CHEMICAL REVIEWS
Review
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Dual Catalysis Strategies in Photochemical Synthesis

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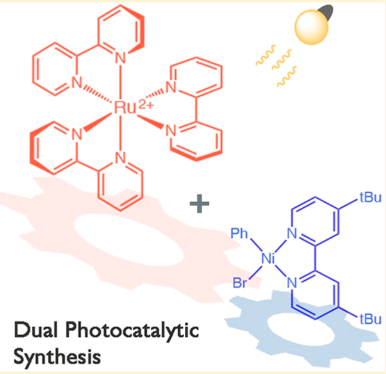
ABSTRACT: The interaction between an electronically excited photocatalyst and an organic molecule can result in the genertion of a diverse array of reactive intermediates that can be manipulated in a variety of ways to result in synthetically useful bond constructions. This Review summarizes dual-catalyst strategies that have been applied to synthetic photochemistry. Mechanistically distinct modes of photocatalysis are discussed, including photoinduced electron transfer, hydrogen atom transfer, and energy transfer. We focus upon the cooperative interactions of photocatalysts with redox mediators, Lewis and Brønsted acids, organocatalysts, enzymes, and transition metal complexes.



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1. INTRODUCTION

Catalysis has played a central role in the development of all major areas of contemporary synthetic chemistry. A remarkably diverse range of catalyst structures, both metal-based and purely organic, have been developed to increase the rate and practicality of important chemical transformations. These entities are capable of providing high levels of control over the stereo- and regioselectivity of complexity-building reactions, and, perhaps most importantly, enabling novel bond constructions that can only be achieved using catalysis.

In the context of synthetic organic photochemistry, photocatalysts play a unique but no less critical role. The interaction of simple organic molecules with light is generally weak. Moreover, electronically excited states are often only available upon irradiation with quite short wavelengths of ultraviolet (UV) light. These high-energy photons can cause uncontrolled photodecomposition processes to occur, a factor that has limited the broad utility of photochemical synthesis in the construction of complex organic molecules. In contrast, photocatalysts are powerfully enabling in synthetic applications because they absorb light with greater efficiency and at longer wavelengths than do simple organic small molecules. These species operate by converting the energy of an absorbed photon into chemical potential that can be used to transform organic substrates in a multitude of ways. Photocatalysis provides a direct means to

Special Issue: Photochemistry in Organic Synthesis

Received: January 12, 2016
Published: April 25, 2016

ACS Publications

DOI: 10.1021/acs.chemrev.6b00018
Chem. Rev. 2016, 116, 10035−10074

access the chemistry of reactive intermediates that often cannot readily be generated using other nonphotochemical strategies. Thus, many of the most practical synthetic strategies involving radical ions, diradicals, and electronically excited organic compounds rely upon the use of photocatalysts.

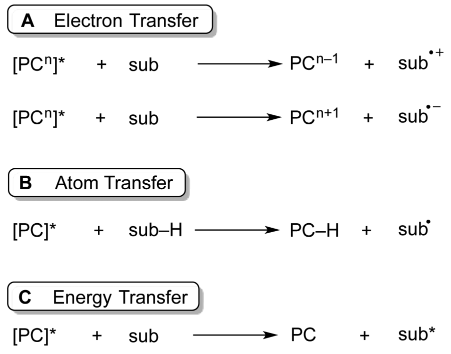
An intriguing synergy emerges when photocatalysis is combined with other, nonphotochemical catalytic strategies. In these dual-catalyst systems, one catalyst is used to absorb light and activate organic substrates, and a second, independent catalyst species is used to further manipulate the reactivity of the resulting photogenerated intermediates. In the past several years, the synthetic chemistry community's interest in photocatalysis has enjoyed tremendous growth, and one of the most remarkable emerging features in this body of recent literature is the frequency with which dual catalysis approaches are utilized. The purpose of this Review is to provide an overview of the ways in which cocatalyst strategies have been applied to synthesis, covering both contemporary developments in organic photochemistry and the important precedents that paved the way for the recent surge of renewed interest in photocatalytic synthesis.

1.1. Mechanisms of Photocatalysis

The interaction between an electronically excited photocatalyst and an organic molecule can result in the generation of a diverse array of reactive intermediates. By taking advantage of the distinctive chemistry of each, a wide range of powerful complexity-building synthetic transformations has been developed.[1] To provide a conceptual framework for discussing the impact of cocatalysis on the reactivity of these varied intermediates, we have organized this Review around three common photocatalytic activation steps.

First, much of the recent renewal of interest in photochemical synthesis has been based upon the propensity of photoexcited molecules to participate in electron-transfer (or "photoredox") processes.[2] A molecule in an electronically excited state is both a stronger oxidant as well as a stronger reductant than its ground-state analogue. Thus, one common class of photochemically initiated reactions involves activation via either a one-electron oxidation or a one-electron reduction of an organic substrate by the photocatalyst (Scheme 1A). The resulting organic radical ion species can directly react in a number of different bond-forming reactions. Alternatively, the radical ion can undergo mesolytic fragmentation to afford separate radical and ionic intermediates, either of which can be productively intercepted in synthetic transformations.

Scheme 1. Mechanisms of Homogeneous Photocatalysis



Second, radical intermediates can also result from the reaction of excited-state photocatalysts via direct hydrogen atom abstraction, rather than by stepwise electron transfer and bond scission as independent processes (Scheme 1B). This is a characteristic reaction of photoexcited aromatic ketones such as benzophenone or acetophenone.[3] More recently, polyoxometalates have also been exploited as photocatalysts for this mechanism of photoactivation as well.[4] The distinction between electron and hydrogen atom-transfer mechanisms is an important one for a number of reasons. Among the most critical is the identity of the thermodynamic parameters that best determine the feasibility of the activation step; while for photoredox activation the success of electron transfer is governed by the redox potentials of the substrate and excited photocatalyst, in hydrogen atom-transfer reactions, the bond strength is typically more predictive.

Third, electronically excited photocatalysts can also activate an organic substrate via energy transfer (Scheme 1C).[5] The transfer of excited-state energy from a photocatalyst to an organic substrate can occur through one of several mechanisms, but the most common in synthetic applications is Dexter energy transfer. This can be conceptualized as the bilateral electron exchange between the excited-state photocatalyst and an organic substrate, resulting in the nonradiative relaxation of the photocatalyst coupled to the simultaneous generation of an excited-state substrate. For this process to be efficient, transfer of excited-state energy from the photocatalyst to the substrate must be thermodynamically feasible. Photosensitization of reactions via this mode of activation is quite common in synthesis; however, the lifetime of the resulting electronically excited substrates is generally quite short. Thus, strategies to use exogenous catalysts to manipulate their reactivity have been substantially more challenging to develop.

Several of the most common photocatalysts used in synthetic applications are shown in Figure 1. The structures of this family of catalysts are dominated by highly conjugated systems, as one might expect for a class of molecules designed to interact with light. Beyond this trivial similarity, however, a cursory glance at these compounds reveals their remarkable diversity. These include simple aromatic chromophores, both neutral and charged, functionalized organic dyes, inorganic clusters, and transition metal complexes whose properties can be easily tuned by ligand modification. The availability of diverse photocatalyst structures that span a broad range of triplet energies and redox potentials is an important benefit of photocatalytic synthesis; the appropriate choice of photocatalyst can be used to control the mechanistic outcome of many reactions where direct substrate photoexcitation might lead unselectively to multiple reaction pathways.

Because this diverse collection of photocatalyst structures nevertheless operates by only a few fundamentally distinct mechanisms of photoactivation, we have elected to organize the material in this Review broadly on the basis of the mode by which the photoacatalyst acts, that is, by electron transfer (section 2), by hydrogen atom abstraction (section 3), or by energy transfer (section 4). However, these various photoactivation processes often lead to similar open-shell reactive intermediates, and because of the short lifetimes of the species involved, it is often difficult to unambiguously determine which mechanism of photoactivation is operative in a given transformation. The mechanisms provided herein reflect the best reasonable hypotheses of the publishing authors, and we present them as such. Given the understandable focus of the field on synthetic advances, experimental validation of several frequently invoked phenomena such as the persistent radical effect[6−8] and the relative contribution of closed catalytic versus radical propagative

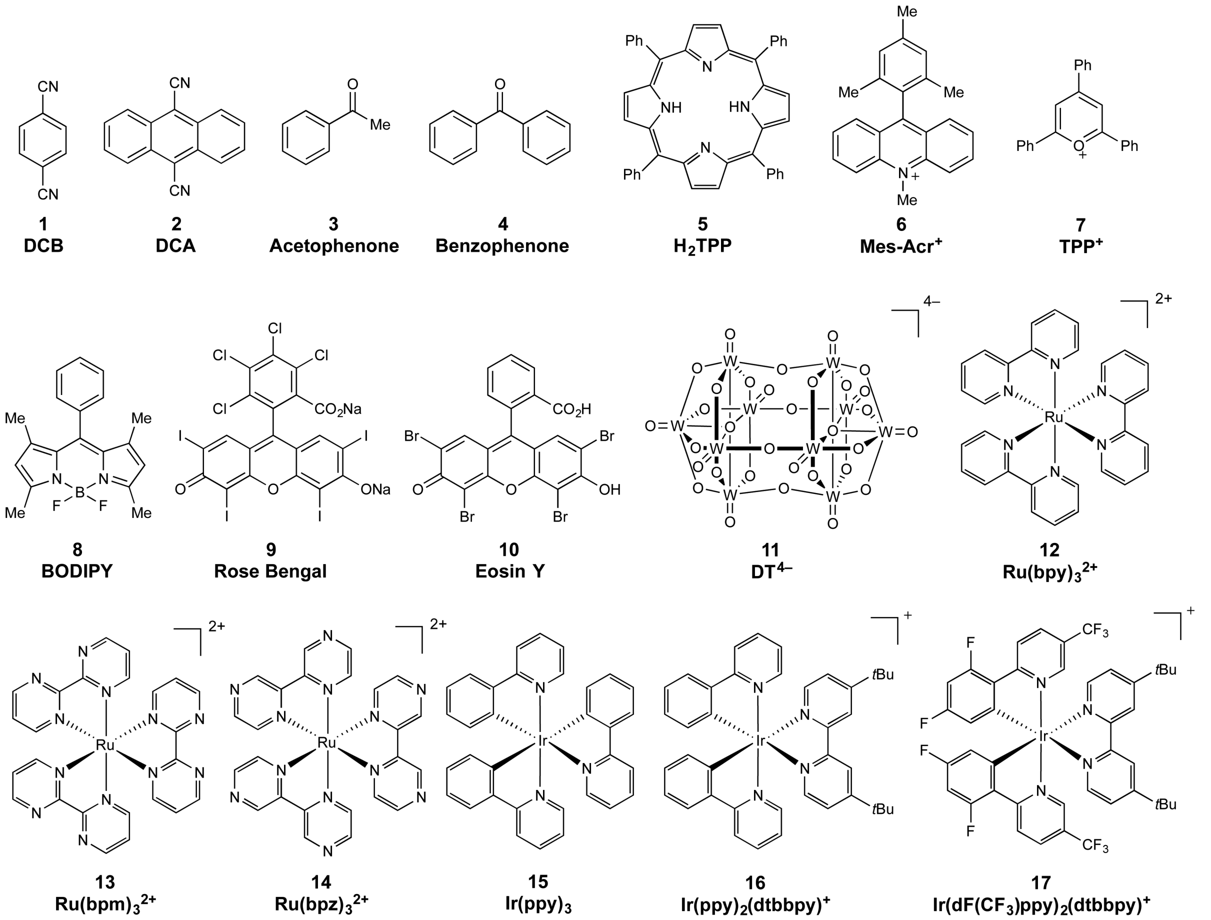


Figure 1. Chemical structures of common photocatalysts.

pathways[9] has not yet been performed for the majority of these reactions. Thus, certain details may be revised as the community's mechanistic understanding expands.

1.2. Scope of the Review

Synthetic organic photochemistry, like many interdisciplinary fields, is informed by the language and culture of several independent scholarly traditions. One significant challenge in interpreting this literature is the existence of a multitude of competing definitions of common terms such as "catalysis" that are used in different communities.[10−13] Can templating moieties that interact with the substrate only via noncovalent interactions be considered "catalysts"? Must a "catalyst" be used substoichiometrically? It might be possible to mount a compelling argument that some of these definitions are more useful than others. However, for the purposes of this Review, we will consider an entity a catalyst if it increases the macroscopic rate of the organic transformation in question while neither being formed nor consumed in the balanced reaction.

We have limited this discussion herein to the use of well-defined small-molecule photocatalysts and cocatalysts in the construction of complex organic molecules. This restriction unfortunately omits the substantial body of work involving semiconductor photocatalysis[14−17] as well as the study of photochemical reactions in supramolecular hosts.[18−21] These two themes of research within synthetic photochemistry are quite extensive, and while we cannot adequately cover them here, a number of excellent, comprehensive reviews on both fields are available. Earlier reviews covering the concept of molecular photocatalysis in synthetic applications have also been published, focusing upon carbon−carbon bond-forming reactions,[22−29] the synthesis of natural products or complex molecular scaffolds,[30−34] as well as asymmetric synthesis.[35−38] The application of both transition metal[39−43] and organic photocatalysts[44−46] has also been discussed previously. Finally, we note that an excellent tutorial review on photochemical dual-catalyst strategies was recently published by Glorius, focusing on the revival of visible light photoredox catalysis over the past decade.[47]

2. PHOTOINDUCED ELECTRON TRANSFER

The emergence of useful redox properties in the excited state is a common feature of molecular chromophores. Photoinduced promotion of an electron from the molecule's HOMO to its LUMO results in the formation of an electronically excited state that can formally be conceptualized as a charge-separated electron−hole pair. If the lifetime of this excited state is sufficiently long to engage in subsequent intermolecular reactions, it can either donate its high-energy electron to an appropriate acceptor (**A**) or fill its partially occupied orbital from a suitable electron donor (**D**). Thus, by virtue of having an electron−hole pair, an excited photocatalyst can engage in both reductive and oxidative chemistry and is typically both a stronger reductant and a stronger oxidant than its ground-state counterpart. As a result, a commonly exploited feature of a photocatalytic species is its ability to convert the energy of an incident photon into synthetically useful electrochemical potential.

Figure 2 outlines the generalized photoredox processes available to a photocatalyst. Absorption of a photon results in

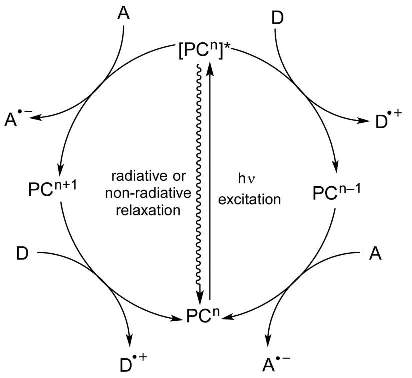


Figure 2. Photoinduced electron transfer (PET).

the generation of an electronically excited state; this can undergo relaxation back to the ground state via a number of unimolecular emissive and nonemissive pathways at relatively rapid rates. The redox properties of the excited state, however, can be exploited upon fast electron transfer to an electron-deficient acceptor species (**A**) or from an electron-rich donor species (**D**). These species are referred to as oxidative and reductive quenchers, respectively, because they result in the formation of a different oxidation state of a photocatalyst in its electronic ground-state configuration. Regeneration of the photochemically active state requires a second electron-transfer process from a complementary donor or acceptor species. Thus, photoredox catalysis typically results in a formal transfer of an electron from one reagent to another, which produces a pair of reactive radical ions comprising the oxidized donor ($\mathbf{D}^{\bullet+}$) and reduced acceptor ($\mathbf{A}^{\bullet-}$).

Both radical cations and radical anions exhibit intriguing, synthetically useful reactivity that is often not available to closed-shell organic molecules.[48−57] However, in photoredox catalysis, it is relatively rare for both radical ion equivalents to be simultaneously engaged in the same organic transformation. More commonly, a single synthetically relevant organic substrate is activated by photoinduced electron transfer, and a balancing redox equivalent is independently introduced to the reaction.

There are two mechanistic scenarios by which this can occur. First, the substrate may directly quench the excited state of the photocatalyst, in which case the balancing redox equivalent is required to regenerate the photocatalyst (Figure 3A). This pathway is viable when electron transfer between the substrate and the excited photocatalyst is thermodynamically feasible. When it is not, however, the excited state can also be engaged by a secondary quencher (Figure 3B). This produces an oxidized or reduced ground-state catalyst that is more powerfully redox-active than the excited state and thus capable of performing a broader range of electron-transfer processes. Interaction with the substrate generates the corresponding substrate radical ion and returns the catalyst to its resting state. Prototypical oxidative quenchers include pyridinium salts, quinones, and nitroarenes. Reductive quenching is typically carried out by electron-rich tertiary amines, sulfides, or phosphines. The kinetics of these quenching processes with a variety of photocatalytic species have been extensively documented.[58]

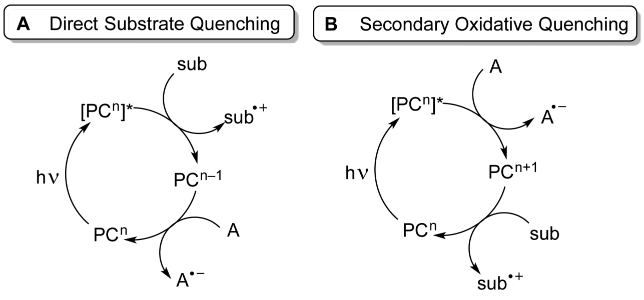


Figure 3. Direct and secondary quenching for an oxidative reaction.

Cocatalysts can be used to influence photoredox transformations by mediating the electron transfer, by independently generating an intermediate species that undergoes photocatalytic activation in situ, or by controlling a reactive intermediate downstream of the photoinduced electron-transfer process itself. The first strategy (redox mediation) constitutes the largest body of research and is treated separately (section 2.1). The remainder of this section is organized according to the identity of the cocatalyst (sections 2.2−2.6).

2.1. Redox Mediation

The feasibility of a given photoredox activation step is primarily determined by the relative half cell potentials of the photocatalyst and substrate, respectively. In general, synthetically useful photoredox reactions have been designed around exergonic electron-transfer processes. However, the kinetics of electron transfer are also important; many PET processes that are thermodynamically favorable are nevertheless kinetically too slow to be useful. In addition, photoredox reactions involving modestly endergonic electron transfer are possible, although Marcus theory considerations predict slow rates of reaction for these processes. A common strategy to address either of these situations is the use of a redox mediator.

The redox mediator is a particular type of quencher that undergoes redox processes with both the photocatalyst and the substrate in separate electron-transfer events (Figure 4). These cocatalysts are commonly referred to in the photochemistry literature as cosensitizers, and occasionally as electron mediators, redox photosensitizers, redox catalysts, electron relays, or electron-transfer agents.[59−62] There are three main mechanistic scenarios in which a redox mediator may increase the rate of a reaction. For a hypothetical oxidative reaction, these are as follows:

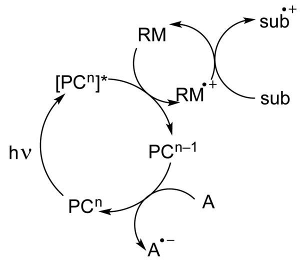


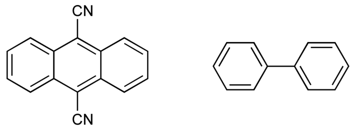
Figure 4. Redox mediation of an oxidative transformation.

(I) The most straightforward use of redox mediators is for transformations in which direct oxidation of the substrate by the photocatalyst is exergonic, but inefficient rates of electron transfer result in a slow overall reaction. In this case, the appropriate choice of a redox mediator that reacts rapidly with both **PC*** and the substrate can mitigate the unfavorable kinetics of the direct electron-transfer process.

(II) Redox mediators can also be beneficial in reactions that involve endergonic PET. Although the electron transfer from $\mathbf{RM}^{\bullet+}$ to the substrate must also be endergonic, it is kinetically more feasible than direct quenching because **RM**$^{\bullet+}$ is in its electronic ground-state configuration and thus has a significantly longer lifetime than **PC***.

(III) Finally, a redox mediator may aid in generation of a solvent-separated ion pair.[63−66] One common source of low quantum efficiency is the occurrence of back-electron transfer (BET) before the intimate ion pair arising from collisional electron transfer ($\mathbf{PC}^{n-1}\cdot\mathbf{sub}^{\bullet+}$) can diffuse apart. A redox mediator may undergo BET more slowly and thus escape the solvent cage more efficiently. Subsequent electron transfer from the substrate to **RM**$^{\bullet+}$ results in the same reactive species but as a solvent-separated ion pair ($\mathbf{PC}^{n-1}$ + $\mathbf{sub}^{\bullet+}$) that is more resistant to BET.

Common photocatalyst/redox mediator pairs such as 9,10-dicyanoanthracene (DCA, **2**) and biphenyl (BP, **18**) are often employed with little discussion of which mechanistic scenario is operative (Figure 5).[67−70] As such, this section is organized by transformation, but we will attempt to highlight these mechanistic distinctions where possible.



2
DCA

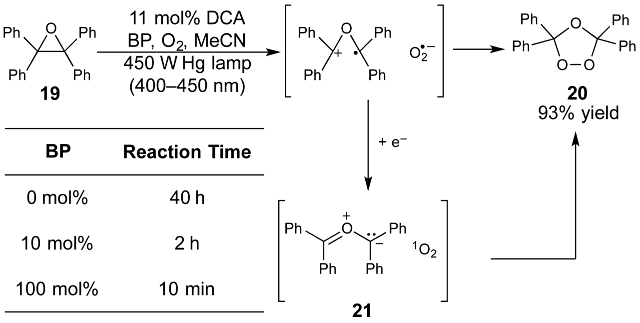
18
BP

Figure 5. Common photocatalyst/redox mediator pair 9,10-dicyanoanthracene (DCA) and biphenyl (BP).

2.1.1. Photooxygenation.

One of the most prolific areas of study for this type of cocatalysis is the photooxygenation of cycloalkanes and small saturated heterocycles.[71] In the 1980s, the Schaap group discovered that biphenyl provided a dramatic rate increase to the DCA-catalyzed oxidation of cyclopropanes,[72] epoxides,[73−76] and aziridines.[77] For example, the photooxygenation of epoxide **19** to **20** is a slow reaction upon photocatalysis using DCA alone (Scheme 2). However, addition of 10 mol % biphenyl (BP) decreased the reaction time to 2 h, and complete conversion could be achieved in just 10 min using a stoichiometric loading of BP. The proposed explanation for this effect was in line with mechanistic situation II (section 2.1). Substrate **19** is an ineffective quencher of DCA*, whereas BP quenches rapidly (k_q = 3.1 × 10^{9} M^{-1} s^{-1}). Secondary electron transfer from BP$^{\bullet+}$ to **19** is endergonic, but still kinetically feasible due to the long lifetime of BP$^{\bullet+}$ relative to DCA*.

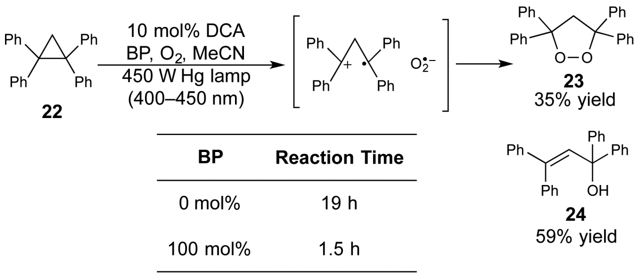
Scheme 2. Redox-Mediated Epoxide Photooxygenation



BP	Reaction Time
0 mol%	40 h
10 mol%	2 h
100 mol%	10 min

The photooxygenation of cyclopropanes exhibited similar rate increases in the presence of biphenyl (Scheme 3), although a different mechanistic rationale was proposed.[72,77] Although substrate **22** quenches DCA* at close to a diffusion-controlled rate (k_q = 1.1 × 10^{10} M^{-1} s^{-1}), the rate of formation of photooxygenated products **23** and **24** nevertheless increased 10-fold upon the addition of biphenyl. This observation is most consistent with mechanistic scenario III. Rapid PET results in the formation of a contact ion pair (DCA$^{\bullet-}$·**22**$^{\bullet+}$), and escape from the solvent cage is inefficient with respect to the rate of back-electron transfer. In contrast, while BP quenches the photoexcited catalyst more slowly, BP$^{\bullet+}$ can undergo more efficient dissociation. Subsequent electron transfer to this redox mediator affords the solvent-separated (DCA$^{\bullet-}$ + **22**$^{\bullet+}$) ion pair, which can more readily react with oxygen to afford the endoperoxide.

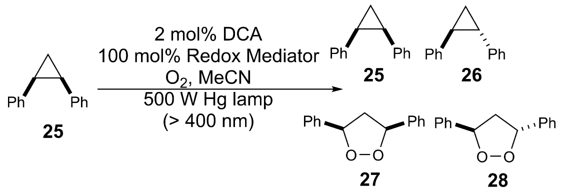
Scheme 3. Redox-Mediated Cyclopropane Photooxygenation



BP	Reaction Time
0 mol%	19 h
100 mol%	1.5 h

Similar effects were observed in the photooxygenation of diarylcyclopropanes,[78] vinylcyclopropanes,[79−81] and 8-methoxypsoralen.[82] In each case, DCA* is quenched more efficiently by the substrate than by BP, but the addition of redox mediator nevertheless accelerates the overall rate of reaction. Tamai et al. quantified this effect in a study of the photoisomerization and photooxygenation of 1,2-diphenylcyclopropane **25**.[83,84] The addition of various polyphenylene redox mediators such as biphenyl, terphenyl, and phenanthrene was shown to result in an increase in the quantum yield for separation of RM$^{\bullet+}$ and DCA$^{\bullet-}$ (Scheme 4).

Scheme 4. Effect of Redox Mediator on Ion Pair Separation for Cyclopropane Isomerization and Photooxygenation



Redox Mediator	k_q (M^{-1} s^{-1})	E_{ox} (V)[a]	Φ_{sep}
None	1.1 x 10^{10}	1.38[b]	0.12
Biphenyl	3.6 x 10^{9}	1.45	0.72
o-Terphenyl	7.0 x 10^{9}	1.42	0.64
m-Terphenyl	5.5 x 10^{9}	1.40	0.32
Napthalene	1.4 x 10^{10}	1.22	0.58
Phenanthrene	1.4 x 10^{10}	1.17	0.62

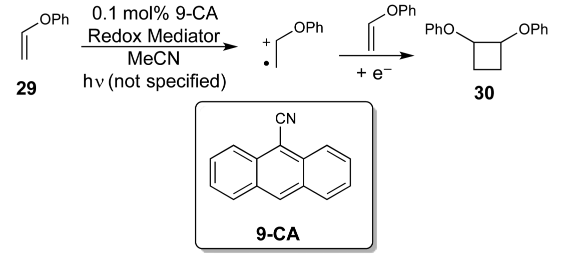
[a] Oxidation potentials vs Ag/AgClO$_4$ in MeCN. [b] Oxidation potential of cyclopropane **25**.

2.1.2. Alkene Oxidation.

Alkene radical cations have immense versatility in organic synthesis. They can readily participate in nucleophilic additions,[51,85] cyclizations,[52,86] cycloadditions,[48,49,51,57] fragmentations,[54] and rearrangement processes.[53,86] Photoredox catalysis offers a convenient method to generate these reactive intermediates, and redox mediation has been frequently utilized in tandem with photocatalysis to maximize the rate of reaction.

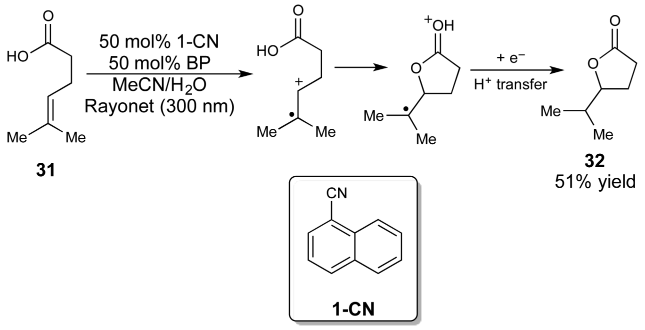
One of the earliest examples of this strategy was reported by Farid in the dimerization of phenyl vinyl ether **29** (Scheme 5) using 9-cyanoanthracene (9-CA) as a photocatalyst.[87] Direct quenching of [9-CA]* by **29** is endergonic and too slow to be measured. Consistent with this inefficient electron transfer, the dimerization reaction proceeds with low quantum yield ($\Phi = 7.3 \times 10^{-3}$). However, addition of redox mediators such as phenanthrene, alkylnaphthalenes, or durene improved the quantum yield, up to 200-fold. This finding is consistent with the production of a long-lived arene radical cation that improves the efficiency by which the alkene radical cation can be generated.

Scheme 5. Dimerization of Phenyl Vinyl Ether by Redox-Mediated PET



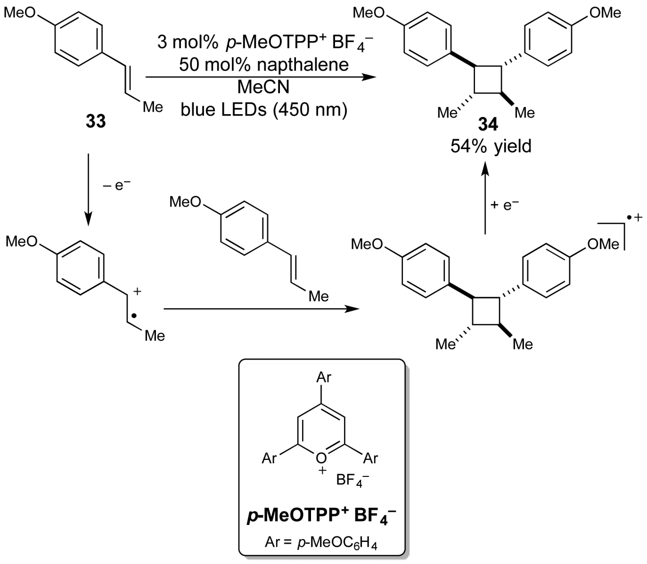
Gassman reported that a combination of 1-cyanonapthalene (1-CN) and biphenyl could be used to oxidize trisubstituted alkenes such as **31** (Scheme 6). The resultant radical cations could be trapped with oxygen nucleophiles in both intramolecular[88,89] and intermolecular[90] functionalization reactions. Arnold achieved similar reactivity using diphenylethene substrates.[91,92] Silyl enol ethers could also be oxidized and selectively desilylated in the presence of alkyl silyl ethers,[93] and Hintz et al. later reported a DCA/Phen photocatalytic system for the cyclization of silyl enol ethers with pendant olefins.[94] The Roth laboratory observed altered chemoselectivity in the PET cyclization of geraniol, although the influence of the redox mediator was small.[95]

Scheme 6. Alkene Photooxygenation and Trapping



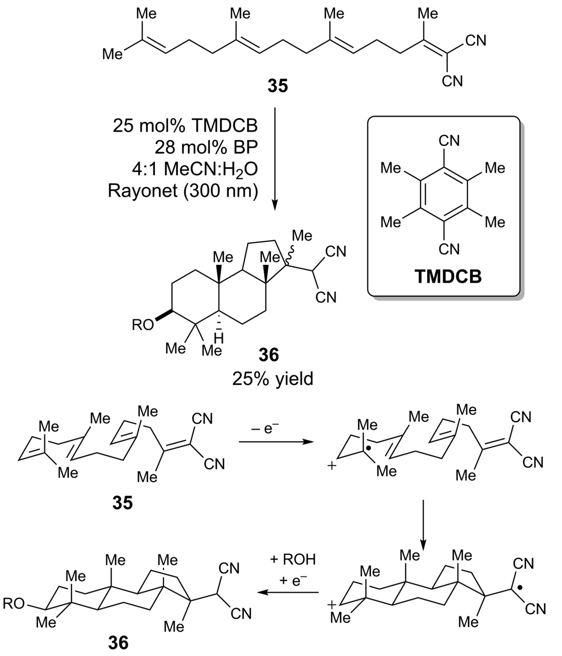
Nicewicz reported a conceptually similar strategy for the [2+2] cycloaddition of styrenes such as **33** using 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (p-MeOTPP$^+$BF$_4^-$) as a photocatalyst (Scheme 7). Optimal yields of cycloadduct **34** required the addition of aromatic hydrocarbons such as naphthalene or anthracene.[96] The authors proposed that the redox mediators improve the rate of substrate oxidation as compared to direct quenching.

Scheme 7. [2+2] Cycloaddition of Styrenes by PET



Alkene oxidation by PET/redox mediation has also been leveraged for the rearrangement of polyunsaturated compounds such as aza-1,4-dienes[97,98] and 1,5-hexadienes,[99] as well as tautomerization of styrenes,[100] nucleophilic addition to 1,3-dienes,[101] and the valence isomerization of norbornadiene.[102] Among the most synthetically powerful transformations in this class are the radical cation cascades developed by Warzecha, Demuth, and Görner (Scheme 8). Photocatalytic oxidation of polyene **35** by 1,4-dicyano-2,3,4,5-tetramethylbenzene

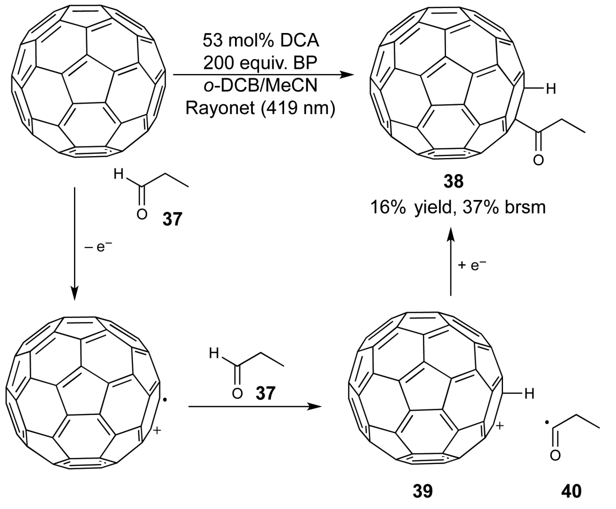
Scheme 8. Photooxidative Radical Cation Cascade Employing Redox Mediation



(TMDCB) resulted in the formation of polycyclic scaffold **36**.[103−105] In these reactions, biphenyl was employed as a redox mediator.[106,107] Stern−Volmer analysis revealed that BP is able to quench [TMDCB]* at rates comparable to those of the terpene substrates. Furthermore, given its high loading and the long lifetime of $BP^{\bullet+}$ relative to [TMDCB]*, it dramatically increases the rate of substrate oxidation. Transient absorption spectroscopy also revealed the presence of $BP^{\bullet+}$ under these conditions, as well as the unexpected result that $TMDCB^{\bullet-}$ may reduce the substrate as well. Subsequent studies showed that other donors such as *trans*-stilbene or *N*,*N*-dimethylaniline were also competent as redox mediators when coupled with 2,4,6-triphenylpyrylium tetrafluoroborate ($TPP^+BF_4^-$).[108] This method was utilized in the synthesis of several steroid natural products.[109,110] Furthermore, a remote chiral auxiliary could be used to control the stereochemical outcome of the overall transformation.[111−113]

The combination of PET sensitization and redox mediation enables the facile generation of $C_{60}^{\bullet+}$, a process that has traditionally required γ-irradition. Foote demonstrated that *N*-methylacridinium hexafluorophosphate ($MA^+PF_6^-$) could photocatalytically generate this radical cation, as observed by transient absorption spectroscopy. Addition of biphenyl increased the signal strength of $C_{60}^{\bullet+}$ by an order of magnitude.[114,115] Subsequent work by Mattay and co-workers focused on the reaction of the $C_{60}^{\bullet+}$ radical cation with alcohols, ethers, and aldehydes using DCA photocatalysis (Scheme 9).[116]

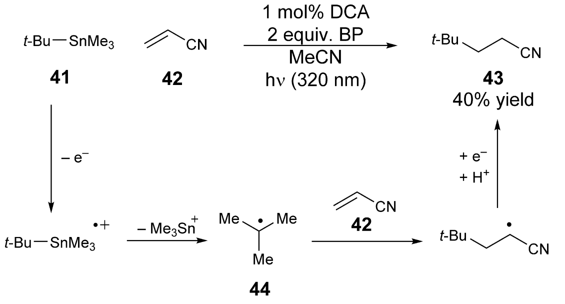
Scheme 9. Acylation of C_{60} Using PET and Redox Mediation



For instance, the reaction with propionaldehyde **37** affords **38**, consistent with a process involving H atom abstraction by $C_{60}^{\bullet+}$ followed by attack of the resulting acyl radical **40** on $H{-}C_{60}^{+}$ **39**.[117,118]

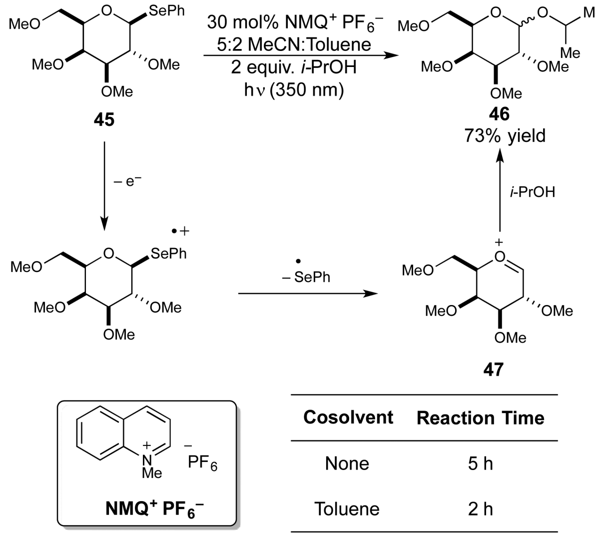
2.1.3. Heteroatom Oxidation. Fagnoni and Albini reported that the photooxidation of organostannane **41** followed by mesolytic fragmentation of the C−Sn bond results in the formation of alkyl radical **44**, which subsequently can react with electron-poor acceptors such as **42** to give **43** (Scheme 10).[62,119] Although the process can be conducted using single photocatalysts such as 1,4-dicyanonapthalene (DCN) or phenanthrene, the rates were increased in the presence of biphenyl as a redox mediator. Enantioselective, chiral auxiliary controlled versions of this reaction have also been reported.[120]

Scheme 10. Oxidative Destannylation and Radical Addition



Cumpstey and Crich reported a procedure for photocatalytic glycosylation using selenosugars as donors (Scheme 11).[121]

Scheme 11. Oxidative Deselenation and Nucleophilic Trapping

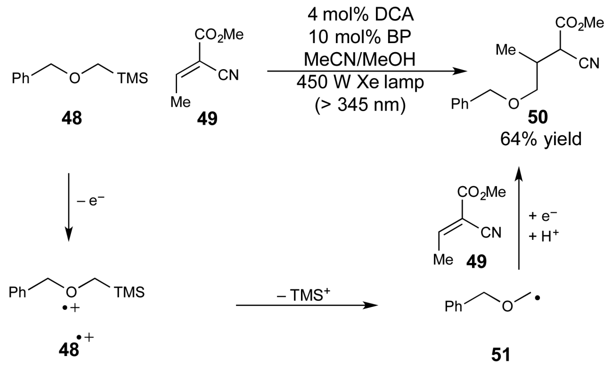


Cosolvent	Reaction Time
None	5 h
Toluene	2 h

Photoxidation of **45** with a *N*-methylquinolinium photocatalyst ($NMQ^+PF_6^-$) results in elimination of the selenyl radical to give glycosyl cation **47**, which can in turn be trapped by an alcoholic acceptor moiety to form **46**. The reaction was accelerated upon addition of toluene as a cosolvent, which the authors proposed was serving as a redox mediator.

Steckhan, Blechert, and co-workers used the DCA/BP pair for the functionalization of α-silyl amines,[122] ethers, acetals,[123] and carbamates.[124] Scheme 12 shows that following oxidation and

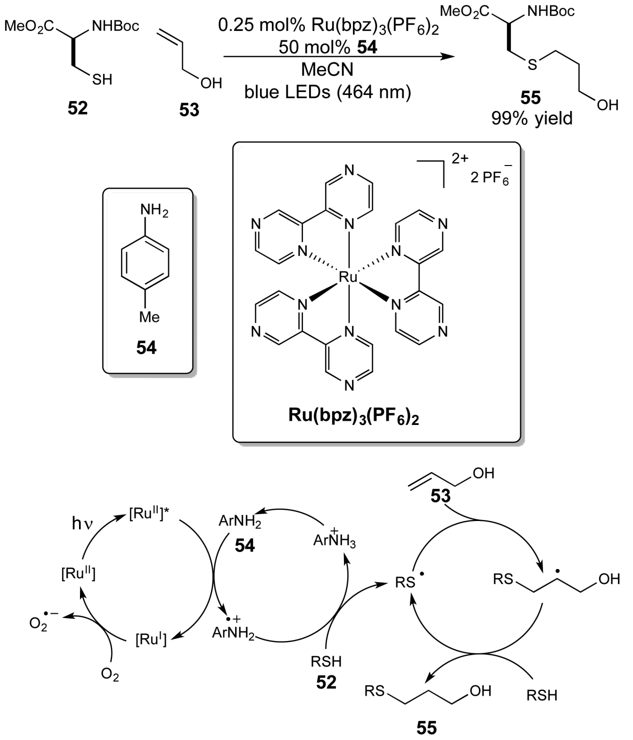
Scheme 12. Photooxidative Desilylation and Radical Addition



desilylation of **48**, α-alkoxy radical **51** can add to alkenes such as **49** to afford **50**. The analogous reaction with a single photocatalyst was inefficient, presumably due to rapid BET from DCA$^{\bullet-}$. As has been discussed previously, the redox mediator helps to form **48**$^{\bullet+}$ free in solution and thus avoid this problem.

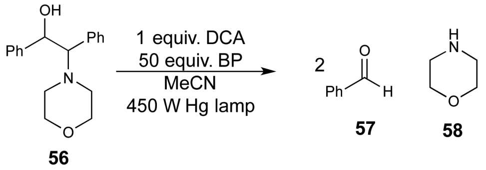
The Yoon laboratory reported a radical thiol–ene reaction initiated by photooxidation of sulfur-containing compounds by Ru(bpz)$_3$(PF$_6$)$_2$ (Scheme 13).[125] Several amine additives provided a dramatic rate increase, particularly those such as **54**, whose redox potentials were between that of the excited photocatalyst and that of the thiol substrate. As direct quenching of the photocatalyst by thiol **52** was proposed to be quite slow, the authors suggested that sequential PET events from and to the redox mediator (**54**) allowed for the increase in reaction rate. This case then falls into the first mechanistic scenario described in section 2.1, wherein the mediator provides a more kinetically feasible pathway for electron transfer. Boyer subsequently utilized this method for the postsynthetic radical functionalization of polymers.[126]

Scheme 13. Radical Thiol–Ene Reaction with Anilines as Redox Mediators



In some cases, redox mediators can alter the distribution of reaction products or otherwise influence the chemoselectivity of a photocatalytic transformation. Whitten studied the oxidative fragmentation of 1,2-aminoalcohols to give aldehydes (Scheme 14) and found that redox mediation with biphenyl improved reaction rates due to its efficient quenching of DCA*.[127] Moreover, while photooxidation of *syn*-**56** using DCA alone afforded higher quantum yields than *anti*-**56**, both diastereomers underwent cleavage at equivalent efficiencies in the presence of BP. The authors proposed that the former conditions involve the reaction of contact ion pairs while the latter give solvent-separated ion pairs.

Scheme 14. Oxidative Fragmentation of α,β Amino Alcohols

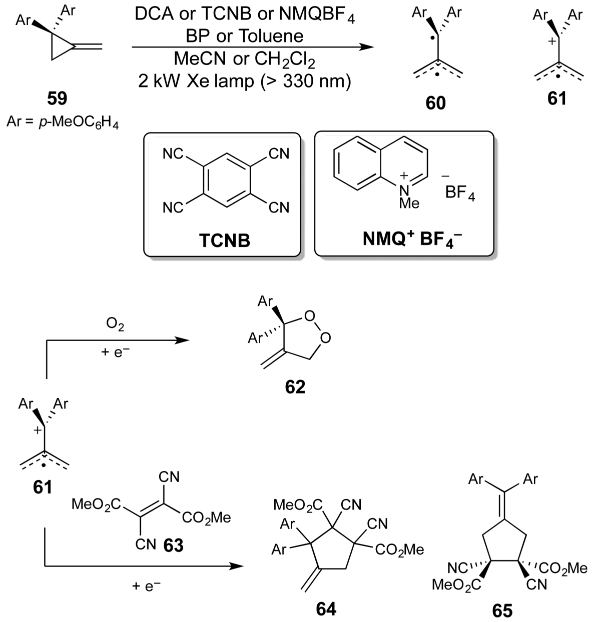


Photocatalyst	Φ_{ox}
DCA	0.0017
DCA/BP	1.10

2.1.4. Oxidative Rearrangement.

Ikeda studied the rearrangement and cycloaddition of methylenecyclopropanes such as **59** under photocatalytic conditions (Scheme 15).[128]

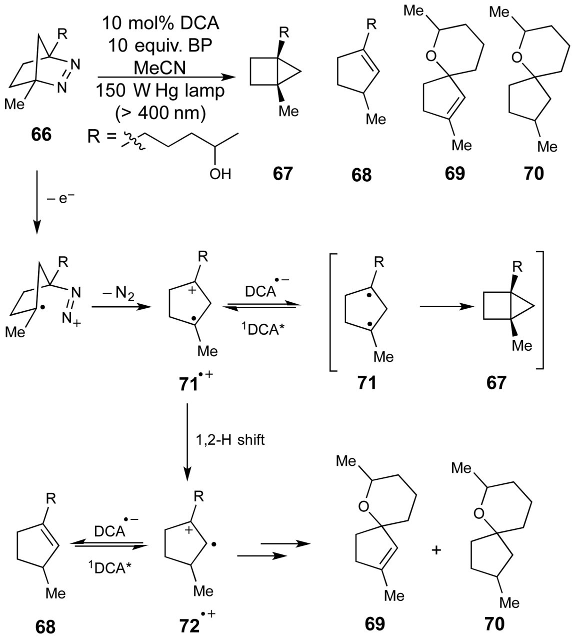
Scheme 15. Methylene Cyclopropane Rearrangement and Cycloadditions



Transient absorption spectroscopy revealed both diradical **60** and radical cation **61** as intermediates, and their relative concentration could be controlled by photocatalyst identity. Moreover, the addition of redox mediators such as biphenyl or toluene increased the formation of **61** relative to **60**. Although the ability of these species to undergo cycloadditions with oxygen to form **62** or with fumarate **63** to form **64** and **65** was examined, the photocatalyst/redox mediator pairs were not directly compared.

Adam and Sendelbach demonstrated that photooxidation of azoalkane **66** led to extrusion of dinitrogen, followed by ring closure to housane **67**, rearrangement to cyclopentene **68**, or intramolecular trapping of the pendant alcohol to produce spiroethers **69** and **70** (Scheme 16).[129,130] Addition of biphenyl as a redox mediator results in an increase in the rate of reaction and also changes the distribution of products. The authors proposed that BET from DCA$^{\bullet-}$ to **71**$^{\bullet+}$ leads to 1,3-diradical **71**, which can rapidly form housane **67**. Thus, the DCA-only conditions, proposed to produce a contact radical ion pair from which back-electron transfer is rapid, generate a large amount of

Scheme 16. Effect of Redox Mediator on Chemoselectivity of a Photooxidative Azoalkane Rearrangement



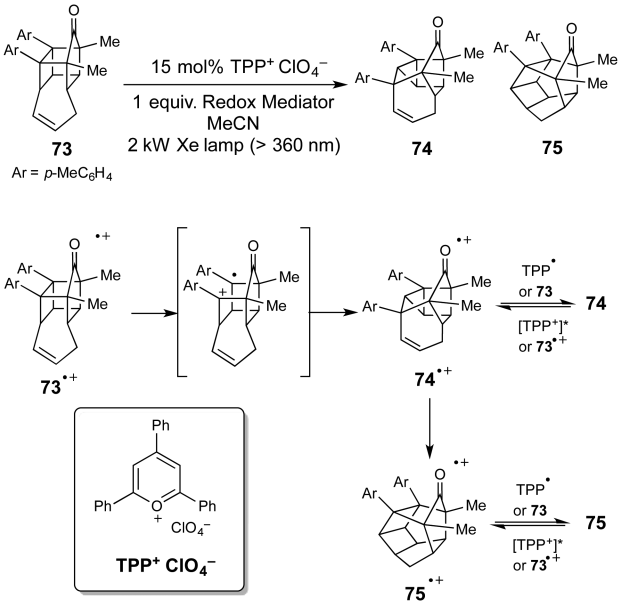
Photocatalyst	Conv.	67	68	69	70
DCA	30%	52%	48%	--	--
DCA/BP	40%	25%	62%	7%	6%

this product. In contrast, redox mediation with biphenyl generates **71**$^{\bullet+}$ as a solvent-separated ion pair with DCA$^{\bullet-}$. The free radical cation intermediate has a lifetime sufficient to undergo 1,2-hydrogen migration to form **72**$^{\bullet+}$, which in turn leads to alkene **68** and spiroethers **69** and **70**.

Yamashita studied the rearrangement of cage ketone **73** catalyzed by 2,4,6-triphenylpyrylium perchlorate (TPP$^+$ClO$_4^-$).[131] The proposed mechanism involves oxidation of **73**, rearrangement via **74**$^{\bullet+}$ and **75**$^{\bullet+}$, and chain-propagating electron transfer to afford **74** and **75** (Scheme 17). The addition of aromatic hydrocarbons such as biphenyl, phenanthrene, and pyrene resulted in a significant rate increase, consistent with their role as redox mediators. Furthermore, the product distribution proved to be sensitive to the structure of the mediator. Interestingly, the rate increases as the reaction progresses, and on the basis of quantum yield measurements, the authors suggested that the product can also act as an autocatalytic redox mediator.

2.1.5. Photoreduction. While reductive redox mediators are regularly utilized in electrochemical transformations,[132−136] they have found relatively few applications in synthetic photoredox chemistry. An interesting example was described by Darwent and Kalyanasundaram (Scheme 18),[137] who found that methyl viologen (MV^{2+}) can act as a redox mediator between a Ru(bpy)$_3$Cl$_2$ photocatalyst and benzoquinone **76**. Although **76** can quench the photocatalyst directly, a high concentration of superior quencher MV^{2+} results in the accumulation of MV$^{\bullet+}$. This in turn can reduce **76** to **76**$^{\bullet-}$, which upon protonation and disproportionation affords phenol **77**. More recently, this type of redox mediation has been applied to the Meerwein−Ponndorf−Verley-type reduction of ketones, although in this case the viologen is involved in hydride transfer as well as electron transfer.[138]

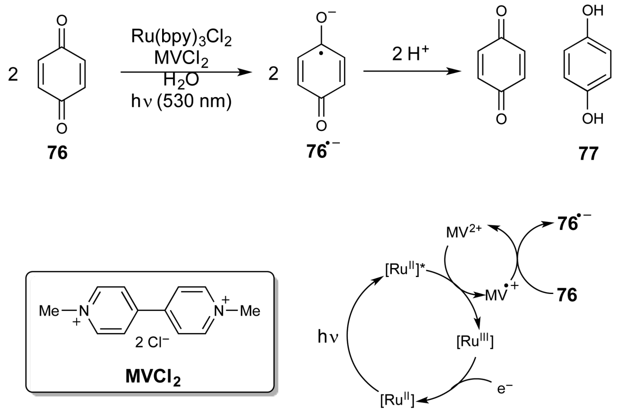
Scheme 17. Oxidative Cage Ketone Rearrangement and Influence of Redox Mediators



Redox Mediator	E_{ox} (V)[a]	Time	73	74	75
None	—	60 min	93%	--	7%
Pyrene	1.15	5 min	100%	--	trace
Phenanthrene	1.58	5 min	41%	59%	--
Biphenyl	1.90	5 min	46%	46%	--

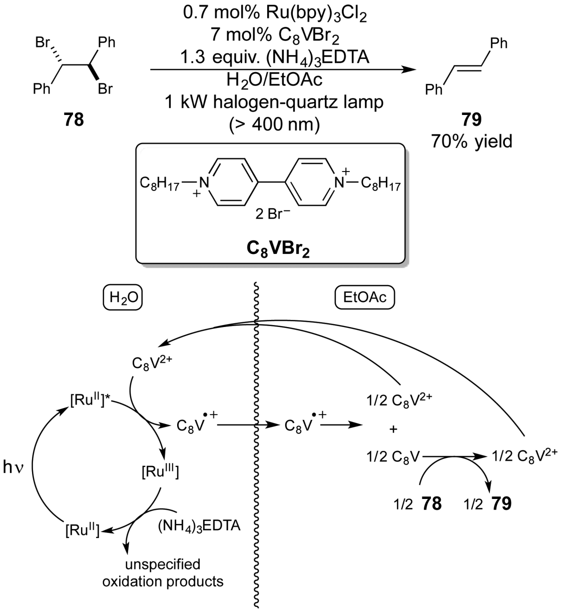
[a] Oxidation potentials vs SCE in MeCN.

Scheme 18. Redox Mediation Applied to Benzoquinone Reduction



Willner merged this approach with phase transfer catalysis in the reductive dehalogenation of vicinal dibromides (Scheme 19).[139−141] In his system, *N*,*N*′-dioctyl viologen (C$_8$V^{2+}) is reduced by photoexcited Ru*(bpy)$_3$Cl$_2$. The resultant C$_8$V$^{\bullet+}$ is lipophilic, and migrates to the organic phase of the reaction mixture, where it can disproportionate to C$_8$V^{2+} and C$_8$V. The former returns to the aqueous phase to reenter the catalytic cycle, and the latter carries out the two-electron reduction of dibromide

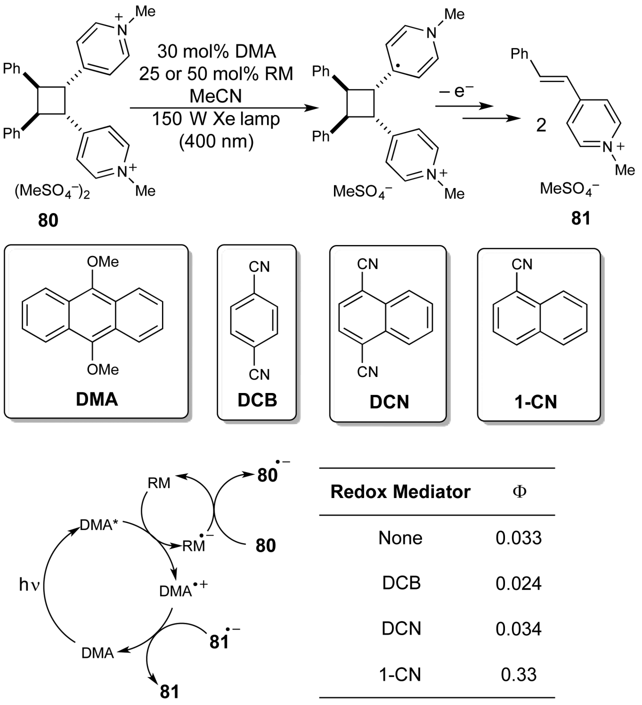
Scheme 19. Reductive Mediation Combined with Phase Transfer Catalysis



78 to **79**. Further work from this group incorporated enzymes as cocatalysts and will be discussed later (section 2.6).

Sawaki reported that the photoreduction and fragmentation of stilbazolium cyclobutane **80** could be carried out with 9,10-dimethoxyanthracene (DMA) as a photocatalyst and 1-CN, DCN, or DCB as redox mediators (Scheme 20).[142] The authors postulated that the mediator quenches DMA* and dissociates from the solvent cage to reduce the substrate. The most dramatic increase in quantum yield was observed using 1-CN as the redox mediator, with less pronounced effects using DCN and DCB. The authors attributed this difference to an increased proclivity for the $DMA^{\bullet+}\cdot 1\text{-}CN^{\bullet-}$ intimate ion pair to undergo dissociation.

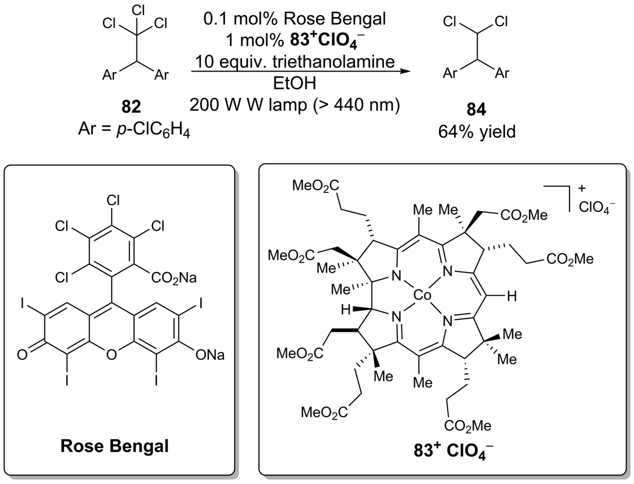
Scheme 20. Effect of Redox Mediators on Photoreductive Cycloreversion



Redox Mediator	Φ
None	0.033
DCB	0.024
DCN	0.034
1-CN	0.33

More recently, Tahara and Hisaeda reported a reductive dehalogenation protocol using Rose Bengal as a photocatalyst (Scheme 21).[143] In their proposed mechanism, the photoexcited catalyst is quenched by vitamin B12 derivative **83**$^+$, and the resulting Co^I species reduces **82**.

Scheme 21. Reductive Dehalogenation Using a Co^{II} Redox Mediator



2.2. Lewis Acid Catalysis

The use of Lewis acids to activate heteroatom-containing organic moieties is a ubiquitous strategy in organic synthesis that has found use in a wide variety of applications. Photochemistry is no exception, and the prevalence of ketone and enone functional groups has made this a fertile area for exploration. Coordination of a Lewis acid to heteroatom-containing substrates can impact a number of critical reactivity parameters, including electrophilicity and reduction potential. They can also impact the rate of a reaction by stabilizing a ketyl radical or other photoreduced anionic intermediate.

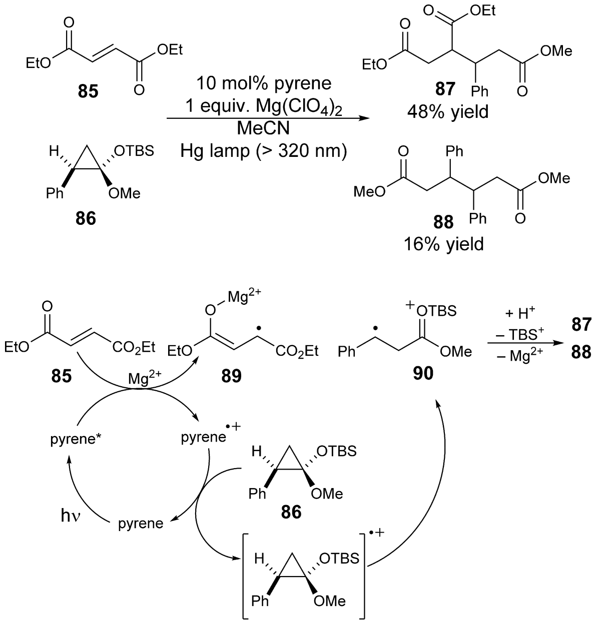
2.2.1. Substrate–Lewis Acid Interactions.

Abe and Oku studied the pyrene-catalyzed PET reaction between diethyl fumarate **85** and cyclopropane **86** to give crossed product **87** and homodimer **88** (Scheme 22).[144] This reaction proceeds only in the presence of $Mg(ClO_4)_2$ as a Lewis acidic cocatalyst. The authors proposed that stabilization of allylic ketyl radical **89** by Mg^{2+} suppresses back-electron transfer to the photocatalyst and enables the coupling with **90** to proceed efficiently. Saito and coworkers observed a similar effect of a Mg^{2+} Lewis acid in the reductive cleavage of the benzoyloxy moiety from **91** (Scheme 23).[145]

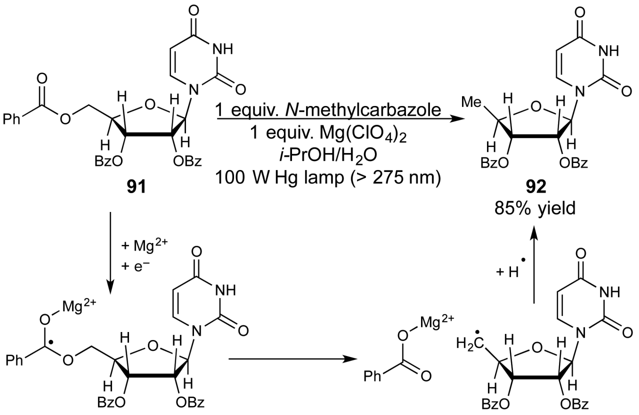
Pac reported an intriguing example of a Lewis acid effect that does not require precoordination to the substrate. The rate of photoreduction of olefins by $Ru(bpy)_3^{2+}$ and a NADH analogue enjoys a dramatic increase in the presence of $Mg(ClO_4)_2$ (Scheme 24).[146] Although the Mg^{2+} does not exhibit appreciable binding to starting alkene **93**, there is a strong stabilizing interaction with the corresponding radical anion **93**$^{\bullet-}$. This interaction thus facilitates the one-electron reduction of the substrate.[147]

Mizuno, Nakanishi, and Otsuji also observed that the substitution of dicyanobenzene **1** with group 14 allyl metal species such as **95** became more efficient upon addition of

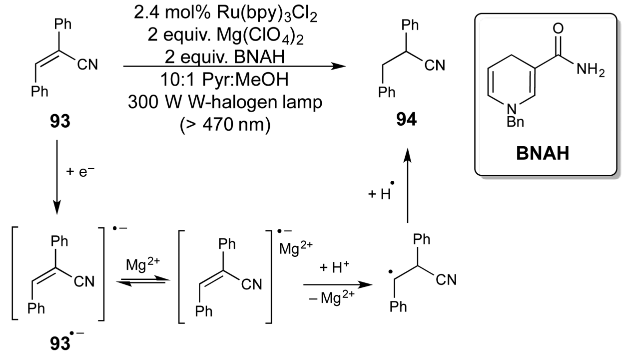
Scheme 22. Photoreduction of Fumarate Promoted by Lewis Acid Coordination

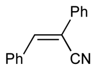
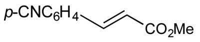
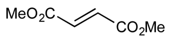


Scheme 23. Reductive Deoxygenation by Lewis Acid-Promoted PET



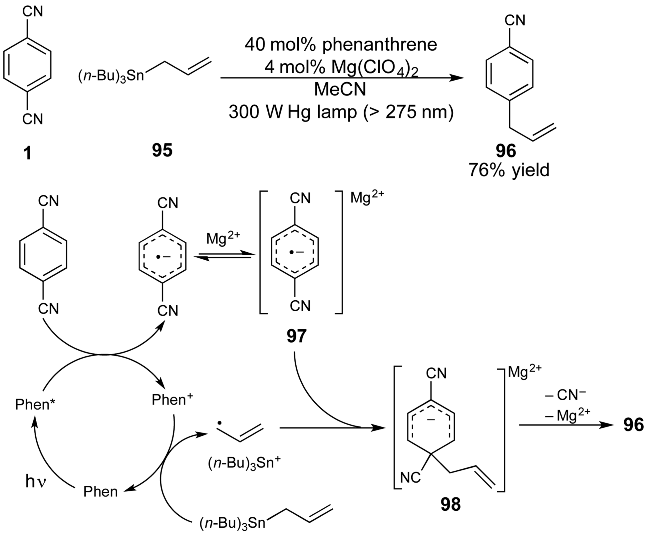
Scheme 24. Effect of Mg^{2+} on Photocatalytic Alkene Reduction



Substrate	E_{red}(V)[a,b]	Φ_{Mg}/Φ	Yield[b]
	−1.95 (−1.82)	3.6	30% (47%)
	−1.80 (−1.63)	1.3	100% (100%)
	−1.72 (−1.49)	1.6	70% (80%)

[a] Reduction potential vs $Ag/AgNO_3$ in MeCN. [b] The listed values are in the absence of Mg^{2+}. The parenthetical values are when Mg^{2+} is added.

Scheme 25. Photoreductive Substitution with $Mg(ClO_4)_2$ Cocatalyst



$Mg(ClO_4)_2$ (Scheme 25).[148] Again, the magnesium salt was proposed to stabilize the radical anion of the substrate and inhibit back-electron transfer to the photocatalyst. The resulting complex **97** can combine with an allyl radical to form **98**, which then undergoes loss of cyanide and the Lewis acid to provide **96**.

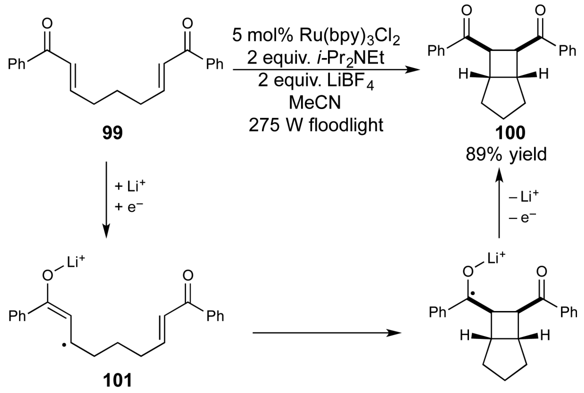
The effect of a Lewis acid on the reduction potential of organic substrates has found use in recent reports of photocatalytic methods as well. The Yoon group has applied this strategy to a variety of photocatalytic cycloaddition reactions. For example, the intrinsic reduction potential of bis(enone) **99** is roughly −1.6 V vs SCE in DMF,[149] which lies outside the range accessible using $Ru(bpy)_3^{2+}$ (Scheme 26). However, coordination of $LiBF_4$ to the substrate results in a more positive reduction potential, thereby enabling photoreduction. The resulting allylic ketyl radical **101** is able to engage with the pendant Michael acceptor to afford cyclobutane product **100**.[150] Intermolecular versions of this reaction have also been developed.[151,152]

Because the enone substrates do not absorb in the visible region, no background reaction occurs in the absence of photocatalyst or Lewis acid. Thus, a highly enantioselective [2+2] cycloaddition could be realized using a chiral Eu^{3+} Lewis acid without any competing racemic process due to direct excitation or uncatalyzed photoreduction (Scheme 27).[153]

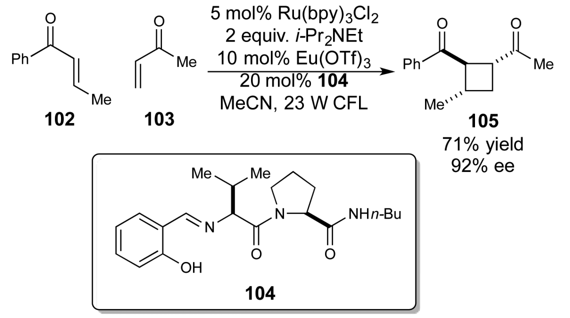
Similar photoreductive conditions were applied to the [4+2] hetero-Diels−Alder cycloaddition of bis(enone) **106** (Scheme 28).[154] In this study, Yoon found empirically that $Mg(ClO_4)_2$ was the optimal Lewis acid that balanced the rate of photoreductive activation of the enone substrate and that of an undesired reductive decomposition of the product.

Yoon utilized a conceptually analogous approach in the design of a [3+2] cycloaddition of acyl cyclopropanes with alkenes, where coordination of a Lewis acid to the ketone modulates the

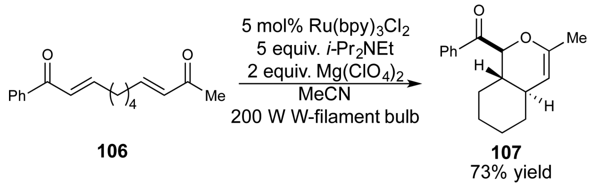
Scheme 26. Photoreductive [2+2] Cycloaddition with $LiBF_4$



Scheme 27. Enantioselective [2+2] Cycloaddition Using a Chiral Lewis Acid Cocatalyst



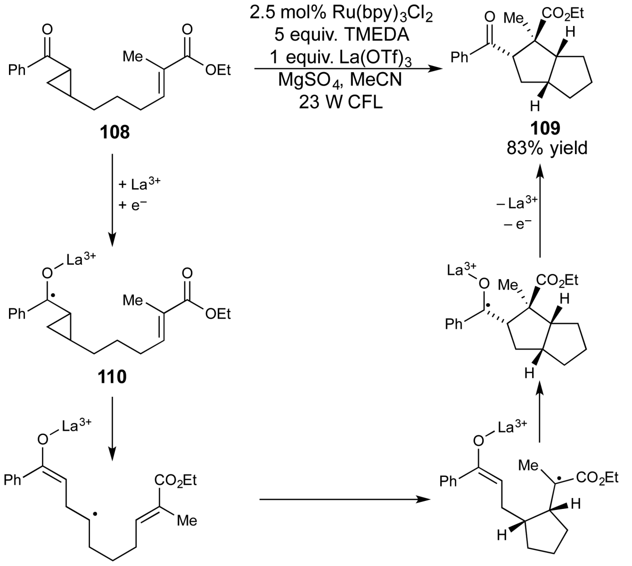
Scheme 28. $Ru(bpy)_3Cl_2/Mg(ClO_4)_2$-Catalyzed [4+2] Bis(enone) Cycloaddition



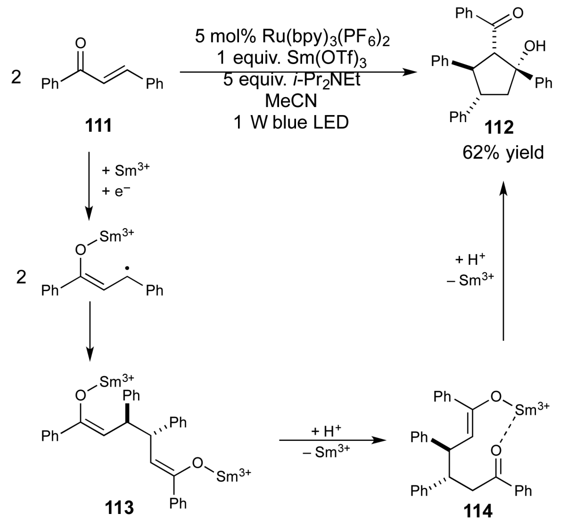
reduction potential of **108**. The resultant α-cyclopropyl ketyl radical **110** can undergo ring opening followed by alkene addition and reoxidation to yield [3.3.0]bicyclooctane **109** (Scheme 29).[155] In this reaction, $LiBF_4$ was insufficiently Lewis acidic to enable photoreductive activation of the cyclopropyl ketone. Instead, the more strongly Lewis acidic additive $La(OTf)_3$ was found to be the optimal Lewis acid cocatalyst for this transformation. An asymmetric intermolecular variant of this reaction was recently reported.[156]

Xia demonstrated that lanthanide Lewis acids are also effective in promoting the reductive dimerization of chalcones using photoredox catalysis (Scheme 30).[157] The authors proposed that $Sm(OTf)_3$ facilitates the reduction of **111** and stabilizes the resulting radical anion, which dimerizes to form dienolate **113**. The Lewis acid also guides the subsequent cyclization step of **114** to **112**. Importantly, this reaction is a net-reductive cyclization reaction and thus differs in an important mechanistic regard from the previous examples of $Ru(bpy)_3^{2+}$-catalyzed cycloadditions.

Scheme 29. Photoreductive [3+2] Cycloadditions by Lanthanide Cocatalysis



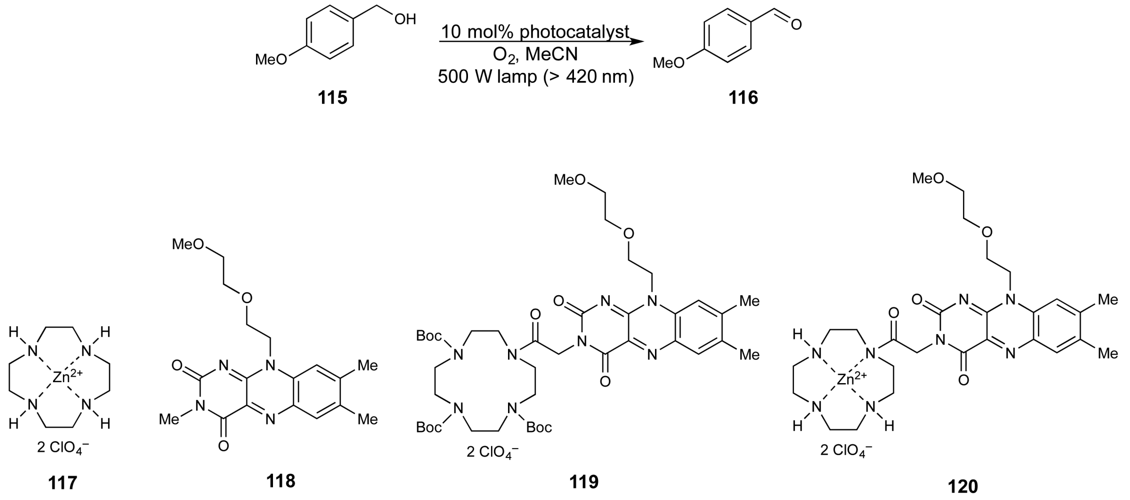
Scheme 30. Reductive Chalcone Dimerization Catalyzed by Sm^{3+} and $Ru(bpy)_3(PF_6)_2$



Lewis acidic metal ions can also be used as templating reagents to recruit and localize Lewis basic substrates. While this strategy is common in many applications involving homogeneous catalysis, few examples related to photocatalytic transformations have been reported. Cibulka, Vasold, and König designed flavin-derived photocatalyst **119** with a tetraamine binding site.[158] The latter chelates Mg^{2+}, which in turn coordinates benzyl alcohol **115**. By increasing the local concentration of the substrate, the quantum efficiency of photooxidation by the flavin is increased significantly (Scheme 31).

2.2.2. Photocatalyst−Lewis Acid Interactions. The use of Lewis acids to activate electron-deficient organic substrates toward photocatalytic reduction is a logical cocatalyst strategy that follows from their ability to increase the electrophilicity of a wide range of organic substrates. However, examples of Lewis acid cocatalysis of oxidative photochemical transformations are also known. Neither the organic substrates nor their radical cations would be expected to engage in redox-relevant interactions with a Lewis acid. On the other hand, the radical anion resulting from a reduced photocatalyst can readily be stabilized by a Lewis acid, which could serve to minimize the rate of back-electron transfer. The application of this concept to photoinduced electron-transfer chemistry has been a topic of investigation for several decades.[66,159−161]

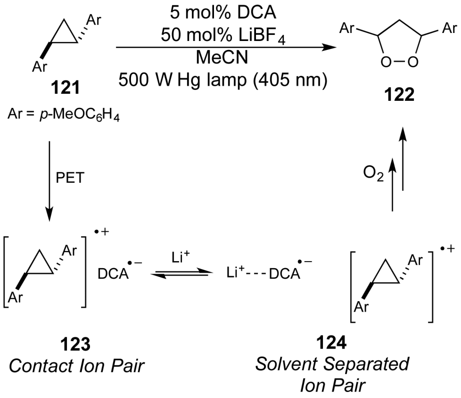
Scheme 31. Lewis Acid-Templated Photocatalytic Alcohol Oxidation



Photocatalyst(s)	Φ	Conv. at 1 h
None	--	0%
117 + **118**	1.8×10^{-3}	2%
119	9.1×10^{-4}	1%
120	3.8×10^{-2}	51%

Mizuno discovered that a range of Lewis acids increase the quantum yield for photoisomerization and oxygenation of cyclopropane **121** (Scheme 32).[162] One major source of inefficiency in this reaction arises from recombination of the photogenerated ion pair **123**, composed of oxidized $\mathbf{121}^{\bullet+}$ and reduced $DCA^{\bullet-}$. However, coordination of a Lewis acid to $DCA^{\bullet-}$ is proposed to stabilize the radical anion and decrease the rate of unproductive back-electron transfer. A similar strategy has been applied to a number of other transformations, including the photooxygenation of cyclopropanes,[78,84,163] disiletenes,[164] biphenyls,[165,166] and 1,5-dienes,[167] as well as the addition of methanol to 1,1-diaryl alkenes.[168]

Scheme 32. Lewis Acid Accelerated Cyclopropane Photooxidation by BET Suppression



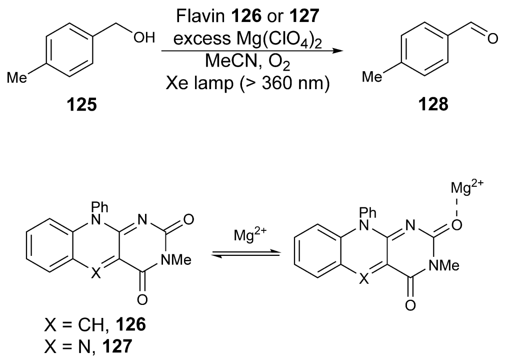
Lewis acids can alter the photoelectrochemical properties of photocatalysts by coordination to heteroatom binding sites in much the same way as they can change the redox potential of Lewis basic organic substrates (section 2.2.1). Fukuzumi, Kuroda, and Tanaka showed that the excited-state oxidation potential of flavin photocatalysts **126** and **127** is increased substantially upon complexation with Mg^{2+} or Zn^{2+} ions (Scheme 33).[169] Under these conditions, the oxidation of benzyl alcohol **125** to **128** was achieved in considerably shorter reaction times.[170,171]

2.2.3. Lewis Acid Catalysis of Non-Redox Steps. Lewis acid strategies that alter the redox properties of the substrate or photocatalyst or interfere with back-electron transfer exert their influence primarily on the dynamics of the electron-transfer process itself. These constitute the majority of synthetic applications of photoredox/Lewis acid cocatalysis to date. However, Lewis acids can also affect processes downstream of the PET step. This can be particularly important when the photogeneration of reactive intermediates is facile but their subsequent reactions are relatively inefficient. For example, Zhu and Rueping recently reported the photocatalytic α-functionalization of glycyl esters (Scheme 34).[172] After oxidation of **129**, a $Zn(OAc)_2$ cocatalyst decomposes photogenerated hemiaminal intermediate **132**; the resulting imine **133** is activated toward nucleophilic addition by indole **130** to afford **131**. Cheng and coworkers observed a similar effect, although they proposed a slightly different order of steps.[173]

In their study on photocatalytic radical cation cascades using Eosin Y, Yang et al. found that substrates such as **134** did not provide appreciable conversion, presumably due to the low nucleophilicity of the 1,3-diketone terminus. However, the addition of LiBr helped to favor the enol tautomer, allowing facile cyclization to **135** (Scheme 35).[174]

$Ru(bpy)_3^{2+}$ and other photoredox sensitizers can be used to photooxidatively desilylate α-silylamine **136**; the chemistry of the resulting α-amino radical intermediate **139** has been

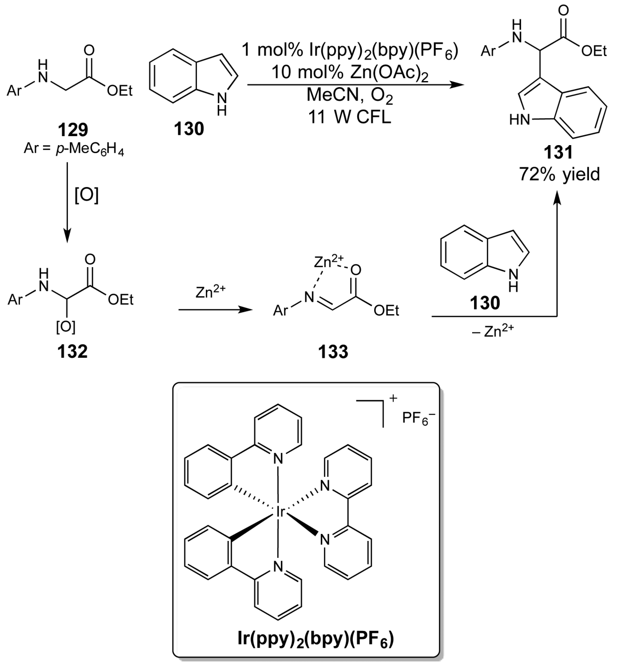
Scheme 33. Effect of Mg^{2+} Binding of Flavin Photoredox Properties



Flavin	$K_{assoc.}$	$E(fl^{*}/fl^{\bullet-})(V)^{a,b}$
126	1.1×10^3	1.85 (2.16)
127	1.7×10^2	2.06 (2.35)

[a] Redox potentials determined indirectly on the basis of the oxidation potentials of various arenes vs SCE in MeCN. See ref 169 for details. [b] The listed values are in the absence of Mg^{2+}. The parenthetical values are when Mg^{2+} is added.

Scheme 34. Lewis Acid Accelerated Addition after PET

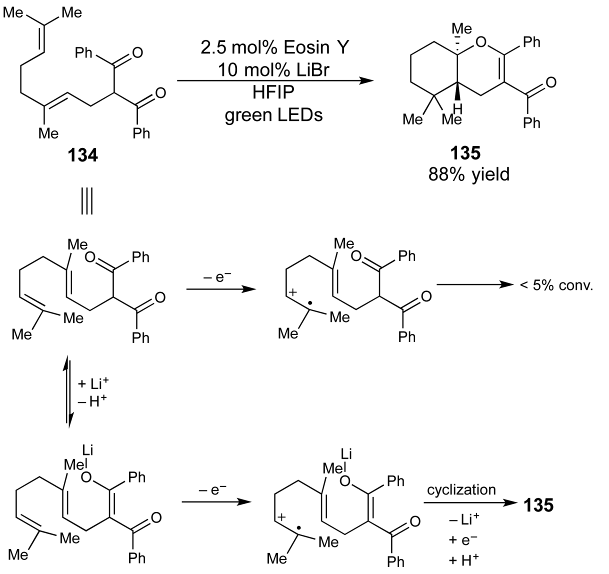


thoroughly investigated.[175] While this class of nucleophilic radical is sufficiently reactive to add to Michael acceptors unassisted,[176] Yoon found that the rate of the conjugate addition increases significantly upon addition of Lewis acid cocatalysts. In particular, a chiral (pybox)Sc^{III} complex is able to accelerate the reaction and control the enantioselectivity of the conjugate addition step (Scheme 36).[177]

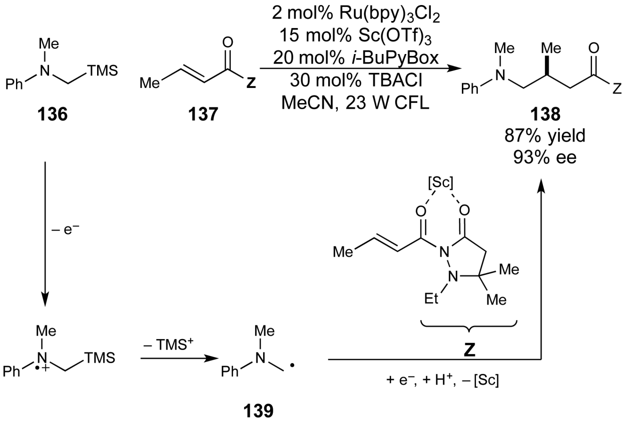
2.3. Brønsted Acid/Base Catalysis

Like Lewis acid coordination, the protonation of organic functional groups can have a similarly diverse range of effects on the redox properties and reactivities of organic substrates.

Scheme 35. Radical Cation Cascade Promoted by Lewis Acid Activation



Scheme 36. Enantioselective Lewis Acid-Catalyzed Addition of Radical Generated by PET



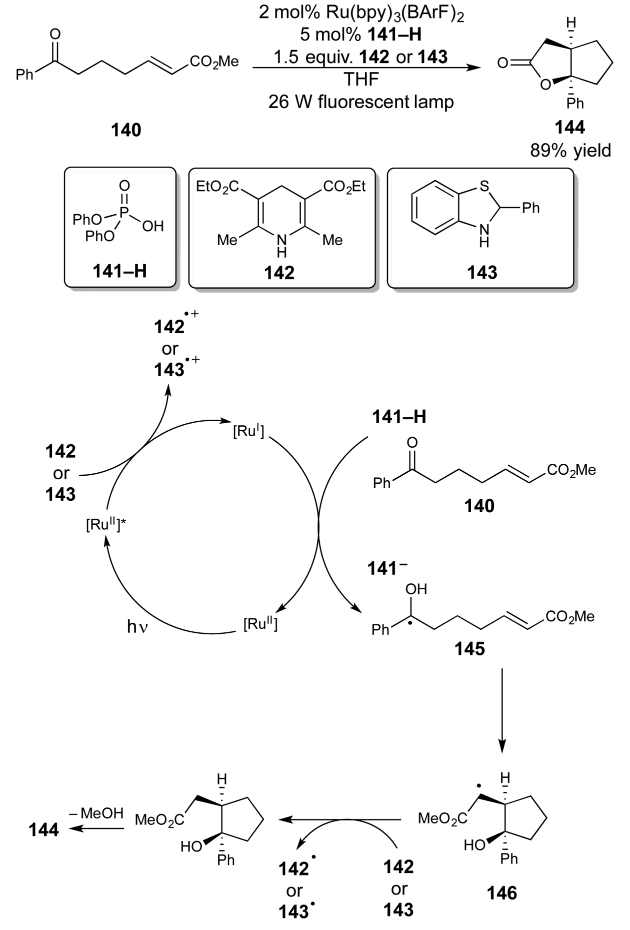
Thus, the use of Brønsted acid cocatalysts in photocatalytic transformations has also emerged as a powerful strategy for novel synthetic methods.

2.3.1. Proton-Coupled Electron Transfer (PCET).

Brønsted acids can catalyze the photoreduction of organic substrates in a manner analogous to that of Lewis acids. However, in many cases, these electron-deficient functional groups possess a pK_a too low to result in a significant concentration of protonated substrate. Proton-coupled electron transfer (PCET) involves the concomitant transfer of a proton and an electron to an organic substrate in a single concerted process. This activation strategy enables the facile generation of radical intermediates that would be kinetically inaccessible via separate proton- and electron-transfer steps. This subject has been reviewed recently,[178−180] and we focus here on its applications to photocatalytic synthesis.

The Knowles laboratory has pioneered the development of synthetic methods that exploit PCET as a means of generating open-shell reactive intermediates. They have shown that aryl ketones are reduced and cyclized using a combination of Brønsted acid and transition metal photoredox catalysts (Scheme 37).[181] The authors propose a mechanism wherein photoexcited

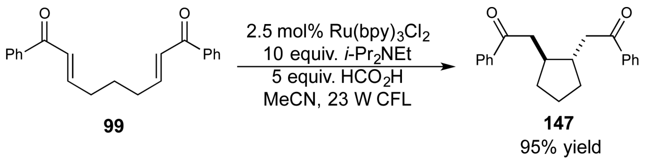
Scheme 37. Reductive Cyclization of Ketones by PCET



Ru(bpy)$_3$(BArF)$_2$ is quenched by hydrogen atom donor **142** or **143** to provide Ru^I; transfer of an electron from this species to the ketone substrate is assisted by a phosphoric acid cocatalalyst (**141-H**) in a PCET step. The resulting ketyl radical **145** undergoes cyclization to the pendant alkene to **146**, followed by hydrogen atom transfer from **142** or **143** and lactonization to afford ester **144**. The oxidized hydrogen atom donors **142**$^•$ or **143**$^•$ can lose another electron and proton to regenerate the active Ru^I reductant and the Brønsted acid cocatalyst **141-H**. Subsequently, the authors developed an enantioselective addition of photogenerated ketyl radicals to hydrazones in which chiral BINOL-derived phosphoric acid cocatalysts both activated the ketone substrate toward PCET and controlled the stereochemistry of the subsequent radical addition.[182]

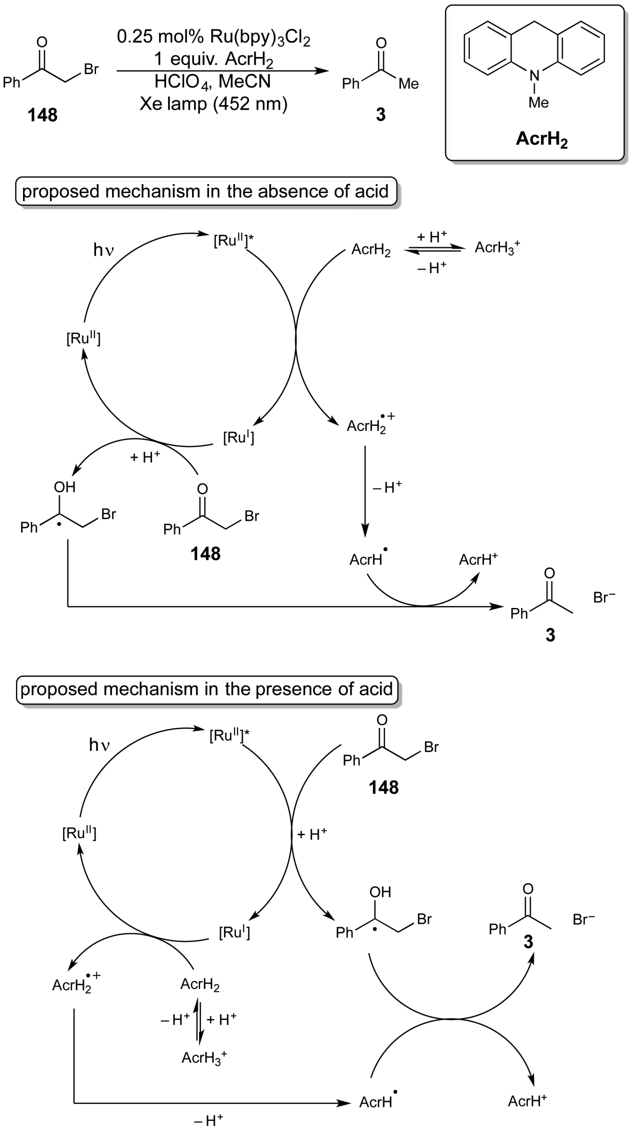
Yoon and co-workers utilized a similar combination of Brønsted acid and photoredox catalysts in the reductive cyclization of bis(enone) **99** to **147** (Scheme 38).[183] The optimal activating Brønsted acid utilized in this case proved to be formic acid. While the authors did not propose that the photoreduction step involved PCET, the analogy to the ketyl radical cyclization studied by Knowles suggests that the same mechanism of activation is likely to be operative here. Notably, only the identity of the acidic cocatalyst differs from the Lewis acid-catalyzed [2+2] method that the Yoon laboratory reported for the same bis(enone) substrates earlier.[150] The authors argued that the chemistry of the neutral radical intermediate generated under Brønsted acid conditions is fundamentally distinct from the reactivity of the radical anion generated under Lewis acidic conditions.

Scheme 38. Reductive Cyclization of Bis(enones)



Fukuzumi and co-workers studied the effect of Brønsted acids on the reductive dehalogenation of phenacyl bromide **148** (Scheme 39).[184] They found that addition of $HClO_4$ substantially improves the reaction rate, and engages substrates that are otherwise unreactive, such as phenacyl chlorides. In the absence of acid, the authors propose that photoexcited [Ru*(bpy)$_3$]$^{2+}$ is reductively quenched by 9,10-dihydro-10-methylacridine (AcrH$_2$) and the resultant Ru^I species is capable of reducing the α-bromoketone substrate. Direct quenching by the substrate is not observed. In the presence of Brønsted acid, however, AcrH$_2$ is protonated to AcrH$_3^+$, which is a less effective

Scheme 39. Effect of Brønsted Acid on Rates of Electron Transfer to α-Bromoketones

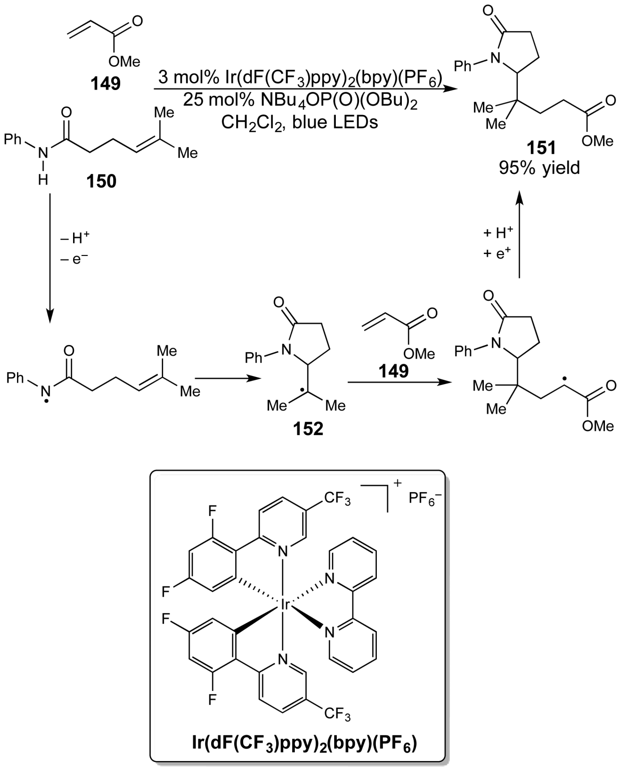


reductive quencher. Nevertheless, the rate of dehalogenation is increased, and the authors suggest a change in mechanism to explain this observation. Rather than reductive quenching by $AcrH_2$ or $AcrH_3^+$, they propose direct oxidative quenching by the substrate, which is known to be accelerated by Brønsted acids.[185,186] Under these conditions, quenching rates for the ketones match or exceed those measured for $AcrH_2$ in the absence of acid. The exact nature of this acid catalysis, and the possibility of PCET, is not discussed.

Bissember and co-workers recently disclosed a reaction between maleimides and dialkylanilines that utilizes TFA as a cocatalyst.[187] The authors propose that the role of this Brønsted acid is to facilitate the aerobic oxidation of the photoexcited $[Cu^I]^*$ catalyst to $[Cu^{II}]$, although they do not comment on the exact mechanism by which this takes place. They also consider that the TFA may accelerate downstream steps as well, which is a general phenomenon discussed in section 2.3.2.

PCET may also be used to remove a net hydrogen atom, rather than add one. For example, Knowles showed that amides could be oxidized to amidyl radicals and cyclized onto tethered alkenes (Scheme 40).[188] The key PCET step is thought to involve simultaneous deprotonation of **150** by a catalytic phosphate base and electron transfer to photoexcited $[Ir^{III}]^*$. Following cyclization, alkyl radical **152** can either add to **149** and gain a net hydrogen atom to form **151**,[188] or directly abstract a hydrogen atom from an appropriate donor (hydrogen atom-transfer cocatalysis is discussed further in section 2.4.2).[189]

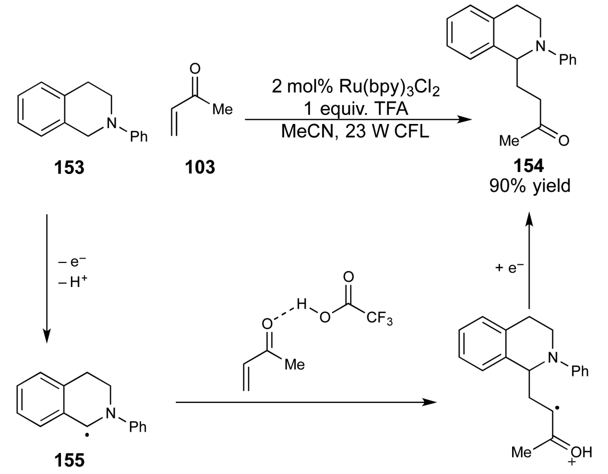
Scheme 40. PCET and Amide Cyclization



2.3.2. Brønsted Acid Catalysis of Non-Redox Steps.

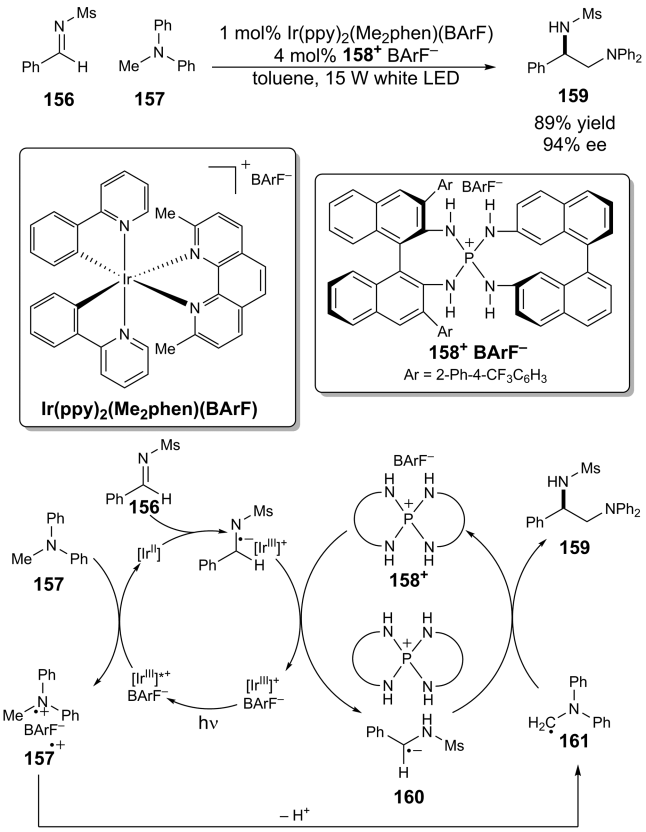
Brønsted acids can control nonphotochemical processes downstream of the photoactivation step in a manner analogous to that of Lewis acid cocatalysts. For example, the Yoon group studied the addition of photocatalytically generated α-amino radical **155** to methyl vinyl ketone (Scheme 41).[190] This reaction was accelerated by acidic additives such as TFA, which the authors proposed could increase the net electrophilicity of the Michael acceptor.

Scheme 41. Brønsted Acid-Catalyzed Addition of PET-Generated α-Amino Radicals to Enones



Ooi recently disclosed a highly enantioselective radical coupling based on the idea of ion pairing.[191] In their proposed mechanism (Scheme 42), amine **157** quenches the photoexcited iridium catalyst, which can then reduce imine **156** to the corresponding radical anion. Hydrogen-bond donor **158**$^+$ undergoes counterion exchange with this species to form chiral

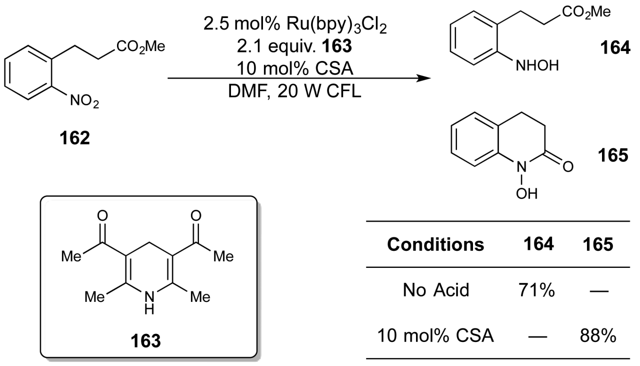
Scheme 42. Enantioselective Radical Coupling Reaction Using Chiral Ion Pairing



ion pair **160**. At the same time, oxidized **157**$^{\bullet+}$ is deprotonated to form α-amino radical **161**, which adds to **160** to form **159**.

The Yoon laboratory reported the photocatalytic reduction of nitroarenes such as **162** (Scheme 43).[192] The addition of a catalytic amount of camphorsulfonic acid (CSA) was required for the formation of cyclized hydroxamic acid **165**; in the absence of this cocatalyst, only hydroxylamine **164** was observed.

Scheme 43. Nitroarene Reduction and Post-PET Cyclization



Conditions	164	165
No Acid	71%	—
10 mol% CSA	—	88%

Brønsted acid additives have been empirically shown to be beneficial in a number of other photoredox transformations as well, although the precise nature of their effect is not always clear. For example, Maity and Zheng reported a photocatalytic oxidative indole synthesis that is accelerated by the addition of silica gel.[193] Yu employed a catalytic amount of *p*-chlorobenzenesulfonic acid in the photocatalytic synthesis of azaarenes, presumably to facilitate formation of an acyl oxime precursor rather than to influence PET.[194] Qi and Zhang found that catalytic TsOH improved their synthesis of α-alkoxybenzamides.[195] König observed enhanced performance of photocatalytic amine deprotection at low pH, although the mechanistic basis of this effect was not determined.[196]

2.4. Organocatalysis

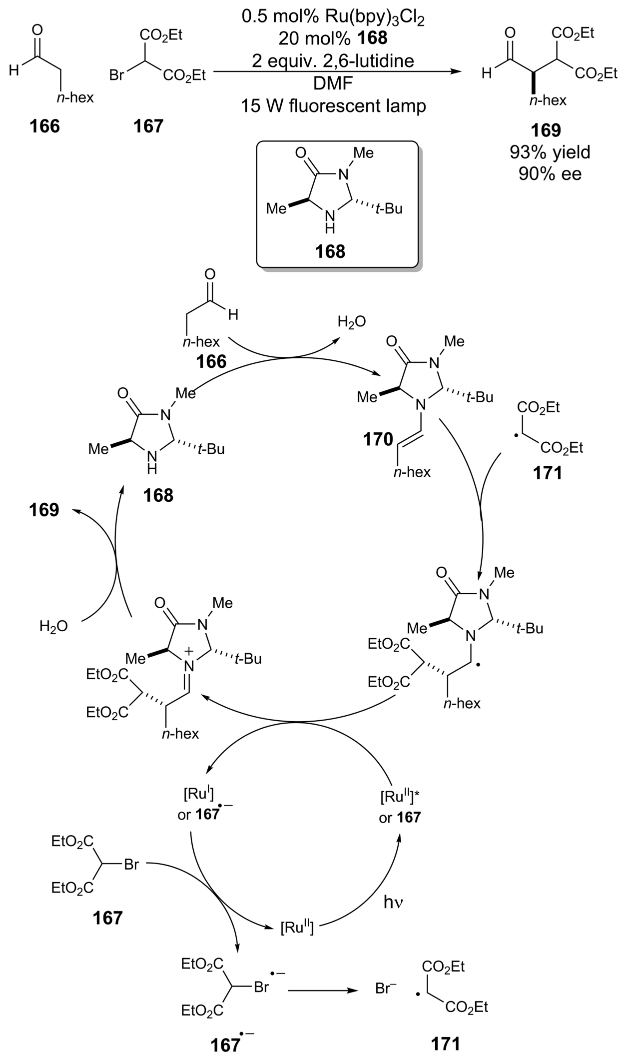
Over the past two decades, organocatalysis has evolved into a robust and diverse theme of contemporary synthetic research. A wide range of organocatalytic activation modes have been used in conjunction with photoredox catalysis. The majority of these cocatalysts influence the photocatalytic activation step itself, either by facilitating electron transfer or by catalytically generating a transient species that participates directly in the PET process. Other cocatalysts impact the rate of downstream steps by interacting with a reactive intermediate produced by photoactivation but not with the photocatalyst itself. The organization of this section will be based upon the class of organocatalyst utilized.

2.4.1. Enamine/Iminium Catalysis.

Some of the earliest applications of organocatalysis to photoredox reactions were developed by MacMillan, who reported several protocols for the α-functionalization of aldehydes. The general mechanism for these reactions is exemplified by Scheme 44, and is proposed to be operative for the addition of α-carbonyl,[197] fluoroalkyl,[198] α-cyanoalkyl,[199] benzyl,[200] and carbamoyl groups.[201]

The condensation of chiral secondary amine **168** with aldehyde **166** provides enamine **170**. A sacrificial quantity of this species quenches the photoexcited $Ru(bpy)_3^{2+}$ catalyst, forming $Ru(bpy)_3^{+}$. This reduces alkyl halide **167** to **167**$^{\bullet-}$, which then undergoes dehalogenation to afford electron-deficient α-ketoradical **171**. The SOMOphilic enamine **170** undergoes radical addition to **171**, and the resulting α-amino radical can be oxidized by either photoexcited $Ru(bpy)_3^{2+}$ or another equivalent of the alkyl halide in a chain propagative manner.[9] Finally, the iminium ion can be hydrolyzed to release the α-functionalized product and regenerate the amine organocatalyst. In addition to high yields under mild conditions, these reactions produce highly enantioenriched products due to the exquisite facial selectivity afforded by this class of organocatalyst in the radical addition step.

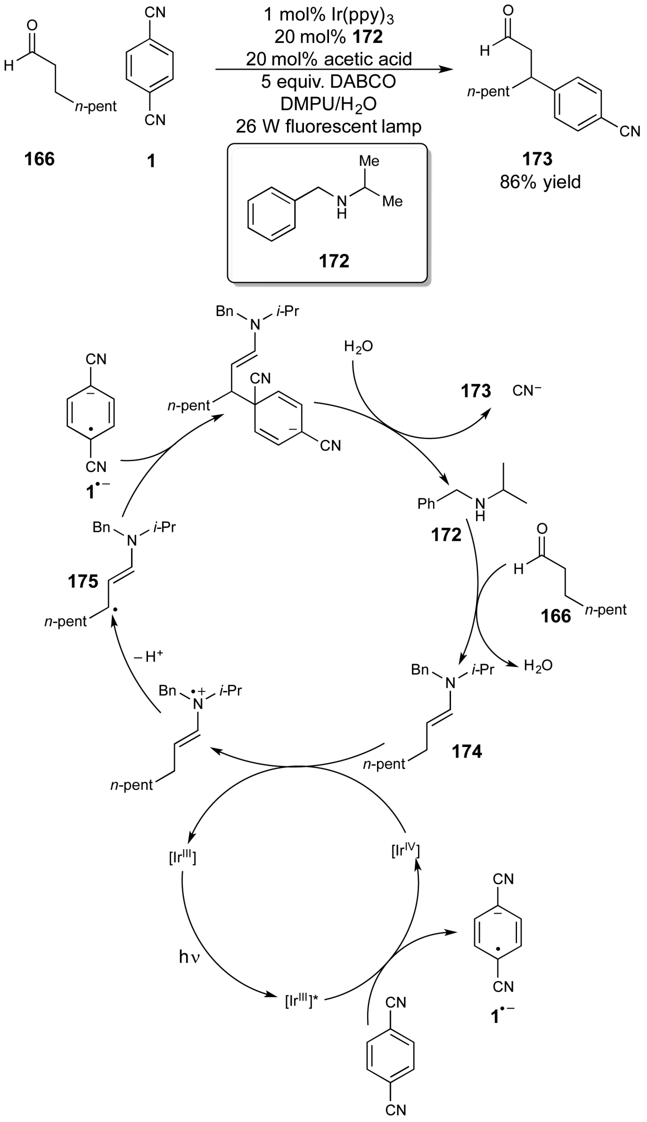
Scheme 44. Aldehyde α-Alkylation by Tandem Photo-/Organocatalysis



Following MacMillan's initial report, several other research groups have merged enamine organocatalysis with photoredox catalysis. For example, Luo developed a highly enantioselective photoredox alkylation protocol that was able to construct a variety of acyclic, cyclic, and spirocyclic quaternary stereocenters using a secondary amine organocatalyst.[202] Koike and Akita demonstrated that organocatalytically generated chiral enamines could be oxidized and trapped with TEMPO,[203] and the Jang group showed that the chiral enamine intermediate for this α-oxygenation could be accessed via chiral iminium-catalyzed conjugate addition.[204] Gualandi reported that an inexpensive $Fe(bpy)_3Br_2$ catalyst could be used in place of a Ru photocatalyst,[205] while the Zeitler[206,207] and Ferroud[208] groups independently showed that transition metal photocatalysts could often be replaced by photoredox-active organic dyes such as Eosin Y and Rose Bengal.

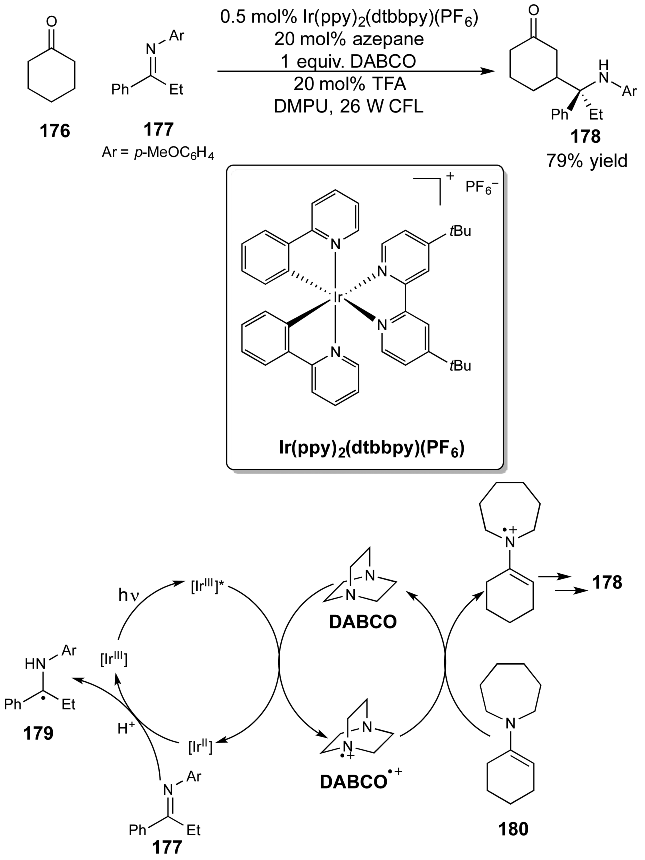
MacMillan also demonstrated that selective β-functionalization of aldehydes and ketones could be accomplished using a related cocatalytic system (Scheme 45). Photoexcited Ir(ppy)$_3$ can reduce electron-poor cyanoarenes such as **1** to **1**$^{\bullet -}$. Concomitantly, aldehyde **166** can condense with secondary amine **172** to afford enamine **174**, which is then oxidized by Ir(ppy)$_3^+$ and deprotonated to form the 5π e$^-$ β-enamine radical **175**. The authors propose these two radical species undergo heterocoupling, and upon loss of cyanide and hydrolysis this affords β-arylated product **173**.[209]

Scheme 45. Aldehyde β-Arylation by Tandem Photo-/Organocatalysis



MacMillan also developed a similar reaction that utilized ketones[210] and imines[211] in place of cyanoarenes (Scheme 46). In this case, formation of α-amino radical **179** was proposed to be facilitated by a catalytic amount of acid, presumably via PCET activation. These protocols also employ 1,4-diazabicyclo[2.2.2]-octane (DABCO) as a redox mediator. This base quenches the Ir*(ppy)$_2$(dtbbpy)PF$_6$ photocatalyst more rapidly than either substrate, and the resultant DABCO$^{\bullet +}$ can oxidize enamine **180**.

Scheme 46. Formal β-Mannich Reaction Using Several Types of Cocatalysis

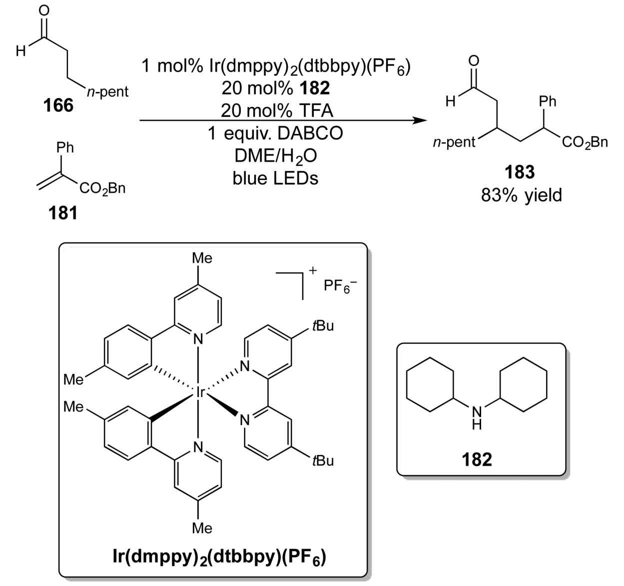


The mediator is also able to shift the reaction selectivity, as it generates exclusively β-Mannich product **178**, while the reaction intrinsically gives a mixture of α- and β-products in its absence. In the case of ketones, LiAsF$_6$ proved to be important in minimizing the occurrence of ketyl radical dimerization by stabilizing this intermediate. Thus, in addition to the iridium photocatalyst, this reaction is influenced by an organocatalyst, a redox mediator, and a Brønsted and Lewis acid catalyst.

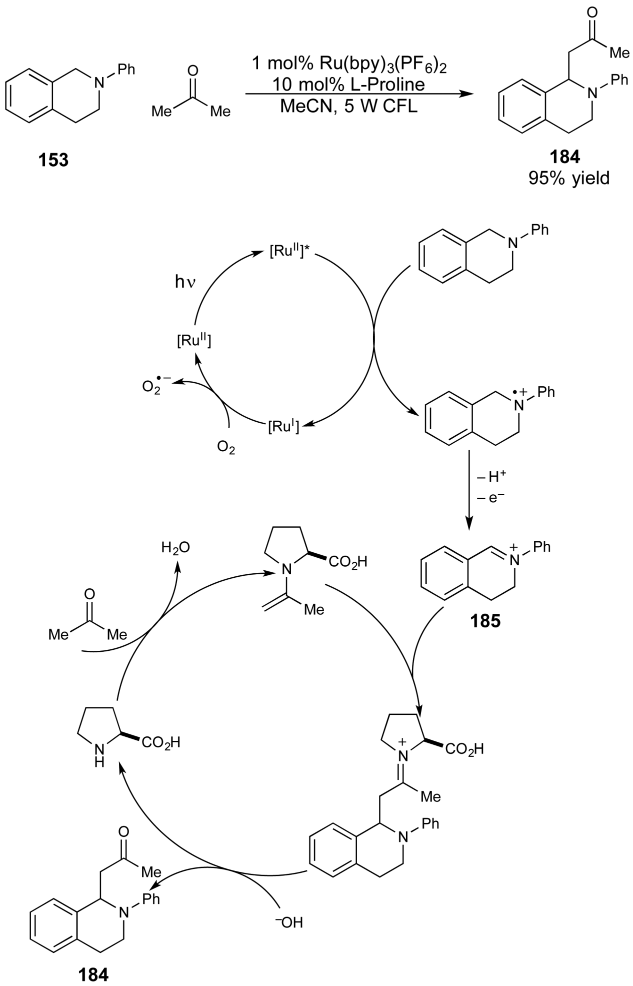
The MacMillan laboratory developed an analogous coupling with electron-deficient alkenes (Scheme 47).[212] In this case, however, oxidation of the enamine was proposed to be from direct quenching of the excited photocatalyst, Ir(dmppy)$_2$(dtbbpy)PF$_6$. The β-enamine radical could then add to Michael acceptors such as **181** and be subsequently reduced to afford the β-alkylated product **183**.

The photooxidation of amines constitutes a major theme of research in synthetic photochemistry. Many classical[213,214] and contemporary[215,216] methods have exploited the photogeneration of iminium ions via amine oxidation and subsequently trapped them using a range of nucleophiles. Among the most thoroughly studied transformations in this context is the oxidation of *N*-phenyltetrahydroisoquinoline (THIQ) **153**, which is particularly susceptible toward oxidative functionalization. Several reports of tandem photocatalytic/organocatalytic Mannich reactions have been published on the basis of this reactivity. For example, Rueping and co-workers demonstrated that iminium ion **185** could be coupled with ketones using proline as an organocatalyst (Scheme 48).[217] Zeitler expanded this method to other amine scaffolds and also improved throughput by carrying out the reactions in a flow photo-

Scheme 47. Aldehyde β-Alkylation



Scheme 48. Oxidation of THIQ and Interception by an Organocatalytic Nucleophile

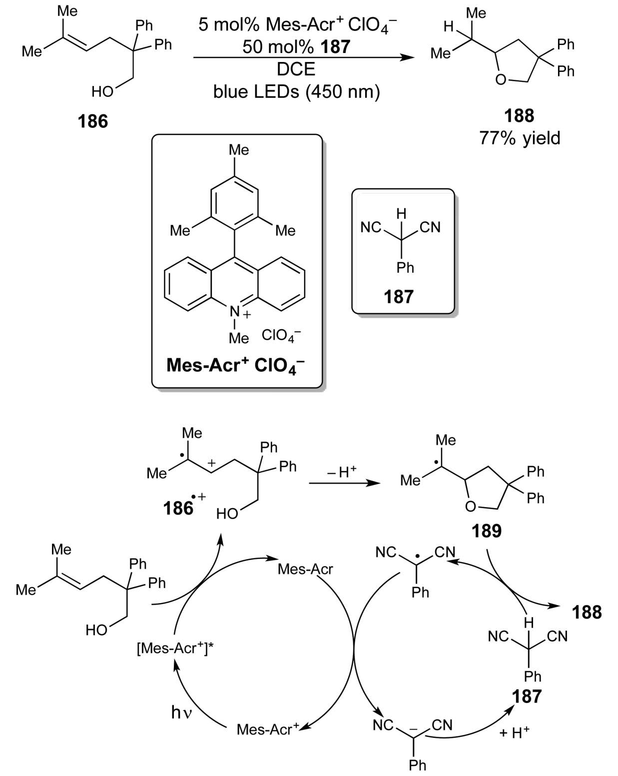


reactor.[207] Organic photoredox sensitizers have also been utilized for these reactions. For example, Tan accomplished the amine oxidation/organocatalytic coupling with Rose Bengal,[218] while Zhao employed a variety of BODIPY photocatalysts.[219]

2.4.2. Hydrogen Atom-Transfer (HAT) Catalysis. Photoinduced electron-transfer processes result in the formation of open-shelled intermediates, and production of closed-shell products via efficient termination of open-shell reaction manifolds often proves to be somewhat challenging. One strategy that has proven to be particularly important in photoredox chemistry has been the use of organic hydrogen atom-transfer (HAT) cocatalysts.

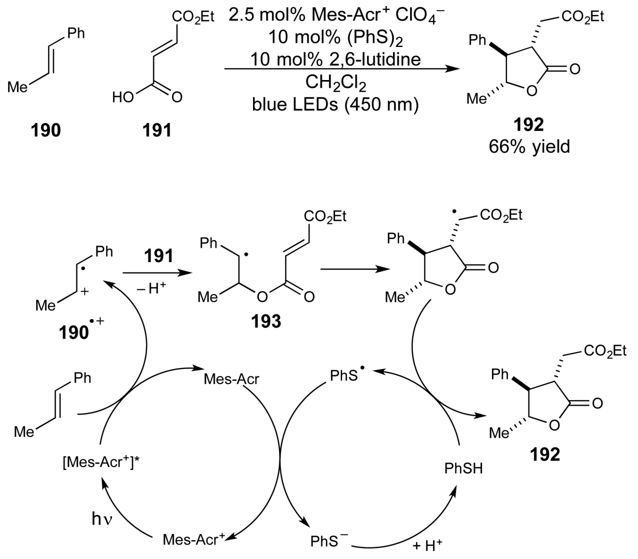
Nicewicz has exploited this strategy extensively to develop high-yielding anti-Markovnikov alkene functionalization reactions (Scheme 49).[220] Photoexcitation of 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$ClO$_4^-$) and quenching by alkene **186** gives radical cation **186$^{•+}$**. Alkene radical cations are susceptible to attack by a range of nucleophiles;[51−53,85,86] intramolecular cyclization of the pendant alcohol in this case affords **189**. This tertiary alkyl radical is insufficiently oxidizing to directly react with **186** in chain propagating electron transfer or with the reduced photocatalyst to regenerate the photochemically active acridinium. With no cocatalyst, therefore, the rate of product formation is relatively slow. However, the introduction of 2-phenylmalononitrile **187** as a hydrogen atom shuttle that reacts with **189** affords the closed-shell product **188**. This HAT cocatalyst is then regenerated by electron transfer from the reduced Mes-Acr photocatalyst. In addition to **187**, subsequent work from this laboratory showed that methylthiosalicylate,[221] thiophenol,[222] and phenylsulfinic acid[223] could also act as HAT catalysts. Thiophenol in particular could be generated in situ from operationally benign phenyldisulfide.[224]

Scheme 49. Photooxidative Cyclization Merged with HAT Catalysis



Using a similar strategy, Nicewicz has also achieved anti-Markovnikov functionalization of alkenes with ethers,[220,225,226] amines,[222,224] trifluoromethyl groups,[221] halogens,[227] carboxylic acids,[223] amides, and thioamides.[228] Complex heterocyclic scaffolds are accessible using an intermolecular coupling partner with an additional π system (Scheme 50). Initial addition of **191** to radical cation **190**$^{\bullet+}$ affords radical **193**, which can cyclize on a pendant alkene[229,230] or oxime[231] before being trapped by the HAT catalyst to afford **192**.

Scheme 50. Alkene–Acid Coupling by Photocatalysis/HAT Catalysis

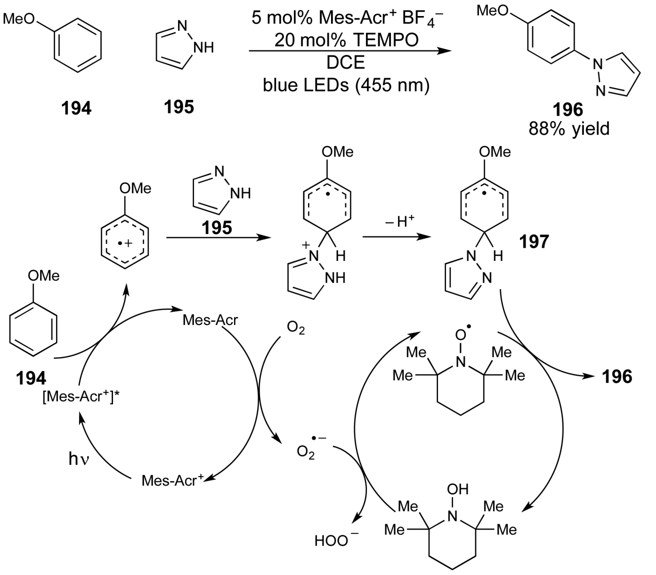


Thiyl HAT cocatalysts can also be used to terminate radical intermediates that are photogenerated in other ways. For example, the photooxidation of carboxylic acids is a well-established method to produce carbon-centered radicals via decarboxylation.[232] Nicewicz demonstrated that these radicals could be productively intercepted by thiyl HAT cocatalysts; in their absence, these radicals primarily undergo homodimerization.[233−235]

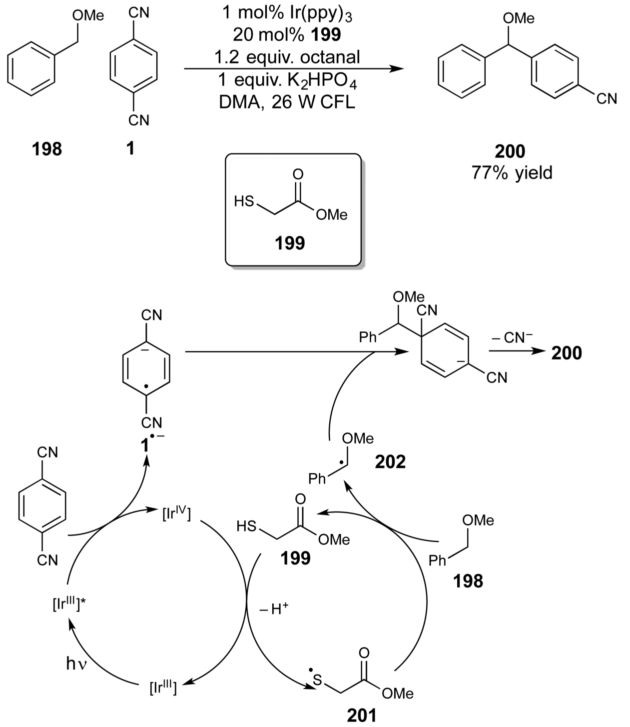
Nicewicz has also recently reported a protocol for C–H amination of arenes with nitrogen nucleophiles.[236] In the proposed mechanism (Scheme 51), [Mes-Acr$^+$]* oxidizes arene **194**, which can be attacked by an amine nucleophile **195**. Following deprotonation to neutral radical **197**, TEMPO is used to abstract a hydrogen atom, affording the closed-shell product. The HAT cocatalyst can then be regenerated by a reactive oxygen species.

MacMillan has also developed several reactions that employ thiols as HAT cocatalysts (Scheme 52). In an early example, methyl 2-mercaptoacetate **199** was deprotonated and oxidized by Ir(ppy)$_3^+$ to afford thiyl radical **201**; this intermediate can abstract a hydrogen atom from benzylic ethers such as **198**. The resulting radical **202** can add to both cyanoarenes[237] and imines.[238] The Tan group carried out benzylic bromination using a similar strategy with morpholine as the HAT catalyst.[239] Li reported the oxidation of primary alcohols using tandem photoredox/TEMPO catalysis.[240] The authors proposed a mechanism in which photoexcited Ru(bpy)$_3$(PF$_6$)$_2$ oxidizes TEMPO to the corresponding oxammonium, a known reagent for alcohol oxidation.

Scheme 51. Aromatic C–H Amination Using Photocatalysis and TEMPO as an HAT Catalyst



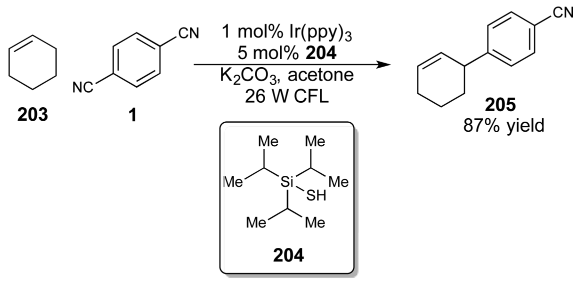
Scheme 52. Benzylic C–H Arylation by Photo/HAT Cocatalysis



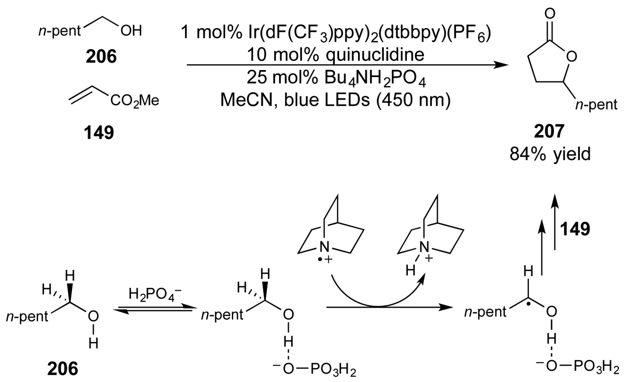
This method has been expanded to include the activation of other compounds with weak C–H bonds. The direct allylic coupling of simple alkenes such as **203** with cyanoarenes was achieved using HAT organocatalyst **204** (Scheme 53).[241] Primary alcohols can also be used, and their coupling with heteroarenes was followed by an intriguing spin-center shift rearrangement.[242] The presence of a base proved advantageous for these reactions, presumably by facilitating sulfur oxidation through a PCET process (see section 2.3.1).

This Brønsted acid/base synergy was further exploited for the site-selective activation of aliphatic alcohols (Scheme 54).[243] In these reactions, the radical cation of the catalytic quinuclidine is proposed to abstract a hydrogen atom adjacent to the alcohol. The phosphate cocatalyst in this process forms a hydrogen bond

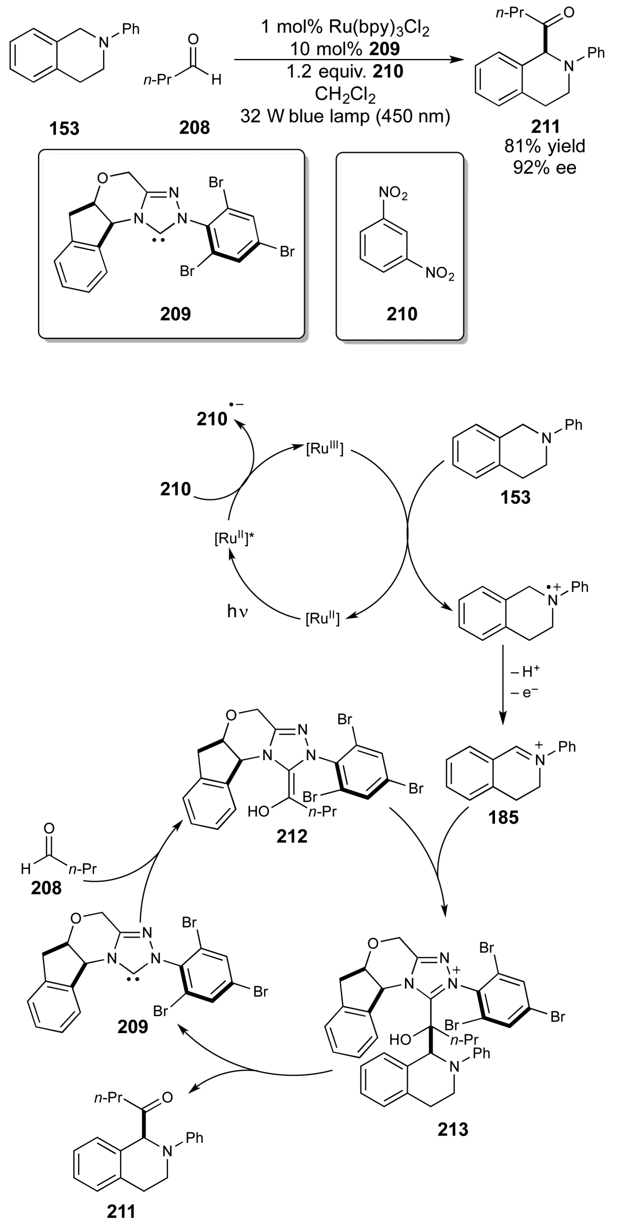
Scheme 53. C−H Arylation of Simple Alkenes



Scheme 54. Alkene−Alcohol Coupling Catalyzed by Site-Selective HAT



Scheme 55. Umpolung Reactivity Using Dual Photo/NHC Catalysis



with the hydroxyl functionality; the resulting increase in hydricity facilitates the HAT process.

2.4.3. Other Modes of Organocatalysis. Rovis demonstrated that photoredox chemistry can also be merged with the use of chiral *N*-heterocyclic carbene (NHC) organocatalysis (Scheme 55).[244] Addition of NHC **209** to propionaldehyde **208** results in the formation of Breslow intermediate **212**. This nucleophilic species was used to trap THIQ iminium ion **185**, which was generated by photoquenched Ru^{III}.[245−247] The resulting amino alcohol **213** could fragment to form α-amino ketone **211** in good enantioselectivity and regenerate the NHC catalyst.

Stephenson reported a procedure for the synthesis of symmetric anhydrides from carboxylic acids using photocatalysis (Scheme 56).[248] Their reaction is carried out in DMF, which is proposed to catalyze the dehydration by formation of the Vilsmeyer reagent **216** in situ. The authors propose a mechanism in which photoexcited $Ru(bpy)_3Cl_2$ promotes reductive dehalogenation of CBr_4 to form $^\bullet CBr_3$. Addition of this radical to DMF, followed by oxidation and bromide exchange, forms **216**. This can in turn act as an acyl transfer reagent for the formation of anhydride **215** from **214** with concomitant regeneration of DMF.

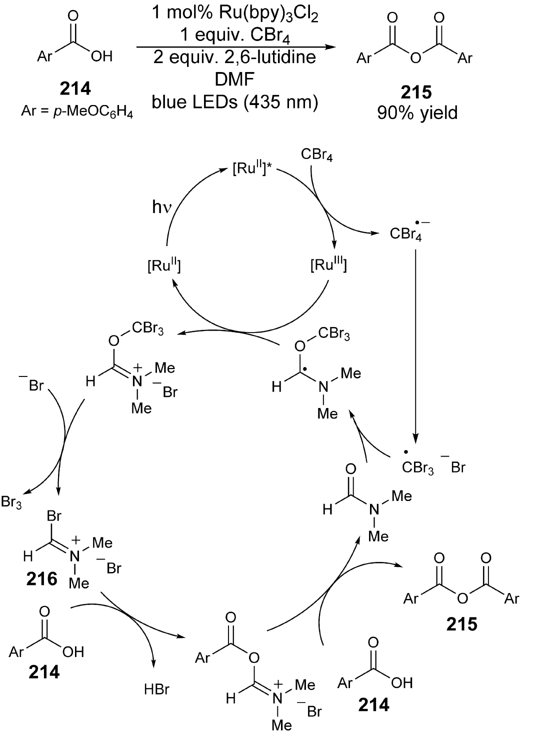
Finally, Hopkinson, Glorius, and co-workers merged a typical photoredox cycle with a catalytic halide salt to achieve the oxidative trifluoromethylthiolation of styrenes (Scheme 57).[249] In the mechanism proposed by these authors, the bromide additive reacts with *N*-(trifluoromethylthio)phthalimide **218** to afford highly reactive trifluoromethylsufenyl bromide **220** in situ. This species undergoes photoreduction and mesolytic cleavage to form $^\bullet SCF_3$ and to regenerate Br^-. Addition of the sulfur-centered radical to styrene **217** followed by radical-polar crossover affords product **219**. Lu and Xiao proposed a conceptually similar application of halide catalysis to generate allyl iodides in situ, which could then be coupled with *N*-aryltetrahdroisoquinolines.[250]

2.5. Transition Metal Catalysis

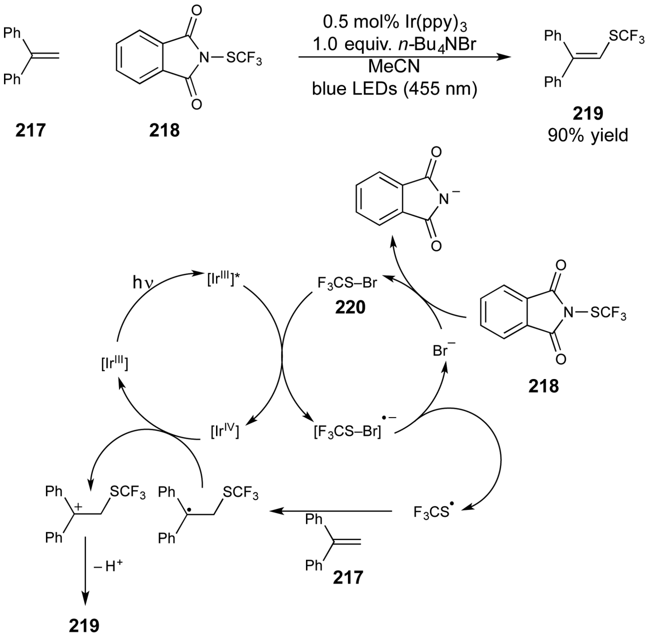
Transition metal catalysis has become an indispensable tool in all areas of synthetic chemistry, for a variety of reasons. Among the most important features in the design of new organometallic transformations is the ability of a transition metal center to exist in multiple oxidation states, each of which can access distinct reactivity patterns. Thus, the combination of transition metal catalysis and photoredox catalysis offers unique opportunities for the innovative design of powerful synthetic transformations.

Because the use of transition metal catalysts in tandem with photoredox catalysts is a relatively recent development, few of these reactions have been subject to detailed mechanistic interrogation, and there is still considerable ambiguity regarding many mechanistic subtleties in these processes. Broadly speaking, however, there are a handful of dominant reaction

Scheme 56. Photocatalytic Carboxylic Acid Dehydration with Acyl Transfer Cocatalysis



Scheme 57. Dual Halide/Photoredox Catalysis



modes that effectively describe most current examples of photoredox/transition metal dual catalysis.

The following section is organized according to the manner in which the transition metal catalyst and the photocatalyst interact in the mechanisms proposed by the authors. First, we will discuss transition metal-catalyzed reactions where photocatalysis produces an oxidation state change that facilitates an otherwise sluggish organometallic step (Figure 6A). These can either occur by direct electron transfer between the organometallic complex and the photocatalyst or be mediated by a photogenereated reactive intermediate such as superoxide. Second, we will discuss reactions in which a photogenerated reactive intermediate is intercepted by an organometallic complex (Figure 6B). In these reactions, the redox balance is often proposed to be maintained by a secondary back-electron transfer between the organometallic fragment and the photocatalyst; however, the principal role of the photocatalyst in these methods is the independent production of the key reactive intermediate.

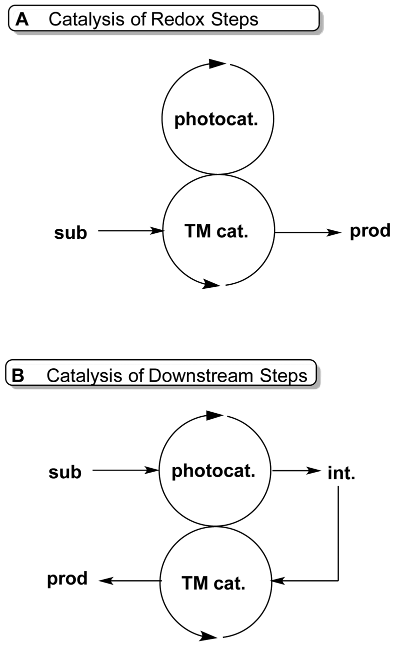


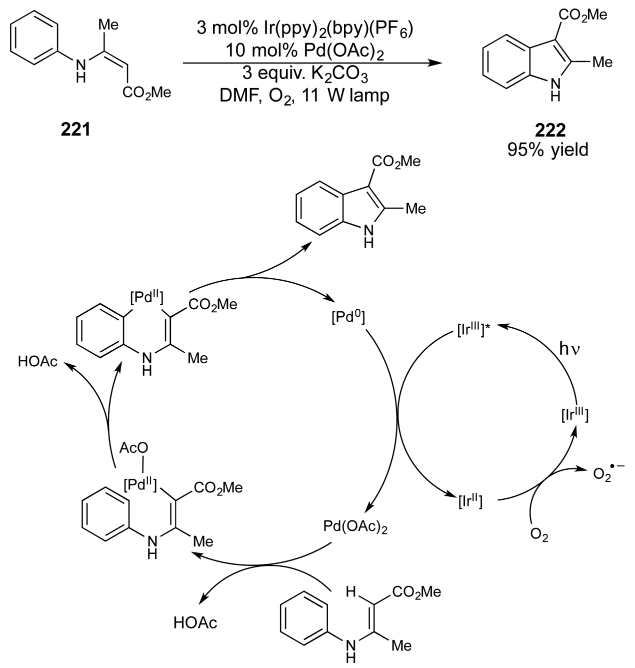
Figure 6. Common modes of tandem transition metal/photocatalysis.

2.5.1. Catalysis of Redox Steps.

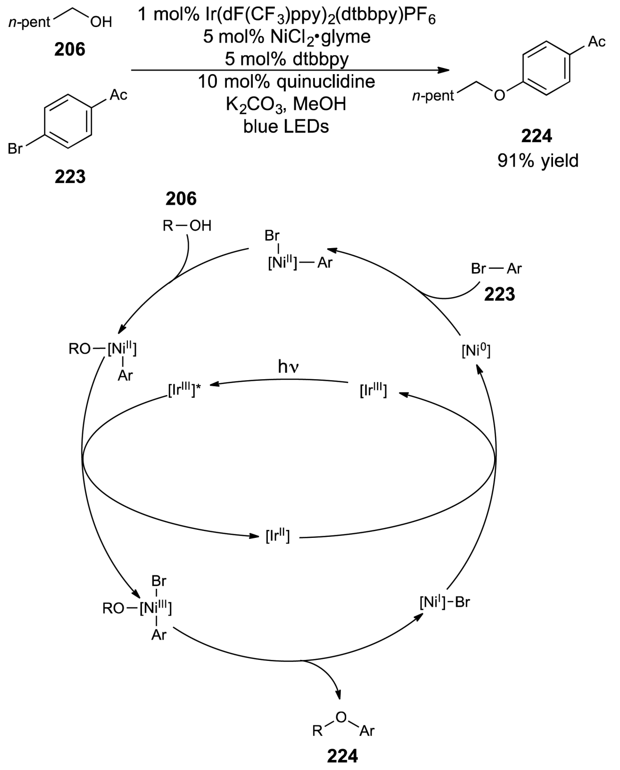
Catalyst turnover by reoxidation of a reduced transition metal is often the rate-limiting process in oxidative organometallic transformations. To address this challenge, Rueping developed an indole synthesis based upon the intramolecular oxidative C−H arylation of enamides (Scheme 58).[251] The authors proposed a mechanism in which the organometallic steps are rapid but where aerobic oxidation of the Pd^0 catalyst is slow. The authors hypothesized that a photocatalyst could facilitate this reoxidation process. The details of the oxidation have not yet been elucidated, but given the two-electron oxidation state change required, the mechanism must presumably be somewhat more complicated than a simple bimolecular photoinduced single electron transfer. Rueping has utilized a similar design strategy in oxidative Heck reactions of aryl amides[252] and phenols[253] catalyzed by rhodium and ruthenium, respectively.

Photocatalysts may also be used to enable novel or unusual reactivity by accessing higher metal oxidation states. The MacMillan laboratory demonstrated this concept in the coupling of simple alcohols with aryl bromides (Scheme 59).[254] Nickel-catalyzed cross couplings of this type are difficult because C−O reductive elimination from Ni^{II} is predicted to be thermodynamically uphill. However, oxidation to Ni^{III} by photoexcited $Ir(dF(CF_3)ppy)_2(dtbbpy)\ (PF_6)$ renders this step energetically favorable. In the proposed catalytic cycle, Ni^{I} is returned to Ni^{0} by the reduced Ir^{II} photocatalyst. A similar mechanism was invoked for the decarboxylative coupling of acids and acid chlorides,[255] as well as the oxidative coupling of anilines with alkenes reported by Jamison.[256]

Scheme 58. Oxidative Heck Reaction Employing Photocatalytic Palladium Turnover



Scheme 59. Nickel-Catalyzed Cross Coupling Enabled by Photocatalysis



A limited number of examples utilizing this strategy have been reported using other transition metal cocatalysts. Kobayashi disclosed a copper-catalyzed Chan−Lam protocol that employs Ir(ppy)$_3$ as a cocatalyst.[257] The key bond-forming step is postulated to require reductive elimination from Cu^{III}, which can be accessed either by PET to the photoexcited [Ir^{III}]* or by superoxide. You, Cho, and co-workers reported a Pd/Ir-dual catalysis strategy for the formation of carbazoles.[258] The photocatalyst is proposed to oxidize the intermediate complexes to either Pd^{III} or Pd^{IV} to facilitate the transformation.

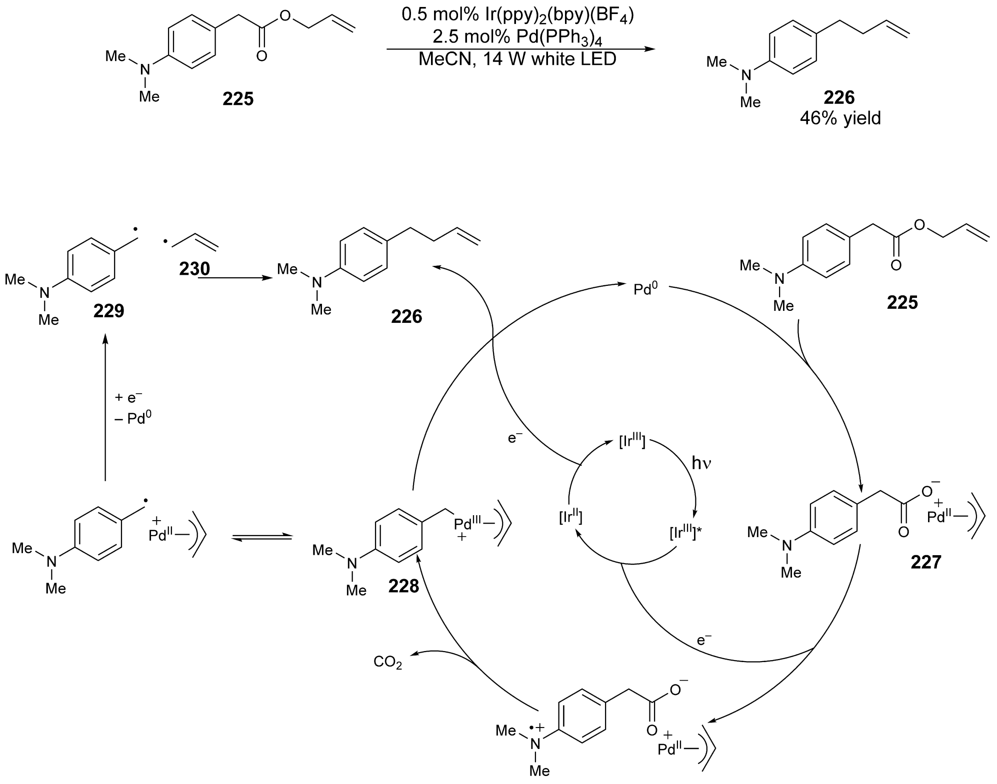
Tunge developed a method for the decarboxylative allylation of alkanoic esters using a combination of Pd(PPh$_3$)$_4$ and Ir(ppy)$_2$(bpy) (BF$_4$).[259] In their proposed mechanism (Scheme 60), reaction of allylic ester **225** with Pd^0 affords π-allyl complex **227**. Subsequent photooxidation of the aniline triggers radical decarboxylation. Palladium complex **228** may undergo reductive elimination and SET from Ir^{II} to form product **226**, which has been suggested in related systems.[260] Alternatively, reduction of **228** could liberate *p*-aminobenzylic radical **229**, which would undergo heterodimerization with allyl radical **230**, giving rise to **226**. This pathway was postulated on the basis of the observation of side products consistent with homodimerization of **229** and **230**, as well as stereochemical probe experiments.[261] A similar transformation was reported by Lu, Xiao, and co-workers using an allyl phosphate in place of the ester.[262] In both cases, the extent to which palladium is involved in the bond-forming step seems to depend on the stability of the possible radical intermediate, with more stable species favoring the latter pathway, and less stable radicals favoring the former.

2.5.2. Catalysis of Downstream Steps. The facile photooxidation of tetrahydroisoquinoline **153** to the corresponding iminium ion **185** has become a relatively common means to test the compatibility of photoredox catalysis with complementary activation modes. As such, several recent reports have described the reaction of the photogenerated iminium electrophile with organometallic nucleophiles. Stephenson[263] and Rueping[264] independently reported that metal acetylides are good nucleophiles in this context. These groups reported cross dehydrogenative coupling reactions in which silver or copper salts activate terminal alkyne **231** and the resulting metal acetylide **233** adds to iminium ion **185** (Scheme 61). An asymmetric adaptation of this method was reported by Li and co-workers using (*R*)-QUINAP as a chiral ligand for copper.[265] Zhao demonstrated that BODIPY photocatalysts could also be used to perform the amine oxidation in place of ruthenium or iridium species.[266]

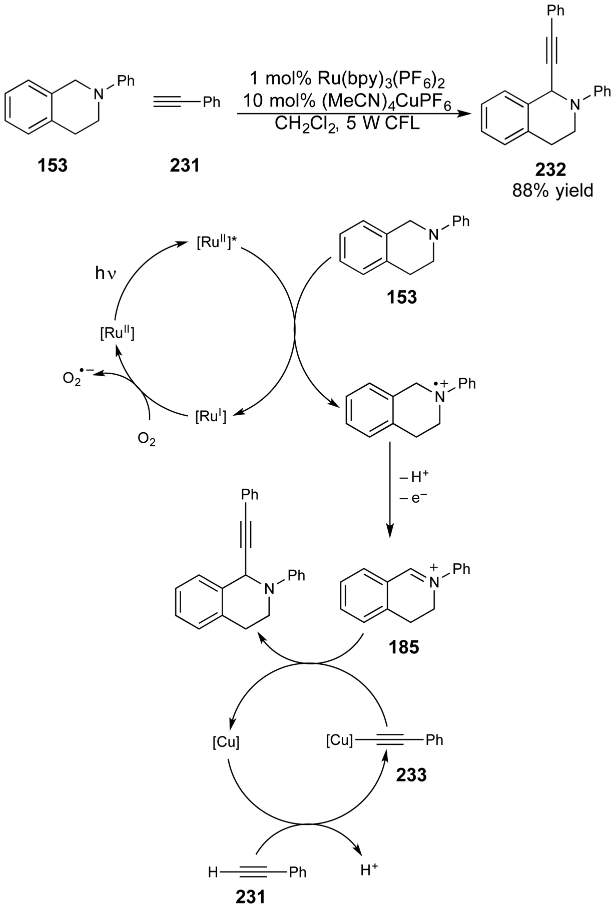
Sanford reported an early example of photoredox/transition metal dual catalysis (Scheme 62).[267,268] Her laboratory's detailed mechanistic studies of the Pd-catalyzed oxidative C−H arylation of phenylpyridines had revealed that the metalation of the C−H bond is relatively facile but that oxidation of the resulting cyclometalated Pd^{II} intermediate **237** by hypervalent iodoarene oxidants is inefficient and rate-limiting. Thus, Sanford developed a strategy to utilize photogenerated aryl radicals as more reactive oxidants in these reactions. Taking advantage of an insight reported by Cano-Yelo and Deronzier,[269] Sanford generated aryl radical **238** by the photocatalytic reduction of aryl diazonium salt **235**. This species reacts rapidly at room temperature with cyclometalated intermediate **237** to generate arylated Pd complex **239** at a higher oxidation state, which is poised to undergo rapid reductive elimination. This dual-catalyst strategy enabled the Pd-catalyzed C−H arylation reaction to be conducted at room temperature under conditions considerably milder than previously reported.

Gold complexes have become recognized as synthetically powerful soft Lewis acidic catalysts for the activation of carbon−carbon multiple bonds. Several reactions involving the interception of photogenerated aryl radicals with organometallic gold complexes have recently been described. Glorius reported a strategy for combining gold and photoredox catalysis to effect the

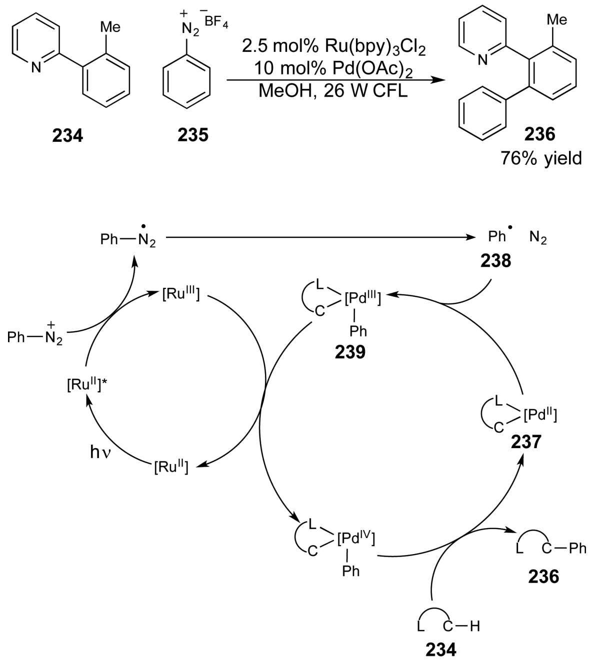
Scheme 60. Decarboxylative Allylation Using Palladium and Photocatalysis



Scheme 61. Oxidation of THIQ and Trapping with Metal Acetylides

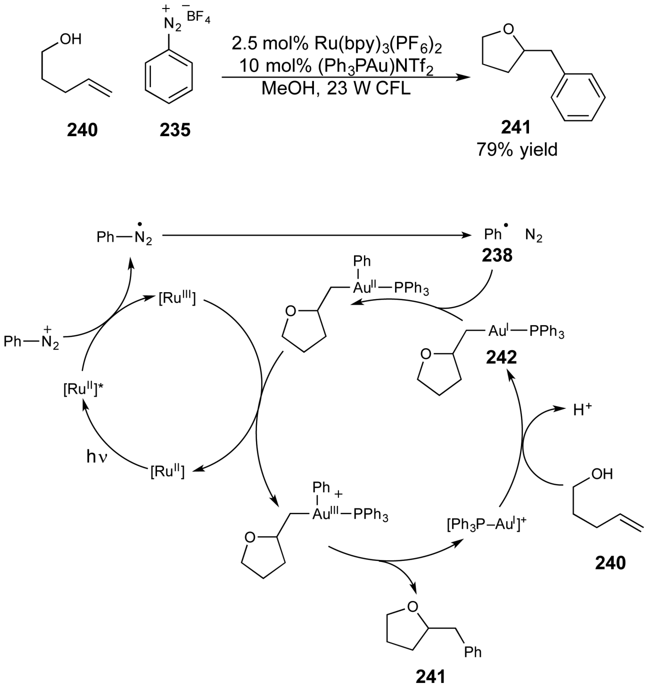


Scheme 62. Photocatalytic Diazonium Reduction and Palladium Catalysis with Resulting Aryl Radical



alkoxyarylation of alkenes (Scheme 63).[270,271] In this process, the role of the π-acidic catalyst $(Ph_3PAu)NTf_2$ is to activate the alkene of substrate **240** toward alcohol addition. The authors proposed that the resulting alkyl gold species **242** is attacked by a photocatalytically generated aryl radical **238**. This combination would produce a high-valent organogold species that is poised to undergo facile reductive elimination, in conceptual analogy to the

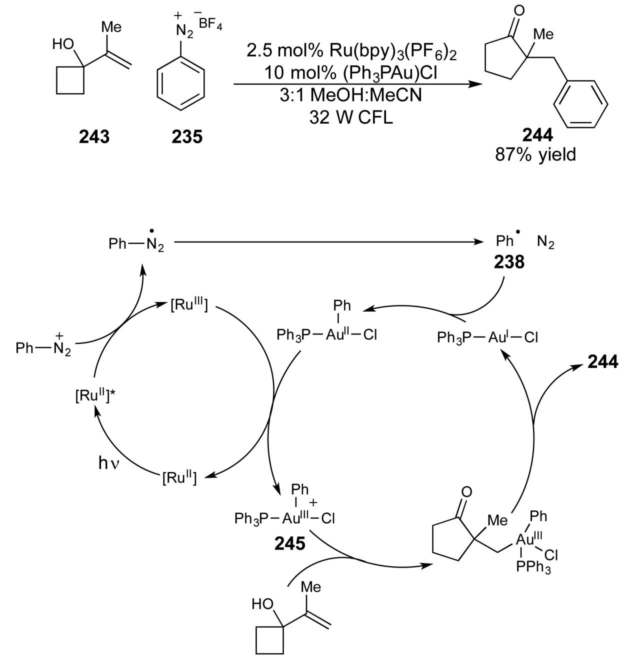
Scheme 63. Tandem Gold/Photocatalyzed Cyclization/Arylation Reaction



photocatalytic Pd-catalyzed arylation developed by Sanford (Scheme 62).[267]

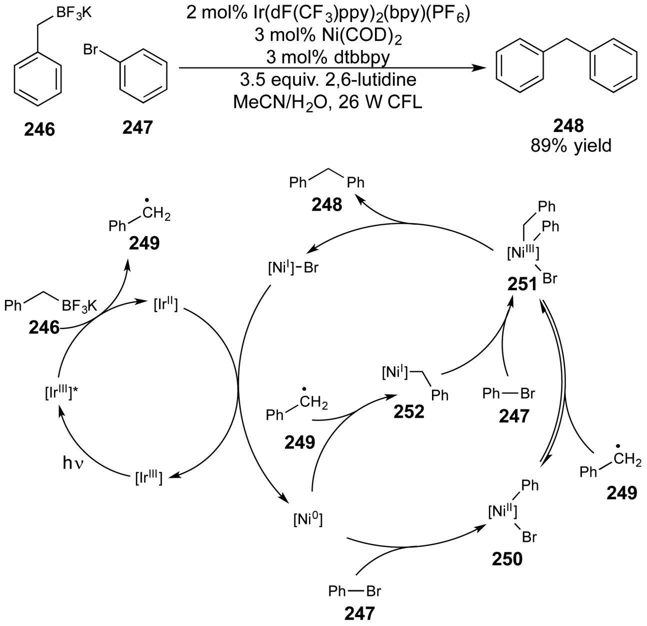
Toste suggested a slightly different mechanism for the gold-catalyzed arylative ring expansion of vinyl cyclobutanol **243** (Scheme 64).[272,273] In his proposal, Au^{I} first adds to photochemically generated aryl radical **238**, before alkene coordination and oxidation. The resultant high-valent intermediate **245** is well-suited to catalyze the ring expansion and reductive elimination giving rise to product **244**. This strategy has since been utilized for a variety of methods, including the coupling of arenes with terminal alkynes[274,275] and propargyl alcohols,[276,277] as well as the hydroarylation of alkynes[277] and the formation of sp^2 C−P bonds.[278]

Scheme 64. Tandem Gold/Photocatalyzed Alkene Functionalization



First-row transition metals are particularly promising partners for dual catalytic systems involving photoredox catalysis due to the relative ease by which they undergo one-electron redox changes. Molander exploited this behavior in several examples of organoboron cross coupling using nickel chemistry in tandem with photoredox catalysis.[279] The initial studies investigating this combination involved the reaction of trifluoroborate **246** and aryl bromide **247** (Scheme 65). Oxidation of **246** by the photoexcited iridium catalyst generates benzylic radical **249**. Concomitantly, the aryl bromide substrate undergoes oxidative addition to Ni^0. The resulting $\mathrm{Ni}^{\mathrm{II}}$ complex **250** then intercepts the benzylic radical to afford $\mathrm{Ni}^{\mathrm{III}}$ **251**. Reductive elimination from this species releases cross-coupled product **248**, along with Ni^{I}, which can be reduced by $\mathrm{Ir}^{\mathrm{II}}$. Alternatively, computational studies suggest that benzylic radical **249** may instead add directly to Ni^0 to form Ni^{I} complex **252**, and that the oxidative addition of aryl bromide **247** and subsequent reductive elimination occur after this step.[280] Interestingly, the dissociation of benzyl radical from $\mathrm{Ni}^{\mathrm{III}}$ complex **251** is facile, meaning that there is a rapid equilibrium between **250** and **251** prior to reductive elimination, even if initial formation of **251** proceeds through Ni^{I} complex **252**. This has important ramifications for stereoinduction in this system (vide infra).

Scheme 65. Nickel-Catalyzed Cross-Coupling Employing Photocatalytically Generated Benzylic Radicals



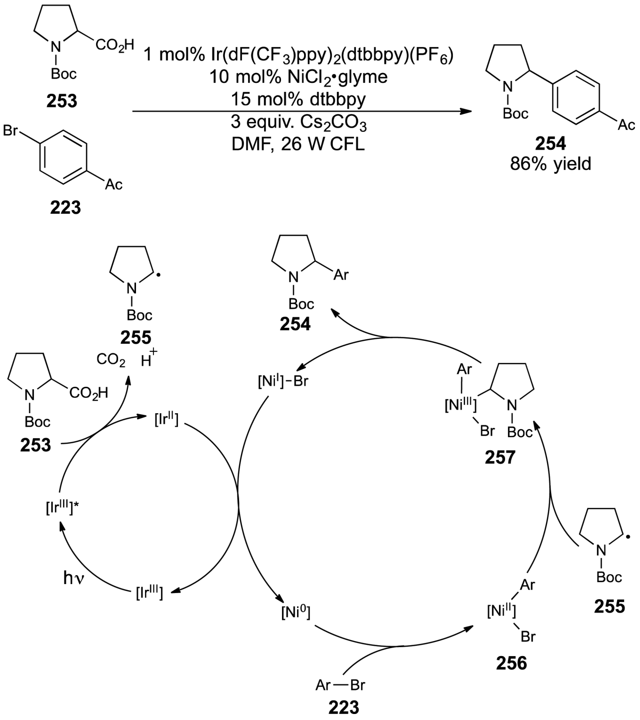
This strategy has been applied to benzylic,[279,281] secondary alkyl,[282] alkoxymethyl,[283,284] and α-amino[285] boron nucleophiles. Notably, the mild conditions utilized for the photooxidation of the trifluoroborate salts do not affect other organoboron species. Thus, Molander has described conditions for the use of aryl halides bearing boronate esters and other less reactive boron functional groups in photoredox reactions, affording products poised for further elaboration by cross-coupling.[286] Finally, preliminary reports have demonstrated asymmetric induction using chiral ligands on the nickel catalyst,

DOI: 10.1021/acs.chemrev.6b00018
Chem. Rev. 2016, 116, 10035−10074

although enantioselectivities reported to date are moderate.[279,280] The facile dissociation of benzylic radical from Ni^{III} scrambles the stereocenter, thereby rendering the transformation stereoconvergent. Moreover, the rapid equilibration between Ni^{II} and both diastereomers of Ni^{III} creates a dynamic kinetic resolution in which the stereoselectivity is determined in the final reductive elimination.[280]

MacMillan and Doyle published a concurrent report of a similar Ir/Ni dual catalytic system that employs carboxylic acids in place of organoboron reagents (Scheme 66).[287] Photooxidative decarboxylation of **253** affords α-amino radical **255**. The authors proposed that this radical serves the same function as the benzylic radical in the Molander system; addition to Ni^{II} adduct **256** affords a high-valent Ni^{III} complex **257** that is prone toward reductive elimination, resulting in the formation of product **254**. This method was employed for the cross-coupling of aryl and vinyl halides to radicals derived from α-amino, α-oxy, and alkyl carboxylic acids.[288] Acyl radicals, generated from α-keto acids, can be added to indoles[289] and aryl halides.[290] The latter intermediates can also participate in palladium-catalyzed cross coupling to afford direct C−H acylation of acetamides.[291] Furthermore, Luo and Zhang showed that organic donor−acceptor fluorophores are effective photocatalysts for these transformations.[292] Lastly, MacMillan and Fu recently developed an asymmetric variant of the α-amino acid/aryl halide coupling using semicorrin-type bis(oxazoline) ligands for nickel.[293] The reaction is stereoconvergent and dictated entirely by nickel, as the radical intermediate following decarboxylation is achiral.

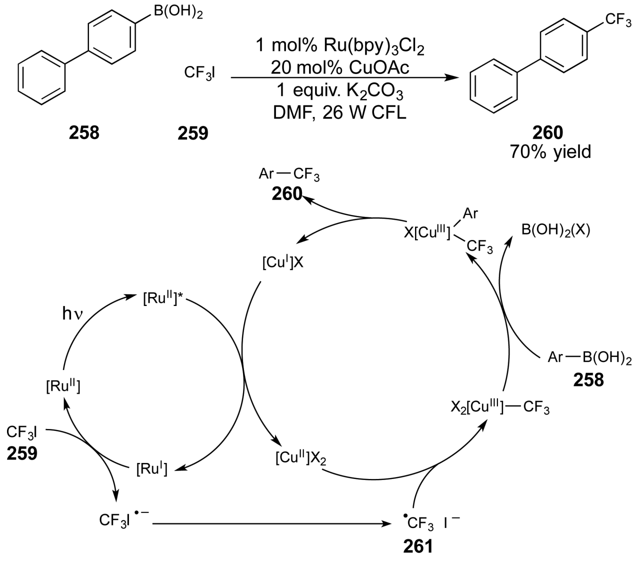
Scheme 66. Nickel-Catalyzed Cross Coupling Using Photocatalytic Decarboxylation To Generate α-Amino Radicals



Several other noteworthy developments have been reported recently in this area. Investigators at AstraZeneca demonstrated that both Molander and MacMillan's protocols can be carried out using Ni^{II} salts under aerobic conditions.[294] Independently, Molander[295,296] and Fensterbank[297,298] showed that hypervalent silicon compounds can be oxidized and fragment to alkyl radicals, which can engage in nickel-catalyzed cross-coupling as previously described. In addition to C−C bonds, this dual-catalyst system is capable of forging C−S bonds by reacting with thiyl radicals, which can be generated from thiols either by oxidation/deprotonation[299] or by HAT to an alkyl radical.[300] Analogously, Lu, Xiao, and co-workers were able to achieve C−P cross-couplings using phosphorus-centered radicals, generated by oxidation/deprotonation of the phosphine oxide.[301]

Copper has also been utilized in dual catalytic systems of this type. Sanford reported the trifluoromethylation of boronic acids using $Ru(bpy)_3Cl_2$ and CuOAc (Scheme 67).[302] Photocatalytic reductive dehalogenation of trifluoromethyl iodide **259** affords trifluoromethyl radical **261**, which can be intercepted by Cu^{II}. Transmetalation with the arylboronic acid and reductive elimination provides product **260** along with Cu^{I}, which is proposed to undergo photooxidation to generate Cu^{II}.

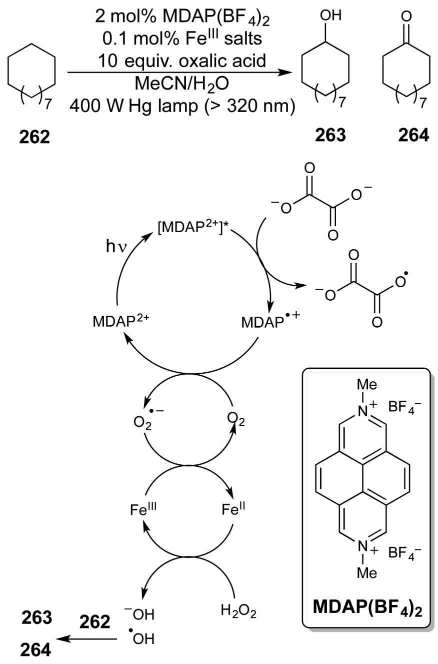
Scheme 67. Aryl Trifluoromethylation Using Tandem Copper/Photocatalysis



A conceptually distinct photocatalytic system was reported by Saito, who performed the oxidation of adamantane and cyclododecane **262** using *N*,*N*′-dimethyl-2,7-diazapyrenium ($MDAP^{2+}$) and iron cocatalysts (Scheme 68).[303] The mechanism of this process is likely to be a Fenton-type alkane oxidation by hydroxyl radical.[304] The role of the photocatalyst would thus be to photoreduce dioxygen in situ, and the Fe catalyst would result in subsequent homolytic production of hydroxyl radical.

Wu has reported several examples of acceptorless dehydrogenative reactions that use $Co(dmgH)_2(DMAP)Cl$ in tandem with a photocatalyst such as $Ru(bpy)_3(PF_6)_2$[305,306] or Eosin Y.[307] The proposed mechanism of one representative example is depicted in Scheme 69. Photooxidation and deprotonation[308] of **265** affords thioamidyl radical **267**, which undergoes cyclization to afford **268**.[309] The Co^{III} catalyst is then proposed to be sequentially reduced by Ru^{I} and by radical **268**. Proton transfer from the pentadienyl cation to the Co^{I} complex results in the formation of rearomatized benzothiazole **266** and regenerates the Co^{III} catalyst with evolution of hydrogen gas. Wu has exploited a similar design strategy for the addition of β-keto esters to photocatalytically generated oxocarbenium ions.[310]

Scheme 68. Alkane Oxidation by Photogenerated Hydroxyl Radical



2.6. Enzymatic Catalysis

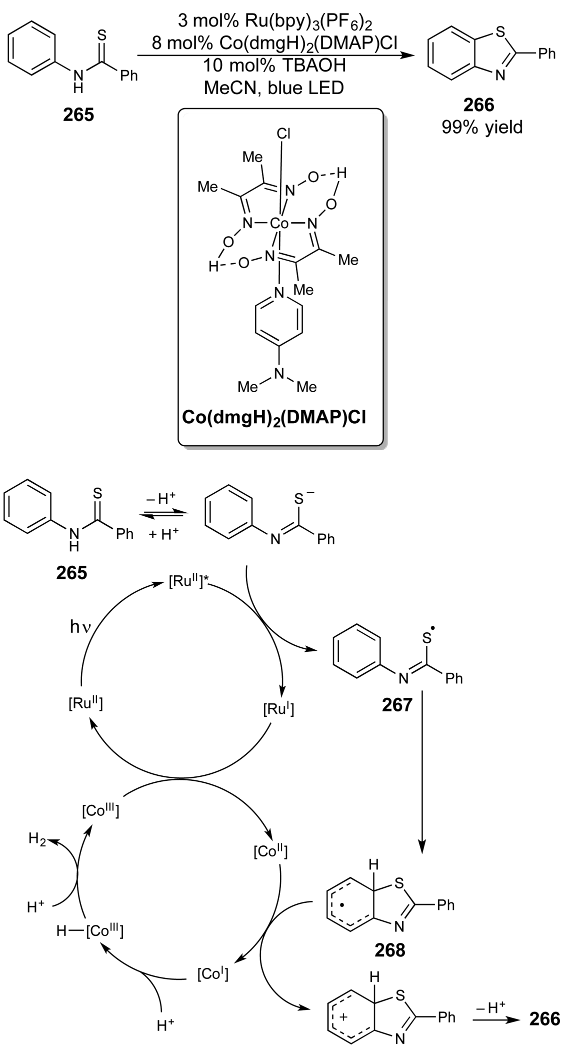
Enzymes can offer several attractive features in synthetic applications, including high chemo-, regio-, and stereoselectivity, as well as the ability to use environmentally benign terminal oxidants and reductants. However, relatively few reports have described strategies to couple the catalytic reactivity of enzymes to photocatalytic reactions to date. Willner developed several systems for reductive enzymatic processes that utilize these cooperative effects (Scheme 70). Ru(bpy)$_3^{2+}$ transfers reducing equivalents from a terminal reductant (EDTA) to a redox mediator (MV^{2+}), which then proceeds to turn over enzymatic reduction of NADP$^+$ to NADPH. The resulting NADPH is subsequently utilized in enzymatic ketone reductions[141,311] and reductive aminations.[312,313] Park used a similar strategy for the enzymatic conversion of α-ketoglutarate to L-glutamate. In these studies, $[\mathrm{Cp^*Rh(bpy)(H_2O)}]^{2+}$ was employed as a redox mediator to facilitate enzymatic reduction of NADP$^+$.[314,315] In other cases, these cofactors were proposed to turn over the photocatalyst directly.[316]

Oxidative transformations have also been carried out using enzymatic cocatalysis, including the oxidation of alcohols,[317] hydroxylation of C−H bonds, epoxidation of alkenes,[318] oxidative decarboxylation of fatty acids,[319] and Baeyer−Villiger reactions of ketones.[320] These processes typically involve the photochemical generation of oxidants such as H$_2$O$_2$ or NADP$^+$, which then participate in downstream enzyme catalysis.

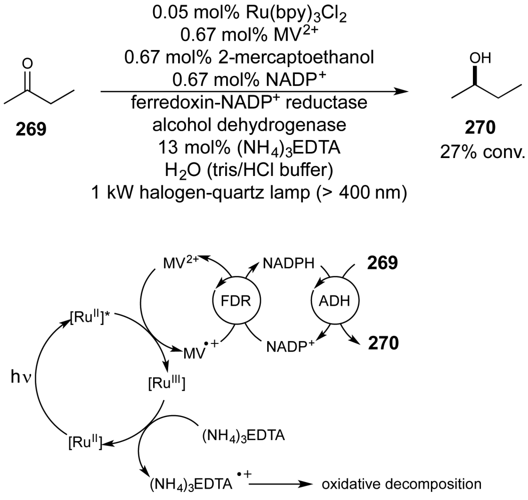
3. PHOTOINDUCED HYDROGEN ATOM TRANSFER

A second important mechanism of photocatalytic activation involves production of radical intermediates via the transfer of a hydrogen atom from an organic substrate directly to a photoexcited chromophore. The previous section discussed several examples of transformations that involve two discrete photooxidation and deprotonation steps, which can produce similar reactive radical intermediates. However, the feasibility of concerted hydrogen atom transfer is largely determined by C−H bond strength, while redox potential is the relevant thermodynamic parameter in photoinduced electron-transfer processes. The previous section also discussed C−H abstraction using HAT cocatalysts as a strategy for photoredox catalysis (section 2.4.2).

Scheme 69. Dehydrogenative Cross Coupling Using Both Cobalt and Photocatalysis



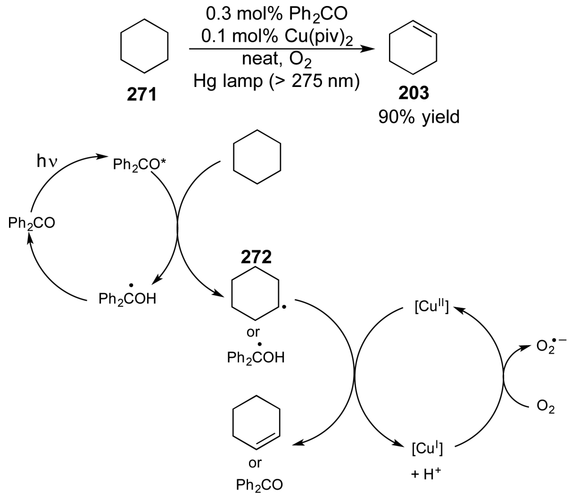
Scheme 70. Enzymatic/Photocatalytic Ketone Reduction



The transformations discussed in the following section, however, involve direct cleavage of a C−H bond by the photocatalyst and thus do not require a secondary catalyst to generate the key radical intermediate.

Jones, Edwards, and Parr reported an example using benzophenone in conjunction with Cu^{II} to perform the aerobic dehydration of alkanes (Scheme 71).[321] The authors proposed a mechanism in which photoexcited benzophenone abstracts $H^{\bullet}$ from cyclohexane to generate alkyl radical **272**. Cu^{II} subsequently serves to both oxidize this radical and regenerate the photocatalyst, and Cu^{I} can be reoxidized by oxygen.

Scheme 71. Benzophenone/Copper Tandem Catalysis for Alkane Dehydrogenation

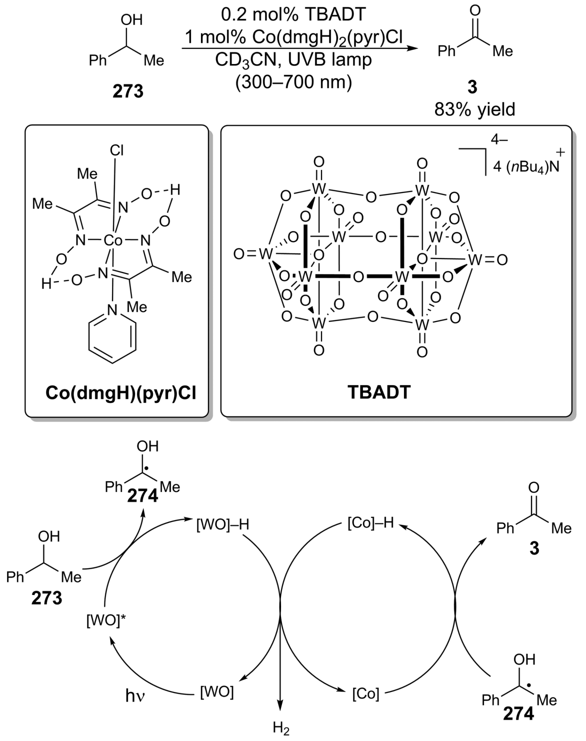


More recently, Sorensen reported similar reactivity using polyoxotungstate TBADT and a cobaloxime cocatalyst.[322] This dual catalytic system was effective for the dehydrogenation of both alkanes and alcohols (Scheme 72). After excitation, the polyoxometalate photocatalyst can abstract a hydrogen atom from **273**, and the resulting radical can undergo a second HAT step with the cobalt catalyst, generating oxidized product **3**. The tandem catalytic cycle is turned over by evolution of H_2 from the cobaloxime complex.

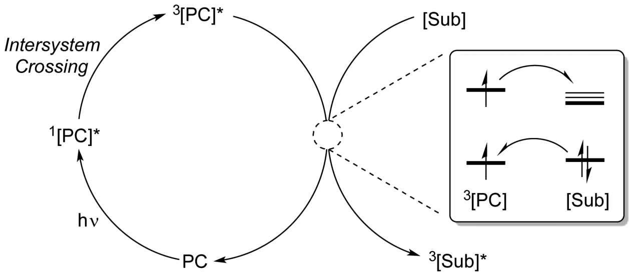
4. PHOTOINDUCED ENERGY TRANSFER

A third major mechanism of photocatalytic activation involves the sensitization of organic substrates via energy transfer. In the context of organic synthesis, the predominant mechanism for activation of substrates by this method has been the Dexter electron exchange mechanism.[5] This process can be conceptualized as simultaneous photoinduced electron transfer both to and from the excited state of the photocatalyst. This results in the generation of an electronically excited substrate molecule and concomitant relaxation of the photocatalyst to its electronic ground state (Scheme 73). Importantly, the electron exchange process results in no net redox chemistry. Thus, electrochemical potentials are not typically useful predictors of reactivity for these reactions. Instead, the relative triplet state energies for both photocatalyst and substrate are more important determinants in the feasibility of energy transfer.

Scheme 72. Alcohol Dehydrogenation by Tandem Polyoxotungstate and Cobaloxime Catalysis



Scheme 73. Dexter Mechanism for Triplet Energy Transfer



Photosensitization by energy transfer provides a means to access the distinctive reactivity of electronically excited molecules, with several important advantages over direct photoexcitation of the substrate. First, direct irradiation of ground-state, closed-shell organic molecules leads to the formation of excited singlets; these often do not undergo efficient intersystem crossing to longer-lived triplet states and thus relax rapidly to the ground state before useful bimolecular reactions can occur. Useful triplet sensitizers, on the other hand, generally undergo rapid intersystem crossing and provide a more efficient route for the production of triplet state organic compounds. Additionally, direct photoexcitation of most organic compounds requires relatively high-energy UV light that can be incompatible with common organic functional groups such as organohalides and nitroarenes. Most common photocatalytic chromophores, however, typically absorb at longer wavelengths that are more compatible with the densely functionalized, complex organic structures common in synthetic applications.

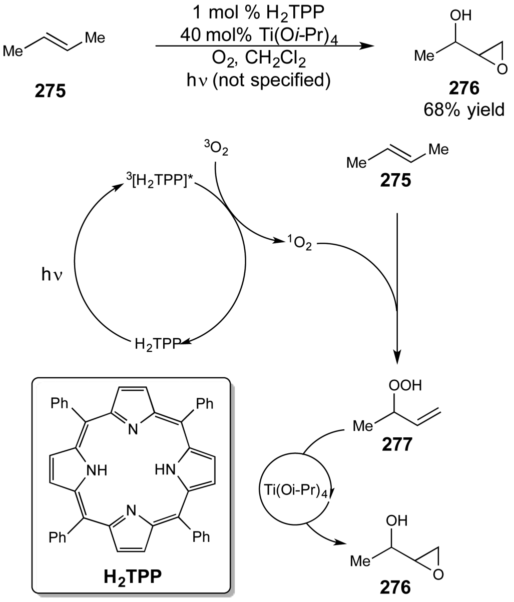
On the other hand, the use of cocatalysts to modulate the reactivity of photocatalytically generated excited-state intermediates presents unique challenges. The lifetimes of the open-shell radical intermediates generated through electron transfer or hydrogen atom-transfer photocatalysis, although short, are nevertheless substantially longer than the lifetimes of electronically excited intermediates. A variety of distinctive deactivation modes are available to photoexcited compounds, including unimolecular emissive and vibrational relaxation pathways that are generally fast. As such, the ability of a second molecular catalyst to intercept the electronically excited substrate and impact its reactivity is limited.

Nevertheless, several reports of dual-catalyst systems have proposed that the photocatalytic component engages in an energy transfer process. Many of these reactions involve the photochemical generation of singlet oxygen, the lifetime of which is on the order of several hundreds of microseconds,[323] much longer than the lifetimes of simple excited-state organic compounds. This section covers the use of energy transfer photocatalysis in conjunction with a second organic, transition metal, or Brønsted acid cocatalyst.

4.1. Transition Metal Catalysis

Adam reported an early example in which a transition metal catalyst is used to activate the ground-state product of a photosensitization reaction. Tetraphenylporphyrin (H_2TPP) is a common photocatalyst for the production of singlet oxygen via energy transfer. Reaction of $^1O_2$ with alkene **275** affords allylic hydroperoxide **277**, which subsequently reacts with a Ti^{IV} alkokide catalyst (Scheme 74). This results in O atom transfer to the alkene to generate α-epoxy alcohol **276**.[324]

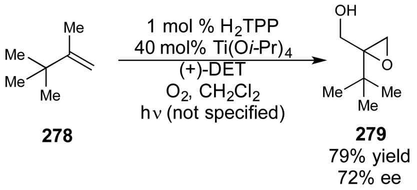
Scheme 74. Tandem Allylic Oxidation and Alkene Epoxidation



The scope for this transformation is remarkably broad, and the primary competing reactions are reduction of the allylic hydroperoxide for electron-deficient substrates in which the epoxidation step is slow. Additionally, the authors demonstrate that the use of (+)-diethyl tartrate (DET) as a chiral element in the epoxidation generates enantioenriched products in good yields and moderate enantioselectivities (Scheme 75).

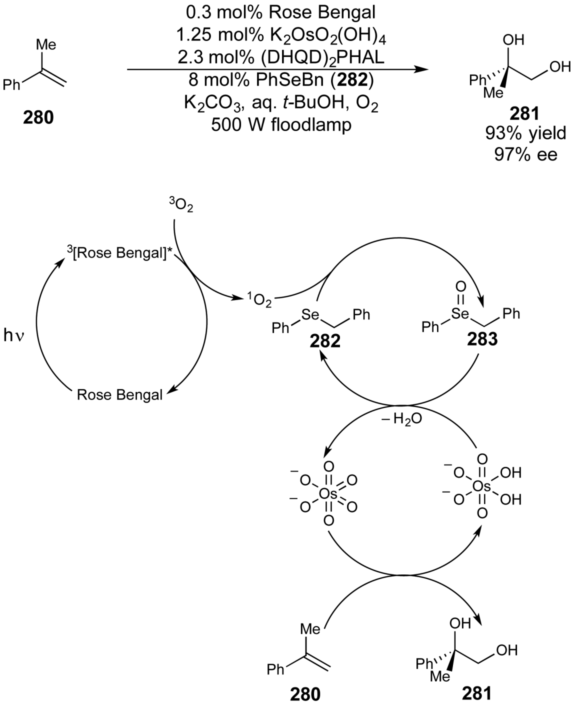
Campestrini recently demonstrated a similar transformation using $Mo(CO)_6$ as a catalyst.[325] However, because the molybdenum catalyst consumes 2 equiv of hydroperoxide for each epoxide formed, a maximum theoretical yield of 50% is possible for each olefin substrate. Nevertheless, yields of up to 38% (77% of theoretical maximum) were obtained under the optimized conditions.

Scheme 75. Asymmetric Epoxidation Applied in Dual Photo/Transition Metal Catalysis



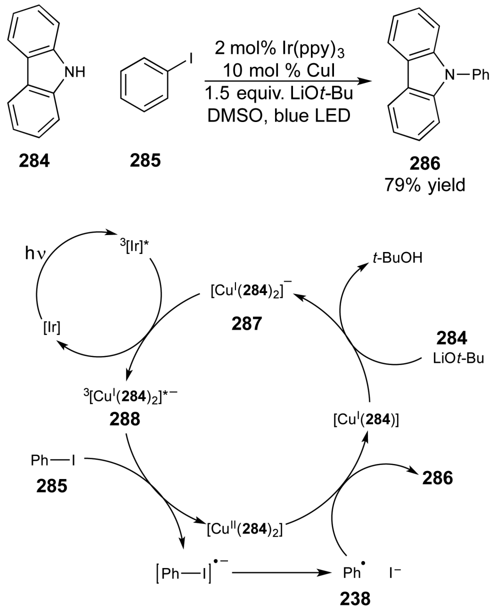
Krief developed a multicatalytic cascade process exploiting singlet oxygen sensitization for olefin dihydroxylation (Scheme 76).[326] Earlier work by this group had shown that photochemically generated singlet oxygen can oxidize selenides such as **282**.[327] The resulting selenoxide **283** is capable of oxidizing Os^{VI} to Os^{VIII}.[328] Thus, by combining Rose Bengal as a photocatalyst for singlet oxygen generation, benzyl phenyl selenide **282**, and catalytic $K_2OsO_2(OH)_4$, the authors were able to develop a high-yielding protocol for an aerobic version of the Sharpless asymmetric dihydroxylation[329] of **280** to **281**.

Scheme 76. Aerobic Alkene Dihydroxylation via Photocatalytic Generation of Selenoxides



The use of photocatalysts to directly interact with a second catalytic transition metal species can be considered a conceptually different strategy from the preceding examples. Kobayashi proposed such a mechanism[330] to rationalize the observation that the addition of $Ir(ppy)_3$ accelerates the rate of a photochemical Ullman coupling developed recently by Fu and Peters (Scheme 77).[331−333] The key step of the original, single-catalyst system involves photoinduced electron transfer between Cu^I bis(carbazole) complex **287** and iodoarene **285**; this process results in the formation of aryl radical **238** that recombines with the oxidized Cu^{II} complex to furnish a product featuring a new C−N bond. Kobayashi[330] suggests that the formation of excited $[Cu^I]^*$ complex **288** can arise from sensitization of **287** by $^3[Ir]^*$. The main benefit of the dual-catalyst system is the ability to excite

Scheme 77. Ullmann-Type Coupling Using Ir/Cu Dual Catalysis

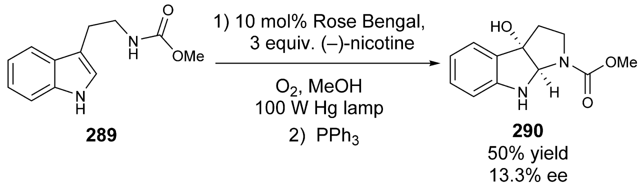


the Ir complex at longer wavelengths than the Cu^{I} carbazole complex.

4.2. Organocatalysis

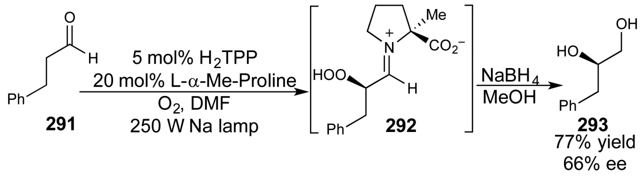
A pioneering example of the use of chiral amines to influence energy transfer photoreactions was reported by Shioiri,[334] who investigated the enantioselective photooxygenation of *N*-Moc tryptamine **289** using photogenerated singlet oxygen and (−)-nicotine (Scheme 78). Although the mechanism of stereoinduction was not proposed, experimentally significant levels of enantiomeric excess were reported.

Scheme 78. Enantioselective Photooxygenation of Tryptamine



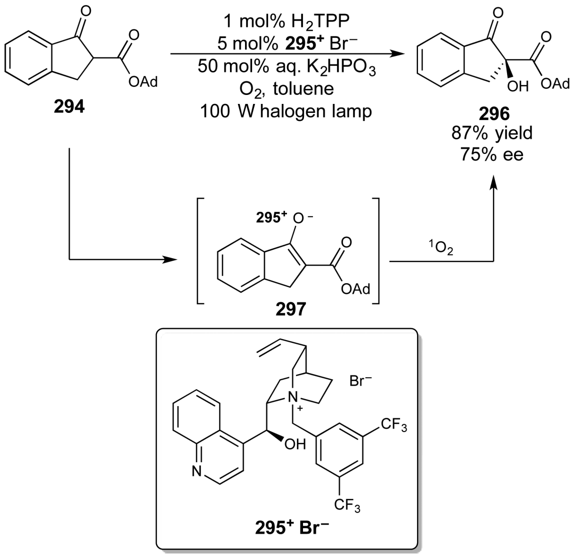
Subsequent work by Córdova also utilized chiral amine cocatalysts in asymmetric photooxygenation reactions (Scheme 79). This work took advantage of the enantiocontrol offered by amino acids and derivatives such as the Jørgensen−Hayashi diarylprolinol[335] in a range of aldehyde[336,337] and ketone[338] functionalization reactions. Reaction of the transient chiral enamine intermediate with photogenerated singlet oxygen was proposed to furnish hydroperoxide **292** in situ, which was reduced to diol **293** upon workup with NaBH$_4$. Gryko has reported that the formation of trace $^1O_2$-derived oxidative byproducts can be observed by GC−MS to support the intermediacy of both enamine and singlet oxygen in this reaction.[339]

Scheme 79. Aldehyde α-Oxygenation by Dual Enamine and Photocatalysis



Meng demonstrated that asymmetric phase-transfer catalysis could also be used to control the stereochemistry of photocatalytic enolate oxidation reactions (Scheme 80).[340] The optimal system utilized quaternized cinchona alkaloid salt **295$^+$Br$^-$** as the phase transfer catalyst and H_2TPP as the sensitizer for singlet oxygen generation. Upon deprotonation, *β*-ketoester **294** was converted to enolate **297**, and the addition of $^1O_2$ was controlled by chiral counterion **295$^+$**. The activation of oxygen by energy transfer was validated using experiments showing that the reaction rate was retarded in the presence of a singlet oxygen trap (DABCO)[341] but not in the presence of a trap for superoxide (*p*-benzoquinone).[342]

Scheme 80. Asymmetric Phase Transfer Cocatalysis Applied to Photochemical Enolate Oxidation

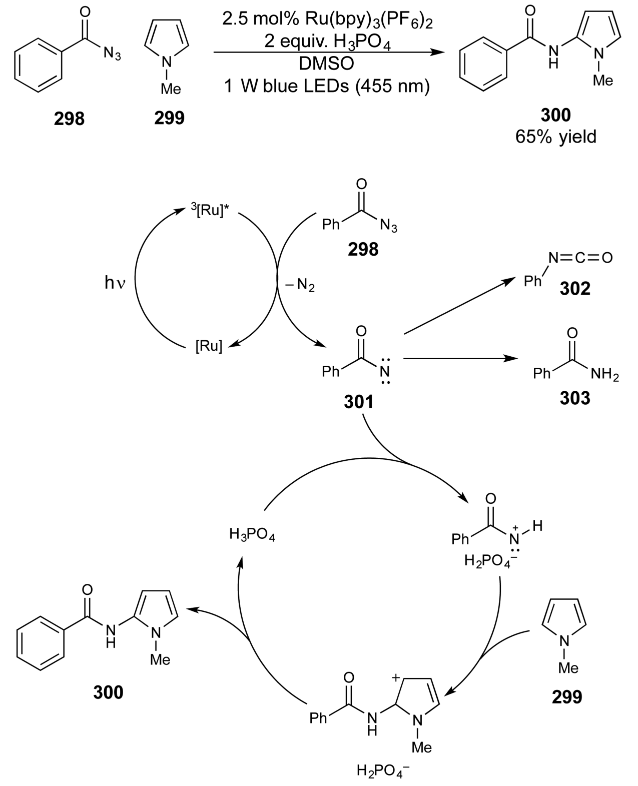


4.3. Brønsted Acid Catalysis

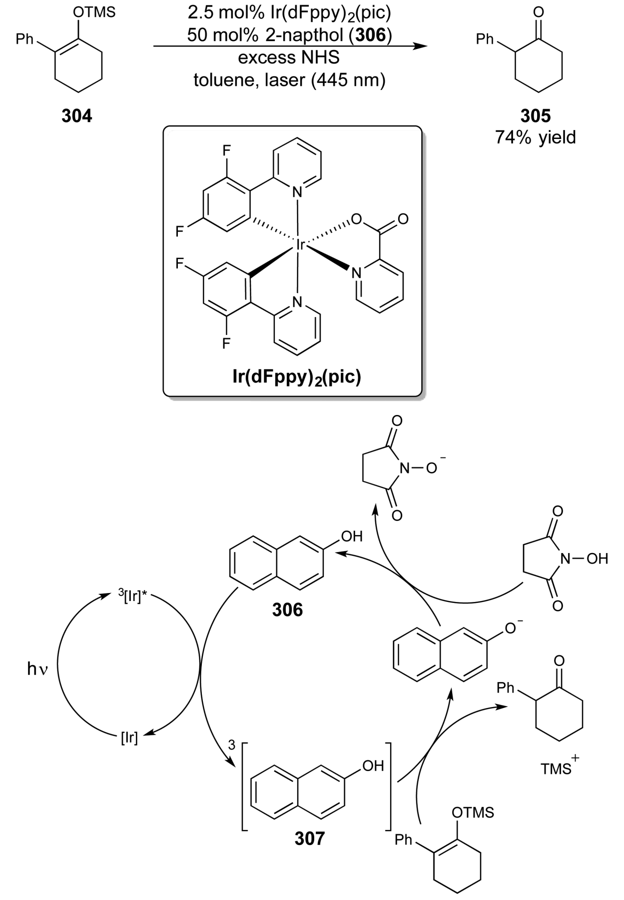
König has studied the photocatalytic amination of electron-rich heteroarenes with benzoyl azides and reported that the use of a Brønsted acid cocatalyst is necessary for optimal reactivity (Scheme 81).[343] The authors propose photocatalytic activation of benzoyl azide **298** using Ru(bpy)$_3$Cl$_2$ as a triplet sensitizer, which liberates dinitrogen to generate free nitrene **301**. Under neutral reaction conditions, this intermediate can undergo rapid unimolecular Curtius rearrangement to a phenyl isocyanate **302** or perform a C−H abstraction to yield benzamide **303**. However, under the strongly acidic reaction conditions, the authors suggest that protonation of the nitrene minimizes these side reactions and promotes electrophilic attack onto electron-rich aromatic systems to afford C−H amination product **300**.

Hanson has reported that excited-state proton transfer chemistry can be sensitized using transition metal chromophores (Scheme 82).[344] The hydroxyl moiety of an excited-state naphthol **307** is significantly acidified relative to the ground state **306** and is capable of protonating silyl enol ethers. While this reaction can be accessed directly by UV irradiation of

Scheme 81. Arene C−H Amination Using Triplet Energy Transfer and Brønsted Acid Cocatalysis



Scheme 82. Silyl Enol Ether Protonation by Photosensitized Naphthol



appropriate naphthols, the authors show that the addition of an Ir sensitizer enables longer wavelengths of light to be used.

5. CONCLUSION AND OUTLOOK

There has recently been an increasing awareness among synthetic chemists that the use of two catalysts in a single chemical reaction is a powerful design strategy that can effect transformations that are either difficult or impossible to achieve otherwise. It is interesting to reflect on the observation that dual-catalyst strategies have been a major theme of research in organic photochemistry for many decades, long predating the recent renewal of interest in synthetic photoredox catalysis. Non-photoactive cocatalysts have been used to alter the rate of all aspects of photocatalytic reactions. They can be used to impact the properties of the photocatalyst or the rate of the photoactivation steps; they can be used to transiently generate intermediates that intersect with the excited state of the photocatalyst; or they can be used to control the rate and selectivity of steps that occur downstream of the photoactivation step itself.

One might rationalize the uniquely enabling impact of dual-catalyst strategies in photochemistry as a consequence of the ways in which photocatalysis differs from other modes of catalysis. The ability to absorb and convert the energy of a photon into useful chemical potential does not necessarily require strongly bonding interactions with the substrate. Thus, photocatalysts often do not need to possess potentially reactive binding sites, and the range of cocatalysts that consequently have been shown to be compatible with photocatalysis spans a remarkably broad range, from simple protic additives to enzymes and structurally complex transition metal assemblies. As photochemistry becomes an increasingly common tool for synthesis, the development of new dual catalytic approaches will surely continue to be a powerfully enabling strategy for the photochemical construction of complex organic molecules.

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Notes

The authors declare no competing financial interest.

Biographies

Kaz Skubi attended Carleton College, where he carried out research in the laboratories of David Alberg and Gretchen Hofmeister on enantioselective desymmetrization reactions using organocatalysis. After earning his bachelor's degree in 2011, he began graduate studies at the University of Wisconsin−Madison in the group of Tehshik Yoon. His current research focuses on new strategies to control the absolute stereochemistry of photocatalytic processes.

Travis Blum received his bachelor's degree in Biochemistry from Hobart and William Smith Colleges in 2010 studying the total synthesis of bioactive depsipeptide natural products. In 2016, he completed graduate studies in both electron transfer and energy transfer photocatalysis at the University of Wisconsin−Madison under Prof. Tehshik Yoon. He is currently a postdoctoral fellow in the laboratory of Prof. David Liu at Harvard University.

Tehshik Yoon has been on the faculty at the University of Wisconsin−Madison since 2005. He received his M.S. at Caltech working with Erick

Carreira and his Ph.D. from the same institution with David MacMillan. After a postdoc at Harvard studying with Eric Jacobsen, he established an independent research program at the University of Wisconsin focusing on synthetic aspects of photochemistry and radical chemistry. His teaching and scholarship have recently been recognized through a Bessel Award from the Humboldt Foundation (2015) and UW−Madison's Kiekhofer Distinguished Teaching Award (2013).

ACKNOWLEDGMENTS

We are grateful to the NIH (GM09888) and the Sloan Foundation for financial support.

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