Oxidase Reactions in Photoredox Catalysis

Nicholas L. Reed, **Tehshik P. Yoon**[*]

[a]Department of Chemistry, University of Wisconsin–Madison, 1101 University Avenue, Madison, WI 53706, USA

Abstract

The nature of the terminal oxidant in oxidation reactions is an important reaction variable that can profoundly impact the mechanism, efficiency, and practicality of a synthetic protocol. One might reasonably categorize catalyitic oxidation reactions into either "oxygenase" type reactions, in which the oxidant serves as an atom- or group-transfer reagent, or "oxidase" type reactions, where the oxidant is involved in catalyst turnover but does not become structurally incorporated into the product. As the field of photoredox catalysis has matured over the past decade, many successful oxygenase type photoreactions have been reported. The development of photocatalytic oxidase reactions, on the other hand, has been somewhat slower. This tutorial review presents selected examples of some of the key classes of terminal oxidants that have been used in the design of photoredox oxidase transformations, along with the mechanistic features and benefits of each.

1. Introduction

The realization that many visible light-absorbing chromophores can efficiently convert photonic energy into synthetically useful chemical potential has motivated a recent renaissance in organic photochemistry.[1,2,3] Photocatalysis offers a uniquely facile strategy for the generation of a wide variety of open-shell intermediates, and the development of new photoredox transformations based upon their reactivity has been a major theme of research in the past decade. An important aspect of these reactions is the involvement of balanced photocatalyst-mediated electron transfer steps. That is, the initiating step of a photoredox reaction is a photoinduced one-electron oxidation or reduction. Turnover of the photocatalytic cycle, therefore, requires a complementary redox step to regenerate the photocatalyst. This mechanistic requirement may explain why many of the most successful early applications of photoredox catalysis were net redox-neutral in nature.

Recently, significant efforts have led to the development of complementary net-oxidation and reduction reactions that leverage the unique reactivity accessible from photoredox catalysis. These transformations have been somewhat more difficult to develop, however, because photocatalyst regeneration requires the use of stoichiometric terminal oxidants or reductants. Appropriate redox reagents must be compatible with the photocatalyst,

tyoon@chem.wisc.edu .

Conflicts of interest
There are no conflicts to declare.

the organic substrates, any photogenerated intermediates, and the products in each transformation. Thus, the identification of compatible terminal oxidants and reductants is a key consideration in the development of this class of reactions. Tertiary amines and dihydropyridines have long been recognized as practical, inexpensive terminal reductants in photocatalytic solar energy applications. This insight enabled the early, rapid development of a wide range of photocatalytic reduction reactions.[4]

The development of efficient photocatalytic oxidation reactions has been somewhat slower. The most widely utilized terminal oxidants have been group transfer reagents in which a portion of the terminal oxidant becomes structurally incorporated into the final product. An excellent example of this strategy is the photocatalytic decarboxylative fluorination strategy developed initially by Sammis[5] and later expanded by MacMillan[6] that uses Selectfluor as a terminal oxidant (Scheme 1). Photooxidation of the carboxylate of acid **1** affords organoradical **2**, which can be intercepted by Selectfluor to produce the desired C–F bond. Aminyl radical **3**, generated during C–F bond formation, serves to either turn over the photocatalyst or oxidize another equivalent of **1** in a chain propagation pathway. This mechanistic manifold has proven quite powerful, enabling the transfer of a variety of functional groups under photoredox conditions (Figure 1).

Stahl has drawn an analogy between transition metal-catalyzed group-transfer oxidation reactions and biological "oxygenase" reactions, in which metalloenzymes use molecular oxygen to install oxygen-containing functionalities.[7] Aerobic oxidation reactions in which oxygen is simply used as an electron acceptor to turn over a transition metal catalyst, in contrast, are comparable to enzymatic "oxidase" reactions. The generalization of the chemical oxidase paradigm has informed synthetic methods development by enabling the coupling of O_2 reduction to a variety of oxidative transformations, including those that do not introduce any new atoms at all (e.g., dehydrogenation). The extension of the oxidase/oxygenase analogy to other classes of redox transformations can also be conceptually quite useful.

In the context of photoredox catalysis, the group-transfer reactions that might be categorized as oxygenase-type reactions are relatively well developed (*vide supra*). In contrast, oxidase reactions have been much more difficult to develop. This observation could be due to the fact that photoredox catalysis introduces several unique challenges related to the choice of terminal oxidant. For example, many terminal oxidants that are commonly used in ground-state transition metal catalysis react rapidly and unproductively with photogenerated radical intermediates and can quench the excited states of many photocatalysts. Furthermore, these oxidants can react through multiple, diverse mechanistic pathways that can be difficult to deconvolute and rationalize. Thus, the identification of an appropriate terminal oxidant for a given photocatalytic reaction is often the result of laborious empirical screening. This review is designed to present a targeted survey of the major classes of terminal oxidants that have been used in photocatalytic oxidase chemistry. As this review is intended to be tutorial rather than comprehensive, examples have been chosen to illustrate unifying themes and common pitfalls that we hope could aid in future reaction development. Protocols that rely on the preactivation of an organic substrate in a separate, prior step (e.g. the conversion

of a carboxylic acid to a redox-active ester) will not be discussed because the photocatalytic process would then be oxygenase in nature.

2. Molecular Oxygen

Molecular oxygen is often considered an ideal terminal oxidant due to its abundance, low toxicity, and environmentally benign byproducts.[8] Its use in photocatalytic oxidase reactions, however, presents significant challenges. Molecular oxygen exists as a triplet in its ground state and efficiently quenches the excited state of many common photocatalysts.[9] Furthermore, it reacts rapidly with the radical and radical ion intermediates that typify modern photoredox catalysis.[10] Nevertheless, its successful use has been reported in a variety of photocatalytic transformations operating via several distinct mechanisms. Photoreduction of O_2 generates superoxide anion, a potent hydrogen atom transfer reagent.[11] Molecular oxygen can also mediate photocatalyst quenching or turnover by serving as an electron/proton acceptor.

Stephenson and coworkers reported an oxidative aza-Henry reaction of tetrahydroisoquinolines using an aerobic photoredox catalyst system (Scheme 2).[12] Tetrahydroisoquinoline **4** was oxidized by photoexcited $[Ir(ppy)_2(dtbbpy)]PF_6$ to afford radical cation **5** and an Ir(II) complex. Photocatalyst turnover generated superoxide anion, which can abstract a hydrogen atom from radical cation **5** to generate iminium **6**. Interception of **6** by nitromethane enolate delivered **7**. Mechanistic experiments strongly suggested that photocatalyst turnover was mediated primarily by molecular oxygen and not nitromethane. These conclusions were subsequently confirmed by König, Gshwind, and coworkers who found that O_2 was integral to both efficient hydrogen atom transfer and photocatalyst turnover.[13] The success of this system hinged on the highly selective hydrogen atom transfer between photogenerated superoxide anion and radical cation **5**, a result of severe weakening of its α-amino C–H bonds.

Reactive oxygen species such as superoxide anion react with many common organic functional groups and can result in undesired decomposition pathways. The oxidative amination of arenes developed by Nicewicz and coworkers offers an instructive case study (Scheme 3).[14] Photooxidation of anisole by acridinium **8** afforded an electrophilic arene radical cation (**9**) which could be intercepted by N–H heterocycles. Subsequent oxidation generated aryl amine **11** via the intermediacy of delocalized radical **10**. Turnover of the photocatalyst can occur via reduction of molecular O_2. However, Nicewicz found that the resulting superoxide decomposed both acridinium **8** and the anisole starting materials. The addition of catalytic TEMPO was found to prevent decomposition and resulted in significantly higher isolated yields of aminated products. TEMPO was proposed to sequester reactive oxygen species via hydrogen atom transfer. Subsequent reports have found that the addition of radical scavengers is not necessary in all cases, presumably because the rates of catalyst turnover and reduction of hydroperoxyl radical are sufficiently matched to avoid these decomposition pathways entirely.[15,16] These studies also highlight a key limitation of using molecular oxygen as a terminal oxidant in photocatalytic reactions: the presence of weak C–H bonds can result in significant oxidative decomposition and often requires the identification of alternate terminal oxidants to achieve the desired reactivity.

Reoxidation of a transition metal catalyst can often be the rate-limiting step in catalytic oxidation reactions. Photoredox catalysis offers a particularly attractive solution to this problem because it can rapidly oxidize organometallic complexes via photoinduced electron transfer, and these processes can be readily coupled to the reduction of O_2 to regenerate the photocatalyst. Kobayashi and coworkers reported a photocatalytic Chan–Evans–Lam coupling that utilized a dual photoredox/Cu(II) system (Scheme 4).[17] Irradiation of a solution of catalytic Ir(ppy)$_3$ under Chan–Evans–Lam conditions rapidly afforded high yields of *N,N*-diaryl amine products. Kobayashi proposed that photooxidation of an intermediate Cu(I)–aryl complex to regenerate their Cu(II) catalyst was responsible for the significantly enhanced rates of reaction. Rapid oxidative quenching of *Ir(ppy)$_3$ by molecular oxygen generated the Ir(IV) complex necessary to oxidize the intermediate Cu(I)–aryl species.

3. Persulfates

Persulfate salts are among the most potent chemical oxidants that are commercially available, inexpensive, and conveniently handled. As such, they have found extensive use as radical initiators, bleaching agents, and chemical oxidants.[18] In the context of photocatalytic oxidase chemistry, persulfate oxidants have primarily been used to generate sulfate radical anion, a potent hydrogen atom transfer reagent. Unlike superoxide, sulfate radical anion does not readily engage in atom transfer radical addition and generates only innocuous sulfate byproducts. One distinctive limitation of persulfate oxidants, however, is their limited solubility in most organic solvents, which can lead to slow rates of reaction. This practical consideration often dominates the design of new photocatalytic reactions using this class of oxidants. In fact, some of the most successful early applications of these oxidants (e.g. water oxidation[19] and protein-protein cross-linking[20]) use H_2O as the reaction medium.

MacMillan and coworkers leveraged the high reactivity of persulfate oxidants in the development of a photocatalytic Minisci reaction (Scheme 5).[21] The direct oxidation of ethers occurs at high positive reduction potentials and can be difficult to achieve using most photocatalysts. Oxidative quenching of the photocatalyst by $Na_2S_2O_8$ generated sulfate radical anion, which can abstract a hydrogen atom from the weak C–H bonds of tetrahydropyran to generate radical **12**. The high reactivity of sulfate radical anion allowed for a range of cyclic and acyclic ethers to be used as radical precursors. Radical **12** underwent addition to protonated heteroarenes such as **13** in Minisci fashion to generate α-amino radicals (**14**). Photocatalyst turnover was accomplished by oxidation of **14**, furnishing α-arylation product **15**. In contrast to molecular oxygen, persulfate oxidants generate benign sulfate byproducts that cannot promote further oxidative side reactions.

A common method of taming the high reactivity of sulfate radical anion is to generate a highly activated hydrogen atom donor via photooxidation as a coupled process. Using this strategy, Woo and coworkers reported a photocatalytic deprotection of *para*-methoxybenzyl (PMB) ethers utilizing $(NH_4)_2S_2O_8$ as a terminal oxidant (Scheme 6).[22] Woo found that the use of aqueous MeCN was necessary to ensure high solubility of the persulfate oxidant and consequently attain high yields of deprotected alcohol products. Photooxidation of arene **16** generated radical cation **17** while subsequent photocatalyst turnover generated sulfate radical

anion. Hydrogen atom transfer between **17** and sulfate radical anion afforded oxocarbenium **18** which underwent hydrolysis to reveal alcohol **19**. By coupling generation of sulfate radical anion to the generation of an activated hydrogen atom donor, these processes minimize unproductive side reactions.

While the use of aqueous cosolvents can often be beneficial, Yoon and coworkers provided an alternative strategy in the development of a photocatalytic [3+2] cycloaddition between phenols and styrenic olefins using persulfate as a terminal oxidant (Scheme 7).[23] The photooxidation of electron-rich phenols and their subsequent cycloadditions with styrenic olefins was found to proceed in high yields and diastereoselectivity using catalytic $[Ru(bpz)_3](PF_6)_2$ and $(NH_4)_2S_2O_8$ as a terminal oxidant. Yoon found that these reactions exhibited a significant induction period and rationalized this observation by proposing a salt metathesis between $[Ru(bpz)_3](PF_6)_2$ and $(NH_4)_2S_2O_8$ to generate catalytically active $[Ru(bpz)_3](S_2O_8)$. Upon photoexcitation, $[Ru(bpz)_3](S_2O_8)$ underwent oxidative quenching within the ion pair to generate the highly oxidizing $[Ru(bpz)_3](SO_4)^+$ complex ($[Ru]^{3+/2+} = +1.98$ V vs. SCE), which was capable of oxidizing the phenolic starting materials. Evidence for this pathway was obtained via independent synthesis of $[Ru(bpz)_3](S_2O_8)$, which proved to be both competent as a catalyst for this reaction and to exhibit no induction period. Thus, even though $[Ru(bpz)_3](S_2O_8)$ was only sparingly soluble in MeCN, the generation of this salt as the active photocatalyst *in situ* meant that oxidative quenching occurred rapidly within the ion pair upon irradiation.

4. Peroxides and Peresters

Peroxides and peresters have been used relatively infrequently as terminal oxidants in photocatalytic oxidase reactions because the intermediate oxyradicals are highly reactive and exhibit limited functional group tolerance. They do, however, undergo single-electron reduction to afford oxygen-centered radical intermediates that are capable of hydrogen atom transfer with organic substrates. Given the relative scarcity and limited mechanistic diversity of peroxides in photocatalytic oxidase chemistry, an extensive treatment of the available synthetic methods would not likely be instructive. Instead, we present a single illustrative example in the synthesis of elbasvir, a collaboration between the Merck Research Laboratories and the Knowles group at Princeton University (Scheme 8).[24]

During the development of a process route to elbasvir, an inhibitor of heptatitis C virus NS5A protein, dehydrogenation of indoline **24** proved troublesome due to facile epimerization of the hemiaminal stereocenter. An exhaustive screen of oxidation protocols revealed that photocatalytic dehydrogenation using $[Ir(dF,CF_3-ppy)_2(dtbbpy)]PF_6$ as a photocatalyst and *tert*-butylperbenzoate (*t*-BPB) as a terminal oxidant enabled selective oxidation of **24** to indole **26** without epimerization. This transformation proved highly scalable, and a continuous flow method enabled the synthesis of 100 g of this key intermediate. Detailed mechanistic investigations revealed that selective hydrogen atom transfer between photogenerated *t*-butoxy radical and indoline **24** was the key step responsible for maintaining stereochemical fidelity. Fortuitously, the indoline α-amino hydrogen atom was found to have the lowest bond dissociation free energy and other oxidation methods that proceeded via oxidation of the nitrogen atom resulted in significant

epimerization of the adjacent stereocenter. This reaction was found to be a radical chain process, and propagation was proposed to occur via benzoyl transfer between *t*-BPB and radical **25**.

5. Halocarbons

Halocarbon oxidants undergo facile single-electron reduction under photoredox conditions to generate highly electrophilic carbon-centered radicals that react rapidly with a variety of unsaturated organic functionality.[25] In the presence of photogenerated organoradical intermediates, however, these halocarbon oxidants react primarily by halogen atom transfer to generate stable, closed shell organohalides which can then undergo elimination or substitution in a subsequent step. Furthermore, the halomethyl radical byproducts do not readily participate in hydrogen atom transfer reactions with organic substrates. For these reasons, reactions that utilize these oxidants typically display expanded scope and functional group tolerance compared to their aerobic or persulfate-mediated counterparts. Additionally, halocarbon oxidants are freely soluble in most organic solvents, rendering issues of mass transport or gas diffusion inconsequential. The main drawback of these reagents is that they are quite toxic and environmentally problematic on scale. Although many halocarbons might be used as terminal oxidants, in practice, carbon tetrabromide (CBr_4), carbon tetrachloride (CCl_4), and bromotrichloromethane ($BrCCl_3$) have been the most frequently employed for photoredox applications (Figure 3).

Stephenson and coworkers dramatically expanded the scope of viable nucleophiles in their photocatalytic aza-Henry reaction (see Section 1.2) by utilizing $BrCCl_3$ as a terminal oxidant instead of molecular oxygen (Scheme 9).[26] The aerobic conditions suffered from slow photocatalyst turnover, and Stephenson found that the use of $BrCCl_3$ as a terminal oxidant afforded high yields of aza-Henry adduct **30**. Stephenson proposed that amine radical cation **28**, generated by photooxidation of **27**, afforded highly reactive bromide **29** after reaction with $BrCCl_3$. Photocatalyst turnover was accomplished via reduction of trichloromethyl radical by the reduced photocatalyst. Bromide **29** could then be subjected to nucleophilic substitution with a variety of nucleophiles to afford high yields of functionalized tetrahydroisoquinoline products. A diverse range of nucleophiles, including allyl silanes (**32**), silyl enol ethers (**33**, **35**), malonates (**34**), and aza-heterocycles (**36**), could be used.

In a subsequent report, Stephenson and Jacobsen reported that these photogenerated α-aminohalide intermediates serve as excellent iminium ion precursors in the presence of chiral anion-binding catalysts (Scheme 10).[27] The generation of a stable, closed shell intermediate (**38**) from **37** was crucial to the success of this method as the photochemical oxidation and alkylation steps required drastically different solvents to achieve both high yields and enantioselectivities. This method clearly demonstrates a key advantage of using this class of terminal oxidants: the organohalide intermediates are relatively stable and can generally be isolated. Thus, they can be utilized in subsequent transformations much more readily than photogenerated radical intermediates, which are rarely stable at high concentrations.

6. Hypervalent Iodine Reagents

Hypervalent iodine reagents have been used extensively in organic synthesis as mild oxidants with diverse chemical reactivity.[28] Hypervalent iodine reagents are most often utilized as group transfer oxidants in photoredox catalysis due to their proclivity to undergo facile single electron reduction and subsequent fragmentation, which offers a valuable route to diverse organoradical intermediates.[29] The most widely studied members of this class are the cyclic benziodoxole and periodinane reagents due to their greater stability (Figure 4). In contrast, their use as terminal oxidants in photocatalytic oxidase reactions has only recently been reported. Under photoredox conditions, they typically serve to activate an organic substrate *in situ* towards single-electron reduction and fragmentation. Hypervalent iodine reagents can also mediate radical generation via a wide range of unconventional mechanistic manifolds, however, and optimization of the oxidant structure can often reveal new modes of reactivity.

In 2015, Y. Chen and coworkers demonstrated that the oxidative coupling of acrylic acids and organotrifluoroborate salts could be accomplished using benziodoxole terminal oxidants under photoredox conditions (Scheme 11).[30] Chen proposed that BI-OAc served to activate acrylic acid **40** towards reduction by $Ru(bpy)_3^{2+}$ via condensation to initiate the reaction. Turnover of the photocatalyst was accomplished by oxidation of the organotrifluoroborate salt to liberate alkyl radical **42**, which underwent addition to **41** to give radical **43**. Fragmentation of **43** released carboxyl radical **44** and alkenylation product **45**. Carboxyl radical **44** could then be reduced by $Ru(bpy)_3^+$ to turn over the photocatalyst and continue the reaction. This strategy allowed for the direct use of a wide array of carboxylic acids without the need for preactivation.

G. Chen and coworkers have probed the mechanistic diversity available to this class of terminal oxidants. Chen utilized BI-OAc as a terminal oxidant in a photocatalytic alkylation of aza-arenes, finding that BI-OAc generated organoradical intermediates from trifluoroborate salts via an unusual radical "ate" mechanism (Scheme 12).[31] Oxidative quenching of $[Ru(bpy)_3]Cl_2$ by BI-OAc resulted in formation of the corresponding carboxyl radical, which formed metastable complex **46** with *n*-butyl boronic acid, generated by hydrolysis of the corresponding trifluoroborate salt. This complex decomposed to afford *n*-butyl radical. Addition of the alkyl radical to heteroarene **47** and subsequent oxidation by the photocatalyst afforded the desired alkylated heterocycle **48**. This unusual radical "ate" pathway allowed for the use of a wide variety of alkyl trifluoroborate salts as radical precursors.

The same group found that highly electrophilic hypervalent iodine oxidants could also mediate hydrogen atom transfer reactions (Table 1).[32] Reasoning that the increased stability of the benziodoxole oxidant was responsible for their poor hydrogen atom transfer reactivity, a series of increasingly electrophilic benziodoxole reagents were examined. Chen found that **49** cleanly effected hydrogen atom transfer to afford organoradical intermediates, which delivered hydroxylated or amidated products in excellent yields upon oxidation and solvolysis.

7. Transition Metals

Transition metals have most often been used as co-catalysts in photoredox catalysis[33] while their use as stoichiometric terminal oxidants has been much less common. This is surprising given the fact that many transition metals undergo facile reduction via outer-sphere photoinduced electron transfer, making them especially well-suited to mediate photocatalyst turnover. Furthermore, the reduced metal by-products are relatively unreactive and avoid many of the decomposition pathways that can occur using other classes of terminal oxidants (e.g. hydrogen atom transfer). The use of transition metal complexes as terminal oxidants does impose several practical limitations, however. Many transition metals are prohibitively expensive and can require complicated ligand scaffolds for good reactivity. Transition metal terminal oxidants should ideally be commercially available or easily synthesized from commodity chemicals, air- and moisture-stable, and non-toxic. For these reasons, they are generally limited to simple, first row transition metal salts.

A seminal example comes from the work of Okhubo and coworkers who utilized chiral-at-metal ruthenium catalysts in an oxidative dimerization of naphthols (Scheme 13).[34] The photocatalyst, a menthol derivative of $Ru(bpy)_3^{2+}$, underwent oxidative quenching by $Co(acac)_3$ upon excitation and the resulting Ru(III) complex was capable of oxidizing naphthol **50** to radical **51**. Radical **51** underwent dimerization and oxidation with another equivalent of naphthol **50** to furnish biaryl **52**. The terminal oxidant was found to have a negligible impact on enantioinduction as enantiopure Λ- or -Co(acac)$_3$ did not impart significant enantioselectivity. This is consistent with the fact that the Co(III) oxidant is not intimately involved in the oxidation of the organoradical intermediates and serves only to mediate redox state changes of the photocatalyst.

Cu(II) has found use as a terminal oxidant in thermal catalysis, but its utilization in photoredox catalysis has only recently gained attention. Cu(II) readily oxidizes organoradical intermediates to their corresponding carbocations, which can then be intercepted by a wide variety of nucleophilic functionality. The reduction of Cu(II) also provides a strong thermodynamic driving force to drive a wide array of oxidative transformations. Additionally, the reduced metal byproducts are innocuous and easily removed at the end of a reaction by aqueous washing or filtration.

Yoon and coworkers developed an approach to photocatalytic alkene difunctionalization that utilized triphenyl pyrylium tetrafluoroborate (TPPT) as a photocatalyst and Cu(II) salts as terminal oxidants (Scheme 14).[35] Initial photooxidation of **53** resulted in formation of styrene radical cation **54** which underwent cyclization with tethered carbamates to afford radical **55**. The role of Cu(II) in this reaction was proposed to be twofold: (1) to oxidize **55** and (2) to turn over the photocatalyst. Cyclization of the carbamoyl oxygen and loss of *tert*-butyl cation upon oxidation of **55** afforded oxazolidone **56**. Interestingly, Yoon found that one equivalent of Cu(II) was able to effect both oxidations, resulting in formation of Cu(0) which could be observed precipitating from solution. Due to the oxidase nature of this reaction, alkene diamination and dioxygenation could also be accomplished under very similar conditions by changing the identity of the heteroatomic nucleophile.

Realizing that the oxidation of radical intermediates by Cu(II) should be agnostic to the method of radical generation, Yoon subsequently developed a direct benzylic alkoxylation reaction between electron-rich arenes and alcohols (Scheme 15).[36] Oxidation and subsequent deprotonation of **57** generated radical **58**. Oxidation of **58** by Cu(II) afforded quinone methide cation **59** which was then intercepted by oxygen nucleophiles to generate benzylic functionalization products (**60**). Disproportionation of Cu(I) generated Cu(II), which effected photocatalyst turnover. The mild reaction conditions enabled the late stage functionalization of several arene natural products with complex alcohols. In conceptually related work, Tunge and coworkers demonstrated that the outcome of organoradical oxidation can be diverted towards alkene formation to accomplish the decarboxylative alkenylation of amino acid derivatives.[37]

8. Hydrogen Evolution Catalysis

One particularly attractive approach to the development of photocatalytic oxidase reactions is to couple the oxidation of an organic substrate to the reduction of H^+ and generation of H_2 gas. The use of hydrogen evolution catalysis in combination with photoredox catalysis has allowed for the development of a wide variety of "external oxidant-free" reactions in which the protons and electrons necessary for hydrogen evolution come from the organic substrate upon photooxidation. The most commonly utilized catalysts for this purpose are the Co(III) diglyoxime complexes first reported by Connolly and Espenson (Figure 5)[38] whose synthesis, reactivity, and applications have been examined in detail elsewhere.[39] The main advantage of these systems is that they eliminate the need for stoichiometric bases and oxidants and generate H_2 as the byproduct. While the mechanism of hydrogen evolution can be quite complex, a simplified mechanism under photoredox conditions is presented in Scheme 16. Reduction of a Co(III) complex by two sequential single-electron transfers gives rise to an intermediate Co(I) complex. Protonation affords a Co(III)–H which, after an additional proton transfer, liberates H_2 to regenerate the starting Co(III) catalyst.

Lei and coworkers used a dual photoredox/hydrogen evolution strategy to develop a photocatalytic C–H thiolation reaction (Table 2).[40] Using catalytic Ru(bpy)$_3^{2+}$ and **64** Lei observed quantitative yields of benzothiazole **67**. They found these conditions applicable to the synthesis of a wide variety of substituted benzothiazoles and found no traces of overoxidation. To demonstrate the advantages of this strategy, Lei used other common terminal oxidants in place of hydrogen evolution catalyst **64** and found that they resulted in mixtures of **67** and amide **68**, with **68** favored in all cases. Thus, the use of hydrogen evolution catalysis avoids this deleterious pathway entirely. Lei has since demonstrated the broad generality of this approach, developing a wide variety of oxidative transformations, including hydration, phosphonylation, arene amination, dehydrogenative lactonization, and oxidative annulation reactions.[41] In all cases, the protons and electrons needed for hydrogen evolution are provided by the organic substrate upon photooxidation. Sorenson and coworkers reported that this strategy can also be used to effect the dehydrogenation of simple alkanes and alcohols when used in combination with a decatungstate photocatalyst.[42]

Nearly simultaneous reports by the groups of Ritter[43] and Tunge[44] described the application of dual photoredox/hydrogen evolution catalysis approaches to decarboxylative olefination.

Ritter's system converted alkyl carboxylic acids to alkenes using an iridium photocatalyst and **63** as a hydrogen evolution catalyst (Scheme 17a) and olefination proceeded in excellent yields using a wide variety of carboxylic acids. Interestingly, stoichiometric experiments of isolated alkyl–Co(III) complexes showed that alkene formation occurs from discrete organocobalt complexes upon irradiation with visible light. Tunge and coworkers reported a similar strategy for the decarboxylative olefination of *N*-acyl amino acid derivatives (Scheme 17b). Tunge found that enamides and enecarbamates could be readily synthesized upon irradiation of the corresponding amino acids in the presence of an acridinium photocatalyst and **61**. This method greatly expanded the scope of decarboxylative elimination as initially described by Kochi by eliminating the need for stoichiometric Pb(OAc)$_4$ and Cu(OAc)$_2$, which afforded only low yields of the desired products and significant decomposition.

9. Electrochemistry

There has been a significant renewal of interest in synthetic organic electrochemistry over the last two decades. While the combination of photoredox catalysis and electrochemistry has only recently been explored in depth, it represents an exciting new frontier in photocatalytic reaction development. The main advantage of this strategy is that anodic oxidation can be coupled to the cathodic reduction of an innocuous terminal oxidant (e.g., H$^+$). Consequently, these reactions typically require acidic additives although they afford H$_2$ gas as the sole by-product. There are, however, several limitations that must be considered in the development of such a reaction. Anodic oxidation of organic compounds typically requires high electrode potentials, which can lead to decomposition, and the resulting organoradical intermediates can undergo further oxidation at the electrode surface, leading to electrode passivation. Finally, electrochemical synthesis comes with significant barriers to entry in terms of equipment and experimental expertise and has long been viewed as a "specialist" branch of synthetic organic chemistry.

These barriers have been lowered substantially through the publication of tutorial reviews and the introduction of standardized instruments for electrochemical synthesis.[45,46] Methods that combine electrochemical and photochemical activation of organic substrates have been enabled primarily by indirect electrolysis strategies in which a redox mediator, often the photocatalyst, is oxidized at the anode surface, diffuses into the bulk solution, and oxidizes an organic substrate (Scheme 18).[47] Turnover of the electrochemical system is most often coupled to cathodic generation of H$_2$ from H$^+$. This strategy allows for many oxidative transformations to be performed at low applied potentials (*ca.* <1 V versus SCE), limiting overoxidation and electrode passivation. Indirect electrolysis also allows for efficient irradiation of commonly used electrochemical cells, significantly simplifying the experimental intricacies associated with the development of these methods.

Several recent pioneering studies have clearly demonstrated the power and unique reactivity accessible by combining these two modes of activation. Xu and coworkers demonstrated that electrochemical oxidation could be used in place of persulfate oxidants during the development of a Minisci reaction of heteroarenes (Scheme 19).[48] Their proposed mechanism involved photooxidation of a trifluoroborate salt (**74**) by MesAcrMe$^+$ to generate

an alkyl radical intermediate that subsequently adds to an aza-arene (**73**). Subsequent oxidation by either the photocatalyst or at the anode surface afforded the desired functionalized heteroarenes (**75–78**). Photocatalyst turnover was accomplished via anodic oxidation and was coupled to cathodic reduction of H^+. Lin and coworkers recently reported an elegant study on the oxidation of unactivated alcohols using riboflavin tetraacetate (RFT) as a photocatalyst (Scheme 20).[49] Unactivated alcohols could not be directly oxidized by the excited state photocatalyst but Lin found that addition of thiourea **79** as a catalytic redox mediator afforded high yields of aldehyde and ketone products. These reactions were proposed to proceed via hydrogen atom transfer between photogenerated thiourea radical **80** and the alcohol substrates to afford an electron-rich α-oxy radical which undergoes subsequent oxidation at the anode surface.

Stahl and Wang greatly expanded the scope of the traditional Hoffman-Löffler-Freytag (HLF) reaction by merging the photochemical cleavage of N–I bonds with the electrochemical oxidation of an iodide catalyst (Scheme 21).[50] Stahl found that tetrabutylammonium iodide (TBAI) could be oxidized at low applied potentials to generate catalytic I_2. Subsequent reaction with sulfonamide or imidate nucleophiles generated iodoamine intermediates, like **86,** which underwent homolysis to generate nitrogen-centered radical **87** upon irradiation with visible light. The reaction then proceeded via 1,5-HAT, iodination, and base-promoted nucleophilic ring closure to deliver aza-heterocycle **88** and this method proved applicable to the synthesis of a wide range of aza-heterocyclic scaffolds (**89–92**). Photochemical cleavage of the N–I bond proved crucial to the success of this method as β-hydride elimination of the iodoamine intermediates predominated under thermal conditions.

Lambert and coworkers reported the trisaminocyclopropenium ion (**TAC**) as a privileged catalyst for dual photoredox/electrochemical applications. The relevant mechanism for oxidase chemistry is outlined in Scheme 22. Anodic oxidation of TAC generates a radical dication (**TAC⁺**), which, upon excitation with visible light, affords an extremely oxidizing excited state (***TAC⁺**, $E_{ox} = +3.33$ V vs SCE). Oxidation of an organic substrate regenerates the ground state monocationic catalyst. Lambert initially applied this catalyst system to the oxidative amination of arenes using nitrogen heterocycles which was proposed to proceed via the intermediacy of arene radical cations (Scheme 23a).[51] In comparison to Nicewicz's arene amination (see Scheme 3),[14] Lambert's conditions displayed expanded scope due to the highly oxidizing nature of the excited state radical dication and, as such, even electron-deficient arenes were viable reaction partners. The use of **TAC** as a photochemical redox mediator was crucial as bulk electrolysis led to polymerization and poor yields of aminated product.

Lambert demonstrated that the excited state radical dication can mediate hydrogen atom transfer to generate organoradical intermediates (Scheme 23b).[52] Using this new mode of reactivity, a Minisci reaction between alkyl ethers and heteroarenes was developed. The oxidase nature of this process allowed electron deficient olefins and N–H heterocycles to be used in place of the heteroarene reaction partner with no change to the catalytic conditions. This process is noteworthy because the hydrogen atom transfer reagent is generated catalytically as turnover of the electrochemical system is coupled to cathodic

reduction of H^+. Cathodic generation of H_2 also turns over the TAC catalyst and allows the photocatalytic cycle to continue. This contrasts most photocatalytic oxidase reactions which use stoichiometric terminal oxidants to generate hydrogen atom transfer reagents upon photoreduction (see Sections 2–4).

10.   Other Oxidants

A variety of organic compounds have also been used as terminal oxidants in photocatalytic oxidase reactions. A unifying theme among these reagents is that the reduced oxidant (often an organoradical species itself) must not promote deleterious side reactions. This is most commonly accomplished by a subsequent reaction in which the reduced oxidant generates a closed shell organic molecule. An early example is the seminal work of Cano-Yelo and Deronzier, who reported a photocatalytic oxidation of benzyl alcohols to benzaldehydes using aryl diazonium salts as terminal oxidants (Scheme 24).[53] Diazonium salt **93** oxidatively quenches the excited state photocatalyst, generating aryl radical **94** as a byproduct. Aryl radicals are normally quite reactive and might be expected to engage in unproductive side reactions, but **94** underwent Pschorr cyclization to yield fluorenone **95** as a stable byproduct instead. A more recent example comes from DiRocco and Rovis who reported the asymmetric α-acylation of tertiary amines using a combination of photoredox and *N*-heterocyclic carbene catalysis.[54] They showed that *meta*-dinitrobenzene acts as an excellent terminal oxidant for this process; its absence results in decomposition and low yields. Other oxidants, like bromotrichloromethane, also resulted in significant decomposition of both the amine substrate and *N*-heterocyclic carbene catalyst presumably due to the highly reactive nature of the trichloromethyl radical intermediate.

Conclusions

The identification of terminal oxidants for photoredox applications has resulted in the development of a variety of synthetically useful oxidative transformations. While the majority of these proceed *via* group-transfer pathways, there has been an increasing appreciation for the power of oxidase-type processes where the identity of the terminal oxidant is critical to the success of the methods. Under this paradigm, the terminal oxidants can react through a diverse array of mechanistic pathways enabled by photoredox catalysis. They can quench the photocatalyst to generate highly reactive intermediates; they can activate an organic substrate towards reaction with an excited state photocatalyst; they can directly oxidize photogenerated radical intermediates; or they can mediate photocatalyst turnover by outer sphere electron transfer. In most cases, several of these processes are performed in concert to accomplish a single photocatalytic transformation.

Our purpose in crafting this tutorial review has been to survey the major classes of terminal oxidants that have been utilized in photocatalytic oxidase chemistry and to provide instructive guidance using selected examples. The most important insight that arises from this analysis is that terminal oxidants that are ideal for thermal catalysis are often not ideal for photoredox applications, and it is not uncommon to see highly unconventional terminal oxidants (e.g. diazonium salts) employed under photoredox conditions. Thus, the design of new photocatalytic oxidase reactions requires a high degree of flexibility and creativity in

the selection of appropriate terminal oxidants. While this might seem like a daunting task at first, it also affords exciting opportunities to develop fundamentally new strategies in catalytic oxidation chemistry. Our hope is that this review will provide an appreciation for the critical role of the terminal oxidant in these processes and aid in the future development of novel photocatalytic transformations.

Acknowledgements

Notes and references

1. See: Narayanam JMR and Stephenson CRJ, Chem. Soc. Rev, 2011, 40, 102–113 [PubMed: 20532341]

2. See:Prier CK, Rankic DA, and MacMillan DWC, Chem. Rev, 2013, 113, 5322–5363 [PubMed: 23509883]

3. See:Romero NA and Nicewicz DA, Chem. Rev, 2016, 116, 10075–10166 [PubMed: 27285582]

4. For a leading modern example, see: Narayanam JMR, Tucker JW, and Stephenson CRJ, J. Am. Chem. Soc. 2009, 131, 8756–8757. [PubMed: 19552447]

5. Rueda-Becerril M, Mahé O, Drouin M, Majewski MB, West JG, Wolf MO, Sammis GM, and Pacquin J-F, J. Am. Chem. Soc, 2014, 136, 2637–2641. [PubMed: 24437369]

6. Ventre S, Petronijevic FR, and MacMillan DWC, J. Am. Chem. Soc, 2015, 137, 5654–5657. [PubMed: 25881929]

7. See:Stahl SS, Angew. Chem., Int. Ed, 2004, 43, 3400–3420

8. See:Stahl SS, Science, 2005, 309, 1824–1826 [PubMed: 16166508]

9. Winterle JS, Kliger DS, and Hammond GS, J. Am. Chem. Soc, 1976, 98, 3719–3721.

10. Maillard B, Ingold KU, and Scaiano JC, J. Am. Chem. Soc, 1983, 105, 5095–5099.

11. See:Hayyan M, Hashim MA, and AlNashef IM, Chem. Rev, 2016, 116, 3029–3085 [PubMed: 26875845]

12. Condie AG, González-Goméz JC, and Stephenson CRJ, J. Am. Chem. Soc, 2010, 132, 1464–1465. [PubMed: 20070079]

13. Bartling H, Eisenhofer A, König B, and Gschwind RM, J. Am. Chem. Soc, 2016, 138, 11860–11871. [PubMed: 27541322]

14. Romero NA, Margrey KA, Tay NE, and Nicewicz DA, Science, 2015, 349, 1326–1330. [PubMed: 26383949]

15. McManus JB and Nicewicz DA, J. Am. Chem. Soc, 2017, 139, 2880–2883. [PubMed: 28177237]

16. Margrey KA, Levens A, and Nicewicz DA, Angew. Chem., Int. Ed, 2017, 56, 15644–15648.

17. Yoo W-J, Tsukamoto T, and Kobayashi S, Angew. Chem., Int. Ed, 2015, 54, 6587–6590.

18. See:Mandal S, Bera T, Dubey G, Saha J, and Laha JK, ACS Catal, 2018, 8, 5085–5144

19. See:Yagi M and Kaneko M, Chem. Rev, 2001, 101, 21–35 [PubMed: 11712192]

20. Fancy DA and Kodadek T, Proc. Natl. Acad. Sci. U.S.A, 1999, 96, 6020–6024. [PubMed: 10339534]

21. Jin J and MacMillan DWC, Angew. Chem., Int. Ed, 2015, 54, 1565–1569.

22. Ahn DK, Kang YW, and Woo SK, J. Org. Chem, 2019, 84, 3612–3623. [PubMed: 30781954]

23. Blum TR, Zhu Y, Nordeen SA, and Yoon TP, Angew. Chem., Int. Ed, 2014, 53, 11056–11059.

24. Yayla HG, Peng F, Mangion IK, McLaughlin M, Campeau L-C, Davies IW, DiRocco DA, and Knowles RR, Chem. Sci, 2016, 7, 2066–2073. [PubMed: 29899932]

25. For a leading modern example, see: Nguyen JD, Tucker JW, Konieczynska MD, and Stephenson CRJ, J. Am. Chem. Soc, 2011, 133, 4160–4163. [PubMed: 21381734]

26. Freeman DB, Furst L, Condie AG, and Stephenson CRJ, Org. Lett, 2012, 14, 94–97. [PubMed: 22148974]

27. Bergonzini G, Schindler CS, Wallentin C-J, Jacobsen EN, and Stephenson CRJ, Chem. Sci, 2014, 5, 112–116.

28. See: Yoshimura A and Zhdankin VV, Chem. Rev. 2016, 116, 3328–3435 [PubMed: 26861673]

29. See: Wang L and Liu J, Eur. J. Org. Chem, 2016, 10, 1813–1824

30. Huang H, Jia K, and Chen Y, Angew. Chem., Int. Ed, 2015, 54, 1881–1884.

31. Li G-X, Morales-Rivera CA, Wang Y, Gao F, He G, Liu P, and Chen G, Chem. Sci, 2016, 7, 6407–6412. [PubMed: 28451096]

32. Li G-X, Morales-Rivera CA, Gao F, Wang Y, He G, Liu P, and Chen G, Chem. Sci, 2017, 8, 7180–7185. [PubMed: 29081950]

33. See: Twilton J, Le C, Zhang P, Shaw MH, Evans RW, and MacMillan DWC, Nat. Rev. Chem, 2017, 1, 0052

34. Hamada T, Ishida H, Usui S, Watanabe Y, Tsumura K, and Ohkubo K, J. Chem. Soc., Chem. Commun, 1993, 909–911.

35. Reed NL, Herman MI, Miltchev VP, and Yoon TP, Org. Lett, 2018, 20, 7345–7350. [PubMed: 30407833]

36. Lee BJ, DeGlopper KS, and Yoon TP, Angew. Chem., Int. Ed, 2019, 58, 1–7.

37. Cartwright KC, Lang SB, and Tunge JA, J. Org. Chem, 2019, 84, 2933–2940. [PubMed: 30785754]

38. Connolly P, and Espenson JH, Inorg. Chem, 1986, 25, 2684–2688.

39. See:Dempsey JL, Brunschwig BS, Winkler JR, and Gray HB, Acc. Chem. Res, 2009, 42, 1995–2004 [PubMed: 19928840]

40. Zhang G, Liu C, Yi H, Meng Q, Bian C, Chen H, Jian J-X, Wu L-Z, and Lei A, J. Am. Chem. Soc, 2015, 137, 9273–9280. [PubMed: 26158688]

41. See: Wang H, Goa X, Lv Z, Abdelilah T, and Lei A, Chem. Rev, 2019, 119, 6769–6787 [PubMed: 31074264]

42. West JG, Huang D, and Sorensen EJ, Nat. Commun, 2015, 6, 10093. [PubMed: 26656087]

43. Sun X, Chen J, and Ritter T, Nat. Chem, 2018, 10, 1229–1233. [PubMed: 30297751]

44. Cartwright KC and Tunge JA, ACS Catal, 2018, 8, 11801–11806.

45. See: Feng R, Smith JA, and Moeller KD, Acc. Chem. Res, 2017, 50, 2346–2352 [PubMed: 28858480]

46. See: Moeller KD, Chem. Rev, 2018, 118, 4817–4833 [PubMed: 29498518]

47. For a recent review on the combination of electrochemistry and photoredox catalysis, see:Liu J, Lu L, Wood D, and Lin S, ACS Cent. Sci, 2020, 6, 1317–1340 [PubMed: 32875074]

48. Yan H, Hou Z-W, and Xu H-C, Angew. Chem., Int. Ed, 2019, 58, 4592–4595.

49. Zhang W, Carpenter KL, and Lin S, Angew. Chem., Int. Ed, 2020, 59, 409–417.

50. Wang F and Stahl SS, Angew. Chem., Int. Ed, 2019, 58, 6385–6390.

51. Huang H, Strater ZM, Rauch M, Shee J, Sisto TJ, Nuckolls C, and Lambert TH, Angew. Chem., Int. Ed, 2019, 58, 13318–13322.

52. Huang H, Strater ZM, and Lambert TH, J. Am. Chem. Soc, 2020, 142, 1698–1703. [PubMed: 31904939]

53. Cano-Yelo H and Deronzier A, Tetrahedron Lett, 1984, 25, 5517–5520.

54. DiRocco DA and Rovis T, J. Am. Chem. Soc, 2012, 134, 8094–8097. [PubMed: 22548244]
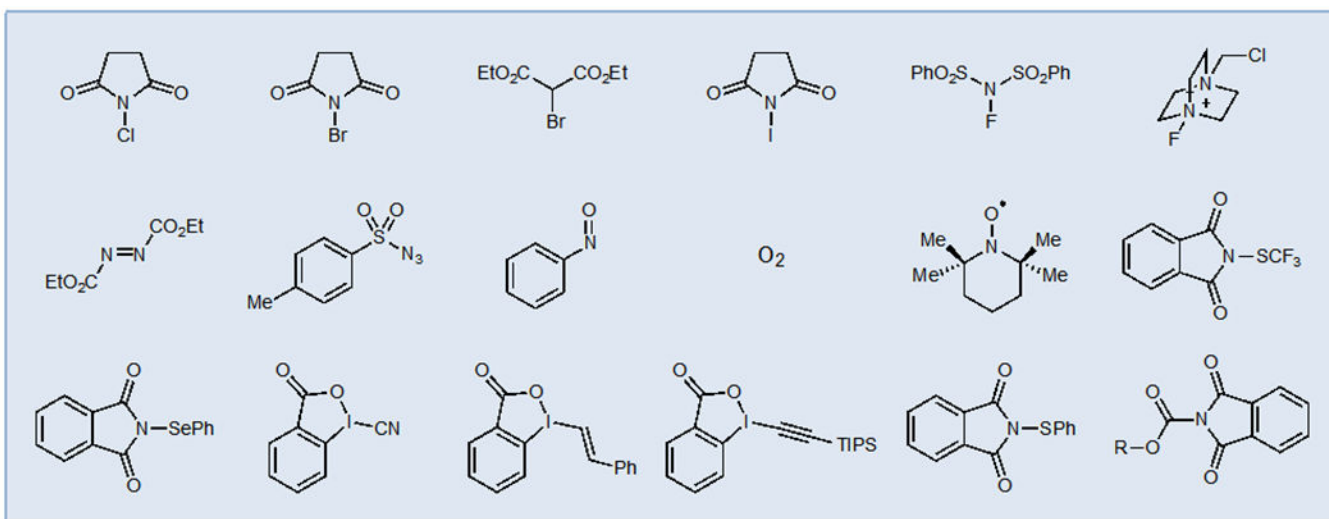
Figure 1.
Representative Terminal Oxidants Commonly Used for Atom- or Group-transfer Photoredox Reactions
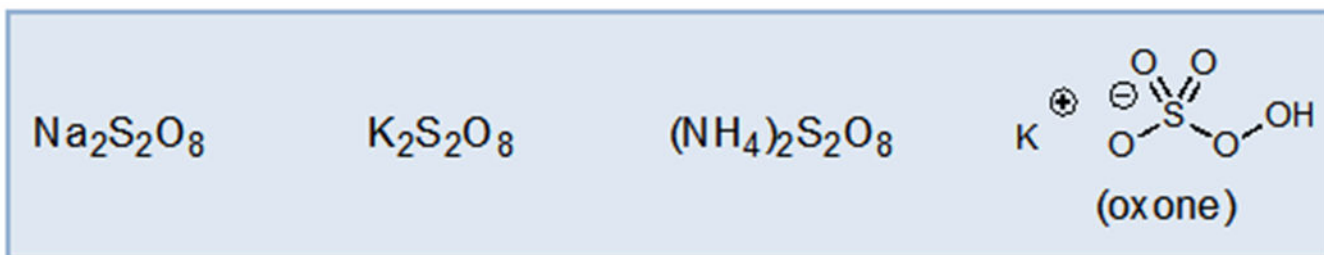
Fig. 2.
Common Persulfate Oxidants
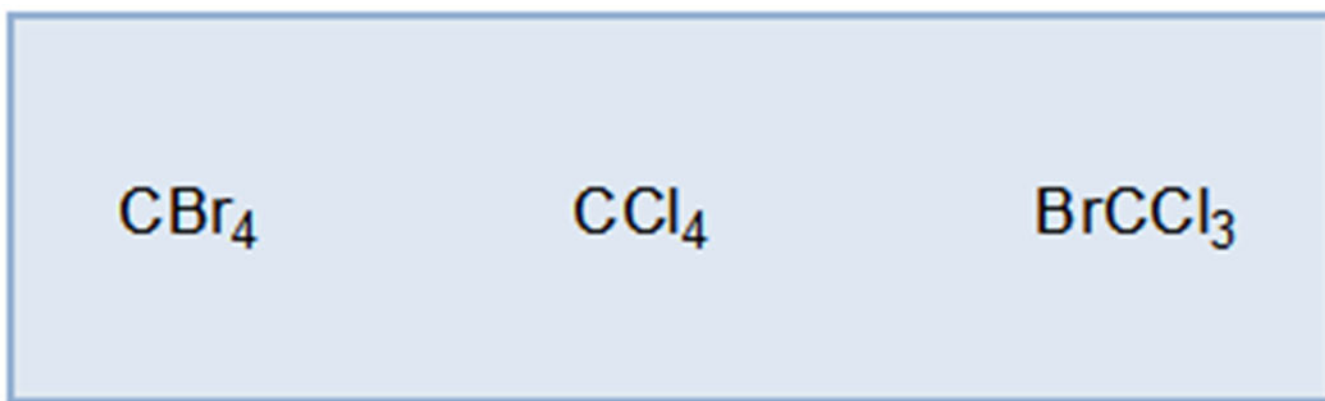
Figure 3.
Common Halocarbon Oxidants
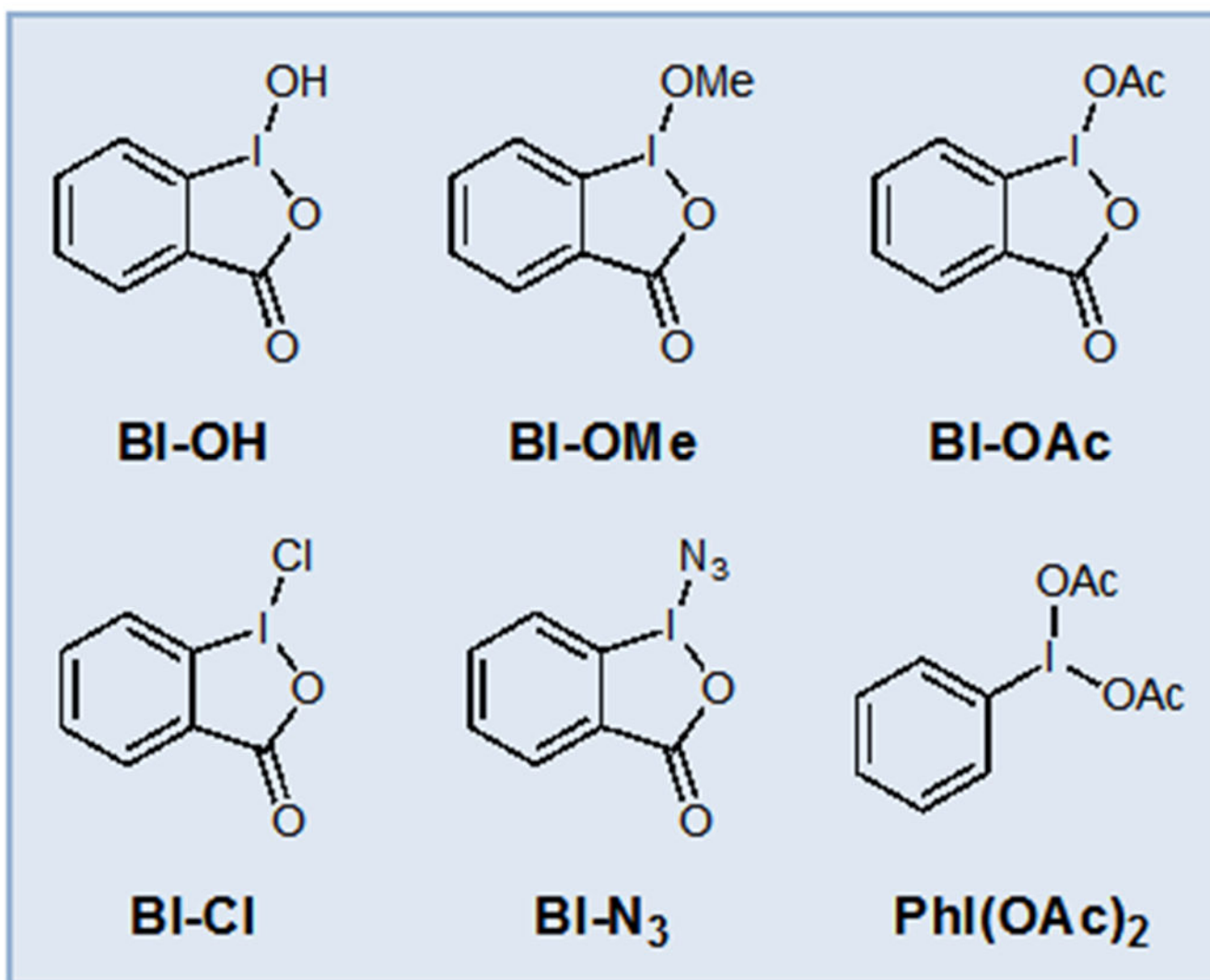
Figure 4.
Common Hypervalent Iodine Oxidants
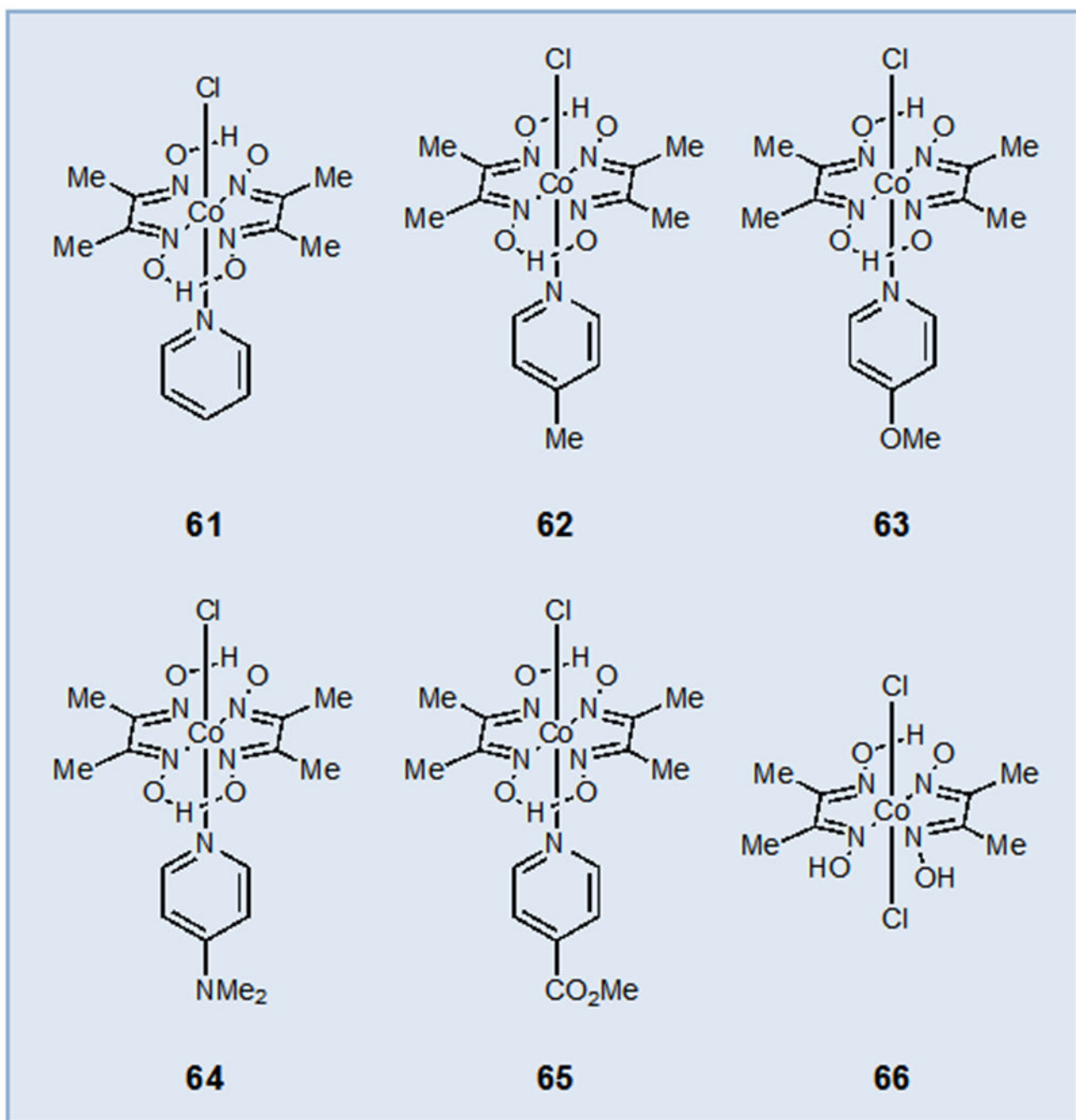
Fig. 5.
Common Hydrogen Evolution Catalysts
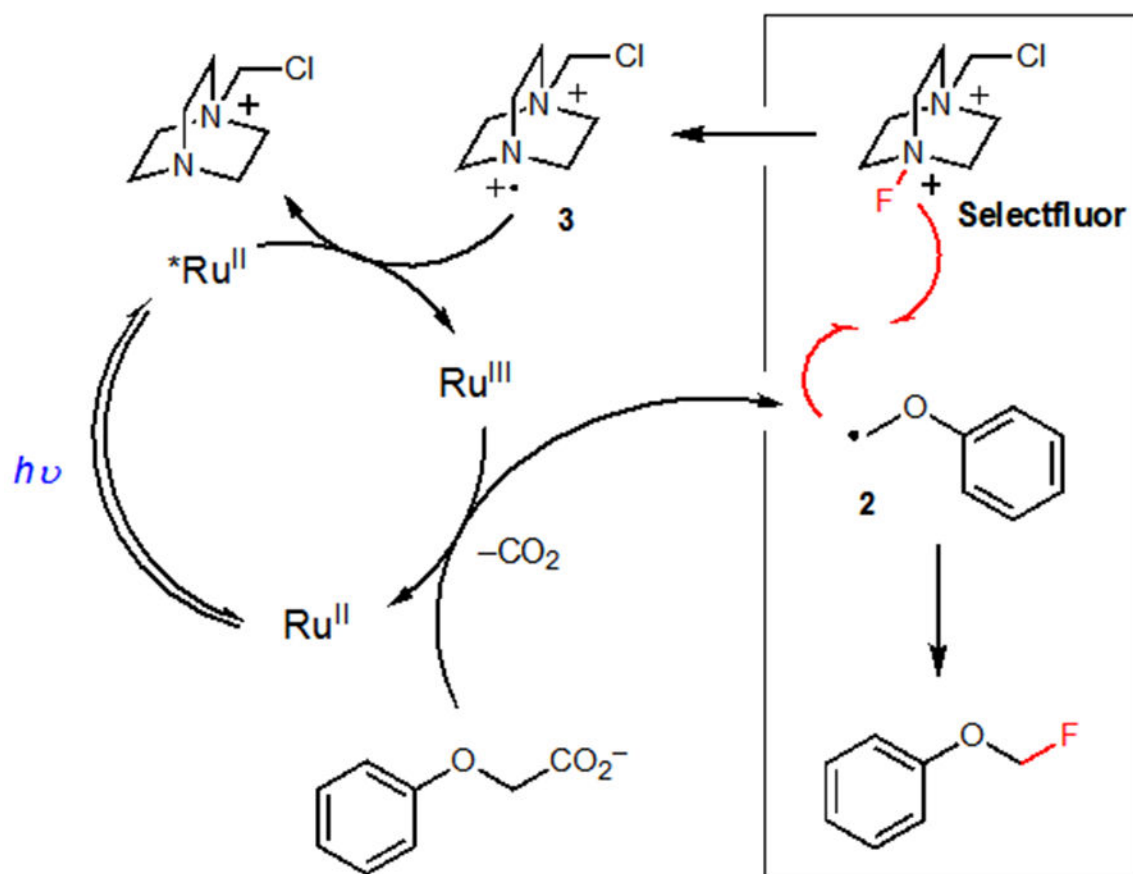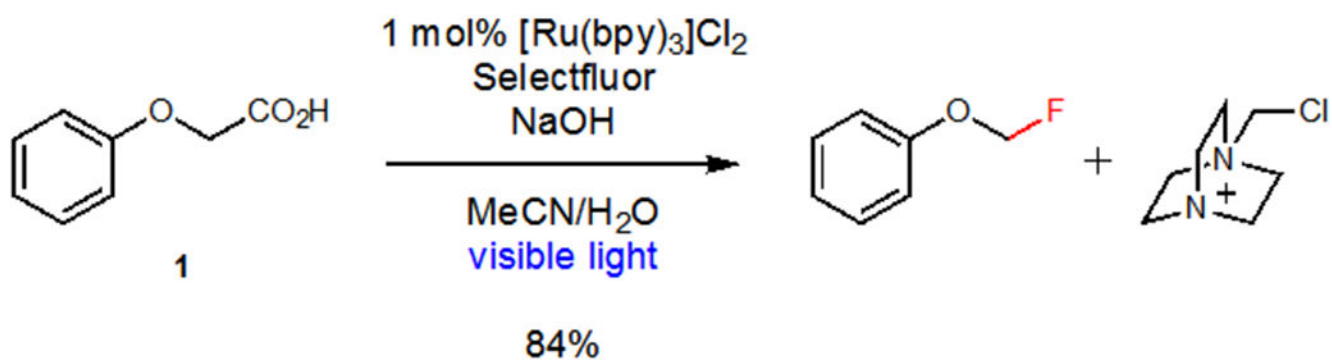
Scheme 1.
Decarboxylative Fluorination using Selectfluor as a Group Transfer Oxidant
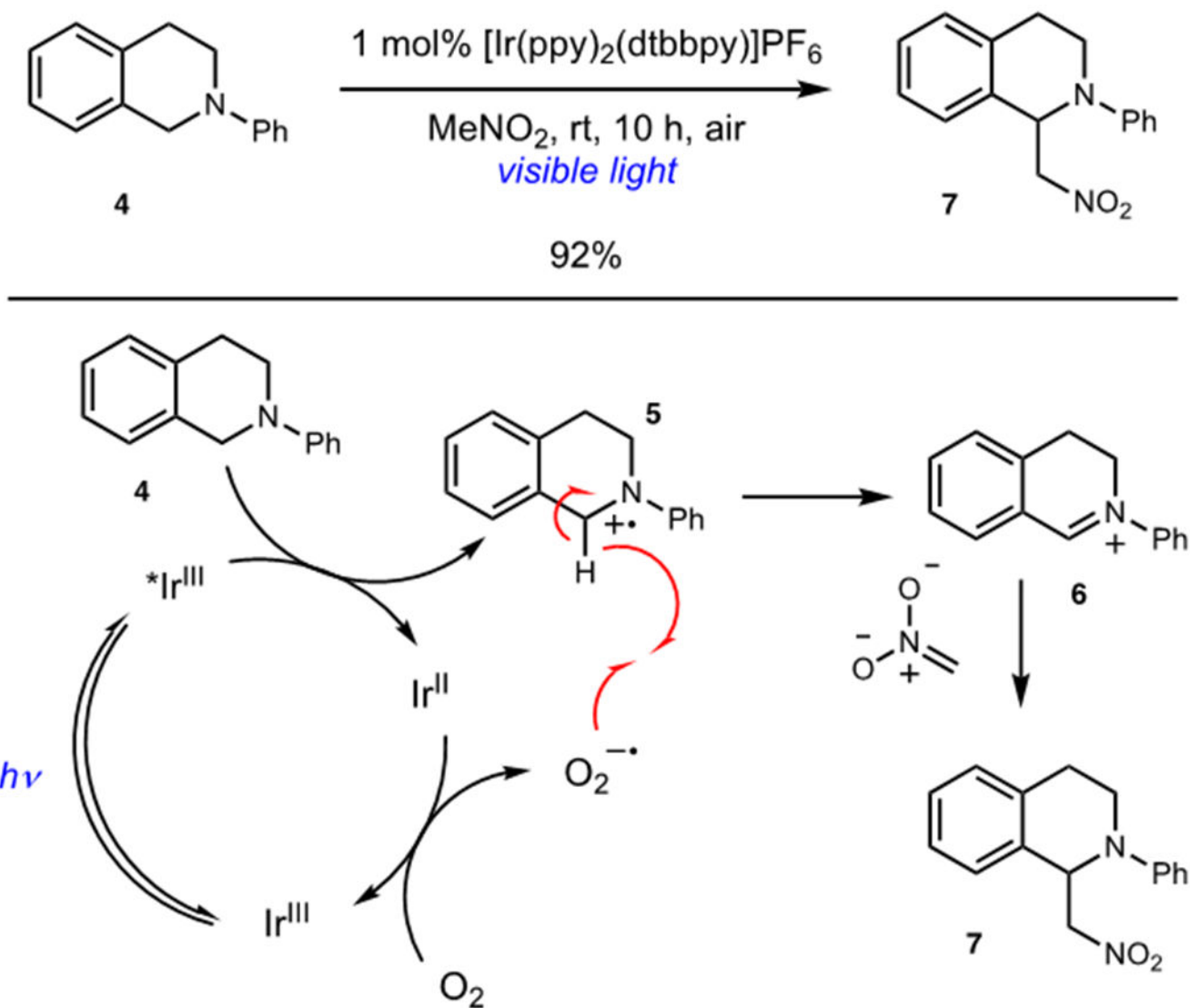
Scheme 2.
Photocatalytic Oxidative Aza-Henry Reaction
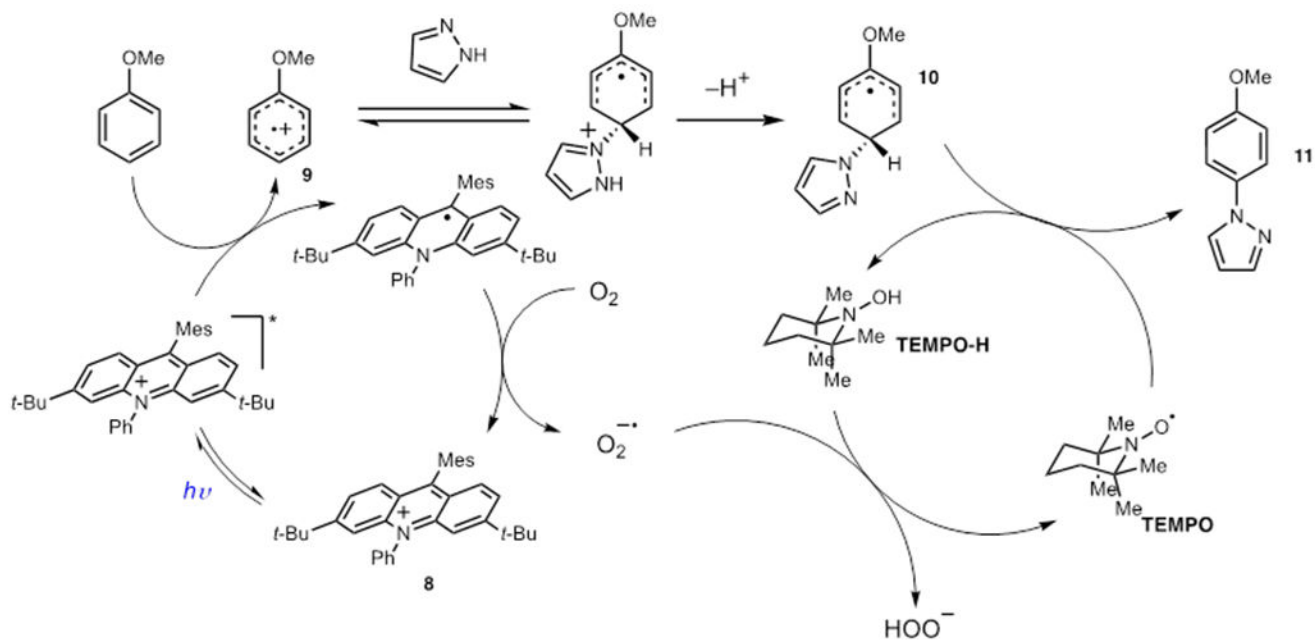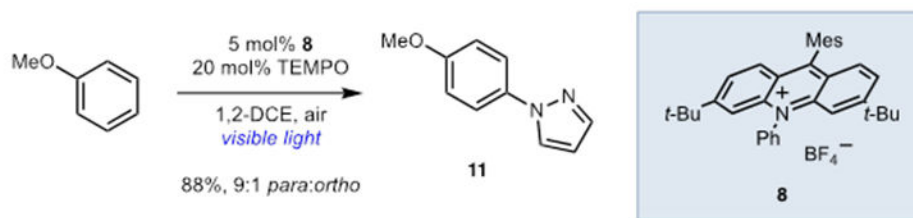
Scheme 3.
Arene Amination via Organic Photoredox Catalysis

10 mol% Cu(OAc)$_2$
20 mol% myristic acid
1 mol% *fac*-[Ir(ppy)$_3$]
1 equiv 2,6-lutidine

toluene/MeCN, 35 °C, air
visible light

93%

100%

91%

85%
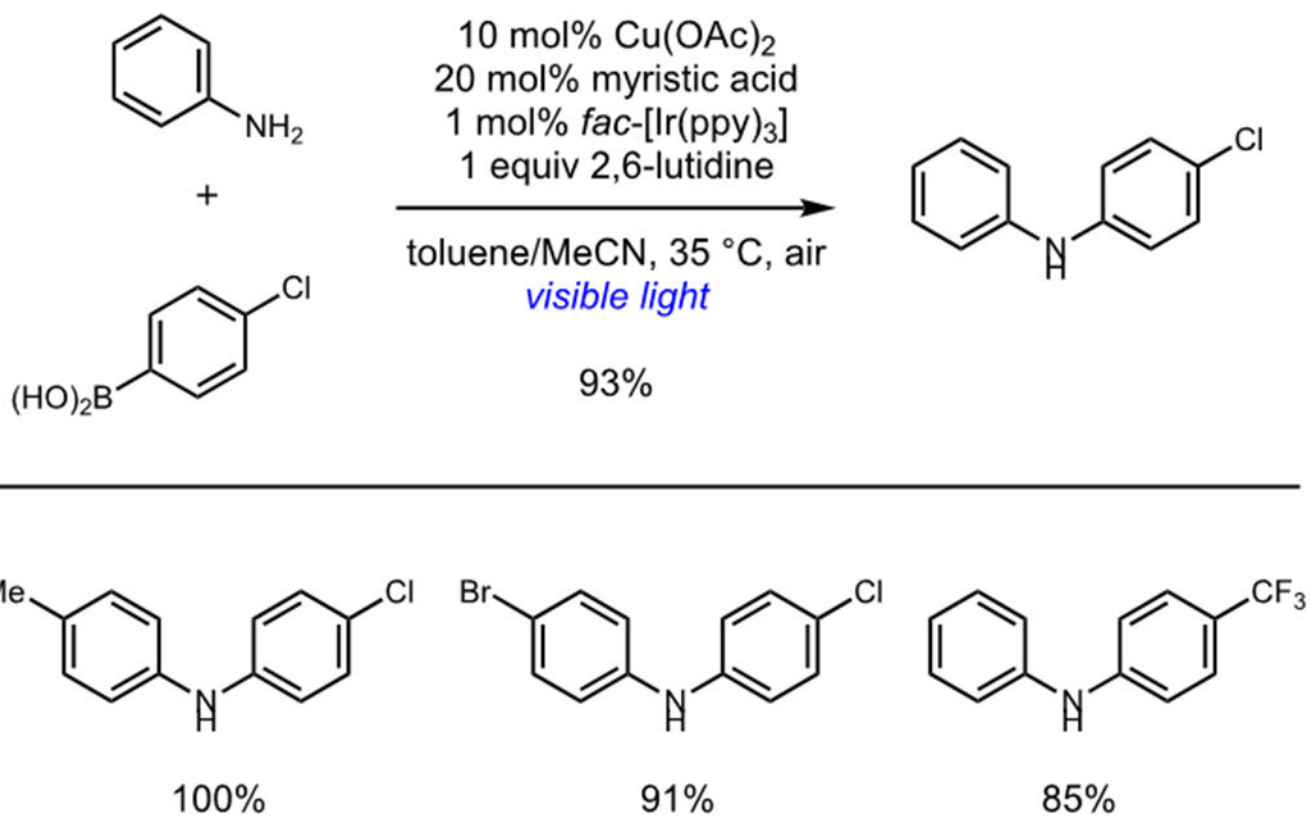
Scheme 4.
Photocatalytic Chan–Evans–Lam Coupling
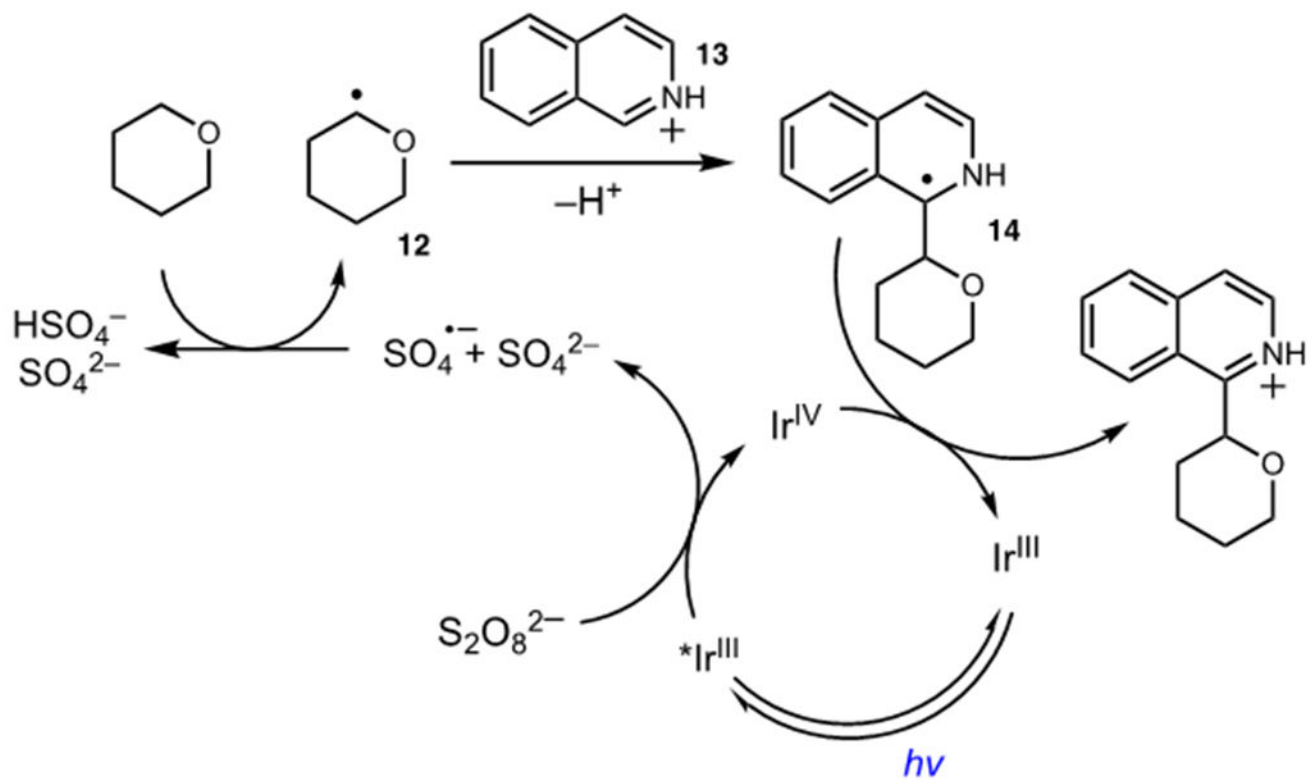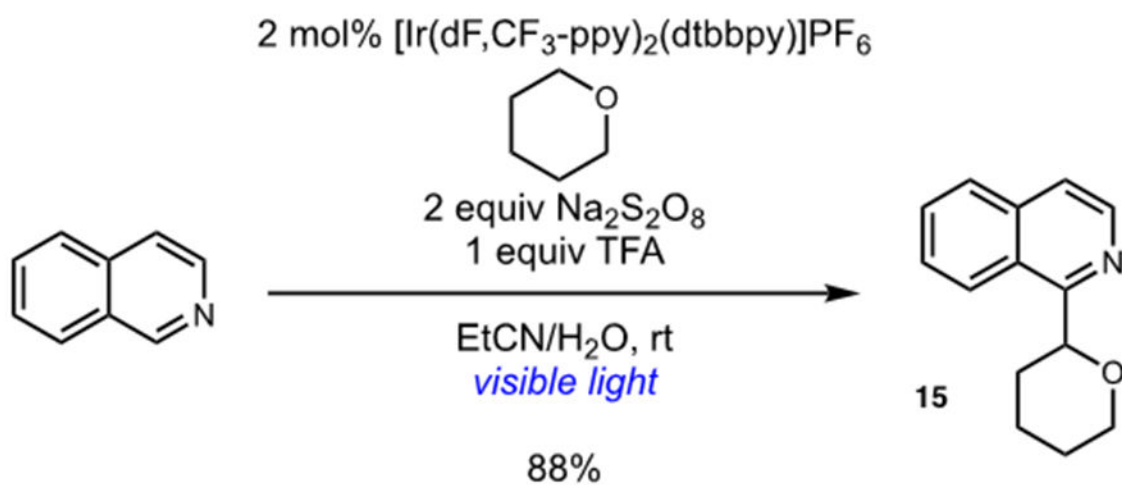
Scheme 5.
Arylation of Ethers via C–H Abstraction and Minisci-Type Addition
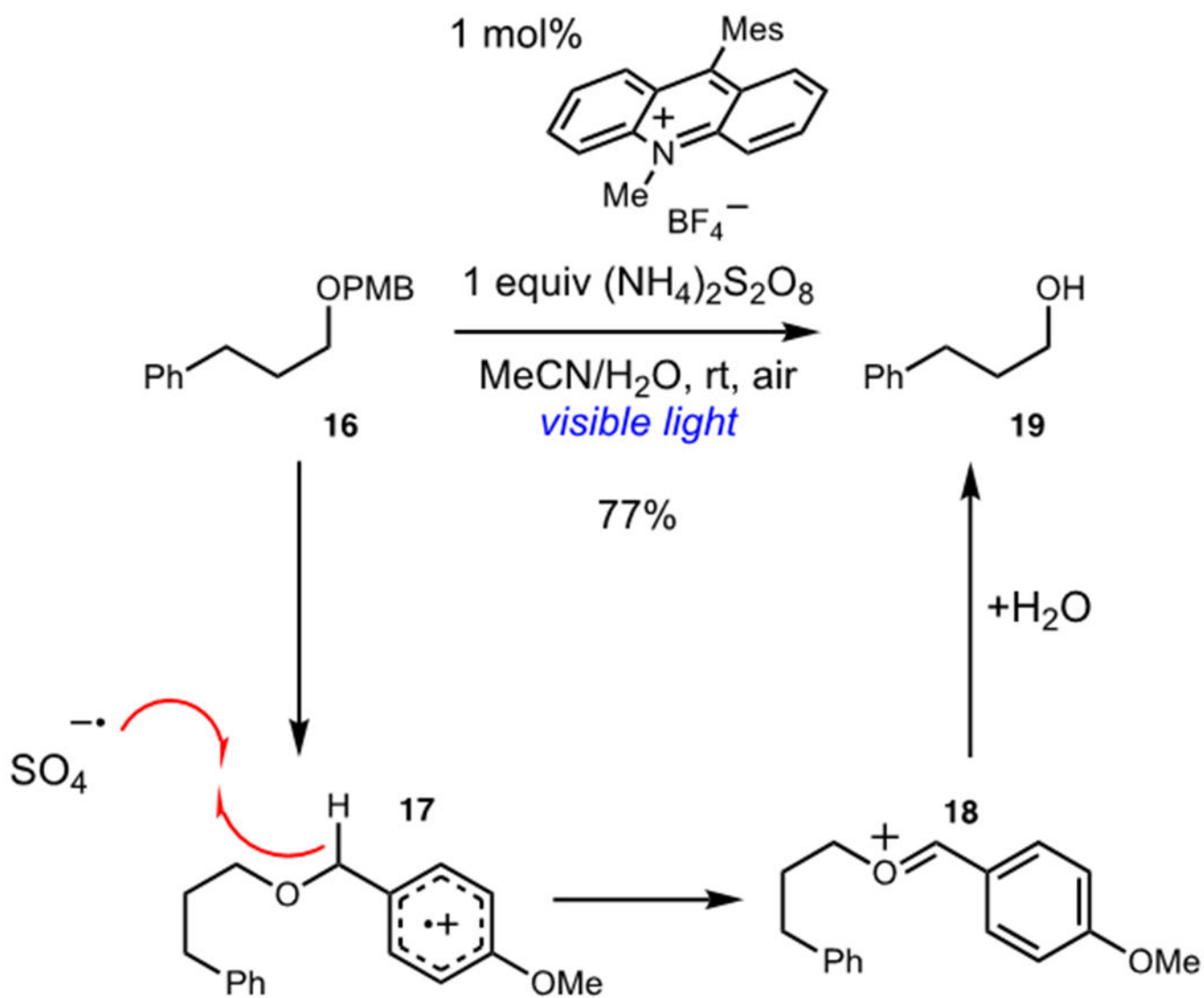
Scheme 6.
Photocatalytic Deprotection of *para*-Methoxybenzyl Ethers
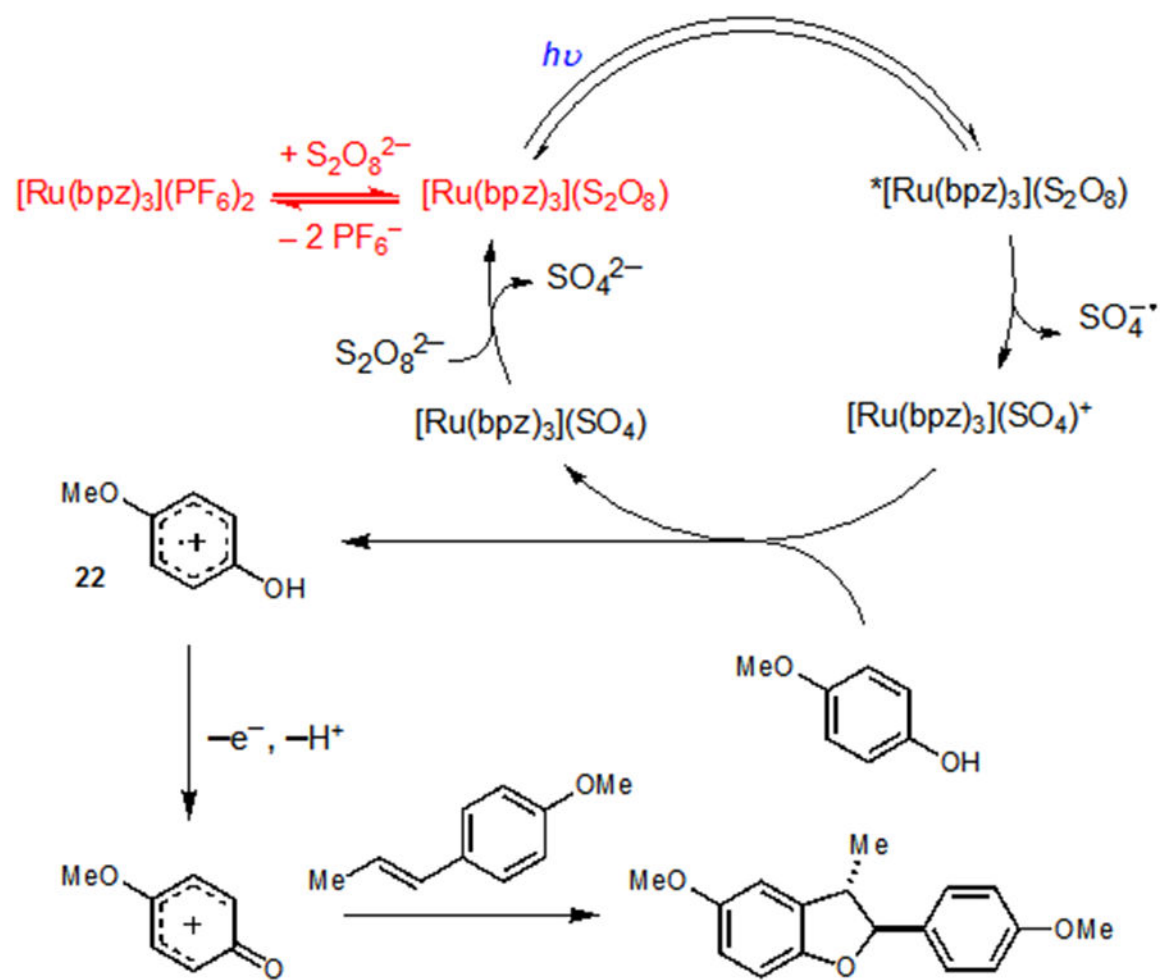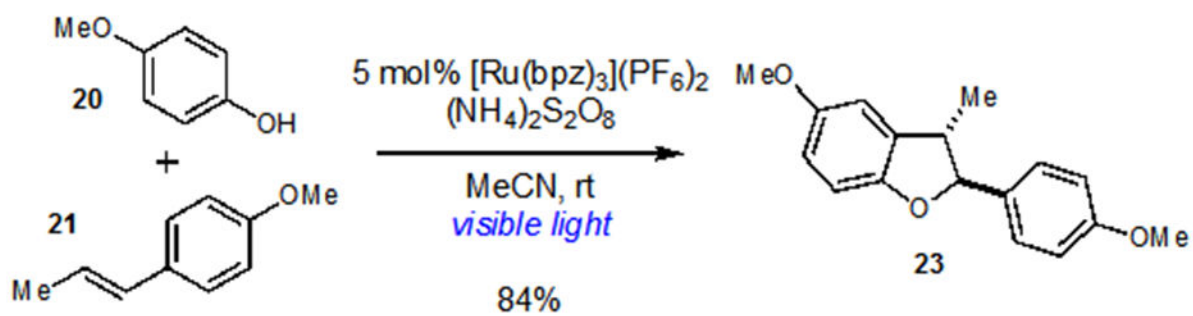
Scheme 7.
Photocatalytic [3+2] Cycloaddition of Phenols
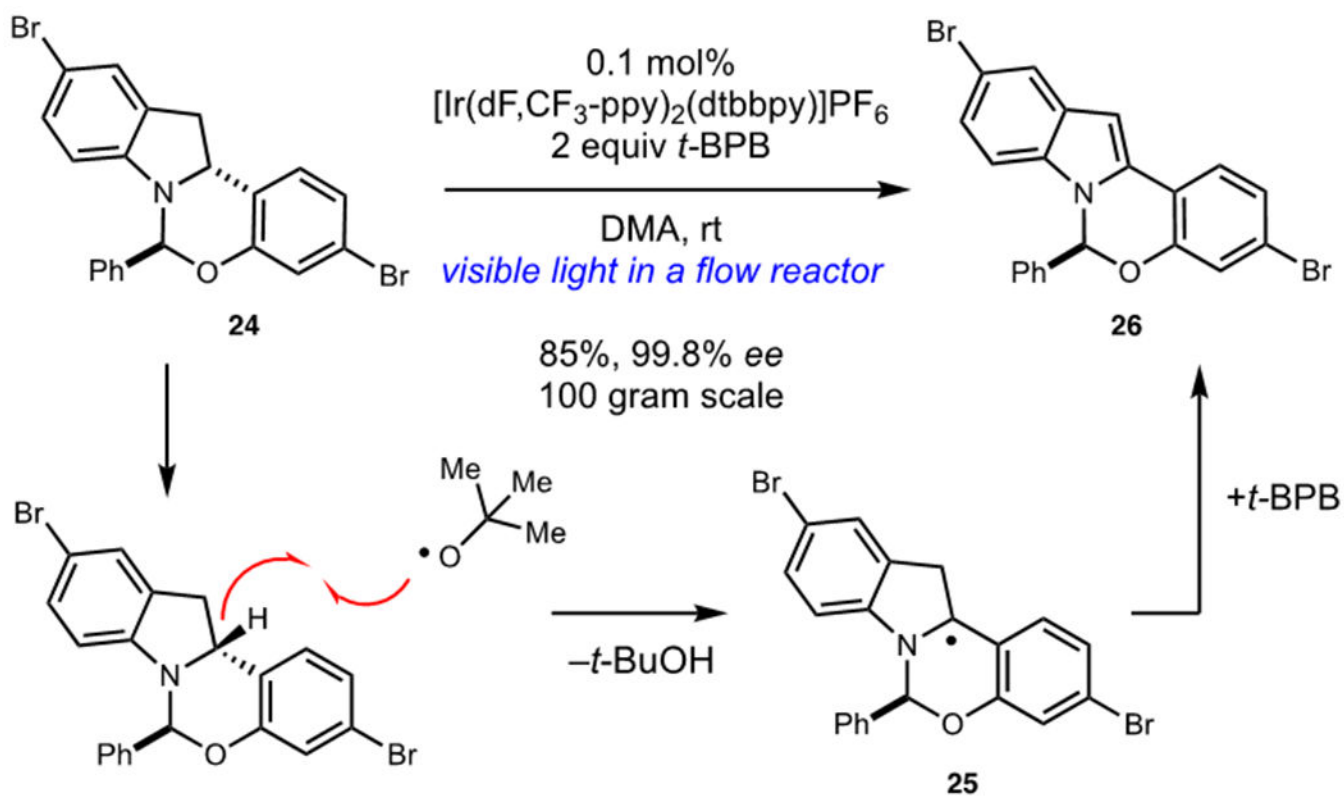
Scheme 8.
Photocatalytic Indoline Dehydrogenation in the Synthesis of Elbasvir
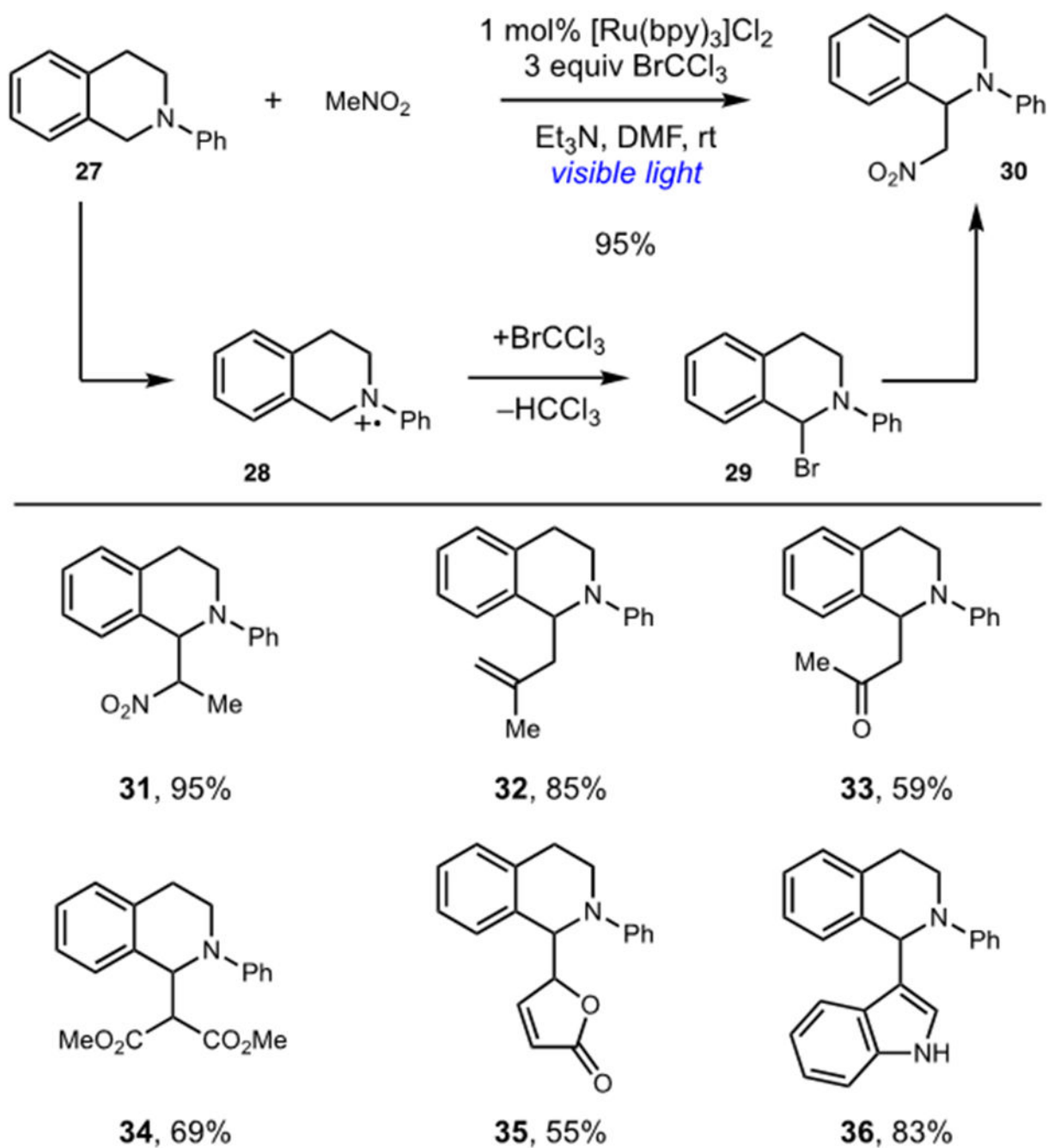
Scheme 9.
Nucleophilic Trapping of Photogenerated Iminium Ions
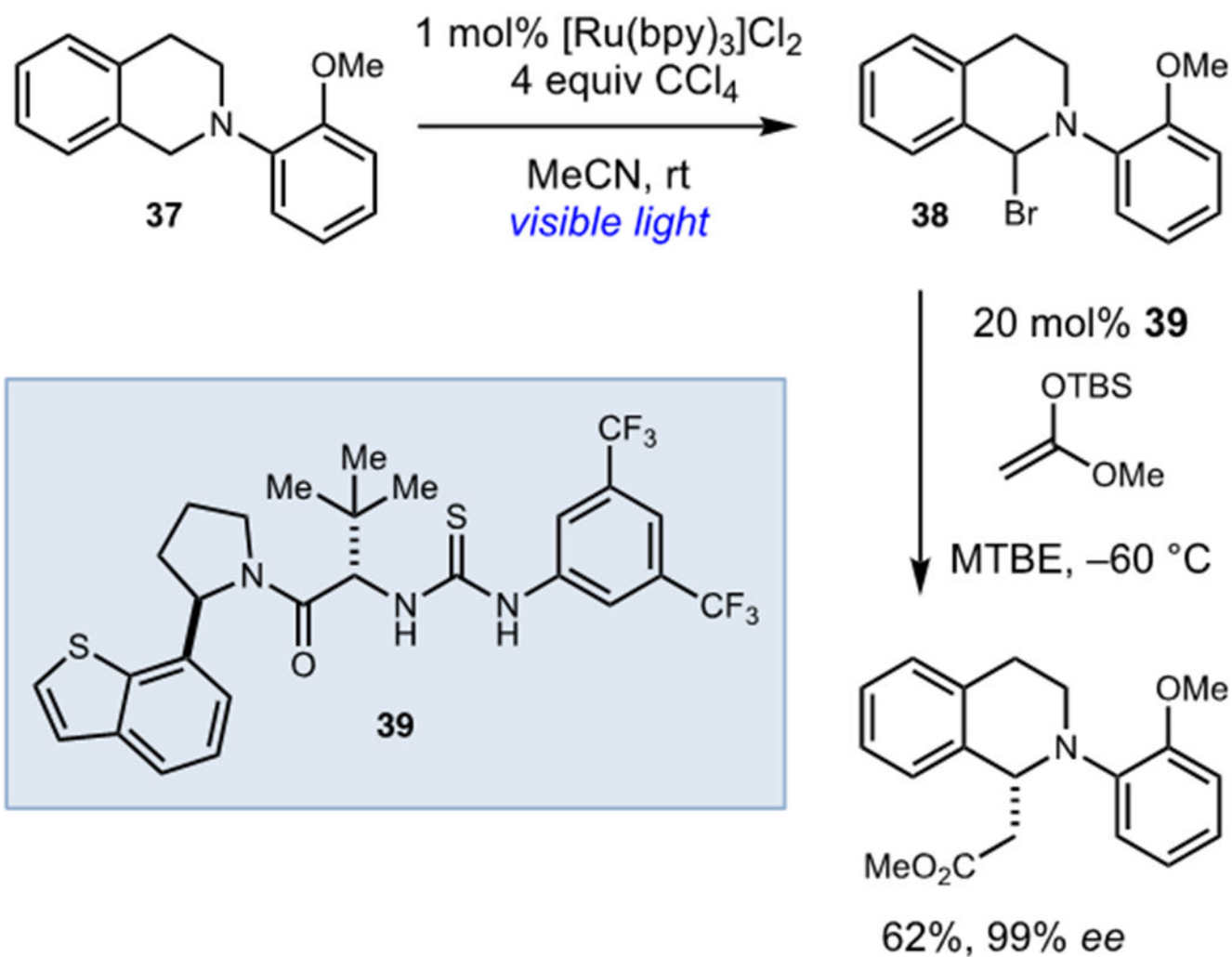
Scheme 10.
Enantioselective Oxidative Alkylation of Tetrahydroisoquinolines
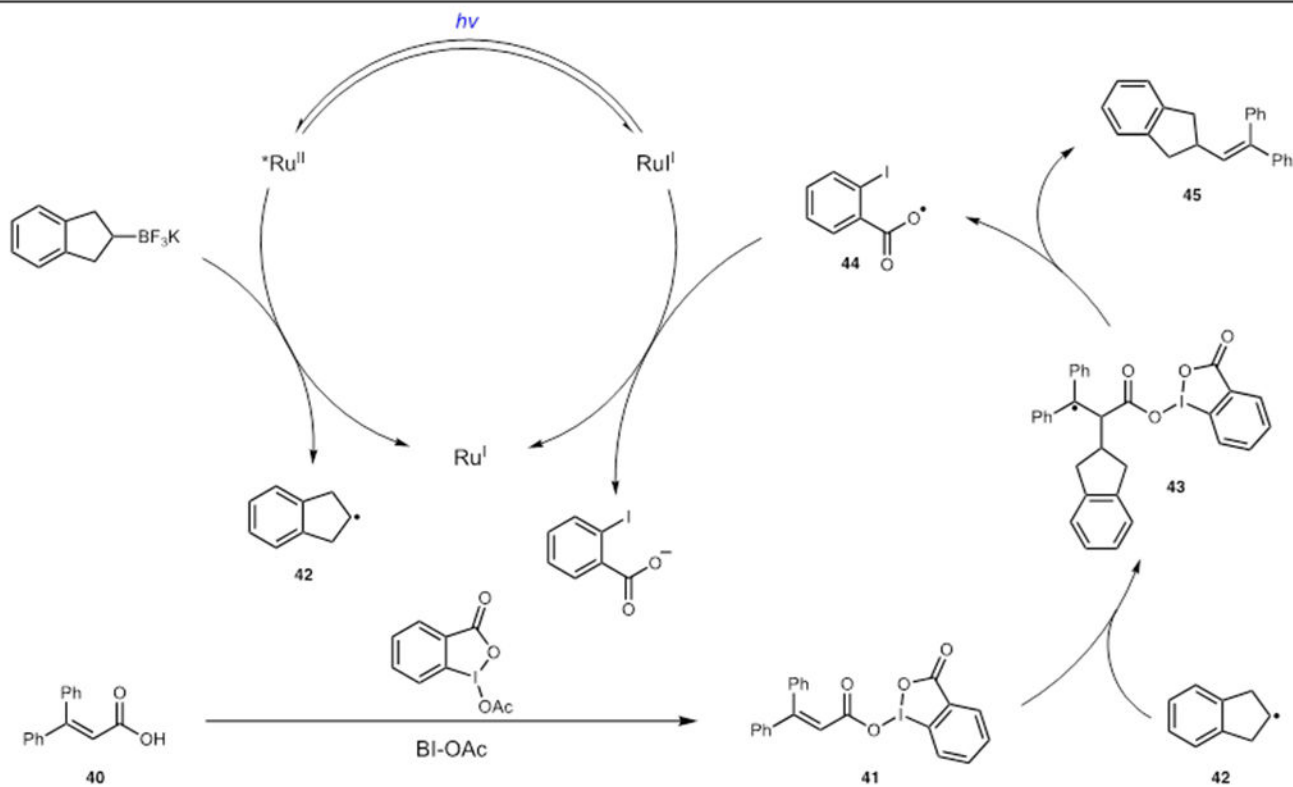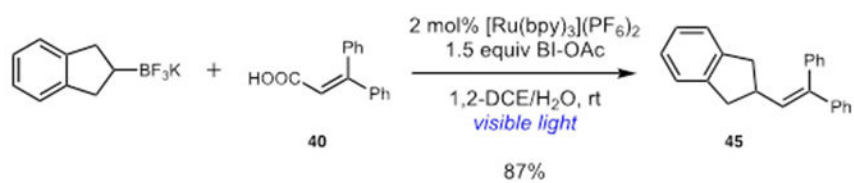
Scheme 11.
Decarboxylative Alkenylation via Photoredox Catalysis
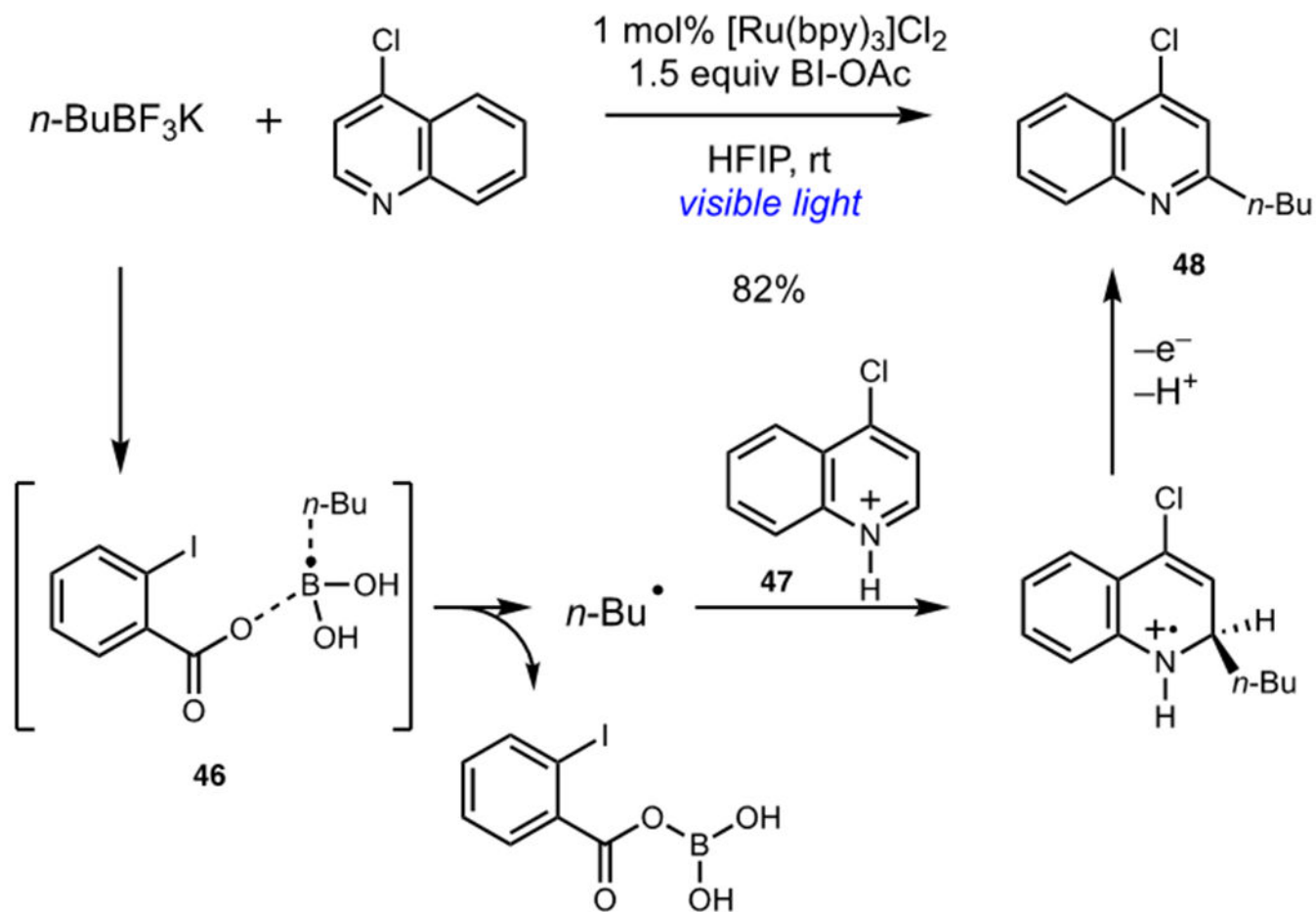
Scheme 12.
Photocatalytic Alkylation of Aza-Arenes Using Trifluoroborate Salts
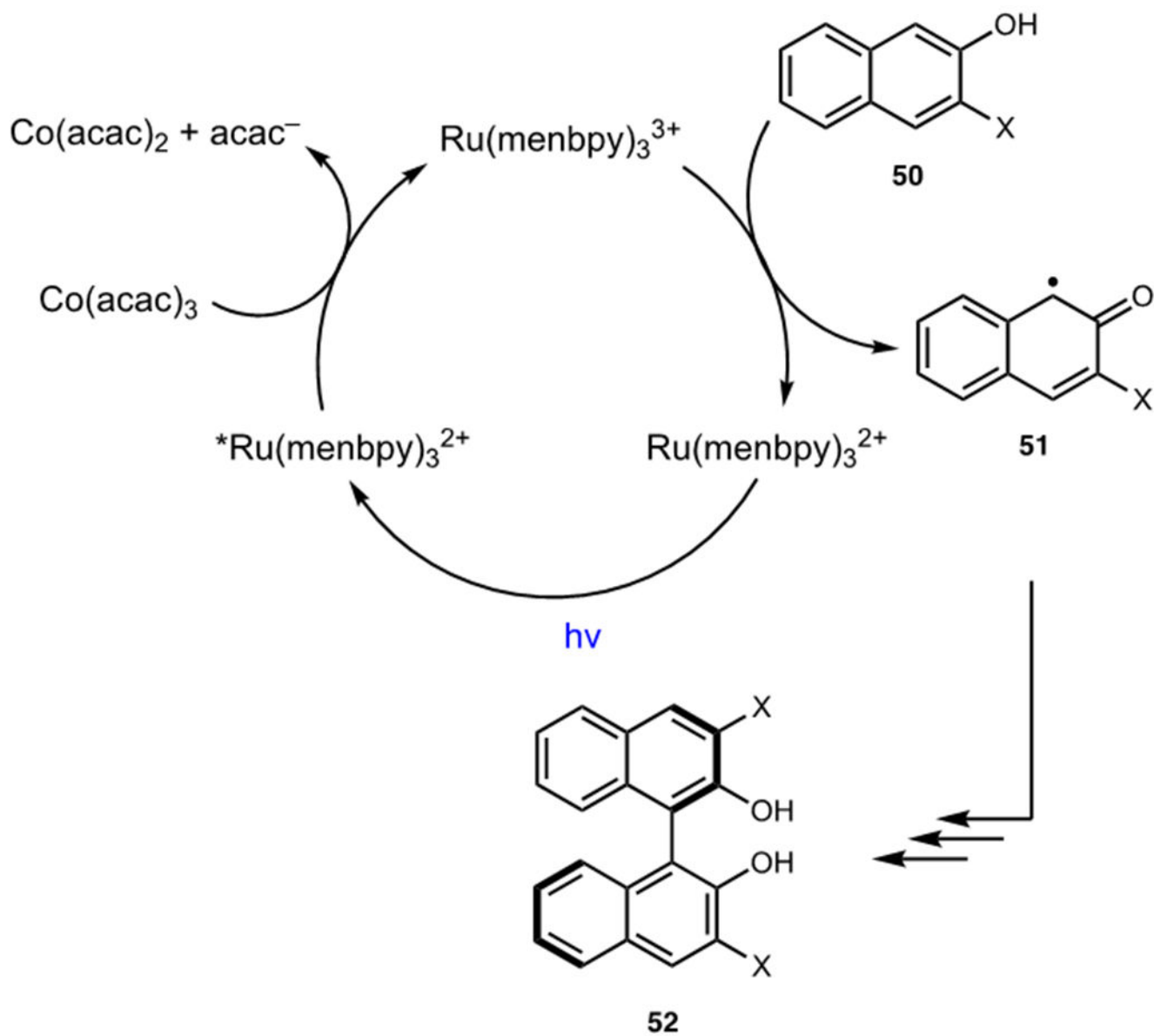
Scheme 13.
Okhubo's Mechanism for the Dimerization of Naphthols using $Ru(menbpy)_3^{2+}$
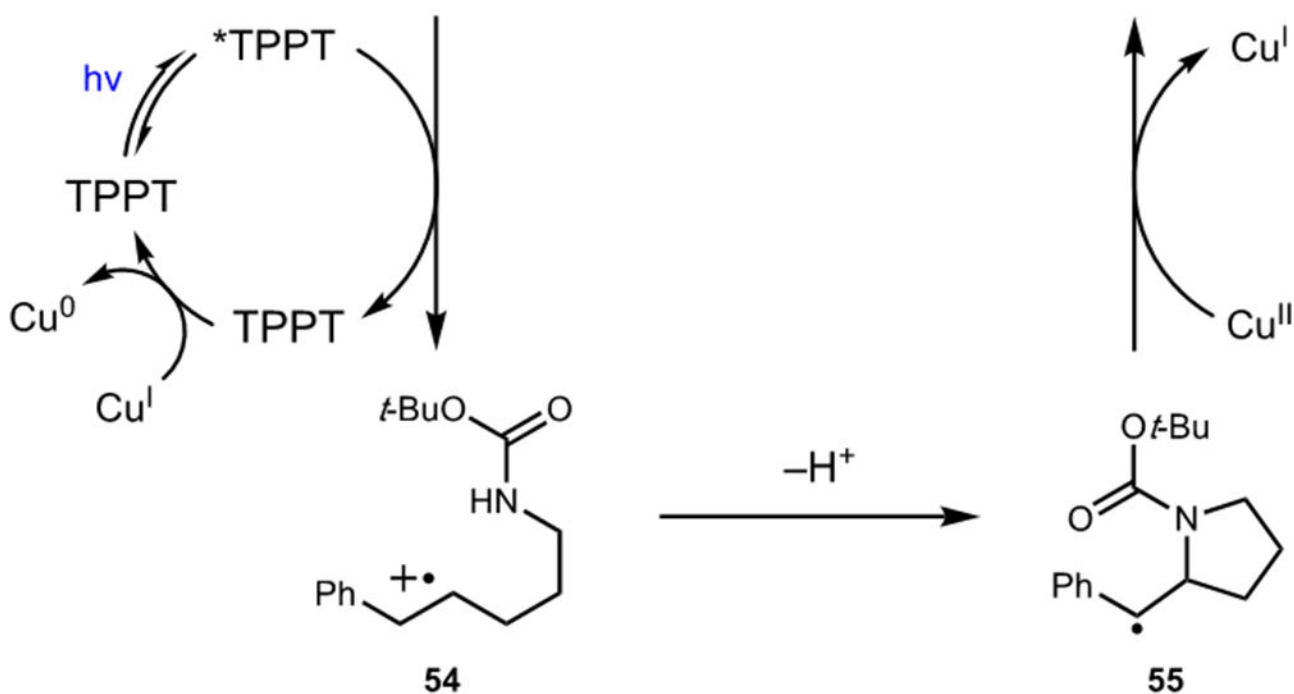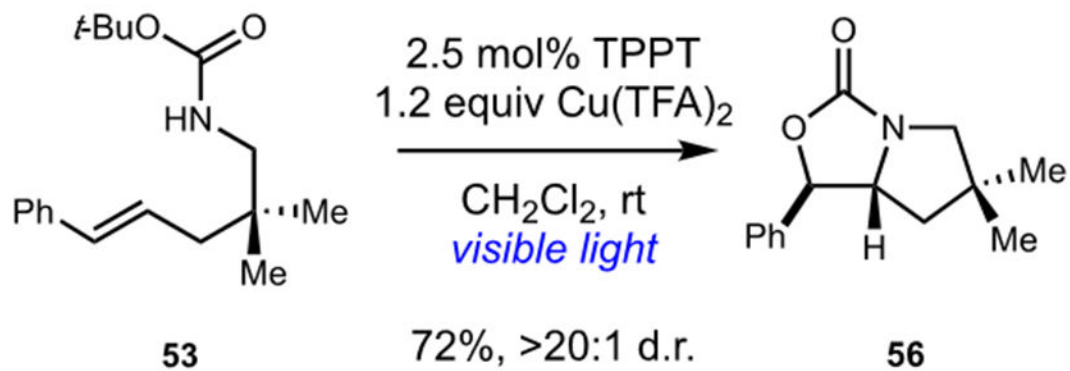
Scheme 14.
Photocatalytic Oxidative Alkene Difunctionalization

1 mol% [Ir(dF(CF$_3$)ppy)$_2$(5,5'-dCF$_3$bpy)]PF$_6$
1.2 equiv Cu(TFA)$_2$
2.0 equiv MeOH
3.0 equiv K$_2$HPO$_4$

MeCN, rt, 6 h
visible light

70%

2 Cu(I) $\rightleftharpoons$ Cu(II) + Cu(0)
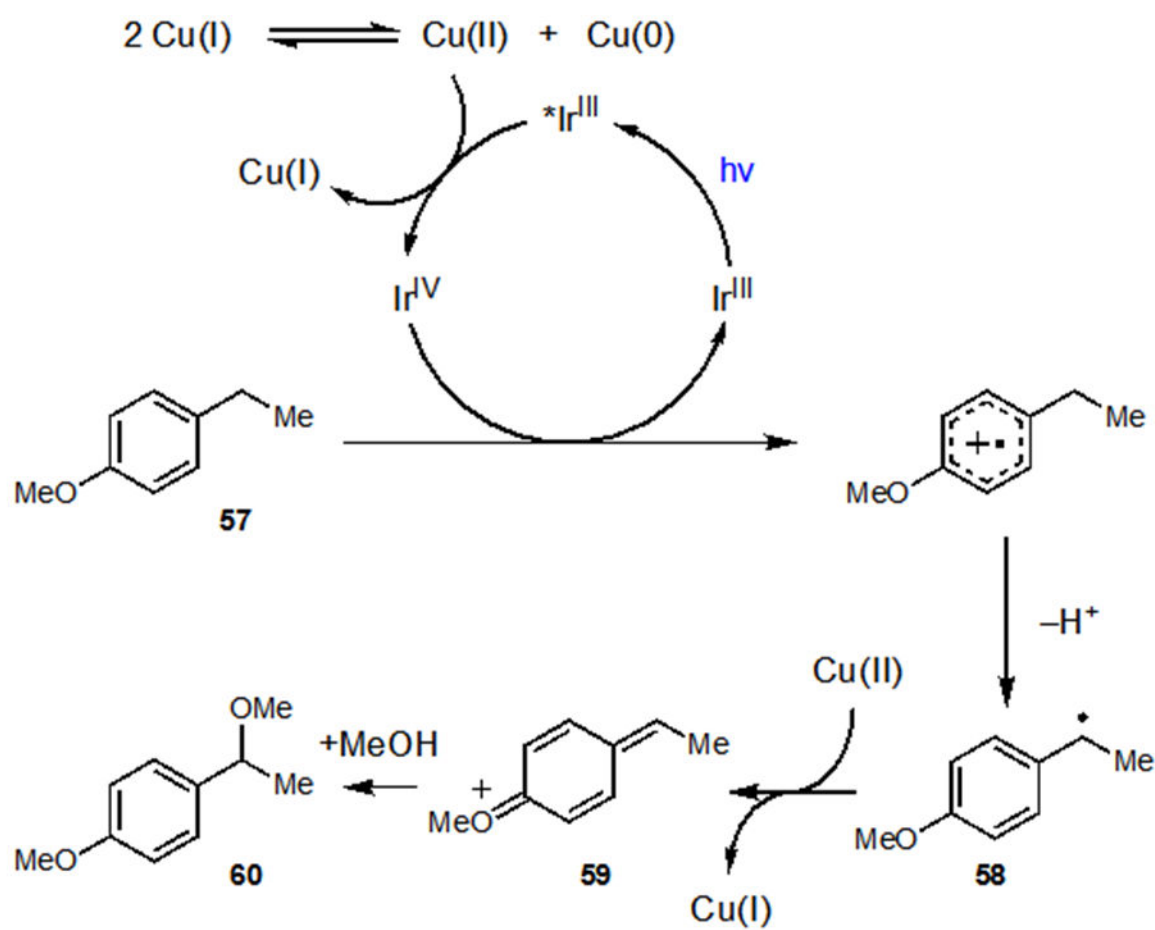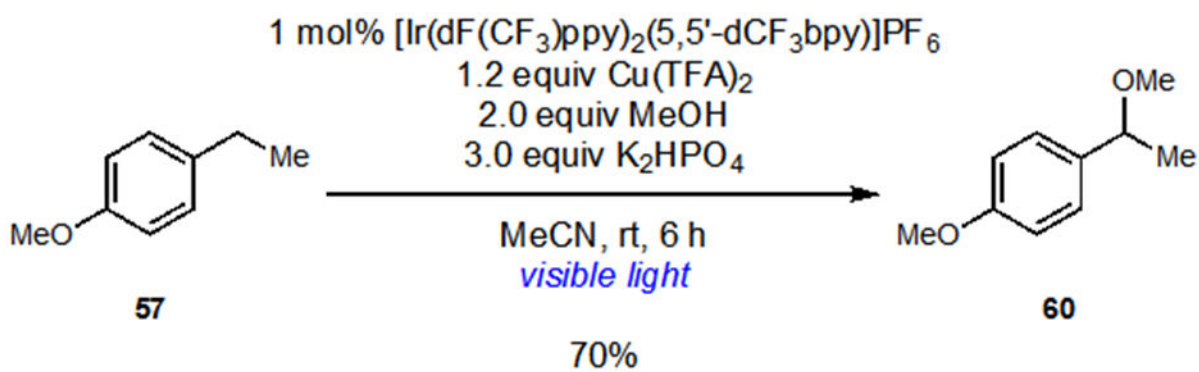
Scheme 15.
Photocatalytic Benzylic Alkoxylation
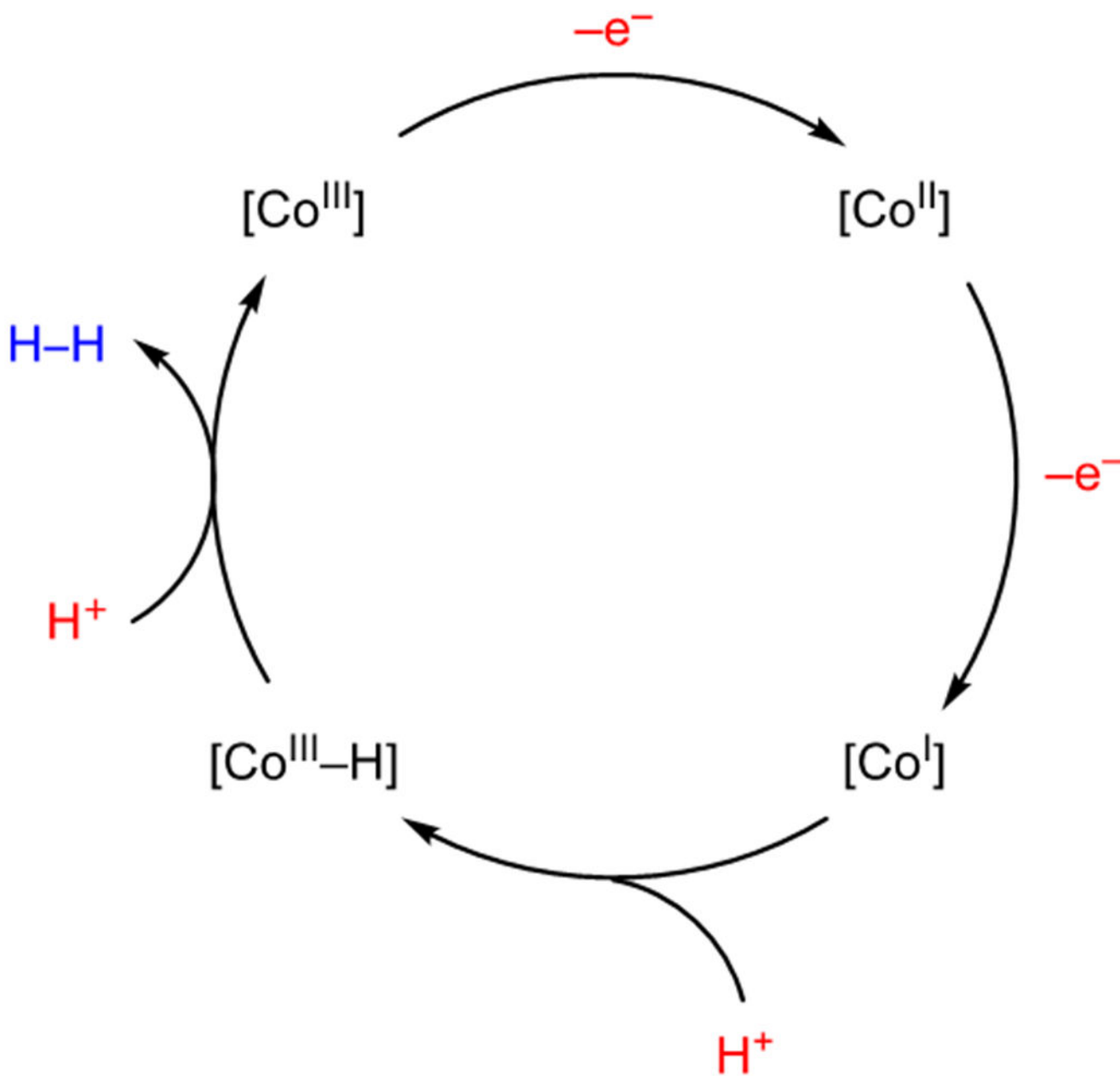
Scheme 16.
Common Mechanism for Hydrogen Evolution by Cobalt Diglyoxime Catalysts under Photoredox Conditions

A Ritter's decarboxylative olefination
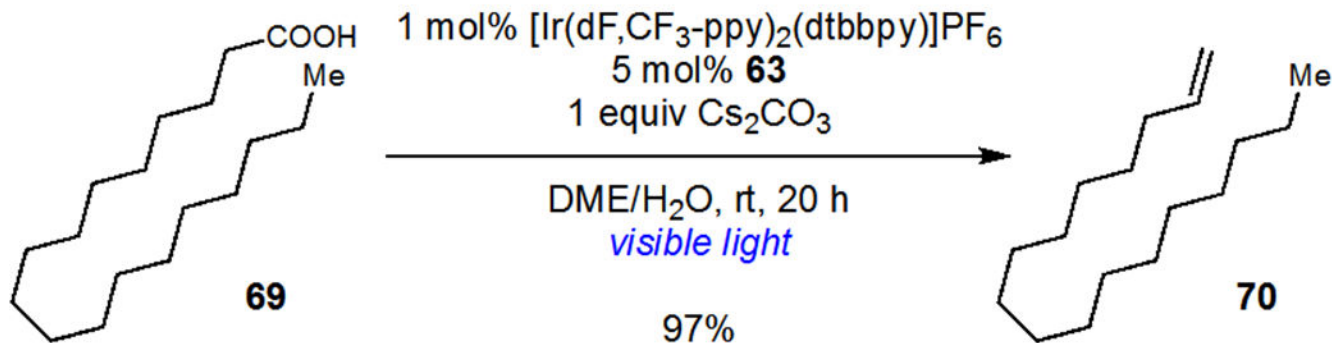
B Tunge's decarboxylative elimination of *N*-acyl amino acids
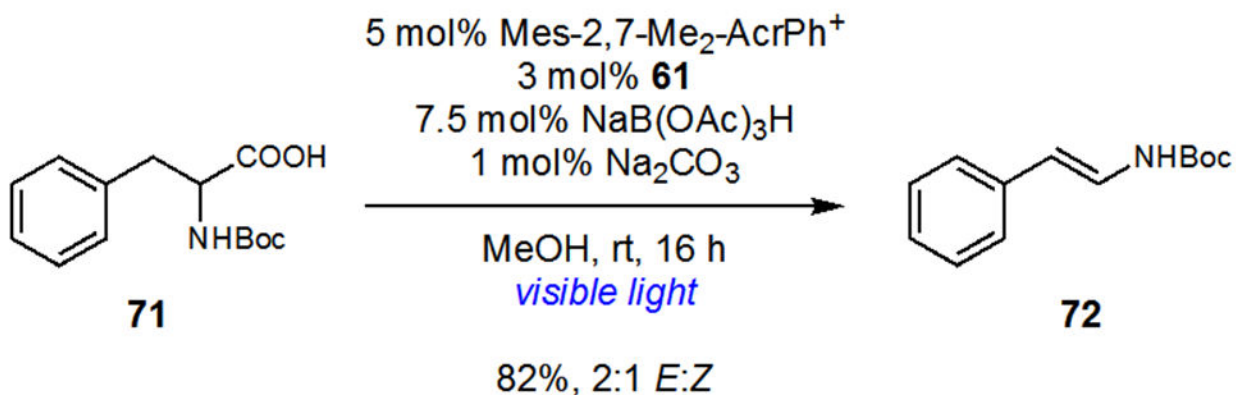
Scheme 17.
(a) Ritter's Decarboxylative Olefination and (b) Tunge's Decarboxylative Elimination of
N-Acyl Amino Acids
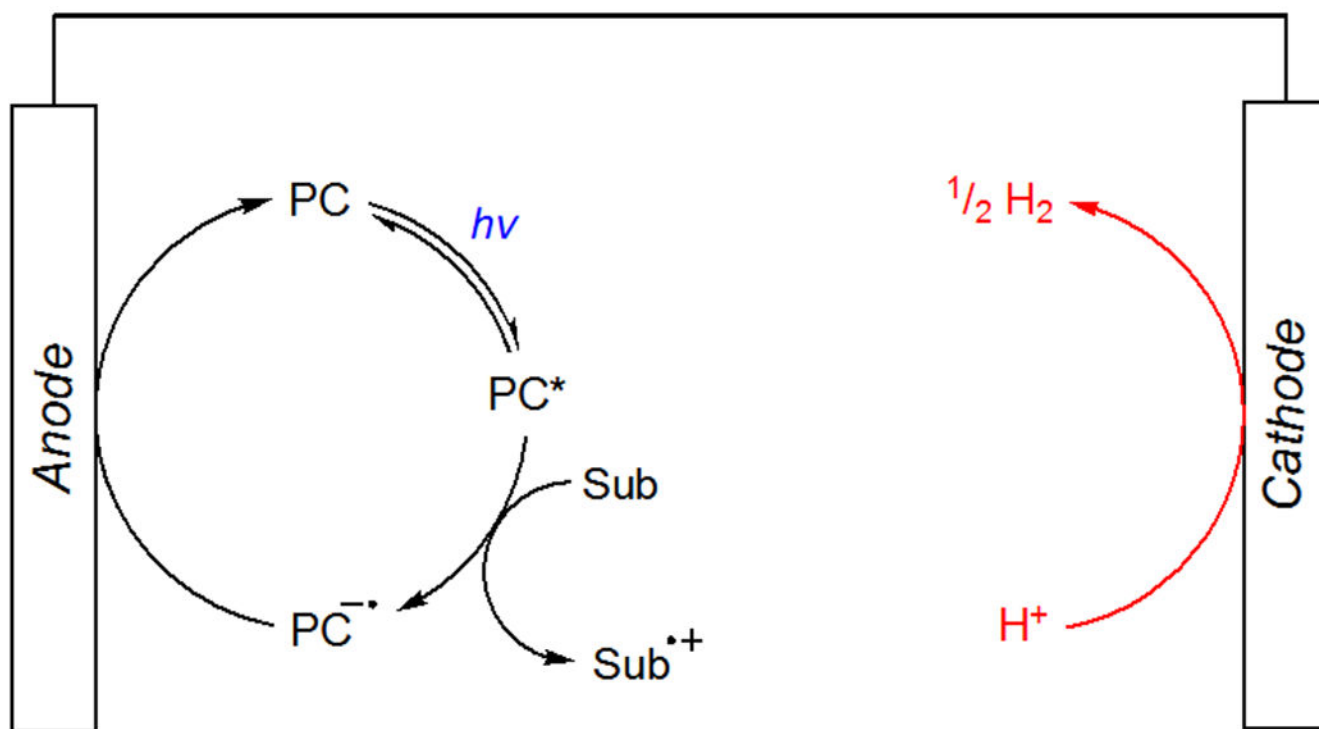
Scheme 18.
General Mechanism for Dual Photoredox/Electrochemical Oxidase Reactions
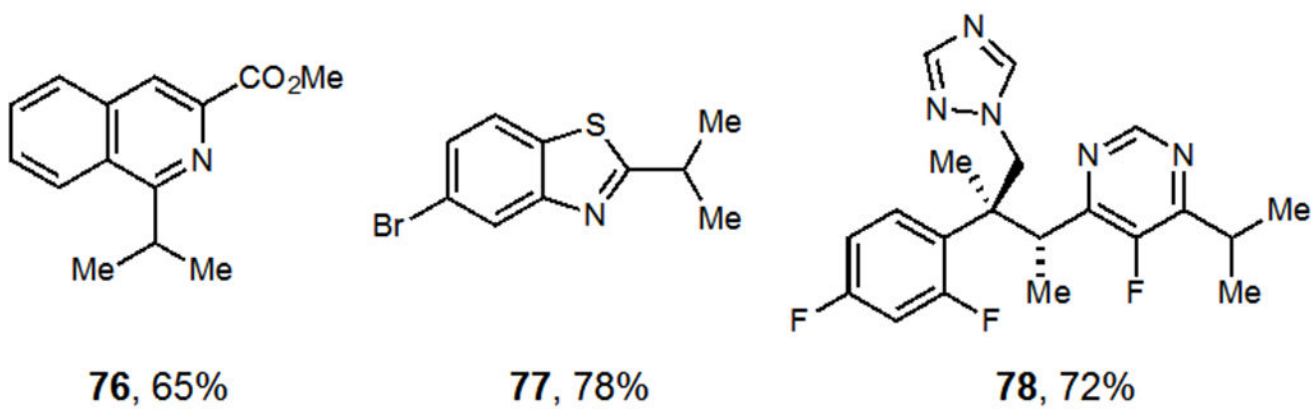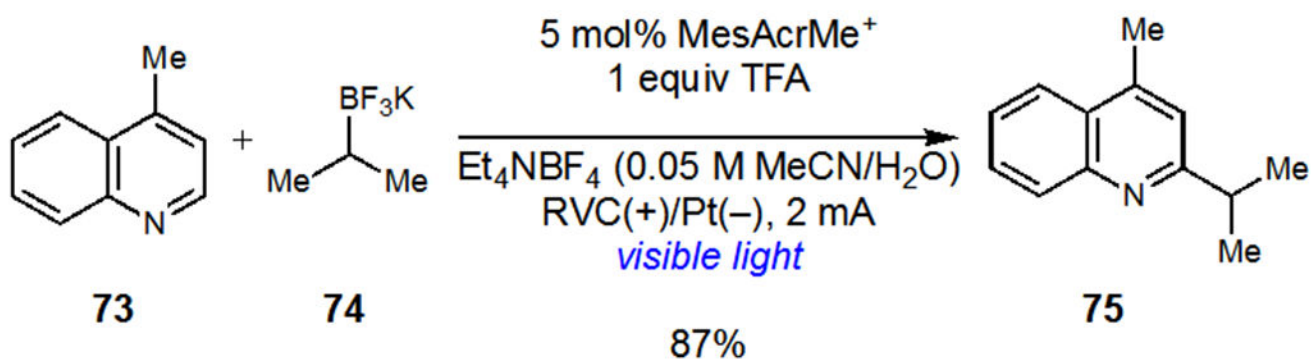
Scheme 19.
Xu's Alkylation of Heteroarenes
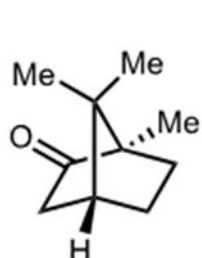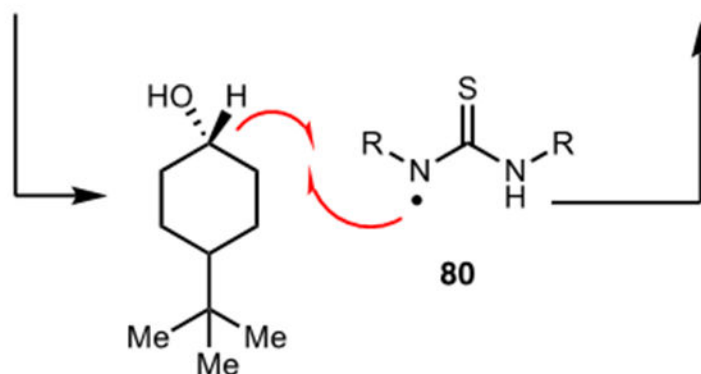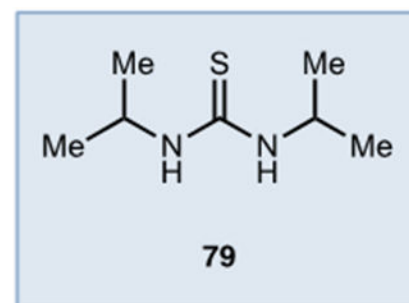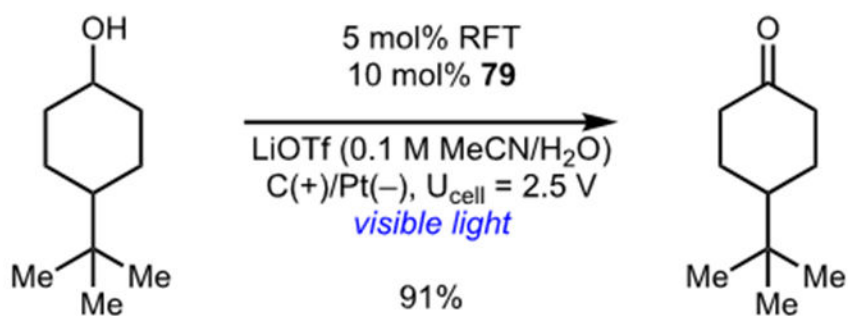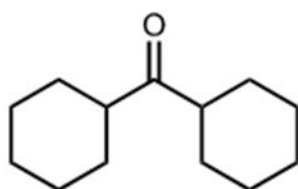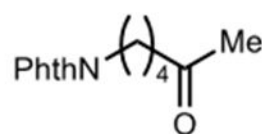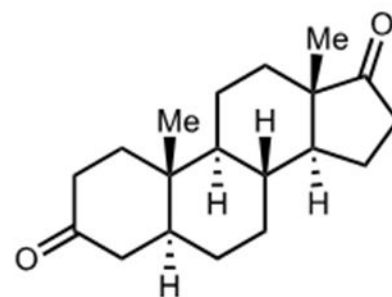
Scheme 20.
Lin's Oxidation of Unactivated Alcohols
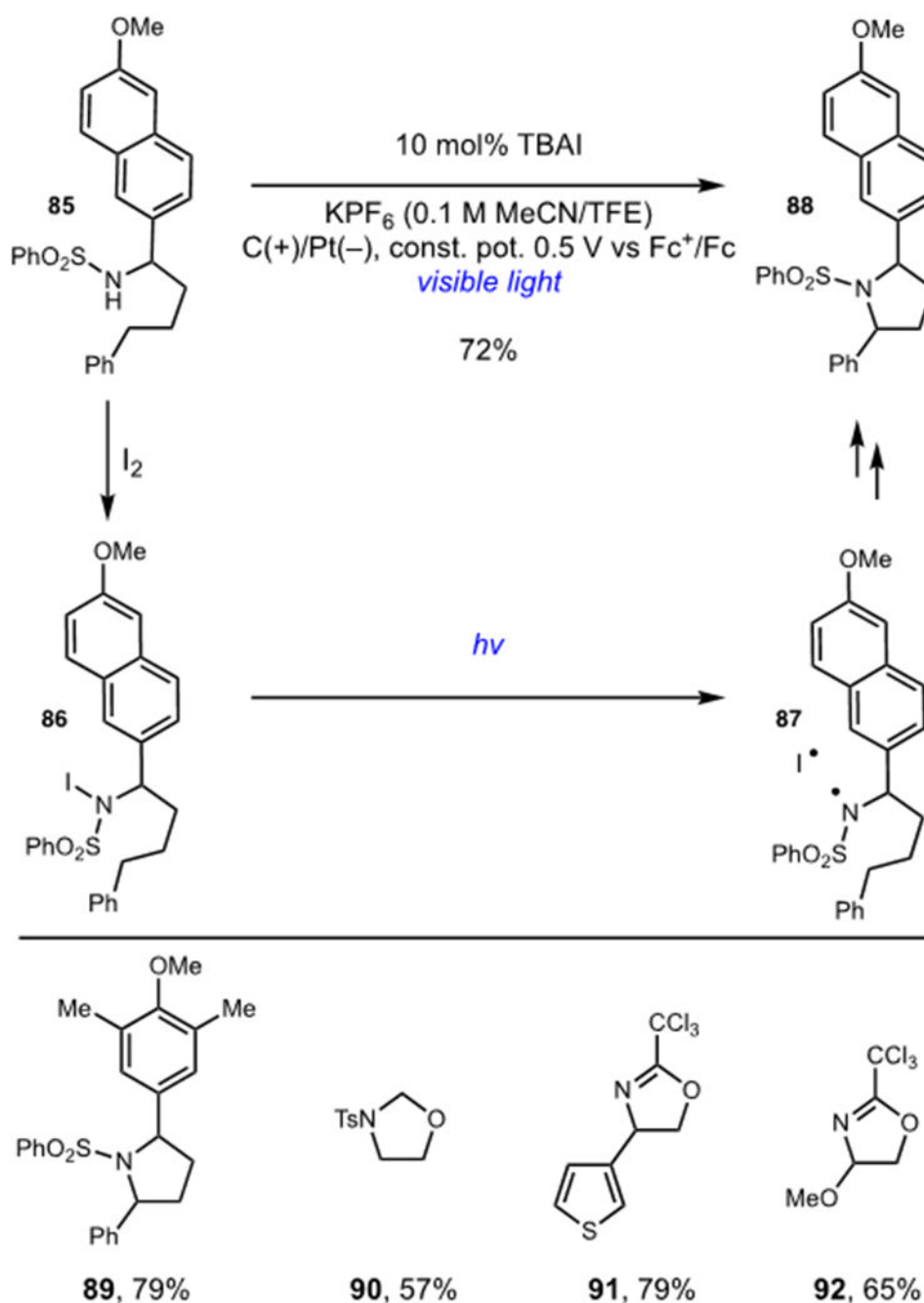
Scheme 21.
Stahl's Hoffman-Löffler-Freytag Reaction
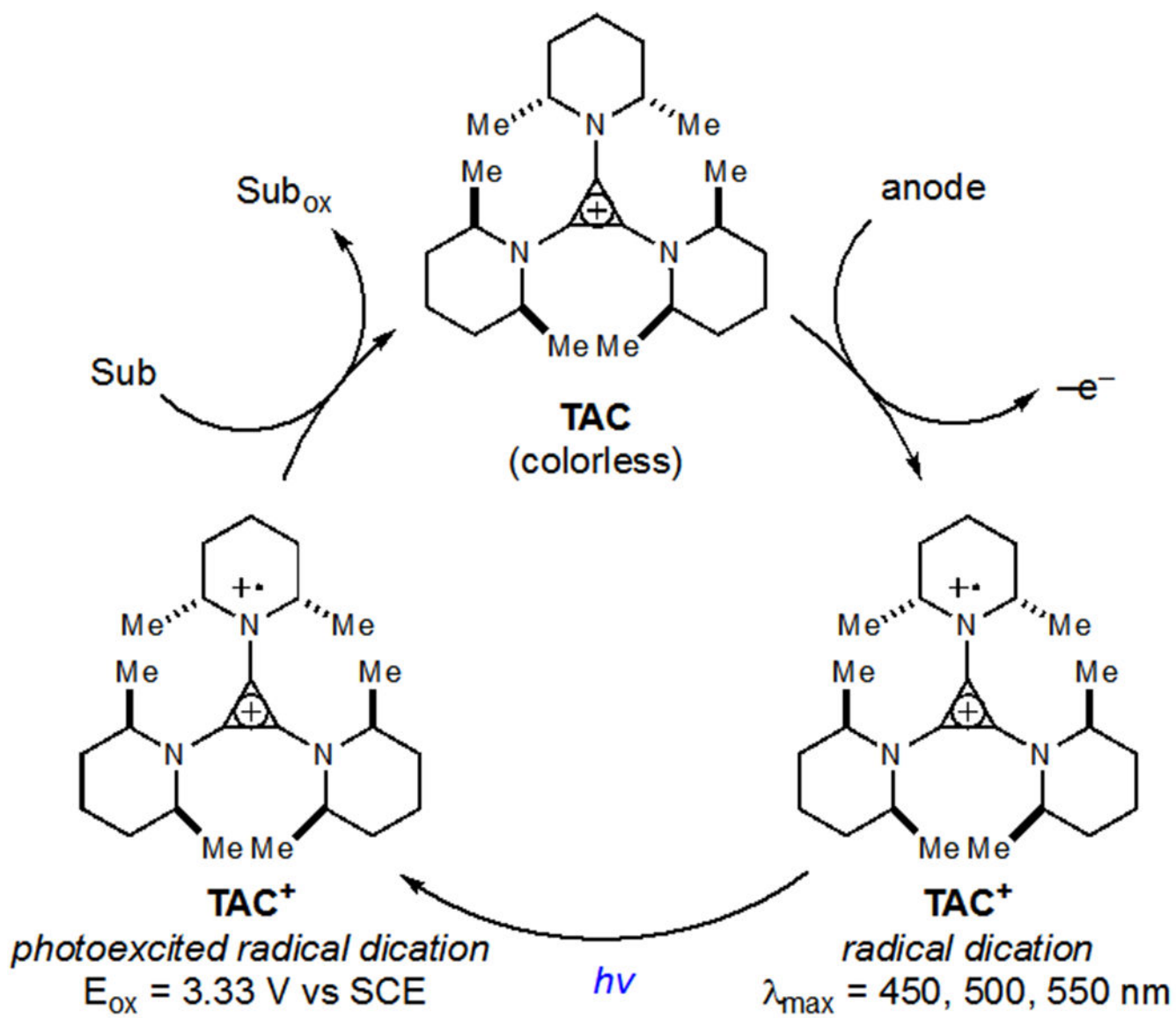
Scheme 22.
Photophysical and Electrochemical Properties of **TAC**

A TAC-Catalyzed Oxidative Amination of Arenes

56% + 30% recovered starting material
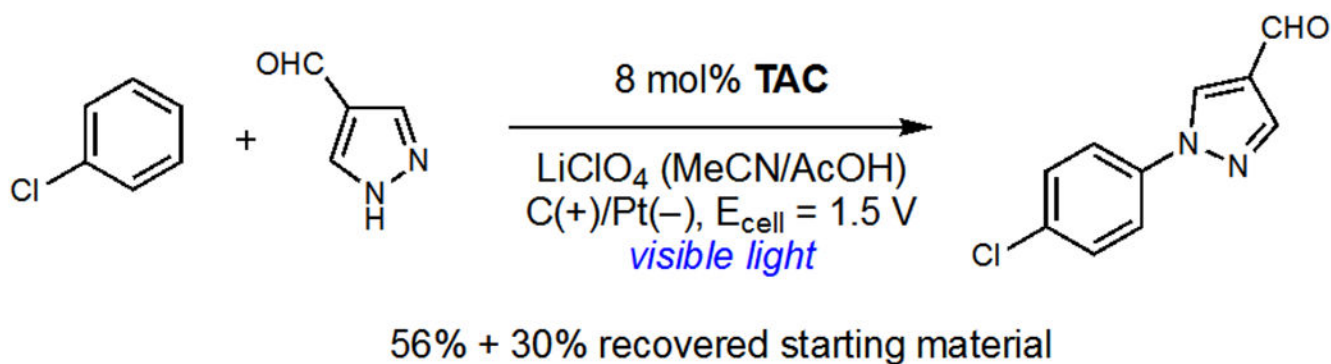
B TAC-Catalyzed Oxidative Ether Synthesis

80%
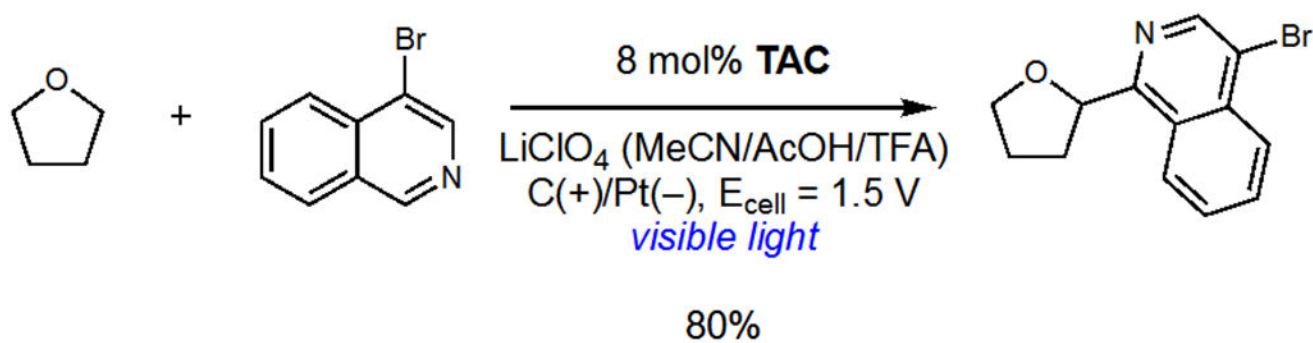
Scheme 23.
Lambert's (a) Oxidative Amination of Arenes and (b) Oxidative Ether Synthesis
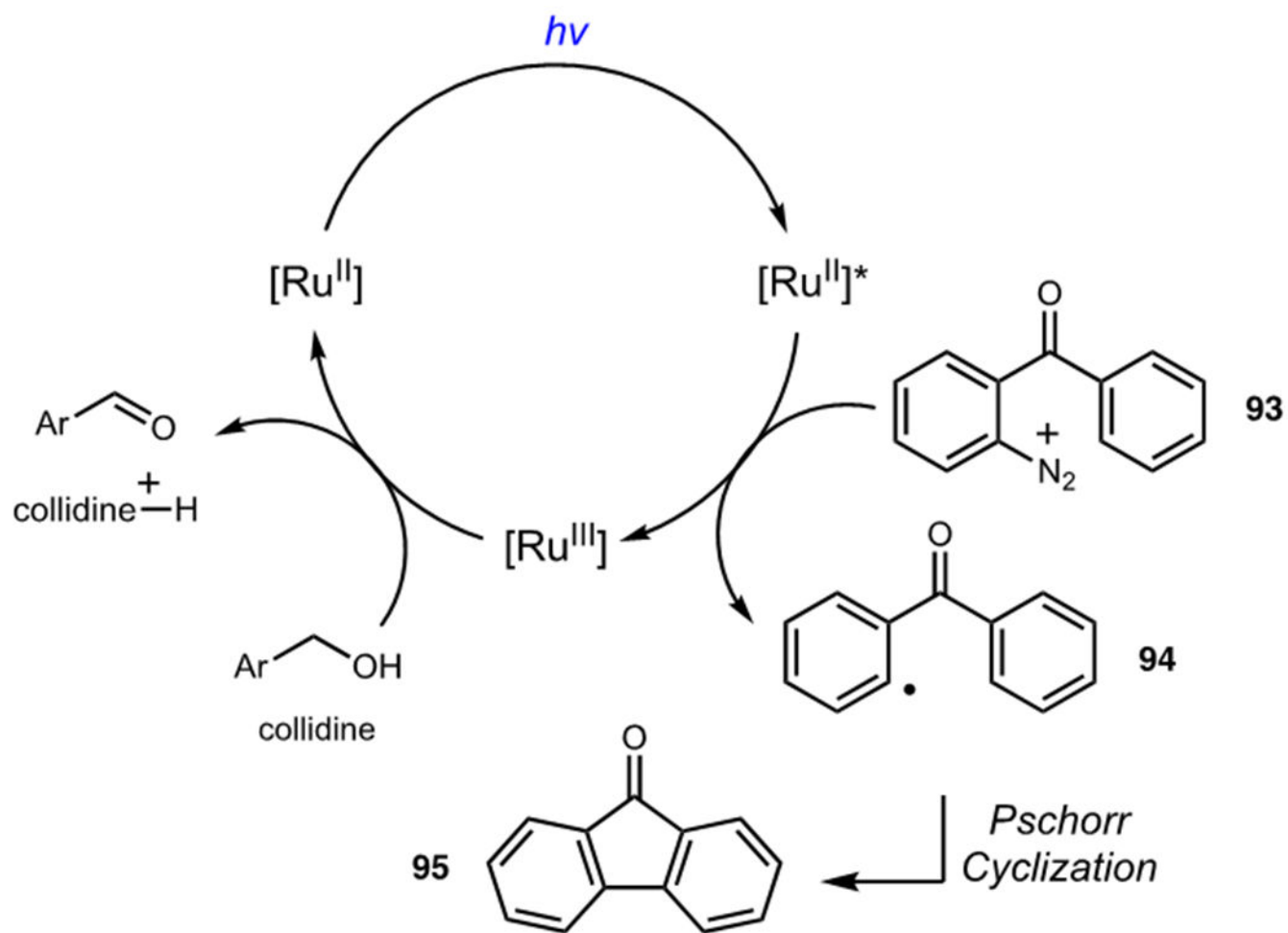
Scheme 24.
Mechanism for Photocatalytic Oxidation of Carbinols

Table 1.

Effect of Benziodoxole Structure on Photocatalytic Hydroxylation
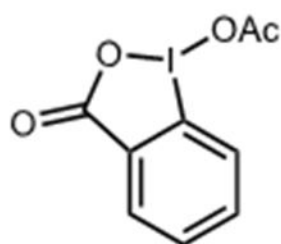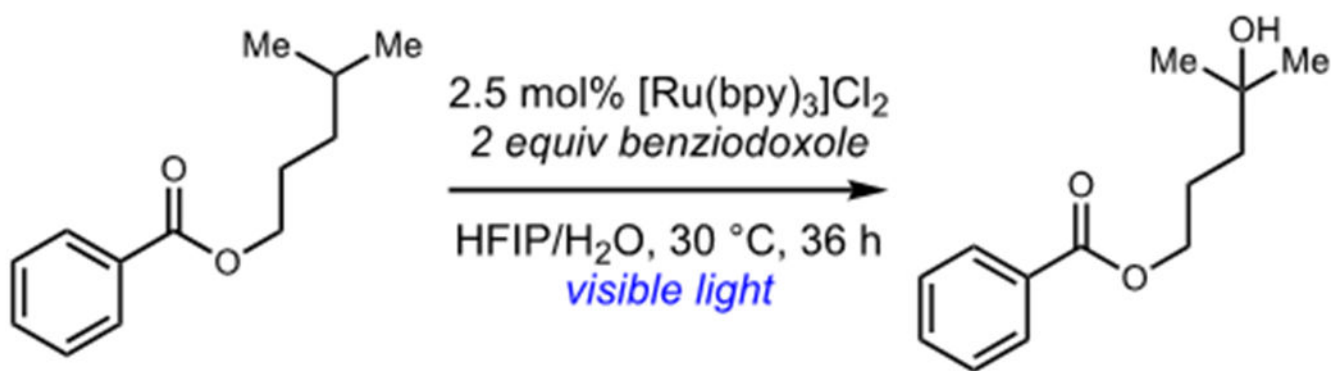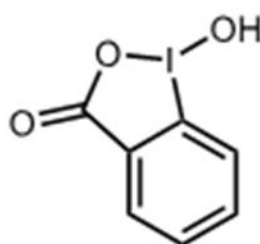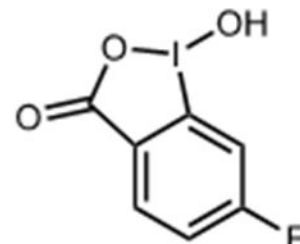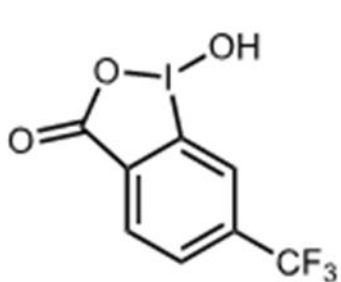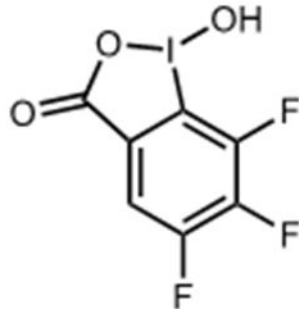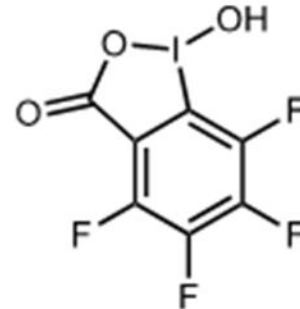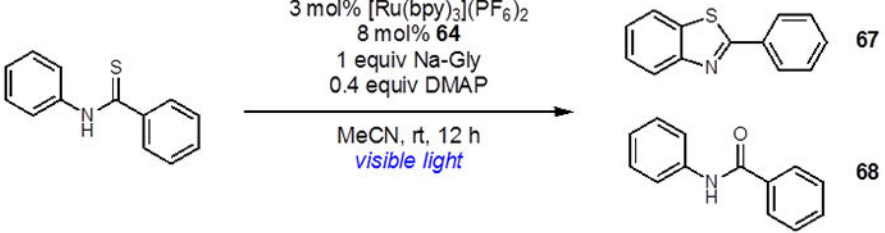
Table 2.

Effect of the Oxidant on Photocatalytic Thiolation

entry	oxidant	yield (67:68)
1	–	99%:0%
2	O_2	7%:49%
3	$K_2S_2O_8$	26%:38%
4	H_2O_2	16%:17%