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Photocatalytic Oxyamination of Alkenes: Copper(II) Salts as Terminal Oxidants in Photoredox Catalysis

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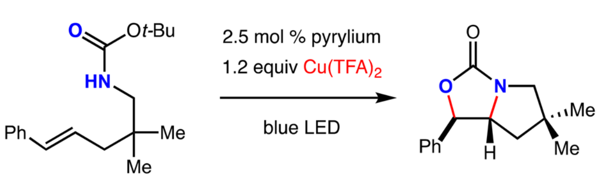
Supporting Information

ABSTRACT: A photocatalytic method for the oxyamination of alkenes using simple nucleophilic nitrogen atom sources in place of prefunctionalized electrophilic nitrogen atom donors is reported. Copper(II) is an inexpensive, practical, and uniquely effective terminal oxidant for this process. In contrast to oxygen, peroxides, and similar oxidants commonly utilized in non-photochemical oxidative methods, the use of copper(II) as a terminal oxidant in photoredox reactions avoids the formation of reactive heteroatom-centered radical intermediates that can be incompatible with electron-rich functional groups. As a demonstration of the generality of this concept, it has been shown that diamination and deoxygenation reactions can also be accomplished using similar photooxidative conditions.

Photocatalytic Oxidative Alkene Difunctionalization with Simple Nucleophiles

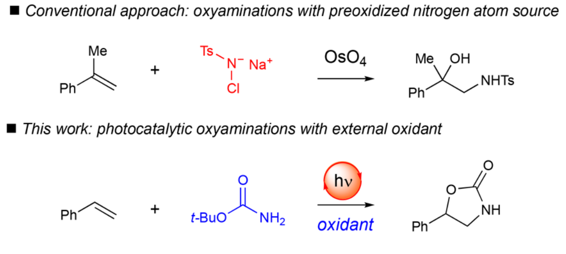


31 examples – oxyamination, diamination, dioxygenation

Oxyamination of alkenes remains an important problem in synthetic chemistry due to the prominence of amino alcohol derived subunits in many important classes of bioactive natural products, pharmaceutical compounds, and chiral reagents for stereoselective synthesis.[1] However, the most extensively developed oxyamination methods, including the Sharpless aminohydroxylation and its derivatives, require preoxidized, electrophilic nitrogen donors such as chloramines, iminoiodinanes, or hydroxylamines that can be difficult to synthesize, are often explosive, and can be challenging to handle because of their chemical instability. One important objective in oxidative functionalization methodology has therefore been the development of new oxyamination protocols that can be conducted directly with simple nucleophilic nitrogen and oxygen atom donors (Figure 1).[2]

The design of effective net-oxidative transformations is a fundamental problem in catalysis, but it poses a particular challenge for photoredox chemistry.[3] Although many powerful oxidative photoredox processes have been reported, the majority have exploited the reactivity of preoxidized electrophilic group-transfer reagents where some portion of the terminal oxidant is structurally incorporated into the product (e.g., halogenation,[4] amination,[5] or perfluoroalkylation[6]). In contrast, an oxyamination protocol using simple heteroatom nucleophiles requires an "oxidase" strategy[7] in which the terminal oxidant serves as an electron acceptor and not a functional group donor.[8] Unfortunately, terminal oxidants that are suitable for nonphotochemical reactions can be problematic in photoredox applications. For instance, molecular oxygen,[9] often identified as an ideal oxidant for organometallic catalysis,[10] is an efficient quencher of the excited states of many photocatalysts[11] and reacts rapidly with the organoradical intermediates that are ubiquitous in photoredox chemistry.[12] Similarly, photoredox activation of peroxides affords promiscuously reactive oxygen-centered radicals that can be incompatible with common electron-rich functional groups.[13] Organic oxidants (e.g., perhaloalkanes, nitroarenes, amine *N*-oxides, or arene diazonium salts)[14] can avoid these problems but are relatively expensive and produce unattractive stoichiometric byproducts. The identification of a general terminal oxidant that is free from these drawbacks would thus represent a significant advance in photochemical synthesis.

We began by examining Nicewicz's pioneering examples of photocatalytic alkene hydrofunctionalization reactions[15] (Scheme 1). In these studies, photooxidation of an alkene affords an electrophilic radical cation intermediate (**1**$^{\bullet+}$). Subsequent trapping of a heteroatomic nucleophile such as an



Goals
- low-cost, bench-stable, environmentally benign oxidant
- compatible with photocatalytic reaction conditions
- avoids promiscuous heteroatom-centered radical intermediates

Figure 1. Oxyamination reactions with and without preoxidized nitrogen atom donors.

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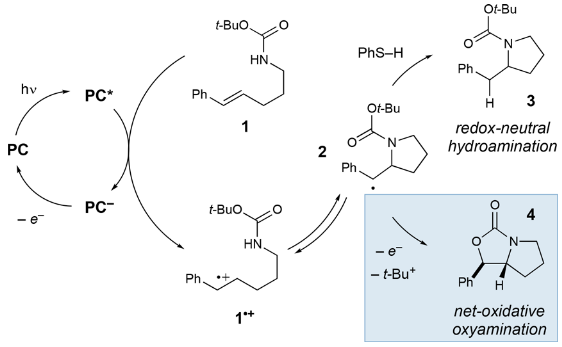
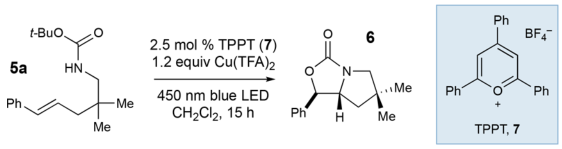
Scheme 1. Diverting Photogenerated Radical Intermediates toward Net Oxidative Functionalization Reactions



alkyl carbamate results in the generation of a carbon-centered radical intermediate (**2**). Interception by a hydrogen atom donor, often a malononitrile or thiophenol, affords the product of a redox-neutral hydrofunctionalization reaction (**3**). A recent report has also described interception of **2** by catalytic $CuCl_3$ as an atom-transfer reagent to effect an oxidative aminochlorination.[4c] We speculated that an appropriate alternative oxidant could react with this radical to produce a formally cationic intermediate; cyclization with facile loss of *tert*-butyl cation would afford oxazolidone products (**4**), effecting a net-oxidative oxyamination reaction.

We began by examining the effect of several photocatalysts and potential terminal oxidants on the oxidative cyclization of carbamate **5a**. Irradiation with a 15 W blue LED for 15 h in the presence of a commercially available pyrylium photocatalyst (TPPT, **7**) and $Cu(TFA)_2$ as an oxidant affords oxazolidone **6** in 82% yield as a single diastereomer (Table 1, entry 1).

Table 1. Effect of Reaction Variables on Oxyamination[a]



entry	variation from standard conditions	yield (%)
1	none	82
2	MesAcrMe$^+$BF$_4^-$ instead of TPPT	72
3	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ instead of TPPT	5
4	no $Cu(TFA)_2$	0[b]
5	$Cu(OTf)_2$ instead of $Cu(TFA)_2$	24
6	$Cu(OAc)_2$ instead of $Cu(TFA)_2$	7
7	$PhI(OAc)_2$, TEMPO, MnO_2, or $FeCl_3$ instead of $Cu(TFA)_2$	0[b]
8	Air, DDQ, or *t*-BuOOH instead of $Cu(TFA)_2$	0[c]
9	no TPPT	1
10	no light	0[b]

[a] Unless otherwise noted, all reactions were conducted in degassed CH_2Cl_2 and irradiated with a 15 W blue LED flood lamp for 15 h. Yields determined by ^1H NMR analysis of the unpurified reaction mixtures using phenanthrene as an internal standard. [b] No conversion. [c] Substrate decomposition.

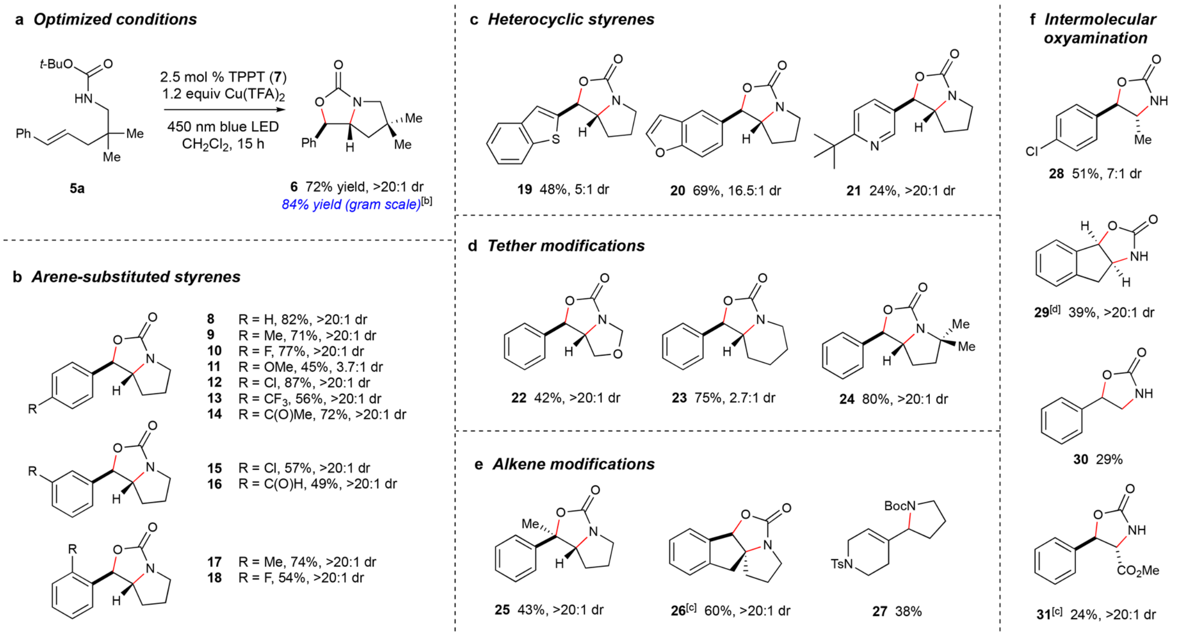
Although other strongly oxidizing organic photocatalysts afford similar results, transition-metal photoredox catalysts with less positive excited-state reduction potentials are ineffective (entries 2 and 3). The addition of a terminal oxidant is required for conversion to oxazolidone (entry 4), and importantly, the identity of the oxidant is critical. Other Cu(II) salts provide diminished yields of the oxyamination product (entries 5 and 6), but an extensive screen of alternate oxidants spanning several different classes revealed that only Cu(II) oxidants are effective. For example, $PhI(OAc)_2$, TEMPO, MnO_2, and $FeCl_3$ provide no conversion to **6**, while air, DDQ, and *t*-BuOOH result in extensive decomposition, which is consistent with the formation of reactive oxygen-centered radical intermediates (entries 7 and 8). Finally, control experiments validated the photocatalytic nature of this reaction; no product is observed in the absence of light or photocatalyst (entries 9 and 10).

The unique suitability of Cu(II) salts in this reaction is consistent with seminal investigations by Kochi, demonstrating that Cu(II) salts are exceptionally rapid and efficient oxidants of carbon-centered radicals.[16] Moreover, copper compounds do not interfere with the photochemistry of common photoredox catalysts and have been utilized as co-catalysts in several recently reported photocatalytic methods.[17] Additionally, Cu(II) salts are attractive, practical stoichiometric oxidants that are readily handled on the benchtop and removed from a reaction mixture by simple extraction or filtration through silica.[18] Copper(II) salts are generally less toxic[19] and less expensive than many common organic terminal oxidants. Although the cost of $Cu(TFA)_2$ itself is unusually high, on par with common organic oxidants, it can be synthesized from inexpensive $CuCO_3$ and trifluoroacetic acid, and reactions using either commercial or freshly prepared $Cu(TFA)_2$ give identical results.

These optimized conditions proved to be effective on a gram-scale batch, affording the oxyamination product in 84% yield (Scheme 2a). A variety of styrenic alkenes undergo facile oxyamination. The arene could be substituted at all positions with common functional groups, including halides, ketones, and aldehydes (Scheme 2b, **8**–**18**). Heteroaryl styrenes can also undergo oxyamination; while pyridines provide diminished rates, less basic O and S heterocycles were readily tolerated (Scheme 2c, **19**–**21**). The diastereoselectivity was excellent, except in the cases of very electron-rich styrenes (**11** and **19**).[20] Increasing the length of the tether, incorporating heteroatoms, or substituting the carbon chain had little effect on the rate of the cyclization (Scheme 2d, **22**–**24**). The styrene could be substituted on the alkene moiety as well, both at the α and β positions (Scheme 2e, **25** and **26**). Trisubstituted aliphatic alkenes, however, instead afforded an allylic carbamate (**27**), suggesting that although the excited-state photocatalyst could oxidize the substrate, the resulting cationic intermediate undergoes elimination faster than trapping by the carbamoyl oxygen. Finally, we examined intermolecular oxyaminations using simple Boc carbamate as the amine source (Scheme 2f). Both *cis* and *trans* 1,2-disubstituted styrenes (**28** and **29**) react with good yields. Interestingly, methyl cinnamate also underwent oxyamination, despite the presence of the highly electron-withdrawing ester moiety, affording direct access to a highly functionalized oxazolidone scaffold (**31**).

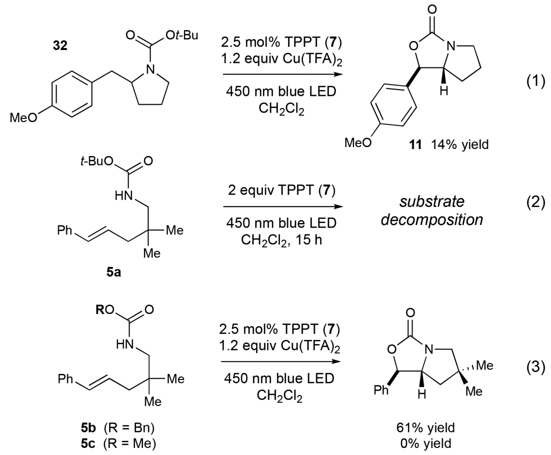
Scheme 3 summarizes several experiments supporting the mechanism proposed in Scheme 4a. First, subjecting hydroamination product **32** to the optimized reaction conditions resulted in the formation of oxazolidone product **11** in 14% yield (Scheme 3, eq 1). Thus, the benzylic radical produced by photooxidation of the arene[21] can re-enter the catalytic cycle, supporting its role as an intermediate in this process. Second, irradiation of **5a** in the presence of 2 equiv of TPPT, but in the

Scheme 2. Scope Studies for Photocatalytic Oxyamination Reactions[a]



[a] Unless otherwise noted, all reactions were conducted using 2.5 mol % of 7, 1.2 equiv of Cu(TFA)$_2$ in degassed CH$_2$Cl$_2$ and irradiated with a 15 W blue LED flood lamp for 15−48 h. Isolated yields are reported. [b] Reaction time 48 h. [c] Reaction time 72 h. [d] Reaction time 7 days.

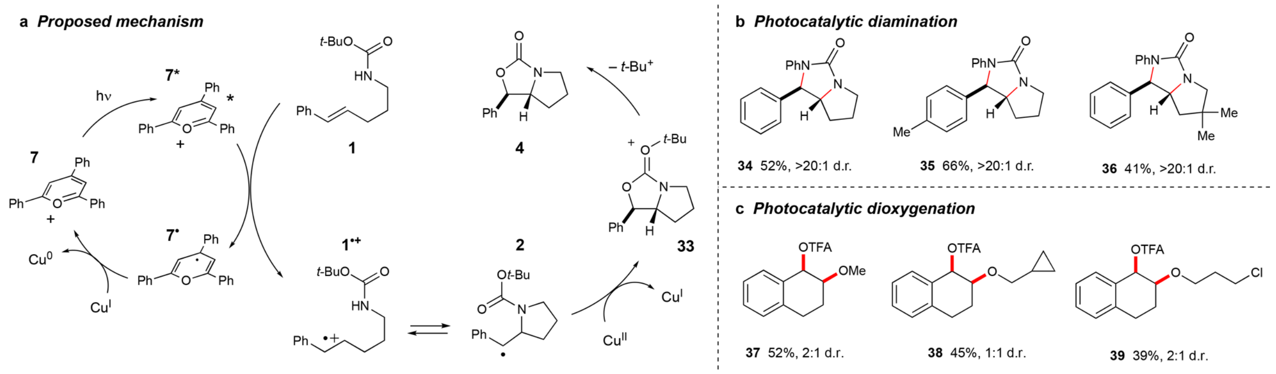
Scheme 3. Experiments Supporting the Proposed Mechanism



absence of Cu(TFA)$_2$, resulted in complete decomposition of the substrate without formation of the oxyamination product (Scheme 3, eq 2). This result is consistent with the hypothesis that Cu(II) is not merely a terminal oxidant but is intimately involved in oxidation of the organoradical intermediate, as expected from Kochi's studies. Third, the formation of the final product by loss of *tert*-butyl cation is consistent with the observation that while Cbz carbamates cyclize effectively, Moc carbamates provide no product (Scheme 3, eq 3), in line with the poor stability of the methyl cation. Finally, because the reaction requires only 1.2 equiv of Cu(TFA)$_2$, Cu(II) must be acting as a net two-electron oxidant. It is unclear whether the Cu(I) intermediate directly turns over the photocatalyst by oxidation of 7$^{\bullet}$ or disproportionates to Cu(II) and Cu(0). Both mechanisms would be consistent with the observed precipitation of copper metal from solution during the course of the reaction.

Oxyamination reactions are representative of a broader class of synthetically important oxidative alkene difunctionalizations.[22]

Scheme 4. Working Mechanistic Hypothesis and Extension to Alkene Difunctionalization



[a] Reactions conducted using MesAcrMe$^+$BF$_4^-$ as the photocatalyst and Cu(OAc)$_2$ as the terminal oxidant. [b] Reactions conducted using 4 equiv of alcohol, TPPT as photocatalyst, and Cu(TFA)$_2$ as terminal oxidant.

If this Cu(II)-mediated photocatalytic strategy could be generalized to the use of alternate nucleophilic reaction partners, it would provide a novel, flexible approach toward the photocatalytic synthesis of a wide range of vicinal heteroatom arrays. Indeed, the use of ureas in place of carbamates affords the products of net alkene diamination (Scheme 4b). The optimal photocatalyst ($\mathrm{MesAcrMe^+}$) and oxidant [$\mathrm{Cu(OAc)_2}$] were slightly different in this case, which demonstrates that these variables can be tuned to achieve optimal reactivity in different transformations. Moreover, the irradiation of dihydronaphthalene with various alcohols in the presence of $\mathrm{Cu(TFA)_2}$ and TPPT results in alkene dioxygenation (Scheme 4c). Thus, these preliminary results indicate that the identity of each of the heteroatoms introduced across the alkene can be varied and suggest that this reaction design plan might be generalizable to a much wider range of oxidative functionalization reactions.

In summary, copper(II) salts are effective oxidants that enable the oxidative difunctionalization of alkenes using photoredox catalysis. More broadly, these results are exciting because organoradical intermediates are common in photoredox reactions. The ability to divert these intermediates toward cationic reactivity using convenient Cu(II) oxidants suggests a powerful and conceptually novel approach toward the design of a wide range of new oxidative functionalization reactions. Studies toward this broader goal are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03345.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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