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Photoredox-Catalyzed Reductive Carbamoyl Radical Generation: A Redox-Neutral Intermolecular Addition−Cyclization Approach to Functionalized 3,4-Dihydroquinolin-2-ones

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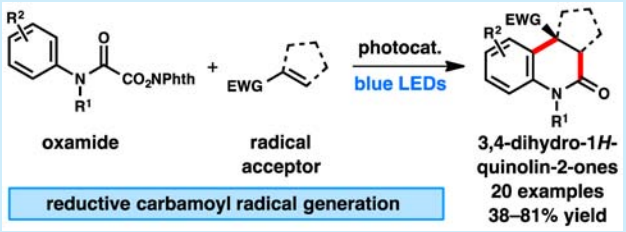
Supporting Information

ABSTRACT: The first reductive generation of carbamoyl radicals using photoredox catalysis for their formation is reported. This approach facilitated the development of a redox-neutral synthesis of functionalized 3,4-dihydroquinolin-2-ones via the novel intermolecular addition−cyclization of carbamoyl radicals across electron-deficient alkenes. To illustrate the versatility of this reaction, a diverse collection of 3,4-dihydroquinolin-2-ones, including fused cyclic and spirocyclic systems inspired by natural products, has been prepared.

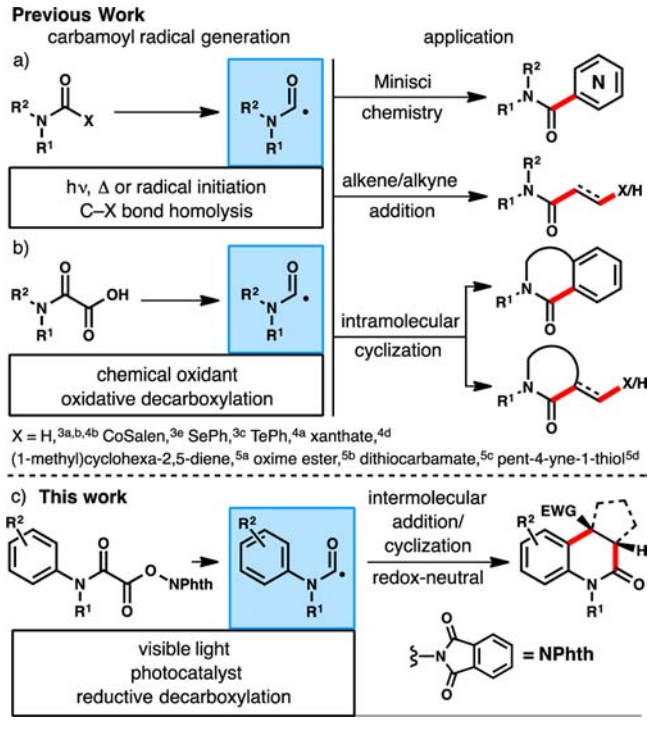


The field of photoredox catalysis has expanded exponentially over the past decade, becoming an extremely powerful platform for the development of novel chemistry.[1] This approach makes use of visible light, a mild, safe, and environmentally friendly form of energy, to drive reactions. The utilization of photoredox catalysis in single-electron transfer (SET) processes has fuelled exploration of alternatives to traditional radical chemistry, eliminating toxic reagents and harmful, unselective ultraviolet (UV) light; it has also facilitated the development of previously unknown and unattainable reactions that exploit the simultaneous and continual generation of strongly oxidizing and reducing species within the same reaction vessel.

Carbamoyl radicals are versatile reactive intermediates especially well-suited to the synthesis of amide-containing compounds.[2−4] However, existing methods for the generation of carbamoyl radicals are limited to two general strategies, which restricts further development of their application in synthesis. These are (i) a classical radical chemistry approach involving homolytic C−X cleavage of a suitably functionalized acyl precursor induced by either a radical initiator, heat, or UV light (Scheme 1a)[3a−c,e,4a,b,d,5] and (ii) an oxidative approach via SET from an α-amidocarboxylate to a stoichiometric chemical oxidant with subsequent decarboxylation (Scheme 1b).[3d,f,4c,e]

We reasoned that an unprecedented reductive approach to carbamoyl radicals would provide a basis for the development of chemistry not possible under existing modes of generation. The photoredox-catalyzed single-electron reduction of *N*-hydroxyphthalimido esters has been developed by Overman and co-workers as a general tactic for the generation of alkyl and methoxycarbonyl radicals.[6,7] We proposed that the single-electron reductive decarboxylation of *N*-hydroxyphthalimido oxamides would allow a novel entry into carbamoyl radicals (Scheme 1c). To validate our approach and showcase its utility, we proposed that the novel intermolecular addition of *N*-aryl carbamoyl radicals across electron-deficient alkenes would form

Scheme 1. Generation and Application of Carbamoyl Radicals



two new C−C bonds and construct the 3,4-dihydroquinolin-2-one architecture.[8] Since restoration of aromaticity after radical addition necessitates single-electron oxidation and loss of H^+, carbamoyl radical generation via a *reductive* SET would render the process redox-neutral and hence highly suitable for

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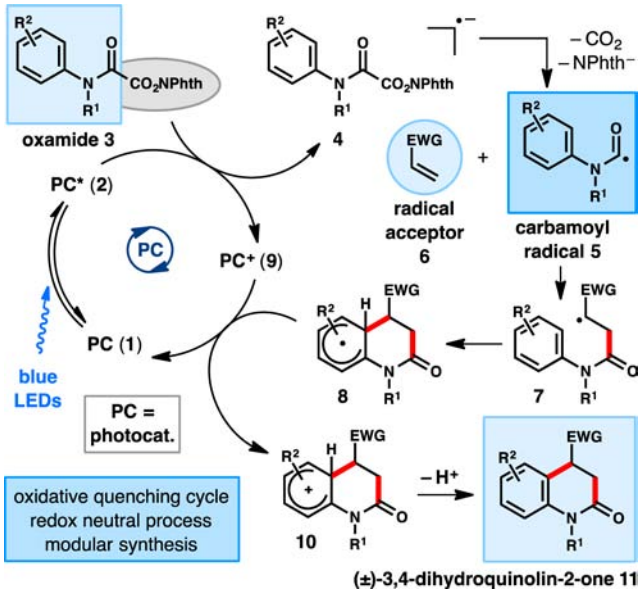
photoredox catalysis, which notably would represent the first application of this strategy to carbamoyl radical chemistry.[9]

The proposed mechanistic cycle is depicted in Scheme 2. Irradiation of an appropriate photocatalyst, **PC** (**1**), such as

Scheme 2. Proposed Mechanism



$Ru(bpy)_3{\cdot}6H_2O$ or *fac*-$Ir(ppy)_3$ with visible light, would lead to the long-lived photoexcited state **PC*** (**2**) [Ru τ = 1.1 μs, Ir τ = 1.9 μs], which is a single-electron reductant [$E_{1/2}(Ru^{III}/Ru^{II*})$ = −0.81 V, $E_{1/2}(Ir^{IV+}/Ir^{III*})$ = −1.73 V vs SCE][10] capable of reducing *N*-hydroxyphthalimido oxamide **3** to the transient radical anion **4**, which should undergo homolytic cleavage to afford carbamoyl radical intermediate **5** with the loss of CO_2 and $NPhth^-$.[6,7] The nucleophilic carbamoyl radical **5**[4b] is anticipated to add readily to electron-deficient alkene **6**, generating the electrophilic conjugate radical **7**, which can then engage in homolytic aromatic substitution (HAS) with the anilide to produce cyclohexadienyl radical **8**. Oxidation of the electron-rich intermediate **8** by the oxidized-state photocatalyst **PC**$^+$ (**9**) [$E_{1/2}(Ru^{III}/Ru^{II})$ = +1.29 V, $E_{1/2}(Ir^{IV+}/Ir^{III})$ = +0.77 V vs SCE] would regenerate the ground-state photocatalyst **PC** (**1**) and liberate cyclohexadienyl cation **10**, which can rearomatize with the loss of H^+ to give 3,4-dihydroquinolin-2-one **11**.[10]

3,4-Dihydroquinolin-2-ones are a class of heterocycles with proven medicinal value, present within top-selling pharmaceuticals (e.g., **12**), natural product families (e.g., **13** and **14**),[11,12] and other bioactive molecules (Figure 1).[13] Herein, as part of our program to develop new strategies for the synthesis of

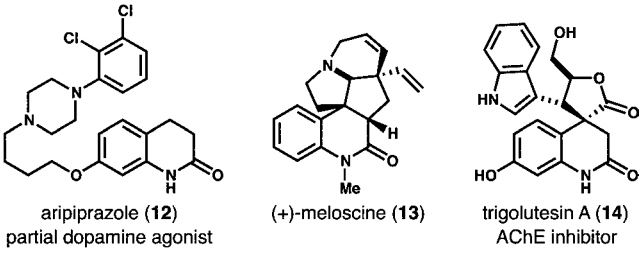
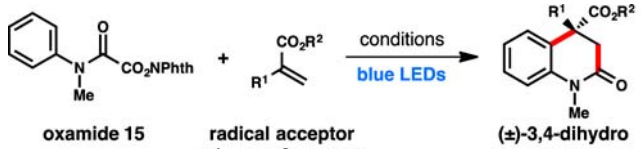


Figure 1. Pharmaceutical and natural products with the 3,4-dihydroquinolin-2-one core.

medicinally relevant nitrogen-containing ring systems,[14,15] we demonstrate the realization of this novel lactam-forming strategy with the preparation of a diverse library of 3,4-dihydroquinolin-2-ones.

A general route to access the *N*-hydroxyphthalimido oxamide radical precursors on gram-scale was developed via the acylation of anilines with chloro-*N*-phthalimidoyl oxalate (see Supporting Information).[16] The resulting oxamides were easily purified by recrystallization to afford bench-stable solids. The novel addition−cyclization process was initially evaluated for the formation of 3,4-dihydroquinolin-2-ones **18** and **19** using the oxamide derived from *N*-methylaniline **15** and acrylates **16** and **17**. Selected optimization results are summarized in Table 1.

Table 1. Reaction Optimization



entry	acceptor (equiv)	photocatalyst (2 mol %)	solvent (M)	product, yield (%)[a]
1[b]	**16** (1.0)	$Ru(bpy)_3Cl_2$[c]	MeCN (0.12)	**18**, 19
2[b]	**16** (1.0)	*fac*-$Ir(ppy)_3$	MeCN (0.12)	**18**, 27
3[b]	**16** (1.0)	Eosin Y	MeCN (0.12)	**18**, 13
4[b]	**16** (1.5)	*fac*-$Ir(ppy)_3$	CH_2Cl_2 (0.12)	**18**, 26
5[b]	**16** (1.5)	*fac*-$Ir(ppy)_3$	THF (0.12)	**18**, 17
6[b]	**16** (1.5)	*fac*-$Ir(ppy)_3$	PhMe (0.12)	**18**, 37
7[b]	**16** (1.5)	*fac*-$Ir(ppy)_3$	PhMe (0.24)	**18**, 25
8[b]	**16 (1.5)**	***fac*-Ir(ppy)$_3$**	**PhMe (0.04)**	**18**, 48, 43[d]
9[b]	**16** (1.5)	*fac*-$Ir(ppy)_3$	PhMe (0.02)	**18**, 49
10[b]	**17 (1.5)**	***fac*-Ir(ppy)$_3$**	**PhMe (0.04)**	**19**, 70[d]
11[b]	**17** (1.5)		PhMe (0.04)	**19**, 0
12[e]	**17** (1.5)	*fac*-$Ir(ppy)_3$	PhMe (0.04)	**19**, 0

[a]Determined by ^{1}H NMR spectroscopy against an internal standard (BnOAc). [b]Irradiated with 60 W blue LEDs and fan cooling for 24 h. [c]Hexahydrate. [d]Isolated yield. [e]Conducted in the dark.

With oxamide **15**, radical acceptor **16**, and 2 mol % of $Ru(bpy)_3{\cdot}6H_2O$, after 24 h irradiation with blue LEDs in MeCN, we observed the desired product **18** in 19% yield (entry 1). Variation of the photocatalyst significantly influenced reaction efficiency, with *fac*-$Ir(ppy)_3$ found to be superior to both $Ru(bpy)_3{\cdot}6H_2O$ and eosin Y, leading to a 27% yield (entries 2 and 3). Next, a solvent screen identified toluene to be optimal, affording lactam **18** in 37% yield (see entries 4−6). A more dilute set of conditions (0.04 M) was also determined to be beneficial, affording a 48% yield by ^{1}H NMR analysis, which translated into a 43% isolated yield (entries 6−9). We then applied the reaction conditions to methyl methacrylate (**17**), an acceptor anticipated to better stabilize the intermediate conjugate radical. Gratifyingly, 3,4-dihydroquinolin-2-one **19** was isolated in 70% yield (entry 10). Finally, control experiments revealed that no product formation was observed in the absence of either photocatalyst or light (entries 11 and 12).

At this juncture, the reaction conditions were evaluated across a range of electron-deficient alkene radical acceptors (Scheme

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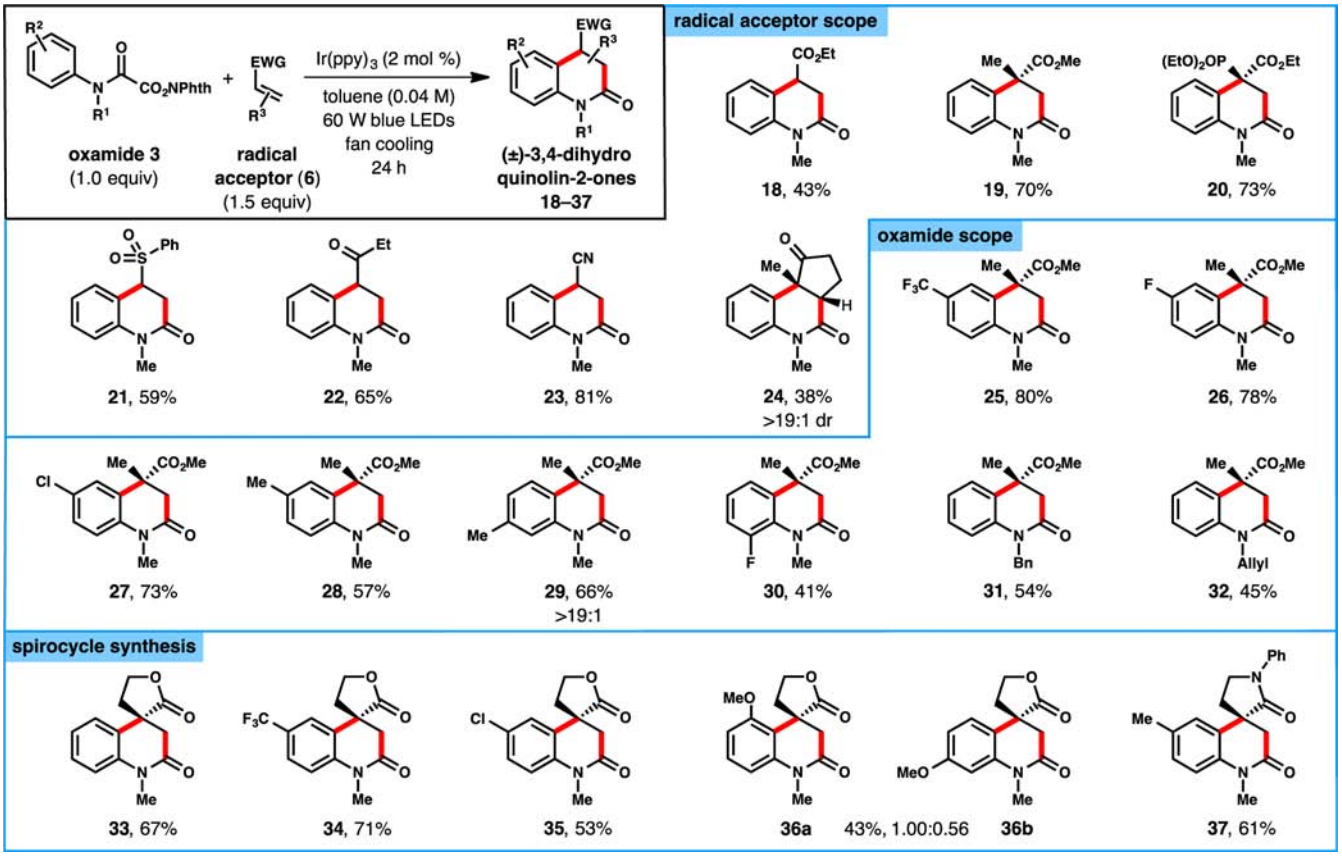
Scheme 3. Substrate Scope



3).[17] In addition to quinolin-2-one **19**, a second quaternary substituted example **20** was obtained in good yield. Several monosubstituted alkenes were competent reaction partners in this chemistry, offering ester, sulfone, ketone, and nitrile-substituted products **18** and **21**–**23** in 43–81% yields. The yield of the reactions correlated with the electron-withdrawing and radical-stabilizing ability of the alkene substituent.

Fused cyclopentane **24** was isolated in modest yield as a single diastereomer, unambiguously determined as the anticipated *cis*-fusion by the observation of an NOE correlation between the benzylic methyl group and the proton at the ring junction. Notably, compound **24** contains the [6,6,5]-core of meloscine (**13**) and many of the other *melodinus* alkaloids.

We next investigated the scope in terms of the oxamide inputs **3** using methyl methacrylate (**17**) as the common acceptor. A series of *p*-substituted *N*-methyl oxamides were subjected to the reaction, affording 3,4-dihydroquinolin-2-ones **25**–**28** in 57–80% yield with a range of electron-withdrawing and electron-donating substituents and potentially useful functional groups. Taken together with compound **19**, there is a clear trend of increasing yield for more electron-deficient oxamides. Interestingly, the *m*-methyl-substituted oxamide afforded lactam **29** in 66% yield as a single regioisomer, owing to steric-directing effects. In contrast, none of the desired lactam was observed when the analogous *o*-methyl-substituted oxamide was employed in the process. Pleasingly, the smaller and more electron-withdrawing *o*-fluoro substituent was compatible with the method, providing quinolin-2-one **30** in 41% yield. Finally, the formation of products **31** and **32** is notable as they bear removable *N*-protecting groups[18] and also because the intramolecular cyclization occurred preferentially onto the anilide rather than the pendant *N*-benzyl[3f] and *N*-allyl groups,[5c,b] which has previously been observed in the literature.

The Taylor group has had a long-running interest in the synthesis of spirocyclic natural products and natural product-like scaffolds.[14,15a] Inspired by (+)-meloscine (**13**) and trigolutesin A (**14**), we questioned if a radical acceptor with an exocyclic alkene might provide an entry into spirocycles. The reaction of oxamide **15** with α-methylene-γ-butyrolactone produced the spirocyclic lactone lactam **33** in 67% yield under the standard conditions. Similarly, *p*-trifluoromethyl and chloro-spirocycles were prepared in good yields (**34** and **35**). To access substitution reflecting that found in trigolutesin A (**14**), a *m*-methoxy oxamide was subjected to the reaction, which afforded the spirocyclic product as a mixture of two inseparable regioisomers **36a** and **36b** in a ratio of 1.00:0.56, respectively, and 43% combined yield. Interestingly, in this case, steric effects seem to play a less significant role in controlling regioselectivity, with orbital coefficients dominating the position of HAS. When 3-methylidene-1-phenylpyrrolidin-2-one was used to trap the carbamoyl radical intermediate, spirorocyclic bislactam **37** was produced in 61% yield.

This proof-of-principle study demonstrates how the novel reductive generation of carbamoyl radicals under photoredox catalysis provides a basis for the development of new chemistry, as exemplified by a redox-neutral intermolecular addition–cyclization process to access functionalized 3,4-dihydroquinolin-2-ones. Under a general set of conditions, variation of the electron-deficient alkenes and readily prepared oxamides allows functionality at all available positions of the 3,4-dihydroquinolin-2-one core via this new disconnection, giving access to structures which would be difficult or lengthy to prepare using existing

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methods.[15c] We are currently using this reductive carbamoyl radical generation for the development of methods to target other heterocyclic systems and for applications in synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00022.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Butyl vinyl ether did not provide detectable levels of 3,4-dihydroquinolin-2-one formation; this was expected given the electron-rich nature of the olefin and the nucleophilic character of carbamoyl radicals; see ref 4b and references cited therein. Similar reactivity was observed by Overman for related methoxycarbonyl radicals; see ref 8.

(18) No 3,4-dihydroquinolin-2-one formation was observed with an oxamide bearing an electron-withdrawing *N*-Boc substituent.

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