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Oxyamination of Unactivated Alkenes with Electron-Rich Amines and Acids via a Catalytic Triiodide Intermediate

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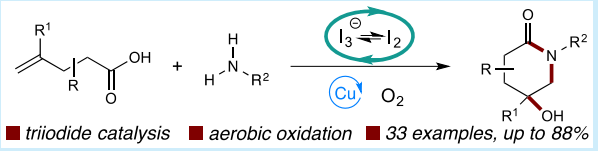
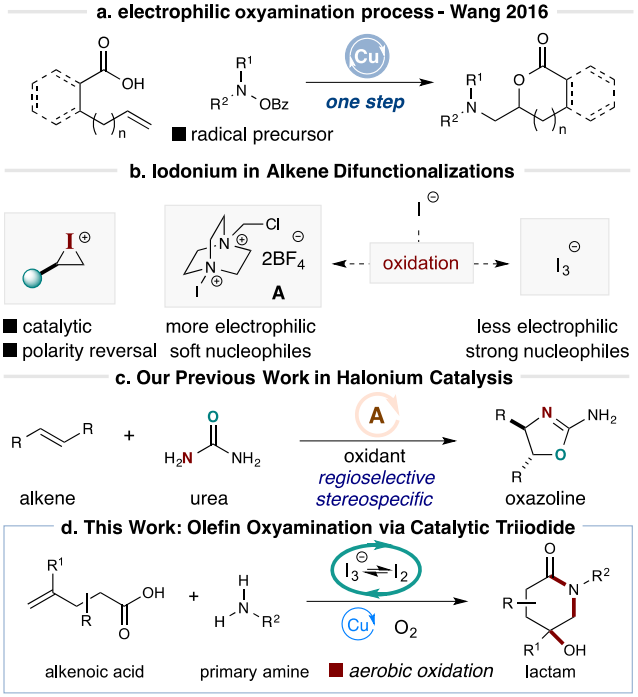
ABSTRACT: An aerobic catalytic oxidation process is described for the olefin oxyamination using acids and primary amines as the sources of O and N. Our mechanistic findings point to the formation of triiodide as a critical catalytic intermediate to account for the tolerance of electron-rich nucleophiles. This dual iodide and copper catalytic system is suitable for a formal [5+1] annulation process to access valuable lactam structures and highlighted by the synthesis of the pharmaceutical Zamifenacin.



Alkene difunctionalization represents a broadly adopted and powerful strategy for the rapid assembly of molecular complexity.[1] This class of reactions offers intriguing and disruptive opportunities in terms of bond disconnection logics, as exemplified by the recent works of Brown,[2] Engle,[3] Giri,[4] and others.[5,6] A subclass of alkene difunctionalizations, the alkene oxyamination reaction, is among the most studied catalytic reactions since the pioneering osmium-catalyzed process developed by Sharpless.[7] To circumvent the inherent challenges in this reaction such as regio- and enantioselectivity, a nontoxic catalyst, an abundant substrate, etc., a variety of transition metal-catalyzed processes, including osmium,[8] palladium,[9] copper,[10] iron,[11] iridium,[12] etc.,[13,14] have been developed. While tremendous progress has been made in this area, aerobic catalytic processes that directly utilize unadorned oxygen and nitrogen precursors remain challenging and rare.[15] A notable example that inspired our work in this area is a recent example by Wang et al., in which an *O*-benzoylhydroxylamine was utilized as both an oxidant and the electron-rich amine source (Scheme 1a).[16]

We are interested in the utilization of halonium as a catalytic template to achieve alkene difunctionalizations (Scheme 1b).[17] The catalytic polarity reversal of an alkene to a dielectrophile renders the use of simple nucleophiles for alkene difunctionalizations. In this regard, the understanding of the oxidation process of the precatalyst, the halide salt, is critical in defining the scope and nature of reagents that can be used in the desired reaction settings. Recently, we have reported an iodide-catalyzed intermolecular alkene oxyamination using Selectfluor as a terminal oxidant (Scheme 1c).[18] The activated iodenium intermediate **A**, being a highly electrophilic halogen source, allowed the use of a soft nucleophile such as urea to function as the source of oxygen and nitrogen. On the other hand, we reason that the anionic triiodide species, as demonstrated in the classic "iodine clock" experiment, while less electrophilic, may engage stronger nucleophiles in alkene oxyamination reaction.[19] Herein, we report an aerobic oxyamination of unactivated alkenes via catalytic triiodide using electron-rich primary amines and carboxylic acids (Scheme 1d).

Scheme 1. Background and Mechanistic Questions



We recently reported a copper-catalyzed aminolactonization reaction with a stoichiometric iodide additive.[20] Regardless of

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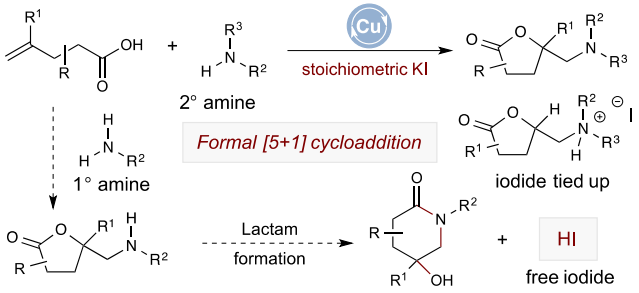
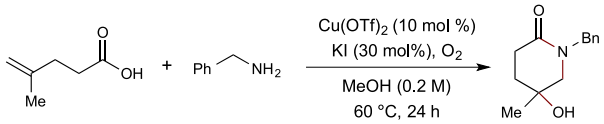


Figure 1. Our hypothesis for facilitating iodide turnover.

Scheme 2. Optimization Studies[a]



entry	Cu catalyst (%)	halide (%)	solvent (M)	yield (%)[b]
1[c]	$Cu(OTf)_2$ (10)	KI (100)	ACN/MeOH (0.5)	49
2[c]	$Cu(OTf)_2$ (10)	KI (30)	ACN/MeOH (0.5)	18
3[c]	$Cu(OTf)_2$ (10)	KI (100)	MeOH (0.5)	67
4	$Cu(OTf)_2$ (10)	KI (100)	MeOH (0.5)	69
5	$Cu(OTf)_2$ (10)	KI (30)	MeOH (0.5)	56
6	$Cu(OTf)_2$ (10)	KI (30)	MeOH (2.0)	39
7	$Cu(OTf)_2$ (10)	KI (30)	MeOH (0.2)	75(74)
8	$Cu(OTf)_2$ (10)	KI (30)	MeOH (0.1)	63
9	$Cu(OTf)_2$ (10)	KI (20)	MeOH (0.2)	47
10	$CuCl_2$ (10)	KI (30)	MeOH (0.2)	68
11	$Cu(OAc)_2$ (10)	KI (30)	MeOH (0.2)	49
12	-	KI (30)	MeOH (0.2)	0
13	$Cu(OTf)_2$ (10)	-	MeOH (0.2)	0
14[d]	$Cu(OTf)_2$ (10)	KI (30)	MeOH (0.2)	0

[a]Reaction conditions: alkenoic acid **1** (0.5 mmol), amine **2** (1.5 mmol), copper catalyst (10 mol %), halide salt (30 mol %), solvent (2.5 mL), 60 °C, 24 h. [b]Yields were determined by crude ^1H NMR using 1,3-benzodioxole as the internal standard. The yield shown in parentheses is the isolated yield. [c]With 1.0 mmol of amine. [d]Under an atmosphere of nitrogen with a nitrogen balloon.

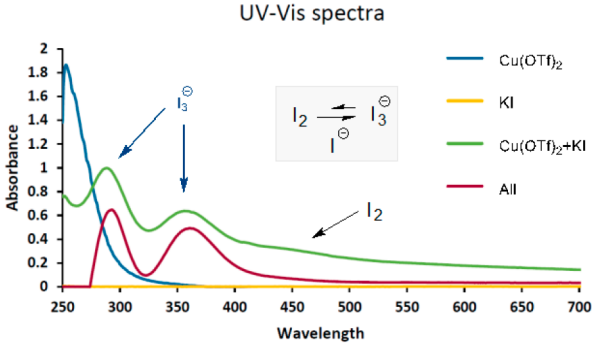


Figure 2. UV−vis studies.

the conditions utilized, the catalytic turnover of the iodide salt was problematic. We reasoned that the aminolactone product, bearing a tertiary amine, may tie up the proton and iodide source in a salt form that prevented them from being turned over (Figure 1). To circumvent this problem, we thought that if a primary amine was used instead, an intramolecular lactam formation could follow suit to generate a lactam product.[21] The much less basic amide functionality in the product will allow free HI to reenter the catalytic cycle. The overall process enables primary amines to react with alkenoic acids directly to furnish γ-lactams, a valuable pharmaceutical motif with limited synthetic protocols, via a dual catalytic process.[22]

We began our optimization with copper(II) triflate [$Cu(OTf)_2$], potassium iodide (KI), acetonitrile (ACN), and methanol (MeOH) as a solvent mixture under an oxygen atmosphere. We were delighted that desired lactam product **3** was obtained in 49% yield (Scheme 2, entry 1). However, when the amount of KI was decreased to a catalytic amount (30 mol %), only 18% of **3** was observed, suggesting no catalytic turnover of the halide salt (Scheme 2, entry 2). Evaluation of the solvent revealed that the polar protic methanol was the optimal choice, indicating that instead the solubility of the resulting iodide could be crucial for catalytic turnover (Scheme 2, entries 3 and 4). Indeed, reevaluation of KI as a catalyst with methanol revealed that catalytic turnover could be achieved with a 56% yield of the lactam product (Scheme 2, entry 5). Examination of concentration demonstrated that 0.2 M gave the optimal conditions, producing a 75% yield of the product and validating the catalytic capacity of the iodide additive (Scheme 2, entries 6−8). Furthermore, decreasing the iodide catalyst load or changing the copper catalyst identity could also lead to the desired product formation, albeit in diminished efficiency (Scheme 2, entries 9−11). Finally, control reactions revealed that the absence of either the copper catalyst or the iodide catalyst resulted in a 0% yield (Scheme 2, entries 12 and 13).

With the optimized conditions in hand, we wanted to first gain insights into the reaction tolerance to strong nucleophiles such as electron-rich amines and acids. As documented in the literature, these reagents are prone to oxidation, decarboxylation, and other decomposition pathways in aerobic copper catalysis or halogen-based conditions.[23] To comprehend this compatibility feature, we performed UV−vis studies to elucidate the exact nature of potential catalytic species (Figure 2). The mixing of $Cu(OTf)_2$ and KI resulted in the immediate formation of the triiodide with trace iodine present compared to the controls.[24] The formation of the triiodide helps to explain the compatibility to both the electron-rich amines and acids. Specifically, the facile oxidation of the iodide by a Cu(II) catalyst keeps the copper catalyst at the Cu(I) oxidation state, a less oxidizing species. The triiodide formation critically minimizes the presence of iodine in an equilibrium similar to the classic "iodine clock" experiment. Finally, the mixing of the acid and amine likely results in the formation of either the ammonium or copper carboxylate, a more efficient nucleophile at consuming any iodine present than the acid. The rate acceleration based on stronger nucleophiles in halocyclization has recently been elegantly documented by Borhan et al.[25] Thereby, constant and rapid consumption of the iodine from the triiodide−iodine equilibrium further minimizes the presence of iodine. With the mixing of all of the reagents, triiodide was again observed with complete $Cu(OTf)_2$ consumption.

The clarification of the active catalytic intermediate suggests that an extensive substrate scope can be achieved. With that in mind, we first evaluated the primary amine substrate scope. A series of substitutions, including *m*-OMe, *p*-Br, and *p*-F, on the benzene ring of primary benzyl amines all worked efficiently (Scheme 3, products **4**−**6**, respectively). Notably, the electron-

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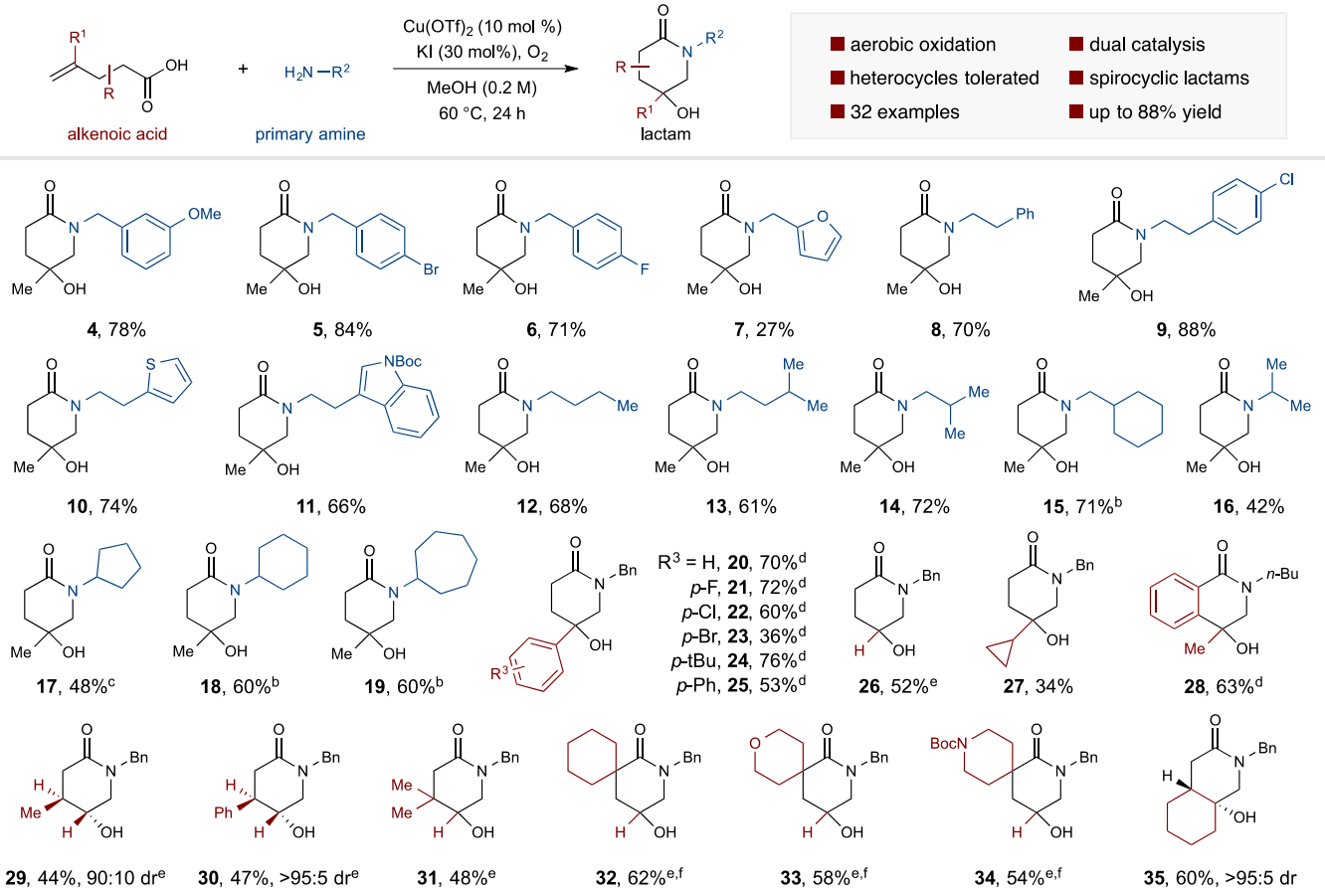
Scheme 3. Substrate Scope of Primary Amines and Alkenoic Acids.[a]



[a]Standard reaction conditions. [b]MeOH (0.14 M), 36 h. [c]At 48 h. [d]At 36 h. [e]KI (100 mol %). [f]See the Supporting Information for the detailed procedure.

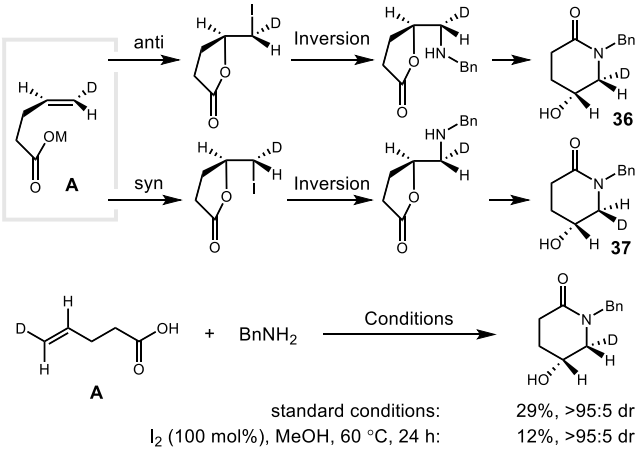


Figure 3. Stereochemical analysis and results.

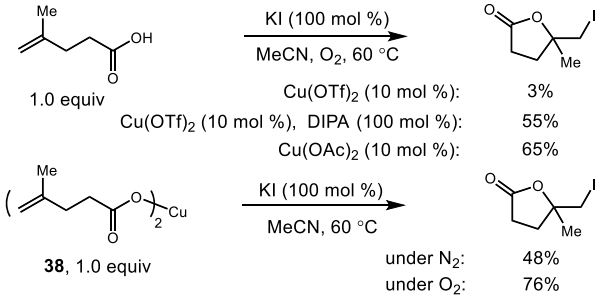


Figure 4. Role of the copper catalyst in iodolactonization.

rich heteroarene furan was also tolerated in diminished yield (Scheme 3, product **7**). The coupling of primary homobenzylic amines proceeded with exceptional yields, including substrates containing heteroaromatics such as thiophene and tryptamine (Scheme 3, products **8**–**11**). Encouraged by these findings, we ventured to test aliphatic primary amine substrates. In this case, a range of aliphatic amines produced the desired products in good yields (Scheme 3, products **12**–**15**). Even the sterically hindered isopropylamine produced the desired product in 42% yield (Scheme 3, product **16**). Furthermore, cyclic primary amines such as cyclopentylamine, cyclohexylamine, and cycloheptamine could all afford the lactam product in 48%, 60%, and 60% yields (Scheme 3, products **17**–**19**, respectively).

Satisfied with the broad scope of primary amine substrates, we then examined the range of alkenoic acid substrates for this reaction. A number of 1,1-disubstituted styrenyl 4-pentenoic acids with *p*-F, -Cl, -Br, -*t*-Bu, and -Ph substitutions all proceeded smoothly to provide the lactam products in reasonable yields (Scheme 3, products **20**–**25**, respectively). Coupling of 4-pentenoic acid also affoded the lactam **26** in 52% yield (Scheme 3, product **26**). Interestingly, the cyclopropyl-substituted 4-pentenoic acids resulted in product formation with a 34% yield (Scheme 3, product **27**).[26] A

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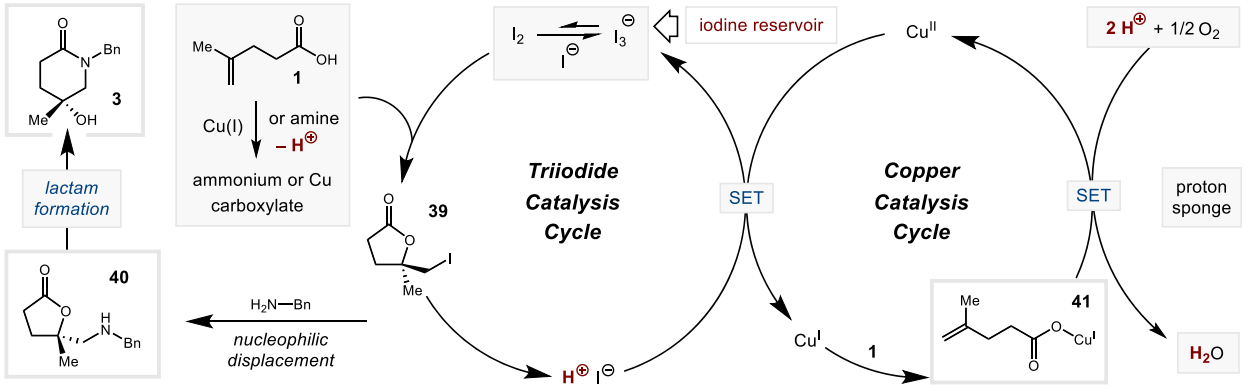
Scheme 4. Proposed Mechanism



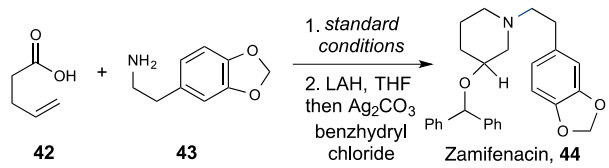


Figure 5. Synthesis of Zamifenacin.

benzene backbone in the lactam ring was also tolerated with good efficiency (Scheme 3, product **28**). 4-Pentenoic acids with 3-methyl, -phenyl, or -dimethyl substituents afforded the lactam products in slightly diminished yields, presumably due to increased steric demand during the lactam formation step (Scheme 3, products **29**–**31**). Notably, for products **29** and **30**, excellent diastereoselectivities were observed. Initially, the α-disubstituted 4-pentenoic acids proved to be challenging substrates, producing the amino lactone intermediates in high efficiency but with trace lactam formation. However, the addition of $AlMe_3$, as a Lewis acid in a second step, could facilitate the intramolecular cyclization to generate the lactam products in reasonable yields (Scheme 3, products **32**–**34**).[27] In this manner, interesting spirocyclic lactam structures, containing both carbo- and heterocyclic motifs, can be obtained. In addition, a fused bicyclic lactam product was also produced smoothly with excellent diastereoselectivity (Scheme 3, product **35**).

We have conducted a number of experiments to gain further insights into the reaction mechanism. First, the catalytic cycle is initiated with a single-electron oxidation of the iodide to triiodide, which was confirmed by our UV–vis studies by mixing the copper(II) salt with KI (Figure 2). The equilibrium between the triiodide and iodine simply functions as an iodine "reservoir" that (1) minimizes the presence of iodine and (2) maintains the copper catalyst at the Cu(I) oxidation state. This phenomenon explains the origin of compatibility to all of the nucleophiles present in the reaction. Meanwhile, the carboxylate, either a copper carboxylate or ammonium carboxylate, can proceed via two possible pathways: (1) a copper-catalyzed *syn* oxycupration followed by iodine trapping[28] or (2) an *anti* iodolactonization with the in situ-generated iodine at a low concentration. To understand the alkene addition process, we synthesized deuterium-labeled substrate **A**, a substrate commonly used to probe the *syn* or *anti* nature of the alkene addition step based on stereochemical analysis.[29] Because the amination step is a stereoinvertive S_N2 step and the intramolecular lactam formation has no bearing on the stereochemical outcome, the stereochemistry of the alkene addition step can be traced through the final product stereochemistry. If the reaction followed pathway (2) with the iodine-catalyzed process, product **36** would be generated (Figure 3). On the other hand, with pathway 1 of a copper-catalyzed alkene addition process, the resulting product would be **37**. We directly compared the stereochemical outcome of this reaction with the iodine-mediated reaction. In both cases, we observed product **36** as the only diastereomer, suggesting that the anti-addition process across the alkene is most likely operative here. Therefore, our deuterium-labeled substrate study here strongly supports iodine-promoted pathway (2).

To illustrate the nature of the carboxylate that underwent the iodolactonization, we have conducted the reactions as shown in Figure 4. When $Cu(OTf)_2$ was used as the catalyst, only 3% iodolactone product was observed. However, the addition of 1 equiv of non-nucleophilic amine base, diisopropylamine (DIPA), restored the capacity to conduct the iodolactone formation. When $Cu(OAc)_2$ was used as the catalyst, no base was needed to generate the iodolactone product in 65% yield. These data suggest that an initial ligand exchange on the copper catalyst was necessary to facilitate the copper catalyst turnover. Furthermore, a presynthesized copper carboxylate **38** could also generate the iodolactone product in 48% and 76% yields under both anaerobic and aerobic conditions, respectively.[30] These data, collectively, suggest that the formation of copper carboxylate is crucial for the reaction turnover in the iodolactonization process.

With all of this information, a summary for our proposed mechanism is shown in Scheme 4. Oxidation of the iodide by the Cu(II) catalyst generated the triiodide, which, in this case, functions as an iodine reservoir for slow iodine release. Either the copper or ammonium carboxylate then reacts with iodine to produce iodolactone **39**. Amine displacement of **39** then affords amino lactone **40**, which was also observed in the cases for products **32**–**34**. Subsequent lactam formation can occur spontaneously to provide desired lactam product **3**.[31] Simultaneously, the reduced Cu(I) catalyst can undergo ligand exchange to generate requisite Cu(I) carboxylate **41** for the ensuing aerobic oxidation with the proton sources released from the formation of the lactam. In this case, the aerobic oxidation process not only regenerates the active Cu(II) intermediate but also functions as an acid sponge to free up more amine nucleophiles in the reaction (Scheme 4). Discernible features of this dual catalytic approach include the utilization of a triiodide–iodine equilibrium and a benign oxidant (O_2) with water as the byproduct.

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To highlight the synthetic utility of this reaction, we turned our focus to its application in pharmaceutical synthesis. In this regard, we targeted (±)-Zamifenacin, a potent gut M3 selective anti-muscarinic drug (Figure 5).[32] The synthesis was carried out with commercially available alkenoic acid **42** and amine **43**. The reaction proceeded smoothly to generate the corresponding lactam product in 52% yield. LAH reduction of the lactam product directly followed by S_N1 with benzhydryl chloride and Ag_2CO_3 produced the desired (±)-Zamifenacin **44** in 58% yield in two steps.

In summary, we have demonstrated a dual catalytic protocol of copper and iodide catalysis for the aerobic oxyamination of alkenes with electron-rich amines and acids. This oxyamination protocol afforded a formal [5+1] annulation process via multiple C−O and C−N bond formations. Privileged lactam structures with a broad scope were synthesized in a single operation. This reaction was further highlighted in the synthesis of a pharmaceutical Zamifenacin. Finally, the mechanistic insights demonstrated here provided interesting iodide oxidation features for future reaction designs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04432.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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