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Copper-Catalyzed Amino Lactonization and Amino Oxygenation of Alkenes Using *O*-Benzoylhydroxylamines

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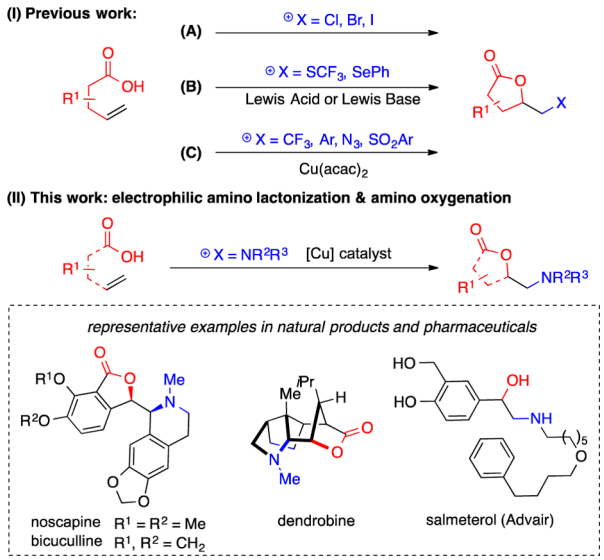
Supporting Information

ABSTRACT: A copper-catalyzed amino lactonization of unsaturated carboxylic acids has been achieved as well as the analogous intermolecular three-component amino oxygenation of olefins. The transformation features mild conditions and a remarkably broad substrate scope, offering a novel and efficient approach to construct a wide range of amino lactones as well as 1,2-amino alcohol derivatives. Mechanistic studies suggest that the reaction proceeds via a distinctive *O*-benzoylhydroxylamine-promoted electrophilic amination of alkenes.

Electrophilic functionalization of unsaturated carboxylic acids has proven to be a powerful strategy toward synthesis of highly valued lactones (Scheme 1, I). For example, halolactonization of unsaturated carboxylic acids by electrophilic halides has been extensively studied for the synthesis of 5-halomethyl-γ-lactones (Scheme 1, A).[1] The use of other electrophiles to construct diversely functionalized lactones has also attracted great interest. With Lewis acid or Lewis base, chalco-lactonization has been achieved using sulfur and selenium electrophiles (Scheme 1, B).[2] Moreover, an elegant copper-catalyzed lactonization strategy has been developed with electrophilic CF_3, aryl, azide, and sulfonyl groups (Scheme 1, C).[3] Yet amino electrophile-promoted lactonization is absent, despite the importance of amino lactones and its related 1,2-amino alcohol derivatives in organic synthesis and medicine (Scheme 1).

Scheme 1. Electrophilic Functionalization of Alkenes for the Syntheses of Valuable Lactones



Herein, we report *O*-benzoylhydroxylamines as a new type of electrophile for copper-catalyzed amino lactonization and the corresponding intermolecular alkene amino oxygenation with carboxylic acids (Scheme 1, II). Despite remarkable advances in metal-catalyzed amination using *O*-benzoylhydroxylamines as electrophilic amino trapping agents,[4] there are no examples of *O*-benzoylhydroxylamines for the initial electrophilic activation of alkenes, to the best of our knowledge.[5] This report describes the first examples of *O*-benzoylhydroxylamine-initiated alkene difunctionalization as a rapid and efficient access to amino lactones[6] and 1,2-amino alcohol derivatives,[7] which represent an important class of structural motifs prevalent in natural products and pharmaceuticals (Scheme 1).[8] Currently, the syntheses of amino lactones rely on laborious and, in many cases, ineffective multiple-step sequences. With amino lactones as versatile synthetic intermediates, this method also offers a unique entry to many valuable scaffolds such as tetrahydrofurans and tetrahydropyrans.[9] Furthermore, the dual role of *O*-benzoylhydroxylamines as an oxidant and amino source in the reaction is advantageous. It eliminates the need of external oxidants and offers a general amino precursor, enabling the direct introduction of electron-rich amines that remain as a challenge in current metal-mediated oxyamination of alkenes.[7]

Our studies began with the amino lactonization reaction for the formation of **3a** using unsaturated carboxylic acid **1a** and 4-benzoyloxymorpholine **2a** as model substrates (Table 1). In the absence of a catalyst, both **1a** and **2a** were recovered, and no desired product **3a** was obtained (entry 1). Copper salts were found effective to promote the desired transformation, with $Cu(OTf)_2$ serving as the most effective catalyst in 1,2-dichloroethane at 80 °C (entries 2−7). Upon the examination of different ligands (entries 8−12), $Cu(OTf)_2$/bathocuproine (BCP) proved to be the most general and efficient catalytic system and was chosen as standard conditions (entry 12).[10]

With these established conditions, we examined the alkene scope of this amino lactonization transformation with **2a** as the standard *O*-benzoylhydroxylamine (Table 2). 2-Vinylbenzoic acids, such as **1a**−**d**, all underwent 5-*exo* cyclization and readily afforded the desired amino lactones (entries 1−4). The efficient formation of **3e**−**h** illustrated that either electron-rich or -deficient substituents were tolerated on the aryl ring (entries

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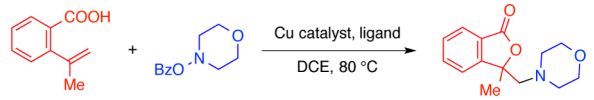
Table 1. Optimization for Copper-Catalyzed Amino Lactonization of Unsaturated Carboxylic Acid 1a[a]



entry	catalyst	ligand	3a (yield)[b]
1	–	–	0
2	$Cu(OTf)_2$	–	57
3	$Cu(OAc)_2$	–	39
4	$Cu(eh)_2$	–	38
5	$Cu(acac)_2$	–	21
6	$CuCl_2$	–	40
7	CuOAc	–	36
8	$Cu(OTf)_2$	BINAP	54
9	$Cu(OTf)_2$	bipyridine	86
10	$Cu(OTf)_2$	di(2-pyridyl)ketone	77
11	$Cu(OTf)_2$	phenanthroline	84
12	**$Cu(OTf)_2$**	**bathocuproine (BCP)**	**84 (75)**[c]

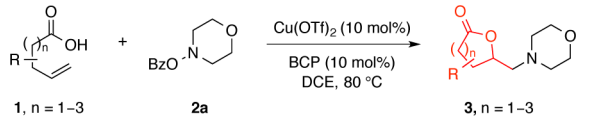
[a]Conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (2.0 equiv), catalyst (10 mol %), ligand (10 mol %), DCE (1.0 mL), 80 °C. [b]Yields determined by ^{1}H NMR with CH_2Br_2 as an internal standard. [c]Isolation yield in parentheses. eh = 2-ethylhexanoate, acac = acetylacetonate.

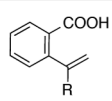
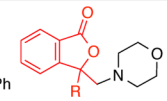
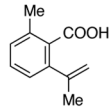
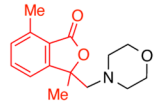
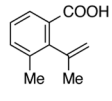
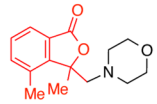
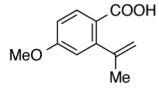
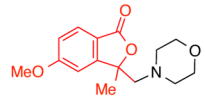
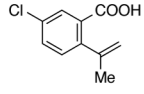
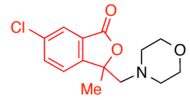
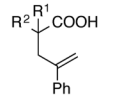
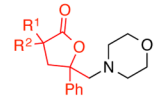
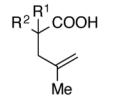
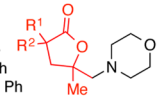
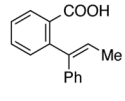
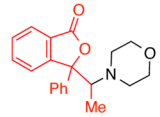
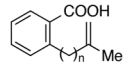
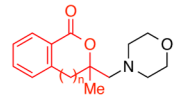
5−8). Besides aromatic substrates, the amino lactonization was compatible with aliphatic acids for the formation of lactones **3i**−**n** (entries 9−14).[11] Note that this transformation was successful even for olefin substrates containing no backbone elements to favor cyclization (**1i** and **1k**). Furthermore, internal alkene **1o** was a viable substrate, providing **3o** in 99% yield (entry 15). This result was remarkable as internal alkenes are challenging in metal-catalyzed alkene difunctionalization due to competing β−H elimination issues.[4o,12] Finally, this transformation was amenable for the formation of 3,4-dihydroisocoumarin **3p** and even seven-membered oxepanone **3q** (entries 16 and 17). Overall, this amino lactonization reaction proved to be effective on a broad scope of olefin substrates that encompass diverse substitutions on both alkenes and backbones.

The scope of *O*-benzoylhydroxylamines **2** was examined in the reactions with **1a** and **1p**, for the formation of γ-lactones **4** and δ-lactones **5**, respectively (Table 3). Six- membered cyclic *O*-benzoylhydroxylamines all readily participated in the amino lactonization reaction to afford **4a**−**d** and **5a**−**d**. The reactions of seven-membered *O*-benzoylhydroxylamines derived from 1,4-diazepane and azepane provided the desired lactones **4e**−**f** and **5e**−**f**, albeit in reduced yields, similar to the reactions with five-membered *O*-benzoylhydroxylpyrrolidine in the formation of **4g** and **5g**. In addition, acyclic hydroxylamines derived from *N*,*N*-diethylamine and *N*-methyl-*N*-benzylamine were both viable amino precursors for the formation of γ- and δ-lactones **4h**−**i** and **5h**−**i**. The higher efficiency observed for the formation of γ-lactones **4** than δ-lactones **5** indicates that this transformation was influenced by the rate of the nucleophilic lactonization, especially in the reactions of highly reactive *O*-benzoylhydroxylamines.[4o]

To obtain mechanistic insights on this amino lactonization reaction, we conducted a series of control experiments (Scheme 2). First, both stereoisomers of 2-styrylbenzoic acid, (*E*)- and (*Z*)-**1r**, were subjected to the reaction with **2a** under standard conditions. Both reactions provided a trace amount of **3r**, yet with **3r′** resulting from *endo*-lactonization as the major product. Strikingly, the *endo* product **3r′** was only observed in *anti*-

Table 2. Alkene Scope of Amino Lactonization[a]



entry	alkene		product		yield (%)[b]
1		**1a**, R = Me **1b**, R = H **1c**, R = Ph **1d**, R = 4-Cl-Ph		**3a** **3b** **3c** **3d**	75 43[c] 82 89
2					
3					
4					
5		**1e**		**3e**	77
6		**1f**		**3f**	75
7		**1g**		**3g**	73
8		**1h**		**3h**	72
9		**1i**, R^1 = R^2 = H **1j**, R^1 = R^2 = Me		**3i** **3j**	45[c] 53[c]
10					
11		**1k**, R^1 = R^2 = H **1l**, R^1 = R^2 = Me **1m**, R^1 = R^2 = Ph **1n**, R^1 = H, R^2 = Ph		**3k** **3l** **3m** **3n**	35[c] 30[c] 55 44 (dr = 1.2:1)[d]
12					
13					
14					
15		**1o**		**3o**	99 (dr = 1.4:1)[d]
16		**1p**, n = 1 **1q**, n = 2		**3p** **3q**	89 27
17					

[a]Conditions: **1** (0.4 mmol, 1.0 equiv), **2a** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), BCP (10 mol %), DCE (1.0 mL), 80 °C, 0.5−2 h. [b]Isolation yields. [c]Without BCP. [d]dr = diasteriomeric ratio, determined by ^{1}H NMR of the crude mixture.

stereochemistry, regardless of the olefin geometry of **1r** (*E* or *Z*). Likewise, the reactions of (*E*)- and (*Z*)-**1s** both led to the formation of *exo* product **3s** in 1.8:1 ratio of diasteroselectivity, along with a trace amount of *endo* product **3s′**. Furthermore, the reaction of **1t** containing two methyl groups at the β-position formed *exo* product **3t** in 30% yield along with 16% yield of 6-*endo* product **3t′**. All these results suggest the possible involvement of radical intermediates, which contributed to the observed regio- and stereoselective outcomes.

To further investigate the formation of radical intermediates, carboxylic acids **1u** and **1v**, containing a standard radical clock cyclopropane moiety at either vinyl position, were subjected to the reaction with **2a** (Scheme 2). The reaction of **1u** readily formed **3u** along with a trace amount of 6-*endo* product **3u′** detected by GCMS, while no ring opening product was observed (e.g., **6**). In the reaction of **1v**, lactone **3v** was observed along with compound **7**, which was likely formed from a ring opening and

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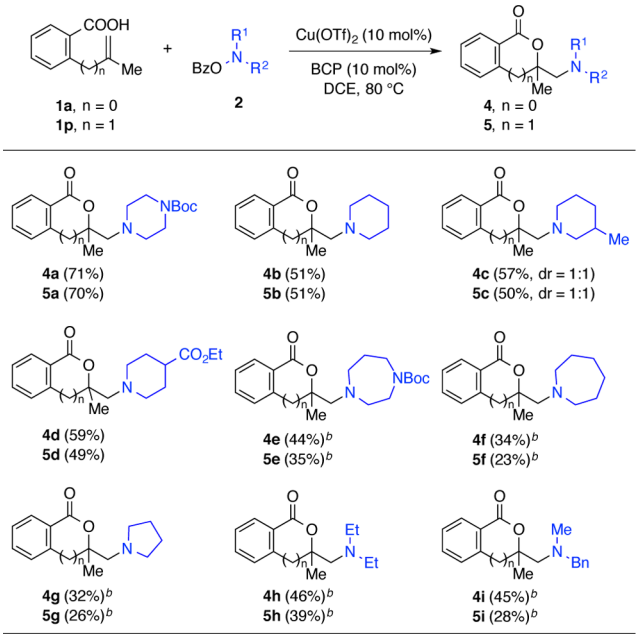
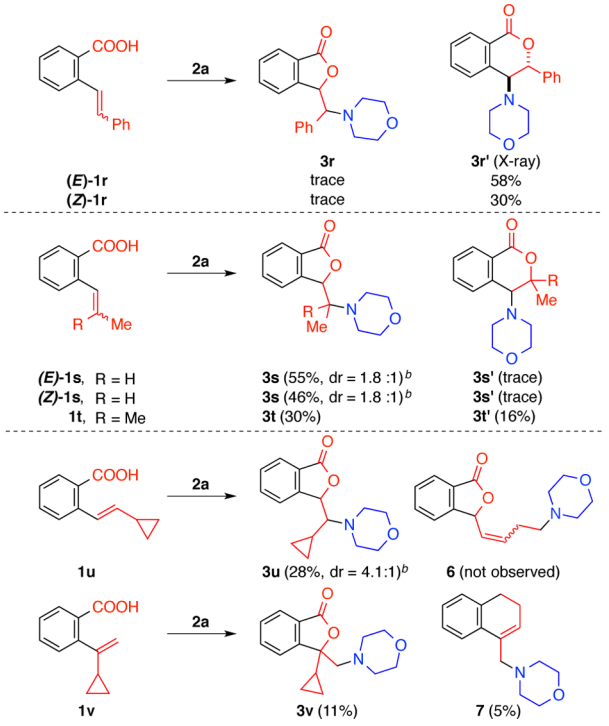
Table 3. Amine Scope of Amino Lactonization[a]



[a]Conditions: **1** (0.4 mmol, 1.0 equiv), **2** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), BCP (10 mol %), DCE (1.0 mL), 80 °C, 0.5−2 h. [b]Without BCP using 20 mol % $Cu(OTf)_2$. dr determined by ^1H NMR of the crude mixture.

Scheme 2. Mechanistic Investigations[a]

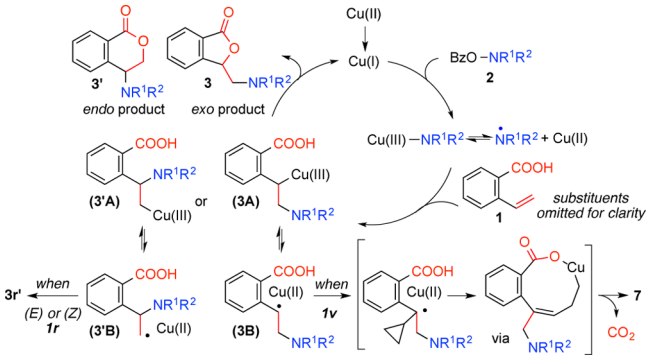


[a]Isolation yields shown. [b]dr determined by ^1H NMR of the crude mixture.

decarboxylation cascade (see Scheme 3). Finally, the reaction of **1a** and **2a** in the presence of a radical scavenger TEMPO led to the full recovery of **1a**, with no cyclization observed.[10]

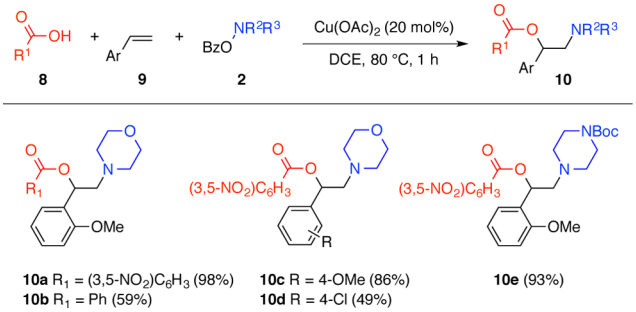
Based on the current results, the plausible reaction pathways of this copper-catalyzed amino lactonization are outlined in Scheme 3, although a detailed mechanism remains unclear. Upon the reaction of Cu salt with *O*-benzoylhydroxylamine, a highly reactive amino-Cu(III) complex would form and initiate an electrophilic amination of olefins via either a two- or one-electron-transfer mechanism.[13] The regioselectivity in the amination (**3A** vs **3′A**) is influenced by the vinyl substituents and would determine the formation of lactone products **3** or **3′** in a *5-exo* or *6-endo* cyclization manner. Furthermore, the amino lactonization reaction involves radical intermediates (e.g., **3B** and **3′B**), as implied by the formation of ring-opened product **7** from **1v** as well as **3r′** from both (*E*)- and (*Z*)-**1r**. Note that such electrophilic amination−initiation pathways have not been observed, even in the related Cu-catalyzed alkene diamination involving *O*-benzoylhydroxylamines.[4o]

Scheme 3. Plausible Reaction Pathways



Finally, we demonstrated the potential of this electrophilic amination strategy for the intermolecular amino oxygenation of alkenes **9** using carboxylic acids **8** and *O*-benzoylhydroxylamines **2** (Scheme 4). In this three-component version, 1,2-amino

Scheme 4. Three-Component Intermolecular Amino Oxygenation of Styrenes[a]



[a]Conditions: **8** (3.0 equiv), **9** (3.0 equiv), **2** (0.4 mmol, 1.0 equiv), $Cu(OAc)_2$ (20 mol %), DCE (2.0 mL), 80 °C, 1 h.

alcohols **10a−10b**, resulting from different carboxylic acids, were readily obtained under optimized conditions.[14] Simiarly, **10c** and **10d**, with either an electron-rich or -deficient group on styrenes, as well as *N*-Boc-piperazine **10e** derived from a different amino precursor, all formed efficiently. The remarkably higher efficacy observed on electron-rich styrenes is consistent with the proposed pathways for amino lactonization in Scheme 3, due to the involvement of more stable radical intermediates. These results also suggest the potential of *O*-benzoylhydroxylamine for a new alkene difunctionalization strategy incorporating diverse external nucleophiles.

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In summary, we have developed a copper-catalyzed amino lactonization of unsaturated carboxylic acids as well as the three-component intermolecular amino oxygenation of alkenes using *O*-benzoylhydroxylamines as an electrophilic amination agent. This transformation offers a unique and efficient approach to directly access a wide range of amino γ- and δ-lactones as well as 1,2-amino alcohol derivatives that are of great value in organic synthesis and medicine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02840.

Experimental details and data (PDF)
crystallographic data for **3r′** (CIF)

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Notes

The authors declare no competing financial interest.

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