Published in final edited form as:

ACS Catal. 2019 November ; 9(11): 10070–10076. doi:10.1021/acscatal.9b03076.

Copper-Catalyzed 1,2-Amino Oxygenation of 1,3-Dienes: A Chemo-, Regio-, and Site-Selective Three-Component Reaction with *O*-Acylhydroxylamines and Carboxylic Acids

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Abstract

A three-component reaction for 1,2-amino oxygenation of 1,3-dienes has been achieved using *O*-acyl hydroxylamines and carboxylic acids. The reaction occurs through copper-catalyzed amination of olefins followed by nucleophilic addition of carboxylic acids, offering high levels of chemo-, regio-, and site-selectivity. The method is effective for both terminal and internal 1,3-dienes, including those bearing multiple, unsymmetrical substituents. The amino oxygenation conditions also exhibited remarkable selectivity toward 1,3-dienes over alkenes, good tolerance of sensitive functional groups, and reliable scalability.

Graphical Abstract

- site- and regio-selective 1,2-addition
- selectivity toward 1,3-dienes over alkenes
- compatible with diverse, sensitive functional groups
- broad scope of 1,3-dienes and carboxylic acids
- >50 examples, including 2-mmol scale reaction in 79% yield

Keywords

amino oxygenation; 1,3-diene; copper catalysis

INTRODUCTION

Difunctionalization of 1,3-dienes is fundamentally important as a powerful strategy to introduce molecular complexity onto simple 1,3-diene skeletons and to create diverse, highly valuable compounds from readily available materials.¹ In comparison to significant advances

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, additional screening data, and characterization data including NMR spectra.

The authors declare no competing financial interest.

in the construction of new carbon–carbon bonds from diene difunctionalization,^{1d,2} selective installation of two different heteroatoms onto 1,3-dienes remains underdeveloped.^{3–4} For example, 1,2-amino oxygen containing skeletons are ubiquitously found in natural products, bioactive compounds, and functional materials.⁵ However, a modular and selective three-component amino oxygenation reaction remains lacking and challenging. There are several distinctive challenges to control site- and regioselectivity in such a modular amino oxygenation of 1,3-dienes (Scheme 1A). First, 1,3-dienes possess two possible olefins at which to react, leading to the potential for two distinct reaction sites. Secondly, the conjugated nature of 1,3-dienes allows for either direct 1,2-addition or conjugated 1,4-addition. Furthermore, unless the reaction occurs in a concerted fashion, a stepwise pathway for difunctionalization may allow for the resonance of its intermediate, leading to the loss of the original geometry of the unreacted olefin. Finally, a mixture of products resulting from a non-selective reaction often presents another difficulty in their separation under conventional means.

Several approaches have been developed to overcome these challenges in amino oxygenation of 1,3-dienes (Scheme 1B). For example, [4+2] cycloaddition of 1,3-dienes and nitroso compounds allows for exclusive 1,4-addition, preserving alkene geometry via a concerted process, yet suffers from a narrow substrate scope.⁶ Site-selective 1,2-addition reactions for terminal dienes or symmetrically-substituted dienes have been achieved via a sophisticated strategy using tethered oxygen/nitrogen sources, and afforded complementary regioselectivity with different metal catalysts.⁷ In another example, rhodium-catalyzed amino oxygenation was achieved with chemo- and site-selectivity through a diene-tethered nitrogen group yet gave a nearly equal mixture of 1,2- and 1,4-addition products.⁸ Despite these seminal developments, a three-component modular and selective amino oxygenation reaction incorporating a diverse range of 1,3-dienes remains lacking, and is greatly desired.⁹

In this work, we have developed a copper-catalyzed three-component 1,2-amino oxygenation reaction of 1,3-dienes, using *O*-acyl hydroxylamines as the electrophilic nitrogen source and carboxylic acids as the nucleophilic oxygen source (Scheme 1C). The transformation is envisioned to be initiated by a copper-catalyzed amination of dienes with electrophilic *O*-acyl hydroxylamines¹⁰ followed by the nucleophilic addition of carboxylic acids. Such amination/oxygenation pathways are distinctly different from previous 1,3-diene methods and thus would allow for a chemo-, regio- and site-selective addition to 1,3-dienes. This study has demonstrated that such an approach is effective on a wide range of 1,3-dienes, including those substrates that are known to be challenging such as those bearing multiple substituents and internal dienes. Interestingly, these amino oxygenation conditions show remarkable selectivity toward 1,3-dienes over non-conjugated olefins, which are also known to undergo similar amino oxygenation reactions.¹⁰ This method also tolerates a diverse scope of carboxylic acids, even those that contain sensitive functional groups. Studies on the reaction pathways offer further mechanistic insights on the radical intermediates and pathways under reaction conditions.

Our studies began with amino oxygenation of (*E*)-1-phenyl-1,3-butadiene **2a** as the model reaction, with pentafluorobenzoic acid **1a** as the nucleophilic oxygen source, and *O*-benzoyl-*N*-hydroxylmorpholine **3a** as the electrophilic nitrogen source (Table 1). We expected that

the reaction might form both 1,2- and 1,4-addition products **4a** and **4a'**, as well as **4b** resulting from the competitive trapping of benzoate which was released from the *O*-benzoylhydroxylamine. Using copper(II) acetate as a catalyst in dichloroethane (DCE) at 80 °C, the reaction with stoichiometric amounts of each reactant provided 1,2-addition product **4a**, with no detection of 1,4-addition product **4a'** and only a trace amount of benzoate trapped product **4b** (entry 1). Probing the stoichiometric amount of each reagent in this three-component reaction offered several notable observations. Increasing the equivalents of **1a** gave an increased amount of 1,4 trapping (entry 2), while increasing the equivalents of **2a** or **3a** led to more benzoate trapped product (entries 3 and 4). Increasing the equivalents of both **1a** and **2a** improved the reaction efficiency and also inhibited the undesired benzoate trapping, yet at the cost of poor 1,2- and 1,4-selectivity (entries 6 and 7). Remarkably, reducing the catalyst loading from 20 mol % to even 1 mol % did not diminish the reaction efficacy (entries 8 and 9). Decreasing the reaction temperature resulted in a longer time yet with little effect on the efficacy (entries 10 and 11). Surveying different solvents revealed that etherated solvents, such as dimethoxyethane (DME) and 2-methyltetrahydrofuran (2-MeTHF) significantly reduced the formation of 1,4-addition **4a'** (entries 12 and 13). Yet the use of exclusively 2-MeTHF as the solvent was found incompatible with many acid sources.¹¹ Finally, the conditions of a 1:1 co-solvent system of DCE/2-MeTHF were found more generally effective for this reaction (entry 14), which were adopted as standard conditions in our studies.

To examine the scope of this three-component reaction, we started with different carboxylic acids (Table 2). First, a series of substituted benzoic acids successfully delivered 1,2-addition products. These reactions exhibited good tolerance of functional groups, including nitro (**4c**), cyano (**4d**), alkoxy (**4e**), acetate (**4f**), and even diazo group (**4g**), albeit in reduced yields. Poly substituted benzoic acids were also effective (**4h–4i**), and even steric hindrance had no effect on the yield (*e.g.*, **4i**). A heteroaromatic carboxylic acid was also tolerated (**4j**). We noticed that the reaction with benzoic acid gave **4b** in a slightly higher yield of 76% than others. Thus, we decided to probe if matching the leaving group on the *O*-benzoylhydroxylamine with the corresponding carboxylic acid nucleophile could improve the yield. The use of pentafluoro-benzoyl-derived **3b** in the reaction of matching acid **1a** showed no effect on the formation of **4a**. However, using 3,4,5-trimethoxybenzoyl-derived **3c** in the reaction of matching acid **1h** led to a notable increase in the formation of **4h**, when compared to using the standard **3a**, from 63% to 76% yield. We next evaluated this reaction with a broad range of diversely functionalized carboxylic acids. Acrylic acid and *E*-cinnamic acid proved compatible in the reaction to form **4k–4l**, with the alkene group intact. Diene-bearing sorbic acid afforded the desired product **4m** while the poor yield suggested the conjugated diene system may undergo side reactions under these conditions. Even propiolic acid gave rise to the desired product **4n**, with the terminal alkyne tolerated without the canonic activation pathway under the reaction conditions.¹² Simple alkyl carboxylic acids were found capable of providing desired products **4o–4p** in modest yields. When matching acid-derived **3d** was used instead of **3a** for the formation of **4p**, an increased yield was also observed. Functionalized alkyl-derived carboxylic acids were also tested, including alkyl halides (**4q**), thioethers (**4r**), and ketones (**4s–4t**). Even acids bearing sensitive functional groups that are known to interfere with transition metals via strong coordination,¹³ such as

cyclic disulfide lipoic acid (**4u**), oxetanes (**4v**), and amino acid derivatives (**4w–4x**), were all effective. Finally, the use of crushed ibuprofen tablets in the reaction afforded desired product **4y** in 46% yield, which proved the practicality of this transformation and its good tolerance of impure material.

We briefly examined the scope for *O*-benzoyl-hydroxylamines in the reaction (Table 3). Similar to the alkene amino oxygenation reactions from our previous studies,¹⁰ piperazine and piperidine derivatives proved to be the most compatible in the reaction (**5a–5c**). Acyclic amines such as *N*-methylbenzyl amine (**5d**), *N*-methylphenethyl amine (**5e**), and diethyl amine (**5f**) were also compatible, whereas highly sterically-hindered dicyclohexylamine was ineffective (**5g**). Functional groups on the nitrogen source were well tolerated, such as carbamate (**5a**) and ester (**5b**).

The scope of dienes was extensively examined in the amino oxygenation reaction with **3a** (Table 4). In comparison to the model substrate 1-phenyl-1,3-butadiene **2a**, different substituents on the aryl group were examined (**6a–6j**). While *para*-substitution with methyl (**6a**), phenyl (**6b**), or electron-withdrawing halogens (**6c–6f**) showed little effect on the reaction, electron-donating groups, such as dimethylamino (**6c**) and methoxy (**6d**) were found to be deleterious. Substituents at the *meta* position, either electron donating methoxy (**6g**) or electron-withdrawing trifluoromethyl (**6h**), showed no influence. For substituents at the *ortho* position, electron-donating methoxy (**6i**) showed a decrease in the reaction yield, while electron-withdrawing chloro (**6j**) did not. Besides 1-aryldienes, 1-alkyl-substituted dienes were tested, providing 1,2-addition products exclusively (**6k–6l**). Note that 1-methyl-1,3-diene gave a mixture of **6l** and **6l'** with a 5:1 ratio of site selectivity, favoring the 1,2-addition at the unsubstituted olefin as **6a–6j**. Interestingly, the reactions with 2-substituted dienes successfully afforded 1,2-addition products (**6m–6o**), while site selectivity favored the branched olefin. The site selectivity of **6a–6l** may largely result from steric influence of substituent, which may impede the initial amination of the olefin. Rather, the site selectivity observed in the cases of **6m–6o** might be influenced by the nucleophilic trapping step that favors the more stable intermediate bearing more substituents. Next, disubstituted 1,3-dienes were examined. The reaction with 2,3-dimethyl-1,3-butadiene **2p** successfully provided 1,2-addition product **6p** while the reaction with 1-phenyl-3-methyl-1,3-butadiene failed to deliver desired product **6q**. The reactions with 1,2-, and 1,2-disubstituted-dienes all gave amino oxygenation products **6r–6t** with 1,2-addition selectively occurring at the less substituted olefin site. It is worth noting that in the reaction forming **6r**, no amino oxygenation was observed on the isolated alkene, suggesting different reactivity between 1,3-dienes and isolated alkenes.

Reaction of internal 1,3-dienes, one of the most challenging and complex systems, were next evaluated for efficiency and selectivity. First, the formation of **6u** in 60% yield was encouraging, as the comparable efficacy between **6u** and **6t** suggests that the presence of methyl group did not impede the reaction. The reactions of terminally fully substituted dienes also delivered products **6v–6w** successfully. The formation of 1,4-addition product **6w'** was observed (structure not shown), which likely resulted from the isomerization of 1,2-addition product **6w**.¹¹ A 1,4-non-symmetrically disubstituted-1,3-diene was examined to

evaluate the selectivity between two differentially-substituted olefin sites. Despite the low yield, the formation of 1,2-addition products **6x** and **6x'** in a 3.5:1 ratio suggested site selectivity in favor of the methyl-substituted olefin, possibly because of the steric difference. Among an extensive range of 1,3-dienes tested, electron-deficient dienes were found ineffective, such as ethyl sorbate (**6y**).

During our studies, we noticed some difference in reactivity of *E* vs *Z* dienes in their reactions (Scheme 2). The reaction of a methyl-substituted *E* isomer (**E-2z**) produced 1,2-addition products **6z** in a 7:1 ratio of the *E*:*Z* isomers along with recovery of the *E* diene. The reaction of **Z-2aa**, a chloromethyl-substituted *Z* isomer, showed no detection of 1,2-addition product (**6aa**) and gave nearly quantitative recovery of **Z-2aa**. These results indicate the absence of reversibility in the amino addition to the diene and possibly the potentially impotent nature of this *Z*-isomer under reaction conditions.

We next examined the selectivity between 1,3-dienes and alkenes under copper-catalyzed amino oxygenation conditions by a number of competition experiments (Scheme 3). First, in the reaction with 4-vinylbenzoic acid, 4-vinylbenzoate **4z** was formed as 1,2-addition to diene **2a** while the styrene-addition product **7** was not observed (Scheme 3A). Secondly, in the reactions of 2-vinylbenzoic acids, **4aa** and **4ab** were formed as the 1,2-addition products to diene **2a**, in 58% and 55% yields, respectively (Scheme 3B). We detected only trace amounts of **8a** and **8b**, the amino lactonization products resulting from alkene addition. These results suggest that the intermolecular amino oxygenation of 1,3-diene **2a** occurs even faster than the intramolecular amino oxygenation of alkenes under such conditions. When both the model diene (**2a**) and styrene (**9**) were present under the reaction conditions, the diene addition product **4c** was formed with no detection of the alkene addition product **10** (Scheme 3C). Note that the formation of **4c** in 61% yield in this competitive experiment is comparable to its formation of 63% yield in the reaction with the absence of alkene **9** (Table 2). All these results suggest the remarkable selectivity of this amino oxygenation reaction favoring 1,3-dienes over alkenes, even when expedient intramolecular trapping of alkenes was possible.

Our previous studies on copper-catalyzed amino oxygenation of alkenes using *O*-benzoylhydroxylamines have suggested the presence of radical pathways under similar reaction conditions.¹⁰ To probe the involvement of any possible radical intermediates in the reaction of dienes, the reaction of diene **2a** was performed in the presence of radical scavengers (Scheme 4). With the presence of one equivalent of butylated hydroxytoluene (BHT) as a radical scavenger in the reaction of **2a**, the desired product **4c** was obtained in a decreased 30% yield, along with the formation of two BHT-derived products, **11** and **12**. The control experiments in the absence of diene **2a**, acid **1c**, or both were conducted. The formation of **12** was confirmed independent from the reaction of 1,3-dienes. On the other hand, the formation of the 1,4-aminocarbonation addition product **11** suggested the formation of an allylic radical intermediate after the initial amination step of 1,3-diene and the involvement of resonance through the conjugated system, providing additional insights on the pathways in this reaction. Further studies for a better understanding of observed selectivity will be disclosed in future work.

Finally, a representative example for the synthetic utility of this method is highlighted in its application for a rapid entry to amino alcohol **13**, by the amino oxygenation of diene **2a** and subsequent hydrolysis (Scheme 5). Note that the formation of **13** in 79% yield on the 2.0 mmol-scale reaction is more efficient than the reaction on the 0.2 mmol-scale in 68% yield, further demonstrating the scalability and practicality of the reaction protocol.

In conclusion, we have developed a copper-catalyzed, three-component 1,2-amino oxygenation reaction of 1,3-dienes. The reaction proceeds through a copper-catalyzed amination of the diene followed by a rapid nucleophilic trapping by the carboxylic acid. The amino oxygenation conditions show remarkable selectivity toward 1,3-dienes over alkenes, excellent tolerance of sensitive functional groups, and reliable scalability. This method is general and applicable to an extensive range of terminal and internal 1,3-dienes as well as a wide range of carboxylic acids, presenting high levels of chemo-, regio-, and site-selectivity. Further studies for a better understanding of the selectivity will be disclosed in our future work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The authors acknowledge financial support from Duke University, the National Institutes of Health (GM118786), and the GAANN fellowship from US Department of Education (P200A150114) to B.N.H. The authors thank Dr. Peter Silinski (Duke University Mass Spectrometry Facility) and Dr. Michael Walla (University of South Carolina Mass Spectrometry Facility) for assistance with high-resolution mass spectrometry. The authors thank Dr. Ben Bobay and the Duke University NMR Center for assistance with NMR experimentation. The authors also thank Colton Ku and Jiaqi Zhao for collaborative efforts on *O*-benzoylhydroxylamine synthesis.

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(A) Difunctionalization of 1,3-dienes: challenges in site- and regio-selectivity **(B) Current method: two-component reactions by tethering strategy**

[4+2] cycloaddition: 1,4-addition

tethered nucleophile and electrophile: 1,2-addition

tethered diene and electrophile: both 1,2- and 1,4-addition

(C) This work: a three-component, modular reaction initiated by copper-catalyzed amination

Scheme 1.
Amino Oxygenation Reactions of 1,3-Dienes.

Scheme 2. Comparison of Diene Geometry in the Amino Oxygenation of 1,3-Dienes.

Ar = 3,5-dinitrophenyl. ^aRatio determined by ¹H NMR of the crude reaction. ^bAverage of two runs.

Scheme 3. Competition Experiments for the Amino Oxygenation of 1,3-Dienes or Alkenes.

Isolated yields as an average of two runs on 0.4 mmol scale. Ar = 3,5-dinitrophenyl. ^aND =

Not detected by GCMS. ^bObserved by ¹H NMR of the crude reaction (with the ratio of **4aa**:

8a >40:1). ^cObserved by GCMS.

Scheme 4. Radical Trapping Experiments for the Amino Oxygenation of 1,3-Dienes.
Isolated yields as an average of two runs on 0.4 mmol scale. Ar = 3,5-dinitrophenyl.

Scheme 5.

Rapid Synthesis of the 1,2-Amino Alcohol via Amino Oxygenation Reaction/Hydrolysis Sequence.

Table 1.

Condition Optimization for 1,2-Amino Oxygenation of (*E*)-1-Phenyl-1,3-butadiene.

entry	1a	2a (equiv)	3a	Cu(OAc) ₂ (mol%)	solvent	temp (°C)	time (h)	4a ^b (%)	4a' ^b (%)	4b (equiv) ^c
1	1	1	1	20	DCE	80	2.0	36	0	0.07
2	3	1	1	20	DCE	80	0.5	36	19	0.01
3	1	3	1	20	DCE	80	2.0	53	1	0.12
4	1	1	3	20	DCE	80	0.5	31	0	0.27
5	1	3	3	20	DCE	80	2.0	48	0	1.53
6	2	3	1	20	DCE	80	0.5	50	12	0
7	3	3	1	20	DCE	80	0.5	46	20	0
8	2	3	1	10	DCE	80	0.5	51	16	0
9	2	3	1	1	DCE	80	0.5	47	18	0
10	2	3	1	1	DCE	60	2.5	48	21	0
11	2	3	1	1	DCE	40	24	40	21	0
12	2	3	1	1	DME	60	7	55	4	0
13	2	3	1	1	2-MeTHF	60	1.5	56	2	0
14	2	3	1	1	DCE/2-MeTHF (1:1)	60	5	62 ^d	7	0
15	2	3	1	0	DCE/2-MeTHF (1:1)	60	5	0	0	0

^aReactions on 0.2 mmol scale.^bDetermined by ¹⁹F NMR of the crude reaction with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard.^cDetermined by ¹H NMR of the crude reaction with dibromomethane as a quantitative internal standard.^dIsolated yield.

Table 2.

Scope of Carboxylic Acids in Amino Oxygenation of 1,3-Dienes.

Isolated yields as an average of two runs on 0.4 mmol scale.

^aRun with 3b.^bRun without 2-MeTHF.

^cRun with **3c**.

^dRun with **3d**.

^eDetermined by chiral HPLC of the crude reaction.

^fRun with crushed ibuprofen.

^gDetermined by ¹H NMR of the crude reaction.

Table 3.Scope of *O*-Benzoylhydroxylamines in Amino Oxygenation of 1,3-Dienes.

Isolated yields as an average of two runs on 0.4 mmol scale. Ar = 3,5-dinitrophenyl.

^aRun without 2-MeTHF.

Table 4.

Scope of Dienes in the Amino Oxygenation of 1,3-Dienes.

$\text{Ar-COOH} + \text{2 (3 equiv)} + \text{3a (1 equiv)} \xrightarrow[\text{DCE/2-MeTHF, 60 } ^\circ\text{C}]{\text{Cu(OAc)}_2 \text{ (1 mol \%)}} \text{6}$				
dienes bearing a terminal olefin				
6a, R = 4-Me, 52%	6b, R = 4-Ph, 56%	6c, R = 4-NMe ₂ , ND	6d, R = 4-OMe, trace	6e, R = 4-Cl, 57%
6f, R = 4-Br, 64%	6g, R = 3-OMe, 63%	6h, R = 3-CF ₃ , 53%	6i, R = 2-OMe, 43%	6j, R = 2-Cl, 57%
6k, 49% ^a	6l, 47% (5:1 <i>E/Z</i>) ^b	6m, R = Me, 73% ^c (6:1 <i>E/Z</i>) ^b	6n, R = CH_2CMe_2 , 61% ^c (3:1 <i>E/Z</i>) ^b	6o, R = Ph, 39% ^{a,c,d} (8:1 <i>E/Z</i>) ^b
6p, 49%	6q, ND	6r, 32% (1:3:1 <i>dr</i>) ^b	6s, 49% (3:1 <i>E/Z</i>) ^b	6t, 59%
internal dienes				
6u, 60% (1:1 <i>dr</i>) ^b	6v, R = Ph, 59% ^{c,e}	6w, R = Me, 76% ^c (8:1) ^b	6x, 26% (1.4:1 <i>dr</i>) ^b	6y, ND
			6x', 26% (3.5:1 <i>dr</i>) ^b	

Isolated yields as an average of two runs on 0.4 mmol scale. Ar = 3,5-dinitrophenyl.

^aSecond run on 0.2 mmol scale.^bDetermined by ¹H NMR of the crude reaction.^cRun without 2-MeTHF.^dYield of major isomer.

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f_e Determined by chiral HPLC of the crude reaction.

f_f Starting from 1.2:1 *E:Z* diene.

f_g Ratio of 1.2:1.4 addition products.

f_h Determined by ^1H NMR of the crude reaction eluted through silica gel.