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Copper-Catalyzed Aerobic Oxidation of Hydroxamic Acids Leads to a Mild and Versatile Acylnitroso Ene Reaction

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Supporting Information

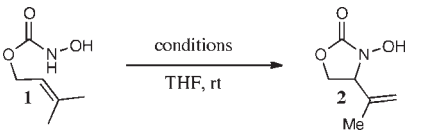
ABSTRACT: A mild formation of transient acylnitroso intermediates using a copper chloride catalyst and 1 atm of air as the terminal oxidant is described. The mild reaction conditions enable the inter- and intramolecular acylnitroso ene reaction with a wide range of functionalized alkene partners, as well as the first asymmetric variant. Notably, this transformation provides a practical and operationally simple method for effecting allylic amidation using an environmentally benign oxidant and a readily abundant transition metal.

Acylnitroso intermediates are exceptionally reactive electrophiles with a rich history in the hetero-Diels–Alder reaction.[1] Several variants of the acylnitroso Diels–Alder reaction have been developed, and since the pioneering report by Kirby in 1973, it has found widespread application in the synthesis of natural products.[2] In contrast, the acylnitroso ene reaction,[3] which can be used for the direct allylic amination of olefins, is vastly underdeveloped despite the synthetic utility of allylic amines for the construction of α- and β-amino acids, alkaloids, and carbohydrate derivatives.[4]

The most common method to conduct an acylnitroso ene reaction was independently developed by Keck[5] and Kirby.[6] Their elegant two-step transfer protocol generates acylnitroso intermediates by a thermo retro-cleavage of the corresponding Diels–Alder adducts. While Keck's and Kirby's two-step process allowed for the preliminary development of the acylnitroso ene reaction, it also revealed the main challenge. Due to their high reactivity, acylnitroso intermediates can only be generated in situ and thus are conveniently obtained from the oxidation of hydroxamic acid derivatives using periodate salts.[3] However, this in situ oxidation protocol commonly used in the Diels–Alder reaction is not compatible with the acylnitroso ene reaction because the initially formed hydroxylamine ene product is susceptible toward subsequent decomposition reactions such as oxidation, disproportionation, and elimination.[3a]

Notably absent from current acylnitroso ene methods are examples with functionalized alkene partners and the development of an asymmetric manifold. In addition, excess olefin is often required to obtain high yields of the ene product. A possible reason for the slow advance of acylnitroso ene reactions has been an inability to identify a general and practical oxidant.[7] In this Communication, we describe our initial efforts in this area using copper(I) chloride catalyst and air as the terminal oxidant for the in situ oxidation of *N*-hydroxycarbamates.[8] This new process provides straightforward access to a range of functionalized allylic hydroxycarbamates via the inter- and intramolecular acylnitroso ene reaction and enables the first intermolecular asymmetric acylnitroso ene reaction.

Table 1. Screening Reaction Conditions[a]



entry	catalyst	additive	oxidant	time	% yield[b]
1	$FeCl_3$	–	HOOH	3 h	25
2	$RuCl_3$	Et_3N	HOOH	6 h	53
3[c]	$NiCl_2$	–	HOOH	6 h	0
4	$CuCl_2$	–	HOOH	20 min	79
5	CuCl	–	HOOH	30 min	78
6	$CuCl_2$	–	air	144 h	68
7	CuCl	–	air	29 h	87
8	CuCl	pyridine	air	6 h	93
9	CuCl	DTBMP[d]	air	29 h	94
10[c]	CuCl	pyridine	–	48 h	0

[a] All reactions were performed with reagent-grade THF containing 250 ppm BHT inhibitor. The following amounts of reagents were used according to Table 1: 5 mol % catalyst, 120 mol % peroxide, 1.25 mol % pyridine, and 1.25 mol % DTBMP. [b] Isolated yields. [c] Starting material recovered. [d] DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

The recent work of Iwasa, Whiting, and others led us to initially focus on oxidation methods that relied on transition metals and stoichiometric peroxides as the terminal oxidant.[7b,9] A preliminary screen revealed copper salts in combination with hydrogen peroxide were optimal for the intramolecular ene reaction of *N*-hydroxycarbamate **1** (Table 1, entries 1–5). Treatment of **1** with 5 mol % copper(II) chloride and hydrogen peroxide gave the intramolecular ene product in up to 79% yield (entry 4). Unfortunately, obtaining consistent isolated yields proved problematic due to the rate of product decomposition under the reaction conditions.[10] Consequently, an alternative, milder method to oxidize the hydroxamic acids was sought.

After extensive screening, we discovered that 1 atm of air and 5 mol % copper catalyst at room temperature provided a mild oxidation system (Table 1, entries 6 and 7).[11] *Importantly, these conditions suppress the rate of ene product decomposition.*[10]

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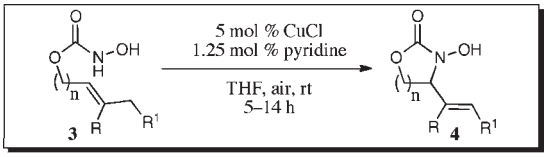
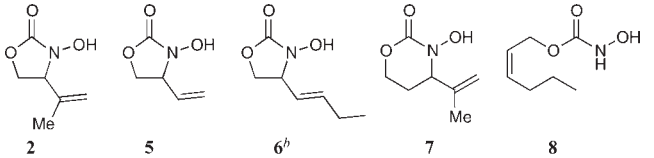
Table 2. Substrate Scope Studies for the Intramolecular Ene Reaction[a]





2	5	6[b]	7	8
93%	71%	96%[c] 3:1 (*E*:*Z*)	88%	0%[d]

[a] All reactions were performed with reagent-grade THF containing 250 ppm BHT inhibitor. [b] Product **6** resulted from the reaction of *trans*-2-hexenyl hydroxycarbamate. [c] The yield is a combined yield of both olefin isomers. [d] Starting material decomposed.

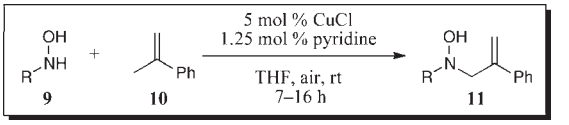
Furthermore, air is the ideal oxidant because it is readily available, inexpensive and the byproducts are environmentally benign.[12] Addition of catalytic pyridine ensured cleaner and more efficient reactions (entry 8). No rate enhancement was observed when 2,6-di-*tert*-butyl-4-methylpyridine was used, which suggests the role of pyridine is not simply as a base (entry 9). In addition, no reaction was observed under anaerobic conditions (entry 10).

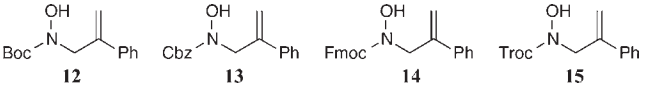
With the optimized reaction conditions (5 mol % copper(I) chloride, 1.25 mol % pyridine, reagent grade THF, air, rt), we investigated the scope of the intramolecular acylnitroso ene reaction (Table 2). The allylic and homoallylic nitrosoformate esters both cyclize by a Type I mechanism, according to Oppolzer and Snieckus's classification,[13] to construct the 2-oxazolidinone and 1,3-oxazin-2-one scaffold (**2**, **5**−**7**). Olefin geometry plays an important role and currently the intramolecular reaction does not accommodate substrates bearing a *Z*-alkene (**8**).

Having established a mild, single-pot method for the intramolecular acylnitroso ene reaction, we evaluated the bimolecular reaction which provides a simple method for effecting allylic amidation. Our investigations focused on *N*-hydroxycarbamates bearing protecting groups that were easy to prepare, commonly used in synthesis and could be orthogonally deprotected. Hydroxylamines protected with Boc, Cbz, Fmoc and Troc groups all participated in the intermolecular ene reaction in greater than 80% yield (Table 3). Significantly, with the exception of *tert*-butyl-*N*-hydroxycarbamate, comparable yields were also obtained with only 1.1 equivalents of α-methylstyrene. Based on reaction trends, *vide infra*, we currently believe the copper−air catalyst system is oxidizing the *N*-hydroxycarbamate and generating a transient acylnitroso intermediate. However, the nature of the copper-oxidant species and the oxidation mechanism require further studies. Under the aerobic oxidation conditions tetrahydrofuran can form peroxides, however, alternative solvents like 2-methyltetrahydrofuran (2-MeTHF) can be used to reduce the risk of peroxide formation.[14]

We chose to investigate the scope of the intermolecular ene reaction with 1.2 equiv of the alkene partner and the carbobenzyloxy (Cbz)-protected hydroxylamine (**16**) (Table 4). The reaction tolerated a series of alkene reaction partners and furnished allylic *N*-hydroxycarbamate derivates in moderate to excellent yields

Table 3. Substrate Scope Studies for the Intermolecular Ene Reaction[a]





AMS[b]	12	13	14	15
5 equiv ⟶	90%	87%	83%	83%
1.1 equiv ⟶	57%	80%	76%	81%

[a] Reactions were performed with reagent-grade THF containing 250 ppm BHT inhibitor. [b] AMS = α-methylstyrene.

(entries 1−9). The best results were generated from substrates with electron-rich olefins, which is consistent with other ene processes.[3] The reaction can also tolerate alkenes that are deactivated by electron-withdrawing substituents, as well as an alkene bearing a free hydroxyl group (entries 6−8). Geranyl acetate was used to further probe the reactivity of electronically differentiated alkenes (entry 9). The major product arose from reaction at the 6,7-double bond, since the allylic acetate electronically deactivates the 2,3-double bond (9:1 mixture was obtained). Similar to ArNO enophiles, the acylnitroso abstracts a hydrogen atom from the *geminal* alkyl group on the more substituted side of the alkene (entries 5−9).[3] In addition, 1-methyl-1-cyclohexene revealed the preference for acylnitroso enophiles to approach the alkene with a *skew* geometry. Hydrogen atom abstraction predominately occurred from the *twix* position (*twix:twin* ratio 6:1, entry 5),[15] consistent with typical ene reaction patterns.[3]

We next turned our attention to bimolecular reactions with tiglic acid derivatives because they provide rapid access to α,*β*-disubstituted amino acids. Direct methods to access this important structural motif are limited.[16] Nitroso reactions with tiglic acid derivatives, electron-deficient ene substrates, are often low yielding, especially with acylnitroso enophiles.[7a] Therefore, we were thrilled when we discovered that use of 1.2 equiv of methyl tiglate resulted in a 73% yield of the desired ene product (entry 10). The unprotected amide and acid derivates also afforded product in 72% and 37%, respectively (entry 11 and 12). The benzamide analogue underwent clean reaction; however, it cyclized in situ to form α-methylene isoxazolidinone (entry 13).

Inspired by these results we set out to control the absolute stereochemistry of the newly formed carbon−nitrogen bond by employing a chiral auxiliary on the tiglic acid derivative. Guided by Adam's work, we prepared the tiglic-acid with Oppolzer's derived sultam (**19**) and subjected it to our optimized reaction conditions (eq 1).[17]

To our gratification, the α-methylene isoxazolidinone (**20**) was produced in situ as predominately a single enantiomer (98.5:1.5 er) and Oppolzer's chiral auxiliary could be quantitatively recovered from the reaction. This represents the first example of an asymmetric intermolecular acylnitroso ene reaction.[18,19]

Single-crystal X-ray analysis was used to establish the *S*-configuration of the newly formed stereocenter in ene product **20** (Scheme 1).[20] To explain the observed selectivity we postulate a

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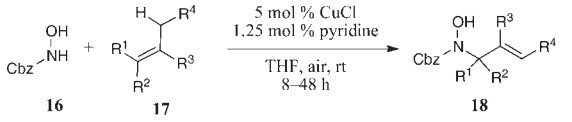
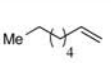
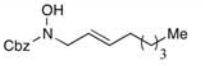
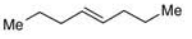
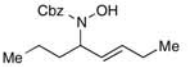
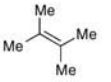
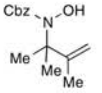
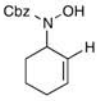
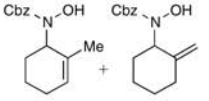
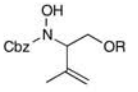
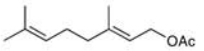
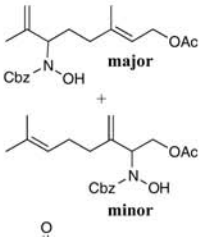
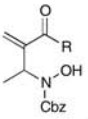
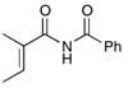
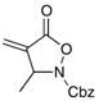
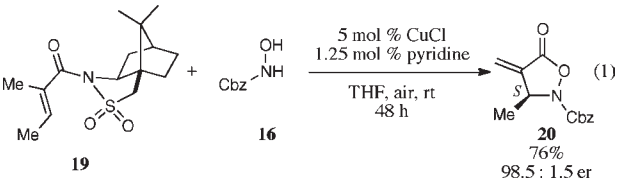
Table 4. Substrate Scope Studies for the Intermolecular Ene Reaction[a]



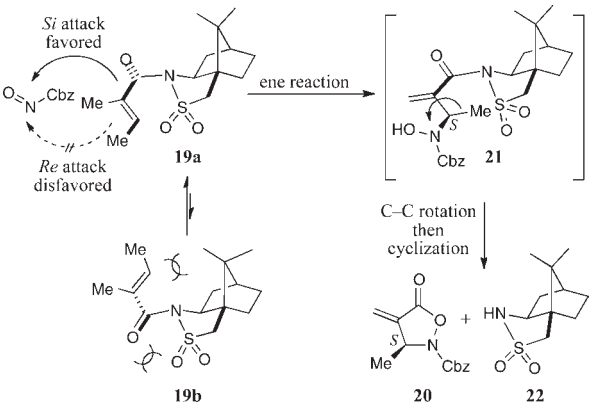
entry	olefin (1.2 equiv)	product	% yield[b] (E/Z)
1			42[c] (3:1)
2			73[c] (3:1)
3			98
4			71
5[d]			66[e] twix:twin ratio 6:1
			
6	R = H	R = H	85
7	R = Ac	R = Ac	77
8	R = TBS	R = TBS	88
9		 major + minor	87[e] ratio 9:1
			
10	R = OMe	R = OMe	73
11	R = NH_2	R = NH_2	72
12	R = OH	R = OH	37
13			78

[a] Reactions were performed with reagent-grade THF containing 250 ppm BHT inhibitor. [b] Isolated yields. [c] The yield is a combined yield of both olefin isomers. [d] A third product resulting from reaction at the *lone* position was also isolated in 5%; see Supporting Information for details. [e] The yield is a combined yield of both regioisomers.

reactive conformation of **19a** based on literature precedent.[17,21] The favored conformation features an *anti*-orientation between the carbonyl group and the sulfonyl functionality and an *s-trans* conformation of the carbonyl group and the double bond. A *skewed* approach of the enophile from the less hindered *Si*-face is



Scheme 1. Asymmetric Acylnitroso Ene Reaction and Proposed Stereochemical Model



favored because the sulfonyl oxygen atoms shield the *Re*-face. Since both enantiomers of the camphorsultam chiral auxiliary are commercially available, both stereoisomers of the ene product are available.

Preliminary studies demonstrate α-methylene isoxazolidinone compounds have similar biological activity as α-methylidene-γ-lactones and are potent against mouse L-1210 as well as human HL-60 and NALM-6 leukemia cell lines.[22] The precise mechanism of activity is currently unknown, but these compounds are believed to react as Michael-type acceptors with bionucleophiles. Despite their potential as possible novel therapeutics, access to α-methylene isoxazolidinone compounds is virtually unknown,[17,22] especially in an asymmetric sense. Moreover, isoxazolidinones represent well-established building blocks that can serve as synthons for α,β-disubstituted amino acids.[16]

In conclusion, we have developed mild reaction conditions for the in situ formation of transient acylnitroso compounds. The new strategy is operationally simple and provides a practical solution for the acylnitroso ene reaction and should allow for future advances in the field of acylnitroso chemistry. Reactions are performed with reagent grade THF, employ 1 atm of air as the terminal oxidant and the only byproduct is water. In addition, the mild reaction conditions enabled the development of the first asymmetric acylnitroso ene reaction using a traceless chiral auxiliary. Further investigations are underway to clarify the mechanism of this transformation and to explore the scope of acylnitroso chemistry.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental details and spectral data for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) While this manuscript was in review, a similar copper-catalyzed aerobic oxidation was reported and developed for the acylnitroso Diels–Alder reaction: Chaiyaveij, D.; Cleary, L.; Batsanov, A.; Marder, T. B.; Shea, K. J.; Whiting, A. *Org. Lett.* **2011** , DOI: 10.1021/ol201188d.

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(10) Ene product decomposition was observed within 30 min when **2** was resubjected to the reaction conditions found in entries 4 and 5. The rate of product decomposition was slighly slower when copper(I) chloride was used. Only slight product decomposition was observed for entry 8, even after 24 h. Overall, the degree of product decomposition varied depending on the nature of the substrate when stoichiometric peroxide was used as the terminal oxidant.

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(13) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed.* **1978**, *17*, 476.

(14) **13** was produced in 75% yield in 2-MeTHF. The reaction to form product **13** can also be conducted in methanol (68%), ethyl acetate (77%), and toluene (77%). Further studies with these more environmentally friendly solvents are currently under investigtion.

(15) (a) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791. (b) Quadrelli, P.; Romano, S.; Piccanello, A.; Caramella, P. *J. Org. Chem.* **2009**, *74*, 2301.

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