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Copper-Catalyzed Aerobic Oxidation of *N*-Substituted Hydroxylamines: Efficient and Practical Access to Nitroso Compounds

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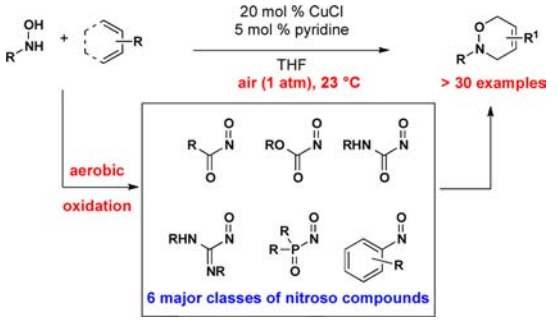
ABSTRACT



A general and efficient aerobic oxidation of *N*-substituted hydroxylamines is described. The mild reaction conditions employed provide a catalytic and sustainable alternative to stoichiometric oxidation methods to gain access to a range of nitroso compounds, such as acylnitroso, nitrosoformate, nitrosoformamide, iminonitroso, arylnitroso, and *P*-nitrosophosphine oxide derivatives in excellent yield.

Aerobic oxidations have recently emerged as a promising new area capable of replacing hazardous classical oxidation protocols.[1] From an economical and environmental viewpoint, molecular oxygen represents the ideal oxidant due to its low cost and lack of toxic byproduct.[2] Aerobic oxidation methodology has largely focused on the oxidation of alcohol-based systems, despite the important role oxidation chemistry plays in other functional group transformations.[3−5] For example, the analogous aerobic oxidation of hydroxylamines to nitroso compounds has remained underdeveloped, despite its potential synthetic utility and environmetal impact.

Hydroxylamines not only represent an important structural motif prevalent in natural products and biologically active molecules but also serve as a precursor to nitroso compounds. During the past four decades, nitroso compounds have been utilized as synthetically useful intermediates for organic synthesis.[6] In spite of the significant achievements, most methods used for the preparation of nitroso compounds still rely on the use of stoichiometric oxidants, which impose constraints on nitroso chemistry, such as functional group

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(3) For select examples using copper catalysts, see: (a) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044. (b) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433.

(4) For select examples using palladium catalysts, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854.

(5) For select examples using ruthenium catalysts, see: (a) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661. (b) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4538. (c) Zhan, B.-Z.; White, M. A.; Sham, T.-K.; Pincock, J. A.; Doucet, R. J.; Rao, K. V. R.; Robertson, K. N.; Cameron, T. S. *J. Am. Chem. Soc.* **2003**, *125*, 2195. (d) Mori, S.; Takubo, M.; Makida, K.; Yanase, T.; Aoyagi, S.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Chem. Commun.* **2009**, 5159.

(6) For select reviews on the use of nitroso compounds in synthesis, see: (a) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107. (b) Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (d) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131. (e) Iwasa, S.; Fakhruddin, A.; Nishiyama, H. *Mini-Rev. Org. Chem.* **2005**, *2*, 157. (f) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031. (g) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630.

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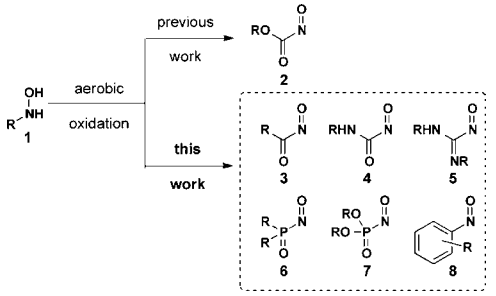
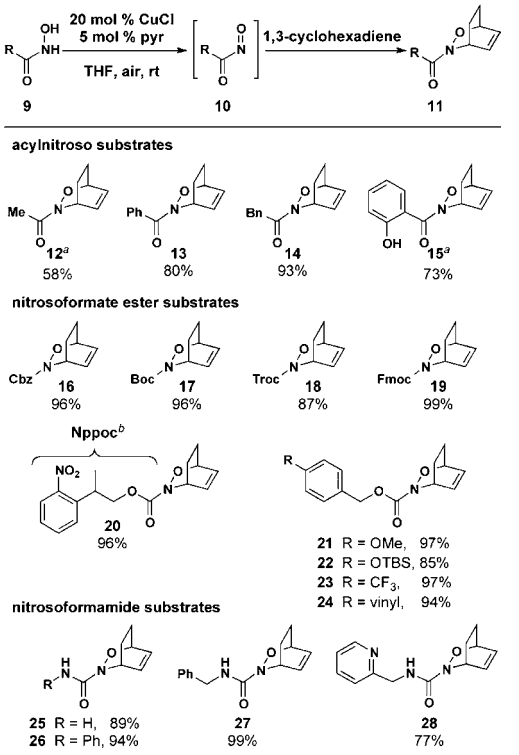
Scheme 1. Aerobic Oxidation of Substituted Hydroxylamines



Scheme 2. Aerobic Oxidation of *N*-Substituted Hydroxylamines



[a] Reactions conducted at 50 °C. [b] Nppoc = 2′-nitrophenylpropyloxycarbonyl.

compatibility, new reaction development, and removal of a potentially toxic oxidation byproduct.[7,8]

During our study of the nitroso ene reaction, we discovered an efficient, mild, and environmentally benign *in situ* process for the oxidation of *N*-hydroxycarbamates to nitrosoformate esters (Scheme 1).[9] This system, based on a Cu(I)-catalyzed aerobic oxidation, enabled the development of a practical and general acylnitroso ene reaction. Simultaneously, Shea, Whiting and co-workers independently reported a similar Cu(II)-catalyzed aerobic oxidation protocol.[10] Their process provides straightforward access to carbobenzyloxy(Cbz)-protected oxazines via a nitroso hetero-Diels–Alder (HDA) reaction. At present, aerobic oxidation protocols are limited to the formation of nitrosoformate derivatives (**2**), with the exception of two intramolecular reactions.[11] Given the importance of nitroso chemistry and the myriad of *N*-substituted nitroso compounds used in synthesis, such as acylnitroso **3**, nitrosoformamide **4**, iminonitroso **5**, *P*-nitroso phosphine oxide **6**, *P*-nitroso phosphate **7**, and arylnitroso **8** derivatives, the development of a general aerobic oxidation of *N*-substituted hydroxylamines is still desired.[6] Herein, we describe a Cu(I)-catalyzed oxidation of these major classes of substituted hydroxylamines at rt using air as the terminal oxidant (Scheme 1). The process provides a general, catalytic, and sustainable alternative to stoichiometric oxidation methods to gain access to a range of nitroso compounds.

Due to the instability and transient nature of nitroso compounds **2**–**7**, we elected to use the nitroso HDA reaction to investigate the generality of our catalytic aerobic oxidation protocol. It is well-known that nitroso compounds that are directly connected to an electron-withdrawing group (**2**–**7**) undergo rapid [4 + 2] cycloaddition reactions with conjugated dienes.[6] Furthermore, the HDA reaction is a valuable transformation that plays a central role in the synthesis of natural products and biologically active molecules. These advantageous properties were key factors in our selection of the nitroso HDA reaction as a platform to test our new oxidation methodology.

Our investigations began with our previously developed oxidation conditions (5 mol % CuCl, 1.25 mol % pyridine, reagent grade THF, and 1 atm air). Under these conditions, reactions with acyl-substituted hydroxylamines required long reaction times and proved impractical. However, it was found that the aerobic oxidation protocol was more efficient and tolerant of a variety of *N*-substituted hydroxylamines when the catalyst loading was increased to 20 mol % CuCl and 5 mol % pyridine (Scheme 2). Generally, compounds containing a more electron-withdrawing group on the nitrogen substituent reacted slower. Within the acyl-substituted series, *N*-hydroxyacetamide and *N*,2-dihydroxybenzamide afforded the lowest yields (58% and 73% respectively) and required heating to 50 °C to help facilitate the reaction. Under these conditions, decomposition of the acylnitroso species became competitive with the HDA reaction, which resulted in the lower yields.

(7) For select examples, see: (a) Kirby, G. W.; Mackinnon, J. W. M.; Sharma, R. P. *Tetrahedron Lett*. **1977**, *18*, 215. (b) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007. (c) Adam, W.; Bottke, N.; Krebs, O.; Saha-Möller, C. R. *Eur. J. Org. Chem*. **1999**, *1999*, 1963. (d) Gowenlock, B. G.; Richter-Addo, G. B. *Chem. Rev*. **2004**, *104*, 3315. For an asymmetric example, see: (e) Yamamoto, Y; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 4128.

(8) More recently, some progress has been made in metal-catalyzed oxidations with stoichiometric peroxides, see: (a) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *Chem. Commun*. **2001**, 1812. (b) Iwasa, S.; Tajima, K.; Tsushima, S.; Nishiyama, H. *Tetrahedron Lett*. **2001**, *42*, 5897. (c) Adamo, M. F. A.; Bruschi, S. *J. Org. Chem*. **2007**, *72*, 2666 and references therein.

(9) Frazier, C. P.; Engelking, J. R.; Read de Alaniz, J. *J. Am. Chem. Soc*. **2011**, *133*, 10430.

(10) Chaiyaveij, D.; Cleary, L.; Batsanov, A. S.; Marder, T. B.; Shea, K. J.; Whiting, A. *Org. Lett*. **2011**, *13*, 3442.

(11) Shea, Whiting and co-workers examined the intramolecular trapping of an acyl-substituted hydroxylamine and an acyl-substituted hydrazide.

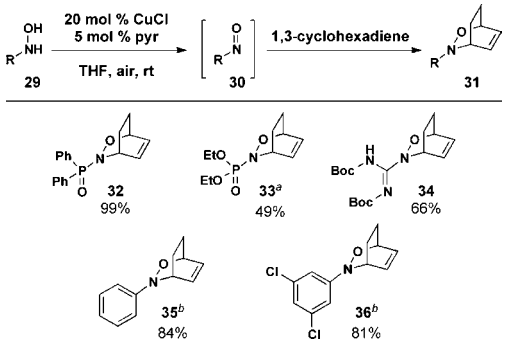
Hydroxylamines bearing orthogonal formate-based protecting groups, such as Cbz, Boc, Troc, Fmoc, and Nppoc, all participated in the acylnitroso HDA reaction in greater than 87% yield (**16**–**20**). Other Cbz-derived *N*-hydroxycarbamates bearing *p*-substituted functional groups proceeded under the reaction conditions with no complications. Nitrosoformamide compounds **25**–**28** reacted analogously and universally afforded products in high yield. Importantly, this includes the formation of hydroxyurea cycloaddition adduct **25** that previously resulted in low isolated yield when stoichiometric periodate oxidation was used.[12] Finally, the mild oxidation protocol can be performed successfully in a number of reagent grade solvents, such as 2-MeTHF, MeOH, EtOH, *i*-PrOH, EtOAc, and toluene (see Supporting Information for more details).

We next explored the capacity of these conditions to catalyze the aerobic oxidation of other known classes of *N*-substituted hydroxylamines (Scheme 3). Although less studied, HDA reaction with *P*-nitrosophoshine oxide and nitrosoamidine allows for the direct installation of phosphinamide and guanidine functional groups, which are prevalent in asymmetric catalysts and biologically active molecules.[13] In addition, King and co-workers have shown that *N*-phosphinoylnitroso compounds hydrolyze to liberate nitroxyl (HNO), the biologically important reduced form of nitric oxide.[14] Therefore, we were encouraged to observe that *N*-hydroxyphosphinamide and *N*-hydroxyphosphoramidate could be oxidized and readily trapped with 1,3-cyclohexadiene in excellent to moderate yield, **32** and **33**. Phosphorus migration is a known problem with *N*-hydroxyphosphoramidates and may contribute to the reduced yield of **33**.[14b] The oxidation protocol also worked with *N,N*′-bis-Boc-*N*″-hydroxylguanidine.[13c]

Arylnitroso compounds are benchtop stable and consequently much less reactive in the hetero-Diels–Alder reaction in comparison to acylnitroso compounds.[6g] In general, a considerable drop in yield is observed for these reactions. In addition, *in situ* oxidation of the arylhydroxylamine is usually avoided because it is difficult to prevent overoxidation and formation of a coupling byproduct, such as azoxybenzene.[15] Initially, subjection of phenylhydroxylamine to the optimized reaction conditions resulted in the exclusive formation of azoxybenzene. To circumvent this undesired side reaction, we added the arylhydroxylamine via syringe pump over the course of 2 h. Utilizing this protocol, the azoxybenzene formation could be minimized and the nitroso HDA adducts **35** and **36** were isolated in high yield (84% and 81%). This approach represents a viable solution to the arylnitroso Diels–Alder cycloaddition.

HDA trapping of transient nitroso species is not limited to the use of 1,3-cyclohexadiene; other more elaborate and less

Scheme 3. Aerobic Oxidation of *N*-Substituted Hydroxylamines



[a] Synthesis of **33** commenced from diethyl (trimethylsilyl)oxyphosphoramidate, see Supporting Information. [b] The arylhydroxylamines were added over 2 h via syringe pump.

reactive dienes can also be used (Table 1). Good functional group compatibility was observed (entries 1–7). For example, nitroso Diels–Alder adducts of ergosterol **46** and ergosteryl acetate **47** were isolated and produced in good yield and excellent regioselectivity (16:1 and 35:1 respectively).[16] Derivatives of these and other diene-containing natural products have been studied for their biological activity.[17]

Shea and Whiting showed that by using their mild oxidation protocol they could accurately determine the product distribution for dienes that are capable of undergoing both Diels–Alder cycloaddition and ene reactions.[10] As expected, we observed similar results with 2,3-dimethylbuta-1,3-diene (DMB) **50** and 2-methyl-buta-1,3-diene **52** (entries 6–7). The combined yields were high, and the Diels–Alder adducts could be isolated in 71% and 43% yield, respectively. 2-Substituted 1,3-dienes often provide the oxazine with moderate selectivity; we observed a 2:1 ratio of regioisomeric Diels–Alder adducts **53** and **54** when isoprene was used.

We were curious about the origin of the competing ene reaction when DMB and isoprene were used. It is generally believed that the HDA reaction is more rapid if the free nitroso compound is present. A number of studies have indicated the involvement of a metal-bound nitroso complex when the ene adduct is observed as a major product in the presence of a Diels–Alder trapping agent.[18] These control experiments are typically conducted with DMB as the Diels–Alder trapping agent. However, it is well-known that DMB exists as a mixture of *s*-trans and *s*-cis conformers.[19] We hypothesized that the formation of the ene product could be a reflection of the diene

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(14) (a) Ware, R. W.; King, S. B. *J. Am. Chem. Soc.* **1999**, *121*, 6769. (b) Ware, R. W.; King, S. B. *J. Org. Chem.* **2000**, *65*, 8725. (c) Ware, R. W.; Day, C. S.; King, S. B. *J. Org. Chem.* **2002**, *67*, 6174.

(15) Møller, E. R.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 5770.

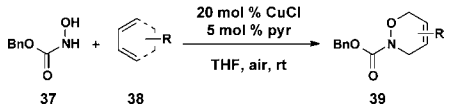
(16) (a) Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 887. (b) Yang, B.; Miller, P. A.; Mollmann, U.; Miller, M. J. *Org. Lett.* **2009**, *11*, 2828.

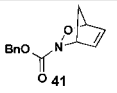
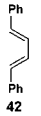
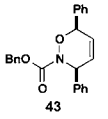
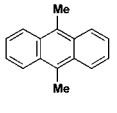
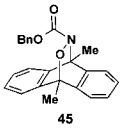
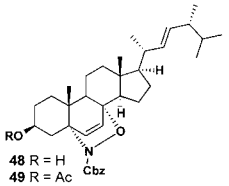
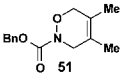
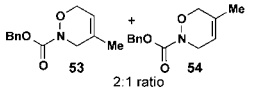
(17) Krchnak, V.; Zajicek, J.; Miller, P. A.; Miller, M. J. *J. Org. Chem.* **2011**, *76*, 10249.

(18) (a) Srivastava, R. S.; Nicholas, K. M. *Chem. Commun.* **1996**, 2335. (b) Ho, C.-M.; Lau, T.-C. *New J. Chem.* **2000**, *24*, 859. (c) Srivastava, R. S.; Khan, M. A.; Nicholas, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 7278 and references therein.

(19) Squillacote, M. E.; Semple, T. C.; Mui, P. W. *J. Am. Chem. Soc.* **1985**, *107*, 6842.

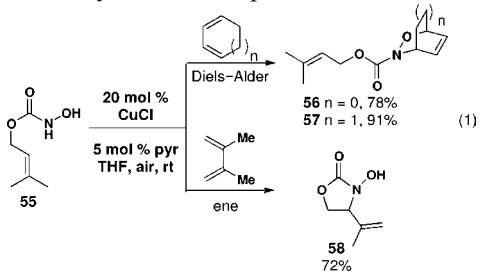
Table 1. Hetero-Diels–Alder Reaction with Various Dienes



entry	diene	product	yield[b] %
1	 40	 41	94
2	 42	 43	80
3	 44	 45	96
4	ergosterol 46	 48 R = H 49 R = Ac	99[a]
5	ergosteryl acetate 47		86[b]
6	 50	 51	71[c]
7	 52	 53 + 54 2:1 ratio	43[d]

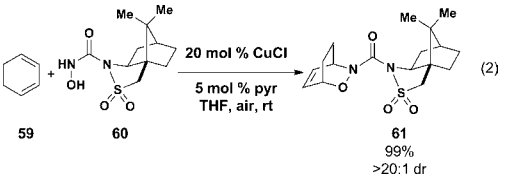
[a] Isolated as a nonseparable mixture of regioisomers (16:1). [b] Isolated as a nonseparable mixture of regioisomers (35:1). [c] 17% of the acylnitroso ene product was isolated. [d] 36% of the acylnitroso ene product was isolated.

conformation/reactivity and not the involvement of a metal-bound acylnitroso complex.



(1)

In order to further evaluate the rate difference, a competition experiment between an intermolecular HDA cycloaddition and an intramolecular ene reaction was designed using prenyl alcohol derived *N*-hydroxycarbamate **55**. Cyclic dienes locked in the required and reactive *s*-cis conformation were found to out-compete the intramolecular ene reaction (eq 1). No product derived from the intramolecular ene reaction was observed. In contrast, in the presence of DMB the predominant product resulted from an intramolecular ene reaction (72%). The overall ratio of products for this transformation was 14:3:1 (intramolecular ene (72%)/nitroso HDA cycloaddition (16%)/intermolecular ene with **50** (6%)). These results reveal that DMB is less reactive in the acylnitroso HDA cycloaddition than cylopentadiene and 1,3-cyclohexadiene.[20] They also suggest that the use of less reactive dienes could result in the ene reaction proceeding in preference to the Diels–Alder cycloaddition. The involvement of a metal-bound acylnitroso complex cannot be ruled out at this time.



(2)

Finally, we wanted to investigate a diastereoselective nitroso HDA reaction. While there are a number of elegant methods for performing asymmetric nitroso HDA reactions, the most common method for inducing chirality utilizes a chiral auxiliary on the acylnitroso dienophile. We chose to investigate the asymmetric HDA reaction using Oppolzer's camphorsultam derivative **60**. As shown in eq 2 exposure of **60** to the optimized reaction conditions produced **61** as a single diastereomer in 99% yield.

In conclusion, we have developed a highly general copper-catalyzed aerobic oxidation of *N*-substituted hydroxylamines for the *in situ* formation of nitroso compounds. These transient nitroso compounds were efficiently trapped using an HDA reaction, and a variety of *N*-substituted oxazines were formed in high to moderate yields. Importantly, this oxidation protocol is operationally simple, using reagent grade solvents, 1 atm of air, and only a slight excess of diene. Further investigations are underway to explore the scope of aerobic oxidations and nitroso chemistry.

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Supporting Information Available. Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) To our knowledge, the reactivity of different dienes with acylnitroso compounds have not been measured. For related studies using different dienes with cycloalkenones, see: (a) Dols, P. PM. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 8515. (b) Paton, R. S.; Kim, S.; Ross, A. G.; Danishefsky, S. J.; Houk, K. N. *Angew. Chem. Int., Ed.* **2011**, *50*, 10366 and references therein.