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Metal-Free, Aerobic Dioxygenation of Alkenes Using Simple Hydroxamic Acid Derivatives

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Supporting Information

ABSTRACT: The dioxygenation of alkenes using molecular oxygen and a simple hydroxamic acid derivative has been achieved. The reaction system consists of readily prepared methyl *N*-hydroxy-*N*-phenylcarbamate and molecular oxygen with a radical initiator, offering an alternative to common dioxygenation processes catalyzed by precious transition metals. This transformation capitalizes on the unique reactivity profile of hydroxamic acid derivatives in radical-mediated alkene addition processes.

Direct dioxygenation of alkenes is a valuable synthetic tool for the preparation of 1,2-diol derivatives, which have high utility in organic synthesis. There are a number of transition-metal-catalyzed processes capable of achieving this goal.[1] A common drawback to these methods is the requirement of toxic and/or expensive transition metals. In an effort to develop a metal-free direct dioxygenation of alkenes using molecular oxygen or air as the sole oxidant, we recently developed an aerobic intramolecular dioxygenation of alkenes using unsaturated hydroxamic acids.[2] This reaction utilizes the amidoxyl radical as a synthetic substitute for the typically highly reactive oxygen-centered radical[3] and provides differentiated diols as cyclization products from a variety of tethered alkenes.

In an effort to expand the capabilities of this dioxygenation process, we targeted the development of a variant proceeding via an intermolecular addition, as depicted in Scheme 1. This variant would not require tethering of the hydroxamic acid to the alkene functionality, facilitating the direct dioxygenation of unsaturated hydrocarbons using molecular oxygen as the sole oxidant. A number of challenges had to be addressed in developing such a transformation. For instance, there are no examples of general synthetic methods proceeding by way of intermolecular additions of oxygen-centered radicals to alkenes.[4,5] Furthermore, such a process would have a greater activation entropy than the previously disclosed intramolecular dioxygenation. We report herein the successful development of an intermolecular direct aerobic dioxygenation of alkenes employing a simple hydroxamic acid derivative that overcomes these significant challenges.

We initially explored the intermolecular aerobic dioxygenation of styrene utilizing simple acylated *N*-phenylhydroxylamine derivatives such as *N*-hydroxy-*N*-phenylacetamide (**1**, R = Me) under conditions similar to those in our previous intramolecular studies. However, reaction of *N*-hydroxy-*N*-phenylacetamide (1.0 equiv) and styrene (1.2 equiv) under 1 atm O_2 at 60 °C in AcOH with 2.5 mol % dilauroyl peroxide (DLP) as an initiator led to no observed dioxygenation product. Substituting DMSO for AcOH did provide the desired dioxygenation product after an extended reaction time (3 d), albeit in low yield. We next attempted the dioxygenation using methyl *N*-hydroxy-*N*-phenylcarbamate (**2**), a related simple hydroxamic acid derivative that is easily obtained by the reaction of *N*-phenylhydroxylamine and methyl chloroformate. Under our optimized reaction conditions employing *n*BuOAc as the solvent,[6] the aerobic dioxygenation of styrene utilizing **2** delivered a single product regioisomer in high yield following mild in situ workup with Me_2S (Table 1, entry 1).[7] Our optimization studies revealed that the addition of DLP as an initiator was not required for the reaction to proceed (entry 2) but

Scheme 1. Alkene Dioxygenation Using *N*-Aryl Hydroxamic Acids

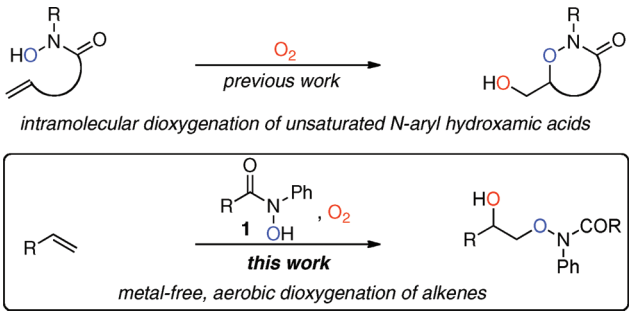
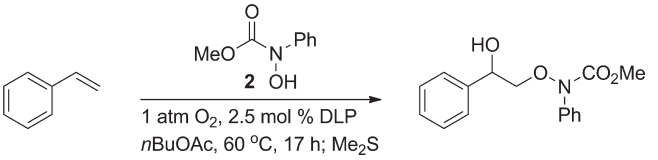


Table 1. Initial Aerobic Dioxygenation Studies[a]



entry	variation from standard conditions above	% yield[b]
1	none	93
2	no DLP, 25 h	90
3	DMSO instead of *n*BuOAc, 17 h	52
4	AcOH instead of *n*BuOAc, 8 h	80
5	1.0 equiv alkene instead of 1.2 equiv alkene, 3 d	49
6	1.0 equiv alkene and 1.2 equiv **2**, 26 h	74

[a] All of the reactions were run using 1.0 equiv of **2** and 1.2 equiv of styrene. [b] Yields of isolated products.

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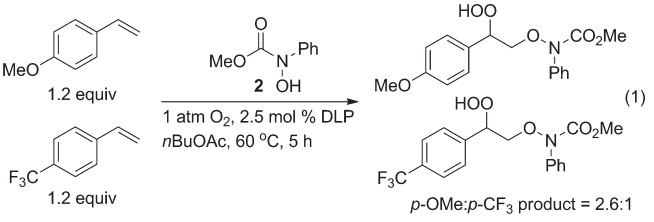
did increase the reaction rate. We attribute the reaction in the absence of the initiator to formation of the amidoxyl radical from **2** via autoxidation processes. The use of solvents employed in our previously reported intramolecular cyclizations, such as DMSO or AcOH, decreased the reaction efficiency (entries 3 and 4). The use of exactly 1.0 equiv of alkene with either 1.0 or 1.2 equiv of **2** led to reduced yields (entries 5 and 6), which we attribute to side reactions of styrene. Notably, the aerobic dioxygenation could be run on a gram scale with no loss in reaction efficiency (92% isolated yield).

We next explored the reaction scope using our optimized dioxygenation protocol. Styrenes proved to be excellent substrates for the aerobic dioxygenation (Table 2). Both electron-rich and electron-poor styrenes were dioxygenated in high yield (entries 1−4). Notably, these reactions all produced a single differentiated diol regioisomer as the product, as did all of the other substrates shown in Table 2. Styrenes containing α- or β-alkyl substitution were also viable substrates (entries 5−7), with β-methylstyrene favoring the *anti* dioxygenation product with a moderate level of stereoselection (78:22 dr). This aerobic, radical-mediated dioxygenation is also compatible with common functional groups that are susceptible to oxidation (entry 8). The bicyclic substrates 2-vinylnapthalene (entry 9) and 1-methylene-1,2,3,4-tetrahydronapthalene (entry 10) also reacted efficiently under our dioxygenation protocol. Trisubstituted styrenes were also excellent substrates under these conditions (entry 11).

We also explored the dioxygenation of a variety of other unsaturated hydrocarbons to define the scope of our current reaction system (Table 3).[8] The heterocyclic substrates 2-vinylthiophene (entry 1) and 2-(prop-1-en-2-yl)furan (entry 2) yielded dioxygenation products in 84 and 48% yield, respectively. A number of reactions employing dienes were successful (entries 3−5), with the potential for both 1,2- and 1,4-dioxygenation. Enynes were viable substrates as well, displaying high chemoselectivity for difunctionalization of the alkene. The dioxygenation of norbornene proceeded efficiently, delivering a 1.2:1 mixture of product diastereomers (entry 7). Reactions involving methacrylic acid (entry 8) and methyl methacrylate (entry 9) additionally demonstrated the ability of this system to dioxygenate electron-poor conjugated alkenes.

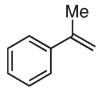
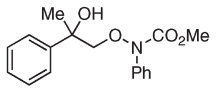
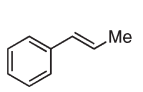
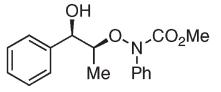
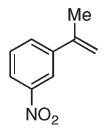
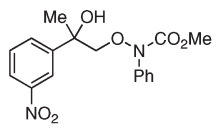
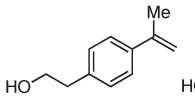
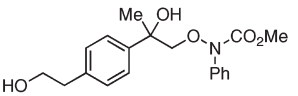
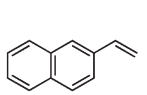
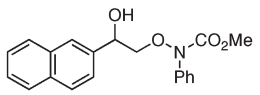
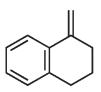
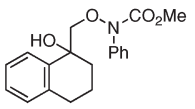
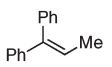
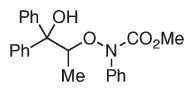
Heteroatom-centered radicals are generally considered to be electron-poor species, favoring additions to more electron-rich alkenes. In order to study the electronic nature of the putative amidoxyl radical, we performed a competition experiment involving the dioxygenation of a 1:1 mixture of *p*-methoxy- and *p*-trifluoromethylstyrene (eq 1). A 2.6:1 ratio of initially formed hydroperoxides favoring the reaction of the more electron-rich *p*-methoxystyrene was observed. This result is consistent with the amidoxyl radical functioning similarly to other oxygen-centered radicals as electron-poor species. Thus, the amidoxyl radical can function as a general synthetic substitute for the promiscuous alkoxy radical for applications in chemical synthesis.



(1)

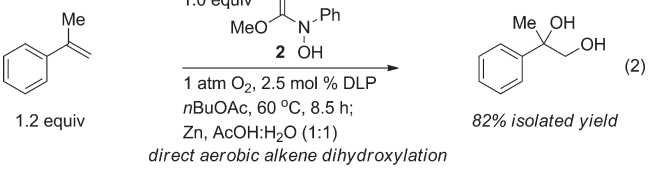
We also developed a simple one-pot protocol for direct aerobic dihydroxylation of alkenes. Following initial dioxygenation,

Table 2. Aerobic Dioxygenation of Styrenic Alkenes[a]

entry	substrate	product	time (h)	% yield[b,c]
1	R = 4-OMe		5	82
2	R = 4-Me		12	83
3	R = 2-Br		11	89
4	R = 4-CF_3		15	84
5			8.5	92
6			7.5	86 78:22 dr
7			5	83
8			5	78
9			24	89
10			3	79
11			5	87

[a] All of the reactions were run using 1.0 equiv of **2** and 1.2 equiv of substrate with $[\mathbf{2}]_0$ = 1.0 M in *n*BuOAc at 60 °C under 1 atm O_2 with 2.5 mol % DLP. [b] Yields of isolated products after Me_2S workup. [c] The diastereomeric ratio in entry 6 was determined by ^1H NMR analysis of the crude reaction mixture.

direct reduction of the N−O bond and the hydroperoxide moiety is easily accomplished using Zn metal as the reductant. For instance, the one-pot dihydroxylation of α-methylstyrene yielded 2-phenylpropane-1,2-diol in 82% yield (eq 2). Thus, while a synthetic advantage of this dioxygenation system is the highly regioselective production of a differentiated diol as demonstrated in Tables 1−3, aerobic alkene dihydroxylation can also be readily achieved if desired.



(2)

In conclusion, we have developed an aerobic alkene dioxygenation method that uses a simple hydroxamic acid derivative and is applicable to a variety of alkenes. The reaction proceeds

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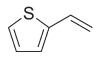
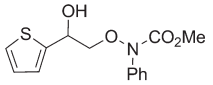
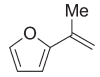
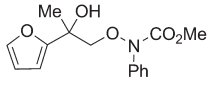
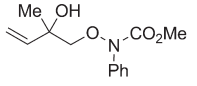
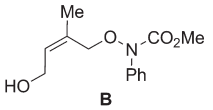
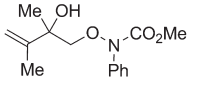
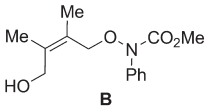
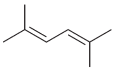
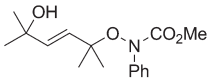
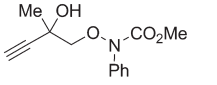
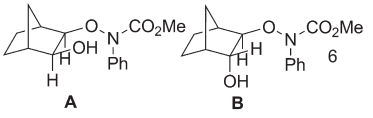
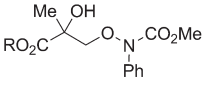
Table 3. Aerobic Dioxygenation of a Variety of Unsaturated Hydrocarbons[a]

entry	substrate	product	time (h)	% yield[b,c]
1			7	84[d]
2			2	48[d]
3		 **A**  **B** 3.2:1 Z:E	6	88 2:1 **A:B**
4		 **A**  **B** 5.1:1 Z:E	3	88 5.9:1 **A:B**
5			2	59[d]
6			7	68
7		 **A** **B**	6	77 1.2:1 **A:B**
8 9		 R = H R = Me	7 20	45 84

[a] All of the reactions were run using 1 equiv of **2** and 5.0 equiv of substrate with $[\mathbf{2}]_0$ = 1.0 M in *n*BuOAc at 60 °C under 1 atm O_2 with 2.5 mol % DLP. [b] Yields of isolated products after Me_2S workup. [c] The ratios of product regioisomers were determined by ^1H NMR analysis of the crude reaction mixtures. [d] 2.0 equiv of substrate was used.

without the use of precious and/or toxic transition-metal catalysts common to related alkene difunctionalization processes and uses molecular oxygen as the sole oxidant. This process capitalizes on the synthetic versatility of the amidoxyl radical, which is formed under mild conditions from simple hydroxamic acid derivatives and can serve as a useful source of oxygen-centered radicals for chemical synthesis. Harnessing this unique reactivity has led to the first example of a general synthetic transformation involving the intermolecular addition of an oxygen-centered radical to alkenes. Future work will continue to explore the use of the amidoxyl radical in the development of new synthetic reactions, including asymmetric variants of these difunctionalization processes.

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

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(2) (a) Schmidt, V. A.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4491–4494. For a metal-free oxyamination of alkenes using hydroxamic acids, see: (b) Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 11402–11405.

(3) (a) Hartung, J. *Eur. J. Org. Chem.* **2001**, 619–632. (b) Zlotorzynska, M.; Zhai, H.; Sammis, G. M. *Org. Lett.* **2008**, *10*, 5083–5086.

(4) Reactions of isolated amidoxyl radicals with alkenes (anaerobic conditions) have been shown to provide 1,2-diaddition products in limited cases. See: Hussain, S. A.; Jenkins, T. C.; Perkins, M. J.; Siew, N. P. Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2803–2808.

(5) Addition of the highly reactive imidoxyl radical derived from *N*-hydroxyphthalimide to norbornene was observed in a cobalt-catalyzed alkane oxidation study. See: Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520–4526.

(6) Other alkyl acetates (e.g., EtOAc) could be employed as the solvent, but *n*BuOAc proved to be the most convenient because of its lower volatility.

(7) The reported yields are relative to the 1.0 equiv of hydroxamic acid **2** utilized in all of the reactions, as the alkene was employed in slight excess.

(8) The increased amounts of substrate in the reactions of Table 3 were utilized to ensure adequate concentrations because of the volatility of several of these compounds.