Synthetic Methods

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# Metal-Free, Aerobic Dioxygenation of Alkenes Using Hydroxamic Acids**

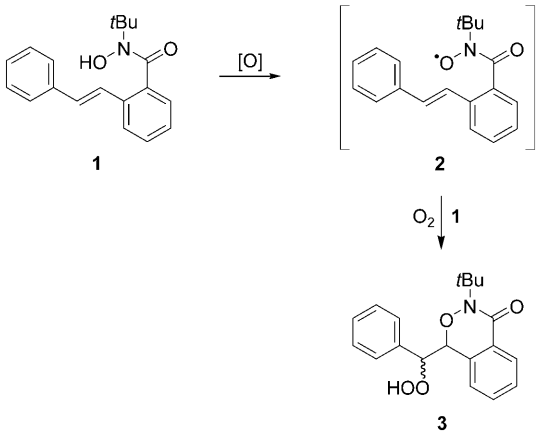
*Valerie A. Schmidt and Erik J. Alexanian**

Methods for achieving the vicinal difunctionalization of alkenes greatly facilitate the preparation of functionalized organic compounds. Examples of useful transformations include alkene dioxygenations,[1] aminooxidations,[2] and diaminations,[3] with many notable recent developments employing palladium catalysis. A common drawback to these processes is the use of precious and/or toxic transition-metal catalysts. We report herein a convenient, general method for alkene dioxygenation that utilizes oxygen as an environmentally friendly and inexpensive oxidant, while circumventing the use of metal catalysts.

As a persistent triplet diradical in its ground state, molecular oxygen reacts rapidly with carbon-centered radicals.[4] This mode of reactivity was witnessed by Gomberg during his historic studies on the first organic free radical, triphenylmethyl,[5] and is an important step in classical radical autoxidation.[6] Radical oxygenation has proven to be of value in modern organic synthesis, especially in cases where the generation of carbon-centered radicals proceeds in a regioselective manner. For example, radical decarboxylation,[7] dehalogenation,[8] demercuration,[9] and carbocyclization[10] processes have all utilized molecular oxygen to selectively deliver radical oxidation products.

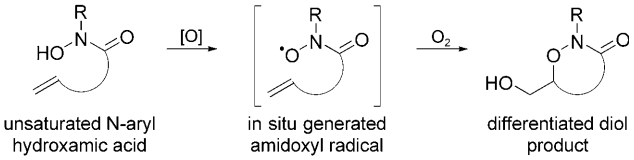
During their pioneering work on the fundamental reactivity of amidoxyl radicals with alkenes, Perkins and coworkers observed a single remarkable example of an amidoxyl radical cyclization followed by oxygenation (Scheme 1).[11] While attempting to prepare the highly conjugated stilbene-substituted *tert*-butyl amidoxyl radical **2**, the parent hydroxamic acid **1** underwent spontaneous oxidation and intramolecular cyclization followed by radical oxygenation to deliver hydroperoxide **3** as a mixture of diastereomers.[12] These nitroxyl radicals, which contain electron-withdrawing acyl groups, are destabilized relative to persistent dialkyl nitroxyl radicals (e.g. TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl),[13] and can be generated by oxidation of *N*-aryl or alkyl hydroxamic acids under mild conditions.[14]

We envisioned an alkene cyclization with a tethered amidoxyl radical that is formed in situ from readily obtained




***Scheme 1.*** Spontaneous aerobic radical cyclization of stilbene-substituted *tert*-butyl hydroxamic acid **1** as reported by Perkins and coworkers.[11]

*N*-aryl hydroxamic acids, and subsequent reaction with molecular oxygen, as a potentially general approach to the dioxygenation of alkenes (Scheme 2). This strategy utilizes amidoxyl radicals as a substitute for highly reactive alkoxy radicals,[15] and allows the production of vicinal diols by subsequent facile reductive cleavage of the N–O bond. Furthermore, this method differentiates the oxygen atom functionality delivered to the alkene, which is difficult using current dioxygenation methods.




***Scheme 2.*** Proposed alkene dioxygenation using *N*-aryl hydroxamic acids and $O_2$.

We began our studies with *N*-phenyl hydroxamic acid **4**. To facilitate cyclization, initial experiments explored the use of simple, inexpensive cobalt salts as catalysts, which assist the formation of amidoxyl radicals under aerobic conditions.[16] Treatment of **4** with either 2 mol% $Co(OAc)_2$ or 2 mol% $[Co(acac)_3]$ under one atmosphere of $O_2$ in acetic acid provided the desired dioxygenated [1,2]-oxazinone **5** in 55 and 54% yield, respectively (Table 1, entries 1 and 2). A control experiment revealed that dioxygenation proceeded under 1 atmosphere of $O_2$ alone, in the absence of any metal catalyst, to afford [1,2]-oxazinone **5** in 80% yield following

[*] V. A. Schmidt, Prof. E. J. Alexanian
Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 (USA)
Fax: (+1) 919-962-2388
E-mail: eja@email.unc.edu

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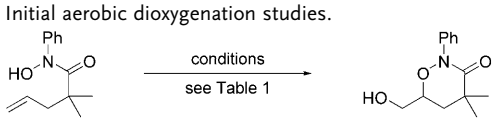
***Table 1:*** Initial aerobic dioxygenation studies.




**4** **5**

| Entry | Metal | Solvent | Conditions | $T$ [°C]/$t$ [h] | Yield [%] |
|---|---|---|---|---|---|
| 1 | 2% $Co(OAc)_2$ | AcOH | 1 atm $O_2$ | 60/4 | 55[a] |
| 2 | 2% $[Co(acac)_3]$ | AcOH | 1 atm $O_2$ | 60/4 | 54[a] |
| 3 | None | AcOH | 1 atm $O_2$ | 60/4 | 80[b] |
| 4 | None | AcOH | 1 atm Ar | 60/4 | trace |
| 5 | None | DMSO | 1 atm $O_2$ | 90/9 | 65[c] |

[a] Yield determined by GC analysis. [b] Yield of isolated product after $PPh_3$ workup. [c] Yield of isolated product.

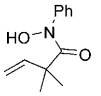
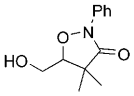
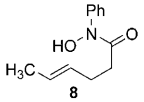
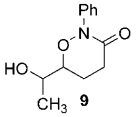
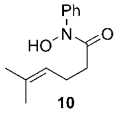
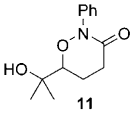
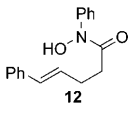
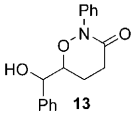
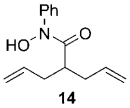
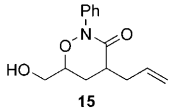
mild in situ reductive work up with $PPh_3$ (Table 1, entry 3). Under these conditions, no reaction took place under one atmosphere of Ar (Table 1, entry 4). Substituting dimethyl sulfoxide for acetic acid as solvent and heating at 90°C directly delivered dioxygenation product **2** in 65% yield (Table 1, entry 5).

Encouraged by these initial findings, we explored the generality of this metal-free aerobic alkene dioxygenation in a variety of synthetic contexts (Table 2). The difunctionalization of substrate **6** by 5-*exo* ring closure proceeded well, delivering isoxazolidinone **7** in 88% yield (Table 2, entry 1). Further substitution on the alkene moiety is well-tolerated in the dioxygenation process, as demonstrated by the successful reactions involving 1,2-disubstituted and trisubstituted substrates **8** and **10** (Table 2, entries 2 and 3). Conjugated alkenes also participate in the dioxygenation process, as styrene-substituted hydroxamic acid **12** reacts smoothly to deliver oxazinone **13** in 63% yield (Table 2, entry 4). We also prepared α-diallyl hydroxamic acid substrate **14** to explore the potential for selective oxidation of diene substrates. Upon heating under one atmosphere of $O_2$ in dimethyl sulfoxide, **14** cyclizes to monoallyl [1,2]-oxazinone product **15** in 75% yield (Table 2, entry 5). This selectivity is dictated by the intramolecular amidoxyl radical cyclization. Oxidation of similar substrates by using intermolecular protocols would likely lead to a mixture of mono- and bis-difunctionalization products.

The results presented in Table 1 and Table 2 demonstrate the unique chemoselectivity of the amidoxyl radical in 6-*exo* alkene-cyclization reactions. Oxygen-centered radicals are generally incapable of providing access to six-membered ring systems through alkene cyclization reactions, owing to the marked predominance of 1,5-hydrogen abstraction at the allylic position.[17] However, we observed no by-products resulting from these allylic oxidation pathways, which we attribute to the attenuated reactivity profile of the amidoxyl radical. The amidoxyl radical thus performs admirably well as an oxygen-centered radical substitute for the promiscuous alkoxy radical in this important context.

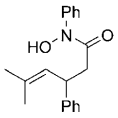
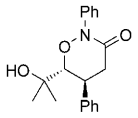
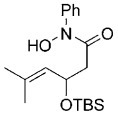
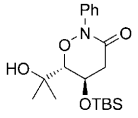
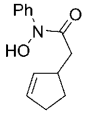
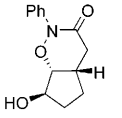
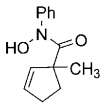
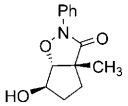
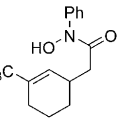
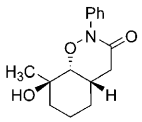
To assess the potential for diastereocontrol in the dioxygenation process, we studied a number of different substrates (Table 3). β-Phenyl-substituted hydroxamic acid **16** underwent a highly stereoselective 6-*exo* cyclization, providing product **17** as a single diastereomer in 62% yield (Table 3, entry 1). β-Silyloxy substrate **18** performed equally well,

***Table 2:*** Aerobic dioxygenations of alkenyl *N*-aryl hydroxamic acids[a]

| Entry | Substrate | Conditions[b] | Product | Yield [%][c,d] |
|---|---|---|---|---|
| 1 |  **6** | A |  **7** | 88 |
| 2 |  **8** | B |  **9** | 66 (55:45 d.r.) |
| 3 |  **10** | C |  **11** | 79 |
| 4 |  **12** | B |  **13** | 63 (60:40 d.r.) |
| 5 |  **14** | B |  **15** | 75 (62:38 d.r.) |

[a] All reactions run in 0.1 M solvent, 1 atm $O_2$, 3–40 h. [b] Conditions A: AcOH, 60°C, $PPh_3$ work up. B: DMSO, 90°C. C: DMSO, 60°C, $PPh_3$ workup. [c] Yield of isolated product. [d] The diastereomeric ratios were determined by $^1H$ NMR spectroscopic analysis of the crude reaction mixtures.

***Table 3:*** Studies of alkene dioxygenation stereoselectivity.[a]

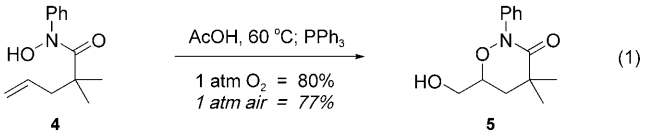
| Entry | Substrate | Conditions[b] | Product | Yield [%][c,d] |
|---|---|---|---|---|
| 1 |  **16** | A |  **17** | 62 (>95:5 d.r.) |
| 2 |  **18** | C |  **19** | 69[e] (>95:5 d.r.) |
| 3 |  **20** | A |  **21β** | 91[e] (78:22 d.r. β:α) |
| 4 |  **22** | A |  **23β** | 98 (66:33 d.r. β:α) |
| 5 |  **24** | A |  **25β** | 64[e] (84:16 d.r. β:α) |

[a]–[d] See Table 2. [e] Reactions initiated with 10 mol% dilauroyl peroxide.

delivering the fully differentiated masked triol **19** in 69% yield and >95:5 d.r. (Table 3, entry 2). This reaction was initiated by the addition of dilauroyl peroxide, as the reaction in the absence of an initiator was slow. Although not necessary for the majority of substrates, we found this to be a simple way to increase reaction rates, as required.

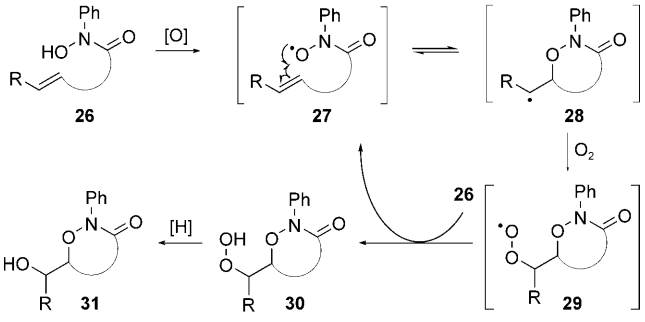
We also explored the potential of the dioxygenation process for reactions involving cyclic alkenes. Cyclopentenyl substrate **20** underwent 6-*exo* cyclization to provide [5,6]-*cis*-fused product **21** as a 78:22 mixture of β:α hydroxy diastereomers in high yield (91%; Table 3, entry 3). Difunctionalization of cyclopentenyl substrate **22** gave [5,5]-*cis*-fused product **23** in 98% yield, also favoring the β-hydroxy diastereomer (Table 3, entry 4). Cyclohexenes are also viable substrates for stereoselective dioxygenation, as hydroxamic acid **24** delivered [6,6]-*cis*-fused bicyclic oxazinone **25** as an 84:16 mixture of β:α hydroxy diastereomers (Table 3, entry 5). These results indicate that the aerobic dioxygenation of cyclic substrates favors *trans*-alkene difunctionalization, providing a useful alternative to *cis*-selective metal-catalyzed alkene dioxygenation processes.[1]

We further hypothesized that the dioxygenation could be promoted by air alone. Remarkably, dioxygenation of alkenyl hydroxamic acid **4** at 60°C in acetic acid delivered [1,2]-oxazinone **5** in four hours using one atmosphere of air as the sole oxidant and external oxygen atom source [Eq. (1)]. To the best of our knowledge, this represents the first such example of a metal-free dioxygenation of simple alkenes using air.



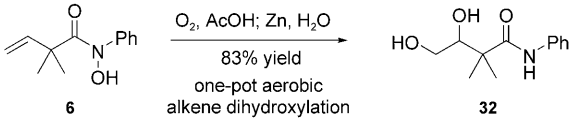
4 5 (1)

A plausible reaction mechanism is shown in Scheme 3. Following initiation of the reaction via formation of the amidoxyl radical, a reversible cyclization produces carbon-centered radical **28**.[18] This intermediate reacts with oxygen to deliver alkylhydroperoxy radical **29**, which subsequently performs a hydrogen atom abstraction from the substrate hydroxamic acid,[19] generating amidoxyl radical **27** and affording alkylhydroperoxide **30**. We have verified the production of alkylhydroperoxides by isolating and characterizing the parent hydroperoxide of dioxygenation product **11** (Table 2, entry 3).[20] Subsequent reduction by $Me_2S$, formed in situ from the disproportionation of dimethyl sulfoxide[21] or added $PPh_3$, produces dioxygenation product **31**.



***Scheme 3.*** Proposed mechanism for aerobic dioxygenation.

Access to 1,2-diols is readily accomplished through reduction of the N–O bond. For example, we have developed a one-pot alkene dihydroxylation reaction by adding zinc metal directly into the reaction mixture prior to work-up. As shown in Equation 2, substrate **6** undergoes aerobic dioxygenation and in situ reduction of the N–O bond with zinc to produce diol **32** in 83% yield.



6 32 (2)

In conclusion, we have developed a metal-free, aerobic dioxygenation of alkenes using hydroxamic acids. This reaction avoids the use of precious transition-metal catalysts that are typically required in related difunctionalization processes and employs oxygen or air as green oxidants and external oxygen atom sources. The dioxygenation reaction is applicable to a wide range of unsaturated substrates and affords dioxygenation products with differentiated oxygen atom functionality, which is a unique feature of this process. This method also exhibits the potential for high reaction stereoselectivity, and results in *trans* difunctionalization with cyclic alkenes, complementing transition-metal-catalyzed *cis*-selective dioxygenation reactions. The mild reaction conditions, simple substrate preparation, and generality of this dioxygenation procedure are attractive aspects for organic synthesis. Future studies will explore the unique reactivity of amidoxyl radicals in the development of new reactions and in complex synthetic applications.

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