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Metal-Free Oxyaminations of Alkenes Using Hydroxamic Acids

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Supporting Information

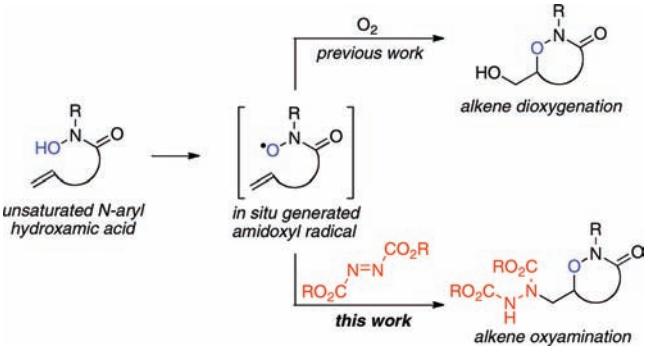
ABSTRACT: A radical-mediated approach to metal-free alkene oxyamination is described. This method capitalizes on the unique reactivity of the amidoxyl radical in alkene additions to furnish a general difunctionalization using simple diisopropyl azodicarboxylate (DIAD) as a radical trap. This protocol capitalizes on the intramolecular nature of the process, providing single regioisomers in all cases. Difunctionalizations of cyclic alkenes provide *trans* oxyamination products inaccessible using current methods with high levels of stereoselectivity, complementing *cis*-selective oxyamination processes.

Vicinal amino alcohols are highly valuable compounds in chemical synthesis, comprising a multitude of biologically active compounds and natural products.[1] Alkene oxyamination enables the direct synthesis of 1,2-aminoalcohols from simple unsaturated hydrocarbons and is, therefore, a most useful synthetic transformation for accessing this important motif.[2] There are a number of synthetic methods capable of facilitating alkene oxyamination; however, these processes commonly rely on the use of precious and/or toxic transition-metal catalysts[3] or hypervalent iodine(III)-based oxidants.[4] In addition, the control of oxyamination regioselectivity is often a major challenge using metal-catalyzed intermolecular difunctionalization protocols. Herein, we report a transition-metal-free approach to alkene oxyamination employing easily prepared hydroxamic acids and commercially available azodicarboxylates. This approach offers high levels of reaction regio- and stereoselectivity and constitutes a general approach to the direct *trans* oxyamination of cycloalkenes, complementing *cis*-selective metal-catalyzed protocols.

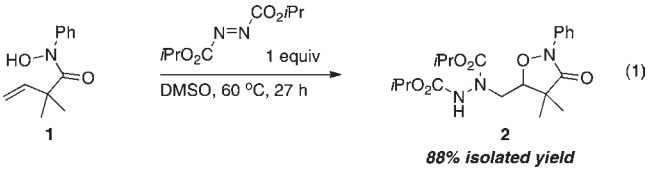
Our radical-based approach to alkene oxyamination is outlined in Scheme 1. Readily prepared *N*-aryl hydroxamic acids are easily converted to amidoxyl radicals upon exposure to mild oxidants or radical initiators.[5] These reactive species are then capable of addition to alkenes, producing an intermediate carbon-centered radical. We have previously shown that interception of this carbon-centered radical with molecular oxygen provides a radical-based approach to alkene dioxygenation.[6] We hypothesized that simple substitution of molecular oxygen for an N-atom radical trap could provide the analogous oxyamination product. Importantly, the regioselectivity of this process should be easily controlled by the intramolecular addition step of the tethered amidoxyl radical.

We commenced our studies utilizing azodicarboxylates as an N-atom source, as these readily available compounds have demonstrated ability as carbon-centered radical traps.[7] We began by exploring the oxyamination of unsaturated hydroxamic acid **1**. Heating this substrate in DMSO at 60 °C in the presence of

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



1 equiv of diisopropyl azodicarboxylate (DIAD) delivered the isoxazolidinone oxyamination product **2** in 88% isolated yield (eq 1). While the reaction utilizing 1 equiv of DIAD was successful, reaction using an excess of DIAD (3 equiv) proceeded in higher yield (94% vs 88%) and a much shorter reaction time (5 vs 27 h). Reactions of substrate **1** employing other simple azodicarboxylates such as diethyl azodicarboxylate (DEAD) and di-*tert*-butyl azodicarboxylate (DTAD) were also successful, delivering the corresponding oxyamination products in 92% and 68% yield, respectively.[8] Notably, *this alkene difunctionalization proceeded without any additional reagents*. We attribute this reactivity to the formation of a small amount of the amidoxyl radical (autoxidation) prior to the start of the reaction, capable of initiating the radical chain process.[9]



We next explored the scope of this metal-free alkene oxyamination utilizing a variety of unsaturated hydroxamic acids as substrates (Table 1). The difunctionalization of hydroxamic acid **3** involving 6-*exo* ring closure proceeded efficiently, affording oxazinone **4** in 83% yield (Table 1, entry 1). This reaction was initiated by the addition of commercially available, low temperature radical initiator V-65 (2,2′-azobis(2,4-dimethyl valeronitrile)), as reaction without added initiator was slow. Although not necessary in reactions with most substrates, we found this to be a simple way to increase reaction rates, as desired. Reactions involving 1,

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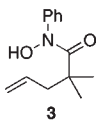
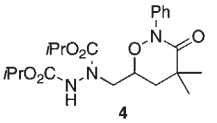
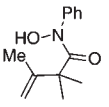
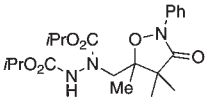
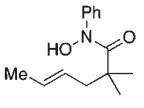
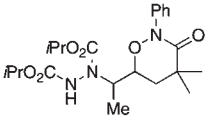
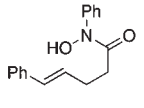
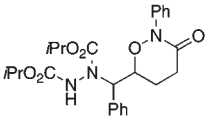
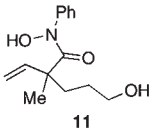
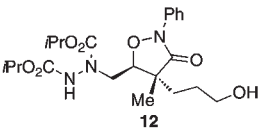
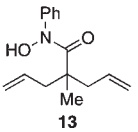
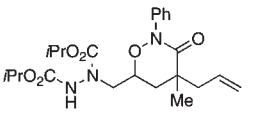
Table 1. Oxyaminations of Alkenyl *N*-Aryl Hydroxamic Acids[a]

entry	substrate	product	time (h)	% yield[b,c]
1	 **3**	 **4**	18	83[d]
2	 **5**	 **6**	4	74
3	 **7**	 **8**	10	86[e] 55:45 dr
4	 **9**	 **10**	14	61[f] 50:50 dr
5	 **11**	 **12**	12	64[d] 75:25 dr
6	 **13**	 **14**	9	59 50:50 dr

[a] All reactions run 0.5 M in DMSO with 3 equiv of DIAD at 60 °C. [b] Yields of isolated product. [c] The diastereomeric ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d] 10 mol % V-65 azo initiator added at 40 °C. [e] Reaction temp 40 °C. [f] 10 mol % dilauroyl peroxide (DLP) initiator added.

1- and 1,2-disubstituted alkenes were also successful, as demonstrated by the reactions of substrates **5** and **7**, respectively (Table 1, entries 2 and 3).[10] Conjugated alkenes also participate in the oxyamination process, as styrenyl substrate **9** afforded oxazinone **10** (Table 1, entry 4). In order to test the functional group compatibility of the oxyamination, we prepared substrate **11** containing a free primary hydroxyl group. Reaction of **11** afforded isoxazolidinone **12** in 64% yield, demonstrating the compatibility of this mild, radical-mediated protocol with functional groups susceptible to oxidation (Table 1, entry 5). The intramolecular nature of the oxyamination process also permits chemoselective single difunctionalization of diene substrates, as demonstrated by the reaction of α-diallyl hydroxamic acid **13** (Table 1, entry 6). The utilization of common intermolecular oxyaminations would likely lead to mixtures of mono- and bis-difunctionalized products.

Following the oxyamination process, direct reductive cleavage of the N−O or N−N bond is easily accomplished to provide the acyclic difunctionalization product (Scheme 2). For example, selective mild reduction of the isoxazolidinone N−O bond of **2** proceeds using Zn in a 1:1 AcOH/H_2O solvent mixture. Reduction using Raney Ni under ultrasonic conditions[11] results in one-pot cleavage of the N−O and N−N bond of **2**, delivering **16** in 63% yield.[12]

Scheme 2. Selective Reduction of Difunctionalization Products

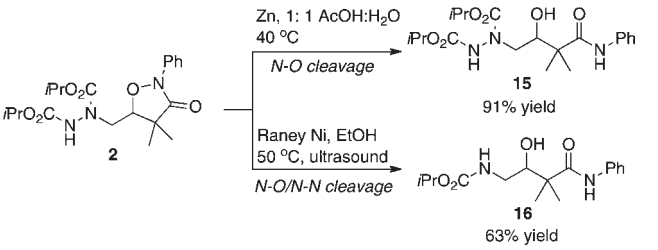
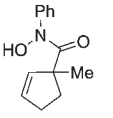
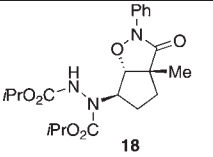
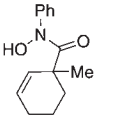
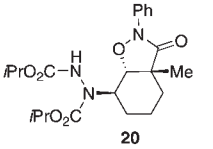
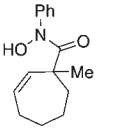
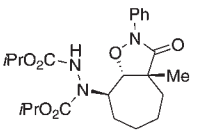
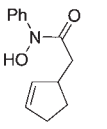
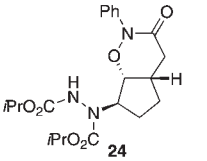


Table 2. Stereoselective Oxyaminations of Cycloalkenes[a]

entry	substrate	product	time (h)	% yield[b,c]
1	 **17**	 **18**	6	80 >95:5 dr β:α
2	 **19**	 **20**	3	92 >95:5 dr β:α
3	 **21**	 **22**	3	89 >95:5 dr β:α
4	 **23**	 **24**	24	52 >95:5 dr β:α

[a] All reactions run 0.5 M in DMSO with 3 equiv of DIAD at 60 °C. [b] Yields of isolated product. [c] The diastereomeric ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures.

In contrast to the variety of methods available for *cis*-selective oxyamination, there are few methods capable of the direct, stereoselective *trans* oxyamination of cycloalkenes.[13] An intramolecular oxyamination process using unsaturated *O*-alkyl hydroxamates by Wardrop is a notable exception, though this process requires stoichiometric quantities of hypervalent iodine(III) reagents.[4b] In order to assess the stereoselectivity of the oxyamination process using cycloalkenes, we studied the oxyamination of a number of cycloalkenyl hydroxamic acids (Table 2). Our studies began with the study of cyclopentenyl substrate **17**, which delivered *trans* oxyamination product **18** as a single diastereomer in 80% yield (Table 2, entry 1). Both cyclohexenyl hydroxamic acid **19** and cycloheptenyl substrate **21** also produced *trans* difunctionalization products in high yield as single diastereomers (Table 2, entries 2−3). The difunctionalization of

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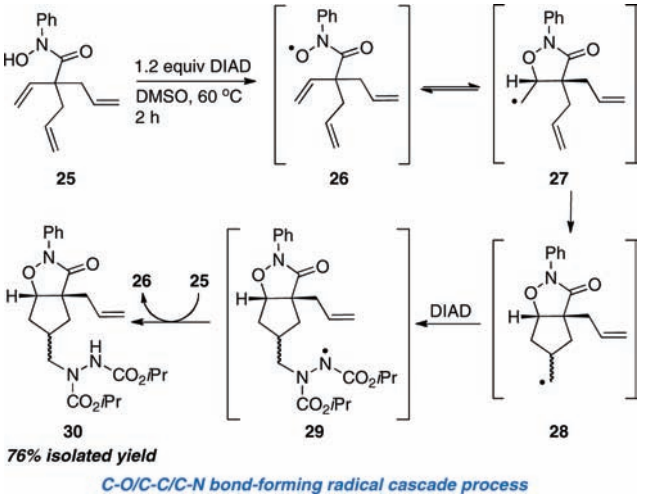
Scheme 3. Cascade Cyclization of Triene Substrate 25



cyclic substrates is also not limited to 5-*exo* cyclizations, as cyclopentenyl substrate **23** reacted to provide product **24** as a single diastereomer, albeit in lower yield (52%, Table 2, entry 4).

This highly *trans*-selective radical-mediated oxyamination of cycloalkenes therefore complements *cis*-selective transition-metal-catalyzed protocols. In addition, the tethered nature of the difunctionalization processes described in Tables 1 and 2 facilitates the production of single regioisomers of the alkene difunctionalization products, which is an important advantage of the present method. Control of oxyamination regioselectivity using sterically or electronically unbiased alkenes is a major challenge using common transition-metal-catalyzed processes.[14] Furthermore, current methods for intramolecular alkene oxyamination involve cyclizations of N-atom functionality. This oxyamination using unsaturated hydroxamic acids involves initial O-atom alkene addition, providing access to products of opposite regioselectivity.

Radical-mediated cascade reactions of polyunsaturated compounds have long served as outstanding synthetic platforms for the rapid generation of molecular complexity.[15] As the oxyamination protocol involves carbon-centered radicals as intermediates, we hypothesized that it may be possible to perform cascade-type sequences by inserting a carbon−carbon bond-forming step prior to final carbon-centered radical trapping by the azodicarboxylate. Our studies have initially focused on triene hydroxamic acid substrate **25** (Scheme 3). Upon heating **25** at 60 °C in DMSO in the presence of 1.2 equiv of DIAD, we isolated desired *cis*-fused bicyclic isoxazolidinone **30** in good yield. A mechanistic proposal is shown. Following amidoxyl radical formation, reversible alkene cyclization can produce isoxazolidinone **27**. Intermediate **27** is well positioned for a subsequent C−C bond-forming addition step, which is followed by azodicarboxylate addition to deliver **30**.

Notably, this cascade process is a rare example of a synthetic transformation capable of the construction of three distinct bond types in a single reaction: C−O, C−C, and C−N. The capability of this radical-based approach to oxyamination to generate functionalized, complex products via cascade sequences is a useful feature uncommon to transition-metal-mediated or ionic oxyamination processes.[16] We view the controlled reactivity of amidoxyl radicals in alkene additions, particularly in light of the facile formation of these species from simple hydroxamic acids, as constituting a promising approach to radical-mediated organic synthesis harnessing the powerful synthetic potential of oxygen-centered radicals.

In conclusion, we have developed a metal-free approach to alkene oxyamination using hydroxamic acids and simple azodicarboxylates. These reactions proceed without the use of transition-metal catalysts and/or hypervalent iodine(III) reagents common to related alkene difunctionalization processes. This tethered oxyamination reaction is applicable to a wide range of unsaturated substrates, delivering single regioisomers in all cases, which is often a challenge using intermolecular protocols. In addition, this process exhibits high *trans*-stereoselectivity using cycloalkene substrates, complementing transition-metal-catalyzed *cis*-selective oxyaminations. Initial extensions of the radical-mediated difunctionalization to multibond-forming cascade processes are also described. Future work will continue to harness the unique reactivity of the amidoxyl radical in new synthetic reaction development, as well as explore applications in complex molecule synthesis.

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

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(8) For reactions employing additional azodicarboxylates, see Supporting Information.

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