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Alkene Hydrofunctionalization Using Hydroxamic Acids: A Radical-Mediated Approach to Alkene Hydration

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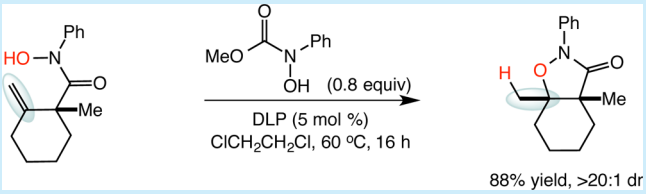
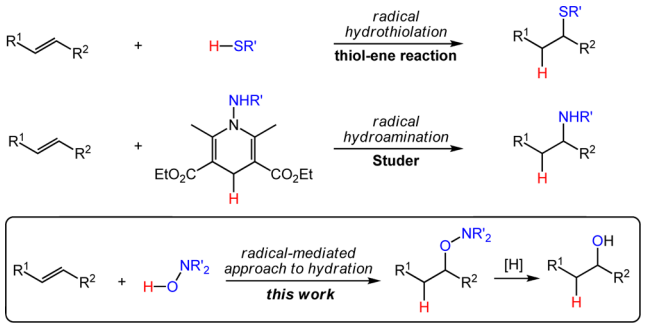
Supporting Information

ABSTRACT: A radical-mediated approach to alkene hydration is described. The present strategy capitalizes on the unique radical reactivity of hydroxamic acids, which are capable of functioning as both synthetically useful oxygen-centered radical species and suitable hydrogen atom-based donors. This reaction manifold has been applied to both alkene hydrations and tandem alkene−alkene carbocyclization processes.



The hydration of alkenes is a fundamental synthetic transformation, commonly performed using water and an acid catalyst.[1] Recent efforts have demonstrated the impressive potential of transition metal or photoredox catalysts in facilitating catalytic hydrations (or hydroalkoxylations).[2] Alternatively, despite the success of heteroatom-centered radical additions in hydrofunctionalizations, including hydrothiolations[3] and hydroaminations,[4] radical-mediated approaches to hydration remain undeveloped (Scheme 1).[5] It is not

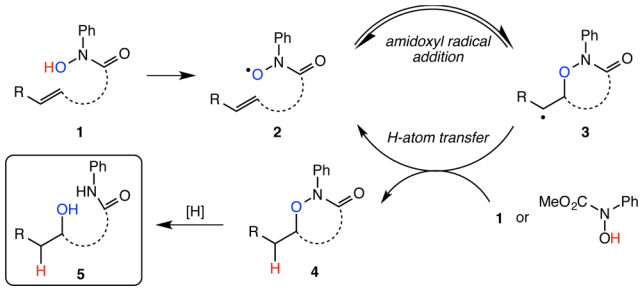
Scheme 1. Alkene Hydrofunctionalization Using Heteroatom-Centered Radicals



difficult to understand why this is the case; such a transformation requires two steps with limited precedent: oxygen-centered radical addition to an alkene[6] and hydrogen-atom transfer from a hydroxyl group to a carbon-centered radical.[7] The successful development of a radical-mediated approach to hydration would require solutions to both of these challenges.

We postulated that hydroxamic acids could enable such a transformation. We have developed a platform for alkene functionalization capitalizing on the addition of amidoxyl radicals to alkenes in intra- and intermolecular processes.[8] We sought to develop an approach to alkene hydration by combining this addition process with H atom transfer from the hydroxamic acid substrate (Scheme 2). We anticipated that

Scheme 2. An Approach to Alkene Hydration Using Hydroxamic Acids



such an H atom transfer would be possible based on the relatively low O−H bond strength of *N*-phenyl hydroxamic acids (~80 kcal/mol).[9] Furthermore, appending additional unsaturation to the hydroxamic acid substrate could enable cascade-type radical cyclizations, producing complex polycycles. Such C−O/C−C/C−H bond-forming cascades would constitute rare examples of synthetic transformations forming three distinct bond types in a single step.

Our studies commenced with the cyclization of tiglic acid derived *N*-phenyl hydroxamic acid **6** (Table 1). Simply heating the substrate to 60 °C in the presence of 5 mol % of the radical initiator dilauroyl peroxide (DLP) provided a moderate yield (65%) of isoxazolidinone product **8**. We discovered that the addition of a substoichiometric amount of methyl *N*-hydroxy-*N*-phenyl carbamate (**7**), a reagent previously developed in our laboratory for intermolecular alkene dioxygenations,[8c] increased both reaction conversion and yield (entries 1−2). A diverse set of alternative hydrogen atom donors were studied, including silanes,[10] catechols,[7a] and thiols;[11] however these reactions provided lower conversions and yields (entries 3−5). The addition of both DLP and reagent **7** were crucial to the reaction

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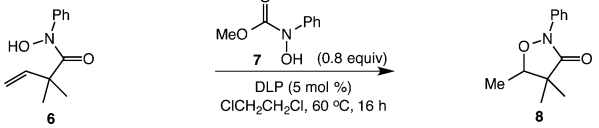
Table 1. Radical Cyclization of Unsaturated Hydroxamic Acid 6



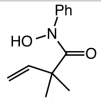
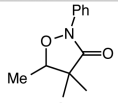
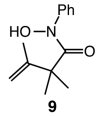
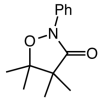
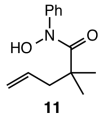
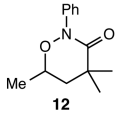
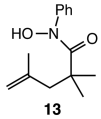
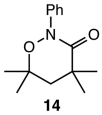
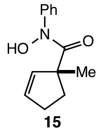
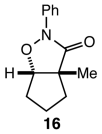
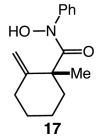
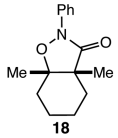
entry	variation from conditions above	% conversion[a]	% yield[b]
1	**none**	100	**90**
2	no 7 added	80	65
3	$(Me_3Si)_3SiH$ instead of 7	69	69
4	4-*tert*-butylcatechol instead of 7	77	55
5	*tert*-dodecylmercaptan instead of 7	73	47
6	no DLP added	78	67
7	no DLP and no 7 added	48	38

[a]Calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [b]Yield of isolated product.

(entries 6–7). Reaction conversion in the absence of DLP is attributed to trace aerobic oxidation of the hydroxamic acid prior to reaction.

With a viable system for the radical cyclization in hand, we next surveyed the reaction scope using a diverse set of acyclic and cyclic alkenyl hydroxamic acids (Table 2). Cyclizations proceeding via both 5-*exo* and 6-*exo* reaction pathways were possible (entries 1–4). Interestingly, substrates **9** and **17** possessing 1,1-disubstituted alkenes delivered good yields of isoxazolidinone products even in the absence of reagent **7** (entries 2 and 6). Substrate **11** containing a terminal alkene reacted sluggishly via a 6-*exo* cyclization (43% conversion after 42 h) and delivered a low yield of [1,2]-oxazinone product **12** even in the presence of an excess of **7** (1.6 equiv, entry 3). We hypothesize that the decreased efficiency of this reaction versus previously reported alkene difunctionalizations using **11**[8d,e] is a consequence of the relatively slow rate of radical hydrogen atom transfer involved. In contrast, the 6-*exo* cyclization of methallyl substrate **13** proceeded to complete conversion and produced product **14** in 71% yield (entry 4). Cyclopentenyl substrate **15** afforded **16** in good yield and high diastereoselectivity favoring *cis* ring fusion (entry 5). The reaction of methylene cyclohexenyl substrate **17** also proceeded in good yield and high stereoselectivity (entry 6).

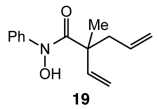
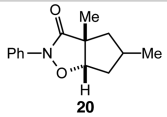
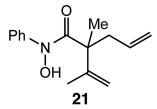
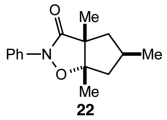
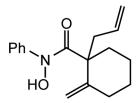
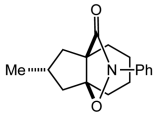
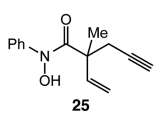
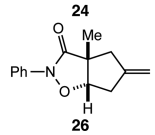
Table 2. Cyclizations of Alkenyl *N*-Aryl Hydroxamic Acids

entry	substrate	product	% yield[a,b]
1	 **6**	 **8**	90
2[c]	 **9**	 **10**	85
3[d]	 **11**	 **12**	32
4	 **13**	 **14**	71
5	 **15**	 **16**	77 >20:1 dr
6[c]	 **17**	 **18**	88 >20:1 dr

[a]Standard reaction conditions: 0.1 mmol of substrate, 5 mol % DLP, 0.80 equiv of **7**, $ClCH_2CH_2Cl$, 60 °C, 16–72 h. [b]Yield of isolated product. [c]Reaction performed on 0.5 mmol scale with 2.5 mol % DLP (no **7** required). [d]1.6 equiv of **7** added.

Cascade-type radical cyclizations are among the premier methods for the rapid construction of complex carbocycles and heterocycles from unsaturated substrates.[12] We postulated that introducing additional unsaturation to the simple alkenyl hydroxamic acids of Table 2 would enable the construction of a variety of complex polycyclic products via cascade-type cyclizations. As shown in Table 3, we have successfully applied this approach to the synthesis of a number of [5,5]- and [5,6]-fused and bridged polycyclic compounds. Minor changes in the standard reaction conditions were required to prevent decomposition and premature reduction of the intermediate carbon-centered radical prior to the C–C bond-forming step: reagent **7** was excluded from these reactions, the reaction solvent was switched from $ClCH_2CH_2Cl$ to benzene, and the cascade reactions were performed at a higher dilution (0.1 M instead of 0.5 M). The cascade cyclizations of substrates **19** and **21** containing either a terminal or 1,1-disubstituted alkene and a pendant allyl group delivered [5,5]-*cis*-fused isoxazolidinone products **20** and **22**, respectively (entries 1 and 2). Cyclohexenyl hydroxamic acid **23** provided an efficient approach to complex propellane-type bridged isoxazolidinone **24** (entry 3). The modest diastereoselectivity observed in the cascade reactions of entries 1–3 is a consequence of the carbon–carbon bond-forming step. The cascade cyclization of alkynyl

Table 3. Cascade-Type Polycyclizations of Unsaturated Hydroxamic Acids

entry	substrate	product	% yield[a,b]
1	 **19**	 **20**	54 1.2:1 dr
2[c]	 **21**	 **22**	82 2.9:1 dr
3[c]	 **23**	 **24**	82 2.7:1 dr
4	 **25**	 **26**	41 >20:1 dr

[a]Standard reaction conditions: 0.1 mmol of substrate, 5 mol % DLP, benzene, 60 °C, 16–72 h. [b]Yield of isolated product. [c]Entries 2 and 3 were performed on a 0.5 mmol scale.

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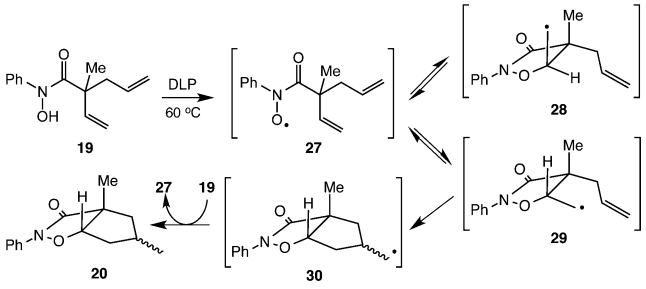
hydroxamic acid **25** provides *cis*-fused bicyclic isoxazolidinone **26** as a single diastereomer, consistent with this hypothesis (entry 4).

Indeed, all products in Table 3 exclusively contain *cis* ring fusion. The basis for stereoselectivity is easily understood by considering the likely mechanism for these cascade processes (Scheme 3). Following an initial, reversible amidoxyl radical

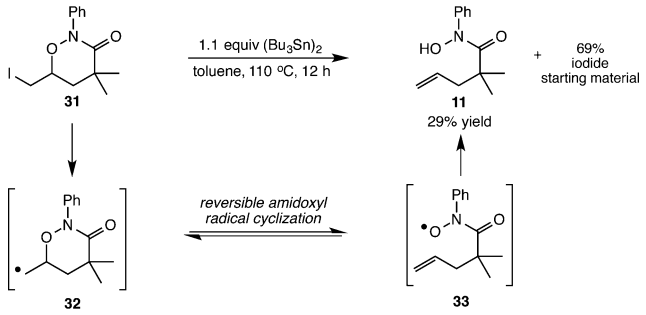
Scheme 3. Reversible Amidoxyl Radical Cyclizations Lead to *cis* Ring Fusion in Cascade-Type Processes



cyclization, the intermediate carbon-centered radical may be formed on either the opposite (**28**) or same (**29**) face of the isoxazolidinone ring as the pendant alkene. Intermediate **29** undergoes a fast 5-*exo* cyclization, whereas isomer **28** is incapable of alkene addition and reverts to the amidoxyl species **27**. This equilibration ultimately leads to exclusive formation of the *cis*-fused product.

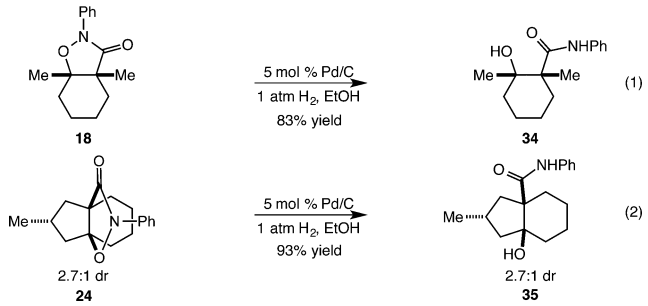
We hypothesize that the amidoxyl radical cyclizations involved in the reactions presented herein, and in related alkene difunctionalizations, are reversible.[8] We therefore sought to provide experimental evidence for this reversibility by independently demonstrating the viability of a radical elimination of an amidoxyl species in a ring-opening process (Scheme 4). Standard radical deiodination of iodide **31** using

Scheme 4. Hydroxamic Acid Formation via a Radical Ring Opening Process



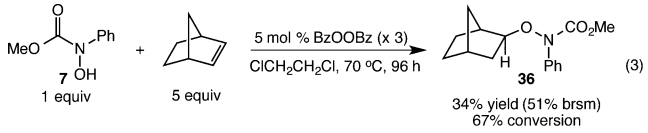
$(Bu_3Sn)_2$ in toluene at 110 °C delivered ring-opened alkenyl hydroxamic acid **11** in 29% yield (69% recovered **31**). This result demonstrates the potential for carbon-centered radical **32** to undergo radical ring opening to deliver amidoxyl species **33**, and provides evidence for the reversibility of amidoxyl radical cyclizations.

The isoxazolidinone products of these cyclization reactions may be easily elaborated by cleavage of the weak N−O bond. This reduction can be conveniently performed using palladium-catalyzed hydrogenation (eqs 1 and 2). For example, hydrogenation of bicyclic isoxazolidinone **18** (formed from substrate **17**) delivered the formal hydration product **34**.



Reduction of propellane-type isoxazolidinone **24** provides substituted hydrindane **35** in high yield.

While our radical-mediated approach to alkene hydration was successful in a variety of intramolecular contexts, the development of intermolecular transformations proved challenging. This is likely a consequence of the reversibility of the amidoxyl radical alkene addition, combined with a relatively slow rate of H atom transfer (see Scheme 2). Nevertheless, we have obtained a proof-of-principle result for an intermolecular amidoxyl radical addition by using norbornene as a substrate under modified reaction conditions (eq 3). This reaction required extended reaction times (96 h) and did not proceed to completion. At this stage, our efforts to engage other alkenes have been unsuccessful.



In conclusion, we have developed a free-radical-mediated approach to the formal hydration of alkenes using hydroxamic acids. This method capitalizes on the unique ability of hydroxamic acids to participate in both alkene additions and hydrogen atom transfers. These modes of reactivity have enabled both simple and cascade-type cyclization processes, although extensions to intermolecular contexts are currently limited. The isoxazolidinones produced are easily elaborated to a variety of mono- and bicyclic products.

■ ASSOCIATED CONTENT

Supporting Information

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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Notes

The authors declare no competing financial interest.

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