JOC Article
pubs.acs.org/joc

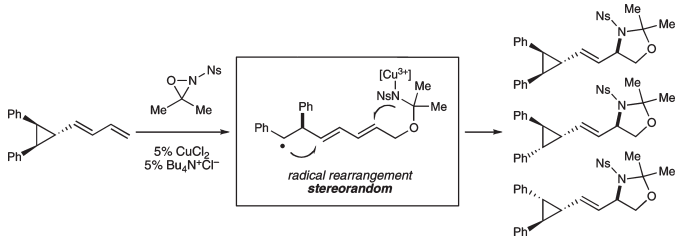
Anionic Halocuprate(II) Complexes as Catalysts for the Oxaziridine-Mediated Aminohydroxylation of Olefins

Tamas Benkovics, Juana Du, Ilia A. Guzei, and Tehshik P. Yoon*

Department of Chemistry, University of Wisconsin–Madison, 1101 University Avenue, Madison, Wisconsin 53706

tyoon@chem.wisc.edu

Received April 30, 2009



We have discovered that the oxaziridine-mediated copper-catalyzed aminohydroxylation reaction recently discovered in our laboratories is dramatically accelerated in the presence of halide additives. The use of this more active catalyst system enables the efficient aminohydroxylation of electronically and sterically deactivated styrenes and also enables the use of nonstereogenic 3,3-dialkyl oxaziridines as terminal oxidants in the aminohydroxylation reaction. We present evidence that anionic halocuprate(II) complexes are the catalytically active species responsible for the increased reactivity under these conditions. This unexpected observation has led us to re-evaluate our mechanistic understanding of this reaction. On the basis of the results of a variety of radical trapping experiments, we propose a modified mechanism that involves a homolytic reaction of the olefin with a copper(II)-activated oxaziridine. Together, the observation that anionic additives significantly increase the oxidizing ability of oxaziridines and the recognition of the radical nature of reactions of oxaziridines under these conditions suggest that a variety of new oxidative transformations catalyzed by halocuprate(II) complexes should be possible.

Introduction

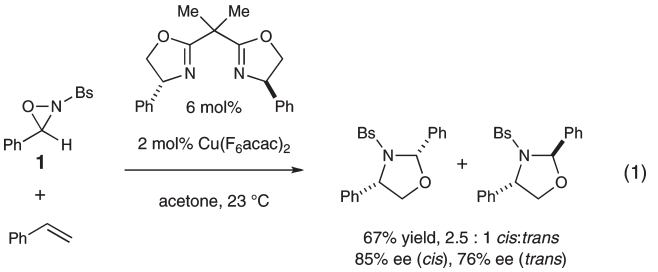
Halocuprates(II) are anionic cupric halide complexes that typically possess the empirical formula $[ACuX_3]$ or $[A_2CuX_4]$, where X is a halide anion and A is a cationic metal or ammonium counterion. Due to the constitutional and stereochemical diversity of their solid-state structures[1] and their unusual magnetic properties,[2] the physical and electronic structure properties of these compounds have been investigated in great depth.[3] In contrast, only a handful of reports describing organic reactions catalyzed by halocuprate(II) complexes have been published.[4,5] Some of the most intriguing of these papers, beginning with a report in the Japanese patent literature, describe the beneficial effect of lithium and ammonium chloride salts in $CuCl_2$-catalyzed

(1) Arnby, C. H.; Hagner, S.; Dance, I. *CrystEngComm* **2004**, *6*, 257–275.
(2) (a) O'Brien, S.; Gaura, R. M.; Landee, C. P.; Ramakhrishna, B. L.; Willett, R. D. *Inorg. Chim. Acta* **1988**, *141*, 83–89. (b) Willett, R. D.; Twamley, B.; Montfrooij, W.; Granroth, G. E.; Nagler, S. E.; Hall, D. W.; Park, J.-H.; Watson, B. C.; Meisel, M. W.; Talham, D. R. *Inorg. Chem.* **2006**, *45*, 7689–7697.
(3) (a) Smith, D. W. *Coord. Chem. Rev.* **1976**, *21*, 93–158. (b) Willett, R. D. *Coord. Chem. Rev.* **1991**, *109*, 181–205.
(4) (a) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063–3073.bAsakawa, Y.; Matsuda, R.; Hashimoto, T. Jpn. Patent 39847 (1984); *Chem. Abstr.* 1984, *101*, 130395x. (c) Takehira, K.; Shimizu, M.; Watanabe, Y.; Orita, H.; Hayakawa, T. *Tetrahedron Lett.* **1989**, *30*, 6691–6692. (d) Shimizu, M.; Watanabe, Y.; Orita, H.; Hyakawa, T.; Takehira, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1522–1526. (e) Sasaki, T.; Zhong, C.; Tada, M.; Iwasawa, Y. *Chem. Commun.* **2005**, 2506–2508.
(5) Halocuprate(I) compounds, on the other hand, are used synthetically and have been shown to be convenient sources of nucleophilic chloride. See: (a) Muscio, O. J. Jr.; Jun, Y. M.; Philip, J. B. Jr. *Tetrahedron Lett.* **1978**, *19*, 2379–2382. (b) Elsevier, C. J.; Meijer, J.; Tadema, G.; Stehouwer, P. M.; Bos, H. J. T.; Vermeer, P.; Runge, W. *J. Org. Chem.* **1982**, *47*, 2194–2196. (c) Elsevier, C. J.; Bos, H. J. T.; Vermeer, P.; Spek, A. L.; Kroon, J. *J. Org. Chem.* **1984**, *49*, 379–381. (d) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1984**, *49*, 1649–1650. (e) Liedholm, B.; Nilsson, M. *Acta Chem. Scand. A.* **1984**, *38*, 555–562.

DOI: 10.1021/jo900902k Published on Web 06/09/2009

aerobic oxidations of phenols and speculate that the formation of halocuprate(II) complexes is responsible for the observed rate accelerations.[4b−4d] To the best of our knowledge, however, the effect of halide additives in other copper-catalyzed oxidation reactions has not been extensively investigated, despite the community's increasing interest in the development of new copper-catalyzed oxidative transformations.[6] In this paper, we report that the oxaziridine-mediated aminohydroxylation reaction recently developed in our laboratory[7] is also significantly accelerated in the presence of anionic halide additives, and we present evidence that a halocuprate(II) complex formed in situ is responsible for this effect.

The need to develop a more reactive catalyst system became apparent to us in the course of our investigations toward a highly enantioselective version of our aminohydroxylation protocol. We recently reported our initial efforts toward an asymmetric aminohydroxylation.[8] Synthetically useful levels of enantioselectivity (up to 86% ee) can be achieved in the aminohydroxylation of styrenes with *N*-sulfonyl oxaziridine **1** ("Davis' oxaziridine")[9] when a copper(II) bis(oxazoline) complex is used as the catalyst (eq 1), and the enantiopurity of the amino alcohol products can be increased to very high levels (>99% ee) upon recrystallization. Thus, this method represents a useful osmium-free complement to the highly enantioselective Sharpless aminohydroxylation reaction[10] that remains the state-of-the-art method for olefin oxyamination.

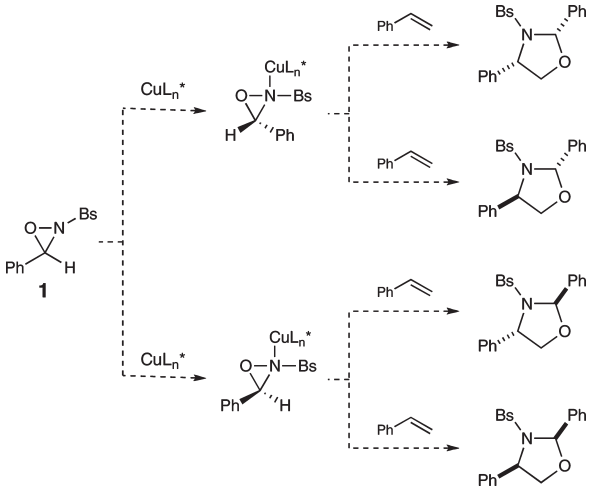


(1)

We quickly recognized, however, that the use of a chiral, racemic oxaziridine as the terminal oxidant for the copper(II)-catalyzed asymmetric aminohydroxylation was nonideal, for several reasons. First, we have been unable to control the orientation of the benzylidene aminal stereocenter in any oxaziridine-mediated aminohydroxylations we have studied to date. Fortunately, both diastereomers of the product produced in the enantioselective reaction depicted in eq 1 possess the same orientation at the benzylic amine stereocenter, and the same major enantiomer of the *N*-sulfonyl aminoalcohol is revealed upon acid-catalyzed hydrolysis of either diastereomer. Nevertheless, the product mixture arising from the lack of control over the stereogenic benzylidene aminal moiety makes purification difficult and complicates spectroscopic analysis of the reaction mixture.

More critically, the chirality of oxaziridine **1** is a significant impediment to further improving the enantioselectivity of the asymmetric process. Coordination of racemic **1** to a chiral copper catalyst results in the formation of a matched and mismatched set of diastereomeric oxaziridine−metal complexes, each of which would be expected to react at different rates and with different stereoselectivities in the aminohydroxylation reaction. Thus, the stereoinduction in this transformation consists of two separate stereodifferentiating steps: (1) initial coordination of the racemic oxaziridine to the enantiopure chiral copper catalyst, followed by (2) the aminohydroxylation process itself (Scheme 1). These two steps are not stereochemically well-coupled, and during the course of our optimization studies, we found that variations of the reaction conditions that improved the selectivity of one step often decreased the selectivity of the other.

SCHEME 1



A possible approach to address the complexity of this system would be to utilize oxaziridines that are not stereogenic at carbon (i.e., symmetrically 3,3-disubstituted oxaziridines). This approach would simplify the system by avoiding the problematic formation of diastereomeric copper−oxaziridine complexes in the enantioselective reaction altogether. In addition, the aminohydroxylation reaction would not produce mixtures of diastereomeric products, and thus the nonstereogenic aminal moiety could be used as a convenient protecting group during a multistep synthetic sequence. Unfortunately, 3,3-dialkyloxaziridines are much less reactive oxidants than monosubstituted 1-aryl oxaziridines such as **1** and fail to produce useful yields of aminohydroxylation products with any combination of bis(oxazoline) ligand and copper precursor we have investigated to date. Thus, the development of a highly enantioselective aminohydroxylation protocol is predicated on the discovery of a more reactive catalyst system capable of engaging these sterically and electronically deactivated oxaziridines in the aminohydroxylation reaction.

In this paper, we report that an anionic halocuprate(II) complex is a significantly more active catalyst for the oxaziridine-mediated aminohydroxylation of olefins. While the initial goal for this research was the development of conditions that

(6) For recent reviews, see: (a) Punniyamurthy, T.; Rout, L. *Coord. Chem. Rev.* **2008**, *252*, 134–154. (b) van der Vlught, J. I.; Meyer, F. *Top. Organomet. Chem.* **2007**, *22*, 191–240.

(7) (a) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 1866–1867. (b) Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610–6615.

(8) Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. *Tetrahedron* **2009**, *65*, 5118−5124.

(9) (a) Davis, F. A.; Nadir, U. K.; Kluger, E. W. *J. Chem. Soc., Chem. Commun.* **1977**, 25–26. (b) Davis, F. A.; Jenkins, R.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, *52*, 5171–5174.

(10) Sharpless, K. B.; Chong, A. O.; Oshima, J. *J. Org. Chem.* **1976**, *41*, 177–179.

enable the use of 3,3-dialkyl oxaziridines as the terminal oxidant for this reaction, we show that these improved reaction conditions also dramatically accelerate the reactions of a variety of sterically and electronically deactivated styrene substrates, as well. Moreover, the surprising observation that anionic copper complexes provide dramatically superior rates of reaction led us to probe the mechanism of this transformation in greater depth, and we also describe the results of mechanistic studies that suggest that the oxaziridine-mediated aminohydroxylation involves a radical intermediate, rather than the cationic intermediate we had originally proposed. Together, the discovery of these more reactive reaction conditions coupled with our understanding of the unique ability of halocuprate(II) complexes to initiate one-electron oxidation reactions of oxaziridines should enable us to design new approaches to other copper-catalyzed oxidative functionalization reactions.

Results and Discussion

A. Anionic Halocuprate(II) Complexes as Catalysts for Aminohydroxylation. Figure 1 outlines the features that we considered to be desirable in the design of an ideal terminal oxidant for the copper-catalyzed aminohydroxylation reaction (e.g., **2**). As outlined above, the most critical element of our design plan is the absence of a stereogenic carbon in the oxaziridine ring. We considered the use of 3,3-unsubstituted and 3,3-diaryl oxaziridines, but the former could not be synthesized in useful yields, and the latter decompose readily and are not suitable for long-term storage. Thus, we focused our attention upon aminohydroxylations using 3,3-dialkyl oxaziridines, which can be easily synthesized using the method of Jennings[11] and appear to be indefinitely stable when stored in the refrigerator. Second, we were interested in the reactivity of oxaziridines bearing N-substituents that can be removed from the 1,3-oxazolidine products under mild conditions. Oxaziridines bearing *N*-carbamate[12] and *N*-phosphinoyl[13] groups failed to afford aminohydroxylation products. On the other hand, *N*-nosyl oxaziridines possess reactivity similar to that of the analogous *N*-benzenesulfonyl oxaziridines and afford products that can be deprotected under conditions much milder than the dissolving metal reduction conditions required for removal of an *N*-benzenesulfonyl group.

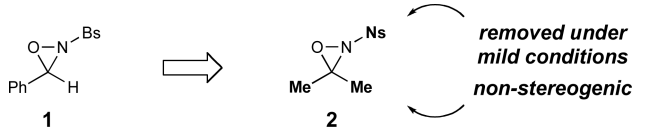
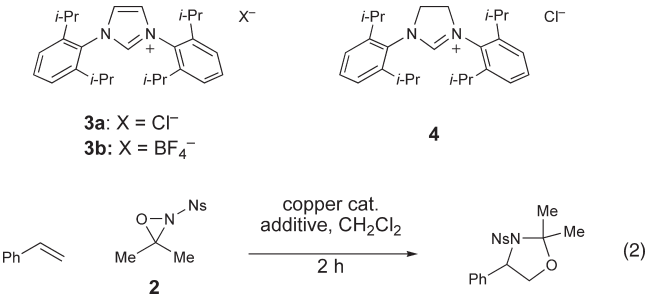


FIGURE 1. Design considerations for oxaziridines used in aminohydroxylation. Bs = benzenesulfonyl; Ns = 4-nitrobenzenesulfonyl.

Table 1 summarizes our experiments probing the utility of oxaziridine **2** in the copper-catalyzed aminohydroxylation reaction. As we stated previously, 3,3-dialkyloxaziridines are significantly poorer oxidants than 3-phenyloxaziridine **1**, and no aminohydroxylation products are observed using

TABLE 1. Effect of Additives on Copper-Catalyzed Aminohydroxylations Using Oxaziridine 2[a]



entry	copper source	additive	yield
1	$Cu(TFA)_2$ (2 mol %)	HMPA (10 mol %)	< 5%
2	$CuCl_2$ (5 mol %)	HMPA (10 mol %)	19%
3	$CuCl_2$ (5 mol %)	IPr·Cl (**3a**) (6 mol %)	82%
4[b]	$CuCl_2$ (5 mol %)	IPr·BF_4 (**3b**) (6 mol %)	< 5%
5	**$CuCl_2$ (5 mol %)**	**$Bu_4N^+Cl^-$ (6 mol %)**	**80%**
6	none	$Bu_4N^+Cl^-$ (6 mol %)	< 5%
7[b]	$CuCl_2$ (5 mol %)	$Bu_4N^+ClO_4^-$ (6 mol %)	< 5%
8	$CuCl_2$ (5 mol %)	$Bu_4N^+Br^-$ (6 mol %)	59%
9	$CuCl_2$ (5 mol %)	$Bu_4N^+OAc^-$ (6 mol %)	70%

[a] Reactions were conducted using 1.5 equiv of oxaziridine in CH_2Cl_2 (2 M) under argon. [b] $CuCl_2$ was insoluble under these conditions.

the $Cu(TFA)_2$/HMPA catalyst system that we previously reported (entry 1). Extensive optimization of copper source and reaction conditions resulted in only modest improvement in the reactivity when $CuCl_2$ was used as the copper source instead of $Cu(TFA)_2$ (entry 2). Thus, we performed a survey of ligands that might modify the reactivity of the copper catalyst, which revealed a significant increase in the efficiency of aminohydroxylation upon the addition of a variety of imidazolium chloride salts (e.g., IPr·Cl **3a**, entry 3), precursors to the corresponding N-heterocyclic carbene (NHC) ligands.[14] We were able to obtain diffractable crystals of a putative catalyst complex upon combining dihydroimidazolium chloride **4** (SIPr·Cl) with $CuCl_2$ in deuterochloroform. Surprisingly, the X-ray structure of these crystals revealed that a chloride-bridged copper dimer had been formed rather than the expected NHC−copper complex (see Supporting Information). We wondered, therefore, if the observed increase in catalytic efficiency was attributable to the presence of an anionic chloride additive, rather than a carbene ligand. Indeed, the addition of imidazolium salts bearing noncoordinating counterions (e.g., IPr·BF_4 **3b**, entry 4) failed to accelerate the reaction. On the other hand, tetrabutylammonium chloride had the same dramatic effect on the rate of the aminohydroxylation as imidazolium chloride **3a** (entry 5).

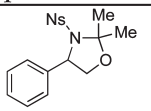
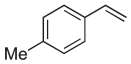
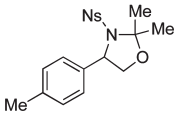
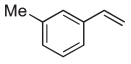
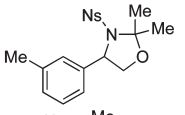
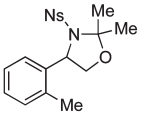
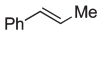
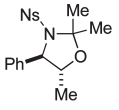
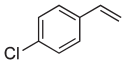
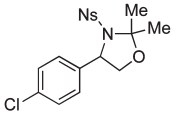
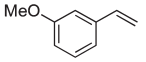
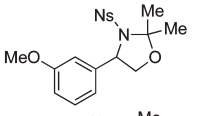
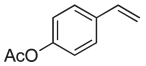
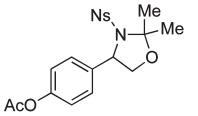
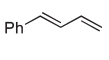
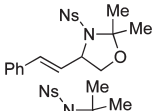
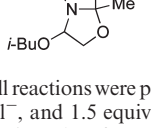
Further control experiments showed that no reaction occurs in the absence of copper(II) additives (entry 6), which rules out the possibility that the aminohydroxylation could be catalyzed by the halide alone.[15] We also found that reactions using tetrabutylammonium salts of noncoordinating anions

(11) Jennings, W. B.; Watson, S. P.; Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1988**, 931–932.
(12) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem.—Eur. J.* **1997**, *3*, 1691–1709.
(13) Boyd, D. R.; Jennings, W. B.; McGuckin, R. M.; Rutherford, M.; Saket, B. M. *J. Chem. Soc., Chem. Commun.* **1985**, 582–583.
(14) The direct formation of metal−NHC complexes from the reaction of imidazolium salts with metal complexes bearing basic ligands is well-precedented: Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371–2374.
(15) For a rare example of halogen-catalyzed aziridination, see: Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844–6845.

(e.g., $Bu_4N^+ClO_4^-$) were inefficient (entry 7). On the other hand, a variety of additives possessing coordinating anions, including $Bu_4N^+Br^-$ and $Bu_4N^+OAc^-$, were also effective at increasing the rate of aminohydroxylation (entries 8 and 9). Together, these results suggest that an anionic halocuprate(II) complex formed upon coordination of the halide or pseudohalide additive to $CuCl_2$ constitutes a more reactive catalyst for the aminohydroxylation than the neutral $CuCl_2$ species itself.

An important initial goal for this study was to demonstrate that dimethyloxaziridine **2** is indeed a competent terminal oxidant for the aminohydroxylation using these halocuprate catalysts for a range of olefinic substrates, which is demonstrated by the experiments summarized in Table 2. As was the case with our previous aminohydroxylation protocol that utilized the more reactive oxaziridine **1**, aminohydroxylations with **2** require some electron-stabilizing group in order to provide reasonable product yields. In addition to styrene itself (entry 1), styrenes that are substituted at various positions on the ring (entries 2−4) and styrenic olefin (entry 5) undergo efficient aminohydroxylation. Similarly, styrenes bearing electron-donating and -withdrawing substituents are also well-tolerated (entries 6−8). Finally, other stabilized olefinic substrates such as dienes (entry 9) and vinyl ethers (entry 10) are also competent substrates for aminohydroxylation with oxaziridine **2** using the more reactive $CuCl_2/Bu_4N^+Cl^-$ catalyst system.

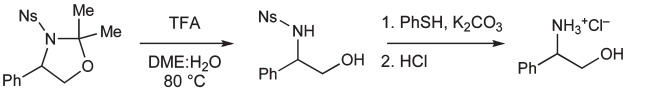
TABLE 2. Aminohydroxylations Using Oxaziridine 2[a]

entry	substrate	product	time	yield[b]
1			2.5 h	74%
2			2 h	79%
3			1 h	78%
4[c]			4 h	80%
5[c]			4.5 h	60%[d]
6			3 h	78%
7			3 h	86%
8			2 h	71%
9[e]			2 h	71%[f]
10			2 h	62%

[a]Unless otherwise noted, all reactions were performed using 5 mol % of $CuCl_2$, 5 mol % of $Bu_4N^+Cl^-$, and 1.5 equiv of oxaziridine in CH_2Cl_2 (2 M). [b]Yields are the averaged results of two reproducible experiments. [c]Reaction performed using 10 mol % of $CuCl_2$ and 10 mol % of $Bu_4N^+Cl^-$ and at 1 M. [d]>20:1 *trans*/*cis*. [e]Reaction performed using 2 mol % $CuCl_2$ and 2 mol % $Bu_4N^+Cl^-$. [f]>20:1 olefin selectivity.

Unlike the products of aminohydroxylations using 3-phenyloxaziridine **1**, the aminohydroxylation products shown in Table 2 are formed as single diastereomers, which simplifies the purification and analysis of these reactions considerably. Moreover, the isopropylidene aminal moiety can be quantitatively removed under standard acidic hydrolysis conditions, and the *N*-nosyl group is also efficiently removed using a protocol (PhSH, K_2CO_3)[16] that is much milder than the strongly reducing conditions required for cleavage of other benzenesulfonyl groups. Both deprotections are clean and high yielding, and they can be conducted on gram scale without the need for chromatographic purification after either step (Scheme 2, 91% yield).

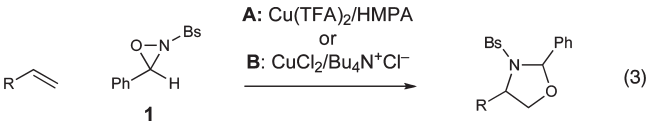
SCHEME 2

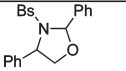
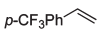
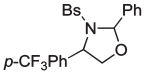
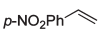
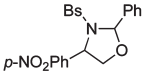
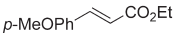
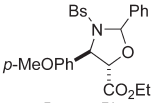
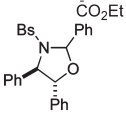
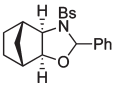


The effect of the halocuprate(II) catalyst on the efficiency of the reaction is also dramatically evident in aminohydroxylations that utilize the more reactive 3-phenyloxaziridine **1** as the terminal oxidant (Table 3). We previously reported that styrene is efficiently aminohydroxylated by **1** in the presence of $Cu(TFA)_2$/HMPA system, and that the reaction requires 11 h to proceed to completion (entry 1). Using the $CuCl_2/Bu_4N^+Cl^-$ system, however, the reaction is complete in just 2 h, and the yield of the reaction is not negatively affected (entry 2). Similarly, *p*-(trifluoromethyl)styrene, which previously required 36 h to proceed to completion, affords good yields of the aminohydroxylation product under these improved conditions after 3 h (entries 3 and 4). Given the dramatic rate increase we observed in the reaction of this electron-deficient styrene, we wondered if the halocuprate(II) catalyst would enable successful aminohydroxylation of styrenes bearing strongly electron-withdrawing groups, which were not useful substrates using our original system. Indeed, the reaction of *p*-nitrostyrene, which did not proceed to completion even after extended reaction times using the $Cu(TFA)_2$/HMPA system (entry 5), requires only 4.5 h to generate the aminohydroxylated product in 76% yield (entry 6), and the rate of reaction with ethyl *p*-methoxycinnamate is also increased to synthetically useful levels (entries 7 and 8). Sterically encumbered styrenes also react efficiently under these improved conditions; in re-examining the aminohydroxylation of *cis*-stilbene, we found that the yield was improved and the reaction time was

(16) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253–5256.

TABLE 3. Comparison of Catalyst Systems with Less Reactive Substrates[a]



entry	alkene	product	catalyst	time	yield
1[b]			**A** (2%)	11 h	87%
2			**B** (2%)	2 h	92%
3[b]			**A** (2%)	36 h	73%
4			**B** (2%)	3 h	80%
5			**A** (2%)	24 h	46%
6			**B** (2%)	4.5 h	76%
7			**A** (2%)	24 h	23%
8			**B** (2%)	24 h	74%
9[b]			**A** (10%)	24 h	58%
10			**B** (2%)	12 h	80%
11			**A** (2%)	6 h	54%
12			**B** (2%)	6 h	72%

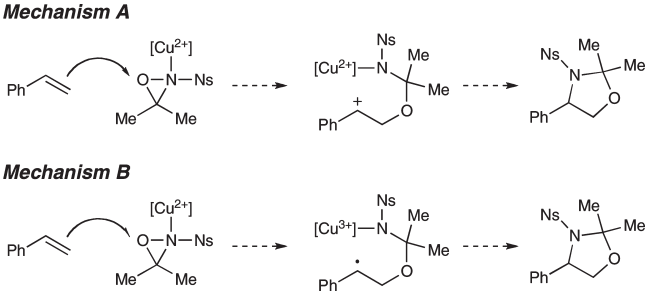
[a] Reactions conducted using catalyst system **A** were performed using 2 mol % of $Cu(TFA)_2$, 10 mol % of HMPA, and 1.5 equiv of **1** in CH_2Cl_2 (0.5 M). Reactions conducted using catalyst system **B** were performed using 2 mol % of $CuCl_2$, 2 mol % of $Bu_4N^+Cl^-$, and 1.5 equiv of **1** in CH_2Cl_2 (0.5 M). [b] Data reported are from ref 7a.

reduced even when the loading of the copper catalyst was reduced from 10 to 2 mol % (entries 9 and 10). As was the case with the original $Cu(TFA)_2$/HMPA catalyst system, this reaction is not stereospecific, and the *cis*-olefin exclusively generates products in which the two vicinal phenyl substituents are *trans* on the oxazolidine ring. Finally, we also observed a rate acceleration using non-aromatic substrates, but the effect was less pronounced. The aminohydroxylations of strained aliphatic olefins such as norbornene are faster using the halocuprate(II) catalyst (entries 11 and 12), but reactions involving less reactive primary aliphatic olefins are not high-yielding, and further explorations will be required to increase the reactivity of these substrates to synthetically useful levels. These studies will benefit from a deeper understanding of the origins of the rate acceleration in the presence of halide additives. Our recent investigations have therefore been focused on a detailed examination of the mechanism of this reaction, and these studies are described in the next section.

To summarize this section, halocuprate(II) complexes generated in situ by coordination of exogenous anionic halide additives to copper salts are superior catalysts for the oxaziridine-mediated aminohydroxylation developed in our laboratories. This discovery is significant for a number of reasons. First, the halocuprate(II) complex is freely soluble in many common organic solvents, and thus reactions conducted using the $CuCl_2/Bu_4N^+Cl^-$ catalyst system do not require the use of HMPA as a solubilizing additive. Second, these more powerfully oxidizing conditions increase the efficiency of aminohydroxylations using sterically and electronically deactivated styrenes and also enable the use of nonstereogenic 3,3-dimethyl oxaziridine **2** as the terminal oxidant for the aminohydroxylation, which is an important step toward the development of a highly enantioselective aminohydroxylation protocol. Finally, examples of synthetically useful reactions catalyzed by halocuprate(II) complexes are relatively rare, and while the beneficial effects of halide additives in palladium-catalyzed reactions[17] are well-appreciated, their effect in copper-catalyzed reactions has not been systematically explored. The possibility of developing a general understanding of halide effects in copper-catalyzed oxidations prompted us to examine the mechanism of the aminohydroxylation in greater detail.

B. Revision of the Mechanism of Aminohydroxylation. Our previous investigations of the mechanism of the aminohydroxylation under our original $Cu(TFA)_2$/HMPA conditions had led us to propose a two-step, cationic mechanism (Scheme 3, Mechanism A) in which the copper catalyst serves as a Lewis acid that activates the oxaziridine toward nucleophilic attack by the styrenic olefin. This hypothesis was based on several observations, including the following: (1) styrenes bearing electron-donating groups react more rapidly than those bearing electron-withdrawing groups; (2) aminohydroxylations of *cis*- and *trans*-olefins are stereoconvergent, indicating an intermediate that enables free rotation about the bond arising from the alkene; and (3) vinyl ethers and dienes that would be expected to give rise to stabilized radical or cationic intermediates are excellent substrates for aminohydroxylation. However, it seems unlikely that the anionic $CuCl_3^-$ fragment would be a more powerful Lewis acid than a neutral $CuCl_2$•HMPA complex. Thus, the results of these studies seem to be at odds with our original mechanistic hypothesis. Instead, we wondered if our observation of the anion acceleration effect suggested a non-redox-innocent role for the copper catalyst.

SCHEME 3



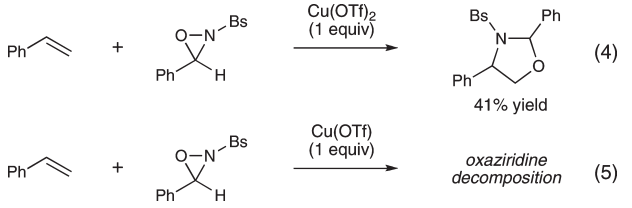
It seems unlikely, given the strongly oxidizing conditions of the aminohydroxylation, that a copper(I) salt would be the catalytically relevant species in this process.[18,19] Evidence against this possibility is provided by the results of stoichiometric experiments.

(17) (a) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321. (c) Fairlamb, I. J. S.; Taylor, R. J. K.; Serrano, J. L.; Sanchez, G. *New J. Chem.* **2006**, *30*, 1695–1704.

(18) Radical rearrangements of *N*-alkyloxaziridines initiated upon one-electron reduction by copper(I) catalysts have been studied in detail by Aubé. See: (a) Aube, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009–9018. (b) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269–277.

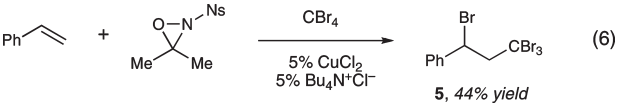
(19) An intramolecular aminohydroxylation of olefins using *N*-benzoyloxyamines catalyzed by copper(I) salts has been reported: Noack, M.; Göttlich, R. *Chem. Commun.* **2002**, 536–537.

First, we showed that styrene reacts with oxaziridine **1** in the presence of 1 equiv of $Cu(OTf)_2$ in acetonitrile to produce the expected aminohydroxylation product, albeit in modest yield (eq 4, 41% yield). In contrast, no aminohydroxylation is observed when 1 equiv of CuOTf is used as the stoichiometric promoter (eq 5).[20] Instead, the oxaziridine is rapidly consumed upon addition, and the colorless copper(I) solution immediately turns blue-green, suggesting that copper(I) is oxidized to copper(II) by the oxaziridine under the reaction conditions. Thus, it seems very unlikely that copper(I) generated upon disproportionation of copper(II) is the mechanistically relevant resting state of the catalyst.



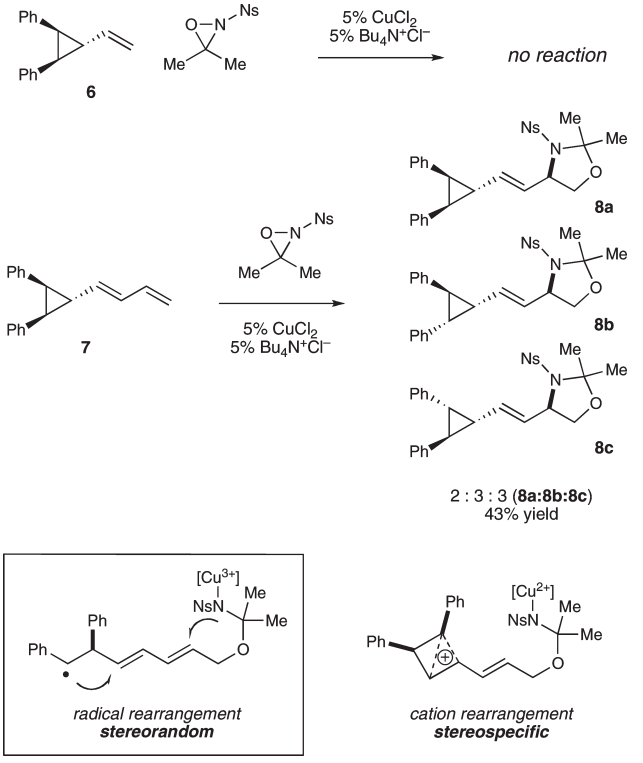
Thus, we propose instead that this reaction proceeds via a copper(II/III) catalytic cycle. Our modified mechanistic hypothesis is depicted in Scheme 3, Mechanism B, in which the copper-activated oxaziridine undergoes an initial homolytic reaction with the alkene substrate. The intermediate of this reaction would involve a transient copper(III) sulfonamide that reacts with a benzylic radical to produce the cyclic aminal product and regenerate the copper(II) catalyst.[21] Previous computational studies of oxaziridine reactivity provide support for a radical mechanism. Houk reported that the transition state for oxaziridine-mediated epoxidations is concerted but features a significant buildup of unpaired spin density on one of the carbons of the alkene and on the oxaziridine nitrogen.[22] Thus, Mechanism B is consistent with the propensity of oxaziridines to react with significant homolytic character. In addition, a key feature of this mechanism is the generation of a highly oxidized copper(III) intermediate. We would expect that an anionic halocuprate(II) would be more easily oxidized than a neutral copper−HMPA complex and could thus be a more active catalyst.[23−25]

In order to obtain evidence to support Mechanism B, we first investigated the possibility that an exogenous trapping reagent might intercept the putative benzylic radical intermediate. The strongly oxidizing conditions of the aminohydroxylation limited the choice of radical trap; most standard trapping reagents such as TEMPO and trialkyltin hydrides are rapidly oxidized by the oxaziridine under the reaction conditions. Ultimately, we discovered that carbon tetrabromide, although stable to the oxaziridine and copper(II) catalyst alone, could inhibit formation of the aminohydroxylation product. In the presence of excess CBr_4, we observed exclusive formation of Kharasch addition product **5** (eq 6).[26] No reaction was observed in the absence of the oxaziridine. These data are consistent with interception of a short-lived benzylic radical intermediate by CBr_4, which would generate tribromomethyl radical and initiate the radical chain addition of CBr_4 across the styrenic bond. Thus, this experiment provides strong evidence that a radical species is indeed generated under the reaction conditions, although we could not demonstrate that this radical was a productive intermediate en route to the aminohydroxylation product.



We also investigated the aminohydroxylation of cyclopropane-substituted alkenes in an attempt to observe products resulting from ring opening of a cyclopropylcarbinyl radical (Scheme 4). *cis*-1,2-Diphenyl-3-vinylcyclopropane **6** proved to be unreactive under our optimized reaction conditions. On the other hand, the analogous 1-(*cis*-2,3-diphenylcyclopropyl)butadiene **7** reacted smoothly under the same conditions and produced a 43% isolated yield of aminohydroxylation

SCHEME 4



(20) These stoichiometric studies were conducted using copper(I) and copper(II) triflate because of the limited solubility of the chloride and TFA salts in methylene chloride.

(21) This mechanism would be similar to the "molecule-induced homolysis" pathway proposed by Minisci to explain dioxirane-mediated epoxidations: Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Zhao, L. *J. Org. Chem.* **1998**, *63*, 254–263.

(22) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147–10152.

(23) Margerum's studies on copper(II)−peptide complexes indicate that multiple anionic ligands facilitate electrochemical oxidation of the metal by stabilizing the copper(III) oxidation state: Bossu, F. P.; Chellappa, K. L.; Margerum, D. W. *J. Am. Chem. Soc.* **1977**, *99*, 2195–2203.

(24) A copper(III) intermediate has been implicated in the decomposition of hypochlorite and hypobromite salts by anionic hydroxycuprate(II) catalysts: Gray, E. T. Jr.; Taylor, R. W.; Margerum, D. W. *Inorg. Chem.* **1977**, *16*, 3047–3055.

(25) We have also ruled out a mechanism involving initial homolytic ring opening of the oxaziridine. One-electron reduction of the oxaziridine would be expected to produce a copper alkoxide and a nitrogen-centered radical, in analogy to Aubé's studies with copper(I),[18] which would give rise to the opposite regiochemical outcome. Moreover, as shown in eq 5, copper(I) complexes reduce the oxaziridine but fail to produce any aminohydroxylation products, which suggests that reductive cleavage of the N−O bond is not the initial step of the mechanism.

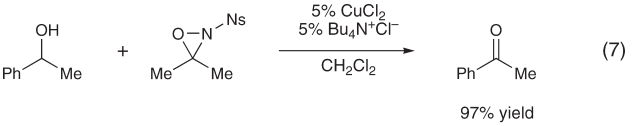
(26) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *J. Am. Chem. Soc.* **1946**, *68*, 154–155.

products. Surprisingly, we obtained a 2:3:3 mixture of three diastereomeric products (**8a**−**c**) possessing varying stereochemistry about the cyclopropane. Control reactions indicated that the stereochemical fidelity of the *cis*-diphenylcyclopropane unit was preserved when diene substrate **7** was subjected to the copper catalyst and when the isomerically pure product **8a** was isolated and resubjected to the reaction conditions. Thus, both the substrate and the product are stereochemically stable to the reaction conditions; stereomutation of the cyclopropane must therefore occur at an intermediate en route to the aminohydroxylation products.

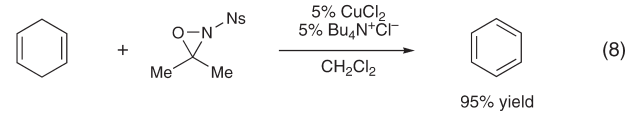
These observations provide strong evidence for a benzylic radical intermediate, as proposed in Mechanism B. The diastereomeric mixture of products obtained in this experiment is consistent with ring-opening of a cyclopropylcarbinyl radical to afford an acyclic intermediate where the stereochemical fidelity of the cyclopropane ring is lost. On the other hand, cyclopropylcarbinyl *cations* are nonclassical,[27] and their rearrangements are stereospecific in nature.[28] Therefore, the lack of stereochemical fidelity in this experiment seems inconsistent with cationic Mechanism A and is better explained by the radical Mechanism B.[29]

Thus, our investigations into the oxaziridine-mediated aminohydroxylation under the influence of halocuprate(II) catalysts have two principal conclusions. First, the reactivity of oxaziridines is dramatically increased in the presence of halocuprate(II) catalysts, enabling both less reactive oxaziridines and less electron-rich olefins to participate readily in the aminohydroxylation reaction. Second, our mechanistic investigations suggest that the aminohydroxylation involves a radical mechanism, rather than the cationic mechanism we originally proposed. Together, these observations prompted us to explore whether we might be able to design new oxaziridine-mediated oxidation reactions of less reactive, non-olefinic functional groups using halocuprate(II) catalysts. In particular, we wondered if activated C−H bonds might be prone to oxidation under these conditions.

In our preliminary studies toward this goal, we found that *sec*-phenethylalcohol is rapidly and quantitatively oxidized to acetophenone within 4 h in the presence of oxaziridine **2** and $CuCl_2/Bu_4N^+Cl^-$ under an atmosphere of argon (eq 7). Only a trace of acetophenone (2% yield) is observed using the $Cu(TFA)_2$/HMPA system, and control experiments indicate that the oxaziridine and the copper catalyst are both required for this reaction to occur. Similarly, 1,4-hexadiene is oxidized to benzene in 20 min under the same conditions (eq 8), presumably by oxidation of the doubly allylic C−H bond. This substrate is also much less reactive using the $Cu(TFA)_2$/HMPA catalyst system (8% yield). These intriguing results suggested that we should be able to design synthetically useful oxidative functionalization reactions initiated by oxaziridine-mediated C−H bond abstraction. We have made significant progress along this line of investigation, and these results will be reported shortly.



(7)



(8)

Conclusion

In the context of our research program on the activation of oxaziridines, the discovery that anionic halocuprate(II) complexes serve as significantly more active catalysts for aminohydroxylation than neutral copper(II) salts is significant for several reasons. First, these more reactive conditions engage less reactive oxaziridines, 3,3-dimethyl oxaziridines that are completely unreactive under our original conditions are suitable terminal oxidants when the $CuCl_2/Bu_4N^+Cl^-$ catalyst system is used. The ability to utilize these nonstereogenic oxaziridines is an important prerequisite for our plans to develop a highly asymmetric aminohydroxylation reaction, and the greater ease of deconvoluting the product mixtures enabled us to conduct a more thorough investigation of the reaction mechanism. Second, the efficiency of aminohydroxylation reactions using a variety of sterically and electronically deactivated styrenes is dramatically increased. Substrates bearing very electron-withdrawing groups that failed to proceed to completion under our original conditions even with extended reaction times can now be aminohydroxylated in a matter of hours. Finally, our efforts to understand the origins of this effect led us to significantly revise our understanding of the mechanism of this transformation. The surprising discovery that an anionic halocuprate(II) complex is a superior catalyst for activation of oxaziridines toward homolytic reactions suggests that other copper-catalyzed oxidative functionalization processes might also be designed that take these observations into account.

In addition to these considerations, the rate acceleration we observe for the aminohydroxylation in the presence of halide additives seems similar to the acceleration previously observed in copper-catalyzed aerobic oxidations of phenols.[4b−4d] These observations raise the intriguing possibility that halocuprate(II) complexes, whose reactivity as catalysts has not been extensively studied to date, may be suitable catalysts for a broader range of other copper-catalyzed oxidations that employ a variety of terminal oxidants. Thus, the studies reported in this paper should have broad significance in light of the chemistry community's increased interest in the development of new oxidation reactions mediated by inexpensive and relatively nontoxic copper catalysts.

(27) For reviews, see: (a) Richey, H. G. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; John Wiley: New York, 1972; Vol. III, pp 1201−1294. (b) Wiberg, K. B.; Hess, B. A., Jr.; Ashe, A. J. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; John Wiley: New York, 1972; Vol. III, pp 1295−1346. (c) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. Chem. Rev. 1992, 92, 69–95.

(28) (a) Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1968**, *90*, 4195–4196. (b) Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1970**, *92*, 571–579. (c) Majerski, Z.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 665–671.

(29) The radical mechanism may also help to explain the observed reactivity of allyl silanes. Previously, we found that allyltriisopropylsilane reacts with oxaziridine **1** in the presence of $Cu(TFA)_2$/HMPA to afford the expected aminohydroxylation product in 66% yield. However, this reaction required extended reaction times (36 h) to proceed to completion. The ability of β-silicon groups to stabilize both cations and radicals is well-known, but the former stabilization energy has been estimated to be 29−30 kcal/mol, while the latter is closer to 3−5 kcal/mol. Thus the observation that allyl silanes react more readily than primary aliphatic olefins but still require longer reaction times than styrenes is more consistent with a radical mechanism than with our originally proposed cationic mechanism. For a recent review of α- and β-silicon effects in organic synthesis, see: Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173–3199.

Experimental Section

Full experimental details for this work are available in the Supporting Information.

General Producedure for Aminohydroxylations Using Dimethyloxaziridine 2. In a nitrogen atmosphere glovebox, copper(II) chloride and tetrabutylammonium chloride were placed in a 2 dram vial with a stirbar. The vial was capped with a septum and transferred out of the glovebox. The vessel was charged with CH_2Cl_2, and the mixture was stirred under argon for 30 min. Styrene was then added by syringe. The septum was removed, oxaziridine **2** was quickly added, and the vessel was sealed and flushed with argon. The reaction progress was monitored by ^{1}H NMR or TLC. Upon completion of the reaction, the remaining oxaziridine was quenched with dimethylsulfide, the solvent was removed by rotary evaporation, and the remaining residue was loaded directly onto silica for purification by flash column chromatography.

***N*-(4-Nitrobenzenesulfonyl)-2,2-dimethyl-4-phenyl-1,3-oxazolane (Table 2, entry 1).** Prepared according to the general procedure using 52.3 mg (0.502 mmol) of styrene, 3.6 mg (0.025 mmol) of $CuCl_2$, 7.0 mg (0.025 mmol) of $Bu_4N^+Cl^-$, 191 mg (0.75 mmol) of oxaziridine **2**, and 0.25 mL of CH_2Cl_2. Reaction time was 2.5 h. The silica gel was loaded using 6:1 hexane/acetone, and the product was eluted using 5:1 hexane/acetone. Isolated 134 mg (0.371 mmol, 74% yield) white solid. Yield 2: 51.2 mg (0.492 mmol) of styrene, 3.5 mg (0.025 mmol) of $CuCl_2$, 7.1 mg (0.025 mmol) of $Bu_4N^+Cl^-$, 191 mg (0.75 mmol) of oxaziridine **2**, and 0.25 mL of CH_2Cl_2. Isolated 132 mg (0.365 mmol, 74% yield): IR (neat) 3005, 1535, 1346, 1155; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dt, J = 9.5, 2.4 Hz, 2H), 7.48 (dt, J = 9.5, 2.4 Hz, 2H), 7.16 (m,1H), 7.10 (dt, J = 4.3 Hz, 4H), 4.94 (dd, J = 7.0, 2.7 Hz, 1H), 4.44 (dd, J = 9.1, 7.0 Hz, 1H), 3.94 (dd, J = 9.2, 2.7 Hz, 1H), 1.84 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 146.9, 139.5, 128.8, 128.7, 128.4, 127.7, 123.5, 99.4, 71.7, 62.9, 27.2, 26.6; HRMS (EI^+) calcd for $[C_{16}H_{15}N_2O_5S]^+$ $(M - CH_3)^+$ requires m/z 347.0697, found m/z 347.0700 (mp = 103−105 °C).

Acknowledgment. We thank Prof. Clark Landis and Chris Shaffer for their insights on the mechanistic studies described in this paper, and David Michaelis and Justin Woods for optimizing the large-scale preparation of oxaziridine **2**. Financial support from the NSF (CHE-0645447), the NIH (R01-GM084022), and the ACS Petroleum Research Fund (44783-G1) is gratefully acknowledged. The NMR spectroscopy facility at UW−Madison is funded by the NIH (S10 RR04981-01) and NSF (CHE-9629688).

Supporting Information Available: 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.