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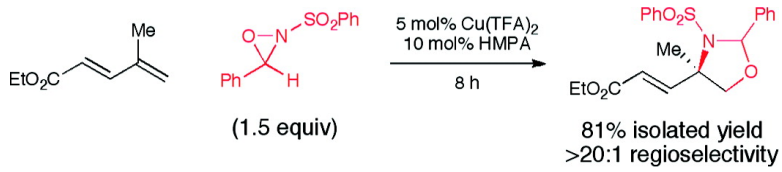

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Activation of *N*-Sulfonyl Oxaziridines Using Copper(II) Catalysts: Aminohydroxylations of Styrenes and 1,3-Dienes

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Abstract: *N*-Sulfonyl oxaziridines are susceptible to electrophilic activation using copper(II) catalysts and react with styrenes under these conditions to provide 1,3-oxazolidines in a formal aminohydroxylation of the alkene. We propose a two-step mechanism involving a cationic intermediate to account for the rate differences and regioselectivities observed using a variety of styrenes. In accord with our hypothesis, aminohydroxylations of a range of substrates bearing electron-stabilizing groups are successful, and 1,3-dienes are particularly good substrates for copper(II)-catalyzed aminohydroxylation. Reactions of unsymmetrical dienes provide good to excellent olefin selectivity, the sense and magnitude of which can be rationalized upon consideration of the stability of the cationic intermediates suggested by our mechanism. Diastereoselective synthesis of a diverse range of densely functionalized structures can be achieved by polyfunctionalization of dienes using aminohydroxylation as a key complexity-increasing step.

Introduction

The 1,2-aminoalcohol motif is a common substructure of a variety of natural products, bioactive compounds, and chiral reagents for the stereoselective construction of organic molecules. Vicinal aminoalcohols are also amenable to a variety of synthetic manipulations that lead to a diverse array of molecular architectures. As a result of the versatility and importance of 1,2-aminoalcohols in synthesis, the osmium-catalyzed aminohydroxylation reported by Sharpless in 1976[1] has enjoyed widespread use in the construction of complex target molecules. Nevertheless, due to the cost and toxicity of osmium compounds as well as the moderate regioselectivities often observed using the Sharpless protocol,[1,2] there has continued to be significant interest in the development of complementary methods for the addition of nitrogen- and oxygen-containing functional groups across carbon−carbon double bonds.[3]

Our group is interested in the discovery of new oxidative transformations that employ oxaziridines as the terminal oxidant. These three-membered nitrogen−carbon−oxygen heterocycles are stable, easily synthesized, and easily handled analogues of dioxiranes and have been shown to perform a similar range of oxygen atom-transfer reactions, including epoxidations, thioether oxidations, and Rubottom oxidations.[4] Very electron-deficient oxaziridines have also been shown to oxidize aliphatic C−H bonds.[5] In general, however, oxaziridines are significantly less reactive than dioxiranes, and oxidations mediated by oxaziridines often require elevated temperatures or extended reaction times.

Notably, the reactivity profiles of oxaziridines is significantly influenced by the nature of the nitrogen substituent. While *N*-sulfonyl oxaziridines typically transfer oxygen to organic substrates, *N*-acyl and *N*-unsubstituted oxaziridines react predominantly as electrophilic nitrogen-transfer reagents that can aminate sulfides, alkoxides, amines, and enolates.[6] Aziridination of olefins has been observed using *N*-H and *N*-Boc oxaziridines, although these transformations require forcing reaction conditions.[7] Reactions of oxaziridines that involve transfer of both nitrogen and oxygen to an organic substrate are quite rare. Prior to our work in this area, we were only aware of two isolated studies in which an oxaziridine was shown to participate in the formal aminohydroxylation of an olefin. The scope of each reaction was reported to be limited, either to very electron-poor[8] or electron-rich[9] carbon−carbon double bonds. In this report, we describe the development of a new copper(II)-catalyzed

(1) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177–179.
(2) (a) Brunko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483–1486. (b) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207–1217.
(3) (a) Noack, M.; Göttlich, R. *Chem. Commun.* **2002**, 536–537. (b) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. (c) Liu, G. S.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181. (d) Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460–1461.
(4) For reviews of oxaziridines in synthesis: (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703–5742. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919–934. (c) Petrov, V. A.; Resnati, G. *Chem. Rev.* **1996**, *96*, 1809–1823. (d) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499–3548.
(5) (a) Arnone, A.; Cavicchioli, M.; Montanari, V.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 5511–5513. (b) Arnone, A.; Foletto, S.; Metrangolo, P.; Pregnolato, M.; Resnati, G. *Org. Lett.* **1999**, *1*, 281–284. (c) Brodsky, B. H.; Du Bois, J. *J. Am. Chem. Soc.* **2005**, *127*, 15391–15393.
(6) Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327–341.
(7) (a) Schmitz, E.; Jahnisch, K. *J. Geterozikl. Soedin.* **1974**, *12*, 1629. (b) Armstrong, A.; Edmonds, I. D.; Swarbrick, M. E. *Tetrahedron Lett.* **2005**, *46*, 2207–2210.
(8) Lam, W. Y.; DesMarteau, D. D. *J. Am. Chem. Soc.* **1982**, *104*, 4034–4035.
(9) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159–1160.

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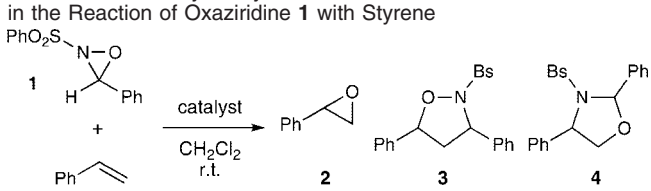
Table 1. Preliminary Study of Brønsted and Lewis Acid Additives in the Reaction of Oxaziridine **1** with Styrene



			yield (%)		
entry	catalyst	time	**2**	**3**	**4**
1	none	8 days	6[a]		
2	20 mol % AcOH	8 days	25[a]		
3	20 mol % $Sc(OTf)_3$	24 h		53[b]	
4	20 mol % $Cu(OAc)_2$	24 h			87[c]

[a] Conversion, determined by ^{1}H NMR spectroscopy. [b] 2.6:1 *cis*:*trans*. [c] 3.3:1 *cis*:*trans*. Bs = benzenesulfonyl.

reaction of oxaziridines that results in the regioselective aminohydroxylation of a diverse range of styrenes and 1,3-dienes.[10]

Results and Discussion

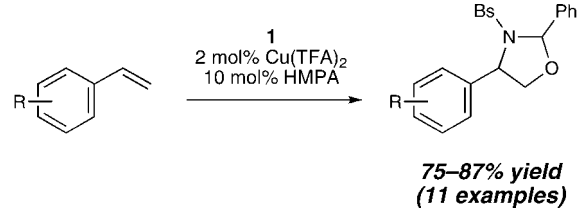
A. Initial Observations. In general, oxaziridines can be considered electrophilic oxidants. Accordingly, the introduction of electron-withdrawing substituents onto an oxaziridine can significantly increase its reactivity. We became interested in exploring whether the reactivity of oxaziridines toward organic substrates could also be increased upon activation by exogenous electrophilic catalysts. At the time we began these investigations, a few studies describing Brønsted[11] or Lewis[12] acid-accelerated oxidations of thioethers using *N*-alkyl oxaziridines had been reported. In each of these examples, however, stoichiometric amounts of the promoter were required, and oxidations of less nucleophilic substrates such as alkenes were not described. We surmised that these limitations were due to the poor inherent oxidizing ability of the *N*-alkyl oxaziridines that were employed. Moreover, the greater basicity of the imine byproduct compared to the unusually non-basic ring nitrogen of the oxaziridine[13] would explain the lack of catalyst turnover in these reactions.

We elected, therefore, to study the effect of electrophilic catalysts on reactions of *N*-sulfonyl oxaziridines (Davis oxaziridines),[14] which are significantly more reactive as oxygen atom donors than *N*-alkyl oxaziridines. Our initial studies probed the reaction of oxaziridine **1** with styrene in the presence of a variety of Brønsted and Lewis acids (Table 1). In the absence of any additives, the reaction is very slow at room temperature, and only a trace of epoxide **2** is generated after several days (entry 1). Upon addition of 20 mol % of AcOH (entry 2), the rate of epoxidation was increased 4-fold, which was a gratifying validation our hypothesis that oxaziridine **1** is indeed susceptible to electrophilic activation. The results of reactions using transition metal catalysts, however, were more interesting. In the presence of 20 mol % $Sc(OTf)_3$, 1,2-isoxazolidine **3** is formed within 24 h instead of the expected epoxide product, presumably by Lewis acid-catalyzed rearrangement of the oxaziridine to the nitrone followed by [3+2] cycloaddition. Alternatively, in the presence of 20 mol % $Cu(OAc)_2$, we observed the formation of 1,3-oxazolidine **4** instead of either the previously observed epoxide or isoxazolidine products.

Several features of this exploratory study are notable. First, these data demonstrate that the reactivity of oxaziridines can indeed be significantly increased upon addition of substoichiometric quantities of electrophilic Brønsted or Lewis acids. Second, the reaction observed (epoxidation, nitrone cycloaddition, or aminohydroxylation) is dependent upon the nature of the catalyst used (protic acid, early transition metal, or late transition metal, respectively). Finally, unlike the oxenoid reactivity typically observed in reactions between oxaziridines and alkenes, the novel reactions observed in the presence of copper(II) and scandium(III) catalysts install both nitrogen- and oxygen-bearing functional groups in a single transformation, either as a masked 1,3-aminoalcohol (**3**) or as a masked 1,2-aminoalcohol (**4**).

Both of these new transition metal-catalyzed reactions are under development in our laboratory.[10,15] However, recognizing the synthetic potential of a new osmium-free method for olefin aminohydroxylation, we concentrated our initial efforts on a more detailed study of the scope, mechanism, and synthetic utility of the copper(II)-catalyzed process.

B. Mechanistic Considerations in Copper(II)-Catalyzed Aminohydroxylations. Under our optimized conditions, efficient aminohydroxylations were observed using as little as 2 mol % of $Cu(TFA)_2$. The addition of a small amount of HMPA (10 mol %) solubilized the copper catalyst, improving both the rate and the reproducibility of the reaction. We found that a wide range of styrenes react efficiently with oxaziridine **1** to produce the corresponding 1,3-oxazolidine as a mixture of two diastereomers (eq 1). The benzylidene aminal moiety of the products is readily hydrolyzed under standard acidic conditions to reveal *N*-sulfonyl 1,2-aminoalcohols in excellent yields. The regioselectivity of the aminohydroxylation is superb; we have not observed the formation of the regioisomeric aminals in the aminohydroxylations of any styrenic substrates investigated to date.



(1)

Three possible mechanisms that account for this newly discovered reactivity are depicted in Scheme 1. Non-oxenoid reactions of *N*-sulfonyl oxaziridines are rare, and thus we initially considered the possibility that the copper(II) catalyst was promoting epoxidation of the olefin followed by subsequent

(10) A preliminary communication describing some of this work has been published: Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P *J. Am. Chem. Soc.* **2007**, *129*, 1866–1867.

(11) (a) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 2817–2818. (b) Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 155–166.

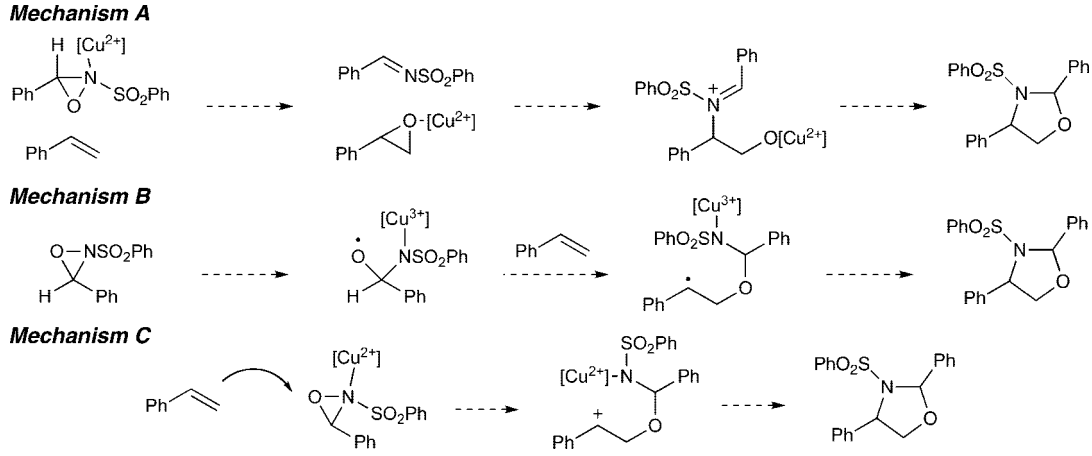
(12) (a) Schoumacker, S.; Hamelin, O.; Téti, S.; Pécaut, J.; Fontecave, M. *Eur. J. Org. Chem.* **2005**, 301. Two papers describing enantioselective Lewis acid-catalyzed reactions involving *N*-sulfonyl oxaziridines as electrophilic oxygen sources have recently been published; however, the possibility of oxaziridine activation is not discussed in either report: (b) Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5810–5814. (c) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488–16489.

(13) (a) Butler, A. R.; Challis, B. C.; Lobo, A. M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1035–1038. (b) Butler, A. R.; White, J. G.; Challis, B. C.; Lobo, A. M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1039–1044.

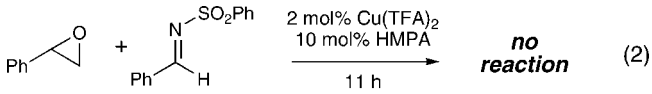
(14) Davis, F. A.; Jenkins, R.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171–5174.

(15) Partridge, K. M.; Anzovino, M. E.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 2920–2921.

Scheme 1

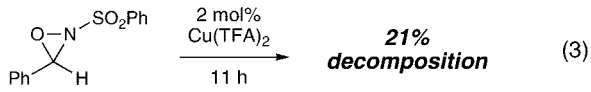


Lewis acid-mediated ring-opening and acetal formation (Mechanism A). The copper(II)-catalyzed ring expansion of aryl epoxides with aldehydes to give 1,3-dioxolanes is known[16] and is conceptually similar to the second step of this proposed mechanism. However, the combination of styrene oxide and *N*-sulfonylimine **5** under the reaction conditions does not result in formation of the aminohydroxylation product (eq 2), which rules out Mechanism A.



5

We also considered the possibility that the copper(II) salt could be serving as a one-electron reductant of the oxaziridine (Mechanism B). An analogous mechanism was proposed by Aubé for the copper(I)-catalyzed radical rearrangements of *N*-alkyl oxaziridines developed in his laboratories.[17] We disfavor a mechanism involving initial heterolytic N−O bond cleavage to rationalize the aminohydroxylation, however, for two major reasons. First, one-electron reduction of **1** would be expected to result in a sulfonyl-stabilized nitrogen-centered radical instead of an unstabilized oxygen-centered radical; reaction of this intermediate with styrene would produce the aminal regioisomeric to **4**. Second, we would expect the radical intermediate generated by homolysis to be very unstable and to decompose rapidly in the absence of an alkene. Control experiments, however, indicate that the rate of oxaziridine decomposition in the absence of styrene is too slow for this to be the initial, rate-limiting step of the aminohydroxylation (eq 3).



For these reasons, we propose a mechanism involving Lewis acid activation of the oxaziridine and nucleophilic attack by the styrenic olefin, as depicted in Mechanism C.[18] Ring closure of the sulfonamide onto the resulting benzylic cation would produce the observed aminoalcohol-derived benzylidene aminal. Consistent with this hypothesis, reactions of electron-rich styrenes require considerably shorter reaction times than those of styrenes bearing electron-withdrawing substituents. Also consistent with Mechanism C are the results of our investigations of 1,2-disubstituted olefins in this reaction (Scheme 2). Aminohydroxylation of either *cis*- or *trans*-stilbene gives a 2:1 mixture of diastereomeric aminals (**6** and **7**) in which both stilbene-derived phenyl substitutents are oriented *trans* to one another, suggestive of an intermediate in which the geometry of the stilbene is not maintained.

Mechanism C predicts that alkenes unable to stabilize a carbocationic intermediate should be poor substrates for aminohydroxylation. As anticipated, yields of reactions using monosubstituted aliphatic olefins were not synthetically useful (Table 2, entry 1). In contrast, a variety of electron-rich alkenes are excellent substrates for aminohydroxylation, including enol ethers (entry 2) and allyl silanes (entry 3). We were also intrigued to find that dienes are particularly effective substrates

Scheme 2

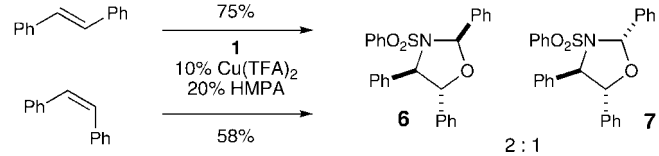
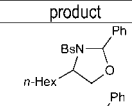
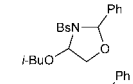
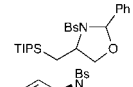
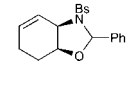


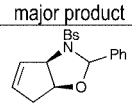
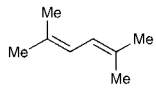
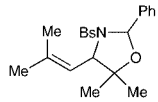
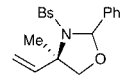
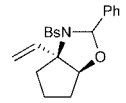
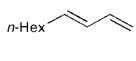
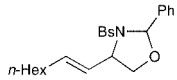
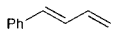
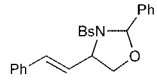
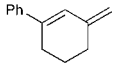
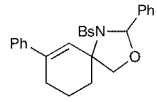
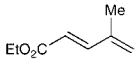
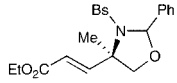
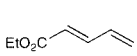
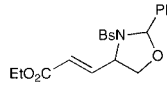
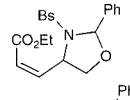
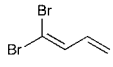
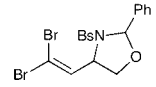
Table 2. Aminohydroxylations of Non-styrenic Olefins

entry	olefin	product	time	yield[c,d]
1[a]	*n*-Hex		24 h	15%
2[b]	*i*-BuO		30 min	71%
3[a]	TIPS		32 h	66%
4[b]			1 h	72%

[a] Reactions performed using 1.5 equiv of oxaziridine, 2 mol % Cu(TFA)$_2$, and 10 mol % HMPA at ambient temperature. [b] Reactions performed using 2 equiv of oxaziridine, 10 mol % Cu(TFA)$_2$, and 20 mol % HMPA at 35 °C. [c] Isolated yields represent the averaged results of two reproducible experiments. [d] Diastereomer ratios ranged from 1.3:1 to 2.4:1.

(16) Krasik, P.; Bohemier-Bernard, M.; Yu, Q. *Synlett* **2005**, 854–856.
(17) (a) Aubé, J.; Peng, X.; Wang, Y.; Takusagawa, F. *J. Am. Chem. Soc.* **1992**, *114*, 5466–5467. (b) Aubé, J.; Gülgeze, B.; Peng, X. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2461–2464. (c) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269–277.
(18) Dmitrienko proposed a similar cationic mechanism to rationalize the uncatalyzed aminohydroxylation of 2,3-dialkylindoles by **1**. See ref 9.

Table 3. Aminohydroxylations of 1,3-Dienes

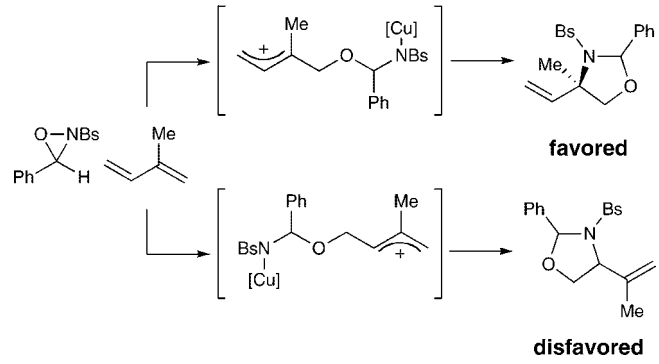
entry[a]	diene	major product	time	yield[b]	olefin selectivity[b,c]
1			1.5 h	84%	---
2[d]			30 min	62%	---
3[d]			45 min	80%	6 : 1
4[d]			1 h	63%	7 : 1
5			2 h	73%	4 : 1
6			2.5 h	89%	>20 : 1
7			1 h	72%	>20 : 1
8			8 h	81%	>20 : 1
9[d]			12 h	66%	>20 : 1
10[d]			10 h	71%	>20 : 1
11[d]			5 h	73%	>20 : 1

[a] Unless otherwise noted, reactions were performed using 1.5 equiv of oxaziridine, 5 mol % of $Cu(TFA)_2$, and 10 mol % of HMPA in CH_2Cl_2 at ambient temperature. Diastereoselectivities ranged from 1:1 to 2.5:1. [b] Isolated yields and olefin selectivities represent the averaged results of two reproducible experiments. [c] Olefin selectivity ratios determined by ^1H NMR analysis of the unpurified reaction mixture. [d] Reaction performed at 35 °C with 2 equiv of oxaziridine.

for aminohydroxylation using our methodology (entry 4). Examples of osmium-catalyzed aminohydroxylation of 1,3-dienes are rare. Donohoe and co-workers[19] have reported tethered, intramolecular aminohydroxylations of dienes that are regioselective and quite efficient, but in general, osmium-catalyzed *intermolecular* aminohydroxylations of dienes reported in the literature are low-yielding[1] and of limited synthetic utility.

Thus, our copper(II)-catalyzed method enables the aminohydroxylation of an important class of alkenes that are not suitable substrates for the osmium-catalyzed process. The products arising from the monoaminohydroxylation of dienes possess an unreacted olefin that can serve as a synthetic handle for a wide range of subsequent structurally diversifying transformations. Moreover, the proximity of a newly formed stereocenter to this olefin led us to consider whether these further

Scheme 3. Origins of Selectivity in Aminohydroxylation of Unsymmetrical Dienes



manipulations could be performed in a stereocontrolled manner. Recognizing the synthetic versatility of this class of substrates, we elected to explore the aminohydroxylation of dienes in greater detail as an entry into a diverse polyfunctionalized structures commonly found in natural products and other bioactive compounds.[20]

C. Aminohydroxylations of Conjugated 1,3-Dienes. Conditions optimized for the aminohydroxlation of styrenes translated smoothly to a wide range of diene substrates (Table 3). As expected, both cyclic (entry 1) and acyclic (entry 2) symmetrical dienes undergo aminohydroxylation in good yield with no observable formation of alternate *N*,*O*-regioisomers. More gratifying was the observation that unsymmetrical dienes can also undergo efficient aminohydroxylation and provide good levels of selectivity between the two chemically distinct double bonds (entries 3–11).

In all cases, both the direction and the magnitude of the observed chemoselectivity can be rationalized by examining the stabilities of the two possible allylic cation intermediates. For instance, electrophilic attack of the oxaziridine upon isoprene (entry 3) could result in formation of either a 1,1-disubstituted or a 1,2-disubstituted allyl cation (Scheme 3). The major product observed in the aminohydroxylation would be expected from the more stable putative 1,1-disubstituted allylic cation intermediate. Similar levels of olefin selectivity are observed using a variety of cyclic (entry 4) and linear (entry 5) dienes. Aminohydroxylations of dienes substituted with strongly electron-stabilizing groups, however, demonstrate complete olefin selectivity (entries 6 and 7).

A variety of electron-deficient dienes are also suitable substrates for this process and undergo aminohydroxylation upon the more electron-rich double bond with complete selectivity (entries 8–11). Surprisingly, we observed that the geometry of the non-reacting olefin is preserved in the event (entries 9 and 10), which suggests that the rate of ring closure must be faster than the rate of geometric isomerization of the allyl cation.[21,22] We were also delighted to discover that 1,1-dibromobutadiene

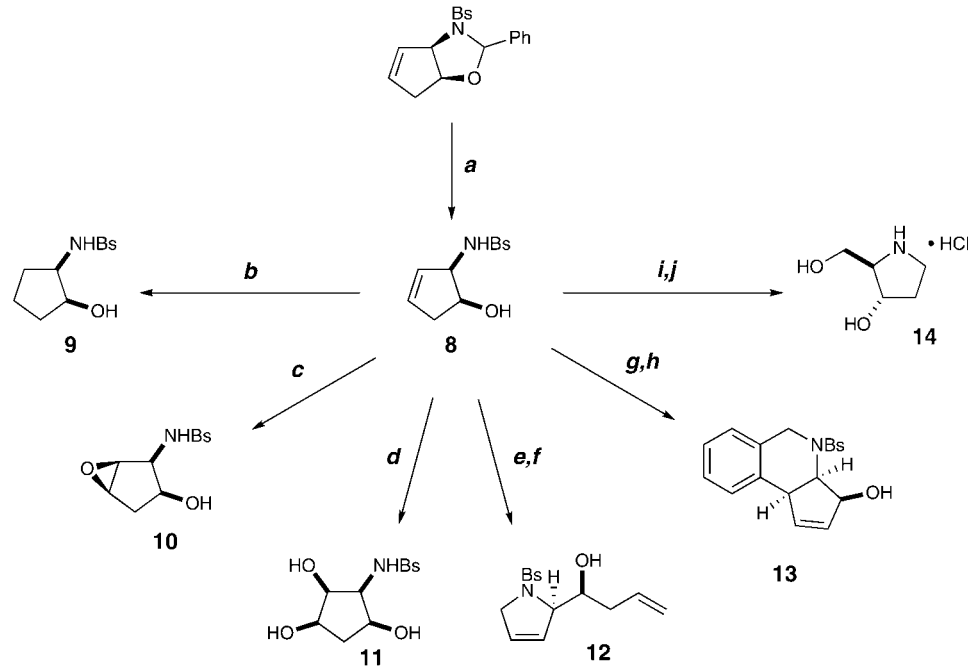
(19) (a) Donohoe, T. J.; Johnson, P. D.; Helliwell, M.; Keenan, M. *Chem. Commun.* **2001**, 2078–2079. (b) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725–1728.

(20) For copper(I)- and palladium(II)-catalyzed diaminations of dienes mediated by diaziridinones, see: (a) Du, H. F; Zhao, B. G.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762–763. (b) Du, H. F.; Yuan, W. C; Zhao, B. G.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496–7497. (c) Yuan, W. C.; Du, H. F.; Zhao, B. G.; Shi, Y. *Org. Lett.* **2007**, *9*, 2589–2591. (d) Du, H. F.; Yuan, W. C.; Zhao, B. G.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689.

(21) Aminohydroxylations of (*Z*)-1,3-decadiene also maintain the geometric integrity of the non-reacting olefin.

(22) The rotational barrier for *cis*−*trans* isomerization in allyl cations has been measured to be 18–24 kcal/mol: (a) Schleyer, P. v. R.; Su, T. M.; Saunders, M.; Rosenfeld, J. C. *J. Am. Chem. Soc.* **1969**, *91*, 5174–5176. (b) Bollinger, J. M.; Brinich, J. M.; Olah, G. A. *J. Am. Chem. Soc.* **1970**, *92*, 4025–4033.

Scheme 4. Structural Diversification of Aminohydroxylated Cyclopentadiene[a]



[a] Reagents and conditions: (a) TFA, dioxane, 80 °C, 90%; (b) H_2 (1 atm), Pd/C (7 mol %), MeOH, 77%; (c) *m*-CPBA, CH_2Cl_2, 86%; (d) OsO_4 (1.1 equiv), TMEDA, CH_2Cl_2, then HCl, MeOH, 80%; (e) allyl bromide, K_2CO_3, DMF, 98%; (f) ethylene (1 atm), Grubbs II (5 mol %), CH_2Cl_2, 53%; (g) *o*-bromobenzyl bromide, K_2CO_3, DMF, 94%; (h) $Pd(PPh_3)_4$ (10 mol %), K_2CO_3, dioxane, 110 °C, 78%; (i) O_3, CH_2Cl_2, −78 °C, then $NaBH_3CN$, 63%; (j) sodium naphthalide, DME, −78 °C, 99%.

reacts smoothly, providing a product bearing a synthetic handle that could be manipulated to synthesize alkynes[23] or trisubstituted olefins[24] (entry 11).

Having demonstrated that a range of dienes are excellent substrates for aminohydroxylation, we next considered strategies for the synthetic manipulation of the products (Scheme 4). First, as expected, deprotection of cyclopentadiene-derived aminal proceeds in high yield to produce aminoalcohol **8**, and subsequent hydrogenation of the remaining olefin produces 1-aminocyclopentan-2-ol (**9**), which is not accessible by direct aminohydroxylation of cyclopentene using our standard method. *This approach effectively circumvents the major synthetic limitation of our method by enabling the synthesis of 1,3-oxazolidines bearing aliphatic substituents at C4.* Directed epoxidation[25] and dihydroxylation[26] of the double bond are also successful using conventional protocols for these oxidations, and in both cases exclusive formation of the all-*syn* diastereoisomer of the oxidized product is observed (**10** and **11**).

Construction of heterocyclic structures by further synthetic manipulation of the olefin is also possible. Allylation of the sulfonamide, followed by ring-opening/ring-closing metathesis[27] under an atmosphere of ethylene, affords dihydropyrrole **12**. *N*-Alkylation with 2-bromobenzyl bromide and intramolecular Heck cyclization results in formation of isoquinoline **13** with exclusive formation of the all-*cis* stereoisomer. Finally, ozonolysis of the olefin coupled with a reductive borohydride workup affords a single diastereomer of an *N*-protected 3-hydroxyprolinol; removal of the sulfonyl group upon treatment with sodium naphthalenide reveals (±)-CYB-3 (**14**), a natural product[28] with modest gyclosidase inhibitory activity against a variety of insect and mammalian targets[29] and a synthetic precursor to the indolizidine alkaloids.[30]

Thus, the copper(II)-catalyzed method we have discovered is uniquely suited for aminohydroxylations of dienes. High levels of olefin selectivity can be observed in a range of structurally varied non-symmetrical dienes, and both the direction and the degree of this selectivity are accounted for by a two-step, cationic mechanism. The 1,2-aminoalcohols resulting from this transformation are versatile scaffolds for further stereoselective elaboration into a diverse range of

(23) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
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(25) Diastereoselective epoxidations directed by allylic sulfonamides: (a) Bäckvall, J.-E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B *J. Org. Chem.* **1979**, *44*, 1953–1957. (b) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M *Org. Lett.* **2003**, *5*, 4955–4957. Diastereoselective epoxidations directed by homoallylic alcohols: (c) Zurflüh, R.; Wall, E. N.; Siddall, J. B.; Edwards, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 6224–6225.
(26) (a) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027–5030. (b) Donohoe, T. J.; Blades, K.; Moore, P. R.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *J. Org. Chem.* **1999**, *64*, 2980–2981. (c) Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Bell, A.; Newcombe, N. J. *Tetrahedron Lett.* **2001**, *42*, 8951–8954. (d) Donohoe, T. J. *Synlett* **2002**, 1223–1232.
(27) (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640. (b) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325–4329.
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densely functionalized structures of interest in the synthesis of biologically active compounds.

Conclusions

The new copper(II)-catalyzed methodology for aminohydroxylation of olefins that we have discovered is a practical and synthetically useful complement to existing methods for the construction of 1,2-aminoalcohols, for a number of reasons. First, it employs bench-stable copper(II) catalysts that are relatively inexpensive and non-toxic compared to osmium compounds. Second, the regioselectivity of the aminohydroxylation is high, as is the chemoselectivity observed in aminohydroxylations of 1,3-dienes, and both can be predicted on the basis of the cationic mechanism we have proposed for this transformation. Finally, our method enables the straightforward polyfunctionalization of dienes, which is a powerful and versatile strategy for the construction of a wide range of densely functionalized structures. We anticipate that the copper(II)-catalyzed aminohydroxylation will be of significant utility in a variety of synthetic applications.

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Supporting Information Available: 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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