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Copper(II)-Catalyzed Aminohydroxylation of Olefins

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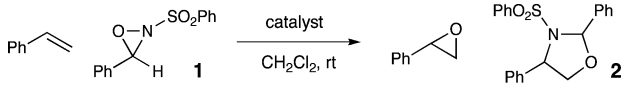
The osmium-catalyzed aminohydroxylation of olefins was first discovered in 1976 by Sharpless and co-workers[1] and remains the method of choice for construction of β-amino alcohols. This structural motif is common to a variety of bioactive natural products and chiral reagents for stereoselective synthesis. However, given the poor regioselectivity observed in the osmium-catalyzed aminohydroxylation of styrenes[2] as well as the expense and toxicity of osmium compounds, there has been significant interest in the discovery of complementary protocols. Several groups have recently reported palladium(II)-catalyzed olefin aminohydroxylation utilizing $PhI(OAc)_2$ as the terminal oxidant.[3] In this communication, we report that copper(II) salts catalyze the regioselective aminohydroxylation of olefins using *N*-sulfonyl oxaziridines.[4] This process represents a novel reaction of oxaziridines and a promising new alternative to the known osmium- and palladium-catalyzed aminohydroxylation methods.

The discovery of this new reactivity arose from our interest in developing Lewis acid-catalyzed oxidation reactions. Hypothesizing that Lewis acid activation of oxaziridines[5] would increase their electrophilicity and, consequently, their ability to epoxidize olefins, we initially explored the effect of metal salts on the reaction between oxaziridine **1** and styrene (Table 1). As expected from earlier reports of oxaziridine reactivity,[6] only a trace of styrene oxide is formed in the absence of Lewis acidic additives even after extended reaction times (entry 1). Upon addition of 10 mol % of $Cu(OAc)_2$, however, we observed the regioselective formation of aminal **2** instead of the expected epoxide (entry 2). This new aminohydroxylation reaction occurs in the presence of a variety of copper(II) salts (entries 2−5). Using $Cu(TFA)_2$, the most effective metal salt screened, efficient aminohydroxylation was observed at catalyst loadings as low as 2 mol % (entry 6). Under our optimized conditions,[7] the addition of 10 mol % of HMPA increased the solubility of the copper catalyst and improved the reproducibility of the reaction (entry 7).[8,9]

Table 1. Development of Optimized Aminohydroxylation Conditions



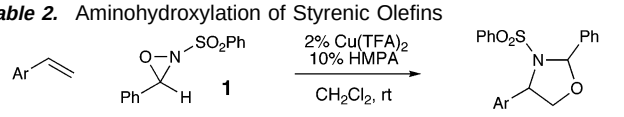
entry[a]	conditions	time (h)	% conversion[b] epoxide	% conversion[b] aminal	dr[b] *cis*:*trans*
1	no catalyst	192	6	−	−
2	10 mol % of $Cu(OAc)_2$	24	−	62	1.8:1
3	10 mol % of $Cu(OTf)_2$	24	−	91	>9:1
4	10 mol % of $CuCl_2$	24	−	>95	1:1.6
5	10 mol % of $Cu(TFA)_2$	24	−	>95	2.5:1
6	2 mol % of $Cu(TFA)_2$	24	4	92	3.3:1
7	2 mol % of $Cu(TFA)_2$ + 10 mol % of HMPA	24	−	>95	1.8:1

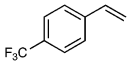
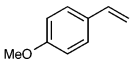
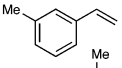
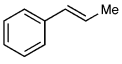
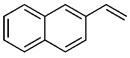
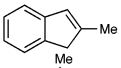
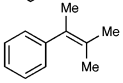
[a] Reactions were performed with 1 equiv of styrene and 2 equiv of oxaziridine in CH_2Cl_2 (0.5 M) at ambient temperature. [b] Conversions and diastereomeric ratios were determined by ^1H NMR analysis of the unpurified reaction mixture.

This new aminohydroxylation constitutes a rare example of a non-oxenoid reaction of oxaziridine **1**. To the best of our knowledge, the only previous report of a reaction in which both heteroatoms of an *N*-sulfonyl oxaziridine are transferred to an organic substrate was an unexpected aminohydroxylation of indoles observed by Dmitrienko during studies toward a synthesis of the alkaloid FR900482.[10] This reaction only occurred using electron-rich 2,3-dialkyl indoles, and other electron-rich olefins such as enamines failed to undergo aminohydroxylation.

In contrast, the scope of this new copper-catalyzed process seems to be significantly broader. Experiments probing the range of styrenes that undergo this new reaction are summarized in Table 2. Styrenes bearing electron-withdrawing (entry 2) and electron-donating (entry 3) *para* substituents can be aminohydroxylated

Table 2. Aminohydroxylation of Styrenic Olefins



entry[a]	olefin	time	yield[b]	d.r. *cis*:*trans*[b,c]
1		11 h	87%	1.7 : 1
2		36 h	73%	1.2 : 1
3		6 h	84%	1.1 : 1
4		6.5 h	84%	1.0 : 1
5		11h	83%	1.9 : 1
6[d]		2 h	75%	2.1 : 1
7		4 h	85%	1.2 : 1[e]
8		1.5 h	81%	3.5 : 1
9		5 h	83%	1.6 : 1
10[d]		2 h	84%	1.6 : 1
11[d]		2 h	81%	>10 : 1

[a] Unless otherwise noted, reactions were performed using 1.5 equiv of oxaziridine, 2 mol % of $Cu(TFA)_2$, and 10 mol % of HMPA in CH_2Cl_2 (0.5 M) at ambient temperature. [b] Isolated yields and diastereomeric ratios represent the averaged results of two reproducible experiments. [c] Ratios were determined by ^1H NMR analysis of the unpurified reaction mixture. [d] Reaction was conducted with 10 mol % of $Cu(TFA)_2$ in CH_2Cl_2 (0.125 M) at 35 °C. [e] Refers to the 4,5-*trans*-isomers. Only traces of the 4,5-*cis*-isomers could be observed.

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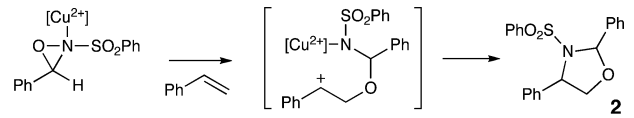
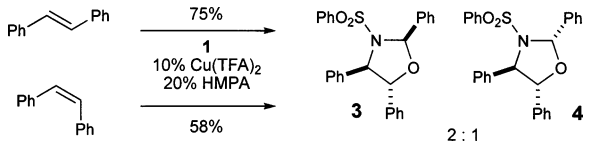
Scheme 1

Proposed mechanism



Scheme 2



easily, although the former require extended reaction times to achieve good yields. Substitution at the *ortho* and *meta* positions of the arene is also tolerated (entries 4 and 5), as are α and *β* substituents on the alkene (entries 6 and 7). Cyclic (entry 8) and condensed polycyclic styrenes (entry 9) are also excellent substrates for aminohydroxylation, as are tri- and tetrasubstituted styrenic olefins (entries 10 and 11).[11]

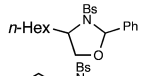
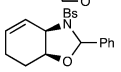
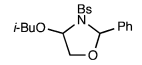
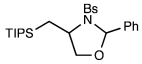
In order to rationalize this unusual reactivity, we initially considered a mechanism involving Lewis acid-catalyzed ring opening of a transient epoxide intermediate, as the copper(II)-catalyzed synthesis of 1,3-dioxolanes from aryl epoxides and aldehydes is well precedented.[12] However, treatment of styrene oxide with *N*-benzylidene benzenesulfonamide in the presence of $Cu(TFA)_2$ does not produce aminohydroxylated product **2**, which precludes the intermediacy of an epoxide.

We also considered the possibility that the copper(II) salt was serving as a one-electron reductant of the oxaziridine, in analogy to the copper(I)-catalyzed radical rearrangements of *N*-alkyl oxaziridines developed by Aubé.[13] We disfavor this mechanism for two major reasons: (1) one-electron reduction of **1** should result in a nitrogen-centered radical, which would be expected to produce the aminal regioisomeric to **2**; and (2) this mechanism would require a copper(III) intermediate that is unlikely to form in the absence of strongly donating coordination environment, yet aminohydroxylation proceeds efficiently even using electron-poor $Cu(OTf)_2$ without added ligands (Table 1, entry 2).

Our current working hypothesis is depicted in Scheme 1. The available data are consistent with Lewis acid activation of the oxaziridine and nucleophilic attack by the styrenic olefin. Ring closure of the sulfonamide onto the resulting benzylic cation results in the observed aminoalcohol-derived benzylidene aminal. This ionic mechanism is consistent with the observation that styrenes bearing electron-rich substituents react considerably more rapidly than those bearing electron-withdrawing substituents (Table 2, entries 2 and 3).

The reaction of stilbenes in this transformation provides additional evidence for a cationic mechanism (Scheme 2). Aminohydroxylation of either *cis*- or *trans*-stilbene gives aminals **3** and **4** as a 2:1 mixture of diastereomers. This stereoconvergent behavior is consistent with the carbocationic intermediate in Scheme 1. Also consistent with a polar mechanism is the diminished reactivity of aliphatic alkenes such as 1-octene (Table 3, entry 1). Conversely, non-styrenic substrates that would produce stabilized carbocationic intermediates react smoothly under our standard conditions. Thus, enol ethers (entry 2), dienes (entry 3), and allyl silanes (entry 4) can be aminohydroxylated using our new methodology.

Table 3. Aminohydroxylations Using Non-styrenic Olefins

entry	olefin	product	time	yield	d.r. *cis*:*trans*[c]
1[a]			24 h	15%	1.9 : 1
2[b]			1 h	72%	2.4 : 1
3[b]			30 min	71%	1.4 : 1
4[a]			32 h	66%	1.3 : 1

[a] Reactions were performed using 2 mol % of $Cu(TFA)_2$ and 10 mol % of HMPA at ambient temperature. [b] Reactions were performed using 10 mol % of $Cu(TFA)_2$ and 20 mol % of HMPA at 35 °C. [c] Diastereomeric ratios were determined by ^1H NMR analysis of the unpurified reaction mixture.

In summary, we have discovered a novel copper(II)-catalyzed reaction of oxaziridines that effects regioselective aminohydroxylation of styrenes and electron-rich olefins. Studies to better elucidate the mechanism of this reaction, further explore the substrate scope, and develop enantioselective aminohydroxylations based on this new methodology are currently underway in our laboratory.

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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.

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(5) The activation of an *N*-alkyl oxaziridine toward sulfoxidation using a stoichiometric zinc(II) additive has been reported: Schoumacker, S.; Hamelin, O.; Teti, S.; Pecaut, J.; Fontecave, M. *J. Org. Chem.* **2005**, *70*, 301—308.
(6) Davis, F. A.; Abdul-Malik, N. F.; Awad, S. B.; Harakal, M. E. *Tetrahedron Lett.* **1981**, *22*, 917—920.
(7) The use of $Cu(OTf)_2$ as a catalyst leads to higher diastereoselectivities, presumably by Lewis acid-catalyzed epimerization of the aminal stereocenter, albeit with diminished yields.
(8) Among additives screened, HMPA provided the fastest rates of reaction, but less toxic ligands can be used instead. For example, aminohydroxylation of styrene proceeds in 81% and 89% yield using 5 mol % of DMPU and pyridine, respectively (see Supporting Information).
(9) The benzylidene aminal of **2** is readily hydrolyzed using TFA in dioxane/H_2O (4 h, 80 °C, 95% yield; see Supporting Information).
(10) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159—1160.
(11) We have not observed regioisomeric aminal products in the aminohydroxylations of any styrenic olefins investigated to date.
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