

## Oxaziridine-Mediated Intramolecular Amination of $sp^3$ -Hybridized C–H Bonds

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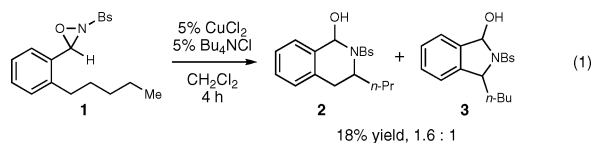
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Dioxiranes and oxaziridines are members of a class of three-membered heterocyclic oxidants that perform a variety of atom-transfer reactions.<sup>1,2</sup> Among the most intriguing of these reactions is the dioxirane-mediated hydroxylation of unactivated  $sp^3$ -hybridized C–H bonds.<sup>3</sup> The intramolecular version of this reaction, first reported by Yang, exhibits high regioselectivity for the  $\delta$  position of the dioxirane.<sup>4</sup> Oxaziridines, which are significantly more stable than dioxiranes, also perform a variety of hydrocarbon oxidations; however, only oxaziridines that bear strongly electron-withdrawing substituents have previously been shown to be reactive enough to oxidize C–H bonds.<sup>5</sup> In this communication, we report that activation of *N*-sulfonyl oxaziridines using copper(II) induces the regioselective intramolecular amination of  $sp^3$ -hybridized C–H bonds.

Our lab has been investigating novel reactions of oxaziridines that occur in the presence of transition-metal catalysts.<sup>6</sup> Recently, we discovered that the copper(II)-catalyzed aminohydroxylation developed in our lab exhibits a marked rate acceleration in the presence of anionic halide and pseudohalide additives.<sup>7</sup> The increased reactivity of this system led us to consider whether these conditions might also enable the oxidative functionalization of more challenging substrates such as alkanes.

As a starting point for our investigations, we prepared *N*-sulfonyl oxaziridine **1** bearing an ortho alkyl substituent on the *C*-aryl group. Subjecting **1** to conditions optimized for the aminohydroxylation<sup>7</sup> afforded low yields of two regioisomeric amins (**2** and **3**) resulting from C–H bond amination (eq 1):

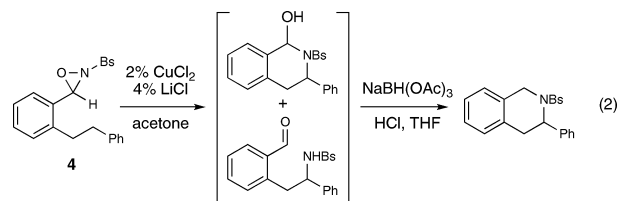


This result was remarkable for several reasons. First, we were surprised to observe formation of a new C–N bond, as we had expected to observe oxygen atom transfer reactivity consistent with the characteristic oxenoid reactivity of oxaziridines.<sup>8</sup> To the best of our knowledge, this represents the first example of formal nitrogen atom transfer from an *N*-sulfonyl oxaziridine. Second, there has been considerable interest in the development of methods for the amination of  $sp^3$ -hybridized C–H bonds.<sup>9</sup> Our approach is a mechanistically distinct complement to the metal nitrenoid chemistry that has enjoyed the most success in this field. Finally, despite the low regioselectivity observed in this initial experiment, we were intrigued by the observation that the major product arose from functionalization of the stronger, unactivated  $\delta$  C–H bond rather than the weaker neighboring benzylic  $\gamma$  C–H bond.

Given these results, we wondered whether an oxaziridine bearing electronically similar  $\gamma$  and  $\delta$  methylene units might exhibit a stronger regiochemical preference. Indeed, under optimized conditions (2 mol %  $\text{CuCl}_2$ , 4 mol %  $\text{LiCl}$ , 0.1 M in acetone), dihydrostilbene-derived oxaziridine **4** undergoes efficient intramolecular C–H amination with exclusive functionalization at the  $\delta$  position (eq 2); no trace of reaction

at the  $\gamma$  methylene could be observed by  $^1\text{H}$  NMR analysis of the unpurified reaction mixture. The product of the reaction is formed as an inseparable mixture of ring-opened and -closed isomers, which undergo efficient reductive amination to furnish a single tetrahydroisoquinoline product in 81% yield over two steps.

**Table 1.** Aminations with Dihydrostilbene-Derived Oxaziridines<sup>a</sup>



entry	oxaziridine	product	time	yield <sup>b</sup>
1			2 h	81%
2			75 min	81%
3			75 min	87%
4			75 min	76%
5			1 h	74%
6			1 h	72%
7			1 h	67%
8			3.5 h	61%
9			4 h	84% <sup>c</sup>

<sup>a</sup> See the Supporting Information for full experimental details.

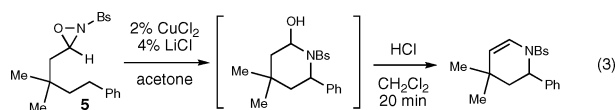
<sup>b</sup> Isolated yields of the product after reductive amination. <sup>c</sup> Refers to the yield of the isolated aminal, which was not stable under the reductive amination conditions. Only the syn diastereomer was observed.

Table 1 summarizes experiments probing structural variation of the dihydrostilbene-derived oxaziridine. The reaction appears to be relatively insensitive to electronic perturbation of the tethering arene (entries 2 and 3). Electron-donating and -withdrawing substituents on the terminal arene are also tolerated (entries 4–8), although the reaction times in the latter case prove to be longer. A variety of functional groups are tolerated in the cyclization; the presence of ethers, esters, aryl halides, carbamates, and alcohols do not affect the efficiency of the reaction. In all cases, the amination is highly regioselective; functionalization of the  $\gamma$  position is observed only when the length of the tether is shortened by one carbon, although this modification results in somewhat longer reaction times (entry 9).

We also explored the reactions of substrates bearing aliphatic linkers (Table 2). Oxaziridine **5** undergoes efficient cyclization under our optimized conditions and eliminates  $\text{H}_2\text{O}$  upon treatment with acid to furnish the corresponding enamide in good yield (entry 1). The presence of substituents that bias the conformation of the chain toward cyclization proved to be essential for efficient amination; the corresponding substrate lacking *gem*-dimethyl substituents produced the cyclized product in only 13% yield (entry 2). On the other hand, dioxolane-linked oxaziridines are also suitable substrates for this method; acidic hydrolysis furnishes the corre-

sponding 4-piperidones in good yield (entries 3–6). The amination is not limited to benzylic C–H bonds; alkynes are efficient activating groups as well (entry 7). Notably, cyclizations of oxaziridines with aliphatic tethers are  $\delta$ -selective even when the functionalization occurs at unactivated methylene units (entry 8). This high positional selectivity is observed even when an adjacent benzylic methylene is present in the substrate (entry 9).<sup>10,11</sup>

**Table 2.** Aminations with Oxaziridines Bearing Aliphatic Tethers<sup>a</sup>



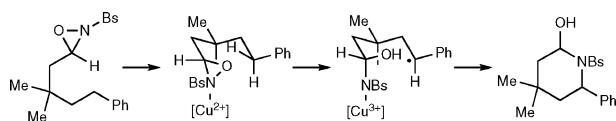
entry	oxaziridine	product	time	yield <sup>b</sup>
1			2 h	74%
2			5 h	13%
3			2 h	73%
4			2 h	92%
5			75 min	63%
6			75 min	69%
7 <sup>c</sup>			90 min	69%
8			3 h	37%
9			3 h	40%

<sup>a</sup> See the Supporting Information for full experimental details.

<sup>b</sup> Isolated yields of the dihydropyridine product after treatment with acid. <sup>c</sup> Reaction conducted using 10 mol % CuCl<sub>2</sub> at 40 °C.

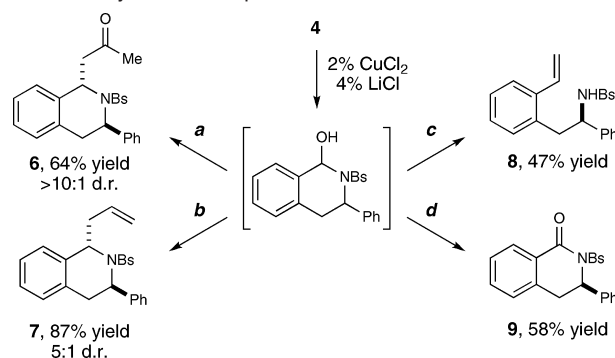
To account for the C–N bond-forming process, we propose a mechanism consistent with our proposal for oxaziridine-mediated aminohydroxylation<sup>7</sup> (Scheme 1). Upon coordination to the copper catalyst, the oxaziridine becomes activated toward substrate-induced homolysis; regioselective abstraction of the  $\delta$  C–H bond followed by ring closure of the copper(III) sulfonamide onto the carbon-centered radical yields the hemiaminal product of this process. The regioselectivity observed in this reaction is identical to that observed in intramolecular C–H bond oxidations mediated by dioxiranes.<sup>4</sup> Thus, we deduce that the transition states of these two oxidative processes share a similar geometry. The regioselectivity of the hydrogen atom abstraction could be due to the combined influence of the stereoelectronic preferences of the oxaziridine and the geometrical constraints imposed by the cyclic conformation of the transition state.

**Scheme 1.** Proposed Mechanism



While the *N,O*-aminal intermediates are generally not isolated, they are amenable to a variety of synthetic manipulations (Scheme 2). Treatment of the unpurified reaction mixture from **4** with a silyl enol ether in the presence of BF<sub>3</sub>·OEt<sub>2</sub> produces the Mannich addition product **6** in 58% yield with excellent diastereocontrol (>10:1 trans:cis). Similarly, the same iminium intermediate can be intercepted by an allyl silane under the identical conditions to afford the allylated product **7** in 87% yield, again with good selectivity for the trans diastereomer (5:1 d.r.). The aminal–aldehyde equilibrium can also be exploited, and the open-chain aldehyde form can undergo Wittig olefination to produce alkene **8** in 49% yield. Finally, oxidation of the ring-closed aminal using IBX affords *N*-sulfonyl isoquinoline **9** in 58% yield.

**Scheme 2.** Synthetic Manipulations of Aminal Intermediates<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) 2-(trimethylsilyloxy)propene, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 to 23 °C; (b) allyltrimethylsilane, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 to 23 °C; (c) methyltriphenylphosphonium bromide, *n*-BuLi, –78 to 23 °C; (d) IBX, DMSO, 90 °C.

In summary, we have demonstrated that *N*-sulfonyl oxaziridines participate in efficient, regioselective intramolecular C–H bond amination reactions. This new reactivity is the first example of formal nitrogen atom transfer from *N*-sulfonyl oxaziridines and constitutes a fundamentally novel method for amination of sp<sup>3</sup>-hybridized C–H bonds. The ability to construct the structurally diverse heterocyclic compounds produced by this reaction should be useful in the synthesis of biologically active and medicinally relevant organic compounds.

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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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