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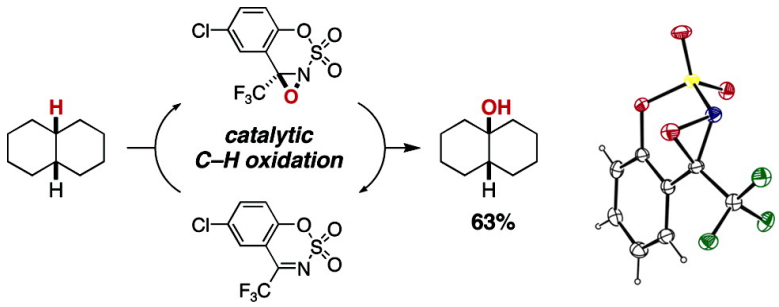

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Oxaziridine-Mediated Catalytic Hydroxylation of Unactivated 3° C−H Bonds Using Hydrogen Peroxide

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Alkane hydroxylation poses a formidable challenge in reaction design.[1] Processes for the selective oxyfunctionalization of C−H bonds have potential application for the synthesis of both commodity and fine chemicals, and thus the development of such tools has been a focal point of numerous investigations. Despite many notable advances in this arena, a general, catalytic method that offers predictable and high levels of chemo-, regio-, and stereocontrol continues to be sought.[2] Herein, we disclose our first step toward achieving this goal.

Oxaziridines constitute a class of strained organic heterocycles that, in stark contrast to highly reactive dioxiranes, exhibit remarkable stability (Figure 1).[3] These compounds are easily prepared from imine-based starting materials and are known to react as electrophilic O-atom transfer agents with strong nucleophiles, such as metal enolates.[4,5] Substrate oxidation regenerates the parent imine and thus provides an opportunity for catalysis that has been rarely exploited.[6,7]

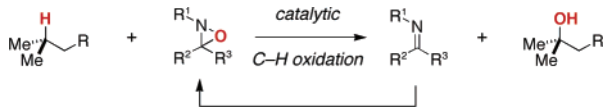


Figure 1. Proposed oxaziridine-catalyzed C−H hydroxylation.

The ability to influence the oxidizing power of oxaziridines through steric and electronic modulation is a distinguishing property of these heterocycles.[8] Perfluorinated oxaziridines are representative, as such agents will convert select alkanes to alcohols.[9,10] The difficulties associated with the preparation of these compounds have limited their use, however, and to our knowledge, no reports of catalytic oxidations employing these systems have been described. Nevertheless, such findings convinced us that an appropriately configured electron-deficient imine would allow for oxaziridine formation and C−H hydroxylation under catalytic conditions. The 1,2,3-benzoxathiazine-2,2-dioxide platform was chosen for its numerous advantages, which include ease of synthesis, stability, and electronic tunability (Figures 2 and 3).

To evaluate the oxidizing potential of benzoxathiazine oxaziridines, we first conducted a limited series of DFT calculations (B3LYP/6-31G*).[11,12] These experiments were designed to compare activation energies for ethylene and methane oxidation by model oxaziridine **1** and related derivatives to those reported for dimethyldioxirane (DMDO), a stoichiometric organic oxidant capable of hydroxylating aliphatic C−H bonds (Figure 2).[5,13,14] Stationary points consistent with transition structures for epoxidation and hydroxylation of ethylene $\mathbf{TS_E^1}$ and methane $\mathbf{TS_M^1}$ by **1** were located. $\mathbf{TS_E^1}$ adopts the expected spiro-geometry with a calculated activation energy (ΔE) of 22.6 kcal/mol. A ΔE value of 18.2 kcal/mol has been computed for ethylene epoxidation with DMDO.[15] In the case of methane hydroxylation, $\mathbf{TS_M^1}$ ($\Delta E = 50.8$ kcal/mol) assumes a similar nuclear orientation to that found for $\mathbf{TS_M^{DMDO}}$ ($\Delta E = 45.8$ kcal/mol), with slightly more advanced C−H bond

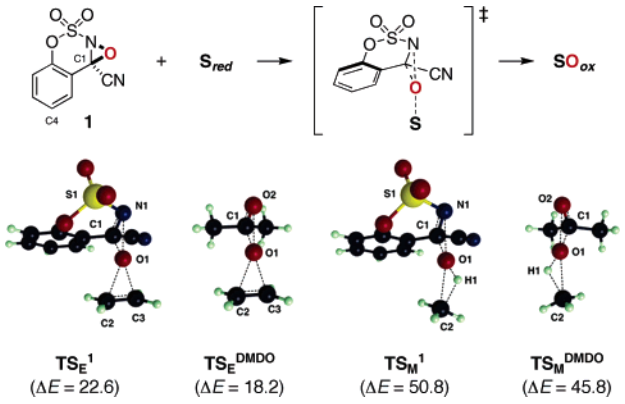


Figure 2. B3LYP/6-31G* transition structures for ethylene epoxidation by **1** ($\mathbf{TS_E^1}$), ethylene epoxidation by DMDO ($\mathbf{TS_E^{DMDO}}$), methane hydroxylation by **1** ($\mathbf{TS_M^1}$), and methane hydroxylation by DMDO ($\mathbf{TS_M^{DMDO}}$).[15,16] Calculated ΔE values are in kcal/mol.

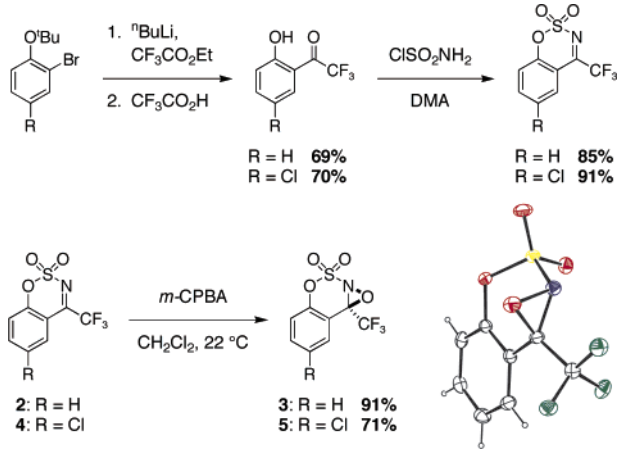


Figure 3. Synthesis and X-ray crystallographic analysis of novel *N*-alkoxysulfonyl oxaziridines.

breakage evident in the former construct.[16,17] Intrinsic reaction coordinate analysis of $\mathbf{TS_M^1}$ supports a concerted asynchronous hydroxylation event akin to the DMDO-promoted reaction.[18] Overall, the similarities of the calculated transition structures $\mathbf{TS_M^1}$ and $\mathbf{TS_M^{DMDO}}$ led us to conclude that C−H oxidation by such intermediates should be feasible. In addition, these studies indicated that substituents at the C1 and C4 positions of the benzoxathiazine ring would have the most pronounced influence on reactivity.

Synthesis of our first-generation benzoxathiazine catalysts **2** and **4** comprises three to four steps and furnished gram-quantities of each material (Figure 3). To ensure that the active oxaziridine species could be formed and to gauge their oxidizing potential, **2** and **4** were treated with *m*-CPBA. Under these conditions, the desired oxaziridines **3** and **5** were produced in high yields and isolated as stable crystalline solids. X-ray crystallographic analysis

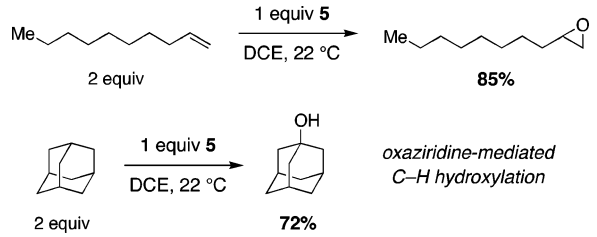


Figure 4. Stoichiometric alkene and C−H oxidation reactions with oxaziridine **5**.

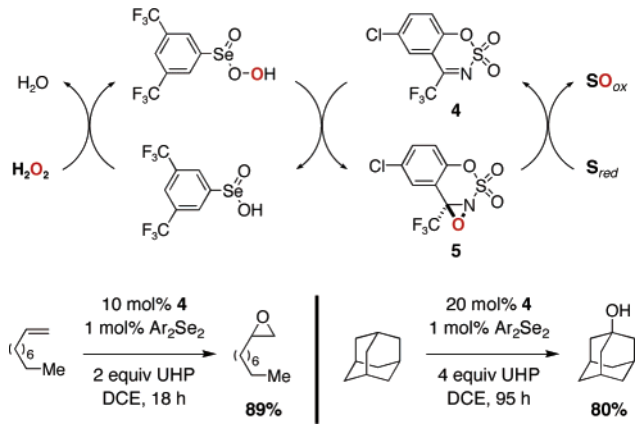


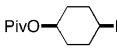
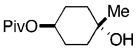
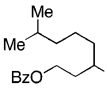
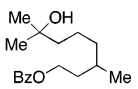
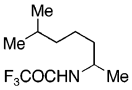
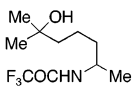
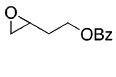
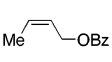
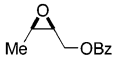
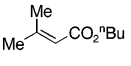
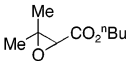
Figure 5. Alkene and C−H oxidation with H_2O_2 catalyzed by Ar_2Se_2 and benzoxathiazine **4**.

confirmed the identity of one of these unique heterocycles, **3**. The striking stability of these compounds belies their extraordinary reactivity, as **5** was found to convert 1-decene to decene epoxide in 85% yield (Figure 4).[19] When adamantane was employed as substrate, efficient 3° C−H oxidation occurred to give 72% of the hydroxylated product.[20] In both cases, benzoxathiazine **4** was returned, thereby making viable the development of a catalytic process.

Having established the oxidizing ability of oxaziridine **5**, reaction conditions suitable for catalytic turnover were examined. Importantly, oxaziridines may be prepared using a variety of terminal oxidants, a salient advantage over dioxirane-based systems.[3,5] By employing H_2O_2 as the O-atom source and a suitable cocatalyst, oxaziridine generation could be promoted with minimal byproduct formation. Bis(3,5-bis(trifluoromethyl)phenyl) diselenide (Ar_2Se_2), known to react with H_2O_2 to give perseleninic acid, was tested in this capacity and found to catalyze efficiently the production of oxaziridine **5** (Figure 5).[21] When this same reaction was performed with 10 mol % of benzoxathiazine **4**, 2 equiv of urea·H_2O_2 (UHP), and 1 equiv of 1-decene, the product epoxide was furnished in 89% yield.[22] Most notably, a 20 mol % charge of **4** also promoted the selective oxidation of adamantane to 1-adamantanol (80%). Collectively, these results show for the first time that 1 mol % of Ar_2Se_2 in combination with UHP is an effective means for conducting catalytic oxaziridine oxidations.[23]

The two-stage catalytic process using 10−20 mol % of **4**, 1 mol % of Ar_2Se_2, and UHP can be applied to the oxidation of other saturated and unsaturated aliphatic substrates (Table 1). Tertiary C−H hydroxylation is strongly preferred, even for starting materials in which methylene oxidation enjoys a significant statistical advantage.[24] Substrates possessing equatorial C−H groups on cyclohexane rings are optimal, as highlighted by the reaction of *cis*-decalin (entry 1). The *trans*-isomer, on the other hand, gives a markedly reduced yield of 3° alcohol product.[25] Nonetheless, in both examples and in entry 2, oxidation is stereospecific. As highlighted by the reaction of dihydrocitronellol benzoate (entry 3), C−H functionalization occurs preferentially at the 3° site distal to the electron-withdrawing group.[26] This pattern of reactivity together with the stereospecific nature of the process is consistent with a concerted oxidation event by an electrophilic species.[16,27] Although the turnover frequency and product yields for entries 2−4 are reduced from that of *cis*-decalin, such results constitute an important advance for catalytic oxidation of unactivated C−H centers. Stereospecific C−H hydroxylation is a hallmark of this chemistry and provides rapid entry to optically pure tetrasubstituted alcohols.[28]

Table 1. Catalytic Oxidations with UHP, Ar_2Se_2, and **4**

Entry	Substrate	Product	mol% 4	Time (h)	Yield[a]
1			20	48	**63**[b]
2			20	72	**36**[c]
3			20	96	**43**[c]
4			20	72	**39**[c]
5			20	72	**70**
6			10	36	**92**
7			10	12	**94**
8			20	45	**96**

[a] Reactions conducted at 22−50 °C using 1 mol % of Ar_2Se_2 and 2−4 equiv of UHP, 0.5−1.0 M in substrate; see Supporting Information for experimental details. [b] Reaction performed at 35 °C. [c] Reaction performed at 50 °C.

The oxidizing ability and potential versatility of oxaziridine **5** is further showcased in reactions with alcohol and alkene substrates. Cyclohexanol oxidation is accomplished in high yield and gives cleanly ϵ-caprolactone (entry 5) through perseleninic acid-catalyzed Baeyer−Villiger rearrangement of the intermediate ketone.[21a] Additionally and perhaps of greater consequence, we have found that this process is most efficient for epoxidation reactions, including those with weakly nucleophilic olefins (entries 6−8).[23] Given the synthetic flexibility of the benzoxathiazine heterocycle, the possibility for H_2O_2-mediated catalytic asymmetric alkene oxidation is evident.

Unique oxaziridines have been designed and evaluated as oxidants using both theoretical and experimental techniques. By employing a two-stage reaction cycle, this oxidation process is made catalytic with H_2O_2 serving as the terminal O-atom source. The ease by which benzoxathiazines may be synthesized will enable systematic catalyst modification with the aim of improving turnover efficiency and substrate scope. Such studies are advanced by the predictive power of DFT calculations, which have provided invaluable insights for this work. We believe that our findings

represent a significant step toward the development of general methodology for the catalytic hydroxylation of C−H bonds.

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Supporting Information Available: A complete list of authors for ref 11 can be found in ref 2, page S9. Experimental details, X-ray crystallographic, and analytical data for all compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A comparative table of selected bond lengths and angles for $\mathbf{TS_M^1}$ and $\mathbf{TS_M^{DMDO}}$ is included in the Supporting Information.

(18) The restricted B3LYP wave function exhibits an RHF → UHF instability similar to that observed for $\mathbf{TS_M^{DMDO}}$. Calculations using the stable unrestricted B3LYP wave function on $\mathbf{TS_M^1}$ led to a decrease in energy by 2.3 kcal/mol. A lowering of energy by 1.9 kcal/mol was noted for methane oxidation by dioxirane; see ref 16. Also see: (a) Du, X.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 6480−6483. (b) Shustov, G. V.; Rauk, A. *J. Org. Chem.* **1998**, *63*, 5413−5422.

(19) The reaction of oxaziridine **3** and 1-decene or adamantane affords the oxidized products with reaction times and product conversions comparable to that of **5**. Difficulties associated with the chromatographic separation of the benzoxathiazine byproduct from the desired compounds in addition to the high cost of the starting 2-bromophenol caused us to favor the use of benzoxathiazine **4** for all subsequent experiments.

(20) 1,3-Adamantanediol was produced in small quantities (∼5%) along with trace levels of 2-adamantanone. The absence of halogenated products suggests that freely diffusing radical species are not formed.

(21) Ar_2Se_2 is very easily prepared in a single operation (80%). See: (a) ten Brink, G.-J.; Vis, J.-M.; Arends, I. W. C. E.; Sheldon, R. A. *J. Org. Chem.* **2001**, *66*, 2429−2433. (b) ten Brink, G.-J.; Fernandes, B. C. M.; van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Chem Soc., Perkin Trans. 1* **2001**, 224−228.

(22) For a brief discussion on the various uses of UHP, see: Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533−535.

(23) Aqueous H_2O_2 was tested and found to be ineffective. No C−H oxidation was observed in the absence of Ar_2Se_2 and/or **4**. In control experiments, the combination Ar_2Se_2 and UHP gave <10% conversion to epoxide.

(24) Attempts to oxidize benzylic substrates afforded mixtures of products presumably due to aromatic functionalization.

(25) *Trans*-decalin affords ∼15% yield of *trans*-9-decalinol with no isomerization to the *cis* product detected by GC. DMDO oxidizes *trans*-decalin to *trans*-9-decalinol in 20% yield. See: Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470−2472.

(26) Oxidation of dihydrocitronellol benzoate affords the corresponding 3° alcohol with >10:1 selectivity as determined by ^{1}H NMR. Under the same catalytic conditions, isoamyl benzoate showed 5% conversion to the hydroxylated product after 24 h. Collectively, these data suggest that the selectivity observed in the hydroxylation of dihydrocitronellol benzoate is principally determined by electronic effects.

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