Synthetic Methods

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C–H Hydroxylation Using a Heterocyclic Catalyst and Aqueous H_2O_2**

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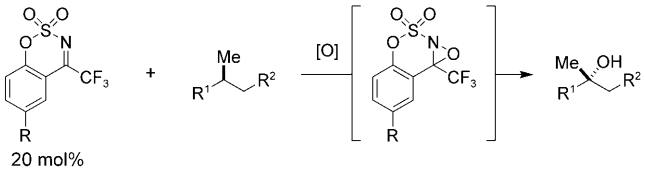
Catalytic reaction processes for selective C–H bond hydroxylation are at the fore of modern synthetic chemical methods development. Such technologies attempt to mimic the extraordinary performance and precision of enzymatic systems.[1] Following this approach, most inventions have relied on transition-metal based complexes to support reactive metal–oxo or metal–peroxo species that can effect the desired C–H oxidation event.[2,3] Far fewer catalytic methods make use of strained, electrophilic organic heterocycles (e.g., dioxiranes and oxaziridines).[4,5] We have capitalized on the unique properties of oxaziridines—ease of synthesis, modularity of design, tunable reactivity—and have described the first example of an oxaziridine-based catalytic process for C–H hydroxylation.[6,7] In contrast to most metal-mediated hydroxylation reactions, for which the high, indiscriminant reactivity of the oxidant often limits product selectivity and catalyst turnover, our first-generation oxaziridine system is hampered by its modest activity, thus restricting its use to a very small number of substrates. As such, we have sought new catalyst designs with enhanced performance and application potential. Mechanistic insights gained through computational and kinetics experiments have made possible the advent of a catalyst for C–H hydroxylation that: 1) can be employed with a number of architecturally diverse substrates; 2) displays positional selectivity towards tertiary C–H bonds; and 3) functions under aqueous conditions with H_2O_2 as the terminal oxidant.[8] These findings are described herein.

Computational data paired with experimental observations have guided the development of new catalysts for C–H hydroxylation. The benzoxathiazine heterocycle functions as a unique platform from which a reactive oxaziridine intermediate may be generated using a terminal oxidant (Scheme 1). Oxaziridine-mediated O-atom transfer to a saturated C–H bond or an alkene π-bond likely occurs through a concerted, asynchronous process, a conclusion supported by both theory and experiment.[9] We have performed density functional theory calculations (B3LYP/6-31G*) to examine further the electronic structure of the activated complex in the oxaziridine O-atom transfer event.[10,11] Despite their similarity in structure, oxaziridines **1** and **2** are predicted to react with disparate activation energies, the former having a barrier more than 3 kcal mol^{-1} lower than the latter (Figure 1). This difference appears to stem from the ability of the benzoxathiazine system **1** to support the build-up of electron density on the phenolic oxygen in the transition structure. Such data suggest that the incorporation of an electron-withdrawing group *para* to the phenolic oxygen (i.e., C6) should lower further the activation barrier for oxidation. Additionally, the use of polar solvents and/or hydrogen-bond donor additives could help to stabilize the transition structure. Insights gained from these computational data provide the basis for examining both C6-substituent effects and polar protic solvent to improve catalyst activity and performance.



Scheme 1. Benzoxathiazine-catalyzed C–H hydroxylation.

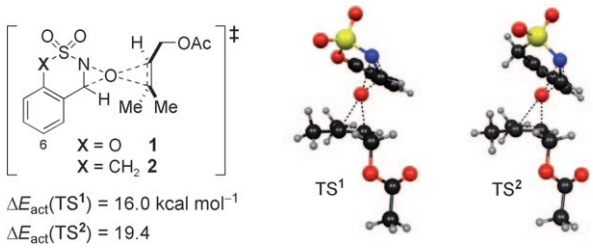


Figure 1. Calculated transition structures (B3LYP/6-31G*, CPCM (DCE)) for alkene epoxidation by oxaziridines **1** and **2**.

The influence of electronic substitution on catalyst activity was systematically explored using the eight oxaziridines highlighted in Figure 2. These particular derivatives were selected due to their ready availability in just two steps from commercial C5-substituted salicylaldehydes.[12] Initial rate measurements were recorded for the stoichiometric reaction between these oxidants and an alkene substrate **3** (Figure 2). Olefin epoxidation was used as a model reaction for C–H hydroxylation as both processes proceed through concerted, asynchronous transition states.[9,13] The rate of the oxaziridine-promoted epoxidation reaction, however, is significantly faster than the insertion process, thus facilitating

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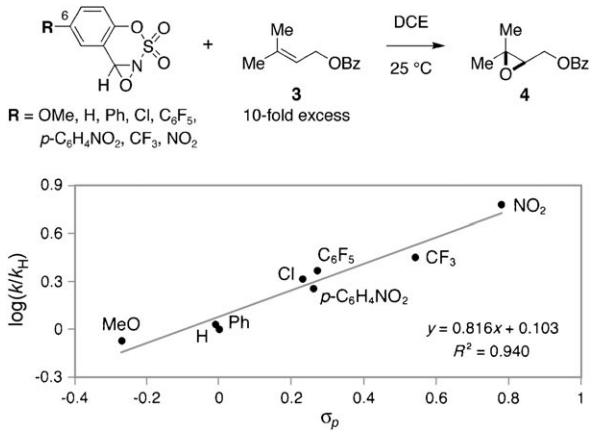
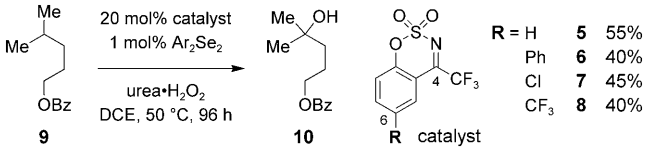


Figure 2. Hammett analysis of oxaziridine-promoted epoxidation.

kinetic analysis. Determination of k_{obs} for each oxaziridine was made under pseudo-first order conditions using a 10-fold excess of alkene **3**. When these data were plotted against the respective σ_p-substituent constants, a small positive ρ value of 0.83 was obtained; such a ρ value is consistent with an electrophilic O-atom transfer process.[14] The observed rate enhancement for the CF_3 and NO_2 derivatives prompted us to synthesize the corresponding 4-trifluoromethylbenzoxathiazines (see Scheme 2) and to evaluate these heterocycles as catalysts for C–H hydroxylation.[15]

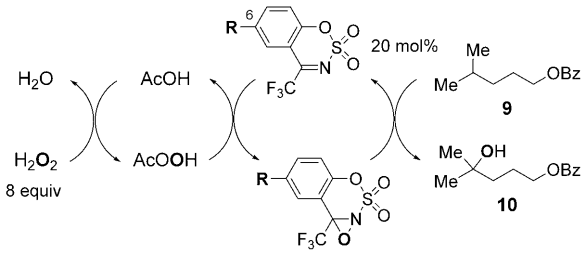


Scheme 2. Reduced performance with electron-deficient catalysts.

Although benzoxathiazines **6–8** proved competent as catalysts for C–H hydroxylation under our previously reported conditions (4 equiv urea·H_2O_2, 1 mol% 3,5-bis-trifluoromethylphenyldiselenide), the production of tertiary alcohol did not differ substantially between experiments and, surprisingly, no other heterocycle outperformed the parent structure **5**.[16] Despite the greater oxidizing power of the oxaziridines afforded from catalysts such as **7** and **8**, other factors clearly conspire to limit catalytic turnover in these reactions. One possibility is that the more electron-deficient benzoxathiazines favor to a greater extent hydration at C4, a factor that could retard the rate at which the oxaziridine is regenerated.[17] These somewhat disappointing results, particularly in light of the Hammett data, made evident the need for alternative strategies in order to improve the effectiveness of this family of hydroxylation catalysts.

Concomitant with investigations of the benzoxathiazine electronic structure on catalytic function, the influence of solvent, oxidant type, and polar additives was also explored. These studies revealed that catalytic C–H hydroxylation with benzoxathiazine **5** could be achieved using a combination of aqueous H_2O_2, acetic acid, and H_2O (Table 1). Under such

Table 1: A simplified catalytic scheme for C–H hydroxylation with aqueous H_2O_2.



Entry	R	Cat.	σ_p	Conversion [%][a]
1	H	**5**	0	40
2	Ph	**6**	0	50
3	Cl	**7**	0.23	70
4	CF_3	**8**	0.54	60
5	C_6F_5	**11**	0.27	95
6	p-$C_6H_4NO_2$	**12**	0.26	20

[a] Conversion determined by ^{1}H NMR integration of the unpurified reaction mixture. Reaction conditions: 20 mol% catalyst, 8 equiv 50% H_2O_2, 0.25 M 1:1 AcOH/H_2O, 50 °C, 96 h.

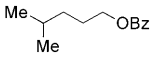
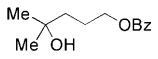
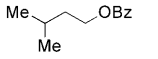
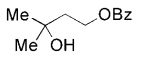
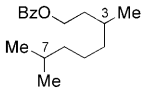
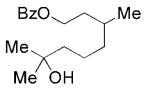
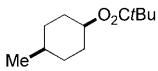
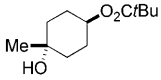
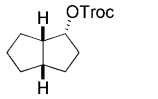
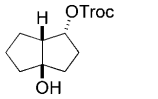
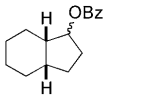
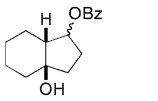
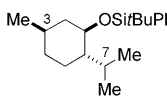
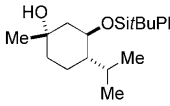
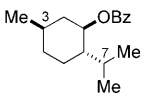
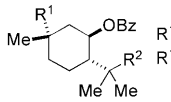
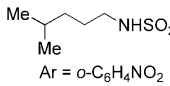
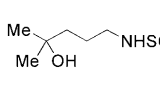
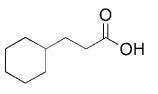
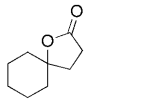
conditions, peracetic acid is formed and is likely the oxidant responsible for converting **5** to the corresponding oxaziridine.[18] The role of acetic acid is also as a co-solvent to help solubilize apolar substrates. While initial exploratory reactions employing this protocol with catalyst **5** gave modest returns, discernible improvement in product conversion with the C6-Ph (**6**), C6-Cl (**7**), and C6-CF_3 (**8**) derivatives was observed (Table 1, entries 2–4). Optimal performance under these new conditions seemed to peak with the Cl-substituted catalyst **7**. Also intriguing was the fact that the C6-Ph catalyst **6** was more effective than **5** despite the apparent similarity in the electronic structures of these two systems. This latter result, albeit small, caused us to question the influence of catalyst shape (i.e., polar surface area, molecular volume) and solubility on catalytic function. To examine these effects, two additional benzoxathiazines were designed with C6-aryl substituent groups chosen to match closely the σ_p parameter of Cl (Table 1, entries 5 and 6).[14]

Oxaziridines generated from catalysts **11** and **12** were assumed to possess nearly identical electrophilic reactivity, a conclusion supported by the Hammett analysis data shown in Figure 2. Accordingly, the function of both catalysts should be comparable if this parameter were the principal determinant of reaction efficiency under the aqueous conditions. The results from hydroxylation reactions with **11** and **12** are markedly disparate, however, with the pentafluorophenyl (PFP) catalyst **11** clearly outshining **12** and all others (Table 1). It is evident that C–H hydroxylation using benzoxathiazine-based catalysts in aqueous media is responsive to factors other than oxidant reactivity. Moreover, it appears that the mechanistic details underlying catalytic turnover are considerably more complex than initially envisioned. At present, we believe that the fluorocarbon moiety in **11** may present a large hydrophobic surface area that promotes catalyst–substrate aggregation and thus elevates the effective molarity between these two reacting partners.[19] Studies are currently in progress to test this hypothesis.[20] As highlighted

below, this first-generation catalyst displays marked performance for tertiary C–H bond hydroxylation.

Results depicted in Table 2 define the substrate profile for reactions catalyzed by the PFP-substituted benzoxathiazine

Table 2: Substrate profile for reactions catalyzed by **11**.[a]

Entry	Substrate	Product	Yield [%][b]
1			75
2			44
3			70[c]
4			61
5			38
6			82
7			34
8			47[d]
9			66
10			40[e]

[a] Troc = trichloroethoxycarbonyl; Bz = benzoyl. [b] Optimized reaction conditions: 20 mol% catalyst **11**, 8 equiv 50% H_2O_2, 0.25 M 1:1 AcOH/H_2O, 50 °C, 96 h. [c] Yield of isolated product after 48 h. [d] The ratio of C3/C7 hydroxylation products is ca. 1:1. An additional 10–15% of the product resulting from benzoate migration to the C7-OH is also obtained. [e] Product volatility accounts for some diminution in yield.

11 under aqueous acetic acid/H_2O_2 reaction conditions. The active oxidant is exquisitely selective for tertiary C–H bonds, the products of secondary hydroxylation having never been observed for any of the substrates shown. As predicted based on prior knowledge, the catalyst is sensitive to the electronic environment of the C–H bond undergoing reaction.[3,4,6,21] In substrates possessing two tertiary C–H bonds, the center furthest removed from the electron-withdrawing moiety reacts preferentially (Table 2, entries 3, 5, 6). Catalytic hydroxylation of a starting material possessing a stereogenic CH center (Table 2, entries 5–7) gives a single stereoisomeric product.[22] While reaction times are somewhat prolonged, it is notable that the reaction can proceed for an extended period without observable catalyst or substrate decomposition.[23]

Stereospecific C–H hydroxylation of mono- and bicyclic ring systems to afford tetrasubstituted carbinol centers is a desirable transformation for complex molecule synthesis. Through judicious choice of protecting groups, positional selectivity in substrates such as menthol (Table 2, entries 7 and 8) can be controlled. Although the total conversion to product is efficient for the *O*-benzyl ester derivative, hydroxylation occurs indiscriminately at C3 and C7. In the former example, the steric demands of the larger *t*$BuPh_2Si$ group are presumably enough to steer the reaction towards C3. Oxidation at fused ring junctures is highlighted for both *cis*-fused 5,5 and 5,6 ring systems (Table 2, entries 5, 6). Applications for this type of transformation are potentially high, as angular hydroxy groups appear with some regularity as structural motifs in natural products. Finally, we note that the reaction conditions are tolerant to a number of common functional groups including esters, silyl ethers, sulfonylated amines, and carboxylic acids.

We have advanced a unique catalytic process for C–H hydroxylation from a proof-of-principle to that of an effective tool for chemical synthesis. In doing so, aqueous H_2O_2 conditions have been identified that greatly simplify the experimental protocol and facilitate the large-scale application of this method. More importantly, our findings suggest a possible strategy for promoting kinetically slow C–H hydroxylation events through the hydrophobic aggregation of catalyst and substrate. Continued efforts to elucidate the reaction pathways that limit catalyst turnover and to exploit secondary catalyst–substrate interactions to optimize reaction performance are expected to bear additional, salient discoveries.

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Keywords: benzoxathiazines · C–H hydroxylation · hydrogen peroxide · organocatalysis · oxaziridines

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[10] Calculations performed using Gaussian 03, Revision C.02, M. J. Frisch, et al. Gaussian, Inc., Wallingford, CT, **2004**. Activation energies were calculated relative to isolated reactants.
[11] A comparative table of selected bond lengths and angles for **TS[1]** and **TS[2]** is included in the Supporting Information.
[12] Oxaziridines were synthesized from C5-substituted salicylaldehydes by sulfamoylation followed by oxidation with buffered Oxone. Salicylaldehydes not commercially available were synthesized from 5-bromosalicyclaldehyde by Suzuki cross-coupling (see Supporting Iinformation for details).
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[15] The incorporation of a 4-trifluoromethyl group is necessary for generating an oxaziridine capable of effecting C–H hydroxylation. Salicylaldehyde-derived benzoxathiazines (see Figure 2) are only able to catalyze olefin epoxidation.
[16] A catalytic reaction with the C6-NO_2 derived benzoxathiazinane afforded $< 10\,\%$ of the desired product.
[17] It is possible that other nucleophilic species (e.g., H_2O_2, urea) could add at C4, thus inhibiting oxaziridine regeneration.
[18] Control reactions show that AcOH is required for benzoxathiazine oxidation with H_2O_2. In addition, peracetic acid will react with **7** and **11** to afford the corresponding oxaziridines.
[19] M. R. Biscoe, R. Breslow, *J. Am. Chem. Soc.* **2005**, *127*, 10812.
[20] It appears that the improved performance of **11** over other benzoxathiazines is not due to its greater stability under the reaction conditions. More than 90% of the starting benzoxathiazine is recovered from reactions performed with either catalyst **5** or **11**.
[21] a) J. Du Bois, *Chemtracts*: *Org. Chem.* **2005**, *18*, 1; b) K. W. Fiori, C. G. Espino, B. H. Brodsky, J. Du Bois, *Tetrahedron* **2009**, *65*, 3042.
[22] Only a single diastereomer is observed within the limits of ^{1}H NMR.
[23] A reaction conducted for 48 h with the substrate appearing in entry 1 of Table 2 returned $> 90\,\%$ of the benzoxathiazine catalyst. The combination of starting material and product accounts for more than 80% of the total mass balance.

