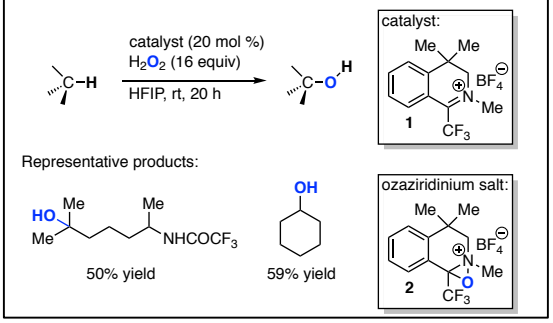
PRF# 56158-DNI1
New Organocatalysts for Chemoselective Aliphatic C–H Hydroxylation
P.I.: Michael Hilinski, University of Virginia

Research Progress

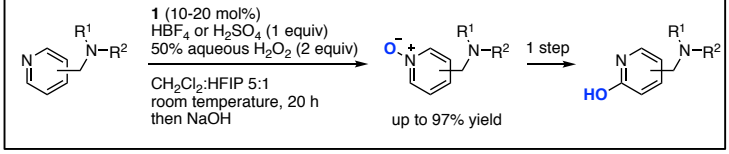
The overall goal of the research funded by this award is to develop new organocatalytic methods for selective C–H oxidation reactions. Two classes of organocatalysts, ketones and iminium salts, were proposed. Efforts for this year focused on the development of iminium salt catalysts for C–H hydroxylation. We have reported that iminium salt catalyst **1** was capable of catalyzing the site-selective hydroxylation of tertiary aliphatic C–H bonds at room temperature using aqueous hydrogen peroxide as the terminal oxidant. In the absence of steric effects, these reactions are selective for the most electron-rich C–H bond on a given molecule. When tertiary C–H bonds are not available to react, secondary C(sp^3)–H bonds can also be selectively oxidized, as in the case of cyclohexane (Figure 1). We obtained evidence that the active oxidant for these reactions is oxaziridinium salt **2**.

Figure 1. Iminium catalysis of C-H hydroxylation



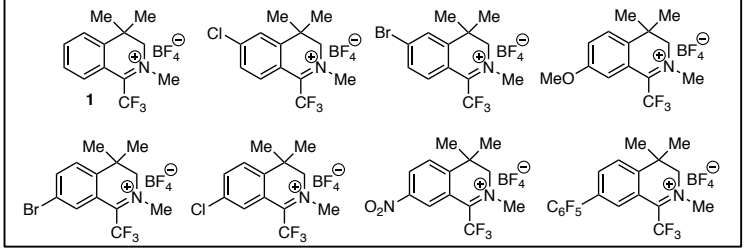
While further exploring the capabilities of this new C–H hydroxylation catalyst, we discovered that substrates containing more than one nucleophilic nitrogen atom could be selectively oxidized at the less nucleophilic nitrogen atom under acidic conditions (Figure 2). This addressed an unsolved problem in selective N-oxidation chemistry and, by extension, in selective C–H hydroxylation chemistry given that the resulting heteroaromatic N-oxides could be converted into hydroxylated heteroarene products in one step (Figure 2).

Figure 2. Selective heteroaryl N-oxidation of amine-containing molecules



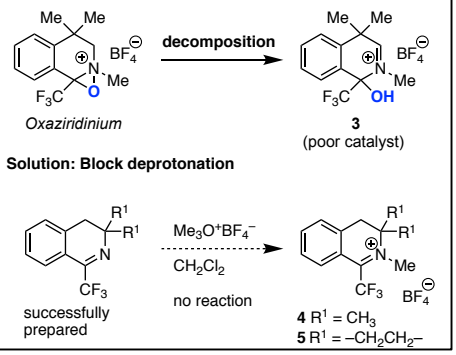
In order to improve yields, selectivities, and the scope of substrates that can be selectively hydroxylated using iminium salt catalysts, our current work emphasizes the synthesis and evaluation of structurally modified catalysts based either on the dihydroisoquinolinium scaffold used for catalyst **1** or on other scaffolds that might offer complementary reactivity and selectivity. The original design of catalyst **1** incorporated an unsubstituted aryl ring that was intended to function as a handle for electronic modification of the catalyst. New catalysts have been synthesized that incorporate electron-withdrawing and/or electron-donating groups at the 6- and 7-positions of the dihydroisoquinolinium ring. Representative examples are shown in Figure 3. All of these new iminium salts are capable of catalyzing the C–H hydroxylation reaction, and the differences in their capabilities are currently being evaluated in order to inform the future design of superior catalysts.

Figure 3. Recently prepared, competent C–H hydroxylation catalysts



Expansion of the capabilities of iminium salt-catalyzed C(sp^3)–H hydroxylation also requires overcoming limitations inherent in the design of the first-generation catalysts. In the course of investigating the fate of catalyst **1** in a typical hydroxylation reaction, we observed the formation of iminium salt **3**, which presumably arises from the observable, but not isolable oxaziridinium **2**. Iminium salt **3** is a poor hydroxylation catalyst, and therefore this pathway contributes substantially to limitations in conversion and catalyst loading associated with catalyst **1**. Consequently, the synthesis of alternative catalyst scaffolds that avoid this oxaziridinium decomposition pathway was

Figure 4. Catalyst decomposition and design and synthesis of longer-lived catalysts



investigated, focusing on blocking the 3-position of the catalyst from deprotonation (Figure 4). Unfortunately, the synthesis of proposed catalysts **4** and **5** could not be completed due to the failure of the final alkylation step on the penultimate imine intermediate. The increased steric bulk of the *gem*-dimethyl and cyclopropyl groups presumably reduced the imine nucleophilicity in this reaction. To overcome this synthetic issue, other strategies to avoid the known oxaziridinium decomposition pathway are currently being investigated.

Evaluation of ketones as catalysts for C–H hydroxylation was a focus of year 1 of the award period. During this second year of funding, we sought to expand the capability of ketone-catalyzed C–H hydroxylation by evaluating the capability of chiral ketone catalysts to promote asymmetric C–H hydroxylation of simple alkanes. A number of chiral ketone catalyst scaffolds have been prepared. Evaluation of the capability of these catalysts is ongoing.

Impact of the Research

This work has enabled the development of two distinct organocatalytic approaches to selective C(sp^3)–H hydroxylation. Although other organocatalytic and transition metal catalyzed methods have previously been developed, current challenges in the field including those associated with site selectivity and stereoselectivity are considerable and the development of a more diverse set of catalytic approaches will enable more rapid progress. The choice of ketone and iminium salt catalysts was made due to the large body of literature describing use of these catalysts for related reactions, including epoxidation. The large known variety of catalyst scaffolds that incorporate these motifs can be explored for C–H hydroxylation now that catalysis of these reactions has been developed.

This ACS PRF support has enabled the Hilinski laboratory to initiate a major project in organocatalytic C–H hydroxylation. Data obtained in the course of these investigations was used as preliminary data for a funded R01 award from the National Institutes of Health (NIGMS). Two graduate research assistants have been supported using PRF funds, and this support has enabled their training in standard synthetic organic chemistry techniques. One of the students completed his Ph.D. requirements during this current award year.