Organic Letters

Letter

pubs.acs.org/OrgLett

An Iminium Salt Organocatalyst for Selective Aliphatic C−H Hydroxylation

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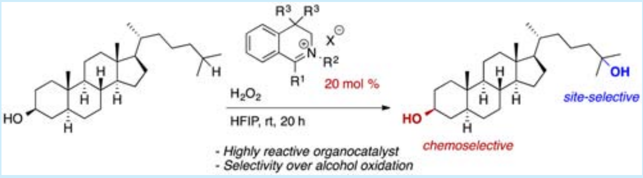
Supporting Information

ABSTRACT: The first examples of catalysis of aliphatic C−H hydroxylation by an iminium salt are presented. The method allows the selective organocatalytic hydroxylation of unactivated 3° C−H bonds at room temperature using hydrogen peroxide as the terminal oxidant. Hydroxylation of an unactivated 2° C−H bond is also demonstrated. Furthermore, improved functional group compatibility over other catalytic methods is reported in the form of selectivity for aliphatic C−H hydroxylation over alcohol oxidation. On the basis of initial mechanistic studies, an oxaziridinium species is proposed as the active oxidant.



Over the past decade, the development of catalytic methods for site-selective hydroxylation has provided elegant solutions to the problem of discriminating among several potential sites of oxidation on complex molecules, leading to improvements in synthetic efficiency.[1] However, there are still considerable challenges preventing the widespread adoption of hydroxylation as a synthetic strategy. Specific challenges include incompatibility with more easily oxidized functional groups[2] and limitations on the degree and nature of site selectivity that can be achieved in the absence of directing groups.[3] Herein we present the first disclosure of a new class of organocatalysts for C−H hydroxylation, iminium salts, which begin to address some of these limitations.

The majority of efforts toward site-selective hydroxylation methods have been directed at the development of transition-metal-based catalysts.[4] In contrast, organocatalytic methods are relatively unexplored despite potential advantages.[5] The most thoroughly investigated are the benzoxathiazine catalysts developed by Du Bois,[6] which demonstrate a high degree of site selectivity. We have sought to identify new classes of organocatalysts with advantages in reactivity and selectivity over existing catalytic methods,[7] and herein we report a trifluoromethyl-substituted *N*-methyliminium salt that is capable of catalyzing the selective hydroxylation of aliphatic C−H bonds by hydrogen peroxide at room temperature, demonstrating improved reactivity over benzoxathiazine catalysts. More importantly, we report that the catalyst is selective for tertiary aliphatic C−H hydroxylation over 1° and 2° alcohol oxidation, demonstrating a significant advantage over other hydroxylation methods in terms of functional group compatibility.

To date, the development of organocatalysts has focused on harnessing the reactivity of dioxiranes[7] and *N*-sulfonyl oxaziridines[6] in a catalytic cycle (Figure 1). The ability of dioxiranes[8] and oxaziridines[9] to hydroxylate unactivated aliphatic C−H bonds intermolecularly in a site-selective manner had been previously established. *N*-Alkyl oxaziridinium salts,[10] a separate but related class of oxidants, have been developed as reagents[11] and catalytic intermediates[12] for epoxidation and other oxidation reactions, including asymmetric transformations. However, the analogous C−H hydroxylation reactions employing oxaziridinium salts remain unexplored. We hypothesized that these cationic oxidants, if properly developed, would potentially be more reactive than dioxiranes or oxaziridines in a C−H oxidation process because of the increased electrophilicity of the oxygen atom.

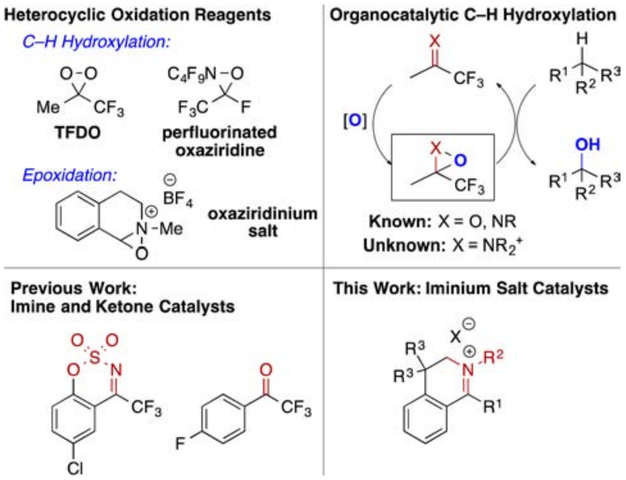


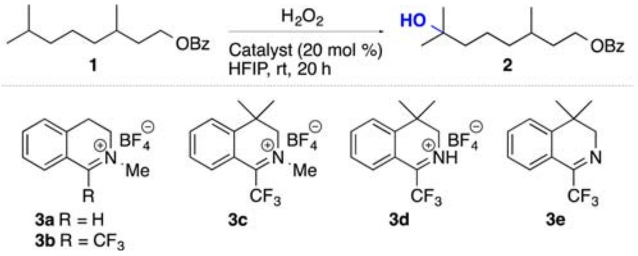
Figure 1. Stoichiometric and catalytic C−H oxidation by heterocyclic oxidants and organocatalysts.

We first investigated known epoxidation catalyst **3a**[12d] at 20 mol % loading using an excess of hydrogen peroxide as the terminal oxidant but observed no hydroxylation of ester **1** at room temperature (Table 1, entry 1). Trifluoromethyl substitution as in catalyst **3b** (entry 2) led to improved

Received: June 22, 2016
Published: July 8, 2016

DOI: 10.1021/acs.orglett.6b01832
Org. Lett. 2016, 18, 3826–3829

Table 1. Summary of Optimization Studies[a]



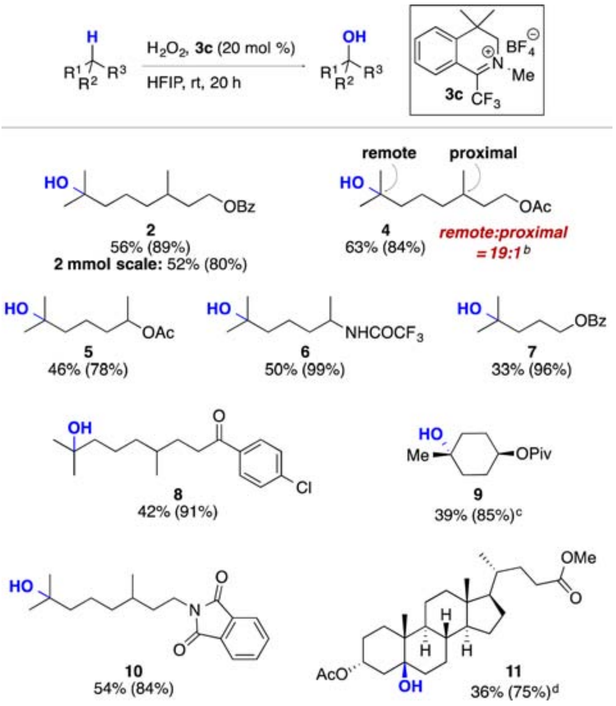
entry	catalyst	deviation from initially optimized conditions[b]	conversion (%)[c]	yield of **2** (%)[d]
1	**3a**	–	<1	<1
2	**3b**	–	12	3
3	**3c**	–	70	57
4	**3d**	–	<1	<1
5	**3e**	–	<1	<1
6	**3c**	DCE (200 μL)	31	21
7	**3c**	MeCN (200 μL)	2	<1
8	**3c**	t = 4 °C	46	43
9	**3c**	t = 50 °C	49	25
10	**3c**	100 μL of HFIP	59	47
11	**3c**	200 μL of HFIP	74	64
12	**3c**	250 μL of HFIP	68	59

[a] Reactions were performed with 0.2 mmol of substrate, 0.04 mmol of **3c**, and 180 μL of H_2O_2 (50% aqueous solution) in 150 μL of HFIP at room temperature for 20 h, unless otherwise noted. [b] Entries 6 and 7: DCE and MeCN were used as cosolvents in addition to HFIP. Entries 10–12: The amount of HFIP was varied. [c] Determined by GC. [d] Corrected GC yields.

reactivity, generating the product of hydroxylation at the site remote from the benzoate ester. Incorporating *gem*-dimethyl substitution at the benzylic position to limit the possibility of catalyst aromatization[12d] led to a dramatic improvement (entry 3). Importantly, *N*-methyl substitution of the catalyst is required; neither the corresponding imine nor its HBF_4 salt are competent hydroxylation catalysts under these conditions (entries 4 and 5). The use of hexafluoroisopropanol (HFIP), which is known to activate H_2O_2,[13] as a solvent was essential, and varying the amount used allowed the identification of the fully optimized conditions (entry 11).

Notably, iminium salt **3b** demonstrated improved reactivity over other organocatalysts, which require elevated temperatures and in some cases extended reaction times to achieve similar results. Thus, we investigated a variety of substrates to evaluate the functional group compatibility and electronic effects on the yield and selectivity (Scheme 1). As is the case for other catalysts, hydroxylation using **3c** is consistently selective for 3° over 2° oxidation. Additionally, we observed a high degree of selectivity for a single site of hydroxylation. In many cases other hydroxylation products could be observed, but only in trace amounts. Furthermore, this catalyst demonstrates a high degree of selectivity for hydroxylation of 3° C–H bonds that are remote rather than proximal to an electron-withdrawing group. For example, we directly compared the selectivity of hydroxylation of 3,7-dimethyloctyl acetate (generating **4** as the major product) using **3c** to the selectivity obtained using the White–Chen catalyst. In the latter case, the reported selectivity for hydroxylation of the remote over the proximal 3° C–H bond is 5:1.[4b] In contrast, with catalyst **3c** we observed 19:1 selectivity. Hydroxylation catalyzed by **3c** is also stereospecific (product **9**).

Scheme 1. Hydroxylation of 3° C–H Bonds[a]

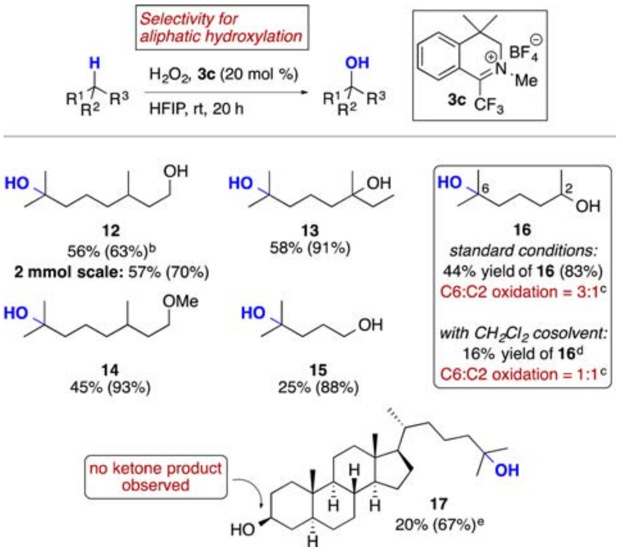


[a] Reactions were performed on a 0.4 mmol scale unless otherwise noted. Yields of isolated products and, in parentheses, combined yields of product and recovered starting material following chromatography are shown. [b] Determined by GC of the crude reaction mixture using authentic standards. [c] 40 mol % **3c** was used. [d] Reaction time = 48 h. **3c** and H_2O_2 were added in two portions at 0 and 24 h.

We also observed an unexpected preference for aliphatic hydroxylation in the presence of sterically unencumbered 1° and 2° alcohols (Scheme 2). To our knowledge, this type of chemoselectivity is unprecedented for organocatalysts or transition-metal catalysts that exhibit site selectivity; the use of ester protecting groups is generally required to avoid alcohol oxidation.[4−9] In our case, the oxidation of 1° alcohols (e.g., products **12** and **15**) using **3c** generates no more than trace amounts of carboxylic acid or aldehyde products.[14] Aliphatic hydroxylation also occurs selectively over oxidation of 2° alcohols (e.g., product **16**), although the degree of selectivity (3:1 preference) is somewhat diminished. These counter-intuitive results can potentially be explained by unexpected hydrophobic effects elucidated by Breslow for iminium salt-catalyzed epoxidations.[15] To test this hypothesis, we performed a hydroxylation of 6-methylheptan-2-ol using our standard conditions but with the inclusion of dichloromethane as a cosolvent (1:1 ratio with HFIP; Scheme 2). Consistent with our hypothesis, there was no selectivity for aliphatic hydroxylation in this less polar solvent system; a 1:1 mixture of **16** and 6-methylheptane-2-one was observed. The addition of a smaller amount of CH_2Cl_2 (1:2 ratio with HFIP) to solubilize dihydrocholesterol was sufficient to maintain the selectivity for aliphatic hydroxylation (product **17**). Notably, in this case no 2° alcohol oxidation was observed.

Hydroxylation of unactivated 2° aliphatic C–H bonds has been reported using transition-metal catalysts but not organocatalysts, a drawback we surmised might be overcome by the improved reactivity of **3c**. Furthermore, one current limitation of aliphatic 2° bond hydroxylation by site-selective catalysts is

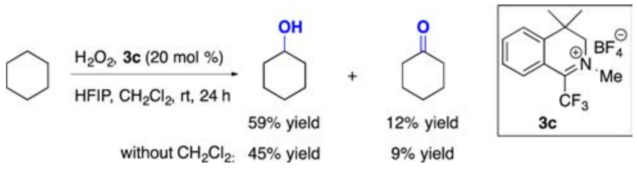
Scheme 2. Aliphatic Hydroxylation of Alcohol and Ether Substrates[a]



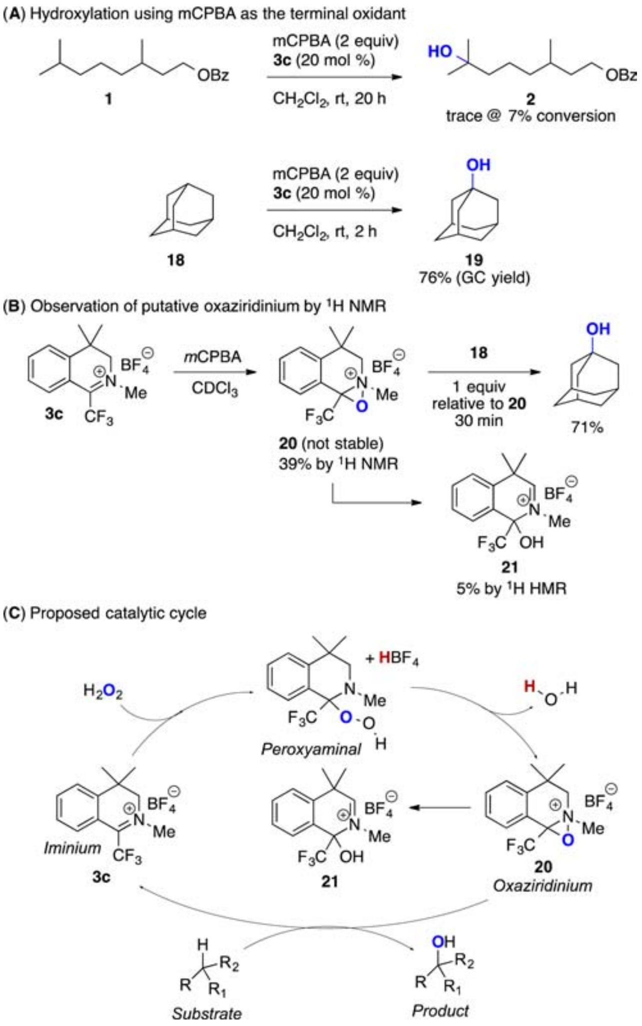
[a]Reactions were performed on a 0.4 mmol scale unless otherwise noted. Yields of isolated products and, in parentheses, combined yields of product and recovered starting material following chromatography are shown. [b]Recovery of starting material was low because of difficult reisolation. [c]Ratios were determined by GC. [d]Corrected GC yield. The reaction was performed with the addition of 400 μL of CH_2Cl_2. [e]CH_2Cl_2 (200 μL) was used as a cosolvent.

that ketones are typically observed as the only products.[4] In contrast, not only is **3c** capable of catalyzing the oxidation of cyclohexane, but the typically observed overoxidation to the ketone is suppressed (Scheme 3).[16] In this case the addition of CH_2Cl_2 modestly improved the yield, presumably because of the increased solubility of the substrate in the biphasic solvent mixture (the ratio of products did not change).

Scheme 3. Selective Catalytic Oxidation of Cyclohexane to Cyclohexanol



Scheme 4. Investigation of the Reaction Mechanism



Initial attempts to observe the formation of an oxaziridinium species under the standard reaction conditions were unsuccessful. Thus, to investigate the mechanism further, we performed catalytic oxidations using mCPBA, the oxidant of choice for oxaziridinium synthesis,[10] as the terminal oxidant (Scheme 4A). In this case, hydroxylation of **1** to form **2** was low-yielding, but adamantane was smoothly converted to adamantanol in just 2 h. The formation of a species consistent with an oxaziridinium could be observed by ^1H NMR spectroscopy, but this species could not be isolated because of its considerable instability (Scheme 4B). Iminium **21**, the result of a known decomposition pathway of oxaziridinium species,[10b] was also observed and could be isolated. In the same experiment, addition of adamantane to the NMR tube led to the consumption of **20** and concomitant formation of 1-adamantanol. Thus, the evidence suggests that an oxaziridinium species is capable of hydroxylation at room temperature and is therefore the likely active oxidant. In support of this, the formation of **21** is also observed under the optimized reaction conditions. A proposed catalytic cycle is outlined in Scheme 4C. We propose that fluoroboric acid liberated upon addition of hydrogen peroxide promotes oxaziridinium formation, which is consistent with a pH of 2 observed for the standard reaction conditions. Catalyst decomposition product **21** can catalyze the hydroxylation of **1** under the standard reaction conditions but in a much lower yield (5%), suggesting an explanation for the limitations in reaction conversion.

In conclusion, we have disclosed the first example of an iminium salt catalyst for aliphatic C−H hydroxylation. Advantages over previously reported organocatalysts include efficient hydroxylation at room temperature and hydroxylation of unactivated 2° C−H bonds. Furthermore, chemoselectivity for aliphatic hydroxylation over alcohol oxidation provides advantages over existing catalysts (including transition-metal catalysts), including the ability to oxidize a 2° aliphatic C−H bond selectively to a 2° alcohol with limited overoxidation. Overall, these results further establish organocatalysis as a competitive alternative to transition-metal catalysis for aliphatic C−H hydroxylation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01832.

> Experimental details, analytical and spectroscopic data, and copies of spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Virginia for financial support.

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