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Organocatalytic, Dioxirane-Mediated C−H Hydroxylation under Mild Conditions Using Oxone

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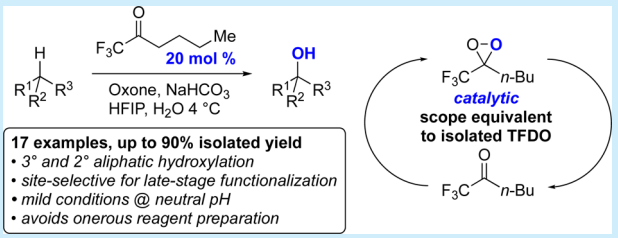
Supporting Information

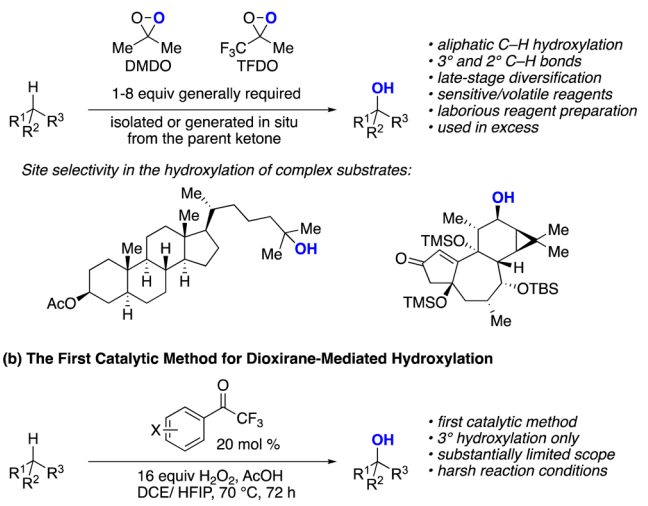
ABSTRACT: Dioxiranes are among the most selective and useful reagents for C(sp^3)−H hydroxylation, but the development of a general dioxirane-mediated catalytic method has been an elusive goal. A trifluoromethyl ketone catalyst in combination with Oxone is shown to enable the first dioxirane-mediated catalytic hydroxylations that approximate the reactivity and selectivity of isolated dioxiranes. The mild reaction conditions allow for selective 3° hydroxylation and 2° oxidation and are tolerant of acid-sensitive functionality and electron-neutral arenes.



The appeal of precise control of selectivity in the conversion of C−H bonds to more synthetically tractable functional groups has spurred investigations into general catalytic methods for intermolecular, site-selective aliphatic hydroxylation.[1,2] Transition-metal complexes[3] and organocatalysts[4] that are capable of effecting oxygen atom transfer have been investigated for this purpose, resulting in considerable recent advances in the ability to selectively oxidize one of many unactivated C(sp^3)−H bonds, even on highly complex, druglike substrates. While these developments have opened the door to the prospect of C−H hydroxylation as a routine synthetic transformation, significant challenges remain in addressing issues of regioselectivity, stereoselectivity, and functional group compatibility that necessitate the development of new catalytic strategies.

Some of the most extensively studied reagents capable of selective C−H hydroxylation are dioxiranes (Scheme 1a), particularly dimethyldioxirane (DMDO) and its more reactive derivative methyl(trifluoromethyl)dioxirane (TFDO).[5] The high degree of site selectivity they demonstrate in the oxidation of complex molecules makes them paradigmatic reagents for this purpose,[5,6] but for many applications their use is impractical, given that they must be prepared in advance as dilute solutions under carefully controlled conditions.[7] Methods for C−H hydroxylation that involve the in situ generation of TFDO from 1,1,1,-trifluoroacetone avoid this complication but require an excess amount of the highly volatile parent ketone to achieve synthetically useful conversion.[8] In contrast, oxidation of more reactive functional groups can be achieved using a catalytic amounts of ketone. In particular, the development of dioxirane-mediated catalytic epoxidations by Shi, Denmark, and Yang helped to usher in the advent of modern organocatalysis two decades ago.[9] The considerable advantages of ketone catalysis as applied to enantioselective epoxidations,[10] in particular, illustrate the appeal of expanding this platform to include catalytic enantioselective C−H hydroxylation. Despite a longstanding interest in this possibility,[11] and success in achieving organocatalytic hydroxylation with structurally related oxaziridine[4c−e] and oxaziridinium[4a] oxidants, to date no intermolecular methods that are catalytic in ketone and that replicate the broad substrate scope and site selectivity of TFDO and DMDO have been disclosed. This creates a substantial barrier to pursuing tunable site-selective and enantioselective organocatalytic methods for C−H hydroxylation.

Scheme 1. C−H Hydroxylation by Dioxiranes: Prior Art



We have recently reported the first examples of ketone-catalyzed C−H hydroxylation (Scheme 1b).[4b] While that study established that catalytic turnover in a dioxirane-mediated C−H hydroxylation could indeed be achieved, hydroxylation of aliphatic C−H bonds was limited to highly reactive adamantane

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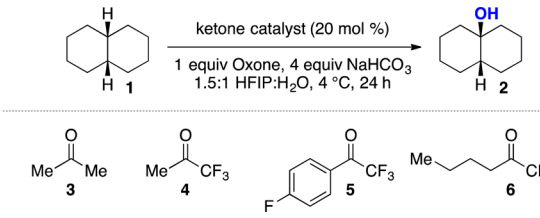
and decalin substrates. In addition, a large excess of 50% aqueous H_2O_2 (16 equiv), high temperature, and acidic reaction conditions were required, likely precluding the possibility of developing enantioselective and functional group tolerant transformations. This has led us to seek new strategies that would enable ketone catalysis as a widely applicable platform for hydroxylation. We report herein substantially milder reaction conditions using Oxone as the terminal oxidant that allow for greatly expanded substrate scope. Reactivity of this catalytic system is analogous to that observed using isolated TFDO[5] and thereby reduces the need for onerous reagent preparation and storage. Our findings also expand the range of competent ketone catalysts to include alkyl trifluoromethyl ketones in addition to the previously reported aryl trifluoromethyl ketones,[4b] enabling greater flexibility in catalyst design to address current challenges in selective hydroxylation.

Although Oxone is a typical oxidant used for in situ generation of dioxiranes[12] and has the advantages of being inexpensive, safe, and environmentally benign, our previous investigations were structured to deliberately avoid its use. Our hypothesis was that the demonstrated instability of dioxiranes in its presence[13] contributed to earlier unsuccessful attempts to achieve catalysis of intermolecular hydroxylation.[11] Ultimately, this led to the discovery that catalytic turnover could be achieved when 50% aqueous H_2O_2 was used as the terminal oxidant at elevated temperature (70 °C).[4b] Importantly, the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a cosolvent was essential to realize the highest yields and lowest catalyst loading.[8] In related work, Du Bois has reported that *N*-sulfonyloxaziridines, which are structurally and mechanistically related to dioxiranes, are stabilized in aqueous fluoro alcohol solvent mixtures.[4c,8] In light of these previous observations, we now report that the use of HFIP as a cosolvent can enable dioxirane-mediated catalysis in the presence of Oxone.

Initial investigations into the hydroxylation of *cis*-decalin (**1**) revealed that catalytic turnover using Oxone (1 equiv relative to 4 equiv of $NaHCO_3$) could be achieved at 4 °C using 20 mol % catalyst loading and a 1.5:1 mixture of HFIP/H_2O as the solvent (Table 1, entries 1−4). DMDO precursor acetone gave only trace conversion, but TFDO precursor 1,1,1-trifluoroacetone (**4**) and commercially available 1,1,1-trifluorohexan-2-one (**6**) gave promising initial results. Interestingly trifluoroacetophenones, which demonstrated superior catalytic ability using our previously reported protocol, were inferior to the alkyl trifluoromethyl ketone catalysts (entry 3). Ketone **6** was chosen for further investigation due to superior performance as well as ease of handling (boiling point of 90 °C versus 22 °C for **4**). Optimal yields were achieved with addition of 5 mol % of a tetraalkylammonium salt phase-transfer catalyst (entry 6). As shown by entries 7−10, both the choice of organic solvent and its ratio to water are critical. 2,2,2-Trifluoroethanol (TFE) was inferior to HFIP, and the use of a typical cosolvent for dioxirane-mediated oxidations, acetonitrile,[10] did not result in catalytic turnover.

For less reactive substrates, up to 3 equiv of Oxone were required to achieve the highest yields. This necessitated the development of a portionwise addition protocol (Table 2).[13] Hydroxylation of 3,7-dimethyloctyl acetate (**7**) using a single equivalent of Oxone gave only a modest yield (46%). Doubling the amount of oxidant and base gave no improvement in yield after 24 h, with no additional conversion observed thereafter. However, increasing the reaction time to 48 h in combination

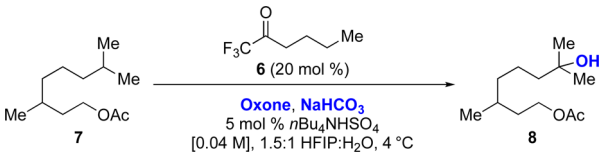
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent adjustment[b]	additive (5 mol %)	yield of **2**[c] (%)
1	**3**			4
2	**4**			49
3	**5**			13
4	**6**			61
5	**6**		18-crown-6	76
6	**6**		nBu$_4$NHSO$_4$	80
7	**6**	5:1 HFIP/H_2O	nBu$_4$NHSO$_4$	26
8	**6**	1:5 HFIP/H_2O	nBu$_4$NHSO$_4$	9
9	**6**	1.5:1 TFE/H_2O	nBu$_4$NHSO$_4$	40
10	**6**	1.5:1 CH_3CN/H_2O	nBu$_4$NHSO$_4$	25

[a]Reaction conditions: 0.1 mmol of **1**, 0.02 mmol of catalyst, 0.1 mmol of Oxone, 0.4 mmol of $NaHCO_3$, 0.04 M in 1.5:1 HFIP/H_2O at 4 °C for 24 h unless otherwise noted. [b]The solvent mixture noted replaced 1.5:1 HFP/H_2O while maintaining a concentration of 0.04 M in **1**. [c]Corrected GC yield using dodecane as an internal standard.

Table 2. Portionwise Addition of Reagents Improves Yield[a]



Oxone (equiv)	$NaHCO_3$ (equiv)	addition protocol	total reaction time (h)	yield of **8**[b] (%)
1	4	single portion	24	46
2	8	single portion	24	46
2	8	two portions (t = 0, 24 h)	48	73
3	12	three portions (t = 0, 24, 48 h)	72	85[c]

[a]Reaction conditions unless otherwise noted: 0.1 mmol of **7**, 0.02 mmol of **6**, 0.04 M in 1.5:1 HFIP/H_2O using amounts of oxidant, base, and addition protocol noted. [b]Corrected GC yield using dodecane as an internal standard unless otherwise noted. [c]Isolated yield on 0.5 mmol scale.

with portionwise addition of Oxone and $NaHCO_3$ gave substantially improved conversion. Ultimately, portionwise addition of 3 equiv of Oxone and 12 equiv of $NaHCO_3$ over 72 h was found to be optimal.

Investigations of the substrate scope of this new catalytic method revealed a strong preference for 3° hydroxylation, characteristic of dioxirane reactivity (Table 3). As expected, regioselectivity is strongly influenced by substituent effects, with products of 3° hydroxylation remote to electron-withdrawing groups strongly preferred when multiple sites of oxidation are available (Table 3, entries 5−7).[5] Ester, primary ether, and imide groups are tolerated (Table 3, entry 1). Cyclic substrates can be selectively hydroxylated in up to 98% yield. The remote oxidation of cyclic substrate **31**, rather than the unusual proximal hydroxylation we observed for our first-generation method, supports our earlier conclusion that proximal hydroxylation is specific to trifluoroacetophenone catalysts.[4b]

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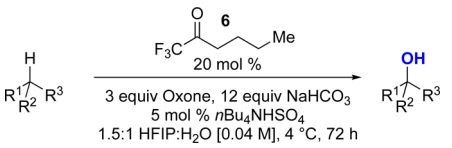
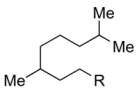
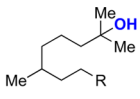
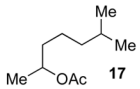
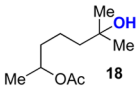
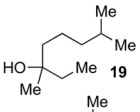
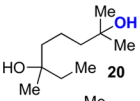
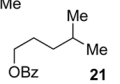
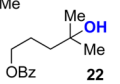
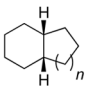
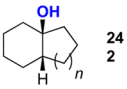
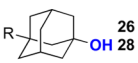
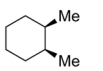
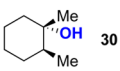
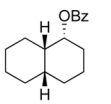
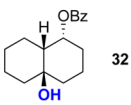
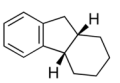
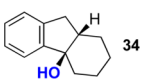
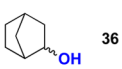
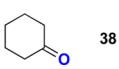
Table 3. C−H Hydroxylation Catalyzed by Ketone 6[a]



entry	substrate	product	yield (%)[b]
1	 **7** R = OAc; **9** R = OBz; **11** R = OTBS; **13** R = OMe; **15** R = NPhth	 **8** R = OAc; **10** R = OBz; **12** R = OTBS; **14** R = OMe; **16** R = NPhth	85; 71; 42; 82; 71
2	 **17**	 **18**	37
3	 **19**	 **20**	34
4	 **21**	 **22**	30
5	 **23** n = 1; **1** n = 2	 **24**; **2**	90; 78
6	 **25** R = H; **27** R = OH	 **26**; **28**	81[c]; 39
7	 **29**	 **30**	98[d]
8	 **31**	 **32**	59
9	 **33**	 **34**	47[c]
10	 **35**	 **36**	32; 3:1 exo:endo
11	 **37**	 **38**	29[e]

[a]Reaction conditions: 0.5 mmol of substrate, 1.5 mmol of Oxone, and 6 mmol of sodium bicarbonate added in three portions, 0.025 mmol of nBu$_4$HSO$_4$, 0.04 M in 1.5:1 HFIP/H$_2$O, 4 °C. [b]Isolated yield after chromatography unless otherwise noted. [c]0.75 mL of CH$_2$Cl$_2$ added to improve substrate solubility. [d]Corrected GC yield. Isolated yield 41% due to product volatility. [e]Corrected GC yield.

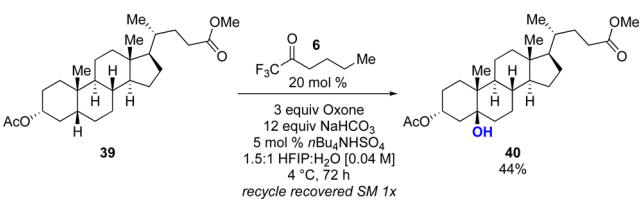
Importantly, retention of configuration was observed, suggesting no deviation from the current mechanistic understanding of dioxirane hydroxylations.[8,14] A strong preference for benzylic rather than aliphatic hydroxylation was revealed by substrate **33**. Consistent with the reactivity of isolated TFDO,[5] oxidation of unactivated 2° C−H bonds is also possible, as demonstrated for both norbornane and cyclohexane (Table 3, entries 10 and 11). Overall, oxidations using this catalytic method generate products consistent with dioxirane reactivity[15] and provide isolated products in moderate to excellent yields with a substrate scope that approximates that of TFDO.[16]

Comparison of results observed for substrates **7** and **9** reveal advantages of this catalytic method over the use of stoichiometric amounts of TFDO generated in situ from 1,1,1-trifluoroacetone as reported by Wong and co-workers.[17] Using the latter method, hydroxylation proceeds in 33% yield for **7** and 34% yield for **9**, compared to 85% and 71% respectively using the conditions outlined in Table 3. Substantial improvement in the ratio of 3° hydroxylation at the position remote rather than proximal to the ester were also observed for our catalytic conditions. For substrate **7**, the stoichiometric TFDO method provides the product in a 4:1 ratio favoring product **8** over the product of hydroxylation of the proximal 3° C−H bond, compared to a ratio of ≥28:1 using our catalytic conditions.[18] For substrate **9**, product **10** was generated in quantitative yield based on recovered starting material, indicating complete selectivity for remote over proximal hydroxylation (compared to 7:1 selectivity observed by Wong). This high degree of selectivity is consistent with selectivities observed for other hydroxylation reactions that employ the strong hydrogen bond donor HFIP[19] as a cosolvent,[4a] which might arise through deactivation of the proximal C−H bond as a result of H-bond donation by HFIP to the ester. Confirming that these high selectivities are primarily due to the modified conditions rather than the bulkier catalyst, the use of **4** as a TFDO precursor under our catalytic conditions gave a ratio of ≥19:1 favoring the remote hydroxylation product for substrate **7** (41% yield).[20]

The mild conditions identified for catalytic hydroxylation lead to advantages in functional group tolerance over other catalytic methods. For example, under the essentially neutral reaction conditions (pH approximately 7.5) no cleavage of a pH-sensitive 1° TBS ether is observed (product **12**). In comparison, representative catalysts capable of site-selective modification of complex molecules, such as Du Bois' benzoxathiazine organocatalyst[4c] and White's nonheme iron catalyst,[3g] require acidic reaction conditions. Attempts to hydroxylate substrate **11** using these catalysts led to a substantial degree of silyl ether cleavage and at most only a trace amount of hydroxylation product **12**.[20] Further oxidation of the liberated primary alcohol to the corresponding aldehyde and carboxylic acid was also observed in trace amounts.[4a] Incompatibility of catalytic C(sp^3)−H hydroxylation conditions with electron-rich or electron-neutral arenes has also been noted.[1,4c] Using catalyst **6**, benzylic oxidation of substrate **33** is preferred over arene oxidation, illustrating an additional advantage of this approach over previously reported catalytic hydroxylations.[21]

A highly valued characteristic of dioxirane reactivity is the retention of a substantial degree of site selectivity when used for the late-stage oxidation of highly complex, biologically relevant substrates.[6] To evaluate whether this characteristic is maintained using this new catalytic protocol, we attempted the hydroxylation of bile acid derivative **39** and observed selective 3° hydroxylation at the A/B cis ring junction that occurred with retention of configuration (Scheme 2).[22] No other products were observed in more than trace amounts. This steroidal substrate bearing 36 aliphatic C−H bonds (including

Scheme 2. Application to Late-Stage Hydroxylation



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six 3° centers) illustrates that substrate- and catalyst-controlled selectivity can combine to make this a useful method for late-stage functionalization.

In summary, we have demonstrated that ketone-catalyzed C−H hydroxylation can be achieved using a combination of Oxone and an aqueous fluoro alcohol solvent system. The substrate scope achieved using this catalytic protocol rivals that observed using typical stoichiometric or superstoichiometric dioxirane protocols, which can require large excesses of difficult-to-handle reagents. Compared to our previously reported method, the inclusion of acyclic substrates and realization of 2° C−H bond oxidation greatly expand the range of substrates amenable to ketone-catalyzed hydroxylation. In addition, the mild reaction conditions at essentially neutral pH and decreased temperature led to initial observations of compatibility with sensitive functionality. More importantly, this catalytic protocol overcomes a significant limitation in dioxirane chemistry that had previously prevented the development of ketone catalysts to address issues of stereoselectivity, regioselectivity, and chemoselectivity in intermolecular C−H oxidation. Future efforts will focus on catalyst design to address these limitations and to further expand the utility of organocatalytic aliphatic oxidations in synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02178.

Experimental details as well as spectroscopic and analytic data for all hydroxylation products (PDF)

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Notes

The authors declare no competing financial interest.

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(22) Recycling recovered starting material one time allowed for an increase in the initial yield of 33% to 44%.

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