Chemical Science

EDGE ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/c3sc52649f

Organocatalytic C–H hydroxylation with Oxone® enabled by an aqueous fluoroalcohol solvent system†

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Received 21st September 2013
Accepted 1st November 2013

DOI: 10.1039/c3sc52649f

www.rsc.org/chemicalscience

Selective hydroxylation of 3° and benzylic C–H bonds is made possible using a non-metal-based catalyst system, Oxone as the terminal oxidant, and an aqueous fluoroalcohol solvent mixture. The choice of solvent is uniquely effective for this process, but seemingly at odds with our finding that H_2O promotes reduction of the oxaziridine intermediate. Our studies suggest that the hydroxylation reaction is occurring within a fluoroalcohol microdroplet, which both concentrates the reactants and mitigates the deleterious impact of H_2O on oxaziridine stability. These discoveries have led to demonstrable improvements in the organocatalytic oxygenation of hydrocarbon substrates and, for the first time, the successful use of Oxone with this catalyst system. Reactions generally afford product and unreacted starting material in near quantitative amounts and display outstanding selectivity for 3° and benzylic C–H bond oxidation.

Introduction

The pursuit of general methods for C–H hydroxylation has focused predominantly on the application of well-defined transition metal complexes to effect oxo-atom transfer.[1–13] Oxidants such as peracids,[14,15] dioxiranes,[16–20] and perfluorinated oxaziridines,[21,22] however, offer viable alternatives for the conversion of C–H to C–O bonds. The outstanding reactivity and selectivity of these reagents notwithstanding, successful application of such compounds generally necessitates the use of a large number of excess equivalents (Fig. 1A). The preparation of these reagents is also laborious and potentially hazardous.[23]

Organocatalytic methods for C–H oxidation have witnessed little in the way of advancement. This problem is challenged by the facility with which oxidants such as dioxiranes decompose under ambient conditions and in the presence of reagents such as Oxone.[24–28] To our knowledge, no solution involving catalytic, dioxirane-mediated C–H hydroxylation has appeared in the literature.

We have disclosed a catalytic method for C–H hydroxylation that relies on the generation of a reactive oxaziridine **1** from a benzoxathiazine heterocycle **2** (Fig. 1B).[29,30] While our initial report demonstrated that **1** is selective for 3° C–H bond hydroxylation, the process is strictly limited to a handful of simple hydrocarbon substrates, and suffers from prolonged reaction times (≥96 h) as well as the need for super-stoichiometric amounts of H_2O_2 oxidant (≥8 equivalents). Studies aimed at understanding the factors that adversely influence reaction performance have led to the surprising result that both H_2O and 3° alcohol promote

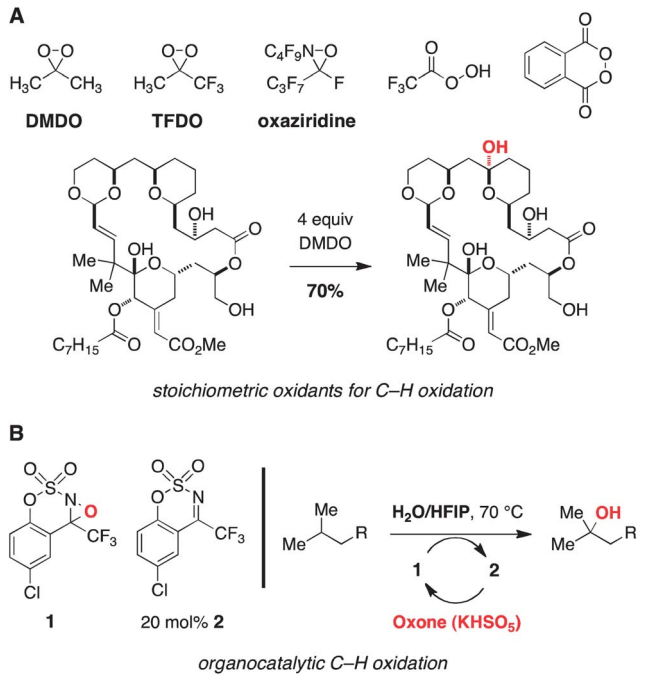

Fig. 1 Selective C–H bond hydroxylation. (A) Representative non-metal-based oxidants used as stoichiometric reagents for C–H hydroxylation;[14–22] (B) a unique, non-metal-based catalytic system for C–H hydroxylation promoted by oxaziridine **1** in an aqueous fluoroalcohol solvent mixture.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3sc52649f

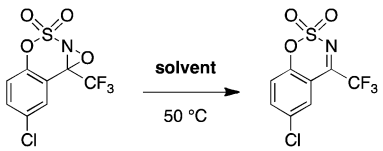
decomposition of oxaziridine **1**, a finding with important consequences for subsequent method development. To mitigate the undesired reaction with H_2O, we have explored the use of fluoroalcohol solvent mixtures, postulating that solvation of **1** in a fluorous phase could effectively 'shield' this intermediate from polar reactants (*e.g.*, H_2O, $KHSO_5$). Our discovery enables, for the first time, C–H hydroxylation with a non-metal-based catalyst and Oxone as the terminal oxidant. Additionally, use of a fractional quantity of fluoroalcohol in H_2O as solvent effectively concentrates substrate and oxidant, thus accelerating the overall rate of reaction. Demonstrable improvement in the performance of this method – substrate scope, efficiency, reaction time – is thus achieved. Our findings should have general value for related redox reaction processes that may profit from the segregation of reaction components and microencapsulation of reactants.

Results and discussion

Oxaziridine stability

Oxaziridine **1** is easily prepared and isolable as a solid material, features that enable stoichiometric experiments to measure the stability of **1** as a function of solvent, added reagents, and temperature. Following our earlier work, which relied on the use of large excesses of H_2O_2 with catalytic amounts of benzoxathiazine to promote modest yields of alcohol products, the rate of oxaziridine decomposition was assessed in binary solvent mixtures, including aqueous AcOH and CH_3CN.[31] In both cases, complete consumption of **1** was noted after 6 h at 50 °C (entries 1, 2, Table 1). Analogous experiments with other solvent systems strongly implicate a role for H_2O or 3° alcohol (entry 5) in the reduction of oxaziridine **1**. In halogenated solvents such as $CHCl_3$, CH_2Cl_2, 2,2,2-trifluoroethanol (TFE), 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), the rate of conversion of **1** to benzoxathiazine **2** is significantly slowed (entries 6–9). Adding a 1/2 volume equivalent of H_2O to TFE or HFIP solutions accelerates oxaziridine **1** reduction, but to a much lesser extent than noted with AcOH or CH_3CN co-solvents. Collectively, these data implicate both H_2O- and *t*-BuOH-promoted reduction of **1** through a pathway *that cleanly and quantitatively generates* **2**.[32]

Table 1 Solvent influence on oxaziridine **1** stability at 50 °C[a]



1 **2**

Entry	Solvent	Remaining oxaziridine **1**[a] $t = 4$ h	$t = 6$ h	$t = 30$ h
1	1 : 1 H_2O–AcOH	25	0	0
2	1 : 1 H_2O–CH_3CN	0	0	0
3	1 : 1 AcOH–CH_3CN	90	85	80
4	1 : 1 : 1 H_2O–AcOH–CH_3CN	45	15	0
5	*t*-BuOH	90	88	70
6	$CHCl_3$	95	95	95
7	CH_2Cl_2	95	95	90
8	**CF_3CH_2OH (TFE)**	**95**	**95**	**90**
9	**$(CF_3)_2CHOH$ (HFIP)**	**95**	**95**	**90**
10	1 : 1 H_2O–TFE	60	40	0
11	1 : 1 H_2O–HFIP	85	80	20

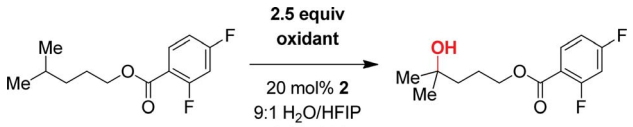
[a] All data points are an average of two independently run experiments and are quantified by ^{19}F and ^{1}H NMR against internal standards. [**1**] = 0.05 M.

Reaction optimization

Although the stability of oxaziridine **1** is compromised in aqueous solvent mixtures, we were intrigued by the marked differences between the rates of reversion to **2** in fluoroalcohol and AcOH or CH_3CN mixtures. Prior work has shown that TFE and HFIP aggregate in H_2O to form microdroplets.[33–37] Additional data establish that HFIP clusters to a greater extent in aqueous solution than TFE. We infer that the extended half-life of **1** in aqueous TFE and HFIP (entries 10 and 11, Table 1) is due to the hydrophobic solvation environment of the fluoroalcohol phase, which limits the accessibility of H_2O to **1**.[38] In principle, this fluoroalcohol phase could also serve to concentrate substrate and catalyst, and thereby accelerate the C–H oxidation event. A solvent combination of H_2O–HFIP might also enable use of terminal oxidants such as Oxone, segregating **1** from the aqueous salt mixture and, thus, limiting deleterious off-pathway processes.

We have examined the stability and hydroxylating performance of oxaziridine **1** with ester **3** (Table 2) in varying combinations of H_2O and fluorous solvents, and have identified 9 : 1 H_2O–HFIP as the optimal solvent mixture.[39] Rather remarkably, the 10% v/v of HFIP is sufficient to solubilize most substrates; assuming complete dissolution, the small volume of HFIP ensures a starting substrate concentration of 2.5 M. The new reaction conditions also allow for dramatic reductions in the time (from 96 to 12–24 h) required for the hydroxylation reaction.

Table 2 Evaluation of terminal oxidants for hydroxylation with catalytic benzoxathiazine **2** in a H_2O–HFIP solvent system



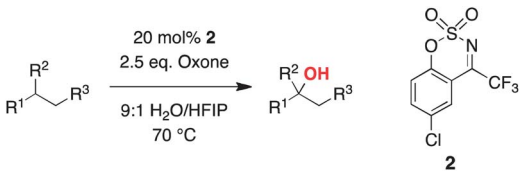
3 **4**

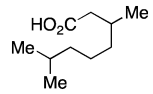
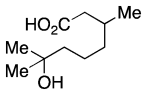
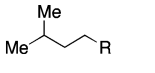
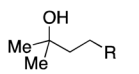
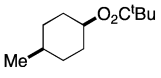
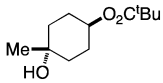
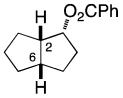
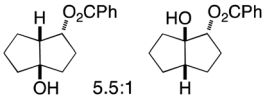
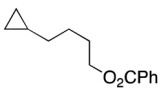
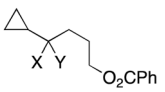
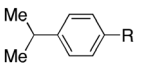
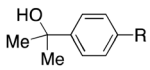
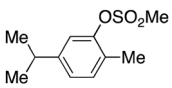
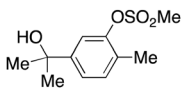
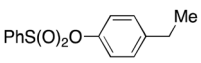
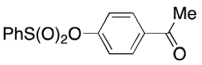
Entry	Oxidant	% oxaziridine[a]	% **4**[a]
1	**Oxone**	**80%**	**30%**
2	Oxone[b]	0%	<5%
3	***m*-CPBA**	**90%**	**30%**
4	*m*-CPBA[b]	0%	10%
5	**MMPP**	**0%**	**<5%**
6	MMPP[b]	0%	<5%

[a] The percentage of oxaziridine **1** and product **4** at 13 h was measured by both ^{1}H and ^{19}F NMR against internal standards. [b] Reactions conducted without addition of benzoxathiazine **2**. MMPP = magnesium bis(monoperoxyphthalate).

The uniqueness of 9 : 1 H_2O–HFIP as a solvent mixture is further displayed in the reaction of terminal oxidants with benzoxathiazine **2**. In this milieu, both Oxone and *m*-CPBA will engage **2** to generate oxaziridine **1** (entries 1, 3, Table 2).[40,41] When substrate **3** is present, ^1H and ^{19}F NMR signals corresponding to oxaziridine and alcohol **4** are recorded. The same reaction conducted with magnesium bis(monoperoxyphthalate) (MMPP) fails to show any detectable amounts of **1** and affords only trace quantities of **4** (also formed in the control experiment, see entry 6). The inability of MMPP, a H_2O-soluble oxidant, to react with **2** lends support to the conclusion that oxaziridine formation and substrate hydroxylation occur principally in a fluoroalcohol solvation sphere. Although both Oxone and *m*-CPBA can be employed successfully, the former is chosen in preference due to ease of product purification, as well as its low cost as a commodity chemical.

Table 3 C–H hydroxylation catalyzed by benzoxathiazine **2**[a]



Entry	Substrate	Product	Yield[b]
1			**85** (92)[c]
2		 R = OBz = CH_2OBz = $NHSO_2CF_3$	**50** (85)[d] **71** (90) **40** (97)
3			**75** (90)[d]
4		 5.5:1	**46** (80)[e]
5		 X, Y = O X = H, Y = OH	**29** (93)[f] **11**
6		 R = NO_2 = OSO_2Me	**50** (98)[c] **55** (98)[c]
7			**30** (88)[c]
8			**53** (97)

[a] *Reaction conditions*: 20 mol% **2**, 2.5 equiv. Oxone, 9 : 1 H_2O–HFIP, 70 °C, 24 h, 1.0 mmol scale. [b] Values in bold are isolated yields; values in parentheses indicate the combined yield of product and recovered starting material following silica gel chromatography. [c] Reaction time = 12 h. [d] Reaction time = 48 h. [e] The mass loss in this reaction is due principally to the decomposition of the major product under the reaction conditions. [f] Reaction conducted with 3.5 equiv. Oxone.

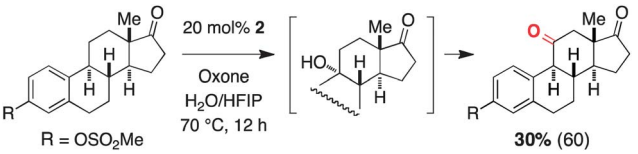


Fig. 2 Estrone oxidation gives C11-ketone product. This reaction is believed to first form a tertiary benzylic alcohol, which is prone to ionization.

Reaction performance

Oxidation of 3° C–H bonds occurs with outstanding selectivity using catalytic **2** (20 mol%), Oxone, and 9 : 1 H_2O–HFIP solution. In general, reactions are complete within 12–24 h and mass balances (*i.e.*, total amount of product and recovered starting material) are >90% (highlighted in parentheses). As shown in entries 1 and 2 (Table 3), the intermediate oxaziridine is responsive to substituent group effects that influence the relative reactivity of C–H bonds. Hydroxylation of substrates bearing multiple 3° bonds favors the site furthest removed from polar functional groups (entries 1 and 4). Other starting materials containing sulfonamide and ester groups are smoothly converted to 3° alcohols (entries 2 and 3). Despite the strong predilection of this catalyst system to oxidize 3° C–H bonds, functionalization of a methylene center adjacent to a cyclopropane ring is possible (entry 5). In this example, the ketone product is obtained as the major isolate, along with ~10% of the 2° alcohol.[42,43]

With the combination of H_2O–HFIP and Oxone, the substrate scope of our organocatalytic oxidative process has been expanded to include benzylic C–H bonds on electron-deficient arene rings.[44] Both tertiary and secondary benzylic sites react to give alcohol and ketone products, respectively (entries 5–7, Table 3). Under our previously reported protocol arene substrates were incompatible due to their limited solubility and the acidity of the media.

Attempts to functionalize other, more complex arene derivatives, have led us to examine a modified estrone substrate (Fig. 2). In this example, the C11-ketone is obtained as the principal product. We speculate that the ketone forms through the C9-alcohol, a product demonstrated to be prone to C9–C11 alkene formation.[45] Epoxidation of the putative alkene under the reaction conditions and subsequent 1,2-shift would yield the C11-ketone. Notably, we have found no evidence of Baeyer–Villiger-derived lactone products in this reaction.[46,47]

Conclusions

We have discovered an unprecedented reduction reaction of oxaziridine **1** by H_2O (and *tert*-butanol), which results in quantitative formation of **2**. This finding has led to the identification of H_2O–HFIP as a particularly effective reaction medium for conducting organocatalytic C–H oxidation reactions.[41] The advantages of this solvent combination are

manifold, as the rate of undesired reaction between **1** and H_2O is slowed, and the water-soluble triple salt, Oxone, can be employed as the terminal oxidant. This disclosure is one of a very small number of examples of catalytic C–H oxidation processes that uses peroxysulfate.[48] Under these conditions and in comparison to our earlier protocols, demonstrable improvements in reaction times, substrate scope, and product yields have been realized. The impressive selectivity displayed by oxaziridine **1** for oxidation of fine chemicals motivates future studies aimed at understanding the details of its reaction with H_2O and further advancing this technology. It should be noted that, currently, benzoxathiazine heterocycles such as **2** remain the only non-metal-based catalysts capable of promoting O-atom insertion into C–H bonds.

Acknowledgements

This work has been supported by the National Science Foundation under the CCI Center for Selective C–H Functionalization, CHE-1205646.

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