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Chemoselective Hydroxylation of Aliphatic sp^3 C–H Bonds Using a Ketone Catalyst and Aqueous H_2O_2

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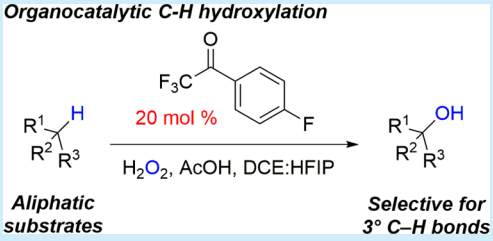
Supporting Information

ABSTRACT: The first ketone-catalyzed method for the oxidation of aliphatic C–H bonds is reported. The reaction conditions employ aryl trifluoromethyl ketones in catalytic amounts and hydrogen peroxide as the terminal oxidant. Hydroxylation is stereospecific and chemoselective for tertiary over secondary C–H bonds. A catalytic cycle invoking a dioxirane as the active oxidant is proposed.



The development of methods for chemoselective aliphatic C–H bond hydroxylation is a considerable challenge.[1] Over the past decade, impressive new transition-metal and organocatalysts for C–H hydroxylation have emerged that are able to discriminate among similarly reactive sp^3 C–H bonds in complex molecules.[2] These developments, along with the increasingly successful use of late-stage C–H oxidations in complex molecule synthesis,[3] highlight the great potential value of aliphatic hydroxylation as a retrosynthetic disconnection. Thus, the search for new catalytic processes is currently an area of substantial research activity. In this regard, dioxiranes have long been known as highly chemoselective stoichiometric reagents for sp^3 C–H hydroxylation (Figure 1).[4] These reactions typically require that representative dioxiranes DMDO or TFDO be used in excess as dilute solutions prepared in advance by oxidation of the corresponding ketone or that they be generated in situ using a substantial excess of the ketone.[5] Although ketones have been used with great success for over 30 years as catalysts for other dioxirane-mediated transformations such as asymmetric epoxidations,[6] the development of an analogous catalytic hydroxylation has remained an elusive goal. Herein we report the first examples of C–H hydroxylation using a catalytic amount of ketone.

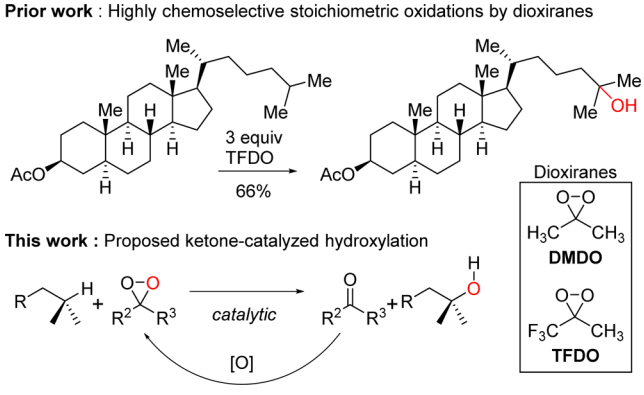


Figure 1. C–H hydroxylation by dioxiranes.

Progress toward a catalytic method has been impeded by the ease with which dioxiranes decompose under the conditions employed for their formation, most commonly requiring the use of Oxone as the terminal oxidant under slightly basic conditions with precise control of pH.[7] Previous reports suggest that under these conditions ketone-catalyzed C–H hydroxylation is not achievable.[8] However, over time the available methods for in situ dioxirane formation have become more diverse and include reports of catalytic dioxirane-mediated epoxidations that employ alternative terminal oxidants such as hydrogen peroxide (H_2O_2).[9] H_2O_2 has been successfully used in closely related imine-catalyzed C–H hydroxylations (involving the intermediacy of an oxaziridine) to avoid Oxone-mediated decomposition.[2c,e,k] However, to our knowledge, no analogous dioxirane-mediated hydroxylation using H_2O_2 as a terminal oxidant has been reported. As part of a larger research effort aimed at selective C–H functionalization, we became interested in exploring whether this change in oxidant could allow for ketone-catalyzed hydroxylation.

Initially, we investigated the hydroxylation of adamantane using H_2O_2 in the presence of a stoichiometric amount of a ketone. 2,2,2-Trifluoroacetophenone[10] was selected for evaluation due to reports of reduced incidence of decomposition through a Baeyer–Villiger reaction in dioxirane-mediated epoxidations[11] and the potential to tune catalyst activity through variations in aryl substitution. Unfortunately, no reaction was observed after 48 h using any of the known methods for dioxirane- or oxaziridine-mediated oxidation (Table 1). However, by modifying conditions originally reported for oxaziridine formation[2e] to include an organic cosolvent and increased reaction temperature (70 °C), successful hydroxylation was achieved, providing 1-adamantanol from adamantane in 54%

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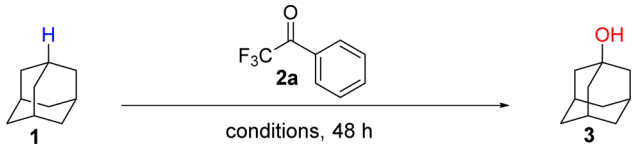
Table 1. Screening of Reaction Conditions



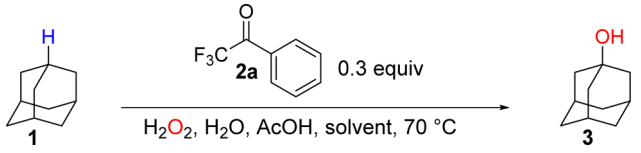
entry	conditions	temp (°C)	yield[a] (%)
1	H_2O_2 (aq), K_2CO_3, MeCN, DMM[b]	rt	0
2	H_2O_2 (aq), MeCN, DCE	rt	0
3	urea·H_2O_2, Ph_2Se_2, DCE	50	0
4	H_2O_2 (aq), Ph_2Se_2, DCE	70	0
5	urea·H_2O_2, 1:1 AcOH/H_2O, DCE	70	0
6	H_2O_2 (aq), 1:1 AcOH/H_2O	70	0
7	H_2O_2 (aq), 1:1 AcOH/H_2O, DCE	70	54
8	H_2O_2 (aq), 1:1 AcOH/H_2O, DCE[c]	70	53
9	H_2O_2 (aq), 1:1 AcOH/H_2O, DCE[d]	70	29

[a]Corrected GC yield using dodecane as an internal standard. 1.0 equiv of **2a** used except where otherwise noted. [b]In 0.0004 M Na_2EDTA. [c]30 mol % of **2a**. [d]0.0 equiv of **2a**.

yield using 50% aqueous H_2O_2 as the terminal oxidant. Decreasing the amount of **2a** to 0.3 and 0 equiv (entries 8 and 9, Table 1) revealed a clear effect of the ketone on the extent of hydroxylation. Consequently, these conditions were selected for further optimization.

Initial studies revealed that hydroxylation in the absence of **2a** could be suppressed by reducing the amount of acetic acid to 0.5 equiv, allowing for clearer identification of a potential ketone-catalyzed method.[12] In light of reports of substantial solvent effects on both the rate and chemoselectivity of dioxirane- and oxaziridine-mediated oxidations,[2k,5b] we then proceeded to investigate the effect of solvent on adamantane hydroxylation in the presence of 30 mol % of **2a**. A summary of key results is outlined in Table 2. Mixtures of 1,2-dichloroethane with EtOAc or hexafluoroisopropanol (HFIP) proved especially advantageous and provided the first evidence of catalytic turnover.

Table 2. Effect of Solvent on Reaction Progress[a]



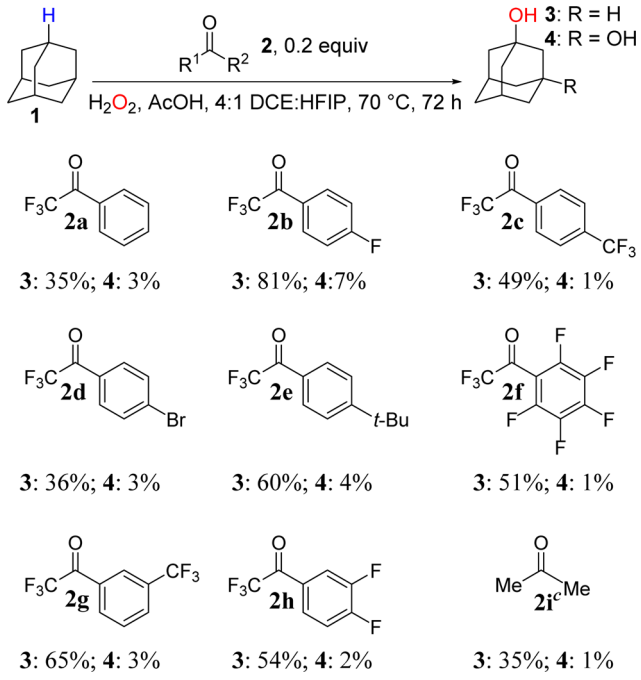
entry	solvent	yield[b] (%)
1	DCE	5
2	MeCN	0
3	EtOAc	0
4	HFIP	0
5	1:1 DCE/EtOAc	26
6	1:1 DCE/EtOAc[c]	55
7	4:1 DCE/HFIP	30
8	4:1 DCE/HFIP[c]	57
9	4:1 DCE/HFIP[d]	8
10	1:1 DCE/EtOAc[d]	5

[a]All reactions were carried out on 0.4 mmol of adamantane using 30 mol % of **2a**, 16.0 equiv of H_2O_2, 0.5 equiv of AcOH, 0.5 mL of H_2O, 0.4 M concentration in indicated solvent. [b]Corrected GC yield using dodecane as an internal standard. [c]Concentration = 0.8 M, no additional H_2O. [d]Concentration = 0.8 M, no additional H_2O, no added ketone.

Reaction times up to 72 h were required for optimum conversion. Notably, it has been reported that the presence of fluoroalcohols greatly increases the stability of oxaziridines.[2k] Anticipating that a similar effect on dioxirane stability could ultimately allow for lower catalyst loading, the 4:1 DCE/HFIP mixture was used for all subsequent experiments.

In order to probe the effect of aryl substitution of the trifluoroacetophenone, a collection of commercially available ketones **2b–h** were screened at 20 mol % loading and compared to the parent ketone **2a** (Scheme 1). At this reduced loading a

Scheme 1. Catalyst Optimization[a,b]



[a]All reactions carried out on 0.4 mmol of adamantane as a 0.8 M solution in 4:1 DCE:HFIP, 16.0 equiv H_2O_2, 0.5 equiv AcOH. [b]Reported yields are corrected GC yields obtained using dodecane as an internal standard. [c]1.0 equiv acetone used.

substantial dependence of reaction progress on the pattern of substitution was apparent. Given that both the rates of dioxirane formation and subsequent hydroxylation of the substrate can in principle be affected by these changes, it is not entirely surprising that general trends were difficult to discern.

Ketone **2b** (bearing a fluorine in the *para*-position) gave optimal conversion, providing 1-adamantanol in 81% yield as determined by GC. In all cases, the dihydroxylation product 1,3-adamantanediol (**4**) and unreacted adamantane were the only other species observed in greater than trace amounts. This high degree of chemoselectivity for 3° C–H bond hydroxylation is consistent with that observed for reactions of adamantane with stoichiometric amounts of DMDO or TFDO.[4b] Not surprisingly, under these conditions the use of 1 equiv of DMDO precursor acetone also promoted chemoselective hydroxylation, albeit in comparatively low yield. A more thorough study on the effects of ketone structure is currently underway.

This catalytic method can be applied to other substrates, giving products resulting from oxidation of both unactivated and activated sp^3 C–H bonds (Table 3).[13] The moderate isolated yields observed for the majority of substrates are on par with existing catalytic methods for aliphatic hydroxylation.[2] No more

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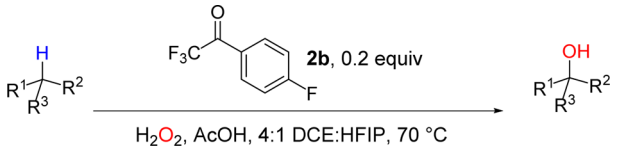
Table 3. Oxidations Using Catalyst 2b



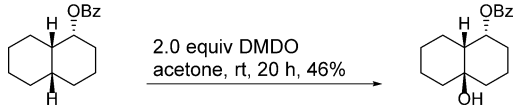
substrate	product	GC yield[a]	yield (%)[b]
1	3	83(97)	81
5	6	38(77)	33
7	8 + 9 (1:1.5)	56(83)	49
10	9	54(64)[c]	46
11	12	37(87)[d]	31
13	14	48(81)[e]	40
15	16 + 17 (2.5:1)	49(91)	49

[a]Corrected GC yield, yield based on recovered starting material shown in parentheses. [b]Isolated yield. Optimized reaction conditions: 20 mol % of catalyst **2b**, 16 equiv of H_2O_2, 0.5 equiv of AcOH, 0.8 M in 4:1 DCE/HFIP, 72 h. [c]Reaction time = 96 h. [d]Reaction time = 120 h. [e]1.0 equiv of ketone.

than trace amounts of other products were observed. This high degree of chemoselectivity is characteristic of dioxirane reactivity. Notably, hydroxylation of alkanes at 3° positions is preferred even when 2° C−H bonds are substantially more abundant. Hydroxylation using catalyst **2b** is both stereospecific and less efficient for substrates bearing electron-withdrawing groups, consistent with a concerted, electrophilic oxygen insertion mechanism proposed for dioxiranes.[14] Initially, the formation of *trans*-9,10-decalindiol (Table 3, product **9**) as the major product of oxidation of both *cis*- and *trans*-decalin was surprising; however, control experiments suggest this product is formed by elimination of water from the monohydroxylated product followed by epoxidation and ring opening and does not arise from a second, nonstereospecific C−H hydroxylation.[15] Chemoselective oxidation of 2° C−H bonds can be achieved using this method, as in the case of ethyl tetrahydrofurfuryl ether (Table 3, product **14**); however, an activated bond and stoichiometric amounts of **2b** are required.

Overall, the patterns in reactivity and chemoselectivity observed for these substrates mirror closely what has been previously observed or would be predicted for oxidation using DMDO or TFDO. However, both the degree and nature of chemoselectivity observed for catalytic oxidation using **2b** suggests potential advantages to this method over the use of conventional stoichiometric dioxirane oxidations or other catalytic methods. In particular, when *trans*-decalin is oxidized by TFDO a substantial degree of 2° C−H bond oxidation is observed (2:1 ratio of 3°/2° oxidation products).[4b] In contrast, oxidation of *trans*-decalin using catalyst **2b** gives exclusively 3° hydroxylation, suggesting a higher degree of chemoselectivity for 3° over 2° C−H bonds using this catalytic method. Additionally and in contrast to other catalytic oxidation methods, including both oxaziridine-mediated and nonheme iron-catalyzed oxidations, hydroxylation with **2b** occurs preferentially at a site proximal to an electron-withdrawing group (Table 3, product **12**). To confirm this complementary chemoselectivity, we attempted to hydroxylate substrate **11** using an excess of DMDO. As expected, hydroxylation occurred exclusively at the 3° C−H bond distal to the ester (Scheme 2). This

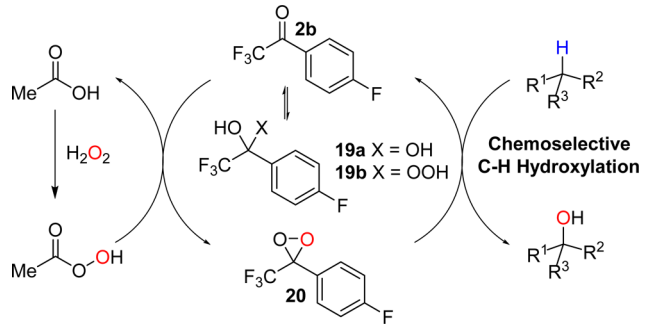
Scheme 2. Hydroxylation of Substrate 11 by DMDO



complementary chemoselectivity suggests potential advantages for trifluoroacetophenone-catalyzed hydroxylations over other methods. A more thorough investigation of chemoselectivity is currently underway.

A proposed catalytic cycle that accounts for the use of substoichiometric amounts of both acetic acid and **2b** is outlined in Scheme 3.[16] When ketone **2b** is exposed to the reaction

Scheme 3. Proposed Catalytic Cycle



conditions in the absence of substrate, the rapid formation of an equilibrium between it and the corresponding hydrate (**19a**) and peroxyhydrate[17] (**19b**) is observed. Control experiments indicate that no component of this mixture is the active oxidant.[18] Over longer reaction times (72 h), slow decomposition of **2b** to 4-fluorophenol is observed. This product of Baeyer−Villiger oxidation provides evidence of peracetic acid addition into the carbonyl, a critical step on the path to dioxirane formation. Reaction progress is not affected by the presence of up to 1 equiv of the radical inhibitor 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT).[19] These results, along with evidence of stereospecific hydroxylation and dioxirane-like chemoselectivity (vide supra, Table 3 and related discussion), suggest that under the reaction conditions dioxirane **20** is transiently formed and subsequently hydroxylates the substrate. This is the first reported

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use of a combination of H_2O_2 and acetic acid to generate dioxiranes in situ.

In summary, this new organocatalytic method for C−H oxidation enables for the first time the use of ketones as catalysts for C−H hydroxylation. This method is applicable to the hydroxylation of unactivated C−H bonds and is highly chemoselective. Aqueous hydrogen peroxide serves as an inexpensive and readily available terminal oxidant. To our knowledge, the trifluoroacetophenones reported here are only the second nonmetal catalysts shown to promote C−H hydroxylation. We expect that this method will provide entry to a much more thorough inquiry into dioxirane-mediated catalytic C−H hydroxylation with the goal of improving substrate scope, increasing catalyst turnover, and developing asymmetric methods.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data for hydroxylation products, as well as details for additional experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) Yield of 1-adamantanol from adamantane in the presence of of 1.0 equiv of BHT: 75%. A simultaneous control experiment run in the absence of BHT gave 77% yield of 1-adamantanol. See the Supporting Information for details.