Regioselective Intramolecular Oxidation of Unactivated C−H Bonds by Dioxiranes Generated *in Situ*

Dan Yang,* Man-Kin Wong, Xue-Chao Wang, and Yeung-Chiu Tang

Department of Chemistry
The University of Hong Kong
Pokfulam Road, Hong Kong

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Regioselective oxidation of unactivated C−H bonds has been a challenging problem in organic synthesis.[1,2] Intramolecular oxidation, due to its geometric constraint, has become a very effective approach. In particular, significant progress has been made in remote oxidation of rigid substrates such as steroids.[3,4a,b] For flexible substrates, selective oxidation of remote carbons four bonds away from a heteroatom has been successfully achieved by using the radical reactions that undergo intramolecular radical 1,5-hydrogen abstractions (Figure 1).[4] However, for oxidation of more remote C−H bonds in flexible molecules, there is no general method available.[5] Here we report a novel method for selective oxidation of unactivated C−H bonds at the δ site of ketones.

Dioxiranes, a new generation of oxidants, have excellent reactivity toward unactivated C−H bonds under mild and neutral conditions.[6] The oxidation reaction is stereospecific and has strong preference for tertiary C−H bonds over secondary ones.[6,7] We previously reported a homogeneous solvent system that allows dioxiranes to be generated *in situ* from ketones and Oxone at neutral pH.[8] This makes it possible to develop a ketone-catalyzed intramolecular C−H bond oxidation method.

We first examined the activities of various ketones in catalyzing oxidation of adamantane under our *in situ* conditions. As shown in Table 1, 1,1,1-trifluoroacetone and methyl pyruvate were found

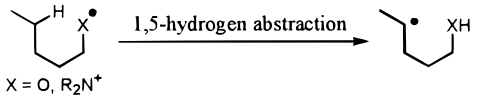
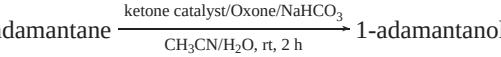
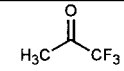
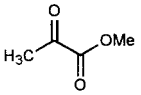
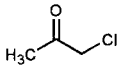
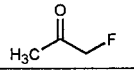


Figure 1. Radical oxidation.

Table 1. Oxidation of Adamantane Catalyzed by Ketones[a]



entry	ketone catalyst	product ratio (adamantane : 1-adamantanol)[b]
1		1 : 0.22
2		1 : 0.17
3		1 : 0.13
4		1 : 0.11

[a] Reaction conditions: all the oxidation reactions were carried out at room temperature with 0.1 mmol of ketone and 0.1 mmol of adamantane, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, and 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M) for 2 h. [b] The product ratios were determined by ^{1}H NMR.

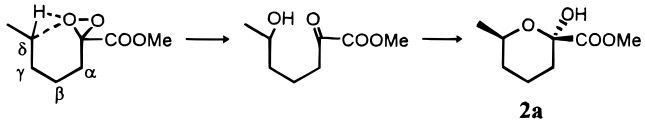


Figure 2.

to exhibit higher activities than fluoroacetone and chloroacetone. These ketone units were then attached to a series of hydrocarbon skeletons and oxidation reactions were carried out at 10 mM concentration (Table 2). Oxidation of linear α-keto esters **1** and **2** was found to give hemiketal **1a** (70% yield) and **2a** (86% yield), respectively, as the major oxidation products in 24 h (entries 1−2, Table 2). Despite the presence of several other secondary C−H bonds, the δ C−H bonds were selectively oxidized. Methyl 2-oxohexanoate failed to give the desired oxidation product, because its δ C−H bonds are primary and extremely unreactive. In each of the branched substrates **3**−**8**, there is one tertiary C−H bond in addition to several secondary ones, and interestingly, only the δ site was oxidized (entries 3−8, Table 2). Here intermolecular C−H bond oxidation by dioxiranes is unlikely as the reactions of compounds **3**−**5** proceeded via selective oxidation of secondary C−H bonds despite the presence of tertiary C−H bonds. These results indicate the predominance of stereoelectronic control on the transition state for hydroxylation. Furthermore, the observed regioselectivity (i.e., δ-selectivity) is different from that of a typical intramolecular radical reaction (i.e., γ-selectivity), suggesting the nonradical nature of this oxidation reaction.[9] We propose a concerted C−H bond oxidation mechanism (Figure 2).[6b,7a,c] Oxidation of a δ C−H bond generates a δ-hydroxy ketone which cyclizes to give a hemiketal. The hemiketal formation prevents further oxidation at the δ site.

For concerted C−H bond oxidation by dioxiranes, there are two possible transition states (TS's), i.e., the planar TS and the spiro TS (Figure 3).[7c,10] Under a spiro TS, oxidation of the

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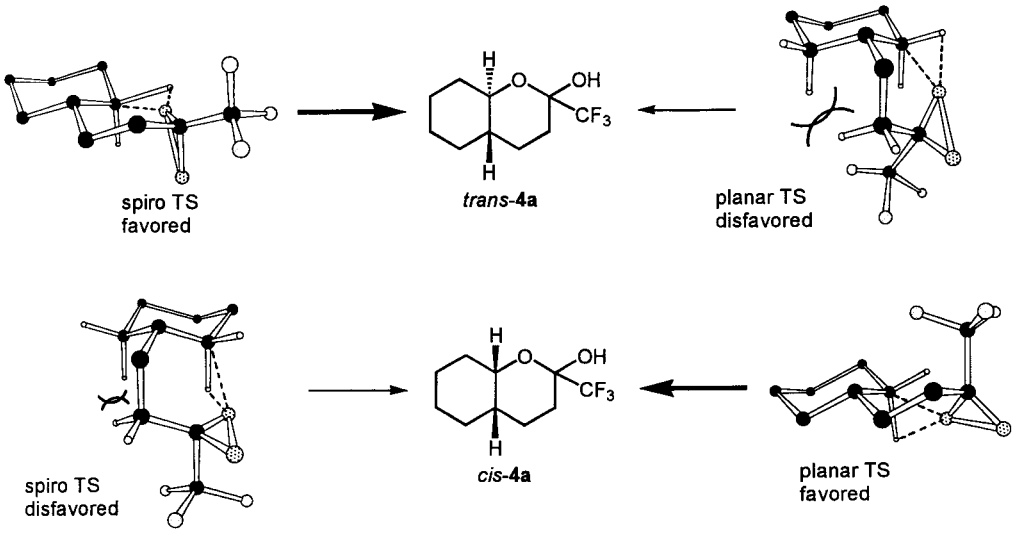
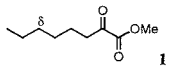
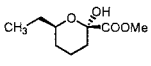
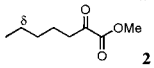
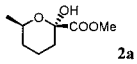
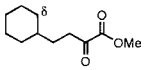
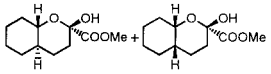
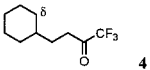
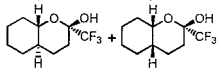
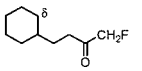
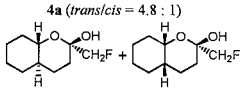
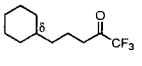
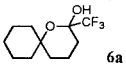
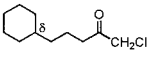
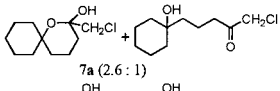
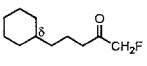
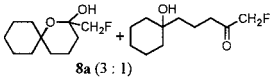
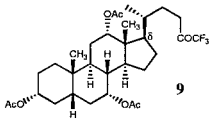
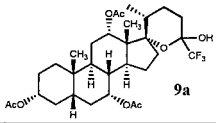


Figure 3.

Table 2. Selective Oxidation of the δ C−H Bond[a]

ketone (10 mM) $\xrightarrow[CH_3CN/H_2O,\ rt,\ 24\ h]{Oxone/NaHCO_3}$ product

entry	ketone	product	Yield (%)[b]
1	 **1**	 **1a**	70
2	 **2**	 **2a**	86
3	 **3**	 **3a** (*trans*/*cis* = 4.0 : 1)	83[c]
4[d]	 **4**	 **4a** (*trans*/*cis* = 4.8 : 1)	87[c]
5	 **5**	 **5a** (*trans*/*cis* = 4.2 : 1)	70[c,e]
6[d]	 **6**	 **6a**	78
7	 **7**	 **7a** (2.6 : 1)	77[f]
8	 **8**	 **8a** (3 : 1)	73[f,g]
9[d]	 **9**	 **9a**	58

[a] Unless otherwise indicated, all reactions were carried out with a 1.0×10^{-2} M solution of ketone in a 1.5:1 mixture of CH_3CN and aqueous Na_2·EDTA solution (4×10^{-4} M) containing 5.0 equiv of Oxone and 15.0 equiv of $NaHCO_3$ for 24 h at room temperature. [b] Isolated yield after flash column chromatography. [c] The *trans*/*cis* ratio was determined by using NMR. [d] 15.5 equiv of $NaHCO_3$. [e] Isolated yield based on 55% conversion after 120 h. [f] The reaction time was 72 h. The product ratio (hemiketal/hydroxy ketone) was determined by ^{1}H NMR in C_6D_6. [g] Isolated yield based on 75% conversion.

equatorial δ C−H bond (leading to *trans*-product) is strain-free whereas oxidation of the axial one (leading to *cis*-product) is disfavored by one gauche-butane interaction (ca. 0.85 kcal/mol),

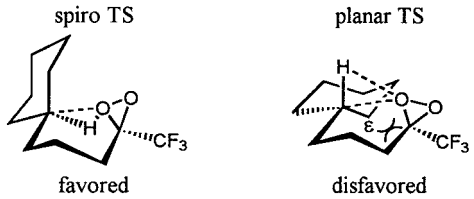


Figure 4.

which would predict a trans/cis ratio of 4.3:1 at 20 °C. In contrast, under a planar TS, *cis*-product is expected to be the major product with a trans/cis ratio of 1:4.3. The observed *trans*-selectivity in **3a**−**5a** (entries 3−5, Table 2) supports the spiro TS model. Furthermore, oxidation of the tertiary C−H bonds in compounds **6**−**8** could only be possible under a spiro TS, because under a planar TS there are severe steric interactions between the dioxirane group and the ϵ CH_2 group (Figure 4).[11]

As shown in Table 2, compounds **1**−**8** of different substituents, i.e., CO_2CH_3, CF_3, CH_2Cl, and CH_2F, were found to give the same δ selectivity.[12] This δ-selective C−H bond oxidation method allows incorporation of various substituents into the tetrahydropyran products. To further demonstrate the synthetic potential of this method, cholic acid triacetate was converted into the trifluoromethyl ketone **9**, which upon treatment with Oxone gave selective hydroxylation at the 17-position with retention of configuration.

In summary, we have discovered that intramolecular C−H bond oxidation by dioxiranes is highly regioselective, and established a spiro transition state for this reaction. Future work will be directed at exploring the applications of this reaction in asymmetric synthesis as well as remote functionalization of steroids.

Acknowledgment. This work was supported by the Hong Kong Research Grants Council and The University of Hong Kong (CRCG grant and postdoctoral fellowships to M.K.W. and X.C.W.). This paper is dedicated to Prof. Ronald Breslow for his mentorship.

Supporting Information Available: Preparation and characterization data of compounds **1**−**9**; experimental details for oxidation reactions; and characterization data of compounds **1a**−**9a** (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) A similar spiro transition state has been found for dioxirane epoxidation reactions. See: (a) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (b) Reference 8c. (c) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

(12) The CH_2OAc analogue of compound **4** did not undergo oxidation in 72 h at room temperature. This indicates that strong electron-withdrawing groups at α-positions of ketones are important for their intramolecular C−H bond oxidation.