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Direct Construction of 1,3-Diaxial Diol Derivatives by C−H Hydroxylation

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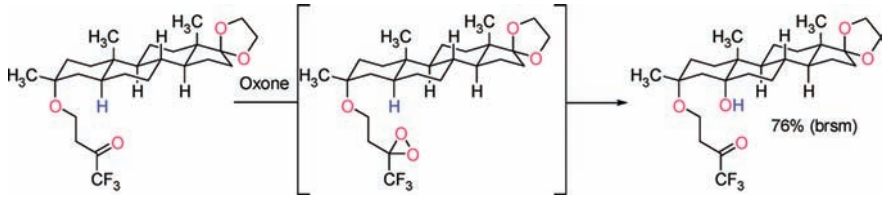
ABSTRACT

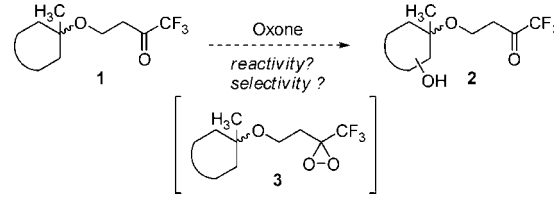


Direct hydroxylation of tertiary C−H bonds for construction of 1,3-diaxial diol derivatives was achieved by devising a new detachable dioxirane precursor containing a trifluoromethyl ketone moiety and ethylene tether. Oxone treatment of the ketones led to the corresponding dioxiranes, enabling hydroxy group installment into cyclohexane and steroid derivatives in a regio- and stereoselective manner through intramolecular oxygen insertion.

Direct hydroxylation of sp^3 C−H bonds has attracted intense attention from the chemical community since such transformations generally minimize functional group manipulations, adjustments of oxidation states, and use of protective groups for syntheses of natural products with highly complex structures.[1] Although recent advances have provided many effective direct C−H bond functionalizations,[2] sp^3 C−H bond oxidation of multiply substituted carbocycles continues to be challenging in terms of yields and selectivities. Here we report a new strategy of regio- and stereocontrolled C−H bond hydroxylation for construction of 1,3-diaxial diols in carbocyclic matrices.

Stereoselective hydroxylation of sp^3 C−H bonds could be achieved by incorporating a detachable oxidant into a substrate since spatial proximity between the oxidant and the C−H bond is expected to accelerate the desired transformation at a specific position in a predictable manner. To test this idea, we designed a covalently attached dioxirane precursor containing a trifluoromethyl ketone moiety and an ethylene tether (**1**, Scheme 1).[3,4] Treatment of **1** with Oxone

Scheme 1. Plan of Intramolecular C−H Oxidation of Carbocycles



($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) would generate dioxirane **3**, which was expected to transfer oxygen to the carbocycle to provide **2**. We were especially interested in the reactivity of various sp^3 C−H bonds on methine, methylene, and methyl groups and the influence of the three-dimensional relationship

(1) For recent reviews, see: (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (b) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L., Jr. *Chem. Rev.* **2004**, *104*, 939. (c) *Activation and Functionalization of C−H Bonds*; Goldberg, K. I., Goldman, A. S., Eds.; American Chemical Society: Washington, DC, 2004. (d) *Hanbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vols. 1 and 2. (e) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (f) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (g) Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2740. (h) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

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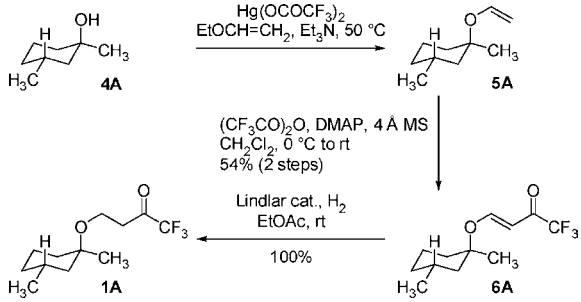
Scheme 2. Introduction of Trifluoroketone Moiety

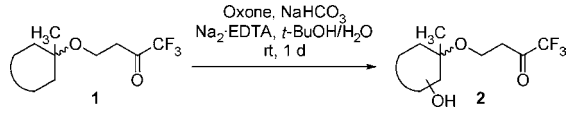


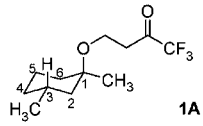
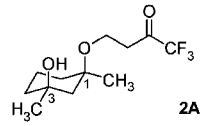
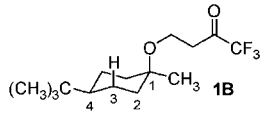
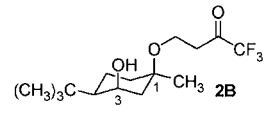
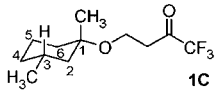
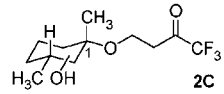
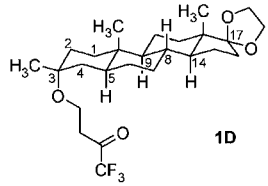
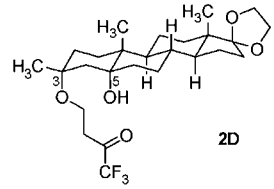
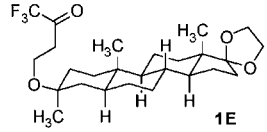
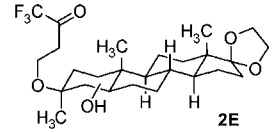
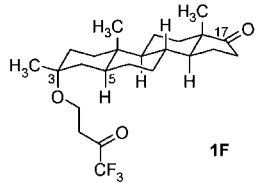
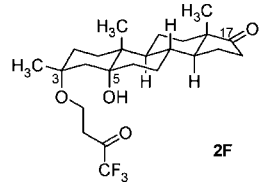
between the dioxirane and reacting C−H bond in the starting carbocycle.

Introduction of the dioxirane-generating moiety to the hydroxy group is illustrated in Scheme 2 The axial tertiary alcohol of 1,3-dimethylcyclohexanol **4A** was reacted with ethyl vinyl ether in the presence of $Hg(OCOCF_3)_2$ to produce vinyl ether **5A**,[5] treatment of which with trifluoroacetic anhydride and DMAP[6] resulted in installment of the trifluoromethyl ketone group to provide enone **6A**. Then, hydrogenation of the double bond of **6A** using the Lindlar catalyst gave β-alkoxy ketone **1A**.[7] By following this protocol, the trifluoromethyl ketones were successfully introduced into various starting materials (**1A**−**F**) as shown in Table 1.

Exposure of **1A** to Oxone in the presence of $NaHCO_3$[8] in *t*-BuOH/H_2O regio- and stereoselectively furnished 1,3-diaxial diol derivative **2A** through intramolecular oxygen insertion in 74% yield based on the recovered starting material (entry 1, Table 1).[9,10] Remarkably, the most hindered tertiary C−H at C3 was oxidized with retention of the configuration in the presence of other proximal C−H bonds at C1−CH_3, C2, C5, and C6. In the case of 4-*t*-butyl-1-

Table 1. Construction of 1,3-Diaxial Diol Derivatives from Various Carbocycles[a]



entry	starting material (sm)	product	yield, % product (sm)	yield, % brsm[b]
1	 **1A**	 **2A**	51 (31)	74
2[c]	 **1B**	 **2B**	14 (43)	25
3	 **1C**	 **2C**	0 (64)	0
4	 **1D**	 **2D**	47 (38)	76
5	 **1E**	 **2E**	0 (63)	0
6[c]	 **1F**	 **2F**	33 (16)	39

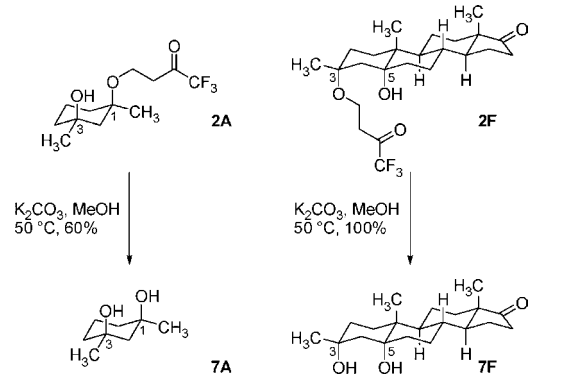
[a] The starting material was treated with Oxone (5 equiv) and $NaHCO_3$ (15 equiv) in *t*-BuOH/0.4 mM aq Na_2·EDTA solution = 3/2 (0.01 M) at rt for 1 d. [b] Yield based on the recovered starting material. [c] MeCN/0.4 mM aq Na_2·EDTA solution = 3/2 (0.0015 M) was used as a solvent.

methylcyclohexanol **1B**, the oxidation again gave the 1,3-diaxially substituted structure **2B** as the sole isolable compound but in low yield (entry 2). Both regioselective formation of the tertiary alcohol of **2A** over other alcohols and the inefficient formation of the secondary alcohol of **2B** should originate from the general lower reactivity of the secondary C−H than the tertiary C−H toward oxirane oxidation.[11] Interestingly, **1C**, the C1-epimer of **1A**, possessing a β-alkoxy ketone at the equatorial position, did not afford any oxidized products of **2C** under the same conditions (entry 3). Overall, these results indicate the importance of the specific three-dimensional orientation between the dioxirane-generating carbonyl moiety and the tertiary C−H bond for efficient intramolecular hydroxylation.

We next investigated the applicability of the present transformation to steroid skeletons, possessing four reactive tertiary C−H bonds at C5, C8, C9, and C14 (Table 1). Oxidation of **1D** with the axially substituted dioxirane precursor gave rise to the corresponding 1,3-diaxial diol derivative **2D** in 76% yield (brsm) in a regio- and stereoselective fashion (entry 4), even though C5−H is more sterically shielded than C9−H and C14−H. On the other hand, the oxidation of its C3-epimer **1E** resulted in recovery of the starting material (entry 5). The C17-ketone of diketone **1F** survived under oxirane-generating conditions (entry 6). The oxygen functionalities in the 1,3-diaxial relationship of **2F** were constructed from **1F** in 39% yield (brsm).

The trifluoromethyl ketone moieties of the obtained compounds were efficiently removed under basic conditions (Scheme 3). For instance, oxidized compounds **2A** and **2F**

Scheme 3. Removal of Trifluoroketone Moiety



were treated with K_2CO_3 in methanol to generate 1,3-diaxial diols **7A** and **7F**, respectively. The structures of thus obtained diols were unambiguously determined by NMR.

In conclusion, we have achieved the intramolecular direct hydroxylation of tertiary C−H bonds for construction of 1,3-diaxial diols by devising a new detachable dioxirane precursor. Hydroxylation in the present system consistently proceeded with retention of the configuration in a regio- and stereoselective fashion. Further studies on the synthetic application of the present strategy are currently underway.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901367M

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(6) Moriguchi, T.; Endo, T.; Takata, T. *J. Org. Chem.* **1995**, *60*, 3523.

(7) Trifluoromethyl ketones of compounds **1A**−**F** were in equilibrium with their corresponding hydrate forms.

(8) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.

(9) MeCN, dimethoxymethane, or 1,4-dioxane can be used as a solvent without decreasing the yield of the C−H oxidation. On the other hand, use of K_2CO_3 instead of $NaHCO_3$ significantly decreased the yield, presumably due to the base sensitivity of the β-alkoxy ketone.

(10) Attempted intermolecular oxidation of 1,3-dimethylcyclohexanol **4A** using in situ generated dioxirane [trifluoroacetone (1 equiv), Oxone (5 equiv), and $NaHCO_3$ (15 equiv) in *t*-BuOH/0.4 mM aq Na_2·EDTA solution = 3/2 (0.01 M) at rt for 1 d] did not give 1,3-dimethyl-cyclohexane-1,3-diol **7A**, and the starting material was recovered.

(11) Reactivity toward oxirane oxidation: $R_3CH > R_2CH_2 > RCH_3$. (a) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470. (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749.