Mild and Selective Oxyfunctionalization of Hydrocarbons by Perfluorodialkyloxaziridines

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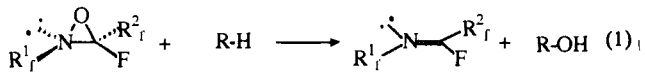
The conversion of a C–H bond to C–OH, while carried out routinely in nature by a variety of enzymes,[1] has not so far found wide application in organic synthesis. Much effort has been devoted to developing reagents for this purpose; in particular, the hydroxylation of C–H bonds remote from functional groups is a challenging goal and the object of continuing interest.

Perfluoro-*cis*-2,3-dialkyloxaziridines **1** are indefinitely stable, neutral, aprotic oxidizing agents. They have been proven to be powerful yet selective reagents for the oxidation of alkenes to epoxides,[2] alcohols to ketones,[3] and sulfides to sulfoxides or sulfones.[4] These oxaziridines are easily prepared in sizable quantities and good yields from commercially available perfluorotrialkylamines in two steps: conversion of $(R^1_f)_3N$ to azaalkenes **3** by SbF_5[5] followed by oxidation with *m*-chloroperbenzoic acid (MCPBA).

We wish to report that perfluorodialkyloxaziridines **1** effect in good yields and high regio- and stereoselectivities the hydroxylation of unactivated tertiary aliphatic C–H bonds at room temperature in the condensed phase (eq 1); reaction times range from several hours to a few minutes.[6] Typical results and yields are presented in Table I.



1a,b **2a-g** **3a,b** **4a-g**

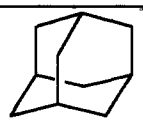
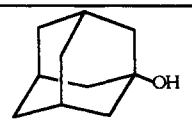
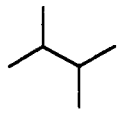
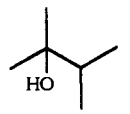
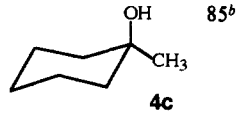
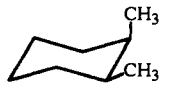
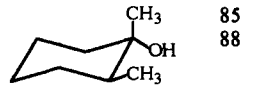
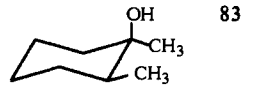
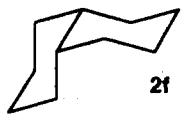
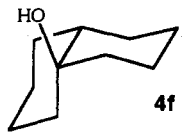
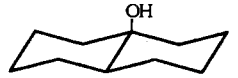
	R^1_f	R^2_f
1a, 3a:	C_4F_9	C_3F_7
1b, 3b:	C_6F_{13}	C_5F_{11}

The reactions were carried out by adding to a ca. 1 M solution of the hydrocarbon substrate **2** in $CFCl_3$ a slight molar excess of oxaziridine **1a** or **1b** and stirring the reaction mixture at room temperature for a few minutes (**2a**), a few hours (**2b,d,f**), or several hours (**2c,e,g**). Reactions were monitored by GC, and the identities and quantities of formed products **4** were established by GC, MS, and ^1H, ^{13}C, and ^{19}F NMR against authentic samples.

Some halogenated solvents other than $CFCl_3$ could also be employed with good results (CCl_4, $CHCl_3$) despite the fact that the reactions became two-phase systems, as only in $CFCl_3$ were oxaziridines **1** completely soluble.

The data reported in Table I deserve some comments. In all cases, products of monohydroxylation were formed in good yields and a remarkable tertiary to secondary selectivity for the attack at C–H bond was noted.[8] Oxidation of primary C–H bonds or

Table I. Reactions of Oxaziridines **1** with Hydrocarbons **2**

substrate	oxaziridine	product	yield, %
 **2a**	**1a**	 **4a**	90[a]
	1b		90
 **2b**	**1a**	 **4b**	84
 **2c**	**1a**	 **4c**	85[b]
 **2d**	**1a**	 **4d**	85
	1b		88
 **2e**	**1a**	 **4e**	83
 **2f**	**1a**	 **4f**	88[c]
	1b		85
 **2g**	**1a**	 **4g**	73[d]

[a] 2-Adamantanone (0.8%). [b] 2-Methylcyclohexanone (1.2%), 3-methylcyclohexanone (3.7%), 4-methylcyclohexanone (0.7%). [c] *cis*-1-Decalone (1.4%), *cis*-2-decalone (0.4%). [d] *trans*-1-Decalone (6.1%), *trans*-2-decalone (0.6%).

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(6) MCPBA (*m*-chloroperbenzoic acid) was washed free of *m*-chlorobenzoic acid with a phosphate buffer (pH 7) and dried over P_2O_5 in a vacuum desiccator. To 19.0 g (110 mmol) of MCPBA thus purified, suspended in 150 mL of dry acetonitrile, was added (*Z*)-azaalkene **3a** (36.0 g, 83 mmol) in one portion with rapid stirring. After 3 h at room temperature, the reaction mixture was diluted with acetonitrile until the precipitated *m*-chlorobenzoic acid dissolved. The lower layer was separated and distilled in vacuum, collecting 24.2 g of **1a** (65% yield) at 68–69 °C/190 mmHg. IR (film): 1414 cm^{-1}. ^{19}F NMR ($CFCl_3$, 188 MHz) $CF_3{}^A CF_2{}^G CF_2{}^F CF^C CF^D N(O)CF^E CF_2{}^I CF_2{}^K CF_3{}^B$: A,B –81.4 (6 F); C,D –99.2 (dddt) and –106.5 (ddt) (2 F); E –139.7 (m); G,F,I,K –125.0 to –127.1 (8 F); J_{CD} = 208 Hz. **1b** has been prepared similarly. Full experimental details are given in ref 7.

(7) Synthesis of perfluoro-*cis*-2,3-dialkyloxaziridines **1** by oxidation of azaalkenes **3** with: (a) Peracids, Petrov, V. A.; DesMarteau, D. D. *J. Org. Chem.*, submitted for publication; Eur. Pat. Appl. EP 496 414, 1992, *Chem. Abstr.* **1992**, *117*, 191830n. (b) Fluoroxy compounds, Petrov, V. A.; DesMarteau, D. D. *Mendeleev Commun.*, in press. Eur. Pat. Appl. EP 496 413, 1992, *Chem. Abstr.* **1992**, *117*, 191831p.

(8) A foretold exception was norbornane. Its reaction with **1a** was sluggish and afforded only products derived from reaction at C-2 secondary C–H bonds. After 24 h, traces of *exo*-norborneol (1.8%) were formed and the main reaction product was norcamphor (7.5%). A similar preference for oxidation at C-2 was shown by ozone[9] and methyl(trifluoromethyl)dioxirane.[10] On various other substrates, both reagents[9-11] revealed a high selectivity for attack at tertiary to secondary to primary C–H bonds.

(9) Giamalva, D. H.; Church, D. F.; Pryor, W. A. *J. Org. Chem.* **1988**, *53*, 3429–3442.

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dioxyfunctionalization[12] of substrates **2** was not observed. Minor amounts of ketones were formed, probably through further oxidation of initially produced secondary alcohols.[3] The amount of these byproducts was larger when longer reaction times were needed. For instance, akin to oxyfunctionalization by dry ozone,[13] some peracids,[14] and (trifluoromethyl)dioxirane,[10] the regioselectivity was nearly quantitative with adamantane (**2a**), the most reactive substrate. *cis*-Dimethyl cyclohexane (**2d**) and *cis*-decalin (**2f**) were more reactive than their *trans* isomers **2e** and **2g**, respectively, which gave less clean reactions. The last four substrates also show the stereoselectivity of oxaziridines **1**. A high retention of configuration (>98%) occurred in all cases. Similar behavior was shown by dioxiranes,[10,15] ozone,[11,13] peracids,[14] and fluorine.[16]

While *N*-sulfonyloxaziridines are established as versatile oxidants in organic chemistry,[17] the hydroxy dehydrogenation of unactivated C–H bonds by **1** was so far unreported with any other compound of the class.

The perfluorinated compounds **1**, in being much more powerful oxidants than their hydrocarbon analogs, follow a well-documented trend. Indeed, whenever hydrogen-substituted oxidizers have been compared with their fluorinated analogs, the latter were found more active, e.g., trifluoroacetates of lead(IV),[18] cobalt(III),[19] thallium(III),[20] mercury(II),[21] [bis(trifluoroacetoxy)iodo]benzene,[22] trifluoroacetyl hypohalites,[23] metalloporphyrins with fluorinated residues,[24] and methyl(trifluoromethyl)dioxirane.[25] A further example relates to two of the most potent oxidizers used in organic chemistry, cesium fluoroxysulfate and potassium persulfate. The couple SO_4F^-/HSO_4^- has a potential of 2.5 V vs 1.4 V for HSO_5^-/HSO_4^-.[26] In the field of oxaziridines, substitution of phenyl with pentafluorophenyl at the ring carbon[27] or fluorination at an α-exocyclic position[28] increased the rates of oxidations.

In all these cases, the electron-withdrawing character of fluorine or fluorinated substituents provides only a partial rationale. In the present case, we believe that the molecular structure of **1** must also play a crucial role. At room temperature, compounds **1** are indefinitely stable from the chemical and stereochemical points of view, so it becomes unattractive to explain their reactivity by way of weak C–O or N–O bonding. Thermal decomposition of oxaziridines **1a** and **1b** leads quantitatively to perfluoro-2-aza-1-propoxyhex-1-ene and -1-pentoxyoct-1-ene, respectively.[29] On the contrary, when they behave as oxidizers, the azaalkenes (*Z*)-(**3**) form quantitatively with complete retention of stereochemistry.

Several mechanisms could be envisaged for the reaction under consideration, including hydride abstraction, hydrogen atom abstraction, and a concerted insertion into the C–H bond. While none of the experiments yet was specifically designed to gain insight into this aspect, an examination of the product distribution can provide useful hints as to the likely mechanism. The high tertiary to secondary selectivity is an argument for carbocationic vs radical process. But the C-1 and C-2 positions of adamantane (**2a**) should be similar in reactivity in a cationic process, while in a radical pathway C-1 (bridgehead) should react primarily[9] as oberved. If freely diffusing alkyl radicals are involved, they should be intercepted by the halogenated solvents to give alkyl halides as side products. For instance, even in the ozone oxidation of adamantane (**2a**), chlorinated products accounted for up to 40% of the products when CCl_4 was used as the solvent.[9] Differently, when oxaziridines **1** were reacted with **2a** in $CFCl_3$, CCl_4, or $CHCl_3$, the formation of chlorinated products could not be detected. Furthermore, the stereospecificity in hydroxylation of stereoisomeric 1,2-dimethylcyclohexanes (**2d,e**) and decalins (**2f,g**) could hardly be rationalized through mechanisms involving cationic or radical species. The reactivities and stereospecificities of oxaziridines **1** are similar to those of dioxiranes,[10,15,25] both classes of compounds having their active sites as part of a three-membered ring.

It seems convenient and reasonable to extend the similarity to the mechanistic aspect and assume that the simplest pathway of hydrocarbon oxidation by oxaziridines is an "oxenoid" O-atom insertion into C–H bonds.[30] Some radical or ionic character might develop in the transition state. However, as a consequence of the high stereoselectivity observed, the suggestion of actual ionic or radical caged pairs would require the introduction of the additional assumption that collapse of the pairs to alcohols **4** and azaalkenes **3** occurs faster than loss of stereochemistry on the side of either substrates **2** or oxidants **1**. A further argument for a concerted O-atom insertion is the more rapid reaction of alicyclic hydrocarbons carrying equatorial tertiary C–H bonds with respect to isomers having axial C–H bonds. Specifically, in competitive experiments at 21 °C, *cis*-1,2-dimethylcyclohexane (**2d**) and *cis*-decalin (**2f**) reacted 4.5 and 13 times faster than the corresponding *trans* isomers **2e** and **2g**. A 7.1 ratio was observed for (trifluoromethyl)dioxirane oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane.[10] Similar trends were shown by dimethyldioxirane[15] and some peracids.[14]

Finally, the economy in producing **1a,b** in combination with their indefinite storage stability at room temperature should make these reactants attractive as general purpose high oxidants.

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Supplementary Material Available: Prototype experimental procedure for oxyfunctionalization reactions; structure assignment and identification (2 pages). Ordering information is given on any current masthead page.

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