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Highly Enantiospecific Oxyfunctionalization of Nonactivated Hydrocarbon Sites by Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine

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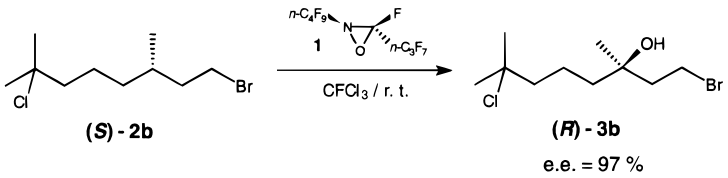
ABSTRACT



Nonactivated hydrocarbon sites of enantiopure compounds are oxyfunctionalized enantiospecifically by perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine under remarkably mild reaction conditions. The reaction occurs with retention of configuration at the oxidized stereogenic center, and the enantiospecificity is highly independent from both the carbon framework of the substrate and the presence of functional groups.

Oxyfunctionalized molecules are principal building blocks in organic synthesis.[1] The most straightforward approach to these compounds is the direct hydroxylation of corresponding hydrocarbons.

However, saturated hydrocarbons possess neither an unbounded electron pair or low-lying empty orbitals[2] and as a consequence the selective oxyfunctionalization of nonactivated C−H bonds under homogeneous and mild conditions is recognized as an important and challenging objective.[3]

A survey of the literature revealed that different approaches have been employed spanning from the catalytic methods (microorganisms,[4] enzymes,[5] and transition metals[6]) to the stoichiometric reagents (ozone,[7] fluorine,[8] peroxides and peroxy acids[9]). However, to the best of our knowledge only very limited examples of stereospecific oxyfunctionalizations at nonactivated hydrocarbon sites have been described. Efficient regio- and diastereoselective oxidations of hydrocarbons have been achieved with dimethyldioxirane[10] and its methyltrifluoromethyl analogue while a single example

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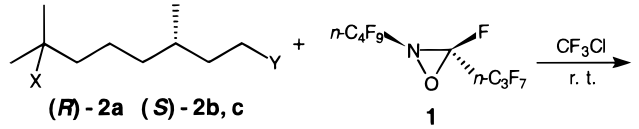
of oxidation at purely aliphatic sites with 70−85% retention of configuration has been reported by action of chromic acid.[11]

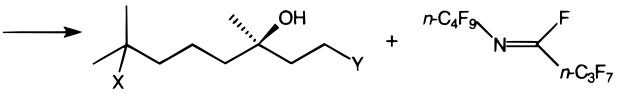
Perfluoro-*cis*-2,3-dialkyloxaziridines are powerful yet selective oxidizing reagents[12] and have already proven their efficiency also in the *regioselective, site-selective, and diastereoselective hydroxylation of various hydrocarbon substrates*.[13] Herein we describe the effectiveness of perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) in the *enantiospecific oxyfunctionalization of nonactivated hydrocarbons* under remarkably mild reaction conditions.

Treatment of (*R*)-2,6-dimethyloctane (**2a**) with oxaziridine **1** at room temperature cleanly furnished 3-octanol **3a** having the (*S*) absolute configuration (Table 1).[14,15] The reaction did

Table 1. Enantiospecific Oxyfunctionalization of Citronellyl Derivatives **2a**−**c**



(*R*) - **2a** (*S*) - **2b, c** **1**



(*S*) - **3a** (*R*) - **3b, c** **4**

substr	X	Y	reactn time (h)	added salt[a]	% ee **2**	% ee **3**	configuration retention %
(*R*)-**2a**	H	H	1		81	78	96
(*R*)-**2a**	H	H	9		81	48	59
(*R*)-**2a**	H	H	1	KF (1 equiv)	81	79	97
(*R*)-**2a**	H	H	9	KF (1 equiv)	81	78	96
(*R*)-**2a**	H	H	9	CsF (1 equiv)	81	72	89
(*R*)-**2a**	H	H	9	CsF (2 equiv)	81	71	88
(*S*)-**2b**	Cl	Br	30		99	97	98
(*S*)-**2c**	OH	Br	21		99	96	97

[a] Equivalents of added salt with respect to 1 equiv of substrate **2**.

occur with retention of configuration[16] as demonstrated by chemical correlation with 3-octanol **3a** obtained from the oxidation of (*R*)-**2a** with peracids which are known to work with preferential retention of configuration.[17]

The enantiospecificity of the reaction changed from high to moderate on prolonging the reaction time. Assuming that this decrease in the enantiospecificity was due to in situ racemization of the formed alcohol **3a** under catalysis by traces of hydrofluoric acid (generated by the hydrolytic decomposition of azaalkene **4** or present in oxaziridine **1**), we performed the oxyfunctionalization reaction in the presence of metal fluorides which are known to work as effective scavengers of HF.[18] Indeed, the decrease of optical purity at long reaction times was definitively retarded and potassium fluoride was slightly more effective than cesium fluoride.

On treatment of the two citronellyl derivatives **2b**,**c**[19] with oxaziridine **1**, almost complete retention of configuration[20] has been observed, thus confirming the enantiospecific character of the hydroxylation reaction performed by the oxaziridine. Oxyfunctionalization reactions in general[21] and those performed by oxaziridines too[13] are retarded by the presence of electron-withdrawing functional groups near the reaction center. This is consistent with the fact that oxidation reactions are electrophilic in nature and the presence of functionalities decreases the electron density at the reaction

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(14) All the reactions here described have been performed on both racemic and nonracemic substrates **2**, **5**, and **7**. The optical purity of any substrate and product (but **2a**) was established unequivocally through GLC analyses on chiral columns (see Supporting Information), and the stereospecificity of the process was thus established. The optical purity of **2a** could not be established by chiral GLC and was determined through the optical purity of (*R*)-2,6-dimethyl-2-octanol (**3d**, ref 15) whose signals in the ^{1}H NMR spectrum showed a clear splitting in the presence of Eu(hfc)$_3$ (see Supporting Information).

(15) Oxyfunctionalization by oxaziridine **1** is known to occur selectively at tertiary sites (ref 13). Consistent with this regioselectivity (*R*)-**2a** was attacked by the oxaziridine **1** at both C-6 and C-2 to give (*S*)-3,7-dimethyl-3-octanol (**3a**) and (*R*)-2,6-dimethyl-2-octanol (**3d**), respectively, in an approximate 1:1 ratio.

(16) Substrates **2**, **5**, and **7** and corresponding oxyfunctionalized products **3**, **6**, and **8** which have the same geometry at the stereogenic center are assigned to the opposite absolute configuration due to the CIP rules.

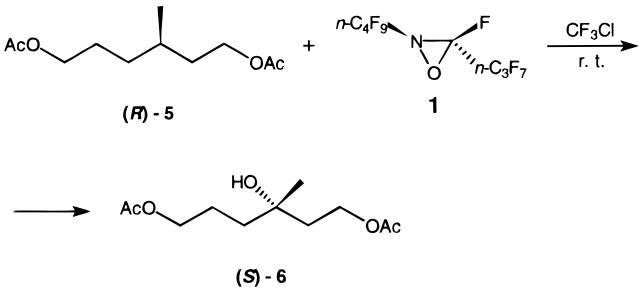
(17) Schneider, H. J.; Muller, W. *J. Org. Chem.* **1985**, *50*, 4609. Kirmse, W.; Rauleder, G.; Ratajczak, H.-J. *J. Am. Chem. Soc.* **1975**, *97*, 4142.

(18) This hypothesis was also supported by control experiments where HF was bubbled in the solution of **3a** prior to the addition of **1**. The formed alcohol **3a** was nearly racemic.

center. The reduced in situ racemization of **3b**,**c** compared to **3a** can also be ascribed to the decreased electron density at the oxyfunctionalized center due to the presence of functional groups.

To show that the enantiospecificity in the oxyfunctionalization is highly independent of both the carbon framework of the substrate and the presence of functional groups, 3-methyladipic acid derivative **5**[22] (Table 2) and isoamyl

Table 2. Enantiospecific Oxyfunctionalization of 3-Methyladipic Acid Derivative **5**



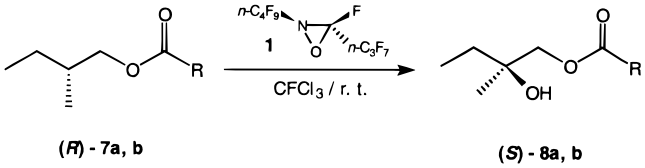
reactn time (h)	added salt[a]	% ee **5**	% ee **6**	configuration retention %
24		99	93	94
38		99	89	90
72		99	47	48
48	NaF (1 equiv)	99	94	95
31 (days)	CsF (1 equiv)	99	88	89

[a] Equivalents of added salt with respect to 1 equiv of substrate **5**.

alcohol derivatives **7a**,**b**[23,24] (Table 3) have been reacted with oxaziridine **1** under standard reaction conditions.

In all cases the oxidation did occur with very high retention of configuration. Consistent with the presence of electron-withdrawing functionalities in the substrate molecules, reaction times were quite long. As expected, the in situ racemization of **6** was slow and it was retarded by the presence of alkaline fluorides. The ee of the alcohol (*S*)-**6** was as high as 89% even after a reaction time of 31 days when cesium fluoride was used as hydrofluoric acid scavenger during the reaction.

Table 3. Enantiospecific Oxyfunctionalization of Isoamyl Alcohol Derivatives **7**



substr	R	reactn time (h)	% ee **7**	% ee **8**	configuration retention %
(*S*)-**7a**	CH_3	24	99	95	96
(*S*)-**7a**	CH_3	31	99	93	94
(*S*)-**7b**	$(CH_3)_2CBr$	22	99	93	94
(*S*)-**7b**	$(CH_3)_2CBr$	72	99	82	83

In general the oxidative properties of oxaziridine **1** recall those of dioxiranes[10,25] which also have been successfully employed in the oxyfunctionalization of various hydrocarbons. Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is confirmed to be an interesting alternative to these reagents. While the enantiospecificity in the oxidation by dioxiranes has been tested only on benzylic positions,[26] oxaziridine **1** performs the oxyfunctionalization reaction with very high enantiospecificity on quite different trialkyl-substituted hydrocarbon sites and the presence of various functional groups (carbalkoxy, chloro, bromo, hydroxyl residues) is tolerated.

Useful aspects of the employment of **1** are the mild reaction conditions, the simple reaction workup procedure, and the indefinite storage stability of the oxaziridine. The reactions here described thus represent a general procedure for the chemical generation of aliphatic chirons possessing a tertiary carbinol site on quite different carbon skeletons and in the presence of various functional groups.

As far as mechanistic considerations are concerned, the observed retarding effect of electron-withdrawing substituents is consistent with an electrophilic process having an ionic or concerted or radical nature. Among others,[27] high enantiospecificity has been used as a proof of a concerted mechamism in oxyfunctionalization reactions.[28] However,

(19) Substrates **2b**,**c** have been obtained starting from (*S*)-citronellyl bromide (Aldrich) by addition of hydrochloric acid (HCl, *n*-pentane, rt) and water (H_2O, H_2SO_4, THF, rt), respectively. Selected spectral and physical properties of (*S*)-**2b**: $[\alpha]^{20}_D = -5.30$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.47−3.43 (m, 2H), 1.58 (s, 6H), 2.00−1.20 (m, 9H), 0.91 (d, $J = 7.0$ Hz, 3H). Selected spectral and physical properties of (*R*)-**3b**: $[\alpha]^{20}_D = +2.41$ ($c = 0.3$, $CHCl_3$); ^{1}H NMR (250 MHz,$CDCl_3$) δ 3.49 (m, 2H), 2.10 (m, 2H), 2.03 (brs, 1H), 1.59 (s, 6H), 1.80−1.30 (m, 6H), 1.22 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 73.02 (o), 70.87 (o), 46.29 (o), 45.00 (o), 42.33 (o), 32.52 (e), 32.44 (e), 28.08 (o), 26.61 (e), 19.50 (o); GC-MS (CI) 273 ($M^+ + 2$), 255 ($M^+ - H_2O$), 219 ($M^+ - HCl$).

(20) The oxyfunctionalization of substrates **2**, **5**, and **7** has been assumed to occur with preferential retention of configuration for analogy with the proven stereochemical course in the oxidation of **2a**.

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(22) (*R*)-3-Methyl-1,6-diacetyloxyhexane (**5**) has been prepared from (*R*)-3-methyladipic acid through esterification (methanol, H_2SO_4, reflux), reduction ($LiAlH_4$, ethyl ether, rt), and acetylation (Ac_2O, pyridine, rt).

(23) Esters (*R*)-**7a**,**b** have been obtained by acylation of (*R*)-2-methyl-1-buthanol (Aldrich) with Ac_2O/pyridine and with 2-bromo-2-methylpropionic acid/DCC/4-DMAP/CH_2Cl_2, respectively.

(24) The presence of the ester residue strongly deactivates the nearby tertiary site. As a consequence, the oxaziridine **1** attacked also the less deactivated secondary position (C-3). Indeed, alcohols **8a**,**b** and 3-methyl-4-carbalkoxy-2-butanones (generated through in situ further oxidation of the initially formed 3-methyl-4-carbalkoxy-2-butanols) were formed in nearly equimolar amounts.

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radical reactions can occur enantiospecifically;[29] therefore, in our opinion the results here reported do not allow us to make any definitive statement on the mechanism of the described process.

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Supporting Information Available: General procedure for the oxyfunctionalization reaction; tecniques (^{1}H NMR, chiral GC) and conditions for enantiomer separation of compounds **2**, **3**, **5**, **6**, **7**, and **8**; spectral data (^{1}H and ^{13}C NMR) for the products **3**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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