Selective Oxidation of Optically Active *sec,sec*-1,2-Diols by Dioxiranes. A Practical Method for the Synthesis of Homochiral α-Hydroxy Ketones in High Optical Purity

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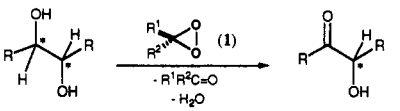
Summary: By employing either dimethyldioxirane or its trifluoromethyl analog, the direct, high-yield conversion of one cyclic and three open chain optically *sec,sec*-1,2-diols to the corresponding α-hydroxy ketones in high optical yield has been achieved.

Several studies have been directed to the stereoselective synthesis of enantiomomerically pure α-hydroxy ketones,[1] since these compounds are important synthons in the asymmetric synthesis of natural products and fine chemicals.[2] A proficient direct method consists in the asymmetric oxidation of enolates.[3-5] Thus, by using enantiomerically pure *N*-sulfonyloxaziridines, Davis and coworkers[3] were able to achieve good to excellent enantioselectivities in reagent-controlled[2d] asymmetric oxidations of prochiral enolates. On the other hand, in the chiral auxiliary approach, the diastereoselective oxidation of chiral enolates has been performed using oxidants such as achiral sulfonyloxaziridines, dibenzyl peroxydicarbonate, and Vedejs' MoOPH reagent.[4] Along these lines, an important addition has been recently devised by Sharpless and co-workers;[5] indeed, these authors have shown that α-hydroxy ketones in high enantiomeric excess can be obtained by the well-established osmium-catalyzed asymmetric dihydroxylation (AD)[6] of the corresponding enol ethers or silyl enol ethers.[5]

We report herein on the selective conversion of representative optically active *sec,sec*-diols into the corresponding α-hydroxy ketones, using isolated dimethyldioxirane (**1a**: $R^1 = R^2 = CH_3$)[7,8] or methyl(trifluoromethyl)dioxirane (**1b**: $R^1 = CH_3$; $R^2 = CF_3$)[9] (eq 1).



(1)

As a preliminary screening, optically active 1,2-cyclohexanediol (**2**), 2,3-butanediol (**4**), 1,2-diphenyl-1,2-ethanediol (**6**), and *threo*-1-phenyl-1,2-propanediol (**8**) were examined as representative substrates.[10] The dioxiranes (**1a** and **1b**) could be obtained in the isolated form by following a described general protocol.[7-9] Typical reaction conditions and results are shown in Table I.

Reactions were carried out by addition of an aliquot (usually from 4 to 10 mL) of standardized[7-9] cold solution of ca. 0.1 M **1a** in acetone or of ca. 0.8 M **1b** in 1,1,1-trifluoro-2-propanone (TFP) to a stirred solution of the diol (100–300 mg) in CH_2Cl_2 (5–10 mL) at 0 °C. The reactions were monitored by GC, GC/MS, and/or TLC; product isolation simply entailed removal of solvent in vacuo. Thus, in most of the cases yields of product isolated were just a trifle lower (from 1 to 5%) than GC yields (Table I).

The oxidative dehydrogenation of *vic*-diols into α-hydroxy ketones is difficult to achieve in good yields using common oxidation reagents.[11] Overoxidation to α-dicarbonyls and/or carbon–carbon bond cleavage to form carboxylic acids is the problem most frequently met.[11d-g]

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(10) (a) (1*R*,2*R*)-*trans*-1,2-cyclohexanediol (**2**) (Fluka, $[\alpha]_D$ −39°), (2*R*,3*R*)-2,3-butanediol (**4**) (Aldrich, $[\alpha]_D$ −13.2°), and (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol (**8**) (Aldrich, $[\alpha]_D$ +93°) were commercial products. Osmium-catalyzed AD of *trans*-β-methylstyrene using *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant and dihydroquinidine 4-chlorobenzoate (DHQD) CLB as the chiral ligand (ref 6e) allowed us to obtain (1*R*,2*R*)-*threo*-1-phenyl-1,2-propanediol (**8**) (ref 10b–d): mp 55–57 °C; $[\alpha]_D$ −28.0° (*c* 0.57, EtOH) (lit.[10b] $[\alpha]_D$ −31.4° (*c* 1.79, EtOH)). The ^1H NMR and MS spectral characteristics of diol **8** were in good agreement with literature data. (b) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (c) Foltz, C. M.; Witkop, B. *J. Am. Chem. Soc.* **1957**, *79*, 201. (d) Audier, H. E.; Dupin, J. F.; Jullien, J. *Bull. Soc. Chim. Fr.* **1966**, 2811.

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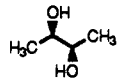
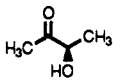
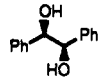
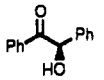
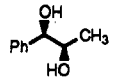
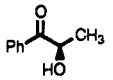
Table I. Selective Oxidation of Some *vic*-Diols to α-Hydroxy Ketones Using Dioxiranes[a]

	substrate							product				
entry	diol	(number)	config	% ee[b]	dioxirane	reactn time	% convn[c]	ketol	(number)	% yield[d]	$[\alpha]_D$[e]	% ee[b] (config)
1		(2)	*R,R*-(−)	95	(1a)	8 h	>96		(3)[f]	>96	+13.4°[g]	94 (*R*)
2		(4)	*R,R*-(−)	>98	(1a)	4 h	92		(5)	>96	−58.6°[h]	>98[i] (*R*)
3		(6)	*R,R*-(+)	96	(1a) (1b)	48 h 100 min	50 92		(7)	92 96	−110.0°[j]	>92 (*R*)
4		(8)	*R,R*-(−)	89	(1a) (1b)	22 h 40 min	94[k] 95		(9)	45[l] 43[l]		86[m] (*R*) 85[m] (*R*)

[a] All reactions routinely run at 0 °C, with initial dioxirane to substrate molar ratio ca. 1.2:1; mixed solvent composition was CH_2Cl_2/TFP ca. 9:1 for oxidations with **1b** and CH_2Cl_2/acetone ca. 7:3 for oxidations with **1a**. [b] Unless noted otherwise, percent enantiomeric excesses (ee) were estimated (±2%) upon comparison of optical rotations with literature values. [c] As determined (±2%) by GC (DB5, 0.20-μm film thickness, 15-m × 0.32-mm i.d., wide-bore capillary column). [d] Yields were determined by GC or GC/MS (Hewlett-Packard Model 5970 mass selective detector and Model 5890 gas chromatograph) and based on the amount of substrate consumed; products were identified upon comparison of their ^{1}H NMR spectra (200 MHz, Varian XL 200) and/or GC/MS with those of reported compounds. [e] Optical rotations (at 20 °C) of product isolated (Perkin-Elmer 241 MC spectropolarimeter). [f] Sheehan, J. C.; O'Neil, R. C.; White, M. A. *J. Am. Chem. Soc.* **1950**, *72*, 3376. [g] (*c* 0.1, $CHCl_3$); cf. $[\alpha]_D$ +14.3° (*c* 0.53, $CHCl_3$) (Whitesides, G. M.; Lee, L. *J. Org. Chem.* **1986**, *51*, 25). [h] *c* 0.12, H_2O; cf. $[\alpha]_D$ −55.4° (*c* 0.15, H_2O) (Givsky, H. *Bull. Soc. Chim. Belg.* **1942**, *51*, 91). [i] As determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$ (Aldrich); cf. Sweeting, L. M. *J. Org. Chem.* **1987**, *52*, 2273. [j] *c* 1.2, acetone; cf. (*S*)-(+)-benzoin (Aldrich); $[\alpha]$ +115° (*c* 1.5, acetone). [k] Initial dioxirane to substrate ratio ca. 2.2:1. [l] Accompanied by 1-phenyl-1,2-propanedione (11–15%) and (*R*)-(−)-1-hydroxy-1-phenyl-2-propanone (**10**) (35–38%); for the latter, ca. 82% ee was estimated by ^{1}H NMR of the product mixture using Eu(hfc)$_3$ (cf., ref 3b). [m] As determined by HPLC (Hewlett-Packard Model 1050 and UV detector Model 35900) of the reaction mixture, employing a chiral stationary phase (DAICEL Chiracel OD, 25-cm × 0.46-cm i.d.; 2% i-PrOH/98% *n*-hexane, 1 mL/min); cf. ref 6.

By contrast, data collected in Table I demonstrate that application of dioxiranes to the oxidation of *vic*-diols led to α-hydroxy ketones in good to excellent yields.[12] However, regioselectivity was low in the oxidation of (1*R*,2*R*)-*threo*-1-phenyl-1,2-propanediol (**8**). In fact, this unsymmetrically substituted diol gave, along with (*R*)-2-hydroxy-1-phenyl-1-propanone (**9**),[13] its regioisomer (*R*)-1-hydroxy-1-phenyl-2-propanone PhC*H(OH)C(:O)CH_3 (**10**)[3b,14] in ca. 35% yield using both dioxiranes **1a** and **1b**; nevertheless, the overall (**9** plus **10**) ketol yield ranged from 78 to 83% (Table I).

In the oxidation of substrates **6** and **8**, similar results were obtained using either dioxirane **1a** or **1b** (entries 3 and 4, Table I), except for percent conversions; as expected, transformations were much faster with the more reactive[9] methyl(trifluoromethyl)dioxirane (**1b**). Under the given conditions (Table I), overoxidation of the α-hydroxy ketone to α-diketone became appreciable (ca. 10–15%) only in the transformation of diol **8** (last entry). However, α-diketone formation was just trifling at lower substrate conversions (e.g., ca. 2% 1-phenyl-1,2-propanediol at 50% conversion of **8**).

Inspection of the data in Table I reveals that the transformation of the diols investigated into α-hydroxy ketones occurs selectively with practically complete retention of configuration at the chiral center adjacent to the one undergoing transformation into carbonyl. In each of the cases examined, the conservation of optical purity is excellent. The observed preservation of stereochemical integrity at the residual C*HOH moiety in the ketol product argues against a radical mechanism;[15] instead, similar to oxidation of secondary alcohols by dioxiranes,[16] an "oxenoid" *O*-insertion mechanism[8a] is likely to apply.

The high selectivities recorded in the transformations at hand should be ascribed to the remarkably mild conditions, close to neutrality, attainable by using isolated dioxiranes. Furthermore, product isolation is quite simple. Also attractive is the easy access to the optically active *vic*-diol starting materials by the Sharpless procedure; indeed, with recent improvements, the asymmetric dihydroxylation of alkenes has attained outstanding levels of enantioselectivity and simplicity.[6] Therefore, the high-yield transformation of chiral *vic*-diols into homochiral α-hydroxy ketones by dioxiranes, with virtually no loss in enantiomeric purity, is likely to further broaden the scope the AD reaction. Thus, the synthetic route to optically active α-hydroxy ketones reported herein shows promise of considerable practical value because of its efficiency and simplicity of approach.

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Supplementary Material Available: Chromatogram showing chiral-column HPLC ee determination of ketol **9** resulting from dioxirane oxidation of diol **8** and spectral data for diol **8** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) We find that isolated dioxiranes **1a** and **1b** also afford the conversion of tertiary,secondary bicyclic or tricyclic diols into the corresponding α-hydroxy ketones in high yields. In the oxidation of commercial (Aldrich) optically active (1*S*,2*S*,3*R*,5*S*)-(+)-pinane-2,3-diol, (1*S*,2*S*,5*S*)-(−)-2-hydroxy-3-pinanone is obtained in optical yield >97% with retention of configuration (Curci, R.; Eaton, P. E.; Takeuchi, K.; et al., to be published).

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