Asymmetric C−H Oxidation of *vic*-Diols to α-Hydroxy Ketones by a Fructose-Derived Dioxirane: Electronic Effects on the Enantioselectivity of Oxygen Transfer

Waldemar Adam,* Chantu R. Saha-Möller, and Cong-Gui Zhao

Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany

Received May 12, 1999

A mechanistic study on the enantioselective C−H oxidation of *vic*-diols with the in-situ-generated dioxirane from the fructose-derived ketone **1** is presented. The asymmetrization of meso-configured and the kinetic resolution of racemic *vic*-diols **2** afforded the optically active α-hydroxy ketones **3** in opposite configurations with moderate to good ee values. Significant electronic effects on the enantioselectivity of C−H insertion have been observed, which are explained in terms of the hydrogen-bonded transition-state structures for the concerted C−H oxygen insertion.

Introduction

Dioxiranes, either in isolated form[1] or in-situ-generated,[2] have been established as very reactive yet highly selective oxidants.[3] One of the highlights of dioxirane chemistry is the efficient oxyfunctionalization of unactivated as well as activated C−H bonds.[4] Although the possibility of a radical-chain reaction has been recently raised,[5] convincing experimental evidence[6] as well as theoretical work[7] have confirmed the concerted mechanism for this insertion reaction, especially under carefully controlled experimental conditions.[6a] The concerted nature of this oxidation process provides an opportunity to conduct enantioselective C−H oxidations,[8] which still present a formidable challenge in organic chemistry.[9]

Several methods are available for the preparation of optically active α-hydroxy ketones, which are valuable building blocks in asymmetric synthesis.[10] In metal-free methods, silyl enol ethers and enol esters have been oxidized to optically active α-hydroxy ketones[11] by the in-situ-generated dioxirane from the fructose-derived ketone **1**.[12] Moreover, it is well-known that *vic*-diols may be readily oxidized by dioxiranes to yield the corresponding α-hydroxy ketones.[13] When optically active *vic*-diols were used, the resulting α-hydroxy ketones were obtained with complete retention of configuration.[13b] Since optically active dioxiranes have been established as efficient oxidants for the asymmetric epoxidation of unfunctionalized olefins,[12,14] we envisaged that optically active α-hydroxy ketones should be accessible through asymmetrization of meso-configured *vic*-diols or kinetic resolution of racemic *vic*-diols by enantioselective C−H oxidation. In a recent paper,[15] we described such an oxidation of *vic*-diols to enantiomerically enriched α-hydroxy ketones by the in-situ-generated, fructose-derived dioxirane in eq 1 and demonstrated the preparative convenience of this direct and metal-free asymmetric oxidation. Presently, we report the electronic substituent effects on the

* To whom correspondence should be addressed. Tel: +49-931-8885340. Fax: +49-931-8884756. E-mail: adam@chemie.uni-wuerzburg.de.

(1) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847−2853. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. P. *Chem. Ber.* **1991**, *124*, 2377.

(2) Curci, R.; Fiorentino, M.; Triosi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758−4760. (b) Adam, W.; Hadjiarapogolou, L. P.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227−232. (c) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887−3889. (d) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964−8965. (e) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810−2811. (f) Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425−6426.

(3) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205−211. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187−1201. (c) Curci, R. In *Advances in Oxygenated Process*; Baumstark, A. L., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, Chapter I, pp 1−59. (d) Adam, W.; Hadjiarapoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; Chapter 4, pp 195−219. (e) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811−822. (f) Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581−599. (g) Adam, W.; Smerz, A. K.; Zhao, C.-G. *J. Prakt. Chem.* **1997**, *339*, 298−300.

(4) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470−2472. (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749−6757.

(5) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Zhao, L. *J. Org. Chem.* **1998**, *63*, 254−263. (b) Vanni, R.; Garden, S. J.; Banks, J. T.; Ingold, K. U. *Tetrahedron Lett.* **1995**, *36*, 7999−8002.

(6) Adam, W.; Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gasparrini, F.; Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkötz, S.; Winde, R. *Chem. Eur. J.* **1997**, *3*, 105−109. (b) Simakov, P. A.; Choi, S.-Y.; Newcomb, M. *Tetrahedron Lett.* **1998**, *39*, 8187−8190.

(7) Shustov, G. V.; Rauk, A. *J. Org. Chem.* **1998**, *63*, 5413−5422. (b) Du, X.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 6480−6483. (c) Glukhovtsev, M. N.; Canepa, C.; Bach, R. D. *J. Am. Chem. Soc.* **1998**, *120*, 10528−10533.

(8) Punniyamurthy, T.; Miyafuji, A.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 8295−8298. (b) Miyafuji, A.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10339−10348. (c) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337−6350. (d) Södergen, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577−7580. (e) Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10017−10028. (f) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628−3634.

(9) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146−153. (b) Arndsten, B. A.; Bergman, R. G.; Mobley, A.; Peterson, P. H. *Acc. Chem. Res.* **1992**, *25*, 504−512. (c) Asensio, G.; González-Núñez, M. E.; Bernardini, C. B.; Mello, R.; Adam, W. *J. Am. Chem. Soc.* **1993**, *115*, 7250−7253. (d) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 69−72.

(10) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon: New York, 1983; Chapter 2. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934.

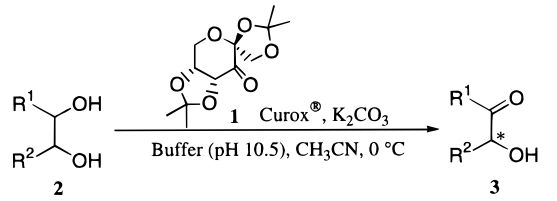
(11) Adam, W.; Fell, R. T.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 397−401. (b) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819−7822.

(12) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806−9807. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328−2329. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224−11235.

(13) Curci, R.; D'Accolti, L.; Detomaso, A.; Fusco, C.; Takeuchi, K.; Ohga, Y.; Eaton, P.; Yip, Y.-C. *Tetrahedron Lett.* **1993**, *34*, 4559−4562. (b) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, *58*, 3600−3601. (c) Bovicelli, P.; Lupattelli, P.; Sanetti, A.; Mincione, E. *Tetrahedron Lett.* **1995**, *36*, 3031−3034. (d) Bovicelli, P.; Sanetti, A.; Lupattelli, P. *Tetrahedron* **1996**, *52*, 10969−10978.

10.1021/jo9907843 CCC: $18.00
Published on Web 09/11/1999

enantioselectivity of this C−H insertion in an effort to optimize its efficiency through such a mechanistic study.



(eq 1)

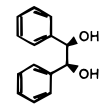
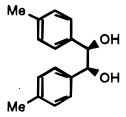
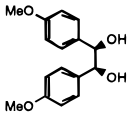
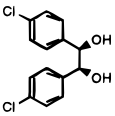
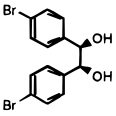
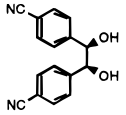
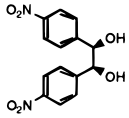
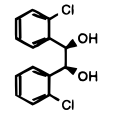
Results

Of the several recently reported optically active ketones, which were employed as precursors of dioxiranes in asymmetric epoxidation, the ones prepared from binaphthol[14d,e,g] and TADDOL[14d] proved to be ineffective. The fructose-derived ketone **1**[12] was the best choice for the enantioselective oxidation of *vic*-diols to optically active α-hydroxy ketones. The results are presented below, separately for the various substrate types.

Asymmetrization of *meso*-Diols. Our initial investigation started with the asymmetrization of *meso*-hydrobenzoins (Table 1). Under standard conditions (pH of 10.5 and 3.0 equiv of ketone **1**), a conversion of 89% for *meso*-hydrobenzoin (**2a**) and an ee value of 45% for the α-hydroxy ketone **3a** were achieved (Table 1, entry 1), with about 50% of ketone **1** recovered after the reaction. Under these conditions, similar high conversions were obtained with the electron-rich methyl- and methoxy-substituted *meso* diols **2b** (Table 1, entry 2) and **2c** (Table 1, entry 3), but with still lower ee values for the products **3b** and **3c**. The electron-poorer fluoro-, chloro-, or bromo-substituted *meso*-diols **2d**−**f** (Table 1, entries 4−6) are less reactive (except the fluoro derivative), but exhibit higher ee values, which are considerably better than the previously reported ones.[16a] Of the electron-poor substrates, the cyano derivative **2g** (Table 1, entry 7) was barely oxidized, but the highest ee value was achieved, while the nitro-subsituted *meso*-diol **2h** was unreactive under these conditions (Table 1, entry 8). The *o*-chloro substitution in *meso*-**2i** is disadvantageous since a low conversion and the worst ee value was obtained (Table 1, entry 9).

Since the enantiomers of the racemic α-hydroxy ketones **3e** and **3f** are not baseline-separated on chiral OD-H or OB-H columns, these enantiomerically enriched products were acetylated with acetic anhydride/pyridine to their acetates and readily separated on an OD-H column to determine their ee values. The *R* configurations were assigned to the major enantiomers of **3a**−**f**, obtained by asymmetric oxidation of *meso*-diols **2a**−**f**, on the basis of the known sign of the optical rotations.[16] The major enantiomers of the products **3g** and **3i** were tentatively assigned as the *R*-configured ones based on

Table 1. Enantioselective Oxidation of *meso*-Diols 2 by the in-Situ-Generated Dioxirane from the Fructose-Derived Ketone 1

entry	substrate[a]	time (h)	convn (%)[b]	ee (%)[c]	confign of **3**[d]
1	 (*meso*-**2a**)	3	89	45	*R*(-) [13b]
2	 (*meso*-**2b**)	3	92	30	*R*(-) [16]
3	 (*meso*-**2c**)	3	95	24	*R*(-) [16]
4	 (*meso*-**2d**)	3	95	58	*R*(-) [16]
5	 (*meso*-**2e**)	2.5	56	54[e]	*R*(-) [16]
6	 (*meso*-**2f**)	2	61	58[e]	*R*(-) [16]
7	 (*meso*-**2g**)	3	≤5	60	*R*(+)[f]
8	 (*meso*-**2h**)	3	0	---	----
9	 (*meso*-**2i**)	4	17	17	*R*(-)[f]

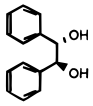
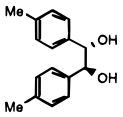
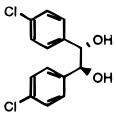
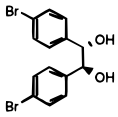
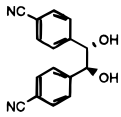
[a] Diols **2** (0.1 mmol), ketone **1** (0.3 mmol), Curox (0.15 mmol), K_2CO_3 (0.63 mmol), and Bu_4NHSO_4 (4 μmol) in CH_3CN (1.5 mL) and 0.05 M $Na_2B_4O_7$ (1.0 mL) at 0 °C. [b] Determined by ^1H NMR analysis, error ≤5% of the stated values. [c] Determined by chiral HPLC analysis, error ≤2% of the stated values. [d] Configuration of the major isomer was determined by comparison of the specific rotation with literature values, numbers in brackets are the references. [e] Determined for the acetate of the α-hydroxy ketone by chiral HPLC analysis. [f] Configuration tentatively assigned.

(14) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491−492. (b)Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311−11312. (c) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622−8623. (d) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995−3998. (e) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S.-g.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921−2926. (f) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi. H. *J. Org. Chem.* **1997**, *62*, 8288−8289. (g) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943−5952. (h) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659−7660. (i) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621−622. (j) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475−8485.

(15) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 4117−4122.

(16) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217−1221. (b) Gu, J. X.; Li, Z. Y.; Lin, G. Q. *Chin. Chem. Lett.* **1995**, *6*, 457−458.

Table 2. Enantioselective Oxidation of *d,l*-Diols 2 by the in-Situ-Generated Dioxirane from the Fructose-Derived Ketone 1

entry	substrate[a]	time (h)	convn (%)[b]	ee (%)[c]	confign of **3**[d]
1	 (*d,l*-**2a**)	3	51	65[e]	*S*(+) [13b]
2	 (*d,l*-**2b**)	3	12	61[e]	*S*(+) [16]
3		1.5	10	71 (11)	*S*(+) [16]
4[f]	(*d,l*-**2d**)	3	31	69 (28)	
5	 (*d,l*-**2e**)	2	11	70[e,g]	*S*(+) [16]
6	 (*d,l*-**2f**)	2	10	74[e,g]	*S*(+) [16]
7	 (*d,l*-**2g**)	2.5	6	75[e]	*S*(-)[h]

[a] Diols **2** (0.1 mmol), ketone **1** (0.3 mmol), Curox (0.075 mmol), K_2CO_3 (0.32 mmol), and Bu_4NHSO_4 (4 μmol) in CH_3CN (1.5 mL) and 0.05 M $Na_2B_4O_7$ (1.0 mL) at 0 °C, unless otherwise indicated. [b] Determined by ^1H NMR analysis, error ≤5% of the stated values. [c] Determined by chiral HPLC analysis, error ≤2% of the stated values, numbers in parentheses are the ee values of the remaining diol. [d] Configuration of the major isomer was determined by comparison of the specific rotation with literature values; numbers in the brackets are the references. [e] The ee value of the remaining diol was not determined. [f] 0.15 mmol of Curox and 0.63 mmol of K_2CO_3 were used. [g] Determined for the acetate of the α-hydroxy ketone by chiral HPLC analysis. [h] Configuration tentatively assigned.

the mechanism discussed below (vide infra). Moreover, the major enantiomer of **3i** has the same elution order and sign of optical rotation as the known *R*-configured α-hydroxy ketones **3a**−**f**.

Kinetic Resolution of *d,l*-Diols. The results of this asymmetric oxidation are collected in Table 2. The kinetic resolution of the *d,l* diastereomers led to higher enantioselectivities (ee ≥ 61%) than for the corresponding meso substrates (Table 1), with the *S* rather than the *R* enantiomer as the major product. Again, the highest ee value (75%) was observed for the poorly reactive cyano-substituted substrate *d,l*-**2g** (Table 2, entry 7). Generally, the conversions of the *d,l* substrates were much lower than that for their meso counterparts; however, the conversions could be increased by using Curox (potassium monoperoxysulfate) in excess. For example, the conversion of *d,l*-4,4′-difluorohydrobenzoin (*d,l*-**2d**) was raised from 10 to 31% by using 1.5 instead of 0.75 equiv of Curox, with the same ee value (69 vs 71%) of the product (*S*)-**3d** within the experimental error (Table 2, entries 3 and 4). The ee values of the remaining diols were not determined since the enantiomers were inseparable on either OD-H or OB-H columns. For this case, the ee values of the remaining diol were determined to be 11% at 10% conversion and 28% at 31% conversion because the two enantiomers of the diol *d,l*-**2d** are easily separated on an OD-H column.

Kinetic Resolution of Unsymmetric *vic*-Diols. These results are summarized in Table 3. The oxidation of the unsymmetrical *threo*-1-phenyl-1,2-propanediol (*threo*-**2j**) led to the two regioisomeric *S*-configured products 2-hydroxy-1-phenyl-1-propanone (**3j**) and 1-hydroxy-1-phenyl-2-propanone (**3j′**) in a ratio of 84:16,[18] with ee values of 69% and 44% (Table 3, entry 1). The oxidation of the *erythro*-**2j** also yielded these two regioisomeric α-hydroxy ketones in a ratio of 89:11 (entry 2),[18] with ee values of only 23% (*S*) and 8% (*R*). Although some nonbenzylic C−H oxidation was observed with *erythro*- and *threo*-**2j**, attempted oxidation of *cis*-1,2-cyclohexanediol and *meso*-2,3-butanediol failed completely (data not shown). The oxidation of *cis*- and *trans*-1,2-indanediol (**2k**) and of *cis*- and *trans*-1,2,3,4-tetrahydronaphthalene-1,2-diol (**2l**) gave α-hydroxy ketones **3k** and **3l** in low ee values and again in opposite configurations (Table 3, entries 3−6).

Enantioselective Oxidation of Acetals. Since the acetals of *vic*-diols are also known to be oxidized by (trifluoromethyl)methyldioxirane (TFD), and even DMD, with complete retention of configuration,[19] the enantioselective oxidation of some acetals of the above-mentioned diols was examined (Table 3). The *cis*-**4a** derived from *meso*-**2a** (Table 3, entry 7) and *cis*-**4b** derived from *meso*-**2b** (entry 8) gave almost the same ee values (63 vs 65%) for the products (*S*)-**3a** and **3b**, but in very low conversions (ca. 10%), even when a large excess of Curox was used. The *trans*-**4a** is still less reactive, and no consumption could be achieved (data not shown). The oxidation of the *cis*- and *trans*-**4c** acetals took place regioselectively[20] (Table 3, entries 9 and 10) to yield exclusively the (*S*)-2-hydroxy-1-phenyl-1-propanone (**3j**). In both cases, the conversions were very low and the enantioselectivities inferior to those observed in oxidations of the corresponding diols *erythro*- and *threo*-**2j**.

Discussion

Stereoselectivity. In the asymmetrization of *meso*-hydrobenzoins (Table 1) and kinetic resolution of *d,l*-hydrobenzoins (Table 2), noteworthy is the finding that α-hydroxy ketones of opposite configurations were formed

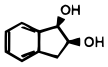
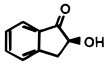
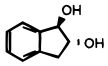
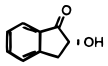
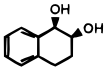
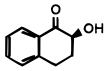
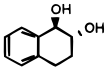
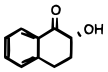
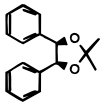
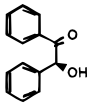
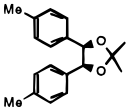
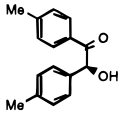
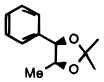
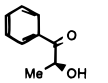
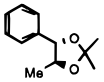
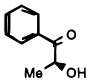
(17) Adam, W.; Díaz, M. T.; Fell, R. T.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2207−2210. (b) Davis, F. A.; Shepperd, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679−6690.

(18) The oxidation of 1-phenyl-1,2-propanediol by dimethyldioxirane (DMD) gave a mixture of 2-hydroxy-1-phenyl-1-propanone, 1-hydroxy-1-phenyl-2-propanone, and 1-phenyl-1,2-propanedione in a ratio of 52:32:16 (see ref 13d).

(19) Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Rosa, A. *Tetrahedron Lett.* **1996**, *37*, 115−118.

(20) DMD oxidizes acetal-**4c** regioselectively to give the 2-hydroxy-1-phenyl-1-propanone as the only product (see refs 13c and 19).

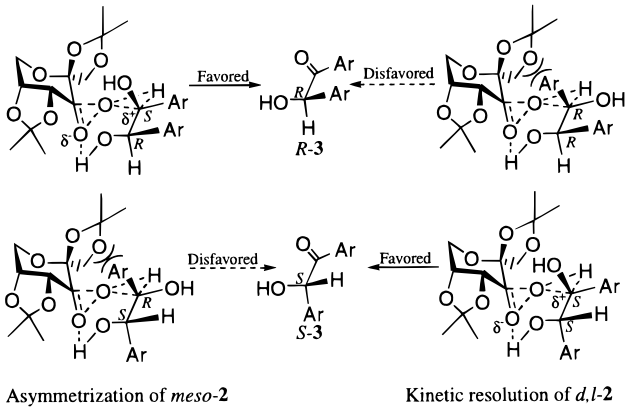
Table 3. Enantioselective Oxidation of Unsymmetric *vic*-Diols and Acetals by the in-situ-Generated Dioxirane from the Fructose-Derived Ketone 1

entry	substrate[a]	Curox® (equiv.)	time (h)	convn (%)[b]	product **3**	ee (%)[c]	confign of **3**[d]
1	 (*threo*-**2j**)	0.75	2	20[e]	 (**3j**)	69	*S*(-) [17]
					 (**3j'**)	44	*S*(+) [17]
2	 (*erythro*-**2j**)	0.75	2	34[f]	 (**3j**)	23	*S*(-) [17]
					 (**3j'**)	8	*R*(-) [17]
3	 (*cis*-**2k**)	0.75	2	30	 (**3k**)	9	*S*(+) [17]
4	 (*trans*-**2k**)	0.75	2	26	 (**3k**)	20	*R*(-) [17]
5	 (*cis*-**2l**)	0.75	2	18	 (**3l**)	14	*S*(-) [17]
6	 (*trans*-**2l**)	0.75	2	8	 (**3l**)	5	*R*(+) [17]
7[g]	 (*cis*-**4a**)	4.5	5	10	 (**3a**)	63	*S*(+) [13b]
8[g]	 (*cis*-**4b**)	4.5	5	10	 (**3b**)	65	*S*(+) [16]
9[h]	 (*cis*-**4c**)	2.3	5	6	 (**3j**)	44	*S*(-) [17]
10[h]	 (*trans*-**4c**)	2.3	5	<5	 (**3j**)	11	*S*(-) [17]

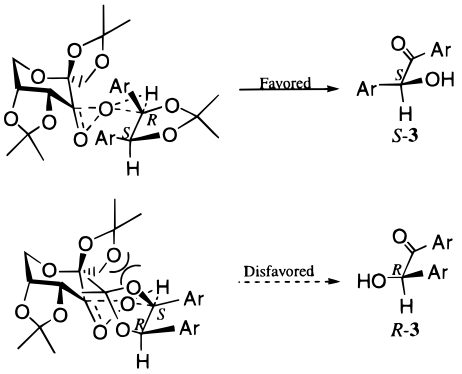
[a] In CH_3CN (1.5 mL) and 0.05 M $Na_2B_4O_7$ (1.0 mL) at 0 °C as described in Table 2, unless otherwise indicated. [b] Determined by ^1H NMR analysis, error ≤5% of the stated values. [c] Enantiomeric excess of α-hydroxy ketones **3** determined by chiral HPLC analysis, error ≤2% of the stated values; ee values of the remaining diols or acetals were not determined. [d] Configuration of the major isomer was determined by comparison of the specific rotation with literature values, in brackets are given the references. [e] Ratio of 2-hydroxy-1-phenyl-1-propanone to 1-hydroxy-1-phenyl-2-propanone is 84:16. [f] Ratio of 2-hydroxy-1-phenyl-1-propanone to 1-hydroxy-1-phenyl-2-propanone is 89:11. [g] In 3.0 mL of CH_3CN−dimethoxymethane (DMM) (1:2) and 2.0 mL of 0.05 M $Na_2B_4O_7$ with 1.89 mmol of K_2CO_3 at 0 °C. [h] In 3.0 mL of CH_3CN−DMM (1:2) and 2.0 mL of 0.05 M $Na_2B_4O_7$ with 0.95 mmol of K_2CO_3 at 0 °C.

in the oxidation of the *d*,*l*-diols (*S* configuration) and that of the *meso*-diols (*R* configuration). This may be explained in terms of the transition-state structures for the concerted oxygen transfer[6,7,13], in which hydrogen bonding of the remote hydroxy group is a key feature[7,13] (Scheme 1). Thus, the *S*-configured site is more readily oxidized than the *R*-configured one since the sterically demanding aryl group minimally interacts with the exocyclic dioxolane ring of the dioxirane. Consequently, the asymmetric oxidation of *meso*-**2** (Scheme 1, left) gives the α-hydroxy ketone (*R*)-**3**, while in the case of the kinetic resolution of *d*,*l*-**2** (Scheme 1, right) (*S*)-**3** is formed. Clearly, in both cases the *same sense of stereoselection* applies. Also, the oxidation of the unsymmetrical *threo*-1-phenyl-1,2-propanediol (*threo*-**2j**) and the *erythro*-**2j** (Table 3, entries 1 and 2) may be rationalized in terms of the concerted mechanism depicted in Scheme 1, with the exception of the benzylic oxidation of *erythro*-**2j** to the (*S*)-2-hydroxy-1-phenyl-1-propanone [(*S*)-**3j**], for which the *R*-configured product [(*R*)-**3j**] would be expected according to Scheme 1. The enantioselective oxidation of the cis and trans diastereomers of cyclic diols **2k** and **2l** (Table 3, entries

Scheme 1



Scheme 2



3−6) also afforded the α-hydroxy ketones **3k** and **3l** in opposite configurations. In these cyclic cases, in contrast to the acyclic diols, it is not possible to form the intermolecular hydrogen bonds between the dioxirane and the diol due to the constraints imposed by the ring structures. An alternative mechanism has been proposed by us previously[15] for the asymmetric oxidation of these cyclic diols.

In the asymmetrization of the acetals *cis*-**4a** and *cis*-**4b** (Table 3, entries 7 and 8), again there is no possibility to form intermolecular hydrogen bonds since both hydroxy groups are protected. As depicted in the respective transition-state structures in Scheme 2, there is no steric interaction between the dioxolane ring of the acetals **4** and the exocyclic dioxolane ring of the dioxirane in the upper transition state (Scheme 2), so that the *R*-configured center is the favored site of oxidation and, therefore, (*S*)-**3a** and (*S*)-**3b** are formed as the major products. This is to be contrasted with the *meso*-diols **2a** and **2b** (the precusor to the cis acetals **4a** and **4b**), which afford the *R* enantiomers (Scheme 1) due to hydrogen bonding (Table 1, entries 1 and 2). The formation of (*S*)-2-hydroxy-1-phenyl-1-propanone [(*S*)-**3j**] from the acetal *cis*-**4c** (Table 3, entry 9) may also be explained by the transition structures depicted in Scheme 2, but preferential production of the *S* enantiomer from the *trans*-**4c** diastereomer (Table 3, entry 10) cannot be reconciled in this manner. However, as in the case of the oxidation of *erythro*-**2j**, for which our mechanistic rationale also fails, the low ee values of the product **3j** reflect remote steric interactions that are difficult to diagnose.

Electronic Effects on the Enantioselectivity. It is also evident from Tables 1 and 2 that the electronic properties of the para substituents in the hydrobenzoins

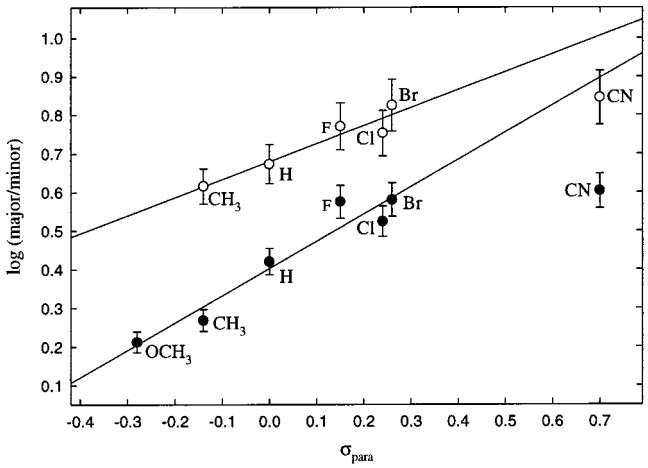


Figure 1. Electronic effects in the asymmetrization of *meso*-diols [● log (*R*/*S*) vs σ_{para}, $r^2 = 0.9338$] and in the kinetic resolution of *d*,*l*-diols [○ log (*S*/*R*) vs σ_{para}, $r^2 = 0.9047$] by enantioselective oxidation with the fructose-derived dioxirane from ketone **1**.

2 (Table 1, entries 1−7, and Table 2) influence the enantioselectivity of the C−H oxidation. This electronic effect is more pronounced in the case of the asymmetrization of *meso*-diols; that is, the enantioselectivities drop considerably in the order CN (60%) > Br (58%) ≈ F (58%) > Cl (54%) > H (45%) > CH_3 (30%) > OCH_3 (24%). The diminution of the enantioselectivity can hardly be of steric origin because the para substituent is too far away from the reaction center (Scheme 1); besides, these groups are not sufficiently sterically demanding.

To confirm that electronic effects operate, a Hammett correlation was constructed by plotting the logarithmic values of the ratio of major to minor enantiomers [log (major/minor)], which provide the energy difference ($\Delta\Delta G^{\ddagger}$) between the favored and disfavored transition states (Scheme 1), against the Hammett σ_{para} values[21] of the substituents. As is evident in Figure 1, with the exception of the cyano-substituted *meso*-**2g** and *d*,*l*-**2g** cases, reasonably good linear correlations were found for the asymmetrization of the *meso* diols ($r^2 = 0.9338$) and for the kinetic resolution of the *d*,*l*-diols ($r^2 = 0.9047$); clearly, the observed enantioselectivity is controlled by electronic effects. The positive ρ values (0.71 for the asymmetrization and 0.47 for the kinetic resolution) indicate that *electron-withdrawing groups yield higher enantioselectivities*.

The present dependence of the enantioselectivity on the electronic nature of the para substituents may be understood by considering hydrogen bonding in the transition-state structures of the oxidations (Scheme 1). From experimental evidence,[13] it has been established that intermolecular hydrogen bonding plays an important role in the oxidation of *vic*-diols by dioxiranes. The transition state for the dioxirane C−H insertion is a polar one,[7,13] in which the carbon atom that is oxidized bears a partial positive charge (δ^+), while the hydrogen-bonded oxygen atom of the dioxirane bears a partial negative charge (δ^-). Thus, the electron-accepting para substituent of the aryl group will increase the positive charge at the carbon atom through electron withdrawal, which will lower the reac-

(21) Exner, O.; In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 10. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

tivity of the diol substrate toward the electrophilic C−H insertion. At the same time, the electron withdrawal of the para group on the adjacent phenyl ring of the *vic*-diol will enhance the acidic character of the hydroxy group and facilitate hydrogen bonding to the negatively charged dioxirane oxygen atom. In the disfavored transition state for the asymmetrization of *meso*-diols (Scheme 1, lower left), there is steric interaction between the aryl group and the exocylic dioxolane ring of the dioxirane. Since a stronger hydrogen bond will generate a more tightly bound transition-state structure, this steric interaction will be increased in such a more rigid structure and thereby disfavor this transition state even more. Consequently, the stronger hydrogen bonding promoted by the electron-accepting aryl groups leads to a higher enantioselectivity in the asymmetrization of *meso*-diols. The fact that the cyano group falls off the line (Figure 1) suggests that the stabilizing effect of stronger hydrogen bonding has leveled off for the cyano group, but other factors, e.g., competitive intermolecular hydrogen bonding by the water in the aqueous medium in which the optically active dioxiranes are generated in situ, may be responsible for the observed deviation by altering the transition-state structure.

This same mechanistic argument also applies to the kinetic resolution of the *d*,*l*-diols (Scheme 1, right), but in this case the electronic effects are smaller than for the asymmetrization of the *meso*-diols. The better enantioselectivity observed in the kinetic resolution (Table 2) of the *d*,*l*-diols versus the asymmetrization (Table 1) of the *meso*-diols is presumably due to the lower steric repulsions between the adjacent aryl groups for the *d*,*l* diastereomers, which allows better alignment for intermolecular hydrogen bonding, and electronic effects are less pronounced.

In the oxidation of the acetals **4** of the *vic*-diols (Table 3), hydrogen bonding cannot operate in this enantioselective C−H oxidation. Hence, only the electronic effect on the C−H bond polarity of the acetals is manifested. It has been reported that acetals are significantly less reactive toward electrophilic oxygen insertion than the corresponding diols due to the lack of intermolecular hydrogen bonding.[19] As experimentally confirmed, the *cis*-acetals **4** are less reactive than the *meso*-diols **2**; the conversions of the acetals were very low (ca. 10%) even when a large excess of Curox was used.[22] The *cis*-**4a** and *cis*-**4b** derived from *meso*-**2a** (Table 3, entry 7) and *meso*-**2b** (entry 8) gave almost the same ee values (63 vs 65%) for the products **3a** and **3b**, which are significantly higher than for the corresponding *meso*-diols. The better enantioselectivity for *cis*-acetals **4** than for *meso*-diols **2** might be due to an increased energy difference between the favored and disfavored transition-state structures, since the steric interaction of the exocyclic dioxolane ring of the dioxirane with the dioxolane ring of *cis*-acetals **4** should be considerably larger than that with an aryl group in the case of the *meso*-diols **2**. This enhanced steric interaction should be beneficial in developing more effective asymmetric oxidations by chiral dioxiranes.

(22) Steric factors should not be responsible for the low reactivity of the acetals toward the fructose-derived dioxirane since these substrates are also much less reactive towards dimethyldioxirane (DMD) than the corresponding diols (see ref 19).

Conclusion

The oxidation of *vic*-diols by the in-situ-generated fructose-derived dioxirane yields the corresponding optically active α-hydroxy ketones in moderate to good enantioselectivities. By choosing the appropriate diastereomeric substrates, i.e., meso or *d*,*l*, both enantiomers of the α-hydroxy ketones may be obtained with the same chiral dioxirane. Electronic effects of the para substituents display a pronounced influence on the enantioselectivity of the oxidation of meso and *d*,*l* hydrobenzoins and good linear correlations between the log(major/minor) and σ_{para} were found for both processes. Electron-withdrawing substituents decrease the reactivity of the diol, but with increased enantioselectivity of the oxygen transfer. The results are explained in terms of the counteracting electronic effects of the electron-accepting para substituent: On one hand, the reactivity of the C−H bond is reduced through the inductive electron withdrawal, and on the other hand, the intermolecular hydrogen bonding is strengthened in the transition state for these electrophilic C−H insertions.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm "Peroxidchemie: Mechanistische und präparative Aspekte des Sauerstofftransfers") and the Fonds der Chemischen Industrie. The generous gift of Curox (potassium monoperoxysulfate) from Peroxid-Chemie GmbH (Höllriegelskreuth, Germany) is gratefully appreciated. C.-G.Z. thanks the DAAD (Deutscher Akademischer Austauschdienst) for a doctoral fellowship.

Supporting Information Available: Experimental details; characterization data for new compounds **3g** and *cis*-**4b**; ^{1}H NMR and ^{13}C NMR data, as well as HPLC conditions for the separation of the enantiomers of **3g** and all other known α-hydroxy ketones **3**. This material is available free of charge from the Internet at http://pubs.acs.org.

JO9907843