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Enantioselective oxidation of *vic*-diols to optically active α-hydroxy ketones by a fructose-derived dioxirane

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Abstract

Optically active α-hydroxy ketones **3** have been prepared in moderate to good enantioselectivities through asymmetrization of *meso*-, and kinetic resolution of, racemic *vic*-diols **2** by enantioselective oxidation with the in situ generated dioxirane from the fructose-derived ketone **1**; the opposite sense in the enantioselectivity of the two processes is explained in terms of the hydrogen-bonded transition-state structures for the concerted C–H oxygen insertion.

Dioxiranes,[1] either in isolated form[2] or in situ generated,[3] have been established as very reactive yet highly selective oxidants. 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. The latter fact provides the opportunity to conduct enantioselective C–H oxidations, which still present a formidable challenge in organic chemistry.[8]

Several methods are available for the preparation of optically active α-hydroxy ketones, which are valuable building blocks in synthetic chemistry.[9] Recently we have reported a metal-free method in which silyl enol ethers have been oxidized to optically active α-hydroxy ketones by the in situ generated dioxirane from the fructose-derived ketone **1**.[10] Furthermore, it is known that *vic*-diols may be readily oxidized by dioxiranes to yield the corresponding α-hydroxy ketones.[11] When optically active *vic*-diols were used, the resulting α-hydroxy ketones were obtained with complete retention of configuration.[11b] While optically active dioxiranes have been established as efficient oxidants for the asymmetric epoxidation of unfunctionalized olefins,[12] there is as yet no report on the enantioselective oxidation of C–H bonds.[13] Thus, we envisaged that optically active α-hydroxy ketones should be accessible through asymmetrization of *meso*-*vic*-diols or kinetic resolution of racemic *vic*-diols by enantioselective oxidation with an optically active dioxirane. We report herein the first example of such an

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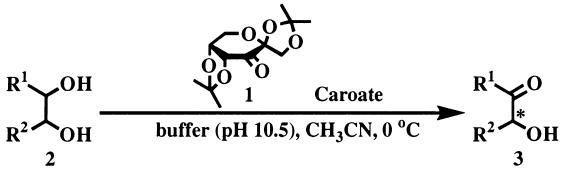
oxidation of *vic*-diols to enantiomerically enriched α-hydroxy ketones by the optically active dioxirane, generated in situ from the fructose-derived ketone **1**[12a] (Scheme 1).

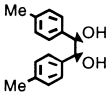
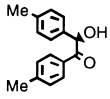
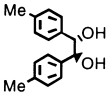
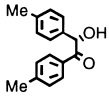
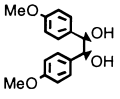
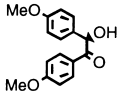
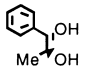
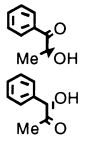
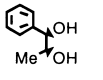
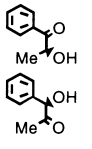
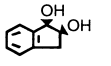
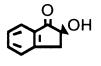
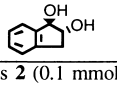
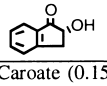
Of the several recently reported optically active ketones which were employed as precursors of dioxiranes for asymmetric epoxidation, in particular the ones prepared from binaphthol,[12c–e] TADDOL,[12d] and the fructose-derived ketone **1**,[12a] the latter was the best choice for the enantioselective oxidation of *vic*-diols to optically active α-hydroxy ketones (Scheme 1). The results are summarized in Table 1. Under nearly neutral conditions ($NaHCO_3$ buffer, pH ca. 8), there was no conversion of *meso*-hydrobenzoin **2a**, even with a stoichiometric amount of ketone **1** (Table 1, entry 1). However, at the higher pH of 10.5[12a] a conversion of 67% and an ee value of 46% for the α-hydroxy ketone **3a** was achieved (Table 1, entry 2). The use of a catalytic amount (0.3 equiv.) of ketone **1** resulted in a lower conversion, but the ee value remained unchanged (Table 1, entry 3); thus, the direct oxidation by Caroate is negligible under such conditions. A control experiment also showed that the resulting α-hydroxy ketone **3a** racemizes slowly (ca. 10% ee in 3 h) under the reaction conditions. To guarantee complete conversion of **2a** within a short reaction time, 3 equiv. of the ketone **1** were used (Table 1, entry 4). While 89% conversion of the diol **3a** was obtained, the ee value remained the same; about 50% of ketone **1** could be recovered after reaction.[16] Under these conditions, similiar conversions and enantioselectivities were obtained with the *meso*-diols **2b** (entry 6) and **2c** (entry 8). It can also be seen from Table 1 that the electronic nature of the *para* substituents in the *meso*-hydrobenzoins **2a–c** (Table 1, entries 4, 6, 8) influences the enantioselectivity of the C–H oxidation in the order H (45%)>CH_3 (30%)>OCH_3 (24%); in all these cases, the (*R*)-(−) enantiomers of the α-hydroxy ketones **3a–c** were formed preferentially. The diminution of the enantioselectivity can hardly be of steric origin because the *para* substituent is too far away from the reaction center; besides, these groups are not sufficiently sterically demanding.



Scheme 1. Enantioselective oxidation of *vic*-diols by the dioxirane generated in situ from the fructose-derived ketone **1**

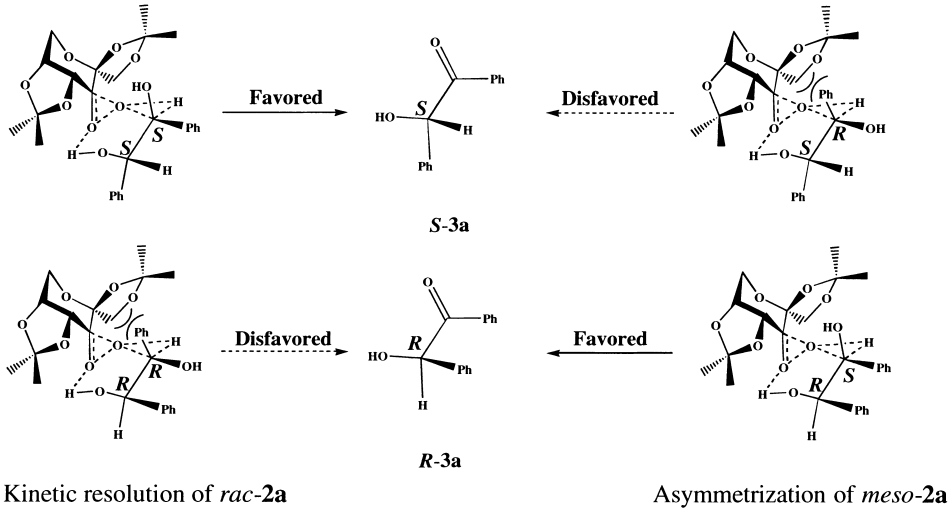
For the kinetic resolution of the racemic diols by enantioselective oxidation, the conversion of the substrate was controlled below 50% by employing an insufficient amount of Caroate. With 3 equiv. of ketone **1**, the diol *rac*-**2a** gave a good ee value of 65% for the α-hydroxy ketone (*S*)-(+)-**3a** at 51% conversion (Table 1, entry 5). In addition, a good enantioselectivity (ee 61%) was observed for the diol *rac*-**2b** at 12% conversion (Table 1, entry 7). Noteworthy is the finding that the sense of enantioselectivity in the oxidation of the racemic diols (*S* configuration) is reversed from that of the *meso*-diols (*R* configuration). These results may be explained in terms of the transition-state structures for the concerted oxygen transfer[6,7] in Scheme 2, in which assistance through hydrogen bonding by the remote hydroxy group plays a central role.[7,11] Thus, the *S*-configured site is more readily oxidized than the *R*-configured one since the sterically demanding phenyl group minimally interacts with the exocyclic dioxolane ring of the dioxirane. In the case of the kinetic resolution of *rac*-**2a** (Scheme 2, left), the *S*,*S*-configured diol is oxidized preferentially to give the *S*-**3a**, while in the asymmetric oxidation of *meso*-**2a** (Scheme 2, right) the *S*-configured site is favored to give the *R*-**3a**. The better enantioselectivity observed in the kinetic resolution of *rac*-**2a** (65% ee) than in the asymmetric oxidation of *meso*-**2a** (45% ee) appears to be a consequence of the hydrogen bonding between the diol and dioxirane, which is known to accelarate the oxidation, since a considerably polarized transition state applies in the oxygen transfer.[7,11] In the oxidation of the *meso*-**2a** diastereomer, steric hindrance operates between the two phenyl groups, even in

Table 1
Enantioselective oxidation of *vic*-diols by the in situ generated dioxirane from the fructose-derived ketone **1**

Entry	Substrate[a]	**1** (equiv.)	Time (h)	Convn.[b] (%)	Product **3**	ee[c] (%)	Configuration[d]
1[e]		1.0	1.5	0		---	---
2		1.0	1.5	67		46	(*R*)-(-)[11b]
3	(*meso*-**2a**)	0.3	1.5	30		44	(*R*)-(-)
4		3.0[f]	3.0	89		45	(*R*)-(-)
5	 (*rac*-**2a**)	3.0[f]	3.0	51		65[g]	(*S*)-(+)[11b]
6	 (*meso*-**2b**)	3.0[f]	3.0	92		30	(*R*)-(-)[14]
7	 (*rac*-**2b**)	3.0[f]	3.0	12		61[g]	(*S*)-(+)[14]
8	 (*meso*-**2c**)	3.0[f]	3.0	95		24	(*R*)-(-)[14]
9	 (*threo*-**2d**)	3.0[f]	2.0	20[h]		69[g] 44	(*S*)-(-)[15] (*S*)-(+)[15]
10	 (*erythro*-**2d**)	3.0[f]	2.0	34[i]		23[g] 8	(*S*)-(-)[15] (*R*)-(-)[15]
11	 (*cis*-**2e**)	3.0[f]	2.0	30		9[g]	(*S*)-(+)[15]
12	 (*trans*-**2e**)	3.0[f]	2.0	26		20[g]	(*R*)-(-)[15]

[a]For diols **2** (0.1 mmol) with ketone **1** (0.3-3.0 equiv. based on **2**), Caroate (0.15 mmol; for kinetic resolution 0.075 mmol), K_2CO_3 (0.63 mmol; for kinetic resolution 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 ^{1}H-NMR analysis, error ≤ 5% of the stated values. [c]Enantiomeric excess of α-hydroxy ketones **3** determined by chiral HPLC analysis (Chiralcel OD-H or OB-H column, UV detection at 220 nm, 90:10 or 95:5 hexane/isopropanol, flow rate 0.5-0.6 mL/min), error ≤2% of the stated values. [d]Configuration of the major isomer was determined by comparison of the specific rotation with literature values. [e]Carried out at pH ca. 8 with Caroate (0.5 mmol), $NaHCO_3$ (1.55 mmol) in CH_3CN (1.5 mL) and 4 × 10^{-4} M aqueous Na_2EDTA (1.0 mL). [f]40-50% of ketone **1** recovered. [g]ee value of the remaining diol could not determined because inseparable on Chiralcel OD-H or OB-H columns. [h]Ratio of 2-hydroxy-1-phenyl-1-propanone to 1-hydroxy-1-phenyl-2-propanone 84:16. [i]Ratio of 2-hydroxy-1-phenyl-1-propanone to 1-hydroxy-1-phenyl-2-propanone 89:11.

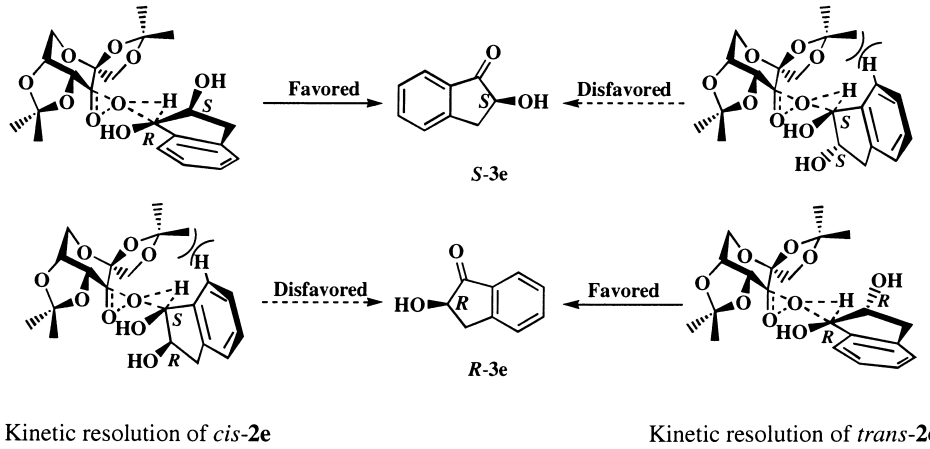
the favored *S*,*R* configuration, which is absent in the case of the favored *S*,*S* configuration of the *rac*-**2a** diastereomer.



Scheme 2. Transition-state structures for the kinetic resolution of *rac*-**2a** and the asymmetrization of *meso*-**2a** by oxidation with the fructose-derived dioxirane

The oxidation of the unsymmetrical *threo*-1-phenyl-1,2-propanediol (*threo*-**2d**) led to the two *S*-configured products 2-hydroxy-1-phenyl-1-propanone and 1-hydroxy-1-phenyl-2-propanone in a ratio of 84:16[17] with ee values of 69% and 44% (Table 1, entry 9). The oxidation of the *erythro*-**2d** also yielded these two products in a ratio of 89:11 (Table 1, entry 10)[17] with ee values of 23% (*S*) and 8% (*R*). Two facts are remarkable about these data: the drastically lower (less than one-third) extent of enantioselectivity for the *erythro* diastereomer and the opposite configuration of the product 1-hydroxy-1-phenyl-2-propanone derived from this diastereomer. These results may also be rationalized in terms of the concerted mechanism depicted in Scheme 2, with the exception of the (*S*)-2-hydroxy-1-phenyl-1-propanone from the *erythro*-**2d**. The oxidation of *cis*- and *trans*-1,2-indanediol **2e** both gave low ee values for the α-hydroxy ketone **3e** and again opposite configurations (entries 11 and 12). However, in these cyclic cases it is not possible to form the intermolecular hydrogen bonds because of constraints imposed by the ring structures and, therefore, the mechanism depicted in Scheme 3 applies. As shown in Scheme 3, the *R*-configured site is favored for oxidation because steric interactions between the exocyclic dioxolane ring and the *peri*-hydrogen of the phenyl ring are avoided in the transition state. Thus, in the kinetic resolution of *cis*-**2e** (Scheme 3, left), the α-hydroxy ketone (*S*)-**3e** is formed preferentially, while in the case of *trans*-**2e** the α-hydroxy ketone (*R*)-**3e** is favored (Scheme 3, right). Although the *trans*-**2e** diastereomer is oxidized in a substantially higher enantioselectivity than the corresponding *cis*-**2e** one, the extent of stereocontrol is low and hardly of synthetic value.

In summary, we have shown that optically active α-hydroxy ketones **3** may be prepared in moderate to good ee values by the asymmetrization of *meso*- and kinetic resolution of racemic diols **2**, through enantioselective oxidation with the fructose-derived dioxirane generated in situ from **1**. The different sense in the enantioselectivity is explained in terms of steric interaction in the transition states for these concerted C–H oxygen insertions.



Scheme 3. Transition-state structures for the kinetic resolution of *cis*- and *trans*-**2e** by the fructose-derived dioxirane

Acknowledgements

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16. *General procedure*: To a solution of *meso*-diol **2a** (21.43 mg, 0.10 mmol), ketone **1** (77.48 mg, 0.30 mmol) and Bu_4NHSO_4 (1.5 mg, 4.0 μmol) in 1.5 ml CH_3CN at 0°C, was added 1.0 ml of 0.05 M $Na_2B_4O_7$ in 4×10^{-4} M aqueous Na_2EDTA while stirring. Both solutions of Caroate (92.0 mg, 0.15 mmol) and K_2CO_3 (87.0 mg, 0.63 mmol) in 0.65 ml of 4×10^{-4} M aqueous Na_2EDTA were added simultaneously by means of separate syringes over ca. 2 h. The mixture was further stirred for 1 h and then diluted with H_2O (20 ml), extracted with ether (3×20 ml), washed with H_2O (2×10 ml), and dried over $MgSO_4$. After removal of the solvent (20°C/20 mbar), the residue was purified by silica-gel chromatography to give the recovered ketone **1** (38.0 mg, 49%) and benzoin **3a** (17.5 mg, 82%).
17. 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. 11d).