

## Metal-Template Effect in the Asymmetric Weitz–Scheffer Epoxidation of $\alpha,\beta$ -Enones by an Optically Active Hydroperoxide

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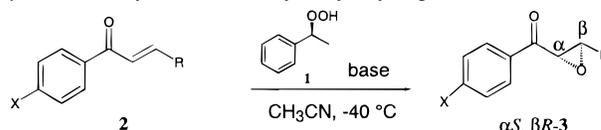
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Recently we have reported the synthesis of optically active hydroperoxides by enzymatic kinetic resolution<sup>1</sup> and utilized these hydroperoxides in the Ti(IV)-catalyzed asymmetric oxidation of sulfides and allylic alcohols.<sup>2</sup> To date, such optically active hydroperoxides have not been employed for the asymmetric epoxidation of electron-deficient olefins, for example, in the Weitz–Scheffer epoxidation of  $\alpha,\beta$ -enones. After the seminal work of Wynberg and co-workers,<sup>3</sup> this preparatively valuable oxidation of  $\alpha,\beta$ -enones under basic conditions has received much attention during the past few years. For this purpose, a variety of asymmetric methods has been developed, which include the use of molecular oxygen and diethylzinc in the presence of (*R,R*)-*N*-methylpseudoephedrine<sup>4</sup> or optically active polybinaphthyl derivatives.<sup>5</sup> Good enantioselectivities have also been achieved with hydrogen peroxide in the presence of polypeptides<sup>6</sup> or chiral platinum(II) complexes.<sup>7</sup> Achiral alkyl peroxides in conjunction with optically active lanthanide–binaphthol complexes<sup>8</sup> or with diethyl (+)-tartrate<sup>9</sup> as chiral auxiliaries have provided as well high enantioselectivities. Lately, Wynberg's approach of using optically active quarternary ammonium salts as phase-transfer catalysts for such epoxidations has been significantly extended.<sup>10</sup>

Herein we report our preliminary results on the first application of the optically active *S*-(–)-(1-phenyl)ethyl hydroperoxide (**1**) for the enantioselective Weitz–Scheffer epoxidation of  $\alpha,\beta$ -enones, in which we demonstrate that enantioselectivities up to 90% ee may be achieved, if the appropriate substrates and

**Table 1.** Enantioselective Weitz–Scheffer Epoxidation of  $\alpha,\beta$ -Enones **2** by *S*-(–)-(1-Phenyl)ethyl Hydroperoxide (**1**)<sup>a</sup>



entry	X	R	base	yield <sup>b</sup> (%)	ee <sup>c,d</sup> (%)	
1	2a	H	KOH	99	51	
2	2a	H	KOH/ 18-crown-6	94	6	
3 <sup>e</sup>	2a	H	DBU	84	9	
4	2b	Me	KOH	98	54	
5	2c	OMe	KOH	97	53	
6	2d	Br	KOH	95	48	
7	2e	H	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	KOH	97	57
8	2f	H	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	KOH	96	61
9	2g	H	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	KOH	98	42
10	2h	H	Me	KOH	99	46
11	2i	H	<i>t</i> -Bu	KOH	95	75
12	2i	H	<i>t</i> -Bu	KOH/ 18-crown-6	91	11
13	2j		KOH	90	90	

<sup>a</sup> Epoxidations were carried out on 0.1–0.5 mmol of the enone **2**, 1.0 equiv of hydroperoxide **1** and 2–3 equiv of base; quantitative consumption of both the enone **2** and hydroperoxide **1** was observed.

<sup>b</sup> Yield of isolated epoxide **3**; no *cis*-epoxide was observed. <sup>c</sup> Determined by HPLC analysis on chiral columns with 2-propanol–hexane as eluent and detection at 260 nm; for entries 1–3 and 8–12 an OD column and for entries 4–6 and 13 an OB–H column were used, error  $\leq 3\%$  of the stated values. <sup>d</sup> Configuration of the major enantiomer was determined by comparison with literature data; for refs see Supporting Information. <sup>e</sup> The epoxidation was carried out at  $\sim 20^\circ\text{C}$ ;  $\alpha R,\beta S$ -**3a** is the major enantiomer.

conditions are utilized. These results are summarized in Table 1, which are rationalized mechanistically in terms of steric effects between the  $\beta$  substituent in the enone substrate and the groups on the chirality center of the hydroperoxide oxygen donor in the potassium-coordinated template.

After screening diverse inorganic bases and solvents under a variety of experimental conditions, we found that the asymmetric epoxidation of enone **2a** by the hydroperoxide *S*-(–)-**1** proceeded smoothly with KOH as a base in CH<sub>3</sub>CN. At  $-40^\circ\text{C}$ , within 10–20 min the epoxide **3a** is obtained quantitatively with an ee value of 51% and preference for the (+)-enantiomer (entry 1, Table 1). Comparison of the sign of the optical rotation with the literature data<sup>11</sup> revealed that the (+)-enantiomer of the epoxy ketone **3a** possesses the  $\alpha S,\beta R$  configuration. Thus, the observed enantioselectivity derives from the preferential attack of the chiral hydroperoxide on the *Re* face of the *S*-*cis* conformation of the *E* enone **2a** to afford the ( $\alpha S,\beta R$ )-**3a** epoxide as major enantiomer, whereas the attack at the *Si* face leads to the ( $\alpha R,\beta S$ )-epoxy ketone **3a** (Scheme 1). Substitution on the aromatic ring of the enone carbonyl function by *p*-Me, *p*-OMe, *p*-Br groups (entries 4–6) does not change the enantioselectivity, the ee values are within the experimental error. In contrast, a definite trend to higher ee values is displayed by para substituents on the  $\beta$ -phenyl group in the order *p*-OMe > *p*-Me > *p*-NO<sub>2</sub> (entries 7–9). Thus, electron-donating  $\beta$ -aryl groups enhance the enantioselectivity, but to a minor extent. Also the  $\beta$ -methyl substituent in the enone **2h** (entry

(11) Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312–2314.

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(1) (a) Adam, W.; Hoch, U.; Lazarus, M.; Saha-Möller, C. R.; Schreiber, P. *J. Am. Chem. Soc.* **1995**, *117*, 11898–11901. (b) Adam, W.; Fell, R. T.; Hoch, U.; Saha-Möller, C. R.; Schreiber, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1047–1050.

(2) (a) Adam, W.; Korb, M. N.; Roschmann, K. J.; Saha-Möller, C. R. *J. Org. Chem.* **1998**, *63*, 3423–3428. (b) Adam, W.; Korb, M. N. *Tetrahedron: Asymmetry* **1997**, *8*, 1131–1142.

(3) (a) Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, *17*, 1831–1834. (b) Wynberg, H.; Greijdanus, B. *J. Chem. Soc., Chem. Commun.* **1978**, 427–428. (c) Wynberg, H.; Marsman, B. *J. Org. Chem.* **1980**, *45*, 158–161. (d) Plum, H.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2498–2502.

(4) Enders, D.; Zhu, J.; Kramps, L. *Liebigs Ann./Recl.* **1997**, 1101–1113. (5) Yu, H.-B.; Zheng, X.-F.; Lin, Z.-M.; Hu, Q.-S.; Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 8149–8155.

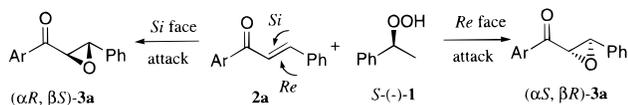
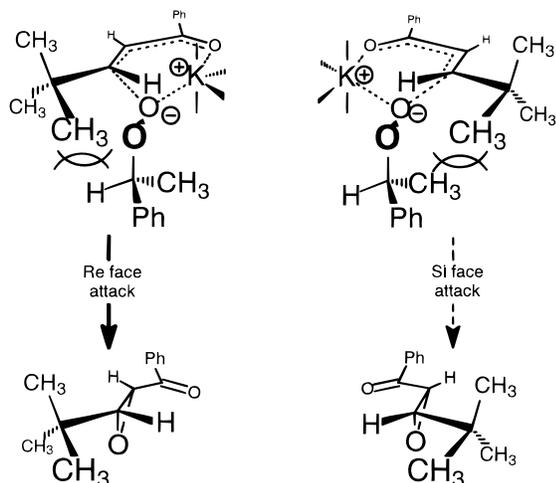
(6) (a) Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929–931. (b) Kroutil, W.; Lasterra-Sanchez, M. E.; Maddrell, S. J.; Mayon, P.; Morgan, P.; Roberts, S. M.; Thornton, S. R.; Todd, C. J.; Tüter, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2837–2844. (c) Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047–6049. (d) Pu, L. *Tetrahedron: Asymmetry* **1998**, *9*, 1457–1477. (e) Ebrahim, S.; Wills, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3163–3173. (f) Porter, M. J.; Roberts, S. M.; Skidmore, J. *Bioorg. Med. Chem.* **1999**, *7*, 2145–2156.

(7) Baccin, C.; Gusso, A.; Pinna, F.; Strukul, G. *Organometallics* **1995**, *14*, 1161–1167.

(8) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329–2330.

(9) Elston, C. L.; Jackson, R. F. W.; MacDonald, S. J. F.; Murray, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 410–412.

(10) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289–6300. (b) MacDonald, G.; Alcaraz, L.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 5433–5436. (c) Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563–7566. (d) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287–1290.

**Scheme 1.** Enantioselectivity for the Epoxidation of Enone **2a****Scheme 2.** Metal Template Effect for the Epoxidation of Enone **2i**

10) leads to ee values similar to those by the  $\beta$ -phenyl one in the enone **2a** (entry 1); but more significantly, the same sense in the enantioselectivity is observed, namely *Re* face attack, to afford the  $\alpha S, \beta R$ -enantiomer. For the sterically more demanding  $\beta$ -*tert*-butyl group in the substrate **2i** (entry 11), an ee value as high as 75% has been achieved, which represents a substantial improvement in the *Re*-face stereocontrol.

When the epoxidation of substrate **2a** was carried out with DBU as organic base (entry 3), compared to the inorganic base KOH (entry 1), the ee value is reduced from 51 to 9%, and even the opposite enantiomer is favored. Evidently, the potassium metal ion is important for the high enantio-control, and to substantiate this, the reaction with KOH was performed in the presence of 18-crown-6 ether as chelating agent under otherwise identical reaction conditions. It is mechanistically noteworthy that in the epoxidation of the  $\beta$ -phenyl enone **2a** (entry 2), and even more so, the *tert*-butyl one **2i** (entry 12), the enantioselectivity was almost negligible in the presence of 18-crown-6 ether. As anticipated, the potassium ion is playing a pivotal role in generating preferentially the  $(\alpha S, \beta R)$ -epoxides **3**, that is, the potassium ion steers the *Re*-face attack on the enone (Scheme 2). The  $\beta$ -*tert*-butyl-substituted enone **2i** has been chosen as the substrate in Scheme 2 because it displays the highest ee value of the derivatives in Table 1 discussed as far and, thus, the pertinent steric interactions are most pronounced, which facilitates their illustration.

What is the electronic and structural nature of this metal-ion steering effect? It is the simultaneous coordination (*template effect*) of the metal ion to the lone pair of the carbonyl oxygen atom in the enone **2a** and the distal oxygen atom of the peroxide functionality of the *S*-(-)-**1** hydroperoxide, which presumably governs the  $\pi$ -facial differentiation. For effective nucleophilic

oxygen-atom transfer from the  $K^+$ -coordinated peroxide anion to the  $\beta$  carbon atom of the  $K^+$ -ligated enone substrate, the latter must assume a *S-cis* conformation. But this does not suffice, because an additional structural requirement is that during the oxygen-atom transfer the energetically favored 90–120° dihedral angle of the peroxide bond should be fulfilled,<sup>12</sup> as exhibited in the transition structures of Scheme 2. The pertinent steric interactions that ensue in these geometrical arrangements are between the substituents of the hydroperoxide chirality center and the  $\beta$ -*tert*-butyl group of the enone **2i** substrate in the  $K^+$ -coordinated template. The sterically largest group, namely the phenyl one, needs to point away (outward of the paper plane), which brings either the hydrogen atom (*Re*-face attack) or the methyl group (*Si*-face attack) in close proximity of the *tert*-butyl group at the reaction center (the  $\beta$  carbon atom of the enone substrate). Evidently, oxygen transfer from the *Re* face is energetically preferred and the  $\alpha S, \beta R$ -epoxide enantiomer formed predominantly, as is observed experimentally (Table 1). Complexation of the  $K^+$  ion by the crown ether (entries 2 and 12) destroys the template effect, and enantio-control breaks down. Alternatively, for the organic base DBU (entry 3), a template is not possible and again low enantioselectivity results.

One structural feature in the transition state in Scheme 2 may be controlled at will, namely the *S-cis* conformation of the enone, by selecting a substrate in which this arrangement is rigidly fixed. For this purpose, the cyclic derivative **2j** (entry 13) with an exomethylene substituent was chosen. Gratifyingly, an ee value as high as 90% was achieved for the  $(\alpha S, \beta R)$ -epoxide **3i** (*Re*-face attack). This is the highest enantioselectivity ever obtained in the asymmetric oxyfunctionalization with optically active hydroperoxides.<sup>2,13</sup> The high enantioselectivity that has been achieved for the rationally designed substrate **2i** validates the mechanistic construct offered in Scheme 2.

In summary, in this novel asymmetric Weitz–Scheffer epoxidation mode, the attack of the optically active hydroperoxide *S*-(-)-**1** on the *Re* face of the *S-cis* conformation of enone **2** has been rationalized in terms of minimized steric repulsions between the substituents at the hydroperoxide chirality center and the enone  $\beta$ -substituent. Responsible for the good enantioselectivity is the simultaneous coordination of the metal ion to the  $\alpha, \beta$ -enone **2** and hydroperoxide *S*-(-)-**1** (template effect). This unprecedented methodology, that is, the direct use of an optically active oxidant, offers attractive opportunities in asymmetric synthesis.

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**Supporting Information Available:** Experimental procedure for the asymmetric epoxidation and conditions for the chiral HPLC analysis of the epoxides **3** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) Kalinowski, H. O. In *Methods of Organic Chemistry (Houben Weyl)*, 4th ed.; Kropf, H., Ed; G. Thieme: Stuttgart, New York, 1995; Vol. E 13, pp 5–24.

(13) Hamann, H.-J.; Hoefl, E.; Mostowicz, D.; Mishnev, A.; Urbanzyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **1997**, *53*, 185–192.