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Enantioselective Epoxidation of Nonconjugated *cis*-Olefins by Chiral Dioxirane

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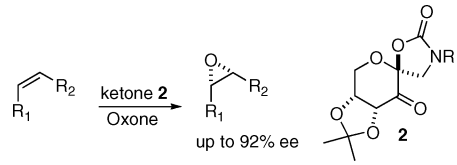
ABSTRACT



A variety of nonconjugated *cis*-olefins has been enantioselectively epoxidized with chiral ketones 2, and up to 92% ee has been obtained. The two prochiral faces of an olefin are likely stereodifferentiated by the relative hydrophobicity of the olefin substituents and/or allylic oxygen functionality.

Chiral ketones have been shown to be effective catalysts for asymmetric epoxidation of olefins.[1] In our own studies, fructose-derived ketone **1** (Figure 1) has been shown to be a very effective catalyst for the epoxidation of *trans*- and trisubstituted olefins.[2] It has also been found that oxazolidinone-bearing ketones **2** can give high ee's for olefins such as conjugated aromatic *cis*-olefins,[3a,c−e,g] conjugated *cis*-dienes,[3k] enynes,[3a,c,l] styrenes,[3b−d,f] and certain trisubstituted[3h,j] and tetrasubstituted olefins.[3i,j,4] For epoxidation of

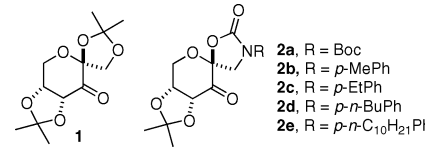


Figure 1. Ketones **1** and **2**.

cis-olefins with ketones **2**, the reacting C−C double bond has usually been conjugated with an aromatic group, an alkene, or an alkyne which directs the enantioselective epoxidation via an apparent attraction with the spiro-oxazolidinone of the ketone catalyst (Figure 2). For asymmetric epoxidation of nonconjugated *cis*-olefins, 67% ee was

(1) For leading reviews, see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (d) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (e) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

(2) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

(3) (a) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (b) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. (c) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. (d) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293. (e) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115. (f) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715. (g) Wong, O. A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973. (h) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429. (i) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455. (j) Wang, B.; Shen, Y.-M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519. (k) Burke, C. P.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4475. (l) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093. (m) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 6320.

(4) For leading reviews on metal-catalyzed asymmetric epoxidation of unfunctionalized olefins, see: (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter *4.2*. (b) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404. (c) Mukaiyama, T. *Aldrichim. Acta* **1996**, *29*, 59. (d) Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000; Chapter *6B*. (e) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563. (f) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603. (g) Barlan, A. U.; Zhang, W.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 6075. (h) Matsumoto, K.; Sawada, Y.; Katsuki, T. *Pure Appl. Chem.* **2008**, *80*, 1071.

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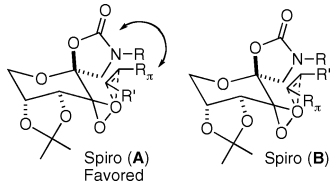
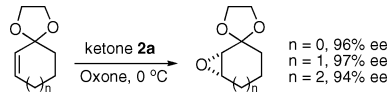


Figure 2. Transition states for the epoxidation with ketone **2**.

obtained for *cis*-1-cyclohexyl-1-propene, and 94−97% ee was obtained for 3,3-ethylenedioxycycloalkenes with ketone **2a** (Scheme 1).[3a,c,5,6] To expand the substrate scope of chiral

Scheme 1



ketone-catalyzed epoxidation of nonconjugated *cis*-olefins and gain better understanding of stereodifferentiation factors, we undertook further investigations on asymmetric epoxidation of this class of olefins with glucose-derived ketones **2**. Herein we report our studies on this subject.

During our studies on asymmetric epoxidation of conjugated *cis*-dienes and enynes with ketones **2**, it became apparent that the relative hydrophobicity of the olefin substituents had a significant effect on enantioselectivity.[3k,l] To further probe this hydrophobic effect on stereodifferentiation, *cis*-2-nonene was epoxidized with ketones bearing different *N*-substituents, giving 44%, 56%, 58%, 64% (Table 1, entry 1), and 54% ee, respectively, for ketones **2a**−**e**.[7] The ee initially increased with increasing length of the *p*-alkyl chain on the aryl ring of catalysts **2b**−**d** (from Me to *n*-Bu) but decreased with further increasing length of the alkyl chain (*n*-$C_{10}H_{21}$) (**2e**). The epoxidations are run in aqueous solvent mixtures, and although the absolute configuration of the epoxide[8a] could not be unambiguously determined yet, the results suggest that the enantioselectivity is likely derived from hydrophobic interactions between the substrate and the catalyst with the hydrophobic *n*-hexyl group of the olefin aligned adjacent to the *N*-aryl group of the catalyst in the transition state (spiro **C** favored over spiro **D**) (Figure 3, X = H, n = 6).

The ee increased when the other substituent on the olefin became more hydrophilic (Table 1, entries 2−5) likely due to spiro **C** being further favored over spiro **D** (Figure 3).[9]

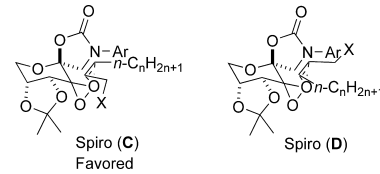


Figure 3. Stereodifferentiation via hydrophobicity.

Up to 91% ee was obtained for *cis*-dec-4-enoic acid (entry 4). For entries 4 and 5, the products were obtained as five- and six-membered lactones, respectively.[10] The lactone in entry 4 is the enantiomer of a natural product isolated from *Streptomyces griseus* and has been the subject of several synthetic investigations.[11] The high enantioselectivity observed for entries 4 and 5 (Table 1) is likely due to the extreme difference in hydrophilicity between the two olefin substituents. The carboxylic acids are presumably deprotonated under the basic reaction conditions to give the corresponding carboxylates which are charged polar groups.

Good ee's can also be obtained for certain allylic ethers (Table 1, entries 6−8). An allylic acetal was a very effective substrate (Table 1, entry 10), but an acyclic allylic ketal (entry 11) was not, in contrast to the cyclic ketals previously studied (Scheme 1). All-carbon analogues of an aromatic ether and a cyclic ketal gave much lower ee's than their oxygen-containing counterparts (Table 1, entries 9 and 12), indicating the oxygen atoms are important for stereodifferentiation. The absolute configurations of the epoxides from 3,3-ethylenedioxycyclohexene (Scheme 1) and the allylic ethers of entries 6 and 8 (Table 1) indicate that ketal and ether substituents prefer to be proximal to the oxazolidinone of **2a** during the transition states (Figure 4) (for methods

(5) For leading references on metal- and enzyme-catalyzed asymmetric epoxidation of nonconjugated *cis*-olefins, see: (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323. (c) Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1994**, 479. (d) Mikame, D.; Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 827. (e) Sawada, Y.; Matsumoto, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4559. (f) Allain, E. J.; Hager, L. P.; Deng, L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 4415.

(6) 94% ee has been obtained for 3,3-ethylenedioxycyclohexene with chiral (salen)Mn(III) catalyst; see refs 5a and 5b.

(7) For a recent report on Ti-catalyzed asymmetric epoxidation of nonactivated *cis*-olefins (70−97% ee), see ref 5e.

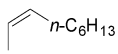
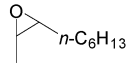
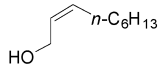
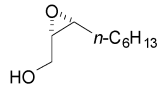
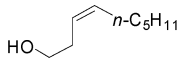
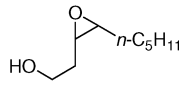
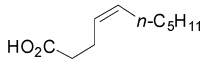
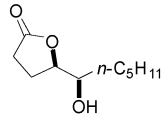
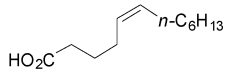
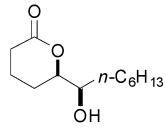
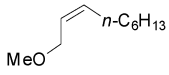
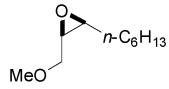
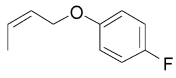
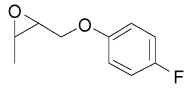
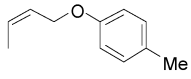
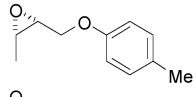
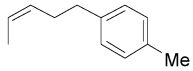
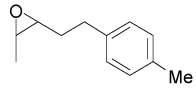
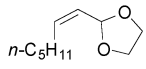
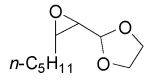
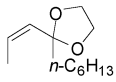
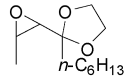
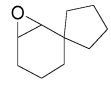
(8) (a) Asami, M.; Kanemaki, N. *Tetrahedron Lett.* **1989**, *30*, 2125. (b) Utaka, M.; Konishi, S.; Takeda, A. *Tetrahedron Lett.* **1986**, *27*, 4737. (c) Zaks, A.; Dodds, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 10419.

(9) For leading references on asymmetric epoxidation of allylic and homoallylic alcohols, see: (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis;* Ojima, I. Ed.; VCH: New York, 2000; Chapter *6A*. (c) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389. (d) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286.

(10) For entry 5, the epoxide did not completely cyclize under the reaction conditions; a mixture of epoxy acid and lactone were isolated from the crude reaction mixture. Refluxing this crude mixture overnight in cyclohexane gave the lactone product in overall 88% yield; see: Ochiai, M.; Ukita, T.; Iwaki, S.; Nagao, Y.; Fujita, E. *J. Org. Chem.* **1989**, *54*, 4832.

(11) For leading references, see: (a) Gräfe, U.; Reinhardt, G.; Schade, W.; Krebs, D.; Eritt, I.; Fleck, W. F.; Hienrich, E.; Radics, L. *J. Antibiot.* **1982**, *35*, 609. (b) Gräfe, U.; Eritt, I. *J. Antibiot.* **1983**, *36*, 1592. (c) Cooper, R. D.; Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1984**, *45*, 5215. (d) Mori, K.; Otsuka, T. *Tetrahedron* **1985**, *41*, 3253. (e) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636. (f) Fujisawa, T.; Kojima, E.; Itoh, T.; Sato, T. *Chem. Lett.* **1985**, 1751. (g) Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417. (h) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407.

Table 1. Asymmetric Epoxidation of Non-conjugated *cis*-Olefins[a]

entry	substrate	product	ketone	temp (°C)	time (h)	yield (%)[b]	ee (%)
1[e]			**2d**	0	8	52	64[d,8]
2			**2d**	-10	8	71	79[e,f,12]
3			**2d**	-10	4	89	82[e,13]
4			**2d**	-10	8	75	91[d,f,11h]
5			**2d**	-10	8	85	86[g,14]
6			**2a**	-10	8	79	61[d,h]
7[i,j,k]			**2a**	-10	12	73	86[d]
8[i,j,k]			**2a**	-10	12	71	85[d,h]
9			**2a**	-10	12	80	32[l]
10[i,j]			**2a**	-10	12	76	92[d]
11[i,j]			**2a**	0	12	39	51[d]
12			**2a**	0	8	87	59[d,5b,15]

[a] For ketone **2d**: unless otherwise stated, all reactions were carried out with olefin (1.0 equiv), catalyst (0.25 equiv), Oxone (1.6 equiv), and K_2CO_3 (6.7 equiv) in DME/DMM (3:1, v/v) and buffer (0.1 M K_2CO_3−AcOH in 4×10^{-4} M aq EDTA, pH 9.3) (1.5:1, v/v). For ketone **2a**: unless otherwise stated, all reactions were carried out with olefin (1.0 equiv), catalyst (0.25 equiv), Oxone (1.6 equiv), and K_2CO_3 (3.8 equiv) in DME/DMM/*n*-BuOH (3:1:2, v/v/v) and buffer (0.1 M K_2CO_3−AcOH in 4×10^{-4} M aq EDTA, pH 8.0) (4:1, v/v). In both cases, Oxone and K_2CO_3 were added separately and simultaneously over the time and temperature specified. [b] Isolated yield. [c] DME was used as solvent. [d] The ee was determined by chiral GC (Chiraldex B-DM column). [e] The ee was determined by chiral GC (Chiraldex B-DM column) of the methyl ether derivative. [f] Absolute stereochemistry was determined by comparing the optical rotation of the epoxide or its derivate with the reported one. [g] Relative stereochemistry indicated. The ee was determined by chiral HPLC (Chiralpak AD column) of the benzoate derivative. [h] Absolute stereochemistry was determined by converting a compound of known configuration to the epoxide of interest and comparing the optical rotation and chiral GC elution order. [i] 0.30 equiv catalyst was used. [j] 2.9 equiv of Oxone and 6.9 equiv of K_2CO_3 were used. [k] DME/DMM (3:1, v/v) was used as solvent; the solvent/buffer ratio was 1.5:1 (v/v). [l] The ee was determined by chiral HPLC (Chiralcel OD column).

used to determine absolute configuration, see the Supporting Information).

All these results suggest that there are two main mechanisms of stereodifferentiation operating for these olefins. For substrates in entries 1−5 (Table 1), the relative hydrophobicity of the olefin substituents is the dominant mechanism of stereodifferentiation, and ketone **2d** is most effective. The second mechanism differentiates substituents that contain an allylic oxygen functionality from those that do not, and ketone **2a** is most effective when this mechanism dominates. In the case of an allylic alcohol (Table 1, entry 2), both mechanisms might be operating in competition with each other. In this case, the free hydroxyl group is apparently hydrophilic enough to override the second mechanism to give the observed epoxide configuration. Based purely on hydrophobic considerations, *cis*-3-nonen-1-ol (Table 1, entry 3) would be expected to give lower ee than *cis*-2-nonen-1-ol (entry 2) since the alkyl substituent is one carbon shorter

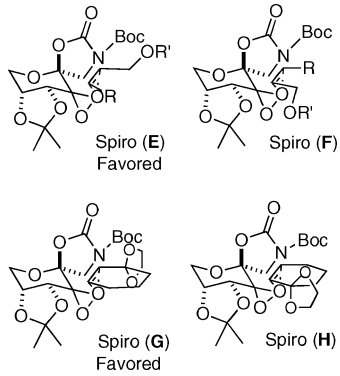


Figure 4. Transition states for ether/ketal-containing olefins.

and the alcohol substituent is one carbon longer. However, higher ee is observed (82% vs 79% ee). This result indicates that the apparent attraction between oxygen-containing functionality and the oxazolidinone of the catalyst is significantly weakened when the oxygen-containing functionality is not in the allylic position.

Entry 6 is another case where both mechanisms of stereodifferentiation appear to be operating in competition with each other. However, in this case, the methyl ether substituent is not hydrophilic enough to override the apparent ether-oxazolidinone attraction with ketone **2a**, so the (2*R*,3*S*) enantiomer predominates. With ketone **2c** hydrophobic properties again dominate, but only slightly, giving 14% ee of the (2*S*,3*R*) enantiomer.[16] The high enantioselectivity observed in the epoxidation of the allylic acetal of entry 10 (Table 1) along with the previous observations of high ee with spirocyclic ketals (Scheme 1) indicate that two allylic oxygens on the same side of the olefin create an even stronger apparent attraction to the oxazolidinone of the catalyst than one. The allylic ketal of entry 11 (Table 1) was an ineffective substrate possibly because the olefin is too hindered or because it cannot adopt the optimal conformation for the interaction between the ketal of the olefin and the oxazolidinone of the catalyst due to $A_{1,3}$ strain.

The origin of enantioselectivity for substrates which rely on differences in hydrophobicity of the olefin substituents is fairly straightforward (Figure 3). However, the origin of the apparent attraction for allylic oxygen functionality to the oxazolidinone of the catalyst is not clear, and there are several possible rationales. One possibility is that there is an attraction between the electron lone pairs on the oxygen atoms and a partial or transient positive charge on the oxazolidinone (Figure 5) which would favor spiro **G** (Figures 4 and 5). Another possibility is that repulsion exists between the electron lone pairs of the oxygen atoms of the substrate and the fused ketal of the catalyst in spiro **H**, thus disfavoring this transition state. A better understanding awaits further studies.

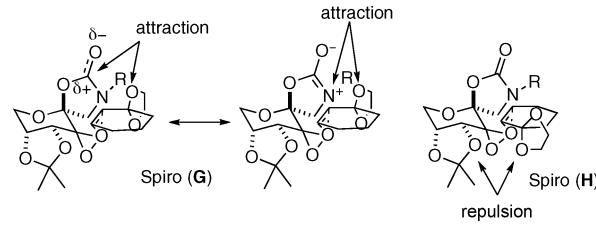


Figure 5. Possible electronic interactions in transition states.

In summary, the scope of the ketone-catalyzed asymmetric epoxidation reaction has been expanded to include several types of nonconjugated *cis*-olefins, and good to high ee's have been obtained for a number of substrates. If the two substituents of nonconjugated *cis*-olefins have substantially different hydrophobic or electronic properties, this system could provide a good opportunity for asymmetric induction. This study opens up a new avenue for this system that will be valuable for further studies and designing new ketone catalysts in the future.

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Supporting Information Available: Synthesis and characterization of olefins and epoxides, as well as the data for the determination of the enantiomeric excess and the NMR spectra of the epoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) It was found that ketone **2a** was the most effective catalyst. No ee was obtained with ketone **2b**, and 14% ee of the opposite enantiomer was obtained with ketone **2c** for *cis*-1-methoxy-2-nonene using DME/DMM (3:1, v/v) as solvent.