Highly Enantioselective Epoxidation of *trans*-Stilbenes Catalyzed by Chiral Ketones

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Catalytic asymmetric epoxidation of unfunctionalized olefins has been a great challenge in organic synthesis.[1] For *cis*-olefins,[2] trisubstituted olefins,[2d,3] tetrasubstituted olefins,[4] and styrenes,[2d,5] highly enantioselective catalysts based on metal−oxo complexes have been developed. However, there is no general and effective method available for catalytic asymmetric epoxidation of *trans*-olefins.[6,7] Here, we report on a series of novel chiral ketone catalysts that give the highest enantioselectivities reported to date for epoxidation of *trans*-stilbenes. In addition, using chiral ketones as probes, we provide convincing experimental evidence for a spiro transition state of dioxirane epoxidation.[8]

We recently reported that C_2 symmetric chiral dioxirane **1a**, generated *in situ* from chiral ketone **1** and Oxone, is selective for asymmetric epoxidation of *trans*-olefins and trisubstituted olefins (33−87% ee).[7] The X-ray structure of ketone **1** revealed that the two naphthalene rings were located on the opposite faces of the keto group.[7] As shown in Figure 1, H-3 and H-3′ are closer to the dioxirane group than other atoms on the chiral binaphthalene unit and may therefore be the steric sensors in the oxygen transfer process.[9,10] We expected that, by increasing steric bulkiness at the 3 and 3′ positions, the resulting chiral ketones would have better enantioselectivity than ketone **1**.[11] New chiral ketones **2**−**8** were thus designed and synthesized.[12]

The results for asymmetric epoxidation of *trans*-stilbene with catalysts **1**−**8** (10 mol %) are summarized in Table 1. Several trends were observed. (1) As the size of the steric sensor became larger (from H to Cl to Br to I, see entries 1−4; from H to Me to MOM to acetal to TMS, see entries 1 and 5−8), enantioselectivity was first increased and then decreased. This implies that ketones with the appropriate size of steric sensor are desirable. (2) While Cl is smaller in size than Me, higher ee was obtained with chloro ketone **2** than methyl ketone **5**, which suggests that the presence of electronegative atoms on the steric sensor is also important. (3) Among ketones **1**−**8**, acetal ketone **7** was found to be the most reactive one.

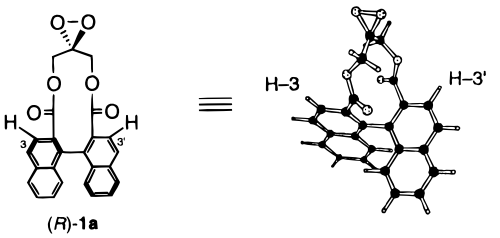
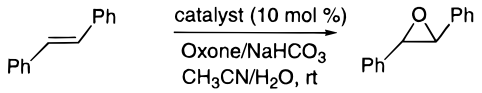


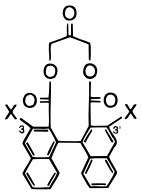
Figure 1.

Table 1. Asymmetric Epoxidation of *trans*-Stilbene with Catalysts **1**−**8**[a]



entry	catalyst[b]	reaction time	epoxide yield (%)[c]	epoxide confign[d]	ee (%)[e]
1	(*R*)-**1**	1 h	91	(−)-(*S*,*S*)	47
2	(*R*)-**2**	2 h	95	(−)-(*S*,*S*)	76
3	(*R*)-**3**	3 h	92	(−)-(*S*,*S*)	75
4	(*R*)-**4**	22 h	90[f]	(−)-(*S*,*S*)	32
5	(*S*)-**5**	1 h	93	(+)-(*R*,*R*)	56
6	(*R*)-**6**	1.8 h	92	(−)-(*S*,*S*)	66
7	(*R*)-**7**	0.7 h	95	(−)-(*S*,*S*)	71
8	(*S*)-**8**	20 h	nc[g]	(+)-(*R*,*R*)	44

[a] All epoxidation reactions were carried out at room temperature with 0.1 mmol of *trans*-stilbene, 0.01 mmol of catalyst, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, and 1 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [b] Optical purity: 98% ee. All chiral ketones were recovered in over 80% yield without loss of catalytic activity and chiral induction. [c] Isolated yield. [d] Determined by circular dichroism spectroscopy. [e] Determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$. [f] Yield based on recovered *trans*-stilbene (50% conversion). [g] Not completed.



1 X = H **5** X = Me

2 X = Cl **6** X = CH_2OCH_3

3 X = Br **7** X = 

4 X = I **8** X = $SiMe_3$

It is interesting to note that *trans*-stilbene has a phenyl group and a hydrogen atom on one side of the double bond. When encountering *trans*-stilbene, C_2 symmetric chiral dioxirane (*R*)-**1a** has two possible orientations (favored and disfavored based on steric considerations) under either a spiro or a planar transition state (Figure 2).[13,14] The favored orientation has the phenyl group of *trans*-stilbene positioned away from the naphthalene rings of the dioxirane. When the steric sensors at the 3 and 3′ positions become larger up to certain size (e.g., from H to Br), there is little increase of steric interaction in the favored orientation, whereas steric interaction is significantly increased in the disfavored orientation, thereby giving higher enantioselectivity.[15] However, when the steric sensors become

(1) For recent reviews on catalytic 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.

(2) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055. (c) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320. (d) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457. (e) Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055. (f) Hosoya, N.; Hatayama, A.; Irie, R.; Sasaki, H.; Katsuki, T. *Tetrahedron* **1994**, *50*, 4311.

(3) (a) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378. (b) Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197.

(4) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123.

(5) (a) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333. (b) Naruta, Y.; Ishihara, N.; Tani, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 158.

(6) (a) Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533. (b) Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939. (c) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937. (d) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489. (e) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004.

(7) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491.

(8) For excellent reviews on dioxirane chemistry, see: (a) Adam, W.; Curci, R.; Edward, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.

(9) In the X-ray structure of ketone **1**, the distance between H−3 or H−3′ and the keto group is ca. 5 Å, approximately the length of a phenyl ring.

(10) The structure of chiral dioxirane (*R*)-**1a** was created using the Chem 3D program on the basis of the coordinates from the X-ray structure of ketone **1**.

(11) When the C_2 symmetric chiral element was changed from 1,1′-binaphthyl-2,2′-dicarboxylic acid to 6,6′-dinitro-2,2′-diphenic acid, similar ee values were observed. Unpublished results.

(12) All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, HRMS, and LRMS (see Supporting information).

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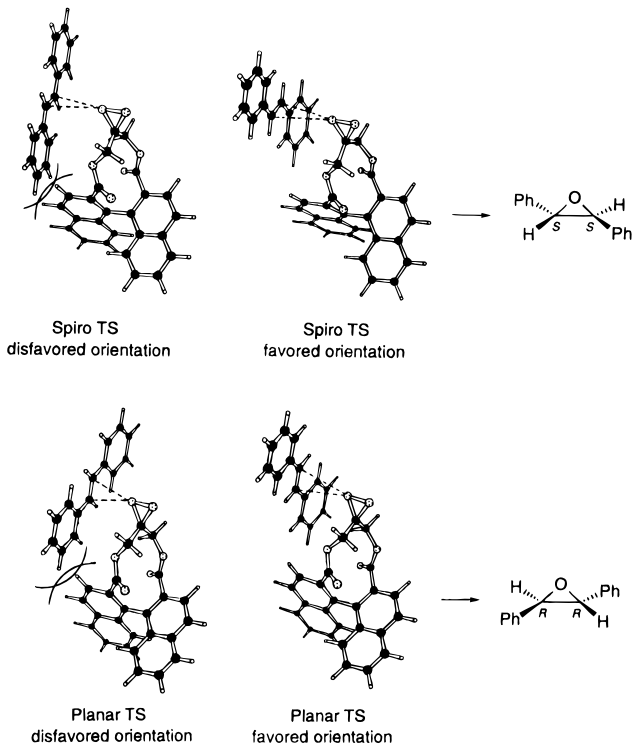
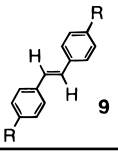


Figure 2.

even larger (e.g., from Br to I), the nonbonded steric interaction is increased significantly in the favored as well as the disfavored orientations, resulting in lower enantioselectivity and slower epoxidation.

As effective chiral catalysts for asymmetric epoxidation, ketones **2**, **3**, and **7** can be used as probes to address an important question of whether dioxirane epoxidation follows a spiro or a planar transition state (TS).[13] As illustrated in Figure 2, with (*R*)-ketones as catalysts, (*S*,*S*)-epoxides of *trans*-stilbenes are expected to be the major products under a spiro TS, whereas (*R*,*R*)-epoxides are expected under a planar TS. Results summarized in Table 2 show that enantiomerically enriched (*S*,*S*)-epoxides of *trans*-stilbenes were formed with catalysts (*R*)-**2**, (*R*)-**3**, and (*R*)-**7**, which is consistent with a spiro TS. In addition, docking experiments using the MacroModel program[16] suggest that the steric sensors recognize the *meta*/*para* positions of *trans*-stilbene under a spiro TS but the *ortho*/*meta* positions under a planar TS (Figure 2). It is interesting to observe that, when the *para* substituents of *trans*-stilbenes **9a**−**e** became larger (from H to Me to Et to *i*-Pr to *t*-Bu), higher ee values were obtained with ketones (*R*)-**2**, (*R*)-**3**, and (*R*)-**7** as catalysts (Table 2). This again lends support to a spiro TS.

Table 2. Asymmetric Epoxidation of *trans*-Stilbenes **9a**−**e** by Catalysts **2**, **3**, and **7**[a]



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		ee (%)[b]			
entry	Substrate	(*R*)-**2**[c,d]	(*R*)-**3**[c,d]	(*R*)-**7**[c,e]	(*R*)-**7**[f,g]
1	**9a** (R = H)	76	75	71	84
2	**9b** (R = Me)	80	85	84	88
3	**9c** (R = Et)	85	88	82	91
4	**9d** (R = *i*-Pr)	85	90	88	91
5	**9e** (R = *t*-Bu)	91	93	90	95

[a] Optical purity: 98% ee. [b] Determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$. The reaction products isolated in over 90% yield were predominently the (−)-(*S*,*S*)-epoxides. [c] Condition A: room temperature, 0.1 mmol of substrate, 0.01 mmol of catalyst, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, and 1 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [d] Completed in 2−3 h. [e] Completed in 40 min. [f] Condition B: 0 °C, 0.1 mmol of substrate, 0.01 mmol of catalyst, 1 mmol of Oxone, 3.1 mmol of $NaHCO_3$, 1.5 mL of DME, and 1 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [g] Completed in 20 h.

We also discovered that, when epoxidation was carried out in an aqueous DME (1,2-dimethoxyethane) solution at 0 °C, further increases in ee (up to 13%) were obtained (Table 2). Most significantly, with ketone (*R*)-**7** as the catalyst, 84−95% ee values were achieved for epoxides of *trans*-stilbenes **9a**−**e**.[17] To our knowledge, this represents the highest ee for direct epoxidation of unfunctionalized *trans*-olefins by any synthetic catalyst.[18]

In summary, due to their unique geometry, C_2 symmetric chiral ketones are excellent catalysts for asymmetric epoxidation of *trans*-olefins. With better understanding of the transition state geometry of dioxirane epoxidation, future work should be directed at developing chiral ketone catalysts that recognize other substituents of *trans*-olefins and trisubstituted olefins.

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Supporting Information Available: Experimental details for catalytic asymmetric epoxidation reactions; preparation of ketones **2**, **3**, and **7**; characterization data of ketones **2**−**8** and *trans*-stilbenes and their epoxides; assignment of absolute configurations of epoxides; determination of enantiomeric excess of epoxides; and stereoviews of favored and disfavored orientations of both spiro and planar transition states (24 pages). See any current masthead page for ordering and Internet access instructions.

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(13) Baumstark *et al*. proposed a spiro TS rather than a planar TS for dioxirane epoxidation on the basis of the observation that certain *cis*-dialkyl alkenes were ca. 7−10 times more reactive than their *trans*-isomers. However, for phenyl-substituted alkenes, certain *trans*-isomers were slightly more reactive than *cis*-isomers. (a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311. (b) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437. (c) Baumstark, A. L.; Harden, D. B. *J. Org. Chem.* **1993**, *58*, 7615. For computational studies on dioxirane epoxidation, see: (d) Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207.

(14) Stereoviews of the favored and disfavored orientations for both spiro TS and planar TS are provided as Supporting Information.

(15) The higher enantioselectivity observed for chloro ketone **2** compared to methyl ketone **5** may be attributed to the unfavorable n−π repulsive electronic interaction between the Cl atom and the phenyl rings of *trans*-stilbene in the disfavored orientation. See also: Homada, T.; Irie, R.; Katsuki, T. *Synlett* **1994**, 479.

(16) MacroModel version 4.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(17) Although giving similar enantioselectivities, ketones (*R*)-**2** and (*R*)-**3** were less reactive than (*R*)-**7** at 0 °C.

(18) For highly enantioselective epoxidation of α,β-unsaturated ketones such as *trans*-chalcones, see: Juliá, S.; Masana, J.; Vega, C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929.