Design and Synthesis of Chiral Ketones for Catalytic Asymmetric Epoxidation of Unfunctionalized Olefins

Dan Yang,* Man-Kin Wong, Yiu-Chung Yip, Xue-Chao Wang, Man-Wai Tang, Jian-Hua Zheng, and Kung-Kai Cheung

Contribution from the Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

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Abstract: A series of C_2 symmetric chiral ketones were designed and synthesized for catalytic asymmetric epoxidation of unfunctionalized olefins. Among those ketones screened, (*R*)-**7**, (*R*)-**9**, and (*R*)-**10** were found to be highly efficient catalysts for epoxidation of *trans*-stilbenes with enantioselectivities in the range of 84−95%. Convincing evidence was provided for a spiro transition state of dioxirane epoxidation. Through the ^{18}O-labeling experiment, chiral dioxiranes were found to be the intermediates in chiral ketone catalyzed epoxidation reactions.

Introduction

Catalytic asymmetric epoxidation of unfunctionalized olefins has attracted a lot of attention for two reasons. First, chiral epoxides are important building blocks for natural product synthesis. Second, asymmetric induction based on molecular recognition of olefin substitution patterns has been a particularly challenging problem for modern organic chemistry.[1] In the past several years substantial progress has been made in developing catalysts for asymmetric epoxidation of a broad range of unfunctionalized olefins. The most notable catalysts include chiral Mn-salen complexes,[2−5] metalloporphyrins,[6] and biocatalysts.[7]

We have initiated a program using chiral dioxiranes for asymmetric epoxidation of unfunctionalized olefins. Dioxiranes

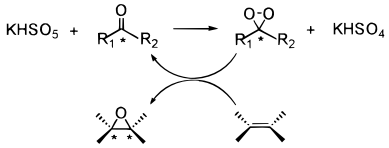

Figure 1.

are powerful organic oxidants under mild and neutral conditions.[8] Epoxidation mediated by dioxiranes is stereospecific and highly efficient toward both electron-rich[9] and electron-deficient olefins.[10] Furthermore, dioxirane epoxidation can be a catalytic process as dioxiranes can be generated *in situ* from ketones and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).[11] Therefore, chiral ketones[12−16] are expected to be catalysts for asymmetric epoxidation (Figure 1). In 1984, Curci *et al.* reported the first asymmetric epoxidation of olefins catalyzed by chiral ketones (up to 20% ee for *trans*-β-methylstyrene epoxide).[12]

Recently, we reported an efficient epoxidation protocol that used *in situ* generated methyl(trifluoromethyl)dioxirane in a

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(3) For highly enantioselective epoxidation of trisubstituted olefins using chiral Mn-salen catalysts, see: (a) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378. (b) Fukada, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197.

(4) For highly enantioselective epoxidation of tetrasubstituted olefins using chiral Mn-salen catalysts, see: Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123.

(5) For highly enantioselective, low-temperature epoxidation of styrene using chiral Mn-salen catalysts, see: Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.

(6) For asymmetric epoxidation of unfunctionalized olefins using chiral metalloporphyrins, see: (a) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (b) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (c) Collman, J. P.; Lee, V. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1993**, *115*, 3834. (d) Collman, J. P.; Lee, V. J.; Kellen-Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, *117*, 692. (e) Naruta, Y.; Ishihara, N.; Tani, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 158.

(7) For biological catalysts in asymmetric epoxidation of unfunctionalized olefins, see: (a) Allain, E. J.; Hager, L. P.; Deng, L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 4115. (b) Dexter, A. F.; Lakner, F. J.; Campbell, R. A.; Hager, L. P. *J. Am. Chem. Soc.* **1995**, *117*, 6412. (c) Koch, A.; Reymond, J.; Lerner, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 803.

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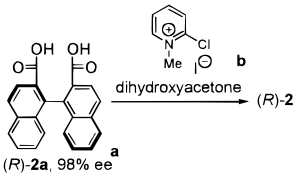
Scheme 1[a]



[a] (**a**) Preparation: see ref 21; (**b**) Et_3N, CH_3CN, reflux, 12 h, 25%.

homogeneous acetonitrile−water solvent system under neutral reaction conditions.[17] This simple protocol allowed us to perform catalytic asymmetric epoxidation with various chiral ketones. In particular, we focused on developing C_2 symmetric chiral ketones. Herein we report the preparation of a series of novel C_2 symmetric chiral ketones and their activities in catalytic asymmetric epoxidations. A portion of this work was published earlier.[18,19]

Results and Discussion

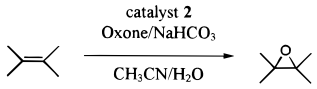
I. Rational Design of Binap Ketone 2 for Catalytic Asymmetric Epoxidation of Unfunctionalized Olefins. In our screening for efficient ketone catalysts,[20] cyclic ketone **1** was found to have high activity in catalytic epoxidation of olefins by Oxone, and therefore became an ideal template for introduction of chiral elements. Since ketones with chiral centers at α positions are prone to racemization, we chose to put the C_2 symmetric chiral element away from the catalytic center (i.e., the keto group). Therefore, a C_2 symmetric, 11-membered-ring chiral ketone **2** was designed when the diphenic unit of ketone **1** was replaced by a chiral binaphthalene unit. This C_2 symmetric chiral ketone was found to be a promising catalyst for asymmetric epoxidation of unfunctionalized *trans*-olefins and trisubstituted olefins.

Preparation of Binap Ketone (*R*)-2. Chiral ketone (*R*)-**2** was synthesized in one step from chiral (*R*)-1,1′-binaphthyl-2,2′-dicarboxylic acid **2a**[21] and 1,3-dihydroxyacetone using 2-chloro-1-methylpyridinium iodide (Mukaiyama reagent) in 20−30% yield[22] (Scheme 1).

Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Ketone (*R*)-2. Results of asymmetric epoxidation of unfunctionalized olefins catalyzed by chiral ketone **2** are summarized in Table 1.

Several interesting features were observed. (1) It is important to note that ketone (*R*)-**2** gave moderate to good enantioselectivities for epoxidation of *trans*-olefins (entries 1−6) and trisubstituted olefins (entry 8−9) but not for *cis*-olefins or terminal olefins (entries 10−12). (2) When the *para* substituents of *trans*-stilbenes became larger (from methyl to ethyl to isopropyl to *tert*-butyl to phenyl), the ee values of *trans*-epoxides increased gradually from 47% to 87% (entries 1−6). (3) When epoxidation of (*E*)-4,4′-diphenylstilbene **20** was catalyzed by ketone (*R*)-**2**, the enantiomerically enriched (*S*,*S*)-epoxide with 87% ee was obtained (entry 6) whereas epoxidation catalyzed by ketone (*S*)-**2** gave enantiomerically enriched (*R*,*R*)-epoxide (entry 7). This suggests that enantiomerically enriched epoxides can be obtained by using ketone catalysts of proper configurations. (4) Ketone **2** was stable under the reaction conditions and can be recovered in over 80% yield by flash column chromatography with Et_3N buffered silica gel and reused without loss of catalytic activity and chiral induction.

Table 1. Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Ketone **2**[a]



entry	catalyst[b]	substrate	time (min)	yield[c] (%)	epoxide confign	epoxide ee[d] (%)
1[e]	(*R*)-**2**	**15**	20	99	(−)-(*S*,*S*)[f]	47
2	(*R*)-**2**	**16**	40	99	(−)-(*S*,*S*)[f]	50
3	(*R*)-**2**	**17**	40	96	(−)-(*S*,*S*)[f]	60
4	(*R*)-**2**	**18**	40	98	(−)-(*S*,*S*)[f]	71
5	(*R*)-**2**	**19**	40	95	(−)-(*S*,*S*)[f]	76
6	(*R*)-**2**[g]	**20**	480	82[h]	(−)-(*S*,*S*)[f]	87
7	(*S*)-**2**[g]	**20**	480	80[h]	(+)-(*R*,*R*)[f]	87
8	(*R*)-**2**	**22**	75	97	(+)-(*S*)[i]	48
9[j]	(*R*)-**2**	**23**	90	83	(−)-(*S*,*S*)[i]	33
10[k]	(*R*)-**2**	**24**	210	70	nd[l]	18
11[k]	(*R*)-**2**	**25**	80	85	nd[l]	<5
12[k]	(*R*)-**2**	**26**	60	83	(−)-(*S*)[m]	18

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.1 mmol of substrate, 0.01 mmol of ketone **2**, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 2.0 mL of CH_3CN, 1.7 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [b] Optical purity: 98% ee. Ketone **2** was recovered in over 80% yield by flash column chromatography with Et_3N buffered silica gel (Merck 230-400 mesh) and reused without loss of catalytic activity and chiral induction. [c] Isolated yield after flash column chromatography. [d] Enantiomeric excess was determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$ (Aldrich catalog no. 16,474-7). [e] 0.1 mmol of substrate, 0.1 mmol of ketone **2**. [f] Determined by circular dichroism spectroscopy. [g] Ketone **2** was not recovered. [h] Isolated yield after washing with CH_2Cl_2 (see experimental section). [i] Reference 3a. [j] 0.5 mmol of substrate, 0.1 mmol of ketone **2**. [k] 0.2 mmol of substrate, 0.1 mmol of ketone **2**. [l] Not determined. [m] Reference 6a.

X-ray analysis revealed that ketone-**2**[18] has a rigid and C_2 symmetric structure: the keto group lies on the C_2 axis of the molecule; the two ester groups, antiparallel to each other, retain the favorable *s-trans* geometry and are nearly perpendicular to the macrocyclic ring plane; and the dihedral angle of the two naphthalene rings is ca. 70°. With the Chem 3D program, the structure of C_2 symmetric chiral dioxirane (*R*)-**2b** was created by using the coordinates of the X-ray structure of ketone **2** (Figure 2). The distance between H-3 or H-3′ and the dioxirane group is ca. 5 Å, which is approximately the length of a phenyl ring. In addition, 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 atom transfer process.

Importance of Ester Groups in Ketone 2. To examine whether the ester groups in the ketone skeleton were essential for chiral induction, a nine-membered-ring cyclic ketone **3**[23] was prepared where the ester groups were replaced by the ether

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(16) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995.

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(20) Manuscript in preparation.

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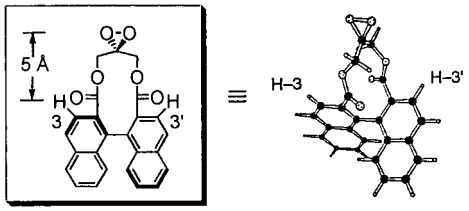
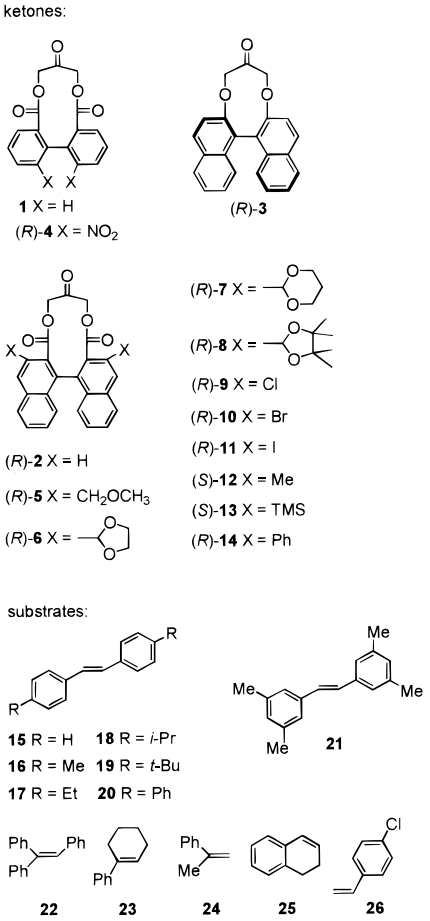


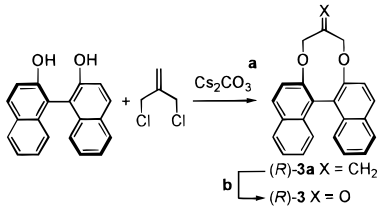
(*R*)-**2b**

Figure 2.

Chart 1



Scheme 2[a]



[a] (**a**) DMF, 60 °C, 12 h; (**b**) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, room temperature, 10 h.

groups. The chiral element used was the commercially available (*R*)-1,1′-bi-2-naphthol (Scheme 2).

The ketone (*R*)-**3** (10 mol %) was examined in asymmetric epoxidation of *trans*-stilbene **15** under the same reaction conditions as that for (*R*)-**2**. It was found that the epoxidation reaction proceeded with 10% conversion (determined by ^{1}H NMR) after 6 h, and the ee value of *trans*-stilbene epoxide was 12%. The poor reactivity of the ketone could be attributed to the fact that an ether group is a weaker electron withdrawing group than an ester group. The X-ray structure of ketone (*R*)-**3** was shown in Figure 3, which suggests a non C_2 symmetric conformation in contrast to that of ketone **2**. The ester groups that gave rigid and C_2 symmetric structures of cyclic ketones seemed to be essential for effective asymmetric epoxidation.

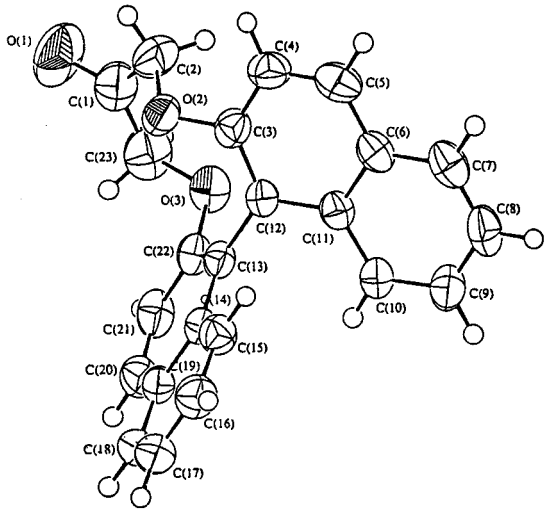


Figure 3. X-ray structure of (*R*)-**3** (ORTEP view).

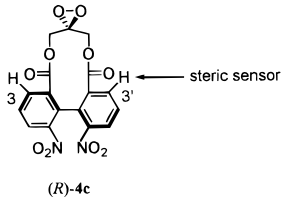


Figure 4.

Effect of Chiral Elements in Ketone 2. To test the effect of chiral elements, a new ketone catalyst (*R*)-**4** was obtained when the C_2 symmetric chiral element was changed from (*R*)-1,1′-binaphthyl-2,2′-dicarboxylic acid to (*R*)-6,6′-dinitro-2,2′-diphenic acid. If the H-3 and H-3′ in the chiral dioxiranes (*R*)-**2b** and (*R*)-**4c** are the steric sensors in the oxygen atom transfer process, (*R*)-**2** and (*R*)-**4** are expected to give similar ee values for epoxidation (Figures 2 and 4).

Optical resolution of 6,6′-dinitro-2,2′-diphenic acid[24] was achieved by the use of (*R*)−(+)-1,1′-bi-2-naphthol (98% ee). Since the (*R*)-form of the binaphthol could only react with the (*R*)-form of dinitrodiphenic acid to form the cyclic diolide (*R*,*R*)-**4b**, the kinetic resolution of racemic diacid took place. Both ^{1}H and ^{13}C NMR spectra showed that only one diastereomer, i.e., diolide (*R*,*R*)-**4b**, was formed (31% yield). After a mild basic hydrolysis, (*R*)-6,6′-dinitro-2,2′-diphenic acid (*R*)-**4a** was obtained in quantitative yield with (*R*)−(+)-1,1′-bi-2-naphthol recovered. Ketone (*R*)-**4** was easily prepared in one step from the corresponding diacid (*R*)-**4a** and 1,3-dihydroxyacetone using the Mukaiyama reagent (22% yield).

As shown in Table 2, similar enantioselectivities were observed for epoxidation catalyzed by ketones (*R*)-**2** and (*R*)-**4**. This confirms that H-3 and H-3′ in both C_2 symmetric dioxiranes

(23) After our experimental work was completed, a report by Song *et al.* appeared on the preparation of ketone (*R*)-**3**. Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S.-g.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921.

(24) Synthesis of 6,6′-dinitro-2,2′-diphenic acid was carried out according to the literature procedures: (a) Whitmore, F. C.; Culhane, P. J.; Neher, H. T. *Organic Syntheses*; Wiley: New York, Collect. Vol. 1; 1976; p 56. (b) Culhane, P. J. *Organic Syntheses*; Wiley: New York, Collect. Vol. 1; 1976; p 125. (c) Ingersoll, A. W.; Little, J. R. *J. Am. Chem. Soc.* **1934**, *56*, 2123. (d) Newman, P.; Rutkin, P.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 465.

Table 2. Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Ketone (*R*)-**2**[a] and (*R*)-**4**[b]

entry	catalyst[c]	substrate	time (min)	yield[d] (%)	epoxide config	ee[e] (%)
1[f]	(*R*)-**2**	**15**	20	99	(−)-(*S*,*S*)[g]	47
2	(*R*)-**4**	**15**	35	94	(−)-(*S*,*S*)[g]	50
3	(*R*)-**2**	**18**	40	98	(−)-(*S*,*S*)[g]	71
4	(*R*)-**4**	**18**	35	94	(−)-(*S*,*S*)[g]	66
5	(*R*)-**2**	**19**	40	95	(−)-(*S*,*S*)[g]	76
6	(*R*)-**4**	**19**	35	91	(−)-(*S*,*S*)[g]	77
7	(*R*)-**2**	**22**	75	97	(+)-(*S*)[h]	48
8	(*R*)-**4**	**22**	60	82	(+)-(*S*)[h]	49

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.1 mmol of substrate, 0.01 mmol of ketone (*R*)-**2**, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 2.0 mL of CH_3CN, 1.7 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [b] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.1 mmol of substrate, 0.01 mmol of ketone (*R*)-**4**, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [c] Optical purity: 98% ee. Ketone (*R*)-**2** and (*R*)-**4** were recovered in over 80% yield by flash column chromatography with Et_3N buffered silica gel (Merck 230−400 mesh). [d] Isolated yield after flash column chromatography. [e] Enantiomeric excess was determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$. [f] 0.1 mmol of substrate, 0.1 mmol of ketone (*R*)-**2**. [g] Determined by circular dichroism spectroscopy. [h] Reference 3a.

Table 3. Effect of Solvent System on the Enantiomeric Excess of (*E*)-4,4′-Di-*tert*-butylstilbene Epoxide **19a**[a]

entry	solvent system	time (h)	yield[b] (%)	epoxide config[c]	ee[d] (%)
1	DME−H_2O	0.5	92	(−)-(*S*,*S*)	77
2	CH_3CN−H_2O[e]	0.7	95	(−)-(*S*,*S*)	76
3	dioxane−H_2O	24	91[f]	(−)-(*S*,*S*)	76
4	THF−H_2O	24	93[g]	(−)-(*S*,*S*)	75

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.1 mmol of (*E*)-4,4′-di-*tert*-butylstilbene **19**, 0.01 mmol of ketone (*R*)-**2**, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of organic solvent, 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [b] Isolated yield after flash column chromatography. [c] Absolute configuration was determined by circular dichroism spectroscopy. [d] Enantiomeric excess was determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$. [e] 2.0 mL of CH_3CN, 1.7 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [f] Yield based on 57% conversion. [g] Yield based on 44% conversion.

(*R*)-**2b** and (*R*)-**4c** are the steric sensors in the oxygen atom transfer process (Figures 2 and 4).

Effect of Solvent System on the Enantiomeric Excess of (*E*)-4,4′-Di-*tert*-butylstilbene Epoxide 19a. To optimize the reaction conditions, asymmetric epoxidation of (*E*)-4,4′-di-*tert*-butylstilbene **19** catalyzed by 10 mol % of ketone (*R*)-**2** was investigated in four solvent systems (CH_3CN−H_2O, DME-H_2O, dioxane−H_2O, THF−H_2O) (Table 3).

Both (*E*)-4,4′-di-*tert*-butylstilbene **19** and ketone (*R*)-**2** were completely soluble in the four solvent systems. The time for complete epoxidation was 30 min in the homogeneous DME−H_2O solvent system, even shorter than that required in the CH_3CN−H_2O system (ca. 45 min). It seems that there is no appreciable change in the ee values of *trans*-epoxide **19a** in the four solvent systems. This suggests that the ketone catalyst recognizes various olefin substitution patterns entirely through the nonbonded steric interactions.

Effect of Reaction Temperature on the Enantiomeric Excess of (*E*)-4,4′-Di-*tert*-butylstilbene Epoxide 19a. Asymmetric epoxidation of (*E*)-4,4′-di-*tert*-butylstilbene **19** catalyzed by 10 mol % of ketone (*R*)-**2** in DME−H_2O solvent system was carried out at different temperatures (Table 4).

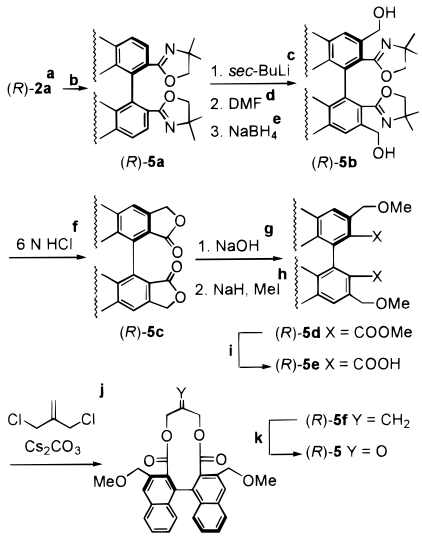
When the reaction temperature was decreased from 25 to −20 °C, the ee values of *trans*-epoxide **19a** increased from 77% to 84%. However, the isolated yield of *trans*-epoxide **19a** at −20 °C was only 2% (entry 3) with 95% of recovery of the starting material. It seemed that the most suitable reaction temperature was 0 °C at which both excellent yield (91%) and high ee value (83%) of *trans*-epoxide **19a** were achieved (entry 2).

Table 4. Effect of Reaction Temperature on the Enantiomeric Excess of (*E*)-4,4′-Di-*tert*-butylstilbene Epoxide **19a**[a]

entry	temp (°C)	time	yield[b] (%)	epoxide config[c]	ee[d] (%)
1	25	45 min	97	(−)-(*S*,*S*)	77
2	0[e]	20 h	91	(−)-(*S*,*S*)	83
3	−20[e]	20 h	2[f]	(−)-(*S*,*S*)	84

[a] Unless otherwise indicated, reaction conditions were as follows: 0.1 mmol of (*E*)-4,4′-di-*tert*-butylstilbene **19**, 0.01 mmol of ketone (*R*)-**2**, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of DME, 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [b] Isolated yield after flash column chromatography. [c] Absolute configuration was determined by circular dichroism spectroscopy. [d] Enantiomeric excess was determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$. [e] 1.0 mmol of Oxone and 3.1 mmol of $NaHCO_3$ were used. [f] Substrate **19** was recovered in 95%.

Scheme 3. Synthetic Pathway of Ketone (*R*)-**5**[a]



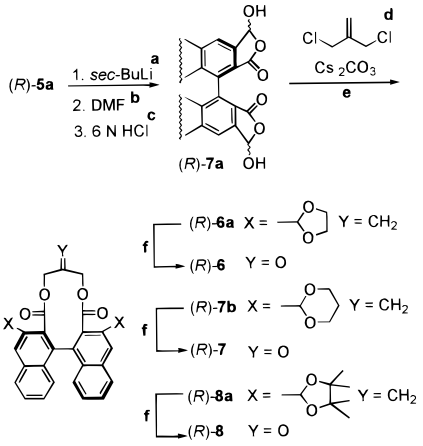
[a] (**a**) Preparation: see ref 21; (**b**) oxalyl chloride, catalyst DMF, CH_2Cl_2, room temperature, 1.5 h; 2-amino-2-methyl-1-propanol, CH_2Cl_2, room temperature, $SOCl_2$, CH_2Cl_2, room temperature, 6 h; (**c**) TMEDA, THF, −78 °C, 1 h; (**d**) −78 °C; 3 h; (**e**) MeOH, room temperature, 20 h; (**f**) reflux; (**g**) MeOH, reflux; (**h**) DMF, room temperature, 1 h; (**i**) 10% NaOH, MeOH, reflux; (**j**) DMF, 90 °C, 8 h; (**k**) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 0 °C, 1 h.

II. Design and Synthesis of Ketone Catalysts with Larger Sensor Groups. From structural analysis of (*R*)-**2b** (Figure 2), we expected that, by replacing the H-3 and H-3′ of the binaphthyl unit with sterically bulky substituents, the resulting chiral ketones would give better enantioselectivities than ketone **2**.

Preparation of Bis-MOM Ketone (*R*)-5. As shown in Scheme 3, binap bisoxazoline (*R*)-**5a** was prepared from (*R*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (*R*)-**2a** according to literature procedure.[25] Hydroxymethyl groups were introduced by the *ortho*-directed lithiation, followed by quenching with DMF and reduction with $NaBH_4$ to afford (*R*)-**5b**.[26] The bislactone (*R*)-**5c** obtained after acidic hydrolysis (95% yield) was converted to the diester (*R*)-**5d** (76% yield) which gave the *ortho*-substituted carboxylic acid (*R*)-**5e** (80% yield) after basic hydrolysis. However, cyclization with Mukaiyama reagent failed to give ketone (*R*)-**5**. An alternative approach was taken.

(25) Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010.
(26) Meyers, A. I.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881.

Scheme 4. Synthetic Pathways of Ketones (*R*)-**6**−**8**[a]



[a] (**a**) TMEDA, THF, −78 °C, 1 h; (**b**) −78 °C to room temperature, 4 h; (**c**) reflux; (**d**) DMF, 45 °C, 8 h; (**e**) 1,2-ethanediol for (*R*)-**6a**; 1,3-propanediol for (*R*)-**7b**; pinacol for (*R*)-**8a**; catalyst *p*-TsOH, benzene; (**f**) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, room temperature.

Treatment of (*R*)-**5e** with 3-chloro-2-chloromethyl-1-propene and cesium carbonate in DMF[27] at 95 °C for 24 h gave (*R*)-**5f** as a single product (25% yield). The oxidative cleavage of (*R*)-**5f** was achieved using the conditions reported by Sharpless *et al.* (30% yield).[28]

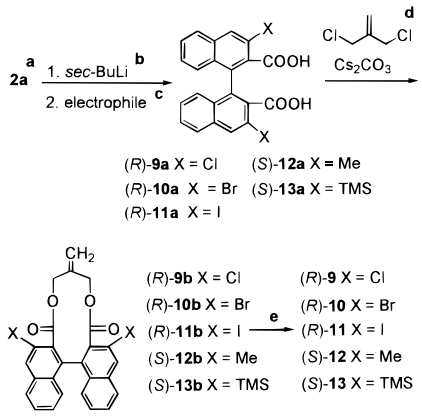
Preparation of Diacetal Ketones (*R*)-6−8. Dilithiation of (*R*)-**5a** using *sec*-BuLi/TMEDA in THF at −78 °C for 1 h followed by addition of DMF and treatment with 6 N HCl afforded the hydroxylactone (*R*)-**7a** in 51% yield (Scheme 4). Cyclization of (*R*)-**7a** with 3-chloro-2-chloromethyl-1-propene in the presence of Cs_2CO_3 in DMF at 45 °C for 8 h and protection with the corresponding diols afforded (*R*)-**6a**, **7b**, and **8a** (23−35% yield). Using the Sharpless procedure, cleavage of (*R*)-**6a**, **7b**, and **8a** with $RuCl_3/NaIO_4$ gave ketones (*R*)-**6**−**8** after flash column chromatography (23−59% yield).

Preparation of Ketones 9−14. We found it difficult to introduce other *ortho*-substituents using the synthetic schemes outlined above, because the hindered oxazolines could not be cleaved without the assistance of a neighboring hydroxyl group.

Recently, Jacques Mortier *et al*. reported the use of carboxylic acid group as an effective director for *ortho*-lithiation.[29] This immediately drew our attention to the possibility of using carboxylic acid group as an *ortho*-metalation directing group in our ketone synthesis. We found the resulting synthetic scheme for the ketone catalysts **9**−**13** more efficient and convergent (Scheme 5).

1,1′-Binaphthyl-2,2′-dicarboxylic acid **2a** ((*R*)-**2a** for ketones (*R*)-**9**, (*R*)-**10**, and (*R*)-**11**; (*S*)-**2a** for ketones (*S*)-**12** and (*S*)-**13**) was treated with *sec*-BuLi/TMEDA in THF at −90 °C and quenched with the corresponding electrophiles. The *ortho*-substituted carboxylic acids **9a**−**13a** were coupled with 3-chloro-2-chloromethyl-1-propene in the presence of cesium carbonate in DMF at 95−100 °C. Oxidative cleavage of **9b**−**13b** to ketones **9**−**13** was carried out successfully. On the other hand, ketone (*R*)-**14** was synthesized in 59% yield from (*R*)-**11** by cross-coupling with phenyl boric acid in the presence of Pd-$(PPh_3)_4$ and K_3PO_4 in DMF.[30]

Scheme 5. Synthetic Pathways of Ketones **9**−**13**[a]



[a] (**a**)Preparation: see ref 21; (**b**) TMEDA, THF, −90 °C; (**c**) hexachloroethane for (*R*)-**9a**; 2,4,4,6-tetrabromo-2,5-cyclohexadienone for (*R*)-**10a**; 1,2-diiodoethane for (*R*)-**11a**; MeI for (*S*)-**12a**; TMSCl for (*S*)-**13a**; −78 °C to room temperature; (**d**) DMF, 90−100 °C; (**e**) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, room temperature.

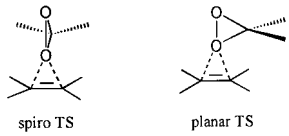


Figure 5.

Chiral Ketones as Probes for Transition State of Dioxirane Epoxidation: Evidence for a Spiro Transition State. While dioxirane epoxidation follows a concerted and stereospecific pathway, there are two extreme transition states, i.e., spiro and planar (Figure 5). Baumstark *et al.* proposed a spiro TS rather than a planar TS for dioxirane epoxidation based on the observation that certain *cis*-dialkyl alkenes were ca. 7−10 times more reactive than their *trans*-isomers.[31] However, for phenyl-substituted alkenes, certain *trans*-isomers were slightly more reactive than *cis*-isomers. Besides, computational studies by Bach *et al.*[32] and Houk *et al.*[33] showed that the optimized transition state for oxygen atom transfer from dioxirane to ethylene was spiro.

The 10 new chiral ketones **5**−**14** were therefore used as probes to address the question of whether dioxirane epoxidation follows a spiro or a planar transition state. Epoxidation results obtained using ketones **5**−**14** are summarized in Table 5 in comparison with that of ketone (*R*)-**2**.

Several interesting trends are observed. (1) As the size of the steric sensor X became larger (from H to Cl to Br to I, see entries 1−4; from H to Me to MOM to acetal to Ph to TMS, see entries 5−9; and also see entries 10−12), enantioselectivity first increased and then decreased. This means that ketones with steric sensors of appropriate sizes are desirable. (2) While Cl is smaller in size than Me, higher ee was obtained with chloro ketone **9** than methyl ketone **12**, which suggests that the presence of electronegative atoms on the steric sensors is also important. (3) With (*R*)-ketones as catalysts, (*S*,*S*)-epoxides of *trans*-stilbenes were obtained as the major enantiomers.

Note that *trans*-stilbene **15** has a large phenyl group and a small hydrogen atom on one side of the double bond. When

(27) (a) Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1976**, *41*, 1373. (b) Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I. D. *J. Org. Chem.* **1977**, *42*, 1286.

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(29) Mortier, J.; Moyroud, J. *J. Org. Chem.* **1994**, *59*, 4042.

(30) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

(31) (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.

(32) Bach, R. D.; Andres, J. L.; Su, M.-D.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5768.

(33) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147.

Table 5. Asymmetric Epoxidation of *trans*-Stilbene **15**[a] Catalyzed by Ketones **2** and **5**−**14**

entry	catalyst[b]	time (h)	yield[c] (%)	epoxide config[d]	ee[e] (%)
1[f]	(*R*)-**2**	1	91	(−)-(*S*,*S*)	47
2	(*R*)-**9**	2	95	(−)-(*S*,*S*)	76
3	(*R*)-**10**	3	92	(−)-(*S*,*S*)	75
4	(*R*)-**11**	22	90[g]	(−)-(*S*,*S*)	32
5	(*R*)-**12**	1	93	(+)-(*R*,*R*)	56
6	(*R*)-**5**	1.8	92	(−)-(*S*,*S*)	66
7	(*R*)-**7**	0.7	95	(−)-(*S*,*S*)	71
8	(*R*)-**14**	24	50[h]	(−)-(*S*,*S*)	55
9	(*R*)-**13**	20	nc[i]	(+)-(*R*,*R*)	44
10[j]	(*R*)-**6**	20	90	(−)-(*S*,*S*)	77
11[j]	(*R*)-**7**	20	93	(−)-(*S*,*S*)	84
12[j]	(*R*)-**8**	20	91	(−)-(*S*,*S*)	75

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.1 mmol of *trans*-stilbene **15**, 0.01 mmol of ketone, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [b] Optical purity: 98% ee. All ketones listed were recovered in over 80% yield by flash column chromatography with Et_3N buffered silica gel (Merck 230-400 mesh). [c] Isolated yield after flash column chromatography. [d] Determined by circular dichroism spectroscopy. [e] Enantiomeric excess was determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$. [f] 0.1 mmol of *trans*-stilbene **15**, 0.1 mmol of ketone (*R*)-**2**. [g] Yield based on recovery of *trans*-stilbene (50% conversion). [h] Yield based on recovery of *trans*-stilbene (44% conversion). [i] Not completed. [j] 0−1 °C, 0.1 mmol of *trans*-stilbene **15**, 0.01 mmol of ketone, 1.0 mmol of Oxone, 3.1 mmol of $NaHCO_3$, 1.5 mL of DME, 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M).

encountering *trans*-stilbene, C_2 symmetric chiral dioxirane (*R*)-**2b** has two possible orientations (favored and disfavored orientations based on steric considerations) under either a spiro or a planar transition state (Figure 6). 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 of dioxirane become larger up to a certain size (e.g., from H to Cl to Br), there is little increase of steric interactions in the favored orientation, whereas steric interactions are significantly increased in the disfavored orientation, thereby giving higher enantioselectivity. However, when the steric sensors become even larger (e.g., from Br to I), the nonbonded steric interactions are increased significantly in both favored and disfavored orientations, resulting in lower enantioselectitivity and slower epoxidation.

As illustrated in Figure 6, 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 listed in Table 5 are consistent with a spiro TS. In addition, docking experiments using the MacroModel program[34] suggested that the steric sensors recognize the *para*/*meta* positions of *trans*-stilbene under a spiro TS but *ortho*/*meta* positions under a planar TS. It is thus expected that, under a spiro TS, higher ee values are obtained when the *para* substituents of *trans*-stilbenes **15**−**19** become larger. As shown in Table 6, this was indeed the case for effective chiral catalysts (*R*)-**7**, (*R*)-**9**, and (*R*)-**10**. The *meta* substituents of substrate **21** seemed to have little effect on enantioselectivity. Our results suggest that those chiral ketones recognize *para* substituents much better than *meta* substituents of *trans*-stilbenes.

We also discovered that when epoxidation was carried out in an aqueous DME solution at 0 °C, further increases in enantioselectivities (up to 13%) were obtained (Table 6). Most significantly, with the most active ketone (*R*)-**7** as the catalyst, high enantioselectivities (84−95% ee) were achieved for epoxidation of *trans*-stilbenes **15**−**19**.

Asymmetric Epoxidation of Trisubstituted Olefins. As chiral ketones (*R*)-**7**, (*R*)-**9**, and (*R*)-**10** are excellent catalysts for asymmetic epoxidation of *trans*-olefins, they are expected to be effective for trisubstituted olefins. Results for asymmetric epoxidation of trisubstituted olefins **22** and **23** are summarized in Table 7.

For triphenylethylene **22**, approach of chiral dioxiranes from the disubstituted side of the olefin double bond would be sterically hindered by the two phenyl rings under a spiro TS. On the monosubstituted side, there are a large phenyl ring and a small hydrogen atom present, similar to the steric environment of *trans*-stilbene **15**. Therefore, for any given catalyst, similar enantioselectivities were obtained for epoxidation of **15** and **22** (compared Table 6 with Table 7).

On the other hand, the two identical methylene groups of 1-phenylcyclohexene **23** are not bulky enough to block dioxiranes approaching from the disubstituted side. Competing approaches from the monosubstituted and disubstituted sides of **23** would occur. Therefore, lower enantioselectvities as compared with *trans*-stilbene **15** were observed for the epoxidation of **23** catalyzed by ketones (*R*)-**9** and (*R*)-**10**. Ketone (*R*)-**7** with more extended steric sensors seemed to be suitable for recognizing olefin **23**.

III. Evidence for the Involvement of the Dioxirane Intermediates in Epoxidation of *trans*-Stilbene 15 Catalyzed by Ketone (*S*)-2. Recently, based on an ^{18}O-labeling experiment, Armstrong *et al.* suggested that dioxirane intermediates might not be involved in ketone-catalyzed epoxidation by Oxone in a biphasic system (CH_2Cl_2/aqueous buffer).[35] This intrigued us to investigate whether dioxirane intermediates are involved in our epoxidation reactions.[36]

An ^{18}O-labeling experiment was designed to probe whether dioxirane intermediate (*S*)-**2b** was involved in epoxidation of *trans*-stilbene **15** catalyzed by ketone (*S*)-**2**.

A 1:1 mixture of unlabeled and ^{18}O-labeled ketones (*S*)-**2** was prepared by stirring a solution of ketone (*S*)-**2** in a $CH_3CN-H_2{}^{18}O$ solvent system at room temperature for 1 h. Evidence for ^{18}O-label incorporation was provided by mass spectrometry and ^{13}C NMR analysis. The mass spectrum of ketone (*S*)-**2** showed two peaks at *m*/*z* 397 ($M^+ + 1$) and 399 (($M^+ + 1$) + 2) in a 1:1 ratio. Also, the ^{13}C NMR spectrum showed two carbonyl resonances at δ 202.15 and 202.10 in a 1:1 ratio. There was ca. 0.05 ppm upfield shift for the ^{18}O-labeled carbonyl group.

When epoxidation of *trans*-stilbene **15** was carried out using the 1:1 mixture of unlabeled and ^{18}O-labeled ketones (*S*)-**2** with Oxone/$NaHCO_3$ in a $CH_3CN-H_2{}^{18}O$ solvent system, ^{18}O-label incorporation into the epoxide was observed (Scheme 6). The reaction was complete in 2.5 h. The mass spectrum of the resulting *trans*-stilbene epoxide revealed two peaks at *m*/*z* 197 ($M^+ + 1$) and 199 (($M^+ + 1$) + 2) in a ratio of 1:0.31. The ^{13}C NMR spectrum also showed two epoxide carbon resonances at δ 62.85 and 62.82; there was ca. 0.03 ppm upfield shift for the ^{18}O-labeled epoxide. Since addition of $KHSO_5$ to ketone (*S*)-**2** is nonstereoselective, dioxirane intermediate (*S*)-**2b** would result in 25% ^{18}O-label incorporation into the epoxide, provided that (i) both ^{16}O and ^{18}O oxygen atoms of the dioxirane group

(34) 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.

(35) Armstrong, A.; Clarke, P. A.; Wood, A. *J. Chem. Soc., Chem. Commun*. **1996**, 849.

(36) Denmark *et al.* recently reported that dioxiranes are the active agents in ketone-catalyzed epoxidation reactions with Oxone. This is consistent with our conclusion. See: Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964.

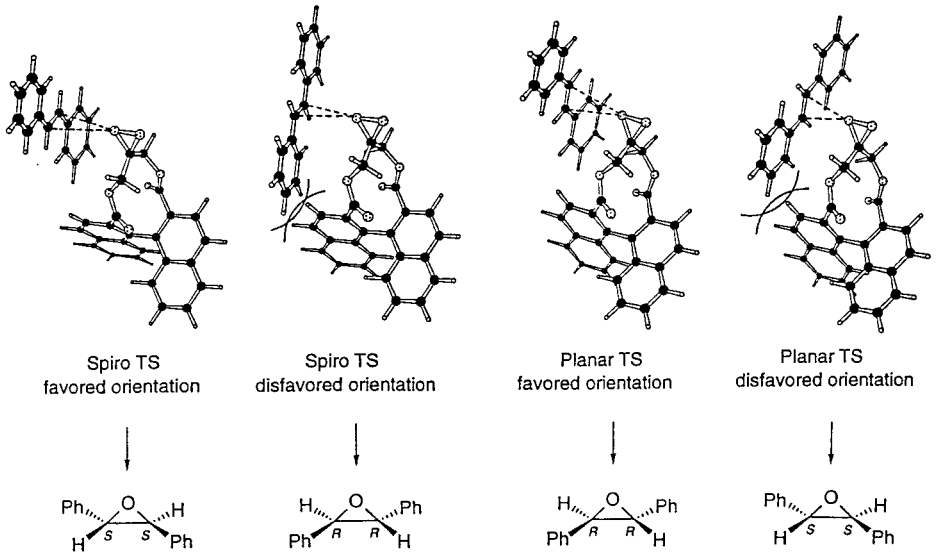


Figure 6. Proposed TS for epoxidation of olefins.

Table 6. Enantioselective Epoxidation of *trans*-Stilbenes **15**−**19** and **21** Catalyzed by Ketones **7**, **9**, and **10**[a]

entry	substrate	epoxide ee[b] (%) (*R*)-**9**[c,d]	(*R*)-**10**[c,d]	(*R*)-**10**[e]	(*R*)-**7**[c,f]	(*R*)-**7**[e,g]
1	**15** (R = H)	76	75	80[h]	71	84
2	**16** (R = Me)	80	85	88[g]	84	88
3	**17** (R = Et)	85	88	92[i]	82	91
4	**18** (R = *i*-Pr)	85	90	92[j]	88	91
5	**19** (R = *t*-Bu)	91	93	95[k]	90	95
6	**21**		74		73	

[a] Optical purity of ketone catalysts: 98% ee. [b] Enantiomeric excess was determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$. The reaction products isolated were predominantly the (−)-(*S*,*S*)-epoxides as determined by circular dichroism spectroscopy. [c] Method 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 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). The epoxides were isolated in over 90% yield. [d] Reaction was complete in 2−3 h. [e] Method B: 0−1 °C, 0.1 mmol of substrate, 0.01 mmol of catalyst, 1.0 mmol of Oxone, 3.1 mmol of $NaHCO_3$, 1.5 mL of DME, and 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [f] Reaction was complete in 40 min. [g] The epoxides were isolated in over 90% yield. Reactions were complete in 20 h. [h] 94% yield based on 88% conversion after 25 h. [i] 85% yield based on 60% conversion after 24 h. [j] 83% yield based on 60% conversion after 21 h. [k] 55% yield based on 40% conversion after 18 h.

can be transferred to *trans*-stilbene with little rate difference;[37] and (ii) the equilibrium ratio of unlabeled and ^{18}O-labeled ketones (*S*)-**2** remains unchanged during epoxidation reaction. The experimental result showed ca. 23% ^{18}O-label incorporation into the epoxide. In addition, as suggested by ^{1}H NMR no detectable amount of epoxides was formed under identical conditions in the absence of ketone (*S*)-**2**. The excellent agreement between the prediction and experimental observation supports the conclusion that the dioxirane intermediate (*S*)-**2b** is responsible for epoxidation of *trans*-stilbene **15** catalyzed by ketone (*S*)-**2**.

Conclusion

In this paper, we have demonstrated the potential of C_2 symmetric chiral ketones for catalytic asymmetric epoxidation of *trans*-olefins and trisubstituted olefins. Epoxidation reactions can be performed with only 10 mol % of ketone catalysts, which can be recovered and reused without loss of activity and chiral induction. Convincing evidence for a spiro transition state of dioxirane epoxidation was provided. Through the ^{18}O-labeling experiment, chiral dioxiranes were found to be the intermediates in chiral ketone catalyzed epoxidation reactions.

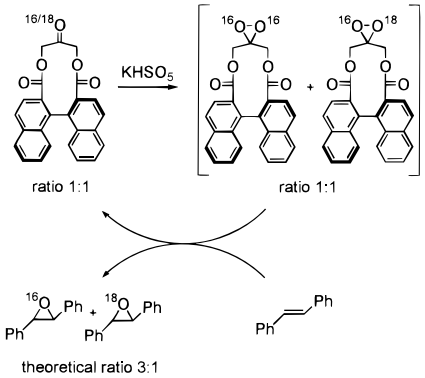
(37) The primary kinetic isotope effect k_{16O}/k_{18O} for C−O bond cleavage was estimated to be 1.073 at 25 °C. Melander, L.; Saunders, Jr., W. H. In *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980; p 272−275.

Table 7. Enantioselective Epoxidation of Trisubstituted Olefins Catalyzed by Ketones **5**, **7**, **9**, and **10**[a]

entry	substrate	catalyst[b]	time (h)	yield[c] (%)	epoxide config	ee[d] (%)
1	**22**	(*R*)-**9**	24	96	(+)-(*S*)[e]	76
2	**22**	(*R*)-**10**	24	82	(+)-(*S*)[e]	81
3	**22**	(*R*)-**5**	2.3	95	(+)-(*S*)[e]	67
4	**22**	(*R*)-**7**	3	90	(+)-(*S*)[e]	73
5	**23**	(*R*)-**9**	1.5	75	(−)-(*S*,*S*)[e]	65
6	**23**	(*R*)-**10**	4	81	(−)-(*S*,*S*)[e]	64
7	**23**	(*R*)-**5**	1.5	80	(−)-(*S*,*S*)[e]	67
8	**23**	(*R*)-**7**	1.3	90	(−)-(*S*,*S*)[e]	71

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.1 mmol of substrate, 0.01 mmol of ketone, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, 1.0 mL of aqueous Na_2·EDTA solution (4×10^{-4} M). [b] Optical purity: 98% ee. [c] Isolated yield after flash column chromatography. [d] Enantiomeric excess was determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$. [e] Reference 3a.

Scheme 6



Experimental Section

General Methods. All reactions were performed in oven-dried apparatus. Air and moisture-sensitive compounds were introduced via syringes through a rubber septum. THF was distilled from sodium-

benzophenone. Dichloromethane and acetonitrile were distilled from calcium hydride. Flash column chromatography was performed using the indicated solvent system on Merck silica gel 60 (230−400 mesh ASTM). Enantioselectivity (% ee) of epoxides was determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$ (Aldrich Cat. No. 16,474-7). Absolute configuration was determined by circular dichroism spectroscopy (ethanol as solvent) with a JASCO J-720 spectropolarimeter. The olefins and Oxone were purchased from Aldrich Chemical Co. and used without further purification. The known epoxides were identified by comparison of the spectral and physical data with those reported. Synthesis of various substituted stilbenes **16**−**19** and **21** were carried out according to the literature procedure.[38]

Preparation of Ketones (*R*)-7, (*R*)-9 and (*R*)-10. (*R*)-2,10-Bis-(1,3-dioxan-2-yl)-5*H*-dinaphtho[2,1-g:1′,2′-i][1,5]dioxacycloundecin-3,6,9(7H)-trione ((*R*)-7). To a THF solution (50 mL) of bisoxazoline (*R*)-**5a** (0.68 g, 1.51 mmol) at −78 °C under N_2 atmosphere was added TMEDA (1.2 mL, 7.58 mmol) and *sec*-butyllithium (5.8 mL, 1.3 M in cyclohexane, 7.58 mmol). The reaction mixture was stirred at −78 °C for 1 h. DMF (0.6 mL, 6.06 mmol) was added. The mixture was slowly warmed to room temperature for 4 h and quenched with aqueous NH_4Cl (5 mL). After dilution with EtOAc (100 mL), the reaction mixture was washed with water (100 mL), dried ($MgSO_4$), and concentrated. The crude substituted bisoxazoline was treated with 6 N HCl (40 mL) and refluxed overnight. After dilution with water (200 mL), the mixture was extracted with EtOAc (200 mL). The EtOAc layer was treated with saturated $NaHCO_3$ solution (200 mL) and separated. The organic layer was discarded. The aqueous layer was acidified to pH 3 with 2 N HCl, saturated with NaCl salts, and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous $MgSO_4$, filtered through a pad of silica gel (Merck, 230−400 mesh), and concentrated to give a pale yellow viscous liquid (*R*)-**7a** (0.31 g, 51% yield). Analytical TLC (silica gel 60), EtOAc, R_f = 0.29; ^{1}H NMR (500 MHz, CD_3CN) δ 8.32 (s, 1H), 8.31 (s, 1H), 8.21−8.20 (m, 2H), 7.72−7.69 (m, 2H), 7.45−7.41 (m, 2H), 7.26−7.23 (m, 2H), 6.81 (d, J = 6 Hz, 1H), 6.77 (d, J = 6 Hz, 1H), 6.01 (d, J = 6 Hz, 1H), 5.87 (d, J = 6 Hz, 1H) (a mixture of diastereomers); ^{13}C NMR (125.77 MHz, CD_3CN) δ 167.04, 166.98, 140.97, 140.94, 140.81, 140.79, 135.95, 135.90, 135.86, 133.72, 133.66, 133.55, 133.50, 133.25, 133.05, 128.86, 128.83, 128.82, 128.78, 128.75, 128.69, 127.71, 127.65, 127.63, 127.56, 126.54, 126.51, 126.40, 126.35, 123.40, 123.37, 123.25, 123.22, 122.90, 122.67, 122.63, 122.42, 96.90, 96.76 (a mixture of diastereomers); IR (Nujol mull) 3453 (br), 1745, 1629, 1463, 1093, 932 cm^{-1}; FABMS *m*/*z* 398 (M^+, 13), 380 (20), 252 (14), 250 (23), 153 (68), 136 (41), 108 (15), 107 (62), 106 (24), 77 (100).

Hydroxylactone (*R*)-**7a** (80 mg, 0.2 mmol) and 3-chloro-2-chloromethyl-1-propene (25 mg, 0.2 mmol) were dissolved in anhydrous DMF (20 mL), and then cesium carbonate (138 mg, 0.42 mmol) was added. The resulting solution was stirred at 45 °C under N_2 atmosphere for 8 h. The reaction mixture was diluted with EtOAc (100 mL), washed with water (4 × 50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the crude aldehyde (32 mg, 94% yield based on 38% conversion) which was used in the next step without further purification. The aqueous layer was acidified to pH 3 with 2 N HCl, and extracted with EtOAc (100 mL). The EtOAc layer was washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated to give back the hydroxylactone (*R*)-**7a** (50 mg, 62% yield of recovery) which was reused in the cyclization step.

The crude aldehyde (160 mg, 0.36 mmol) and 1,3-propanediol (100 mg, 1.3 mmol) were dissolved in anhydrous benzene (15 mL). Anhydrous *p*-toluenesulfonic acid (2−3 mg) was added. The resulting solution was refluxed under N_2 for 5 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (20 mL), and dried (Na_2SO_4). After evaporation of solvents, the residue was purified by flash column chromatography: 20 g of silica gel (Merck, 230−400 mesh) in hexane (100 mL) with NEt_3 (2 mL) was poured into a column of 20 mm diameter. The column was eluted with hexane (100 mL), 30% EtOAc in hexane (100 mL), and 40% EtOAc in hexane (200 mL) to give the acetal (*R*)-**7b** (47 mg, 23% yield) as a white solid. Analytical TLC (silica gel 60), 50% EtOAc in hexane, R_f = 0.33; mp 362−363 °C (hexane−CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 2H), 7.91 (d, J = 8 Hz, 2H), 7.46 (t, J = 7 Hz, 2H), 7.20 (t, J = 7 Hz, 2H), 6.97 (d, J = 8 Hz, 2H), 5.90 (s, 2H), 5.53 (d, J = 14.1 Hz, 2H), 5.15 (s, 2H), 4.43 (dd, J = 12 Hz, 4.9 Hz, 2H), 4.25−4.04 (m, 6H), 3.91 (td, J = 12 Hz, 2.4 Hz, 2H), 2.28−2.17 (m, 2H), 1.47 (br d, J = 13.5 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 167.16, 141.34, 134.96, 133.08, 132.79, 132.37, 129.28, 128.54, 127.66, 127.38, 127.17, 126.02, 112.68, 99.44, 67.46, 67.23, 64.05, 25.77; CIMS *m*/*z* 567 (M^+ + 1, 100), 154 (38).

A stock solution of $NaIO_4$ (877 mg, 4.1 mmol) and ruthenium trichloride hydrate (5 mg, 0.024 mmol) in water (5 mL) was prepared. The acetal (*R*)-**7b** (47 mg, 0.083 mmol) was dissolved in CCl_4 (2 mL), CH_3CN (2 mL) and water (2.6 mL). The stock solution (0.4 mL) was transferred to the reaction mixture. The biphasic mixture was stirred vigorously for 6 h at room temperature. Then CH_2Cl_2 (30 mL) and water (20 mL) were added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography: 20 g of silica gel (Merck, 230−400 mesh) in hexane (100 mL) and NEt_3 (2 mL) was poured into a column of 20 mm diameter. The column was eluted with hexane (100 mL), followed by 40% EtOAc in hexane (200 mL) to give ketone (*R*)-**7** (28 mg, 59% yield) as a white solid. Analytical TLC (silica gel 60), 50% EtOAc in hexane, R_f = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 2H), 7.94 (d, J = 8 Hz, 2H), 7.49 (t, J = 7 Hz, 2H), 7.23 (t, J = 7 Hz, 2H), 6.98 (d, J = 8 Hz, 2H), 5.86 (s, 2H), 5.63 (d, J = 15.3 Hz, 2H), 4.41 (dd, J = 11 Hz, 4.9 Hz, 2 H), 4.19 (dd, J = 11 Hz, 4.9 Hz, 2H), 4.11−4.01 (m, 4H), 3.87 (td, J = 12 Hz, 2.4 Hz, 2H), 2.30−2.14 (m, 2H), 1.48 (br d, J = 13.6 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 203.24, 165.78, 135.00, 132.97, 132.90, 132.49, 128.63, 128.24, 127.63, 127.57, 126.48, 99.39, 67.51, 67.27, 66.17, 25.69; IR (CCl_4) 2928, 2856, 1765, 1738, 1378, 1248, 1121 cm^{-1}; HRMS for $C_{33}H_{28}O_9$ (M^+), calcd 568.1733, found 568.1727; EIMS (20 eV) *m*/*z* 568 (M^+, 83), 509 (21), 495 (100), 437 (29), 395 (34); FABMS *m*/*z* 568 (M^+, 64), 509 (19), 495 (100), 437 (28), 395 (36); CD (EtOH) λ_{max} (θ) 296 (5.3 × 10^5), 263 (−5.2 × 10^5), 231 (−9.2 × 10^6), 219 (8.2 × 10^6).

(*R*)-2,10-Dichloro-5*H*-dinaphtho[2,1-g:1′,2′-i][1,5]dioxacycloundecin-3,6,9(7*H*)-trione ((*R*)-9). A solution of (*R*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (*R*)-**2a**[21] (0.20 g, 0.58 mmol; azeotroped three times with toluene) and TMEDA (0.7 mL, 4.6 mmol) in THF (20 mL) was treated dropwise with *sec*-butyllithium (3.2 mL, 1.3 M in cyclohexane, 4.2 mmol) at −90 °C for 1.5 h. A solution of hexachloroethane (1.40 g, 5.8 mmol) in THF (5 mL) was added dropwise at −78 °C. Stirring was continued at this temperature for 1 h. The mixture was warmed slowly to room temperature, quenched with aqueous NH_4Cl (5 mL), and diluted with CH_2Cl_2 (30 mL). The resulting mixture was extracted with 0.5 N NaOH solution (40 mL). The aqueous phase was acidified with concentrated HCl and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by preparative TLC (1% acetic acid in EtOAc, three elutions) to provide diacid (*R*)-**9a** (0.121 g, 50% yield) as a solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.19 (s, 2H), 7.95 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 7 Hz, 2H), 7.35 (t, J = 7 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 155.78, 121.35, 121.28, 120.56, 118.45, 116.13, 115.35, 114.58, 114.51, 114.25; HRMS for $C_{22}H_{12}Cl_2O_4$ (M^+), calcd 410.0113, found 410.0117; EIMS (20 eV) *m*/*z* 410 (100), 366 (10), 348 (13), 286 (15).

Diacid (*R*)-**9a** (0.132 g; 0.32 mmol, azeotroped three times with toluene) and 3-chloro-2-chloromethyl-1-propene (0.040 g, 0.32 mmol) were dissolved in anhydrous DMF (32 mL). Cesium carbonate (0.229 g, 0.704 mmol) was added to this solution. The resulting reaction mixture was stirred at 100 °C under N_2 atmosphere for 17 h, poured into water (50 mL), and extracted with EtOAc (100 mL). The organic layer was washed three times with water and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (30% EtOAc in hexane) to give (*R*)-**9b** (88.5 mg, 60% yield) as a white solid. Analytical TLC (silica gel 60), 30% EtOAc in hexane, R_f = 0.48; ^{1}H

(38) Ogawa, K.; Sano, T.; Yoshimura, S.; Takeuchi, Y.; Toriumi, K. *J. Am. Chem. Soc*. **1992**, *114*, 1041.

NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.52 (t, J = 7 Hz, 2H), 7.26 (t, J = 7 Hz, 2H), 6.90 (d, J = 8.2 Hz, 2H), 5.46 (d, J = 14 Hz, 2H), 5.18 (s, 2H), 4.43 (d, J = 14 Hz, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 165.65, 139.72, 134.95, 133.70, 131.54, 131.07, 129.10, 128.21, 127.60, 127.36, 127.21, 113.62, 65.18; IR (CCl_4) 1752 cm^{-1}; HRMS for $C_{26}H_{16}Cl_2O_4$ (M^+), calcd 462.0426, found 462.0422; EIMS (20 eV) *m*/*z* 462 (100), 418 (8), 348 (14).

A stock solution of $NaIO_4$ (877 mg, 4.1 mmol) and ruthenium trichloride hydrate (5 mg, 0.024 mmol) in water (5 mL) was prepared. To a solution of (*R*)-**9b** (0.046 g, 0.103 mmol) in a mixture of CCl_4 (2 mL), CH_3CN (2 mL), and H_2O (2.5 mL) was added the stock solution (0.5 mL). Stirring was continued at room temperature for 17 h. CH_2Cl_2 (20 mL) and water (20 mL) were added to this mixture. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (30% EtOAc in hexane) to provide ketone (*R*)-**9** (10 mg, 21% yield) as a white solid. Mp 256−258 °C (hexane−CH_2Cl_2); analytical TLC (silica gel 60), 30% EtOAc in hexane, R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.56 (t, J = 7 Hz, 2H), 7.29 (t, J = 7 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 5.57 (d, J = 15.4 Hz, 2H), 4.23 (d, J = 15.4 Hz, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 201.36, 164.32, 135.03, 133.90, 131.36, 130.17, 129.44, 128.63, 127.88, 127.50, 127.42, 127.25, 67.06; IR (CCl_4) 1762, 1281, 1247, 1160, 1141 cm^{-1}; HRMS for $C_{25}H_{14}Cl_2O_5$ (M^+), calcd 464.0218, found 464.0223; EIMS (20 eV) *m*/*z* 464 (100), 406 (26), 376 (20), 348 (61); CD (EtOH) λ_{max} (θ) 300 (1.1×10^4), 263 (-1.4×10^4), 234 (-2.9×10^5), 219 (1.9×10^5).

(*R*)-2,10-Dibromo-5*H*-dinaphtho[2,1-g:1′,2′-i][1,5]dioxacyclo-undecin-3,6,9(7*H*)-trione ((*R*)-10). A solution of (*R*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (*R*)-**2a** (0.205 g, 0.58 mmol; azeotroped three times with toluene) and TMEDA (0.7 mL, 4.6 mmol) in THF (20 mL) was treated dropwise with *sec*-butyllithium (3.2 mL, 1.3 M in cyclohexane, 4.2 mmol) at −90 °C for 1.5 h. A solution of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (3.8 g, 9.3 mmol) in THF (10 mL) was added dropwise at −78 °C. Stirring was continued at this temperature for 1 h. The mixture was warmed slowly to room temperature, quenched with aqueous NH_4Cl (5 mL), and diluted with CH_2Cl_2 (30 mL). The resulting mixture was extracted with saturated $NaHCO_3$ solution (40 mL). The aqueous phase was acidified with concentrated HCl and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by preparative TLC (1% acetic acid in EtOAc, three elutions) to provide diacid (*R*)-**10a** (0.061 g, 21% yield) as a solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.33 (s, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 173.35, 139.44, 135.24, 133.51, 132.35, 128.64, 128.56, 128.41, 128.29, 127.80, 116.42.

Diacid (*R*)-**10a** (0.171 g, 0.342 mmol; azeotroped three times with toluene) and 3-chloro-2-chloromethyl-1-propene (0.047 g, 0.376 mmol) were dissolved in anhydrous DMF (34 mL). Cesium carbonate (0.244 g, 0.748 mmol) was added to this solution. The resulting reaction mixture was stirred at 100 °C under N_2 atmosphere for 18 h, poured into water, and extracted with EtOAc (100 mL). The organic layer was washed three times with water and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (30% EtOAc in hexane) to give (*R*)-**10b** (71 mg, 39% yield) as a white solid. Analytical TLC (silica gel 60), 30% EtOAc in hexane, R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.51 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 5.46 (d, J = 14 Hz, 2H), 5.18 (s, 2H), 4.43 (d, J = 14 Hz, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 165.99, 139.72, 134.81, 134.05, 132.69, 132.61, 131.84, 128.18, 127.76, 127.28, 127.24, 115.42, 113.56, 65.09; IR (CCl_4) 1751 cm^{-1}; HRMS for $C_{26}H_{16}Br_2O_4$ (M^+), calcd 551.9572, found 551.9586; EIMS (20 eV) *m*/*z* 552 (100), 508 (10), 438 (12), 399 (15). Anal. Calcd for $C_{26}H_{16}Br_2O_4$: C, 56.13; H, 2.93. Found: C, 55.95; H, 3.01.

A stock solution of $NaIO_4$ (877 mg, 4.1 mmol) and ruthenium trichloride hydrate (5 mg, 0.024 mmol) in water (5 mL) was prepared. To a solution of (*R*)-**10b** (0.043 g, 0.081 mmol) in a mixture of CCl_4 (2 mL), CH_3CN (2 mL), and H_2O (2.6 mL) was added the stock solution (0.4 mL). Stirring was continued at room temperature for 19 h. CH_2Cl_2 (20 mL) and water (20 mL) were added to this mixture. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (30% EtOAc in hexane) to provide ketone (*R*)-**10** (17 mg, 40% yield) as a white solid. Mp 252−254 °C (hexane−CH_2Cl_2); analytical TLC (silica gel 60), 20% EtOAc in hexane, R_f = 0.3; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 2H), 7.86 (d, J = 8.2 Hz, 2H), 7.56 (t, J = 7.1 Hz, 2H), 7.31 (t, J = 7.1 Hz, 2H), 6.91 (d, J = 8.2 Hz, 2H), 5.56 (d, J = 15.4 Hz, 2H), 4.23 (d, J = 15.4 Hz, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 201.42, 164.64, 134.89, 134.25, 133.01, 131.71, 131.67, 128.58, 128.03, 127.40, 127.27, 115.42, 67.00; IR (CCl_4) 1763, 1743, 1278, 1246, 1159, 1140 cm^{-1}; HRMS for $C_{25}H_{14}Br_2O_5$ (M^+), calcd 553.9208, found 553.9216; EIMS (20 eV) *m*/*z* 554 (100), 496 (17), 438 (49); CD (EtOH) λ_{max} (θ) 301 (3.0×10^4), 267 (-3.9×10^4), 253 (8.8×10^4), 236 (-9.1×10^5), 220 (6.1×10^5).

General Epoxidation Procedure. Method A. General *in Situ* Epoxidation Procedure in CH_3CN-H_2O Solvent System at Room Temperature (Table 6, Entry 1). To an CH_3CN solution (1.5 mL) of *trans*-stilbene **15** (18 mg, 0.1 mmol) and ketone (*R*)-**9** (4.6 mg, 0.01 mmol) at room temperature was added an aqueous Na_2·EDTA solution (1 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone (307 mg, 0.5 mmol) and sodium bicarbonate (130 mg, 1.55 mmol). The reaction was complete in 2 h at room temperature as shown by TLC. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography: 20 g of silica gel (Merck, 230−400 mesh) in hexane (100 mL) and NEt_3 (2 mL) was poured into a column of 20 mm diameter. The column was eluted with hexane (50 mL), followed by 5% EtOAc in hexane (100 mL) to give *trans*-stilbene epoxide **15a** (18.6 mg, 95% yield), and 35% EtOAc in hexane (100 mL) to recover ketone (*R*)-**9** (3.7 mg, 81% recovery).

Method B. General *in Situ* Epoxidation Procedure in DME−H_2O Solvent System at 0−1 °C (Table 6, Entry 1). To a 1,2-dimethoxyethane (DME) solution (1.5 mL) of *trans*-stilbene **15** (18 mg, 0.1 mmol) and ketone (*R*)-**7** (5.7 mg, 0.01 mmol) at 0−1 °C was added an Na_2·EDTA solution (1 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone (614.8 mg, 1.0 mmol) and sodium bicarbonate (260.4 mg, 3.1 mmol). The reaction was complete in 20 h at 0 °C as shown by TLC. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography: 20 g of silica gel (Merck, 230−400 mesh) in hexane (100 mL) and NEt_3 (2 mL) was poured into a column of 20 mm diameter. The column was eluted with hexane (50 mL), followed by 5% EtOAc in hexane (100 mL) to give *trans*-stilbene epoxide **15a** (17.7 mg, 90% yield), and EtOAc (100 mL) to recover ketone (*R*)-**7** (4.6 mg, 80% recovery).

Preparation of (*E*)-4,4′-Diphenylstilbene Epoxide 20a (Table 1, Entry 6). To an CH_3CN solution (2.0 mL) of (*E*)-4,4′-diphenylstilbene **20** (33.2 mg, 0.1 mmol) and ketone (*R*)-**2** (3.9 mg, 0.01 mmol) at room temperature was added an aqueous Na_2·EDTA solution (1.7 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone (307 mg, 0.5 mmol) and sodium bicarbonate (130 mg, 1.55 mmol). The reaction was complete in 8 h at room temperature. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue solid was triturated carefully with CH_2Cl_2 (2 × 4 mL) to give epoxide **20a** (27.8 mg, 80% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.59 (m, 8H), 7.48−7.43 (m, 8H), 7.39−7.34 (m, 2H), 3.96 (s, 2H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 141.39, 140.67, 136.12, 128.84, 127.47, 127.36, 127.10, 125.98, 62.77; HRMS for $C_{26}H_{20}O$ (M^+), calcd 348.1514, found 348.1512; EIMS (20 eV) *m*/*z* 348 (11), 333 (27), 332 (100), 320 (15), 319 (56), 181 (9).

Evidence for Involvement of Dioxirane Intermediate in Epoxidation of *trans*-Stilbene 15 Catalyzed by Ketone (*S*)-2. To an CH_3CN solution (0.6 mL) of ketone (*S*)-**2** (7.9 mg, 0.02 mmol) at room temperature was added $H_2{}^{18}O$ (Aldrich, 95 at. % ^{18}O, 0.4 mL). After stirring at room temperature for 1 h, the solution mixture was divided into two portions by using a micro-pipet. The first portion of the solution mixture (0.2 mL) was diluted with CH_2Cl_2 (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The recovered ketone (*S*)-**2** was subjected to mass spectrometry (CIMS) and ^{13}C NMR analysis. The mass spectrum of ketone (*S*)-**2** showed two peaks at *m*/*z* 397 ($M^+ + 1$) and 399 (($M^+ + 1$) + 2) in a 1:1 ratio. Also, the ^{13}C NMR spectrum (125.77 MHz, $CDCl_3$) showed that two carbonyl resonances at δ 202.15 and 202.10 in a 1:1 ratio were observed; there was ca. 0.05 ppm upfield ^{13}C shift for the ^{18}O-labeled ketone.

To the second portion of solution mixture (0.8 mL) was added *trans*-stilbene **15** (3.6 mg, 0.02 mmol). To this reaction mixture was added a mixture of Oxone (61.5 mg, 0.1 mmol) and sodium bicarbonate (26 mg, 0.31 mmol). The reaction was complete in 2.5 h at room temperature as shown by TLC. After dilution with CH_2Cl_2 (10 mL), the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to mass spectrometry (CIMS) and ^{13}C NMR analysis. The mass spectrum of *trans*-stilbene epoxide **15a** revealed two peaks at *m*/*z* 197 ($M^+ + 1$) and 199 (($M^+ + 1$) + 2) in a 1:0.31 ratio. There was ca. 23% ^{18}O-label incorporation into the epoxide. The ^{13}C NMR spectrum showed two epoxide resonances at δ 62.85 and 62.82; there was ca. 0.03 ppm upfield ^{13}C shift for the ^{18}O-labeled epoxide.

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Supporting Information Available: Experimental details for preparation of ketones **2**−**6**, **8**, and **11**−**14**; characterization data for ketones **2**−**6**, **8**, and **11**−**14**, *trans*-stilbenes **16**−**19** and **21** and epoxides **15a**−**19a** and **21a**−**26a**; CI-MS and ^{13}C NMR spectra of ^{18}O-labeled ketone (*S*)-**2** and epoxide **15a**; CD spectra for assignment of absolute configurations of epoxides **15a**−**21a**; determination of enantiomeric excess of epoxide **19a**; and X-ray structural analysis of ketone (*R*)-**3** containing tables of atomic coordinates, thermal parameters, bond lengths, and angles (33 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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