

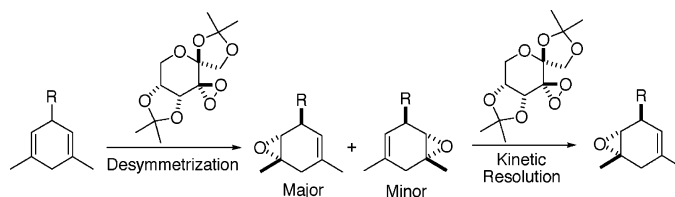
## Transition State Studies on the Dioxirane-Mediated Asymmetric Epoxidation via Kinetic Resolution and Desymmetrization

Jon C. Lorenz, Michael Frohn, Xiaoming Zhou, Jian-Rong Zhang, Yong Tang, Christopher Burke, and Yian Shi\*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

yian@lamar.colostate.edu

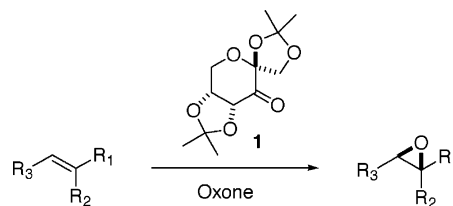
Received October 8, 2004



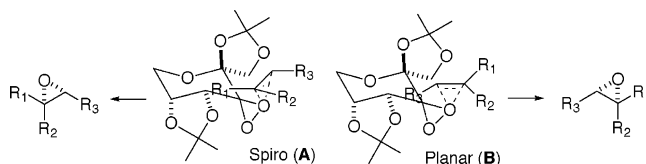
This paper describes an efficient kinetic resolution process of trisubstituted cyclic olefins via a chiral dioxirane generated in situ from a fructose-derived ketone and Oxone. The substrates presented include a variety of 1,3-disubstituted and 1,6-disubstituted cyclohexenes with the stereogenic centers at allylic positions. A sequential desymmetrization and kinetic resolution of 1,4-cyclohexadienes by the chiral dioxirane was also found to be feasible. The initially formed monoepoxides can be kinetically resolved by continuing the reaction, leading to the increase or decrease of the ee values of monoepoxides depending on the diene systems. In some cases, a prochiral directing group is not required and the first formed epoxide stereoselectively directs the second epoxidation. When the coupled desymmetrization and kinetic resolution is used synergistically, high enantiopurity can be obtained for an epoxide from an intrinsically less enantioselective substrate. The observed absolute and relative stereochemistry as well as the changing optical purity can be effectively rationalized by transition state analysis.

Dioxiranes generated in situ from chiral ketones have been shown to be effective reagents for asymmetric epoxidation of olefins.<sup>1–3</sup> Recently we reported that fructose-derived ketone **1** gives high ee values for a variety of trans-substituted and trisubstituted olefins (Scheme 1).<sup>4,5</sup> Our studies with various prochiral olefins show that the epoxidation catalyzed by ketone **1** proceeds through spiro transition state **A** with planar transition state **B** being the major competing mode (Scheme 2).<sup>4a,b</sup> The extent of the competition between spiro **A** and planar **B** is dependent on the steric nature of the substituents

### SCHEME 1



### SCHEME 2



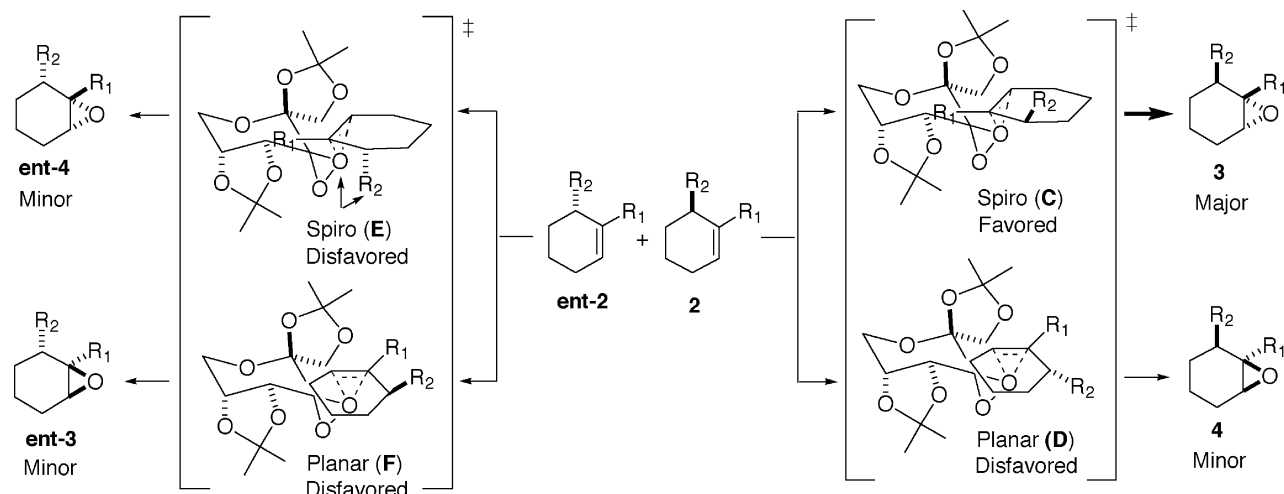
on the olefins.<sup>4b</sup> Generally speaking, higher ee can be obtained by decreasing the size of R<sub>1</sub> (favoring spiro **A**) and/or increasing the size of R<sub>3</sub> (disfavoring planar **B**). In an effort to further explore the catalytic and mecha-

\* Address correspondence to this author. Phone: 970-491-7424. Fax: 970-491-1801.

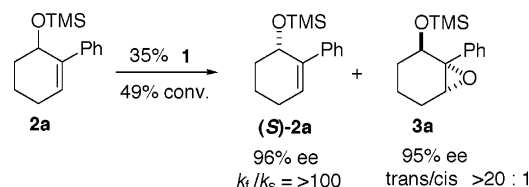
(1) For general leading references on dioxiranes see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R.; Dinioi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (d) Clennan, E. L. *Trends Org. Chem.* **1995**, *5*, 231. (e) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, 219.

(2) For reviews on chiral ketone catalyzed asymmetric epoxidations see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979.

SCHEME 3



SCHEME 4



nistic features of this asymmetric epoxidation, we investigated the kinetic resolution of chiral olefins and found that high-resolution efficiency could be obtained for a number of trisubstituted cyclic olefins.<sup>6</sup> Since our initial report, we have further examined the asymmetric epoxidation of symmetric cyclic dienes to couple the desymmetrization with a subsequent kinetic resolution. In all these cases, the results are highly consistent with the

spiro-planar transition state model, and therefore further contribute to our general mechanistic understanding of the asymmetric epoxidation catalyzed by ketone **1**, which further enhances the ability to rationalize or predict stereochemical outcomes of this epoxidation process for a given substrate. Herein we wish to report our detailed studies on this subject.

## Results and Discussion

**Kinetic Resolution of Cyclohexenes.** The transition state model presented in Scheme 2 suggests that an existing stereogenic center adjacent to the reacting double bond might influence the epoxidation, providing the possibility for kinetic resolution.<sup>7,8</sup> Our initial studies focused on cyclic olefins with the stereogenic centers at allylic positions. The rigid conformation and proximity of the stereogenic center to the olefin make these substrates promising systems for kinetic resolution. Therefore, 1,6-disubstituted cyclohexenes (**2**) were chosen for initial studies (Scheme 3). Among the competing transition states, spiro **C** and spiro **E** are expected to be

(3) For selected examples of asymmetric epoxidation mediated in situ by chiral ketones see: (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831. (c) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (d) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S. G.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (e) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. (f) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (g) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (h) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (i) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659. (j) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749. (k) Solladie-Cavallo, A.; Bouerat, L. *Org. Lett.* **2000**, *2*, 3531. (l) Solladie-Cavallo, A.; Bouerat, L.; Jierry, L. *Eur. J. Org. Chem.* **2001**, 4557. (m) Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113. (n) Seki, M.; Furutani, T.; Imashiro, R.; Kuroda, T.; Yamanaka, T.; Harada, N.; Arakawa, H.; Kusama, M.; Hashiyama, T. *Tetrahedron Lett.* **2001**, *42*, 8201. (o) Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* **2002**, *43*, 631. (p) Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545. (q) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Forlani, R.; Maietti, S.; Pedrini, P. *J. Org. Chem.* **2002**, *67*, 5802. (r) Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943. (s) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479. (t) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610. (u) Chan, W.-K.; Yu, W.-Y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* **2003**, *68*, 6576. (v) Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* **2003**, *44*, 7403.

(4) For examples of asymmetric epoxidation mediated by fructose-derived ketone **1** see: (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. (d) Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1. (e) Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth.* **2003**, *80*, 9.

(5) For some applications of ketone **1** see: (a) Bluet, G.; Campagne, J.-M. *Synlett* **2000**, 221. (b) Tokiwa, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335. (c) Hioki, H.; Kanehara, C.; Ohnishi, Y.; Umemori, Y.; Sakai, H.; Yoshio, S.; Matsushita, M.; Kodama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2552. (d) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831. (e) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328. (f) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (g) Morimoto, Y.; Iwai, T.; Kinoshita, T. *Tetrahedron Lett.* **2001**, *42*, 6307. (h) Guz, N. R.; Lorenz, P.; Stermitz, F. R. *Tetrahedron Lett.* **2001**, *42*, 6491. (i) Shen, K.-H.; Lush, S.-F.; Chen, T.-L.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 8106. (j) McDonald, F. E.; Wei, S. *Org. Lett.* **2002**, *4*, 593. (k) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515. (l) Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813. (m) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 2489. (n) Morimoto, Y.; Takaishi, M.; Iwai, T.; Kinoshita, T.; Jacobs, H. *Tetrahedron Lett.* **2002**, *43*, 5849. (o) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574. (p) Altmann, K.-H.; Bold, G.; Caravatti, G.; Denni, D.; Flörshiemer, A.; Schmidt, A.; Rihs, G.; Wartmann, M. *Helv. Chim. Acta* **2002**, *85*, 4086. (q) Madhushaw, R. J.; Li, C.-L.; Su, H.-L.; Hu, C.-C.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2003**, *68*, 1872. (r) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514. (s) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123. (t) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. (u) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36. (v) Smith, A. B., III; Fox, R. J. *Org. Lett.* **2004**, *6*, 1477.

(6) For a preliminary report of a portion of this work, see: Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718.

TABLE 1. Kinetic Resolution of Representative Olefins by Ketone 1 Catalyzed Asymmetric Epoxidation<sup>a</sup>

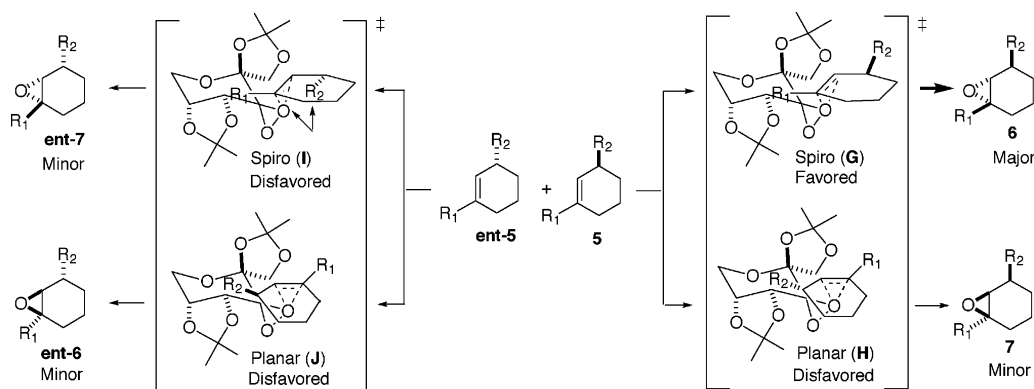
entry	substrate	temp (°C)	conv. (%) <sup>b</sup>	recovered S.M. ee (%) <sup>c</sup>	epoxide ee (%)	epoxide (trans/cis) <sup>d</sup>	<i>k</i> <sub>rel</sub> <sup>e</sup> ( <i>k</i> <sub>f</sub> / <i>k</i> <sub>s</sub> )
1 <sup>f</sup>	R = TMS	-10	49	96 <sup>o</sup> (S) <sup>t</sup>	95 <sup>o</sup>	>20	>100
2 <sup>g</sup>	R = Me	-10	65	99 <sup>p</sup> (S)	85 <sup>w</sup>	6	16
3 <sup>h</sup>	R = COMe	0	54	96 <sup>q</sup> (S)	88 <sup>p</sup>	12	39
4 <sup>i</sup>	R = COOEt	-10	51	94 <sup>o</sup> (S)	97 <sup>p</sup>	>20	70
5 <sup>j</sup>		0	71	89 <sup>r</sup> (S) <sup>t</sup>	nd	6	6
6 <sup>k</sup>		0	56	89 <sup>r</sup> (S) <sup>u</sup>	nd	6	16
7 <sup>l</sup>		-10	70	99 <sup>o</sup> (R)	81 <sup>x</sup>	4	11
8 <sup>m</sup>		-10	49	75 <sup>s</sup> (R)	nd	13	18
9 <sup>m</sup>		20	66	96 <sup>s</sup> (R)	nd	8	11
10 <sup>n</sup>	R = OTMS	-10	61	91 <sup>q</sup> (R)	76 <sup>w</sup>	4	11
11 <sup>g</sup>	R = <sup>i</sup> Pr	-10	59	93 <sup>q</sup> (S)	85 <sup>w</sup>	8	15
12 <sup>i</sup>	R = <sup>t</sup> Bu	-10	54	99 <sup>q</sup> (R) <sup>v</sup>	84 <sup>w</sup>	>20	61

<sup>a</sup> All reactions were carried out with substrate (1 equiv), ketone (0.20–1.0 equiv), Oxone (2.3–2.8 equiv), and K<sub>2</sub>CO<sub>3</sub> (9.5–12.5 equiv) in CH<sub>3</sub>CN–DMM–0.05 M Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10H<sub>2</sub>O in aqueous EDTA (4 × 10<sup>-4</sup> M) solution (1:2:2, v/v/v). Oxone was added over 2.5 h except for entries 5 and 6 (2 h), and entry 7 (1.5 h). For entries 1, 4, 6, 10, and 12, 2.8 equiv of Oxone and 12.5 equiv of K<sub>2</sub>CO<sub>3</sub> were used. For entries 2, 3, 5, 7, and 11, 2.5 equiv of Oxone and 11.0 equiv of K<sub>2</sub>CO<sub>3</sub> were used. For entries 8 and 9, 2.3 equiv of Oxone and 9.5 equiv of K<sub>2</sub>CO<sub>3</sub> were used. <sup>b</sup> The conversion was determined by <sup>1</sup>H NMR of the crude reaction mixture after workup except entry 5 where the conversion was determined by GC (Restec Corporation RTX-5). In cases where the ee of the epoxide was determined and one diastereomer of the epoxide was formed predominately (entries 1, 4, and 12), the conversion could be cross-checked applying the ee values of the olefin and epoxide to the following equation: ee (olefin)/ee (epoxide) = C/(1 - C). In these cases the measured conversion was consistent with the calculated conversion. <sup>c</sup> The absolute configuration was tentatively assumed based on the spiro reaction mode unless otherwise noted. <sup>d</sup> The ratio of trans and cis epoxides was determined by <sup>1</sup>H NMR except entry 5 where the ratio was determined by GC (Restec Corporation RTX-5). <sup>e</sup> The relative rate was calculated by using the equation  $k_{rel} = k_f/k_s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ , where *C* is the conversion and ee is the percent enantiomeric excess of the recovered starting material (ref 14). <sup>f</sup> 0.35 equiv of ketone was used. <sup>g</sup> 0.45 equiv of ketone was used. <sup>h</sup> 0.50 equiv of ketone was used. <sup>i</sup> 0.60 equiv of ketone was used. <sup>j</sup> 0.20 equiv of ketone was used. <sup>k</sup> 1.0 equiv of ketone was used. <sup>l</sup> 0.40 equiv of ketone was used. <sup>m</sup> 0.25 equiv of ketone was used. <sup>n</sup> 0.75 equiv of ketone was used. <sup>o</sup> Enantioselectivity was determined by chiral HPLC (Chiralcel OD). <sup>p</sup> Enantioselectivity was determined by chiral HPLC (Chiralpak AD). <sup>q</sup> Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). <sup>r</sup> Enantioselectivity was determined by chiral GC (Chiraldex G-TA) after conversion to the acetate. <sup>s</sup> Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation with TBAF. <sup>t</sup> The configuration was determined by comparing the measured optical rotation with the known alcohol after desilylation (for entry 1 see ref 13; for entry 5 see ref 16). <sup>u</sup> The configuration was determined by comparing the measured optical rotation of the corresponding acetate with the reported one (ref 17). <sup>v</sup> The configuration was determined by comparing the measured optical rotation with the known ketone after hydrolysis (ref 13). <sup>w</sup> Enantioselectivity was determined by <sup>1</sup>H NMR shift analysis, using Eu(hfc)<sub>3</sub>. <sup>x</sup> Enantioselectivity was determined by chiral HPLC (Chiralpak AD) of the corresponding benzoate.

the main reaction modes for the epoxidation of each enantiomer. Spiro **E** was expected to be disfavored compared to spiro **C** due to the unfavorable steric interactions between R<sub>2</sub> and one of the dioxirane oxygens, thus one enantiomer would be epoxidized faster than the

other. To test this hypothesis, (±)-1-phenyl-6-(trimethylsiloxy)cyclohexene (**2a**) was used as our initial substrate (Scheme 4). When the epoxidation was carried out with 35% ketone **1** at -10 °C for 2.5 h, a 49% conversion was obtained as judged by <sup>1</sup>H NMR assay of the reaction

## SCHEME 5

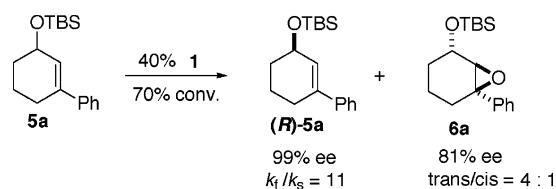


mixture (Scheme 4). The  $^1\text{H}$  NMR spectra showed the trans epoxide was formed predominantly (trans/cis > 20/1).<sup>9</sup> A 96% ee was obtained for the unreacted substrate and 95% ee for the trans epoxide as determined by HPLC, using a chiral support (Chiralcel OD) (Table 1, entry 1). The fact that the major epoxide was trans and the unreacted olefin was enriched in the *S* isomer is consistent with the above transition state analysis.

When 1-methyl-6-[(*tert*-butyldimethyl)siloxy]cyclohexene was subjected to the kinetic resolution process, the  $k_{\text{rel}}$  value was reduced to 6 as shown in Table 1 (entry 5). This result suggests that in addition to spiro **E**, planar **F** might also be accessible to epoxidize less reactive **ent-2** in this case, since a methyl group is a larger group and diminishes the favored spiro **C**.<sup>10</sup> The effect of planar **F** on  $k_{\text{rel}}$  is further supported by the observation that the  $k_{\text{rel}}$  increased to 16 when gem dimethyl groups at the 3-position of the substrate are introduced to reduce the competing planar **F** (Table 1, entry 6).

A similar transition state analysis suggested that the kinetic resolution might also be feasible for 1,3-disubstituted cyclohexenes (**5**) (Scheme 5). Subjecting the TBS ether of 3-phenyl-2-cyclohexenol (**5a**)<sup>11</sup> to the typical reaction conditions (with 40% ketone catalyst **1** at  $-10^\circ\text{C}$  for 1.5 h) led to 70% conversion of the substrate

## SCHEME 6



(Scheme 6, Table 1, entry 7). The enantiomeric excess of the unreacted substrate was determined to be 99%. The trans epoxide was obtained as the major product (trans/cis = 4/1),<sup>12</sup> indicating that spiro **G** is the favored transition state. Further studies showed that efficient resolution could also be obtained with other 1,3-disubstituted cyclohexenes (Table 1, entries 8–12). The results obtained in these cases are also consistent with the transition state analysis outlined in Scheme 5. For example, the unreacted substrate presented in entry 12 is expected to have the *R* configuration. To confirm the prediction, the pivaloate was converted to 3-*tert*-butylcyclohexanone by hydrolysis (NaOMe–MeOH). The resulting ketone was determined to indeed have the *R* configuration by comparing the measured optical rotation with the reported value for the ketone.<sup>13</sup>

**Desymmetrization and Subsequent Kinetic Resolution of 1,4-Cyclohexadienes.** Asymmetric desymmetrization of a symmetrical bifunctional molecule coupled with a subsequent kinetic resolution provides a unique opportunity to generate chiral molecules and probe the reaction mechanism. In such a process, the minor enantiomer from the first asymmetric transformation could be preferentially consumed in a second transformation as the reaction proceeds, leading to an enhancement of the optical purity of the major enantiomer. This powerful feature has been elegantly demonstrated in a number of asymmetric transformations.<sup>18–21</sup> The feasibility of the

(7) For leading references on kinetic resolution by asymmetric epoxidation see: (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1. (c) Vander Velde, S. L.; Jacobsen, E. N. *J. Org. Chem.* **1995**, *60*, 5380. (d) Noguchi, Y.; Irie, R.; Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4533. (e) Linker, T.; Rebien, F.; Tóth, G.; Simon, A.; Kraus, J.; Bringmann, G. *Chem. Eur. J.* **1998**, *4*, 1944.

(8) For kinetic resolution of acyclic olefins with chiral dioxirane see: Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Lai, T.-H.; Wong, M.-K. *J. Org. Chem.* **2001**, *66*, 4619.

(9) The trans configuration of the major isomer was assigned based on the following comparison: Epoxide **3a** was desilylated with TBAF. The  $^1\text{H}$  NMR analysis showed that the resulting epoxy alcohol matched the minor isomer (trans epoxide) of the epoxidation products of 2-phenyl-2-cyclohexenol with *m*-CPBA. It is known that the epoxidation of an allylic alcohol with *m*-CPBA gives cis epoxide as a major product due to the directing effect of the hydroxy group. For a leading reference on this subject see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(10) The epoxidation of 1-phenylcyclohexene with ketone **1** gives 98% ee, showing that the phenyl group acts as a small group due to its flat nature, favoring spiro **A** (Scheme 2). A lower 81% ee obtained with 1-methylcyclohexene indicates that the methyl group is larger than the phenyl group and spiro **A** is somewhat disfavored, leading to the substantial involvement of planar **B** (for detailed discussions see ref 4b).

(11) For kinetic resolution of related systems using asymmetric dihydroxylation see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2503.

(12) The trans configuration was assigned as epoxide **3a**.  
(13) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040.  
(14) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.  
(15) Allen, J. V.; Williams, J. M. *J. Tetrahedron Lett.* **1996**, *37*, 1859.  
(16) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Pharm. Bull.* **1985**, *33*, 52.

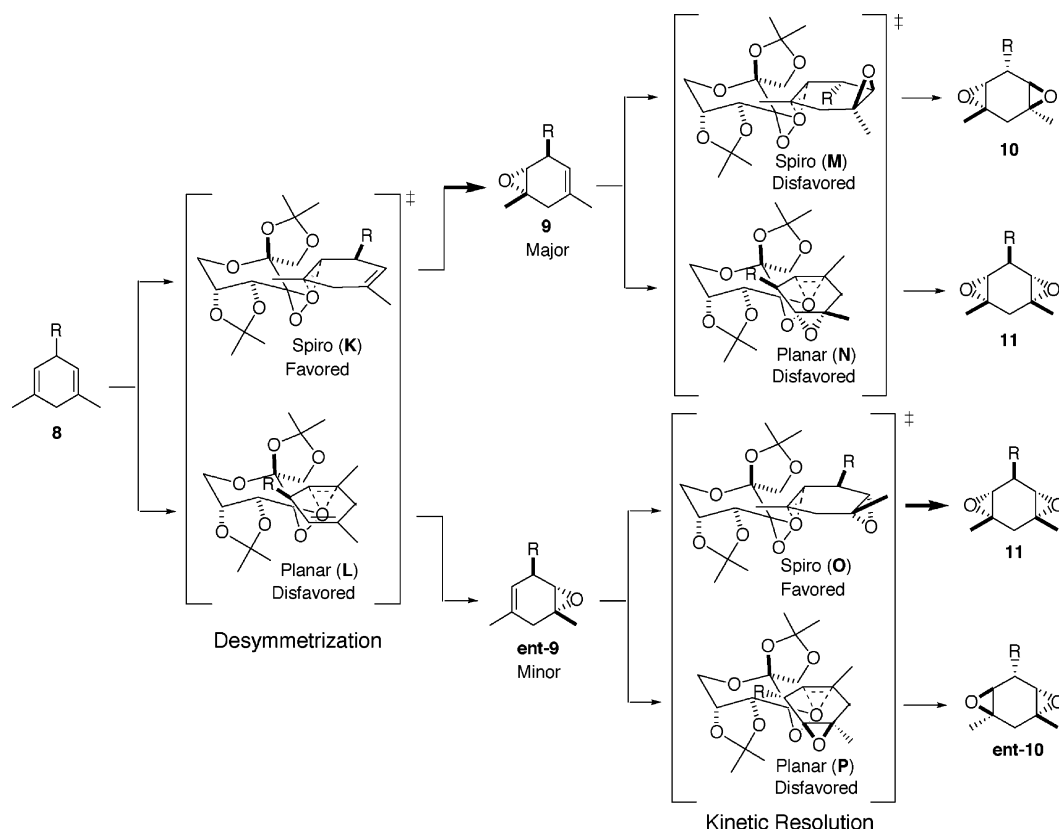
(17) Mori, K.; Puapoomchareon, P. *Liebigs Ann. Chem.* **1991**, 1053.

(18) For reviews see: (a) Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63. (b) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (c) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765.

(19) For additional discussions see: (a) Ward, D. E.; How, D.; Liu, Y. *J. Am. Chem. Soc.* **1997**, *119*, 1884. (b) Kroutil, W.; Kleewein, A.; Faber, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3251. (c) DeMello, N. C.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 329.



## SCHEME 7



kinetic resolution of cyclohexenes mediated by ketone **1** prompted us to investigate the desymmetrization and subsequent kinetic resolution of symmetrical cyclohexadienes,<sup>22</sup> with the aim of further exploring the mechanistic features of this asymmetric epoxidation.

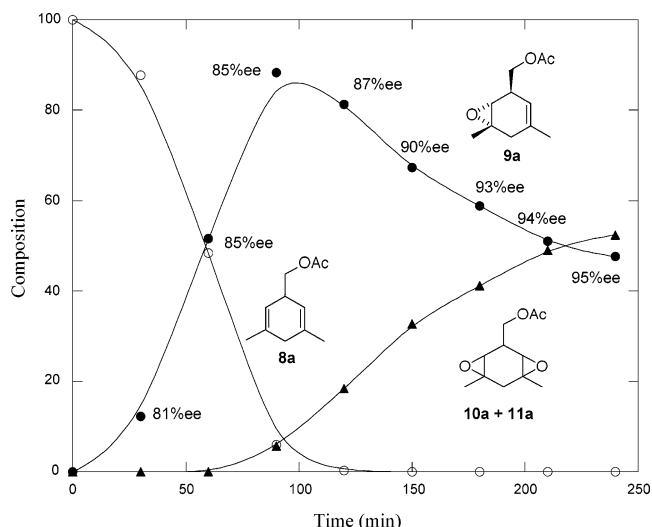
Dimethylcyclohexadiene **8**, with the prochiral center proximal to the two olefins, became our initial substrate for studies (Scheme 7). Diene **8a** (R = CH<sub>2</sub>OAc) was subjected to the standard epoxidation conditions, and the reaction composition and ee of the monoepoxide **9a** were analyzed by GC at different reaction times. As shown in Figure 1, the ee of the monoepoxide **9a** gradually

increased with reaction time (81% to 95% from 30 to 240 min). The initial desymmetrization where the spiro **(K)** and planar **(L)** transition states delivered the oxygen preferentially anti to the R group gave monoepoxide **9a** in 81% ee (Scheme 7). In a second epoxidation, the minor enantiomer (**ent-9a**) was preferentially epoxidized through spiro **(O)**, resulting in an increase of the optical purity of monoepoxide **9a**. Thus, the monoepoxide could be obtained in high ee (>90%) from an initially less enantioselective epoxidation (81% ee) by a slight sacrifice of the monoepoxide. Additional dienes examined also showed

(20) For examples of enzymatic processes see: (a) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. (b) Wu, S.-H.; Zhang, L.-Q.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *Tetrahedron Lett.* **1985**, *26*, 4323. (c) Kazlauskas, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953. (d) Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942. (e) Akai, S.; Naka, T.; Fujita, T.; Takebe, Y.; Tsujino, T.; Kita, Y. *J. Org. Chem.* **2002**, *67*, 411.

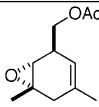
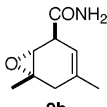
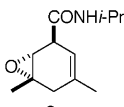
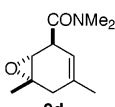
(21) For examples of nonenzymatic processes see: (a) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055. (b) Doku-zovic, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034. (c) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (d) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793. (e) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529. (f) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K.-I. *Organometallics* **1993**, *12*, 4188. (g) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101. (h) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (i) Aggarwal, V. K.; Esquivel-Zamora, B. N.; Evans, G. R.; Jones, E. *J. Org. Chem.* **1998**, *63*, 7306. (j) Harada, T.; Egusa, T.; Oku, A. *Tetrahedron Lett.* **1998**, *39*, 5535. (k) Spivey, A. C.; Woodhead, S. J.; Weston, M.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 769.

(22) For desymmetrization of cyclohexadienes with asymmetric dihydroxylation and aminohydroxylation see: (a) Angellaud, R.; Landais, Y. *J. Org. Chem.* **1996**, *61*, 5202. (b) Landais, Y.; Zekri, E. *Eur. J. Org. Chem.* **2002**, 4037.



**FIGURE 1.** Epoxidation of diene **8a** with ketone **1** (100 mol % of **1** used).

TABLE 2. Desymmetrization and Kinetic Resolution of Cyclohexadienes by Ketone 1<sup>a</sup>

entry	epoxide	time (h)	cat. (%)	yield (%) <sup>b</sup>	ee (%)
1		1.5	30	87	79 <sup>c</sup>
		4	100	53	95 <sup>c</sup>
2		1.5	30	78	89 <sup>d</sup>
		4	60	69	95 <sup>d</sup>
3		1.5	30	73	89 <sup>d</sup>
		4	60	68	95 <sup>d</sup>
4		1.5	30	63	83 <sup>d</sup>
		3	60	57	91 <sup>d</sup>

<sup>a</sup> All reactions were carried out with substrate (1 equiv), ketone (0.3–1.0 equiv), Oxone (1.38 equiv), and K<sub>2</sub>CO<sub>3</sub> (5.8 equiv) in CH<sub>3</sub>CN–DMM–0.05 M Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10H<sub>2</sub>O of aqueous EDTA (4 × 10<sup>−4</sup> M) solution (1:2:1.5, v/v) at 0 °C for the time indicated. When 60 or 100 mol % of **1** used, the amount of Oxone and K<sub>2</sub>CO<sub>3</sub> solution was doubled and added over the time indicated. <sup>b</sup> Isolated yield. <sup>c</sup> Enantioselectivity was determined by chiral GC (Chiraldex G-TA). <sup>d</sup> Enantioselectivity was determined by HPLC (Chiralpak AD).

that the ee values of the monoepoxides improved by using longer reaction times, and the monoepoxides could be isolated in good yields and high ee values (Table 2).<sup>23</sup>

Previous desymmetrization–kinetic resolution processes required an existing prochiral center proximal to the reacting sites to direct the transformations.<sup>18–21</sup> Further studies showed that the desymmetrization–kinetic resolution also proceeded efficiently for diene **12** (Figure 2). The ee of monoepoxide **13** increased from 80% to 98% after prolonged reaction time (Figure 2).<sup>24</sup> This result was rather interesting, considering diene **12** contains no prochiral center adjacent to the reacting olefins. A possible rationalization for this increase in optical purity with reaction time is shown in Scheme 8. The first epoxide directs the second epoxidation to the opposite face,<sup>25,26</sup> preferentially consuming the minor enantiomer (**ent-13**). The second epoxidation of **12** was much more rapid compared to diene **8** due to the lack of steric crowding of the monoepoxide.

Additional evidence for the directing effect of the first epoxide in the second epoxidation is displayed with diene

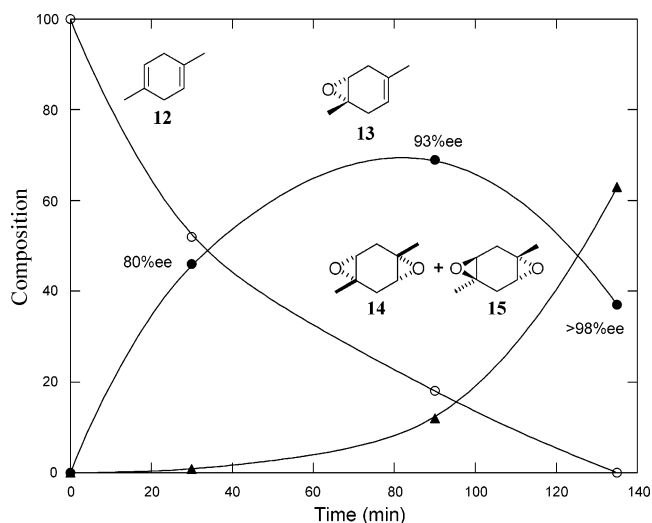


FIGURE 2. Epoxidation of diene **12** with ketone **1** (30 mol % of **1** used).

(23) The stereochemistry of the epoxides was tentatively assigned based on mechanistic considerations. A crystal structure was obtained for monoepoxide **9c** showing the relative stereochemistry of the epoxide and amide to be trans, providing support for the proposed transition state analysis of Scheme 7.

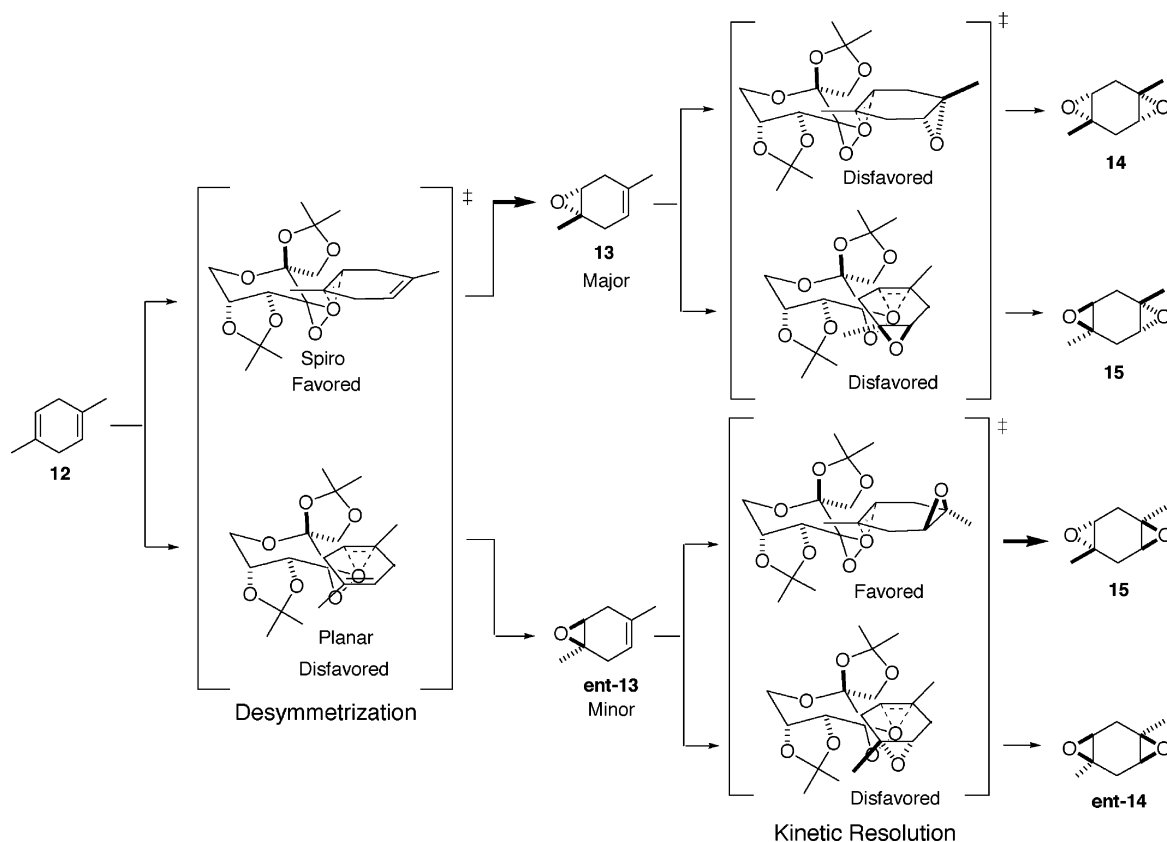
(24) Each data point was taken from a separate run.

(25) The epoxidations of 1,4-cyclohexadiene with peracids and MTO–H<sub>2</sub>O<sub>2</sub> systems have shown that the trans bisepoxide is formed predominately see: (a) Craig, T. W.; Harvey, G. R.; Berchtold, G. A. *J. Org. Chem.* **1967**, 32, 3743. (b) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, 119, 6189.

(26) For conformational studies of epoxycyclohexanes and related compounds see: Aumelas, A.; Casadevall, E.; Casadevall, A. *Tetrahedron* **1978**, 34, 2481.

**16** (Figure 3). In contrast to **13**, the ee of monoepoxide **17** dropped as the reaction progressed. As shown in Scheme 9, the trans epoxidation was favored in the second step, and the major enantiomer of monoepoxide **17** was preferentially epoxidized, leading to the decrease of its ee as the reaction proceeded.<sup>25</sup> The fact that the bisepoxide was found to be optically active indicated that the epoxide rings must be trans to each other, since the *cis*-bisepoxide is a meso compound. As the reaction proceeded, the ee of the bisepoxide also decreased, as the

## SCHEME 8



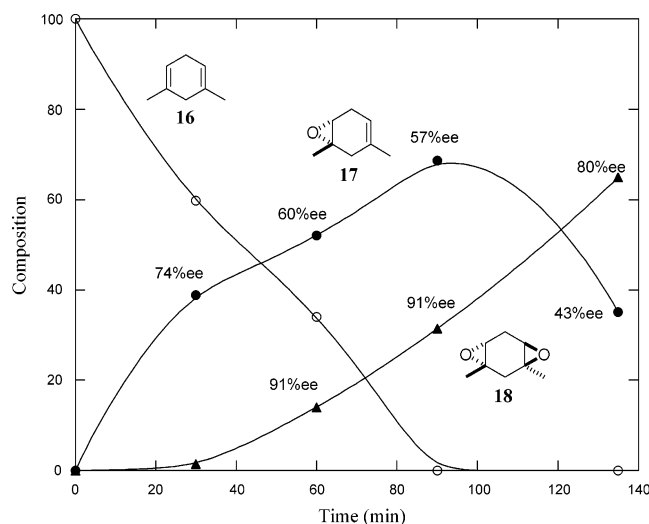
pool of monoepoxide became deficient in the major monoepoxide.<sup>24,27</sup>

In summary, we have shown that the kinetic resolution of 1,3- and 1,6-disubstituted cyclohexenes via chiral dioxirane is feasible. Resolution was obtained for a number of trisubstituted cyclohexenes. Furthermore, we have shown that ketone **1** can successfully desymmetrize cyclohexadienes and kinetically resolve the monoepoxides in situ, leading to the increase or decrease of the monoepoxide ee depending on the diene system. In some cases, a prochiral directing group is not required and the

first formed epoxide stereoselectively directs the second epoxidation. When the coupled desymmetrization and kinetic resolution is used synergistically, high enantiopurity can be obtained for an epoxide from an intrinsically less enantioselective substrate. Importantly, in the cases studied, the spiro-planar transition state model provides effective rationalization for the observed absolute and relative stereochemistry as well as optical purity. The current study provides useful insight to analyze and predict the stereochemical outcome for various olefin systems. Efforts will be devoted to investigate other systems to further reveal the catalytic properties of this asymmetric epoxidation.

## Experimental Section

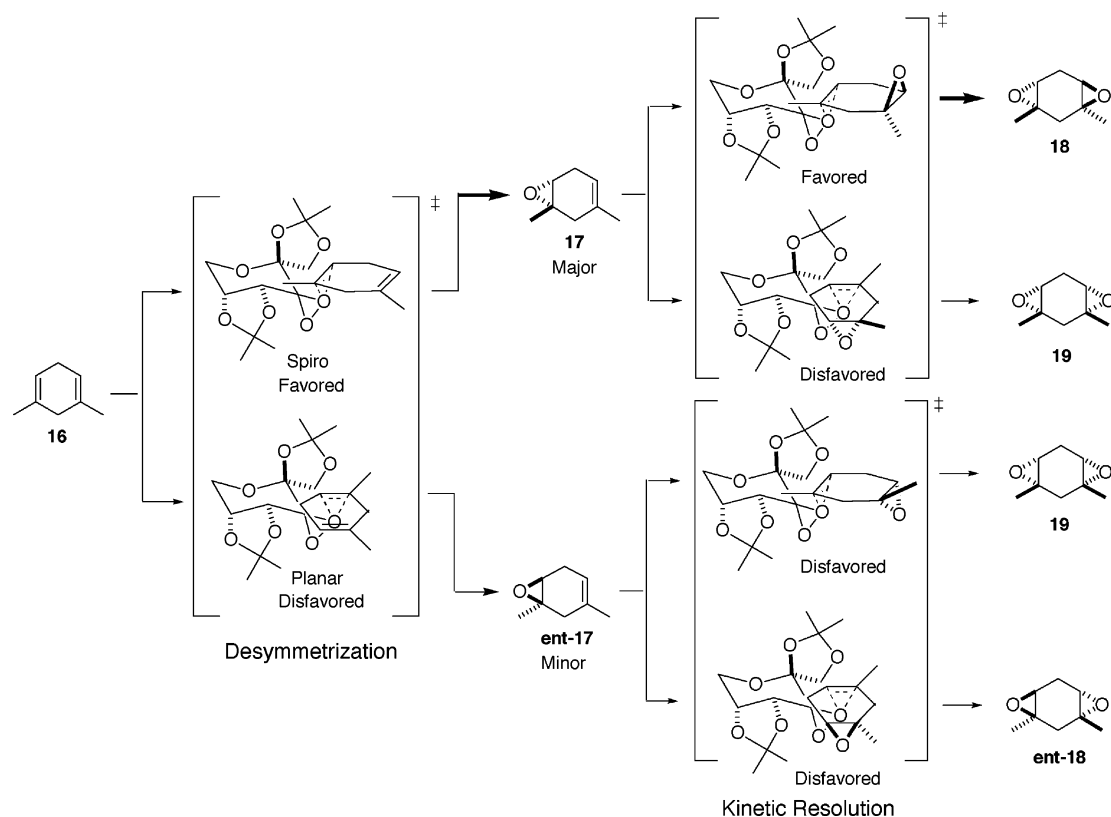
**General Methods.** Oxone was purchased from Aldrich (it has been found that the oxidation activity of the purchased Oxone occasionally varies with different batches). All glassware used for the epoxidation was carefully washed in order to be free of any trace metals which catalyze the decomposition of Oxone. The symmetrical dienes were prepared by Birch reduction of the appropriate benzene derivatives and subsequent transformations. Column chromatography was done with 60 Å 230–400 mesh Whatman silica gel. The quality and acidity of the silica gel are very important for repeatable yields (buffering acidic silica gel with bases results in deprotonation of the mono epoxide leading to aromatization). High-resolution mass spectra were performed at the mass spectrometry facility of Colorado State University. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). X-ray crystal-



**FIGURE 3.** Epoxidation of diene **16** with ketone **1** (30 mol % of **1** used).

(27) As the minor monoepoxide **ent-17** accumulated with reaction time, **ent-18** was formed from the epoxidation of **ent-17** via a planar transition state, decreasing the ee of **18**.

## SCHEME 9



lographic analyses of epoxide **9c** were performed at the X-ray Crystallographic Laboratory of Colorado State University.

**Representative Kinetic Resolution Procedure (Table 1, Entry 3).** To a vigorously stirred solution of 1-phenyl-6-acetoxycyclohexene (0.108 g, 0.50 mmol), ketone **1** (0.064 g, 0.25 mmol), and tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol) in dimethoxymethane (10 mL), acetonitrile (5 mL), and buffer (0.05 M  $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$  in  $4 \times 10^{-4}$  M  $\text{Na}_2\text{EDTA}$ , 10 mL) were added a solution of Oxone (0.760 g, 1.24 mmol) in aq  $\text{Na}_2\text{EDTA}$  ( $4 \times 10^{-4}$  M, 9.8 mL) and a solution of  $\text{K}_2\text{CO}_3$  (0.76 g, 5.5 mmol) in water (9.8 mL) separately at a rate of 4 mL/h (via syringe pump) at 0 °C over 2.5 h. The reaction mixture was quenched with water, extracted with pentane, washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, concentrated, and purified by column chromatography [the silica gel was buffered with 1%  $\text{NEt}_3$  in hexane, hexane/ethyl acetate (60/1 v/v) was used as eluent] to give recovered starting

material (0.046 g, 43%) as a colorless oil and the trans epoxide (0.037 g, 32%) as a colorless oil.

**Acknowledgment.** We are grateful to the generous financial support from the General Medical Sciences of the National Institutes of Health (GM59705-05) and the Camille and Henry Dreyfus Foundation. J.C.L. thanks Boehringer Ingelheim for a graduate fellowship.

**Supporting Information Available:** Experimental procedure for the epoxidation reactions, the characterization of the compounds, and the data for the determination of the enantiomeric excess of the unreacted olefins and epoxides. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO048217P