Kinetic Resolution of Racemic Cyclic Olefins via Chiral Dioxirane

Michael Frohn,† Xiaoming Zhou,† Jian-Rong Zhang,† Yong Tang, and Yian Shi*

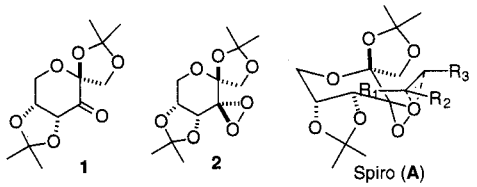
Department of Chemistry, Colorado State University Fort Collins, Colorado 80523

Received August 21, 1998

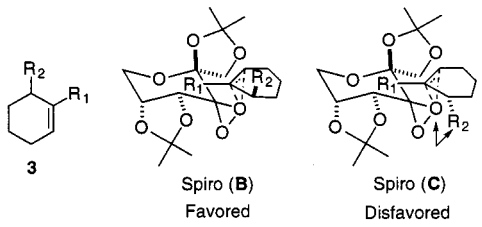
Chiral dioxiranes have been shown to be effective reagents for asymmetric epoxidation of olefins.[1,2] Recently we reported a highly enantioselective epoxidation method for trans- and trisubstituted olefins using a fructose-derived ketone **1** as catalyst and Oxone as oxidant.[3] The epoxidation has been shown to proceed primarily through a well ordered spiro transition state **A** (Scheme 1).[3b] Since dioxiranes are expected to be sensitive to sterics, an existing chiral center adjacent to the double bond provides the possibility for kinetic resolution.[4] Herein we wish to report our preliminary studies in this area.

Our initial studies have been focused on cyclic olefins with the chiral center at the allylic position. The rigid conformation and proximity of the chiral center to the olefin make them promising candidates for kinetic resolution. Therefore, we began the study with 1,6-disubstituted cyclohexenes (**3**) (Scheme 2). Transition states **B** and **C** represent the spiro transition states for the epoxidation of each enantiomer. Transition state **C** is expected to be disfavored compared to transition state **B** due to the steric interaction between R_2 and one of the dioxirane oxygens. Consequently one enantiomer would be epoxidized faster than the other.

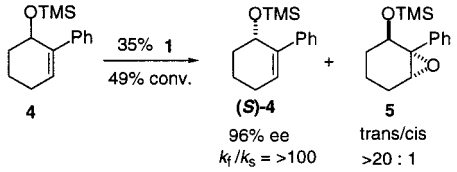
Scheme 1



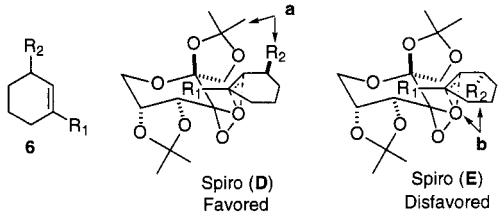
Scheme 2



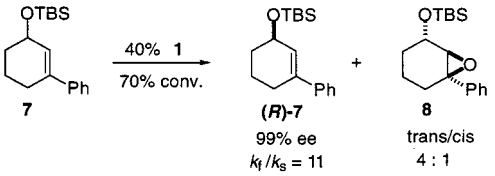
Scheme 3



Scheme 4



Scheme 5



To test this hypothesis, we used (±)-1-phenyl-6-(trimethylsiloxy)cyclohexene (**4**) as our initial substrate. 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 ^{1}H NMR assay of the crude reaction mixture (Scheme 3). The ^{1}H NMR spectra showed that the trans epoxide was formed predominantly (trans/cis > 20:1).[5] Analysis of the unreacted substrate using HPLC on a chiral support (Chiralcel OD) showed a 96% ee. The fact that the major epoxide product was trans and the recovered olefin was enriched in the *S* isomer supports the above transition state analysis.

* Corresponding author. Phone: 970-491-7424. Fax: 970-491-1801. Email: yian@lamar.colostate.edu.

† M. F., X. Z., and J.R.Z. contributed equally to this work.

(1) For general leading references on dioxiranes see: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res*. **1989**, *22*, 205. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem*. **1995**, *67*, 811. (d) Clennan, E. L. *Trends Org. Chem*. **1995**, *5*, 231. (e) Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg*. **1996**, *105*, 581.

(2) For leading references on asymmetric epoxidation mediated 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) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L *Tetrahedron* **1995**, *51*, 3587. (d) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem*. **1995**, *60*, 1391. (e) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc*. **1996**, *118*, 491. (f) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc*. **1996**, *118*, 11311. (g) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S. G.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (h) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. (i) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem*. **1997**, *62*, 8288. (j) Bergbreiter, D. E. *Chemtracts: Org. Chem*. **1997**, *10*, 661. (k) Armstrong, A.; Hayter, B. R. *Chem. Commun*. **1998**, 621. (l) Dakin, L. A.; Panek, J. S. *Chemtracts: Org. Chem*. **1998**, *11*, 531. (m) 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.

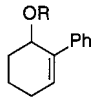
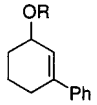
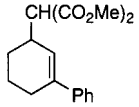
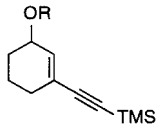
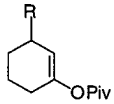
(3) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc*. **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224. (c) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 2948. (d) Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 3099. (e) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 4425. (f) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819. (g) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 8475.

(4) Many excellent kinetic resolution methods have been developed. 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.

(5) The trans configuration of the major isomer was assigned on the basis of the following comparison: Epoxide **5** was desilylated with TBAF. The ^{1}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 the 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.

10.1021/ja9830039 CCC: $18.00
Published on Web 08/06/1999

Table 1. Kinetic Resolution of Representative Olefins by Ketone **1** Catalyzed Asymmetric Epoxidation[a]

entry	substrate	temp (°C)	con. (%)[b]	recov'd SM ee (%)[c]	trans epoxide ee (%)	epoxide (trans/cis)[d]	k_{rel}[e] (k_f/k_s)
							
1[f]	R = TMS	−10	49	96[g] (S)[h]	95[g]	>20	>100
2[i]	R = Me	−10	65	99[j] (S)	85[k]	6	16
3[l]	R = COMe	0	54	96[m] (S)	88[j]	12	39
4[n,o]	R = COOEt	−10	51	94[g] (S)	97[j]	>20	70
							
5[p]	R = TBS	−10	70	99[g] (R)	81[q]	4	11
6[r]	R = Me	−10	61	95[g] (R)	nd	6	14
							
7[r]		0	72	81[m] (R)	nd	1.7	4
							
8[r]	R = TBS	−10	49	75[s] (R)	nd	13	18
9[r]	R = TBS	20	66	96[s] (R)	nd	8	11
							
10[n]	R = OTMS	−10	61	91[m] (R)	76[k]	4	11
11[t]	R = ^{i}Pr	−10	59	93[m] (S)	85[k]	8	15
12[i]	R = ^{t}Bu	−10	54	99[m] (R)[u]	84[k]	>20	61

[a] All reactions were carried out with substrate (1 equiv), ketone (0.25−0.75 equiv), Oxone (2.3 equiv), and K_2CO_3 (9.5 equiv) in CH_3CN-DMM-0.05 M $Na_2B_4O_7 \cdot 10H_2O$ in aqueous EDTA (4×10^{-4} M) solution (1:2:2, v/v/v). Oxone was added over 2.5 h except for entry 5 and entry 6 (1.5 h). [b] Conversion was determined by ^{1}H NMR of the crude reaction mixture after workup. 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's of the olefin and epoxide to the following equation: ee(olefin)/ee(epoxide) = $C/(1 - C)$. In these cases the meassured conversion was consistent with the calculated conversion. [c] The absolute configuration was tentatively assumed on the basis of the spiro reaction mode unless otherwise noted. [d] The ratio of trans and cis epoxides was determined by ^{1}H NMR. [e] The relative rate was calculated 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 12). [f] 0.35 equiv of ketone used. [g] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [h] The configuration was determined by comparing the measured optical rotation with the known alcohol after desilylation (ref 11). [i] 0.45 equiv of ketone used. [j] Enantioselectivity was determined by chiral HPLC (Chiralcel AD). [k] Enantioselectivity was determined by ^{1}H NMR shift analysis using Eu(hfc)$_3$. [l] 0.50 equiv of ketone used. [m] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [n] 0.60 equiv of ketone used. [o] 2.8 equiv of Oxone used. [p] 0.40 equiv of ketone used. [q] Enantioselectivity was determined by chiral HPLC (Chiralcel AD) of the corresponding benzoate. [r] 0.25 equiv of ketone used. [s] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation with TBAF. [t] 0.75 equiv of ketone used. [u] The configuration was determined by comparing the measured optical rotation with the known ketone after hydrolysis (ref 9).

The feasibility of the kinetic resolution of (±)-2-phenyl-2-cyclohexenol derivatives led us to investigate the kinetic resolution of 1,3-disubstituted cyclohexenes (**6**) (Scheme 4). The kinetic resolution efficiency would be dependent on the energy difference between repulsive interactions **a** and **b**. Subjecting the TBS ether of 3-phenyl-2-cyclohexenol (**7**)[6] to the typical reaction conditions (with 40% ketone catalyst **1** at −10 °C for 1.5 h) led to a 70% conversion of the substrate (Scheme 5). The product was a 4:1 mixture of trans and cis epoxides (**8**) favoring the trans isomer.[7] This result demonstrates that transition state **D** is favored over **E**, suggesting that the interaction **b** is greater than the interaction **a**.[8] The enantiomeric excess of the unreacted substrate was determined to be 99%.

Encouraged by the result obtained for compound **7**, we prepared and investigated a number of 1,3-disubstituted cyclohexenes (Table 1, entries 6−12). The resolution efficiency for these substrates is reasonably good. On the basis of the reaction model presented in Scheme 4, the unreacted substrates presented in entries 5−10 and 12 are likely to have *R* configurations. To confirm the configuration, the pivaloate in entry 12 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.[9]

In summary, we have shown that the kinetic resolution of 1,3 and 1,6-disubstituted cyclohexenes via chiral dioxirane is feasible. High-resolution efficiency was obtained for a number of trisubstituted cyclic olefin substrates,[10] which provides a valuable way to prepare certain chiral intermediates in a straightforward manner. Since the dioxirane-mediated resolution is expected to rely largely on steric interactions, this process could potentially be applied to olefins with a variety of substituents. Extension of this resolution to other classes of substrates is currently under study. In addition to the synthetic value, such a study will yield useful mechanistic information.

Acknowledgment. We are grateful to the generous financial support from the Beckman Young Investigator Award Program, the General Medical Sciences of the National Institutes of Health (GM55704-01), the Camille and Henry Dreyfus New Faculty Award Program, Alfred P. Sloan Foundation, and Colorado State University.

Supporting Information Available: Experimental procedure for the kinetic resolution reaction and the characterization data of the compounds in Table 1 along with the HPLC and NMR spectral data for the determination of the enantiomeric excess of the unreacted substrates and the epoxide products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9830039

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

(7) The trans configuration was assigned as epoxide **5**.

(8) In addition to the spiro transition state (**C** or **E**), the epoxidation of the less reactive enantiomer of the substrate could proceed via an alternative planar transition state to give the trans epoxide, particularly when R_2 is large (e.g., Table 1, entry 12) (for further discussion of the effects of sterics on the transition state, see ref 3b).

(9) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc*. **1987**, *109*, 2040.

(10) For a Zr-catalyzed kinetic resolution of cyclic allylic ethers see: (a) Visser, M. S.; Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 3779. (b) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1997**, *119*, 1488.

(11) Allen, J. V.; Williams J. M. J. *Tetrahedron Lett.* **1996**, *37*, 1859.

(12) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem*. **1988**, *18*, 249.