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

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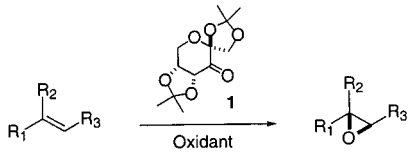
Received August 16, 2000

Asymmetric epoxidation of olefins presents a powerful strategy for the synthesis of enantiomerically enriched epoxides.[1−3] For the epoxidation of unfunctionalized *cis*-olefins, chiral salen and porphyrin complexes give very high enantioselectivities. Jacobsen's Mn salen catalyst is particularly successful and practical. Dioxiranes generated in situ from chiral ketones have been shown to be highly enantioselective for the asymmetric epoxidation of *trans*-olefins and trisubstituted olefins.[4−6] However, highly enantioselective epoxidation of *cis*-olefins using chiral dioxiranes still remains a challenging problem. Herein we wish to report our preliminary efforts on this subject.

Recently, we reported that the fructose-derived ketone **1** is an effective epoxidation catalyst and gives high ee values for a variety of *trans*-olefins and trisubstituted olefins (eq 1).[6] However,



(eq. 1)

epoxidation of *cis*-olefins using this ketone led to rather poor enantioselectivity.[6c] For example, a 39% ee was obtained for *cis*-β-methylstyrene, giving the (1R,2S) epoxide as the major enantiomer. Spiro transition states **A** and **B** are likely to be the two major competing transition states (Chart 1).[6c] The low ee obtained suggests that the ketone catalyst does not provide the necessary structural environment to sufficiently differentiate between the phenyl and methyl groups of the olefin in these two transition states (Chart 1).

Chart 1

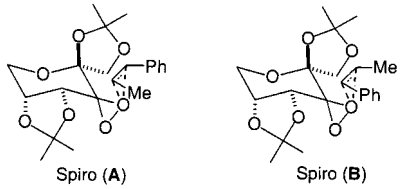
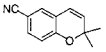
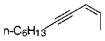


Table 1. Asymmetric Epoxidation of Olefins Catalyzed by Ketone **2**[a]

Entry	Substrate	Yield(%)[b]	ee (%)	Configuration
1[c]		87	91[h]	(-)-(1R,2S)[m,9a,b]
2[c]		91	92[i]	(-)-(1R,2S)[n]
3[d]		88	83[j]	(-)-(1R,2S)[m,9c]
4[c]		88	84[j]	(+)-(1R,2S)[m,9b,7d]
5[d]		77	91[k]	(-)-(5R,6S)[m,9d,e]
6[e]		61	91[l]	(+)-(3R,4R)[m,9f,g]
7[f]		82	91[l]	(-)-(2S,3R)[o,7a,d]
8[g]		77	87[l]	(-)-(2S,3R)[o]
9[g]		47	96[h]	(+)
10[g]		61	97[h]	(+)[9h]
11[g]		88	94[h]	(+)
12[g]		65	94[l]	(+)-(R,R)[m,9i,6c]
13[c]		91	77[h]	(+)-(R,R)[m,9a]
14[c]		78	95[h]	(+)[6c]
15[c]		55	80[l]	(+)[6c]

[a] All reactions were carried out with olefin (0.5 mmol), ketone (0.075−0.15 mmol), Oxone (0.89 mmol), and K_2CO_3 (2.01 mmol) in DME/DMM (3:1, v/v) (7.5 mL) and buffer (0.2 M K_2CO_3−AcOH, pH 8.0) (5 mL) at −10 or 0 °C unless otherwise stated. The reactions were stopped after 3.5 h. [b] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [c] With 0.075 mmol of ketone at −10 °C. [d] With 0.10 mmol of ketone at −10 °C. [e] With 0.075 mmol of ketone at 0 °C. [f] With 0.15 mmol of ketone at −10 °C. [g] With 0.15 mmol of ketone at 0 °C. [h] Enantioselectivity was determined by chiral GC (Chiraldex G-TA). [i] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [j] Enantioselectivity was determined by chiral HPLC (Chiralcel OB). [k] Enantioselectivity was determined by chiral HPLC (Chiralpak AD). [l] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [m] The absolute configurations were determined by comparing the measured optical rotations with the reported ones. [n] The epoxide was reduced to 1-(2-naphthyl)propanol with $LiAlH_4$, and the absolute configuration was determined by comparing the measured optical rotation of the alcohol with the reported one (ref 10). [o] The epoxide was reduced with $LiAlH_4$ to the corresponding homopropargyl alcohol, and the absolute configuration was determined by a correlation of the resulting alcohol with a prepared authentic sample by a different route.

During the course of our continuing studies of structural effects of ketones on catalysis, ketone **2**, a nitrogen analogue of **1**, was

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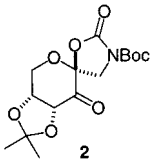
10.1021/ja003049d CCC: $19.00
Published on Web 11/02/2000

designed and investigated for epoxidation. Although our initial



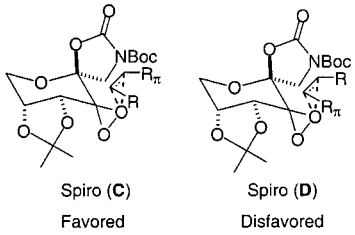
2

studies showed that ketone **2** did not give as high enantioselectivity as **1** for *trans*-olefins, its behavior toward *cis*-olefins was strikingly different. When the epoxidation of *cis*-β-methylstyrene was carried out with 15 mol % ketone **2** at −10 °C, (1*R*,2*S*)-*cis*-β-methylstyrene oxide was obtained in 87% yield with 91% ee. Furthermore, like other dioxirane-mediated epoxidations, the epoxidation of *cis*-β-methylstyrene was found to be stereospecific, with no *trans*-β-methylstyrene oxide formed during the reaction, as judged by ^{1}H NMR and GC assays of the crude reaction mixture.

Encouraged by this result, we investigated the asymmetric epoxidation of a variety of *cis*-olefins to explore the generality of ketone **2**. The enantiomeric excesses were generally high for a variety of acyclic and cyclic *cis*-olefins conjugated with aromatics (Table 1, entries 1−6). The epoxidation of *cis*-1-cyclohexyl-1-propene with ketone **2** resulted in the formation of the (2*R*,3*S*)-2-cyclohexyl-3-methyloxirane in 67% ee, indicating that a conjugated aromatic group is beneficial for the enantioselectivity. The epoxidation of acyclic enynes was also found to be both highly enantioselective and stereospecific, providing *cis*-epoxides with high ee values (Table 1, entries 7 and 8).[7] High ee values were obtained for 3,3-ethylenedioxycycloalkenes as well (Table 1, entries 9−11). The enantioselectivity for *trans*-olefins and trisubstituted olefins was found to be substrate dependent (Table 1, entries 12−15).[8]

The high ee values obtained with ketone **2** for *cis*-olefins are rather intriguing. Spiro **C** and **D** are the two most plausible

Chart 2



transition states (Chart 2). The determination of the absolute configurations of some selected epoxides (Table 1, entries 1−8) showed that groups with a π system preferred to be proximal to the spiro oxazolidinone. It appears that spiro **C** is favored over **D** for substrates containing a π system. A clear mechanistic understanding awaits further investigation.

In summary, we report a highly enantioselective epoxidation for *cis*-olefins using chiral ketone **2** as catalyst and Oxone as oxidant. High ee values have been obtained for a number of cyclic and acyclic *cis*-olefins. The epoxidation was stereospecific with no isomerization observed in the epoxidation of acyclic systems. The source of the enantioselectivity is not known at this time. The results described show that chiral dioxiranes can also epoxidize *cis*-olefins in addition to *trans*-olefins and trisubstituted olefins in a high degree of enantioselectivity. Ketone **2** reveals a promising structural element required for the ketone to induce the high enantioselectivity for the epoxidation of *cis*-olefins, which provides a basis for further optimization of the ketone structure to enhance both enantioselectivity and catalytic activity.

Acknowledgment. We are grateful for the generous financial support from the General Medical Sciences of the National Institutes of Health (GM59705-02), the Arnold and Mabel Beckman Foundation, the Camille and Henry Dreyfus Foundation, Alfred P. Sloan Foundation, DuPont, Eli Lilly, GlaxoWellcome, and Merck.

Supporting Information Available: Experimental procedures for the preparation of ketone **2** and for the asymmetric epoxidation reaction and the characterization of the ketone and epoxides along with the GC and HPLC data for the determination of the enantiomeric excess of the epoxides (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Up to 40% ketone could be recovered after extracting the aqueous layer of the reaction mixture with CH_2Cl_2−EtOAc, and purification by flash chromatography. The recovered ketone gave a similar conversion and ee for the epoxidation.

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