Design and Synthesis of Binaphthol-Derived Chiral Ketone Catalysts for Dioxirane-Mediated Asymmetric Epoxidation of Olefins

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Received April 17, 1999

Binaphthol-derived chiral ketones **1a-c** were synthesized and were shown to serve as active catalysts for asymmetric epoxidation of olefins using Oxone®, although their enantioselectivities were not high. However, very interestingly, the stereochemical outcome of the resulting epoxides implicates that in the epoxidation using **1a-c**, the planar transition state may be more favorable than the spiro transition state.

Catalytic asymmetric epoxidation of olefins presents a powerful strategy for the synthesis of enantiomerically enriched epoxides.[1] Among many other methods, chiral dioxiranes generated *in situ* from chiral ketone catalysts and Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) have been shown to be remarkably promising oxidation reagents.[2] Recently Yang *et al.* reported C_2-symmetric chiral ketones derived from binaphthyl dicarboxylic acids for asymmetric epoxidation which afforded modest to good enantioselectivities.[2a-c] Yang's ketones have conformationally flexible 11-membered ring structure. Intuitively speaking, the higher enantioselectivity could be achieved when chiral dioxirane has more rigid conformation and the stereogenic center is closer to one of the diastereotopic oxygen atoms of the dioxirane since the efficient stereochemical communication between substrate and catalyst is more likely to be expected. Based on this idea, we designed and prepared (*R*)-(+)-1,1'-bi-2-naphthol-derived 9-membered ketone **1a**,[2k] in which the chiral moiety in **1a** is closer to the oxygen-transfer site compared to that of Yang's ketones. However, it is discouraging that the observed enantioselectivity is significantly lower compared to that of Yang's ketones. For *trans*-stilbene as a substrate at pH 8.0, the corresponding chiral epoxide was obtained with an ee value of only 27%.[2k,3] However, very interestingly, the (*R,R*)-configuration of resulting epoxide is opposite to that obtained using Yang's ketones, which afforded the (*S,S*)-configured *trans*-stilbene oxide.[2a-c] This stereochemical outcome has been explained by Yang *et al*. that epoxidations proceeded mainly *via* spiro transition state.[2a-c] It is generally believed that dioxirane-mediated epoxidation proceeds more favorably *via* spiro transition state, in which steric repulsions of the dioxirane and olefin substituents are minimized.[6] For the planar-type arrangement of the oxygen transfer, usually more severe steric repulsions between the olefin substituents and the dioxirane would give the minor epoxide enantiomer. A spiro-like transition state also benefits from the stabilizing interaction of an oxygen lone pair with the π^* orbital of alkene.[7]

To improve the enantioselectivity and to understand the transition state geometry, we prepared 3,3'-substituted C_2-symmetric binaphthol-derived chiral ketones **1b,c**. In chiral

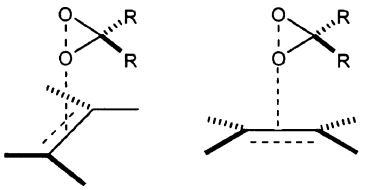
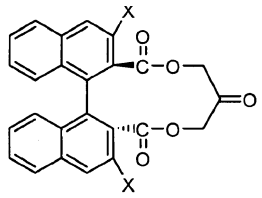


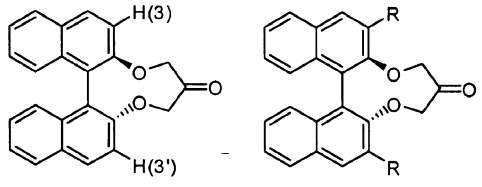
Figure 1. Spiro and planar transition state in dioxirane-mediated epoxidation.

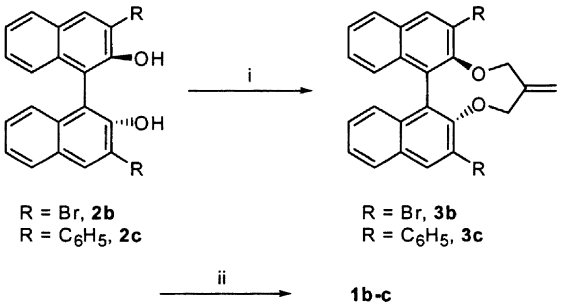


ketone **1a**, H-3 and H-3' are closer to the dioxirane group than other atoms on the chiral binaphthalene unit. Therefore the protons of C-3 and C-3' positions as well as the substituents at those positions may be the chiral sensors in the oxygen transfer process.[2b-c] Thus, the chiral ketones **1b** and **1c** which have steric bulkiness at the 3 and 3' positions would give better enantioselectivity than ketone **1a**.

The chiral ketones **1b** and **1c** were readily synthesized by the reaction of 3,3'-substituted (*R*)-(+)-1,1'-bi-2-naphthols **2b**[4] and **2c**[4] with 3-chloro-2-chloromethyl-1-propene, followed by ozonolysis as shown in Scheme 1.

In order to examine the catalytic efficiency of ketones **1a-c**, the epoxidations of olefins were carried out in a homoge-



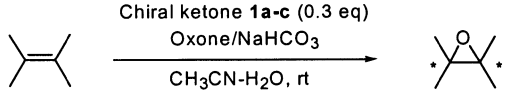


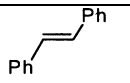
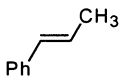
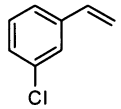
Scheme 1. Reagents and conditions: i) KOH/DMSO, $ClCH_2C(=CH_2)CH_2Cl$, rt; ii) O_3/CH_2Cl_2 then PPh_3, -78 °C.

neous CH_3CN-H_2O solvent system under alkaline conditions (pH-10.5). The epoxidation efficiency can generally be enhanced at high pH due to the decrease of the decomposition of ketone catalysts *via* Baeyer-Villiger oxidation. Moreover, at high pH, the nucleophilicity of Oxone® could be enhanced which increases the formation of dioxirane.[2e,h] At low pH, a substantial amount of the racemic epoxides can also be produced by Oxone® itself.[2e,h] The results of dioxirane-mediated epoxidation using ketones **1a-c** are summarized in Table 1.

In a 0.3 : 1 ketone : olefin ratio at room temperature, epoxidation catalyzed by ketones **1a-c** proceeded within 4-6 h, and afforded the epoxides in good yields. However, very low ees were observed. Moreover, the steric bulk at 3,3'-positions in the ketones **1b,c** did not affect the enantioselectivity. The ketone **1c** possessing the phenyl substituent at 3,3'-positions is far from increasing the enantioselectivity. It gave the nearly racemic product (2% ee). Nevertheless, very interestingly, all of the resulting epoxides showed the opposite absolute configurations to those expected usually.

Table 1. Asymmetric epoxidation of unfunctionalized olefins catalyzed by chiral ketones **1a-c** under alkaline conditions[a]



Olefin	Catalyst	time	% yield[b]	% ee[c]	config.[d]
	**1a**	4h	72	20	R,R
	1b	4h	58	24	R,R
	1c	4h	90	2	R,R
	**1a**	6h	91	19	R,R
	**1a**	6h	68	10	R
	**1a**	6h	65	7	R

[a]All the epoxidations were carried out with substrate (1 equiv.), ketone (0.3 equiv.), Oxone® (5 equiv.), and $NaHCO_3$ (15.5 equiv.) in CH_3CN/aqueous EDTA (4×10^{-4} M) (1.5/1). [b]GC yields. [c]Determined by chiral HPLC or chiral GC (conditions: see experimental section). [d]The configurations were determined by comparison of reported $[\alpha]_D$ values.[5]

As depicted in Figure 2, the spiro transition state of the favored orientation of chiral dioxirane and *trans*-stilbene would give the epoxides with *S,S*-configuration, whereas the planar transition state would afford *R,R*-configuration. Hence our results implicate that the epoxidation using **1a-c** may proceed mainly *via* planar transition state, not *via* spiro transition state. The steric repulsion between binaphthalene unit and olefin substituent in spiro transition state may outweigh the stabilizing interaction of oxygen lone pair with π^* orbital of the alkene. However, the low ees may be caused by the small energy difference between two transition states. The similar results have been recently observed by Adams and coworkers in the epoxidation of silyl enol ethers.[8]

Conclusions

We have prepared new binaphthol-derived chiral ketones **1b-c**, which were shown to be active catalysts in dioxirane-mediated asymmetric epoxidation of alkenes, although their enantioselectivities were not high enough. It is noticeable that the resulting epoxides showed the opposite absolute configurations to those expected usually. This result implicates that the epoxidation using **1a-c** may proceeded mainly

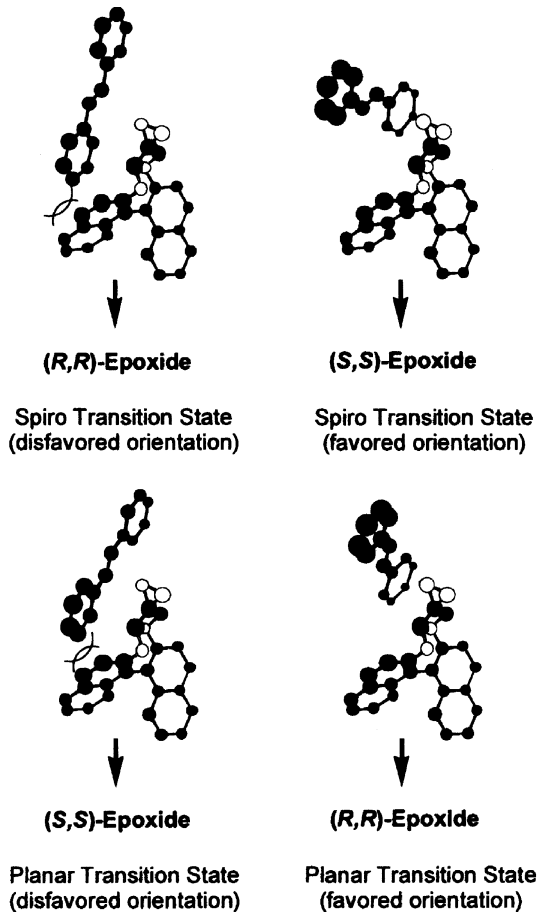


Figure 2

via planar transition state. The steric repulsion between binaphthalene unit and olefin substituent in spiro transition state outweighs the stabilizing interaction of oxygen lone pair with π^* orbital of the alkene. Efforts will be devoted to further understanding of the factors involved in the transition state in epoxidation reactions.

Experimental Section

General. Chromatographic purification of products was carried out by flash chromatography using Merck silica gel 60 (230-400 mesh). Thin layer chromatography was carried out on Merck silica gel 60F plates. Melting points were measured with a Thomas Hoover capillary melting point apparatus and were uncorrected. Optical rotation was measured on a AUTOPOL III polarimeter (Rudolph Research). ^{1}H NMR (300 MHz) and ^{13}C NMR (75.0 Hz) spectra were recorded on a Varian Gemini 300 spectrometer using TMS as an internal standard. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer and main absorption frequencies were given in cm^{-1}.

(*R*)-1,12-Dibromo-15-methylene-14*H*,16*H*-naphtho[1,2-*h*]naphtho[2,1-*f*]1,5-dioxonane (3b). To a stirred solution of (*R*)-(+)-3,3'-dibromo-1,1'-bi-2-naphthol (**2b**) (1.65 g, 3.70 mmol) in DMSO (100 mL) was added powered KOH (0.52 g, 9.25 mmol) at room temperature. After stirring for 15 min at room temperature, 3-chloro-2-chloromethyl-1-propene (0.46 g, 3.70 mmol) was added dropwise and stirring continued for 3 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl solution and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc : hexane = 1 : 10) to give **3b** (1.04 g, 56.6%) as a white solid: mp 179-182 °C; $[\alpha]^{25}_D$ -326.3 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (s, 4H, OCH_2-), 5.24 (s, 2H, C = CH_2), 7.09 (d, *J* = 9.0 Hz, 2H), 7.33 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.35, 141.48, 131.84, 130.23, 129.88, 128.93, 127.87, 123.58, 122.04, 120.55, 118.53, 76.17; HRMS (FAB) *m/z* calcd for $C_{24}H_{16}Br_2O_2$: 495.9498. Found: 495.9496.

(*R*)-1,12-Dibromo-14*H*,16*H*-naphtho[1,2-*h*]naphtho[2,1-*f*]1,5-dioxonan-15-one (1b). A solution of olefin **3b** (1.04 g, 2.09 mmol) in CH_2Cl_2 (50 mL) was ozonized at -78 °C by passing the O_3/O_2 stream. The progress of reaction was monitored by TLC. After completion of reaction, excess O_3 was removed by O_2 stream, and triphenylphosphine (1.10 g, 4.17 mmol) was added portionwise to the reaction mixture at -78 °C. After stirring for 30-40 min at the same temperature, the mixture was allowed to warm to room temperature. The solvent was evaporated, and the residue was purified by column chromatography (EtOAc : hexane = 1 : 6) to give **1b** (749 mg, 72.0%) as a white solid: mp 136-140 °C; $[\alpha]^{25}_D$ -438.6 (*c* 1.04, $CHCl_3$); IR (neat) 1722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (d of ABq, *J* = 16.5 Hz, 2H), 4.95 (d of ABq, *J* = 16.5 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 7.33 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 2H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 8.07 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.49, 156.06, 131.67, 130.31, 130.22, 129.82, 128.06, 120.94, 119.43, 118.92, 79.23; HRMS (FAB) *m/z* calcd for $C_{23}H_{14}Br_2O_3$: 497.9291. Found: 497.9295.

(*R*)-1,12-Diphenyl-15-methylene-14*H*,16*H*-naphtho[1,2-*h*]naphtho[2,1-*f*]1,5-dioxonane (3c). To a stirred solution of (*R*)-(+)-3,3'-diphenyl-1,1'-bi-2-naphthol **(2c)** (0.31 g, 0.71 mmol) in DMSO (35 mL) was added powered KOH (0.10 g, 1.77 mmol) at room temperature. After stirring for 15 min at room temperature, 3-chloro-2-chloromethyl-1-propene (0.09 g, 0.71 mmol) was added dropwise and stirring continued for 3 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl solution and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc : hexane = 1 : 10) to give **3c** (0.27 g, 77.1%) as a white solid: mp 127-130 °C; $[\alpha]^{25}_D$ -309.8 (*c* 0.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (s, 4H, OCH_2-), 5.25 (s, 2H, C = CH_2), 7.36-7.57 (m, 12H), 7.69 (d, *J* = 8.5 Hz, 4H), 8.03 (d, *J* = 9.0 Hz, 2H), 8.11 (d, *J* = 1.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.12, 141.93, 137.21, 132.66, 130.82, 130.03, 128.85, 127.32, 127.21, 126.20, 126.10, 123.75, 121.80, 119.87, 76.21; HRMS (FAB) *m/z* calcd for $C_{36}H_{26}O_2$: 490.1932. Found: 490.1939.

(*R*)-1,12-Diphenyl-14*H*,16*H*-naphtho[1,2-*h*]naphtho[2,1-*f*]1,5-dioxonan-15-one (1c). A solution of chiral olefin **3c** (0.78 g, 1.58 mmol) in CH_2Cl_2 (30 mL) was ozonized at -78 °C by passing the O_3/O_2 stream. The reaction was monitored by TLC. After completion of reaction, excess O_3 was removed by O_2 stream, and triphenyl phosphine (0.83 g, 3.17 mmol) was added portionwise to the reaction mixture at -78 °C. After stirring for 30-40 min at the same temperature, the mixture was allowed to warm to room temperature. The solvent was evaporated, and the residue was purified by column chromatography (EtOAc : hexane = 1 : 4) to give **1c** (616 mg, 79.2%) as a white solid: mp 138-140 °C; $[\alpha]^{25}_D$ -319.4 (*c* 0.40, $CHCl_3$); IR (neat) 1722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (d of ABq, *J* = 16.2 Hz, 2H), 4.94 (d of ABq, *J* = 16.2 Hz, 2H), 7.28-7.50 (m, 12H), 7.62 (d, *J* = 8.5 Hz, 4H), 8.01 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.11, 155.91, 140.78, 137.52, 132.36, 130.87, 128.93, 127.30, 127.14, 126.47, 126.08, 121.11, 118.70, 79.35; HRMS (FAB) *m/z* calcd for $C_{35}H_{24}O_3$: 492.1725. Found : 492.1727.

General procedure for asymmetric epoxidation of olefins catalyzed by chiral ketones 1a-c. To a solution of the olefinic substrate (0.1 mmol), chiral ketone (0.03 mmol) and Bu_4NHSO_4 (1.5 mg, 4.0 mol) in CH_3CN (1.5 mL) was added a buffer solution of 0.05 M $Na_2B_4O_7$ in 4×10^{-4} M Na_2EDTA (1.0 mL) with stirring at room temperature. Solutions of Oxone® (85 mg, 0.138 mmol) in 4×10^{-4} M Na_2EDTA (0.65 mL) and K_2CO_3 (80 mg, 0.58 mmol) in H_2O (0.65 mL) each were added simultaneously by means of separate syringes over a period of 1.5 h. The reaction mix-

ture was further stirred for 2.5-4.5 h, diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, concentrated *in vacuo*. The residue was purified by chromatography on silica gel (deactivated with 1% Et_3N solution in EtOAc-hexane) with EtOAc-hexane (1 : 4 to 1 : 20) as the eluent, to afford the corresponding epoxide. Determination of enantiomeric excess: for *trans*-stilbene oxide, HPLC conditions (Chiralcel OD column, *i*-PrOH : *n*-hexane = 10 : 90, flow rate: 0.8 mL/min) 6.60 min (*S*,*S*), 8.82 min (*R*,*R*); *trans*-β-methylstyrene oxide, GC conditions [Chiraldex-α column, carrier : nitrogen, oven temperature : 110 °C, initial time: 3 min, injection temperature: 250 °C, detection temperature (FID): 250 °C] 19.14 min (*S*,*S*), 19.84 (*R*,*R*); styrene oxide, GC conditions [Chiraldex-α column, oven temperature: 110 °C, initial time: 3 min, injection temperature: 250 °C, detection temperature (FID): 250 °C] 16.76 min (*S*), 17.13 (*R*); *m*-chlorostyrene oxide, GC conditions [Chiraldex-α column, carrier: nitrogen, oven temperature: 110 °C (3 min) at 2.5 °C/min, injection temperature: 250 °C, detection temperature (FID): 250 °C] 22.29 min (*S*), 22.51 (*R*).

Acknowledgment. This work was supported by a grant from Ministry of Science and Technology in Korea.

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