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Asymmetric epoxidation catalyzed by novel azacrown ether-type chiral quaternary ammonium salts under phase-transfer catalytic conditions

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Abstract—Asymmetric epoxidation of (*E*)-chalcone with alkaline hydrogen peroxide by novel chiral phase-transfer catalysts (chiral PTCs) with quaternary ammonium salts of azacrown ether proceeded in high yield and good enantioselectivity. Remarkably, this reaction depended on the length of the carbon chain on the nitrogen atom with the chiral PTCs and on the bulk of the base.

Chiral phase-transfer catalyst (chiral PTC) reaction has been increasingly useful for asymmetric synthesis, where there is no necessity to perform it under strict reaction conditions such as inert gas or dehydrated circumstance. In particular, quaternary ammonium salts derived from cinchona alkaloids have been more widely used in chiral PTC,[1] although there are many restrictions in the catalyst design. Therefore, some developments of novel chiral PTCs have been reported for asymmetric alkylation of glycine imine esters recently,[2] and the progress of new chiral PTCs is a challenging theme in asymmetric synthesis. For example, in asymmetric epoxidation of electron-deficient olefins under PTC conditions,[3] it has been reported by Maruoka and co-workers that spiro-type quaternary ammonium salts, prepared via multi-steps from BINOL, have been effective in this reaction.[4]

Chiral PTC has been generally classified into two systems: one is chiral onium salts which function as surfactant in liquid–liquid phase (aqueous solution/less polar organic solvent), and the another is chiral crown ethers which have high ability of molecular recognition in solid–liquid phase (inorganic salt/less polar organic solvent).[1] Since we thought it would be interesting to devise a compound which functions not only as a surfactant but also a chiral recognition molecule, we constructed the C_2-symmetry chiral PTC $\mathbf{5}_{\boldsymbol{n}}$ with long-alkyl chains (***n*** denotes the carbon number of two alkyl chains on their nitrogen), in which quaternary ammonium salts of chiral azacrown ether worked as a molecular recognition site and were easier to prepare. In this letter, we wish to describe the synthesis of novel PTC (*S*,*S*)-$\mathbf{5}_{\boldsymbol{n}}$ derived from (*S*)-BINOL and its application to asymmetric epoxidation of chalcones under PTC conditions (Fig. 1, Scheme 1).

The chiral quaternary ammonium salts (*S*,*S*)-$\mathbf{5}_{\boldsymbol{n}}$ were readily prepared via four steps (Scheme 2). The ether (*S*,*S*)-**1**, which was obtained from two (*S*)-BINOLs,[5] reacted with N-protected diethanolamine ester **2** to give the azacrown ether precursor (*S*,*S*)-**3** in 52% yield. Deprotection of the *p*-nitrobenzenesulfonyl group in (*S*,*S*)-**3** by *p*-toluenethiol[6] afforded the azacrown ether

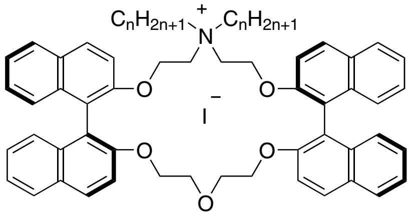

Figure 1. Structure of (*S*,*S*)-$\mathbf{5}_{\boldsymbol{n}}$ (***n*** = 1 and 6–10).

Keywords: Chiral phase-transfer catalyst; Azacrown ether; Asymmetric epoxidation.

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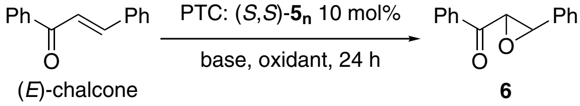
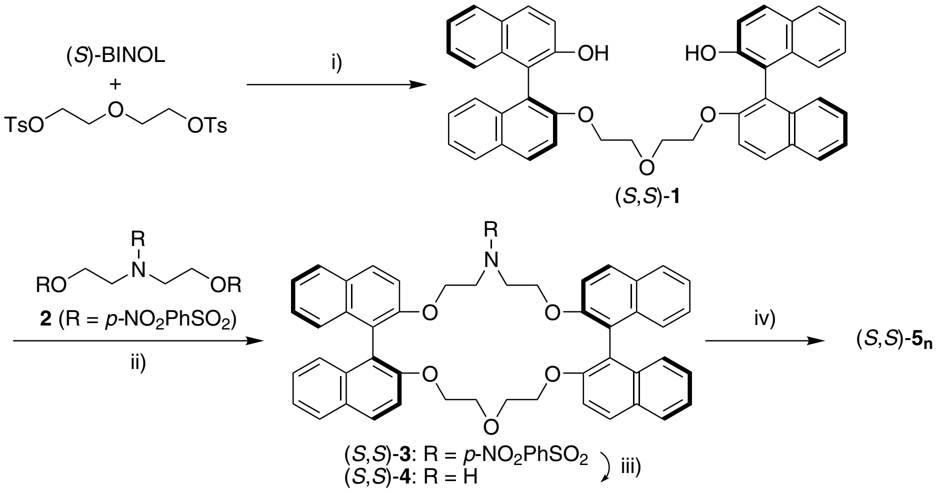


Scheme 1. Asymmetric epoxidation of (*E*)-chalcone.

(*S*,*S*)-**4** in 78% yield. The desired chiral quaternary ammonium salts (*S*,*S*)-$\mathbf{5}_n$ were prepared by treatment of (*S*,*S*)-**4** with alkyl iodides and potassium carbonate in high yield (ca. 80%).

In a preliminary investigation on the potentiality of (*S*,*S*)-$\mathbf{5}_n$ as chiral PTC, we applied it to asymmetric epoxidation of (*E*)-chalcone. Typical results are summarized in Table 1. The epoxidation using an aqueous solution of NaOH as a base and hydrogen peroxide in the presence of (*S*,*S*)-$\mathbf{5}_1$ gave the corresponding epoxy compound **6** in quantitative yield, while in the absence of catalyst only in 7% yield, which showed the effectiveness of (*S*,*S*)-$\mathbf{5}_1$ for the epoxidation, though enantioselectivity was low (Table 1, run 1). At 0 °C, the reaction catalyzed by (*S*,*S*)-$\mathbf{5}_8$, of which two carbon chains on the quaternary nitrogen atom were longer than those of (*S*,*S*)-$\mathbf{5}_1$, improved the enantioselectivity to 46% ee (run 3).

Interestingly, it was found that the kind of base was important in this reaction (runs 5–8). There was a tendency that the use of the hydroxide having a large cation such as K^+, Cs^+, and tetramethylammonium ion gave good enantioselectivity. To examine the interaction between $\mathbf{5}_n$ and the counter cation of the base, (*S*,*S*)-**7**, in which the aliphatic ether oxygen atom of (*S*,*S*)-$\mathbf{5}_8$ was converted to a methylene group (Fig. 2), was applied to this reaction. The lower enantioselectivity in run 9 indicates complexation ability of the azacrown ether ring of $\mathbf{5}_8$ with the counter cation would be necessary.



Scheme 2. Synthesis of (*S*,*S*)-$\mathbf{5}_n$. Reagents and conditions: (i) NaH, THF, reflux 24 h; (ii) K_2CO_3, methyl ethyl ketone, reflux 24 h; (iii) *p*-MePhSH, K_2CO_3, DMF, rt 24 h; (iv) $C_nH_{2n+1}I$, K_2CO_3, MeCN, reflux 24 h.

Table 1. Asymmetric epoxidation of (*E*)-chalcone catalyzed by PTC (*S*,*S*)-$\mathbf{5}_n$[a]

Run	PTC	Solvent	Oxidant	Base	Temperature	Yield[b] (%)	% ee
1	(*S*,*S*)-$\mathbf{5}_1$	Toluene	30% aq H_2O_2	2 M aq NaOH	rt	100	6
2	(*S*,*S*)-$\mathbf{5}_1$	Toluene	30% aq H_2O_2	2 M aq NaOH	0 °C	13	3
3	(*S*,*S*)-$\mathbf{5}_8$	Toluene	30% aq H_2O_2	2 M aq NaOH	0 °C	53	46
4	(*S*,*S*)-$\mathbf{5}_8$	Toluene	10% aq NaClO	—	0 °C	73	2
5	(*S*,*S*)-$\mathbf{5}_8$	Toluene	30% aq H_2O_2	$LiOH{\cdot}H_2O$[c]	0 °C	43	43
6	(*S*,*S*)-$\mathbf{5}_8$	Toluene	30% aq H_2O_2	2 M aq KOH	0 °C	85	70
7	(*S*,*S*)-$\mathbf{5}_8$	Toluene	30% aq H_2O_2	2 M aq CsOH	0 °C	38	65
8	(*S*,*S*)-$\mathbf{5}_8$	Toluene	30% aq H_2O_2	2 M aq Me_4NOH	0 °C	86	71
9	(*S*,*S*)-**7**	Toluene	30% aq H_2O_2	2 M aq KOH	0 °C	61	4
10	(*S*,*S*)-$\mathbf{5}_8$	CH_2Cl_2	30% aq H_2O_2	2 M aq KOH	0 °C	72	0
11	(*S*,*S*)-$\mathbf{5}_8$	$^nBu_2O$	30% aq H_2O_2	2 M aq KOH	0 °C	79	14
12	(*S*,*S*)-$\mathbf{5}_8$	Et_2O	30% aq H_2O_2	2 M aq KOH	0 °C	70	44
13	(*S*,*S*)-$\mathbf{5}_8$	EtOH	30% aq H_2O_2	2 M aq KOH	0 °C	69	3

[a] Reaction conditions: 2 M aqueous solution of base (1.25 mmol) was added to a solution of (*E*)-chalcone (0.5 mmol) and PTC (0.05 mmol) in solvent (1.5 mL) at room temperature. After stirring for 20 min, aqueous solution of oxidant (4.93 mmol) was added to the above mixture at appropriate temperature, and then the mixture was stirred for 24 h.

[b] The yield was determined by ^1H NMR.

[c] Solid $LiOH{\cdot}H_2O$ was used.

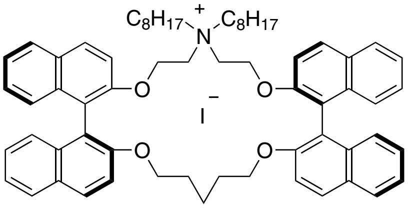


Figure 2. Structure of (*S*,*S*)-**7**.

In addition, use of toluene gave the best result in 85% yield and 70% ee among the several solvents (runs 6 and 10–13).[7,8]

Based on the results of (*S*,*S*)-$\mathbf{5_1}$ and (*S*,*S*)-$\mathbf{5_8}$ (Table 1, runs 2 and 3), the length of two carbon chains on the nitrogen of $\mathbf{5}_n$ was investigated in this epoxidation with aqueous KOH and H_2O_2 in toluene (Table 2). It was noted that the octyl group ((*S*,*S*)-$\mathbf{5_8}$) was the best length; in other words, longer or shorter alkyl groups caused reduction of the catalytic ability. These results may be ascribed to the distribution rate of $\mathbf{5}_n$ for toluene and the aqueous phase was important. Furthermore, applications of (*S*,*S*)-$\mathbf{5}_n$ to the epoxidation in an aqueous phase (without organic solvent) were examined (runs 6–8 in Table 2), which indicated that (*S*,*S*)-$\mathbf{5_{12}}$ functioned as both a surfactant and PTC.

With the optimized conditions, the scope of the epoxidation catalyzed by (*S*,*S*)-$\mathbf{5_7}$–$\mathbf{5_9}$ was explored (Table 3). The product from chalcone **7** was obtained in 90% yield with 83% ee when (*S*,*S*)-$\mathbf{5_9}$ was used, and for the reaction of 4′-chlorochalcone **9**, (*S*,*S*)-$\mathbf{5_7}$ was suitable (runs 1–3 and 7–9). It should be noted that the optimized length of $\mathbf{5}_n$ varied with chalcones. However, that of 4-chlorochalcone **8** decreased the enantioselectivity (runs 4–6) and electron-rich chalcones such as **10** and flavanone **11** were ineffective (runs 10 and 11) (Scheme 3).

In conclusion, we have synthesized a new type chiral PTC $\mathbf{5}_n$ and have applied it to asymmetric epoxidation of chalcones to give the corresponding epoxy compound in excellent yield and good enantioselectivity. This study shows that the application of $\mathbf{5}_n$ would be able to achieve asymmetric PTC reactions by control of the length of the carbon chains in the quaternary ammonium salts. Further studies of related PTC-catalyzed chemistry are currently in progress.

Table 2. Effect of functional group with nitrogen atom on (*S*,*S*)-$\mathbf{5}_n$[a]

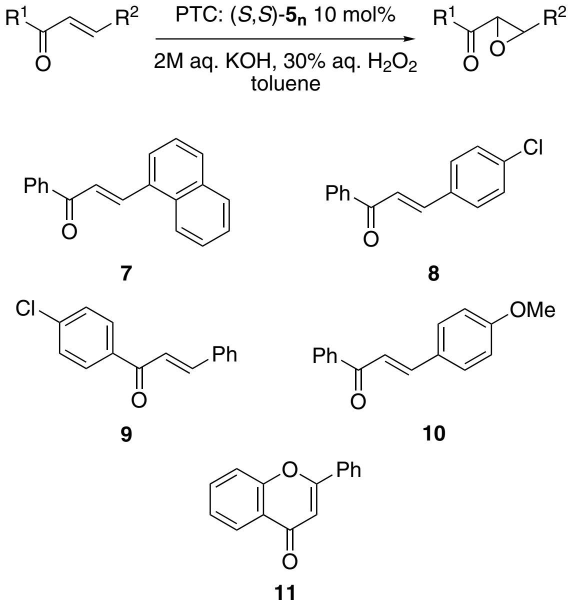
Run	PTC	*n*	Yield[b] (%)	% ee
1	(*S*,*S*)-$\mathbf{5_6}$	6	11	1
2	(*S*,*S*)-$\mathbf{5_7}$	7	75	54
3	(*S*,*S*)-$\mathbf{5_8}$	8	85	70
4	(*S*,*S*)-$\mathbf{5_9}$	9	42	32
5	(*S*,*S*)-$\mathbf{5_{10}}$	10	11	32
6[c]	(*S*,*S*)-$\mathbf{5_8}$	8	Trace	ND
7[c]	(*S*,*S*)-$\mathbf{5_{10}}$	10	18	5
8[c]	(*S*,*S*)-$\mathbf{5_{12}}$	12	57	11

[a] The reaction condition is given in Table 1, run 6.
[b] The yield was determined by ^{1}H NMR.
[c] These reactions performed without toluene.

Table 3. Asymmetric epoxidation of chalcones in the presence of (*S*,*S*)-$\mathbf{5}_n$[a]

Run	Substrate	PTC	Yield[b] (%)	% ee
1	**7**	(*S*,*S*)-$\mathbf{5_7}$	91	72
2		(*S*,*S*)-$\mathbf{5_8}$	95	75
3		(*S*,*S*)-$\mathbf{5_9}$	90	83
4	**8**	(*S*,*S*)-$\mathbf{5_7}$	96	32
5		(*S*,*S*)-$\mathbf{5_8}$	70	41
6		(*S*,*S*)-$\mathbf{5_9}$	68	22
7	**9**	(*S*,*S*)-$\mathbf{5_7}$	85	71
8		(*S*,*S*)-$\mathbf{5_8}$	72	32
9		(*S*,*S*)-$\mathbf{5_9}$	69	66
10	**10**	(*S*,*S*)-$\mathbf{5_8}$	—[c]	—
11	**11**	(*S*,*S*)-$\mathbf{5_8}$	—[d]	—

[a] The reaction condition is given in Table 1, run 6.
[b] The yield was determined by ^{1}H NMR.
[c] The complex mixture was obtained.
[d] No reaction.



Scheme 3. Asymmetric epoxidation of various chalcones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.142.

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7. Representative asymmetric epoxidation of (E)-chalcone procedure. To a solution of (E)-chalcone (104.1 mg, 0.50 mmol) and (S,S)-$\mathbf{5_8}$ (53.2 mg, 0.050 mmol) in toluene (1.5 mL) was added 2 M aq KOH (0.63 mL, 1.25 mmol), and then the resultant mixture was stirred vigorously at 0 °C for 20 min. After the mixture was added 30% aq H_2O_2 (0.50 mL, 4.93 mmol) and was stirred vigorously at 0 °C for 24 h, the reaction mixture was quenched by addition of 10% aq $NaHSO_3$ (20 mL) and extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford a crude product. The yield was determined by ^{1}H NMR spectroscopy of the mixture of the crude product and anthracene (17.8 mg, 0.1 mmol) as internal standard, which used the ratio of the integral value between the signal of **6** (δ 4.08 (d, $J = 1.7$ Hz, 1H)) and of anthracene (δ 8.43 (s, 2H)). The enantiomeric excess was determined by HPLC analysis (n-hexane/2-propanol = 98:2), flow rate; 0.5 mL/min, retention time; 32.4 and 34.3 min.
8. The absolute configuration of **6** was $(\alpha R,\beta S)$, which was determined by comparison of HPLC data with the reference.[4]