Catalytic Asymmetric Epoxidation of Naphthoquinone Derivatives Under Phase-Transfer Catalyzed Conditions

Shigeru Arai,* Makoto Oku, Motoko Miura, and Takayuki Shioiri*

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

Fax:+81-52-834-4172. E-mail: shioiri@phar. nagoya-cu.ac.jp

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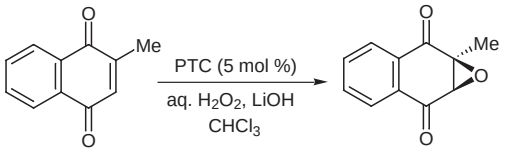
Abstract: 2-Alkyl-1,4-naphthoquinones were smoothly transformed to the corresponding epoxides in moderate to good yields with good enantioselectivities (up to 76% ee) under mild reaction conditions by use of a catalytic amount of chiral quaternary ammonium salts derived from quinidine as a phase-transfer catalyst.

Recently, we have succeeded in the establishment of a useful methodology for the preparation of α,β-epoxyketones from (*E*)-enones such as chalcone and its derivatives using chiral quaternary ammonium salts as a phase-transfer catalyst (PTC).[1] Known successful examples of the PTC-catalyzed epoxidation of enones were limited in (*E*)-enones such as chalcone and its derivatives as substrates.[1a,2] On the other hand, few results were reported by use of (*Z*)-enones in catalytic asymmetric epoxidation. Wynberg[3a-d] and the others[3e,f] reported the PTC-catalyzed asymmetric epoxidation of cycloalkenones or α-substituted naphthoquinones with moderate enantiomeric excess. Recently, Taylor and co-workers[4] revealed that the epoxidation of a dienone proceeded with good enantiomeric excess (89%) under PTC conditions. In this paper, we report our own results on the catalytic asymmetric epoxidation of naphthoquinone derivatives promoted by modified chiral PTCs derived from cinchona alkaloids under mild reaction conditions.

Our first target was vitamin K because the role of vitamin K and its epoxide is interesting in its biological activity.[5] Since many quinones have been shown to possess antimicrobial and antitumor activity and, since the corresponding epoxides seem to play an important role in metabolic processes, development of the practical synthesis of quinone epoxides as their optically active forms is an important goal. As a result, commercially available naphthoquinone derivative **1a** (vitamin K_3) was employed for initial studies and transformed to the corresponding epoxide with a safety oxidant, H_2O_2, under a biphase-system in the presence of a catalytic amount of quaternary ammonium salts derived from quinidine as a chiral PTC. The reaction proceeded smoothly to give the corresponding epoxide **2a** in good yield but with low enantioselectivities in a usual solvent system such as toluene or diethyl ether. After screening of solvents, PTCs, bases, and reaction conditions, we have found that the desired product **2a** was obtained in the presence of 5 mol % of PTC **A** with 30% H_2O_2 and a stoichiometric amount of LiOH in chloroform at rt with 31% ee in good chemical yield (Table 1, entry 1).[6-8] On the other hand, treatment of **1a** in the absence of PTC afforded **2a** with much lower chemical yield. The chiral PTC plays an important role in not only asymmetric induction but acceleration of the reaction rate in this reaction system. Since **2a** has low values of optical rotation in any solvent, its enantioselectivity was determined by HPLC analysis. In order to obtain **2a** with higher enantioselectivity, we turned to use new PTCs derived from quinidine. As the result, PTCs including an *ortho*-substituted benzyl moiety were found to give better results in this asymmetric epoxidation. Particularly, the PTC involving the α-naphthyl unit on the nitrogen atom of quinuclidine gave the best result to afford **2a** with 34% ee in chloroform at -10°C (Table 1, entry 2). Encouraged by this result, we have paid attention to epoxidize other easily prepared α-alkyl substituted 1,4-naphthoquinones under the same reaction conditions. As shown in Table 2, by use of 5 mol % of PTC **A**, *N*-(α-naphthylmethyl)quinidinium chloride,[9] in the presence of aqueous H_2O_2, the corresponding epoxides **2** were obtained with moderate to good enantiomeric excess. In comparison with the case of **1a**, substrates involving more bulky alkyl groups at the α-position gave good enantioselectivities (Table 2, entries 2-6). These results imply that the PTC recognized two unequivalent carbonyl groups to afford the corresponding epoxides with moderate ee. In particular, 2-isopropyl (**1d**) and 2-phenyl-1,4-naphthoquinone (**1g**) were transformed to the corresponding epoxides **2d** and **2g** with 70 and 76% ee, respectively.[10] And also the α-alkynylated quinone was oxidized smoothly under the same reaction conditions to afford the desired products with modest enantioselectivities (Table 2, entry 7). According to our best knowledge,



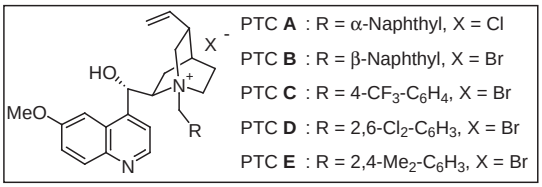


Table 1. Asymmetric Epoxidation of **1a** Under PTC Conditions

entry	PTC	temp & time	yield of **2a** (%)	ee of **2a** (%)
1	**A**	rt, 1 h	82	31
2	**A**	-10°C, 1 h	86	**34**
3	**B**	rt, 1 h	84	27
4	**C**	rt, 1 h	87	18
5	**D**	rt, 1 h	92	30
6	**E**	rt, 1 h	93	26

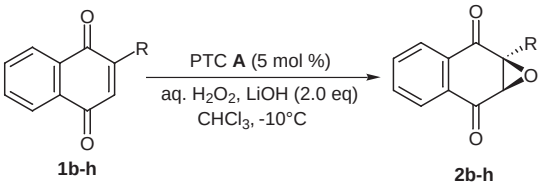


Table 2. Substrate Effect on Asymmetric Epoxidation

entry	quinone	time (h)	yield of **2** (%)	ee of **2** (%)
1	**1b** : R = Et	16	**2b** : 99	41
2	**1c** : R = *n*-Pr	7	**2c** : 95	40
3	**1d** : R = *i*-Pr	5	**2d** : 93	**70**
4	**1e** : R = *i*-Bu	30	**2e** : 100	28
5	**1f** : R = *c*-Hex	23	**2f** : 60	**64**
6	**1g** : R = Ph	23	**2g** : 47	**76**
7	**1h** : R = C≡CPh	21	**2h** : 84	40

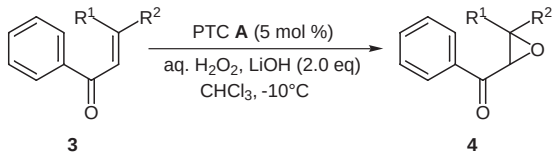


Table 3

entry	enone	time (h)	yield of **4** (%)	ee of **4** (%)	(config.)
1	**3a**:R^1 = H, R^2 = Ph	44	**4a** :85	17	(α*S*,β*R*)
2	**3b**:R^1 = H, R^2 = *i*-Pr	14	**4b** :97	35	(α*S*,β*R*)
3	**3c**:R^1 = H, R^2 = *c*-Hex	48	**4c** :34[a]	26	(α*S*,β*R*)
4	**3d**:R^1 = H, R^2 = Et	44	**4d** :88[b]	21	(α*S*,β*R*)
5	**3e**:R^1 = Et, R^2 = H	44	**4d** :61[b]	29	(α*R*,β*S*)

a) Conversion yield. b) Twenty mol % of PTC **A** was used.

these results are the first establishment of the generality on catalytic asymmetric epoxidation of 2-substituted-1,4-naphthoquinone derivatives to obtain the corresponding epoxides with moderate to good enantioselectivities.

Next, we attempted to examine the application of PTC **A** to the (*E*)-enone system. As shown in Table 3, the substrates which involve the same partial moiety relative to α-alkylnaphthoquinones **3a-d** were easily oxidized to the corresponding *trans* epoxides **4a-d** under similar reaction conditions, respectively. These enantiomeric excesses were found to be much lower. Indeed, the (*Z*)-enone **3e** was also transformed to the corresponding epoxide **4d** in 61% yield with 29% ee, and its absolute configuration was found to be (α*R*,β*S*). These results represent that PTC **A** seems to act as a quite effective phase-transfer catalyst in the naphthoquinone system.

In conclusion, we have realized the catalytic asymmetric epoxidation of α-substituted naphthoquinones under phase-transfer catalyzed conditions with the achievement of a dramatic increase in enantioselectivities in comparison to the known results. *N*-(α-Naphthylmethyl)quinidinium salt appears to act as a quite effective PTC in this reaction system. This methodology can be a practical synthesis for the preparation of optically active quinone epoxides. Although it is not clear that stereo and electronic effects between PTC and substrates determine the asymmetric induction in this reaction system at present, these results described here will lead to further progress.

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6. Wynberg *et al*. reported that **2a** was obtained via asymmetric epoxidation with 5% ee in 60-70% yield under phase-transfer catalyzed conditions, see ref. 3c,d.
7. The absolute configuration of epoxides was determined by $[\alpha]_D$ and CD spectral data by comparison with the literature results, see ref. 3c,d.
8. Enantiomeric excess of the epoxide **2a** (34% ee) can be easily increased to 98% ee (as white needles) after recrystallization from hexane-Et_2O.[3d]
9. All PTCs used in this reaction system were easily prepared from quinidine and commercially available arylmethyl halide derivatives. PTCs having alkyl groups on the phenyl ring afforded **2** with better ee than PTCs having other electron-withdrawing or donating groups.
10. A typical procedure for the catalytic asymmetric epoxidation under phase-transfer catalyzed conditions: Synthesis of **2d** (Table 2, entry 3). PTC **A** (29.6 mg, 0.05 mmol) and LiOH (47.9 mg, 2.0 mmol) were added to a solution of naphthoquinone **1d** (201 mg, 1.0 mmol) in chloroform (3.0 mL) and 30% aqueous H_2O_2 (1.0 mL) at -10°C. After being stirred for 5 h at -10°C, the reaction mixture was quenched with 1*N* HCl and extracted with diethyl ether (15 mL x 3). The combined organic layer was dried over Na_2SO_4. Removal of the solvent followed by flash column chromatography (silica gel, hexane:Et_2O = 3:1) gave the desired product **2d** (201.8 mg, 93%, 70% ee) as a colorless oil. Ee was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane:*i*-PrOH = 50:1, flow rate = 0.5 mL/min, retention time; 12.5 min (minor) and 13.0 min (major)).