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Asymmetric Epoxidation of α,β-Unsaturated Ketones Under Phase-Transfer Catalyzed Conditions

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Abstract: Asymmetric epoxidation of a,b-unsaturated ketones with H_2O_2 was developed using a chiral quaternary ammonium salt as the phase-transfer catalyst. A catalytic amount of *N*-[4-(iodo)benzyl]cinchoninium bromide, easily prepared from cinchonine, was effective in the asymmetric epoxidation for producing the corresponding desired products with up to 92% ee under mild reaction conditions. © 1998 Elsevier Science Ltd. All rights reserved.

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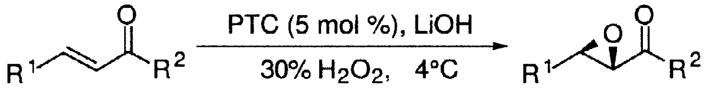
The catalytic asymmetric epoxidation of alkenes is one of the most potential methodologies used to obtain optically active organic compounds.[1] In 1980, Sharpless *et al.*[2] reported the titanium promoted asymmetric epoxidation of allylic alcohols with *t*-BuOOH, which was later used to construct a catalytic cycle by the addition of molecular sieves.[3] Excellent results for the catalytic enantioselective epoxidation of isolated olefins using salen-manganese complexes were reported by Jacobsen *et al.*[4] and Katsuki *et al.*[5] The first example of asymmetric epoxidation under phase-transfer-catalyzed conditions using electron deficient alkenes as the substrate was reported by Wynberg *et al.*[6] in 1976. Using a catalytic amount of chiral quaternary ammonium salt as the phase-transfer catalyst (PTC) and hydrogen peroxide afforded oxygenated products with modest enantiomeric excess. Also the high enantioselectivities for the catalytic asymmetric epoxidation were achieved using polypeptides as a PTC.[7] Enders *et al.*[8] also reported an efficient zinc reagent for the stoichiometric asymmetric epoxidation of enones. Quite recently, Shibasaki *et al.*[9a] and Jackson *et al.*[9b] independently reported the catalytic asymmetric epoxidation of enones promoted by metal catalysis with high generalities and enantioselectivities. Herein we report our own results on the efficient catalytic asymmetric epoxidation of chalcone and its derivatives promoted by a new class of quaternary ammonium salts derived from cinchonine, which reacts as a phase-transfer catalyst in the presence of a safe oxidant, H_2O_2, in a two phase system under mild reaction conditions.[10]

Phase-transfer catalyzed reaction systems are one of the most useful methodologies for practical syntheses because of the mild reaction conditions which enable the use of water as a co-solvent, safety, and operational simplicity.[11] We aimed to develop an efficient and direct method for the practical asymmetric synthesis that would afford optically active organic compounds promoted by a PTC involving the above mentioned advantages (Scheme 1).[12] During the preparation of this manuscript, Lygo and co-worker reported similar successful results on the asymmetric phase-transfer mediated epoxidation of α,β-unsaturated ketones using catalysts derived from cinchona alkaloids and sodium hypochlorite as the oxidant.[12b]

Scheme 1



At the outset, we attempted to develop methods that would afford the catalytic asymmetric epoxidation of enones. Thus compound **1a** was easily oxidized in the presence of a catalytic amount of a quaternary

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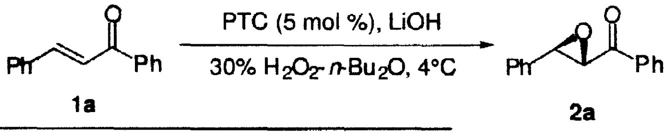
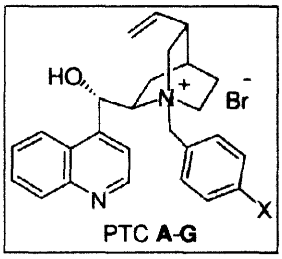
ammonium salt derived from cinchonine using an inorganic base such as LiOH or NaOH and aqueous H_2O_2 in an organic solvent. After screening a variety of inorganic bases and solvents, we were pleased to find that the asymmetric epoxidation reaction proceeded smoothly in the presence of a catalytic amount (5 mol %) of a commercially available chiral quaternary ammonium salt, *N*-(4-trifluoromethylbenzyl)cinchoninium bromide[13] using a LiOH (3.0 equiv)-dibutyl ether-30% H_2O_2 biphase system, at 4° C for 36 h, which gave the desired epoxide **2a** in 72% yield with 73% ee in the *trans* form (entry 1, Table 1).[14] Encouraged by this result, we prepared and examined new chiral quaternary salts derived from cinchonine in order to obtain **2a** with a higher enantiomeric excess using the phase-transfer catalyzed asymmetric epoxidation. After optimization for the substituent effect on the phenyl ring of the *N*-benzyl group, we realized that PTCs that introduced the electron withdrawing groups at the 4-position on the phenyl ring of *N*-benzyl unit are quite effective.[15] These results are summarized in Table 1. Using the *N*-4-iodobenzyl derivative[16] as a PTC gave **2a** in 97% yield with 84% ee (entry 5, Table 1).

Table 1. Effect of PTC on Asymmetric Epoxidation of Chalcone[a]



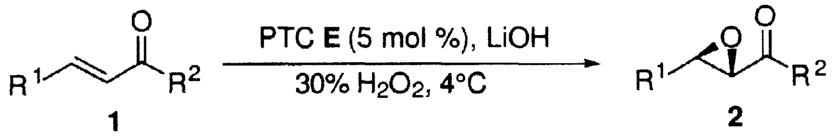
entry	PTC	X	time (h)	yield (%)	ee (%)[b]
1	**A**	CF_3	26	72	73
2	**B**	F	88	24	3
3	**C**	Cl	41	68	65
4	**D**	Br	36	56	77
5	**E**	I	37	97	84
6	**F**	NO_2	37	61	72
7	**G**	H	74	72	1



PTC **A-G**

a) Absolute configuration of **2a** was determined by comparison of literature data, see ref. 8 and 9. b) Ee was determined by HPLC analysis.

Table 2. Catalytic Asymmetric Epoxidation of Various Enones



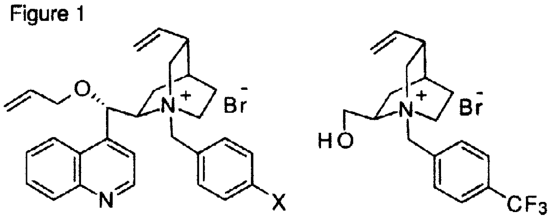
entry	enone	solvent	product	time (h)	yield of **2** (%)	ee of **2** (%)
1	**1b** : R^1=Ph, R^2=3-Me-C_6H_4	*n*-Bu_2O	**2b**	36	**2b** : 99	87
2	**1c** : R^1=Ph, R^2=4-Me-C_6H_4	*n*-Bu_2O	**2c**	36	**2c** : 95	89
3	**1d** : R^1=3-Me-C_6H_4, R^2=Ph	*n*-Bu_2O	**2d**	64	**2d** :100	92
4	**1e** : R^1=2-Me-C_6H_4, R^2=Ph	*n*-Bu_2O	**2e**	64	**2e** : 96	67
5	**1f** : R^1=2-Cl-C_6H_4, R^2=Ph	*n*-Bu_2O	**2f**	47	**2f** : 88	65
6	**1g** : R^1=*t*-BuCH$_2$, R^2=Ph	*n*-Bu_2O	**2g**	68	**2g** : 41	57
7	**1h** : R^1=*t*-Bu, R^2=Ph	$CHCl_3$	**2h**	43	**2h** : 90	55
8	**1i** : R^1=*c*-Hex, R^2=Ph	$CHCl_3$	**2i**	37	**2i** : 70	53[a]
9	**1j** : R^1=*i*-Pr, R^2=Ph	$CHCl_3$	**2j**	43	**2j** : 82	42

a) PTC **G** was used in this reaction system.

Next we turned our attention to establish the generality of the phase-transfer catalyzed asymmetric epoxidation. As shown in Table 2, other chalcone derivatives **1b-j** as reactive olefins afforded the corresponding epoxides **2b-j** with modest to high enantiomeric excesses. It was found that chalcone derivatives, which are methylated on their phenyl ring such as **1b**, **1c**, and **1d**, were much more effective, and gave the corresponding desired products **2b**, **2c**, and **2d** in high yields with 87, 89, and 92% ee, respectively,[17] under similar biphase reaction conditions to those described above (entries 1 to 3, Table 2). Other chalcone derivatives such as **1e** and **1f** also afforded the corresponding epoxides **2e** and **2f** but only with modest enantiomeric excess (entries 4 and 5). Also, β-alkyl substituted substrates such as **1g-1j** were oxidized to give the corresponding products **2g-2j** with only a modest enantiomeric excess using a dibutyl ether or $CHCl_3$[18]-aqueous H_2O_2 system (entries 6 to 9).

We believe that the chiral secondary alcohol, the *N*-benzyl and quinoline units in the PTC skeleton play an important role in this asymmetric epoxidation reaction by constructing an effective reaction site, though complete details are not presently clear. For example, the *O*-protected PTC **H** or **I**, easily prepared from the cinchoninium salt,[19] and PTC **J** derived from chiral quinuclidine derivative were quite ineffective for asymmetric induction in this reaction system (Figure 1). These catalysts gave the desired product **2a** with 0% ee under similar reaction conditions.

Figure 1



PTC H: X=CF_3,
2a:61% yield (0% ee)
PTC I: X=I,
2a:72% yield (2% ee)

PTC J,
2a:20% yield (0% ee)

In conclusion, we have realized that the easily prepared PTC **E** derived from cinchonine is quite an effective catalyst for asymmetric epoxidation under phase-transfer catalyzed conditions. These results described above will lead to further progress.

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13. Purchased from Aldrich Chemical Co., Ltd.
14. Using a stronger base such as NaOH or KOH instead of LiOH gave the **2a** with a slightly lower ee in this reaction system.
15. PTCs including electron donating groups on the phenyl ring such as MeO, or bulky and electron withdrawing groups such as CF_3SO_2, CCl_3 and CBr_3, alkyl groups induced derivatives, or regioisomers of 4-iodo derivatives such as 2-iodo or 3-iodo ones were less effective in this reaction system and afforded the desired products with lower ee.
16. The preparation of *N*-[4-(iodo)benzyl]cinchoninium bromide (PTC **E**) is as follows: A mixture of cinchonine (1.47g, 5.0 mmol) and 4-iodobenzyl bromide (1.48g, 5.0 mmol) in THF (20 mL) was refluxed for 133 h. The precipitated solid was filtered and washed with benzene, and recrystallized from MeOH to give the desired compound as colorless crystals (1.04g, 35%), mp 218° C (decomp.) $[\alpha]_D^{19}$ +103 (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{26}H_{28}Br_2IN_2O \cdot 1/2H_2O$: C, 52.02; H, 4.87; N, 4.67. Found: C, 51.96; H, 5.16; N, 4.61. According to this procedure, the other PTCs described in Table 1 can be easily prepared.
17. A typical procedue for catalytic asymmetric epoxidation under PTC conditions is as follows: A mixture of enone **1d** (222 mg, 1.0 mmol) and *N*-(4-iodobenzyl)cinchoninium bromide (PTC **E**) (29.6 mg, 0.05 mmol) in a biphase-system, dibutyl ether (3.0 mL) and 30% aqueous H_2O_2 (1.0 mL), was stirred at 4℃ for 20 min. After lithium hydroxide (72.0 mg, 3.0 mmol) was added, the reaction mixture was stirred at 4℃ for 37 h. The mixture was quenched with 1*N* HCl (3.0 mL), extracted with diethyl ether (15 mL x 3), washed with brine, and dried over Na_2SO_4. Removal of the solvent followed by flash column chromatography (silica gel, hexane:diethyl ether = 9:1) gave the desired product **2d** as a colorless solid (238.3 mg, quantitative, 92% ee). Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL AD, hexane:*i*-PrOH = 50:1, flow rate:1.0 mL/min. The retention time was 19.0 min for the ($\alpha S,\beta R$)-isomer and 25.1 min for the ($\alpha R,\beta S$)-isomer, with detection at 254 nm.
18. Chloroform gave the best results using the β-alkyl enones as substrates except for **1g**.
19. According to Corey's procedure,[12a] PTC **H** and **I** were easily prepared from the corresponding ammonium salt.