Pergamon

Tetrahedron 55 (1999) 6375–6386

TETRAHEDRON

Phase-Transfer-Catalyzed Asymmetric Darzens Reaction

Shigeru Arai,[†]* Yoshiki Shirai,[†] Toshimasa Ishida,[‡] and Takayuki Shioiri[†]*

[†]*Faculty of Pharmaceutical Sciences, Nagoya City University*
Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan
[‡]*Osaka University of Pharmaceutical Sciences*
4-20-1 Nasahara, Takatsuki, Osaka 569-1041, Japan

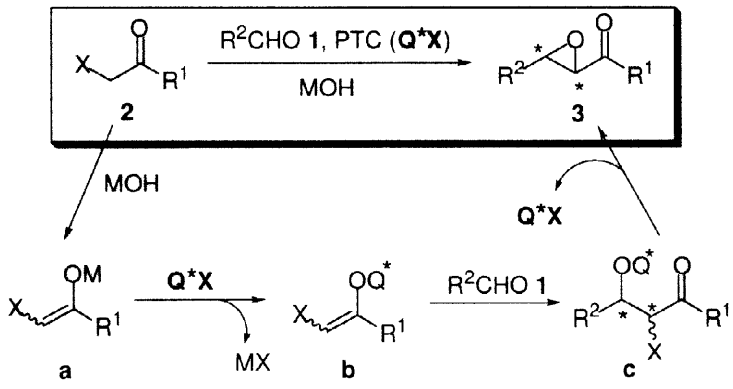
Received 30 November 1998; accepted 20 January 1999

Abstract: Catalytic asymmetric Darzens reaction promoted by a chiral phase-transfer catalyst derived from cinchonine is described. The desired α,β-epoxy ketones were obtained by use of α-chloro acyclic and cyclic ketones as substrates with moderate to high enantiomeric excesses under mild reaction conditions. This methodology can be quite an effective protocol for practical asymmetric synthesis.

Keywords: asymmetric catalyst, Darzens reactions, epoxides, phase transfer

The Darzens reaction is one of the more important carbon-carbon bond forming reactions in synthetic organic chemistry because of the multifunctionality and utility of the α,β-epoxy carbonyl products. Although many examples are known with diastereoselective control in the Darzens reaction,[1] few successful results involving enantiocontrol using chiral catalysts or reagents have been reported. Thus, obtaining a reasonable enantiomeric excess in the catalytic asymmetric Darzens reaction still remains a challenge. A significant problem to be solved is the establishment of an efficient catalytic cycle in which the inorganic salts or related compounds generated from both substrates and reagents are converted into effective reactive species. Past enantioselective Darzens reactions promoted by metal reagents required stoichiometric amounts of chiral sources because of the metal reagents and harsh reaction conditions employed.[1]

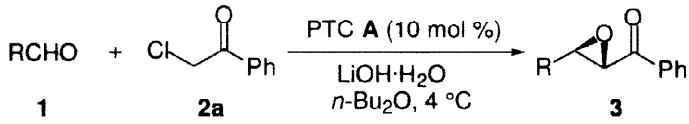
Scheme 1. Proposed Catalytic Cycle for Asymmetric Darzens Reaction



PII: S0040-4020(99)00213-6

To overcome these problems, we chose to explore the use of chiral quaternary ammonium salts as phase-transfer catalysts (PTC) in the Darzens reactions. Phase-transfer catalysis has been recognized as a practical methodology for organic synthesis due to its operational simplicity, mild reaction conditions, safety considerations, and environmental concerns.[2] In addition, the development of novel PTC catalyzed asymmetric reactions is of considerable industrial interest. In the case of the Darzens reaction, a reactive and soluble ammonium halide (QX), which can be considered to be equivalent to an inoragnic salt in the case of the stoichiometric reaction, could be transformed into a chiral active species in the presence of an inorganic base (MOH) and, as shown in Scheme 1, lead to an effective catalytic cycle. We reported preliminary results concerning the catalytic asymmetric Darzens reaction using a catalytic amount of chiral quaternary ammonium salts derived from commercially available chiral amines such as cinchonine and quinine.[3] In this paper, we describe further studies of the PTC-catalyzed asymmetric Darzens reaction as well as unusual mechanistic aspects observed in this reaction system.[4]

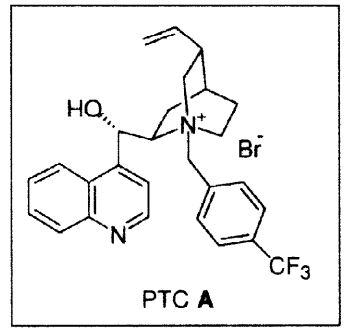
Initial work focused on the reaction using commerically available α-chloroketone **2a** with various aldehydes **1**.[3a] Although the desired epoxyketones **3a** or **3b** were readily obtained using a catalytic amount of the chiral quaternary ammonium salt together with a stoichiometric amount of strong base (NaOH or KOH), the enantiomeric excesses observed were low. In these systems, the reaction proceeded smoothly to give racemic product **3** in the absence of chiral PTC, presumably via the achiral alkaline metal enolate. Screening studies involving different solvents, bases and conditions have led to an improved system which gives reasonable inductions: *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (PTC **A**)[5] (10 mol %), LiOH monohydrate (2.0 eq),and the aldehyde **1** (2.0 eq) in dibutyl ether (0.1 M) at 4 °C. The results of the PTC-catalyzed asymmetric Darzens reaction using **2a** with various aldehydes **1** are summarized in Table 1.



1 **2a** **3**

Table 1

entry	aldehyde	time (h)	yield of **3** (%)	ee of **3** (%)
1	**1a** : R = *i*-Pr	60	**3a** : 80	53
2	**1b** : R = Et	117	**3b** : 32	79
3	**1c** : R = *n*-Pr	60	**3c** : 82	57
4	**1d** : R = *i*-Bu	134	**3d** : 73	69
5	**1e** : R = *t*-BuCH$_2$	91	**3e** : 50	62
6	**1f** : R = Et$_2$CH	117	**3f** : 76	58
7	**1g** : R = Ph(CH$_2$)$_2$	114	**3g** : 83	44
8	**1h** : R = *c*-Hex	61	**3h** : 47	63
9	**1i** : R = Ph	69	**3i** : 43	42

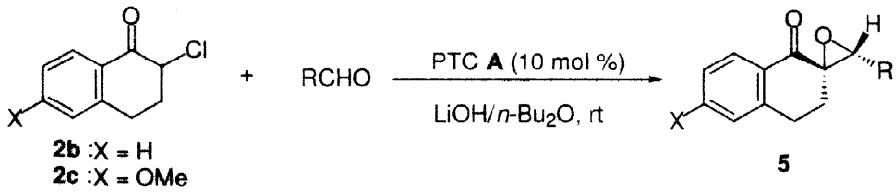


PTC **A**

The reaction of **2a** with aliphatic aldehydes proceeded smoothly to give the corresponding epoxides **3** with good stereocontrol and yield under quite mild conditions. Of note are the reactions in which the products were obtained in greater than 60% ee (entries 2,4,5 and 8), especially the reaction with propionaldehyde to give the product **3b** in 79% ee. In other cases with sterically non-demanding aldehydes (entries 3 and 7), in which it is expected to be difficult to obtain good enantioselectivities, the

desired products were still obtained with reasonable selectivities (57 and 44% ee, respectively). The reaction with benzaldehyde, an aromatic aldehyde, was also quite effective, giving epoxide **3i** with 42% ee. The absolute configurations of products **3a**, **3b**, **3c** and **3i** were determined to be ($\alpha S,\beta R$) by comparison of the optical rotation of these products with literature data.[6] To the best of our knowledge, these are the first successful results obtained in the catalytic asymmetric Darzens reaction promoted by chiral quaternary ammonium salts as PTC.[7] Catalyst **A** was found to be the best catalyst in this reaction system; other related catalysts, such as the 4-MeO, 4-NO_2, 2,4-$(CF_3)_2$, 3,5-$(CF_3)_2$, and 4-CH_3 benzyl derivatives, were found to be quite ineffective.[8]

The use of α-chloro cyclic ketones (**2b** and **2c**) as starting substrate was investigated next (Table 2). In this case the intermediate ammonium enolate would necessarily be in the *Z*-form. Starting materials **2b** and **2c** were readily prepared from 1-tetralone and its derivatives. The Darzens reaction of **2b** and **2c** with various aldehydes proceeded smoothly to afford the desired coupling products **5** with high diastereoselectivites under quite mild reaction conditions (*room temperature*). The stereochemistry of the desired product was determined to be *trans* by X-ray crystallographic analysis (Fig. 1) and comparison of the ^{1}H NMR spectra. The higher diastereoselectivites observed in this reaction system are likely due to the generation of the single *Z*-enolate species. In general, both the chemical yields and the enantioselectivities were higher in these systems. In particular, the α-chloroketone **2b** reacted smoothly with aldehydes **1e** and **1f** to give products **5c** and **5d** in 86 and 84% ee (86 and 67% yields), respectively (entries 3 and 4). Benzaldehyde was also found to be an effective substrate to yield **5f** with moderate ee and chemical yield (entry 6). Unfortunately, the reaction of more bulky substrates, such as pivalaldehyde, with **2b** was quite ineffective. In this case, the reaction was difficult to proceed to give an unknown product.



2b :X = H
2c :X = OMe

5

Table 2

entry	ketone	aldehyde	time (h)	yield of **5** (%)	ee of **5** (%)
1	**2b**	**1a** : R = *i*-Pr	61	**5a** : 99	69
2	**2b**	**1d** : R = *i*-Bu	63	**5b** : 86	74
3	**2b**	**1e** : R = *t*-BuCH$_2$	84	**5c** : 86	**86**[a]
4	**2b**	**1f** : R = Et$_2$CH	252	**5d** : 67	**84**
5	**2b**	**1h** : R = *c*-Hex	62	**5e** : 80	69
6	**2b**	**1i** : R = Ph	43	**5f** : 67	59
7	**2c**	**1d** : R = *i*-Bu	48	**5g** : 65	50
8	**2c**	**1e** : R = *t*-BuCH$_2$	63	**5h** : 90	75
9	**2c**	**1a** : R = *i*-Pr	94	**5i** : 96	35

a) 85% de

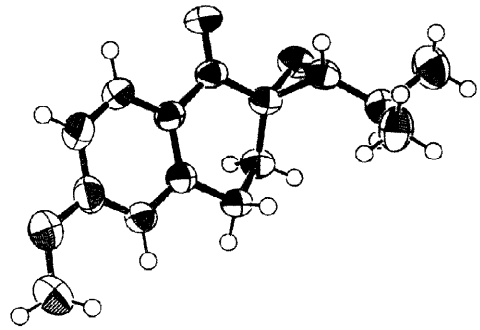
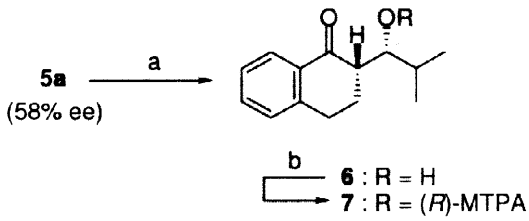


Figure 1. The ORTEP diagram of **5i**

The absolute configuration of the desired *trans* epoxide **5** was determined by the transformation of **5a** to the corresponding Mosher ester **7**[9] (Scheme 2) and comparison of the ^{1}H NMR spectra. Treatment of **5a** (58% ee) with SmI_2 in THF-MeOH[10] at -78 °C afforded the β-hydroxyketone **6** as the sole product in 53% yield, without epimerization or racemization. The stereochemistry of this product was determined by comparison with literature data.[11] Subsequent esterification of **6** with (*R*)-MTPA in the presence of DCC

with a catalytic amount of DMAP gave product **7**. As noted earlier for the acyclic systems, PTC **A** was found to be the optimal catalyst for these reactions.

Scheme 2. Tranformation of **5a** to MTPA ester



a) SmI_2, 53%, b) (*R*)-MTPA, 85%

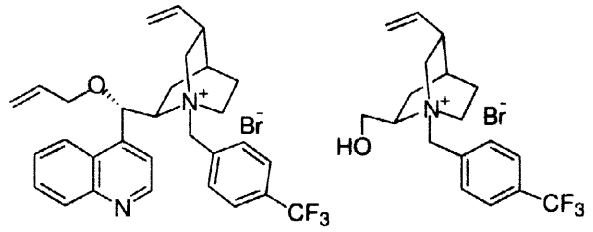


Figure 2

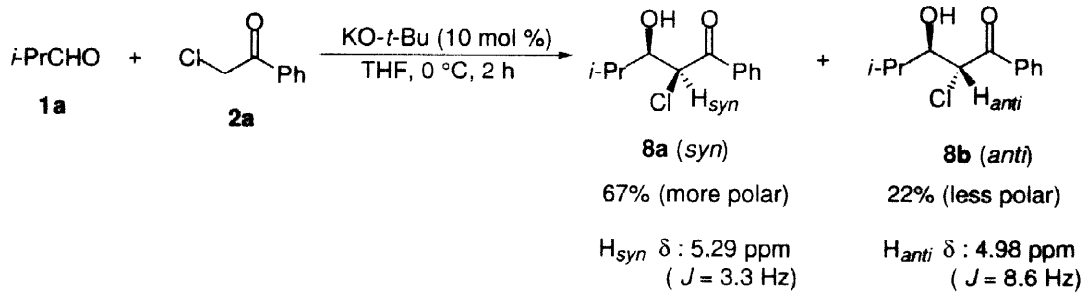
The important substituent effect of the 4-trifluoromethyl group in the catalyst PTC **A** is unclear at present. Other types of cinchoninium salt derivatives, which include electron-withdrawing groups such as NO_2, electron-donating groups like OMe, and alkyl groups instead of the CF_3 are all quite ineffective catalysts in both the cyclic and acyclic systems. The corresponding 4-methyl derivative gave a lower ee, which implies that the electron-withdrawing ability of the CF_3 plays an important role in the asymmetric induction. The chiral secondary alcohol in the PTC was also found to be quite important to realize reasonable asymmetric inductions. The catalyst in which the hydroxyl is protected as an allyl ether[12] or the primary alcohol catalyst (Figure 2), were both found to be very ineffective catalysts, providing the product in racemic form. These results suggest that the hydrogen bond between the oxygen atom in the substrate and the chiral alcohol in the catalyst plays an important role in the enantiocontrol.[13] Related studies from our laboratory have shown that chloromethyl phenylsulfone, which possesses a strong Lewis base functionality, can also serve as an effective carbon nucleophile with aromatic aldehydes in catalytic asymmetric Darzens reactions.[3c]

Mechanistic Insights

The proposed reaction mechanism (Scheme 1) would suggest that the two newly generated stereogenic centers are controlled by reaction of the aldehyde with the chiral ammonium enolate **b**, which is considered as the active catalyst species. According to this mechanism, both the product epoxyketone **3** as well as its precursor aldol intermediate **c** would exist in optically active forms during the reaction.

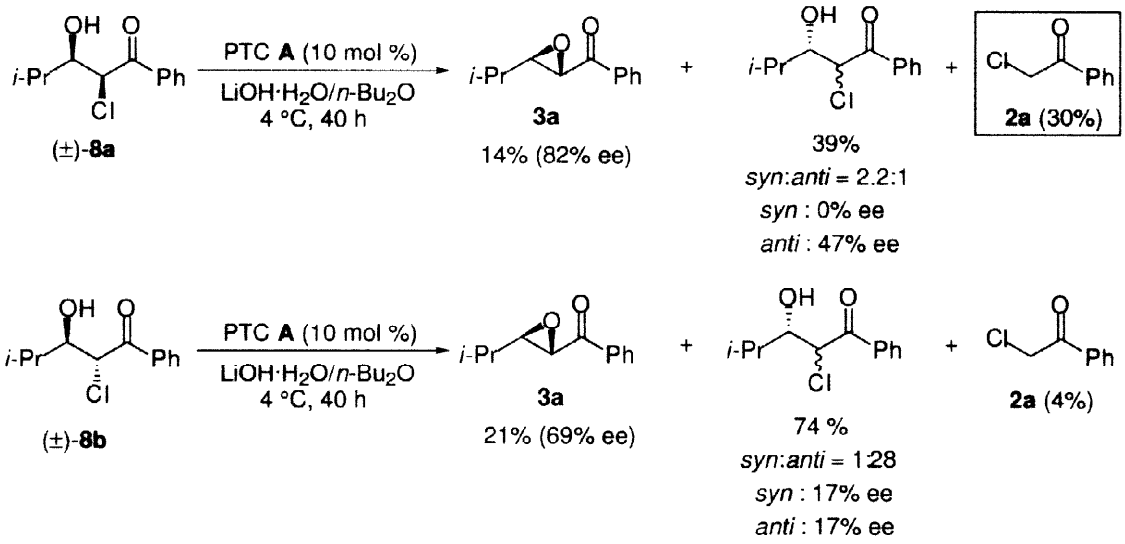
In spite of this reasonable hypothesis, the real reaction pathway to optically active product was found to involve a kinetic resolution process of the racemic aldol intermediate **c**. In the acyclic system, the desired products **3** were obtained with complete stereocontrol in the *trans* form because of epimerization at the stereogenic center adjacent to the carbonyl group and then ring closure from the antiperiplaner conformer to give the product *trans* epoxides. Even though these processes, epimerization followed by cyclization, were expected to be facile in the basic reaction medium, the aldol intermediates could be detected by TLC following immediate disappearance of the starting material **2a**. Since this seemed unusual, the behavior of the aldol intermediates was investigated further. The racemic aldol adducts were prepared by reacting aldehyde **1a** with phenacyl chloride **2a** in the presence of a catalytic amount of KO-*t*-Bu (10 mol %) in THF at 0 °C for 2 h, as shown in Scheme 3. *Syn* and *anti* isomers, **8a** and **8b**, were isolated as the major and minor diastereomers, respectively, and only a trace amount of the Darzens product was detected by TLC. The relative configurations of products **8a** and **8b** were determined from the ^1H NMR coupling constants of the α and β protons.

Scheme 3. Preparation of α-Chloro-β-hydroxyketone



Transformation of the racemic *anti* and *syn* aldolates (**8a** and **8b**) to the corresponding epoxides **3** under phase-transfer conditions similar to those used in the original reaction revealed that both compounds reacted smoothly to give the same optically active *trans* epoxide **3a** together with differing amounts of **2a** (Scheme 4). The yield of recovered **2a** from *syn* aldolates **8a** was 30%, whereas it was only 4% from the *anti* aldolates **8b**. These results suggest that the key reaction process involves not C-C and/or C-O bond formation, but a C-C bond-breaking process due to the retro aldol reaction. Because of steric repulsion between the *i*-Pr and PhCO substitutents, it is difficult to fix the *syn* isomer (alkoxide of **8a**) in the requisite antiperiplaner conformation for the final ring closure to a Darzens product. Instead, the alkoxides of **8a** undergo a retro aldol reaction to give starting materials **1a** and **2a**. These starting materials then recondense to form more *anti* isomer, which undergoes cyclization to the product **3a**.

Scheme 4. Transformation of **8a** and **8b** to Epoxides Under PTC-Catalyzed Conditions

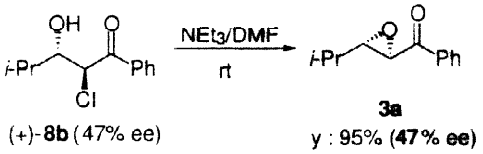


Although the absolute configuration of the epoxides was the same as that of the Darzens product, the recovered aldol **8b** was found to be the antipodal form. Treatment of **8b** (47% ee) with triethylamine in DMF[14] resulted in the smooth conversion to the corresponding epoxide **3a** without racemization. This product was shown, by chiral HPLC analysis, to possess the opposite absolute configuration to that formed in the regular PTC-promoted Darzens reaction (Scheme 5). These results suggest that the most important factor in determining the stereoselectivity of the Darzens product is not the chiral enolate anion process, but

the retro aldol reaction and kinetic resolution.

In order to confirm this hypothesis, the behavior of all the products generated in this system was studied over time. The first experiments involved monitoring the chemical yields of the observed products over time. As shown in Table 3 and Figure 3, the starting material **2a** disappeared smoothly and an increase of the aldol intermediates **8** was observed. This was also followed qualitatively by TLC. A gradual decrease in the amount of **8** occurred while the desired epoxide product **3a** was formed. Figure 3 demonstrates that the catalytic Darzens reaction includes both a rapid carbon-carbon bond formation and a slow rate-determining intramolecular C-O bond-forming process. Indeed, the diastereoselectivity of the aldol intermediates was found to be constant at approximately *syn*:*anti* = 1:2, even at the end of the reaction (Table 3 and Figure 4). This implies that the epimerization at the α-stereogenic center of **8** is not facile, in spite of the basic reaction conditions. As shown in Scheme 4, the pure *syn* isomer **8a** was never completely transformed to the *anti* isomer to give the diastereo-mixture *syn*:*anti* = 2.2:1. On the other hand, the % ee of product **3a** was constant. Although the chiral ammonium enolate seemed to act as an active species, the corresponding *syn* and *anti* aldolates were found to show low enantiomeric excess relative to the Darzens product, as determined by chiral HPLC analysis (Table 3 and Figure 5).

Scheme 5. Transformation of (+)-**8b** to **3a**



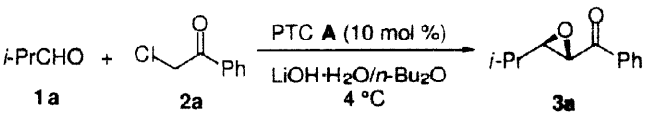


Table 3

run	time (h)	yield of **8** (%)	*syn* : *anti* (% de)	ee of **8a** (%)	ee of **8b** (%)	yield of **3a** (%)	ee of **3a** (%)
1	2.5	52	1:1.0 (0)	0	8	5	57
2	5	60	1:1.1 (5)	0	14	11	58
3	10	51	1:1.1 (5)	5	24	28	53
4	20	44	1:1.5 (20)	11	17	46	51
5	40	41	1:2.0 (33)	16	17	55	54
6	60	<20	1:2.0 (33)	11	3	80	53
7	80	<20	1:2.0 (33)	29	-5	74	46

Figure 3. The Change of Chemical Yields

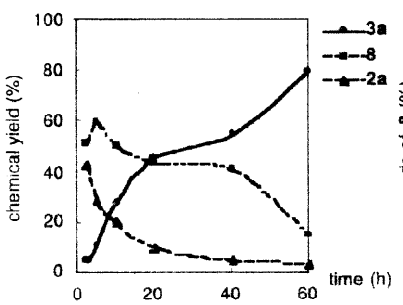


Figure 4. The Change of De of **8**

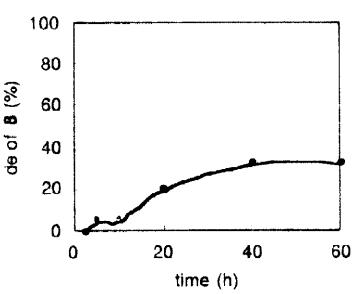
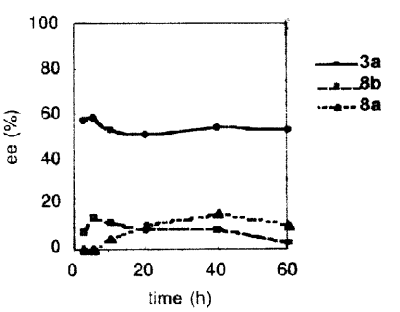


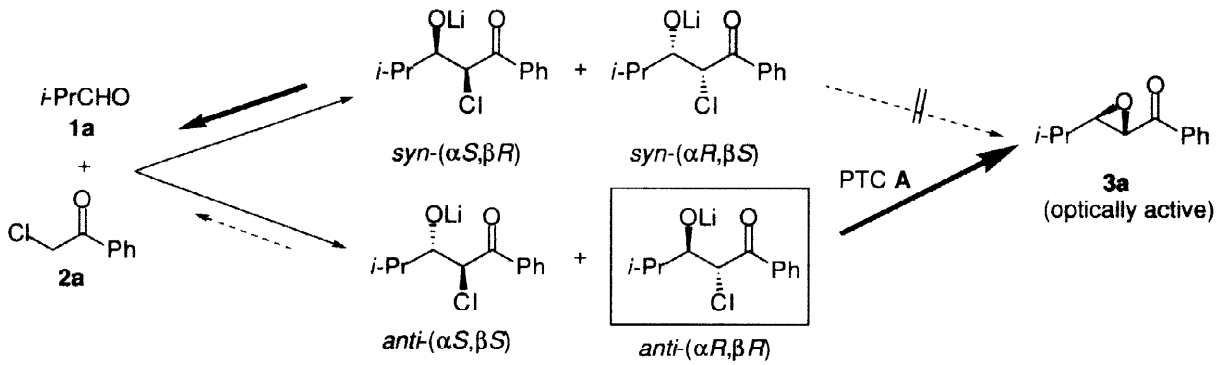
Figure 5. The Change of Ee of **3a** and **8**



We have shown that the Darzens reaction in an acyclic system does not involve a chiral enolate process but, rather, a kinetic resolution, which leads to optically active product because of a slow cyclization step to form the final epoxide product. The long lifetime of the racemic lithium alkoxide intermediates formed from the aldol reaction implies that these intermediates could easily be converted into the corresponding chiral ammonium alkoxides and lithium bromide by an ion-exchange process. This exchange would give mixtures of diastereomeric intermediates and would preceed the kinetic resolution in the cyclization step. In the acyclic phase-transfer catalyzed reaction, all four possible stereoisomers

(enantiomers and diastereomers) can exist. The chiral cinchonine-derived PTC is able to recognize one aldolate ($\alpha R,\beta R$) and promotes the final cyclization step to afford the desired product in optically active form. Since the equilibrium to produce **1a** and **2a** is possible via the retro aldol reaction, the consumed *anti*-($\alpha R,\beta R$)-intermediate yields the ($\alpha S,\beta R$)-Darzens product **3a** in moderate to high ee, as shown in Scheme 6. In contrast to the acyclic system, no aldol intermediates were detected in the cyclic case. Although, at present, we have no further information in the cyclic system, the cyclic chiral enolate seems to act as a relatively active intermediate.

Scheme 6. Possible Reaction Pathway to the Optically Active Product



Conclusion

We have demonstrated that a chiral ammonium salt derived from cinchonine acts as an effective phase-transfer catalyst to afford Darzens products in moderate to high enantioselectivities using mild reaction conditions. This synthesis, which involves chiral PTC, is potentially a very powerful synthetic strategy for making optically active α,β-epoxy ketones. Further studies into the origin of the enantioselection and the effect of substituents in the catalyst are in progress.

Experimental Section

^{1}H and ^{13}C NMR were measured at 270 and 67.8 MHz, respectively, with Me_4Si as an internal reference and $CDCl_3$ as the solvent. Flash chromatography was performed on Cica-MERCK Silica Gel 60 (230-400 mesh ASTM). Analytical thin layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. All the solvents were dried prior to use.

A General Procedure for the Asymmetric Darzens Reaction under Phase-Transfer Catalyzed Conditions in Acyclic System. (2*S*,3*R*)-2,3-Epoxy-4-methylpentanophenone (3a): To a solution of phenacyl chloride **2a** (154 mg, 1.0 mmol) and isobutyraldehyde **1a** (0.14 mL, 1.5 mmol) in dibutyl ether (10 mL) was added *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (PTC **A**) (53.3 mg, 0.1 mmol) at room temperature. After 20 min of stirring at 4 °C, lithium hydroxide monohydrate (84 mg, 2.0 mmol) was added and the reaction mixture was stirred for 72 h. The reaction 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 = 15:1) gave the desired product **3a** as a colorless oil (152.0 mg, 80%, 53% ee), $[\alpha]_D^{19}$ -11.2 (*c* 2.6, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OD, hexane:*i*-PrOH = 50:1. The retention time was 8.3 min for the ($\alpha S,\beta R$)-isomer and 9.9 min for the ($\alpha R,\beta S$)-isomer: ^{1}H-NMR δ : 1.07 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.72-1.84 (m, 1H), 2.97 (dd, J = 2.0, 6.0 Hz, 1H), 4.07 (d, J = 2.0 Hz, 1H), 7.47-7.56 (m, 2H), 7.58-7.66 (m, 1H), 8.02 (d, J = 8.6 Hz, 2H); ^{13}C-NMR δ : 18.0 (CH_3), 18.6 (CH_3), 30.3 (CH), 56.2 (C-O), 64.8

(C-O), 127.9 (Ph, CH), 128.6 (Ph, CH), 133.6 (Ph, CH), 135.2 (Ph, 4°), 194.5 (C=O); IR (neat) ν_{max}: 2964, 1691 cm^{-1}; MS *m/z*: 190 (M^+), 147, 105 (base peak); Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.46; H, 7.28.

(2*S*,3*R*)-2,3-Epoxypentanophenone (3b): ^{1}H-NMR δ : 1.10 (t, *J* = 7.6 Hz, 3H), 1.68-1.92 (m, 2H), 3.15 (dt, *J* = 2.0, 5.3 Hz, 1H), 4.03 (d, *J* = 2.0 Hz, 1H), 7.48-7.57 (m, 2H), 7.59-7.70 (m, 1H), 8.02 (dd, *J* = 1.7, 8.6 Hz, 2H); ^{13}C-NMR δ : 9.5 (CH_3), 24.8 (CH_2), 56.9 (C-O), 60.7 (C-O), 128.0 (Ph, CH), 128.6 (Ph, CH), 133.6 (Ph, CH), 135.3 (Ph, 4°), 194.5 (C=O); IR (neat) ν_{max}: 2973, 1690 cm^{-1}; MS *m/z*: 176 (M^+), 147 (M^+-Et), 105 (base peak), 77; Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.74; H, 7.07; $[\alpha]_D^{24}$ -11.8 (*c* 2.0, $CHCl_3$), (79% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*- PrOH = 50:1, retention time 10.0 min, 11.2 min.

(2*S*, 3*R*)-2,3-Epoxyhexanophenone (3c): ^{1}H-NMR δ : 0.95 (t, *J* = 7.3 Hz, 3H), 1.47-1.64 (m, 2H), 1.65-1.84 (m, 2H), 3.13 (dt, *J* = 2.0, 7.3 Hz, 1H), 4.03 (d, *J* = 2.0 Hz,1H), 7.44-7.53 (m, 2H), 7.56-7.64 (m, 1H), 8.01 (d, *J* = 7.9 Hz, 2H); ^{13}C-NMR δ : 13.6 (CH_2), 19.0(CH_3), 33.7 (CH_2), 57.0 (C-O), 59.6 (C-O), 128.0 (Ph, CH), 128.5 (Ph, CH), 133.5 (Ph, CH), 135.3 (Ph, 4°), 194.4 (C=O); IR (neat) ν_{max}: 2737, 1694 cm^{-1}; MS *m/z*: 190 (M^+), 147, 105 (base peak); $[\alpha]_D^{24}$ +5.4 (*c* 3.3, $CHCl_3$), (57% ee); Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.46; H, 7.52; HPLC: DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 50:1, retention time 9.2 min, 10.2 min.

(2*S*,3*R*)-2,3-Epoxy-5-methylhexanophenone (3d): ^{1}H-NMR δ : 1.01 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.60-1.78 (m, 2H), 1.85-1.95 (m, 1H), 3.14-3.21 (m, 1H), 4.00 (d, *J* = 2.0 Hz, 1H), 7.43-7.52 (m, 2H), 7.58-7.62 (m, 1H), 8.06-7.98 (m, 2H); ^{13}C-NMR δ : 22.3 (CH_3), 22.6 (CH_3), 26.3 (CH_2), 40.8 (CH_2), 57.1 (C-O), 58.9 (C-O), 128.1 (Ph, CH), 128.6 (Ph, CH), 133.7 (Ph, CH), 135.4 (Ph, 4°), 194.5 (C=O); IR (neat) ν_{max}: 2959, 1690 cm^{-1}; MS *m/z*: 205 (M^++H), 105 (base peak), 77; $[\alpha]_D^{24}$ +10.3 (*c* 3.1, $CHCl_3$), (69% ee); Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.45; H, 7.89. Found: C, 76.06; H, 7.79; HPLC: DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 50:1, retention time 8.6 min, 9.3 min.

(2*S*,3*R*)2,3-epoxy-5,5-dimethylhexanophenone (3e): ^{1}H-NMR δ : 1.03 (s, 9H), 1.55 (dd, *J* = 6.9, 14.2 Hz, 1H), 1.72 (dd, *J* = 4.6, 14.2 Hz, 1H), 3.21 (ddd, *J* = 2.0, 4.6, 6.9 Hz, 1H), 3.97 (d, *J* = 2.0 Hz, 1H), 7.46-7.55 (m, 2H), 7.58-7.67 (m, 1H), 8.03 (dd, *J* = 1.3, 7.3 Hz, 2H); ^{13}C-NMR δ : 29.4 (*t*-Bu, CH_3), 30.5 (*t*-Bu, 4°), 45.8 (CH_2), 56.6 (C-O), 57.5 (C-O), 128.0 (Ph, CH), 128.6 (Ph, CH), 133.6 (Ph, CH), 135.3 (Ph, 4°), 194.4 (C=O); IR (neat) ν_{max}: 2959, 1694 cm^{-1}; MS *m/z*: 218 (M^+), 215 (M^+-Me), 162, 147, 105 (base peak); $[\alpha]_D^{24}$ +3.0 (*c* 3.7, CH_2Cl_2), (62% ee); Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.79; H, 8.18; HPLC: DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 50:1, retention time 7.7 min, 8.3 min.

(2*S*,3*R*)-2,3-Epoxy-5-ethylpentanophenone (3f): ^{1}H-NMR δ : 0.96 (t, *J* = 7.3 Hz, 3H), 1.00 (t, *J* = 7.3 Hz, 3H), 1.17-1.34 (m, 2H), 1.37-1.61 (m, 3H), 2.97 (dd, *J* = 2.0, 7.9 Hz, 1H), 4.06 (*J* = 2.0 Hz, 1H), 7.46-7.55 (m, 2H), 7.59-7.67 (m, 1H), 8.05 (d, *J* = 8.3 Hz, 2H); ^{13}C-NMR δ : 10.9 (CH_3), 11.6 (CH_3), 23.4 (CH_2), 24.7 (CH_2), 44.0 (CH), 56.6 (C-O, CH), 63.6 (C-O, CH_2), 128.2 (Ph,CH), 128.7 (Ph, CH), 133.7 (Ph, CH), 135.5 (Ph, 4°), 194.7 (C=O); IR (neat) ν_{max}: 2965, 1690 cm^{-1}; MS *m/z*: 218 (M^+), 215 (M^+-Me), 147, 105 (base peak); $[\alpha]_D^{24}$ -7.3 (*c* 3.3, CH_2Cl_2), (58% ee); Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.76; H, 8.43; HPLC: DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 50:1, retention time 7.4 min, 8.4 min.

(2*S*,3*R*)-2,3-Epoxy-5-phenylpentanophenone (3g): ^{1}H-NMR δ : 2.00-2.22 (m, 2H), 2.72-3.00 (m, 2H), 3.20 (ddd, *J* = 2.0, 5.3, 7.3 Hz, 1H), 3.98 (d, *J* = 2.0 Hz, 1H), 7.08-7.37 (m, 5H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.3 Hz, 2H); ^{13}C-NMR δ : 31.6 (CH_2), 33.1 (CH_2), 57.0 (C-O), 59.3 (C-O), 126.0 (Ph, CH), 128.0 (Ph, CH), 128.1 (Ph, CH), 128.4 (Ph, CH), 128.5 (Ph, CH), 135.6 (Ph, CH), 135.2 (Ph, 4°), 140.3 (Ph, 4°), 194.3 (C=O); IR (neat) ν_{max}: 1688 cm^{-1}; MS *m/z*: 252 (M^+), 234, 105 (base peak), 77; Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.73; H, 6.52; $[\alpha]_D^{24}$ +6.2 (*c* 6.9, $CHCl_3$), (44% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 16.6 min, 18.3 min.

(2*S*,3*R*)-2,3-Epoxy-3-cyclohexylpropiophenone (3h): ^{1}H-NMR δ : 1.08-2.09 (m, 11H), 2.96 (dd, *J* = 2.0, 6.6 Hz, 1H), 4.09 (d, *J* = 2.0 Hz, 1H), 7.39-7.74 (m, 3H), 8.02 (d, *J* = 6.9 Hz, 2H); ^{13}C-NMR δ : 25.4 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 28.9 (CH_2), 29.5 (CH_2), 40.1 (CH_2), 56.4 (C-O), 64.2 (C-O), 128.2 (Ph, CH), 128.8 (Ph, CH), 133.7 (Ph, CH), 135.6 (Ph, 4°), 194.8 (C=O); IR (neat) ν_{max}: 1691 cm^{-1}; MS *m/z*: 230 (M^+), 214, 147, 105 (base peak); Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.02; H, 7.93; $[\alpha]_D^{24}$ +2.5 (*c* 3.8, $CHCl_3$), (63% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 0.5 ml/min, hexane:*i*-PrOH = 20:1, retention time 15.4 min, 16.7 min.

(2*S*,3*R*)-2,3-Epoxy-3-phenylpropiophenone (3i): ^{1}H-NMR δ : 4.08 (d, *J* = 2.0 Hz, 1H), 4.30 (d, *J* = 2.0 Hz, 1H), 7.33-7.58 (m, 7H), 7.60-7.73 (m, 1H), 8.02 (d, *J* = 7.3 Hz, 2H); ^{13}C-NMR δ : 59.9 (C-O), 61.5 (C-O), 126.3 (Ph, CH), 128.9 (Ph, CH), 129.3 (Ph, CH), 129.4 (Ph, CH), 129.6 (Ph, CH), 134.5 (Ph, 4°), 136.0 (Ph, 4°), 193.6 (C=O); IR (neat) ν_{max}: 3018, 1688 cm^{-1}; MS *m/z*: 224 (M^+), 207 (M^+-OH), 105 (base peak); Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.11; H, 5.32; $[\alpha]_D^{24}$ +125 (*c* 1.0, CH_2Cl_2), (42% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 0.5 ml/min, hexane:*i*-PrOH = 20:1, retention time 25.4 min, 27.5 min.

A Typical Procedure for the Catalytic Asymmetric Darzens Reaction in Cyclic System. (2*S*,1'*R*)-2,1'-Epoxy-2-(2'-methylpropyl)-1-tetralone (5a): To a suspension of **2b** (53.0 mg, 0.3 mmol), PTC **A** (16.0 mg, 0.03 mmol) and aldehyde **1a** (0.06 mL, 0.6 mmol) in dibutyl ether (1.5 mL) was added anhydrous lithium hydroxide (28.4 mg, 1.2 mmol) at room temperature. After the mixture was stirred for 45 h, more **1a** (0.06 mL, 0.6 mmol) was added, and the mixture was stirred for additional 16 h and the reaction 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 = 5:1) gave the desired coupling adduct **5a** as a colorless oil (64.2 mg, 99%, 69% ee). $[\alpha]_D^{25}$ +55.0 (*c* 2.1, $CHCl_3$). Ee was determined by HPLC analysis by use of DAICEL CHIRALCEL OD+OD, hexane-*i*-PrOH = 20:1, retention time, 16.9 min (major) and 18.6 min (minor): ^{1}H-NMR δ : 1.03 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.64-1.76 (m, 1H), 2.14 (ddd, *J* = 4.3, 9.2, 12.8 Hz, 1H), 2.43-2.56 (m, 1H), 3.00 (d, *J* = 9.2 Hz, 1H), 3.15 (dd, *J* = 4.3, 8.3 Hz, 2H), 7.26-7.41 (m, 2H), 7.53 (dd, *J* = 1.3, 7.6 Hz, 1H), 8.08 (d, *J* = 6.9 Hz, 1H); ^{13}C-NMR δ : 19.0 (CH_3), 19.9 (CH_3), 26.1 (CH_2), 27.3 (CH(Me_2)), 27.9 (CH_2), 62.5 (C_α), 70.1 (CH, C-O), 126.7 (CH), 127.4 (CH), 128.5 (CH), 132.4 (4°), 133.9 (CH), 143.1 (4°), 194.1 (C=O); IR (neat) ν_{max} : 1694 cm^{-1}; MS *m/z*:216, (M^+), 173 (M^+-*i*-Pr, base peak), 132; HRMS calcd for $C_{14}H_{16}O_2$ 216.1151, found 216.1152.

(2*S*,1'*R*)-2,1'-Epoxy-2-(3'-methylbutyl)-1-tetralone (5b): ^{1}H-NMR δ : 1.00 (d, J = 6.6 Hz, 3H), 1.06 (d, *J* = 6.3 Hz, 3H), 1.64-1.76 (m, 1H), 1.52 (dd, *J* = 6.9, 14.2 Hz, 1H), 1.68 (ddd, *J* = 4.3, 6.9, 14.2 Hz, 1H), 1.82-1.96 (m, 1H), 2.13 (dt, *J* = 4.3, 13.9 Hz, 1H), 2.44-2.55 (m, 1H), 3.13 (dd, *J* = 4.6, 7.6 Hz, 2H), 3.30 (dd, *J* = 4.3, 7.6 Hz, 1H), 7.27-7.38 (m, 2H), 7.52 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 8.06 (dd, *J* = 1.2, 7.9 Hz, 1H); ^{13}C-NMR δ : 22.6 (CH_3), 22.7 (CH_3), 26.4 (CH_2), 26.8 (CH(Me_2)), 27.8 (CH_2), 36.8 (CH_2), 61.6 (C_α), 63.4 (CH, C-O), 126.9 (CH), 127.6 (CH), 128.6 (CH), 132.7 (4°), 134.0 (CH), 143.3 (4°), 194.5 (C=O); IR (neat) ν_{max}: 1694, 1601 cm^{-1}; MS *m/z*:230 (M^+), 215 (M^+-Me), 173 (M^+-*i*-Bu, base peak), 146; HRMS calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1305; $[\alpha]_D^{24}$ +56.0 (*c* 2.5, $CHCl_3$), (74% ee); HPLC:DAICEL CHIRALCEL OD+OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 16.6 min, 18.6 min.

(2*S*,1'*R*)-2-(3',3'-Dimethylbutyl)-2,1'-epoxy-1-tetralone (5c): ^{1}H-NMR δ : 1.04 (s, 9H), 1.48 (dd, *J* = 7.9, 14.3 Hz, 1H), 1.73 (dd, *J* = 3.3, 14.3 Hz, 1H), 2.14 (dt, *J* = 4.6, 13.9 Hz, 1H), 2.42-2.55 (m, 1H), 3.07-3.17 (m, 2H), 3.34 (dd, *J* = 3.3, 7.9 Hz, 1H), 7.26-7.38 (m, 2H), 7.53 (ddd, *J* = 1.3, 5.9, 6.3 Hz, 1H), 8.07 (dd, *J* = 1.3, 7.9 Hz, 1H); ^{13}C-NMR δ : 26.3 (CH_2), 27.6 (CH_2), 29.3 (CH_3), 30.6 (4°), 41.5 (CH_2), 60.8 (C_α), 61.7 (CH, C-O), 126.8 (CH), 127.5 (CH), 128.6 (CH), 132.6 (4°), 134.0 (CH), 143.3 (4°), 194.6 (C=O); IR (neat) ν_{max}: 1693, 1601 cm^{-1}; MS *m/z*:244 (M^+), 229 (M^+-Me), 188 (M^++H-*t*-Bu, base peak), 173; HRMS calcd for $C_{16}H_{20}O_2$ 244.1464, found 244.1465; $[\alpha]_D^{19}$ +50.8 (*c* 2.4, $CHCl_3$), (86% ee); HPLC:DAICEL CHIRALPAK AD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 8.7 min, 12.1 min.

(2*S*,1'*R*)-2,1'-Epoxy-2-(2'-ethylbutyl)-1-tetralone (5d): ^{1}H-NMR δ : 0.91 (t, *J* = 7.6 Hz, 3H), 1.02 (t, *J* = 7.6 Hz, 3H), 1.21-1.69 (m, 5H), 2.11-2.22 (m, 1H), 2.39-2.58 (m, 1H), 3.10-3.20 (m, 3H), , 7.23-7.40 (m, 2H), 7.53 (ddd, *J* = 1.6, 7.6, 7.6 Hz, 1H), 8.07 (dd, J = 1.2, 7.9 Hz, 1H); ^{13}C-NMR δ : 10.9 (CH_3), 11.4 (CH_3), 24.0 (CH_2), 24.7 (CH_2), 26.4 (CH_2), 27.6 (CH_2), 39.5 (CH), 61.5 (C_α), 68.6 (CH, C-O), 126.9 (CH), 127.7 (CH), 128.7 (CH), 132.7 (4°), 134.0 (CH), 143.3 (4°), 194.6 (C=O); IR (neat) ν_{max}: 1690, 1603 cm^{-1}; MS *m/z*:244 (M^+), 228 (M^++H-Me), 216 (M^++H-Et, base peak), 173 (base peak), 132; HRMS calcd for $C_{16}H_{20}O_2$ 244.1464, found 244.1461; $[\alpha]_D^{24}$ +31.8 (*c* 2.1, $CHCl_3$), (84% ee); HPLC:DAIPAK CHIRALCEL AD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 7.0 min, 8.1 min.

(2*S*,1'*R*)-2-(1'-Cyclohexylmethyl)-2,1'-epoxy-1-tetralone (5e): ^{1}H-NMR δ : 1.14-1.43 (m, 5H), 1.58-1.85 (m, 5H), 1.93-2.05 (m, 1H), 2.10-2.18 (m, 1H), 2.44-2.55 (m, 1H), 3.02 (d, *J* = 8.9 Hz, 1H), 3.12-3.17 (m, 2H), 7.28-7.37 (m, 2H), 7.53 (ddd, *J* = 1.7, 7.6, 7.6 Hz, 1H), 8.07 (dd, *J* = 1.0, 6.6 Hz, 1H); ^{13}C-NMR δ : 25.27 (CH_3), 25.34 (CH_2), 26.0 (CH_2), 26.3(CH_2), 28.2 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 36.9 (CH), 62.3 (C_α), 69.1 (CH, C-O), 126.9 (CH), 127.6 (CH), 128.6 (CH), 132.7 (4°), 134.0 (CH), 143.2 (4°), 194.4 (C=O); IR (neat) ν_{max}: 1691, 1603 cm^{-1}; MS *m/z*:256 (M^+), 173 (M^+-*c*-Hex, base peak), 161 (M^+-*c*-Hex-C), 132; HRMS calcd for $C_{16}H_{20}O_2$ 256.1464, found 256.1461; Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.33; H,7.88; $[\alpha]_D^{22}$ +23.3 (*c* 1.6, $CHCl_3$), (69% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 9.2 min, 11.3 min.

(2*S*,1'*R*)-2,1'-Epoxy-2-(1'-phenylmethyl)-1-tetralone (5f): ^{1}H-NMR δ : 1.86 (dt, *J* = 4.3, 13.5 Hz, 1H), 2.45 (dt, *J* = 8.6, 13.5 Hz, 1H), 2.83 (dd, *J* = 4.3, 8.6 Hz, 2H), 4.37 (s, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.34-7.40 (m, 6H), 7.53 (ddd, *J* = 2.3, 7.6, 7.6 Hz, 1H), 8.12 (dd, *J* = 1.2, 7.9 Hz, 1H); ^{13}C-NMR δ : 25.2 (CH_2), 26.3(CH_2), 27.3 (CH_2), 64.0 (C_α), 64.3 (CH, C-O), 126.6 (CH), 126.9 (CH), 127.5 (CH), 128.30 (CH), 128.26 (CH), 128.7 (CH), 132.6 (4°), 134.0 (4°), 134.2 (CH), 143.3 (4°), 193.5 (C=O); IR (neat) ν : 1694, 1601 cm^{-1}; MS *m/z*:250 (M^+, base peak), 231, 115; HRMS calcd for $C_{16}H_{20}O_2$ 250.0994, found 250.0993; $[\alpha]_D^{24}$ +102 (*c* 2.2, $CHCl_3$), (59% ee); HPLC:DAICEL CHIRALCEL OD+OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 18.3 min, 19.7 min.

(2*S*,1'*R*)-2,1'-Epoxy-6-methoxy-2-(3'-methylbutyl)-1-tetralone (5g): ^{1}H-NMR δ : 0.99 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.43-1.57 (m, 1H), 1.62-1.72 (m, 1H), 1.81-1.93 (m, 1H), 2.10 (dt, *J* = 4.6, 10.1 Hz, 1H), 2.40-2.51 (m, 1H), 3.06-3.10 (m, 2H), 3.11-3.31 (m, 1H), 3.87 (s, 3H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 2.3, 8.9 Hz, 1H), 8.04 (d, J = 8.9 Hz, 1H); ^{13}C-NMR δ : 22.66 (CH_3), 22.70 (CH_3),26.5 (CH_2), 26.8 (CH), 28.1 (CH_2), 36.8 (CH_2), 55.5 (OCH_3), 61.4 (C_α), 63.1 (CH, C-O), 112.6 (CH), 113.3 (CH), 126.4 (4°), 130.1 (CH), 145.8 (4°), 164.1 (4°),193.1 (C=O); IR (neat) ν_{max}: 1682, 1497, 1464 cm^{-1}; MS *m/z*:260 (M^+), 245 (M^+-Me), 218 (M^++H-*i*-Pr), 203 (base peak), 176; HRMS calcd for $C_{16}H_{20}O_3$ 260.1413, found 260.1408; Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.56; H,7.66; $[\alpha]_D^{26}$ +29.1 (*c* 2.5, $CHCl_3$), (50% ee); HPLC:DAICEL CHIRALCEL OD+OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 27.8 min, 30.3 min.

(2*S*,1'*R*)- 2-(3',3'-Dimethylbutyl)-2,1'-epoxy-6-methoxy-1-tetralone (5h): ^{1}H-NMR δ : 1.04 (s, 9H), 1.43-1.75 (m, 2H), 2.09-2.15 (m, 1H), 2.40-2.49 (m, 1H), 3.06-3.10 (m, 2H), 3.32-3.36 (m, 1H), 3.88 (s, 3H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 2.3, 8.9 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 1H); ^{13}C-NMR δ : 26.4 (CH_2), 28.0 (CH_2), 29.6 (CH_3), 30.6 (4°), 41.6 (CH_2), 55.4 (OCH_3), 60.6 (C_α), 61.4 (CH, C-O), 112.5 (CH), 113.3 (CH), 126.3 (4°), 130.1 (CH), 145.8 (4°), 164.0 (4°), 193.2 (C=O); IR (nujol) ν_{max}: 1676, 1599, 1462, 1373 cm^{-1}; MS *m/z*:274 (M^+), 259 (M^+-Me), 218 (base peak), 203; HRMS calcd for $C_{17}H_{22}O_3$ 274.1570, found 274.1571; $[\alpha]_D^{21}$ +48.5 (*c* 2.1, $CHCl_3$), (75% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:*i*-PrOH = 20:1, retention time 11.2 min, 12.4 min.

(2*S*,1'*R*)-2,1'-Epoxy-6-methoxy-2-(2'-methylpropyl)-1-tetralone (5i): mp; 85.5-88.6 °C (colorless crystals, hexane-diethyl ether); ^{1}H-NMR δ : 1.02 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.58-1.77 (m, 1H), 2.07-2.17 (m, 1H), 2.40-2.52 (m, 1H), 2.99 (d, *J* = 9.2 Hz, 1H), 3.07-3.14 (m, 2H),

3.88 (s, 3H), 6.74 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 2.4, 8.9 Hz, 1H), 8.05 (d, J = 8.9 Hz, 1H); ^{13}C-NMR δ : 19.1 (CH_3), 20.1(CH_3), 26.3 (CH_2), 27.5 (CH_2), 28.5 (CH), 55.5 (OCH_3), 62.4 (C_α), 70.0 (CH, C-O), 112.6 (CH), 113.4 (CH), 126.3 (4°), 130.2 (CH), 145.7 (4°), 164.1 (4°), 192.8 (C=O); IR (nujol) ν_{max}: 2361, 1676, 1597, 1460 cm^{-1}; MS m/z:246 (M^+), 231 (M^+-Me), 203 (base peak), 162; Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.88; H,7.21; $[\alpha]_D^{23}$ +7.1 (c 2.4, $CHCl_3$), (35% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:i-PrOH = 20:1, retention time 15.7 min, 17.9 min. The X-ray crystallographic data of **5i** have been depositted at the Cambridge Crystallographic Data Centre.

(2*S*,1'*R*)-2-(1'-Hydroxy-2-methylpropyl)-1-tetralone (6): To a stirred solution of SmI_2 (1.11 mmol) in THF (0.1 M solution) at -78 °C was added a solution of **5a** (95.7 mg, 0.44 mmol) in MeOH (1.0 mL) under argon atmosphere. After stirring for 20 minutes, the reaction mixture was quenched with H_2O at -78 °C, extracted with diethyl ether (15 mL X 3), and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvents and the following flash column chromatography (silica gel, hexane:diethyl ether = 4:1) gave the desired product **6** as a sole diastereomer as a colorless oil (51.1 mg, 53% yield). Stereochemistry of **6** was determined by comparison of the literature data.[11] Enantiomeric excess of **6** was determined by HPLC analysis which revealed the reaction proceeded without racemization. $[\alpha]_D^{28}$ -13.8 (c 2.7, $CHCl_3$), (58% ee); HPLC:DAICEL CHIRALCEL OD, flow rate 1.0 ml/min, hexane:i-PrOH = 20:1, retention time 7.9 min (minor), 9.1 min (major).

α-Chloro-β-hydroxyketone (8): To a stirred solution of phenacyl chloride **2a** (267 mg, 1.7 mmol) and isobutyraldehyde **1a** (0.24 mL, 2.6 mmol) in THF (8.7 mL) at 0 °C was added a catalytic amount of KO-t-Bu (19 mg, 0.17 mmol). After stirring for 2 h, the reaction mixture was quenched with 1N HCl (3.0 mL), extracted with diethyl ether (15 mL X 3), and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4. Removal of solvents followed by flash column chromatography (silica gel, hexane:diethyl ether = 3:1) gave the desired coupling products **8a** (152.1 mg, 67% yield) as a more polar ingredient and **8b** (49.1 mg, 22% yield) as a less polar one, respectively.

***syn*-2-Chloro-3-hydroxy-4-methylpentanophenone (8a, more polar)**: ^{1}H-NMR δ : 1.03 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 1.96 (dq, J = 6.9, 7.3 Hz, 1H), 3.09 (d, J = 4.3 Hz, 1H), 3.84 (ddd, J = 3.3, 4.3, 7.3 Hz, 1H), 5.29 (d, J = 3.3 Hz, 1H), 7.47-7.56 (m, 2H), 7.60-7.68 (m, 1H), 7.99 (dd, J = 1.3, 7.6 Hz, 2H); ^{13}C-NMR δ : 18.0 (CH_3), 19.0 (CH_3), 30.9 (CH), 59.4 (C-Cl, CH), 76.0 (C-O, CH), 128.8 (Ph, CH), 128.9 (Ph, CH), 134.1 (Ph, CH), 134.3 (Ph, 4°), 194.5 (C=O); IR (nujol) ν_{max}: 1682 cm^{-1}; MS m/z:191 (M^+-Cl), 105 (base peak); Anal. Calcd. for $C_{12}H_{15}ClO_2$: C, 63.58; H, 6.67. Found: C, 63.40; H, 6.78; HPLC: DAICEL CHIRALPAK AD, flow rate 1.0 ml/min, hexane:i-PrOH = 20:1, retention time 15.0 min, 17.1 min.

***anti*-2-Chloro-3-hydroxy-4-methylpentanophenone (8b, less polar)**: ^{1}H-NMR δ : 1.01 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 2.14-2.32 (m, 1H), 2.58 (d, J = 5.6 Hz, 1H), 4.04-4.15 (m, 1H), 4.98 (d, J = 8.6 Hz, 1H), 7.46-7.55 (m, 2H), 7.58-7.67 (m, 1H), 8.04 (d, J = 8.3 Hz, 2H); IR (nujol) ν_{max}: 1682 cm^{-1}; MS m/z:191 (M^+-Cl), 154, 156, 105 (base peak); $[\alpha]_D^{24}$ +32.0 (c 0.41, $CHCl_3$), (47% ee, (α*S*,β*S*)); Anal. Calcd. for $C_{12}H_{15}ClO_2$: C, 63.58; H, 6.67. Found: C, 63.28; H, 6.65; HPLC: DAICEL CHIRALPAK AD, flow rate 1.0 ml/min, hexane:i-PrOH = 20:1, retention time 9.0 min, 11.0 min.

The Transformation of (+)-8b to Epoxide 3a: According to the Mukaiyama procedure,[13] the desired product **3a** was obtained without retro aldol or epimerization process. To a stirred solution of (+)-**8b** (5.8 mg, 0.026 mmol, 47% ee) in DMF (0.2 mL) was added NEt_3 (30 μL, 0.22 mmol) at rt. After stirring for 46 h, the reaction mixture was quenched with 1N HCl (1.0 mL), extracted with diethyl ether (1.0 mL X 3), and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvents followed by chromatography (silica gel, hexane:diethyl ether = 5:1) gave **3a** as colorless oil (4.7 mg, 95% yield). Enantiomeric excess of the obtained product was determined by HPLC analysis.

Acknowledgments: We thank Professor M. J. O' Donnell of Indiana University-Purdue University at Indianapolis for critical reading of the manuscript. One of the authors (S.A.) is grateful to the Ciba-Geigy Foundation (Japan) for the Promotion of Science for their financial support. This work was also supported by Grants-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan and the Ohara Award in Synthetic Organic Chemistry, Japan.

References and Notes

1. (a) Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* **1996**, 2411-2412. (b) Takahashi, T.; Muraoka, M.; Capo, M.; Koga, K. *Chem. Pharm. Bull.* **1995**, *43*, 1821-1823.
2. For recent books on PTC, see: (a) *Phase-Transfer Catalysis. Mechanism and Syntheses*; Halpern, M. E., Ed.; American Chemical Society, Washington D C, 1997. (b) *Handbook of Phase Transfer Catalysis*; Sasson, Y; Neumann, R. Ed.; Blackie A. & M., London, 1997.
3. Preliminary reports of this and related works have appeared, see: (a) Arai, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2145-2148. (b) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Chem. Commun.* **1999**, 49-50. See also (c) Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 8299-8302.
4. Quite recently, we have reported the successful asymmetric reactions promoted by chiral PTC, see (a) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997-3000. (b) Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563-7566. (c) Arai, S.; Oku, M.; Miura, M.; Shioiri, T. *Synlett* **1998**, 1201-1202. (d) Arai, S.; Nakayama, K. Hatano, K.; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 9572-9575. (e) Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 9739-9742.
5. PTC **A** was purchased from Aldrich, Co. Ltd.
6. Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.*, **1997**, *119*, 2329-2330. (b) Elston, C. L.; Jackson, R. F. W.; MacDonald, S. J. F.; Murry, P. J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 410-412.
7. Recently, the chiral crown ether catalyzed asymmetric Darzens reaction was reported, see: Bako, P.; Szollosy, A.; Bombicz, P.; Toke, L. *Synlett*, **1997**, 291-292.
8. Unpublished results.
9. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.
10. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29-68, and references cited therein.
11. Hojo, M.; Harada, H.; Itoh, H.; Hosomi, A. *J. Am. Chem. Soc.* **1997**, *119*, 5459-5460.
12. O'Donnell and co-workers reported experiments leading to the proposal of the *O*-alkylated salt as an active catalyst in alkylation reaction: O'Donnell, M. J.; Wu, S.; Huffmann, J. C. *Tetrahedron* **1994**, *50*, 4507-4518.
13. Quite recently, successful examples of the asymmetric reactions promoted by the *O*-allyl-cinchonine or cinchonidine derived PTCs have been reported, see (a) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347-5350. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599-1602. (d) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775-8778.
14. Mukaiyama,T.; Haga, T.; Iwasawa, N.; *Chem. Lett.* **1982**, 1601-1604. No transformation to epoxide or epimerization of α–hydrogen occurred by use of the corresponding *syn* adduct **8b** as a starting material under similar conditions.