Synthesis and Investigation of C_2-Symmetric Optically Active Pyrrolidinium Salts as Chiral Phase-Transfer Catalysts

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Received June 22, 1994; accepted August 4, 1994

C_2-Symmetric optically active pyrrolidinium salts were synthesized by the reaction of 2,3 : 4,5-di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-(2*S*,5*S*)-bis(hydroxymethyl)pyrrolidine (2), (3*R*,4*R*)-dimethoxy-(2*S*,5*S*)-bis(methoxymethyl)-pyrrolidine (3), 2,3 : 4,5-Di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-*N*-(2-hydroxyethyl)-(2*S*,5*S*)-bis(hydroxymethyl)-pyrrolidine (5), and (3*R*,4*R*)-dimethoxy-*N*-(2-hydroxyethyl)-(2*S*,5*S*)-bis(methoxymethyl)pyrrolidine (7) with methyl iodide or α,ω-dibromoalkanes. They exhibited low chiral induction activity in the epoxidation of chalcone and in the Darzens condensation of *p*-chlorobenzaldehyde and phenacyl chloride under phase-transfer conditions.

Keywords chiral phase-transfer catalyst; asymmetric induction; C_2-symmetric quaternary pyrrolidinium salt; epoxidation of chalcone; Darzens condensation

Asymmetric synthesis using phase-transfer catalysts (PTCs) is a topic of much current interest,[1] although the efficiency of the chiral induction has generally been low. So far, the most widely employed chiral PTCs have been essentially limited to the quaternary ammonium salts of cinchona alkaloids and ephedrine, such as *N*-benzylcinchoninium chloride[2a] and *N*-methyl-*N*-dodecylephedrinium chloride.[2b] In addition, the dominant structural factor of chiral PTCs in invoking asymmetric induction has remained obscure. Therefore, in order to gain more insight into this kind of asymmetric synthesis and to open the way for design of new high-efficiency chiral PTCs, it is necessary to prepare some structurally modified simple chiral quaternary ammonium salts and examine their asymmetric induction ability under phase-transfer conditions.

C_2-Symmetric chiral reagents, including auxiliaries and catalyst ligands, have proved to be remarkably useful in asymmetric synthesis and have attracted much attention.[3] This prompted us to prepare some C_2-symmetric chiral quaternary ammonium salts in the hope that they would also have high efficiency in asymmetric synthesis under phase-transfer conditions. Previously, we have reported that 2,3 : 4,5-di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-(2*S*,5*S*)-bis(hydroxymethyl)pyrrolidine (**1**), (3*R*,4*R*)-dimethoxy-(2*S*,5*S*)-bis(methoxymethyl)pyrrolidine (**2**), and related chiral C_2-symmetric pyrrolidine derivatives could be conveniently synthesized from D-mannitol in high yields, and a high chiral induction of 82% ee was observed in the addition reaction of diethylzinc to benzaldehyde using these amines as chiral catalyst ligands.[4] In this paper, we wish to report the synthesis of C_2-symmetric pyrrolidinium salts from **1** and **2** and to disclose their utility as chiral PTCs.

Results and Discussion

Although 2,3 : 4,5-di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-(2*S*,5*S*)-dihydroxymethyl-*N*,*N*-dimethylpyrrolidinium iodide (**3a**) was readily prepared by the reaction of **1** with an excess of methyl iodide in acetonitrile in the presence of potassium carbonate under reflux, no quaternary ammonium salts could be obtained by alkylation using benzyl bromide or long-chain alkyl halides such as heptyl or octyl bromide; these gave only the corresponding *N*-alkylpyrrolidine derivatives under the same reaction conditions (Chart 1). On the other hand, Littmann and Marvel have reported that bromoalkylamines of the general type $Br(CH_2)_nN(CH_3)_2$ ($n=4$—6) gave cyclic quaternary ammonium salts by heating in water.[5] This interesting result stimulated us to investigate further the reaction of **1** and **2** with some α,ω-dibromoalkanes and 2,2'-bis(bromomethyl)biphenyl as shown in Chart 2.

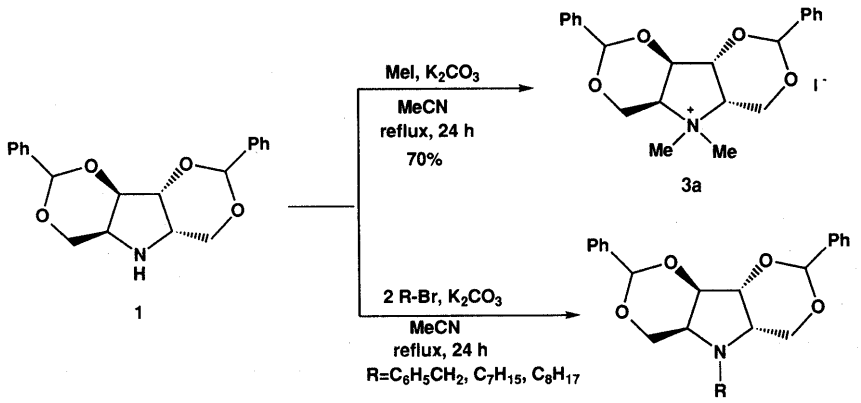


Chart 1

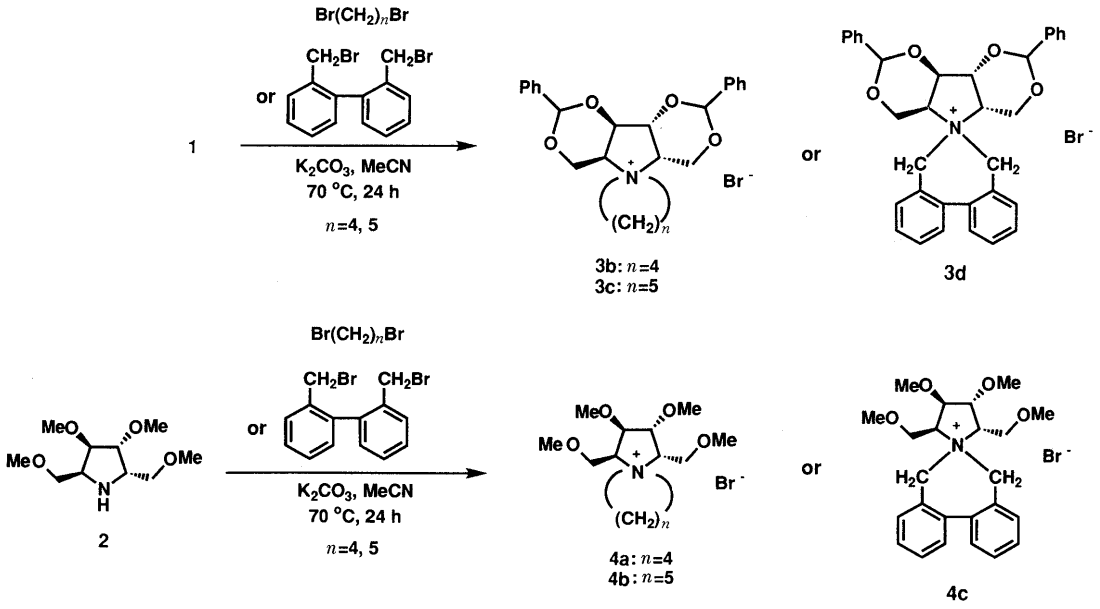


Chart 2

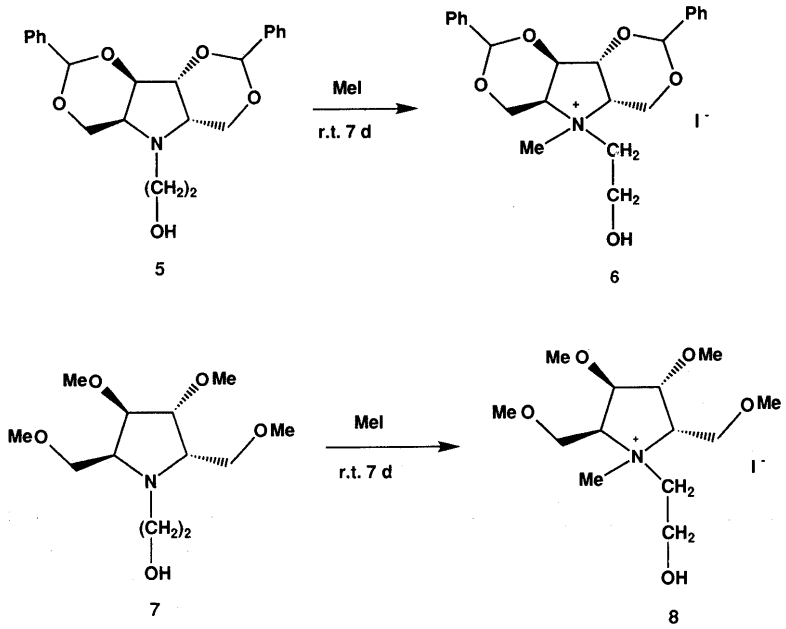


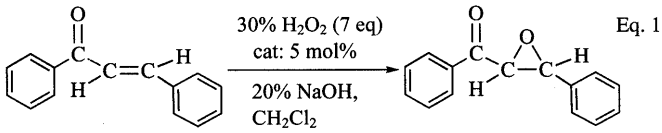
Chart 3

The C_2-symmetric quaternary spiro-ammonium salts (**3b—d**, **4a—c**) could be readily obtained by the reaction of **1** and **2** with 1,4-dibromobutane, 1,5-dibromopentane, and 2,2′-bis(bromomethyl)biphenyl, respectively in acetonitrile in the presence of potassium carbonate at 70 °C (Chart 2).

Previous data obtained by using quaternary ammonium salts of cinchona alkaloids and ephedrine as chiral PTCs implied that a hydroxyl group at the position β to the onium function is important in order to achieve asymmetric induction under phase-transfer conditions.[6] Thus, two C_2-symmetric quaternary ammonium salts (**6** and **8**) having a β-hydroxyl group with respect to the onium function were also synthesized by stirring the tertiary amines (**5** and **7**), which were prepared from the starting materials (**1** and **2**),[4] with an excess of methyl iodide at room temperature for 7 d as shown in Chart 3. It should be mentioned that mild reaction conditions seemed to be necessary for the preparation of **6** and **8** because the reaction product was **3a** rather than **6** when the reaction of **5** with excess methyl iodide was carried out by heating at 80 °C in a sealed tube.

It is well known that the quaternary ammonium salts of cinchona alkaloids are excellent chiral phase-transfer catalysts in epoxidation reactions.[7] Therefore, the reactions examined using the obtained catalysts **3a—d**, **4a—c**, **6**, and **8** were (1) the asymmetric epoxidation of chalcone, which was carried out with 30% H_2O_2 in a

two-phase system of dichloromethane (CH_2Cl_2)–20% sodium hydroxide (NaOH) aqueous solution in the presence of a catalytic amount (5 mol%) of the ammonium salts (Eq. 1) and (2) the Darzens reaction of *p*-chlorobenzaldehyde and phenacyl chloride in a mixture of 20% NaOH and CH_2Cl_2 using 5 mol% of quaternary ammonium salts as a catalyst (Eq. 2). These results are summarized in Tables I and II, respectively.



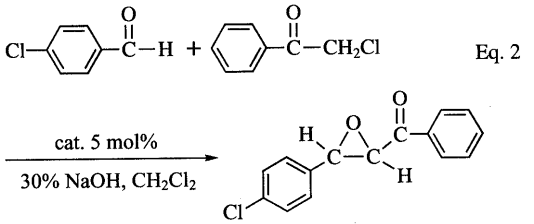
Eq. 1

9a

TABLE I. Epoxidation of Chalcone with 30% H_2O_2 in 20% NaOH–CH_2Cl_2 in the Presence of the Chiral Catalyst

Entry	Reaction conditions			Yield[a] (%)	$[\alpha]_D$ (°)	Optical purity[b] (%)
	Cat.	Temp. (°C)	Time (h)			
1	**3a**	0	24	14	+1.0	0.9
2	**3c**	0	24	69	−2.0	1.8
3	**4b**	0	24	70	−7.7	6.7
4	**4c**	0	24	82	−4.0	3.5
5	**6**	0	24	20	+1.0	0.9

a) Isolated yields. *b*) The optical purities of **9a** were calculated from the specific optical rotation on the basis of the reported data. $[\alpha]_D$ −6.2° (*c*=1, $CHCl_3$), 5.4% ee.[8]



Eq. 2

9b

TABLE II. Darzens Condensation of Benzaldehyde and Phenacyl Chloride with 30% NaOH–CH_2Cl_2 in the Presence of Chiral PTCs

Entry	Reaction conditions			Yield[a] (%)	$[\alpha]_D$ (°)	Optical purity[b] (%)
	Cat.	Temp. (°C)	Time (h)			
1	**3b**	0	10	82	+3.0	2.6
2	**3c**	0	10	85	+3.4	3.0
3	**3d**	0	10	80	+2.4	2.1
4	**4a**	0	10	83	−2.5	2.2
5	**4b**	0	10	66	−2.0	1.8
6	**6**	0	10	98	−3.0	2.6
7	**8**	0	10	90	+2.6	2.3

a) Isolated yields. *b*) The optical purities of **9b** were calculated from the specific optical rotation on the basis of the reported data. $[\alpha]_D$ −13.0° (*c*=1, $CHCl_3$), 8.6% ee.[8]

Although the chiral inductions attained were low, the results at least indicate that C_2-symmetric chiral pyrrolidinium salts can act as chiral PTCs. Further work is in progress.

Experimental

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined in a solution of $CHCl_3$ or CH_3OH at 20 °C by using a Jasco DIP-360 digital polarimeter. ^{1}H-NMR spectra were determined for solutions in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard on a JNM-GX270 spectrometer. Mass spectra were recorded with a JMS D-300 instrument. All compounds reported in this paper gave satisfactory CHN microanalyses with a Perkin-Elmer Model 240 analyzer. The optical purities of **9a** and **9b** were determined from the specific optical rotation according to the literature [the epoxy ketone (**9a**): $[\alpha]_D$ −6.2° (*c*=1, $CHCl_3$), ee=5.4%; the epoxy ketone (**9b**): $[\alpha]_D$ −13.0° (*c*=1, $CHCl_3$), ee=8.6%].[8]

2,3:4,5-Di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-(2*S*,5*S*)-bis(hydroxymethyl)pyrrolidine (**1**), (3*R*,4*R*)-dimethoxy-(2*S*,5*S*)-bis(methoxymethyl)pyrrolidine (**2**), 2,3:4,5-di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-*N*-(2-hydroxyethyl)-(2*S*,5*S*)-bis(hydroxymethyl)pyrrolidine (**5**), and (3*R*,4*R*)-dimethoxy-*N*-(2-hydroxyethyl)-(2*S*,5*S*)-bis(methoxymethyl)-pyrrolidine (**7**) were synthesized from D-mannitol according the literature.[4,9]

Preparation of 2,3:4,5-Di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-(2*S*,5*S*)-dihydroxymethyl-*N*,*N*-dimethylpyrrolidinium Iodide (3a) An acetonitrile solution of **1** (200 mg, 0.59 mmol), an excess of methyl iodide, and potassium carbonate (81.6 mg, 0.59 mmol) was stirred vigorously for 24 h under reflux. After cooling, the white precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was recrystallized from ethanol and ether to give **3a** as a colorless solid $[\alpha]_D$ +42.4° (*c*=0.58, $CHCl_3$) mp 248 °C (dec.). IR (KBr) *v*: 3450, 3050, 3025, 2950, 2900, 2850, 1460, 1400, 1350, 1300, 1240, 1220, 1140, 1090, 1050, 980, 920, 760, 700 cm^{-1}. ^{1}H-NMR (CD_3CN) δ: 3.48 (6H, s), 4.14 (2H, br), 4.50—4.56 (2H, m), 4.80—4.86 (4H, m), 5.79 (2H, s), 7.37—7.63 (10H, m, Ar). *Anal.* Calcd for $C_{22}H_{26}INO_4$: C, 53.34; H, 5.29; N, 2.82. Found: C, 53.21; H, 5.26; N, 2.79.

Preparation of the Spiro-ammonium Bromide (3b) An acetonitrile solution of **1** (200 mg, 0.59 mmol), 1,4-dibromobutane (128 mg, 0.59 mmol), and potassium carbonate (81.6 mg, 0.59 mmol) was stirred vigorously for 24 h at 70 °C. After cooling, the white precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was recrystallized from ethanol and ether to give **3b** as a colorless solid (145 mg, 52%). $[\alpha]_D$ +27.9° (*c*=1.0, CH_3OH) mp 172—174 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.50 (4H, m, CH_2), 4.05—4.20 (2H, m, CH_2), 4.27 (2H, s), 4.25—4.50 (2H, m, CH_2), 4.60 (2H, dd, *J*=15.1, 2.0 Hz), 4.76 (2H, d, *J*=2.0 Hz), 5.0 (2H, d, *J*=15.1 Hz), 5.68 (2H, s), 7.20—7.60 (10H, m, Ar). *Anal.* Calcd for $C_{24}H_{28}BrNO_4 \cdot 0.5H_2O$: C, 59.63; H, 6.05; N, 2.90. Found: C, 59.60; H, 6.13; N, 2.95.

Preparation of Spiro-ammonium Bromide (3c) This compound was prepared in the same manner as described above (187 mg, 65%). $[\alpha]_D$ +17.0° (*c*=1.0, CH_3OH) mp 177—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.12 (4H, m, CH_2), 2.12—2.30 (2H, m, CH_2), 4.10—4.40 (4H, m, CH_2), 4.27 (2H, s), 4.60 (2H, dd, *J*=15.1, 2.4 Hz), 4.79 (2H, d, *J*=2.4 Hz), 5.53 (2H, d, *J*=15.1 Hz), 5.75 (2H, s), 7.30—7.55 (10H, m, Ar). *Anal.* Calcd for $C_{25}H_{30}BrNO_4 \cdot 0.5H_2O$: C, 60.36; H, 6.28; N, 2.82. Found: C, 60.24; H, 6.23; N, 2.89.

Preparation of Spiro-ammonium Bromide (3d) This compound was prepared in the same manner as described above (211 mg, 60%) (highly hygroscopic). $[\alpha]_D$ +58.0° (*c*=1, CH_3OH) mp 233—236 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.97 (2H, d, *J*=15.63 Hz), 4.38 (2H, d, *J*=13.2 Hz), 4.63 (2H, d, *J*=13.2 Hz), 4.85 (2H, d, *J*=14.7 Hz), 5.27 (2H, s), 5.43 (2H, s), 5.64 (2H, s), 7.20—8.10 (18H, m, Ar). High FAB-MS *m*/*z*: 518.2329 (M^+ −Br) ($C_{34}H_{32}NO_4$ requires 518.2333). *Anal.* Calcd for $C_{34}H_{32}BrNO_4$: C, 68.23; H, 5.39; N, 2.34. Found: C, 70.20; H, 5.61; N, 2.68.

Preparation of Spiro-ammonium Bromide (4a) This compound was prepared in the same manner as described above (110 mg, 53%). $[\alpha]_D$ +27.2° (*c*=1, CH_3OH) mp 176—179 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.30 (2H, m, CH_2), 2.30—2.62 (2H, m, CH_2), 3.39 (6H, s, OCH_3), 3.52 (6H, s, OCH_3), 3.70—4.0 (8H, m), 4.18 (2H, d, *J*=5.8 Hz), 4.78—4.85 (2H, q, *J*=5.4 Hz). *Anal.* Calcd for $C_{14}H_{28}BrNO_4$: C, 47.46; H, 7.97; N, 3.95. Found: C, 47.28; H, 7.85; N, 3.89.

Preparation of Spiro-ammonium Bromide (4b) This compound was prepared in the same manner as described above and recrystallized from acetone and ether (141 mg, 65%). $[\alpha]_D$ +47.5° (*c*=0.5, CH_3OH) mp 181—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.82 (2H, m, CH_2), 2.0—2.20 (2H, m, CH_2), 2.25—2.50 (2H, m, CH_2), 3.30—3.46 (2H, m), 3.40 (6H, s, OCH_3), 3.54 (6H, s, OCH_3), 3.58—3.74 (2H, m), 3.78 (2H, dd, *J*=12.7, 2.9 Hz), 3.93 (2H, dd, *J*=12.7, 6.4 Hz), 4.16 (2H, d, *J*=6.84 Hz), 4.96—5.20 (2H, m). *Anal.* Calcd for $C_{15}H_{30}BrNO_4$: C, 48.92; H, 8.21; N, 3.80. Found: C, 48.54; H, 8.04; N, 3.78.

Preparation of Spiro-ammonium Bromide (4c) This compound was prepared in the same manner as described above (169 mg, 60%). $[\alpha]_D$ +32.2° ($c=1$, CH_3OH) mp 178—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.15 (6H, s, OCH_3), 3.63 (6H, s, OCH_3), 3.65—4.0 (4H, m), 4.10—4.67 (4H, m), 4.51 (2H, d, $J=2.9$ Hz), 4.92 (2H, q, $J=5.4$ Hz), 7.42—7.85 (8H, m, Ar). *Anal.* Calcd for $C_{24}H_{32}BrNO_4$: C, 60.25; H, 6.74; N, 2.93. Found: C, 60.08; H, 6.66; N, 2.98.

Preparation of 2,3 : 4,5-Di-*O*-benzylidene-(3*R*,4*R*)-dihydroxy-*N*-(2-hydroxyethyl)-(2*S*,5*S*)-bis(hydroxymethyl)-*N*-methylpyrrolidinium Iodide (6) A mixture of **5** (690 mg, 1.80 mmol) and methyl iodide (2 ml) was stirred at room temperature for 7 d. Excess methyl iodide was removed under reduced pressure, and the residue was purified by silica gel column chromatography and recrystallized from ethanol and ether to give **6** as colorless crystals (650 mg, 69%). mp 231—232 °C. IR (KBr) ν: 3300, 1400, 1140, 1100, 1080, 1040, 980, 970, 760 cm^{-1}. *Anal.* Calcd for $C_{23}H_{28}INO_5$: C, 52.58; H, 5.37; N, 2.67. Found: C, 52.29; H, 5.32; N, 2.74.

Preparation of (3*R*,4*R*)-Dimethoxy-*N*-(2-hydroxyethyl)-(2*S*,5*S*)-bis-(methoxymethyl)-*N*-methylpyrrolidinium Iodide (8) This compound was prepared from **7** (65%) in the same manner as described for **5**. $[\alpha]_D$ +13.34° ($c=1.15$, $CHCl_3$) mp 96—97 °C. IR (KBr) ν: 3300, 2920, 1450, 1180, 1100, 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.37 (3H, s), 3.44 (3H, s), 3.76—3.86 (1H, m), 3.90—3.97 (3H, m), 3.50 (3H, s), 3.76—3.86 (1H, m), 3.90—3.97 (3H, m), 4.09—4.11 (1H, m), 4.19—4.20 (2H, m), 4.34—4.43 (2H, m), 4.69 (1H, dd, $J=11.72$, 5.37 Hz). *Anal.* Calcd for $C_{13}H_{28}INO_5$: C, 38.53; H, 6.96; N, 3.46. Found: C, 38.45; H, 6.96; N, 3.54.

General Procedure for the Chiral Phase-Transfer Reaction. 1. Epoxidation of Chalcone A solution of 20% aqueous NaOH (0.4 ml) and 30% aqueous H_2O_2 (1.0 ml) was added to a solution of chalcone (200 mg, 0.96 mmol) and **3c** (23.4 mg, 5 mol%) in dichloromethane (2.0 ml) and the reaction mixture was vigorously stirred at 0 °C for 24 h. After usual work-up, the residue was separated by thin layer chromatography (eluant : chloroform/hexane = 1/1) to afford the known epoxide (**9a**) (138 mg, 69%). ^{1}H-NMR ($CDCl_3$) δ: 4.08 (1H, d, $J=2.0$ Hz), 4.30 (1H, d, $J=2.0$ Hz), 7.30—7.70 (8H, m, Ar), 7.90—8.10 (2H, m, Ar). EI-MS m/z: 224 (M^+, 10), 105 (M^+-119, 100), 77 (M^+-147, 30).

2. Darzens Condensation Reaction *p*-Chlorobenzaldehyde (141 mg, 1.0 ml) and phenacyl chloride (154 mg, 1.0 mmol) were stirred in a mixture of 20% NaOH (2 ml) and CH_2Cl_2 (5 ml) with 5 mol% catalyst of **3b** at 0 °C for 10 h. After usual work-up, the residue was purified by flash column chromatography (SiO_2) (eluant : chloroform/hexane = 1/2) to give the known epoxide (**9b**) (212 mg, 82%). ^{1}H-NMR ($CDCl_3$) δ: 4.06 (1H, d, $J=2.0$ Hz), 4.25 (1H, d, $J=2.0$ Hz), 7.10—8.10 (9H, m, Ar). EI-MS m/z: 258 (M^+, 10), 105 (M^+-153, 100), 77 (M^+-147, 30).

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