Pergamon

Tetrahedron Letters 39 (1998) 8299–8302

TETRAHEDRON
LETTERS

Asymmetric Synthesis of α,β-Epoxysulfones Under Phase-Transfer Catalyzed Darzens Reaction

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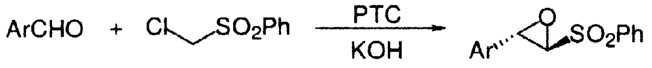
Received 6 August 1998; accepted 28 August 1998

Abstract: Enantioselective synthesis of α,β-epoxysulfones by the Darzens reaction was achieved under phase-transfer catalyzed conditions. The reaction of chloromethyl phenylsulfone with various aromatic aldehydes smoothly proceeded in the presence of a catalytic amount (10 mol %) of chiral quaternary ammonium salt derived from quinine with KOH at room temperature to afford the desired coupling products in good yield with up to 81% ee.

Keywords: Asymmetric reactions, Darzens reactions, Phase transfer, Sulfones

The Darzens reaction is one of the most potential methodologies for the construction of α,β-epoxy carbonyl and its related compounds. Since the reaction mechanism includes both the C-C and C-O bond forming processes which lead to the generation of stable salts as side products, the construction of an effective catalytic cycle for asymmetric synthesis has been recognized to be a major challenge in these decades. Recently, we have succeeded in the establishment of an efficient catalytic cycle for the asymmetric Darzens reaction utilizing α-chloroketone with both an inorganic base and a catalytic amount of a chiral quaternary ammonium salt derived from an easily available chiral amine such as cinchonine to afford the desired α,β-epoxy ketones as the optically active form.[1] Quaternary salts seem to act as an effective phase-transfer catalyst (PTC) in this reaction system. According to this methodology, other types of carbon nucleophiles such as chloromethylsulfone, which can be transformed to the corresponding carbanion and not the enolate anion in basic media, would react with electrophiles more effectively to give the Darzens product with higher enantioselectivities due to the closer distance between the reactive carbon atom and the chiral quaternary ammonium cation in carbanion species. In this communication, we report the first example of catalytic asymmetric synthesis of α,β-epoxysulfones via the Darzens reaction under PTC conditions (Scheme 1).[2]



Scheme 1

Optically active α,β-epoxysulfones are useful chiral building blocks for the synthesis of natural products.[3a] Mori and co-workers have revealed its utility as effective carbon nucleophiles for the

PII: S0040-4039(98)01811-5

stereoselective synthesis of complex molecules.[3b,c] We began investigations of the catalytic asymmetric Darzens reaction using commercially available chloromethyl phenylsulfone **2** with various aromatic aldehydes in the presence of both an inorganic base such as KOH[4] and a catalytic amount of quaternary salts which are easily prepared from quinine.[5] Initially, we attempted to investigate the effect of solvent and PTC in this reaction system. Although the reaction smoothly proceeded to afford the desired product in any solvent, the use of diethyl ether and dichloromethane gave **3a** with 30 and 46% ee, respectively. On the other hand, in the case of utilizing toluene as the solvent with benzaldehyde **1a** and **2** as the substrates in the presence of 10 mol % of PTC **A** at room temperature, the desired *trans*-epoxide **3a** was obtained as the sole product in high yield with 69% ee with preference for the ($\alpha S,\beta S$)-isomer (entry 3).[6]

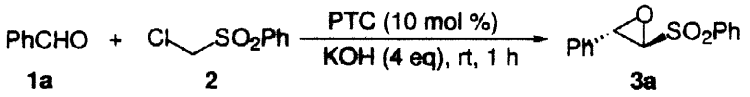
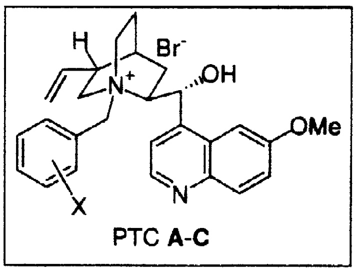


Table 1

entry	solvent	PTC	yield of **3a** (%)	ee of **3a** (%)[a]
1	Et_2O	**A**: X = 4-CF_3	45	30
2	CH_2Cl_2	**A**: X = 4-CF_3	57	46
3	toluene	**A**: X = 4-CF_3	85	**69**[b]
4	toluene	**B**: X = 2,4-$(CF_3)_2$	41	7
5	toluene	**C**: X = 3,5-$(CF_3)_2$	47	32

a) Ee was determined by HPLC analysis using DAICEL CHIRALCEL OD (hexane:*i*-PrOH = 9:1, flow rate = 1.0 ml/min, 13.9 (minor) and 18.9 min (major)). b) $[\alpha]_D^{20}$ -36.0 (*c* 1.0, CH_2Cl_2)



PTC **A-C**

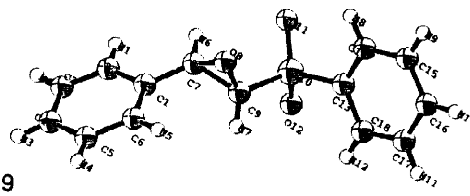


Figure 1

In the case of using other types of quaternary salts including disubstituted benzyl moieties such as PTC **B** or **C**, the desired epoxide was obtained with a lower ee in toluene under similar reaction conditions (entries 4 and 5, respectively). These results are summarized in Table 1. The absolute configuration of **3a** was determined by X-ray crystallographical analysis. The ORTEP diagram shown in Figure 1 was measured using **3a** obtained by use of a catalytic amount of PTC derived from quinidine (pseudo enantiomer to quinine) under similar reaction conditions followed by recrystallization from hexane-AcOEt (96% ee).[7] The results described above indicate that the 4-substituted derivative is quite effective in this asymmetric induction. Although the role of the trifluoromethyl group at the 4-position of the phenyl ring on PTC is not clear at present, it seems to be dependent on the steric effect rather than the electronic one in this asymmetric induction in comparison with the results using other types of PTCs. PTCs that contain electron donating or withdrawing substituents at the 4-position gave **3a** with a slightly lower ee.[8] Also the PTCs, which possess the *o*- or *m*-substituted benzyl moiety, were quite ineffective to afford the product with low ee. Encouraged by these results, we investigated other substituted aromatic aldehydes in this reaction system under the optimized reaction conditions described above (10 mol % of PTC **A**, KOH, toluene, rt). The reaction smoothly proceeded to afford the corresponding α,β-epoxysulfones with good enantioselectivities. Especially, the 4-methyl and 4-*t*-butylbenzaldehydes gave the Darzens products, **3d** and **3e**, in good yield with 78 and 81% ee, respectively.[9] Since the reaction will analogously proceed to form **3a**, the absolute configuration of the predominant isomers were tentatively assigned to be *αS*,*βS*. These results are summarized in Table 2. Although the substituent effects on the above-described PTCs in asymmetric induction are unclear, this procedure will offer a practical methodology for the preparation of optically active α,β-epoxysulfones due to its safe and operational simplicity together with quite mild reaction conditions. In the case of using chiral metal reagents for the asymmetric Darzens reactions, a stoichiometric amount of chiral source is required to obtain the desired product with reasonable yield because of the impossible regeneration of the chiral base catalysts due to the inevitable formation of a stable, insoluble and less reactive metal halide.

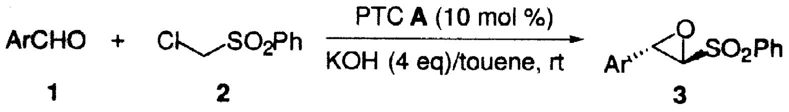


Table 2

entry	aldehyde **1**	time (h)	yield of **3** (%)	ee of **3** (%)[a]	$[\alpha]_D^{20}$
1	**1b** : Ar = 4-Br-C_6H_4	1	**3b** : 80	64	-16.9
2	**1c** : Ar = 3-Br-C_6H_4	1.5	**3c** : 69	71	-24.2
3	**1d** : Ar = 4-Me-C_6H_4	2	**3d** : 84	**78**	-29.6
4	**1e** : Ar = 4-*t*-Bu-C_6H_4	2	**3e** : 70	**81**	-32.4
5	**1f** : Ar = 4-Ph-C_6H_4	1.5	**3f** : 71	72	-8.5
6	**1g** : Ar = 3-PhO-C_6H_4	1.5	**3g** : 83	65	-27.7
7	**1h** : Ar = 3-Me-C_6H_4	1	**3h** : 82	74	-43.1
8	**1g** : Ar = β-Naphthyl	1	**3i** : 94[b]	68	-13.7

a) Ee was determined by HPLC analysis. b) 2.4 eq of **1g** was used.

In conclusion, we have realized the facile and effective asymmetric Darzens reaction promoted by the easily prepared chiral PTC under mild reaction conditions. These results will propose a useful methodology for the synthesis of α,β-epoxysulfones as the optically active form, and the results will lead to further progress.

Acknowledgments: One of the authors (S. A.) is grateful to 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 Ohara Award in Synthetic Organic Chemistry, Japan.

References and Notes

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2. Recently, the chiral crown ether catalyzed asymmetric Darzens condensation was reported, see (a) Bako, P.; Szollosy, A.; Bombicz, P.; Toke, L. *Synlett*, **1997**, 291-292. Other examples of asymmetric Darzens condensation using stoichiometric amount of chiral source are reported, see (b) Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *J. Chem. Soc. Chem. Commun.* **1996**, 2411-2412. (c) Takahashi, T.; Muraoka, M.; Capo, M.; Koga, K. *Chem. Pharm. Bull.* **1995**, *43*, 1821-1823. Other examples of the catalytic asymmetric Darzens condensation using chloromethyl phenylsulfone and its

derivatives with quaternary salts as PTC derived from ephedrine have been reported, see (d) Colonna, S.; Fornasier, R.; Pfeiffer, U. *J. Chem. Soc. Perkin I* **1978**, 8-11.

3. Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557-4558. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158-8159. (c) Mori, Y.; Yaegashi, K.; Iwase, K.; Yamamori, Y.; Furukawa, H. *Tetrahedron Lett.* **1996**, *37*, 2605-2608.
4. KOH gave the best results on enantioselectivities in comparison with the other metal hydroxides.
5. PTC **A** was easily prepared with quinine and 4-trifluoromethylbenzyl bromide under reflux conditions in THF followed by recrystallization from hexane-MeOH, mp 185-187℃, $[\alpha]_D^{24}$ -153.3° (*c* 0.18, MeOH). Other quaternary salts were synthethized using the corresponding benzyl bromides under similar reaction conditions.
6. Benzene gave results similar to toluene.
7. Use of a catalytic amount of *N*-(4-trifluoromethybenzyl)quinidinium bromide (10 mol %) or commercially available *N*-(4-trifluoromethylbenzyl)cinchoninium bromide gave **3a** with 49 and 27% ee in ($\alpha R,\beta R$)-configuration under similar reaction conditions, respectively. The absolute configuration was determined by X-ray crystallographical analysis by use of anomalous dispersion of the sulfer atom.
8. Other types of 4-substituted PTCs derived from quinine gave **3a** with the following results under similar reaction conditions: 4-OMe (58% yield, 51% ee), 4-NO_2 (31% yield, 56% ee), 4-H (68% yield, 54% ee), 4-Me (76% yield, 53% ee), 4-*t*-Bu (81% yield, 66% ee), and 4-halogenated PTCs (59-80% yield, 60-67% ee).
9. A typical procedure for the asymmetric Darzens reaction is as follows: To a solution of 4-*tert*-butylbenzaldehyde **1e** (0.1 mL, 0.6 mmol), chloromethyl phenylsulfone **2** (95 mg, 0.5 mmol) and PTC **A** (28 mg, 0.05 mmol) in toluene (3.0 mL) was added a portion of KOH (113 mg, 2.0 mmol) at room temperature. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with 1*N* HCl (3.0 mL), and the mixture was extracted with ethyl acetate (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:AcOEt = 10:1) gave **3e** as a colorless solid (111.0 mg, 70%, 81% ee): mp: 93-94℃; $[\alpha]_D^{20}$ -32.4° (*c* 1.0, CH_2Cl_2); Ee was determined by HPLC analysis: DAICEL CHIRALCEL OD, hexane:*i*-PrOH = 9:1, flow rate: 1.0 mL/min, retention time: 10.0 min (minor) and 10.9 min (major). ^1H NMR ($CDCl_3$, 270 MHz) δ: 1.30 (s, 9H), 4.18 (d, *J* = 1.7 Hz, 1H), 4.57 (d, *J* = 1.7 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.56-7.68 (m, 2H), 7.70-7.77 (m, 1H), 7.99 (dd, *J* = 7.3, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 31.1, 34.6, 57.3, 70.8, 125.6, 125.8, 128.7, 129.3, 129.5, 134.4, 136.8, 152.7; IR (nujol): 1325, 1154 cm^{-1}; MS *m/z*: 316 (M^+), 301 (M^+-Me), 287 (M^++1-Me_2), 177 (base peak); Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.33; H, 6.37; Found C, 68.18; H, 6.34.