The Highly *trans*-Selective Darzens Reaction via Ammonium Ylides

Tetsutaro Kimachi,* Hiroyo Kinoshita, Kumiko Kusaka, Yukiko Takeuchi, Mai Aoe, Motoharu Ju-ichi

Faculty of Pharmaceutical Sciences, Mukogawa Women's University, 9-11-68, Koshien, Nishinomiya 663-8179, Hyogo, Japan
Fax +81(798)412792; E-mail: tkimachi@mwu.mukogawa-u.ac.jp

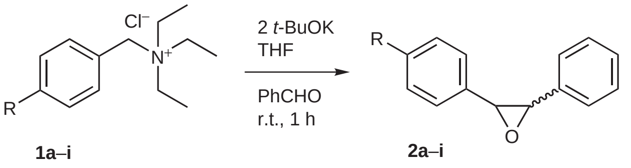
Received 16 November 2004

Abstract: The Darzens reaction using electron deficient *p*-substituted benzyltriethylammonium chlorides with aromatic aldehydes afforded 2,3-diaryl epoxides with *trans* selectivity (>99%) while the corresponding reaction with electron releasing *p*-substituted benzyltriethylammonium salts gave the epoxides as diastereomeric mixtures. Epoxide formation of *p*-trifluoromethylbenzylammonium salt, prepared from *p*-trifluoromethylbenzyl chloride and DABCO, afforded the corresponding 2,3-diaryl epoxide in high yield (>98%).

Key words: Darzens reaction, ammonium ylides, 2,3-diaryl epoxides

Recent progress on asymmetric Darzens glycidic ester formation catalyzed by phase-transfer catalysts[1] or chiral sulfur ylides[2] includes the development of environmentally benign and mild conditions. A novel Darzens reaction via ammonium ylides was reported by Jonczyk et al.,[3] which, however, is unsatisfactory in chemical yield and stereoselectivity compared with that using phase-transfer catalysts or sulfur ylides. Encouraged by Jonczyk's report, we undertook to study the scope and limitations of Darzens reaction via ammonium ylides. Here we report the high *trans*-selective Darzens reaction of various substituted benzyl ammonium chlorides with aromatic aldehydes. Furthermore, we demonstrate successive formation of *trans*-2,3-diaryl epoxides without isolation of derived ammonium salts. The substituted benzylic quaternary ammonium salts (**1a**–**i**) were prepared from the corresponding benzylic chlorides by treatment with triethylamine under reflux conditions.[4,5] After a screening of suitable conditions, we found that epoxides were formed when *p*-substituted benzyltriethylammonium chlorides and benzaldehyde were treated with 2 equivalents of *t*-BuOK in THF under anhydrous conditions.[6] The results are summarized in Table 1. Remarkably, starting ammonium chlorides having electron-withdrawing group exclusively afforded *trans*-2,3-diaryl epoxides in moderate to good yields at room temperature (Table 1, entries 4–9). On the other hand, using electron-rich substrates (entries 1–3) resulted low to moderate epoxide formation with poor diastereoselectivity (Table 1, entries 1–3). The *trans*-selectivity in the reaction of ammonium ylides and aldehydes appears to proceed via formation of the *anti*- or *syn*-betaine intermediates same as that of sulfonium ylides and aldehydes.[2] In the addition of benzylsulfonium ylides to aldehydes, *trans*-epoxides are derived from formation of the *anti*-betaine intermediates and *cis*-epoxides are derived from formation of the *syn*-betaine intermediates. Our results suggest that aromatic bearing electron-withdrawing groups stabilizes an *anti*-betaine or promotes formation of an *anti*-betaine which then leads to a *trans*-epoxide.

Table 1 Diastereoselective Synthesis of 2,3-Diaryl Epoxides from *p*-Substituted Benzyltriethylammonium Chlorides and Benzaldehyde



Entry	Substrate (*R*)	Product	Yield (%)	dr (*cis*:*trans*)[b]
1	**1a** (-CH_3)	**2a**	67	57:43
2	**1b** (-OCH_3)	**2b**	18	67:33
3	**1c** (-H)	**2c**	26	23:73
4	**1d (-$CONEt_2$)**	**2d**	**89**	**<1:>99**
5	**1e** (-CO_2*t*-Bu)	**2e**	70	<1:>99
6	**1f** (-CO_2Et)	**2f**	68	<1:>99
7	**1g** (-CN)	**2g**	54	<1:>99
8	**1h (-CF_3)**	**2h**	**96**	**<1:>99**
9[a]	**1i** (-NO_2)	**2i**	30	<1:>99

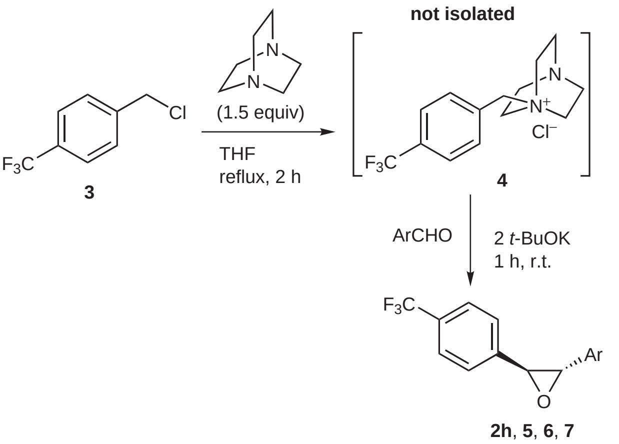
[a] 50% aq NaOH was used as a base. The reaction mixture was continuously stirred for 18 h.
[b] *trans*-Configuration was confirmed by X-ray analysis.

The reaction between a *p*-substituted benzylchloride and benzaldehyde under the same conditions resulted in recovery of starting materials (Table 3, entry 1). Advantages in using ammonium salts are easy formation of the reactive ammonium ylides and recovery of the reusable tertiary amines after completion of the reaction. However, it is not practical to use triethylammoium salts as a leaving group because of the ready volatility of triethylamine, causing poor recovery in the work up procedure. We found DABCO (diazabicyclo[2,2,2]-octane) to be a suitable amine candidate to improve the recovery of tertiary amine. DABCO, which is more nucleophilic than triethylamine, led to the rapid formation of the corresponding ammonium salt in reaction with *p*-trifluoromethylbenzyl chloride (**3**) in acetone. Using isolable ammonium salts **4**,

SYNLETT 2005, No. 5, pp 0842–0844
Advanced online publication: 09.03.2005
DOI: 10.1055/s-2005-864799; Art ID: U30904ST

reaction with benzaldehyde afforded epoxide with 91% *trans*-selectivity. DABCO was recovered in >90% as described in the typical experimental section. Furthermore, the ammonium salt prepared from DABCO and *p*-trifluoromethylbenzyl chloride (**3**) in THF, upon in situ treatment with *t*-BuOK (2 equiv) and benzaldehyde, afforded the corresponding epoxide (**2h**) quantitatively. Hence, no isolation and purification of prepared ammonium salt is required.[7] Formation of epoxides using other aryl aldehydes was carried out and the results are summarized in Table 2.[8] In order to investigate the nature of the counter anion, chloride was replaced by Br^-, I^-, and NO_3^-. Thus, using the corresponding benzylic ammonium bromide, benzylic ammonium iodide, and benzylic ammonium nitrate afforded the 2,3-diaryl epoxides (in 77%, 31%, 81%, respectively) with *trans*-selectivity.

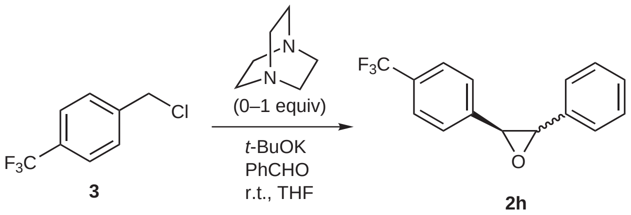
Table 2 One-Pot and Successive Preparation of *trans*-2,3-Diaryl Epoxides



Ar	Product	Yield (%)	dr (*cis*:*trans*)
C_6H_5-	**2h**	quant.	<1:>99
4-$CH_3OC_6H_4$-	**5**	83	<1:>99
4-ClC_6H_4-	**6**	81	<1:>99
4-NCC_6H_4-	**7**	55	5:95

p-Trifluoromethylbenzyl chloride (**3**) undergoes reaction with DABCO to slowly form the corresponding ammonium salt even at room temperature. This encouraged us to study catalytic potency of DABCO in one-pot procedure. Various amounts of DABCO [0, 0.01, 0.1, 1 equivalent to *p*-trifluoromethylbenzyl chloride (**3**)] and **3**, benzaldehyde and *t*-BuOK were mixed at once and the mixture was stirred for the appropriate times described in Table 3. As illustrated in Table 3, the presence of DABCO was necessary for the formation of epoxides, but observed diastereoselectivity was quite low (entries 1–4). In order to investigate the role of catalytic amount of DABCO, we attempted the reactions of *p*-trifluoromethylbenzyl chloride (**3**) and benzaldehyde with or without catalytic amount of DABCO, and together with catalytic amount of quaternary ammonium salt (**4**) prepared from **3** and DABCO. In these events, 2,3-diaryl epoxide (**2h**) was obtained in 43%, 67%, respectively, as *cis* and *trans* mixture (*cis*:*trans* = 43:57). These results suggest that one-pot catalytic epoxide formation shown in Table 3 proceeds not only via ammonium salt which can form *anti*-betaine intermediate to preferentially afford *trans*-epoxide, but also via another pathway to afford *cis*- and *trans*-epoxide mixture as a result. One of the probable pathways other than that via ammonium salt consists of a route via chlorohydrin intermediate directly formed from benzylic chloride and benzaldehyde, catalyzed by DABCO itself or ammonium salt (**4**).[9]

Table 3 Catalytic Potency of DABCO in One-Pot Preparation of **2h**



Entry	DABCO (equiv)	Yield (%)	dr (*cis*:*trans*)	Time (h)
1	0	0	–	16
2	0.01	35	43:57	16
3	0.1	45	50:50	4
4	1	48	40:60	1

In conclusion, we have achieved a highly *trans*-selective Darzens reaction of electron deficient *p*-substituted benzylammonium chlorides with aromatic aldehydes to give 2,3-diaryl epoxides. *p*-Trifluoromethylbenzylammonium salt of DABCO not only provide the corresponding *trans*-2,3-diaryl epoxide in high yield but also allowed recovery of DABCO in 90% by extraction. Studies on the enantioselective version of this *trans*-selective Darzens reaction using optically active tertiary amines (e.g. chiral diazabicyclo[2,2,2]octane derivatives or chiral quinuclidine derivatives) and the development of the environmentally benign synthesis using resin-supported tertiary amines are in progress.

Acknowledgment

We thank Professor Yoshiji Takemoto (Graduate School of Pharmaceutical Sciences, Kyoto University, Japan) for informative discussion and advice. We also thank Professor Toshihiro Hashimoto (Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima, Japan) for the X-ray crystal structure analysis of epoxide **2d**.

References

(1) (a) Arai, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2145. (b) Arai, S.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1407; and references cited therein.

(2) (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (b) Aggarwal, V. K.; Calamai, S.; Ford, J. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 593. (c) Aggarwal, V. K.; Ford, J. G.; Fonquerna, S.; Adams, H.; Jones, R. V. H.; Fieldhouse, R. *J. Am. Chem. Soc.* **1998**, *120*, 8328. (d) Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731. (e) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611.

(3) Jonczyk, A.; Konarska, A. *Synlett* **1999**, 1085.

(4) **Typical Procedure for the Preparation of *p*-Substituted Benzyltriethylammonium Chlorides (1d).**
A mixture of 4-chloromethyl-*N*,*N*-diethylbenzamide (2.25 g, 10 mmol) and Et_3N (5.5 mL, 40 mmol) in acetone (5 mL) was heated under reflux for 16 h. Acetone was removed in vacuo and EtOAc was added. The formed colorless solid was filtered off to afford 4-diethylcarbamyl-benzyltriethylammonium chloride (**1d**, 2.27 g, 6.95 mmol) in 70% yield as white solid; mp 125–127 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (m, 3 H), 1.26 (m, 3 H), 1.48 (t, 9 H, $J = 7.3$ Hz), 3.44 (m, 2 H), 3.47 (q, 8 H, $J = 7.3$ Hz), 5.03 (s, 2 H), 7.45 (d, 2 H, $J = 8.4$ Hz), 7.7 (d, 2 H, $J = 8.1$ Hz). ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 8.5$, 12.9, 14.3, 39.4, 43.4, 53.2, 61.1, 127.3, 128.4, 133.0, 139.6, 170.0. IR ($CHCl_3$): $\nu_{max} = 2900$, 1615, 1565, 1510 cm^{-1}. HRMS (FAB^+): *m*/*z* calcd for $[C_{18}H_{31}N_2O]^+$: 291.2436; found: 291.2434. Anal. Calcd for $C_{18}H_{31}N_2OCl{\cdot}H_2O$: C, 62.7; H, 9.65; N, 8.12. Found: C, 62.55; H, 9.99; N, 8.12.

(5) Quaternary ammonium salts containing methyl groups are known to promote 2,3-Stevens-type rearrangement reaction under strong basic condition. See: Marko, I. E. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B., Ed.; Pergamon Press: Oxford England, **1991**, 913.

(6) **Typical Procedure.**
To an ice cooled stirred solution of 4-diethylcarbamyl benzyltriethylammonium chloride (**1d**, 326.8 mg, 1 mmol) and benzaldehyde (0.1 mL, 1 mmol) in THF (4 mL) was slowly added *t*-BuOK (224.4 mg, 2 mmol). Yellow colored suspension was stirred for 1 h at r.t. The mixture was diluted with $CHCl_3$ and sat. aq NH_4Cl. The mixture was separated and the aqueous layer was washed with H_2O, brine, and then dried over $MgSO_4$. Removal of the solvent and purification by flash chromatography (hexane–EtOAc = 1:1) afforded *N*,*N*-diethyl-4-(3-phenyloxiranyl)benzamide (**2d**, 264 mg, 89%) as a colorless solid; mp 83–85 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.20$ (m, 6 H), 3.30 (m, 2 H), 3.54 (m, 2 H), 3.86 (d, 1 H, $J = 1.83$ Hz), 3.88 (d, 1 H, $J = 1.83$ Hz), 7.32–7.41 (m, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 13.0$, 14.2, 39.3, 43.3, 62.4, 62.9, 125.6, 126.7, 128.5, 128.6, 136.9, 137.4, 138.2, 170.9. IR ($CHCl_3$): $\nu_{max} = 3000$, 1612, 1565, 1510 cm^{-1}. HRMS (EI^+): *m*/*z* calcd for $C_{19}H_{21}NO_2$: 295.1572; found: 295.1572. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74. Found: C, 77.13; H, 7.28; N, 4.71. DABCO dissolved in the aqueous layer as an ammonium ion was recovered when the aqueous layer was basified by KOH and extracted with CH_2Cl_2.

(7) Quinuclidine (the second N of DABCO is replaced by CH) was also tried as an amine candidate. The ammonium salt was formed but it was too moisture sensitive to be isolated. When one-pot and successive preparation of *trans*-2,3-diaryl epoxide was carried out using quinuclidine, **2h** was obtained in 89%. Thus, the role of the second N of DABCO is not clear to date.

(8) When carbonyl compounds such as aliphatic aldehydes and ketones, other than aryl aldehydes were used under the reaction condition, no epoxides were formed and carbonyl compounds were recovered.

(9) According to the literature method,[10] we have tried the reaction using benzylic chloride [e.g. (*p*-chloromethyl)benzonitrile, *p*-nitrobenzyl chloride] and benzaldehyde in the presence of phase-transfer catalyst. Corresponding epoxides were obtained in 88% and 70%, respectively, as diastereomeric mixtures.

(10) (a) Dilling, W. L.; Hickner, R. A.; Farber, H. A. *J. Org. Chem.* **1967**, *32*, 3489. (b) Taranko, L. B.; Perry, R. H. Jr. *J. Org. Chem.* **1969**, *34*, 226.