

## Efficient Synthesis of $\alpha,\beta$ -Epoxy Carbonyl Compounds in Acetonitrile: *Darzens* Condensation of Aromatic Aldehydes with Ethyl Chloroacetate

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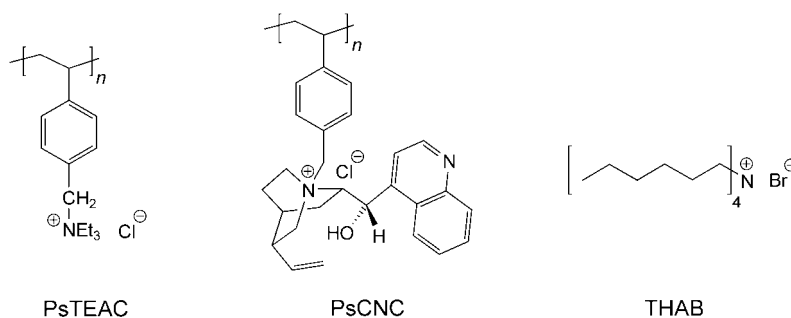
The *Darzens* reaction of ethyl 2-chloroacetate (**1**) with aromatic aldehydes **2** in the presence of polymer-supported or nonsupported quaternary ammonium salts proceeds under mild conditions by phase-transfer catalysis to give the corresponding epoxides **3** in satisfactory yields (Tables 1 and 2). With both MeCN as solvent and polystyrene-supported catalysts, diastereoselective *Darzens* reactions proceed in excellent yields and short times, with a fair degree of stereoinduction.

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**Introduction.** – The *Darzens* condensation plays an important role in catalytic asymmetric C–C bond-forming reactions [1], and is one of the most powerful methodologies for the synthesis of  $\alpha,\beta$ -epoxy carbonyl compounds and derivatives thereof [2–5]. Although dramatic progress has been achieved in the past two decades, the classical *Darzens* condensation is still performed in the presence of a strong base (RONa, ROK, NaNH<sub>2</sub>) in organic solvents (THF, toluene, CH<sub>2</sub>Cl<sub>2</sub>) under anhydrous conditions and at low temperatures (–78 to 0°) [6]. Alternative methods are laborious and costly, and are often not suitable for large-scale preparations.

The *Darzens* reactions of chloroketones and sulfones, promoted by phase-transfer catalysts, have been reported recently [7]. The use of a phase-transfer catalysis (PTC) [8] has many advantages with respect to economics, operational simplicity, and ecology. PTC can even promote diastereoselective *Darzens* reactions *via* a catalytic cycle [9]. Although recent advances have made this route more attractive, development of cheaper, simpler, and more-efficient and recyclable catalysts is highly desirable. One of the most important technical problems in industrial PTC applications with soluble phase-transfer catalysts, such as quaternary ammonium salts, is the need to separate the catalysts from the reaction mixture for subsequent reuse or disposal. Immobilization of the catalyst on a polymeric matrix can provide a simple solution to this problem [10]. Polymer-supported catalysts can be separated from the products easily and used repeatedly, and, thus, have been widely used in green chemistry [11].

The control of diastereo- and enantioselectivities in asymmetric *Darzens* reactions leading to  $\alpha,\beta$ -epoxy carbonyl compounds is still a challenging goal. In this paper, we report the *Darzens* condensation between ethyl chloroacetate (**1**) and aromatic aldehydes **2** for the synthesis of  $\alpha,\beta$ -epoxy carbonyl compounds, as catalyzed by PsTEAC (polystyrene–triethylammonium chloride), PsCNC (polystyrene–cinchonidin chloride), or THAB (tetrahexylammonium bromide).



**Results and Discussion.** – First, we investigated the *Darzens* reaction of ethyl chloroacetate (**1**) with benzaldehyde (**2a**), catalyzed by PsTEAC, in a mixture of THF and powdered KOH. The results are summarized in *Table 1*. As expected, the desired epoxide **3a** was obtained in good yield (82%; *Entry 2*). The same product was obtained in much lower yield (10%) in the absence of phase-transfer catalyst. In the catalyzed reaction, we found that *cis*-**2a** was dominating (*cis/trans* 6.5 : 1). However, the filtration and reuse of PsTEAC was difficult since the reaction mixture became a gum in THF. To solve this problem, MeCN and toluene were tested as solvents. With toluene under PTC conditions, the workup was also difficult, and the yield of **2a** was low (54%; *cis/trans* 3.1 : 1). Surprisingly, the same transformation was greatly accelerated in MeCN, both with PsTEAC and PsCNC as catalysts, leading to **3a** in good yield (*Entries 5 and 6*). It is noteworthy that the diastereoselectivity in MeCN was reversed (*cis/trans* 1 : 1.6 for PsTEAC). To the best of our knowledge, this is the first report of a *Darzens* reaction in MeCN in which the *trans*-product dominates. Of course, the type of catalyst is very important for the control of the diastereo- and enantioselectivity. However, we noticed that the solvent also affects the outcome of this reaction, THF being comparable to MeCN in terms of yield, in contrast to Et<sub>2</sub>O, which gave poor selectivities and low yields (*Table 1*).

Next, we compared the results of the reaction between **1** and **2a** in MeCN/KOH in the presence of either polymer-supported catalysts (PsCNC or PsTEAC) *vs.* non-supported THAB. From the three quaternary ammonium salt catalysts tested, THAB gave rise to the highest diastereoselectivity (*cis/trans* 1 : 6.7; *Entry 7* in *Table 1*) with only slightly lower yield (83% *vs.* 92% in case of PsCNC; *Entry 5*). These results indicate that both the catalyst and the solvent play important roles in determining the stereochemical course of the *Darzens* condensation.

Initially, we were worried that MeCN would react with benzaldehyde under the basic condition used in the above *Darzens* condensation. Fortunately, GC, <sup>13</sup>C-NMR, and <sup>1</sup>H-NMR experiments showed that this was not the case.

Encouraged by these results, a series of aromatic substrates (**2b–i**) with either electron-withdrawing or -releasing substituents were examined in the reaction with **1** to afford **3b–i** (*Table 2*). Again, a catalytic amount (10 mol-%) of either polymer-supported (PsTEAC, PsCNC) or non-supported (THAB) phase-transfer catalyst was used in MeCN/KOH at room temperature. In this reaction, aromatic aldehydes with electron-donating groups (Me, Br, Cl, *etc.*) tended to afford higher yields compared to

Table 1. Solvent Effects in the Phase-Transfer-Catalyzed Darzens Reaction of Ethyl Chloroacetate (**1**) with Benzaldehyde (**2a**) Leading to **3a**

$\text{C}_6\text{H}_5\text{CHO} + \text{ClCH}_2\text{CO}_2\text{Et} \xrightarrow[\text{Solvent, KOH, r.t.}]{\text{Cat. (0.1 equiv.)}} \text{C}_6\text{H}_5\text{CH}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$

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

Entry	Solvent	Catalyst	Time [h]	Isolated yield [%]	cis/trans <sup>a)</sup>
1	THF	PsCNC	23	63	3.6 : 1
2	THF	PsTEAC	23	82	6.5 : 1
3	THF	THAB	24	78	3.4 : 1
4	Et <sub>2</sub> O	PsCNC	22	34	1.4 : 1
5	MeCN	PsCNC	6.5	92	1 : 1.3
6	MeCN	PsTEAC	11	81	1 : 1.6
7	MeCN	THAB	10.5	83	1 : 6.7

<sup>a)</sup> Determined by <sup>1</sup>H-NMR and GC.

substrates with electron-withdrawing or sterically more-demanding groups (NO<sub>2</sub>, MeO). Notably, some transformations proceeded with fairly high diastereoselectivities (e.g., Entries 6 and 10 in Table 2).

Table 2. Substrate and Catalyst Effects in the Phase-Transfer-Catalyzed Darzens Reaction of **1** with Aromatic Aldehydes **2**

$\text{R-C}_6\text{H}_4\text{CHO} + \text{ClCH}_2\text{CO}_2\text{Et} \xrightarrow[\text{MeCN, KOH, r.t.}]{\text{Cat. (0.1 equiv.)}} \text{R-C}_6\text{H}_4\text{CH}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$

**2b – i**                      **1**    **3b – i**

Entry	Aldehyde	R	Catalyst	Time [h]	Yield [%] <sup>a)</sup>	cis/trans
1	<b>2c</b>	4-Cl	THAB	16	89	1 : 2.5
2	<b>2i</b>	4-Me	THAB	10.5	71	1 : 4.4
3	<b>2c</b>	4-Cl	PsTEAC	18	85	1 : 2.8
4	<b>2i</b>	4-Me	PsTEAC	18	67	1 : 4.1
5	<b>2b</b>	4-Br	PsCNC	15.5	72	1 : 1.4
6	<b>2c</b>	4-Cl	PsCNC	15	86	1 : 12.7
7	<b>2d</b>	2-Cl	PsCNC	23	80	1 : 1.2
8	<b>2e</b>	2,6-Dichloro	PsCNC	33.5	26	1 : 1.6
9	<b>2f</b>	4-NO <sub>2</sub>	PsCNC	33	52	1 : 1.6
10	<b>2g</b>	4-MeO	PsCNC	25	27	1 : 10.2
11	<b>2h</b>	2-MeO	PsCNC	33.5	39	1 : 0.8
12	<b>2i</b>	4-Me	PsCNC	8	90	1 : 1.4

<sup>a)</sup> Isolated yields of **3b – i** after column chromatography.

We then tested whether the catalysts could be reused in the above type of transformation. When PsCNC was used three times for the reactions between **1** and **2a**, the yield of **3a** decreased slightly, but the diastereoisomer ratio remained constant.

In conclusion, we discovered that the readily available polymer-supported phase-transfer catalysts PsTEAC and PsCNC are effective for the clean and green *Darzens* synthesis of aromatic  $\alpha,\beta$ -epoxy carbonyl compounds under mild conditions; the same holds for THAB. We noticed for the first time that the diastereoselectivity of the reaction can be reversed by the choice of MeCN instead of THF as solvent. Further investigations, such as the detailed mechanisms of PTC in MeCN and the development of an enantioselective catalytic process, are now in progress.

### Experimental Part

*General.* All solvents and reagents were used without purification. Thin-layer chromatography (TLC) was performed on silica-gel  $F_{254}$  plates; visualization under UV light. Flash-column chromatography (FC) was performed over silica gel (100–200 mesh). IR Spectra were recorded on an FT-IR apparatus.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Spectra were recorded at 400 and 100 MHz, respectively, and were referenced to internal solvent signals;  $\delta$  in ppm,  $J$  in HZ. All compounds were fully characterized, including GC/MS (*Agilent 6890N MS/5973N MS, HP-5MS*).

*Preparation of PsTEAC and PsCNC.* To a flask containing chloromethyl resin (5.0 g; 200–400 mesh, loading: 3.5 mmol Cl/g) was added DMF (15 ml), and the resin was stirred for 2 h. Then,  $\text{NEt}_3$  (20 ml; for PsTEAC) or cinchonidine (20 mmol; for PsCNC) was added, and the mixture was heated at  $80^\circ$  for 24 h. The resin was filtered under reduced pressure, washed with anh. EtOH, stirred for 12 h at  $80^\circ$ , filtered, and dried in vacuum. The concentration of onium ions, which is the same as that of chloride ions, was determined by titration with  $\text{AgNO}_3$ .

*Typical Procedure of Polymer-Supported Phase-Transfer-Catalyzed Darzens Reaction.* To a soln. of, e.g., **2a** (318 mg, 3.0 mmol), benzaldehyde (**1**; 441 mg, 3.6 mmol) and PsCNC (300 mg, ca. 10 mol-%) were added in MeCN (9 ml). After stirring at r.t. for 5 min, solid KOH (200 mg, 3.6 mmol) was added, and the mixture was stirring for 5 h at r.t., during which KOH (100 mg, 1.8 mmol) was added twice. The reaction was quenched with  $\text{H}_2\text{O}$ , when **2a** was fully consumed (TLC). The mixture was extracted with AcOEt ( $3 \times 15$  ml), the catalyst was filtered off, the combined org. layer was washed with brine and AcOEt, and concentrated under reduced pressure. Purification by FC (petroleum ether/AcOEt 50:1) gave pure **3a** as a semicrystalline pale cloudy oil. Yield: 530 mg (92%; see Table 1).  $^1\text{H}$ -NMR (400 MHz;  $\text{CDCl}_3$ ): a) *trans*-isomer: 1.01 (t,  $J = 7.2$ , Me); 3.82 (d,  $J = 4.4$ , 1 H); 4.25 (d,  $J = 4.4$ , 1 H); 3.99 (t,  $J = 7.2$ ,  $\text{OCH}_2$ ); 7.28–7.42 (5 arom. H); b) *cis*-isomer: 1.32 (t,  $J = 7.2$ , Me); 3.50 (d,  $J = 1.6$ , 1 H); 4.09 (d,  $J = 1.6$ , 1 H); 4.28 (t,  $J = 7.2$ ,  $\text{OCH}_2$ ); 7.28–7.42 (5 arom. H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ): 13.9; 55.4; 56.4; 56.9; 57.5; 61.0; 125.7–132.8; 166.0.

This study was financially supported in part by the *Natural Science Foundation of China* (29933050 and 20373082).

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Received April 17, 2004