



Diastereoselective Darzens reactions of α -chloroesters, amides and nitriles with aromatic aldehydes under phase-transfer catalyzed conditions

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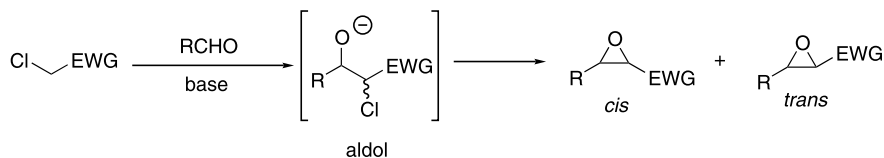
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Abstract—The development of the highly diastereoselective catalytic synthesis of glycidic acid derivatives via Darzens reaction is described. The reaction of α -chloroesters and amides with aromatic aldehydes smoothly proceeds in the presence of a quaternary ammonium salt as a phase-transfer catalyst to give the corresponding *cis* and *trans* desired products in satisfactory yields, respectively. © 2002 Elsevier Science Ltd. All rights reserved.

The use of phase-transfer catalysts (PTC) have many advantages with respect to economics, operational simplicity and environmental consciousness in modern organic synthesis so that PTC chemistry has been utilized in green chemistry.¹ In particular, Darzens reaction, which is promoted by using bases, has been widely recognized as one of the most potential methodologies to obtain α,β -epoxy carbonyl compounds (Scheme 1).² Their diastereo and enantio controls are still a challenging goal. We have already reported some examples of the asymmetric Darzens reaction utilizing chiral PTCs by use of α -chloroketones³ and a sulfone⁴ as the carbon nucleophiles with complete diastereo control. The observed diastereoselectivities in the products are strongly dependent on the kinetics of the corresponding aldol intermediates during the cyclization step and *trans* isomers are generally formed. On the other hand, few examples of the catalytic diastereoselective synthesis of α,β -epoxyesters via carbon–carbon⁵ and carbon–oxygen⁶ bond forming reactions are reported. In this communication, we wish to report the PTC-con-

trolled highly diastereoselective synthesis of glycidic acid derivatives (EWG = CO₂R, CN and CONPh₂).

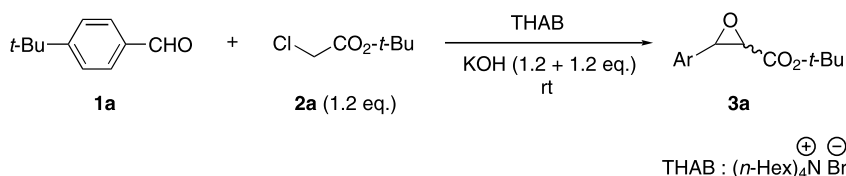
Initially, the solvent effect was examined using 4-*tert*-butylbenzaldehyde (**1a**) and *tert*-butyl chloroacetate (**2a**) in the presence of KOH and 10 mol% of tetrahexylammonium bromide (THAB) as the PTC,^{7,8} as shown in Table 1. First of all, toluene was used under PTC conditions. Initial survey of reaction conditions in toluene using 1.2 equiv. of KOH revealed that the reaction became slow after 5 h and addition of more 1.2 equiv. of KOH after 5 h not only accelerated the reaction but also increased the chemical yields.⁹ Thus, the reaction was conducted through the twice addition of KOH. As expected, the desired product **3a** was formed in good yield and fortunately, **3a** was obtained in a much lower yield in the absence of the PTC (entry 1 versus 2). The diastereoselectivity of entry 1 was found to be 3.9:1. When the chloroester **2a** was used in large excess from the initial stage of the reaction, the diastereoselectivity of **3a** greatly decreased because the



Scheme 1.

Keywords: Darzens reactions; diastereoselection; epoxides; phase-transfer.

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Table 1. Solvent effect

Entry	Solvent	THAB (mol %)	Time (h)	3a (%)	<i>cis:trans</i>
1	Toluene	10	19	77	3.9:1
2	Toluene	None	19	4	1.3:1
3	CH ₂ Cl ₂	10	19	70	3.1:1
4	Et ₂ O	10	19	77	9.7:1
5	THF	10	25	61	<i>cis</i> only
6	THF	None	21	46	1.2:1
7	THF	10	18	82 ^a	3.4:1
8	BTF ^b	10	19	86	3.5:1

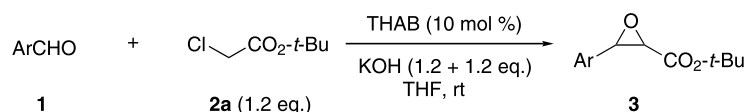
^a Excess amount of **2** (2.4 equiv.) was used.

^b Benzotrifluoride.

potassium enolate, probably a mixture of *cis*- and *trans*-isomers, may be produced in large amount and the reaction may proceed without PTC. Each isomer was easily separated by flash column chromatography and their stereochemistry was determined by ¹H NMR analysis to be *cis* as the major product. Dichloromethane was found not to be effective because of the lower de (entry 3). Fortunately, diethyl ether gave a better diastereoselectivity in good yield (entry 4). We were pleased to find that THF was quite effective for exclusively producing the *cis* isomer in satisfactory chemical yield. Surprisingly, the *trans* isomer was also formed in an almost equal ratio in the absence of PTC (entry 5 versus 6) in THF.¹⁰ This result is the obvious evidence that PTC plays a very important role in determining the diastereomeric ratio of the product in the PTC-catalyzed Darzens reaction. Using an excess of **2** resulted in a lower diastereomeric ratio, as shown in entry 7. Weaker bases such as LiOH or K₂CO₃ were not strong enough to abstract the α proton of **2** and little or no reaction proceeded. Encouraged by these results, other substrates were examined under similar reaction conditions for further investigation.¹¹

As shown in Table 2, the combination of a catalytic amount of THAB and KOH in THF at room temperature was investigated in other aromatic aldehydes. As expected, these conditions were quite sufficient to give the desired Darzens adduct **3** as the sole product with complete *cis*-diastereoselectivity. For example, 2-substituted aldehydes such as **1b** and **1c** gave the corresponding Darzens adducts in 54 and 43% yield, respectively (entries 1 and 2). Aldehydes **1d** and **1e** also gave similar results to **1a** (entries 3 and 4). Electron withdrawing groups such as CF₃ and NO₂ were also found to be applied to this system, though the chemical yields were reduced (entries 5 and 6). Although other aliphatic aldehydes were examined, the reaction did not smoothly proceed due to decomposition of the aldehydes under strong basic conditions.

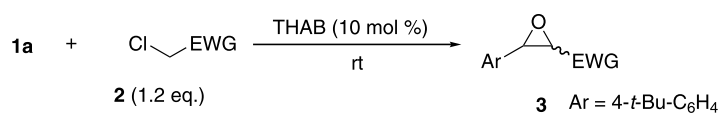
Finally, we attempted to use a various carbon nucleophiles for the investigation of the broad generality. In the case of the aryl ester **2b**, weaker base should be used to avoid its decomposition and the reaction smoothly proceeded to give **3b** in 87% yield using benzotrifluoride as a solvent and Rb₂CO₃ as a base in which no product

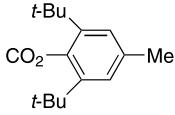
Table 2.

Entry	Aldehyde	Time (h)	3 (%) ^a
1	1b : α-Naphthyl	25	3b : 54
2	1c : 2-Cl-C ₆ H ₄	23	3c : 43
3	1d : Ph	22	3d : 52
4	1e : 4-Me-C ₆ H ₄	24	3e : 59
5	1f : 4-CF ₃ -C ₆ H ₄	23	3f : 36
6	1g : 4-NO ₂ -C ₆ H ₄	27	3g : 31

^a Only *cis*-isomer was formed.

Table 3.



Entry	2	Conditions ^a	3 (%)	cis:trans
1	2b: EWG = 	Rb ₂ CO ₃ , BTF, 34 h	3b: 54	1:3
2	2c: EWG = CN	KOH, THF, 27 h	3c: 86	0.8:1
3	2c: EWG = CN	KOH, Et ₂ O, 29 h	3c: 21	40:1
4	2d: EWG = CONPh ₂	KOH, THF, 31 h	3d: 40	30:1
5	2d: EWG = CONPh ₂	LiOH, THF, 25 h	3d: 91	trans only

^a Excess amount of base (2.4 equiv.) was used in all entries.

was produced in the absence of PTC, though its diastereoselectivity was found to be lower than **2a**. On the other hand, nitrile **2c** gave the satisfactory diastereoselectivity to produce **3c** in a ratio of 40:1 when the reaction was carried out in diethyl ether instead of THF though the yield decreased (entry 2 versus 3). The Darzens reaction of the *N,N*-diarylamide **2d** using KOH gave the epoxy-amide **3d** with good *cis* selectivity though in low yield (entry 4). Surprisingly, however, the use of milder base (LiOH) afforded **3d** in good yield with complete stereocontrol, as shown in Table 3.

In summary, we have realized that commercially available THAB acts as quite an effective PTC under mild reaction conditions to achieve high diastereoselectivities in the Darzens reaction using *tert*-butyl chloroacetate, chloroacetonitrile and *N,N*-diphenylacetamide with aromatic aldehydes. Further investigations will lead more satisfactory results, and the application of new chiral PTCs is under development.

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- Trials to use other commercially available quaternary ammonium salts such as (*n*-Bu)₄NBr, BnNEt₃Br and CetNMe₃Br gave no better results than THAB.
- In the case of the initial addition of 2.4 equiv. of KOH, the reaction was slow to afford **3a** in 61% (*cis:trans* = 3:1) even after 32 h.
- A successful result for the synthesis of chiral *trans*-glycidic esters with a stoichiometric amount of base via Darzens reaction was reported, see: (a) Takahashi, T.; Muraoka, M.; Capo, M.; Koga, K. *Chem. Pharm. Bull.* **1995**, *43*, 1821–1823. Moderate de in the stoichiometric asymmetric Darzens reaction was achieved, see: (b) Takagi, R.; Kimura, J.; Shinohara, Y.; Ohba, Y.; Takezono, K.; Hiraga, Y.; Kojima, S.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 689–698 and references cited therein. See also Ref. 6b.
- Typical procedure of PTC-catalyzed Darzens reaction, synthesis of **3a**: To a solution of **1a** (0.5 mL, 3.0 mmol), **2a** (0.52 mL, 3.6 mmol), and THAB (130 mg, 0.3 mmol) in THF (9.0 mL) was added KOH (200 mg, 3.6 mmol) in one portion at room temperature. After the mixture was

stirred for 5.5 h, additional KOH (200 mg, 3.6 mmol) was added to the reaction mixture. After stirring for 19.5 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate (15 mL×3). The combined organic layer was washed with brine and solvent, and concentrated under reduced pressure. Purification by flash column chromatography (hexane:AcOEt=50:1) exclusively gave **3a** as a pale yellow oil (508 mg, 61%). ¹H NMR

(CDCl₃, 270 MHz) δ : 1.16 (s, 9H), 1.29 (s, 9H), 3.69 (d, $J=4.6$ Hz, 1H), 4.21 (d, $J=4.6$ Hz, 1H), 7.34 (s, 4H); ¹³C NMR (CDCl₃, 67.8 MHz) δ : 27.5 (CH₃×3), 31.3 (CH₃×3), 34.5 (4°), 55.9 (CH), 56.9 (CH), 82.2 (4°), 124.7 (CH×2), 126.4 (CH×2), 130.2 (4°), 151.3 (4°), 166.0 (4°); IR (neat) ν_{max} : 2967, 1752, 1368, 1159 cm⁻¹; MS m/z : 220 (M⁺-Me₃CH), 163 (base peak), 57. Anal. calcd for C₁₇H₂₄O₃: C, 73.88; H, 8.75. Found: C, 73.84; H, 8.83.