ENANTIOSELECTIVE DARZENS REACTION : ASYMMETRIC SYNTHESIS OF *trans*-GLYCIDIC ESTERS MEDIATED BY CHIRAL LITHIUM AMIDES

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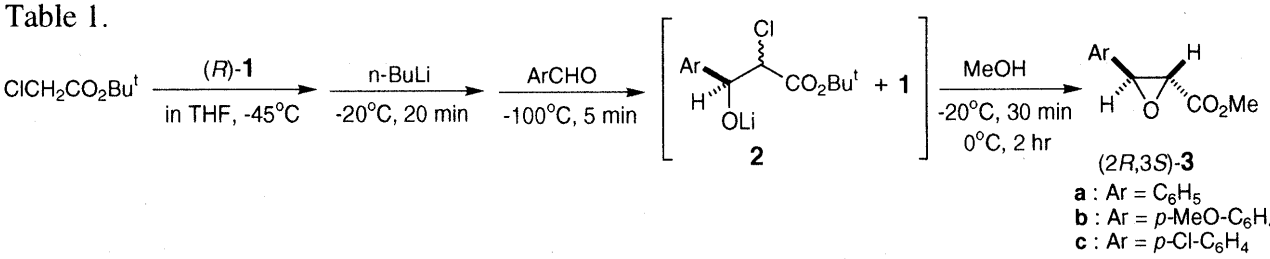
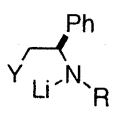
Enantioselective and diastereoselective Darzens reaction mediated by chiral lithium amides was achieved between *tert*-butyl chloroacetate and aromatic aldehydes to give the corresponding *trans*-glycidic esters in up to 84% enantiomeric excess.

KEY WORDS enantioselective reaction; diastereoselective reaction; asymmetric Darzens reaction; chiral lithium amide; *trans*-glycidic ester

The Darzens reaction[1] involves condensation of an aldehyde or ketone with an α-halo ester in the presence of a base to afford a glycidic ester (α,β-epoxy ester). Since chiral glycidic esters can serve as chiral building blocks in organic synthesis, various methods[2] involving Darzens reaction[1,3] have been developed to obtain them in optically active forms.

We previously reported enantioselective aldol reaction between some methylketones and aldehydes mediated by chiral lithium amides.[4] We intended to apply this reaction condition to enantioselective Darzens reaction between *tert*-butyl chloroacetate and aromatic aldehydes by using chiral lithium amides ((*R*)-**1**), because the initial step of the reaction should be the formation of the corresponding aldol-type intermedites (**2**) as shown below, which then undergo intramolecular ring closure to form the glycidic esters (**3**). Some results under optimized conditions are summarized in Table 1.





(*R*)-**1**

	Y	R
a	N-Me	$CHMe_2$
b		$CHMe_2$
c		CH_2Me
d		$(CH_2)_6Me$
e		$CH_2CH_2CHMe_2$
f		CH_2CH_2-H
g		CH_2CH_2OMe
h		$(CH_2)_5OMe$
i		$CH_2CH_2OCH_2CH_2OMe$
j		$CH_2CH_2OCH_2CH_2NMe_2$
k		$CH_2CH_2N(Me)CH_2CH_2NMe_2$
l		$CH_2CH_2N(Me)CH_2CH_2OMe$

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Table 1. Enantioselective Darzens Reaction[a)]

Entry	(*R*)-**1**	Ar-CHO (Ar)	Product (2*R*,3*S*)-**3**	Chem. y. (%)	E. e. (%)
1	**1a**	C_6H_5	**3a**	77	67
2	**1b**	C_6H_5	**3a**	74	79
3	**1c**	C_6H_5	**3a**	74	76
4	**1d**	C_6H_5	**3a**	78	77
5	**1e**	C_6H_5	**3a**	76	81
6	**1f**	C_6H_5	**3a**	73	80
7	**1g**	C_6H_5	**3a**	62	58
8	**1h**	C_6H_5	**3a**	54	78
9	**1i**	C_6H_5	**3a**	75	76
10	**1j**	C_6H_5	**3a**	75	72
11	**1k**	C_6H_5	**3a**	69	80
12	**1l**	C_6H_5	**3a**	62	84
13	**1e**	*p*-MeO-C_6H_4	**3b**	53[b)]	80
14	**1e**	*p*-Cl-C_6H_4	**3c**	69	72

a) For procedure, see text. b) The corresponding diol was isolated in 15% yield.

A typical experimental procedure (Table 1, entry 5) is as follows. A solution of lithium amide ((*R*)-**1e**) was prepared under argon atmosphere by adding a solution of *n*-butyllithium (1.2 mmol) in hexane (1.64 M solution) to a solution of the corresponding chiral amine (1.1 mmol) in THF (10 ml) under stirring at -45°C. A solution of *tert*-butyl chloroacetate (1.0 mmol) in THF (5 ml) was added, and the whole was stirred at -45°C for 10 min. A solution of *n*-butyllithium (1.2 mmol) in hexane (1.64 M solution) was added, and the resulting solution was warmed to -20°C and stirred for 20 min. The mixture was cooled to -100°C, and then a cooled solution of benzaldehyde (1.2 mmol) in THF (8 ml) was added. The mixture was stirred at -100°C for 5 min. After addition of methanol (6 ml), the reaction mixture was stirred at -20°C for 30 min, and then at 0°C for 2 h. After addition of saturated aqueous ammonium chloride (20 ml) and water (20 ml), the mixture was extracted with chloroform. The organic extracts were combined, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to dryness to give a pale yellow oil,[5)] which was purified by column chromatography (silica gel, hexane-ethyl acetate (20:1)) to give (2*R*,3*S*)-**3**[6,7)] (76% yield) as a colorless oil. Enantiomeric excess (81%) of this product was determined by HPLC using a chiral column (OD-H, Daicel Co.).

Using (*R*)-**1**, it is shown that the reaction gives (2*R*,3*S*)-**3** enantioselectively and diastereoselectively. It should be noted that the reaction is highly dependent on reaction conditions. Thus, after deprotonation of *tert*-butyl chloroacetate, addition of one equivalent of *n*-butyllithium is essential to get effective asymmetric induction.[8)] Without addition of *n*-butyllithium at this stage in entry 1, racemic product was obtained in almost the same chemical yield. It is also essential to use THF as a solvent, because the degree of asymmetric induction is very low in toluene, ether, or DME.[9)] As was observed in aldol reaction reported previously,[4)] warming the reaction mixture before addition of aldehyde raised the enantiomeric excess of the product.[10)] These facts suggest that the complex formation in solution between the lithium enolate of *tert*-butyl chloroacetate and chiral lithium amide is crucial for the present enantioselective Darzens reaction.

Further studies on the stereochemical mechanisms are underway.

REFERENCES AND NOTES

1) Rosen T., "Comprehensive Organic Synthesis," Vol 2, ed. by Heathcock H., Pergamon Press, Oxford, 1991, pp. 409-454.

2) For examples: a) *via* Sharpless asymmetric epoxidation: Denis J.-N., Greene A. E., Serra A. A., Luche M.-J., *J. Org. Chem.*, **51**, 46-50 (1986); Mulzer J., Lammer O., *Chem. Ber.*, **119**, 2178-2190 (1986); Legters J., Thijs L., Zwanenburg B., *Tetrahedron Lett.*, **30**, 4881-4884 (1989); Caldwell C. G., Bondy S. S., *Synthesis*, **1990**, 34-36. b) *via* enzyme-catalyzed reaction: Akita H., Matsukura H., Oishi T., *Tetrahedron Lett.*, **27**, 5397-5400 (1986); Gentile A., Giordano C., Fuganti C., Ghirotto L., Servi S., *J. Org. Chem.*, **57**, 6635-6637 (1992); Tsuboi S., Furutani H., Ansari M. H., Sakai T., Utaka M., Takeda A., *J. Org. Chem.*, **58**, 486-492 (1993). c) *via* asymmetric dihydroxylation: Denis J.-N., Correa A., Greene A. E., *J. Org. Chem.*, **55**, 1957-1959 (1990). d) *via* deaminative bromination of optically active serine: Petit Y., Sanner C., Larcheveque M., *Synthesis*, **1988**, 538-540. e) *via* asymmetric Michael addition: Baures P. W., Eggleston P. S., Flisak J. R., Gombatz K., Lantos I., Mendelson W., Remich J. J., *Tetrahedron Lett.*, **31**, 6501-6504 (1990). f) *via* resolution: Yamamoto M., Hayashi M., Masaki M., Nohira H., *Tetrahedron: Asymmetry*, **2**, 403-406 (1991).

3) a) Shisido K., Nakanishi O., Nozaki H., *J. Org. Chem.*, **26**, 4878-4881 (1961). b) Colonna S., Fornasier R., Pfeiffer U., *J. Chem. Soc., Perkin 1*, **1978**, 8-11. c) Annunziata R., *Synth. Commun.*, **9**, 171-178 (1979). d) Hummelen J. C., Wynberg H., *Tetrahedron Lett.*, **1978**, 1089-1092. e) Annunziata R., Banfi S., Colonna S., *Tetrahedron Lett.*, **26**, 2471-2474 (1985). f) Abdel-Magid A., Pridgen L. N., Eggleston D. S., Lantos I., *J. Am. Chem. Soc.*, **108**, 4595-4602 (1986). g) Evans D. A., Sjogren E. B., Weber A. E., Conn R. E., *Tetrahedron Lett.*, **28**, 39-42 (1987). h) Baldoli C., Buttero P. D., E. Licandro, Maiorana S., Papagni A., *J. Chem. Soc., Chem. Commun.*, **1987**, 762-764. i) Corey E. J., Choi S., *Tetrahedron Lett.*, **32**, 2857-2860 (1991). j) Corey E. J., Lee D.-S., Choi S., *Tetrahedron Lett.*, **33**, 6735-6738 (1992).

4) Muraoka M., Kawasaki H., Koga K., *Tetrahedron Lett.*, **29**, 337-338 (1988).

5) By proton NMR analysis, this crude product was found to contain a small amount (ca. 3%) of *cis*-isomer as *tert*-butyl ester.

6) Coupling constant (J=1.7 Hz) of the protons attached to the epoxide ring determines the *trans* stereochemistry. For example, see: Hoffman R. V., Kim H.-O., *J. Org. Chem.*, **56**, 6759-6764 (1991).

7) The absolute configuration was determined by converting the product (72% ee) to the known methyl (*R*)-3-phenyllactate (Feenstra R. W., Stokkingreef E. H. M., Nivard R. J. F., Ottenheijm H. C. J., *Tetrahedron*, **44**, 5583-5595 (1988)) by catalytic hydrogenation (5% Pd-C/H_2 in MeOH).

8) By ^{15}N NMR studies, it is shown that deprotonation of *tert*-butyl chloroacetate by [^{6}Li,$^{15}N_2$]-(*R*)-**1e** in THF gives a solution in which the chiral amine exists in free state. However, by addition of one equivalent of *n*-butyllithium to this solution, the signals of ^{6}Li and ^{15}N NMR spectra becomes very complicated, indicating the existence of the interactions between lithium enolate and lithium amide in solution.

9) In entry 1, under the condition where benzaldehyde was added to the reaction mixture at -78°C, the product was found to be 45% ee (68% yield), 0% ee (10% yield), 9% ee (26% yield), and 4% ee (53% yield), in THF, toluene, ether, and DME, respectively.

10) Before and after warming, the reaction mixture was quenched with trimethylsilyl chloride to isolate silyl enol ethers of *tert*-butyl chloroacetate. It is shown that *E/Z* ratio was 1/2 before warming, while it was 1/9 after warming.

(Received August 4, 1995; accepted August 29, 1995)