

## Phase-transfer Catalysis Using Chiral Catalysts. Synthesis of Optically Active 2-Phthalimido-esters

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**Summary** Reaction between ( $\pm$ )-2-bromoalkanoates and potassium phthalimide, under solid-liquid phase-transfer conditions, using either (-)-1-benzylcinchonidinium chloride or (+)-1-benzylcinchoninium chloride as chiral phase-transfer catalysts, gives optically active 2-phthalimido-esters.

THE application of phase-transfer catalysis (PTC)<sup>1</sup> in asymmetric synthesis is a topic of current interest. Quaternary ammonium salts derived from naturally occurring optically active amines (ephedrine,<sup>2</sup> chinine<sup>3</sup>) have been used as catalysts in recent reports. However *N*-alkylation of potassium phthalimide has been carried out by solid-liquid PTC using quaternary phosphonium salts.<sup>4</sup> Since 2-phthalimido-esters are immediate synthetic precursors of the corresponding amino-acids, it would be of interest to

attempt their asymmetric synthesis by PTC. We report here the synthesis of optically active 2-phthalimido-esters by reaction of ( $\pm$ )-2-bromo-esters and potassium phthalimide, by solid-liquid PTC using chiral catalysts, (+)-1-benzylcinchoninium chloride (BCNC) and (-)-1-benzylcinchonidinium chloride (BCDC). No examples of *N*-alkylations under these conditions have been reported.

A typical experiment involves heating to reflux a solution containing 20 mmol of the ( $\pm$ )-2-bromo-ester in 60 ml of solvent (liquid phase), 25 mmol of powdered potassium phthalimide (solid phase), and 1 mmol of the catalyst (only partially soluble in liquid phase). The catalyst and its degradation products are carefully removed and 2-phthalimido-esters are isolated in *ca.* 30–40% yield by washing the reaction mixture with dilute acid and water, chromatography over silica gel, and recrystallization from *n*-hexane.

TABLE

Exp. No.	Substrate	Catalyst	Solvent	$[\alpha]_D^{20}$	Optical purity/% <sup>b,c</sup>
1	(±)-MeCH(Br)CO <sub>2</sub> Et	BCDC	A	0	0
2	"	"	B	-0.12	0.63 (S)
3	"	"	C	-1.47	7.7 (S)
4	"	"	D	-2.30	12.1 (S)
5	"	"	E	-1.80	9.5 (S)
6	"	BCNC	E	3.62	19.1 (R)
7	(-)-MeCH(Br)CO <sub>2</sub> Et	BCDC	E	2.20	11.6 (R)
8	"	BCNC	E	9.94	52.3 (R)
9	(±)-EtCH(Br)CO <sub>2</sub> Me	BCDC	E	-2.06	—
10	(±)-EtCH(Br)CO <sub>2</sub> Pr <sup>1</sup>	"	E	-3.42	—
11	(±)-PhCH(Br)CO <sub>2</sub> Me	"	E	-0.10	—

<sup>a</sup> A, Acetonitrile; B, methyl ethyl ketone; C, ethyl acetate; D, dioxan; E, tetrahydrofuran. <sup>b</sup> Optical purity is defined as  $[\alpha]_{obs} / [\alpha]_{max} \times 100$ . <sup>c</sup> In order to calculate the optical purity, the compound (S)-(-)-ethyl 2-phthalimidopropionate was prepared from (+)-alanine (E. Fisher, *Ber.*, 1907, **40**, 489). The rotatory power obtained ( $[\alpha]_D^{20} - 19.0$ ) is higher than that reported previously ( $[\alpha]_D^{20} - 12.6$ ). No data has been found for the other compounds.

As can be seen in the Table, optical yields are greatly affected by solvent polarity.<sup>5</sup> Non-polar solvents such as dichloromethane, chloroform, or benzene cannot be used because of the low chemical yields obtained. Using a catalyst with different configuration (BCNC and BCDC differ in configuration at C-8 and C-9) gives the opposite enantiomer in high yield (*cf.* Table, exp. nos. 5 and 6).

In order to obtain information about the reaction mechanism, we have carried out experiments (7 and 8) with

(S)-(-)-ethyl 2-bromopropionate as substrate from which the following conclusions can be drawn: (a) the reaction takes place with partial inversion of configuration and, (b) it seems to be a kinetic racemate resolution induced by the catalyst. These conclusions are supported by the recovery, in some cases, of optically active unchanged substrate (Table, exp. no. 6).

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<sup>1</sup> E. V. Dehmlov, *Angew. Chem. Internat. Edn.*, 1974, **13**, 170; 1977, **16**, 493.

<sup>2</sup> S. Colonna, J. Balcells, and R. Fornasier, *Synthesis*, 1977, 266; J. P. Masse and E. R. Parayre, *J.C.S. Chem. Comm.*, 1976, 438.

<sup>3</sup> J. C. Hummelen and H. Wynberg, *Tetrahedron Letters*, 1978, 1089.

<sup>4</sup> D. Landini and F. Rolla, *Synthesis*, 1976, 389.

<sup>5</sup> This has also been recently observed by H. Wynberg and B. Greijdanus, *J.C.S. Chem. Comm.*, 1978, 427, in homogeneous asymmetric catalysis.