Phase-transfer Catalysis Using Chiral Catalysts. Influence of the Structure of the Catalyst on Stereoselectivity. Part 3.[1]

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Some chiral catalysts have been tested in the reaction of ethyl 2-bromopropionate with potassium phthalimide and in the borohydride reduction of phenyl t-butyl ketone under phase-transfer conditions. The mechanism of the *N*-alkylation reaction and the influence of the molecular structure of the catalysts on stereoselectivity are analysed.

ASYMMETRIC synthesis by phase-transfer methods using chiral ammonium salts as catalysts has been a subject of interest by several authors in the last few years.[2] The optical purity of the resulting products is, in general, low. However this method could become a valuable synthetic tool owing to its simplicity, and by analogy with enzyme-type reactions. It seems necessary, in order to improve this method, to understand fully the factors influencing the stereoselectivity in these type of reactions.

Several authors have showed that the stereoselectivity is affected by: (*i*) polarity of the solvent employed;[3,4] (*ii*) molecular structure of the chiral phase-transfer catalyst;[2,3,5,6] (*iii*) molecular structure of the substrate;[2,3] and (*iv*) conditions of reaction (temperature, time, and catalyst-substrate molar ratio).[2,6] Of these factors, the elucidation of the structural requirements of the chiral catalyst seems to be the most important aspect. This has been proved by Wynberg [7] but only in Michael reactions carried out in homogeneous media in the presence of catalysts derived from cinchona alkaloids. However, few data are available in the literature for reactions done under phase-transfer conditions.

RESULTS AND DISCUSSION

Thus we have investigated the behaviour of a series of ammonium quaternary salts (1)—(14) in the previously reported [3] kinetic resolution of ethyl 2-bromopropionate with potassium phthalimide and in the asymmetric borohydride reduction of phenyl t-butyl ketone.[2] The chosen ammonium salts differ in molecular structure, nature of the alkyl substituent at cationic nitrogen, and/or configurations at chiral centres. Since experimental conditions (*e.g.* solvent) can affect the enantiomeric excess of the products, these were kept constant throughout the series of experiments. The *N*-alkylations of phthalimide were performed under solid–liquid (SL) phase-transfer † conditions (PTC) (Experimental section), while the borohydride reductions were carried out under liquid–liquid (LL) conditions, as previously described.[2] The results obtained are listed in Tables 1 and 2.

The optically active ethyl 3-phthalimidopropionates were carefully purified in order to avoid measurements of their optical activity (see Experimental section). No changes in rotation were observed between the product eluted from the column and the product solidified by treatment with n-hexane. In order to elucidate the mechanism of the formation of the optically active 2-phthalimidopropionates some experiments were carried

† *N*-Alkylations of phthalimide gave poor results under LL conditions.

TABLE 1

Synthesis of optically active ethyl 2-phthalimidopropionates in the presence of the catalysts (1)—(14) under SL PTC

No.	Catalyst [a]	Yield [b]	$[\alpha]_{546}^{20}$	Optical purity (%) [c]	Configuration
1	(1)	28	−1.10	5.0	*S*
2	(2)	17	−0.70	3.1	*S*
3	(3)	23	−2.10	9.5	*S*
4	(4)	24	−2.30	10.4	*S*
5	(5)	27	−0.29	1.3	*S*
6	(6)	29	−0.54	2.5	*S*
7	(7)	33	−0.89	4.0	*S*
8	(8)	28	+4.10	18.6 [d]	*R*
9	(9)	28	+3.40	15.4	*R*
10	(10)	16	−0.69	2.5	*S*
11	(11)	30	−0.37	1.7	*S*
12	(12)	30	−0.19	0.85	*S*
13	(13)	33	−0.33	1.5	*S*
14	(14)	37	0	0	

[a] 0.05 mol per mol of substrate. [b] Based on material isolated after chromatography over silica gel. [c] Optical purity; maximum value for $[\alpha]_{546}^{20} = -22.1°$ (*c* 7.6 in MeOH).[3] [d] Determination of the enantiomeric excess by ^{1}H n.m.r. (100 MHz) in the presence of Eu(hfc)$_3$ as chiral displacement reagent afforded a value of 17%.

TABLE 2

Asymmetric borohydride reduction of phenyl ketones in the presence of several chiral catalysts under LL PTC [a]

No.	R	Catalyst	Yield [b]	$[\alpha]_D^{20}$	Optical purity (%) [c]	Configuration
15	Bu^t	(1)	95	+8.70	28.5	*R*
16	Bu^t	(2)	60	+4.10	13.4	*R*
17	Bu^t	(3)	95	+6.48	21.2	*R*
18	Bu^t	(4)	95	+6.38	21	*R*
19	Bu^t	(11)	77	+4.20	7.6	*R*
20	Bu^t	(12)	45	+2.30	13.7	*R*
21	Bu^t	(13)	74	−1.50	5.2	*S*
22	Bu^t	(14)	85	0	0	
23	Me	(3)	82	−1.96	4.7	*S*
24	Me	(8)	82	+0.73	1.7	*R*

[a] Experimental conditions described in ref. 2. [b] Based on material isolated after silica gel column chromatography. [c] Optical purity; maximum value $[\alpha]_D^{20}$ +39.6° (*c* = 3.64 in Me_2CO).[2]

out with racemic and laevorotatory 2-bromopropionate (Table 3). From these results we conclude that: (*i*) recovery of unreacted optically active starting product (Experiments 25 and 26, Table 3), shows that there is a partial kinetic resolution of substrate induced by the ion pair phthalimido-chiral ammonium cation; (*ii*)

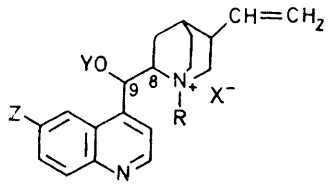
TABLE 3

Mechanism of kinetic resolution of ethyl 2-bromopropionate under SL PTC with chiral catalysts [a]

		Enantiomeric composition		
No.	Catalyst	Starting substrate	Final product	Recovered substrate
25	(3)	50% *R*–50% *S*	45% *R*–55% *S*	49.2% *R*–50.8% *S*
26	(8)	50% *R*–50% *S*	59% *R*–41% *S*	51.5% *R*–48.5% *S*
27	(3)	10% *R*–90% *S*	55% *R*–45% *S*	
28	(8)	10% *R*–90% *S*	74% *R*–26% *S*	
29	TEBA	10% *R*–90% *S*	60% *R*–40% *S*	

[a] Reactions were performed under the same conditions as in Table 1. TEBA = Benzyltriethylammonium chloride.

nucleophilic substitution occurs with inversion of configuration, because the prevailing enantiomer in the final product, and in recovered starting material (experiments 25 and 26) has the same configuration; (*iii*) the rate of nucleophilic substitution is different for each enantiomer of the substrate and depends on the catalyst used [for example, with catalyst (3) the (*R*)-enantiomer reacts faster than the (*S*)-enantiomer (Experiments 25 and 28); the reverse occurs with catalyst (8)]; (*iv*) the



				Configuration		
Catalysts	X	Y	Z	C-8	C-9	R
(1)	Cl	H	OMe	*S*	*R*	CH_2Ph
(2)	Cl	OAc	OMe	*S*	*R*	CH_2Ph
(3)	Cl	H	H	*S*	*R*	CH_2Ph
(4)	Cl	OAc	H	*S*	*R*	CH_2Ph
(5)	Cl	H	H	*S*	*R*	Me
(6)	Br	H	H	*S*	*R*	Et
(7)	Br	H	H	*S*	*R*	Bu
(8)	Cl	H	H	*R*	*S*	CH_2Ph
(9)	Cl	H	OMe	*R*	*S*	CH_2Ph

inversion is partial because some racemization is produced, both in substrate and final product during the reaction as is demonstrated when a racemic catalyst is used (Experiment 29) or by the enantiomeric balance of the recovered substrate and final product in Experiments 25 and 26. Furthermore, control experiments were performed (see Experimental section) showing that racemization occurs with 2-bromopropionate (*ca.* 15%) and of 2-phthalimidopropionate (*ca.* 40%).

The chemical yields of *N*-alkylation are low in all cases. They can be improved by removing the solid phase and adding a fresh amount of phthalimide and catalyst. After two recyclings of the solid phase, yields are *ca.* 70% (Table 4). Logically, the optical yield varies with the chemical yield, the reaction being a kinetic resolution.

From the results in Tables 1 and 2, the following inferences about the relationship between the structure of the catalyst and optical purity can be made.

(*a*) Catalysts derived from cinchona alkaloids are better than those derived from ephedrin and darvon (Experiments 1—9 and 15—18, 10—14, and 19—22

TABLE 4

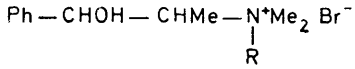
Relation between chemical and optical yield in reaction of ethyl (±)-2-bromopropionate with potassium phthalimide under SL PTC [a]

No.	Number of recyclings of solid phase	Yield	Optical Purity (%)	Configuration
30	0	23	9.5	*S*
31	1	42	6.1	*S*
32	2	69	3.4	*S*

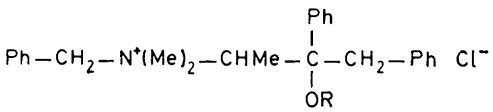
[a] Experiments were performed in same conditions as in Table 1 with catalyst (3).

respectively). In fact, the former are the best catalysts to date that have been used in reported syntheses by PTC methods.[2-4]

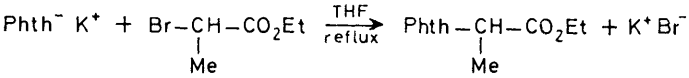
(*b*) The configuration at C-8 and C-9 in catalysts (1)—(9) determines the prevailing enantiomer in ethyl 2-phthalimidopropionate. If the configuration at these C-atoms is inverted, the resulting ethyl 2-phthalimidopropionate is also enriched in the opposite enantiomer

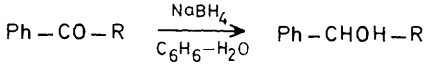


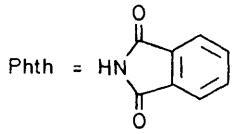
(10) R = Me
(11) R = CH_2Ph
(12) R = n—$C_{12}H_{25}$



(13) R = H
(14) R = EtCO







(Experiments 1—9, Table 1). This tallies with the results obtained by Wynberg and Kobayashy in the reaction of α-ketoesters with methyl vinyl ketone catalysed by cinchona alkaloids [7] and by cinchona alkaloid–acrylonitrile copolymers.[8]

(*c*) Chiral nitrogen and the other asymmetric carbons (C-3, C-4) having the same configuration in the catalysts (1)—(9) do not determine the prevailing enantiomer in both reactions (Experiments 1—9, Table 1, and 23, 24, Table 2).

(*d*) The degree of stereoselectivity depends on the configuration at C-8 and C-9. Probably the configuration at C-9 is more important because of the presence of the hydroxy-substituent which can lead to differences in the diastereoisomeric transition states. In Table 1, the stereoselectivity is greater when the configuration at C-8 is *R* and C-9 is *S* in the alkylation reaction (Experiments 8 and 9 *vs.* Experiments 1 and 3), while in the borohydride reduction the reverse occurs (Experiments 23 and 24, Table 2).

(*e*) A similar effect on the stereoselectivity is observed for the Z-substituent. The methoxy-group enhances stereoselectivity in the borohydride reduction (Experiment 15 *vs.* 17, Table 2) and reduces it in the other reaction (Experiments 1, 9 *vs.* 3, 8, Table 1). It seems probable that both structural factors jointly determine a favoured conformation in the transition state in each case.

(*f*) In order to study the influence of the hydroxy-group, the acylated catalysts (2), (4), and (14) were assayed. No conclusions can be made from experiments 2 and 4 (Table 1) and 16 and 18 (Table 2) because there is evidence that these catalysts are deacetylated in the two-phase systems (see Experimental section). However, when the hydroxy-group of catalyst (13), derived from darvon alcohol, was replaced by a propoxy-group (14) no optically active product was obtained (Experiment 14, Table 1). This result indicates that the hydroxy-group influences the stereoselectivity of the *N*-alkylation reaction. It has already been pointed out that the hydroxy-group of the catalyst plays an important role on the stereochemical course of the borohydride reduction [2] and in the Michael additions under homogeneous conditions,[7] and in the presence of chiral alkaloid–acrylonitrile copolymers.[8] Additional support for these observations were obtained from other experimental results: (*i*) the reduction of acetophenone using benzylbrucinium chloride, a conformationally rigid catalyst without an OH substituent, afforded racemic alcohol under the same LL conditions (89% yield); (*ii*) Michael addition of $MeNO_2$ to chalcone by PTC using catalyst (14) produced the racemic adduct (85% yield); (iii) as a conclusive test of the crucial role played by the hydroxy-group of the catalyst, the kinetic resolution of ethyl 2-bromopropionate and the borohydride reduction were repeated in the presence of *N*-benzyldeoxyquininium chloride. In the *N*-alkylation no reaction occurred, while the reduction of phenyl t-butyl ketone with $NaBH_4$ afforded racemic alcohol.[9]

(*g*) The benzyl group is the best *N*-alkyl substituent in the kinetic resolution of ethyl 2-bromopropionate (Experiments 3—7 and 11, 12, Table 1). In contrast, in the reduction of ketones using ephedrine derivatives the *N*-dodecyl group seems more convenient (Experiments 19, 20, Table 2). Probably, in the former case the benzyl group interacting with the aromatic nucleus allows a more rigid conformation of the catalyst, which enhances the differences between the diastereoisomeric transition states.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer model 157, ^1H n.m.r. spectra were recorded on an R-24 Perkin-Elmer 60-Mz spectrometer, and optical rotations were measured on a Perkin-Elmer 141 polarimeter.

Optically Active Catalysts.—(−)-*N*-Benzylquininium chloride (1) and (−)-(1*R*, 2*S*)-*N*-dodecyl-*N*-methylephedrinium bromide (12) were commercial products (Fluka AG). (−)-*N*-Benzylcinchonidinium chloride (3), (−)-*N*-methylcinchonidinium chloride (5), (+)-*N*-benzylcinchoninium chloride (8), (+)-*N*-benzylquinidinium chloride (9), and (−)-(1*R*,2*S*)-*NN*-dimethylephedrinium iodide (10) were prepared as previously described.[10-12]

(−)-O-*Acetyl*-N-*benzylquinium chloride* (2). (−)-*N*-Benzylquininium chloride (3 g, 7 mmol) and acetic anhydride (3 g, 30 mmol) were heated at 100 °C until the mixture became a homogeneous oil (30 min). After cooling, the residue was crystallised three times from benzene–ethanol, yield 1.33 g (40%), m.p. 186—190 °C, $[\alpha]_D^{20}$ −138.8° (*c* 1.6 in EtOH) (Found: C, 70.8; H, 7.0; Cl, 7.2; N, 5.0. $C_{29}H_{33}ClN_2O_3$ requires C, 70.6; H, 6.7; Cl, 7.2; N, 5.7%).

(−)-O-*Acetyl*-N-*benzylcinchonidinium chloride* (4). (−)-*N*-Benzylcinchonidinium chloride (2.59 g, 6.1 mmol) and acetic anhydride (3 g, 30 mmol) were heated at 100 °C with one drop of H_2SO for 2.5 h. After cooling, the product was precipitated by adding diethyl ether (300 ml) and crystallised twice from benzene–ethanol; yield 1.75 g (59%), m.p. 172—175 °C (decomp.), $[\alpha]_D^{20}$ −85.6° (*c* 2.7 in EtOH) (Found: C, 72.65; H, 6.6; Cl, 7.5; N, 5.95. $C_{28}H_{31}ClN_2O_2$ requires C, 72.63; H, 6.75; Cl, 7.66 N, 6.05%).

(−)-N-*Ethylcinchonidinium bromide* (6). Cinchonidine (5 g, 17 mmol), ethyl bromide (3.7 h, 34 mmol), and acetone (150 ml) were refluxed for 70 h. After cooling the solid was filtered off. The precipitate was boiled with water, the hot solution was filtered, and the product crystallised on cooling, yield 4.0 g (58%), m.p. 262—265 °C from water (decomp.), $[\alpha]_D^{20}$ −95.9° (*c* 1.8 in MeOH) (Found: C, 62.2; H, 7.05; Br, 19.8; N, 7.0. $C_{21}H_{27}BrN_2O$ requires C, 62.2; H, 6.73; Br, 19.8; N, 6.9%).

(−)-N-*benzyl*-N-*methylephedrinium chloride* (11). *N*-Methylephedrine (2.2 g, 12 mmol), benzyl chloride (1.5 ml), and absolute ethanol were refluxed for 18 h. After solvent evaporation the product was precipitated by adding ethyl acetate–n-hexane, yield 3 g (82%), m.p. 198—199°, $[\alpha]_D^{25}$ −8.67° (*c* 2.0 in EtOH) (Found: C, 70.0; H, 7.6; N, 4.4; $C_{18}H_{24}NOCl$ requires C, 70.6; H, 7.9; N, 4.6%).

The following catalysts were prepared by the same procedure: (+)-*N*-benzyldarvonium chloride [(2*R*,3*S*)-*N*-benzyl-*N*-(3-hydroxy-2-methyl-3,4-diphenylbutyl)-*NN*-dimethylammonium chloride) (13), yield 28%, m.p. 210 °C, $[\alpha]_D^{20}$ +12.1° (*c* 0.74 in CH_2Cl_2: (−)-*N*-butylcinchonidinium bromide (7), yield 73%, m.p. 232—234 °C from acetonitrile (decomp.), $[\alpha]_D^{20}$ −90.9° (*c* 1.9 in MeOH): (−)-*N*-benzylpropoxyphene chloride [(2*R*,3*S*)-N-benzyl-*NN*-dimethyl-*N*-(3-propoxy-2-methyl-3,4-diphenylbutyl)ammonium chloride] (14), yield 90%, m.p. 194—195 °C, $[\alpha]_D^{20}$ −9.1° (*c* 2.4 in MeOH).

Ethyl (−)-(S)-2-*phthalimidopropionate.* In a Pyrex tube at 150 °C (−)-alanine (2.67 g, 0.03 mol) and phthalic anhydride were heated until evolution of H_2O vapour ceased (5 min). The mixture was cooled and extracted with diethyl ether. n-Hexane was added and an oil was precipitated, which spontaneously solidified, yield 2.63 g (40%), m.p. 150 °C from cyclohexane, $[\alpha]_D^{20}$ −22.3° (*c* 1.0 in MeOH). This product was esterified by the azeotropic method, yield 2.46 g (83%), m.p. 61—62 °C, $[\alpha]_D^{20}$ −19.0° (*c* 7.6 in MeOH).

Kinetic Resolutions by PTC. Synthesis of Optically Active Ethyl 2-*Phthalimidopropionates.*—Ethyl (±)-2-bromopropionate (3.6 g, 20 mmol), potassium phthalimide (4.63 g, 25 mmol), catalysts (1)—(14) (1 mmol), and tetrahydrofuran were mixed in a 100-ml Erlenmeyer flask with magnetic stirring and were refluxed for 4 h. After cooling, tetrahydrofuran was removed and chloroform (100 ml) was added. This solution was washed with 3% HCl (400 ml) and water (200 ml), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (eluant benzene), and the resulting oil was solidified by treatment with n-hexane. The solid was dried under vacuum. Yields, optical rotations, optical purity, and the configuration of the prevailing enantiomer are reported in Table 1; m.p. 61—62 °C, i.r. and n.m.r. spectra in agreement with the structure.

Tests of Racemization.—(*a*) Ethyl (−)-2-phthalimidopropionate (10 mmol) was dissolved in tetrahydrofuran (30 ml) and catalyst (8) (0.5 mmol) and powdered potassium phthalimide (12.5 mmol) added. The mixture was refluxed with stirring for 4 h. After filtration through silica gel, solvent was evaporated; $[\alpha]_{578}^{20}$ (before) −19.4°; $[\alpha]_{578}^{20}$ (after) −7.7° (*c* 1.29 in MeOH).

(*b*) Ethyl (+)-2-bromopropionate (2 mmol) was mixed with powdered potassium phthalimide (2.5 mmol) and tetrahydrofuran (6 ml). Following procedure (*a*) the product was isolated; $[\alpha]_{578}^{20}$ (before) +14.4; $[\alpha]_{578}^{20}$ (after) +12.2 (*c* 3.03 in Me_2CO).

Stability of Acetylated Catalysts in the Reaction Media.—Potassium phthalimide (2 g, 10 mmol) and (−)-*O*-acetyl-*N*-benzylquininium chloride (0.35 g, 0.71 mmol) were dissolved in tetrahydrofuran (25 ml). The mixture was refluxed with stirring for 4 h, and the precipitate was then filtered off and washed with chloroform (25 ml). The organic phases were combined and solvent partially evaporated. The resulting solution was passed through a cationic exchange resin (Dowex 50 W) and eluted with methanol. After elution of phthalimide, the ammonium salt was eluted with MeOH–HCl (10 : 1) affording a product identical (physical constants and spectroscopic data) with *N*-benzylquininium dichloride. In a test control a sample (−)-*O*-acetyl-*N*-benzylquininium chloride (2) chromatographed by the same procedure remained unaltered.

Identical results were obtained using catalyst (4) instead of (2), and in the borohydride reduction.

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