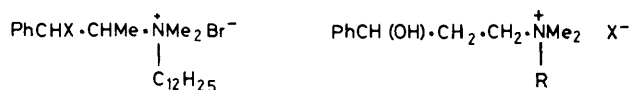


Asymmetric Induction in the Borohydride Reduction of Carbonyl Compounds by Means of Chiral Phase-transfer Catalysts. Part 2.¹

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Reaction of carbonyl compounds with sodium borohydride in a two-phase system, in the presence of chiral ammonium salts containing a secondary hydroxy-group affords the corresponding carbinols with 0–32% enantiomeric excess. The optical yields are higher when the hydroxy group is β to the 'onium' function and the catalyst is conformationally more rigid.

In the last few years growing attention has been devoted to asymmetric synthesis under phase-transfer conditions in the presence of optically active 'onium' salts as catalysts.^{1,2} In particular, carbonyl compounds having a chiral atom α to the carbonyl group and/or sterically hindered undergo borohydride reduction in the presence of *N*-alkyl-*N*-methylephedrinium bromide (1) to afford

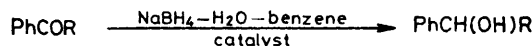
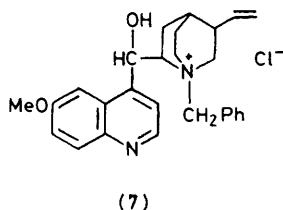
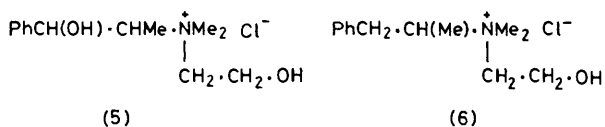


(1) X = OH

(2) X = H

(3) R = C₁₂H₂₅, X = Br

(4) R = CH₂Ph X = Cl



(8)–(11)

(12)–(15)

(8), (12) R = Me

(9), (13) R = Et

(10), (14) R = Pri

(11), (15) R = Bu^t

optically active carbinols.¹ The highest optical yield (13.7%) was obtained for phenyl *t*-butyl ketone. The presence of a hydroxy-group in the catalyst was essential to achieve asymmetric induction.

A readily available chiral reagent affording consistently high stereoselectivity would represent a valuable synthetic tool for optically active carbinols.

† The excellent behaviour of benzylquininium chloride (7) as phase-transfer catalyst is in accord with the 25% enantiomeric excess obtained by Wynberg in epoxidation reactions.^{2f,g}

For this reason we have now investigated the behaviour of the series of 'onium' salts (1)–(7) in the borohydride reduction of carbonyl compounds under phase-transfer conditions, in order to ascertain the influence of structural variations within the catalyst on asymmetric induction. The ammonium salts chosen not only differ in the position and in the number of hydroxy-groups, but also in the degree of conformational freedom.

Alkyl phenyl ketones (8)–(11) were reduced with sodium borohydride at 0 °C in the two-phase system benzene-water in the presence of catalytic amounts (0.05 mol. equiv.) of (1)–(7). The results are listed in Tables I and 2.

TABLE I

Reduction of phenyl *t*-butyl ketone with sodium borohydride^a in benzene-water in the presence of the catalysts (1)–(7)^b at 0 °C

Catalyst	Reaction time	Yield (%) ^c	$[\alpha]_D^{25}$ ^e	E.e. % ^d	Configuration
(1)	1	77	+4.20	13.7	(+)-(R)
(2)	1	75	0		
(3)	2	86	+0.34	1.1	(+)-(R)
(4)	4	80	+0.34	1.1	(+)-(R)
(5)	20	77	0		
(5)	120 ^e	93	+1.15	3.8	(+)-(R)
(6)	7	25	0		
(7)	2	95	+9.75	32.0	(+)-(R)
(7)	2 ^f	100	+7.70	25.2	(+)-(R)

^a 0.6 mol per mol of substrate. ^b 0.05 Mol per mol of substrate. ^c Based on material isolated. ^d Enantiomeric excess; maximum value for $[\alpha]_D^{20}$ +30.6 (*c* 3.64 in Me₂CO); W. Winstein, B. K. Morse, *J. Amer. Chem. Soc.*, 1952, **74**, 1133. ^e In absence of water. ^f At 25 °C.

Among the catalysts tested, benzylquininium chloride (7) is generally the best optically active phase-transfer catalyst.† Indeed in the reduction of phenyl *t*-butyl ketone (11), catalyst (7) afforded (+)-(R)-(15) in an optical purity of 32%. To our knowledge, this is the highest enantiomeric excess found in asymmetric syntheses using chiral ammonium salts as catalysts under phase-transfer conditions.

¹ Part I, J. Balcells, S. Colonna and R. Fornasier, *Synthesis*, 1976, 266.

² (a) S. Colonna and R. Fornasier, *Synthesis*, 1975, 531; (b) T. Hijama, T. Mishima, H. Sawada and H. Nozaki, *J. Amer. Chem. Soc.*, 1975, **97**, 1626; (c) T. Hijama, H. Sawada, M. Tsukanaka, and H. Nozaki, *Tetrahedron Letters*, 1975, 3012; (d) J. C. Fiaud, *ibid.*, 1975, 3495; (e) T. Hijama, T. Mishima, H. Sawada, and H. Nozaki, *J. Amer. Chem. Soc.*, 1976, **98**, 641; (f) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. C. Wiering, and H. Wynberg, *Tetrahedron Letters*, 1976, 1831; (g) H. Wynberg, *Chimia*, 1976, **30**, 445; (h) J. P. Massé and E. R. Parayre, *J.C.S. Chem. Comm.*, 1976, 438.

With the 'onium' salts (3) and (4), whose reactivity was similar to that of the ephedrinium salt (1), (+)-(R)-(phenyl-t-butylcarbinol) (15) was obtained in 1.1% enantiomeric excess.

When *N*-(2-hydroxyethyl)-*N*-methylamphetaminium chloride (5) was used, the reduction was much slower and the isolated alcohol was racemic. This is because (5) is very soluble in the aqueous phase, with a partition coefficient in benzene-water of *ca.* 1:99. Furthermore, when the reaction was repeated with (5) under solid-liquid phase-transfer conditions, phenyl-t-butylcarbinol (15) was obtained in 3.8% enantiomeric excess. This

and (+)-(R) for R = Prⁱ and Bu^t. The stereochemical course of the borohydride reduction of alkyl phenyl ketones in the benzene-water system is consistent with that previously found⁴ in alkyl-metal asymmetric reduction. Such results can be rationalised if account is taken of the increased steric effects of the bulkier isopropyl and t-butyl groups over that of a phenyl substituent.

In a previous paper we reported¹ that reduction of acetophenone (8) at 25 °C with sodium borohydride catalysed by the ephedrinium salt (1) (0.05 mol. equiv.) in a benzene-water system afforded the corresponding

TABLE 2
Reduction of the ketones (8)–(10) with sodium borohydride^a in benzene-water in presence of the catalysts (1) and (7)^b

R	Catalyst	Reaction time (h)	Temp./°C	Yield (%) ^c	$[\alpha]_D^{25}$	E.e. %	Configuration
Me	(1)	1	0	97	0		
Me	(7)	6	0	75	-1.90	4.5 ^d	(-)-(S)
Me	(7)	1	25	96	-2.62	6.2	(-)-(S)
Me	(7)	0.5	45	95	-2.55	6.1	(-)-(S)
Et	(1)	2	0	87	0		
Et	(7)	6	0	85	-1.16	3.3 ^e	(-)-(S)
Et	(7)	1	25	85	-2.00	5.7	(-)-(S)
Pr ⁱ	(1)	16	0	100	+1.70	3.6	(+)-(R)
Pr ⁱ	(1)	6	25	100	+1.50	3.1	(+)-(R)
Pr ⁱ	(7)	3	0	55	+2.43	5.1	(+)-(R)
Pr ⁱ	(7)	2	25	60	+1.60	3.35	(+)-(R)

^a 0.6 Mol. equiv. ^b 0.05 Mol. equiv. ^c Based on material isolated. ^d Maximum value for $[\alpha]_D^{20}$ -42.0° (*c* 3.7 in MeOH)⁷. ^e Maximum value for $[\alpha]_D^{20}$ +34.8 (*c* 8 in Et₂O); P. A. Levene and L. A. Mikeska, *J. Biol. Chem.* 1926, **70**, 355. ^f Maximum value for $[\alpha]_D^{20}$ +47.7 (*c* 6.8 in Et₂O); see ref in *e*.

probably implies that in the benzene-water system only the uncatalysed reduction takes place.

The quinium salt (7) in contrast to the ephedrinium salt (1) also gave asymmetric induction in the reduction of acetophenone (8) and propiophenone (9).

The results as a whole (Table 2) seem to indicate that two factors are important in order to achieve asymmetric induction in the borohydride reduction of carbonyl compounds under phase-transfer conditions: (i) the catalyst must be conformationally rigid, as is the quininium salt (7); (ii) the hydroxy-group must be in the β position to the 'onium' function, possibly in order to interact with the carbonyl group and to favour one of the diastereomeric transition states which lead to carbinol (15); asymmetric induction is much lower with a γ-hydroxy-group.

The degree of asymmetric induction is similar for the carbinols (12)–(14) and substantially lower with respect to phenyl-t-butylcarbinol (15) (see Table 1). For acetophenone (8) and propiophenone (9) the enantiomeric purity of the alcohols obtained increased with the temperature. This behaviour which is difficult to account for, parallels that found in the asymmetric reduction of acetophenone by lithium aluminium hydride-quinine reagents in tetrahydrofuran.³

In the case of catalyst (7) the absolute configurations of the alcohols (12)–(15) were (-)-(S) for R = Me, Et,

optically inactive alcohol (12). In contrast, Massé^{2h} reported that the same reaction carried out at 20 °C in a water-1,2-dichloroethane system, in the presence of the salt (1) (0.01 mol. equiv.), afforded (+)-(R)-phenylmethylcarbinol (12), 0.35% optically pure. It was also claimed that the optical purity of the carbinol (12) increased with the amount of (1) used, to give a 39% enantiomeric excess with a 0.4 mol. equiv. of (1). We have now repeated the latter experiment and obtained (-)-(S)-phenylmethylcarbinol (1) enantiomerically enriched by 4.7%.

When the borohydride reduction of acetophenone (8) was performed at 20 °C in the presence of 0.05 and 0.4 mol. equiv. of benzylquinium chloride (7), the resulting (S)-methylphenylcarbinol had values of $[\alpha]_D^{25}$ of -3.42 and -2.50° respectively which corresponded to enantiomeric purities of 8.1 and 5.9%. Furthermore, reduction in the same reaction conditions of phenyl t-butyl ketone (11) in the presence of 0.05 and 0.4 mol. equiv. of catalyst (7) gave (+)-(R)-(15) having enantiomeric purities of 19.2 and 18.3% respectively.

These results (i) throw doubts on the high values of enantiomeric purity for methylphenylcarbinol (12) claimed by Massé^{2h}; (ii) indicate that only with the ephedrinium salt (1) does asymmetric synthesis increase with the concentration of the catalyst; and (iii) variation of the concentration of catalysts (1) and (7) in the

³ J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice-Hall, New Jersey, 1971, p. 210.

⁴ G. P. Giacomelli, R. Menicagli, and L. Lardicci, *J. Amer. Chem. Soc.*, 1975, **97**, 4009.

range 0.05—0.4 mol. equiv. may affect the nature of the reaction medium and thus influence the asymmetric induction.

EXPERIMENTAL

Light petroleum had b.p. 40—60 °C. ¹H N.m.r. spectra were recorded on a Varian A-60 spectrometer and optical rotations were measured on a 141 Perkin-Elmer polarimeter.

Optically Active Catalysts.—(–)-(1*R*,2*S*)-*N*-Dodecyl-*N*-methylephedrinium bromide (1), (–)-(1*R*)-*N*-dodecyl-*NN*-dimethylamphetaminium bromide (2), (+)-*N*-dodecyl-*NN*-dimethyl-(3-hydroxy-3-phenylpropyl)ammonium bromide (3), and (+)-*N*-benzyl-(3-hydroxy-3-phenylpropyl)-*NN*-dimethylammonium chloride (4) were prepared as previously described.^{1,5}

(–)-*N*-(2-Hydroxyethyl)-*N*-methylephedrinium chloride (5). This compound was prepared by dropwise addition of ethylene chlorohydrin (11 mmol) to a solution of *N*-methylephedrine (10 mmol) in ethanol (10 ml). The reaction mixture was refluxed for 5 days after which the solvent was evaporated under reduced pressure to give (4) (70%), m.p. 158—160 °C (from MeCN-PrⁱOH), $[\alpha]_D^{25} -34^\circ$ (*c* 0.24 in EtOH) (Found: C, 60.0; H, 8.5; N, 5.35. C₁₃H₂₂ClNO₂ requires C, 60.1; H, 8.5; N, 5.4%).

(–)-*Benzylquininium chloride* (7). This compound was prepared by adding benzyl chloride (10 mmol) to a solution of quinine (10 mmol) in benzene (10 ml) and ethanol (2 ml). After 26 h at room temperature the solvent was evaporated off and the residue washed with pentane to give (7) (79% yield) as a monohydrate, m.p. 169—172 °C (decomp.), $[\alpha]_D^{25} -212.5^\circ$ (*c* 0.5 in EtOH) (lit.,⁶ m.p. 183—188 °C as anhydrous salt), $[\alpha]_D^{22} -230.5^\circ$ (*c* 1.479 in H₂O), Cl[–] content 97% by Volhard method.

(–)-*N*-(2-Hydroxyethyl)-*NN*-dimethylamphetaminium chloride (6). This compound was prepared by dropwise

addition of ethylene chlorohydrin (12 mmol) to a solution of (–)-(1*R*)-*NN*-dimethylamphetamine (10 mmol), $[\alpha]_D^{25} -13.5^\circ$ (*c* 10 in H₂O, hydrochloride salt),^{2a} in dimethylformamide (5 ml) and heating of the mixture under reflux for 4 days. The reaction mixture was cooled and diluted with hexane to precipitate (5), which was filtered off (92% yield), m.p. 124—125 °C (hygroscopic), $[\alpha]_D^{25} -5.12^\circ$ (*c* 3 in EtOH) (Found: C, 64.1; H, 9.0; N, 5.6. C₁₃H₂₂ClNO requires C, 64.2; H, 9.05; N, 5.75%).

Reduction of Ketones.—Carbonyl compound (10 mmol), sodium borohydride (6 mmol), benzene (6 ml), water (10 ml), and the catalyst were mixed in a flask and stirred at 0, 25, or 45 °C for a suitable time (see Tables 1 and 2). The reaction was followed by g.l.c. or t.l.c. The organic layer was separated, the aqueous phase extracted with methylene chloride, and the combined organic fraction dried (Na₂SO₄). After evaporation of the solvent the residue was chromatographed on silica with ether–light petroleum (2 : 8) as eluant. Yields, optical rotations, and enantiomeric excesses are reported in Tables 1 and 2.

Reduction of acetophenone was also carried out in 1,2-dichloroethane as described in the literature.^{2b} After work up (–)-(1*S*)-1-phenylethanol (12) was obtained in 97% yield; $[\alpha]_D^{25} -2.0$ (*c* 3.7 in MeOH) which corresponds to an optical purity of 4.7%.⁷ Reduction of acetophenone (8) under the same reaction conditions in the presence of 0.05 and 0.4 mol. equiv. of catalyst (7) gave, in 40 and 94% yield, the (–)-(1*S*)-carbinol (12), $[\alpha]_D^{20} -3.42^\circ$ and $[\alpha]_D^{20} -2.50^\circ$ (*c* 3 in MeOH), 8.1 and 5.9% enantiomerically pure, respectively. Reduction of phenyl t-butyl ketone (11) in (CH₂Cl)₂ under the conditions already described, in the presence of 0.05 and 0.4 mol. equiv. of (7) afforded in 95 and 100% yield, the (+)-(1*R*)-carbinol (15), $[\alpha]_D^{20} +5.88$ and $+5.60^\circ$ (*c* 3.6 in Me₂CO), 19.2 and 18.3% enantiomerically pure, respectively.

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⁵ S. Colonna, R. Fornasier, and U. Pfeiffer, *J.C.S. Perkin I*, 1978, 8.

⁶ W. A. Jacobs and M. Heidelberger, *J. Amer. Chem. Soc.*, 1919, **41**, 2090.

⁷ G. Barbieri, V. Davoli, I. Moretti, F. Montanari, and G. Torre, *J. Chem. Soc. (C)*, 1969, 731.