

Asymmetric Reduction of Ketones by Phase Transfer Catalysis

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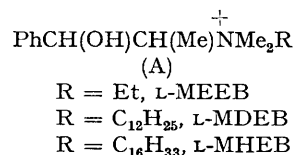
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Summary *N*-Methyl-*N*-dodecyl- or *N*-methyl-*N*-hexadecyl-ephedrinium bromides and sodium borohydride stereoselectively reduce ketones by phase transfer catalysis in aqueous 1,2-dichloroethane; the optical yield depends on chain length and concentration of the surfactants.

BECAUSE of its insolubility, NaBH₄ cannot be used in reduction reactions in nonpolar solvents. Long chain quaternary ammonium borohydrides are soluble in nonpolar solvents, and thus have better reducing ability.¹ Lithium alkyl(hydro)dipinan-3 α -ylborates have also been used for asymmetric reduction of ketones² and imines³ in hydrocarbon solvents.

Phase transfer-catalysed reactions in preparative organic chemistry have recently been reviewed.⁴ Reduction of carbonyl compounds with boron hydrides has led to interest-

ing results,^{5,6} but there are no examples of reactions involving stereoselective reduction. We report the first examples of stereoselective reduction of ketones by NaBH₄ in a water-1,2-dichloroethane system, catalysed by ephedrinium surfactants, *L*-*N*-methyl-*N*-dodecyl- (*L*-MDEB) and *L*-*N*-methyl-*N*-hexadecyl- (*L*-MHEB) ephedrinium bromides (A) prepared from *L*-ephedrine.⁷



Reduction of acetophenone or isobutyl methyl ketone (0.05 mol in 20 cm³ ClCH₂CH₂Cl) with 1 equiv. of a 2*N*

TABLE

Ketone	Surfactant	Surfactant : ketone	Derived alcohol	
			$[\alpha]_D$	Optical purity/% ^a
PhC(O)Me	L-MDEB	1:100	+0.145°	0.35
	"	1:10	+4.07°	8.95
	"	2:10	+6.03°	13.20
	"	4:10	+17.6°	39.0
	L-MHEB	1:100	+0.23°	0.50
	"	5:100	+0.805°	1.78
	"	1:10	+1.9°	4.20
	"	2:10	+0.575°	1.27
Me ₂ CHCH ₂ C(O)Me	L-MDEB	1:100	+0.257°	1.15
	"	1:10	+1.019°	4.55
	L-MHEB	1:100	+0.23°	1.02
	"	1:10	+0.38°	1.71

^a Optical purity is defined as $[\alpha]_{\text{obs}}/[\alpha]_{\text{max}} \times 100$. $[\alpha]_{D_{\text{max}}} = +45.5^\circ$ for (*R*)-1-phenylethanol (L. Horner and D. Degner, *Tetrahedron Letters*, 1968, **56**, 5889; and $[\alpha]_{D_{\text{max}}} = +22.4^\circ$ for (*S*)-4-methylpentan-2-ol. ('Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965).

NaOH-NaBH₄ solution was very slow (incomplete after 2 weeks at 20 °C) in the absence of the surfactant. When *L-N*-methyl-*N*-ethyl ephedrinium bromide (*L*-MEEB) was used, the reaction was slow and low stereoselectivity was observed, probably because *L*-MEEB is a poor phase transfer catalyst owing to the less bulky alkyl group and greater solubility in the aqueous phase. In the presence of the surfactant *L*-MDEB or *L*-MHEB, however, reaction rates increased markedly, as previously reported for non-stereoselective borohydride reductions.⁶

Catalysis of the reaction in aqueous 1,2-dichloroethane was dependent on alkyl chain length of the catalyst, as was the stereoselectivity. Data presented in the Table show

that a better stereoselectivity is obtained with the surfactant *L*-MDEB. *L*-Surfactants produced (+)-alcohols, whereas *D*-surfactants gave (-)-alcohols of similar optical purities under the same conditions.

The results seem to indicate asymmetric phase transfer catalysis in the two-phase reductions studied, the alkyl ephedrinium tetrahydroborate extracted from water into 1,2-dichloroethane causing stereoselective reduction.

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