Asymmetric Reduction of Ketones by Phase Transfer Catalysis

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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, $NaBH_4$ 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-3α-ylborates have also been used for asymmetric reduction of ketones[2] and imines[3] 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 interesting results,[5,6] but there are no examples of reactions involving stereoselective reduction. We report the first examples of stereoselective reduction of ketones by $NaBH_4$ 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]

$$PhCH(OH)CH(Me)\overset{+}{N}Me_2R$$

(A)

R = Et, L-MEEB

R = $C_{12}H_{25}$, L-MDEB

R = $C_{16}H_{33}$, L-MHEB

Reduction of acetophenone or isobutyl methyl ketone (0·05 mol in 20 cm³ $ClCH_2CH_2Cl$) 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
$Me_2CHCH_2C(O)Me$	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 $[\alpha]_{obs}/[\alpha]_{max} \times 100$. $[\alpha]_{D_{max}} = + 45·5°$ for (*R*)-1-phenylethanol (L. Horner and D. Degner, *Tetrahedron Letters*, 1968, **56**, 5889; and $[\alpha]_{D_{max}} = + 22·4°$ for (*S*)-4-methylpentan-2-ol. ('Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965).

$NaOH–NaBH_4$ 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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