Unusual Effect of a Mixed Solvent on the Asymmetric Reduction of Chiral α-Keto-amides with Sodium Borohydride

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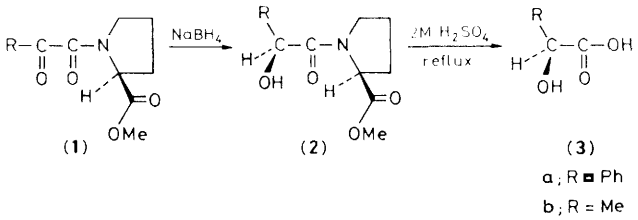
The mixed solvent tetrahydrofuran + methanol (99 : 1) was much more effective than the individual solvents in the asymmetric reduction of chiral α-keto-amides with sodium borohydride; this solvent effect in asymmetric induction is unprecedented.

Despite the importance of the role of solvents in asymmetric synthesis, mixed solvents have been used very rarely.[1] We report the first example of a solvent effect on asymmetric induction in which a mixed solvent caused much higher asymmetric induction than either of the individual solvents.

In general, diastereoselectivities are low in the asymmetric reduction of chiral α-keto-esters or -amides with complex metal hydrides,[2] especially with sodium borohydride.

α-Keto-amides (**1a**, **b**),[3] derived from (*S*)-proline methyl ester and α-keto-acids using dicyclohexylcarbodi-imide, were reduced with readily available $NaBH_4$ at 0 °C to afford (**2a**, **b**). Acidic hydrolysis of (**2a**, **b**) afforded the optically active α-hydroxy-acids (**3a**, **b**). When (**1a**) was reduced in tetrahydrofuran (THF) or methanol alone, the resulting enantiomeric excess (e.e.) of the mandelic acid (**3a**) produced was 36% (THF) and 4% (MeOH).†

A striking solvent effect was observed, however, when a THF + methanol (99:1 by volume) co-solvent was used.



The optical purity of the resulting (*S*)-(+)-mandelic acid {$[\alpha]_D^{25}$ +101° (*c* 1.9, H_2O)} increased to 64% e.e.† Using the same mixed solvent, (*S*)-(+)-lactic acid {(**3b**), $[\alpha]_D^{25}$ −7.4° (*c* 2.9, 1.5 M NaOH)} was obtained in 55% e.e.‡ from (**1b**). Water, instead of MeOH, was also found to be effective.

In either mixed solvents, a catalytic amount of the protic solvent (MeOH or H_2O) in the aprotic THF was found to be essential for good asymmetric induction. The results are summarized in Table 1.

† Enantiomeric excesses were determined by ^{1}H-n.m.r. analysis of (**2a**) and/or by reported specific optical rotation of (**3a**). (*S*)-(+)-Mandelic acid, $[\alpha]_D$ +158° (H_2O), S. Mitsui and A. Kanai, *Nippon Kagaku Zasshi*, 1965, **86**, 627.

‡ Based on the value of (*S*)-(+)-lactic acid $[\alpha]_D^{20}$ −13.5° (*c* 2.5, 1.5 M NaOH), 'Aldrich Catalog Handbook of Fine Chemicals,' Aldrich Chemical Co. Inc., Wisconsin, 1980.

Table 1. Effect of solvent on asymmetric reduction.

Ratio (v/v) THF : MeOH	(**3a**) (% e.e.)
100 : 0	36
99 : 1	64
0 : 100	4
THF : H_2O	
99 : 1	50
85 : 15	0

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