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Stereoselectivity in the Reduction of Cyclic Ketones with Sodium Borohydride. Effect of the Ratio of the Components of a Mixed Solvent of Tetrahydrofuran and Methanol

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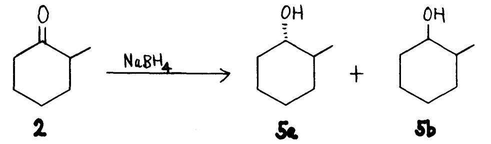
Synopsis. Reduction of relatively conformationally rigid cyclic ketones with sodium borohydride was examined in a mixed solvent of tetrahydrofuran(THF) and methanol(MeOH) with varying the ratio of the components. The highest stereoselectivities of the reductions were observed in the *mixed solvent*, and not in each *individual solvent.*

Sodium borohydride(NaBH$_4$, **1**) has been used widely,[1] and its chemoselectivity is affected by the solvent.[2] Several reports have appeared on the stereoselectivity of the reduction of cyclic ketones with **1**.[3] However, nearly all the reductions have been carried out in a *single solvent.* To the best of our knowledge, the effect of *mixed solvents* on the stereoselectivity of **1** has not been closely examined.[4]

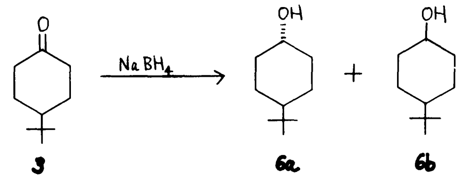
During our continuing study on asymmetric synthesis,[5] we reported that diastereoselectivity is higher in the reduction with **1** of chiral α-keto-amides in a mixed solvent of THF and MeOH than in either individual solvent.[6]

In the present paper, we describe the reduction of relatively conformationally rigid cyclic ketones with **1** in a mixed solvent of THF and MeOH. Cyclic ketones (**2**—**4**) were reduced with **1** at 0 °C in the mixed solvent of THF and MeOH with varying ratio of the components. Stereoselectivities were determined by GLC analyses of the isomeric alcohols formed. Predominant isomers from the reductions of 2-methylcyclohexanone(**2**), 4-*t*-butylcyclohexanone(**3**), and camphor(**4**) were *trans*-2-methylcyclohexanol (**5a**), *trans*-4-*t*-butylcyclohexanol(**6a**), and isoborneol (**7a**) respectively (Eq. 1—3. Only one enantiomer is shown in Eqs. 1 and 3. The actual products were racemic mixtures).

As shown in Figs. 1—3, in each case, stereoselectivities {shown as diastereomeric excesses (% d.e.)} of the product alcohols depended upon the volumetric ratio of THF and MeOH. The highest stereoselectivities in the reduction of cyclic ketones (**2**—**4**) were observed *in mixed solvent of THF and MeOH, and not in each individual solvent.* Diastereomeric excesses in the above mixed solvent of the appropriate ratio of components were higher than in the single solvent



(1)



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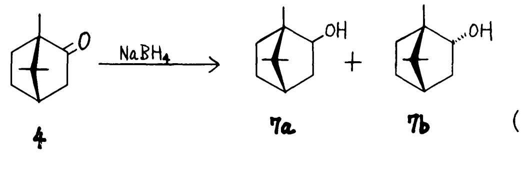

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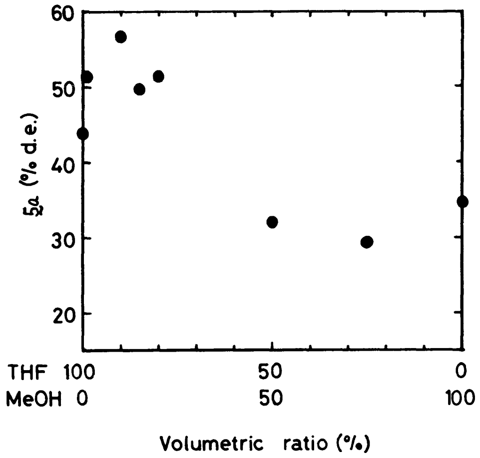

Fig. 1. Relation between Stereoselectivity of the Reduction of **2** and the Ratio of the Components of Mixed Solvent.

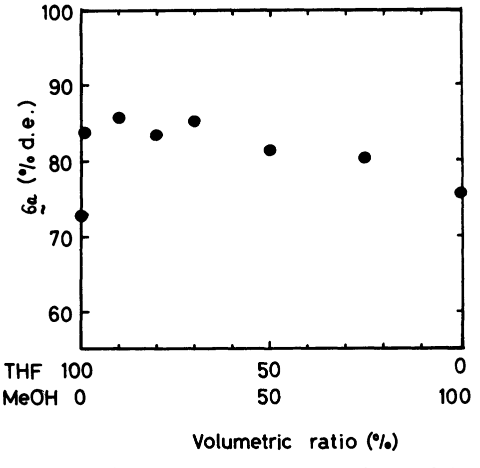

Fig. 2. Relation between Stereoselectivity of the Reduction of **3** and the Ratio of the Components of Mixed Solvent.

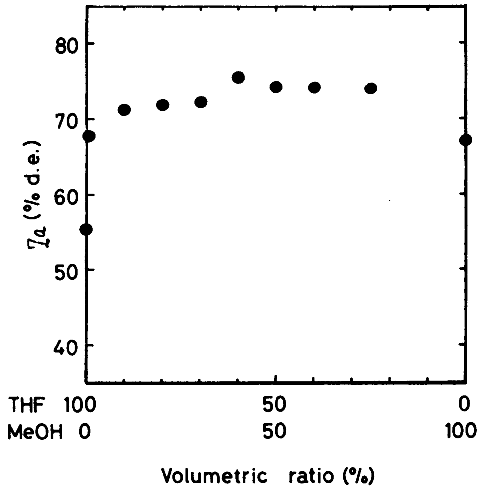

Fig. 3. Relation between Stereoselectivity of the Reduction of **4** and the Ratio of the Components of Mixed Solvent.

2-propanol. In the present mixed solvent of THF-MeOH, diastereomeric excesses of **5a**, **6a**, and **7a** reached 57, 86, and 75% d. e. respectively. On the other hand, reductions of **2**, **3**, and **4** with **1** in 2-propanol give **5a**, **6a**, and **7a** of 38, 66, and 72% d. e. respectively.[7,8] Therefore this mixed solvent may achieve higher stereoselectivities in the reduction of complicated cyclic ketones. Ketones **3** and **4** are conformationally rigid regardless of the ratio of the components of the mixed solvent.[9] Therefore the higher stereoselectivities in mixed solvent may be attributed, at least partly, to other than the ketones themselves, *i.e.* nature of the reducing species or mechanism of the reduction.

As described, mixed solvent of THF–MeOH is an influential factor on the stereoselective reduction of cyclic ketones with **1**.

Experimental

General Procedure for the Reduction of Ketones. Mixed solvent (1ml, THF–MeOH) was added to 1mmol of **1** with cooling in ice-bath, and was stirred for 5min. Ketone (1mmol) in 3ml of the above mixed solvent was added over a period of 15min. The mixture was stirred for 7—10h (ketones except camphor disappeared by TLC analysis). For the reduction of camphor, 3 molar amounts of **1** was used (reaction time 10 h). 1MHCl ($1\ \mathrm{M}=1\ \mathrm{mol\ dm^{-3}}$) was added to quench the reaction. Aqueous layers were extracted with ether and chloroform. The extracts were condensed, and were subjected to GLC analyses. In GLC analyses, all the products were identical with authentic samples purchased. GLC [poly(ethylene glycol)(PEG)-20 M or silicone SE-30, 25 m capillary column, flame ionization detector]. Column temp for 2-methylcyclohexanol; 65 °C, retention time, *cis*-**5b**; 21.1 min., *trans*-**5a**; 23.6 min., 4-*t*-butylcyclohexanol; 120 °C, *cis*-**6b**; 8.0 min., *trans*-**6a**; 9.2 min., isoborneol(**7a**); 5.9 min., borneol(**7b**); 6.1 min. 120 °C.

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