Short Communication

Asymmetric Reduction by an NADH Model Compound with L-Prolinamide in the N_1 -Substituent

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In asymmetric reductions by NADH Model compounds carrying a chiral center in the N_1 -substituent of the dihydropyridine, the optical yields so far reported have been rather low ($\leq 27\%$)¹⁾ as compared with those with the chiral center at the 3-position.

Here, we described the high stereoselectivities achieved with the novel NADH model compound **1** in which L-prolinamide was introduced in the N_1 -substituent.

Preparation Scheme.

Typically, a solution of the model reductant **1** (40 mg, 0.1 mmol), the substrate ethyl benzoylformate (17 mg, 0.1 mmol) and dry magnesium perchlorate (10.7 mg, 0.05 mmol) in dry acetonitrile (20 ml) was stirred at room temperature for 14 hr. The usual work-up²⁾ of the reaction mixture afforded pure ethyl man-

FIG. 1. Optical (—) and Chemical (-----) Yields in the Asymmetric Reduction of Ethyl Benzoylformate by the Models **1** (○), **2** (□) and **3** (●) with a Varying Amount of Magnesium Perchlorate.

delate in a 39% chemical yield and 90% *e.e.* (Fig. 1). The optical yield was the highest among these recorded so far with mono (NADH) models in which the chirality does not reside at the reaction center.³⁾ Of particular interest is that an excellent stereoselectivity was observed even with the model carrying the chiral center in an N_1 -substituent far removed from the reaction site. Such a remote asymmetric induction constitutes an interesting example in the field of asymmetric synthesis. To understand the mechanism of the remote asymmetric induction, another system involving the achiral model **2** in the presence of the chiral fragment from the chiral reductant **1** was examined. In this system, significant *e.e.*'s (26%) were obtained by *intermolecular* transmission of the asymmetry from the chiral fragment to the reductant and then to the product or *via* some complex involving the reductant, L-prolinamide fragment, magnesium ion and/or the substrate, since interaction of ethyl benzoylformate with the metal ion is imperceptible by UV and ¹³C NMR.

However, the *e.e.*'s obtained here were found to be considerably lower than those

Scheme for Model Structures.

observed with model 1. Thus, it can be safely concluded that the high stereoselectivity exhibited by model 1 is ascribed to a sort of *intramolecular proximity effect* on the asymmetric transmission from prolinamide to the reaction site mediated by chelation with metal ions. This deduction is further supported from the chelative property⁴⁾ of model 1 with a metallic ion, as revealed by the significant changes in UV⁵⁾ and ¹³C NMR spectra (Table I) by the addition of magnesium perchlorate to a solution of the model in acetonitrile.

Another NADH model 3 was prepared, in which L-proline ethyl ester was introduced at the 3-position of the dihydropyridine in place of L-prolinamide. Asymmetric reduction of ethyl benzoylformate afforded (*S*)-ethyl mandelate in a 21~26% *e.e.* This is in marked contrast to those reported^{3d,6)} with other *C*₁-symmetric models which carry L-prolinamide at the 3-position of the dihydropyridine and gave unexceptionally the (*R*)-enantiomer in preponderance.

In the present NADH model systems, satisfactory stereoselectivity as well as the product of opposite configurations were obtained under mild conditions, and the remote asymmetric induction presented here could provide information concerning the factors which control the product stereochemistry.

TABLE I. ¹³C NMR DATA OF MODEL 1 (ppm from TMS)

Carbon	Mg(ClO ₄) ₂ /1 (mol ratio)		$\Delta\delta$
	0.0	1.0	
-CONH ₂	175.63	177.38	+1.75
-CONH-	172.99	176.44	+3.45
-CON<	168.66	169.37	+0.71

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