

Highly Enantioselective Synthesis of Optically Active Hydroxyaldehydes Using a Chiral Catalyst

Kenso Soai,* Hiroshi Hori, and Masato Kawahara

Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Shinjuku, Tokyo, 162, Japan.

(Received 19 October 1990)

Abstract: Optically active hydroxyaldehydes are synthesized in 88-94% e.e. by the catalytic enantioselective addition of dialkylzinc using *N,N*-dibutylnorephedrine.

Optically active hydroxyaldehydes are versatile synthetic intermediates.¹ However, tedious steps are required for their synthesis because of the exceeding reactivity of the aldehyde group, and only limited methods have been reported on the asymmetric synthesis of hydroxyaldehydes.²

On the other hand, increasing interest has been centered on liquid crystals.³ Most liquid crystals possess a rigid chain (mesogen group), and a flexible polar group. Optically active hydroxyaldehydes possessing the structure of (**3**) are potentially useful chiral building blocks for the formation of liquid crystals. The reasons are as follows: (i) **3** has a chiral center, (ii) the aldehyde group can be converted to azomethine to form an aromatic linear rigid chain (mesogen group), (iii) a polar flexible group such as an ester and an ether can be formed with alcohol of **3**. Although racemic **3** has been prepared by the oxidation of the diol,⁴ no report has appeared on the asymmetric synthesis of **3**.

We wish to report a highly enantioselective catalytic asymmetric synthesis of optically active **3** by the enantioselective addition of dialkylzinc reagents to 4-(diethoxymethyl)benzaldehyde (**1**)^{5a} using *N,N*-dibutylnorephedrine (DBNE)⁶ as a chiral catalyst. When **1** was reacted with diethylzinc using (1*R*,2*S*)-(+)-DBNE (10 mol %), the corresponding hydroxyacetal (**2b**) was obtained. Hydroxyacetal **2b** was relatively unstable, and the subsequent acidic hydrolysis afforded (*R*)-(+)-**3b**⁷ of 94 % e.e. (determined by HPLC analysis using a chiral column) in 76 % isolated overall yield. Generality of the present method is shown in the

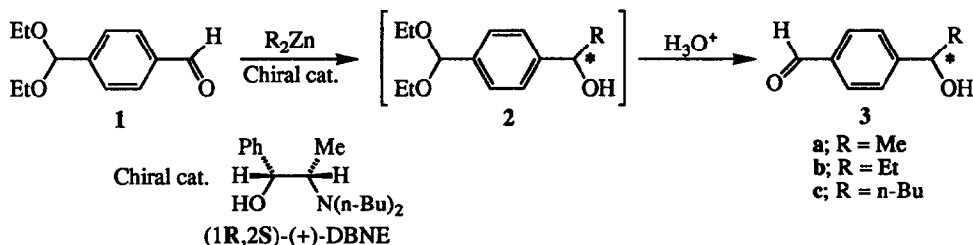


Table Catalytic asymmetric synthesis of hydroxyaldehydes (**3**) using DBNE

| Entry | R ₂ Zn | Time(h) | [α] _D | (R)- 3a | | Yield (%) ^b | E.e. (%) ^c |
|-------|------------------------|---------|------------------|--------------------------------------|--------|------------------------|-----------------------|
| | | | | (c, CHCl ₃) | | | |
| 1 | Me ₂ Zn | 41 | a | [α] _D ²⁴ +50.2 | (3.11) | 74 | 88 |
| 2 | Et ₂ Zn | 7 | b | [α] _D ²⁶ +37.0 | (1.18) | 76 | 94 |
| 3 | (n-Bu) ₂ Zn | 15 | c | [α] _D ²⁶ +29.7 | (2.76) | 60 | 91 |

a) For the assignment of configuration, see the text. b) Isolated total yield from **1**.
c) Determined by HPLC analyses using a chiral column (Chiralcel OB).

asymmetric synthesis of **3a** and **3c**. When Me₂Zn and (n-Bu)₂Zn were employed, (+)-**3a** and **3c** were obtained in 88 and 91 % e.e.'s respectively (Table). Using the appropriate enantiomer of DBNE,^{5b} either enantiomer of **3a-c** desired can be synthesized.

In a typical experiment, Et₂Zn (2.1 mmol, 2.1 ml of 1M hexane solution) was added to an ice-cooled mixture of **1** (1.0 mmol) and (+)-DBNE (0.026 g, 0.1 mmol) in hexane (1 ml). The mixture was stirred at r.t. for 7 h, and was quenched with water. The resulting precipitate was filtered off using celite, and the filtrate was extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated. Crude **2b** was hydrolyzed with 1 M HCl (at r.t., 15 h), extracted with ethyl acetate, and dried over sodium sulfate. Purification by silica gel TLC (CHCl₃/MeOH = 50/1) afforded (+)-**3a** (95%).⁸

As described, the present method provides a convenient catalytic path to optically active hydroxyaldehydes.⁹

References and Notes

- For the application to polyoxygenated natural products, see S. Masamune, M. Hirama, S. Mori, S.A. Ali, and D.S. Garvey, *J. Am. Chem. Soc.*, 1981, **103**, 1568.
- (a) T. Mukaiyama and N. Iwasawa, *Chem. Lett.*, 1982, 1903; (b) N. Iwasawa and T. Mukaiyama, *ibid.*, 1983, 297.
- Reviews. R. Zentel, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1407; R. Eidenschink, *ibid.*, 1989, **28**, 1424.
- S. Kanemoto, H. Tomioka, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 105.
- (a) Available from Aldrich Chemical Co.; (b) Both enantiomers are available from Tokyo Kasei Co.
- (a) K. Soai, S. Yokoyama, K. Ebihara, and T. Hayasaka, *J. Chem. Soc., Chem. Commun.*, 1987, 1690; (b) K. Soai, T. Hayasaka, and S. Ugajin, *ibid.*, 1989, 516; (c) K. Soai, S. Yokoyama, T. Hayasaka, and K. Ebihara, *Chem. Lett.*, 1988, 843.
- Configuration is tentatively assigned. Using (1*S*,2*R*)-(-)-DBNE, R₂Zn reacts from the Si-face of simple aromatic aldehydes (such as benzaldehyde) to afford (S)-(-)-alcohols.^{6a}
- Satisfactory results were obtained for **3a-c** from ¹H-NMR, IR, and High Resolution MS spectra.
- Partial financial support by the Chisso Award in Synthetic Organic Chemistry, Japan, to K.S. is gratefully acknowledged.