Asymmetric Synthesis of Alcohols with Two Chiral Centres from a Racemic Aldehyde by the Selective Addition of Dialkylzinc Reagents using (1*S*,2*R*)-(−)-*N*,*N*-Dibutylnorephedrine and (*S*)-(+)-Diphenyl-(1-methylpyrrolidin-2-yl)methanol as Chiral Catalysts

Kenso Soai,* Seiji Niwa, and Toshihiro Hatanaka

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

Optically active alcohols with two chiral centres were obtained in up to 93% enantiomeric excess by the selective addition of dialkylzinc reagents to the racemic aldehyde, 2-phenylpropanal, using the title compounds as chiral catalysts.

Increasing interest has centred on catalytic asymmetric carbon–carbon bond-forming reactions.[1] Addition of dialkylzinc reagents to aldehydes is usually very slow, but β-aminoalcohol derivatives catalyse the addition of diethylzinc to benzaldehyde.[2] Although we[3] and others[4] have reported the enantioselective addition of dialklyzinc reagents to aldehydes, the structures of the alcohols prepared have been limited to those with a single chiral centre. In connection with the synthesis of alcohols with two chiral centres, the diastereoselective addition of organometallic reagents to racemic

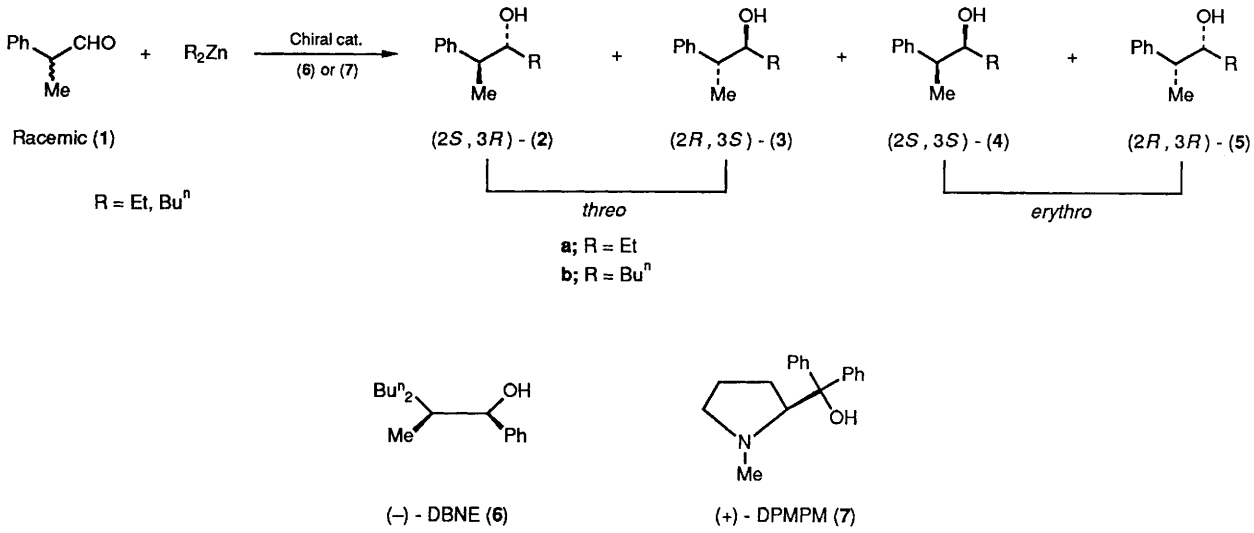

Table 1. Selective addition of R_2Zn to racemic (**1**) using (**6**) or (**7**) as chiral catalysts.

			Alcohols (**2**)—(**5**)						
						threo-[(**2**), (**3**)]		*erythro*-[(**4**), (**5**)]	
Entry	R	Catalyst		Yield[a]/%		E.e.[b]/%	Config.	E.e.[b]/%	Config.
1[c]	Et	(**6**)	**a**	60	(3.0)	93	(**3a**)	65	(**4a**)
2[c]	Bu^n	(**6**)	**b**	32	(5.0)	92	(**3b**)	84	(**4b**)
3[d]	Et	(**6**)	**a**	58	(4.3)	89	(**3a**)	73	(**4a**)
4[e]	Et	(**6**)	**a**	62[f]	(6.2)	76	(**3a**)	76	(**4a**)
5[c]	Et	(**7**)	**a**	63	(6.3)	68	(**3a**)	24	(**4a**)
6[g]	Bu^n	(**6**)	**b**	16[f]	(6.8)	75	(**3b**)	72	(**4b**)

[a] Isolated total yield of (**2**)—(**5**). Figures in parentheses are the ratio of *erythro*-[(**4**) and (**5**)] to *threo*-[(**2**) and (**3**)] determined by HPLC analyses. [b] Determined by HPLC analyses using a chiral column [Chiralcel OD, 250 mm; 254 nm UV detector; eluant 0.5% propan-2-ol in hexane; flow rate 0.4 ml/min; column temperature 35 °C]; retention time (min) 27.9, 30.9, 33.2, 39.5 for (**3a**), (**2a**), (**4a**), (**5a**), respectively; Chiralcel OJ, 250 mm; flow rate 0.5 ml/min; column temperature 20 °C; retention time (min) 29.8, 33.7, 38.9, 43.2 for (**4b**), (**3b**), (**2b**), (**5b**). Configurations were assigned by comparison with optically active authentic samples [(**2**)—(**5**)] prepared from optically active (*S*)-(**1**) and RMgBr (R = Et, Bu^n). [c] Mol ratio (**1**) : R_2Zn : catalyst, 1 : 2 : 0.1. [d] (**1**) : Et_2Zn : (**6**), 1 : 1 : 0.1. [e] (**1**) : Et_2Zn : (**6**), 1 : 0.5 : 0.05. [f] Based on R_2Zn. [g] (**1**) : $Bu^n{}_2Zn$: (**6**), 1 : 0.5 : 0.025.

2-phenylpropanal (**1**) without using optically active auxiliaries has been reported. However, these methods afford only racemic alcohols.[5]

We now report the first asymmetric synthesis of optically active alcohols with two chiral centres from the racemic aldehyde (**1**) by the addition of dialkylzinc reagents using (1*S*,2*R*)-(−)-*N*,*N*-dibutylnorephedrine (DBNE)[3b,c,e,6] and (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM)[3a,c,e,] as chiral catalysts.

Reaction of racemic (**1**) with diethylzinc (2 equiv.) in hexane at room temperature using 10 mol% of (−)-DBNE as a chiral catalyst afforded 2-phenylpentan-3-ol in 60% yield (*threo*/*erythro* 1/3.0). Among the two pairs of enantiomers, (2*S*,3*R*)-*threo*-(**2a**) and (2*R*,3*S*)-*threo*-(**3a**), and (2*S*,3*S*)-*erythro*-(**4a**) and (2*R*,3*R*)-*erythro*-(**5a**), (**3a**) predominated for the *threo*-isomers and (**4a**) for the *erythro*-isomers. The enantiomeric excess (e.e.) of (**3a**) and (**4a**) reached 93 and 65%, respectively (determined by HPLC analysis using a chiral column) (Table 1, entry 1).† Under slightly different conditions (1 equiv. of Et_2Zn), (**3a**) and (**4a**) were obtained in 89 and 73% e.e., respectively (entry 3).

In the reaction of $Bu^n{}_2Zn$ with racemic-(**1**) using (−)-DBNE as a chiral catalyst, 2-phenylheptan-3-ol (32%; *threo*/*erythro* 1/5.0) was obtained. HPLC analysis showed that *threo*-(**3b**) and *erythro*-(**4b**) were formed, predominantly in 92 and 84% e.e., respectively. This selectivity of the predomi-

† Typical experimental procedure. Racemic (**1**) (0.98 mmol) was added to a solution of (−)-DBNE (0.1 mmol) in hexane (1.3 ml) at room temperature. The mixture was cooled to 0 °C, and a solution in hexane (2 ml) of Et_2Zn (2.0 mmol) was added. The mixture was stirred at room temperature for 46 h. The reaction was quenched at 0 °C by the addition of HCl (1 M; 5 ml). The resulting mixture was extracted with CH_2Cl_2 (4 × 15 ml), dried (Na_2SO_4), and evaporated under reduced pressure, and was purified by silica gel TLC (eluant AcOEt–hexane, 1 : 5).

nant *threo*-isomer of (**3b**) in the alkylation may be explained as follows. Because both (**3**) and (**4**) are (3*S*)-alcohols, formation of these isomers is considered to be the result of the selective addition of R_2Zn to racemic (**1**) from the *Si*-face of the aldehyde (**1**), regardless of the configuration of (**1**).‡

Because both enantiomers of DBNE are available, it should be possible to synthesise either enantiomer of alcohols.

Received, 1st February 1990; Com. 0/00486C

References

1 Review: 'Asymmetric Catalysis,' ed. B. Bosnich, Martinus Nijhoff, Dordrecht, 1986.

2 T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *J. Am. Chem. Soc.*, 1979, **101**, 1455.

3 (a) K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111; (b) K. Soai, H. Hori, and S. Niwa, *Heterocycles*, 1989, **29**, 2065; (c) K. Soai, Y. Kawase, and S. Niwa, *ibid.*, 1989, **29**, 219; (d) K. Soai, S. Niwa, Y. Yamada, and H. Inoue, *Tetrahedron Lett.*, 1987, **28**, 4841; K. Soai, S. Niwa, and M. Watanabe, *J. Chem. Soc., Perkin Trans. 1*, 1989, 109; K. Soai and M. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1990, 43; (e) K. Soai, M. Watanabe, and M. Koyano, *ibid.*, 1989, 534, and references cited therein.

4 M. Yoshioka, T. Kawakita, and M. Ohno, *Tetrahedron Lett.*, 1989, **30**, 1657; N. N. Joshi, M. Srebnik, and H. C. Brown, *ibid.*, 1989, **30**, 5551; A. Oeveren, W. Menge, and B. L. Feringa, *ibid.*, 1989, **30**, 6427; M. Kitamura, S. Okada, S. Suga, and R. Noyori, *J. Am. Chem. Soc.*, 1989, **111**, 4028; K. Tanaka, H. Ushio, and H. Suzuki *J. Chem. Soc., Chem. Commun.*, 1989, 1700, and references cited in ref. 3e.

5 M. T. Reetz, S. H. Kyung, and M. Hullmann, *Tetrahedron*, 1986, **42**, 2931; S. Matsuzaka, M. Isaka, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, 1989, **30**, 1975; K. Maruoka, T. Itoh, and H. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 4573; Y. Yamamoto and J. Yamada, *ibid.*, 1987, **109**, 4395.

6 K. Soai, S. Yokoyama, T. Hayasaka, and K. Ebihara, *J. Org. Chem.*, 1988, **53**, 4148; K. Soai, T. Hayasaka, S. Ugajin, and S. Yokoyama, *Chem. Lett.*, 1988, 1571; K. Soai, T. Hayasaka, and S. Ugajin, *J. Chem. Soc., Chem. Commun.*, 1989, 516.

‡ This selectivity might be termed 'pseudo-enantioselectivity.' It should be noted that the conventional diastereoselective addition affords alcohols of different configuration of C-3 depending on the configuration of (**1**).