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

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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-amino-alcohol 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

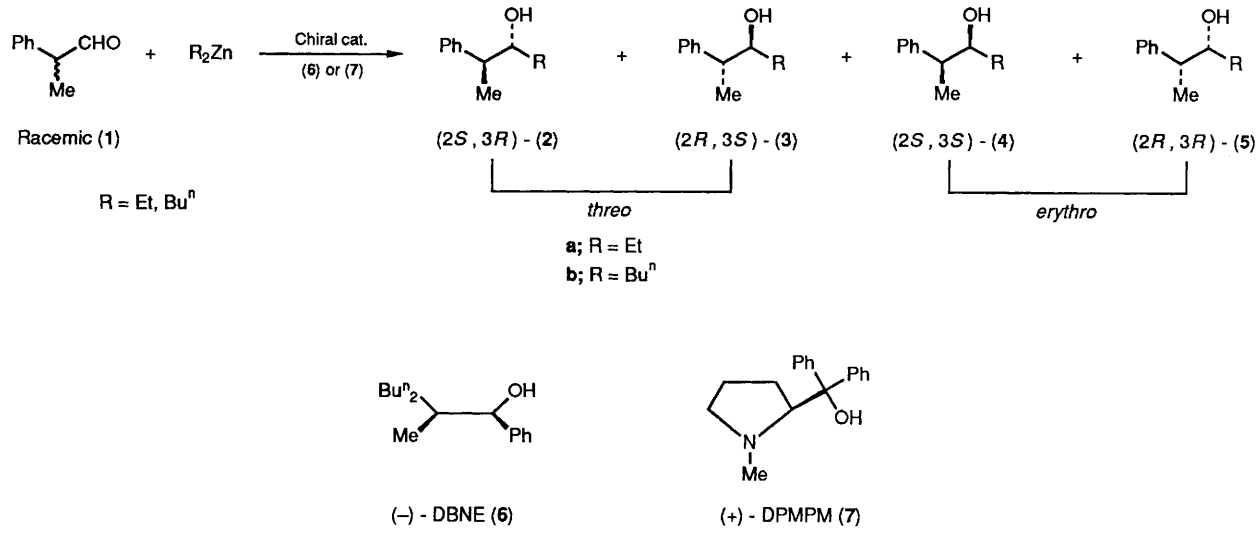

Table 1. Selective addition of R_2Zn to racemic (**1**) using (**6**) or (**7**) as chiral catalysts.

			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[e]	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.

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‡ 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**).