

# Asymmetric Synthesis of Optically Active Alcohols with Two Chiral Centres from a Racemic Aldehyde by the Selective Addition of Dialkylzinc Reagents Using Chiral Catalysts

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Optically active alcohols with two chiral centres have been obtained in good to high e.e.s (enantiomeric excesses) from racemic 2-phenylpropanal **1** by diastereo- and enantio-selective addition of dialkylzinc reagents using (1*S*,2*R*)-(–)-*N,N*-dibutylnorephedrine (DBNE) and (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) as chiral catalysts. It was found that in the presence of (1*S*,2*R*)-(–)-DBNE, dialkylzinc selectively attacked racemic **1** from the *Si*-face of the aldehyde **1** regardless of the configuration of **1** and that (*S*)-**1** reacted faster with dialkylzinc than did (*R*)-**1**.

Addition of organometallic reagents to carbonyl compounds has wide synthetic application. Thus, the asymmetric alkylation of chiral carbonyl compounds has been studied by many workers, and useful models for predicting their relative stereochemistry have been provided.<sup>1</sup> Among the chiral carbonyl compounds 2-phenylpropanal **1** has been extensively used as a fundamental indicator of the diastereoselectivity of 1,2-asymmetric induction (Cram's open-chain<sup>2</sup> and Felkin's<sup>3</sup> models) in addition reactions of organometallic reagents.

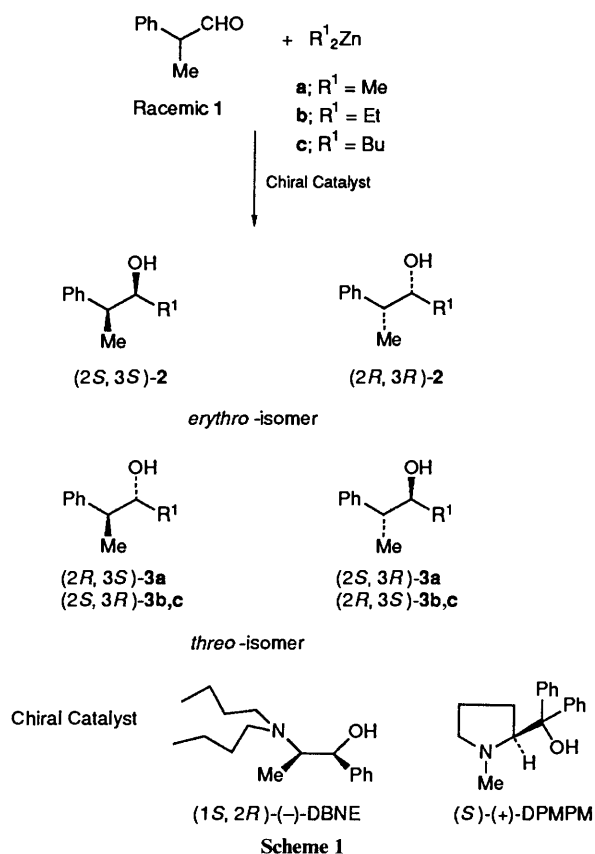
On the other hand, catalytic asymmetric carbon-carbon bond forming reactions have attracted much attention in organic synthesis.<sup>4</sup> The addition of dialkylzinc reagents to aldehydes are usually very slow, but a β-amino alcohol catalyses the addition of diethylzinc to benzaldehyde.<sup>5</sup> Although the enantioselective addition of dialkylzinc reagents to aldehydes has been reported, the alcohols prepared have been limited to those containing one chiral centre.<sup>6,7</sup> In connection with the synthesis of an alcohol with two chiral centres, the diastereoselective addition of organometallic reagents to racemic chiral 2-phenylpropanal **1** without using optically active auxiliaries has been reported. However, these methods afford only racemic alcohols.<sup>8,†</sup>

We report here the 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)<sup>6a</sup> and (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM)<sup>6b</sup> as chiral catalysts.<sup>10</sup>

## Results and Discussion

We examined the asymmetric synthesis of alcohols with two chiral centres from racemic 2-phenylpropanal **1** by the diastereo- and enantio-selective addition of dialkylzinc reagents using DBNE and DPMPM as chiral catalysts (Scheme 1).

The reaction of racemic **1** with diethylzinc (2 equiv.) in hexane at room temperature using 10 mol% of (1*S*,2*R*)-(–)-DBNE as a chiral catalyst afforded 2-phenylpentan-3-ol in 60% yield



(*erythro*:*threo* = 75:25) (Table 1, entry 2). Of the two pairs of enantiomers (2*S*,3*S*)-*erythro*-**2b**/(2*R*,3*R*)-*erythro*-**2b** and (2*S*,3*R*)-*threo*-**3b**/(2*R*,3*S*)-*threo*-**3b**,<sup>‡</sup> (2*S*,3*S*)-**2b** for the *erythro*-isomer and (2*R*,3*S*)-**3b** for the *threo*-isomer were found to be the predominant isomers, respectively. Enantiomeric excesses of **2b** and **3b** reached 65 and 93% e.e., respectively (determined by HPLC analysis using a chiral column).§ HPLC analysis also showed that the d.e.s (diastereoisomeric excesses) of alcohol from (*S*)-**1** and (*R*)-**1** were 97% (Cram selectivity) and 29% (anti-Cram selectivity), respectively. With (*S*)-(+)-DPMPM as a catalyst, diastereoselectivity was increased to 86:14 (*erythro*:*threo*), though enantioselectivity was lower than DBNE (entry 3).

In contrast, when 1 equiv. of Et<sub>2</sub>Zn was employed in the presence of (–)-DBNE (10 mol%), diastereoselectivity was

† We have reported the highly diastereoselective 1,2-asymmetric addition of dialkylzinc reagents to 2-phenylpropanal catalysed by achiral amino alcohols which predominantly produced racemic *erythro*-**2**.<sup>9</sup>

‡ The position numbers of the carbon to which the hydroxy groups are attached are 2 and 3 for **3a** and **3b, c**, respectively.

§ Authentic optically active **2** and **3** were prepared by the reaction of optically active (*S*)-**1** with Grignard reagents (*erythro*-isomer was formed predominantly as a result of Cram selectivity).<sup>2</sup>

**Table 1** Selective addition of  $R_2Zn$  to racemic **1** using (1*S*,2*R*)-(–)-DBNE or (*S*)-(+)-DPMPM as chiral catalysts

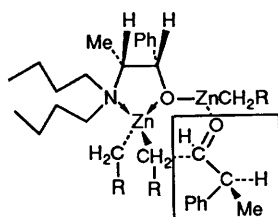
| Entry | $R_2Zn$ |        | Catalyst (equiv.) | Yield (%) <sup>b</sup> | <i>erythro</i> : <i>threo</i> <sup>a</sup><br>2:3 | E.e. (%) <sup>c</sup> |    |
|-------|---------|--------|-------------------|------------------------|---|-----------------------|----|
|       | R       | equiv. |                   |                        |   | 2                     | 3  |
| 1     | Et      | 2      | DBNE (0.05)       | 71                     | 73:27   | 67                    | 93 |
| 2     | Et      | 2      | DBNE (0.10)       | 60                     | 75:25   | 65                    | 93 |
| 3     | Et      | 2      | DPMPM (0.10)      | 63                     | 86:14   | 24                    | 68 |
| 4     | Et      | 0.5    | DBNE (0.025)      | 51 <sup>d</sup>        | 88:12   | 61                    | 72 |
| 5     | Et      | 2      | DBNE (0.2)        | 66                     | 71:29   | 70                    | 95 |
| 6     | Et      | 1      | DBNE (0.10)       | 58                     | 81:19   | 73                    | 89 |
| 7     | Et      | 0.5    | DBNE (0.05)       | 62 <sup>d</sup>        | 86:14   | 76                    | 76 |
| 8     | Me      | 2      | DBNE (0.10)       | 53                     | 80:20   | 68                    | 76 |
| 9     | Bu      | 2      | DBNE (0.10)       | 32                     | 83:17   | 84                    | 92 |
| 10    | Bu      | 0.5    | DBNE (0.025)      | 16 <sup>d</sup>        | 87:13   | 72                    | 75 |

<sup>a</sup> The ratio of *erythro*-**2** and *threo*-**3** were determined by HPLC analyses. <sup>b</sup> Isolated total yield of **2** and **3**. <sup>c</sup> For the determination of e.e.s, see the Experimental section. <sup>d</sup> Yields were based on  $R_2Zn$ .

**Table 2** Effect of reaction time in the selective addition of  $Et_2Zn$  to **1**<sup>a</sup>

| Entry          | Time   | Yield (%) <sup>b</sup> | <i>erythro</i> : <i>threo</i> <sup>c</sup> | E.e. (%) <sup>c</sup>                |                                      |
|----------------|--------|------------------------|--|--------------------------------------|--------------------------------------|
|                |        |                        |  | (2 <i>S</i> ,3 <i>S</i> )- <b>2b</b> | (2 <i>R</i> ,3 <i>S</i> )- <b>3b</b> |
| 1              | 3 min  | 17                     | 84:16                                      | 87                                   | 88                                   |
| 2              | 10 min | 32                     | 83:17                                      | 82                                   | 85                                   |
| 3              | 1 h    | 61                     | 77:23                                      | 78                                   | 93                                   |
| 4              | 3 h    | 69                     | 73:27                                      | 70                                   | 93                                   |
| 5              | 46 h   | 60                     | 75:25                                      | 65                                   | 93                                   |
| 6 <sup>d</sup> | 1 h    | 49                     | 81:19                                      | 80                                   | 87                                   |

<sup>a</sup> The reactions were carried out in hexane in the presence of (1*S*,2*R*)-(–)-DBNE at room temperature unless otherwise noted. Molar ratio, **1**: $Et_2Zn$ :DBNE = 1.0:2.0:0.1. <sup>b</sup> Isolated total yield. <sup>c</sup> Determined by HPLC analyses using chiral column. See footnote *d* of Table 1. <sup>d</sup> The reaction was carried out at 0 °C.



R = H, Me, Pr

**Fig. 1**

increased to 81:19 (Table 1, entry 6). The e.e. of *erythro*-**2b** increased to 73%, while the e.e. of *threo*-**3b** decreased to 89%.

As for the molar ratio of (–)-DBNE (Table 1, entries 1, 2 and 5), the e.e. of *threo*-**3b** reached 95% using 20 mol% of the catalyst (entry 5). In entries 5–7, the amount of aldehyde **1** was changed while the molar ratio of  $Et_2Zn$  and (–)-DBNE was constant. *erythro*-Selectivity and the e.e. of *erythro*-**2b** increased with an increase in the amount of **1**. For example, reaction of **1** and  $Et_2Zn$  in the molar ratio of 2:1 afforded **2b** and **3b** in 86:14, and the e.e. of **2b** reached 76% (entry 7). In contrast, the e.e. of *threo*-**3b** increased with a decrease in the amount of **1**.

In the reaction of  $Bu_2Zn$  with racemic-**1** under similar reaction conditions to entry 2 (Table 1), 2-phenylheptan-3-ol (32%, *erythro*:*threo* = 83:17) was obtained (entry 9). HPLC analysis showed that (2*S*,3*S*)-*erythro*-**2c** and (2*R*,3*S*)-*threo*-**3c** were predominantly formed in 84 and 92% e.e., respectively. Similarly, 3-phenylbutan-2-ol was obtained (53%, *erythro*:*threo* = 80:20) in 68% e.e. for (2*S*,3*S*)-*erythro*-**2a** and in 76% e.e. for (2*S*,3*R*)-*threo*-**3a** (entry 8).

For both *erythro*-**2** and *threo*-**3**, of the predominant isomers formed in the presence of (1*S*,2*R*)-(–)-DBNE, the configuration of the carbon atom to which the hydroxy group is attached, is *S* in all cases. Formation of a specific and predominant isomer is the result of selective addition of  $R_2Zn$  to (*S* and *R*) racemic-**1** from the *Si*-face of the aldehyde **1**, regardless of the configuration of **1**. This selectivity is in sharp contrast to the diastereoselectivity using an achiral catalyst<sup>9</sup> in which the face of the aldehyde attacked is determined by the configuration of **1**, i.e., *S*-**1** and *R*-**1** are attacked from the *Si*-face and *Re*-face, respectively. Thus, the sense of the addition of dialkylzinc to **1** is determined by the chiral catalysts and not by the configuration of **1**.

Next, the effect of reaction time was examined during the addition of diethylzinc to **1** using (–)-DBNE (10 mol%) as a catalyst (Table 2). The result showed that *erythro*-selectivity and the e.e. of *erythro*-**2b** were high when the reaction time was short. On the other hand, the e.e. of *threo*-**3b** was increased to 93% e.e. as the reaction proceeded. The relation between the reaction time and the yield of each enantiomer is shown in Table 3. The total yields of (2*S*,3*S*)-**2b** and (2*S*,3*R*)-**3b** are higher than those of (2*R*,3*R*)-**2b** and (2*R*,3*S*)-**3b**. This result suggests that, in the presence of (1*S*,2*R*)-(–)-DBNE, (*S*)-**1** reacted with  $Et_2Zn$  faster than did (*R*)-**1**.

We postulate that the reaction complex for the addition of diethylzinc to **1** in the presence of (1*S*,2*R*)-(–)-DBNE is that shown in Fig. 1. Dialkylzinc may be chelated to form a five-membered ring with nitrogen and oxygen atoms from the zinc alkoxide. The aldehyde **1**, regardless of the configuration, approaches from the opposite side of the phenyl and *C*-methyl groups of the five-membered chelation ring. The reaction may proceed *via* a six-centre mechanism. Thus, the (3*S*)-alcohol is predominantly formed. In addition, (*S*)-**1**, which has a lower steric hindrance than (*R*)-**1** in the reaction complex, reacts more rapidly to afford (2*S*,3*S*)-*erythro*-**2b**.

Because both enantiomers of DBNE are available, it should be possible to synthesize either enantiomer of the alcohols. The present method provides optically active alcohols with two chiral centres in good to high e.e.s even from a racemic aldehyde **1**.

## Conclusions

Optically active alcohols with two chiral centres were obtained in good to high e.e.s from the racemic 2-phenylpropanal by a diastereo- and enantio-selective addition of dialkylzinc using (1*S*,2*R*)-(–)-*N,N*-dibutylnorephedrine (DBNE) and (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) as chiral catalysts.

**Table 3** Relation between reaction time and the yield of each enantiomers<sup>a</sup>

| Entry | Time   | Total yield (%)<br>(2 + 3) | Yield <i>erythro</i> -2b (%) <sup>b</sup> |                           | Yield <i>threo</i> -3b (%) <sup>b</sup> |                           | Yield (%)  |  |
|-------|--------|----------------------------|---|---------------------------|---|---------------------------|--|--|
|       |        |                            | (2 <i>S</i> ,3 <i>S</i> )                 | (2 <i>R</i> ,3 <i>R</i> ) | (2 <i>R</i> ,3 <i>S</i> )               | (2 <i>S</i> ,3 <i>R</i> ) | (2 <i>S</i> ,3 <i>S</i> )-2b<br>+ (2 <i>S</i> ,3 <i>R</i> )-3b | (2 <i>R</i> ,3 <i>R</i> )-2b<br>+ (2 <i>R</i> ,3 <i>S</i> )-3b |
| 1     | 3 min  | 17                         | 13.3                                      | 1.0                       | 2.5                                     | 0.2                       | 13.5   | 3.5  |
| 2     | 10 min | 32                         | 24.1                                      | 2.4                       | 5.1                                     | 0.4                       | 24.5   | 7.5  |
| 3     | 1 h    | 61                         | 41.5                                      | 5.2                       | 13.8                                    | 0.5                       | 42.0   | 19.0   |
| 4     | 3 h    | 69                         | 42.9                                      | 7.7                       | 17.7                                    | 0.6                       | 43.5   | 25.5   |

<sup>a</sup> For the reaction conditions, see footnote *a* in Table 2. <sup>b</sup> Determined by HPLC analyses using a chiral column. See footnote *d* in Table 1.

## Experimental

**General.**—HPLC analyses were carried out with a Shimadzu LC-6A. Hexane was distilled over lithium aluminium hydride. All the reactions were performed under an argon atmosphere. 2-Phenylpropanal **1** was purchased from Tokyo Kasei, Inc. Diethylzinc (hexane solution) was purchased from Kanto Chemical Co. Dibutylzinc was prepared according to a literature procedure.<sup>11</sup>

**Typical Procedure for the Asymmetric Synthesis of Alcohols with Two Chiral Centres (Table 1, entry 2).**—Racemic **1** (131 mg, 0.98 mmol) was added to a solution of (–)-DBNE (26.5 mg, 0.1 mmol) in hexane (1.3 cm<sup>3</sup>) at room temperature. The mixture was cooled to 0 °C and a hexane solution of Et<sub>2</sub>Zn (1 mol dm<sup>-3</sup>; 2 cm<sup>3</sup>, 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 mol dm<sup>-3</sup>; 5 cm<sup>3</sup>). The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 15 cm<sup>3</sup>), and the extract dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure; the residue was purified by silica-gel TLC (AcOEt–hexane, 1:5 *v/v* as developing solvent). A mixture of 2-phenylpentan-3-ol (*erythro*-**2b** and *threo*-**3b**) was isolated in total 60% yield.

2-Phenylpentan-3-ol had  $\nu_{\max}/\text{cm}^{-1}$  3400, 3030, 2970, 1605, 1500 and 1460;  $\delta(\text{CDCl}_3)$  0.70–1.70 (8 H, m), 1.96 (1 H, s), 2.55–3.05 (1 H, m), 3.45–3.75 (1 H, m) and 7.33 (5 H, s).

When Bu<sub>2</sub>Zn was used instead of Et<sub>2</sub>Zn, 2-phenylheptan-3-ol (*erythro*-**2c** and *threo*-**3c**) was obtained in 32% yield (Table 1, entry 9).

2-Phenylheptan-3-ol had  $\nu_{\max}/\text{cm}^{-1}$  3400, 3030, 2960, 2930, 1605, 1500, 1460 and 1390;  $\delta(\text{CDCl}_3)$  0.70–1.70 (13 H, m), 2.55–3.05 (1 H, m), 3.45–3.75 (1 H, m) and 7.20 (5 H, s).

<sup>1</sup>H NMR and IR spectra of **2a–c** and **3a–c** were identical with those of authentic samples prepared by the reaction of **1** with EtMgBr. Retention times of HPLC analyses were identical with those of authentic samples.

**Determination of the Ratio of erythro-2 and threo-3 and Their Enantiomeric Excesses: Assignment of the Configurations.**—Ratios for *erythro*-**2** and *threo*-**3** were determined by HPLC analyses. Enantiomeric excesses were determined by HPLC analyses using a chiral column [Chiralcel OD 250 mm; 254 nm UV detector; eluent 0.5% propan-2-ol in hexane; flow rate 0.4 cm<sup>3</sup> min<sup>-1</sup>; column temperature 35 °C; retention time (min) 27.9, 30.9, 33.2, 39.5 for (2*S*,3*R*)-**3b**, (2*R*,3*S*)-**3b**, (2*S*,3*S*)-**2b**, (2*R*,3*R*)-**2b**, respectively]. [Chiralcel OJ 250 mm; eluent 0.5% propan-2-ol in hexane; flow rate 0.5 cm<sup>3</sup> min<sup>-1</sup>; column temperature 20 °C; retention time (min) 29.8, 33.7, 38.9, 43.2 for (2*S*,3*S*)-**2c**, (2*R*,3*S*)-**3c** and (2*S*,3*R*)-**3c**, (2*R*,3*R*)-**2c**, 63.9, 69.1, 74.9, 80.8 for (2*S*,3*R*)-**3a**, (2*R*,3*S*)-**3a**, (2*S*,3*S*)-**2a** and (2*R*,3*R*)-**2a**, respectively]. Configurations were assigned by the comparison with optically active authentic samples **2** and **3** prepared from optically active (*S*)-**1** and RMgBr (R = Me, Et, Bu).

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