

## Notes

**Asymmetric Synthesis of Chiral Secondary Alcohols with Isopropyl Substituents by the Catalytic Enantioselective Addition of Diisopropylzinc to Aldehydes using *N,N*-Dialkylnorephedrine as Chiral Catalysts**

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Catalytic enantioselective addition of dialkylzincs to aldehydes has attracted much attention for the asymmetric synthesis of secondary alcohols.<sup>1</sup> With regard to the structure of the dialkylzinc reagents employed, di-(primary alkyl)zincs such as diethylzinc has been the most often utilized in the reaction. Only scattered examples have been reported on the enantioselective addition of ( $\alpha$ -branched) di(secondary alkyl)zincs such as diisopropylzinc.<sup>2,3</sup> Recently the catalytic diastereoselective addition of diisopropylzinc to a chiral aldehyde using chiral catalysts was reported to afford Tacalcitol [(+)-(5*Z*,7*E*,24*R*)-9,10-secosteroid-5,7,10(19)-triene-1 $\alpha$ ,3 $\beta$ ,24-triol monohydrate (Bonalfa, an active vitamin D<sub>3</sub> drug)].<sup>3</sup> On the other hand, from the standpoint of the design of chiral catalysts, a chiral alcohol with a sterically bulky secondary substituent (isopropyl) shows higher asymmetric induction in an asymmetric autocatalytic reaction than that shown with primary substituent (ethyl).<sup>2b,c</sup> Thus, the importance of the enantioselective addition of diisopropylzinc to aldehydes is increasing.

We here report in detail the enantioselective addition of diisopropylzinc to aldehydes using (1*S*,2*R*)-*N,N*-dialkylnorephedrine **2** as chiral catalysts.

The effect of the structure of the chiral catalysts was examined in the enantioselective addition of diisopropylzinc to benzaldehyde. The ee's of (*S*)-2-methyl-1-phenylpropan-1-ol (**3a**) obtained by the addition of diisopropylzinc to benzaldehyde was found to depend upon the structure of the *N*-alkyl substituents of (1*S*,2*R*)-**2**. The results are shown in Table 1.

The ee of **3a** increased according to the increase in carbon number of the *N*-alkyl substituent (entries 1-3). The ee's are comparable among *N,N*-dipropyl-, dibutyl-, and dipentylnorephedrine (90.2-92.1% ee) (entries 3-5).<sup>4</sup>

(1) Reviews: Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(2) (a) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264. (b) Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982. (c) Soai, K.; Hayase, T.; Shimada, C.; Isobe, K. *Tetrahedron: Asymmetry*, **1994**, *5*, 789.

(3) Okamoto, M.; Tabe, M.; Fujii, T.; Tanaka, T. The 114th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March, 1994; Abstract No. 30[32]15-3.

(4) Ee was determined by HPLC analysis using a chiral column. In our previous paper,<sup>2a</sup> we have described the DBNE catalyzed synthesis of (*S*)-**3a** with 75% ee based on the reported value of the optical rotation (MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876). However, the ee must be higher as determined in the present experiment (Table 1, entry 4).

**Table 1. The Effect of the *N*-Alkyl Substituents of (1*S*,2*R*)-**2** as Chiral Catalysts in the Enantioselective Addition of Diisopropylzinc to Benzaldehyde**

entry <sup>a,b</sup>	<i>N</i> -alkyl substituent of <b>2</b> : R <sup>2</sup>	(S)- <b>3a</b>	
		yield (%)	ee (%)
1	Me	69.4	36.4
2	Et	71.9	88.1
3	<i>n</i> -Pr (DPNE)	72.9	92.1
4	<i>n</i> -Bu (DBNE)	72.7	90.7
5	<i>n</i> -pentyl	60.5	90.2
6	allyl	62.5	86.9
7	-(CH <sub>2</sub> ) <sub>4</sub> -	67.6	85.6
8	-CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> -	72.1	87.7

<sup>a</sup> Preparation of the chiral catalysts **2**. For entries 1-7, see ref 2a. For entry 8, see Soai, K.; Hatanaka T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097. <sup>b</sup> Reaction time was 24 h.

**Table 2. Effect of the Amount of Chiral Catalysts [(1*S*,2*R*)-DPNE] in the Enantioselective Addition of Diisopropylzinc to Benzaldehyde**

entry	mol % of DPNE	(S)- <b>3a</b>	
		yield (%)	ee (%)
1	5.0	58.9	85.0
2	10	72.9	92.1
3	20	77.6	93.0
4	40	84.9	94.0

However, it should be noted that the ee reached a peak (92.1% ee) when *N,N*-dipropylnorephedrine (DPNE) was employed. This observation contrasts with the result of the enantioselective addition of diethylzinc to aldehydes in which *N,N*-dibutylnorephedrine (DBNE) is the most enantioselective additive.<sup>2a,5</sup> DPNE is less bulky than DBNE. Because diisopropylzinc is more bulky than diethylzinc, the chiral complex between diisopropylzinc and DPNE may be more stable and more enantioselective than the chiral complex between diisopropylzinc and DBNE. Catalysts with cyclic substituents were less enantioselective (entries 7 and 8).

The effect of the amount of DPNE in the enantioselective addition of diisopropylzinc to benzaldehyde is shown in Table 2. When 10 mol % of DPNE was used, compound **3a** with 92.1% ee was obtained. The use of 20 and 40 mol % of DPNE affords **3a** with comparable (93.0-94.0% ee) ee's.

Enantioselective additions of diisopropylzinc to various aldehydes using DPNE or DBNE are summarized in Table 3. The  $\alpha,\beta$ -unsaturated aldehyde, cinnamaldehyde, was isopropylated to afford **3b** with 93.4 and 90.6% ee using DPNE and DBNE as chiral catalysts, respectively (entries 1 and 2).

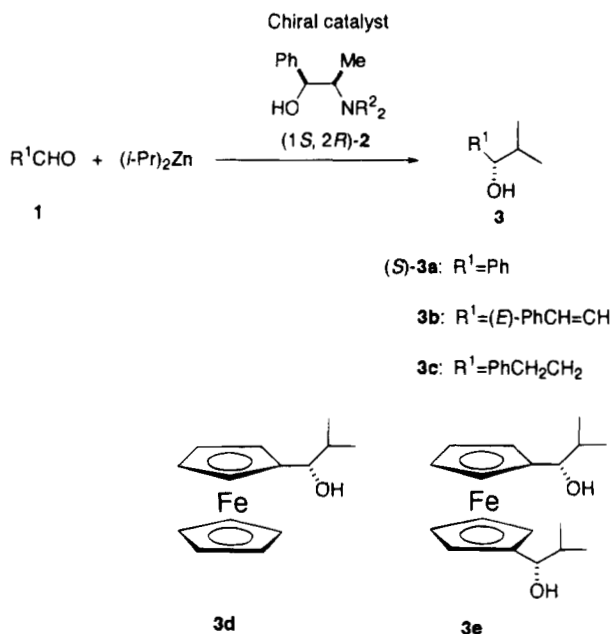
3-Phenylpropanal, which possesses an  $\alpha$ -methylene group, was isopropylated to afford **3c** with 96.1% ee (entry 3). Ferrocenecarbaldehyde was isopropylated to afford (1-hydroxy-2-methylpropyl)ferrocene (**3d**) with 97.0 and 97.7% ee using DPNE and DBNE as chiral catalysts, respectively (entries 4 and 5).<sup>6</sup> This adduct may become a synthetic intermediate for the preparation of optically

(5) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690.

**Table 3. Enantioselective Addition of Diisopropylzinc to Various Aldehydes Catalyzed by (1*S*,2*R*)-DPNE and DBNE**

entry	aldehyde 1	chiral catalyst	time(h)	alcohol 3		
				yield (%)	ee (%) <sup>a</sup>	
1	cinnamaldehyde	DPNE	6	<b>3b</b>	72.7	93.4
2	cinnamaldehyde	DBNE	6	<b>3b</b>	62.9	90.6
3	3-phenylpropanal	DPNE	2.5	<b>3c</b>	62.1	96.1
4	ferrocenecarbaldehyde	DBNE	3.5	<b>3d</b>	96.6	97.7
5	ferrocenecarbaldehyde	DPNE	3.5	<b>3d</b>	91.9	97.0
6	ferrocene-1,1'-dicarbaldehyde	DBNE	4	<b>3e</b>	39.3	100
7	ferrocene-1,1'-dicarbaldehyde	DPNE	4	<b>3e</b>	46.5	99.8

<sup>a</sup> Based on the results that chiral catalyst (1*S*,2*R*)-2 affords (*S*)-**3a**, configurations of **3b**–**e** are tentatively assigned as follows: (*S*)-**3b** and **3d**; (*R*)-**3c**; (*S*,*S'*)-**3e**.



active ferrocenylamine<sup>6b,7</sup> and the related chiral ferrocenylphosphine ligands.<sup>8</sup> It was also found that enantioselective addition of diisopropylzinc to ferrocene-1,1'-dicarbaldehyde<sup>9</sup> using DPNE and DBNE affords 1,1'-bis(1-hydroxy-2-methylpropyl)ferrocene (**3e**) with 99.8 and 100% ee, respectively. The compound **3e** is potentially useful for the preparation of ferrocene-based chiral crown ethers.<sup>10</sup>

### Experimental Section

A hexane solution of diisopropylzinc was purchased from Tri Chemical Inc. All reactions were carried out under an argon atmosphere.

(6) For the preparation of chiral 1-ferrocenylethanol and -propanol, (a) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19. (b) Matsumoto, Y.; A. Ohno, A.; Lu, S.; Hayashi, T.; Oguni, N.; Hayashi, M. *Tetrahedron: Asymmetry*, **1993**, *4*, 1763. (c) Nicolosi, G.; Patti, A.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 251. (d) Boaz, N. M. *Tetrahedron Lett.* **1989**, *30*, 2061.

(7) Gokel, G. W.; Ugi, I. K. *J. Chem. Ed.* **1972**, *49*, 294.

(8) Reviews: Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.

(9) Balavoine, G. G. A.; Doisneau, G.; Fillebeen-Khan, T. *J. Organomet. Chem.* **1991**, *412*, 381.

(10) Czech, B.; Ratajczak, A.; Nagraba, K. *Monatsh. Chem.* **1982**, *113*, 965.

**General Procedure for the Enantioselective Addition of Diisopropylzinc to Aldehydes Catalyzed by *N,N*-Dialkylferrocenylphosphines.** To a solution of a chiral catalyst (0.1 mmol, 10 mol %) in hexane (2 mL) was added an aldehyde (1 mmol) at room temperature. The mixture was stirred for 20 min, and was cooled to 0 °C. Diisopropylzinc (2.2 mL of a 1 M hexane solution, 2.2 mmol) was added to the mixture and was stirred for 2.5–6 h at 0 °C. The reaction solution was diluted by the addition of saturated aqueous NH<sub>4</sub>Cl (5 mL). The mixture was extracted with EtOAc. The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. Purification of the residue by silica gel TLC (developing solvent hexane/EtOAc = 5/1) afforded the corresponding optically active alcohols. The ee's of the obtained alcohols were determined by HPLC analyses using a chiral column as indicated.

**4-Methyl-1-phenyl-1-penten-3-ol (3b):** yield 72.7%, 93.4% ee (Table 3, entry 1). The ee was determined by HPLC analysis using a chiral column (CHIRALCEL OD).  $[\alpha]_D^{25.2} = +18.1^\circ$  (c 1.07, EtOH); IR 3400, 2800, 1380, 1360, 1000, cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz) δ 0.9 (q, 6H), 1.6–2.1 (m, 2H), 4.0 (t, 1H), 6.0–6.8 (m, 2H), 7.2 (m, 5H); HRMS calcd for C<sub>12</sub>H<sub>16</sub>O 176.1201, found 176.1213.

**2-Methyl-5-phenyl-3-pentanol (3c):** yield 62.1%, 96.1% ee (Table 3, entry 3). The ee was determined by HPLC analysis using a chiral column (CHIRALPAK AD).  $[\alpha]_D^{26.0} = +39.0^\circ$  (c 3.08 EtOH); IR 3400, 1400, 1350, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz) δ 0.9 (d, 6H), 1.5 (m, 4H), 2.9 (m, 2H), 3.5 (m, 1H), 7.1 (s, 5H); HRMS calcd for C<sub>12</sub>H<sub>18</sub>O 178.1358, found 178.1366.

**(1-Hydroxy-2-methylpropyl)ferrocene (3d):** Compound **3d** was synthesized according to the general procedure but using 3.0 mmol of diisopropylzinc and 0.2 mmol of chiral catalyst: yield 96.6%, 97.7% ee (Table 3, entry 4). The ee was determined by HPLC analysis using a chiral column (CHIRALCEL OD).  $[\alpha]_D^{24.5} = +86.1^\circ$  (c 0.99, benzene); IR 3500, 2950, 1380, 1360, 1100, 820 cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz) δ 0.9 (m, 6H), 1.7 (m, 1H), 2.1 (s, 1H), 4.2 (m, 10H); HRMS calcd for C<sub>14</sub>H<sub>18</sub>FeO 258.0707, found 258.0695; mp 33.3–33.5 °C.

**1,1'-Bis(1-Hydroxy-2-methylpropyl)ferrocene (3e):** Compound **3e** was synthesized according to the general procedure but using 5.0 mmol of diisopropylzinc and 0.5 mmol of the chiral catalyst: yield 39.3%, 100% ee (Table 3, entry 6). The ee was determined by HPLC analysis using a chiral column (CHIRALPAK AS).  $[\alpha]_D^{24.4} = +96.4^\circ$  (c 1.21, benzene); IR 3361, 2958, 1382, 1367, 1100, 811 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz) δ 0.8 (q, 12H), 1.7 (m, 2H), 3.4 (s, 2H), 4.2 (t, 10H); HRMS calcd for C<sub>18</sub>H<sub>26</sub>O<sub>2</sub>-Fe 330.1283, found 330.1278; mp 58.0–59.7 °C.

**Supplementary Material Available:** Copies of <sup>1</sup>H NMR spectra of **3b**–**e** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.