

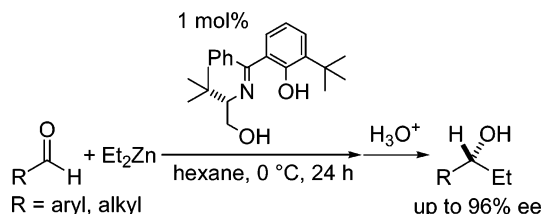
New Chiral Schiff Base as a Tridentate Ligand for Catalytic Enantioselective Addition of Diethylzinc to Aldehydes

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We have developed new chiral Schiff base catalysts for the enantioselective addition of diethylzinc reagents to aldehydes. The reaction of benzaldehyde with diethylzinc in the presence of 1 mol % of the chiral Schiff base catalyst proceeded to afford 1-phenyl-1-propanol in 96% enantiomeric excess (ee).

Since the first discovery by Oguni and Omi in 1984,¹ there have been many reports on enantioselective addition of dialkylzinc to aldehydes. Most of them are catalyzed by bidentate β -amino alcohol or its derivatives.^{2,3} To our knowledge, there are only three reports using tridentate ligands;⁴ furthermore, all of them afforded the alkylated products in lower enantiomeric excess (ee). For example, Corey and Hannon reported enantioselective ethylation of benzaldehyde catalyzed by a tridentate ligand derived from (+)-pseudoephedrine to give 1-phenyl-1-propanol in 87% ee.^{4a} In this paper, we report that our developed tridentate chiral Schiff base catalyzed the alkylation of aldehydes to give the alkylated products in high ee (up to 96% ee).⁵

The chiral Schiff bases used in our alkylation were prepared according to the procedure shown in Scheme 1. The crucial step was the oxidation of alcohol **2** to ketones **3**; that is, the conventional method using CrO₃ afforded ketones only in low

SCHEME 1. Synthesis of the Chiral Schiff Base

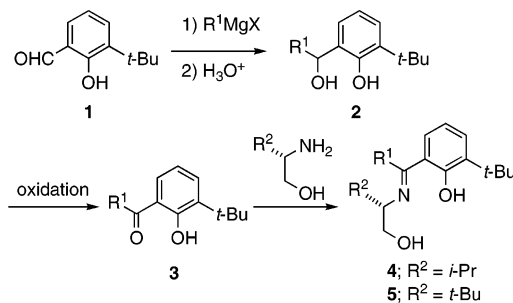


TABLE 1. Effect of Substituents in the Schiff Base on the Asymmetric Addition to Benzaldehyde^a

| entry | ligand | R ¹ | % yield ^b | % ee ^{c,d} |
|----------------|-----------|---|----------------------|---------------------|
| 1 | 4a | H | 36 | 18 |
| 2 | 5a | H | 53 | 21 |
| 3 | 4b | Me | 84 | 88 |
| 4 | 5b | Me | 90 | 94 |
| 5 | 4c | Ph | 95 | 90 |
| 6 | 5c | Ph | 94 | 96 |
| 7 | 4d | 4- <i>t</i> -Bu-C ₆ H ₄ | 90 | 86 |
| 8 | 4e | β -Np | 93 | 87 |
| 9 ^e | 5e | β -Np | 92 | 95 |

^a Conditions: PhCHO/Et₂Zn/Schiff base = 1.0:2.0:0.05, 0 °C, 24 h. ^b Determined by ¹H NMR analysis after silica gel column chromatography. ^c Determined by HPLC using a chiral OD-H column (DAICEL). ^d Absolute configuration was determined as *R* by comparison of the optical rotation values with those in the literature.⁹ ^e 1 mol % of Schiff base was used.

yield (25–35%) because of oxidative decomposition of the phenolic moiety. Fortunately, this oxidation problem was overcome by a hydrogen transfer reaction using a Pd/C–ethylene system.⁶ By the use of 30 wt % of 10% Pd/C under an ethylene atmosphere, we obtained a high yield (83%) of ketone in the case of R¹ = Ph. Thus, the obtained ketones **3** were condensed with chiral β -amino alcohols that are now prepared by direct reduction of α -amino acid as developed by Meyers⁷ and Abiko.⁸

We examined the reaction of benzaldehyde with diethylzinc in the presence of 5 mol % of chiral Schiff bases in hexane. Hexane or toluene was the choice for this reaction after screening of the solvent effect. The obtained results are summarized in Table 1. As shown in entry 6, the Schiff base **5c** derived from *L*-*tert*-leucinol and 3-*tert*-butyl-2-hydroxybenzophenone afforded (*R*)-1-phenyl-1-propanol in 94% yield and 96% ee. When the amount of chiral Schiff base **5c** was decreased to 1 mol %, the same level of chemical yield and enantiomeric excess were obtained (Table 2, entry 1).

The effect of the *tert*-butyl group at the ortho position on the phenolic hydroxy group should be mentioned. That is, in the case of the use of 5 mol % of Schiff base without a *tert*-butyl

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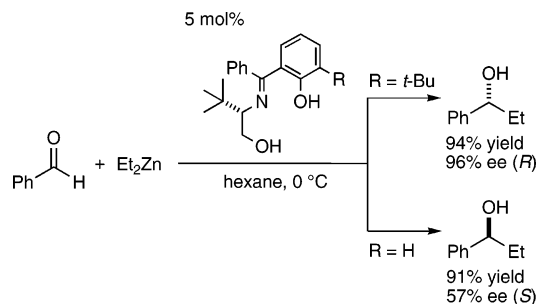
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SCHEME 2. Effect of the *tert*-Butyl Group at the Ortho Position on the Phenolic Hydroxy Group

TABLE 2. Asymmetric Addition to Various Aldehydes^a

| entry | R | % yield ^b | % ee ^{c,d} |
|-------|--|----------------------|---------------------|
| 1 | Ph | 88 (86) | 96 (95) |
| 2 | 4-Cl-C ₆ H ₄ | 92 | 90 |
| 3 | 4-MeO-C ₆ H ₄ | 96 (90) | 80 (84) |
| 4 | (<i>E</i>)-PhCH=CH | 69 (55) | 75 (76) |
| 5 | PhC≡C | 85 | 60 |
| 6 | PhCH ₂ CH ₂ | 75 (81) | 81 (83) |
| 7 | <i>n</i> -C ₅ H ₁₁ | 45 | 81 ^e |
| 8 | <i>c</i> -C ₆ H ₁₁ | 67 | 94 ^e |
| 9 | 2-furyl | 82 | 90 ^e |
| 10 | 2-thienyl | 99 | 95 ^e |

^a Conditions: RCHO/Et₂Zn/Schiff base = 1.0:2.0:0.01, 0 °C, 24 h. The values in parentheses indicated the one when toluene was used as a solvent. ^b Isolated yield after Kugelrohr distillation. ^c Determined by HPLC analysis using a chiral OD-H column (DAICEL). ^d All absolute configurations were determined as *R* by comparison of the optical rotation values with those in the literature.⁹ ^e Determined by HPLC analysis of the corresponding benzoate using a chiral AD-H column (DAICEL).

group at the ortho position, the opposite enantiomer *S* was obtained in 91% yield and 57% ee (Scheme 2). These results mean that from the single stereogenic center of *tert*-leucine both enantiomers were obtained in good to high ee in the case of R¹ = Ph (when 10 mol % of Schiff base without a *tert*-butyl group was used, 63% ee of the *S*-product was obtained in 90% yield).

We then examined the reaction of a variety of aldehydes with diethylzinc in the presence of 1 mol % of **5c** in hexane at 0 °C (Table 2). It should be noted that the present zinc–Schiff base catalyst system is effective not only for aromatic aldehydes but also for aliphatic aldehydes. For example, the reaction of cyclohexanecarbaldehyde with diethylzinc aided by 1 mol % of chiral Schiff base **5c** gave the ethylated product in 94% ee.¹⁰

We also examined the nonlinear effect (asymmetric amplification) in our zinc–Schiff base system. Actually, the nonlinear effect was observed as shown in Figure 1. The degree of amplification, however, is not so remarkable compared with the case of DAIB¹¹ and PDB.¹² It is ascertained that aggregation of the zinc species should participate in the catalytic cycle.

(9) For determination of the absolute configuration of the products. See Supporting Information.

(10) The reaction of dimethylzinc with benzaldehyde in the presence of 5 mol % of **5c** in hexane afforded (*R*)-1-phenylethanol in 72% yield and in 64% ee (30 °C, 24 h).

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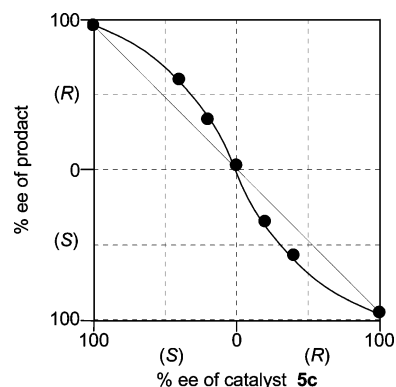


FIGURE 1. Nonlinear effect in the catalytic enantioselective ethylation of benzaldehyde in the presence of **5c**. Conditions: PhCHO/Et₂Zn/Schiff base = 1.0:2.0:0.01, 0 °C, 24 h. The ee was determined by HPLC using a chiral OD-H column (DAICEL).

In the cases of DAIB and PDB reported by the Noyori¹¹ and Oguni¹² groups, the difference in stability between the heterodimeric zinc complex and the homodimeric zinc complex was explained; that is, the easiness of dissociation in the presence of aldehydes caused a high nonlinear effect.

However, in our tridentate ligand case, the origin of the observed nonlinear effect is unclear at present and is now under investigation.

As for the reaction mechanism, we carefully confirmed by ¹H NMR analysis that two of the ethyl groups in diethylzinc reacted with both hydroxy groups in Schiff base (phenolic and amino alcohol) resulting in the disappearance of the ethyl groups in diethylzinc. Therefore, the ethyl groups should add to aldehyde activated by the chiral zinc Schiff base as an ethyl transfer from diethylzinc.

Experimental Section

Oxidation of Alcohol 2 by the Pd/C–Ethylene System. A dry Schlenk tube under an ethylene atmosphere was charged with alcohol **2** (R¹ = Ph, 3.9 g, 15.2 mmol) and acetonitrile (20 mL). To this mixture was added 10% Pd/C (1.17 g). The mixture was stirred vigorously at 80 °C for 7 h under an ethylene atmosphere using a balloon (1 atm). After confirmation of completion of the reaction by TLC, the palladium precipitate was filtered off. After removal of the solvent, the residue was column chromatographed on silica gel using hexane as an eluent to afford the corresponding ketone **3** (R¹ = Ph, 3.2 g, 12.6 mmol, 83%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.47 (s, 9H), 6.79 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.50 (m, 2H), 7.57 (s, 1H), 7.66 (d, *J* = 6.8 Hz, 1H), 12.9 (brs, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ 29.2, 34.9, 119.2, 120.6, 132.0, 134.1, 138.2, 161.2, 197.2.

General Procedure for Asymmetric Ethylation (Table 2). To a solution of chiral Schiff base (0.018 mmol) in solvent (4 mL) at –40 °C was added diethylzinc (0.37 mL, 3.6 mmol). The solution was warmed to 0 °C, stirred for 30 min, and then cooled to –40 °C again, when aldehyde (1.8 mmol) was added. The mixture was stirred for 24 h at 0 °C and was then quenched by 1 N HCl aq (20 mL). After extraction with diethyl ether (20 mL × 3), silica gel column chromatography [eluent, hexanes–ethyl acetate (10:1)], and Kugelrohr distillation, a product was obtained. The ee was determined by HPLC analysis using a chiral column.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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