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Stereocontrolled Enantioselective Addition of Diethylzinc to Aldehydes Using New Chiral Aminoalcohols

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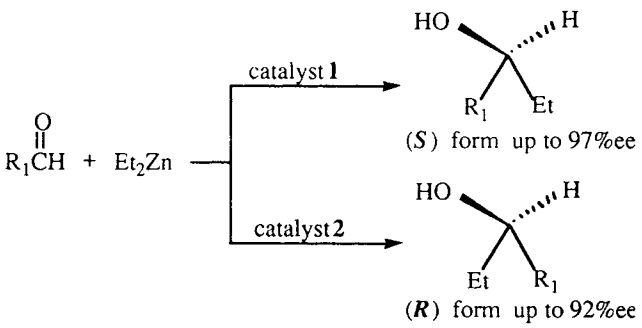
ABSTRACT

The new chiral β-aminoalcohols of indolinylmethanols (**1**) *and their reduced derivatives* (**2**) *were synthesized from* (S)*-indoline-2-carboxylic acid. Both* (R) *and* (S) *enantiomers of the optically active secondary alcohols have been successfully obtained in high enantiomeric excess from the stereoselective addition of diethylzinc to the aldehydes catalyzed by the chiral aminoalcohols* (**1** *and* **2**). *The sense of the asymmetric induction and the degrees of enantioselectivities turned out to be highly dependent on the structure of the catalysts: The presence of the catalyst* **1** *afforded the* (S)*-configuration of the corresponding alcohols; on the other hand, the presence of* **2** *afforded the* (R)*-configuration of the alcohols in high enantiomeric selectivity.*

INTRODUCTION

Intensive studies on the enantioselective addition of organometallic reagents to aldehydes using chiral ligands have been reported [1]. An asymmetric addition of the alkyl group of the dialkylzinc to aldehydes catalyzed by the chiral β-aminoalcohols has been developed for the preparation of optically active alkylated secondary alcohols. Various types of chiral β-aminoalcohols have been synthesized and examined as possible chiral ligands to provide an enantioselective addition of dialkylzinc to aldehydes [2–6]. Although several efficient catalysts that can convert aldehydes to the corresponding alcohols in high optical yields have been discovered, they provide one excess enantiomer of the chiral alcohols: Namely, most β-aminoalcohols of (*S*)-configuration afford (*S*)-configuration alcohols in enantiomeric excess. Even if (*S*)-β-aminoalcohols are used, if the structures of their derivatives are quite different and inhibit the same side approach of the aldehyde to a zinc complex intermediate due to their steric effects, the opposite (*R*)-alcohols can be formed in enantiomeric excess depending on the substituent effects of the (*S*)-β-aminoalcohols [4]. Thus, a series of new chiral β-amino alcohols (**1a**, **1b**, **2a**, and **2b**) were prepared from (*S*)-indoline-2-carboxylic acid and examined to determine whether they can bring about a stereocontrolled enantioselective ethylation of aldehydes.

In this article, we describe a remarkable reversal of enantiofacial selectivity in the asymmetric addition of diethylzinc to the aldehydes by use of the new catalysts of the chiral aminoalcohols (**1** and **2**) as shown in Scheme 1.



SCHEME 1

Dedicated with love and admiration to Professor Ernest L. Eliel on the occasion of his seventieth birthday.

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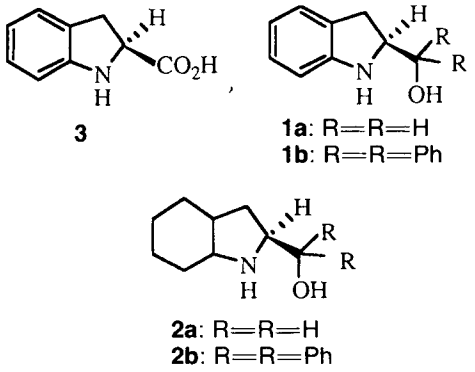
RESULTS AND DISCUSSION

A series of new chiral β-aminoalcohols (**1** and **2**) were synthesized from (*S*)-indoline-2-carboxylic acid (**3**):



To examine the effects of the structures of the catalysts, enantioselective addition of diethylzinc to benzaldehyde was carried out at 0 °C in the presence of a catalytic amount (5 mol%) of indolinylmethanol (**1** and **2**). Table 1 shows the relation between the enantiomeric excess of 1-phenylpropanol produced and the catalysts used. The chemical yields of 1-phenylpropanol were more than 90%. The effects of the structures of the (*S*)-β-aminoalcohol derivatives were compared in the asymmetric additions. The presence of the aminoalcohols (**1a** and **1b**) afforded (*S*)-1-phenylpropanol in enantiomeric excess. On the other hand, the presence of **2a** and **2b** afforded (*R*)-1-phenylpropanol in enantiomeric excess. As shown in Table 1, **1b** and **2a**, respectively, resulted in high optical yields of 1-phenylpropanol of the opposite configuration.

Catalysts **1b** and **2a** were chosen to examine the asymmetric ethylation of other aldehydes. The results are summarized in Table 2. As shown in Table 2, the presence of aminoalcohol **1b** led to high optical yields of (*S*)-secondary alcohols (96–97% ee), but the presence of **2a** led to high optical yields of (*R*)-secondary alcohols (90–92% ee).

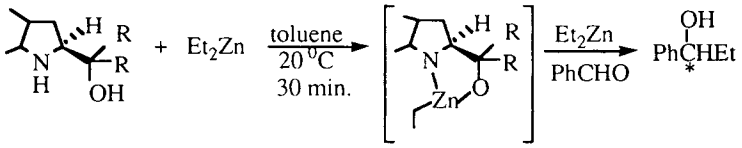
In Table 2, the chemical yields of the alcohols are almost all higher than 90%. It is the first time that such a high enantiomeric excess of the opposite (*R*)-ethylated alcohols from the (*S*)-β-aminoalcohols has been obtained. Even aliphatic 3-methylbutyraldehyde was ethylated in 76% ee. In general, asymmetric ethylation of 3-methylbutyraldehyde has been known to give a lower optical yield [4].

The asymmetric addition of diethylzinc to the aldehydes and a possible mechanism are illustrated in Figure 1. From Table 2, it is considered that the structures of **1b** and **2a**, which result in high enantioselective ethylations (*S*: 96% ee by **1b**, *R*: 90% ee by **2a**, respectively), play an important role in controlling the asymmetric induction.

As shown in Table 1, the steric effect of diphenyl groups in **1b** seems to be important in the formation of intermediate **I** by an *si* face approach of the aldehyde. The fact that the enantioselectivity from **1a** (*S*: 72% ee) when compared with that of **1b** (*S*: 96% ee) shows higher enantioselectivity for **1b** may be attributed to the larger steric effects of two bulky phenyl groups of **1b** (R = Ph). Thus, intermediate **I** seems to be more favorable than **I'**. The steric effect of the cyclohexyl group in **2a** appears to enforce the opposite side approach of the aldehyde (*re* side) to the zinc complex favoring the formation of **II**.

In the cases of **2a** and **2b** (Table 1) the presence of **2a** resulted in higher enantioselective induction (**2a**: *R*: 90% ee and **2b**: *R*: 56% ee). The low steric repulsion between the larger moiety (Ar) of the aldehyde substrate may also play an important role.

TABLE 1 Asymmetric Addition of Et_2Zn to Benzaldehyde



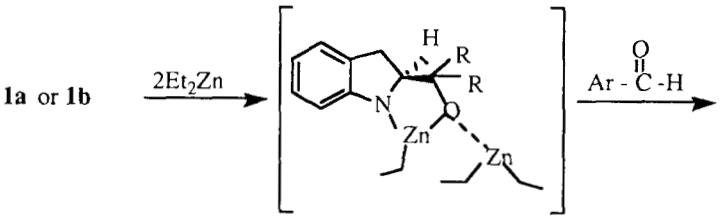
Aminoalcohol	Chemical yield (%)[a]	Optical yield (%ee)[b]	Configuration[c]
1a	96	72	*S*
1b	94	96	*S*
2a	94	90	*R*
2b	93	56	*R*

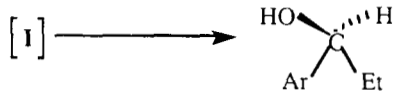
[a]Isolated yield.
[b]Determined by GC analysis of (−)-menthyloxycarbonyl derivatives using capillary OV-17 [8].
[c]Based on $[\alpha]_D$ [9].

TABLE 2 Asymmetric Addition of Et_2Zn to Aldehydes

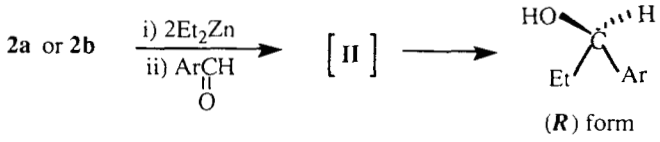
		Ethylated Products		
Aldehydes	*Aminoalcohols*	*% yield*[a]	$[\alpha]_D$, *deg (c, solvent)*	*% ee (confign)*[b]
Benzaldehyde	**1b**	94	−43.6 (5.1, $CHCl_3$) [9]	96 (*S*)[c]
	2a	93	+41.0 (5.2, $CHCl_3$) [9]	90 (*R*)[c]
4-Chlorobenzaldehyde	**1b**	93	−23.3 (5.2, C_6H_6)[10]	97 (*S*)
	2a	92	+26.1 (5, C_6H_6) [4]	92 (*R*)
4-Methoxybenzaldehyde	**1b**	95	−32.4 (5.1, C_6H_6)[10]	96 (*S*)
	2a	94	+32.8 (5, C_6H_6) [4]	90 (*R*)
(E)-Cinnamaldehyde	**1b**	91	−5.70 (3.2, $CHCl_3$) [2]	96 (*S*)
	2a	92	+5.9 (3.1, $CHCl_3$) [4]	91 (*R*)
3-Methylbutyraldehyde	**1b**	90	+16.1 (3.1, $CHCl_3$)[11]	76 (*S*)
	2a	89	−13.6 (4.0, $CHCl_3$)[11]	64 (*R*)

[a]Isolated yield.
[b]Based on $[\alpha]_D$ reported.
[c]Determined by GC analysis [8].

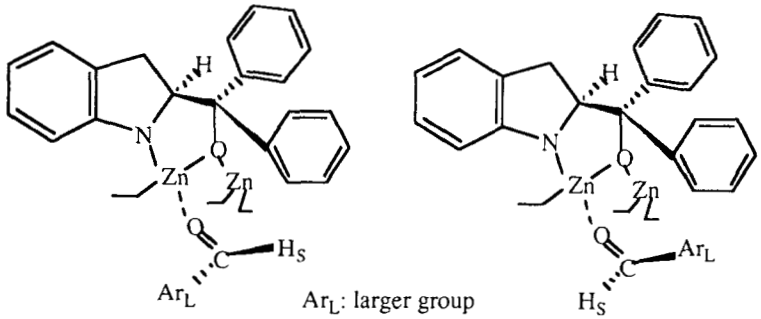




(*S*) form

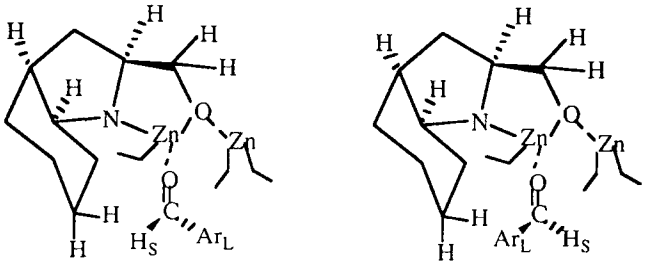


(*R*) form



I (*si* face)
favorable

I'
unfavorable



II (*re* face)
favorable

II'
unfavorable

FIGURE 1 Enantioselective Ethylation of Aldehydes

Thus, in the case of **2a**, intermediate **II** seems to be more favorable than **II'**.

In the asymmetric reduction of aryl alkyl ketones to alcohols using **1b** and **2a** in the presence of borane, the same results were obtained: from **1b**, a high optical yield of (*R*)-alcohols was obtained, but from **2a**, a high enantiomeric excess of (*S*)-alcohols [7] resulted.

In summary, the structure of the added β-aminoalcohols plays an essential role in stereocontrolling the asymmetric induction of the alkylation of aldehydes to give both isomers of the alcohols produced. In comparing **1a** with **2a**, the structure of **2a** is different from **1a** in that it has a cyclohexane ring moiety instead of a benzene ring as in **1a**. It is noteworthy that **2a**, which has the (*S*) configuration at the β-carbon, like **1a**, induced high enantioselectivity of the opposite (*R*) configuration of alcohols.

EXPERIMENTAL

^{1}H-NMR spectra were recorded with Varian T-60A, FT-80A,and Bruker AM-300 spectrometers. Infrared spectra were taken on a Perkin-Elmer Model 238B and Bomem MB-100 FT-IR spectrometer. Mass spectra were obtained on a Hewlett Packard GC/MS 5985B instrument. GLC analyses were performed on a Varian 3700 gas chromatography using an FID detecter. Optical rotations were taken on a Autopoll III automatic polarimeter using a 1-dm cell. Diethylzinc in toluene solution was purchased from Aldrich.

General Procedure for the Enantioselective Addition of Diethylzinc to Aldehydes Using Indolinylmethanol as Catalyst

The mixture containing chiral indolinylmethanol (0.02 mmol) and aldehyde (1.0 mmol) in toluene (5 mL) solution was stirred for 20 min and was cooled at 0 °C. Diethylzinc in toluene (1 M solution, 2.2 mL) was added to the ice-cooled mixture over a period of 5 min, and the mixture was stirred for an additional 4–24 h. HCl (1 M) was added to quench the reaction. The mixture was extracted with dichloromethane, and the extracts were dried and evaporated under reduced pressure. The residue was purified by use of a silica gel column. The synthetic yield was calculated at this stage. Optical rotation was measured after the isolated product was further purified by preparative LC. The product was identified by comparing the ^{1}H NMR and IR spectra with those of authentic samples. Experimental results are summarized in Tables 1 and 2. The chiral β-aminoalcohol was recovered in over 90% yield after usual workup of the dilute aqueous acid solution. Optical purities (% ee) were determined by GC analysis of the menthyloxycarbonyl ester, or by optical rotation.

(S)-*1-Phenylpropanol* $[\alpha]_D$ −43.6 (c 5.0, $CHCl_3$) (lit. [9] $[\alpha]_D$ −45.45 (c 5.15, $CHCl_3$)). Optical yield was determined by GC analysis of the corresponding menthyloxycarbonyl derivatives [8]: column, OV-17 capillary column, 0.25 mm × 25 m, carrier gas, N_2, column temperature, 170 °C; retention time (min) 7.57 (*S*) and 8.06 (*R*).

(S)-*1-(4-Chlorophenyl)propanol* $[\alpha]_D$ −23.28 (c 5.0, C_6H_6)(lit. [10] $[\alpha]_D$ −10.4 (c 5, C_6H_6) for (*S*)-1-(4-chlorophenyl-propanol in 43% ee).

(S)-*1-(4-Methoxyphenyl)propanol* $[\alpha]_D$ −32.40 (c 5.1, C_6H_6)(lit. [10] $[\alpha]_D$ −17.2 (c 5, C_6H_6) for (*S*)-1-(4-methoxyphenyl)propanol in 51% ee).

(S)-*1-Phenylpent-1-en-3-ol* $[\alpha]_D$ −5.70 (c 3, $CHCl_3$) (lit. [2] $[\alpha]_D$ −5.7 (neat $CHCl_3$) in 96% ee).

(*S*)-*5-Methylhexanol* $[\alpha]_D$ 16.1 (c 3, $CHCl_3$) (lit. [11] $[\alpha]_D$ 21.23 (neat)).

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