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Enantioselective addition of diethylzinc to aldehydes with novel chiral C_2-symmetric dimeric ligands

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Abstract

Novel (*S*)-valinol-based chiral C_2-2,2′-ethylenediiminodiethanol derivatives **4a** and **4b** have been synthesized and used as chiral catalysts in the enantioselective addition of diethylzinc to aldehydes. (*R*)-1-Phenylpropanol has been obtained in up to 91% enantiomeric excess.

Keywords: aldehyde; alkylation; organozinc; enantioselective; C_2-symmetric 2,2′-ethylenediiminodiethanol derivatives.

Development of catalytic asymmetric synthesis is important for synthetic chemistry.[1] In the past decade, a number of efficient chiral ligands have been reported in this field.[2] Among the possible reactions, catalytic enantioselective addition of organozinc to aldehydes is a typical reaction to construct a chiral center. A number of aminoalcohols,[3] diamines,[4] and diols[5] have been used successfully to promote this enantioselective reaction.

Uemura and co-workers demonstrated that chiral imines bearing a tricarbonylchromium group undergo highly diastereoselective coupling reactions with samarium diiodide to give coupling products in high chemical and optical yields.[6] Recently, we also succeeded in preparation of (*S*)-valinol-based chiral C_2-2,2′-ethylenediiminodiethanol (C_2-dimeric aminoalcohol) derivatives by a highly diastereoselective intermolecular pinacol-like coupling reaction using optically active imines and metallic samarium.[7] In this report, we describe the synthesis and use of novel chiral C_2-dimeric aminoalcohols as catalysts for the enantioselective addition of diethylzinc to aldehydes. We anticipated that enantioselective addition reaction of diethylzinc to arylaldehydes in the presence of a catalytic amount of C_2-dimeric aminoalcohols could occur to yield chiral aryl ethyl carbinol in high yields and high enantioselectivities.

The chiral compounds **2a** and **2b** were prepared according to our imine coupling method in 70–80% yield.[7] Compounds **3a** and **3b** were obtained in quantitative yield by five-membered ring formation with aqueous formaldehyde in methanol. Demethylation of these compounds gave the C_2-dimeric aminoalcohols **4a**[8] and **4b**[9] with BBr_3 in hexane–chloroform at room temperature in 70–80% yields

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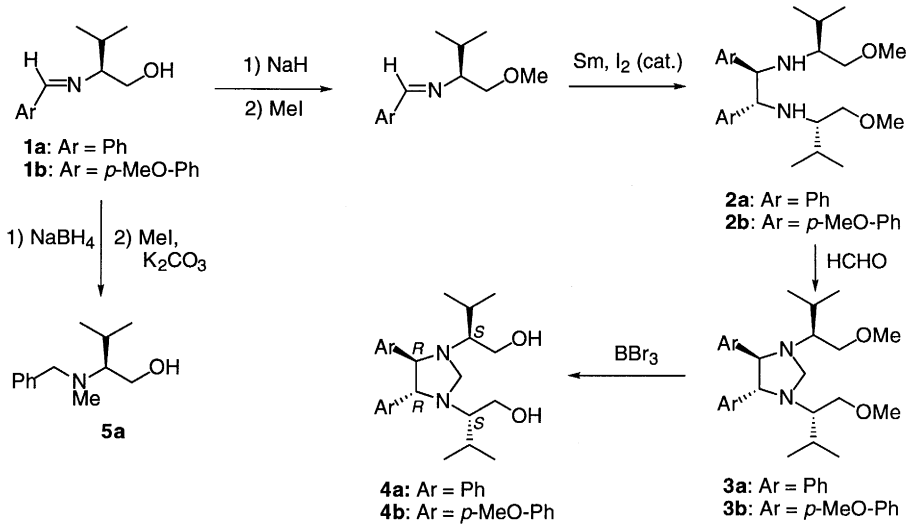
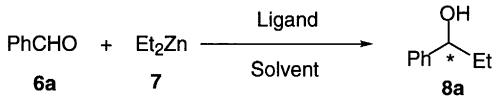
(Scheme 1). A monomeric ligand **5** was prepared in order to compare the difference in asymmetric induction ability between the C_2-dimeric aminoalcohol ligand **4a** and the monomeric ligand **5a**.



Scheme 1.

Table 1
Enantioselective addition of diethylzinc to benzaldehyde with chiral ligands[a]



Entry	Ligand	mol %	Solvent	Temp. (°C)	Time (h)	Yield (%)	ee (%)[b]
1	**4a**	5	Hexane	0	24	75	88 (*R*)
2	**4a**	5	Hexane	0	84	94	89 (*R*)
3	**4a**	1	Hexane	20	24	73	71 (*R*)
4	**4a**	5	Hexane	20	24	90	82 (*R*)
5	**4a**	10	Hexane	20	24	94	85 (*R*)
6	**4a**	10	Hexane	0	24	88	90 (*R*)
7	**4a**	10	Hexane	-20	24	53	84 (*R*)
8	**4a**	10	Toluene	20	24	77	79 (*R*)
9	**4a**	10	Toluene	0	24	69	85 (*R*)
10	**4b**	10	Hexane	0	40	97	91 (*R*)
11	**4b**	10	Toluene	0	40	82	87 (*R*)
12	**5a**	20	Hexane	0	24	84	10 (*R*)
13	**5a**	20	Toluene	0	24	87	13 (*R*)

[a] Reactions were carried out in 1 mmol scale. 2 equiv. of Et_2Zn hexane (or toluene) solution was used.
[b] Determined by HPLC analyses using DAICEL CHIRALCEL OD. In parentheses, configurations of product **8a** determined by comparison of the optical rotation value with the literature value were shown.

The enantioselectivity of chiral ligand-catalyzed reactions of benzaldehyde with diethylzinc was studied by varying the amount of catalyst, the temperature, and the reaction time. Exposure of benzaldehyde to diethylzinc (2 equiv.) and the chiral ligand **4a** (5 mol%) at 0°C for 24 h afforded alcohol **8a** in 75% yield and 88% ee (Table 1, entry 1). When the same reaction was run for 84 h under otherwise identical reaction conditions, the chemical yield was considerably improved (entry 2). The yield and enantiomeric excess of the reactions increased with an increase in the amount of the chiral catalyst **4a** (entries 3–5). The highest enantiomeric excess (90% ee) was realized by reacting in hexane at 0°C (compare entry 6

with entries 5 and 7). Hexane is the solvent of choice rather than toluene (compare entries 5 and 6 with entries 8 and 9). Next, we used the chiral ligand **4b** as a catalyst. The ligand **4b** also catalyzed the addition reaction effectively in hexane to afford (*R*)-1-phenylpropanol (97% yield, 91% ee) (entry 10). However, the chiral aminoalcohol **5a** was found to be a less effective catalyst. Thus, reaction of benzaldehyde with diethylzinc in the presence of 20 mol% of the ligand **5a** afforded an alcohol with only 10–13% ee (entries 12 and 13).

The substituents at the α- or β-position of chiral aminoalcohol play an important role in asymmetric induction.[2a,10] It is known that the α-position of aminoalcohol becomes more bulky, the degree of asymmetric induction becomes higher.[10] Thus far, the addition reaction of diethylzinc to benzaldehyde using chiral C_2-primary aminoalcohol gave 1-phenylpropanol in low to moderate enantiomeric excess.[3d,11] In spite of our ligands **4a** and **4b** having primary alcohol moiety, 1-phenylpropanol was obtained in high enantiomeric excess (90 and 91% ee). As shown in Fig. 1, the *anti*-transition state is predominant. The steric hindrance between the methylene bridge of the ligand and the hydrogen of the aldehyde carbon would disfavor a *syn*-transition state, leading to a decrease in the enantioselectivity. Consequently, it is thought that diethylzinc attacked predominantly from the *re*-face of benzaldehyde.

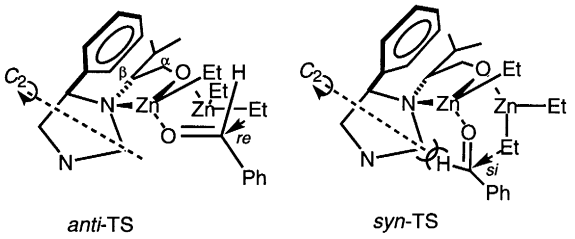
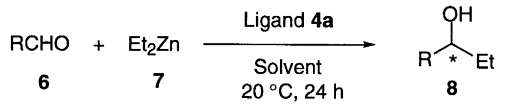


Fig. 1. Plausible mechanism of asymmetric induction using ligand **4a**

Table 2
Enantioselective addition of diethylzinc to aldehydes with chiral ligand **4a**[a]



6 **7** **8**

Entry	R		Solvent	Yield (%)	ee (%)[b]
1	Ph	**6a**	Hexane	94	85 (*R*)
2	Ph	**6a**	Toluene	77	79 (*R*)
3[c]	1-naphthyl	**6b**	Hexane	62	88 (*R*)
4	1-naphthyl	**6b**	Toluene	82	82 (*R*)
5	2-MeO-C_6H_4	**6c**	Toluene	91	77 (*R*)
6	4-MeO-C_6H_4	**6d**	Toluene	81	71 (*R*)
7	4-Cl-C_6H_4	**6e**	Toluene	55	77 (*R*)
8	*trans*-PhCH=CH	**6f**	Toluene	78	27 (*R*)
9	$PhCH_2CH_2$	**6g**	Toluene	30	33 (*R*)

[a] Reactions were carried out in 1 mmol scale. (Molar ratio **6a - g** : **7** : **4a** = 1.0 : 2.0 : 0.1).
[b] Determined by HPLC analyses using DAICEL CHIRALCEL OD. In parentheses, configurations of product **8a - g** determined by comparison of the optical rotation values with the literature values were shown.
[c] Reaction temperature was 0 °C.

The chiral ligand **4a** was found to be an effective catalyst in the addition reaction of diethylzinc to various aldehydes to afford good enantiomeric excess (Table 2, entries 1–7). Due to the low solubility of aldehydes to hexane, toluene was used as a solvent (entries 5–9). The reaction using aromatic aldehydes bearing an electron-donating group (**6c** and **6d**) increased the isolated yields. On the other hand, the reaction using aromatic aldehyde bearing an electron-withdrawing group (**6e**) reduced the isolated

yield. The reaction using α,β-unsaturated aldehyde (**6f**) or aliphatic aldehyde (**6g**) proceeded in low enantioselectivity.

Next, we examined an asymmetric amplification. A slightly positive non-linear relationship was observed between the enantiomeric excess of the product and the enantiomeric excess of the ligand **4a** in the addition reaction (Fig. 2).

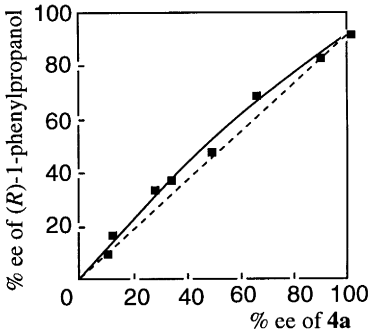


Fig. 2. Correlation between % ee of **4a** and % ee of (*R*)-1-phenylpropanol

In conclusion, this paper is the first report of high enantiomeric excess that was obtained in the reaction of diethylzinc to aromatic aldehyde using C_2-dimeric aminoalcohols **4a** and **4b** bearing primary alcohols. The good enantioselectivity apparently arises from their stereostructural rigidity and bulkiness.

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8. Compound **4a**: ^{1}H NMR ($CDCl_3$) δ: 0.83 (d, 6H, *J*=6.6 Hz), 1.01 (d, 6H, *J*=6.6 Hz), 1.75 (ddd, 2H, *J*=6.6, 6.6, 7.6 Hz), 2.42 (ddd, 2H, *J*=4.3, 7.3, 7.6 Hz), 3.76 (dd, 2H, *J*=7.3, 11.9 Hz), 3.84 (dd, 2H, *J*=4.3, 11.9 Hz), 4.09 (s, 2H), 4.27 (s, 2H), 7.13–7.25 (m, 10H).
9. Compound **4b**: ^{1}H NMR ($CDCl_3$) δ: 0.82 (d, 6H, *J*=6.9 Hz), 1.00 (d, 6H, *J*=6.6 Hz), 1.73 (m, 2H), 2.40 (ddd, 2H, *J*=4.3, 4.6, 7.6 Hz), 3.74 (dd, 2H, *J*=4.6, 11.9 Hz), 3.77 (s, 6H), 3.82 (dd, 2H, *J*=4.3, 11.9 Hz), 4.00 (s, 2H), 4.23 (s, 2H), 6.78 (d, 4H, *J*=8.9 Hz), 7.08 (d, 4H, *J*=8.9 Hz).
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