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Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Diastereomeric 1,4-Amino Alcohols with *o*-Xylylene Skeleton

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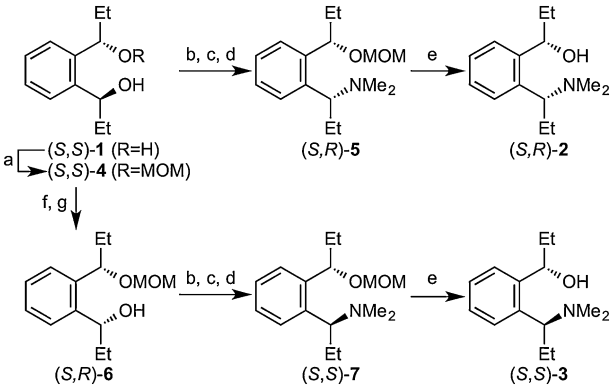
Two diastereomeric 1,4-amino alcohols with *o*-xylylene structure (*S*,*R*)-**2** and (*S*,*S*)-**3**, synthesized from chiral 1,4-diol (*S*,*S*)-**1**, were utilized as chiral ligands for the enantioselective addition of diethylzinc to aldehydes. The stereochemical outcome of the reactions was controlled solely by the absolute configuration of the benzylic carbon bearing amino group, and both enantiomers of 1-substituted propanol were obtained with up to 98% (*S*) and 96% (*R*) enantiomeric excesses.

Chiral 1,2- and 1,3-amino alcohols have been widely investigated as chiral ligands and chiral auxiliaries in various asymmetric transformations.[1] Catalytic enantioselective addition of organozinc compounds to aldehydes is a well-studied asymmetric reaction using amino alcohol ligands. Since the initial report by Oguni and Omi in 1984,[2] a number of chiral 1,2- and 1,3-amino alcohols have been utilized as chiral ligands in the reaction.[3–5] On the other hand, 1,4-amino alcohols have been less investigated and the induction of high levels of enantioselectivity is generally difficult owing to relatively flexible seven-membered chelate ring structures in active chiral catalysts prepared in situ from organozinc compounds and 1,4-amino alcohol ligands.[6] Previously, we reported the synthesis of a chiral 1,4-diol with *o*-xylylene structure, 1,2-bis(1-hydroxypropyl)benzene (**1**),[7] and the derivatization to a novel chiral *N*-heterocyclic carbene ligand[8a,8b] as well as its use in asymmetric reactions as chiral auxiliary.[8c,8d] We expected that 1,4-amino alcohols derived from **1** would form a rigid seven-membered chelate ring structure due to the *o*-xylylene backbone, and therefore should act as effective chiral ligands for various asymmetric reactions. Herein, we report the synthesis of two diastereomers of *o*-xylylene-type 1,4-amino alcohols (*S*,*R*)-**2** and (*S*,*S*)-**3**, and their use in the enantioselective addition of diethylzinc to aldehydes.

Novel diastereomeric 1,4-amino alcohols (*S*,*R*)-**2** and (*S*,*S*)-**3** were synthesized from enantiomerically pure 1,4-diol **1**[7] (Scheme 1). The selective methoxymethylation of one of the two benzylic hydroxy group of (*S*,*S*)-**1** by butyllithium and chloromethyl methyl ether afforded monomethoxymethyl ether (*S*,*S*)-**4** in 92% yield. Stereoinversion of the remaining hydroxy group of (*S*,*S*)-**4** by Mitsunobu azidation followed by the reduction of azide group and the stepwise methylation of the resulting primary amino group gave tertiary amine (*S*,*R*)-**5** in 71% yield from (*S*,*S*)-**4**. The methoxymethyl group of (*S*,*R*)-**5** was removed by treating with 4 M aqueous HCl to give 1,4-amino alcohol (*S*,*R*)-**2** in 81% yield. Similarly, 1,4-amino alcohol (*S*,*S*)-**3**, which is the diastereomer of (*S*,*R*)-**2** at the chiral carbon bearing amino group, was also synthesized from (*S*,*S*)-**1**. At first, the chiral carbon bearing free hydroxy group of (*S*,*S*)-**4** was inverted by the Mitsunobu esterification, and the hydrolysis

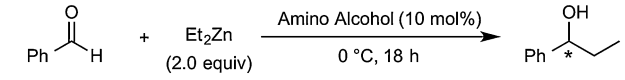


Scheme 1. Synthesis of diastereomeric 1,4-amino alcohols **2** and **3**. (a) *n*-BuLi, MOMCl, Et_2O, −78 °C to rt, 92%; (b) PPh_3, $EtO_2CN{=}NCO_2Et$, $(PhO)_2P(O)N_3$, THF, −20 °C or −20 °C to rt; (c) H_2, 10% Pd/C, MeOH, rt, then HCO_2Et, rt; (d) $LiAlH_4$, THF, reflux, then $(HCHO)_n$, H_2, 10% Pd/C, MeOH, rt, 71% from (*S*,*S*)-**4**, 62% from (*S*,*R*)-**6**; (e) 4 M aq. HCl, rt, 81% from (*S*,*R*)-**5**, 75% from (*S*,*S*)-**7**; (f) PPh_3, $EtO_2CN{=}NCO_2Et$, $PhCO_2H$, THF, −20 °C; (g) 4 M aq. NaOH, THF, rt, 70% from (*S*,*S*)-**4**.

of the resulting ester group afforded (*S*,*R*)-**6** in 70% yield. The alcohol (*S*,*R*)-**6** was then stereospecifically converted to (*S*,*S*)-**7** in 62% yield by using the same manner as the one used for the preparation of (*S*,*R*)-**5**, and the removal of the methoxymethyl group of (*S*,*S*)-**7** gave 1,4-amino alcohol (*S*,*S*)-**3** in 75% yield.

Enantioselective addition of diethylzinc to benzaldehyde was examined by using 1,4-amino alcohol (*S*,*R*)-**2**. In the presence of 10 mol % of (*S*,*R*)-**2**, benzaldehyde and 2.0 equivalents of diethylzinc in toluene were stirred at 0 °C for 18 h to give (*S*)-1-phenyl-1-propanol in 83% yield with high enantiomeric excess (96% ee, Table 1, Entry 1). After the screening of the reaction solvents (Entries 2–4), the best result was obtained by using Et_2O (84%, 97% ee, Entry 3).[9] The reaction was then examined by using 1,4-amino alcohol (*S*,*S*)-**3** in place of (*S*,*R*)-**2** under the same reaction conditions, and (*R*)-1-phenyl-1-propanol was obtained with almost the same enantioselectivity (95% ee, Entry 5). These results indicate that the enantioselectivity of the reaction is controlled solely by the absolute configuration of the benzylic carbon having an amino group, and the stereochemistry of another benzylic carbon bearing a hydroxy group has little influence on the stereochemical outcome of the reaction.[10] The results are in contrast with the results obtained by diastereomeric 1,2-amino alcohols where the enantioselectivity of the products was usually determined by a hydroxy-containing chiral carbon.[3,11]

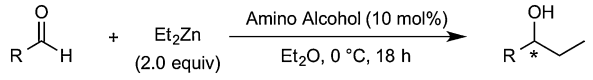
Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by 1,4-amino alcohols **2** and **3**



Entry	Solvent	Amino alcohol	Yield /%[a]	ee /%[b]
1	Toluene	(*S*,*R*)-**2**	83	96 (*S*)
2	Cyclohexane	(*S*,*R*)-**2**	86	73 (*S*)
3	Et_2O	(*S*,*R*)-**2**	84	97 (*S*)
4	THF	(*S*,*R*)-**2**	36	96 (*S*)
5	Et_2O	(*S*,*S*)-**3**	84	95 (*R*)

[a]Isolated yield. [b]Determined by HPLC analysis.

Table 2. Enantioselective addition of diethylzinc to various aldehydes catalyzed by 1,4-amino alcohols **2** and **3**



Entry	R	Amino alcohol	Yield /%[a]	ee /%[b]
1	2-BrC_6H_4	(*S*,*R*)-**2**	88	94 (*S*)
2		(*S*,*S*)-**3**	86	94 (*R*)
3	1-Naphthyl	(*S*,*R*)-**2**	85	95 (*S*)
4		(*S*,*S*)-**3**	78	95 (*R*)
5	2-$MeOC_6H_4$	(*S*,*R*)-**2**	92	95 (*S*)
6		(*S*,*S*)-**3**	87	92 (*R*)
7	4-$MeOC_6H_4$	(*S*,*R*)-**2**	67	87 (*S*)
8		(*S*,*S*)-**3**	78	88 (*R*)
9	*c*-C_6H_{11}	(*S*,*R*)-**2**	80	98 (*S*)
10		(*S*,*S*)-**3**	74	96 (*R*)
11	(*E*)-PhCH=CH	(*S*,*R*)-**2**	70	76 (*S*)
12		(*S*,*S*)-**3**	85	69 (*R*)
13	$PhCH_2CH_2$	(*S*,*R*)-**2**	86	80 (*S*)
14		(*S*,*S*)-**3**	95	77 (*R*)

[a]Isolated yield. [b]Determined by HPLC analysis.

As both enantiomers of 1-phenyl-1-propanol were obtained with high enantioselectivities by using the two diastereomeric 1,4-amino alcohols (*S*,*R*)-**2** and (*S*,*S*)-**3**, the reactions of various aldehydes were then examined (Table 2). In all cases, the corresponding chiral secondary alcohols with *S* and *R* configurations were obtained predominantly by using (*S*,*R*)-**2** and (*S*,*S*)-**3**, respectively. The reactions of aromatic aldehydes with bromo or methoxy groups, 1-naphthaldehyde, and cyclohexanecarboxaldehyde afforded the corresponding chiral secondary alcohols with high enantioselectivities, and the values of the enantiomeric excesses were almost the same between the reactions using (*S*,*R*)-**2** and (*S*,*S*)-**3** (Entries 1–10). Although the reported enantioselectivities of products were often low in the reactions of sterically less-hindered (*E*)-cinnamaldehyde and 3-phenylpropanal using 1,4-amino alcohols,[6] the corresponding products were obtained with good enantioselectivities by using (*S*,*R*)-**2** and (*S*,*S*)-**3** (Entries 11–14).

The proposed catalytic cycles and transition-state structures for the enantioselective addition using (*S*,*R*)-**2** or (*S*,*S*)-**3** are summarized in Figure 1.[6,12] Initially, the zinc catalyst **A** with a seven-membered ring is generated by the reaction of 1,4-amino alcohol ligand (*S*,*R*)-**2** or (*S*,*S*)-**3** with diethylzinc. In both cases, the most suitable conformation of the seven-membered ring would be a pseudo boat conformation for the coordination of another diethylzinc and aldehyde from the less hindered side of the complex to form a transition structure **B** and **C**. The ethyl group of the benzylic carbon bearing the amino group is thought to occupy the pseudo-equatorial position to avoid the steric hindrance of the dimethylamino group, and the absolute configuration of the benzylic carbon having a hydroxy group has little influence on the formation of the boat structure. As a result, both *S*- and *R*-chiral secondary alcohols should selectively be obtained from the transition state **B** and **C** generated from (*S*,*R*)-**2** and (*S*,*S*)-**3**, respectively.

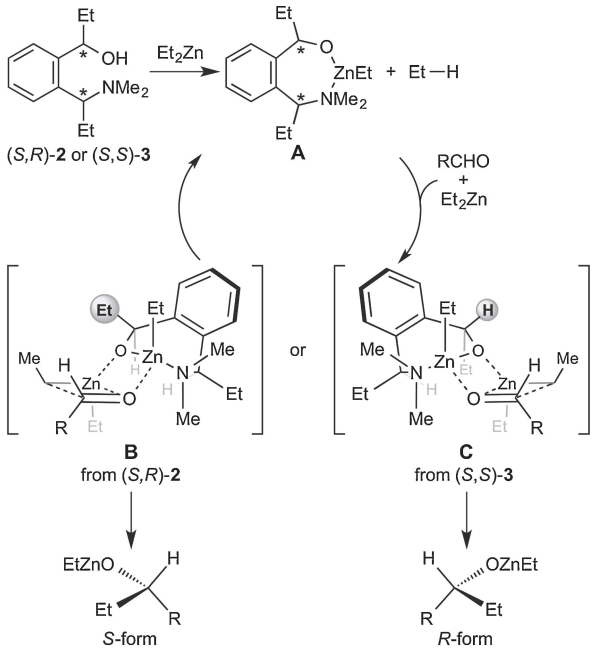


Figure 1. Proposed reaction mechanism for enantioselective addition of diethylzinc to aldehydes using (*S*,*R*)-**2** and (*S*,*S*)-**3**.

In conclusion, both enantiomers of 1-substituted 1-propanols were obtained by the enantioselective addition of diethylzinc to various aldehydes in the presence of two diastereomeric 1,4-amino alcohols (*S*,*R*)-**2** and (*S*,*S*)-**3**, both of which were obtained from the same chiral source (*S*,*S*)-**1**. The stereochemical outcome of the reaction was controlled solely by the absolute configuration of the benzylic carbon bearing amino group. Further studies are now in progress on the use of the novel 1,4-amino alcohols for other asymmetric reactions.

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Supporting Information is available electronically on J-STAGE.

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9 **Typical experimental procedure**: To an Et_2O (3.0 mL) solution of (*S*,*R*)-**2** (33 mg, 0.15 mmol) under an atmosphere of argon was added a hexane solution of diethylzinc (1 M, 3.0 mL) through a syringe at 0 °C, and the mixture was stirred at room temperature for 30 min. After the mixture was cooled to 0 °C, an Et_2O (2.0 mL) solution of benzaldehyde (160 mg, 1.5 mmol) was added and the reaction mixture was stirred at 0 °C for 18 h. Saturated ammonium chloride solution (2 mL) and 2 M HCl (10 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ether three times. The combined organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, crude product was purified by preparative TLC (hexane/Et_2O = 2:1) to give (*S*)-1-phenyl-1-propanol (171 mg, 84%). The ee was determined to be 97% by HPLC analysis using a chiral column (Daicel Chiralcel OD-H (25 cm × 0.46 cm i.d.); 254 nm UV detector; eluent, hexane/*i*-PrOH = 97/3; flow rate, 0.5 mL min^{-1}; *t*, 18.4 min for minor peak, 22.1 min for major peak).

10 Similar results were obtained in the reactions using ferrocenyl 1,4-amino alcohols.[6i]

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