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Enantioselective addition of diethylzinc to aldehydes catalyzed by (*R*)-1-phenylethylamine-derived 1,4-amino alcohols

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ABSTRACT

A series of *o*-xylylene-type 1,4-amino alcohols, synthesized from (*R*)-1-phenylethylamine, were used as chiral ligands for the enantioselective addition of diethylzinc to benzaldehyde. (*S*)-1-Phenyl-1-propanol was obtained with high enantioselectivity in all cases since the stereochemical outcome of the reaction was controlled by the chiral benzylic carbon bearing amino group. Highest catalytic activity was obtained by using (*R*)-1-{2-[1-(pyrrolidin-1-yl)ethyl]phenyl}cyclohexan-1-ol (**1n**) derived from (*R*)-1-(1-phenylethyl)pyrrolidine and cyclohexanone. Various chiral secondary alcohols were obtained by the reaction of diethylzinc and aldehydes in the presence of **1n** within 2 h with good to high enantioselectivities.

1. Introduction

During the past few decades, a number of chiral 1,2- and 1,3-amino alcohols have been developed and utilized as chiral ligands and chiral auxiliaries in various asymmetric reactions.[1] The asymmetric alkylation of aldehydes is one of the important method for the preparation of chiral secondary alcohols, which are useful as intermediate of natural products and pharmaceuticals.[2] Since the initial report by Oguni and Omi in 1984,[3] the enantioselective addition of organozinc compounds to aldehydes has been well-investigated using chiral 1,2- and 1,3-amino alcohol ligands.[2,4–6] Meanwhile, little attention has been paid to the reaction using chiral 1,4-amino alcohols, since the high levels of enantioinduction are generally difficult by chiral zinc catalysts containing relatively flexible seven-membered ring structures generated from organozinc compounds and 1,4-amino alcohol ligands.[7]

Recently, we reported the synthesis of novel diastereomeric 1,4-amino alcohols **2** with *o*-xylylene structure from an enantiopure chiral 1,4-diol, (*S,S*)-1,2-bis(1-hydroxypropyl)benzene, and their use in the enantioselective addition of diethylzinc to aldehydes (Fig. 1a and b).[8] Both enantiomers of the corresponding chiral secondary alcohols were obtained with high enantioselectivities by using the diastereomeric 1,4-amino alcohols (*R,S*)-**2** and (*S,S*)-**2** with different absolute configurations at the chiral carbon bearing amino group. The results are in contrast with those using 1,2-amino alcohols where the stereochemical outcome of the reaction is generally determined by the chiral carbon bearing hydroxy group.[2,4,9] Although the high selectivities were achieved in the reactions using our novel 1,4-amino alcohols, the preparation of them required multistep synthesis from commercially available compounds. This prompted us to develop novel chiral 1,4-amino alcohols with similar structure to **2** starting from chiral 1-phenylethylamine (**3**) as both enantiomers of **3** are commercially available. Herein, we report a short step synthesis of various 1,4-amino alcohols **1** with *o*-xylylene structure starting from **3** and their use in the enantioselective addition of diethylzinc to aldehydes (Fig. 1c).

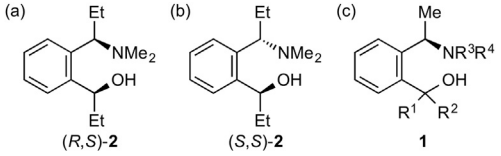

Fig. 1. 1,4-Amino alcohols with *o*-xylylene structure.

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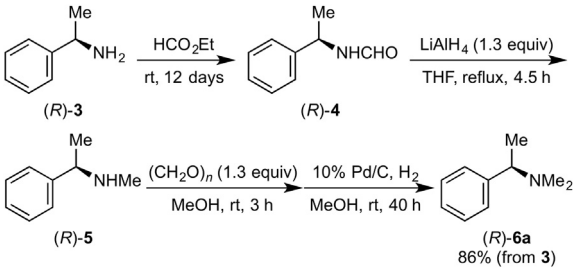
2. Results and discussion

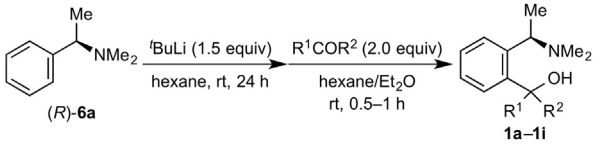
First, a stepwise methylation of (*R*)-1-phenylethylamine (**3**) was carried out as shown in Scheme 1. Primary amine (*R*)-**3** was stirred in ethyl formate at room temperature for 12 days, and the reduction of the resulting formamide (*R*)-**4** with lithium aluminum hydride in refluxing tetrahydrofuran gave (*R*)-*N*-methyl-1-phenylethylamine (**5**). The secondary amine **5** was mixed with paraformaldehyde in methanol at room temperature, followed by the hydrogenation in the presence of palladium on carbon afforded (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (**6a**) in 86% yield from (*R*)-**3**.



Scheme 1. Synthesis of (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (**6a**).

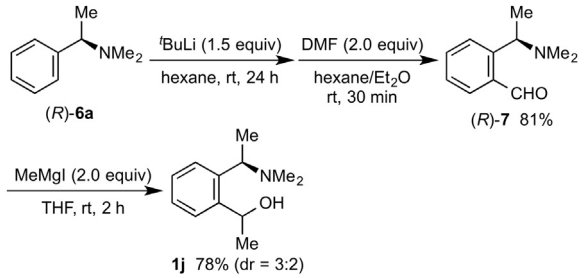
Next, a series of chiral 1,4-amino alcohols **1a**–**1i** were synthesized from (*R*)-**6a** and various carbonyl compounds (Table 1). The tertiary amine (*R*)-**6a** was treated with *tert*-butyllithium in hexane at room temperature for 24 h, and the reaction of the resulting *ortho*-lithiated species with propanal in hexane/diethyl ether at room temperature gave 1,4-amino alcohol **1a** in 83% yield as a diastereomeric mixture (dr=3:2, entry 1). Similarly, the reaction with isobutyraldehyde and benzaldehyde afforded the corresponding 1,4-amino alcohols **1b** and **1c** in 83% and 79% yields as diastereomeric mixtures, respectively (entries 2 and 3). When paraformaldehyde and symmetric ketones were used as electrophile, the corresponding 1,4-amino alcohols **1d**–**1i**, in which benzylic carbon bearing hydroxy group is achiral, were obtained in 23–62% yield (entries 4–9). 1,4-Amino alcohol **1j** was synthesized in two steps from (*R*)-**6a** (Scheme 2). The addition of the *ortho*-lithiated (*R*)-**6a** to *N*,*N*-dimethylformamide afforded aldehyde (*R*)-**7** in 81% yield. The reaction of (*R*)-**7** with methylmagnesium iodide in tetrahydrofuran at room temperature gave **1j** in 78% yield as a diastereomeric mixture (dr=3:2).

Table 1
Synthesis of amino alcohols **1a**–**1i**



Entry	1,4-Amino alcohol	R^1	R^2	Yield (%)
1	**1a**	Et	H	83[a]
2	**1b**	*i*-Pr	H	83[a]
3	**1c**	Ph	H	79[a]
4	**1d**	H	H	45
5	**1e**	Me	Me	37
6	**1f**	Et	Et	62
7[b]	**1g**	$-(CH_2)_4-$		23
8[b]	**1h**	$-(CH_2)_5-$		55
9[c]	**1i**	$-(CH_2)_6-$		54

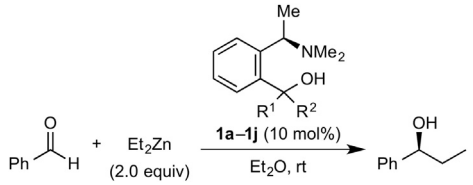
[a] Diastereomeric ratio was 3:2 by ^{1}H NMR analysis.
[b] The reaction with ketone was carried out at −78 °C.
[c] *t*-BuLi (1.0 equiv) and cycloheptanone (1.0 equiv) were used. The lithiation time was 3.5 h.



Scheme 2. Synthesis of 1,4-amino alcohol **1j**.

Enantioselective addition of diethylzinc to benzaldehyde was examined by using various 1,4-amino alcohols **1a**–**1j** (Table 2). When the reaction of benzaldehyde with 2.0 equiv of diethylzinc was carried out in the presence of **1a** in diethyl ether at room temperature, the reaction was completed in 8 h to afford (*S*)-1-phenyl-1-propanol in 84% yield with 95% ee (entry 1). The chiral secondary alcohol was obtained with high enantiomeric excess, although a diastereomeric mixture of **1a** (dr=3:2) was used in the reaction. This result confirms that the enantioselectivity of the reaction is controlled solely by the chiral carbon bearing amino group, as was observed in our previous publication.[8a] Diastereomeric mixtures of 1,4-amino alcohols **1b**, **1c**, and **1j** were then used in the same reaction, and the products were obtained with high enantiomeric excesses (>90% ee) in all cases (entries 2, 3, and 10). Moreover, the reaction using **1d** with single chiral carbon center also produced (*S*)-1-phenyl-1-propanol in 87% yield with 92% ee, clearly indicating that the chirality at the benzylic carbon bearing hydroxy group is unnecessary for the high levels of enantioinduction in this reaction (entry 4).[10] The introduction of two alkyl groups at benzylic carbon bearing hydroxy group was effective to enhance the reaction rate (entries 5–9), even though the reaction required 15 h when **1d** was used. Among them, good results were obtained by using **1g** (1.5 h, 82%, 95% ee) and **1h** (2.5 h, 87%, 95% ee) containing cyclopentane or cyclohexane rings, respectively (entries 7 and 8).

Table 2
Enantioselective addition of diethylzinc to benzaldehyde catalyzed by 1,4-amino alcohols **1a**–**1j**



Entry	1,4-Amino alcohol	R^1	R^2	Time (h)	Yield (%)	ee[a] (%)
1	**1a**[b]	Et	H	8	84	95
2	**1b**[b]	*i*-Pr	H	6	88	94
3	**1c**[b]	Ph	H	9	85	90
4	**1d**	H	H	15	87	92
5	**1e**	Me	Me	6	88	91
6	**1f**	Et	Et	6	89	93
7	**1g**	$-(CH_2)_4-$		1.5	82	95
8	**1h**	$-(CH_2)_5-$		2.5	87	95
9	**1i**	$-(CH_2)_6-$		4	87	93
10	**1j**[b]	Me	H	14	88	94

[a] Determined by HPLC analysis.
[b] Diastereomeric ratio was 3:2 by ^{1}H NMR analysis.

To examine the effect of substituents on the amino group of the 1,4-amino alcohols, cyclic tertiary amines (*R*)-**6b**–**6d** were synthesized from (*R*)-**3** (Table 3). In the presence of 4.0 equiv of potassium carbonate, the reaction of (*R*)-**3** with 1,3-dibromopropane in acetonitrile at 50 °C gave (*R*)-1-(1-phenylethyl)azetidine (**6b**) in