Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by (*S*)-2-(*N*,*N*-Disubstituted aminomethyl)pyrrolidine

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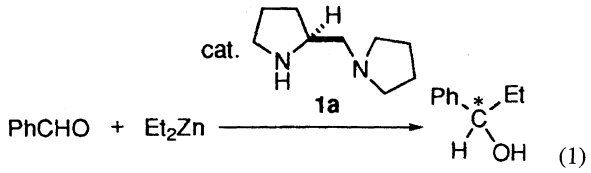
The enantioselective addition of diethylzinc to aldehydes in the presence of a catalytic amount of several chiral diamines, (*S*)-2-(*N*,*N*-disubstituted aminomethyl)pyrrolidines, was studied. Relatively high selectivity was achieved in the case of aromatic aldehydes by employing 15 mol% of (*S*)-2-(1-pyrrolidinylmethyl)pyrrrolidine.

The catalytic enantioselective alkylation of aldehydes is a potentially important method for preparing chiral secondary alcohols.[1] Since Oguni and Omi reported[2] on the reaction of diethylzinc and benzaldehyde in the presence of a catalytic amount of chiral alcohol, amine, or amino alcohol, a number of chiral catalysts have been reported.[3,4] Most of the successful results have been obtained by using β-amino alcohols. Although diamines were also reported to show catalytic activity,[5] the selectivity has not been very high, except for a few cases.[5b,5e]

In our continuing studies[6] of chiral β-diamines derived from (*S*)-proline in highly stereoselective asymmetric reactions, we have demonstrated that a chelated *cis*-fused bicyclic 5-membered ring structure is effective for asymmetric induction. We then examined the effectiveness of diamine, (*S*)-2-(*N*,*N*-disubstituted aminomethyl)pyrrolidine (**1**), as a chiral catalyst in the enantioselective addition of diethylzinc to aldehydes. Relatively high selectivities were achieved in the case of aromatic aldehydes by using 15 mol% **1a**.

Results and Discussion

In the first place, the reaction of diethylzinc and benzaldehyde was examined using diamine **1a** (Eq. 1).



(1)

The reaction was carried out as follows: To a cyclohexane (4.5 ml) solution of benzaldehyde (1.5 mmol) and 5 mol% of **1a** (0.075 mmol) was added a hexane solution (2.7 ml) of diethylzinc (2.7 mmol) at 0 °C. The reaction mixture was then stirred at r.t. for 15 h. After the reaction mixture was worked up (see Experimental section) (*S*)-1-phenyl-1-propanol was obtained with 25%ee in 72%. Since the selectivity was poor, the reaction was then examined by using an increased amount of the catalyst. The selectivity was dramatically improved by using 15—20 mol% of **1a** (Table 1, Entries 1—5). Next, the effect of the reaction solvent on the selectivity was examined using 15 mol% of **1a**. Nonpolar solvents gave better selectivity, and the selectivity was decreased in ether (Table 1, Entries 6—8). The selectivity was further improved by increasing the amount of the solvent (Table 1, Entries 9, 10). This was probably due to

Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by **1a**[a]

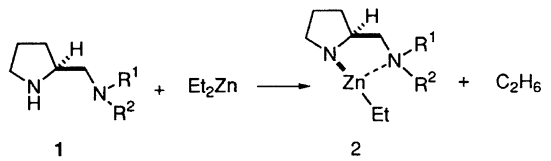
Entry	**1a**/mol%	Solvent	Yield/%	ee/%[b]
1	5	Cyclohexane–Hexane	72	25
2	10	Cyclohexane–Hexane	84	66
3	15	Cyclohexane–Hexane	85	73
4	20	Cyclohexane–Hexane	79	76
5	25	Cyclohexane–Hexane	66	66
6[c]	15	Hexane	83	72
7	15	Toluene–Hexane	78	64
8	15	Ether–Hexane	65	36
9[d]	15	Cyclohexane–Hexane	80	80
10[e]	15	Cyclohexane–Hexane	76	81
11[d,f]	15	Cyclohexane–Hexane	80	76
12[d,g]	15	Cyclohexane–Hexane	82	80
13[d,h]	15	Cyclohexane–Hexane	56	4
14[d,i]	15	Cyclohexane–Hexane	83	67
15[d,j]	15	Cyclohexane–Hexane	81	78

a) The reaction of benzaldehyde (1.5 mmol) and diethylzinc (2.7 mmol) was carried out using 4.5 ml of cyclohexane, toluene, or ether and 2.7 ml of hexane at r.t. for 15 h unless otherwise noted. b) Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OB (25 cm×0.46 cm i.d.); 254 nm UV detector, 2% 2-propanol in hexane; flow rate, 0.5 ml min^{-1}; t_R, 23.0 min for (*S*)-1-phenyl-1-propanol, 29.3 min for (*R*)-1-phenyl-1-propanol). (*S*)-1-Phenyl-1-propanol was obtained preferentially in all runs. c) Hexane (7.2 ml) was used. d) Cyclohexane (6.0 ml) was used. e) Cyclohexane (9.0 ml) was used. f) Diethylzinc (3.3 mmol) was used. g) The reaction was carried out at 0 °C for 17 h. h) The lithium salt of **1a** was used as catalyst. i) DBU (15 mol%) was used as an additive. j) HMPA (15 mol%) was used as an additive.

the solubility of complex **2a** (Chart 1), generated by the reaction of diethylzinc and **1a**, which is supposed to be the actual catalyst. The use of an increased amount of diethylzinc did not improve the yield (Table 1, Entry 11), and the selectivity was not improved even though the reaction was carried out at 0 °C for 17 h (Table 1, Entry 12). The reaction was also examined using the lithium salt of **1a** and in the presence of an additive, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or hexamethylphosphoric triamide (HMPA), which were effective in improving the selectivity in the reaction of our previous studies using the lithium salt of **1a** and its analogues.[6a,6b,6e] Although lithium salt was effective in some cases,[5b,5e,7] an almost racemic alcohol was obtained using the lithium salt of **1a** (Table 1, Entry 13). The additives could not improve the selectivity (Table 1, Entries 14, 15) either, probably because the additives coordinated to the zinc in complex **2a** and partially prevented the formation of a rigid 5-membered bicyclic chelate structure. These results are in accordance with the low selectivity observed using ether as the solvent.

Then, the effect of the substituent of diamine **1** was examined under the reaction conditions of Entry 9 in Table 1. The selectivity of the reaction was varied by a small change in the structure of diamine **1**. In the case of diamine **1b** with a piperidine ring, the selectivity was significantly decreased. The introduction of an oxygen (**1c**) or nitrogen atom (**1d**) into the substituent for an intramolecular coordination to a zinc atom showed higher selectivity, compared with the carbocyclic one (**1b**). Although diamine prepared from acyclic aliphatic amine (**1e**) showed moderate selectivity, diamine prepared from *N*-methyaniline (**1f**) gave (*R*)-1-phenyl-1-propanol with low selectivity. This result also indicates the importance of the rigid complex formation, since the nitrogen atom substituted by the phenyl group would not coordinate to the zinc atom as strongly as the others. Diamine with a pyrrolidine ring (**1a**) gave the best selectivity in the reaction of diethylzinc and benzaldehyde. The results are summarized in Table 2.

Since a good selectivity was achieved in the reaction of diethylzinc and benzaldehyde using 15 mol% of **1a** in cyclohexane, the reactions of diethylzinc with various aldehydes, i.e., *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde, (*E*)-cinnamaldehyde, heptanal, and 3-phenylpropanal were examined. In all cases, the corresponding alcohols having the *S*-configuration were obtained, and relatively high selectivity was achieved in the case of aromatic aldehydes (76—87%ee). The poor yields obtained in reactions with heptanal and 3-phenylpropanal were probably due to the formation of enolate by zinc amide. The results are summarized in Table 3.



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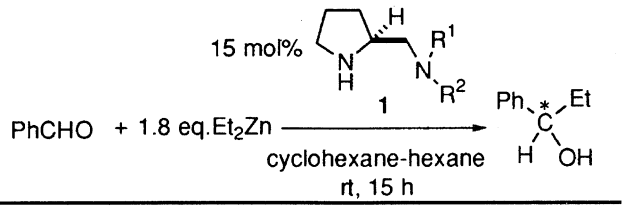
a: $R^1,R^2 = -(CH_2)_4-$ **d**: $R^1,R^2 = -(CH_2)_2-NMe-(CH_2)_2-$
b: $R^1,R^2 = -(CH_2)_5-$ **e**: R^1,R^2 = Et
c: $R^1,R^2 = -(CH_2)_2-O-(CH_2)_2-$ **f**: R^1 = Ph, R^2 = Me

Chart 1.

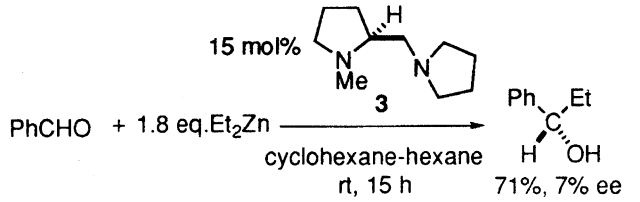
Table 2. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by **1a—f**[a]



Entry	1	R	R′	Yield/%	ee/%[b]
1	**a**	$-(CH_2)_4-$		80	80
2	**b**	$-(CH_2)_5-$		81	45
3	**c**	$-(CH_2)_2-O-(CH_2)_2-$		81	69
4	**d**	$-(CH_2)_2-N(Me)-(CH_2)_2-$		80	63
5	**e**	Et	Et	82	67
6	**f**	Ph	Me	54	8[c]

a) The reaction was carried out under the same conditions described in Table 1, Entry 9. b) Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OB). (*S*)-1-Phenyl-1-propanol was obtained preferentially in Entries 1—5. c) (*R*)-1-Phenyl-1-propanol was obtained preferentially.

With regard to an enantioselective addition of diethylzinc to aldehydes catalyzed by chiral diamines, Salvadori et al. described that moderate selectivity was achieved not by the formation of a zinc-nitrogen bond, but only by the coordination of an aprotic ligand, (*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-2,2′-diamino-1,1′-binaphthyl.[5a] They also reported a protic diamine, (1*S*,3*S*)-*N*,*N*′-dibenzyl-1,3-diphenyl-1,3-propanediamine,[5c] which acted as a coordinating ligand, and showed low selectivity in the reaction of diethylzinc and aromatic aldehydes. Since we assumed that a zinc–nitrogen bond would be formed by the reaction of diamine **1** and diethylzinc, and that the resulting complex would be an effective catalyst, we examined the reaction of diethylzinc and benzaldehyde in the presence of 15 mol% of aprotic diamine, (*S*)-1-methyl-2-(1-pyrrolidinylmethyl)pyrrolidine (**3**) (Eq. 2).

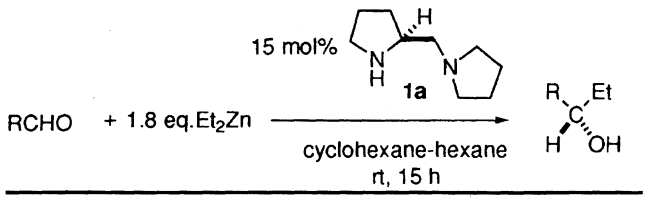


(2)

As (*S*)-1-phenyl-1-propanol was obtained in 71% with only 7%ee by the reaction, a zinc–nitrogen bond must have been formed by the reaction of **1** and diethylzinc, and this bond must be important for the enantioselective addition of diethylzinc to aldehydes.

From these observations, we tentatively postulate that the stereochemical course of the reaction was as follows based on an argument from the literature.[3a] Initially, *cis*-fused 5-membered bicyclic complex **2a** (Chart 1) was generated by

Table 3. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by **1a**[a)]



Entry	R	Yield/%	$[\alpha]_D^{20}$ (c, solv)	ee/%
1	Ph	80	−38.4 (5.20, $CHCl_3$)	80[b)]
2	*p*-ClC_6H_4	86	−24.5 (6.08, C_6H_6)	87[c)]
3	*p*-$MeOC_6H_4$	75	−28.1 (3.96, C_6H_6)	76[d)]
4	(*E*)-PhCH=CH	66	−0.3 (3.60, $CHCl_3$)	5[e)]
5	*n*-C_6H_{13}	25	+4.5 (1.64, $CHCl_3$)	46[f)]
6	$PhCH_2CH_2$	22	+9.4 (0.92, EtOH)	35[g)]

a) The reaction was carried out under the same conditions described in Table 1, Entry 9. All products are of *S*-configuration based on the specific rotation.[8)] b) Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OB). c) Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); 254 nm UV detector, 2% 2-propanol in hexane; flow rate, 0.5 ml min^{-1}; t_R, 23.5 min for major peak, 25.4 min for minor peak). d) Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OB (25 cm×0.46 cm i.d.); 254 nm UV detector, 10% 2-propanol in hexane; flow rate, 0.5 ml min^{-1}; t_R, 16.3 min for major peak, 19.8 min for minor peak). e) Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); 254 nm UV detector, 5% 2-propanol in hexane; flow rate, 0.5 ml min^{-1}; t_R, 22.3 min for minor peak, 36.9 min for major peak). f) Ee was determined by ^{13}C NMR spectroscopy after esterification with (−)-MTPACl.[9)] g) Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OB (25 cm×0.46 cm i.d.); 254 nm UV detector, 1% 2-propanol in hexane; flow rate, 0.5 ml min^{-1}; t_R, 22.5 min for minor peak, 24.4 min for major peak).

the reaction of **1a** and diethylzinc. Another diethylzinc may have been chelated with one nitrogen atom to form the dinuclear zinc complex. The carbonyl oxygen of the aldehyde approached the more Lewis acidic diamine-chelated Zn_A in such a manner as to prevent a nonbonded repulsion between R in the aldehyde and a terminal ethyl group attached to Zn_B. Then, the bridging ethyl group attached to Zn_A migrated to the aldehyde to give *S*-alcohol preferentially (Fig. 1).

In summary, chiral β-diamines derived from (*S*)-proline are effective catalysts for the enantioselective alkylations of aldehydes with diethylzinc. The best result was obtained by using (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine (**1a**), and chiral secondary alcohols were obtained up to 86%ee. A rational stereochemical model for the transition state of the reaction is also proposed.

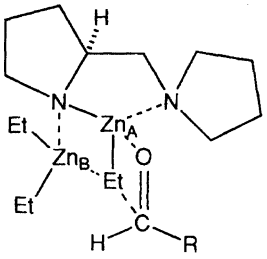


Fig. 1. Transition state model for the reaction of diethylzinc and aldehyde catalyzed by **1a**.

Experimental

Most manipulations were carried out under an atmosphere of argon. Solvents were dried and purified in the usual manner, and stored under an atmosphere of argon.

Infrared spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR and ^{13}C NMR spectra were measured with a JEOL JNM-EX-270 spectrometer, using tetramethylsilane as the internal standard. $CDCl_3$ was used as the solvent. Specific rotations were measured on a Horiba SEPA-200. HPLC analyses were carried out with Tosoh instruments (pump, CCPS; detector, UV-8020).

Diamines **1a—f** and **3** were prepared according to the literature.[6b,10)] Commercial aldehydes were distilled before use, except for *p*-chlorobenzaldehyde, and the products were identified by ^1H NMR and IR with authentic samples.

Typical Procedure for the Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by 1 (Table 1, Entry 9): To a cyclohexane (6.0 ml) solution of benzaldehyde (159 mg, 1.5 mmol) and **1a** (35 mg, 0.225 mmol) was added a hexane (2.7 ml) solution of diethylzinc (2.7 mmol) at 0 °C. The reaction mixture was then stirred at r.t. for 15 h. A saturated ammonium chloride solution (3 ml) and 2 mol m^{-3} HCl (3 ml) were added to the reaction mixture and it was extracted with ether. The organic layer was washed with water and brine, and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the resulting oily substance was purified by preparative TLC (silica gel/hexane : ether=2 : 1) to give 1-phenyl-1-propanol (164 mg, 80%). The alcohol was further purified by bulb-to-bulb distillation for the measurement of the specific rotation ($[\alpha]_D^{20}$ −38.4° (*c* 5.20, $CHCl_3$)). The ee was determined by HPLC analysis using a Daicel Chiralcel OB column.

The Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by the Lithium Salt of 1a: To a cyclohexane (1.5 ml) solution of **1a** (35 mg, 0.225 mmol) was added a hexane solution (0.14 ml) of butyllithium (0.225 mmol) at 0 °C; the reaction mixture was stirred at 0 °C for 30 min. Then, a cyclohexane (4.5 ml) solution of benzaldehyde (159 mg, 1.5 mmol) and a hexane (2.7 ml) solution of diethylzinc were added to the reaction mixture successively at 0 °C. The reaction mixture was stirred at r.t. for 15 h and worked up in the same manner as described above to give 1-phenyl-1-propanol (115 mg, 56%). The ee was determined by HPLC analysis using a Daicel Chiralcel OB column to be 4%ee.

The Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by 1a in the Presence of an Additive: To a cyclohexane (3.0 ml) solution of **1a** (35 mg, 0.225 mmol) and additive (0.025 mmol) was added a cyclohexane (3.0 ml) solution of benzaldehyde (159 mg, 1.5 mmol) followed by a hexane (2.7 ml) solution of diethylzinc (2.7 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 15 h and worked up in the same manner as described above to give 1-phenyl-1-propanol. The ee was determined by HPLC analysis using a Daicel Chiralcel OB column.

The Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by 3: To a cyclohexane (6.0 ml) solution of benzaldehyde (159 mg, 1.5 mmol) and **3** (38 mg, 0.225 mmol) was added a hexane (2.7 ml) solution of diethylzinc (2.7 mmol) at 0 °C. The reaction mixture was then stirred at r.t. for 15 h and worked up in the same manner as described above to give 1-phenyl-1-propanol (145 mg, 71%). The ee was determined by HPLC analysis using a Daicel Chiralcel OB column to be 7%ee.

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