Asymmetric Synthesis Using Chiral Piperazines. Part 3. Enantioselective Addition of Dialkylzincs to Aryl Aldehydes Catalysed by Chiral Piperazines[1]

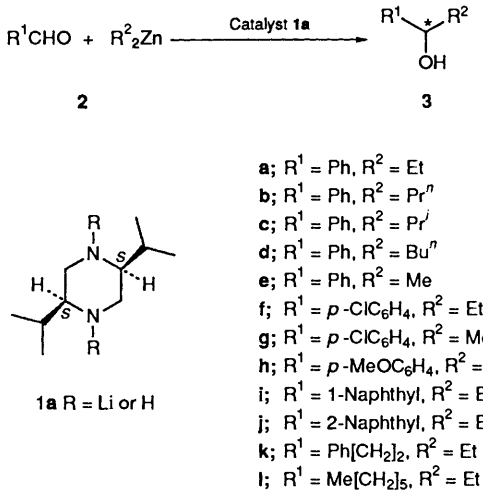
Seiji Niwa and Kenso Soai *
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Shinjuku, Tokyo 162, Japan

The use of chiral piperazines (cyclic diamines) **1** as chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes is described. (2*S*,5*S*)-2,5-Dialkyl substituted piperazines **1** catalysed the enantioselective addition of dialkylzincs to aryl aldehydes. It was found that the presence of the dilithium salt of **1** was more effective in producing the corresponding alcohols in high e.e.s (up to 96% e.e.) and that the catalyst **1** with branched carbon chains as the substituents on the piperazine ring was effective for highly enantioselective reaction.

The catalytic asymmetric carbon–carbon bond forming reaction is an important problem in asymmetric synthesis.[2] Enantioselective addition of organometallic reagents in the presence of a chiral auxiliary affords optically active *secondary* alcohols. We have reported the enantioselective addition of organozinc reagents to aldehydes catalysed by chiral amino alcohols[3,4] [*N*,*N*-dibutylnorephedrine (DBNE),[3a] diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM),[3b] polymer[3c] and inorganic solid-bound[3d] norephedrine derivatives, secondary amino tertiary alcohols[3e]], chiral pyridyl alcohols (asymmetric self-catalyst),[3f] and chiral quaternary ammonium salts.[3h]

However, chiral piperazines have rarely been utilized as a chiral auxiliary in asymmetric reactions, although we have reported the diastereoselective alkylation of diamides derived from chiral piperazine.[5]

We describe here that chiral piperazines serve as effective catalysts for the enantioselective addition of dialkylzincs to aryl aldehydes.[6]



Scheme 1

Results and Discussion

The reaction conditions in the enantioselective addition of diethylzinc to benzaldehyde were examined using the dilithium salt of (2*S*,5*S*)-2,5-diisopropylpiperazine **1a** (R = Li) as a chiral catalyst (Table 1). As to the effect of solvent, hydrocarbons, especially toluene, were effective. On the other hand, ether and tetrahydrofuran (THF) were ineffective (Entries 4 and 5). As regards the molar ratio of catalyst **1a**, 6 mol% of the dilithium salt of **1a** gave the best result and a 92% e.e. of (*R*)-(+)-**3a** was obtained (Entry 8). Also, reaction at 0 °C did not change the e.e. of **3a** (Entry 9). The effect of solvent was further examined using aromatic hydrocarbons in the presence of 6 mol% catalyst. Benzene–hexane was also effective and afforded (*R*)-(+)-**3a** in 90% e.e. (Entry 11), whereas when toluene was used as a single solvent, an increase in the enantioselectivity was not observed (Entry 12). Thus, the reaction in toluene–hexane as a mixed solvent at room temperature using 6 mol% dilithium salt **1a** gave the best result (92% e.e.) (Entry 8).

Various aldehydes and dialkylzincs reacted in the presence of a catalytic amount of **1a** (Scheme 1). The results are shown in Table 2. The addition of diethylzinc to benzaldehyde using 6 mol% of **1a** (R = H) afforded (*R*)-(+)-1-phenylpropanol **3a** in 81% e.e. (Entry 1). It was found that the presence of the dilithium salt **1a** (R = Li) [6 mol%, prepared *in situ* from the reaction of **1a** (R = H) and 2 mol equiv. of butyllithium] was more effective than **1a** (R = H) and produced (*R*)-(+)-**3a** in 90% e.e. (based on HPLC analysis using chiral column) (Entry 2). Using the dilithium salt of **1a** as a catalyst, various aromatic aldehydes were enantioselectively alkylated by diethylzinc at room temperature for 20–45 h to afford the corresponding alcohols in good to high e.e.s (Entries 2, 7 and 9–11). In addition, enantioselective propylation, isopropylation, and butylation afforded the corresponding alcohols in 73–96% e.e.s (Entries 3–5). Corresponding *primary* alcohols were obtained as by-products by the reduction of aldehydes with dialkylzincs. For example, the reaction of benzaldehyde with diethyl-, dipropyl- and dibutyl-zinc afforded benzyl alcohol in 11, 18, and 24% yield, respectively. Also, alkylation of *p*-chlorobenzaldehyde with dimethylzinc afforded (*R*)-(+)-1-(*p*-chlorophenyl)ethanol **3g** in 94% e.e. (Entry 8). However, dimethylzinc was less reactive than diethylzinc and the corresponding alcohols were obtained in low chemical yield after 7 d. The enantioselective alkylation of aliphatic aldehydes was also examined; however, the e.e.s of the corresponding aliphatic alcohols were low (Entries 12 and 13). Thus, chiral piperazine **1a** is most effective in catalytic asymmetric induction for the enantioselective addition of dialkylzincs to aryl aldehydes.

Next, we examined the effect of substituents on the piperazine ring (Scheme 2, Table 3). Various chiral piperazines were obtained by the reduction of the corresponding diketopiperazines, prepared from amino acids according to the literature method,[7] with sodium borohydride–titanium tetrachloride[8] or borane–tetrahydrofuran (BH_3·THF)[9] in dimethoxyethane (DME).

Dilithium salts (6 mol%) of various piperazines [(2*S*,5*S*)-

Table 1 Effect of solvent, molar ratio of catalyst and temperature[a]

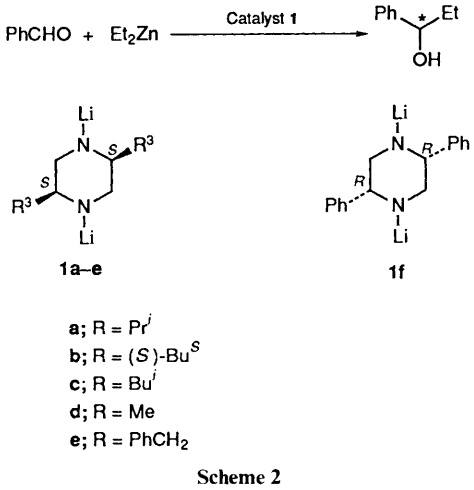
Entry	Solvent (v/v)	(2S,5S)-**1a** mol%	(R)-**3a** Yield (%)	$[\alpha]_D$ (c in $CHCl_3$)	E.e. (%)[b]
1	toluene–hexane (2:1)	10	81	+29.6 (5.49)	65
2	cyclohexane–hexane (2:1)	10	65	+19.4 (5.18)	43
3	hexane	10	55	+17.5 (5.21)	39
4	Et_2O–hexane (2:1)	10	67	+10.3 (5.15)	23
5	THF–hexane (2:1)	10	74	+1.70 (5.47)	4
6	toluene–hexane (2:1)	2	62	+20.6 (3.32)	45
7	toluene–hexane (2:1)	4	63	+30.7 (5.15)	68
8	toluene–hexane (2:1)	6	69	+41.6 (5.21)	92
9[c]	toluene–hexane (2:1)	6	55	+41.7 (5.10)	92
10	toluene–hexane (2:1)	8	72	+37.0 (5.20)	81
11	benzene–hexane (2:1)	6	83	+41.8 (5.18)	90
12	toluene	6	79	+36.5 (5.16)	80

[a] Dilithium salt of **1a** was used as catalyst. Reaction was carried out at room temperature unless otherwise noted. [b] Based on the reported value $[\alpha]_D$ +45.45 (c, 5.15 in $CHCl_3$).[13] [c] Reaction was carried out at 0 °C.

Table 2 Enantioselective addition of dialkylzincs to aldehydes catalysed by (2S,5S)-**1a**[a]

Entry	(R)-**3** R^1	R^2		Yield (%)	$[\alpha]_D$ (c, solvent)	E.e. (%)
1[b]	Ph	Et	**a**	73	+36.9 (5.03, $CHCl_3$)	81[c]
2	Ph	Et	**a**	69	+41.6 (5.21, $CHCl_3$)	92[c] (90)[d]
3	Ph	Pr^n	**b**	48	+40.0 (4.39, C_6H_6)	92[c]
4	Ph	Pr^i	**c**	44	+34.8 (4.90, Et_2O)	73[c]
5	Ph	Bu^n	**d**	44	+30.1 (3.01, C_6H_6)	96[c]
6	Ph	Me	**e**	21	+19.4 (2.20, cyclo-C_5H_{10})	45[c]
7	*p*-ClC_6H_4	Et	**f**	77	+23.7 (5.05, C_6H_6)	98[c] (90)[d]
8	*p*-ClC_6H_4	Me	**g**	23	+47.1 (1.64, Et_2O)	94[c]
9	*p*-$MeOC_6H_4$	Et	**h**	65	+26.6 (5.12, C_6H_6)	79[c]
10	1-naphthyl	Et	**i**	69	+37.1 (4.17, $CHCl_3$)	63[d,e]
11	2-naphthyl	Et	**j**	69	+24.7 (3.81, C_6H_6)	59[c]
12	$Ph[CH_2]_2$	Et	**k**	55	−8.42 (5.01, EtOH)	31[c]
13	$Me[CH_2]_5$	Et	**l**	60	−2.39 (8.09, $CHCl_3$)	25[c]

[a] The reactions were carried out in toluene–hexane (2:1) at room temperature in the presence of the dilithium salt of (2S,5S)-**1a** unless otherwise noted. Molar ratio, aldehyde–dialkylzinc–catalyst = 1.0:2.0:0.06. [b] Compound **1a** was used without lithiation. [c] Based on the reported value $[\alpha]_D$ +45.45 (c, 5.15 in $CHCl_3$) for (R)-**3a**,[13] $[\alpha]_D^{20}$ +43.6 (c, 4.18 in PhH) for (R)-**3b**,[14] $[\alpha]_D^{20}$ +47.7 (c, 7 in Et_2O) for (R)-**3c**,[15] $[\alpha]_D^{20}$ +31.3 (c, 3 in PhH) for (R)-**3d**,[16] $[\alpha]_D^{20}$ −43.1 (c, 7.19 in *cyclo*-C_5H_{10}) for (S)-**3e**,[17] $[\alpha]_D$ −10.4 (c, 5 in PhH) for (S)-**3f** in 43% e.e.,[18] $[\alpha]_D$ +49.9 (c, 2 in Et_2O) for (R)-**3g**,[19] $[\alpha]_D$ −17.2 (c, 5 in PhH) for (S)-**3h** in 51% e.e.,[18] $[\alpha]_D^{26}$ +13.9 (c, 5 in PhH) for (R)-**3j** in 33% e.e.,[3d] $[\alpha]_D$ +26.8 (c, 5 in EtOH) for (S)-**3k**,[20] $[\alpha]_D$ +9.6 (c, 8.3 in $CHCl_3$) for (S)-**31**.[21] [d] Determined by HPLC analyses using chiral column [Bakerbond DNBPG, 250 mm; 254 nm UV detector. For **3a**, eluent 0.25% propan-2-ol in hexane; flow rate 0.44 cm^3 min^{-1}; t_R/min, 62.1 for major peak, 63.7 for minor peak. For **3f**, eluent 0.20% propan-2-ol in hexane; flow rate 0.9 cm^3 min^{-1}; t_R/min, 38.5 for major peak, 39.8 for minor peak. For **3i**, eluent 0.25% propan-2-ol in hexane; flow rate 1.2 cm^3 min^{-1}; t_R/min 44.9 for major peak, 48.3 for minor peak]. [e] Configuration is tentatively assumed.



Scheme 2

1a–e and (2R,5R)-**1f**] were used as chiral catalysts for the addition of diethylzinc to benzaldehyde. The results are shown in Table 3. As already described, (R)-(+)-**3a** was obtained in 90% e.e. in the presence of the dilithium salt of (2S,5S)-**1a** (Entry 1). The dilithium salt of (2S,5S)-**1b**, derived from L-isoleucine with two asymmetric carbons, catalysed the addition of diethylzinc to benzaldehyde and (R)-(+)-**3a** was obtained in 89% e.e. (Entry 2). Catalyst (2S,5S)-**1c** with isobutyl groups (β-branched alkyl group) as substituents on the piperazine ring was also effective in affording (R)-(+)-**3a** (Entry 3). These results were comparable to the case of catalyst **1a** (Entry 1). No asymmetric induction was observed when catalyst **1d**, which has a simple methyl group, was used (Entry 4). When the substituent had a benzyl group as in (2S,5S)-**1e**, (R)-(+)-**3a** was afforded in 68% e.e. (Entry 5). However, with (2R,5R)-**1f** which has phenyl groups attached directly to the piperazine ring, the e.e. of **3a** was decreased to 13% (Entry 6).

Thus, the catalyst with a branched carbon chain as a substituent on the piperazine ring was effective for the highly enantioselective addition of dialkylzincs to aldehydes.

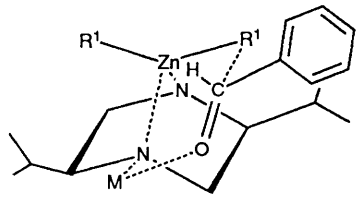
We tentatively postulate the probable reactive complexes in the enantioselective addition of dialkylzincs to benzaldehyde as shown in Fig. 1.

Table 3 Effect of the structure of piperazine in the enantioselective addition of diethylzinc to benzaldehyde

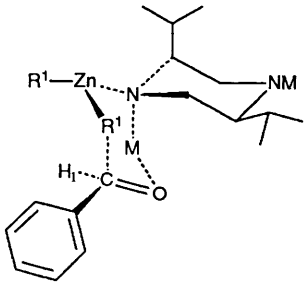
	1		3a			
Entry		R	Yield (%)	$[\alpha]_D$ (c, in $CHCl_3$)	E.e. (%)[a]	Config.
1	(2*S*,5*S*)-**1a**	Pr^i	69	+41.6 (5.21)	92 (90)[b]	*R*
2	(2*S*,5*S*)-**1b**	(*S*)-Bu^s	75	+40.5 (5.02)	89	*R*
3	(2*S*,5*S*)-**1c**	Bu^i	76	+41.5 (5.18)	91	*R*
4	(2*S*,5*S*)-**1d**	Me	54	0 (5.15)	0	—
5	(2*S*,5*S*)-**1e**	$PhCH_2$	70	+30.7 (5.04)	68	*R*
6	(2*R*,5*R*)-**1f**	Ph	32	−6.08 (1.90	13	*S*

[a] Based on the reported value $[\alpha]_D$ +45.45 (c, 5.15 in $CHCl_3$) for (*R*)-**3a**.[13] [b] Determined by HPLC analyses using chiral column. See footnote *d* of Table 2.

Dialkylzinc may be chelated with the two nitrogen atoms of the piperazine ring, which has the boat configuration with two bulky isopropyl substituents in the *pseudo*-equatorial positions (**A** in Fig. 1).* The chiral complex formed has a C_2 symmetry



A



B

Fig. 1 M = Li, ZnR^2

axis which is useful in asymmetric synthesis.[10] The aldehyde approaches this complex from a direction which avoids the bulky isopropyl group of the piperazine and reacts *via* a six-centre [3b,11] mechanism.† Thus, the *R*-alcohol is formed.

It is also possible that the piperazine ring takes a chair conformation with one isopropyl substituent in the equatorial position and with the other in the axial position. It should be noted that the ring inversion of the *cis*-2,5-disubstituted piperazine affords the parent molecule. In this conformation, the environments of the two nitrogen atoms of the ring differ from each other. The addition of dialkylzinc to benzaldehyde *via* a six-centre transition state may involve the nitrogen atom nearer to the *axial*-isopropyl substituent (**B** in Fig. 1). If the other nitrogen atom, which is nearer to the equatorial isopropyl substituent, should be involved in the transition state, the transition state should suffer from the severe 1,3-biaxial repulsion.[12] Thus, again, the *R*-alcohol is formed.

* From X-ray analysis, 1,4-dimethylpiperazine is known to act as a bidentate ligand. a boat-form chelate ring being formed. See, L. J. Guggenberger and R. R. Schrock, *J. Am. Chem. Soc.*, 1975, **97**, 2935.

† Dimethylzinc is a straight chain molecule (the bond length of C–Zn is 1.95 Å) and inactive to aldehydes. However, X-ray analysis of the adduct of dimethylzinc with amine (1,3,5-trimethylhexahydro-1,3,5-triazine) shows that the zinc atom is tetrahedral (the bond angle of C–Zn–C is 145°) and that the bond length of C–Zn is longer (1.98 Å) than the free dimethylzinc (*i.e.*, dimethylzinc coordinated with amine is more reactive). See, M. B. Hursthouse, M. Motevalli, P. O'Brien, J. R. Walsh and A. C. Jones, *J. Mater. Chem.*, 1991, **1**, 139.

Conclusions

Chiral piperazines derived from amino acids were examined in the catalytic asymmetric induction in enantioselective addition of dialkylzincs to aryl aldehydes. It was found that the catalyst with a branched carbon chain as substituents on the piperazine ring was effective for highly enantioselective reaction.

Experimental

General.—M.p.s were measured with a YAMATO MP-21 melting point apparatus and are uncorrected. IR spectra, ^1H NMR spectra (60 MHz), and optical rotations were recorded with a Hitachi 260-10 spectrophotometer, JEOL JNM-PMX-60 NMR spectrometer and a JASCO DIP-181 polarimeter, respectively. Values of $[\alpha]_D$ are quoted in 10^{-1} deg cm^2 g^{-1}. HPLC analysis was carried out with a Hitachi 634 liquid chromatograph. Bulb-to-bulb distillation was carried out with a Shibata Glass Tube Oven GTO-250. Hexane, THF, DME, ether and toluene were distilled over lithium aluminium hydride. All the reactions were performed under an argon atmosphere. Diethylzinc in hexane was purchased from the Kanto Chemical Co. Other dialkylzincs were prepared according to the literature procedure.[22]

Chiral Piperazines **1**.—These compounds were prepared from the corresponding diketopiperazine by the reduction with $NaBH_4$–$TiCl_4$ [8] or BH_3·THF [9] (dimethoxyethane was used as the solvent instead of THF) according to the literature procedure. Analytical data for new compounds were as follows. Synthesis of **1a** and **1c** were reported by our group.[8] Compound **1d** was synthesized according to the literature.[9]

(2S,5S)-2,5-*Di*-sec-*butylpiperazine* **1b**. Compound **1b** was obtained in 61% yield as a dihydrobromide,[9] m.p. 268.0–269.1 °C (decomp.) as dihydrobromide; $[\alpha]_D^{26}$ −17.34 (c, 2.01 in H_2O) as dihydrobromide; ν_{max}/cm^{-1} 3300, 2960, 2880, 1460 and 1380 as dihydrobromide; $\delta(CDCl_3)$ 0.83–1.00 (12 H, m), 1.23–1.87 (8 H, m), 2.17–2.50 (2 H, m) and 2.73–2.83 (4 H, m) [Found: M^+(EI), 198.2082. $C_{12}H_{26}N_2$ requires M, 198.2098].

(2S,5S)-2,5-*Diisobutylpiperazine* **1c**. Compound **1c** was obtained in 65% yield as dihydrobromide,[9] m.p. 302.5–305.0 °C (decomp.) as dihydrobromide; $[\alpha]_D^{25}$ +4.02 (c, 2.00 in H_2O) as dihydrobromide; ν_{max}/cm^{-1} 3350, 3000, 2960, 2800, 1560 and 1480 as dihydrobromide; $\delta(CDCl_3)$ 0.78–1.03 (12 H, m), 1.23–1.69 (8 H, m) and 2.52–2.85 (6 H, m); [Found: M^+(EI), 198.2092. $C_{12}H_{26}N_2$ requires M, 198.2098].

(2R,5R)-2,5-*Diphenylpiperazine* **1f**. Compound **1f** was obtained in 78% yield as a dihydrochloride,[9] m.p. 313.0–313.8 °C

(decomp.) as dihydrochloride; $[\alpha]_D^{26}$ +33.67 (*c*, 1.0 in H_2O) as dihydrochloride; ν_{max}/cm^{-1} 3400, 2950, 1540, 1500 and 1460 as dihydrochloride; $\delta(CDCl_3)$ 1.87 (2 H, s), 3.07–3.20 (4 H, m), 3.93 (2 H, m) and 7.17–7.67 (10 H, m) [Found: M^+(EI), 238.1465. $C_{16}H_{18}N_2$ requires *M*, 238.1471].

Typical Procedure for the Enantioselective Addition of Dialkylzinc to Aldehyde. (*Table* 2, *Entry* 2).—To an ice-cooled solution of **1a** (0.0313 g, 0.184 mmol) in toluene (12.3 cm^3), butyllithium (0.368 mmol, 0.245 cm^3 of 1.5 mol dm^{-3} hexane solution) was added. After 10 min, Et_2Zn (6.2 mmol, 6.2 cm^3 of 1 mol dm^{-3} hexane solution) was added over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.31 cm^3, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 20 h at room temperature and 1 mol dm^{-3} HCl was added to quench the reaction. The mixture was extracted with CH_2Cl_2, the organic extract was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by silica-gel TLC ($CHCl_3$ as a developing solvent).

Acknowledgements

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References

1 For part 2 and for a preliminary communication, see K. Soai, S. Niwa, Y. Yamada and H. Inoue, *Tetrahedron Lett.*, 1987, **28**, 4841.
2 *Asymmetric Catalysis*, ed. B. Bosnich, Martinus Nijhoff, Dordrecht, 1986, ch. 3; *Asymmetric Synthesis*, vol. 5, ed. J. D. Morrison, Academic Press, Orlando, 1985.
3 (*a*) K. Soai, S. Yokoyama, K. Ebihara and T. Hayasaka, *J. Chem. Soc., Chem. Commun.*, 1987, 1690; K. Soai, S. Yokoyama and T. Hayasaka, *J. Org. Chem.*, 1991, **56**, 4264; (*b*) K. Soai, A. Ookawa, K. Ogawa and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467; K. Soai, A. Ookawa, T. Kaba and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111; (*c*) K. Soai, S. Niwa and M. Watanabe, *J. Org. Chem.*, 1988, **53**, 927; K. Soai, S. Niwa and M. Watanabe, *J. Chem. Soc., Perkin Trans. 1*, 1989, 109; K. Soai and M. Watanabe, *Tetrahedron Asymmetry*, 1991, **2**, 97; (*d*) K. Soai, M. Watanabe and A. Yamamoto, *J. Org. Chem.*, 1990, **55**, 4832; (*e*) K. Soai, M. Watanabe, A. Yamamoto and T. Yamashita, *J. Mol. Cat.*, 1991, **64**, L27; (*f*) K. Soai, S. Niwa and H. Hori, *J. Chem. Soc., Chem. Commun.*, 1990, 982; (*g*) K. Soai, H. Hori and S. Niwa, *Heterocycles*, 1989, **29**, 2065; K. Soai, Y. Kawase and S. Niwa, *Heterocycles*, 1989, **29**, 219; (*h*) K. Soai and M. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1990, 43; (*i*) S. Niwa and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 1990, 937; (*j*) K. Soai, H. Hori and M. Kawahara, *Tetrahedron Asymmetry*, 1990, **1**, 769; (*k*) K. Soai, M. Watanabe and M. Koyano, *J. Chem. Soc., Chem. Commun.*, 1989, 534.
4 For the related reactions, N. N. Joshi, M. Srebnik and H. C. Brown, *Tetrahedron Lett.*, 1989, **30**, 5551; W. Oppolzer and R. N. Radinov, *Tetrahedron Lett.*, 1988, **29**, 5645; A. Oeveren, W. Menge and B. L. Feringa, *Tetrahedron Lett.*, 1989, **30**, 6427; H. Takahashi, T. Kawakita, M. Yoshioka, S. Kobayashi and M. Ohno, *Tetrahedron Lett.*, 1989, **30**, 7095; P. A. Chaloner and E. Langadianou, *Tetrahedron Lett.*, 1990, **31**, 5185; M. Kitamura, S. Okada, S. Suga and R. Noyori, *J. Am. Chem. Soc.*, 1989, **111**, 4028; K. Tanaka, H. Ushio and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1989, 1700; R. Noyori, S. Suga, S. Okada, M. Kitamura, N. Oguni, M. Hayashi, T. Kaneko and Y. Matsuda, *J. Organomet. Chem.*, 1990, **382**, 19; E. J. Corey, P.-W. Yuen and F. J. Hannon, *J. Org. Chem.*, 1990, **55**, 784; S. Itsuno and J. M. J. Fréchet, *J. Org. Chem.*, 1987, **52**, 4140; M. Watanabe, S. Araki, Y. Butsugan and M. Umemura, *J. Org. Chem.*, 1991, **56**, 2218; M. Asami and S. Inoue, *Chem. Lett.*, 1991, 685.
5 K. Soai, H. Hayashi, A. Shinozaki, H. Umebayashi and Y. Yamada, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3450.
6 After our preliminary communication,[1] enantioselective addition of diethylzinc to aldehydes using chiral piperazines was reported. See, T. Shono, N. Kise, E. Shirakawa, H. Matsumoto and E. Okazaki, *J. Org. Chem.*, 1991, **56**, 3063. For the enantioselective reduction using chiral piperazines, see M. Falorni and L. Lardicci, *Tetrahedron Lett.*, 1989, **30**, 3551.
7 T. Ueda, M. Saito, T. Kato and N. Izumiya, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 568; D. E. Nitecki, B. Halpern and J. W. Westley, *J. Org. Chem.*, 1968, **33**, 864.
8 K. Soai, H. Hayashi and H. Hasegawa, *Heterocycles*, 1986, **24**, 1287; *cf.* S. Kano, Y. Tanaka, E. Sugino and S. Hibino, *Synthesis*, 1980, 695.
9 M. Jung and J. C. Rohloff, *J. Org. Chem.*, 1985, **50**, 4909.
10 J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.
11 E. C. Ashby and R. S. Smith, *J. Org. Chem.*, 1977, **42**, 425; E. C. Ashby and R. S. Smith, *J. Organomet. Chem.*, 1982, **225**, 71.
12 E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, 1962, ch. 8.
13 R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1914, 1115.
14 R. MacLeod, F. J. Welch and H. S. Mosher, *J. Am. Chem. Soc.*, 1960, **82**, 876.
15 J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 1936, 128.
16 D. Seebach, H. O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. C. Nüssler, Hoc-An Oie and M. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 301.
17 S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 1870.
18 J. Capillon and J. Guétté, *Tetrahedron*, 1979, **35**, 1817.
19 T. Ishizaki, H. Miura and H. Nohira, *Nippon Kagaku Kaishi*, 1980, 1381.
20 T. Sato, Y. Gotoh, Y. Wakabayashi and T. Fujisawa, *Tetrahedron Lett.*, 1983, **24**, 4123.
21 T. Mukaiyama and K. Hojo, *Chem. Lett.*, 1976, 893.
22 C. R. Noller, *Org. Synth.*, Coll. Vol. 2, 1966, 184.

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