APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. **14**, 709–714 (2000)

Enantioselective addition of diethylzinc to aldehydes catalyzed by 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol (BINOL-Box) ligands derived from 1,1′-bi-2-naphthol

Hidehiko Kodama, Junji Ito, Aiichiro Nagaki, Tetsuo Ohta* and Isao Furukawa
Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University,
Kyotanabe, Kyoto 610-0394, Japan

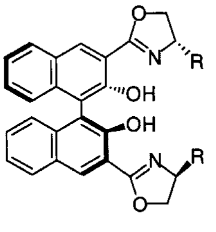
With 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthols (BINOL-Box) synthesized from 1,1′-bi-2-naphthol (BINOL), the enantioselective addition of diethylzinc to aryl aldehydes proceeded smoothly to give secondary aryl alcohols in good yield with good enantioselectivity. Interestingly, the yields and enantioselectivities were affected by the mixing sequence of the reactants. Furthermore, the synthesis of both enantiomers of the addition products has been achieved using the same ligands by choosing achiral additives, $Ti(O\text{-}iPr)_4$ and 4A molecular sieves. Copyright © 2000 John Wiley & Sons, Ltd.

Keywords: asymmetric catalysis; asymmetric catalyst; enantioselective addition; diethylzinc; aldehyde; secondary alcohol; optically active alcohol

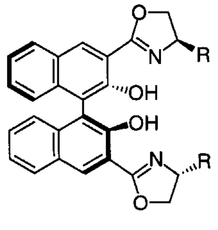
Received 27 March 2000; accepted 12 June 2000

1 INTRODUCTION

The enantioselective addition of diethylzinc to aldehydes is among the most widely used methods for carbon–carbon bond formation in organic synthesis.[1] Previously, in most of the studies of this reaction, β-amino alcohols derived from α-amino acids have been used as a chiral catalyst.[2] On the other hand, binaphthyl derivatives have been used for various asymmetric catalytic reactions as ligands. The prime role for these ligands is played by the C_2-symmetrical 2,2′-disubstituted 1,1′-binaphthyls bearing identical coordinating groups, in particular BINOL[3] and BINAP.[4] Their congeners with nonidentical substituents at the 2,2′-positions have only recently been developed; among these, MOP[5] and NOBIN[6] have risen to prominence, but these ligands are not necessarily available for this enantioselective addition reaction. Recently, Katsuki and co-workers reported that the addition of diethylzinc to benzaldehyde in the presence of *N*,*N*,*N*′,*N*′-tetraisopropyl-2,2′-dihydroxyl-1,1′-binaphthyl-3,3′-dicarboxamide, which has amides at the 3,3′-carbon atoms of 1,1′-bi-2-naphthol, proceeded with high enantioselectivities (99% *ee*).[7]



(*S*,*S*)-**1a**: R = Ph
(*S*,*S*)-**1b**: R = *i*-Pr
(*S*,*S*)-**1c**: R = Bn



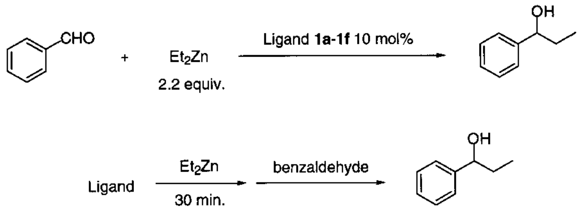
(*S*,*R*)-**1d**: R = Ph
(*S*,*R*)-**1e**: R = *i*-Pr
(*S*,*R*)-**1f**: R = Bn

We have designed 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol (BINOL-Box; **1a**–**1f**) chiral ligands and reported their use in asymmetric 1,3-dipolar cycloaddition in combination with $Sc(OTf)_3$.[8] From their good performance in this 1,3-dipolar cycloaddition, the BINOL-Box ligands are expected to be used for other asymmetric reactions. We found that the enantioselective addition of diethylzinc to aryl aldehydes using these ligands proceeded in good yield with good enantioselectivity.

---

* Correspondence to: Tetsuo Ohta, Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-0394, Japan.

Contract/grant sponsor: Research Promotion Fund, Doshisha University.
Contract/grant sponsor: Ministry of Education, Japan.



Scheme 1 Enantioselective addition of diethylzinc to benzaldehyde (Path A).

Table 1 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by BINOL-Box (Path A)[a]

Entry	Ligand	Yield (%)[b]	*ee* (%)[c]	Config.[d]
1	(*S*,*S*)-**1a**	43	20	*S*
2	(*S*,*S*)-**1b**	8	5	*S*
3	(*S*,*S*)-**1c**	Trace	n.d.[e]	n.d.[e]
4	(*S*,*R*)-**1d**	99	60	*S*
5	(*S*,*R*)-**1e**	91	24	*S*
6	(*S*,*R*)-**1f**	75	30	*S*

[a] Reaction conditions: see the Experimental section.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by chiral GC (CP-cyclodextrin β 236M, 0.25 mm × 25 m).
[d] Absolute configurations were determined by comparison of optical rotations (Ref. 9).
[e] n.d., not determined.

2 RESULTS AND DISCUSSION

The enantioselective addition of diethylzinc to benzaldehyde was carried out using 10 mol% of 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol (BINOL-Box) in toluene as the solvent at 0 °C. Initially, the reaction followed the conventional method as shown in Path A (Scheme 1). That is, ligands and hexane solution of diethylzinc were stirred in toluene for 0.5 h, and then benzaldehyde was added. The reactions using (*S*,*R*)-ligands ((*S*,*R*)-**1d**–**1f**) gave much higher yields than the (*S*,*S*)-ligands ((*S*,*S*)-**1a**–**1c**) (Table 1). This large effect of the diastereomeric structure on the yield of the reaction is explained by considering the structural models of the ligands (Fig. 1). Usually, the addition of diethylzinc to aldehyde is considered to be catalyzed by the monomeric amino alcohol–Zn complex, and not by the dimeric complex.[9] In the case of the (*S*,*S*)-ligands, the two substituents on the oxazoline rings are located on the same side as the hetero atoms, which can coordinate to the Zn center. On the other hand, the (*S*,*R*)-ligands have their two substituents on the oxazoline rings on the opposite side to the binaphthyl backbone. Due to these different steric demands, the (*S*,*S*)-ligand–Zn complexes are easily dimerized, while association of the monomeric (*S*,*R*)-ligand–Zn complexes with each other is difficult. Consequently, in the case of the (*S*,*S*)-ligands, a small amount of active mono-

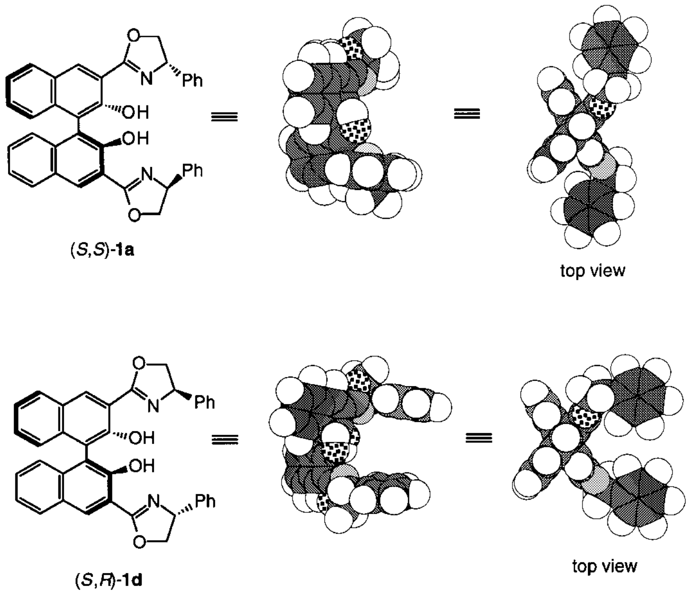
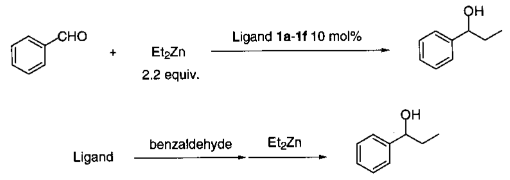


Figure 1 Molecular models of (*S*,*S*)-**1a** and (*S*,*R*)-**1d**.

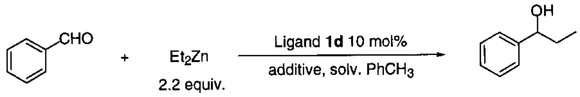


Scheme 2 Enantioselective addition of diethylzinc to benzaldehyde (Path B).

Table 2 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by BINOL-Box (Path B)[a]

Entry	Ligand	Solvent	Yield (%)[b]	*ee* (%)[c]	Config.[d]
1	(*S*,*S*)-**1a**	PhMe	77	50	*S*
2	(*S*,*S*)-**1b**	PhMe	79	58	*S*
3	(*S*,*S*)-**1c**	PhMe	60	58	*S*
4	(*S*,*R*)-**1d**	PhMe	78	64	*S*
5	(*S*,*R*)-**1e**	PhMe	75	14	*S*
6	(*S*,*R*)-**1f**	PhMe	58	48	*S*
7	(*S*,*R*)-**1d**	CH_2Cl_2	56	41	*S*
8	(*S*,*R*)-**1d**	$CHCl_3$	21	38	*S*
9	(*S*,*R*)-**1d**	THF	26	12	*S*
10	(*S*,*R*)-**1d**	Et_2O	68	63	*S*
11	(*S*,*R*)-**1d**	CH_3CN	90	61	*S*
12[e]	(*S*,*R*)-**1d**	PhMe	89	47	*S*
13[f]	(*S*,*R*)-**1d**	PhMe	12	60	*S*

[a] Reaction conditions: see the Experimental section.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by chiral GC (CP-cyclodextrin β 236M, 0.25 mm × 25 m).
[d] Absolute configurations were determined by comparison of optical rotations (Ref. 9).
[e] Ambient reaction temperature.
[f] Reaction temperature was -30 °C.



Scheme 3 Enantioselective addition of diethylzinc to benzaldehyde with a BINOL–Box (*S*,*R*)-**1d** as a ligand.

meric species, or none, is formed in the reaction mixture.

Therefore, as shown by Path B (Scheme 2), the ligands, the benzaldehyde and the hexane solution of diethylzinc were added in this order. The results are shown in Table 2.

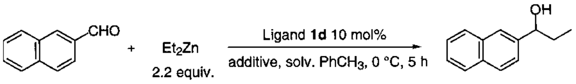
The reaction through Path B using the (*S*,*S*)-ligands proceeded faster than that through Path A and with better stereoselectivity, while the results using (*S*,*R*)-ligands were the same in both cases. This shows that the results of the reaction through Path B exhibit the real steric and diastereomeric effects of the BINOL-Box ligands for the stereodifferentiation ability of the catalyst. The reaction using phenyl-substituted (*S*,*R*)-**1d**, derived from (*R*)-phenylglycinol, gave a high yield and enantioselectivity (78%, 64% *ee*; Table 2, Entry 4). Therefore, the effect of solvents was examined for the reaction with (*S*,*R*)-**1d** (Table 2, Entries 7–11). The reaction proceeded faster in toluene, diethyl ether or acetonitrile as the solvent and with good enantioselectivity, while in dichloromethane, chloroform or tetrahydrofuran the enantioselectivity was lower. The effect of temperature was also examined (Table 2, Entries 4, 12 and 13). The reaction at 0 °C gave the best result.

Moreover, Nakai,[11a] Chan[11b] and co-workers reported that the enantioselective addition of

Table 3 Effect of additives on enantioselective addition of diethylzinc to benzaldehyde catalyzed by (*S*,*R*)-**1d**[a]

Entry	Additive	Temp. (°C)	Yield (%)[b]	*ee*. (%)[c]	Config.[d]
1[e]	None	0	78	64	*S*
2	$Ti(O\text{-}iPr)_4$	0	80	55	*R*
3	$Ti(O\text{-}iPr)_4$ + MS4A (50 mg)	0	63	70	*R*
4[e]	None	-30	12	60	*S*
5	$Ti(O\text{-}iPr)_4$	-30	21	57	*R*
6	$Ti(O\text{-}iPr)_4$ + MS4A (50 mg)	-30	45	71	*R*

[a] Reaction conditions: see the Experimental section.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by chiral GC (CP-cyclodextrin β 236M, 0.25 mm × 25 m).
[d] Absolute configurations were determined by comparison of optical rotations (Ref. 9).
[e] Reaction conditions: see the Experimental section (Path B).



Scheme 4 Enantioselective addition of diethylzinc to 2-naphthaldehyde with (*S*,*R*)-**1d** as a ligand.

diethylzinc to aldehydes using a BINOL–Ti(O-iPr)$_2$ complex as an asymmetric precatalyst proceeded smoothly in good yield with high enantioselectivity. In addition, the carbonyl–ene reactions and hetero Diels–Alder reactions in the presence of 4A molecular sieves proceeded with higher enantioselectivity than in the absence of 4A molecular sieves.[11c] Based on the above results, the effect of Ti(O-iPr)$_4$ and 4A molecular sieves as an additive was examined for this reaction using (*S*,*R*)-**1d** as the ligand in toluene (Scheme 3 and Table 3).

Interestingly, the absolute configuration of the secondary aryl alcohols in the presence of additives was *R*, while that in the absence of additives was *S*. The addition of 4A molecular sieves combined with Ti(O-iPr)$_4$ to the reaction mixture leads to an increase in the enantioselectivity (Table 3, Entries 3 and 6). This tendency has been observed in the asymmetric reactions catalyzed by Ti(O-iPr)$_4$–chiral ligands, in which 4A molecular sieves act at the stage of the formation of the active chiral catalyst.[12] Although there is no experimental evidence about the real active species of the zinc and titanium catalysts, the differences in the absolute configuration of the products from the reaction using additives and no additives may be explained by the structure of the active species. In the absence of Ti(O-iPr)$_4$,[7,13] the active species is proposed as the complex consisting of two zinc atoms, ligand and aldehyde. On the other hand, in the presence of Ti(O-iPr)$_4$,[11a,14] chiral ethyltitanium reagent is once generated from Ti–BINOL-Box complex and diethylzinc, and then it reacts with an aldehyde to form the alkoxytitanium species, which then reacts with Ti(O-iPr)$_4$ to give the titanium alkoxide product.

Finally, the enantioselective addition of diethylzinc to 2-naphthaldehyde instead of benzaldehyde using (*S*,*R*)-**1d** as a ligand proceeded in good yield (80%) with good enantioselectivity (81% *ee*) (Table 4, Entry 3). Moreover, the effect of the amount of catalyst was also examined. The enantioselective addition of diethylzinc to 2-naphthaldehyde using 1 mol% (*S*,*R*)-**1d** as a ligand proceeded to give 1-(2-naphthyl)-1-propanol in 60% yield with 80% *ee* (Scheme 4; Table 4, Entry 4).

3 CONCLUSION

The enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol (BINOL-Box) ligands has been developed. The reaction of diethylzinc with 2-naphthaldehyde catalyzed by 10 mol% (*S*,*R*)-**1d** in the presence of Ti(O-iPr)$_4$ and 4A molecular sieves proceeded to give a secondary alcohol in 80% yield with 81% *ee*. We found that the choice of additives and ligand was very important for this reaction.

4 EXPERIMENTAL

All experiments were carried out under an argon atmosphere. Commercial reagents were used as

Table 4 Enantioselective addition of diethylzinc to 2-naphthaldehyde catalyzed by (*S,R*)-**1d**[a]

Entry	Additive	Yield (%)[b]	*ee* (%)[c]	Config.[d]
1	None	80	49	*S*
2	Ti(O-iPr)$_4$	89	68	*R*
3	Ti(O-iPr)$_4$ + MS4A (50 mg)	80	81	*R*
4[e]	Ti(O-iPr)$_4$ + MS4A (50 mg)	60	80	*R*

[a] Reaction conditions: see the Experimental section.

[b] Isolated yield.

[c] Determined by HPLC analysis using a Daicel Chiralcel OD-H column (eluent 2-propanol/hexane (10:90); flow rate 0.3 ml min^{-1}; detection UV 254 nm).

[d] Absolute configurations were determined by comparison of optical rotations (Ref 15.).

[e] Using 1 mol% (*S*,*R*)-**1d** as a ligand.

received without further purification. All solvents were dried using standard procedures. The ^{1}H NMR (400 MHz) spectra were recorded on a JEOL JNM A-400 spectrometer with tetramethylsilane (TMS) as the internal standard. Optical rotations were recorded using a Horiba SEPA-200 polarimeter. Enantiomeric excesses (% *ee*) were determined by HPLC analyses or GC analysis. Preparations of 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol (BINOL-Box) ligands were carried out according to the reported method.[8]

4.1 Typical procedure for enantioselective addition of diethylzinc to aldehydes through Path A

To a solution of (*S*,*R*)-**1d** (0.10 mmol, 0.058 g) in toluene (3 ml), 1.0 mol l^{-1} hexane solution of diethylzinc (2.2 mmol, 2.2 ml) was added, and the mixture was stirred at 0 °C under an argon atmosphere for 30 min. Then aldehyde (1.0 mmol) was added, and the mixture was stirred at 0 °C for 5 h. The reaction mixture was quenched with 10% hydrochloric acid, extracted with dichloromethane and dried over anhydrous sodium sulfate. The organic layer was evaporated to dryness, and the residue was purified by column chromatography (hexane ethyl acetate = 4:1). The enantiomeric excess was determined by Chiral GC analysis (CP-Cyclodextrin β 236M; 0.25 mm × 25 m; retention times 11.1 min (*R*) and 11.3 min (*S*)) for 1-phenyl-1-propanol. The absolute configuration was assigned by comparison of the optical rotation with that in the literature.[9]

4.2 Typical procedure for enantioselective addition of diethylzinc to aldehydes through Path B

To a solution of (*S*,*R*)-**1d** (0.10 mmol, 0.058 g) in toluene (3 ml), aldehyde (1.0 mmol) and a 1.0 mol l^{-1} hexane solution of diethylzinc (2.2 mmol, 2.2 ml) were added, and the mixture was stirred at 0 °C for 5 h. The reaction mixture was treated by standard work-up (see above). The enantiomeric excess was determined by the method described above for 1-phenyl-1-propanol or chiral HPLC analysis (Daicel Chiralcel OD-H column [eluent 2-propanol hexane (10:90), flow rate 0.3 ml min^{-1}; detection UV 254 nm; retention times 28.3 min (*S*) and 30.3 min (*R*)]) for 1-(2-naphthyl)-1-propanol. The absolute configuration was assigned by comparison of the optical rotation with that in the literature.[9,10,15]

4.3 Typical procedure for enantioselective addition of diethylzinc to aldehydes in the presence of Ti(O-iPr)$_4$

To a solution of (*S*,*R*)-**1d** (0.10 mmol, 0.058 g) in toluene (3 ml), Ti(O-iPr)$_4$ (1.2 mmol, 0.34 ml) was added and the mixture was stirred at 50 °C under an argon atmosphere for 30 min. Then 1.0 mol l^{-1} hexane solution of diethylzinc (2.2 mmol, 2.2 ml) and aldehyde (1.0 mmol) were added, and the mixture was stirred at 0 °C for 5 h. Work-up and determination of enantiomeric excesses and the absolute configurations were performed by the method described above.

Acknowledgements We thank Dr Takayuki Yamashita for helpful discussions during the course of this work. We also thank undergraduate project students Naoki Kunisada and Taku Hasobe. This work was partially supported by Doshisha University's Research Promotion Fund and a grant to RCAST at Doshisha University from the Ministry of Education, Japan.

REFERENCES

1. (a) Seyden-Penne J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*. John Wiley: New York, 1995; (b) Solladie G. In: *Asymmetric Synthesis*, Morrison JD (ed.). Academic Press: New York, 1983, Vol. **2A**, Chapter 6.
2. (a) Oguni N, Omi T. *Tetrahedron Lett.* 1984; **25**: 2823; (b) Noyori R, Kitamura M. *Angew. Chem., Int. Ed. Engl.* 1991; **30**: 49; (c) Kitamura M, Suga S, Kawai K, Noyori R. *J. Am. Chem. Soc.* 1986; **108**: 6071; (d) Soai K, Niwa S. *Chem. Rev.* 1992; **92**: 833; (e) Bolm C, Schlingloff G, Harms K. *Chem. Ber.* 1992; **125**: 1191; (f) Soai K, Hayasa T, Takai K, Sugiyama T. *J. Org. Chem.* 1994; **59**: 7908; (g) Delair P, Einhorn J, Luche JL. *Tetrahedron* 1995; **51**: 165; (h) Belliczey J, Giffels G, Kragl U, Wandry C. *Tetrahedron: Asymmetry* 1997; **8**: 1529; (i) Dosa PL, Ruble JC. *J. Org. Chem.* 1997; **62**: 444; (j) Cho BT, Chun YS. *Tetrahedron: Asymmetry* 1998; **9**: 1489.
3. (a) Noyori R, Tomino I, Tanimoto Y. *J. Am. Chem. Soc.* 1979; **101**: 3129; (b) Noyori R, Tomino I, Tanimoto Y, Nishizawa M. *J. Am. Chem. Soc.* 1984; **106**: 6709; (c) Terada M, Mikami K, Nakai T. *J. Chem. Soc., Chem. Commun.* 1990; 1623; (d) Wang JT, Fan X, Feng X, Qian YM. *Synthesis* 1989; 291; (e) Shibasaki M, Sasai H, Arai T. *Angew. Chem., Int. Ed. Engl.* 1997; **36**: 1236; (f) Keller E, Veldman N, Spek AL, Feringa BL. *Tetrahedron: Asymmetry* 1997; **8**: 3403.
4. (a) Miyashita A, Yasuda A, Takaya H, Toriumi K, Ito T,

Souchi T, Noyori R. *J. Am. Chem. Soc.* 1980; **102**: 7932; (b) Takaya H, Mashima K, Koyano K, Yagi M, Kumobayashi H, Taketomi T, Akutagawa S, Noyori R. *J. Org. Chem.* 1986; **51**: 629.

5. (a) Uozumi Y, Hayashi T. *J. Am. Chem. Soc.* 1991; **113**: 9887; (b) Hayashi T, Iwamura H, Naito M, Matsumoto Y, Uozumi Y, Miki M, Yanagi K. *J. Am. Chem. Soc.* 1994; **116**: 775.
6. (a) Smrcina M, Lorenc M, Hanus V, Kocovsky P. *Synlett* 1991; 231; (b) Smrcina M, Lorenc M, Hanus V, Sedmera P, Kocovsky P. *J. Org. Chem.* 1992; **57**: 1917; (c) Smrcina M, Polakova J, Vyskocil S, Kocovsky P. *J. Org. Chem.* 1993; **58**: 4534.
7. Kitajima H, Ito K, Aoki Y, Katsuki T. *Bull. Chem. Soc. Jpn.* 1997; **70**: 207.
8. Kodama H, Ito J, Hori K, Ohta T, Furukawa I. *J. Organomet. Chem.* in press.
9. Noyori R, Suga S, Kawai K, Okada S, Kitamura M, Oguni N, Hayashi M, Kaneko T, Matsuda Y. *J. Organomet. Chem.* 1990; **382**: 19.
10. Kitamura M, Suga S, Niwa M, Noyori R. *J. Am. Chem. Soc.* 1995; **117**: 4832.
11. (a) Mori M, Nakai T. *Tetrahedron Lett.* 1997; **38**: 6233; (b) Zhang FY, Yip CW, Cao R, Chan ASC. *Tetrahedron: Asymmetry* 1997; **8**: 585; (c) Mikami K, Terada M, Narisawa S, Nakai T. *Synlett* 1992; 255.
12. (a) Minamikawa H, Hayakawa S, Yamada T, Iwasawa N, Narasaka K. *Bull. Chem. Soc. Jpn.* 1988; **61**: 4379; (b) Narasaka K, Inoue M, Yamada T. *Chem. Lett.* 1986; 1967.
13. Kitamura M, Okada S, Suga S, Noyori R. *J. Am. Chem. Soc.* 1989; **111**: 4028.
14. Takahashi H, Kawakita T, Yoshioka M, Kobayashi S, Ohno M. *Tetrahedron Lett.* 1989; **30**: 7095.
15. Soai K, Ookawa A, Kaba T, Ogawa K. *J. Am. Chem. Soc.* 1987; **109**: 7111.