Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 1513–1516

A new approach to enantioselective cyanation of imines with Et_2AlCN

Shuichi Nakamura, Naoki Sato, Masashige Sugimoto and Takeshi Toru*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

Received 1 March 2004; accepted 25 March 2004

Abstract—An enantioselective Strecker-type reaction of imines with Et_2AlCN in the presence of chiral additives has been examined. The enantioselectivity varied depending on the substituents of the imino group as well as the chiral additives used. Thus, α-aminonitriles were obtained in good yields with good enantioselectivities in the reaction of *N*-benzylidenebenzhydrylamine with Et_2AlCN and BINOL. The reaction with excess BINOL gave the aminonitrile with reversed configuration.

1. Introduction

Natural and unnatural homochiral α-amino acids are widely used as chiral building blocks for components of modified proteins.[1] The asymmetric Strecker-type reaction is one of the most efficient methods for the synthesis of these chiral α-amino acids. A number of enantioselective approaches for the synthesis of optically active α-aminonitriles have been reported.[2] We focused on an enantioselective Strecker-type reaction of imines with diethylaluminum cyanide[3] (Et_2AlCN). To the best of our knowledge, the enantioselective version of this type of reaction has not been reported, in contrast to a number of reports on diastereoselective reactions.[4] We expected Et_2AlCN to behave as a good cyanation reagent due to its Lewis acidity. During our study, it was reported that the addition of triethylaluminum to aldehydes or epoxides is accelerated by a Lewis base such as phosphines, arsines, antimonies, and amines.[5] We report herein the first enantioselective Strecker-type reaction using Et_2AlCN as a cyanation reagent activated by chiral additives.

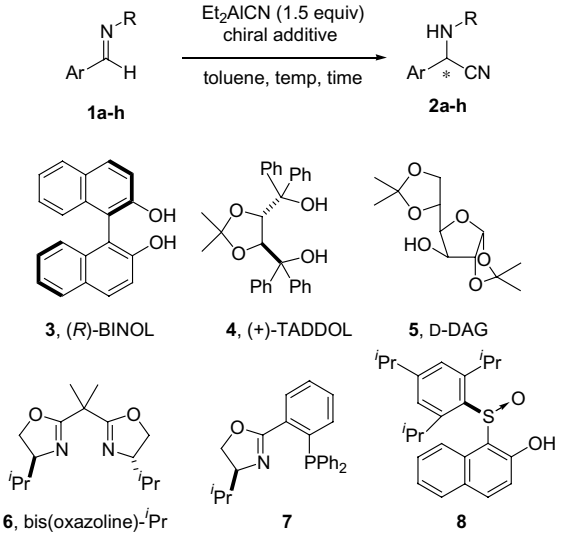
2. Results and discussion

First, we examined various chiral additives in the reaction of *N*-benzylideneaniline **1a** with Et_2AlCN. The reaction was carried out as follows: Et_2AlCN was added to a solution of a chiral additive in toluene at 0 °C under argon. After being stirred for 30 min,[6] the mixture was cooled to −78 °C and stirred for an additional 30 min. A solution of *N*-benzylideneaniline **1a** was then added. When the reaction was carried out at −78 °C without a chiral additive, the formation of only a trace amount of product was observed (Table 1, entry 1). On the other hand, the reaction in the presence of a chiral additive such as (*R*)-BINOL **3**, (+)-TADDOL **4**, or diacetone D-glucose **5** (DAG) proceeded smoothly and was complete within 30 min at −78 °C (entries 2–4). The reaction of imine **1a** with Et_2AlCN (1.5 equiv) in the presence of (*R*)-BINOL **3** (1.5 equiv) in toluene at −78 °C gave α-aminonitrile **2a** in good yield with moderate enantioselectivity (entry 2). Chiral additives **6** and **7** did not promote the reaction with Et_2AlCN, resulting in low enantioselectivity (entries 5 and 6). Although the chiral sulfoxide **8** accelerated the cyanation, the enantioselectivity was poor (entry 7).[7,8] α-Aminonitrile **2a** was formed with good enantioselectivity (61% ee) when 1.5 equiv of Et_2AlCN and 1.2 equiv of (*R*)-BINOL **3** were used (entry 8). Interestingly, when the reaction was carried out with excess (4.5 equiv) (*R*)-BINOL **3**, the configuration of **2a** was reversed from that with 1.2 equiv of (*R*)-BINOL **3** (entry 9).[9] Cyanation of **1a** with Et_2AlCN/(*R*)-BINOL **3** in solvents other than toluene, such as CH_2Cl_2, Et_2O, or THF, resulted in low enantioselectivities (entries 10–12). The reaction of substrates with other substituents was examined, but treatment of *N*-benzylidene-2-methoxyaniline **1b** and *N*-benzylidene-9-fluorenylamine **1c** with Et_2AlCN/

* Corresponding author. Tel./fax: +81-52-735-5217; e-mail: toru@nitech.ac.jp

0957-4166/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2004.03.040

(*R*)-BINOL **3** showed low enantioselectivity (entries 13 and 14). Imine **1d** with a benzhydryl group, a good protecting group of amines,[10] led to reversed enantiofacial selectivity giving (*S*)-**2d** with high enantioselectivity (70% ee, entry 15).[11] The reaction of **1d** with 4.5 equiv of (*R*)-BINOL **3** also showed a reversal of the enantioselectivity affording (*R*)-**2d** with 15% ee (entry 16). The absolute configurations of **2c** and **2d** were determined by comparison of the values of the specific rotation with those already reported.[12] The reaction of *N*-sulfonylimines **1e** and **1f** with Et_2AlCN/BINOL gave **2e** and **2f** with low enantioselectivities (entries 17 and 18). Imines **1g** and **1h** bearing the benzhydryl group and derived from 1-naphthaldehyde and *p*-chlorobenzaldehyde, gave **2g** and **2h** with good enantioselectivities (entries 19 and 20).



A dramatic change in stereochemistry was observed when a threefold excess of BINOL over Et_2AlCN was used (Table 1, entries 8 and 9). It has not often been reported that the stereochemistry of the product changes when the amount of the chiral ligand increases,[13] although there are a few reactions affording each enantiomer separately with the same chiral ligand but by different additives[14] or at different temperatures.[15] The aggregation state of Lewis acids and BINOL has been suggested to play an important role in controlling the stereochemistry of the product.[16] In the present reaction, it is likely that the 2:1 complex of (*R*)-BINOL and Et_2AlCN affords the product possessing reversed stereochemistry from that obtained in the reaction of the 1:1 complex of BINOL and Et_2AlCN, although the solvents and temperature may also influence the enantioface selection.[17] The detailed reaction mechanism remains to be solved.

3. Conclusion

In conclusion, Et_2AlCN has been demonstrated to be a useful cyanation reagent in the enantioselective formation of α-aminonitriles. Further work to improve the enantioselectivity and to clarify the reaction mechanism in the enantioselective Strecker-type reaction using Et_2AlCN is currently in progress in our laboratory.

Table 1. Enantioselective cyanation of imines in the presence of chiral additives[a]

Entry	Substrate	Ar	R	Chiral additive	Temperature (°C)	Time (min)	Product	Yield (%)	Ee (%)[b]
1	**1a**	Ph	Ph	None	−78	90	**2a**	Trace	—
2	**1a**	Ph	Ph	**3** (1.5 equiv)	−78	30	**2a**	90	48
3	**1a**	Ph	Ph	**4** (1.5 equiv)	−78	30	**2a**	91	35
4	**1a**	Ph	Ph	**5** (3.0 equiv)	−78	30	**2a**	96	22
5	**1a**	Ph	Ph	**6** (1.5 equiv)	−78 → rt	1 day	**2a**	90	8
6	**1a**	Ph	Ph	**7** (1.5 equiv)	−78 → rt	2 days	**2a**	62	3
7	**1a**	Ph	Ph	**8** (1.5 equiv)	−78	60	**2a**	52	3
8	**1a**	Ph	Ph	**3** (1.2 equiv)	−78	30	**2a**	96	61[c]
9	**1a**	Ph	Ph	**3** (4.5 equiv)	−78 → 10	360	**2a**	97	−52[d]
10[e]	**1a**	Ph	Ph	**3** (1.2 equiv)	−78	60	**2a**	94	28
11[f]	**1a**	Ph	Ph	**3** (1.2 equiv)	−78 → rt	1 day	**2a**	30	9
12[g]	**1a**	Ph	Ph	**3** (1.2 equiv)	−78 → rt	1 day	**2a**	52	4
13	**1b**	Ph	*o*-$MeOC_6H_4$	**3** (1.2 equiv)	−78 → −40	180	**2b**	98	0
14	**1c**	Ph	Flu	**3** (1.2 equiv)	−78	360	**2c**	93	22 (*R*)
15	**1d**	Ph	Ph_2CH	**3** (1.2 equiv)	−78	90	**2d**	98	70 (*S*)
16	**1d**	Ph	Ph_2CH	**3** (4.5 equiv)	−78 → 0	420	**2d**	93	15 (*R*)
17	**1e**	Ph	$TolSO_2$	**3** (1.2 equiv)	−78	120	**2e**	76	2
18	**1f**	Ph	2-$PySO_2$	**3** (1.2 equiv)	−78 → rt	960	**2f**	52	2
19	**1g**	1-Naph	Ph_2CH	**3** (1.2 equiv)	−78	60	**2g**	99	70 (*S*)
20	**1h**	*p*-ClC_6H_4	Ph_2CH	**3** (1.2 equiv)	−78	90	**2h**	99	64 (*S*)

[a] The reaction was carried out in toluene with 1.5 equiv of Et_2AlCN unless otherwise noted.
[b] Ee was determined by HPLC analysis using chiral columns.
[c] Absolute configuration of the product was not determined.
[d] Stereochemical outcome was reversed.
[e] The reaction was carried out in CH_2Cl_2.
[f] The reaction was carried out in Et_2O.
[g] The reaction was carried out in THF.

4. Experimental section

4.1. Synthesis of diethylaluminum cyanide

Diethylaluminum cyanide was prepared according to a reported method.[18] To a solution of trimethylaluminum in toluene (15 mL, 0.99 mol/L, 14.9 mmol) was added trimethylsilyl cyanide 1.95 mL (14.9 mmol) at room temperature and the mixture stirred for 3 h. The reaction mixture was then warmed to 170 °C to remove volatile components. The resulting crude oil was distilled under high vacuum using a mercury diffusion pump (bath temperature; 170 °C/5×10^{-3} mmHg) to afford the product (1.47 g, 89%). The diethylaluminum cyanide thus obtained was dissolved in degassed toluene to make 1.0 mol/L solution.

4.2. Typical procedure for the cyanation of *N*-benzylidenebenzhydrylamine

(S)-2-(Diphenylmethyl)amino-2-phenylacetonitrile **2d**.[12a] To a solution of (*R*)-BINOL **3** (127 mg, 0.44 mmol) in toluene (22 mL) was added Et_2AlCN (1.0 mol/L solution in toluene, 0.55 mL, 0.55 mmol) at 0 °C and the mixture stirred for 30 min. The mixture was cooled to −78 °C and stirred for 30 min after which was added a solution of *N*-benzylidenebenzhydrylamine **1d** (102 mg, 0.38 mmol) in toluene (1.8 mL). After being stirred for 1.5 h, aq HCl was added to make the solution acidic and the mixture extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was purified by column chromatography (silica gel 30 g, hexane/ethyl acetate 99:1) to afford **2d** (110 mg, 98%). The enantiomeric excess of **2d** was determined to be 70% by HPLC analysis using chiralpak AD. TLC $R_f = 0.50$ (hexane/ethyl acetate = 80:20); $[\alpha]_D^{24} = -40.5$ (*c* 0.31, $CHCl_3$), lit.[12a] $[\alpha]_D^{24} = -64.2$ (*c* 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.14 (d, 1H, $J = 11.6$ Hz, —NH), 4.60 (d, 1H, $J = 11.6$ Hz, –CH–), 5.25 (s, 1H, –CH–), 7.20–7.59 (m, 15H, Ar). Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.22; H, 6.19; N, 9.28. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min) t_R 12 (*R*) and 19 (*S*) min (70% ee).

4.3. 2-Phenylamino-2-phenylacetonitrile 2a[19]

TLC $R_f = 0.40$ (hexane/ethyl acetate = 80:20); $[\alpha]_D^{21} = +91.0$ (*c* 0.178, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.00 (d, 1H, $J = 8.2$ Hz, –NH), 5.42 (d, 1H, $J = 8.2$ Hz, –CH–), 6.70–6.90 (m, 3H, Ar), 7.16–7.65 (m, 7H, Ar); HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min) t_R 25 and 30 min (61% ee).

4.4. 2-(2-Methoxyphenyl)amino-2-phenylacetonitrile 2b[20]

TLC $R_f = 0.20$ (hexane/ethyl acetate = 80:20); ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H, –OMe), 4.68 (d, 1H, $J = 8.5$ Hz, –NH), 5.46 (d, 1H, $J = 8.5$ Hz, –CH–), 6.71–7.68 (m, 9H, Ar); HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min) t_R 22 and 23 min (0% ee).

4.5. (*R*)-2-(9-Fluorenyl)amino-2-phenylacetonitrile 2c[12b]

TLC $R_f = 0.28$ (hexane/ethyl acetate = 80:20); $[\alpha]_D^{24} = -4.45$ (*c* 0.10, $CHCl_3$), lit.[12b] $[\alpha]_D^{24} = -14.0$ (95% ee, *c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) 2.43 (br, 1H, –NH), 4.58 (br, 1H, –CH–), 5.16 (s, 1H, –CH–), 7.30–7.80 (m, 13H, Ar); HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min) t_R 28 (*S*) and 43 (*R*) min (22% ee).

4.6. 2-(*p*-Tolylsulfonyl)amino-2-phenylacetonitrile 2e

TLC $R_f = 0.25$ (hexane/ethyl acetate/triethylamine = 50:50:1); ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H), 5.05 (br, 1H), 5.49 (s, 1H), 7.33–7.48 (m, 7H), 7.82 (d, 2H, $J = 8.4$ Hz); HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 70:30, flow rate 0.7 mL/min) t_R 13 and 16 min.

4.7. 2-(2-Pyridylsulfonyl)amino-2-phenylacetonitrile 2f

TLC $R_f = 0.14$ (hexane/ethyl acetate = 70:30); ^1H NMR (DMSO-d_6) δ 5.92 (s, 1H), 7.32–7.46 (m, 5H, Ar), 7.67 (dd, 1H, $J = 4.6$, 7.4 Hz), 7.96 (d, 1H, $J = 7.8$ Hz), 8.08 (dd, 1H, $J = 7.4$, 7.8 Hz), 8.72 (d, 1H, $J = 4$, 6 Hz); ^{13}C NMR (DMSO-d_6) δ 47.8, 117.8, 121.6, 126.9, 127.4, 128.7, 128.9, 133.9, 138.6, 149.9, 156.8; IR (KBr) 3097, 1348, 1185 cm^{-1}; EIMS *m*/*z* (rel intensity) 273.5 (M^+, 0.43), 208.4 (11), 130.2 (12), 78 (100), 77 (24). Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37. Found: C, 57.24; H, 3.99; N, 15.33. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 70:30, flow rate 1.0 mL/min) t_R 14 and 15 min.

4.8. (*S*)-2-Diphenylamino-2-(1-naphthyl)acetonitrile 2g[12a]

TLC $R_f = 0.48$ (hexane/ethyl acetate = 80:20); $[\alpha]_D^{22} = -130.2$ (*c* 0.876, $CHCl_3$), lit.[12a] $[\alpha]_D^{22} = -182.2$ (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.22 (d, 1H, $J = 11.8$ Hz, –NH–), 5.18 (d, 1H, $J = 11.8$ Hz, –CH–), 5.35 (s, 1H, –CH–), 7.16–7.96 (m, 17H, Ar); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min) t_R 11 (*R*) and 15 (*S*) min (70% ee).

4.9. (*S*)-2-Diphenylamino-2-(4-chlorophenyl)acetonitrile 2h[10]

$R_f = 0.59$ (hexane/ethyl acetate = 80:20); $[\alpha]_D^{23} = -22.9$ (*c* 0.528, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.13 (d, 1H, $J = 12.2$ Hz, –NH–), 4.56 (d, 1H, $J = 12.2$ Hz, –CH–), 5.21 (s, 1H, –CH–), 7.22–7.60 (m, 14H, Ar); HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, flow rate 1.0 mL/min) t_R 19 (*R*) and 53 (*S*) min (64% ee).

Acknowledgements

This work was partly supported by an NIT research promotion program and by the Tatematsu Foundation.

References and notes

1. *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985.
2. For reviews of the enantioselective Strecker-type reactions, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; (b) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875–877; For more recent reports, see: (c) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657–2658; (d) Byrne, J. J.; Chavarot, M.; Chavant, P. Y.; Vallée, Y. *Tetrahedron Lett.* **2000**, *41*, 873–876; (e) Nogami, H.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 279–283; (f) Liu, B.; Feng, X.; Chen, F.; Zhang, G.; Cui, X.; Jiang, Y. *Synlett* **2001**, 1551–1554; (g) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594–11599; (h) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147–1150; (i) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; (j) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635; (k) Keith, J. M.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153–155.
3. (a) Nagata, W.; Yoshioka, M.; Hirai, S. *Tetrahedron Lett.* **1962**, *3*, 461–466; (b) Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1972**, *94*, 4635–4643.
4. (a) Davis, F. A.; Reddy, R. E.; Portonovo, P. S. *Tetrahedron Lett.* **1994**, *35*, 9351–9354; (b) Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1995**, *36*, 6949–6952; (c) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y. *J. Org. Chem.* **1996**, *61*, 440–441; (d) Portonovo, P.; Liang, B.; Joullié, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 1451–1455; (e) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704–8708; (f) Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663–7666; (g) Andrés, J. M.; Martínez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron: Asymmetry* **2001**, *12*, 347–353; (h) Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759–762; (i) Mabic, S.; Cordi, A. A. *Tetrahedron* **2001**, *57*, 8861–8866; (j) Davis, F. A.; Prasad, K. R.; Carroll, P. J. *J. Org. Chem.* **2002**, *67*, 7802–7806.
5. (a) Schneider, C.; Brauner, J. *Tetrahedron Lett.* **2000**, *41*, 3043–3046; (b) Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* **2001**, 4445–4450.
6. When a solution of Et_2AlCN and a chiral ligand was stirred longer, it took much longer time to complete the cyanation.
7. The intramolecular coordination of the sulfinyl group to Et_2AlCN accelerates cyanation: (a) Ruano, J. L. G.; Castro, A. M. M.; Rodríguez, J. H. *J. Org. Chem.* **1992**, *57*, 7235–7241; (b) Escribano, A.; Ruano, J. L. G.; Castro, A. M. M.; Rodríguez, J. H. *Tetrahedron* **1994**, *50*, 7567–7578; (c) Ruano, J. L. G.; Gamboa, A. E.; Castro, A. M. M.; Rodríguez, J. H.; López-Solera, M. I. *J. Org. Chem.* **1998**, *63*, 3324–3332; (d) Ruano, J. L. G.; García, M. C.; Laso, N. M.; Castro, A. M. M.; Ramos, J. H. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2507–2509; (e) Ruano, J. L. G.; García, M. C.; Castro, A. M. M.; Ramos, J. H. R. *Org. Lett.* **2002**, *4*, 55–57, See also Refs. 4c,e,f,h,j.
8. We have recently reported a newly designed chiral ligand having a sulfinyl group: Nakamura, S.; Fukuzumi, T.; Toru, T. *Chirality* **2004**, *16*, 10–12.
9. The absolute stereochemistry of **2a** was not determined.
10. Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.
11. No enantioselectivity was observed in the reaction of **1d** with trimethylsilyl cyanide in the presence of Et_2AlCl/BINOL. No reaction of the oximes (R = OH or OBn in **1d**) and the hydrazone ($R = NH_2$) with Et_2AlCN/ BINOL gave the corresponding cyanated products.
12. (a) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284–4285; (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650–1652.
13. Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719–755.
14. (a) Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721–15730; (b) Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299–302; (c) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083–4084; (d) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623–11636; (e) Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron Lett.* **1996**, *37*, 3027–3030; (f) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099–6110; (g) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483–5488; (h) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3831–3842.
15. (a) Sinou, D. *Tetrahedron Lett.* **1981**, *22*, 2987–2990; (b) Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201–3204; (c) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675–8676.
16. The dimeric Zr-BINOL complex gives the product having stereochemistry opposite that obtained with the monomeric catalyst: (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979–981; (b) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220–4221.
17. We observed a negative nonlinear effect in the reaction with BINOL, indicating that the aggregation state of the reactive species should be involved.
18. Fauss, R.; Findeisen, K.; Haebich, D. *Ger. Offen.* **1986**, DE 3430019 A1.
19. McEwen, W. E.; Grossi, A. V.; MacDonald, R. J.; Stamegna, A. P. *J. Org. Chem.* **1980**, *45*, 1301–1308.
20. Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186–3188.