Designed binaphthyl-derived titanium complexes: a new type of asymmetric catalyst for the carbonyl-ene reaction with glyoxylate

Koichi Mikami*, Yukihiro Motoyama and Masahiro Terada
Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152 (Japan)

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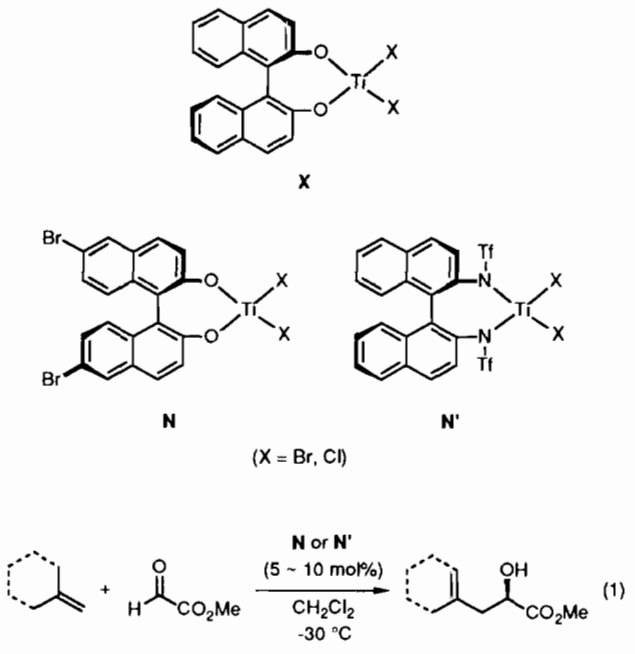
Abstract

A new type of titanium complex (**N**) derived from modified binaphthyl, 1,1′-bi-6-bromo-2-naphthol (6-Br-BINOL, **1**) (98% e.e.) is found to be an extremely efficient asymmetric catalyst for the glyoxylate-ene reaction with α-methylstyrene to give the ene product with 97.5% e.e. in 94% yield. A certain level of positive non-linear effect (asymmetric amplification) is also observed in the present glyoxylate-ene reaction. The 6-Br-BINOL-derived titanium complex (98% e.e.) affords the glyoxylate-ene product of methylenecyclohexane with more than 99% e.e.! in 82% yield. Furthermore, 70% e.e. of 6-Br-BINOL leads eventually to 85% e.e. of the glyoxylate-ene product with α-methylstyrene. A higher level of asymmetric induction is observed in a less polar solvent, toluene, suggesting that dipolar repulsion is operative in controlling the conformation of the ligand 6-Br-BINOL (**1**). Unfortunately, however, the titanium complex **N′** derived from the binaphthyl ligand **2** with the sterical demanding trifylamine moiety gave a disappointingly low level of asymmetric induction in the glyoxylate-ene reaction.

Key words: Titanium complexes; Binaphthyl complexes; Asymmetric catalysis

Introduction

The development of an asymmetric catalyst for carbon–carbon bond formation, in particular, is a most challenging and formidable endeavor in organic synthesis [1]. Such an organometallic catalyst not only accelerates the carbon–carbon bond forming reactions of complexed substrates, but also differentiates diastereomeric transition states to control eventually the product stereochemistry in the absolute sense. Thus, the selection of the central metals and molecular designing of the chiral ligands are particularly important. We have recently developed an enantioselective catalysis of the carbonyl-ene reaction [2] with glyoxylate catalyzed by chiral binaphthol-derived titanium dihalide complexes (**X**) [3] which provides an efficient access to the asymmetric synthesis of α-hydroxyesters of biological and synthetic importance [4]. We now wish to report herein a new class of designed binaphthyl-derived titanium complexes (**N**), which are found to be an efficient asymmetric catalyst for the glyoxylate-ene reaction.



*Author to whom correspondence should be addressed.

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Results and discussion

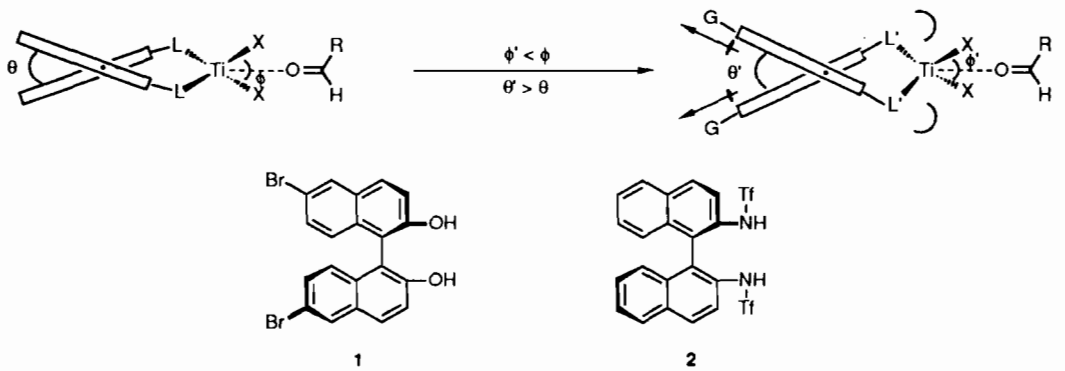
The chiral titanium dihalide catalysts (**X**) were prepared *in situ* from optically pure binaphthol (BINOL) and diisopropoxytitanium dihalide ($(i\text{-PrO})_2TiX_2$: X = Br or Cl) in the presence of molecular sieves (MS 4 Å) [3]. In the original titanium dihalide catalysts (**X**), the halide ligands would act as the stereocontrolling element to direct the enantiofacial selective attack of olefins (ene components) to the glyoxylates. Therefore, the compression of the internal bond angle X–Ti–X (ϕ') would lead to the accomplishment of a higher level of asymmetric induction, hopefully due to the better shielding effect over the enantioface of the glyoxylate by the halide ligands (X). Here, the design to set the larger dihedral angle of binaphthyls (θ') and/or sterically bulky moieties (L') rendering the higher Lewis acidity for titanium complexes is the guiding principle in modifying the binaphthyl ligands (Scheme 1). We have thus designed a new class of titanium complexes (**N** or **N'**) prepared from modified binaphthyls (**1** or **2**) and $(i\text{-PrO})_2TiX_2$ (X = Br or Cl) in the presence of MS 4 Å hoping to provide a higher level of asymmetric catalysis (enantiofacial selectivity and catalytic activity, namely Lewis acidity) for the glyoxylate-ene reaction.

TABLE 1. Asymmetric catalytic glyoxylate-ene reactions[a]

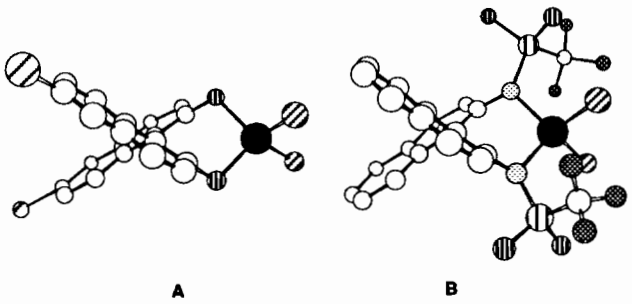
Entry	Ene	Catalyst	% Yield	% e.e.[b]
1[c]		N(X = Cl)	92	85
2		N(X = Br)	82	> 99
3		N(X = Cl)	94	97.5
4[d]		N(X = Cl)	99	99.0
5[e]		N'(X = Cl)	69	0
6[e]		N'(X = Br)	58	0

[a]Unless otherwise noted, reactions were carried out in CH_2Cl_2 using 1.0 mmol of glyoxylate, 1.5 mmol of ene and 0.05 mmol of chiral titanium catalyst. [b]Enantiomeric purity was determined by HPLC analysis. [c]70.4% e.e. of 1,1'-bi-6-bromo-2-naphthol (**1**) was used as the chiral ligand. [d]In toluene. [e]0.1 mmol of chiral titanium catalyst (**N'**) was used.

First, the titanium complexes **N** derived from 1,1'-bi-6-bromo-2-naphthol (6-Br-BINOL) were examined to hopefully bear a larger dihedral angle (θ') presumably because of the dipolar repulsion between the two 6-brominated binaphthyl rings. 6-Br-BINOL was thus prepared through bromination in acetic acid, according to the literature procedure [5]. The titanium complex (**N**: X = Cl) obtained from 6-Br-BINOL and $(i\text{-PrO})_2TiX_2$ (X = Cl) in the presence of MS 4 Å gave only a moderate level of 85% enantiomeric excess (e.e.) in the glyoxylate-ene reaction with α-methylstyrene (Table 1, entry 1). However, we have found that the enantiomeric purity of the 6-Br-BINOL thus prepared is only 70.4% e.e. by chiral HPLC analysis. Consequently, a certain level of positive non-linear effect [6] (asymmetric amplification) [7] is also observed using the present type of chiral ligands. Indeed, the titanium complex (**N**: X = Br) derived from the purified 6-Br-BINOL (up to 98.0% e.e.) affords the glyoxylate-ene product of methylenecyclohexane with more than 99% e.e.! in 82% chemical yield using 5 mol% of complex **N** (entry 2). An extremely high level of asymmetric induction is also obtained with 98.0% e.e. of 6-Br-BINOL in the glyoxylate-ene reaction with α-methylstyrene to give the ene product with 97.5% e.e. and in 94% yield (entry 3). Furthermore, an enhanced level of asymmetric induction (99.0% e.e.) is observed for the glyoxylate-ene reaction with α-methylstyrene in a less polar solvent, toluene (entry 4) suggesting that dipolar repulsion is indeed operative in controlling the conformation of the modified binaphthyl ligand **1** [8], as shown in the 3-D structure **A**, rendered with the Molecular Mechanics Version 2 run on a Tectronix



Scheme 1.



A B

Fig. 1. 3-D structures.

CAChe® molecular modeling workstation (Fig. 1). The chiral titanium complexes **N** are thus found to be a new type of efficient asymmetric catalyst for the glyoxylate-ene reaction [9].

Second, the titanium complexes **N'** (X = Br or Cl) derived from the binaphthyl ligand **2** with a sterically demanding trifylamine moiety were examined. After several trials, we found the procedure for the bistrifylation of binaphthyldiamine [10]. Unfortunately, however, the titanium complexes **N'** thus obtained from binaphthylamine ditriflate (**2**) and $(i\text{-PrO})_2TiX_2$ (X = Br or Cl) in the presence of MS 4 Å gave a disappointingly low level of e.e. in the glyoxylate-ene reaction (Table 1, entries 4 and 5). There would be a competing controlling effect of the trifylamine part versus the halide ligands (X) of **2** as shown in the 3-D structure **B** (Fig. 1).

In summary, we have disclosed herein the designed binaphthyl-derived titanium complexes (**N**) as a new type of extremely efficient asymmetric catalyst for the glyoxylate-ene reaction.

Experimental

General

Molecular sieves 4 Å (activated powder) were purchased from Aldrich Chemical Co. (*R*)-(+)- and (*S*)-(−)-1,1'-bi-2-naphthol were purchased from Wako Pure Chemical Ltd. Melting points and boiling points were uncorrected. ^1H and ^{13}C NMR spectra were measured on Varian EM390 (90 MHz), Gemini 200 (200 MHz) or 300 (300 MHz), and Jeol FX-90Q (90 MHz) or GSX-500 (500 MHz) spectrometers. Chemical shifts of ^1H NMR were described in ppm downfield from tetramethylsilane as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in ppm in $CDCl_3$ as an internal standard ($\delta = 77.1$). IR spectra were measured on a Jasco FT/IR-5000 spectrometer. Optical rotations were measured on a Jasco DIP-140. Mass spectra were obtained with a Jeol JMS-300 or AX-500. Liquid chromatographic analyses were conducted on a Jasco TRI ROTAR SR or Shimadzu LC-6A instrument equipped with a model SPD-6A spectrometer as a UV light (at the indicated wave length) detector. Peak area was calculated by a Shimadzu model C-R6A or C-R3A as an automatic integrator. Analytical thin layer chromatography (TLC) was performed on glass plates and aluminium sheets pre-coated with silica gel (Merck, Kieselgel 60 F_{254}, layer thickness 0.25 and 0.2 mm, respectively). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$. All experiments were carried out under argon atmosphere. Toluene was distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane and hexane were freshly distilled from CaH_2.

Diisopropoxytitanium(IV) dichloride

A 30-ml, two-necked, round-bottomed flask equipped with a magnetic stirring bar and argon inlet was charged with 5 ml of hexane and titanium(IV) isopropoxide (2.98 ml, 10 mmol). To the solution was added titanium(IV) chloride (1.10 ml, 10 mmol) slowly at ambient temperature from a syringe. The addition of titanium(IV) chloride caused the mixture to warm to about 40 °C. After stirring for 10 min, the solution was allowed to stand for 6 h at room temperature, and the precipitate which forms was isolated. This was accomplished by removing the supernatant with a syringe. The solid residue was washed with hexane (2 ml × 2) and recrystallized from hexane (3 ml). The crystallization was carried out in the same flask by heating to reflux and then leaving the solution at room temperature overnight. Again the supernatant was removed with a syringe and the crystalline was vacuum dried to give 3.6 g of highly moisture sensitive product. The crystalline was stored in a refrigerator. ^1H NMR (500 MHz, $CDCl_3$): δ 1.45 (d, $J = 6.0$ Hz, 12H), 4.91 (br, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 87.6.

Diisopropoxytitanium(IV) dibromide

Diisopropoxytitanium(IV) dibromide was prepared in a similar manner described for the preparation of the diisopropoxytitanium(IV) dichloride. Lumps of titanium(IV) bromide (3.67 g, 10 mmol) were dissolved in hexane (5 ml) at room temperature. To the resultant solution titanium(IV) isopropoxide (2.98 ml, 10 mmol) was added slowly. Heat evolved on addition of titanium(IV) isopropoxide. The reaction mixture was stirred for 10 min and allowed to stand for 6 h at room temperature. After recrystallization from hexane, the crystalline was stored in a refrigerator.

(R)-1,1'-Bi-6-bromo-2-naphthol

Br_2 (3.2 g) dissolved in glacial AcOH (5 ml) was added continuously within 60 min to a solution of (*R*)-1,1'-bi-2-naphthol (2.86 g, 10 mmol) in glacial AcOH (20 ml) at 60 °C. After stirring for 30 min at that

temperature, the reaction mixture was cooled to room temperature. The resultant solution was slowly poured into saturated $NaHCO_3$ solution (300 ml) at 0 °C. The mixture was extracted with AcOEt (100 ml) and washed with brine (50 ml). Usual work-up followed by silica gel column chromatography afforded (*R*)-1,1′-bi-6-bromo-2-naphthol in 85% yield (3.77 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.02 (bs, 2H), 6.96 (d, J=9.2 Hz, 2H), 7.37 (dd, J=1.9, 9.2 Hz, 2H), 7.39 (d, J=9.2 Hz, 2H), 7.89 (d, J=9.2 Hz, 2H), 8.05 (d, J=1.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 110.8, 118.1, 119.1, 126.0, 130.6, 130.7, 130.8, 131.0, 132.0, 153.1. IR (KBr) 3420, 1510, 1460, 1440, 1100, 720 cm^{-1}. $[\alpha]_D^{29}$ −38.5° (*c* 0.905, THF) (70.4% e.e.). HPLC (Daicel CHIRALPAK AS, eluent, hexane/isopropanol=3:1, flow rate 0.5 ml/min, detection 254-nm light), t_R of (*R*)-isomer 14.3 min and (*S*)-isomer 11.9 min.

Preparation of 1,1′-bi-6-bromo-2-naphthol in 98% e.e.

The partially resolved 1,1′-bi-6-bromo-2-naphthol (70.4% e.e., 2.39 g) obtained as above was dissolved in a mixture of hexane (30 ml) and CH_2Cl_2 (10 ml). The solution was left to stand overnight at room temperature. The resultant crystalline was filtered off to provide 1,1′-bi-6-bromo-2-naphthol in low enantiomeric purity (34.6% e.e., 1.04 g). The filtrate was concentrated under reduced pressure to give 1,1′-bi-6-bromo-2-naphthol in high enantiomeric purity (98.0% e.e., 1.35 g): $[\alpha]_D^{29}$ −52.3° (*c* 1.15, THF) (98.0% e.e.).

(R)-1,1′-Binaphthyl-2,2′-N,N′-bis(trifluoromethanesulfonyl)amine

To a solution of (*R*)-1,1′-binaphthyl-2,2′-diamine (285 mg, 1.00 mmol) in dichloromethane (10 ml) was added diisopropylethylamine (1.1 ml, 6.47 mmol) at −78 °C. After stirring for 10 min, trifluoromethanesulfonic anhydride (620 mg, 2.20 mmol) was added and stirred for 1 h. Then the reaction mixture was quenched by the addition of 3 N HCl (5 ml) and extracted twice with dichloromethane (totally 20 ml). The combined organic layer was washed with brine (10 ml), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by silica gel chromatography (ethyl acetate) gave (*R*)-1,1′-binaphthyl-2,2′-*N*,*N*′-bis(trifluoromethanesulfonyl)amine in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.30 (s, 2H), 7.06 (d, J=8.5 Hz, 2H), 7.41 (dd, J=8.5, 6.9 Hz, 2H), 7.57 (dd, J=8.2, 6.9 Hz, 2H), 7.93 (d, J=9.1 Hz, 2H), 8.02 (d, J=8.2 Hz, 2H), 8.15 (d, J=9.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 117.3, 120.1, 121.5, 122.5, 124.7, 127.3, 128.8, 128.9, 131.9, 132.0, 132.2. IR (KBr): 3266, 1624, 1417, 1201, 1139, 994, 818, 735 cm^{-1}. $[\alpha]_D^{24}$ +69.5° (*c* 0.45, $CHCl_3$).

General procedure for BINOL-Ti catalyzed ene reaction: preparation of methyl 2-hydroxy-4-phenyl-4-pentenoate

To a suspension of activated powder molecular sieves 4 Å (250 mg) in CH_2Cl_2 (5 ml) was added a crystalline of diisopropoxytitanium dichloride (11.8 mg, 0.05 mmol) and (*R*)-1,1′-bi-6-bromo-2-naphthol (22.2 mg, 0.05 mmol) at room temperature under an argon atmosphere. After stirring for 1 h at room temperature, the catalyst solution was cooled to −30 °C, then α-methylstyrene (177 mg, 1.5 mmol) and a solution of freshly-distilled methyl glyoxylate (88 mg, 1.0 mmol) in CH_2Cl_2 (0.5 ml) was added into the catalyst solution. After stirring for 2 h, the reaction mixture was poured into saturated $NaHCO_3$ (10 ml). Molecular sieves 4 Å was filtered off through a pad of Celite and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with brine. The extract was then dried over $MgSO_4$ and evaporated under reduced pressure. Separation by silica gel chromatography (hexane/ethyl acetate=20:1) gave methyl 2-hydroxy-4-phenyl-4-pentenoate.

(−)-Methyl 2-hydroxy-4-phenyl-4-pentenoate

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.76 (bs, 1H), 2.88 (dd, J=8.1, 13.5 Hz, 1H), 3.13 (dd, J=4.5, 13.5 Hz, 1H), 3.68 (s, 3H), 4.33 (m, 1H), 5.28 (bs, 1H), 5.48 (bs, 1H), 7.4 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.4, 52.2, 69.2, 116.5, 126.6, 127.9, 128.6, 140.4, 143.7, 175.1. IR (neat): 3450, 2940, 1730, 1440, 1030, 910, 780, 710 cm^{-1}. $[\alpha]_D^{23}$ −30.55° (*c* 4.83, $CHCl_3$) (97% e.e.). HRMS for $C_{12}H_{14}O_3$: calc. 206.0943, found 206.0936. HPLC (SUMICHIRAL OA-2500I, eluent, hexane/1,2-dichloroethane/ethanol=200:40:1, flow rate 0.5 ml/min, detection 254-nm light), t_R of (−)-isomer 16.8 min and (+)-isomer 18.3 min.

(+)-Methyl 3-(1′-cyclohexenyl)-2-hydroxypropionate

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.60 (m, 4H), 1.98 (m, 4H), 2.27 (dd, J=7.5, 13.5 Hz, 1H), 2.40 (b, 1H), 2.48 (dd, J=5.5, 13.5 Hz, 1H), 3.77 (s, 3H), 4.30 (dd, J=7.5, 5.5 Hz, 1H), 5.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.1, 22.8, 25.3, 28.4, 43.2, 52.4, 69.4, 125.8, 133.2, 175.7. IR (neat): 3490, 2950, 1740, 1440, 1100, 760, 740, 700 cm^{-1}. $[\alpha]_D^{19}$ +12.27° (*c* 3.35, $CHCl_3$) (98% e.e.). HRMS for $C_{10}H_{16}O_3$: calc. 184.1100, found 184.1107. HPLC (SUMICHIRAL OA-2500I, eluent, hexane/1,2-dichloroethane/ethanol=400:40:1, flow rate 0.5 ml/min, detection 218-nm light), t_R of (+)-isomer 32.0 min and (−)-isomer 33.5 min.

References

1 (a) R. Noyori and M. Kitamura, in R. Schefford (ed.), *Modern Synthetic Methods,* Vol. 5, Springer, Berlin, 1989, p. 115; (b) B. Bosnich, *Asymmetric Catalysis,* Martinus Nijhoff, Dordrecht, 1986; (c) H.B. Kagan, in G. Wilkinson (ed.), *Comprehensive Organometallic Chemistry,* Vol. 8, Pergamon, Oxford, 1982, p. 463; (d) Y. Hayashi and K. Narasaka, *J. Synth. Org. Chem. Jpn., 48* (1990) 280; K. Narasaka, *Synthesis,* (1991) 1; (e) K. Mikami, M. Terada, S. Narisawa and T. Nakai, *Synlett,* (1992) 255.

2 (a) K. Mikami and M. Shimizu, *Chem. Rev., 92* (1992) 1021; (b) B.B. Snider, *Comprehensive Organic Synthesis,* Vols. 2 and 5, Pergamon, London, 1991; (c) W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed. Engl., 17* (1978) 476; (d) J.M. Conia and P. Le Perchec, *Synthesis,* (1975) 1; (e) H.M.R. Hoffmann, *Angew. Chem., Int. Ed. Engl., 8* (1969) 556.

3 (a) K. Mikami, M. Terada, S. Narisawa and T. Nakai, *Org. Synth., 71* (1992) 14; (b) K. Mikami, M. Terada and T. Nakai, *J. Am. Chem. Soc., 111* (1989) 1940; *112* (1990) 3949.

4 S. Omura, *J. Synth. Org. Chem. Jpn., 44* (1986) 127; S. Hanessian, *Total Synthesis of Natural Products: The Chiron Approach,* Pergamon, New York, 1983, Ch. 2; K. Mori, in J. Apsimon (ed.), *The Total Synthesis of Natural Products,* Wiley, New York, 1981, Ch. 1; D. Seebach and E. Hungerbuhler, in R. Schefford (ed.), *Modern Synthetic Methods,* Verlag Chemie, Frankfurt, Germany, 1980.

5 M. Vondenhof and J. Mattay, *Tetrahedron Lett., 31* (1990) 985, and refs. therein.

6 K. Mikami and M. Terada, *Tetrahedron, 48* (1992) 5671.

7 R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl., 30* (1991) 49; N. Oguni, Y. Matsuda and T. Kaneko, *J. Am. Chem. Soc., 110* (1988) 7877; C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami and H.B. Kagan, *J. Am. Chem. Soc., 108* (1986) 2353.

8 M.W. Wong, M.J. Frisch and K.B. Wiberg, *J. Am. Chem. Soc., 113* (1991) 4776.

9 R. Feld and P.L. Cowe, *The Organic Chemistry of Titanium,* Butterworths, London, 1965; D. Seebach, B. Weidmann and L. Widler, in R. Schefford (ed.), *Modern Synthetic Methods,* Vol. 3, Springer, Berlin, 1989; M.T. Reetz, *Organotitanium Reagents in Organic Synthesis,* Springer, Berlin, 1986.

10 H. Takahashi, T. Kawakita, M. Ohno, M. Yoshioka and S. Kobayashi, *Tetrahedron, 48* (1992) 5691.