Chiral Titanium Complex-Catalyzed Carbonyl-Ene Reaction with Glyoxylate: Remarkable Positive Nonlinear Effect

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Abstract: The enantioselective glyoxylate-ene reaction catalyzed by chiral titanium complex derived from partially resolved binaphthol (BINOL) is shown to exhibit a remarkable level of asymmetric amplification (positive nonlinear effect). Thus, the optical yield of the ene product significantly exceeds the enantio-purity of the chiral ligand (BINOL).

The development of efficient processes for the asymmetric synthesis of chiral molecules is an important task in organic synthesis.¹ Among others, the asymmetric catalysis by chiral metal complexes maximizes the synthetic efficiency.^{1,2} A non-classical phenomenon in recent progress of asymmetric catalysis is the nonlinear effect between ee values of the chiral ligands and the products.³ A deviation from the usually assumed linear relationship between the ee of a chiral auxiliary and the extent of the asymmetric induction has recently been observed in certain asymmetric processes (Fig. 1).⁴ The Hajos-Wiechert intramolecular addol reaction shows a concave deviation from the linear relationship, which we wish to call <u>negative</u> nonlinear effect ((-)-NLE): the partially resolved proline catalyst provides the product in % ee lower than that calculated by linearity. By contrast, the Sharpless epoxidation of geraniol by a stoichiometric use of chiral titanium complex exhibits the convex deviation from the linear relationship, which can be referred to as <u>positive</u> nonlinear effect ((+)-NLE).



Fig. 1

Since then considerable attention has been focused on the (+)-NLE particularly in the asymmetric catalysis of C-C bond formations, from a practical and/or mechanistic point of view. Quite recently the remarkable level of (+)-NLE (asymmetric amplification) has been found in the addition of diethylzinc to benzaldehyde catalyzed by β -amino alcohols, wherein the optical yield of the products significantly exceeds the enantio-purity of the chiral auxiliaries employed.⁵ We have recently developed an enantioselective catalysis of the carbonyl-ene reaction with glyoxylate catalyzed by the chiral titanium complexes (1), which provides an efficient access to the asymmetric synthesis of α -hydroxyesters of biological and synthetic importance.⁶ Reported herein is a full account on a remarkable (+)-NLE in the asymmetric catalytic glyoxylate-ene reaction (eq. 1).⁷



We have already reported the asymmetric glyoxylate-ene reaction catalyzed by the chiral titanium complex (1) prepared *in situ* from enantiomerically pure binaphthol (BINOL) and diisopropoxytitanium dihalide (X=Cl or Br) in the presence of molecular sieves (MS 4A).⁶ A remarkable level of (+)-NLE is further observed by a similar use (1 mol%) of chiral titanium catalyst (1a) (X=Br) prepared however from a partially resolved (*R*)-BINOL. For instance, the use of 1a having 33.0% ee provides the ene product (4) with 91.4% ee in 92% chemical yield (eq. 1, Table 1). Fig. 2 graphically shows the ee's of the carbonyl-ene products as a function of the ee of BINOL ligand: similarly high levels of (+)-NLE are obtained with the dichloro catalyst (1b), indicating that the use of BINOL of 35-40% ee is good enough to provide the same level of % ee as obtained with enantiomerically pure BINOL. Furthermore, the degree of asymmetric amplification is found to increase significantly with decrease in the molar ratio (concentration) of the catalyst with a given optical purity of BINOL (31.0% ee) to the constant concentration of glyoxylate and α -methylstyrene (Table 2).

la (% ee)	4 (% ee)	% yield
13.0	59.9	94
33.0	91.4	92
46.8	92.9	88
66.8	94.4	96
100	94.6	98

^{*a*} All reactions were carried out using 1.0 mmol of methyl glyoxylate (3), 2.0 mmol of α -methylstyrene (2), and 0.01 mmol of **1a** in CH₂Cl₂ (5.5 ml).



Fig. 2. (+)-NLE in asymmetric glyoxylate-ene reaction catalyzed by 1 (1.0 mol%).

mol% ^{b,c}	concentration (mM)	% ee	% yield
1	1.7	87.6	97
5	8.4	83.9	93
10	17	81.3	99
20	34	80.6	96
100	170	74.9	88

Table 2. Effect of catalyst molar ratio (concentration) on (+)-NLE.a

^{*a*} All reactions were carried out in a constant concentration; methyl glyoxylate (3) (1.0 mmol) and α methylstyrene (2) (2.0 mmol) in CH₂Cl₂ (5.5 mL). ^{*b*} (*i*-PrO)₂TiCl₂/BINOL (31.0% ee) was used as a chiral catalyst. ^{*c*} Mol% was defined on the basis of 3.

In view of the dinuclear chelate structure of similar titanium complexes such as diphenoxytitanium dichloride,^{8b} it appears likely that the remarkable NLE is a result of a marked difference in the catalytic activity between the diastereomeric dimers (R)(R)- $(1)_2$ (A) and (R)(S)- $(1)_2$ (B) (Fig. 3).⁹ In fact, simple kinetic studies reveal that the catalytic activity (initial reaction rate) by the chiral titanium complex derived from 100% ee of BINOL is 35 times greater than that of the complex derived from 0% ee of BINOL (10 mol% catalytic scale in 17 mM concentration) (Fig. 4). It therefore appears that the catalyst thus formed from racemic BINOL is not a racemic mixture of homochiral dimers (R)(R)- $(1)_2$ and (S)(S)- $(1)_2$ which should exhibit equally high level of catalytic activity to give however the completely racemic ene product, but rather the meso dimer (R)(S)- $(1)_2$ (B) which is more stable (*vide infra*) and hence less reactive. Thus, the racemic BINOL with diisopropoxytitanium

dichloride would readily form the meso type (C_i symmetric) dinuclear complex (**B**) possessing the coplanar Ti_2O_2 four membered ring. On the other hand, the enantio-pure BINOL could afford the chiral dimer (**A**) with C_2 symmetry possessing the distorted Ti_2O_2 four membered ring.



Fig. 4. Initial reaction rates of ene reactions catalyzed by **1b** (10 mol%) derived from 100% and 0% ee of BINOL.

The dimeric nature of the BINOL-derived complex (1) was proven by the vapor pressure osmometric molecular weight measurement in dichloromethane at 30 °C (Fig. 5). Both the homo- and heterochiral titanium complexes (1b), prepared through azeotropic (toluene) removal of isopropanol from the mixture of BINOL and $(i-PrO)_2TiCl_2$, were found to exsist in the dimeric form in 30 mM concentration (obsd. around 800, calcd. 806 for $(C_{20}H_{12}O_2TiCl_2)_2)$.¹⁰ Furthermore, the MW of homochiral (R)(R)-(1b)₂, prepared *in situ* from (*i*-PrO)₂TiCl₂ and optically pure BINOL in the presence of MS 4A, indicated the presence of *i*-PrOH¹¹ and was

concentration-dependent, ranging from 864 (calcd. 866 for $(C_{20}H_{12}O_2TiCl_2)_2 \cdot i$ -PrOH) in 37 mM solution to 762 (9.2 mM solution), suggesting that the homochiral dimer dissociates to the monomeric form to some extent in dilute solutions. By contrast, the MW of the meso dimer (*R*)(*S*)-(**1b**)₂ is not concentration-dependent, 872 (37 mM) and 874 (9.2 mM), indicating the stability of the heterochiral dimer. The observed concentration effect on the MW of the homochiral dimer indicates its lability to dissociate to the monomers, thus accounting for the higher degree of (+)-NLE in lower concentration of the chiral titanium catalyst (Table 2). In other words, the origin of the (+)-NLE in our asymmetric catalysis can be explained on the basis of diastereomeric self-recognition by the chiral titanium catalyst (1): the stability of the readily formed heterochiral dimer and the lability of the homochiral dimer to dissociate to the monomeric complex eventually with glyoxylate.¹² Interestingly, the observed dependence of the degree of asymmetric amplification on the catalyst concentration is opposite to that reported by Noyori et al. in their excellent mechanistic study of the β-aminoalcohol-catalyzed addition reaction of dialkylzinc to benzaldehyde,^{5b} wherein only the reaction rate catalyzed by the racemic DAIB is surprisingly decreased with increase in the ratio of racemic DAIB to the dialkylzinc and/or aldehyde.¹³



c: 1b (100% ee) in situ prepared.

Finally, the observed relationship of ee's of the ene products to the ee's of BINOL of less than 33.3% ee R somewhat departs from the nonlinear curve calculated on the basis of 35 times rate difference (K = k_{homo}/k_{hetero} = 35 in 10 mol% scale) between the homo- and heterochiral BINOL-Ti dimers (1)₂ (Fig. 7). A refined explanation of such departure from the calculated curve could be provided by considering the involvement of a trinuclear complex.¹⁴ The trimer (*e.g.* (*R*)(*S*)(*R*)-(1)₃) would dissociate more slowly into the reactive monomer than the homochiral dimer. Indeed, the presence of trimer of the BINOL-derived complex in 33.3% ee was proven by the MW measurement though in higher concentration (Fig. 5).



Fig. 7. Nonlinear curve and (+)-NLE of ene reaction catalyzed by 1b (10 mol%).

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EXPERIMENTAL

General. Melting points and boiling points were uncorrected. ¹H and ¹³C NMR spectra were measured on a Varian EM390 or GEMINI 300 or a JEOL GSX-500 spectrometer. 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. Liquid chromatographic analyses were conducted on a JASCO TRI ROTAR SR or a Shimadzu LC-6A instrument equipped with SPD-6A as a ultra violet light detector. Molecular weight

measurements were conducted on a KNAUER vapor pressure osmometer. All experiments were carried out under an argon atmosphere. Dichloromethane and toluene were freshly distilled from CaH₂ and sodium benzophenone ketyl, respectively. Molecular sieves 4A (activated powder) and (\pm) -1,1'-bi-2-naphthol were purchased from Aldrich Chemical Co. (R)- And (S)-1,1'-bi-2-naphthol were purchased from Wako Pure Chemical Industries Ltd.

Enantiomeric Purity of Partially Resolved Binaphthol. The enantiomeric purity was determined by the HPLC analysis using chiral column. HPLC (SUMICHIRAL OA-2500I, eluent, hexane/1,2-dichloroethane/ethanol = 200: 40: 5, flow rate 1.0 mL/min, detection 254-nm light), t_R, (S)-isomer: 10.9 min; (R)-isomer: 12.3 min.

Positive Nonlinear Effect.

Preparation of Catalyst Solution (for Catalyst 1b). A catalyst solution suspended with molecular sieves 4A was prepared from partially resolved binaphthol and diisopropoxytitanium dichloride as follows. To a suspension of activated powder molecular sieves 4A (1.0 g) in CH₂Cl₂ (5 mL) was added partially resolved binaphthol (13.0 ~ 66.8% ee) (57.3 mg, 0.20 mmol) at room temperature under an argon atmosphere. The suspension was stirred until binaphthol was completely dissolved. To the resultant suspension was added diisopropoxytitanium dichloride (47.4 mg, 0.20 mmol) at one portion. The resultant mixture was allowed to stand for 1 h at room temperature. The catalyst solution (0.25 mL of a 40 mM CH₂Cl₂ solution, 0.01 mmol) thus obtained was transferred to a 30-mL two necked flask charged with CH₂Cl₂ (4.75 mL). In all cases total volume of CH₂Cl₂ was 5.0 mL at this point.

Catalytic Glyoxylate-Ene Reaction. The catalyst solution prepared from the method above was cooled down to -30 °C. To the solution was added dropwise α -methylstyrene (236 mg, 2.0 mmol) and a solution of freshly-distilled methyl glyoxylate (88 mg, 1.0 mmol) in CH₂Cl₂ (0.5 mL). The reaction mixture was stirred for 3 h at -30 °C. The reaction was monitored for completion by thin layer chromatography. The resultant mixture was poured into saturated NaHCO₃ (10 mL). Molecular sieves 4A was filtered off through a pad of Celite, and the filtrate was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (10 mL x 2). The extract was then dried over MgSO₄ and evaporated under reduced pressure. Separation by silica gel column chromatography (hexane/ethyl acetate = 15 : 1) gave methyl 2-hydroxy-4-phenyl-4-pentenoate (4). The enantiomeric purity was determined by HPLC analysis using chiral column.

(*R*)-(-)-Methyl 2-Hydroxy-4-phenyl-4-pentenoate (4). ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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, CHCl₃) (97% ee); HRMS for C₁₂H₁₄O₃ calcd. 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, (*R*)-(-)-isomer: 16.8 min; (*S*)-(+)-isomer: 18.3 min.

Kinetic Studies. To a suspension of activated powder molecular sieves 4A (0.5 g) in CH₂Cl₂ (5 mL) was added (*R*)- or (\pm)-binaphthol (28.6 mg, 0.10 mmol) and biphenyl (30.0 mg) as an internal standard at room temperature under an argon atmosphere. The suspension was stirred until binaphthol was completely dissolved. To the resultant suspension was added diisopropoxytitanium dichloride (23.7 mg, 0.10 mmol) at one portion. After stirring for 1 h at room temperature, the resultant mixture was cooled down to -30 °C. To the catalyst solution was added α -methylstyrene (236 mg, 2.0 mmol) and subsequently a CH₂Cl₂ (0.5 mL) solution of

freshly-distilled methyl glyoxylate (88 mg, 1.0 mmol) over 0.5 min period at that temperature. At 0.7 ~ 18 min intervals, a portion (ca. 0.5 mL) was quickly transferred by using well-cooled syringe (the syringe was surrounded by polyethylene sheets cooled down to -78 °C by using dry-ice/acetone bath) to a mixture of saturated NaHCO₃ (0.5 mL) and ether (1 mL) at 0 °C. The yield was quantitated by capillary GC analysis of the organic layers. The yield was calculated by the comparison with the integration of the internal standard and that of the ene product (4). Capillary GLC (OV-1, 30 m, Column Temp. 160 °C, detection FID). t_R of biphenyl: 6.3 min, t_R of the ene product (4): 11.2 min.

Concentration Effect of the Catalyst. A 40 mM CH₂Cl₂ solution of the catalyst (31.0% ee) was prepared according to the method above. The 40 mM catalyst solution (0.25 mL ~ 5.0 mL, 0.01 mmol ~ 0.2 mmol) was added to a 30-mL two-necked flask charged with an appropriate volume of CH₂Cl₂ (~ 4.75 mL). In all cases total CH₂Cl₂ volume was 5.0 mL at this point. To the catalyst solution thus obtained was added α -methylstyrene (236 mg, 2.0 mmol) at -30 °C. Subsequent addition of a CH₂Cl₂ (0.5 mL) solution of freshly-distilled methyl glyoxylate (88 mg, 1.0 mmol) at -30 °C furnished the reaction mixture in the constant concentration of the substrates (methyl glyoxylate, 170 mM; α -methylstyrene, 340 mM). At this point, the catalyst concentration was ranged from 1.7 to 34 mM. After stirring for 3 h at -30 °C, the reaction mixture was poured into saturated NaHCO₃ (10 mL). Molecular sieves 4A was filtered off through a pad of Celite, and the filtrate was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (10 mL x 2). The extract was dried over MgSO₄ and evaporated under reduced pressure. Separation by silica gel column chromatography (hexane/ethyl acetate = 15 : 1) gave methyl 2-hydroxy-4-phenyl-4-pentenoate (4). The enantiomeric purity was determined by HPLC analysis using chiral column.

Equimolar Use of the Catalyst. The ene reaction was performed as described above except for the use of equimolar amount of titanium complex. To a suspension of activated powder molecular sieves 4A (5.0 g) in CH_2Cl_2 (5 mL) was added partially resolved binaphthol (31.0% ee) (286 mg, 1.00 mmol) at room temperature under an argon atmosphere. The suspension was stirred until binaphthol was completely dissolved. To the resultant suspension was added diisopropoxytitanium dichloride (237 mg, 1.00 mmol) at one portion. The resultant mixture was allowed to stand for 1 h at room temperature. To the resultant suspension was added α -methylstyrene (2.0 mmol) and methyl glyoxylate (1.0 mmol) according to the above method.

Molecular Weight Measurement.

Preparation *via* **Toluene Azeotrope** from **Binaphthol** (100% or 0% ee) and **Diisopropoxytitanium Dichloride**. A 200-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, and argon inlet was charged with powdered molecular sieves 4A (15.0 g), binaphthol (859 mg, 3.00 mmol), and 150 mL of toluene. After stirring for 20 min at ambient temperature, the resulting suspension was added diisopropoxytitanium dichloride (711 mg, 3.00 mmol) at one portion. At this point, the reaction mixture was turned to red-brown suspension. After stirring for 20 h at that temperature, the resulting suspension was transferred to a centrifuging tube capped with rubber septum and centrifuged at 4000 rpm for 20 min. Again the resultant supernatant was transferred to 200-mL two-necked round-bottomed flask equipped with azeotropic apparatus and magnetic stirring bar. The resulting suspension was heated to reflux under argon atmosphere with azeotropic removal of isopropanol, when all solvents were removed over 2 h period. The resulting solid residue was suspended by adding 50 mL of pentane. The suspension was stirred for 20 min and pentane was then decanted with a syringe. The resulting precipitate was vacuum dried to give the binaphthol-titanium complex (1b) in 90 - 95 % yield.

free of *i*-PrOH for molecular weight measurements. Three to four CH₂Cl₂ solutions (10.0 mL) with graduated concentrations of 1b ($14.6 \sim 120.7$ mg) were prepared.

In situ Preparation from Binaphthol (100%, 33%, or 0% ee) and Diisopropoxytitanium Dichloride. A 200-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, and argon inlet was charged with powdered molecular sieves 4A (15.0 g), binaphthol (859 mg, 3.00 mmol) (100%, 33%, or 0% ee), and 90 mL of CH₂Cl₂. After stirring for 20 min at ambient temperature, the resulting suspension was added diisopropoxytitanium dichloride (711 mg, 3.00 mmol) at one portion. At this point, the reaction mixture was turned to red-brown suspension. After stirring for 3 h at that temperature, the resulting suspension was ransferred to a centrifuging tube capped with rubber septum and centrifuged at 4000 rpm for 20 min. Again the resultant supernatant was transferred to 200-mL two-necked round-bottomed flask equipped with distillation apparatus and magnetic stirring bar. The stirred mixture was evaporated at 30 °C under reduced pressure to give deep reddish residue. The resulting residue was suspended by adding 50 mL of pentane. The suspension was stirred for 20 min and pentane was then decanted with a syringe. The resultant precipitate was vacuum dried to give the titanium complex in 90 - 95 % yield. The binaphthol-titanium complex thus obtained was used as samples including ca. 0.5 equiv. of *i*-PrOH for molecular weight measurements. Three to four CH₂Cl₂ solutions (10.0 mL) with graduated concentrations of **1b** (30.2~ 236.5 mg) were prepared.

Molecular Weight Measurement of the Titanium Complex. The determination of molecular weight was carried out with a vapor pressure osmometer. Three solutions with graduated concentrations of 1,1'-bi-2-methoxynaphthalene were prepared for the calibration. By dividing the measurement value by the molar concentration S value was obtained, which represented the slope of the calibration line, according to the following equation: $S = M/K_{calib}$, where, $K_{calib} =$ measurement value for calibration, M = molar concentration of solute (in this case 1,1'-bi-2-methoxynaphthalene) in 1000 mL of solvent. S value of this osmometer was calculated to be 3.70×10^3 on the basis of the calibration of a CH₂Cl₂ (10.0 mL) solution of 1,1-bi-2-methoxynaphthalene (25.3 ~ 101.0 mg). The molecular weight was calculated in each case from: $MW = (S \times \omega)/K_{mess}$, where, MW = molecular weight, $\omega =$ weight (g) of solute in 1000 mL of solvent, $K_{mess} =$ measurement value of the samples. The value of X-axis (mM) in Figure 5 was calculated by dividing the ω by molecular weight of a monomeric form, where the 433 and 403 was used for the monomeric molecular weight of the samples prepared through *in situ* and toluene azeotrope, respectively.

General Procedure for NMR Studies. All FID collections at the appropriate timing were stored on a floppy diskette. Samples for NMR experiment were prepared from the complexes of which preparation were described above. (*R*)- or (\pm)-1b (0.02 mmol) (prepared through *in situ* or toluene azeotrope) was placed in a well-dried 5 mm NMR tube replaced by argon. The complex was dissolved in CDCl₃ (1.0 mL) to give the NMR sample.

Calculation of the Nonlinear Curve. The nonlinear curve was calculated on the basis of the following hypothesis. The reactions using 50% ee of **1b**, for instance, would be catalyzed independently by the 1 : 1 mixture of homo- and heterochiral dimers. The nonlinear curve was thus calculated by the following equation: $\% \text{ ee}_{calcd} = \% \text{ ee}_{max} \times (K \times \% \text{ ee}_{BINOL})/[K \times \% \text{ ee}_{BINOL} + 1 \times (100 - \% \text{ ee}_{BINOL})]$, where, $\% \text{ ee}_{calcd} = \text{ calculated}$ value of the % ee of the ene product, $\% \text{ ee}_{max} = \%$ ee obtained by the use of enantio-pure catalyst, K (k_{homo}/k_{hetero}) = the ratio of initial reaction rates of enantio-pure and (±)-1b catalyzed reactions (In Fig. 7, K = 35 and 10 were represented).

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- 9. These 3-D structures were rendered with the Macintosh program Chem-3D⁺. Bond length/angle of Ti₂O₂ four membered ring and titanium binaphthoxide framework were based on the X-ray crystal analysis data of a similar type of diphenoxytitanium dichloride (ref. 8b) and diisopropoxytitanium binaphthoxide, which was generously provided by Professor Sharpless: C. A. Martin, Ph.D. Thesis, MIT, 1989.
- 10. Unfortunately however, the ¹H and ¹³C NMR spectra of the homochiral dimer are essentially equivalent to those of heterochiral dimer (Fig. 6a and 6b).
- 11. Indeed, ¹H NMR analysis of the titanium complex indicates the presence of *i*-PrOH (Fig. 6c).
- 12. There is some possibility for the homochiral dimer involving the carbonyl-ene reactions below -65 °C. Indeed, the optical yield of the carbonyl-ene reactions is surprisingly decreased when lowering the reaction temperature. For example, the glyoxylate-ene reaction at -70 °C with α-methylstyrene (2) was found to give the ene product with only 80% ee and in 12% chemical yield after 8 h even by the use of the enantio-pure BINOL-Ti complex (1b) to give 95% ee at higher temperature (-30 °C) (10 mol%).
- 13. In sharp contrast, the reaction rate using pure (-)-DAIB is not affected by the ratio (ref. 3a).
- 14. Trinuclear structure has been reported for diisopropoxytitanium binaphthoxide (see: ref. 9).