Remarkable Positive Nonlinear Effect in the Enantioselective Glyoxylate–Ene Reaction Catalysed by a Chiral Titanium Complex

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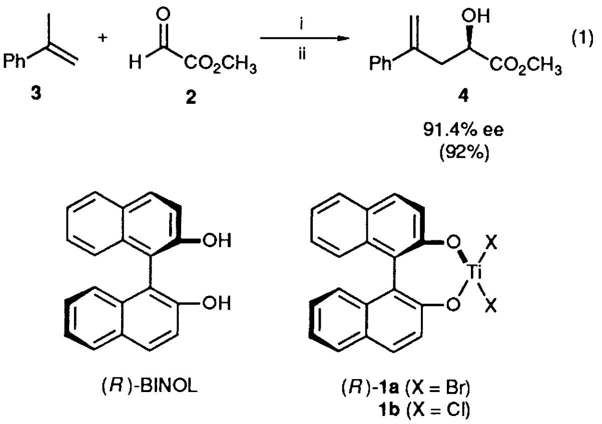
The enantioselective glyoxylate–ene reaction catalysed by chiral titanium complex derived from partially resolved BINOL is found to exhibit a remarkable level of asymmetric amplification, wherein the optical yield of the product significantly exceeds the enantiomeric purity of the chiral auxiliary employed.

Recently the so-called nonlinear effect (NLE) has been observed in the epoxidation of geraniol promoted by chiral titanium complex[1] and the addition of diethylzinc to benzaldehyde catalysed by β-aminoalcohols,[2] wherein the optical yield of the products significantly exceeds the enantiomeric purity of the chiral auxiliaries employed.[3] Oguni has referred to such phenomenon as 'asymmetric amplification',[2a] which is of mechanistic interest and synthetic value. We now wish to disclose a remarkable asymmetric amplification (positive NLE) in enantioselective glyoxylate–ene reaction catalysed by the chiral titanium complex (Scheme 1).

In previous papers,[4] we have reported the remarkable levels of enantioselection (>90% ee) in the glyoxylate–ene reaction catalysed by the chiral titanium complexes **1** prepared *in situ* from diisopropoxytitanium dihalide (X = Cl or Br) and optically pure binaphthol (BINOL) in the presence of molecular sieves 4 Å. We have now found that a similar use of chiral catalyst **1a** (X = Br) prepared from a partially resolved (*R*)-BINOL of 33.0% ee, for instance, provides the ene product **4** with 91.4% ee in 92% chemical yield.† Fig. 1 shows remarkable levels of positive NLE observed with both the dibromo **1a** and dichloro **1b** catalysts, indicating that the use of BINOL of 35–40% ee provides the same level of % ee as previously observed with enantiomerically pure BINOL.[4]

In view of the dinuclear chelate structure of diphenoxytitanium dichloride,[5] it appears likely that the remarkable NLE is a result of a marked difference in the catalytic activity between the diastereomeric dimers (*R*)(*R*)-$\mathbf{1}_2$ (**A**) and (*R*)(*S*)-$\mathbf{1}_2$ (**B**) (Fig. 2).‡ In fact, simple kinetic studies reveal that the catalytic activity of the complex derived from 100% ee of BINOL was at least 30 times greater than that of the complex derived from racemic BINOL. It, therefore, appears that the catalyst thus formed from racemic BINOL is not a racemic mixture of (*R*)(*R*)-$\mathbf{1}_2$ and (*S*)(*S*)-$\mathbf{1}_2$, but the *meso*-dimer (*R*)(*S*)-$\mathbf{1}_2$ (**B**) which is less reactive and more stable (*vide infra*).

The dimeric structure of the BINOL-derived complex was proven by the ebullioscopic molecular weight measurement in dichloromethane. Both the hetero- and homo-chiral titanium complexes **1b**, prepared from BINOL dilithium salt and $TiCl_4$, were found to exist in the dimeric form [M_w obs. *ca.* 800, calcd. 806 for $(C_{20}H_{12}O_2TiCl_2)_2$]. However, the M_w of (*R*)(*R*)-$\mathbf{1b}_2$, prepared *in situ* from diisopropoxytitanium di-



Scheme 1 *Reagents and conditions*: i, $(Pr^iO)_2TiBr_2$/BINOL (33.0% ee) (1.0 mol% each); ii, MS 4 Å, CH_2Cl_2, −30 °C

Table 1 Effect of catalyst molar ratio on positive NLE in the reaction of α-methylstyrene **3** and methyl glyoxylate **2** catalysed by **1b** (31.0% ee)[a]

Mol%[b,c]	(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

[a] All reactions were carried out in a constant concentration; methyl glyoxylate **2** (1.0 mmol) and α-methylstyrene **3** (2.0 mmol) in CH_2Cl_2 (5.5 ml). [b] $(Pr^iO)_2TiCl_2$/BINOL (31.0% ee) was used as a chiral catalyst. [c] Mol% was defined on the basis of **2**.

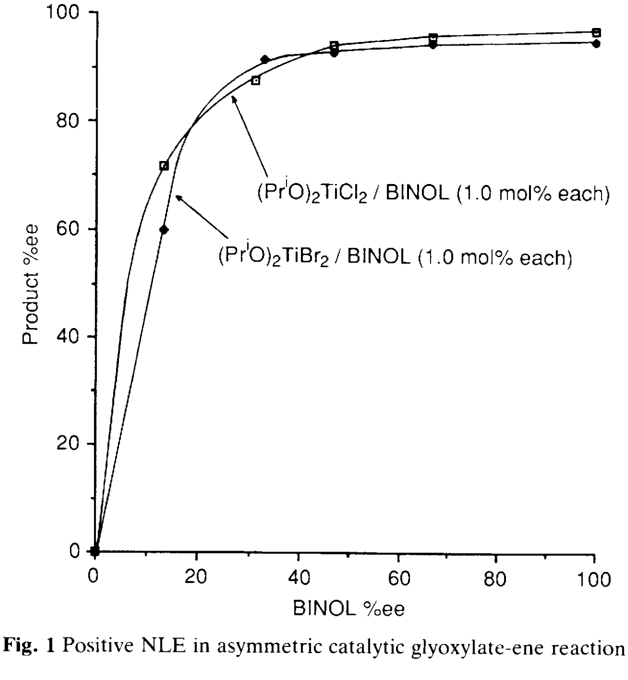


Fig. 1 Positive NLE in asymmetric catalytic glyoxylate-ene reaction

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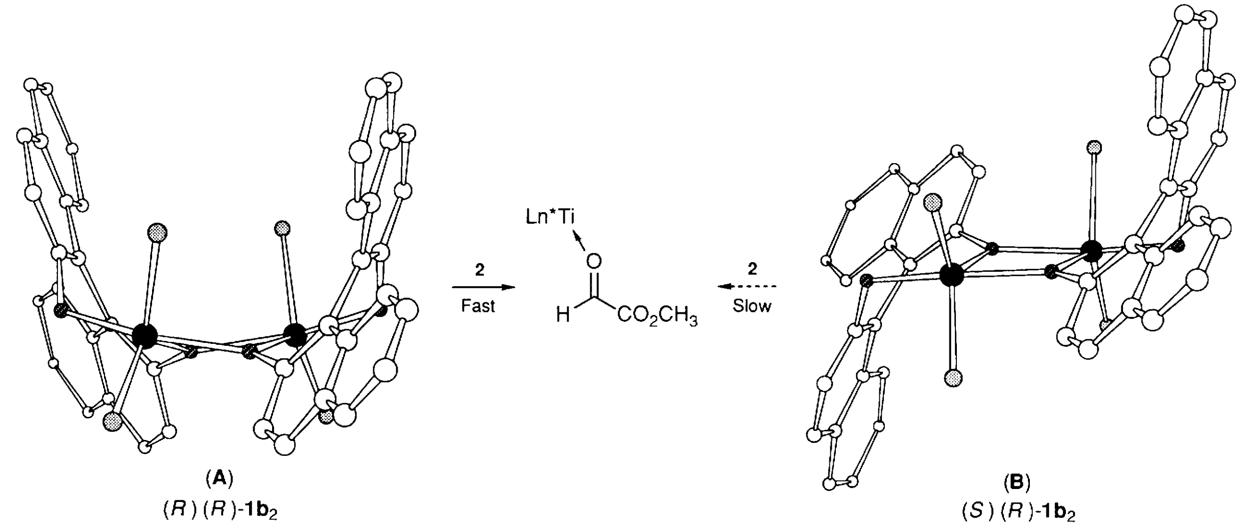
† A similar level of positive NLE was observed in the use of methylenecyclohexane instead of α-methylstylene **3**.

‡ These 3-D representations were rendered with the Machintosh program CHEM-3D+. Bond lengths/angles of the Ti_2O_2 four-membered ring and titanium binaphthoxide framework were based on the X-ray crystal analysis of a similar type of diphenoxytitanium dichloride (ref. 5) and diisopropoxytitanium binaphthoxide, which was generously presented by Professor Sharpless.



(**A**)
(*R*)(*R*)-$\mathbf{1b}_2$

(**B**)
(*S*)(*R*)-$\mathbf{1b}_2$

Fig. 2 3-D representation of (**A**) and (**B**)

chloride and optically pure BINOL in the presence of molecular sieves 4 Å, was concentration-dependent, ranging from 864 [calcd. 866 for $(C_{20}H_{12}O_2TiCl_2)_2Pr^iOH$]§ in 37 mM solution to 762 (9.2 mM solution), suggesting that in dilute solutions the homochiral dimer dissociates to the monomeric form to some extent. By contrast, the M_w of the *meso*-dimer (*R*)(*S*)-$\mathbf{1b}_2$ is not concentration-dependent, 872 (37 mM) and 874 (9.2 mM), indicating the stability of the *meso*-dimer. Furthermore, the level of asymmetric amplification was found to significantly increase with a decrease in the molar ratio of the catalyst with a given optical purity of BINOL (31.0% ee) to the constant concentration of glyoxylate and α-methylstylene.¶ This finding suggests that the monomeric species is responsible for the enantioselective catalysis (Table 1).

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§ ^1H NMR analysis of the titanium complex, **1b**, indicates the presence of 0.5 equiv. of Pr^iOH.

¶ In the diethylzinc/benzaldehyde reaction, however, Noyori *et al.* have reported that the level of NLE increases with increasing the molar ratio of the chiral catalyst (β-aminoalcohol) (ref. 2b).