

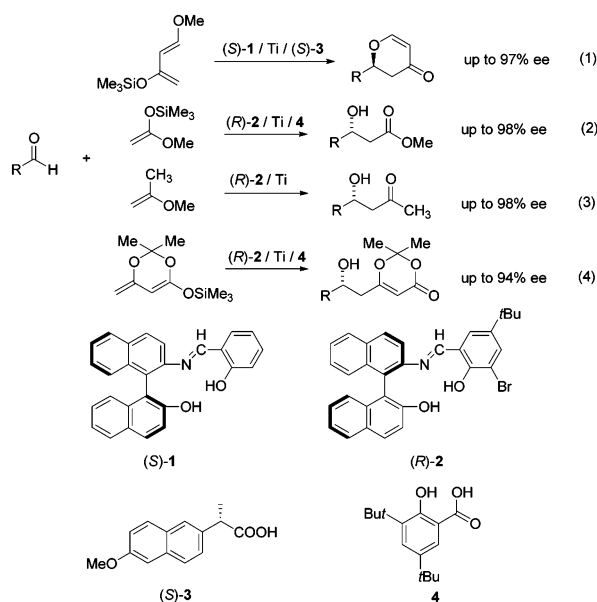
## To Probe the Origin of Activation Effect of Carboxylic Acid and (+)-NLE in Tridentated Titanium Catalyst Systems

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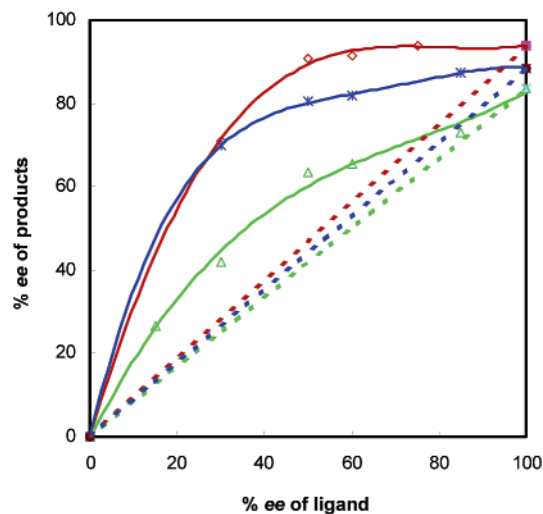
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Since the first report on the nonlinear effect in asymmetric catalysis by Kagan,<sup>1</sup> it has been an extensively studied theme in asymmetric catalysis.<sup>1–3</sup> Particularly, the catalytic system involving the titanium complex of 1,1'-bi-2-naphthol (BINOL) showed a significant positive nonlinear effect in various reactions.<sup>2,4</sup> The generally accepted explanation for this phenomenon is that the homochiral dimeric  $\mu$ -oxo-titanium complex dissociates more readily than the corresponding heterochiral one to give monomeric species which are responsible for the catalysis.<sup>4</sup> However, the direct isolation and X-ray characterization of the homochiral and heterochiral dimeric complexes have not yet been successful. In this communication, we report our results on the first direct probing of the origin of positive nonlinear effect ((+)-NLE) in catalytic enantioselective hetero Diels–Alder (HDA) and aldol-type reactions with tridentated titanium catalysts by X-ray single-crystal structure analysis of homochiral and heterochiral titanium complexes.



The research was initiated by our recent observations of the activation effect of carboxylic acid additives and (+)-NLE in Schiff base/titanium complex-catalyzed enantioselective HDA reaction between Danishefsky's diene and aldehydes (eq 1).<sup>5</sup> The reaction was accelerated by the acid **3** at 1 order of magnitude to give the product in up to 97% ee. On the basis of these findings, we supposed that the (+)-NLE might exist in similar catalyst systems developed by Carreira for aldol-type reactions (eqs 2–4).<sup>6</sup> Accordingly, we examined the nonlinear effect of aldol addition of aldehydes with

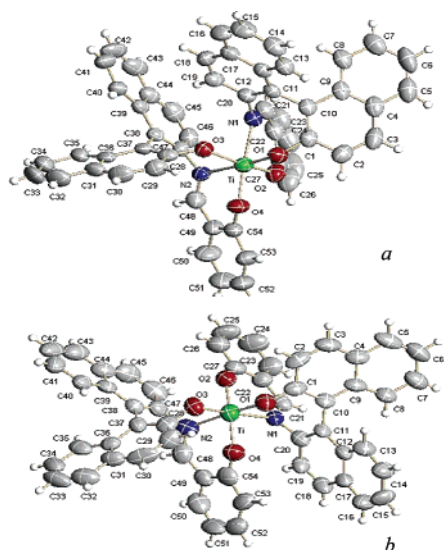


**Figure 1.** Enantioselectivities for the reactions of benzaldehyde with ethyl acetate *O*-silylenolate (red line), cinnamaldehyde with methoxypropene (green line), and hydrocinnamaldehyde with dienolate of acetoacetate (blue line) catalyzed by the titanium complex of partially resolved Schiff base ligand **2**.

ethyl acetate *O*-silyl enolate, methoxypropene, and silyl dienolate of acetoacetate, respectively. As shown in Figure 1, the (+)-NLE was readily observed in Carreira's catalyst systems. Our previous results obtained in the HDA reaction combined with these new facts prompted us to probe the origin of (+)-NLE in these reaction systems.

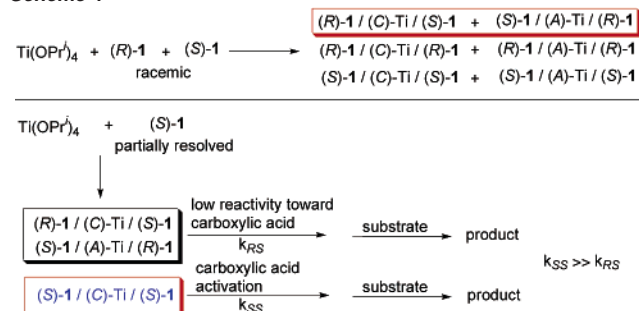
An effort was then made to elucidate the structure of racemic and enantiopure titanium complexes. The titanium complexes of  $[(\pm)\text{-1}]_2\text{Ti}$  and  $[(\text{S})\text{-1}]_2\text{Ti}$  were prepared by the reaction of racemic and enantiopure (S)-**1** with titanium(IV) isopropoxide (2:1 molar ratio) in toluene, respectively. X-ray single-crystal structure analysis revealed that both complexes adopt a similar coordination pattern around the titanium atom (Figure 2).<sup>7a</sup> It is obvious that all six coordination sites of Ti(IV) are occupied by the chelating atoms of two tridentated ligands.<sup>7b</sup> This unique structural feature of titanium complexes clearly explained the reason why the HDA reaction of Danishefsky's diene with benzaldehyde proceeds very slowly to afford the product with very low ee value in the absence of acids.<sup>5a</sup> Therefore, the dramatically synergistic effect of carboxylic acid additives on the reactivities and enantioselectivities of the reaction can be attributed to the reaction of carboxylic acid with stable  $[(\text{S})\text{-1}]_2\text{Ti}$  complex, which breaks the coordination sphere of  $[(\text{S})\text{-1}]_2\text{Ti}$  to accommodate the aldehyde substrate. In fact, the reaction of Danishefsky's diene with benzaldehyde promoted with a catalyst obtained by the reaction of isolated  $[(\text{S})\text{-1}]_2\text{Ti}$  (10 mol %) with (S)-naproxen (5 mol %) afforded 2-phenyl-2,3-dihydro-

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**Figure 2.** ORTEP drawings of [(±)-1]<sub>2</sub>Ti (a) and [(S)-1]<sub>2</sub>Ti (b).

### Scheme 1



4*H*-pyran-4-one in 94% ee and 92% yield, which were essentially identical to those obtained by using the catalyst prepared in situ.<sup>5</sup>

Although the coordination patterns of racemic and enantiopure titanium complexes are similar, the spatial orientations of the Schiff base ligands around the central metallic ion are quite different. As shown in Figure 2, the imino nitrogen atom and two phenoxy oxygen atoms of **1** coordinate in cis form with Ti(IV) atom. In the case of [(±)-1]<sub>2</sub>Ti complex, the imino nitrogen atom of one ligand and phenolate oxygen atom of its enantiomer bond to Ti(IV) in trans form, and the complex possesses C<sub>1</sub> symmetry (Figure 2a). Alternatively, in the case of [(S)-1]<sub>2</sub>Ti complex, two phenolate oxygen atoms of the ligands coordinate to Ti(IV) in trans form, and the complex has C<sub>2</sub> symmetry (Figure 2b). Due to this specific arrangement of the two ligands, the octahedral chirality is formed, and the configuration can be assigned as *C* for [(S)-1]<sub>2</sub>Ti complex according to the literature.<sup>8</sup> In the unit cell of [(±)-1]<sub>2</sub>Ti crystal, there exist two enantiomers of titanium complex molecules.<sup>7b</sup> Their octahedral chiralities can be assigned as *C* (Figure 2a) and *A*, respectively. In principle, there will be six enantiomers of titanium complexes involved in the reaction system when racemic **1** is utilized (Scheme 1). In fact, only two enantiomers, (*R*)-1/(*C*)-Ti/(*S*)-1 and (*R*)-1/(*A*)-Ti/(*S*)-1, have been formed under the experimental conditions because of essentially same <sup>1</sup>H NMR spectra of single crystal of [(±)-1]<sub>2</sub>Ti complex and [(±)-1]<sub>2</sub>Ti complex prepared in situ. When enantiopure (*S*)-1 was employed for the preparation of titanium complex, (*S*)-1/(*C*)-Ti/(*S*)-1 was produced exclusively. In an experiment employing partially resolved (*S*)-1 (50% ee) for the reaction with Ti(OPr<sup>*i*</sup>)<sub>4</sub>, both the enantiopure (*S*)-1/(*C*)-Ti/(*S*)-1 and racemic [(±)-1]<sub>2</sub>Ti complexes including (*R*)-

1/(*C*)-Ti/(*S*)-1 and (*R*)-1/(*A*)-Ti/(*S*)-1 were produced in 1:1 molar ratio.

The reactivity difference of [(*S*)-1]<sub>2</sub>Ti and [(±)-1]<sub>2</sub>Ti with carboxylic acid **3** was demonstrated by <sup>1</sup>H NMR study on the reactions of enantiopure and racemic titanium complexes with (*S*)-naproxen in CDCl<sub>3</sub>. [(*S*)-1]<sub>2</sub>Ti reacted with **3** smoothly to give the new species of titanium complexes which contain the carboxylate group. However, [(±)-1]<sub>2</sub>Ti was very inert to the acid **3** and the <sup>1</sup>H NMR signals of (*S*)-naproxen underwent almost no change even the reaction time was extended to 4 h. On the basis of these facts, it can be concluded that when partially resolved **1** is used, the stable and less reactive heterochiral Schiff base–titanium complex will be formed preferentially in the catalytic system. As a result, the remaining homochiral Schiff base–titanium complex [(*S*)-1]<sub>2</sub>Ti with higher ee than that of starting ligand will react with carboxylic acid additive to form the active species which predominates in the catalytic process (Scheme 1). The higher reactivity of homochiral versus that of heterochiral titanium complexes with carboxylic acid can be considered as the direct origin of the (+)-NLE in the catalytic system.

In conclusion, the activation effect of carboxylic acid and (+)-NLE in tridentate titanium catalyst systems has been first elucidated on the basis of X-ray crystal structural analysis of homochiral and heterochiral titanium complexes and the observation of their reactivities with carboxylic acid additive. The results disclosed in this work provided an important understanding for the rational design of other catalyst systems using tridentate titanium complexes.

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**Supporting Information Available:** Experimental details for the preparation, spectral characterization, and X-ray crystal structural determination of [(±)-1]<sub>2</sub>Ti and [(*S*)-1]<sub>2</sub>Ti, <sup>1</sup>H NMR spectra of [(±)-1]<sub>2</sub>Ti and [(*S*)-1]<sub>2</sub>Ti complexes in the presence of and in the absence of (*S*)-naproxen, and the data for search of NLE (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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