

# Asymmetric cyano-ethoxycarbonylation of aldehydes catalyzed by self-assembled titanium catalyst

Shaohua Gou,<sup>a</sup> Xiaohua Liu,<sup>a</sup> Xin Zhou<sup>a</sup> and Xiaoming Feng<sup>a,b,\*</sup>

<sup>a</sup>Key Laboratory of Green Chemistry and Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China

<sup>b</sup>State Key Laboratory of Biotherapy, Sichuan University, Chengdu 610041, China

Received 26 March 2007; revised 16 May 2007; accepted 17 May 2007

Available online 21 May 2007

**Abstract**—A new self-assembled catalyst based on titanium complex has been developed for the effective enantioselective cyano-ethoxycarbonylation of aldehydes. The self-assembled catalyst was readily prepared from (*R*)-3,3'-bis((methyl(*S*)-1-phenylethyl)amino)methyl)-1,1'-binaphthyl-2,2'-diol (**1h**), *N*-((*1S,2R*)-2-hydroxy-1,2-diphenylethyl)acetamide (**2b**), and tetraisopropyl titanate (Ti(O*i*Pr)<sub>4</sub>). A variety of aromatic aldehydes, aliphatic aldehydes, and  $\alpha,\beta$ -unsaturated aldehydes were found to be suitable substrates in the presence of the self-assembled titanium catalyst (5 mol % **1h**, 5 mol % **2b**, and 5 mol % Ti(O*i*Pr)<sub>4</sub>). The desired cyanohydrin ethyl carbonates were afforded with high isolated yields (up to 95%) and moderate to good enantioselectivities (up to 92% ee) under mild conditions (at  $-15\text{ }^{\circ}\text{C}$ ). A possible catalytic cycle based on the experimental observation was proposed.

© 2007 Elsevier Ltd. All rights reserved.

## 1. Introduction

The asymmetric cyanation of carbonyl compounds is a useful synthetic method to prepare optically active cyanohydrins, which are versatile building blocks for the synthesis of natural products and biologically active compounds.<sup>1</sup> However, in contrast to the cyanation of aldehydes and ketones employing trimethylsilyl cyanide (TMSCN) or hydrogen cyanide (HCN) as the cyanide source in which considerable progress has been made,<sup>2,3</sup> the one-pot catalytic asymmetric cyanation-O-protection reaction is still less developed. Recently, several successful catalyst systems employing cyanofornate (ROCOCN), acetyl cyanide or diethyl cyanophosphonate have been studied.<sup>4–7</sup> Among these precedents, Deng reported a dimeric cinchona alkaloid derivative for the one-pot enantioselective cyanation of aliphatic ketones.<sup>4</sup> Shibasaki and Sansano et al. reported heterobimetallic complex {YLi<sub>3</sub>[tris(binaphthoxide)]} and BINOLAM–Al or –Ti(IV) complex for the addition of cyanofornate (ROCOCN) to aldehydes.<sup>5</sup> Belokon', North, and Moberg developed a bimetallic titanium complex, and obtained the desired *O*-alkoxycarbonyl cyanohydrins with excellent results.<sup>6</sup> Very recently, our group investigated multicomponent titanium complex, *N,N*-dioxide titanium complex, mononuclear salen titanium, and heterobimetallic aluminum lithium bis(binaphthoxide)

in cyano-ethoxycarbonylation of aldehydes, with good yields and enantioselectivities.<sup>7</sup>

In a different reaction, Mikami and Chan et al. reported self-assembly of two different chiral ligand components into a highly enantioselective titanium catalyst for carbonyl-ene reaction and addition of alkynylzinc to aldehydes.<sup>8</sup> Inspired by this method, we continued to search for a new highly efficient catalyst system using BINOL derivatives in combination with amino alcohol to achieve structural diversity. Thus, a set of BINOL derivatives **1a–i** and some chiral amino alcohol ligands **2a–i** were investigated (synthesis for ligands: see Section 4 for details). Herein, we wish to report these ligands that engender a more effective catalyst by self-assembly for the cyano-ethoxycarbonylation of aldehydes.

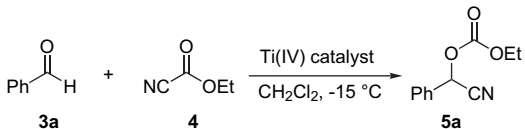
## 2. Results and discussion

### 2.1. Catalyst precursor screening

In the preliminary studies, 10 mol % complexes of **1**-Ti(O*i*Pr)<sub>4</sub> were evaluated for the addition of ethyl cyanofornate to benzaldehyde in dry CH<sub>2</sub>Cl<sub>2</sub> at  $-15\text{ }^{\circ}\text{C}$  (Table 1, entries 1–10). It was found that the complex of **1h**-Ti(O*i*Pr)<sub>4</sub> gave the best result (55% ee and 96% yield after 24 h, Table 1, entry 8). The reaction with complex of **1g**-Ti(O*i*Pr)<sub>4</sub> was slower, although it showed comparable enantioselectivity with **1h**-Ti(O*i*Pr)<sub>4</sub> (Table 1, entry 7). In contrast, the titanium complexes of binol (**1a**), phosphorus-containing **1b** or

**Keywords:** Asymmetric catalysis; Binol; Cyanation; Self-assembly; Titanium.

\* Corresponding author. Fax: +86 28 85418249; e-mail: [xmfeng@scu.edu.cn](mailto:xmfeng@scu.edu.cn)

**Table 1.** Catalyst precursor screening


Entry <sup>a</sup>	Ti(O <i>i</i> Pr) <sub>4</sub> (mol %)	<b>1a–i</b> (mol %)	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	10	<b>1a</b> (10)	48	0	—
2	10	<b>1b</b> (10)	48	0	—
3	10	<b>1c</b> (10)	48	0	—
4	10	<b>1d</b> (10)	48	0	—
5	10	<b>1e</b> (10)	48	0	—
6	10	<b>1f</b> (10)	48	85	14( <i>S</i> )
7	10	<b>1g</b> (10)	48	95	53( <i>S</i> )
8	10	<b>1h</b> (10)	24	96	55( <i>S</i> )
9	10	<b>1i</b> (10)	40	87	27( <i>S</i> )
10	5	<b>1h</b> (5)	48	87	87( <i>S</i> )

<sup>a</sup> Concentration of benzaldehyde: 0.5 M; EtOCOCN: 1.5 equiv.

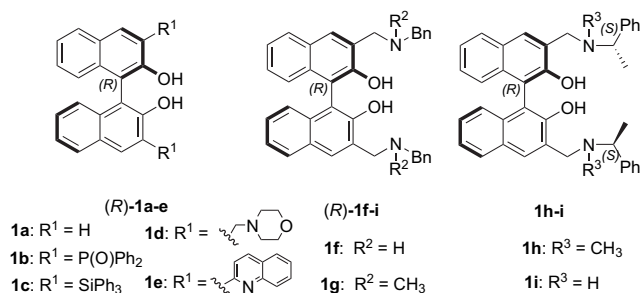
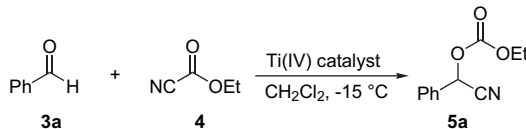
<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC on Chiral OD-H column analysis, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Ref. 5a).

silicon-containing **1c**, nitrogen-containing BINOL derivatives **1d** and **1e**, did not catalyze the reaction under same reaction conditions (Table 1, entries 1–5). Gratifyingly, when the loading of **1h**-Ti(O*i*Pr)<sub>4</sub> complex was decreased from 10 to 5 mol %, higher enantioselectivity was achieved, although longer reaction time was required (87% ee after 48 h, Table 1, entry 10) (Fig. 1).

## 2.2. Chiral activator screening

To gain higher reactivity, some chiral activators<sup>8a,b</sup> **2a–i** were investigated fixing 5 mol % **1h**-Ti(O*i*Pr)<sub>4</sub> complex as the catalyst precursor (Table 2, entries 2 and 3, and 5–11). To our delight, when 5 mol % chiral acetamide **2b** was added together with 5 mol % **1h**-Ti(O*i*Pr)<sub>4</sub> complex, higher enantioselectivity was obtained and the reactivity was increased dramatically (Table 2, entry 3 vs 1), which might be attributed to the hydrogen bonding between the N–H moiety of acetamide with the oxygen atom of ethyl cyanofornate. Other combinations of chiral ligand with **1h**-Ti(O*i*Pr)<sub>4</sub> complex gave lower ee's, although higher reactivity was observed (Table 2, entries 2, 5–11). The combination of titanium binol complex with acetamide **2b** was also tested, but no product was detected (Table 2, entry 4). Therefore, **2b** was selected as the best chiral activator in the self-assembled catalytic system (Fig. 2).

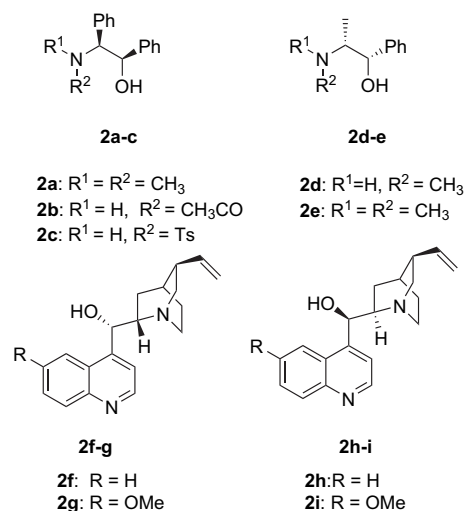
**Figure 1.** Structures of the ligands evaluated in this study.**Table 2.** Chiral activator screening


Entry <sup>a</sup>	<b>1h</b> or <b>1a</b> (5 mol %)	<b>2a–i</b> (5 mol %)	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>1h</b>	None	48	87	87( <i>S</i> )
2	<b>1h</b>	<b>2a</b>	20	99	17( <i>S</i> )
3	<b>1h</b>	<b>2b</b>	24	88	91( <i>S</i> )
4	<b>1a</b>	<b>2b</b>	48	0	—
5	<b>1h</b>	<b>2c</b>	24	97	60( <i>S</i> )
6	<b>1h</b>	<b>2d</b>	24	99	65( <i>S</i> )
7	<b>1h</b>	<b>2e</b>	30	99	63( <i>S</i> )
8	<b>1h</b>	<b>2f</b>	15	99	7( <i>S</i> )
9	<b>1h</b>	<b>2g</b>	20	90	15( <i>S</i> )
10	<b>1h</b>	<b>2h</b>	15	99	26( <i>S</i> )
11	<b>1h</b>	<b>2i</b>	24	90	3( <i>S</i> )

<sup>a</sup> Concentration of benzaldehyde: 0.5 M; Ti(O*i*Pr)<sub>4</sub>: 5 mol %, EtOCOCN: 1.5 equiv.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC on Chiral OD-H column analysis, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Ref. 5a).

**Figure 2.** Structures of the chiral activators evaluated in this study.

## 2.3. Catalyst system optimization

In the further studies, we found that the optimum ratio of chiral ligands (**1h** and **2b**) to Ti(O*i*Pr)<sub>4</sub> was 5/5/5 (Table 3, entry 1 vs entries 2–8). Other ratios gave moderate enantioselectivity and reactivity (Table 3, entries 3 and 4, and 6–8). Changing the ratio of chiral ligands **1h**, **2b**, and Ti(O*i*Pr)<sub>4</sub> to 2.5/5/2.5 greatly decreased the reactivity (Table 3, entry 5). We also found that the desired product could not be obtained when titanium chiral acetamide **2b** was used as the catalyst (Table 3, entry 2).

Reaction solvent and other metal reagents were also examined (Table 4, entries 1–10). Among the investigated solvents, ether solvents (THF or Et<sub>2</sub>O) were found to afford the product in very low yields (Table 4, entries 2 and 3). Toluene gave moderate enantioselectivity and reactivity

Download English Version:

<https://daneshyari.com/en/article/5230098>

Download Persian Version:

<https://daneshyari.com/article/5230098>

[Daneshyari.com](https://daneshyari.com)