

# Titanium (IV) as an essential promoter in the asymmetric addition of diethylzinc to aldehydes catalyzed by aminonaphthol and imine ligands based on 3-substituted binaphthol

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Received 20 March 2007; received in revised form 30 June 2007; accepted 3 July 2007

Available online 12 July 2007

## Abstract

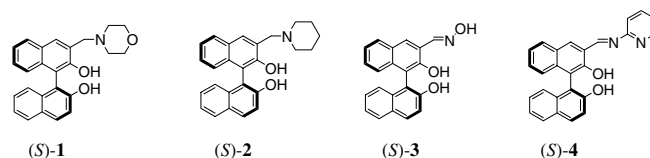
By using indirect reductive amination and condensation, two types of aminonaphthol and imine ligands based on 3-substituted binaphthol have been synthesized, respectively. When their catalytic effectiveness was tested by the ethylation of aldehydes with diethylzinc, titanium tetraisopropoxide was found essential to get good results with ee up to 90%.  
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**Keywords:** Reductive amination; BINOL; Diethylzinc; Titanium tetraisopropoxide

## 1. Introduction

Over the past decades, the enantioselective alkylation of carbonyl compounds has been dramatically improved, owing to the use of organozinc reagents in the presence of a wide variety of chiral auxiliaries [1]. And a large number of chiral catalysts such as  $\beta$ -amino alcohols (particularly those possessing a tertiary amino group) [2], amino thiols [3], aminonaphthols [4], imines [5] and titanium complexes [6] have been developed and high enantioselectivities have been achieved. Thus, the reaction of diethylzinc with aldehydes has become a classical test in the design of new ligands for catalytic asymmetric synthesis. Despite the enormous success of axially chiral ligands in asymmetric reactions, a limited number of aminonaphthol [7] and imine [8] type ligands based on BINOL are reported for diethylzinc addition to aldehydes. To the best of our knowledge, there have never been such type ligands prepared from 3-formyl BINOL [9] in the long catalyst list of the asymmetric addition of diethylzinc to aldehydes. Therefore, it should be of interest to explore the catalytic ability of the aminonaph-

thol and imine ligands with a scaffold of 3-substituted BINOL. In this paper, we report the synthesis of chiral aminonaphthol ligands (*S*)-1 and (*S*)-2 as well as imine ligands (*S*)-3 and (*S*)-4, together with their catalytic applicability in the addition of diethylzinc to aldehydes.



Among the four ligands, (*S*)-1 is a known compound synthesized as a byproduct in a short but severe Mannich-type procedure with partial racemization [10]. Here (*S*)-1 is synthesized under mild reaction condition in high yield without racemization.

## 2. Results and discussion

(*S*)-1 and (*S*)-2 were easily prepared in high yield by indirect reductive amination of (*S*)-3-formyl BINOL with

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morpholine and piperidine in the presence of  $\text{NaBH}_4$ , respectively [11]. (*S*)-**3** and (*S*)-**4** were also conveniently prepared from condensation of (*S*)-**3**-formyl BINOL with hydroxylamine hydrochloride and 2-aminopyridine in good yield (Scheme 1) [12].

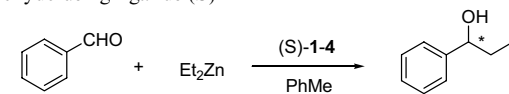
A pale yellow single crystal of *rac*-**3** · THF was obtained from THF-petroleum ether solution. The crystal structure was determined by X-ray diffraction as shown in Fig. 1 [13]. The oxime has a *trans* configuration. The torsion angle of C(20)–C(19)–C(21)–N(1) is 2.1°, and the dihedral angle between the two naphthalene systems is 82.3°.

First, the effectiveness of the four ligands as chiral catalysts for the ethylation of aldehydes with  $\text{Et}_2\text{Zn}$  was tested. The addition reaction was carried out in toluene at room temperature. Unfortunately, neither the chemical yields nor the enantioselectivities were satisfactory (Table 1). Ligand (*S*)-**3** (5 mol%) only gave a 67% yield and 32% ee as the best result (Entry 3). In addition, the reduced benzyl alcohol products were also observed in about 15% yield for (*S*)-**1** and (*S*)-**2** (Entry 1 and 2).

Titanium (IV) complexes with various chiral ligands have been extensively confirmed as an effective promoter for the asymmetric addition of diethylzinc to aldehydes in the last years. Hence, aimed at improving the catalytic performance of the four ligands (*S*)-**1**–**4**,  $\text{Ti}(\text{O}^i\text{Pr})_4$  was added

Table 1

Catalytic asymmetric addition of diethylzinc (1.5 M in hexane) to benzaldehyde using ligands (*S*)-**1**–**4**



Entry	Ligand (mol%) <sup>a</sup>	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	Config. <sup>d</sup>
1	( <i>S</i> )- <b>1</b> (10)	51 (13)	13	<i>S</i>
2	( <i>S</i> )- <b>2</b> (10)	38 (16)	16	<i>S</i>
3	( <i>S</i> )- <b>3</b> (5)	67	32	<i>S</i>
4	( <i>S</i> )- <b>4</b> (5)	57	15	<i>S</i>

<sup>a</sup>  $\text{Et}_2\text{Zn}$ /benzaldehyde = 3:1; reaction temperature: r.t.; reaction time: 48 h.

<sup>b</sup> Isolated yield and the data in brackets refers to the amount of benzyl alcohol product.

<sup>c</sup> Data were determined by GC analysis using a chiral column (Chiral beta-DEX 120 capillary column).

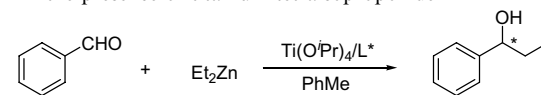
<sup>d</sup> The absolute configuration of the products were determined by comparison to the literature data.

and it resulted in a dramatic enhancement not only in chemical yields but in ee values (Table 2). Again, (*S*)-**3** (20 mol%) gave the best result with a 93% yield and 89% ee in the presence of 1.2 equiv.  $\text{Ti}(\text{O}^i\text{Pr})_4$  (Entry 4). Furthermore, the reduced benzyl alcohol products were not detected at all for (*S*)-**1** and (*S*)-**2** (Entry 1–3).

With conditions optimized for benzaldehyde, the use of ligand (*S*)-**3** was extended to the asymmetric ethylation of other aromatic and  $\alpha,\beta$ -unsaturated aldehydes (Table 3). The additions were completed within 5 h at room temperature with good yields and ee values for all the aldehydes. For anisaldehyde possessing an electron-donating group in *para* position and *trans*-cinnamaldehyde, a slight decreased enantioselectivity was observed (Entry 4 and 6). The best enantioselectivities up to 90% ee were obtained with *p*-bromobenzaldehyde and *o*-methoxybenzaldehyde (Entry 3 and 5).

Table 2

Addition of diethylzinc (1.5 M in hexane) to benzaldehyde using ligands (*S*)-**1**–**4** in the presence of titanium tetraisopropoxide



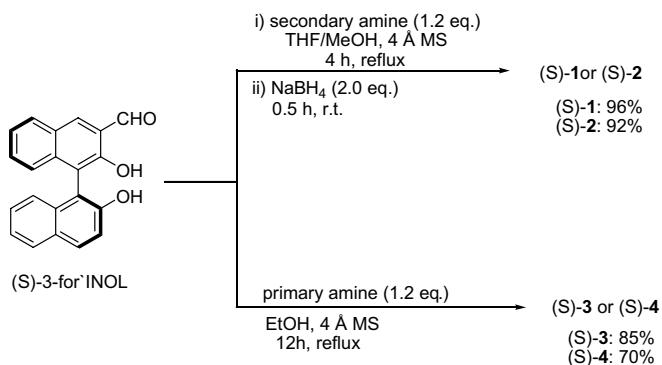
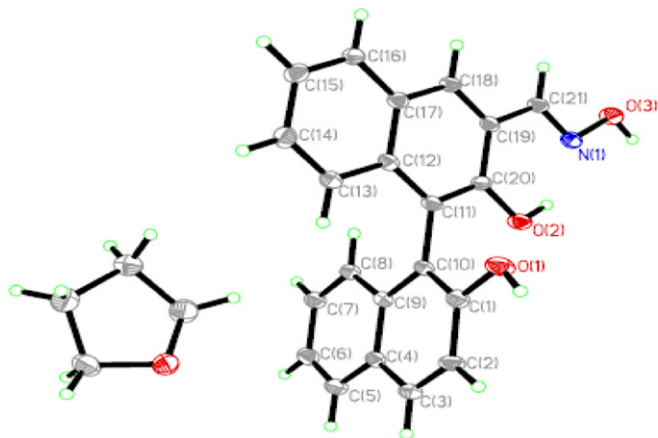
Entry	Ligand (mol%) <sup>a</sup>	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	Config. <sup>d</sup>
1	( <i>S</i> )- <b>1</b> (20)	85	76	<i>S</i>
2	( <i>S</i> )- <b>1</b> (10)	83	72	<i>S</i>
3	( <i>S</i> )- <b>2</b> (10)	80	56	<i>S</i>
4	( <i>S</i> )- <b>3</b> (20)	93	89	<i>S</i>
5	( <i>S</i> )- <b>3</b> (10)	90	81	<i>S</i>
6	( <i>S</i> )- <b>3</b> (5)	94	64	<i>S</i>
7	( <i>S</i> )- <b>4</b> (10)	92	31	<i>S</i>

<sup>a</sup>  $\text{Ti}(\text{O}^i\text{Pr})_4/\text{Et}_2\text{Zn}/\text{benzaldehyde}$  = 1.2:3:1; reaction temperature: r.t.; reaction time: 5 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Data were determined by GC analysis using a chiral column (Chiral beta-DEX 120 capillary column).

<sup>d</sup> The absolute configuration of the products were determined by comparison to the literature data.

Scheme 1. Synthesis of (*S*)-**1**–**4**.Fig. 1. The molecular structure of **3** including one THF molecule.

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