

SYNTHESES OF CHIRAL SOLID CATALYSTS AND APPLICATION TO ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO BENZALDEHYDE

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Abstract : A chiral solid catalyst as a heterogeneous Lewis acid prepared from titanium tetraisopropoxide, (R,R)-(+)-1,2-bis(1-naphthalenesulfonamido)cyclohexane and 4,4'-biphenol has been found to promote the enantioselective addition of diethylzinc to benzaldehyde and is a reusable catalyst.

Introduction

The enantioselective addition of dialkylzinc reagents to aldehydes is one of the most widely studied carbon-carbon bond forming reactions. A variety of catalysts have been employed which facilitate this process with high enantioselectivity.¹ Yoshioka, Zhang and co-workers reported the enantioselective addition of diethylzinc to benzaldehyde using sulfonamide ligands as the chiral catalysts.^{2,3} On the other hand, polymer-bound ligands as a heterogeneous Lewis acid have been widely utilized in organic synthesis due to the easy product isolation and work-up. Several reports on the use of polymer-bound ligands for the enantioselective addition of dialkylzinc to aldehydes have appeared.⁴ In a previous study, the authors developed new type of chiral solid catalysts which contain aluminum as building block of the polymer chain.⁵ In this paper, we report the syntheses of several new types of chiral solid catalysts and application to the enantioselective addition of diethylzinc to benzaldehyde.

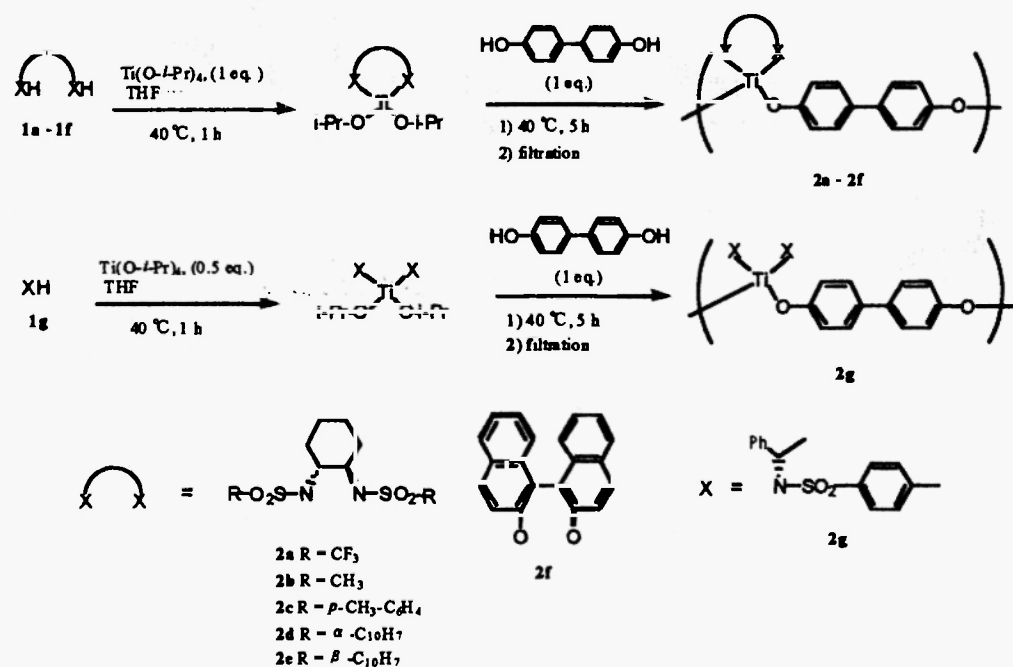
Results and Discussion

Chiral ligands **1a - e** were synthesized according to Yoshioka's method.^{1c} The chiral solid catalysts **2a - e** were easily prepared as shown in scheme 1. The reaction of several disulfonamides **1a - e** with tetraisopropoxytitanium gave a clear solution of titanium-complexes at 40 °C for 1 h. To the obtained solution was added 4,4'-biphenol, and almost immediately, insoluble dark red precipitates appeared. The reaction solution was then stirred for 5 h. The solid was collected by filtration, and **2a**, **2b**, **2c**, **2d**, and **2e** were obtained in 97, 97, 95, 96, and 65 % yields, respectively. The obtained solid **2d** was quenched with 1M HCl, and the ratio of the disulfonyl derivative **1d** and 4,4'-biphenol in the residue was determined to be 1:1 based on ¹H NMR spectrometry. Solid catalysts **2f** using (R)-1,1'-di-2-naphthol (BINOL) or **2g** using 4-methyl-*N*-(1-(*S*)-phenylethyl)benzenesulfonamido as a chiral source were also obtained by the same procedure in 96 and 95 % yields, respectively.

The reaction of benzaldehyde with diethylzinc was carried out in hexane at room temperature for 50 h in the presence of 20 mol % of these solid catalysts. The results are shown in Table 1. Among them, solid catalyst **2d** produced

1-(*S*)-phenylpropanol in 71 %ee with the best enantioselectivity (entries 1, 2, 3, 4, and 7). In addition, differences in the chiral sources of the solid catalysts strongly influence to the enantiomeric excess of the product (entries 3, 8, and 9). The recovered chiral solid catalyst 2d could be reused without reducing the yield and enantioselectivity of the product (entries 5 and 6). In order to deny the participation of the soluble catalysts, the reaction of benzaldehyde with diethylzinc was carried out in the presence of the filtrate obtained from 2d. Consequently, there was no product. This result indicates that the catalytically active species was the solid catalyst in the reaction. We propose a model to explain these results as shown in Figure 1. The orientation of the benzaldehyde could be well controlled by the two arene rings on the sulfonyl groups. Thus, the ethyl group of the diethylzinc can be transferred to the *Si* face of the substrate.

In summary, we have designed and synthesized several chiral solid catalysts which contain titanium as a building block of the polymer chain. The solid catalyst 2d is an effective catalyst for the enantioselective addition of diethylzinc to benzaldehyde. The synthesis of this solid catalyst is quite simple, and a variety of carbon-carbon bond forming reactions would be possible by carefully selecting the chiral source and organic metal.



Scheme 1. Syntheses of chiral solid catalysts 2a - 2g.

Experimental

General Procedure for the Preparation of Solid Catalysts 2d.

To a solution of (*R,R*)-(+)-1,2-bis(1-naphthalenesulfonamido)cyclohexane 1d (197 mg, 0.4 mmol) in absolute THF (2 ml) was added Ti(O-*i*Pr)₄ (0.118 ml, 0.4 mmol), which was stirred at 40 °C for 1 h. To the reaction solution was added 4,4'-biphenol (74.4 mg, 0.4 mmol) in THF (4 ml) at the same temperature, and quickly, insoluble dark red precipitates appeared. The reaction solution was then stirred for 5 h. The solid catalyst 2d was collected by filtration under argon atmosphere, and 2d was obtained in 96 % (278 mg).

General procedure for the asymmetry addition of diethylzinc to benzaldehyde

To a suspension of the solid catalyst 2d (278 mg, 0.384 mol) in absolute hexane (2 ml) was added a 1.0 M hexane solution of Et₂Zn (2.3 ml, 2.3 mmol) at room temperature under an argon atmosphere and stirred for 30 min. To the

mixture was added benzaldehyde (203 mg, 1.92 mol) at $-50\text{ }^{\circ}\text{C}$, and this was stirred at the same temperature for 50 h. The catalyst was removed by filtration and washed several times with hexane under an argon atmosphere. The filtrate was quenched by adding sat. aqueous NH_4Cl , and then extracted with ether. The extract was dried over anhydrous sodium sulfate and concentrated to give pure 1-(*S*)-phenylpropanol, $[\alpha]_{20}^{\text{D}} -32.3^{\circ}$ ($c = 5.0$, CHCl_3) in 93 % (243 mg) yield and in 71 %ee.

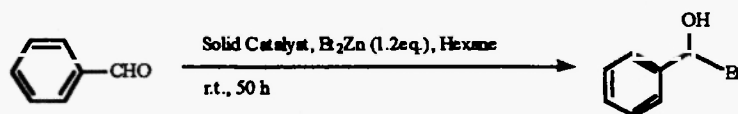


Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by Chiral Solid Catalysts

Entry	Solid Catalyst	Yield of 1-Phenylpropanol (%) ^{a)}	ee (%) ^{b)} (Config.)
1	2a	87	36 (S)
2	2b	88	17 (S)
3	2c	94	30 (S)
4	2d	93	71 (S)
5 ^{c)}	2d	88	68 (S)
6 ^{d)}	2d	90	70 (S)
7	2e	84	3 (S)
8	2f	60	0
9	2g	55	22 (S)

a) Isolated yield. b) Absolute configuration in parentheses was determined by comparison of optical rotation with reported values. c) Once used catalyst was used. d) Twice used catalyst was used.

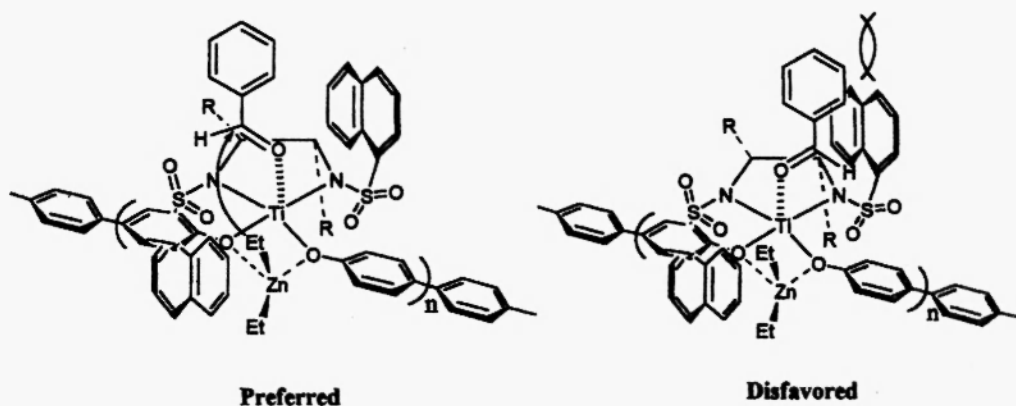


Figure 1. Proposed transition state model

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