

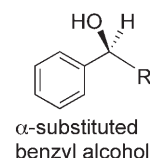
Asymmetric Addition

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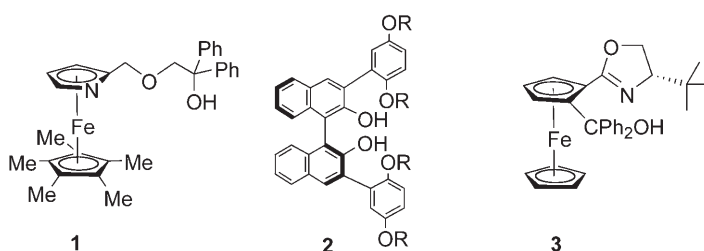
Highly Enantioselective Addition of Diphenylzinc to Aliphatic and Aromatic Aldehydes Catalyzed by a Readily Available H₈-Binol Derivative**

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Chiral α -substituted benzyl alcohols are ubiquitous in the structure of organic compounds. A straightforward synthesis of these compounds involves the nucleophilic addition of a phenyl-metal reagent to an aldehyde which produces a carbon-carbon bond and a stereogenic center simultaneously. Because of the high activity of phenyl-lithium and phenyl Grignard reagents, their asymmetric reactions with aldehydes need to be conducted in the presence of stoichiometric or excess amount of chiral reagents.^[1-5]



Among the catalytic asymmetric additions of the phenyl group to aldehydes,^[6-16] the use of diphenylzinc has received much attention in recent years as the reagent is readily available.^[10-16] In 1997, Fu and co-workers reported the addition of diphenylzinc to aldehydes catalyzed by **1** with



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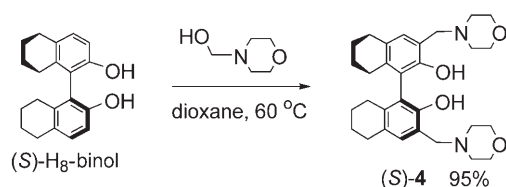
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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

moderate enantioselectivity.^[10] In 1999, we found that compound **2** showed high enantioselectivity for this reaction.^[11] At about the same time, Bolm and co-workers reported good results with the use of **3**.^[12] Other chiral ligands were also developed for the asymmetric addition of diphenylzinc.^[13–16] A few of these compounds catalyze the addition of diphenylzinc to aromatic and α -branched aliphatic aldehydes with high enantioselectivity (> 90% *ee*). However, the enantioselectivity for the addition to linear aliphatic aldehydes is generally lower, and no catalyst has been reported to give over 90% *ee* for the addition of diphenylzinc to a linear aliphatic aldehyde. Thus, the search for generally applicable catalysts for the asymmetric addition of diphenylzinc to aldehydes continues.

We have been interested in using 2,2'-dihydroxy-1,1'-binaphthyl (binol) and its derivatives in asymmetric processes such as catalysis and sensing. Recently, we reported a one-step synthesis of the 3,3'-substituted partially hydrogenated binol compound (*S*)-**4** from the reaction of (*S*)-H₈-binol with morpholinomethanol (Scheme 1).^[17,18] This compound is a



Scheme 1. Synthesis of the 3,3'-bismorpholinylmethyl H₈-binol (*S*)-**4**.

precursor to a class of bifunctional Lewis acid–base catalysts.^[19] That is, the dihydroxy groups of (*S*)-**4** can produce a Lewis acidic center by reacting with a metal alkyl and the 3,3'-morpholinylmethyl groups of (*S*)-**4** can provide two Lewis basic nitrogen atoms. We found that (*S*)-**4** in combination with diethylzinc and Ti(O^{*i*}Pr)₄ catalyzed the addition of phenylacetylene to aldehydes with high enantioselectivity.^[17] Herein we disclose that this compound also catalyzes the reaction of diphenylzinc with aldehydes with excellent enantioselectivity, especially in the case of linear aliphatic aldehydes.

We modified the preparation of (*S*)-**4**^[18] and studied its application in the addition of diphenylzinc to valeraldehyde under various conditions at room temperature (Table 1). In solvents such as dichloromethane, toluene, and diethyl ether, (*S*)-**4** showed very low enantioselectivity (Table 1, entries 1–3; 35–39% *ee*). However, a dramatic increase in enantioselectivity was observed when the reaction was carried out in THF (Table 1, entry 4; 92% *ee*). The absolute configuration of the alcohol product was determined to be *R* by comparing its optical rotation with that reported in the literature.^[20] Slow addition of the aldehyde did not change the enantioselectivity significantly (Table 1, entry 5). The use of diethylzinc and/or methanol as an additive decreased the enantioselectivity slightly (Table 1, entries 6, 7, and 8). Both increasing and decreasing the amount of the chiral ligand gave lower *ee* values (Table 1, entries 9 and 10).

We then used (*S*)-**4** to catalyze the reaction of diphenylzinc with various aliphatic and aromatic aldehydes by

Table 1: Results for the (*S*)-**4**-catalyzed addition of diphenylzinc to valeraldehyde under various conditions.^[a]

Entry	(<i>S</i>)- 4 [mol %]	Solvent	Ph ₂ Zn [equiv]	<i>ee</i> [%] ^[b,c]
1	10	CH ₂ Cl ₂	1.2	35
2	10	toluene	1.2	38
3	10	Et ₂ O	1.2	39
4	10	THF	1.2	92
5 ^[d]	10	THF	1.2	93
6 ^[e]	10	THF	1.0	91
7 ^[f]	10	THF	1.6	89
8 ^[e,f]	10	THF	1.6	91
9	5	THF	1.2	84
10	20	THF	1.4	87

[a] Unless indicated otherwise, the following procedure was used: Solvent (2 mL, dried) was added under nitrogen to a flask containing (*S*)-**4** (12.3 mg, 0.025 mmol) and diphenylzinc (66.0 mg, 0.3 mmol). The solution was stirred at room temperature for 1 h. Valeraldehyde (0.25 mmol) was then added, and the resulting solution was stirred for 12 h. Aqueous workup and column chromatography on silica gel gave 1-phenyl-1-pentanol. [b] The products were isolated in 82–89% yield in all these reactions. [c] The *ee* values were determined by HPLC-Chiral OD column. [d] Valeraldehyde was added dropwise over 2 h. [e] (*S*)-**4** was pretreated with diethylzinc (20 mol %) for 1 h followed by the addition of diphenylzinc and aldehyde. [f] MeOH (40 mol %) was added after (*S*)-**4** was treated with diphenylzinc or diethylzinc.

applying the conditions of entry 4 in Table 1. As summarized in Table 2, (*S*)-**4** exhibited generally high enantioselectivity for all the substrates. For the reactions of linear (Table 2, entries 1–3), α -branched (Table 2, entries 4 and 5) and β -branched (Table 2, entry 6) aliphatic aldehydes, selectivities in the range 92–98% *ee* were attained. Selectivities of 89–96% *ee* were found for the reactions of aromatic aldehydes and an α,β -unsaturated aldehyde (Table 2, entries 6–13). In all cases, the products were isolated in yields of 75–97%. Optical rotation measurements showed that the addition to aliphatic aldehydes gave *R* alcohols (Table 2, entries 1 and 5)^[20a,b] and the addition to aromatic aldehydes gave *S* alcohols (Table 2, entries 9 and 10).^[11,20c]

The relationship between the enantiomeric composition of the chiral ligand (*S*)-**4** and those of the products of the addition of diphenylzinc was investigated. Figure 1 displays the results obtained for the reactions of valeraldehyde and 4-fluorobenzaldehyde with diphenylzinc in the presence of (*S*)-**4** at various enantiomeric compositions. Both reactions gave a linear relationship between the *ee* value of the chiral ligand and that of the product. This suggests that the addition of diphenylzinc to either aliphatic or aromatic aldehydes might be catalyzed by a monomeric H₈-binol catalyst.

We conducted an NMR spectroscopic study for the catalytic addition of diphenylzinc to trimethylacetaldehyde in the presence of (*S*)-**4**. Trimethylacetaldehyde was chosen as the substrate for its simple ¹H NMR spectrum. We first monitored the interaction of (*S*)-**4** with diphenylzinc in [D₈]toluene by using ¹H NMR spectroscopy. Addition of diphenylzinc (1 equiv with respect to (*S*)-**4**) gave only partial

Table 2: Diphenylzinc addition to various aldehydes catalyzed by (*S*)-4.

Entry	Aldehyde	Product	<i>t</i> [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1			12	87	92
2			12	78	93
3			12	75	92
4			8	96	98
5			6	93	98
6			16	82	92
7			16	90	89
8			16	91	89
9			16	90	89
10			16	92	94
11			16	91	91
12			16	97	89
13			12	88	96

[a] Yield of isolated products. [b] Determined by HPLC-chiral column or GC-chiral column (see the Supporting Information for details).

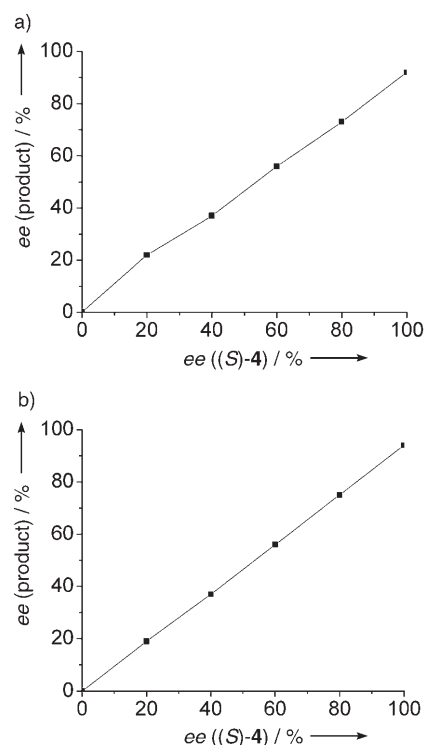
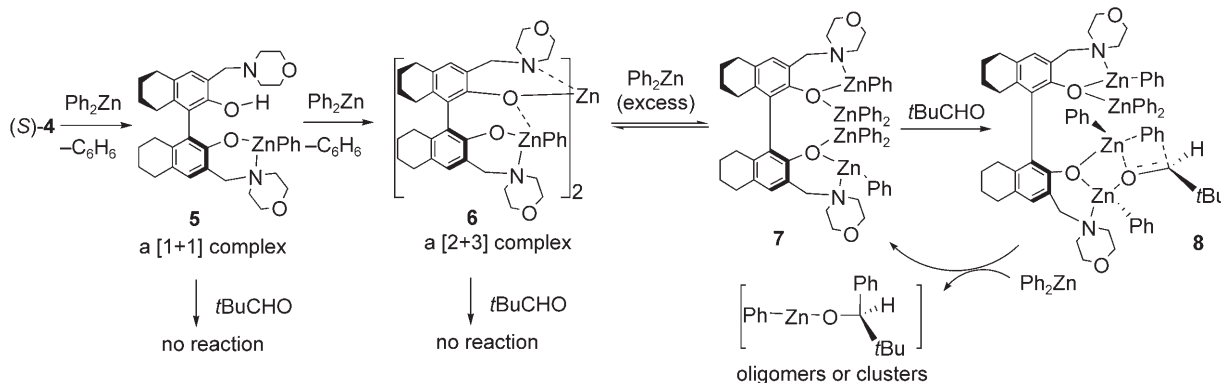


Figure 1. Relationship between *ee* values of (*S*)-4 and those of the products of addition of diphenylzinc to a) valeraldehyde and b) 4-fluorobenzaldehyde.

deprotonation of (*S*)-4. The original singlet at $\delta = 9.99$ ppm for the dihydroxy protons of (*S*)-4 diminished but multiple peaks appeared in the range of $\delta = 9.45$ – 9.96 ppm together with a signal indicating the formation of free benzene. Besides the signal for free benzene, the aromatic region displayed additional complicated peaks. This indicates that only one of the two hydroxy groups of (*S*)-4 could be deprotonated by 1 equivalent of diphenylzinc and the resulting complex should contain a monophenylzinc unit {ZnPh} and a hydroxy group with a number of isomeric structures. This is understandable since the multiple Lewis basic sites of (*S*)-4 could coordinate to the Lewis acidic {ZnPh} unit in various patterns. In Scheme 2, compound **5** represents one such [1+1] complex. When diphenylzinc (1.5 equiv with respect to (*S*)-4) was



Scheme 2. Tentative mechanism for the catalytic addition of diphenylzinc.

added, all the hydroxy proton signals disappeared and the aromatic region gave sharp, clean signals at $\delta = 7.68$ (d, $J = 7.2$ Hz, 2H); 7.55 (s, 1H); 7.48 (d, $J = 7.2$ Hz, 2H); 7.27 (t, $J = 7.2$ Hz, 2H); 7.20 (t, $J = 7.2$ Hz, 2H); 7.18–7.10 (m, overlapping with the free benzene signal); 6.56 (s, 1H); 6.47 (s, 1H); 6.45 ppm (s, 1H). On the basis of gradient double-quantum-filtered (gDQ-COSY) and gradient heteronuclear single-quantum (gHSQC) correlation spectroscopy experiments, this complex was characterized as a [2+3] complex containing two H_8 -binol ligands, three Zn centers, and a total of two phenyl groups on the Zn atoms. The four singlets in the aromatic region were assigned to the aromatic protons of two unsymmetrical H_8 -binol ligands. The two doublets, two triplets, and the multiplet were assigned to the two unsymmetrical phenyl groups on the Zn centers. The ^{13}C NMR spectrum of this compound displayed six downfield singlets at $\delta = 160.1, 158.5, 157.1, 156.7, 156.0$ and 154.8 ppm: four were assigned to the aryl carbon atoms bearing the oxygen atom in the two unsymmetrical ligands and two are due to the *ipso* phenyl carbon atom connected to the Zn atom in the {ZnPh} units.^[21] Compound **6** in Scheme 2 is proposed as a possible structure for the [2+3] complex generated from the reaction of diphenylzinc with the proposed [1+1] complex **5**.

Addition of trimethylacetaldehyde to the above [1+1] or [2+3] complex separately showed no reaction. This demonstrates that the phenyl group in the {ZnPh} units of **5** and **6** cannot migrate to the aldehyde. With the addition of up to 12 equivalents (with respect to (*S*)-**4**) of diphenylzinc in the absence of the aldehyde, the [2+3] complex probably dissociated completely to form a compound that may contain only one H_8 -binol ligand and multiple coordinated {ZnPh₂} units. Its ^1H NMR spectrum showed only one singlet at $\delta = 6.65$ ppm for the aromatic hydrogen atom of the ligand, indicating the formation of a C_2 -symmetric complex as represented by **7**. The conversion of **6** into **7** may involved a metathesis process between diphenylzinc and the zinc center in **6** that contains no phenyl group to form the monophenylated zinc centers in **7**. Addition of trimethylacetaldehyde to this complex immediately led to phenyl migration to the aldehyde. Catalysis by this monomeric H_8 -binol complex is consistent with the observed linear relationship between the *ee* value of the ligand and that of the product. The transition state **8** is proposed for this reaction on the basis of previous mechanistic work in the area of catalytic asymmetric organozinc additions.^[22] Multiple peaks at $\delta = 4.85$ – 4.25 (tBuCHPh) and at 0.95–0.60 ppm ((CH₃)₃C) suggest the formation of various zinc alkoxide products from the addition of phenyl to the aldehyde. These zinc alkoxides probably existed as oligomers or clusters. After complete consumption of diphenylzinc by excess trimethylacetaldehyde, the [2+3] complex reappeared. Addition of D₂O to the reaction mixture converted the zinc alkoxide products into 2,2-dimethyl-1-phenyl-1-propanol with two singlets observed at $\delta = 4.01$ and 0.89 ppm in the ^1H NMR spectrum. The ligand (*S*)-**4** was also regenerated. The mechanism depicted in Scheme 2 on the basis of the NMR study illustrates our current understanding of this catalytic process and more work will be conducted.

In summary, (*S*)-**4** allows high enantioselectivity in the reaction of diphenylzinc with both aliphatic and aromatic

aldehydes and, especially, is the most enantioselective catalyst for linear aliphatic aldehydes. Unlike other catalysts developed for the addition of diphenylzinc—which often require the addition of a significant amount of diethylzinc with cooling (or heating) the reaction mixture to ensure high enantioselectivity—the use of (*S*)-**4** avoids the need for additive and gives excellent results at room temperature. The one-step synthesis of this ligand from H_8 -binol and the mild asymmetric reaction conditions make this chiral catalyst practically useful for general synthesis. The NMR study has also revealed a few interesting mechanistic characteristics of this catalytic process.

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