

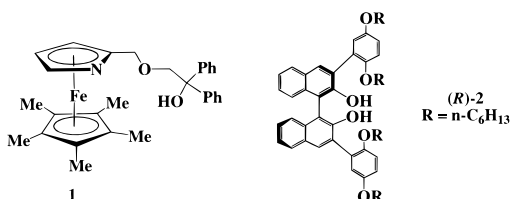
## The First Highly Enantioselective Catalytic Diphenylzinc Additions to Aldehydes: Synthesis of Chiral Diarylcarbinols by Asymmetric Catalysis

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Since the early reports on catalytic enantioselective diethylzinc additions,<sup>1</sup> the asymmetric reaction of aldehydes with dialkylzinc reagents has been studied very extensively.<sup>2,3</sup> A number of excellent catalysts have been discovered and have found many applications in the synthesis of optically active secondary alcohols. However, compared to the work on dialkylzinc additions, very little work has been carried out on asymmetric diarylzinc additions to aldehydes.<sup>4,5</sup> In 1997, Fu and co-workers reported the first enantioselective catalytic addition of diphenylzinc to aldehydes by using a catalyst based on planar-chiral ligand **1**.<sup>4a</sup> In the presence of a catalytic amount of **1**, the addition of diphenylzinc to *p*-chlorobenzaldehyde has generated *p*-chlorophenylphenylcarbinol but with only 57% ee. Unlike the diethylzinc addition to aldehydes which is extremely slow in the absence of a catalyst, the uncatalyzed diphenylzinc addition can even be competitive with the catalyzed reaction (vide infra). This makes the development of an enantioselective catalyst for the diphenylzinc addition much more challenging.



In our laboratory, we are interested in the synthesis of chiral diarylcarbinols by using the asymmetric diarylzinc addition to aromatic aldehydes because chiral diarylcarbinols are synthetically useful intermediates but are difficult to obtain by asymmetric catalysis.<sup>6</sup> Secondary alcohols are generally prepared by either reduction of ketones or addition of organometallic reagents to aldehydes. Because of the similar electronic and steric properties between the two aryl groups in a prochiral diaryl ketone, it is inherently more difficult to obtain chiral diarylcarbinols with high enantiomeric purity through asymmetric reduction. That is, the chiral bias of a catalyst toward the two

prochiral faces of a diaryl ketone should be small. Nevertheless, Corey and co-workers have shown that ketones containing two sterically and/or electronically *very different* aryl groups can be reduced with high enantioselectivity when using chiral oxazaborolidines as the catalysts.<sup>6b,7</sup> Unlike the reduction of diaryl ketones, the addition of organometallic aryl reagents to aryl aldehydes should be more suitable for asymmetric induction because of the large steric and electronic differences between the aryl group and the hydrogen atom in an aromatic aldehyde. However, very few reports on the catalytic enantioselective addition of organometallic aryl reagents to aryl aldehydes have appeared.<sup>4,8,9</sup>

Recently, we have shown that chiral binaphthyl ligand (*R*)-**2** catalyzes the addition of diethylzinc to a large number of aldehydes, including *o*-, *m*-, or *p*-substituted benzaldehyde, linear or branched aliphatic aldehydes, and alkyl- or aryl-substituted  $\alpha,\beta$ -unsaturated aldehydes, with very high enantioselectivity.<sup>10</sup> The excellent catalytic properties of (*R*)-**2** have prompted us to explore its application to the asymmetric diarylzinc addition to aldehydes. We find that (*R*)-**2** is also highly enantioselective for this reaction. Particularly, its high enantioselectivity for the catalytic addition of diphenylzinc to aromatic aldehydes allows the synthesis of chiral diarylcarbinols that are generally difficult to access. Herein, these results are reported.

We have first investigated the reaction of propionaldehyde with diphenylzinc in the presence of (*R*)-**2**. The reaction is conducted at 0 °C in a toluene solution in the presence of 10 mol % of (*R*)-**2** which produces (*S*)-1-phenylpropanol in 87% ee. This is the first example of a catalytic diphenylzinc addition to aldehydes with high enantioselectivity. The *S* configuration of the product indicates that the phenyl addition occurs at the *re* face of the aldehyde, the same as the diethylzinc addition catalyzed by (*R*)-**2**.<sup>10</sup> This suggests that the catalytic diphenylzinc addition should be mechanistically similar to the diethylzinc addition. In the case of the diethylzinc addition to benzaldehyde in the presence of (*R*)-**2**, the *R* product is obtained. Thus, both the *R* and *S* enantiomers of 1-phenylpropanol can be obtained by carrying out either diethylzinc addition to benzaldehyde or diphenylzinc addition to propionaldehyde in the presence of (*R*)-**2**.

Encouraged by the result obtained for the diphenylzinc addition to the aliphatic aldehyde, we have studied the diphenylzinc addition to aromatic aldehydes for the synthesis of chiral diarylcarbinols. The results are summarized in Table 1. The reaction of organozinc reagents with aromatic aldehydes is normally much faster than with aliphatic aldehydes.<sup>2,3,10</sup> Therefore, the catalytic asymmetric diphenylzinc addition to aromatic aldehydes is expected to be even more challenging than its addition to aliphatic aldehydes because of the more competitive uncatalyzed background reaction. Entry 2 in Table 1 shows that at 0 °C the diphenylzinc addition to *p*-anisaldehyde can proceed even without a catalyst. Because of the competitive background reaction, a low ee was observed when a 5 mol % of (*R*)-**2** was used (entry 3). When a larger amount of (*R*)-**2** is pretreated with diethylzinc, the resulting chiral zinc complex

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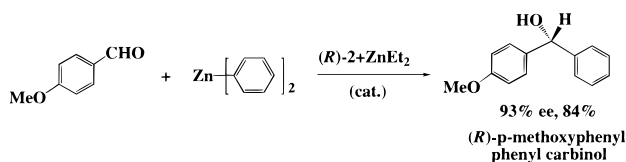
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**Table 1. Asymmetric Diphenylzinc Additions to Aldehydes Catalyzed by (*R*)-2**

Aldehyde	Ph <sub>2</sub> Zn (equiv)	( <i>R</i> )-2 or ( <i>R</i> )-2+Additive (mol%)	Aldehyde Concentration (mM)	Solvent	Temperature (°C)	Time (h)	Isolated Yield (%)	ee (%)	Configuration <sup>c</sup>	Entry
	1.2	10	100	Toluene	0	20	90	87 <sup>a</sup>	S <sup>2</sup>	1
	1	0	50	Toluene	0	10	61	0		2
	2	5	50	Toluene	0	10	76	54 <sup>a</sup>	R <sup>5</sup>	3
	1	5 + 10 Et <sub>2</sub> Zn	50	Toluene	0	10	87	77 <sup>a</sup>	R	4
	1	20 + 40 Et <sub>2</sub> Zn	50	Toluene	-30	24	84	93 <sup>a</sup>	R	5
	1	20 + 40 Et <sub>2</sub> Zn	50	Et <sub>2</sub> O	r.t.	10	70	57 <sup>b</sup>	R	6
	1	20 + 40 Et <sub>2</sub> Zn	5	Et <sub>2</sub> O	r.t.	10	86	94 <sup>b</sup>	R <sup>11</sup>	7
	1	20 + 40 Et <sub>2</sub> Zn	5	THF	-10	96	66	87 <sup>a</sup>	R <sup>9a</sup>	8
	1	20 + 40 Et <sub>2</sub> Zn	5	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	28	98	50 <sup>a</sup>	S <sup>5</sup>	9
	1	20 + 80 Et <sub>2</sub> Zn + 40 MeOH	5	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	22	92	77 <sup>a</sup>	S	10
	1	20 + 80 Et <sub>2</sub> Zn + 40 MeOH	5	CH <sub>2</sub> Cl <sub>2</sub>	reflux	10	94	83 <sup>a</sup>	S	11

a. Determined by HPLC-Chiracel-OD column. b. Determined by analyzing the acetate derivative of the alcohol product on a HPLC-Chiracel-OD column. c. Determined by comparing the optical rotation with the literature data.

### Scheme 1. Asymmetric Addition of Diphenylzinc to *p*-Anisaldehyde Catalyzed by (*R*)-2



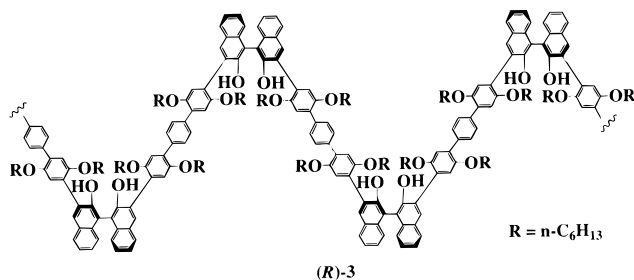
catalyzes the reaction of diphenylzinc with *p*-anisaldehyde to generate (*R*)-*p*-methoxyphenylphenylcarbinol with 93% ee and 84% yield at -30 °C in toluene (entry 5) (Scheme 1).

Through variation of the solvents, reaction temperatures, concentrations of the aldehydes, and amount of the catalyst (*R*)-2, and with the use of additives such as diethylzinc and methanol, excellent enantioselectivity for the addition of diphenylzinc to various aromatic aldehydes and an  $\alpha,\beta$ -unsaturated aldehyde has been achieved. The factors that influence the enantioselectivity of these reactions are summarized below: (1) Pretreatment of the chiral ligand (*R*)-2 with diethylzinc generally increases the enantioselectivity. This indicates that the zinc complex generated from the reaction of diethylzinc with (*R*)-2 is a better catalyst than that generated from the reaction of diphenylzinc with (*R*)-2. (2) Reducing the concentration of the substrates leads to dramatically increased enantioselectivity (entries 6 and 7). This is probably because the uncatalyzed reaction is suppressed at lower concentration. (3) In the case of the  $\alpha,\beta$ -unsaturated aldehyde, addition of methanol might have modified the structure of the catalyst formed from the reaction of (*R*)-2 with diethylzinc, leading to a much improved enantioselectivity (entries 10 and 11). The use of alcohol additives to enhance the enantioselectivity of an organozinc addition was reported by Fu.<sup>4b</sup> It is interesting to notice that *higher* temperature in methylene chloride solution actually leads to higher ee for the reaction of diphenylzinc with *trans*-cinnamaldehyde (entry 11). A more active catalyst may be produced at higher temperature for this reaction.

As an example, the experimental procedure for the diphenylzinc addition to *p*-chlorobenzaldehyde catalyzed by (*R*)-2 is given here. To a Schlenk flask were added diethyl ether (50 mL, dried, and degassed with N<sub>2</sub>), (*R*)-2 (42 mg, 0.05 mmol), and Et<sub>2</sub>Zn (10  $\mu$ L, 0.1 mmol). After stirring at

rt for 15 min, Ph<sub>2</sub>Zn (55 mg, 0.25 mmol) was added. Stirring was continued for another 15 min, and then *p*-chlorobenzaldehyde (35 mg, 0.25 mmol) was added. The reaction mixture was stirred at rt for 10 h and quenched with 1 N HCl. Usual workup gave (*R*)- $\alpha$ -phenyl-4-chlorobenzyl alcohol in 86% yield (47 mg). The alcohol product was converted to its acetate and was analyzed by HPLC on a Chiracel-OD column without purification. The ee of the ester was found to be 94%.

We have further found that polymer (*R*)-3,<sup>12</sup> a rigid and sterically regular polymer containing (*R*)-2 as the chiral ligand units, can also carry out the diphenylzinc addition to aldehydes in a preliminary study. For example, the reaction of diphenylzinc with propionaldehyde in the presence of 20 mol % (based on the binaphthyl repeating units) of (*R*)-3 produces (*S*)-1-phenylpropanol with 85% ee and 82% yield. Both the reaction condition and result are similar to



those when the monomer catalyst (*R*)-2 is used. The polymer (*R*)-3 can be easily recovered with almost quantitative yield by simple precipitation with methanol after workup. The convenient recyclability of the polymer makes the new asymmetric catalytic diphenylzinc addition very practical.

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**Supporting Information Available:** Detailed experimental procedures for the catalytic asymmetric reactions and for the determination of the ee's of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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