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# New and improved ligands for highly enantioselective catalytic diphenylzinc additions to aryl aldehydes

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**Abstract**

By introducing electron-withdrawing fluorine atoms to a chiral 1,1′-binaphthyl ligand (*R*)-**1**, a new catalyst (*S*)-**5d** has been obtained which shows improved catalytic properties for the asymmetric diphenylzinc addition to aldehydes. This new ligand allows the synthesis of chiral diarylcarbinols with high enantioselectivity in shorter reaction time under simple reaction conditions. © 1999 Elsevier Science Ltd. All rights reserved.

Chiral diarylcarbinols are synthetically useful in the preparation of some biologically active molecules.[1–6] In recent years, Corey and coworkers have developed a synthesis of chiral diarylcarbinols by a catalytic asymmetric reduction of prochiral ketones containing electronically and/or sterically very different diaryl groups.[4–6] Although the asymmetric addition of an aryl reagent to an aryl aldehyde seems more suitable for chiral induction because of the large steric and electronic differences between an aryl group and a hydrogen on an aldehyde substrate, no highly enantioselective catalysts are obtained for this reaction until recently.[7–12] In 1994, Weber and Seebach found that an in situ generated $(RO)_3Ti$–Ph reagent can add to aryl aldehydes in the presence of a chiral titanium catalyst with high enantioselectivity.[8] Recently, we have achieved the first highly enantioselective diphenylzinc addition to aryl and alkyl aldehydes by using (*R*)-**1** as the catalyst ligand.[11] Shortly after, Bolm and co-workers also reported a chiral ferrocenyl hydroxy oxazoline compound **2** to catalyze the addition of diphenylzinc to certain aldehydes with good enantioselectivity.[12]

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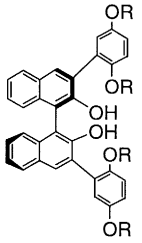
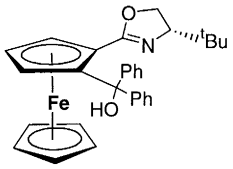



(*R*)-**1**
R = *n*-$C_6H_{13}$



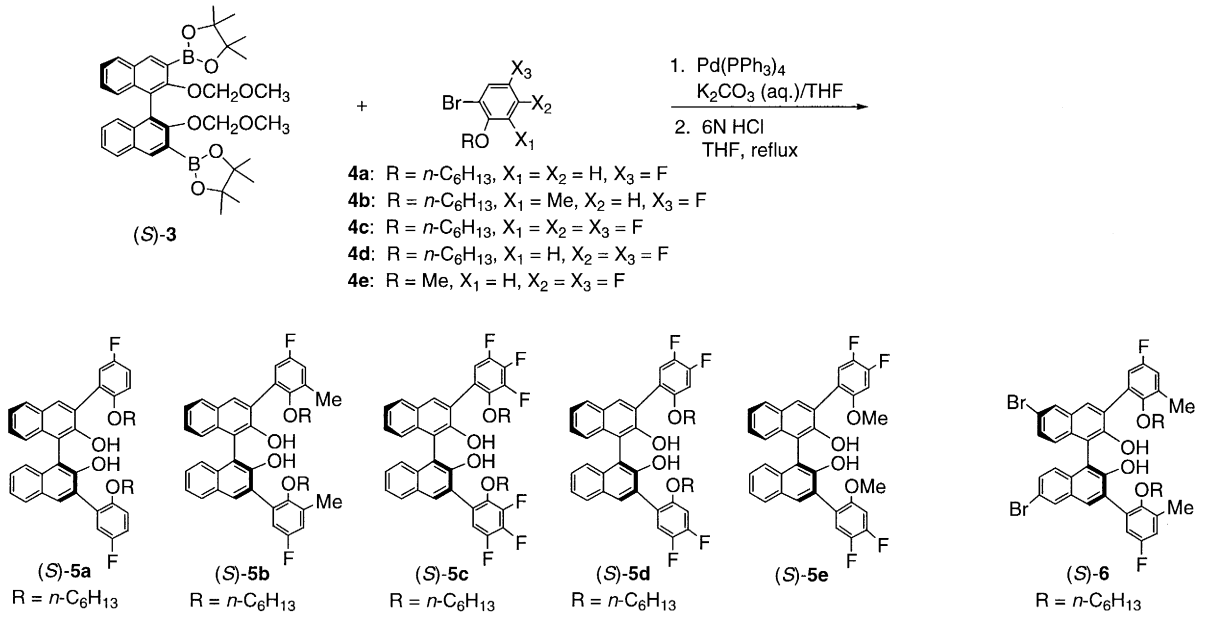

**2**

Compound (*R*)-**1** in combination with 2 equiv. of diethylzinc catalyzes the diphenylzinc addition to 4-chlorobenzaldehyde with 94% ee and to cinnamaldehyde with 83% ee.[11] The reaction with cinnamaldehyde requires the use of methanol as an additive in a refluxing methylene chloride solution. In order to gain further information about this chiral ligand and also to improve this catalytic process, we have modified (*R*)-**1** mainly by tuning its electronic effects and have discovered a new ligand with improved catalytic properties. Herein, these results are reported.

During our study of the catalytic diphenylzinc addition, we have realized that the main challenge is to overcome the uncatalyzed reaction of diphenylzinc with aldehydes.[11] This requires the chiral catalyst-mediated reaction to be much faster than the background reaction in order to achieve efficient chiral induction. A strategy to increase the catalytic activity of ligand (*R*)-**1** is therefore undertaken by introduction of electron-withdrawing substituents in order to increase the Lewis acidity of the catalytically active zinc centers that are generated in situ from the reaction of (*R*)-**1** with 2 equiv. of diethylzinc.

A series of new chiral ligands (*S*)-**5a**–**e** where multiple electron-withdrawing fluorine atoms are introduced to the 3,3′-aryl groups were synthesized by the Suzuki coupling[13] of (*S*)-**3**[14] with aryl bromides **4a**–**e** followed by acidic hydrolysis (Scheme 1). Treatment of (*S*)-**5b** with bromine specifically introduced bromine atoms to the 6,6′-positions of the binaphthyl unit to generate ligand (*S*)-**6**. Ligands (*S*)-**5a**–**d** and (*S*)-**6** were used to catalyze the diphenylzinc addition to cinnamaldehyde without using the methanol additive. The catalytic properties of these new ligands are compared with (*R*)-**1**, and the results are summarized in Table 1. In these reactions, each ligand was first treated with 2 equiv. of diethylzinc in methylene chloride and then a 20 mol% of the in situ generated zinc complex was used to catalyze the diphenylzinc addition to cinnamaldehyde. As shown in Table 1, with the introduction of the electron-withdrawing substituents, all these new ligands exhibit much better enantioselectivity than (*R*)-**1**. Without addition of methanol, (*R*)-**1** gave only 50% ee. However, under the same conditions, ligand (*S*)-**5d** showed up to 87% ee. This compound has the highest enantioselectivity among all the ligands tested. No improvement was observed with the addition of methanol when (*S*)-**5d** was used.

A six-membered ring transition state as shown in **7** is proposed to account for the electronic effects of these ligands.[15] In transition state **7**, introduction of an electron-withdrawing substituent X onto the 3-aryl substituent of the binaphthyl unit should reduce the electron density of the etheral oxygen atom coordinated to the catalytically active zinc center, thus increasing the Lewis acidity of the zinc and further activating the aldehyde. A more active catalyst makes the chiral ligand-controlled reaction more competitive than the uncatalyzed reaction, further enhancing the enantioselectivity. Compound (*S*)-**5d** has two fluorine atoms on each of the 3,3′-aryl substituents and exhibits much higher enantioselectivity than the more electron rich ligand (*R*)-**1**. However, ligand (*S*)-**5c** though with three fluorine atoms on each of the 3,3′-aryl substituents does not show further enhancement in enantioselectivity over (*S*)-**5d**. In the 3,3′-aryl groups of (*S*)-**5c**, there is a fluorine atom *ortho* to an alkoxy group. This fluorine



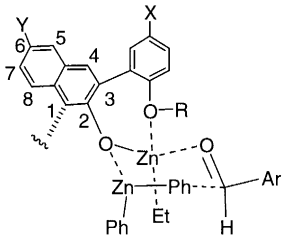

Scheme 1. Synthesis of the chiral binaphthyl ligands (*S*)-**5a**–**e** and (*S*)-**6**

Table 1
Reaction of cinnamaldehyde with diphenylzinc in the presence of the chiral ligands[a]

| Entry | Ligand | Isolated yield (%) | ee (%) | Configuration |
|---|---|---|---|---|
| 1 | (*R*)-**1** | 88 | 50 | S |
| 2 | (*S*)-**5a** | 90 | 73 | R |
| 3 | (*S*)-**5b** | 88 | 81 | R |
| 4 | (*S*)-**5c** | 90 | 81 | R |
| 5 | (*S*)-**5d** | 92 | 87 | R |
| 6 | (*S*)-**6** | 88 | 70 | R |

a. The reaction was carried out under nitrogen at room temperature in $CH_2Cl_2$ in the presence of 20 mol% of the chiral ligand and 40 mol% of $Et_2Zn$. The concentration of aldehyde was 5 mM. The reaction was quenched in 5 h. The ee was determined by HPLC-Chiracel-OD column. The absolute configuration of the product was determined by comparing the optical rotation with the literature data.[7g]

atom may be able to participate in the coordination to a zinc center with the adjacent alkoxy group and thus perturb the catalyst structure. Contrarily, the *ortho* methyl groups in (*S*)-**5b** may provide a better steric control for the diphenylzinc addition than (*S*)-**5a** and give a higher enantioselectivity. In transition state **7**, when a strong electron-withdrawing substituent Y is introduced to the position 6, it may reduce the diphenylzinc coordination to the 2-oxygen atom and thus disfavor the chiral ligand-controlled diphenylzinc addition. Therefore, the bromine atoms at the 6,6′-positions of the binaphthyl unit in (*S*)-**6** lead to reduced enantioselectivity from (*S*)-**5b**.




**7**

The high enantioselectivity of ligand (*S*)-**5d** for the addition of diphenylzinc with cinnamaldehyde has prompted us to examine its use for the reaction of various aryl aldehydes in order to prepare optically active diarylcarbinols. These results are summarized in Table 2. Unlike (*R*)-**1** which requires longer reaction time, in some cases ≤0°C and also very different reaction conditions for different substrates in order to achieve high enantioselectivity, (*S*)-**5d** can catalyze the reaction of various aryl aldehydes with diphenylzinc at room temperature in methylene chloride in 5 h with high enantioselectivity. For example, the reaction of 2-naphthaldehyde catalyzed by (*R*)-**1** took 4 days at −10°C with incomplete conversion and 66% isolated yield. However, in the presence of (*S*)-**5d**, this reaction was completed in 5 h at room temperature with 90% isolated yield (entry 4). We have also studied the use of (*S*)-**5d** and (*S*)-**5e** to catalyze the diphenylzinc addition to 3-pyridinecarboxaldehyde. Ligand (*S*)-**5e** where the hexyloxy groups of (*S*)-**5d** were replaced with the smaller methoxy groups gave a lower ee (entry 6) than (*S*)-**5d** (entry 5). When the nitrogen of 3-pyridinecarboxaldehyde was protected with triethylborane, its reaction with diphenylzinc in the presence of (*S*)-**5d** gave 86% ee and 89% yield (entry 7).[16]

Table 2
Synthesis of chiral diarylcarbinols by the diphenylzinc addition to aryl aldehydes catalyzed by (*S*)-**5d**[a]

| Entry | Aldehyde | Isolated Yield (%) | ee (%) | Configuration[f] |
|---|---|---|---|---|
| 1 | cinnamaldehyde | 92 | 87[b] | R[7g] |
| 2 | 4-chlorobenzaldehyde | 92 | 95[c] | S[17] |
| 3 | 2-methylbenzaldehyde | 87 | 91[b] | S[18] |
| 4 | 2-naphthaldehyde | 90 | 88[b] | S[7a] |
| 5 | 3-pyridinecarboxaldehyde | 86 | 80[b] | (+)[19] |
| 6 | 3-pyridinecarboxaldehyde | 90 | 70[b,d] | (+) |
| 7 | 3-pyridinecarboxaldehyde | 89 | 86[b,e] | (+) |

a. The reaction was carried out under nitrogen at room temperature in $CH_2Cl_2$ in the presence of 20 mol% of (*S*)-**5d** and 40 mol% of $Et_2Zn$ unless otherwise indicated. The concentration of aldehyde was 5 mM. The reaction was quenched in 5 h. b. Determined by HPLC-Chiracel-OD column. c. Determined by analyzing the acetate derivative of the alcohol product by HPLC-Chiracel-OD column. d. (*S*)-**5e** was used in place of (*S*)-**5d**. e. $Et_3B$-pretreated aldehyde was used. f. Determined by comparing the optical rotation with the literature data.

In summary, through a systematic tuning of the electronic properties of ligand (*R*)-**1**, we have obtained a new catalyst (*S*)-**5d** with improved catalytic properties for the asymmetric diphenylzinc additions. The fluorine substituents in (*S*)-**5d** can increase the Lewis acidity of the corresponding zinc complex, leading to higher catalytic activity and better catalyst control over the uncatalyzed background reaction. This new ligand allows the synthesis of chiral diarylcarbinols with high enantioselectivity in shorter reaction time under simple reaction conditions.

## Acknowledgements

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