JOC Article

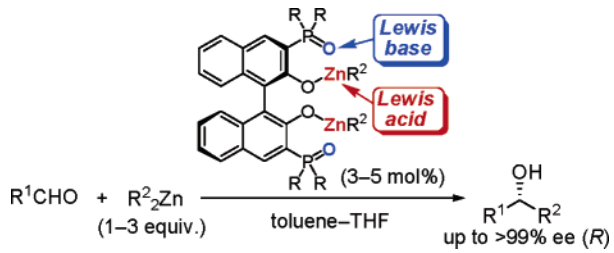
# 3,3′-Diphosphoryl-1,1′-bi-2-naphthol−Zn(II) Complexes as Conjugate Acid−Base Catalysts for Enantioselective Dialkylzinc Addition to Aldehydes

Manabu Hatano, Takashi Miyamoto, and Kazuaki Ishihara*

*Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan*

*ishihara@cc.nagoya-u.ac.jp*

*Received May 2, 2006*




A highly enantioselective dialkylzinc ($R^2{}_2Zn$) addition to a series of aromatic, aliphatic, and heteroaromatic aldehydes (**5**) was developed based on conjugate Lewis acid−Lewis base catalysis. Bifunctional BINOL ligands bearing phosphine oxides [P(═O)$R_2$] (**7**), phosphonates [P(═O)$(OR)_2$] (**8** and **9**), or phosphoramides [P(═O)$(NR_2)_2$] (**10**) at the 3,3′-positions were prepared by using a phospho-Fries rearrangement as a key step. The coordination of a NaphO−Zn(II)−$R^2$ center as a Lewis acid to a carbonyl group in a substrate and the activation of $R^2{}_2Zn$(II) with a phosphoryl group (P═O) as a Lewis base in the 3,3′-diphosphoryl-BINOL−Zn(II) catalyst could promote carbon−carbon bond formation with high enantioselectivities (up to >99% ee). Mechanistic studies were performed by X-ray analyses of a free ligand (**7**) and a tetranuclear Zn(II) cluster (**21**), a $^{31}P$ NMR experiment on Zn(II) complexes, an absence of nonlinear effect between the ligand (**7**) and Et-adduct of benzaldehyde, and stoichiometric reactions with some chiral or achiral Zn(II) complexes to propose a transition-state assembly including monomeric active intermediates.

## Introduction

Modern advanced asymmetric catalysis demands both maximum efficiency in terms of yield and enantioselectivity and minimal waste derived from catalysts, reagents, solvents, salts, etc.[1,2] Catalytic enantioselective dialkylzinc addition to aldehydes is one of the most important reactions involving carbon−carbon bond formation, in which optically active secondary alcohols are obtained as synthetically and pharmaceutically useful compounds.[3] To date, numerous efficient chiral ligands such as amino alcohols (*N*,*O*-ligands), diamines (*N*,*N*-ligands), and diols (*O*,*O*-ligands) have been developed.[4−8] We can classify organometal alkylation into three types: (a) double activation by only Lewis acidic organometal reagents, (b) double activation

(1) (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis I−III*; Springer: Berlin, 1999. (b) Ahluwalia, V. K.; Kidwai, M. *New Trends in Green Chemistry*; Kluwer Academic: Dordrecht, The Netherlands, 2004.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705.

(3) (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188. (b) Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Oxford University Press: New York, 1999. (c) Knochel, P. *Handbook of Functionalized Organometallics*; Wiley-VCH: Weinheim, Germany, 2005.

(4) Reviews for catalytic enantioselective dialkylzinc additions to aldehydes and ketones: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (c) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308. (d) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886. (e) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2006**, in press.

(5) (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 40−69. (c) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19−37.

(6) (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99−101. (b) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321−1323. (c) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384. (d) Weber, B.; Seebach, D.; *Tetrahedron* **1994**, *50*, 7473−7484. (e) Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J.; Gramlich, V. *Org. Lett.* **1999**, *1*, 55−58.

10.1021/jo060908t CCC: $33.50 
Published on Web 07/21/2006

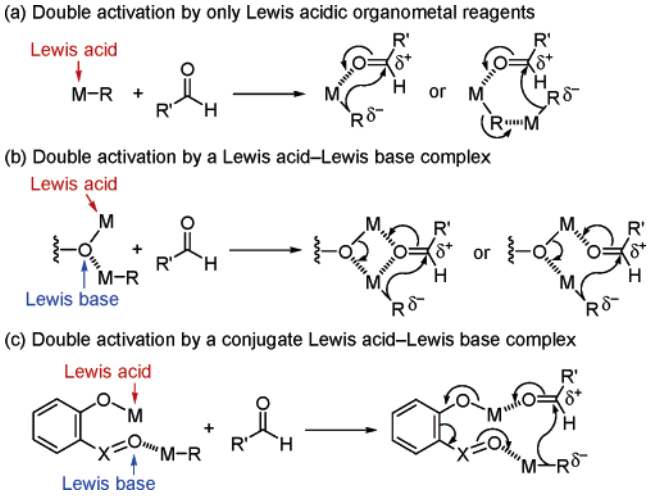



**FIGURE 1.** Double activation of aldehyde and organometal reagents (M−R).

by a Lewis acid−Lewis base, and (c) double activation by a conjugate Lewis acid−Lewis base (Figure 1). Usually, organomagnesium and organoaluminum reagents belong to type a. Most of the reported enantioselective dialkylzinc additions to aldehydes are type b in which the Lewis acid and the Lewis base are attached each other.[4,9] To the best of our knowledge, there have been no reports on conjugate acid−base catalysis such as type c in enantioselective dialkylzinc additions, which involves an electron charge transfer at the ligand interior.[4] Thus, type c catalysis offers an advantage at enhancing catalytic activity because the direct linkage between the acid and base in type b may weaken or negate both activities.

In principle, catalysis with *N*,*O*-ligands such as Noyori's DAIB (**1**) is based on type b as a neighboring acid−base catalytic system to activate aldehyde and dialkylzinc, respectively (Figure 2).[5] For *O*,*O*-ligands, 1,1′-bi-2-naphthol (BINOL) derivatives are important because of their simple $C_2$-symmetric structures and synthetic utility. Particularly, Ti(IV)−BINOLate complex (**2**) has been developed by using type b catalysis.[8b,10] The 3,3′-di(*o*-alkoxyphenyl)-BINOL (**3**) described by Pu and co-workers, which has overcome the problem associated with the use of excess $Ti(O^iPr)_4$, can be also classified as a neighboring acid−base catalytic system, type b.[11,12] In brief, these type b catalyses involve only the terminal acid and base functions without conjugation inside the ligands.

In contrast, in the present study we explored a conjugate Lewis acid−Lewis base catalysis with **4** (Figures 1c and 3). The key to designing the catalysts is a conjugation between a 2-naphthol moiety and a 3-phosphoryl group (P═O) to doubly activate electrophile and nucleophile.[13,14] In particular, we examined the enantioselective dialkylzinc addition to aldehydes (**5**) using BINOL−Zn(II) catalysts bearing phosphine oxides [$P(═O)R_2$], phosphonates [$P(═O)(OR)_2$], or phosphoramides [$P(═O)(NR_2)_2$] at the 3,3′-positions (Figure 3).[15−17]

## Results and Discussion

**Evaluation of Conjugate Acid−Base Catalyst, 3,3′-Diphenylphosphoryl-BINOL−Zn(II).** First, 10 mol % of 3,3′-diphenylphosphoryl-BINOL, (*R*)-**7**, was used to catalyze the addition of diethylzinc (3 equiv) to aldehydes (**5**) in THF/toluene (1:1) at room temperature.[4−8] The results are summarized in Table 1. In particular, aromatic aldehydes with electron-donating or -withdrawing groups showed high enantioselectivities (up to 95% ee) (entries 1−11). The reactions also proceeded smoothly for heteroaromatic aldehydes and α,*β*-unsaturated aldehydes (entries 12−14 and 21−25). For aliphatic aldehydes, in which competitive reduction often occurs along with ethylation, the corresponding secondary aliphatic alcohols were obtained with high enantioselectivities (up to 94% ee) (entries

(7) (a) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 497−501. (b) Wu, Y.; Yun, H.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3543−3552. (c) Shen, X.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321−4327. (d) Yun, H.; Wu, Y.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron Lett.* **2000**, *41*, 10263−10266. (e) Mikami, K.; Angeland, R.; Ding, K.; Ishii, A.; Tanaka, A.; Sawada, N.; Kudo, K.; Senda, M. *Chem.−Eur. J.* **2001**, *7*, 730−737. (f) Du, H.; Ding, K. *Org. Lett.* **2003**, *5*, 1091−1093. (g) Ding, K.; Du, H.; Yuan, Y.; Long, J. *Chem.−Eur. J.* **2004**, *10*, 2872−2884. (h) Du, H.; Zhang, X.; Wang, Z.; Ding, K. *Tetrahedron* **2005**, *61*, 9465−9477.

(8) (a) Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 6929−6941. (b) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336−10348. (c) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971. (d) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739−749. (e) García, C.; Walsh, P. *J. Org. Lett.* **2003**, *5*, 3641−3644. (f) Joen, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448−455. (g) Costa, A. M.; García, C.; Carroll, P. J.; Walsh, P. J. *Tetrahedron* **2005**, *61*, 6442−6446. (h) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416−16425.

(9) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464−2465.

(10) Pioneering BINOL−Ti catalysis: (a) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233−6236. (b) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585−589. (c) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651−3655.

(11) (a) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364−1365. (b) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145−149. (c) Simomson, D. L.; Kingsbury, K.; Xu, M.-H.; Hu, Q.-S.; Sabat, M.; Pu, L. *Tetrahedron* **2002**, *58*, 8189−8193.

(12) (a) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427−7430. (b) Qin, Y.-C.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 273−277.

(13) Resonance behaviors of conjugate aromatic compounds involving $C(sp^2)−P═O/C(sp^2)−O−H$ and $C(sp^2)═P−O−/C(sp^2)═O\cdots H^+$ have been studied. For an excellent textbook on organophosphorus chemistry see Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000, and the references therein.

(14) (a) Griffin, C. E.; Polsky, R. A. *J. Org. Chem.* **1961**, *26*, 4772−4773. (b) Goetz, H.; Nerdel, F.; Wiechel, K.-H. *Liebigs Ann. Chem.* **1963**, *665*, 1−13. (c) Albright, T. A.; Freeman, W. J.; Schweizer, E. E. *J. Org. Chem.* **1975**, *40*, 3437−3441. (d) Symmes, C., Jr.; Quin, L. D. *J. Org. Chem.* **1976**, *41*, 1548−1551. (e) Pacchioni, G.; Bagus, P. S. *Inorg. Chem.* **1992**, *31*, 4391−4398. (f) Gilheany, D. G. *Chem. Rev.* **1994**, *94*, 1339−1374.

(15) Bifunctional nonconjugate BINOLs with phosphoryl groups: (a) Hamasima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641−2642. (b) Kanai, M.; Hamashima, Y.; Takamura, M.; Shibasaki, M. *J. Synth. Org. Chem., Jpn.* **2001**, *59*, 766−778. (c) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989−1999. (d) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. **2005**, 1419−1508. (e) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Pure Appl. Chem.* **2005**, *77*, 2047−2052. (f) Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470−3474.

(16) Precedent chiral ligands bearing P═O moieties: (a) Soai, K.; Hirose, Y.; Ohno, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1473−1474. (b) Hulst, R.; Heres, H.; Fitzpatrick, K.; Peter, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2755−2760. (c) Shibata, T.; Tabira, H.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 177−178. (d) Brunel, J.-M.; Constantieux, T.; Legrand, O.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 2961−2964. (e) Legrand, O.; Brunel, J.-M.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 9419−9422. (f) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3319−3325. (g) Legrand, O.; Brunel, J.-M.; Buono, G. *Tetrahedron Lett.* **2000**, *41*, 2105−2109. (h) Shi, M.; Sui, W.-S. *Chirality* **2000**, *12*, 574−580.

(17) Part of this work has been published as a preliminary communication: (a) Hatano, M.; Miyamoto, T.; Ishihara, K. *Adv. Synth. Catal.* **2005**, *347*, 1561−1568. (b) Hatano, M.; Miyamoto, T.; Ishihara, K. *Synlett.* **2006**, 1762−1764.

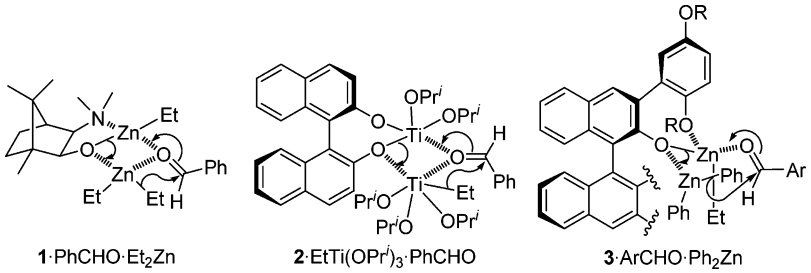



**FIGURE 2.** Precedent acid−base catalytic systems by type b.

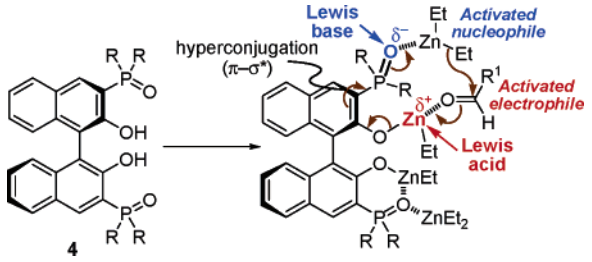


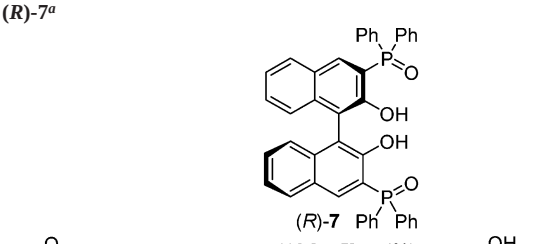

**FIGURE 3.** Expected conjugate acid−base catalysis using 3,3′-diphosphoryl-BINOL−Zn(II) complexes.

15−20). An increase in the catalytic activity of (*R*)-**7** was observed at 50 °C with a bit loss of enantioselectivity, and the catalyst loading could be decreased to 5 mol % (brackets in Table 1).

**BINOL−Zn(II) Catalysts Bearing Phosphonates [P(═O)(OR)$_2$] or Phosphoramides [P(═O)(NR$_2$)$_2$].** To achieve strong Lewis basicity for P═*O*, chiral ligands ((*R*)-**8** and (*R*)-**9**), which had electron-donating P-substitutions, were examined (Table 2). The reaction with 3 mol % of (*R*)-**7** proceeded with high enantioselectivity (93% ee), but was slow. However, even 3 mol % of (*R*)-**8** or (*R*)-**9** was more effective than (*R*)-**7** for the enantioselective addition of diethylzinc (1.5 equiv) to benzaldehyde in THF/toluene at room temperature (Table 2, entries 1−3). This preference for (*R*)-**9** to (*R*)-**8** was probably because of the strong electron-donation and compact structure required by a fixed ring conformation. For a promising ligand with strong Lewis basicity, we next examined the BINOL−Zn(II) catalyst bearing conjugate phosphoramide [P═(O)(NR$_2$)$_2$] moieties. The reaction proceeded smoothly with 3 mol % of (*R*)-**10** and 1.5 equiv of Et$_2$Zn at room temperature for 24 h to give the product in 98% yield and 97% ee (entry 4). Therefore, the catalytic activity of (*R*)-**10** was higher than those of **7**, **8**, and **9**, and the order of reactivity was **10** > **9** > **8** > **7**, according to their electron-donating abilities to P═O moieties.[18] By using **8**−**10**, a warm temperature (50 °C) increased the reactivity with almost the same enantioselectivity (within 0−2% ee) (entries 6−8). Particularly for (*R*)-**10**, the Et-adduct was obtained in quantitative yield with 95% ee after only 4 h (entry 8).

Encouraged by the high efficiency of (*R*)-**10**−Zn(II) catalyst in the enantioselective ethylation of benzaldehyde, we next examined the generality of this method for other aldehydes (Table 3). For mono- or disubstituted aromatic aldehydes and

**TABLE 1. Enantioselective Diethylzinc Addition to Aldehydes with (*R*)-7**[a]



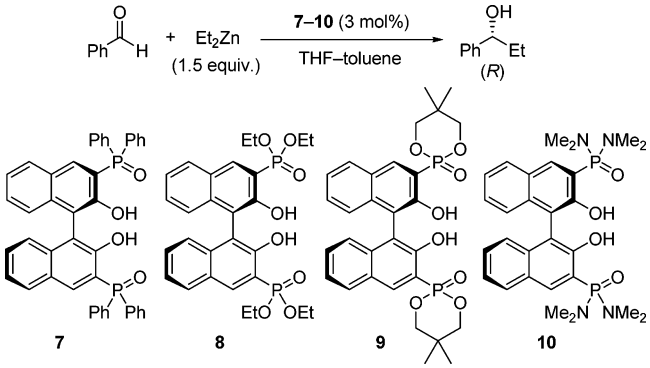

| entry | R$^1$CHO (**5**) | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | PhCHO | 3 [2] | 95 [84] | 95 [88] |
| 2 | 4-MeOC$_6$H$_4$CHO | 18 [7] | 89 [95] | 89 [85] |
| 3 | 4-MeC$_6$H$_4$CHO | 8 [3] | >99 [96] | 93 [88] |
| 4 | 4-PhC$_6$H$_4$CHO | 4 [2] | >99 [98] | 93 [85] |
| 5 | 2-FC$_6$H$_4$CHO | 9 | 89 | 86 |
| 6 | 4-FC$_6$H$_4$CHO | 3 [1] | 94 [98] | 94 [90] |
| 7 | 4-ClC$_6$H$_4$CHO | 1 [0.5] | 98 [92] | 94 [90] |
| 8 | 4-CF$_3$C$_6$H$_4$CHO | 0.5 [0.1] | >99 [98] | 94 [90] |
| 9 | 1-naphthylCHO | 6 | 82 | 80 |
| 10 | 2-naphthylCHO | 4 [1.5] | 95 [92] | 95 [93] |
| 11 | 3,4-(OCH$_2$O)C$_6$H$_3$CHO | 4 [1] | 95 [93] | 95 [89] |
| 12 | PhC≡CCHO | 1 | 86 | 86 |
| 13 | *trans*-PhCH═CHCHO | 24 | 82 | 75 |
| 14 | *trans*-MeCH═CMeCHO | 24 | 63 | 81 |
| 15 | PhCH$_2$CH$_2$CHO | 6 [4] | 73 [50] | 82 [86] |
| 16 | *n*-C$_5$H$_{11}$CHO | 12 | 71 | 94 |
| 17 | *c*-C$_6$H$_{11}$CHO | 12 | 55 | 91 |
| 18 | *n*-C$_7$H$_{15}$CHO | 12 | 69 | 80 |
| 19 | *n*-C$_9$H$_{19}$CHO | 12 | 72 | 90 |
| 20 | *n*-C$_{11}$H$_{23}$CHO | 6 | 66 | 93 |
| 21 | 2-furylCHO | 3 [1.5] | 90 [93] | 84 [80] |
| 22 | 3-furylCHO | 3 | 90 | 73 |
| 23 | 3-thienylCHO | 2 [1.5] | 94 [95] | 92 [83] |
| 24 | 3-pyridylCHO | 0.5 | 30 | 81 |
| 25 | 4-pyridylCHO | 0.5 | 41 | 79 |

[a] An amount of 10 mol % of (*R*)-**7** and 3 equiv of Et$_2$Zn were used at room temperature, while 5 mol % of (*R*)-**7** and 3 equiv of Et$_2$Zn were used at 50 °C (data in brackets). [b] Isolated yield. [c] Absolute configurations of **6** were *R*. The ee values were determined by chiral GC analysis or chiral HPLC (see Supporting Information).

2-naphthaldehyde, high enantioselectivities and high yields were observed under optimized reaction conditions with 3 mol % of (*R*)-**10** and 1.5 equiv of Et$_2$Zn (entries 1−11). The general reactivities were higher with electron-withdrawing aromatic aldehydes than electron-donating ones, although high enantioselectivities were not affected by the type of substitution or its position. Heteroaromatic aldehyde, α,β-unsaturated aldehyde, and aliphatic aldehydes were also effective (entries 12−14). It should be noted that (*R*)-**9** was also useful because (*R*)-**9** showed high enantioselectivities and was easily prepared in two steps, in contrast to the more elaborate preparation of (*R*)-**10**. In some cases, however, the reactivities with (*R*)-**9** were not as high as with (*R*)-**10** (brackets in Table 3).

(18) The P═O bond in P(═O)Ph$_2$ has been known to be less basic than that of P(═O)(OR)$_2$ or P(═O)(NMe$_2$)$_2$. While the greater electronegitivity of the oxygen in P−OR over the carbon in P−Ph will decrease the basicity of the P═O in some extents, resonance donation of the OR or NMe$_2$ lone pair to P makes the P═O more basic effectively. See Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* **1974**, *96*, 3875−3891.

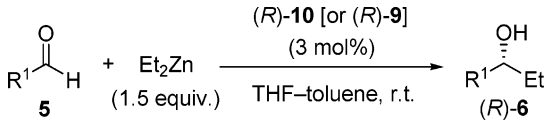
**TABLE 2. Enantioselective Diethylzinc Addition to Benzaldehyde with Conjugate Acid−Base BINOL−Zn(II) Catalysts**




| entry | ligand | temp | time (h) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | (*R*)-**7** | rt | 72 | 77 | 93 |
| 2 | (*R*)-**8** | rt | 48 | 70 | 94 |
| 3 | (*R*)-**9** | rt | 48 | 81 | 97 |
| 4 | (*R*)-**10** | rt | 24 | 98 | 97 |
| 5 | (*R*)-**7** | 50 °C | 12 | 60 | 91 |
| 6 | (*R*)-**8** | 50 °C | 12 | 65 | 94 |
| 7 | (*R*)-**9** | 50 °C | 12 | 76 | 96 |
| 8 | (*R*)-**10** | 50 °C | 4 | >99 | 95 |

[a] Isolated yield. [b] Absolute configuration of product was *R*. The ee values were determined by chiral GC analysis.

**TABLE 3. Highly Enantioselective Diethylzinc Addition to Aldehydes with (*R*)-10 [or (*R*)-9][a]**

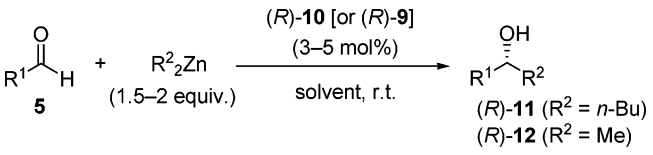



| entry | $R^1$CHO (**5**) | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | PhCHO | 24 [48] | 98 [81] | 97 [97] |
| 2 | 4-MeOC$_6$H$_4$CHO | 48 | 91 | 94 |
| 3 | 2-MeC$_6$H$_4$CHO | 24 | 90 | 96 |
| 4 | 4-MeC$_6$H$_4$CHO | 24 | 90 | 96 |
| 5 | 4-PhC$_6$H$_4$CHO | 24 | 85 | 93 |
| 6 | 2-ClC$_6$H$_4$CHO | 12[24] | 92 [92] | 94 [91] |
| 7 | 3-ClC$_6$H$_4$CHO | 8 [24] | 95 [96] | 98 [96] |
| 8 | 4-ClC$_6$H$_4$CHO | 12 [36] | 93 [98] | 95 [93] |
| 9 | 4-CF$_3$C$_6$H$_4$CHO | 1 [3] | 95 [95] | 97 [97] |
| 10 | 2-naphthylCHO | 12 [24] | 94 [87] | >99 [97] |
| 11 | 3,4-(OCH$_2$O)C$_6$H$_3$CHO | 24 [48] | 87 [86] | 95 [90] |
| 12 | PhC≡CCHO | 12 [24] | 70 [98] | 79 [90] |
| 13 | *n*-C$_5$H$_{11}$CHO | 24 | 85 | 77 |
| 14 | 3-thienylCHO | 12 [48] | 94 [86] | 95 [95] |

[a] An amount of 3 mol % of (*R*)-**9** was used instesd of (*R*)-**10** (data in brackets). [b] Isolated yield. [c] Absolute configulations of **6** were *R*. The ee values were determined by chiral GC or HPLC analyses (see Supporting Information).

**Enantioselective *n*-Bu$_2$Zn and Me$_2$Zn Addition to Aldehydes.** Other catalytic enantioselective additions of dialkylzinc to aldehydes were examined (Table 4). Despite the general difficulties in *n*-Bu- or Me-addition reactions,[19,20] (*R*)-**10** (3−5 mol %) and 1.5−2 equiv of *n*-Bu$_2$Zn or Me$_2$Zn gave smooth conversion at room temperature. High enantioselectivities were observed in aromatic aldehydes without competitive reductions into ArCH$_2$OH. Particularly, dialkylzinc addition to benzaldehyde with 5 mol % of (*R*)-**10** showed high enantioselectivities (96% ee, entries 1 and 8).[21] Instead of (*R*)-**10**, 5 mol % of (*R*)-**9** was also effective for both *n*-butylation and methylation of aldehydes to give the products with high enantioselectivities (82−95% ee), although longer reaction times were necessary (brackets in Table 4).

**TABLE 4. Highly Enantioselective Dialkylzinc Addition to Aromatic Aldehydes with (*R*)-10 [or (*R*)-9][a]**




| entry | $R^1$CHO (**5**) | $R^2$ | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | PhCHO | *n*-Bu | 24 [48] | 94 [92] | 96 [93] |
| 2 | 4-MeC$_6$H$_4$CHO | *n*-Bu | 72 | 78 | 95 |
| 3 | 3-ClC$_6$H$_4$CHO | *n*-Bu | 48 | 87 | 92 |
| 4 | 4-ClC$_6$H$_4$CHO | *n*-Bu | 24 [48] | 94 [89] | 90 [95] |
| 5 | 4-CF$_3$C$_6$H$_4$CHO | *n*-Bu | 12 [24] | 91 [98] | 97 [93] |
| 6[d] | 4-CF$_3$C$_6$H$_4$CHO | *n*-Bu | 48 | 92 | 92 |
| 7 | 3-thienylCHO | *n*-Bu | 36 | 83 | 89 |
| 8 | PhCHO | Me | 72 | 82 | 96 |
| 9 | 4-MeC$_6$H$_4$CHO | Me | 72 | 80 | 90 |
| 10 | 3-ClC$_6$H$_4$CHO | Me | 72 | 84 | 87 |
| 11 | 4-ClC$_6$H$_4$CHO | Me | 48 | 90 | 95 |
| 12 | 4-CF$_3$C$_6$H$_4$CHO | Me | 24 [48] | 88 [60] | 91 [82] |
| 13[e] | 4-CF$_3$C$_6$H$_4$CHO | Me | 48 | 84 | 86 |

[a] Unless otherwise noted, 5 mol % of (*R*)-**10** and 2 equiv of $R^2_2$Zn were used in THF/toluene for methylation and in THF/heptane for butylation. An amount of 5 mol % of (*R*)-**9** was used instead of (*R*)-**10** (data in brackets). [b] Isolated yield. [c] Absolute configulations of products were *R*. The ee values were determined by chiral GC or HPLC analyses (see Supporting Information). [d] An amount of 3 mol % of (*R*)-**10** and 1.5 equiv of *n*-Bu$_2$Zn were used. [e] An amount of 3 mol % of (*R*)-**10** and 2 equiv of Me$_2$Zn were used.

**Enantioselective Ph$_2$Zn Addition to Aldehydes.** Enantioselective phenylation to aldehydes (**5**) with 1 equiv of Ph$_2$Zn was examined in the presence of conjugate Lewis acid−Lewis base BINOL−Zn(II) catalyst and 10 mol % of Et$_2$Zn.[12b,22,23] Unexpectedly, low yield and low enantioselectivity were observed in phenylation of 4-chlorobenzaldehyde by using (*R*)-

(19) Examples of catalytic enantioselective *n*-Bu$_2$Zn or Me$_2$Zn addition to aldehydes have been limited with or without Ti(O$^i$Pr)$_4$. Pioneering works of dialkylzinc transfer can be found in the following examples: (a) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19−37. (b) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264−4268. (c) Jones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 261−272.

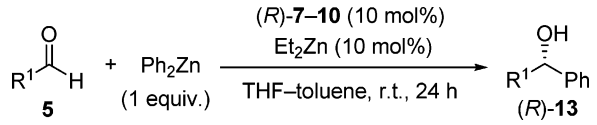
(20) Recent Me$_2$Zn addition: (a) Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608−13609. (b) Garcìa-Delgado, N.; Fontes, M.; Pericàs, M. A.; Riera, A.; Verdaguer, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2085−2090. (c) Sprout, C. M.; Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2004**, *69*, 6666−6673. (d) García-Delgado, N.; Fontes, M.; Pericàs, M. A.; Riera, A.; Verdaguer, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2085−2090. (e) Blay, G.; Fernández, I.; Hernández-Olmos, V.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1953−1958. (f) Cozzi, P. G.; Rudolph, J.; Bolm, C.; Norrby, P.-O.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 5733−5736. (g) Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 15453−15456. (h) Cozzi, P. G.; Kotrusz, P. *J. Am. Chem. Soc.* **2006**, *128*, 4940−4941.

(21) As much as 10 mol % of (*R*)-**7** and 3 equiv of Me$_2$Zn to benzaldehyde gave low conversion (29% yield) and moderate enantioselectivity (71% ee) for 120 h.

(22) Pioneering work of Ph$_2$Zn transfer: (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. (b) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488−1490. (c) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308. (d) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem., Int. Ed.* **2003**, *42*, 3002−3005.

(23) Recent progress in Ph$_2$Zn transfer: (a) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *60*, 2532−2543. (b) Castellnou, D.; Fonte, M.; Jimeno, C.; Font, D.; Solà, L.; Verdaguer, X.; Pericàs, M. A. *Tetrahedron* **2005**, *61*, 12111−12120. Also see ref 12b.

**TABLE 5. Highly Enantioselective Diphenylzinc Addition to Aromatic Aldehydes with (*R*)-7−10**




| entry | ligand | $R^1CHO$ (**5**) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1[c] | **10** | 4-$ClC_6H_4CHO$ | 65 | 49 |
| 2[c] | **9** | 4-$ClC_6H_4CHO$ | 62 | 52 |
| 3 | **8** | 4-$ClC_6H_4CHO$ | 78 | 87 |
| 4 | **7** | 4-$ClC_6H_4CHO$ | 96 | 88 |
| 5 | **7** | 4-$FC_6H_4CHO$ | >99 | 86 |
| 6 | **7** | 4-$CF_3C_6H_4CHO$ | 93 | 88 |
| 7 | **7** | 4-$MeC_6H_4CHO$ | 86 | 85 |
| 8 | **7** | 4-$PhC_6H_4CHO$ | 93 | 82 |
| 9 | **7** | 4-$MeOC_6H_4CHO$ | 77 | 73 |
| 10 | **7** | 1-naphthylCHO | 97 | 77 |
| 11 | **7** | 2-naphthylCHO | 95 | 81 |

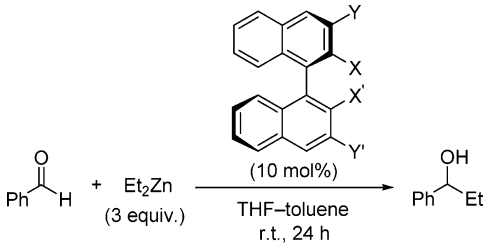
[a] Isolated yield. [b] Absolute configurations of **13** were *R*. The ee values were determined by chiral GC or HPLC analysis (see Supporting Information). [c] Reaction time was 48 h.

**10**, (*R*)-**9**, and (*R*)-**8** (Table 5, entries 1−3). However, (*R*)-**7** bearing conjugate phosphine oxide moieties showed good reactivities, and the corresponding Ph-adduct was obtained in 96% yield and 88% ee (entry 4). For other aromatic aldehydes bearing electron-donating or -withdrawing groups, (*R*)-**7** was so effective that the reactions proceeded smoothly to give the corresponding 1,1-diarylcarbinols with 73−88% ee. The unexpected reversal of catalytic activity between phenylation (**7** > **8** > **9** > **10**) and alkylations (**10** > **9** > **8** > **7**) has not been clear and further examinations are necessary, but for one reason a steric factor involving $\pi-\pi$ interactions among the catalysts and $Ph_2Zn$ cannot be denied completely.[24] Eventually, our Lewis acid−Lewis base BINOL−Zn(II) catalysts (i.e., (*R*)-**7** and (*R*)-**10**) gave complementary results in enantioselective phenylation and alkylation, respectively.

**Effects of Phosphoryl Groups in the Binaphthyl Backbone.** The presence of P═O in the BINOL structure was critical (Table 6). (*R*)-BINOL, (*R*)-BINAP, and (*R*)-BINAPO were ineffective under our reaction conditions even though they have the same $C_2$-symmetric binaphthyl structures (entries 2−4). Medium enantioselectivities and reactivities were observed with the use of **14** and **15**, which have bulky substituents at the 3,3′-positions but lack the key P═O units (entries 5 and 6). These results mean that mere bulkiness at the 3,3′-positions is insufficient to improve the enantioselectivity. Hydroxycarbonyl groups as conjugate moieties at the 3,3′-positions (**16**) were also ineffective because of weaker basicity of C═*O* than that of P═*O* (entry 7). Furthermore, *two* $C_2$-symmetric P═O moieties at the 3,3′-positions in the BINOL skeleton are necessary to achieve high catalytic activity, since **17**, which has a diphenylphosphine oxide on only one side, was ineffective for this catalysis (entry 8). A low reactivity of **18**, which has OH and P═O moieties at the 2- and 2′-positions in a binaphthyl backbone, was also attributable to the lack of a $C_2$-symmetric structure (entry 9). The low performance of **17** and **18** with respect to **7** is probably due not only to the rigidity of the chelation network, but also to the fact that the missing second $P(=O)Ph_2$ moiety in the appropriate position induces a competing chelation mode. $H_8$-**19** with a 5,5′,6,6′,7,7′,8,8′-$H_8$-BINOL backbone and **20** bearing 3,3′-$[P(=S)Ph_2]_2$ moieties in BINOL backbone could catalyze the reaction, but the yield and enantioselectivity were inferior to those with the original **7** (entries 10 and 11).

**Characteristics of Zn(II) Cluster and Dinuclaer Zn(II) Complexes through Stoichiometric Reaction.** We should address the association between the characteristics of the Zn-(II) catalysts and mechanistic aspects. The first key to studying this catalysis should be to clarify whether the P═*O* moiety coordinates to the Zn(II) center as a Lewis base. Fortunately, a single crystal was obtained for X-ray analysis from a mixture of (*R*)-**7** and $Et_2Zn$ (1 equiv each) in $CH_2Cl_2$−hexane at room temperature for 24 h under open air conditions. The ORTEP drawings are shown in Figure 4. The structure of the obtained Zn(II) cluster $\{Zn_4[(R)$-3,3'-bis(diphenyphosphinoyl)-BINOLate$]_3(\mu_4$-O)$\}\cdot(CH_2Cl_2)_3$ (**21**) was self-assembled from four Zn-(II) metals and three units of (*R*)-**7**. At the center of this cluster,

**TABLE 6. Diethylzinc Addition to Benzaldehyde Catalyzed by Chiral Binaphthyl Ligand−Zn(II) Complex[a]**




| entry | ligand | X | X′ | Y | Y′ | yield (%)[b] | ee (%)[c] | config |
|---|---|---|---|---|---|---|---|---|
| 1[d] | **7** | OH | OH | $P(=O)Ph_2$ | $P(=O)Ph_2$ | 95 | 95 | R |
| 2 | BINOL | OH | OH | H | H | 17 | 39 | R |
| 3 | BINAP | $PPh_2$ | $PPh_2$ | H | H | 21 | 0 | |
| 4 | BINAPO | $P(=O)Ph_2$ | $P(=O)Ph_2$ | H | H | 67 | 2 | R |
| 5 | **14** | OH | OH | $PPh_2$ | $PPh_2$ | 76 | 66 | R |
| 6[e] | **15** | OH | OH | Ph | Ph | 87 | 49 | R |
| 7 | **16** | OH | OH | $CO_2H$ | $CO_2H$ | 18 | 0 | |
| 8 | **17** | OH | OH | $P(=O)Ph_2$ | H | 34 | 21 | R |
| 9 | **18** | OH | $P(=O)Ph_2$ | H | H | 44 | 41 | R |
| 10[f] | $H_8$-**19** | OH | OH | $P(=O)Ph_2$ | $P(=O)Ph_2$ | 72 | 87 | R |
| 11 | **20** | OH | OH | $P(=S)Ph_2$ | $P(=S)Ph_2$ | 85 | 83 | R |

[a] Unless otherwise noted, 10 mol % of (*R*)-binaphthyl ligand and 3 equiv of $Et_2Zn$ were used for bezaldehyde in THF/toluene (1:1) at room temperature for 24 h. [b] Isolated yield. [c] The ee values were determined by chiral GC analysis. [d] Reaction time was 3 h. [e] Solvent was THF/hexane (1:1). [f] $H_8$-**19** is 5,5′,6,6′,7,7′,8,8′-$H_8$-BINOL derivative.

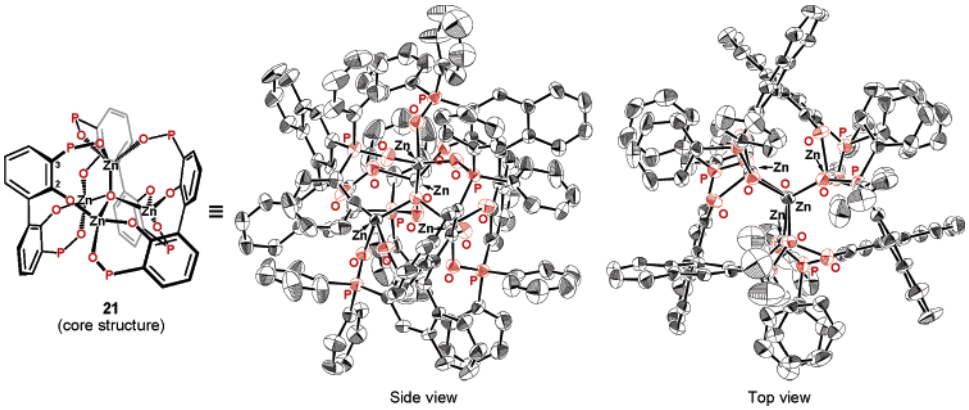



**FIGURE 4.** ORTEP drawings of self-assembled Zn(II) cluster **21** (hydrogen atoms are omitted for clarity).

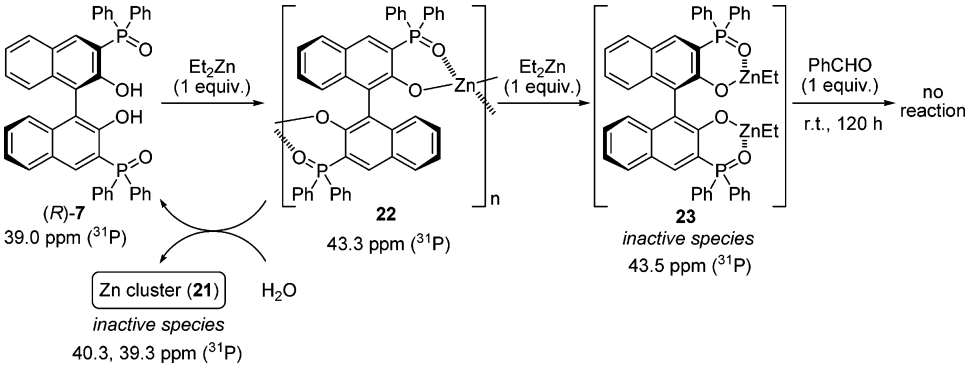



**FIGURE 5.** Postulated oligonuclear and dinuclear BINOL−Zn(II) complexes.

$\mu_4$-*O*, which might be derived from adventitious water during recrystallization, coordinates to four Zn(II) centers.[25] The Zn(II) center in the top position coordinates to $\mu_4$-*O* (1.93 Å) and three P═*O* (1.92-1.95 Å) in three different units of **7**. Each of the other three Zn(II) centers at bottom positions coordinates to $\mu_4$-*O* (1.94-1.96 Å), Naph−*O* (1.87-1.88 Å), and *O*═P−C═C−*O* (1.98-2.01 Å and 1.94-1.95 Å, respectively) through chelation. The position of P═O was not in extension of the naphthyl plane, and the torsion angles of O═P−C(3)−C(2) were 50.9−58.1°. The R*$O_2$Zn [R*$(OH)_2$ = (*R*)-**7**] chelation to the Zn(II) center did not exist in **21**.

As expected, this Zn(II) cluster (**21**) was not an active species; ethylation of benzaldehyde proceeded with 3.3 mol % of isolated crystal **21** under the typical reaction conditions at room temperature for 24 h to give (*R*)-1-phenylpropanol in 38% yield and 20% ee. In fact, in a $^{31}$P NMR study in $CDCl_3$ under anhydrous conditions, the addition of 1 equiv of $Et_2Zn$ to (*R*)-**7** led to a new complex (**22**) with a singlet peak at 43.3 ppm (major, >98%), with downfield shifts from 39.0 ppm for (*R*)-**7** (Figure 5). In this case, 2 equiv of ethane gas were trapped, and Zn(II) cluster **21** was also obtained as a minor product at 39.3 and 40.3 ppm (<2%). Complex **22** was highly moisture sensitive and decomposed to the inactive cluster **21** almost quantitatively with the partial release of (*R*)-**7** for 24 h under open air conditions. Complex **22** with one singlet peak with large downfield shifts in the NMR study suggested a symmetrical structure with two P═O units coordinating to Zn(II) centers, namely oligomeric $[-OR^*O-Zn-]_n$ ($n \geq 2$) besides Zn···O═P coordination but without R*$O_2$Zn chelation.[26] This postulated structure of **22** was also supported by X-ray analysis of **21**. Moreover, the addition of another 1 equiv of $Et_2Zn$ to **22** caused no release of gas to provide a probable $C_2$-symmetric dinuclear Zn(II) complex **23** [R*$(OZnEt)_2$] with two independent NaphO−ZnEt···O═P chelations. The optical rotation ($[\alpha]^{21.0}_D$ in toluene) of **23** (−39.5°, $c$ = 3.22) changed from that of **22** (−94.6°, $c$ = 2.61), although **23** showed one major singlet peak at 43.5 ppm with almost no changes from **22**. The addition of benzaldehyde (1 equiv) to dinuclear **23** (1 equiv), which was prepared by adding either directly two or one then 1 equiv $Et_2Zn$ to **7**, showed no reactivity, and therefore **23** was the inactive species.

**Absence of Nonlinear Effect.** The relation between the ee values of (*R*)-**7** and those of the Et-adduct of benzaldehyde, (*R*)-1-phenylpropanol, provided additional information. For benzaldehyde, 10 mol % of (*R*)-**7** (0−100% ee) and 3 equiv of $Et_2Zn$ were used in THF/toluene at room temperature for 3−5 h to give (*R*)-1-phenylpropanol in >95% yield, and a linear relationship was observed between the ee values of (*R*)-**7** and those of (*R*)-1-phenylpropanol (Figure 6 and Supporting Information).

**Characteristics of Trinuclear and Tetranuclear Zn(II) Complexes through Stoichiometric Reactions.** This linear

(24) Uncatalyzed background reaction of diphenylzinc should occur. See refs 22 and 23. For another reason, particularly in **10**, the steric hiderance around the catalyst might interrupt the central coordination such as R*$O_2$-$ZnPh_2$ [R*$(OH)_2$ = **10**]. As discussed later in this paper, that central coordination should be critical for a transition-state assembly in *diethylzinc* addition (i.e., **37**).

(25) Tetranuclaer Zn(II) cluster with a central $\mu$-$O_4$ structure: Murugavel, R.; Sathiyendiran, M.; Walawalker, M. G. *Inorg. Chem.* **2001**, *40*, 427−434.

(26) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940−7956.

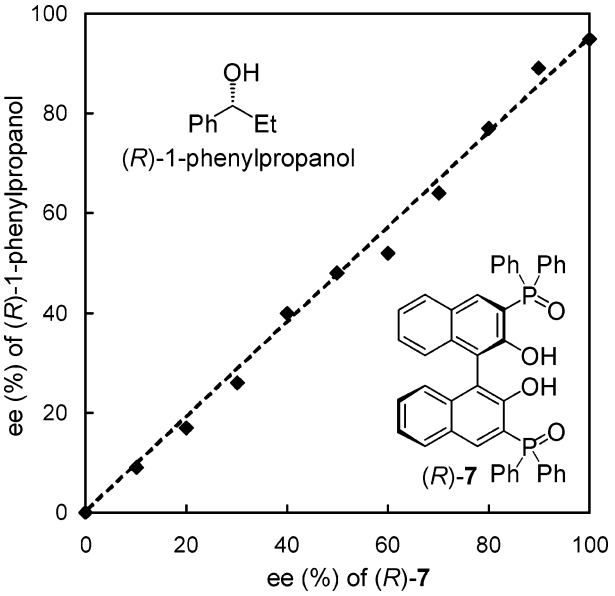



**FIGURE 6.** An absence of nonlinear effect between the ee values of (*R*)-**7** and those of Et-adduct.

relationship suggests that, for one possibility, monomeric species such as **24**−**27** by way of **23** may be involved in the enantioselective addition of $Et_2Zn$ (Figure 7).[27] Unexpectedly, however, these assumed trinuclear complexes (**24**−**27**), which were directly prepared from **7** (1 equiv instead of 10%) and $Et_2Zn$ (3 equiv), showed low reactivity; the stoichiometric reaction to benzaldehyde (1 equiv) gave the product in 13% yield and 87% ee after 72 h at room temperature (Chart 1, eq 1). But the stoichiometric reaction with benzaldehyde (1 equiv) and the complex prepared from **7** (1 equiv) and $Et_2Zn$ (3.5 equiv) resulted in 57% yield and 91% ee (Chart 1, eq 2). From these

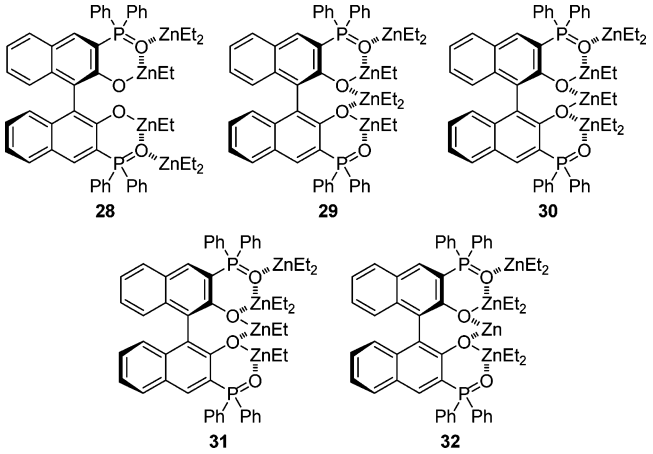



**FIGURE 8.** Possible tetranuclear monomeric complexes.

results, trinuclear complexes (**24**−**27**) would not be the active species, and the equilibrium between the trinuclear complex and another complex such as tetranuclear **28**−**32** should be considered (Figure 8). In fact, the stoichiometric reaction with benzaldehyde (1 equiv) and the expected tetranuclear **28**−**32** (1 equiv), which was prepared from **7** (1 equiv) and $Et_2Zn$ (4 equiv), could proceed and (*R*)-1-phenylpropanol was obtained in 94% yield and 91% ee (Chart 1, eq 3). Interestingly, the reactivity under the stoichiometric conditions in eq 3 was lower than that under the catalytic conditions (Table 1, entry 1). We thus ultimately can assume that the active species in the presence of excess $Et_2Zn$ under normal catalytic reaction conditions may be derived from the tetranuclear complexes (i.e., **28**−**32**) or likely the $C_2$-symmetric pentanuclear complex (**33**) (Figure 9). In two postulated catalytic cycles, (1) less active precursor **23** would be regenerated via **28**−**32** and (2) likely precursors **28**−

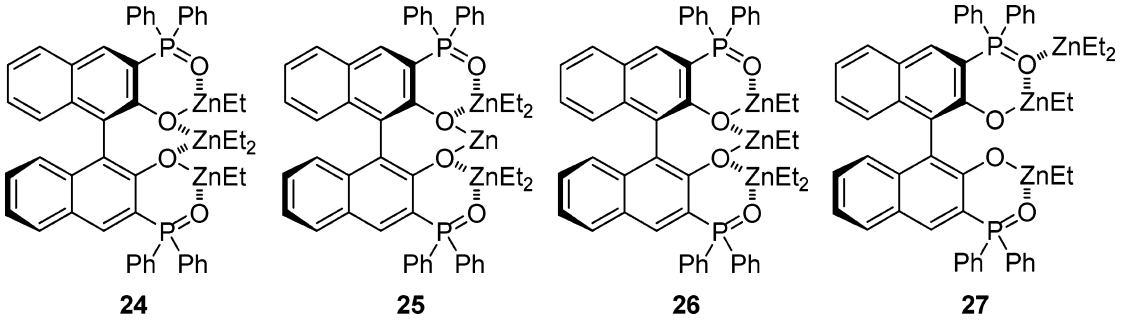



**FIGURE 7.** Possible trinuclear monomeric complexes.

**CHART 1**

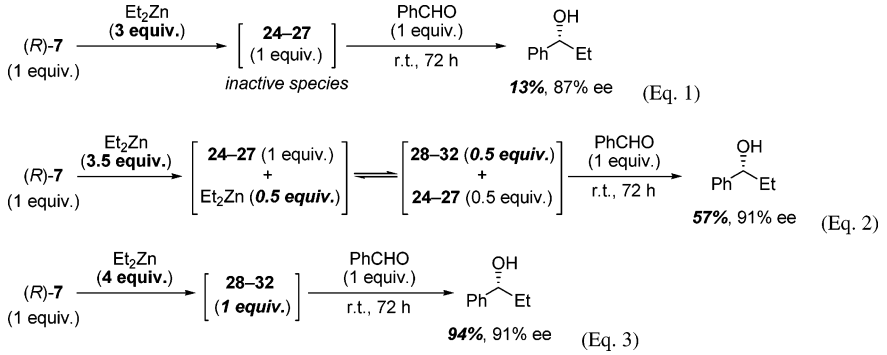
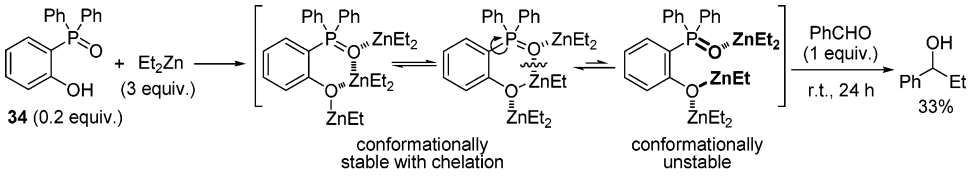
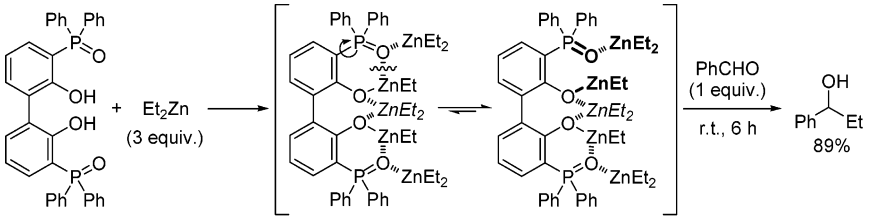


**CHART 2**




(Eq. 4)




(Eq. 5)

**32** would be regenerated through **33**, after carbon−carbon bond formation with $R^1CHO$ (**5**).

**Effect of Phenol and Biphenol Structures.** We next examined the effect of phenol and biphenol onto the catalytic activity. Thus, catalytic diethylzinc addition to benzaldehyde was explored with achiral ligands, such as **34** and **35** (Chart 2, eqs 4 and 5). The catalytic activity of **34** (20 mol %) bearing a phenol backbone was low, and 33% of Et-adduct was given for 24 h (Chart 2, eq 4). Probably, low reactivity of **34** could be rationalized by a six-membered Zn(II)-chelation as a stabilized structure. In high contrast, 10 mol % of **35** with a biphenol backbone could catalyze the reaction smoothly, and Et-adduct was obtained in 89% for 6 h (Chart 2, eq 5). Therefore, biphenol moiety might be an essential structure to enhance the reactivity.[28] These results indicated that a new seven-membered chelation of $Et_2Zn$ with $R(OZnEt)_2$ [$R(OH)_2$ = biphenol] could trigger the dissociation of the original six-membered Zn(II)-chelation to relieve a steric hindrance before the transition states (Chart 2, eq 5).

**Conformation of P═O and NaphO−Zn(II) Moieties and Crystal Structures of 7.** The direction of the P═O bond in ligand **4** depends on the (bi)naphthyl plane (Figures 10, 11a, and 11b): either (a) a "flat" conformation which has a $\pi$-orbital network and a six-membered ring by metal-chelation or (b) a "nonflat" conformation with hyperconjugation through $\pi$(2-naphthol)−$\sigma$*(P−O) is possible.[29] Therefore, a BINOL moiety is suitable for controlling the direction of conjugate P═O (Lewis base), which can be away from the metal ion (Lewis acid) (Figure 11b). Our design of **4**−Zn(II) can be unique to a phosphoryl moiety and distinctive from **36** with C(═O)$NR_2$, for example (Figure 10).[30] For **36**, which was described by

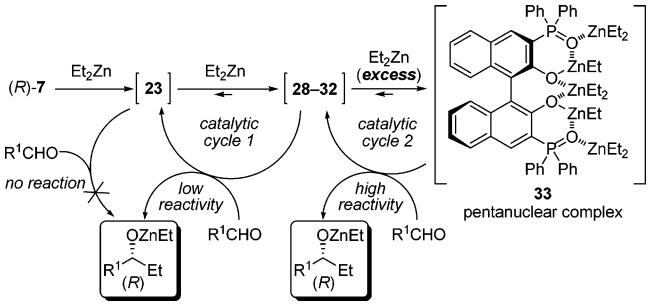



**FIGURE 9.** Proposed catalytic cycle involving monomeric active species.

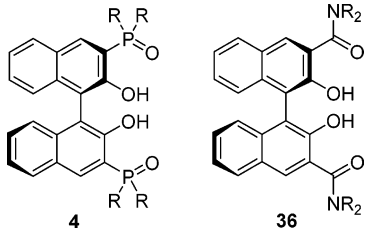



**FIGURE 10.** 3,3′-Disubstituted BINOL ligands.

Katsuki and co-workers, a catalysis by a nonflat conformation as Figure 11d is probably disfavored because the $\sigma$* orbital of C−O is smaller than that of P−O. Therefore, the conjugation in **36**−Zn(II) would be stabilized by metal-chelation in the most-expected conformation like Figure 11c, and eventually the catalytic activity would be weakened by the neighboring acid−base.

To assist the proposed conformations such as shown in Figure 11b, an X-ray analysis of (*R*)-**7** is shown in Figure 12. Hydrogen bonding, which was observed in NaphO−*H*···O═P (1.86 and 1.93 Å) to form a six-membered ring, supports the notion that the chelation to Zn(II) (instead of H) is in this manner, unlike as with $R^*O_2Zn$ [$R^*(OH)_2$ = **7**]. This hydrogen bonding in (*R*)-**7** was responsible for the observed large downfield shift, such as 10.57 ppm in $^1H$ NMR in $CDCl_3$. Interestingly, the positions of P═O were not in extension of the naphthyl plane, probably because of the $\pi$(2-naphthol)−$\sigma$*(P−O) interaction (see also Figure 11a and b.);[13,14] torsion angles were 45.4° for C(2)−C(3)−P(1)−O(2) and 45.0° for C(12)−C(13)−P(2)−O(4). Fortunately, another conformation could be observed by X-ray

(27) Major population of $C_2$-symmetric trinuclear complexes such as **24** and **25** were estimated because the further addition of $Et_2Zn$ to **23** gave a major singlet peak at 38.0 ppm in $^{31}P$ NMR.

(28) Certainly **34** and **35** are sterically very different. However, these results could reflect our assumption described, because a preliminary examination by using the model compound, a *t*-Bu group ortho to the OH in **34**, also resulted in poor reactivities (20 mol %, room temperature, 24 h, 48% yield).

(29) For the nonflat model like Figure 11b, considerable interaction between vacant d-orbital of phosphorous and $\pi$-orbital of 2-naphthol is also possible. See refs 13 and 14.

(30) (a) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343−344. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 207−217. (c) Ito, K.; Tomita, Y.; Katsuki, T. *Tetrahedron Lett.* **2005**, *46*, 6083−6086.

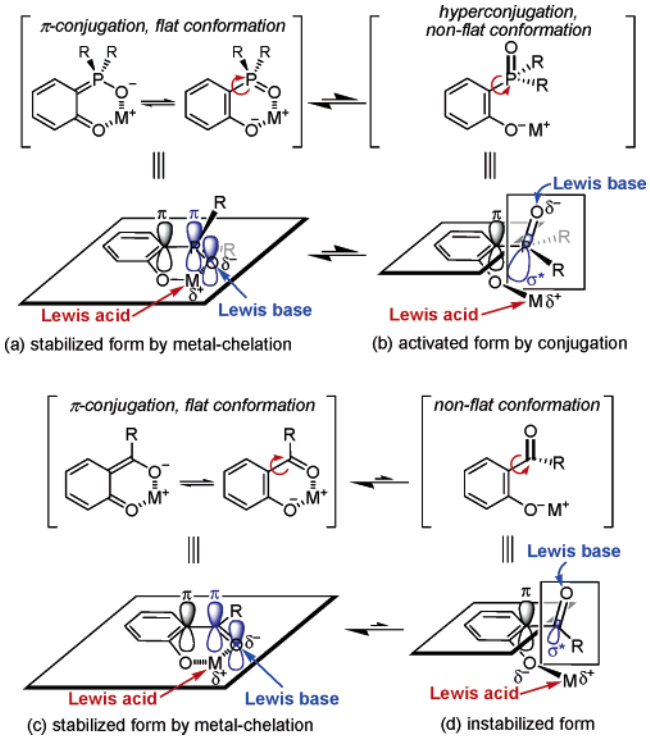



**FIGURE 11.** Conjugate acid−base catalyst bearing P═O or C═O in a BINOL backbone.

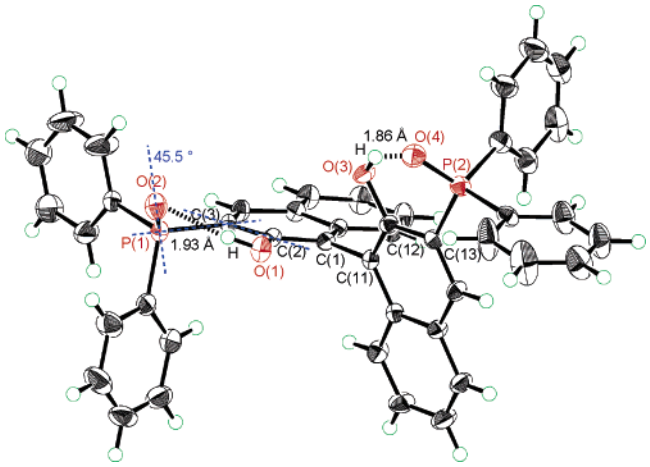



**FIGURE 12.** ORTEP drawing of (*R*)-**7** with hydrogen bondings.

analysis of (*S*)-**7** (Figure 13). In that crystal structure, hydrogen bonding was *not* observed in NaphO−*H*···O═P. Torsion angles were 67.9° for C(2)−C(3)−P(1)−O(2) and 66.6° for C(12)−C(13)−P(2)−O(4), which were larger than those of (*R*)-**7** involving hydrogen bondings. These structures of (*R*)-**7** with hydrogen bondings and (*S*)-**7** without hydrogen bondings may support the existence of $\pi$(2-naphthol)−$\sigma$*(P−O) interaction.

**Proposed Transition-State Assembly with Conjugate Acid−Base BINOL−Zn(II) Catalysts.** Finally, we turned our attention to the mechanistic aspect of the transition-state assembly which should be regarded as a working model. On the basis of X-ray analyses of **7** and **21**, NMR experiments, and the absence of a nonlinear relationship between the ee of (*R*)-**7** and the ee of (*R*)-1-phenylpropanol, the active Zn(II) complex in our catalysis is likely to be a tetra- or pentanuclear monomeric species. Taking advantage of the ligand effect (**10** > **9** > **8** >

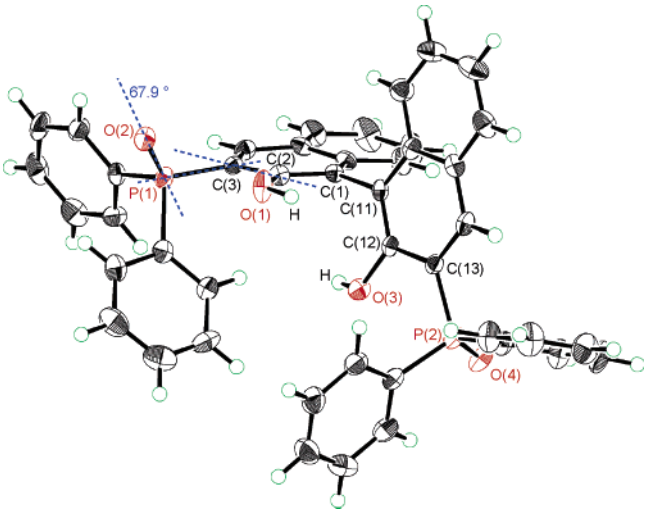



**FIGURE 13.** ORTEP drawing of (*S*)-**7** without hydrogen bondings.

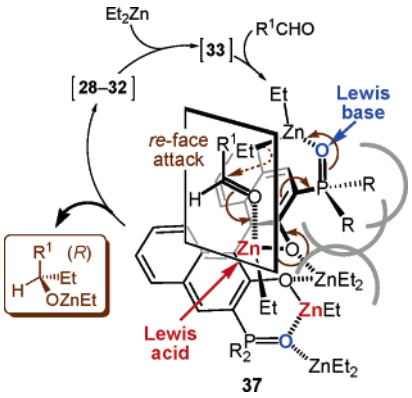


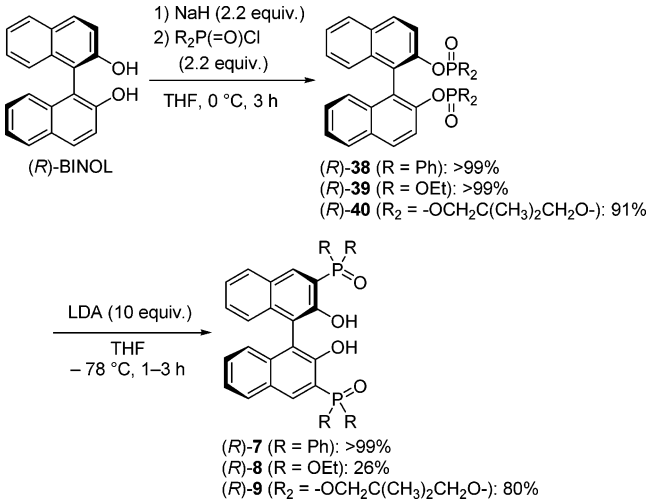

**FIGURE 14.** Proposed transition-state assembly including conjugate acid−base activation and catalytic cycle.

**7**) on reactivity in alkylations based on the strength of Lewis basicity of P═*O*, a new plausible mechanism including tetranuclear **28**−**32**, pentanuclear **33**, and **37** is shown in Figure 14.[17a] Compound **37** may provide the conformation as shown in Figure 11b with $\pi$(2-naphthol) orbital interactions to $\sigma$*(P−O) through hyperconjugation. Compound **37** has two conjugate Lewis acidic NaphO−Zn(II)−Et centers to activate aldehyde and Lewis basic phosphoryl groups to activate $Et_2Zn$. From the results of the catalysis by phenol and biphenol (eqs 4 and 5), tetranuclear complexes **28**−**32** might change to $C_2$-symmetric **33** with a central chelation of R*$O_2$ZnEt [R*$(OH)_2$ = **4**] and then a dissociation of P═O···Zn in **33** would lead to **37**. Because of the steric hindrance between the aldehyde and two substituents (R) to the phosphoryl moiety at the 3-position in the binaphthyl backbone, reface attack should be favored exclusively in **37**. Eventually, (*R*)-products can be obtained with smooth release from the catalyst along with the regeneration of **28**−**32**.

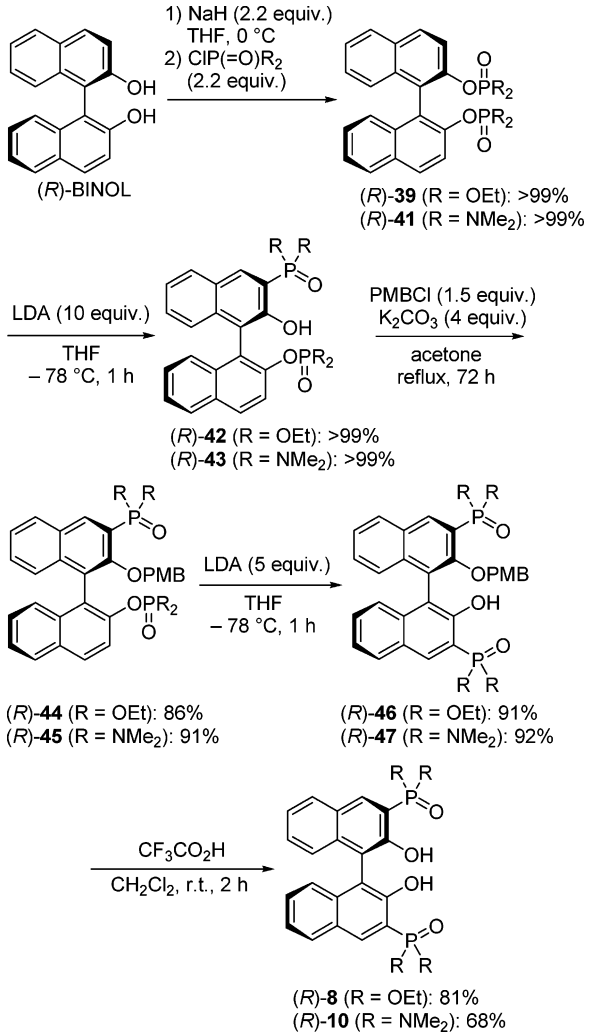
**Preparation of (*R*)-3,3′-Diphosphoryl-BINOLs.** (*R*)-3,3′-Bis(diphenyphosphinoyl)-BINOL (**7**) was prepared almost quantitatively from commercially available (*R*)-BINOL in two steps via phospho-Fries rearrangement (Scheme 1).[31] Our method has an advantage with regard to yield and purification in comparison

(31) Synthesis of **7** via asymmetric oxidative biaryl coupling. Li, X.; Hewgley, J.; Mulrooney, C. A.; Yang, J.; Konzlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500−5511.

**SCHEME 1. Preparation of (*R*)-3,3′-Disubstituted BINOLs Bearing P═O Groups**




**SCHEME 2. Preparation of 3,3′-Disubstituted BINOLs Bearing Phosphoramides Groups**




with a coupling method that uses halide compounds, expensive diphenylphosphine oxide [$Ph_2P(=O)H$], and palladium or nickel catalysts. First, (*R*)-BINOL in THF was treated with NaH. Subsequent dropwise addition of diphenylphosphinic chloride gave the corresponding phosphinates (*R*)-**38** quantitatively without further purification.[32] The rearrangement of (*R*)-**38** proceeded with LDA in THF at − 78 °C for 1 h to give (*R*)-**7** quantitatively as colorless crystals after recrystallization from toluene/hexane (ca. 1/5).[33] Phosphonates [$P(=O)(OR)_2$] ligands (*R*)-**8** and (*R*)-**9** which had substituents that were more electron-donating than phenyl groups in (*R*)-**7** were also prepared in a similar manner via phospho-Fries rearrangement of **39** and **40**.

Unfortunately, promising (*R*)-**10** could not be prepared by the usual simple procedures described above because the key phospho-Fries rearrangement could not proceed on both sides. However, protection of 2-naphthol in (*R*)-**43** with a *p*-methoxybenzyl (PMB) group after the first phospho-Fries rearrangement enabled the second rearrangement to (*R*)-**47**, and (*R*)-**10** was obtained after deprotection of the PMB group (Scheme 2). Other protective groups such as Bn, Piv, and Ac did not work well. This synthetic method was also effective for preparing (*R*)-**8**, which was obtained in low yield by simple phospho-Fries rearrangement, as shown in Scheme 1. The total yields of (*R*)-**8** in Scheme 2 were improved from 26% in Scheme 1 to 59%.

## Conclusion

We have developed a highly efficient enantioselective dialkylzinc ($R^2{}_2Zn$) addition to aldehydes (**5**) by using a conjugate Lewis acid−Lewis base BINOL−Zn(II) catalyst bearing phosphine oxides [$P(=O)R_2$], phosphonates [$P(=O)(OR)_2$], or phosphoramides [$P(=O)(NR_2)_2$] at the 3,3′-positions, namely **7**−**10**. A series of 3,3-diphosphoryl-BINOL derivatives were synthesized by phospho-Fries rearrangement as a key reaction. The coordination of an $R^2Zn$(II) moiety as a Lewis acid to a carbonyl group in a substrate and the activation of $R^2{}_2Zn$ with a phosphoryl (P═O) group as a Lewis base in our BINOL−Zn(II) catalyst could promote carbon−carbon bond formation. The reactions proceeded with high enantioselectivities (up to >99% ee), and showed good reductions in the amounts of both catalysts and dialkylzinc that had to be loaded, unlike other previous catalysts that have been examined for dialkylzinc addition to aldehydes. Detailed mechanistic studies by X-ray analysis of **7** and **21**, a $^{31}P$ NMR experiment of Zn(II) complexes, an absence of nonlinear effect between ee values of the chiral ligand (**7**) and the Et-adduct product (**6**), and stoichiometric and catalytic reactions with various complexes could suggest the transition-state assembly (**37**) including a pentanuclear monomeric intermediate (**33**). Further studies for other enantioselective catalyses are underway by using the conjugate Lewis acid−Lewis base complexes to develop more efficient reactions.

## Experimental Section

**Typical Procedure for the Enantioselective Dialkylzinc Addition to Aldehydes.** A solution of (*R*)-**10** (16.6 mg, 0.03 mmol) in THF (3 mL) was stirred in a well-dried Pyrex Schlenk tube at room temperature for 5 min under nitrogen atmosphere. To the solution was added dialkylzinc (1.5 mmol) at −78 °C. This solution was stirred for 30 min, and aldehyde (**5**) (1.0 mmol) was added. The resulting mixture was then gradually warmed to room temperature (or 50 °C), and stirred for 1−72 h. After hydrolysis with 10 mL of saturated $NH_4Cl$ aqueous solution, the product was

(32) Au-Yeung, T.-L.; Chan, K.-Y.; Haynes, R. K.; Williams, I. D.; Yeung, L. L. *Tetrahedron Lett.* **2001**, *42*, 453−456.

(33) (a) Au-Yeung, T.-L.; Chan, K.-Y.; Haynes, R. K.; Williams, I. D.; Yeung, L. L. *Tetrahedron Lett.* **2001**, *42*, 457−460. (b) Taylor, C. M.; Watson, A. J. *Curr. Org. Chem.* **2004**, *8*, 623−636.

extracted with ether (10 mL × 3) and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the crude product was purified by neutral silica gel column chromatography (eluent: hexane/EtOAc or pentane/ether) to give the desired products. The enantiomeric purity was determined by GC or HPLC on a chiral column.

**1-Phenylpropanol** (Table 1, entry 1; Table 2, entries 1−8; Table 3, entry 1). A solution of (*R*)-**10** (16.6 mg, 0.03 mmol) in THF (3 mL) was stirred in a well-dried Pyrex Schlenk tube at room temperature for 5 min under nitrogen atmosphere. To the solution was added $Et_2Zn$ (1.35 mL of 1.10 M solution in toluene, 1.5 mmol) at −78 °C. This solution was stirred for 30 min, and benzaldehyde (106.1 mg, 1.0 mmol) was added. The resulting mixture was then gradually warmed to room temperature and stirred for 24 h. After hydrolysis with 10 mL of saturated $NH_4Cl$ aqueous solution, the product was extracted with ether (10 mL × 3) and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the crude product was purified by neutral silica gel column chromatography (eluent: hexane/EtOAc = 10/1) to give the desired product (133.4 mg, 98%). The enantiomeric purity was determined by GC on chiral column (97% ee). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 7.5 Hz, 3H), 1.69−1.77 (m, 2H), 2.24 (br, 1H), 4.56 (t, $J$ = 6.9 Hz, 1H), 7.25−7.38 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 10.2 ($CH_3$), 31.9 ($CH_2$), 75.9 (CH), 126.0 (CH), 127.5 (CH), 128.4 (CH), 144.7 (C). IR (film): 3360, 2963, 1492, 1454, 1377, 1200, 1097, 1013, 974 cm$^{-1}$. HRMS(FAB): calcd for $C_9H_{13}O$ $[M + H]^+$, 137.0966; found, 137.0964. Chiral GC: CP-cyclodextrin-$\beta$-2,3,6-M-19 [115 °C, $t_R(R)$ = 13.3 min, $t_R(S)$ = 13.7 min].

**1-Phenylpentanol** (Table 4, entry 1). A solution of (*R*)-**10** (27.7 mg, 0.05 mmol) in THF (3 mL) was stirred in a well-dried Pyrex Schlenk tube at room temperature for 5 min under nitrogen atmosphere. To the solution was added *n*-$Bu_2Zn$ (2.00 mL of 1.00 M solution in heptane, 2.0 mmol) at −78 °C. This solution was stirred for 30 min, and benzaldehyde (106.1 mg, 1.0 mmol) was added. The resulting mixture was then gradually warmed to room temperature and stirred for 24 h. After hydrolysis with 10 mL of saturated $NH_4Cl$ aqueous solution, the product was extracted with ether (10 mL × 3) and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the crude product was purified by neutral silica gel column chromatography (eluent: hexane/EtOAc = 10/1), to give the desired product (154.3 mg, 94%). The enantiomeric purity was determined by HPLC on chiral column (96% ee). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 7.5 Hz, 3H), 1.22−1.46 (m, 4H), 1.65−1.87 (m, 2H), 2.06 (br, 1H), 4.65 (t, $J$ = 6.9 Hz, 1H), 7.24−7.38 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0 ($CH_3$), 22.7 ($CH_2$), 28.0 ($CH_2$), 38.9 ($CH_2$), 74.8 (CH), 126.0 (CH), 127.5 (CH), 128.5 (CH), 145.0 (CH). IR (film): 3360, 2956, 1492, 1455, 1377, 1107, 1041, 1108, 1071, 1044, 1011, 911 cm$^{-1}$. HRMS(FAB): calcd for $C_{11}H_{17}O$ $[M + H]^+$, 165.1279; found, 165.1274. Chiral HPLC (OB−H; hexane/IPA = 80/1, 1 mL/min) [$t_R(R)$ = 18.4 min, $t_R(S)$ = 13.9 min].

**1-Phenylethanol** (Table 4, entry 8). A solution of (*R*)-**10** (27.7 mg, 0.05 mmol) in THF (3 mL) was stirred in a well-dried Pyrex Schlenk tube at room temperature for 5 min under nitrogen atmosphere. To the solution was added $Me_2Zn$ (1.00 mL of 2.00 M solution in toluene, 2.0 mmol) at −78 °C. This solution was stirred for 30 min, and benzaldehyde (106.1 mg, 1.0 mmol) was added. The resulting mixture was then gradually warmed to room temperature and stirred for 72 h. After hydrolysis with 10 mL of saturated $NH_4Cl$ aqueous solution, the product was extracted with ether (10 mL × 3) and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the crude product was purified by neutral silica gel column chromatography (eluent: hexane/EtOAc = 10/1) to give the desired product (100.1 mg, 82%). The enantiomeric purity was determined by GC on chiral column (96% ee). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.46 (d, $J$ = 6.6 Hz, 3H), 2.03 (br, 1H), 4.86 (q, $J$ = 6.6 Hz, 1H), 7.22−7.36 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 25.3 ($CH_3$), 70.6 (CH), 125.4 (CH), 127.5 (CH), 128.5 (CH), 145.9 (C). IR (film): 3358, 2973, 1698, 1558, 1507, 1451, 1369, 1283, 1203, 1077, 1011, 899 cm$^{-1}$. HRMS-(FAB): calcd for $C_8H_{11}O$ $[M + H]^+$, 123.0810; found; 123.0809. Chiral GC: CP-cyclodextrin-$\beta$-2,3,6-M-19 [110 °C, $t_R(R)$ = 10.0 min, $t_R(S)$ = 10.6 min].

**Typical Procedure for the Enantioselective Diphenylzinc Addition to Aldehydes.** A well-dried Pyrex Schlenk tube was charged with diphenylzinc (43.9 mg, 0.20 mmol) at the room temperature under nitrogen atmosphere. THF (2 mL) was added followed by $Et_2Zn$ (18.2 $\mu$L of 1.10 M solution in toluene, 0.02 mmol). The mixture was stirred for 30 min, and then (*R*)-**7** (13.7 mg, 0.02 mmol) was added. This solution was stirred for 30 min, and then aldehyde (**5**) (0.20 mmol) was added. The resulting mixture was stirred at room temperature for 24 h. After hydrolysis with 10 mL of saturated $NH_4Cl$ aqueous solution, the product was extracted with ether (10 mL × 3) and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the crude product was purified by neutral silica gel column chromatography (eluent: hexane/EtOAc) to give the desired products. The enantiomeric purity was determined by GC or HPLC on chiral column.

**(4-Chlorophenyl)(phenyl)methanol** (Table 5, entries 1−4). A well-dried Pyrex Schlenk tube was charged with diphenylzinc (43.9 mg, 0.20 mmol) at the room temperature under nitrogen atmosphere. THF (2 mL) was added followed by $Et_2Zn$ (18.2 $\mu$L of 1.10 M solution in toluene, 0.02 mmol). The mixture was stirred for 30 min, and then (*R*)-**7** (13.7 mg, 0.02 mmol) was added. This solution was stirred for 30 min, and then 4-chlorobenzaldehyde (28.1 mg, 0.20 mmol) was added. The resulting mixture was stirred at room temperature for 24 h. After hydrolysis with 10 mL of saturated $NH_4Cl$ aqueous solution, the product was extracted with ether (10 mL × 3) and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the crude product was purified by neutral silica gel column chromatography (eluent: hexane/EtOAc = 10/1), to give the desired product (41.9 mg, 96%). The enantiomeric purity was determined by HPLC on chiral column (88% ee). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.69 (br, 1H), 5.78 (s, 1H), 7.18−7.40 (m, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 75.6 (CH), 125.4 (CH), 126.6 (CH), 127.9 (CH), 128.6 (CH), 128.7 (CH), 133.3 (C), 142.3 (C), 143.5 (C). IR (KBr): 3358, 3026, 1485, 1453, 1402, 1346, 1189, 1082, 1071, 918 cm$^{-1}$. HRMS(FAB): calcd for $C_{13}H_{12}$-ClO $[M + H]^+$, 219.0577; found, 219.0579. Chiral HPLC (OB−H; hexane/IPA = 9/1, 0.5 mL/min) [$t_R(R)$ = 31.5 min, $t_R(S)$ = 49.5 min].

**Acknowledgment.** Financial support for this project was provided by the JSPS. KAKENHI (Grant 15205021) and the 21st Century COE Program "Nature-Guided Materials Processing" of MEXT.

**Supporting Information Available:** General information, characterization data, and copies of $^1$H and $^{13}$C NMR spectra for ligands and products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060908T