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Highly Active Chiral Phosphoramide–Zn(II) Complexes as Conjugate Acid–Base Catalysts for Enantioselective Organozinc Addition to Ketones

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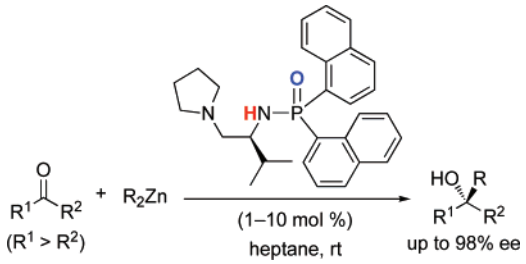
ABSTRACT



A highly efficient enantioselective organozinc (R_2Zn) addition to ketones catalyzed by chiral phosphoramide–Zn(II) complexes (1–10 mol %) has been developed. These complexes serve as conjugate Lewis acid–Lewis base catalysts. Chiral phosphoramides are derived from an inexpensive natural amino acid (i.e., L-valine). From a variety of nonactivated aromatic and aliphatic ketones, the corresponding optically active tertiary alcohols were obtained in high yields with high enantioselectivities (up to 98% ee) under the mild reaction conditions.

Optically active secondary and tertiary alcohols are versatile building blocks for the synthesis of natural products and pharmaceuticals.[1] In particular, the enantioselective addition of organometal reagents to carbonyl compounds is an important synthetic method that gives the enantioenriched alcohols via carbon−carbon bond formation under the mild conditions.[2,3] However, there are few examples of catalytic enantioselective organozinc addition to ketones, in sharp contrast to aldehydes, due to steric and electronic constraints regarding the substrates and/or reagents, and hence it is still a challenge to establish a high level of asymmetric induction as well as a high yield.[4−6] We report here highly active and simple chiral phosphoramide−Zn(II) complexes as conjugate Lewis acid−Lewis base catalysts[7] for the enantioselective organozinc addition to ketones to obtain the desired tertiary

(1) (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (c) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149−183.

(2) (a) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841−842. (b) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823−2824. (c) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (d) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117−6128.

(3) For reviews: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886. (d) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127−157.

(4) (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446. (b) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239−1242. (c) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971. (d) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641−3644. (e) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544−9545. (f) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538−6539. (g) Li, H.; Garica, C.; Walsh, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5425−5427.

(5) For reviews: (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284−287. (b) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749−760.

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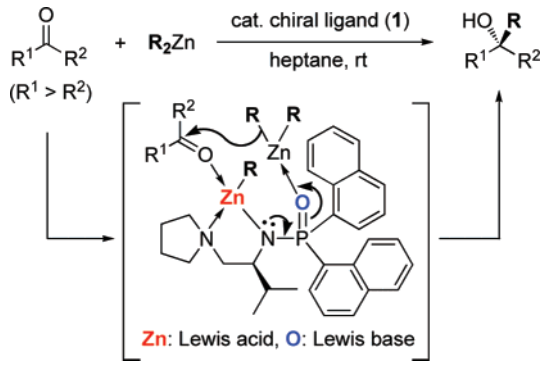
Scheme 1. Chiral Phosphoramide **1**-Zn(II) Complex as a Conjugate Lewis Acid−Lewis Base Catalyst



alcohols in high to excellent yields (Scheme 1). These chiral Zn(II) catalysts, which are simply prepared in situ, are derived from an inexpensive natural amino acid (i.e., L-valine).

In our preliminary study of catalytic enantioselective organozinc addition to aldehydes, chiral Zn(II)−BINOLates bearing phosphoramides at the 3,3′-positions were designed as highly effective conjugate Lewis acid−Lewis base catalysts.[8−10] However, these Zn(II)−BINOLates did not catalyze the reaction of ketones and organozinc reagents, and a significant amount of the aldol products was obtained instead of the desired products. To develop conjugate Lewis acid−Lewis base catalysts with ketones, we first investigated the L-valine-derived chiral phosphoramide ligand (**1**, 10 mol %) in the catalytic enantioselective phenylation of 4′-chloroacetophenone (**2a**) with Ph_2Zn (1 equiv) and Et_2Zn (2 equiv) in heptane at room temperature (Figure 1).[11] Fortunately, simply designed **1a** gave **3a** with high enantioselectivity (80% ee), although the yield was low (30%). Chiral ligand **1b** or **1c** bearing a pyrrolidinyl or piperidinyl group instead of a NMe_2 group in **1a** showed improved catalytic activity, but the enantioselectivitiy was the same or decreased. However, **1d** bearing a *P*-(1-naphthyl) moiety showed a considerable improvement in both yield and enantioselectivity (up to 95% ee). After optimization, **3a** was obtained in 98% yield with 92% ee by using 1 mol % of **1d**.

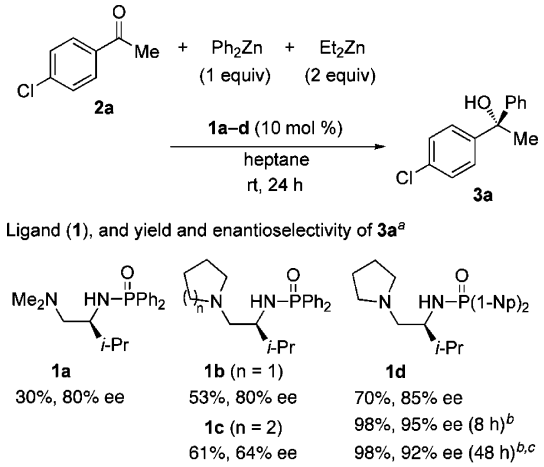


Figure 1. Catalytic enantioselective phenylation to **2a**. Conditions: (a) Reactions were examined in 0.25 M heptane unless otherwise noted. (b) Reactions were examined in 0.5 M heptane. (c) 1 mol % of **1d** was used.

We next examined the generality of this catalysis for other ketones (Figure 2). For aryl ketones with either an electron-withdrawing or electron-donating group (**2a**−**c** and **2g**), cyclic ketones (**2d**−**f**), heteroaryl ketones (**2h** and **2i**), and α,β-unsaturated ketone (**2j**) with 10 mol % of (*S*)-**1d**, high enantioselectivities (91−98% ee) and high yields (up to 98%) were observed in products **3a**−**j**. Moreover, aliphatic ketones (**2k** and **2*l***) also provided the corresponding tertiary alcohols (**3k** and **3*l***) with 80−82% ee in high yields. In particular, a 1-g-scale (5 mmol) preparation of (*R*)-**3a** was established in 91% yield with 93% ee by using 3 mol % of (*R*)-**1d** in heptane at room temperature for 24 h, which is the key intermediate in the synthesis of the antihistamine drug clemastine (**4**) (Scheme 2).[12]

Encouraged by the efficient phenylation to ketones, we next examined ethylation with Et_2Zn (Figure 3). As expected, the reaction of aryl and heteroaryl ketones with 3 equiv of Et_2Zn proceeded smoothly at room temperature for 16−24

(6) (a) Hui, A.; Zhang, J.; Fan, J.; Wang, Z. *Tetrahedron*: *Asymmetry* **2006**, *17*, 2101−2107. (b) Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448−455. (c) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416−16425. (d) Forrat, V. J.; Pieto, O.; Ramón, D. J.; Yus, M. *Chem. Eur. J.* **2006**, *12*, 4431−4445.

(7) Shibasaki's pioneering work of bifunctional nonconjugate acid−base chemistry. See reviews: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187−2209. (b) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989−1999. (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491−1508. (d) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Pure Appl. Chem.* **2005**, *77*, 2047−2052. (e) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269−279. In particular, with P═O moieties: (f) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641−2642. (g) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652. (h) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328. (i) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. (j) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784−10785.

(8) (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. (c) Hatano, M.; Miyamoto, T.; Ishihara, K. *J. Org. Chem.* **2006**, *71*, 6474−6484. For our account, see: (d) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686−703.

(9) Precedent chiral phosphoramide ligands in Et_2Zn addition to aldehydes: (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) Brunel, J.-M.; Constantieux, T.; Legrand, O.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 2961−2964. (d) Shi, M.; Sui, W.-S. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3319−3325.

(10) Chiral phosphine oxides in asymmetric catalysis, for reviews see: (a) Brunel, J. M.; Buono, G. *Top. Curr. Chem.* **2002**, 79−105. (b) Molt, O.; Schrader, T. *Synthesis* **2002**, 2633−2670.

(11) Pionnering work of phenylation to aldehydes with Ph_2Zn/Et_2Zn systems: Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. Also see: (a) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm. C. *Chem. Soc. Rev.* **2006**, *35*, 454−470.

(12) (a) Ebnöther, A.; Weber, H.-P. *Helv. Chim. Acta* **1976**, *59*, 2462−2468. (b) Nikiforov, T.; Stanchev, S.; Milenkov, B.; Dimitrov, V. *Synth. Commun.* **1990**, *20*, 1977−1981.

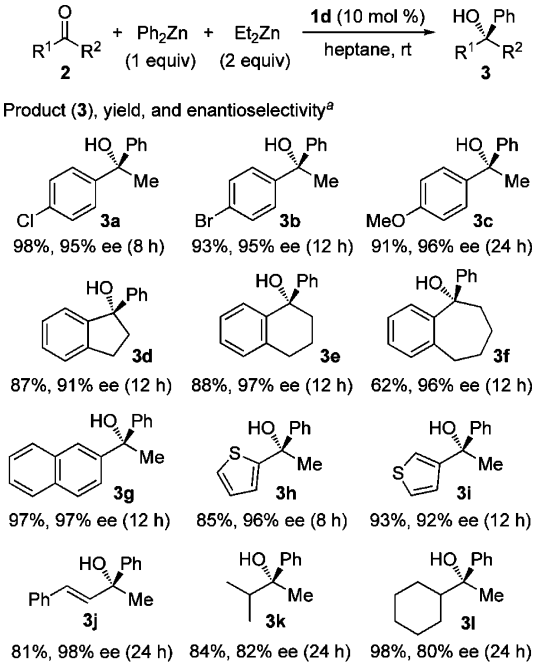
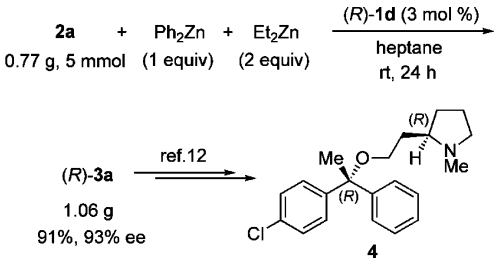


Figure 2. Catalytic enantioselective phenylation to ketones. Conditions: (a) Reactions were examined in 0.5 M heptane.

h in the presence of 10 mol % of (*S*)-**1d**, and the desired tertiary alcohols (**5**) were obtained in high yields with high enantioselectivities (91−96% ee). To the best of our knowledge, this is the first example of the highly efficient ethylation of ketones under mild reaction conditions by simply mixing substrate, Et_2Zn, and the chiral ligand in a solvent.

Scheme 2. A 1-g-Scale Synthesis of (*R*)-**3a** toward Clemastine



Finally, plausible transition-state assemblies in catalytic enantioselective ethylations are shown in Figure 4, which should be regarded as a working model. Chiral ligand (*S*)-**1** and Et_2Zn would make up the *N*,*N*-chelated EtZn(II) center as a Lewis acid to activate a ketone (**2**, R^1COR^2, $R^1 > R^2$).[13] The P═O moiety as a Lewis base, which is electrodonatively activated through conjugation among Zn−N−P═O bonds, would coordinate to the Et_2Zn reagent, leading to six-membered chelation in a chair conformation with a ketone (**TS-1** and **TS-2**; also see Scheme 1). Cyclic amino groups of **1b** and **1c**, having more basic and less hindered characters due to electronic and steric factors, would smoothly coordinate to the Zn(II) center rather than the NMe_2 group of **1a**. Thus, yields with **1b** and **1c** were improved from that with **1a**, although a piperidinyl group of **1c** might cause too much hindrance to ketones leading to lower enantioselctivity (see Figure 1). Unlike the *P*-phenyl moieties of **1a**−**c**, sterically demanding *P*-(1-naphthyl) moieties of **1d** would coordinate to the Zn(II) centers with a more appropriate conformation. Probably the *i*-Pr moiety ("up" in Figure 4)

(13) We confirmed that 1 equiv of ethane gas was released when 1 equiv each of Et_2Zn and **1d** were mixed at room temperature.

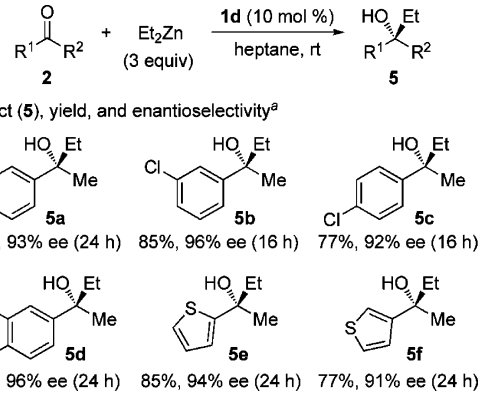


Figure 3. Catalytic enantioselective ethylation to ketones. Conditions: (a) Reactions were examined in 0.33 M heptane.

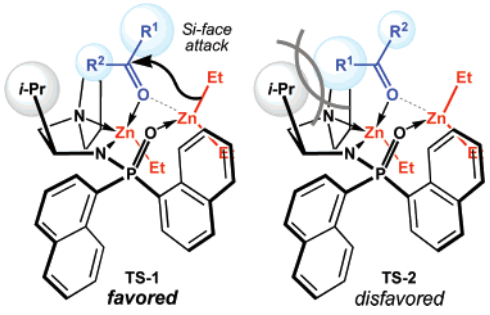


Figure 4. Proposed transition state assemblies.

of the L-valine backbone might relay the direction of two 1-naphthyl moieties, "down" and "up", respectively. Ultimately, the bulkiness of the "up"-1-naphthyl moiety would preferentially induce the coordination of the Et_2Zn reagent, which is activated by the P═O moiety, to the C═O moiety of **2**. Therefore, six-membered cyclic transition states would be stabilized by using **1d**. In particular, *Si*-face attack via **TS-1**, which leads to (*S*)-product, should be favored exclusively without conspicuous steric repulsion between the *i*-Pr and pyrrolidinyl moieties of (*S*)-**1d** and the R^1 group of **2**.

In summary, we have developed a highly efficient enantioselective organozinc addition to not only aldehydes[14] but

also ketones using conjugate Lewis acid−Lewis base phosphoramide−Zn(II) catalysts. These chiral Zn(II) catalysts, which are simply prepared in situ, are derived from an inexpensive natural amino acid (i.e., L-valine). From a variety of aromatic and aliphatic ketones, optically active tertiary alcohols were obtained in high yields with high enantioselectivities (up to 98% ee) under the mild reaction conditions. Further investigations on the scope and mechanistic aspects are under way.

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Note Added after ASAP Publication. References 7 and 8 were incomplete in the version published ASAP September 29, 2007; the revised version was published ASAP October 2, 2007, with apologies to Prof. Masakatsu Shibasaki and co-workers for the omission of their work.

Supporting Information Available: Experimental procedures and spectral data, as well as copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) 10 mol % of (*S*)-**1b** catalyzed the reaction of benzaldehyde and Et_2Zn (3 equiv) in toluene at 0 °C for 12 h, and the corresponding (*S*)-Et-adduct was obtained in 97% yield with 95% ee.