

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

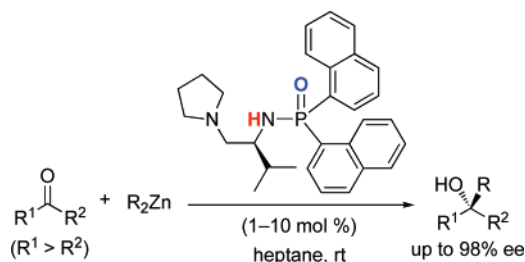
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## ABSTRACT



A highly efficient enantioselective organozinc ( $R_2Zn$ ) addition to ketones catalyzed by chiral phosphoramidate–Zn(II) complexes (1–10 mol %) has been developed. These complexes serve as conjugate Lewis acid–Lewis base catalysts. Chiral phosphoramidates 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.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4–6</sup> We report here highly active and simple chiral phosphoramidate–Zn(II) complexes as conjugate Lewis acid–Lewis base catalysts<sup>7</sup> for the enantioselective organozinc addition to ketones to obtain the desired tertiary

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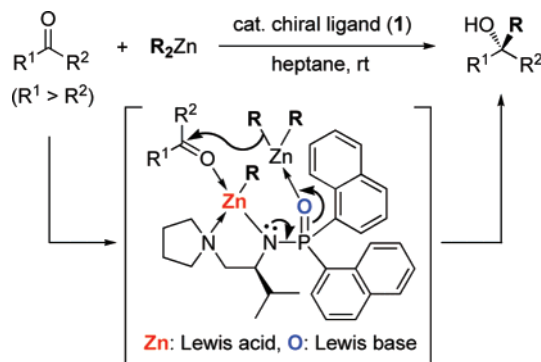
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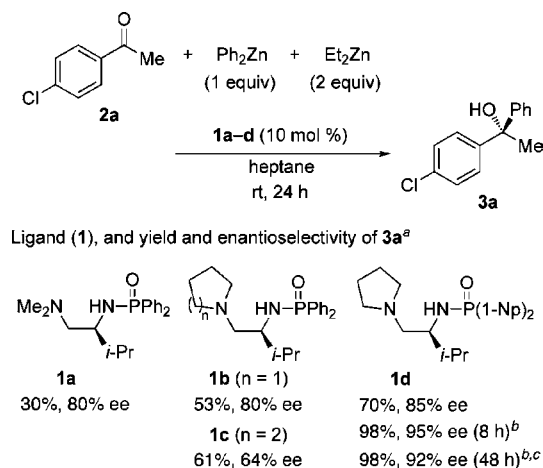
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**Scheme 1.** Chiral Phosphoramidate **1**-Zn(II) Complex as a Conjugate Lewis Acid–Lewis Base Catalyst



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 phosphoramidates at the 3,3′-positions were designed as highly effective conjugate Lewis acid–Lewis base catalysts.<sup>8–10</sup> 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 phosphoramidate ligand (**1**, 10 mol %) in the catalytic enantioselective phenylation of 4′-chloroacetophenone (**2a**) with Ph<sub>2</sub>Zn (1 equiv) and Et<sub>2</sub>Zn (2



**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.

equiv) in heptane at room temperature (Figure 1).<sup>11</sup> 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<sub>2</sub> group in **1a** showed improved catalytic activity, but the enantioselectivity 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**.

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  $\alpha,\beta$ -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 **2l**) also provided the corresponding tertiary alcohols (**3k** and **3l**) 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).<sup>12</sup>

Encouraged by the efficient phenylation to ketones, we next examined ethylation with Et<sub>2</sub>Zn (Figure 3). As expected, the reaction of aryl and heteroaryl ketones with 3 equiv of Et<sub>2</sub>Zn proceeded smoothly at room temperature for 16–24

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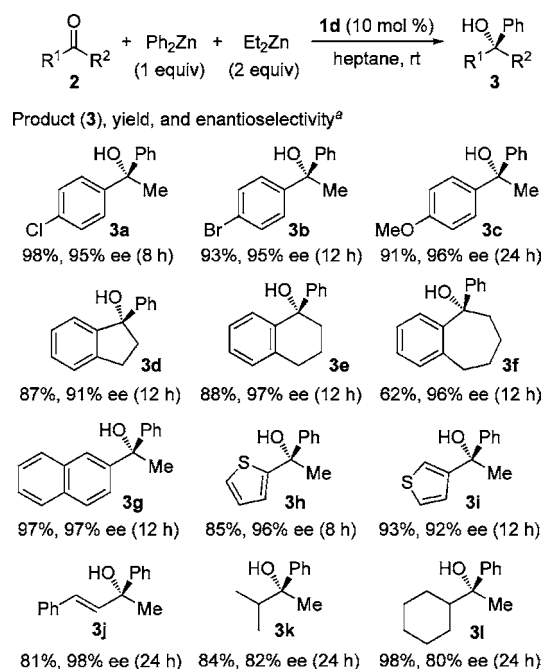
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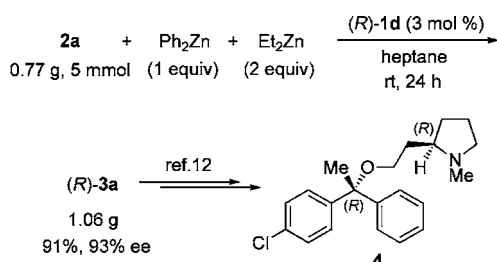
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**Figure 2.** Catalytic enantioselective phenylation to ketones. Conditions: (a) Reactions were examined in 0.5 M heptane.

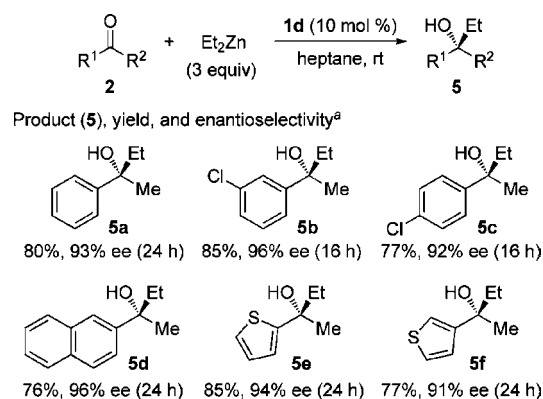
h in the presence of 10 mol % of (*S*)-**1d**, and the desired tertiary alcohols (**5**) were obtained in high yields with high enantioselectivities (91–96% ee). To the best of our knowledge, this is the first example of the highly efficient ethylation of ketones under mild reaction conditions by simply mixing substrate, Et<sub>2</sub>Zn, and the chiral ligand in a solvent.

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



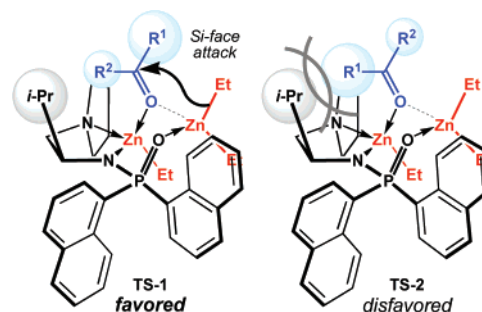
Finally, plausible transition-state assemblies in catalytic enantioselective ethylations are shown in Figure 4, which should be regarded as a working model. Chiral ligand (*S*)-**1** and Et<sub>2</sub>Zn would make up the *N,N*-chelated EtZn(II) center as a Lewis acid to activate a ketone (**2**, R<sup>1</sup>COR<sup>2</sup>, R<sup>1</sup> > R<sup>2</sup>).<sup>13</sup> 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<sub>2</sub>Zn reagent, leading to six-

(13) We confirmed that 1 equiv of ethane gas was released when 1 equiv each of Et<sub>2</sub>Zn and **1d** were mixed at room temperature.



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

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<sub>2</sub> 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 enantioselectivity (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)



**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<sub>2</sub>Zn 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<sup>1</sup> group of **2**.

In summary, we have developed a highly efficient enantioselective organozinc addition to not only aldehydes<sup>14</sup> but

also ketones using conjugate Lewis acid–Lewis base phosphoramidate–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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(14) 10 mol % of (*S*)-**1b** catalyzed the reaction of benzaldehyde and Et<sub>2</sub>Zn (3 equiv) in toluene at 0 °C for 12 h, and the corresponding (*S*)-Et-adduct was obtained in 97% yield with 95% ee.

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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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