

Novel *N,N,P*-Tridentate Ligands for the Highly Enantioselective Copper-Catalyzed 1,4-Addition of Dialkylzincs to Enones

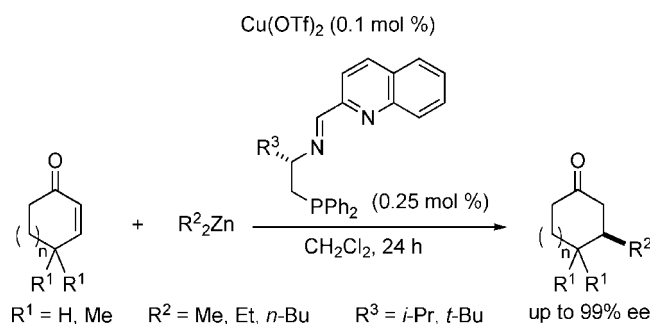
Kenjiro Kawamura, Hitomi Fukuzawa, and Masahiko Hayashi*

Department of Chemistry, Graduate School of Science, Kobe University,
Kobe 657-8501, Japan

mhayashi@kobe-u.ac.jp

Received June 4, 2008

ABSTRACT



Use of 0.25 mol % of the *N,N,P*-tridentate ligand containing the 2-quinolyl moiety (**1** and **2**) and 0.1 mol % of $\text{Cu}(\text{OTf})_2$ enabled the enantioselective 1,4-addition of dialkylzincs to cyclic enones to produce 1,4-adducts in up to 99% ee.

The enantioselective 1,4-addition of organometallic species to enones is one of the most important asymmetric carbon–carbon bond forming reactions in organic synthesis.¹ Some reports on the enantioselective 1,4-addition of dialkylzincs to enones are available.² Following the first report of copper-catalyzed 1,4-addition of diethylzinc to enones by Alexakis et al.,³ several reports of chiral phosphites,⁴

phosphoramidites,⁵ and other types of ligands, such as chiral bis(oxazolines)⁶ and *N*-heterocyclic carbene ligands,⁷ have emerged. For example, Escher and Pfaltz reported a new type of chiral oxazoline-phosphate ligand,^{4a} and Reiser and co-workers reported bis(oxazoline) ligands^{6a} for the asymmetric 1,4-addition of dialkylzinc to enones.⁸

We have developed *O,N,O*-tridentate ligands having the Schiff base framework type I for use in various asymmetric carbon–carbon bond forming reactions. Some examples include the asymmetric silylcyanation of aldehydes,⁹ the enantioselective addition of diketenes to aldehydes,¹⁰ and

(1) (a) Perlmutter, P. In *Conjugate Addition Reaction in Organic Synthesis*, *Tetrahedron Organic Chemistry Series No. 9*; Pergamon Press: Oxford, 1992. (b) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Verlag, Berlin, Heidelberg, 1999; Chapter 31.1. (c) Tomioka, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Verlag, Berlin, Heidelberg, NY, 2004; Supplement to Chapter 31.1.

(2) For a review: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236.

(3) Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, 4, 2427–2430.

(4) (a) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, 56, 2879–2888. (b) Cramer, N.; Laschat, S.; Baro, A. *Organometallics* **2006**, 25, 2284–2291.

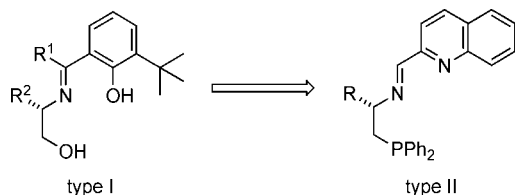
(5) (a) Boeda, F.; Rix, D.; Clavier, H.; Crévisy, C.; Mauduit, M. *Tetrahedron: Asymmetry* **2006**, 17, 2726–2729. (b) Ref 4b.

(6) (a) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, 3, 4259–4262. (b) Barros, M. T.; Maycock, C. D.; Phillips, A. M. F. *Tetrahedron: Asymmetry* **2005**, 16, 2946–2953.

(7) Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P.; Alexakis, A. *J. Organomet. Chem.* **2005**, 690, 5672–5695.

the enantioselective addition of dialkylzincs to aldehydes.¹¹ Considering the affinity to transition metal, we designed and synthesized new chiral *N,N,P*-tridentate ligands (type II). Here we report newly designed *N,N,P*-tridentate ligands (Scheme 1) and their application to the copper-catalyzed

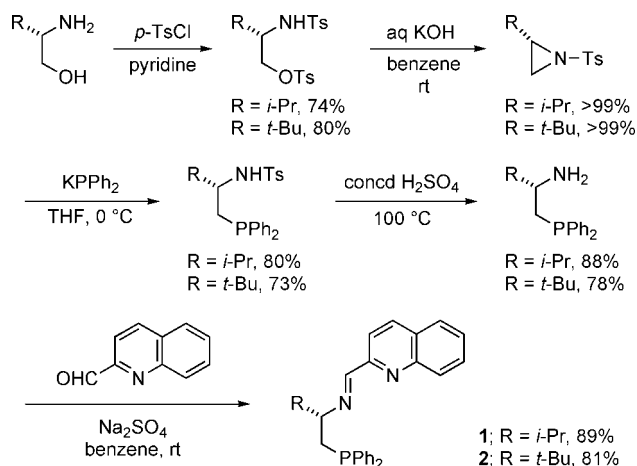
Scheme 1



enantioselective addition of dialkylzincs to enones.

The *N,N,P*-ligands were simply prepared as follows (Scheme 2): Starting from β -amino alcohols such as L-valinol

Scheme 2



(*R* = *i*-Pr) and *L*-tert-leucinol (*R* = *t*-Bu), ditosylation of β -amino alcohols followed by the treatment of KOH afforded

substituted aziridines in high yield. The thus obtained aziridines were treated with KPPH_2 to give the corresponding amino phosphines.¹² Condensation of 2-quinolylcarbaldehyde with these amino phosphines gave the desired *N,N,P*-ligands in high yield.

Table 1 lists the optimized reaction conditions, such as

Table 1. Enantioselective 1,4-Addition of Diethylzinc to 2-Cyclohexene-1-one (**3**)

entry	R	Cu(OTf) ₂ /mol % ^a	temp/°C	time/h	convn/% ^b	ee/% ^b
1	<i>i</i> -Pr	1.0	0	5	>99	97 (<i>S</i>)
2	<i>i</i> -Pr	0.5	0	5	>99	97 (<i>S</i>)
3	<i>i</i> -Pr	0.2	0	5	>99	97 (<i>S</i>)
4	<i>i</i> -Pr	0.2	-20	5	>99	98 (<i>S</i>)
5	<i>i</i> -Pr	0.2	-40	5	66	99 (<i>S</i>)
6	<i>i</i> -Pr	0.1	0	5	89	96 (<i>S</i>)
7	<i>i</i> -Pr	0.1	-40	24	>99	98 (<i>S</i>)
8	<i>t</i> -Bu	1.0	0	5	>99	99 (<i>S</i>)
9	<i>t</i> -Bu	0.2	0	5	>99	95 (<i>S</i>)
10	<i>t</i> -Bu	0.1	0	5	95	95 (<i>S</i>)
11	<i>t</i> -Bu	0.1	-40	24	>99	96 (<i>S</i>)

^a Cu(OTf)₂:ligand = 1:2.5. ^b The conversions and ee values were determined by GC analysis (Supelco γ -DEX-225).

the amount of catalyst ($\text{Cu}(\text{OTf})_2$ and ligand), the reaction temperature, and the substituent effect on the ligand (**1**: *R* = *i*-Pr, **2**: *R* = *t*-Bu), in the reaction of 2-cyclohexen-1-one with diethylzinc. We observed high enantioselectivity in both cases of *R* = *i*-Pr and *t*-Bu in this reaction. Even if the catalyst load was decreased to 0.1 mol % of $\text{Cu}(\text{OTf})_2$ and 0.25 mol % of ligand, the reaction proceeded to afford (*S*)-3-alkylcyclohexanone in 98% ee at -40 °C. In most of the previously reported reactions, 1 mol % or more of catalyst was necessary to obtain high ee. Compared with those reported methods,^{1,2} our present catalyst system exhibited high catalytic activity and enantioselectivity.

Regarding the utility of the 2-quinolyl moiety, Pfaltz and co-workers pointed out an asymmetric Heck reaction and asymmetric hydrogenation.¹³ The ligand having the 2-quinolyl moiety exhibited higher ee than the one having the pyridyl moiety. That is, when the pyridyl moiety was used instead of the 2-quinolyl moiety under the same reaction conditions, only 55% ee of product was obtained even if 1 mol % of

(8) Other examples of use of *N,P*-ligands: (a) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518–3521. (b) Morimoto, T.; Yamaguchi, Y.; Suzuki, M.; Saitoh, A. *Tetrahedron Lett.* **2000**, *41*, 10025–10029. (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755–756. (d) Krauss, I. J.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3201–3203. (e) Hajra, A.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2006**, *8*, 4153–4155. (f) Soeta, T.; Selim, K.; Kuriyama, M.; Tomioka, K. *Adv. Synth. Catal.* **2007**, *349*, 629–635. (g) Morimoto, T.; Obara, N.; Yoshida, I.; Tanaka, K.; Kan, T. *Tetrahedron Lett.* **2007**, *44*, 3093–3095. (h) Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2007**, *48*, 8590–8594.

(9) (a) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1752–1753. (b) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515–1522.

(10) (a) Hayashi, M.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 341–342. (b) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385–4398. (c) Hayashi, M.; Yoshimoto, K.; Hirata, N.; Tanaka, K.; Oguni, N.; Harada, K.; Matsushita, A.; Kawachi, Y.; Sasaki, H. *Isr. J. Chem.* **2001**, *41*, 241–246.

(11) (a) Tanaka, T.; Yasuda, Y.; Hayashi, M. *J. Org. Chem.* **2006**, *71*, 7091–7093. (b) Tanaka, T.; Sano, Y.; Hayashi, M. *Chem. Asian J.* **2008**, in press.

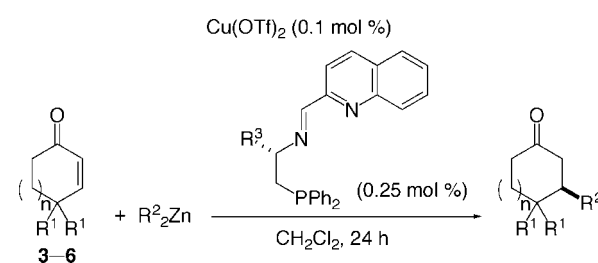
(12) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195–2202.

(13) (a) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16–22. (b) Drury, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 70–74.

Cu(OTf)₂ and 2.5 mol % of chiral ligand were used.^{8b} This result clearly indicates that the 2-quinolyl moiety is essential to achieve high enantioselectivity. It should be mentioned that remarkable rate enhancement was observed by the addition of *N,N,P*-ligands. That is, in the absence of ligands, the product was obtained only in 31% conversion under the same condition of entries 7 and 11 in Table 1 (>99% conversion, 0.1 mol % of Cu(OTf)₂, -40 °C, 24 h).

Under optimum conditions, that is, use of 0.1 mol % of Cu(OTf)₂ and 0.25 mol % of chiral ligand, we examined the reaction of various cyclic enones, such as 2-cyclopenten-1-one (**4**), 2-cyclohexene-1-one (**3**), 4,4-dimethyl-2-cyclohexene-1-one (**5**), and 2-cyclohepten-1-one (**6**), with dimethylzinc and diethylzinc. Unfortunately, the reaction of *n*-Bu₂Zn with enones **3** and **4** gave *n*-butylated ketones in low ee (12–36% ee) (entries 5, 6, 13, and 14, Table 2). We

Table 2. Enantioselective 1,4-Addition of Dialkylzinc to Cyclic Enones

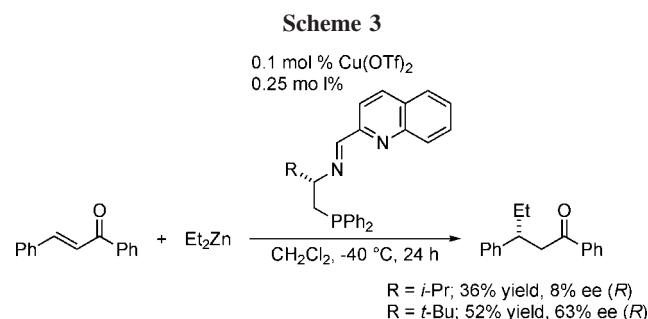
							
entry	<i>n</i>	R ¹	R ²	R ³	temp/°C	convn/% ^a	ee/% ^a
1	0	H	Me	<i>i</i> -Pr	-20	74	58 (<i>S</i>)
2	0	H	Me	<i>t</i> -Bu	-20	88	92 (<i>S</i>)
3	0	H	Et	<i>i</i> -Pr	-40	70	44 (<i>S</i>)
4	0	H	Et	<i>t</i> -Bu	-40	85	93 (<i>S</i>)
5	0	H	<i>n</i> -Bu	<i>i</i> -Pr	-40	64	36 (<i>S</i>)
6	0	H	<i>n</i> -Bu	<i>t</i> -Bu	-40	67	14 (<i>S</i>)
7	1	H	Me	<i>i</i> -Pr	-40	59	99 (<i>S</i>)
8	1	H	Me	<i>t</i> -Bu	-40	35	97 (<i>S</i>)
9	1	H	Me	<i>i</i> -Pr	-20	88	98 (<i>S</i>)
10	1	H	Me	<i>t</i> -Bu	-20	77	98 (<i>S</i>)
11	1	H	Et	<i>i</i> -Pr	-40	>99	98 (<i>S</i>)
12	1	H	Et	<i>t</i> -Bu	-40	>99	96 (<i>S</i>)
13	1	H	<i>n</i> -Bu	<i>i</i> -Pr	-40	58	12 (<i>S</i>)
14	1	H	<i>n</i> -Bu	<i>t</i> -Bu	-40	66	18 (<i>S</i>)
15	1	Me	Et	<i>i</i> -Pr	-20	9	86 (<i>R</i>)
16	1	Me	Et	<i>t</i> -Bu	-20	6	82 (<i>R</i>)
17	2	H	Me	<i>i</i> -Pr	-40	44	88 (<i>S</i>)
18	2	H	Me	<i>t</i> -Bu	-40	32	83 (<i>S</i>)
19	2	H	Et	<i>i</i> -Pr	-40	61	79 (<i>S</i>)
20	2	H	Et	<i>t</i> -Bu	-40	47	68 (<i>S</i>)

^a The conversions and ee values were determined by GC analysis (Supelco γ -DEX-225 for entries 1–16; Supelco β -DEX-225 for entries 17–20).

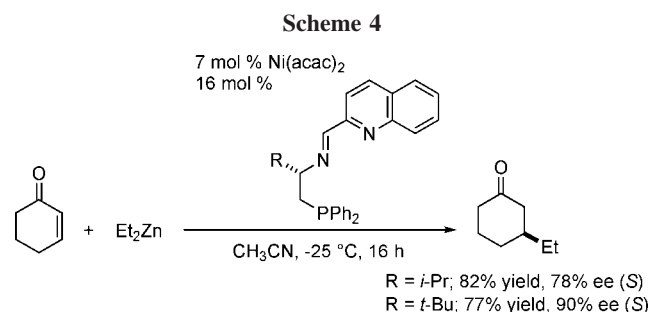
suppose the bulkiness of substituents of ligands and dialkylzincs totally affects the structure of the transition state at which stage the enantioselection will be determined. For 2-cyclopenten-1-one (**4**), the effect of substituents R³ in the ligand was remarkable, and enantioselectivity was increased dramatically; that is, ee was increased from 58% to 92% (in

the case of Me₂Zn) and from 44% to 93% (in the case of Et₂Zn) (entries 1–4, Table 2). In the case of enones **3** and **5**, the nature of R³ did not markedly influence reactivity and selectivity. For the reaction of 2-cyclohepten-1-one (**6**), the ligand having an *i*-Pr group gave higher ee than the one having a *t*-Bu group, contrasting the results of the reaction of 2-cyclopenten-1-one (**4**) (entries 17–20, Table 2).

The reaction of an acyclic enone, chalcone, with Et₂Zn using 0.1 mol % of Cu(OTf)₂ and *N,N,P*-ligands **1** and **2** gave the 1,4-adduct in 8% ee (36% yield) and 63% ee (52% yield), as shown in Scheme 3.



The combination of Ni(acac)₂–*N,N,P*-ligands **1** and **2** afforded the 1,4-adduct in 78% ee (82% yield) and 90% ee (77% yield), respectively, as shown in Scheme 4.



Although a large amount of catalyst is required in the Ni system, compared with the Cu system, our newly developed ligands **1** and **2**, particularly ligand **2**, have high enantioselectivity even in combination with Ni (Scheme 4). It should be noted that in hitherto reported studies of the utility of the Ni catalyst system in the enantioselective addition of dialkylzincs to enones most involved the addition to acyclic enones, and reports on the addition to cyclic enones are few. Thus, this Ni catalyst system proved to be useful for cyclic enones.

In conclusion, we have revealed a new entry of chiral *N,N,P*-tridentate ligands that promote the highly enantiose-

lective 1,4-addition of dialkylzinc to enones (up to 99% ee) in combination with Cu(OTf)₂.¹⁴

(14) A typical experimental procedure for asymmetric 1,4-addition is as follows (Table 1, entry 8): A solution of Cu(OTf)₂ (3.6 mg, 0.01 mmol) and ligand (10.6 mg, 0.025 mmol) in dichloromethane (1.5 mL) was stirred under an argon atmosphere at room temperature for 0.5 h. To the solution was added 2-cyclohexen-1-one (96 mg, 1 mmol) followed by dropwise addition of Et₂Zn (1.5 mmol, 1.5 mL of 1.0 M solution in hexane) at 0 °C. After stirring for 5 h at 0 °C, the reaction mixture was quenched with 1 N HCl solution (2 mL) and was extracted with Et₂O (10 mL × 3). The combined organic layer was washed with saturated aq NaHCO₃ and dried over Na₂SO₄. After the solvent was evaporated, an oily residue was purified by silica gel column chromatography (hexane/Et₂O = 4/1) to afford 106 mg (84%) of 3-ethylcyclohexanone (99% ee (*S*)). [α]_D²⁸ −15.6° (*c* 1.0, CHCl₃) (lit.^{8e} [α]_D²⁶ −8.8° (*c* 1.6, CHCl₃) for 82% ee (*S*)). Data of the conversion and the ee value of the product were determined by chiral-phase GC analysis with a γ -DEX-225 (Supelco) column (30 m × 0.25 mm). The absolute configuration was determined by comparison with literature values.^{8c}

Acknowledgment. This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday. This work was supported by Grants-in-Aid for Scientific Research on Priority Areas “Advanced Molecular Transformations of Carbon Resources” and No. B17340020 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Details of experimental procedures and characterization data (¹H and ¹³C NMR, IR, mass spectrometry, and elementary analyses) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL801259U