# The Catalytic Asymmetric Addition of Diethylzinc to *N*-(Diphenylphosphinoyl) Imines Catalyzed by $Cu(OTf)_2$-Chiral *N*-(Binaphthyl-2-yl)thiophosphoramide Ligands

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Received: February 15, 2003; Accepted: March 27, 2003

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

**Abstract:** Chiral *N*-(binaphthyl-2-yl)thiophosphoramide **L7** [*O,O*-diethyl 2′-(ethylamino)-1,1′-binaphthyl-2-ylamidothiophosphate] prepared from the reaction of diethyl chlorothiophosphate with (*R*)-(+)-*N*-ethyl-1,1′-binaphthyl-2,2′-diamine was used as a catalytic chiral ligand in the first $Cu(OTf)_2$-promoted catalytic asymmetric addition of diethylzinc to *N*-(diphenylphosphinoyl) imines in which ~85% ee can be realized.

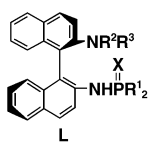
**Keywords:** *N*-(arylmethylene)-*P,P*-diphenylphosphinic amides; asymmetric addition; asymmetric catalysis; chiral *N*-(thiophosphoryl)-1,1′-binaphthyl-2,2′-diamine; copper(II) triflate; diethylzinc; imines; N ligands

Efficient and asymmetric preparation of amines is one of the most promising methodologies in organic synthesis.[1] In addition to the asymmetric reduction of imines, the enantioselective addition of alkylmetals to imines is a convenient route to optically active amines. Among these, chiral amine ligand-catalyzed addition of alkyllithium,[2] copper-amidophosphine,[3] and Zr-peptide-based chiral ligand-catalyzed asymmetric addition of organozinc,[4] chiral allylpalladium-catalyzed allylation with allylstannane,[5] and rhodium-monophosphine-catalyzed arylation with arylstannane[6] showed very good enantioselectivities. Recently, the use of *N*-(diphenylphosphinoyl) imines as activated substrates in combination with diethylzinc as the nucleophillic reagent and an amino alcohol promoter is receiving increasing attention.[7] However, many aspects of this chemistry still need to be developed. Additions to *N*-(diphenylphosphinoyl) imine derived from benzaldehyde have been almost exclusively studied, and as a result of the poor electrophilic character of *N*-(diphenylphosphinoyl) imines, stoichiometric amounts of amino alcohol ligand are normally required to ensure high conversion and enantioselectivity.

We are interested in syntheses and applications of novel chiral ligands based on axially chiral binaphthenediamine (BINAM), which has been much less popular in contrast to the widely used other axially chiral binaphthyl structures such as BINOL and NOBIN and other chiral diamines such as 1,2-cyclohexanediamine, 1,2-diphenylethenediamine.[8] Herein, we wish to report the catalytic asymmetric addition of diethylzinc to *N*-(diphenylphosphinoyl) imines using $Cu(OTf)_2$ as the catalytic precursor and novel chiral *N*-(binaphthyl-2-yl)thiophosphoramides as ligands.[9]

These chiral ligands **L1** – **L8** are easily obtained from (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (see Supporting Information) (Figure 1).[10] In addition, they are quite stable and can be easily recovered from the reaction mixture simply by column chromatography. Using *N*-(diphenylphosphinoyl) imine as the substrate and diethylzinc as the nucleophilic addition reagent, we examined this asymmetric addition in toluene using copper salts (5 mol %) and ligands **L1** – **L7** (5.5 mol %) under various reaction conditions to develop the optimal reaction conditions. The results are summarized in Table 1.

Initially, an examination of the temperature profile of $Cu(CH_3CN)_4BF_4$/**L4**-catalyzed asymmetric addition of diethylzinc to imines was performed. There was a temperature dependence on the yield and enantioselectivity. At room temperature, the reaction was com-



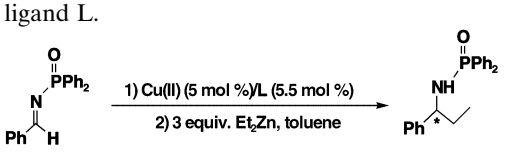

L

| | $R^1$ | $R^2$ | R3 | X |
|---|---|---|---|---|
| **L1** | Me | H | H | S |
| **L2** | Me | H | Et | S |
| **L3** | Ph | H | H | S |
| **L4** | Ph | H | Et | S |
| **L5** | Ph | Me | Me | S |
| **L6** | OEt | H | H | S |
| **L7** | OEt | H | Et | S |
| **L8** | Ph | H | Et | O |

**Figure 1.** The structures of chiral ligands **L1 – L8**.

 **DOI: 10.1002/adsc.200303041**  

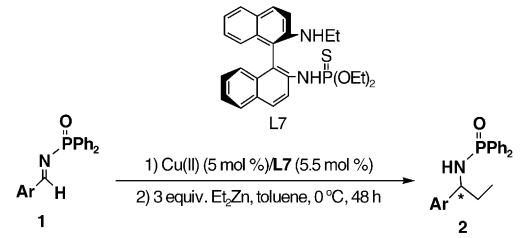
**Table 1.** The enantioselective addition reaction of $ZnEt_2$to diphenylphosphionyl imine catalyzed by copper salt and chiral ligand L.




| Entry | Copper salt | Ligand | Temp. [°C] | Time [h] | Yield[a] [%] | ee[b] [%] | Config.[c] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu(MeCN)_4BF_4$ | **L4** | 20 | 24 | 78 | 51 | *R* |
| 2 | $Cu(MeCN)_4BF_4$ | **L4** | 0 | 48 | 76 | 59 | *R* |
| 3 | $Cu(MeCN)_4BF_4$ | **L4** | −20 | 48 | 54 | 43 | *R* |
| 4 | $Cu(MeCN)_4BF_4$ | **L1** | 0 | 48 | 66 | 9 | *R* |
| 5 | $Cu(MeCN)_4BF_4$ | **L2** | 0 | 48 | 68 | 13 | *R* |
| 6 | $Cu(MeCN)_4BF_4$ | **L3** | 0 | 48 | 70 | 33 | *R* |
| 7 | $Cu(MeCN)_4BF_4$ | **L5** | 0 | 48 | 66 | 7 | *R* |
| 8 | $Cu(MeCN)_4BF_4$ | **L6** | 0 | 48 | 62 | 62 | *R* |
| 9 | $Cu(MeCN)_4BF_4$ | **L7** | 0 | 48 | 72 | 84 | *R* |
| 10 | $Cu(MeCN)_4ClO_4$ | **L7** | 0 | 48 | 70 | 83 | *R* |
| 11 | $CuOTf \cdot 1/2C_6H_6$ | **L7** | 0 | 48 | 80 | 84 | *R* |
| 12 | $Cu(OTf)_2$ | **L7** | 0 | 48 | 80 | 85 | *R* |

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] The absolute configuration was assigned by comparison of the optical rotation with reported data.[7b]

**Table 2.** The asymmetric addition reactions of diethylzinc to various diphenylphosphinoyl imines in the presence of $Cu(OTf)_2$(5 mol % and chiral ligand **L7** (5.5 mol%)




| Entry | Ar | imines | product | Yield[a] [%] | ee[b] [%] | Config.[c] |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **1a** | **2a** | 80 | 85 | *R* |
| 2 | *p*-$MeC_6H_4$ | **1b** | **2b** | 85 | 82 | *R* |
| 3 | *m*-$MeC_6H_4$ | **1c** | **2c** | 89 | 82 | *R* |
| 4 | *p*-$MeOC_6H_4$ | **1d** | **2d** | 61 | 66 | *R* |
| 5 | *p*-$FC_6H_4$ | **1e** | **2e** | 83 | 85 | *R* |
| 6 | *p*-$ClC_6H_4$ | **1f** | **2f** | 84 | 84 | *R* |
| 7 | *p*-$BrC_6H_4$ | **1g** | **2g** | 80 | 84 | *R* |
| 8 | *o*-$BrC_6H_4$ | **1h** | **2h** | 89 | 82 | *R* |
| 9 | *1*-naphthyl | **1i** | **2i** | 82 | 83 | *R* |

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] The absolute configuration was assigned by comparison of the optical rotation with reported data.[7b]

pleted within 24 h and gave the addition product in 78% yield (51% ee) (Table 1, entry 1). Lowering the temperature to 0 °C, the yield of the addition product was 76% with 59% ee (Table 1, entry 2). However, when the reaction was carried out at −20 °C, the reaction was sluggish and the achieved ee was remarkably reduced to 43% (Table 1, entry 3). **L7** is the best chiral ligand for this enantioselective addition reaction in 70–80% yield with 83–85% ee (Table 1, entries 9–12). It should be noted that chiral ligand **L5** having *N*,*N*-dimethyl groups gave the addition product only in 7% ee under the same conditions (Table 1, entry 7) and the *N*-unsubstituted chiral ligands **L1**, **L3**, and **L6** gave the addition products in low to moderate ee (Table 1, entries 4, 6, and 8). These results suggest that the substituents of the amino group in the binaphthyl structure play the important role in chiral induction in this asymmetric addition reaction. The copper salts $Cu(CH_3CN)_4BF_4$, $Cu(CH_3CN)_4ClO_4$, $CuOTf \cdot 1/2\,C_6H_6$, and $Cu(OTf)_2$ showed the same catalytic activities (Table 1, entries 9–12). $Cu(OTf)_2$ was utilized in this study due to its greater air stability and associated convenience in handing. Thus, the best reaction conditions are using $Cu(OTf)_2$ (5 mol %) and **L7** (5.5 mol %) in toluene at 0 °C. The reaction can be completed within 48 h in 85% ee and 80% yield.

Encouraged by the result obtained for the *N*-(diphenylphosphinoyl) imine of benzaldehyde, we investigate a variety of other imines to probe their behaviors under the optimized reaction conditions in this catalytic system. The results are summarized in Table 2. As can been seen from Table 2, most of the reactions proceeded smoothly to provide the corresponding chiral diphenylphosphinic amides in high yields and good enantioselectivities (Table 2, entries 1–3 and 5–9). The enantioselectivity was not affected by introduction of a bromine atom into the *ortho*-position of benzaldehyde (Table 2, entries 1 and 8). The lower yield and ee was obtained for imines having a strongly electron-donating group (Table 2, Entry 4). Based on this catalytic asymmetric addition, a variety of optically active amines can easily be obtained by acidic hydrolysis of the obtained diphenylphosphinic amides.[11]

The heteroatom on phosphorus is crucial for this catalytic asymmetric reaction to be so effective because the corresponding axially chiral *N*-(binaphthyl-2-yl)diphenylphosphoramide ligand **L8** showed no enantioselectivity for this reaction. The addition product was formed only in 25% yield along with a large amount of unreacted starting materials under the same conditions. We believe that this family of *N*-(binaphthyl-2-yl)diphenylthiophosphoramide **L1**–**L7** are bidentate ligands in this catalytic asymmetric reaction. It is well known that sulfur atom can strongly coordinate to some late transition metals.[12] $^{31}P$ NMR studies of a 1:1 mixture of **L7** and $Cu(CH_3CN)_4BF_4$ in $CDCl_3$ at room temperature were carried out. In the absence of $Cu(CH_3CN)_4BF_4$, the phosphorus signal of **L7** appeared at $\delta = 66.571$. While, the upfield shift of phosphorus atom connecting to the

sulfur atom at $\delta = 64.988$ in **L7** was observed in the presence of $CuBF_4$ (see Supporting Information). This result may indicate that $CuBF_4$ can be potentially coordinated by S, N atom in **L7** ligand.

In conclusion, the catalytic asymmetric addition of diethylzinc to *N*-(diphenylphosphinoyl) imines in generally good yields and enantioselectivities has been achieved using $Cu(OTf)_2$ and easily available, very stable and recoverable axially chiral *N*-(binaphth-2-yl)thiophosphoramide ligands. Efforts are underway to elucidate the mechanistic details of this catalytic system and to extend the scope and limitations of those novel chiral ligands in other asymmetric C-C bond forming processes.

## Experimental Section

### Typical Procedure for the Cu(II)-Catalyzed Asymmetric Addition of Diethylzinc to *N*-(Diphenylphosphinoyl) Imines

A solution of $Cu(OTf)_2$ (5.4 mg, 0.015 mmol) and ligand **7** (8.4 mg, 0.018 mmol) in dry toluene (3 mL) was stirred for 1 h at room temperature under an argon atmosphere. *N*-(Diphenylphosphinoyl) imine of benzaldehyde (92 mg, 0.3 mmol) was added and the solution was stirred for a further 10 min, then $Et_2Zn$ (0.9 mL, 0.9 mmol, 1.0 M solution in hexane) was added dropwise at 0 °C. The resulting mixture was stirred for about 48 h at the same temperature, saturated $NH_4Cl$ (10.0 mL) was added. After extraction with ethyl acetate ($3 \times 10.0$ mL), the combined organic layers were dried over $MgSO_4$. The residue obtained upon removal of volatiles under vacuum was purified by column chromatography on silica gel (eluent: petroleum/ethyl acetate = 1:1) to afford the addition product *N*-(1-phenylpropyl)-*P,P*-diphenylphosphinic amide as a colorless solid; yield: 80 mg (80%).

The experimental procedures for the preparation of the ligands and the spectroscopic and analytical data for the ligands **L1 – L8** and products **2** shown in Table 2 are included in the supporting information

## Acknowledgements

*We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China (20025206 and 20272069) for financial support.*

## References and Notes

[1] a) H.-J. Federsel, A. N. Collins, G. N. Sheldrake, J. Crosby, *Chirality in Industry II*, John Wiley & Sons, Chichester, **1997**; pp. 225 – 244; for a review on catalytic asymmetric addition to imines, see: b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069 – 1094.

[2] a) S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, *J. Am. Chem. Soc.* **1994**, *116*, 8797 – 8798; b) S. E. Denmark, C. M. Stiff, *J. Org. Chem.* **2000**, *65*, 5875 – 5878; c) K. Tomioka, I. Inoue, M. Shindo, K Koga, *Tetrahedron Lett.* **1991**, *32*, 3095 – 3098.

[3] H. Fujihara, K. Nagai, K. Tomika, *J. Am. Chem. Soc.* **2000**, *122*, 12055 – 12056.

[4] a) J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.* **2001**, *123*, 984 – 985; b) during our preparation of manuscript, we found that Charette has reported the first example of catalytic enantioselective addition of dialkylzinc to *N*-(diphenylphosphinoyl) imines, see: A. A. Boezio, A. B. Charette, *J. Am. Chem. Soc.* **2003**, *125*, 1692 – 1693.

[5] a) H. Nakamura, K. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 4242 – 4243; b) M. Bao, H. Nakamura, Y. Yamaoto, *Tetrahedron Lett.* **2000**, *41*, 131 – 134.

[6] T. Hayashi, M. Ishigedani, *J. Am. Chem. Soc.* **2000**, *122*, 976 – 977.

[7] a) K. Soai, T. Hatanaka, T. Miyazawa, *J. Chem. Soc. Chem. Commun.* **1992**, 1097 – 1098; b) P. G. Andersson, D. Guijarro, D. Tanner, *J. Org. Chem.* **1997**, *62*, 7364 – 7375; c) P. Brandt, C. Hedberg, K. Lawonn, P. Pinho, P. G. Andersson, *Chem. Eur. J.* **1999**, *5*, 1692 – 1699; d) C. Jimeno, K. S. Reddy, L. Sola, A. Moyano, M. A. Pericas, A. Riera, *Org. Lett.* **2000**, *2*, 3157 – 3159; e) X. M. Zhang, L. Z. Gong, A. Q. Mi, X. Cui, Y. Z. Jiang, M. C. K. Choi, A. S. C. Chan, *Tetrahedron Lett.* **2001**, *42*, 6369 – 6372, f) K. J. M. Beresford, *Tetrahedron Lett.* **2002**, *43*, 7175 – 7177.

[8] a) I. Ojima, Ed. *Catalytic Asymmetric Synthesis*, VCH, New York, **1993**; b) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds. *Comprehensive Asymmetric Catalysis.* Springer-Verlag, Germany, **2001**.

[9] a) M. Shi, W.-S. Sui, *Chiraliy*, **2000**, *12*, 574 – 580; b) M. Shi, W.-S. Sui, *Tetrahedron:Asymmetry* **2000**, *11*, 773 – 779; c) M. Shi, W.-S. Sui, *Tetrahedron Asymmetry* **2000**, *11*, 835 – 841; d) M. Shi, W.-S. Sui, *Tetrahedron Asymmetry* **1999**, *10*, 3319 – 3325.

[10] S. Miyano, M. Nawa, A. Mori, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2171 – 2176.

[11] R. Ramage, D. Hopton, M. J. Parrot, G. W. Kenner, G. A. More, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1357 – 1370.

[12] For selected X-ray structures of Cu complexes coordinated by S,N ligands, see: a) D. M. Koten, D. M. Grove, W. J. Smeets, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **1992**, *114*, 3400 – 3410; b) G. R. Brubaker, J. N. Brown, M. K. Yoo, T. M. Kutchan, E. A. Mottel, *Inorg. Chem.* **1979**, *18*, 299 – 302.