

Asymmetric Addition of Diethylzinc to Diphenylphosphinoyl-Imines Catalyzed by Copper(II) Trifluoromethanesulfonate-Chiral (2'-Ethylamino-[1,1']binaphthalenyl-2-yl)-thiophosphoramidic Acid *O,O'*-Diaryl Ester Ligands

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Received: March 23, 2006; Revised: July 22, 2006; Accepted: August 3, 2006



Supporting information for this article is available on the WWW under <http://asc.wiley-vch.de/home/>.

Abstract: The chiral binaphthylthiophosphoramidate **L1** prepared from the reaction of *O,O*-diphenyl chlorothiophosphate with (*R*)-(+)-*N*-ethyl-1,1'-binaphthyl-2,2'-diamine was used as a catalytic chiral ligand in the copper(II) trifluoromethanesulfonate-promoted asymmetric addition of diethylzinc to diphenylphosphinoyl-imines to give the corresponding adducts in 90–98% *ee* and good yields under mild conditions.

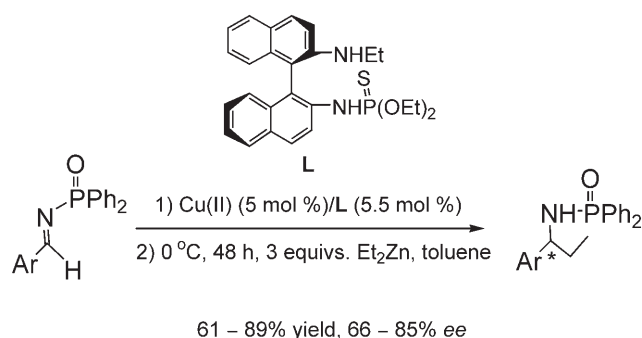
Keywords: asymmetric addition; asymmetric catalysis; chiral binaphthylthiophosphoramidates; copper(II) trifluoromethanesulfonate; diethylzinc; diphenylphosphinoyl-imines

Introduction

The 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, the chiral amine ligand-catalyzed addition of alkyllithium,^[2] copper-amidophosphine,^[3] Zr-peptide-based chiral ligand and copper(II) triflate/diphosphine complex-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 diphenylphosphinoyl-imines as activated substrates in combination with diethylzinc as the nucleophilic reagent and an amino alcohol promoter is receiving increasing attention.^[7] However, many as-

pects of this chemistry still need to be developed. Additions to diphenylphosphinoyl-imine derived from benzaldehyde have been studied almost exclusively, and as a result of the poor electrophilic character of diphenylphosphinoyl-imines, stoichiometric amounts of amino alcohol ligand are normally required to ensure high conversion and enantioselectivity.

We are interested in the syntheses and applications of novel chiral ligands based on axially chiral binaphthenediamine (BINAM), which has been much less popular in comparison to the other widely used axially chiral binaphthyl structures such as BINOL and NOBIN as well as chiral diamines such as 1,2-cyclohexanediamine and 1,2-diphenylethylenediamine.^[8,9] Previously, we reported that the catalytic asymmetric addition of diethylzinc to diphenylphosphinoyl-imines in 61–89% yields and 66–85% *ee* had been achieved using Cu(OTf)₂ and easily available, stable and the recoverable axially chiral binaphthylthiophosphoramidate ligand, (2'-ethylamino-[1,1']binaphthalenyl-2-yl)-thiophosphoramidic acid *O,O'*-diethyl ester (Scheme 1).^[9] On the basis of above results, we envisioned that



Scheme 1. Catalytic asymmetric addition with the chiral thiophosphoramidate ligand.

enantioselectivity of this addition reaction can be improved by replacement of the *O,O'*-diethyl group with the sterically more bulky *O,O'*-aryl group in the binaphthylthiophosphoramidate ligand system. Herein, we report the catalytic asymmetric addition of diethylzinc to diphenylphosphinoyl-imines using Cu(OTf)₂ as the catalytic precursor and novel chiral binaphthylthiophosphoramidates, (2'-ethylamino-[1,1']binaphthalenyl-2-yl)-thiophosphoramidic acid *O,O'*-diaryl esters, as ligands to give the corresponding adducts in good yields and 90–98 % *ee* (Figure 1).

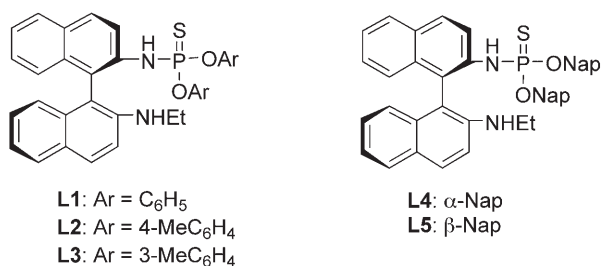
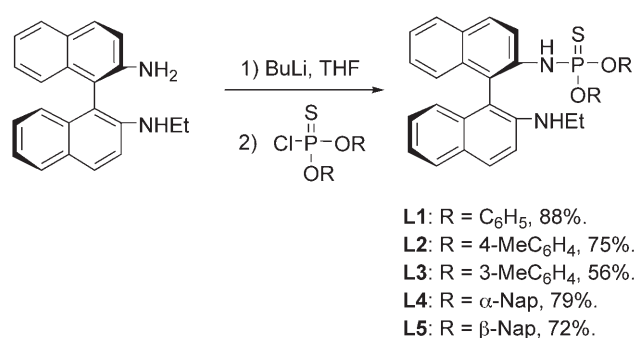


Figure 1.

Results and Discussion

These chiral ligands **L1–L5** are easily obtained from the reaction of *N*²-ethyl-[1,1']binaphthalenyl-2,2'-diamine, derived from (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine,^[10] with the corresponding thiophosphorochloridic acid *O,O'*-diaryl ester (Scheme 2 and Supporting Information).



Scheme 2. Preparation of (2'-ethylamino-[1,1']binaphthalenyl-2-yl)-thiophosphoramidic acid *O,O'*-diaryl ester ligands.

Using diphenylphosphinoyl-imine as substrate and diethylzinc as nucleophilic addition reagent, we examined this asymmetric addition in toluene using copper salt Cu(OTf)₂ (5–10 mol %) and ligand **L1** (5–10 mol %) to develop the optimal reaction conditions. The results are summarized in Table 1. Initially, solvent effects in this asymmetric addition reaction were examined at room temperature (20 °C). We found that in toluene, the corresponding adduct **1a** was obtained in 85 % yield and 67 % *ee*, but in dichloromethane, acetonitrile or tetrahydrofuran (THF), neither reaction occurred or the corresponding adduct **1a** was formed in trace (Table 1, entries 1–4). Next, an examination of the temperature profile of Cu(OTf)₂/**L1**-catalyzed asymmetric addition of diethylzinc to diphenylphosphinoyl-imines was performed. The yield and enantioselectivity are both dependent on the temperature. At 0 °C, the reaction was completed within 48 h

Table 1. Optimization of the reaction conditions of ZnEt₂ to diphenylphosphinoyl-imine catalyzed by the copper salt Cu(OTf)₂ and chiral ligand **L1**.

Entry	Solvent	Temp. [°C]	L1 [mol %]	Cu(OTf) ₂ [mol %]	Time [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	CH ₂ Cl ₂	20	5	5	48	trace	–
2	CH ₃ CN	20	5	5	48	NR	–
3	THF	20	5	5	48	trace	–
4	PhMe	20	5	5	36	85	67
5	PhMe	0	5	5	48	78	82
6	PhMe	–20	5	5	96	67	89
7	PhMe	0	7.5	5	48	86	83
8	PhMe	0	10	5	48	90	83
9	PhMe	0	5	10	48	41	10
10	PhMe	–20	10	10	48	70	92
11	PhMe	–20	15	10	48	87	92

^[a] Isolated yields.

^[b] Determined by chiral HPLC.

to give the addition product **1a** in 78% yield and 82% *ee* (Table 1, entry 5). Lowering the temperature to -20°C , the yield of the addition product **1a** was 67% with 89% *ee* (Table 1, entry 6). However, when the reaction was carried out at -20°C , the reaction was sluggish and a prolonged reaction time is required (Table 1, entry 6). Increasing the amounts of chiral ligand, we found that the yield of the addition product **1a** can be improved at 0°C (Table 1, entries 7–9). At -20°C using 15 mol% of **L1** and 10 mol% of $\text{Cu}(\text{OTf})_2$, we found that the corresponding adduct **1a** can be obtained in 87% yield and 92% *ee* (Table 1, entry 11).

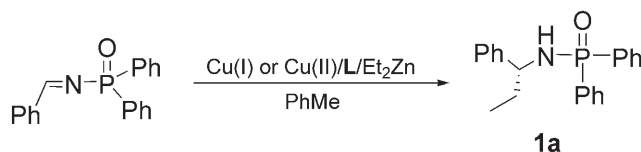
Using **L2–L5** as ligands (5 mol%) and $\text{Cu}(\text{OTf})_2$ (5 mol%) as the catalytic precursor in the reaction, we found that the corresponding adduct **1a** was obtained in 83–93% yields and 67–79% *ee* at 0°C in toluene (Table 2, entries 1–3 and 5). It seems to us that ligand **L4** gave the better result under identical conditions. Using **L4** (15 mol%) and $\text{Cu}(\text{OTf})_2$ (10 mol%) at -20°C in toluene, we found that the corresponding adduct **1a** was formed in 80% yield and 88% *ee* (Table 2, entry 4). Therefore, **L1** is the best ligand in this reaction under similar conditions. Using copper salt $\text{Cu}(\text{CH}_3\text{CN})_4\text{ClO}_4$ as catalytic precursor and **L1** as ligand, the adducts were formed in lower yields and *ee* under our standard conditions (Table 2, entries 6 and 7). $\text{Cu}(\text{OTf})_2$ was therefore utilized in this study due to its greater air stability and associated convenience in handling. Thus, the best reaction conditions are using $\text{Cu}(\text{OTf})_2$ (10 mol%) and **L1** (15 mol%) in toluene at -20°C . The reaction can be completed within 48 h in 87% yield and 92% *ee*.

Encouraged by the result obtained for the diphenylphosphinoyl-imine of benzaldehyde, we investigated a variety of other imines to probe their behaviors under these optimized reaction conditions in this catalytic system. The results are summarized in Table 3. As can

been seen from Table 3, most of the reactions proceeded smoothly to provide the corresponding chiral diphenylphosphinoyl-amides **1** in good yields (75–87%) and high enantioselectivities (90–98% *ee*) (Table 3, entries 1–8). The enantioselectivity was not affected by introduction of a chlorine atom into the *ortho*-position of benzaldehyde (Table 3, entries 7 and 8). Lower yields and *ees* were obtained for imines having a strongly electron-donating group (Table 3, entry 4). Based on this catalytic asymmetric addition, a variety of optically active amines can be easily obtained by acidic hydrolysis of the obtained diphenylphosphinoyl-amides (Scheme 3).^[11] Using the sulfinic adduct of *N*-phosphinoylbutylimine as substrate to examine aliphatic *N*-diphenylphosphinoyl-imines according to Charette's procedure,^[4c] we found that the corresponding adduct was formed in traces under the standard conditions (Scheme 4).

As we mentioned before, the heteroatom on phosphorus is crucial for this catalytic asymmetric reaction to be so effective because the corresponding axially chiral binaphthyl-diphenylphosphoramidate ligand showed no enantioselectivity for this kind of addition reaction.^[9] We believe that this family of binaphthyl-diphenylthiophosphoramidates **L1–L5** are bidentate ligands in this catalytic asymmetric reaction.^[12] ³¹P NMR spectroscopic studies of a 1:1 mixture of **L1** and $\text{Cu}(\text{OTf})_2$ in CDCl_3 at room temperature were carried out. In the absence of $\text{Cu}(\text{OTf})_2$, the phosphorus signal of **L1** appeared at $\delta = +58.03$ as a sharp singlet (see Supporting Information). In contrast, a slightly upfield shift of the signal of the phosphorus atom connecting to the sulfur atom to $\delta = +57.83$ in **L1** was observed in the presence of $\text{Cu}(\text{OTf})_2$, suggesting coordination of the sulfur atom to the copper center and this signal broadened after 12 h, presumably due to the reduction of $\text{Cu}(\text{II})$ into $\text{Cu}(\text{I})$ (see Supporting Information). Secondly, in order to obtain

Table 2. Screening of chiral ligands in the asymmetric addition reaction.

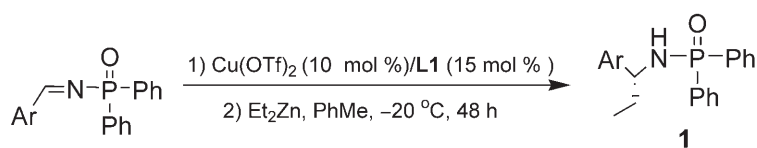


Entry	Copper salt [mol %]		Ligand [mol %]		Temp. [$^{\circ}\text{C}$]	Time [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	$\text{Cu}(\text{OTf})_2$	5	L2	5	0	48	89	67
2	$\text{Cu}(\text{OTf})_2$	5	L3	5	0	48	83	58
3	$\text{Cu}(\text{OTf})_2$	5	L4	5	0	48	93	79
4	$\text{Cu}(\text{OTf})_2$	10	L4	15	-20	48	80	88
5	$\text{Cu}(\text{OTf})_2$	5	L5	5	0	48	86	70
6	$\text{Cu}(\text{MeCN})_4\text{ClO}_4$	5	L1	7.5	0	48	79	48
7	$\text{Cu}(\text{MeCN})_4\text{ClO}_4$	10	L1	15	-20	48	77	61

^[a] Isolated yields.

^[b] Determined by chiral HPLC.

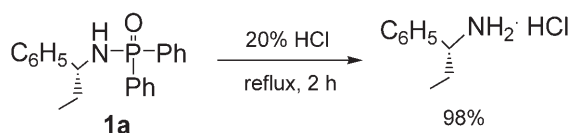
Table 3. Asymmetric addition reaction of ZnEt_2 to diphenylphosphinoyl-imines in the presence of chiral ligand **L1** and $\text{Cu}(\text{OTf})_2$ in toluene.



Entry	Ar	Product	Yield [%] ^[a]	ee [%] ^[b]	Configuration
1	C_6H_5	1a	87	92	<i>R</i>
2	<i>p</i> - MeC_6H_4	1b	83	98	<i>R</i>
3	<i>m</i> - MeC_6H_4	1c	87	91	<i>R</i>
4	<i>p</i> - MeOC_6H_4	1d	75	90	<i>R</i>
5	<i>p</i> - ClC_6H_4	1e	87	93	<i>R</i>
6	<i>p</i> - BrC_6H_4	1f	82	95	<i>R</i>
7	<i>o</i> - ClC_6H_4	1g	82	98	<i>R</i>
8	2,4- $\text{Cl}_2\text{C}_6\text{H}_3$	1h	82	95	<i>R</i>

^[a] Isolated yields.

^[b] Determined by chiral HPLC.



Scheme 3. Preparation of optically active amines.

evidence for the coordination of the nitrogen atom of the aniline moiety ($\text{ArNHCH}_2\text{CH}_3$) to the copper compound, ^{13}C NMR studies of the **L1**/ $\text{Cu}(\text{OTf})_2$ complex (1:1 mixture) in CDCl_3 were also carried out. In the absence of $\text{Cu}(\text{OTf})_2$, the carbon signals of the two carbons in the ethyl group of **L1** appeared at $\delta = 38.17$ and $\delta = 14.95$, but the two corresponding carbons signals appeared at $\delta = 38.88$ and $\delta = 14.76$ along with a new signal at $\delta = 13.40$ in the presence of $\text{Cu}(\text{OTf})_2$, respectively, and these signals broadened as well (see Supporting Information). These observations may indicate that $\text{Cu}(\text{OTf})_2$ can be potentially coordinated by the S, N atoms in the **L1** ligand.

Conclusions

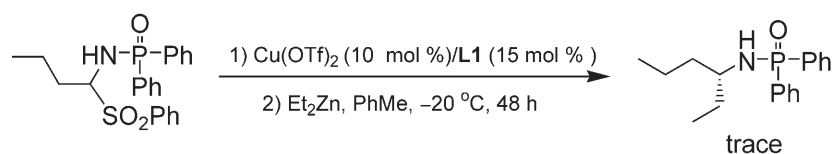
In conclusion, the catalytic asymmetric addition of diethylzinc to diphenylphosphinoyl-imines in generally

good yields and $>90\%$ enantioselectivities has been achieved using $\text{Cu}(\text{OTf})_2$ and easily available, stable axially chiral binaphthylthiophosphoramidate ligands (2'-ethylamino-[1,1']binaphthalenyl-2-yl)-thiophosphoramidic acid *O,O'*-diaryl esters. 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

General Remarks

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in CDCl_3 with tetramethylsilane (TMS) as internal standard; *J* values are in Hz. Mass spectra were recorded with an HP-5989 instrument. All of the solid compounds reported in this paper gave satisfactory CHN microanalyses as determined with a Carlo–Erba 1106 analyzer or HR-MS. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF₂₅₄ silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure. Enantiomeric ratios were determined by chiral HPLC analysis. Racemic products were synthesized



Scheme 4. Asymmetric addition reaction of ZnEt_2 to the sulfinic adduct of *N*-phosphinoylimine in the presence of chiral ligand **L1** and $\text{Cu}(\text{OTf})_2$ in toluene.

by addition of substrates with ethylmagnesium bromide (1.0 M in THF) at 0 °C.

Representative Experimental Procedure for the Synthesis of Ligands 1–5

To a solution of (*R*)-(+)-*N*-ethyl-1,1'-binaphthyl-2,2'-diamine (200 mg, 0.64 mmol) in THF (10.0 mL) was added dropwise *n*-butyllithium (1.12 mL, 1.8 mmol, 1.6 M solution in hexane) at –40 °C over 40 min, and the reaction mixture was stirred for 1 h at the same temperature. Then, *O,O*-diphenyl chlorothiophosphate (365 mg, 1.28 mmol) in 5.0 mL of THF was added dropwise and the reaction solution was slowly warmed to room temperature. After 2 h, THF was removed under vacuum. The residue was purified by alumina column chromatography to give the corresponding **ligand 1** (**L1**) as a colorless solid; yield: 316 mg (88 %).

General Procedure for the Cu(II)-Catalyzed Asymmetric Addition of Diethylzinc to Diphenylphosphinoyl-Imines

A solution of Cu(OTf)₂ (5.4 mg, 0.015 mmol) and ligand **L1** (12.6 mg, 0.0225 mmol) in dry toluene (3.0 mL) was stirred for 1 h at room temperature under an argon atmosphere. The diphenylphosphinoyl-imine of benzaldehyde (47 mg, 0.15 mmol) was added and the solution was stirred for a further 10 min, then Et₂Zn (0.45 mL, 0.45 mmol, 1.0 M solution in hexane) was added dropwise at –20 °C. The resulting mixture was stirred for 48 h at the same temperature and saturated aqueous NH₄Cl solution (10.0 mL) was added. After extraction with ethyl acetate (3 × 10.0 mL), the combined organic layers were dried over MgSO₄. The residue obtained upon removal of the 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*-diphenylphosphinoylamide **1a** as a colorless solid; yield: 43.5 mg (87 %).

Supporting Information

The spectroscopic and analytical data for the compounds shown in Tables 1, 2 and 3 and the detailed description of experimental procedures are included in supporting information for this article, which is also available from the author.

Acknowledgements

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology (04 JC14083), and the National Natural Science Foundation of China for financial support (20472096, 203900502 and 20272069).

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