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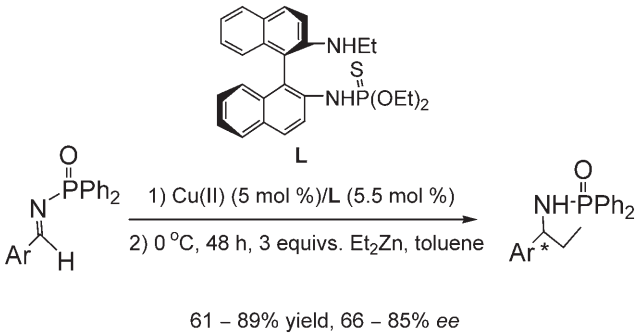
Abstract: The chiral binaphthylthiophosphoramide **L1** prepared from the reaction of *O,O*-diphenyl chlorothiophosphate with (*R*)-(+)-*N*-ethyl-1,1′-binaphthyl-2,2′-diamine was used as a catalytic chiral ligand in the copper(II) trifluoromethanesulfonate-promoted asymmetric addition of diethylzinc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

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

Introduction

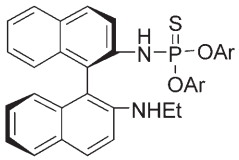
The efficient and asymmetric preparation of amines is one of the most promising methodologies in organic synthesis.[1] In addition to the asymmetric reduction of imines, the enantioselective addition of alkylmetals to imines is a convenient route to optically active amines. Among these, the chiral amine 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 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 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 thesyntheses 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-diphenylethenediamine.[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 binaphthylthiophosphoramide ligand, (2′-ethylamino-[1,1′]binaphthalenyl-2-yl)-thiophosphoramidic acid *O,O′*-diethyl ester (Scheme 1).[9g] On the basis of above results, we envisioned that

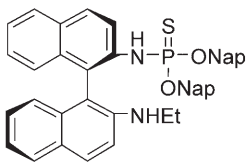


Scheme 1. Catalytic asymmetric addition with the chiral thiophosphoramide ligand.

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 binaphthylthiophosphoramide 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 binaphthylthiophosphoramides, (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).



L1: Ar = C_6H_5
L2: Ar = 4-MeC_6H_4
L3: Ar = 3-MeC_6H_4

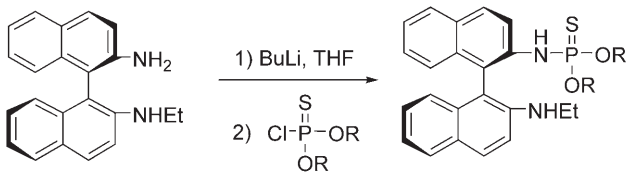


L4: α-Nap
L5: β-Nap

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).

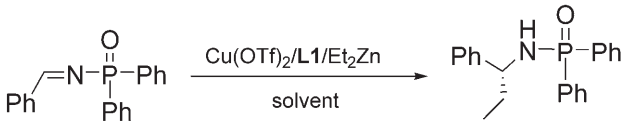


L1: R = C_6H_5, 88%.
L2: R = 4-MeC_6H_4, 75%.
L3: R = 3-MeC_6H_4, 56%.
L4: R = α-Nap, 79%.
L5: R = β-Nap, 72%.

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 $ZnEt_2$ to diphenylphosphinoyl-imine catalyzed by the copper salt $Cu(OTf)_2$ and chiral ligand **L1**.



1a

Entry	Solvent	Temp. [°C]	**L1** [mol%]	$Cu(OTf)_2$ [mol%]	Time [h]	Yield [%][a]	*ee* [%][b]
1	CH_2Cl_2	20	5	5	48	trace	–
2	CH_3CN	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.

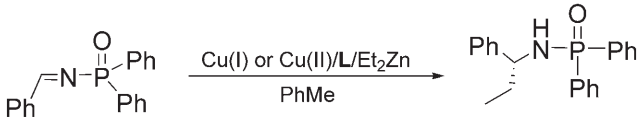
to give the addition product **1a** in 78% yield and 82% *ee* (Table 1, entry 5). Lowering the temperature to −20 °C, the yield of the addition product **1a** was 67% with 89% *ee* (Table 1, entry 6). However, when the reaction was carried out at −20 °C, the reaction was sluggish and a prolonged reaction 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 $Cu(OTf)_2$, 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 $Cu(OTf)_2$ (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 $Cu(OTf)_2$ (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 $Cu(CH_3CN)_4ClO_4$ 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). $Cu(OTf)_2$ was therefore utilized in this study due to its greater air stability and associated convenience in handling. Thus, the best reaction conditions are using $Cu(OTf)_2$ (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 *ee*s 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,[4e] 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 binaphthyldiphenylphosphoramide ligand showed no enantioselectivity for this kind of addition reaction.[9] We believe that this family of binaphthyldiphenylthiophosphoramides **L1**–**L5** are bidentate ligands in this catalytic asymmetric reaction.[12] ^{31}P NMR spectroscopic studies of a 1:1 mixture of **L1** and $Cu(OTf)_2$ in $CDCl_3$ at room temperature were carried out. In the absence of $Cu(OTf)_2$, 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 $Cu(OTf)_2$, suggesting coordination of the sulfur atom to the copper center and this signal broadened after 12 h, presumably due to the reduction of Cu(II) into Cu(I) (see Supporting Information). Secondly, in order to obtain

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

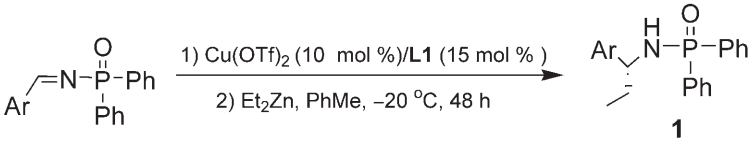


1a

Entry	Copper salt [mol%]		Ligand [mol%]		Temp. [°C]	Time [h]	Yield [%][a]	*ee* [%][b]
1	$Cu(OTf)_2$	5	**L2**	5	0	48	89	67
2	$Cu(OTf)_2$	5	**L3**	5	0	48	83	58
3	$Cu(OTf)_2$	5	**L4**	5	0	48	93	79
4	$Cu(OTf)_2$	10	**L4**	15	−20	48	80	88
5	$Cu(OTf)_2$	5	**L5**	5	0	48	86	70
6	$Cu(MeCN)_4ClO_4$	5	**L1**	7.5	0	48	79	48
7	$Cu(MeCN)_4ClO_4$	10	**L1**	15	−20	48	77	61

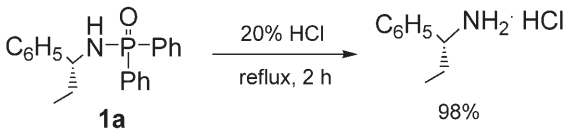
[a] Isolated yields.
[b] Determined by chiral HPLC.

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



Entry	Ar	Product	Yield [%][a]	*ee* [%][b]	Configuration
1	C_6H_5	**1a**	87	92	*R*
2	*p*-MeC_6H_4	**1b**	83	98	*R*
3	*m*-MeC_6H_4	**1c**	87	91	*R*
4	*p*-$MeOC_6H_4$	**1d**	75	90	*R*
5	*p*-ClC_6H_4	**1e**	87	93	*R*
6	*p*-BrC_6H_4	**1f**	82	95	*R*
7	*o*-ClC_6H_4	**1g**	82	98	*R*
8	2,4-$Cl_2C_6H_3$	**1h**	82	95	*R*

[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 ($ArNHCH_2CH_3$) to the copper compound, ^{13}C NMR studies of the **L1**/$Cu(OTf)_2$ complex (1:1 mixture) in $CDCl_3$ were also carried out. In the absence of $Cu(OTf)_2$, 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 $Cu(OTf)_2$, respectively, and these signals broadened as well (see Supporting Information). These observations may indicate that $Cu(OTf)_2$ can be potentially coordinated by the S, N atoms in the **L1** ligand.

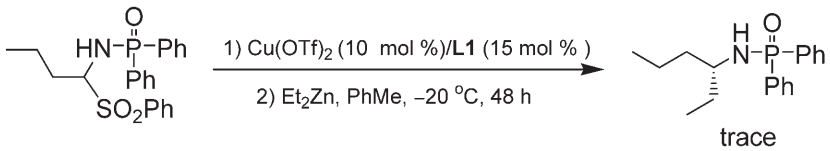
Conclusions

In conclusion, the catalytic asymmetric addition of diethylzinc to diphenylphosphinoyl-imines in generally good yields and $>90\%$ enantioselectivities has been achieved using $Cu(OTf)_2$ and easily available, stable axially chiral binaphthylthiophosphoramide 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 deetrmined 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 GF_{254} 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 $Cu(OTf)_2$ 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 Et_2Zn (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 aqueousNH_4Cl solution (10.0 mL) was added. After extraction with ethyl acetate (3 × 10.0 mL), the combined organic layers were dried over $MgSO_4$. 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-*p*henylpropyl)-*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.

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