Enantioselective Conjugate Addition of Dialkylzinc and Diphenylzinc to Enones Catalyzed by a Chiral Copper(I) Binaphthylthiophosphoramide or Binaphthylselenophosphoramide Ligand System

Min Shi,* Chun-Jiang Wang, and Wen Zhang[a]

Abstract: The enantioselective conjugate addition of dialkylzinc or diphenylzinc to enones was catalyzed by a copper(I)-axially chiral binaphthylthiophosphoramide or binaphthylselenophosphoramide ligand system at room temperature (20 °C) or 0 °C, affording the Michael adducts in high yields with excellent *ee* for cyclic and acyclic enones. The enantioselectivity and reaction rate achieved here are one of the best results yet for the Cu-catalyzed conjugate addition to enones. It was revealed that this series of chiral phosphoramides was a novel type of S,N-bidentate ligands on the basis of ^{31}P NMR and ^{13}C NMR spectroscopic investigations. The mechanism of this asymmetric conjugate addition system has been investigated as well. We found that the acidic proton of phosphoramide in these chiral ligands play a significant role in the formation of the active species. A bimetallic catalytic process has been proposed on the basis of previous literature. The linear effect of product *ee* and ligand *ee* further revealed that the active species is a monomeric Cu^{I} complex bearing a single ligand [Cu^{I}:ligand 1:1].

Keywords: asymmetric synthesis · chiral ligands · conjugate addition reaction · enantioselectivity

Introduction

The conjugate addition of various organometallic reagents to α,β-unsaturated carbonyl compounds is an important process for C–C bond formation in organic synthesis.[1] Many chiral auxiliaries and stoichiometric reagents have been described during the last few years, which allow enantioselective addition.[2] A prominent position in this rapidly expanding field is occupied by the copper-catalyzed and chiral-ligand-accelerated conjugate addition of organozinc reagents originally introduced and rendered practical by Alexakis, Feringa and Pfaltz.[3] In particular, chiral phosphoramidites,[4a–c] phosphites,[4d–k] phosphines,[4l] aminophosphanes,[4m–o] sulfonamides,[4p,q] peptide-based phosphines[4r] and diaminocarbene compounds[4s–u] were used as ligands in the addition to cyclic enones with very good enantioselectivities. Most of them are derived from axially chiral binaphthalenediol, and are trivalent phosphorus ligands, which are very sensitive to ambient air and moisture. However, the development of an air-stable and all-encompassing ligand effective in the conjugate addition of dialkylzincs to all of the five-, six-, and seven-membered cyclic enones and acyclic enones has been less successful.[4q,5]

Recently, we are interested in the syntheses and applications of novel ligands based on a series of chiral diamines.[6] Axially chiral binaphthalenediamine (BINAM)[7] has been much less popular in contrast to the widely used other axially chiral binaphthalene skeletons such as 1,1′-bi-2-naphthol (BINOL) and 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) and other chiral diamines such as 1,2-cyclohexanediamine and 1,2-diphenylethylenediamine in the field of catalytic asymmetric synthesis.[8] Researches in our laboratory, involving novel axially chiral binaphthylthiophosphoramide ligands **L1**–**L7** derived from axially chiral binaphthalenediamine (BINAM), has led to the development of AgOTf-promoted enantioselective allylation of aldehydes with allyltributyltin (up to 98% *ee*),[9] and Cu^{I}-promoted catalytic asymmetric addition of diethylzinc to sulfonylimines (up to 93% *ee*)[10] and Cu^{II}-promoted catalytic asymmetric addition of diethylzinc to diphenylphosphinoylimines (up to 85% *ee*).[11] The effectiveness of chiral binaphthylthiophosphoramide ligands **L1**–**L7** in the aforementioned programs led us to investigate their utilities in other asymmetric C–C bond forming transformations.

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. ^{1}H and ^{13}C NMR spectral and analytic data for **L1**–**L10** and conjugate addition products and experimental details.

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Herein, we wish to report the results of our studies on the catalytic enantioselective conjugate addition of dialkylzinc or diphenylzinc to enones. The method described here allows efficient, catalytic and highly enantioselective functionalization of not only six- and seven-membered cyclic enones, but also of cyclopentenone, acyclic aromatic enones and aliphatic enones.[12]

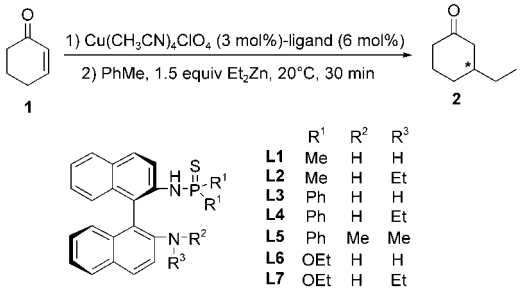
Results and Discussion

Ligand survey: The chiral S,N-ligands **L1**–**L7** are easily obtained from (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine only in 1–2 steps in very high yields through lithiation of the relevant diamines with butyllithium and then, phosphorylation with dialkyl-, dialkoxyl- or diarylthiophosphoryl chloride (see Supporting Information).[10] In addition, they are rather stable and can be easily recovered from the reaction mixture in 80–85% through column chromatography after usual workup and can be reused in this asymmetric reaction without loss of enantioselectivity.

By using 2-cyclohexen-1-one (**1**) as the substrate and diethylzinc as the Michael addition reagent, we examined the conjugate addition reaction in the presence of $Cu(CH_3CN)_4ClO_4$ and ligands **L1**–**L7** to select the optimal ligand.[13] The chiral catalyst was in situ prepared by stirring a solution of the chiral thiophosphoramide ligand and $Cu(CH_3CN)_4ClO_4$ in toluene in a molar ratio of 2:1 at room temperature. Without the isolation of catalyst, the reaction was carried out by adding 2-cyclohexen-1-one (**1**) into the catalyst solution at the same temperature, followed by the addition of diethylzinc and treatment with 1 N HCl at the end of reaction. The desired 3-ethylcyclohexanone (**2**) was afforded. The enantioselectivity of product **2** was determined by chiral GC. The absolute configuration was established by comparing the sign of optical rotation of the product with that reported in the literature.[4q] The screening of ligands revealed that in our ligand system, all of the asymmetric reactions can be finished very quickly within 30 min, and the product **2** was formed in high yields and the achieved enantioselectivities depending on the employed chiral ligands. The results were summarized in Table 1.

As can be seen from Table 1, **L2** and **L4** are the best chiral ligands for this enantioselective conjugate addition reaction with 94% *ee* (90% yield) and 92% *ee* (95% yield) in toluene at room temperature (20 °C), respectively (Table 1, entries 2 and 4). It is noteworthy that a clear trend in favor of N-substituted chiral thiophosphoramide ligands can be delineated from the results detailed in Table 1. The chiral induction effect of the N-ethyl chiral ligands **L2**, **L4**, and **L7** is generally better than that of those N-unsubstituted chiral ligands **L1**, **L3**, and **L6** (Table 1, entries 1, 3, 6 and 2, 4, 7). However, chiral ligand **L5** having a N,N-dimethyl group gave the conjugate addition product in low *ee* with opposite absolute configuration under the same conditions (Table 1, entry 5). These results suggest that the substituents of amino group in binaphthalenediamine skeleton play an important role in this asymmetric conjugate addition reaction. In addition, since in the absence of ligand, this addition reaction is sluggish, the enantioselective conjugate addition by our catalytic ligand system is apparently a ligand-accelerated process.[14]

Table 1. Asymmetric 1,4-addition reaction of 2-cyclohexen-1-one with $ZnEt_2$ catalyzed by $Cu(CH_3CN)_4ClO_4$ and chiral binaphthylthiophosphoramide ligands at room temperature.



Entry	Ligand	Yield[a] [%]	*ee*[b] [%]	Config.[c]
1	**L1**	92	71	*R*
2	**L2**	90	94	*R*
3	**L3**	88	75	*R*
4	**L4**	95	92	*R*
5	**L5**	64	16	*S*
6	**L6**	72	78	*R*
7	**L7**	87	81	*R*

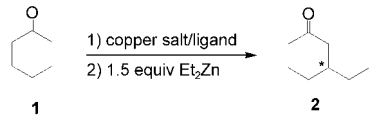
[a] Isolated yield. [b] Determined by chiral GC. [c] Determined by the sign of the specific rotation.

Reaction condition optimization: Encouraged by the obtained results described above, we then investigated the effects of solvent, catalyst precursor, temperature and the ratio of ligand to copper salt to optimize the reaction conditions. The results were summarized in Table 2.

The catalytic ability of $Cu(CH_3CN)_4ClO_4$/**L4** complex in representative solvents was determined by using the standard procedure. The solvent survey revealed a dramatic solvent effect. Toluene was the optimal solvent for this transformation, providing the product of asymmetric conjugate addition reaction in high yield with high enantioselectivity (Table 2, entry 4). In solvents containing a precoordinative oxygen atom such as THF and Et_2O, the reaction not only became sluggish but also afforded the product in lower yield with lower enantionselectivities (Table 2, entries 2 and 3). Dichloromethane was also found to give similar results to those of Et_2O, although the reaction in CH_2Cl_2 proceeded more smoothly than that in Et_2O (Table 2, entry 1).

Besides $Cu(CH_3CN)_4ClO_4$/**L4** complex, other copper salt/**L4** complexes prepared in situ by stirring a solution of **L4** and the corresponding copper salts were also screened in this asymmetric reaction. Among the examined copper salts, the results of catalytic ability using Cu^I salts as the precursors were generally better than that using Cu^{II} salt as precursor because the $Cu(OTf)_2$/**L4** complex provided the product in moderate yield and enantioselectivity under the same conditions (Table 2, entries 4, 5, 6 and 7). Our results showed that $Cu(CH_3CN)_4BF_4$ was the same excellent catalyst precursor as $Cu(CH_3CN)_4ClO_4$, which gave high yield of the asymmetric conjugate addition reaction in even a little higher *ee* (Table 2, entries 4 and 5).

Table 2. Effects of solvents, copper salts, reaction temperature and the ratio of copper salt to ligand on the asymmetric 1,4-addition reaction of 2-cyclohexen-1-one with $ZnEt_2$.



1 2

Entry	Copper salt	Solvent	Ligand	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]
1	$Cu(MeCN)_4ClO_4$	CH_2Cl_2	**L4**	20	3	70	55
2	$Cu(MeCN)_4ClO_4$	Et_2O	**L4**	20	20	89	51
3	$Cu(MeCN)_4ClO_4$	THF	**L4**	20	6	48	12
4	$Cu(MeCN)_4ClO_4$	PhMe	**L4**	20	0.5	95	92
5	$Cu(MeCN)_4BF_4$	PhMe	**L4**	20	0.5	94	93
6	$CuOTf\cdot{}^1/_2C_6H_6$	PhMe	**L4**	20	0.5	95	88
7	$Cu(OTf)_2$	PhMe	**L4**	20	0.5	87	68
8	$Cu(MeCN)_4BF_4$	PhMe	**L4**	0	0.5	89	89
9	$Cu(MeCN)_4BF_4$	PhMe	**L4**	−20	6	92	45
10	$Cu(MeCN)_4BF_4$	PhMe	**L2**	0	0.5	95	97
11[c]	$Cu(MeCN)_4BF_4$	PhMe	**L4**	20	0.5	90	91
12[d]	$Cu(MeCN)_4BF_4$	PhMe	**L4**	20	0.5	95	89
13[e]	$Cu(MeCN)_4BF_4$	PhMe	**L4**	20	0.5	91	92
14[f]	$Cu(MeCN)_4BF_4$	PhMe	**L4**	20	6	80	83
15[g]	$Cu(MeCN)_4BF_4$	PhMe	**L4**	20	0.5	95	94

[a] Isolated yield. [b] Determined by chiral GC. [c] Copper salt is 3 mol% and ligand is 3 mol%. [d] Copper salt is 3 mol% and ligand is 9 mol%. [e] Copper salt is 0.5 mol% and ligand is 1.0 mol%. [f] Copper salt is 0.1 mol% and ligand is 0.2 mol%. [g] Recovered **L4** was used.

Interestingly, when **L4** was used as a chiral ligand and $Cu(CH_3CN)_4BF_4$ as a catalytic precursor, lowering the temperature from +20 to 0 and −20 °C, the *ee* of the product **2** remarkably decreased to 89 and 45%, respectively (Table 2, entries 8 and 9). However, when **L2** was used as a chiral ligand, the optimal reaction temperature for obtaining the highest enantioselectivity (97%) is 0 °C (Table 1, entry 2 and Table 2, entry 10).

The effect of the ratios of **L4** to $Cu(CH_3CN)_4BF_4$ on enantioselectivity was also examined. The catalyst prepared from $Cu(CH_3CN)_4BF_4$:**L4** 1:1 and 1:2 showed the very similar results on yields and enantioselectivities (Table 2, entries 5 and 11). The addition of more than two equivalents of ligand had little effect on the enantioselectivity (Table 2, entry 12). In addition, the reaction was completed in 30 min without loss of yield and *ee* even with only 0.5 mol% of copper salt and 1 mol% of ligand (Table 2, entry 13). But when Cu^I:chiral ligand was reduced to 0.1 mol%:0.2 mol%, the reaction became sluggish and the achieved *ee* became lower under the same conditions (Table 2, entry 14). Moreover, the recovered **L4**, isolated from the reaction mixture by column chromatography after usual workup, gave the addition product in the similar yield and enantioselectivity (Table 2, entry 15). The best reaction conditions are using $Cu(CH_3CN)_4BF_4$ or $Cu(CH_3CN)_4ClO_4$ as a catalytic precursor and **L4** or **L2** as a chiral ligand in toluene at room temperature or 0 °C, the ratio of chiral ligand to Cu^I salt is 1:1 or 1:2. The reaction can be completed within 30 min under these optimized conditions.

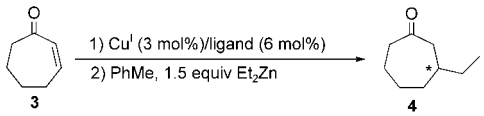
Thus, based on the abovementioned results, it is very clear that the asymmetric conjugate addition reaction can be carried out under mild conditions with high enantioselectivity in our catalytic system, which offers another advantage of our chiral thiophosphoramide ligands over most of other ligands that normally needed a lower temperature.[3,4a–f] Furthermore, our chiral thiophosphoramide ligand system is quite stable, easily available, recoverable and reusable in asymmetric catalysis.

Substrate generality: Until now, the most widely studied substrate for copper-promoted enantioselective conjugate addition reaction has been 2-cyclohexen-1-one.[3,4d–f] For most of the chiral ligands reported in literature, higher enantioselectivities can be obtained only when six or larger than six-membered cyclic enones are used as the substrates. 2-Cyclopenten-1-one and acyclic enones are the more problematic substrates, which usually afforded the addition product in lower enantioselectivity than 2-cyclohexen-2-one by means of the same chiral ligand. But recently Zhang,[4n] Hoveyda,[4r,5a–c] Alexakis,[4b,5d] and Pflatz[3b,4d] made significant progresses on the enantioselective conjugate addition for these two kinds of substrates.

The reactivity of larger than six-membered ring enones is similar to that of 2-cyclohexen-1-one in our asymmetric catalytic system as well. Under the optimized reaction conditions, 2-cyclohepten-1-one (**3**) also gave the corresponding conjugate addition product **4** in very high yield and *ee* within 30 min at room temperature, especially when **L2** was used as a chiral ligand at room temperature, the enantioselectivity of the corresponding product **4** was up to 97% (Table 3, entry 2).

Then, we turned our attention to the most problematic substrate cyclopentenone **5**. The performance was similar to

Table 3. Asymmetric 1,4-addition reaction of 2-cyclohepten-1-one with $ZnEt_2$ catalyzed by $Cu(CH_3CN)_4BF_4$ and chiral phosphoramide ligands.



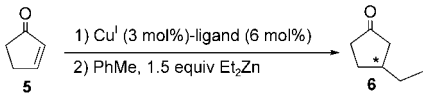
3 4

Entry	Ligand	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]	Config.[c]
1	**L4**	20	0.5	94	91	*R*
2	**L2**	20	0.5	93	97	*R*
3	**L2**	0	0.5	93	95	*R*

[a] Isolated yield. [b] Determined by chiral GC. [c] Determined by the sign of the specific rotation.

that of 2-cyclohexen-1-one or 2-cyclohepten-1-one as that mentioned above. To our great delight, we found that in our catalytic system, the desired 3-ethylcyclopentanone **6** was produced within 30 min in good yield (75%) and excellent enantioselectivity (up to 98%) (Table 4, entry 3). It is worth noting that all the results were obtained at room temperature or 0°C, which are the milder reaction conditions than those reported in the previous literature.[3,4d,q]

Table 4. Asymmetric 1,4-addition reaction of 2-cyclopenten-1-one with $ZnEt_2$ catalyzed by $Cu(CH_3CN)_4BF_4$ and chiral phosphoramide ligands.



5 6

Entry	Ligand	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]	Config.[c]
1	**L4**	20	0.5	62	85	*R*
2	**L2**	20	0.5	73	96	*R*
3	**L2**	0	0.5	75	98	*R*

[a] Isolated yield. [b] Determined by chiral GC. [c] Determined by the sign of the specific rotation.

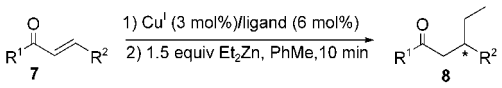
for asymmetric addition of diethylzinc to chalcone, several other acyclic aromatic enones **7** with various substituents on the benzene ring were successfully transformed to the corresponding addition products **8** in excellent yields and extremely high *ee* (95–97%) at room temperature within 10 min (Table 5, entries 5–9). The enantioselectivity achieved was not affected by the electron effect of the substituents on the benzene rings in the employed substrates. The recovered **L4**, isolated from the reaction mixture by column chromatography after usual workup, gave the addition product in the similar yield and enantioselectivity (Table 5, entry 10). Therefore, our catalytic system is the most efficient system for various acyclic aromatic enones so far.[4n,q,5a–d]

This highly catalytic enantioselective conjugate addition reaction system also can be applied to a variety of acyclic aliphatic enones, which have been much less studied despite the fact that they can provide wider applications in the synthesis of biologically active compounds.[3,5] The results were summarized in Table 6. Thus, as can be seen from entry 1 in Table 6, treatment of 3-octen-2-one **9a** with diethylzinc by using **L4** as a chiral ligand at room temperature led to generate the desired addition product only in 30% *ee* and 77% yield (Table 6, entry 1). However, by using **L2** as a chiral ligand under the same conditions, the enantioselectivity was remarkably increased to 93% *ee* within 30 min (Table 6, entry 3). We also found that the yield and enantioselectivity were slightly affected by the sequence of addition of diethylzinc and substrate to the reaction solution of the Cu^I/ligand mixture because treatment a solution of Cu^I/ligand mixture with diethylzinc before the addition of enone led to a little higher yield and *ee*, which is similar to the case reported by Hoveyda using peptide-based phosphines as ligands

Encouraged by the results obtained especially for 2-cyclopenten-1-one **5**, we next investigated a variety of acyclic aromatic enones **7** such as chalcone and its derivatives to probe their behavior by the current catalytic system and under the similar conditions. To the best of our knowledge, there is only one case that 95–98% *ee* was obtained for this kind of substrate, in which the reaction must be performed at −20°C for 48 h.[4n]

Chalcone **7a** was firstly selected as the substrate for testing the reaction conditions. The results using chiral thiophosphoramide ligands **L2** and **L4** were summarized in Table 5. We were delightful to find that the reactions were also finished within 10 min at room temperature in almost quantitative yields (Table 5, entries 1–4). This should be the most efficient catalytic system for conjugate addition reaction of acyclic aromatic enones. Although ligand **L2** showed a little higher asymmetric induction than **L4** for cyclic enones, the opposite trend was observed for chalcone. By using **L2** as a chiral ligand, the enantioselectivity of the asymmetric conjugate addition reaction product **8a** was 87% *ee* at 0°C or room temperature. However, up to 96% *ee* was obtained when **L4** was used as a chiral ligand under the same conditions (Table 5, entries 1, 2 and 3). We can not exactly explain the above results at the present stage, but we can postulate that it is presumably caused by the potential π–π interaction of aromatic rings between the aromatic substrate **7a** and the ligand **L4**, which is beneficial to the improvement of the enantioselectivity. Under the optimal conditions

Table 5. Asymmetric 1,4-addition reaction of chalcone and its derivatives with $ZnEt_2$ catalyzed by $Cu(CH_3CN)_4BF_4$ and ligand **L4** or **L2**.



7 8

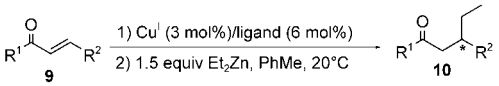
Entry	R^1	R^2	Substrate	Ligand	T [°C]	Yield[a] [%]	*ee*[b] [%]	Config.[c]
1	C_6H_5	C_6H_5	**7a**	**L2**	20	97	87	*S*
2	C_6H_5	C_6H_5	**7a**	**L2**	0	96	87	*S*
3	C_6H_5	C_6H_5	**7a**	**L4**	20	98	96	*S*
4[e]	C_6H_5	C_6H_5	**7a**	**L4**	20	95	96	*S*
5	1-$C_{10}H_7$	C_6H_5	**7b**	**L4**	20	98	96	−[d]
6	C_6H_5	*p*-BrC_6H_4	**7c**	**L4**	20	99	96	+[d]
7	C_6H_5	*p*-$MeOC_6H_4$	**7d**	**L4**	20	98	96	*S*
8	*p*-BrC_6H_4	C_6H_5	**7e**	**L4**	20	97	95	−[d]
9	p-$MeOC_6H_4$	C_6H_5	**7f**	**L4**	20	87	97	*S*
10[f]	C_6H_5	C_6H_5	**7a**	**L4**	20	98	97	*S*

[a] Isolated yield. [b] Determined by chiral HPLC. [c] The absolute configuration was assigned by the optical rotation. [d] Sign of the optical rotation. [e] $Cu(CH_3CN)_4BF_4$ is 3 mol% and **L4** is 3 mol%. [f] Recoverd **L4** was used.

(Table 6, entries 2 and 3).[5] For other substrates described above, no such phenomenon could be observed.

In order to further probe the steric effects of the acyclic aliphatic enones on this catalytic asymmetric conjugate addition system, we synthesized several aliphatic acyclic enones **9b–e** with sterically bulky substituents at the side of either double bond or carbonyl group.[15] As shown in entries 3–6 of Table 6, the enantioselectivity, yield and reaction rate decreased gradually along with the enhancement of the steric hindrance of the substituent group in the substrates, but for acyclic enones **9b–d**, the conjugate addition products (**10b–d**) were still obtained in 82–92% yields with 80–90% *ee* (Table 6, entries 4–6). Only for enone **9e** having the sterically bulkiest *tert*-butyl group beside the carbonyl group, the desired addition product **10e** was detected in trace under the same conditions (Table 6, entry 7). Therefore, our chiral thiophosphoramide ligand system is also very effective for some aliphatic acyclic enones.

Table 6. Asymmetric 1,4-addition reaction of acyclic aliphatic enones with $ZnEt_2$ catalyzed by $Cu(CH_3CN)_4BF_4$ and ligand **L4** or **L2**.



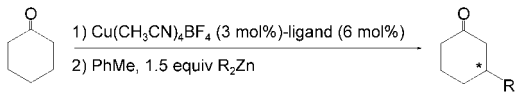
9 **10**

Entry	R^1	R^2	Substrate	Ligand	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1	Me	*n*-butyl	**9a**	**L4**	0.5	77	30
2	Me	*n*-butyl	**9a**	**L2**	0.5	80	92
3[c]	Me	*n*-butyl	**9a**	**L2**	0.5	89	93
4[c]	Me	isopropyl	**9b**	**L2**	1	82	90
5[c]	isobutyl	*n*-butyl	**9c**	**L2**	1	92	85
6[c]	isopropyl	*n*-butyl	**9d**	**L2**	3	92	80
7[c]	*tert*-butyl	*n*-butyl	**9e**	**L2**	8	trace	–

[a] Isolated yield. [b] Determined by chiral GC. [c] Diethylzinc was first added into the reaction mixture before the addition of the corresponding enone.

Scope of organozinc reagents: Organozinc compounds represent ideal reagents for copper-catalyzed enantioselective Michael addition because of their low reactivity towards the substrate in the absence of a copper catalyst. Moreover, one of the major advantages of dialkylzinc reagents is their functional compatibility. This variation of the diorganozinc reagent allows for high synthetic versatility. Among the asymmetric conjugate addition reaction of dialkylzinc reagents to enones catalyzed by copper salt, diethylzinc is nearly always the alkylating agent probed. Dimethylzinc and diphenylzinc have seldom been used, which are much less reactive and generally need longer reaction times than diethylzinc.[4f] In order to clarify the scope and limitations of organozinc reagents in our Cu^I/thiophosphoramide ligand system. We examined the asymmetric conjugate addition reaction of dimethylzinc and diphenylzinc to 2-cyclohexen-1-one (**1**) in the presence of **L2** or **L4** under the optimized conditions. The results were shown in Table 7. As can be seen from Table 7, the relatively less reactive Me_2Zn and Ph_2Zn can be employed in the asymmetric conjugate addition of **1** efficiently with appreciable asymmetric induction in our catalytic system as well. By using **L2** as a chiral ligand, transformation with Me_2Zn delivered the desired product in 71% yield with 87% *ee* at room temperature and in 77% yield with 85% *ee* at 0°C, respectively within 4–6 h (Table 7, entries 1 and 2). Using **L4** as a chiral ligand, similar results were obtained (Table 7, entries 3 and 4). For Ph_2Zn in the presence of **L2** and **L4**, the reaction was much more sluggish, but still gave the product in almost quantitative yield with up to 89% *ee*, which was better than the result reported in the literature (Table 7, entries 5 and 6).[16] Thus, our catalytic system presented here is not limited to diethylzinc and should be suitable to a broad spectrum of organozinc reagents.

Table 7. The asymmetric 1,4-addition reaction of 2-cyclohexen-1-one with ZnR_2 catalyzed by $Cu(CH_3CN)_4BF_4$ and chiral binaphthylthiophosphoramide ligands.



1 **11**

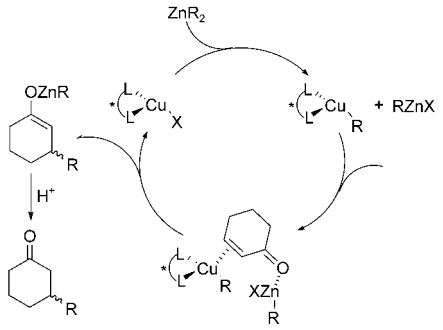
Entry	Ligand	R	Product	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]	Config.[c]
1	**L2**	Me	**11a**	0	6	77	85	*R*
2	**L2**	Me	**11a**	20	4	71	87	*R*
3	**L4**	Me	**11a**	0	6	73	79	*R*
4	**L4**	Me	**11b**	20	4	70	85	*R*
5	**L2**	Ph	**11b**	0	8	97	89	*R*
6	**L4**	Ph	**11b**0	8	98	77	*R*	

[a] Isolated yield. [b] Determined by chiral HPLC or GC. [c] Determined by the sign of the specific rotation.

Reaction mechanism: According to the previous literature,[2f] the proposed pathway for the catalytic asymmetric conjugate addition is shown in Scheme 1. The mechanism of the reaction calls for the transfer of an alkyl group from zinc to a chiral copper complex, which is subsequently capable of delivering the alkyl group to the enone enantioselectively.

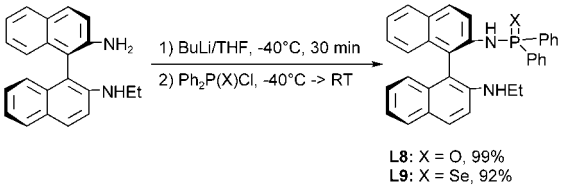
While, a mechanistic insight should be given to explain why this type of ligands combined with Cu^I salt can be so effective in the asymmetric conjugate addition reaction with dialkylzinc or diphenylzinc. The first question that we need to elucidate is the potentially coordinated atoms of the chiral phosphoramide ligands to Cu^I in our catalytic system.

Although the real active species is not yet fully understood in this catalytic addition reaction, we believe that the



Scheme 1.

series of phosphoramides **L1–L7** are bidentate ligands in this catalytic asymmetric reaction. It is well known that sulfur atom can strongly coordinate to late transition metal[17] and Cu^I compounds have a greater affinity for soft ligands (olefins, sulfur, phosphorus and selenium atoms).[18] In order to further verify this speculation, we synthesized diphenylphosphoramide ligand **L8** and diphenylselenophosphoramide ligand **L9** using the same way as that described above and applied them in the asymmetric conjugate addition reaction of diethylzinc to cyclic and acyclic enones (Scheme 2).

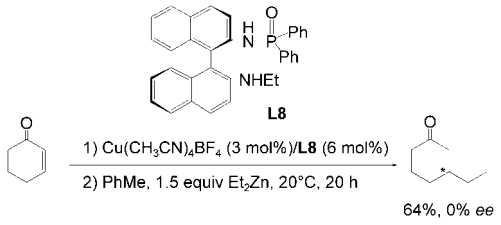


Scheme 2.

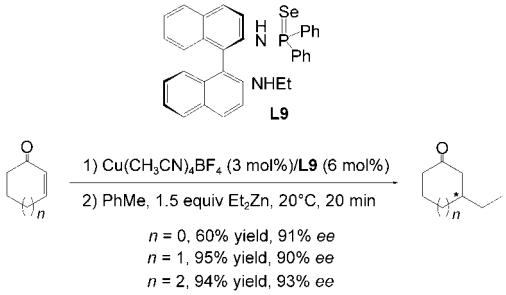
As a result, it was found that the sulfur atom on phosphorus was crucial for this catalytic asymmetric reaction to be so effective because the corresponding axially chiral diphenylphosphoramide ligand **L8** showed no enantioselectivity for this conjugate addition reaction under the same conditions.[19] The reason of this phenomenon maybe due to that oxygen atom is a harder ligand than sulfur atom (Scheme 3). It can not smoothly coordinate to softer metal center such as Cu^I center according to the soft/hard acid and base theory.

On the other hand, the selenium atom is thought to have the great affinity to Cu^I compounds according to the soft/hard acid and base theory.[20] Consequentially, we believe that chiral ligand **L9** should indicate the similar catalytic abilities as those of **L4**. The results were shown in Scheme 4 and Table 9.

As can be seen from the Scheme 4, when using **L9** as a chiral ligand under the optimal reaction conditions, excellent



Scheme 3.

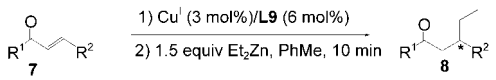


Scheme 4.

enantioselectivities and moderate to high yields were also obtained not only for 2-cyclohexen-1-one and 2-cyclohepten-1-one but also for 2-cyclopenten-1-one within 20 min at room temperature (20 °C), which are very similar to the transformations using **L4** as a chiral ligand. The reaction rates even became faster, because the reaction time could be reduced to 20 min under the same conditions. In addition, the asymmetric conjugate addition reactions of chalcone and its derivatives using chiral ligand **L9** provided the excellent enantioselectivies and quantitative yields of the corresponding adducts within 10 min at room temperature (20 °C) as well (Table 8, entries 1, 2 and 4–7). The recovered ligand **L9**, isolated from the reaction mixture by column chromatography after usual workup, gave the addition product in the similar yield and enantioselectivity (Table 8, entry 3). To the best of our knowledge, this is the first case for a chiral selenophosphoramide ligand used in the asymmetric conjugate addition to enones to achieve excellent *ee* in good yields.

In order to get more information on the coordination of thiophosphoramide and selenophosphoramide ligands to

Table 8. The asymmetric 1,4-addition reaction of chalcone and its deriveatives with $ZnEt_2$ catalyzed by $Cu(CH_3CN)_4BF_4$ and ligand **L9**.



Entry	R^1	R^2	Substrate	Yield [%][a]	*ee* [%][b]	Config.[c]
1	C_6H_5	C_6H_5	**7a**	98	96	*S*
2	1-$C_{10}H_7$	C_6H_5	**7b**	95	96	*S*
3[e]	1-$C_{10}H_7$	C_6H_5	**7b**	98	96	–[d]
4	C_6H_5	*p*-BrC_6H_4	**7c**	99	96	+[d]
5	C_6H_5	*p*-$MeOC_6H_4$	**7d**	98	96	*S*
6	*p*-BrC_6H_4	C_6H_5	**7e**	97	95	–[d]
7	*p*-$MeOC_6H_4$	C_6H_5	**7f**	87	97	*S*

[a] Isolated yield. [b] Determined by chiral HPLC. [c] The absolute configuration was assigned by the optical rotation. [d] Sign of the optical rotation. [e] Recovered **L9** was used.

Cu^I, the ^{31}P NMR spectra measurements of ligands **L2**, **L4**, **L7** and **L9** were carried out in the absence or presence of Cu^I salt. The apparent changes of chemical shift were observed through comparing the corresponding ^{31}P NMR spectra of chiral ligands **L2**, **L4**, **L7** and **L9** with those in the presence of $Cu(CH_3CN)_4BF_4$ (1:1 mixture) in $CDCl_3$ at room temperature. In the absence of $Cu(CH_3CN)_4BF_4$, the phosphorus signal of **L2**, **L4**, **L7** and **L9** appeared at δ 56.68, 53.28, 66.57 and 50.40, respectively. While, the downfield shift of phosphorus atom connected to the sulfur or selenium atom at δ 62.37 55.52 and 57.36 for **L2**, **L4** and **L9** as well as upfield shift at δ 64.99 for **L7** were observed in the presence of $CuBF_4$. While, for **L8** (P=O), no chemical shift was observed (Table 9, entries 1 and 2) (see also Supporting Information). These results clearly suggest that the sulfur or selenium atom on the phosphorus atom indeed coordinate to Cu^I-metal center.

Table 9. The ^{31}P NMR chemical shift of chiral ligands before and after addition of equal molar amount of $Cu(CH_3CN)_4BF_4$.

Entry	L2	L4	L7	L8	L9
1[a]	+56.68	+53.28	+66.57	+17.89	+50.40
2[b]	+62.37	+55.52	+64.99	+17.88	+57.36

[a] Before addition of $Cu(CH_3CN)_4BF_4$. [b] After addition of $Cu(CH_3CN)_4BF_4$.

Besides the sulfur atom, another precoordinative atom in our chiral thiophosphoramide or selenophosphoramide ligand system is the nitrogen atom of $ArNR^1R^2$. Firstly, we can preliminarily draw this conclusion from the experiments on the screening of chiral ligands. The results shown in Table 1 has already suggested that the asymmetric induction effect of the N-ethyl chiral ligands **L2**, **L4**, or **L7** was generally better than that of those N-unsubstituted chiral ligands **L1**, **L3**, or **L6**, that is, one ethyl group on the nitrogen of aniline ($ArNHCH_2CH_3$) is the best choice in our thiophosphoramide ligand system. In comparison with $ArNHCH_2CH_3$, the steric hindrance of nitrogen atom of $ArNMe_2$ in chiral Ligand **L5** is so large that the corresponding nitrogen atom can not effectively coordinate to Cu^I. Although less hindered nitrogen atom of aniline ($ArNH_2$) should coordinate to copper better than more hindered nitrogen atom of aniline ($ArNMe_2$), the lower catalytic ability lever is still attained, which may be caused by its less steric bulkiness in comparison with that of $NHCH_2CH_3$. Namely, an appropriate steric bulkiness around nitrogen atom is required for this novel thiophosphoramide ligand system to achieve high *ee*. Secondly, in order to get the further evidence of the coordination of nitrogen atom of aniline ($ArNHCH_2CH_3$) to Cu^I compound, the ^{13}C NMR studies of **L4**/$Cu(CH_3CN)_4BF_4$ complex (1:1 mixture) and **L9**/$Cu(CH_3CN)_4BF_4$ complex (1:1 mixture) in $CDCl_3$ at room temperature were carried out, respectively (Table 10 and see also Supporting Information). In the absence of $Cu(CH_3CN)_4BF_4$, the carbon signals of the two carbons in the ethyl group of **L4** appeared at δ 38.31 and 15.00, but the two corresponding carbons signals appeared at δ 40.92 and 14.88 in the presence of $Cu(CH_3CN)_4BF_4$, respectively. Meanwhile, another new carbon signal was observed at δ 1.88, which was attributed to the carbon of methyl group in acetonitrile. Similar results were observed for chiral ligand **L9** (Table 10, and see Supporting Information). All these results may suggest that $Cu(CH_3CN)_4BF_4$ can be potentially coordinated by S,N atoms in the phosphoramide ligands, although at present we do not have a crystal structure of this chiral Cu^I–ligand complex.

Table 10. The ^{13}C NMR chemical shift of CH_2CH_3 in the chiral ligand **L4** and **L9** before and after addition of equal molar amount of $Cu(CH_3CN)_4BF_4$.

Entry	L4		L9	
	CH_2	CH_3	CH_2	CH_3
1[a]	38.31	15.00	38.37	15.15
2[b]	40.92	14.88	41.49	14.92

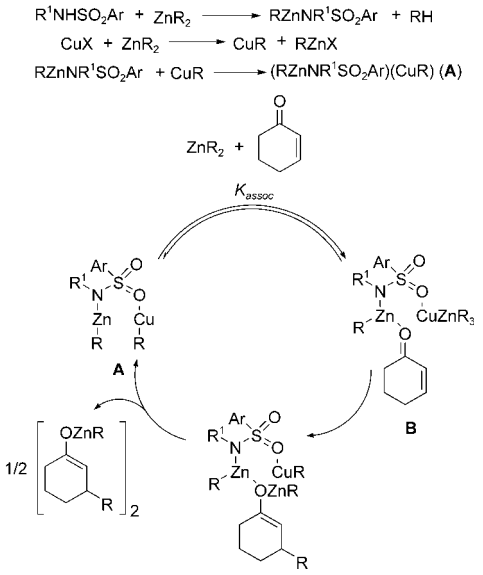
[a] Before addition of $Cu(CH_3CN)_4BF_4$. [b] After addition of $Cu(CH_3CN)_4BF_4$.

Comparing our catalytic system with those reported in the previous literature,[3,4] the significant advantages are the extremely fast reaction rate, mild reaction conditions and the general applicability for almost all of the common cyclic and acyclic enones besides the advantage of the thiophosphoramide ligands themselves mentioned above. The second question we need to clarify is the potential reason leading to such remarkably ligand-accelerated effect.

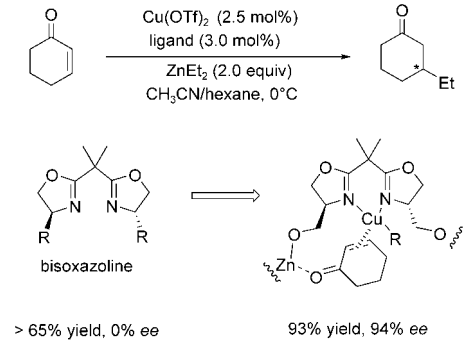
After consulting the previous literature, we noticed that Noyori and Kitamura reported that a mixture of CuCN and N-benzylbenzenesulfonamide catalyzed the conjugate addition of dialkylzinc or diarylzinc to enones to give the desired products in nearly quantitative yields.[21] They found that N-monosubstituted sulfonamides worked much better than N-unsubstituted compounds, but a bulky group on the nitrogen atom considerably lowered the reaction rate. Moreover, N,N-dibenzylbenzenesulfonamide was totally ineffective. In their proposed catalytic cycle, they suggested that the first step was N-benzylbenzenesulfonamide reacted with ZnR_2 to form $RZnNR'SO_2Ar$ complex by elimination of hydrocarbon RH; it was then combined with CuR formed by metathesis to give the mixed complex **A**, which acted as a bimetallic catalyst (Cu/Zn) for the reaction. That is, the acidic proton (H) played a significant role in their catalytic system (Scheme 5).

Recently, Reiser et al.[16] reported that the famous bisoxazoline ligands, which have been widely applied in the Cu^I-catalyzed asymmetric reactions, showed no catalytic abilities in the enantioselective conjugate addition reactions. However, when a hydroxymethylene side chain was introduced in this ligand system, up to 94% *ee* and 74% *ee* of conjugate addition products were obtained for 2-cyclohexen-1-one by using diethylzinc and diphenylzinc as the Michael addition reagents, respectively (Scheme 6). They also postulated that a possible bimetallic complex was decisive for their catalytic system and the two hydroxyl groups in the modified bisoxazoline ligands were the key factor for achieving high enantioselectivity.

Based on the reported literature and the obtained results, we can assume that our catalytic ligand system also undergo



Scheme 5.



Scheme 6.

a similar bimetallic catalytic process. Besides the Cu^I center being coordinated by S,N-bidentate ligand, the Zn center formed through the acidic proton (H) of thiophosphoramide in the ligand with R_2Zn is the other key factor in the potential catalytic active species (Figure 1).

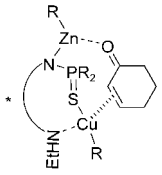
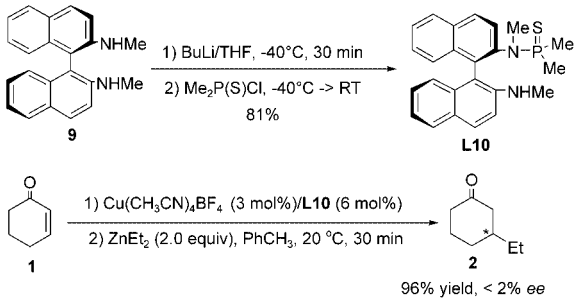


Figure 1. The possible active species in our catalytic system.

In order to verify the postulation, we synthesized the ligand **L10** from compound **9**[7] using the same method as that mentioned above (Scheme 7). **L10** is a phopshoramide in which the acidic proton (H) is replaced by a methyl group. Under the optimal reaction conditions, chiral ligand **L10** showed no asymmetric induction effect for the addition of diethylzinc to cyclohexenone (<2% *ee*), although the reaction can be also finished within 30 min at room temperature (Scheme 7). From the remarkable change of enantioselectivity caused by the modification of ligand structure, we can draw the conclusion that the acidic H of thiophosphoramide in our thiophosphoramide ligand system also played a significant role in the catalytic reaction process, which was very similar to those reported in the previous literature.[16,21] In addition, we also confirmed that in the ^1H NMR spectrum of **L2**, the acidic proton in NH-P(S)Me_2 moiety at 4.61 ppm (a doublet) disappeared in the presence of Et_2Zn (sees Figure 13 and 14 in the Supporting Information); its ^{31}P NMR spectrum with Cu^I clearly indicated a chemical shift to 61.56 in the presence of Et_2Zn (see Table 9 and Figure 15 in the Supporting Information). All these results suggest that the active species shown in Figure 1 could exist in the reaction system.



Scheme 7.

In order to gain further mechanistic insight into the nature of the possible active species that is formed in our catalytic system, we have examined the relationship between product *ee* and ligand *ee*. As shown in Figure 2, using **L4** as chiral ligand, we observed a clear linear effect in the asymmetric conjugate addition of diethylzinc to chalcone. Such a linear correlation between product *ee* and ligand *ee* indicates that the active species is a monomeric Cu^I complex bearing a single chiral ligand [Cu^I:ligand 1:1] (also see Table 2, entries 5, 11, 12 and Table 5 entries 3, 4).[22] All these results suggest that our thiophosphoramide or selenophosphoramide ligands system in Cu^I-promoted conjugate addition reaction is a single bidentate ligand to Cu^I combined with a bimetallic catalytic cycle.

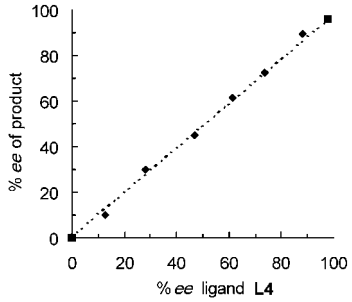


Figure 2. Linear effect for the asymmetric 1,4-addition reaction of diethylzinc to chalcone catalyzed by **L4**/$Cu(CH_3CN)_4BF_4$.

Conclusion

We described in this paper an efficient catalytic ligand system for the enantioselective conjugate addition of diethylzinc to enones catalyzed by Cu^I and axially chiral binaphthylthiophosphoramides, which are easily available, quite stable, recoverable and reusable. The system allows efficient, catalytic and highly enantioselective functionalization of not only six and seven-membered cyclic enones (97% *ee*), but also of cyclopentenone (98% *ee*) and acyclic enones (up to 97% *ee*). Moreover, other zinc reagents such as Me_2Zn and Ph_2Zn can be also employed in this ligand system. In addition, most of the reactions can be completed under mild conditions (20 or 0 °C) within 10–30 min. To the best of our knowledge, the enantioselectivities and reaction rates achieved here are one of the best yet results for the Cu-catalyzed enantioselective conjugate addition to enones. In addition, we confirmed that this series of chiral phosphoramides was a novel type of S,N-bidentate ligands through ^{31}P NMR, ^{13}C NMR spectroscopic experiments. We deduced that the mechanism of asymmetric Michael addition in our reaction system may be a bimetallic catalytic process and the acidic proton (H) of thiophosphoamide in the ligands plays a significant role in the formation of the active species. The linear effect of product *ee* and ligand *ee* further revealed that the active species is a monomeric Cu^I complex bearing a single ligand [Cu^I:ligand 1:1].

Acknowledgement

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