Asymmetric 1,4-Addition of Diethylzinc to Cyclic Enones Catalyzed by Cu(I)-Chiral Sulfonamide-Thiophosphoramide Ligands and Lithium Salts

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Abstract: The chiral sulfonamide-thiophosphoramide ligand **L1**, prepared from the reaction of (1*R*,2*R*)-(−)-1,2-cyclohexanediamine with diphenylthiophosphoryl chloride and *p*-toluenesulfonyl chloride, was used as a chiral ligand in $Cu(MeCN)_4ClO_4$-promoted catalytic asymmetric addition of diethylzinc to cyclic enones using LiCl as an additive in which up to 90% ee can be realized under mild conditions within 0.5 h. This chiral ligand is stable and recoverable after usual work-up and can be reused in the same catalytic asymmetric reaction. Moreover, it was found that this series of chiral ligands represents a type of S,O-bidentate ligands on the basis of ^{1}H NMR, ^{31}P NMR and ^{13}C NMR spectroscopic investigations. The linear effect of ligand ee and product ee further revealed that the active species is a monomeric Cu(I) complex bearing a single ligand.

Keywords: additive; asymmetric 1,4-addition; chiral sulfonamide-thiophosphoramide ligand; cyclic enones; diethylzinc; linear effect; lithium chloride

Introduction

Conjugate addition reactions of organometallic reagents to α,β-unsaturated carbonyl compounds constitute an important part of our standard repertoire of synthetic methods for C–C bond formation.[1,2] Many chiral catalysts have been developed to promote such transformations.[2] Previously, the enantioselective conjugate addition of organometallic reagents (Grignard reagents, organolithium derivatives, and dialkylzinc species) has been assisted more or less efficiently by chiral copper[3] and nickel catalysts.[4] A prominent position in this rapidly expanding field is occupied by the copper-catalyzed and chiral ligand-accelerated 1,4-addition of organozinc reagents originally introduced and rendered practical by Alexakis,[2g,5] Feringa,[6] Hoveyda,[7] Pfaltz[3h,8] and others.[3e,9] In particular, chiral phosphoramidites,[6c,10a,b] phosphites,[8e,5d,10c–h] phosphines,[10i] aminophosphanes,[10j–l] sulfonamides,[10m,n] peptide-based phosphines[7e] and diaminocarbene compounds[10o,p] were used as ligands in the addition to cyclic enones with very good enantioselectivities.

Recently, we are interested in the synthesis of a novel type of air- and moisture-stable chiral thiophosphoramide ligand[11] based on a series of chiral binaphthalenediamine (BINAM), (1*R*,2*R*)-(−)-1,2-cyclohexanediamine or (1*R*,2*R*)-(+)-1,2-diphenylethane-1,2-diamime and the applications of these novel chiral ligands in asymmetric catalysis.[12]

Herein, we report the results of our novel chiral sulfonamide-thiophosphoramide ligands derived from (1*R*,2*R*)-(−)-1,2-cyclohexanediamine and (1*R*,2*R*)-(+)-1,2-diphenylethane-1,2-diamime on the catalytic enantioselective 1,4-conjugate addition of diethylzinc to cyclic enones. The method described here allows the efficient, catalytic and moderate to high enantioselective functionalization of six- and seven-membered cyclic enones within 0.5 h. In addition, the chiral ligands can be easily recovered and reused in the same enantioselective addition without loss of efficiency and enantioselectivity.

Results and Discussion

The chiral sulfonamide-thiophosphoramide ligands **L1**–**L7** are readily synthesized by the reaction of (1*R*,2*R*)-(−)-1-*N*-diphenylthiophosphorylcyclohexane-1,2-diamine **1** and (1*R*,2*R*)-(+)-1-*N*-diphenylthiophosphoryl-1,2-diphenylethane-1,2-diamine **2**[12d] with various sulfonyl chlorides. In Scheme 1, we illustrate the reaction procedures for the preparation of chiral ligands **L1** –

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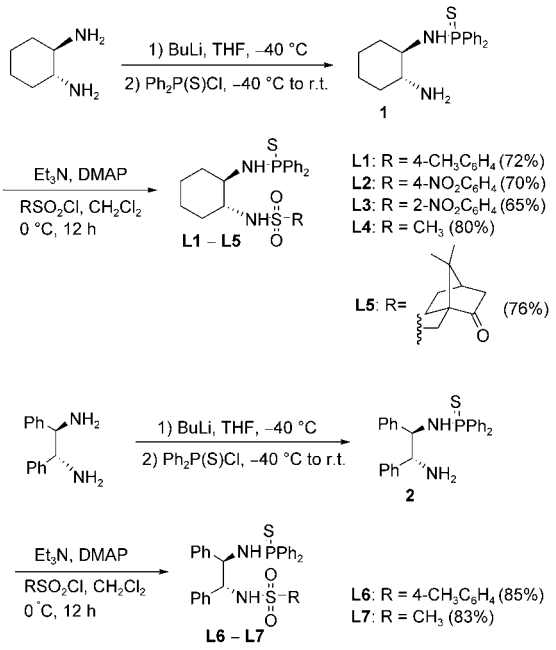
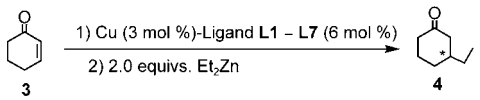


Scheme 1. Synthesis of sulfonamide-thiophosphoramide ligands **L1 – L7**.

L7. In general, they can be synthesized by the reaction of **1** and **2** with the corresponding sulfonyl chlorides in the presence of Et_3N and a catalytic amount of DMAP in dichloromethane at 0 °C for 12 h in moderate yields.[13] These obtained chiral ligands **L1 – L7** are air- and moisture-stable compounds under ambient conditions.

Using 2-cyclohexen-1-one **3** as the substrate and diethylzinc as the Michael addition reagent, we examined the 1,4-addition reaction in the presence of novel sulfonamide-thiophosphoramide ligands **L1 – L7** with various copper salts in a variety of solvents at different temperatures to develop the optimal reaction conditions. The results are summarized in Table 1. As can be seen from Table 1, **L1** is the best chiral ligand for this enantioselective 1,4-addition reaction to give the product **4** with 62% ee in 97% yield at 25 °C within 0.5 h with the *S* configuration (Table 1, entry 1). Chiral ligands **L2** to **L5** gave the addition product **4** in lower ee as compared with **L1** under identical conditions (Table 1, entries 2 to 6). These results suggest that the substituent of aryl group in the sulfonamide-thiophosphoramide ligands plays an important role in chiral induction for the asymmetric 1,4-addition reaction. Using **L6** or **L7** synthesized from (1*R*,2*R*)-(+)-1,2-diphenylethane-1,2-diamine as a chiral ligand, **4** was obtained in lower ee than with ligands **L1** to **L5** under identical conditions (Table 1, entries 7 and 8). In addition, since this addition reaction is sluggish in the absence of ligand, the enantioselective conjugate addition by our catalytic ligand system is apparently a ligand-accelerated process.[14] At lower temperature, **L1** is still active for this reaction but the adduct **4** was generally obtained in lower ee. For example, it was

Table 1. The enantioselective 1,4-addition reaction of 2-cyclohexen-1-one with $ZnEt_2$ catalyzed by copper salt and chiral ligand.[a]



Entry	Copper salt	Ligand	Solv.	Temp. [°C]	Time [h]	Yield[b] [%]	ee[c] [%]	Config.[d]
1	$Cu(MeCN)_4ClO_4$	**L1**	PhMe	25	0.5	97	62	*S*
2	$Cu(MeCN)_4ClO_4$	**L2**	PhMe	25	0.5	98	32	*S*
3	$Cu(MeCN)_4ClO_4$	**L3**	PhMe	25	0.5	95	28	*S*
4	$Cu(MeCN)_4ClO_4$	**L4**	PhMe	25	0.5	97	58	*S*
5	$Cu(MeCN)_4ClO_4$	**L5**	PhMe	25	0.5	94	45	*S*
6	$Cu(MeCN)_4ClO_4$	**L5**	Et_2O	25	0.5	95	55	*S*
7	$Cu(MeCN)_4ClO_4$	**L6**	PhMe	25	0.5	94	18	*S*
8	$Cu(MeCN)_4ClO_4$	**L7**	PhMe	25	0.5	95	37	*S*
9	$Cu(MeCN)_4ClO_4$	**L1**	PhMe	0	1	92	60	*S*
10	$Cu(MeCN)_4ClO_4$	**L1**	PhMe	–10	2	97	53	*S*
11	$Cu(MeCN)_4ClO_4$	**L1**	PhMe	–20	8	90	45	*S*
12	$CuOTf \cdot 1/2C_6H_6$	**L1**	PhMe	25	0.5	94	44	*S*
13	$Cu(OTf)_2$	**L1**	PhMe	25	0.5	94	37	*S*
14	$Cu(MeCN)_4BF_4$	**L1**	PhMe	25	0.5	95	61	*S*
15	$Cu(MeCN)_4ClO_4$	**L1**	Et_2O	25	0.5	95	65	*S*
16	$Cu(MeCN)_4ClO_4$	**L1**	THF	25	24	NR[e]	-[f]	-
17	$Cu(MeCN)_4ClO_4$	**L1**	CH_2Cl_2	25	10	92	45	*S*
18[g]	$Cu(MeCN)_4ClO_4$	**L1**	Et_2O	25	0.5	95	23	*S*
19[h]	$Cu(MeCN)_4ClO_4$	**L1**	Et_2O	25	0.5	94	53	*S*
20[i]	$Cu(MeCN)_4ClO_4$	**L1**	Et_2O	25	0.5	97	69	*S*

[a] Et_2Zn was added after the addition of 2-cyclohexene-1-one.
[b] Isolated yield.
[c] Determined by chiral GLC.
[d] Determined by the sign of the specific rotation.
[e] No reaction took place.
[f] Not determined.
[g] 2-Cyclohexene-1-one was added after the addition of Et_2Zn.
[h] Only 3 mol % of ligand was used.
[i] Recovered **L1** was used as ligand in this reaction.

found that, at 0 °C, the enantioselectivity of this addition reaction was decreased to 60% ee for 1 h while at –10 °C, the enantioselectivity was sharply decreased to 53% ee for 2 h and at –20 °C, the enantioselectivity was further decreased to 45% ee for a prolonged reaction time (8 h), respectively (Table 1, entries 9 to 11). From these results, the best condition for this reaction is at room temperature (25 °C). Copper(I) salts such as $Cu(CH_3CN)_4ClO_4$ or $Cu(CH_3CN)_4BF_4$ showed higher catalytic activity and chiral induction ability than $CuOTf \cdot 1/2C_6H_6$ or $Cu(OTf)_2$ under the same conditions (Table 1, entries 12 to 14). Solvent effects have been also examined using **L1** as a chiral ligand at 25 °C under otherwise identical conditions. Although not routine, this Cu(I)-catalyzed reactions can be carried out in solvents such as Et_2O, toluene, dichloromethane or THF.[15] Et_2O is the solvent of choice for this asymmetric addition re-

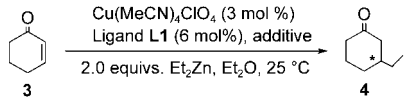
action (Table 1, entries 15 to 17). When 2-cyclohexen-1-one was added after the addition of Et_2Zn compared with the formal procedure, the ee was distinctly decreased to 23% (Table1, entry 18). If 3 mol % of ligand was used in this reaction, the achieved ee of **4** was slightly decreased to 53% (Table 1, entry 19). The best reaction conditions are using $Cu(CH_3CN)_4ClO_4$ (3 mol %) as a catalyst precursor and **L1** (6 mol %) as a chiral ligand in Et_2O at room temperature. This asymmetric addition reaction is complete within 0.5 h under this reaction conditions. Moreover, this chiral ligand is quite stable and can be recovered in 96% yield after usual work-up. The recovered ligand **L1** after usual work-up can be reused in this reaction without loss of catalytic ability and enantioselectivity (Table 1, entry 20).

The detailed mechanism of organocuprate addition to α,β-unsaturated compounds has been studied before.[16] A Cu(III) species has been suggested as the key intermediate in the conjugate addition of cuprate to enone,[17] which can be dissolved by admixture with LiX as an additive.[18] In addition, in some asymmetric catalysis, the addition of LiX can improve the enantiopurity of the reaction product.[3k,8b,9b] Based on these results, we also examined the addition of some LiX in our reaction system to improve the enantioselectivity. The results are indicated in Table 2. As can be seen from these results, using 10 mol % of LiCl as the additive gives the best results (Table 2, entries 2 to 8). LiCl only acts as an additive in this reaction because no reaction occurred in the absence of $Cu(MeCN)_4ClO_4$ (Table 2, entry 1). The reaction proceeded more quickly at ambient temperature (25 °C) than at −20 °C to give the adduct in similar enantioselectivities of 87% ee and 88% ee, respectively (Table 2, entries 3 and 4). Solvent Et_2O is better than isopropyl ether (*i*-PrOPr-*i*) to obtain higher enantioselectivity (Table 2, entries 3 and 5). Other lithium salts such as LiBr, $LiClO_4$, LiOAc are not as effective as LiCl in this reaction system (Table 2, entries 9 to 11). LiCl is the best additive in this asymmetric catalytic system (Table 2, entries 3, 9 to 11). Moreover, we found that the ee of **4** can be slightly increased to 90% in the presence of 9 or 12 mol % of ligand **L1** (Table 2, entries 12 and 13).

Therefore, on the basis of the above-mentioned results, it is very clear that the asymmetric conjugate addition reaction can be carried out under mild conditions (room temperature) with high enantioselectivity in our catalytic system in the presence of LiCl which offers another example of lithium salts as additives that increase the enantioselectivity in asymmetric catalysis. Furthermore, our chiral sulfonamide-thiophosphoramide ligand system is quite stable, easily available, recoverable and reusable in asymmetric catalysis.

Under the optimized reaction conditions, the 1,4-addition of diethylzinc to 2-cyclopenten-1-one and 2-cyclohepten-1-one have been also examined. It was found that for 2-cyclopenten-1-one, the corresponding 1,4-addition product **5** was obtained in moderate yield with 47% ee in the presence of ligand **L1** and for 2-cyclohepten-1-one, the corresponding 1,4-addition product **6** was obtained in 95% yield with moderate ee (73% ee), respectively (Scheme 2).

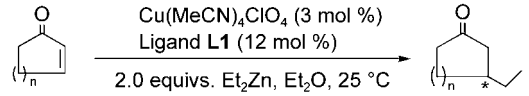
Table 2. The enantioselective 1,4-addition reaction of 2-cyclohexen-1-one with $ZnEt_2$ catalyzed by copper salt, chiral ligand and additives.[a]



3 4

Entry	Additive	Time [h]	Yield[b] [%]	ee[c] [%]	Config.[d]
1[e]	LiCl (10 mol %)	24	NR	-	-
2	LiCl (5 mol %)	0.5	95	75	*S*
3	LiCl (10 mol %)	0.5	95	87	*S*
4[f]	LiCl (10 mol %)	1	94	88	*S*
5[g]	LiCl (10 mol %)	0.5	95	67	*S*
6	LiCl (20 mol %)	0.5	87	86	*S*
7	LiCl (60 mol %)	0.5	86	83	*S*
8	LiCl (100 mol %)	0.5	87	86	*S*
9	LiBr (10 mol %)	0.5	94	61	*S*
10	$LiClO_4$ (10 mol %)	0.5	92	25	*S*
11	LiOAc (10 mol %)	0.5	89	65	*S*
12[h]	LiCl (10 mol %)	0.5	95	89	*S*
13[i]	LiCl (10 mol %)	0.5	95	90	*S*

[a] Additive was added to Cu(I) and ligand in Et_2O and the solution was stirred at room temperature for 1 h before 2-cyclohexen-1-one and Et_2Zn were added.
[b] Isolated yield.
[c] Determined by chiral GLC.
[d] Determined by the sign of the specific rotation.
[e] No Cu(I) was used.
[f] The reaction was carried out at −20 °C.
[g] Diisopropyl ether was used as solvent.
[h] 9 mol % of ligand was used.
[i] 12 mol% of ligand was used.



n = 0 or 2

5 n = 0: 64% yield, 47% ee.
6 n = 2: 95% yield, 73% ee.

Scheme 2.

Conclusion

We disclosed an efficient catalytic system for the enantioselective 1,4-conjugate addition of diethylzinc to cyclic enones catalyzed by Cu(I) and novel chiral sulfonamide-thiophosphoramide ligands using LiCl as an additive, which are easily available, quite stable, recoverable and reusable in asymmetric catalysis. The catalytic

system allows the efficient, catalytic and moderately to high enantioselective functionalization of six- and seven-membered cyclic enones, although it is not effective for five-membered cyclic enones. Results of mechanistic studies on this type of chiral S,O-bidentate ligands to the copper center through ^{1}H NMR, ^{31}P NMR and ^{13}C NMR spectroscopic experiments and the linear effect of ligand ee and product ee revealed that the active species is a monomeric Cu(I) complex bearing a single ligand are shown in the Supporting Information. Efforts are underway to extend the scope of these novel chiral ligands in other asymmetric C–C bond forming transformations.

Experimental Section

General Remarks

All reactions were conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of dry argon or nitrogen. Toluene was distilled from sodium metal; dichloromethane was distilled from calcium hydride; diethyl ether, tetrahydrofuran and toluene were distilled from sodium metal/benzophenone ketyl. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded at 300, 75 and 121 MHz, respectively. Mass spectra were recorded by the EI method. All of the solid compounds reported in this paper gave satisfactory C,H,N microanalyses. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel coated plates. P-Arus reagent [prepared by dissolving *p*-anisaldehyde (10 mL), acetic acid (7.5 mL), and concentrated H_2SO_4 (25 mL) in 95% ethanol (500 mL)] was used for those substrates which do not have absorptions in UV region. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure. Enantiomeric ratios were determined by chiral GLC or HPLC analysis. The absolute configuration was assigned by comparison the optical rotation with reported data.[19] Racemic products were synthesized according to the literature.[20] Melting points are uncorrected.

Typical Procedure: Synthesis of (1*R*,2*R*)-(+)-*N*-diphenylthiophosphoryl-*N*′-4-methylbenzenesulfonamidecyclohexane-1,2-diamine (L1)

The (1*R*,2*R*)-(−)-*N*-diphenylthiophosphorylcyclohexane-1,2-diamine (**1**; 231 mg, 0.7 mmol), Et_3N (293 μL, 2.1 mmol), and a catalytic amount of DMAP (10 mg) were combined in dichloromethane (5 mL) and cooled to −78 °C. *p*-Toluenesulfonyl chloride (144 mg, 0.75 mmol) in dichloromethane (3 mL) was added dropwise to the cooled, magnetically stirred solution over 20 minutes. After the addition was completed, the solution was allowed to stand at 0 °C overnight. The resulting mixture was washed with 1.0 N hydrochloric acid (2 × 10 mL) aqueous solution, saturated aqueous sodium bicarbonate (2 × 10 mL), saturated brine (2 × 15 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product which was purified by a flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 4/1) to afford **L1** as a white solid.

General Procedure for the Cu(I)-Catalyzed 1,4-Conjugate Addition

A solution of $Cu(CH_3CN)_4ClO_4$ (5.0 mg, 0.015 mmol) and **L1** (15.0 mg, 0.03 mmol) in anhydrous Et_2O (3 mL) was stirred for 1 h at room temperature under an argon atmosphere. Then, 2-cyclohexen-1-one (**3**; 48 μL, 0.5 mmol) was added into the reaction mixture and the solution was stirred for another 10 min. Et_2Zn (1.0 mL, 1.0 mmol, 1.0 M solution in hexane) was added dropwise within 30 seconds. The resulting mixture was stirred at 25 °C for 0.5 h. The reaction was quenched by the addition of 1 N hydrochloric acid aqueous solution (4.0 mL). After extraction with ether (3 × 5.0 mL), the combined organic layers were dried over anhydrous $MgSO_4$. The residue obtained upon removal of volatiles under vacuum was purified by a flash column chromatography on silica gel (eluent: pentane/ether = 30/1) to afford (*S*)-(−)-3-ethylcyclohexanone (**4**) as a colorless oil; yield: 61 mg (97%). The ligand **L1** was recovered in 96% yield after chromatography.

Supporting Information Available

The linear effect study, mechanistic work on the basis of ^{1}H NMR, ^{31}P NMR and ^{13}C NMR spectroscopic measurements of **L1** in the absence or presence of Cu(I) salt, characterization data for ligands **L1** – **L7**, and analytical data of the conjugate adducts (chiral GC) are available as Supporting Information

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