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(±)-*trans*-1,2-Cyclohexanediamine-Based Bis(NHC) Ligand for Cu-Catalyzed Asymmetric Conjugate Addition Reaction

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Received: 31 August 2019; Accepted: 16 September 2019; Published: 19 September 2019

Abstract: Bis(NHC) ligand precursors, **L1**, based on *trans*-1,2-diaminocyclohexane were designed and synthesized. To introduce chirality at the hydroxyamide side arm on the NHC of **L1**, a chiral *β*-amino alcohol, such as enantiopure leucinol, was used. Cu-catalyzed asymmetric conjugate addition reactions of cyclic and acyclic enones with Et_2Zn were selected to evaluate the performance of **L1** as a chiral ligand. For the reaction of cyclic enone, a combination of [bis(trimethylsilyl)acetylene]-(hexafluoroacetylacetonato)copper(I) (Cu(hfacac)(btmsa)) with a (±)-*trans*-1,2-cyclohexanediamine-based bis(NHC) ligand precursor, (*rac*; *S*,*S*)-**L1**, which was prepared from (*S*)-leucinol, was the most effective. Thus, treating 2-cyclohexen-1-one (**3**) with Et_2Zn in the presence of catalytic amounts of Cu(hfacac)(btmsa) and (*rac*; *S*,*S*)-**L1** afforded (*R*)-3-ethylcyclohexanone ((*R*)-**4**) with 97% *ee*. Similarly, use of (*rac*; *R*,*R*)-**L1**, which was prepared from (*R*)-leucinol, produced (*S*)-**4** with 97% *ee*. Conversely, for the asymmetric 1,4-addition reaction of the acyclic enone, optically pure (−)-*trans*-1,2-cyclohexanediamine-based bis(NHC) ligand precursor, (*R*,*R*; *S*,*S*)-**L1**, worked efficiently. For example, 3-nonen-2-one (**5**) was reacted with Et_2Zn using the CuOAc/(*R*,*R*; *S*,*S*)-**L1** catalytic system to afford (*R*)-4-ethylnonan-2-one ((*R*)-**6**) with 90% *ee*. Furthermore, initially changing the counterion of the Cu precatalyst between an OAc and a ClO_4 ligand on the metal reversed the facial selectivity of the approach of the substrates. Thus, the conjugate addition reaction of **5** with Et_2Zn using the $Cu(ClO_4)_2$/(*R*,*R*; *S*,*S*)-**L1** catalytic system, afforded (*S*)-**6** with 75% *ee*.

Keywords: asymmetric catalysis; conjugate addition; reversal of enantioselectivity; *N*-heterocyclic carbene; ligand design

1. Introduction

Synthesizing efficient chiral ligands for asymmetric catalysis is currently a major challenge in synthetic organic chemistry [1–4]. In recent years, *N*-heterocyclic carbenes (NHCs) have become recognized as versatile ligands [5–25]. There have been several recent reports on chiral bis(NHC) ligands (Figure 1) [26–30].

Douthwaite et al. synthesized a chiral bis(NHC)-Pd(II) complex from optically pure *trans*-1,2-diaminocyclohexane [31,32]. In 2003, Shi et al. developed a bidentate axially chiral bis(NHC)-Rh(III) complex [33]. They succeeded in creating a large variety of asymmetric transformations by using this versatile chiral ligand [34–47]. Nagel et al. showed the enantioselective transfer hydrogenation of ketones catalyzed by Rh(I) and Ir(I) complexes derived from (*S*)-valinol [48,49]. Iglesias and Sánchez et al. reported the asymmetric hydrogenation of alkenes with bis(NHC) derived from tartaric acid [50,51]. A chiral palladium allyl complex bearing bis(NHC)/cyclophane ligand for 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one was synthesized by Veige et al. [52,53].

To the best of our knowledge, there are two bis(NHC) ligands based on chiral *trans*-1,2-diaminocyclohexane for asymmetric catalytic transformations (Figure 1). Herrmann and Kühn et al. demonstrated the enantioselective hydrogenation of alkenes catalyzed by Rh(I) complexes derived from 1,2,4-triazole and [54,55]. Zhang et al. reported asymmetric catalytic Suzuki–Miyaura couplings employing a bis(NHC)-Pd(II) complex [56–59]. However, the appearance of an efficient asymmetric catalytic system using a chiral bis(NHC) ligand remains rare.

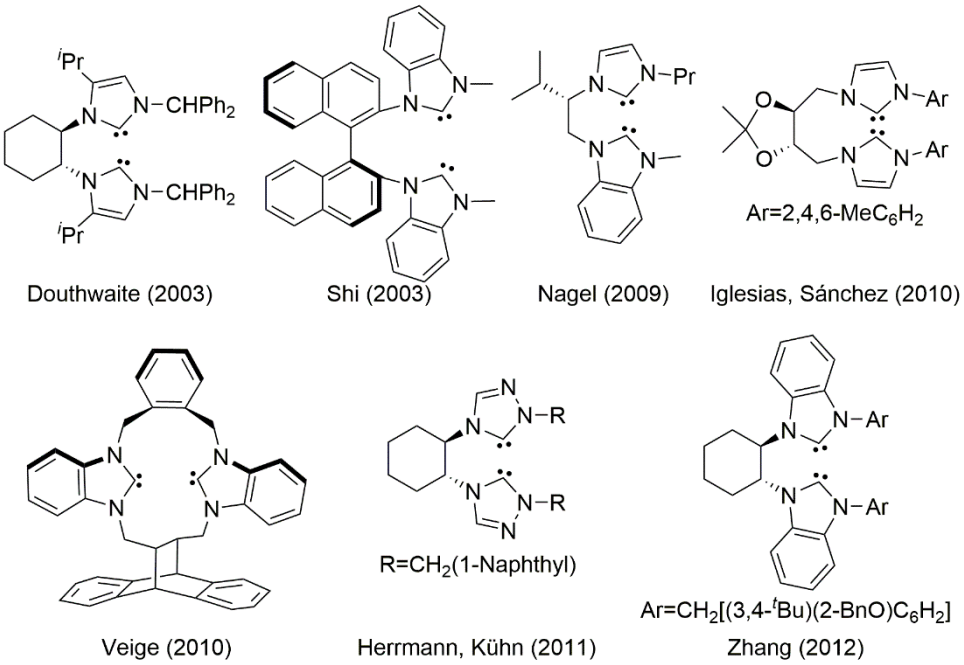
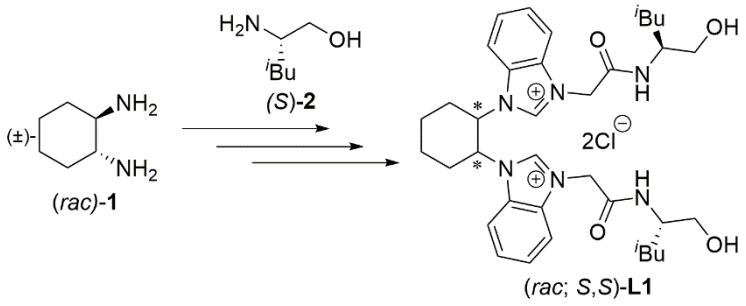


Figure 1. Selected examples of chiral bis-*N*-heterocyclic carbenes bis(NHC)s.

Introducing an appropriate hemilabile chiral donor group at the NHC side arm provides a chelating NHC-based ligand [60–67]. As part of our research program on developing chiral NHC ligand precursors, we have reported a Cu-catalyzed enantioselective conjugate addition reaction of enone with Et_2Zn, using a chiral hydroxyamide-functionalized azolium ligand precursor [68–76]. Much attention has been given to the 1,4-addition reaction [77–80]. We previously synthesized a new chiral azolium salt, (*rac*; *S*,*S*)-**L1**, which serves as a bis(NHC) ligand precursor [81]. The (*rac*; *S*,*S*)-**L1** was prepared by using (±)-*trans*-1,2-diaminocyclohexane ((*rac*)-**1**) and (*S*)-leucinol ((*S*)-**2**) (Scheme 1). Thus, (*rac*; *S*,*S*)-**L1** was obtained as a 1:1 diastereoisomeric mixture and used for the catalytic asymmetric reaction. Importantly, a highly enantioselective Cu-catalyzed conjugate addition reaction of cyclic enone with dialkylzinc in the presence of (*rac*; *S*,*S*)-**L1** was successfully achieved [81].



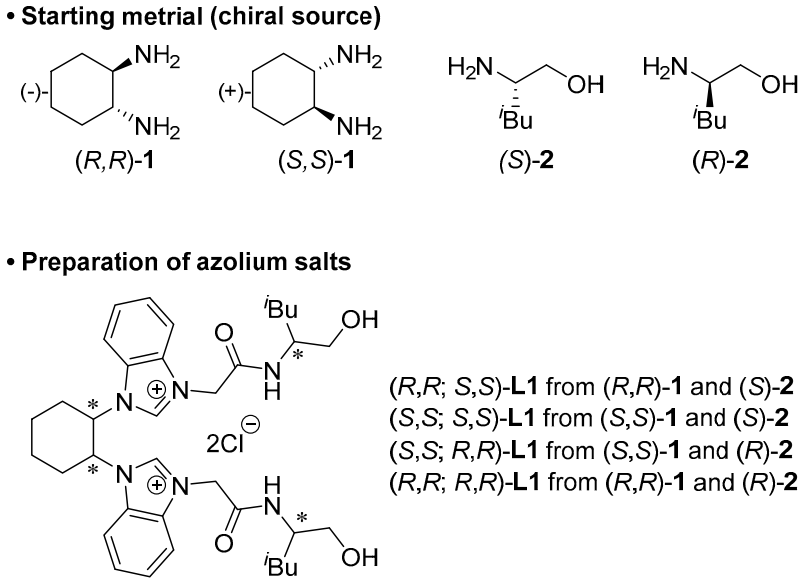
Scheme 1. Previously reported bis(NHC) ligand precursor.

However, the 1,4-addition reaction employing the bis(NHC) ligand precursor derived from an optically active *trans*-1,2-diaminocyclohexane (**1**) remains unclarified. In this paper, we show the synthesis of the corresponding bis(NHC) ligand precursor **L1** from a single enantiomer of *trans*-1,2-diaminocyclohexane ((-)-**1** or (+)-**1**). Systematic studies on the catalytic asymmetric 1,4-addition reaction using this promising class of enantiomerically pure bis(NHC) ligand are described.

2. Results and Discussion

2.1. Catalytic Asymmetric Conjugate Addition Reaction of Cyclic Enone

Enantiomerically pure **L1** was synthesized from enantiopure *trans*-1,2-diaminocyclohexane ((*R*,*R*)-**1** or (*S*,*S*)-**1**) [81]. To introduce chirality at the hydroxyamide side arm at **L1**, we chose (*S*)-leucinol ((*S*)-**2**) or (*R*)-leucinol ((*R*)-**2**) as a chiral source. In this study, we wanted to determine the influence of the chirality of the cyclohexanediamine skeleton of **L1** on the catalytic asymmetric transformation. Thus, four sets of bis(NHC) azolium ligands were synthesized (Scheme 2).



Scheme 2. Preparation of a series of chiral ligands **L1** used in this study.

The previously reported bis(NHC) azolium ligand (*rac*; *S*,*S*)-**L1** consists of a 1:1 diastereoisomeric mixture of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** (Scheme 1) [81]. With a set of diastereomerically and enantiomerically pure azolium salts in hand (Scheme 2), we performed an NMR study of these compounds (Figures 2–4). Initially, temperature dependence was observed in the ^{1}H NMR spectrum of the bis(NHC) azolium precursor (Figure 2). For example, ^{1}H NMR signals of (*R*,*R*; *R*,*R*)-**L1** at 25 °C were extremely broad, indicating that several conformers, slowly interconverting on the NMR timescale, were present at room temperature. Conversely, increasing the temperature (to 80 °C) provided sharp, well-defined signals in the NMR spectra (Figure 2). Thus, a fully assignable NMR spectrum was obtained.

Furthermore, the methyl group signals of the isobutyl substituent in the ^{1}H NMR spectra of a series of azolium salts **L1** was considered. Figure 3 shows the expanded spectra of the methyl group regions of (*rac*; *S*,*S*)-**L1**, (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1**. Their C-H resonances appeared at δ = 0.87/0.82 ppm (J = 6.9 Hz) for (*R*,*R*; *S*,*S*)-**L1** and δ = 0.88/0.83 ppm (J = 6.9 Hz) for (*S*,*S*; *S*,*S*)-**L1**. Thus, the methyl group signals in (*rac*; *S*,*S*)-**L1** could be assigned, as shown in Figure 3.

Similarly, in the ^{13}C NMR spectrum of (*rac*; *S*,*S*)-**L1**, two signals were observed in the methine carbon adjacent to the isobutyl substituent (Figure 4). This is because of the presence of a diastereoisomeric mixture. The ^{13}C NMR spectra of the diastereoisomerically pure isomers revealed

that the signal at δ 48.6 ppm could be attributed to the methine carbon on (*R*,*R*; *S*,*S*)-**L1** and that at δ 48.5 ppm, it could be attributed to the methine carbon on (*S*,*S*; *S*,*S*)-**L1**.

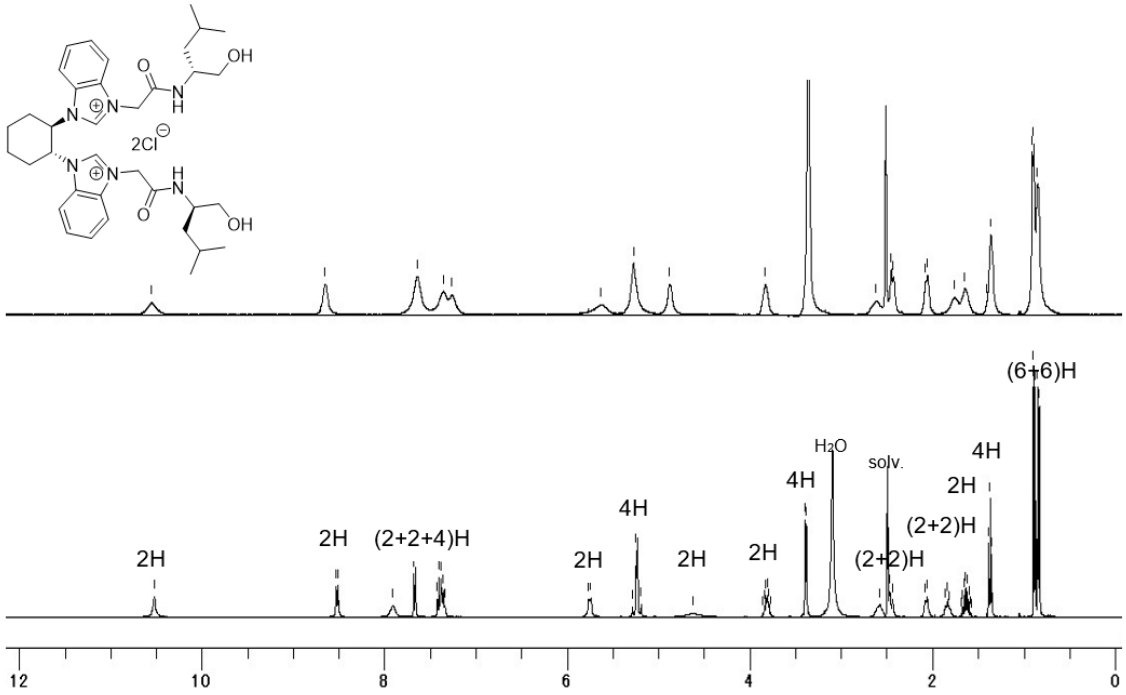
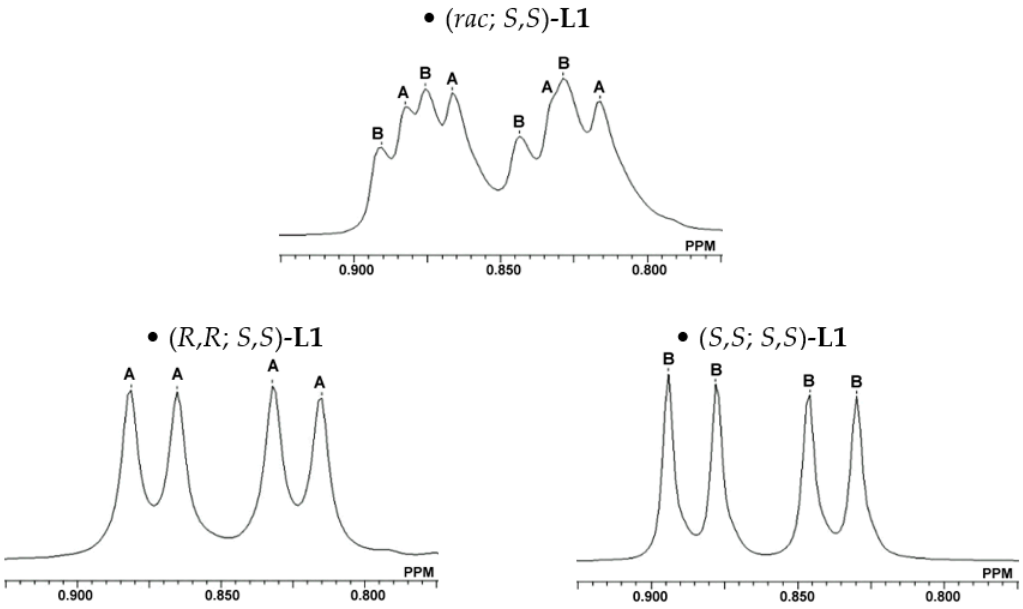


Figure 2. ^{1}H NMR spectrum of (*R*,*R*; *R*,*R*)-**L1** in $(CD_3)_2SO$ at 25 °C (upper) and 80 °C (lower).



A: the signal of the methyl proton on (*R*,*R*; *S*,*S*)-**L1**;
B: the signal of the methyl proton on (*S*,*S*; *S*,*S*)-**L1**

Figure 3. ^{1}H NMR spectrum of the methyl proton on selected **L1** (at 80 °C).

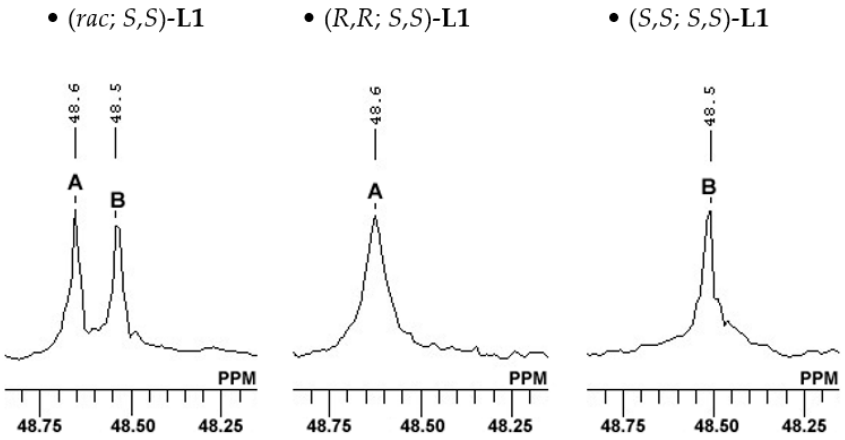
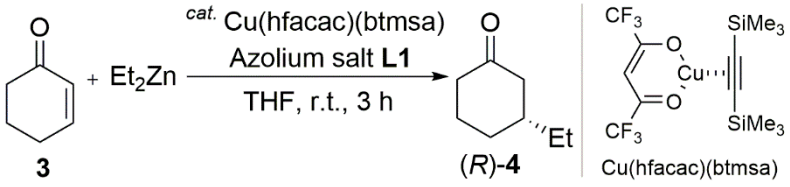


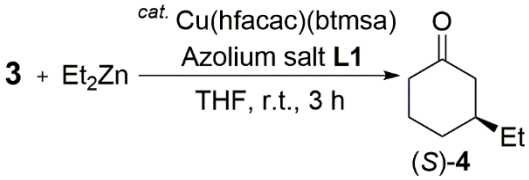
Figure 4. ^{13}C NMR spectrum of the methine carbon adjacent to isobutyl substituent.

To test the performance of the chiral bis(NHC) ligand precursors **L1**, the conjugate addition reaction of 2-cyclohexen-1-one (**3**) with Et_2Zn catalyzed by [bis(trimethylsilyl)acetylene](hexafluoroacetylacetonato)copper(I) (Cu(hfacac)(btmsa)), combined with **L1**, was examined (Table 1).

Table 1. Effect of chiral ligands **L1** in the conjugate addition reaction of cyclic enone **3**.



Entry [a]	(*R,R; S,S*)-L1:(*S,S; S,S*)-L1	Yield (%) [b]	*ee* (%) [c]
1	1:0	57	16
2	1:1 ≡ (*rac*; *S,S*)-**L1**	99	97
3	0:1	34	26



Entry [a]	(*S,S; R,R*)-L1:(*R,R; R,R*)-L1	Yield (%) [b]	*ee* (%) [c]
4	1:0	59	12
5	1:1 ≡ (*rac*; *R,R*)-**L1**	91	97
6	0:1	39	24

[a] To a solution of Cu(hfacac)(btmsa) (6.0 mol%) and **L1** (4.5 mol%) in THF (9 mL), Et_2Zn (3 mmol) was added first, then **3** (1 mmol). The reaction mixture was stirred at room temperature for 3 h. [b] Determined by GC analysis using the internal standard technique. [c] Determined by GC analysis of a chiral stationary phase.

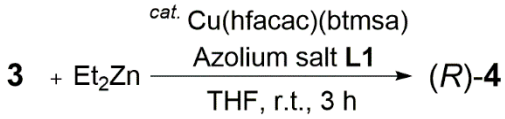
In our previous publication, we briefly described a highly stereoselective transformation that was achieved using (*rac*; *S,S*)-**L1** [81]. Thus, the reaction of **3** with Et_2Zn in the presence of catalytic amounts of Cu(hfacac)(btmsa) and (*rac*; *S,S*)-**L1** in THF at room temperature afforded (*R*)-3-ethylcyclohexanone ((*R*)-**4**) in 99% yield, with excellent enantioselectivity (97% *ee*) (Table 1, entry 2). We then investigated

the 1,4-addition reaction using the diastereomerically and enantiomerically pure ligand. Notably, use of (*R*,*R*; *S*,*S*)-**L1** in place of (*rac*; *S*,*S*)-**L1** under these reaction conditions resulted in a lower yield (57%) of (*R*)-**4** with poor enantioselectivity (16% *ee*) (entry 1). As with (*R*,*R*; *S*,*S*)-**L1**, a combination of Cu(hfacac)(btmsa) and (*S*,*S*; *S*,*S*)-**L1** led to (*R*)-**4** in 34% yield with 26% *ee* (entry 3).

Next, we synthesized (*rac*; *R*,*R*)-**L1**, (*S*,*S*; *R*,*R*)-**L1** and (*R*,*R*; *R*,*R*)-**L1** (Scheme 2). Clearly, the Cu-catalyzed 1,4-addition reaction of **3** with Et_2Zn in the presence of (*rac*; *R*,*R*)-**L1** afforded (*S*)-**4** with 97% *ee* (Table 1, entry 5). Conversely, it was difficult to obtain the desired 1,4-adduct, (*S*)-**4**, with high yield and enantioselectivity by using (*S*,*S*; *R*,*R*)-**L1** or (*R*,*R*; *R*,*R*)-**L1** (entries 4 and 6). These results strongly suggest that the chirality of the hydroxyamide side arm plays a critical role in the asymmetric 1,4-addition reaction of **3** with Et_2Zn.

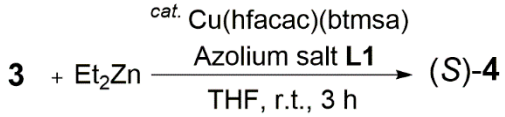
It is noteworthy that the asymmetric catalytic 1,4-addition reaction occurred efficiently when using a 1:1 mixture of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** ((*rac*; *R*,*R*)-**L1**). To highlight the importance of both components in the catalytic reaction, we then varied the ratio of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** (Table 2).

Table 2. Influence of the ratio of chiral ligands **L1** in the conjugate addition reaction of **3**.



Ratio [a]	Yield (%)	*ee* (%)	Graphical Presentation of *ee* Value
10:0	57	16	
9:1	94	89	
8:2	95	94	
6:4	96	96	
5:5	99	97	
4:6	95	96	
2:8	94	95	
1:9	86	89	
0:10	34	26	

[a] (*R*,*R*; *S*,*S*)-**L1** : (*S*,*S*; *S*,*S*)-**L1**.



Ratio [b]	Yield (%)	*ee* (%)	Graphical Presentation of *ee* Value
10:0	59	12	
9:1	86	90	
8:2	90	97	
6:4	91	98	
5:5	91	97	
4:6	90	98	
2:8	90	97	
1:9	88	94	
0:10	39	24	

[b] (*S*,*S*; *R*,*R*)-**L1** : (*R*,*R*; *R*,*R*)-**L1**.

We carefully prepared various mixtures of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** (with (*R*,*R*; *S*,*S*)-**L1**/(*S*,*S*; *S*,*S*)-**L1** ratios of 10:0, 9:1, 8:2, 6:4, 5:5, 4:6, 2:8, 1:9 and 0:10). Notably, **3** was reacted with Et_2Zn catalyzed by Cu(hfacac)(btmsa) in the presence of a 9:1 mixture to afford (*R*)-**4** in 94% yield with 89% *ee* (Table 2). Use of (*R*,*R*; *S*,*S*)-**L1** alone resulted in poor enantioselectivity (16% *ee*) of (*R*)-**4**. The best result (99% yield, 97% *ee*) was obtained at the 5:5 ratio. Furthermore, surprisingly, the yield and stereoselectivity of

the 1,4-addition reaction using a 1:9 mixture were comparable to those obtained by using a 9:1 mixture. These results suggest that the presence of a small amount of each component of these two chiral ligands is enough to achieve an optimum asymmetric catalytic performance. This will be discussed later (vide infra; see Table 3).

The same experiment was conducted using (*S*,*S*; *R*,*R*)-**L1** and (*R*,*R*; *R*,*R*)-**L1** to provide (*S*)-**4** in the Cu-catalyzed reaction of **3** with Et_2Zn (Table 2). In a similar manner, a 9:1 or 1:9 mixture facilitated the highly enantioselective conjugate addition reaction to afford (*S*)-**4** with 90% or 94% *ee*, respectively. These results confirm the importance of the presence of both stereoisomers of the cyclohexanediamine moiety in the chiral ligands for reaction efficiency and stereoselectivity.

The relationship between the catalyst *ee* and the product *ee* was also investigated (Figure 5). Various mixtures of (*rac*; *S*,*S*)-**L1** and (*rac*; *R*,*R*)-**L1** were carefully prepared. The enantioselective conjugate addition reaction of cyclic enone **3** with Et_2Zn provided sufficient chiral amplification (Figure 5).

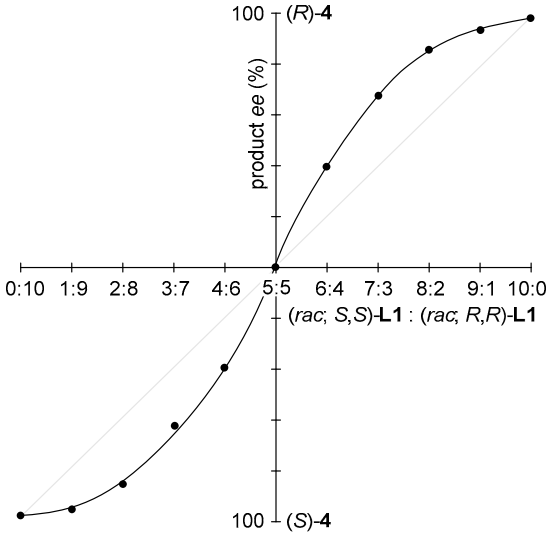


Figure 5. Chiral amplification in the conjugate addition reaction of **3** using (*rac*; *S*,*S*)-**L1** and (*rac*; *R*,*R*)-**L1**.

As shown in Table 2, we have clearly demonstrated that a 9:1 or 1:9 mixture of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** promotes the enantioselective catalytic reaction. These reactions were performed in the presence of 6.0 mol % of Cu salt and 4.5 mol % of the chiral ligand mixtures. We assumed that an excess of (*R*,*R*; *S*,*S*)-**L1** would not be needed in the catalytic reaction with a 9:1 mixture of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** and that a small amount of a 1:1 mixture of these ligands, with respect to the Cu precatalyst, would be sufficient to facilitate the catalytic reaction. This assumption prompted us to study the asymmetric 1,4-addition reaction of **3** with Et_2Zn catalyzed by Cu(hfacac)(btmsa), with a reduced amount of the chiral ligand mixtures (Table 3).

As expected, the 1,4-addition reactions with Cu/ligand ratios of 1:0.75, 1:0.3, 1:0.225, and 1:0.15 occurred in a similar manner to afford the corresponding adduct with 97%, 93%, 96%, and 97% *ee*, respectively (entries 1–4). These results indicate that the same catalytic active species were probably formed. It is also noteworthy that the loading of chiral ligand could be dramatically reduced.

No reaction was observed in the absence of **L1**. Additionally, two bis(NHC) ligands, **L2** and **L3**, were synthesized to investigate the effect of the ligand structure on the catalytic performance. Changing the alkyl substituent at the chiral carbon center of the ligand from the isobutyl group ((*rac*; *S*,*S*)-**L1**) to the more sterically hindered *tert*-butyl group (**L2**) led to the conjugate adduct, (*S*)-**4**, in lower yield and enantioselectivity with the opposite configuration (Table 3, entry 6). This might be due to the highly hindered *tert*-butyl group blocking the approach of the reagents. Furthermore, **L3** was synthesized from

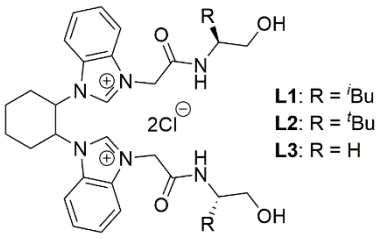
1-aminoethanol. However, it was difficult to react **3** with Et_2Zn in the presence of Cu(hfacac)(btmsa) in combination with **L3** (entry 7).

The catalytic performance of the Cu(hfacac)(btmsa)/(*rac*; *R*,*R*)-**L1** system in the asymmetric 1,4-addition reaction of various cyclic enones was investigated, as described in our previous publication [81].

Table 3. Effect of the amount of chiral ligand and ligand structure on the conjugate addition reaction of **3** [a].

Entry	(*rac*; *S*,*S*)-L1 (mol%)	Yield (%) [b]	*ee* (%) [c]
1 [d]	4.5	99	97
2	1.8	97	93
3	1.35	91	96
4	0.9	82	97
5	0.45	13	Nd [e]
6	**L2**, 4.5	48	*ent*-27
7	**L3**, 4.5	18	0

[a] To a solution of Cu(hfacac)(btmsa) (6.0 mol%) and (*rac*; *S*,*S*)-**L1** (0.45-4.5 mol%) in THF (9 mL), Et_2Zn (3 mmol) was added first, then **3** (1 mmol). The reaction mixture was stirred at room temperature for 3 h. [b] Determined by GC analysis using the internal standard technique. [c] Determined by GC analysis of a chiral stationary phase. [d] The same data is shown in Table 1, entry 2. [e] Not determined.



2.2. Catalytic Asymmetric Conjugate Addition Reaction of Acyclic Enone

In contrast to the conjugate addition reactions of organometallic compounds with cyclic enones, few highly enantioselective reactions of acyclic enones have been reported [71,82–93]. We then focused on studying the Cu-catalyzed asymmetric 1,4-addition reaction of acyclic enone with Et_2Zn using this promising class of bis(NHC) chiral ligand **L1**.

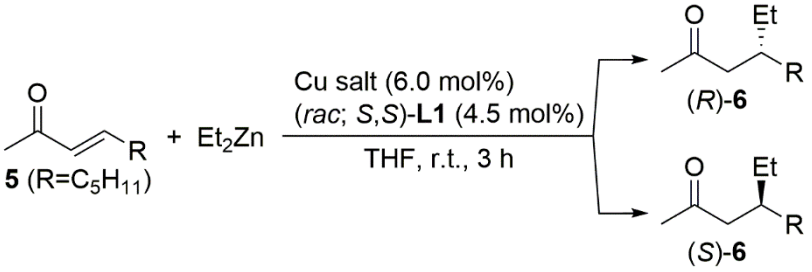
In our previous publication, we briefly reported that 3-nonen-2-one (**5**) was reacted with Et_2Zn catalyzed by Cu(hfacac)(btmsa) and (*rac*; *S*,*S*)-**L1** at room temperature to afford (*R*)-4-ethylnonan-2-one ((*R*)-**6**) in 90% yield with moderate stereoselectivity (49% *ee*) (Table 4, entry 1) [81]. Replacing Cu(hfacac)(tmsa) with cyclooctadiene(hexafluoro-2,4-pentanedionato)copper(I) (Cu(hfacac)(cod)) improved the stereoselectivity (61% *ee*) of the 1,4-addition reaction (entry 2).

Encouraged by this success, we continued to test various Cu precatalysts for further reaction optimization (Table 4). Although the reaction was catalyzed by bis(hexafluoroacetylacetonato)-copper(II) ($Cu(hfacac)_2$) and (*rac*; *S*,*S*)-**L1** to afford (*R*)-**6** with moderate enantioselectivity (53% *ee*), $CuOCOCF_3$ did not work efficiently (entries 3 and 4). The promising result was achieved when the reaction was performed with CuOAc. Thus, the combination of CuOAc and (*rac*; *S*,*S*)-**L1** catalyzed the reaction to furnish the corresponding adduct, (*R*)-**6**, in 78% yield and with 60% *ee* (entry 5). Despite achieving the same enantioselectivity (63% *ee*), $Cu(OAc)_2$ decreased the product yield (entry 6).

Interestingly, during this study, we found that simply changing the copper catalyst precursor with the same ligand reversed the stereochemistry. The reaction of **5** with Et_2Zn using the $CuCl_2$/(*rac*; *S*,*S*)-**L1** catalytic system afforded (*R*)-**6** in 50% yield and with 39% *ee* (entry 7). In contrast, $Cu(OTf)_2$ in place of $CuCl_2$ led to the 1,4-adduct, (*S*)-**6**, with the opposite configuration with 33% *ee* (entry 8). Developing a synthetic methodology for switching enantioselectivity is an essential and challenging

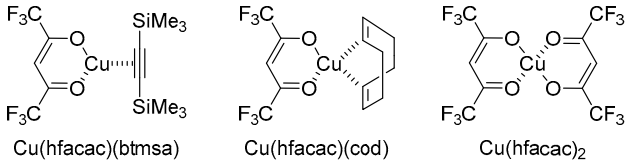
research topic. Recently, many papers have been published to provide a comprehensive overview of the importance of stereodivergent catalytic transformations [94–100].

Table 4. Switching of stereoselectivity in the conjugate addition reaction of acyclic enone **5** [a].



Entry	Cu Salt	Product	Yield (%) [b]	*ee* (%) [c]
1 [d]	Cu(hfacac)(btmsa)	(*R*)-**6**	90	49
2 [d]	Cu(hfacac)(cod)	(*R*)-**6**	87	61
3	$Cu(hfacac)_2$	(*R*)-**6**	85	53
4	$CuOCOCF_3$	(*R*)-**6**	73	27
5	CuOAc	(*R*)-**6**	78	60
6	$Cu(OAc)_2$	(*R*)-**6**	37	63
7	$CuCl_2$	(*R*)-**6**	50	39
8	$Cu(OTf)_2$	(*S*)-**6**	58	33
9	$CuOTf{\cdot}0.5C_6H_6$	(*S*)-**6**	57	2
10	$Cu(NO_3)_2$	(*S*)-**6**	62	9
11	$Cu(ClO_4)_2$	(*S*)-**6**	31	50

[a] To a solution of Cu salt (6.0 mol%) and (*rac*; *S*,*S*)-**L1** (4.5 mol%) in THF (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). The reaction mixture was stirred at room temperature for 3 h. [b] Determined by GC analysis using the internal standard technique. [c] Determined by GC analysis of a chiral stationary phase. [d] Previously reported data [81].



Based on this finding, we decided to evaluate several Cu salts. $CuOTf{\cdot}0.5C_6H_6$ and $Cu(NO_3)_2$ resulted in racemic **6** (Table 4, entries 9 and 10). $Cu(ClO_4)_2$ led to a marked increase in the enantioselectivity of the 1,4-addition reaction to provide (*S*)-**6** as a major product (entry 11). Previously, we showed that the reversal of enantioselectivity was achieved in the Cu-catalyzed conjugate addition reaction of cyclic enone using a mono-NHC azolium ligand **L4** with a chiral hydroxyamide side-arm (Figure 6) [76]. For example, **3** was reacted with Et_2Zn catalyzed by $Cu(OTf)_2$/**L4** to afford (*S*)-**4**, whereas (*R*)-**4** was obtained in the same reaction with the $Cu(acac)_2$/**L4** catalytic system [74]. However, no reversal of enantioselectivity was observed in the Cu-catalyzed 1,4-addition reaction of acyclic enone when changing the Cu precatalyst in the presence of **L4** [71]. Therefore, to the best of our knowledge, this is the first example of switchable enantioselectivity in a catalytic conjugate addition reaction of acyclic enone, with the same chiral ligand.

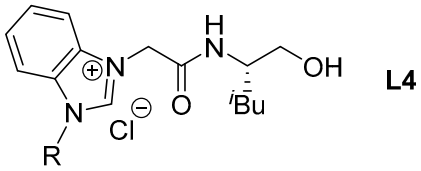


Figure 6. Previously reported chiral ligand **L4**.

The combination of transition metal complex and chiral ligand can provide a chiral environment for the metal, where high enantioselectivity requires only small differences in transition state energies in the catalytic reaction. The transition metal complex consists of a cationic metal and an achiral counter anion. While the chiral ligand design is critical to achieving a highly stereoselective catalytic reaction, the choice of the achiral counter anion of the transition metal complex is also an important factor. In the literature, it appears that changing the achiral counter anion of the metal catalyst precursor has sometimes switched the stereochemistry of the catalytic reaction [76,101–107].

Table 5 summarizes the switching of enantioselectivity in the asymmetric 1,4-addition reaction of **5** with Et_2Zn catalyzed by CuOAc or $Cu(ClO_4)_2$ using the chiral bis(NHC) ligand precursor, (*rac*; *S*,*S*)-**L1**, under selected reaction conditions. To optimize the reaction conditions, various reaction parameters, including the ratio of Cu salt/chiral ligand, solvents and reaction temperatures were screened with CuOAc (entries 1–8) or $Cu(ClO_4)_2$ (entries 9–16). Further evaluations of the reaction parameters with both catalytic systems are presented in Tables S1 and S2, respectively (see Supplementary Materials).

Table 5. Switching of stereoselectivity in the conjugate addition reaction of **5** under selected conditions [a].

Entry	Cu/L1 (mol%)	Solv	Temp./Time	Product	Yield (%)	*ee* (%)
1 [b,c]	6/4.5	THF	r.t./3 h	(*R*)-**6**	78	60
2 [b]	4.5/6	THF	r.t./3 h	(*R*)-**6**	72	56
3 [b]	4/4	THF	r.t./3 h	(*R*)-**6**	79	60
4 [b]	4/4	Et_2O	r.t./3 h	(*R*)-**6**	46	39
5 [b]	4/4	DME	r.t./3 h	(*R*)-**6**	43	70
6 [b]	4/4	DME	0 °C/24 h	(*R*)-**6**	49	78
7 [b]	4/4	DME	0 °C/48 h	(*R*)-**6**	78	73
8 [b]	4/4	DME	−10 °C/48 h	(*R*)-**6**	69	75
9 [d,e]	6/4.5	THF	r.t./3 h	(*S*)-**6**	31	50
10 [d]	4.5/6	THF	r.t./3 h	(*S*)-**6**	44	34
11 [d]	6/3	THF	r.t./3 h	(*S*)-**6**	39	46
12 [d]	6/3	2-MeTHF	r.t./3 h	(*S*)-**6**	26	43
13 [d]	6/3	DME	r.t./3 h	(*S*)-**6**	28	34
14 [d]	6/3	THF	0 °C/24 h	(*S*)-**6**	89	70
15 [d]	6/3	THF	−5 °C/24 h	(*S*)-**6**	82	67
16 [d]	6/3	THF	−10 °C/24 h	(*S*)-**6**	90	69
17 [d,f]	6/3	DME	0 °C/24 h	(*S*)-**6**	93	69

[a] To a solution of Cu salt and (*rac*; *S*,*S*)-**L1** in solvent (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). [b] CuOAc was used as a copper precatalyst. [c] The same data entry is shown in Table 4, as entry 5. [d] $Cu(ClO_4)_2$ was used as a copper precatalyst. [e] The same data entry is shown in Table 4, as entry 11. [f] DME (6 mL) was used.

In the CuOAc/(*rac*; *S*,*S*)-**L1** catalytic system, a 1:1 ratio of Cu/ligand was most effective (entries 1–3). We thus investigated the solvent effect on the reaction in the presence of 4 mol% of a 1:1 mixture of CuOAc and (*rac*; *S*,*S*)-**L1** (entries 3–5; *also see* Table S1). Although slightly lower enantioselectivity was observed in the catalytic reaction with Et_2O, a promising result was achieved with 1,2-dimethoxyethane (DME) (entries 4 and 5). Furthermore, a decrease in the reaction temperature to 0 °C improved the enantioselectivity (73–78% *ee*), even though a longer reaction time was needed (entries 6 and 7). The desired product (*R*)-**6** was obtained in 69% yield with 75% *ee* when the reaction was performed in DME at −10 °C for 48 h (entry 8). The facial selectivities of the 1,4-addition reaction using the $Cu(ClO_4)_2$/(*rac*; *S*,*S*)-**L1** catalytic system were reversed, compared to those of the CuOAc-catalyzed

reaction (Table 5, entries 9–17). Compound **5** was reacted with Et_2Zn catalyzed by 6 mol% of $Cu(ClO_4)_2$ and 4.5 mol% of (*rac*; *S*,*S*)-**L1** in THF at room temperature to afford (*S*)-**6** in 31% yield with 50% *ee* (entry 9). Changing the Cu/ligand ratio from 6/4.5 to 4.5/6 decreased the *ee* value (entry 10). Therefore, the reaction was performed in the presence of a catalytic amount of $Cu(ClO_4)_2$/(*rac*; *S*,*S*)-**L1** (6/3 mol%) to explore the effect of solvent (entries 11–13). Among the solvents examined, THF gave moderate enantioselectivity, providing (*S*)-**6** with 46% *ee* (entry 11). Fortunately, performing the catalytic reaction at a lower temperature remarkably increased the stereoselectivity (entries 14–16). Thus, treatment of **5** with Et_2Zn in the presence of $Cu(ClO_4)_2$ and (*rac*; *S*,*S*)-**L1** in THF at 0 °C for 24 h produced (*S*)-**6** in 89% yield with 70% *ee* (entry 14). Almost the same result was observed for the catalytic 1,4-addition reaction in DME at 0 °C for 24 h (entry 17).

In the Cu-catalyzed conjugate addition reaction of acyclic enone using the bis(NHC) ligand, we described successful enantioselectivity reversal by simply changing of the counter anion of the Cu salt. We then assumed that combining copper chloride with a silver salt facilitates the catalytic reaction and that a silver salt additive would control the setereoselectivity of the 1,4-addition reaction (Table 6).

Table 6. Switching of stereoselectivity in the $CuCl_n$-catalyzed conjugate addition reaction of **5** in the presence of an additive.

Entry	Cu Salt	Additive	(mol%)	Product	Yield (%)	*ee* (%)
1 [a,b]	CuOAc	none		(*R*)-**6**	49	78
2 [a]	CuCl	none		(*R*)-**6**	12	35
3 [a]	CuCl	AgOAc	4	(*R*)-**6**	47	86
4 [a]	CuCl	AgOAc	6	(*R*)-**6**	54	85
5 [a]	CuCl	AgOAc	8	(*R*)-**6**	21	74
6 [c,d]	$Cu(ClO_4)_2$			(*S*)-**6**	89	70
7 [c]	$CuCl_2$	none		(*R*)-**6**	79	48
8 [c]	$CuCl_2$	$AgClO_4$	12	(*S*)-**6**	93	68
9 [c]	$CuCl_2$	$AgClO_4$	15	(*S*)-**6**	90	66
10 [c]	$CuCl_2$	$AgClO_4$	6	(*S*)-**6**	80	66

[a] To a solution of Cu salt (4 mol%) and (*rac*; *S*,*S*)-**L1** (4 mol%) in DME (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). The reaction mixture was stirred at 0 °C for 24 h. [b] The same data entry is shown in Table 5, as entry 6. [c] To a solution of Cu salt (6 mol%) and (*rac*; *S*,*S*)-**L1** (3 mol%) in THF (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). The reaction mixture was stirred at 0 °C for 24 h. [d] The same data entry is shown in Table 5, as entry 14.

First, we tested the reaction of **5** with Et_2Zn catalyzed by CuCl (4 mol%) in the presence of (*rac*; *S*,*S*)-**L1** (4 mol%). This reaction afforded (*R*)-**6** in lower enantioselectivity, compared with the reaction using the CuOAc/(*rac*; *S*,*S*)-**L1** catalytic system (entries 1 and 2). As expected, adding AgOAc (4 mol%) to the CuCl-catalyzed reaction led to a remarkable increase in the stereoselectivity (86% *ee*) (entry 3). This result was comparable to that of the CuOAc-catalyzed reaction, meaning that the acetate anion would play an important role through interaction with a copper ion having the (*rac*; *S*,*S*)-**L1** ligand. Based on this assumption, an excess of AgOAc additive, with respect to the CuCl catalyst, was employed. The catalytic 1,4-addition reaction with a 1:1.5 molar ratio of CuCl/AgOAc provided (*R*)-**6** in 54% yield with 85% *ee*, whereas a greater excess (8 mol%) of AgOAc decreased its catalytic activity (entries 4 and 5).

Next, to test the influence of $AgClO_4$, the reaction of **5** with Et_2Zn catalyzed by $CuCl_2$ (6 mol%) in the presence of (*rac*; *S*,*S*)-**L1** (3 mol%) was performed as a control experiment. As with the CuCl-catalyzed reaction, the combination of $CuCl_2$ with (*rac*; *S*,*S*)-**L1** produced (*R*)-**6** (Table 6, entry 2 vs. entry 7). Interestingly, adding $AgClO_4$ to this catalytic system dramatically affected the facial selectivity of the approach of the substrates to the Cu species. Thus, the reaction of **5** with Et_2Zn in the presence of catalytic amounts of $CuCl_2$ (6 mol%), (*rac*; *S*,*S*)-**L1** (3 mol%), and $AgClO_4$ (12 mol%) afforded (*S*)-**6** in 93% yield with 68% *ee* (entry 8). This result was comparable to that of the $Cu(ClO_4)_2$-catalyzed reaction, as expected (entry 6 vs. entry 8). Using excess $AgClO_4$ (15 mol%) did not drastically affect the outcome

(entry 9). The reversal of enantioselectivity was also achieved in the $CuCl_2$-catalyzed conjugate reaction, using half the amount of $AgClO_4$ (6 mol%) (entry 10).

To evaluate the substrate scope and limitations of the developed catalytic reactions, several α,β-unsaturated enones were investigated (Table 7). The conjugate addition reaction of 5-methyl-3-hexen-2-one (**7**) with Et_2Zn in the presence of catalytic amounts of CuOAc and (*rac*; *S*,*S*)-**L1** yielded (*S*)-4-ethyl-5-methylhexan-2-one ((*S*)-**8**) with 69% *ee* (entry 3). In this reaction, a somewhat lower yield was probably due to steric hindrance in the substrate. In contrast, the 1,4-addition reaction of **7** catalyzed by $Cu(ClO_4)_2$ gave reversed enantioselectivity, affording (*R*)-**8** in 44–59% yield with 80–82% *ee* (entries 4 and 5). Additionally, when **7** was allowed to react with Et_2Zn using the combined catalytic system comprising $Cu(ClO_4)_2$ and the bis(NHC) azolium ligand having a *tert*-butyl group, (*rac*; *S*,*S*)-**L2**, (*R*)-**8** was obtained, with satisfactory enantioselectivity (75% *ee*) (entry 6).

Table 7. Exploring substrate scope.

Entry	Enone	Conjugate Adduct	Yield (%)	*ee* (%)
1 [a,b]	**5**	(*R*)-**6**	49	78
2 [c,d]	**5**	(*S*)-**6**	89	70
3 [a]	^{i}PrCH = CHCOMe (**7**)	(*S*)-**8**	15	69
4 [c]	**7**	(*R*)-**8**	44	82
5 [c,e]	**7**	(*R*)-**8**	59	80
6 [c,e,f]	**7**	(*R*)-**8**	64	75
7 [a]	PhCH = CHCOMe (**9**)	(*S*)-**10**	55	63
8 [c]	**9**	(*R*)-**10**	21	57
9 [a]	PhCH = CHCOPh (**11**)	(*S*)-**12**	33	55
10 [c]	**11**	(*R*)-**12**	16	15
11 [a]	**3**	(*R*)-**4**	38	57
12 [c]	**3**	(*S*)-**4**	64	47

[a] To a solution of CuOAc (4 mol%) and (*rac*; *S*,*S*)-**L1** (4 mol%) in DME (9 mL), Et_2Zn (3 mmol) was added first, then enone (1 mmol). The reaction mixture was stirred at 0 °C for 24 h. [b] The same data entry is shown in Table 5, as entry 6. [c] To a solution of $Cu(ClO_4)_2$ (6 mol%) and (*rac*; *S*,*S*)-**L1** (3 mol%) in THF (9 mL), Et_2Zn (3 mmol) was added first, then enone (1 mmol). The reaction mixture was stirred at 0 °C for 24 h. [d] The same data entry is shown in Table 5, as entry 14. [e] Reaction was conducted for 48 h. [f] **L2** in place of (*rac*; *S*,*S*)-**L1** was used.

Switching of stereoselectivity was also observed in the 1,4-addition reaction of benzalacetone (**9**). Treatment of **9** with Et_2Zn in the presence of catalytic amounts of CuOAc and (*rac*; *S*,*S*)-**L1** afforded (*S*)-4-phenylhexan-2-one ((*S*)-**10**) in 55% yield and 63% *ee* (entry 7), whereas (*R*)-**10** was obtained using $Cu(ClO_4)_2$ catalyst combined with the same ligand (entry 8). The results of the conjugate addition reaction of chalcone (**11**) differ from those for the reaction of **9**. Although the CuOAc/(*rac*; *S*,*S*)-**L1** system catalyzed the reaction of **11** with Et_2Zn to produce (*S*)-1,3-diphenylpentan-1-one ((*S*)-**12**) with 55% *ee* (entry 9), the $Cu(ClO_4)_2$/(*rac*; *S*,*S*)-**L1** catalytic system gave poor yield and stereoselectivity of (*R*)-**12** (entry 10).

The performance of both catalytic systems for in the Cu-catalyzed conjugate addition of cyclic enone were evaluated (Table 7, entries 11 and 12). As mentioned above, we previously reported successful enantioselectivity reversal of the Cu-catalyzed 1,4-addition reaction of **3** with Et_2Zn using the mono-NHC azolium ligand, **L4** (Figure 6), by changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$ [76]. The bis(NHC) azolium ligand, (*rac*; *S*,*S*)-**L1**, was suitable for achieving the enantioselectivity switch in the 1,4-addition reaction of both acyclic and cyclic enones. The combination of CuOAc and (*rac*; *S*,*S*)-**L1** catalyzed the reaction of **3** with Et_2Zn to afford the corresponding adduct (*R*)-**4** in 38% yield with 57% *ee* (entry 11). The facial selectivity of the 1,4-addition reaction using the $Cu(ClO_4)_2$/(*rac*; *S*,*S*)-**L1** catalytic system was reversed compared to that of the reaction using CuOAc (entry 12).

As shown in Table 2, a mixture of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** promoted the Cu-catalyzed conjugate addition reaction of *cyclic enone* with Et_2Zn, and using (*R*,*R*; *S*,*S*)-**L1** or (*S*,*S*; *S*,*S*)-**L1** alone led to a poor stereoselectivity. Based on this finding, we next investigated the catalytic reaction of *acyclic*

enone using a set of diastereomerically and enantiomerically pure azolium salts, (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** (Table 8).

Table 8. Effect of chiral azolium ligand **L1** in the conjugate addition reaction of **5**.

Entry	(*R*,*R*; *S*,*S*)-L1 (mol%)	(*S*,*S*; *S*,*S*)-L1 (mol%)	Product	Yield (%)	*ee* (%)
1 [a]	4	0	(*R*)-**6**	79	88
2 [a,b]	2	2	(*R*)-**6**	49	78
3 [a]	0	4	(*R*)-**6**	17	48
4 [a]	3	0	(*R*)-**6**	70	91
5 [c]	3	0	(*S*)-**6**	70	75
6 [c,d]	1.5	1.5	(*S*)-**6**	89	70
7 [c]	0	3	(*S*)-**6**	82	66

[a] To a solution of CuOAc (4 mol%) and **L1** in DME (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). The reaction mixture was stirred at 0 °C for 24 h. [b] The same data entry is shown in Table 5, as entry 6. [c] To a solution of $Cu(ClO_4)_2$ (6 mol%) and **L1** in THF (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). The reaction mixture was stirred at 0 °C for 24 h. [d] The same data entry is shown in Table 5, as entry 14.

Compound **5** was treated with Et_2Zn in the presence of catalytic amounts of CuOAc and (*R*,*R*; *S*,*S*)-**L1** in DME at 0 °C for 24 h to afford (*R*)-**6** in good yield and stereoselectivity (79% yield, 88% *ee*, entry 1). This is in contrast to the catalytic reaction of cyclic enone, where the Cu/(*R*,*R*; *S*,*S*)-**L1** catalytic system was inert (see Table 2). It is noteworthy that (*R*,*R*; *S*,*S*)-**L1** showed a superior catalytic performance compared a diastereomeric mixture of ligands, such as (*rac*; *S*,*S*)-**L1**, in the 1,4-addition reaction of acyclic enone (entry 1 vs. entry 2). In contrast to the catalytic conjugate addition reaction of **5** using (*R*,*R*; *S*,*S*)-**L1**, the reaction using (*S*,*S*; *S*,*S*)-**L1** proceeded, with difficulty, to produce the desired (*R*)-**6** (17% yield and 48% *ee*, entry 3). These results suggest that (*S*,*S*; *S*,*S*)-**L1** acts as a catalyst poison in the catalytic reaction with (*rac*; *S*,*S*)-**L1**. Additionally, an excellent *ee* value of 91% of (*R*)-**6** was obtained in the conjugate addition reaction of **5** with Et_2Zn using 4 mol% of CuOAc and 3 mol% of (*R*,*R*; *S*,*S*)-**L1** (entry 4).

Next, in the switchable enantioselective reaction using $Cu(ClO_4)_2$ precatalyst to provide (*S*)-**6**, the performances of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** were examined (Table 8, entries 5–7). With 6 mol% of $Cu(ClO_4)_2$, 3 mol% of chiral ligand containing (*R*,*R*; *S*,*S*)-**L1** and/or (*S*,*S*; *S*,*S*)-**L1** was employed in the conjugate addition reaction. These experiments showed the formation of the desired (*S*)-**6** with almost the same yields and enantioselectivities (66–75% *ee*) in each of the catalytic reactions (entries 5–7). These results differed from those of the CuOAc/**L1** catalytic system (entries 1–3). It could be assumed that the chiral hydroxyamide side arm of the bis(NHC) ligand would play an important role in the $Cu(ClO_4)_2$-catalyzed asymmetric conjugate addition reaction.

Finally, we highlighted the greater reactivity of the 1,2-diaminocyclohexane-based bis(NHC) ligand **L1** compared with those of chiral ligands based on other bis(NHC) skeletons. We synthesized three chiral ligands **L5**, **L6** and **L7** from 1,2-diaminoethane, 1,3-diaminobenzene and 1,2-benzenedimethanamine, respectively (Table 9).

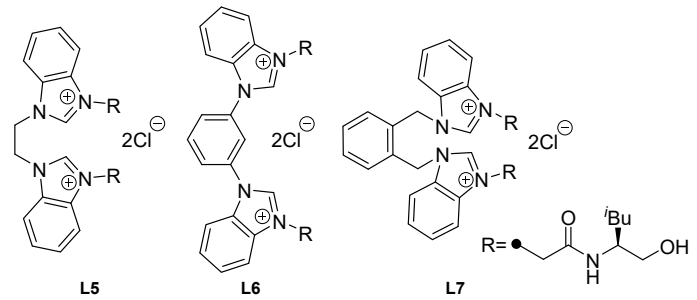
The reaction of **5** with Et_2Zn catalyzed by CuOAc in the presence of 1,2-diaminoethane-based bis(NHC) ligand **L5** provided the corresponding 1,4-adduct, (*R*)-**6**, in poor yield and stereoselectivity (entry 1). When the same reaction was conducted using the $Cu(ClO_4)_2$/**L5** catalytic system, the enantioselectivity of the reaction was reversed, affording (*S*)-**6** in 73% yield and 58% *ee* (entry 2). However, no reversal of enantioselectivity was observed in the catalytic reactions using 1,3-diaminobenzene-based chiral ligand **L6** (entries 3 and 4). Additionally, treatment of **5** with Et_2Zn catalyzed by CuOAc combined with 1,2-benzenedimethanamine-based ligand **L7** gave an almost racemic mixture of conjugate adduct **6** (entry 5). Conversely, the $Cu(ClO_4)_2$/**L7** catalytic system offered an efficient enantioselective protocol for the 1,4-addition reaction of **5** with Et_2Zn to afford (*S*)-**6** in 87% yield and 69% *ee* (entry 6). Based on the screening test using a series of

bis(NHC) ligands, the 1,2-diaminocyclohexane-derived skeleton is critically important for successful enantioselectivity switching.

Table 9. Effect of chiral ligand structure on switching of stereoselectivity in the conjugate addition reaction of **5**.

Entry	Cu Salt	Ligand	Product	Yield (%)	*ee* (%)
1 [a]	CuOAc	**L5**	(*R*)-**6**	12	27
2 [b]	$Cu(ClO_4)_2$	**L5**	(*S*)-**6**	73	58
3 [a]	CuOAc	**L6**	(*S*)-**6**	27	16
4 [b]	$Cu(ClO_4)_2$	**L6**	(*S*)-**6**	94	42
5 [a]	CuOAc	**L7**	(*S*)-**6**	31	5
6 [b]	$Cu(ClO_4)_2$	**L7**	(*S*)-**6**	87	69

[a] To a solution of CuOAc (4 mol%) and ligand (4 mol%) in DME (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). The reaction mixture was stirred at 0 °C for 24 h. [b] To a solution of $Cu(ClO_4)_2$ (6 mol%) and ligand (3 mol%) in THF (9 mL), Et_2Zn (3 mmol) was added first, then **5** (1 mmol). The reaction mixture was stirred at 0 °C for 24 h.



3. Experimental

3.1. General Procedures

All chemicals were obtained from commercial sources and were used as received. ^1H and ^{13}C NMR spectra were recorded on spectrometers at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra. $CDCl_3$ and $(CD_3)_2SO$ were used as the NMR solvent. Thin-layer chromatography (TLC) analysis was performed with glass-backed plates, pre-coated with silica gel and examined under UV (254 nm) irradiation. Flash column chromatography was executed on silica gel 60 (230–400; particle size: 0.040–0.063 nm).

3.2. Procedure for Preparation of Azolium Salt *L1*

Azoles were synthesized from *trans*-1,2-cyclohexanediamine (**1**) according to the literature procedure [47,59]. The reaction mixture of azole (485 mg, 1.5 mmol) and α-chloroacetamide (580 mg, 3.0 mmol), derived from chloroacetyl chloride and luecinol, was heated to 110 °C and stirred for 2 days. After the reaction, the solvent was removed under reduced pressure. The desired product was isolated from the crude residue by column chromatography (SiO_2, CH_2Cl_2/CH_3OH = 8/2) to yield the light yellow solution after removing the solvent. The residue was dissolved in methanol, and then activated carbon (ca. 1 g) was added. After 3 h, the activated carbon was removed by filtration. After removing the CH_3OH in vacuo from the filtrate, the azolium salt **L1** was purified by reprecipitation using CH_3OH and $CH_3CO_2C_2H_5$ affording white solid (yield: 710 mg, 62%). Compounds (*rac*; *S*,*S*)-**L1**, (*rac*; *R*,*R*)-**L1**, **L5** and **L6** were reported in our previous publication [81].

(*R*,*R*; *S*,*S*)-**L1**. White solid. ^1H-NMR ($(CD_3)_2SO$, 400 MHz): δ 10.66 (s, 2H, NCHN), 8.60 (d, *J* = 8.2 Hz, 2H, NCCH), 7.94 (br, 2H, NH), 7.69 (d, *J* = 7.8 Hz, 2H, NCCH), 7.39–7.33 (m, 4H, NCCHC*H*), 5.81–5.79 (m, 2H, NCH), 5.31 (d, *J* = 16.0 Hz, 2H, NCH_2CO), 5.23 (d, *J* = 16.0 Hz, 2H, NCH_2CO), 4.69 (br, 2H, OH), 3.86–3.78 (m, 2H, NHC*H*)), 3.41 (br, 4H, CH_2OH), 2.61 (br, 2H), 2.46–2.43 (m, 2H), 2.07–2.05 (m,

2H), 1.87–1.85 (m, 2H), 1.67–1.57 (m, 2H, $CH_{i\mathrm{Bu}}$), 1.37 (t, *J* = 7.1 Hz, 4H, $CH_{2i\mathrm{Bu}}$), 0.87 (d, *J* = 6.9 Hz, 6H, $CH_{3i\mathrm{Bu}}$), 0.82 (d, *J* = 6.9 Hz, 6H, $CH_{3i\mathrm{Bu}}$); ^{13}C-NMR (100 MHz): δ 163.1 (CO), 142.5 (NCHN), 130.2, 129.9, 126.3, 126.2, 112.7 (NC), 112.4 (NC), 63.1 (CH_2OH), 60.0 (CH_2CO), 49.8 (NCH), 48.6 (NHCH), 39.5, 30.7, 23.9 ($CH_{2i\mathrm{Bu}}$), 23.5 ($CH_{i\mathrm{Bu}}$), 22.6 ($CH_{3i\mathrm{Bu}}$), 21.6 ($CH_{3i\mathrm{Bu}}$).

(*S*,*S*; *S*,*S*)-**L1**. White solid. ^{1}H-NMR ($(CD_3)_2SO$, 400 MHz): δ 10.65 (s, 2H, NCHN), 8.63 (d, *J* = 8.7 Hz, 2H, NCCH), 8.00 (br, 2H, NH), 7.69 (d, *J* = 7.8 Hz, 2H, NCCH), 7.41–7.34 (m, 4H, NCCHC*H*), 5.84–5.82 (m, 2H, NCH), 5.30 (d, *J* = 16.0 Hz, 2H, NCH_2CO), 5.25 (d, *J* = 16.0 Hz, 2H, NCH_2CO), 4.68 (br, 2H, OH), 3.85–3.77 (m, 2H, NHC*H*), 3.39 (br, 4H, CH_2OH), 2.61 (br, 2H), 2.46–2.43 (m, 2H), 2.06–2.04 (m, 2H), 1.88–1.86 (m, 2H), 1.70–1.56 (m, 2H, $CH_{i\mathrm{Bu}}$), 1.37 (t, *J* = 7.3 Hz, 4H, $CH_{2i\mathrm{Bu}}$), 0.88 (d, *J* = 6.9 Hz, 6H, $CH_{3i\mathrm{Bu}}$), 0.83 (d, *J* = 6.9 Hz, 6H, $CH_{3i\mathrm{Bu}}$); ^{13}C-NMR (100 MHz): δ 163.1 (CO), 142.5 (NCHN), 130.3, 129.8, 126.3, 112.7 (NC), 112.5 (NC), 63.2 (CH_2OH), 60.1 (CH_2CO), 49.8 (NCH), 48.5 (NHCH), 39.6, 30.7, 24.0 ($CH_{2i\mathrm{Bu}}$), 23.5 ($CH_{i\mathrm{Bu}}$), 22.6 ($CH_{3i\mathrm{Bu}}$), 21.6 ($CH_{3i\mathrm{Bu}}$).

(*S*,*S*; *R*,*R*)-**L1**. White solid. ^{1}H-NMR ($(CD_3)_2SO$, 400 MHz): δ 10.65 (s, 2H, NCHN), 8.59 (d, *J* = 8.5 Hz, 2H, NCCH), 7.93 (br, 2H, NH), 7.69 (d, *J* = 7.6 Hz, 2H, NCCH), 7.39–7.32 (m, 4H, NCCHC*H*), 5.81–5.79 (m, 2H, NCH), 5.30 (d, *J* = 15.7 Hz, 2H, NCH_2CO), 5.22 (d, *J* = 15.7 Hz, 2H, NCH_2CO), 4.68 (br, 2H, OH), 3.86–3.78 (m, 2H, NHC*H*), 3.42–3.39 (m, 4H, CH_2OH), 2.61 (br, 2H), 2.46–2.43 (m, 2H), 2.07–2.05 (m, 2H), 1.87–1.85 (m, 2H), 1.67–1.56 (m, 2H, $CH_{i\mathrm{Bu}}$), 1.37 (t, *J* = 7.0 Hz, 4H, $CH_{2i\mathrm{Bu}}$), 0.87 (d, *J* = 6.7 Hz, 6H, $CH_{3i\mathrm{Bu}}$), 0.82 (d, *J* = 6.7 Hz, 6H, $CH_{3i\mathrm{Bu}}$); ^{13}C-NMR (100 MHz): δ 163.1 (CO), 142.5 (NCHN), 130.2, 129.9, 126.3, 126.2, 112.7 (NC), 112.3 (NC), 63.1 (CH_2OH), 60.1 (CH_2CO), 49.8 (NCH), 48.6 (NHCH), 39.5, 30.8, 23.9 ($CH_{2i\mathrm{Bu}}$), 23.5 ($CH_{i\mathrm{Bu}}$), 22.6 ($CH_{3i\mathrm{Bu}}$), 21.6 ($CH_{3i\mathrm{Bu}}$).

(*R*,*R*; *R*,*R*)-**L1**. White solid. ^{1}H-NMR ($(CD_3)_2SO$, 400 MHz): δ 10.53 (s, 2H, NCHN), 8.52 (d, *J* = 8.5 Hz, 2H, NCCH), 7.91 (br, 2H, NH), 7.68 (d, *J* = 8.1 Hz, 2H, NCCH), 7.43–7.34 (m, 4H, NCCHC*H*), 5.77–5.75 (m, 2H, NCH), 5.26 (d, *J* = 16.0 Hz, 2H, NCH_2CO), 5.22 (d, *J* = 16.0 Hz, 2H, NCH_2CO), 4.63 (br, 2H, OH), 3.86–3.78 (m, 2H, NHC*H*), 3.43–3.36 (m, 4H, CH_2OH), 2.58 (br, 2H), 2.47–2.44 (m, 2H), 2.09–2.06 (m, 2H), 1.86–1.82 (m, 2H), 1.69–1.57 (m, 2H, $CH_{i\mathrm{Bu}}$), 1.38 (t, *J* = 7.0 Hz, 4H, $CH_{2i\mathrm{Bu}}$), 0.89 (d, *J* = 6.7 Hz, 6H, $CH_{3i\mathrm{Bu}}$), 0.85 (d, *J* = 6.7 Hz, 6H); ^{13}C-NMR (DMSO, 100 MHz): δ 163.1 (CO), 142.5 (NCHN), 130.3, 129.8, 126.3, 112.7 (NC), 112.5 (NC), 63.1 (CH_2OH), 60.1 (CH_2CO), 49.8 (NCH), 48.5 (NHCH), 39.6, 30.7, 24.0 ($CH_{2i\mathrm{Bu}}$), 23.5 ($CH_{i\mathrm{Bu}}$), 22.6 ($CH_{3i\mathrm{Bu}}$), 21.6 ($CH_{3i\mathrm{Bu}}$).

L2. White solid. ^{1}H-NMR ($(CD_3)_2SO$, 400 MHz): δ 10.69 (br, 2H, NCHN), 8.48 (br, 2H, NCCH), 7.96 (br, 2H, NH), 7.72 (br, 2H, NCCH), 7.35 (br, 4H, NCCHC*H*), 5.80 (br, 2H, NCH), 5.43–5.31 (m, 4H, NCH_2CO), 4.55 (br, 2H, OH), 3.65–3.60 (m, 4H, CH_2OH), 3.48–3.45 (m, 2H, NHC*H*), 2.61 (br, 2H), 2.50–2.44 (m, 2H), 2.02 (br, 2H), 1.85 (br, 2H), 0.88 (m, 18H, $CH_{3t\mathrm{Bu}}$). Because of the presence of the diastereoisomeric mixture, so many broad signals appeared in ^{1}H-NMR, that the failure of ^{13}C-NMR measurement in $(CD_3)_2SO$ was observed. Elemental analysis: Calculated for $C_{36}H_{52}Cl_2N_6O_4{\cdot}3H_2O$: C, 57.06; H, 7.72; N, 11.09. Found: C, 56.74; H, 7.41; N, 10.86%. M.p. 204-216 °C (decompose).

L3. White solid. ^{1}H-NMR ($(CD_3)_2SO$, 400 MHz): δ 10.65 (s, 2H, NCHN), 8.86 (br, 2H, NCCH), 8.00 (br, 2H, NH), 7.70 (d, *J* = 7.7 Hz, 2H, NCCH), 7.40–7.30 (m, 4H, NCCHC*H*), 5.83 (br, 2H, NCH), 5.30 (d, *J* = 16.3 Hz, 2H, NCH_2CO), 5.24 (d, *J* = 16.3 Hz, 2H, NCH_2CO), 4.77 (br, 2H, OH), 3.49–3.47 (m, 4H, CH_2OH), 3.22–3.19 (m, 4H, NH(CH_2)$_2$OH), 2.61 (br, 2H), 2.44–2.41 (m, 2H), 2.03–2.01 (m, 2H), 1.85 (br, 2H). Failure of ^{13}C-NMR measurement in $(CD_3)_2SO$ was observed. Elemental analysis: Calculated for $C_{28}H_{36}Cl_2N_6O_4{\cdot}3H_2O$: C, 52.09; H, 6.56; N, 13.02. Found: C, 51.67; H, 6.36; N, 12.88%. M.p. 86.4–89.5 °C.

L7. White solid. ^{1}H-NMR ($(CD_3)_2SO$, 400 MHz) δ 9.94 (s, 2H, NCHN), 8.71 (d, *J* = 8.5 Hz, 2H), 8.02–7.97 (m, 4H, NH), 7.71–7.64 (m, 4H), 7.41–7.38 (m, 2H), 7.16–7.14 (m, 2H), 6.17 (s, 4H, NCH_2C), 5.42 (d, *J* = 16.4 Hz, 2H, NCH_2CO), 5.35 (d, *J* = 16.4 Hz, 2H, NCH_2CO), 4.88 (br, 2H, OH), 3.83–3.77 (m, 2H, NHC*H*), 3.40–3.32 (br, 4H, CH_2OH), 1.64–1.57 (m, 2H, $CH_{i\mathrm{Bu}}$), 1.36–1.30 (m, 4H, $CH_{2i\mathrm{Bu}}$), 0.86 (d, *J* = 6.4 Hz, 6H, $CH_{3i\mathrm{Bu}}$), 0.79 (d, *J* = 6.4 Hz, 6H, $CH_{3i\mathrm{Bu}}$); ^{13}C-NMR (100 MHz) δ 164.0 (CO), 143.9 (NCHN), 132.2, 131.6, 130.8, 129.3, 128.4, 126.9, 126.8, 114.1 (NC), 113.7 (NC), 63.5 (CH_2OH), 49.7, 48.8, 47.5, 39.5 ($CH_{2i\mathrm{Bu}}$),

24.2 ($CH_{i\mathrm{Bu}}$), 23.3 ($CH_{3i\mathrm{Bu}}$), 21.8 ($CH_{3i\mathrm{Bu}}$). Elemental analysis: Calculated for $C_{38}H_{50}Cl_2N_6O_4 \cdot 1.5H_2O$: C, 59.91; H, 7.15; N, 11.03. Found: C, 60.13; H, 6.96; N, 10.95%. M.p. 165–174 °C (decompose).

3.3. General Procedure for Cu-Catalyzed Asymmetric Reaction of Enone with Et_2Zn

Cu salt and azolium salt were added to anhydrous THF. After stirring at room temperature for 1 h, the mixture was cooled to 0 °C. Then, Et_2Zn (3 mmol, 1 M in hexanes, 3 mL) was added to the reaction vessel. After the resulting mixture was stirred at room temperature for 30 min, a solution of enone (1 mmol) in anhydrous THF was added dropwise over a period of 10 min. After stirring at room temperature for 3 h, the reaction was quenched with 10% HCl aq. The product yield was determined by GC using internal standard technique. The enantiomeric excess was measured by the chiral GC (see Supplementary Materials). The conjugate adduct was isolated as follows: After quenching the reaction mixture with 10% HCl aq., the resulting mixture was extracted with diisopropyl ether (3 × 10 mL) and dried over Na_2SO_4. The product was purified by silica gel column chromatography (hexane/Et_2O).

4. Conclusions

We demonstrated that a chiral bis(NHC) ligand precursor **L1**, which is a dibenzimidazolium salt having a hydroxyamide side arm, efficiently performs Cu-catalyzed asymmetric conjugate addition of Et_2Zn to cyclic or acyclic enones. In the catalytic 1,4-addition reaction of cyclic enone **3** with Et_2Zn, an excellent enantioselectivity (up to 97% *ee*) was achieved with the Cu(hfacac)(btmsa)/(*rac*; *S*,*S*)-**L1** catalytic system. Further investigations revealed that a 9:1 or 1:9 mixture of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S*; *S*,*S*)-**L1** promoted the highly enantioselective catalytic reaction. A potential application of the Cu/**L1** catalytic system was investigated in the enantioselective 1,4-addition reaction of acyclic enones with Et_2Zn. Interestingly, the stereoselectivity switching was observed in the Cu-catalyzed 1,4-addition reaction of **5** with Et_2Zn in the presence of **L1** when changing the counter anion on the Cu precatalyst.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/9/780/s1: NMR charts; Selected chiral GC and LC traces in the catalytic reactions; Table S1: CuOAc-catalyzed reaction of **5** with E_2Zn yielding (*R*)-**6**; Table S2: $Cu(ClO_4)_2$-catalyzed reaction of **5** with E_2Zn yielding (*S*)-**6**.

Author Contributions: Conceptualization, Methodology and Writing—original draft preparation, S.S.; Investigation—experiments and analyses, A.I., S.K., and Y.I.; Writing—review and editing, S.S.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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