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C_2-symmetric functionalized azolium salt from serine ester for Cu-catalyzed asymmetric conjugate addition reaction

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ABSTRACT

C_2-symmetric ester-amide functionalized azolium salt was synthesized from readily available α-amino ester such as *L*-serine methyl ester. The combination of a Cu salt and the chiral azolium salt promoted the asymmetric conjugate addition reaction of enones with dialkylzincs. Thus, treatment of acyclic enone such as chalcone with Et_2Zn afforded the corresponding 1,4-adduct with up to 85% ee. An excellent ee value of 93% was obtained when 3-nonen-2-one was reacted with Et_2Zn. The present catalytic system was found to be useful for the 1,4-addition reaction of cyclic enone. For example, the reaction of 2-cyclohepten-1-one with Et_2Zn produced (*R*)-3-ethylcycloheptanone with 80% ee.

1. Introduction

The synthesis of efficient enantiopure ligands that provide a chiral environment to metals for asymmetric catalysis is currently one of the major challenges in synthetic organic chemistry. Natural amino acids provide an easily accessible, inexpensive, and optically pure source for the chiral ligand design [1]. In the last decade, N-heterocyclic carbenes (NHCs) have attracted increasing attention because of their function as efficient ligands in coordination chemistry and homogeneous catalysis [2]. For the design of an efficient chiral ligand, the introduction of an appropriate hemilabile chiral donor group at the NHC side-arm provides a relatively inflexible chelating NHC-based ligand, which is expected to offer a key structure for constructing an efficient stereodirecting group [3].

The Cu-catalyzed asymmetric conjugate addition (ACA) of alkylating reagents to enones is one of the most important and versatile strategies for enantioselective carbon–carbon bond formation [4]. An impressive array of chiral ligands have been developed to control the stereochemistry of 1,4-addition reactions [5,6]. Among the different systems investigated for ACA, NHC and phosphorus-based polydentate ligands have shown significant promise. Despite efficiency, ACA can still be improved in terms of enantioselectivity and substrate scope. For example, much attention has been paid to the enantioselective conjugate addition of organometallic reagents to *cyclic enones* catalyzed by NHC–Cu complexes; however, the highly enantioselective catalytic reaction of *acyclic enones* has been rarely reported. The difficulty in the stereoselective reaction of acyclic enones is assumed to be caused by the *s*-cis/*s*-trans conformational flexibility [6a,7]. To the best of our knowledge, only one report by Katuski and Uchida showed the reaction of alkenyl phenyl ketones with Et_2Zn catalyzed by $Cu(OTf)_2$ and a chiral NHC, where the ligand precursor was an imidazolium compound containing 1,2-diphenylethylenediamine skeleton as the chiral source [8].

As a part of our research program on developing chiral NHC ligand precursors from natural amino acid derivatives, we reported the Cu-catalyzed enantioselective conjugate addition reaction of *cyclic enone* using a C_2-symmetric bis(hydroxy-amide)-functionalized azolium ligand precursor [9,10a]. Recently, we also reported that structurally similar bis(ester-amide)-functionalized azolium compound can be synthesized from amino esters such as serine ester [10b]. Fortunately, the combination of a Cu salt and the bis(ester-amide)-functionalized NHC ligand promoted the 1,4-addition of *acyclic enones*. While the C_2-symmetric chiral ligand derived from serine ester has been studied in a few examples of ACA reaction of acyclic enones, their applications in ACA reaction of both acyclic and cyclic enones have not been yet studied. This prompted us to continue to study the potential of this promising class of C_2-symmetric functionalized NHC ligand to expand the substrate scope of ACA reaction. Herein, we report the Cu-catalyzed ACA reaction under the influence of bis(ester-amide)-functionalized NHC ligand precursors for both *acyclic* and *cyclic enones*.

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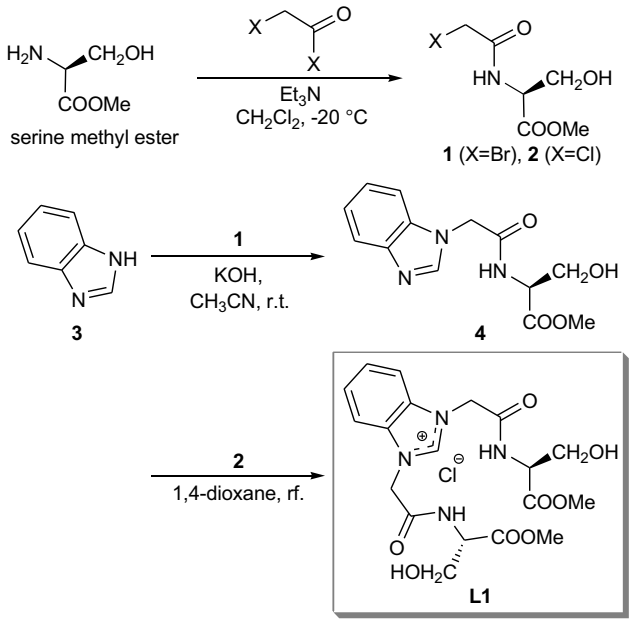


Scheme 1. Facile synthetic route to C_2-symmetric azolium salt **L1** from serine ester.

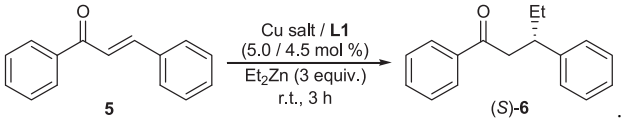
2. Results and discussion

C_2-symmetric azolium compound **L1**, which is the NHC ligand precursor developed in our laboratory, was prepared by a three-step synthesis from a natural amino ester (Scheme 1). The reaction of serine methyl ester with bromoacetyl bromide or chloroacetyl chloride afforded the corresponding α-bromo- or α-chloroacetamide derivative, **1** or **2**, respectively, in almost quantitative yield. The ester-amide group was attached to the benzimidazole ring by reacting **1** with benzimidazole (**3**) in the presence of KOH in CH_3CN at room temperature. Subsequently, the reaction of functionalized benzimidazole **4** with **2** afforded benzimidazolium salt **L1** in 71% yield. This synthetic approach offers several advantages: (i) the starting materials are readily available; (ii) all reaction conditions are simple; (iii) azolium ligand precursor **L1** is air-stable and easy to handle.

For the catalytic ACA, the reaction of chalcone (**5**) with Et_2Zn to afford 1,3-diphenylpentan-1-one (**6**) was selected as the model reaction [6,8]. The performance of azolium salt **L1** in the Cu-catalyzed ACA was evaluated (Table 1). The reaction in the presence of catalytic amounts of $Cu(OTf)_2$ and **L1** at room temperature afforded (*S*)-**6** in 79% yield and with 74% ee (entry 1). The use of a Cu(I) salt, such as $[Cu(CH_3CN)_4](OTf)$, resulted in almost same enantioselectivity with a slightly lower yield (entry 2). Although the reaction was catalyzed by $Cu(hfacac)_2$ and **L1** to afford (*S*)-**6** with moderate enantioselectivity (73% ee), the Cu precatalysts such as $Cu(acac)_2$ and Cu(hfacac)(btmsa) did not work efficiently (entries 3–5). The first promising result was achieved when the reaction was performed with inexpensive $Cu(NO_3)_2$. Thus, a combination of $Cu(NO_3)_2$ and **L1** catalyzed the reaction of **5** with Et_2Zn in THF at ambient temperature to afford the corresponding adduct (*S*)-**6** in 95% yield and with 77% ee (entry 6).

The solvent effect was also examined. Other ethereal solvents such as 2-methyltetrahydrofuran and diethyl ether afforded (*S*)-**6** with difficulty (entries 7 and 8). The reaction using a nonpolar solvent such as toluene significantly decreased the enantioselectivity (only 2% ee), whereas the enantioselectivity of the reaction in a polar solvent such as EtOAc was similar to that in THF (entries 9 and 10). Recently, Zhang and co-workers reported that the combination of $Cu(OAc)_2$ and phosphoramidite ligands bearing a D_2-symmetric biphenyl backbone promoted the conjugate addition of Et_2Zn to **5**. In their catalytic system, the use of THF afforded the 1,4-adduct with *R* configuration (99% ee), whereas the use of toluene afforded the adduct with *S* configuration (92% ee) [6c]. In contrast, such a reversal of enantioselectivity based on the solvent employed was not observed in this catalytic system.

Table 1
ACA reaction of **5** with Et_2Zn catalyzed by Cu salt and **L1** to afford (*S*)-**6**.[a]



Entry	Cu salt	Solvent	Yield (%)[b]	Ee (%)[c]
1	$Cu(OTf)_2$	THF	79	74
2	$[Cu(CH_3CN)_4](OTf)$	THF	64	76
3	$Cu(hfacac)_2$[d]	THF	44	73
4	$Cu(acac)_2$	THF	23	46
5	Cu(hfacac)(btmsa)[e]	THF	15	23
6	$Cu(NO_3)_2$	THF	95	77
7	$Cu(NO_3)_2$	2-MeTHF[f]	76	62
8	$Cu(NO_3)_2$	Et_2O	30	53
9	$Cu(NO_3)_2$	Toluene	22	2
10	$Cu(NO_3)_2$	EtOAc	30	76
11[g]	$Cu(NO_3)_2$	THF	99	72
12[h]	$Cu(NO_3)_2$	THF	82	78
13[i]	$Cu(NO_3)_2$	THF	86	72
14[j]	$Cu(NO_3)_2$	THF	84	75
15[k]	$Cu(NO_3)_2$	THF	74	79
16[l]	$Cu(NO_3)_2$	THF	22	85
17[m]	$Cu(NO_3)_2$	THF	93	82
18[m]	$Cu(hfacac)_2$	THF/EtOAc	80	85

[a] **5** (1 mmol), Et_2Zn (3 mmol), Cu salt (5.0 mol%), **L1** (4.5 mol%), solvent (9 mL), r.t., 3 h.
[b] Determined by ^{1}H-NMR analysis using 1-methylnaphthalene as the internal standard.
[c] Determined by HPLC analysis.
[d] Bis(hexafluoroacetylacetonato)copper(II).
[e] [Bis(trimethylsilyl)acetylene](hexafluoroacetylacetonato)copper(I).
[f] 2-Methyltetrahydrofuran.
[g] Catalyst loading Cu/**L1** (4.5/4.5 mol%).
[h] Catalyst loading Cu/**L1** (6.0/4.5 mol%).
[i] Catalyst loading Cu/**L1** (4.0/4.5 mol%).
[j] Catalyst loading Cu/**L1** (6.0/3.0 mol%).
[k] Reaction was conducted at 0 °C for 3 h.
[l] Reaction was conducted at −20 °C for 3 h.
[m] Reaction was conducted at −20 °C for 24 h.

The effects of the copper/ligand ratio and catalyst loading on the stereoselectivity of the reaction of **5** with Et_2Zn in THF were examined (entries 11–14). The reaction with a Cu/ligand ratio of 1:1, 1.3:1, and 2:1 occurred in a similar manner to afford the corresponding adduct in 72% ee, 78% ee, and 75% ee, respectively (entries 11, 12, and 14). These results show that probably the same catalytic active species were formed under these reaction conditions. The decrease in the reaction temperature to −20 °C improved the enantioselectivity (82–85% ee), even though the longer reaction time was needed (entries 16 and 17). At −20 °C, **5** reacted with Et_2Zn in the presence of catalytic amounts of $Cu(hfacac)_2$ and **L1** to afford (*S*)-**6** in 80% yield and with good enantioselectivity (85% ee) (entry 18).

With the encouraging results obtained using C_2-symmetric azolium ligand precursor **L1**, a series of NHC-based ligands were screened (Tables 2 and 3). The chiral ligands evaluated in this study are ester-amide-functionalized azolium salts **L1–L6** derived from serine, leucine, or *tert*-leucine (Scheme 2).

First, the enantiomer of benzimidazolium salt *ent*-**L1** was prepared from commercially available *D*-serine methyl ester by a similar procedure used for **L1** (Scheme 1). The Cu-catalyzed conjugate addition reaction of **5** with Et_2Zn under the influence of *ent*-**L1** proceeded in a similar manner as the reaction under **L1** to

Table 2
Evaluation of chiral azolium ligands **L1–L4** derived from serine ester in the $Cu(NO_3)_2$-catalyzed reaction of **5** with Et_2Zn to afford (*R*)- or (*S*)-**6**.[a]

Entry	Azolium salt	Yield (%)[b]	Ee (%)[b]
1	**L1**	95	77 (*S*)
2[c]	*ent*-**L1**	92	76 (*R*)
3	**L2**	87	68 (*S*)
4	**L3**	99	52 (*S*)
5	**L4**	99	45 (*S*)
6[d]	**L1**	63	80 (*S*)
7[e]	**L1**	63	76 (*S*)
8[f]	**L1**	60	67 (*S*)

[a] **5** (1 mmol), Et_2Zn (3 mmol), $Cu(NO_3)_2$ (5.0 mol%), azolium salt (4.5 mol%), THF (9 mL), r.t., 3 h.
[b] See Table 1 b and c.
[c] Azolium ligand precursor was prepared from D-serine methyl ester.
[d] Result for the reaction of 4-chlorochalcone yielding (*S*)-3-(4-chlorophenyl)-1-phenylpentan-1-one.
[e] Result for the reaction of 4′-chlorochalcone yielding (*S*)-1-(4-chlorophenyl)-3-phenylpentan-1-one.
[f] Result for the reaction of 4-methoxychalcone yielding (*S*)-3-(4-methoxyphenyl)-1-phenylpentan-1-one.

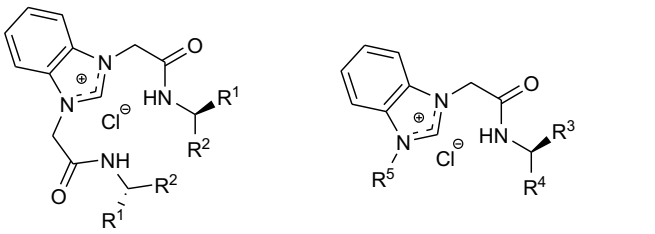
Table 3
Further investigations on the Cu-catalyzed ACA of Et_2Zn to **5** under the influence of azolium salts **L5–L7** to afford (*R*)- or (*S*)-**6**.[a]

Entry	Cu salt	Azolium	Yield (%)[b]	Ee (%)[b]
1	$Cu(NO_3)_2$	**L5**	65	18 (*S*)
2	$Cu(NO_3)_2$	**L6**	8	36 (*S*)
3	$Cu(NO_3)_2$	**L7**	70	37 (*S*)
4	$Cu(OTf)_2$	**L7**	41	7 (*S*)
5	$[Cu(CH_3CN)_4](OTf)$	**L7**	26	26 (*S*)
6[c]	$[Cu(CH_3CN)_4](OTf)$	**L7**	98	74 (*S*)
7[c,d]	$[Cu(CH_3CN)_4](OTf)$	**L7**	87	56 (*S*)

[a] **5** (1 mmol), Et_2Zn (3 mmol), Cu salt (5.0 mol%), azolium salt (4.5 mol%), THF (9 mL), r.t., 3 h.
[b] See Table 1 b and c.
[c] Et_2Zn (4 mmol), $[Cu(CH_3CN)_4](OTf)$ (4.0 mol%), azolium salt (6.0 mol%), 2-MeTHF (6 mL).
[d] Reaction was conducted at −20 °C for 24 h.

afford (*R*)-**6** in 92% yield and with 76% ee (Table 2, entries 1 and 2). The replacement of the methyl ester (azolium ligand **L1**) by an ethyl ester (azolium ligand **L2**) slightly decreased the yield and enantioselectivity (entry 3).

It is important to highlight the greater selectivity of the C_2-symmetric ligand such as bis(ester-amide)-functionalized azolium salt **L1** than that of the chiral ligand precursor with both the ester-amide and alkyl functional groups on the azolium ring. Two azolium ligand precursors with N-methyl and N-benzyl substituents, **L3** and **L4**, respectively, were selected. The reaction of **5** with Et_2Zn catalyzed by $Cu(NO_3)_2$ and **L3** afforded (*S*)-**6** in 99% yield and with moderate enantioselectiviy (52% ee) (entry 4). Almost similar result was obtained in the case of the reaction under the influence of **L4** (45% ee) (entry 5). The pincer-type ligands act as tightly coordinating polydentate ligands and provide C_2-symmetric and meridional environment around the metal center [11]. Therefore, the metal complex of the pincer ligand such as **L1** may become a suitable catalyst to recognize the prochiral face of a substrate rather than **L3** or **L4**. Additionally, the ACA reaction of several chalcone derivatives with Et_2Zn by the $Cu(NO_3)_2$/**L1** catalytic system was investigated (entries 6–8). Unfortunately, however, the product yields and enantioselectivities were slightly lowered under these reaction conditions, respectively.



- ***From serine ester***
  L1 (R^1=CH_2OH, R^2=COOMe)
  L2 (R^1=CH_2OH, R^2=COOEt)
  L3 (R^3=CH_2OH, R^4=COOMe, R^5=Me)
  L4 (R^3=CH_2OH, R^4=COOMe, R^5=Bn)
- ***From leucine, tert-leucine and tert-leucinol***
  L5 (R^1=^{t}Bu, R^2=COOMe)
  L6 (R^1=^{t}Bu, R^2=COOMe)
  L7 (R^1=^{t}Bu, R^2=CH_2OH)

Scheme 2. List of chiral azolium ligand precursors.

Encouraged by the results using C_2-symmetric chiral NHC ligand **L1** derived from natural amino acid such as serine (Tables 1 and 2), we next investigated the structurally similar azolium ligand precursors **L5** and **L6** prepared from commercially available chiral α-amino ester, leucine and *tert*-leucine, respectively (Scheme 2 and Table 3).

The replacement of the hydroxymethyl group (azolium **L1**) to isobutyl group (azolium **L5**) at the stereogenic center on the NHC side-arm decreased the enantioselectivity (18% ee) in the Cu-catalyzed conjugate addition of Et_2Zn to **5** (Table 3, entry 1). Although the use of more sterically hindered *tert*-butyl group (azolium **L6**) slightly improved the stereoselectivity (36% ee), the conjugate adduct was obtained in a very low yield (8%) (entry 2).

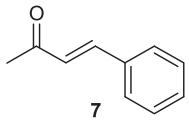
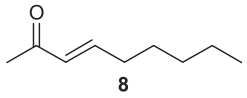
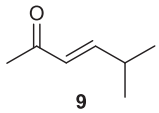
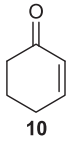
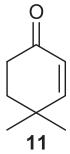
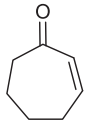
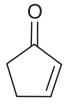
We previously designed and synthesized a C_2-symmetric bis(hydroxy-amide)-functionalized benzimidazolium salt **L7** from a chiral β-amino alcohol such as *tert*-leucinol that could be prepared easily by the reduction of *tert*-leucine [11a]. When **5** was reacted with Et_2Zn catalyzed by $Cu(NO_3)_2$ and **L7** in THF at room temperature, the desired product (*S*)-**6** was obtained in 70% yield (Table 3, entry 3). The enantioselectivity obtained using **L7** was comparable to that obtained using **L6** (entry 2 vs. entry 3). After several experiments, we were pleased to find that the use of **L7** increased the enantioselectivity of the ACA reaction (entry 6). The treatment of **5** with Et_2Zn in the presence of catalytic amounts of $[Cu(CH_3CN)_4](OTf)$ and **L7** at room temperature afforded (*S*)-**6** in 98% yield and with good enantioselectivity (74% ee). However, lowering the reaction temperature to −20 °C decreased the enantioselectivity (entry 7). This is in contrast to the result of the reaction using $Cu(NO_3)_2$/**L1** catalytic system where a high enantioselectivity was achieved (up to 85% ee) in the conjugated addition reaction at −20 °C (Table 1, entries 16–18).

Finally, to evaluate the substrate scope and limitations of the developed catalytic reaction, a set of seven α,β-unsaturated enones was investigated regarding the effect of the structural differences of the substrates on the product yield and enantioselectivity. To demonstrate the versatility of bis(ester-amide)-functionalized NHC ligand precursor **L1**, two catalytic systems were selected as follows: **Method A**: the combination of $Cu(NO_3)_2$ and **L1**; **Method B**: the combination of $Cu(hfacac)_2$ and **L1** (Table 4).

These catalytic systems were suitable for the 1,4-addition reaction of benzalacetone (**7**). The reaction of **7** with Et_2Zn in the presence of catalytic amounts of $Cu(NO_3)_2$ and **L1** in THF at room temperature afforded (*S*)-4-phenylhexan-2-one in 86% yield and with 85% ee (entry 1). The facial selectivity of the addition of the alkylating reagent to **7** was similar to that observed in the reaction of **5** with Et_2Zn as shown in Table 1. Almost the same result was obtained when the reaction of **7** with Et_2Zn was performed using $Cu(hfacac)_2$/**L1** catalytic system (entry 2).

An excellent ee value of 93% was obtained when 3-nonen-2-one (**8**) was reacted with Et_2Zn catalyzed by $Cu(NO_3)_2$ and **L1** to afford (*R*)-4-ethylnonan-2-one (entry 3). Similar enantioselectivity (92% ee) was achieved in the $Cu(hfacac)_2$-catalyzed reaction (entry 4).

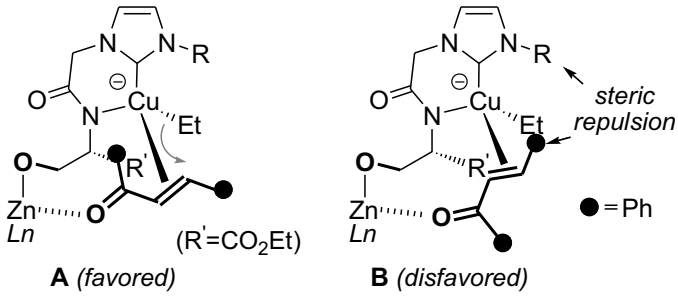
Table 4
ACA reaction of acyclic and cyclic enones.[a]

Entry	Enone	Method	Yield (%)	Ee (%)
1[b]	 **7**	**A**	86	85
2[b]	**7**	**B**	90	85
3[b]	 **8**	**A**	99	93
4[b]	**8**	**B**	91	92
5[c,d]	**8**	**A**	17[e]	80
6	 **9**	**A**	76	77
7	**9**	**B**	89	86
8	 **10**	**A**	98	71
9	**10**	**B**	99	71
10	 **11**	**A**	17[e]	86
11[d]	**11**	**A**	57[e]	85
12	**11**	**B**	20[e]	84
13	 **12**	**A**	95[e]	71
14	**12**	**B**	78[e]	80
15	 **13**	**A**	–[f]	51

[a] Method **A**: Enone (1 mmol), Et_2Zn (3 mmol), $Cu(NO_3)_2$ (5.0 mol%), **L1** (4.5 mol%), THF (9 mL), r.t., 3 h; Method **B**: $Cu(hfacac)_2$ (5.0 mol%), **L1** (4.5 mol%), THF/AcOEt (4.5/4.5 mL), r.t., 3 h; Yield of the conjugate adduct was determined by GLC analysis.
[b] Data taken from Ref. [10b].
[c] Me_2Zn in place of Et_2Zn was used.
[d] The reaction was conducted for 24 h.
[e] Isolated yield.
[f] Owing to the volatility and low yield of the reaction product, the correct yield could not be determined.

Notably, these high enantioselective reactions were carried out at room temperature without temperature control. However, unfortunately, Me_2Zn was difficult to add to **8** by this catalytic system probably due to the lower nucleophilicity of the alkylating reagent, and the starting materials were recovered almost unchanged (entry 5). The conjugate addition reaction of 5-methyl-3-hexen-2-one (**9**) with Et_2Zn using method B afforded better result than the reaction using method A (entries 6 and 7). Thus, (*S*)-4-ethyl-5-methylhexan-2-one was synthesized in 89% yield and with 86% ee (entry 7).

A potential application of the NHC–Cu catalytic system was investigated in the ACA of cyclic enones with dialkylzinc (Table 4, entries 8–15). As mentioned above, an efficient catalytic system



Scheme 3. Proposed reaction modes.

for both acyclic and cyclic enones has been rarely reported. 2-Cyclohexen-1-one (**10**) efficiently underwent the 1,4-addition with Et_2Zn catalyzed by $Cu(NO_3)_2$/**L1** catalytic system in THF at room temperature to afford (*R*)-3-ethylcyclohexanone in 98% yield and with 71% ee (entry 8). Previously, we have shown that the Cu-catalyzed conjugate addition of Et_2Zn to *cyclic enone* **10** under the influence of the C_2-symmetric bis(hydroxy-amide)-functionalized azolium ligand precursor **L7** afforded the corresponding (*S*)-adduct [10a]. Thus, the facial selectivities of the 1,4-addition reaction of *cyclic enone* catalyzed by (ester-amide)-functionalized NHC ligand **L1** were found to be reversed compared to that of the reaction catalyzed by (hydroxy-amide)-functionalized NHC ligand **L7**. These are in contrast to the results obtained in the reaction of *acyclic enone* **5** catalyzed by **L1** or **L7**, where no switching enantioselectivity was observed (Table 2, entry 1 vs. Table 3, entry 6). At this stage we have no explanation of this interesting difference between cyclic enone and acyclic enone. Further investigations are currently ongoing.

The reaction of 4,4-dimethyl-2-cyclohexen-1-one (**11**) proceeded slowly probably because of the steric hindrance of the substrate, affording the corresponding conjugate adduct in a poor yield, but with a relatively good enantioselectivity (86% ee) (entry 10). A prolonged reaction time afforded the 1,4-adduct in a moderate yield (57%) without any loss of the enantioselectivity (entry 11). The reaction with a cyclic enone comprising a seven-membered ring such as 2-cyclohepten-1-one (**12**) slightly increased the enantioselectivity of the reaction than that of the reaction of **10** (entry 14). The use of method B in the reaction of **12** with Et_2Zn afforded (*R*)-3-ethylcycloheptanone in a moderate yield (78%) and with good enantioselectivity (80% ee) (entry 14). 2-Cyclopenten-1-one (**13**) reacted with Et_2Zn with difficulty catalyzed by this catalytic system (entry 15). The conformations of the five-membered ring differ from those of the six- and seven-membered rings, and there are two puckered conformations such as the envelope and half-chair for the five-membered ring [12]. Hence, the lower enantioselectivity in the asymmetric addition reaction of **13** with Et_2Zn may be caused by the conformational differences between the five-membered ring and six- or seven-membered ring.

We speculated that the present Cu-catalyzed 1,4-addition reaction of chalcone with Et_2Zn might proceed through the formation of an anionic amidate/NHC–Cu species as an intermediate. The proposed reaction modes in the ACA reaction are shown in Scheme 3. A copper ate complex **A** involving a carbene, amidate, and ethyl group, might be generated. An enone would be envisioned to coordinate by approaching from the front side because of the steric repulsion of the stereodirecting group such as ethoxycarbonyl group on the backside. In addition, the formation of a zinc alkolate from the hydroxy group initially on the azolium precursor would facilitate the coordination of the enone by an interaction between the carbonyl group of enone and zinc species. Consequently, an ethyl group would be added to the enone from the backside as shown in **A**. In contrast, model **B** would lead to a conjugate adduct with an opposite configuration. In structural model **B**, however,

there would be significant steric repulsion between the side-arm on the NHC ring and phenyl substituent of chalcone. Consequently, the ACA reaction would be expected to proceed via reaction model **A** to produce (*S*)-1,4-adduct.

3. Conclusion

We demonstrated that a C_2-symmetric bis(ester-amide)-functionalized azolium salt efficiently performs the copper-catalyzed ACA of dialkylzinc reagents to *acyclic* or *cyclic enones*, with up to 93% ee. These air-stable, chiral ligands are particularly useful because of their easy preparation. In addition, the asymmetric catalytic reaction was carried out at ambient temperature without controlling the temperature of the reaction mixture. We believe the preset catalytic system provides an alternative method for catalytic ACA reaction.

4. Experimental

4.1. General procedures

All chemicals were obtained from commercial sources and were used as received. ^{1}H 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 ^{1}H and ^{13}C NMR spectra. $CDCl_3$, CD_3OD, 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).

4.2. General procedure for preparation of azolium salt

To CH_3CN (8 mL) were added KOH (5.9 mmol, 331 mg), benzimidazole (**3**) (3.7 mmol, 437 mg) and α-bromoacetamide derivative **1** (3.7 mmol, 888 mg) derived from bromoacetyl bromide and serine methyl ester. After stirring the reaction mixture at room temperature for 16 h, H_2O was added to form a white precipitate. The white product was separated from the solution by filtration under reduced pressure, and then the solid was dissolved in methanol. The resulting solution was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to obtain the desired product such as substituted benzimidazole derivative **4**. The product **4** could be used without further purification in the next step. Then, to 1,4-dioxane (15 mL) were added **4** (0.5 mmol, 139 mg) and α-chloroacetamide **2** (0.5 mmol, 98 mg) derived from chloroacetyl chloride and serine methyl ester. After stirring the reaction mixture at 110 °C for 2 days, the solvent was removed under reduced pressure. The residue was dissolved in methanol, and then activated carbon (ca. 1 g) was added. After 16 h, the activated carbon was removed by filtration. After removing the methanol in vacuo from the filtrate, the crude residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH = 9/1) to yield the corresponding azolium salt **L1**. Compound **L1** [10b], **L3** [9d], **L4** [9d] and **L7** [10a] were reported previously (See Supporting information).

4.2.1. Compound *L2*

White solid. mp 189.0–192.4 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.38 (s, 1H, $CH_{benzimid}$), 9.24 (d, J = 7.3 Hz, 2H, NH), 7.91–7.89 (m, 2H, $CH_{benzimid}$), 7.70–7.67 (m, 2H, $CH_{benzimid}$), 5.48 (s, 4H, NCH_2CO), 5.31–5.29 (m, 2H, OH), 4.37–4.33 (m, 2H, NHC*H*), 4.11–4.05 (m, 4H, OCH_2CH_3), 3.80–3.75 (m, 2H, CH_2OH), 3.71–3.66 (m, 2H, CH_2OH), 1.15 (t, J = 7.1 Hz, 6H, CH_2CH_3). ^{13}C NMR: δ 169.9 (CO), 164.8 (CO), 144.3, 131.1, 126.7, 113.6, 61.0 (CH_2OH), 60.7 (OCH_2CH_3), 55.2 (CH_2CO), 48.4 (NHCH), 14.0 (OCH_2CH_3). Anal. Calc. for $C_{21}H_{29}ClN_4O_8 \cdot 1.2H_2O$: C, 48.27; H, 6.06; N, 10.72. Found: C, 48.00; H, 5.75; N, 10.82%.

4.2.2. Compound *L5*

White solid. mp 190.8–192.9 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.84 (s, 1H, $CH_{benzimid}$), 9.38 (br, 2H, NH), 7.90–7.87 (m, 2H, $CH_{benzimid}$), 7.70–7.68 (m, 2H, $CH_{benzimid}$), 5.54 (d, J = 16.5 Hz, 2H, CH_2CO), 5.46 (d, J = 16.5 Hz, 2H, CH_2CO), 4.32–4.26 (m, 2H, NHC*H*), 3.60 (s, 6H, OCH_3), 1.75–1.51 (m, 6H, CH_2CH ^{i}Bu), 0.91 (d, J = 6.4 Hz, 6H, CH_3 ^{i}Bu), 0.84 (d, J = 6.4 Hz, 6H, CH_3 ^{i}Bu). ^{13}C NMR: δ 172.3 (CO), 164.8 (CO), 144.3, 131.1, 126.7, 113.6, 52.0 (CH_2CO), 50.8 (CH_3O), 48.3 (NHCH), 24.2 (CH ^{i}Bu), 22.7 (CH_2 ^{i}Bu), 21.2 (CH_3 ^{i}Bu). Anal. Calc. for $C_{26}H_{39}ClN_4O_6 \cdot 2.2H_2O$: C, 53.96; H, 7.56; N, 9.68. Found: C, 53.56; H, 6.67; N, 10.11%.

4.2.3. Compound *L6*

White solid. mp 169.6–170.5 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.88 (s, 1H, $CH_{benzimid}$), 9.21 (br, 2H, NH), 7.93–7.91 (m, 2H, $CH_{benzimid}$), 7.69–7.67 (m, 2H, $CH_{benzimid}$), 5.65 (d, J = 16.5 Hz, 2H, CH_2CO), 5.55 (d, J = 16.5 Hz, 2H, CH_2CO), 4.14 (d, J = 8.2 Hz, 2H, NHC*H*), 3.61 (s, 6H, OCH_3), 0.99 (s, 18H, CH_3 ^{t}Bu). ^{13}C NMR: δ 170.9 (CO), 165.0 (CO), 144.3, 131.1, 126.7, 113.5, 61.2 (CH_2CO), 51.5 (CH_3O), 48.3 (NHCH), 33.7 (C ^{t}Bu), 26.5 (CH_3 ^{t}Bu). Anal. Calc. for $C_{26}H_{39}ClN_4O_6 \cdot 2H_2O$: C, 54.30; H, 7.54; N, 9.74. Found: C, 54.16; H, 7.21; N, 9.82%.

4.3. General procedure for Cu-catalyzed asymmetric reaction of enone with Et_2Zn

To a solution of azolium salt (0.045 mmol) in THF (9 mL) were added $Cu(NO_3)_2 \cdot 5H_2O$ (0.050 mmol) and enone (1 mmol). After the mixture was cooled to 0 °C, Et_2Zn (3 mmol, 1 mol/L in hexanes, 3 mL) was added to the reaction vessel. The color immediately changed from yellow to dark brown. After stirring at room temperature for 3 h, the reaction was quenched 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). The enantiomeric excess was measured by the chiral GLC or chiral LC (See Appendix A. Supplementary data).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2014.08.006.

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