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CHIRAL BENZIMIDAZOLIUM N-HETEROCYCLIC CARBENE LIGANDS WITH HYDROXYAMIDE- OR HYDROXYALKYL-FUNCTIONALIZED WINGTIP FOR Cu-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION

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Abstract – An asymmetric allylic alkylation (AAA) reaction of allyl phosphates with dialkylzinc was studied using a combination of a Cu salt and a bis(hydroxyamide)-functionalized benzimidazolium salt ((*R*,*R*; *S*,*S*)-**L1**) derived from (1*R*, 2*R*)-(−)-1,2-cyclohexanediamine and (*S*)-leucinol as a catalyst. Treatment of (*E*)-cinnamyl diethyl phosphate (**1**) with Et_2Zn under the influence of the $Cu(acac)_2$/(*R*,*R*; *S*,*S*)-**L1** catalytic system under ambient conditions without temperature control afforded (*R*)-3-phenyl-1-pentene ((*R*)-**2**) in 91% yield with 83% ee. The enantioselectvity of the reaction was investigated by evaluating the relationship between the catalyst ee and the product ee in the AAA reaction of **1** with Et_2Zn, revealing a clear linear relationship. Investigation of the effect of the leaving group in the allylic substrate on the AAA reaction revealed that using a phosphate leaving group was essential to achieve good catalytic performance. 1,2-Diaminocyclohexane-based bis(*N*-heterocyclic carbene) azolium ligand **L1** exhibited higher reactivity than other chiral azolium ligands having a hydroxyamide functional group. Futhermore, it was found that using the $Cu(acac)_2$/*hydroxyalkyl*-functionalized benzimidazolium salt **L7** system to catalyze the AAA reaction of **1** with Et_2Zn led to stereoselectivity reversal to afford (*S*)-**2** in 87% yield with 75% ee. A plausible reaction pathway is proposed.

INTRODUCTION

The development of efficient chiral ligands for enantioselective transition-metal-catalyzed transformations is one of the most important subjects in synthetic organic chemistry. In this context, chiral *N*-heterocyclic

carbene (NHC) ligands stand out for their potential in enantioselective catalysis due to their strong σ donor character, robustness and easily tunable steric and electronic properties.[1] Previously, we reported the preparation of chiral hydroxyamide-functionalized azolium salts as precursors of NHC ligands. A wide variety of benzimidazolium salts could be synthesized from easily accessible natural amino acids and successfully applied to asymmetric catalytic reactions such as the Pd-catalyzed oxidative Heck reaction,[2] Cu-catalyzed conjugate addition,[3] Pd-catalyzed allylic alkylation,[4] Ir- and Ru-catalyzed transfer hydrogenations,[5] and Ir-catalyzed hydrosilylation.[6]

Cu-catalyzed asymmetric allylic alkylation (AAA) reactions are versatile C-C bond formation reactions producing useful chiral building blocks, and new catalysts are continuously being investigated for this benchmark reaction.[7] In 2004, Okamoto and coworkers reported a Cu-catalyzed AAA reaction between allylic chlorides and alkyl Grignard reagents with moderate enantioselectivity of up to 70% ee by employing a C_2-symmetric monodentate NHC-Cu complex.[8] Hoveyda and coworkers reported a breakthrough in the development of new bidentate carbene-based chiral ligands for the highly enantioselective Cu-catalyzed AAA reaction.[9] Tomioka et al. successfully achieved the AAA reaction of aliphatic allylic bromides with aryl Grignard reagents catalyzed by tunable monodentate NHC-Cu complexes.[10] Mauduit et al. developed chelating hydroxyalkyl-functionalized NHC ligands for the Cu-catalyzed AAA reaction of allyl phosphates with dialkylzinc or Grignard reagents.[11] Similarly, Shintani and Hayashi reported that the combination of CuCl with hydroxyalkyl-functionalized azolium salts derived from chiral 1-amino-2-indanol promoted the AAA reaction of allyl phosphates with arylboronates.[12] Alexakis et al. developed a Cu-free AAA reaction of bifunctional allylic bromides with Grignard reagents using chiral bidentate azolium salts as NHC precursors.[13]

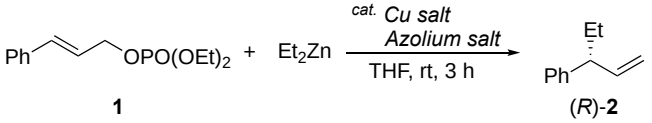
Nowadays, the Cu-catalyzed AAA reaction serves as a model reaction to test the performance of new chiral ligands and chiral NHC-Cu complexes. However, to the best of our knowledge, efficient asymmetric catalytic systems using a chiral bis(NHC) ligand are still rare. The tightly coordinating polydentate bis(NHC) ligand system is expected to enhance the catalyst stability and offer a key structure for constructing efficient stereodirecting elements. Herein we report an enantioselective reaction of allyl phosphate with dialkylzinc catalyzed by the combination of a Cu salt and a *hydroxyamide*-functionalized bis(NHC) ligand. Additionally, during the course of this study, we found that using a *hydroxyalkyl*-functionalized NHC ligand in the Cu-catalyzed AAA reaction led to the enantioselectivity reversal relative to that obtained using the *hydroxyamide*-functionalized NHC ligand.

RESULTS AND DISCUSSION

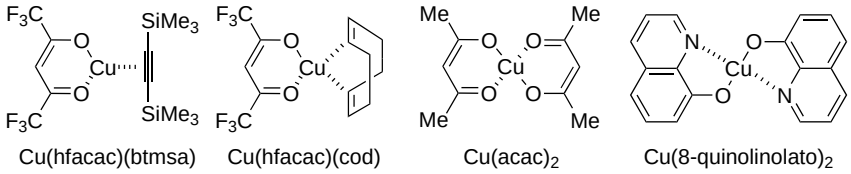
This study commenced with the evaluation of the Cu catalyst precursors and the chiral azolium ligands in the allylic substitution reaction (Table 1). The chiral ligand (*rac*; *S,S*)-**L1** was synthesized starting from (±)-

1,2-cyclohexanediamine and (*S*)-leucinol.[14] Treatment of (*E*)-cinnamyl diethyl phosphate with Et_2Zn in the presence of catalytic amounts of [bis(trimethylsilyl)acetylene](hexafluoro-2,4-pentanedionato)copper(I) (Cu(hfacac)(btmsa)) in combination with (*rac*; *S*,*S*)-**L1** at room temperature afforded (*R*)-3-phenyl-1-pentene ((*R*)-**2**) in 80% yield with moderate enantioselectivity (45% ee) (entry 1). In this reaction, the α-substituted product 1-phenyl-1-pentene was obtained as a side product (γ-product: α-product = 80:20). Using cyclooctadiene(hexafluoro-2,4-pentanedionato)copper(I) (Cu(hfacac)(cod)) resulted in similar product yield and stereoselectivity (entry 2). Changing the Cu catalyst precursor did not affect significantly the reaction outcome (entries 3-5). Notably, (*R*,*R*; *S*,*S*)-**L1** derived from (1*R*, 2*R*)-(−)-1,2-cyclohexanediamine and (*S*)-leucinol showed a superior catalytic performance compared with (*rac*; *S*,*S*)-

Table 1. Evaluation of Cu salts and azolium salts[a]

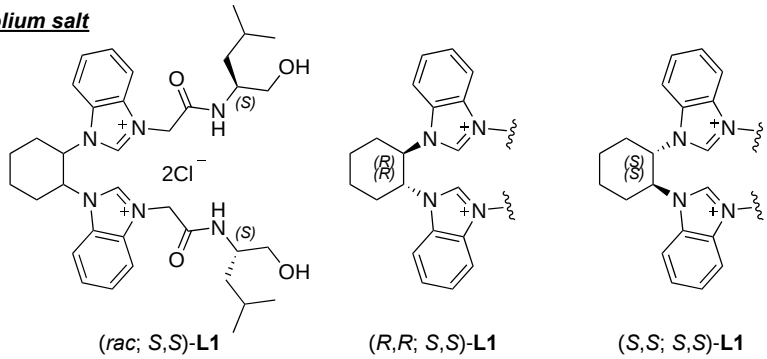


Cu salt



Cu(hfacac)(btmsa) Cu(hfacac)(cod) $Cu(acac)_2$ $Cu(8\text{-quinolinolato})_2$

Azolium salt



(*rac*; *S*,*S*)-**L1** (*R*,*R*; *S*,*S*)-**L1** (*S*,*S*; *S*,*S*)-**L1**

Entry	Cu salt	Azolium salt	Yield [%][b]	*ee* [%][c]
1[d]	Cu(hfacac)(btmsa)	(*rac*; *S*,*S*)-**L1**	80	45
2	Cu(hfacac)(cod)	(*rac*; *S*,*S*)-**L1**	83	49
3	$Cu(OTf)_2$	(*rac*; *S*,*S*)-**L1**	88	39
4	$Cu(acac)_2$	(*rac*; *S*,*S*)-**L1**	91	42
5	$Cu(8\text{-quinolinolato})_2$	(*rac*; *S*,*S*)-**L1**	92	38
6[e]	Cu(hfacac)(btmsa)	(*R*,*R*; *S*,*S*)-**L1**	92	74
7[f]	Cu(hfacac)(btmsa)	(*S*,*S*; *S*,*S*)-**L1**	59	*ent*-26[g]

[a] To a solution of Cu salt (6.0 mol%) and **L1** (4.5 mol%) in THF (6 mL), Et_2Zn (3 mmol) and **1** (1 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 3 h. [b] Yield of γ-product (**2**) determined via GC analysis using the internal standard technique. [c] Determined via GC analysis of a chiral stationary phase. [d] γ-Product: α-Product = 80:20. [e] γ-Product: α-Product = 92:8. [f] γ-Product: α-Product = 65:35. [g] (*S*)-**2** was obtained as a major product.

L1. Thus, **1** reacted with Et_2Zn under the influence of catalytic amounts of Cu(hfacac)(btmsa) and (*R*,*R*; *S*,*S*)-**L1** to produce (*R*)-**2** in 92% yield with 74% ee (entry 6). Fortunately, the regioselectivity of the AAA reaction was also improved (γ-product: α-product = 92:8). In contrast, the catalytic AAA reaction using (*S*,*S*; *S*,*S*)-**L1** instead of (*R*,*R*; *S*,*S*)-**L1** proceeded with difficulty, producing (*S*)-**2** with the opposite configuration in 59% yield with 26% ee (entry 7). These results suggest that (*S*,*S*; *S*,*S*)-**L1** acts as a catalyst poison in the catalytic AAA reaction using (*rac*; *S*,*S*)-**L1**. Similar results have been reported in the Cu-catalyzed asymmetric conjugate addition reaction of acyclic enones with Et_2Zn using **L1** as a chiral ligand.[15] At this stage, we believe that Et_2Zn acts as a base to deprotonate the C-H bond at the C_2 position of the azolium salt to afford a carbene species. It was reported that treatment of an imidazolinium sulfonate with Et_2Zn afforded the corresponding monomeric bidentate NHC-Zn(II) complex.[16]

Encouraged by this success, we continued our investigation by screening the reaction conditions for the Cu-catalyzed AAA reaction of **1** with Et_2Zn in the presence of (*R*,*R*; *S*,*S*)-**L1** (Table 2). Among the Cu catalyst precursors examined, Cu(hfacac)(btmsa) and copper(II) acetylacetonate ($Cu(acac)_2$) gave satisfactory product yields and enantioselectivities (entries 2-5). For practical reasons, we selected $Cu(acac)_2$ as a precatalyst for further studies. Although using 2-MeTHF instead of THF as a solvent furnished (*R*)-**2** in 84% yield with slightly lower enantioselectivity, a poor product yield was observed in the AAA reaction using other ethereal solvents, such as Et_2O (entries 6 and 7). Interestingly, the yield and stereoselectivity of the reaction of **1** with Et_2Zn in EtOAc, which is considered as a greener solvent, were comparable to those obtained using THF as a solvent (entry 8).[17] The AAA reaction at 0 °C did not increase the ee value of (*R*)-**2** (entry 11). Noteworthily, the $Cu(acac)_2$/(*R*,*R*; *S*,*S*)-**L1** catalytic system could be applied under ambient conditions without temperature control.

Table 2. Reaction of **1** with Et_2Zn using (*R*,*R*; *S*,*S*)-**L1**[a]

Entry	Cu salt	Solvent	Yield [%]	*ee* [%]
1[b]	Cu(hfacac)(btmsa)	THF	92	74
2	Cu(hfacac)(cod)	THF	87	77
3	$Cu(OTf)_2$	THF	32	57
4	$Cu(acac)_2$	THF	89	75
5	$Cu(8\text{-quinolinolato})_2$	THF	85	70
6	$Cu(acac)_2$	2-MeTHF	84	62
7	$Cu(acac)_2$	Et_2O	26	52
8	$Cu(acac)_2$	EtOAc	93	69
9	$Cu(acac)_2$	CH_2Cl_2	52	32
10[c]	$Cu(acac)_2$	THF	89	67
11[d]	$Cu(acac)_2$	THF	94	64

[a] To a solution of Cu salt (6.0 mol%) and (*R*,*R*; *S*,*S*)-**L1** (4.5 mol%) in a solvent (6 mL), Et_2Zn (3 mmol) and **1** (1 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 3 h. [b] The same data is shown in Table 1, entry 6. [c] THF (3 mL) was used. [d] The reaction was conducted at 0 °C.

Next, we investigated the effect of the catalyst loading on the AAA reaction (Table 3, entries 1-7). The present tightly coordinating bis(NHC) ligand system allowed significant reduction in the catalyst loading for an efficient conversion of **1**. The AAA reaction with the catalyst loading of $Cu(acac)_2$/(*R*,*R*; *S*,*S*)-**L1** = 3/1.1 mol% afforded (*R*)-**2** in 91% yield with 83% ee (entry 2). Using a 1:1.1 ratio of Cu salt to (*R*,*R*; *S*,*S*)-**L1** afforded (*R*)-**2** with satisfactory yield and stereoselectivity (entry 4), whereas decreasing of the amount of (*R*,*R*; *S*,*S*)-**L1** resulted in lower yield and stereoselectivity (entry 5). As shown in entries 2-4, the AAA reactions with the Cu/ligand ratios of 3:1.1, 2:1.1, and 1:1.1 occurred in a similar manner to afford (*R*)-**2** with 83%, 81%, and 84% ee. These results might suggest that a 1:1 complex of Cu and chiral ligand would be generated as a catalytic Cu species (vide infra). The reaction **1** with Et_2Zn hardly proceeded in the presence of $Cu(acac)_2$ alone (entry 6), indicating a strong ligand-accelerated catalysis effect for the present catalytic system. In addition, the presence of the Cu ion was essential (entry 7). Reducing the reaction time and the amount of alkylating reagent decreased the product yield (entries 8-10). To verify whether the absolute configuration of the stereogenic centers in the ligand exerted a significant effect on the enantiocontrol of the present catalytic reaction, (*S*,*S; R*,*R*)-**L1** was synthesized starting from (1*S*, 2*S*)-(+)-1,2-cyclohexanediamine and (*R*)-leucinol. The reaction of **1** with Et_2Zn catalyzed by the $Cu(acac)_2$/(*S*,*S R*,*R*)-**L1** system furnished (*S*)-**2** in 89% yield with 86% ee (entry 11).

Table 3. Effect of catalyst loading[a]

Entry	Cu [mol %]	Azolium [mol %]	Yield [%]	*ee* [%]
1[b]	6	4.5	89	75
2	3	1.1	91	83
3	2	1.1	87	81
4	1	1.1	82	84
5	1	0.5	62	73
6	6	0	<2	-
7	0	1.1	0	-
8[c]	3	1.1	83	73
9[d]	3	1.1	43	70
10[e]	3	1.1	64	83
11[f]	3	1.1	89	*ent*-86[g]

[a] To a solution of $Cu(acac)_2$ and (*R*,*R*; *S*,*S*)-**L1** in a solvent (6 mL), Et_2Zn (3 mmol) and **1** (1 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 3 h. [b] The same data is shown in Table 2, entry 4. [c] The reaction was conducted for 1 h. [d] The reaction was conducted for 0.5 h. [e] Et_2Zn (1.5 mmol) was used. [f] (*S*,*S*; *R*,*R*)-**L1** was used instead of (*R*,*R*; *S*,*S*)-**L1**. [g] (*S*)-**2** was obtained as a major product.

To gain more insight into the enantioselectivity of the catalytic reaction, we investigated the relationship between the catalyst ee and the product ee using various carefully prepared mixtures of (*R*,*R*; *S*,*S*)-**L1** and (*S*,*S; R*,*R*)-**L1** (Figure 1). The AAA reaction of **1** with Et_2Zn provided no sufficient chiral amplification to

reach an enantiopure end state. This clear linear relationship might indicate that only one molecule of the chiral auxiliary participates in the active catalyst species.

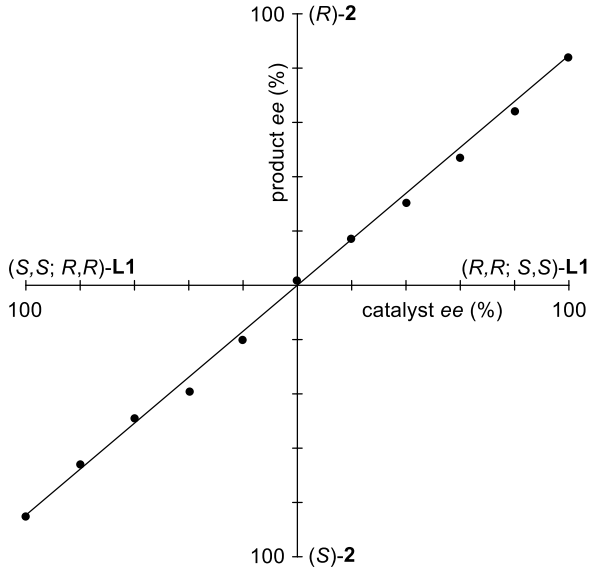
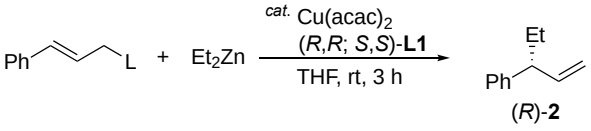


Figure 1. Relationship between the catalyst *ee* and the product *ee*

Next, we investigated the effect of the leaving group in the allylic substrate on the AAA reaction (Table 4). When (*E*)-cinnamyl bromide was reacted with Et_2Zn using the $Cu(acac)_2$/(*R*,*R*; *S*,*S*)-**L1** catalytic system, a racemic mixture of the corresponding allylic substitution product **2** was obtained (enry 2). In stark contrast, treatment of (*E*)-cinnamyl acetate with Et_2Zn resulted in no reaction under the present reaction conditions (entry 3). The different reactivity between the phosphate and bromide leaving group was further studied.

Table 4. Effect of the leaving group in the substrate[a]



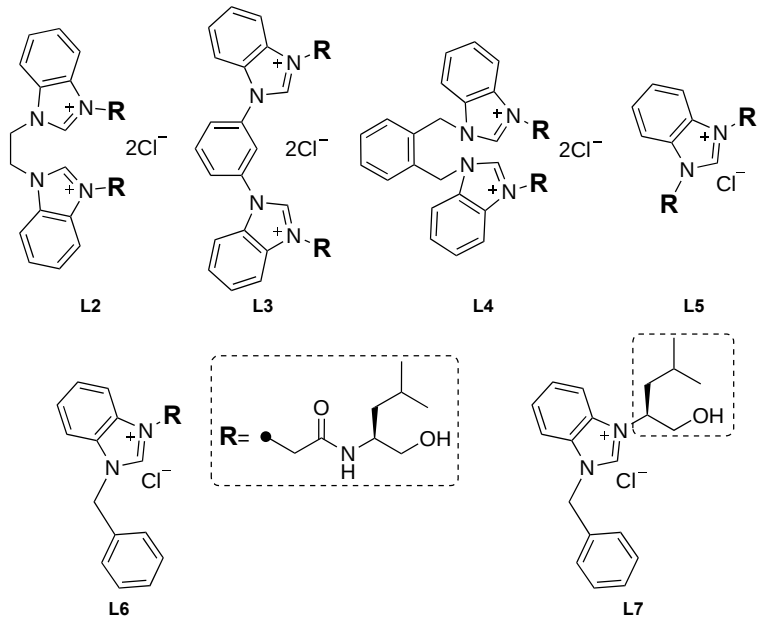
Entry	Cu [mol %]	Leaving group	Yield [%]	*ee* [%]
1[b]	6	-OPO(OEt)$_2$	89	75
2	6	-Br	59	<5
3	6	-OAc	0	-
4[c,d]	6	-OPO(OEt)$_2$	<2	-
5[c]	6	-Br	77	-
6[c]	0	-Br	20	-

[a] To a solution of $Cu(acac)_2$ (0 or 6 mol%) and (*R*,*R*; *S*,*S*)-**L1** (4.5 mol%) in THF (6 mL), Et_2Zn (3 mmol) and the substrate (1 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 3 h. [b] The same data is shown in Table 2, entry 4. [c] The reaction was conducted in the absence of (*R*,*R*; *S*,*S*)-**L1**. [d] The same data is shown in Table 3, entry 6.

The Cu-catalyzed reaction of **1** with Et_2Zn proceeded with difficulty in the absence of (*R*,*R*; *S*,*S*)-**L1** (entry 4), whereas (*E*)-cinnamyl bromide reacted with Et_2Zn under the influence of the $Cu(acac)_2$ catalyst alone to afford racemic **2** in 77% yield (entry 5). This result indicates that $Cu(acac)_2$ accelerates the racemic background reaction in the reaction of (*E*)-cinnamyl bromide with Et_2Zn. Additionally, **2** was obtained in 20% yield in the reaction of (*E*)-cinnamyl bromide with Et_2Zn in the absence of both $Cu(acac)_2$ and (*R*,*R*; *S*,*S*)-**L1** (entry 6). These results strongly suggest that the interaction between the phosphate moiety of substrate **1** and the chiral Cu species generated from the $Cu(acac)_2$/(*R*,*R*; *S*,*S*)-**L1** catalytic system is important for the success of the present AAA reaction (see Figure 2).

Finally, we investigated in the reactivity of the 1,2-diaminocyclohexane-based chiral azolium ligand **L1** compared with that of other chiral azolium ligands (Table 5). Three chiral ligands **L2**, **L3**, and **L4** derived from 1,2-ethanediamine, 1,3-diaminobenzene, and 1,2-benzenedimethanamine, respectively, were selected as the bis(NHC) skeleton. Although the combination of $Cu(acac)_2$ with **L2** promoted the AAA reaction of

Table 5. Investigation of chiral azolium salts[a]



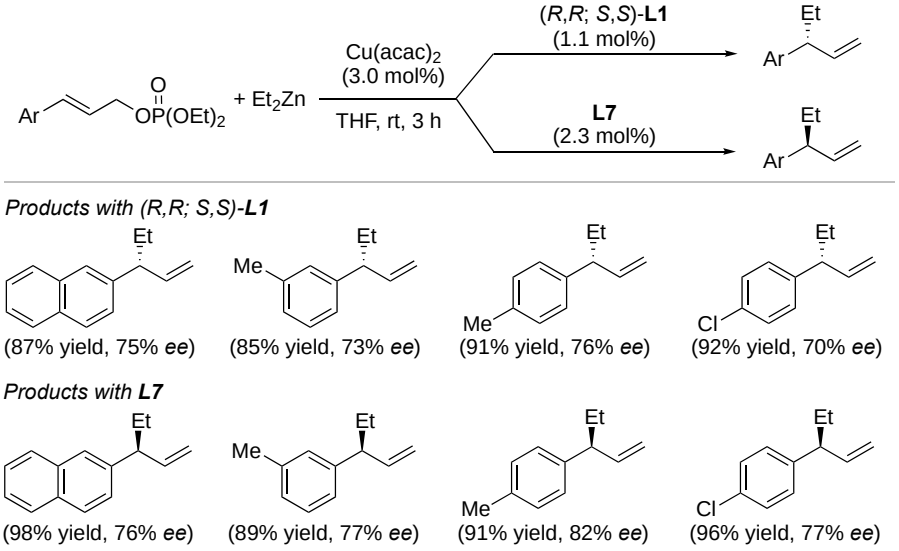
Entry	Azolium salt	[mol %]	Yield [%]	*ee* [%]
1[b]	(*R*,*R*; *S*,*S*)-**L1**	1.1	91	83
2	**L2**	1.1	82	30
3	**L3**	1.1	98	30
4	**L4**	1.1	98	26
5	**L5**	1.1	73	37
6	**L5**	2.3	90	40
7	**L6**	2.3	93	38
8	**L7**	2.3	99	*ent*-80[c]

[a] To a solution of $Cu(acac)_2$ (3 mol%) and azolium salt (1.1 or 2.3 mol%) in THF (6 mL), Et_2Zn (3 mmol) and **1** (1 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 3 h. [b] The same data is shown in Table 3, entry 2. [c] (*S*)-**2** was obtained as a major product.

1 with Et_2Zn, the enantioselectivity was lower (30% ee) than that observed in the reaction using **L1** (entry 2). The reactions using **L3** and **L4** proceeded in a similar manner as that using **L2** to afford (*R*)-**2** with 30% ee and 26% ee, respectively (entries 3 and 4). These results indicate the importance of the conformational rigidity of the cyclohexyl skeleton of **L1**. Meanwhile, we also assumed that the presence of two hydroxyamide moieties in the chiral ligand might contribute to the high enantioselectivity. Therefore, C_2-symmetric bis(hydroxyamide)-functionalized benzimidazolium salt **L5** was next examined. However, the $Cu(acac)_2$/**L5** catalytic system gave low enantioselectivity (entries 5 and 6). In addition, the result of the AAA reaction using **L5** was comparable to that obtained with hydroxyamide-functionalized benzimidazolium salt **L6** having a benzyl group as the side-arm of the azolium ring (entry 7).

In connection with another project, we also investigated the asymmetric catalytic reaction using *hydroxyalkyl*-functionalized benzimidazolium salt **L7**. Notably, an enantioselectivity reversal was observed in the AAA reaction of **1** with Et_2Zn using the $Cu(acac)_2$/**L7** catalytic system. Thus, (*S*)-**2** was preferentially obtained in 99% yield and with 80% ee (Table 5, entry 8).

The switching of the enatioselectvity was also observed in the AAA reaction of diethyl (2*E*)-3-(2-naphthalenyl)-2-propen-1-yl phosphate with Et_2Zn (Scheme 1). The $Cu(acac)_2$/(*R*,*R*; *S*,*S*)-**L1** catalytic system produced (*R*)-3-(2-naphthalenyl)-1-pentene in 87% yield with 75% ee. The corresponding (*S*)-product was obtained when the catalytic reaction was conducted under the influence of *hydroxyalkyl*-functionalized azolium chiral ligand **L7**. Similary, both enatiomers of the substituted products could be synthesized by allowing several substrates to react with Et_2Zn in the presence of catalytic amounts of $Cu(acac)_2$ and (*R,R; S,S*)-**L1** or **L7**. These results were also summaried in Scheme 1. Further investigations on the performance of the Cu/**L7** catalytic system in the AAA reaction are currently ongoing in our laboratory.



Scheme 1. Switching of enantioselectivity

Although the mechanism of these reactions remains unclear, the enantioselectivity reversal in the Cu-catalyzed AAA reaction might proceed through an ordered transition state involving a precoordinating catalyst structure (Figure 2).

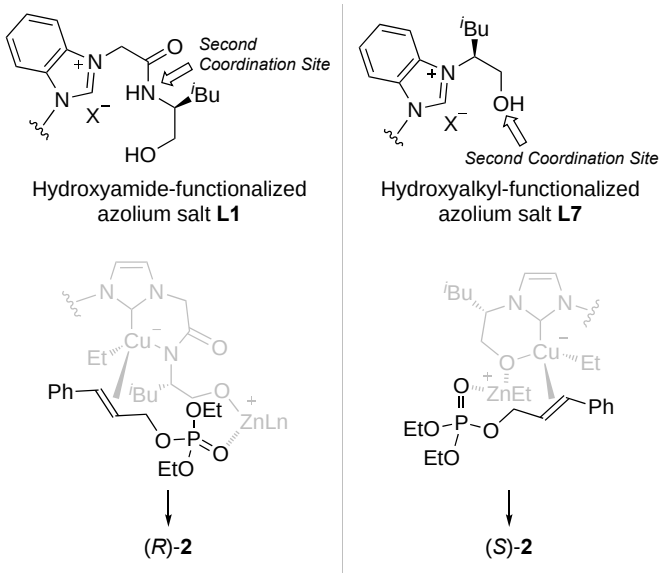


Figure 2. Plausible mechanism for switching of stereoselectivity

Thus, when the chiral ligand **L1** was used, an anionic amidate/NHC-Cu species would be formed. In our previous works, we isolated and fully characterized an anionic amidate/NHC-Pd complex from the reaction of a hydroxyamide-functionalized NHC ligand with $PdCl_2(MeCN)_2$.[2] In addition to the formation of the amidate/NHC-Cu species, an ethyl anion and an alkene might coordinate to generate a cuprate(I) species. Additionally, a Zn alcoholate might be formed to facilitate the coordination of the alkene in a fixed position via the interaction between the P=O group and the Zn species. This might explain effect of the leaving group in the substrate on the reaction outcome as shown in Table 4. Consequently, an ethyl group would attack the alkene from the backside to afford (*R*)-**2**.

Meanwhile, an anionic alcoholate/NHC-Cu species might be generated from *hydroxyalkyl*-substituted azolium salt **L7**. Subsequently, an ethyl anion and an alkene would coordinate in a similar manner to that described for the reaction with **L1**. Additionally, the Zn species would act as a Lewis acid to lock the alcoholate-Cu species and the substrate in a fixed conformation, leading to the formation of (*S*)-**2** in the stereoselective allylic substitution reaction.

CONCLUSIONS

We investigated the performance of a chiral bis(hydroxyamide)-functionalized benzimidazolium NHC ligand in the Cu-catalyzed AAA reaction, finding that the combination of $Cu(acac)_2$ with (*R*,*R*; *S*,*S*)-**L1**

promoted the reaction of **1** with Et_2Zn to afford (*R*)-**2** with satisfactory yield and enantioselectivity. Using a phosphate leaving group in the allylic substrate was essential to achieve the high catalytic performance in the AAA reaction. Additionally, investigation of a series of chiral benzimidazolium ligands revealed that treating **1** with $E_{t2}Zn$ in the presence of a combination of the *hydroxyalkyl*-functionalized benzimidazolium salt **L7** and $Cu(acac)_2$ furnished (*S*)-**2** as a major product. Considering that both ligand precursors **L1** and **L7** are prepared from a natural α-amino acid, enantioselectivity reversal was successfully achieved by structurally modifying the chiral ligands. The application of chiral chelating *hydroxyalkyl*-functionalized NHC catalysts in catalytic enantioselective transformations is the subject of ongoing research in our laboratory.

EXPERIMENTAL

All chemicals were obtained from commercial sources and used as received. ^1H and ^{13}C NMR spectra were recorded on spectrometers at 400 and 100 MHz, respectively. The chemical shifts in the ^1H and ^{13}C NMR spectra are reported in ppm relative to TMS. $CDCl_3$ and $(CD_3)_2SO$ were used as NMR solvents. A thin-layer chromatography analysis was performed using glass-backed plates precoated with silica gel and examined under UV (254 nm) irradiation. Flash column chromatography was executed on silica gel 60 (230-400 mesh; particle size: 0.040-0.063 nm). Compounds (*rac*; *S*,*S*)-**L1**, (*R*,*R*; *S*,*S*)-**L1**, (*S*,*S*; *S*,*S*)-**L1**, **L2**, **L3**, **L4**,[15] **L5**[18] and **L6**[3] were reported in our previous publications.

Procedure for preparation of azolium salt L7

A mixture of (*S*)-2-benzimidazol-1-yl-4-methylpentan-1-ol (3 mmol, 655 mg, 1.0 equiv; synthesized according to a published procedure[19]) and benzyl chloride (3.3 mmol, 418 mg, 1.1 equiv) in 1,4-dioxane (10 mL) was stirred at 110 °C for 2 days. After the reaction, the solvent was removed under reduced pressure and the crude residue was subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH = 95/5) to yield a light yellow liquid after removing the solvent. The residue was dissolved in MeOH, and activated carbon (ca. 1 g) was then added. After 3 h, the activated carbon was removed via filtration. After removing the MeOH in vacuo from the filtrate, azolium salt **L7** was purified via reprecipitation using MeOH and EtOAc affording a white solid (yield: 1.5 mmol, 517 mg, 50%); mp 173.7-174.0 °C; ^1H-NMR ($CDCl_3$, 400 MHz): δ 11.10 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.54-7.43 (m, 5H), 7.34-7.27 (m, 3H), 5.91-5.77 (m, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 4.93 (br, 1H), 4.14-4.03 (m, 2H), 2.12-2.04 (m, 1H), 1.91-1.84 (m, 1H), 1.56-1.49 (m, 1H), 0.93 (t, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 142.4, 132.9, 131.9, 131.0, 129.1, 128.8, 128.1, 126.6, 126.6, 113.6, 113.5, 62.7, 59.9, 51.3, 39.5, 24.9, 22.4, 22.2; HRMS (ESI^+): *m/z* calcd for $C_{20}H_{25}N_2O^+$: 309.1961; found: 309.1961.

General procedure for Cu-catalyzed AAA reaction of 1 with Et_2Zn

The Cu and azolium salts 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 stirring the resulting mixture at 0 °C for 15 min, a solution of **1** (1 mmol) in anhydrous THF (2 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred at room temperature for 3 h and then quenched with 10% HCl aq. The product yield was determined via GLC using the internal standard technique. The ee was measured using chiral GLC. The substitution product was isolated as follows: after quenching the reaction mixture with 10% HCl aq., the resulting mixture was extracted with diisopropyl ether (3 x 10 mL) and dried over Na_2SO_4. The product was purified via silica gel column chromatography (hexane).

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