JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

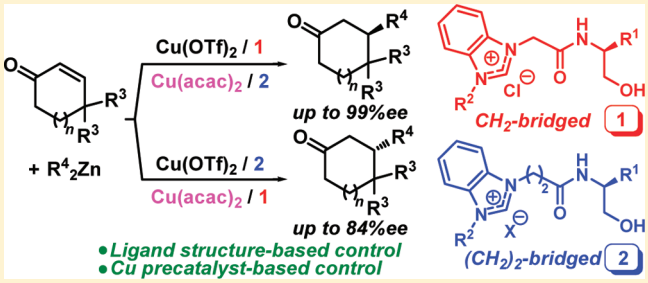
Hydroxy-amide Functionalized Azolium Salts for Cu-Catalyzed Asymmetric Conjugate Addition: Stereocontrol Based on Ligand Structure and Copper Precatalyst

Naoatsu Shibata, Misato Yoshimura, Haruka Yamada, Ryuichi Arakawa, and Satoshi Sakaguchi*

Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan

Supporting Information

ABSTRACT: A series of hydroxy-amide functionalized azolium salts have been designed and synthesized for Cu-catalyzed asymmetric conjugate addition reaction. The $(CH_2)_2$-bridged hydroxy-amide functionalized azolium ligand precursors **2**, in addition to the previously reported CH_2-bridged azolium salts **1**, have been prepared from readily available enantiopure β-amino alcohols. The combination of a Cu species with **1** or **2** efficiently promoted the 1,4-addition reaction of cyclic enones with dialkylzincs. For example, the reaction of 2-cyclohepten-1-one (**17**) with Bu_2Zn in the presence of catalytic amounts of $Cu(OTf)_2$ and **1** gave (*S*)-3-butylcycloheptanone (**20**) in 99% yield and 96% ee. On the other hand, when the reaction was carried out under the influence of $Cu(OTf)_2$ combined with **2**, (*R*)-**20** in preference to (*S*)-**20** was obtained in 98% yield and 80% ee. In this manner, the enantioselecvity was switched by controlling the structure of chiral ligand. Additionally, the reversal of enantioselectivity was also achieved by changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$ with the same ligand. The combination of $Cu(acac)_2$ with CH_2-bridged azolium salt **1** in the reaction of **17** with Bu_2Zn led to formation of (*R*)-**20** as a major product in 55% yield and 80% ee. This result was in contrast to the $Cu(OTf)_2$/**1** catalytic system, where the 1,4-adduct with opposite configuration was obtained. Moreover, use of the $Cu(acac)_2$/**2** catalytic system produced (*S*)-**20**, while (*R*)-**20** was formed by the $Cu(OTf)_2$/**2** catalytic system. Thus, it was found that either varying the linker of the chiral ligands or changing the counterion of Cu species between a OTf and acac ligand initially on the metal led to dual enantioselective control in the 1,4-addition reaction.



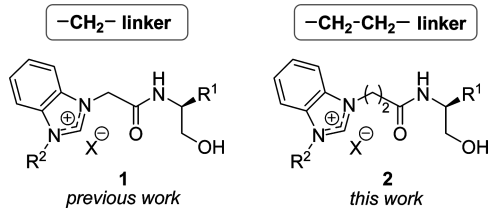
INTRODUCTION

The selection of either enantiomer via transition-metal-catalyzed asymmetric reaction is typically achieved by preparing both enantiomers of a chiral ligand.[1] For the preparation of the chiral ligand, chiral induction may often be realized by using chiral molecules of natural origin such as amino acids. However, in some cases where the ligand is a natural product or derived from a natural product, the necessary antipodes may not be easily available. From a single chiral source, the reversal of enantioselectivity of a reaction has been achieved so far by design and control of the ligand structure. However, the preparation of both enantiomers of a target molecule using a single ligand derived from a natural product remains a challenging endeavor.[2]

The Cu-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated compounds is a powerful method for the efficient construction of carbon−carbon bonds. In the past decade, catalytic asymmetric conjugate addition reactions with high enantioselectivities have been successfully achieved by using a variety of chiral ligands.[3] Among the growing number of the chiral ligands, N-heterocyclic carbenes (NHCs) have been recognized as useful ligands since the first publications by Alexakis and Mangeney in 2001.[4,5] One of the most attractive features that make NHCs a very interesting class of ligands is the easy access to their ligand precursors (mostly azolium salts). The azolium salts are very easy to functionalize often by simple reactions that allow the introduction of manifold of N-substituents (or wingtips). Thus, numerous functionalized azolium salts have been developed so far.[4,6]

Recently, we designed and synthesized the CH_2-bridged hydroxy-amide functionalized azolium salt **1** shown in Scheme 1.

Scheme 1. Ligand Design



Received: March 4, 2012
Published: March 29, 2012

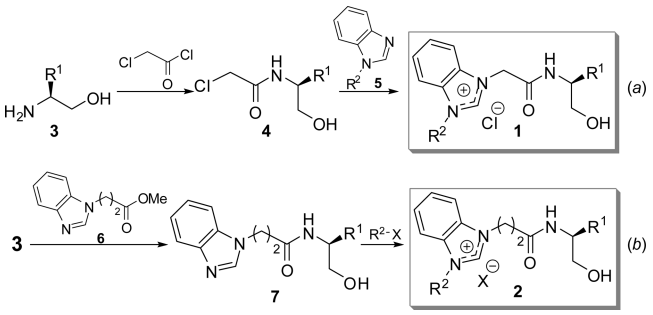
   dx.doi.org/10.1021/jo300472r | J. Org. Chem. 2012, 77, 4079−4086

Compound **1** acts as a chelating ligand with a carbene unit and a second coordinating group on the side arm at NHC. This combination generates a strongly coordinating polydentate ligand that can lock stereodirecting functional groups in a fixed conformation. Thus, Pd-catalyzed intermolecular Heck-type couplings[7] as well as Ir-catalyzed hydrosilane reduction of ketones[8] with high enantioselectivities (over 90% ee) have been developed. In addition, the functionalized azolium salt **1** was tested in the Cu-catalyzed asymmetric conjugate addition of dialkylzincs to cyclic enones.[9] Interestingly, the reversal of enantioselectivity with the same ligand could be achieved by changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$. Encouraged by this success, we have now designed $(CH_2)_2$-bridged hydroxy-amide functionalized azolium salt **2** for asymmetric conjugate addition reaction (Scheme 1). We assumed that a metal chelate generated from chiral ligand precursor **2** would differ from a species generated from **1**. This might cause changing of the highly hindered face that would block approach of the reaction substance. It was found that in comparison with the product that was obtained in the 1,4-addition reaction by $Cu(OTf)_2$ combined with **1**, the combination of $Cu(OTf)_2$ and **2** led to the formation of the 1,4-adduct with opposite configuration. Additionally, dual enantioselective control of the 1,4-addition reaction with the ligand precursor **2** was achieved by changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$. Now, we have synthesized a series of azolium compounds **2a−m** having the *N*-hydroxy-amide functional groups with the $(CH_2)_2$ linker and studied the influence of the structure of the ligand and the Cu precatalyst on the stereoselective induction for optimization of the conjugate addition reaction. Herein, we describe the systematic studies of the dependence of reaction stereocontrol on the ligand structure and Cu precatalyst.

RESULTS AND DISCUSSION

Synthesis of Hydroxy-amide Functionalized Azolium Salt 2. Due to increasing economic and ecological pressure, the development of a readily accessible chiral ligand that can be prepared from a commercially available chiral source via one- or two-step syntheses has become important.[10] As we have described previously, the CH_2-bridged hydroxy-amide functionalized azolium ligand precursor **1** could be prepared by coupling reaction between *N*-alkylbenzimidazole **5** and α-chloroacetamide derivative **4**, which was prepared from chloroacetyl chloride and enantiopure β-amino alcohol **3** (Scheme 2, route *a*).[7c] However,

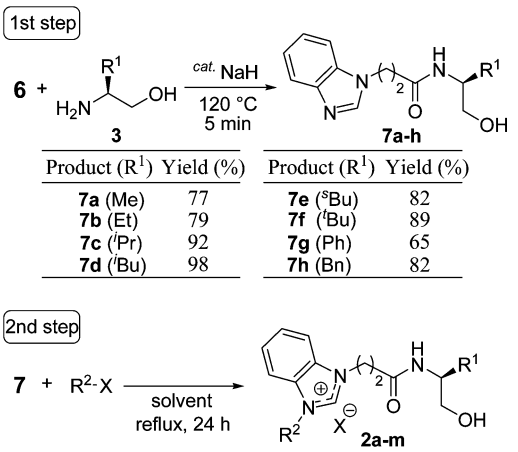
Scheme 2. Facile Route to Azolium Ligand Precursors 1 and 2 from Enantiopure β-Amino Alcohol 3



attempts to prepare the $(CH_2)_2$-bridged hydroxy-amide functionalized azolium salt **2** by the use of 3-chloropropionyl chloride in place of chloroacetyl chloride failed due to the formation of the corresponding acryl amide derivative. Therefore, we proposed an alternative synthetic route to azolium compound **2** (route *b*). The first step involved the formation of hydroxy-amide functionalized azole derivative **7** by reacting **3** with ester **6**, which was synthesized in quantitative yield through an aza-Michael reaction between methyl acrylate and benzimidazole.[11] Subsequent treatment of **7** with an alkyl halide yielded the desired $(CH_2)_2$-bridged hydroxy-amide functionalized azolium salt **2**.

Scheme 3 summarizes the results of the preparation of the desired azolium compounds, namely, **2a−2m**, and their

Scheme 3. Preparation of Ligand Precursors 2



Product (R^1)	Yield (%)	Product (R^1)	Yield (%)
7a (Me)	77	**7e** (^{s}Bu)	82
7b (Et)	79	**7f** (^{t}Bu)	89
7c (^{i}Pr)	92	**7g** (Ph)	65
7d (^{i}Bu)	98	**7h** (Bn)	82

R^1=	Me	Et	^{i}Pr	^{i}Bu	^{s}Bu	^{t}Bu	Ph	Bn
R^2=Me, X=I	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
R^2=Bn, X=I		**2l**		**2k**		**2m**		
R^2=Bn, X=Cl				**2i**				
R^2=Bn, X=Br				**2j**				

Substrate 7	R^2-X	Solvent	Product	Yield (%)
7a	Me-I	1,4-dioxane	**2a**	80
7b	Me-I	1,4-dioxane	**2b**	82
7c	Me-I	1,4-dioxane	**2c**	79
7d	Me-I	1,4-dioxane	**2d**	49
7e	Me-I	1,4-dioxane	**2e**	81
7f	Me-I	1,4-dioxane	**2f**	83
7g	Me-I	1,4-dioxane	**2g**	77
7h	Me-I	1,4-dioxane	**2h**	20
7d	Bn-Cl	Toluene	**2i**	27
7d	Bn-Br	DME	**2j**	60
7d	Bn-I	DME	**2k**	77
7b	Bn-I	DME	**2l**	77
7f	Bn-I	1,4-dioxane	**2m**	61

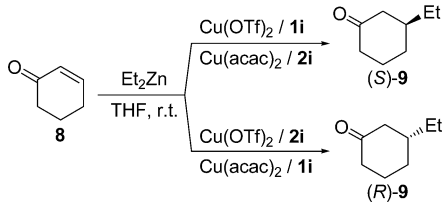
intermediates, namely, **7a−7h**. We were also interested in the influence of the counterion of the azolium ligand on the stereoselectivity of the 1,4-addition reaction. Therefore, azolium halides **2i−2k** were prepared by coupling of **7d** with benzyl chloride, bromide, and iodide, respectively. Thus, a series of $(CH_2)_2$-bridged hydroxy-amide functionalized azolium salts **2a−2m** having both an alkyl group at the stereogenic center and a methyl or benzyl substituent at the azolium ring could be obtained in two steps from commercially available β-amino alcohols **3**.

Cu-Catalyzed Asymmetric Conjugate Addition Reaction. To test the possibility of achieving an asymmetric conjugate addition by using the chiral ligand precursor, we chose azolium salt **2i** (R^1 = ^{i}Bu, R^2 = Bn), prepared from (*S*)-leucinol, for the reaction of 2-cyclohexen-1-one (**8**) with Et_2Zn catalyzed by a Cu salt. To compare the relative abilities between $(CH_2)_2$-bridged azolium salt and CH_2-bridged azolium salt, the

dx.doi.org/10.1021/jo300472r | J. Org. Chem. 2012, 77, 4079−4086

results of the reaction employing **1i** (R^1 = ^{i}Bu, R^2 = Bn) are also listed in Table 1 as entries 1 and 2. The treatment of **8** with

Table 1. Initial Studies on Stereocontrol Based on Ligand Structure and Cu Precatalyst in 1,4-Addition Reaction[a]



entry	Cu catalyst	azolium salt (R^1, R^2, X)	method	yield (%)	ee (%)
1[b]	$Cu(OTf)_2$	**1i** (^{i}Bu, Bn, Cl)	A	99	81 (*S*)
2[b,c]	$Cu(acac)_2$	**1i**	A	69	41 (*R*)
3	$Cu(OTf)_2$	**2i** (^{i}Bu, Bn, Cl)	A	99	61 (*R*)
4[c]	$Cu(acac)_2$	**2i**	A	92	24 (*S*)
5[c]	$Cu(acac)_2$	**2i**	B	91	65 (*S*)

[a]**8** (1 mmol), Et_2Zn (3 mmol), Cu precatalyst (6 mol %), azolium salt (4.5 mol %), THF (9 mL), rt, 3 h. Method A: to a solution of Cu precatalyst and azolium salt in THF, **8** was added first, then Et_2Zn. Method B: Et_2Zn was added first, then **8**. Yields were determined by GLC using an internal standard technique. [b]Previously reported data (see ref 9b). [c]With Cs_2CO_3 (8 mol %).

Et_2Zn in THF in the presence of catalytic amounts of $Cu(OTf)_2$ and **2i** afforded 3-ethylcyclohexanone (**9**) in almost quantitative yield (entry 3). It is worth noting that the use of azolium ligand **2i**, whose sole difference is the $(CH_2)_2$ linker, produced (*R*)-**9** (61% ee) in preference to (*S*)-**9**, while (*S*)-**9** (81% ee) was obtained with $Cu(OTf)_2$ combined with azolium ligand **1i** (entry 1 vs entry 3). In this manner, enantioselectivity was reversed by controlling the structure of the chiral ligand.[12]

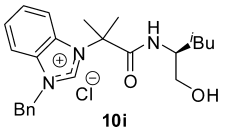
As mentioned in the Introduction, switching the stereoselectivity in the conjugate addition reaction using the azolium ligand **1** was achieved by simply changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$ (Table 1, entries 1 vs 2).[9] It was also found that a similar reversal of enantioselectivity occurred by changing the Cu precatalyst with azolium salt **2**. When the reaction of **8** with Et_2Zn was carried out under the influence of $Cu(acac)_2$ combined with **2i** in the presence of Cs_2CO_3, (*S*)-**9** instead of (*R*)-**9** was formed with a 24% ee (entry 4). The effect of additives such as Cs_2CO_3 in the $Cu(acac)_2$-catalyzed reaction will be described later (Table 3). Additionally, it was found that the order of substrate addition influenced this reaction.[13] Slightly better enantioselectivity (65% ee) was obtained by first adding the R_2Zn and then the enone (entry 5). Thus, it can be said from the results in Table 1 that dual enantioselective control was achieved not only through the structural modification of the chiral ligand but also through a change of Cu precatalyst. Moreover, one of the most attractive features of this reaction is that it can be carried out at ambient temperature without temperature control.

The easy access to the hydroxy-amide functionalized azolium ligand precursors **2** allowed us to synthesize a series of derivatives to optimize the reaction. Table 2 and Figure 1 show the representative results of the 1,4-addition reaction of **8** with Et_2Zn with the $Cu(OTf)_2$/**2** catalytic system and the $Cu(acac)_2$/**2** catalytic system with different ligand derivatives. First, we studied the $Cu(OTf)_2$ catalyst system. To investigate the effect of the stereodirecting group in the chiral ligand, we screened several azolium chlorides **2a**–**2h** (entries 1–8, left column).

Table 2. Evaluation of Various Azolium Ligands 2 for $Cu(OTf)_2$- or $Cu(acac)_2$-Catalyzed 1,4-Addition Reaction of 8 with Et_2Zn[a]

		with $Cu(OTf)_2$ method A		with $Cu(acac)_2$ method B[b]	
entry	azolium	yield (%)	ee (%)	yield (%)	ee (%)
1	**2a**	96	39 (*R*)	77	80 (*S*)
2	**2b**	99	45 (*R*)	93	82 (*S*)
3	**2c**	99	44 (*R*)	71	57 (*S*)
4	**2d**	95	47 (*R*)	98	72 (*S*)
5	**2e**	78	47 (*R*)	5	3 (*S*)
6	**2f**	94	58 (*R*)	11	7 (*R*)
7	**2g**	70	12 (*R*)	60	66 (*S*)
8	**2h**	90	33 (*R*)	73	59 (*S*)
9	**2i**	99	61 (*R*)	16	60 (*S*)
10	**2j**	92	58 (*R*)	19	72 (*S*)
11	**2k**	91	60 (*R*)	91	65 (*S*)
12	**2l**	76	46 (*R*)	93	78 (*S*)
13	**2m**	87	66 (*R*)	3	
14	**10i**[c]	46	44 (*R*)	8	32 (*R*)

[a]See Table 1, footnote *a*. [b]With Cs_2CO_3 (8 mol %). [c]Structure:



10i

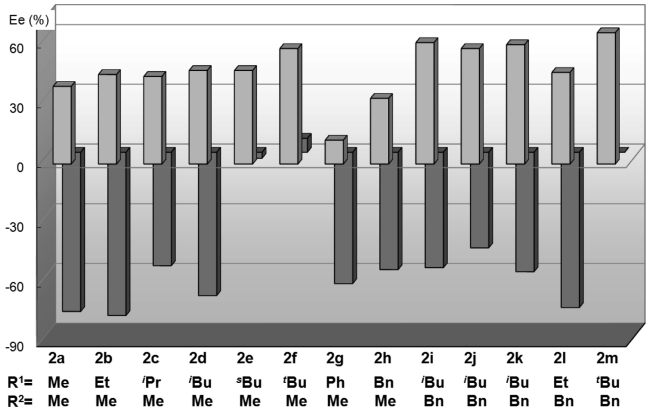


Figure 1. Screening of various azolium ligands **2** in the $Cu(OTf)_2$-catalyzed conjugate addition reaction of **8** with Et_2Zn (front) or the $Cu(acac)_2$-catalyzed conjugate addition reaction of **8** with Et_2Zn (back). Data are shown in Table 2.

Clearly, the increase in the steric demand of the alkyl substituent on the ligand led to improved enantioselectivites. Compound **2f**, having a sterically hindered *tert*-butyl group, efficiently produced (*R*)-**9** in 94% yield and 58% ee (Table 2 entry 6 and Fugure 1). We were also interested in the influence of the counterion of the azolium ligand on the stereoselectivity of the 1,4-addition reaction. It was found that the yield and stereoselectivity obtained by the $Cu(OTf)_2$-catalyzed conjugate addition reaction using **2i** was very similar to those obtained by using **2j** or **2k** (entries 9–11). The ligand screening test also revealed that replacement of the methyl with a benzyl substituent on the azolium ring, which is far from the stereogenic center of the chiral ligand, led to a marked increase in enantioselectivity (entry 4 vs entry 11). Thus, we designed and synthesized azolium ligand **2m** with (*S*)-*tert*-leucinol and benzyl iodide. As expected, **8** was reacted with Et_2Zn under the

dx.doi.org/10.1021/jo300472r | J. Org. Chem. 2012, 77, 4079–4086

influence of $Cu(OTf)_2$ in combination with **2m** to afford (*R*)-**9** with 66% ee (entry 13).

Next, we focused on the $Cu(acac)_2$/**2** catalytic system that produced (*S*)-configured product **9** (Table 2, right column). In contrast to the $Cu(OTf)_2$/**2** catalytic system, the results of the reaction with a series of azolium halides **2a**−**2h** indicated an unusual relationship between the steric factor of the ligand and the enantioselectivity of the reaction (Table 2 entries 1−8 and Figure 1). Decreased steric bulkiness of the alkyl substituent at the ligand led to greater enantioselectivity. For instance, azolium salts **2a** and **2b**, having a methyl and an ethyl group at the stereogenic center, respectively, gave the highest enantioselectivities in excellent yields (entries 1 and 2). By contrast, ligands **2e** and **2f**, derived from (*S*)-*sec*-leucinol and (*S*)-*tert*-leucinol, respectively, gave adduct **9** in poor yields as nearly racemic mixtures (entries 5 and 6). Ligand **2f** actually favored the opposite absolute configuration, albeit slightly (entry 6). In contrast to the above-mentioned $Cu(OTf)_2$-catalyzed reaction, the halide ion of the azolium salts has a significant influence on the yields in the $Cu(acac)_2$-catalyzed reaction (entries 9−11). The combination of $Cu(acac)_2$ and azolium iodide, **2k**, gave the conjugate addition product in 91% yield (entry 11). However, use of the corresponding azolium chloride and bromide, **2i** and **2j**, resulted in poor yields, although the enantioselectivities of these reactions were comparable to that obtained in the reaction catalyzed by the $Cu(acac)_2$/**2k** system (entries 9 and 10).

We also designed hydroxy-amide functionalized azolium ligand **10i**, in which the azolium ring and amide group were connected by a (dimethyl)methylene bridge. Although the combination of $Cu(OTf)_2$ and **10i** provided (*R*)-configured product **9** in moderate yield and ee, no reversal of enantioselectivity was observed by changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$ (entry 14). The reaction with the $Cu(acac)_2$/**10i** system took place with difficulty under these reaction conditions. These results indicated that selection of the linker on the chiral ligand was an important factor for dual enantiocontrol.

Having established the catalytic activity of the $Cu(acac)_2$/**2b** system, we turned our attention to the effect of an additive such as Cs_2CO_3. Table 3 summarizes the $Cu(acac)_2$-catalyzed 1,4-addition reaction with the $Cu(acac)_2$/**2b** system under the influence of various bases. The reaction in the absence of Cs_2CO_3 proceeded with some difficulty to afford (*S*)-**9** in 62% yield and 74% ee (entry 1). Almost all of the bases except for Na_2CO_3 promoted the reaction rate (entries 2−12). Additionally, we found that the 1,4-addition of Et_2Zn to **8** could also be catalyzed by bis(8-quinolinato)Cu(II), which has similar chelation to $Cu(acac)_2$ (entry 13). Advantageously, the reaction with the bis(8-quinolinato)Cu(II)/**2b** catalytic system proceeded even in the absence of a base (entry 1 vs entry 13).

Finally, we studied the scope and the limitations of the reaction protocol (Table 4). Despite an excellent yield, the reaction of 2-cyclopenten-1-one (**11**) with Et_2Zn by the $Cu(OTf)_2$/**2m** system resulted in the formation of a racemic mixture of the corresponding conjugate adduct **12** (entry 1). On the other hand, the same reaction with the $Cu(acac)_2$/**2b** system produced (*S*)-**12** in 82% ee (entry 2). The asymmetric conjugate addition of Et_2Zn to **11** using the CH_2-bridgied azolium salt **1** was difficult to be achieved in both $Cu(OTf)_2$ and $Cu(acac)_2$ catalytic systems, leading to poor enantioselectivities of the product **12**.[9] Therefore, it should be noted that a significant improvement was observed in the combination of $Cu(acac)_2$ with the $(CH_2)_2$-bridged azolium ligand precursor **2** (entry 2).

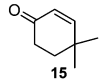
Again, unfortunately, the reaction of **8** with Me_2Zn with the $Cu(OTf)_2$/**2m** system gave poor enantioselectivity (entry 3). By contrast, the use of $Cu(acac)_2$ as a precatalyst led to a dramatic increase in ee (97% ee) to give 3-methylcyclohexanone (**13**) with the opposite configuration (entry 4). In the literature, Hoveyda and Mauduit mentioned that it is impossible to generate a general catalyst for all conjugate

Table 3. Reaction of 8 with Et_2Zn by the $Cu(acac)_2$/2b Catalytic System Under the Influence of Various Bases[a]

entry	base	yield (%)	ee (%)
1	none	62	74 (*S*)
2	Li_2CO_3	82	77 (*S*)
3	Na_2CO_3	60	76 (*S*)
4	K_2CO_3	92	77 (*S*)
5	Rb_2CO_3	90	77 (*S*)
6	Cs_2CO_3	93	82 (*S*)
7	AcOK	93	76 (*S*)
8	AcOCs	94	75 (*S*)
9	$KHCO_3$	71	79 (*S*)
10	KOH	91	72 (*S*)
11	^{t}BuOK	90	76 (*S*)
12	pyridine	90	77 (*S*)
13[b]	none	97	86 (*S*)

[a]See Table 1, footnote *a* (method B). [b]Bis(8-quinolinato)Cu(II) was used instead of $Cu(acac)_2$.

Table 4. Switching of Enantioselectivity in Cu-Catalyzed 1,4-Addition Reaction[a]

Entry	Substrates	Catalyst	Product	Yield/Ee (%)
1	 11 Et_2Zn	$Cu(OTf)_2$/**2m**	**12**	99/0
2	Et_2Zn	$Cu(acac)_2$/**2b**	(*S*)-**12**	99/82
3[b]	**8** Me_2Zn	$Cu(OTf)_2$/**2m**	(*R*)-**13**	98/35
4[b]	**8** Me_2Zn	$Cu(acac)_2$/**2b**	(*S*)-**13**	99/97
5	**8** Bu_2Zn	$Cu(OTf)_2$/**2m**	(*R*)-**14**	97/68
6	**8** Bu_2Zn	$Cu(acac)_2$/**2b**	(*S*)-**14**	99/81
7	 15 Et_2Zn	$Cu(OTf)_2$/**2m**	(*S*)-**16**	43/84
8	Et_2Zn	$Cu(acac)_2$/**2b**	(*R*)-**16**	68/99
9[b]	 17 Me_2Zn	$Cu(OTf)_2$/**2m**	(*R*)-**18**	92/52
10[b]	Me_2Zn	$Cu(acac)_2$/**2b**	(*S*)-**18**	99/96
11[c]	**17** Et_2Zn	$Cu(OTf)_2$/**1m**	(*S*)-**19**	99/91
12[c]	**17** Et_2Zn	$Cu(acac)_2$/**1i**	(*R*)-**19**	99/82
13	**17** Et_2Zn	$Cu(OTf)_2$/**2m**	(*R*)-**19**	92/80
14	**17** Et_2Zn	$Cu(acac)_2$/**2b**	(*S*)-**19**	95/81
15[c]	**17** Bu_2Zn	$Cu(OTf)_2$/**1m**	(*S*)-**20**	99/96
16[c]	**17** Bu_2Zn	$Cu(acac)_2$/**1i**	(*R*)-**20**	55/80
17	**17** Bu_2Zn	$Cu(OTf)_2$/**2m**	(*R*)-**20**	98/80
18	**17** Bu_2Zn	$Cu(acac)_2$/**2b**	(*S*)-**20**	97/86

[a]Enone (1 mmol), R_2Zn (3 mmol), Cu (6 mol %), azolium (4.5 mol %), THF (9 mL), rt, 3 h. For $Cu(OTf)_2$-catalyzed reaction: to a solution of $Cu(OTf)_2$ and azolium in THF, enone was added first, then R_2Zn. For $Cu(acac)_2$-catalyzed reaction: to a solution of $Cu(acac)_2$, azolium and Cs_2CO_3 (8 mol %) in THF, R_2Zn was added first, then enone. [b]Reaction was run for 27 h. [c]Previously reported data (see ref 9b).

dx.doi.org/10.1021/jo300472r | J. Org. Chem. 2012, 77, 4079−4086

addition and more difficult to anticipate the reactivity or the stereoselectivity.[3c,6r,14]

The dual enantioselective control was observed in the reactions of **8** with Bu_2Zn to produce 3-butylcyclohexanone (**14**) and 4,4-dimethyl-2-cyclohexen-1-one (**15**) with Et_2Zn to furnish 3-ethyl-4,4-dimethylcyclohexanone (**16**) (entries 5−8). For example, treatment of **15** with Et_2Zn in the presence of catalytic amounts of $Cu(OTf)_2$ combined with **2m** produced (*S*)-**16** in 84% ee, whereas (*R*)-**16** was produced in 99% ee with the $Cu(acac)_2$/**2b** catalytic system (entries 7 and 8).

The catalytic systems were suitable for the reaction of 2-cyclohepten-1-one (**17**) with various dialkylzincs (entries 9−18). The 1,4-addition reaction of **17** with Me_2Zn proceeded efficiently under the influence of the $Cu(OTf)_2$/**2m** system to afford (*R*)-3-methylcycloheptanone (**18**) in 92% yield with moderate enantioselectivity (entry 9). The use of $Cu(acac)_2$ in place of $Cu(OTf)_2$ resulted in the opposite configuration forming (*S*)-**18** with 96% ee (entry 10). It is noteworthy that excellent enantioselectivity was obtained in the reaction using Me_2Zn under ambient conditions. The synthetic utility of the Cu-catalyzed asymmetric 1,4-addition of Me_2Zn has been demonstrated by its application as a key step in numerous syntheses of natural products and biologically active compounds.[3a]

In the conjugate addition reactions of **17** with Et_2Zn, the ligand structure and copper precatalyst exerted remarkable control over the outcomes (entries 11−14). The combination of azolium salt **1m** and $Cu(OTf)_2$ produced (*S*)-3-ethylcycloheptanone (**19**) in good yield with excellent 91% ee, and $Cu(acac)_2$/**2b** gave a similarly good yield at 81% ee (entries 11 and 14). By contrast, the *R*-configured conjugate adduct **19** was successfully obtained by using the $Cu(acac)_2$/**1i** and $Cu(OTf)_2$/**2m** catalytic systems (entries 12 and 13). In the reaction of **17** with Bu_2Zn, an excellent ee value of 96% was obtained with the $Cu(OTf)_2$/**1m** system, while the same reaction using $Cu(acac)_2$ afforded the corresponding conjugate adduct of the opposite configuration (entries 15 and 16). Enantioselectivity was also reversed by changing the copper precatalyst when the reaction was carried out with azolium salt **2** (entries 17 and 18).

Previously, we have shown the synthesis of the NHC-Pd, NHC-Ag, and NHC-Ir complexes by employing the hydroxy-amide functionalized azolium salt **1** as NHC precursor.[7,8] However, it was difficult to obtain a NHC-Cu complex from the hydroxy-amide functionalized azolium salt. Attempt to prepare a NHC-Cu species by allowing **1** to react with Cu_2O or with CuCl in the presence of ^{t}BuOK failed due to the formation of an unidentified product.[15] Recently, two important reports concerning the synthesis of NHC-Cu complexes by Nechaev and Cazin have been independently published.[16] They showed that some of the NHC-Cu compounds were unstable and difficult to synthesize from azolium salts, owing to the formation of haloamidinium salts or azolidin-2-ones instead of NHCs. In the literature, the most common methods for the catalytic asymmetric 1,4-addition reaction involve the *in situ generated catalyst* from azolium salt and a Cu species.[6,17] We believe that this class of transformations can be performed under operationally simple conditions. Although it might be better from the mechanistic viewpoint to use a well-defined copper complex, we could not obtain such a complex from the hydroxy-amide functionalized azolium salt at this stage.[18]

CONCLUSION

We have described a switchable enantioselectivity in a Cu-catalyzed conjugate addition reaction. Hydroxy-amide functionalized azolium salts were found to be versatile chiral ligand precursors for dual enantioselective control. The stereoselectivity of the conjugate addition could be controlled not only by the structure of the chiral ligand but also by the copper precatalyst. Either varying the linker of the chiral ligands or changing the counterion of Cu species between a OTf and acac ligand initially on the metal led to a complete reversal in the facial selectivity of approach of the substrates. Considering that both the ligand precursors **1** and **2** are prepared from natural α-amino acids, it can be said that obtaining both enantiomers in the asymmetric catalytic reaction was successfully achieved.

EXPERIMENTAL SECTION

General. 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. $(CD_3)_2SO$ or $CDCl_3$ was used as the NMR solvent. Thin-layer chromatography (TLC) analysis was performed with 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; particle size 0.040−0.063 nm). Compounds **6** and **7** were synthesized according to the literature procedures.[11,2i]

General Procedure for Preparation of Hydroxy-amide Derivatives 7. Amino alcohol (2 mmol) was placed in a Schlenk tube, and methyl 3-(1-benzimidazolyl)propionate (**6**) (2 mmol, 408 mg) and NaH 60% w/w dispersion in mineral oil (20 mol %, 16 mg) were then added. The mixture was heated at 120 °C for 5 min. After removing the formed methanol *in vacuo*, the crude residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 97/3) to yield compound **7**.

3-(Benzimidazol-1-yl)-*N*-((*S*)-1-hydroxypropan-2-yl)-propanamide (7a). White solid (380 mg, 77%); mp 149.8−150.0 °C. ^{1}H NMR (DMSO): δ 8.10 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.63−7.58 (m, 2H), 7.25−7.16 (m, 2H), 4.63 (t, J = 5.5 Hz, 1H), 4.44 (t, J = 6.6 Hz, 2H), 3.74−3.67 (m, 1H), 3.27−3.21 (m, 1H), 3.12−3.06 (m, 1H), 2.60 (t, J = 6.6 Hz, 2H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR: δ 169.0, 144.0, 143.3, 133.6, 122.2, 121.4, 119.3, 110.4, 64.2, 46.5, 40.7, 35.7, 17.0. Anal. Calcd for $C_{13}H_{17}N_3O_2{\cdot}0.125CHCl_3{\cdot}0.125H_2O$: C, 60.59; H, 6.78; N, 16.15. Found: C, 60.38; H, 6.64; N, 15.94.

3-(Benzimidazol-1-yl)-*N*-((*S*)-1-hydroxybutan-2-yl)-propanamide (7b). White solid (413 mg, 79%); mp 150.6−150.8 °C. ^{1}H NMR (DMSO): δ 8.10 (s, 1H), 7.64 (br,1H), 7.62−7.58 (m, 2H), 7.25−7.16 (m, 2H), 4.59 (br, 1H), 4.45 (t, J = 7.6 Hz, 2H), 3.59−3.51 (m, 1H), 3.28−3.24 (m, 1H), 3.16−3.11 (m, 1H), 2.70−2.58 (m, 2H), 1.51−1.41 (m, 1H), 1.21−1.10 (m, 1H), 0.65 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 169.2, 143.9, 143.3, 133.6, 122.1, 121.3, 119.2, 110.4, 62.7, 52.1, 40.7, 35.7, 23.4, 10.1. Anal. Calcd for $C_{14}H_{19}N_3O_2{\cdot}0.25H_2O$: C, 63.26; H, 7.39; N, 15.81. Found: C, 63.14; H, 7.28; N, 15.60.

3-(Benzimidazol-1-yl)-*N*-((*S*)-1-hydroxy-3-methylbutan-2-yl)-propanamide (7c). White solid (506 mg, 92%); mp 151.9−152.1 °C. ^{1}H NMR (DMSO): δ 8.10 (s, 1H), 7.62−7.58 (m, 2H), 7.56 (br, 1H), 7.25−7.16 (m, 2H), 4.49 (t, J = 5.5 Hz, 1H), 4.47−4.43 (m, 2H), 3.57−3.50 (m, 1H), 3.27 (t, J = 5.5 Hz, 2H), 2.73−2.61 (m, 2H), 1.75−1.66 (m, 1H), 0.71 (d, J = 6.9 Hz, 3H), 0.65 (d, J = 6.9 Hz, 3H). ^{13}C NMR: δ 169.3, 143.8, 143.3, 133.6, 122.0, 121.3, 119.2, 110.4, 61.1, 55.5, 35.6, 27.9, 19.4, 17.9. Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.36; H, 7.67; N, 15.23.

3-(Benzimidazol-1-yl)-*N*-((*S*)-1-hydroxy-4-methylpentan-2-yl)propanamide (7d). White solid (567 mg, 98%); mp 136.6−136.8 °C. ^{1}H NMR ($CDCl_3$): δ 7.82 (s, 1H), 7.73−7.71 (m, 1H), 7.41−7.38 (m, 1H), 7.30−7.24 (m, 2H), 6.22 (d, J = 8.2 Hz, 1H), 4.56−4.42 (m, 2H) 4.01−3.95 (m, 1H), 3.53−3.49 (m, 1H), 3.41−3.37 (m, 1H), 2.71−2.59 (m, 2H), 1.36−1.33 (m, 1H), 1.26−1.19 (m, 2H),

dx.doi.org/10.1021/jo300472r | J. Org. Chem. 2012, 77, 4079−4086

0.83 (d, J = 3.2 Hz, 3H), 0.81 (d, J = 3.2 Hz, 3H). ^{13}C NMR: δ 169.8, 143.3, 143.2, 133.3, 123.1, 122.3, 120.0, 109.6, 64.9, 49.7, 41.0, 39.9, 36.7, 24.7, 22.8, 22.1. Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.21; H, 8.10; N, 14.39.

3-(Benzimidazol-1-yl)-*N*-((*S*)-1-hydroxy-3-methylpentan-2-yl)propanamide (7e). White solid (475 mg, 82%); mp 162.8−163.0 °C. ^{1}H NMR (DMSO): δ 8.10 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.62−7.58 (m, 2H), 7.25−7.15 (m, 2H), 4.59 (br, 1H), 4.50−4.39 (m, 2H), 3.58−3.52 (m, 1H), 3.30−3.29 (m, 2H), 2.74−2.59 (m, 2H), 1.47−1.37 (m, 1H), 1.25−1.14 (m, 1H), 0.90−0.79 (m, 1H), 0.70 (t, J = 7.3 Hz, 6H). ^{13}C NMR: δ 169.2, 143.9, 143.3, 133.6, 122.1, 121.3, 119.3, 110.4, 60.8, 54.6, 40.8, 35.6, 34.6, 24.5, 15.3, 11.2. Anal. Calcd for $C_{16}H_{23}N_3O_2{\cdot}0.35H_2O$: C, 64.99; H, 8.08; N, 14.21. Found: C, 64.92; H, 8.08; N, 14.21.

3-(Benzimidazol-1-yl)-*N*-((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)propanamide (7f). White solid (515 mg, 89%); mp 197.5−197.7 °C. ^{1}H NMR (DMSO): δ 8.12 (s, 1H), 7.61 (br, 1H), 7.60−7.52 (m, 2H), 7.25−7.15 (m, 2H), 4.51−4.41 (m, 2H), 4.44 (br, 1H), 3.61−3.56 (m, 1H), 3.27−3.15 (m, 2H), 2.78−2.64 (m, 2H), 0.72 (s, 9H). ^{13}C NMR: δ 169.6, 143.9, 143.3, 133.6, 122.1, 121.3, 119.3, 110.4, 60.5, 58.6, 40.8, 35.6, 33.4, 26.7. Anal. Calcd for $C_{16}H_{23}N_3O_2{\cdot}0.5H_2O$: C, 64.40; H, 8.11; N, 14.08. Found: C, 64.74; H, 7.93; N, 14.05.

3-(Benzimidazol-1-yl)-*N*-((*S*)-2-hydroxy-1-phenylethy)-propanamide (7g). White solid (402 mg, 65%); mp 158.5−158.7 °C. ^{1}H NMR (DMSO): δ 8.33 (d, J = 8.2 Hz, 1H), 8.09 (s, 1H), 7.64−7.59 (m, 2H), 7.25−7.15 (m, 7H), 4.82 (t, J = 5.7 Hz, 1H), 4.83−4.78 (m, 1H), 4.45 (t, J = 6.9 Hz, 2H), 3.52−3.42 (m, 2H), 2.74 (t, J = 6.6 Hz, 2H). ^{13}C NMR: δ 169.2, 144.0, 143.3, 140.8, 133.6, 128.0, 126.8, 126.7, 122.2, 121.4, 119.3, 110.4, 64.5, 54.9, 40.6, 35.5. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.69; H, 6.18; N, 13.46.

3-(Benzimidazol-1-yl)-*N*-((*S*)-1-hydroxy-3-phenylpropan-2-yl)propanamide (7h). White solid (530 mg, 82%); mp 119.4−119.6 °C. ^{1}H NMR (DMSO): δ 8.05 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.64−7.56 (m, 2H), 7.27−7.07 (m, 7H), 4.74 (t, J = 5.3 Hz, 1H), 4.38 (t, J = 6.6 Hz, 2H), 3.90−3.82 (m, 1H), 3.29−3.16 (m, 2H), 2.77−2.72 (m, 1H), 2.59 (t, J = 6.6 Hz, 2H), 2.54−2.41 (m, 1H). ^{13}C NMR: δ 169.1, 143.9, 143.3, 138.9, 133.6, 129.0, 128.0, 125.8, 122.1, 121.4, 119.3, 110.4, 62.2, 52.3, 40.6, 36.3, 35.6. Anal. Calcd for $C_{19}H_{21}N_3O_2{\cdot}0.5H_2O$: C, 68.28; H, 6.70; N, 12.57. Found: C, 68.36; H, 6.63; N, 12.34.

General Procedure for Preparation of Azolium Salts 2. To compound 7 (1 mmol) were added alkyl halide (1 mmol) and 5 mL of solvent, and the reaction mixture was stirred under reflux for 24 h. Evaporation of all volatile materials and purification of the residue by chromatography (SiO_2, CH_2Cl_2/MeOH 95/5) gave the corresponding coupling product.

1-[3-((*S*)-1-Hydroxy-2-propanylamino)-3-oxopropyl]-3-methylbenzimidazolium Iodide (2a). Colorless liquid (311 mg, 80%). ^{1}H NMR (DMSO): δ 9.69 (s, 1H), 8.07−8.06 (m, 1H), 8.01−7.99 (m, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.70−7.68 (m, 2H), 4.69 (t, J = 6.8 Hz, 1H), 4.66−7.63 (m, 1H), 4.07 (s, 3H), 3.74−3.65 (m, 1H), 3.24−3.10 (m, 2H), 2.77−2.74 (m, 2H), 0.89 (d, J = 6.8 Hz, 3H). ^{13}C NMR: δ 168.3, 143.1, 131.6, 130.8, 126.4, 126.4, 113.6, 113.5, 64.1, 46.5, 43.2, 34.4, 33.2, 16.9. HRMS (ESI$^+$) calcd for $C_{14}H_{20}H_3O_2^+$: 262.1556, found 262.1550.

1-[3-((*S*)-1-Hydroxy-2-butanylamino)-3-oxopropyl]-3-methylbenzimidazolium Iodide (2b). Colorless liquid (330 mg, 82%). ^{1}H NMR (DMSO): δ 8.10 (s, 1H), 7.64 (br, 1H), 7.62−7.58 (m, 2H), 7.25−7.16 (m, 2H), 4.58 (br, 1H), 4.45 (t, J = 6.6 Hz, 2H), 3.59−3.51 (m, 1H), 3.33 (s, 3H), 3.25−3.24 (m, 2H), 3.16−3.11 (m, 1H), 2.70−2.58 (m, 2H), 1.51−1.41 (m, 1H), 1.21−1.10 (m, 1H), 0.66 (t, J = 7.3 Hz, 3H). ^{13}C NMR: δ 168.6, 143.2, 142.9, 131.6, 130.7, 126.4, 113.6, 113.6, 62.6, 52.2, 34.4, 33.1, 31.6, 23.3, 10.0. HRMS (ESI$^+$) calcd for $C_{15}H_{22}N_3O_2^+$: 276.1712, found 276.1717.

1-[3-((*S*)-1-Hydroxy-3-methyl-2-butanylamino)-3-oxopropyl]-3-methylbenzimidazolium Iodide (2c). Colorless liquid (330 mg, 79%). ^{1}H NMR (DMSO): δ 9.66 (s, 1H), 8.09−8.07 (m, 1H), 8.02−7.99 (m, 1H), 7.70−7.67 (m, 3H), 4.71 (t, J = 6.4 Hz, 1H), 4.50 (t, J = 5.0 Hz, 1H), 4.06 (s, 3H), 3.54−3.46 (m, 1H), 3.27−3.24 (m, 2H), 2.87−2.77 (m, 2H), 1.69−1.61 (m, 1H), 0.68 (d, J = 6.4 Hz, 3H), 0.61 (d, J = 6.4 Hz, 3H). ^{13}C NMR: δ 168.8, 143.1, 131.6, 130.7, 126.5, 126.4, 113.7, 113.5, 61.0, 55.7, 43.4, 34.4, 33.2, 28.0, 19.3, 17.9. HRMS (ESI$^+$) calcd for $C_{16}H_{24}N_3O_2^+$: 290.1869, found 290.1864.

1-[3-((*S*)-1-Hydroxy-4-methyl-2-pentanylamino)-3-oxopropyl]-3-methylbenzimidazolium Iodide (2d). Colorless liquid (211 mg, 49%). ^{1}H NMR ($CDCl_3$): δ 10.38 (s, 1H), 7.89−7.87 (m, 1H), 7.70−7.64 (m, 3H), 7.33 (d, J = 8.8 Hz, 1H), 5.00−4.93 (m, 1H), 4.82−4.76 (m, 1H), 4.21 (s, 3H), 4.03−3.93 (m, 2H), 3.52−3.49 (m, 1H), 3.21 (br, 1H), 3.12−3.06 (m, 1H), 1.96−1.34 (m, 2H), 1.26−1.12 (m, 1H), 0.83 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H). ^{13}C NMR: δ 169.2, 142.1, 131.6, 131.5, 127.4, 127.3, 113.5, 112.4, 64.6, 50.4, 43.8, 39.7, 35.4, 34.1, 24.7, 22.8, 22.1. HRMS (ESI$^+$) calcd for $C_{17}H_{26}N_3O_2^+$: 304.2025, found 304.2017.

1-[3-((*S*)-1-Hydroxy-3-methyl-2-pentanylamino))-3-oxopropyl]-3-methylbenzimidazolium Iodide (2e). Colorless liquid (349 mg, 81%). ^{1}H NMR (DMSO): δ 9.62 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 8.09−8.07 (m, 1H), 8.01−7.99 (m, 1H), 7.71−7.67 (m, 2H), 7.24−7.19 (m, 3H), 7.12−7.10 (m, 2H), 4.71 (t, J = 6.4 Hz, 2H), 4.46 (t, J = 5.5 Hz, 1H), 4.01 (s, 3H), 4.07 (s, 3H), 3.56−3.49 (m, 1H), 3.30−3.24 (m, 2H), 2.87−2.76 (m, 2H), 1.41−1.31 (m, 1H), 1.20−1.10 (m,1H), 0.84−0.77 (m, 1H), 0.69−0.65 (m, 6H). ^{13}C NMR: δ 168.5, 143.1, 131.6, 130.7, 126.5, 126.4, 113.7, 113.5, 60.7, 54.7, 43.4, 34.7, 34.4, 33.1, 24.5, 15.2, 11.1. HRMS (ESI$^+$) calcd for $C_{17}H_{26}N_3O_2^+$: 304.2025, found 304.2021.

1-[3-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-3-oxopropyl]-3-methylbenzimidazolium Iodide (2f). Colorless liquid (358 mg, 83%). ^{1}H NMR (DMSO): δ 9.63 (s, 1H), 8.11−8.09 (m, 1H), 8.01−7.98 (m, 1H), 7.70−7.68 (m, 2H), 7.63 (d, J = 9.6 Hz, 1H), 4.72 (t, J = 6.2 Hz, 2H), 4.37 (t, J = 5.0 Hz, 1H), 4.05 (s, 3H), 3.58−3.49 (m, 2H), 3.20−3.14 (m, 1H), 2.87−2.83 (m, 2H), 0.70 (s, 9H). ^{13}C NMR: δ 169.0, 143.0, 131.6, 130.7, 126.5, 126.4, 113.6, 113.5, 60.2, 58.8, 43.4, 34.3, 33.2, 33.1, 26.6. HRMS (ESI$^+$) calcd for $C_{17}H_{26}N_3O_2^+$: 304.2025, found 304.2018.

1-[3-((*S*)-1-Hydroxy-2-phenyl-2-ethanylamino)-3-oxopropyl]-3-methylbenzimidazolium Iodide (2g). Colorless liquid (347 mg, 77%). ^{1}H NMR (DMSO): δ 9.62 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 8.09−8.07 (m, 1H), 8.01−7.99 (m, 1H), 7.71−7.67 (m, 2H), 7.24−7.19 (m, 3H), 7.12−7.10 (m, 2H), 4.85 (t, J = 5.5 Hz, 1H), 4.81−4.75 (m, 1H), 4.70 (t, J = 6.4 Hz, 1H), 4.01 (s, 3H), 3.50−3.39 (m, 2H), 2.95−2.83 (m, 2H). ^{13}C NMR: δ 168.6, 143.1, 140.7, 131.6, 130.7, 128.0, 126.7, 126.6, 126.5, 126.4, 113.6, 113.5, 64.4, 55.0, 43.2, 34.1, 33.1. HRMS (ESI$^+$) calcd for $C_{19}H_{22}N_3O_2^+$: 324.1712, found 324.1703.

1-[3-((*S*)-1-Hydroxy-3-phenyl-2-propanylamino)-3-oxopropyl]-3-methylbenzimidazolium Iodide (2h). Colorless liquid (93 mg, 20%). ^{1}H NMR (DMSO): δ 9.58 (s, 1H), 8.05−8.00 (m, 2H), 7.91 (d, J = 8.2 Hz, 1H), 7.71−7.68 (m, 5H), 4.74 (t, J = 5.5 Hz, 1H), 4.62 (t, J = 7.3 Hz, 2H), 4.04 (s, 3H), 3.90−3.82 (m, 1H), 3.28−8.20 (m, 2H), 2.79−2.66 (m, 3H). ^{13}C NMR: δ 163.9, 143.5, 138.7, 131.4, 131.2, 129.1, 128.1, 126.6, 126.4, 126.0, 113.6, 113.1, 62.4, 53.0, 48.4, 36.6, 34.3, 33.3. HRMS (ESI$^+$) calcd for $C_{20}H_{24}N_3O_2^+$: 338.1869, found 338.1861.

1-[3-((*S*)-1-Hydroxy-4-methyl-2-pentanylamino)-3-oxopropyl]-3-benzilbenzimidazolium Chloride (2i). Colorless liquid (112 mg, 27%). ^{1}H NMR ($CDCl_3$): δ 11.02 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.60−7.55 (m, 1H), 7.50−7.47 (m, 4H), 7.38−7.29 (m, 3H), 5.82 (d, J = 15.1 Hz, 1H), 5.75 (d, J = 15.1 Hz, 1H), 4.98−4.93 (m, 1H), 4.82−4.78 (m, 1H), 4.47 (br, 1H), 3.87−3.83 (m, 1H), 3.51−3.40 (m, 3H), 3.09−3.04 (m, 1H), 1.47−1.41 (m, 1H), 1.35−1.28 (m, 1H), 1.23−1.11 (m, 1H), 0.79 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H). ^{13}C NMR: δ 168.8, 142.7, 132.6, 131.9, 130.8, 129.2, 129.1, 128.1, 127.0, 127.0, 113.5, 113.3, 64.3, 51.5, 50.2, 43.9, 39.8, 35.1, 24.6, 22.7, 22.3. HRMS (ESI$^+$) calcd for $C_{23}H_{30}N_3O_2^+$: 380.2338, found 380.2324.

1-[3-((*S*)-1-Hydroxy-4-methyl-2-pentanylamino)-3-oxopropyl]-3-benzilbenzimidazolium Bromide (2j). Colorless liquid (276 mg, 60%). ^{1}H NMR ($CDCl_3$): δ 10.80 (s, 1H), 7.84−7.82 (m, 1H), 7.82 (m, 2H), 7.63−7.59 (m, 1H), 7.55−4.48 (m, 4H), 7.40−7.35 (m, 3H), 5.81 (d, J = 15.1 Hz, 1H), 5.74 (d, J = 15.1 Hz, 1H), 5.01−4.94 (m, 1H), 4.76−4.71 (m, 1H), 3.94−3.86 (m, 1H), 3.60−3.53 (m, 3H),

dx.doi.org/10.1021/jo300472r | J. Org. Chem. 2012, 77, 4079−4086

3.47−3.38 (m, 2H), 3.09−3.03 (m, 1H), 1.52−1.43 (m, 1H), 1.39−1.32 (m, 1H), 1.22−1.14 (m, 1H), 0.83 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{13}C NMR: δ 168.9, 142.4, 132.4, 131.8, 130.8, 129.3, 129.1, 128.2, 128.2, 127.1, 127.0, 113.5, 113.3, 64.4, 51.6, 50.2, 44.0, 39.8, 35.3, 24.6, 22.7, 22.2. HRMS (ESI$^+$) calcd for $C_{23}H_{30}N_3O_2^+$: 380.2338, found 380.2325.

1-[3-((*S*)-1-Hydroxy-4-methyl-2-pentanylamino)-3-oxopropyl]-3-benzilbenzimidazolium Iodide (2k). Colorless liquid (391 mg, 77%). ^{1}H NMR (DMSO): δ 9.93 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.68−7.60 (m, 2H), 7.51−7.47 (m, 2H), 7.42−7.35 (m, 3H), 5.78 (s, 2H), 4.78−4.71 (m, 2H), 4.58 (t, J = 5.6 Hz, 1H), 3.76−3.67 (m, 1H), 3.22−3.12 (m, 2H), 2.90−2.76 (m, 2H), 1.28−1.06 (m, 3H), 0.70 (d, J = 6.3 Hz, 3H), 0.66 (d, J = 6.3 Hz, 3H). ^{13}C NMR: δ 168.4, 143.0, 133.9, 131.1, 130.5, 128.8, 128.6, 128.2, 128.0, 126.5, 113.9, 113.7, 63.5, 49.7, 48.7, 43.5, 40.1, 39.9, 39.7, 39.5, 39.2, 39.0, 38.8, 34.0, 24.0, 23.0, 21.6. HRMS (ESI$^+$) calcd for $C_{23}H_{30}N_3O_2^+$: 380.2338, found 380.2337.

1-[3-((*S*)-1-Hydroxy-2-butanylamino)-3-oxopropyl]-3-benzilbenzimidazolium Iodide (2l). Colorless liquid (369 mg, 77%). ^{1}H NMR (DMSO): δ 9.91 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.68−7.60 (m, 2H), 7.48−7.46 (m, 2H), 7.40−7.34 (m, 3H), 5.77 (s, 2H), 4.75 (t, J = 6.4 Hz, 1H), 4.60 (t, J = 5.5 Hz, 1H), 3.59−3.49 (m, 1H), 3.26−3.17 (m, 2H), 2.89−2.76 (m, 2H), 1.47−1.37 (m, 1H), 1.22−1.09 (m, 1H), 0.59 (t, J = 7.3 Hz, 3H). ^{13}C NMR: δ 168.6, 143.0, 133.9, 131.1, 130.6, 128.9, 128.6, 113.9, 113.8, 62.6, 52.2, 49.7, 48.5, 43.5, 34.0, 23.4, 10.1. HRMS (ESI$^+$) calcd for $C_{21}H_{26}N_3O_2^+$: 352.2025, found 352.2021.

1-[3-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-3-oxopropyl]-3-benzilbenzimidazolium Iodide (2m). Colorless liquid (309 mg, 61%). ^{1}H NMR ($CDCl_3$): δ 10.52 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.61−7.57 (m, 1H), 7.51−7.48 (m, 4H), 7.38−7.33 (m, 3H), 7.22 (d, J = 9.6 Hz, 1H), 5.79 (d, J = 15.1 Hz, 1H), 5.73 (d, J = 15.1 Hz, 1H), 5.02−4.95 (m, 1H), 4.90−4.84 (m, 1H), 3.84−3.80 (m, 1H), 3.70−3.62 (m, 3H), 3.17−3.10 (m, 1H), 0.84 (s, 9H). ^{13}C NMR (DMSO): δ 164.7, 143.5, 133.9, 131.6, 130.4, 129.0, 128.7, 128.1, 126.7, 126.6, 113.8, 113.6, 60.2, 59.7, 49.7, 48.7, 41.5, 33.6, 26.8. HRMS (ESI$^+$) calcd for $C_{23}H_{30}N_3O_2^+$: 380.2338, found 380.2327.

1-[3-((*S*)-1-Hydroxy-4-methyl-2-pentanylamino)-2,2-dimethyl-3-oxopropyl]-3-benzilbenzimidazolium Chloride (10i). Colorless liquid (159 mg, 37%). ^{1}H NMR (DMSO): δ 10.28 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.78−7.75 (m, 1H), 7.59−7.55 (m, 5H), 7.42−7.35 (m, 3H), 5.81 (s, 2H), 4.73 (t, J = 5.5 Hz, 1H), 3.79 (br, 1H), 3.27−3.15 (m, 2H), 1.98 (s, 3H), 1.92 (s, 3H), 1.26−1.10 (m, 3H), 0.68 (d, J = 2.3 Hz, 3H), 0.67 (d, J = 2.3 Hz, 3H). ^{13}C NMR: δ 169.1, 143.0, 134.0, 131.2, 130.1, 128.8, 128.5, 128.2, 126.3, 126.2, 114.9, 114.1, 64.8, 63.4, 50.0, 49.8, 25.1, 24.6, 24.0, 23.2, 21.6. HRMS (ESI$^+$) calcd for $C_{24}H_{31}N_3O_2^+$: 394.2495, found 394.2491.

General Procedure for Cu(OTf)$_2$-Catalyzed Asymmetric Reaction of Enone with Et$_2$Zn (Method A). To a solution of azolium salt (0.045 mmol) in THF (9 mL) were added Cu(OTf)$_2$ (0.06 mmol, 21.7 mg) and enone (1 mmol). After the mixture was cooled to 0 °C, Et$_2$Zn (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 and dried over Na_2SO_4. The product was purified by silica gel column chromatography (hexane/EtOAc). Enantiomeric excess was measured by chiral GLC.

General Procedure for Cu(acac)$_2$-Catalyzed Asymmetric Reaction of Enone with Et$_2$Zn (Method B). To a solution of azolium salt (0.045 mmol) in THF (9 mL) were added Cs_2CO_3 (0.08 mmol, 26.0 mg) and Cu(acac)$_2$ (0.06 mmol, 15.7 mg), and then the mixture was cooled to 0 °C. Then, Et$_2$Zn (3 mmol, 1 mol/L in hexanes, 3 mL) was added to the reaction vessel, and the mixture was stirred at room temperature for 15 min. The color changed from blue to dark brown. Then, enone (1 mmol) was added. and the reaction mixture was stirred at room temperature for 3 h.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra for products and chiral GC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*satoshi@kansai-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by a Grant-in-Aid for Scientific Research (C) (23550128) from Japan Society for the Promotion of Science (JSPS), Kansai University Research Grant: Grant-in-Aid for Encouragement of Scientists, 2011, and the Sumitomo Foundation.

■ REFERENCES

(1) (a) Bartók, M. *Chem. Rev.* **2010**, *110*, 1633. (b) Tanaka, T.; Hayashi, M. *Synthesis* **2008**, 3361. (c) Zanoni, G.; Castronovo, F.; Franzini, M.; Vidari, G.; Giannini, E. *Chem. Soc. Rev.* **2003**, *32*, 115. (d) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719.

(2) For selected recent examples, see: (a) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738. (b) Inagaki, T.; Ito, A.; Ito, J.; Nishiyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9384. (c) Liu, Y.; Shang, D.; Zhou, X.; Zhu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010**, *12*, 180. (d) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3779. (e) Kim, H. Y.; Shih, H. J.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420. (f) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682. (g) Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724. (h) Abermil, N.; Masson, G.; Zhu, J. P. *Org. Lett.* **2009**, *11*, 4648. (i) Schneider, N.; César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2005**, *21*, 4886.

(3) For selected recent reviews, see: (a) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039. (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (c) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779. (d) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

(4) For selected recent reviews, see: (a) *N-Heterocyclic Carbenes*; Díez-González, S., Ed.; RSC-Publishing: Cambridge, 2011. (b) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* **2011**, *111*, 2705. (c) Kühl, O. *Functionalised N-Heterocyclic Carbene Complexes*; Wiley-VCH: Weinheim, 2010. (d) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (e) Wencel, J.; Mauduit, M.; Hénon, H.; Kehrli, S.; Alexakis, A. *Aldrichim. Chim. Acta* **2009**, *42*, 43. (f) Snead, D. R.; Seo, H.; Hong, S. *Curr. Org. Chem.* **2008**, *12*, 1370. (g) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer-Verlag: Berlin/Heidelberg, 2007. (h) Douthwaite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702. (i) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (j) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768. (k) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239. (l) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619. (m) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

(5) (a) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083. (b) Pytkowicz, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2087.

(6) Selected recent publications: (a) O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7712. (b) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736. (c) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 3040. (d) Tissot, M.; Hernández, A. P.; Müller, D.; Mauduit, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1524. (e) Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.;

Alexakis, A. *Chem.—Eur. J.* **2010**, *16*, 9890. (f) Rix, D.; Labat, S.; Toupet, L.; Crévisy, C.; Mauduit, M. *Eur. J. Org. Chem.* **2009**, 1989. (g) Lee, K.-s.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455. (h) Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2009**, *50*, 4741. (i) Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578. (j) Moore, T.; Merzouk, M.; Williams, N. *Synlett* **2008**, 21. (k) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904. (l) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358. (m) Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122. (n) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097. (o) Clavier, H.; Guillemin, J.-C.; Mauduit, M. *Chirality* **2007**, *19*, 471. (p) Lee, K.-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182. (q) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416. (r) Clavier, H.; Coutable, L.; Toupet, L.; Guillemin, J.-C.; Mauduit, M. *J. Organomet. Chem.* **2005**, *690*, 5237. (s) Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. *Tertahedron: Asymmetry* **2005**, *16*, 921. (t) Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P.; Alexakis, A. *J. Organomet. Chem.* **2005**, *690*, 5672. (u) Arnold, P. L.; Rodden, M.; Davis, K. M.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2004**, 1612. (v) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345.

(7) (a) Sakaguchi, S.; Yoo, K. S.; O'Neill, J.; Lee, J. H.; Stewart, T.; Jung, K. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 9326. (b) Yoo, K. S.; O'Neill, J.; Sakaguchi, S.; Giles, R.; Lee, J. H.; Jung, K. W. *J. Org. Chem.* **2010**, *75*, 95. (c) Sakaguchi, S.; Kawakami, M.; O'Neill, J.; Yoo, K. S.; Jung, K. W. *J. Organomet. Chem.* **2010**, *695*, 195. (d) Kamisue, R.; Sakaguchi, S. *J. Organomet. Chem.* **2011**, *696*, 1910.

(8) (a) Chiyojima, H.; Sakaguchi, S. *Tetrahedron Lett.* **2011**, *52*, 6788. (b) Kawabata, S.; Tokura, H.; Chiyojima, H.; Okamoto, M.; Sakaguchi, S. *Adv. Synth. Catal.* **2012**, *354*, 807.

(9) (a) Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *Chem. Commun.* **2009**, 7363. (b) Shibata, N.; Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *J. Org. Chem.* **2010**, *16*, 5707. (c) Harano, A.; Sakaguchi, S. *J. Organomet. Chem.* **2011**, *696*, 61.

(10) (a) Wencel-Delord, J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2010**, *12*, 4335. (b) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67.

(11) Hou, X.; Hemit, H.; Yong, J.; Nie, L.; Aisa, H. A. *Synth. Commun.* **2010**, *40*, 973.

(12) We previously reported the ligand design for dual enantioselective control by using *β*-amino alcohols and *α*-amino esters, which are derived from natural amino acids: Yoshimura, M.; Shibata, N.; Kawakami, M.; Sakaguchi, S. *Tetrahedron* **2011**, DOI: 10.1016/j.tet.2011.04.028.

(13) The influence of the order of addition of the substrates in NHC-Cu catalyzed asymmetric conjugate addition reaction has been reported; see ref 6q.

(14) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779.

(15) In ^{13}C NMR of the unidentified product, the absence of the characteristic signal for the carbene carbon, which is expected to be shifted to low field (typically ca. 200 ppm), was observed.[16] The ^{13}C NMR signal of the product, which was obtained by the reaction of **1** with Cu_2O or CuCl, appeared at 154 ppm instead of 200 ppm.

(16) (a) Kolychev, E. L.; Shuntikov, V. V.; Khrustalev, V. N.; Bush, A. A.; Nechaev, M. S. *Dalton Trans.* **2011**, *40*, 3074. (b) Citadelle, C. A.; Nouy, E. L.; Bisaro, F.; Slawin, A. M. Z.; Cazin, C. S. J. *Dalton Trans.* **2010**, *39*, 4489.

(17) Díez-González, S.; Nolan, S. P. *Aldrichim. Chim. Acta* **2008**, *41*, 43.

(18) Quite recently, Hoveyda proposed the reaction mechanistic model in the NHC-Cu-catalyzed asymmetric allylic substitution reaction: Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490. We speculate that the present Cu-catalyzed-1,4-addition reaction might proceed through similar mechanistic models. In the $Cu(OTf)_2$/**1** catalytic system, the anionic amidate/NHC-Cu species **A** might be involved. On the other hand, the 1,4-addition reaction catalyzed by $Cu(acac)_2$ combined with **1** may take place through the model **B**, where anionic acetylacetonate ligand coordinates to a Cu center.