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Reversal of Stereoselectivity in the Cu-Catalyzed Conjugate Addition Reaction of Dialkylzinc to Cyclic Enone in the Presence of a Chiral Azolium Compound

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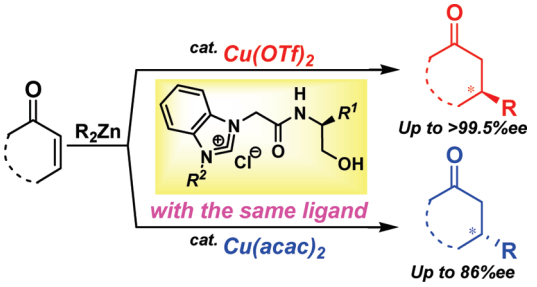

Reversal of enantioselectivity in a Cu-catalyzed asymmetric conjugate addition reaction of dialkylzinc to cyclic enone with use of the same chiral ligand was successfully achieved. The reaction of 2-cyclohexen-1-one (**30**) with Et_2Zn catalyzed by $Cu(OTf)_2$ in the presence of an azolium salt derived from a chiral β-amino alcohol gave (*S*)-3-ethylcyclohexanone (**31**) in good enantioselectivity. Among a series of chiral azolium compounds examined, the benzimidazolium salt (**10**) having both a *tert*-butyl group at the stereogenic center and a benzyl substituent at the azolium ring was found to be the best choice of ligand in the $Cu(OTf)_2$-catalyzed reaction. Good enantioselectivity was observed when the reaction was conducted by employing a benzimidazolium derivative rather than an imidazolium derivative. The influence of the substituent at the azolium ring on the stereoselectivity of the reaction was also examined. In addition, from the results of the reaction catalyzed by $Cu(OTf)_2$ combined with an azolium compound derived from (*S*)-leucine methyl ester, it was found that the hydroxy side chain in the chiral ligand is probably crucial for the enantiocontrol of the conjugate addition reaction. On the other hand, it was discovered from a screening test of copper species that the reversal of enantioselectivity was realized by allowing **30** to react with Et_2Zn in the presence of $Cu(acac)_2$ combined with the same ligand precursor to afford (*R*)-**31** as a major product. The influence of the stereodirecting group at the chiral ligand on the stereoselectivity in the $Cu(acac)_2$-catalyzed reaction differed completely from that observed in the $Cu(OTf)_2$-catalyzed reaction. Reaction with a cyclic enone consisting of a seven-membered ring such as 2-cyclohepten-1-one (**40**) resulted in increasing the enantioselectivity of the reaction. Thus, treatment of **40** with Et_2Zn catalyzed by $Cu(OTf)_2$ combined with a benzimidazolium salt produced the corresponding (*S*)-conjugate adduct in a 92:8 enantiomer ratio (er), while the $Cu(acac)_2$-catalyzed reaction with the same ligand afforded (*R*)-product in a 9:91 er.

Introduction

The preparation of both enantiomers of a chiral compound with high enantioselectivity is an important challenge because both enantiomers are increasingly needed in organic synthesis and medical and bioorganic chemistry.[1] This preparation is typically achieved in asymmetric catalysis by using chiral ligands with different configuration. However, several of the chiral ligands derived from natural products such as amino acids are available in only one enantiomeric form. The reversal of enantioselectivity of a reaction without employing the antipode of the chiral source has been achieved by design and control of the ligand

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structure.[2] However, the development of effective catalytic asymmetric methods to induce a switch in the enantioselectivity of a reaction *with the same chiral ligand* is an attractive possibility.[3]

The Cu-catalyzed enantioselective conjugate addition (ECA) reaction has received increasing interest during the past few years. A great number of successful chiral phosphorus donor ligands have been developed so far.[4] In addition, several chiral *N*-heterocyclic carbenes (NHCs) that have emerged as a new family of ancillary ligands have been introduced for the ECA reaction of cyclic enones with dialkylzincs.[5,6] The monodentate Arduengo-type diaminocarbene ligands afforded moderate enantioselectivity in the 1,4-addition of Et_2Zn to 2-cyclohexen-1-one, whereas the bidentate chelating NHC ligands were clearly superior in the ECA reaction.[7]

The first example of enantioselective Cu-catalyzed conjugate addition with a chiral anionic tethered bidentate NHC ligand was reported by Arnold et al. in 2004.[8] Hoveyda et al. have developed anionic phenoxy- or sulfonate-bearing chiral bidentate NHC ligands. These ligands were successfully used not only in asymmetric catalytic allylic alkylation, but also in ECA reactions.[9,10] Mauduit et al. introduced a second coordination site at the NHC ligand, provided by an alcohol moiety, to achieve higher stereoselectivity.[11] By using the same ligand, an efficient 1,4-addition of Grignard reagents to β-substituted cyclic enones, generating all-carbon chiral quaternary centers, has been developed. As a result, anionic tethered polydentate NHC chemistry has received attention.[12,13]

Recently, we designed and synthesized a new chiral tridentate NHC ligand, which is composed of benzimidazole and a chiral amino alcohol. The tridentate anionic amidate/alkoxy/NHC palladium(II) complex successfully catalyzed oxidative Heck-type reactions of arylboronic acids with alkenes to offer high enantioselectivities unprecedented in intermolecular Heck-type couplings.[14a,b] An important feature of our NHC ligand is that it bears both a chiral center and hard chelating sites such as anionic amidate and alkoxy groups. Furthermore, easy tuning of both the *N*-anionic functional groups and the *N*-alkyl groups of the ligand allowed the development of various tridentate NHC ligands. Thus, an efficient synthetic route to various chiral tridentate and anionic tethered NHC ligands with their Pd complexes has been developed.[14c]

Ligand precursors, such as azolium chlorides, have also been tested in the Cu-catalyzed asymmetric conjugate addition of

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SCHEME 1. Reversal of Stereoselectivity with the Same Ligand

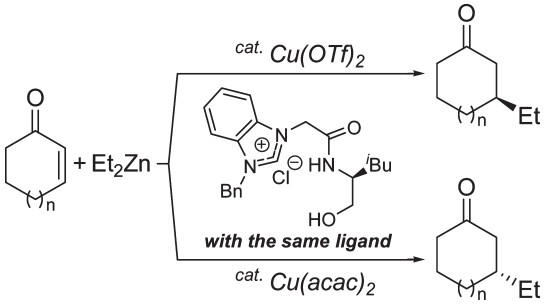
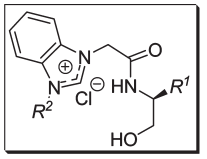
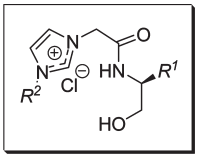
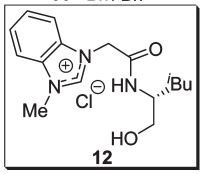


CHART 1. Chiral Azolium Salts





	R^1, R^2
1	Me, Me
2	Et, Me
3	^{i}Pr, Me
4	^{i}Bu, Me
5	^{t}Bu, Me
6	^{s}Bu, Me
7	Ph, Me
8	Bn, Me
9	^{i}Bu, Bn
10	^{t}Bu, Bn
11	Bn, Bn



12

	R^1, R^2
13	^{i}Bu, Me
14	Me, Bn
15	Et, Bn
16	^{i}Pr, Bn
17	^{i}Bu, Bn
18	^{t}Bu, Bn
19	^{s}Bu, Bn
20	Ph, Bn
21	Bn, Bn
22	^{t}Bu, Me
23	^{t}Bu, Bu
24	^{t}Bu, ^{i}Pr
25	^{t}Bu, CH_2(1-Naphthyl)
26	^{t}Bu, $CH_2C_6H_4$(*p*-OMe)
27	^{t}Bu, $CH_2C_6H_4$(*p*-CO_2Me)
28	^{t}Bu, $CH_2C_6H_4$(*p*-F)
29	^{t}Bu, Allyl

dialkylzincs to cyclic enones. Interestingly, we discovered that reversal of enantioselectivity with the same ligand was achieved by changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$ (Scheme 1).[15a] For example, reaction of 2-cyclohepten-1-one with Et_2Zn catalyzed by $Cu(OTf)_2$ combined with benzimidazolium salt derived from (*S*)-leucinol gave the corresponding (*S*)-adduct in a 92:8 enantiomer ratio (er), while the (*R*)-adduct was obtained as a major product in a 9:91 er by using $Cu(acac)_2$ in combination with the same azolium compound. To the best of our knowledge, this is the first example of the dual enantioselective control on the Cu-catalyzed ECA reaction.

Now, we have prepared a huge variety of azolium compounds **1**−**29** having both the *N*-hydroxyamide functional groups and the *N*-alkyl groups (Chart 1), and studied the influence of the structure of the ligand and the copper precatalyst on the stereoselective induction for optimization of the ECA reaction. Herein, we report the entire results of the dual enantioselective control in the NHC−Cu-catalyzed 1,4-addition by simply changing the copper catalyst precursor from $Cu(OTf)_2$ to $Cu(acac)_2$ with the same ligand.

Results and Discussion

1. $Cu(OTf)_2$-Catalyzed ECA Reaction. The reaction of 2-cyclohexen-1-one (**30**) with Et_2Zn yielding 3-ethylcyclohexanone (**31**) was selected as a model reaction, and the $Cu(OTf)_2$-catalyzed ECA reaction in the presence of benzimidazolium salt **1**−**12** was examined (Table 1). The reaction catalyzed by $Cu(OTf)_2$ (6 mol %) and **4** ($R^1 = {}^i$Bu, R^2 = Me) (4.5 mol %) derived from (*S*)-leucinol afforded (*S*)-**31** in preference to (*R*)-**31** in an 87:13 er (74% ee) with quantitative yield (entry 1), although decreasing the amount of catalysts resulted in somewhat lower conversion of **30** (entries 1−3). To investigate the effect of the stereodirecting group of the chiral ligand, we screened several benzimidazolium chlorides **1**−**8** for the $Cu(OTf)_2$-catalyzed ECA reaction (entries 4−10). It was found that a sterically hindered substituent such as a *tert*-butyl group proved efficient to produce (*S*)-**31** in an 88.5:11.5 er (entry 7).

TABLE 1. ECA Reaction of 30 with Et_2Zn Catalyzed by $Cu(OTf)_2$ Combined with Benzimidazolium Salt[a]

			er[b]	
entry	azolium salt	yield[b] (%)	*S*	*R*
1	**4**	> 99	87	13
2[c]	**4**	63	80.5	19.5
3[d]	**4**	85	85	15
4	**1**	> 99	82	18
5	**2**	> 99	84.5	15.5
6	**3**	> 99	86	14
7	**5**	> 99	88.5	11.5
8	**6**	> 99	87	13
9	**7**	89	67	33
10	**8**	> 99	76	24
11	**9**	> 99	90.5	9.5
12	**10**	> 99	91	9
13	**11**	> 99	78.5	21.5
14[e]	**9**	84	90.5	9.5
15[f]	**9**	> 99	88	12
16	**12**	> 99	14	86

[a] **30** (1 mmol), Et_2Zn (3 mmol), $Cu(OTf)_2$ (6 mol %), benzimidazolium salt (4.5 mol %), THF (9 mL), rt, 3 h. [b] Yield and enantiomer ratio (er) were determined by GLC analysis. Average of two runs. [c] Et_2Zn (1.5 mmol), $Cu(OTf)_2$ (2 mol %), **4** (3 mol %), THF (3 mL). [d] $Cu(OTf)_2$ (4 mol %), **4** (3 mol %). [e] 0 °C. [f] 45 °C.

Moreover, we found that replacement of the methyl by a benzyl substituent at the azolium ring led to a marked increase in enantioselectivity. Thus, the use of **9** ($R^1 = {}^i$Bu, R^2 = Bn) in place of **4** ($R^1 = {}^i$Bu, R^2 = Me) gave (*S*)-**31** in an 90.5:9.5 er (entry 11). Similar results were obtained with **10** or **11** instead of **5** or **8**, respectively (entries 7 and 10 vs entries 12 and 13). The ee of **31** increased to 82% with **10** (entry 12). The influence of the R^2 group at the azolium ring on enantioselectivity will be discussed later (see Table 3). Raising the reaction temperature to 45 °C or decreasing it to 0 °C did not have a drastic effect on the outcome (entries 14 and 15).

At this stage of the study, it was necessary to verify whether the absolute configuration of the stereogenic center in the ligand showed a significant influence on the enantiocontrol of the conjugate addition. Thus, by using the β-amino alcohol derived from unnatural *d*-leucine, the enantiomer of benzimidazolium chloride **12** ((*ent*)-**4**) was prepared. Almost the same enantioselectivity was observed with **12** in the ECA reaction (entry 1 vs entry 16).

It was reported that the azolium moiety plays a critical role in the NHC−Ir-catalyzed asymmetric transfer hydrogenation of ketones.[16] Therefore, next we investigated the ECA reaction

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TABLE 2. ECA Reaction of 30 with Et_2Zn Catalyzed by $Cu(OTf)_2$ Combined with Imidazolium Salt[a]

entry	azolium salt	yield[b]	er[b] *S*	er[b] *R*
1[c]	**13**	38	68	32
2[c]	**17**	61	72	28
3[c]	**18**	88	82.5	17.5
4	**18**	>99	82	18
5	**14**	81	62.5	37.5
6	**15**	87	66	34
7	**16**	91	73.5	26.5
8	**17**	84	73.5	26.5
9	**19**	92	74.5	25.5
10	**21**	86	52	48

[a] **30** (1 mmol), Et_2Zn (3 mmol), $Cu(OTf)_2$ (2 mol %), imidazolium salt (3 mol %), THF (3 mL), rt, 3 h. [b] See Table 1, footnote *b*. [c] Reaction condition: see Table 1, footnote *a*.

TABLE 3. Influence of the R^2 Group at Imidazolium Salt on Enantioselectivity in the $Cu(OTf)_2$-Catalyzed ECA Reaction of 30 with Et_2Zn[a]

entry	azolium salt	yield[b] (%)	er[b] *S*	er[b] *R*
1	**22**	90	77.5	22.5
2	**23**	80	76.5	23.5
3	**24**	42	76	24
4	**18**	>99	82	18
5	**25**	89	81.5	18.5
6	**26**	98	81.5	18.5
7	**27**	>99	80.5	19.5
8	**28**	96	80.5	19.5
9	**29**	97	81.5	18.5

[a] Reaction condition: see Table 2, footnote *a*. [b] See Table 1, footnote *b*.

catalyzed by $Cu(OTf)_2$ combined with various chiral imidazolium compounds (Table 2). Treatment of **30** with Et_2Zn in the presence of catalytic amounts of $Cu(OTf)_2$ (6 mol %) and **13** ($R^1 = {}^t$Bu, R^2 = Me) (4.5 mol %) derived from (*S*)-leucinol afforded the adduct **31** in 38% yield and 68:32 er (entry 1). In a manner similar to that found in the ECA reaction with benzimidazolium derivatives, changing the *N*-methyl unit in **13** to a benzyl group improved the stereoselectivity and the product yield (entry 2). Using these results, we selected the benzyl group at the azolium ring for further studies of the catalyst performance.

The imidazolium salt **18** ($R^1 = {}^t$Bu, R^2 = Bn) derived from (*S*)-*tert*-leucinol led to slightly better enantioselectivity (entry 3). After optimization of the reaction conditions, product **31** was obtained in quantitative yield and an 82:18 er (entry 4, and Table S1, Supporting Information). The effect of the choice of the solvent on the catalyst selectivity was investigated for the $Cu(OTf)_2$-catalyzed ECA reaction by using **18** (Table S2, Supporting Information). This study showed that THF, DMA, and AcOEt afford high levels of enantioselectivity. On the basis of these results, we screened several imidazolium chlorides **14**−**21** (Table 2, entries 5−10). Because of the highly hydroscopic character of compound **20** (R^1 = Ph, R^2 = Bn) that was prepared from (*S*)-2-phenylglycinol, we did not perform the ECA reaction using **20**.

Figure 1 represents the influence of the R^1 group at the azolium salt on enantioselectivity in the $Cu(OTf)_2$-catalyzed ECA reaction of **30** with Et_2Zn giving (*S*)-**31** as a major product. These data have already been shown in Tables 1 and 2. It was clear that a relatively higher stereoselectivity was

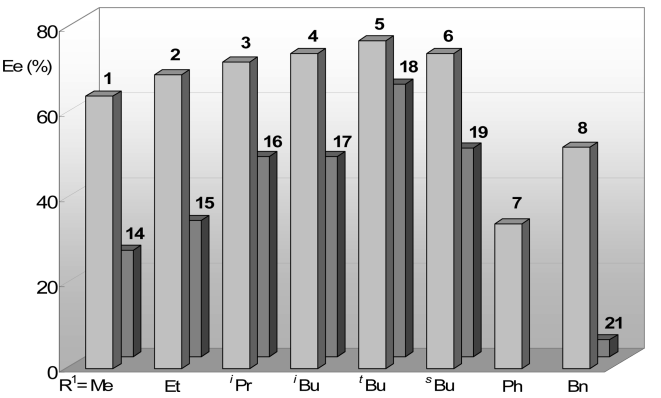


FIGURE 1. Influence of R^1 group at benzimidazolium salt (**1**−**8**, front) and imidazolium salt (**14**−**21**, back) on enantioselectivity in the $Cu(OTf)_2$-catalyzed ECA reaction.

obtained when benzimidazolium compounds are used as compared to the imidazolium salts, and that the increase in the steric demand of the alkyl substituent at the ligand led to improved product ee.

Note that our catalytic system does not require an additional base to generate the NHC species from azolium compounds by deprotonation. This is in contrast with the Mauduit and Williams reaction systems that need an appropriate base such as ^{t}BuOK or BuLi.[11e,13c] Recently, Alexakis and Tomioka demonstrated independently that the Cu-catalyzed conjugate addition of EtMgBr to an enone under the influence of an azolium salt takes place in the absence of a base.[11d,13b] In addition, Hoveyda et al. reported excellent results from the preparation of a NHC−Zn complex by allowing an azolium compound to react with Et_2Zn, where Et_2Zn acts as a base to generate the NHC species.[9b] Therefore, Et_2Zn possibly serves as a base to generate the NHC species as well as an alkylating reagent in our catalytic system.

On the other hand, as mentioned above, a slightly better result was obtained upon changing the R^2 substituent, which is far from the stereogenic center of the chiral ligand, from a methyl to a benzyl group (Table 2, entries 1 and 2). We were interested in the influence of the R^2 substituent at the imidazolium compound on the stereoselectivity in the $Cu(OTf)_2$-catalyzed ECA reaction of **30** with Et_2Zn. A series of imidazolium derivatives **22**−**29** were synthesized from (*S*)-*tert*-leucinol and the asymmetric conjugate addition reaction was examined (Table 3).

Ligands **22**−**24** bearing Me, Bu, and ^{i}Pr groups at the R^2 position, respectively, resulted in almost the same product ratio (76−77.5:24−22.5 er), though the yield decreased with the use of a sterically hindered ligand such as **24** (entries 1−3). The stereoselectivity in the ECA reaction with ligand **25** was similar to that observed with ligand **18** (entries 4 and 5). The substituent on the benzene ring in ligands **26**−**28** did not show a significant influence on the enantiocontrol of the conjugate addition (entries 6−8). These results strongly suggest that the stereoselectivity was not affected by either steric factors or the electronic properties of the R^2 substituent. In addition, we were surprised that the product ratio obtained with **29** (R^2 = allyl) was very comparable to that obtained with **18** (R^2 = benzyl) (entry 9).

Although the role of the R^2 substituent is unclear at this stage, it may be assumed that a benzyl or an allyl moiety coordinates with a NHC−Cu during the catalytic cycle as shown in Scheme 2. The intermediate **A**, where the substrate coordinates with the Cu species, undergoes the ECA reaction

SCHEME 2. Tentative Catalytic Cycle

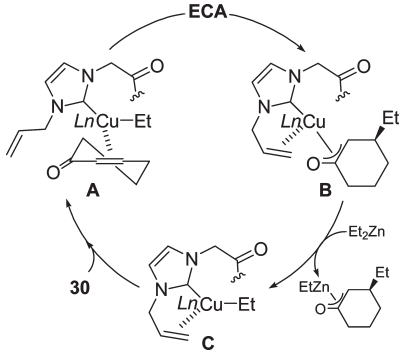
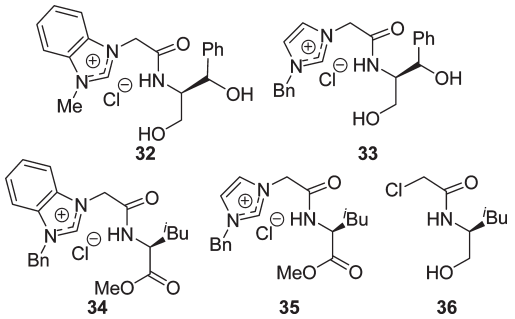


TABLE 4. ECA Reaction of 30 with Et_2Zn Catalyzed by $Cu(OTf)_2$ Combined with Several Chiral Ligands



				er[b]	
entry	ligand	condition[a]	yield[b] (%)	*S*	*R*
1	**32**	A	> 99	78.5	21.5
2	**33**	B	98	60	40
3	**34**	A	72	51.5	48.5
4	**34**	B	98	50.5	49.5
5	**35**	B	50	35	65
6	**36**	A	< 5	50	50

[a]Condition A: see Table 1, footnote *a*. Condition B: see Table 2, footnote *a*. [b]See Table 1, footnote *b*.

to give **B** in which the reaction would be facilitated by coordination of the Cu species with the π-bond. **B** then reacts with Et_2Zn to form **C**, followed by coordination of substrate **30** to regenerate **A**. Similar observations have been reported in the Ir-catalyzed transfer hydrogenation of ketones, where the NHC−Ir complex having a hemilabile alkene moiety generated a vacant site in the iridium coordination sphere during the reaction.[17]

In addition, several chiral ligands **32**−**36** were tested (Table 4). Azolium compounds **32** and **33** derived from (1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol, which has an additional hydroxy moiety, were not effective for the present ECA reaction (entries 1 and 2). On the other hand, ligand **34**, prepared by the same procedure as **9** by employing (*S*)-leucine methyl ester instead of (*S*)-leucinol, provided racemic **31** (entries 3 and 4). This indicates that the hydroxy side chain in the NHC ligand is probably crucial for the enantiocontrol of the conjugate addition. Interestingly, the corresponding imidazolium salt **35** preferred (*R*)-**31** over (*S*)-**31** (entry 5). The use of this new ligand is currently under investigation. Treatment of **30** with Et_2Zn in the presence of $Cu(OTf)_2$ and 2-chloro-*N*-[(*1S*)-1-(hydroxymethyl)-3-methylbutyl]acetamide (**36**) produced a racemic mixture of **31** in < 5% yield (entry 6). This suggests that the complexation of the Cu species with the 2-hydroxyamide moiety of the azolium salt to form the catalytic active species is not essential.

TABLE 5. Screening of Cu Salts for ECA Reaction of 30 with Et_2Zn in the Presence of 9[a]

			er[b]	
entry	Cu salt	yield[b] (%)	*S*	*R*
1	$Cu(OTf)_2$	> 99	90.5	9.5
2	$[Cu(OTf)]_2(C_6H_6)$	90	88	12
3	$[Cu(CH_3CN)]_4OTf$	89	89	11
4	$[Cu(CH_3CN)]_4BF_4$	91	80	20
5	$Cu(NO_2)_3$	15	72	28
6	$Cu(OAc)_2$	84	54	46
7	Cu(I) salt[c]	31	54	46
8	Cu(II) salt[d]	33	53	47
9	$Cu(acac)_2$	84	39	61
10[e]	$Cu(acac)_2$	69	29.5	70.5
11[e]	Cu(II) oxinate[f]	21	31	69
12	$CuCl_2$	9	32	68
13	none	< 5	50	50

[a]**30** (1 mmol), Et_2Zn (3 mmol), Cu salt (6 mol %), **9** (4.5 mol %), THF (9 mL), rt, 3 h. [b]See Table 1, footnote *b*. [c][Bis(trimethylsilyl)acetylene](hexafluoroacetylacetonato)copper(I). [d]Bis(hexafluoroacetylacetonato)copper-(II). [e]Cs_2CO_3 (8 mol %) was added. [f]Bis(8-hydroxyquinolinato)copper(II).

2. $Cu(acac)_2$-Catalyzed ECA Reaction. Alexakis et al. reported the systematic study of the ECA reaction of **30** with Et_2Zn using Cu precursors and a chiral phosphoramidite ligand.[18] Mauduit et al. also examined several copper precatalysts in combination with a bidentate NHC ligand.[11e] The reactions in their copper species screening tests always yielded the conjugate adduct, possessing the same absolute configuration. In contrast, we achieved a dual enantioselective control of the product on screening tests of copper species combined with a chiral azolium salt (Table 5).

Table 5 summarizes the results of 1,4-addition of Et_2Zn to **30** catalyzed by several Cu compounds in the presence of benzimidazolium salt **9** ($R^1 = {}^i$Bu, R^2 = Bn). Cu(I) salts such as $[Cu(OTf)]_2(C_6H_6)$, $[Cu(CH_3CN)_4]OTf$, and $[Cu(CH_3CN)_4]BF_4$ could be used in the same manner as $Cu(OTf)_2$ to produce (*S*)-**31** as a major product (entries 1−4). $Cu(NO_3)_2$ afforded (*S*)-adduct in low yield, whereas $Cu(OAc)_2$ led to a racemic mixture of **31** in good yield (entries 5 and 6). We were then surprised to discover that the combination of $Cu(acac)_2$ with **9** furnished (*R*)-**31** as the major product (entry 9). The addition of a base such as Cs_2CO_3 improved the enantiomer ratio slightly (entry 10). Reversal of enantioselectivity was also observed in the case of bis(8-hydroxyquinolinato)Cu(II)/**9** and in the $CuCl_2$/**9** catalytic system, but the yield of **31** was very low (entries 11 and 12). The present ECA reaction did not take place in the absence of a copper precatalyst (entry 13), although Hoveyda et al. recently demonstrated enantioselective allylic alkylation of allylic phosphates with dialkylzinc catalyzed by chiral bidentate imidazolium salt under Cu-free conditions, where a chiral Zn-based NHC complex that was formed by the reaction of the imidazolium salt with dialkylzinc promoted enantioselective allylic alkylation.[9b]

Next, we studied the influence of the stereodirecting group of several azolium chlorides **1**−**21** on the $Cu(acac)_2$-catalyzed ECA

(17) (a) Corberán, R.; Sanaú, M.; Peris, E. *Organometallics* **2007**, *26*, 3492–3498. (b) Corberán, R.; Peris, E. *Organometallics* **2008**, *27*, 1954–1958.

(18) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263.

TABLE 6. Screening of Azolium Salts for ECA Reaction of 30 with Et_2Zn in the Presence of $Cu(acac)_2$ and Cs_2CO_3[a]

entry	azolium salt	yield[b] (%)	er[b] *S*	er[b] *R*
1	**1**	>99	45.5	54.5
2	**2**	>99	41	59
3	**3**	78	33	67
4	**4**	>99	38	62
5	**5**	30	57.5	42.5
6	**6**	73	32	68
7	**7**	97	44	56
8	**8**	83	25	75
9	**9**	69	29.5	70.5
10	**10**	73	63	37
11	**11**	93	40	60
12	**14**	>99	44	56
13	**15**	>99	36.5	63.5
14	**16**	94	40.5	59.5
15	**17**	91	35.5	64.5
16	**18**	78	70	30
17	**19**	95	35.5	64.5
18	**21**	90	46	54

[a]Reaction condition: see Table 5, footnotes *a* and *e*. [b]See Table 1, footnote *b*.

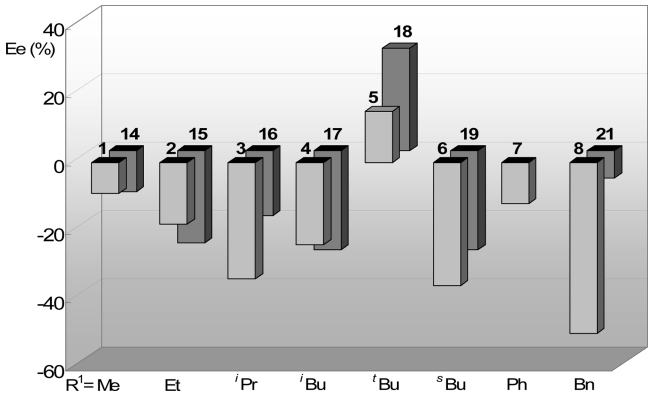
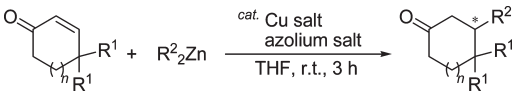


FIGURE 2. Influence of the R^1 group at benzimidazolium salt (**1**−**8**, front) and imidazolium salt (**14**−**21**, back) on enantioselectivity in the $Cu(acac)_2$-catalyzed ECA reaction.

reaction (Table 6 and Figure 2). These results differed completely from the observations in the $Cu(OTf)_2$-catalyzed ECA reaction: (i) ligands **5**, **10**, and **18** derived from (*S*)-*tert*-leucinol produced (*S*)-**31** as the major product, while (*R*)-**31** was obtained with other ligands (entries 5, 10, and 16); (ii) an unusual relationship between the steric factor of the ligand and the enantioselectivity of the reaction was observed (Figure 2); and (iii) ligand **8** (R^1 = Bn, R^2 = Me) gave a 25:75 er, a slightly better result than otained with **9** (R^1 = ^{i}Bu, R^2 = Bn) (entries 8 and 9).

In addition, we examined several Cu catalyst precursors in the presence of ligand **29** having a ^{t}Bu group (Table S3, Supporting Information). All of these reactions produced (*S*)-**31** in preference to the (*R*)-enantiomer, implying no reversal of stereoselectivity was observed in this case. It is difficult to explain why the ligands having a ^{t}Bu group at the R^1 position, such as **5**, **10**, **18**, and **29**, afford the (*S*)-enantiomer in the $Cu(acac)_2$-catalyzed ECA reaction in contrast to that provided by other ligands. We assume that the complex, which is an active catalytic species derived from $Cu(acac)_2$ and **18**, would be structurally different from the complex derived from **11**−**21** excuding **18** beause of the steric hindrance of the ^{t}Bu moiety.

TABLE 7. Reversal of Enantioselectivity by Changing the Cu Salts[a]



entry	enone *n*	enone R^1	$R^2{}_2Zn$ R^2	Cu salt	azolium salt	yield[b] (%)	er[c] *S*	er[c] *R*
1	1	H	Bu	$Cu(OTf)_2$	**9**	92	92	8
2	1	H	Bu	$Cu(OTf)_2$	**10**	>99	94	6
3	1	H	Bu	$Cu(acac)_2$	**9**	82	26	74
4[d]	1	H	Bu	$Cu(acac)_2$	**8**	63	19	81
5	1	Me	Et	$Cu(OTf)_2$	**9**	49	14	86
6	1	Me	Et	$Cu(OTf)_2$	**10**	84	<0.5	>99.5
7	1	Me	Et	$Cu(acac)_2$	**9**	44	85	15
8[d]	1	Me	Et	$Cu(acac)_2$	**8**	35	73	27
9	2	H	Et	$Cu(OTf)_2$	**9**	>99	92	8
10	2	H	Et	$Cu(OTf)_2$	**10**	>99	95.5	4.5
11	2	H	Et	$Cu(acac)_2$	**9**	>99	9	91
12[d]	2	H	Et	$Cu(acac)_2$	**8**	>99	7	93
13	2	H	Bu	$Cu(OTf)_2$	**9**	>99	88	12
14	2	H	Bu	$Cu(OTf)_2$	**10**	>99	98	2
15	2	H	Bu	$Cu(acac)_2$	**9**	>99	11	89
16[d]	2	H	Bu	$Cu(acac)_2$	**8**	55	10	90

[a]Reaction condition: see Table 1, footnote *a*. [b]Isolated yield. [c]Enantiomer ratio (er) was determined by GLC analysis. [d]Reaction condition: see Table 5, footnotes *a* and *e*, and also text (the improved experimental procedure).

Before the study on a scope of cyclic enones with our catalytic system, we reexamined the experimental procedure to improve the ee in the ECA reaction catalyzed by $Cu(acac)_2$ combined with **8**. The above-mentioned reaction was conducted by adding first the enone and then Et_2Zn to a THF solution containing catalytic amounts of $Cu(acac)_2$ and **8** to give (*R*)-**31** in a 25:75 er (Table 6, entry 8). This is the same procedure used for the $Cu(OTf)_2$-catalyzed ECA reaction shown above. Additional optimization revealed that (*R*)-**31** could be obtained in a 15.5:84.5 er by adding enone **30** to the mixture of $Cu(acac)_2$, **8**, and Et_2Zn (see the Experimental Section).

Finally, on the basis of these results, we examined the ECA reaction of several cyclic enones with dialkylzinc reagents catalyzed by $Cu(OTf)_2$ or $Cu(acac)_2$ in the presence of the appropriate azolium compound as a chiral ligand (Table 7). Replacement of Et_2Zn by Bu_2Zn resulted in a slight improvement of the reversal of enantioselectivity (entries 1−4). For example, the reaction of **30** with Bu_2Zn, catalyzed by $Cu(OTf)_2$, combined with **9** gave (*S*)-3-butylcyclohexanone (**37**) as a major product in a 92:8 er (entry 1), while the use of $Cu(acac)_2$ with the same ligand induced a reversed enantioselectivity to afford (*R*)-**37** in a 26:74 er (entry 3). The dual enantioselective control was also observed in the reaction of 4,4-dimethyl-2-cyclohexen-1-one (**38**) with Et_2Zn producing 3-ethyl-4,4-dimethylcyclohexanone (**39**) (entries 5−8). An excellent ee value of >99.5% was obtained in the ECA reaction, which was catalyzed by the $Cu(OTf)_2$/**10** system (entry 6). Although the reversed isomer of adduct **39** was the main product in both the $Cu(acac)_2$/**9** and $Cu(acac)_2$/**8** catalytic systems, the yields were lower (entries 7 and 8).

Reaction of a cyclic enone consisting of a seven-membered ring such as 2-cyclohepten-1-one (**40**) was found to increase the enantioselectivity of the reaction (entries 9−16). A similar observation was reported in the monodentate NHC−Cu-catalyzed conjugate addition of dialkylzinc to cyclic enone.[7b] Treatment of **40** with Et_2Zn catalyzed by $Cu(OTf)_2$ combined with **10** afforded (*S*)-3-ethylcycloheptanone (**41**) in a 95.5:4.5 er (entry 10). On the other hand, (*R*)-**41** was produced as a major

product in a 7:93 er by reacting **40** with Et_2Zn in the presence of $Cu(acac)_2$ combined with **8** (entry 12). In the $Cu(OTf)_2$-catalyzed ECA reaction of **40** with Bu_2Zn ligand **9** provided 76% ee, whereas 96% ee was recorded by using **10** leading to (*S*)-adduct (entries 13 and 14).

Conclusions

We conducted systematic studies on the Cu-catalyzed asymmetric conjugate addition of Et_2Zn to cyclic enones using a wide variety of chiral azolium compounds that are readily accessible, highly stable, and easily tunable. The most important feature of our ligands was that almost complete reversal of enantioselectivity with the same ligand was achieved simply by changing the Cu species employed. Reaction of cyclic enones with dialkylzinc catalyzed by $Cu(OTf)_2$ combined with an appropriate chiral benzimidazolium compound afforded the corresponding optically active conjugate adducts in moderate to excellent yields and 91:9 to >99.5:<0.5 enantiomer ratio (82% to >99.5% ee), whereas $Cu(acac)_2$ in place of $Cu(OTf)_2$ led to the adducts with opposite configurations in 19:81 to 7:93 er (62% to 86% ee). The present method might provide a new synthetic strategy for obtaining both enantiomers of a given compound in the Cu-catalyzed ECA reaction. Further studies focusing on coordination chemistry and organometallic chemistry of the catalytic active Cu species that would be formed by the reaction of $Cu(OTf)_2$ or $Cu(acac)_2$ with the azolium compounds to gain insight into the mechanisms of the reversal of enantioselectivity are currently in progress. In addition, applications of the chiral chelating polydentate NHC catalysts for development of efficient catalytic enantioselective transformations are the subject of ongoing research in our laboratory.

Experimental Section

General. All chemicals were obtained from commercial sources and were used as received. *N*-Alkylated azoles except for 1-methylbenzoimidazole, 1-methylimidazole, 1-byutylimidazole, 1-benzylimidazole, and 1-allylimidazole have been prepared according to the literature procedure.[19] Chiral azolium salts **1**−**29** and **32**−**35** have been synthesized according to our previous papers.[14] ^1H and ^{13}C NMR spectra were recorded on spectrometers at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra. CD_3OD, $(CD_3)_2SO$, 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 (Merck, mesh: 230−400; particle size: 0.040−0.063 nm).

General Procedure for the Prepation of Azolium Salts. To 1,4-dioxane were added *N*-benzylbenzimidazole (0.293 M) and α-chloroacetoaminde derived from chloroacetyl chloride and *β*-aminoalcohol[20] (0.267 M). After the reaction mixture was stirred at 110 °C for 16 h, the solvent was removed under reduced pressure. The residue was dissolved in methanol, and then activated carbon was added. After 16 h, the activated carbon was removed by filtration. The filtrate was concentrated under reduced pressure to obtain a solid, which was purified by reprecipitation with ethyl acetate and methanol to afford the corresponding coupling product as a white solid. The compounds **3**, **4**, **5**, **7**, **9**, **12**, **13**, **16**, and **17** were reported in our previous papers.[14,15]

1-[2-((*S*)-1-Hydroxy-2-propanylamino)-2-oxoethyl]-3-methylbenzimidazolium chloride (1): yield 72%; mp 117.6−117.8 °C; ^1H NMR (DMSO) δ 9.78 (s, 1H), 8.68 (br, 1H), 8.05−7.93 (m, 2H), 7.74−7.66 (m, 2H), 5.31 (s, 2H), 4.87 (t, J = 6.0 Hz, 1H), 4.14 (s, 3H), 3.81−3.77 (m, 1H), 3.39−3.30 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 163.9, 143.7, 131.5, 131.4, 126.7, 126.4, 113.6, 113.5, 64.0, 48.5, 47.4, 33.3, 16.9. Anal. Calcd for $C_{13}H_{18}ClN_3O_2 \cdot 0.5H_2O$: C, 53.33; H, 6.54; N, 14.35. Found: C, 52.96; H, 6.36; N, 14.29.

1-[2-((*S*)-1-Hydroxy-2-butanylamino)-2-oxoethyl]-3-methylbenzimidazolium chloride (2): yield 70%; mp 164.8−165.1 °C; ^1H NMR (DMSO) δ 9.76 (s, 1H), 8.52 (br, 1H), 8.05−8.03 (m, 1H), 7.93−7.92 (m, 1H), 7.72−7.69 (m, 2H), 5.36 (d, J = 16.4 Hz, 1H), 5.29 (d, J = 16.4 Hz, 1H), 4.82 (t, J = 5.6 Hz, 1H), 4.14 (s, 3H), 3.67−3.59 (m, 1H), 3.43−3.33 (m, 2H), 1.64−1.53 (m, 1H), 1.42−1.32 (m, 1H), 0.84 (t, J = 7.6 Hz, 3H); ^{13}C NMR δ 164.1, 143.5, 131.3, 131.3, 126.5, 126.3, 113.5, 113.2, 62.4, 52.8, 48.3, 33.2, 23.4, 10.3. Anal. Calcd for $C_{14}H_{20}ClN_3O_2$: C, 56.47; H, 6.77; N, 14.11. Found: C, 56.12; H, 6.58; N, 14.06.

1-[2-((*S*)-1-Hydroxy-3-methyl-2-pentanylamino)-2-oxoethyl]-3-methylbenzimidazolium chloride (6): yield 48%; mp 177.3−177.5 °C; ^1H NMR (DMSO) δ 9.83 (s, 1H), 8.66 (d, J = 8.7 Hz, 1H), 8.03−8.01 (m, 1H), 7.96−7.94 (m, 1H), 7.69−7.67 (m, 2H), 5.42 (d, J = 16.3 Hz, 1H), 5.34 (d, J = 16.3 Hz, 1H), 4.78 (t, J = 11.0 Hz, 1H), 4.13 (s, 3H), 3.63−3.56 (m, 1H), 3.46−3.36 (m, 2H), 1.59−1.58 (m, 1H), 1.46−1.41 (m, 1H), 1.13−1.02 (m, 1H), 0.83 (d, J = 7.3 Hz, 3H), 0.79 (d, J = 7.3 Hz, 3H); ^{13}C NMR δ 164.3, 143.7, 131.5, 131.3, 126.6, 126.4, 113.6, 113.4, 60.8, 55.5, 48.5, 34.8, 33.3, 24.7, 15.4, 11.2. Anal. Calcd for $C_{16}H_{24}ClN_3O_2 \cdot 1.25H_2O$: C, 55.17; H, 7.67; N, 12.06. Found: C, 55.05; H, 7.47; N, 12.05.

1-[2-((*S*)-1-Hydroxy-3-phenyl-2-propanylamino)-2-oxoethyl]-3-methylbenzimidazolium chloride (8): yield 68%; mp 208.8−209.1 °C; ^1H NMR (DMSO) δ 9.75 (s, 1H), 8.86 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.71−7.63 (m, 3H), 7.24−7.16 (m, 5H), 5.30 (d, J = 16.4 Hz, 1H), 5.24 (d, J = 16.4 Hz, 1H), 5.02 (t, J = 5.7 Hz, 1H), 4.12 (s, 3H), 3.96−3.92 (m, 2H), 3.43−3.35 (m, 2H), 2.90−2.86 (m, 1H), 2.71−2.36 (m, 1H); ^{13}C NMR δ 164.0, 143.6, 138.9, 131.4, 131.2, 129.1, 128.1, 126.6, 126.4, 126.0, 113.5, 113.3, 62.5, 53.2, 48.5, 36.5 33.3. Anal. Calcd for $C_{19}H_{22}ClN_3O_2$: C, 63.42; H, 6.16; N, 11.68. Found: C, 63.26; H, 6.10; N, 11.63.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-benzilbenzimidazolium chloride (10): yield 62%; mp 230.6−230.8 °C; ^1H NMR (DMSO) δ 9.95 (d, J = 4.1 Hz, 1H), 8.37 (br, 1H), 7.99−7.91 (m, 2H), 7.69−7.62 (m, 2H), 7.49−7.35 (m, 5H), 5.84 (s, 2H), 5.43 (d, J = 16.3 Hz, 1H), 5.32 (d, J = 16.3 Hz, 1H), 4.63 (br, 1H), 3.63−3.55 (m, 2H), 3.45−3.32 (m, 1H), 0.86 (s, 9H); ^{13}C NMR δ 164.7, 143.5, 133.9, 131.6, 130.4, 128.9, 128.7, 128.1, 126.7, 126.6, 113.8, 113.6, 60.2, 59.7, 49.7, 48.7, 33.5, 26.8. Anal. Calcd for $C_{22}H_{28}ClN_3O_2$: C, 65.74; H, 7.02; N, 10.45. Found: C, 65.46; H, 6.93; N, 10.31.

1-[2-((*S*)-1-Hydroxy-3-phenyl-2-propanylamino)-2-oxoethyl]-3-benzilbenzimidazolium chloride (11): yield 53%; mp 195.7−195.9 °C; ^1H NMR (DMSO) δ 9.97 (s, 1H), 8.89 (d, J = 8.2 Hz, 1H), 7.99−7.96 (m, 1H), 7.65−7.60 (m, 3H), 7.49−7.48 (m, 2H), 7.43−7.37 (m, 3H), 7.24−7.12 (m, 5H), 5.83 (s, 2H), 5.32 (d, J = 16.5 Hz, 1H), 5.25 (d, J = 16.5 Hz, 1H), 5.04 (t, J = 5.2 Hz, 1H), 3.98−3.91 (m, 1H), 3.42 (t, J = 5.2 Hz, 2H), 2.91−2.86 (m, 1H), 2.70−2.65 (m, 1H); ^{13}C NMR δ 163.9, 143.4, 138.9, 134.0, 131.5, 130.4, 129.1, 129.0, 128.7, 128.2, 128.1, 126.8, 126.6, 126.0, 113.9, 113.6, 62.5, 53.3, 49.7, 48.7, 36.6. Anal. Calcd for $C_{25}H_{26}ClN_3O_2 \cdot 0.25H_2O$: C, 68.17; H, 6.06; N, 9.54. Found: C, 68.29; H, 5.92; N, 9.58.

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1-[2-((*S*)-1-Hydroxy-2-butanylamino)-2-oxoethyl]-3-benzylimidazolium chloride (14): yield 72%; ^{1}H NMR (DMSO) δ 9.40 (br, 1H), 8.60 (br, 1H), 7.86−7.84 (m, 1H), 7.72−7.70 (s, 1H), 7.45−7.38 (m, 5H), 5.50 (s, 2H), 5.02 (s, 2H), 4.91 (d, J = 5.9 Hz, 2H), 3.81−3.72 (m, 1H), 3.42−3.26 (m, 2H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 164.1, 137.4, 134.9, 129.0, 128.7, 128.2, 124.2, 121.8, 64.0, 51.9, 50.7, 47.2, 16.9. Because of the highly hydroscopic character collection of analytical data failed.

1-[2-((*S*)-1-Hydroxy-2-propanylamino)-2-oxoethyl]-3-benzylimidazolium chloride (15): yield 68%; mp 136.8−137.0 °C; ^{1}H NMR (DMSO) δ 9.31 (s, 1H), 8.34 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.46−7.39 (m, 5H), 5.48 (s, 2H), 5.03 (d, J = 16.4 Hz, 1H), 4.98 (d, J = 16.4 Hz, 1H), 4.78 (t, J = 4.0 Hz, 1H), 3.66−3.57 (m, 1H), 3.40−3.30 (m, 2H), 1.63−1.52 (m, 1H), 1.40−1.29 (m, 1H), 0.84 (t, J = 7.6 Hz, 3H); ^{13}C NMR δ 164.4, 137.4, 134.8, 129.0, 128.7, 128.2, 124.2, 121.8, 62.5, 52.9, 51.8, 50.7, 23.5, 10.4. Anal. Calcd for $C_{16}H_{22}ClN_3O_2 \cdot 0.125H_2O$: C, 58.94; H, 6.88; N, 12.89. Found: C, 58.77; H, 6.64; N, 12.89.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-benzylimidazolium chloride (18): yield 81%; mp 213.8−214.0 °C; ^{1}H NMR (DMSO) δ 9.33 (s, 1H), 8.21 (d, J = 9.2 Hz, 1H), 7.82 (t, J = 1.6 Hz, 1H), 7.73 (t, J = 1.6 Hz, 1H), 7.44−7.39 (m, 5H), 5.49 (s, 2H), 5.08 (d, J = 16.4 Hz, 1H), 5.02 (d, J = 16.4 Hz, 1H), 4.55 (t, J = 5.6 Hz, 1H), 3.63−3.57 (m, 2H), 3.38−3.31 (m, 1H), 0.87 (s, 9H); ^{13}C NMR δ 164.9, 137.4, 134.9, 128.9, 128.7, 128.1, 124.1, 121.8, 60.3, 59.6, 51.8, 50.9, 33.6, 26.8. Anal. Calcd for $C_{18}H_{26}ClN_3O_2 \cdot 0.125CH_3OH$: C, 61.17; H, 7.51; N, 11.81. Found: C, 61.04; H, 7.46; N, 11.83.

1-[2-((*S*)-1-Hydroxy-3-methyl-2-pentanylamino)-2-oxoethyl]-3-benzylimidazolium chloride (19): yield 54%; mp 159.6−159.8 °C; ^{1}H NMR (DMSO) δ 9.31 (s, 1H), 8.30 (d, J = 8.6 Hz, 1H), 7.81 (t, J = 1.6 Hz, 1H), 7.73 (t, J = 1.6 Hz, 1H), 7.45−7.38 (m, 5H), 5.48 (s, 2H), 5.05 (d, J = 16.5 Hz, 1H), 4.98 (d, J = 16.5 Hz, 1H), 4.66 (t, J = 5.4 Hz, 1H), 3.64−3.60 (m, 1H), 3.44 (t, J = 5.4 Hz, 2H), 1.61−1.56 (m, 1H), 1.49−1.40 (m, 1H), 1.09−1.05 (m, 1H), 0.86−0.80 (m, 6H); ^{13}C NMR δ 164.4, 137.4, 134.9, 128.9, 128.7, 128.2, 124.1, 121.8, 60.7, 55.5, 51.8, 50.7, 34.9, 24.7, 15.3, 11.3. Anal. Calcd for $C_{18}H_{26}ClN_3O_2 \cdot 0.25CH_3OH$: C, 60.91; H, 7.56; N, 11.68. Found: C, 60.74; H, 7.18; N, 11.80.

1-[2-((*S*)-1-Hydroxy-2-phenyl-2-ethanylamino)-2-oxoethyl]-3-benzylimidazolium chloride (20): yield 83%; ^{1}H NMR (DMSO) δ 9.33 (s, 1H), 9.19 (d, J = 6.8 Hz, 1H), 7.81 (s, 1H), 7.74 (s, 1H), 7.41−7.24 (m, 10H), 5.47 (s, 2H), 5.12 (s, 1H), 4.87−4.82 (m, 1H), 3.59 (d, J = 6.3 Hz, 2H); ^{13}C NMR δ 164.5, 140.5, 137.5, 134.9, 129.0, 128.8, 128.2, 128.1, 126.9, 124.3, 121.8, 64.6, 55.8, 51.8, 50.8. Because of the highly hydroscopic character collection of analytical data failed.

1-[2-((*S*)-1-Hydroxy-3-phenyl-2-propanylamino)-2-oxoethyl]-3-benzilimidazolium chloride (21): yield 83%; ^{1}H NMR (DMSO) δ 9.27 (s, 1H), 8.59 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 1.6 Hz, 1H), 7.62 (t, J = 1.6 Hz, 1H), 7.42−7.37 (m, 5H), 7.27−7.14 (m, 5H), 5.45 (s, 2H), 4.99−4.90 (m, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.92 (d, J = 16.0 Hz, 1H), 3.92−3.84 (m, 1H), 3.48−3.35 (m, 2H), 2.85−2.80 (m, 1H), 2.68−2.63 (m, 1H); ^{13}C NMR δ 164.3, 138.8, 137.3, 134.8, 129.1, 129.0, 128.8, 128.2, 128.2, 126.0, 124.1, 121.8, 62.1, 53.3, 51.9, 50.7, 36.5. Because of the highly hydroscopic character collection of analytical data failed.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-methylimidazolium chloride (22): yield 97%; mp 239.8−240.0 °C; ^{1}H NMR (DMSO) δ 9.09 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 7.68−7.66 (m, 2H), 5.04 (d, J = 16.5 Hz, 1H), 4.98 (d, J = 16.5 Hz, 1H), 4.55 (t, J = 4.6 Hz 1H), 3.88 (s, 3H), 3.61−3.56 (m, 2H), 3.41−3.30 (m, 1H), 0.85 (s, 9H); ^{13}C NMR δ 165.1, 137.7, 123.7, 123.0, 60.3, 59.7, 50.7, 35.8, 33.7, 26.8. Anal. Calcd for $C_{12}H_{22}ClN_3O_2$: C, 52.26; H, 8.04; N, 15.24. Found: C, 52.32; H, 7.96; N, 15.28.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-butylimidazolium chloride (23): yield 58%; mp 205.6−205.9 °C; ^{1}H NMR (DMSO) δ 9.26 (s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.81 (t, J = 1.6 Hz, 1H), 7.74 (t, J = 1.6 Hz, 1H), 5.09 (d, J = 16.4 Hz, 1H), 5.04 (d, J = 16.4 Hz, 1H), 4.60 (d, J = 16.4 Hz, 1H), 4.23 (t, J = 7.2 Hz, 2H), 3.62−3.57 (m, 2H), 3.39−3.33 (m, 1H), 1.81−1.74 (m, 2H), 1.30−1.21 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR δ 165.0, 137.2, 123.8, 121.7, 60.3, 59.6, 50.8, 48.5, 33.6, 31.3, 26.8, 18.7, 13.2. Anal. Calcd for $C_{15}H_{28}ClN_3O_2$: C, 56.68; H, 8.88; N, 13.22. Found: C, 56.41; H, 8.77; N, 13.19.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-(2-methylethyl)imidazolium chloride (24): yield 78%; mp 210.0−210.4 °C; ^{1}H NMR (DMSO) δ 9.29 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.73 (s, 1H), 5.04 (d, J = 16.4 Hz, 1H), 4.99 (d, J = 16.4 Hz, 1H), 4.73−4.67 (m, 1H), 4.57 (t, J = 4.8 Hz, 1H), 3.62−3.57 (m, 2H), 3.38−3.32 (m, 1H), 1.49 (d, J = 6.4 Hz, 6H), 0.87 (s, 9H); ^{13}C NMR δ 164.9, 136.0, 123.9, 119.8, 60.3, 59.6, 52.2, 50.7, 33.6, 26.8, 22.3, 22.3. Anal. Calcd for $C_{14}H_{26}ClN_3O_2$: C, 55.34; H, 8.63; N, 13.83. Found: C, 55.32; H, 8.43; N, 13.82.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-(naphthalen-1-ylmethyl)imidazolium chloride (25): yield 62%; mp 230.7−230.9 °C; ^{1}H NMR (DMSO) δ 9.30 (s, 1H), 8.23−8.16 (m, 2H), 8.04−8.01 (m, 2H), 7.83 (d, J = 1.6 Hz, 1H), 7.74 (d, J = 1.6 Hz, 1H), 7.65−7.49 (m, 4H), 6.01 (s, 2H), 5.08 (d, J = 16.6 Hz, 1H), 5.02 (d, J = 16.6 Hz, 1H), 4.56 (t, J = 4.8 Hz, 1H), 3.60−3.56 (m, 2H), 3.36−3.30 (m, 1H), 0.85 (s, 9H); ^{13}C NMR δ 165.0, 137.6, 133.4, 130.3, 130.3, 129.6, 128.8, 127.3, 127.2, 126.4, 125.6, 124.1, 122.9, 122.2, 60.3, 59.6, 50.9, 49.7, 33.6, 26.8. Anal. Calcd for $C_{22}H_{28}ClN_3O_2$: C, 65.74; H, 7.02; N, 10.45. Found: C, 65.71; H, 6.98; N, 10.46.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-(4-methoxybenzyl)imidazolium chloride (26): yield 75%; mp 244.7−245.0 °C; ^{1}H NMR (DMSO) δ 9.28 (s, 1H), 8.22 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 7.71 (s, 1H), 7.41 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 5.40 (s, 2H), 5.07 (d, J = 16.6 Hz, 1H), 5.02 (d, J = 16.6 Hz, 1H), 4.56 (t, J = 5.2 Hz, 1H), 3.76 (s, 3H), 3.62−3.56 (m, 2H), 3.39−3.30 (m, 1H), 0.86 (s, 9H); ^{13}C NMR δ 164.9, 159.5, 137.0, 130.0, 126.7, 124.0, 121.6, 114.3, 60.3, 59.6, 55.2, 51.4, 50.8, 33.6, 26.8. Anal. Calcd for $C_{19}H_{28}ClN_3O_3$: C, 59.76; H, 7.39; N, 11.00. Found: C, 59.74; H, 7.28; N, 11.04.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-(4-methylbenoate-1-ylmethyl)imidazolium chloride (27): yield 71%; mp 224.2−224.5 °C; ^{1}H NMR (DMSO) δ 9.34 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.83 (t, J = 1.6 Hz, 1H), 7.76 (t, J = 1.6 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 5.60 (s, 2H), 5.09 (d, J = 16.4 Hz, 1H), 5.03 (d, J = 16.4 Hz, 1H), 4.53 (t, J = 5.2 Hz, 1H), 3.86 (s, 3H), 3.63−3.57 (m, 2H), 3.38−3.32 (m, 1H), 0.87 (s, 9H); ^{13}C NMR δ 164.9, 137.4, 134.9, 129.0, 128.7, 128.2, 124.2, 121.9, 60.3, 59.6, 51.3, 50.9, 33.6, 26.8. Anal. Calcd for $C_{20}H_{28}ClN_3O_4$: C, 58.60; H, 6.89; N, 10.25. Found: C, 58.50; H, 6.76; N, 10.18.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-(4-fluorobenzyl)imidazolium chloride (28): yield 65%; mp 212.3−212.5 °C; ^{1}H NMR (DMSO) δ 9.30 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.81 (t, J = 2.0 Hz, 1H), 7.71 (t, J = 1.6 Hz, 1H), 7.52−7.49 (m, 2H), 7.29−7.25 (m, 2H), 5.46 (s, 2H), 5.07 (d, J = 16.4 Hz, 1H), 5.01 (d, J = 16.4 Hz, 1H), 4.54 (t, J = 5.6 Hz, 1H), 3.60−3.55 (m, 2H), 3.37−3.29 (m, 1H), 0.85 (s, 9H); ^{13}C NMR δ 164.9, 137.3, 131.1, 130.7, 124.1, 121.7, 116.0, 115.7, 60.3, 59.6, 51.0, 50.9, 33.6, 26.8. Anal. Calcd for $C_{18}H_{25}ClFN_3O_2$: C, 58.45; H, 6.81; N, 11.36. Found: C, 58.29; H, 6.70; N, 11.17.

1-[2-((*S*)-1-Hydroxy-3,3-dimethyl-2-butanylamino)-2-oxoethyl]-3-allylimidazolium chloride (29): yield 65%; mp 201.5−201.8 °C; ^{1}H NMR (DMSO) δ 9.21 (s, 1H), 8.26 (d, J = 9.2 Hz, 1H), 7.75−7.72 (m, 2H), 6.12−5.98 (m, 1H), 5.37−5.22 (m, 2H), 5.10 (d, J = 15.9 Hz, 1H), 5.03 (d, J = 15.9 Hz, 1H), 4.89 (d, J = 5.7 Hz, 2H), 4.57 (br, 1H), 3.62−3.54 (m, 2H), 3.44−3.30 (m, 1H), 0.86 (s, 9H); ^{13}C NMR δ 164.9, 137.3, 131.8, 123.9, 121.8, 119.9, 60.3, 59.6, 50.8, 50.7, 33.6, 26.8. Anal. Calcd for $C_{14}H_{24}ClN_3O_2$: C, 55.71; H, 8.02; N, 13.92. Found: C, 55.52; H, 7.79; N, 13.90.

1-[2-((1*R*,2*R*)-1,3-Dihydroxy-1-phenyl-2-propanylamino)-2-oxoethyl]-3-methylbenzimidazolium chloride (32): yield 62%; ^{1}H NMR (DMSO) δ 9.68 (s, 1H), 8.58 (d, J = 12.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.70−7.61 (m, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.38−7.19 (m, 5H), 5.74 (d, J = 4.0 Hz, 1H), 5.27 (d, J = 16.5 Hz, 1H), 5.20 (d, J = 16.5 Hz, 1H), 4.97−4.91 (m, 1H), 4.92 (t, J = 4.0 Hz, 1H), 4.09 (s, 3H), 3.96−3.88 (m, 1H), 3.62−3.58 (m, 1H), 3.40−3.36 (m, 1H); ^{13}C NMR δ 164.2, 143.5, 131.1, 127.7, 126.6, 126.4, 126.1, 113.6, 113.1, 69.6, 60.6, 57.1, 48.3, 33.2. Because of the highly hydroscopic character collection of analytical data failed.

1-[2-((1*R*,2*R*)-1,3-Dihydroxy-1-phenyl-2-propanylamino)-2-oxoethyl]-3-methylimidazolium chloride (33): yield 61%; ^{1}H NMR (DMSO) δ 9.21 (s, 1H), 8.34 (d, J = 9.2 Hz, 1H), 7.77 (t, J = 1.2 Hz, 1H), 7.56 (t, J = 1.2 Hz, 1H), 7.45−7.17 (m, 10H), 5.61 (d, J = 4.8 Hz, 1H), 5.44 (s, 2H), 4.96 (d, J = 16.0 Hz, 1H), 4.90 (d, J = 16.0 Hz, 1H), 4.88−4.84 (m, 1H), 3.90−3.88 (m, 1H), 3.56−3.50 (m, 1H), 3.42−3.27 (m, 2H); ^{13}C NMR δ 164.6, 143.3, 137.3, 134.8, 129.0, 128.7, 128.6, 128.3, 128.2, 127.7, 127.7, 127.4, 126.7, 126.2, 124.0, 121.8, 69.9, 60.4, 57.3, 51.8, 50.8. Because of the highly hydroscopic character collection of analytical data failed.

1-[2-((*S*)-1-(Methoxycarbonyl)-3-methyl-1-butanylamino)-2-oxoethyl]-3-benzylbenzimidazolium chloride (34): yield 60%; mp 135.5−135.8 °C; ^{1}H NMR (DMSO) δ 10.0 (s, 1H), 9.36 (d, J = 7.2 Hz, 1H), 8.01−7.99 (m, 1H), 7.92−7.89 (m, 1H), 7.71−7.64 (m, 2H), 7.52−7.38 (m, 5H), 5.87 (s, 2H), 5.50 (d, J = 16.4 Hz, 1H), 5.43 (d, J = 16.4 Hz, 1H), 4.32−4.30 (m, 1H), 3.62 (s, 3H), 1.71−1.55 (m, 3H), 0.92 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 172.3, 164.9, 143.6, 133.9, 131.6, 130.5, 129.0, 128.7, 128.2, 126.8, 126.7, 113.9, 113.6, 52.0, 50.8, 49.8, 48.4, 24.2, 22.6, 21.2. $C_{23}H_{28}ClN_3O_3 \cdot 0.75H_2O$: C, 62.29; H, 6.71; N, 9.48. Found: C, 62.13; H, 6.40; N, 9.46.

1-[2-((*S*)-1-(Methoxycarbonyl)-3-methyl-1-butanylamino)-2-oxoethyl]-3-benzylimidazolium chloride (35): yield 98%; ^{1}H NMR (DMSO) δ 9.38 (s, 1H), 9.16 (d, J = 7.2 Hz, 1H), 7.84 (t, J = 1.6 Hz, 1H), 7.74 (t, J = 1.6 Hz, 1H), 7.43−7.39 (m, 5H), 5.50 (s, 2H), 5.15 (d, J = 16.4 Hz, 1H), 5.10 (d, J = 16.4 Hz, 1H), 4.33−4.27 (m, 1H), 3.63 (s, 3H), 1.73−1.49 (m, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 172.4, 165.1, 137.5, 134.8, 129.0, 128.7, 128.2, 124.2, 121.8, 52.0, 51.8, 50.7, 50.4, 24.1, 22.6, 21.3. Because of the highly hydroscopic character collection of analytical data failed.

General Procedure for Cu(OTf)$_2$-Catalyzed Asymmetric Reaction of Enone with Et$_2$Zn. To a solution of azolium salt (0.045 mmol) in THF (9 mL) were added Cu(OTf)$_2$ (0.06 mmol) and enone (1 mmol). After the mixture was cooled to 0 °C, Et$_2$Zn (3 mmol, 1 mol/L in hexanes) 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. To a solution of azolium salt (0.045 mmol) in THF (9 mL) were added Cs_2CO_3 (0.08 mmol) and Cu(acac)$_2$ (0.06 mmol), and then the mixture was cooled to 0 °C. Then, Et$_2$Zn (3 mmol, 1 mol/L in hexanes) 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.

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Supporting Information Available: Tables S1−S3 giving ECA reaction of **30** with Et$_2$Zn by the Cu(OTf)$_2$/**18** catalytic system (Table S1), solvet effect for ECA reaction of **30** with Et$_2$Zn by the Cu(OTf)$_2$/**18** catalytic system (Table S2), and screening of Cu salts for ECA reaction of **30** with Et$_2$Zn in the presence of **29** (Table S3), spectra for products, and chiral GC traces. This material is available free of charge via the Internet at http://pubs.acs.org.