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Ligand design for dual enantioselective control in Cu-catalyzed asymmetric conjugate addition of R_2Zn to cyclic enone

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ABSTRACT

A new chiral *N*-heterocyclic carbene (NHC) ligand derived from a natural α-aminoester has been designed and synthesized. The coupling of *N*-methylbenzimidazole with an α-chloroacetamide derivative, which was prepared from chloroacetyl chloride and (*S*)-serine methyl ester, gave the corresponding ester/amide-functionalized azolium compound **20**. The reaction of 2-cyclohexen-1-one (**17**) with Et_2Zn in the presence of catalytic amounts of $Cu(OTf)_2$ and **20** produced (*R*)-3-ethylcyclohexanone (**18**) as a major product. In contrast, the enantioselective conjugate addition (ECA) reaction catalyzed by $Cu(OTf)_2$ under the influence of a hydroxy-amide-functionalized azolium compound **15**, which was derived from (*S*)-*tert*-leucinol, produced (*S*)-**18** in preference to (*R*)-**18**. A series of azolium salts were synthesized from (*S*)-serine esters, and the reaction conditions for the ECA reaction were optimized to produce (*R*)-**18** with 69% ee. The best results were obtained in the case of the reaction of 4,4-dimethyl-2-cyclohexen-1-one (**34**) with Et_2Zn catalyzed by $Cu(OTf)_2$ in combination with azolium compounds. When the reaction of **34** with Et_2Zn was carried out in the presence of catalytic amounts of $Cu(OTf)_2$ and **20**, (*S*)-3-ethyl-4,4-dimethylcyclohexanone (**35**) was obtained with 97% ee, whereas the ECA reaction under the influence of hydroxy-amide-functionalized azolium **15** afforded (*R*)-**35** with >99% ee. In this manner, the reversal of enantioselectivity was achieved by controlling the structure of chiral ligands.

1. Introduction

The preparation of both enantiomers of a chiral compound is increasingly important not only in life science, including medicine and agricultural chemicals, but also in materials science. The most effective approach for preparing optically active compounds involves asymmetric catalysis using transition metal complexes having appropriately designed chiral ligands. Despite the enormous progress of the catalytic asymmetric syntheses, the efficient preparation of both enantiomers still remains a significant challenge.[1] The use of chiral ligands with opposite configurations in an asymmetric catalysis is the most straightforward method. However, the antipodes of the ligands are not always easily available when the chiral ligands are prepared from chiral molecules of a natural origin, such as amino acids. To overcome this disadvantage the structural modification of the chiral ligands would provide a significant breakthrough in switching the stereoselectivity of a reaction.[2]

The Cu-catalyzed enantioselective conjugate addition (ECA) reaction has emerged as a powerful synthetic tool for the stereoselective formation of carbon–carbon bonds.[3] Several chiral *N*-heterocyclic carbene (NHC) ligands as effective alternatives to phosphine ligands have been prepared and applied to this reaction.[4] Initial studies on the NHC–Cu-catalyzed ECA reaction involved the utilization of a monodentate NHC ligand.[5,6] However, this reaction provided moderate enantioselectivity. In contrast, polydentate NHC ligands exhibited better stabilities and selectivities. Arnold et al. reported a chiral anionic tethered bidentate NHC ligand for Cu-catalyzed ECA reaction of 2-cyclohexen-1-one with Et_2Zn.[7] Later, Mauduit et al. designed and applied chelating hydroxy-alkyl-substituted NHC ligands for achieving high enantioselectivities.[8] Moreover, Hoveyda et al. developed chelating anionic hydroxy-aryl-functionalized NHC ligands for the ECA reaction.[9,10]

Recently, we developed hydroxy-amide-functionalized azolium compounds derived from chiral β-amino alcohols to prepare tridentate anionic amidate/NHC–Pd(II) as well as dianionic alkoxy/amidate/NHC–Pd(II) complexes.[11] The newly designed polydentate ligand can lock the stereocontrol element in a fixed conformation during the entire catalytic processes to afford higher enantioselectivity. Thus, the Pd(II) complex catalyzes the asymmetric oxidative Heck-type reaction of arylboronic acid with alkene with excellent enantioselectivity. Encouraged by this success, we also examined the Cu-catalyzed ECA reaction of cyclic enones with

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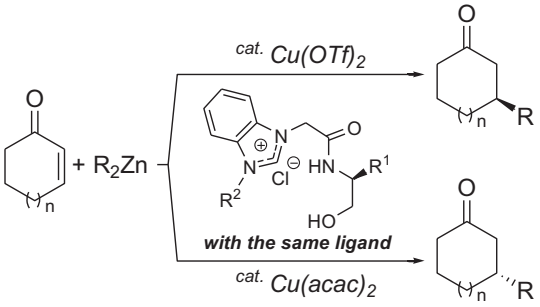
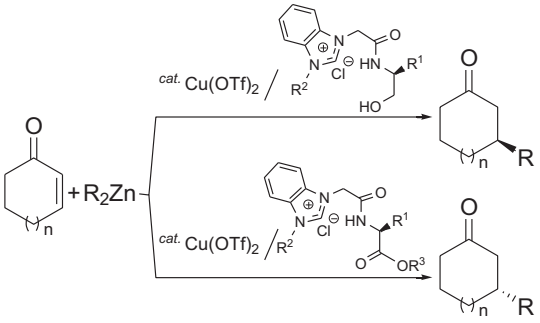
dialkylzincs in the presence of the hydroxy-amide-functionalized NHC ligand precursor.[12] Surprisingly, the reversal of enantioselectivity with the same ligand was achieved by changing the Cu precatalyst from $Cu(OTf)_2$ to $Cu(acac)_2$ (Scheme 1).



Scheme 1. Reversal of enantioselectivity with the same ligand.

As a part of our continuing efforts to design new catalyst systems, we examined the development of new functionalized NHC ligands, which were derived from natural α-aminoesters instead of β-amino alcohols. In the previous paper, we briefly described an ECA reaction catalyzed by $Cu(OTf)_2$ in combination with a chiral imidazolium salt having an ester/amide side chain, which was prepared from (*S*)-leucine methyl ester.[12b] Interestingly, the absolute configuration of the conjugate adduct obtained in the ECA reaction using the ester/amide-functionalized azolium salt differs from that obtained in the ECA reaction using the hydroxy-amide-functionalized azolium salt (Scheme 2). Because both ligand precursors are prepared from natural α-amino acids, it is possible to achieve dual enantioselective control through the structural modification of chiral ligands. Herein, we wish to focus on the design and development of various functionalized NHC ligands derived from natural α-aminoesters for the Cu-catalyzed ECA reaction.

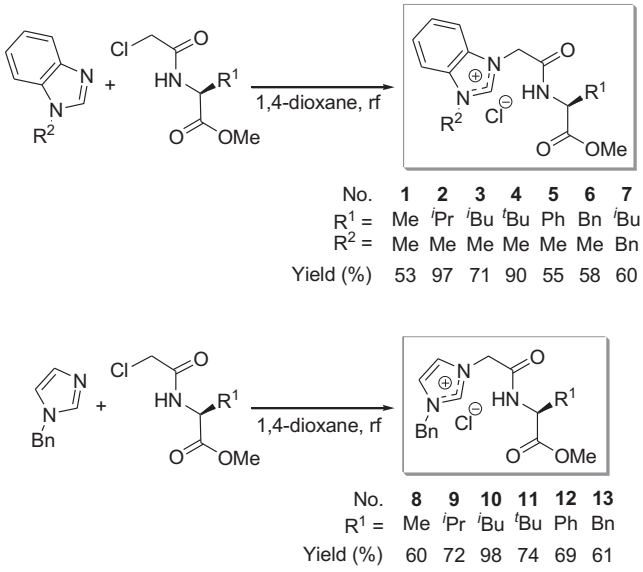


Scheme 2. Strategy for switching of enantioselectivity.

2. Results and discussion

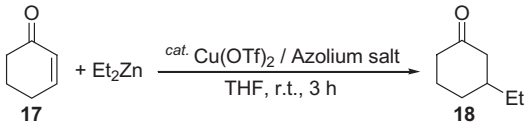
This study commenced with the synthesis of a series of azolium chlorides derived from commercially available α-aminoesters. The coupling of *N*-alkylazoles with α-chloroacetamide derivatives, which were prepared independently from chloroacetyl chloride and α-aminoesters, afforded the corresponding ester/amide-functionalized azolium compounds **1**–**13** (Scheme 3). Unlike hydroxy-amide-functionalized azolium salts, which are stable in air,[11,12] azolium chlorides **1**–**13** have a highly hydroscopic character.

Table 1 summarizes the conjugate addition of Et_2Zn to 2-cyclohexen-1-one (**17**) catalyzed by $Cu(OTf)_2$ combined with **1**–**13**. To compare the relative abilities of azolium salts bearing ester/amide functionality or hydroxy-amide functionality, the results of the ECA reaction employing hydroxy-amide-functionalized



Scheme 3. Synthesis of various azolium salts.

Table 1
ECA reaction of **17** with Et_2Zn catalyzed by $Cu(OTf)_2$ combined with azolium salt[a]

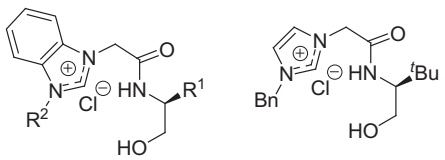


Run	Azolium salt	Yield[b] (%)	er[b]	
			S	*R*
1	**1**	81	52.5	47.5
2	**2**	77	52	48
3	**3**	96	50	50
4	**4**	77	50.5	49.5
5	**5**	77	47.5	52.5
6	**6**	80	55	45
7	**7**	98	50.5	49.5
8[c]	**7**	72	51.5	48.5
9[c]	**14**	>99	**90.5**	9.5
10[c]	**15**	>99	**91**	9
11	**8**	47	44	56
12	**9**	74	33	**67**
13[d]	**9**	78	31	**69**
14	**10**	50	35	65
15	**11**	58	37	63
16	**12**	51	44.5	55.5
17	**13**	51	43.5	56.5
18	**16**	>99	**82**	18

[a] Compound **17** (1 mmol), Et_2Zn (3 mmol), $Cu(OTf)_2$ (2 mol %), azolium salt (3 mol %), THF (3 mL), rt, 3 h.
[b] Yield and enantiomer ratio (er) were determined by GLC analysis. Average of two runs.
[c] $Cu(OTf)_2$ (6 mol %), azolium salt (4.5 mol %), THF (9 mL).
[d] $Cu(OTf)_2$ (6 mol %).

azolium salts **14**–**16**, which were prepared from (*S*)-leucinol or (*S*)-*tert*-leucinol, are also listed in Table 1. The treatment of **17** with Et_2Zn in THF in the presence of catalytic amounts of $Cu(OTf)_2$ and benzimidazolium salt **3**, which was derived from (*S*)-leucine methyl ester, produced 3-ethylcyclohexanone (**18**) in almost quantitative yield (run 3). However, the reaction resulted in a racemic mixture, and stereoselectivity could not be improved by the initial screening of the chiral benzimidazolium salts **1**–**7** (runs 1–7). In contrast, the $Cu(OTf)_2$-catalyzed ECA reaction of **17** with Et_2Zn in the presence of hydroxy-amide-functionalized benzimidazolium salt **15** proceeded efficiently to give (*S*)-**18** in a 91:9 enantiomer ratio (er) (run 10). On

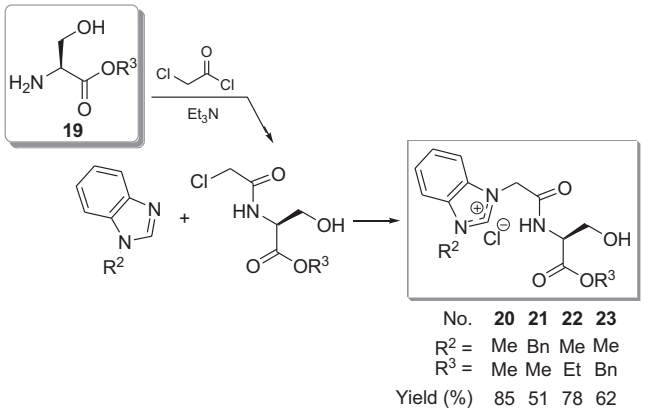
the other hand, the reaction under the influence of the imidazolium salt **9** derived from (*S*)-valine methyl ester afforded (*R*)-**18** in preference to (*S*)-**18** in a 31:69 er (run 13). These results suggest that the reversal of enantioselectivity can be achieved. However, attempts to increase enantioselectivity failed in the reaction of **17** with Et_2Zn catalyzed by a Cu salt combined with **9** (see Table S1).



14 (R^1 = *i*Bu, R^2 = Bn)
15 (R^1 = *t*Bu, R^2 = Bn)

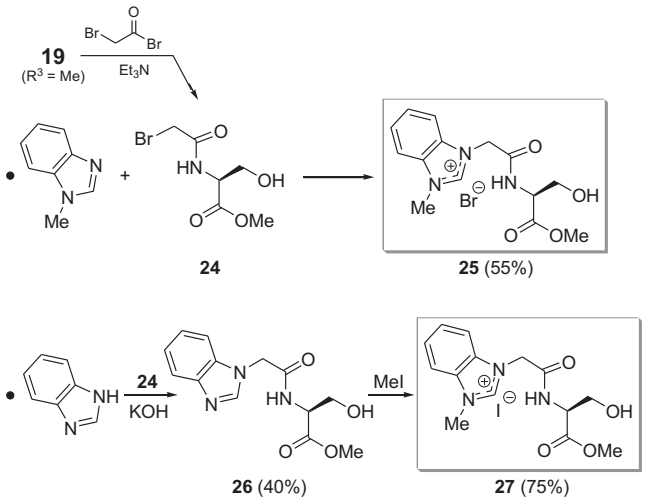
16

Since the variation of the stereodirecting group (R^1=alkyl) on the ester/amide-functionalized NHC ligands **1**–**13** was not effective for achieving stereoselective reaction (Table 1), we next chose a natural (*S*)-serine ester (**19**) as the origin of chiral induction. (*S*)-Serine is an inexpensive α-amino acid bearing a hydroxymethyl substituent. A series of benzimidazolium chlorides, **20**, **21**, **22**, and **23**, were synthesized from (*S*)-serine methyl, ethyl, and benzyl esters, respectively, by a route similar to that shown in Schemes 3 and 4. These compounds are air stable and easy to handle. In addition, we are interested in the influence of the counter ion of the azolium ligand on the stereoselectivity of the Cu-catalyzed ECA reaction. Therefore, the corresponding bromide **25** was synthesized by a coupling reaction of *N*-methylbenzimidazole with an α-bromoacetamide derivative **24**, which was prepared from bromoacetyl bromide and (*S*)-serine methyl ester (Scheme 5). The treatment of benzimidazole with **24** in the presence of KOH gave the corresponding azole derivative **26**. Subsequently, **26** was allowed to react with methyl iodide to produce azolium iodide **27**.



Scheme 4. Synthesis of azolium salts derived from serine ester.

The results for the Cu-catalyzed ECA reaction of **17** with Et_2Zn in the presence of an azolium salt derived from (*S*)-serine ester under various reaction conditions are summarized in Table 2. Fortunately, the reaction under the influence of azolium chloride **20** proceeded smoothly to produce (*R*)-**18**, as desired (run 1). Under the reaction condition that was optimized for the $Cu(OTf)_2$-catalyzed ECA reaction using the hydroxy-amide-functionalized benzimidazolium salt **15** to afford (*S*)-**18** with 82% ee, the ECA reaction catalyzed by $Cu(OTf)_2$ (6 mol %) combined with **20** (4.5 mol %) produced (*R*)-**18** in 90% yield and 67% ee (Table 1 run 10 vs Table 2 run 2). Decreasing the amount of $Cu(OTf)_2$ from 6 mol % to 4.5 mol % slightly improved the stereoselectivity of the reaction, producing (*R*)-**18** with 69% ee (run 3). In the ECA reaction using the hydroxy-amide-



Scheme 5. Synthesis of azolium bromide (**25**) and iodide (**27**).

functionalized azolium salt, the replacement of the *N*-methyl by an *N*-benzyl substituent at the azolium ring led to a significant increase in enantioselectivity.[12b] However, the stereoselectivity of the ECA reaction using an azolium salt **20** was comparable to that obtained using **21** (runs 2 and 4). The use of the azolium chlorides, **22** and **23**, which contained ethyl and benzyl esters, respectively, only slightly reduced the enantioselectivity (runs 5 and 6).

Next, we screened Cu salts and solvents for the ECA reaction. By using $[Cu(OTf)]_2(C_6H_6)$ and $Cu(NO_3)_2$, (*R*)-**18** was obtained in 60% ee and 62% ee, respectively, whereas the use of $Cu(acac)_2$ and $CuCl_2$

Table 2
ECA reaction of **17** with Et_2Zn catalyzed by Cu salt combined with azolium salt derived from serine ester to produce (*R*)-**18**[a]

Run	Cu salt	Azolium	Solvent	Yield[b] (%)	ee[b] (%)
1[c]	$Cu(OTf)_2$	**20**	THF	90	57
2[d]	$Cu(OTf)_2$	**20**	THF	90	67
3	**$Cu(OTf)_2$**	**20**	**THF**	**89**	**69**
4[d]	$Cu(OTf)_2$	**21**	THF	90	67
5[d]	$Cu(OTf)_2$	**22**	THF	80	61
6[d]	**$Cu(OTf)_2$**	**23**	**THF**	**94**	**68**
7	Cu(I) salt[e]	**20**	THF	79	60
8	$Cu(NO)_3$	**20**	THF	86	62
9	$Cu(acac)_2$	**20**	THF	83	29
10	$CuCl_2$	**20**	THF	55	18
11	$Cu(OTf)_2$	**20**	2-Me–THF[f]	92	63
12	$Cu(OTf)_2$	**20**	DME	81	67
13	$Cu(OTf)_2$	**20**	AcOEt	97	53
14	$Cu(OTf)_2$	**20**	1,4-Dioxane	79	51
15	$Cu(OTf)_2$	**20**	Et_2O	87	27
16	$Cu(OTf)_2$	**20**	TBME[g]	95	13
17	$Cu(OTf)_2$	**20**	CH_3CN	39	40
18	$Cu(OTf)_2$	**20**	NMP	44	25
19	$Cu(OTf)_2$	**20**	DMSO	48	26
20	$Cu(OTf)_2$	**20**	DMF	46	38
21	$Cu(OTf)_2$	**20**	DMA	57	17
22[h]	$Cu(OTf)_2$	**20**	THF	85	69
23[i]	$Cu(OTf)_2$	**20**	THF	81	69
24	$Cu(OTf)_2$	**25**	THF	77	43
25	$Cu(OTf)_2$	**27**	THF	88	65

[a] Compound **17** (1 mmol), Et_2Zn (3 mmol), Cu salt (4.5 mol %), azolium salt (4.5 mol %), THF (9 mL), rt, 3 h.
[b] See Table 1 b.
[c] $Cu(OTf)_2$ (2 mol %), **20** (3 mol %), THF (3mL).
[d] $Cu(OTf)_2$ (6 mol %).
[e] $[Cu(OTf)]_2(C_6H_6)$.
[f] 2-Methyltetrahydrofuran.
[g] *tert*-Butyl methyl ether.
[h] Reaction was run at 10 °C.
[i] Reaction was run at −10 °C.

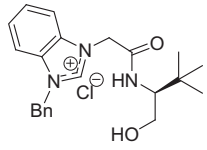
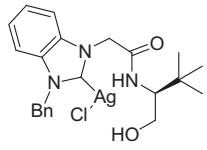
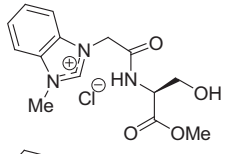
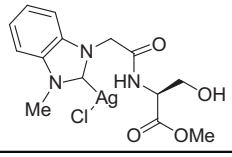
resulted in poor enantioselectivity (runs 7–10). It should be noted that no reversal of enantioselectivity was observed when the Cu precatalyst was changed from $Cu(OTf)_2$ to $Cu(acac)_2$ (run 3 vs run 9). This observation is in contrast to the ECA reaction under the influence of the hydroxy-amide-functionalized azolium salt (Scheme 1), in which the reversal of enantioselectivity was observed. The type of solvent used was also an important parameter in the ECA reaction. The use of THF led to the best ee (69%), followed by DME and 2-methyltetrahydrofuran (runs 3 and 11–21). Decreasing the reaction temperature did not affect the enantioselectivity (runs 22 and 23). The choice of the counter ion of the azolium salt is also an important factor. The ECA reaction catalyzed by $Cu(OTf)_2$ combined with azolium iodide **27** proceeded in a manner comparable to the reaction in which azolium chloride **20** was used, whereas the use of bromide **25** resulted in a somewhat lower ee (runs 3, 24, and 25).

From a mechanical point of view, it seems likely that the present ECA reaction was catalyzed by an NHC–Cu species generated in situ from an azolium compound and a Cu precatalyst under the influence of Et_2Zn. In fact, Hoveyda et al. reported the preparation of an NHC–Zn complex by allowing an azolium compound to react with Et_2Zn, where Et_2Zn acts as a base to form the NHC species.[13] In the preceding papers, we showed that the treatment of a hydroxy-amide-functionalized azolium salt with Ag_2O formed the corresponding NHC–Ag complex, where Ag_2O serves as a mild base and reacts predominantly at the C_2 position of the azolium salt without causing the deprotonation of other acidic protons.[11] Moreover, Alexakis and Roland reported that the use of an NHC–Ag complex instead of an azolium salt carbene precursor in the $Cu(OTf)_2$-catalyzed ECA reaction of **17** with Et_2Zn resulted in increased stereoselectivity.[5c] Therefore, we are interested in the ECA reaction catalyzed by $Cu(OTf)_2$ combined with an NHC–Ag complex (Table 3).

First, an ECA reaction was preformed in the presence of the hydroxy-amide-functionalized NHC–Ag complex **28**. The treatment of **15** with 0.5 equiv of Ag_2O in dichloromethane at room temperature gave **28**. Owing to the light-sensitive property of the silver complex, **28** was used without further purification for the ECA reaction. After the resultant silver complex **28** was treated with $Cu(OTf)_2$ in THF at room temperature for 1 h, enone **17** and Et_2Zn were subsequently added to the reaction vessel. As expected, this reaction afforded (*S*)-**18** as a major product, and the enantiomer ratio (*S*/*R*=91:9) obtained by using **28** was very similar to that obtained by using **15** (runs 1 and 2). These results strongly suggest that a similar catalytic copper species is generated in both cases. On the other hand, (*R*)-**18** was formed with a 17:83 er by employing the NHC–Ag complex **29**, which was prepared from **20** and Ag_2O (run 4).

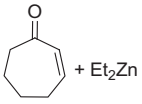
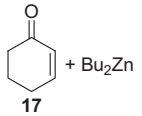
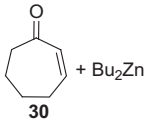
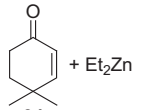
On the basis of these results, we finally investigated the scope of the ECA reactions of different cyclic enones with dialkylzincs. The results for the ECA reaction catalyzed by $Cu(OTf)_2$ combined with **15** (or **28**) or **20** (or **29**) in THF at room temperature for 3 h are summarized in Table 4. The present catalytic systems were found suitable for the reaction of 2-cyclohepten-1-one (**30**) with Et_2Zn. The 1,4-addition of **30** with Et_2Zn proceeded efficiently under the influence of the $Cu(OTf)_2$/**15** system to afford (*S*)-3-ethylcycloheptanone (**31**) in >99% yield with a 95.5:4.5 er, whereas (*R*)-**31** was obtained with a 7.5:92.5 er when the reaction was carried out with the $Cu(OTf)_2$/**20** system (runs 1 and 3). Almost similar results were obtained in the reactions by using the NHC–Ag complexes, **28** and **29** (runs 2 and 4). The reaction of **17** or **30** with Bu_2Zn gave the corresponding adduct in low yield probably due to sterically reason (runs 6 and 8). Excellent ee values of >99% and 97%, respectively, were obtained in the ECA reaction of 4,4-dimethyl-2-cyclohexen-1-one (**34**) with Et_2Zn (runs 9–11). It was found that

Table 3
ECA reaction of **17** with Et_2Zn catalyzed by $Cu(OTf)_2$ salt combined with NHC precursor[a]

Run	NHC precursor		Yield[b] (%)	er[b]	
				S	*R*
1[c]		**15**	>99	**91**	9
2[c]		**28**	>99	**91**	9
3		**20**	89	15.5	**84.5**
4		**29**	87	17	**83**

[a] Compound **17** (1 mmol), Et_2Zn (3 mmol), $Cu(OTf)_2$ (4.5 mol %), NHC precursor (4.5 mol %), THF (9 mL), rt, 3 h.
[b] See Table 1 b.
[c] $Cu(OTf)_2$ (6 mol %).

Table 4
Switching of enantioselectivity[a]

Run	Substrates	Ligand	Yield[b] (%)	er[b]	
				S	*R*
1[c]	 **30**	**15**	>99	**95.5**	4.5
2[c]		**28**	96	**96.5**	3.5
3		**20**	85	7.5	**92.5**
4		**29**	80	9	**91**
5[c]	 **17**	**15**	>99	**94**	6
6		**20**	40	14	**86**
7[c]	 **30**	**15**	>99	**98**	2
8		**20**	22	29	**71**
9[c]		**15**	84	<0.5	>**99.5**
10		**20**	42	**98.5**	1.5
11[d]		**20**	58	**97**	3
12	**34**	**21**	83	**97.5**	2.5

[a] Compound **17** (1 mmol), Et_2Zn (3 mmol), $Cu(OTf)_2$ (4.5 mol %), ligand (4.5 mol %), THF (9 mL), rt, 3 h.
[b] Isolated yield. Enantiomer ratio (er) was determined by GLC analysis. Average of two runs.
[c] $Cu(OTf)_2$ (6 mol %), ligand (4.5 mol %), THF (9 mL).
[d] Et_2Zn (5 mmol).

the yield of the conjugate adduct **35** increased when the reaction was carried out in the presence of **21** instead of **20** (run 12).

3. Conclusion

We developed a series of ester/amide-functionalized azolium compounds derived from natural α-aminoesters for use as chiral NHC precursors for a Cu-catalyzed ECA reaction. The reaction of cyclic enones with dialkylzincs catalyzed by $Cu(OTf)_2$ combined with the appropriate chiral azolium salt **20** derived from an (*S*)-serine ester gave the corresponding optically active conjugate adducts with moderate to excellent enantioselectivities (69–97% ee). In contrast, the use of the hydroxy-amide-functionalized azolium salt derived from β-amino alcohol led to the formation of adducts with opposite configurations in with 82% to >99% ee. Considering that both the ligand precursors are prepared from natural α-amino acids, it can be said that the reversal of enantioselectivity by the structural modification of chiral ligands was successfully achieved. The applications of the chiral chelating polydentate NHC catalysts for efficient catalytic enantioselective transformations including the ECA reaction of acyclic enones are the subject of ongoing research at our laboratory.

4. Experimental

4.1. General procedure for the preparation of azolium compound

To 1,4-dioxane were added azole derivative (0.293 M) and α-chloroacetamide derivative (0.267 M), which was prepared from chloroacetyl chloride and α-aminoester. After stirring the reaction mixture 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 using ethyl acetate and methanol to afford the corresponding azolium compound. Because of the highly hydroscopic character, elemental analyses of **1**–**4**, **6**–**13**, and **25** were not preformed. Azolium salts **7**, **10**, and **14**–**16** were reported in the preceding paper.[12b] Because of the light-sensitive character, elemental analyses of **28** and **29** were not preformed.

4.2. Analytical data

*4.2.1. Compound **1**.* ^{1}H NMR ($CDCl_3$): δ 10.60 (s, 1H), 9.88 (d, *J*=6.9 Hz, 1H), 8.00–7.98 (m, 1H), 7.69–7.58 (m, 3H), 5.80 (d, *J*=16.5 Hz, 1H), 5.76 (d, *J*=16.5 Hz, 1H), 4.41–4.34 (m, 1H), 4.22 (s, 3H), 3.60 (s, 3H), 1.50 (d, *J*=7.3 Hz, 3H); ^{13}C NMR: δ 172.6, 164.7, 143.5, 131.6, 131.4, 127.2, 126.9, 114.1, 112.1, 52.1, 49.2, 48.8, 33.6, 16.7. $[\alpha]_D^{28}$ −5.1 (*c* 0.55 in CH_3OH).

*4.2.2. Compound **2**.* ^{1}H NMR ($CDCl_3$): δ 10.67 (s, 1H), 9.67 (d, *J*=7.3 Hz, 1H), 8.04–8.02 (m, 1H), 7.68–7.60 (m, 3H), 5.94 (d, *J*=16.5 Hz, 1H), 5.88 (d, *J*=16.5 Hz, 1H), 4.29–4.26 (m, 1H), 4.22 (s, 3H), 3.61 (s, 3H), 2.32–2.24 (m, 1H), 1.07 (d, *J*=6.9 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 3H); ^{13}C NMR: δ 171.8, 165.2, 143.5, 131.9, 131.5, 127.4, 127.1, 114.5, 112.0, 59.0, 51.9, 49.4, 33.6, 30.1, 19.1, 18.5. $[\alpha]_D^{28}$ −3.8 (*c* 0.50 in CH_3OH).

*4.2.3. Compound **3**.* ^{1}H NMR ($CDCl_3$): δ 10.49 (s, 1H), 9.63 (d, *J*=6.9 Hz, 1H), 7.96–7.94 (m, 1H), 7.64–7.62 (m, 3H), 5.80 (d, *J*=16.0 Hz, 1H), 5.71 (d, *J*=16.0 Hz, 1H), 4.43–4.37 (m, 1H), 4.21 (s, 3H), 3.61 (s, 3H), 1.82–1.80 (m, 2H), 1.65–1.63 (m, 1H), 0.94 (d, *J*=6.0 Hz, 3H), 0.88 (d, *J*=6.0 Hz, 3H); ^{13}C NMR: δ 173.0, 165.1, 143.6, 131.8, 131.5, 127.2, 127.0, 114.3, 112.1, 52.1, 51.8, 49.4, 39.7, 33.6, 24.8, 22.7, 21.5. $[\alpha]_D^{28}$ −3.6 (*c* 0.50 in CH_3OH).

*4.2.4. Compound **4**.* ^{1}H NMR ($CDCl_3$): δ 10.80 (s, 1H), 9.46 (d, *J*=7.3 Hz, 1H), 8.05–8.03 (m, 1H), 7.66–7.64 (m, 3H), 5.89 (s, 2H), 4.21 (s, 1H), 4.19 (s, 3H), 3.62 (s, 3H), 1.10 (s, 9H); ^{13}C NMR: δ 171.5, 165.3, 143.5, 132.0, 131.6, 127.3, 127.0, 114.5, 112.1, 62.4, 51.7, 49.5, 34.0, 33.6, 26.9. $[\alpha]_D^{29}$ −5.4 (*c* 0.37 in CH_3OH).

*4.2.5. Compound **5**.* White solid; mp 188.9–189.2 °C. ^{1}H NMR ($CDCl_3$): δ 10.67 (s, 1H), 10.10 (d, *J*=7.3 Hz, 1H), 7.95–7.93 (m, 1H), 7.61–7.59 (m, 3H), 7.53–7.51 (m, 2H), 7.33–7.26 (m, 3H), 5.93 (d, *J*=16.1 Hz, 1H), 5.84 (d, *J*=16.1 Hz, 1H), 5.47 (d, *J*=7.3 Hz, 1H), 4.15 (s, 3H), 3.58 (s, 3H); ^{13}C NMR ($(CD_3)_2SO$): δ 170.4, 164.9, 143.7, 135.5, 131.4, 131.3, 128.8, 128.5, 127.8, 126.6, 126.4, 113.6, 113.4, 56.6, 52.4, 48.1, 33.3. Anal. Calcd for $C_{19}H_{20}ClN_3O_3\cdot 0.7H_2O$: C, 59.05; H, 5.58; N, 10.87. Found: C, 58.92; H, 5.48; N, 10.91%. $[\alpha]_D^{30}$ +5.0 (*c* 0.20 in CH_3OH).

*4.2.6. Compound **6**.* ^{1}H NMR ($(CD_3)_2SO$): δ 9.82 (s, 1H), 9.70 (d, *J*=7.8 Hz, 1H), 8.02–8.00 (m, 1H), 7.69–7.63 (m, 3H), 7.28–7.20 (m, 5H), 5.44 (d, *J*=16.5 Hz, 1H), 5.38 (d, *J*=16.5 Hz, 1H), 4.55–4.49 (m, 1H), 4.11 (s, 3H), 3.59 (s, 3H), 3.15–3.07 (m, 1H), 3.01–2.95 (m, 1H); ^{13}C NMR: δ 171.3, 164.8, 143.6, 136.9, 131.4, 131.1, 129.2, 128.3, 126.6, 126.4, 113.6, 113.2, 54.0, 52.0, 48.1, 36.5, 33.3. $[\alpha]_D^{32}$ −0.3 (*c* 0.90 in CH_3OH).

*4.2.7. Compound **8**.* Light yellow liquid. ^{1}H NMR ($(CD_3)_2SO$): δ 9.30 (s, 1H), 9.08 (br, 1H), 7.81 (s, 1H), 7.71 (s, 1H), 7.41–7.38 (m, 5H), 5.47 (s, 2H), 5.09 (d, *J*=16.9 Hz, 1H), 5.04 (d, *J*=16.9 Hz, 1H), 4.36–4.28 (m, 1H), 3.62 (s, 3H), 1.31 (d, *J*=7.3 Hz, 3H); ^{13}C NMR: δ 172.5, 164.8, 137.5, 134.8, 129.0, 128.2, 124.2, 121.8, 52.0, 51.8, 50.4, 47.9, 17.0. $[\alpha]_D^{32}$ −5.1 (*c* 0.43 in CH_3OH).

*4.2.8. Compound **9**.* White solid. ^{1}H NMR ($(CD_3)_2SO$): δ 9.26 (s, 1H), 8.86 (br, 1H), 7.79 (s, 1H), 7.72 (s, 1H), 7.42–7.38 (m, 5H), 5.46 (s, 2H), 5.13 (d, *J*=16.5 Hz, 1H), 5.07 (d, *J*=16.5 Hz, 1H), 4.21 (t, *J*=7.3 Hz, 1H), 3.64 (s, 3H), 2.09–2.01 (m, 1H), 0.89 (t, *J*=6.9 Hz, 6H); ^{13}C NMR: δ 171.5, 165.4, 137.5, 134.8, 129.0, 128.7, 128.2, 124.3, 121.8, 57.8, 51.8, 50.5, 30.1, 18.9, 18.1. $[\alpha]_D^{32}$ −3.5 (*c* 0.63 in CH_3OH).

*4.2.9. Compound **10**.* White solid. ^{1}H NMR ($(CD_3)_2SO$): 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. $[\alpha]_D^{31}$ −3.3 (*c* 0.51 in CH_3OH).

*4.2.10. Compound **11**.* White solid. ^{1}H NMR ($(CD_3)_2SO$): δ 9.36 (s, 1H), 8.93 (br, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.42–7.37 (m, 5H), 5.48 (s, 2H), 5.20 (d, *J*=16.5 Hz, 1H), 5.13 (d, *J*=16.5 Hz, 1H), 4.16 (d, *J*=8.2 Hz, 1H), 3.62 (s, 3H), 0.95 (s, 9H); ^{13}C NMR: δ 170.9, 165.3, 137.5, 134.8, 128.9, 128.7, 128.2, 124.2, 121.8, 60.9, 51.8, 51.5, 50.5, 33.8, 26.4. $[\alpha]_D^{31}$ −3.2 (*c* 0.62 in CH_3OH).

*4.2.11. Compound **12**.* White solid. ^{1}H NMR ($(CD_3)_2SO$): δ 9.53 (br, 1H), 9.35 (s, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.41–7.38 (m, 10H), 5.48 (s, 2H), 5.46 (d, *J*=7.3 Hz, 1H), 5.18 (d, *J*=16.5 Hz, 1H), 5.12 (d, *J*=16.5 Hz, 1H), 3.62 (s, 3H); ^{13}C NMR: δ 170.5, 165.0, 137.5, 135.6, 134.8, 129.0, 128.8, 128.7, 128.5, 128.2, 127.7, 124.3, 121.9, 56.4, 52.4, 51.8, 50.5. $[\alpha]_D^{32}$ +3.2 (*c* 0.63 in CH_3OH).

*4.2.12. Compound **13**.* White solid. ^{1}H NMR ($(CD_3)_2SO$): δ 9.24 (s, 1H), 9.12 (br, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 7.42–7.39 (m, 5H), 7.28–7.21 (m, 5H), 5.45 (s, 2H), 5.05 (d, *J*=16.5 Hz, 1H), 5.00 (d, *J*=16.5 Hz, 1H), 4.54–4.49 (m, 1H), 3.59 (s, 3H), 3.07–3.02 (m, 1H), 2.96–2.90 (m, 1H); ^{13}C NMR: δ 171.4, 165.0, 137.5, 136.7, 134.8, 129.1, 129.0, 128.7, 128.3, 128.2, 126.7, 124.2, 121.8, 54.0, 53.2, 52.0, 50.4, 17.3. $[\alpha]_D^{32}$ +0.7 (*c* 0.56 in CH_3OH).

*4.2.13. Compound **20**.* White solid; mp 165.0–165.3 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.78 (s, 1H), 9.28 (d, J=7.3 Hz, 1H), 8.03–8.01 (m, 1H), 7.91–7.88 (m, 1H), 7.71–7.67 (m, 2H), 5.42 (s, 2H), 5.32 (t, J=6.0 Hz, 1H), 4.39–4.35 (m, 1H), 4.12 (s, 3H), 3.83–3.75 (m, 1H), 3.71–3.66 (m, 1H), 3.62 (s, 3H); ^{13}C NMR: δ 170.4, 164.9, 143.7, 131.5, 131.3, 126.7, 126.5, 113.6, 113.4, 61.0, 55.1, 52.0, 48.3, 33.3. Anal. Calcd for $C_{14}H_{18}ClN_3O_4\cdot 0.6H_2O$: C, 49.66; H, 5.72; N, 12.41. Found: C, 49.55; H, 5.49; N, 12.33%. $[\alpha]_D^{28}$ −3.2 (c 1.00 in CH_3OH).

*4.2.14. Compound **21**.* White solid; mp 213.0–213.3 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.98 (s, 1H), 9.27 (d, J=7.8 Hz, 1H), 7.99–7.97 (m, 1H), 7.92–7.90 (m, 1H), 7.70–7.62 (m, 2H), 7.50–7.48 (m, 2H), 7.43–7.35 (m, 3H), 5.84 (s, 2H), 5.44 (s, 2H), 5.30 (t, J=6.0 Hz, 1H), 4.41–4.37 (m, 1H), 3.81–3.76 (m, 1H), 3.71–3.66 (m, 1H), 3.63 (s, 3H); ^{13}C NMR: δ 170.3, 164.9, 143.6, 133.9, 131.6, 130.4, 129.0, 128.7, 128.1, 126.8, 126.7, 113.8, 113.7, 61.0, 55.0, 52.0, 49.8, 48.4. Anal. Calcd for $C_{20}H_{22}ClN_3O_4$: C, 59.48; H, 5.49; N, 10.40. Found: C, 59.39; H, 5.35; N, 10.37%. $[\alpha]_D^{29}$ −4.0 (c 0.10 in CH_3OH).

*4.2.15. Compound **22**.* White solid; mp 171.0–171.2 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.75 (s, 1H), 9.19 (d, J=7.8 Hz, 1H), 8.04–8.02 (m, 1H), 7.91–7.88 (m, 1H), 7.72–7.67 (m, 2H), 5.41 (s, 2H), 5.28 (t, J=6.0 Hz, 1H), 4.37–4.33 (m, 1H), 4.13 (s, 3H), 4.08 (q, J=6.9 Hz, 2H), 3.80–3.75 (m, 1H), 3.71–3.65 (m, 1H), 1.15 (t, J=6.9 Hz, 3H); ^{13}C NMR: δ 169.8, 164.9, 143.7, 131.5, 131.3, 126.6, 126.5, 113.6, 113.4, 61.0, 60.7, 55.2, 48.2, 33.3, 14.0. Anal. Calcd for $C_{15}H_{20}ClN_3O_4\cdot 0.6H_2O$: C, 51.09; H, 6.06; N, 11.92. Found: C, 51.10; H, 5.82; N, 11.85%. $[\alpha]_D^{28}$ −2.8 (c 0.50 in CH_3OH).

*4.2.16. Compound **23**.* White solid; mp 176.8–177.1 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.77 (s, 1H), 9.31 (d, J=7.8 Hz, 1H), 8.03–8.01 (m, 1H), 7.88–7.86 (m, 1H), 7.71–7.62 (m, 2H), 7.35–7.33 (m, 5H), 5.43 (s, 2H), 5.36 (t, J=6.0 Hz, 1H), 5.13 (s, 2H), 4.46–4.42 (m, 1H), 4.12 (s, 3H), 3.85–3.80 (m, 1H), 3.75–3.70 (m, 1H); ^{13}C NMR: δ 169.8, 164.9, 143.7, 135.8, 131.4, 131.3, 128.3, 127.9, 127.6, 126.6, 126.4, 113.6, 113.3, 66.0, 61.0, 55.2, 48.2, 33.3. Anal. Calcd for $C_{20}H_{22}ClN_3O_4\cdot 0.8H_2O$: C, 57.43; H, 5.69; N, 10.05. Found: C, 57.43; H, 5.46; N, 10.12%. $[\alpha]_D^{28}$ −2.2 (c 0.50 in CH_3OH).

*4.2.17. Compound **24**.* Yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.37 (br, 1H), 4.67–4.64 (m, 1H), 4.06–4.03 (m, 1H), 3.97–3.96 (m, 1H), 3.93 (s, 2H), 3.82 (s, 3H), 2.34 (br, 1H); ^{13}C NMR: δ 170.3, 166.1, 62.8, 55.1, 52.9, 28.5.

*4.2.18. Compound **25**.* Light yellow solid. ^{1}H NMR ($(CD_3)_2SO$): δ 9.79 (s, 1H), 9.27 (d, J=7.3 Hz, 1H), 8.04–8.02 (m, 1H), 7.90–7.87 (m, 1H), 7.70–7.68 (m, 2H), 5.43 (s, 2H), 5.39 (br, 1H), 4.40–4.36 (m, 1H), 4.13 (s, 3H), 3.80–3.76 (m, 1H), 3.69–3.66 (m, 1H), 3.62 (s, 3H); ^{13}C NMR: δ 170.4, 164.9, 143.6, 131.4, 131.3, 126.7, 126.4, 113.6, 113.4, 60.9, 55.1, 52.0, 48.2, 33.3. $[\alpha]_D^{28}$ −1.1 (c 0.57 in CH_3OH).

*4.2.19. Compound **26**.* White solid. ^{1}H NMR ($(CD_3)_2SO$): δ 8.83 (d, J=7.8 Hz, 1H), 8.15 (s, 1H), 7.65–7.63 (m, 1H), 7.45–7.44 (m, 1H), 7.25–7.17 (m, 2H), 5.18 (t, J=6.4 Hz, 1H), 5.03 (s, 2H), 4.41–4.36 (m, 1H), 3.78–3.72 (m, 1H), 3.67–3.65 (m, 1H), 3.62 (s, 3H); ^{13}C NMR: δ 170.7, 166.9, 144.8, 143.2, 134.1, 122.3, 121.4, 119.3, 110.2, 61.1, 54.7, 51.9, 46.5.

*4.2.20. Compound **27**.* Light yellow solid; mp 169.5–169.8 °C. ^{1}H NMR ($(CD_3)_2SO$): δ 9.70 (s, 1H), 9.13 (d, J=7.8 Hz, 1H), 8.05–8.01 (m, 1H), 7.88–7.84 (m, 1H), 7.72–7.68 (m, 2H), 5.42 (d, J=16.5 Hz, 1H), 5.38 (d, J=16.5 Hz, 1H), 5.29 (br, 1H), 4.42–4.38 (m, 1H), 4.12 (s, 3H), 3.81–3.76 (m, 1H), 3.69–3.65 (m, 1H), 3.63 (s, 3H); ^{13}C NMR: δ 170.4, 164.9, 143.6, 131.4, 131.3, 126.7, 126.5, 113.6, 113.3, 61.0, 54.9, 52.0, 48.2, 33.3. Anal. Calcd for $C_{14}H_{18}IN_3O_4$: C, 40.11; H, 4.33; N, 10.02. Found: C, 40.11; H, 4.26; N, 9.98%. $[\alpha]_D^{27}$ −11.0 (c 0.10 in CH_3OH).

*4.2.21. Compound **28**.* White solid. ^{1}H NMR ($(CD_3)_2SO$): δ 8.19 (br, 1H), 7.71–7.63 (m, 2H), 7.41–7.28 (m, 7H), 5.73 (s, 2H), 5.28 (d, J=15.9 Hz, 1H), 5.20 (d, J=15.9 Hz, 1H), 4.58 (br, 1H), 3.63–3.58 (m, 2H), 3.42–3.36 (m, 1H), 0.86 (s, 9H); ^{13}C NMR: δ 166.1, 136.2, 134.0, 133.0, 128.7, 128.0, 127.3, 123.9, 123.9, 112.2, 60.4, 59.2, 51.7, 51.3, 33.6, 26.8, the carbene resonance was not observed.

*4.2.22. Compound **29**.* White solid. ^{1}H NMR ($CDCl_3$): δ 9.01 (br, 1H), 7.77–7.75 (m, 1H), 7.63–7.61 (m, 1H), 7.45–7.43 (m, 2H), 5.27 (br, 1H), 5.27 (s, 2H), 4.38–4.35 (m, 1H), 4.04 (s, 3H), 3.78–3.75 (m, 1H), 3.69–3.65 (m, 1H), 3.63 (s, 3H); ^{13}C NMR: δ 170.6, 166.5, 133.7, 133.7, 123.8, 123.8, 111.9, 111.8, 61.0, 54.8, 51.9, 50.6, 35.5, the carbene resonance was not observed.

4.3. General procedure for the Cu(OTf)$_2$-catalyzed ECA of enone with R$_2$Zn

To a solution of azolium salt (0.045 mmol) in THF (9 mL) were added $Cu(OTf)_2$ (0.045 mmol) and enone (1 mmol). After the mixture was cooled to 0 °C, Et_2Zn (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). The ee was measured by chiral GLC.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.04.028.

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