EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201082

Functionalized N-Heterocyclic Carbene Ligands for Dual Enantioselective Control in the Cu-Catalyzed Conjugate Addition of Dialkylzinc Compounds to Acyclic Enones

Kenta Dohi,[a] Junko Kondo,[a] Haruka Yamada,[a] Ryuichi Arakawa,[a] and Satoshi Sakaguchi*[a]

Keywords: Asymmetric catalysis / Homogeneous catalysis / Copper / Zinc / Ligand design / Carbenes / Conjugate addition / Enantioselectivity

A series of highly tunable, functionalized azolium compounds have been synthesized from chiral α-amino acid derivatives such as β-amino alcohols or α-amino esters. The combination of a Cu salt and a chiral azolium efficiently facilitated the asymmetric conjugate addition (ACA) reactions of acyclic enones with dialkylzinc under ambient conditions without temperature control. Of the (hydroxy amide)-functionalized azolium ligand precursors, which were derived from β-amino alcohols, an azolium salt containing a *tert*-butyl group as the stereodirecting group was found to be the best choice of ligand. Ligand screening revealed that the use of an azolium salt containing a sterically bulky alkyl substituent such as *N*-CHRR′ on the azolium ring led to a marked increase in the enantioselectivity of the ACA reaction. Thus, a new efficient (hydroxy amide)-functionalized azolium ligand precursor such as **26**, which was prepared from 1-(diphenylmethyl)benzimidazole and (*S*)-*tert*-leucinol, has been developed. The treatment of benzalacetone (**30**) with Et_2Zn in the presence of catalytic amounts of $[Cu(OTf)]_2(C_6H_6)$ and **26** at room temperature gave the corresponding 1,4-adduct **31** with excellent enantioselectivity (92 % *ee*). On the other hand, the enantioselectivity of the ACA reactions of acyclic enones with dialkylzinc was successfully reversed by the use of (ester amide)-functionalized azolium salts, which were obtained from α-amino esters. Several functionalized azolium ligand precursors from readily available serine esters have been designed and synthesized. Finally, it was found that **30** could react with Et_2Zn under the influence of a bis(hexafluoroacetylacetonato)copper(II) salt and C_2-symmetric azolium salt **36** to afford *ent*-**31** in almost quantitative yield with 89 % *ee*. A plausible reaction mechanism for the switching of the stereoselectivity in the ACA reaction by these two functionalized azolium compounds is described.

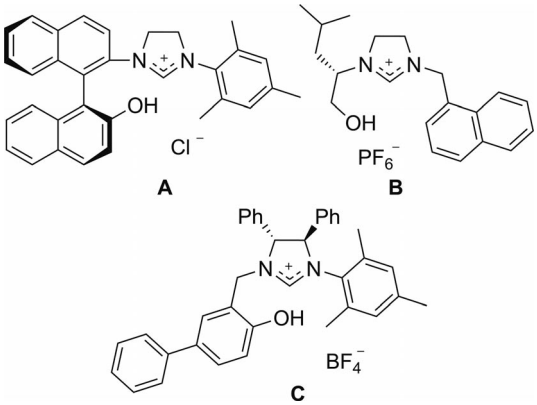
Introduction

The copper-catalyzed asymmetric conjugate addition (ACA) reaction is a powerful and versatile synthetic tool that affords enantiomerically enriched building blocks. Since the 1990s, a wide range of chiral ligands have emerged that have led to excellent selectivities with various alkylating reagents and Michael acceptors.[1] In recent years, N-heterocyclic carbenes (NHCs) have been recognized as versatile ligands in organometallic chemistry due to their strong donating ability.[2] Their most attractive feature is their easy manipulation by the modification of the backbone and substituents leading to stable complexes with a metal center. Thus, during the past decade, a variety of functionalized NHC ligands have been designed and synthesized for use in Cu-catalyzed ACA reactions (Scheme 1).[1d] The pioneers in this field are Hoveyda and co-workers who developed the chelating ligand **A** with a carbene unit and binaphthol as a second coordinating group on the side-arm of the NHC.[3,4] Moreover, the combination of a Cu salt and the chiral hydroxyalkyl-functionalized azolium salt **B**, developed by Mauduit and co-workers, exhibits excellent catalytic activity in the ACA reaction of substituted or unsubstituted cyclic enones with alkylating reagents such as alkylzinc compounds or Grignard reagents.[5]

Most of the above-mentioned studies were performed on the conjugate addition reactions of organometallic compounds with cyclic enones. In contrast, very few highly enantioselective reactions of acyclic enones have been reported. It has been assumed in the literature that the lower stereoselectivity of the ACA reactions of acyclic enones was caused by *s-cis*/*s-trans* conformational flexibility.[6] To the best of our knowledge, there is only one report on the copper-catalyzed ACA of Et_2Zn to an acyclic enone employing a chiral NHC ligand that gives satisfactory enantioselectivity.[7] Katsuki and Uchida described the highly enantioselective ACA reactions of alkenyl phenyl ketones with

[a] Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan
Fax: +81-6-6339-4026
E-mail: satoshi@kansai-u.ac.jp
Homepage: http://www2.ipcku.kansai-u.ac.jp/~satoshi/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201082.



Scheme 1. Representative chelating ligands with a hydroxy group on the side-arm of the NHC.

Et_2Zn catalyzed by $Cu(OTf)_2$ in combination with the biphenol-NHC precursor **C** (Scheme 1), which was based on the 1,2-diphenylethylenediamine skeleton as a source of chirality. Furthermore, Mauduit and co-workers mentioned that it is impossible to generate a general catalyst for all conjugate addition reactions and extremely difficult to anticipate the reactivity or stereoselectivity of reactions.[1d,1h,5e,5g]

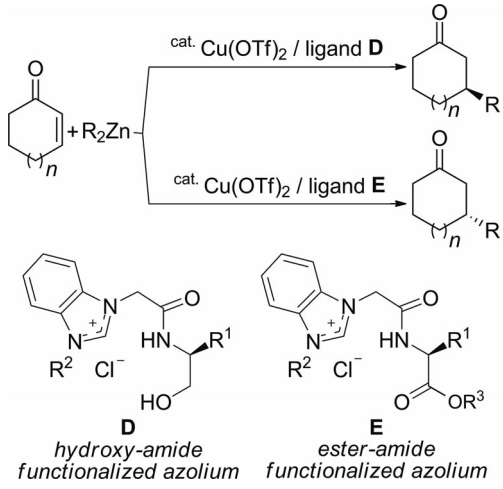
In organic synthesis, it is very important to introduce a versatile ligand that is useful in the ACA reactions of both cyclic and acyclic enones.[1c] For example, the straightforward asymmetric synthesis of (*R*)-muscone, the key flavor component of musk, was accomplished through the conjugate addition of Me_2Zn to a cyclic enone such as (*E*)-cyclopentadec-2-en-1-one under the influence of $Cu(OTf)_2$ in combination with a chiral phosphate ligand.[8] The total synthesis of the antimycobacterial agent erogorgiaene was achieved by the enantioselective 1,4-addition of Me_2Zn to an acyclic enone such as a benzalacetone derivative in the presence of catalytic amounts of $Cu(OTf)_2$ and a phosphane ligand.[9] Therefore the development of an general efficient chiral ligand for enantioselective conjugate addition reactions is urgently needed.

We have previously reported the highly enantioselective conjugate addition reactions of cyclic enones with R_2Zn by using a combined catalyst of a copper salt and a (hydroxy amide)-functionalized azolium salt **D** (Scheme 2).[10] This NHC ligand precursor offers several advantages:

i. The starting materials, such as β-amino alcohols, are readily available from naturally occurring α-amino acids,

ii. the ligand precursors can be prepared by a two-step synthesis from β-amino alcohols, and

iii. the azolium compounds are air-stable and easy to handle. In addition, we have developed a chiral azolium salt containing an ester amide side-chain (**E**), which was prepared from serine ester.[11] Interestingly, the absolute configurations of the conjugate adducts obtained in the ACA reactions of cyclic enones with R_2Zn using the (ester amide)-functionalized azolium salt **E** differed from those obtained in the ACA reactions using the (hydroxy amide)-functionalized azolium salt **D** (Scheme 2).



Scheme 2. Ligand design for dual enantioselective control in the ACA reactions of cyclic enones with dialkylzinc compounds.

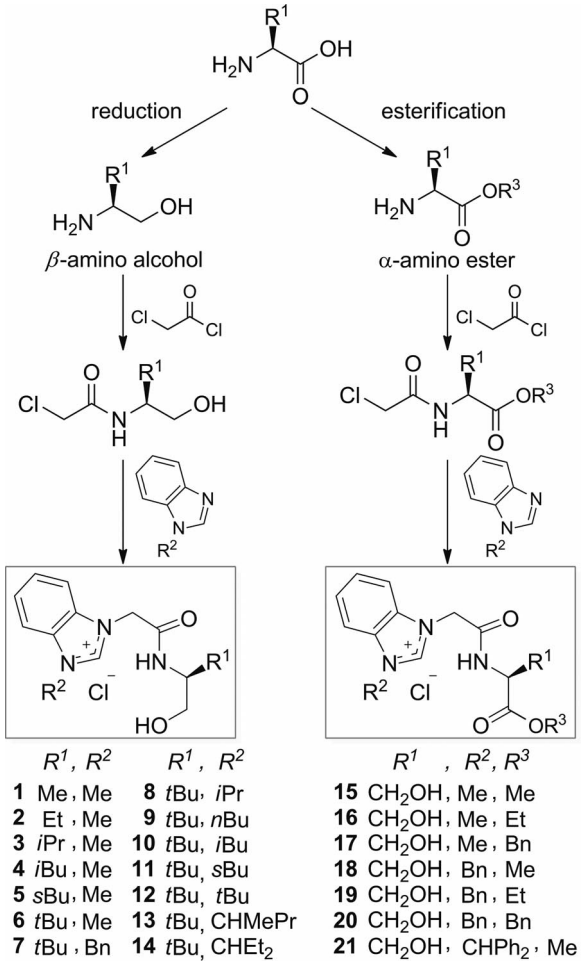
Because both ligand precursors are prepared from natural α-amino acids, it is possible to achieve dual enantioselective control through the structural modification of chiral ligands. To investigate the potential of this promising class of functionalized NHCs, we have continued our efforts to improve the chiral functionalized azolium ligand. In this paper, we describe the systematic study of the copper-catalyzed ACA reactions of acyclic enones with dialkylzinc by using chiral ligands **D** and **E**, and we report on the dual stereoselective control achieved by tuning the chiral ligand in both reactions.

Results and Discussion

Synthesis of Chiral Azolium Salts from α-Amino Acid Derivatives

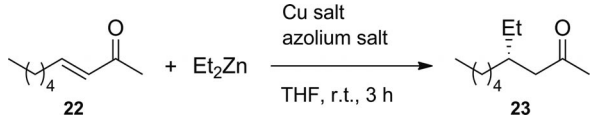
The synthetic routes to enantiopure azolium salts are shown in Scheme 3.[10–12] The reaction of chloroacetyl chloride with β-amino alcohol afforded α-chloroacetamide in almost quantitative yield. This was subsequently coupled with *N*-alkylated benzimidazole to yield the corresponding (hydroxy amide)-functionalized azolium chloride. The *N*-alkylated benzimidazole could be prepared with ease by the reaction between benzimidazole and the corresponding alkyl halide. Because various chiral β-amino alcohols are commercially available, the azolium compounds **1**–**14** can be synthesized by this route.

In addition, (ester amide)-functionalized azolium compounds were obtained by a route similar to the (hydroxy amide)-functionalized azolium salts by using α-amino esters in place of β-amino alcohols. Previously we showed that serine ester with a hydroxymethyl substituent (R^1 = CH_2OH) was the best choice of chiral source among various naturally occurring α-amino esters examined.[11] Therefore we prepared azolium salts **15**–**21** derived from serine esters. These newly prepared azolium ligand precursors were obtained as air-stable, white solids by a two-step synthesis from readily available enantiopure compounds.



Scheme 3. Synthetic routes to a series of (hydroxy amide)- and (ester amide)-functionalized NHC ligand precursors.

Table 1. Evaluation of chiral azolium ligands **1**–**14** and the Cu precatalyst in the ACA reaction of 3-nonen-2-one (**22**) with Et_2Zn.[a]



Entry	Azolium	Cu	Yield [%]	*ee* [%]
1	**1**	$Cu(OTf)_2$	73	35
2	**2**	$Cu(OTf)_2$	93	45
3	**3**	$Cu(OTf)_2$	97	56
4	**4**	$Cu(OTf)_2$	91	46
5	**5**	$Cu(OTf)_2$	93	55
6	**6**	$Cu(OTf)_2$	97	60
7	**7**	$Cu(OTf)_2$	91	64
8	**8**	$Cu(OTf)_2$	88	80
9	**9**	$Cu(OTf)_2$	99	64
10	**10**	$Cu(OTf)_2$	95	65
11	**11**	$Cu(OTf)_2$	90	77
12	**12**	$Cu(OTf)_2$	60	77
13	**13**	$Cu(OTf)_2$	99	79
14	**14**	$Cu(OTf)_2$	99	75
15	**8**	$[Cu(OTf)]_2(C_6H_6)$	90	82
16	**8**	$[Cu(CH_3CN)]_4OTf$	87	83
17	**8**	$[Cu(CH_3CN)]_4BF_4$	88	71
18	**8**	$Cu(acac)_2$	58	70
19	**8**	$Cu(NO_3)_2$	95	85
20	**8**	$CuCl_2$	38	62
21[b]	**8**	$Cu(NO_3)_2$	99	88

[a] Reagents and conditions: **22** (1 mmol), Et_2Zn (3 mmol), Cu salt (6 mol-%), azolium salt (4.5 mol-%), THF (9 mL), room temp., 3 h. Yield and *ee* were determined by GLC analysis. Average of two runs. [b] In this case, 6 mol-% of **8** was used.

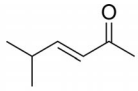
ACA Reactions with (Hydroxy Amide)-Functionalized Azolium Compounds

We started by screening ligand precursors **1**–**14** in the $Cu(OTf)_2$-catalyzed ACA reaction of 3-nonen-2-one (**22**) with Et_2Zn to give (*S*)-4-ethylnonan-2-one (**23**; Table 1). First, the alkyl substituent (R^1 group) at the stereogenic center of the ligand was evaluated. Clearly, of the ligand precursors **1**–**6**, the increase in the steric demand of the alkyl substituent on the ligand led to improved enantioselectivities (entries 1–6). For example, the use of compound **6** containing a sterically hindered *tert*-butyl group efficiently produced **23** in 97% yield with 60% *ee* (entry 6). One of the most attractive features of the functionalized NHC ligand is that the easy tuning of not only the hydroxy amide functional group but also the *N*-alkyl group (R^2) on the ligand allows the development of a huge variety of NHC ligands. The replacement of a methyl group (ligand precursor **6**) by a benzyl group (ligand precursor **7**) at the azolium ring slightly increased the enantioselectivity (entry 7).

We found that the chiral azolium ligand precursor **8** (R^1 = *t*Bu, R^2 = *i*Pr) was also effective in the ACA reaction, producing the desired product **23** with satisfactory stereoselectivity (80% *ee*; entry 8). Note that the isopropyl group on the azolium ring, which is far from the stereogenic center, led to a marked increase in enantioselectivity. The effect of the R^2 substituent will be discussed later. Based on this finding, we decided to evaluate the efficiency of several azolium ligands **7**–**14** containing various *N*-alkyl groups in the ACA reaction as well as the asymmetric induction (entries 7–14). We found that the azolium salts **9** and **10** with an *N*-CH_2R moiety [R^2 = *n*Bu (for **9**) and *i*Bu (for **10**)] gave lower selectivities than the azolium ligands **8**, **11**, **13**, and **14**, which involve an *N*-CHRR′ moiety (entries 9 and 10 vs. entries 8, 11, 13, and 14). Although the stereoselectivity of the ACA reaction with azolium salt **12** (R^2 = *t*Bu) was comparable to that obtained with **8** (R^2 = *i*Pr), the yield was somewhat lower (60%; entry 12). This might be due to the highly hindered *tert*-butyl group at the azolium ring blocking the approach of one of the reagents, such as enone **22**.

The screening of Cu salts showed that $[Cu(OTf)]_2(C_6H_6)$ as well as $Cu(NO_3)_2$ gave the 1,4-adduct **23** in excellent yields and with good enantioselectivities (entries 15–20). Note that no reversal of enantioselectivity was observed when the Cu precatalyst was changed from $Cu(OTf)_2$ to $Cu(acac)_2$ (entry 8 vs. entry 18). This observation is in contrast to the ACA reaction of a cyclic enone with Et_2Zn under the influence of the (hydroxy amide)-functionalized azolium salt.[10] The reaction with $Cu(NO_3)_2$/**8** in a ratio of

1:1 proceeded similarly to afford the corresponding adduct **23** in high yield and with good enantioselectivity (entry 21).



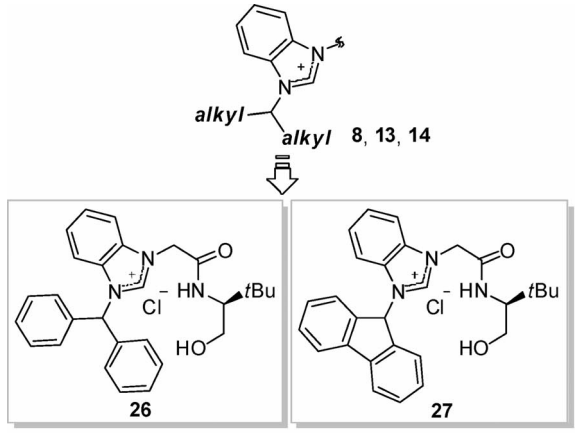
24

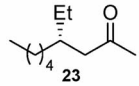
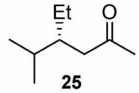
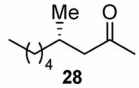
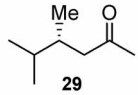
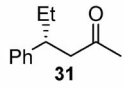
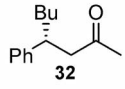
To investigate the influence of the R^1 and R^2 substituents on the ligand precursors in the ACA reaction of an acyclic enone other than **22**, 5-methyl-3-hexen-2-one (**24**) was allowed to react with Et_2Zn in the presence of $Cu(OTf)_2$ and a series of azolium ligands **1**–**14** (see Figure S1 in the Supporting Information). The results obtained from this ligand screening test in the ACA reaction of **24** were similar to those obtained in the ACA reaction of **22**. The sterically hindered *tert*-butyl group at the stereogenic center of the ligand (R^1 group) was the best choice of substituent. Furthermore, the enantioselectivity of the ACA reaction improved when the reaction was conducted with chiral ligands **8**, **13**, and **14**, which involve the *N*-CHRR′ moiety. In addition, further examination of the Cu precatalysts and chiral azolium ligands revealed that the combination of $[Cu(OTf)]_2(C_6H_6)$ and **14** led to the desired product **25** in almost quantitative yield and with good enantioselectivity (84% *ee*; see Table S1 in the Supporting Information).

As shown above, we have clearly demonstrated that a better enantiodiscrimination can be obtained by replacing the linear alkyl substituent (*N*-CH_2R) by a branched alkyl substituent (*N*-CHRR′) at the R^2 group of the chiral ligand. In addition to the successful ligands **8**, **13**, and **14**, we designed and synthesized two other substituted benzyl-based ligands, namely **26** (R^2 = diphenylmethyl) and **27** (R^2 = fluorenyl; Table 2). As expected, the 1,4-addition of **22** to Et_2Zn proceeded efficiently under the influence of the $Cu(NO_3)_2$/**26** catalytic system to give **23** in 99% yield and 89% *ee* (entry 1). Similar results were obtained in the ACA reaction with the $Cu(NO_3)_2$/**27** catalytic system (entry 2). Similarly, **24** and Et_2Zn were converted into the corresponding adduct **25** with good enantioselectivities (entries 3 and 4). Moreover, the ACA reactions of **22** and **24** with Me_2Zn were achieved by using the Cu salt/**26** catalytic system and gave the 1,4-adducts **28** and **29** with 73 and 82% *ee*, respectively, although somewhat longer reaction times were needed (entries 5 and 6).

Under the optimized reaction conditions, the conjugate addition of dialkylzinc compounds to benzalacetone (**30**) was investigated (Table 2, entries 7–12). It was found that the catalytic system of $[Cu(OTf)]_2(C_6H_6)$ in combination with **8**, **13**, or **26** is suitable for the ACA reaction of **30** with Et_2Zn at ambient temperature, furnishing 4-phenyl-2-hexanone (**31**) with good enantioselectivity (89–92% *ee*; entries 7–10). An excellent *ee* of 96% was obtained from the reaction of **30** with Bu_2Zn catalyzed by $[Cu(OTf)]_2(C_6H_6)$ and **26** in THF (entry 12). Moreover, one of the most attractive features of this reaction is that it can be performed at ambient temperature without temperature control.

Table 2. Ligand design for the ACA reactions of acyclic enones with R_2Zn.[a]



Entry	Azolium	Product	Yield [%]	*ee* [%]
1[b]	**26**	 **23**	99 (94)	89
2[b]	**27**	**23**	95	86
3	**26**	 **25**	99 (87)	84
4	**27**	**25**	99	77
5[b,c]	**26**	 **28**	(40)	73
6[c]	**26**	 **29**	(70)[d]	82
7	**8**	 **31**	76	90
8	**13**	**31**	78	90
9[e]	**13**	**31**	94	89
10	**26**	**31**	72	92
11[f]	**8**	 **32**	78	92
12[f]	**26**	**32**	79	96

[a] Reagents and conditions: Acyclic enone (1 mmol), Et_2Zn (3 mmol), $[Cu(OTf)]_2(C_6H_6)$ (6 mol-%), azolium salt (4.5 mol-%), THF (9 mL), room temp., 3 h. The yields and *ee* values were determined by GLC analysis. Data in parentheses show isolated yields. Average of two runs. [b] $Cu(NO_3)_2$ (6 mol-%), azolium salt (6 mol-%). [c] Me_2Zn (3 mmol) was used instead of Et_2Zn. The reaction was run for 24 h. [d] A conversion of >98% was observed by GLC analysis. The moderate yield was due to the volatility of **29**. [e] 2-MeTHF was used instead of THF. [f] Bu_2Zn (3 mmol) was used instead of Et_2Zn. The reaction was run in THF (3 mL).

ACA Reactions with (Ester Amide)-Functionalized Azolium Compounds

We have previously shown that the facial selectivities of the copper-catalyzed 1,4-addition of dialkylzinc compounds

to cyclic enones with the (hydroxy amide)-functionalized NHC ligand **D** are reversed in comparison with the reaction with the (ester amide)-functionalized NHC ligand **E**; the azolium **D** directs the 1,4-addition of R_2Zn to the *Si* face of the cyclic enone, whereas the 1,4-addition under the influence of **E** occurs on the opposite face (Scheme 2).[11] Thus, we anticipated that the chiral ligand **E** derived from an α-amino ester such as serine ester might be suitable for dual enantiocontrol in the ACA reactions of acyclic enones. To test the possibility of achieving an enantioselective catalytic conjugate addition reaction, we chose to study the reaction of benzalacetone (**30**) with Et_2Zn catalyzed by a Cu salt combined with the (ester amide)-functionalized azolium salt **15** (R^1 = CH_2OH, R^2 = R^3 = Me; Scheme 3). Table 3 shows representative results for the ACA reaction performed under various reaction conditions. The treatment of **30** with Et_2Zn in the presence of catalytic amounts of $[Cu(OTf)]_2(C_6H_6)$ and **15** in THF at room temperature afforded the expected *ent*-**31** in 63% yield with 44% *ee* (entry 1). Encouraged by this success, we examined various Cu precatalysts and solvents for further reaction optimization (entries 2–9). The first promising result was obtained with $Cu(NO_3)_2$ and bis(hexafluoroacetylacetonato)copper(II) ([Cu(hfacac)$_2$]) as the Cu precatalyst, furnishing *ent*-**31** in 58 and 66% *ee*, respectively (entries 4 and 5). Variation of the solvent revealed that the yield of the conjugate adduct was improved by using Et_2O or EtOAc (entries 7 and 8). Finally, it was found that **30** underwent 1,4-addition of Et_2Zn in the mixed solvent of THF and EtOAc (1:1, v/v) to afford *ent*-**31** in 96% yield with 65% *ee* (entry 9).

Table 3. Screening of Cu salts and solvents in the ACA reaction of **30** with Et_2Zn under the influence of (ester amide)-functionalized azolium salt **15** to give *ent*-**31**.[a]

Entry	Cu salt	Solvent	Yield [%]	*ee* [%]
1	$[Cu(OTf)]_2(C_6H_6)$	THF	63	44
2	$Cu(OTf)_2$	THF	55	46
3	$Cu(acac)_2$	THF	25	47
4	$Cu(NO_3)_2$	THF	90	58
5[b]	[Cu(hfacac)$_2$]	THF	76	66
6[b,c]	[Cu(hfacac)$_2$]	2-MeTHF	99	49
7[b]	[Cu(hfacac)$_2$]	Et_2O	91	56
8[b]	[Cu(hfacac)$_2$]	EtOAc	98	53
9[b,d]	[Cu(hfacac)$_2$]	THF/EtOAc	96	65

[a] Reagents and conditions: **30** (1 mmol), Et_2Zn (3 mmol), Cu salt (6 mol-%), **15** (4.5 mol-%), solvent (9 mL), room temp., 3 h. The yields and *ee* values were determined by GLC analysis. Average of two runs. [b] [Cu(hfacac)$_2$] = bis(hexafluoroacetylacetonato)copper(II). [c] 2-MeTHF = 2-methyltetrahydrofuran. [d] A 1:1 mixture of THF and EtOAc was used as solvent.

The fact that the functionalized NHC ligand precursors derived from β-amino alcohols and α-amino esters gave the opposite major enantiomer of the product is highly interesting from a conceptual and mechanistic point of view, but not completely satisfying due to the moderate *ee* (65% *ee*) obtained in the formation of the 1,4-adduct, as shown in Table 3. Therefore we next focused on screening the highly tunable (ester amide)-functionalized azolium ligand precursors. Table 4 summarizes the results of the ACA reaction of **30** with Et_2Zn catalyzed by [Cu(hfacac)$_2$] in 1:1 THF/EtOAc (left column) or by $Cu(NO_3)_2$ in THF (right column) with different ligand precursors to produce *ent*-**31**. The stereoselectivities of the [Cu(hfacac)$_2$]-catalyzed 1,4-addition reactions performed with azolium salt **16** or **17**, which contain ethyl (R^3 = Et) or benzyl (R^3 = Bn) esters, were comparable to that obtained with **15** (R^3 = Me; entries 1–3, left column). In contrast, the combination of $Cu(NO_3)_2$ with **17** in place of **15** resulted in slightly improved enantioselectivity (entries 1 and 3, right column). This ligand screening test revealed that *ent*-**31** was obtained in quantitative yield with 72% *ee* when the reaction was performed under the influence of [Cu(hfacac)$_2$] and **18** (R^2 = Bn, R^3 = Me; entry 4, left column). However, unfortunately, the use of **21** (R^2 = $CHPh_2$, R^3 = Me) did not improve the enantioselectivity of either catalytic system (entry 7). This result contrasts that of the above-mentioned ACA reactions of acyclic enones with dialkylzinc compounds in the presence of (hydroxy amide)-functionalized azolium salt **26**, in which the replacement of the *N*-methyl substituent (**6**, R^2 = Me) by the diphenylmethyl substituent (**26**, R^2 = $CHPh_2$) at the azolium ring led to a significant increase in the enantioselectivity (Table 2).

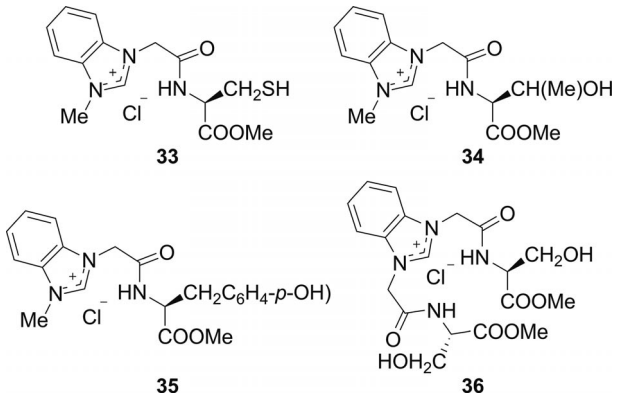
Table 4. [Cu(hfacac)$_2$]- and $Cu(NO_3)_2$-catalyzed ACA reactions of **30** with Et_2Zn using various (ester amide)-functionalized azolium salts to give *ent*-**31**.[a]

Entry	Azolium	With [Cu(hfacac)$_2$][b]		With $Cu(NO_3)_2$	
		Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
1	**15**	96	65	90	58
2	**16**	95	67	72	68
3	**17**	95	67	98	67
4	**18**	99	72	83	59
5	**19**	96	68	99	60
6	**20**	99	70	95	58
7	**21**	95	50	90	62
8	**33**	27	15	16	10
9	**34**	93	40	99	40
10	**35**	46	22	32	9
11	**36**	90	85	86	85
12	**36**	90[c]	89[c]	–	–
13[d]	**36**	91	92	99	93

[a] Reagents and conditions: **30** (1 mmol), Et_2Zn (3 mmol), [Cu(hfacac)$_2$] or $Cu(NO_3)_2$ (6 mol-%), azolium salt (4.5 mol-%), THF (9 mL), room temp., 3 h. The yields and *ee* values were determined by GLC analysis. Average of two runs. [b] A 1:1 mixture of THF and EtOAc was used as solvent. [c] A 1:1 mixture of THF and *t*BuOAc was used as solvent. [d] Acyclic enone **22** (1 mmol) in place of **30** was treated with Et_2Zn (3 mmol) to afford *ent*-**23**.

Because the variation of the R^2 and R^3 groups on the (ester amide)-functionalized azolium ligands **15**–**21** was not effective in achieving a highly stereoselective reaction (Table 4, entries 1–7), the different (ester amide)-functionalized azolium salts **33**–**36**, which could be prepared from inexpensive α-amino esters, were synthesized and evaluated in an attempt to find a more efficient catalytic system. The chiral azolium ligand **33**, which only differs from **15** by the presence of the SH functional group, was synthesized from commercially available L-cysteine methyl ester by a route similar to that shown in Scheme 1. However, the ACA reac-

tion of **30** with Et_2Zn in the presence of catalytic amounts of [Cu(hfacac)$_2$] or $Cu(NO_3)_2$ in combination with **33** resulted in the production of the corresponding conjugate adduct, *ent*-**31**, in low yield and with poor enantioselectivity (entry 8). These results will be discussed later. The 1,4-addition of Et_2Zn to **30** by using the ligand precursor **34** derived from L-threonine methyl ester occurred in the same high yield as in the case of the ligand precursor **15**, however, the reaction proceeded with moderate enantioselectivity (entry 9). We also designed the chiral ligand **35**, which was prepared from a natural amino acid such as L-tyrosine. When **30** was treated with Et_2Zn under the influence of **35**, which bears a hydroxy group at a position far from the stereogenic center of the chiral ligand, the desired product, *ent*-**31**, was obtained with poor enantioselectivity (entry 10).

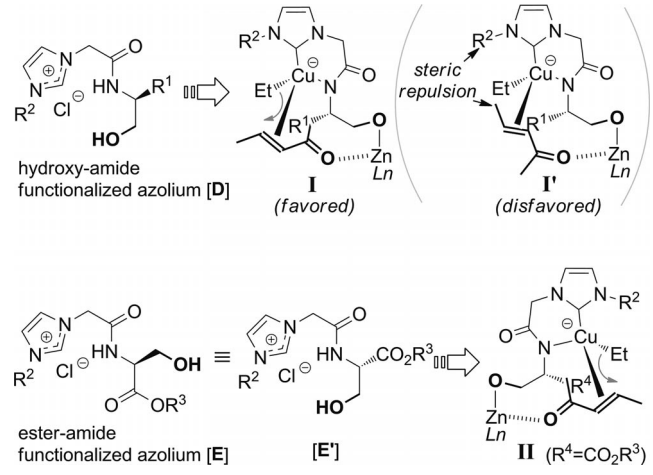


We have previously demonstrated that a C_2-symmetric bis(hydroxy amide)-functionalized benzimidazolium salt efficiently performs a copper-catalyzed ACA addition of R_2Zn to cyclic enones with up to 96% *ee*.[13] Therefore we designed and synthesized a similar bis(ester amide)-functionalized benzimidazolium salt **36** from L-serine methyl ester. We were pleased to find that the use of **36** led to an increase in the enantioselectivity of the ACA reaction (Table 4, entry 11). The treatment of **30** with Et_2Zn by using the combined catalytic system [Cu(hfacac)$_2$] and **36** afforded *ent*-**31** in 90% yield with good enantioselectivity (85% *ee*). Similar results were obtained by using the $Cu(NO_3)_2$/**36** catalytic system (entry 11). Moreover, the ACA reaction catalyzed by [Cu(hfacac)$_2$] and **36** in a mixed solvent of THF/*t*BuOAc at room temperature gave *ent*-**31** in 90% yield and 89% *ee* (entry 12). In addition, the enantioselectivity was reversed in the reaction of **22** with Et_2Zn under the influence of catalytic amounts of [Cu(hfacac)$_2$] or $Cu(NO_3)_2$ in combination with **36**, furnishing *ent*-**23** with up to 93% *ee* (entry 13).[14]

Mechanistic Aspects

Although the mechanism of this reaction remains unclear, it is likely that the reaction proceeds through an ordered transition state involving the catalyst structure bearing a precoordinating substituent. For the ACA reaction catalyzed by a copper salt in combination with the hydroxyalkyl-functionalized azolium ligand **A**, Mauduit and co-workers suggested that a plausible reaction mechanism involves an anionic alkoxy/NHC–Cu complex containing a covalent copper–oxygen bond as a second coordination site.[5c] Recently, a reaction intermediate similar to that formed in the NHC–Cu-catalyzed allylic substitution reaction was proposed by Jung and Hoveyda.[15] On the other hand, we have previously shown that an anionic amidate/NHC–Pd complex was formed from the (hydroxy amide)-functionalized azolium salt **D** and an appropriate palladium precursor such as [$PdCl_2(CH_3CN)_2$].[12] This indicates that the azolium salt **D** acts as a chelating ligand with a carbene unit and a second coordinating group such as an anionic amidate on the side-arm of the NHC. This combination generates a strongly coordinating polydentate ligand that can lock the stereodirecting functional group in a fixed conformation.

We speculate that the Cu-catalyzed 1,4-addition reaction described herein might proceed through the formation of an anionic amidate/NHC–Cu intermediate species (Scheme 4). The proposed reaction mechanisms for the ACA reaction with the (hydroxy amide)-functionalized azolium ligand **D** and the (ester amide)-functionalized azolium ligand **E** are shown in Scheme 4. In the case of the ACA reaction performed with ligand precursor **D**, the copper complex **I** involving a carbene, amidate, and ethyl group might be generated. An enone would be envisioned to coordinate by approaching from the front side because of the steric repulsion of the stereodirecting group such as R^1 group on the back side. In addition, the formation of a zinc alcoholate from the hydroxy group initially on the azolium precursor would facilitate the coordination of the enone by an interaction between the carbonyl group of the enone and the zinc species. Consequently, an ethyl group would add to the enone from the back side as shown in **I**. In contrast, model **I′** would lead to a conjugate adduct with the opposite configuration. In structural model **I′**, however, there would be significant steric repulsion between the R^2 group on the NHC ring and the alkyl substituent at the β position of the enone.

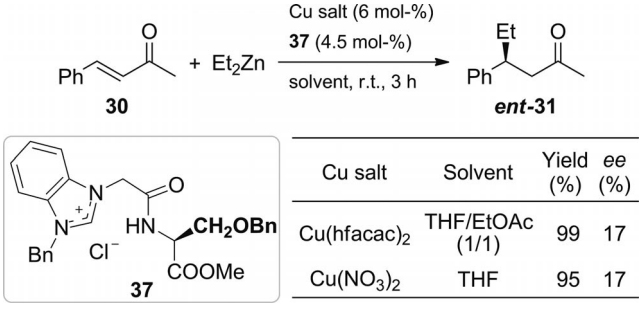


Scheme 4. Proposed reaction mechanisms for the ACA reaction using the functionalized azolium salts **D** and **E**.

As shown in Table 3, the use of the ligand precursor **26**, which contains a sterically bulky diphenylmethyl substituent at the R^2 position, resulted in an increase in the enantioselectivity of the ACA reaction. This suggests that model **I′** would be disfavored because of steric hindrance. Consequently, the ACA reaction with the (hydroxy amide)-functionalized azolium **D** would be expected to proceed via reaction model **I**.

On the other hand, we also speculate that the reversal of enantioselectivity in the ACA reaction with the (ester amide)-functionalized azolium ligand **E** might be explained as shown in Scheme 4. We chose a natural serine ester that bears a hydroxymethyl substituent as the origin of the chiral induction. As indicated in structures **D** and **E′** in Scheme 4, the alkyl group (R^1 group) at the chiral carbon center in ligand **D** is on the front side, whereas the ester group (CO_2R^3 group) at the chiral carbon center of ligand **E** (**E′**) is on the back side. According to this assumption, the CO_2R^3 group in **E′** would correspond to the R^1 group in **D**, that is, **E** (**E′**) is formally the enantiomer of **D**. This might cause significant changes in the enantioselective control of the ACA reaction. Therefore we proposed reaction mechanism **II** in which the CO_2R^3 group is represented by the R^4 group. The intermediate **II** formally becomes the enantiomer of intermediate **I**. In addition, it seems likely that a zinc alcoholate would determine the approaching direction of the enone. As shown in entry 8 of Table 4, the use of **33** (containing a CH_2SH group) in place of **15** (containing CH_2OH group) led to a low yield of the conjugate adduct with poor enantioselectivity. This suggests that the hydroxy amide functionality of the chiral ligand, which might lead to the generation of a zinc alcoholate intermediate in **I** or **II**, is of critical importance for highly enantioselective ACA reactions.

To obtain further information we prepared the functionalized azolium ligand precursor **37** from *O*-benzyl-L-serine methyl ester in which the hydroxy group is protected by a benzyl group (Scheme 5). The treatment of **30** with Et_2Zn in the presence of either the [Cu(hfacac)$_2$]/**37** or Cu(NO$_3$)$_2$/**37** catalytic system afforded *ent*-**31** with reduced enantioselectivity (Scheme 5). These lower enantioselectivities might be caused by preventing the formation of a zinc alcoholate in the intermediate **II** from **37** (Scheme 4). Furthermore, high product yields were observed in the ACA reactions with copper salts in combination with azolium ligand **37** (Scheme 5). An independent reaction revealed that no Cu-catalyzed 1,4-addition reaction of **30** with Et_2Zn occurred in the absence of an azolium ligand precursor. This strongly indicates that the coordination of an appropriate NHC ligand to the metal center not only induces the stereoselectivity of the ACA reaction but also enhances the reaction rate. The strong ligand-accelerated catalysis (LAC) by NHCs in the Cu-catalyzed conjugate addition reactions of enones with dialkylzinc compounds was first reported by Woodward and co-workers.[16]



Cu salt	Solvent	Yield (%)	*ee* (%)
Cu(hfacac)$_2$	THF/EtOAc (1/1)	99	17
Cu(NO$_3$)$_2$	THF	95	17

Scheme 5. Cu-catalyzed ACA reaction of **30** with Et_2Zn using the functionalized azolium salt **37** derived from *O*-benzylserine methyl ester.

Conclusions

Dual enantioselective control in the ACA reactions of acyclic enones with R_2Zn was successfully achieved by the design and tuning of the chiral ligand structure. Highly enantioselective catalytic 1,4-addition reactions were established by using two types of functionalized azolium compounds. These compounds were prepared with ease through a two-step synthesis from readily available enantiopure β-amino alcohols and α-amino esters. The high degree of asymmetric catalysis achieved by using (hydroxy amide)-functionalized azolium salt **D** is presumably due to the facial selection of the enone, which is a result of steric repulsion between the R^2 group on the NHC ring and the alkyl substituent at the β position of the enone (Scheme 4, intermediate **I** vs. **I′**). In addition, the CH_2OH substituent on the (ester amide)-functionalized azolium salt **E** derived from serine ester seems critical for the switching of enantioselectivity. We believe that the catalytic systems described in this report are alternatives to those used previously in the ACA reactions of acyclic enones with dialkylzinc.

Experimental Section

General: All chemicals were obtained from commercial sources and were used as received. ^1H and ^{13}C NMR spectra were recorded with spectrometers at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra. $(CD_3)_2SO$ or $CDCl_3$ was used as the NMR solvent. 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).

General Procedure for the Preparation of Azolium Salts: *N*-Alkylbenzimidazole (3 mmol), 1,4-dioxane (12 mL), and α-chloroacetoamide derivative (3 mmol) derived from chloroacetyl chloride and (*S*)-*tert*-leucinol or serine ester were added to a flask. After stirring the reaction mixture at 110 °C for 24 h, the solvent was removed under reduced pressure. The residue was dissolved in methanol and then activated carbon (ca. 1 g) was added. After 16 h, the activated carbon was removed by filtration. After removing the methanol in vacuo from the filtrate, the crude residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH = 9:1) to yield the corresponding azolium salt. Azolium salts **1**–**7** and **15**–**18** have been reported in preceding papers.[10–12] Because of their

highly hygroscopic character, the elemental analyses of **8**, **11**–**14**, **21**, and **33** were not performed.

3-(2-{[(1*S*)-1-(Hydroxymethyl)-2,2-dimethylpropyl]amino}-2-oxoethyl)-1-(1-methylethyl)-1*H*-benzimidazolium Chloride (8): White solid (yield 75%). $[\alpha]_D^{27}$ = +0.9 (*c* = 0.75, CH_3OH). ^1H NMR (DMSO): δ = 10.09 (s, 1 H, $CH_{benzimid}$), 8.55 (br., 1 H, NH), 8.14–7.67 (m, 4 H, $CH_{benzimid}$), 5.45 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 5.36 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 5.14–5.08 [m, 1 H, C*H*-$(CH_3)_2$], 4.69 (br., 1 H, OH), 3.59 (br., 2 H, C*H*$_2$OH), 3.40–3.48 (m, 1 H, NHC*H*), 1.63 (d, *J* = 6.4 Hz, 6 H, CH_3), 0.87 (s, 9 H, CH_{3tBu}) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.7 (CO), 141.8, 132.4, 130.2, 127.1, 126.7, 114.4, 112.7, 61.1 (CH_2OH), 60.9 (NHCH), 51.5 (*C*H$_2$CO), 49.6 [*C*H$(CH_3)_2$], 33.7 (C_{tBu}), 27.0 (CH_{3tBu}), 22.0 (CH_3), 22.0 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{18}H_{28}N_3O_2^+$ 318.2176; found 318.2155.

1-Butyl-3-(2-{[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]amino}-2-oxoethyl)-1*H*-benzimidazolium Chloride (9): White solid (yield 64%); m.p. 212.9–213.5 °C. $[\alpha]_D^{27}$ = +0.8 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 9.97 (s, 1 H, $CH_{benzimid}$), 8.60 (br., 1 H, NH), 8.13–8.10 (m, 1 H, $CH_{benzimid}$), 8.03–7.99 (m, 1 H, $CH_{benzimid}$), 7.69–7.64 (m, 2 H, $CH_{benzimid}$), 5.50 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 5.40 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 4.70 (br., 1 H, OH), 4.56 (t, *J* = 6.9 Hz, 2 H, C*H*$_2C_3H_7$), 3.62–3.55 (m, 2 H, C*H*$_2$OH), 3.43–3.35 (m, 1 H, NHC*H*), 1.91–1.84 (m, 2 H, CH_2), 1.36–1.27 (m, 2 H, CH_2), 0.90 (t, *J* = 7.3 Hz, 3 H, CH_3), 0.86 (s, 9 H, CH_{3tBu}) ppm. ^{13}C NMR (DMSO): δ = 164.8 (CO), 143.3, 131.5, 130.8, 126.7, 126.6, 113.8, 113.7, 60.3 (CH_2OH), 59.9 (NHCH), 48.8 (*C*H$_2$CO), 46.5 (*C*H$_2C_3H_7$), 33.6 (C_{tBu}), 30.6 (CH_2), 26.9 (CH_{3tBu}), 19.0 (CH_2), 13.4 (CH_3) ppm. $C_{19}H_{30}ClN_3O_2{\cdot}H_2O$: calcd. C 59.13, H 8.36, N 10.89; found C 59.26, H 8.29, N 10.88.

3-(2-{[(1*S*)-1-(Hydroxymethyl)-2,2-dimethylpropyl]amino}-2-oxoethyl)-1-(2-methylpropyl)-1*H*-benzimidazolium Chloride (10): White solid (yield 64%); m.p. 169.9–170.1 °C. $[\alpha]_D^{28}$ = +0.7 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 9.97 (s, 1 H, $CH_{benzimid}$), 8.62 (br., 1 H, NH), 8.16–7.65 (m, 4 H, $CH_{benzimid}$), 5.52 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 5.43 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 4.69 (br., 1 H, OH), 4.42 (d, *J* = 6.9 Hz, 2 H, C*H*$_2C_3H_7$), 3.62–3.55 (m, 2 H, C*H*$_2$OH), 3.44–3.37 (m, 1 H, NHC*H*), 2.26–2.19 (m, 1 H, CH), 0.92 (d, *J* = 6.9 Hz, 6 H, CH_3), 0.86 (s, 9 H, CH_{3tBu}) ppm. ^{13}C NMR (DMSO): δ = 164.8 (CO), 143.6, 131.4, 131.0, 126.6, 126.5, 113.9, 113.6, 60.3 (CH_2OH), 59.9 (NHCH), 53.1 (*C*H$_2$CO), 48.7 (*C*H$_2C_3H_7$), 33.6 (C_{tBu}), 30.7 (CH), 28.3 (CH_3), 26.8 (CH_{3tBu}), 19.3 (CH_3) ppm. $C_{19}H_{30}ClN_3O_2{\cdot}H_2O$: calcd. C 59.13, H 8.36, N 10.89; found C 59.28, H 8.15, N 10.87.

3-(2-{[(1*S*)-1-(Hydroxymethyl)-2,2-dimethylpropyl]amino}-2-oxoethyl)-1-(1-methylpropyl)-1*H*-benzimidazolium Chloride (11): White solid (yield 47%). $[\alpha]_D^{27}$ = +0.8 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 10.20 (s, 1 H, $CH_{benzimid}$), 8.65 (br., 1 H, NH), 8.20–8.16 (m, 1 H, $CH_{benzimid}$), 8.07–8.03 (m, 1 H, $CH_{benzimid}$), 7.71–7.66 (m, 2 H, $CH_{benzimid}$), 5.54–5.39 (m, 2 H, NCH_2CO), 5.02–4.94 [m, 1 H, C*H*$(C_2H_5)(CH_3)$], 4.74 (br., 1 H, OH), 3.63–3.57 (m, 2 H, C*H*$_2$OH), 3.45–3.39 (m, 1 H, NHC*H*), 2.09–1.92 (m, 2 H, CH_2), 1.65 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.89 (s, 9 H, CH_{3tBu}), 0.84 (t, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (DMSO): δ = 164.8 (CO), 142.3, 131.6, 130.5, 126.7, 126.5, 114.0, 113.8, 60.3 (CH_2OH), 59.9 (NHCH), 55.9 (*C*H$_2$CO), 48.9 [*C*H$(C_2H_5)(CH_3)$], 33.6 (C_{tBu}), 28.4 (CH_2), 26.9 (CH_{3tBu}), 19.6 (CH_3), 9.9 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{19}H_{30}N_3O_2^+$ 332.2332; found 332.2311.

1-(2,2-Dimethylethyl)-3-(2-{[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]amino}-2-oxoethyl)-1*H*-benzimidazolium Chloride (12): White solid (yield 65%). $[\alpha]_D^{28}$ = +0.8 (*c* = 1.0, CH_3OH). ^1H NMR ($CDCl_3$): δ = 10.34 (s, 1 H, $CH_{benzimid}$), 8.77 (d, *J* = 9.6 Hz, 1 H, NH), 7.97 (d, *J* = 7.3 Hz, 1 H, $CH_{benzimid}$), 7.85 (d, *J* = 7.3 Hz, 1 H, $CH_{benzimid}$), 7.60–7.53 (m, 2 H, $CH_{benzimid}$), 5.90 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 5.67 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 3.82–3.77 (m, 1 H, NHC*H*), 3.75–3.71 (m, 2 H, C*H*$_2$OH), 3.08 (br., 1 H, OH), 1.89 (s, 9 H, CH_{3tBu}), 0.92 (s, 9 H, CH_{3tBu}) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.8 (CO), 141.9, 133.3, 129.8, 126.8, 126.2, 115.3, 114.5, 61.4 (CH_2OH), 61.0 (NHCH), 60.9 (*C*H$_2$CO), 49.5 (C_{tBu}), 33.7 (C_{tBu}), 29.1 (CH_{3tBu}), 27.0 (CH_{3tBu}) ppm. HRMS (ESI^+): calcd. for $C_{19}H_{30}N_3O_2^+$ 332.2332; found 332.2312.

3-(2-{[(1*S*)-1-(Hydroxymethyl)-2,2-dimethylpropyl]amino}-2-oxoethyl)-1-(1-methylbutyl)-1*H*-benzimidazolium Chloride (13): White solid (yield 60%). $[\alpha]_D^{27}$ = +0.2 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 10.17 (s, 1 H, $CH_{benzimid}$), 8.60 (br., 1 H, NH), 8.18–8.15 (m, 1 H, $CH_{benzimid}$), 8.02–8.00 (m, 1 H, $CH_{benzimid}$), 7.69–7.64 (m, 2 H, $CH_{benzimid}$), 5.47 (dd, *J* = 3.7, 16.0 Hz, 1 H, NCH_2CO), 5.39 (dd, *J* = 3.7, 16.0 Hz, 1 H, NCH_2CO), 5.06–4.98 [m, 1 H, C*H*$(C_3H_7)(CH_3)$], 4.69 (br., 1 H, OH), 3.62–3.55 (m, 2 H, C*H*$_2$OH), 3.44–3.37 (m, 1 H, NHC*H*), 2.07–1.86 (m, 2 H, CH_2), 1.62 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.33–1.13 (m, 2 H, CH_2), 0.87 (s, 9 H, CH_{3tBu}), 0.85 (m, 3 H, CH_3) ppm. ^{13}C NMR (DMSO): δ = 164.8 (CO), 142.3, 131.6, 130.4, 127.0, 126.5, 114.0, 113.8, 60.3 (CH_2OH), 59.9 (NHCH), 54.5 (*C*H$_2$CO), 48.9 [*C*H$(C_3H_7)(CH_3)$], 33.6 (C_{tBu}), 26.8 (CH_{3tBu}), 20.1 (CH_2), 20.1 (CH_2), 18.5 (CH_3), 13.4 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{32}N_3O_2^+$ 346.2489; found 346.2468.

1-(1-Ethylpropyl)-3-(2-{[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]amino}-2-oxoethyl)-1*H*-benzimidazolium Chloride (14): White solid (yield 54%). $[\alpha]_D^{28}$ = +0.7 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 10.19 (s, 1 H, $CH_{benzimid}$), 8.63 (br., 1 H, NH), 8.21–8.16 (m, 1 H, $CH_{benzimid}$), 8.07–8.03 (m, 1 H, $CH_{benzimid}$), 7.70–7.64 (m, 2 H, $CH_{benzimid}$), 5.50 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 5.41 (d, *J* = 16.0 Hz, 1 H, NCH_2CO), 4.84–4.75 [m, 1 H, C*H*$(C_2H_5)_2$], 4.71 (br., 1 H, OH), 3.61–3.54 (m, 2 H, C*H*$_2$OH), 3.43–3.40 (m, 1 H, NHC*H*), 2.05–1.98 (m, 4 H, CH_2), 0.86 (s, 9 H, CH_{3tBu}), 0.77 (t, *J* = 7.3 Hz, 6 H, CH_3) ppm. ^{13}C NMR (DMSO): δ = 164.8 (CO), 142.7, 131.5, 131.0, 126.8, 126.6, 114.0, 113.8, 61.9 (CH_2OH), 60.3 (NHCH), 59.9 (*C*H$_2$CO), 49.0 [*C*H$(C_2H_5)_2$], 33.6 (C_{tBu}), 26.9 (CH_{3tBu}), 26.8 (CH_2), 26.7 (CH_2), 10.0 (CH_3), 10.0 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{32}N_3O_2^+$ 346.2489; found 346.2466.

3-(2-{[(1*S*)-1-(Ethoxycarbonyl)-2-hydroxyethyl]amino}-2-oxoethyl)-1-(1-phenylmethyl)-1*H*-benzimidazolium Chloride (19): White solid (yield 47%); m.p. 210.4–210.5 °C. $[\alpha]_D^{28}$ = –3.0 (*c* = 0.5, CH_3OH). ^1H NMR (DMSO): δ = 10.11 (br., 1 H, $CH_{benzimid}$), 9.44 (br., 1 H, NH), 8.00–7.93 (m, 2 H), 7.68–7.61 (m, 2 H), 7.52–7.49 (m, 2 H), 7.42–7.34 (m, 3 H, Ph), 5.86 (s, 2 H, CH_2Ph), 5.48 (s, 2 H, NCH_2CO), 5.39 (br., 1 H, OH), 4.35–4.31 (m, 1 H, NHC*H*), 4.09–4.04 (m, 2 H, C*H*$_2CH_3$), 3.81–3.68 (m, 2 H, C*H*$_2$OH), 1.13 (t, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (DMSO): δ = 169.8 (CO), 164.9 (CO), 143.6, 134.0, 131.6, 130.4, 129.0, 128.7, 128.2, 126.8, 126.7, 113.9, 113.7, 61.0 (CH_2O), 60.6 (CH_2O), 55.3 (NHCH), 49.8 (CH_2), 48.5 (CH_2), 14.0 (CH_3) ppm. $C_{21}H_{24}ClN_3O_4{\cdot}0.6H_2O$: calcd. C 58.84, H 5.92, N 9.80; found C 58.79, H 5.79, N 9.75.

3-(2-{[(1*S*)-1-(Benzyloxycarbonyl)-2-hydroxyethyl]amino}-2-oxoethyl)-1-(1-phenylmethyl)-1*H*-benzimidazolium Chloride (20): White solid (yield 50%); m.p. 210.0–210.2 °C. $[\alpha]_D^{28}$ = –2.3 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 9.98 (s, 1 H, $CH_{benzimid}$), 9.32 (d, *J* = 7.3 Hz, 1 H, NH), 7.99–7.86 (m, 2 H), 7.64–7.62 (m, 2 H), 7.50–7.48 (m, 2 H), 7.43–7.34 (m, 8 H), 5.84 (s, 2 H, CH_2Ph), 5.45 (s, 2 H, NCH_2CO), 5.38–5.35 (m, 1 H, OH), 5.13 (s, 2 H, OCH_2Ph), 4.47–4.45 (m, 1 H, NHC*H*), 3.86–3.81 (m, 1 H, C*H*$_2$OH), 3.75–3.70 (m, 1 H, C*H*$_2$OH) ppm. ^{13}C NMR (DMSO): δ = 169.8 (CO), 165.0 (CO), 143.6, 135.8, 133.9, 131.6, 130.4, 129.0, 128.7, 128.4,

128.2, 128.0, 127.6, 126.8, 126.7, 113.9, 113.7, 66.0 (CH_2O), 61.1 (CH_2O), 55.3 (NHCH), 49.8 (CH_2), 48.5 (CH_2) ppm. $C_{26}H_{26}ClN_3O_4 \cdot 0.5H_2O$: calcd. C 63.87, H 5.57, N 8.59; found C 63.93, H 5.26, N 8.38.

1-(Diphenylmethyl)-3-(2-{[(1*S*)-2-hydroxy-1-(methoxycarbonyl)-ethyl]amino}-2-oxoethyl)-1*H*-benzimidazolium Chloride (21): White solid (yield 43%). $[\alpha]_D^{27}$ = –2.5 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 9.55 (s, 1 H, $CH_{benzimid}$), 9.49 (d, *J* = 7.3 Hz, 1 H, NH), 7.96–7.94 (m, 1 H), 7.73–7.37 (m, 13 H), 5.46–5.42 (m, 3 H, NCH_2CO, OH), 4.35 (br., 1 H, NHC*H*), 3.80–3.70 (m, 2 H, CH_2OH), 3.61 (s, 3 H, OCH_3), 3.40 (br., 1 H, OH) ppm. ^{13}C NMR (DMSO): δ = 170.4 (CO), 164.9 (CO), 143.1, 136.0, 132.0, 130.7, 129.3, 129.1, 128.3, 127.0, 126.7, 114.4, 113.9, 64.0 (CH_2), 61.0 (CH_2), 55.3 (CH), 52.0 (CH_3), 48.7 (CH) ppm. HRMS (ESI^+): calcd. for $C_{26}H_{26}N_3O_2^+$ 444.19178; found 444.1889.

1-(Diphenylmethyl)-3-(2-{[(1*S*)-1-(hydroxymethyl)-2,2-dimethyl-propyl]amino}-2-oxoethyl)-1*H*-benzimidazolium Chloride (26): White solid (yield 70%); m.p. 159.8–160.2 °C. $[\alpha]_D^{27}$ = +0.5 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 9.49 (s, 1 H, $CH_{benzimid}$), 8.52 (br., 1 H, NH), 8.00–7.98 (m, 1 H), 7.72–7.35 (m, 14 H), 5.47 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 5.37 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 4.66 (t, *J* = 5.5 Hz, 1 H, OH), 3.61–3.54 (m, 2 H, CH_2OH), 3.42–3.37 (m, 1 H, NHC*H*), 0.85 (s, 9 H, $CH_{3t\mathrm{Bu}}$) ppm. ^{13}C NMR (DMSO): δ = 164.8 (CO), 143.0, 138.0, 132.0, 130.7, 129.3, 129.1, 128.3, 126.9, 126.7, 114.3, 113.9, 63.9 (CH_2OH), 60.2 (NHCH), 59.8 (CH_2CO), 33.6 ($C_{t\mathrm{Bu}}$), 30.7, 26.8 ($CH_{3t\mathrm{Bu}}$) ppm. $C_{28}H_{32}ClN_3O_2 \cdot CH_3CO_2C_2H_5 \cdot CH_2Cl_2 \cdot 0.5H_2O$: calcd. C 60.05, H 6.57, N 6.37; found C 59.92, H 6.72, N 6.06.

1-(Fluoren-9-yl)-3-(2-{[(1*S*)-1-(hydroxymethyl)-2,2-dimethyl-propyl]amino}-2-oxoethyl)-1*H*-benzimidazolium Chloride (27): White solid (yield 61%); m.p. 174.5–175.1 °C. $[\alpha]_D^{28}$ = +0.6 (*c* = 1.0, CH_3OH). ^1H NMR ($CDCl_3$): δ = 11.08 (s, 1 H, $CH_{benzimid}$), 9.13 (d, *J* = 8.6 Hz, 1 H, NH), 7.96 (d, *J* = 7.7 Hz, 1 H), 7.82 (d, *J* = 7.7 Hz, 2 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.48–7.43 (m, 4 H), 7.38 (t, *J* = 7.7 Hz, 1 H), 7.30 (s, 1 H), 7.20 (t, *J* = 7.7 Hz, 1 H), 7.12 (t, *J* = 7.7 Hz, 1 H), 7.05 (t, *J* = 7.7 Hz, 1 H), 6.31 (br., 1 H), 6.19 (d, *J* = 15.9 Hz, 1 H, NCH_2CO), 5.95 (d, *J* = 15.9 Hz, 1 H, NCH_2CO), 3.87–3.64 (m, 3 H, CH_2OH, NHC*H*), 0.88 (s, 9 H, $CH_{3t\mathrm{Bu}}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.1 (CO), 145.1, 140.6, 140.5, 139.1, 132.6, 130.3, 130.2, 129.1, 128.6, 128.5, 126.9, 126.5, 126.0, 125.8, 120.5, 114.0, 113.8, 63.3 (CH_2OH), 61.2 (NHCH), 50.1 (CH), 33.7 ($C_{t\mathrm{Bu}}$), 27.0 ($CH_{3t\mathrm{Bu}}$) ppm. $C_{28}H_{30}ClN_3O_2 \cdot 2H_2O$: calcd. C 65.68, H 6.69, N 8.21; found C 65.57, H 6.59, N 7.85.

3-(2-{[(1*S*)-2-Mercapto-1-(methoxycarbonyl)ethyl]amino}-2-oxoethyl)-1-methyl-1*H*-benzimidazolium Chloride (33): White solid; m.p. 145.2–145.5 °C. $[\alpha]_D^{28}$ = –3.3 (*c* = 0.2, CH_3OH). ^1H NMR (DMSO): δ = 9.95 (s, 1 H, $CH_{benzimid}$), 9.83 (br., 1 H, NH), 8.05–7.98 (m, 2 H, $CH_{benzimid}$), 7.68–7.66 (m, 2 H, $CH_{benzimid}$), 5.61 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 5.52 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 4.50–4.45 (m, 1 H, NHC*H*), 4.13 (s, 3 H, NCH_3), 3.61 (s, 3 H, OCH_3), 2.91–2.81 (m, 2 H, CH_2SH) ppm. ^{13}C NMR (DMSO): δ = 170.1 (CO), 165.2 (CO), 143.8, 131.5, 131.3, 126.7, 126.5, 113.7, 113.6, 55.2 (CH_2CO), 52.2 (CH_3O), 48.3 (NHCH), 33.4 (CH_3N), 25.3 (CH_2SH) ppm. $C_{14}H_{18}ClN_3O_2S \cdot 0.8CH_2Cl_2$: calcd. C 43.17, H 4.80, N 10.20; found C 43.36, H 4.77, N 10.39.

3-(2-{[(1*S*)-2-Hydroxy-1-(methoxycarbonyl)propyl]amino}-2-oxoethyl)-1-methyl-1*H*-benzimidazolium Chloride (34): White solid (yield 77%); m.p. 121.1–121.3 °C. $[\alpha]_D^{27}$ = –3.1 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 9.89 (s, 1 H, $CH_{benzimid}$), 9.31 (d, *J* = 8.7 Hz, 1 H, NH), 8.05–8.02 (m, 1 H, $CH_{benzimid}$), 7.95–7.90 (m, 1 H, $CH_{benzimid}$), 7.71–7.66 (m, 2 H, $CH_{benzimid}$), 5.55 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 5.48 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 5.35 (br., 1 H, OH), 4.27 (dd, *J* = 3.7, 8.2 Hz, 1 H, NHC*H*), 4.17–4.13 (m, 1 H, C*H*OH), 4.13 (s, 3 H, NCH_3), 3.61 (s, 3 H, OCH_3), 1.12 (d, *J* = 6.4 Hz, 1 H, CH_3) ppm. ^{13}C NMR (DMSO): δ = 170.6 (CO), 165.4 (CO), 143.8, 131.6, 131.3, 126.7, 126.5, 113.7, 113.3, 66.3 (CHOH), 58.7 (CH_2CO), 52.0 (CH_3O), 48.3 (NHCH), 33.4 (CH_3N), 20.2 (CH_3) ppm. $C_{15}H_{20}ClN_3O_4 \cdot 1.2H_2O$: calcd. C 49.58, H 6.21, N 11.56; found C 49.47, H 5.82, N 11.54.

3-(2-{[(1*S*)-2-(4-Hydroxyphenyl)-1-(methoxycarbonyl)ethyl]amino}-2-oxoethyl)-1-methyl-1*H*-benzimidazolium Chloride (35): White solid (yield 62%). $[\alpha]_D^{27}$ = +1.5 (*c* = 1.0, CH_3OH). ^1H NMR (DMSO): δ = 9.81 (s, 1 H, $CH_{benzimid}$), 9.56–9.48 (m, 2 H, NH, OH), 8.01–7.99 (m, 1 H, $CH_{benzimid}$), 7.69–7.58 (m, 3 H, $CH_{benzimid}$), 7.05 (d, *J* = 8.7 Hz, 2 H, C_6H_4), 6.70 (d, *J* = 8.2 Hz, 2 H, C_6H_4), 5.44 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 5.36 (d, *J* = 16.5 Hz, 1 H, NCH_2CO), 4.48–4.42 (m, 1 H, NHC*H*), 4.11 (s, 3 H, NCH_3), 3.59 (s, 3 H, OCH_3), 3.00–2.95 (m, 1 H, CH_2Ar), 2.88–2.82 (m, 1 H, CH_2Ar) ppm. ^{13}C NMR (DMSO): δ = 171.5 (CO), 164.7 (CO), 156.3, 143.6, 131.5, 131.1, 130.1, 126.8, 126.7, 126.5, 115.2, 113.6, 113.3, 54.3 (CH_2CO), 52.0 (CH_3O), 48.2 (NHCH), 35.9 (CH_2Ar), 33.3 (CH_3N) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{22}N_3O_2^+$: 368.1604; found 368.1581.

1,3-Bis(2-{[(1*S*)-2-Hydroxy-1-(methoxycarbonyl)ethyl]amino}-2-oxoethyl)-1*H*-benzimidazolium Chloride (36): White solid (yield 71%); m.p. 208.7–208.9 °C. $[\alpha]_D^{28}$ = –4.0 (*c* = 0.5, CH_3OH). ^1H NMR (DMSO): δ = 9.80 (s, 1 H, $CH_{benzimid}$), 9.20 (br., 2 H, NH), 7.90–7.88 (m, 2 H, $CH_{benzimid}$), 7.71–7.68 (m, 2 H, $CH_{benzimid}$), 5.46 (s, 4 H, NCH_2CO), 5.28 (t, *J* = 5.5 Hz, 2 H, OH), 4.42–4.37 (m, 2 H, NHC*H*), 3.81–3.65 (m, 4 H, CH_2OH), 3.63 (s, 6 H, OCH_3) ppm. ^{13}C NMR (DMSO): δ = 170.4 (CO), 164.8 (CO), 144.4, 131.2, 126.8, 113.6, 61.1 (CH_2OH), 55.1 (CH_2CO), 52.1 (CH_3O), 48.5 (NHCH) ppm. $C_{19}H_{25}ClN_4O_8 \cdot 0.8H_2O$: calcd. C 46.83, H 5.50, N 11.50; found C 46.74, H 4.96, N 11.21.

3-(2-{[(1*S*)-2-(Benzyloxy)-1-(methoxycarbonyl)ethyl]amino}-2-oxoethyl)-1-(phenylmethyl)-1*H*-benzimidazolium Chloride (37): White solid (yield 53%); m.p. 142.3–142.6 °C. $[\alpha]_D^{28}$ = –1.2 (*c* = 0.5, CH_3OH). ^1H NMR (DMSO): δ = 10.18 (s, 1 H, $CH_{benzimid}$), 9.55 (d, *J* = 7.3 Hz, 1 H, NH), 8.01–7.97 (m, 1 H), 7.90–7.88 (m, 1 H), 7.65–7.61 (m, 2 H), 7.52–7.50 (m, 2 H), 7.42–7.27 (m, 8 H), 5.88 (s, 2 H, CH_2Ph), 5.55 (d, *J* = 16.9 Hz, 1 H, NCH_2CO), 5.50 (d, *J* = 16.9 Hz, 1 H, NCH_2CO), 4.63–4.58 (m, 1 H, NHC*H*), 4.57 (d, *J* = 12.4 Hz, 1 H, OCH_2Ph), 4.50 (d, *J* = 12.4 Hz, 1 H, OCH_2Ph), 3.83–3.79 (m, 1 H, CH_2OBn), 3.71–3.68 (m, 1 H, CH_2OBn), 3.63 (s, 3 H, OCH_3) ppm. ^{13}C NMR (DMSO): δ = 169.9 (CO), 165.1 (CO), 143.6, 143.6, 137.8, 134.0, 131.6, 130.4, 129.0, 128.7, 128.3, 128.2, 127.6, 126.8, 126.7, 113.9, 113.7, 72.2 (CH_2O), 68.9 (CH_2O), 52.8 (CH_2CO), 52.2 (CH_3O), 49.8 (CH_2Ph), 48.5 (NHCH) ppm. $C_{26}H_{26}ClN_3O_4 \cdot 0.4H_2O$: calcd. C 64.10, H 5.54, N 8.63; found C 64.10, H 5.79, N 8.27.

General Procedure for the Cu-Catalyzed Asymmetric Reactions of Enones with R_2Zn: A Cu salt (0.06 mmol) and enone (1 mmol) were added to a solution of the azolium salt (0.045 or 0.06 mmol) in THF (9 mL) . After cooling the mixture to 0 °C, Et_2Zn (3 mmol, 1 mol/L in hexanes, 3 mL) was added to the reaction vessel. The color immediately changed from yellow to dark brown. After stirring at room temperature for 3 h, the reaction was quenched with 10% aq. HCl. The product yield was determined by GLC using a internal standard technique. The enantiomeric excess was measured by chiral GLC or chiral LC (see the Supporting Information). The conjugate adduct was isolated as follows: After quenching the reaction mixture with 10% aq. HCl, the resulting mixture was extracted with diisopropyl ether (3 × 10 mL) and dried with Na_2SO_4. The product was purified by silica gel column chromatography (hexane/

Et_2O). Because of the volatility of conjugate adducts such as **29**, the solvent was removed carefully under reduced pressure. The yields are the average of two runs. The 1,4-adducts **23**,[17] **25**,[17] **28**,[18] **29**,[19] **31**,[17] and **32**[20] have been reported in the literature.

Supporting Information (see footnote on the first page of this article): Evaluation of the chiral azolium ligands used in the ACA reaction of **24** with Et_2Zn catalyzed by $Cu(OTf)_2$, results of the ACA reaction of **24** with Et_2Zn under selected reaction conditions, NMR spectra, and chiral GC and LC traces.

Acknowledgments

This work was financially supported by the Japan Society for the Promotion of Science (JSPS) through a Grant-in-Aid for Scientific Research (grant number 23550128).

[1] For selected recent reviews, see: a) J.-X. Ji, A. S. C. Chan, in: *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), John Wiley & Sons, Hoboken, NJ, **2010**, pp. 439–495; b) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295–7306; c) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2009**, *38*, 1039–1075; d) J. Wencel, M. Mauduit, H. Hénon, S. Kehrli, A. Alexakis, *Aldrichim. Acta* **2009**, *42*, 43–50; e) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796–2823; f) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279–1300; g) F. López, A. J. Minnaard, B. L. Feringa, *Acc. Chem. Res.* **2007**, *40*, 179–188; h) A. H. Hoveyda, A. W. Hird, M. A. Kacprzynski, *Chem. Commun.* **2004**, 1779–1785; i) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221–3236.

[2] For selected recent reviews, see: a) J. Tornatzky, A. Kannenberg, S. Blechert, *Dalton Trans.* **2012**, *41*, 8215–8255; b) F. Wang, L.-j. Liu, W. Wang, S. Li, M. Shi, *Coord. Chem. Rev.* **2012**, *256*, 804–853; c) S. Díez-González (Ed.), *N-Heterocyclic Carbenes*, RSC, Cambridge, **2011**; d) L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Laponnaz, V. César, *Chem. Rev.* **2011**, *111*, 2705–2733; e) O. Kühl, *Funtionalised N-Heterocyclic Carbene Complexes*, Wiley-VCH, Weinheim, **2010**; f) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676; g) D. R. Snead, H. Seo, S. Hong, *Curr. Org. Chem.* **2008**, *12*, 1370–1387; h) F. E. Hahn, M. C. Jahnke, *Angew. Chem.* **2008**, *120*, 3166–3216; *Angew. Chem. Int. Ed.* **2008**, *47*, 3122–3172; i) F. Glorius (Ed.), *N-Heterocyclic Carbenes in Transition Metal Catalysis*, Springer, Berlin/Heidelberg, **2007**; j) R. E. Douthwaite, *Coord. Chem. Rev.* **2007**, *251*, 702–717; k) S. P. Nolan (Ed.), *N-Heterocyclic Carbenes in Synthesis* Wiley-VCH, Weinheim, Germany, **2006**; l) L. H. Gade, S. Bellemin-Laponnaz, *Coord. Chem. Rev.* **2007**, *251*, 718–725; m) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824–2870; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813; n) M. S. Sigman, D. R. Jensen, *Acc. Chem. Res.* **2006**, *39*, 221–229; o) E. Peris, R. H. Crabtree, *Coord. Chem. Rev.* **2004**, *248*, 2239–2246; p) V. César, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Soc. Rev.* **2004**, *33*, 619–636; q) M. C. Perry, K. Burgess, *Tetrahedron: Asymmetry* **2003**, *14*, 951–961; r) W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342–1363; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309.

[3] a) T. L. May, J. A. Dabrowski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 736–739; b) J. M. O'Brien, K.-s. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633; c) K.-s. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900; d) K.-s. Lee, A. H. Hoveyda, *J. Org. Chem.* **2009**, *74*, 4455–4462; e) M. K. Brown, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 12904–12906; f) T. L. May, M. K. Brown, A. H. Hoveyda, *Angew. Chem.* **2008**, *120*, 7466–7472; *Angew. Chem. Int. Ed.* **2008**, *47*, 7358–7362; g) M. K. Brown, T. L. May, C. A. Baxter, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 1115–1118; *Angew. Chem. Int. Ed.* **2007**, *46*, 1097–1100; h) K.-s. Lee, M. K. Brown, A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184; i) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955.

[4] P. L. Arnold, M. Rodden, K. M. Davis, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.* **2004**, 1612–1613.

[5] a) M. Tissot, D. Poggiali, H. Hénon, D. Müller, L. Guénée, M. Mauduit, A. Alexakis, *Chem. Eur. J.* **2012**, *18*, 8731–8747; b) S. Kehrli, D. Martin, D. Rix, M. Mauduit, A. Alexakis, *Chem. Eur. J.* **2010**, *16*, 9890–9904; c) D. Rix, S. Labat, L. Toupet, C. Crévisy, M. Mauduit, *Eur. J. Org. Chem.* **2009**, 1989–1999; d) H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem.* **2008**, *120*, 9262–9264; *Angew. Chem. Int. Ed.* **2008**, *47*, 9122–9124; e) H. Clavier, J.-C. Guillemin, M. Mauduit, *Chirality* **2007**, *19*, 471–476; f) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417; g) H. Clavier, L. Coutable, L. Toupet, J.-C. Guillemin, M. Mauduit, *J. Organomet. Chem.* **2005**, *690*, 5237–5254.

[6] a) J. M. García, A. González, B. G. Kardak, J. M. Odriozola, M. Oiarbide, J. Razkin, C. Palomo, *Chem. Eur. J.* **2008**, *14*, 8768–8771; b) S. R. Harutyunyan, F. López, W. R. Browne, A. Correa, D. Peña, R. Badorrey, A. Meetsma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118.

[7] T. Uchida, T. Katsuki, *Tetrahedron Lett.* **2009**, *50*, 4741–4743.

[8] N. Fuchs, M. D'Augustin, M. Humam, A. Alexakis, R. Taras, S. Gladiali, *Tetrahedron: Asymmetry* **2005**, *16*, 3143–3146.

[9] R. R. Cesati, J. de Armas, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 96–101.

[10] a) N. Shibata, M. Yoshimura, H. Yamada, R. Arakawa, S. Sakaguchi, *J. Org. Chem.* **2012**, *77*, 4079–4086; b) N. Shibata, M. Okamoto, Y. Yamamoto, S. Sakaguchi, *J. Org. Chem.* **2010**, *75*, 5707–5715; c) M. Okamoto, Y. Yamamoto, S. Sakaguchi, *Chem. Commun.* **2009**, 7363–7365.

[11] M. Yoshimura, N. Shibata, M. Kawakami, S. Sakaguchi, *Tetrahedron* **2012**, *68*, 3512–3518.

[12] a) S. Sakaguchi, M. Kawakami, J. O'Neill, K. S. Yoo, K. W. Jung, *J. Organomet. Chem.* **2010**, *695*, 195–200; b) K. S. Yoo, J. O'Neill, S. Sakaguchi, R. Giles, J. H. Lee, K. W. Jung, *J. Org. Chem.* **2010**, *75*, 95–101; c) S. Sakaguchi, K. S. Yoo, J. O'Neill, J. H. Lee, T. Stewart, K. W. Jung, *Angew. Chem.* **2008**, *120*, 9466–9469; *Angew. Chem. Int. Ed.* **2008**, *47*, 9326–9329.

[13] A. Harano, S. Sakaguchi, *J. Organomet. Chem.* **2011**, *696*, 61–67.

[14] One of the reviewers pointed out the possibility of racemization of **36** during its preparation. In the ^1H NMR analysis of **36**, however, only one component was observed (no existence of diastereoisomers). In addition, the high enantioselectivity obtained in the conjugate addition reaction of **22** with Et_2Zn might suggest that **36** was prepared with high purity. The possible racemization of the (ester amide)-functionalized azolium salts **33**–**35** is currently under investigation.

[15] B. Jung, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 1490–1493.

[16] P. K. Fraser, S. Woodward, *Tetrahedron Lett.* **2001**, *42*, 2747–2749.

[17] A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263.

[18] A. Hajra, N. Yoshikai, E. Nakamura, *Org. Lett.* **2006**, *8*, 4153–4155.

[19] A. De Roma, F. Ruffoa, S. Woodward, *Chem. Commun.* **2008**, 5384–5386.

[20] a) C. Monti, C. Gennari, U. Piarulli, *Chem. Eur. J.* **2007**, *13*, 1547–1558; b) G. Delapierre, T. Constantieux, J. M. Brunel, G. Buono, *Eur. J. Org. Chem.* **2000**, 2507–2511.

Received: August 9, 2012
Published Online: November 7, 2012

