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Enantioselective conjugate addition of dialkylzinc to cyclic enones catalyzed by chiral binaphthyldiamine–copper(I) complexes

Manabu Hatano, Takafumi Asai and Kazuaki Ishihara*

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-6603, Japan

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Abstract—The enantioselective conjugate addition of dialkylzinc (R_2Zn) to cyclic enones was examined using chiral binaphthyldiamine–copper(I) catalysts. Under the present reaction conditions, chiral C_2-symmetric $[RZn(II)]_2$-diamine–Cu(I) complexes were formed from chiral binaphthyldiamine, R_2Zn, and copper(I or II) chloride in situ. The reaction of 2-cyclohexenone with Et_2Zn proceeded smoothly in the presence of the corresponding chiral copper(I) complex (5 mol %) and achiral 2,6-diphenylaniline (10 mol %), and the desired Et-adduct was obtained with up to 76% ee in 95% yield.

The catalytic enantioselective conjugate addition to α,β-unsaturated carbonyl compounds is one of the most important methods in organic synthesis for stereoselective carbon–carbon bond formation.[1] In particular, the chiral Cu(I)-catalyzed conjugate addition of dialkylzinc reagents to enones has been extensively investigated, and various efficient catalysts have been developed.[2] To date, several chiral P-ligands, such as phosphoramidites, phosphites, and phosphines, have been shown to be highly useful.[3] Chiral N,N-ligands, such as sulfonamides and bis(oxazoline)s, and chiral P,N-ligands have also been shown to be effective.[4] However, to the best of our knowledge, there have been no reports of the enantioselective conjugate addition of dialkylzinc to enones using chiral N,N-ligands with primary amino groups. We report here for the first time the Cu(I)-catalyzed enantioselective conjugate addition of dialkylzinc to cyclic enones using chiral binaphthyldiamine (**5**), which is a simple and commercially available C_2-symmetric ligand with primary amines.

In principal, a primary amine ($R'NH_2$) has a relatively low pK_a,[5] and $R'NH_2$ can be easily replaced by $R'NHZnR$ through the use of basic dialkylzinc reagents (R_2Zn) in situ. In particular, a primary aniline ($ArNH_2$) should be efficiently converted to the corresponding *N*-ZnR-substituted compound via smooth deprotonation. If we can take advantage of this approach, particularly for chiral aniline compounds toward asymmetric catalysis, N-modification in advance, such as alkylation, arylation, carbonylation, and sulfonation, might not always be necessary. Therefore, we examined the catalysis of sterically demanding chiral C_2-symmetric $[RZn(II)]_2$-diamine–Cu(I) complexes, which would be prepared in situ from diamine–Cu(I) complexes via the deprotonation of primary amino groups with $R_2Zn(II)$, in the enantioselective conjugate addition of dialkylzinc to enones (Fig. 1). In particular, binaphthyldiamine (**5**) would be highly promising because of its low pK_a as an aniline analogue. In the expected chiral catalysis in situ, not only *N*-ZnR substitutions would show a

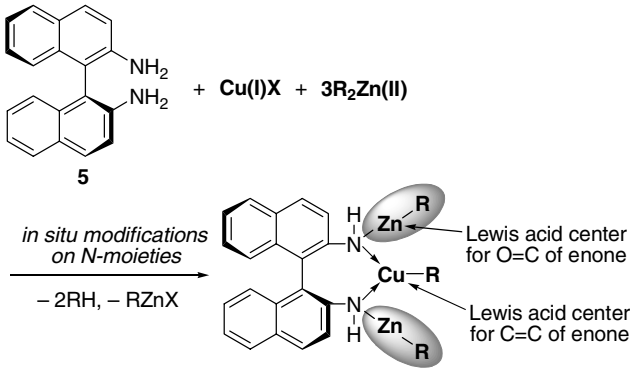

Figure 1. Design of chiral diamine–Cu(I) catalysts with in situ modifications of N-moieties.

* Corresponding author. Tel.: +81 52 789 3331; fax: +81 52 789 3222; e-mail: ishihara@cc.nagoya-u.ac.jp

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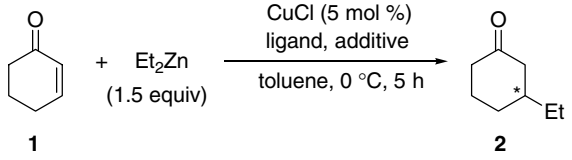
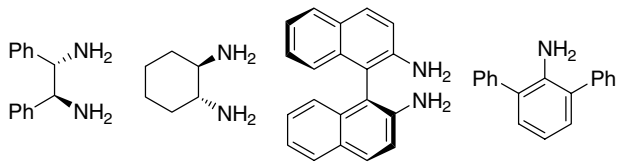
Table 1. Enantioselective conjugate addition of Et_2Zn to **1** catalyzed by chiral Cu(I) complexes in the presence of achiral amines



1 **2**

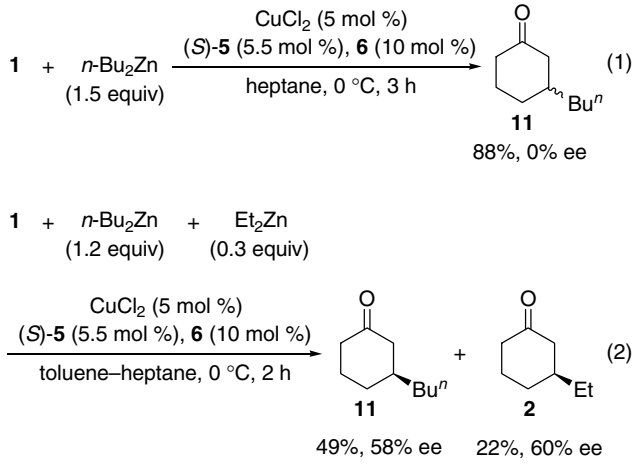
Entry	Ligand (mol %)	Additive (mol %)	Yield (%)	ee % (config.)
1	**3** [5.5]	—	82	3 (*S*)
2	**4** [5.5]	—	29	3 (*R*)
3	**5** [5.5]	—	14	18 (*S*)
4	**5** [20]	—	69	72 (*S*)
5	**3** [5.5]	$PhCH_2NH_2$ [10]	52	0
6	**4** [5.5]	*c*-$C_6H_{11}NH_2$ [10]	21	0
7	**5** [5.5]	**6** [30]	89	74 (*S*)
8	**5** [5.5]	**6** [10]	94	73 (*S*)
9	**5** [5.5]	**6** [5]	93	71 (*S*)



3 **4** **5** **6**

steric preference, but also the RZn(II) centers should act as Lewis acid centers to activate the C=O moiety of an enone. The RCu(I) center should also serve as a Lewis acid center to activate the C=C moiety of an enone. Thus, the resulting trinuclear complexes with one Cu(I) center and two Zn(II) centers should serve as efficient multi-functionalized chiral catalysts in this reaction.[6,7]

First, we examined the conjugate addition of Et_2Zn to 2-cyclohexenone (**1**) with chiral C_2-symmetric N,N-ligands with primary amino groups, such as (*S*,*S*)-1,2-diphenylethylenediamine (**3**), (*R*,*R*)-1,2-cyclohexanediamine (**4**), and (*S*)-binaphthyldiamine (**5**) (Table 1). In the presence of 5 mol % of CuCl and 5.5 mol % of **3** or **4**, the reactions between **1** and Et_2Zn (1.5 equiv) proceeded in toluene at 0 °C for 5 h, but the enantioselectivities of Et-adduct **2** were quite low (entries 1 and 2). The enantioselectivity was slightly improved (18% ee) with the use of **5** although the yield fell to 14%. Surprisingly, however, 20 mol % of **5** triggered the reactivity, and **2** was obtained in 69% yield with 72% ee (entry 4). Considering these interesting results, we suspected that another pathway would give racemic **2**, but with a low yield in the absence of adequate **5**. Therefore, to prevent the expected side pathway, we examined the effect of achiral additives as 'scavengers'. Compound **3** with benzylamine and **4** with cyclohexaneamine were not effective, and **2** was obtained in a racemic manner (entries 5 and 6).[8] However, the addition of 10 mol % of 2,6-diphenylaniline (**6**) to 5.5 mol % of **5** in the presence of 5 mol % of CuCl showed a significant improvement in catalytic activity, and the desired product **2** was obtained in 94% yield with 73% ee (entry 8).[9] The most appropriate amount of **6** was not critical, although a slight decrease in yield or enantioselectivity was observed when 5 or 30 mol % of **6** was used (entries 7 and 9).



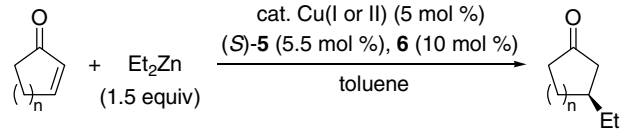
Scheme 1. Enantioselective conjugate addition of *n*-Bu_2Zn to **1**.

Before we examined the conjugate addition of organozinc reagents to other cyclic enones, we further optimized the copper(I or II) precursors (Table 2). CuBr and $(CuOTf)_2{\cdot}C_6H_6$ enhanced the catalytic activity, although the enantioselectivities of **2** were significantly decreased (entries 2 and 3 vs entry 1). $CuCl_2$ in place of CuCl also gave better reactivity, and we finally obtained **2** in 95% yield with 76% ee at 0 °C within 1.5 h (entry 4).[10] (*S*)-5,5′,6,6′,7,7′,8,8′-H_8-Binaphthyldiamine (**5′**) (5.5 mol %) in place of (*S*)-**5** was also effective to achieve higher enantioselectivity (79% ee) (entry 5). With these optimized conditions, the addition of Et_2Zn to 2-cyclopentenone (**7**) and 2-cycloheptenone (**9**) was examined. Although a trace amount of 3-ethylcyclopentanone (**8**) was obtained from **1** even at room temperature (entry 6), 3-ethylcycloheptanone (**10**) was obtained in 96% yield and 65% ee (entry 7). The reaction of **1** with *n*-Bu_2Zn (1.5 equiv) gave the corresponding *n*-Bu-adduct (**11**), but in a racemic manner (Scheme 1, Eq. 1).

Interestingly, however, we found that the addition of 0.3 equiv of Et_2Zn to 1.2 equiv of *n*-Bu_2Zn in the reaction of **1** with the $CuCl_2$/**5**/**6** catalytic system improved the enantioselectivity of *n*-Bu-adduct **11** up to 58% ee in 49% yield and also gave **2** as a minor product (22% yield and 60% ee) (Scheme 1, Eq. 2).[11,12]

We should address the association between the characteristics of the active Cu(I) catalysts and mechanistic aspects. The key to elucidating this topic should be to clarify whether covalent bonds are present between EtZn and N atoms via deprotonation (also see Fig. 1). Thus, we performed stoichiometric experiments to prepare the expected *N*-ZnEt-substituted chiral **5**–Cu(I) complexes (Scheme 2). When 1 equiv each of **5**, CuCl, and Et_2Zn were mixed at room temperature, 1.03 equiv of ethane gas was released, and the corresponding *N*-ZnEt-substituted chiral Cu(I) complexes (**12** and/or **13**) were formed. When another 1 equiv of Et_2Zn was added to that mixture, 0.72 equiv of ethane gas was released

Table 2. Enantioselective conjugate addition of Et_2Zn to cyclic enones catalyzed by chiral (*S*)-**5**–Cu(I) complexes

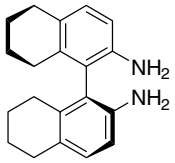


7 (n = 1)
1 (n = 2)
9 (n = 3)

8 (n = 1)
2 (n = 2)
10 (n = 3)

Entry	Enone	Cu	Conditions	Product	Yield (%)	ee (%)
1	**1**	CuCl	0 °C, 5 h	**2**	94	73
2	**1**	CuBr	0 °C, 30 min	**2**	96	61
3	**1**	$(CuOTf)_2{\cdot}C_6H_6$	0 °C, 1.5 h	**2**	94	8
4	**1**	$CuCl_2$	0 °C, 1.5 h	**2**	95	76
5[a]	**1**	$CuCl_2$	0 °C, 1.5 h	**2**	78	79
6	**7**	$CuCl_2$	rt, 8 h	**8**	Trace	—
7	**9**	$CuCl_2$	0 °C, 1.5 h	**10**	96	65

[a] (*S*)-5,5′,6,6′,7,7′,8,8′-H_8-Binaphthyldiamine (**5′**) (5.5 mol %) was used in place of (*S*)-**5**.



5'

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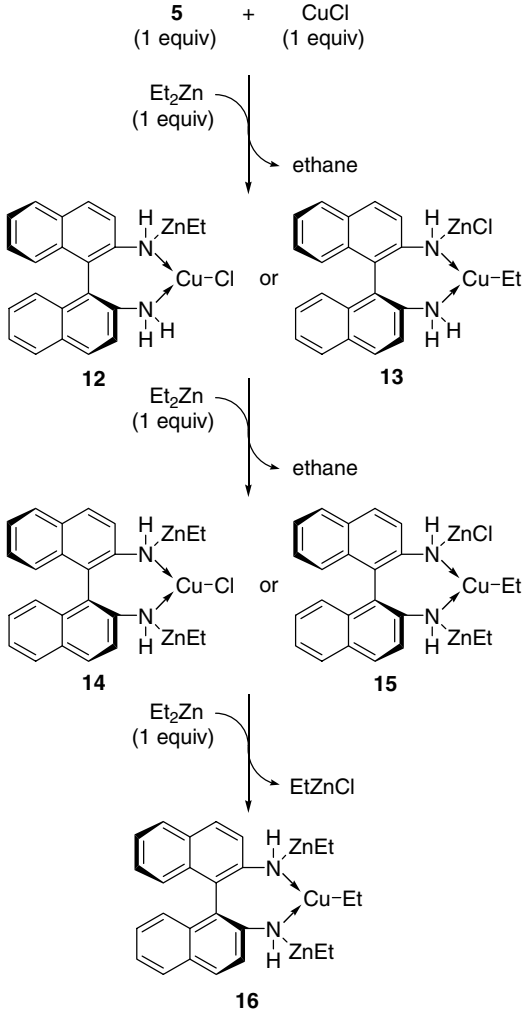

Scheme 2. Characteristics of **5**–Cu(I) catalysts with Et_2Zn.

again. Finally, when another 1 equiv of Et_2Zn was added to the resultant mixture, only 0.06 equiv of ethane gas was released. Therefore, these results suggest that the expected *N*-ZnEt-substituted chiral **5**–CuEt complex (i.e., **16**) should be prepared via **14** and/or **15**.[13]

Next, we turned our attention to mechanistic aspects, including transition states as a working model. As shown in Scheme 2, the expected active species **16** would be generated in addition to EtZnCl from the mixture of $CuCl_2$ (or CuCl), **5**, and Et_2Zn. In the absence of **6**, the equilibrium between **16** and **14**/**15** is expected to shift to the **14**/**15** side, where **14**/**15** might be less active in this catalysis (Table 1, entry 3). However, in the presence of achiral amine **6** as a scavenger of EtZnCl,[9] the equilibrium would be expected to shift the opposite to promote the generation of **16** as an active species (Table 1, entry 8). This is why a catalytic amount of **6** or a large amount of **5** was necessary in this reaction (Table 1, entries 4 and 8). Active catalytic alkylating reagent **16** shows attractive interaction with enone **4** to give the

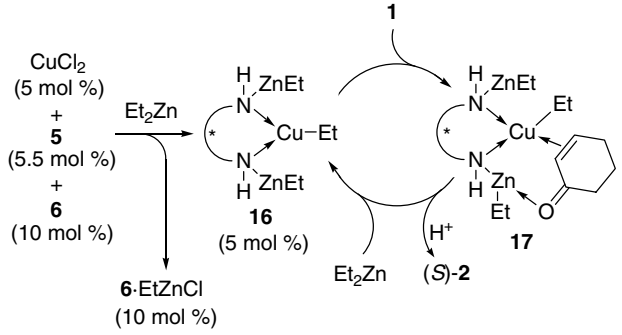

Figure 2. Possible catalytic cycle.

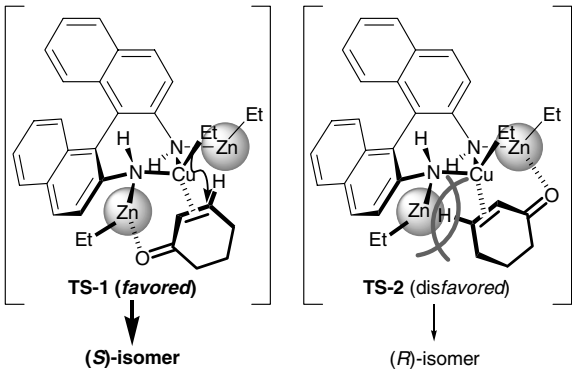

Figure 3. Proposed transition states.

postulated intermediate **17** before carbon–carbon bond-formation (Fig. 2). In the transition states, *si*-face attack (**TS-1**) should be favored to avoid steric repulsion between substrate (**1**) and the *N*-ZnEt moiety (**TS-2**) (Fig. 3). Eventually, (*S*)-product can be obtained with release from the catalyst along with the regeneration of **16** by Et_2Zn.

In summary, the enantioselective conjugate addition of dialkylzinc to cyclic enones was achieved by using chiral binaphthyldiamine–copper(I) catalysts. Sterically less-hindered C_2-symmetric chiral binaphthyldiamine was easily modified in two primary amino groups, and the expected sterically demanding $[RZn(II)]_2$-binaphthyldiamine–Cu(I) complexes were formed via deprotonation by R_2Zn in situ. The reaction of 2-cyclohexenone with Et_2Zn proceeded smoothly in the presence of chiral Cu(I) catalyst (5 mol %) and achiral 2,6-diphenylaniline (10 mol %) at 0 °C for 1.5 h, and the corresponding Et-adduct was obtained with up to 76% ee in 95% yield. Further studies are in progress toward other catalytic enantioselective reactions with the modified catalysts by organometallic reagents in situ.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.061.

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8. The combined use of **1** and **6** or **2** and **6** was not effective, and **2** was obtained in poor yield and low enantioselectivities (<10% ee).
9. It is noted that the reaction between **1** and Et_2Zn with 5 mol % of CuCl and 10 mol % of **6** did not proceed at 0 °C for 5 h.
10. Representative reaction procedure (Table 2, entry 4): $CuCl_2$ (6.7 mg, 0.05 mmol) and (*S*)-binaphthyldiamine (**5**) (15.6 mg, 0.055 mmol) were mixed in a pyrex Schlenk tube under nitrogen atmosphere. To the mixture was added Et_2Zn (1.36 mL of 1.1 M solution in toluene) at 0 °C, and this solution was stirred for 30 min at that temperature. Then 2,6-diphenylaniline (**6**) (24.5 mg, 0.10 mmol) was added, and the mixture was stirred for 15 min at 0 °C. Then, 2-cyclohexenone (**1**) (96.1 mg, 1.0 mmol) was added. The resulting mixture was stirred at 0 °C for 1.5 h by monitoring with TLC. After hydrolysis with 10 mL of saturated NH_4Cl aqueous solution, the product was extracted with ether (10 mL × 3). The combined extracts were washed by brine (10 mL) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the crude product was purified by neutral silica gel column chromatography (eluent: pentane/Et_2O), to give the desired products (**2**) in 95% yield (119.9 mg). The enantiomeric purity was determined by GC on chiral column (γ-TA) (76% ee, *S*).
11. Et_2Zn (1.1 M solution in toluene) and *n*-Bu_2Zn (1.0 M solution in heptane) were used in the reaction without further solvents. Similar procedures using two different organozinc reagents in the enantioselective phenylation of aldehydes have been reported (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465; Also see reviews: (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454; (c) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127.
12. Enantioselective conjugate addition of dialkylzinc to acyclic enones, such as chalcone and diethyl 2-ethylidenemalonate, catalyzed by Cu(II)/**5**/**6** system gave the corresponding products in low yields with low enantioselectivities (<20% ee).
13. Further addition of Et_2Zn (total >3 equiv) to this mixture did not gave additional ethane gas. Therefore, tri-substitutions or tetra-substitutions including $ArN(ZnEt)_2$ did not occur.