

# Practical Asymmetric Henry Reaction Catalyzed by a Chiral Diamine-Cu(OAc)<sub>2</sub> Complex

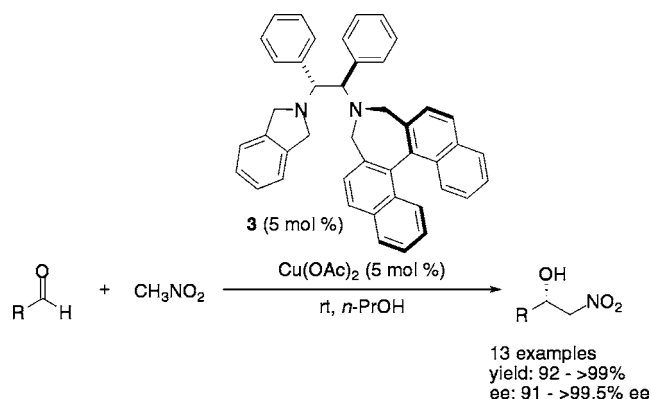
Takayoshi Arai,\* Masahiko Watanabe, and Akira Yanagisawa

Department of Chemistry, Graduate School of Science, Chiba University,  
Inage 263-8522, Japan

tarai@faculty.chiba-u.jp

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## ABSTRACT



The chiral diamine ligand **3** was designed and synthesized from (*R,R*)-1,2-diphenylethylenediamine, (*S*)-2,2'-dibromomethyl-1,1'-binaphthalene, and *o*-xylylene dibromide. The resulting 3-Cu(OAc)<sub>2</sub> complex was a highly efficient catalyst for the Henry reaction, giving the various nitroaldols with over 90% ee (up to >99%). The reaction was performed in *n*-propyl alcohol at room temperature, and the Henry adducts were produced in high yield with excellent enantiomeric excess; these attributes are desirable in a catalyst for practical use.

The requirements for a useful chiral catalyst are that it must provide only the target product, in high yield and excellent enantiomeric excess, and must have broad general application. If the catalyst is to be usefully applied in industry, it is desirable that the reaction can be carried out without strict temperature control or special care for air-sensitive reagents.<sup>1</sup> From the point of view of protecting the environment, it is particularly essential to minimize waste in synthetic processes.<sup>2</sup> These requirements must be taken into account when researching and developing new chiral ligands.

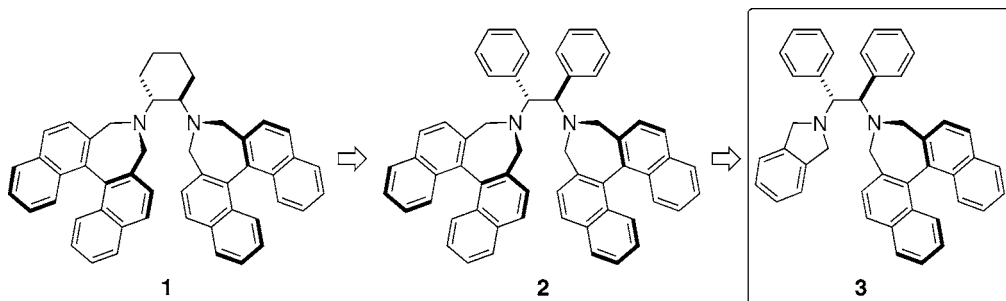
The Henry (nitroaldol) reaction is one of the most atom-economical carbon–carbon bond-forming reactions in synthetic chemistry. The resulting  $\beta$ -hydroxy nitro compounds

have been used in various beneficial transformations to provide chiral  $\beta$ -amino alcohols and  $\alpha$ -hydroxy carboxylic acids. To provide the raw materials for research into these biologically significant building blocks, attention has recently been focused on the development of catalytic, asymmetric versions of the Henry reaction.<sup>3</sup> The most impressive work of heterobimetallic lanthanoid catalysis<sup>4a</sup> has stimulated the successful development of various types of asymmetric catalyst.<sup>4</sup> Among them, the Cu-catalyzed Henry reaction performed at room temperature has received much attention in recent years.<sup>4b,d,j–m</sup>

(3) (a) Shibasaki, M.; Gröger, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. III, pp 1075–1090. (b) Shibasaki, M.; Göger, H.; Kanai, M. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, Germany, 2004; pp 131–133. (c) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.

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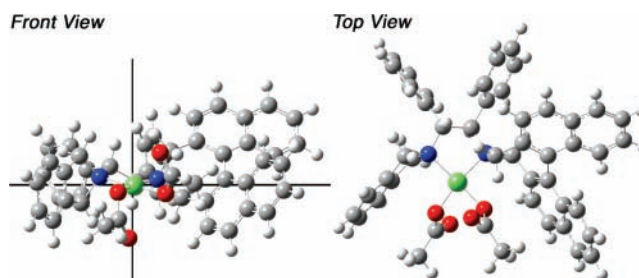
**Figure 1.** Designer chiral diamine **3**.

We previously reported a facile enantioselective Henry reaction catalyzed by a  $C_2$ -symmetric diamine (**1**)-Cu(I) catalyst.<sup>5</sup> The reaction of *o*-nitrobenzaldehyde with nitromethane was catalyzed by **1**-CuCl to provide the corresponding adduct in >99% yield with 90% ee (20 h, rt). However, there are some practical difficulties associated with the use of **1**-CuCl as a catalyst, such as the presence of a hygroscopic cyclohexyl-1,2-diamine structure in **1**. The second drawback of the previously developed catalyst is the use of an air-sensitive Cu(I) salt. A Cu(II)-catalyzed Henry reaction developed by Jørgensen and Evans has apparent advantages for practical application.<sup>4b,d</sup> According to the reaction mechanism proposed by Evans,<sup>4d</sup> the weakly Lewis acidic metal complex bearing a moderately basic charged counteranion would work for the generation of a nitronate species. We envisioned that the tertiary diamine ligands having relatively strong basicity and coordination ability would influence the catalytic activity in the application to the Cu(OAc)<sub>2</sub> catalysis. Here we report a practical and useful Henry reaction catalyzed by the new chiral diamine-Cu(OAc)<sub>2</sub> complex.

The current study was started from the use of an analogue **2** containing more manageable 1,2-diphenylethylenediamine; however, the **2**-CuCl-catalyzed reaction of *o*-nitrobenzaldehyde with nitromethane unfortunately gave the desired product in 98% yield with only 66% ee (24 h, rt); the yield with a Cu(OAc)<sub>2</sub> catalyst was 73%, with 58% ee (30 h, rt). It was assumed that the phenyl groups of the 1,2-diphenylethylenediamine caused steric repulsion of the binaphthyl-

derived azepine ring, resulting in narrowing of the reaction sphere of the **2**-Cu(OAc)<sub>2</sub> catalyst. On the basis of the structure–activity relationship described above, we designed the new chiral diamine ligand **3**, which incorporates a 1,2-diphenylethylenediamine structure, for Cu(OAc)<sub>2</sub> catalysis (Figure 1).

In the design of the new ligand, one of the binaphthyl azepine rings was replaced by a simple isoindoline to obtain a suitable reaction sphere (Figure 1). Computational calculations with the Gaussian 03 program are presented in Figure 2.



**Figure 2.** **3**-Cu(OAc)<sub>2</sub> complex (Cu: green; N: blue; O: red; C: gray; H: white).

Optimization of geometry with the B3LYP/6-31G\* method revealed that the resulting **3**-Cu(OAc)<sub>2</sub> complex should possess a constrained reaction sphere, allowing highly stereocontrolled catalysis by the Cu atom. The new isoindoline ring stands perpendicularly to the square-planar structure of the tetracoordinated Cu(II) complex (see Top View in Figure 2).

The synthesis of **3** was readily carried out by a method analogous to the synthesis of **1**, using (*R,R*)-1,2-diphenylethylenediamine, (*S*)-2,2'-dibromomethyl-1,1'-binaphthalene, and *o*-xylylene dibromide (see the experimental details in the Supporting Information). Compared with the synthesis of **1**, the method used for **3** allowed a reduction in the required amount of chiral (*S*)-2,2'-dibromomethyl-1,1'-binaphthalene, which requires a three-step synthesis from (*S*)-binaphthol.

The newly developed chiral diamine ligand **3** was utilized in the Cu(OAc)<sub>2</sub>-catalyzed Henry reaction of *o*-nitrobenzal-

(4) Selected examples of an enantioselective Henry reaction: (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Christensen, C.; Juhl, C.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222. (c) Trost, B.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861. (d) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692. (e) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2004**, 33, 614. (f) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881. (g) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167. (h) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (i) Mandal, T.; Samanta, S.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 943. (j) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007**, *13*, 829. (k) Ma, K.; You, J. *Chem. Eur. J.* **2007**, *13*, 1863. (l) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616. (m) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151. See also refs 5–7.

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dehyde with nitromethane. We were delighted to find that the presence of 5 mol % of the **3**-Cu(OAc)<sub>2</sub> complex was sufficient to provide the adduct in >99% yield with 98% ee at room temperature (Table 1, entry 1). Because the catalyst

**Table 1.** Enantioselective Henry Reaction

| $\text{R}-\text{CHO} + \text{CH}_3\text{NO}_2 \xrightarrow[n\text{-PrOH, rt}]{\text{3-Cu(OAc)}_2 \text{ (5 mol \%)}} \text{R}-\text{CH(OH)}-\text{NO}_2$ |   |          |                        |        |
|--|---|----------|------------------------|--------|
| entry  | R   | time (h) | yield (%) <sup>b</sup> | ee (%) |
| 1  | <i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>       | 24       | >99                    | 98     |
| 2  | <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>       | 24       | >99                    | 93     |
| 3 <sup>a</sup>   | C <sub>6</sub> H <sub>5</sub>                                 | 120      | 94                     | 91     |
| 4  | <i>o</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>      | 72       | >99                    | 95     |
| 5  | BnOCH <sub>2</sub>  | 48       | >99                    | 95     |
| 6  | C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub> | 48       | 99                     | >99.5  |
| 7  | (CH <sub>3</sub> ) <sub>2</sub> CH                            | 48       | 99                     | 95     |
| 8  | (CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>             | 48       | >99                    | 94     |
| 9  | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>               | 48       | 95                     | 93     |
| 10   | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>               | 48       | 95                     | 93     |
| 11   | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>               | 48       | 94                     | 93     |
| 12   | (CH <sub>3</sub> ) <sub>3</sub> C                             | 48       | 92                     | 93     |
| 13   | <i>c</i> -C <sub>6</sub> H <sub>11</sub>                      | 48       | 96                     | 97     |

<sup>a</sup> The reaction was carried out at 0 °C. <sup>b</sup> Isolated yield.

was prepared with Cu(OAc)<sub>2</sub>·H<sub>2</sub>O, the reaction is apparently moisture proof. Interestingly, the corresponding **3**-CuCl catalyst provided the adduct in 31% yield with only 63% ee (72 h, rt). The broad generality of the **3**-Cu(OAc)<sub>2</sub>-catalyzed enantioselective Henry reaction is illustrated in Table 1.

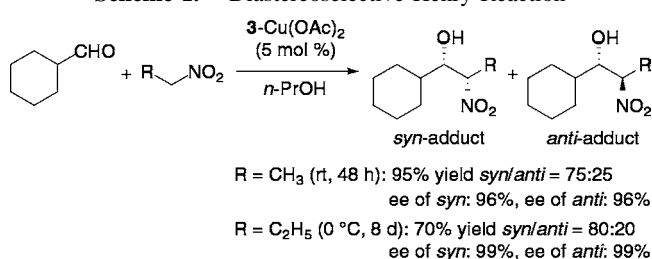
The reaction was suitable not only for electron-deficient substrates (entries 1 and 2), but also for *o*-methoxybenzaldehyde, which was converted to the corresponding adduct in >99% yield with 95% ee (entry 4). For simple benzaldehyde, over 90% ee was obtained when the reaction was carried out at 0 °C (entry 3). Moreover, aliphatic aldehydes were smoothly converted to nitroaldols in good yields with quite high ee (entries 5–13). In particular, the reaction of hydrocinnamaldehyde provided the adduct quantitatively with >99.5% ee (entry 6).  $\alpha$ -Benzyloxy acetoaldehyde was also applicable in the current Henry reaction, providing the corresponding adduct with 95% ee (entry 5). The results in Table 1 demonstrate the practical utility of the **3**-Cu(OAc)<sub>2</sub> catalyst.

In all reactions examined in Table 1, the product was obtained in the (*S*)-form, generated by nucleophilic attack of nitromethane at the *re*-face of the aldehyde. On the basis of the Evans' report, the acetate anion would act as a weak base to generate a nitronate.<sup>4d</sup> Then, in the most reactive transition states, the nitronate stands at the position of the apical site, and the aldehyde would coordinate to the more Lewis acidic equatorial site. In the equatorial coordination, the site adjacent to the isoindoline ring is the most appropriate for reducing the steric repulsion, and the bulky side chain of the aldehyde would be released to a vacant space over the small isoindoline ring. Subsequently, the generated

nitronate would cause nucleophilic addition to the activated aldehyde, giving the (*S*)-nitroaldol adduct.

The catalyst was also applied to the diastereoselective Henry reaction.<sup>6,7</sup> As shown in Scheme 1, the reaction

**Scheme 1.** Diastereoselective Henry Reaction



proceeded in *syn*-selective manner, and both diastereomers were obtained with excellent enantiomeric excess.

This *syn*-selectivity was in contrast with the results of Jørgensen's bis(oxazoline)-Cu(OTf)<sub>2</sub>-catalyzed *anti*-selective Henry reaction with silyl nitronates.<sup>7b</sup> When the reaction with 1-nitropropane was carried out at 0 °C, enantiomeric excesses of 99% were achieved for both diastereomers, although a prolonged reaction time was required. These results indicate that the face of the carbonyl functionality of aldehydes is reliably selected by the chiral reaction sphere produced by **3**-Cu(OAc)<sub>2</sub>.

In conclusion, we designed and developed a new chiral diamine ligand **3**. The ligand can be readily prepared by using a cheap building block, air-stable Cu(OAc)<sub>2</sub>; the reaction is performed in *n*-propyl alcohol at room temperature; and the resulting Henry adducts are produced in high yield with excellent enantiomeric excess. All these points contribute to the practicality and usefulness of this catalytic system.

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**Supporting Information Available:** Experimental procedure and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) *Anti*-selective Henry reaction with silyl nitronates: (a) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (b) Risgaard, T.; Gothelf, K. V.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153.