

and valuable organic compounds.<sup>[1]</sup> The importance of this research topic has stimulated chemists worldwide to develop numerous methods of asymmetric catalysis, although the process of developing new catalysts involves tedious effort, even when modern methods are used. One way to overcome the time-consuming aspect of the process would be to use the technology of combinatorial chemistry for the discovery and optimization of catalysts.<sup>[2]</sup>

For the efficient exploration of novel asymmetric catalysts with the combinatorial approach, a convenient technology of high-throughput screening (HTS) is required for the analysis of both catalytic activity (chemical yield) and enantiomeric excess. Although recent remarkable studies<sup>[3]</sup> have resulted in some useful HTS systems, a more powerful analytical system is required in pursuit of wide application, easy handling, and practical use in broad asymmetric catalysis.<sup>[4]</sup> Herein, a new HTS system has been developed by coupling circular dichroism (CD) detection and solid-phase reactions (Figure 1). The

## Combinatorial Chemistry

DOI: 10.1002/ange.200602255

### Direct Monitoring of the Asymmetric Induction of Solid-Phase Catalysis Using Circular Dichroism: Diamine–Cu<sup>1</sup>-Catalyzed Asymmetric Henry Reaction\*\*

Takayoshi Arai,\* Masahiko Watanabe,  
Akitsugu Fujiwara, Naota Yokoyama, and  
Akira Yanagisawa

The catalytic synthesis of chiral molecules is of crucial importance in fine chemistry to ensure the supply of useful

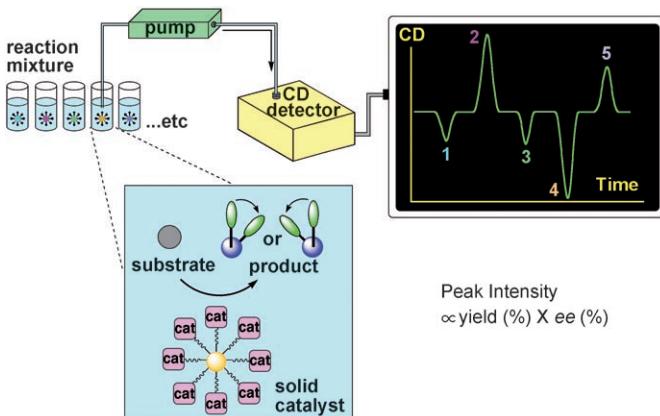


Figure 1. A new high-throughput screening system for analyzing asymmetric induction.

origin of chirality is restricted in this system by the solid support. When the catalytic asymmetric reaction is examined by using an achiral substrate in solution, no asymmetric induction occurs; therefore, when the solution is analyzed by CD, no significant signal should be detected. Because any two enantiomers have exactly opposite CD values at each wavelength, the CD detector could analyze a single appropriate wavelength and record a positive or negative signal that corresponds to the amount of excess enantiomer.

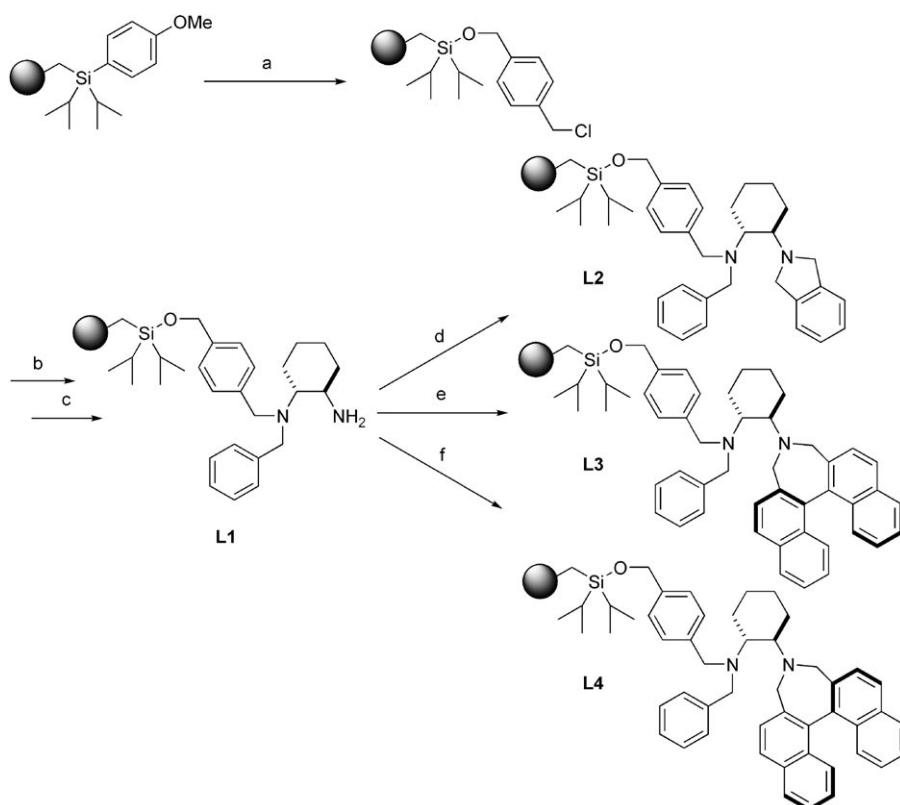
We synthesized chiral amines on polystyrene beads, as outlined in Scheme 1, to demonstrate the newly constructed HTS system. After the introduction of 4-hydroxymethylbenzyl chloride onto the polystyrene beads through formation of a Si–O linkage, the chloromethyl functionality was substituted by 1,3-dimethyl-5-acetylbarbituric acid (DAB)-protected *N*-benzylcyclohexyldiamine.<sup>[5]</sup> Deprotection of the DAB group with hydrazine gave the diamine ligand **L1**, and further alkylation of the terminal primary amine gave the corresponding ligands **L2–L4**. Conversion and product purity were analyzed at each synthetic step by <sup>1</sup>H NMR spectroscopic analysis of the released products.<sup>[6]</sup>

[\*] Prof. Dr. T. Arai, Prof. Dr. A. Yanagisawa  
Department of Chemistry  
Faculty of Science, Chiba University  
Inage, Chiba 263-8522 (Japan)  
Fax: (+81) 43-290-2889  
E-mail: tarai@faculty.chiba-u.jp

M. Watanabe, A. Fujiwara, N. Yokoyama  
Graduate School of Science and Technology  
Chiba University  
Inage, Chiba 263-8522 (Japan)

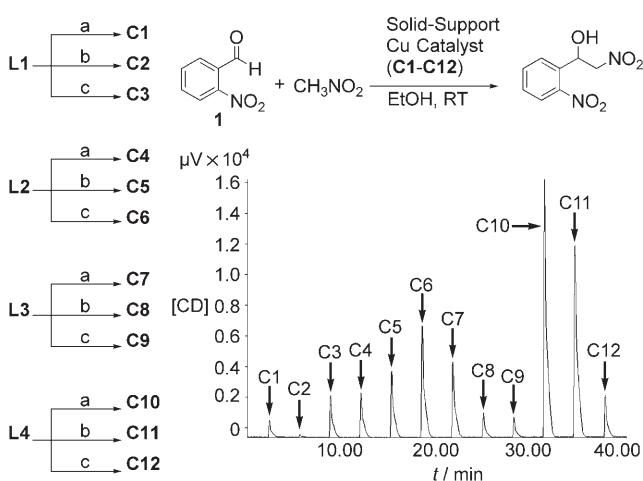
[\*\*] This work was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture and Technology of the Japanese Government and the Industrial Technology Research Grant Program in 2006 from the New Energy and Industrial Technology Development Organization (NEDO) of Japan.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



**Scheme 1.** Synthesis of polymer-supported chiral ligands. a) TfOH, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ; then 4-chloromethylbenzyl alcohol; b) DAB-protected chiral diamine, 2,6-lutidine, NaI, DMF; c)  $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ , THF; d–f) corresponding alkyl bromide,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ . DMF = *N,N*-dimethylformamide; TfOH = trifluoromethanesulfonic acid.

With the polymer-supported chiral diamine ligands **L1–L4** in hand, the desired Cu catalysts **C1–C12** were prepared on a solid support using three kinds of Cu salts (Figure 2). In all cases, the polystyrene beads turned green, which suggested the formation of Cu–diamine complexes. Among the several types of asymmetric reaction examined, the Henry reaction



**Figure 2.** Catalytic asymmetric Henry reaction. The CD was operated at 254 nm. a)  $\text{CuCl}$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ; b)  $\text{CuCl}_2$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{Cu}(\text{OAc})_2$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ .

was found to be catalyzed by the polymer-supported diamine–Cu complexes.<sup>[7,8]</sup> After carrying out the asymmetric Henry reaction for 36 hours, each reaction mixture was analyzed by continuous injection to obtain the profile shown in Figure 2 (see the experimental details in the Supporting Information).

The detectable compounds in the reaction mixtures were the targeted product and the starting material. Despite the catalytic success of  $\text{Cu}(\text{OAc})_2$ <sup>[7b]</sup> in conjunction with **L1** and **L2**, the **L4**– $\text{CuCl}$  catalyst (namely, **C10**) was found to be the most effective for this reaction. The positive intensity of the signal operated at 254 nm indicates the formation of Henry adducts enriched with the *S* isomer in the reaction. All the reaction mixtures were purified by the conventional method to confirm the results shown in Figure 2; the chemical yields were determined using column chromatography on silica gel, and the enantiomeric excess was analyzed with chiral HPLC. The results of the more time-consuming analysis are summarized in Table 1. An analysis of the **C10**-catalyzed Henry reaction by using conventional methods showed

a chemical yield of over 99% with 68% *ee*. It is noteworthy that the CD signals obtained demonstrated considerable sensitivity, even with low levels of enantiomeric excess.

A reaction with a good yield but with low enantiomeric excess should result in a CD signal of low intensity. In the same manner, when catalytic activity is low, thus resulting in a low yield, the intensity of the CD signal is low, even with high enantiomeric excess. The CD signal is of maximum intensity only when both the chemical yield and enantiomeric excess are at their highest. A precise expression of CD signal

**Table 1:** Chemical yields and *ee* values for the Cu-catalyzed asymmetric Henry reaction.

Entry	Catalyst	Yield of <b>1</b> [%]	<i>ee</i> [%]	ACY [%]
1	<b>C1</b>	18	3	7
2	<b>C2</b>	trace	–	0
3	<b>C3</b>	52	20	32
4	<b>C4</b>	15	59	30
5	<b>C5</b>	48	6	17
6	<b>C6</b>	95	32	55
7	<b>C7</b>	91	3	17
8	<b>C8</b>	16	7	11
9	<b>C9</b>	63	5	18
10	<b>C10</b>	>99	68	83
11	<b>C11</b>	50	68	58
12	<b>C12</b>	66	5	18

intensity is represented by Equation (1), in which the square root of the chemical yield multiplied by the enantiomeric excess is defined as the asymmetric conversion yield (ACY).

$$\text{ACY} [\%] = \sqrt{\text{yield} [\%] \times ee [\%]} \quad (1)$$

The most efficient asymmetric catalyst should give the target product in good yield with high enantiomeric excess. This principle is of fundamental importance, although it has not so far been clearly stated. Our HTS system allows us to determine the catalysts that meet the criterion of this new definition of ACY. The **C10**-catalyzed Henry reaction recorded equates to an ACY value of 82%.

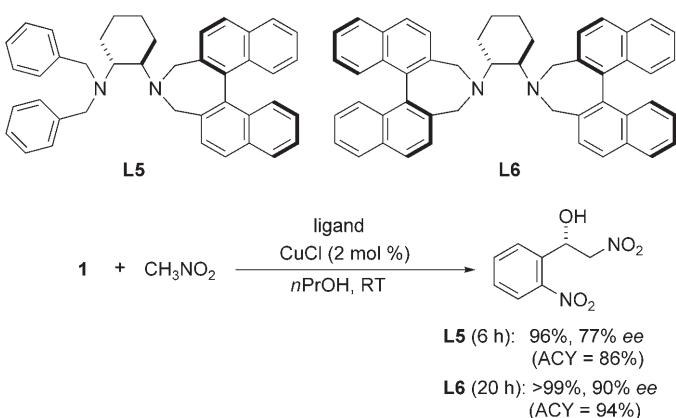
Although Mikami, Ding, and Reetz recently reported pioneering studies on the application of CD-HPLC in a new HTS system, their system requires the use of achiral HPLC to separate the product from the chiral ligands.<sup>[9]</sup> The system currently under discussion does not require any pretreatment of the sample (e.g., quenching) and time-consuming purification, and the efficiency of asymmetric induction can be clearly monitored without chromatographic separation. The success of continuous introduction of the reaction mixtures into the CD detector for the ready comparison of the relative intensity of CD signals is remarkable.

Inspired by the success of exploring the promising asymmetric catalyst, the well-defined ligand **L5** was then prepared by solution synthesis. The **L5**–CuCl complex was revealed as an efficient catalyst that provided the Henry adduct in quantitative yield with 65% *ee* at room temperature. When the reaction was carried out in *n*PrOH, the use of only 2 mol % catalyst was enough to promote the reaction in 96% yield, and the enantiomeric excess of the adduct was improved to 77% *ee* (ACY = 86 %).

Furthermore, with the employment of the  $C_2$ -symmetric concept for decreasing the number of catalyst–substrate interactions, which consequently removes competing reaction pathways, ligand **L6** was prepared as a crystalline compound.<sup>[10]</sup> Finally, the  $C_2$ -symmetric **L6**–CuCl catalyst provided the Henry adduct in quantitative yield with up to 90% *ee* (ACY = 94%). This reaction is the first success of an asymmetric Henry reaction catalyzed by diamine–Cu<sup>I</sup> (Scheme 2).

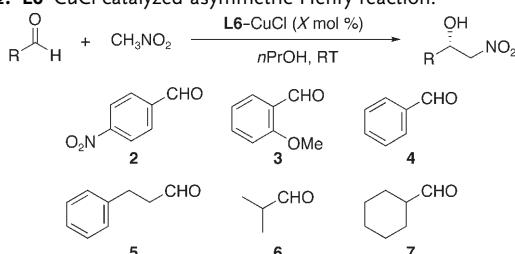
The scope of the asymmetric Henry reaction was studied on various aldehydes using the well-defined **L6**–CuCl catalyst. As summarized in Table 2, high *ee* values were obtained even at room temperature for various aromatic aldehydes. The reaction was promoted even in the presence of 1 mol % catalyst and gave the nitroaldol product with the highest enantiomeric excess of 92 % (Table 2, entry 2). Not only electron-deficient substrates (Table 2, entries 1–3), but *o*-methoxybenzaldehyde was also converted into the corresponding adduct in 82 % yield with 90 % *ee* (Table 2, entry 4). Moreover, the aliphatic aldehydes were smoothly converted into the nitroaldols in good yield and with high enantiomeric excess (Table 2, entries 6–8).

In conclusion, our new HTS system analyzes asymmetric induction in catalytic enantioselective synthesis by direct



**Scheme 2.** Catalytic asymmetric Henry reaction using the well-defined solution-phase catalyst.

Table 2: L6–CuCl-catalyzed asymmetric Henry reaction.



Entry	Aldehyde	X [mol %]	t [h]	Yield [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	<b>1</b>	2	20	>99	90
2	<b>1</b>	1	24	66	92
3	<b>2</b>	3	16	>99	80
4	<b>3</b>	5	96	82	90
5	<b>4</b>	5	48	66	86
6	<b>5</b>	5	48	85	86
7	<b>6</b>	5	48	>99	86
8	<b>7</b>	2	120	99	90

[a] Yield of the isolated product. [b] The enantioselectivity was determined by HPLC analysis with a Chiralcel OD-H column.<sup>[7b]</sup>

introduction of the reaction mixture into a CD detector. In this new HTS system, the Henry reaction catalyzed by the chiral diamine–Cu<sup>I</sup> complex was successfully developed. It is of note that this achievement is impossible to realize without use of the HTS system. This direct monitoring system is of obvious application to the ongoing search for outstanding catalysts among the many contenders and also provides an efficient method of analyzing catalytic asymmetric reactions.

Received: June 6, 2006

Published online: August 9, 2006

**Keywords:** asymmetric catalysis · circular dichroism · combinatorial chemistry · high-throughput screening · solid-phase synthesis

[1] Recent representative books on asymmetric catalysis: a) *Comprehensive Asymmetric Catalysis, Vol. I-III* (Eds.: E. N. Jacobsen, M. S. Stenzel, and K. M. Smith, Wiley-Interscience, New York, 2004).

sen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; b) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley-VCH, New York, **2000**.

[2] Recent representative books on combinatorial chemistry:  
a) *Combinatorial Chemistry* (Ed.: H. Fenniri), Oxford University Press, Oxford, **2000**; b) *Solid-Phase Synthesis and Combinatorial Technologies* (Ed.: P. Seneci), Wiley-Interscience, New York, **2000**; c) *Handbook of Combinatorial Chemistry, Vol. 1 & 2* (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**.

[3] a) M. A. Evans, J. P. Morken, *J. Am. Chem. Soc.* **2002**, *124*, 9020–9021; b) F. Taran, C. Gauchet, B. Mohar, S. Meunier, A. Valleix, P. Y. Renard, C. Crémignon, J. Grassi, A. Wagner, C. Mioskowski, *Angew. Chem.* **2002**, *114*, 132–135; *Angew. Chem. Int. Ed.* **2002**, *41*, 124–127; c) M. T. Reetz, M. H. Becker, H. W. Klein, D. Stöckigt, *Angew. Chem.* **1999**, *111*, 1872–1875; *Angew. Chem. Int. Ed.* **1999**, *38*, 1758–1761.

[4] a) M. T. Reetz, *Angew. Chem.* **2002**, *114*, 1391–1394; *Angew. Chem. Int. Ed.* **2002**, *41*, 1335–1338; b) M. Tsukamoto, H. B. Kagan, *Adv. Synth. Catal.* **2002**, *344*, 453–463; c) M. T. Reetz, *Angew. Chem.* **2001**, *113*, 292–320; *Angew. Chem. Int. Ed.* **2001**, *40*, 284–310.

[5] E. T. da Silva, E. L. S. Lima, *Tetrahedron Lett.* **2003**, *44*, 3621–3624.

[6] J. A. Tallarico, K. M. Depew, H. E. Pelish, N. J. Westwood, C. W. Lindsley, M. D. Shair, S. L. Schreiber, M. A. Foley, *J. Comb. Chem.* **2001**, *3*, 312–318.

[7] Cu<sup>II</sup>-catalyzed asymmetric Henry reaction: a) C. Christensen, K. Juhl, K. A. Jørgensen, *Chem. Commun.* **2001**, 2222–2223; b) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; c) S.-F. Lu, D.-M. Du, S.-W. Zhang, J. Xu, *Tetrahedron: Asymmetry* **2004**, *15*, 3433–3441; d) C. Gan, G. Lai, Z. Zhang, Z. Wang, M.-M. Zhou, *Tetrahedron: Asymmetry* **2006**, *17*, 725–728.

[8] Selected examples of a catalytic asymmetric Henry reaction:  
a) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; b) B. M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889–891; *Angew. Chem. Int. Ed.* **2002**, *41*, 861–863; c) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055; d) Y. Kogami, T. Nakajima, T. Ashizawa, S. Kezuka, T. Ikeno, T. Yamada, *Chem. Lett.* **2004**, *33*, 614–615; e) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem.* **2005**, *117*, 3949–3952; *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884; f) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 943–945; *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.

[9] a) K. Ding, A. Ishii, K. Mikami, *Angew. Chem.* **1999**, *111*, 519–523; *Angew. Chem. Int. Ed.* **1999**, *38*, 497–501; b) K. Mikami, R. Angelaud, K. Ding, A. Ishii, A. Tanaka, N. Sawada, K. Kudo, M. Senda, *Chem. Eur. J.* **2001**, *7*, 730–737; c) M. T. Reetz, K. M. Kühlung, H. Hinrichs, A. Deege, *Chirality* **2000**, *12*, 479–482; d) J. Long, J. Hu, X. Shen, B. Ji, K. Ding, *J. Am. Chem. Soc.* **2002**, *124*, 10–11.

[10] J.-L. Vasse, R. Stranne, R. Zalubovskis, C. Gayet, C. Moberg, *J. Org. Chem.* **2003**, *68*, 3258–3270.