Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 11, pp. 1717–1719, 1997

Printed in Great Britain
PII: S0957-4166(97)00183-3
0957-4166/97 $17.00 + 0.00

# One-pot asymmetric autocatalytic reaction with remarkable amplification of enantiomeric excess

Takanori Shibata, Tadakatsu Hayase, Jun Yamamoto and Kenso Soai *

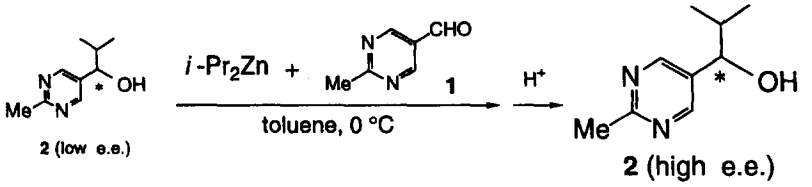
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

***Abstract:*** A trace amount (*ca.* 3 mg) of 2-methylpyrimidyl alkanol with only a slight enantiomeric excess (0.2–0.3% e.e.) was auto-multiplied with dramatic amplification of enantiomeric excess (up to *ca.* 90% e.e.) in one-pot asymmetric autocatalytic reaction using diisopropylzinc and 2-methylpyrimidine-5-carbaldehyde. © 1997 Elsevier Science Ltd

Asymmetric autocatalytic reactions,[1] where a chiral catalyst and the product have the same structure and configuration,[2] are superior to the conventional asymmetric reactions because a trace amount of a chiral source produces itself without the assistance of any other chiral auxiliary and the separation of the product from the catalyst is not needed.[3] We recently reported asymmetric autocatalytic reactions[4] with amplification of enantiomeric excess (e.e.):[5,6] 5-pyrimidyl alkanol with 2% e.e. automultiplied to provide itself with amplified e.e. of 10% in the enantioselective autocatalytic alkylation of pyrimidine-5-carbaldehyde. But in order to utilize the product of one round as the reactant for the next, the stepwise processes of quenching the reaction and purification of the product were inevitable.

This paper discloses a *one-pot asymmetric autocatalytic reaction* with a much more dramatic increase of e.e. using 2-methyl substituted pyrimidyl alkanol as an autocatalyst: A slight imbalance (*R*-:*S*-isomer=50.1:49.9) of chirality in 2-methyl-1-(2-methyl-5-pyrimidyl)propan-1-ol **2** becomes overwhelming in one flask single by the portionwise additions of a pair of diisopropylzinc and 2-methylpyrimidine-5-carbaldehyde **1** without quenching.

An enantioselective autocatalytic isopropylation of aldehyde **1** (0.12 mmol) was examined in the presence of (*R*)-enriched **2** (2.8 mg, 6.4% e.e.) as an autocatalyst at the 0.12 mmol reaction scale, followed by two additions of a pair of *i*-$Pr_2Zn$ and aldehyde **1** at 0.34 and 1.36 mmol reaction scale respectively (Table 1). As a result, 252.9 mg of (*R*)-pyrimidyl alkanol **2** [90 times as much as asymmetric autocatalyst **2** (2.8 mg)] was obtained in 83.2% with a drastically amplified e.e. of 92.1% (Entry 1).[7] The one-pot addition of *i*-$Pr_2Zn$ and aldehyde **1** proves to be effective for this asymmetric autocatalytic system.




Next, an asymmetric autocatalytic amplification using an autocatalyst with extremely low e.e. was examined by the three additions as above; 2.8 mg of (*R*)-**2** with 0.18% e.e. ($[\alpha]_{405}^{26}$ +0.29 (*c* 7.90, $CHCl_3$)) was used as an autocatalyst (Entry 3). After the additions of a pair of *i*-$Pr_2Zn$ and aldehyde **1**, (*R*)-pyrimidyl alcohol **2** was obtained in 65.8% e.e. (204.3 mg). In the same procedure, alkanol **2** with the opposite configuration [(*S*)-isomer] with 0.28% e.e. ($[\alpha]_{405}^{26}$ −0.46 (*c* 4.38, $CHCl_3$)) also

* Corresponding author. Email: ksoai@ch.kagu.sut.ac.jp

**Table 1**. One-pot asymmetric autocatalytic reaction using pyrimidyl alkanol **2**

| Entry | Catalyst 2 | | Obtained alcohol 2 | | |
|---|---|---|---|---|---|
| | Amount / mg | E.e. / % | Amount / mg | Yield / % | E.e. / % |
| 1[a] | 2.8 | 6.4 (*R*) | 252.9 | 83.2 | 92.1 (*R*) |
| 2[b] | 2.7 | 6.4 (*R*) | 54.4 | 72.0 | 60.0 (*R*) |
| 3[c] | 3.3 | 0.18 (*R*) | 297.4 | 84.4 | 83.9 (*R*) |
| 4[c] | 3.2 | 0.28 (*S*) | 323.5 | 92.0 | 87.0 (*S*) |

[a] A pair of *i*-$Pr_2Zn$ and aldehyde **1** was added in three portions (0.12, 0.34, and 1.36 mmol of **1**, respectively).
[b] A pair of *i*-$Pr_2Zn$ and aldehyde **1** was added in two portions (0.10 and 0.34 mmol of **1**).
[c] A pair of *i*-$Pr_2Zn$ and aldehyde **1** was added in three portions (0.10, 0.40, and 1.60 mmol of **1**, respectively).

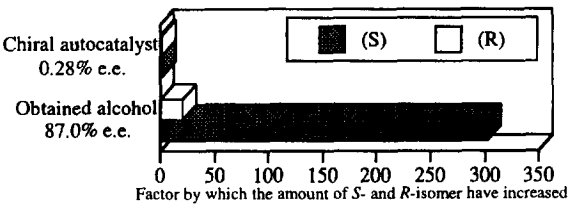



**Figure 1**. Change of the amount of *S*- and *R*-**2** in one-pot reaction (Entry 4).

automultiplied itself along with the enantiomeric amplification to give 323.5 mg (101 times increase in quantity) of alcohol (*S*)-**2** in 87.0% e.e. (Entry 4). As shown in Figure 1, (*S*)-**2** has increased by a factor of 302 times, whereas (*R*)-**2** does by a factor of only 21 times.

The above reaction shows that a trace amount of the chiral alcohol with a slight imbalance of enantiomeric excess is self-replicated to give an enormous amount of alcohol with very high e.e. in one flask only by the addition of a pair of *i*-$Pr_2Zn$ and the aldehyde. This reaction may be called *an asymmetric chemical evolutional automultiplication*. It could be a chemical model for the process, where homochirality of natural amino acids and sugars was achieved.[8]

## Acknowledgements

Financial support by the New Energy and Industrial Technology Development Organization (NEDO) and by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture is gratefully acknowledged.

## References

1. For the implication of asymmetric autocatalysis, see: Wynberg, H. *J. Macromol.-Sci. Chem.*, **1989**, *A26*, 1033–1041.
2. Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.*, **1990**, 982–983.
3. For asymmetric autoinduction, where a chiral source and a product after acid treatment have the same structure and configuration, see Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.*, **1989**, *111*, 7265–7266; ShengJian, L.; Yaozhong, J.; Aiqiao, M.; Guishu, Y. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 885–886; Soai, K.; Inoue, Y.; Takahashi, T.; Shibata, T. *Tetrahedron*, **1996**, *52*, 13355–13362.
4. (a) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.*, **1996**, *118*, 471–472; (b) Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *Chem. Commun.*, **1996**, 751–752.
5. (a) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature*, **1995**, *378*, 767–768; (b) Shibata, T.; Choji, K.; Hayase, T.; Aizu, Y.; Soai, K. *Chem. Commun.*, **1996**, 1235–1236.
6. For *non*-autocatalytic asymmetric amplification, see (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.*, **1986**, *108*, 2353–2357; (b) Oguni, N; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.*, **1988**, *110*, 7877–7878; (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.*,**1989**, *111*, 4028–4036.

7. Typical experimental procedure (Entry 1): After a mixture of a toluene solution (0.6 ml) of alcohol **2** [2.8 mg (0.02 mmol), 6.4% e.e.] and *i*-$Pr_2Zn$ (0.20 ml of 1 M toluene solution, 0.2 mmol) was stirred for 15 min at 0°C, a toluene solution (0.4 ml) of aldehyde **1** (14.1 mg, 0.12 mmol) was added at 0°C. After being stirred for 8 h at 0°C, toluene (1.2 ml) and *i*-$Pr_2Zn$ (0.60 ml of 1 M toluene solution, 0.6 mmol) was added to the reaction mixture at 0°C and the combined mixture was stirred for 15 min, then a toluene solution (1.5 ml) of aldehyde **1** (41.4 mg, 0.34 mmol) was added at 0°C. The reaction mixture was stirred for additional 8 h at 0°C. By the same procedure, toluene (7.6 ml), *i*-$Pr_2Zn$ (2.4 ml of 1 M toluene solution, 2.4 mmol) and a toluene solution (2.2 ml) of aldehyde **1** (165.8 mg, 1.36 mmol) was added and stirred for 8 h. The reaction mixture was quenched and purified by the typical treatment[4a] to give pure **2** (252.9 mg). HPLC analysis of obtained **2** using a chiral column (Daicel Chiralcel OC) showed it had an enantiomeric purity of 92.1% e.e.
8. Bada, J. L. *Nature*, **1995**, *374*, 594–595; Mason, S. *Nature*, **1985**, *314*, 400–401.

*(Received in Japan 15 March 1997; accepted 21 April 1997)*