Communications to the Editor

Highly Enantioselective Catalytic Asymmetric Automultiplication of Chiral Pyrimidyl Alcohol

Takanori Shibata, Hiroshi Morioka, Tadakatsu Hayase, Kaori Choji, and Kenso Soai*

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

Received September 5, 1995

We report here the first highly enantioselective (up to 98.2% ee) catalytic asymmetric automultiplication of chiral pyrimidyl alcohol.

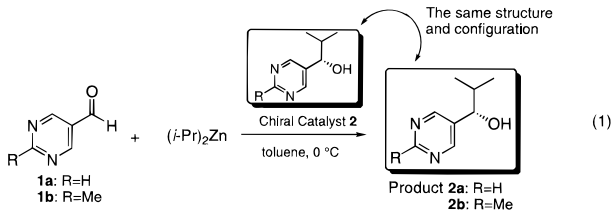
Great progress has been made in enantioselective synthesis.[1] In conventional enantioselective synthesis, regardless of the type (homogeneous, heterogeneous, catalytic, or stoichiometric), the use of chiral auxiliaries with structures different from those of the products as chiral catalysts or ligands is inevitable. Chiral catalysts and ligands are often expensive and can require steps for their preparation. Moreover, separating the catalyst from the products is often very tedious.

In the enantioselective addition of alkyllithium and alkylmagnesium reagents to carbonyl compounds in the presence of chiral ligands, the enantioselectivity varies depending on the molar ratio of the ligands, alkyl metals, and substrates.[2] Furthermore, the chiral products formed during the reaction may affect the enantioselectivity of the reaction.[3]

If a chiral compound acts as a chiral catalyst and produces itself with the same configuration (*i.e.*, catalytic asymmetric automultiplication), the reaction does not require a catalyst with a structure different from that of the product.[4,5] Thus, the catalyst does not need to be separated from the product after the end of the reaction. In addition, catalytic automultiplication of a chiral compound is considered to be the asymmetric version of molecular replication.[6]

With this in mind, we[7] and other groups[8] have investigated the catalytic asymmetric automultiplication of chiral compounds. Although the newly formed compounds have the same configuration as the compounds used as chiral catalysts, early examples of catalytic asymmetric automultiplication reactions have resulted in only moderate enantiomeric excesses. Moreover, the ee's of the products have been much lower than those of the chiral catalysts. Thus, research in this field has remained at a fairly primitive stage. The design of a chiral compound which automultiplies with high enantioselectivity is a challenging problem.

This report describes the highly enantioselective catalytic asymmetric automultiplication reaction of chiral pyrimidyl alcohols in the isopropylation of pyrimidine-5-carbaldehydes (eq 1).



(1)

The asymmetric automultiplication reaction was examined using enantio-riched (*S*)-2-methyl-1-(5-pyrimidyl)-1-propanol (**2a**)[9] as a chiral catalyst. When pyrimidine-5-carbaldehyde (**1a**)[10] (1.0 mmol) was treated with diisopropylzinc (1.2 mmol)[2g,5,11] in the presence of chiral pyrimidyl alcohol **2a** (92.6% ee, 20 mol %) as a catalyst in toluene at 0 °C, 0.83 mmol of (*S*)-**2a** (91.0% ee) was obtained. The recovered catalyst was included in the resulting (*S*)-**2a**. Newly synthesized (*S*)-**2a** with 90.4% ee was formed at a yield of 63% (Table 1, run 1).[12] When (*S*)-**2a** with a higher ee (99.0% ee)[13] was used as a chiral catalyst, the ee of the newly formed **2a** increased to 93.3% ee (run 3). Thus, chiral pyrimidyl alcohol **2a** with high enantiomeric purity regenerates itself in the same configuration with high ee (Figure 1).

It is more surprising that (*S*)-2-methyl-1-(2-methyl-5-pyrimidyl)-1-propanol (**2b**, 20 mol %)[9] with 94.8% ee automultiplied itself *without any loss of ee* during the reaction of 2-methylpyrimidine-5-carbaldehyde (**1b**)[14] and (*i*-Pr)$_2$Zn (run 4). The resulting (*S*)-**2b** (including the catalyst) had an enantiomeric purity of 95.4% ee. **2b** with 94.8% ee automultiplied at a yield of 48% with no loss of its ee (95.7% ee) (run 4).[15] The use of excess (*i*-Pr)$_2$Zn increased the yield of the newly formed **2b** up to 80% with a slight decrease in ee (93.5% ee, run 5). On the

* Correspondence to Prof. Kenso Soai: FAX: 81-3-3235-2214.

(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497.

(2) (a) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455. (b) Soai, K. Ph.D. Dissertation, University of Tokyo, 1979. (c) Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695. (d) Mazaleyrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585. (e) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597. (f) Review: Evans, D. A. *Science* **1988**, *240*, 420. (g) Review: Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

(3) Seebach first noted the role of mixed aggregates which included products: Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(4) For an excellent explanation of the implications of asymmetric automultiplication reactions, see: Wynberg, H. *J. Macromol. Sci., Chem.* **1989**, *A26*, 1033.

(5) Review: Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

(6) For nonasymmetric molecular replication: Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *Acc. Chem. Res.* **1994**, *27*, 198.

(7) (a) Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982. (b) Soai, K.; Hayase, T.; Shimada, C.; Isobe, K. *Tetrahedron: Asymmetry* **1994**, *5*, 789. (c) Soai, K.; Hayase, T.; Takai, K. *Tetrahedron: Asymmetry* **1995**, *6*, 637.

(8) (a) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265. (b) ShengJian, L.; Yaozhong, J.; Aiqiao, M.; Guishu, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 885.

(9) Optically active pyrimidyl alcohols (*S*)-**2a** (77%, 93.4% ee) and **2b** (79%, 94.8% ee) were prepared by the enantioselective isopropylation of the corresponding pyrimidine-5-carbaldehydes (**1a**,**b**) using a catalytic amount of (1*S*,2*R*)-*N*,*N*-dipropylnorephedrine (Soai, K.; Hayase, T.; Takai, K.; Sugiyama, T. *J. Org. Chem.* **1994**, *59*, 7908). The absolute configurations of **2a**,**b** were estimated by the ^{1}H NMR analysis of the corresponding (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters (Otani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092).

(10) Rho, T.; Abuh, Y. F. *Synth. Commun.* **1994**, *24*, 253.

(11) Reviews: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Soai, K.; Hayase, T. *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem., Jpn)* **1995**, *53*, 138.

(12) A preliminary examination of the relation between the reaction time and the yield of the newly formed **2a** using (*S*)-**2a** with 92.6% ee as a chiral catalyst revealed that the reaction rate is accelerated during the initial 2.5 h. Time, yield: 1.0 h, 3.9%; 2.0 h, 19.6%; 2.5 h, 42.0%.

(13) The ee's of **2a**,**b** were increased to 99.0% (**2a**) and 99.9% (**2b**) ee by the recrystallization of their (−)-camphanic esters. Cf.: (a) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169. (b) Lampe, D.; Mills, S. J.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2899.

(14) Gupton, J. T.; Gall, J. E.; Riesinger, S. W.; Smith, S. Q.; Bevirt, K. M.; Sikorski, J. A.; Dahl, M. L.; Arnord, Z. *J. Heterocycl. Chem.* **1991**, *28*, 1281.

(15) The use of (*S*)-**2b** with 89.8% ee as a chiral catalyst afforded (*S*)-**2b** (including catalyst) with 93.1% ee. (Observation by T. Shibata).

0002-7863/96/1518-0471$12.00/0

Table 1. Enantioselective Catalytic Automultiplication of Pyrimidyl Alcohol **2**

run[a]	aldehyde **1**	chiral catalyst (*S*)-**2** (% ee)[b]	time, h	catalyst **2** and product (*S*)-**2**			newly formed product (*S*)-**2**		
					yield, %[c]	ee, %[b]		yield, %	ee, %
1	**1a**	**2a** (92.6)	66	**2a**	83	91.0	**2a**	63	90.4
2	**1a**	**2a** (93.4)	43	**2a**	79	90.8	**2a**	59	89.9
3	**1a**	**2a** (99.0)	40	**2a**	87	94.7	**2a**	67	93.3
4	**1b**	**2b** (94.8)	72	**2b**	68	95.4	**2b**	48	95.7
5[d]	**1b**	**2b** (94.8)	50	**2b**	100	93.8	**2b**	80	93.5
6	**1b**	**2b** (99.9)	108	**2b**	58	98.8	**2b**	38	98.2
7[d]	**1b**	**2b** (99.9)	68	**2b**	103	95.9	**2b**	83	95.0

[a] Unless otherwise noted, molar ratio of **1**:**2**:(i-Pr)$_2$Zn = 1.0:0.2:1.2. [b] Determined by HPLC analysis using a chiral column (Daicel Chiralcel OD). [c] The recovered chiral catalyst (20 mol %) is included. [d] Molar ratio of **1**:**2**:(i-Pr)$_2$Zn = 1.0:0.2:3.2.

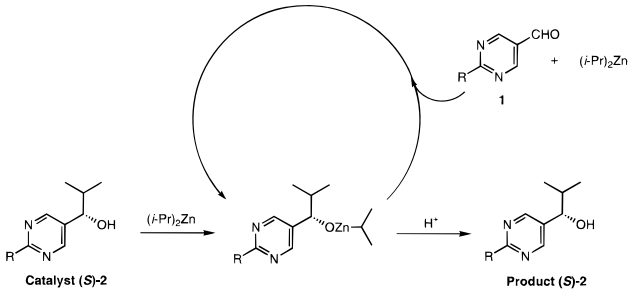


Figure 1. Reaction scheme of the catalytic asymmetric automultiplication of **2**.

other hand, when **2b** with 99.9% ee[13] was used as a catalyst, the ee of the newly formed **2b** reached 98.2% ee (run 6).[16,17]

Typical experimental procedures (Table 1, run 1) were as follows: After a mixture of pyrimidyl alcohol (*S*)-**2a** [30.5 mg (0.20 mmol), 92.6% ee, containing (*S*)-**2a** (29.4 mg), (*R*)-**2a** (1.1 mg)] in toluene (44.8 mL) and (i-Pr)$_2$Zn (1.2 mL of a 1 M toluene solution, 1.2 mmol) was stirred for 30 min at 0 °C, a toluene solution (1.8 mL) of aldehyde **1a** (108.2 mg, 1.00 mmol) was added at 0 °C. The reaction mixture was stirred for 66 h at 0 °C and then quenched by the addition of 1 N hydrochloric acid (5 mL) and saturated aqueous $NaHCO_3$ (15 mL) at 0 °C. The mixture was filtered using Celite, and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude product on silica gel TLC (thin-layer chromatography) gave pyrimidyl alcohol **2a** (126.6 mg), which was a mixture of the newly formed alcohol **2a** and the catalyst alcohol **2a** (30.5 mg). HPLC analysis of the mixture using a chiral column (Daicel Chiralcel OD) showed that it had an enantiomeric purity of 91.0% ee. Therefore, the mixture contained (*S*)-**2a** (120.9 mg) and (*R*)-**2a** (5.7 mg). The amount of newly formed alcohol **2a** was 126.6 − 30.5 = 96.1 mg (0.631 mmol, 63% yield), consisting of major (*S*)-**2a** (120.9 − 29.4 = 91.5 mg) and minor (*R*)-**2a** (5.7 − 1.1 = 4.6 mg). The newly formed (*S*)-enriched alcohol **2a** had an enantiomeric purity of 90.4% ee.

The present enantioselective catalytic automultiplication reaction is unprecedented in two respects. First, the ee of the reaction (up to 98.2% ee) is much higher than those in previously reported automultiplication reactions.[7,8] Second, under certain conditions, the automultiplication proceeds without any loss of the enantiomeric purity of the compound. Thus, once optically active pyrimidyl alcohol **2b** is prepared, it replicates and automultiplies without the assistance of any other chiral auxiliary. The mechanism of this highly enantioselective catalytic asymmetric automultiplication of chiral pyrimidyl alcohol is currently under investigation.

The present automultiplication process provides one of the most direct and resource- and energy-saving methods for asymmetric synthesis.

Acknowledgment. This study was supported in part by a SUT Special Grant for Research Promotion 1994−1995, a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, and the New Energy and Industrial Technology Development Organization (NEDO). We thank S. Sakaguchi, H. Tabira, and S. Tanji for their assistance with experiments.

Supporting Information Available: Experimental details for the synthesis and characterization of **2a,b** and plot of yield of **2a** as a function of reaction time in the automultiplication reaction (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA953066G

(16) Automultiplication of (*S*)-1-(2-ethyl-5-pyrimidyl)-1-propanol (88.5% ee) in the presence of diethylzinc and 2-ethylpyrimidine-5-carbaldehyde was also observed, but with low ee (13.1% ee).

(17) Optically active secondary alcohols with an isopropyl substituent are known. (a) Natural product octalactin A and B: Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511. (b) An active analogue of vitamin D_3: Okamoto, M.; Fujii, T.; Tanaka, T. *Tetrahedron* **1995**, *51*, 5543. Okamoto, M.; Tabe, M.; Fujii, T.; Tanaka, T. *Tetrahedron: Asymmetry* **1995**, *6*, 767.