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Asymmetric Synthesis with a Chiral Catalyst Generated from Asymmetric Autocatalysis

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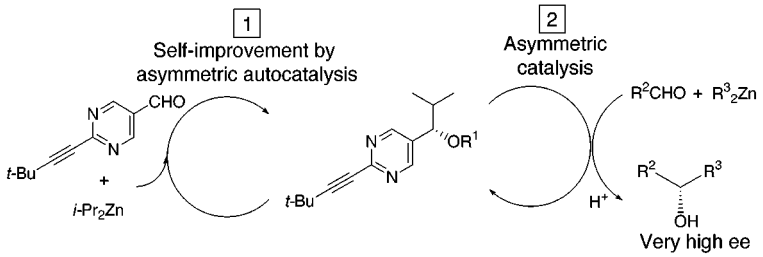
ABSTRACT



A new and efficient one-pot system of asymmetric catalysis is presented in which a chiral catalyst (5-pyrimidyl alkanol) self-improves its ee by asymmetric autocatalysis and then acts as a highly enantioselective chiral catalyst for other asymmetric synthesis (addition of dialkylzincs to aldehydes) to provide products (*sec*-alcohols) with very high ee (up to 99%).

Highly enantioselective catalytic asymmetric synthesis is an important field of research because chirality plays a central role in chemistry and pharmaceutical sciences.[1] For efficient synthesis of chiral compounds with high ee, it has been taken for granted that an enantiomerically pure chiral catalyst is required. It has been assumed that when the ee of the chiral catalyst is low, one cannot expect to obtain the product with high ee. Recently, a positive nonlinear effect of asymmetric catalysis (asymmetric amplification), i.e., the ee of the product is higher than that of chiral catalyst, has been reported and the effect is becoming more and more important in asymmetric synthesis.[2−8] Some of the significant examples of this phenomenon include Sharpless epoxidation,[3] alkylation of aldehydes,[4] ene reaction,[5] conjugate addition,[6] cycloaddition,[7] and miscellaneous reactions.[8] In most cases, however, chiral catalyst with >10% ee are required to obtain the enantioenriched products with very high ee. In asymmetric amplification of the enantioselective alkylation of benzaldehyde with diethylzinc, chiral catalysts with 11%[4a] and 14% ee[4c] afford the *sec*-alcohol with significantly increased ee values of 82%[4a] and 87%,[4c] respectively, with large amplification indexes of 8.2 and 10.5, respectively. Note that amplification index is defined by Kagan as the ratio of the enantiomeric ratio of the product experimentally observed

(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. R., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(2) Reviews: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997−3017. (c) Fenwick, D. R.; Kagan, H. B. In *Topics in Stereochemistry*; Denmark, S. E., Ed.; John Wiley: New York, 1999; pp 257−296. (d) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532−3556. (e) Soai, K.; Shibata, T. In ref 1b, Chapter 9, pp 699−725

(3) (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357. See also: (b) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529−4533.

(4) (a) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877−7888. (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036. (c) Bolm, C.; Schlingloff, G.; Harms, K.; Felder, M. *Chem. Ber.* **1992,** *125*, 1191−1203. (d) Fitzpatrick, K.; Hulst, R.; Kellog, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1861−1864. (e) Rijnberg, E.; Hjovestad, N. J.; Kleij, A. W.; Jastrebski, J. T. B. H.; Boersma, J.; Janssen, M. D.; Spek, A. L.; van Koten, G. *Organometallics* **1997**, *16*, 2847−2857.

(5) Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623−1624.

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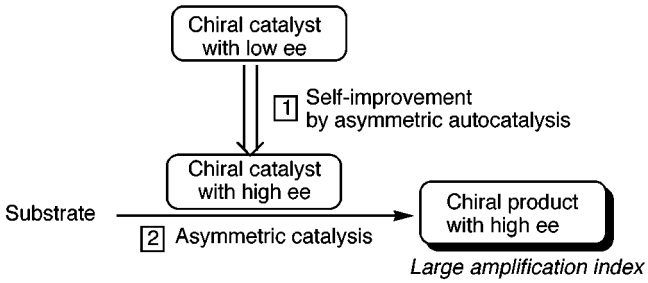
to the enantiomeric ratio of the catalyst.[2c,9] However, when chiral catalysts with lower ee values (3.1[4a] and 2.1%,[4c] respectively) than 10% ee are used in the same reaction, the amplified ee of the product remains low (36[4a] and 39% ee,[4c] respectively) with a considerable decrease in the amplification indexes (2.0 and 2.2, respectively). Thus, asymmetric amplification with a large amplification index starting with an asymmetric catalyst with a very low ee is a challenging problem.

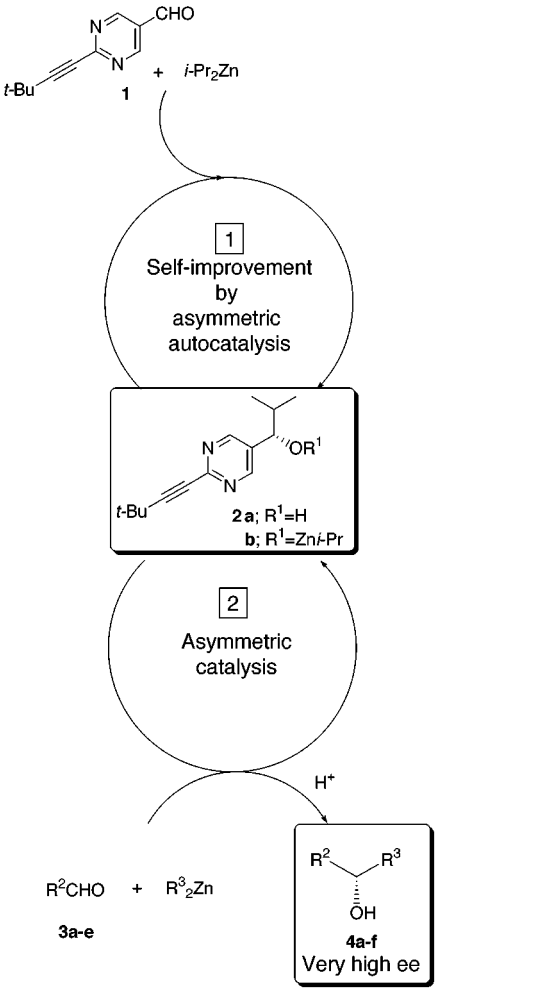
In contrast, during our continuing study on asymmetric autocatalysis,[10−12] in which the chiral product acts as a chiral catalyst for its own production, we found asymmetric autocatalysis with amplification of ee.[10a,d] If an asymmetric autocatalyst acts as a chiral catalyst for some other asymmetric reaction, the opportunity for asymmetric autocatalysis would increase significantly.

We wish to present a new and efficient concept of asymmetric catalysis: a chiral catalyst self-improves its ee by asymmetric autocatalysis and then acts as a highly enantioselective chiral catalyst for some other asymmetric synthesis to provide a product with very high ee (Scheme 1). In other words, the one-pot consecutive system of asymmetric autocatalysis and asymmetric catalysis can afford a highly enantioenriched product by using a compound with a very low ee as the chiral source.

Scheme 1. One-Pot Consecutive System of Asymmetric Autocatalysis and Asymmetric Catalysis



Scheme 2



Due to the very high efficiency of the amplification of ee in asymmetric autocatalysis,[10e] we chose 1-(2-*tert*-butylethynyl-5-pyrimidyl)-2-methylpropanol (**2a**) as the asymmetric autocatalyst and the subsequent asymmetric catalyst in the consecutive system. The one-pot consecutive reaction is shown in Scheme 2: (1) self-improvement of 5-pyrimidyl alkanol by asymmetric autocatalysis with amplification of

(6) (a) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992,** *125*, 1205−1215. (b) de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479−4491. (c) Tanaka, K.; Matsui, J.; Suzuki, H.; Watanabe, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1632−1634. (d) Rossiter, B. E.; Miao, G.; Swingle, N. M.; Eguchi, M.; Hernández, A. E.; Patterson, R. G. *Tetrahedron: Asymmetry* **1992**, *3*, 231−234.

(7) (a) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581−1584. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820. (c) Shimizu, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **1996**, 455−456. (d) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788−1799. (e) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325−6328.

(8) For asymmetric reduction, see: (a) Evans, D. A.; Nelson, S. G.; Gagné, M. R. Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800−9801. For asymmetric allylation, see: (b) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217−1218. (c) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897−7900. (d) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363−2364. For aldol reaction: (e) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363−2365. (f) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851−854. For asymmetric ring-opening of epoxide, see: (g) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924−10925.

(9) In Kagan's definition,[2c] a factor of the enantioselectivity of enantiomerically pure catalyst is included. In this paper, for a practical reason, a value of 1 for the factor is used.

(10) (a) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767−768. (b) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471−472. (c) Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 659−661. (d) Shibata, T.; Hayase, T.; Yamamoto, J.; Soai, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1717−1719. (e) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, 33, 382−390.

(11) Reviews: (a) Soai, K.; Shibata, T. *Yuki Gosei Kagaku Kyokaishi* (*J. Synth. Org. Chem., Jpn.*) **1997**, *55*, 994−1005. (b) Soai, K. *Enantiomer* **1999**, *4*, 591−598. (c) Soai, K.; Sato, I.; Shibata, T. *Chem. Rec.* **2001**, *1*, 321−332.

(12) Reviews: (a) Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1657−1659. (b) Feringa, B. L.; Delden, R. A. van *Angew. Chem., Int. Ed.* **1999**, *38*, 3418−3439. (c) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Chem. Commun.* **2000**, 887−892. (d) Buschmann, H.; Thede, R.; Heller, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4033−4036.

Table 1. Enantioselective Addition of Dialkylzincs to Various Aldehydes Using (*S*)-Pyrimidyl Alkanol **2a** with 1% ee as a Chiral Source

run	aldehydes	R^3	self-improvement	(*S*)-alcohol **4**[a]	yield (%)	ee (%)	amplification index[b]
1[c]	pyridine-3-carbaldehyde (**3a**)	*i*-Pr	none	**4a**	70	9	1.2
2		*i*-Pr	present		84	96	48.0
3[c]	quinoline-3-carbaldehyde (**3b**)	*i*-Pr	none	**4b**	75	7	1.1
4		*i*-Pr	present		87	99	195.1
5[d]		Et	present	**4c**	64	89	16.8
6	5-bromopyridine-3-carbaldehyde (**3c**)	*i*-Pr	present	**4d**	71	90	18.6
7	5-methylpyridine-3-carbaldehyde (**3d**)	*i*-Pr	present	**4e**	73	94	31.7
8	5-*N*,*N*-diisopropylcarbamoylpyridine-3-carbaldehyde (**3e**)	*i*-Pr	present	**4f**	82	86	13.0

[a] ee values were determined by HPLC analysis using a chiral stationary phase (Chiralcel OD-H). The absolute configuration of **4f** was determined by stereospecific conversion into D-valine. See ref 16. The absolute configurations of **4a**−**e** were assigned by analogy. [b] See refs 2c and 9. [c] Reaction was performed without self-improvement using 0.5 mmol of aldehyde **3**, 0.6 mmol of *i*-Pr_2Zn, and 0.1 mmol of pyrimidyl alkanol **2** with 1% ee. [d] Molar ratio. Chiral catalyst:aldehyde:Et_2Zn = 0.5:1.0:1.0.

ee and (2) the subsequent highly enantioselective alkylation of aldehydes using the formed 5-pyrimidyl alkanol as a chiralcatalyst. The results are shown in Table 1. In the presence of (*S*)-**2a** with only 1% ee, 2-(*tert*-butylethynyl)-pyrimidine-5-carbaldehyde (**1**) was reacted with diisopropylzinc (*i*-Pr_2Zn)[13] to give in situ the enantiomerically amplified (isopropylzinc alkoxide of) pyrimidyl alkanol **2b** (run 2).[10a,d] Consecutively, isopropylzinc alkoxide of alkanol **2b** catalyzed highly enantioselective addition of *i*-Pr_2Zn to pyridine-3-carbaldehyde **3a** to give enantioenriched *sec*-3-pyridyl alkanol **4a** with 96% ee in a yield of 84% (run 2).[14] Thus, the 5-pyrimidyl alkanol **2a** originally with only 1% ee improved itself by asymmetric autocatalysis to become a highly enantioselective chiral catalyst for the addition of *i*-Pr_2-Zn to aldehydes to afford the *sec*-alkanol with 96% ee. This result means that the overall amplification index reached 48.0 (run 2), i.e., from 1% ee of 5-pyrimidyl alkanol **2a** to 96% ee of (*S*)-3-pyridyl alkanol **4a**. In marked contrast, ordinary asymmetric amplification using 5-pyrimidyl alkanol **2a** with 1% ee, that is, without autocatalytic self-improvement, gave alcohol **4a** with only 9% ee with a very low amplification index of 1.2, i.e., from 1% ee of **2a** to 9% ee of **4a**, in the catalytic enantioselective addition to aldehyde **3a** (run 1).[15] The self-improving catalyst system also works well in the enantioselective addition to quinoline-3-carbaldehyde (**3b**) (runs 4 and 5). The self-improved chiral catalyst **2b** drove the corresponding enantioselective addition of *i*-Pr_2Zn to aldehyde **3b** efficiently to give (*S*)-3-quinolyl alkanol **4b** with 99% ee in 87% yield. The amplification index reached 195.1, from 1% ee of 5-pyrimidyl alkanol **2b** to 99% ee of 3-quinolyl alkanol **4b** (run 4). The method is also applicable to the addition of diethylzinc to aldehyde **3b** to afford alkanol **4c** with 89% ee with an amplification index of 16.8 (run 5). In contrast, ordinary asymmetric amplification using catalyst **2a** with 1% ee gave (*S*)-**4b** with only 7% ee with a low amplification index of 1.1 (run 3). Thus, as shown in Table 1 (runs 1−4), the consecutive system of asymmetric autocatalysis and asymmetric catalysis (Scheme 2) is apparently advantageous to the ordinary asymmetric amplification. Moreover, enantioselective addition to 5-bromopyridine-3-carbaldehyde (**3c)** and 5-methylpyridine-3-carbaldehyde (**3d)** using the consecutive catalysis system afforded the corresponding alcohols **4c** and **4d** with 90% ee and 94% ee, respectively (runs 6 and 7).

As described above, we have developed asymmetric catalysis mediated with self-improving chiral catalysis by asymmetric autocatalysis. The one-pot consecutive system of asymmetric autocatalysis and asymmetric catalysis provides highly enantioenriched compounds starting from chiral compounds with very low ee with significantly larger

(13) Reviews: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

(14) **Typical experimental procedure for consecutive system** (Table 1, run 2). To a toluene solution (10 mL) of (*S*)-5-pyrimidyl alkanol **2a** (2.3 mg, 0.01 mmol, 1% ee) was added a toluene solution (1.0 M) of *i*-Pr_2Zn (0.75 mmol) at 0 °C. A toluene (5 mL) solution of pyrimidine-5-carbaldehyde **1** (94.1 mg, 0.5 mmol) was then added dropwise, and the mixture was stirred for 3 h at 0 °C. Part of the solution (3.1 mL) was transferred into another two-necked flask using a syringe, toluene (11.4 mL) and a toluene solution (1.0 M) of *i*-Pr_2Zn (0.5 mmol) were added successively, and the mixture was stirred for an additional 15 min. After the solution was cooled to 0 °C, a toluene (2.6 mL) solution of pyridine-3-carbaldehyde **3a** (53.5 mg, 0.5 mmol) was added to the solution over a period of 2 h using a microfeeder, and the mixture was stirred at 0 °C for 19 h. The reaction was quenched by the addition of saturated aqueous sodium chloride (15 mL). The mixture was filtered using Celite, and the filtrate was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Purification of the residue by silica gel thin-layer chromatography (developing solvent, hexane:ethyl acetate = 1:1 v/v) gave (*S*)-2-methyl-1-(3-pyridyl)-propan-1-ol **4a** with 96% ee in an isolated yield of 84% (63.1 mg). In addition, the recovered (*S*)-5-pyrimidyl alkanol **2a** was found to have 92% ee.

(15) **Experimental procedure for the system without self-improving step** (Table 1, run 1). To a toluene solution (14.5 mL) of (*S*)-5-pyrimidyl alkanol **2a** (23.2 mg, 0.1 mmol, 1% ee) was added a toluene solution (1.0 M) of *i*-Pr_2Zn (0.6 mmol) at 0 °C. A toluene (2.6 mL) solution of **3a** (94.1 mg, 0.5 mmol) was then added over a period of 2 h using a microfeeder, and the mixture was stirred for 18 h at 0 °C. The reaction was quenched by the addition of saturated aqueous sodium chloride (15 mL). The mixture was filtered using Celite, and the filtrate was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Purification of the residue by silica gel thin-layer chromatography (developing solvent, hexane:ethyl acetate = 1:1 v/v) gave (*S*)-**4a** with 9% ee in an isolated yield of 70% (53.1 mg).

(16) Soai, K.; Tanji, S.; Kodaka Y.; Shibata, T. *Enantiomer* **1998**, *3*, 241−243.

amplification indexes than those of the existing asymmetric amplification.

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Supporting Information Available: Characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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