Amplification of Chirality

Amplification of Chirality from Extremely Low to Greater than 99.5% *ee* by Asymmetric Autocatalysis**

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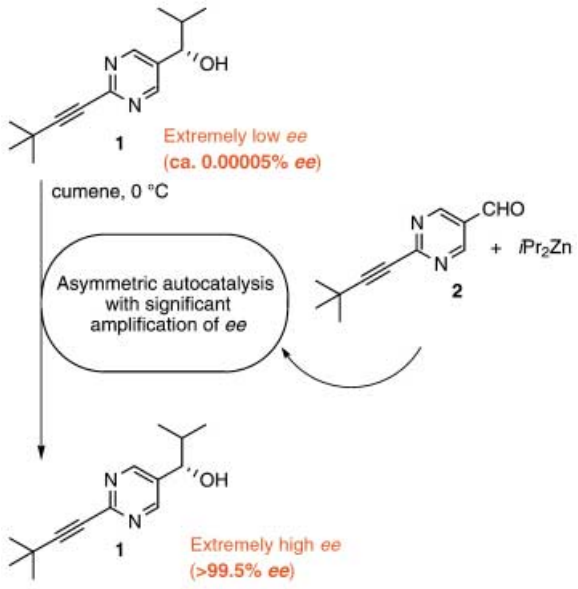
Biomolecules such as amino acids and sugars occur in Nature overwhelmingly as L and D enantiomers, respectively. The origins of chirality and the processes leading to high enantiomeric enrichment of organic compounds have been intriguing puzzles.[1] Several factors have been proposed as the origins of chirality of organic molecules.[2] However, the enantiomeric excesses (*ee*) of organic compounds induced by these factors have usually been very low (from 10^{-4} to < 2% *ee*). Circularly polarized light (CPL) induces very low selectivity (< 2% *ee*) in asymmetric photosynthesis,[2a,b] photoisomerization,[2c] photoequilibration,[2d,e] and photolysis.[2f,g] Asymmetric adsorption on and desorption from chiral surfaces induce a tiny imbalance (< 2% *ee*) in enantiomers.[2h–k] These very low levels of enantiomeric excess require an efficient method of amplification in order to explain the very high enantiomeric enrichment of organic compounds. A tiny imbalance in the enantiomeric composition of a sterically encumbered olefin induces the twist of a nematic phase into a cholesteric phase in liquid crystals.[2d] The positive nonlinear effect of asymmetric catalysis, discovered by Kagan et al.,[3a] explains how a product can have a higher *ee* than the chiral catalyst required for its production.[3] However, the selectivity of the reaction remains low to moderate when the chirality level of the asymmetric catalyst employed is low. For example, the product was produced with only 36% *ee* when a catalyst with 3% *ee* was used.[3b] On the other hand, we reported asymmetric autocatalysis in which the chiral product acts as a chiral catalyst for its own production.[4] The chirality level of the initial catalyst with 0.3–2% *ee* was enhanced to 87–88% *ee*.[5] However, considering the much lower levels of chirality induced by a physical factor,[2l] it is a challenge to develop a method for "amplifying chirality" starting from extremely small enantiomeric imbalances to give practically enantiomerically pure product.

Herein we report efficient chirality amplification by a catalyst with as low as 10^{-5}% *ee* to give practically enantiomerically pure (> 99.5% *ee*) product in only three consecutive cycles. The product formed in situ with enhanced *ee* serves as an asymmetric autocatalyst for the further formation of itself with much higher *ee*.

The initial asymmetric autocatalysts with very low levels of chirality were prepared carefully by adding calculated amounts of standardized solutions of (*S*)- and (*R*)-(2-alkynyl-5-pyrimidyl)alkanol **1** (> 99.5% *ee*)[6] to racemic **1** (Scheme 1).[7] The enantiomeric enrichment of these two solutions was roughly 0.00005% *ee* (i.e. enantiomeric ratio of ca. 50.000025:49.999975).[8] We found that the first asymmetric autocatalysis with (*S*)-**1** of approximately 0.00005% *ee* in the enantioselective addition of diisopropylzinc[9] to 2-alkynylpyrimidine-5-carbaldehyde **2** gave (*S*)-**1** in 96% yield with an enhanced selectivity of 57% *ee* (Table 1, run 1). To take advantage of asymmetric autocatalysis, the (*S*)-**1** obtained was used as an asymmetric autocatalyst for the next reaction (run 2). Indeed, by adding pyrimidine-5-carbaldehyde **2** slowly over a period of 1.5 h to the mixture of asymmetric autocatalyst **1** and iPr$_2$Zn, the *ee* of the pyrimidylalkanol **1** obtained increased to 99% and the yield was 96%. By the third cycle of asymmetric autocatalysis, the chirality level of pyrimidylalkanol reached > 99.5% *ee* (run 3). On the other hand, asymmetric autocatalysis starting with (*R*)-**1** with ca. 0.00005% *ee* instead of (*S*)-**1** produced (*R*)-**1** with 45% *ee* (run 4). The next reaction with this as the asymmetric autocatalyst and a slow addition of aldehyde **2** further enhanced the enantiomeric enrichment of (*R*)-**1** to 95% *ee* (run 5). Finally, the third reaction afforded practically enantiomerically pure (*R*)-**1** with > 99.5% *ee* (run 6).

As shown here, extremely tiny enantiomeric imbalances in the catalyst **1** on the order of 10^{-5}% *ee* with *S* and *R* configurations were effectively amplified to > 99.5% *ee* with



Scheme 1. Alkylation of **2** catalyzed by and yielding (2-alkynyl-5-pyrimidyl)alkanol **1**.

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[**] This work was supported in part by Japan Space Forum, New Energy and Development Organization (NEDO), and a Grant-in-Aid for Scientific Research from the Ministry of Education, Sports, Culture, Science and Technology. This research was presented at the 81st Annual Meeting of The Chemical Society of Japan: H. Urabe, S. Ishiguro, I. Sato, K. Soai, Abstract 4GZ-16, March 2002, Tokyo.

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

  0044-8249/03/11503-0329 $ 20.00+.50/0

Table 1: Amplification of chirality from extremely low levels to >99.5% *ee* by asymmetric autocatalysis.

Run[a]	Set[b]	Initial autocat. **1** *ee* [%]	Config.	Initial and newly formed **1** *ee* [%][c]	Config.	Newly formed **1** Yield [%]
1[d]	A	ca. 0.00005	*S*	57	*S*	96
2[e]		57	*S*	99	*S*	96
3[e]		99	*S*	>99.5	*S*	90
4[d]	A	ca. 0.00005	*R*	45	*R*	96
5[e]		45	*R*	95	*R*	96
6[e]		95	*R*	>99.5	*R*	92
7[f]	B	ca. 0.005	*S*	86	*S*	99
8[f]	B	ca. 0.005	*R*	82	*R*	98
9[f]	C	ca. 0.0005	*S*	76	*S*	95
10[f]	C	ca. 0.0005	*R*	71	*R*	98

[a] All reactions were reproducible. Although very slight enantioselectivity was observed in the initially formed products in runs 1, 4, and 7–10, further asymmetric autocatalysis enhanced in all cases the chirality level of **1** to >99.5% *ee*. [b] The pair of *S* and *R* asymmetric autocatalysts indicated in one set were prepared by the addition of a certain amount of (*S*)- and (*R*)-**1**, respectively, to a racemic mixture. See refs. [7] and [8]. [c] Determined by HPLC analysis with a chiral stationary phase (Chiralcel OD). [d] Reactions were carried out in cumene at 0°C. Molar ratio asymmetric autocatalyst **1**:aldehyde **2**:iPr$_2$Zn = 0.008:1:2. Aldehyde and iPr$_2$Zn were added in four portions. See Experimental Section. [e] Aldehyde **2** and iPr$_2$Zn were added slowly over a period of 1.5 h with a microfeeder. Molar ratio asymmetric autocatalyst **1**:aldehyde **2**:iPr$_2$Zn = 0.02:1:1.5. [f] Molar ratio asymmetric autocatalyst **1**:aldehyde **2**:iPr$_2$Zn = 0.01:1:2. Aldehyde and iPr$_2$Zn were added in three portions.

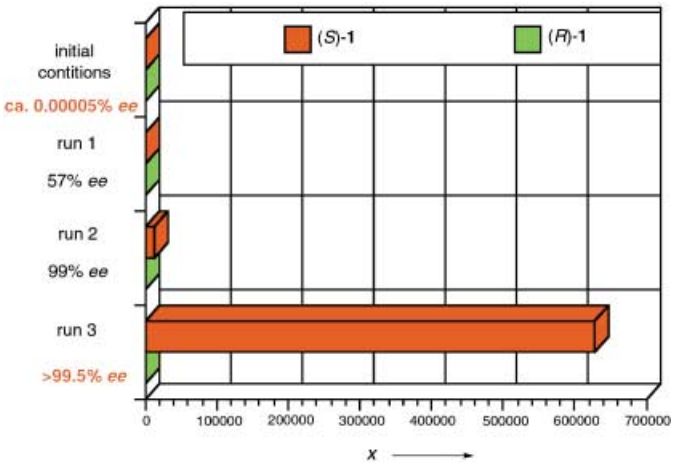

Figure 1. Plot showing the increase in the amount of *S* and *R* isomers by the factor *x* during consecutive asymmetric autocatalyses (Table 1, runs 1–3).

S and *R* configurations, respectively, in the product **1** by three consecutive cycles of asymmetric autocatalysis.[10] As shown in Figure 1, the very slightly major *S* enantiomer in the initial (*S*)-**1** with ca. 0.00005% *ee* has automultiplied by a factor of ca. 630000 after the three consecutive asymmetric autocatalyses (runs 1–3), whereas the very slightly minor enantiomer (*S*)-**1** has automultiplied by a factor of only ca. 950.

We also examined asymmetric autocatalysis using catalysts **1** with 10^{-3}–10^{-4}% *ee*. As expected, (*S*)- and (*R*)-**1** with increased *ee* were formed with (*S*)- and (*R*)-asymmetric autocatalysts **1**, respectively (runs 7–10). It should be mentioned that the subsequent asymmetric autocatalysis with the product **1** as asymmetric autocatalyst amplified the chirality level to >99.5% *ee*.[11,12]

In summary, we have demonstrated that 2-alkynylpyrimidylalkanol with a chirality level of only 10^{-5}% *ee* with *S* and *R* configurations automultiplies with significant amplification of chirality in the addition of iPr$_2$Zn to 2-alkynylpyrimidine-5-carbaldehyde, producing itself with the corresponding configurations in almost enantiomerically pure form. We believe that this reaction provides an efficient method to correlate extremely low levels of chirality induced by factors[13] related to the origin of chirality to very high levels of chirality of organic compounds.

Experimental Section

Typical experimental procedure for asymmetric autocatalysis using alkanol **1** with about 0.00005% *ee* (run 1): A solution of iPr$_2$Zn (0.1 mL of a 1.0 M solution in cumene, 0.1 mmol) was added at 0°C to a solution of (*S*)-**1** (1.3 mL of a 9.9×10^{-3} M solution in cumene, 2.9 mg, 0.013 mmol) with ca. 0.00005% *ee*, and the mixture was stirred for 15 min. A solution of aldehyde **2** (9.4 mg, 0.05 mmol) in cumene (1 mL) was then added over a period of 30 min, and the mixture was stirred for 1.5 h at 0°C. Cumene (1.3 mL), iPr$_2$Zn (0.3 mmol, 0.3 mL of a 1.0 M solution in cumene), and a solution of aldehyde **2** (28.2 mg, 0.15 mmol) in cumene (1.5 mL) were added successively, and the reaction mixture was stirred for 1 h. Then cumene (2.6 mL), iPr$_2$Zn (0.9 mmol, 0.9 mL of 1.0 M solution in cumene), and a solution of aldehyde **2** (84.6 mg, 0.45 mmol) in cumene (3.0 mL) were added successively, and the mixture was stirred at 0°C for another 1 h. After the addition of cumene (9.3 mL), iPr$_2$Zn (1.8 mmol, 1.8 mL of a 1.0 M solution in toluene) and a solution of aldehyde **2** (169 mg, 0.90 mmol) in cumene (5.0 mL), the mixture was stirred for 18 h. The reaction was quenched with hydrochloric acid (1.0 M, 4 mL), and saturated aqueous sodium hydrogencarbonate (13 mL) was then added. The mixture was filtered through Celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (eluent, hexane:ethyl acetate = 3:1 *v*/*v*) gave (*S*)-pyrimidyl alkanol **1** with 57% *ee* (348 mg). The yield of the newly formed **1** was 96%.

Received: August 21, 2002 [Z50015]

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[7] Racemic **1** was prepared by the lithiation of 2-alkynyl-5-bromopyrimidine followed by treatment with 2-methylpropanal.

[8] Preparation of (*S*)-**1** with ca. 0.00005 % *ee*. Pyrimidyl alkanol (*S*)-**1** (1.5 mg, > 99.5 % *ee*) was dissolved in ethyl acetate (or benzene) to make a standardized solution of (*S*)-**1** (3.2×10^{-6} mol L^{-1}). The solution (50 μL) was added to a solution of racemic **1** (75.1 mg) in ethyl acetate (or benzene). Then, a part of the solution was transferred to another flask, and the removal of solvent gave (*S*)-**1** with ca. 0.00005 % *ee* (9.9 mg). Dissolution of the whole (*S*)-**1** in 4.3 mL of cumene produced a 9.9×10^{-3} M solution of (*S*)-**1** with ca. 0.00005 % *ee*.

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[10] After our experiments were completed, Singleton and Vo reported asymmetric autocatalysis using (*R*)-(2-methylpyrimidyl)alkanol[5b] with the order of 10^{-5} % *ee* [a) D. A. Singleton, L. K. Vo, *J. Am. Chem. Soc.* **2002**, *124*, 10010 – 10011]. However, they used only the catalyst with the *R* configuration. We believe that it is essentially important to examine the asymmetric autocatalysts of both configurations. The reasons are as follows: 1) The chirality level of the catalyst on the order of 10^{-5} % *ee* is below the detection level of the instruments typically used, for example, HPLC, CD, polarimeter etc. (for recent advances in the measurement of enantiomeric excesses, see: b) M. Tsukamoto, H. B. Kagan, *Adv. Synth. Catal.* **2002**, *344*, 453 – 463). 2) Only after obtaining results that the asymmetric autocatalyst with *S* configuration affords itself with *S* configuration and the asymmetric autocatalyst with *R* configuration affords itself with *R* configuration one can judge that the autocatalyst works.

[11] Autocatalyst **1** on the order of 10^{-9} % *ee* has been employed, but we have not yet received reproducible results probably because of the effect of some unexpected and unknown chiral factor.

[12] The reaction of 2-methylpyrimidine-5-carbaldehyde with $i Pr_2Zn$ without any added chiral substance had been examined in 100 experiments. After repeated asymmetric autocatalysis, (2-methylpyrimidyl)alkanol with a chirality level above the detection level formed [K. Soai, T. Shibata, Y. Kowata, Japan Kokai Tokkyo Koho JP, 9-268179 **1997**]. However, the probability of the formation of *S* and *R* enantiomers in toluene was not equal, which indicates an unexpected and unknown chiral factor affects the asymmetric induction. Similar observations have been reported by Singleton and Vo.[10a]

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Coordination Networks

Open Network Architectures from the Self-Assembly of $AgNO_3$ and 5,10,15,20-Tetra(4-pyridyl)porphyrin (H_2tpyp) Building Blocks: The Exceptional Self-Penetrating Topology of the 3D Network of $[Ag_8(Zn^{II}tpyp)_7(H_2O)_2](NO_3)_8$**

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The use of suitable predetermined building blocks has assumed an increasing relevance in recent times in the crystal engineering of coordination frameworks[1] that have potential interest as zeolite-like materials.[2] In this regard, much

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[**] This work was supported by MURST within the project "Solid Supermolecules" 2000–2001. F.P. thanks the ISTM Centre for instrument facilities.