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Communication

Determination of absolute configurations of amino acids by asymmetric autocatalysis of 2-alkynylpyrimidyl alkanol as a chiral sensor

Itaru Sato [a,b], Yasushi Ohgo [b], Hirotaka Igarashi [b], Daisuke Nishiyama [b], Tsuneomi Kawasaki [b], Kenso Soai [b,*]

[a] Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo 669-1337, Japan
[b] Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

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Dedicated to Professor Gyula Pályi on the occasion of his 70th birthday.

Abstract

Asymmetric autocatalysis of 2-alkynyl-5-pyrimidyl alkanol is employed as a chiral sensor of 20 amino acids. Asymmetric autocatalysis using amino acids as chiral initiators gave pyrimidyl alkanols of the absolute configurations that were correlated with those of the amino acids. The enantiomeric excesses of pyrimidyl alkanol are invariably high even when the enantiomeric excess of amino acids is as low as 0.1%. Thus, by determining the absolute configuration of pyrimidyl alkanol with high enantiomeric excess, one can determine the absolute configuration of amino acids even when their enantiomeric excess is low.

Keywords: Asymmetric autocatalysis; Amino acid; Chiral sensor; Pyrimidyl alkanol; Chiral initiator; Origin of chirality

1. Introduction

Chiral homogeneity of naturally occurring organic compounds such as L-amino acids and D-sugars has been an intriguing puzzle in the chemical origin of life [1]. It has been thought that the initial fixation of a tiny imbalance of chirality and the amplification of chirality are necessary for the production of highly enantioenriched amino acids. Amino acids exist not only on Earth, but also in extraterrestrial substances such as meteorites. In addition, their existence in Saturn's moon Titan is hypothesized [2a]. In systems that have no chiral factor or nonlinear amplification, the probability of the formation of two enantiomers is 1:1. In this context, it is very interesting that some amino acids found in meteorites exhibit enantioenrichments [3], although the degree is very low, supporting the extraterrestrial origin of chirality of amino acids. This has raised the question of whether amino acids in space are L or D. To address the question, it is necessary to develop a highly sensitive method for detecting the absolute configuration of amino acids [2].

In our continuing study of asymmetric autocatalysis [4,5], we showed that asymmetric autocatalysis of 5-pyrimidyl alkanols proceeds with significant amplification of enantiomeric excess [6]. We also reported that the chiral initiator in the reaction of pyrimidine-5-carbaldehyde and diisopropylzinc (*i*-Pr_2Zn) controls the absolute configuration of the produced 5-pyrimidyl alkanols and that the enantioenrichments of the produced pyrimidyl alkanols are high even when the enantioenrichments of chiral initiators are very low [7].

Thus, development of the method for the detection of the absolute configuration of amino acids with low

* Corresponding author. Tel.: +81 3 5228 8261; fax: +81 3 5261 4631.
E-mail address: soai@rs.kagu.tus.ac.jp (K. Soai).

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enantioenrichment is a challenging problem [8]. We thought that the absolute configuration of amino acids can be determined by determining the absolute configuration of the produced pyrimidyl alkanol with high enantiomeric excess in asymmetric autocatalysis using amino acids as chiral initiators [9]. We previously described only a few examples of asymmetric autocatalysis of 2-methylpyrimidyl alkanol using [10]. We here report asymmetric autocatalysis of 2-alkynyl-5-pyrimidyl alkanol, which is more significant than 2-methylpyrimidyl alkanol in amplification of chirality, using the 20 naturally occurring amino acids as chiral initiators.

2. Results and discussion

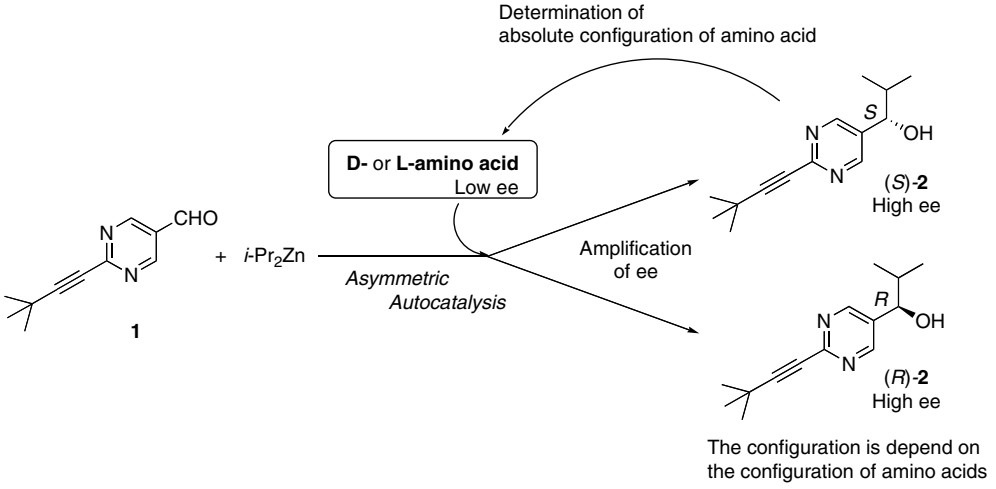
We examined the reaction of 2-(3,3-dimethy-1-butynyl)pyrimidine-5-carbaldehyde **1** and *i*-Pr_2Zn in the presence of the 20 naturally occurring amino acids (Scheme 1). If the chirality of amino acid controls the enantioselectivity of the addition of *i*-Pr_2Zn to aldehyde **1**, the subsequent asymmetric autocatalysis of the produced 5-pyrimidyl alkanol amplifies the enantiomeric excess of 5-pyrimidyl alkanol **2**.

The results of asymmetric autocatalysis induced by amino acids are shown in Table 1. As shown in Entry l, L-alanine induced the production of (*S*)-5-pyrimidyl alkanol **2** with 90% yield and 92% ee. In contrast, D-alanine gave (*R*)-5-pyrimidyl alkanol **2** with 90% ee. These results clearly show that the configuration of alanine determined the configuration of the produced 5-pyrimidyl alkanol. Other amino acids with aliphatic side chains such as valine, leucine, and isoleucine exhibited the same sense of enantioselectivity. Thus, in the presence of L-amino acids, (*S*)-5-pyrimidyl alkanol **2** with high ee was obtained. In the presence of D-amino acids, (*R*)-**2** was obtained (Entries 2, 4–6). It should be noted that, in the presence of leucine or valine, the sense of the enantioselectivity of product **2** is opposite to that of the product in the asymmetric addition to 2-methylpyrimidine-5-carbaldehyde [10]. In addition, asymmetric amplification of **2** with an alkynyl substituent is more significant than that of 2-methylpyrimidyl alkanol [6d].

Results of the asymmetric autocatalysis initiated by other naturally occurring amino acids are shown in Table 1 (Entries 7–21). In all cases, chirality of the amino acids is recognized and highly enantiomerically enriched pyrimidyl alkanol **2** was obtained.

Next, asymmetric autocatalysis initiated by amino acids with low ees was examined (Table 2). Calculated amounts of commercially available D- and L-amino acids were mixed and finely ground using a mortar and pestle. Samples of amino acids with low ees were then washed with diethyl ether and dried in vacuo before use. When L-alanine with ca. 10% ee was used as the chiral initiator, the obtained alkanol **2** with 94% ee possessed the *S* configuration (Entry 1) as predicted from the result when enantiopure amino acid was used as a chiral initiator (Table 1, Entry 1). Even when the ee of the prepared L-alanine was as low as ca. 1% and ca. 0.1% ee, the configuration of the formed (*S*)-5-pyrimidyl alkanol **2** was formed (Entries 2 and 3). It should be noted that the products' ees are almost the same regardless of the ee of chiral initiator. On the other hand, asymmetric autocatalysis in the presence of D-alanine with low ee (ca. 10%, 1%, and 0.1% ees) gave (*R*)–**2** (Entries 4–6). Similarly, the chirality of D- and L-methionine (Entries 7–12), D- and L-histidine (Entries 13–18), and D- and L-valine (Entries 19–22) with low ee was recognized and turned into the amplified ee of the 5-pyrimidyl alkanol product **2**.

We also examined the asymmetric autocatalysis in the presence of D-*allo*-isoleucine, i.e., (2*R*,3*S*)-2-amino-3-methylpentanoic acid. The reaction gave the (*R*)-**2** with 95% ee in 96% yield. To compare this result with the asymmetric autocatalysis in the presence of D- and L-isoleucine (Table 1, Entry 6), the stereogenic center at the 2-position of amino acid controls the absolute configuration of the formed product **2**.



Scheme 1.

Table 1
Asymmetric autocatalysis initiated by various enantiopure amino acids

Entry	Amino acids (enantiopure)	5-Pyrimidyl alkanol **2** (initiated by L-amino acids[a])			5-Pyrimidyl alkanol **2** (initiated by D-amino acids[b])		
		Yield (%)	ee (%)[c]	Configuration[c]	Yield (%)	ee (%)[c]	Configuration[c]
1	Alanine	90	92	*S*	83	90	*R*
2	Valine	85	82	*S*	95	93	*R*
3	Phenylalanine	93	93	*S*	85	89	*R*
4	Leucine	95	96	*S*	98	95	*R*
5	Isoleucine	91	96	*S*	95	96	*R*
6[d]	Isoleucine	91	96	*S*	95	95	*R*
7	Serine	87	73	*S*	91	75	*R*
8	Threonine	95	91	*S*	91	92	*R*
9	Methionine	95	95	*S*	93	94	*R*
10	Lysine	85	85	*S*	92	67	*R*
11	Cysteine	85	73	*R*	80	76	*S*
12	Cystine	95	95	*S*	93	88	*R*
13	Tyrosine	84	73	*R*	88	75	*S*
14	Tryptophan	96	96	*R*	83	95	*S*
15	Histidine	92	91	*R*	89	86	*S*
16	Proline	83	88	*R*	83	92	*S*
17	Aspartic acid	91	81	*S*	91	85	*R*
18	Glutamic acid	97	73	*S*	92	75	*R*
19	Asparagine	87	73	*S*	86	84	*R*
20	Glutamine	90	70	*R*	96	95	*S*
21	Arginine	91	77	*R*	89	79	*S*

[a] Ee and configuration of 5-pyrimidyl alkanol **2** when the L-amino acid was used as a chiral initiator.
[b] Yield, ee and configuration of 5-pyrimidyl alkanol **2** when the D-amino acid was used as a chiral initiator.
[c] Determined by HPLC analysis using a chiral stationary phase (Chiralcel-OD).
[d] A suspension of amino acid and *i*-Pr_2Zn was treated for 12 h. See Section 4.3.

The enantioselectivity observed in this asymmetric reaction may be explained as follows: since the initial reaction of the aldehyde **1** and the *i*-Pr_2Zn proceeded under the influence of the chiral amino acid, a small ee was induced. Then, a subsequent asymmetric autocatalysis with an amplification of the ee afforded alkanol (as zinc alkoxide) with high ee, which showed the corresponding absolute configuration. Further mechanistic details including the relationship between structures of amino acids and the absolute configuration of obtained alkanol are now under investigation.

Table 2
Asymmetric autocatalysis initiated by various amino acids with low ee

Entry	Amino acids (ee/%, configuration)		5-Pyrimidyl alkanol **2**		
			Yield (%)	ee (%)	Configuration
1	Alanine	ca. 10 (L)	98	94	*S*
2		ca. 1 (L)	83	95	*S*
3		ca. 0.1 (L)	91	92	*S*
4		ca. 10 (D)	90	83	*R*
5		ca. 1 (D)	91	89	*R*
6		ca. 0.1 (D)	89	87	*R*
7	Methionine	ca. 10 (L)	89	95	*S*
8		ca. 1 (L)	96	97	*S*
9		ca. 0.1 (L)	96	91	*S*
10		ca. 10 (D)	95	93	*R*
11		ca. 1 (D)	95	93	*R*
12		ca. 0.1 (D)	91	72	*R*
13	Histidine	ca. 10 (L)	89	90	*R*
14		ca. 1 (L)	86	93	*R*
15		ca. 0.1 (L)	94	97	*R*
16		ca. 10 (D)	96	94	*S*
17		ca. 1 (D)	95	85	*S*
18		ca. 0.1 (D)	91	92	*S*
19	Valine	ca. 10 (L)	93	96	*S*
20		ca. 1 (L)	96	92	*S*
21		ca. 10 (D)	96	92	*R*
22		ca. 1 (D)	94	90	*R*

3. Conclusion

We have established the correlation between the chirality of 20 amino acids and the absolute configurations of 2-(3,3-dimethy-1-butynyl)-5-pyrimidyl alkanol formed from the asymmetric autocatalysis using amino acids as chiral initiators. The asymmetric autocatalysis produced highly enantiomerically enriched 5-pyrimidyl alkanol even when the enantiomeric excess of amino acid is low (ca. 0.1% ee). We believe that the present method will be useful for the determination of absolute configuration of amino acids even when the enantioenrichment of amino acid is low.

4. Experimental

*4.1. Representative experimental procedure for the enantioselective addition of diisopropylzinc to 2-(3,3-dimethy-1-butynyl)pyrimidine-5-carbaldehyde **1** using enantiopure amino acids as chiral initiators (Table 1, Entry 1, L-alanine was used as a chiral initiator)*

To enantiopure L-alanine (2.2 mg, 0.025 mmol), 1 M toluene solution (0.125 ml) of diisopropylzinc (*i*-Pr_2Zn) was added at 0 °C. After the mixture was stirred for 30 min at

0 °C, a toluene (0.25 ml) solution of pyrimidine-5-carbaldehyde **1** (4.7 mg, 0.025 mmol) was added to the mixture over a period of 30 min. After the mixture was stirred for 12 h, toluene (1.9 ml), 1 M toluene solution (0.2 ml) of *i*-Pr_2Zn, and pyrimidine-5-carbaldehyde **1** (18.8 mg, 0.1 mmol) in toluene (1.25 ml) were added successively. After 3.5 h, toluene (6.7 ml), 1 M toluene solution (0.8 ml) of *i*-Pr_2Zn, and pyrimidine-5-carbaldehyde **1** (75.3 mg, 0.4 mmol) in toluene (2.5 ml) were added and the mixture was stirred for an additional 2.5 h. The reaction was quenched by adding 1 M hydrochloric acid (2 ml), made alkaline with saturated aq. sodium bicarbonate (8 ml). The mixture was filtered through Celite, and the separated aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated. Purification of the residue by silica gel thin layer chromatography (developing solvent, hexane:ethyl acetate = 2:1 (v/v)) gave 5-pyrimidyl alkanol **2** (110.0 mg) in 90% yield. Enantiomeric excess was determined as 92% by HPLC analysis on a column with a chiral stationary phase (Chiralcel OD).

4.2. Representative procedure for the preparation of amino acids with low ee (D-alanine with 10% ee)

Commercially available D-alanine (1.0000 g) and L-alanine (0.8182 g) were mixed using a mortar and pestle. The mixture was washed with diethyl ether, and dried in vacuo before use. The mixture contains D- and L-alanine in a ratio of 55:45, i.e., ca. 10% ee.

*4.3. Representative experimental procedure for the enantioselective addition of diisopropylzinc to 2-(3,3-dimethy-1-butynyl)pyrimidine-5-carbaldehyde **1** using amino acids with low ee as chiral initiators (Table 2, Entry 4, D-alanine with ca. 10% ee was used as a chiral initiator)*

To D-alanine with ca. 10% ee (4.5 mg, 0.05 mmol), 1 M toluene solution (0.15 ml) of *i*-Pr_2Zn was added at room temperature. After the mixture was stirred at room temperature for 12 h, the mixture was cooled to 0 °C, and 1 M toluene solution (0.05 ml) of *i*-Pr_2Zn was added. Toluene (0.5 ml) solution of pyrimidine-5-carbaldehyde **1** (9.4 mg, 0.05 mmol) was added to the mixture over a period of 30 min. After the mixture was stirred for 6 h, toluene (4.7 ml), 1 M toluene solution (0.4 ml) of *i*-Pr_2Zn, and pyrimidine-5-carbaldehyde **1** (37.6 mg, 0.2 mmol) in toluene (1.5 ml) were added successively. After 3.5 h, toluene (14.4 ml), 1 M toluene solution (1.6 ml) of *i*-Pr_2Zn, and pyrimidine-5-carbaldehyde **1** (151 mg, 0.8 mmol) in toluene (4 ml) were added and the mixture was stirred for an additional 2.5 h. The reaction was quenched by adding 1 M hydrochloric acid (5 ml), made alkaline with saturated aq. sodium bicarbonate (15 ml). The mixture was filtered through Celite, and the separated aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel thin layer chromatography (developing solvent, hexane:ethyl acetate = 2:1 (v/v)) gave 5-pyrimidyl alkanol **2** (219.5 mg, 1.04 mmol) in a yield of 90%. Enantiomeric excess was determined as 83% by HPLC analysis on a column with a chiral stationary phase (Chiralcel OD).

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