Amplification of a Slight Enantiomeric Imbalance in Molecules Based on Asymmetric Autocatalysis: The First Correlation between High Enantiomeric Enrichment in a Chiral Molecule and Circularly Polarized Light

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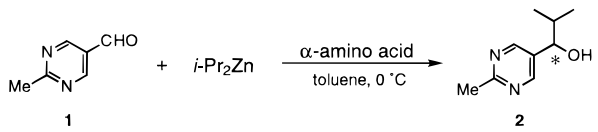
Molecular chirality plays a central role in chemistry, biology, and the pharmaceutical sciences. Considerable attention has been focused on the origin of chiral homogeneity of natural compounds such as L-α-amino acids.[1] Several physical factors have been reported to be possible sources of chirality. Among these factors, circularly polarized light (CPL) is a potent candidate because Kagan,[2] Buchardt,[3] and Bonner[4] reported that chirality can be induced in organic molecules by photosynthesis or photolysis using left or right CPL.[5,6] Moreover, a recent intriguing report[7] disclosed that strong CPL in the infrared region is observed in an area of star formation. However, the degree of enantiomeric imbalance caused by these physical factors (including CPL) is usually too small to be associated with the large enantiomeric imbalance in molecules found in nature.[8,9]

We report here a new concept and a system for the amplification of enantiomeric imbalance starting from a trace amount of chiral initiator with very low ee, which enables us for the first time to correlate a highly enantiomerically enriched compound with a slight enantiomeric imbalance induced by CPL. The principle is as follows: A slight symmetry breaking induced by the presence of a chiral initiator of very low ee is dramatically amplified by asymmetric autocatalysis[10] (Scheme 1). When pyrimidine-5-carbaldehyde undergoes alkylation by diisopropylzinc in the presence of a chiral initiator, the slight enantiomeric excess is enhanced in the alkylated product, pyrimidyl alkanol. The subsequent addition of diisopropylzinc and aldehyde to the reaction mixture leads to an asymmetric autocatalytic reaction by the slightly enantiomerically enriched pyrimidyl alkanol as an asymmetric autocatalyst,[11] and highly enantiomerically enriched pyrimidyl alkanol is obtained. Therefore, the configuration of the product alkanol with a much higher ee is correlated to that of the chiral initiator which was originally used.[12]

Table 1. α-Amino Acids with Low ee as Chiral Initiators



entry	α-amino acid (ee/%)		pyrimidyl alkanol **2** (ee/%)
1[a]	leucine	ca. 2 (L)	21 (*R*)
2[a]	leucine	ca. 2 (L)	23 (*R*)
3[a]	leucine	ca. 2 (D)	26 (*S*)
4[a]	leucine	ca. 2 (D)	16 (*S*)
5[b]	valine	ca. 1 (L)	51 (*R*)
6[b]	valine	ca. 1 (D)	47 (*S*)

[a] Molar ratio of leucine/aldehyde **1**/diisopropylzinc is 0.02:1.0:2.4. Aldehyde **1** and diisopropylzinc were added in three portions. [b] Molar ratio of valine/aldehyde **1**/diisopropylzinc is 0.2:1.0:2.4. Aldehyde **1** and diisopropylzinc were added in two portions.

We first chose leucine as a chiral initiator because it is a biologically important α-amino acid and because slightly enantiomerically enriched L- or D-leucine (ca. 2% ee) can be obtained by photolysis of racemic leucine using right or left CPL.[4] To 13 mg (0.10 mmol, 5 mol %) of L-leucine with ca. 2% ee were added diisopropylzinc and 2-methylpyrimidine-5-carbaldehyde (**1**), in three portions, one after the other. (*R*)-2-Methyl-1-(2-methyl-5-pyrimidyl)propan-1-ol (**2**) was obtained in 82% yield and 21% ee (Table 1, entry 1). Conversely, in the presence of D-leucine with ca. 2% ee, enantioselective alkylation under the same conditions gave the opposite isomer-enriched (*S*)-pyrimidyl alkanol **2** with 26% ee (entry 3). This stereochemical coherency of leucine (L or D) and the resulting pyrimidyl alkanol (*R* or *S*) was reproducible (entries 2 and 4). Another α-amino acid, valine, also acted as a chiral initiator, and (*R*)- and (*S*)-pyrimidyl alkanol **2** were obtained in the presence of 20 mol % of L- and D-valine with ca. 1% ee, respectively, along with adding diisopropylzinc and aldehyde **1** in two portions (entries 5 and 6). The ee of the resulting pyrimidyl alkanol **2** can be easily increased to >95% ee by further asymmetric autocatalytic reaction using pyrimidyl alkanol **2** as an asymmetric autocatalyst.[11a,c] These results imply that a slight CPL-induced imbalance in the chirality of an organic compound is synthetically correlated with a significant enantiomeric imbalance in a chiral molecule.

Trace amounts of various chiral compounds, other than α-amino acids, with very low ee, even less than 1% ee, can also serve as a chiral initiator. For example, to 3 mg (0.02 mmol, 1 mol %) of slightly *S*-enriched methyl mandelate (a sample with ca. 0.1% ee was prepared by mixing a toluene solution of racemic methyl mandelate (9.990 g) and a toluene solution of (*S*)-methyl mandelate (0.010 g)) were added diisopropylzinc (0.24, 1.0, and 3.8 mL of 1 M toluene solution) and 2-methylpyrimidine-5-carbaldehyde **1** (12, 49, and 195 mg, 0.1, 0.4, and 1.6 mmol, respectively) in three portions one after another. The reaction proceeds in homogeneous condition and the resulting pyrimidyl

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Scheme 1. Proposed Scheme for Amplification of ee Induced by Chiral Initiator with Very Low ee

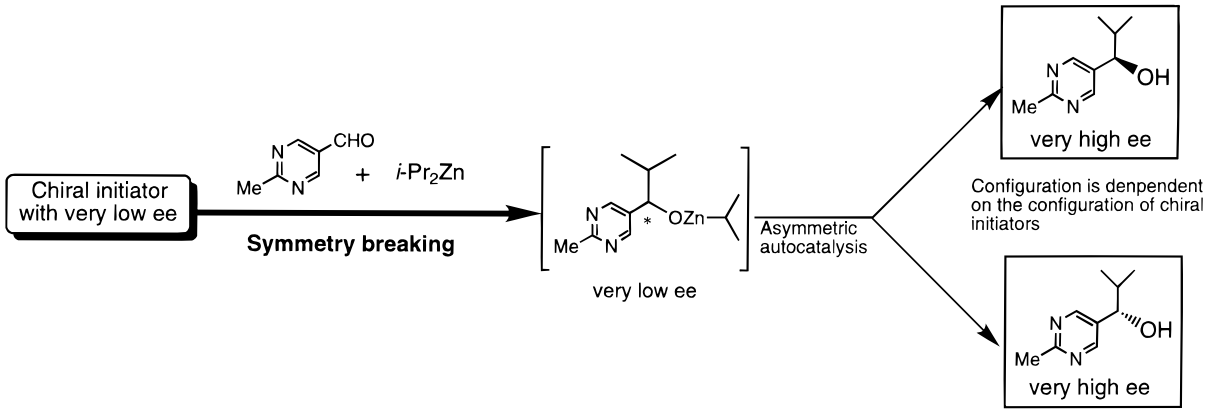
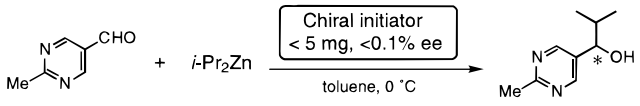
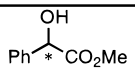
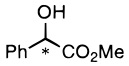
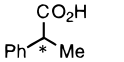
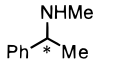


Table 2. Chiral Initiator-Induced Amplification of ee of Pyrimidyl Alkanol



1 2

entry [a]	chiral initiator	pyrimidyl alkanol **2**	
		ee / %	ee. / %
1		ca. 0.1 (*S*)	68 (*R*)
2		ca. 0.1 (*R*)	70 (*S*)
3		ca. 0.05 (*S*)	54 (*R*)[b]
4		ca. 0.05 (*R*)	38 (*S*)[c]
5		ca. 0.1 (*S*)	76 (*R*)
6		ca. 0.1 (*R*)	73 (*S*)
7		ca. 0.1 (*S*)	79 (*R*)
8		ca. 0.1 (*R*)	85 (*S*)
9		ca. 0.1 (*S*)	73 (*S*)
10		ca. 0.1 (*R*)	76 (*R*)

[a] Molar ratio of chiral initiator/aldehyde **1**/diisopropylzinc is 0.01−0.02:1.0:2.4. Aldehyde **1** and diisopropylzinc were added in three portions. [b] An average of three experiments under the same reaction conditions (56, 53, 53% ee). [c] An average of three experiments under the same reaction conditions (40, 37, 38% ee).

alkanol **2** was obtained in 88% yield in *R*-form with 68% ee (Table 2, entry 1). Conversely, in the presence of (*R*)-methyl mandelate with ca. 0.1% ee, the opposite isomer-enriched (*S*)-pyrimidyl alkanol was obtained (entry 2). Methyl mandelate with lower ee (0.05% ee) can be used, and the reproducibility of the stereochemical coherency between methyl mandelate and the resulting pyrimidyl alkanol **2** was ascertained by three experiments for each enantiomer under the same conditions (entries 3 and 4).[13] When racemic methyl mandelate was used under the same conditions, the ee of the resulting pyrimidyl alkanol was below the detection level (<1% ee). Very slight enantiomeric imbalances (ca. 0.1% ee) in a chiral carboxylic acid and a chiral amine possessing a phenyl group were also amplified to more than 70% ee (entries 5−8). Moreover, a phenyl group in the chiral initiator is not essential. In the presence of a simple chiral alcohol, (*S*)-2-butanol with ca. 0.1% ee, pyrimidyl alkanol with 73% ee was obtained in *S*-form, and vice versa (76% ee (*R*)) (entries 9 and 10). Even the very small steric difference between methyl and ethyl substituents on the asymmetric carbon atom is sufficient to induce chirality in the resulting pyrimidyl alkanol. As mentioned above, the ee of the resulting pyrimidyl alkanol can be increased to >95% ee by further asymmetric autocatalytic reaction.

Thus, various organic compounds with only a slight enantiomeric imbalance can be converted into almost enantiomerically pure pyrimidyl alkanol by asymmetric autocatalysis. For the first time, a very small enantiomeric imbalance caused by a physical mechanism can be directly linked to a significant enantiomeric enrichment in a chiral molecule.

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Supporting Information Available: Preparation of L- and D-leucine with ca. 2% ee and L- and D-valine with ca. 1% ee and experimental procedures for entries 1 and 5 in Table 1 (2 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(13) Typical experimental procedure (Table 2, entry 3): All reaction apparatus including a flask, syringes, needles, and a magnetic stirring bar were thoroughly washed by fuming nitric acid, water, and then acetone. The reaction vessel was heated to over 400 °C in vacuo before use. To a toluene solution (0.6 mL) of (*S*)-methyl mandelate with ca. 0.05% ee (3 mg, 0.02 mmol) was added *i*-Pr_2Zn (0.24 mL of 1 M toluene solution, 0.24 mmol) at 0 °C, and the mixture was stirred for 15 min. A toluene solution (0.4 mL) of 2-methylpyrimidine-5-carbaldehyde (**1**) (12 mg, 0.10 mmol) was added at 0 °C. After the reaction mixture was stirred for 8 h at 0 °C, toluene (1.5 mL) and *i*-Pr_2Zn (1.0 mL of 1 M toluene solution, 1.0 mmol) were added to the reaction mixture at 0 °C, and the combined mixture was stirred for 15 min. A toluene solution (1.5 mL) of aldehyde **1** (49 mg, 0.40 mmol) was then added at 0 °C. The reaction mixture was stirred for an additional 8 h at 0 °C. In the same manner, toluene (9.4 mL), *i*-Pr_2Zn (3.8 mL of 1 M toluene solution, 3.8 mmol), and a toluene solution (2.6 mL) of aldehyde **1** (195 mg, 1.60 mmol) were added, and the reaction mixture was stirred for 8 h. The reaction was quenched by adding 1 M hydrochloric acid (3 mL) and saturated aqueous sodium bicarbonate (12 mL). 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 the pure product **2** (311 mg, 89%). Its enantiomeric excess was determined to be 56% ee in the *S*-form by HPLC/CSP analysis using a chiral column (Daicel Chiralcel OC).