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# Spontaneous absolute asymmetric synthesis promoted by achiral amines in conjunction with asymmetric autocatalysis

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## Abstract

The origin of homochirality of organic compounds such as L-amino acids and D-sugars have intrigued many scientists, and several hypotheses regarding its homochirality have been proposed. According to the statistical theory, small fluctuations in the ratio of the two enantiomers are present in a racemic mixture obtained from the reaction of achiral molecules.

We report herein the reaction of pyrimidine-5-carbaldehyde and diisopropylzinc in the presence of achiral amine such as *N,N'*-dimethylpiperazine, *N,N'*-diethylpiperazine or *N*-methylmorpholine but in the absence of a chiral substance. The stochastic formation of (*S*)- and (*R*)-pyrimidyl alkanols with detectable ee was observed. This study shows that the slight fluctuation of the enantiomeric ratio of pyrimidyl alkanol produced at the initial reaction step can be enhanced significantly in conjunction with asymmetric autocatalysis with amplification of enantiomeric excess. We believe that the stochastic behavior in the formation of pyrimidyl alkanol constitutes one of the conditions necessary for spontaneous absolute asymmetric synthesis.

## Background

The origin of biomolecular homochirality such as L-amino acids and D-sugars is an interesting mystery [1-6]. Spontaneous absolute asymmetric synthesis [1], that is, the synthesis of enantioenriched products from achiral conditions in the absence of a chiral substance, has been proposed as one of the origins of chirality. Spontaneous asymmetric crystallization of achiral compounds is another of the proposed mechanisms of homochirality [7-10]. However, spontaneous absolute asymmetric synthesis without using chiral compounds differs from crystallization in that it is possible for an increase in the amount of chiral compound to occur. Experimental realization of spontaneous absolute asymmetric synthesis *via* asymmetric autocatalysis has been a challenge, although the theories have been proposed [11-13].

During our continuing studies of asymmetric autocatalysis [14-25], we have observed asymmetric autocatalysis of 5-pyrimidyl alkanols in the enantioselective addition of diisopropylzinc (*i*-Pr<sub>2</sub>Zn) to pyrimidine-5-carbaldehyde.

It is noteworthy that, even when an asymmetric autocatalyst with an extremely low ee was used as the initial catalyst, an almost enantiomerically pure product, i.e., asymmetric autocatalysis, could be obtained by consecutive reactions [16]. For example, when pyrimidyl alkanol with ca. 0.00005% ee was used as the initial catalyst, almost enantiomerically pure (> 99.5% ee) product was obtained after three consecutive asymmetric autocatalytic reactions [16]. Moreover, a variety of chiral organic compounds [26,27] and inorganic crystals including isotopically chiral compounds [28,29], inorganic crystals such as quartz [30], organic crystals of achiral compounds [31,32] and even a physical chiral factor, that is, right- or left-handed circularly polarized light [33], can act as chiral initiators to afford 5-pyrimidyl alkanol with a high ee in conjunction with asymmetric autocatalysis, with the product having an absolute configuration corresponding to that of the chiral initiators.

On the other hand, from the standpoint of statistics, small fluctuations in the ratio of the two enantiomers are expected to be present in racemic mixtures of chiral molecules [1,34,35]. We envisaged that when the reaction system involves asymmetric autocatalysis with amplification of ee, the initial small imbalance of

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enantiomers in racemic mixtures that arises from the reaction of achiral reactants becomes overwhelming to afford a highly enantiomerically enriched product [36-44].

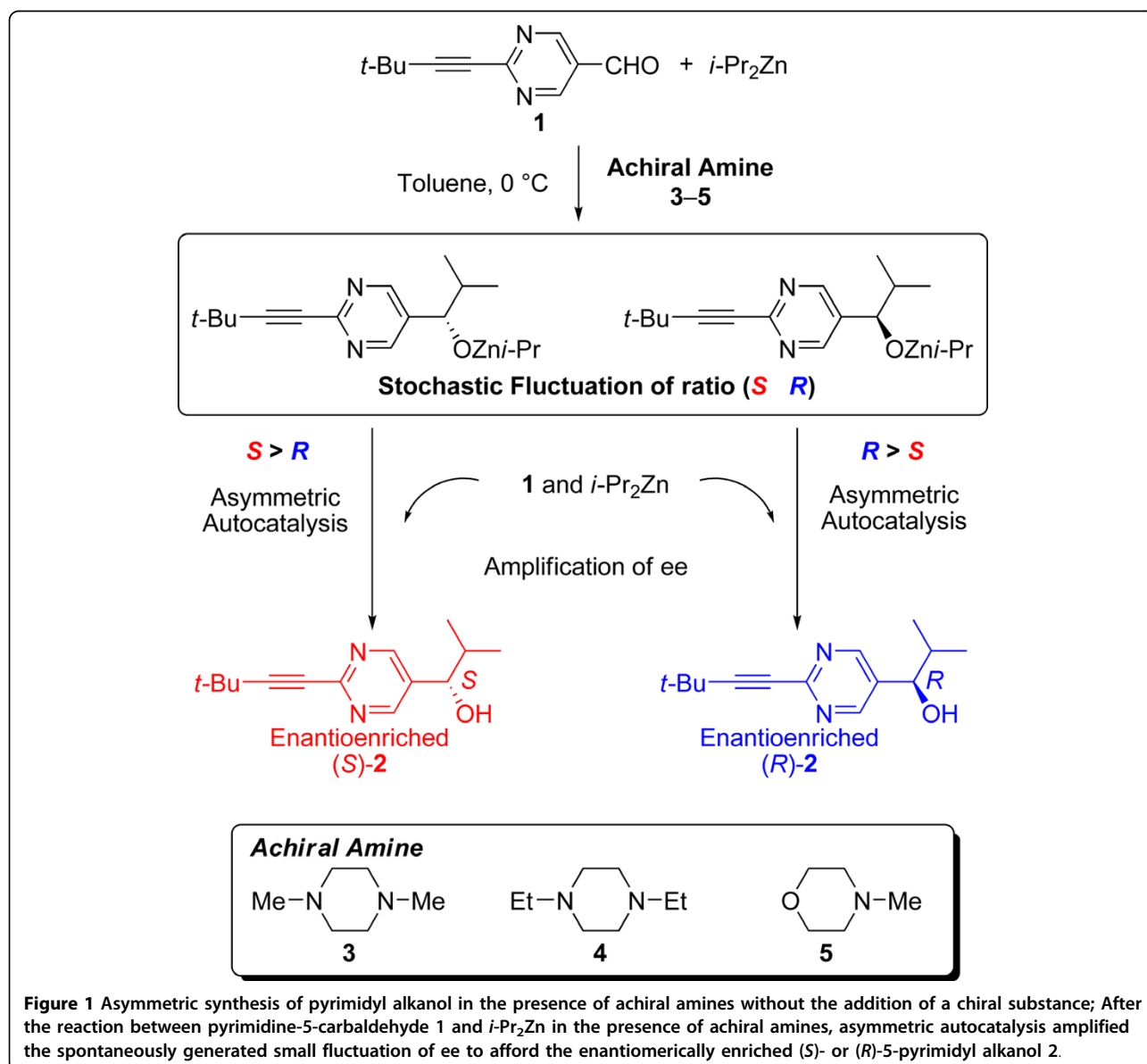
We have reported that without adding any chiral substance, enantioenriched (*S*)- or (*R*)-pyrimidyl alkanol **2** is generated in an approximately stochastic distribution from the reaction between pyrimidine-5-carbaldehyde **1** and *i*-Pr<sub>2</sub>Zn in conjunction with asymmetric autocatalysis [45-48].

## Results and Discussion

We previously reported that dialkylzincs are activated by amines to add to aldehydes [49,50]. Because an amine is a Lewis base, it coordinates to the zinc atom of dialkylzinc

[51], and this coordination enhances the nucleophilic character of the dialkylzinc. We reasoned as follows: when achiral amine is added to the reaction between aldehyde **1** and *i*-Pr<sub>2</sub>Zn, the achiral amine acts as a catalyst to promote the formation of racemic alkanol **2** with statistical fluctuation of chirality. The initial enantioenrichment would be amplified by the subsequent asymmetric autocatalysis to afford (*S*)- or (*R*)-alkanol **2**.

Here, we report that the enantioenriched pyrimidyl alkanol **2** is generated from the reaction between pyrimidine-5-carbaldehyde **1** and *i*-Pr<sub>2</sub>Zn in conjunction with asymmetric autocatalysis under achiral conditions in the presence of an achiral amine, such as *N,N'*-dimethylpiperazine **3**, *N,N'*-diethylpiperazine **4** or *N*-methylmorpholine **5** (Figure 1).

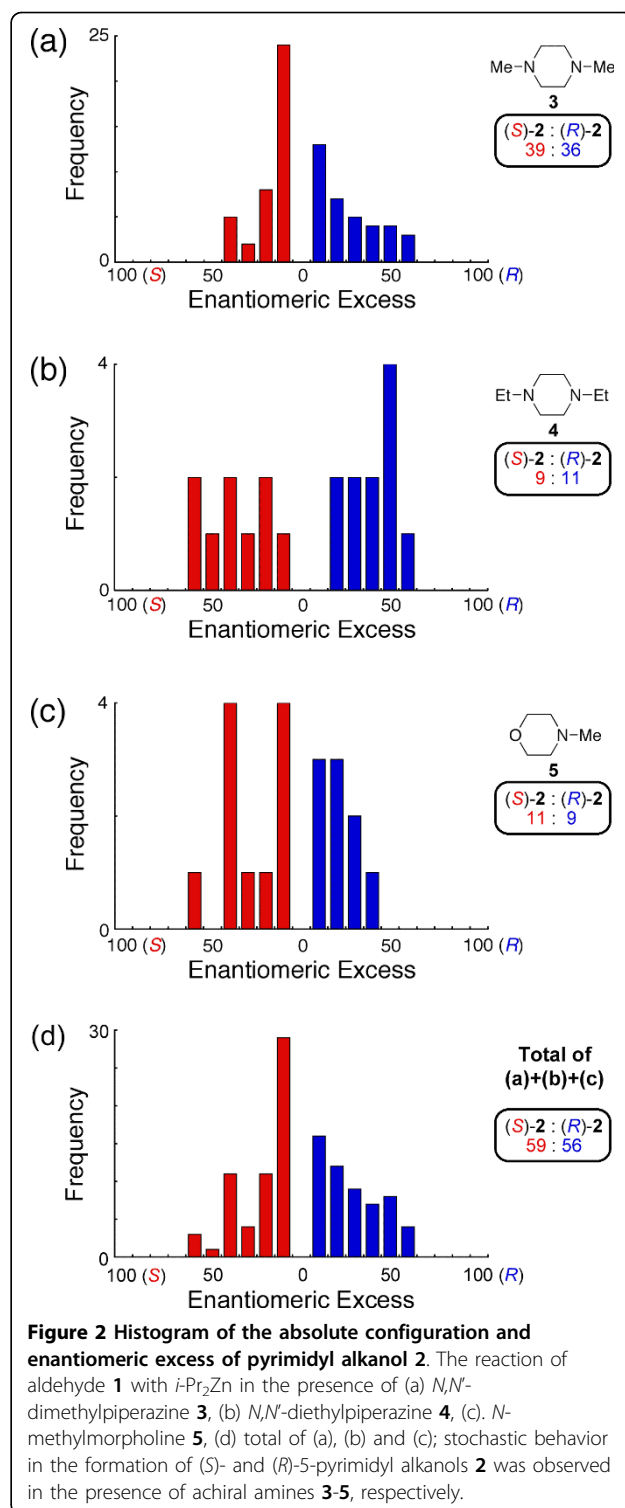


**Figure 1** Asymmetric synthesis of pyrimidyl alkanol in the presence of achiral amines without the addition of a chiral substance; After the reaction between pyrimidine-5-carbaldehyde **1** and *i*-Pr<sub>2</sub>Zn in the presence of achiral amines, asymmetric autocatalysis amplified the spontaneously generated small fluctuation of ee to afford the enantiomerically enriched (*S*)- or (*R*)-5-pyrimidyl alkanol **2**.

First, reaction of pyrimidine-5-carbaldehyde **1** with *i*-Pr<sub>2</sub>Zn in the presence of achiral *N,N'*-dimethylpiperazine **3** in toluene, followed by one-pot asymmetric autocatalysis with amplification of ee, was examined. The enantioenriched (*S*)- or (*R*)-5-pyrimidyl alkanol **2** was obtained. The results are shown in Table 1. To examine the distribution of the absolute configuration of the predominantly formed enantiomer **2**, 75 experiments were run under the same reaction conditions. In all cases, enantioenriched 5-pyrimidyl alkanols **2** with either *S* or *R* configurations were formed. As shown in Figure 2a, the absolute configurations of the resulting 5-pyrimidyl alkanol **2** exhibited an approximate stochastic distribution (the *S* form occurred 39 times and the *R* form occurred 36 times). It should be noted that the ee of the product **2** can be easily amplified significantly by further consecutive asymmetric autocatalytic reactions. That is, by using the alkanol **2** with low to moderate ee obtained in the described method as the asymmetric autocatalyst,

**Table 1 Asymmetric synthesis of pyrimidyl alkanol **2** without adding chiral substances by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde **1** in the presence of *N,N'*-dimethylpiperazine **3**.**

Run	Pyrimidyl alkanol <b>2</b>		Run	Pyrimidyl alkanol <b>2</b>		Run	Pyrimidyl alkanol <b>2</b>	
	ee	Config.		ee	Config.		ee	Config.
1	19	<i>R</i>	26	3	<i>R</i>	52	36	<i>S</i>
2	18	<i>S</i>	27	7	<i>S</i>	53	23	<i>S</i>
3	8	<i>R</i>	28	4	<i>S</i>	54	32	<i>R</i>
4	10	<i>S</i>	29	14	<i>R</i>	55	32	<i>S</i>
5	11	<i>R</i>	30	6	<i>S</i>	56	4	<i>S</i>
6	8	<i>S</i>	31	6	<i>R</i>	57	6	<i>R</i>
7	5	<i>S</i>	32	4	<i>S</i>	58	12	<i>S</i>
8	9	<i>R</i>	33	4	<i>R</i>	59	15	<i>S</i>
9	6	<i>S</i>	34	3	<i>S</i>	60	5	<i>S</i>
10	4	<i>S</i>	35	15	<i>S</i>	61	42	<i>R</i>
11	4	<i>S</i>	36	20	<i>S</i>	62	52	<i>R</i>
12	57	<i>R</i>	37	18	<i>R</i>	63	2	<i>S</i>
13	2	<i>R</i>	38	9	<i>R</i>	64	43	<i>R</i>
14	37	<i>S</i>	39	37	<i>S</i>	65	35	<i>R</i>
15	23	<i>R</i>	40	27	<i>S</i>	66	3	<i>S</i>
16	4	<i>S</i>	41	28	<i>R</i>	67	2	<i>R</i>
17	6	<i>R</i>	42	3	<i>R</i>	68	4	<i>S</i>
18	4	<i>S</i>	43	9	<i>S</i>	69	4	<i>S</i>
19	7	<i>S</i>	44	32	<i>S</i>	70	42	<i>R</i>
20	47	<i>R</i>	45	29	<i>R</i>	71	32	<i>R</i>
21	29	<i>R</i>	46	11	<i>S</i>	72	18	<i>R</i>
22	25	<i>R</i>	47	16	<i>R</i>	73	6	<i>S</i>
23	10	<i>S</i>	48	52	<i>R</i>	74	9	<i>R</i>
24	12	<i>S</i>	49	9	<i>R</i>	75	19	<i>R</i>
25	31	<i>R</i>	50	4	<i>S</i>			
26	12	<i>S</i>	51	19	<i>R</i>			



additional reactions between pyrimidine-5-carbaldehyde **1** and *i*-Pr<sub>2</sub>Zn could afford finally almost enantiomerically pure product **2** with the same absolute configuration as to the submitted asymmetric autocatalyst, in highly reproducible manner [16].

Next, the addition of *i*-Pr<sub>2</sub>Zn to pyrimidine-5-carbaldehyde **1** in the presence of achiral *N,N'*-diethylpiperazine **4** was examined. The results are summarized in Table 2 and Figure 2b. The absolute configurations of the pyrimidyl alkanol **2** formed show an approximate stochastic distribution (formation of *S* 9 times and *R* 11 times). The reaction in the presence of achiral *N*-methylmorpholine **5** gave the results of the stochastic formation of (*S*)- and (*R*)-alkanol **2** (formation of *S* 11 times and *R* 9 times, Table 3 and Figure 2c). The total distribution of alkanol **2** in the presence of achiral amines **3-5** is summarized in Figure 2d. The results of the formation of (*S*)-**2** in 59 times and (*R*)-**2** in 56 times strongly suggest that the reaction is spontaneous absolute asymmetric synthesis.

### Experimental

The typical experimental procedure is as follows: The pyrimidine-5-carbaldehyde **1** (37.6 mg, 0.20 mmol) dissolved in 2.0 mL of toluene was added dropwise over a period of 1 h to a mixture of *i*-Pr<sub>2</sub>Zn (0.40 mL of 1 M toluene solution, 0.40 mmol) and achiral *N,N'*-dimethylpiperazine **3** (1.1 mg, 1.0 × 10<sup>-2</sup> mmol) in toluene (4.0 mL) at 0°C. After the mixture was stirred for a period of 12 h at 0°C, 6.6 mL of toluene and *i*-Pr<sub>2</sub>Zn (0.80 mL of 1 M toluene solution, 0.80 mmol) were added successively, and the mixture was stirred at 0°C for a period of 15 min. The aldehyde **1** (75.3 mg, 0.4 mmol) in 2.0 mL of toluene was added dropwise at 0°C over a period of 40 min. After the mixture was stirred at 0°C for a period of 2 h, the reaction was quenched using 2.4 mL of 1 M hydrochloric acid. Saturated aqueous sodium hydrogen carbonate (7.2 mL) was then added, and the mixture filtered through Celite. The filtrate was extracted using ethyl acetate, dried over anhydrous sodium sulfate, and evaporated. Purification of the residue by silica gel TLC gave the pyrimidyl alkanol **2**.

**Table 2 Asymmetric synthesis of pyrimidyl alkanol 2 without adding chiral substances by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde 1 in the presence of *N,N'*-diethylpiperazine 4**

Run	Pyrimidyl alkanol 2		Run	Pyrimidyl alkanol 2		Run	Pyrimidyl alkanol 2	
	ee	Config.		ee	Config.		ee	Config.
1	50	<i>S</i>	8	53	<i>S</i>	15	36	<i>S</i>
2	57	<i>R</i>	9	39	<i>R</i>	16	24	<i>S</i>
3	47	<i>R</i>	10	40	<i>R</i>	17	22	<i>R</i>
4	55	<i>S</i>	11	37	<i>S</i>	18	5	<i>S</i>
5	14	<i>R</i>	12	20	<i>S</i>	19	35	<i>R</i>
6	27	<i>R</i>	13	47	<i>R</i>	20	11	<i>S</i>
7	10	<i>R</i>	14	47	<i>R</i>			

**Table 3 Asymmetric synthesis of pyrimidyl alkanol 2 without adding chiral substances by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde 1 in the presence of *N*-methylmorpholine 5**

Run	Pyrimidyl alkanol 2		Run	Pyrimidyl alkanol 2		Run	Pyrimidyl alkanol 2	
	ee	Config.		ee	Config.		ee	Config.
1	34	<i>S</i>	8	15	<i>R</i>	15	6	<i>S</i>
2	37	<i>R</i>	9	33	<i>S</i>	16	9	<i>R</i>
3	52	<i>S</i>	10	7	<i>R</i>	17	29	<i>R</i>
4	33	<i>S</i>	11	10	<i>S</i>	18	12	<i>S</i>
5	20	<i>R</i>	12	6	<i>S</i>	19	12	<i>R</i>
6	16	<i>R</i>	13	7	<i>R</i>	20	27	<i>S</i>
7	33	<i>S</i>	14	7	<i>S</i>			

### Conclusions

We have demonstrated the stochastic formation of (*S*)- and (*R*)-5-pyrimidyl alkanol **2** from pyrimidine-5-carbaldehyde **1** and *i*-Pr<sub>2</sub>Zn in the presence of achiral amines without the intervention of a chiral auxiliary. The presence of achiral amines facilitated the initiation of asymmetric autocatalysis by activation of diisopropylzinc. The stochastic behavior of the formation of (*S*)- and (*R*)-5-pyrimidyl alkanol **2** was observed in the presence of achiral amines. We believe that the phenomenon reported here constitutes one of the conditions necessary for a spontaneous absolute asymmetric synthesis. In this reaction system involving asymmetric autocatalysis with amplification of ee, the imbalance of enantiomeric purity in the initially forming racemic mixtures that arises from the reaction of achiral reactants becomes overwhelming to afford an enantiomerically enriched product. The mechanism and reaction model for the spontaneous generation of enantiopurity and amplification of ee in asymmetric autocatalysis [22,35-44,52-56] are now under investigation.

### Methods

All reactions were performed under an argon atmosphere. Toluene was distilled under argon in the presence of sodium benzophenone ketyl before use. Toluene solution of diisopropylzinc (1.0 M) is commercially available. Achiral amines **3-5** are commercial sources and were distilled from potassium hydroxide under reduced pressure before use. Pyrimidine-5-carbaldehyde **1** was synthesized and purified according to a reported procedure and was finally purified by sublimation before use. The ee of 5-pyrimidyl alkanol **2** was determined by HPLC using a chiral stationary phase (Daicel Chiralpak IB, eluent 5% 2-propanol in hexane (*v/v*), flow rate 1.0 mL min<sup>-1</sup>, 254 nm UV detector, retention time 11.4 min for (*S*)-**2**, 15.9 min for (*R*)-**2**).

## Abbreviations

S: sinister; R: rectus; T: tertiary; I: iso; EE: enantiomeric excess PR: propyl; BU: butyl; M: milli; M: mol/L; G: gram; L: liter; ME: methyl; ET: ethyl; TLC: thin-layer chromatography; HPLC: high performance liquid chromatography; MIN: minute.

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## Authors' contributions

KSo conceived the research project and obtained the research funding. KSu, KH and DN performed the asymmetric autocatalytic reactions in the presence of achiral amines. TK performed the project and taught how to perform the experiments. KSu, TK and KSo wrote the paper.

## Competing interests

The authors declare that they have no competing interests.

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