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Asymmetric synthesis of pyrimidyl alkanol without adding chiral substances by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde in conjunction with asymmetric autocatalysis

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Abstract—Enantiomerically enriched pyrimidyl alkanol with either *S* or *R* configuration was obtained stochastically from the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc without adding chiral substances in conjunction with subsequent asymmetric autocatalysis, leading to amplification of the enantiomeric excess.

The origins of optically active organic compounds such as L-amino acids and D-sugars have intrigued many scientists.[1] Spontaneous asymmetric crystallization is one of the proposed mechanisms.[2] On the other hand, asymmetric synthesis in the absence of chiral reagents, differing from crystallization, enables an increase in the amount of chiral compound. Although theories regarding spontaneous asymmetric synthesis[3] have been proposed, its practical realization remains a challenging problem.

During our continuing studies on asymmetric autocatalysis,[4,5] we found asymmetric autocatalysis of pyrimidyl alkanol in the enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) to pyrimidine-5-carbaldehyde. Pyrimidyl alkanol with low ee acts as an asymmetric autocatalyst with amplification of ee to afford itself with significantly high ee.[4d] Even pyrimidyl alkanol with as low as ca. 5×10^{-5}% ee enhances its ee to >99.5% ee during asymmetric autocatalysis.[4f] Moreover, a variety of chiral organic compounds and inorganic crystals act as chiral initiators to afford pyrimidyl alkanol with high ee with the absolute configurations corresponding to that of the chiral initiator used.[6]

According to the theory of Mills,[7] small fluctuations in the ratio of the two enantiomers are present in a given racemic mixture [it has been estimated that if a number of groups of 100,000 chiral molecules are produced under conditions under which the probability of formation of the enantiomers is statistically equal, half the groups will contain statistically an excess of more than 212 molecules of one enantiomer (0.21% ee)[7]].

When the reaction system involves asymmetric autocatalysis with amplification of ee,[4,5] the initial small imbalance of enantiomers in racemic mixtures that arises from the reaction of achiral reactants becomes overwhelming to afford a highly enantiomerically enriched product.

We report herein that, without adding chiral substances, optically active pyrimidyl alkanol is generated from the reaction between pyrimidine-5-carbaldehyde and *i*-Pr_2Zn in conjunction with subsequent asymmetric autocatalysis (Scheme 1).[8] Reaction of 2-alkynylpyrimidine-5-carbaldehyde **1** with *i*-Pr_2Zn in a mixed solvent of ether and toluene and the following one-pot asymmetric autocatalysis with amplification of ee[4] gave

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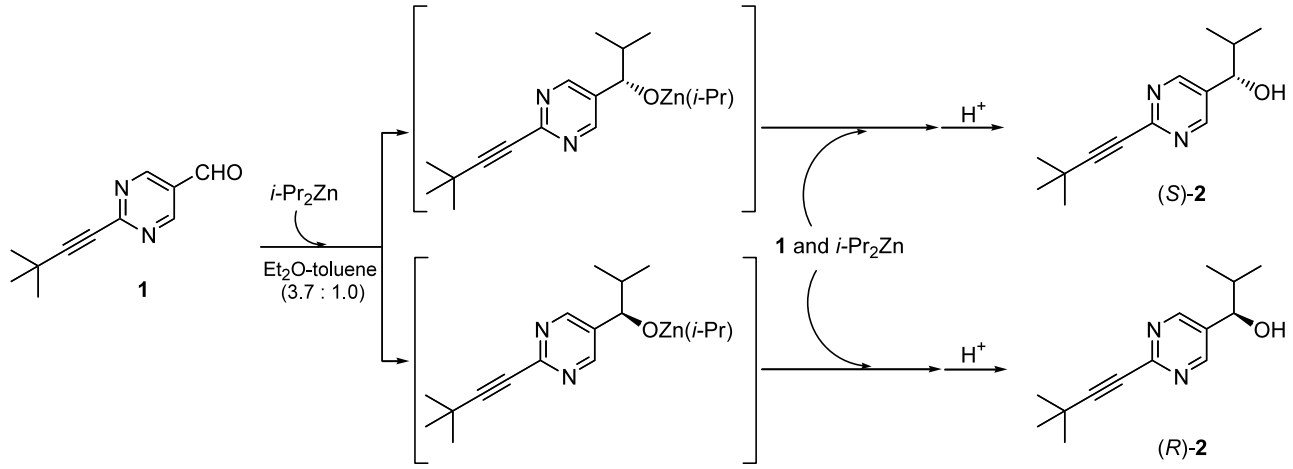

Scheme 1. Asymmetric synthesis of pyrimidyl alkanol without adding chiral substances.

optically active (*R*)-pyrimidyl alkanol **2** with 75% ee (Table 1, run 1). In order to examine the distribution of the predominantly formed enantiomer **2**, an additional 36 experiments were completed using new and clean equipment (glassware, syringe, needle, stirrer, etc.) under the same reaction conditions. In all cases, optically active pyrimidyl alkanol **2** with either *S* or *R* configurations was formed. As shown in Table 1 and Fig. 1, the absolute configurations of the pyrimidyl alkanol formed **2** show an approximate stochastic distribution (19 times formation of *S* and 18 times *R*). It should be noted that the ee of the product **2** can be enhanced significantly by further asymmetric autocatalysis.[4d,4f]

A typical experimental procedure is as follows: (Table 1, run 21): *i*-Pr_2Zn (1 M toluene solution, 0.20 ml, 0.20 mmol) was added dropwise at 0°C to aldehyde **1** (18.8 mg, 0.10 mmol) in diethyl ether (0.7 ml). The mixture was stirred for 1 h at 0°C and a solution of aldehyde **1** (75.3 mg, 0.4 mmol) in diethyl ether (3.0 ml) and *i*-Pr_2Zn (1 M toluene solution, 0.80 ml, 0.80 mmol) were added successively to the reaction mixture. The mixture was stirred for 2 h then quenched by adding 1

Table 1. Asymmetric synthesis of pyrimidyl alkanol **2** without adding chiral substances by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde **1**[a]

	Pyrimidyl alkanol **2**[b]				Pyrimidyl alkanol **2**[b]		
Run	Yield (%)	ee (%)	Config.	Run	Yield (%)	ee (%)	Config.
1	91	75	*R*	20	88	84	*S*
2	84	36	*R*	21	87	82	*R*
3	94	65	*S*	22	82	68	*R*
4	86	63	*R*	23	89	85	*R*
5	73	26	*R*	24	72	86	*R*
6	82	84	*S*	25	86	56	*S*
7	93	45	*R*	26	89	85	*S*
8	91	82	*R*	27	88	54	*R*
9	96	65	*S*	28	80	69	*S*
10	99	81	*S*	29	99	91	*S*
11	86	81	*S*	30	87	64	*R*
12	90	77	*R*	31	99	57	*S*
13	90	15	*S*	32	99	57	*S*
14	86	76	*S*	33	96	66	*R*
15	85	78	*R*	34	92	90	*S*
16	86	75	*S*	35	92	71	*R*
17	99	45	*R*	36	87	83	*S*
18	99	82	*S*	37	96	85	*S*
19	99	29	*R*				

[a] *i*-Pr_2Zn (0.20 ml of 1 M toluene solution, 0.20 mmol) was added dropwise at 0°C to aldehyde **1** (0.10 mmol) in Et_2O (0.7 ml). After the mixture was stirred for 1 h at 0°C, aldehyde **1** (0.4 mmol) in Et_2O (3.0 ml) and *i*-Pr_2Zn (0.80 ml of 1 M toluene solution, 0.80 mmol) were added and the mixture was stirred for 2 h.

[b] The ee and the configuration of pyrimidyl alkanol **2** were determined by HPLC analysis using chiral stationary phase (Daicel Chiralcel OD or OD-H).

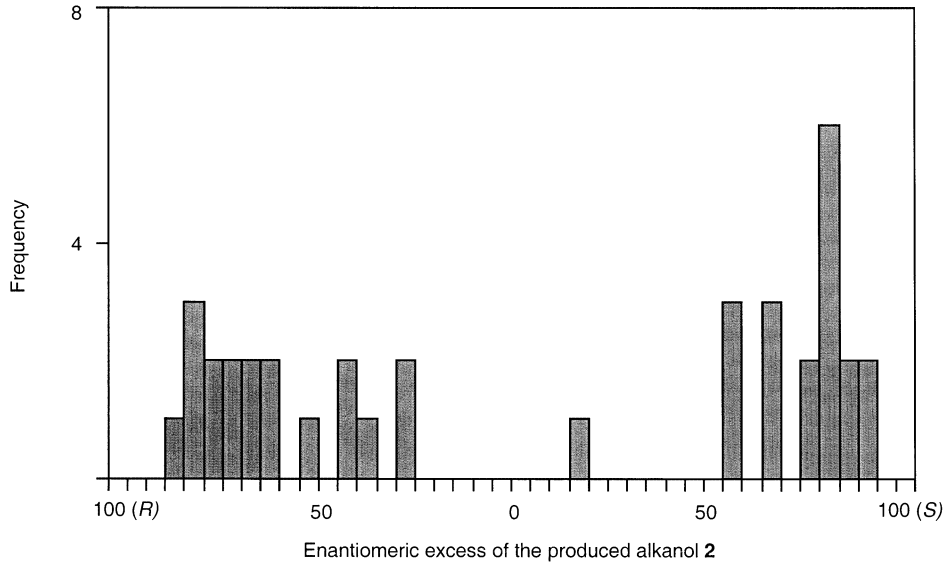

Figure 1. Histogram of the absolute configuration and the enantiomeric excess of pyrimidyl alkanol **2**.

M hydrochloric acid (2 ml). Satd. aq. sodium hydrogen carbonate (5 ml) was added, and the mixture was filtered through Celite. The filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated. Purification of the residue by silica gel TLC gave pyrimidyl alkanol **2** (101 mg, 87%). HPLC analysis of the obtained alkanol **2** by HPLC using a chiral column (Daicel Chiralcel OD) showed that alkanol (*R*)-**2** has 82% ee.

The reaction between pyrimidine-5-carbaldehyde and *i*-Pr_2Zn in toluene without adding chiral substances also gave optically active (*S*)- or (*R*)-pyrimidyl alkanol. However, in our hands, the enantiomer of the predominantly formed pyrimidyl alkanol deviated from the stochastic distribution, which is probably due to unknown chiral factors. Very recently Singleton and Ho reported the formation of the optically active pyrimidyl alkanol from pyrimidine-5-carbaldehyde and *i*-Pr_2Zn in toluene, where a deviation from the stochastic distribution was also observed.[9]

Based on our previous observation on the dramatic solvent effects between ethereal and hydrocarbon solvents in the enantioselective addition of organometallic reagents to aldehydes,[10] we postulate the reason for the different distributions of the enantiomers of **2** when a mixed ether–toluene solvent system and toluene alone were used: The solvation of the reactive intermediate is different for the two systems because Et_2O is able to coordinate to zinc more strongly than toluene. This difference in solvation between the two solvent systems may change the structure of the reactive intermediate. The greater solvation of the reactive intermediate in the mixed Et_2O–toluene solvent system may lessen the effect of unknown chiral factors, enabling the stochastic formation of optically active pyrimidyl alkanol.

In summary, we have demonstrated stochastic formation of (*S*)- and (*R*)-pyrimidyl alkanol from pyrimidine-5-carbaldehyde and diisopropylzinc in a mixed solvent of ether and toluene without adding chiral compounds. We believe that the stochastic behavior in the formation of pyrimidyl alkanols reported here constitutes one of the conditions necessary for spontaneous asymmetric synthesis.

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