Asymmetric Autocatalysis of Pyrimidyl Alkanol Induced by Optically Active 1,1′-Binaphthyl, an Atropisomeric Hydrocarbon, Generated from Spontaneous Resolution on Crystallization

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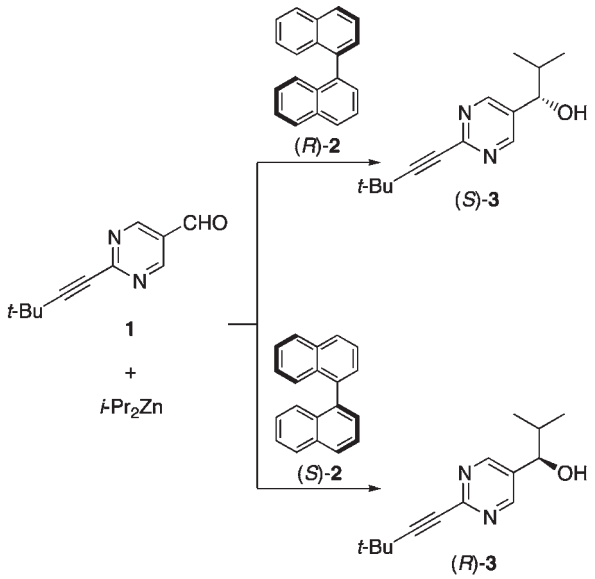
An atropisomeric hydrocarbon, (*R*)-1,1′-binaphthyl, acts as a chiral initiator of asymmetric autocatalysis of pyrimidyl alkanol in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde to afford (*S*)-5-pyrimidyl alkanol **2** with 96% ee. On the other hand, in the presence of (*S*)-1,1′-binaphthyl, the reaction affords (*R*)-**2** with 94% ee.

Origin of chirality of organic compounds has attracted much attention.[1] One of the proposed mechanisms is a spontaneous resolution on crystallization from the racemate. 1,1′-Binaphthyl **2** displays spontaneous optical resolution on crystallization from the melt.[2,3] Crystallization at 150 °C from unstirred melt shows the Gaussian-like distribution of optical activity (mean 20% ee) centered around zero.[2] Recently, Kondepudi and co-workers reported that, in the crystallization from the "stirred" melt at 150 °C, almost all **2** precipitated have the same chirality (mean 77% ee).[3] Although optically active **2** is obtained by the above procedure, **2** racemizes rapidly at melt and moderately in solution (half life time is *ca.* 10 h in benzene at room temperature[3]). Thus, we became interested in synthesizing non-racemizable optically active compound with high ee using optically active **2** as a chiral inducer.

Meanwhile, chiral hydrocarbon has rarely been used as chiral inducer in enantioselective synthesis[4] mainly due to the fact that chiral hydrocarbon doesn't possess any heteroatom which facilitates the chiral recognition by, for example, coordinating with metal atoms of reagents. To the best of our knowledge, optically active **2** (note that it is an atropisomeric hydrocarbon bearing no heteroatom) has never been used successfully as chiral inducer in asymmetric synthesis.[5] During our study on asymmetric autocatalysis[6–8] initiated by chiral organic[9a-d] and inorganic[9e,f] substances, and by chiral metal complexes,[9g] we recently reported asymmetric autocatalysis using optically active helical hydrocarbons, *i.e.*, [6] and [5] helicenes, as chiral initiators.[9a]

We report here asymmetric autocatalysis[8] of pyrimidyl alkanol **3** using **2** as a chiral initiator in the enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) to 2-alkynylpyrimidine-5-carbaldehyde **1**. The objectives of the present paper are as follows: (1) Chiral induction by atropisomeric hydrocarbon **2** in asymmetric autocatalytic reaction. (2) Correlation of the chirality of **2** generated by spontaneous crystallization to that of functionalized pyrimidyl alkanol **3** with high ee.

To (*R*)- or (*S*)-1,1′-binaphthyl **2**, pyrimidine-5-carbaldehyde **1**[6c] and *i*-Pr_2Zn were added in two portions (Method A). The results are shown in Table 1. In the presence of (*R*)-**2** with 81 and 93% ee, (*S*)-pyrimidyl alkanol **3** with 83 and 93% ee were obtained, respectively (Runs 1 and 2). On the other hand, the presence of (*S*)-**2** with 81 and 89% ee afforded the opposite enantiomer (*R*)-**3** with 83 and 82% ee, respectively (Runs 3 and 4). In addition, (*R*)- and (*S*)-**2** with moderate (74% and 78%) ee's served as chiral initiator to afford (*S*)- and (*R*)-**3**, respectively (Runs 5 and 6). When aldehyde **1** and *i*-Pr_2Zn were added further, *i.e.*, in three portions in total (Method B), pyrimidyl alkanol **3** with higher ee was formed. Thus, (*R*)-**2** with 77% ee afforded (*S*)-**3**



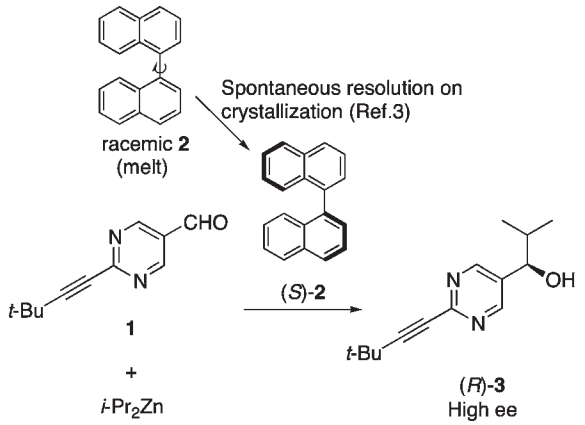
Scheme 1. Asymmetric autocatalysis of pyrimidyl alkanol using 1,1′-binaphthyl, atropisomeric hydrocarbon, as chiral initiator.

Table 1. Highly enantioselective synthesis of pyrimidyl alkanol **3** initiated by 1,1′-binaphthyl **2**[a]

	1,1′-Binaphthyl **2**[b]			Pyrimidyl alkanol **3**[d]		
Run	ee/%	Config.	Method[c]	Yield/%	ee/%	Config.
1	81	*R*	A	87	83	*S*
2	93	*R*	A	92	93	*S*
3	81	*S*	A	87	83	*R*
4	89	*S*	A	84	82	*R*
5	74	*R*	A	86	79	*S*
6	78	*S*	A	84	80	*R*
7	77	*R*	B	99	96	*S*
8	80	*S*	B	95	94	*R*

[a]For experimental details, see the text. [b]Generated from spontaneous resolusion on crystallization of racemic melt (Runs 5 and 6) or resolved by HPLC using a chiral stationary phase (Chiralcel OD, Runs 1–4, 7 and 8). [c]Method A: Molar ratio, 1,1′-Binaphthyl **2**: Aldehyde **1**: *i*-Pr_2Zn = 0.3 : 1 : 2.7. Aldehyde **1** and *i*-Pr_2Zn were added in two portions. Method B: **2** : **1** : *i*-Pr_2Zn = 0.05 : 1 : 2.1. **1** and *i*-Pr_2Zn were added in three portions. [d]The ee value was determined by HPLC analysis using chiral stationary phase (Chiracel OD).

with 96% ee and (*S*)-**2** with 80% ee, (*R*)-**3** with 94% ee (Runs 7 and 8). These results show that the absolute configuration of the produced alkanol **3** is controlled by the chirality of **2**. The reason of the higher ee of alkanol **3** in Method B is attributed to the fact that the process involves asymmetric autocatalysis of pyrimidyl alkanol with amplification of ee.[6–8] The ee of **3** can be amplified significantly by further asymmetric autocatalysis of **3**.[6,7] Thus, the overall process correlates the chirality of **2** generated from spontaneous crystallization[3] to that of functionalized pyrimidyl alkanol **3** with high ee (Scheme 2).



Scheme 2. Correlation of the chirality of 1,1′-binaphthyl generated from spontaneous resolusion on crystallization to that of pyrimidyl alkanol with high ee.

In a typical experiment (Table 1, Run 7), to a solution of aldehyde **1** (9.4 mg, 0.05 mmol) and (*R*)-**2** (12.5 mg, 0.05 mmol, 77% ee) in toluene (0.1 mL), a 1 M toluene solution (0.15 mL) of *i*-Pr_2Zn was added dropwise over a period of 30 min at 0 °C. After the mixture was stirred for 14 h, toluene (4.8 mL), a 1 M toluene solution (0.4 mL) of *i*-Pr_2Zn, and aldehyde **1** (37.6 mg, 0.2 mmol) in toluene (1.5 mL) were added successively. After 5 h, toluene (14 mL), a 1 M toluene solution (1.6 mL) of *i*-Pr_2Zn, and aldehyde **1** (151 mg, 0.8 mmol) in toluene (4 mL) were added and the mixture was stirred for further 3 h. The reaction was quenched by adding 1 M hydrochloric acid (4 mL), made alkaline by saturated aq. sodium bicarbonate (12 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 pyrimidyl alkanol (*S*)-**3** with 96% ee (242 mg, 1.04 mmol) in a yield of 99%.

In summary, we have demonstrated that an atropisomeric hydrocarbon 1,1′-binaphthyl **2** acts as a chiral initiator in the enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **1** to afford, in combination with asymmetric autocatalysis, pyrimidyl alkanol **3** with high ee.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

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