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Asymmetric autocatalysis induced by chiral hydrocarbon [2.2]paracyclophanes

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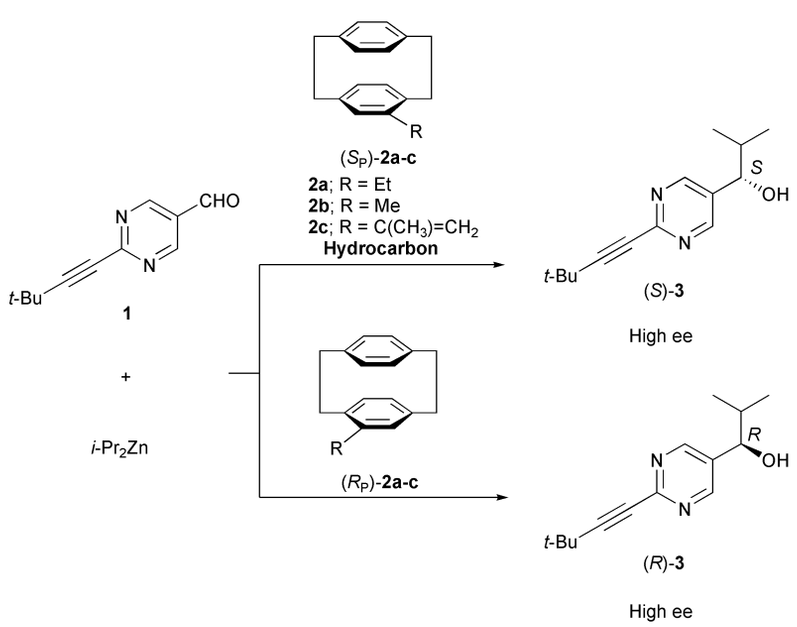
Chiral hydrocarbon [2.2]paracyclophanes act as chiral initiators in asymmetric autocatalysis in the addition of diisopropylzinc to pyrimidine-5-carbaldehyde and give highly enantiomerically enriched 5-pyrimidyl alkanol with a reversed sense of the enantioselectivity to that of other [2.2]paracyclophanes with heteroatoms.

During the last few years, enantioselective synthesis has been reported using chiral ligands or chiral auxiliaries derived from [2.2]paracyclophane.[1–5] For example, chiral bisphosphine ligands derived from [2.2]paracyclophane have been successfully used in enantioselective hydrogenation[2c,g,h] and kinetic resolution.[2d] Chiral Schiff-bases[2a,b,e,f,l] with a [2.2]paracyclophane skeleton have been used in catalytic enantioselective addition of dialkylzincs to aldehydes[2n] or imines.[2o] Mono-substituted [2.2]paracyclophanes are also used as chiral ligands. Enantioselective epoxidation of allylic alcohols using vanadium complexes of chiral mono-substituted [2.2]paracyclophane with a *N*-hydroxy-4-carboxylic amide moiety affords epoxy alcohols with up to 71% ee,[3d,f] and cyclopropanation of olefins using chiral monosubstituted Schiff-base derived from [2.2]paracyclophane shows up to 68% enantioselectivity.[3b,e] Very recently, mono-substituted [2.2]paracyclophanes were employed as chiral ligands in the enantioselective addition of dialkylzincs to aldehydes by us[5] and Ruzziconi and co-workers.[3g] The cyclophane-based chiral ligands possess a carbonyl group or a pyridyl alcohol, which are known to coordinate to alkylmetals. Thus, to the best of our knowledge, chiral hydrocarbon [2.2]paracyclophanes have not been employed in the enantioselective addition of dialkylzincs to aldehydes as well as other kinds of enantioselective synthesis.

Meanwhile, during our continuing study on asymmetric autocatalysis, it was found that asymmetric autocatalysis of 5-pyrimidyl alkanol in the enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) to pyrimidine-5-carbaldehyde proceeds with amplification of ee.[6,7] Moreover, when *i*-Pr_2Zn was reacted with pyrimidine-5-carbaldehyde in the presence of chiral initiators such as amino acids,[8a] deuterated primary alcohols,[8b] quartz[8c] and sodium chlorate,[8d] the absolute configurations of the obtained 5-pyrimidyl alkanols depend on those of the chiral initiators.[8,9] Chiral hydrocarbons such as helicenes,[10a] 1,1′-binaphthyl[10b] and 1,3-disubstituted allenes[10c] act as chiral initiators. Compared to these chiral hydrocarbons, chiral hydrocarbons derived from [2.2]paracyclophanes have unique structures with planar chirality. In addition, mono-substituted [2.2]paracyclophanes possess two similar but slightly different pi faces. One face is an aromatic ring with a substituent, and the other is an aromatic ring without any substituent. Thus, the discrimination and the use of hydrocarbon mono-substituted [2.2]paracyclophane in enantioselctive synthesis is a challenge.

We here report the asymmetric autocatalysis of 5-pyrimidyl alkanol induced by chiral hydrocarbon [2.2]paracyclophane (Scheme 1).

First, chiral 4-ethyl[2.2]paracyclophane **2a**[11] was used as a chiral initiator (Table 1). To an ice cooled methylcyclohexane solution of aldehyde **1** and [2.2]paracyclophane (S_p)-(+)-**2a**, a hexane solution of *i*-Pr_2Zn was slowly added. The solution was then diluted with toluene, and aldehyde **1** and *i*-Pr_2Zn were added portionwise. Aqueous work up gave (*S*)-2-alkynyl-5-pyrimidyl alkanol **3** with 98% ee. In contrast, (*R*)-alkanol **3** with 96% ee was obtained by the corresponding reaction in the presence of (R_p)-(−)-**2a**. Thus, the absolute configuration of



Scheme 1 Highly enantioselective synthesis of chiral 5-pyrimidyl alkanol in the presence of hydrocarbon [2.2]paracyclophanes **2a**–**c**.

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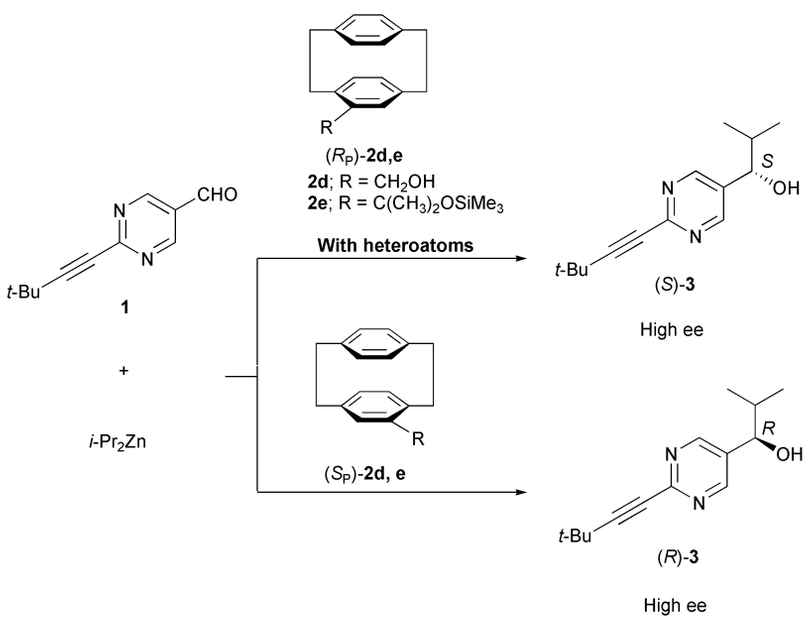
Table 1 Highly enantioselective synthesis of chiral 5-pyrimidyl alkanol in the presence of mono-substituted chiral [2.2]paracyclophanes[a]

Entry	[2.2]Paracyclophane[b]			Solvent	Pyrimidyl alkanol		
		R	Config. (ee/%)		Yield (%)	Ee (%)	Config.
1	**2a**	Et	S_p (94)	Methylcyclohexane–toluene	95	98	*S*
2			R_p (88)		95	96	*R*
3	**2b**	Me	S_p (98)		97	96	*S*
4			R_p (>99.5)		96	93	*R*
5	**2c**	$C(CH_3)=CH_2$	S_p (>99.5)		95	98	*S*
6			R_p (99)		93	92	*R*
7	**2d**	CH_2OH	S_p (>99.5)		89	99	*R*
8			R_p (98)		99	99	*S*
9			S_p (>99.5)	Toluene	93	97	*R*
10			R_p (98)		96	93	*S*
11	**2e**	$C(CH_3)_2OSiMe_3$	S_p (99)[c]		88	90	*R*
12			R_p (99)[c]		87	96	*S*

[a] Reactions were performed at 0 °C. Molar ratio for entries 1–6, [2.2]paracyclophane **2**: aldehyde **1**: *i*-Pr_2Zn = 0.1–0.2: 1: 2. For entries 7–12, **2**: **1**: *i*-Pr_2Zn = 0.01–0.05 : 1 : 2. [b] Unless indicated, the configuration was determined by the comparison of the sign of the specific rotation to the literature. The ee was determined by HPLC analysis on a column fitted with a chiral stationary phase (Chiralcel OD-H for **2a**,**b**. Chiralcel OJ for **2c**. Chiralcel OD for **2d**,**e**). [c] Configuration was assigned by the stereospecific transformation from chiral 4-carboxy[2.2]paracyclophane.



Scheme 2 Highly enantioselective synthesis of chiral 5-pyrimidyl alkanol in the presence of [2.2]paracyclophanes with heteroatom **2d**,**e**.

5-pyrimidyl alkanol formed is dependent on that of the chiral [2.2]paracyclophane. Chiral 4-methyl-,[12] and 4-isopropenyl-[2.2]paracyclophane[13] **2b**,**c** were also used as chiral initiators. In a similar manner of enantioselectivity, the reaction in the presence of (S_p)-(+)-4-methyl[2.2]paracyclophane **2b** and (S_p)-(+)-4-isopropenyl[2.2]paracyclophane **2c** afforded (*S*)-5-pyrimidyl alkanol **3** with 96 and 98% ee, respectively (entries 3 and 5). On the other hand, (R_p)-(−)-**2b** and (R_p)-(−)-**2c** gave (*R*)-pyrimidyl alkanol with 93 and 92% ee, respectively (entries 4 and 6).

Next, chiral [2.2]paracyclophanes with heteroatoms **2d**,**e** were examined as chiral initiators (Scheme 2). Chiral 4-hydroxymethyl[2.2]paracyclophane **2d**[14] as a chiral initiator showed the opposite sense of the enantioselectivity to those of hydrocarbons **2a**–**c**. In the presence of (S_p)-(+)-**2d**, (*R*)-alkanol **3** with 99% ee was obtained from the asymmetric autocatalysis (entry 7), whereas (*S*)-alkanol **3** with 99% ee was obtained in the presence of (R_p)-(−)-**2d** (entry 8). When the reactions were carried out in toluene, the same sense of the enantioselectivity was observed (entries 9 and 10). [2.2]Paracyclophane with trimethylsilyl ether **2e** also worked as a chiral initiator. The reaction in the presence of (S_p)-(+)-**2e** afforded (*R*)-pyrimidyl alkanol with 90% ee, (entry 11). The cyclophane (R_p)-(−)-**2e** with the opposite configuration induced the formation of (*S*)-pyrimidyl alkanol with 96% ee (entry 12).

Thus, the sense of the enantioselectivity in the cases of hydrocarbon [2.2]paracyclophanes **2a**–**c** is opposite to that of [2.2]paracyclophanes with heteroatoms **2d**,**e**. The reversal of the sense of the enantioselectivity may be attributed to the less Lewis basic nature of the alkyl or alkenyl substituent (**2a**–**c**) than the substituents with more basic oxygen atoms (**2d**,**e**). In other words, hydrocarbon substituents of **2a**–**c** may play a role of bulkiness while heteroatom substituents of **2d**,**e** may play a role of coordination with the zinc atom.

A typical experimental procedure is as follows (Table 1, entry 2): to an ice cooled methylcyclohexane solution (3.5 ml) of (R_p)-(−)-4-ethyl[2.2]paracyclophane (**2a**) (23.6 mg, 0.01 mmol, 88% ee) and aldehyde **1** (4.7 mg, 0.025 mmol), *i*-Pr_2Zn (0.05 ml of 1 M hexane solution, 0.05 mmol) was added over a period of 30 min. After the mixture was stirred for 16 h at 0 °C, toluene (2.4 ml) and *i*-Pr_2Zn (0.20 ml of 1 M toluene solution, 0.20 mmol) were added to the reaction mixture and the mixture was stirred for 15 min. A toluene solution (1.5 ml) of aldehyde **1** (18.8 mg, 0.10 mmol) was added and the reaction mixture was stirred for an additional 4 h at 0 °C. Toluene (7.2 ml), *i*-Pr_2Zn (0.80 ml of 1 M toluene solution, 0.80 mmol) and a toluene

solution (2.0 ml) of aldehyde **1** (75.3 mg, 0.40 mmol) were added and stirred for 4 h. The reaction was quenched by adding 1 M hydrochloric acid (3 ml). Satd. aq. sodium hydrogen carbonate (9 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 on silica gel TLC gave pyrimidyl alkanol **3** (117 mg, 95%). HPLC analysis of the obtained alkanol **3** using a chiral column (Daicel Chiralcel OD) showed that alkanol (*R*)-**3** had an ee value of 96%.

In summary, hydrocarbon mono-substituted [2.2]paracyclophanes were successfully used as chiral initiators in asymmetric autocatalysis. Highly enantiomerically enriched 5-pyrimidyl alkanol was obtained from the reaction. The sense of the enantioselectivity of mono-substituted [2.2]paracyclophanes without any heteroatom is opposite to that of other mono-substituted [2.2]paracyclophanes with heteroatoms.

Acknowledgements

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