ORGANIC LETTERS

2001
Vol. 3, No. 2
287−289

Asymmetric Autocatalysis of a Pyrimidyl Alkanol Induced by Chiral Monosubstituted [2.2]Paracyclophanes

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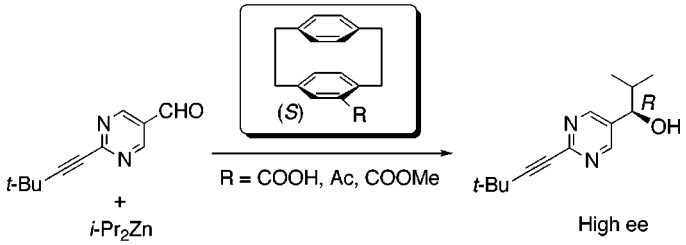
Received November 25, 2000

ABSTRACT



Monosubstituted[2.2]paracyclophanes 3a–c with planar chirality were found to act as chiral initiators in an enantioselective addition of diisopropylzinc to 2-alkynylpyrimidine-5-carbaldehyde 1 to afford 2-alkynylpyrimidyl alkanol 2 with up to 97% ee.

Over the past several years, [2.2]paracyclophanes with planar chirality have received growing interest as chiral ligands in enantioselective reactions. A planar chiral bisphosphine ligand derived from [2.2]paracyclophane has been successfully used in enantioselective hydrogenation[1a,b] and kinetic resolution.[1c] Chiral Schiff-bases of salicylic aldehydes with a [2.2]paracyclophane skeleton have been used in enantioselective cyanation[1d] and oxidation.[1e] A chiral sulfide derivative of [2.2]paracyclophane with an oxazoline ring has been used in enantioselective allylic alkylation.[1f] On the other hand, compared with these disubstituted [2.2]paracyclophanes, chiral monosubstituted [2.2]paracyclophanes exhibit moderate enantioselectivities as chiral ligands. Enantioselective epoxidation of allylic alcohols using vanadium complexes of chiral monosubstituted [2.2]paracyclophane with a *N*-hydroxy-4-carboxylic amide moiety affords epoxy alkanols with up to 71% ee,[2a] and cyclopropanation of olefins using chiral monosubstituted Schiff-base derived from [2.2]paracyclophane shows up to 68% enantioselectivity.[2b,c] The use of bipyridine-type [2.2]paracyclophane as a chiral ligand in enantioselective reduction gives an enantioselectivity of 31%,[2d] while a chiral porphyrin ligand derived from [2.2]paracyclophane-4-carbaldehyde shows an enantioselectivity of 31% in enantioselective epoxidation.[2e]

On the other hand, in the course of our continuing study on asymmetric autocatalysis[3] using pyridyl[4a−d] and pyrimidyl alkanols,[4e,f] 2-alkynylpyrimidyl alkanol was found to be a very efficient asymmetric autocatalyst.[5] Recently, we reported that chiral inorganic crystals[6a,b] and a chiral compound with very low ee possessing an asymmetric carbon atom[6c] induce the enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) to 2-alkynyl-pyrimidine-5-carbaldehyde to afford

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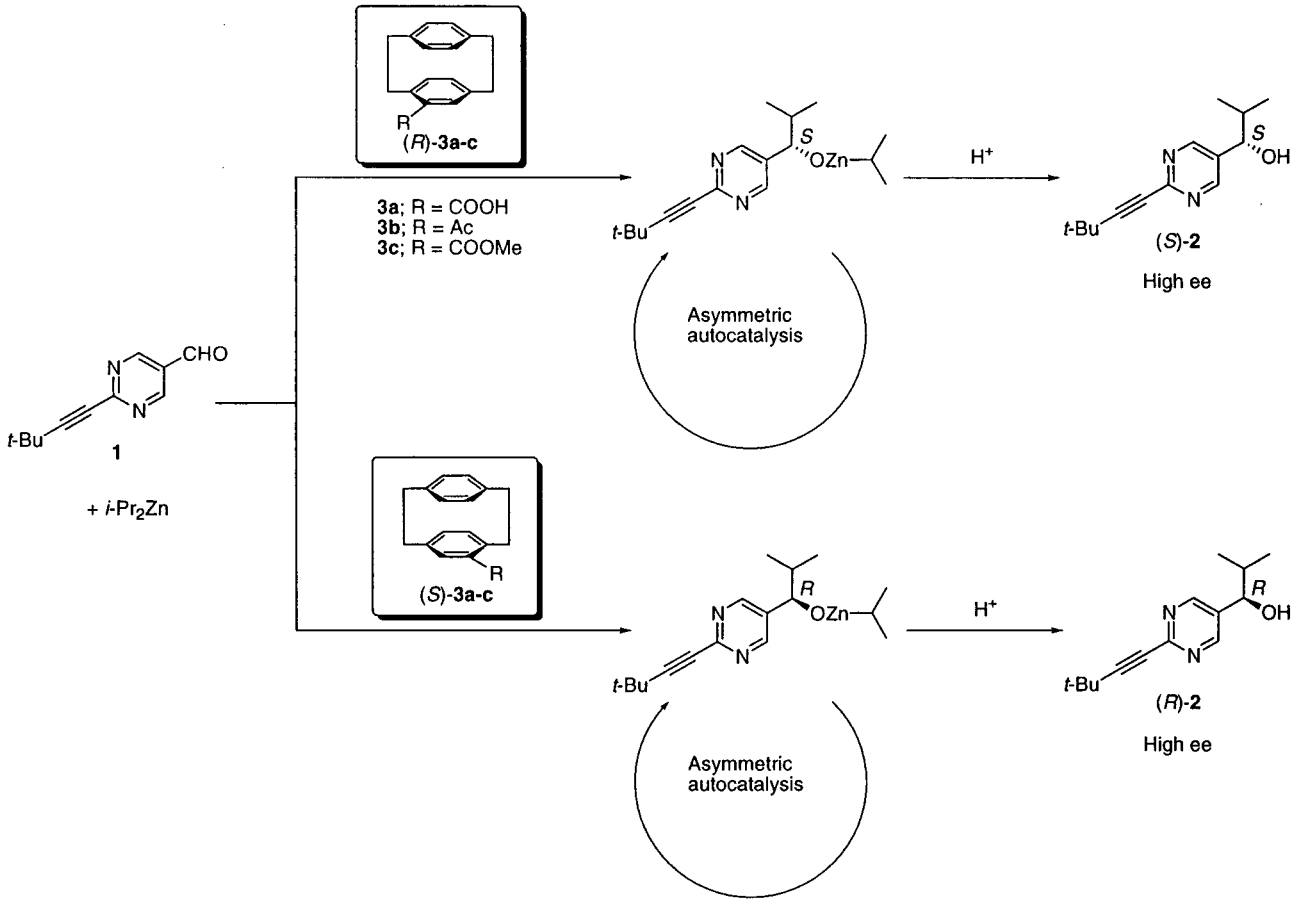
10.1021/ol006921w CCC: $20.00
Published on Web 01/05/2001

Scheme 1



pyrimidyl alkanol with high ee. We report here an asymmetric autocatalytic reaction initiated by monosubstituted [2.2]paracyclophane derivatives with planar chirality (Scheme 1).

First, we examined the enantioselective addition of *i*-Pr_2Zn to 2-(*tert*-butylethynylpyrimidine)-5-carbaldehyde (**1**) in the presence of (*S*)- or (*R*)-4-carboxy[2.2]paracyclophane (**3a**)[7] as a chiral initiator. The results are shown in Table 1. When (*S*)-(+)-**3a** with 99% ee (4.8 mol %) were added 2-alkynylpyrimidine-5-carbaldehyde **1** and *i*-Pr_2Zn in three portions, (*R*)-pyrimidyl alkanol **2** was obtained in 91% yield with a very high ee of 95% (entry 1). On the other hand, in the presence of (*R*)-(−)-**3a** with 93% ee, enantioselective addi-

Table 1. Enantioselective Synthesis of Chiral Pyrimidyl Alkanol **2** in the Presence of (*S*)- or (*R*)-4-Carboxy[2.2]paracyclophane **3a**

	4-carboxy[2.2]-paracyclophane **3a**:	pyrimidyl alkanol **2**	
entry[a]	ee (%)[b]	yield (%)	ee (%)[c]
1	99 (*S*)	91	95 (*R*)
2[d]	99 (*S*)	94	95 (*R*)
3[e]	99 (*S*)	94	94 (*R*)
4	93 (*R*)	94	92 (*S*)
5[d]	93 (*R*)	96	97 (*S*)
6[e]	93 (*R*)	90	91 (*S*)
7	29 (*S*)	90	95 (*R*)
8	27 (*R*)	91	91 (*S*)
9	2.5 (*R*)	95	89 (*S*)

[a] Unless otherwise noted, molar ratio is as follows: 4-Carboxy[2.2]paracyclophane **3a**:**1**:*i*-Pr_2Zn = 0.048:1.0:2.1. [b]Determined by HPLC analyses using a chiral stationary phase (Chiralcel OC). [c]Determined by HPLC analyses using a chiral stationary phase (Chiralcel OD). [d]Molar ratio. **3a**:**1**:*i*-Pr_2Zn = 0.0095:1.0:2.1. [e]Molar ratio. **3a**:**1**:*i*-Pr_2Zn = 0.0024:1.0:2.1.

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tion of *i*-Pr_2Zn to aldehyde **1** gave the opposite enantiomer (*S*)-**2** with 92% ee (entry 4). Thus, it was elucidated that the [2.2]paracyclophane derivative induces chirality in the enantioselective addition of *i*-Pr_2Zn to aldehyde **1**. Even when very small amounts (0.24−0.95 mol % against aldehyde **1**) of chiral **3a** were used, chiral pyrimidyl alkanol **2** with significantly high (91−97%) ee was obtained (entries 2, 3, 5, and 6).

Moreover, it became clear that the chiral initiator **3a** with only low to moderate ee was sufficient to induce the formation of alkanol **2** with high ee. Thus, the reaction using (*S*)- and (*R*)-[2.2]paracyclophane **3a** of 29 and 27% ee gave the highly enantiomerically enriched (*R*)- and (*S*)-pyrimidyl alkanol **2** with 95 and 91% ee, respectively (entries 7 and 8). Paracyclophane (*R*)-**3a** with only a slight enantiomeric imbalance of 2.5% ee induced enantioselective addition and gave chiral pyrimidyl alkanol (*S*)-**2** with 89% ee (entry 9).

Next, chiral monosubstituted [2.2]paracyclophanes, possessing acetyl or methoxycarbonyl groups instead of a carboxylic acid functionality, were examined as chiral initiators in the asymmetric autocatalysis of chiral pyrimidyl alkanol **2**. The results are summarized in Table 2. An asymmetric autocatalytic reaction initiated by (*S*)-(+)-4-acetyl[2.2]paracyclophane (**3b**)[8] (2.4 mol %) gave (*R*)-pyrimidyl alkanol **2** with 95% ee (entry 1). Conversely, in the presence of (*R*)-(−)-[2.2]paracyclophane **3b**, (*S*)-pyrimidyl alkanol **2** with 94% ee was obtained (entry 2). Moreover, in the presence of (*S*)-(+)-4-methoxycarbonyl[2.2]paracyclophane (**3c**),[9] pyrimidyl alkanol **2** with 93% ee in *R*-form was obtained, and the reaction using (*R*)-(−)-**3c** resulted in the formation of (*S*)-**2** with 92% ee (entries 3 and 4).

Table 2. Asymmetric Autocatalytic Reaction Initiated by Chiral [2.2]Paracyclophanes **3b**−**c**

	[2.2]paracyclophane **3**		pyrimidyl alkanol **2**	
entry	R	ee (%)[a,b]	yield(%)	ee (%)[a]
1[c]	(*S*)-**3b** Ac	>99.5	95	95 (*R*)
2[c]	(*R*)-**3b** Ac	88	95	94 (*S*)
3[d]	(*S*)-**3c** COOMe	93	96	93 (*R*)
4[d]	(*R*)-**3c** COOMe	96	88	92 (*S*)

[a] Determined by HPLC analyses using a chiral stationary phase (Chiralcel OD). [b]Ees of the recovered paracyclophanes **3b**,**c** were the same as those of the initial paracyclophanes. [c]Molar ratio. [2.2]Paracyclophane **3b**:**1**:*i*-Pr_2Zn = 0.024:1.0:2.1. [d]Molar ratio. [2.2]Paracyclophane **3c**:**1**:*i*-Pr_2Zn = 0.048:1.0:2.1.

A typical experimental procedure is as follows (Table 2, entry 1): After a mixture of a toluene solution (2.0 mL) of (*S*)-(+)-4-acetyl[2.2]paracyclophane (**3b**) [6.3 mg (0.025 mmol), >99.5% ee] and *i*-Pr_2Zn [0.25 mmol (0.25 mL of 1 M toluene solution)] was stirred for 30 min at 0 °C, a toluene solution (1.0 mL) of aldehyde **1** (9.4 mg, 0.05 mmol) was added. After the mixture was stirred for 14 h at 0 °C, toluene (4.75 mL) and *i*-Pr_2Zn [0.4 mmol (0.40 mL of 1 M toluene solution)] were added to the reaction mixture, and the mixture was stirred for 15 min. A toluene solution (1.5 mL) of aldehyde **1** (37.6 mg, 0.20 mmol) was added, and the reaction mixture was stirred for an additional 2 h at 0 °C. Again, toluene (14.4 mL), *i*-Pr_2Zn [1.6 mmol (1.6 mL of 1 M toluene solution)], and a toluene solution (4.0 mL) of aldehyde **1** (150.6 mg, 0.80 mmol) were added and stirred for 4 h. The reaction mixture was quenched by adding 1 M hydrochloric acid (5 mL). Saturated aq sodium bicarbonate (15 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 under reduced pressure. Purification of the residue on silica gel TLC gave pyrimidyl alkanol **2** (232.7 mg, 95%). HPLC analysis of the obtained alkanol **2** using a chiral column (Daicel Chiralcel OD) showed that alkanol **2** of with an *R*-configuration had an enantiomeric excess of 95%. Chiral initiator (*S*)-**3b** was recovered (6.2 mg) in 98% without any racemization.

In summary, monosubstituted [2.2]paracyclophanes **3a**−**c** with planar chirality induced the enantioselective addition of *i*-Pr_2Zn to 2-alkynylpyrimidine-5-carbaldehyde **1** to afford highly enantiomerically enriched pyrimidyl alkanol **2**. Furthermore, even slightly enantiomerically enriched 4-carboxy-[2.2]paracyclophane **3a** also worked as a chiral initiator.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture and by the Japan Space Forum.

OL006921W

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(7) (*S*)- and (*R*)-4-Carboxy[2.2]paracyclophanes **3a** were prepared by optical resolution according to the literature procedure: Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc*. **1955**, *77*, 6289−6294.

(8) Racemic 4-acetyl[2.2]paracyclophane **3b** was synthesized as described in the literature.[7] Enantiomerically enriched **3b** was obtained by the resolution of racemate on HPLC using a chiral stationary phase (Chiralcel OD).

(9) Racemic 4-methoxycarbonyl[2.2]paracyclophane **3c** was synthesized by the reaction of MeOH with the acid chloride, which was derived from carboxylic acid **3a**. Enantiomerically enriched **3c** was obtained by HPLC separation using a chiral stationary phase (Chiralcel OD).