Highly Enantioselective Asymmetric Autocatalysis of Pyrimidin-5-yl Alkanol Induced by Chiral 1,3-Disubstituted Hydrocarbon Allenes

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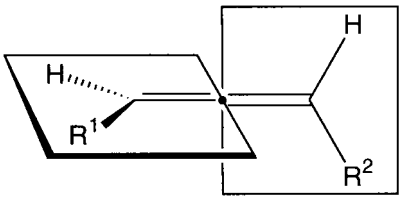
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

1,3-Disubstituted chiral allenes without any heteroatoms act as chiral initiators in the addition of $(i\text{-}Pr)_2Zn$ to pyrimidine-5-carbaldehyde to afford, in combination with the subsequent asymmetric autocatalysis, chiral pyrimidin-5-yl alkanols with up to 98% ee. The absolute configuration of the pyrimidin-5-yl alkanol formed depend on that of the chiral allene.

Introduction. – 1,3-Disubstituted allene is one of the representative chiral compounds without any stereogenic center [1]. Two consecutive π faces are twisted vertically to locate the terminal substituent on the *re* or *si* face of another π face. Recent progress in the synthesis of allenes made it possible to obtain optically active allenes by enantioselective synthesis [2–4]. Hence, applications of optically active allenes as synthetic intermediates have been reported [5]. However, to the best of our knowledge, the use of chiral allenes as chiral catalysts or chiral ligands has rarely been reported.



$R^1, R^2 \neq H$

Meanwhile, during our continuing study of asymmetric autocatalysis [6], it was found that asymmetric autocatalysis of pyrimidin-5-yl alkanol in the addition of $(i\text{-}Pr)_2Zn$ to pyrimidine-5-carbaldehyde proceeds with amplification of ee [6] (for reviews on asymmetric autocatalysis with amplification of ee, see [7a–f]; for reviews including both autocatalytic and non-autocatalytic reactions with amplification of ee, see [7g–i]). Moreover, when $(i\text{-}Pr)_2Zn$ was reacted with pyrimidine-5-carbaldehyde in the presence of chiral initiators such as amino acids, helicenes, deuterated primary alcohols,

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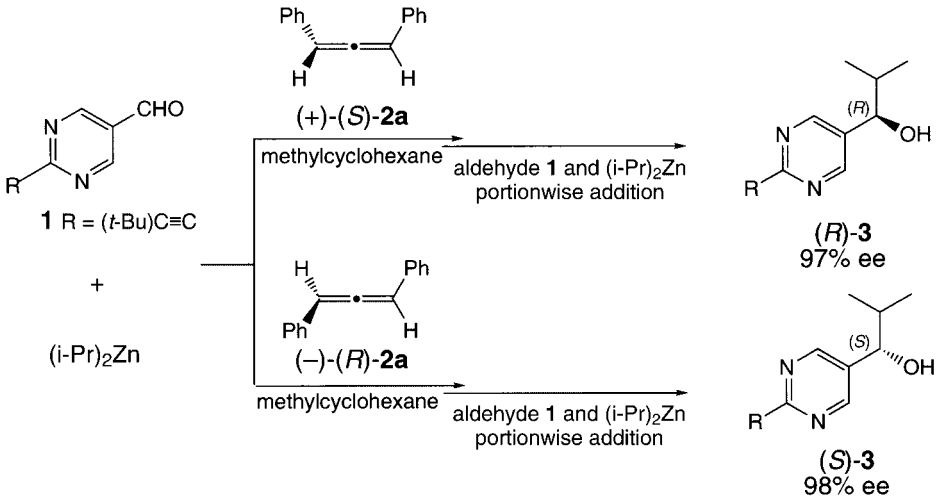
quartz, and sodium chlorate, the absolute configuration of the pyrimidin-5-yl alkanol obtained depends on that of the chiral initiator [8].

We report herein the asymmetric autocatalysis of pyrimidin-5-yl alkanol in the presence of 1,3-disubstituted chiral allenes. Both enantiomers of highly enantiomerically enriched pyrimidin-5-yl alkanols were obtained from axially chiral allenes as the sole chiral source.

Results and Discussion. – Enantioselective addition of $(i\text{-}Pr)_2Zn$ to 2-(alkynyl)pyrimidine-5-carbaldehyde **1** in the presence of chiral allenes **2a**–**e** were examined (*Scheme*). To an ice-cooled methylcyclohexane solution of **1** and chiral allene **2**, a hexane solution of $(i\text{-}Pr)_2Zn$ was slowly added. The solution was then diluted with toluene, and aldehyde **1** and $(i\text{-}Pr)_2Zn$ were added portionwise. Aqueous workup gave enantiomerically enriched 2-(alkynyl)pyrimidin-5-yl alkanol **3**. The results are summarized in the *Table*. As shown in the *Scheme*, when (+)-(*S*)-1,3-diphenylpropadiene **2a** was used as a chiral initiator, (*R*)-pyrimidin-5-yl alkanol **3** with 97% ee was obtained in 95% isolated yield (*Entry 1*). On the other hand, when the other enantiomer of chiral allene (−)-(*R*)-**2a** was used as chiral initiator, (*S*)-pyrimidin-5-yl alkanol **3** with 98% ee was obtained in 95% isolated yield (*Entry 2*). Thus, the absolute configuration of the pyrimidin-5-yl alkanol **3** obtained was dependent on that of the chiral allene. Toluene as a solvent (*Entries 3* and *4*) gave results similar to those with methylcyclohexane as solvent (*Entries 1* and *2*). The reaction in the presence of (+)- or (−)-1-cyclohexyl-3-phenylpropadiene (**2b**) gave (*R*)- and (*S*)-pyrimidin-5-yl alkanol **3** with 97% ee, respectively (*Entries 5* and *6*). According to the *Lowe*'s experimental rule and the subsequent studies based on circular dichroism, the absolute configuration of 1-phenylallenes and 1,3-dialkylallenes have been correlated with the sign of specific rotation [3a][9].

Scheme. *Enantioselective Addition of $(i\text{-}Pr)_2Zn$ to 2-(Alkynyl)peprinidine-5-carbaldehyde* **1** *in the Presence of Chiral Allenes* **2a**–**e**



Therefore, allenes with *dextro* rotation may have the (*S*) configuration similar to the 1,3-diphenylpropadiene [10]. The derivatives of 1-phenylallenes were also used as chiral initiators in asymmetric autocatalysis. When chiral (+)-(*S*)-4-methyl-1-phenylpenta-1,2-diene **2c** [3a] was used as a chiral initiator, (*R*)-pyrimidin-5-yl alkanol **3** with 96% ee was formed in a yield of 96% (*Entry 7*). On the other hand, (*S*)-pyrimidin-5-yl alkanol with 94% ee was obtained in a yield of 94% in the corresponding reaction with (−)-(*R*)-**2c** as a chiral initiator (*Entry 8*). Similarly, chiral (+)- and (−)-1-phenylallene derivatives **2d** with $PhCH_2$ substituents gave (*R*)- and (*S*)-pyrimidin-5-yl alkanol **3** with 94 and 95% ee, respectively (*Entries 9* and *10*). In addition, nonconjugated allene was used as a chiral initiator. (+)-1,5-Diphenylpentadiene (**2e**), *i.e.*, a chiral allene with two $PhCH_2$ substituents, afforded (*R*)-**3** (*Entry 11*), whereas the other enantiomer (−)-**2e** gave (*S*)-**3** (*Entry 12*).

Table. *Highly Enantioselective Synthesis of Pyrimidin-5-yl Alkanol* **3** *with Chiral 1,3-Disubstituted Allenes* **2**[a])

Entry	Allene **2**					Pyrimidin-5-yl alkanol **3**	
		R^1	R^2	ee/%[b])	$[\alpha]_D$ (config.)	Yield/%	ee/% (config.)
1[c])	**2a**	Ph	Ph	>99.5	+ (*S*)	95	97 (*R*)
2[c])				>99.5	− (*R*)	95	98 (*S*)
3[d])				>99.5	+ (*S*)	92	93 (*R*)
4[d])				>99.5	− (*R*)	94	94 (*S*)
5	**2b**	Ph	Cyclohexyl	90	+	88	97 (*R*)
6				94	−	90	97 (*S*)
7	**2c**	Ph	i-Pr	91	+ (*S*)	96	96 (*R*)
8				>99.5	− (*R*)	94	94 (*S*)
9	**2d**	Ph	$PhCH_2$	43	+	96	94 (*R*)
10				56	−	92	95 (*S*)
11	**2e**	CH_2Ph	$PhCH_2$	97	+	97	90 (*R*)
12				92	−	97	97 (*S*)

[a]) Aldehyde **1** (1.3 mmol) and $(i\text{-}Pr)_2Zn$ (2.7 mmol) were added in four portions. Molar ratio: allene **2**/pyrimidine-5-carbaldehyde **1**/$(i\text{-}Pr)_2Zn$ 0.0094/1.0/2.0. [b]) The ee value was determined by HPLC analysis with a chiral stationary phase. [c]) Molar ratio: allene **2a**/pyrimidine-5-carbaldehyde **1**/$(i\text{-}Pr)_2Zn$ 0.037/1.0/2.0. [d]) Toluene was used instead of methylcyclohexane. Aldehyde **1** (1.1 mmol) and $(i\text{-}Pr)_2Zn$ (2.2 mmol) were added in three portions. Molar ratio: allene **2a**/pyrimidine-5-carbaldehyde **1**/$(i\text{-}Pr)_2Zn$ 0.024/1.0/2.0.

Conclusions. – As described, chiral allenes induce asymmetry in the enantioselective addition of $(i\text{-}Pr)_2Zn$ to 2-(alkynyl)pyrimidine-5-carbaldehyde **1**. Highly enantiomerically enriched pyrimidin-5-yl alkanol **3** was obtained by combination asymmetric autocatalysis. In addition, chiral allenes **2a**–**e** are hydrocarbon compounds without any heteroatom. Thus, these results are also significant in that chiral hydrocarbon compounds [8e,g] without any stereogenic center act as chiral initiators in asymmetric synthesis.

Financial support by *Grant-in-Aid* from the *Ministry of Education, Culture, Sports, Science and Technology* and *Japan Space Forum* is gratefully acknowledged.

Experimental Part

Synthesis of Enantiomerically Enriched Allenes. Racemic allenes were synthesized according to the procedure in [11]. The racemic allenes obtained were resolved into enantiomerically enriched form by HPLC with a chiral stationary phase.

*(+)-(*S*)- and (−)-(*R*)-1,3-Diphenylpropa-1,2-diene* (**2a**) [3a]. Racemic **2a** was synthesized [11] and resolved into enantiomerically enriched form by HPLC (*Chiralcel OD* (4 × 250 mm); eluent: 1% i-PrOH in hexane; flow rate: 0.4 ml/min): t_R 12 min for (−)-isomer, 18 min for (+)-isomer.

(+)-1-Cyclohexyl-3-phenylpropa-1,2-diene (**2b**) [3g]. $[\alpha]_D^{28} = +299$ ($c = 0.47$, EtOH) for the sample with 90% ee. HPLC (*Chiralcel OD-H* (4 × 250 mm); eluent: 0.01% i-PrOH in hexane; flow rate: 0.4 ml/min): t_R 15 min for (−)-isomer, 18 min for (+)-isomer.

(−)-1-Cyclohexyl-3-phenylpropa-1,2-diene (**2b**) [3g]. $[\alpha]_D^{29} = -345$ ($c = 0.39$, EtOH) for the sample with 92% ee.

*(+)-(*S*)-4-Methyl-1-phenylpenta-1,2-diene* (**2c**) [3a]. $[\alpha]_D^{32} = +139$ ($c = 0.33$, $CHCl_3$) for the sample with 68% ee ([3a]: $[\alpha]_D^{20} = +345$ (EtOH)). HPLC (*Chiralcel OD-H* (4 × 500 mm), eluent: 0.01% i-PrOH in hexane; flow rate: 0.4 ml/min): t_R 29 min for (−)-isomer, 32 min for (+)-isomer.

*(−)-(*R*)-4-Methyl-1-phenylpenta-1,2-diene* (**2c**) [3a]. $[\alpha]_D^{32} = -277$ ($c = 0.40$, $CHCl_3$) for the sample with 98% ee.

(+)-1,4-Diphenylbuta-1,2-diene (**2d**). HPLC (*Chiralcel OD* (4 × 250 mm), eluent: 0.001% i-PrOH in hexane, flow rate: 0.5 ml/min, r.t.) t_R 27 min for (−)-isomer, 31 min for (+)-isomer. Colorless oil. $[\alpha]_D^{29} = +105$ ($c = 0.64$, EtOH) for the sample with 38% ee. FT-IR (neat): 1948. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.51 (*dd*, *J* = 7.3, 2.5, 2 H); 5.75 (*td*, *J* = 7.3, 6.5, 1 H); 6.20 (*dt*, *J* = 6.5, 2.5, 1 H); 7.2–7.4 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 36.0; 94.9; 95.4; 126.7; 127.1; 127.2; 128.9; 129.0; 135.0; 140.5; 206.1. HR-MS (FAB$^+$): 206.1085 (M^+; $C_{16}H_{14}$; calc. 206.1096.

(−)-1,4-Diphenylbuta-1,2-diene (**2d**). $[\alpha]_D^{29} = -211$ ($c = 0.23$, EtOH) for the sample with 86% ee.

(+)-1,5-Diphenylpenta-2,3-diene (**2e**). HPLC (Chiralcel OD (4 × 250 mm), eluent: 0.5% 2-propanol in hexane, flow rate: 0.5 ml/min): t_R 14 min for (+)-isomer, 16 min for (−)-isomer. Colorless oil. $[\alpha]_D^{25} = +1.9$ (c = 1.75, EtOH) for the sample with 97% ee. FT-IR (neat): 1963. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.3–3.4 (*m*, 4 H); 5.2–5.3 (*m*, 2 H); 7.1–7.3 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 35.6; 91.0; 126.1; 128.3; 128.6; 140.2; 205.1. Anal. calc. for $C_{17}H_{16}$: C 92.68, H 7.32; found: C 92.47, H 7.06.

(−)-1,5-Diphenylpenta-2,3-diene (**2e**). $[\alpha]_D^{25} = -4.87$ ($c = 1.84$, EtOH) for the sample with 92% ee.

Representative Procedure for the Enantioselective Addition of (i-Pr)$_2$Zn to Pyrimidine-5-carbaldehyde in the Presence of Chiral Allenes (*Table*, *Entry 2*). To a methylcyclohexane (1 ml) soln. of (+)-(*R*)-1,3-diphenylpropa-1,2-diene (**2a**, > 99.5% ee; 9.6 mg, 0.05 mmol) and pyrimidine-5-carbaldehyde **1** (9.4 mg, 0.05 mmol) was added dropwise a 1M hexane soln. of (i-Pr)$_2$Zn (0.15 ml, 0.15 mmol) over a period of 30 min at 0°. After stirring for 12 h at 0°, the mixture was diluted with toluene (1.9 ml). A toluene soln. (1M) of (i-Pr)$_2$Zn (0.2 ml, 0.2 mmol) and a toluene (1.0 ml) soln. of **1** (18.8 mg, 0.1 mmol) were added successively at 0°. After stirring the mixture for 30 min at 0°, toluene (7.5 ml), a toluene soln. (1M) of (i-Pr)$_2$Zn (0.8 ml, 0.8 mmol), and a toluene (2.0 ml) soln. of **1** (75.3 mg, 0.4 mmol) were added successively. Then, the mixture was stirred for further 30 min at 0°. Toluene (15 ml), toluene soln. (1M) of (i-Pr)$_2$Zn (1.6 ml, 1.6 mmol), and a toluene (4.0 ml) soln. of **1** (150.6 mg, 0.8 mmol) were added successively, and the mixture was stirred at 0° for 30 min. The reaction was quenched by adding 5 ml of 1M HCl, and the resulting mixture was neutralized with sat. aq. soln. of $NaHCO_3$ (15 ml). The mixture was filtered through *Celite*. The filtrate was extracted with AcOEt and dried (Na_2SO_4). The solvent was removed, and the residue was purified on TLC (hexane/AcOEt 2:1): *(*S*)-1-[2-[2-(*tert*-Butyl)ethenyl]pyrimidin-5-yl]-2-methylpropan-1-ol* (**3**) with 98% ee was obtained in 95% yield (296.4 mg).

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Received June 14, 2002