Asymmetric Autocatalysis Induced by Octahedral Tris(acetylacetonato)chromium(III) Complex as a Homogeneous Chiral Initiator

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Enantioselective addition of diisopropylzinc to 2-*t*-butylethynylpyrimidine-5-carbaldehyde in the presence of chiral Δ- and Λ-tris(acetylacetonato)chromium(III) complex [Cr(acac)$_3$] affords highly enantiomerically enriched (*S*)- and (*R*)-5-pyrimidyl alkanols, respectively, in conjunction with asymmetric autocatalysis. The absolute configuration of the corresponding 2-*t*-butylethynyl-5-pyrimidyl alkanol is dependent upon the chirality of the octahedral chromium(III) complex.

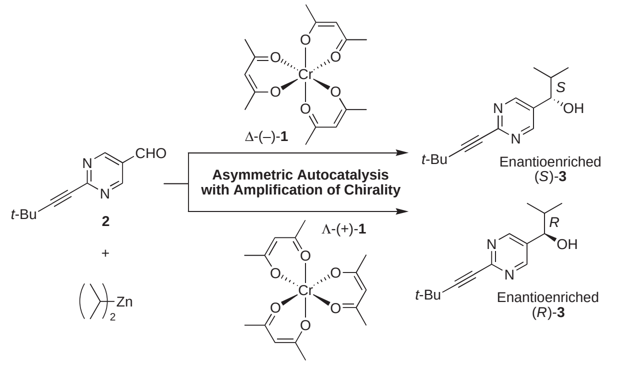
In the field of asymmetric catalysis, the development of efficient catalytic chiral transition-metal complexes is a major focus of research activity.[1] Most chiral metal complexes, which are used in enantioselective synthesis, are constructed from chiral organic ligands. Some of these metal complexes show not only the chirality in their organic ligands, but also chirality due to the topological coordination of the ligands around the metal center.[2] Because of the increasing importance of transition-metal complexes in enantioselective catalysis, the structures of chiral organic ligands have been well investigated to date.[1] However, the effect of chiral coordination at the metal center on enantioselectivity remains an unsolved problem, despite the fact that chiral coordination metal complexes formed from achiral ligands have been known for a long time.[3] To the best of our knowledge, only a limited number of applications of this kind of metal complex to enantioselective synthesis have been reported, although they are used in diastereoselective reactions.[4] Thus, highly enantioselective synthesis using metal complexes with chirality due only to the topology of their achiral ligands is considered an emerging challenge.

Meanwhile, during our continuing study on asymmetric autocatalysis,[5,6] we found that the asymmetric autocatalysis of 5-pyrimidyl alkanol in the enantioselective addition of diisopropylzinc (*i*-Pr$_2$Zn) to pyrimidine-5-carbaldehyde proceeds with an amplification of enantiomeric excess (ee).[5a,7] We also reported that, in this reaction, the chiral initiator[8] controls the absolute configuration of the produced 5-pyrimidyl alkanols, and that the ee of the produced alkanols are high, in conjunction with asymmetric autocatalysis.[8] The stochastic formation of (*S*)- and (*R*)-product is observed in the asymmetric autocatalysis without adding chiral substance.[8i] The cobalt complex with chirality due to the topology of achiral ligands, can work as a heterogeneous chiral initiator of asymmetric autocatalysis.[9] In this system, the chiral metal complex was used in the solid state because of its poor solubility in the organic solvent.

We report here that the chiral octahedral tris(acetylacetonato)chromium(III) complex with achiral ligands, i.e., Cr(acac)$_3$ (**1**),[10] which shows chirality due to the topological coordination of its achiral bidentate ligands, acts as a homogeneous chiral initiator in the enantioselective addition of *i*-Pr$_2$Zn to pyrimidine-5-carbaldehyde **2** to afford, in combination with asymmetric autocatalysis, 5-pyrimidyl alkanol **3** with high enantiomeric excess. The absolute configuration of the corresponding alkanol **3** was controlled efficiently by the chirality of the ligand configuration around the metal center (Scheme 1). Because of its higher solubility in organic solvent, metal complex **1** acts as a homogeneous chiral initiator of the asymmetric autocatalysis.

The enantioselective addition of *i*-Pr$_2$Zn to pyrimidine-5-carbaldehyde **2** was examined in the presence of Cr(acac)$_3$ (**1**) (Table 1). When the *i*-Pr$_2$Zn addition was performed in the presence of Δ-Cr(acac)$_3$ **1** with an ee of 90%, (*S*)-5-pyrimidyl alkanol **3** was obtained in 98% yield with an ee of 96% (Table 1, Entry 1). Conversely, in the presence of Λ-**1** with 91% ee, the opposite enantiomer, (*R*)-**3** with 94% ee was formed in 97% yield (Entry 2). Asymmetric autocatalyses using Δ-**1** with 95% and 93% ee and Λ-**1** with 99% and >99% ee support this reproducibility, that is, Δ-**1** induced the formation of (*S*)-**3** and Λ-**1**, (*R*)-**3**, respectively (Entries 3–6). Thus, the absolute configurations of the resulting alkanols **3** depend on those of the chiral Cr(acac)$_3$ used. Using **1** with a moderate ee as an inducer yielded 5-pyrimidyl alkanol **3** with 59–60% ee (Entries 7 and 8). Even Δ- and Λ-Cr(acac)$_3$ **1** with only 4% and 9% ee were found to serve as chiral initiators of the asymmetric autocatalysis, producing (*S*)-**3** and (*R*)-**3**, respectively (Entries 9 and 10). These results clearly show that the topological chirality of **1** controls the absolute configuration of the formed 5-pyrimidyl alkanol **3**.

In a typical experiment (Table 1, Entry 4), a 1 M hexane solution of *i*-Pr$_2$Zn (0.075 mL, 0.075 mmol) was added dropwise to an Et$_2$O (1.0 mL) solution of Λ-**1** (1.75 mg, 0.005 mmol) with 99% ee and aldehyde **2** (4.7 mg, 0.025 mmol) over a period of 1.5 h at 0 °C. After stirring for 2 h, toluene (1.1 mL) and a 1 M toluene solution of *i*-Pr$_2$Zn (0.2 mL, 0.2 mmol) was added, then a toluene (1.0 mL) solution of **2** (18.8 mg, 0.1 mmol) was added dropwise over a period of 1 h. After the mixture was stirred for 2 h, toluene (3.6 mL) and a 1 M toluene solution of *i*-Pr$_2$Zn (0.8 mL, 0.8 mmol) was added successively, and then a toluene



Scheme 1. Highly enantioselective asymmetric autocatalysis in the presense of chiral octahedral chromium complex **1**.

Table 1. Enantioselective addition of i-Pr_2Zn to pyrimidine-5-carbaldehyde **2** in the presence of chiral Δ- and Λ-Cr(acac)$_3$ (**1**)

Entry[a]	Cr(acac)$_3$ (**1**)[b]		5-Pyrimidyl alkanol **3**		
	Config.[c]	Ee[d]/%	Yield[e]/%	Ee[f]/%	Config.
1	Δ-(−)	90	98	96	*S*
2	Λ-(+)	91	97	94	*R*
3	Δ-(−)	95	78	68	*S*
4	Λ-(+)	99	81	64	*R*
5[g]	Δ-(−)	93	93	59	*S*
6	Λ-(+)	>99	91	51	*R*
7	Δ-(−)	31	81	60	*S*
8	Λ-(+)	38	81	59	*R*
9	Δ-(−)	4	60	45	*S*
10	Λ-(+)	9	89	58	*R*

[a]The molar ratio. **1**:**2**:i-Pr_2Zn = 0.005:1.325:2.675. i-Pr_2Zn and **2** were added in four separate portions. [b]Racemic **1** were resolved into enantiomers by HPLC on a chiral stationary phase (Daicel Chiralpak IA). [c]See Ref. 10b. [d]The ee value was determined by HPLC on a chiral stationary phase (Shiseido Ceramospher RU-1). [e]Isolated yield. [f]The ee value was determined by HPLC on a chiral stationary phase (Daicel Chiralcel OD-H). [g]Cr(acac)$_3$ (**1**) with 83% ee was recovered in near quantitative yield (see also Ref. 10c).

(2.5 mL) solution of **2** (75.3 mg, 0.4 mmol) was added dropwise over a period of 30 min and the reaction mixture was stirred for 2 h at 0 °C. Once again, toluene (7.2 mL) and a 1 M toluene solution of i-Pr_2Zn (1.6 mL, 1.6 mmol) were added, and a toluene (5.0 mL) solution of **2** (150.6 mg, 0.8 mmol) was added slowly. After the mixture was stirred for 1 h at 0 °C, the reaction was quenched with 1 M hydrochloric acid (5 mL) and neutralized with a saturated sodium hydrogen carbonate solution (15 mL). The resulting mixture was filtered through Celite and the filtrate extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue by silic-gel column chromatography (hexane:ethyl acetate = 2:1 to 1:1 and dichloromethane: acetone = 20:1) gave (*R*)-5-pyrimidyl alkanol **3** (249.3 mg, 1.07 mmol) in 81% yield with 64% ee.

The enantiomeric excesses observed in the above asymmetric reactions may be explained as follows: The chromium complex **1** is soluble in Et_2O and is recovered quantitatively after the reaction, despite a small decrease in ee,[10c] so the initial reaction between i-Pr_2Zn and aldehyde **2** may be promoted around the chiral coordination sphere of the metal complex. The initially formed isopropylzinc alkoxide of **3** has a small ee, which possesses the corresponding absolute configuration to the chirality of the Cr(acac)$_3$. Then, the ee is amplified during the subsequent asymmetric autocatalysis[7,11] to afford enantioenriched **3**.

In conclusion, enantioselective addition of i-Pr_2Zn to pyrimidine-5-carbaldehyde **2** in the presence of chiral Δ- and Λ-Cr(acac)$_3$ (**1**) gave (*S*)- and (*R*)-5-pyrimidyl alkanol **3** with high ee, respectively. We have clearly demonstrated that the chirality due to the topological coordination of achiral ligand at the metal center is responsible for the enantioselective addition of i-Pr_2Zn.[12]

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

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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Published on the web (Advance View) December 2, 2006; doi:10.1246/cl.2007.30