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Highly enantioselective asymmetric autocatalysis induced by chiral cobalt complexes due to the topology of the coordination of achiral ligands

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Chiral octahedral cobalt complexes, K[Co(edta)]·2H$_2$O and K[Co(trdta)]·2H$_2$O, induce enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde, affording the pyrimidyl alkanol with high (85–94%) enantiomeric excesses.

Enantioselective reactions are one of the most important areas in organic chemistry.[1] Chiral transition metal complexes play an important role in asymmetric reactions with most chiral metal complexes being prepared using chiral organic ligands. On the other hand, metal complexes such as the octahedral cobalt complex with achiral ethylenediamine (en) ligands, *i.e.* $[Co(en)_3]^{3+}$ shows chirality due to the topology of coordination of the achiral ligand.[2] A 'chiral-at-metal'[3a] complex with achiral ligands has been used in diastereoselective synthesis,[3b] and a 'chiral-at-metal' complex with chiral ligands has been used in enantioselective synthesis.[4] However, the application of 'chiral-at-metal' complexes with achiral ligands towards enantioselective synthesis has been a difficult problem. It is noteworthy that, as early as 1929, Shibata and Tsuchida[5] reported an enantiomer selective asymmetric oxidation of racemic 3,4-dihydroxyphenylalanine using a chiral cobalt complex $[Co(en)_2NH_3Cl]Br_2$. However, highly enantioselective syntheses using chiral metal complexes (due to the topology of achiral ligands) is a challenge.

One of us (H. O.) previously reported the preparation of chiral octahedral cobalt complexes with ethylenediaminetetraacetate (edta) and trimethylenediaminetetraacetate (trdta), *i.e.* K[Co(edta)]·2H$_2$O **1**[6a] and K[Co(trdta)]·2H$_2$O **2**.[6b]

In the course of our continuing study on asymmetric autocatalysis,[7,8] we found that the sense of the enantioselectivity of the addition of diisopropylzinc (*i*-Pr$_2$Zn) to pyrimidine-5-carbaldehydes is affected by chiral materials[9] such as chiral quartz[9a] and sodium chlorate.[9b]

We report here a highly enantioselective addition of *i*-Pr$_2$Zn to 2-(*tert*-butylethynyl)pyrimidine-5-carbaldehyde **3** in the presence of chiral metal complex **1** or **2** (Fig. 1). The absolute configurations of the formed pyrimidyl alkanol with high (85–94%) ee's were controlled by the chirality of the octahedral cobalt complexes **1** and **2**.

Experiments were conducted as illustrated in Scheme 1. To a suspension of finely powdered chiral crystals (0.025 mmol) of cobalt complex **1** or **2**, aldehyde **3**[10] (1.05 mmol) and *i*-Pr$_2$Zn (2.15 mmol)[11] were added portionwise. In the presence of (+)$_{546}$-K[Co(edta)]·2H$_2$O **1**, (*S*)-alkanol **4** with 91% ee was obtained in 91% yield (Table 1, entry 1). On the other hand, in the presence of (−)$_{546}$-K[Co(edta)]·2H$_2$O **1**, (*R*)-alkanol **4** with 94% ee was obtained (entry 3). Thus, the absolute configuration of chiral complex **1** determines the absolute configuration of the newly formed pyrimidyl alkanol **4**.

In a typical experiment (Table 1, entry 3), to a toluene suspension (0.1 ml) of (−)$_{546}$-K[Co(edta)]·2H$_2$O **1** (10.6 mg, 0.025 mmol) and aldehyde **3** (9.4 mg, 0.05 mmol), a toluene solution (1.0 M) of *i*-Pr$_2$Zn (0.15 mmol) was added over a period of 15 min at 0 °C. After the mixture was stirred for 14 h at 0 °C, toluene (4.8 ml), *i*-Pr$_2$Zn (0.4 mmol, 1.0 M toluene solution), and a toluene solution (1.5 ml) of aldehyde **3** (37.6 mg, 0.2 mmol) were added successively, and the reaction mixture was stirred for 3.5 h. Then, toluene (14.4 ml), *i*-Pr$_2$Zn

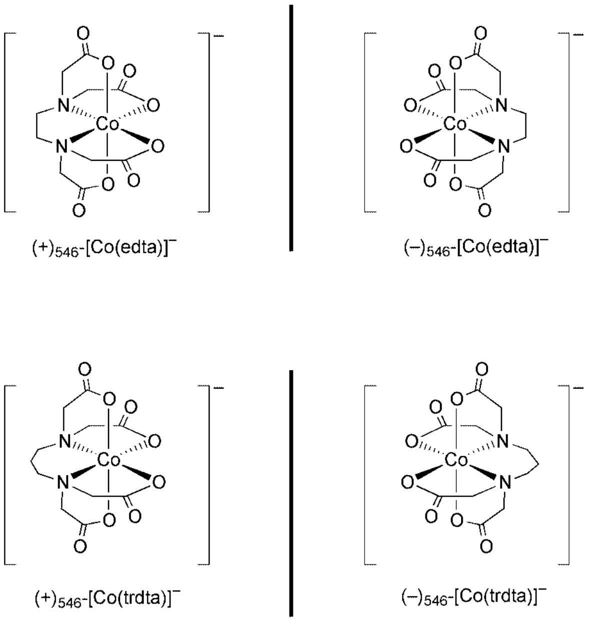
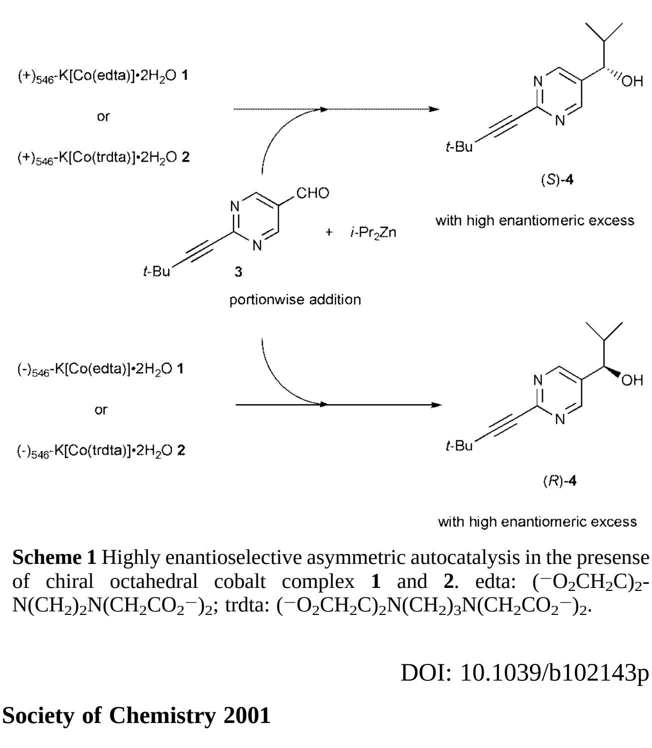

(+)$_{546}$-[Co(edta)]$^-$ (−)$_{546}$-[Co(edta)]$^-$
(+)$_{546}$-[Co(trdta)]$^-$ (−)$_{546}$-[Co(trdta)]$^-$

Fig. 1 Chiral structures of ethylenediaminetetraacetatocobaltate(III) and trimethylenediaminetetraacetatocobaltate(III).



Scheme 1 Highly enantioselective asymmetric autocatalysis in the presense of chiral octahedral cobalt complex **1** and **2**. edta: $(^-O_2CH_2C)_2N(CH_2)_2N(CH_2CO_2^-)_2$; trdta: $(^-O_2CH_2C)_2N(CH_2)_3N(CH_2CO_2^-)_2$.

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(1.6 mmol, 1.0 M toluene solution) and a toluene (4 ml) solution of aldehyde **3** (150.6 mg, 0.8 mmol) were added successively, and the mixture was stirred at 0 °C for an additional 3 h. The reaction was quenched by hydrochloric acid (1 M, 5 ml), and satd. aq. sodium hydrogen carbonate (15 ml) was added. The mixture was filtered using Celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated. Purification of the residue by silica gel thin layer chromatography (developing solvent, hexane–ethyl acetate = 2:1 v/v) gave (*R*)-pyrimidyl alkanol **4** (244 mg) with 94% ee in an isolated yield of 99%.

Since the cobalt complex **1** is practically insoluble in toluene, enantioselective addition seems to occur at the interface between the crystal of metal complex **1** and the solvent. When $(+)_{546}$-K[Co(trdta)]·$2H_2O$ **2** was used instead of $(+)_{546}$-K[Co(edta)]·$2H_2O$ **1**, the formation of (*S*)-**4** with 85% ee was induced (entry 5), and the reaction using $(-)_{546}$-K[Co(trdta)]·$2H_2O$ (**2**) gave (*R*)-**4** with 88% ee (entry 6).

In summary, enantioselective addition of *i*-Pr_2Zn to pyrimidinecarbaldehyde **4** in the presence of $(+)_{546}$-K[Co(edta)]·$2H_2O$ **1** or $(+)_{546}$-K[Co(trdta)]·$2H_2O$ **2** gave (*S*)-**4** with high ee's, respectively, and the reaction in the presence of $(-)_{546}$-K[Co(edta)]·$2H_2O$ (**1**) or $(-)_{546}$-K[Co(trdta)]·$2H_2O$ **2** afforded (*R*)-**4** with high ee's, respectively. We have clearly demonstrated that the chirality at the cobalt is responsible for the enantioselective addition of *i*-Pr_2Zn.

Table 1 Enantioselective addition of diisopropylzinc to aldehyde **3** in the presence of chiral octahedral cobalt complexes **1** and **2**

		Alkanol **4**[a]		
Entry	Cobalt complex	Yield (%)	Ee (%)	Config.
1	$(+)_{546}$-K[Co(edta)]·$2H_2O$ **1**	91	91	*S*
2		98	89	*S*
3	$(-)_{546}$-K[Co(edta)]·$2H_2O$ **1**	99	94	*R*
4		92	90	*R*
5	$(+)_{546}$-K[Co(trdta)]·$2H_2O$ **2**	90	85	*S*
6	$(-)_{546}$-K[Co(trdta)]·$2H_2O$ **2**	90	88	*R*

[a] Ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OD).

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