# **Reusable Cobalt(III) Complex Catalysts for Enantioselective Borohydride Reduction of Ketones**

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A reusable catalytic system was developed for the catalytic enantioselective borohydride reduction of ketones. The optically active 1-chlorovinylketoiminatocobalt(III) complexes were recovered after the reaction by silica gel column chromatography, and then efficiently catalyzed the enantioselective reduction several times without any loss of reactivity as well as enantioselectivity.

Although the demand for various structures of optically active compounds as chiral synthons has been increasing, the varieties supplied from natural products are limited. Catalytic and enantioselective syntheses are one of the most attractive and reasonable solutions for these requirements in order to provide a wide variety of optically active compounds, among which the optically active secondary alcohols obtained by the enantioselective reduction of ketones1 are one of the most reliable building blocks for the syntheses of bioactive compounds or highly functionalized materials. This research group has reported the enantioselective borohydride (= tetrahydridoborato) reduction of various ketones using ketoiminatocobalt complex catalysts to afford the corresponding secondary alcohols with high-to-excellent yields and high enantioselectivities.<sup>2</sup> In this reduction system, analytical and theoretical studies revealed that a catalytic amount of haloalkanes, such as chloroform or trichloroethane, effectively generated the reactive cobalt(III) complex intermediate to achieve high enantioselectivity.3 For the reduction of aromatic ketones, the dichloromethyl group derived from chloroform was crucial to provide the axial ligand for the reactive cobalt(III) intermediate to accomplish high enantioselectivity as well as high yield. For the enantioselective reduction of aliphatic ketones, screening of various haloalkanes as the axial ligand precursors revealed that 1,1,1-tirchloroethane was a suitable additive for high enantioselectivities.<sup>4</sup> The enantioselectivity was remarkably improved in the presence of 1,1,1-trichloroethane and several aliphatic ketones were successfully converted into corresponding alcohols with good-to-high enantioselectivities (Scheme 1). The analytical and experimental examinations revealed that the cobalt(III) complex coordinated by 1-chlorovinyl group was generated and the 1-chlorovinylcobalt(III) complex 2 catalyzed the enantioselective borohydride reduction.<sup>5</sup> Meanwhile, it was also suggested that the cobalt(III) complex 2 was stable enough to be recovered as red-colored fractions by silica gel column chromatography and analyzed by NMR as well as X-ray analyses of a single crystal. Moreover, the recovered complex 2



Scheme 1. Enantioselective reduction of aliphatic ketones catalyzed by 1-chlorovinylketoiminatocobalt(III) complex.

was also found to catalyze the enantioselective borohydride reduction in the presence of 1,1,1-trichloroethane (86% ee) although the enantioselectivity decreased to 66% ee without additional 1,1,1-trichloroethane due to the loss in the activity by the gradual decomposition of the cobalt(III) complex **2** to the cobalt(II) complex **1** (Scheme 2). Encouraged by these results, we tried to develop the reusable and recyclable catalyst system to more efficiently improve the present cobalt catalysis for providing optically active secondary alcohols. In this short article, we describe a reusable catalyst system using the ketoiminatocobalt(III) complex for the enantioselective borohydride reduction of ketones.

Under the previously reported conditions, 1-adamantyl methyl ketone (3) was reduced to the corresponding alcohol 4 in high yield and enantioselectivity (94% yield, 85% ee) using 10 mol % cobalt(II) complex 1 (Table 1, Run 1). During the purification process by silica gel column chromatography, the red-colored fractions were collected with a high-polarity eluent (ethyl acetate (AcOEt)/diethyl ether (Et<sub>2</sub>O) = 4/1) after isolation of the produced alcohols (eluent: AcOEt/hexane = 1/15). In the second run, the recovered red-colored cobalt(III) complex 2 was employed as a catalyst with additional 1,1,1-trichloroethane to give the reduced product in a comparable yield and enantioselectivity. Although the reduction proceeded for five runs, the enantiomeric excesses decreased to 77% ee (Runs 2–5). An improvement in the recovery methods was then required to maintain the high selectivity.

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Scheme 2. Effect of addition of 1,1,1-trichloroethane on the enantioselectivities of the reaction with the recovered cobalt(III) complex.





a) Reaction conditions: [1st run] ketone **3** (0.25 mmol), (*S*,*S*)-**2** (10 mol %), NaBH<sub>4</sub> (0.50 mmol, 2.0 equiv), MeOH (3.0 mmol, 12 equiv), CH<sub>3</sub>CCl<sub>3</sub> (40 mol %) at -20 °C, 24 h. [2nd–5th runs] The complexes recovered in last cycle were used. Yields are of product isolated. Chromatography conditions: the product alcohols were isolated by silica gel chromatography with an eluent (AcOEt/hexane = 1/15). The complexes were recovered with an eluent (AcOEt/Et<sub>2</sub>O = 4/1). Enantiomeric excess was determined by HPLC analysis of 1-naphthoate derivative (Chiralpak IB).

In these procedures, it was confirmed that the red-colored fractions consisted of two contents after simple change to a polar eluent in the silica gel column chromatography purification. After detailed examination, it was found that the yellow-colored fractions<sup>6</sup> came out before the red-colored ones with a lower-polarity eluent. Based on this observation, the red-colored fractions were only collected with the high-polarity eluent (AcOEt/Et<sub>2</sub>O = 4/1) after elimination of the yellow-colored fractions with a lower-polarity eluent (AcOEt/Et<sub>2</sub>O = 4/1) after elimination of the yellow-colored fractions with a lower-polarity eluent (AcOEt/Et<sub>2</sub>O = 1/12) (Figure 1). By using these obtained pure red-colored fractions, the enantioselectivities remained at a high level in every run, 84–86% ee (Table 2).

For the reduction of aliphatic ketones, the recovery and reuse of the cobalt(III) complex were realized using 1,1,1-trichloroethane as a precursor of an axial ligand as well as the enantioselectivity being improved. Application of the reusable catalytic system to aromatic ketones was also expected. According to the original conditions using the complex **8** in the presence



Figure 1. The column chromatography conditions for recovery of the cobalt(III) complexes.

**Table 2.** Reuse of the Cobalt Complex in the Reduction of

 1-Adamantyl Methyl Ketone Using the Improved Recovery Process<sup>a</sup>



a) Reaction conditions: [1st run] ketone **3** (0.25 mmol), (*S*,*S*)-**2** (10 mol %), NaBH<sub>4</sub> (0.50 mmol, 2.0 equiv), MeOH (3.0 mmol, 12 equiv), CH<sub>3</sub>CCl<sub>3</sub> (30 mol %) at -20 °C, 24 h. [2nd–5th runs] The complexes recovered in last cycle were used. Yields are of product isolated. Chromatography conditions: the product alcohols were isolated by silica gel chromatography with an eluent (AcOEt/hexane = 1/15). The complexes were recovered with an eluent (AcOEt/Et<sub>2</sub>O = 1/12 to 4/1). Enantiomeric excess was determined by HPLC analysis of 1-naph-thoate derivative (Chiralpak IB).

of 1,1,1-trichloroethane, butyl phenyl ketone (6) was reduced to 1-phenyl-1-pentanol (7) in a high yield and enantioselectivity (Table 3, Entry 1). However for this reaction, the expected cobalt(III) complex with 1-chlorovinyl group could not be recovered. The color of the reaction mixture changed from



### Table 3. Reduction of Aromatic Ketone with Various Cobalt Complexes<sup>a)</sup>

a) Reaction conditions: ketone **6** (0.25 mmol), cobalt complex (5 mol %), NaBH<sub>4</sub> (0.50 mmol, 2.0 equiv), MeOH (3.0 mmol, 12 equiv), CH<sub>3</sub>CCl<sub>3</sub> (20 mol %) at -20 °C, 24 h. Yields are of product isolated. Chromatography conditions: the product alcohols were isolated by silica gel chromatography with an eluent (AcOEt/hexane = 1/20). Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H). b) The red-colored cobalt complexes could not be recovered. c) (*R*,*R*)-**10** was used.

purple-red to yellow during the isolation process; the chlorovinyl-cobalt(III) complex derived from the cobalt(II) complex **8** seemed less stable than the complex **2**. Thus, complex **1**, the precursor of the sufficiently stable catalyst **2**, was used instead for the reduction of aromatic ketones. The recovery of the catalyst was successful, however, the enantiomeric excess significantly decreased (Entry 2). These results suggested that the ketoimine ligand with sterically demanding aromatic groups on the side chains (R in Table 3) was required to stabilize the corresponding cobalt(III) complex catalyst for recycling. Several ketoimine ligands containing arylketones on their side chains were then examined (Entries 2–4), but the enantioselec-

 
 Table 4. Reuse of the Cobalt Complex in the Reduction of Butyl Phenyl Ketone with Different Recovery Methods<sup>a)</sup>

	1st Run Co(II) 2nd-5th F Reco NaBl	) Complex <b>11</b> <sub>Runs</sub> vered Comple H <sub>4</sub> , MeOH, CH THF, -20 °C	(10 mol%) ix 1 <sub>3</sub> CCl <sub>3</sub>	ОН 7
Run	Method A		Method B	
	Yield/%	ee/%	Yield/%	ee/%
1	95	89	88	89
2	87	86	98 <sup>b)</sup>	87
3	76 <sup>b)</sup>	88	95 <sup>b)</sup>	80
4	71 <sup>c)</sup>	88	91 <sup>b)</sup>	88

a) Reaction conditions: [1st run] ketone **6** (0.25 mmol), (*S*,*S*)-**11** (10 mol %), NaBH<sub>4</sub> (0.375 mmol, 1.5 equiv), MeOH (2.25 mmol, 9 equiv), CH<sub>3</sub>CCl<sub>3</sub> (40 mol %) at -20 °C, 5 h. [2nd–5th runs] The complexes recovered in last cycle were used. Yields are of product isolated. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H). Chromatography conditions: [Method A] the product alcohols were isolated by silica gel chromatography with an eluent (AcOEt/hexane = 1/20). The complexes were recovered with an eluent (AcOEt/Et<sub>2</sub>O = 4/1). [Method B] the product alcohols were isolated by silica gel chromatography with an eluent (THF/hexane = 1/25). The complexes were recovered with an eluent (THF/Et<sub>2</sub>O = 1/10). b) The reaction time was 6 h. c) The reaction time was 8 h.

tivities could not be improved. These ligands were attached by ortho-substituted aromatic ketones in order to stabilize the intermediates with their steric demand. It was found that the cobalt(II) complex **11** with the ligand containing 3,5-dimethylphenyl group effectively catalyzed the reduction of aromatic ketone **6** to afford the corresponding alcohol with high enantioselectivity (Entry 5).

Eventually, the reuse of the catalyst for several times was carried out with the newly designed complex **11** (Table 4). The enantioselectivity was maintained over five runs, but the high yield decreased. It seemed that the cobalt(III) complex derived from the complex **11** was relatively less stable than the complex **2** due to the bulky difference between 3,5-dimethylphenyl group and 2,4,6-trimethylphenyl group. It was expected that the coordinative saturation of the cobalt complex by the solvent, such as tetrahydrofuran (THF), could stabilize the chlorovinyl–cobalt complex during the recovery process. When the eluent used in the silica gel column chromatography was changed from Method A (AcOEt) to Method B (THF), the product yields were improved.

In summary, it was demonstrated that the reusable and recyclable cobalt catalyst system for the enantioselective borohydride reduction of ketones was effectively achieved. The cobalt(III) complex with 1-chlorovinyl group recovered by a silica gel column chromatography could be reused several times along with 1,1,1-trichloroethane. The reusable system of the cobalt complex was also employed after optimization of the ligand and recovery process to efficiently provide optically active secondary alcohols from aliphatic and aromatic ketones.

#### Experimental

**General Information.** All reactions were carried out in dry solvents under a nitrogen atmosphere in dried glassware. The ESI high-resolution mass spectra were obtained using a Waters LCT Premier XE mass spectrometer. Column chromatography was conducted on silica gel (Kanto 60 N). The HPLC analyses were performed by a Shimadzu LC-6A or LC-10A chromatograph using chiral columns (Daicel Chiralcel OD-H, Chiralpak IB); the peak areas were obtained using a Shimadzu SPD-M10AVP diode array detector/Shimadzu Class-VP or Shimadzu SPD-6A UV detector/JASCO ChromNAV. DSC analyses were performed with Shimadzu DSC-60 under nitrogen atmosphere. NaBH<sub>4</sub> was purchased from Kanto Chemical Co., Inc. Anhydrous THF was purchased from Kanto Chemical Co., Inc., and used without further purification. MeOH was distilled over CaH<sub>2</sub> before use.

Procedure for Reusable Catalytic System in Reduction of 1-Adamantyl Methyl Ketone (3). Under a nitrogen atmosphere, NaBH<sub>4</sub> (18.9 mg, 0.50 mmol) and MeOH (121  $\mu$ L, 3.0 mmol) in 3.9 mL of THF was stirred at 20 °C for 2 h. To a solution of cobalt complex 1 (19.5 mg, 25 µmol, 10 mol%) or recovered complex 2, 1-adamantyl methyl ketone (3) (44.6 mg, 0.25 mmol) and 1,1,1-trichloroethane (7.5 µL, 75 µmol, 30 mol%) in THF (2.5 mL) was added the prepared borohydride mixture at -20 °C over 20 min. After stirring for 24 h at -20 °C, the reaction was quenched with 1.5 mL of cooled aqueous THF. To the solution was added water and AcOEt, extracted 3 times with AcOEt, then washed with brine. The combined organic layers were dried over Na2SO4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography pressurized by nitrogen with an eluent (AcOEt/hexane = 1/15) to afford the corresponding alcohol 4. After elimination of the yellowcolored fractions with an eluent (AcOEt/Et<sub>2</sub>O = 1/12), the red-colored fractions were collected with an eluent (AcOEt/  $Et_2O = 4/1$ ). The collected red-colored fractions evaporated under reduced pressure (Do not evaporate completely under high vacuum. When the red-colored fractions were dried completely to obtain the recycled catalyst, the enantiomeric excesses decreased). The secondary alcohol 4 was followed by esterification with 1-naphthoyl chloride for HPLC analysis.<sup>5</sup>

Procedure for Reusable Catalytic System in Reduction of Butyl Phenyl Ketone (6). To a solution of the cobalt complex 11 (18.8 mg, 25  $\mu$ mol, 10 mol %) or recovered complex, butyl phenyl ketone (6) (40.6 mg, 0.25 mmol) and 1,1,1-trichloroethane (10.0  $\mu$ L, 100  $\mu$ mol, 20 mol %) in THF (2.5 mL) was added the prepared borohydride mixture as above at -20 °C over 20 min. After stirring for 5–6 h at -20 °C, the reaction was quenched with 1.5 mL of cooled aqueous THF. To the solution was added water and AcOEt, extracted 3 times with AcOEt. then washed with brine. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography pressurized by nitrogen with an eluent (THF/ hexane = 1/25) to afford the corresponding alcohol 7. HPLC analysis was performed without further purification.<sup>3a</sup> After elimination of the vellow-colored fractions, the red-colored fractions were collected with an eluent (THF/Et<sub>2</sub>O = 1/10). The collected red-colored fractions evaporated under reduced pressure (Do not evaporate completely under high vacuum. When the red-colored fractions were dried completely, the enantiomeric excesses decreased).

#### **Supporting Information**

Analytical data of cobalt complexes **9–11** and recovered cobalt(III) complex derived from cobalt(II) complex **11**. This material is available free of charge on the web at: http://www.csj.jp/journals/bcsj/.

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6 The yellow-colored fractions were assumed to be the cobalt(II) complex 1 based on ESI-MS analysis. However, the reactivity and selectivity of the reaction with the recovered yellow catalyst were different from original cobalt(II) complex 1. The recovered cobalt(II) complex would be damaged by air (especially oxygen) during the recovery process. See Supporting Information.