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Structure Determination of the Cobalt(III) Complex Catalyst for Enantioselective Borohydride Reduction

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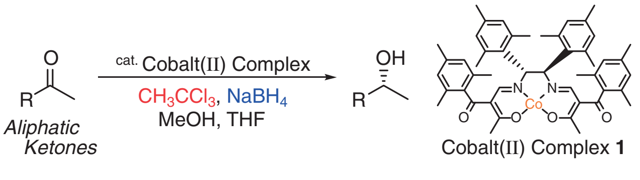
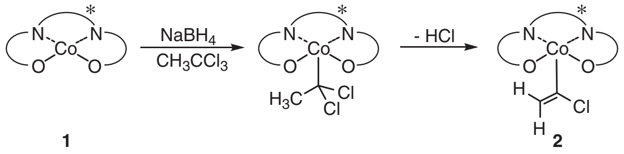
The structure of the reactive cobalt complex catalyst for the enantioselective borohydride reduction of ketones was completely determined by ESI-MS, NMR, and X-ray analyses. It was confirmed that as an axial ligand, 1-chlorovinyl group derived from 1,1,1-trichloroethane was attached. Based on the X-ray analysis, two rotamers on cobalt–carbon bond were found in one unit. The obtained 1-chlorovinylcobalt(III) complex was examined for the enantioselective reduction to afford the reduced product in high yield with a high enantioselectivity.

In the preceding communication,[1] the enantioselective borohydride reduction for aliphatic ketones catalyzed by the optically active ketoiminatocobalt complexes **1** was reported (Scheme 1). Based on the previously proposed transition state[2] in the original catalysis system with chloroform,[3] various haloalkanes were screened as the precursor for the axial ligand activating the cobalt(II) complex catalyst. Eventually, 1,1,1-trichloroethane was found to be the most effective activator for cobalt catalyst to achieve a high enantioselectivity. Several aliphatic ketones were successfully reduced to the corresponding secondary alcohols with good-to-high enantioselectivities. In ESI-MS analysis of the reaction mixture, a peak at m/z 843 in the positive mode could be assigned as the cobalt(III) complex **2** coordinated by 1-chlorovinyl group, derived from the initially generated dichloroethyl–cobalt complex,[4] via elimination of hydrogen chloride due to the acidity of the terminal methyl group (Scheme 2). In this communication, we describe the complete determination of the structure of the cobalt catalyst intermediate generated in the present reaction and also propose the reaction mechanism including the enantioselective sense.



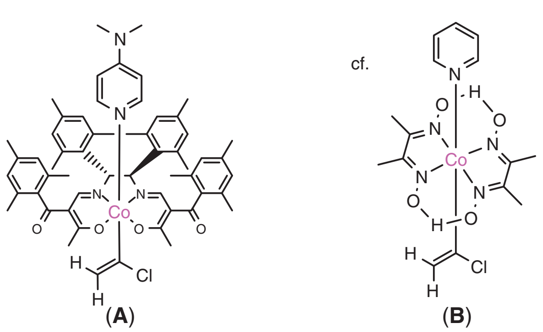
Scheme 1. Enantioselective reduction of aliphatic ketones catalyzed by cobalt complex.



Scheme 2. Mechanism for the generation of 1-chlorovinyl-cobalt(III) complex from 1,1-dichloroethyl–cobalt(III) complex.

In the conventional purification process by silica gel column chromatography, the red-colored fractions came out using a highly polar eluent after the fractions of the organic compounds. The ESI-MS analysis of the red-colored fractions indicated the peak at m/z 843 (in positive mode) assigned as the cobalt(III) complex containing 1-chlorovinyl group **2** as well as the reaction mixture. This observation suggested that the chlorovinyl–cobalt **2** was stable enough to be employed for various analytical methods, such as NMR or single-crystal X-ray structure analyses.

Since the dichloromethylcobalt(III) complexes were proposed by analytical and/or theoretical studies in order to determine the detailed structure, NMR analysis and recrystallization for X-ray analysis have been examined. In NMR analysis, a high-resolution spectrum should be provided for the diamagnetic cobalt(III) complex, however, broadened signals were observed due to decomposition of the cobalt(III) complexes into paramagnetic cobalt(II) complexes. For the present cobalt(III) complex with 1-chlorovinyl group on the axial site, the treatment with 4-(dimethylamino)pyridine (DMAP) was found to effectively stabilize the cobalt(III) structure to afford the orange-colored solid. As a result, a high-resolution spectrum was successfully obtained in ^{1}H and ^{13}C NMR analyses of this orange-colored crystal. As a pair of doublet peaks ($J = 2.2$ Hz) were observed in ^{1}H NMR at 5.03 and 5.32 ppm, they could be assigned as vinyl protons in the estimated 1-chlorovinyl-cobalt(III) complex (Figure 1A). The chemical shift at 120.7 ppm in ^{13}C NMR also supported the vinyl structure. These



(A)
^{1}H : 5.03 ppm (d, 2.2 Hz)
5.32 ppm (d, 2.2 Hz)
^{13}C : 120.7 ppm

(B)
^{1}H : 5.05 ppm (d, 2.1 Hz)
5.24 ppm (d, 2.1 Hz)
^{13}C : 119.3 ppm

Figure 1. Characteristic signals in NMR study of the recovered complex and the reported (ref. 5) complex.

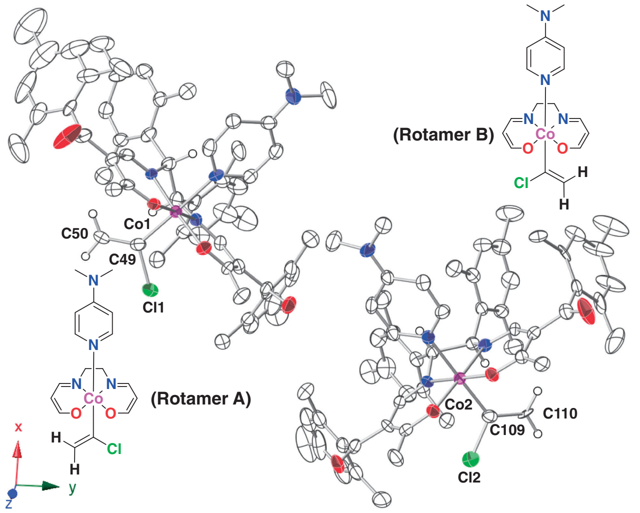
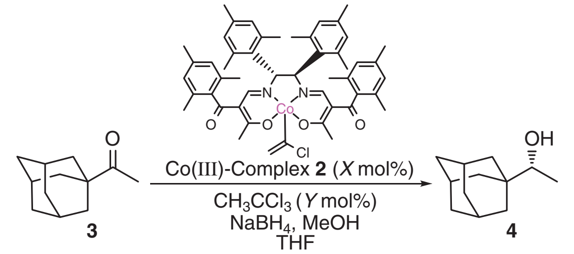


Figure 2. The asymmetry unit is drawn at a 50% probability level including a pair of rotation isomers, A and B. Hydrogen atoms (except for the hydrogen atom around the chiral atoms and on vinyl group), noncoordinated THF molecules and disorderd atoms are omitted for clarity.

observations were reasonably supported by the reported value for the similar structure of the cobalt(III) complexes, (chloroethenyl)cobaloxime complex(es) as shown in Figure 1B.[5]

The orange-colored cobalt(III) complex stabilized by DMAP was successfully recrystallized from dichloromethane/hexane to afford a single crystal as an orange needle. Single-crystal X-ray analysis[6] showed that the compound crystallized in the $P2_1$ space group ($a = 11.3722(3)$ Å, $b = 29.9378(8)$ Å, $c = 19.1540(6)$ Å, $\beta = 105.713(1)°$, $Z = 4$). In Figure 2, the asymmetry unit drawn at a 50% probability was provided including a pair of rotamers on the cobalt–carbon bond. The coordination geometries around the cobalt center were an octahedral, connecting with two N atoms and two O atoms in equatorial ligand, and with N atom in the pyridine ring and C atom in 1-chlorovinyl group in each axial direction. The C–C distances of 1-chlorovinyl group in rotamers A (C49–C50) and B (C109–C110) were 1.40 and 1.42 Å, respectively, longer than the average bond distance for C=C bond (1.32 Å). On the equatorial ketoimine ligand plane, two aromatic rings are attached perpendicular on the ethylene-bridge to form chiral centers. Their distance between aromatics on the ethylene-bridge (e.g., C31–C36) and side-chain (e.g., C11–C16) was 4.0–4.5 Å, assuming π–π interaction. Interestingly, the asymmetric unit consisted of two cobalt complex molecules, a pair of rotation isomers on N–Co–C axis for the pyridine ring and vinyl group. In each isomer, Cl atom on 1-chlorovinyl was located above one of the two O atoms in the planar ketoimine ligand.

Table 1. Examination of catalytic activity of 1-chlorovinylcobalt(III) complex[a]



Entry	X/mol %	Y/mol %	Time/h	Yield/%	ee/%
1	7.2	0	0.5	20	83
2	7.2	0	10	94	56
3	60.0	0	24	90	84
4	5.0	20	24	95	86

[a] Reaction conditions: ketone **3** (0.25 mmol), (R,R)-**2** (X mol %), $NaBH_4$ (0.50 mmol, 2.0 equiv), MeOH (3.0 mmol, 12 equiv), CH_3CCl_3 (Y mol %) at −20 °C. Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by HPLC analysis of 1-naphthoate derivative (Chiralpak IB).

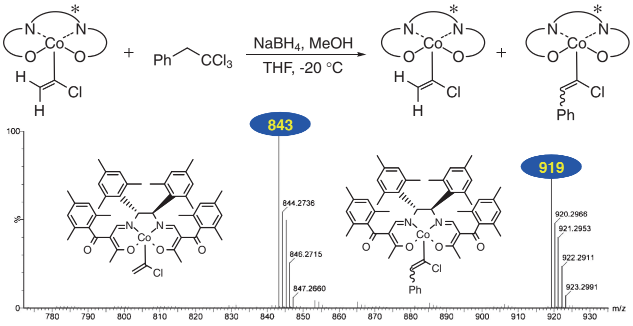


Figure 3. Regeneration of 1-chlorovinyl axial ligand in the crossed reaction.

For the next stage, the catalytic activity of the cobalt(III) complex containing 1-chlorovinyl group was examined.[7] In the presence of 7.2 mol % of the cobalt(III) complex **2**, without 1,1,1-trichloroethane, the enantiomeric excess of the reduced product with 20% yield in 30 min was 83% ee (Table 1, Entry 1), while after 10 h, 94% yield of the product was obtained, but with 56% ee (Entry 2). By loading 60 mol % of the complex catalyst **2**, the selectivity was improved to a level similar to the original system with 1,1,1-trichloroethane, i.e., 84% ee (Entry 3). These results suggested that the complex **2** itself should catalyze the enantioselective borohydride reduction though it could be gradually decomposed to the corresponding starting cobalt(II) complex **1**. In the experiment of Entry 3, the active and effective catalyst still remained after 24 h due to the loading amount. This consideration is consistent with the low resolution in the previous NMR study due to decomposition into the cobalt(II) complexes. In the presence of the axial ligand precursor, 1,1,1-trichloroethane (20 mol %), 5 mol % of catalyst **2** effectively achieved a high chemical yield (95% yield) and high enantioselectivity (86% ee) after 24 h (Entry 4). The effective catalyst intermediate **2** can be reconstructed by adding 1,1,1-trichloroethane to recover the selectivity even when the complex is deactivated due to the cobalt–carbon bond cleavage. The regeneration of cobalt–carbon bond was confirmed in the crossed experiment with another trichloroalkane. The complex **2** and (2,2,2-trichloroethyl)benzene were treated under the reaction conditions. In ESI-MS analysis of the reaction mixture, the peak assigned as the cobalt(III) complex coordinated by 1-chloro-2-phenylethenyl group (m/z 919, in positive mode) was detected in addition to the starting complex **2** (m/z 843) (Figure 3).

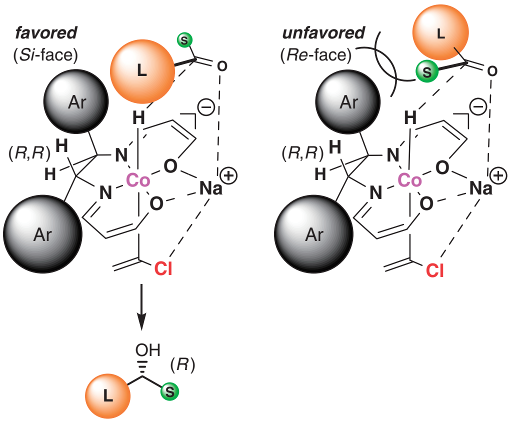


Figure 4. Plausible mechanism for enantioselective sense.

Thus the reaction mechanism of the cobalt-catalyzed borohydride reduction would be proposed as follows: The starting cobalt(II) complex **1** would react with 1,1,1-trichloroethane to provide the dichloroethyl–cobalt(III) complex in the presence of sodium borohydride.[4] The protons in 1,1-dichloroethyl group would be sufficiently acidic to release hydrogen chloride to afford the more stable 1-chlorovinylcobalt(III) complex **2**. The intermediate **2** would capture the hydride from the modified borohydride to generate the chlorovinyl–cobalt(III)–hydride with a sodium cation and then the ketone would be fixed by the sodium cation to construct the quasi-six-membered transition state (Figure 4). The enantiofacial sense would be regulated by the steric demand of the aromatics on the ethylene bridge and the substituent of the ketones. On the proposed quasi-six-membered transition state, *Si*-face attack would be favorable for the (*R*,*R*)-catalyst due to the steric repulsion between the aromatic group (Ar) with the larger substituent (L) in the ketone. The model structure is reasonable for the X-ray structure and the prediction of the enantiosense is consistent with the observed results.

Based on the analytical methods and reference experiments, it was concluded that the 1-chlorovinylcobalt(III) complex was generated as the key catalyst intermediate in the presence of 1,1,1-trichloroethane and catalyzed the present enantioselective borohydride reduction to afford the product with a high enantioselectivity.

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6 The very poor crystallinity due to the several THF molecules included as the crystal solvent resulted in synchrotron radiation being used. The crystallographic data reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-880757. A copy of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

7 Supporting Information is electronically available on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.