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The Reactive Intermediate of Catalytic Borohydride Reduction by Schiff Base–Cobalt Complexes

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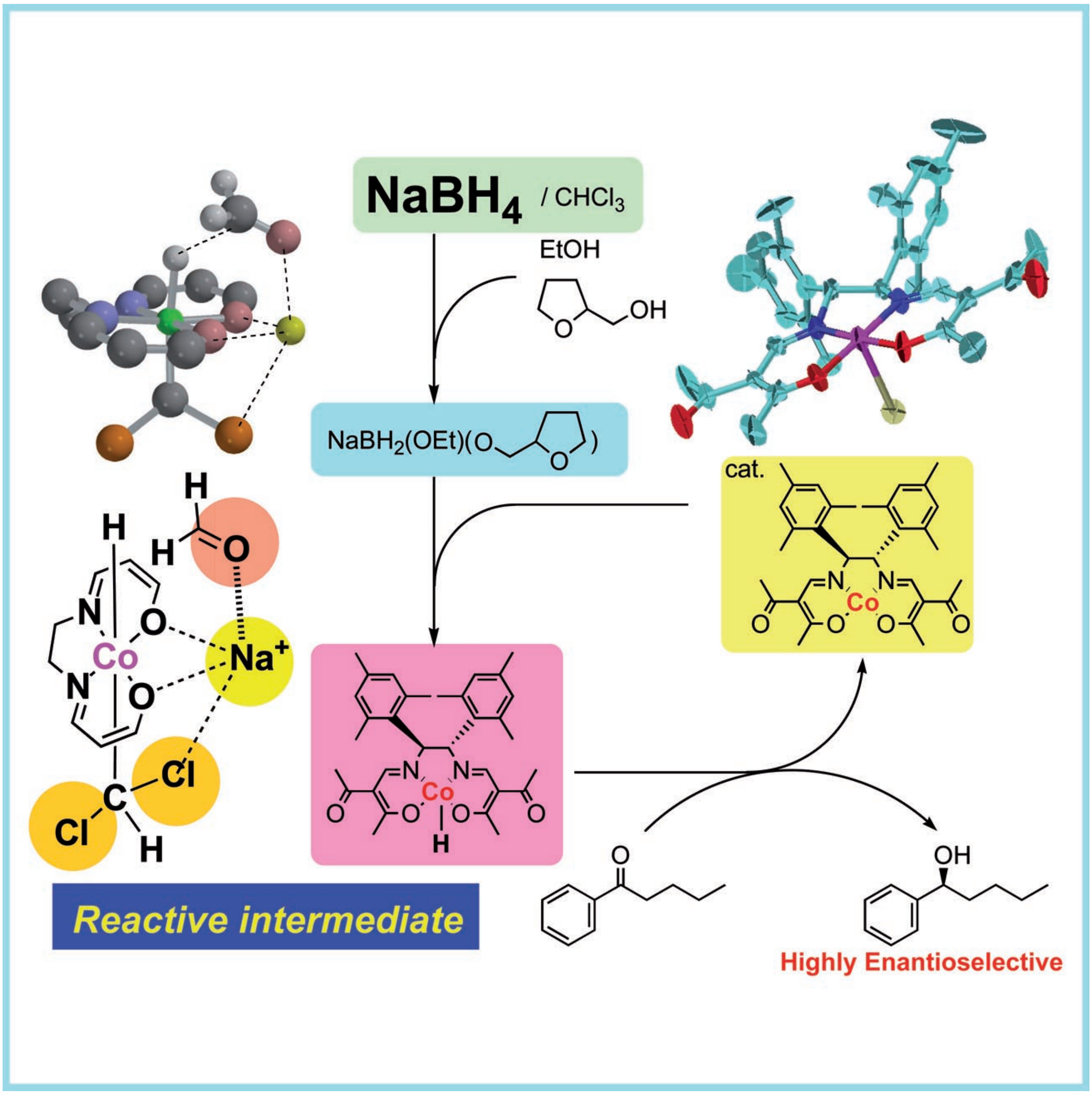

Abstract: The key reactive intermediate of borohydride reduction catalyzed by Schiff base–cobalt complexes is proposed to be the dichloromethylcobalt hydride with a sodium cation, based on experimental and theoretical studies. It was revealed that chloroform is not the solvent but the reactant that activates the cobalt catalyst. The substrate carbonyl compounds are fixed and activated by the alkali cation, which is captured by the oxygen atoms of the planar ligand and the chlorine atom of the axial ligand, and attacked by the hydride on the cobalt atom via a six-membered-like transition state to afford the corresponding alcohol.

Keywords: asymmetric synthesis · cobalt · density functional calculations · reduction · Schiff bases

Introduction

Sodium borohydride is one of the most reliable reducing agents in industry and the laboratory. On the other hand, the ketoiminatocobalt complexes[1] developed by our research group are a unique group of catalysts for the enantioselective borohydride reduction[2] of carbonyl compounds. For instance, various ketones, imines, and α,β-unsaturated carbonyl compounds are reduced to the corresponding secondary alcohols, amines, and carboxylates with high to excellent enantioselectivities and high efficiencies. The protocol of the present cobalt-catalyzed reduction is as follows: A solution of borohydride modified by ethanol and tetrahydrofurfuryl alcohol (THFA) was added to a solution of the carbonyl compound and a catalytic amount of the cobalt complex. The orange solution immediately turned reddish-violet, thus showing that the reduction had occurred (Figure 1). The color change was also observed by the addition of the solution of borohydride to the cobalt complex. The preliminary FAB MS analysis[3] of these solutions revealed that the peak of the original cobalt complex at 697 Da disappeared and a strong peak at 698 Da $[M+1]$ was observed after the borohydride was added and the color changed. These observations support the fact that the cobalt hydrides were generated as the active catalytic species and, therefore, refute the possibility that the borohydride directly reduced the carbonyl compound activated by the cobalt complex and could act as a Lewis acid.

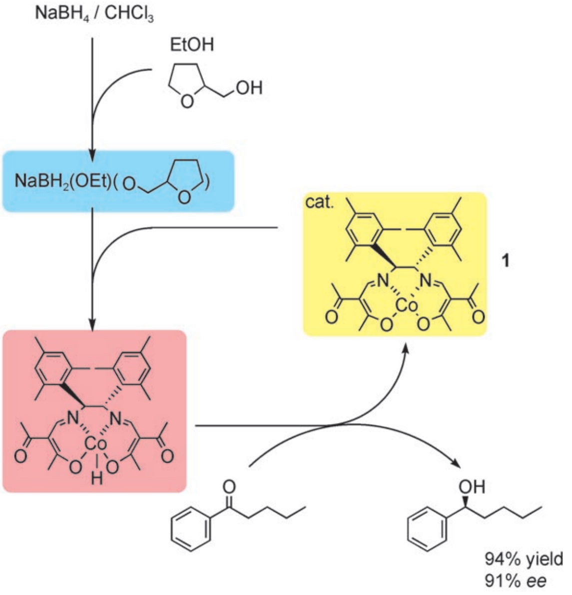

Figure 1. Tentative mechanism for the enantioselective borohydride reduction catalyzed by the cobalt(II) complex **1**.

Herein, we propose the key reactive intermediate of the highly efficient cobalt-catalyzed borohydride reduction based on a mechanistic study involving the experimental and theoretical investigations.

Results and Discussion

Experimental Observations

For the catalytic enantioselective borohydride reduction, chloroform is the only solvent in which both high enantiose-

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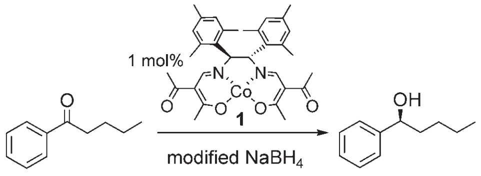
lectivity and efficiency are realized (Table 1, entry 1). In other solvents, such as THF and toluene (Table 1, entries 2 and 3), the reduced product was obtained in high yield, but its *ee* was very low.

Table 1. Borohydride reduction in various solvents catalyzed by the cobalt complex.

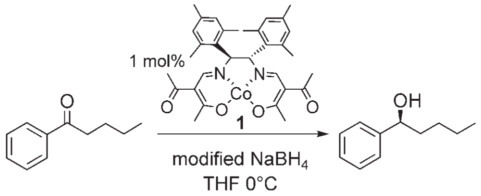


Entry[a]	t [h]	Solvent	Yield [%]	*ee* [%][b]
1	15	$CHCl_3$	94	91
2	4	THF	94	2
3	10	toluene	88	0.4

[a] Reaction conditions: 0.50 mmol substrate, 0.0050 mmol Co catalyst, 0.75 mmol $NaBH_4$, 0.75 mmol EtOH, 10.5 mmol THFA in solvent (8 mL), 0 °C. [b] Determined by HPLC analysis.

It was found that in THF with chloroform, the reduction proceeded enantioselectively (Table 2, entries 1 and 2). Furthermore, even in the presence of a catalytic amount of chloroform, a high enantioselectivity was observed. Only five equivalents of chloroform relative to the cobalt catalyst were needed to obtain high enantioselectivity (Table 2, entry 4). Therefore, the effect of chloroform is not only due to the solvent effect, but chloroform itself reacted with the cobalt complex to generate a key reactive intermediate that catalyzed the present reduction with borohydride.

Table 2. Effect of amount of chloroform on yield and enantioselectivity.



Entry[a]	$CHCl_3$ [equiv][b]	Yield [%]	*ee* [%][c]
1	200	88	82
2	100	85	84
3	25	97	85
4	5	83	85
5	0	74	41

[a] Reaction conditions: 0.50 mmol substrate, 0.0050 mmol Co catalyst, 0.75 mmol $NaBH_4$, 0.75 mmol EtOH, 10.5 mmol THFA in THF (8 mL), 0 °C, 14 h. [b] Relative to catalyst. [c] Determined by HPLC analysis.

Abstract in Japanese:

ケトイミナトコバルト錯体を触媒とする不斉ボロヒドリド還元の反応中間体として、実験結果と理論解析からナトリウムカチオンが配位したジクロロメチル–コバルト–ヒドリド中間体を提唱した。クロロホルムは溶媒ではなく、触媒量でコバルト錯体を活性化する反応剤である。平面配位子の酸素原子とアキシャル配位子のクロロ原子により還元剤のアルカリカチオンは捕捉され、このアルカリカチオンに基質のカルボニル基が配位することにより活性化されると同時に構造が固定化され、高い立体選択性が発現したと考えることができる。

The FAB MS spectrum of the solution of cobalt complex/borohydride was then examined in detail (Figure 2). After treatment of the cobalt solution with the modified borohydride, the peak at $m/z = 697$ Da in the negative mode for the original cobalt complex **2** (Figure 2a) disappeared, and a new peak at $m/z = 698$ Da, assigned to the cobalt hydride complex **3**, appeared (Figure 2b). Another peak was observed at $m/z = 781$ Da, which was assigned to the dichloromethylcobalt hydride **4** ($697 + 1 + 83$ Da). When borodeuteride was employed in place of borohydride, a new peak at $m/z = 782$ Da was also detected, which was assigned to the dichloromethylcobalt deuteride complex, along with the peak at $m/z = 699$ Da assigned to the cobalt deuteride complex (Figure 2c).[4] When [D]chloroform and borodeuteride were used, new peaks at $m/z = 783$ and 699 Da, assigned to the [D]dichloromethylcobalt deuteride and the cobalt deuteride complexes, respectively, were also detected (Figure 2d). These observations suggest that the dichloromethylcobalt hydride intermediate could be generated as the key reactive intermediate in the present reduction system.

To confirm the presence of the dichloromethylcobalt(III) complex, the UV/Vis spectra of the reduction system were also examined (Table 3). The cobalt(II) complex **2** showed a characteristic absorption at about 380 nm, whereas that of the phenylcobalt(III) complex **8** was observed at about 600 nm. After **2** was treated with the modified borohydride, the characteristic absorption for the cobalt(II) complex disappeared, and a new absorption was observed at 631 nm, which was assigned to the corresponding alkylcobalt(III) complex. This UV/Vis spectrum is similar to that of the phenylcobalt(III) complex with borohydride, and in both cases, the catalyst solution turned reddish with the addition of borohydride.

It was previously reported that a dioximatocobalt complex and vitamin B_{12} readily react with an alkyl halide in the presence of sodium borohydride to generate cobalt–alkyl complexes. For example, a dichloromethylcobalt complex was obtained from a dioximatocobalt complex and chloroform in the presence of sodium borohydride.[6] Based on these reports and the present observations, it is reasonable to consider that the dichloromethylcobalt hydride complex was generated as the key reactive intermediate during the cobalt-catalyzed borohydride reduction.

Notably, the alkali-metal cation has a crucial effect on the reaction rate as well as the enantioselectivity during catalytic enantioselective borohydride reduction with the cobalt(II) catalyst. As shown in Table 4, as the amount of [15]crown-5 added as sodium-cation scavenger was increased, not only did the chemical yield and reaction rate significantly decreased, but so did the enantioselectivity.

Borohydrides with various countercations were next examined (Table 5). When lithium borohydride was employed

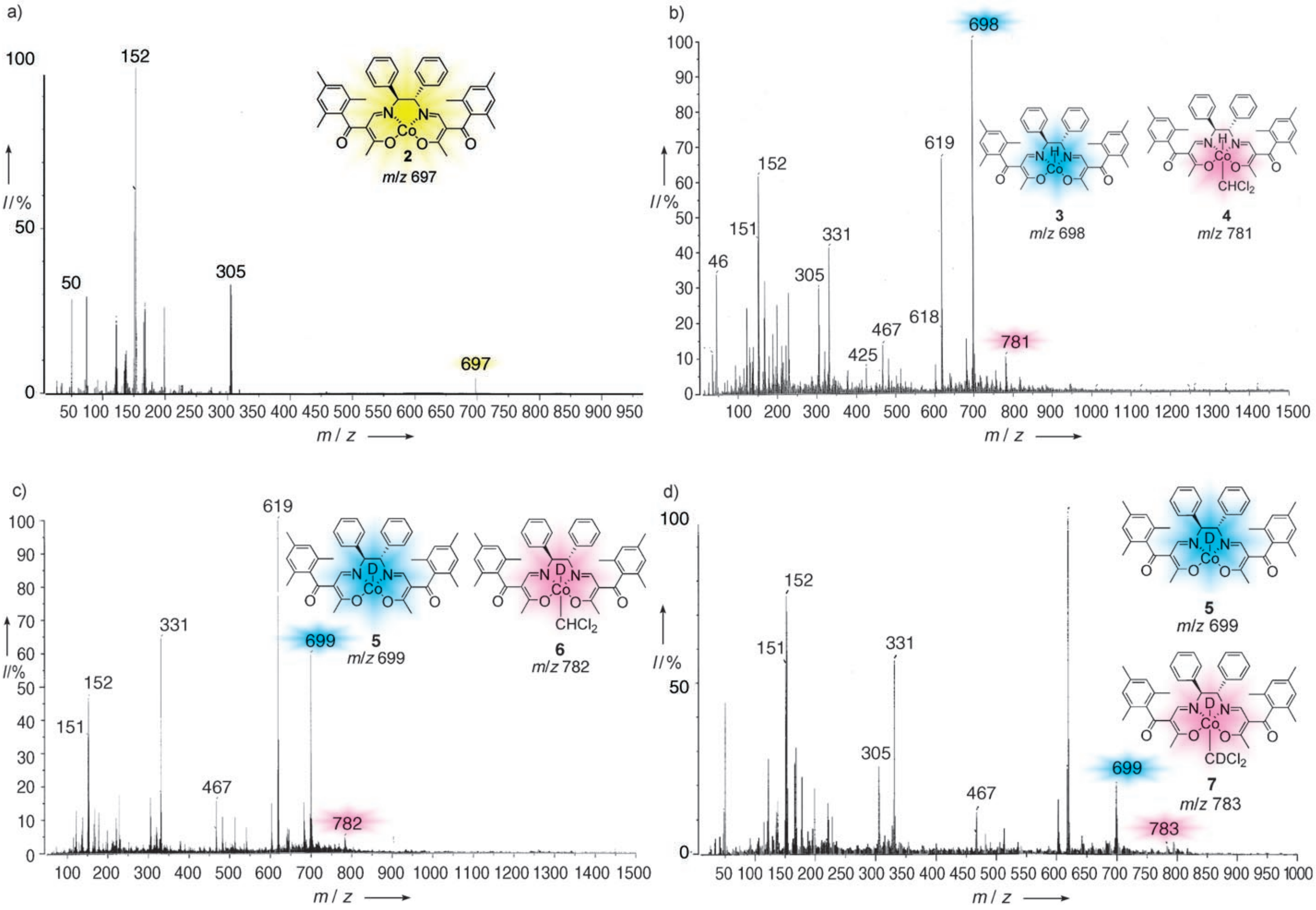
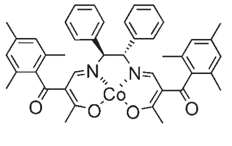


Figure 2. FAB MS spectra of a) the original cobalt complex, b) the cobalt complex treated with borohydride, c) the cobalt complex treated with borodeuteride, and d) the cobalt complex treated with borodeuteride in [D]chloroform.

Table 3. UV/Vis spectra of cobalt complexes.



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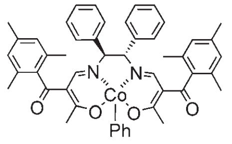
Cobalt(II) complex

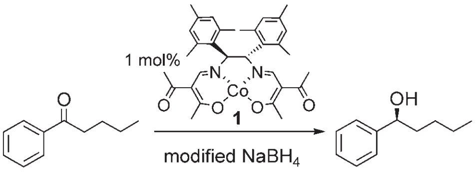


8

Cobalt(III)–Ph complex

Entry	Complex and reagents	λ [nm]				
1	Cobalt(II) complex **2**			378	318	245
2	Cobalt(III)–Ph complex **8**		621		278	244
3	Cobalt(II) complex **2** + modified borohydride	880	631		278	245
4	Cobalt(III)–Ph complex **8** + modified borohydride	973	612		278	253

Table 4. Effect of [15]crown-5 on yield and enantioselectivity.

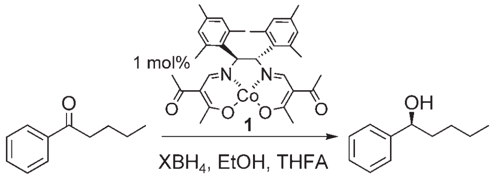


Entry[a]	[15]Crown-5 [equiv][b]	Yield [%]	*ee* [%][c]
1	0.00	94	91
2	0.25	93	90
3	0.50	76	71
4	0.75	72	56
5	1.00	65	41
6	2.00	54	21

[a] Reaction conditions: 0.50 mmol substrate, 0.0050 mmol Co catalyst, 0.75 mmol NaBH$_4$, 0.75 mmol EtOH, 10.5 mmol THFA in CHCl$_3$ (8 mL), 0 °C. [b] Relative to the modified NaBH$_4$. [c] Determined by HPLC analysis.

instead of sodium borohydride, the reduced product was obtained in high yield along with excellent enantioselectivity (Table 5, entry 2). Potassium borohydride produced a product of high optical purity in relatively low yield because of its solubility (Table 5, entry 3). The reaction with unmodified borohydride proceeded in suspension to afford the reduced product with slightly decreased *ee*, but on the whole, the same trend was observed. In contrast, the tetraalkylammonium borohydrides produced the almost-racemic product in low yield (Table 5, entries 4 and 5). These experimental results strongly suggest that the alkali-metal cation plays an essential part in this enantioselective reduction.

Table 5. Effect of the countercations of the borohydrides on yield and enantioselectivity.



Entry	Borohydride	Modified conditions[a]		Unmodified conditions[b]	
		Yield [%]	*ee* [%][c]	Yield [%]	*ee* [%][c]
1	$NaBH_4$	90	94	90	80
2	$LiBH_4$	94	95	86	93
3	KBH_4	13	89	2	72
4	Et_4NBH_4	52	2	30	–
5	Bu_4NBH_4	51	3	46	7

[a] Reaction conditions: The borohydride (0.75 mmol) was treated with EtOH (0.75 mmol) and THFA (10.5 mmol) in $CHCl_3$ until 2 equivalents of H_2 evolved relative to the borohydride. The solution was added to a solution of substrate (0.50 mmol) and **1** (0.005 mmol) in $CHCl_3$ (8 mL) at 0°C. The mixture was then stirred for 20 h. [b] Reaction conditions: A suspension of borohydride (0.75 mmol) in EtOH (0.75 mmol), THFA (10.5 mmol), and $CHCl_3$ was added to a solution of substrate (0.50 mmol) and **1** (0.005 mmol) in $CHCl_3$ (8 mL) at 0°C. The mixture was then stirred for 20 h. [c] Determined by HPLC analysis.

Theoretical Analysis

The following cobalt hydride models were presumed for computational analysis (Figure 3): Model A: the simple cobalt hydride; Model B: the cobalt hydride with an axial ligand such as the dichloromethyl group; and Model C: the cobalt hydride with an axial ligand and a countercation, which is the alkali-metal cation from the borohydride. On the basis of the experimental observations above, the key reactive intermediate was assumed to be the complex of the sodium cation and the dichloromethylcobalt hydride (Model C in Figure 3), although the theoretical analysis of the reaction pathway was examined for each of the presumed Models A–C.

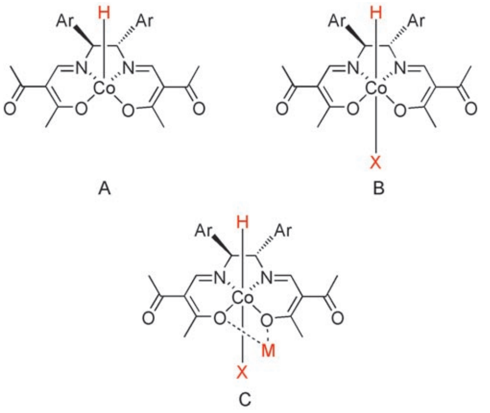


Figure 3. Presumed models of the cobalt hydride intermediates.

As the real cobalt-catalyzed borohydride-reduction system was too large to analyze directly, a model structure was extracted with the principle electronic effect of the reaction (Figure 4). The model cobalt(II) complex **9** has a planar coordination as a simple acacen-type complex (acacen = *N,N′*-ethylenebis(acetylacetonylideneiminato)) instead of 3-oxobutylideneaminato ligands,[7] and formaldehyde was adopted as the representative carbonyl compound. Calculations were performed by using density functional theory at the B3LYP/6-31G*, B3LYP/6-311G**, and B3LYP/6-311+G** levels.[8] The singlet and triplet states were considered for calculation of the d^6 cobalt complexes, and the doublet and quartet states for the d^7 cobalt complexes. The results of the calculations for the B3LYP/6-31G* level are shown below.

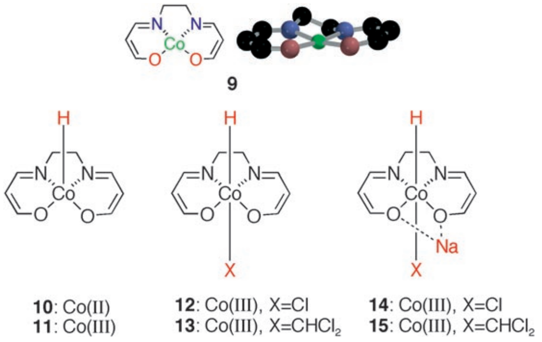


Figure 4. Model and examined cobalt complexes.

The anionic cobalt(II) hydride **10**, which corresponds to Model A, was examined; it could be optimized successfully in both the doublet and quartet states. The latter was more stable than the former by 10 kcal mol^{-1}. The structures and relative energies are shown in Figure 5. However, the transition state (TS) for the reduction of formaldehyde could not be obtained because the alkoxide anion product was quite unstable, with the result that formaldehyde was separated far from **10**. The neutral cobalt(III) hydride **11** could be optimized in the singlet and triplet states. Although the singlet state was found to be more stable than the triplet and the Co–H bond in the former was shorter than that in the latter, the TSs could not be obtained. The cobalt hydrides **12** and **13** were then examined with chloride and dichloromethyl groups as axial ligands (Model B). Optimization of both anionic cobalt hydride complexes in the ground state was successful and revealed that the singlet states were more stable than the triplet, although none of the TSs with **12** and **13** could be obtained due to the reason above. Based on these trials and experiments, Model C, which includes the sodium cation, was then examined to stabilize the increasing anionic character of the oxygen atom of the formaldehyde in the TS. The ground-state structures were successfully optimized (Figure 5).[9] The singlet states were more stable than the triplet, and the Co–H bond shortened slightly by coordination of the sodium cation. The TS of the reduction was first obtained by using the complex **14** with chloride as the axial ligand. However, the energy of the

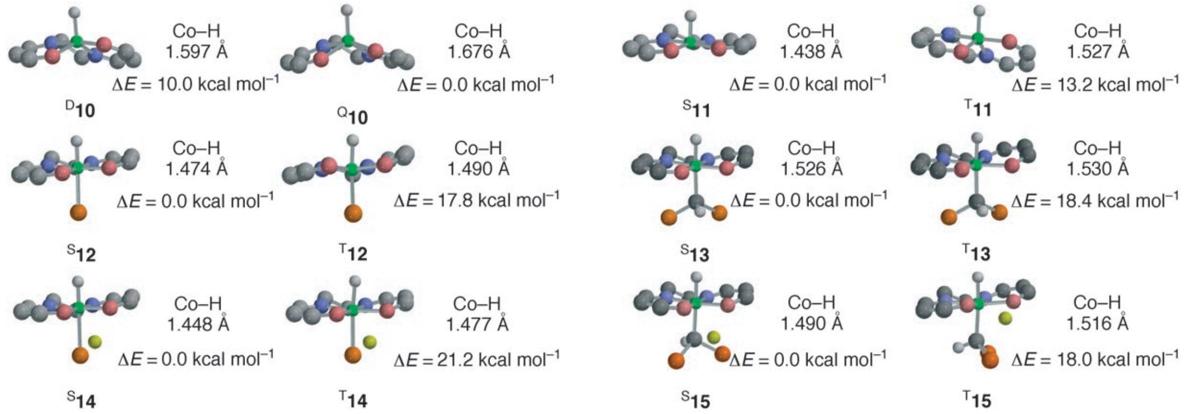


Figure 5. Optimized structures and relative energies of cobalt hydrides at the B3LYP/6-31G*//B3LYP/6-31G* level. S = singlet, D = doublet, T = triplet, Q = quartet.

product obtained by geometry optimization after the intrinsic reaction coordinate (IRC) calculation was higher than that of the reactant.[10] When the dichloromethyl complex **15** was employed, the TS could be optimized, and the product was more stable than the reactant. The optimized TS structures and the energy profile are shown in Figures 6 and 7, respectively.[9,11,12] Throughout the reaction, the singlet state was more stable than the triplet state. The sodium cation was coordinated by two oxygen atoms of the ligand and one chlorine atom of the dichloromethyl group at the axial site. Along the reaction pathway, the distance between the sodium atom and oxygen atoms of the ligand changed only slightly, whereas that between the sodium atom and aldehyde oxygen atom was shortened.

Based on the experimental and theoretical analyses, the mechanism of the cobalt(II)-catalyzed borohydride reduction is proposed as follows: in the presence of chloroform, the original cobalt complex reacts with the hydride reducing agent to generate the corresponding dichloromethylcobalt hydride with the sodium cation intermediate **15**. Ketones coordinate the sodium cation, which leads to the activation and stereochemical alignment of the carbonyl group.[13] From the intermediate, the hydride on the cobalt atom attacks the carbonyl carbon to form a six-membered-like TS. Coordination by both the chlorine and oxygen atoms of the ligand in the TS is essential. After the TS, the anionic character of the oxygen atom is delocalized to the cationic sodium ion.

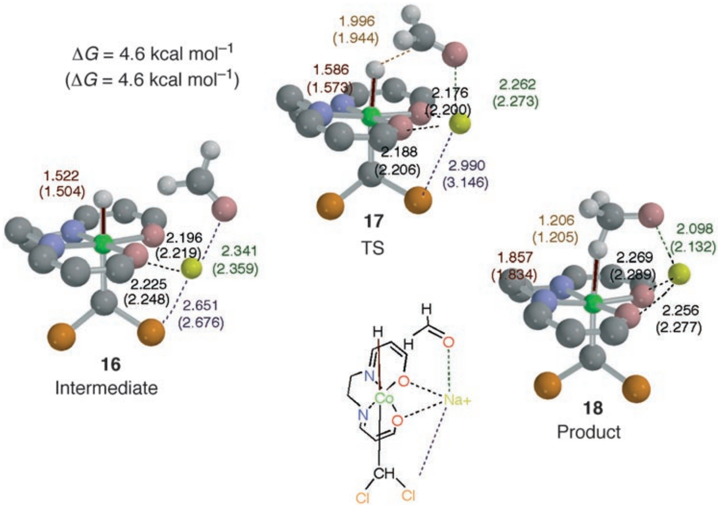


Figure 6. Optimized transition states of cobalt hydride at the B3LYP/6-31G*//B3LYP/6-31G* level. Results at the B3LYP/6-311+G**//B3LYP/6-311+G** level are shown in parentheses.

Conclusions

We have proposed that the dichloromethylcobalt hydride with the sodium cation is the key reactive intermediate of cobalt-catalyzed borohydride reduction on the basis of experimental and theoretical studies. The oxygen atoms of the planar ligand and a chlorine atom of the axial ligand captures the sodium ion, which activates the carbonyl compounds and fixes the stereochemistry (Figure 8).[14]

Experimental Section

General

^{1}H NMR spectra were recorded on a JEOL model EX-270 (270 MHz) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS; 0.00 ppm) as the internal standard. High-performance liquid chromatography (HPLC) was performed with a Shimadzu LC-6A chromatograph and an optically active column (Daicel Chiralcel OD-H); the peak areas were obtained by using the Shimadzu LCsolution software. FAB mass spectra were obtained on a JEOL JMS-700 mass spectrometer with 3-nitrobenzyl alcohol as the matrix and 10-kV acceleration voltages. UV/Vis spectra were recorded on a Shimadzu model UV mini-1240 spectrometer.

Computational Methods

The Gaussian 98 program was used for the structure calculations.[8] Geometry optimizations were performed with density functional theory at the generalized gradient approximation through the use of the B3LYP

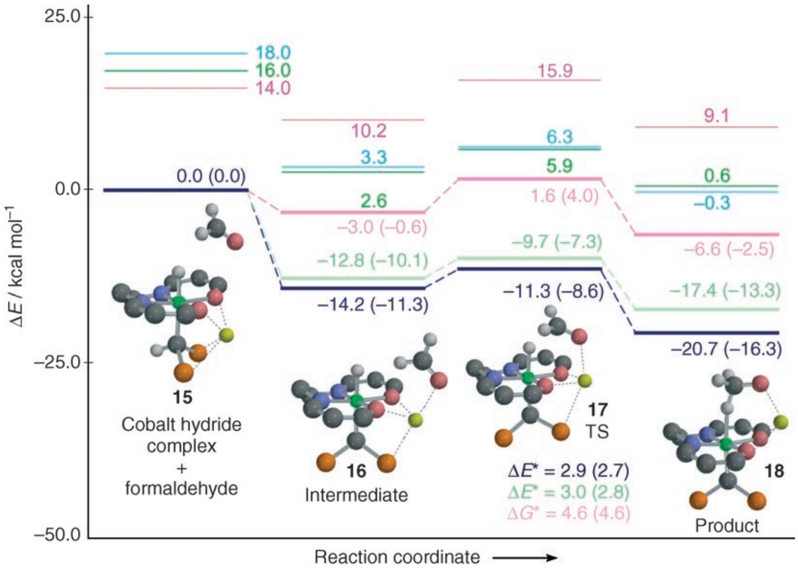


Figure 7. Energy profile of cobalt-catalyzed borohydride reduction at the B3LYP/6-31G*//B3LYP/6-31G* level. Results at the B3LYP/6-311+G**//B3LYP/6-311+G** level are shown in parentheses. —— = Triplet single-point energy, —— = triplet zero-point energy, —— = triplet Gibbs energy, —— = singlet single-point energy, —— = singlet zero-point energy, —— = singlet Gibbs energy.

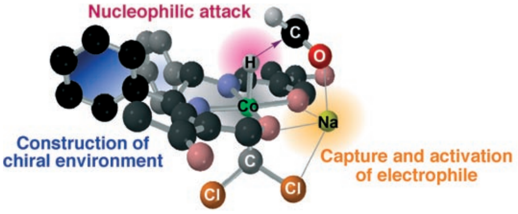


Figure 8. Functions of the cobalt complex.

hybrid functional. The implemented 6-31G*, 6-311G**, and 6-311+G** basis sets were used for the analysis. As for the d orbital, 5d functions were used. The frequency calculations were performed for all the structures obtained at the same level. All the frequencies were real for the ground states, and one imaginary frequency existed for the TSs. Vectors of the imaginary frequencies directed the reaction mode, and the IRC calculations were further performed to confirm that the TSs obtained were the saddle points on the energy profile from the reactant to the product. The zero-point energy correction and Gibbs free energies were calculated without scaling at 0 and 298.15 K, respectively. The stability of all the wavefunctions obtained in the multiplet states was confirmed.

Typical Procedure for the Enantioselective Reduction of Valerophenone

Preparation of the modified sodium borohydride: EtOH (0.06 mL, 1 mmol) and THFA (1.36 mL, 14 mmol) were added to a suspension of $NaBH_4$ (37.8 mg, 1 mmol) in $CHCl_3$ (4 mL) at 0 °C under dry nitrogen. The mixture was stirred for 3 h at 0 °C.

Preparation of the modified lithium borohydride: EtOH (0.06 mL, 1 mmol) and THFA (1.36 mL, 14 mmol) were added to a suspension of $LiBH_4$ (21.8 mg, 1 mmol) in $CHCl_3$ (4 mL) at 0 °C under dry nitrogen. The mixture was stirred for 1 h at 0 °C.

Preparation of the modified potassium borohydride: EtOH (0.06 mL, 1 mmol) and THFA (1.36 mL, 14 mmol) were added to a suspension of KBH_4 (54.0 mg, 1 mmol) in $CHCl_3$ (4 mL) at 0 °C under dry nitrogen. The mixture was stirred for 3 h at 0 °C.

Preparation of the modified ammonium borohydride: EtOH (0.06 mL, 1 mmol) and THFA (1.36 mL, 14 mmol) were added to a suspension of Et_4NBH_4 (145.1 mg, 1 mmol) in $CHCl_3$ (4 mL) at 0 °C under dry nitrogen. The mixture was stirred for 3 h at 0 °C.

Preparation of the unmodified borohydride: EtOH (0.06 mL, 1 mmol) and THFA (1.36 mL, 14 mmol) were added to a suspension of $NaBH_4$ (37.8 mg, 1 mmol) in $CHCl_3$ (4 mL) at 0 °C under dry nitrogen. The mixture was stirred for 2 min at 0 °C.

Enantioselective reduction of valerophenone: Valerophenone (0.05 mmol) and the (*R*,*R*)-cobalt catalyst (**1**, 2.9 mg, 0.0005 mmol, 1.0 mol % relative to valerophenone) were dissolved in $CHCl_3$ (5 mL) and cooled to 0 °C under dry nitrogen. The solution of modified borohydride (4.1 mL, 0.75 mmol) was then added, and the reaction mixture was stirred for 20 h at 0 °C. The reaction was quenched by the addition of phosphate buffer (2 mL). The reaction mixture was extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica-gel column chromatography (hexane/EtOAc) to afford the corresponding 1-phenyl-1-pentanol. The enantioselectivity was determined by HPLC analysis (Daicel Chiralpak OD-H, EtOH/hexane).

1-Phenyl-1-pentanol: ^{1}H NMR (270 MHz, $CDCl_3$, TMS): $\delta = 0.88$ (t, $^3J_{H,H} = 6.8$ Hz, 3 H), 1.22–1.42 (m, 4 H), 1.64–1.82 (m, 2 H), 1.90 (s, 1 H), 4.65 (t, $^3J_{H,H} = 5.2$ Hz, 1 H), 7.26 ppm (m, 5 H); HPLC: Daicel Chiralpak OD-H, 1 % ethanol in hexane, flow 0.8 mL min^{-1}, major 17.3 min, minor 21.3 min.

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[11] Similar energy profiles were obtained at the UB3LYP/6-311G** level. Single-point energy, zero-point energy, and Gibbs energy at that level are shown in square brackets. All energies are in kcal mol^{-1}.**16**: [−14.1, −12.6, −2.8], **17**: [−11.2, −9.7, 1.7], **18**: [−18.1, −15.0, −4.0], ΔE^*: [2.9, 2.9, 4.5].

[12] The solvent effect was evaluated by single-point calculation with the COSMORS method in chloroform and ethanol with the geometry optimized in the gas phase and the dipole model at the B3LYP/6-31G* level. It indicated that the product complex was stabilized by 6 kcal mol^{-1} by the solvent, even though, when complex **14** was used, the product was less stable than the reactant. Therefore, we considered that the solvent effect (solvent conductivity) was not significant, and the dichloromethyl group and sodium cation were crucial for the reduction.

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