Chloroform Is *Not* Solvent but Activator for Cobalt Complex Catalyst of Enantioselective Borohydride Reduction

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For the enantioselective borohydride reduction of carbonyl compounds catalyzed by the optically active ketoiminatocobalt complexes, chloroform has been employed as a unique solvent for achieving a high enantioselectivity, whereas it was found that a catalytic amount of chloroform effectively activated the present catalytic system to convert various ketones into the corresponding reduced product with a high ee in the THF solvent.

Previously, it was reported by our laboratory that the enantioselective borohydride reduction was efficiently catalyzed by the optically active ketoiminatocobalt(II) complexes to convert a wide variety of ketones into the corresponding optically active alcohols in high to excellent yields and enantioselectivities.[1] The drawback in the present reduction system has been pointed out that chloroform is a unique solvent that achieves the high efficiency and high enantioselectivity. For example, the catalytic enantioselective reduction of valerophenone in a pure THF solvent afforded the reduced product with 41% ee, while with 91% ee in the pure chloroform solvent. Due to the troublesome regulation regarding on their waste, halocarbon solvents including chloroform are apt to be prevented from being employed as a solvent in practical applications and non-halogenated solvents have been desired to be employed for the catalytic enantioselective borohydride reduction. During the detailed examination of the reaction system, a small amount of dichloromethane was detected by GC-MS analysis after the reaction was completed. This observation suggested that chloroform could react with the hydride in this reduction system[2] as well as be employed as the suitable solvent. The key reactive intermediate of the borohydride reduction catalyzed by the cobalt complexes was recently proposed to be the dichloromethylcobalthydride with a sodium cation (Figure 1) based on both experimental and theoretical studies.[3] It was revealed that chloroform was not the solvent, but the reactant that activates the cobalt complex catalyst. In this letter, we report that a catalytic amount of chloroform effectively activated the catalytic reduction system in THF solvent to convert various ketones into the corresponding reduced product with a high enantioselectivity.

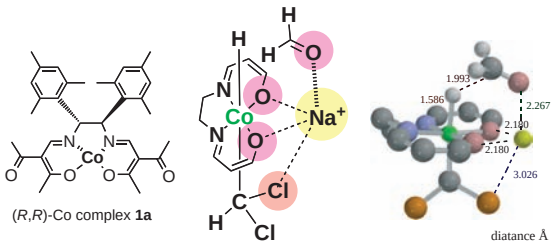
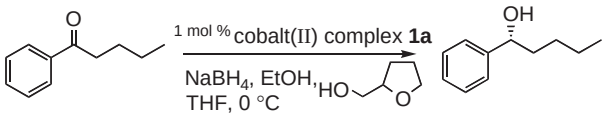


Figure 1. The cobalt complex catalyst and the proposed TS of cobalt-catalyzed borohydride reduction.

The loading amount of chloroform was examined in detail (Table 1). Although in pure THF solvent, the reduced product was obtained with 41% ee, in the presence of 200 equiv. of chloroform vs the cobalt complex, the ee of the reduced product was increased to 82% ee. The remarkable effect of the additive was observed under the conditions of 100, 25, and 5 equiv. of chloroform vs the cobalt complex in THF as the mother solvent, to afford the products with 84, 85, and 85% ee, respectively. Finally, it was found that only 1.5 equiv. of chloroform vs the cobalt complex effectively maintained the enantioselectivity at 81% ee (Entry 4). These results revealed that chloroform was

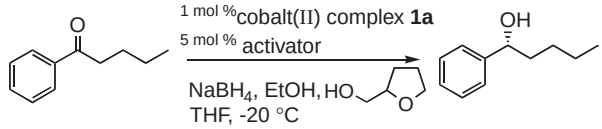
Table 1. The loading amount of chloroform



Entry[a]	Amount of $CHCl_3$/equiv.[b]	Yield/%[c]	ee/% ee[d]
1	solvent	80	91
2	25	97	85
3	5	83	85
4	1.5	80	81
5	none	74	41

[a]Reaction conditions: 0.50 mmol substrate, 0.005 mmol Co catalyst, and 0.75 mmol modified $NaBH_4$ (0.75 mmol $NaBH_4$, 0.75 mmol EtOH, and 10.3 mmol THFA) in THF 8 mL. Reaction time was 15 h. [b]Equivalent vs cobalt complex. [c]Isolated yield. [d]Determined by HPLC analysis (Chiralpak OD-H).

Table 2. Various halocarbons as activators of Co complex



Entry[a]	Activator	Yield/%	ee/% ee
1	CCl_4	90	53
2	CBr_4	87	47
3	$CHBr_3$	98	51
4	CHI_3	93	64
5	ICH_2Cl	95	43
6	$CBrCl_3$	91	81
7	CH_2Cl_2	87	80
8[b]	$CHCl_3$	89	88
9[c]		93	91

[a]Reaction conditions: 0.50 mmol substrate, 0.005 mmol Co catalyst, and 0.75 mmol modified $NaBH_4$ (0.75 mmol $NaBH_4$, 0.75 mmol EtOH, and 10.3 mmol THFA) in THF 8 mL. Reaction time was 15 h. [b]THF (13 mL) was used. [c]2 mol % cat. was used.

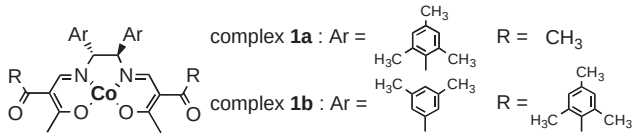
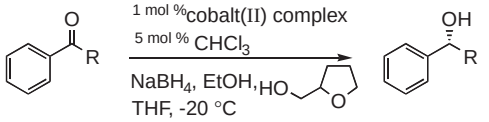
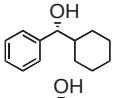
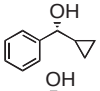
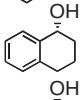
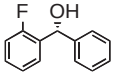
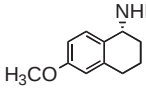
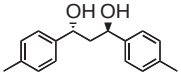
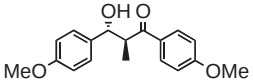
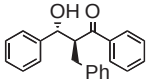
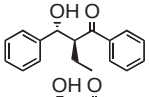
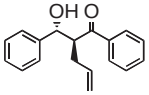
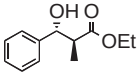


Figure 2. The structure of the cobalt complexes.

Table 3. Catalytic enantioselective borohydride reduction in THF



Entry[a,b]	Reduced product	Time/h	Yield/%[i]	ee/% ee[j]
1		15	80	91
2		15	89	92
3[c]		18	95	90
4[c]		15	87	85[k]
5		9	quant	82[k]
6		25	97	77[k]
7[c,d]		15	88	85
8		10	96	95
9[e,f]		40	77	92 (*dl*:*meso* = 76:24)
10[e,g]		16	84	95[k]
11[e,g]		39	81	87[k]
12[e,g]		16	87	96
13[e,g]		15	90	94[k]
14[h]		60	91	82[k] *dynamic kinetic resolution*

[a]Reaction conditions: 0.50 mmol substrate, 0.005 mmol Co catalyst, and 0.75 mmol modified borohydride (0.75 mmol $NaBH_4$, 0.75 mmol EtOH, and 10.3 mmol THFA) in THF 8 mL. [b]Cobalt complex **1a** was employed for Entries 1, 2, 4, 5, 8–12, and **1b** for Entries 3, 6, and 7. [c]−40 °C, 2.0 mol % Co catalyst, 10 mol % $CHCl_3$. [d]In toluene. [e]5.0 mol % Co catalyst, 25 mol % $CHCl_3$. [f]5.0 equiv. $NaBH_4$. [g]0.8 equiv. $NaBH_4$. [h]4.0 mol % Co catalyst, 20 mol % $CHCl_3$, 1.2 equiv. modified borohydride, 1.0 equiv. NaOMe. [i]Isolated yield. [j]Determined by HPLC analysis (Chiralpak AD-H). [k]Determined by HPLC analysis (Chiralcel OD-H).

not only the appropriate reaction solvent, but also an effective activator of the ketoiminatocobalt complex to realize a highly enantioselective catalytic reduction with sodium borohydride. For the following investigations, the conditions of adding 5 equiv. of chloroform were adopted.

Various halocarbons other than chloroform were examined as the activator for the catalytic enantioselective reduction (Table 2). In the presence of tetrahalocarbons, CCl_4 and CBr_4, the reduction smoothly proceeded, but their enantioselectivities were 53 and 47% ee, respectively (Entries 1 and 2). The haloforms, $CHBr_3$ and CHI_3, were not effective activators to improve the enantioselectivities (Entries 3 and 4). Although chloroiodomethane was not effective (Entry 5), bromotrichloromethane improved the ee of the reduced product (Entry 6). Dichloromethane (Entry 7) was also effective for improving the product ee as did chloroform (Entry 8). After optimization of the reaction conditions, the catalytic enantioselective reduction in THF afforded a product with a 91% ee (Entry 9), which was the same as that obtained in pure chloroform solvent. The examination suggested that halogenated methanes containing more than two chlorine atoms were effective activators, and these observations were quite compatible with the proposed structure in Figure 1.

Thus, the optimized procedure was successfully applied to the enantioselective borohydride reduction catalyzed by the optically active cobalt(II) complexes (Figure 2) in THF solvent. In the presence of 5 mol % of chloroform and 1 mol % of the cobalt complex, various ketones were subjected to the enantioselective borohydride reduction (Table 3). For the isopropyl phenyl ketone (Entry 1), cyclohexyl phenyl ketone (Entry 2), and cyclopropyl phenyl ketone (Entry 3) were converted to the corresponding alcohols in high yields with higher than 90% ee. Tetralone (Entry 4) and 2,2-dimethylchromanone (Entry 5) were also reduced into the corresponding alcohols with 85 and 82% ee, respectively. This reduction system can be applied for the enantioselective reduction of *ortho*-fluorinated benzophenones[4] (Entry 6) and diphenylphosphinylimine derivatives (Entries 7 and 8). The diaryloylmethanes were converted to the corresponding diols with a ca. 3:1 *dl* selectivity and high enantioselectivity (Entry 9). The 2-alkyl substituted 1,3-diketones were reduced to selectively afford the *anti*-alcohol derivatives and their ee's were excellent (Entries 10–13). For the enantioselective reduction along with a dynamic kinetic resolution, this reduction system was effective (Entry 14).

It is noted that a catalytic amount of chloroform effectively activated the cobalt-catalyzed borohydride reduction system that converts various ketones into the corresponding reduced product with a high ee in THF solvent.

Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 80th birthday.

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