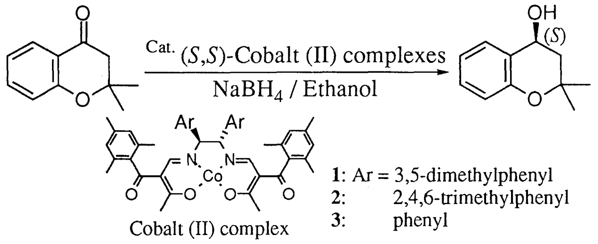
Enantioselective Borohydride Reduction of Ketones Catalyzed by Optically Active Cobalt(II) Complexes: Achievement of High Enantioselection by Modified Borohydrides with Furfuryl Alcohol Derivatives

Kiyoaki D. Sugi, Takushi Nagata, Tohru Yamada, and Teruaki Mukaiyama†
Basic Research Laboratories for Organic Synthesis, Mitsui Petrochemical Industries, Ltd., Nagaura, Sodegaura, Chiba 299-02
†Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

(Received May 14, 1996)

The enantioselective borohydride reduction of ketones catalyzed by optically active (β-oxoaldiminato) cobalt(II) complexes was remarkably improved by using the borohydride which was modified with furfuryl alcohol derivatives and ethanol. In the presence of 1 mol% of the above complex catalysts, asymmetric reduction of aromatic ketones proceeded smoothly to give the corresponding optically active alcohols in quantitative yields within 6-12 h with high enantiomeric excesses (90-97% ee).

The development of various catalytic methods in enantioselective reduction of ketones to optically active alcohols is becoming important tasks in providing alternatives for a synthetic strategy.[1] Among them, the method of borane reduction catalyzed by oxazaborolidine[2] was examined for syntheses of various interests,[3] and also the methods of metal catalyzed hydrogenation[4] and hydrogen transfer[5] were acclaimed as preferential alternatives for using attractive hydride sources. Recently, we have demonstrated that optically active (β-oxoaldiminato) cobalt(II) complex catalysts are effective in the enantioselective reduction of various aromatic ketones using borohydrides; a new category of hydride sources for catalytic enantioselective reduction[6] was made, for example, 2,2-dimethyl-4-chromanone was successfully reduced by sodium borohydride ($NaBH_4$) to afford the corresponding optically active alcohol with 92% ee in the presence of catalytic amount of cobalt(II) complex **1** (Scheme 1).

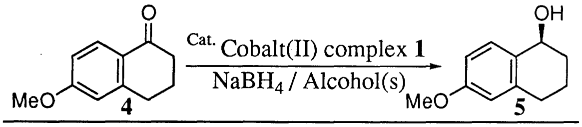


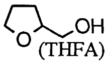
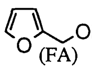
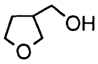
Scheme 1.

It is interesting to note that a limited number of applications concerning metal-complex catalyzed borohydride reductions were reported in the literature[7] in spite of the obvious advantages of easily accessible hydride reagents in carbonyl moiety reductions.[8] Intention was to gain the versatility of borohydrides as the practical hydride source in the enantioselective reduction catalyzed by cobalt(II) complexes and the facial selectivity was significantly improved by proper modification of the borohydrides. Thus this communication now discloses the modification of the borohydrides with furfuryl alcohol derivatives, and the applications to highly practical enantioselective reduction of aromatic ketones which were catalyzed by optically active cobalt(II) complexes.

Preliminary investigations suggested that the addition of an alcohol was indispensable for achieving a high degree of an enantiofacial differentiation. As shown in table 1, alone or in a co-existence of ethanol, $NaBH_4$ showed significant differences in both enantiomeric excess (ee) and chemical yield in the reduction of 6-methoxy-1-tetralone **4**, that is, the obtained alcohols **5** possessed 5% ee with less than 10% yield, and 83% ee with 38% yield, respectively (entries 1 and 2). Higher optical purity of 87% ee as well as higher reaction rate were found when tetrahydrofurfuryl alcohol (THFA) was used to give **5**, and it was obtained in 82% yield (entry 3). The combinational addition of ethanol and THFA or furfuryl alcohol (FA) raised further enhancement in optical purities of **5**, and it possessed 91% ee (entry 4) and 91% ee (entry 7), respectively. On the contrary, the outcomes were lower (75% ee and 70% ee) when structurally similar alcohols such as methoxyethanol and tetrahydro-3-furanmethanol were used (entries 8 and 9). The combinational effects of various alcoholic additives with THFA were examined in the present reduction, and primary alcohols such as ethanol were the suitable combinational additive pair for THFA (or FA). Systematical examination of the ratios of ethanol and THFA was subjected to the catalytic reduction of the ketone **4**, and those indicated an equimolar equivalent of the both alcohols to $NaBH_4$ were at least required for achieving

Table 1. Effects of the various alcohol(s) in the enantioselective borohydride reduction catalyzed by cobalt(II) complex[a]



Entry	Alcohols (mol.-equiv. vs. $NaBH_4$)	Yield /%	Ee /%ee[b]
1	none	<10	5
2	EtOH (6)	38	83
3	 (6) (THFA)	82	87
4	THFA (6) + EtOH (6)	87	91
5	THFA (1) + EtOH (1)	82	91
6[c]	THFA (14) + EtOH (3)	>98[d]	93
7	 (6) (FA) + EtOH (6)	82	91
8	 (6) + EtOH (6)	65	75
9	 (6) + EtOH (6)	27	70

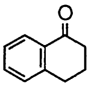
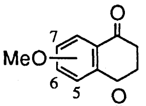
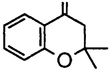
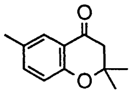
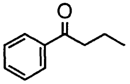
[a]Reaction Conditions: Cobalt(II) complex **1** 0.025 mmol, ketone **4** 0.50 mmol, $NaBH_4$ 0.75 mmol; Solvent $CHCl_3$ 10.0 ml; -20 °C, 24 h. The amount of alcohol was given in parentheses. [b]Determined by HPLC analysis using Daicel Chiralpak AD. [c]Cobalt(II) complex **1** 0.005 mmol (1 mol% vs. ketone **4**). [d]Isolated yield after 6 h.

high ee (91% ee, entry 5). The best result was obtained by adding the excess amount of THFA (14 mol-equiv. vs. $NaBH_4$, entry 6), and **5** was obtained quantitatively with 93% ee in 6 h even when the decreased catalytic amount to 1 mol% was employed. The effect of the non-catalytic path was tested by subjecting the modified borohydride in the absence of the cobalt(II) complex catalyst for 48 h, and the starting substrate was recovered nearly quantitatively (>95%), thus it represented a very small contribution of the path.[9] Thus the addition of THFA (or FA) to this reaction system represented two interesting futures; appropriately modified borohydride which specifically promoted catalytic reduction of the ketones was formed *in situ*, and secondly, a reaction mixture becomes homogenous.

The successful applications[10] using THFA and ethanol modified $NaBH_4$ in the enantioselective reduction of ketones by using the optically active cobalt(II) complex catalyst (**1** or **2**) are summarized in Table 2.

Various aromatic ketones were smoothly converted to the corresponding optically active alcohols in quantitative yields in 6-12 h using 1 mol% of the catalyst, thus these presented a high potential for a practical use. The influence on the facial selectivity is worth noting. The reduction of α-tetralone gave the corresponding alcohols in 90% ee (entry 1), whereas, without addition of THFA, it was 73% ee. Similarly, the reduction of 5-, 6-, and 7-methoxy-1-tetralone(s) led improved ee's of 90%, 95% and 92%, respectively (entries 2-4). For chromanone derivatives; 2,2-dimethyl-4-chromanone and 2,2,6-trimethyl-4-chromanone were reduced to the corresponding alcohols with 91% ee and 93% ee, respectively (entries 5 and 6). For acyclic ketone, optical purity of the resulting alcohol from *n*-butyrophenone was 97% ee (entry 7), and it was 15% enhancement compared with the reduction by employing $NaBH_4$ modified with ethanol alone.

Table 2. Achievement of high enantioselection by modified borohydrides with furfuryl alcohol derivatives

Entry	Ketones	Ee /%ee^a (Yiled /%)		
		Additive(s):	EtOH^b	THFA-EtOH^c
1^g			73 (>98)	90 (>98)
2		5-OMe	71 (91)	90^d (>98)
3		6-OMe	83 (94)	95^d (>98)
4		7-OMe	81 (86)	92^d (>98)
5^g			92 (>98)	92 (>98)
6			87 (74)	93 (>98)
7			82^{e,f} (85)	97^{e,f} (>98)

^{a}Determined by HPLC analysis using Daicel Chiralpak AD. Unless otherwise specified. ^{b}Reaction conditions: Cobalt(II) complex **1** 0.025 mmol, ketone 0.50 mmol, $NaBH_4$ 0.75 mmol, EtOH 4.50 mmol; Solvent $CHCl_3$ 10.0 ml; -20 °C, 120 h. ^{c}Reaction conditions: Cobalt(II) complex **1** 0.005 mmol, ketone 0.50 mmol, $NaBH_4$ 0.75 mmol, EtOH 2.22 mmol, THFA 10.3 mmol; Solvent $CHCl_3$ 10.0 ml; -20 °C, 12 h. Unless otherwise specified. ^{d}Homogeneous mixture of $NaBH_4$-THFA-EtOH was added to the reaction mixture in four successive portions. ^{e}HPLC analysis using Daicel Chiralcel OB. ^{f}Cobalt(II) complex **2** was used in place of **1**. ^{g}The absolute configuration of the corresponding alcohols were assigned as (*S*) by the sign of optical rotations with the literature values; For entry 1 see Ref. 11 and entry 5 see Ref. 12.

Thus the practical alternative method in the syntheses of various optically active alcohols from prochiral ketones was presented. Enantiofacial selectivity and reaction rate in the asymmetric reduction were significantly improved by using the borohydride which was suitably modified with furfuryl alcohol derivatives and ethanol, and the corresponding alcohols were obtained quantitatively with 90-97% ee in 6-12 h using 1 mol% of the catalyst. The study on mechanisms of present reduction system is currently on going.

References and Note

1 Reviews: L. Deloux and M. Strebnik, *Chem. Rev.*, **93**, 763 (1993); V. K. Singh, *Synthesis*, **1992**, 605; R. Noyori, "Asymmetric Catalysis in Organic Synthesis," John Wiley & Sons, New York (1994), Chap. 2.

2 S. Itsuno, Y. Sakurai, K. Ito, A. Hirano, and S. Nakahama, *Bull. Chem. Soc. Jpn.*, **60**, 395 (1987); E. J. Corey, R. K. Bakshi, S. Shibata, C. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987).

3 For examples: Y.-J. Shi, D. Cai, U.-H. Dolling, A. W. Douglas, D. M. Tschaen, and T. R. Verhoeven, *Tetrahedron Lett.*, **35**, 6409 (1994); Y. Hong, Y. Gao, X. Nie, and C. M. Zepp, *Tetrahedron Lett.*, **35**, 5551 (1994).

4 T. Ohkuma, H. Ooka, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **117**, 10417 (1995) and references cited therein.

5 A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **118**, 2521 (1996) and references cited therein.

6 T. Nagata, K. Yorozu, T. Yamada, and T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **34**, 2145 (1995).

7 For examples: U. Leutenegger, A. Madin, and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, **28**, 60 (1989); H. Okawa, T. Katsuki, M. Nakamura, N. Kumagai, Y. Shuin, T. Shinmyozu, and S. Kida, *J. Chem. Soc., Chem. Commun.*, **1989**, 139; T. Okamoto and S. Oka, *J. Mol. Catal.*, **23**, 107 (1984).

8 Review: A. Pelter, K. Smith, and H. C. Brown, "Borane Reagents," Academic Press, London (1988).

9 Even though the quantitative study on non-catalytic path contribution in the present reduction system is currently on going, sequential addition of $NaBH_4$-THFA-EtOH mixture in the system gave **5** in 95% ee, and it might also suggest the presence of non-catalytic path in less than 5%.

10 The typical procedures; Under argon atmosphere, in a pre-cooled vessel at -20 °C were placed 29.0 mg of fine grained $NaBH_4$ (0.75 mmol), 5.0 ml of $CHCl_3$, 0.13 ml of EtOH (2.22 mmol) and 1.0 ml of THFA (10.30 mmol), and the mixture was stirred for 15 min. To the mixture, solution of 3.9 mg of cobalt(II) complex **2** (0.005 mmol) and 74.1 mg of *n*-butyrophenone (0.50 mmol) in 2.0 ml of $CHCl_3$ each were successively added, and the mixture was continued to stirred for 12 h at -20 °C. The mixture was quenched by the addition of saturated aqueous ammonium chloride, and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then the excess solvents were removed under reduced pressure. The purification by column chromatography on silica gel (hexane/ethyl acetate) gave 74.3 mg of the corresponding alcohol; 99% yield. The ee was determined by using Daicel Chiralcel OB (hexane/2-propanol).

11 R. Weidmann, J.-P. Guetté, and M. H. Normant, *C. R. Acad. Sci. ,Ser. C.*, **268**, 2225 (1969).

12 M. Majeriç, M. Gelo-Pujiç, V. Sunjiç, A. Lévai, P. Sebök, and T. Timàr, *Tetrahedron; Asymmetry*, **6**, 937 (1995).