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Catalytic Enantioselective Borohydride Reduction of *Ortho*-Fluorinated Benzophenones

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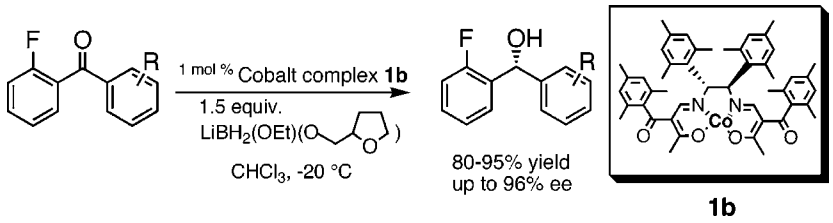
ABSTRACT



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In the presence of the optically active ketoiminatocobalt(II) complexes, the enantioselective borohydride reduction of benzophenones was successfully completed. The fluorine atom on the *ortho* position of the benzophenone and aryl ketones proved effective for obtaining high enantioselectivities. The combined use of modified lithium borohydride afforded the corresponding benzhydrols and arylcarbinols in high yield and high enantioselectivity (88–96% ee).

Although sodium borohydride is an inexpensive, safely handled, and readily available reducing agent that provides various reduction processes both in the laboratory and in industry, a catalytic and enantioselective version has been very limited, except for the catalytic enantioselective 1,4-reduction with semicorrin cobalt(II) complexes.[1] The catalytic enantioselective borohydride reduction catalyzed by the optically active cobalt(II) complexes developed in our laboratory[2] has been a unique practical process that has been applied to various substrates, such as ketones,[3] imine derivatives,[4] α,β-unsaturated carboxylates,[5] 1,3-dicarbonyl compounds,[6] ferrocenyl ketones,[7] etc., to afford the corresponding reduced products with high to excellent enantioselectivities. Optically active benzhydrols are some of the most important frameworks of pharmaceutical compounds, such as neobenodine,[8] carbinoxamine,[9] and orphenadrine. For their synthesis, two strategies have been proposed: the enantioselective reduction of precursory benzophenone derivatives using enantioselective hydrogenation catalyzed by BINAP/ruthenium complexes[10] and the enantioselective CBS reduction catalyzed by oxazaborolidine derivatives,[11] though high pressure or high catalyst loading was sometimes required for high enantioselectivity. An alternative method

(1) (a) Leutengger, U.; Madin, A.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 60−61. (b) Matt, P. V.; Pfaltz, A. *Tetrahedron: Asymmetry* **1991**, 691−700.

(2) (a) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2145−2147. (b) Sugi, K. D.; Nagata, N.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1997**, 493−494. (c) Yamada, T.; Nagata, T.; Sugi, K. D.; Yorozu, K.; Ikeno, T.; Ohtsuka, Y.; Miyazaki, D.; Mukaiyama, T. *Chem.−Eur. J.* **2003**, *9*, 4485−4509.

(3) (a) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1996**, 737−738. (b) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem.* Lett. **1996**, 1081−1082. (c) Nagata, T.; Sugi, K. D.; Yamada, T.; Mukaiyama, T. *Synlett* **1996**, 1076−1078.

(4) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1997**, 493−494.

(5) Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 967−970.

(6) (a) Ohtsuka, Y.; Kubota, T.; Ikeno, T.; Nagata, T.; Yamada, T. *Synlett* **2000**, 535−537. (b) Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 2543−2546.

(7) Sato, H.; Watanabe, H.; Ohtsuka, Y.; Ikeno, T.; Fukuzawa, S.; Yamada, T. *Org. Lett.* **2002**, *4*, 3313−3316.

(8) Muller, P.; Nury, P.; Bernardinelli, G. *Eur. J. Org. Chem.* **2001**, *21*, 4137−4147.

(9) (a) Casy, A. F.; Drake, A. F.; Ganellin , C. R.; Mercer , A. D.; Upton, C. *Chirality* **1992**, *4*, 356−366. (b) Shafi'ee, A.; Hite, G. *J. Med. Chem.* **1969**, *12*, 266−270.

(10) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659−662.

(11) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *50*, 9153−9156.

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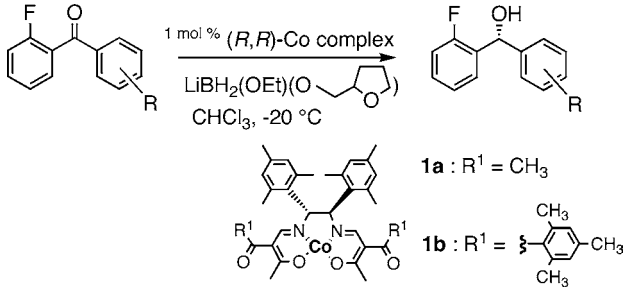
for the enantioselective addition[12] of air-sensitive aryl reagents to aryl aldehydes has been proposed. It was reported that the cobalt(II)-catalyzed enantioselective borohydride reduction operated with less than 1 mol % of catalyst loading in ordinary glass vessels, and the cobalt(II) complexes are stable even in air during handling. In this communication, we report the enantioselective borohydride reduction of *ortho*-fluorinated benzophenones to the corresponding benzhydrols in the presence of a catalytic amount of an optically active cobalt(II) complex (Scheme 1).

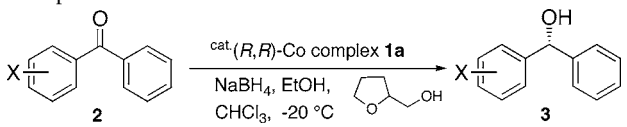
Scheme 1. Asymmetric Borohydride Reduction



The catalytic enantioselective reduction was performed as follows: Powdered $NaBH_4$ was activated with ethanol and tetrahydrofurfuryl alcohol (THFA) to generate the modified borohydride solution, which was added to a solution of the (*R*,*R*)-cobalt(II) catalyst, **1a** or **1b**, and benzophenone derivatives. In the cobalt(II) complex catalyzed borohydride reduction, the *si*/*re* face selection of carbonyl compounds could be regulated by the conjugated π-system. For example, the enantioselective reduction of 1,1′-dibenzoylferrocene in the presence of the (*S*,*S*)-cobalt complex catalyst afforded the (*R*,*R*)-ferrocenyl diol, whereas the (*S*,*S*)-diol was obtained from the 1,1′-dialkanoylferrocene.[7] On the basis of this hypothesis, 4-fluorobenzophenone was subjected to the present reduction system to afford the corresponding benzhydrol in 95% yield with 14% ee (entry 1), whereas 3-fluorobenzophenone produced the racemic benzhydrol (entry 2). In contrast, it was found that the 2-fluorinated benzophenone was converted to the corresponding benzhydrol with 81% enantioselectivity (entry 3).

The highly diastereoselective borohydride reduction of the α-fluoro ketones was recently reported,[13] and the addition of a Lewis acid improved the diastereoselectivity by coordination of both the fluorine on the α-position and the carbonyl oxygen. The chelation between the fluorine atom and the carbonyl oxygen was expected to enhance the differentiation of the two aryl groups of the benzophenones during their enantioselective reduction. Various coordinative substituents were then screened (Table 1). Among the *ortho*-halogenated benzophenones, in the order of F > Br > Cl > I, the enantioselectivity decreased (entries 3−6). It was postulated that the sodium cation of the borohydride should coordinate both the fluorine atom and the carbonyl oxygen to fix the conformation to accelerate the reaction and improve the enantioselectivity. During the reaction of *o*-hydroxybenzophenone, the corresponding alcohol was obtained with moderate enantioselectivity (entry 7), whereas the *o*-methylbenzophenone provided the racemic product (entry 8). Because these results supported the fact that chelation by the *ortho*-fluorine was critical for the highly enantioselective induction in the borohydride reduction of the benzophenones,

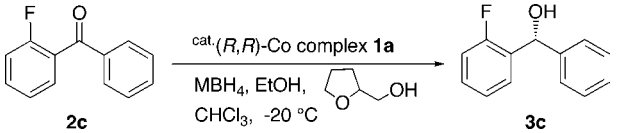
Table 1. Enantioselective Reduction of Various Substituted Benzophenones[a]



entry	benzophenone	X	yield/%	ee/%[b]
1	**2a**	*p*-F	95	14
2	**2b**	*m*-F	76	0
3	**2c**	*o*-F	90	81
4	**2d**	*o*-Cl	89	15
5	**2e**	*o*-Br	74	17
6	**2f**	*o*-I	74	9
7	**2g**	*o*-OH	90	46
8	**2h**	*o*-CH_3	49	0

[a] Reaction conditions: 0.50 mmol of substrate, 0.0050 mmol of Co catalyst, and 0.75 mmol of modified $NaBH_4$ (0.75 mmol of $NaBH_4$, 0.75 mmol of EtOH, and 10.3 mmol of THFA) in $CHCl_3$. Reaction time: 20 h (entries 1−3, 7−8), 4 days (entries 4−6). [b] Determined by HPLC.

Table 2. Effect of the Countercation[a]



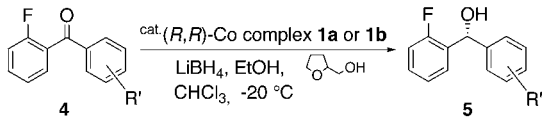
entry	M^+ in MBH_4	yield/%	ee/%[b]
1	K^+	41	63
2[c]	K^+	78	62
3	Na^+	90	81
4	Li^+	93	84
5	Me_4N^+	20	71
6	Et_4N^+	37	37
7	Bu_4N^+	14	63

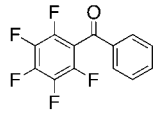
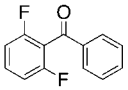
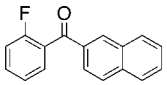
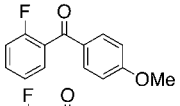
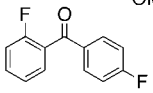
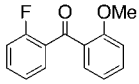
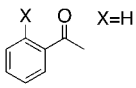
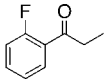
[a] Reaction conditions: 0.50 mmol of substrate, 0.0050 mmol of Co catalyst, and 0.75 mmol of modified MBH_4 (0.75 mmol of MBH_4, 0.75 mmol of EtOH, and 10.3 mmol of THFA) in $CHCl_3$. Reaction time: 20 h. [b] Determined by HPLC. [c] Methanol was used instead of ethanol.

(12) (a) Huang, W. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222−4223. (b) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445. (c) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446. (d) Bolm, C.; Muniz, K. *Chem. Commun.* **1999**, 1295−1296. (e) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. (f) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308.

(13) Mohanta, P. K.; Davis, T. A.; Gooch, J. R.; Flowers, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 11896−11897. A similar chelation effect of the fluorine atom was effectively employed for the stereocontrol of several reactions. Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16.

Table 3. Asymmetric Borohydride Reduction of Various *o*-Fluoroaryl Ketones[a]



entry	ketone		catalyst	yield / %	ee / % [b]
1		**4a**	**1a**	92	96
2		**4b**	**1a**	95	95
3		**4c**	**1b**	76	90
4[c]		**4d**	**1b**	80	90
5		**4e**	**1b**	81	87
6[c]		**4f**	**1a**	75	90
7	 X=H	**4g**	**1a**	85	86
8	X=F	**4h**	**1a**	80	91
9		**4i**	**1a**	86	97

[a] Reaction conditions: 0.50 mmol of substrate, 0.005 mmol of Co catalyst, and 0.75 mmol of modified $LiBH_4$ (0.75 mmol of $LiBH_4$, 0.75 mmol of EtOH, and 10.3 mmol of THFA) in $CHCl_3$. Reaction time: 8 h (entries 1, 2, 6−9), 2 days (entries 3−5). [b] Determined by HPLC. [c] Reaction carried out in 0.05 M solution.

the countercation of the borohydride was then examined (Table 2). As potassium borohydride was not completely dissolved by adding ethanol and THFA, the reaction did not go to completion providing *o*-fluorobenzhydrol in only 41% yield with 63% ee (entry 1). When methanol was used instead of ethanol, the modified KBH_4 solution clearly improved the yield to 78%, but the enantioselectivity did not change (62% ee). Compared to sodium borohydride, using ammonium borohydride, the reaction rate drastically decreased when producing the corresponding alcohol with moderate enantioselectivity and low yield (entries 5−7). In contrast, lithium borohydride provided *o*-fluorobenzhydrol with the highest yield and enantioselectivity (entry 4). Thus, the optimized reaction conditions, using $LiBH_4$ as the reducing agent in the presence of 1 mol % of the catalyst, **1a** or **1b**, were successfully applied to the enantioselective reduction of various *o*-fluorobenzophenones and *o*-fluorinated phenyl ketones (Table 3). Pentafluoro- and 2,6-difluoro-substituted benzhydrols were converted to the corresponding benzhydrols with excellent enantioselectivities, 96% ee and 95% ee, respectively (entries 1 and 2). Various *o*-fluorophenyl aryl ketones and 2-naphthyl, *p*-methoxyphenyl, *p*-fluorophenyl, and *o*-methoxyphenyl ketones were converted into the corresponding products, all with high enantioselectivities (entries 3−6). These results indicated that only the substitution of a fluorine atom on the *ortho* position of the benzophenones effectively afforded the corresponding benzhydrols with high enantioselectivities. The present *ortho*-fluorine effect could also be expected for the enantioselective reduction of aryl alkyl ketones. Actually, the *o*-fluoroacetophenone was reduced with 91% ee in 8 h at −20 °C (entry 8), whereas the acetophenone was reduced with 86% ee under the same conditions (entry 7). The enantioselectivity for the reduction of aryl alkyl ketones with *ortho*-fluoro substitution was similarly improved.

In summary, various benzophenones and aryl alkyl ketones substituted with a fluorine atom on the *ortho* position were effectively converted into the corresponding alcohols with high to excellent enantioselectivities. Further application of the effect of the fluorine atom on the enantioselective borohydride reduction is ongoing as well as the mechanistic study of this remarkable effect.

Supporting Information Available: Experimental details and spectroscopic data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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