Letter

Preparation of optically active deuterated primary alcohols: enantioselective borodeuteride reduction of aldehydes catalyzed by cobalt complexes

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The enantioselective borodeuteride reduction of aldehydes catalyzed by optically active β-ketoiminato cobalt complexes afforded the corresponding chiral deuterated primary alcohols with a high degree of deuteration and good enantiomeric excess.

Isotopically-labeled compounds provide reliable chemical probes for the investigation of the mechanisms in chemical and biochemical processes[1] in order to develop efficient catalysts or specific medicines. As deuteride is one of the most available isotopic atoms, the utilization of an optically active deuterated primary alcohol[2] is a conventional and established strategy for the synthesis of the labeled compounds containing the deuteride on a chiral center. It was reported that the chiral deuterated primary alcohol can be prepared from the corresponding aldehyde by the following two procedures; *e.g.*, the enantioselective reduction of the deuterated aldehyde[3] and the enantioselective deuteride reduction of the aldehyde.[3b,3d,4] Although the latter required less synthetic steps, few methods have been reported for the catalytic and enantioselective reduction[3d,4] because of the limited number of deuteride reducing agents. Sodium borodeuteride is an easily handled reducing agent and a commercially available deuteride source, whereas there has been no report on the catalytic enantioselective borodeuteride reduction of aldehydes. The highly enantioselective reductions of ketones and ketimines with sodium borohydride were realized in the presence of the optically active β-ketoiminato cobalt complexes (Fig. 1) to afford the corresponding secondary alcohols or amines in high yields with high enantiomeric excesses.[5] In this communication, we would like to report that the cobalt-catalyzed reduction system with sodium borodeuteride was applied to aldehydes to provide a convenient and preparative method for chiral deuterated primary alcohols (Scheme 1).

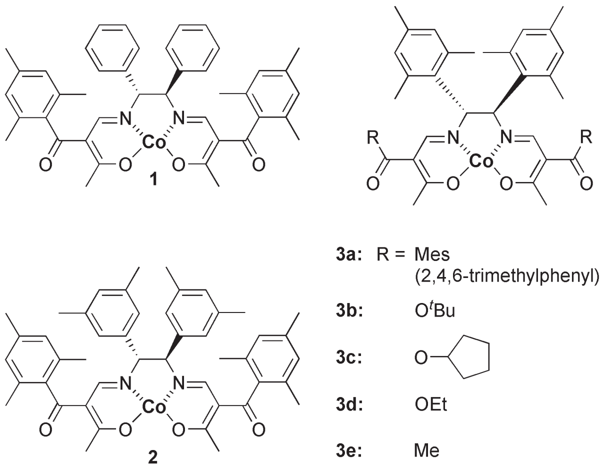
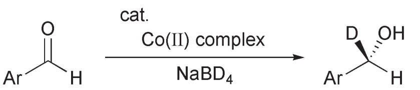
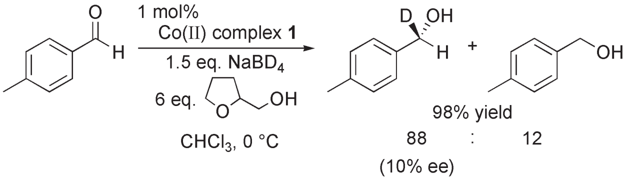


Fig. 1 Various optically active β-ketoiminato cobalt complexes.

The enantioselective reduction of *p*-tolualdehyde was initially examined using sodium borodeuteride modified by tetrahydrofurfuryl alcohol (THFA) in the presence of 1 mol% of a cobalt catalyst **1** (Scheme 2). The reaction was completed in 4 h to afford the corresponding alcohol in high yield. Based on the ^{1}H NMR analysis of the corresponding MTPA ester,[6] the enantiomeric excess of the benzyl-α-*d* alcohol was determined to be 10% ee along with a significant amount of benzyl alcohol due to the reduction with hydride. It was reported that the deuteride of sodium borodeuteride could be exchanged with a proton from the alcohol.[7] The reactive intermediate in the borohydride reduction catalyzed by cobalt complexes has been assumed to be cobalt-hydride species, which were detected by FAB mass analysis.[8] A solution of the cobalt complex **1** with borodeuteride modified by THFA was then analyzed by FAB mass spectroscopy, and it was actually found that cobalt-deuteride existed along with cobalt-hydride (Fig. 2(A)). These observations indicated that the hydrogen of benzyl alcohol should be derived from the proton of THFA, the modifier alcohol of borodeuteride. Accordingly, it was expected that employing tetrahydrofurfuryl alcohol-*d* (THFA-*d*) in place of THFA should generate pure cobalt-deuteride to afford the reduced product with high isotopic purity. As shown in Scheme 3, the THFA-*d* was prepared in two steps; *e.g.*, THFA was treated with chlorotrimethylsilane and triethylamine to form the corresponding trimethylsilyl ether with 85% yield after distillation (bp 82 °C/30 mmHg), and then subsequently hydrolyzed with deuterium oxide in the presence of a catalytic amount of sulfuric acid-d_2 to afford THFA-*d* in 80% yield after distillation (bp 97 °C/50 mmHg). Its isotopic purity was determined by ^{1}H NMR analysis to be more than 99%. In the FAB mass spectrum of the cobalt complex **1** treated with borodeuteride modified by THFA-*d*, the peak of the cobalt-hydride in the FAB mass spectrum disappeared and the corresponding cobalt-deuteride was



Scheme 1 The enantioselective deuteride reduction of aldehydes.

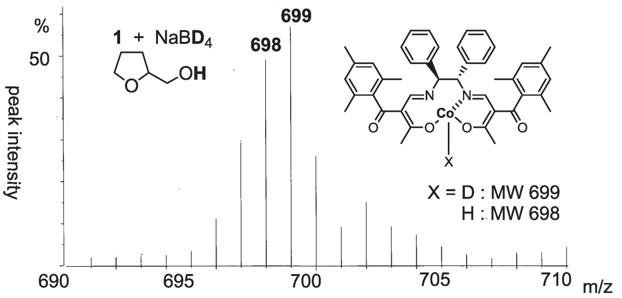


Scheme 2 Enantioselective reduction of *p*-tolualdehyde with sodium borodeuteride modified by tetrahydrofurfuryl alcohol.

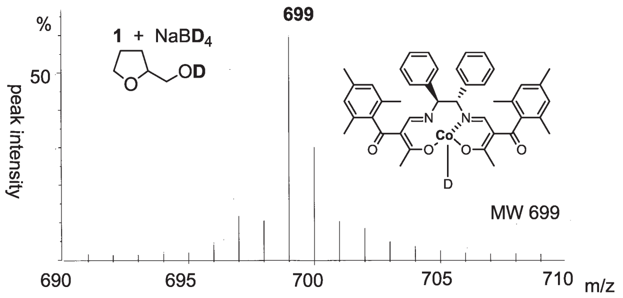
observed (Fig. 2(B)). By using the obtained THFA-*d* for borodeuteride modification, *p*-tolualdehyde was converted to *p*-methylbenzyl-α-*d* alcohol with a greater than 95% deuteration degree.

Various ketoiminato cobalt complexes were next examined (Table 1). Each ligand of the cobalt complex was prepared from the corresponding optically active 1,2-diarylethylenediamine and 1,3-dicarbonyl compound. These complexes exhibited excellent catalytic activity for the reduction of *p*-tolualdehyde to afford the D-labeled alcohols in high yields, whereas their enantiomeric excesses widely varied, being sensitive to the structure of the cobalt complex catalysts (entries 1–7). Catalysts **1** and **2** afforded a low ee of the deuterated alcohol (entries 1 and 2), while the enantioselectivity was remarkably improved when employing the **3** series catalysts derived from the optically active 1,3-bis(2,4,6-trimethylphenyl)ethylenediamine (entries 3–7). Among the series **3** catalysts, it was found that catalyst **3e**, having acetyl groups on both side chains, was the most efficient catalyst for the reduction of *p*-tolualdehyde with sodium borodeuteride (entry 7).

The catalytic and enantioselective borodeuteride reduction was applied to the preparation of various chiral deuterated primary alcohols from the corresponding aldehydes (Table 2). Various aryl aldehydes, such as benzaldehyde, 2-naphthaldehyde, and *p*-phenylbenzaldehyde were converted into the corresponding chiral deuterated primary alcohols in high yields with good enantioselectivities (entries 2–4). A high *ee* was achieved in the reduction of *p*-methoxybenzaldehyde and piperonal; they were converted to the corresponding optically active deuterated primary alcohols with 73% and 72% *ee*, respectively (entries 5 and 6).



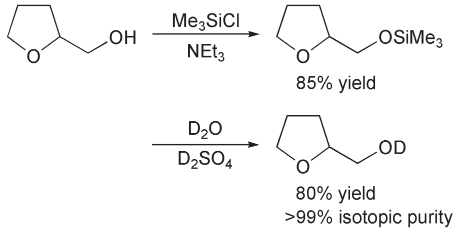
(A) Complex with THFA-modified borodeuteride



(B) Complex with THFA-*d*-modified borodeuteride

acceleration voltage : +10 kV
matrix : 3-nitrobenzyl alcohol
Jeol JMS-700 mass spectrometer

Fig. 2 FAB mass spectra of the cobalt complex treated with borodeuteride: (A) THFA modified and (B) THFA-*d* modified.



Scheme 3 Preparation of tetrahydrofurfurylalcohol-*d*.

The enantioselective reduction of deuterated aldehydes was also attempted with sodium borohydride under similar conditions. However, the optical yields of the chiral deuterated primary alcohols in the present system were not as high as those for the borodeuteride reduction of aldehydes; for example, 2-naphthaldehyde-*d* and *p*-methoxybenzaldehyde-*d* were reduced to 2-naphthalenemethyl-*d* alcohol and *p*-methoxybenzyl-α-*d* alcohol with 21% and 60% *ee*, respectively, while 63% and 73% *ee* were obtained for the enantioselective borodeuteride reduction of 2-naphthaldehyde and *p*-methoxybenzaldehyde (Scheme 4).[9] These contrasting results might be attributed to the isotope effect of the borodeuteride *vs.* borohydride, that is the non-catalytic reduction by borodeuteride itself could be suppressed[10] and the enantioselectivity was higher with the former procedure.

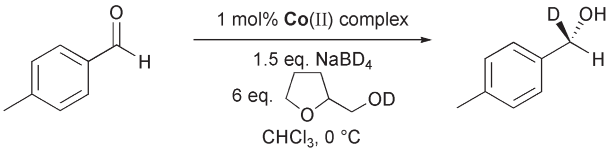
In summary, the enantioselective borodeuteride reduction catalyzed by optically active β-ketoiminato cobalt complexes was used for the preparation of chiral deuterated primary alcohols; high yields and high isotopic purities with good enantiomeric excesses were achieved. Further applications to other various aldehydes and aldimines are currently underway.

Experimental

Preparation of the premodified borodeuteride solution

To a suspension of $NaBD_4$ (125.6 mg, 3 mmol) in $CHCl_3$ (20 mL), tetrahydrofurfuryl alcohol (THFA; 1.16 mL, 12 mmol) was added at 0 °C under a dry nitrogen atmosphere. After stirring for 30 min, the mixture was allowed to stand at room

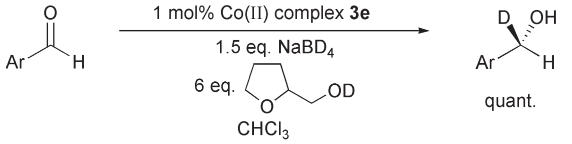
Table 1 Various cobalt catalysts for the enantioselective borodeuteride reduction[a]

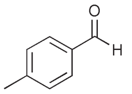
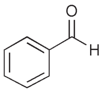
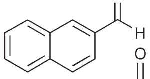
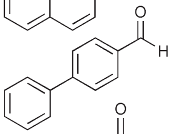
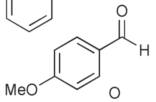
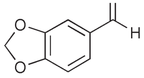


Entry	Catalyst	% Yield[b]	% *ee*[c]
1	**1**	96	8
2	**2**	97	13
3	**3a**	98	48
4	**3b**	100	51
5	**3c**	97	51
6	**3d**	97	50
7	**3e**	100	77

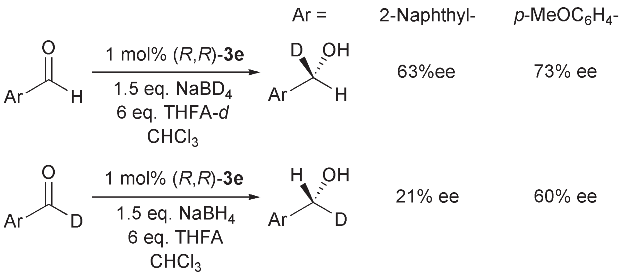
[a] Reaction conditions: to a solution of the cobalt catalyst and the *p*-tolualdehyde was added a solution of the modified borodeuteride, 0.5 mmol of *p*-tolualdehyde, 0.005 mmol (1 mol %) of cobalt catalyst, 0.75 mmol of $NaBD_4$, 3 mmol of THFA-*d* in $CHCl_3$ at 0 °C, 3–4 h. [b] Isolated yield. Isotopic purity was >95%. [c] Determined by ^1H NMR analysis of the corresponding MTPA ester.

Table 2 Enantioselective borodeuteride reduction of various aldehydes[a]



Entry	Aldehyde	% ee[b]
1[c]		77
2[c]		63
3[c]		63
4[c]		61
5[d]		73
6[c]		72

[a] Reaction conditions: to a solution of the cobalt catalyst and the aldehyde was added a solution of the modified borodeuteride, 0.5 mmol of aldehyde, 0.005 mmol (1 mol%) of cobalt catalyst, 0.75 mmol of $NaBD_4$, 3 mmol of THFA-*d* in $CHCl_3$. [b] Determined by ^1H NMR analysis of the corresponding MTPA ester. [c] At 0 °C. [d] At 20 °C.



Scheme 4 Comparison of the synthesis of optically active deuterated primary alcohols by the reduction of deuterated or undeuterated aldehydes.

temperature for 5 h, followed by heating at 40 °C for 1 h. The solution was then cooled and maintained at −20 °C.

Enantioselective borodeuteride reduction of aldehydes

Under a dry nitrogen atmosphere at reaction temperature were placed the (*S*,*S*)-cobalt catalyst **1** (2.9 mg, 0.005 mmol), the aldehyde (0.5 mmol) and $CHCl_3$ (5 mL). The premodified $NaBD_4$ (5.2 mL, 0.75 mmol) was added to the reaction mixture, which was stirred until the reaction was completed. The reaction was quenched by a precooled aqueous THF solution and pH 7 buffer solution, then the crude products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation the residue was purified by silica gel column chromatography (hexane–AcOEt) to give the corresponding optically active deuterated primary alcohol.

Determination of the enantiomeric excess of optically active deuterated primary alcohols

N,*N*′-Dicyclohexylcarbodiimide (24.8 mg, 0.12 mmol) was added to a solution of the optically active deuterated primary alcohol (0.06 mmol) also containing (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (21.0 mg, 0.09 mmol), *N*,*N*-dimethylaminopyridine (14.7 mg, 0.12 mmol) and CH_2Cl_2 (3 mL); then the reaction mixture was stirred at room temperature until the reaction reached completion. The mixture was filtered off to remove the precipitate of *N*,*N*′-dicyclohexylurea. The filtrate was evaporated and the residue was purified by silica gel column chromatography (hexane–AcOEt) to give the corresponding (*R*)-MTPA ester. The enantiomeric excess was determined by ^1H NMR analysis of this ester.

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9 The absolute configuration of the chiral deuterated primary alcohol was determined by comparing the ^1H NMR spectrum of the corresponding MTPA ester with that in the literature.[3d] These results indicated that the cobalt-deuteride or cobalt-hydride species derived from the (*R*,*R*)-cobalt catalyst selectively attacked the (*Si*)-face of the carbonyl in the aldehyde and is in accord with the face selectivity of a carbonyl previously reported for the borohydride reduction of ketones[5d].
10 2-Naphthaldehyde was treated with the modified borodeuteride and borohydride simultaneously to afford 42% of 2-naphthalenemethyl-*d* alcohol and 58% of 2-naphthalenemethyl alcohol, respectively.