Practical and Efficient Enantioselective Borohydride Reduction of Aromatic Ketones Catalyzed by Optically Active Cobalt(II) Complexes Using Pre-Modified Borohydride

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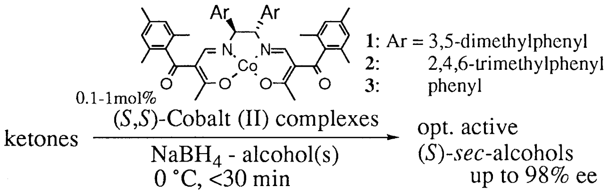
A catalytic enantioselective borohydride reduction of aromatic ketones in presence of 0.1-1 mol% of optically active aldiminato cobalt(II) complex catalysts at 0 °C was successfully achieved using precisely pre-modified borohydride with one equivalent each of tetrahydrofurfuryl alcohol, ethanol and $NaBH_4$. The corresponding secondary alcohols were produced in less than 45 min with high enantiomeric excesses (up to 98% ee). The above method was successfully applied to kinetic and dynamic kinetic resolutions of aromatic ketones.

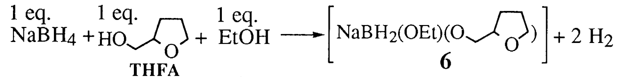
An enantioselective reduction of ketones to optically active alcohols have been widely appreciated even in industrial uses,[1] and highly efficient metal catalyzed hydrogenation[2] and hydrogen transfer[3] using preferable hydrogen sources are worth noting. Optically active aldiminato cobalt(II) complexes[4] were effectively employed as catalysts in enantioselective reduction of prochiral ketones using readily available reducing agent, $NaBH_4$, to afford optically active alcohols. Recently, the combinational addition of a pair of two alcohols, tetrahydrofurfuryl alcohol (THFA) and ethanol, significantly improved the enantioselectivity of the above-mentioned reduction, and various aromatic ketones were quantitatively transformed to optically active alcohols with up to 97% ee using 1 mol% of the cobalt (II) catalysts **1**, **2**, or **3** in 12 h.[5]

Although a number of articles on $NaBH_4$ reduction of ketones in alcoholic solvents have been appeared in literature,[6] an activated borohydride species in the reduction were not even completely characterized. Similarly, in the enantioselective borohydride reduction catalyzed by cobalt(II) catalysts, systematic investigation have never been performed on which alkoxyborohydride was responsible for achieving high enantioselection. Thus, this communication discloses pre-modification procedure for the formation of an active borohydride, and presents a practical method of enantioselective borohydride reduction of ketones by using precisely pre-modified borohydride (Scheme 1).



Scheme 1.

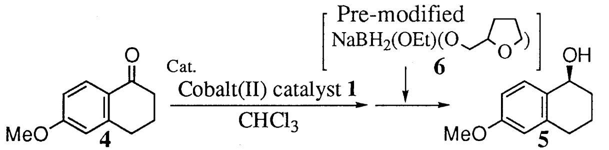
The formation of alkoxyborohydride could be monitored by measuring the evolution of H_2 during the reaction, and nearly 2 molar equivalents of H_2 versus $NaBH_4$ was gradually liberated as reaction proceeded. This implied that $NaBH_4$ consumed two molar equivalents of alcohol(s). The modifications of $NaBH_4$ with THFA or THFA-ethanol was carried out,[7] and the resulting mixture was then applied to the reduction of 6-methoxy-1-tetralone (**4**) in the presence of catalyst **1** at -20 °C. When two equivalents of THFA versus $NaBH_4$ were used, the resulting alcohol **5** possessed 85% ee[8] whereas 91% ee was found in the alcohol **5** when the pre-modified borohydride with one equivalent each of THFA and ethanol were used. Thus, the pre-modified borohydride in the present reaction is tentatively illustrated as formula **6** in Scheme 2.



Scheme 2.

It was revealed that the molar ratio of ethanol to $NaBH_4$ and the modification temperature were critical to form the active borohydride **6** exclusively. The number of molar ratios of ethanol, THFA to $NaBH_4$ varied, and an equimolar ethanol to $NaBH_4$ was definitive. The molar ratio of THFA to $NaBH_4$ was found to be less important, and only one additional mole of THFA was consumed by $NaBH_3(OEt)$ when 10-15 molar excess of THFA was used. The above ratio of alcohols to $NaBH_4$ and the formation temperature at 0 °C were suitable for preparing the borohydride **6** exclusively. Under these conditions, 2 molar equivalents of H_2 were released in 3 h as the result of the formation of **6**.[9] Dramatical acceleration of the reduction was observed when the pre-modified borohydride **6** solution was used to the reduction of 6-methoxy-1-tetralone (**4**) using catalyst **1** at -20 °C (pre-formation method, Table 1). When 1 mol% of catalyst was present (S/C = 100), *the reaction was completed within 20 min* whereas it took 6 h when *in situ* formed borohydride **6** (*in situ* method) was used. The quantitatively obtained alcohol **5** possessed 94 and 95% ee, respectively (entry 1). The modification of borohydride and the

Table 1. Comparitive study of *in situ* and pre-formation of borohydride methods for the reduction of ketone **4**



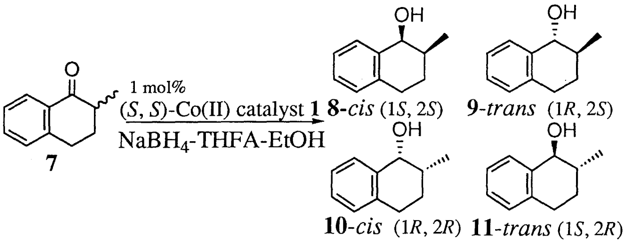
Entry	Reac.temp /°C	S/C	Reaction time /min (Ee /%ee[a]) Method: *in situ*[b]	pre-formation[c]
1	-20	100	360 (95)	<20 (94)
2	0	100	35 (93)	<15 (93)
3	0	1000	900[d](56)	<45[e](93)

[a]Determined by HPLC; Daicel Chiralpak AD. [b]See typical procedure given in Ref. 5. [c]Reaction conditions: $NaBH_4$ 0.75 mmol, EtOH 0.75 mmol, THFA 10.3 mmol; Solvent $CHCl_3$ 5.0 ml, 0 °C, 3 h; Cobalt(II) catalyst **1** given in table, ketone 0.50 mmol; Solvent $CHCl_3$ 5.0ml. [d]Reaction was gradually terminated in 15 h (83% yield). [e]Active borohydride mixture was successively added to the reaction in three portions in 15 min interval.

reduction were carried out at 0 °C throughout, and the reaction was completed within 15 min maintaining the enantioselectivity (93% ee, entry 2). According to the pre-modified method, high efficiency of the catalyst was also noted in the reduction employing 0.1 mol% of the catalyst (S/C = 1000), and it was completed in 45 min with retention of 93% ee (entry 3). Various ketones such as butyrophenone and isopropylphenylketone were examined using pre-modified borohydride **6** with 1 mol% of the cobalt(II) catalyst **2** at 0 °C for 30 min, and the corresponding alcohols were obtained quantitatively with optical purities of 96 and 98% ee, respectively.[10]

The successful application of the present enantioselective reduction to kinetic resolution[11] was carried out by using limited equivalents of pre-modified borohydride **6** (Table 2). When 0.55 equivalent of pre-modified borohydride was used for the kinetic resolution of **7** using 1 mol% of the (*S*, *S*)-cobalt(II) catalyst **1** at 0 °C, the conversion of the reaction was 52%. The obtained reductants possessed *cis-trans* ratio of 98:2 with 51% yield of *cis*-alcohol. The analysis of the recovered ketone **7** indicated 90% ee with (2*R*). The enantiomeric excess of **8**-*cis* (major isomer) to **10**-*cis* was 92%. These results implied that excellent selectivity of the formation of alcohol **8**-*cis* among four possible stereoisomers **8**-**11** was achieved. On the contrary, the conversion of the reaction was 70% when *in situ* method was applied. It suggested the transfer of more than one hydride per sodium borohydride, and the presence of multiple kinds of hydride sources was apparent. Accordingly, the decreased optical purity was found for the resulting *cis*-alcohol (76% ee) and the recovered **7** (2*R*) possessed 92% ee.[12] Similarly, the use of borohydride **6** was effective for dynamic kinetic resolution[13] of 2-ethoxycarbonyl-1-tetralone derivative **12** using 1 mol% of (*S*, *S*)-cobalt (II) catalyst at 0 °C (Scheme 3). The *cis*-alcohol was dominantly obtained in 97% yield with the enantiomerically enriched alcohol **13**-*cis* (1*S*, 2*S*)[14] as 92% ee.[15]

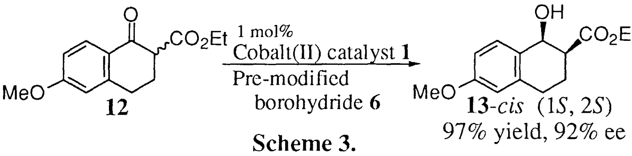
Table 2. Result of kinetic resolution of 2-methyl-1-tetralone (**7**)



Entry	Conv. /%[a]	Prod. distribution (**8** + **10**) : (**9** + **11**)	Ee /%ee[b,c] recov. **7**	Ee /%ee[b,c] **8** vs. **10**
Pre-modification Method				
1	52	98 : 2	90 (2*R*)	92
in situ Method				
2	70	97 : 3	92 (2*R*)	76

[a]Reaction conditions: Cobalt(II) catalyst **1** S/C=100, ketone **7** 0.50 mmol; Solvent $CHCl_3$ 10.0ml total; $NaBH_4$ 0.28 mmol 0.55 equiv. vs ketone **7**; Reaction time 2 h, only expected products were formed; see typical precedure for preperation of modified borohydride Ref. 5 and 10. [b]Determined by HPLC; Daicel Chiralpak AD. [c]Determined by sign of rotation; see Ref. 16.

Dynamic kinetic resolution using pre-modified borohydride **6**



Scheme 3.

Thus, precisely pre-modified borohydride at 0 °C with a catalytic amount of cobalt(II) complexes provided the practical and highly enantioselective borohydride reduction of aryl ketones. The pre-modified borohydride was also shown to be effective for the kinetic and dynamic kinetic resolutions of aromatic ketones. The study on mechanism of present reduction system is currently under investigation.

References and Note

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2 T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, and R. Noyori, *J. Org Chem.*, **61**, 4872 (1996) and references cited therein.
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4 T. Nagata, K. Yorozu, T. Yamada, and T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **34**, 2145 (1995).
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6 Review: D. C. Wigfield, *Tetrahedron* **35**, 449 (1979) and references cited therein.
7 About 90% of expected H_2 gas was released per each molar equivalent of alcohol additive(s) in 24 - 48 h at 30 °C , and unreacted $NaBH_4$ in the mixture was discarded prior to the examination.
8 When THFA alone was used to modify $NaBH_4$, the resulting enantiomeric excesses of optically active alcohol **5** in the reduction of **4** was 75, 85 and 72% ee for one, two and three equivalent(s) of THFA versus $NaBH_4$. When only ethanol was used to modify borohydride, the resulting optically active alcohol **5** possessed non-reproducible values of 61 to 81% ee, and these were probably associated with disproportion of alkoxyborohydrides; B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970) and references cited therein.
9 No further reaction of THFA with borohydride was observed for given conditions for 24 h, and its mixture could be stored for a few days at below 0 °C.
10 The typical procedure: Exclusive formation of pre-modified dialkoxyborohydride **6**; Under argon atmosphere, in a pre-cooled vessel at 0 °C were placed 29.0 mg of fine grained $NaBH_4$ (0.75 mmol), 5.0 ml of $CHCl_3$, 0.044 ml of EtOH (0.75 mmol) and 1.0 ml of THFA (10.32 mmol), and the mixture was continued to stir for 3 h.
Catalytic borohydride reduction; While maintaining solution of **6** at 0 °C, the solution of **6** was slowly added to the solution of 3.7 mg of cobalt(II) catalyst **1** (0.005 mmol, 1 mol%) and 88.1 mg of 6-methoxy-1-tetralone **4** (0.50 mmol) in 5.0 ml of $CHCl_3$, and the mixture was continued to stirred for 30 min at 0 °C. The reaction 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 88.2 mg of the corresponding alcohol **5**; 99% yield. The optical purity was determined by using Daicel Chiralpak AD (hexane/2-propanol).
11 Review: H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, **18**, 249 (1988).
12 When 0.38 equiv. of borohydride was used for *in situ* method, the conversion of the reduction of **7** was 47%. The optical purities of recovered **7** and *cis*-alcohol were 80% and 87% ee, respectively.
13 Review: R. Noyori, M. Tokunaga, and M. Kitamura, *Bull. Chem. Soc. Jpn.*, **68**, 36 (1995).
14 The *in situ* method gave **13**-*cis* in 97% yield with 48% ee.
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16 For ketone **8**: G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, **97**, 4667 (1975); for 1,2,3,4-tetrahydro-2-methyl-1-naphthol: A. Schoofs, J. P. Gutte, and A. Horeau *Bull. Soc. Chim. Fr.*, **1976**, 1215.