New and efficient catalysts for enantioselective borohydride reduction of ketones and imines

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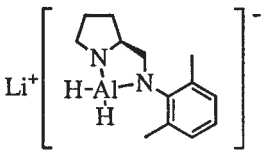
Optically active aldiminato cobalt(II) complexes have been found to catalyze the enantioselective reduction of ketones with sodium borohydride affording the corresponding optically active secondary alcohols in high chemical yields with high enantioselectivities. The enantioselective borohydride reduction is also applicable to not only C=O bonds in aromatic ketones but also to C=N bonds in aromatic imines.

Keywords: cobalt, enantioselective reduction, borohydride, aromatic ketone, secondary alcohol, aromatic imine, primary amine

1. Introduction

The development of methods for the enantioselective reduction of prochiral ketones to the corresponding optically active secondary alcohols has been the subject of intense study in recent years. Since the resulting optically active alcohols are themselves useful and are easily converted to other useful compounds such as optically active amines, the progress regarding this method is significant. Various methods have been developed for the enantioselective reduction of ketones [1].



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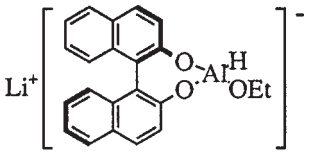

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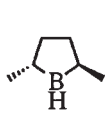

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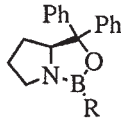

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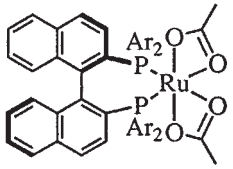

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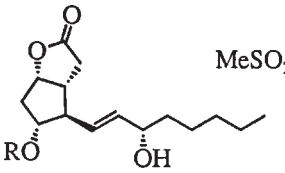
The first example of optically active hydride reagents for asymmetric reduction was reported in 1951: lithium aluminum hydride was modified with a stoichiometric amount of (+)-camphor [2]. Thereafter, metal hydride reagents such as lithium aluminum hydride [3], sodium borohydride [4], and borane [5], have been modified with various optically active ligands (**1**, **2**, **3**, and **4**). Among these, it is noteworthy that the asymmetric reduction of ketones was performed using a catalytic amount of chiral oxazaborolidines **4** [6]. Numerous successful applications have been developed by taking advantage of catalytic reduction; for example, various optically active secondary alcohols such as a prostaglandin precursor **6** [7(a)], potassium channel blockers **7** [7(b)] and trichloromethyl alcohol **8** used for the preparation of unnatural amino acids [7(c)] have all been prepared by enantioselective reduction with oxazaborolidine catalysts.



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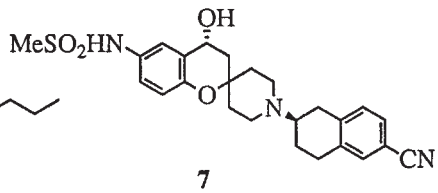

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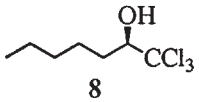

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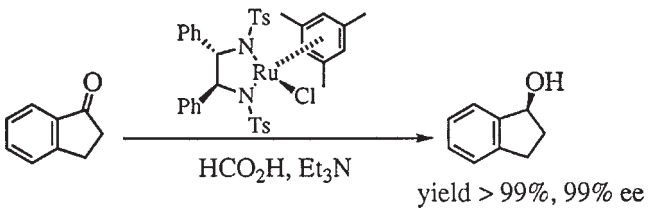
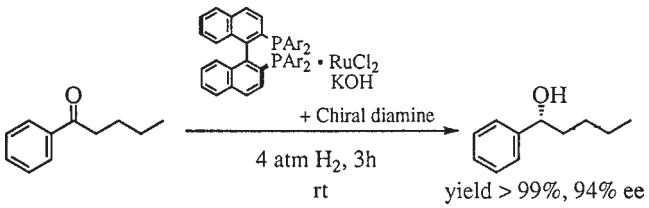
Another approach for the asymmetric reduction of ketones is the use of molecular hydrogen. In 1966, Wilkinson and his coworkers discovered that chlorotris(triphenylphosphine) rhodium can be used as an efficient hydrogenation catalyst [8]. Since then, the idea of replacing triphenylphosphine in the Wilkinson catalyst by a chiral phosphine has been examined by several groups [9]. High enantioselectivities were achieved in the asymmetric hydrogenation of functionalized ketones such as α-amino ketones and β-keto esters by using diphosphine complexes of rhodium [10] and ruthenium (**5**) [11]. Although it has been difficult to attain high enantioselections in the reduction of simple ketones, some complexes of rhodium [12], iridium [13], and ruthenium (equation (1)) [14] with optically active nitrogen ligands were recently shown to be effective for enantioselective transfer hydrogenation of alkyl aryl ketones [15]. More recently, enantioselective hydrogenations of simple ketones were carried out using iridium [16] or ruthenium

complex catalysts. In particular, the combined catalyst system composed of BINAP-ruthenium(II)-optically active diamine-KOH acted as a highly efficient catalyst for the enantioselective hydrogenation of aromatic ketones. This reaction proceeded smoothly with 0.2 mol% of the catalyst under mild conditions to give the optically active alcohols with high enantioselectivities in quantitative yields within 1–24 h (equation (2)) [17].

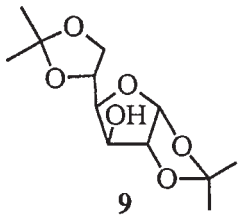


Equation (1).



Equation (2).

Metal borohydrides such as lithium borohydride and sodium borohydride are very popular reagents in organic synthesis due to their stability, high selectivity, and ease of handling. The usefulness of borohydrides in enantioselective reduction has been examined with the combined use of stoichiometric amounts of optically active ligands such as **9** [18] and **10** [19]. For example, reducing agents prepared from lithium borohydride and N-benzoylcystine (**10**) as a chiral auxiliary in the presence of t-butyl alcohol were applied to the enantioselective reduction of ketones. In this reaction, butyrophenone was converted to the corresponding optically active alcohol with 90% ee at $-40\,^{\circ}C$.



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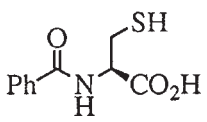

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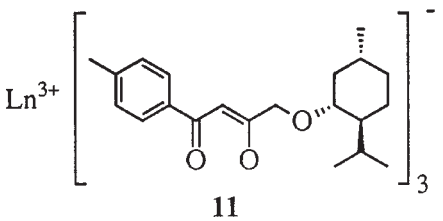

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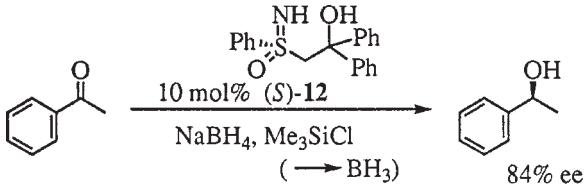
On the other hand, there have been few reports on the use of borohydrides in the enantioselective reduction of ketones using optically active metal complex catalysts. For the stoichiometric borohydride reduction with chiral metal complexes, an interesting example using a lanthanoid complex **11** as a Lewis acid catalyst for enantioselective reduction with sodium borohydride was reported [20]. There has been one example which used a catalytic amount of β-hydroxysulfoxime **12** with a borane-THF complex generated *in situ* from sodium borohydride and trimethylsilyl chloride in the reduction of aromatic ketones (equation (3)) [21].



Equation (3).

With regard to substrates other than ketones, it has been reported that a cobalt-semicorrin catalyst gave high enantioselectivities in the asymmetric 1,4-reduction of α,β-unsaturated esters with sodium borohydride [22].

It is strongly desired to provide new catalytic processes with not only high enantioselection but also high efficiency, such as high turnover of the catalyst, high reaction rate, and mild conditions, and simple procedures, etc.

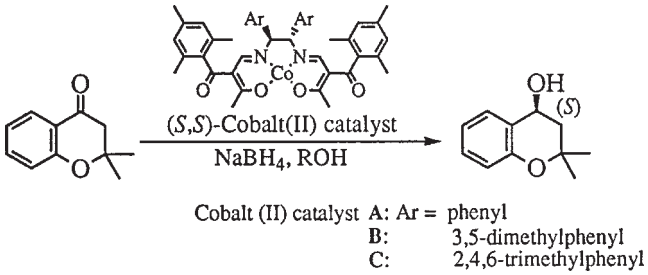
In this paper, recent studies carried out by the authors on the highly enantioselective reduction of ketones catalyzed by cobalt(II) complexes with optically active aldimine ligands are reviewed. The application of the present reaction for the enantioselective reduction of imine compounds are also described.

2. Enantioselective borohydride reduction of ketones catalyzed by cobalt(II) complexes

2.1. Enantioselective reduction using sodium borohydride

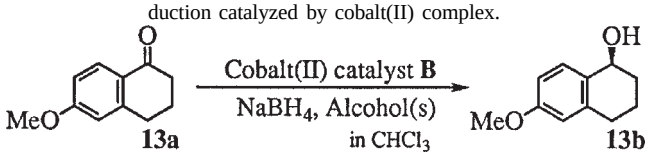
Recently, it was reported by our laboratory that optically active aldimines form a new class of effective ligand for aerobic enantioselective epoxidation of simple olefins with manganese(III) complexes as catalysts [23]. The novel method for enantioselective borohydride reduction of ketones was constructed using the above aldimine ligands. The optically active cobalt(II) complexes containing the aldimine ligand, N,N'-bis(3-oxobutylidene) ethylenediamine have been found to catalyze the enantioselective reduction of aromatic ketones with sodium borohydride (equation (4)) [24].

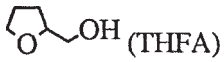
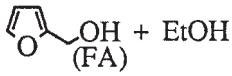
Preliminary investigations suggested that the addition of an alcohol was indispensable for achieving a high enantioselection. As shown in table 1, alone or in a co-existence of ethanol, $NaBH_4$ showed significant differences in both



Equation (4).

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



Entry[a]	Alcohols	Yield /%	Ee /% ee[b]
1	none	<10	5
2	EtOH	38	83
3	 (THFA)	82	87
4	THFA + EtOH	87	91
5	 (FA)	82	91

[a] Reaction conditions: ketone **13a** 0.50 mmol, Co(II) catalyst **B** 0.025 mmol, $NaBH_4$ 0.75 mmol, alcohol(s) 4.50 mmol; Solvent $CHCl_3$ 10.0 ml; −20 °C, 24 h. [b] Determined by HPLC using Daicel Chiralpak AD.

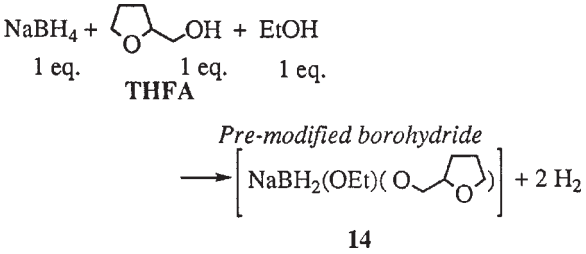
enantiomeric excess (ee) and chemical yield in the reduction of 6-methoxy-1-tetralone (**13a**); that is, the obtained alcohols **13b** possessed 5% ee in less than 10% yield, and 83% ee in 38% yield in 24 h, respectively (entries 1 and 2).

Higher optical purity of 87% ee as well as faster reaction rate were found when tetrahydrofurfuryl alcohol (THFA) was used in the formation of **13b** (entry 3). The combinational addition of ethanol and THFA or furfuryl alcohol (FA) raised further enhancement in optical purities of **13b**, and it possessed 91% ee, each (entries 4 and 5). Thus the addition of THFA (or FA) to this reaction system represented two interesting features; a reaction mixture becomes homogenous. Secondary, an appropriately modified borohydride was formed *in situ* promoting specifically catalytic reduction of the ketones [25].

2.2. Enantioselective reduction using pre-modified borohydride

Although a number of articles on $NaBH_4$ reduction of ketones in alcoholic solvents have appeared in the literature [26], an activated borohydride species in the reduction was not even completely characterized [27]. Thus, the pre-modification procedure for the formation of an active borohydride was examined.

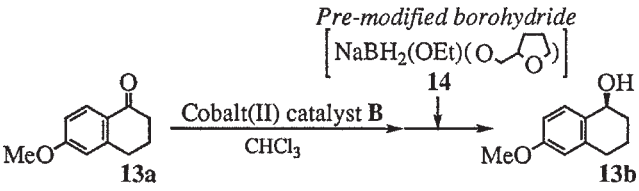
The formation of alkoxyborohydride could be monitored by measuring the evolution of H_2 during the reaction of $NaBH_4$ with alcohols, and nearly 2 molar equivalents of H_2 versus $NaBH_4$ was gradually liberated as the reaction proceeded. This implied that $NaBH_4$ consumed two molar equivalents of alcohol(s). The modifications of $NaBH_4$ with THFA or THFA-ethanol was carried out [28], and the resulting mixture was then applied to the reduction of 6-methoxy-1-tetralone (**13a**) in the presence of catalyst **B** at −20 °C. When two equivalents of THFA versus $NaBH_4$ were used, the resulting alcohol **13b** possessed 85% ee [29] whereas 91% ee was found in the alcohol **13b** 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 **14** in equation (5).



Equation (5).

It was revealed that the molar ratio of ethanol to $NaBH_4$ and the modification temperature were critical to form the active borohydride **14** exclusively. When molar ratios of ethanol and THFA to $NaBH_4$ varied, 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 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 temperature of the modification at 0 °C

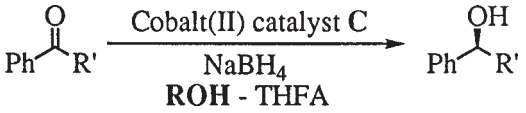
Table 2
Comparitive study of *in situ* and pre-formation of borohydride methods for the reduction of ketone **13a**.

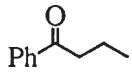
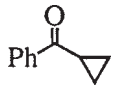
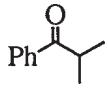
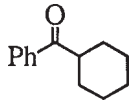


Entry	Temp./°C	S/C	Reaction time/min (Ee /% ee)	
			Method: *in situ*[a]	pre-formation[b]
1	−20	100	360 (95)	<20 (94)
2	0	100	35 (93)	<15 (93)
3	0	1000	900[c] (56)	<45[d] (93)

[a] See typical procedure given in table 1. [b] 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; Co(II) catalyst **B** given in table, ketone 0.50 mmol; Solvent $CHCl_3$ 5.0 ml. [c] Reaction was gradually terminated in 15 h (83% yield). [d] Pre-modified borohydride mixture was successively added to the reaction in three portions in 15 min interval.

Table 3
Combination of additive alcohols with various aromatic ketones.



Entry[a]	Ketone	Optical yield /% ee[b]		
		Additive ROH	MeOH	EtOH
1	 **15a**		90	**97**
2	 **16a**		76	**90**
3	 **17a**		**98**	77
4	 **18a**		**95**	78

[a] Reaction conditions refer to table 1. [b] Determined by HPLC using Chiralcel OB for the corresponding alcohols **15b** and **17b**, Chiralpak AD for **16b**, Chiralcel OD-H for **18b**, respectively.

were suitable for preparing the borohydride **14** exclusively. Under these conditions, 2 molar equivalents of H_2 were released in 3 h [30]. Dramatical acceleration of the reduction was observed when the pre-modified borohydride **14** solution was applied to the reduction of 6-methoxy-1-tetralone (**13a**) using catalyst **B** at $-20\,^{\circ}C$ (pre-formation method, table 2). When 1 mol% of the catalyst was present (S/C = 100), *the reaction was completed within 20 min* whereas it took 6 h when *in situ* formed borohydride **14** (*in situ* method) was used. The quantitatively obtained alcohol **13b** possessed 94 and 95% ee, respectively (entry 1 in table 2). The modification of borohydride and the reduction were carried out at $0\,^{\circ}C$ throughout, and the reaction was completed within 15 min maintaining high enantioselectivity of 93% ee (entry 2) [31].

It is noted that an appropriate choice of alcohol in the combination with THFA also significantly influences the enantioselection, and it is summarized in table 3.

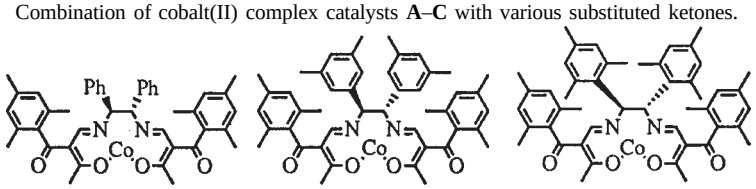
For example, when the borohydride was modified with the combined use of methanol and THFA, the aryl ketone **15a** was converted to the corresponding alcohol **15b** with 90% ee. Whereas, the employment of ethanol in place of methanol in the above experiment afforded the reduced product **15b** with 97% ee (entry 1 in table 3). The similar effect was observed in the enantioselective reduction of **16a** (76% ee with methanol vs. 90% ee with ethanol). On the contrary, methanol was alternatively effective for the reduction of aryl ketones **17a** and **18a** (98 and 95% ee, respectively). Based on these observations, it could be assumed that sodium borohydride was modified *in-situ* with additive alcohols to form $NaBH_2(OR^1)(OR^2)$ (R^1 = Me or Et, R^2OH = THFA) and that the modified borohydride was located closely to both the cobalt complex and the ketone to achieve high enantioselection. The following notes for choosing the suitable additive alcohols to achieve high enantioselection should be shown; (1) The use of ethanol-THFA combination for the modification of borohydride is preferable in case of using sterically less demanding ketones (primary alkyl or cyclopropyl ketone). (2) In the cases of ketones which are sterically more demanding (secondary alkyl ketone), methanol is preferable for combined use with THFA [32].

2.3. Enantioselective borohydride reduction using appropriate ligand of cobalt(II) complex catalysts

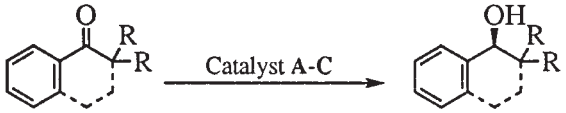
The preliminary investigations of asymmetric borohydride reduction of various ketones by using cobalt(II) complex catalysts **A** [33]–**C** suggested, that the suitable matching of catalyst and substrates plays an important role on achieving high enantioselections, and it is summarized in table 4. For example, the reduction of 2,2-dimethyl-1-tetralone (**19a**) with combined use of MeOH-THFA or EtOH-THFA was catalyzed by the complex **A** to afford the corresponding optically active alcohol in 91% ee or 81% ee, respectively, whereas it was with 75% ee when the complex **B** was used. On the contrary, enantioselectivity in the reduction of 1-tetralone (**20a**) was observed to be higher for the use of the complex **B** (90% ee) than that for the complex **A** or **C** (65% ee or 60% ee, respectively). Similarly, 2,2-dimethyl-4-chromanone (**21a**) was converted to the alcohol with higher enantioselection by the borohydride reduction catalyzed by the complex **B** (with 92% ee) than by using the complex **A** (with 88% ee) or **C** (with 74% ee). In the case of acyclic ketones such as cyclohexylphenyl ketone (**18a**) and butyrophenone (**15a**), the complex **C** [34] was the most matching catalyst to achieve high enantioselection; aryl ketones **18a** and **15a** were converted to the corresponding alcohols with 95% ee and 97% ee, respectively, whereas ranging between 62–87% ee was observed by using the complex **A** and **B**.

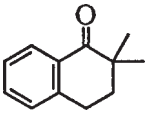
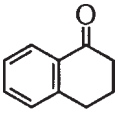
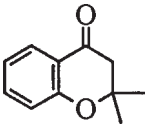
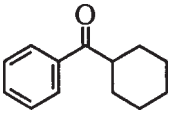
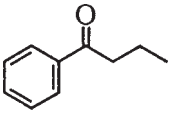
A general rule to choose a suitable catalyst was considered as follows: (1) The complex **A** having the ligand derived from prototypal diphenylethylenediamine was effective in reduction of aryl ketones which are sterically hindered at α-position of carbonyl groups (entry 1 in table 4). (2) The complex **B** having the ligand derived from bis(3,5-dimethylphenyl) ethylenediamine was the most matching to the cyclic aryl ketones which are sterically less demanding (entries 2 and 3). (3) The complex **C** having the ligand derived from the bulky bis(2,4,6-trimethylphenyl) ethylenediamine was effectively employed in enantioselective borohydride reduction of acyclic aryl ketones (entries 4 and 5) [32].

Table 4
Combination of cobalt(II) complex catalysts **A**–**C** with various substituted ketones.



A **B** **C**



Entry[a]	Ketone	Optical yield /% ee[b]		
	Catalyst	**A**	**B**	**C**
1	 **19a**	**91**[c] (81)[d]	75	NR[e]
2	 **20a**	65	**90**	60
3	 **21a**	88	**92**	74
4	 **18a**	62	65	**95**[c]
5	 **15a**	63	87	**97**

[a] Reaction conditions: 0.75 mmol, EtOH 2.25 mmol, THFA 10.3 mmol, (*S*, *S*)-Co(II) catalyst (**A**–**C**) 0.005 mmol, ketone 0.50 mmol; Solvent $CHCl_3$ 10.0 ml total; −20 °C, 12 h. The corresponding (*S*)-alcohols were isolated in 96–99% yields. [b] Determined by HPLC using Chiralcel OD-H for the corresponding alcohols **19b**, Chiralcel OB for **20b**, Chiralpak AD for **21b**, respectively. [c] MeOH was used instead of EtOH. [d] The reaction condition is given in footnote a. [e] No reaction.

2.4. Application of enantioselective borohydride reduction for various aromatic ketones

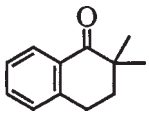
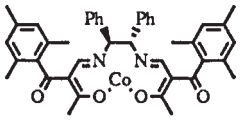
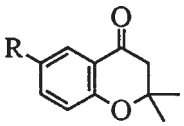
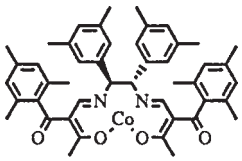
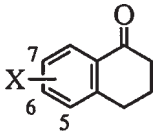
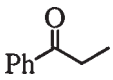
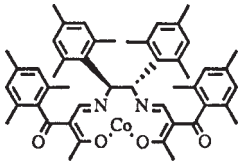
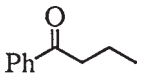
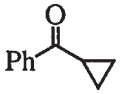
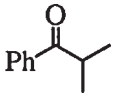
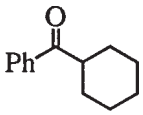
The successful applications using pre-modified borohydride in the enantioselective reduction of ketones by using the optically active cobalt(II) complex catalysts are summarized in table 5. Various aromatic ketones were smoothly converted to the corresponding optically active alcohols in quantitative yields in 1 h using 1 mol% of the catalysts, thus these presented a high potential for a practical use.

The present study illustrates that high enantioselectivities in the asymmetric borohydride reductions of various substituted aryl ketones are achieved by the appropriate choice of the optically active cobalt(II) catalysts together with the matching combination of two alcohols used for modifying borohydride.

2.5. Kinetic resolution using enantioselective borohydride reduction

The successful application of the present enantioselective reduction to kinetic resolution [35] was carried out by using limited equivalents of pre-modified borohydride (equation (6)) [31]. When 0.55 equivalent of a pre-modified borohydride was used for the kinetic resolution of **26a** using 1 mol% of the (*S*, *S*)-cobalt(II) catalyst **B** at 0 °C, the reac-

Table 5
Achievement of high enantioselection by using modified borohydrides and appropriate catalysts.

Entry	Ketone			Catalyst	Modifiers	Ee[a] /%ee
1			**20a**	 Co(II) catalyst **A**	MeOH-THFA	91
2		R=H	**21a**	 Co(II) catalyst **B**	EtOH-THFA	92
3		CH_3	**22a**			93
4		X=H	**19a**			92
5		5-OMe	**23a**			92
6		6-OMe	**13a**			95
7		7-OMe	**24a**			92
8			**25a**	 Co(II) catalyst **C**	EtOH-THFA	90
9			**15a**			97
10			**16a**			90
11			**17a**		MeOH-THFA	98
12			**18a**			95

[a] Optically active alcohols were obtained in quantitative yields in all cases.

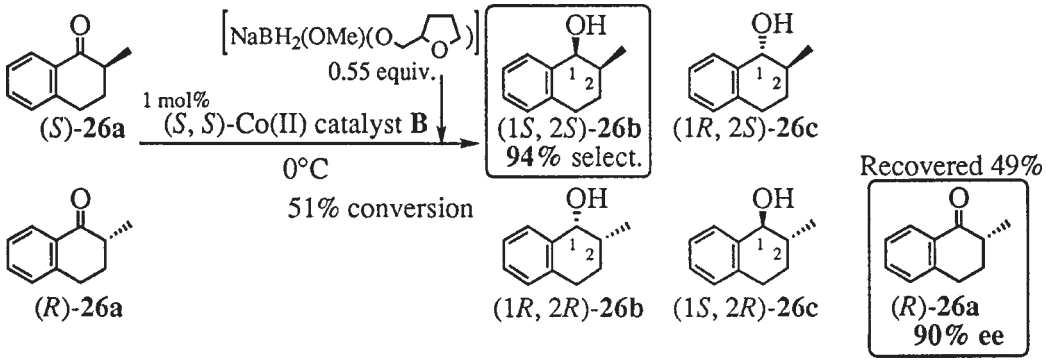
tion was terminated automatically at the conversion of 51%. The obtained alcohols possessed *cis-trans* ratio of 98:2 with 50% yield of *cis*-alcohol. The analysis of the recovered ketone **26a** indicated 90% ee with (R)-configuration [36]. The enantiomeric excess of ($1S, 2S$)-**26b** to ($1R, 2R$)-**26b** was 92% [37]. These results implied that the excellent selectivity in the formation of the ($1S, 2S$)-alcohol among four possible stereoisomers was achieved.

Similarly, the use of pre-modified borohydride **14** was effective for dynamic kinetic resolution [38] of 2-ethoxycarbonyl-1-tetralone derivative **27a** using 1 mol% of (S, S)-cobalt(II) catalyst **B** at 0 °C (equation (7)). The ($1S, 2S$)-alcohol **27b** [39] was dominantly obtained in 92% ee with high chemical yield.

The pre-modified borohydride was also shown to be effective for the kinetic and dynamic kinetic resolutions of aromatic ketones.

2.6. Enantiofacial discrimination of asymmetric borohydride reduction

A crystallographical analysis of molecular structure was performed for the cobalt(III) complex [40] derived from the corresponding cobalt(II) complex **C**. It revealed that the centered cobalt was surrounded by the square planar ligand and that the aryl groups in the optically active diamine and the mesitoyl side chain located nearby [41]. Therefore, the sterically hindered site (site **b**) and the open site (site **a**) could obviously be differentiated (figure 1). The observed enantiofacial selection of corresponding (S)-alcohols to (S, S)-cobalt complexes (*re* facial attack) can be explained by considering the favorable transition state illustrated in figure 2; the substrates, aryl ketones, would approach the postulated cobalt hydride [42] through the open site (*re* facial attack). The aromatic ring of aryl ketones was

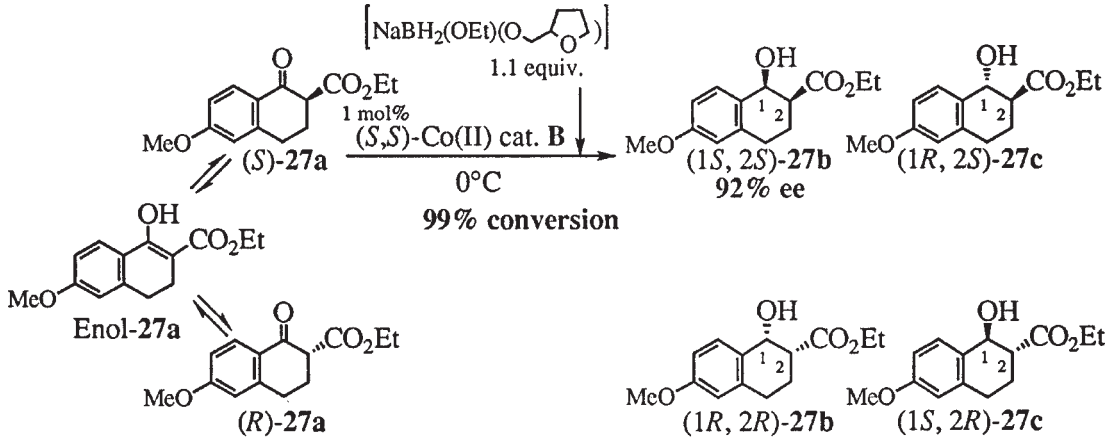


Selectivity / % (Total 50% yield)

(1*S*, 2*S*)-**26b** : (1*R*, 2*R*)-**26b** : (1*R*, 2*S*)-**26c** + (*1S,2R*)-**26c**

94 : 4 : 2

Equation (6).



Selectivity / %

(1*S*, 2*S*)-**27b** : (1*R*, 2*R*)-**27b** : (1*R*, 2*S*)-**27c** + (*1S,2R*)-**27c**

94 : 4 : 2

Equation (7).

placed parallel to the square delocalized π-system plane of the cobalt complex by π-interaction [43]. The approaching carbonyl group of the substrates was oriented away from cobalt complex to avoid a steric hindrance of the bulky aryl groups.

The alternative transition state (*si* facial attack) is not rationalized because of the steric repulsion of the bulky aryl groups of the complex with the carbonyl group of incoming ketones. These closely packed transition state could suggest that the enantiofacial selectivity was fairly dependent on the components of substrates, ligands, and additive alcohols shown in table 3 and 4, respectively.

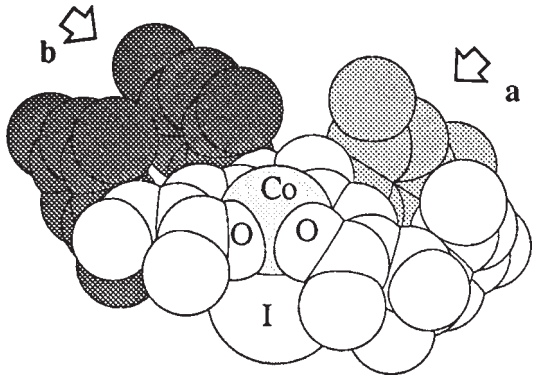


Figure 1. Molecular structure (*S*, *S*)-aldiminato cobalt(III) iodide derived from cobalt(II) complex C (space filling model based on X-ray analysis).

3. Enantioselective borohydride reduction of imines

Various methods for catalytic enantioselective reduction of prochiral ketones have been extensively investigated in order to prepare optically active alcohols in high efficiency [44]. Likewise, analogous catalytic enantioselective

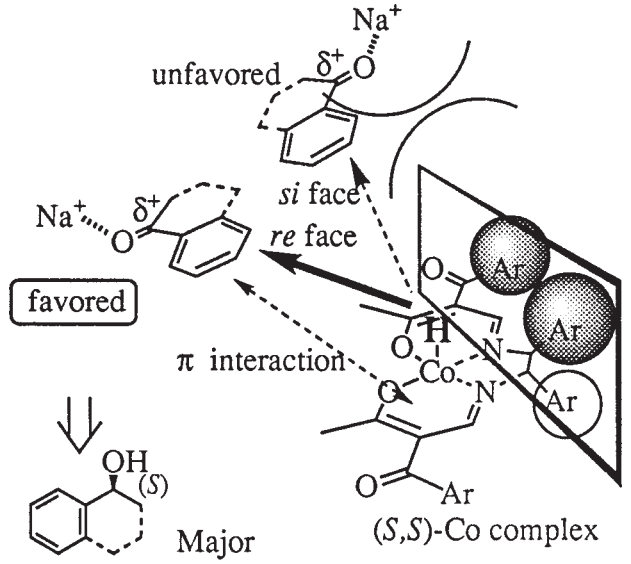
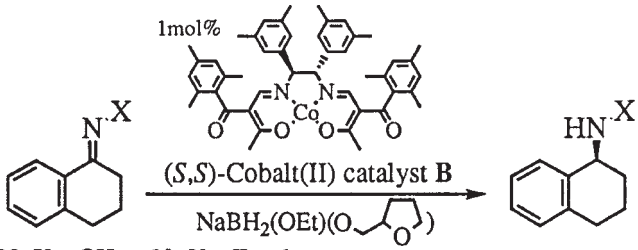


Figure 2. Possible mechanistic explanation for the observed enantioface selection in asymmetric reduction with (S, S)-cobalt complex.

reductions of imines were reported in the literature [45]. However, a few examples were known for the syntheses of optically active amines with satisfactory enantiomeric excesses; for examples, the recent achievements of enantioselective hydrogenations [46], transfer hydrogenation [47], hydrosilylations [48], and borane reduction [49] of imines are worth noting. Therefore, a development of highly efficient enantioselective reduction of imines is still remained as challenging topics in synthetic organic chemistry.

The above-mentioned enantioselective borohydride reduction was applied to compounds having C=N functionality [50], and the reduction of N-substituted ketimines were effectively catalyzed by the cobalt(II) complexes to form the corresponding optically active amines with high enantiomeric purity. This section describes the successful applications of the optically active cobalt(II) complex catalysts to the enantioselective reduction of the imines [51].

Preliminary experiments on synthesis of optically active primary amines from each aryl ketoximes and N-substituted ketimines [52] by the enantioselective borohydride reductions using 1 mol% of the cobalt(II) complex were tried at 0 °C for 4 h (equation (8)).



Equation (8).

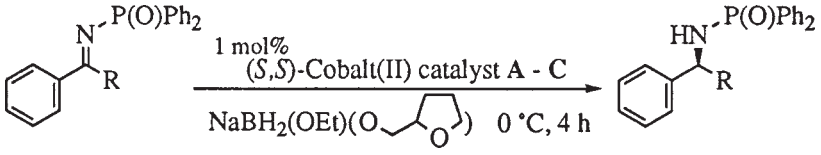
Treatments of oxime **28** or oxime methyl ether **29** by the borohydride reductions using the cobalt(II) complex **B** did not afford the optically active primary amines under the above conditions, and the starting substrates were recovered completely. On the contrary, when the reduction of protected imines such as N-toluenesulfonyl imine **30** (N-tosyl imine) or N-diphenylphosphinyl imine **31** was tried, the reactions took place smoothly and the corresponding optically active amines were obtained in 95 and 85% yields with 71 and 98% ee, respectively. The observed differences in optical purity of the resulted amines could be attributed to competitive direct reduction of imines with borohydrides [53] via non-catalytic reduction pathway. When N-tosyl imine **30** was subjected to the reduction in the absence of the catalyst, the corresponding racemic amine was obtained in **30**% yield. On the other hand, *N*-phosphinyl imine **31** was inert toward pre-modified borohydride alone suggesting that N-phosphinyl imines are suitable substrates for the present reductions. Then, the enantioselective borohydride reduction using optically active cobalt(II) complex catalyst (**A**, **B**, or **C**) was examined using various N-diphenylphosphinyl imines [54], and the results are summarized in table 6.

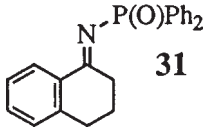
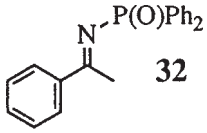
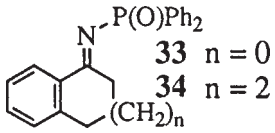
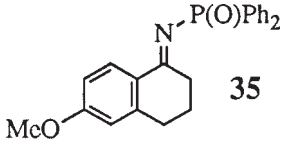
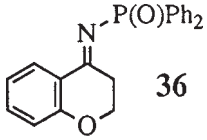
In the presence of 1 mol% of the above catalyst **A**, **B**, or **C**, various aryl N-phosphinyl imines were smoothly converted to the corresponding optically active amines in good yields (up to 97%) at 0 °C within 4 h. As shown in the enantioselective borohydride reduction of aryl ketones, a suitable combination of the cobalt(II) catalyst and aryl imine was one of the important factors in achieving high enantioselection. When the cyclic aryl imine **31** was subjected to the reductions, the cobalt(II) complex **B** was the best choice, and the corresponding amine was obtained in 98% ee whereas complex **A** gave 92% ee (entries 1 and 2). It is noted that when complex **C** was used, no reaction took place (entry 3). It may be attributed to a high degree of steric congestion for N-diphenylphosphinyl imines with cobalt(II) complexes. The complex **C** gave the corresponding amine with the highest optical purity (90% ee, entry 6) in case of acyclic aryl imine **32**. The complexes **A** and **B** gave poorer outcomes as 77 and 80% ee, respectively (entries 4 and 5). The observed combinations of the catalyst and imine are paralleled with the suitable pairs found for the aryl ketone reductions, and thus the cyclic aryl substrates with complex **B** and acyclic aryl substrates with complex **C** are preferable. Accordingly, various cyclic N-phosphinyl imines **33**–**36** were applied to the reductions using 1 mol% of complex **B**, and the corresponding optically active amines were obtained in 91–99% ee (entries 7–10).

The resulting N-phosphinyl amine represents an additional advantage over N-sulfonyl amine since the preparation of optically active primary amine by subsequent removal of the diphenyl-phosphoryl group can be carried out under mild conditions [55]; for example, using HCl/MeOH at 25 °C, the optically active primary amine [56] was obtained in good yield without the loss of optical purity (equation (9)).

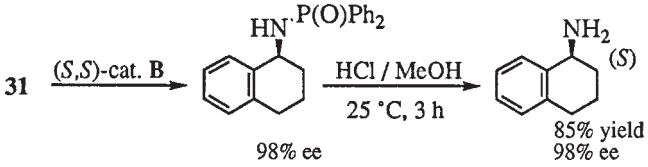
Thus, a new and efficient method for the synthesis of various optically active amines was presented, and the prepa-

Table 6
Enantioselective borohydride reduction of *N*-diphenylphosphinyl imines by cobalt(II) complex catalyst.



Entry[a]	Imine	Catalyst	Ee /% ee[b] (Yield /%[c])	Abs. config.
1	 **31**	**A**	92 (88)	
2		**B**	98 (85)	(*S*)
3		**C**	NR[d]	
4	 **32**	**A**	77 (96)	
5		**B**	80 (95)	(*S*)
6		**C**	90 (97)	
7	 **33** n = 0 **34** n = 2	**B**	91 (86)	(*S*)
8		**B**	94 (81)	ND[e]
9	 **35**	**B**	99 (97)	ND[e]
10	 **36**	**B**	92 (81)	ND[e]

[a] Reaction conditions; same as table 2, ref. b. [b] Determined by HPLC using Chiralpak AD. [c] Isolated yield. [d] No reaction. [e] Not determined.



Equation (9).

ration of the optically active primary amine by subsequent hydrolysis was carried out smoothly.

4. Conclusion

A new and efficient method of enantioselective borohydride reduction has been developed in which aromatic ketones are smoothly converted to the corresponding alcohols quantitatively in the presence of optically active cobalt(II) complex catalyst. This enantioselective reduction is carried out using precisely pre-modified borohydride with alcohols such as tetrahydrofurfuryl alcohol and ethanol or methanol, and high optical yields are obtained by choosing an appropriate alcohols as modifiers and a suitable aldimine ligand of the catalyst.

Also, the enantioselective borohydride reduction has been successfully applied to the reduction of imines protected by a phosphinyl group. The optically active amines are obtained with high chemical and optical yields. The subsequent hydrolysis smoothly gives the corresponding primary amine maintaining a high optical purity.

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