

# Recent development and improvement for boron hydride-based catalytic asymmetric reduction of unsymmetrical ketones

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Catalytic asymmetric reduction of prochiral ketones with hydrides such as boranes and borohydrides is one of the simplest and the most convenient methods for obtaining chiral alcohols. This *tutorial review* describes the most significant advances recently achieved for enhancing the enantioselectivity and practicability of the reduction using this methodology. The review covers the development of new homogeneous and/or immobilized catalysts for asymmetric reduction using borane or borohydride reagents and practical improvement of the well-known oxazaborolidine (OAB)-catalysed reduction through developing more stable, cost effective and recoverable OABs, scalable and environmental friendly borane sources, and one-pot procedures for the reduction.

## 1. Introduction

Enantiomerically pure secondary alcohols are important intermediates or chiral building blocks for the preparation of biologically active substances. One of the simplest and the most convenient methods for obtaining such chiral alcohols is the asymmetric reduction of prochiral ketones with metal hydrides. For this purpose, a great number of asymmetric reducing agents, which are mostly chirally modified aluminium or boron hydrides, have been reported.<sup>1</sup> Despite much remarkable success, stoichiometric reagents have some drawbacks for large-scale applications because at least one equivalent of the reagents is required for the reduction. Their use involves separation and purification steps which can become troublesome and costly. Thus it appeared desirable to develop catalytic processes for the reduction. One of

the most well-known methods for the purpose is the asymmetric reduction catalyzed by oxazaborolidine (OAB) using borane reagents as hydride source, discovered by Itusno in 1981 and developed by Corey in 1987.<sup>2</sup> A large number of asymmetric reductions and synthetic applications using this methodology over the past two decades have been extensively studied.<sup>2,3</sup> This method proves to be very effective and convenient for the catalytic asymmetric reduction of a variety of ketones including most of aryl alkyl ketones and various aromatic functionalized ketones, giving high enantioselectivity with predictable configurations.<sup>2,3</sup> However the method is less effective for the reduction of unhindered linear ketones. On the other hand, sodium borohydride is an inexpensive, highly selective and stable, safe to handle, and environmental friendly reducing agent in organic synthesis. Although sodium borohydride is superior to borane reagents from a practical point of view, studies on the catalytic asymmetric reduction with the hydride have been relatively neglected.

In recent years, significant advances for developing a wide range of new chiral catalysts and improvement studies toward enhancing the enantioselectivity and practicability of boron hydride-based catalytic asymmetric reduction of ketones have been accomplished. However, such results have not been reviewed. This tutorial review will focus on recently developed catalysts and improvement studies that have been shown enantioselectivity over 90% ee in the field of the catalytic asymmetric borane and borohydride reduction of prochiral ketones that mostly appeared in the literature between 2001 and April 2008.

## 2. Catalytic asymmetric borane reduction

### 2.1 Oxazaborolidine (OABs) catalysts

**2.1.1 Preparation and mechanism: brief overviews on the earlier works.** Most of the OABs were prepared from the reaction of chiral 1,2-aminoalcohols with borane-THF (BH<sub>3</sub>-THF), borane-dimethyl sulfide (BMS), alkyl or aryl boronic acids, trimethylboroxine or trialkylborates. For

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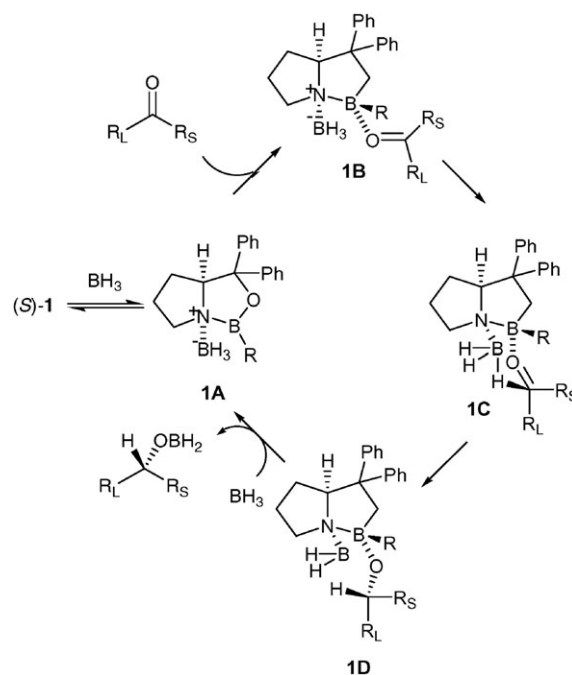
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example, one of the most well-known OABs, Corey–Bakshi–Shibata reagent (CBS reagent **1**) is prepared from (*R*)- or (*S*)- $\alpha,\alpha$ -diphenylprolinol (DPP, **2**), which can be obtained from (*R*)- or (*S*)-proline. Of these, *B*-HCBS (**1a**) and *B*-MeOCBS (**1e**) reagents were usually used as themselves after *in situ* generation from **2** with borane and trimethyl borate, respectively (Scheme 1). The structures of **1a** and **1b** were characterized by  $^1\text{H}$  and  $^{11}\text{B}$  NMR spectrometry, mass spectrometry and X-ray diffraction analyses.

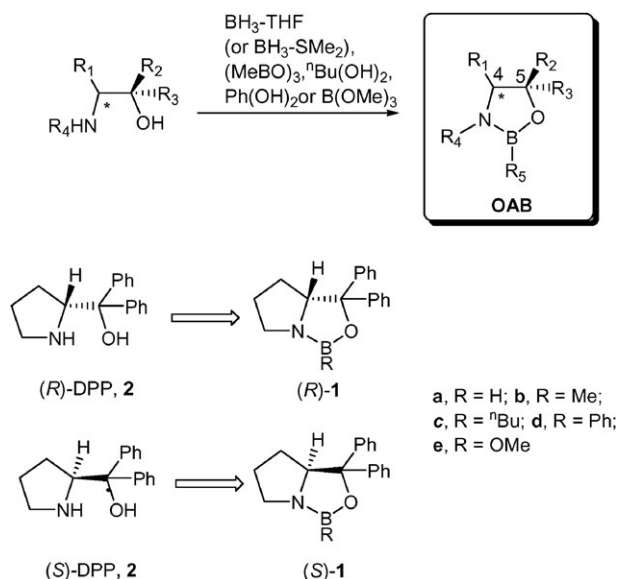
The mechanism for OAB-catalyzed asymmetric borane reduction of prochiral ketones have well been studied.<sup>2</sup> Scheme 2 outlines the general mechanistic model developed for the (*S*)-**1**-catalyzed reduction of ketones. The reductions may occur by the following sequence: (a) *endo* complexation of borane to the nitrogen of (*S*)-**1** to the less hindered site of the OAB ring system; (b) *anti*-coordination of the ketone oxygen to the ring boron of (*S*)-**1**; (c) hydrogen transfer from the coordinated borane to the carbonyl *via* a six-membered cyclic transition state. The initial step in the pathway is rapid coordination of  $\text{BH}_3$  to the Lewis base nitrogen atom on the  $\alpha$  face of (*S*)-**1** to form (*S*)-**1**- $\text{BH}_3$  adduct (**1A**), which is structurally defined by single-crystal X-ray diffraction analysis. This adduct serves to activate  $\text{BH}_3$  as a hydride donor and also to increase the Lewis acidity of the boron atom of the OAB ring, which coordinates with the carbonyl oxygen of the ketone to provide the more stable *anti* form along the direction of the oxygen lone pair. The manner of this coordination minimizes unfavorable steric interactions between (*S*)-**1** and the ketone to form the complex **1B**. The resulting complex produces reduction product **1D** by a face-selective hydride transfer *via* a six-membered transition state **1C**. Finally, the catalyst (*S*)-**1** is regenerated by decomposition of **1D** with excess  $\text{BH}_3$ . In the reaction, of fundamental importance is the fact that OABs themselves do not reduce ketones. They can act as reducing agents only after addition of a second equivalent of borane. In the OAB-catalyzed asymmetric borane reduction of ketones, the OABs play a role as Lewis



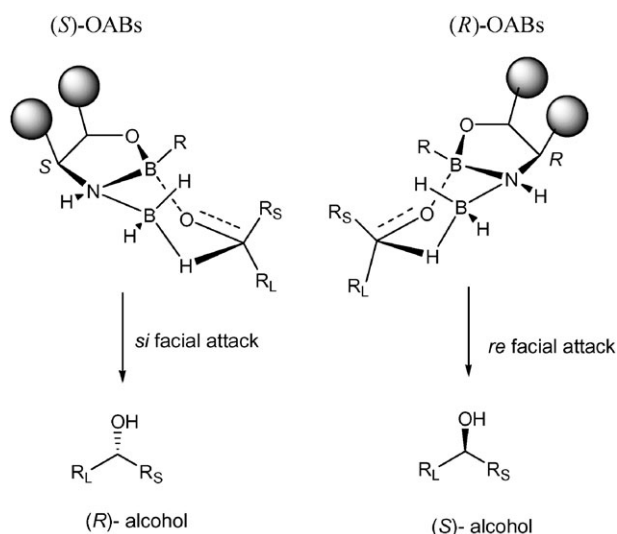
**Scheme 2** Proposed mechanism of the (*S*)-**1**-catalyzed reduction of ketones.

acid–Lewis base bifunctional asymmetric inducing catalyst by activating both ketone and borane to facilitate the reduction more rapidly than borane itself. The enantioselectivity of OAB-catalyzed borane reduction is greatly influenced by various factors such as structural variations of the OAB ring system, stability of OABs, nature of borane source, and reaction conditions (solvent and reaction temperature). The analysis of the literature data<sup>2</sup> and a direct comparison study<sup>4</sup> for the variations of OAB rings show that *cis* relationship between substituent groups at the C4 and C5 is essential for obtaining high enantioselectivity. The presence of a diphenyl group at C5 is more preferable. The sterically rigid OABs bearing fused bicyclic ring structures have proved to work as more effective catalysts than ones with monocyclic ring systems. Especially the stereogenic configurations at C4 are crucial for determining absolute configuration of product alcohols. In most cases, (*S*)-OABs provide (*R*)-alcohols by *si*-facial attack of hydride, while (*R*)-OABs give (*S*)-alcohols by *re*-facial attack of hydride (Fig. 1). On the other hand, to obtain high enantioselectivity, the use of Lewis basic ethereal solvents such as THF and DME is preferably since they can keep a high monomer/dimer ratio of catalyst by breaking the less reactive dimer down to more active monomer form.<sup>2</sup> As for the effects of temperature, the effects remains controversial. Up to date, it is generally accepted that the best enantioselectivity in the OAB reduction can be obtained in the range of temperature 25–50 °C.<sup>2</sup>

**2.1.2 Improvement studies of OAB-catalyzed reduction.** A well-known oxazaborolidine (OAB)-catalyzed asymmetric borane reduction provides an impetus for the asymmetric reduction. Although a number of reductions and their application using this methodology have been developed, there are



**Scheme 1** Preparation of oxazaborolidines (OABs).

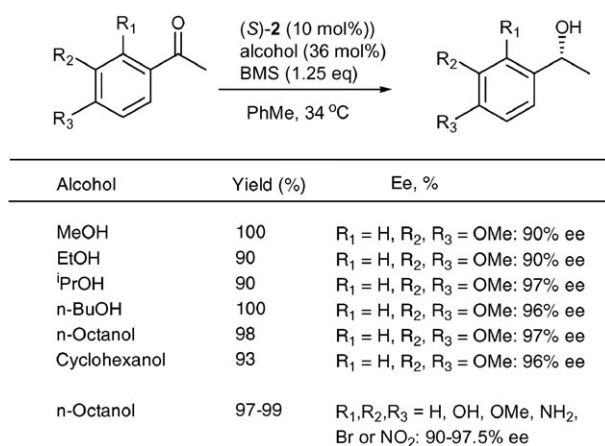


**Fig. 1** Proposed mechanism for enantioselection of OAB-catalyzed reduction.

many problems to be solved for large-scale applications. Therefore, to enhance enantioselectivity and practicability for the reduction, many improvement studies have been made.

**2.1.2.1 Improvement through variation of B-substituents of OABs.** In the OAB-catalyzed reduction, to obtain reproducible results with high enantioselectivity and enhance practicability for a wide range of industrial applications, it is essential to prepare more stable OABs in air and moisture with a simple procedure and cost effectiveness. Although it is known that a commercially available OAB, **1b**, is more stable in air than **1a**, the catalyst is sensitive to moisture so that a trace amount of water content decreases enantioselectivity dramatically.<sup>2</sup> For example, it was found that the presence of 1 mg of water in 1 g of ketone lowers the enantioselectivity from 95 to 50% ee.<sup>2</sup> Moreover, synthesis of B-substituted OABs, **1b–1d**, required not only relatively expensive trimethylboroxine or methyl boronic acid, *n*-butyl boronic acid and phenyl boronic acid, respectively, but also time-consuming operations to remove water formed.<sup>2</sup> Recently asymmetric reduction of ketones employing various B-methoxylated OABs as catalyst has been growing due to several practical advantages: it eliminates the necessity of prior synthesis of the catalyst and provides high reactivity and excellent enantioselectivity.<sup>5,6,16,17,27</sup> For example, comparing the reduction of 3-acetylpyridine using **1b** and **1e** as catalyst, **1e** afforded product alcohol in 99% ee with 10 mol% of the catalyst in contrast to 63% ee with 20 mol% of **1b**. This method is successfully applied to a large-scale synthesis of (*R*)-2-amino-1-(3-pyridyl)ethanol.<sup>5</sup> Furthermore the catalytic reduction has been successfully achieved with B-alkoxylated CBS reagents *in situ* generated from alcohols, BMS and (*S*)-**2** (Scheme 3).<sup>6</sup>

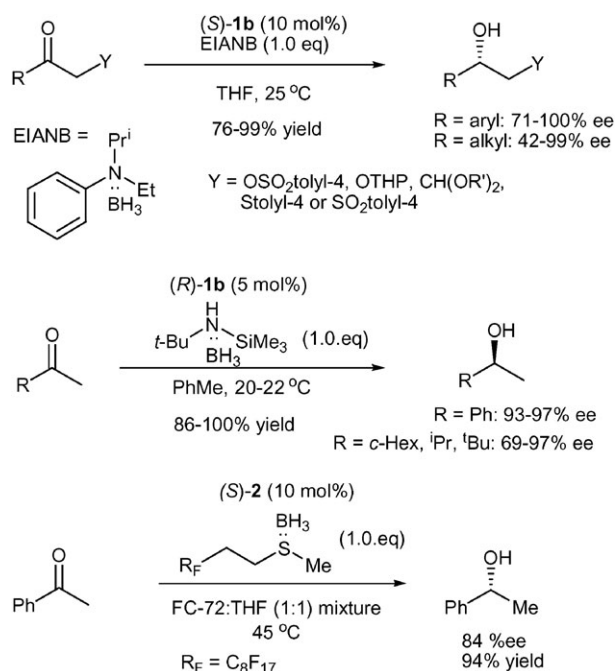
**2.1.2.2 Improvement through variation of borane sources.** In the OAB-catalyzed reduction, the most commonly used borane reagents are  $\text{BH}_3\cdot\text{THF}$ , BMS and catecholborane (CB). However, these borane reagents are not free of certain disadvantages, such as the low concentration and stability of  $\text{BH}_3\cdot\text{THF}$ , and high



**Scheme 3** Asymmetric borane reduction catalyzed by B-alkoxylated CBS reagent generated *in situ* from (*S*)-**2** and alcohol.

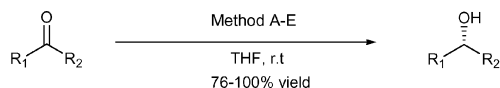
volatility, flammability, unpleasant odor of BMS and high sensitivity to air and moisture. In particular, impurities in commercial  $\text{BH}_3\cdot\text{THF}$  decrease enantioselectivity significantly. For example, the reduction of acetophenone with commercial 1 M  $\text{BH}_3\cdot\text{THF}$  (stabilized with  $\sim 0.005$  M  $\text{NaBH}_4$ , >98% purity) in the presence of 5 mol% of **1b** in THF at ambient temperature gave 1-phenylethanol with 65% ee due to nonselective ketone reduction by a borohydride species, while the same reduction using non-stabilized 1 M  $\text{BH}_3\cdot\text{THF}$  provided 95% ee.<sup>7</sup> Besides, the use of this hydride frequently affords different results due to inconsistent quality of commercial products.<sup>8</sup> These drawbacks could be overcome by using amine–borane complexes, such as *N,N*-diethyl-aniline–borane, *N*-ethyl-*N*-isopropylaniline–borane (EIANB), and *N*-phenylmorpholine–borane. Such amine–borane complexes afford not only excellent enantioselectivities in the reduction of various ketones, but also offer the advantages of being soluble in most common solvents at high concentration and with a lower sensitivity to air and moisture. Of these reagents, it is noticeable that EIANB is very effectively utilized for the reductions of various functionalized ketones including  $\alpha$ -sulfonyloxy ketones,  $\alpha$ -hydroxy ketones,  $\alpha$ -keto acetals,  $\alpha$ -keto sulfides and sulfones (Scheme 4).<sup>3</sup> Nevertheless, use of these reagents may require removal of amine ligands used as borane carrier for the purification of products. On the other hand, *N*-*tert*-butyl-*N*-trimethylsilylamine–borane offers the advantage of easy product isolation through the hydrolysis of the silylamine upon aqueous work-up producing the water-soluble *tert*-butylamine and volatile silicon by-products. (*R*)-**1b**-catalyzed reduction of aryl methyl ketones and pinacolone using this reagent provided excellent enantioselectivities (93–97% ee).<sup>9</sup> A fluoros borane methyl sulfide prepared by complexation of borane gas on 2-(perfluorooctyl)-ethyl methyl sulfide was successfully used for the CBS reduction of acetophenone as reductant.<sup>10</sup> In contrast to BMS, this hydride is found to be an environmental friendly reagent since it is not only odorless and non-pyrophoric solid, but also can be recycled by fluoros extraction (Scheme 4).

**2.1.2.3 Improvement through developing one-pot procedures.** Although several of borane complexes are commercially available, these borane carriers suffer from drawbacks with regard



**Scheme 4** (S)- or (R)-1 catalyzed asymmetric reduction with some new borane carriers.

to their large-scale applications because of difficulties in handling and transporting these reagents. Some of them may require an additional step for eliminating carrier ligands of borane. Based on the reaction of  $\text{NaBH}_4$  with  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{I}_2$ ,  $\text{TMSCl}$ ,  $\text{MeI}$  or  $\text{Me}_2\text{SO}_4$  in THF to easily produce  $\text{BH}_3\cdot\text{THF}$ , simple and convenient OAB reductions through *in situ* 'one-pot' generation of both OABs and borane species have been developed and from a practical view point, this is highly desirable. Although the first 'one-pot' reduction of acetophenone carried out with  $\text{NaBH}_4$  and  $\text{I}_2$  (method A) in the presence of (S)-2 in THF gave 65% ee,<sup>11</sup> the reduction using  $\text{TMSCl}$  or  $\text{BF}_3\cdot\text{OEt}_2$  (method B),<sup>12,24</sup> and  $\text{SnCl}_4$  or  $\text{SnCl}_2$  (method C)<sup>13</sup> in place of  $\text{I}_2$  provided 85–98% ee for aryl methyl ketones and 2-chloroacetophenone. Similar reduction using *n*- $\text{Bu}_4\text{NBH}_4$  with  $\text{MeI}$  (method D) afforded high enantioselectivity.<sup>14</sup>  $\text{BH}_3\cdot\text{THF}$  can be also generated from  $\text{LiH}$  and  $\text{BF}_3\cdot\text{OEt}_2$  (method E). The reduction of aryl methyl ketones employing this method gave 49–95% ee.<sup>15</sup> These results are summarized in Scheme 5. The  $\text{NaBH}_4\text{-Me}_2\text{SO}_4$  system is also effectively used for synthesis of a chiral drug intermediate *via* a one-pot procedure.<sup>8</sup>



Method	Yield, %	Ee, %
A: Ketone (1.0 eq) : $\text{NaBH}_4$ (1.2 eq) : $\text{I}_2$ (0.6 eq) : (S)-2 (0.2 eq)	85	$\text{R}_1 = \text{Ph}$ , $\text{R}_2 = \text{Me}$ : 65% ee
B: Ketone (1.0 eq) : $\text{NaBH}_4$ (1.2 eq) : $\text{TMSCl}$ : (S)-2 (0.1 eq)	93-98	$\text{R}_1 = \text{aryl}$ , $\text{R}_2 = \text{Me}$ , $\text{CH}_2\text{Cl}$ : 90-98% ee
C: Ketone (1.0 eq) : $\text{NaBH}_4$ (1.2 eq) : $\text{SnCl}_2$ (0.6 eq) : (S)-2 (0.1 eq)	91-98	$\text{R}_1 = \text{aryl}$ , $\text{R}_2 = \text{Me}$ , $\text{CH}_2\text{Cl}$ : 85-97% ee; $\text{R}_1 = ^i\text{Pr}$ , <sup><i>t</i></sup> Bu, $\text{R}_2 = \text{Me}$ : 68, 94% ee
D: Ketone: <i>n</i> - $\text{Bu}_4\text{NBH}_4$ (1.0 eq) : $\text{MeI}$ (0.8 eq) : (S)-2 (0.08 eq)	76-89	$\text{R}_1 = \text{aryl}$ , $\text{R}_2 = \text{Me}$ , Et, <sup><i>i</i></sup> Pr, $\text{CH}_2\text{Cl}$ : 76-99% ee
E: Ketone (1.0 eq) : $\text{LiH}$ (2.5 eq) : $\text{BF}_3\cdot\text{OEt}_2$ (3.75 eq) : (S)-1b (0.05 eq)	100	$\text{R}_1 = \text{aryl}$ , $\text{R}_2 = \text{Me}$ : 49-95% ee

**Scheme 5** One-pot CBS-catalyzed asymmetric reduction of prochiral ketones.

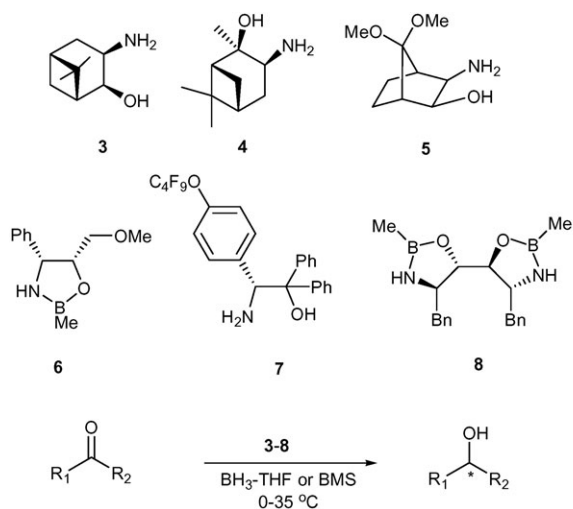
## 2.1.3 New homogeneous and immobilized OAB catalysts

**2.1.3.1 New homogeneous OABs.** Recently a great number of chiral 1,2-aminoalcohols used as new pre-catalysts for OAB-catalyzed reduction have been developed. Among them, chiral ligands **3**<sup>16</sup> and **4**<sup>17</sup> bearing fused bicyclic ring structures derived from naturally occurring (1S)-(-)-β-pinene and (1R,5R)-(-)-α-pinene were utilized as highly effective pre-catalysts for the reduction. B-methoxylated OABs derived from these ligands catalyzed the reduction of aralkyl ketones to give the corresponding alcohols with 61–98% ee. With respect to the application of chiral catalysts, the choice of catalyst being available as both enantiomers is more desirable. Unfortunately, most chiral amino alcohols derived from naturally occurring chiral pools provide only one enantiomer. Therefore the attainment of its antipode is often difficult and economically unfavorable. The chiral ligands or OAB catalysts **5**,<sup>18</sup> **6**,<sup>19</sup> **7**,<sup>20</sup> and **8**<sup>21</sup> are available as both enantiomers, since they can be prepared by asymmetric synthesis or starting from inexpensive chiral pools which are commercially available as both enantiomers such as optically active 4-hydroxyphenylglycine and tartaric acid. They afforded 73–96% ee for the reduction of aralkyl ketones and α-halo ketones. Of these, the reduction with **6** and **7** provided the best results to give 90–96% ee. Noticeably, **6** gave 79% ee and 97% ee for the reduction of cyclohexyl methyl ketone and pinacolone, respectively (Scheme 6).

**2.1.3.2 Immobilized OAB catalysts.** Most of homogeneous OAB catalysts are not suited for separation and recycling of the catalyst. The advantages of chiral ligands immobilized on insoluble or soluble matrices are that they can be used in excess, recovered by filtration or extraction from reaction mixtures and reused. Most of polymer-supported (PS) ligands recently developed are PS-CBS reagents derived from (R)- or (S)-2. Among them, **9**<sup>22</sup> and **10**<sup>23</sup> are CBS reagents anchored on a cross-linked polystyrene, and a PS-CBS reagent **11**<sup>24</sup> is attached to a polyethylene polymer. When the reduction was carried out with 10–50 mol% of these ligands, 61–97% ee for aralkyl ketones, α-halo ketones and pinacolone were obtained (Scheme 7). As for recycling of the catalyst, **10** and **11** are sufficiently chemically stable to withstand many reaction cycles, which can be recycled several times without loss of enantioselectivity for the reduction of acetophenone, while the case of **9** was unsuccessful.

Although heterogenous PS catalysts offer more advantages involving recovery of the catalyst and purification of product

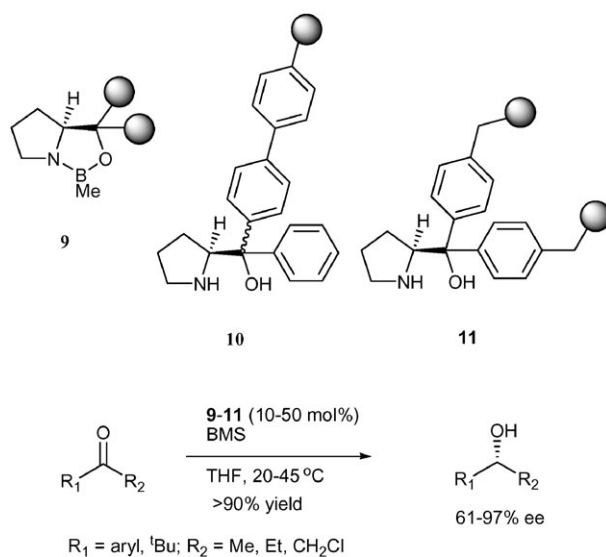




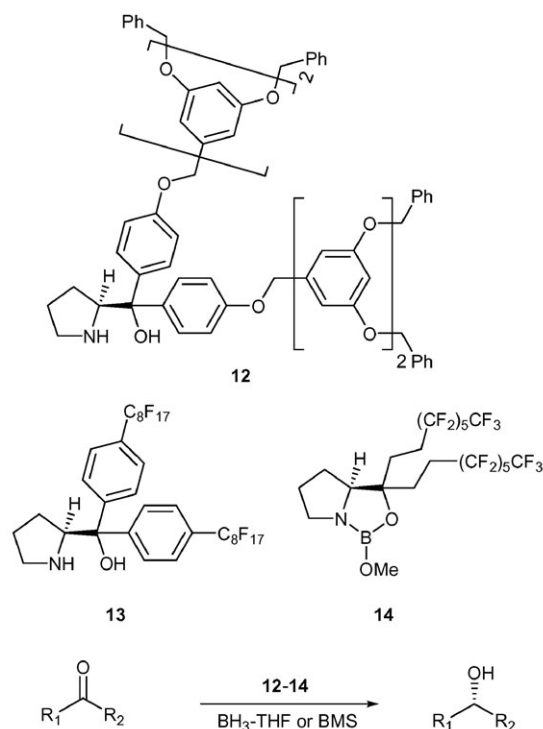
OAB	Yield, %	Ee, %
3 (3 mol%) B(OMe) <sub>3</sub> (3.3 mol%)	92-99	R <sub>1</sub> = aryl, R <sub>2</sub> = Me, Et: 93-98% ee, S R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Cl: 96% ee, R
4 (10 mol%) B(OMe) <sub>3</sub> (10 mol%)	100	R <sub>1</sub> = Ph, R <sub>2</sub> = Me, Et, <sup>i</sup> Pr: 61-96% ee, R R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Cl: 91% ee, S
5 (5 mol%)	68-94	R <sub>1</sub> = aryl, R <sub>2</sub> = Me, Et: 76-93% ee, S R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Br: 95% ee, R R <sub>1</sub> = <sup>t</sup> Bu, <sup>t</sup> Bu, R <sub>2</sub> = Me: 49-72% ee, S
6 (10 mol%)	>99	R <sub>1</sub> = aryl, R <sub>2</sub> = Me, Et, <sup>n</sup> Pr: 90-96% ee, S R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Cl: 94% ee, R R <sub>1</sub> = <i>c</i> -Hex, <sup>t</sup> Bu, R <sub>2</sub> = Me: 79-97% ee, S
7 (10 mol%)	76-80	R <sub>1</sub> = Ph, R <sub>2</sub> = alkyl: 90-96% ee, S R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Cl: 96% ee, R
8 (2.5 mol%)	90-99	R <sub>1</sub> = Ph, 2-Np, R <sub>2</sub> = Me: 73-81% ee, S R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Cl, CCl <sub>3</sub> : 70-95% ee, R Np = naphthyl

**Scheme 6** Asymmetric borane reduction of ketones catalyzed by new chiral OABs.

than homogenous catalysts, they sometimes have drawbacks, such as low catalysis activity or rigorous conditions owing to the polymer matrix restricting the mobility and accessibility to active sites of catalysis. To avoid such inconvenience, a PS-CBS ligand **12**<sup>25</sup> anchored on dendrimer and (*S*)-prolinol-based fluorinated analogues, **13**<sup>26</sup> and **14**,<sup>27</sup> have been developed. Reduction using these ligands as catalysts can be carried out under homogeneous conditions, since they are soluble in THF in contrast to other PS ligands. For the reduction of aryl methyl ketones, these catalysts were very effective to give high enantioselectivity even with relatively small loads (5–10 mol%). Moreover, **12** and **14** afforded high enantioselectivity (90–97% ee) for the reduction of 3- or 4-acetylpyridine. However, they are less effective even for relatively hindered aliphatic ketones (Scheme 8). After a completion of reduction, all of these ligands can be readily recovered by filtration from reaction mixtures by treatment with methanol. However, it has been observed that **12** and **13** can be reused without a significant loss of enantioselectivity, while the use of recovered **14** remarkably decreases enantioselectivity.



**Scheme 7** Asymmetric reduction catalyzed by polymer-supported CBS reagents.



OAB	Yield, %	Ee, %
12 (5 mol%) THF, reflux	77-99	R <sub>1</sub> = aryl, R <sub>2</sub> = Me: 85-97% ee R <sub>1</sub> = <sup>i</sup> Pr, <sup>t</sup> Bu, R <sub>2</sub> = Me: 61-68% ee R <sub>1</sub> = 3-pyridyl, R <sub>2</sub> = Me: 97% ee
13 (10 mol%) THF, rt	83-99	R <sub>1</sub> = aryl, R <sub>2</sub> = Me, Et: 71-95% ee
14 (10 mol%) PhMe, rt	50-99	R <sub>1</sub> = aryl, R <sub>2</sub> = Me: 86-93% ee R <sub>1</sub> = <sup>t</sup> Bu, R <sub>2</sub> = Me: 30% ee R <sub>1</sub> = 4-pyridyl, R <sub>2</sub> = Me: 90% ee

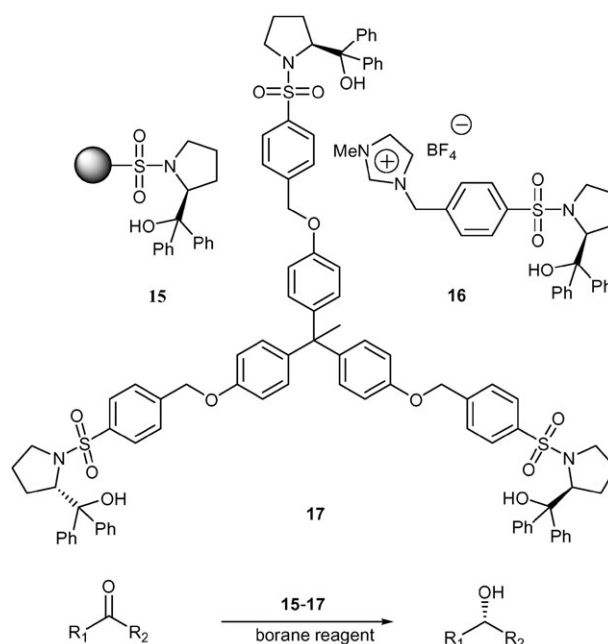
**Scheme 8** Asymmetric borane reduction of ketones catalyzed by dendrimer-supported CBS and fluorinated CBS reagents.

As a different type of PS ligand, a chiral prolinol-based PS-sulfonamide **15** has been prepared from (*S*)-**2** and polymeric sulfonyl chloride. This ligand can not form an OAB ring structure with borane reagents due to the absence of an N–H group. However, this reagent has been found to be highly effective as a catalyst for the borane reduction of aryl methyl ketones, even at 15 mol% level, to provide high enantioselectivity (84–96% ee).<sup>28</sup> Furthermore, the catalyst could be reused five times with no loss of catalytic efficiency (95.8–96.5% ee) for the reduction of 4-nitroacetophenone. When one-pot reduction using NaBH<sub>4</sub>–TMSCl or BF<sub>3</sub>·OEt<sub>2</sub> as borane source was carried out with 25 mol% of **15**, almost the same results as those with BMS were obtained. However, the catalyst is still less effective for the reduction of aliphatic ketones. On the other hand, a chiral ionic liquid-tagged prolinol-based sulfonamide ligand **16**,<sup>29</sup> which acts as a homogeneous recyclable catalyst provides 75–94% ee for the reduction of aryl methyl ketones and  $\alpha$ -halo ketones. Noticeably, this catalyst is found to be highly effective for the reduction of 2'-substituted acetophenones such as 2'-chloroacetophenone (94% ee) and 2'-methylacetophenone (91% ee).<sup>29</sup> An easily recoverable C<sub>3</sub>-symmetric sulfonamide **17**<sup>30</sup> provided 73–97% ee even with a 5 mol% load for reduction of aralkyl ketones and  $\alpha$ -halo ketones (Scheme 9).

## 2.2 Chiral borinate and spiroborate catalysts

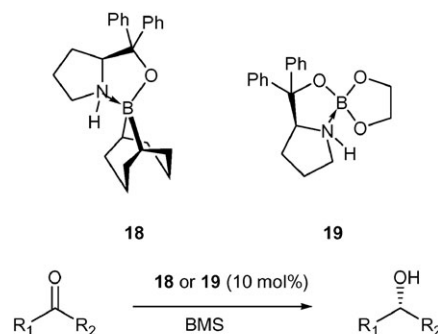
A chiral borinate complex **18**<sup>31</sup> prepared from (*S*)-**2** and 9-BBN acts as a new type of chiral catalyst for asymmetric borane reduction. Its structure is well established by <sup>11</sup>B NMR analysis. The catalyst can be used without isolation and proves to be particularly effective for reduction of the more hindered aralkyl ketones and  $\alpha$ -halo ketones, providing 91.5% ee for pivalophenone and 99.2% ee for 1-acetonaphthone, 95.5% ee for 2-bromoacetophenone and 93.1% ee for 2,2,2-trifluoroacetophenone (Scheme 10).

Recently a series of chiral spiroborates has been prepared by transesterification of borates of various chiral 1,2-aminoalcohols with ethylene glycol or the reaction of aminoalcohols with CB.<sup>32</sup> These compounds were fully characterized by <sup>1</sup>H, <sup>13</sup>C and <sup>11</sup>B NMR, HRMS, IR, and specific rotation. Among them, a chiral spiroborate **19**<sup>32</sup> prepared from (*S*)-**2** and ethylene glycol has been found to be a stable solid even after being exposed to moisture and air for 24 h at 25 °C and provide excellent enantioselectivities for the reduction of various aralkyl ketones and  $\alpha$ -halo ketones. In particular, this catalyst is highly effective for the reduction of cyclic aralkyl ketones such as 1-indanone (97% ee), 1-tetralone (>99% ee) and 8-methoxy-1-tetralone (98% ee). For aliphatic ketones, the catalyst afforded 99% ee for the reduction of a hindered ketone, 1-adamantyl methyl ketone, while is less effective for the reduction of an unhindered ketone, 4-phenylbutan-2-one (72% ee) (Scheme 10). For the reduction of acetophenone, high enantioselectivity (98% ee) was achieved with as low as 0.5 mol% of catalytic load and the enantiomeric excess was still high (89% ee) even with 0.1 mol% of the catalyst.<sup>32</sup> Also, the catalyst is highly effective for the reduction of heterocyclic ketones, such as 3- and 4-acetylpyridines, 5-acetyl-2-methoxypyridine and 2-acetylphenothiazine to give 95–99% ee with 1 mol%.<sup>33</sup> The reaction mechanism and chiral reducing species for the reduction using **18** and **19** are unknown.



ligand	Yield, %	Ee, %
<b>15</b> (15–25 mol%) NaBH <sub>4</sub> –TMSCl or BMS THF, reflux	91–99	R <sub>1</sub> = aryl, R <sub>2</sub> = Me: 84–95.7% ee R <sub>1</sub> = Bn, Tr, <i>c</i> -Hex, Et, R <sub>2</sub> = Me: 50.6–89.5% ee R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Cl: 96.6% ee
<b>16</b> (15 mol%), BMS PhMe, reflux	91–96	R <sub>1</sub> = aryl, R <sub>2</sub> = Me: 75–94% ee R <sub>1</sub> = aryl, R <sub>2</sub> = CH <sub>2</sub> Cl: 71–95% ee
<b>17</b> (5 mol%), BMS THF, reflux	80–95	R <sub>1</sub> = aryl, R <sub>2</sub> = Me, Et: 73–97% ee R <sub>1</sub> = aryl, R <sub>2</sub> = CH <sub>2</sub> Br: 89–92% ee

**Scheme 9** Asymmetric borane reduction of ketones catalyzed by chiral PS-sulfonamides.



ligand	Yield, %	Ee, %
<b>18</b> (10 mol%) BMS, THF, rt	>99	R <sub>1</sub> = aryl, R <sub>2</sub> = alkyl: 73.2–99.2% ee R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Br, CF <sub>3</sub> : 93.1–95.5% ee
<b>19</b> (10 mol%) BMS, THF, 0 °C	81–98	R <sub>1</sub> = aryl, R <sub>2</sub> = alkyl: 61–99% ee R <sub>1</sub> = Ph(CH <sub>2</sub> ) <sub>2</sub> , 1-Adamantyl, R <sub>2</sub> = Me: 72% ee, 99% ee R <sub>1</sub> = aryl, R <sub>2</sub> = CH <sub>2</sub> Cl, CF <sub>3</sub> : 82–95% ee R <sub>1</sub> = 3- and 4-pyridyl, R <sub>2</sub> = Me: 98% ee, 99% ee

**Scheme 10** Asymmetric borane reduction of ketones catalyzed by chiral borinate and spiroborate.

### 2.3 Chiral $\beta$ -hydroxy phosphoramidate and carboxamide catalysts

A number of bifunctional organophosphorus compounds including an N-P=O structural framework as a different type of chiral catalysts for the reduction have been developed. These compounds include chiral phosphoramidates, phosphonamides, phosphinamides and oxazaphospholidine oxides derived from non-racemic 1,2-aminoalcohols and diamines. Of these catalysts, a (*S*)-**2**-based  $C_3$ -symmetric tripodal  $\beta$ -hydroxyphosphoramidate **20**<sup>34</sup> afforded high enantioselectivity (93–98% ee) with 5 mol% load for the borane reduction of most of aryl methyl ketones bearing both electron-withdrawing and electron-donating groups on the phenyl ring and  $\alpha$ -halo ketones (Scheme 11). However, the reduction for isobutyrophenone under the same conditions gave low enantioselectivity (43% ee). The catalyst can be recovered as the solid state from the reaction mixture and reused with no loss of catalytic efficiency on the enantioselectivity. Furthermore, no distinct decrease of enantioselectivity in the reduction was observed carried out by eight continuous additions of borane and acetophenone. Similarly, a  $C_3$ -symmetric  $\beta$ -hydroxy carboxamide **21**<sup>35</sup> also catalyzes the reduction of aryl methyl ketones and pinacolone to provide 74–97% ee in high yields (Scheme 11). In this study, it has been found that the catalytic reduction is sufficiently faster than the reduction of amide group of **21** with BMS.

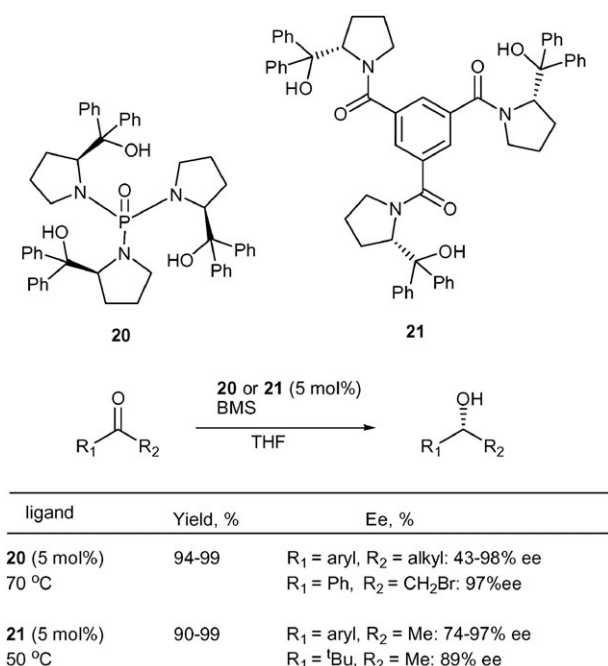
### 2.4 Chiral *N*-squaryl aminoalcohol and diazaborolidine catalysts

Squaric acid is an aromatic four-membered cyclic compound with a cyclobutenedione structure having with acidic hydroxyl groups which can be replaced by various functional groups. A series of chiral *N*-squaryl amino alcohols derived from various chiral 1,2-aminoalcohols has been developed. Since the squaric acid moiety possesses a rigid skeleton and two oxygen atoms

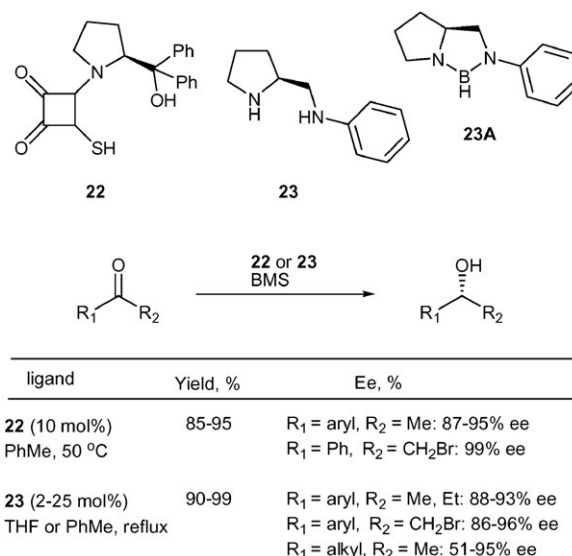
with a Lewis base character of cyclobutenedione structure, it is expected that the new catalysts can form more rigid transition state by facilitating intramolecular coordination between substrates and catalysts. Of these ligands, a prolinol-based thiosquaryl amino alcohol **22**<sup>36</sup> prepared from thiosquaric acid derivative and (*S*)-**2** provides 87–95% ee with 10 mol% of the catalysts for the reduction of aryl methyl ketones. In particular, the catalyst is highly effective for the reduction of  $\alpha$ -halo ketones to give 99% ee for 2-bromoacetophenone (Scheme 12). As another bifunctional chiral ligand, a chiral 1,2-diamine, **23**,<sup>37</sup> has been prepared from (*S*)-proline or more inexpensive (*S*)-pyroglutamic acid. The borane reduction carried out with 25 mol% of **23** at refluxing temperature of THF afforded 82–93% ee for aryl methyl ketones, 96% ee for 2-chloroacetophenone and 95% ee for pinacolone (Scheme 12). In this reduction, it has been realized that initial formation of a diazaborolidine **23A** is essential for obtaining high enantioselectivity. Therefore **23A** should be first prepared by the treatment of **23** with BMS at refluxing temperature of THF or toluene prior to the addition of ketones. When the reduction was carried out at refluxing temperature of toluene, high enantioselectivities (86–91% ee) even with 2 mol% of catalyst for 2-haloacetophenone derivatives was achieved.<sup>37</sup>

### 2.5 Chiral metal alkoxide catalysts

As a chiral Lewis acid catalyst, a gallium complex (LiGa(MTB)<sub>2</sub>, **24**<sup>38</sup>) has been prepared by the reaction of LiGaH<sub>4</sub> with 2 equiv. of non-racemic *S*,*O*-2-hydroxy-2'-mercapto-1,1'-biphenyl (MTBH<sub>2</sub>) in THF. Its structure has been characterized by X-ray crystallography. Carrying out the reduction of ketones with CB in the presence of 2–2.5 mol% of **24** in THF at –15 to –25 °C, the reduction afforded 73–93% ee for most alkyl ketones with two exceptions: 24% ee for relative bulky isobutyrophenone and 59% ee for 1-acetonaphthone. The same reduction for aliphatic ketones is less effective (46–79% ee) (Scheme 13). In this reaction, it has been suggested that an active gallium hydride species, LiGaH(MTB)Y

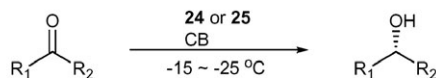
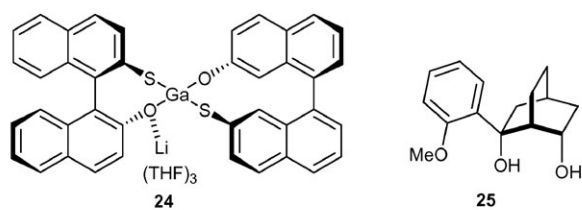


**Scheme 11** Asymmetric borane reduction of ketones catalyzed by chiral  $\beta$ -hydroxyphosphoramidate and carboxamide.



**Scheme 12** Asymmetric borane reduction of ketones catalyzed by chiral *N*-squaryl aminoalcohol and diazaborolidine.





ligand	Yield, %	Ee, %
<b>24</b> (2-2.5 mol%) THF	60-96	R <sub>1</sub> = aryl, R <sub>2</sub> = alkyl: 24-93% ee R <sub>1</sub> = branched alkyl, R <sub>2</sub> = Me: 46-79% ee R <sub>1</sub> = Ph, R <sub>2</sub> = CH <sub>2</sub> Br: 60% ee
<b>25</b> (10 mol%) Ti(OPr <sup>i</sup> ) <sub>4</sub> (10 mol%) <sup>t</sup> BuOMe	50-100	R <sub>1</sub> = aryl, R <sub>2</sub> = Me, Et: 91-98% ee R <sub>1</sub> = <sup>n</sup> Bu, <sup>n</sup> Hex, R <sub>2</sub> = Me: 85-87% ee

**Scheme 13** Asymmetric borane reduction of ketones catalyzed by chiral metal alkoxides.

(**24A**, Y = MTB ligand moiety) formed by the hydride transfer of CB to **24** initiates the reduction as an active catalyst species and the catalytic cycle is made by regeneration of **24A** from a gallium alkoxide of product by selective decomplexation with CB. On the other hand, the asymmetric borane reduction of ketones using a chiral Ti-based catalytic system based on a chiral bicyclo[2.2.2]octane-1,3-diol (**25**, BODOL) framework together with Ti(OPr<sup>i</sup>)<sub>4</sub> as catalyst has been reported.<sup>39</sup> When the reduction was carried out in <sup>t</sup>BuOMe at −15 to −20 °C by adding CB to a mixture of ketones and 10 mol% of a Ti-complex of **25** prepared from an equivalent molar reaction of BODOL and Ti(OPr<sup>i</sup>)<sub>4</sub>, the reduction gave high enantioselectivity (86–98% ee) for aryl methyl ketones. It is particularly noteworthy that the reduction gives 85 and 87% ee, respectively, for unhindered ketones such as 2-heptanone and 2-octanone and 96% ee for an enone, 1-acetylcyclohexene (Scheme 13). The reduction catalyzed by **25** itself without the addition of Ti(OPr<sup>i</sup>)<sub>4</sub> provided the product alcohols with no or negligible enantioselectivity.

### 3. Catalytic asymmetric borohydride reduction

Borane reagents are Lewis acid type hydrides, while borohydride reagents are Lewis base type hydrides. Consequently their reducing characteristics are different. In contrast to enormous progress for the catalytic asymmetric borane reduction of ketones, such reduction employing borohydride as the reducing agent has been relatively neglected. Only few successful examples for catalytic borohydride reduction have been reported.

#### 3.1 Chiral ketoiminocobalt(II) complex catalysts

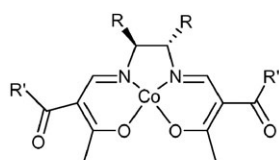
Since Mukaiyama *et al.* discovered catalytic asymmetric reduction of ketones with sodium borohydride using non-racemic β-ketoiminato cobalt(II) complexes as catalysts, a variety of these complexes has been prepared and evaluated as catalysts

for the borohydride reduction of ketones. These compounds were prepared by the treatment of CoCl<sub>2</sub> in the presence of sodium methoxide with the corresponding imine ligands obtained from optically active 1,2-diaryl-1,2-ethanediamines and 1,3-dicarbonyl compounds.<sup>40</sup> Among them, catalysts **26** provided excellent enantioselectivity even with 1 mol% load for the reduction of aralkyl ketones and 1-tetralone derivatives. It is worth noting that both enantiomers of chiral 1,2-diaryl-1,2-ethanediamines are commercially available for the preparation of the catalyst. In the reduction using this catalyst, one of the most important factors to achieve high enantioselectivity and high yield is that the NaBH<sub>4</sub> should be first activated with alcohols in chloroform solvent. For example, comparing the reduction of 6-methoxy-1-tetralone with 5 mol% of **26b** in CHCl<sub>3</sub> at −20 °C in the presence and absence of tetrahydrofurfuryl alcohol (THFA), the reduction using NaBH<sub>4</sub> activated with THFA gave the product alcohol with 87% ee in 82% yield, whereas the reduction with NaBH<sub>4</sub> itself without the alcohol provided only 5% ee and less than 10% yield. From the systematic examination on the effect of alcohols used for modification of NaBH<sub>4</sub> in the reduction, it was realized that the combination of 14 molar equivalents of THFA and 3 molar equivalents of ethanol provided the best result (93% ee and >98% yield). Moreover, it was found that the choice of alcohol in the combination with THFA was also significantly effective for tuning the enantioselectivity. For example, comparing the reduction of butyrophenone in the presence of 1 mol% of **26c**, NaBH<sub>4</sub> modified with THFA–EtOH (hydride A) provided 97% ee, while the pre-modified hydride by THFA–MeOH (hydride B) gave 90% ee under the same conditions. Similarly the reduction of cyclopropyl phenyl ketone gave 90% ee with hydride A and 76% ee with hydride B. On the contrary, hydride B afforded better results than hydride A in the reduction of more hindered ketones such as isobutyrophenone (98% ee with hydride B vs. 77% ee with hydride A) and cyclohexyl phenyl ketone (95% ee with hydride B vs. 78% ee with hydride A). Also, the influence by a match between the bulkiness of ketones and catalysts on the enantioselectivity has been observed. For example, a relatively more bulky catalyst **26c** provided 97% ee for the reduction of less bulky butyrophenone in contrast to 68% ee with less bulky catalyst **26a**. In contrast, the latter catalyst is highly effective (up to 91% ee) for the reduction of more bulky 2,2-dimethyl-1-tetralone, while **26c** does not reduce the ketone (Scheme 14).

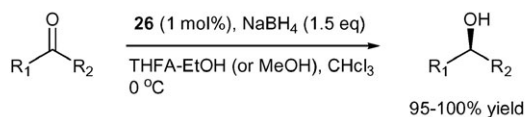
#### 3.2 Chiral aza crown ether catalysts

To develop effective catalysts for the asymmetric reduction of ketones with NaBH<sub>4</sub>, a series of chiral aza crown ethers starting from (*S,S*)-tartaric acid has been prepared.<sup>41</sup> Of these compounds, an aza crown ether **27a** bearing exocyclic hydroxyl groups afforded 80.9% ee and 89.6% ee with 10 mol% load, respectively, for the reduction of acetophenone and pinacolone (Scheme 15). Catalyst **27b**, where both amino and hydroxyl groups are protected with benzyl group, is less effective, giving 62.9% ee and 70.1% ee for reduction of the same ketones, showing that unprotected hydroxyl group and amino group play an important role for increasing enantioselectivity.





**26a:** R = Ph, R' = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>  
**26b:** R = 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R' = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>  
**26c:** R = R' = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>



R <sub>1</sub> COR <sub>2</sub>	26c: Ee, %		
	MeOH	EtOH	
PhCOPr <sup>n</sup>	90	97	
PhCOC <sub>3</sub> H <sub>5</sub> -C	76	90	
PhCOPr <sup>l</sup>	98	77	
PhCOC <sub>6</sub> H <sub>11</sub> -C	95	78	

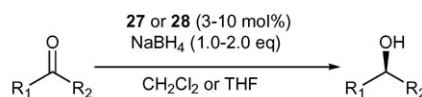
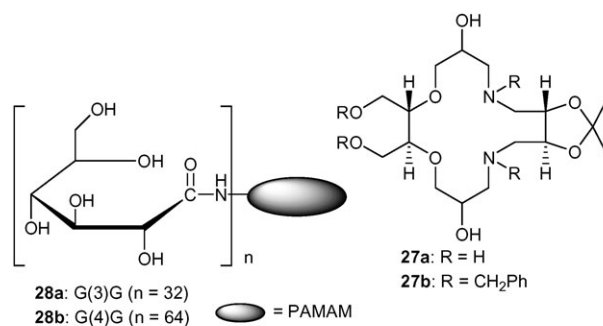
R <sub>1</sub> COR <sub>2</sub>	Ee, %		
	26a	26b	26c
1-Tetralone	65	90	60
2,2-Dimethyl-1-tetralone	81 (91) <sup>a</sup>	75	no reaction
2,2-Dimethyl-4-chromanone	88	92	74

<sup>a</sup>Using MeOH

**Scheme 14** Asymmetric borohydride reduction of ketones catalyzed by chiral cobalt complexes.

### 3.3 Chiral amphiphilic dendrimer catalysts

Since chiral dendrimers have a chiral surface environment with internal cavities, they can be used for chiral recognition and enantioselective binding to guest molecules. Chiral amphiphilic dendrimers **28** prepared from D-glucolactone and polyamidoamine (PAMAM) have been effectively used for the borohydride reduction of prochiral ketones as a chiral inducing catalyst.<sup>42</sup> Comparing the reduction of acetophenone using NaBH<sub>4</sub> in the presence of 3 mol% of **28** in THF, an excellent result (92% yield and 99% ee) was only obtained with the third-generation dendrimer G(3)G (**28a**, *n* = 32). All other dendrimer generations including G(1)G (**28**, *n* = 8), G(2)G (**28**, *n* = 16) and G(4)G (**28b**, *n* = 64) were not able to selectively induce chirality. In particular, the catalyst **28a** proved to be highly effective for the reduction of aralkyl ketones, where the carbonyl is attached to a long linear alkyl chains (82–100% ee). It is noteworthy that high enantioselectivities even for the reduction of unhindered aliphatic ketones, such as 85% ee for 2-pentanone and 96% ee for 2-heptanone were obtained (Scheme 15). In this reduction, it was observed that decrease of temperature significantly improved enantioselectivity: acetophenone (82% ee at 25 °C vs. 99% ee at 0 °C), 2-pentanone (55% ee at 0 °C vs. 85% ee at –20 °C), and 2-heptanone (28% ee at –20 °C vs. 96% ee at –80 °C). Also, the enantioselectivity seems to be sensitive to the structure of substrates. For example, the reduction of 2-heptanone provides 96% ee at –80 °C in contrast to 50% ee for 2-octanone under the same conditions. The same phenomena have been observed in the



ligand	Yield, %	Ee, %
<b>27</b> (10 mol%) CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	>97	R <sub>1</sub> = Ph, R <sub>2</sub> = Me: 80.6% ee R <sub>1</sub> = <sup>t</sup> Bu, R <sub>2</sub> = Me: 89.6% ee
<b>28</b> (3 mol%) THF, rt ~ –80 °C	45–97	R <sub>1</sub> = Ph, R <sub>2</sub> = C1–C6 alkyl: 82–100% ee R <sub>1</sub> = C3–C6 alkyl, R <sub>2</sub> = Me: 50–96% ee R <sub>1</sub> = 2-, 3-, or 4-pyridyl, R <sub>2</sub> = Me: 25–90% ee

**Scheme 15** Asymmetric borohydride reduction of ketones catalyzed by chiral aza crown ether and amphiphilic dendrimer.

reduction of acetylpyridines (Scheme 15). Since the reduction with this catalyst takes place at the solid–liquid interface under heterogeneous conditions in THF, the dendrimer catalyst can be recovered from filtration, regenerated in HCl–MeOH, and recycled up to 10 times without any loss of catalyst activity. When the same reduction for acetophenone was carried out in water, the reduction can be conducted under homogeneous conditions. In water, G(4)G catalyst, **28b**, provided better enantioselectivity (98% ee) than the 50% ee with **28a**. Such a result is attributable to the change of the topology of the chiral surface influenced by hydrogen bonding and solvation of the sugar heads.

## 4. Conclusions

Catalytic asymmetric reduction of unsymmetrical ketones using borane or borohydride as reducing agent is clearly one of the best methods for the preparation of optically active alcohols. For the borane reduction, oxazaborolidine (OAB)-catalyzed reductions are the most well known. To enhance enantioselectivity and practicability of this method for industrial applications, improvement studies through the preparation of inexpensive, more stable OAB, the use of easy-to-handle, scalable borane reagents and the development of one-pot reduction by *in situ* generation of borane species have been accomplished. Also, a variety of new homogeneous and immobilized catalysts (or ligands) to afford high enantioselectivity and/or to be recoverable have been developed. Of the homogeneous catalysts surveyed in this review, the compounds **3**, **6**, **7**, **19**, **20**, **22** and **25** provided high enantioselectivity for the reduction of aralkyl ketones and/or α-halo ketones. It is particularly noteworthy that enantioselectivities with **19** and **20**, which are a chiral prolinol-based spiroborate and

phosphoramidate, respectively, are comparable with those with a CBS reagent, **1b**, which proves to be one of the best catalysts for the borane reduction. From a practical point of view, these catalysts are superior to **1b**, since they are found to be more stable to air and moisture and easily recoverable. The selected catalysts, except for **3**, **6** and **7** are non-OAB catalysts, since they have no N–H group to form an OAB ring structure. Both the reaction mechanism and chiral reducing species for the borane reduction using these non-OAB catalysts are mostly unknown. As for immobilized catalysts, the compounds **12–15** and **17** prove to be the most effective. These catalysts can be recoverable and reusable without loss of the catalyst activity in terms of both reactivity and enantioselectivity. For the borohydride reduction, chiral cobalt complexes **26** and dendrimer catalysts **28** provided high enantioselectivity for the reduction of aryl linear alkyl ketones and some unhindered aliphatic ketones. In both asymmetric reductions with borane and borohydride reagents, most of the catalysts developed are highly effective for aralkyl ketones and relatively hindered aliphatic ketones such as pinacolone and 1-adamantyl methyl ketone. For unhindered aliphatic ketones, only few typical examples are successful. The development of highly effective chiral catalysts for the asymmetric reduction of unhindered aliphatic ketones remains a challenging target.

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