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Recent advances in the synthetic applications of the oxazaborolidine-mediated asymmetric reduction

Byung Tae Cho*

Department of Chemistry, Hallym University, Chuncheon, Kangwondo 200-702, Republic of Korea

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1. Introduction

Optically active alcohols and amines are important compounds utilized widely as starting materials, intermediates, and chiral auxiliaries for preparing biologically active substances including natural products. One of the simplest and most useful methods for the preparation of such compounds is the asymmetric reduction of prochiral ketones and ketimines. Since Itsuno[1] and Corey[2] reported the first oxazaborolidine (OAB; **1** and **2**)-catalyzed borane reduction (Fig. 1), a number of such reductions have been extensively studied.[3] For prochiral ketones, these reductions are very effective not only for most of aryl alkyl ketones, but also for various functionalized ketones, such as heterocyclic ketones, α-halo- and sulfonyloxy ketones, α-hydroxy ketones, diketones, α-keto acetals or thioketals, α,β-enones and ynones, α-azido ketones, *meso*-imides, keto esters, keto phosphates, β-keto sulfides and sulfones, and biaryl ketones and lactones, to furnish high enantioselectivity

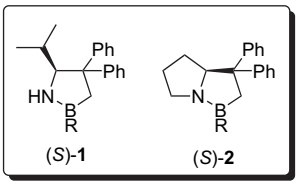

Figure 1.

Keywords: Chiral oxazaborolidine; Asymmetric reduction; Chiral natural products; Chiral bioactive compounds.
* Tel.: +82 33 248 2071; fax: +82 33 251 8491; e-mail: btcho@hallym.ac.kr

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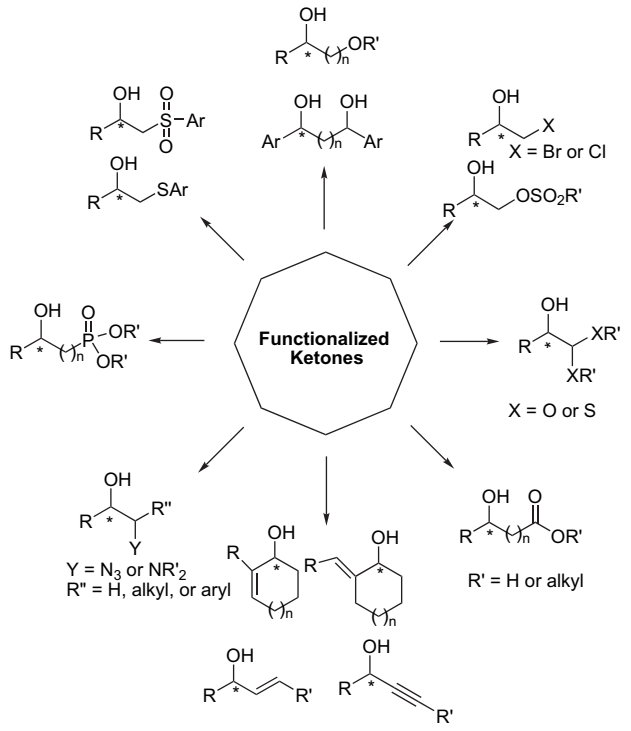


Figure 2.

with predictable configurations, even in the presence of only 2 mol % of OAB (Figs. 2 and 3). Many applications of this methodology for the synthesis of nonracemic natural products, bioactive compounds including chiral drugs and/or their intermediates have therefore been reported.[3] This review will cover only recent advances for the applications published during the years from 1998 through to mid-2005, since such applications reported until 1997 have been adequately reviewed.[3d] On the other hand, the reduction of ketimines using OABs as asymmetric inducers afforded only limited success, in contrast to the enormous progress made in the reduction of ketones. This is attributable to the low electrophilicity of the imine carbon and the rapid equilibration between the *E* and *Z* isomers. In addition, most of the chiral Lewis acids including OABs are trapped by the basic nitrogen atoms of imines and/or product amines, leading to less effective catalytic reactions.[3b] In order to illustrate the methodology, this review will begin with a brief description of the OAB-mediated asymmetric borane reduction.

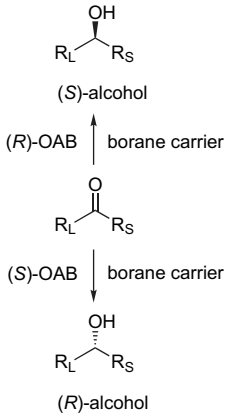


Figure 3.

2. Oxazaborolidine-mediated asymmetric borane reduction

In the OAB-mediated asymmetric borane reduction of ketones and ketimines, OABs play a role as Lewis acid–Lewis base bifunctional asymmetric inducer, which would activate both ketone or imine and borane, respectively, at the defined positions.[4] The dual activation mechanism involves the enantiofacial addition of boron–hydrogen bond to the activated ketone or imine (Fig. 4).[3e] In this reduction, OABs are used as both catalyst and stoichiometric reagent for asymmetric induction. Most of the OABs reported were prepared from chiral 1,2-amino alcohols with boron reagents, such as borane carriers, alkyl- or aryl-boronic acids, trimethylboroxine or trialkyl borate. Among these, CBS[5] reagents and their derivatives **2a**–**e** have been widely applied as some of the most effective asymmetric inducers (or catalysts) for the reduction. These reagents have been prepared from (*R*)- or (*S*)-2,2-diphenylhydroxymethylpyrrolidine (DPP, **3**) with borane–THF (BH_3–THF) or borane-dimethyl sulfide (BMS), trimethylboroxine, *n*-butylboronic acid, 4-*t*-butylphenylboronic acid, and trimethyl (or isopropyl) borate, respectively (Scheme 1).[2,6] Of these, **2a** and **2e** were usually used as themselves after in situ generation from **3** with borane and trimethyl or triisopropyl borate, respectively. The reagent **2b** is commercially available. The OAB-mediated borane reductions are generally performed by the

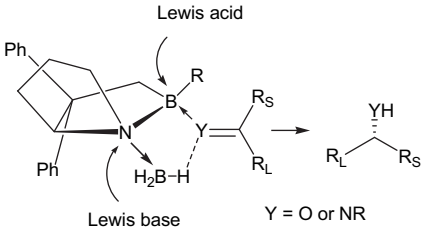
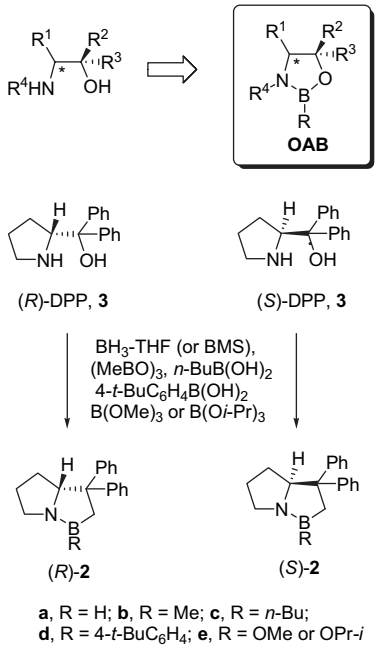


Figure 4.



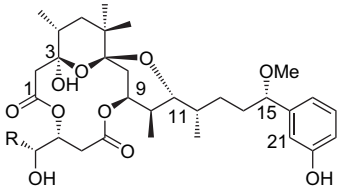
Scheme 1.

addition of prochiral ketones (or imines) to a mixture of OABs and borane carriers in an appropriate solvent at ambient temperature. As borane carriers, BH_3–THF, BMS, catecholborane (CB), and phenylamine–borane complexes, such as *N*,*N*-diethylaniline-borane (DIANB) and *N*-ethyl-*N*-isopropylaniline-borane (EIANB), are commonly used.

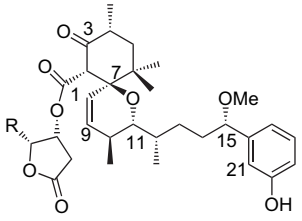
3. Applications

3.1. Synthesis of natural products and related compounds

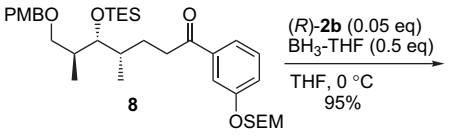
3.1.1. Lactones and macrolides. Aplysiatoxin and oscillatoxin derivatives are a class of natural macrolide products, which are metabolites of some species of tropical marine blue-green algae. Of these, it has been known that the toxic debromoaplysiatoxin (**4**) and oscillatoxin A (**5**) are significant tumor promoters, whereas the nontoxic oscillatoxin D (**6**) and 30-methyloscillatoxin D (**7**) possess antileukemic activity. An approach to the synthesis of a chiral alcohol **9**, which comprises a selectively protected C_9–C_{21} portion of these compounds, using the catalytic CBS reduction has been investigated. The reduction of an aromatic ketone **8** using (*R*)-**2b** and BH_3–THF as catalyst and borane carrier, respectively, provided **9** in 95% yield as a single stereoisomer (Scheme 2).[7]



debromoaplysiatoxin, **4**: R = Me
oscillatoxin A, **5**: R = H



oscillatoxin D, **6**: R = H
30-methyloscillatoxin D, **7**: R = Me



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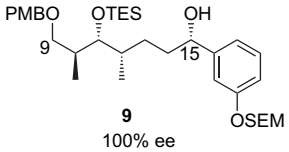
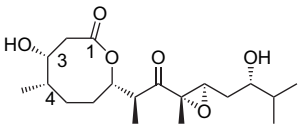


9
100% ee

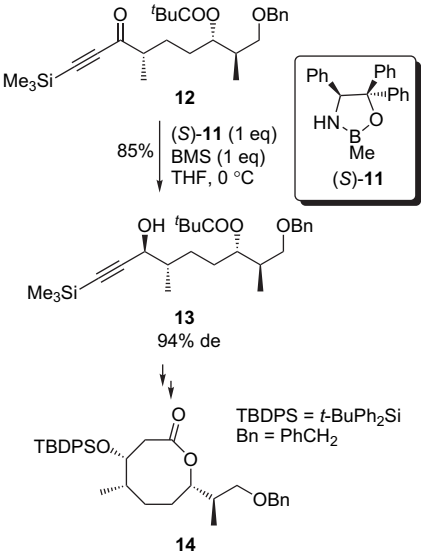
PMB = *p*-methoxybenzyl
TES = Et_3Si
SEM = $Me_3Si(CH_2)_2OCH_2$

Scheme 2.

A stoichiometric OAB-mediated borane reduction of an acetylenic ketone **12** using (*S*)-**11** derived from (*S*)-phenylglycine as asymmetric inducer was applied to the synthesis of C_1–C_4 fragment of the lactone ring of a marine actinomycete, octalactin A (**10**), a potent cytotoxin against some human tumor cell lines. The reduction provided the acetylenic alcohol **13** in 85% yield and 94% diastereomeric excess (de). The chiral alcohol **13** obtained has been used as a precursor for the synthesis of the octalactin lactone ring (**14**) (Scheme 3).[8]



octalactin A, **10**

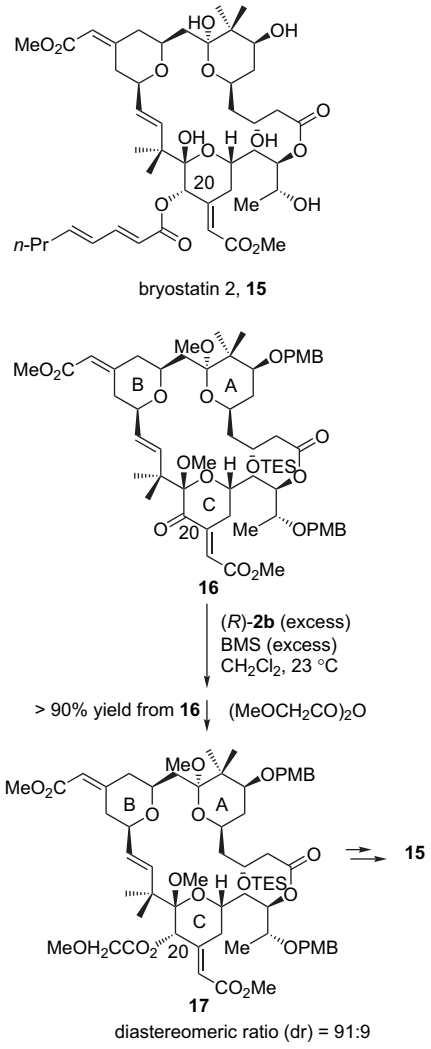


Scheme 3.

For the synthesis of a marine natural macrolide, bryostatin 2 (**15**), exhibiting potent antitumor activity, the stoichiometric CBS reduction of an exocyclic α,β-enone **16** to give the required allylic alcohol functionality at the C_{20} position of the C-ring (**17**) in a 91:9 selectivity has been utilized (Scheme 4).[9]

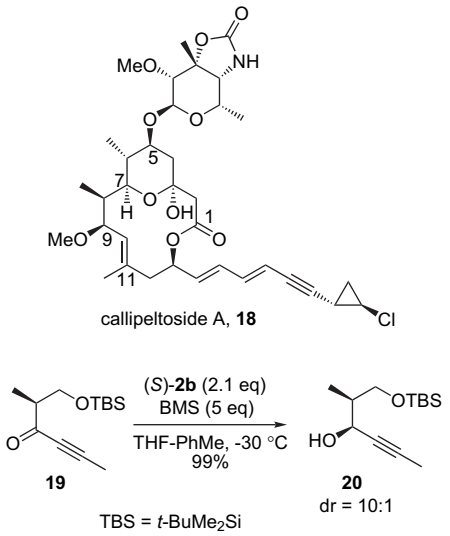
Similarly, the stoichiometric CBS reduction of the acetylenic ketone **19** using 2.1 equiv of (*S*)-**2b** and 5 equiv of BMS at −30 °C afforded the desired propargylic alcohol **20** with a 10:1 diastereoselectivity. This alcohol can be used as a starting material for the synthesis of C_7 to C_{11} fragment of callipeltoside A (**18**), a marine sponge possessing antitumor activity (Scheme 5).[10]

11-Desmethyllaulimalide (**22**), an analogue of the antitumor active laulimalide (**21**) isolated from a marine sponge, has been prepared by the CBS reduction of an acyclic enone **23**, followed by Sharpless epoxidation. The reduction afforded the required (20*S*)-allylic alcohol **24** with very high diastereoselectivity (diastereomeric ratio (dr) = 56.6:1). In contrast, the use of other reducing agents, such as lithium *tert*-butoxyaluminum hydride and L-Selectride, proved to be less effective (Scheme 6).[11]

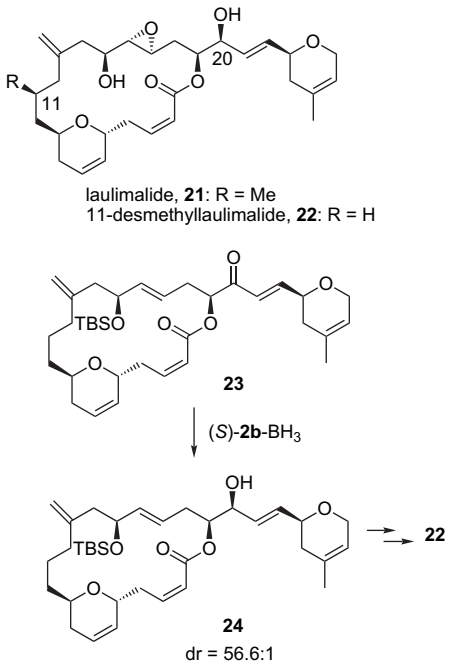


Scheme 4.

Starting from the CBS reduction of 2-methylcyclopentenone **26** using 1 equiv of (*S*)-**2b**·BH_3, a tricyclic spirobutenolide precursor **30**, which can serve as a common intermediate

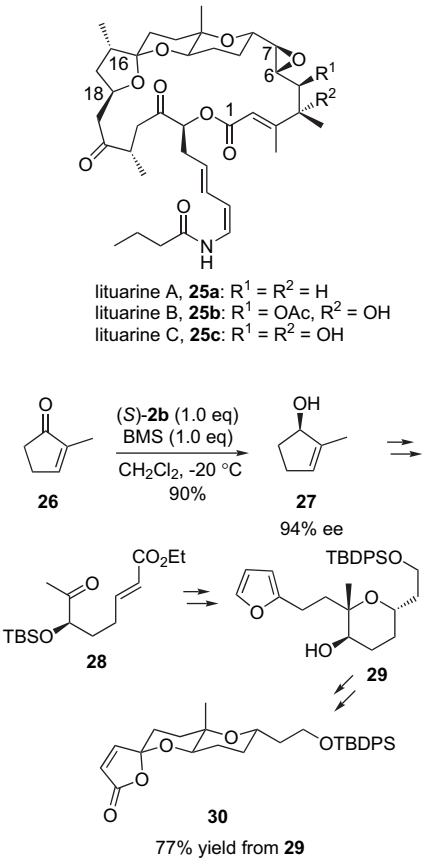


Scheme 5.



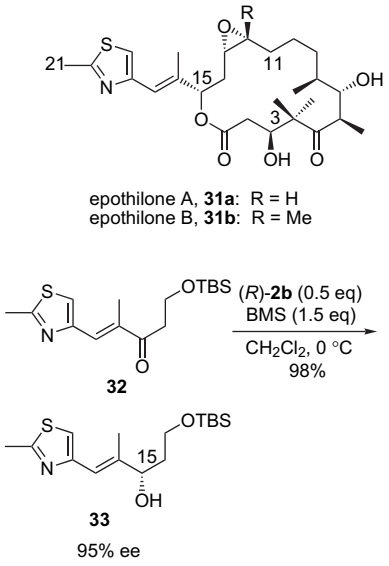
Scheme 6.

for the synthesis of C_7–C_{18} fragment of the antifungal marine natural products, lituarines A–C (**25a**–**c**), has been prepared. The reduction afforded a chiral enol **27** with 94% ee, which was converted into the desired precursor **30** via intermediates **28** and **29** (Scheme 7).[12]



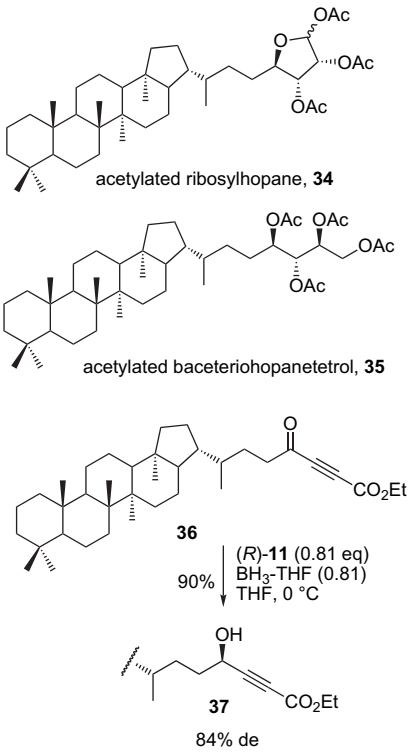
Scheme 7.

A (15*S*)-allylic alcohol **33**, which is the C_{13}–C_{21} fragment of epothilones A and B (**31a** and **31b**) isolated from myxobacteria exhibiting antimitotic activity against multidrug resistant cancer cell lines, has been prepared in 98% yield and 95% ee from the CBS reduction of the enone **32** using 0.5 equiv of (*R*)-**2b** and 1.5 equiv of BMS (Scheme 8).[13]



Scheme 8.

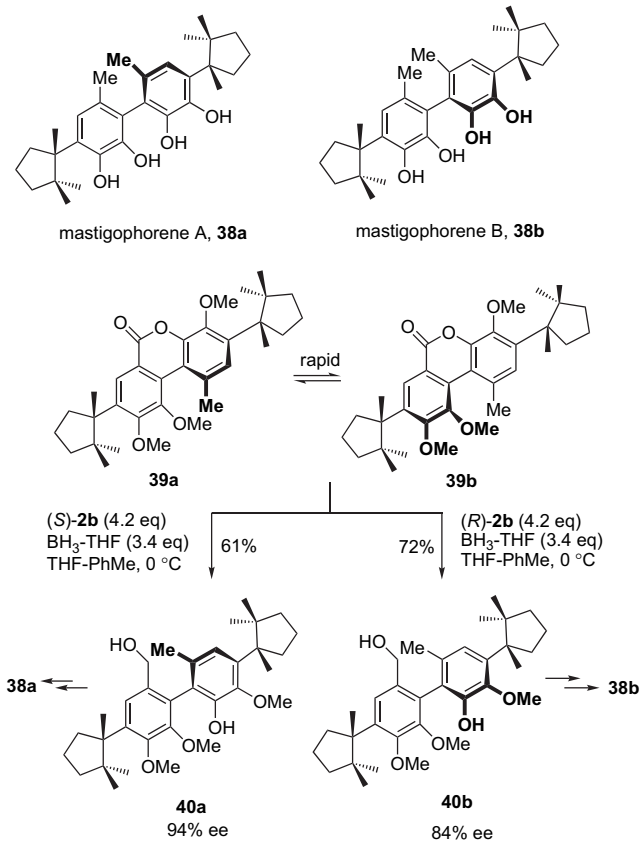
3.1.2. Terpenoids. Hopanoids, a class of triterpenoids, are widely distributed in bacteria and blue-green algae, where they are important cell membrane constituents. Acetylated ribosylhopane **34** and acetylated bacteriohopanetetrol **35** are the putative biosynthetic precursors of bacterial triterpenoids. An OAB-mediated reduction of an acetylenic ketone **36** using (*R*)-**11** as asymmetric inducer has been applied to the synthesis of the desired propargylic alcohol **37** with 90% yield and 84% de, which can serve as a precursor for the synthesis of these hopanoid compounds (Scheme 9).[14]



Scheme 9.

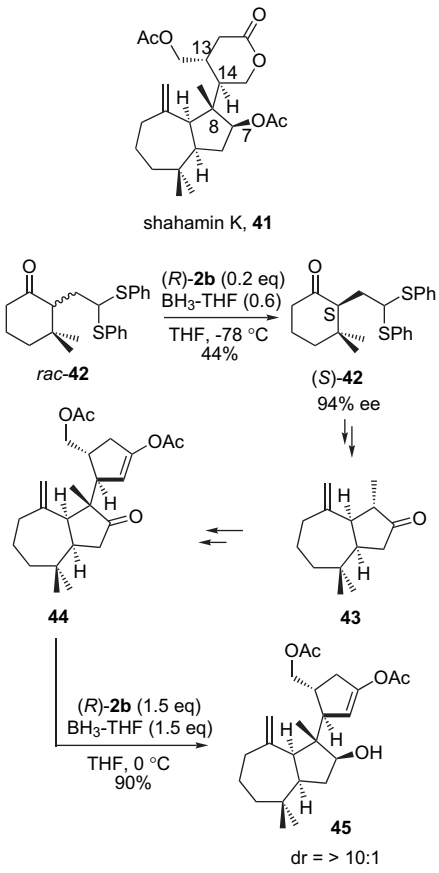
A dynamic kinetic resolution of two rapidly interconverting atropodiastereomeric lactones, **39a** and **39b**, by CBS reduction was utilized for the synthesis of the natural products, mastigophorene A and B (**38a** and **38b**), which are regarded as therapeutic agents for degenerative diseases of the central nervous system such as Parkinson's disease and Alzheimer's disease. These compounds have a C_2-symmetric structure involving elements of both axial and centro chirality. When the reduction of an equilibrium mixture of **39a** and **39b** using a large excess of BH_3–THF in the presence of each of (*S*)-**2b** and (*R*)-**2b** was carried out at 0 °C, the reactions provided **40a** in 61% yield and 94% ee and **40b** in 72% yield and 84% ee, respectively. The chiral products obtained have been converted into **38a** and **38b** by a reductive benzylic deoxygenation and demethylation (Scheme 10).[15]

Shahamin K (**41**) is a marine natural product having a *cis*-hydroazulene unit. This compound has been synthesized starting from an enol acetate alcohol **45**. The CBS reductions were applied to the synthesis of the chiral hydroazulenone **43** and the alcohol **45**, which were used as key intermediates for the synthesis of **41**. A chiral ketone (*S*)-**42** obtained from the kinetic resolution of a racemic ketone *rac*-**42** with (*R*)-**2b**-catalyzed reduction was converted into **43** and a chiral keto enol acetate **44** through multiconversion steps. Finally, a stoichiometric CBS reduction of **44** with (*R*)-**2b**



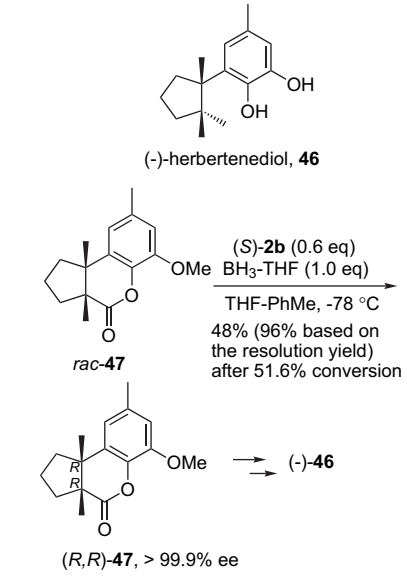
Scheme 10.

gave the desired alcohol **45** in 90% yield with high diastereoselectivity (dr >10:1) (Scheme 11).[16]

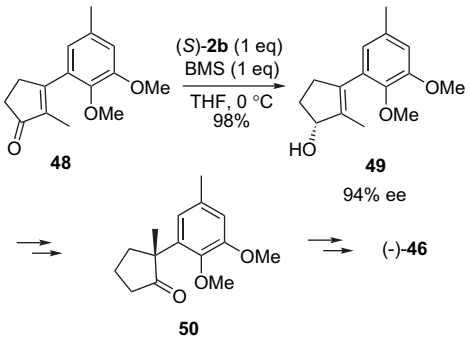


Scheme 11.

(−)-Herbetenediol (**46**) is a sesquiterpene isolated from liverwort exhibiting anti-lipid peroxidation activity. For the synthesis of this compound, two different methods using CBS reduction have been reported. Scheme 12 shows the synthesis of **46** starting from a chiral lactone, (*R*,*R*)-**47**, obtained from the enantiomer-differentiating reduction of *rac*-**47** by CBS reduction under a kinetic resolution condition.[15] The other method begins with a stoichiometric CBS reduction of α,β-enone **48** to give a chiral enol **49** in 94% ee. The enol **49** obtained has been converted into **46** via a chiral cyclopentanone **50** (Scheme 13).[17]

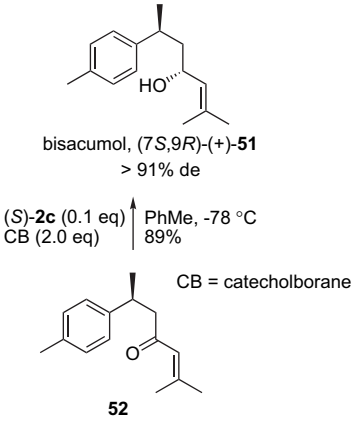


Scheme 12.



Scheme 13.

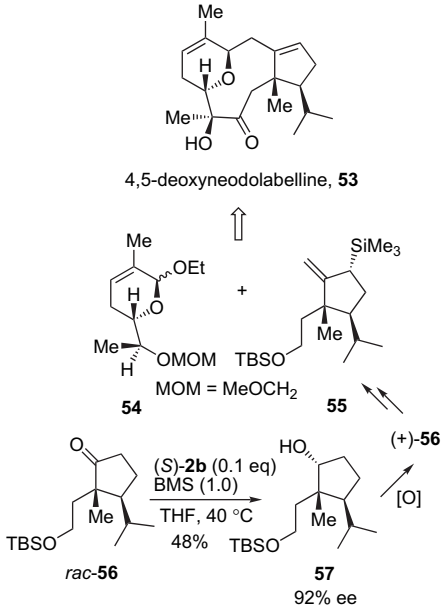
Scheme 14 outlines the (*S*)-**2c**-catalyzed CBS reduction of α,β-enone **52** to provide an antitumor aromatic bisabolane sesquiterpene, (+)-bisacumol **51**, in 89% yield and >91% de.[18]



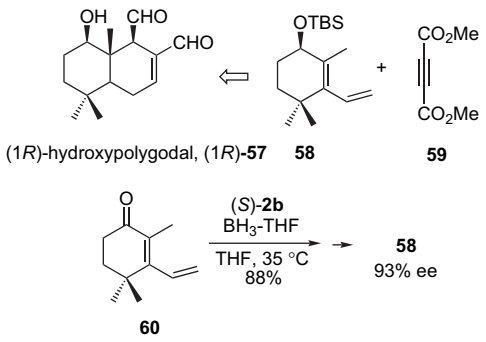
Scheme 14.

4,5-Deoxyneodolabelline (**53**) isolated from a marine bicyclic diterpene is an analogue of dolabellanes showing cytotoxic, antibacterial, and antiviral activity. This compound has been prepared by a reductive coupling of nonracemic dihydropyran **54** and cyclopentenylsilane **55**. Of these intermediates, **55** was prepared via a multistep route, starting from a chiral ketone (+)-**56** obtained from the catalytic CBS reduction of *rac*-**56**, followed by a chromatographic separation of the desired alcohol **57** and subsequent oxidation (Scheme 15).[19]

(1*R*)-Hydroxypolygodal (**57**) is an analogue of polygodal isolated from terrestrial and marine sources possessing a pungent sensation on the human tongue. This compound has been synthesized by Diels–Alder reaction of a chiral protected hydroxydiene derivative **58** and dimethyl acetylenedicarboxylate **59**. Of these, **58** has been prepared in 88% yield and 93% ee by CBS reduction of dienone **60** using (*S*)-**2b** (Scheme 16).[20]



Scheme 15.

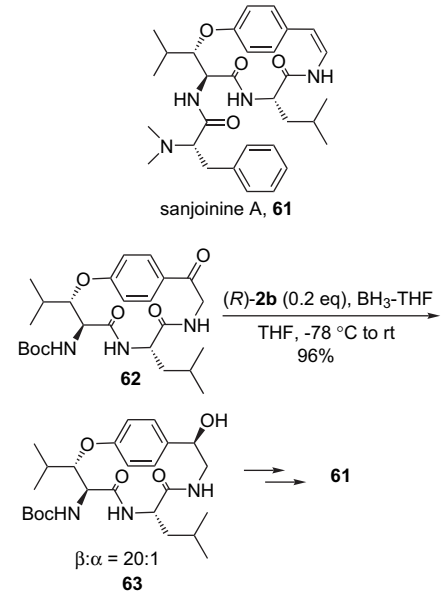


Scheme 16.

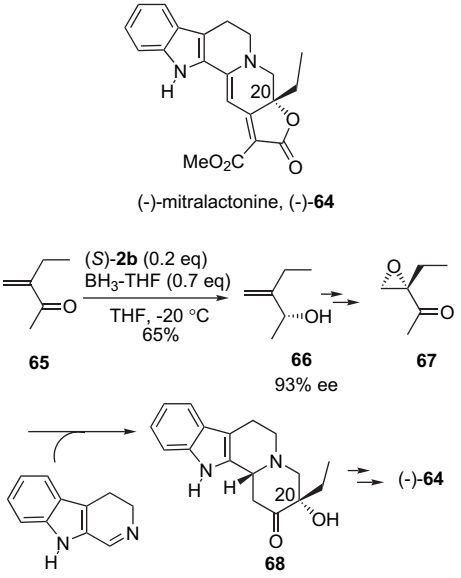
3.1.3. Alkaloids. Sanjoinine A (frangufoline, **61**) is a natural alkaloid used as a sedative herbal medicine in the Orient. A key intermediate, β-hydroxy isomer **63** required for constructing the *cis*-enamine of **61**, has been prepared in 96% yield and 20:1 (β:α) stereoselectivity by a (*R*)-**2b**-catalyzed borane reduction of amido ketone **62** (Scheme 17).[21]

(−)-Mitralactonine (**64**) is a monoterpenoid indole alkaloid, which is known to exhibit narcotic-like actions, such as opioid agonistic properties. The catalytic CBS reduction of α,β-enone **65** provided a chiral allylic alcohol **66** in 65% yield and 93% ee. This alcohol was subjected to Sharpless epoxidation under the kinetic resolution conditions and subsequent oxidation to give a chiral α-epoxy ketone **67** with >99% ee, possessing the desired configuration at the C_{20} position of **64**. The stereoselective condensation of **67** with dihydro-β-carboline gave a chiral hydroxyl ketone **68**. The target compound **64** has been prepared in 46% yield from **67** by Knoevenagel condensation of **68** with dimethyl malonate, followed by elimination (Scheme 18).[22]

The atropoenantioselective ring cleavage reaction of an equilibrium mixture of racemic lactones, **70a** and **70b**, using a stoichiometric CBS reduction in the presence of each of



Scheme 17.

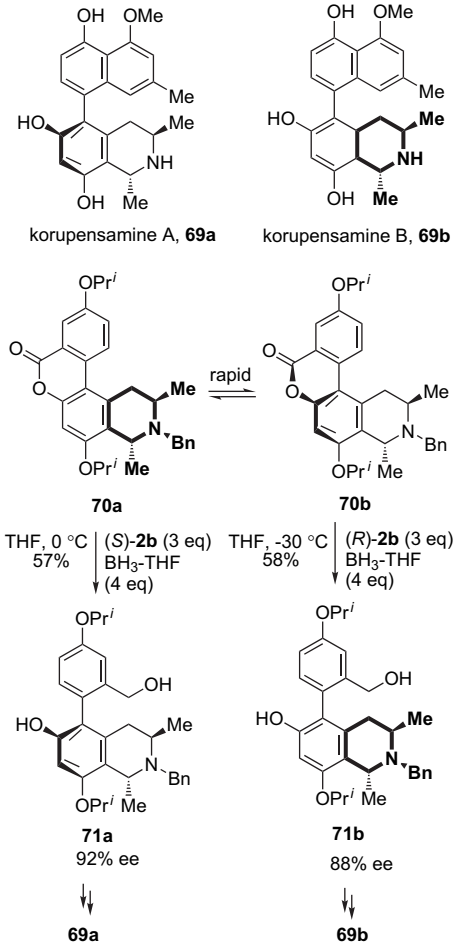


Scheme 18.

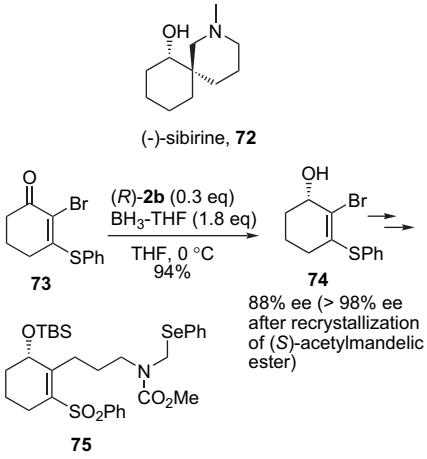
(*S*)- and (*R*)-**2b**, provided **71a** and **71b** with 92 and 88% ee, respectively. From these latter products, the synthesis of dimeric naphthylisoquinoline alkaloids, korupensamines A and B (**69a** and **69b**), which exhibit good antimalarial activities in vitro and in vivo, has been reported (Scheme 19).[23]

The catalytic CBS reduction of α-bromo α,β-enone **73** gave a chiral 2-bromoallylic alcohol **74** in 94% yield and 88% ee. Starting from this alcohol, a natural spiropiperidine alkaloid, (−)-sibirine (**72**), has been prepared via the precursor **75** (Scheme 20).[24]

Compound (+)-*trans*-195A (**76**) is an alkaloid having decahydroquinoline structure isolated from amphibian skin, which shows noncompetitive blocking activity of nicotinic receptor channels and an inhibitory effect against sodium and potassium transport. This compound has been prepared

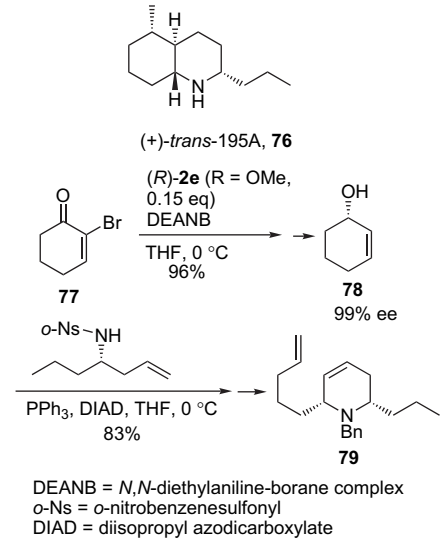


Scheme 19.



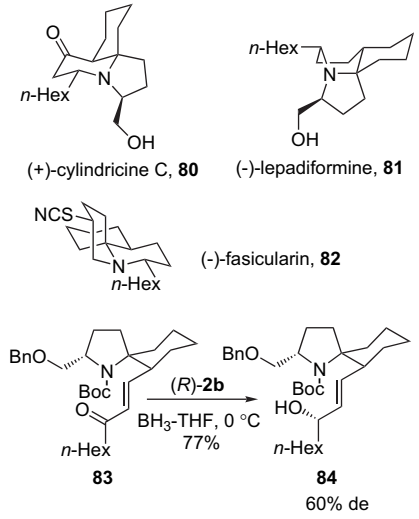
Scheme 20.

by a stereoselective ring-closure reaction of **79**, prepared from (*S*)-cyclohex-2-ol **78**. CBS reduction of 2-bromocyclohex-2-one **77** using (*R*)-**2e** (R=OMe) as catalyst, followed by debromination, provided (*S*)-**78** in 96% yield and 99% ee (Scheme 21).[25]



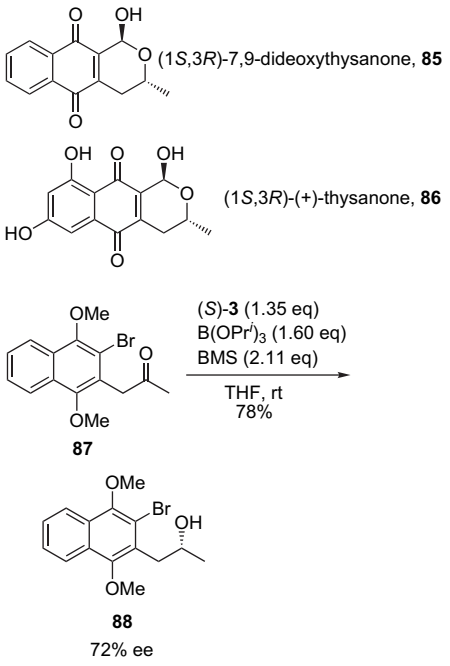
Scheme 21.

Very recently, a total synthesis of the tricyclic marine alkaloids (+)-cylindricine C (**80**), (−)-lepadiformine (**81**), and (−)-fasicularin (**82**), using CBS reduction as a key step have been reported. These compounds were prepared from an intramolecular conjugate azaspirocyclization of a chiral common intermediate **84**, obtained from the CBS reduction of an α,β-enone **83** (Scheme 22).[26]



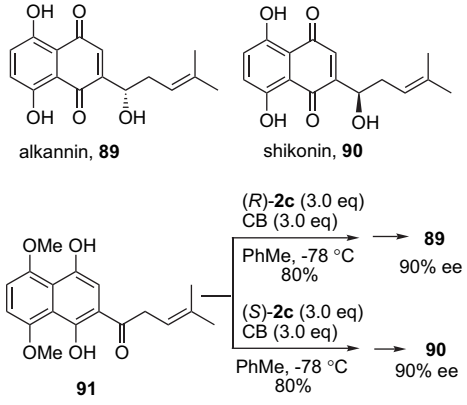
Scheme 22.

3.1.4. Phenolics and propargylic alcohols. (1*S*,3*R*)-7,9-Dideoxythysanone (**85**) is an analogue of (1*S*,3*R*)-(+)-thysanone (**86**), which is a fungal benzoisochromanquinone with potent human rhinovirus 3C protease inhibitory activity, and can be used as a chemotherapeutic agent for the control of common cold. The stoichiometric CBS reduction of bromoketone **87**, using BMS in the presence of an excess of triisopropyl borate and (*S*)-**3**, provided a chiral bromoalcohol **88** in 78% yield and 72% ee, which can serve as a key intermediate for the synthesis of **85** (Scheme 23).[27]



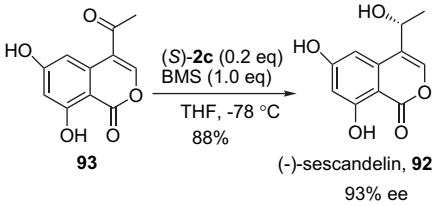
Scheme 23.

Starting from a stoichiometric CBS reduction of **91** with (*R*)-**2c** and (*S*)-**2c**, the natural products, alkannin (**89**) and shikonin (**90**), in 90% ee have been prepared (Scheme 24).[28] These compounds exhibit a very wide spectrum of biological activities including anti-inflammatory, antibacterial, antifungal, anticancer, analgesic, antipyretic, antithrombotic, immunostimulatory, angiostatic, and wound-healing properties.



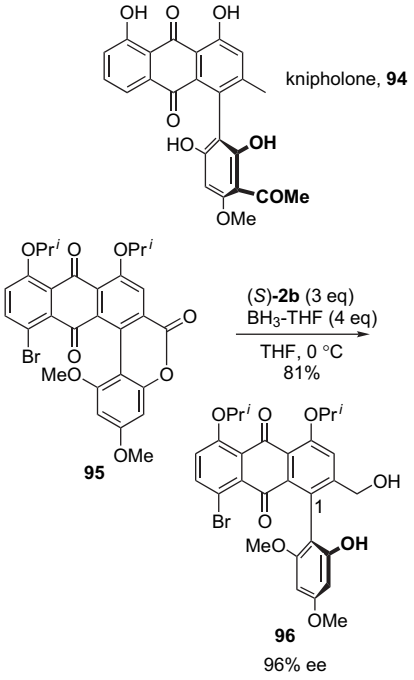
Scheme 24.

CBS reduction of acetylisocoumarin **93**, using (*S*)-**2c** as catalyst, afforded (−)-sescandelin (**92**), a fungal natural product having anti-angiogenic activities, in 88% yield and 93% ee (Scheme 25).[29]



Scheme 25.

Knipholone (**94**) is a natural phenylanthraquinone possessing high antiplasmodial activity in vitro against *Plasmodium falciparum*, the carrier of the most lethal malaria tropica. The enantioselective ring cleavage of a racemic biaryl lactone **95** using stoichiometric CBS reduction gave the desired alcohol **96** with high optical purity, which can serve as a key intermediate for the synthesis of **94** (Scheme 26).[30]

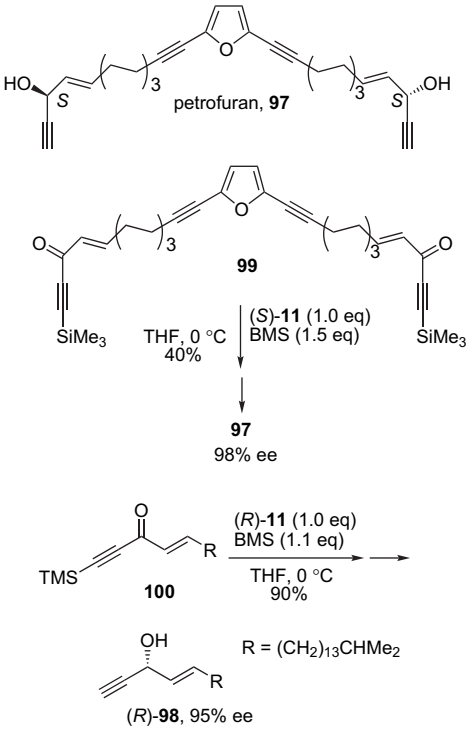


Scheme 26.

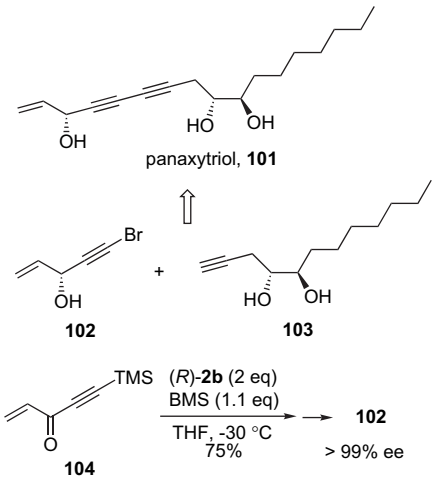
Some long-chain chiral propargylic alcohols, such as petrofuran (**97**)[31a] and (*R*)-**98**,[31b] isolated from marine sponges, exhibit antimicrobial, cytotoxic, immunosuppressive, and antitumor properties. A stoichiometric OAB-mediated reduction of enynones, **99** and **100**, using (*S*)- and (*R*)-**11** as asymmetric inducers, respectively, followed by desilylation, provided **97** in 98% ee and (*R*)-**98** in 95% ee (Scheme 27).

Panaxytriol **101**, isolated from red ginseng widely used as a folk medicine in Oriental regions, is known to have inhibitory activity against a human breast carcinoma cell line and to enhance the cytotoxicity of mitomycin C against human gastric adenocarcinoma cell lines. This compound has been synthesized by a cross-coupling reaction of two chiral alcohols **102** and **103**. Among these, the chiral alcohol **102** with >99% ee has been prepared by a stoichiometric CBS reduction of enynone **104**, followed by bromination (Scheme 28).[32]

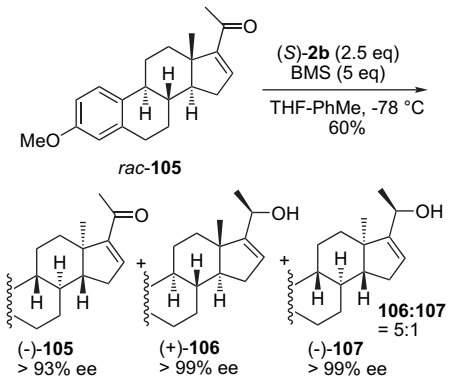
3.1.5. Steroids, lignans, and pheromones. A stoichiometric CBS reduction has been successfully applied to a kinetic resolution of a racemic steroidal ketone *rac*-**105** to give (−)-**105** with high enantiopurity. When the reduction of *rac*-**105** with BMS in the presence of (*S*)-**2b** at −78 °C was quenched at approximately 60% completion, (−)-**105** was isolated in 40% yield with >93% ee, along with a 5:1 mixture of diastereomeric alcohols (+)-**106** and (−)-**107**, each with >99% ee (Scheme 29).[33]



Scheme 27.

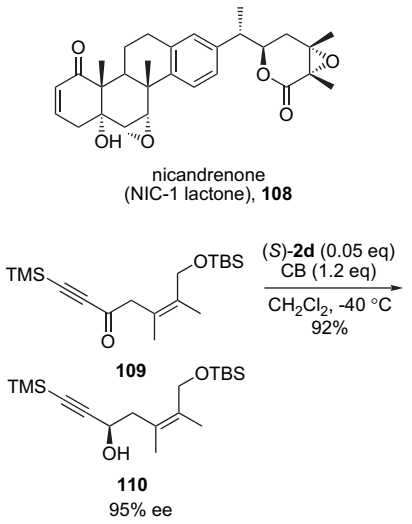


Scheme 28.



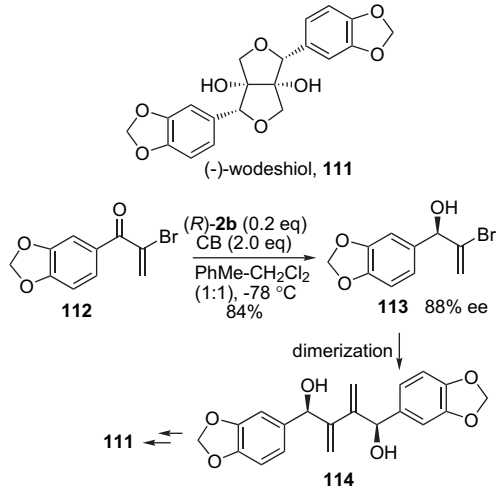
Scheme 29.

Nicandrenone (NIC-1 lactone, **108**) is a steroid-derived natural product, which exhibits insect repellent and antifeedant properties. CBS reduction of acetylenic ketone **109**, using (*S*)-**2d** as catalyst, provided the desired chiral alcohol **110** in 95% ee, which can be utilized as a precursor for the synthesis of the lactone ring component in the side chain (Scheme 30).[34]



Scheme 30.

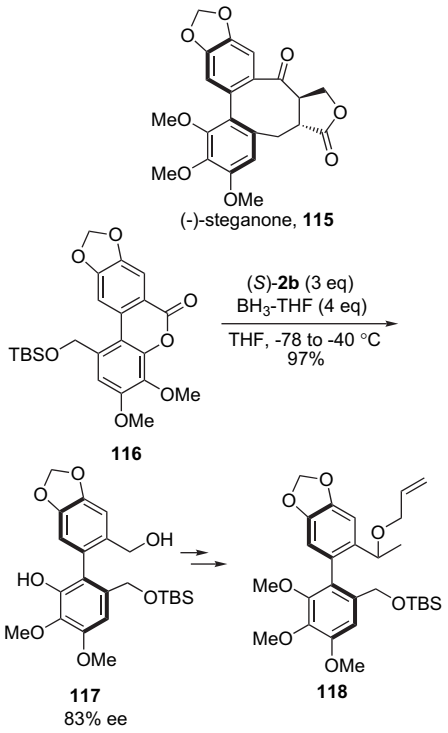
The catalytic CBS reduction of α,β-enone **112**, using (*R*)-**2b** and CB as catalyst and borane carrier, respectively, provided a chiral allylic alcohol **113** in 84% yield and 88% ee. Using **114** obtained from dimerization of **113** as a key intermediate, a natural lignan-containing furan ring, (−)-wodeshiol (**111**), has been prepared (Scheme 31).[35]



Scheme 31.

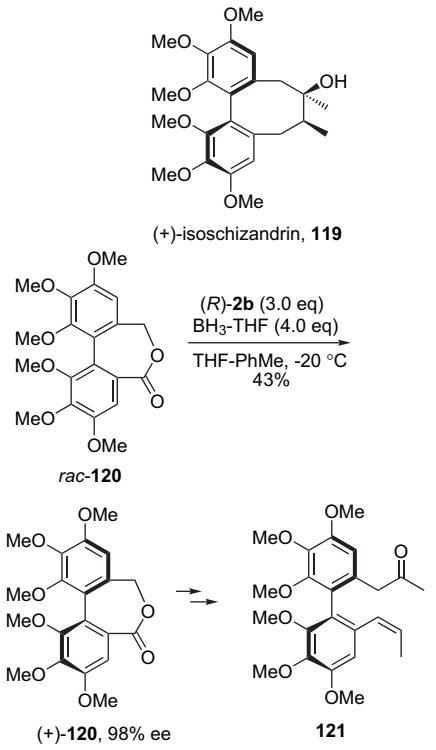
(−)-Steganone (**115**) is a natural lignan bearing an asymmetrical 2,2′-disubstituted biphenyl moiety with an axial chirality. This compound is known to have antileukemic activity. The stoichiometric CBS reduction was utilized for enantioselective construction of the biaryl part of this compound.

The reductive asymmetric lactone ring-opening reaction of racemic lactone **116** based on dynamic optical resolution afforded a chiral biaryl alcohol **117** in 97% yield and 83% ee. From this alcohol, a chiral homoallyl ether **118**, which can be used as a key intermediate for the synthesis of **115**, has been prepared (Scheme 32).[36]



Scheme 32.

A kinetic resolution of a racemic biaryl lactone *rac*-**120**, using the stoichiometric CBS reduction using (*R*)-**2b**, provided a chiral lactone (+)-**120** in 43% yield and 98% ee. Using a chiral keto (*Z*)-olefin **121**, obtained from (+)-**120** as a key intermediate, a dibenzocyclooctadiene lignan, (+)-isoschizandrin (**119**), displaying antirheumatic, antihepatotoxic, and antiulcer activities, has been prepared (Scheme 33).[37]

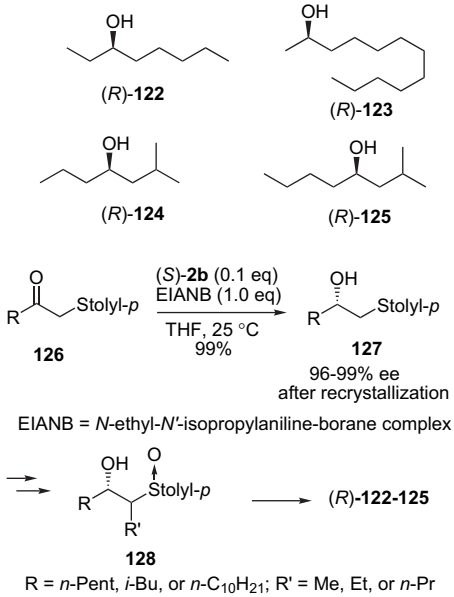


Scheme 33.

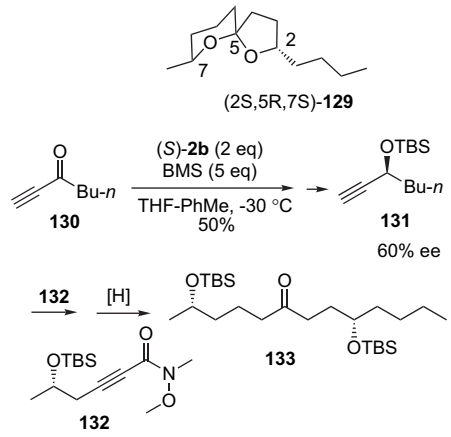
Chiral aliphatic alcohols (*R*)-**122**–**125** are pheromones found in various classes of insects, showing a variety of biological activities. As shown in Scheme 34, these compounds have been prepared by using chiral β-hydroxy sulfides **127** as key intermediates. The catalytic CBS reduction of β-keto sulfides **126** afforded chiral β-hydroxy sulfides **127**, which were converted into (*R*)-**122**–**125** by desulfurization of alkylated sulfoxides **128** obtained from selective oxidation of **126**, followed by alkylation.[38] Although the reduction of **126** initially provided **127** with 74–71% ee, their optical purities were improved to 96–99% ee by recrystallization of their nitrobenzoates.

Scheme 35 illustrates the synthesis of an optically active spiroacetal insect pheromone **129** via intramolecular ketal formation of chiral dihydroxy ketone **133**, prepared from a cross-coupling reaction of two chiral propargylic alcohols **131** and **132**, followed by catalytic hydrogenation. Of these alcohols, **131** was obtained from the stoichiometric CBS reduction of acetylenic ketone **130** (Scheme 35).[39]

3.1.6. Prostanoids, sphinganines, and biotins. The catalytic CBS reduction was applied to the synthesis of a chiral iodoallylic alcohol **136**, which is a precursor for the synthesis of an ω-side chain of prostaglandin E_1 (**134**). The reduction of γ-iodovinyl ketone **135** with CB in the presence of

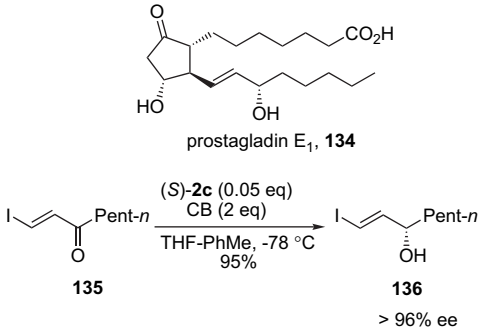


Scheme 34.



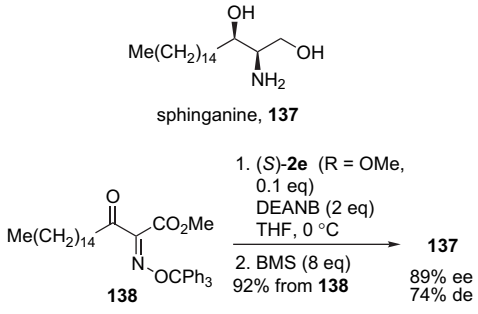
Scheme 35.

0.05 equiv of (*S*)-**2c** at −78 °C provided **136** in 95% yield and >96% ee (Scheme 36).[40]



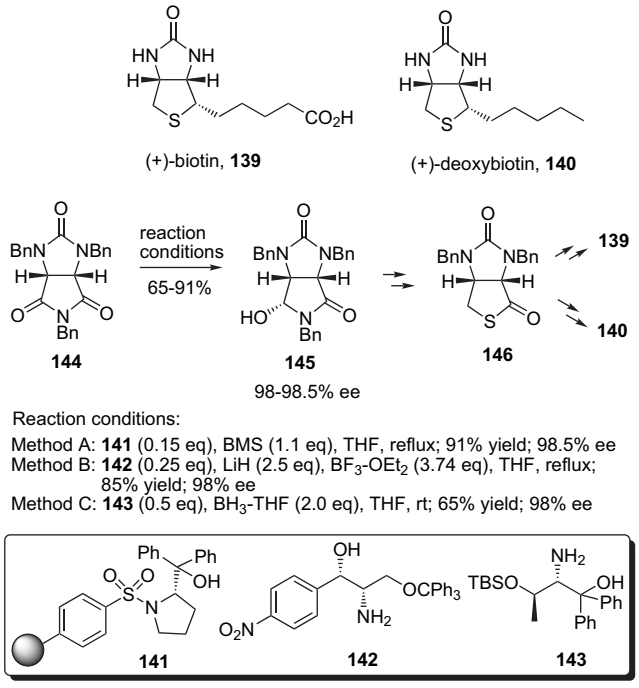
Scheme 36.

Sphinganine (**137**) is an intermediate in the biosynthesis of sphingolipids, which play important roles in cell regulation and signal transduction. The synthesis of this compound was achieved by the catalytic CBS reduction of an α-imino ketone derivative **138** using 2 equiv of DEANB in the presence of 0.1 equiv of (*S*)-**2e** (R=OMe) in situ generated from (*S*)-**3** with $B(OMe)_3$, followed by further reduction with an excess of BMS (Scheme 37).[41]



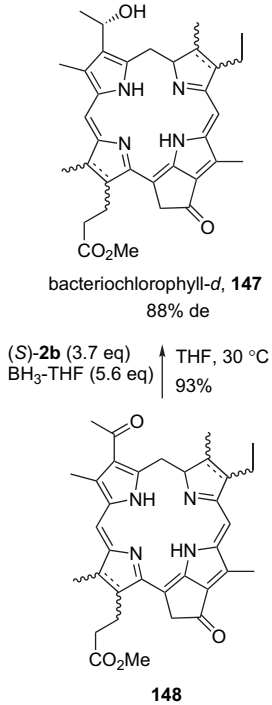
Scheme 37.

(+)-Biotin (**139**) is a water-soluble vitamin showing a significant biological activity for human nutrition and animal health. On the other hand (+)-deoxybiotin **140** is important as a precursor of **139**. The catalytic borane reduction of *meso*-imide **144** using OABs derived from each of **141**,[42a] **142**,[42b] and **143**[42c] as asymmetric inducers provided a chiral hydroxylactam **145** with 98–98.5% ee, which can be then converted into the chiral thiolactone **146**, a common intermediate for the synthesis of **139** and **140** (Scheme 38).[42]



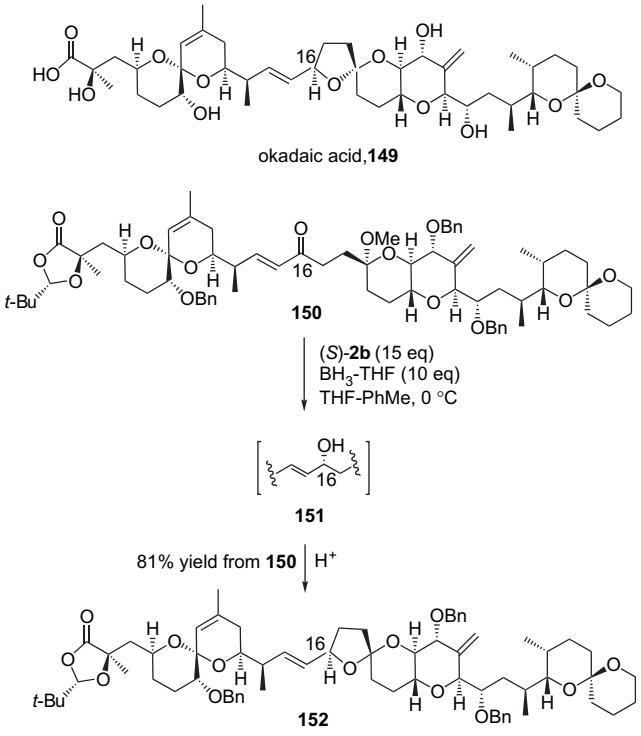
Scheme 38.

3.1.7. Other natural products. The stoichiometric CBS reduction of the corresponding ketone **148** using a large excess of (*S*)-**2b** and borane provided chiral bacteriochlorophyll-*d* (**147**), which is a natural pigment in light-harvesting antennae of green photosynthetic bacteria (Scheme 39).[43]



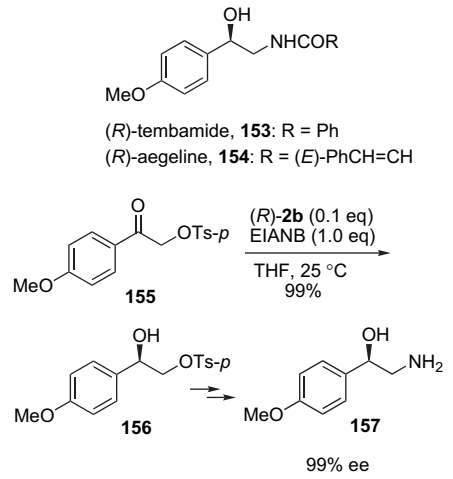
Scheme 39.

Okadaic acid (**149**) is a marine natural product with a rich modern history and is known as a potential anticancer agent. CBS reduction was applied to the introduction of (*R*)-configuration at C_{16} of this compound. The borane reduction of (*E*)-enone **150** in the presence of a large excess of (*S*)-**2b** provided the corresponding enol **151**. This alcohol was converted into the spiroketal **152** by spiroketalization and then **149** was obtained through hydrolysis and debenzylation of **152** (Scheme 40).[44]

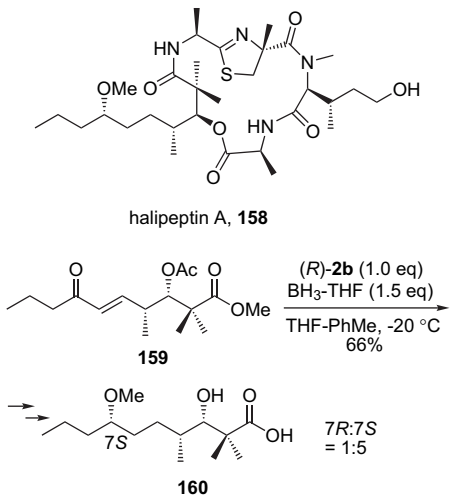


Scheme 40.

The catalytic CBS reduction was successfully utilized for the synthesis of (*R*)-tembamide (**153**) and (*R*)-aegeline (**154**), naturally occurring bioactive substances, which are used in traditional Indian medicine and have been shown to have hypoglycemic activity. The catalytic CBS reduction of α-*p*-tosyloxyketone **155** using (*R*)-**2b** as catalyst provided the chiral 1,2-diol monotosylate **156** with high enantiomeric purity. The target compounds, **153** and **154**, have been prepared from acylation of a chiral amino alcohol **157**, obtained by the reaction of **156** with sodium azide, followed by a catalytic hydrogenation (Scheme 41).[45]



Scheme 41.

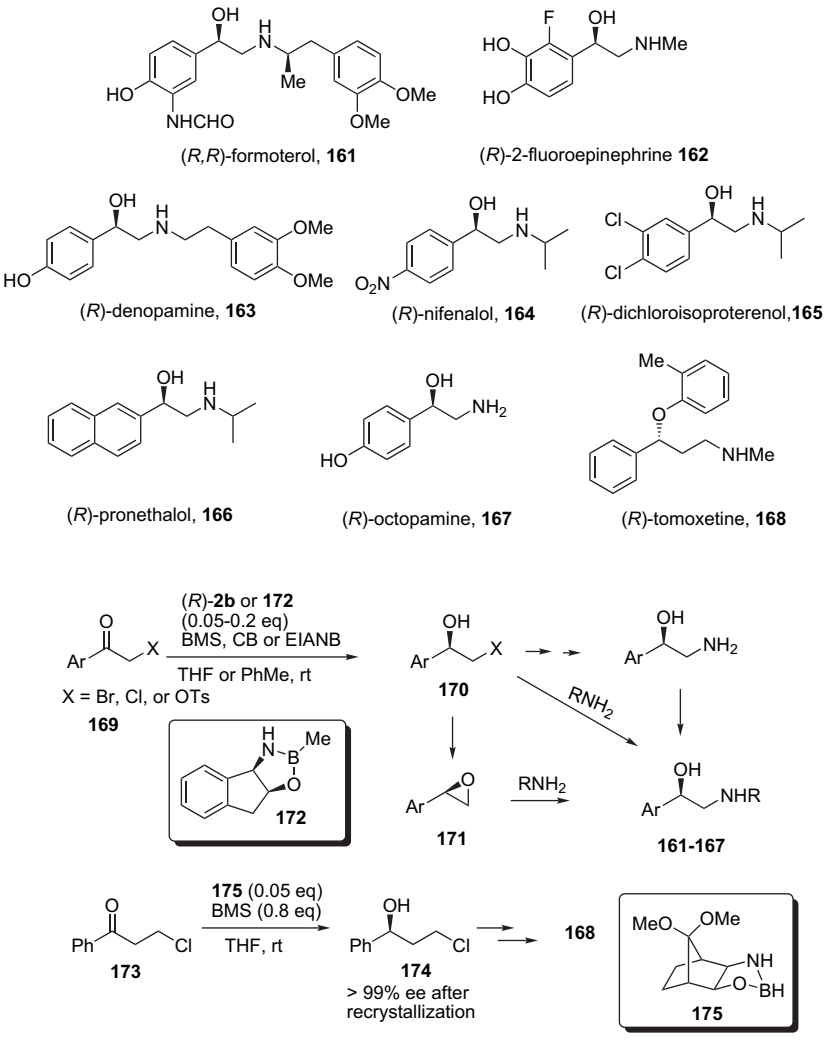


Scheme 42.

Halipeptin A (**158**) is a potent anti-inflammatory cyclic depsipeptide isolated from a marine sponge. The stoichiometric CBS reduction of enone **159** using (*R*)-**2b** as an asymmetric inducer, followed by a catalytic hydrogenation and methylation, was applied for the introduction of (*S*)-configuration at C_7 of a polyketide fragment **160** of this compound (Scheme 42).[46]

3.2. Synthesis of unnatural bioactive compounds

3.2.1. β-Adrenergic agonists. Pharmaceuticals **161–168** having a structural unit of 2-amino-1-arylethanol are of great importance as β-adrenergic agonists in the therapy of asthma, bronchitis, and congestive heart failure. In general, the (*R*)-isomers of these drugs show more potent pharmacological activity than their racemates. The OAB-catalyzed reductions have been effectively applied to the synthesis of these chiral drugs with high optical purity. Scheme 43 shows the synthesis of these drugs from 1,2-diol monotosylates (or halohydrins) **170** or chiral styrene oxides **171** obtained from the asymmetric reduction of α-*p*-tosyloxyketones (or α-halo ketones) **169**. (*R*,*R*)-Formoterol **161** was prepared by amination of the corresponding chiral epoxide obtained from OAB (**172**)-catalyzed reduction of the α-bromo ketone.[47a–c] (*R*)-2-Fluoroepinephrine (**162**),[48] (*R*)-denopamine (**163**), (*R*)-nifenalol (**164**), (*R*)-dichloroisoproterenol (**165**), and (*R*)-pronethalol (**166**) were prepared by direct amination of the corresponding chiral iodohydrin or 1,2-diol monotosylates **170** obtained from (*R*)-**2b**-catalyzed reduction of **169**.[49] (*R*)-Octopamine (**167**) was prepared by azidation of the corresponding 1,2-diol monotosylate, followed by catalytic hydrogenation.[45] The OAB (**175**)-catalyzed reduction of 3-chloropropiophenone **173** provided the (*S*)-chloro alcohol **174** with >99% ee after a single recrystallization, and this was subjected to Mitsunobu inversion with *o*-cresol, followed by amination, to give (*R*)-tomoxetine (**168**).[47d]



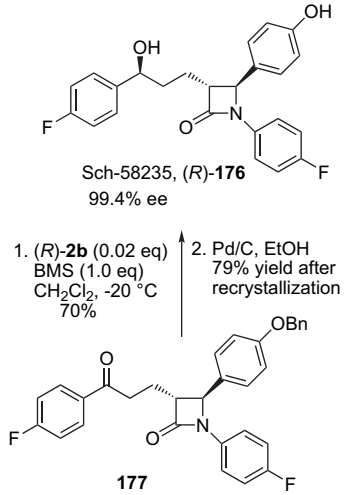
Scheme 43.

3.2.2. Other bioactive compounds. A chiral *trans*-azetidinone (Sch-58235, (*R*)-**176**) is known to be a potent cholesterol absorption inhibitor, which has shown efficacy in clinical trials for reducing cholesterol levels. CBS reduction of a ketone **177**, using (*R*)-**2b** as catalyst, followed by debenzylation, provided (*R*)-**176** in 56% yield and 99.4% ee (Scheme 44).[50]

Scheme 45 illustrates the catalytic CBS reduction of a diaryl ketone–chromium complex **179** to give the desired chiral alcohol **180** in 91% ee. The alcohol **180** can serve as a key intermediate for the synthesis of a selective opioid receptor agonist, (*S*)-diarylmethylamine derivative **178**, via **181**.[51]

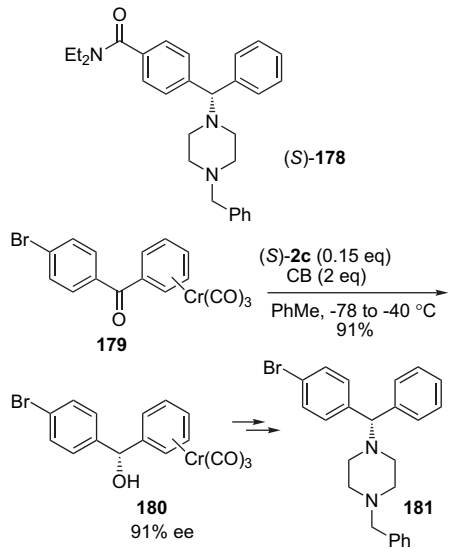
Using the catalytic CBS reduction of a heterocyclic ketone **183** to give a chiral alcohol **184** in 83% yield and 98% ee, the synthesis of an analgesic, (*R*)-cizolirtine **182**, has been reported (Scheme 46).[52]

An enantiopure spiro[(2*S*)-hydroxyindane-1,4′-piperidine] (*S*)-**185** is known as a component of growth hormone secretagogues and also as one of the key constituents of a tachykinin receptor antagonist. The (2*S*)-configuration has been shown to be an essential requirement for more potent binding

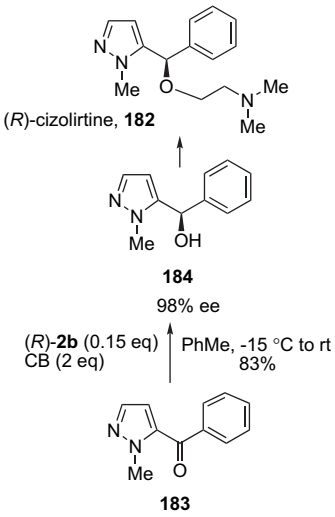


Scheme 44.

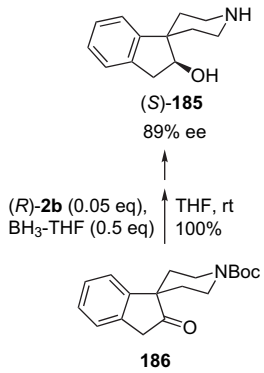
affinities of the tachykinin receptor. This compound has been prepared by the catalytic CBS reduction of a Boc-amino ketone **186** using (*R*)-**2b** as a catalyst (Scheme 47).[53]



Scheme 45.

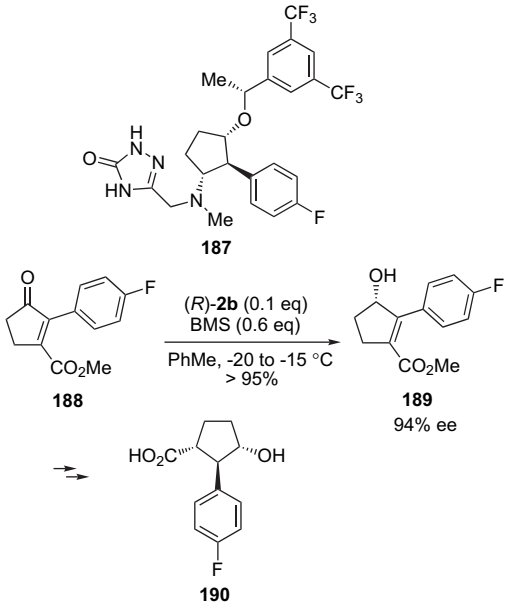


Scheme 46.



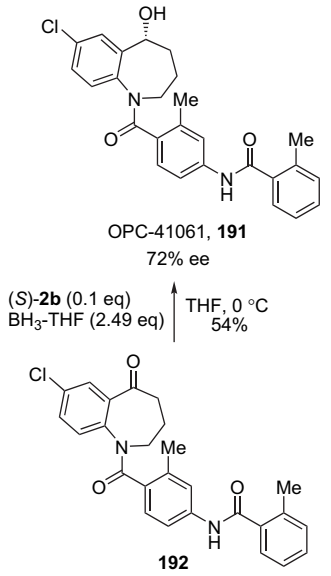
Scheme 47.

Using the catalytic CBS reduction of cyclopentenone derivative **188** as a key step to give the corresponding enol **189** with 94% ee, the synthesis of a cyclopentane-based nonpeptide antagonist (**187**) of human neurokinin-1 receptor, which is under development as an antidepressant has been reported. The chiral enol **189** obtained was used as a starting material for the synthesis of hydroxyacid intermediate **190** bearing the *trans*,*trans*-cyclopentyl structure, which served as the core synthetic intermediate for **187** (Scheme 48).[54]



Scheme 48.

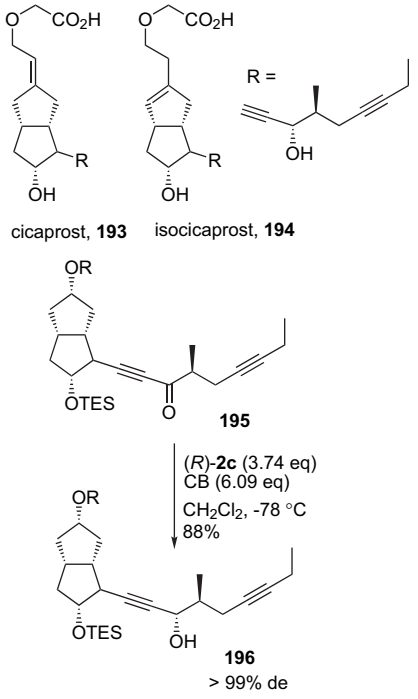
The racemic benzodiazepine derivative, 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-41061, **191**), is a new vasopressin V receptor antagonist under clinical trial as an aquaretic agent. The catalytic CBS reduction of ketone **192** using (*S*)-**2b** as catalyst provided **191** in 54% yield and 72% ee (Scheme 49).[55]



Scheme 49.

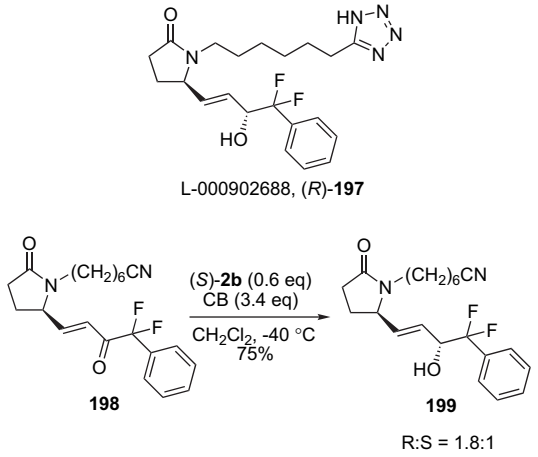
Similarly, the stoichiometric CBS reduction of a diynone **195** using (*R*)-**2c** as an asymmetric inducer was utilized for the synthesis of a key intermediate **196** for cicaprost

(**193**) and isocicaprost (**194**) (Scheme 50).[56] These compounds are known to be attractive drugs for the therapy of solid tumor metastasis and cardiovascular diseases.



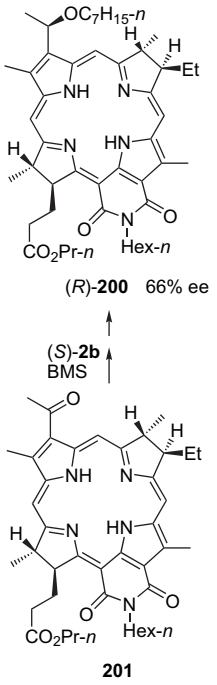
Scheme 50.

Compound L-000902688, **197** is a prostaglandin E_2 analogue, which is an orally bioavailable EP4 receptor agonist exhibiting bone-growth activity in animals. It is known that its (*R*)-isomer shows more potent biological activity than the corresponding (*S*)-isomer. CBS reduction of (*E*)-enone **198** using (*S*)-**2b** as catalyst was applied to the preparation of a key intermediate **199** for the synthesis of **197** (Scheme 51).[57]



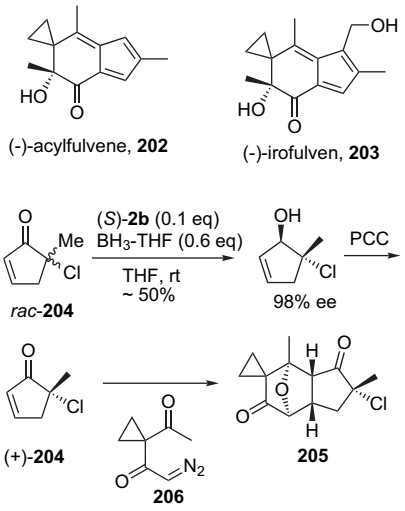
Scheme 51.

The stoichiometric CBS reduction of 3-acetylbacteriopurpurimide **201** using (*S*)-**2b** as an asymmetric inducer, followed by O-alkylation, afforded a bacteriopurpurimide derivative (*R*)-**200**, which is a photosensitizer exhibiting long-wavelength absorption near 800 nm, which can be used for photodynamic therapy in the treatment of various types of tumors. The efficacy of its (*R*)-isomer is greater than that of the (*S*)-isomer (Scheme 52).[58]



Scheme 52.

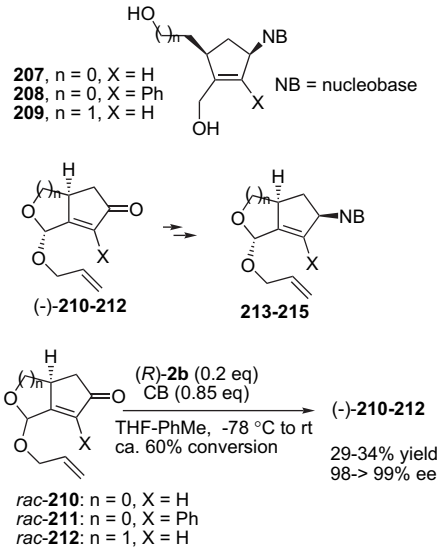
Scheme 53 outlines the synthesis of optically active (−)-acylfulvene (**202**) and (−)-irofulven (**203**) possessing antitumor activity using kinetic resolution of racemic cyclopentenone *rac*-**204** by employing CBS reduction as a key step. The reduction of *rac*-**204** using (*S*)-**2b** as catalyst, followed by oxidation, provided a chiral enone (+)-**204** in 98% ee.[59a] The chiral ketone obtained was reacted with diazoketone **206** to give a chiral diketone **205**, which could be used as a key intermediate for the synthesis of both **202** and **203**.[59b]



Scheme 53.

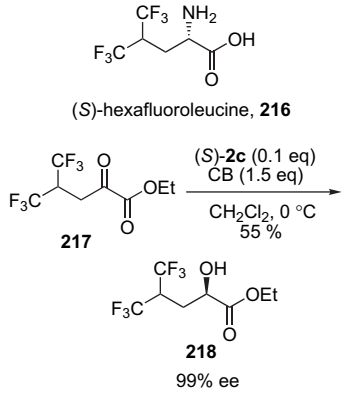
Carbocyclic nucleosides, where the furanose oxygen atom of the normal nucleoside is replaced by a methylene group,

play important roles as antiviral or antitumor drugs. The monoprotected, 2′,3′-unsaturated carbocyclic nucleoside analogues **207**–**209** were prepared via the precursors **213**–**215**, starting from chiral bicyclic enones (−)-**210**–**212**. The kinetic resolution of *rac*-**210**–**212** by CBS reduction using (*R*)-**2b** as catalyst provided (−)-**210**–**212** in 29–34% yields and 98–99% ee. The precursors **213**–**215** have been prepared by stereoselective reduction and subsequent introduction of various pyrimidine and purine nucleobases by means of Pd-catalyzed allylic substitution of (−)-**210**–**212** (Scheme 54).[60]



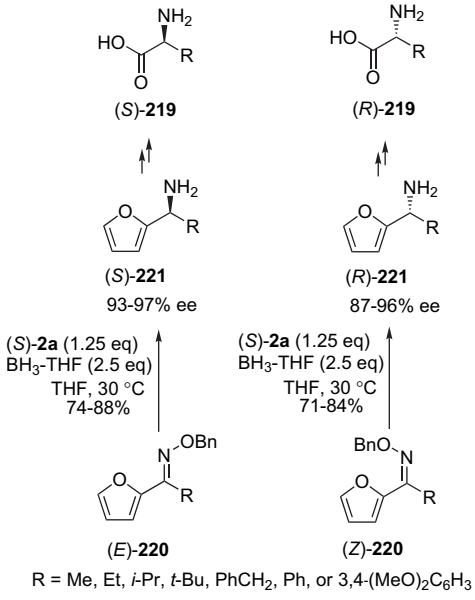
Scheme 54.

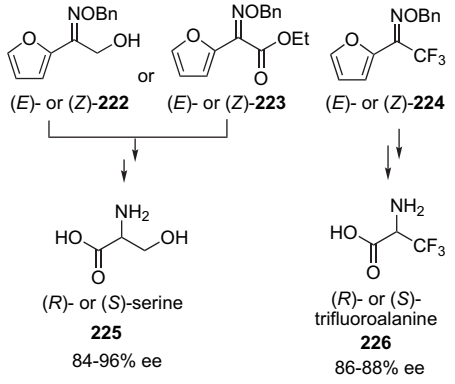
3.2.3. Amino acid derivatives. CBS reduction of an α-keto ester **217** using (*S*)-**2c** as catalyst provided a chiral hydroxyl ester **218** in 55% yield and 99% ee. This alcohol was converted into an *F*-containing α-amino acid, (*S*)-hexafluoroleucine **216**, by a S_N2 reaction with an amine (Scheme 55).[61]



Scheme 55.

Scheme 56 shows an asymmetric synthesis of α-amino acids **219** using a stoichiometric CBS reduction of (*E*)- or (*Z*)-2-furyl alkyl ketone oxime ethers **220**. The reduction using 1.25 equiv of (*S*)-**2a** provided optically active 2-furyl amines **221** in 87–97% ee, which could be converted into (*R*)- or (*S*)-**219** by oxidative cleavage of the furan ring. In this reduction, the absolute configurations of **221** formed depend upon the geometry of **220**: (*E*)-oximes led to the (*S*)-amines, while (*Z*)-oximes gave rise to the (*R*)-amines.[62a] Using the same methodology (*R*)- or (*S*)-serine **225** and trifluoroalanine **226** were obtained from the oxime ethers of furyl hydroxymethyl ketone **222** or α-imino ester **223**[62b] and furyl trifluoromethyl ketone oxime **224**,[62c] respectively.

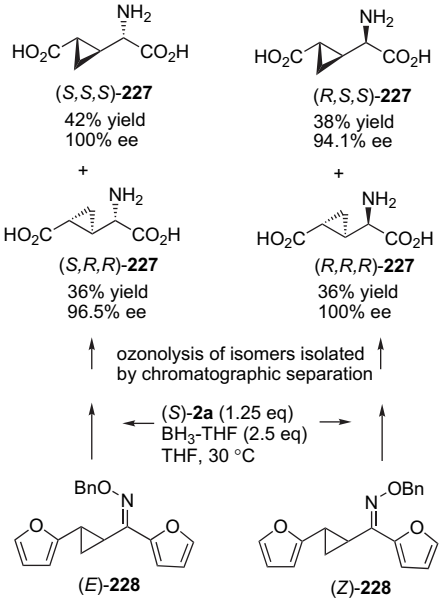




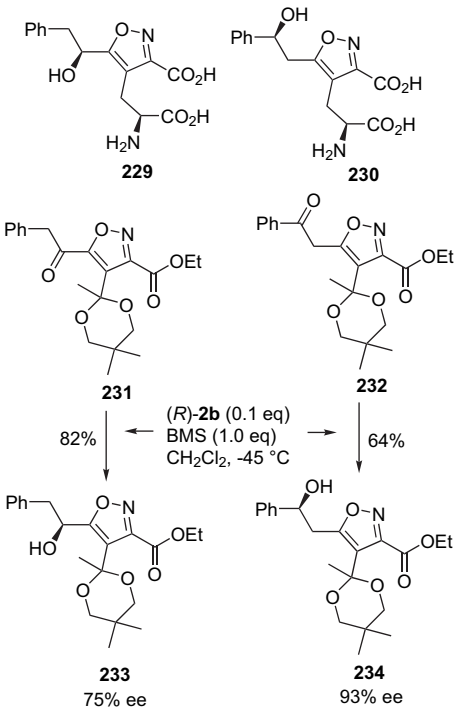
Scheme 56.

The same methodology has been applied to the synthesis of optically active α-amino acids **227** containing a cyclopropyl ring, which are conformationally constrained L-glutamate analogues, from the reduction of oxime ethers **228** (Scheme 57).[63]

L-Glutamate analogues having an isoxazole ring, **229** and **230**, play important roles as neurotransmitters in the human CNS. The catalytic CBS reduction of ketones **231** and **232** provided the corresponding alcohols, **233** with 75% ee and **234** with 93% ee, respectively. These alcohols obtained were converted into **229** and **230** through further steps including hydrolysis of ketal groups and asymmetric Strecker synthesis (Scheme 58).[64]

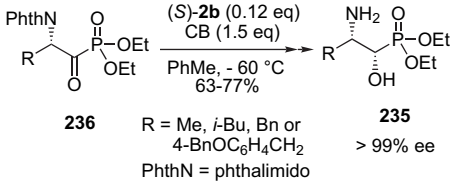


Scheme 57.



Scheme 58.

CBS reduction has been utilized for the synthesis of chiral 2-amino-1-alkylhydroxyphosphonic acids **235**, known as inhibitors of proteolytic enzymes such as renin and HIV protease. The diastereoselective reduction of chiral phthalimido keto phosphonates **236** using (*S*)-**2b** as the catalyst and CB as reductant, followed by deprotection of phthalimido group, provided **235** with >99% ee. In this reduction, however, the use of BMS instead of CB as the borane source gave diastereoisomeric mixtures of **235** (Scheme 59).[65]



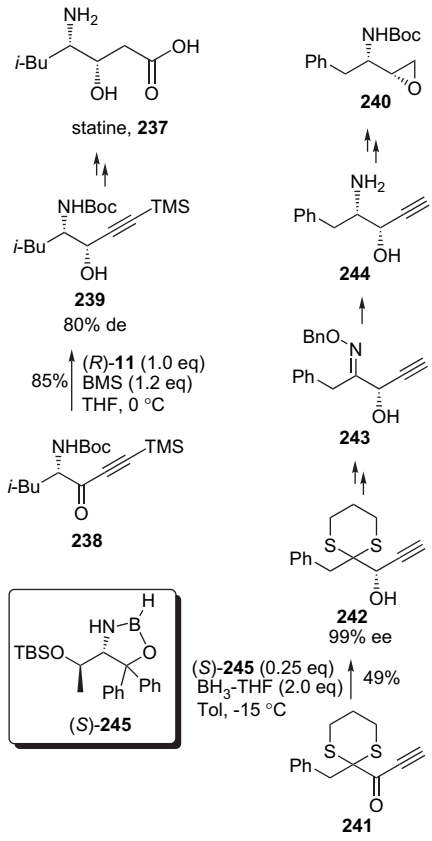
Scheme 59.

3.3. Synthesis of chiral intermediates, ligands, and building blocks

The chiral *syn*-3-hydroxy-4-amino acid moiety has been the focus of much attention in connection with the development of new pharmaceuticals based on protease inhibitors e.g., statine **237** is an essential component of pepstatine, a natural hexapeptide antibiotic, which acts as an inhibitor of aspartic acid protease. Starting from a stoichiometric OAB-mediated reduction of chiral α-amido acetylenic ketone **238** using (*R*)-**11** as asymmetric inducer, **237** has been prepared.[66a] The reduction gave **239** in 85% yield and 80% de, which was converted into **237** by transformation of the acetylenic group to a carboxylic acid group using hydroboration and subsequent oxidation. On the other hand, the chiral amino epoxide **240** is a key intermediate for the synthesis of HIV protease inhibitors, such as saquinavir and palinavir. This compound has also been prepared by using OAB-catalyzed reduction as a key step. The reduction of an acetylenic ketone **241**, using (*S*)-**245** derived from (*S*)-threonine as asymmetric inducer, provided a chiral propargylic alcohol **242** with 99% ee. After conversion of **242** into a chiral imino alcohol **243** by deprotection of the 1,3-dithianyl group and subsequent benzyloxyimination, diastereoselective reduction of **243** gives a *syn*-amino alcohol **244**, which can be used as a key intermediate for the synthesis of **240** (Scheme 60).[66b]

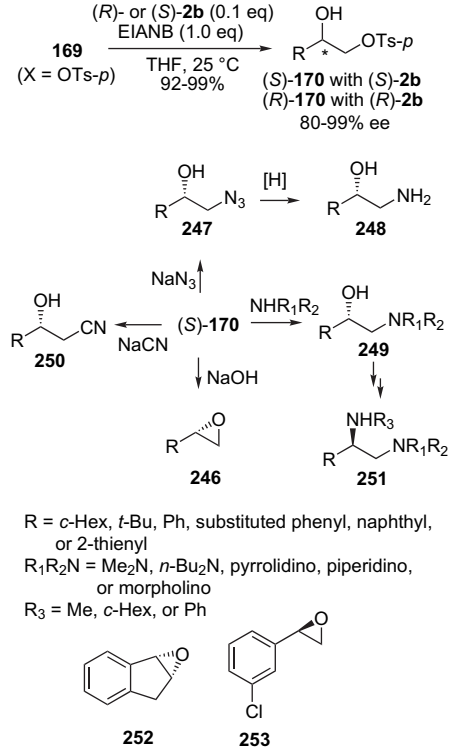
Chiral 1,2-diol monotosylates **170** prepared by the catalytic CBS reduction of **169** have been widely utilized for the synthesis of a variety of chiral intermediates such as chiral epoxides **246**,[67a] β-azido and amino alcohols **247**–**249**,[45] β-hydroxy cyanides **250**,[67b] and 1,2-diamines **251**[67c] (Scheme 61). This methodology has also been applied to the synthesis of enantiopure (1*S*,2*R*)-indene oxide **252**[67d] and (*R*)-3-chlorostyrene oxide **253**,[67e] which can be used as essential intermediates for the synthesis of an HIV protease inhibitor, indinavir, and β_3-agonists possessing antiobesity and antidiabetic activities, respectively.

Scheme 62 outlines the synthesis of other synthetically useful chiral β-functionalized alcohols, such as 1,2-diols **254**,[68] α-hydroxy acetals **255**,[69] β-azido alcohols **247**,[70] β-hydroxy sulfides **127**,[71a,b] β-hydroxy sulfones **256**,[72] and β-amido alcohols **257**,[73] via the catalytic CBS reduction of the corresponding ketones. Among these, chiral β-hydroxy sulfides **127** were successfully used as starting materials for the synthesis of chiral epoxides,[71c] diols,[71c] and unhindered aliphatic alcohols.[71d] In particular, the successful application of **127** for the synthesis of near-enantiopure unhindered aliphatic alcohols **258** possessing a similar steric bias between the two alkyl groups adjacent to the carbinyl group is noteworthy.

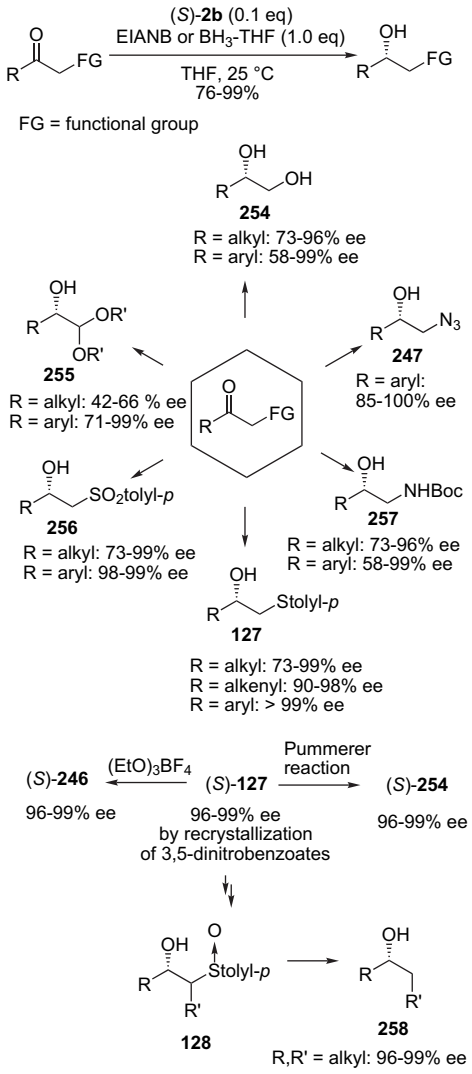


Scheme 60.

Homochiral 2-amino-1,2-diarylethanols **259** and 1,2-diaryl-1,2-ethanediols **262** are widely used as chiral building blocks and ligands for organic synthesis. When α-keto oxime ethers



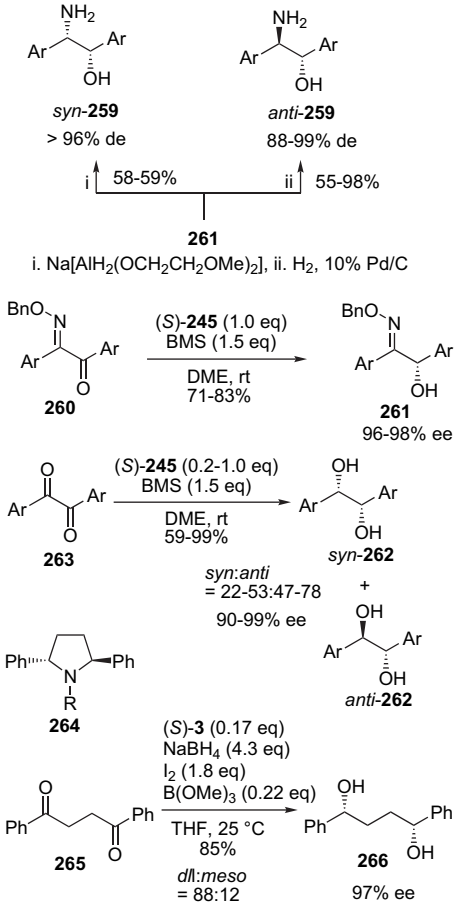
Scheme 61.



Scheme 62.

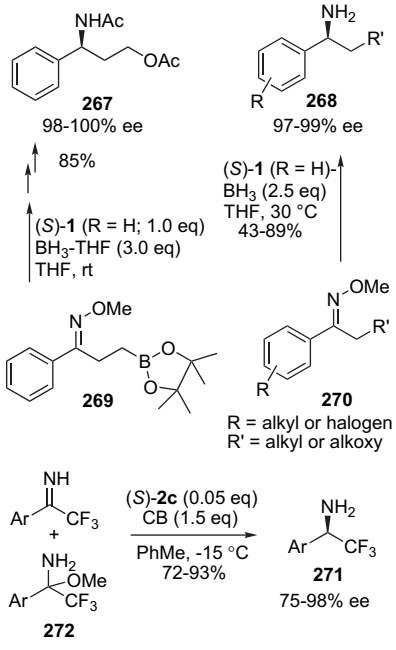
260 were reacted with 1.5 equiv of BMS using 1.0 equiv of (*S*)-**245** as asymmetric inducer in DME at room temperature, the carbonyl group was reduced much faster than the imine to give the chiral imino alcohols **261** in 73–83% yield and 96–98% ee. Further reduction of **261** using $Na[AlH_2(OCH_2CH_2OMe)_2]$ produced *syn*-**259** in >96% de, whereas the reduction with catalytic hydrogenation on Pd/C gave the *anti*-isomers with 88–99% de. The asymmetric reduction of 1,2-diketones **263** using the same methodology provided the chiral 1,2-diols *syn*-**262** with 90–99% ee. This reduction, however, afforded a low diastereoselectivity.[74] Similarly, CBS reduction was applied to the synthesis of chiral *trans*-2,5-diphenylpyrrolidines **264**, which is utilized as C_2-symmetric chiral auxiliaries or ligands for asymmetric synthesis. When the reduction of 1,4-diketone **265** was carried out in the presence of trimethyl borate, the reduction provided (*S*,*S*)-diol **266** in 85% yield and 97% ee with *dl*/*meso* ratio of 88:12, and this diol is easily converted into **264** by dimesylation, followed by a S_N2 reaction with an amine.[75] These results are summarized in Scheme 63.

Scheme 64 illustrates the stoichiometric OAB-mediated reduction of oxime ethers **269** and **270** using Itsuno's reagent,



Scheme 63.

(*S*)-**1** (R=H), derived from (*S*)-valine as asymmetric inducer to give the chiral benzylic amine derivatives **267** and **268** with high enantiopurity.[76] Very recently, the asymmetric synthesis of chiral trifluoromethylated amines **271** with good enantiopurity by the catalytic CBS reduction has been reported. The reduction of a mixture **272** obtained from the methanolysis of *N*-silylimines of the corresponding ketones using 1.5 equiv of CB in the presence of 0.05 equiv of (*R*)-**2c** at −15 °C in toluene afforded **271** in 72–95% yields and 75–98% ee.[77]



Scheme 64.

4. Summary and outlook

Chiral OAB-mediated borane reductions of prochiral ketones and ketimines have been very widely utilized for the highly effective asymmetric synthesis of a broad range of chiral natural products, bioactive compounds, intermediates, ligands, and building blocks, which include a chiral alcohol or amine functionality in their structures. Such applications of this methodology continue to increase rapidly in number. The effective asymmetric reduction of ketimine derivatives using this methodology, however, remains a challenging target, since only a few examples of the successful asymmetric reduction of prochiral ketimine derivatives in contrast to those for ketones have been reported.

Acknowledgements

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Biographical sketch

Byung Tae Cho was born in Seoul and grew up in Kang Nung, Republic of Korea. He received his B.S. degree in pharmacy from Seoul National University in 1967, MSc degree in 1971 and PhD degree in 1982 from Sogang University. After his military service for 3 years, he worked in the Korea Institute of Science and Engineering (KIST) for 4 years and in Dong Wha Pharmaceutical Company for 8 years. In 1982, he joined Hallym University as an assistant professor of chemistry. From 1985 to 1987, he undertook a postdoctoral fellowship with Professor Herbert C. Brown at Purdue University, where he worked on the development of new chiral borohydrides and their applications to the asymmetric reduction of ketones. Since 1993, he has been working at Hallym University as a full professor. His research interests include the catalytic asymmetric reductions, enantioselective carbonyl alkylations, and the synthesis of chiral drugs.