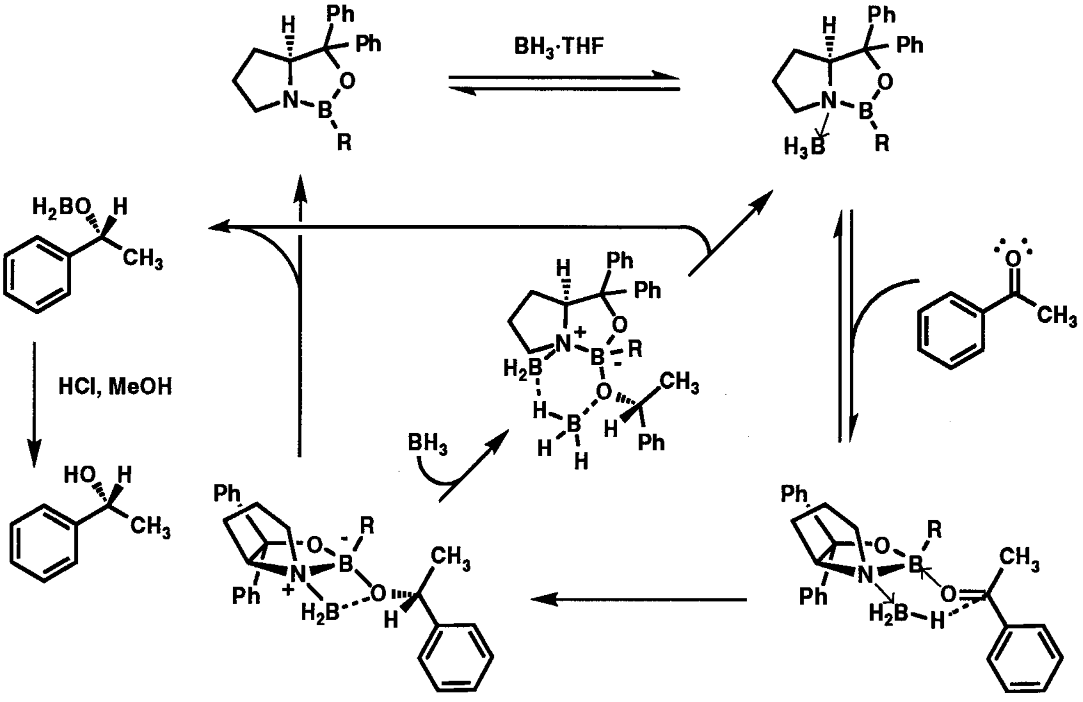
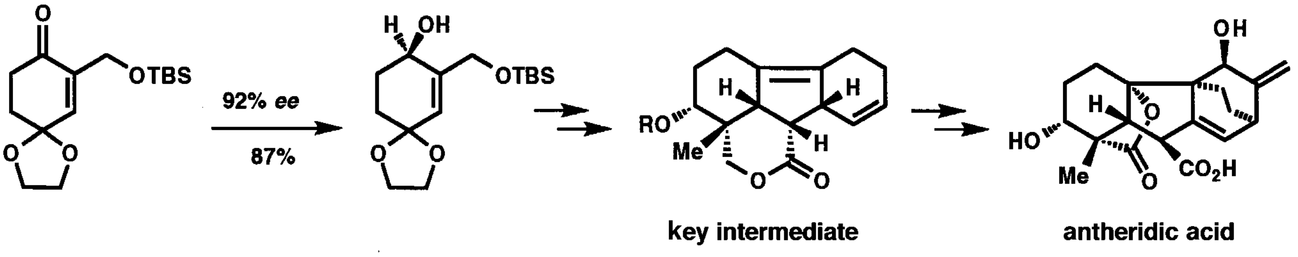
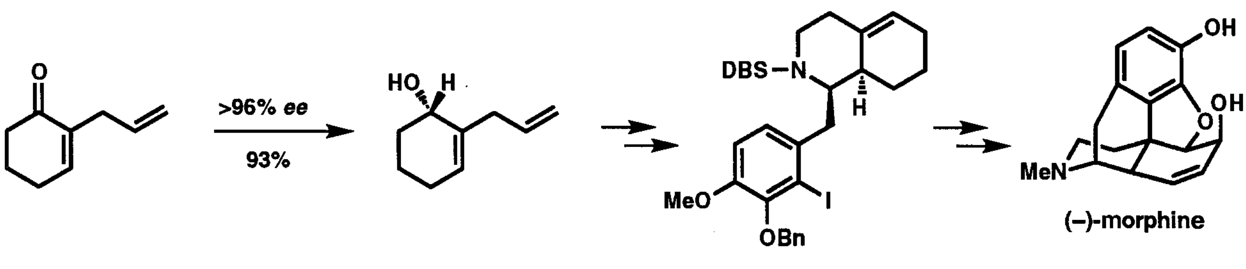


Remarkable advances in catalytic methods for enantioselective synthesis of chiral organic molecules have made the past decade truly momentous for organic chemistry. Great progress has been made not only in the discovery of useful new reactions, but also in our understanding of the fundamental mechanistic principles underlying enantioselective catalysis.





ANGEWANDTE CHEMIE

Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method**

Elias J. Corey* and Christopher J. Helal

The introduction of complex metal hydrides such as lithium aluminum hydride and sodium borohydride into synthetic organic chemistry half a century ago greatly accelerated progress in this field. For many years, efforts to combine these reducing agents with various chiral ligands for the purpose of achieving efficient asymmetric synthesis proved disappointing. However, promising results obtained by Itsuno and his collaborators in the 1980s with mixtures of chiral 1,2-amino alcohols and borane paved the way for the discovery of oxazaborolidines as chiral catalysts for the borane-mediated enantioselective reduction of a wide variety of achiral ketones (CBS reduction). The well-defined structure of the catalyst and the straightforward reaction pathway have allowed the rapid expansion of the scope of the CBS reduction and the rational modification of catalyst structure to achieve optimal enantioselectivity for a particular type of substrate. This enantioselective catalytic reduction is now established as a major synthetic method for the asymmetric synthesis of chiral medicinals, catalytic ligands, complex natural products, and synthetic intermediates.

Keywords: asymmetric catalysis · boron · ketones · reductions · total synthesis

1. Introduction

The introduction of aluminum and boron hydrides for the reduction of carbonyl groups half a century ago had an enormous impact on the field of synthetic chemistry, and helped to usher in a golden age for the rationally planned multistep construction of complex organic molecules.[1] These reagents not only provided predictable site selectivity in multifunctional substrates, but often predictable diastereoselectivity as well. The versatile parent compounds $LiAlH_4$,[2] AlH_3,[3] $NaBH_4$,[4] and $BH_3 \cdot THF$[5] have been modified in almost every conceivable way to generate a large collection of derivatives, each of which has a special reactivity and utility, for example $NaBH(OMe)_3$, $NaBH(OAc)_3$, $NaBH_3CN$, LiBH(sBu)$_3$, Cl_2BH, (cyclohexyl)$_2$BH, catecholborane, (RS)$_2$BH, $NaBH_4 \cdot CeCl_3$, LiAlH(OtBu)$_3$, $LiAlH(OMe)_3$, $NaAlH_2(OR)_2$, and iBu$_2$AlH.[6] The literature on carbonyl reduction by this extensive family of hydride/hydrogen donors is so vast that a comprehensive review would require several large volumes. However, despite five decades of research and countless thousands of applications of hydride donors, much remains to be learned regarding detailed reaction mechanisms and transition-state structures.[6, 7] One consequence of this primitive understanding of transition-state structure is that it is difficult to predict how a new reagent will behave.

In view of the enormous utility of Al–H and B–H reagents for the reduction of carbonyl groups, it is natural that the modification of these structures by the emplacement of chiral ligands would be investigated for the purpose of achieving absolute stereochemical control (*re*- or *si*-face selectivity) in the synthesis of chiral alcohols. For more than thirty years there have been numerous studies of mixtures of $LiAlH_4$, $NaBH_4$, or $BH_3 \cdot THF$ with chiral 1,2-diols, 1,2-amino alcohols, or 1,2-diamines as reagents for enantioselective carbonyl reduction.[8] Specific examples of such "mixture reagents" include *cis*-2,3-pinanediol and $LiAlH_4$;[9a] (2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (Darvon alcohol) and $LiAlH_4$;[9b, c, d] (−)-*N*-methyl-*N*-(1-phenylethyl)amine · HCl and $LiAlH_4$;[9e] hydroxymethyl oxazolines and $LiAlH_4$;[9f] (−)-*N*-methylephedrine, various phenols, and $LiAlH_4$;[9g, h, i] (*S*)-leucine methyl ester · BH_3 and BF_3;[9j] 2,2′-dihydroxy-1,1′-binaphthol, ethanol, and $LiAlH_4$ (BINAL-H);[9k, l] (*S*)-2-(*N*-arylaminomethyl)pyrrolidines and $LiAlH_4$;[9m] (*S*)-4-anilinyl-3-methylamino-1-butanol and $LiAlH_4$;[9n, o] 2,2′-dihydroxy-6,6′-dimethylbiphenyl, $BH_3 \cdot THF$, and various amines;[9p] (−)-*N*-methylephedrine, 2-alkylaminopyridines, and $LiAlH_4$;[9q] *N*-

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[**] A list of abbreviations used is provided in the Appendix.

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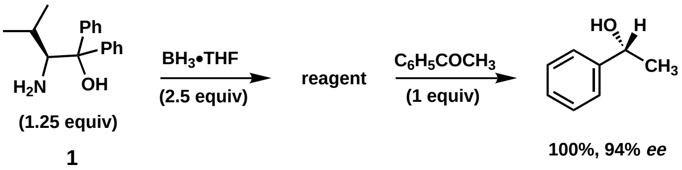
benzoylcysteine, $LiBH_4$, and *tert*-butyl alcohol;[9r] and (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol and $BH_3 \cdot Me_2S$.[9s]

While good levels of enantioselectivity have been reported for some of these early empirical studies, these reducing systems have seen very limited use in synthesis. In addition, because the reactive species are generally unknown, and in many cases insoluble as well, there has been no reliable information on the mechanistic basis for enantioselectivity. This is the situation for the Darvon alcohol – $LiAlH_4$ complex, introduced by Mosher and Yamaguchi,[9b] and used with some success by others.[9c, d] It is probably the best known of these mixture reagents. The Noyori reagent BINAL-H[9k, l]—which is made from (*S*)- or (*R*)-BINOL, $LiAlH_4$, and ethanol, and seems to be structurally better defined—also has seen very little use although it reacts with very high enantioselectivity with certain substrates; clearly high cost and marginal practicality are factors which detract from the usefullness of this reducing system.

After a survey of the extensive literature of these mixture reagents for hydride reduction and in an attempt to rationalize the basis for the observed enantioselectivities, we became very interested in a system introduced by Itsuno et al. in 1981.[10] In this initial work, the authors reported the novel finding that mixtures of chiral amino alcohols such as (*S*)-valinol and $BH_3 \cdot THF$ in a ratio of 1:2 in THF at 30 °C effected the enantioselective reduction of a number of achiral ketones to chiral secondary alcohols in nearly 100 % yield with enantiomeric excesses in the range of 10 – 73 % *ee*.[11] The most thoroughly studied substrate, butyrophenone, was reduced by this reagent to (*R*)-1-phenylbutan-1-ol with 69 % enantiomeric purity. Upon screening numerous amino alcohols, it was discovered that the tertiary amino alcohol **1** derived from (*S*)-valine together with two equivalents of $BH_3 \cdot THF$ at -78 to 0 °C over several hours converted acetophenone into (*R*)-1-phenylethanol with a much improved enantiomeric excess (94 %, Scheme 1).[12] The dependence of the enantioselectivity of this process on the ratio of BH_3 to amino alcohol, the quantity of hydride present in the reagent, and the steric bulk of the ketone substituents was studied. However, no mechanistic rationale was proposed by Itsuno et al. for either the sense or magnitude of this surprisingly good enantioselectivity. No applications were reported by other groups. Studies of this intriguing reaction were initiated by our group on the basis of mechanistic insights which were subsequently confirmed and which led to a new and powerful catalytic version of the original stoichiometric Itsuno reduction.



Scheme 1. Highly enantioselective ketone reduction reported by Itsuno.

2. Development of the CBS Catalytic Enantioselective Reduction[13]

From the outset it appeared reasonable that the primary reaction product of the tertiary amino alcohol **1** would be an oxazaborolidine of structure **2**. This was confirmed in 1986 – 1987 by Bakshi and Shibata of our laboratories. They found that the reaction of amino alcohol **1** with two equivalents of BH_3 in THF at 35 °C produced two equivalents of hydrogen gas and the oxazaborolidine **2**, which was obtained in pure form upon sublimation (105 – 130 °C, 0.05 Torr) after removal of the solvent and excess BH_3 in vacuo (see Scheme 2). Its structure was demonstrated by FT-IR and ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI). Although solutions of **2** in THF did not reduce acetophenone after several hours at 23 °C, mixtures of **2** and $BH_3 \cdot THF$ (0.6 equiv) effected the rapid reduction of acetophenone in less than one minute at 23 °C to afford (*R*)-1-phenylethanol in 94.7 % *ee*, which is

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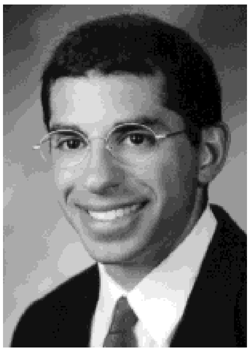
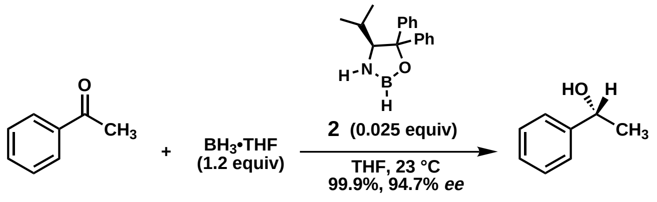
Christopher J. Helal, born in 1969 in Columbus, OH, received his Bachelor of Science degree in chemistry in 1991 from the Ohio State University. He enrolled in the graduate program at Harvard University, where he was a National Science Foundation Graduate Fellowship recipient. He earned his doctorate in 1997 under the direction of Professor E. J. Corey on the investigation of novel electronic and steric effects in the enantioselective oxazaborolidine-catalyzed reduction of ketones, and is currently employed at Pfizer Central Research, Groton, CT, where he is involved in drug discovery.

E. J. Corey



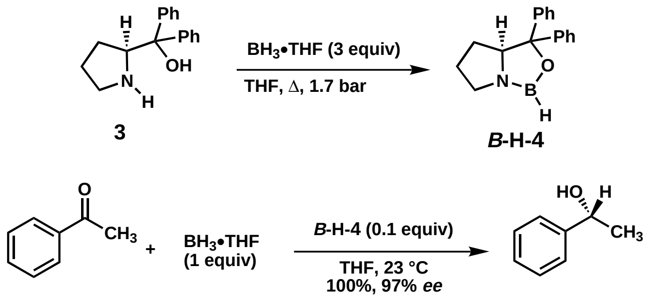
C. J. Helal

comparable to the results reported by Itsuno.[12] In the absence of **2**, acetophenone was reduced relatively slowly with $BH_3 \cdot THF$ at 23 °C. The rate acceleration with **2** immediately suggested that substoichiometric quantities of **2** could effect an asymmetric reduction of a ketone. This was readily verified by an experiment with 2.5–5 mol% of **2** and 1.2 equivalents of $BH_3 \cdot THF$, which produced (*R*)-1-phenylethanol with 94.7% *ee* (Scheme 2). Thus, the careful investigation of an impressive yet, in the original report, poorly understood reaction led to the discovery of a highly enantioselective *catalytic* reduction of ketones mediated by an *isolable* and *structurally defined* catalyst.



Scheme 2. Oxazaborolidine-catalyzed reduction with borane.

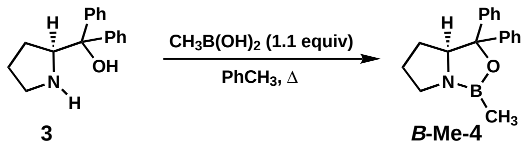
The demonstration of the catalytic activity of oxazaborolidine **2** and mechanistic considerations (see Section 3) led to the expectation that oxazaborolidine **4** should be a superior reagent (Scheme 3). Treatment of amino alcohol **3**[14a, b] with $BH_3 \cdot THF$ gave oxazaborolidine *B*-H-**4** (CBS catalyst named after *C*orey, *B*akshi, and *S*hibata), which was characterized by ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI).



Scheme 3. A superior oxazaborolidine catalyst for the enantioselective reduction of ketones.

Oxazaborolidine **4** was indeed found to be generally superior to **2** as an enantioselective reduction catalyst. For example, the reduction of acetophenone with 1.2 equivalents of $BH_3 \cdot THF$ and 0.1 equivalents of *B*-H-**4** in THF at 25 °C gave (*R*)-1-phenylethanol with 97% *ee* and in quantitative yield.

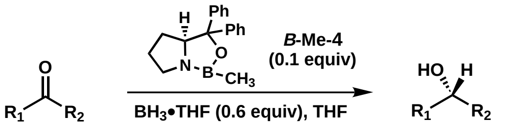
The methyl-substituted oxazaborolidine *B*-Me-**4** was prepared as shown in Scheme 4 and characterized by ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI). An improvement in the selectivity and practicality of the CBS reduction was realized with this catalyst relative to the *B*-H analogue. The reduction of ketones with *B*-Me-**4** as the catalyst frequently resulted in appreciably higher enantioselectivity than with *B*-H-**4**. Additionally, *B*-H-**4** is extremely air- and moisture-sensitive, and its formation requires extended heating with BH_3 under increased pressure. On the other hand, *B*-Me-**4** is less sensitive and can be stored in closed containers, weighed or transferred in air, and is readily formed by heating **3** and methaneboronic acid at reflux in toluene for 4 h with removal of water.

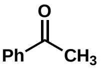
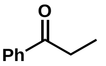
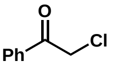
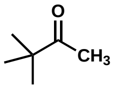
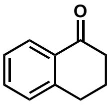
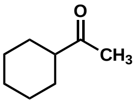
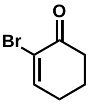
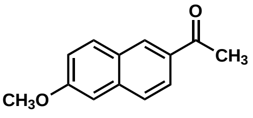
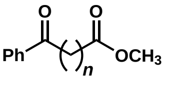


Scheme 4. A more stable and enantioselective catalyst.

Table 1 summarizes the results for the reduction of a variety of different ketones with *B*-Me-**4** as the catalyst.[13b] These data show that the CBS reduction process results in excellent enantioselectivities, near quantitative yields, and short reaction times, and leads to a product whose absolute configuration can be predicted from the relative effective steric bulk of the two carbonyl appendages. Another notable attribute of

Table 1. CBS reduction of ketones catalyzed by *B*-Me-**4**.[13b]



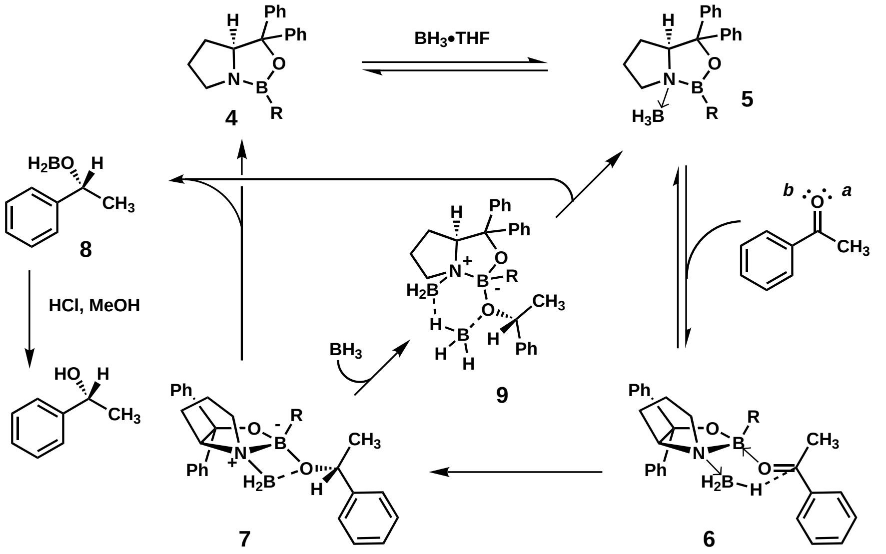
Ketone		Config. (*ee* [%])	*T* [°C]
		*R* (96.5)	2
		*R* (96.7)	–10
		*S* (95.3)	32
		*R* (97.3)	–10
		*R* (86)[a]	–15
		*R* (84)	–10
		*R* (91)	23
		*R* (97.6)	23
	$n=2$	*R* (94)	0[b]
	$n=3$	*R* (96.7)	0[b]

[a] 0.25 equiv of *B*-Me-**4**. [b] The reaction time was 25 min.

this methodology is the easy recovery of the catalyst precursor **3** by precipitation from organic solvent as the hydrochloride salt and efficient recycling.[14c]

3. Mechanistic Rationale[13, 15]

The general mechanistic model which was developed for reduction of ketones with oxazaborolidine catalyst **4** (and analogous catalysts such as **2**) is outlined in Scheme 5. The mechanistic model explains 1) the absolute stereochemistry of the reduction, 2) the outstanding enantioselectivity obtained for the reduction, 3) the exceptional rate enhancement of the reduction, and 4) the turnover of the catalyst.

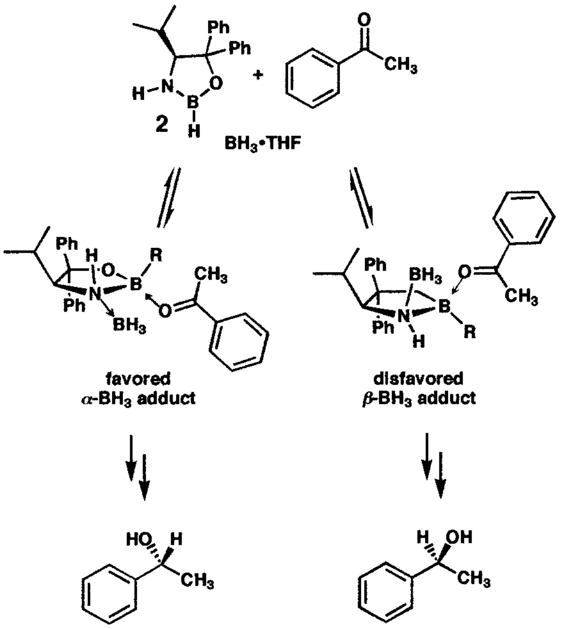


Scheme 5. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidines **4**.

The initial step in the pathway is the rapid (and probably reversible) coordination of BH_3 to the Lewis basic nitrogen atom on the *α* face of oxazaborolidine **4** to form the *cis*-fused oxazaborolidine · BH_3 complex **5**. Unambiguous support for the initial step comes from the observation by ^{11}B NMR spectroscopy[16] that **4** and BH_3 · THF form the 1:1 complex *B*-H-**5** and the fact that crystalline *B*-Me-**5** (**5**, R = Me) can be isolated and structurally defined by single-crystal X-ray diffraction analysis.[17] The coordination of the electrophilic BH_3 to the nitrogen atom of **4** serves to activate BH_3 as a hydride donor and also to increase strongly the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex **5** then readily binds to the ketonic substrate, for example acetophenone, at the more sterically accessible electron lone pair (*a* in the case of acetophenone) and *cis* to the vicinal BH_3 group (→**6**). This manner of binding minimizes unfavorable steric interactions between the oxazaborolidine and the ketone, and aligns the electronically deficient carbonyl carbon atom and the coordinated BH_3 for stereoelectronically favorable, face-selective hydride transfer via a six-membered transition state to form the reduction product **7**. Thus, the rate enhancement for the oxazaborolidine-catalyzed reduction is due to the activation of the stoichiometric reducing agent BH_3 by coordination with the Lewis basic nitrogen atom of **4** with simultaneous intensification of the Lewis acidity of the boron atom in the heterocycle for coordination to the ketone. This leads to subsequent enthalpically and entropically favorable face-selective intramolecular hydride transfer.[18]

Dissociation of the reduction product from **7** to regenerate the oxazaborolidine catalyst may occur by two different pathways: 1) reaction of the alkoxide ligand attached to the endocyclic boron atom with the adjacent boron atom of **7** to regenerate **4** and form the borinate **8** by cycloelimination;[13d, 15] or 2) by the addition of BH_3 to **7** to form a six-membered BH_3-bridged species **9**, which decomposes to produce the catalyst – BH_3 complex **5** and borinate **8**.[19, 20] The facile disproportionation of **8** to afford dialkoxyborane $(RO)_2BH$ and BH_3 allows the efficient use of the three hydrogen atoms of the stoichiometric reductant.[21]

The mechanism proposed in Scheme 5 provides a simple explanation for the superior effectiveness of oxazaborolidine **4** relative to **2**. As shown in Scheme 6, the selective binding of BH_3 to one face of **2** is the result of a steric preference for a *trans* relationship between the isopropyl substituent and BH_3. Competing formation of the *cis* adduct leads to lower enantioselectivity of the reduction. The rigid [3.3.0] ring system of **4**, however, strictly requires the *α* coordination



Scheme 6. A possible reduction pathway for catalyst **2** with low enantioselectivity.

of BH$_3$ to the Lewis basic nitrogen atom (see **6**); β coordination would result in a very strained (by ca. 10 kcal mol^{-1}) *trans*-fused [3.3.0]pentalane. Thus, production of the undesired alcohol enantiomer through a diastereomeric BH$_3$ coordination mode is energetically precluded with CBS catalyst **4**.

A final issue posed by the mechanistic model in Scheme 5 is whether the complexation of the ketone by **5** or the subsequent hydride transfer to form **7** is the rate-limiting step of the reduction. To answer this question, the rates of reduction of acetophenone and the p-NO$_2$ and p-MeO derivatives catalyzed by B-Me-**4** were measured.[22a] The relative rates of reduction were 3.4 (p-NO$_2$), 1.8 (p-MeO), and 1.0 (p-H).[22b] This implies that the coordination of the ketone to **5** is not strictly rate-limiting for these substrates. Additional information was obtained from the ^{1}H–^{2}H kinetic isotope effect (k_H/k_D) for hydride transfer, which was measured with an excess of a 1:1 mixture of B^{1}H$_3$ and B^{2}H$_3$ (6 equiv of each) in THF with two equivalents of oxazaborolidine B-Me-**4** and one equivalent of acetophenone. The ratio of ^{1}H to ^{2}H in the reduction product 1-phenylethanol at low conversion was determined by mass spectrometry to be 1.7, which is then the approximate value of k_H/k_D.[22a] This low value is indicative of an early transition state for highly exothermic transfer of hydride from the boron atom to the carbonyl group. Thus, both association to the carbonyl comound and hydride transfer are probably fast and comparably rate-limiting. In agreement with these experimental results, semiempirical molecular orbital calculations with the AM1 Hamiltonian provided similar transition state enthalpies for ketone complexation and hydride transfer.[18c] The calculated kinetic isotope effect for the oxazaborolidine-catalyzed reduction of 2-propanone was 1.8 at 23 °C, which is in agreement with the experimentally determined value of 1.7.[23]

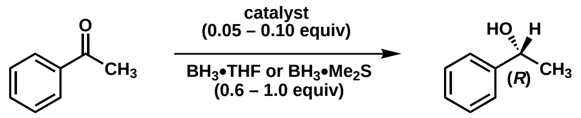
4. Further Studies in the Optimization of the CBS Reduction

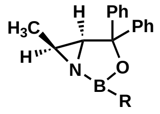
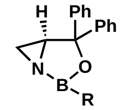
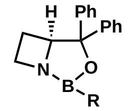
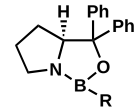
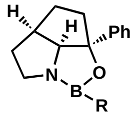
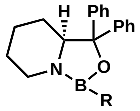
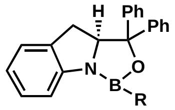
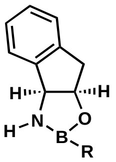
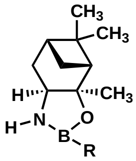
The high enantioselectivity, generality, and profound mechanistic understanding of the CBS reduction have led to a number of other studies aimed at further elucidating in ever increasing detail the effect of five variations in the structure of the oxazaborolidine catalyst on enantioselectivity over a wide range of substrates. Described in the following are results from investigations of varying 1) the oxazaborolidine ring system, 2) the *gem*-diphenyl substituents, 3) the group on the endocyclic boron atom, 4) the stoichiometric reducing agent, and 5) the mode of catalyst preparation.

4.1. Variations in the Oxazaborolidine Ring System

Subsequent to the discovery of the high enantioselectivity imparted by the proline-derived oxazaborolidine catalyst **4** in the reduction of ketones with BH$_3$, many other fused bicyclic oxazaborolidines have been prepared by other research groups and by our own to demonstrate the relationship between catalyst structure and enantioselectivity. The effectiveness of the various oxazaborolidine catalysts for the enantioselective reduction of acetophenone is summarized in Table 2. For example, the aziridine (entries 1 and 2),[24] azetidine (entry 3),[25] and pyrrolidine catalysts (entry 4, **4**)[13] afford (R)-1-phenylethanol in very high enantiomeric excess (94–97 %). The structurally constrained tricyclic oxazaborolidine in entry 5 is among the most effective of all the oxazaborolidines synthesized, as it has demonstrated exceptional enantioselectivity for the reduction of acetophenone (98 % *ee*) as well as numerous other substrates.[26] The use of a catalyst with a more flexible [4.3.0] ring system (entry 6) resulted in lower enantioselectivity.[27] Entry 7 reveals that the

Table 2. Fused bicyclic oxazaborolidine catalysts for the enantioselective reduction of acetophenone.



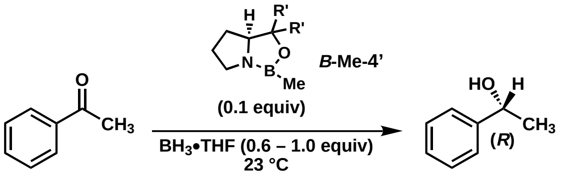
Entry	Catalyst	R	*ee* [%]	Solvent, T [°C]
1		H	94	THF, 23
2		H	94	PhCH$_3$, 23
3		H Me	97 75	THF, 23 PhCH$_3$, 23
4		H Me	97 97	THF, 23 THF, 23
5		Me	98	THF, 0
6		H	87	THF, 0
7		H Me	96 92	THF, 23 PhCH$_3$, 27
8		Me	86	THF, 0
9		H Me	94 93	THF, 25–30 THF, 0–5

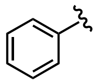
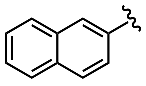
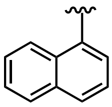
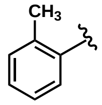
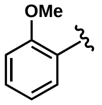
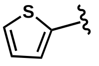
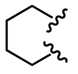
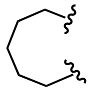
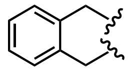
enantioselectivity of the reduction is not strongly affected by decreased Lewis basicity of the endocyclic nitrogen atom of the catalyst owing to conjugation with the fused aromatic ring (up to 96% *ee* for the reduction of acetophenone).[28] Industrial interest in the large-scale application of CBS reductions has led to the search for other inexpensive and readily available enantiopure amino alcohols as precursors to chiral oxazaborolidines. Towards this end, enantiopure *cis*-1-amino-2-indanol (entry 8, prepared in four steps from indene)[29] and an amino alcohol derived from α-pinene (entry 9, prepared from α-pinene)[30] have been used to generate bicyclic oxazaborolidine catalysts which mediate the reduction of acetophenone with high enantioselectivity (86 and 94% *ee*, respectively).

4.2. Variation of the Carbinol Substituents

The effects of the *gem*-diphenyl substituents of the carbinol center (R′) on the enantioselectivity of acetophenone reduction are summarized in Table 3. Replacing the phenyl group (entry 1, *B*-Me-**4**) by the somewhat bulkier β-naphthyl group (entry 2) leads to a slight increase in enantioselectivity (98% *ee*) in this and some other cases.[31] The use of still bulkier *ortho*-substituted aromatic groups such as α-naphthyl (entry 3),[25c] *ortho*-tolyl (entry 4),[32] or *ortho*-anisyl (entry 5),[32] however, results in considerably lower enantioselectivity, as does the use of the smaller 2-thienyl group (entry 6).[32] Substitution with straight-chain alkyl (*n*-butyl, entry 7)[25c] and spiroalkyl groups (entries 8 and 9),[33] did not provide useful catalysts. However, a catalyst containing the rigid spiro-2-indanyl substituent (entry 10) afforded the reduction product with high enantioselectivity (96% *ee*).[34] Emplacement of two strongly electron-withdrawing trifluoromethyl groups on the oxazaborolidine ring system (entry 11), which should inductively increase the Lewis acidity of the heterocyclic boron atom, led to a catalyst which provided relatively poor enantioselectivity.[35, 36]

Table 3. Influence of the substituents R′ at the carbinol center.



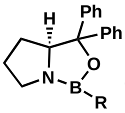
Entry	R′	*ee* [%]
1		97
2		98
3		62
4		76
5		28
6		82
7	$CH_3CH_2CH_2CH_2$	55
8[a]		67
9[a]		71
10[a]		96
11[b]	CF_3	60

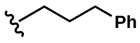
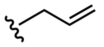
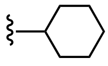
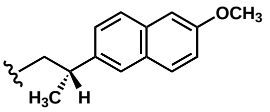
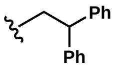
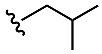
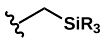
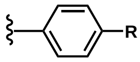
[a] The oxazaborolidine (0.15 equiv) was formed from the corresponding precursor by reaction with $BH_3\cdot THF$ and contains a hydrogen atom on boron instead of the methyl group. The reduction was carried out at 0 °C. [b] The group on the oxazaborolidine boron atom was *n*-pentyl.

4.3. Variation of the Substituent on the Heterocyclic Boron Atom

The group R on the heterocyclic boron atom can play an important role in determining the selectivity of complexation by the catalyst to the two possible ketone electron lone pairs. Because of differential steric interactions between R and the carbonyl substituents (see **6**, Scheme 5), a discrimination is crucial to the enantioselectivity of the reduction. Table 4 lists several groups which have been studied as boron substituents in our laboratory[37] for the CBS reduction of a range of ketonic substrates. Besides the compounds *B*-H-**4** (entry 1) and *B*-Me-**4** (entry 2) previously discussed, a variety of other catalysts containing *n*-alkyl (entries 3,[38] 4,[39] 5[35]), 3-phenylpropyl (entry 6),[40] allyl (entry 7),[37] *s*-alkyl (entry 8),[40] and β-branched attachments both with chiral centers (entry 9)[41] and without (entries 10[40] and 11[42]) have been synthesized and tested in the enantioselective reduction. In general, the R group exerts a steric effect in proximity to the boron atom to which it is attached that can influence the selectivity of binding at one of the oxygen lone pairs. In addition, it has been possible to design substituents, such as trialkylsilylmethyl (entry 12)[43] and *p*-substituted aryl groups (entry 13),[44] which interact sterically with more remote sites on the coordinated ketone and thus influence dramatically the enantioselectivity of reduction (see Sections 5, 6.3, and 6.4). The optimal R group for enantioselective reduction can be expected to depend on the structure of the substrate, as discussed in Section 5.

Table 4. Boron substituents in CBS catalysts.


4

Entry	R
1	H
2	CH_3
3	CH_2CH_3
4	$CH_2CH_2CH_2CH_3$
5	$CH_2CH_2CH_2CH_2CH_3$
6	
7	
8	
9	
10	
11	
12	
13	

4.4. Variation of the Stoichiometric Reducing Agent

Since the initial use of $BH_3 \cdot THF$ as the stoichiometric reductant in the CBS reduction, a number of other BH_3 complexes have been employed—including $BH_3 \cdot Me_2S$,[44b] $BH_3 \cdot$ 1,4-thioxane,[45] and $BH_3 \cdot$ diethylaniline[46]—all of which lead to comparable enantioselectivity. An advantage of these reagents over $BH_3 \cdot THF$ is lower sensitivity to moisture and oxygen. The coordination of Me_2S, THF, etc. to BH_3 generally does not effect the level of enantioselection except at temperatures below −30 °C.[47] At this temperature the equilibria between BH_3, the coordinated ligand, the oxazaborolidine catalyst, and the ketone are sufficiently altered to allow the intervention of competing reduction pathways; this then results in diminished enantioselectivity. The use of catecholborane,[48] a less reactive monohydridic reagent that requires no ancillary ligand for stabilization, permits CBS reductions to occur at temperatures as low as −126 °C in noncoordinating solvents (CH_2Cl_2 or toluene) with excellent enantioselectivity.[31, 47] Furthermore, the decreased reactivity of catecholborane as compared to BH_3, especially at lower temperatures, minimizes both uncatalyzed ketone reduction and hydroboration of sensitive functional groups (e.g., C=C, C≡C, C=O) within the ketonic substrate.

4.5. Variations in Oxazaborolidine Formation

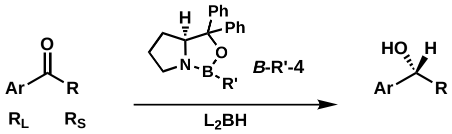
The preparation of chiral oxazaborolidines in pure form was vital to the discovery of the CBS catalyst *B*-H-**4** and the demonstration of the mechanism outlined in Scheme 5. Catalyst purity is essential for the attainment of high enantioselectivity and reproducibility in the reduction of ketones. As a result, considerable effort has been extended towards the development of effective procedures for the generation of pure oxazaborolidines without the need for a purification step. The first-generation CBS catalyst *B*-H-**4** was originally prepared by the extended heating of amino alcohol **3** with three equivalents of $BH_3 \cdot THF$ under argon (1.7 bar) followed by sublimation.[13a] Subsequently, a more convenient procedure was developed for the synthesis of *B*-H-**4** that consists of heating **3** and $BH_3 \cdot Me_2S$ in toluene at reflux for 17 h and then removing solvent in vacuo without further purification.[49, 50] The alkyl- and aryl-substituted oxazaborolidines (Section 4.3) are easily prepared by heating a solution of **3** and the corresponding boronic acid $RB(OH)_2$ or boroxine $(RBO)_3$ at reflux in toluene for 12–24 h with removal of water with molecular sieves.[51] To shorten the time required for complete catalyst formation, the more reactive boronic acid equivalents bis(trifluoroethyl)alkyl boronates ($RB(OCH_2CF_3)_2$) have been developed; they allow for quantitative oxazaborolidine formation in less than one hour.[52]

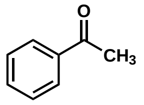
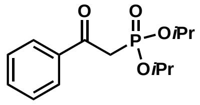
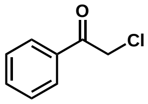
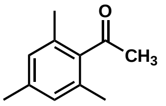
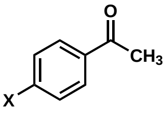
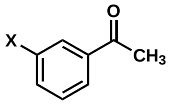
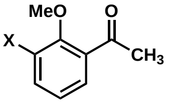
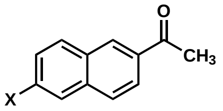
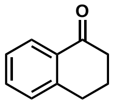
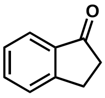
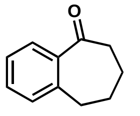
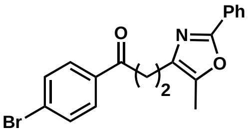
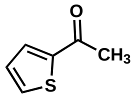
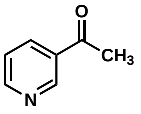
5. Scope of Oxazaborolidine-Catalyzed Reductions

The well-defined mechanistic pathway of the enantioselective reduction of ketones mediated by chiral oxazaborolidine **4** greatly simplified application of this reaction to the enantioselective reduction of many different types of ketones and to the expansion of its scope and generality. As shown in Table 5, many conjugated aryl ketones of varying structure undergo highly enantioselective reduction with BH_3 or catecholborane in the presence of the proline-derived oxazaborolidine **4**. For example, acetophenone[46] and derivatives with functional groups on the alkyl side chain such as $P(O)(O\mathit{i}Pr)_2$[53] or Cl[44a] are reduced with high enantioselectivity, as are the *para*-,[17b] *meta*-,[13b, 54] and *ortho*-substituted[55] aryl ketones and the cyclic aryl ketones 1-tetralone,[46] 1-indanone,[17b] and 1-benzosuberone.[17b] The presence of nitrogen and other heteroatoms in the ketonic substrate is tolerated in the oxazaborolidine-catalyzed reduction, but often requires the use of an additional equivalent of the stoichiometric reductant L_2BH to coordinate to the Lewis basic site.[50a, 56] Representative procedures for the CBS reduction of acetophenone and α-chloroacetophenone are detailed in reference [57].

Recently, the oxazaborolidine-catalyzed reduction of essentially isosteric electronically biased benzophenones[58, 59] as well as *ortho*-substituted benzophenones[59] and 2-benzoyl pyridinium triflates[59] has been shown to be strikingly selective as a result of gearing effects between the aromatic rings. This reaction provides an efficient route to optically active benzhydrols (Table 6).[60] The presence of an *ortho*-substituent on the aromatic ring also proved to be very

Table 5. Oxazaborolidine-catalyzed reduction of aryl ketones.



Ketone	*ee* [%]	Catalyst	L$_2$BH	*T* [°C]	Ketone	*ee* [%]	Catalyst	L$_2$BH	*T* [°C]
	99[46]	*B*-Me-**4**	BDEA	30		91[53]	*B*-*n*Bu-**4**	CB	−20
	98[44a]	*B*-Me-**4**	BDEA	31		99.7[55a]	*B*-*n*Bu-**4**	CB	−78
	97 (X = F)[17b] 99 (X = OMe)[17b]	*B*-Me-**4**·BH$_3$	BMS	−20		96 (X = Br)[54] 97 (X = OMe)[54]	*B*-Me-**4**	BTHF	23
	97 (X = OMe)[55b] 94 (X = H)[55b]	*B*-Me-**4**	BMS	23		96 (X = H)[54] 98 (X = OMe)[13b]	*B*-Me-**4**	BTHF	23
	≥99[46]	*B*-Me-**4**	BDEA	20		98[17b]	*B*-Me-**4**·BH$_3$	BMS	−20
	99[17b]	*B*-Me-**4**·BH$_3$	BMS	−20		94[56]	*B*-Me-**4**	BMS	25
	94[56]	*B*-Me-**4**	BMS	25		99[50a]	**3** + (MeO)$_3$B	BMS	23

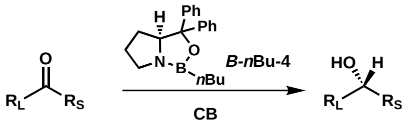
important for the enantioselective reduction of aryl diisopropylphosphono ketones.[53]

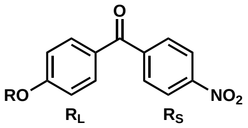
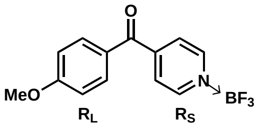
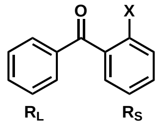
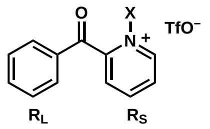
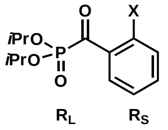
α,β-Enones have been extensively investigated as CBS reduction substrates since enantiopure allyl alcohols are extremely versatile intermediates which can participate in many useful synthetic elaborations, for example the Claisen rearrangement or S_N2' displacement reactions with organometallic reagents that allow transfer of chirality by cleavage of C−O bonds and formation of C−C bonds to new chiral centers. It is interesting to note that in the case of acyclic enones (Table 7) the olefinic portion generally behaves as the large group R_L, especially in the presence of a β substituent such as aryl,[58] trimethylsilyl, tri-*n*-butylstannyl,[61] or alkyl groups.[62b–f]. Even an α substituent[62a, f] (see below) can serve to reinforce the intrinsic preference for lone pair coordination. For cyclic α,β-enones with endocyclic unsaturation, α substitution of the C−C double bond with alkyl[47, 63] or halogen[64] is crucial for effective steric differentiation of the carbonyl oxygen electron lone pairs (Table 8). The reduction of cyclic α,β-enones with an exocyclic double bond has not been extensively studied. However, it can be expected that β substitution is not crucial for high enantioselectivity, but helps to minimize reduction of the conjugated double bond.[65, 66]

The oxazaborolidine-catalyzed reduction of α,β-ynones to afford propargyl alcohols of high optical purity has recently been accomplished by two different reaction protocols (Table 9). The use of (*S*)-*B*-Me-**4** as catalystand $BH_3\cdot Me_2S$ as reductant in THF leads to (*S*)-alcohols, with ethynyl behaving as the small group R_S.[67] In contrast, the use of (*S*)-*B*-CH_2SiMe_3-**4**[43] or (*S*)-*B*-*p*-*t*BuC_6H_4-**4**[44a] and catecholborane in CH_2Cl_2 for the reduction of triisopropylsilyl or trimethylsilylacetylene ketones furnishes (*R*)-propargyl alcohols, with ethynyl behaving as the large group R_L.[68] This intriguing reversal in the enantioselectivity of the reduction is the consequence of repulsive interactions between the remotely situated bulky substituents on the triple bond and the heterocyclic boron atom of the catalyst.[43]

Ketones with two sp^3-hydridized carbon atoms attached to the carbonyl center can also be reduced with high enantio-

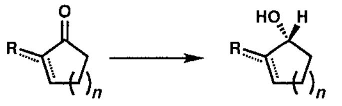
Table 6. Oxazaborolidine-catalyzed reduction of diaryl- and aryl diisopropylphosphono ketones.[a]



Ketone	*ee* [%]	*T* [°C]
	95[58]	−78
	93[59]	−78
	97 (X = Br,Me)[59]	−40
	> 90 (X = Me)[59] 99 (X = allyl)[59]	−40
	91–97 (X = F,Cl,Br,I,Me)[53]	−20

[a] A procedure for the CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)-pyridinium triflate is provided in reference [60].

Table 8. Oxazaborolidine-catalyzed reduction of cyclic α,β-enones.



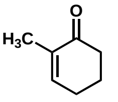
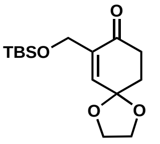
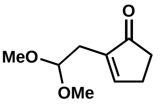
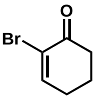
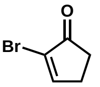
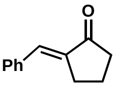
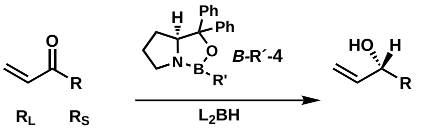
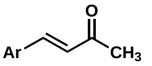
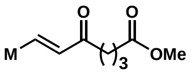
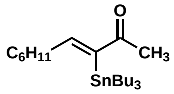
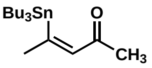
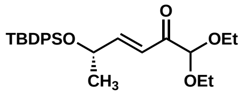
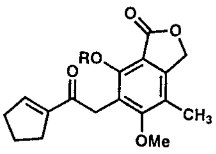
Enone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	93[47]	*B*-*n*Bu-**4**	CB	−78
	92[63a]	*B*-*n*Bu-**4**	BTHF	37
	93[63b]	*B*-Me-**4**	BTHF	10
	96[64a]	*B*-Me-**4**	BMS	−15
	90[64b]	*B*-Me-**4**	BTHF	23
	96[65]	*B*-Me-**4** $\cdot BH_3$	BMS	−20

Table 7. Oxazaborolidine-catalyzed reduction of acyclic α,β-enones.[a]

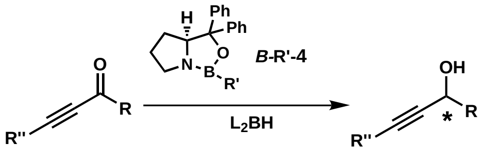


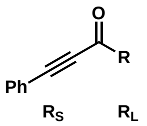
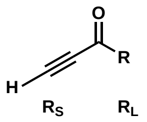
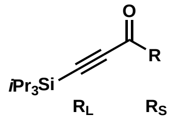
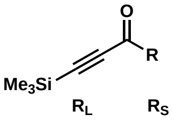
Enone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	97 (Ar = Ph)[58] 95 (Ar = 4-$MeOC_4H_4$)[58]	*B*-*n*Bu-**4**	CB	−78
	94 (M = $SiMe_3$)[61] 88 (M = $SnBu_3$)[61]	*B*-CH_2SiMe_3-**4**	CB	−78 −60
	94[62a]	*B*-*n*Bu-**4**	CB	−78
	85[62b,c]	*B*-Me-**4**	CB	−30
	95[62d,e]	*B*-*n*Bu-**4**	BMS	23
	92–97[62f]	*B*-Me-**4**	BMS	−30

[a] A procedure for the CBS reduction of (*E*)-4-(4′-methoxyphenyl)-3-buten-2-one is provided in reference [66].

selectivity whenever there are substantial differences in the accessibility of the two oxygen electron lone pairs for coordination (Table 10). For example, ketones having a *tert*-alkyl group and a primary or *n*-alkyl-type group as carbonyl appendages can be reduced with high enantioselectivity.[44a, 46] The reduction of some ketones, especially those in which the carbonyl group is quite hindered, often proceeds with better stereoselectivity at higher temperatures (30–120 °C), possibly due to accelerated removal of the bulky boronate product from the oxazaborolidine.[55a, 69a, b] The highly enantioselective reduction of *s*-alkyl ketones such as cyclohexyl methyl ketone and isopropyl methyl ketone was recently accomplished by the use of $BH_3 \cdot$ diethylaniline as stoichiometric reductant.[46] In the CBS reduction of cyclopropyl isopropyl ketone, the strong influence of electronic factors is clearly evidenced, as the π electron rich cyclopropyl group behaves as R_L in comparison to the sterically similar isopropyl group.[58] Methyl *n*-alkyl ketones are reduced with modest selectivity with *n*-alkyl as R_L,[70] but the factors responsible for enantiodifferentiation of di-*n*-alkyl ketones can be quite subtle;[71] further study of the reduction of such challenging substrates represents an attractive area for future research.

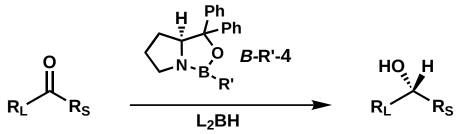
Table 9. Oxazaborolidine-catalyzed reduction of α,β-ynones.

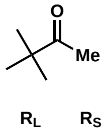
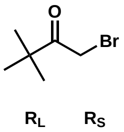
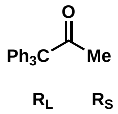
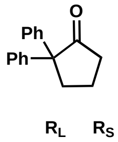
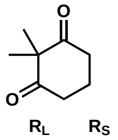
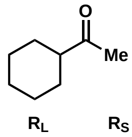
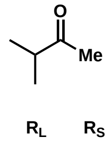
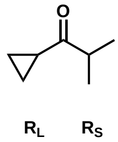
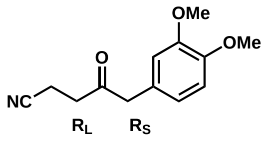
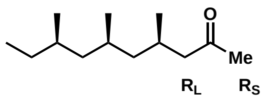


Ynone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	71–88 (R = *n*-alkyl)[67] 94–96 (R = *s*-alkyl)[67]	*B*-Me-**4**[a]	BMS	−30
	95 (R = *n*-alkyl)[67] 98 (R = *c*-Hexyl)[67]	*B*-Me-**4**[a]	BMS	−30
	90–97 (R = *n*-, *s*-alkyl)[43]	*B*-CH_2SiMe_3-**4**	CB	−78
	91–97 (R = CH_3, *n*-alkyl)[44a]	*B*-*p*-*t*BuC_6H_4-**4**	CB	−40

[a] 2 equiv of *B*-Me-**4**.

Table 10. Oxazaborolidine-catalyzed reduction of dialkyl ketones.



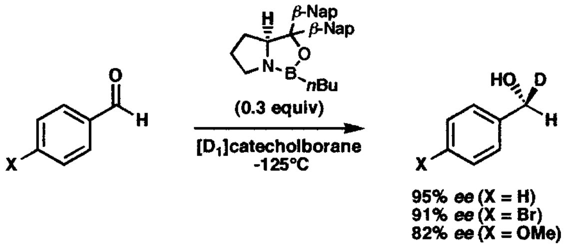
Ketone	*ee* [%]	Catalyst	L_2BH	*T* [°C]	Ketone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	97.4[46]	*B*-Me-**4**	BDEA	20		97[44a]	*B*-*n*Bu-**4**	BMS	23
	97[55a]	*B*-Me-**4**	BTHF	120		92[69a]	*B*-Me-**4**	BMS	40
	93[70]	*B*-*n*Bu-**4**	CB	25		≥ 99[46]	*B*-Me-**4**	BDEA	20
	91[46]	*B*-Me-**4**	BDEA	20		91[58]	*B*-*n*Bu-**4**	CB	−78
	82[71]	*B*-Me-**4**	BMS	−15		–[a]	*B*-Me-**4**	BTHF	23

[a] 70 % *de*.[70]

Transition metal π complexes of achiral ketones can often be reduced with high enantioselectivity. Thus, the CBS reduction of a variety of ketones π-complexed with chromium,[72] cobalt,[58] iron,[73] or ruthenium[73b] has been investigated with outstanding results (Table 11). The resulting optically active products are useful for the synthesis of pharmaceutically important compounds[72] and chiral ligands for asymmetric catalysis.[73]

The study of trihalomethyl ketones has provided deep insights into the connection between ketone conformation and reactivity.[22, 74] The electron-withdrawing nature of the trihalomethyl group results in a stereoelectronically favorable deformation of the carbonyl group towards CX_3. Together with the steric bulk of the trihalomethyl group, this leads to highly selective catalyst binding *anti* to CX_3 and subsequent fast hydride transfer[22] to furnish trihalomethyl carbinols of high enantiopurity across a wide range of ketonic structures (Table 12).[75]

Primary alcohols deuterated in the 1-position have been prepared by the reduction of the corresponding aldehydes with [D_1]catecholborane at low temperature (Scheme 7).[31] 1-Octanal (90 % *ee*) and cyclohexanecarbaldehyde (92 % *ee*) also undergo highly selective reduction under these conditions.

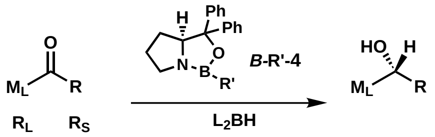


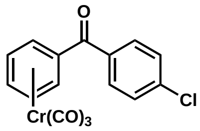
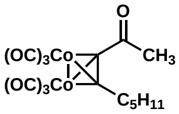
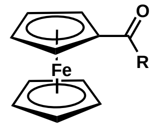
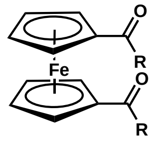
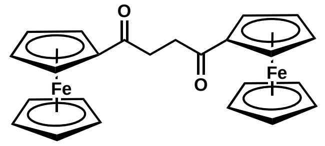
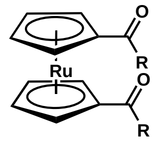
Scheme 7. Preparation of primary alcohols deuterated in the 1-position.

6. Applications of the Oxazaborolidine-Catalyzed Reduction of Ketones

The ever-increasing need for absolute stereochemical control in the construction of organic molecules has resulted

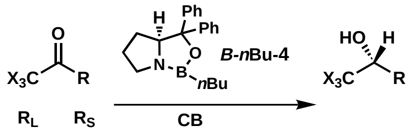
Table 11. Oxazaborolidine-catalyzed reduction of ketones in ligands of metal complexes.

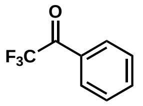
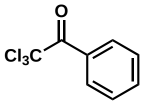
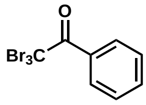
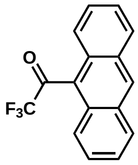
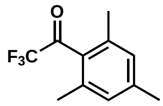
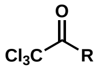


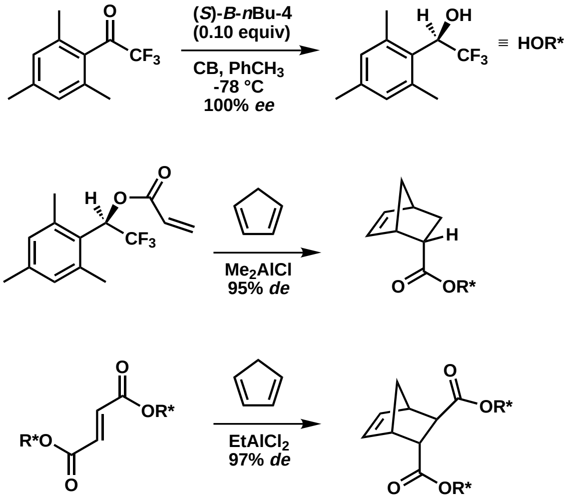
Complex	*ee* [%]	Catalyst	L_2BH	*T* [°C]
	98[72]	*B*-*n*Bu-**4**	CB	− 40
	97[58]	*B*-CH_2SiMe_3-**4**	CB	− 78
	> 95 (R = Me, Et, Ph, *i*Pr)[73a]	*B*-Me-**4**	BTHF	0
	> 99 (R = *n*-, *s*-alkyl, Ph)[a][73b]	*B*-Me-**4**	BTHF	0
	> 98[b][73c]	*B*-Me-**4**	BTHF	0
	> 99 (R = Me, *n*-pentyl)[c][73b]	*B*-Me-**4**	BTHF	0

[a] 74–94 % *de*. [b] 74 % *de*. [c] 68–78 % *de*.

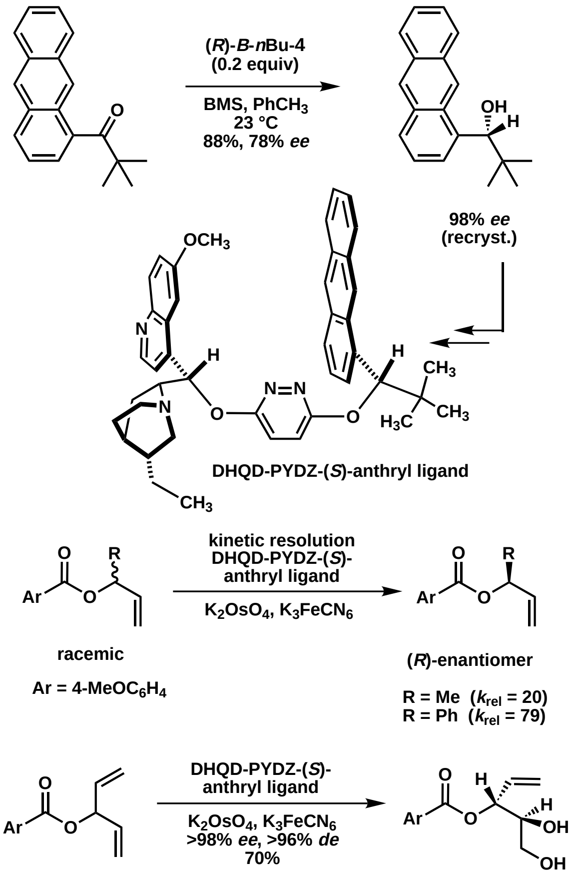
Table 12. Oxazaborolidine-catalyzed reduction of trihalomethyl ketones.



Ketone	*ee* [%]	*T* [°C]
	90[47]	− 78
	96[22]	− 23
	98[22]	− 23
	94[47]	− 78
	100[55a]	− 78
	92 – 98 (R = *n*-, *s*-, *t*-alkyl)[75]	− 23 bis − 78



Scheme 8. Synthesis of (*R*)-(−)-mesityl-2,2,2-trifluoroethanol, an outstanding chiral auxiliary for the Lewis acid catalyzed Diels – Alder reaction.



Scheme 9. Highly selective kinetic resolution of allyl alcohol derivatives with a catalyst for asymmetric dihydroxylation.

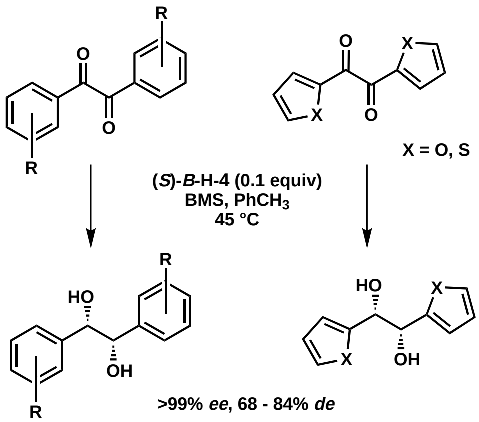
in a large number of applications of the CBS reduction to asymmetric synthesis. These applications include the preparation of 1) chiral ligands for enantioselective synthesis, 2) highly useful chiral intermediates, 3) synthetic bioactive compounds, and 4) natural products.

6.1. Preparation of Enantiopure Ligands for Asymmetric Synthesis

The CBS reduction of 1-mesityl trifluoromethyl ketone provided the corresponding (*R*)-alcohol with greater than 99.8 % *ee* (Scheme 8).[55a] This product served as a useful chiral controller in Lewis acid catalyzed Diels – Alder reactions. The corresponding acrylate and fumarate esters react with cyclopentadiene to form Diels – Alder adducts with excellent diastereoselectivity.[76]

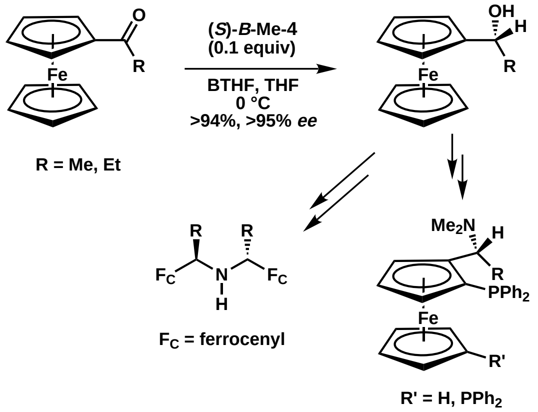
The Sharpless asymmetric dihydroxylation (AD) of olefins is broadly useful in organic synthesis. To increase the scope of this reaction, the DHQD-PYDZ-(*S*)-anthryl ligand (designed under guidance from the dihydroxylation mechanism) was prepared from enantioenriched *tert*-butyl anthryl alcohol (Scheme 9).[77] This catalyst has a deep binding pocket that can accommodate olefinic substrates with remote binding groups, such as allyl 4-methoxybenzoates.[78] It is highly effective for kinetic resolution of racemic allyl 4-methoxybenzoate (Scheme 9).

Chiral 1,2-diols have been extensively utilized as ligands and chiral controllers for the asymmetric preparation of C – X and C – C stereocenters. The CBS reduction of 1,2-diketones, in particular benzil derivatives and heterocyclic analogues, with $BH_3 \cdot Me_2S$ in the presence of (*S*)-*B*-H-**4** furnishes the optically active (*S,S*)-hydrobenzoins with outstanding enantiomeric excess and good diastereomeric excess (Scheme 10).[79]



Scheme 10. Enantioselective reduction of 1,2-diketones to valuable chiral 1,2-diols.

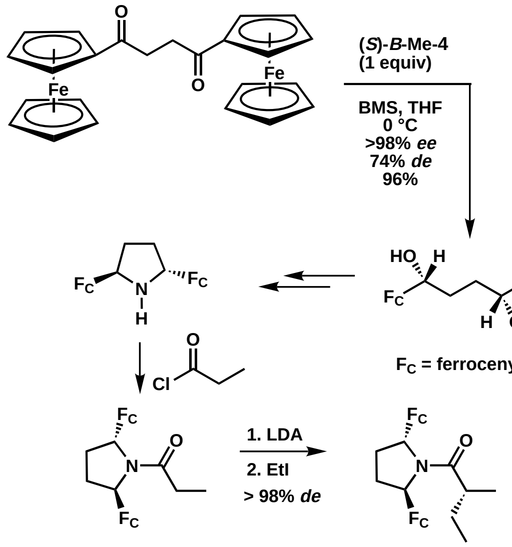
The oxazaborolidine-catalyzed reduction of ferrocenyl ketones, F_CCOR, proceeds with excellent enantioselectivity (>95% *ee*, Scheme 11 and Table 11).[76] The resultant optically active ferrocenyl carbinols can be converted into chiral ferrocenylamines with complete retention of configuration. This affords useful chiral bases for asymmetric deprotonation or chiral ligands for transition metal catalyzed reactions.



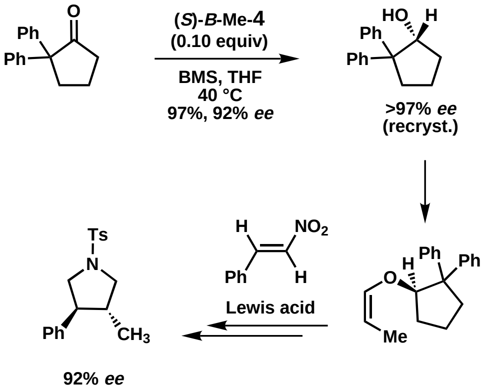
Scheme 11. CBS reduction of acylferrocenes to useful chiral ligands.

The asymmetric reduction of 1,2-bis(ferrocenoyl)ethane occurs with high enantioselectivity (>98% *ee*) and diastereoselectivity (74% *de*) to form a diol which was converted into a chiral C_2-symmetric pyrrolidine. This is a useful chiral auxiliary for diastereoselective alkylation (Scheme 12).[73c]

(*R*)-2,2-Diphenylcyclopentanol was obtained by oxazaborolidine-catalyzed reduction (92% *ee*) and converted into vinyl ethers for Lewis acid promoted [4+2] cycloaddition with 2-substituted 1-nitroalkenes. Hydrogenation of the resulting cycloadducts affords a route to chiral 3,4-disubstituted pyrrolidines (Scheme 13).[69a, 80]



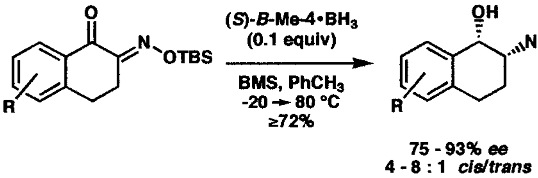
Scheme 12. A C_2-symmetric ferrocenylpyrrolidine is an effective chiral auxiliary.



Scheme 13. Preparation of a useful auxiliary for nitroalkene–vinyl ether cycloadditions.

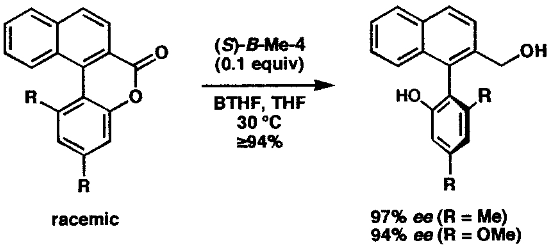
6.2. Preparation of Useful Chiral Building Blocks

Enantiopure amino alcohols are of interest because of their biological activity and value as chiral ligands in metal-catalyzed organic reactions. The catalytic oxazaborolidine-mediated reduction of α-keto oximes results in reduction of C=O followed by C=N to give primarily the *cis*-amino alcohol (Scheme 14).[81]



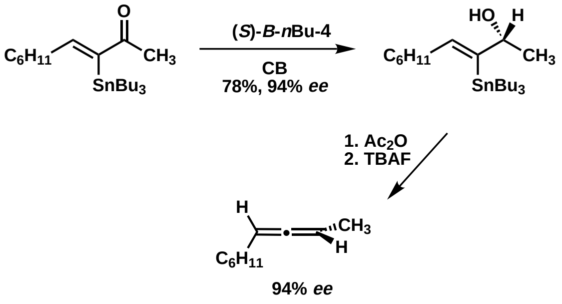
Scheme 14. One-step synthesis of optically active *cis*-amino alcohols.

In a particularly striking example of the broad applicability of the CBS methodology, the enantioselective reduction of axially prostereogenic biaryl lactones affords one atropisomer in a ratio of 97:3 or higher (Scheme 15).[82] It was proposed that the product-determining step is the selective reduction of an equilibrating mixture of enantiomeric hydroxy aldehydes.



Scheme 15. Selective ring opening to an atropisomer of axially chiral biaryl compounds.

The chiral stannylated allyl alcohol shown in Scheme 16 was readily obtained by CBS reduction and transformed into a chiral allene by fluoride-catalyzed elimination.[62a]

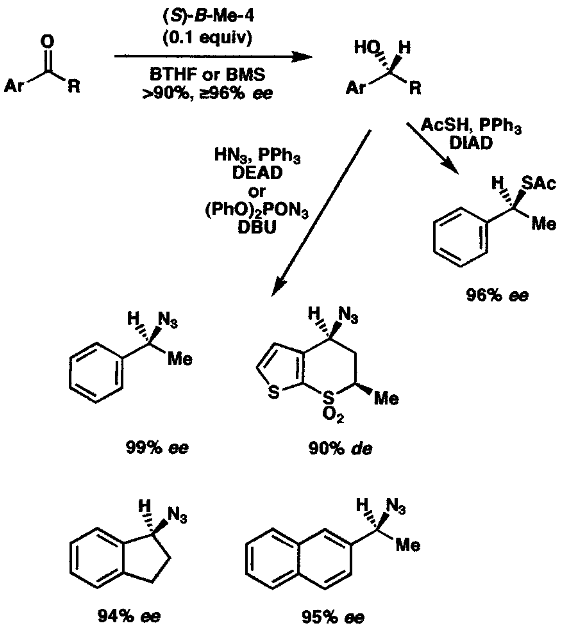


Scheme 16. A different route to optically active allenes.

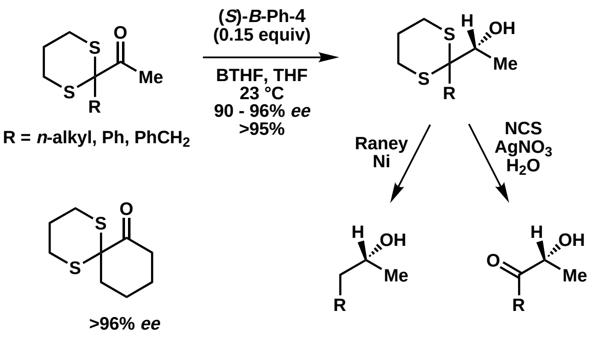
Whereas chiral C–O stereocenters can be readily accessed by oxazaborolidine-catalyzed reduction of ketones, the asymmetric reductions of other heteroatom–carbon double bonds are not as efficient. To overcome these limitations, the displacement of the hydroxyl group of chiral secondary alcohols from the CBS reduction with either nitrogen or sulfur nucleophiles under Mitsunobu-type conditions has been investigated and found to occur by S_N2 inversion; this yields optically active nitrogen[54, 83] and sulfur compounds[86] (Scheme 17). These results are especially noteworthy considering the tendency of benzyl substrates to undergo S_N1 displacement with loss of configuration.

The dithiane protecting group for ketones has been utilized as a steric control element in the CBS reduction to differentiate the carbonyl oxygen electron lone pairs (Scheme 18).[85] The reductions were highly enantioselective for both acyclic and cyclic compounds. Subsequent desulfurization (with Raney Ni) gave aliphatic carbinols, whereas hydrolysis gave α-hydroxy ketones.

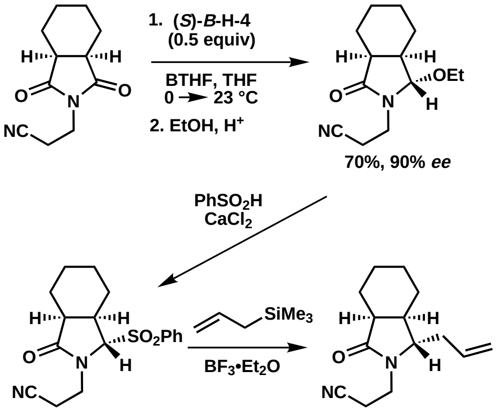
The desymmetrization of a *meso*-imide by the selective reaction of one of the two prochiral carbonyl groups is extremely powerful as three new chiral centers result. As shown in Scheme 19, oxazaborolidine-catalyzed reduction accomplishes this transformation with good enantiomeric excess (90% *ee*). This provides a route to enantioenriched starting materials for *N*-acyliminium ion chemistry.[86]



Scheme 17. The Mitsunobu route to chiral nitrogen and sulfur compounds.

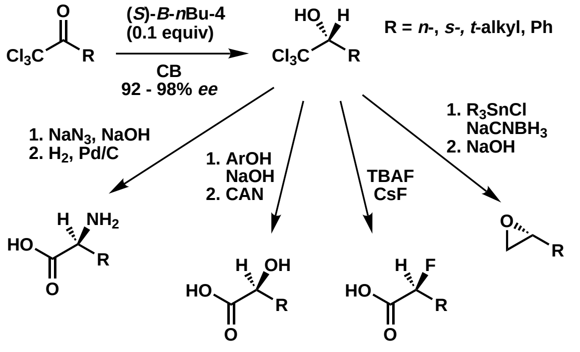


Scheme 18. Dithiane as the large group R_L in the CBS reduction.



Scheme 19. CBS reduction of *meso*-imides yields chiral pyrrolidinones.

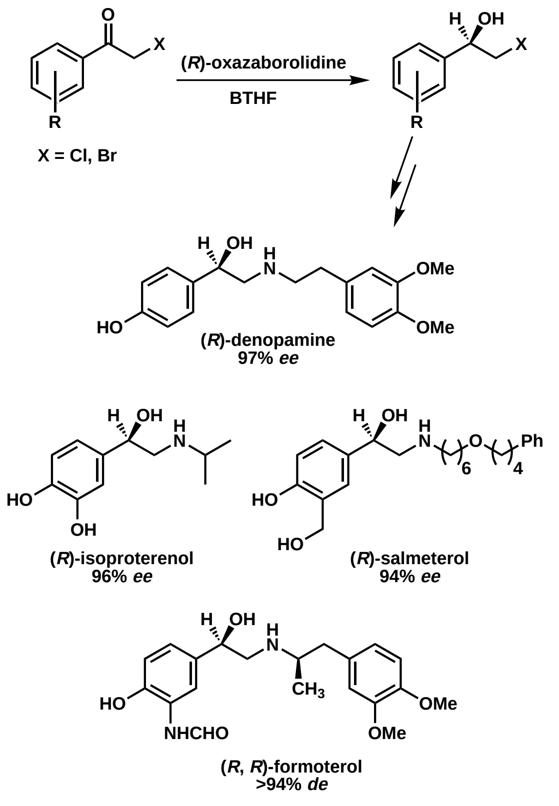
Trichloromethyl carbinols, which are available with very high levels of enantioselectivity by the asymmetric reduction of achiral trichloromethyl ketones,[87] are readily converted into α-amino,[75] α-hydroxy,[88] and α-fluoro acids[89] under basic conditions via a highly reactive 1,1-dichloro epoxide (Scheme 20). The selective dechlorination of trichloromethyl carbinols to chlorohydrins followed by ring closure provides a straightforward route to optically active terminal oxiranes.[90]



Scheme 20. Trichloromethyl alcohols give access to many useful chiral intermediates.

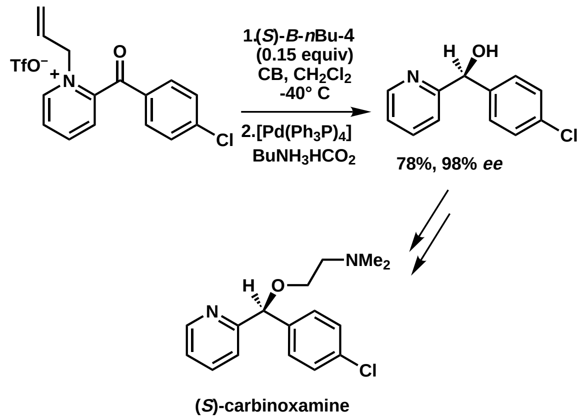
6.3. Synthesis of Bioactive Compounds

Many β-agonists, which are useful in the treatment of asthma and bronchitis, are currently sold as racemates despite the demonstration of enhanced efficacy of the *R* isomers. The oxazaborolidine-catalyzed reduction of α-haloacetophenones has permitted the highly efficient preparation of a number of β-agonists in enantiomerically pure form by amination of the corresponding optically active styrene oxide or O-silyl halohydrin (Scheme 21).[91]



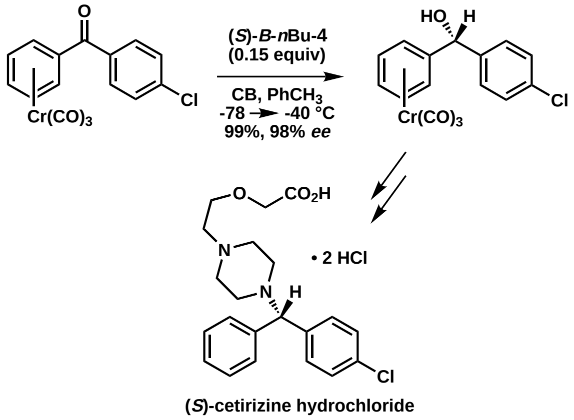
Scheme 21. Enantioselective synthesis of β-agonists.

The commercial histamine antagonist carbinoxamine has been prepared as essentially a single enantiomer (98% *ee*); the key steps are a CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate followed by in situ deallylation (Scheme 22).[59, 60] The allyl group serves both to prevent coordination of the pyridine nitrogen atom to the stoichiometric reductant catecholborane and/or the oxazaborolidine catalyst, and to provide the necessary steric bias for the selective binding of one of the carbonyl oxygen electron lone pairs to the catalyst.



Scheme 22. Enantioselective synthesis of (*S*)-carbinoxamine.

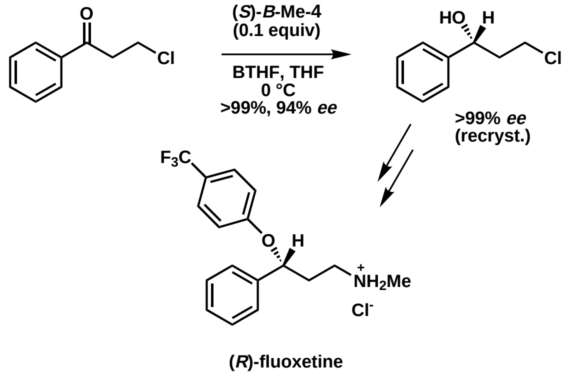
Cetirizine hydrochloride (zyrtec), an antihistamine that is notable for its nonsedating properties and potency, contains an amino-substituted benzhydril stereocenter. This stereocenter has been established by a highly selective CBS reduction of a benzophenone–$Cr(CO)_3$ π complex (Scheme 23).[75] The complexed $Cr(CO)_3$ group behaves as R_L both for steric and electronic reasons, and functions as a controller for the enantiospecific displacement of the hydroxyl group by amine with retention of configuration.



Scheme 23. Enantioselective synthesis of (*S*)-cetirizine hydrochloride.

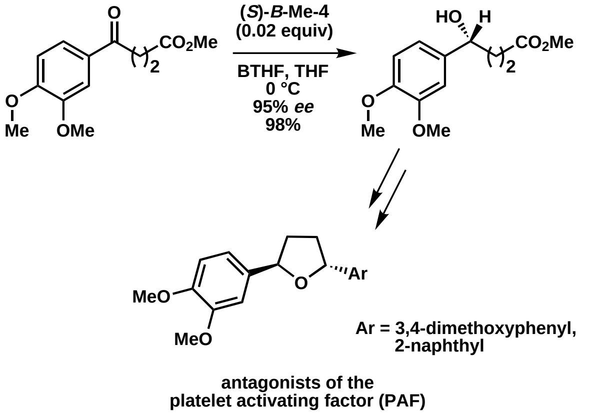
The antidepressant fluoxetine hydrochloride (prozac, Eli Lilly) has been synthesized in enantiomerically pure form by the oxazaborolidine-catalyzed reduction of β-chloropropiophenone as a key step (Scheme 24).[92] This four-step synthesis proceeds in high overall yield (77–82%) and does not require chromatographic purification.

Chiral *trans*-2,5-diaryltetrahydrofurans, inhibitors of the platelet activating factor, have been prepared by CBS



Scheme 24. Enantioselective synthesis of (R)-fluoxetine.

reduction of a γ-ketoester followed by lactonization, reduction, and stereoselective arylation (Scheme 25).[93]



Scheme 25. Enantioselective synthesis of antagonists of the platelet activating factor (PAF).

The chiral thioether L-691,698, an antagonist of leukotriene D_4, has also been synthesized by the oxazaborolidine-catalyzed reduction (Scheme 26).[94]

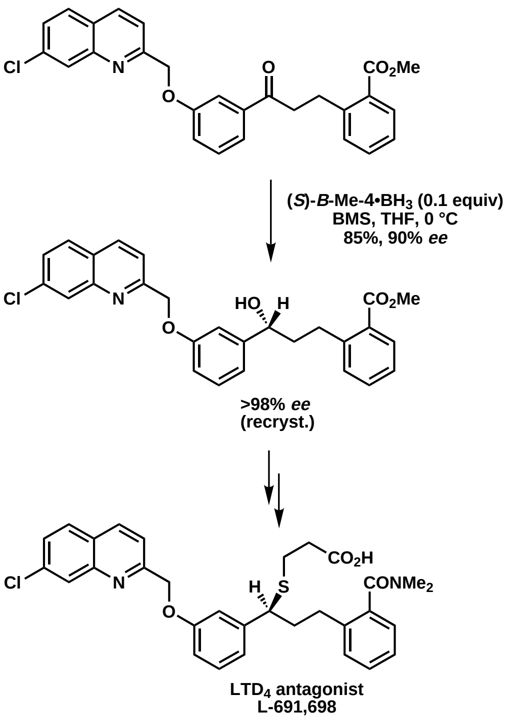
The carbonic anhydrase inhibitor MK-0417 has been prepared on a large scale by the oxazaborolidine-catalyzed reduction of the heterocyclic ketone shown in Scheme 27.[44b]

The synthesis of the potassium channel blocker MK-0499 utilized a variant of the CBS reduction in which one equivalent of 2-propanol was added prior to $BH_3 \cdot SMe_2$ (Scheme 28).[21] The use of 2-propanol as additive increased the diastereoselectivity from 93 to 98%.

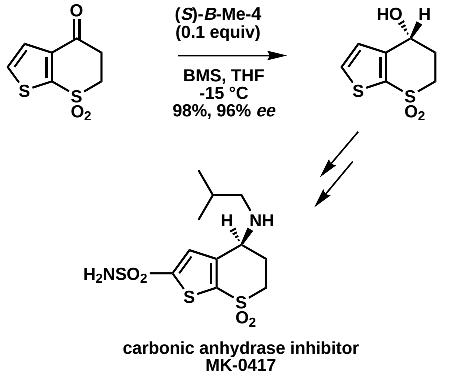
The CBS reduction of the acyclic α,β-enone shown in Scheme 29 proceeded diastereoselectively to form the corresponding allyl alcohol, which was used for the synthesis of an isomer of colletallol.[62d, e]

Oxazaborolidine-catalyzed reduction of the α,β-enone in Scheme 30 to the optically pure allyl alcohol provided the first chiral center in the synthesis of the antiinflammatory and immunosuppressive agent RS-97613.[62f] Subsequent stereoselective orthoester Johnson–Claisen rearrangement, diastereoselective α-methylation, and hydrolysis completed the synthesis of this analogue of mycophenolic acid.

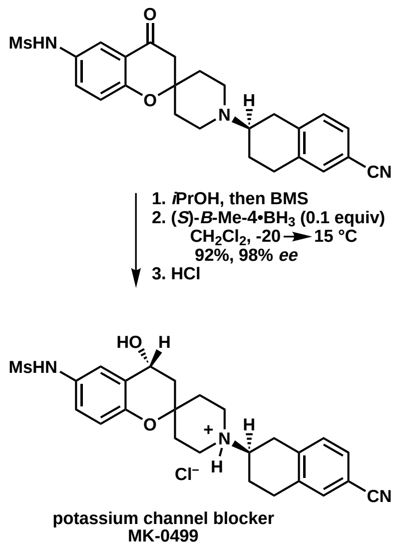
The 3-deoxy-3-thia analogue of vitamin D was synthesized by CBS reduction of the cyclic α,β-enone shown in Scheme 31.



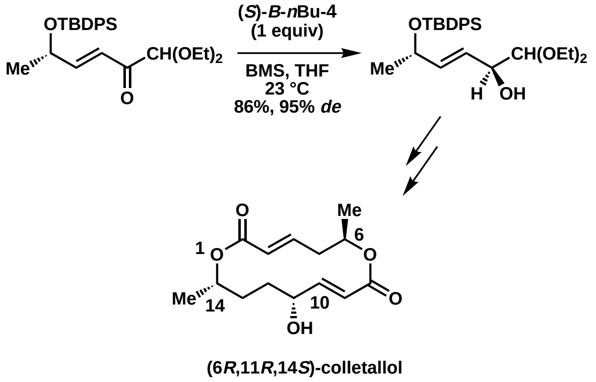
Scheme 26. Enantioselective synthesis of a leukotriene D_4 antagonist.



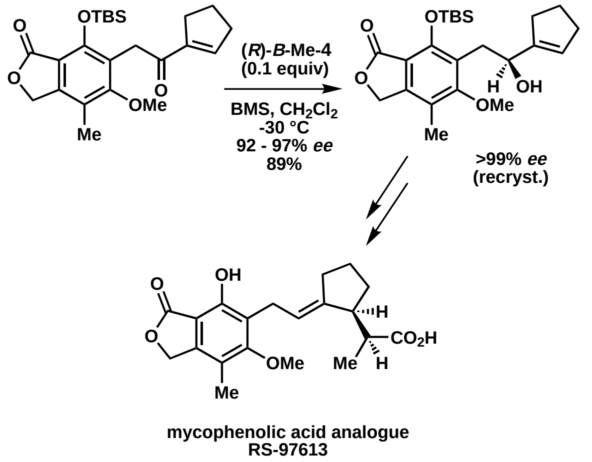
Scheme 27. Enantioselective synthesis of a carbonic anhydrase inhibitor.



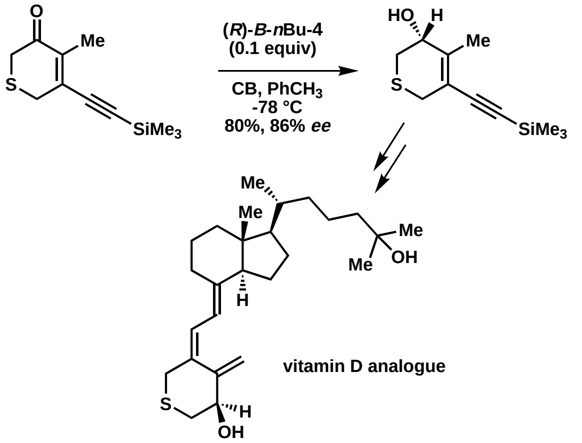
Scheme 28. Enantioselective synthesis of a potassium channel blocker.



Scheme 29. Asymmetric synthesis of (6*R*,11*R*,14*S*)-colletallol.



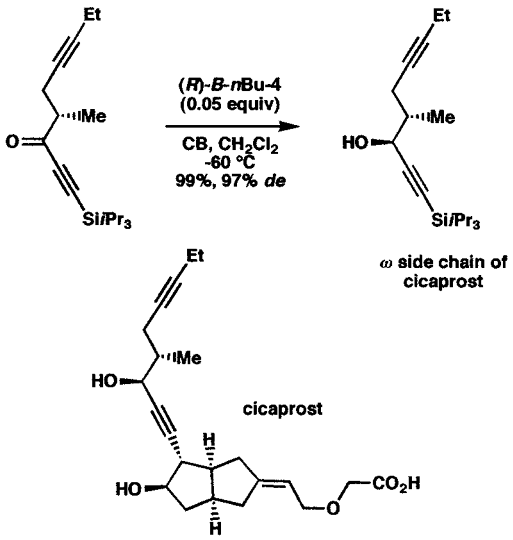
Scheme 30. Enantioselective synthesis of an immunosuppressive and antiinflammatory agent.



Scheme 31. Asymmetric synthesis of a vitamin D analogue.

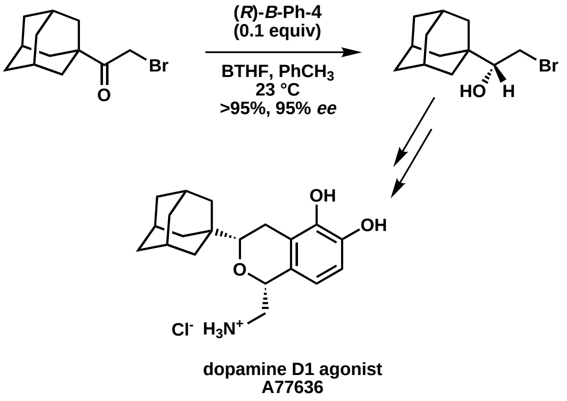
This provided a chiral allyl alcohol corresponding to the A ring.[95]

Cicaprost, an orally active, metabolically stable prostaglandin I$_2$ (PGI$_2$) analogue, contains a complex side chain which was constructed by oxazaborolidine-catalyzed reduction (Scheme 32).[96] Long-range steric interactions between *n*-butyl group on the boron atom of the catalyst and the triisopropylsilyl group of the ketonic substrate cause ethynyl to behave as the large group R$_L$. The chirality of the starting ketone does not affect the selectivity of the reduction since the use of the enantiomeric (*S*)-oxazaborolidine catalyst gave the other diastereomer with high diastereomeric excess (96 %).



Scheme 32. Asymmetric synthesis of the ω side chain of cicaprost.

The dopamine D1 agonist A77636 was recently prepared in optically pure form by oxazaborolidine-catalyzed reduction of adamantyl bromomethyl ketone (Scheme 33).[97] Conversion of the chiral bromohydrin into the corresponding epoxide, ring opening with an aryllithium reagent, intramolecular acetal cyclization, and deprotection gave the desired product in very good yield.

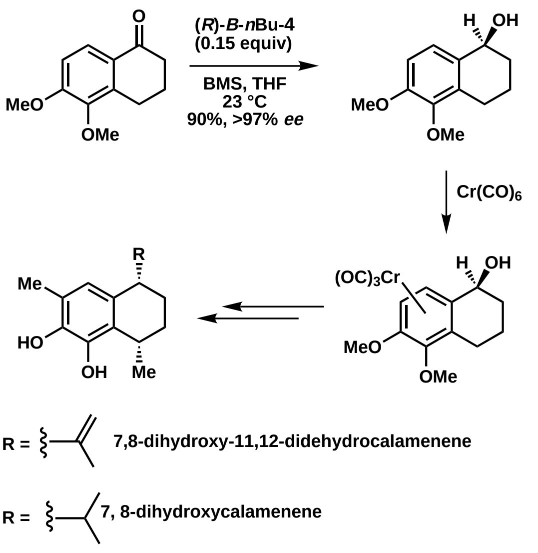


Scheme 33. Asymmetric synthesis of A77636.

6.4. Synthesis of Natural Products

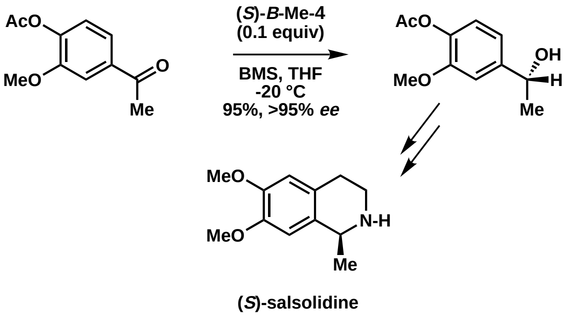
The antiinfective compounds 7,8-dihydroxycalamenene and 7,8-dihydroxy-11,12-didehydrocalamenene were synthesized by CBS reduction of 5,6-dimethoxy-1-tetralone, hydroxyl-directed face-selective complexation of a Cr(CO)$_3$ moiety, and subsequent hydrogenolysis, metalation/alkylation, and decomplexation (Scheme 34).[98]

The tetrahydroisoquinoline (*S*)-salsolidine was prepared efficiently by oxazaborolidine-catalyzed reduction of a substituted acetophenone followed by Mitsunobu displacement



Scheme 34. Enantio- and stereocontrolled synthesis of chiralen antiinfective tetralins.

of the hydroxyl group with a sulfonamide and intramolecular cyclization (Scheme 35).[99] This approach should be applicable to the synthesis of a number of enantiopure tetrahydroisoquinoline derivatives.

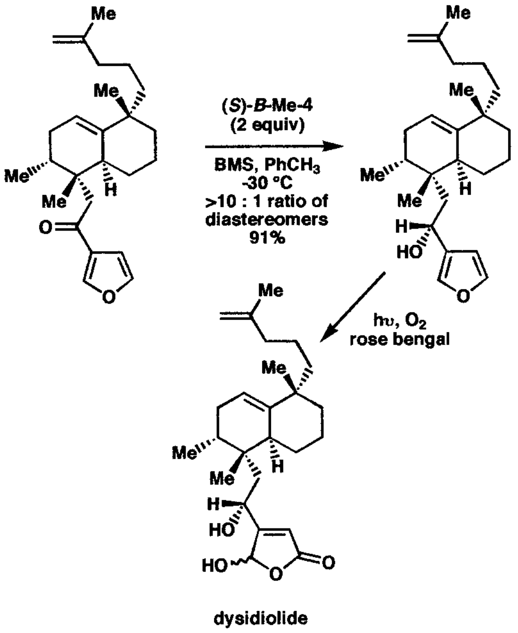


Scheme 35. Enantioselective synthesis of (S)-salsolidine.

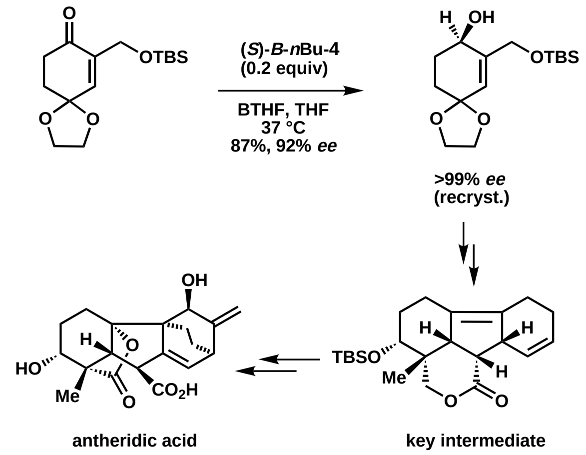
In a recent total synthesis of the sesterterpene dysidiolide, a marine sponge metabolite that has been shown to exhibit antitumor activity, oxazaborolidine-catalyzed reduction afforded greater than 10:1 selectivity for the required alcohol; the 3-furyl group acted effectively as R_L, and the bicyclic ring system as R_S (Scheme 36).[100] Importantly, this route permitted conversion of the *S* diastereomer into the desired *R* isomer by oxidation and subsequent asymmetric reduction. Mitsunobu displacement of the hydroxyl group of the *S* diastereomer was nonstereoselective.

The fern hormone antheridic acid was initially synthesized in racemic form. An enantioselective synthesis of a key intermediate was achieved by the oxazaborolidine-catalyzed reduction and subsequent conversions depicted in Scheme 37.[63a]

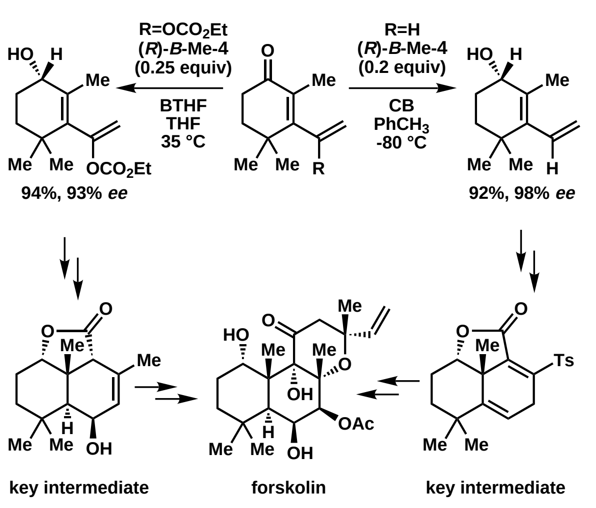
Two different routes to optically active intermediates for the synthesis of forskolin, a potent activator of adenylate cyclase, have been devised utilizing CBS reduction of the dieneones shown in Scheme 38.[101, 102]



Scheme 36. Enantioselective synthesis of dysidiolide.

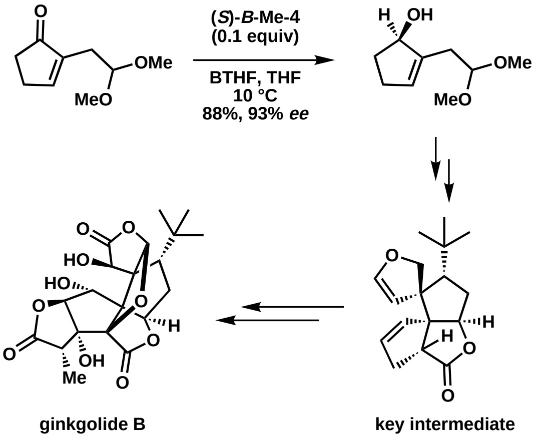


Scheme 37. Enantioselective synthesis of antheridic acid.

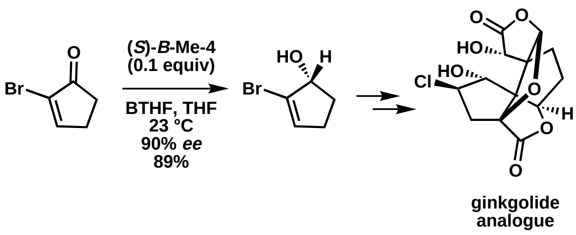


Scheme 38. Enantioselective synthesis of forskolin.

Ginkgolide B, a potent antagonist of the platelet activating factor, has been synthesized enantioselectively by CBS reduction of a α-functionalized cyclopentenone to introduce chirality (Scheme 39).[63b] The resulting optically active allyl alcohol was then elaborated in a stereocontrolled fashion via a tetracyclic lactone to ginkgolide B. The CBS reduction of 2-bromo-2-cyclopentenone served as a key step in the synthesis of a truncated analogue of ginkgolide B (Scheme 40).[64b]

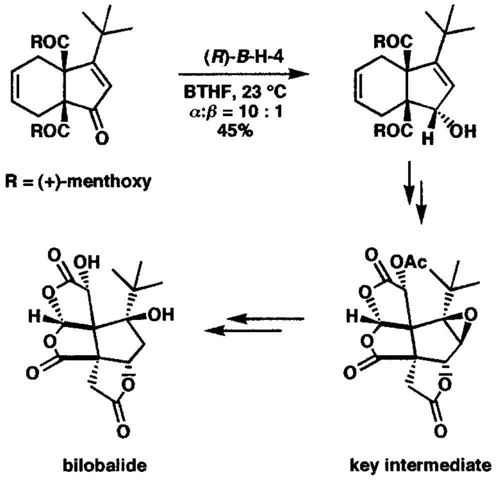


Scheme 39. Enantioselective synthesis of ginkgolide B.



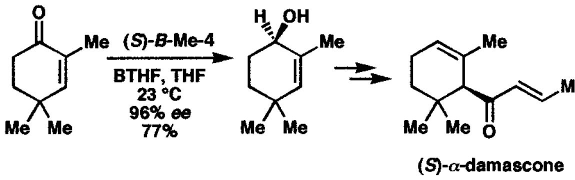
Scheme 40. Enantioselective synthesis of a ginkgolide analogue.

An asymmetric synthesis of bilobalide, an unusual substance produced by the gingko tree *Ginkgo biloba*, has been carried out starting from the bicyclic enone depicted in Scheme 41.[103] Attempts to reduce this chiral ketone to the α-epimer with a number of reagents ($NaBH_4$, $Zn(BH_4)_2$, SmI_2 in THF/MeOH, $BH_3 \cdot THF$, Na powder in 2-propanol/toluene) gave unsatisfactory results. The oxazaborolidine-mediated reduction of this substrate, however, provided greater than 10:1 selectivity for the α-epimer, which was then transformed into bilobalide via the tetracyclic trilactone shown.



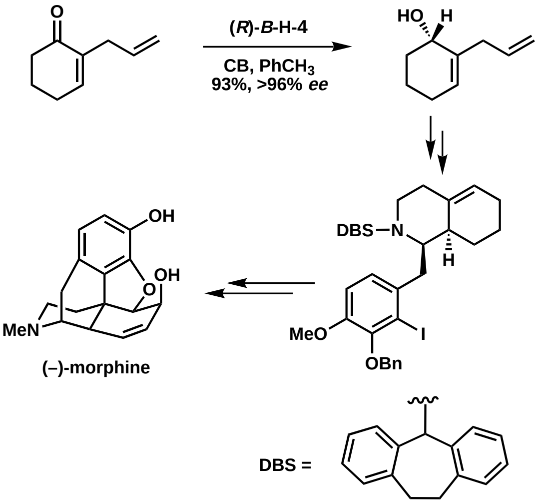
Scheme 41. Enantioselective synthesis of bilobalide.

The important fragrance (*S*)-α-damascone could be prepared by a sequence involving CBS reduction of the cyclic α-methyl-α,β-enone shown in Scheme 42, transfer of chirality from C–O to C–C by the Still variant of the [2,3] Wittig rearrangement to set the tertiary chiral center, oxidation, and introduction of the side chain.[104]



Scheme 42. Enantioselective synthesis of (*S*)-α-damascone.

A recent elegant synthesis of (–)-morphine also employed a highly enantioselective CBS reduction (Scheme 43).[105] Stereospecific conversion of the hydroxyl group into dimethylphenylsilyl and the terminal vinyl moiety into an amino substituent (*N*-DBS) set the stage for an intramolecular iminium ion–allylsilane cyclization to give the bicyclic system shown in Scheme 43. The bridgehead ring system was established by an intramolecular Heck reaction.

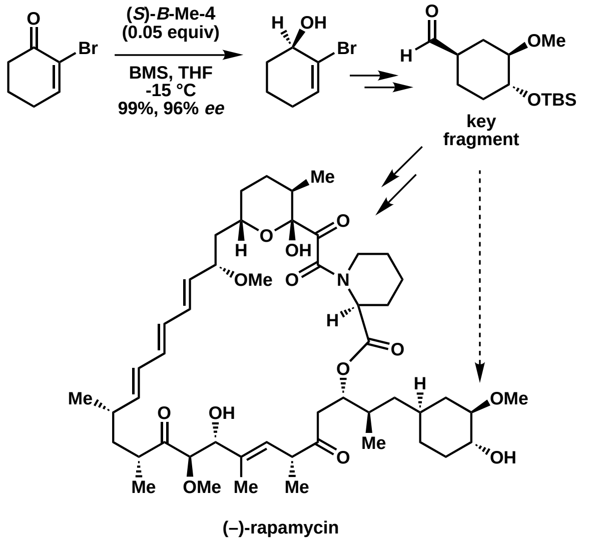


Scheme 43. Enantioselective synthesis of (–)-morphine.

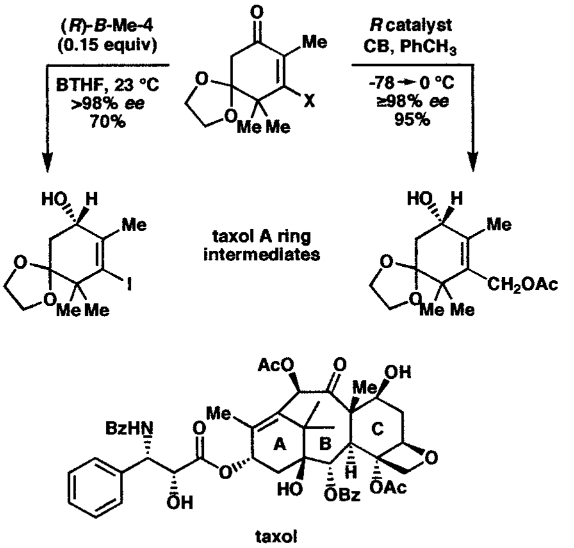
In the synthesis of the powerful immunosupressive agent (–)-rapamycin, oxazaborolidine-catalyzed reduction of 2-bromo-2-cyclohexen-1-one was used to generate the functionalized cyclohexyl subunit (Scheme 44).[64a, 106]

Two conceptually similar routes to the A ring of taxol have been developed by CBS reduction of functionalized cyclohexenones (Scheme 45).[107]

While many conjugated cyclic α,β-enones with *endocyclic* (*s-trans*) unsaturation have been reduced to allyl alcohols in



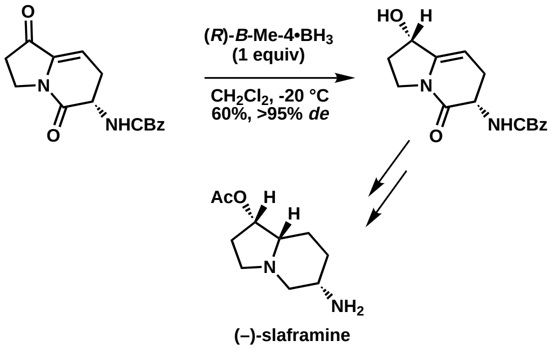
Scheme 44. Asymmetric synthesis of the cyclohexyl moiety of (−)-rapamycin.



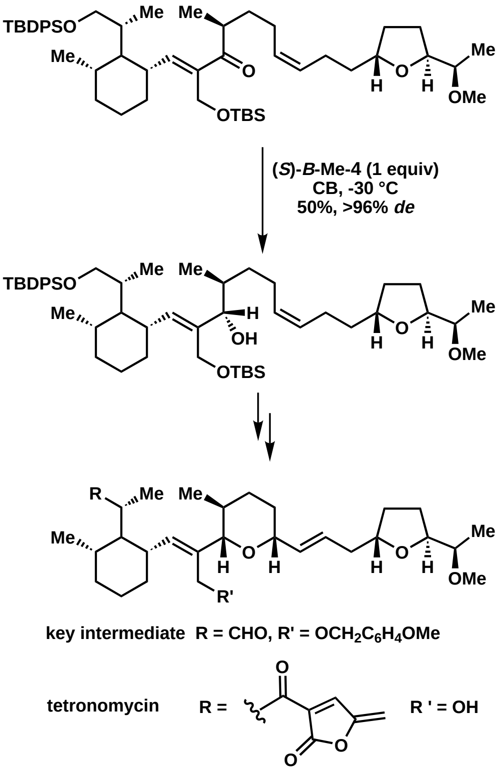
Scheme 45. Enantioselective synthesis of taxol A ring intermediates.

the presence of chiral oxazaborolidines, the reduction of such compounds with *exocyclic* (*s-cis*) double bonds has been reported only recently in connection with the synthesis of the alkaloid (−)-slaframine.[108] The chiral α,β-enone shown in Scheme 46 was reduced with one equivalent of the (*R*)-*B*-Me-**4**·BH_3 complex (*B*-Me-**5**) to provide the required allyl alcohol with excellent diastereomeric purity. In contrast, the use of the enantiomeric oxazaborolidine–BH_3 complex afforded the other diastereomer with high selectivity.

An approach to the synthesis of the ionophore antibiotic tetronomycin utilized the CBS reduction outlined in Scheme 47[109] (>96% *de*) followed by an intramolecular Pd^{II}-mediated cyclization to establish the central *cis*-substituted tetrahydropyran ring. Attempts to prepare the same allyl alcohol by addition of vinyllithium to an aldehyde yielded a 1:2 ratio of desired to undesired diastereomeric alcohols.



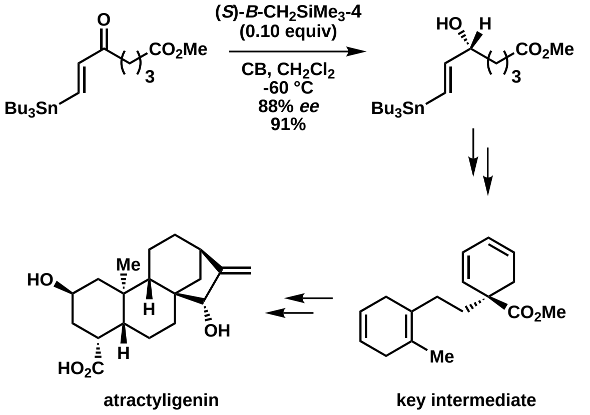
Scheme 46. Asymmetric synthesis of (−)-slaframine.



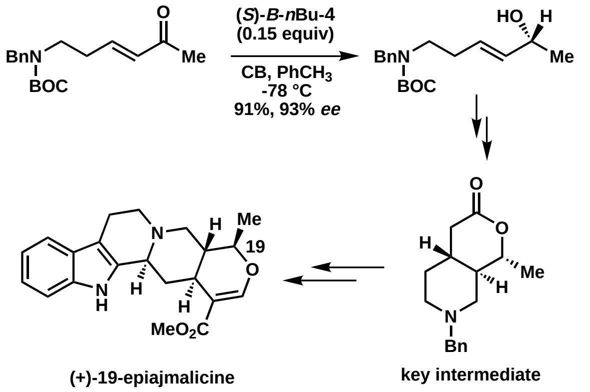
Scheme 47. Diastereoselective CBS reduction of a chiral ketone on the way to tetronomycin.

The naturally occurring adenosine diphosphate transport inhibitor atractilygenin was originally synthesized as the racemate; the first key chiral intermediate in the enantioselective CBS reduction is the substituted 1,3-cyclohexadiene shown in Scheme 48.[61] The use of the β-trialkylstannyl substituent on the enone to provide temporary steric bulk and the CH_2SiMe_3 group on the boron atom of the catalyst to maximize long-range steric interactions were crucial for high enantioselectivity in the oxazaborolidine-catalyzed reduction. Subsequent steps including a Claisen rearrangement effected the transfer of chirality from C–O to C–C to form the quaternary carbon stereocenter of the key intermediate.

A recent study on the synthesis of heteroyohimbine alkaloids utilized a CBS reduction of the acyclic α,β-enone shown in Scheme 49 to the allyl alcohol; the *B*-*n*Bu-oxazaborolidine catalyst (93% *ee*) was superior to the *B*-Me-oxazaborolidine catalyst (81% *ee*).[110] Orthoester Johnson–



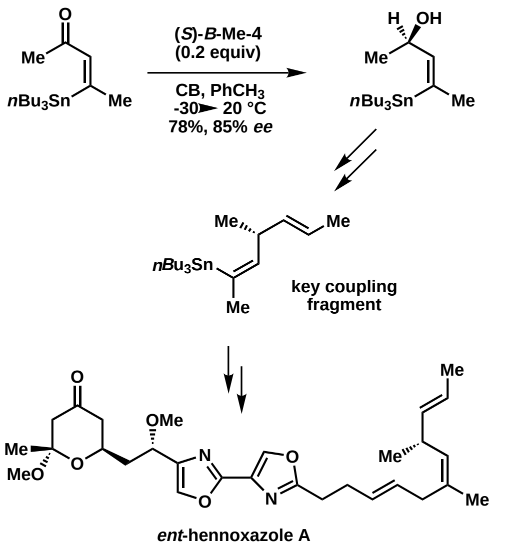
Scheme 48. Enantioselective synthesis of atractyligenin.



Scheme 49. Asymmetric synthesis of a key intermediate on the way to (+)-19-epiajmalicine.

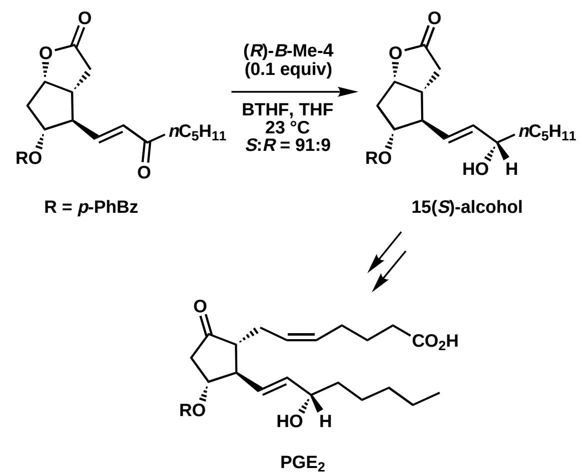
Claisen rearrangement and iminium ion biscyclization provided the bicyclic amino lactone.

The relative and absolute configurations of the marine alkaloid hennoxazole A, which actively inhibits the herpes simplex virus, were unambiguously determined by enantioselective total synthesis. CBS reduction of the *cis*-β-stannylenone as depicted in Scheme 50 followed by hydroxyl activation and stereospecific displacement with a propenyl cuprate gave the indicated chiral 1,4-diene fragment.[62b, c] Transmetalation of this key coupling fragment from the tin to the zinc derivative facilitated a palladium-mediated coupling with an allyl bromide to afford the carbon framework of the natural product.



Scheme 50. Enantioselective synthesis of *ent*-hennoxazole A.

A long-standing challenge in the synthesis of prostanoids has been the selective introduction of the C(15) hydroxyl-bearing stereocenter by reduction of the α,β-enone. While a number of reagents and reaction conditions have been designed to effect this transformation, the CBS reduction provides a pleasing catalytic solution, and furnishes a 10:1 ratio of the diastereomeric alcohols under exceedingly mild conditions (Scheme 51).[13b]

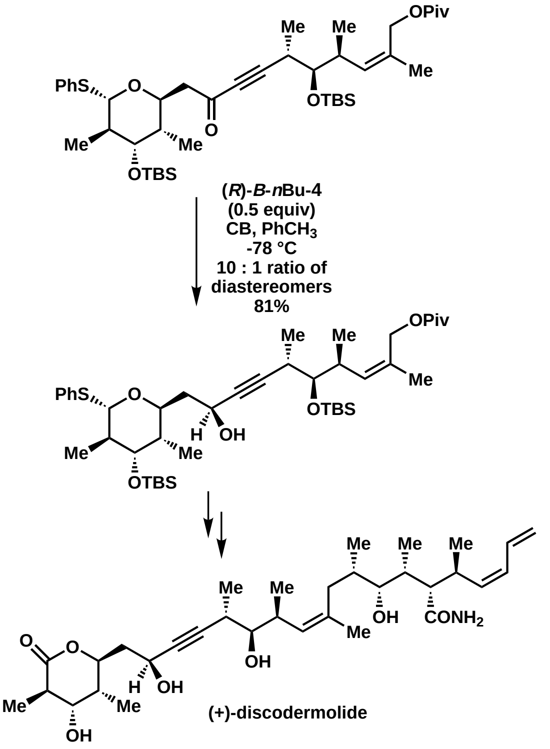


Scheme 51. Asymmetric synthesis of prostaglandins.

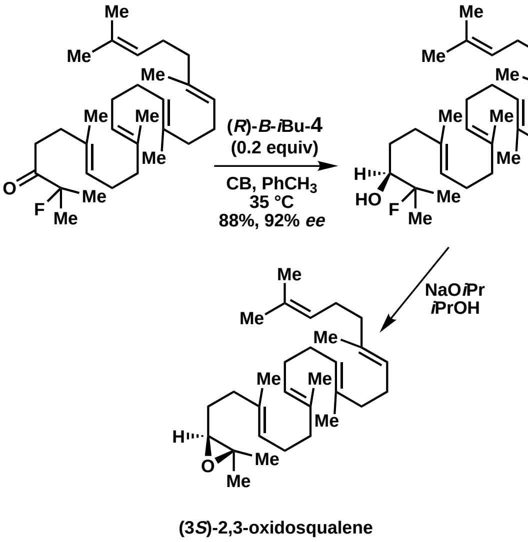
The scarce marine natural product (+)-discodermolide has been observed to possess impressive immunosuppressive activity and, as a result, has been the object of total synthesis. Oxazaborolidine-catalyzed reduction of the propargylic ketone shown in Scheme 52 gave a 10:1 mixture of isomers with the desired antipode predominating.[111] The alkynyl group behaved as R_L in this CBS reduction in a nonpolar solvent and with catecholborane as stoichiometric reductant, which is in agreement with other studies (see Table 9).[43]

(3*S*)-2,3-Oxidosqualene is the biosynthetic precursor to numerous steroids and polycyclic triterpenoids. Asymmetric reduction of the α-fluoro ketone shown in Scheme 53 followed by oxirane ring closure gave (3*S*)-2,3-oxidosqualene with 92% *ee*.[42] The choice of α-fluoro ketone was crucial for high enantioselectivity in the reduction, since the use of the α-chloro or β-bromo ketone resulted in slow reaction rates and only modest enantioselectivities. The magnitude and sense of enantioselectivity were highly dependent on temperature: The enantiomeric ratio *S*:*R* is 96:4 at 35 °C, 93:7 at 23 °C, and 20:80 at −23 °C.

In a recent improved synthesis of the right half of halichondrin B, a potent antitumor agent, a Nozaki–Kishi coupling of vinyl iodide with aldehyde afforded a 4:1 ratio of diastereomers favoring the desired alcohol.[112] Dess–Martin oxidation of the mixture of alcohols to the α-substituted α,β-

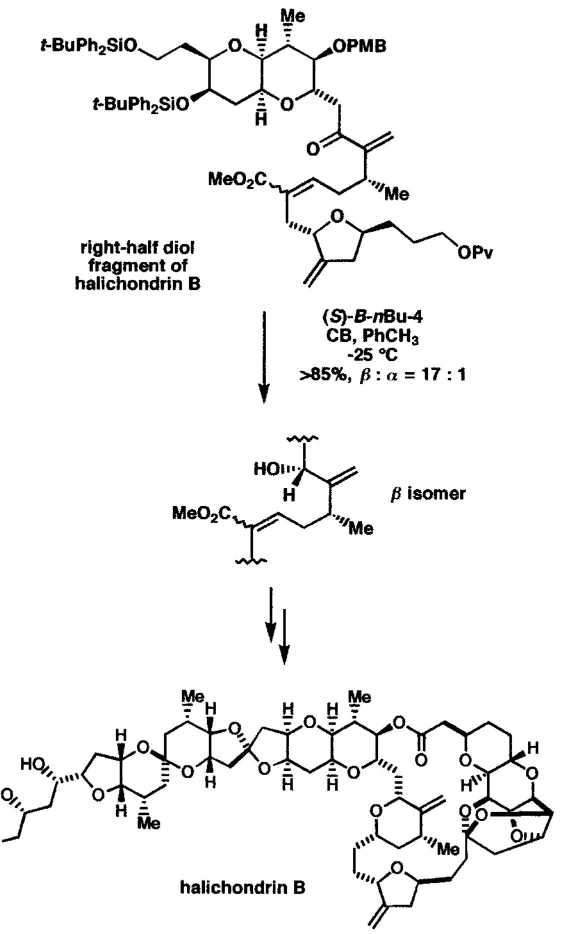


Scheme 52. Enantioselective synthesis of discodermolide.



Scheme 53. Enantioselective synthesis of (3*S*)-2,3-oxidosqualene.

enone followed by CBS reduction gave a much improved 17:1 ratio of diastereomers at the carbinol center and permitted the efficient stereoselective construction of the central pyran unit of the right-half diol fragment (Scheme 54).



Scheme 54. Asymmetric synthesis of halichondrin B.

7. Summary and Outlook

Chiral oxazaborolidine-catalyzed reduction of ketones with coordinated borane or catecholborane as stoichiometric reductant provides access to a broad range of chiral secondary alcohols. These products, in turn, can serve as key intermediates for the synthesis of an enormous range of compounds with regard to functionality, size, and topological complexity. Thus, many types of chiral natural products and bioactive molecules can be synthesized efficiently without the need for optical resolution. The applications of this methodology continue to increase rapidly in number and could become commercially important.

Appendix: Abbreviations Used

BDEA = $BH_3 \cdot$ diethylaniline, BMS = $BH_3 \cdot Me_2S$, Bn = benzyl, BOC = *tert*-butoxycarbonyl, BTHF = $BH_3 \cdot$ THF, Bz = benzoyl, CAN = cerammonium nitrate, CB = catecholborane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DEAD = diethyl azodicarboxylate, DIAD = iiisopropyl azodicarboxylate, Ms = methanesulfonyl, Nap = naphthyl, NCS = *N*-chlorosuccinimide, Piv = pivaloyl, PMB = *p*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl.

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[51] a) Preparation of (*S*)-*B*-*n*Bu-**4**: Toluene (15–20 mL) was added to amino alcohol **3** (253 mg, 1 mmol) and nBuB(OH)$_2 \cdot n H_2O$ (164 mg) in a 25-mL round-bottom flask fitted with a Dean–Stark apparatus (sidearm filled with 4-Å molecular sieves) and a reflux condenser. The mixture was vigorously heated at reflux for 12 h. The toluene was removed by distillation through the Dean–Stark sidearm until about 3 mL were left. After the reaction mixture was cooled to 23°C, the Dean–Stark apparatus was replaced by a rubber septum and the remaining toluene was removed in vacuo at 40°C. Toluene (5.0 mL) was added to provide a 0.20M solution of (*S*)-*B*-*n*Bu-**4** (>95% conversion as determined by ^1H NMR spectroscopy). Spectral data were indentical to that reported in the literature.[14a] The catalyst was stored by placing an additional rubber septum on the flask followed by cooling the solution to −78°C under a positive pressure of nitrogen. The nitrogen source was removed, and the catalyst solution was stored in a jar containing Drierite at −20°C. This precooling procedure prevents possible introduction of air into the flask due to a pressure difference. b) *n*BuB(OH)$_2$ was prepared by a known method (H. C. Brown, T. E. Cole, *Organometallics* **1983**, *2*, 1316–1319) except that aqueous 1N HCl was used instead of anhydrous HCl in the workup. The amount of water in the *n*BuB(OH)$_2$ prepared by this method varies. Therefore, ^1H NMR analysis of the catalyst formation is required to ascertain the exact amount of the boronic acid necessary for complete catalyst formation. Once this is known for a specific batch of *n*BuB(OH)$_2$, however, the proper amount of boronic acid (1.05 equiv) can be added at the start of the reaction. c) Preparation of *B*-Me-**4**: The catalyst was prepared from amino alcohol **3** (253 mg, 1 mmol) and MeB(OH)$_2$ (72 mg, 1.2 mmol) as described above for (*S*)-*B*-*n*Bu-**4**, except that 1) the reaction mixture was heated at 60°C for 1 h before heating at reflux temperature and 2) heating at reflux was maintained for 5 h. The material so obtained showed identical spectral properties with those reported.[14a]

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[57] a) Reduction of acetophenone with *B*-Me-**4** as catalyst and $BH_3 \cdot$diethylaniline (BDEA) as stoichiometric reductant (from reference [46]): A dry 100-mL two-necked flask equipped with an addition funnel, magnetic stirring bar, thermocouple, and septum inlet was charged with a solution of (*R*)-*B*-Me-**4** (0.84 mmol, 0.084M in toluene, 10 mL) followed by BDEA (2.74 g, 16.8 mmol). The reaction vessel was immersed in a water bath, and acetophenone (2.0 mL, 16.6 mmol) in toluene (5 mL) was added through the addition funnel over 1–1.5 h. After ketone addition was complete, the reaction mixture was stirred for an additional hour. MeOH (5 mL) was then slowly added (hydrogen evolution) followed by aqueous 1N HCl (10 mL). After 15–20 min the organic and aqueous layers were separated, and the aqueous layer was extracted with toluene or Et_2O (3×10 mL). The combined organic layers were washed with aqueous 1N HCl (2×10 mL), water, and brine, and then dried ($MgSO_4$). Analysis of the organic layer by gas chromatography (CDX-B column, 30 m × 0.25 mm, J&W Scientific) showed the product to be (*S*)-1-phenylethanol with 94.7% *ee*. Removal of the solvent in vacuo followed by distillation gave (*S*)-1-phenylethanol that was spectroscopically identical with an authentic sample. b) Reduction of α-chloroacetophenone with *B*-*n*Bu-**4** as catalyst and $BH_3 \cdot Me_2S$ (BMS) as stoichiometric reductant: This protocol requires the *simultaneous* addition of ketone and BMS to a solution of the catalyst (0.01 equiv) in order to suppress uncatalyzed reduction pathways and is practical on multigram scale. Dry THF (10 mL) was added to (*S*)-*B*-*n*Bu-**4** (0.647 mmol, 0.2M in toluene, 3.2 mL) and BMS (65 μL, 0.65 mmol, 10M (neat)) under nitrogen. Separate solutions of α-chloroacetophenone (10 g, 64.7 mmol, azeotropically dried with benzene) in dry THF (40 mL) and BMS (4.5 mL, 45 mmol, 10M (neat)) in dry THF (40 mL) were then added simultaneously to the solution of the oxazaborolidine catalyst over 1 h. After addition of ketone and BMS was complete no starting material remained, as determined by thin-layer chromatography. A solution of HCl in MeOH (0.5M, 1.5 mL, 1.2 equiv; prepared by adding acetyl chloride to MeOH at 0°C) was then slowly added (hydrogen evolution), and the solution was stirred for 30 min. THF was removed in vacuo, Et_2O (75 mL) added, and the HCl salt of the amino alcohol that precipitated as a white solid removed by filtration. The Et_2O layer was washed with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (2×10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. HPLC analysis (Chiralcel OD, 2-propanol/hexane 2.5/97.5, 1 mL min^{-1}, $\lambda = 254$ nm) showed the product to be of 98.5% *ee*; t_R: 17.2 min, major; 22.5 min, minor isomer. Purification by filtration through a small plug of silica gel with hexanes/EtOAc (4/1) afforded 10 g (99%) of (*S*)-2-chloro-1-phenylethanol. See reference [13c] for the first report of this procedure with (*S*)-*B*-Me-**4** as catalyst and $BH_3 \cdot$THF (BTHF).

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[60] CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate and in situ deallylation: A flame-dried flask was charged with a solution of (*S*)-*B*-*n*Bu-**4** (370 μL, 0.074 mmol, 0.20 M in toluene), and the toluene was removed in vacuo. CH_2Cl_2 (370 μL) was added followed by catecholborane (104 μL, 0.98 mmol). The solution was cooled to −78°C, and *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate (200 mg, 0.49 mmol, azeotropically dried with CH_2Cl_2) in CH_2Cl_2 (2 mL) was added. After 5 min the heterogeneous mixture was warmed to −40°C and vigorously stirred for 36 h, over which period the mixture became homogeneous. MeOH (300 μL) was added, the solution was warmed to 23°C, and [Pd(PPh$_3$)$_4$] (30 mg, 0.025 mmol) and *n*-butylammonium

formate (300 µL) were added. The solution was stirred for 3 h at 23 °C, and Et_2O (60 mL) was then added. The organic layer was washed with buffer (pH = 13) until the aqueous washings were colorless. The solution was then washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by chromatography (silica gel, hexane/EtOAc 4/1 →2/1) provided 84 mg (78 %) of (*S*)-(4-chlorophenyl)-2-pyridylmethanol as a colorless oil. $[\alpha]_D^{23} = +119$ (c = 0.50 in $CHCl_3$, literature value for the *R* isomer: $[\alpha]_D^{16} = -132.5$ (c = 0.7 in $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.55$ (d, $J = 4.8$ Hz, 1 H), 7.63 (td, $J = 1.7$, 7.7 Hz, 1 H), 7.33 – 7.28 (m, 4 H), 7.20 (dd, $J = 5.0$, 7.5 Hz, 1 H), 7.12 (dd, $J = 0.4$, 7.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.426$, 147.987, 141.789, 137.023, 133.666, 128.774, 128.457, 122.678, 121.283, 74.338. HPLC analysis (Chiralpak AD, 2-propanol/hexane 5/95, 1 mL min^{-1}, $\lambda = 254$ nm) showed the product to be of 98 % *ee*; t_R: 17.7 min, major; 23 min, minor isomer.

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[66] CBS reduction of *E*-4-(4′-methoxyphenyl)-3-buten-2-one: (*E*)-4-(4′-methoxyphenyl)-3-buten-2-one (50 mg, 0.28 mmol, azeotropically dried with toluene) was treated with (*S*)-*B*-*n*Bu-**4** (86 µL, 0.043 mmol, 0.20 M in toluene) and toluene (900 µL). Upon being cooled to −78 °C the solution became heterogeneous. Catecholborane (51 mg, 46 µL, 0.43 mmol) in toluene (138 µL) was added directly into the rapidly stirred reaction mixture, and the color immediately turned dark red (this is unique for 4-aryl-3-buten-2-ones). After the mixture was stirred for 20 h at −78 °C the dark red color had faded to light pink. MeOH (200 µL) was added down the side of the flask, and the solution was warmed to 23 °C, diluted with Et_2O (40 mL), and washed with buffer (pH = 13, 1 N NaOH/saturated $NaHCO_3$ 2/1) until the aqueous washings were colorless. The dark aqueous washes were extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to a volume of about 10 mL. A solution of HCl in MeOH (0.5 M, 86 µL, 0.043 mmol) was added, the HCl salt of the amino alcohol removed by filtration, and the solution concentrated in vacuo. Purification by chromatography (silica gel, hexane/EtOAc 4/1) provided 44 mg (88 %) of the alcohol as a while solid. $[\alpha]_D^{22} = +36.9$ (c = 1.15 in $CHCl_3$); m.p. 96 – 97 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, $J = 8.7$ Hz, 2 H), 6.85 (d, $J = 8.8$ Hz, 2 H), 6.50 (d, $J = 15.9$ Hz, 1 H), 6.12 (dd, $J = 6.6$, 15.9 Hz, 1 H), 4.46 (m, 1 H), 3.80 (s, 3 H), 1.78 (br s, 1 H), 1.36 (d, $J = 6.3$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.25, 131.43, 129.44, 129.01, 127.65, 114.01, 69.11, 55.31, 23.48. HPLC analysis (Chiralcel OD, 2-propanol/hexane 2.5/97.5, 1 mL min^{-1}, λ = 254 nm) showd the product to be of 95 % *ee*; t_R: 42.2 min, major; 49.3 min, minor isomer.

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