Boron Reagents in Process Chemistry: Excellent Tools for Selective Reductions

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1. Introduction and Scope

Boranes and borohydride reagents have found utility in synthesis routes to a number of pharmaceutical and other products. Boron reagents have become increasingly important for catalytic reactions and other organic transformations of highly complex functionalized molecules. Some of the highlights include asymmetric reductions, Suzuki−Miyaura cross-coupling, and the introduction of functional groups such as alcohols and amines. Because of their unique properties and high selectivities, these reagents have become a valuable part of the organic chemistry toolbox and found their way into a number of commercial applications.

Much of the exploratory research on the synthetic application of borane chemistry was conducted in the laboratories of H. C. Brown. Borane (BH_3) is an electrophilic reducing agent; that is, it is not nucleophilic or hydridic in nature. This electrophilicity of borane can be viewed as Lewis acid character since the boron is electron deficient. Due to the electrophilic nature of borane and complexation with the electron-rich center of the functional group, reductions with borane are very selective and specific.

The catalytic effect of ethers in the hydroboration reaction led to the development of more stable borane ligand complexes (BH_3-L) as the preferred borane sources at commercial scale. Borane adducts of Lewis bases such as tetrahydrofuran (THF), dimethyl sulfide (DMS), and some aromatic and hindered amines have been used very effectively for hydroboration of double and triple bonds as well as in reductions of other functional groups.

The strength of the Lewis base determines the reactivity of the borane complex. Borane tetrahydrofuran complex (BTHF) is the most reactive. At the other extreme, numerous amine boranes possess low reactivity even toward proton sources such as water, alcohols, and carboxylic acids. Sulfide boranes, dialkylaniline boranes, and bulky amine boranes are intermediate in reactivity.The amine and sulfide borane complexes offer concentration advantages over BTHF. For example, dimethyl sulfide borane (DMSB) is 10 times more concentrated than BTHF. Both amine and sulfide borane complexes are more stable than BTHF at ambient or higher temperatures.

The availability of boron reagents, specifically borane complexes, substituted borohydride reagents, and chiral boron compounds, at commercial scale, has dramatically expanded the uses of these compounds in process chemistry. In the last 25 years, the development of new synthetic methodologies using boranes has allowed the preparation of very complex molecular structures in high selectivities and excellent overall yields. This review captures the diversity of borane synthetic applications at the pharmaceutical and industrial scales.

Since utilization of boron reagents in process chemistry has not previously been reviewed, the literature from the 1980s up to mid-2005 is included. The purpose of this review is to highlight some relevant processes to give guidance and inspiration for the large scale use of these reagents. Many commercial processes that did not provide details about the step involving a boron reagent are included, as well as small scale synthetic schemes with emphasis on reaction protocol.

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Elizabeth R. Burkhardt, R&D Technical Coordinator at BASF Corporation in Evans City, Pennsylvania, was born in Creighton, Nebraska (USA), in 1962. She received her Bachelors Degree in Chemistry from the University of Nebraska—Lincoln in 1984 after research work for Prof. Reuben Rieke. She received a Ph.D. in Synthetic Chemistry from the University of California—Berkeley in 1989 after completing graduate research on transition metal enolates under the direction of Profs. Robert G. Bergman and Clayton H. Heathcock. She did postdoctoral work on organolanthanides for use in synthesis in Prof. Gary A. Molander's group at the Univeristy of Colorado—Boulder. She joined Callery Chemical Company (now part of BASF Corporation) in 1990 and has had numerous projects involving potassium metal and boron reagents. She has written numerous patents, journal articles, and technical marketing bulletins.

Karl Matos, Research Manager at BASF Corporation at Evans City, Pennsylvania, was born in 1970 in New Haven, Connecticut (USA). He received his B.S. in 1991 and his Ph.D. in 1998 under the supervision of Professor John A. Soderquist from the University of Puerto Rico. His graduate work at the University of Puerto Rico focused on the mechanistic features of the Suzuki–Miyaura alkyl group transfer and organoborane conversions with borabicyclo[3.3.2]decanes. In 1999, he worked as a postdoctoral research associate with Professor John A. Soderquist (University of Puerto Rico) to develop a scalable process to prepare chiral borabicyclo[3.3.2]decane derivatives for asymmetric synthesis. After completing his postdoctoral assignment, he joined Callery Chemical Company (now part of BASF Corporation) in 1999. His industrial scientific work has involved developing large scale processes of new boron reagents for technologies such as the Suzuki–Miyaura coupling reaction and optimizing key parameters in the asymmetric reduction of ketones with the Corey catalyst.

The reaction schemes list as much detail as possible about reaction conditions, solvents, and reagents from the literature or patent examples. We did not include reactions utilizing boronic acids or esters in Suzuki−Miyaura C−C coupling reactions since these topics have been recently reviewed.[1] Other excellent reviews covering borohydride reductions,[2] hydroborations,[3] and boranes in asymmetric synthesis[4] have appeared recently but are not specifically at a particular scale. A number of processes cannot be discussed in detail due to their proprietary nature.

2. Hydroboration

The hydroboration reaction is the *syn*-addition of a boron−hydrogen bond across a carbon−carbon multiple bond to generate the corresponding organoborane. Due to the electrophilic nature of borane reagents, the regioselectivity of the addition gives predominantly anti-Markovnikov products. Early in the development of the reaction, Brown found that ethers catalyze hydroboration. The reaction of diethyl ether with diborane (B_2H_6) results in the formation of weak readily dissociated borane adducts which are more reactive than the B_2H_6 dimer.

The hydroboration of simple olefins with borane complexes such as DMSB or BTHF results in the formation of trialkylboranes. With more hindered olefins, the hydroboration can be stopped at the mono- or disubstituted organoborane. For example, hydroboration of 2-methyl-2-butene proceeds only to the dialkyl stage, generating the corresponding disiamylborane. A very useful regioselective hydroborating agent, 9-borabicyclo[3.3.1]nonane (9-BBN), is prepared via reaction of borane with *cis*,*cis*-1,5-cyclooctadiene.[5]

In contrast to borane complexes, which give mixtures of Markovnikov and anti-Markovnikov products (up to 93% favoring the anti-Markovnikov adduct), dialkylboranes are the reagents of choice where high regioselectivity in the addition across the double bond is required. The low solubility and thermal instability of some dialkylboranes, such as dicyclohexylborane, disiamylborane, thexylborane, and di-isopinocampheylborane, requires *in situ* formation from a borane complex. The main decomposition pathway of these reagents at ambient or higher temperatures is via dehydroboration. Because 9-borabicyclo[3.3.1]nonane (9-BBN) cannot dehydroborate, it is thermally stable and well suited for large scale applications where high regioselectivity is required in the hydroboration. 9-BBN is commercially available as a 0.5 M solution in THF or hydrocarbon solvent, because the solid 9-BBN dimer is pyrophoric, making it difficult to handle for a large scale process.

Hydroboration of optically active substituted alkenes, such as α-pinene, with borane complexes generates asymmetric hydroborating agents. Diisopinocampheylborane (DIPBH) is the reagent of choice for the asymmetric hydroboration of *Z*-alkenes. Enantioselectivities of higher than 90% ee are reported in most of the cases.[6] Unfortunately, DIPBH is also prone to dehydroboration at ambient temperatures.

Dialkoxyboranes can also be used in hydroboration reactions generally at higher temperatures than borane complexes. These compounds are prepared via reaction of a borane complex and a diol, such as pinacol and catechol. Transition metal catalyzed hydroboration with catecholborane (CATB) and pinacolborane (PINB) dramatically increases the rate of hydroboration of alkenes. However, the regioselectivity of the catalyzed reaction can be opposite to that of the uncatalyzed reaction depending on the catalyst used. The use of catalytic amounts of dialkylboranes such as dicyclohexylborane in CATB or PINB reactions also increases the rate of hydroboration.[7]

The organoborane compound formed through hydroboration is not the final stage in the pharmaceutical synthesis but can be used in a number of different ways. Oxidation of

the boron−carbon bond is often used to regioselectively introduce a hydroxyl functionality into a molecule.[8] Other transformations include halogenation, amination, and formation of carbon−carbon bonds through Suzuki−Miyaura coupling reactions. Although hydroboration followed by oxidation to an alcohol is the most common application of the organoborane generated, Suzuki−Miyaura coupling reactions will probably dominate the future of borane intermediates in synthesis schemes because of the ability to rapidly construct large molecular fragments.

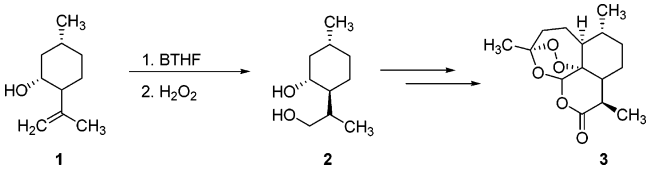
In this section, the hydroboration reaction for the synthesis of active pharmaceutical ingredients is reviewed.

2.1. Conversion to Alcohol

An especially important application of the hydroboration reaction is the conversion of organoborane to an alcohol via oxidation of the B−C bond. Excellent control of regio- and stereochemistry in the hydroboration is based mainly on steric differentiation, although sometimes the electronic bias of the double bond can direct the placement of boron on the carbon. The oxidation of the organoborane intermediates can be accomplished with various oxidizing agents such as hydrogen peroxide (H_2O_2),[9] sodium perborate ($NaBO_3 \cdot H_2O$),[10] trimethylamine *N*-oxide,[11] and, more recently, Oxone.[12] Mild oxidating agents such as sodium perborate are generally used for the oxidation of organoborane intermediates that contain other functionalities sensitive to strong oxidation. Basic hydrogen peroxide oxidation has been the method most commonly used at large scale. Because excess hydrogen peroxide at high pH releases oxygen, measures such as purging the reactor with an inert gas during the oxidation to lower the amount of oxygen in the headspace are required to minimize potential hazardous conditions for large scale hydroboration/oxidation processes.[13]

In the synthesis of Artemisinin (**3**), Deshpande and co-workers hydroborated a double bond in intermediate **1** with BTHF.[14] The intermediate organoborane was oxidized with basic hydrogen peroxide, delivering the diol **2** in high yield (Scheme 1).

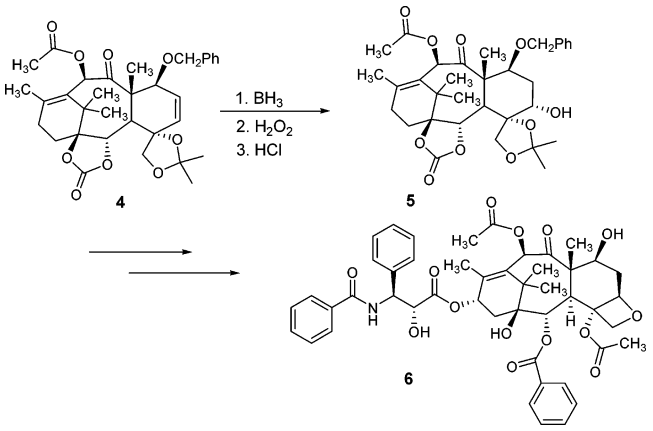
Scheme 1



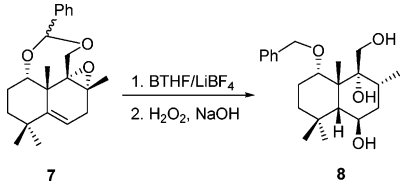
Nicolaou and co-workers used the hydroboration/oxidation strategy to make one of the key intermediates in the synthesis of Taxol (**6**) (Scheme 2). In their approach, the hydroboration took place chemo- and regioselectively upon the disubstituted cyclohexene **4** preferentially over the ketone and tetrasubstituted alkene functionalities.[15]

Calvo and co-workers utilized hydroboration with BTHF to prepare one of the intermediates in the synthesis of the antiglaucoma agent forskolin.[16] The important step in their synthesis was that, by using a $LiBF_4$/BTHF mixture, the acetal ring in **7** opened, thus facilitating the diastereoselective hydroboration of the double bond to the desired diastereomer **8** (Scheme 3). Couturier and co-workers also reported the propensity of acetal cleavage in the presence of BF_3 during borane reductions.[17]

Scheme 2

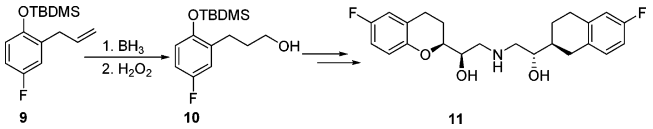


Scheme 3



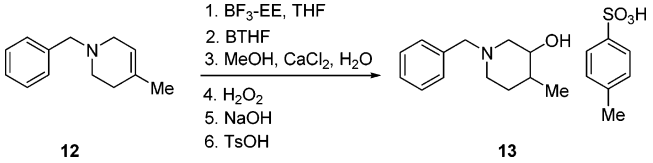
Chandrasekhar efficiently hydroborated a terminal alkene group in **9** to generate a primary alcohol after basic oxidation for the synthesis of Nebivolol (**11**), used as a β-adrenoreceptor antagonist (Scheme 4).[18] They obtained gram quantities of the corresponding alcohol **10**.

Scheme 4



Brown and co-workers developed a scalable synthesis route to cis-*N*-benzyl-3-methylamino-4-methylpiperidine during manufacturing of a clinical drug candidate.[19] One of the key steps of the reaction involved carrying out the hydroboration of **12** using BTHF (Scheme 5). Initially, they needed

Scheme 5



2.2 equiv of BH_3 to drive the reaction to completion because the amino group in the molecule complexed with 1 equiv of borane. Addition of BF_3-EE (1.2 equiv) to complex the amino group in **12** allowed the hydroboration to be carried out with 1.4 equiv of borane rather than the 2.2 equiv usually required for consistent results. BF_3−etherate complex also facilitated the work-up step because less hydrogen was evolved during the methanol quench.

To quench excess borane in the reaction, the authors found that the addition of a mixture of 1 N HCl in methanol and calcium chloride destroyed most of the excess B−H and decomplexed the amine−borane complex. The calcium chloride trapped the fluoride liberated from the release of BF_3 from the amine−borane complex. Interestingly, Brown

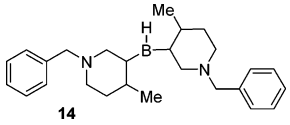


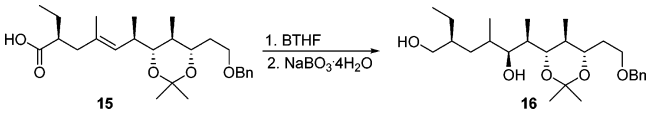
Figure 1.

and co-workers noticed that, despite the strong acidic conditions, some B−H still remained in the product mixture. Heating did not push the hydrolysis further, but it converted the initially formed borinic ester to the corresponding borinic acid.

The oxidation of organoborane intermediate **14** (Figure 1) of the hydroboration was evaluated with Oxone, in general a good alternative process to basic hydrogen peroxide oxidation.[20] One of the major drawbacks of Oxone oxidation is the large solvent volume required to dissolve all the Oxone needed for the oxidation. For that reason, the authors tried the oxidation with a mixture of Oxone and hydrogen peroxide (10:90 for Oxone/peroxide, respectively). However, only 60% conversion of the alkylborane to the corresponding alcohol resulted. Fortunately, using hydrogen peroxide under acidic conditions provided rapid oxidation of the alkylborane intermediate without requiring extended reaction times at elevated temperatures. This process also allowed lower volumes of solvents than with the Oxone procedure. After subsequent transformations of the amino alcohol intermediate, they obtained multiple kilograms of the desired piperidine hydrotosylate salt **13**, demonstrating the feasibility of the hydroboration/oxidation process on a large scale.

Nicolaou and co-workers introduced a critical stereogenic center at C38 in the synthesis of Sanglifehrin A via substrate-controlled regio- and stereoselective hydroboration of a trisubstituted alkene acetonide carboxylic acid **15** with borane complex (Scheme 6). The authors obtained a 5:1 mixture of

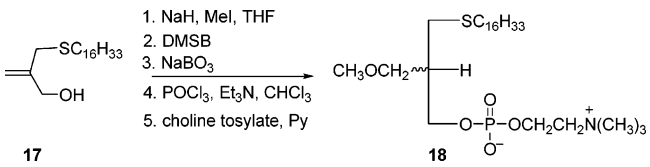
Scheme 6



diastereomeric diols in favor of the desired *trans*-acetonide **16** when they carried out the reaction at −25 °C.[21] The use of more bulky hydroborating agents such as thexylborane was not successful, because of the low reactivity of the alkene. Above −25 °C, byproducts resulting from intramolecular reduction of the acetonide function were obtained.

Ilmofosine, a very potent antineoplastic ether-linked phosphocholine, was synthesized via a milder hydroboration/oxidation protocol (Scheme 7). The oxidation of the organo-

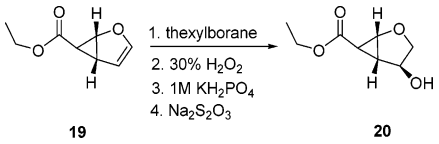
Scheme 7



borane to the corresponding phosphate **18** was carried out with sodium perborate to avoid oxidation of the sulfide.[22]

One of the most effective methods to introduce hydroxyl functionality in five-membered heterocycles at the 3-position is via hydroboration. Massey and co-workers prepared carboxylate **20** via highly chemo- and regioselective hydroboration of a dihydrofuran **19** with thexylborane (Scheme

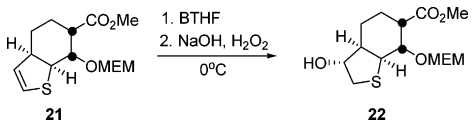
Scheme 8



8) (the hydroborating agent was prepared from reaction of DMSB with 2,3-dimethyl-2-butene).[23] The reaction was carried out at temperatures between −20 and 25 °C, and the oxidation of the organoborane intermediate was accomplished with hydrogen peroxide in the presence of a base or aqueous buffer in a pH range from 5 to 14.

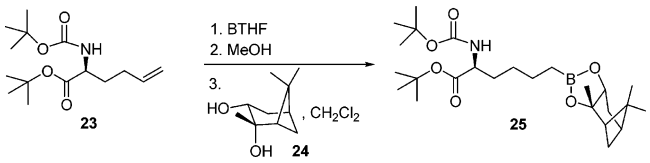
Smith and co-workers also used a similar hydroboration sequence to introduce the hydroxyl group at the 3-position of a vinyl-dihydrothiophene derivative **21** (Scheme 9).[24] They exploited the convex bias of the bicyclic skeleton to favor the exo stereochemistry.

Scheme 9



Due to the importance of arginine catabolism in the regulation of diverse metabolic pathways, significant efforts have been devoted to evaluate nonreactive arginine analogues as enzyme inhibitors or receptor antagonists. Christianson and co-workers prepared the compound 2-(*S*)-amino-6-boronohexanoic acid as the first example of a boronic acid-based arginine isotere.[25] The authors used a chemoselective hydroboration protocol followed by methanolysis and conversion to the pinanediol boronic ester product **25** (Scheme 10). The BOC protecting group on the amine **23** was not

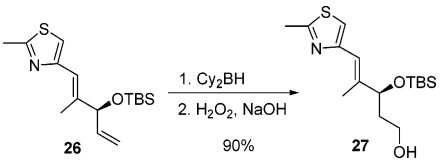
Scheme 10



reduced during the hydroboration. The boronohexanoic acid compound proved to be a very potent inhibitor of Mn^{2+} arginase. This example shows the usefulness of borane adducts as active pharmaceutical ingredients.

Dialkylboranes provide superior selectivities in the hydroboration of primary alkenes compared to simple borane (BH_3) complexes. For example, Panek and co-workers selectively hydroborated a terminal olefin with dicylcohexylborane followed by oxidation to give gram quantities of the alcohol **27**, a key intermediate in the synthesis of epothilone A (Scheme 11).[26] Notice that the internal alkenyl group in **26** was not hydroborated under the reaction conditions.

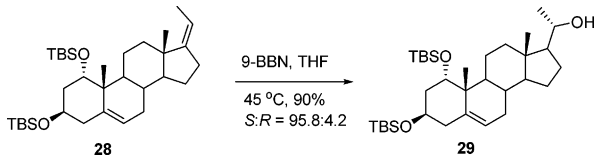
Scheme 11



Diastereoselective hydroboration/oxidation of a diene intermediate **28** in the synthesis of Maxacalcitol gave the

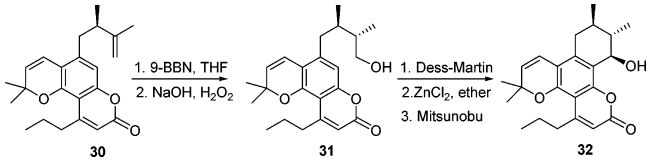
corresponding secondary alcohol **29** in 91.6% de without affecting the internal olefin in **28** (Scheme 12).[27] The desired *S*-isomer **29** crystallized in 90% yield (17 kg), leaving the undesired alcohol in the mother liquor.

Scheme 12



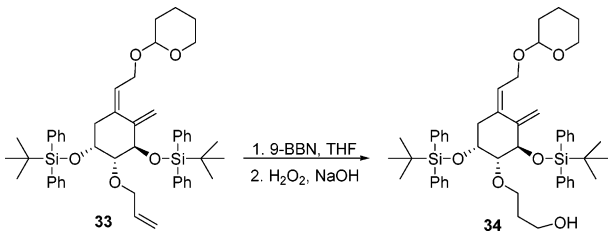
Trost and co-workers used 9-BBN to chemoselectively hydroborate chromene **30** (Scheme 13). Oxidation of the organoborane intermediate with basic hydrogen peroxide followed by Dess−Martin reagent resulted in the formation of an aldehyde intermediate. The aldehyde was converted to the desired *ent*-calonolide A (**32**) via a sequence of $ZnCl_2$ cyclization and Mitsunobu inversion.[28]

Scheme 13



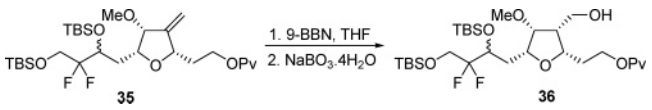
Similarly, Takashashi and co-workers selectively hydroborated tetrahydropyran-2-yl ether intermediate **33** with 9-BBN (Scheme 14). Aqueous basic peroxide oxidation provided the desired primary alcohol **34**, one of the key intermediates in the synthesis of drug candidate ED-71.[29]

Scheme 14



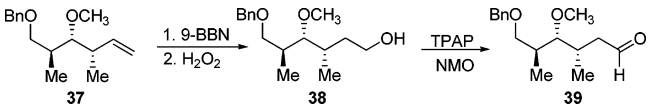
Littlefield and co-workers used 9-BBN to selectively hydroborate 1,1-disubstituted olefin **35**, an intermediate in the synthesis of halichondrin analogues, which have shown anticancer activity (Scheme 15).[30] To oxidize the organoborane intermediate, they used mild oxidation conditions of sodium perborate.

Scheme 15



During the preparation of pironetin, a natural product possessing immunosuppressant activity, Keck and co-workers found that the selective hydroboration of terminal olefin **37** followed by direct oxidation to aldehyde gave low yields.[31] A better strategy was to oxidize the organoborane intermediate and isolate the corresponding alcohol **38** (Scheme 16). Subsequent oxidation using the Ley method (TPAP/NMO, tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide) provided the desired aldehyde intermediate **39**.

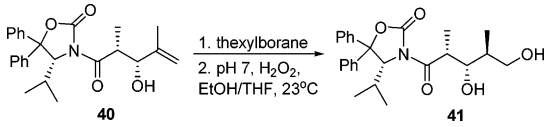
Scheme 16



Presumably, the cyclooctanediol byproduct was interfering with direct oxidation to the aldehyde.

The isolation of desired alcohol product via hydroboration with 9-BBN followed by oxidation sometimes can be difficult because of the 1,5-cyclooctanediol byproduct generated during the oxidative workup. Loiseleur and co-workers found that thexylborane was the preferred hydroborating agent to convert 1,1-disubstituted alkene to the corresponding diol **41**, because it not only gave similar diasteroselectivities as 9-BBN but it also facilitated the isolation of the diol due to the higher volatility of 2,3-dimethyl-2-butanol byproduct after oxidative workup (Scheme 17).[32]

Scheme 17



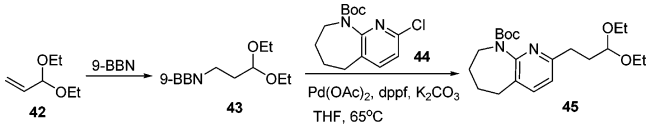
The major drawback of using thexylborane as a hydroborating agent on a large scale is the need to prepare the reagent *in situ* due to its known propensity to undergo thermal dehydroboration to other borane adducts at ambient temperature.

2.2. Suzuki–Miyaura Substrate Formation

The Suzuki−Miyaura cross-coupling reaction is regarded as an extremely efficient method for the coupling of aromatic halides with aryl or alkenyl boron compounds. However, the coupling of aryl halides with alkyl boron compounds has suffered from dehydroboronation of the boron substrate. Alkyl 9-BBN reagents, prepared via hydroboration of terminal alkenes, provide the best effective entry into alkyl replacement of a halide because of the stability of 9-BBN derivatives to the Suzuki−Miyaura conditions.

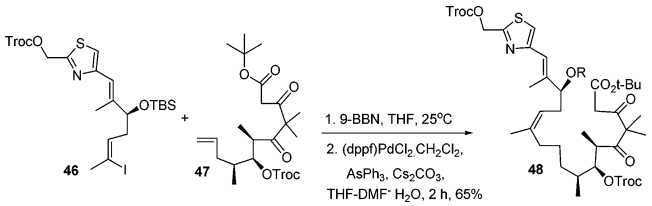
Keen and co-workers used the hydroboration/Suzuki−Miyaura cross-coupling protocol to prepare one of the intermediates in the synthesis of a nonpeptidic avb3 antagonist. The hydroboration of commercially available acrolein diethyl acetal **42** with 9-BBN generated the trialkylborane intermediate **43** (Scheme 18). Gratifyingly, the cross-coupling of trialkylborane with chloride **44** cleanly afforded desired acetal **45** in 98% yield.[33]

Scheme 18



Danishefsky and co-workers effectively used a similar reaction sequence to synthesize one of the intermediates for the synthesis of an epothilone analogue, 12,13-desoxyepothilone F, which is active against tumor cells. The unprecedented coupling of 9-BBN intermediate with iodotrisubstituted alkene **46** proceeded smoothly to the desired diketone **48** in 60% yield (Scheme 19).[34] The key to the reaction was the Lewis acidity of the 9-BBN derivative,

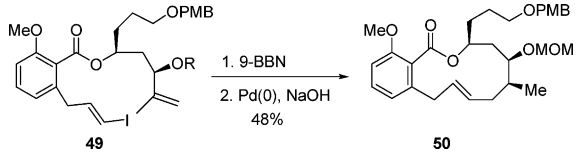
Scheme 19



which facilitated the transmetalation of the alkyl group to the palladium prior to C−C bond formation.[35]

Bauer and Maier recently reported an intramolecular version of the 9-BBN hydroboration/Suzuki−Miyaura reaction in the synthesis of the core system of salicylihalamide A.[36] The authors envisioned a diasteroselective hydroboration followed by Suzuki−Miyaura coupling. Unfortunately, the hydroboration of **49** was slow and required 5 equiv of 9-BBN. The best conditions to carry out the intramolecular Suzuki coupling consisted of adding the intermediate borane to a heated mixture of solvent, base, and palladium catalyst. Under these conditions, the desired intermediate **50** was formed in 48% yield and high diastereoselectivity (Scheme 20).

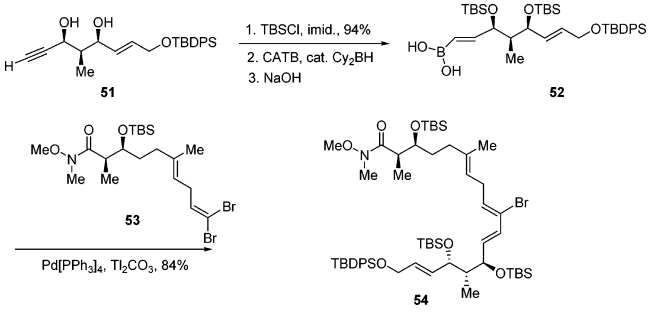
Scheme 20



Others have used the same strategy to conveniently build complex molecules, demonstrating the huge potential of this sequence scheme strategy for pharmaceutical and industrial applications.[37]

Dialkoxyboranes such as catecholborane are the reagents of choice to hydroborate triple bonds because diboration byproducts are not formed. Evans and Starr chemoselectively hydroborated the triple bond in **51** followed by hydrolysis to produce the desired alkenylboronic acid intermediate **52** in excellent yields (91%) (Scheme 21). Palladium catalyzed

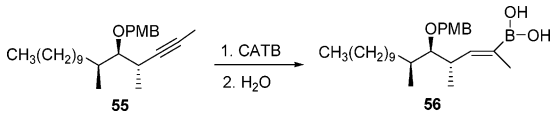
Scheme 21



cross-coupling of **52** with fragment **53** provided an 84% yield of the key intermediate **54** for the synthesis of (−)-FR182877, a compound that exhibits potent cytotoxicity toward tumor cell lines.[38]

Similarly, Kobayashi and co-workers prepared Khafrefungin, a novel inhibitor of fungal sphingolipid synthesis, via CATB hydroboration of an alkyne. The hydroboration of **55** with CATB and hydrolysis gave the desired alkenylboronic acid **56**, which was subsequently used in the Suzuki−Miyaura cross-coupling reaction (Scheme 22).[39]

Scheme 22



Jensen and co-workers prepared gram quantities of the alkenylboronate **58** from propargylic alcohol and 2 equiv of CATB. The boronic acid was used in the synthesis of carbapenem intermediates **57** via subsequent Suzuki−Miyaura reaction (Figure 2).[40] These examples demonstrate the usefulness of CATB to prepare vinylborane intermediates for alkenyl transfer in the Suzuki−Miyaura reaction.

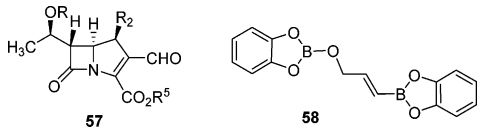


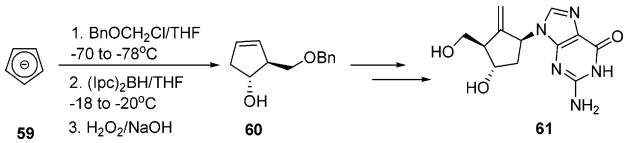
Figure 2.

2.3. Asymmetric Hydroboration

Chiral dialkylboranes can effectively be used for asymmetric hydroboration. The reaction of BTHF with α-pinene generates the corresponding chiral diisopinocampheylborane ($(Ipc)_2BH$). This reagent easily dehydroborates and has limited solubility in THF and other typical solvents. To use technical grade α-pinene, the slurry of crystalline $(Ipc)_2BH$ must be held at 0 °C for 1−3 days to increase the incorporation of *dd* or *ll* isomers in the solid state. Use of upgraded $(Ipc)_2BH$ for the hydroboration of alkenes can result in high enantioselectivity of the corresponding organoborane product. The oxidation of the organoborane proceeds with retention of configuration to yield the desired chiral alcohol in high % ee.

Kotnis and co-workers used the chiral hydroboration/oxidation reaction to prepare entecavir, a novel carbocyclic 2′-deoxyguanosine analogue with potent and selective anti-HBV activity. The most challenging part of the sequence was the separation of the desired intermediate **60** from α-pinene, benzyl alcohol, and pinanol after oxidative workup (Scheme 23). The authors found that the use of continuous-

Scheme 23



counter-current steam distillation was the most effective way to isolate the desired intermediate **60**. With the steam distillation, the pinanol contamination was reduced to less than 7%.[41]

The examples in this section clearly demonstrate the power of borane reagents to introduce hydroxyl into a molecule. Although many examples concentrated on process optimization at smaller volumes, the hydroboration reaction and subsequent chemistry of the trialkylboranes are very attractive and applicable for large scale processes. The unique advantages of the hydroboration reaction, such as high stereoselectivity, chemical purity, and yields of isolated pharma-

ceutical and natural products, coupled with the commercial availability of borane compounds promise to increase the uses and importance of these reagents at commercial scale.

3. Reduction to Alcohol

One of the most desirable characteristics of boranes is the mildness of the reaction conditions required for reductions. The chemoselectivity of borane reduction is highly valued by organic process chemists.

Aldehyde, ketone, amide, and carboxylic acid functional groups are effectively reduced by borane complexes in the presence of other functional groups, such as nitro, halo, ester, and lactone. The chemoselectivity trend listed below is demonstrated by many examples in the following sections.

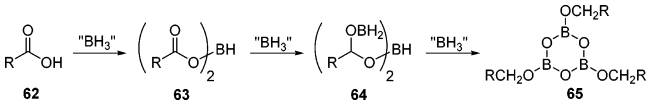
carboxylic acids > aldehydes > ketones > olefins, imines > nitriles, amides, epoxides > esters

Ester, lactone, and anhydride reduction, as well as cleavage of an amide to the alcohol, often requires a nucleophilic alkylborohydride reagent.

3.1. Carboxylic Acid Reduction

The carboxylic acid functional group is reduced at a faster rate by borane complexes than most other groups, including nonconjugated alkene, and is therefore the reagent of choice for the reduction of carboxylic acids. Commonly, halogen, nitro, carbamate, and ester groups remain intact under borane reduction of a carboxylic acid. The mechanism of the carboxylic acid reduction is stepwise. Initially, the acidic proton reacts giving diacyloxyborane intermediate **63** and hydrogen is evolved (Scheme 24). The carbonyl group in

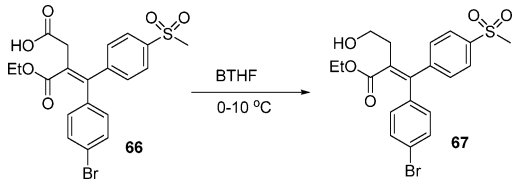
Scheme 24



63 is then reduced with two hydrides from free borane in the solution. Redistribution occurs such that the intermediate before protic quenching is a trialkoxyboroxin **65**. Three hydride equivalents are required for the carboxylic acid reduction, since, in the redistribution process, borane is released from the intermediates. The amounts of borane required for the process could be minimized by the addition of BF_3 to the reaction mixture.

Lobben and co-workers studied the thermodynamics of the carboxylic acid reduction by borane during the scale-up of a COX-2 inhibitor.[42] The BTHF reduction of a carboxylic acid shown in Scheme 25 had a delayed exotherm during

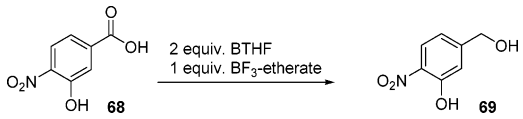
Scheme 25



scale-up. The carbonyl reduction is about 3.5 times more exothermic than the initial diacyloxyborane formation. From these measurements on the heat evolution, the kinetic model proposed control of the BTHF addition rate based on the cooling capacity of the reaction vessel. Thus, a safe controlled scale-up of this reduction was achieved.

The following example demonstrates the mild borane reduction, where the nitro group is unharmed by the reduction conditions, to produce large quantities of 3-hydroxy-4-nitrobenzyl alcohol, a key intermediate.[43] A convenient reduction of 3-hydroxy-4-nitrobenzoic acid (**68**) with BTHF and BF_3−etherate was found to deliver the desired alcohol in 91% yield (Scheme 26). Other highly functionalized

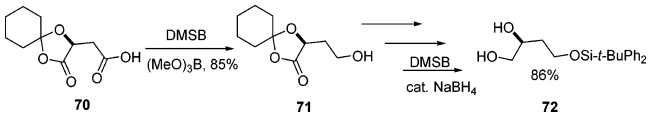
Scheme 26



aromatic carboxylic acids also gave clean high yielding reductions with this combination of reagents. The optimum ratio was 2 equiv of BTHF and 1 equiv of BF_3−etherate per carboxylic acid. The boron trifluoride presumably acts as a Lewis acid to activate the carbonyl toward borane reduction.

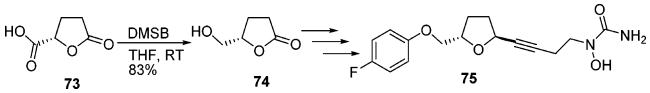
Malic acid and esters of malic acid have been used as building blocks to provide the chiral center in several drugs. To selectively protect the terminal alcohols after reduction of (*l*)-malic acid in the synthesis of Tetrahydrolipstatin, the reduction was conducted stepwise.[44] First, the free alcohol and the C1-acid were cyclized with cyclohexanone, and then the C4-acid **70** was reduced with DMSB in the presence of trimethylborate (Scheme 27). Following protection of the newly formed alcohol, the other acid in **71** was reduced with DMSB and catalytic sodium borohydride.

Scheme 27



DMSB has been used in the ambient temperature reduction of (*S*)-(+)-butyrolactonecarboxylic acid **73** to the 2-hydroxybutyrolactone **74** in 83% yield (Scheme 28).[45] Compound **74** was converted to CMI-997 (**75**), a potent 5-lipoxygenase inhibitor for the treatment of asthma. 2-Hydroxybutyrolactone was also an intermediate in the synthesis of Epothilone B.[46]

Scheme 28

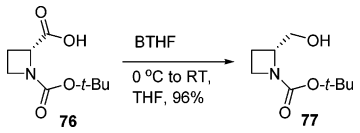


The reduction of amino acids to the corresponding amino alcohols has delivered chiral raw materials for drug candidates. In the preparation of Zolmitriptan, BF_3 was used to bind the amine, followed by DMSB reduction of the carboxylic acid of L-4-nitrophenylalanine (gram scale) at 80 °C to give a 72% yield of amino alcohol.[47]

Tebanicline, a pain relieving analgesic, required a carboxylic acid reduction of a BOC-protected azetidine carboxylic acid **76**. Gram quantities of the carboxylic acid intermediate **76** were reduced with BTHF to give a 96% yield of the BOC-aminoalcohol (Scheme 29).[48]

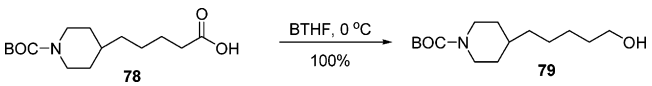
Similarly, L-ethyl phenylglycine was reduced with BTHF to the aminoalcohol during the synthesis of kilogram quantities of a drug candidate for clinical trials.[49] Unfortunately, yield and conditions were not described.

Scheme 29



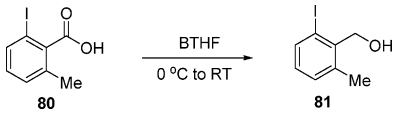
Another drug intermediate was prepared via the reduction of carboxylic acid **78** containing a BOC-protected piperidine.[50] Reduction with BTHF gave quantitative yield of **79** without BOC cleavage (Scheme 30). Although small scale, the reaction yield and tolerance of the BOC protecting group are remarkable.

Scheme 30



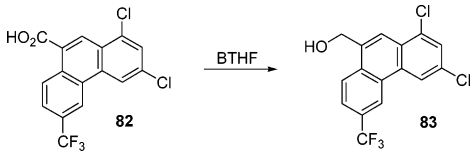
The mildness of the carboxylic acid reduction with BTHF is demonstrated on a gram scale by the absence of iodo-cleavage byproducts in the reduction of 2-iodo-6-methylbenzoic acid (**80)** (Scheme 31).[51] In another example of halo-substituted aromatic carboxylate reduction, 2-bromo-5-methoxybenzoic acid was reduced with DMSB on a gram scale, yielding 94% for the preparation of drug candidate J-104132.[52]

Scheme 31



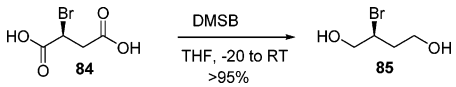
Recently, BTHF complex was used to reduce carboxylic acid **82** in the presence of two chloro groups during the preparation of an antimalaria drug, Halofantrine (Scheme 32).[53]

Scheme 32



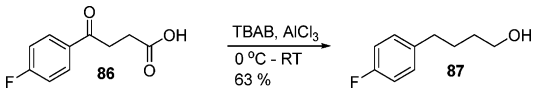
In the synthetic route to Sulopenem, reduction of 2-(*S*)-bromosuccinic acid (**84**) to the bromodiol was completed with DMSB (Scheme 33).[54] Due to the high water solubility of the diol **85**, the reduction workup was accomplished with a methanol quench of the reaction mixture followed by azeotropic removal of the trimethylborate and methanol.

Scheme 33



Reduction of 3-(4-fluorobenzoyl)propionic acid (**86**) with an excess of *tert*-butylamine borane (TBAB) in the presence of $AlCl_3$ provided 4-(4-fluorophenyl)-1-butanol (**87**) in 63% yield (Scheme 34) for the synthesis of LM-1507 sodium salt, a drug candidate in early clinical trials.[55] *tert*-Butylamine strongly complexes with $AlCl_3$, freeing the borane for reduction. $AlCl_3$ also acts as a Lewis acid facilitating the reduction. In the process, the carboxylic acid is converted

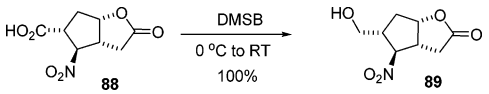
Scheme 34



to an alcohol and the acetophenone carbonyl to the hydrocarbon "CH_2" with this combination of reagents.

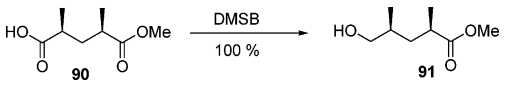
Trimoprostil, a cardiovascular agent and drug for labor induction, required a carboxylic acid reduction. The carboxylic acid **88** with nitro and lactone functionalities present in the structure was cleanly and efficiently reduced with DMSB (Scheme 35).[56] In an early step of Smith's synthesis

Scheme 35



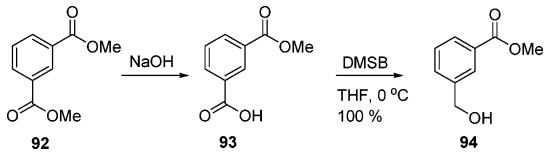
of Rapamycin, DMSB cleanly reduced the carboxylic acid **90** in the presence of the methyl ester functionality (Scheme 36).[57] Another example of carboxylic acid reduction in the

Scheme 36



presence of an ester was demonstrated in the synthesis of an anti-HIV antagonist for the CCR5 coreceptor. Dimethyl isophthalate (**92**) was treated with base to obtain the monomethyl ester of isophthalic acid (**93)** (Scheme 37). Selective reduction of the carbocyclic acid functionality with DMSB in THF gave methyl 3-hydroxymethylbenzoate (**94**) in quantitative yield.[58]

Scheme 37

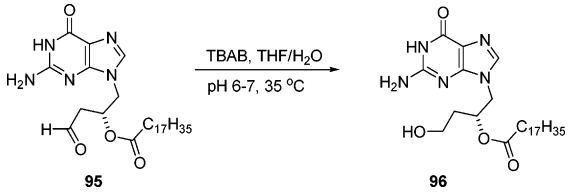


In summary, the borane mediated reduction of carboxylic acids delivers excellent yields of the desired alcohol product and is tolerant to a number of functional groups. The examples in this section clearly demonstrate the chemoselectivity of the borane reduction of a carboxylic acid in the presence of nitro, ester, lactone, and halo groups which are often reduced by other methods such as transition metal catalyzed hydrogenation or lithium aluminum hydride. New commercial applications that take advantage of the highly effective borane reduction of a carboxylic acid functional group are expected to emerge in the coming years.

3.2. Aldehyde, Ketone, and Ester Reduction

The reduction of aldehydes and ketones can be effectively accomplished with borane compounds. In some cases, water stable amine boranes are ideal for these reductions. For example, the selective reduction of aldehyde **95** to the corresponding alcohol **96** during the synthesis of Valomaciclovir stearate, an anti-Varicella Zoster virus drug, was preferentially carried out with TBAB (Scheme 38).[59] The reduction was conducted in a THF/water system at neutral pH.

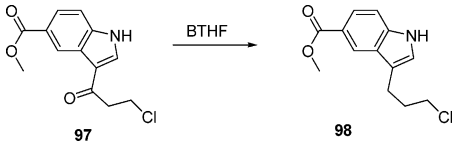
Scheme 38



The reductions of ketones and the carbonyl groups of enones are efficiently carried out with BTHF. The addition of borohydride to the reaction solution is advantageous for accelerated reduction[60] as well as higher selectivity toward carbonyl reduction in ketones and enones.[61] However, trace borohydride is detrimental when conducting asymmetric reduction of ketones with an oxazaborolidine catalyst (see section 5.4 on asymmetric ketone reduction).[62]

The reduction of the ketone moiety in **97** with BTHF is described, but conditions and yield for the reduction are not given (Scheme 39).[63] In the examples, 1 kg and 2 kg of the

Scheme 39



drug candidate Vilazodone hydrochloride was compounded and formed into tablets, so we assume the borane reduction was conducted on greater than one kilogram scale during synthesis of Vilazodone hydrochloride.

Although borane complexes are quite effective for racemic reduction of ketones, asymmetric reduction of prochiral ketones is widely used and is covered extensively in section 5.4.

Reduction of the ester functionality with borane complexes generally requires refluxing conditions to effectively push the reduction to completion. Several examples exist using BTHF or DMSB for this purpose. When DMSB is used, the dimethyl sulfide is usually distilled from the refluxing solution to drive the reduction to completion. At elevated temperatures, BTHF can cleave the tetrahydrofuran ring, producing butyl borate and thus decreasing the amount of borane available for the desired reduction.

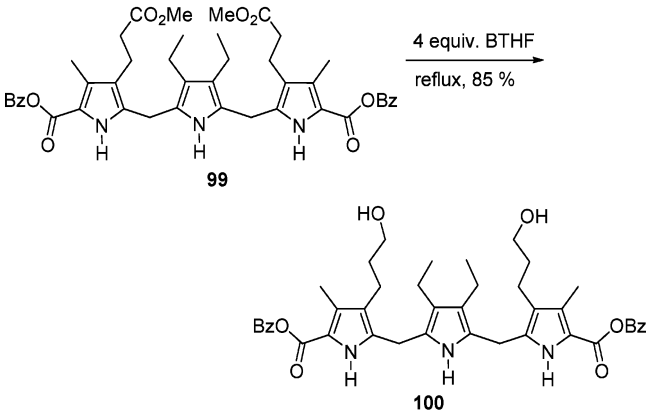
Gadolinium texaphyrin, an anticancer agent, is a lanthanide complex of texaphyrin. The synthesis of the porphyrin macrocycle required the reduction of two methyl esters in the presence of two benzyl esters.[64] The reduction of **99** with 4 equiv of BTHF resulted in 85% yield of the desired diol **100** (gram scale, Scheme 40).

Selective reduction of one ester of L-malic acid dimethyl ester using DMSB successfully produced 3-(*S*)-4-dihydroxybutryic acid methyl ester. This diol has been utilized for preparation of intermediates in the syntheses of the anticholesterol drug Fluvastatin sodium,[65] Ruboxistaurin hydrochloride,[66] and a glaucoma drug candidate, AL-12182.[67]

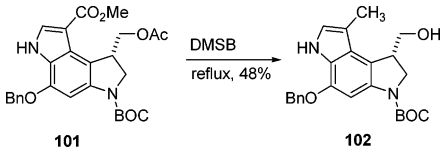
During the synthesis of Carzelesin, an antitumor agent, a methyl ester and acetate were reduced with dimethyl sulfide borane in refluxing THF. The methyl ester **101** was converted to the methyl derivative (**102**) in the process (Scheme 41).[68]

The reduction of an ester to an alcohol is more effectively conducted with lithium trialkylborohydride reagents than borane complexes, as shown in the following examples.

Scheme 40

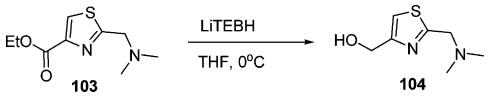


Scheme 41



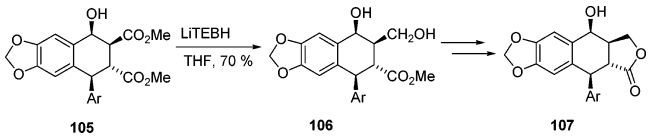
For the synthesis of a Nizatidine drug intermediate, reduction of the ester **103** with lithium triethylborohydride (LiTEBH) gave a 66% yield of alcohol **104** (Scheme 42).[69]

Scheme 42



Several approaches to the drug Podophyllotoxin and derivatives have used lithium triethylborohydride for the reduction of methyl ester **105** adjacent to a hydroxyl group functionality in the presence of another methyl ester (Scheme 43).[70] In a subsequent step the lactone ring is closed to give epiisopodophyllotoxin **107**.

Scheme 43



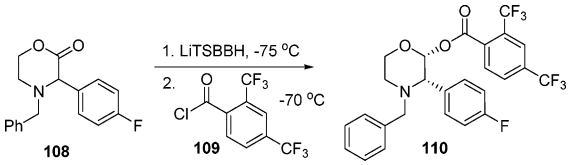
In summary, the reduction of aldehydes and ketones by borane reagents provides the corresponding alcohols in high yields, demonstrating the attractiveness of the transformation for commercial applications. Although the reduction of esters can be carried out with borane complexes, lithium triethylborohydride is a better alternative than boranes because the alkylborohydride reagents reduce esters under milder reaction conditions, increasing the chemoselectivity of the reaction toward the ester functionality.

3.3. Lactone Reduction to Lactol

The reduction of a lactone to a lactol is difficult since many reducing agents convert the lactone to the corresponding diol. This specialized reduction of a lactone to the corresponding lactol was effectively accomplished using lithium tri-*sec*-butylborohydride (LiTSBBH) in the synthesis of the Aprepitant drug.[71] The intermediate lithium salt of the lactol could be trapped directly with substituted benzoyl chlorides or

triflate esters. An example in the patent demonstrates this reduction on a multi-kilogram scale to give 70% yield of **110** (Scheme 44).

Scheme 44

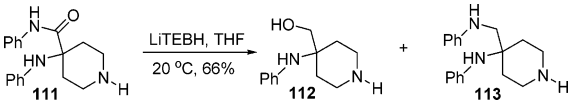


3.4. Amide Reduction to Alcohol

Amides can be selectively reduced to alcohols with alkali metal trialkyl borohydride reagents such as lithium triethylborohydride and lithium dialkylaminoborohydrides.

The synthesis of the drug Alfentanil hydrochloride required the reduction of an amide to the alcohol.[72] Use of lithium aluminum hydride (LAH) for the reduction gave a poor yield of alcohol and several side products. Fortunately, the reduction to the alcohol **112** was successful with excess of LiTEBH (Scheme 45). One complication in the reaction was

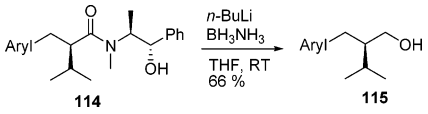
Scheme 45



that, after oxidative workup, product was lost to the water layer. Killgore and collaborators found that quenching the reaction with the theoretical calculated amount of water followed by addition of 2 equiv of NaOH and 3 equiv of 30% H_2O_2 to oxidize the triethylborane was the best work-up conditions. In the example, **112** was obtained in 66% yield on a gram scale. Some reduction of the amide carbonyl to an amine byproduct **113** was observed. The amino alcohol product (**112**) of the reduction was also used for the synthesis of several analogues of Remifentanil.

In the synthesis of CGP60536B, an inhibitor of human renin, the chiral auxiliary was removed via an amide cleavage to the alcohol **115** using lithium aminoborohydride (Scheme 46). The chiral center was not epimerized by the reducing

Scheme 46



agent. $LiNH_2BH_3$ was prepared via *n*-butyllithium deprotonation of ammonia borane, NH_3BH_3.[73] Authors noticed that other amine boranes more readily available than ammonia borane could be used for preparation of this type of reducing agent.

The effectiveness of borane complexes for the reduction of carboxylic acids and other carbonyl groups to alcohols has been demonstrated on greater than kilogram scale for the synthesis of advanced pharmaceutical intermediates. Reduction of esters, lactones, and lactams to the alcohol are more easily accomplished with alkali metal trialkylborohydride reagents.

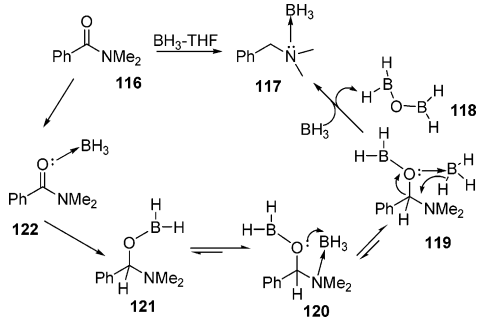
4. Reduction to Amines

Borane reagents are effective for the reduction of amides and nitrile groups to amines. Whereas nitro groups are usually not affected by boranes, the nitro group can be reduced via transition metal catalyzed reaction using amine boranes as the hydrogen source. Reductive aminations can be conducted using either amine boranes or sodium triacetoxyborohydride. The following section elaborates on amine formation via boron reducing agents.

4.1. Amide Reduction

The reduction of an amide to an amine with a borane complex is a key transformation for the development of pharmaceutical drugs such as antibacterials, HIV inhibitors, and ocular hypertension drugs. The mechanism of reduction has been reviewed.[74] To reduce the amide to amine, five hydride equivalents are required (Scheme 47). Two of the

Scheme 47



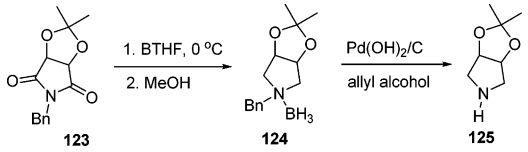
hydrides are used to reduce the amide to amine, and the other three hydrides are utilized to form the amine borane complex. Alternatively, BF_3 can be added to complex the amine and lower the amount of borane required for the reduction to $^2/_3$ of a mole of "BH_3" per mole of substrate. The reduction of tertiary amides is generally faster than that of secondary or primary amides.

Although acids, especially acetic acid,[75] are commonly used to hydrolyze the amine borane product after the reduction is complete, a number of alternative procedures have recently been developed. One method uses an excess of *n*-propylamine to displace the desired amine from the borane.[76] Depending on the steric constraints and electronic nature of the desired amine, from 2 to 5 equiv of *n*-propylamine was required. The *n*-propylamine borane can then be removed from the desired compound through extraction or distillation. This method works well for tertiary amine borane complexes. Some secondary amine borane complexes are decomplexed easily while others require excess *n*-propylamine and extended reaction times. 1,4-Diazabicyclo[2.2.2]octane (DABCO) has also been used to liberate the amine borane product from amide reductions.[77]

Another work-up method uses palladium catalysis to decompose the amine borane.[17] Tertiary amine borane complexes are rapidly hydrolyzed with Pd/C in methanol at 45 °C. In some cases the palladium can make byproducts resulting from hydroboration or cleavage of benzylamines. For example, the amine borane **124** produced during an imide reduction provided an internal hydrogen source for the palladium catalyzed removal of a benzyl group from the amine (Scheme 48).[17] Pearlman's catalyst, $Pd(OH)_2/C$, was used with allyl alcohol to act as a proton source and to scavenge the extra hydrogen released during the reaction.

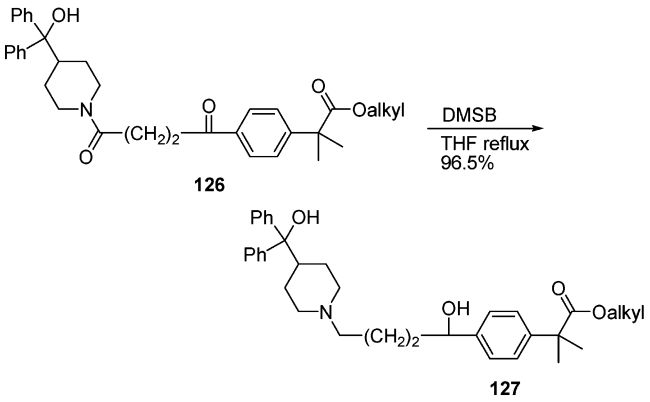
One of the synthesis routes to Terfenadine carboxylate hydrochloride required a ketone and amide reduction.[78] The reduction of the carbonyl groups in **126** with DMSB gave a

Scheme 48



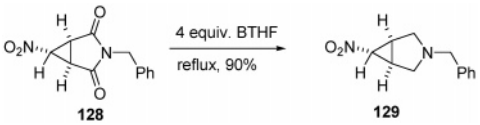
96% yield of product **127** (Scheme 49). For hydrolysis of the resulting amine borane, refluxing in ethanol was preferred over other methods.

Scheme 49



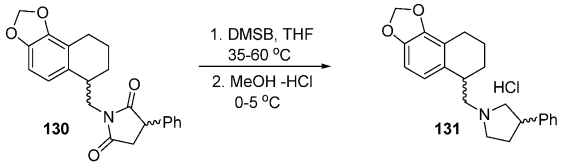
The synthesis of antibacterials Trovafloxacin mesilate and Alatrovafloxacin mesilate required the reduction of an imide in the presence of a nitro group.[79] BTHF was the preferred reagent for the reduction of the imide **128** to the bicyclic amine intermediate **129** (Scheme 50).

Scheme 50



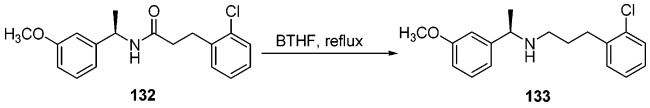
In two of the early synthetic routes to the antidepressant ABT-200, BTHF was used for amide reductions.[80] During the subsequent optimization to produce larger quantities for clinical trials, a variety of reducing agents were tried. Borane mediated amide reduction proved best for the reduction of the succinimide **130 (**Scheme 51). DMSB (80% yield reported) was chosen over BTHF (88% yield reported) because of its higher concentration and stability.

Scheme 51



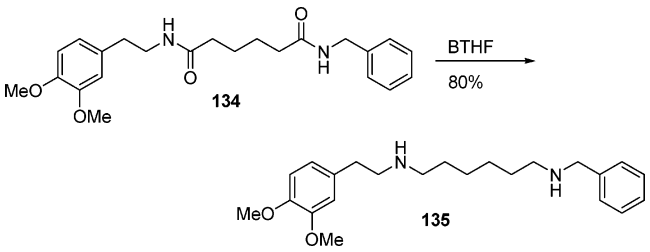
During the preparation of Tecalcet hydrochloride, large scale reduction of amide **132** was conducted with BTHF (Scheme 52).[81]

Scheme 52



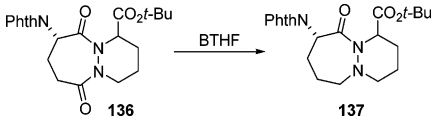
In the synthesis of the heart failure drug Dopexamine, the 1,6-diamide derivative **134** was reduced with BTHF to the bis-amine **135** in 80% yield (Scheme 53).[82]

Scheme 53



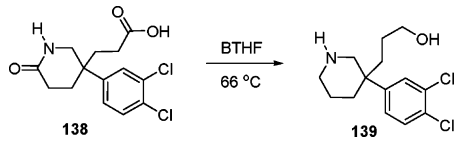
Amide reduction of 2-oxotetrahydrobenzazepine **136** at gram scale with BTHF gave intermediate **137** for the synthesis of SK&F-86466 (Scheme 54).[83] Only the less sterically hindered amide group in **136** was reduced. Unfortunately, no yield was given.

Scheme 54

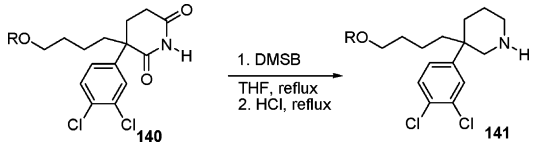


The amide and carboxylic acid in **138** were reduced in one step with BTHF at reflux during the synthesis of an intermediate in the preparation of drug candidate SR 142801 (Scheme 55).[84] In another route to SR 142801, Grugni and co-workers reduced imide **140** with DMSB in THF at reflux on a gram scale (Scheme 56).[85]

Scheme 55

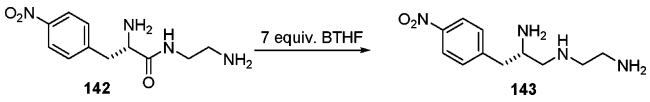


Scheme 56



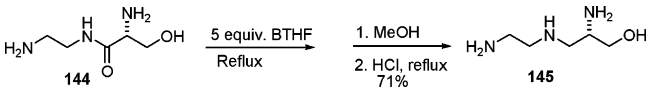
Gadoxate disodium is a contrast agent for magnetic resonance imaging. During one step of the synthesis, amide **142** was reduced on gram scale with BTHF without affecting the chiral center (Scheme 57).[86] Gadofosveset sodium,

Scheme 57



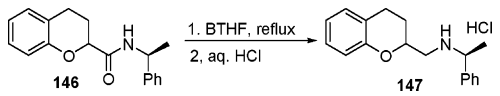
another MRI contrast agent, also required an amide reduction. Amidation of L-serine methyl ester with ethylenediamine gave the amide **144**, which was reduced with BTHF to 2-(*R*)-(hydroxymethyl)diethylenetriamine (**145)** (Scheme 58).[87] Excess BTHF is required because the hydroxyl reacts to liberate hydrogen and both the amine formed during the reduction and the primary amines coordinate with a borane.

Scheme 58



One synthetic route to Repinotan hydrochloride required an amide reduction. High yields of amine **147** as the hydrochloride salt were obtained by reduction of the amide with BTHF at reflux on a multigram scale (Scheme 59).[88]

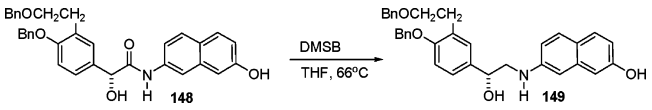
Scheme 59



During the synthesis of the antifungal agent Caspofungin acetate, the reduction of a primary amide, R-CONH$_2$, was required in the presence of other peptide amide linkages.[89] Belyk and co-workers successfully completed this primary amide reduction on a side chain of the macrocyclic 21-membered ring polypeptide on a gram scale with DMSB. The product was isolated in 88−92% yield after preparative high-pressure liquid chromatography (HPLC).

The preparation of an intermediate in the synthesis of KUR-1246 required the reduction of an amide adjacent to a chiral alcohol.[90] Reduction of the amide **148** with DMSB gave the desired product **149** (gram scale, 68% yield) after treatment with triethanol amine at reflux (Scheme 60).

Scheme 60



The reduction of amides and imides with borane complexes is an excellent method to synthesize amine derivatives in high yields. The reaction tolerates other functional groups such as nitro, chloro, and ester. The process has been been demonstrated on small and large scales. The importance of the amino functionality in the synthesis of active pharmaceutical ingredients (APIs) promises to make the amide reduction with boranes one of the preferred synthetic tools to prepare amines at the pharmaceutical level.

4.2. Nitrile Reduction

Reduction of the carbon−nitrogen triple bond to an amine with borane complexes in the presence of other reducible functional groups is a primary example of borane's chemoselectivity. Two hydride equivalents add to the carbon of the nitrile to form a stable borazine structure (**150**, Figure 3). Acidic hydrolysis converts the borazine to the amine as the ammonium salt.

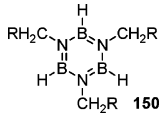
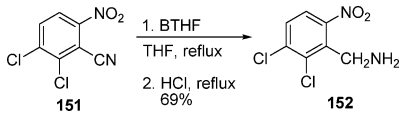


Figure 3.

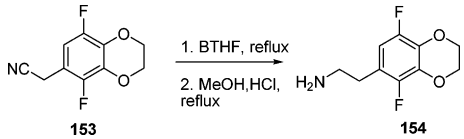
For the preparation of Anagrelide hydrochloride, a highly substituted benzonitrile was reduced with BTHF in the presence of nitro and chloro groups.[91] The reduction was conducted in THF at reflux and then followed by refluxing with HCl to quench the resulting borazine.[92] A yield of 69% was obtained by the patented process. This reduction was conducted on 28 kg of nitrile **151** using DMSB, and a 75% yield was obtained (Scheme 61).[93]

Scheme 61



In the small scale synthesis of analogues of Fenoldapam mesilate, the nitrile of 6-cyanomethyl-5,8-difluoro-1,4-benzodioxane (**153**) was reduced with BTHF at reflux (2 h, Scheme 62). Workup involved methanol quench and HCl addition followed by reflux and neutralization. However, the yield of **154** was not reported.[94]

Scheme 62



One route to (*R*)-Fluoxetine (**155**, Figure 4) used DMSB for the reduction of a nitrile to an amine on a small scale.[95] In summary, the triple bonds of nitrile groups are efficiently reduced to amines with borane complexes.

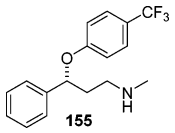


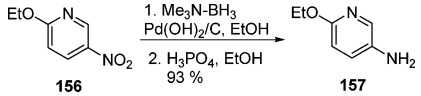
Figure 4.

4.3. Nitro Group Reduction to Amine

Borane reagents do not reduce the nitro functional group. However, amine boranes are a valuable source of hydrogen for transition metal catalyzed hydrogenation. Amine boranes are a clean source of hydrogen that can be utilized in low-pressure vessels to reduce nitro functional groups.

During the synthesis of drug candidates for the treatment of Alzheimer's disease, the reduction of an aromatic nitro group to the aniline was required.[96] Beaudin and co-workers initially used iron powder in ethanol, but to streamline several steps, the nitro reduction was conducted using palladium catalyzed hydrogenation with trimethylamine borane (TMAB) as the source of hydrogen. Pearlman's catalyst (3%) with 1.2 equiv of TMAB at reflux in ethanol effectively reduced the nitro group in **156** (Scheme 63). The product was isolated as a crystalline solid in 93% yield.

Scheme 63



The reduction of nitro groups by borane reagents on a large scale has been less common but nonetheless highly successful.

4.4. Reductive Amination

Reductive amination is an effective way to introduce an amino functionality into a molecule. An aldehyde or ketone

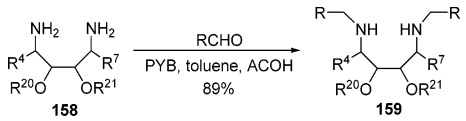
first reacts with an amine to form an imine or enamine intermediate, which can be reduced to the amine in the presence of mild reducing agents.[97] The following sections highlight amine boranes and sodium triacyloxyborohydride reagents for reductive aminations.

4.4.1. Via Amine Boranes

One very useful application of amine boranes is the reduction of imine, enamine, and oxime functionalities. The imine group is reduced to an amine product by an amine borane complex, while leaving a wide variety of substituent functionalities unaffected. The reduction proceeds rapidly when conducted in glacial acetic acid to give secondary amines in excellent yields. Since many amine borane reagents are not hydrolyzed in aqueous solution, they can even be used in water or methanol for mild reductive amination reactions.

The solubility of pyridine borane (PYB) in various aprotic solvents such as toluene and its stability in the presence of acids such as acetic acid make this reducing agent very suitable for reductive amination. Confalone and co-workers prepared intermediates for *N*,*N*′-disubstituted cyclic ureas via reductive amination with PYB.[98] They carried out the reaction in the presence of glacial acetic acid in toluene. Simple extraction with sodium carbonate solution and crystallization with 2-propanol provided the alkylated amine **159** in 89% isolated yield (Scheme 64).

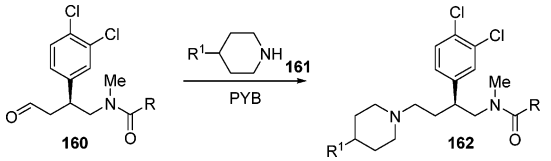
Scheme 64



158 159

To prepare an intermediate for the synthesis of neurokinin antagonists, Parker and co-workers replaced hazardous sodium cyanoborohydride with PYB in a reductive amination.[99] The reaction solvent was changed from methanol to dichloromethane to avoid competing formation of dimethyl acetal byproduct and to allow telescoping the two steps to form ZD6021. The procedure was very effective to produce **162** crude in 76% overall yield at multi-kilogram scale (Scheme 65).

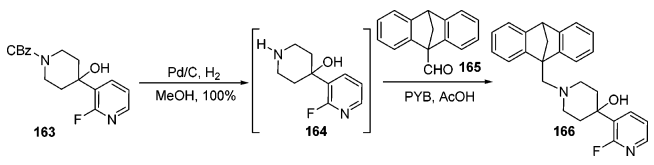
Scheme 65



160 162

Moseley and co-workers reacted crude amino alcohol **164** and aldehyde **165** in the presence of PYB to get the desired alkylated amine product **166** in 73% yield (Scheme 66).[100]

Scheme 66

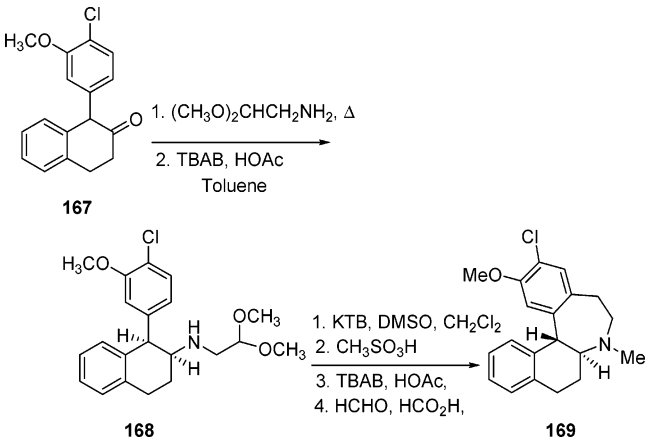


163 164 166

This intermediate was subsequently converted to ZD3638, an antipsychotic agent for the treatment of schizophrenia. The reductive amination was carried out in a methanol and acetic acid mixture. Interestingly, the use of an alternative hydrogenolysis process resulted in only 43% yield of desired product. One of the major problems with the hydrogenolysis was competing reduction of **165** to the alcohol. Process optimization did not improve the overall yields with hydrogenation. The borane reduction not only gave a higher quality product but also proved to be an acceptable process at pilot scale from the hazardous and environmental standpoints.[101]

The use of alkylamine boranes such as TBAB for reductive amination is very advantageous when the reaction is carried out in acidic media. Draper and co-workers effectively used TBAB to reduce enamine intermediates for the synthesis of a dopamine D1 antagonist (Sch 39166).[102] Substituted tetralone **167** was condensed with an amine to the enamine and reduced *in situ* with TBAB to a 9:1 mixture of *cis*/*trans* isomers **168** (Scheme 67). The 9:1 ratio was improved by

Scheme 67

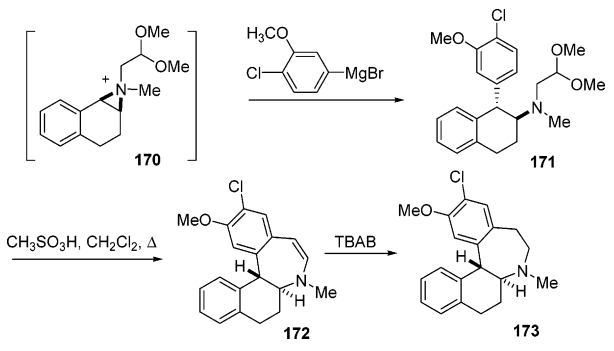


167 168 169

epimerization with KTB in hot DMSO to give the desired *trans* isomer as an 85:15 ratio of diastereoisomers. In a subsequent step, the benzazepine ring was formed via cyclization with CH_3SO_3H followed by reduction using TBAB.

Despite the shorter steps and better diastereoselectivities, this scheme was not enantioselective, requiring a resolution near the end of the synthesis. They were able to develop an enantioselective route based on formation of aziridine **170**, which was converted to benzazepine intermediate **173** using the acid catalyzed cyclization followed by a TBAB reduction protocol (Scheme 68). Some of the problems associated with this route included the use of environmentally unfriendly CH_2Cl_2, a cyclization time of about 2−3 days, and excessive foaming during $NaHCO_3$ neutralization.

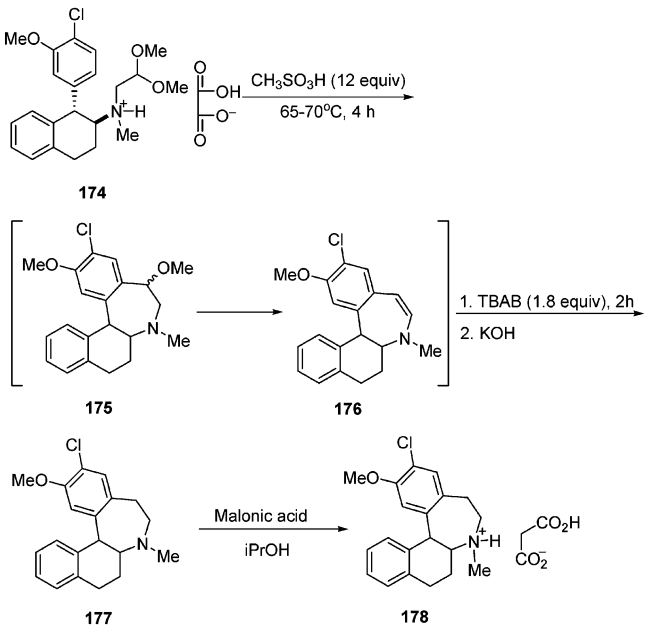
Scheme 68



170 171 172 173

Gala and co-workers developed a more robust, plant-suitable process to make large quantities of Sch 39166. They optimized the previous enamine reduction with TBAB to get **177** in higher yields (Scheme 69).[103] The reaction conditions

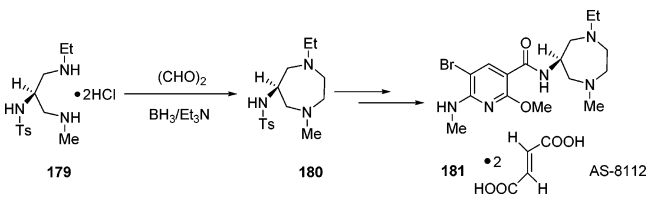
Scheme 69



included addition of **174** to neat $MeSO_3H$ instead of CH_2Cl_2 solvent, followed by heating for 2 h to give **176**. A suspension of TBAB in MTBE was added to the reaction mixture at 0−5 °C, providing the desired product in excellent yields. Gala and co-workers pointed out that the acidity of the reaction mixture was moderated by residual *tert*-butylamine in TBAB complex and the solubility of TBAB in organic solvents made it the ideal reagent for the reduction step. With the above modifications, the processing time was decreased from 7 to 2 days, the throughput was improved 4-fold, and the reaction yield was 20% higher. They also were able to eliminate environmentally unfriendly CH_2Cl_2 and demonstrated the usefulness of TBAB in reductive alkylations on a large scale.

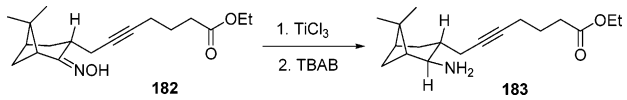
Yoshimi and co-workers used triethylamine borane (TEAB) or trimethylamine borane (TMAB) to effectively carry out the amination of 1,2,3-trisubstituted triaminopropane **179** with 40% aqueous glyoxal to give **180** in quantitative yield (Scheme 70).[104] The key for allowing the reduction to take place was the high stability of amine boranes in aqueous medium.

Scheme 70



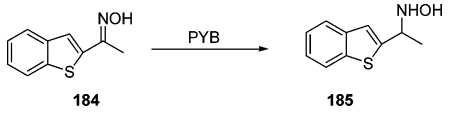
Oximes are usually formed in aqueous media; therefore, amine borane complexes are ideal for this reduction because of their stability in aqueous acidic solution up to pH 5. Cai and co-workers used the amine borane reduction of oximes to synthesize allergy and asthmatic drug candidate S-5751.[105] Aqueous $TiCl_3$ was buffered with sodium acetate, and the oxime was added to this solution at 0 °C followed by reduction with TBAB (Scheme 71). The desired amino ester product **183** was isolated as an oil after extraction and neutralization.

Scheme 71



Summers and co-workers reduced oxime intermediate **184** with PYB to the corresponding hydroxylamine product during the synthesis of Fredericamycin A (Scheme 72). The key aspect of the reaction was the use of 20% HCl solution in ethanol solvent, which allowed the reaction to be completed in just 30 min.[106]

Scheme 72



Overall, the above examples have shown that amine boranes are excellent reagents for reductive amination especially where acidic/aqueous media are required. Amine boranes are very attractive for reductive amination on large scale because of their stability to acidic medium and tolerance to other functional groups such as alkynes and esters.

4.4.2. Via Sodium Triacetoxyborohydride

Sodium triacetoxyborohydride (STAB) is the reagent of choice to carry out reductive aminations especially under nonaqueous conditions. In this process, aldehydes or ketones are reacted with ammonia or with primary or secondary amines in the presence of sodium triacyloxyborohydride reducing agents to produce primary, secondary, and tertiary amines, respectively.

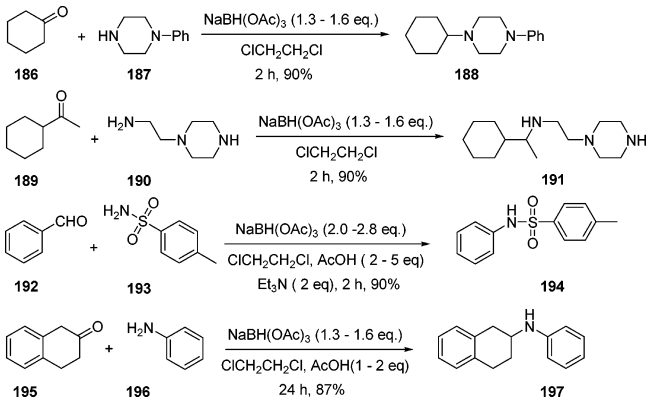
Due to the three electron withdrawing acetoxy groups in STAB, this reagent is a very mild reducing agent which reduces imines and iminium salts in the presence of other functional groups such as ketones, esters, nitro groups, or double or triple bonds. STAB also offers advantages during the workup of the reaction because it does not generate toxic byproducts such as cyanide, which is one the major problems of the alternative reducing agent, sodium cyanoborohydride.[3g]

Abdel-Magid and co-workers reported the reductive alkylation of aldehydes or acyclic and cyclic ketones with a variety of primary, secondary, and weakly basic amines such as aniline. Some examples are shown in Scheme 73.[107]

Their best procedure consisted of mixing the carbonyl compound and the amine (1 and 1.05 equiv, respectively) with STAB without prior formation of the intermediate imine or iminium salt. A slight excess (1.3−1.6 equiv) of STAB was used, and a variety of solvents such as THF, dichloroethane, or acetonitrile were suitable for this reaction at room temperature. The reductive amination with weakly basic and nonbasic amines such as aniline is slower, leading to competing ketone reduction and to overall low yields of the reductive amination products. In these cases, the use of excess ketone or acetic acid (1−3 equiv) is recommended to accelerate the reduction.

It is also important to point out that running reductions with STAB at temperatures higher than 50 °C for extended periods of time may cause degradation of the reducing agent

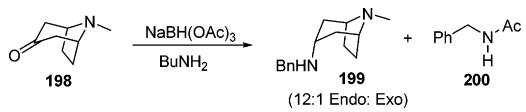
Scheme 73



via acetate reduction, producing acetaldehyde and ethanol byproducts. Acetaldehyde in particular may give unwanted alkylation of the amine substrate, resulting in formation of difficult to separate ethylamine byproducts.

In the preparation of 3-*endo*-tropamine (**198**), an intermediate in the synthesis of Zatosetron, which is useful in the treatment of central nervous system disorders induced by oncolytic drugs, Burks and co-workers used the reductive amination with STAB derivatives (Scheme 74).[108]

Scheme 74

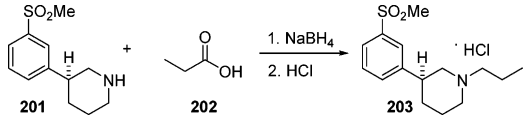


The alternative method to **199**, catalytic hydrogenation, required high catalyst quantities to ensure complete reduction of the imine and removal of the benzyl group. In addition, catalytic hydrogenation produced some unwanted impurities due to incomplete Schiff base formation or decomposition of the imine during reduction. Fortunately, using the standard STAB procedure (1.5 equiv of STAB, acetic acid (1.0 equiv), and 1,2-dichloroethane (DCE)), they obtained a 12:1 mixture (8:1 selectivity via hydrogenation) favoring the desired endo-*N*-benzylamine. The reaction also generated significant amounts of *N*-benzylacetamide probably formed by the addition of benzylamine to acetoxyborohydride. By switching from 1,2-dichloroethane to methylene chloride, the reductive amination of **198** resulted in high yields of **199** and low levels of benzylacetamide (2−4%). Based on statistically designed experiments, the optimal reaction conditions were a stoichiometry of 1.5 equiv of STAB, 0.75 equiv of acetic acid to accelerate the reaction rate, and 1.35 equiv of benzylamine to account for the loss of reagent to benzylacetamide formation.

Interestingly, when Burks and co-workers explored the use of bulky (acyloxy)borohydrides derived from 2-ethylbutyric or 2-ethylhexanoic acid, the stereoselectivity of the reaction for 3-endo-*N*-benzyltropamine (**199**) increased to a >30:1 ratio. These acyloxyborohydride derivates provided additional advantages such as complete solubility of the reagent in methylene chloride and no formation of *N*-benzylacetamide (**200**). One drawback of the more bulky acyloxyborohydrides is a slower reaction rate compared to that with STAB. In reactions with tris(2-ethylhexanoyl)borohydride reagent, the build up of the concentration of imine intermediate in the reaction suggests that hydride transfer in the reduction step is rate limiting. Therefore, it was necessary to use 2 equiv of the tris(2-ethylhexanoyl)borohydride reagent to drive the reaction to completion at rates comparable to those with STAB. The excess 2-ethylhexanoic acid could be recovered via a NaOH wash.[109]

In the final synthesis step of OSU 6162, a potential central nervous system (CNS) agent, a reductive amination was conducted by generation of sodium acyloxyborohydride *in situ*.[110] The propionic acid **202** is reduced *in situ* and aminated, giving the *n*-propylamine derivative **203** in 72% yield after formation of the hydrochloride salt (Scheme 75).

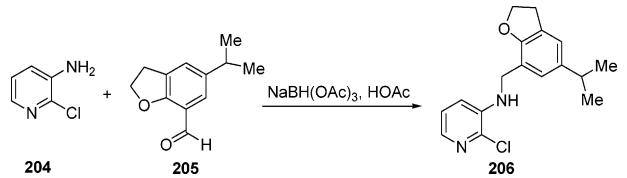
Scheme 75



The key to this successful reductive amination was to add the sodium borohydride in portions to the reactor containing the amine and propionic acid. When the sodium borohydride was added too quickly, a difficult to separate aminoborane impurity formed. In addition, it was necessary to neutralize and extract L-tartaric acid from the prior resolution step to avoid a dimeric impurity resulting from incorporation of the tartaric acid.

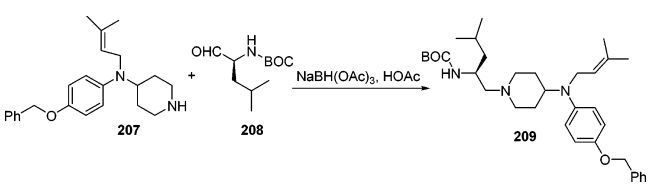
HSP-117 is active for treatment of nausea and vomiting and is a tachykinin NK1 antagonist. The synthesis described in patents required a reductive amination of a substituted benzaldehyde (**205**) with a 3-aminopyridine derivative (**204**). Catalytic hydrogenation was not suitable because of C−Cl bond cleavage. STAB effectively reduced the iminium intermediate at 0−4 °C to generate **206** for the synthesis of HSP-117 (Scheme 76). Ice water quenching, followed by addition of sodium hydroxide and extraction resulted in isolation of desired chloropyridine product (**206**).[111]

Scheme 76



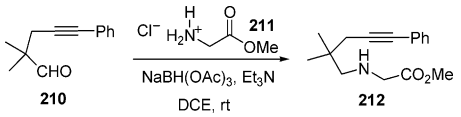
Hu and co-workers described the total synthesis of a piperidine derivative **209**. A key step in the synthesis was the use of STAB to carry out the reductive amination (Scheme 77). The double bond and carbamate group in the molecule were not reduced during the reductive amination. Racemization of the amino aldehyde derivative **208** was not observed.[112]

Scheme 77



Cossy and Belotti efficiently synthesized Licofelone, which is used for the treatment of arthritis. The authors carried out the reductive amination of glycine methyl ester hydrochloride (**211**) with aldehyde **210** in the presence of STAB as reducing agent and Et_3N to deprotonate the glycine compound

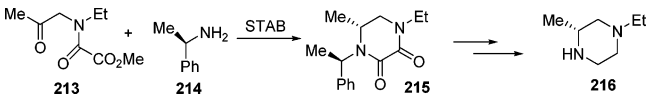
Scheme 78



(Scheme 78). The isolation of **212** and quenching of the reaction was accomplished with an aqueous saturated $NaHCO_3$ solution to give an 80% yield of desired product.[113]

Beshore and Dinsmore recently prepared 1,4-disubstituted 2,3-diketopiperazines and 1,4,5-trisubstituted 2,3-diketopiperazines via tandem reductive amination and acylation (Scheme 79). Interestingly, the use of (*R*)-α-methyl benzyl-

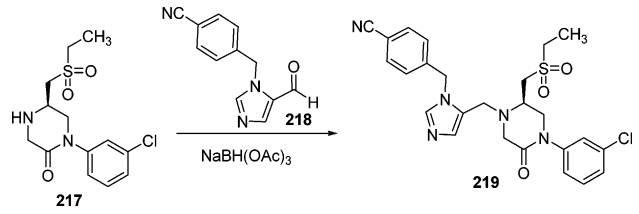
Scheme 79



amine (**214**) as a chiral auxiliary resulted in the diastereoselective formation of diketopiperizine intermediate **215** (6:1 ratio), which was eventually transformed to the piperizine analogue **216**.[114]

During the synthesis of L-779575, Hutchinson and co-workers prepared piperizone derivatives (such as **217**, Scheme 80) using STAB for the reductive amination. The

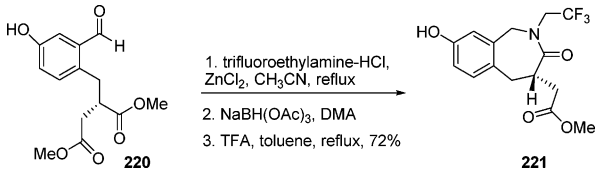
Scheme 80



authors adjusted the pH of the reaction with Et_3N and added crushed molecular sieves to remove water to help drive the reaction to completion.[115,116] Organic acids, such as acetic acid, were also added to accelerate the reduction. For the workup, the authors used a solution of sodium bicarbonate in water to quench the reaction mixture.

Wallace and co-workers used STAB to prepare a benzazepinone derivative (**221**) from a diester aldehyde intermediate **220** during the synthesis of SB-273005 (Scheme 81),

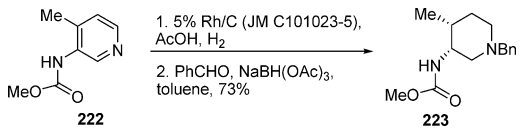
Scheme 81



a vitronectin receptor antagonist, which could be useful in the treatment of inflammation, cardiovascular disorders, cancer, and osteoporosis.[117] The reaction was problematic due to the incomplete formation of Schiff base resulting in contamination of the desired amine product with 10−15% of benzyl alcohol after workup. The authors were able to cyclize the crude amine directly with TFA in refluxing toluene. After acid/base workup (aqueous H_2SO_4, aqueous $NaHCO_3$, and H_2O) and precipitation from toluene, the desired benzazepinone compound was obtained in 72% yield, with 97% purity and free of benzyl alcohol contaminant.

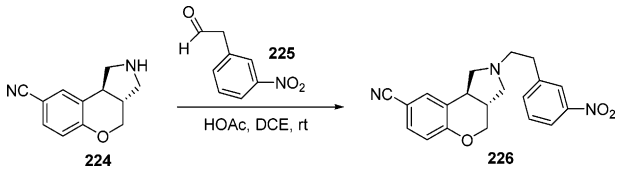
Cai and co-workers developed a large scale production of *cis*-3-methylamino-4-methylpiperidines using reductive amination with STAB.[118] Originally, the reductive amination was carried out in methylene chloride. For environmental reasons, methylene chloride was replaced by toluene. The authors found that the best mode of addition was adding the piperidine and benzaldehyde to a slurry of STAB in toluene. Excess STAB and acetic acid were quenched with aqueous sodium hydroxide. The pH was controlled to about 6−7 to prevent the formation of thick emulsion layers. After precipitation of the amine byproduct with HCl at high temperatures, they cooled and filtered the resulting crystals to isolate 73% yield of **223** (Scheme 82).

Scheme 82



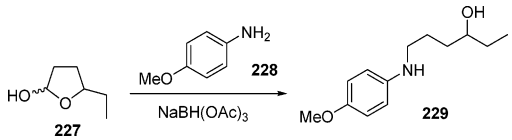
Lejeune and co-workers prepared the tetrahydropyrrole derivative **226** using STAB (Scheme 83). The cyano and nitro functionalities were not attacked under the reaction conditions that included acetic acid, a basic quench, and a relatively long reaction time (15 h), demonstrating the selectivity of STAB for imine reduction.[119]

Scheme 83



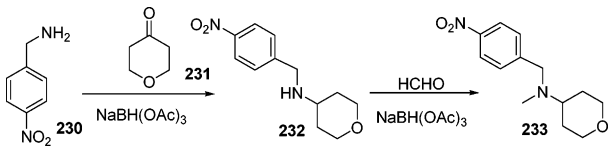
For initial scale-up to kilogram quantities, Urban and co-workers carried out the reductive amination of lactol intermediate **227** in good overall yield (Scheme 84). Even though some of the scale-up batches gave yields comparable to those produced in the lab, **227** proved to be unstable to the reaction conditions, resulting in the generation of complex reaction mixtures. Because of the instability of **227**, Urban and co-workers used an alternative route for the large scale production of desired compound **229**.[120]

Scheme 84



For initial preparation of gram quantities of an aniline dihydrochloride derivative, a key intermediate for the synthesis of TAK-779, a potential drug candidate for HIV-1 therapy, Hashimoto and co-workers carried out two reductive aminations with STAB (Scheme 85). Although **233** was

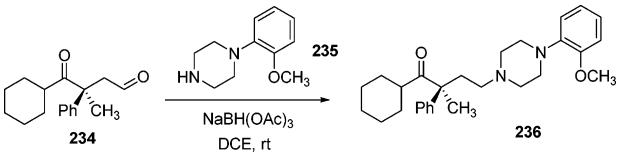
Scheme 85



isolated in excellent yields, the STAB route was abandoned for large scale manufacture of the benzylamine intermediate **233** because of the limited availability of starting material in bulk, separation of a large amount of solid waste including reducing agents, and the use of environmentally unfriendly 1,2-dichloroethane solvent in the reductive amination step.[121,122]

Denmark and Fu recently reported the synthesis of LY426965, a serotonin antagonist. They effectively carried out the reductive amination of aldehyde **234** in the presence of a ketone group with STAB (Scheme 86). The overall yield

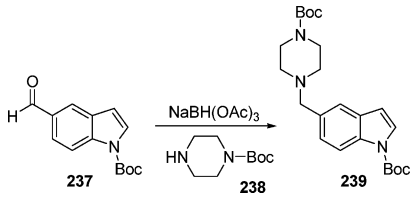
Scheme 86



for the reaction was 93%. The high chemoselectivity was attributed to the β-quaternary center, which would interfere with the formation of imine intermediate, consequently preventing ketone reduction.[123]

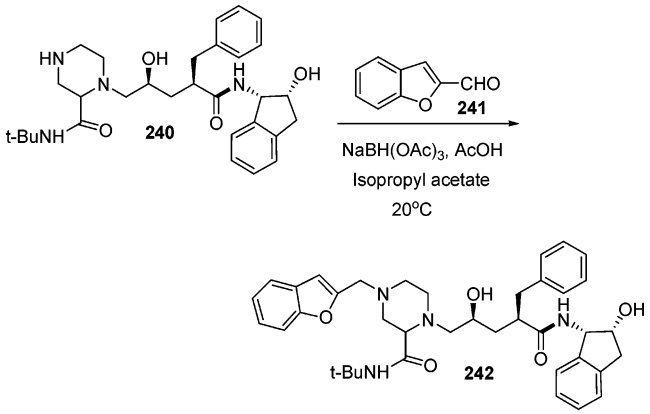
Payack and co-workers developed an efficient synthesis of a potent KDR inhibitor. Intermediate **239** was prepared via reductive STAB amination of BOC-piperazine **238** with aldehyde **237** (Scheme 87). An aqueous workup, followed by crystallization from methanol, gave multi-kilogram quantities of **239**.[124]

Scheme 87



Hoerrner and co-workers prepared L-756423, useful for the treatment of HIV infection, via reductive amination with STAB (Scheme 88). The reaction required 3 kg of STAB. The aldehyde **241** was premixed with the amine intermediate **240** in isopropyl acetate solvent followed by the addition of solid STAB over 15 min at ambient temperature. Glacial acetic acid was also added to assist the reduction. Quenching the reaction mixture with bicarbonate and an extractive workup allowed for the isolation of the desired amine product as free base **242**. The isolation of **242** as free base was critical for the next protonolysis step with sulfuric acid to give a

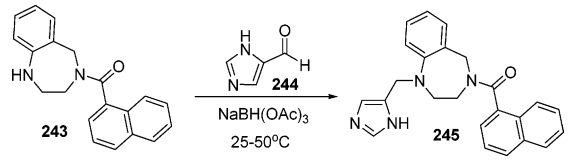
Scheme 88



sulfate salt which was shown to have much greater oral absorption and bioavailability in animal models.[125]

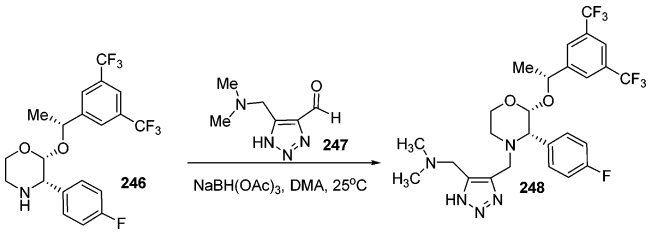
Bhide and co-workers prepared an intermediate (**245**) for the synthesis of BMS-214662, a solid tumor therapy agent, via reductive amination with STAB (Scheme 89).[126] To drive the reaction to completion, they used acetic acid as an additive and stirred the mixture for 2 h at 50 °C.

Scheme 89



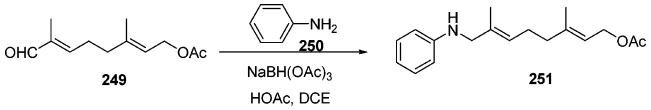
Recently, Cai and co-workers reported a reductive amination reaction with formyl triazole derivative **247** to prepare triazole intermediate **248**, a valuable intermediate in the preparation of pharmaceutical compounds (Scheme 90).[127] It is worth noticing that the hemiacetal functionality in **246** survived the STAB reduction conditions.

Scheme 90



The synthesis of farnesyl pyrophosphate analogues required the preparation of aniline derivative **251**. Chehade and co-workers prepared **251** via mild reductive amination with STAB (Scheme 91). They found that under these mild

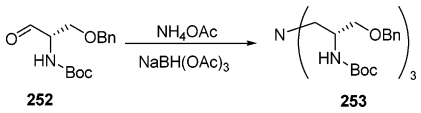
Scheme 91



reducing conditions the yields were consistently higher with fewer side products than was the case for conventional reductive amination reagents such as $NaBH_3CN$/MeOH, PYB or catalytic hydrogenation. This is one of the few examples reported that have used a reductive amination with an α,β-unsaturated aldehyde and the weak base aniline. The corresponding allylic aniline product **251** was obtained in 85% isolated yield.[128]

The synthesis of Gadolinium, a relaxation agent for magnetic resonance imaging, involved an interesting STAB reductive amination of chiral amino aldehyde **252** and ammonium acetate (Scheme 92). The desired tertiary amine **253** was obtained without loss of chirality in the molecule, demonstrating the usefulness of STAB for mild reductions.[129]

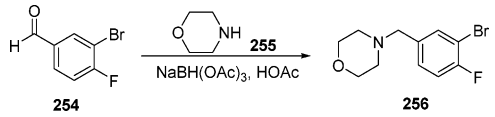
Scheme 92



Thaisrivongs and co-workers chemoselectively reacted 3-bromo-4-fluorobenzaldehyde (**254**) with morpholine fol-

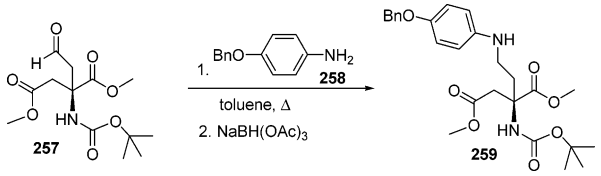
lowed by addition of STAB in portions to get the tertiary amine intermediate **256** (Scheme 93). Contrary to the cases of other methods, the fluoro and bromo functionalities were not reduced in the process.[130,131]

Scheme 93



In some cases, the reductive amination works better by preparing the imine intermediate prior to reduction with STAB. For example, Duan and co-workers heated 4-benzyloxyaniline (**258**) with intermediate **257** using a Dean−Stark apparatus for 6 h followed by addition of STAB (Scheme 94).[132] After 48 h the reaction was still incomplete, requiring

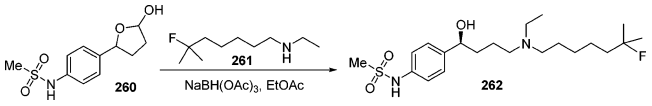
Scheme 94



additional portions of STAB to drive the reaction to completion. As mentioned before, slightly basic amines, such as aniline, are the most challenging substrates to alkylate using STAB.

Recently, Mackey and co-workers reported the synthesis of Trecetilide hemi-fumarate, a compound developed for the treatment of chronic atrial arrythmia. The key amine **262** was synthesized via reductive amination with STAB (Scheme 95).[133] Hydride reduction was preferred for the application

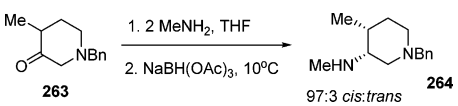
Scheme 95



because equipment limitations did not allow the use of hydrogenation. Other reducing agents, such as sodium cyanoborohydride, were not attractive on a large scale due to the toxicity of the reagent and its byproducts. The iminium intermediate was formed prior to transfer into the STAB slurry at 0−4 °C to afford **262**. Interestingly, the reaction worked well in ethyl acetate solvent. The solvent choice also facilitated the workup of the reaction because the free base amine product (**262**) was completely soluble in the aqueous phase below pH 6.5 while most of the reaction impurities were eliminated with the ethyl acetate organic phase. The free base (**262**) was subsequently extracted at pH 8−8.5 with ethyl acetate. The extractive acid/base workup provided **262** with greater than 90% chemical purity and yield.

Brown and co-workers carried out a reductive amination step during the synthesis of *cis*-*N*-benzyl-3-methylamino-4-methylpiperidine (**264**) (Scheme 96).[134] The reductive amination was more selective with STAB than with $NaBH_4$. On a lab scale, they added 1 equiv of STAB to the imine

Scheme 96

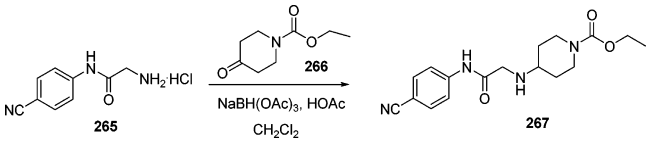


intermediate generated from reaction of ketone **263** with 2 equiv of methylamine in THF and acetic acid. The selectivity of the reaction was in the 97:3 range. When the reaction was done with a solvent mixture of EtOH/THF, a slight drop in selectivity was observed (93:7 ratio). The mode of addition did not influence the selectivity.

On a large scale, 4 equiv of methylamine was needed to ensure rapid and clean conversion to the imine. The mixture was added to a STAB suspension in THF. The imine transfer to the STAB reactor was troublesome because some ketone was regenerated when the imine was transferred to the STAB vessel under partial vacuum. Using extra methylamine and a nitrogen atmosphere solved the problem. Under these conditions, the authors obtained product **264** in 86% purity, with less than 4% of alcohol byproduct.

Kawasaki and co-workers used STAB to carry out the reduction of a Schiff base (Scheme 97). The authors isolated

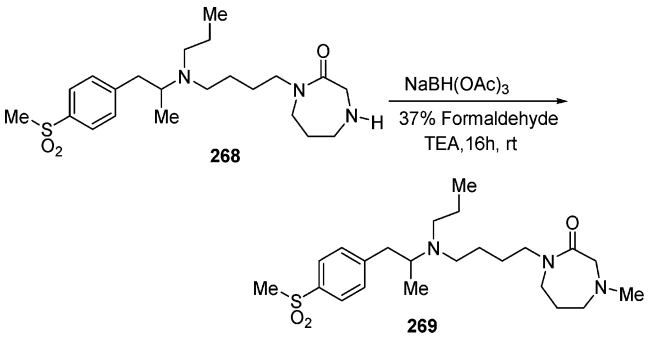
Scheme 97



the alkylated amine **267** via basic quenching with aqueous sodium hydroxide and subsequent extraction. The aqueous basic medium facilitated the removal of borate and acetate byproducts from the organic phase.[135]

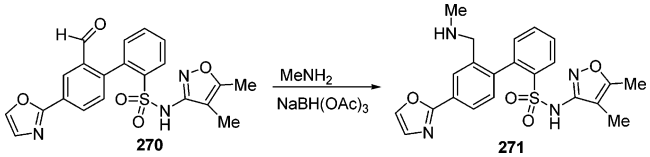
Reductive amination with STAB is an excellent methodology to incorporate methyl groups in an amine compound. For example, Maag and co-workers prepared the methylated diazepan-2-one **269** via reaction of diazepin-2-one **268** in tetrahydrofuran and 37% formaldehyde in the presence of triethylamine and STAB (Scheme 98). The reaction took 16 h at room temperature. Normal basic quenching and concentration provided **269** in high puritities.[136,137]

Scheme 98



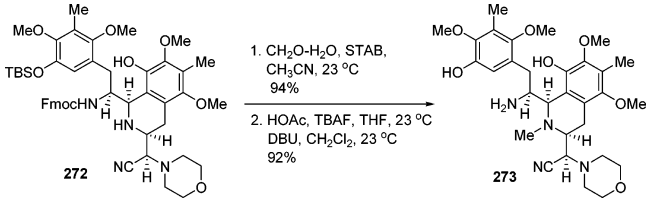
Barrish and co-workers used a modified reductive amination procedure to convert aldehyde **270** to the *N*-methyl benzylamine derivative **271** (Scheme 99). The modification included the use of 3 Å molecular sieves and an acetic acid/sodium acetate buffer solution to control the pH of the reaction.[138,139]

Scheme 99



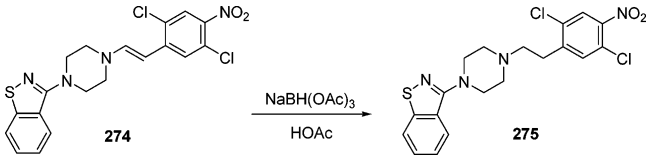
Myers and Kung reported the enantioselective synthesis of (−)-Saframycin A, a potent antitumor agent currently in preclinical trials. The key introduction of the methyl group was accomplished by reaction of **272** with formalin (2 equiv) in the presence of STAB (1.5 equiv) in acetonitrile to give the corresponding *N*-methylated compound **273** in 94% yield (Scheme 100). The labile morpholino nitrile function was unaffected by the mild reductive conditions.[140,141]

Scheme 100



Enamines are also reduced with STAB. Urban and co-workers reported the reduction of enamine **274** with STAB in 1,2-dichloroethane (Scheme 101).[142] Solid STAB was added in portions, and the reaction was complete after overnight stirring. Standard basic workup with sodium carbonate solution and extraction provided the desired amine product **275** in 71% isolated yield.

Scheme 101



Numerous other examples of reductive amination with STAB have been recently reported.[143,144] In general, reductive amination with STAB is an excellent method to alkylate amines. All the applications reviewed in this section demonstrate the great potential of STAB for large scale uses. As shown in this section, the reductive amination with STAB has become one of the preferred methods to synthesize active pharmaceutical ingredients containing secondary and tertiary amines as a structural feature.

5. Stereoselective Reactions with Boranes and Borohydrides

Borane and borohydride reagents have advanced the field of stereoselective reactions through chiral catalysts, chiral reducing agents, and trialkylborohydride reducing agents. The examples in the following sections will illustrate the utility of these reagents.

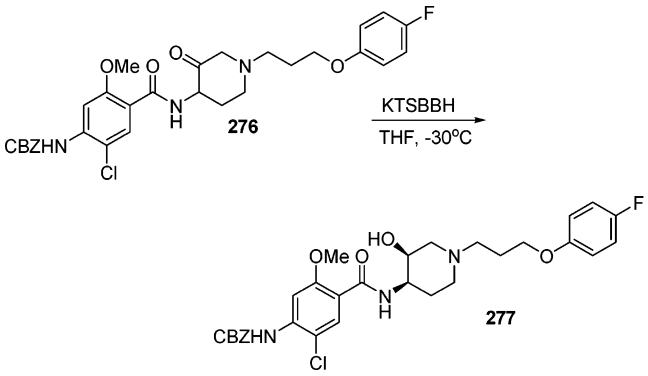
5.1. Stereoselective Ketone Reduction

The stereoselective reduction of cyclic ketones is a difficult task but critical for the synthesis of several drug intermediates. The reduction of a substituted cyclohexanone to a specific diastereomer of the cyclohexanol is often required. Alkali metal tri-*sec*-butylborohydride reagents have fulfilled the requirements of high yield and excellent stereoselectivity for the reduction of cyclohexanones. The bulkiness of the nucleophillic hydride reagents allows addition of hydride to primarily one face of the ketone; thus, an extremely selective reduction is achieved. The stereoselective reduction of cyclic ketones with these hindered reagents has been exploited in several drug syntheses to deliver the correct isomer of the desired intermediate as shown in the examples below.

A note of caution concerning the workup of reductions using alkali metal trialkylborohydride reagents is necessary: trialkylboranes are not hydrolyzed by water or aqueous base and will remain in the organic layer. Trialkylborane that is released from the reducing agent must be chemically oxidized prior to air exposure to avoid rapid unexpected exothermic air oxidation and possible spontaneous combustion upon air exposure.[145]

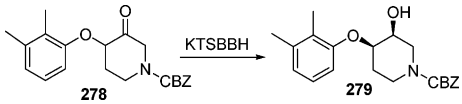
Potassium tri-*sec*-butylborohydride (KTSBBH) was the reagent of choice for the stereoselective reduction of α-amino ketone **276** for the synthesis of Cisapride hydrate (Scheme 102).[146] The reduction was quantitative and stereoselective, giving the desired compound with *cis* orientation of the hydroxyl and amide groups.

Scheme 102



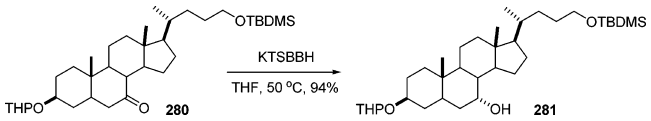
A similar structural feature in Ifoxetine sulfate was achieved by stereoselective reduction of the α-oxo ketone **278** with KTSBBH (Scheme 103). Unfortunately, the yield and stereoselectivity were not given in the patent.[147]

Scheme 103



Squalamine, an antibiotic, required stereoselective reduction of the *B*-ring cyclohexanone on the steroidal structure **280**. Using KTSBBH for this reduction gave the desired 7α-alcohol **281** in 94% yield (gram scale, Scheme 104).[148] Kinney and co-workers recently reported examples where grams of **280** were reduced with KTSBBH to give a 96% yield of **281**.[149]

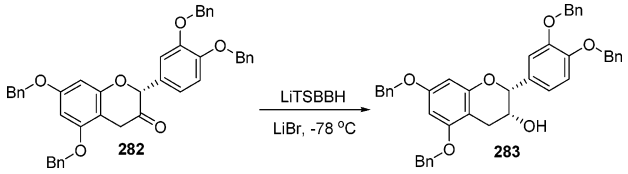
Scheme 104



Small scale stereoselective reduction of the keto group in the substituted flavanone (**282**) with lithium tri-*sec*-butylborohydride (LiTSBBH) gave a 70% yield of product **283** (Scheme 105).[150] This intermediate **283** was used to prepare Procyanidin B-2, a hair growth stimulant in clinical trials.

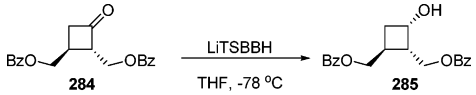
In addition to stereoselective cyclohexanone reduction with hindered borohydride reagents, cyclobutanone was also successfully reduced with the bulky reagent lithium trialkylborohydride. During the synthesis of the antiviral Cygalovir,

Scheme 105



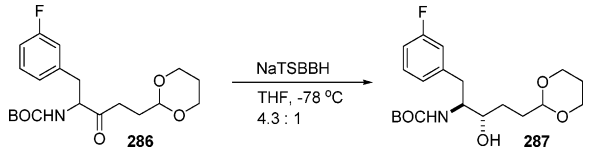
stereoselective reduction of the carbonyl group **284** gave the corresponding alcohol **285** in 80% yield after oxidative workup (Scheme 106).[151] Multi-kilogram quantities of the drug were prepared.

Scheme 106



The stereoselective reduction of acyclic ketones to the desired diastereomer is also important for the synthesis of a number of drug intermediates. Again, alkali metal trialkylborohydrides are very useful for diastereoselective reduction of acyclic ketones. For example, Urban's synthesis of an intermediate for the synthesis of HIV and blood pressure control drugs required the stereoselective reduction of a BOC-protected-amino ketone **286**.[152] Of the hydride reagents tried, sodium tri-*sec*-butylborohydride (NaTSBBH) at −78 °C gave the best selectivity, and a 4.3:1 ratio favoring the desired (*S*,*S*)-isomer **287** was achieved (Scheme 107). In fact, reduction with sodium borohydride and diisobutylaluminum hydride delivered the opposite selectivity (see Table 1).

Scheme 107



Further refinements in the synthesis route to increase the selectivity led to reduction of a similar amino ketone (**288**, **289**) where a 46:1 ratio of the desired isomer **290** was obtained in about 50% overall yield (Scheme 108). Multiple kilograms of lactone were produced with this optimized route.

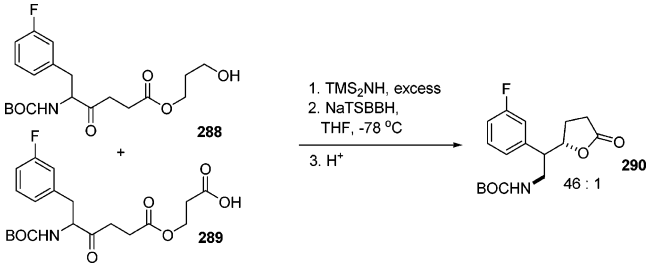
Recently, NaTSBBH was used for the stereoselective reduction of an acetylenic ketone during the synthesis of HAK-2701. Although the work in this paper is no doubt at a small scale, several borohydrides were compared for diastereofacial selectivity in the nucleophilic reduction. A diastereomeric ratio of 33:1 was obtained with NaTSBBH versus one of 20:1 for KTSBBH and low selectivity for STAB and sodium borohydride.[153]

These examples demonstrate that alkali metal trialkylborohydrides are excellent reagents for diastereofacial selectivity in cyclic and acyclic ketone reductions. The selectivity is sometimes governed by the counter-cation, requiring experimental testing to determine the best reagent for highest selectivity.

Table 1. Diastereoselective Reduction of Acyclic Ketone with Various Hydride Reagents

reducing agent	ratio of (*S*,*S*) to (*R*,S)
NaTSBBH	4.3:1
KTSBBH	2:1
LiTSBBH	1.3:1
$NaBH_4$	1:3
$(isobutyl)_2AlH$	1:3.4

Scheme 108

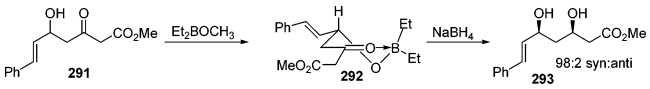


5.2. Diastereoselective Reduction of *β*-Hydroxyketone

Diastereoselective reduction of *β*-hydroxyketones to the corresponding 1,3-*syn*-diols is a very important synthetic transformation because of the occurrence of 1,3-dioxygenated fragments in biologically active natural products such as compactin, macrolides, and others, as well as statins, an important class of pharmaceuticals. Of the available synthetic methods to make 1,3-*syn*-diols from *β*-hydroxyketones, the sodium borohydride reduction of a *β*-hydroxyketone complexed to a borane reagent has proven to be the preferred choice to achieve high stereoselectivity in the ketone reduction.

In early work, Prasad and others used a trialkylborane in the presence of air or other activators to generate an alkoxydialkylborane. The dialkylborane acts as a diastereodirecting group by forming six-membered boron chelate **292** with the substrate (Scheme 109). The substrate alcohol

Scheme 109

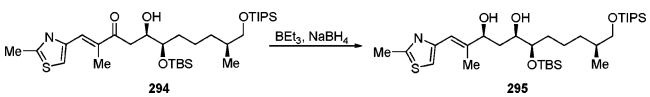


displaces the alkoxy group from the borane reagent, and the ketone coordinates to the boron, which activates the ketone by further polarizing the double bond. The sodium borohydride then delivers the hydride from the less hindered side of the six-membered ring to give the *syn*-diol in high yield.

Recently, alkoxydialkylboranes such as methoxydiethylborane (MDEB) were successfully used directly as chelating agents in the diastereoselective reduction of *β*-hydroxyketones to the corresponding 1,3-*syn*-diols. The alkoxydialkylborane method provides more consistent results than triethylborane. In addition, the lower pyrophorocity of MDEB over trialkylboranes make this reagent more suitable for large scale applications. In this section, examples of *β*-hydroxyketone reduction using trialkylboranes and alkoxydialkylboranes are reviewed.

Bode and Carreira used triethylborane (TEB) to form MDEB *in situ* for the *β*-hydroxyketone reduction to make a key 1,3-*syn* diol intermediate **295** in the synthesis of epothilone A and B (Scheme 110).[154] The reaction required

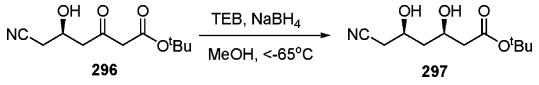
Scheme 110



methanol to convert TEB to MDEB. Interestingly, any excess TEB or MDEB was azeotropically distilled off with methanol. The biggest challenge of the azeotropic distillation was to ensure complete removal of the borane byproduct from the desired product.

In the synthesis of Atorvastatin calcium, Nanninga and co-workers used a strategy similar to Carreira's to make the key 1,3-*syn*-diol intermediate **297** (Scheme 111).[155] To

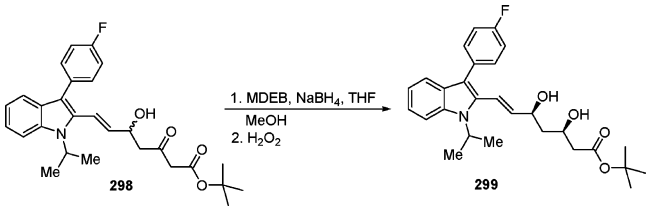
Scheme 111



activate TEB, they utilized a mixture of acetic acid and methanol. The reduction of β-hydroxyketone **296** with $NaBH_4$ in the presence of alkylborane was carried out under cryogenic conditions at temperatures between −65 and −75 °C. The complete removal of borane residues required multiple and lengthy azeotropic distillations using a combination of methanol and acetic acid.

Repic and co-workers found that the use of MDEB and $NaBH_4$ to reduce β-hydroxyketone **298** was a more convenient combination to make the 1,3-*syn*-diol intermediate **299** than TEB.[156] Several reducing agents, chelating agents, solvents, and temperatures were screened during the optimization of the stereoselective reduction of β-hydroxyketones. Interestingly, the selectivity of the reaction significantly increased from 80% to 98% when methanol was added to the triethylborane/sodium borohydride reaction. The authors reasoned that methanol was converting triethylborane into diethylmethoxyborane. The other available methods to activate triethylborane, such as introducing air to the reactor, were difficult to reproduce in the plant. Using MDEB, very high stereoselectivities in the reduction of β-hydroxyketones to *syn*-diols (99%) were achieved (Scheme 112).

Scheme 112



The amount of diethylmethoxyborane was successfully reduced to 0.5 equiv, but the *syn* selectivity of the reduction deteriorated at lower levels of MDEB. Apparently, the reaction is autocatalytic because methanol can displace the product from the boron reagent, regenerating diethylmethoxyborane, which can activate another molecule.

One of the intermediates after the reduction was boronate **300** (Figure 5), which methanolizes much more slowly, thus causing a amount of high boron residue in the desired diol product.

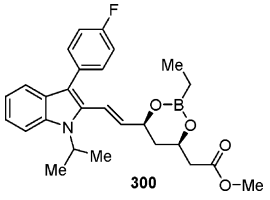
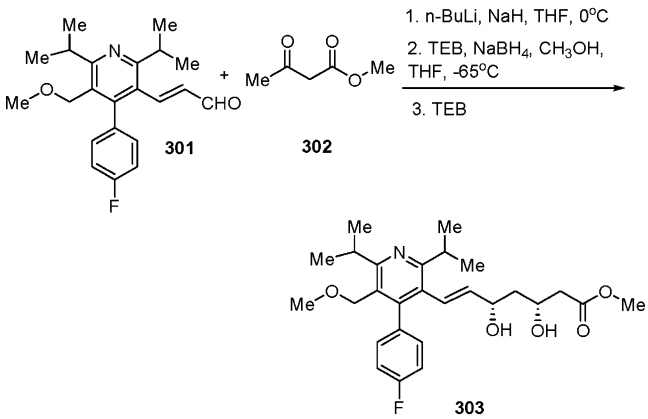


Figure 5.

Instead of multiple azeotropic distillations with MeOH to remove the boron, Repi and co-workers decided to use an oxidative workup with hydrogen peroxide. The oxidation of diethylmethoxyborane and other borane intermediates was essential for clean product isolation.

During the synthesis of Cerivastatin sodium, Angerbauer and co-workers activated TEB by passing air into the reaction mixture for 5 min before the addition of $NaBH_4$ (Scheme 113).[157] Even though the authors isolated 79% of desired

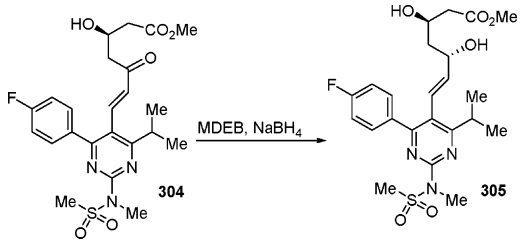
Scheme 113



diol **303**, the biggest challenge of this procedure was to ensure the formation of alkoxydiethylborane intermediates. The selectivity of the reduction depended on formation of enough alkoxydialkylborane in the reaction so that the borohydride did not competitively reduce unchelated β-hydroxyketone.

Hirai and co-workers also used the MDEB/$NaBH_4$ protocol in methanol to make Rosuvastatin calcium.[158] The *syn*-diol **305** was isolated in 85% yield (Scheme 114).

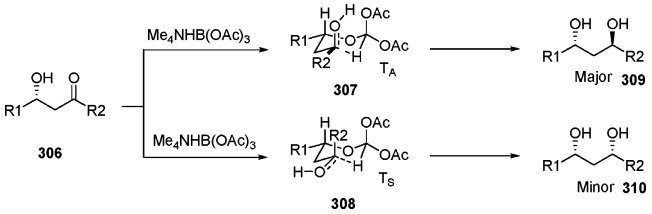
Scheme 114



Other synthetic routes to active pharmaceutical ingredients such as Dalvastatin,[159] Brevastatin,[160] and Nivastatin[161] have used similar MDEB or TEB/$NaBH_4$ protocols, demonstrating the scope of the reaction to prepare *syn*-diols.

Sodium triacetoxyborohydride is a very useful mild reducing agent for the diastereoselective reduction of β-hydroxyketones to the corresponding β-*anti* diols. High diastereoselectivity and good yields are generally observed. Evans and co-workers extensively studied the effect of solvent, temperature, and reducing agent to increase the *anti*-selectivity.[162] The preference of *anti*-diastereoselectivity is explained by exchange of one acetoxy group with the alcohol moiety followed by intramolecular hydride delivery (Scheme 115). Competition between two chairlike transition states, T_A and T_S, accounts for the diastereoselectivity. The 1,3-diaxial interaction of R_2 and OAc destabilizes T_S more than the analogous 1,3-diaxial interaction of OH^+ and OAc in T_A, thus favoring formation of *anti*-diol **309**. Evans used a

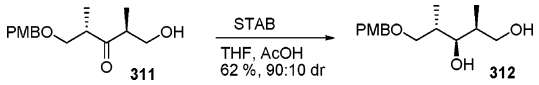
Scheme 115



modified STAB derivative to prepare the key *anti*-diol intermediate in the synthesis of the marine macrolide Bryostatin 2.

Paterson and co-workers recently reported the synthesis of (+)-Discodermolide.[163] The synthesis required the selective formation of diol intermediate **312** (Scheme 116).

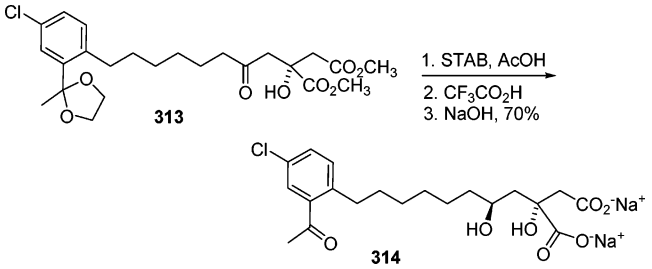
Scheme 116



Carrying out the reduction with STAB in the presence of acetic acid and THF at −20 °C gave an excellent diastereoselectivity (90:10 dr). The diastereomeric mixture was conveniently purified via recrystallization from diethyl ether/hexanes to give pure *anti*-diol **312** in 62% yield.

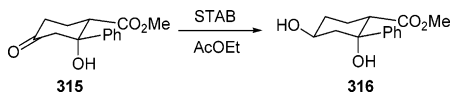
In the synthesis of drug candidates to inhibit cholesterol synthesis, Gribble and co-workers used STAB prepared *in situ* for the reduction of β-keto alcohol **313** (Scheme 117).[164] The desired product **314** was isolated in 70% yield after an acidic removal of a ketal protecting group.

Scheme 117



Turnbull and co-workers reported the synthesis of Milbemycin β1, an insecticidal compound.[165] The synthetic pathway required a dihydroxy cyclohexane carboxylate resulting from a Robinson annelation (without dehydration to an enone) and reduction. Reduction of cyclic hydroxyketoester with $NaBH_4$ in THF or 2-propanol gave a mixture of isomeric diols, with the undesired C5 axial diol predominating. The reduction with STAB gave a higher selectivity to the desired *anti*-diol **316** (C5-equatorial, C7-axial diol, Scheme 118). The authors isolated an 80% yield of **316** after

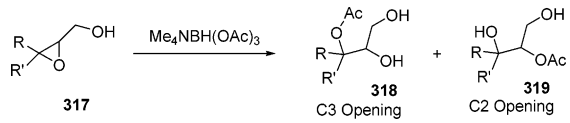
Scheme 118



recrystallization. The undesired isomer was not detected by thin-layer chromatography. The diastereoselectivity is explained by the C7 axial hydroxyl exchanging with an acetoxy group on the borohydride, followed by intramolecular hydride attack on the carbonyl group.

Epoxy derivatives are considered interesting building blocks for the preparation of APIs. Regioselective ring opening of 2,3-epoxy alcohols with nucleophiles is a very important area in multistep synthesis. Honda and collaborators reacted epoxy alcohol **317** with a modified triacetoxyborohydride derivative ($Me_4NBH(OAc)_3$) at 70 °C to provide selectively C3 ring opening product as a 1,2-diol **318** with the C2 alcohol **319** as the acetoxy ester (Scheme 119).[166]

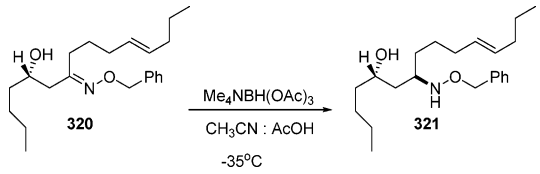
Scheme 119



The triacetoxyborohydride derivative is acting as Lewis acid, increasing the reaction rate and regioselectively via chelation of the metal center and the epoxy alcohol oxygens.

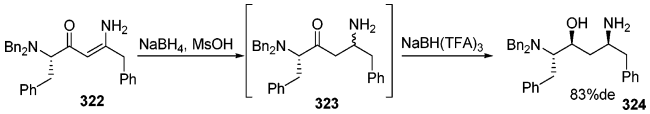
Williams and co-workers reported the convenient preparation of 1,3-amino alcohols via a stereocontrolled reduction of β-hydroxy *o*-benzyl oximes.[167] High selectivities of the desired amino alcohol **321** were obtained (Scheme 120).

Scheme 120



Haight and co-workers developed a practical method to prepare diamino alcohol for the synthesis of Ritonavir, an HIV protease inhibitor.[168] One of the processes involved the reduction of amino ketone **322** with a mixture of trifluoroacetic acid (4 equiv) and sodium tris(trifluoroacetoxy)-borohydride (4 equiv, Scheme 121). The conversion was very

Scheme 121



high (98%), and a significant improvement in the diastereoselectivity was reported over those achieved with other reducing agents (83%).

In general, the complementary reagents MDEB/$NaBH_4$ and STAB are excellent for the stereoselective synthesis of *syn*- and *anti*-diols, respectively. The commercial availability of these compounds on a large scale has enabled the successful implementation of diastereoselective β-hydroxyketones reduction on a technical scale. New industrial and pharmaceutical applications using MDEB/$NaBH_4$ and STAB to make *syn*- or *anti*-diols are expected in years to come.

5.3. 1,2-Enone versus 1,4-Enone Reduction

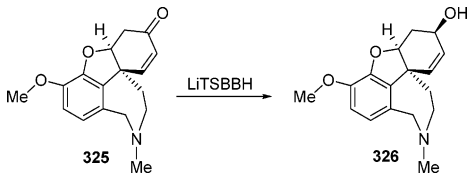
The dual pathways available complicate the reduction of the enone functionality. Addition of hydride across the carbonyl results in a 1,2-enone reduction forming an allyl alcohol. Attack of the hydride on the double bond can form an intermediate enolate anion, which upon quenching with a protic source results in a saturated ketone. Alternatively, the intermediate enolate anion can react with electrophiles. Alkali metal trialkylborohydride reagents are excellent

choices for enone reduction that are proven to give very high regio- and stereoselectivities.

The reduction of enones by alkali metal trialkylborohydrides has been systematically studied.[169] In general, acyclic enones and systems with extended conjugation undergo 1,2-addition to form allyl alcohols after protonation. β- and γ- substituted cyclohexenones give exclusively 1,2-addition, yielding the allyl alcohol. Cyclohexenones with no β-substitution undergo 1,4-addition to give the saturated ketones after protonation. The enolate formed from 1,4-addition can be alkylated.[170] Cyclopentenones and cycloheptenones tend to give a mixture of products with trialkylborohydride reducing agents. Asymmetric reduction of 1,2-enones with chiral reducing agents is covered in section 5.5.

Galantamine hydrochloride has a complex fused ring system. To stereoselectively reduce the carbon−oxygen bond of the cyclohexenone **325** in the final synthetic step, LiTSBBH successfully delivered a 97−99% yield of allyl alcohol product **326** at a multi-kilogram scale. A number of reducing agents were examined, but LiTSBBH proved optimal at −15 °C to give the correct stereoisomer (Scheme 122). In addition, only 1.2 equiv of the lithium trialkylborohydride were necessary on the larger scale when the free base (−)-narwedine was used as substrate instead of narwedine-tartrate salt.[171]

Scheme 122

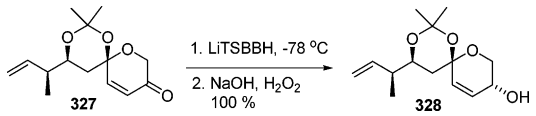


Stereoselective reduction of the carbonyl of an enone with KTSBBH was important to establish the stereochemistry along the chain in the synthesis of (+)-Discodermolide.[172] (+)-Discodermolide is a cytotoxic polyketide with microtubule-stabilizing abilities and is more potent than the anticancer drug Paclitaxel. Stereoselective reduction of the carbonyl of the enone with KTSBBH gave higher diastereoselectivity (9:1) versus the cases with NaTSBBH (3:1) or LiTSBBH (1.2:1). Reduction with (*R*)-MeCBS and DMSB gave a 9:1 diastereomeric ratio, but 2 equiv of chiral reducing agent was required to achieve this selectivity.[173] Other reducing agents did not give the desired allylic alcohol as a primary product.[172] In Paterson's synthesis of Discodermolide, 1,2-reduction of enone with KTSBBH to the required hydroxy lactone in the second to last step gave a 97:3 diastereomeric ratio in 85% yield.[174] Mickel and coworkers' synthesis of (+)-Discodermolide on a 60 g scale successfully used KTSBBH for the 1,2-reduction of an enone in the second to last step of the synthesis.[175] A 97:3 diastereomeric ratio was obtained in 85% yield on a small scale, but upon scale-up, the yield decreased to 60−70%, possibly due to sensitivity of the product to the oxidative workup and chromatography.

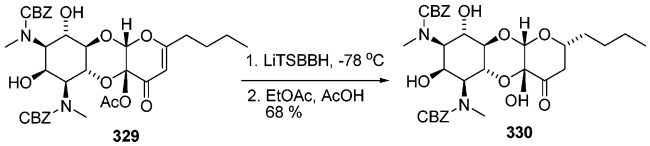
Recently, LiTSBBH was used for the reduction of the spirocyclic enone **327** in the synthesis of Fujimycin (Scheme 123).[176] The regio- and stereospecific reduction was directed by the existing stereocenters, giving 100% yield of desired isomer **328**.

LiTSBBH was successfully used as well in the 1,4-reduction of an enone in the synthesis of the antibiotic Trospectomycin sulfate (Scheme 124).[177] Acetic acid in ethyl acetate was used to quench unreacted LiTSBBH prior to isolation of the desired product **330**.

Scheme 123

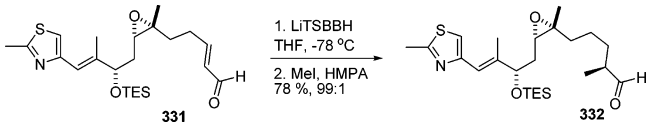


Scheme 124



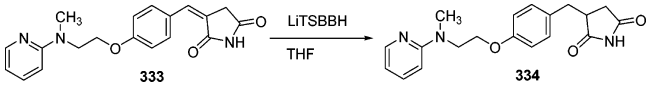
Contrary to the general pattern of 1,2-reduction of acyclic enones, intermediate **331** in an Epithilone B synthesis was reduced in a 1,4-mode with LiTSBBH (Scheme 125). The intermediate boron enolate was methylated with methyl iodode with excellent diastereoselectivity (>99:1).[178]

Scheme 125



In one of several methods to reduce the double bond in the final step of the synthesis of Rogislitazone, LiTSBBH selectively completed the desired 1,4-reduction (Scheme 126). [179]

Scheme 126



In summary, the hindered nature of alkali metal trialkylborohydride reducing agents contributes to the high regio- and stereoselectivity attained in the reduction of unsaturated carbonyl groups. As demonstrated in the previous examples, the trialkylborohydrides selectively reduced enones in the presence of other functionalities such as substituted epoxides and ketals. The 1,2- or 1,4-reduction of enones with trialkylborohydrides to the corresponding alcohols is a very powerful methodology that will find new and interesting applications on the industrial and pharmaceutical scales.

5.4. Enantioselective Ketone Reduction

Enantiomerically pure pharmaceuticals have driven the need for highly selective and high yielding reduction processes. Asymmetric reduction of carbon−oxygen double bonds is of fundamental importance to the synthesis of chiral secondary alcohols. Two classes of chiral boron compounds have contributed to advances in the enantioselective reduction of ketones: chiral oxazaborolidine catalysts and diisopinocampheylchloroborane, $(Ipc)_2BCl$. These chiral compounds have been used on an industrial scale in the production of chiral intermediates for drug candidates.

Asymmetric reduction using chiral oxazaborolidine catalysts is an excellent tool for the synthesis of secondary alcohols in high enantiomeric excess and was recently reviewed.[180] The enantioselective borane reduction of prochiral ketones catalyzed by chiral oxazaborolidine compounds has effectively competed with enzymatic and transition metal

catalyzed hydrogenation reactions, because of the mild reaction conditions, high enantioselectivity, predictability, and high yields. The reduction is highly efficient and operationally simple; therefore, it is well suited to an industrial setting. Several oxazaborolidine compounds have been used in the scale-up of pharmaceutical compounds and will be discussed in further detail.

The oxazaborolidine class of chiral catalysts is formed from chiral amino alcohols and a borane complex, boronic acids, or boroxins. Although the parent HCBS catalyst **335** has been prepared from borane complexes and used *in situ*, the actual amount of active catalyst formed is often questionable. Addition of borane to α,α-diphenylpyrrolidinemethanol (DPP) results in the formation of an aminoborate containing 2 equiv of DPP as the major product.[181] This compound is not active as an asymmetric reduction catalyst.

Patents cover the synthesis and use of oxazaborolidine catalysts.[182] Several oxazaborolidines derived from commercially available amino alcohols are shown in Figure 6.

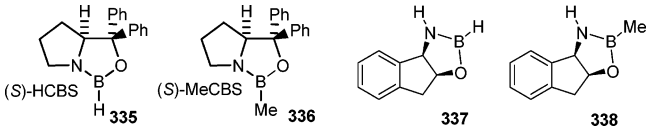
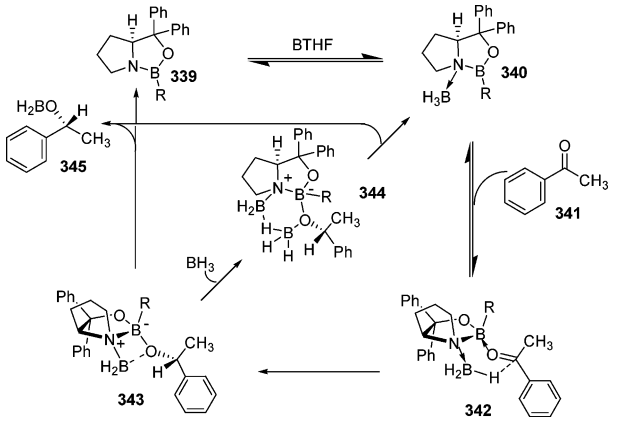


Figure 6.

Despite the fact that numerous structural variations of the amino alcohol have been studied to find an optimum ozaxaborolidine catalyst for ketone reductions, the commercially available Corey catalyst, *S*- or *R*-MeCBS (**336** or the respective *R*-isomer), remains the reagent of choice.

The precise stereocontrol of the reduction arises from a cyclic transition state where the oxazaborolidine holds the ketone via coordination to the Lewis acidic boron while the borane is held in proximity by the amine of the catalyst (Scheme 127).[183] The enantioselectivity of the reduction is

Scheme 127

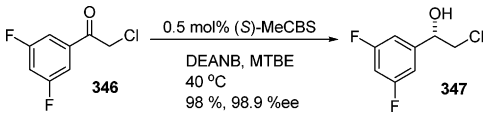


dependent on the oxazaborolidine structure, the substrate structure, and the temperature of the reduction. The enantioselectivity of the oxazaborolidine catalyzed reduction is highest when the groups flanking the carbonyl are vastly different or one group is an aromatic ring. Aromatic substituted ketones and compounds with large steric differences generally give highly predictable enantioselectivities. The nature of the substituents on the boron (H, Me, Ph, Bu, etc.) plays a lesser role in the observed selectivity. Generally, 2−10 mol % of oxazaborolide catalyst is used along with a borane source such as BTHF, DMSB, or *N*,*N*-diethylaniline borane (DEANB). The ketone is usually added slowly to the mixture of catalyst and borane. Simultaneous addition of borane and ketone to the catalyst is also effective for optimizing enantioselectivity.

The presence of borohydride as the stabilizer in commercial BTHF has been shown to be detrimental to the enantioselectivity of oxazaborolidine catalyzed reductions.[62] Borohydride is a competitive nonselective catalyst for ketone reductions;[184] thus, deactivation of the borohydride with an acidic compound is essential for high enantioselectivity when using BTHF.

Very high enantioselectivities and yields can be obtained in the reduction of acetophenone derivatives, especially when electron withdrawing substituents are present on the aromatic ring. For example, in the synthesis of a drug target, Chung and co-workers developed a multi-kilogram route to enantioselectively reduce the readily available 2,4-difluoro-2′-chloroacetophenone **346** (Scheme 128).[185] The (*S*)-MeCBS

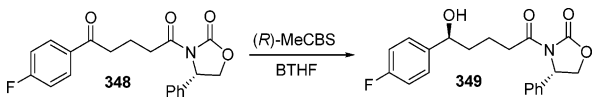
Scheme 128



catalyzed reduction was optimized with DEANB as the borane source at 40 °C. A slow addition of the ketone was also important to achieve high enantioselectivity. A 98% yield of chiral alcohol **347** was obtained with 98.9% ee using 0.5 mol % (*S*)-MeCBS and a 10 h ketone addition time.

In the synthesis of Ezetimbe, several methods have been published using oxazaborolidine catalyzed reduction of an aromatic ketone to the desired chiral alcohol. Wu and co-workers initially used (*R*)-MeCBS with DMSB as the borane source on a gram scale.[186] However, due to the smell of dimethyl sulfide, BTHF was chosen as the borane source for scale-up. Unfortunately, over-reduction of the amide carbonyl bond occurred when the substrate was added to BTHF/(*R*)-MeCBS solution (Scheme 129).[187] Reversing the

Scheme 129

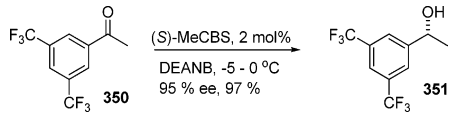


mode of addition overcame the regioselectivity issue, and <1% of the over reduced byproduct and a high diastereoselectivity, 97:3, of the desired chiral alcohol were obtained on a small scale.

This oxazaborolidine catalyzed reduction was subsequently demonstrated on 15−50 kg of ketone with BTHF as the reducing agent in the presence of (*R*)-MeCBS catalyst. The best results were obtained when the reaction temperature was 23−28 °C and the BTHF complex was slowly added to the mixture of ketone and catalyst. After methanolysis and concentration of the reaction mixture, the product **349** was obtained in 97−100% yield with a diastereoselectivity of 93−95% de.

Brands and co-workers compared catalytic asymmetric transfer hydrogenation to oxazaborolidine catalyzed borane reduction of a bis-trifluoromethylacetophenone intermediate **350** in the synthesis of Aprepitant (Scheme 130).[188] Higher enantioselectivity and yield were obtained with (*S*)-MeCBS (2 mol %) catalyzed DEANB reduction of the ketone (95%

Scheme 130



ee, 97%) versus transfer hydrogenation (91% ee, 92%). The reaction was demonstrated on a multi-kilogram scale.

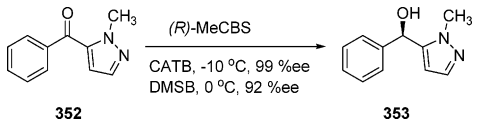
For the asymmetric reduction of ketones with an amine functionality, 1 equiv of borane forms a complex with the amine and is usually not available for the reduction. Therefore, additional borane reagent is required. Duquette and co-workers[189] required kilogram quantities of an amino alcohol derived from 3-acetylpyridine. The desired chiral amino alcohol was obtained via oxazaborolidine catalyzed reduction of 3-acetylpyridine with DMSB. Two equivalents of borane were necessary due to the complexation of one BH_3 to the pyridine nitrogen. The chiral catalyst was prepared *in situ* by stirring methyl borate and (*R*)-diphenylprolinol for 1 h at 25 °C.

In our laboratories, we have observed by ^{11}B NMR that, under these conditions, one methoxy group has exchanged with the alcohol of the diphenylprolinol, but the oxazaborolidine ring had not formed. The actual active catalyst generated under Duquette's conditions may be HCBS instead of methoxy-oxazaborolidine.

Duquette and co-workers found that the enantioselectivity of the reduction was low with a fast ketone addition, but the enantioselectivity increased by slow addition of the ketone and conducting the reaction at 44 °C. Higher enantioselectivity seen at an elevated temperature also supports HCBS as the actual catalyst. A ketone addition time of over 11 h for 1.5 kg resulted in high yield with 96% ee. Slow turnover of the active catalyst due to the electron withdrawing effect of the chloro substitutent was proposed as the reason for the slow reduction.

For an intermediate in the synthesis of Cizolirtine citrate, phenyl pyrazol ketone **352** was asymmetrically reduced using 15 mol % (*R*)-MeCBS as catalyst (Scheme 131).[190] With 2

Scheme 131

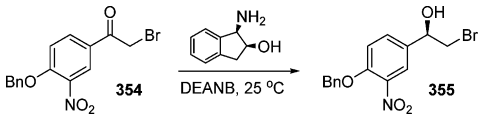


equiv of catecholborane as the reducing agent at −10 °C, the chiral alcohol **353** was obtained in 83% yield with 99% ee, as compared to using 2 equiv of DMSB as the reducing agent at 0 °C, which gave 84% yield and 92% ee. This synthesis was run on a multigram scale.

A key step in the synthesis of (+)-*d*-Sotalol was the asymmetric reduction of 4′-(chloroacetyl)methanesulfonanilide.[191] The reduction using BTHF and 6 mol % (*S*)-MeCBS was optimized to give 96% ee when conducted at ambient temperature in *tert*-butyl methyl ether. Even though the methanesulfonamide proton is acidic, the reduction provided the chiral chloro-alcohol in excellent yield and optical purity.

Hett and co-workers have used the oxazaborolidine derived from (1*R*,2*S*)-1-amino-2-indanol with DMSB for asymmetric reduction of a 3-nitro-α-bromoacetophenone **354** in the synthesis of (*R*,*R*)-Formoterol (Scheme 132).[192] In a comparison study, MeCBS gave a high enantioselectivity in the reduction (95% ee) but −15 °C was required. With *in situ*

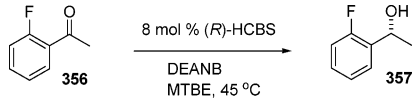
Scheme 132



prepared oxazaborolidine derived from (1*R*,2*S*)-1-amino-2-indanol and BTHF, an acceptable enantioselectivity (90% ee) was obtained at 25 °C. Thus, the asymmetric reduction was conducted efficiently at ambient temperature with the latter oxazaborolidine. Further process optimization lead to use of DEANB as the borane source for the asymmetric reduction.[193] Multiple kilograms of the ketone **355** were reduced at 25 °C to obtain a diastereomeric ratio of 94:6 (*R*:*S*). The diethylaniline from DEANB was efficiently removed via two sulfuric acid extractions and a final brine wash.

Garrett and co-workers developed a practical catalytic process for the enantioselective reduction of 2′-fluoroacetophenone.[194] A number of oxazaborolidine-type catalysts were screened for the reduction of this ketone to obtain an optimized system. The authors compared HCBS, MeCBS, and MeOCBS for the 2′-fluoroacetophenone reduction (**356**) using borane-diethylaniline (DEANB) as a concentrated borane source (5 M, Scheme 133). The simplest procedure

Scheme 133



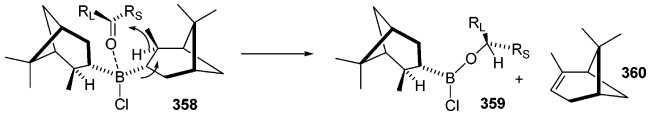
used the catalyst formed *in situ* from (*R*)-α,α-diphenyl-2-pyrrolidinemethanol. The chiral alcohol **357** was produced on a large scale with high enantioselectivity (98% ee).

A membrane reactor for large scale synthesis of chiral fine chemicals has been developed where an oxazaborolidine catalyst was attached to styrene and used in a ceramic membrane reactor for a 2 week run.[195] An optimum space time yield of 1 kg/L·day was obtained with >99% conversion and >96% enantiomer selectivity in the reduction of α-tetralone. This effective use of enantioselective oxazaborolidine catalyzed reduction in a continuous process will advance production and reduce the costs of chiral intermediates.

Oxazaborolidine catalysts were used in the development of the following drugs and drug candidates: KUR-1246,[196] Luliconazole,[197] Tolterodine tartrate,[198] Ro 25-8210,[199] Duloxetine hydrochloride,[200] Fredericamycin A,[201] and Uniprost.[202] It is not known if these processes have been used at a larger scale since the examples show reduction of only several grams of ketone.

Another commercially available chiral boron compound, diisopinocampheylchloroborane ($(Ipc)_2BCl$), is particularly effective for reduction of aromatic ketones to chiral secondary alcohols. The reduction proceeds via a six-membered cyclic transition state where the β-hydrogen of the isopinocampheyl group is transferred to the carbonyl carbon and α-pinene is released (Scheme 134). The reduction is usually conducted at −25 to −30 °C.

Scheme 134

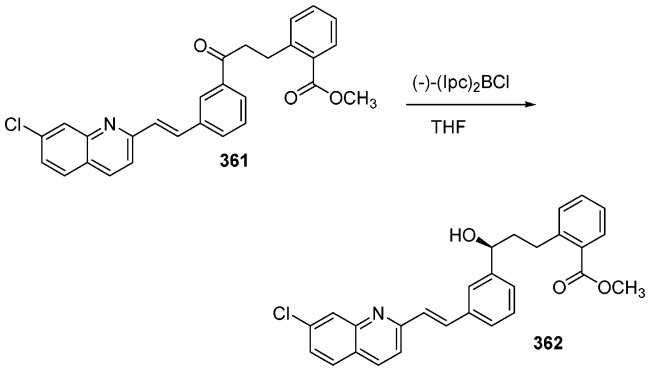


Diisopinocampheylchloroborane derived from 70% ee or higher α-pinene can result in final products of very high enantiomeric purity via asymmetric amplification.[203] In the preparation of $(Ipc)_2BCl$, the minor α-pinene isomer is incorporated into a heterochiral *dl*-diastereomer.[204] This heterochiral isomer reduces ketones more slowly than the *ll*- or *dd*-enantiomers, so by use of excess reducing agent, the chiral secondary alcohol is produced with a very high enantioselectivity. The ability to use lower purity α-pinene and improved processing parameters in the synthesis of diisopinocampheylchloroborane has dramatically lowered the cost of this commercial product. Reductions with diisopinocampheylchloroborane to make enantiomerically pure compounds have been reviewed.[205]

Although asymmetric ketone reductions with diisopinocampheylchloroborane give very high enantioselectivity, the isolation of product from the reaction mixture can be problematic. The isolation of product via extraction into an aqueous layer while leaving the byproducts in the organic layer has been most successful.

Leger and co-workers used (−)-$(Ipc)_2BCl$ in the synthesis of the asthma drug Montelukast.[206] The reduction of the aromatic ketone **361** (Scheme 135) to the chiral (*S*)-alcohol

Scheme 135



362 with (−)-$(Ipc)_2BCl$ gave a 65% yield, but enantioselectivity was not discussed. (*S*)-MeCBS catalysis with BTHF was used to prepare the corresponding (*R*)-alcohol on a multigram scale. The reduction of **361** with (+)-$(Ipc)_2BCl$ prepared from DMSB and (−)-α-pinene was demonstrated on a multi-kilogram scale giving an 87% yield and 99.5% ee.[203] Using *in situ* prepared (−)-$(Ipc)_2BCl$, an excellent enantioselectivity of the reduction (≥99% ee) and a high yield of **362** have been reported in the corresponding patent on a gram scale.[203d]

Another aromatic ketone with a similar structure was reduced with (−)-$(Ipc)_2BCl$ and cyclized to a lactone (88% ee) on a kilogram scale.[207]

Scott and co-workers evaluated several methods to prepare a chiral chlorohydrin **364** by the reduction of α-chloroketone **363** for the development and testing of a *β*-3 adrenergic receptor agonist (Scheme 136).[208]

Scheme 136

(−)-$(Ipc)_2BCl$ reduction of the α-chloroketone was compared to oxazaborolidine catalyzed borane reduction and enzymatic reduction (Table 2). The (−)-$(Ipc)_2BCl$ reduction

Table 2. Reducing Agent's Selectivity

reducing agent	% ee 364
$(Ipc)_2BCl$	91
MeCBS	2−42
Quallich oxazaborolidine	84
enzyme	98

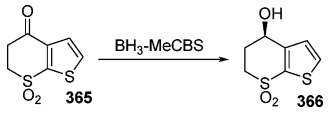
produced the (*R*)-chlorohydrin in 91% ee. Oxidation of the remaining boron−carbon bonds after the reduction was best achieved using the mild oxidant sodium perborate in basic solution. The base effectively formed the epoxide from the chlorohydrin during the workup. The epoxide could not be easily separated from the pinene-related byproducts at this stage, but after the ring opening of epoxide by amine, the product was extracted into acidic aqueous media to obtain a 63% yield. The examples reduced 45 g of substrate, but it is not clear if scale-up was done on this route.

Scott and co-workers then tested oxazaborolidine catalyzed methods to achieve the chiral reduction. MeCBS catalyzed reduction of the α-chloroketone **363** delivered a low enantioselectivity; however, Quallich oxazaborolidine catalyst[209] derived from 2-amino-1,2-diphenylethanol with dimethyl sulfide borane as the borane source gave 84% ee and 95% yield. The oxazaborolidine catalyzed reduction was much cleaner than (−)-$(Ipc)_2BCl$ reduction, and the chlorohydrin product could be isolated via crystallization for an overall 67% yield of (*R*)-chlorohydrin with 95% ee.

The enzymatic reduction of α-**363** with a yeast, *Z. Bailii* ATCC 38924, gave 76% *in situ* yield (57% isolated) and 98% ee with a substrate loading of 16 g/L. Both oxazaborolidine and microbial routes appeared to be promising alternatives to $(Ipc)_2BCl$ mediated reduction for the large scale synthesis.

During the synthesis of MK-0417, used in the treatment of glaucoma, Jones and co-workers screened yeast, $(Ipc)_2BCl$, and (*S*)-MeCBS for the enantioselective reduction of ketone **365**.[210] The oxazaborolidine catalyzed borane reduction was chosen for the high yield (99%) since yeast gave the opposite selectivity and $(Ipc)_2BCl$ made for difficult separations. The catalytic reduction was optimized with (*S*)-MeCBS for kilogram scale production of chiral alcohol **366**, and (*S*)-DPP was recovered in 95% yield (Scheme 137).

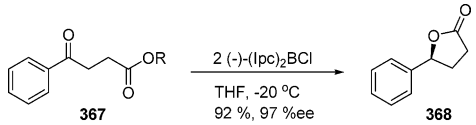
Scheme 137



In the synthesis of (*S*)-Fluoxetine hydrochloride, Senanayake and co-workers compared oxazaborolidine catalyzed ketone reduction and $(Ipc)_2BCl$ reduction at gram scale.[211]

Whereas asymmetric reduction of methyl 3-benzoylpropionate **367** with (−)-$(Ipc)_2BCl$ gave 92% yield with 97% ee (Scheme 138), reduction with oxazaborolidine catalyst derived from (1*R*,2*S*)-1-amino-2-indanol with borane gave high enantiomeric excess and 78% yield of the desired chiral alcohol **368**.

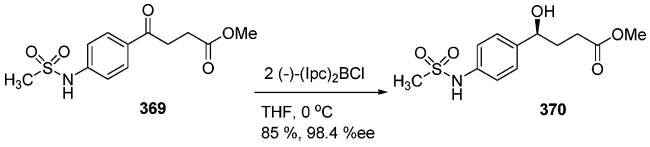
Scheme 138



In another patented route[212] to Fluoxetine hydrochloride, Jurgens and co-workers used catalytic (1*R*,2*S*)-1-amino-2-indanol with DMSB for asymmetric reduction of the aromatic ketone. In the same reduction step, a nitrile is also reduced to the amine.

In a convergent route to Trecetilide hemi-fumarate, Mackey and co-workers found (−)-$(Ipc)_2BCl$ to be the best reagent for the asymmetric reduction of ketone **369** (Scheme 139).[133] The temperature effect on the reduction was

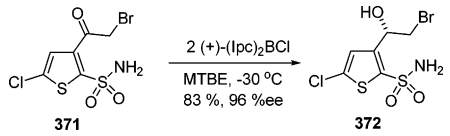
Scheme 139



explored, which showed the best selectivity at −15 °C (97% ee). From the example at 0 °C, 20 g of ketone was reduced in high yield and selectivity (98% ee). The α-pinene was effectively removed from the product through multiple heptane washes.

For the formation of chiral alcohol **372** in the synthesis of Brinzolamide (AL-4862), (+)-$(Ipc)_2BCl$ was used for the reduction of α-bromoketone **371** (multi-kilogram quantities) at −30 °C in *tert*-butyl methyl ether (Scheme 140).[213] MTBE

Scheme 140



as the solvent was superior to THF since it is water-immiscible and relatively nonhygroscopic. The product was obtained in 83% yield, but a tedious chromatographic separation was necessary to separate the product from the α-pinene, isopinocampheol, and other byproducts. A footnote mentions several bottles of $(Ipc)_2BCl$ in MTBE bursting after storage in a refrigerator for >1 month. $(Ipc)_2BCl$ is sold commercially in hexanes or heptane, a nonreactive solvent, and should not be stored in ethers because of ether cleavage decomposition reactions.

The discovery of asymmetric amplification using diisopinocampheylchloroborane has expanded the options for the synthesis of chiral alcohols. Furthermore, the commercial availability of this chiral boron reagent has launched it into the production of multi-kilogram quantities of drug candidates.

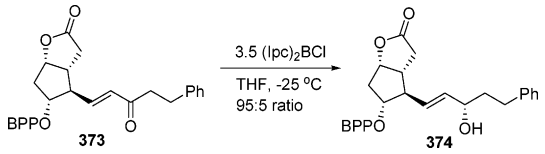
5.5. Enantioselective 1,2-Enone Reduction

For the asymmetric reduction of enones to a chiral alcohol, both oxazaborolidine catalysts and $(Ipc)_2BCl$ have been employed. Over-reduction of the double bond can be a potential problem using borane complexes with oxazaborolidine catalyst but does not occur with $(Ipc)_2BCl$.

In the original synthesis of Latanoprost, sodium borohydride with catalytic cerium chloride was used at −78 °C for the 1,2-enone reduction to obtain the racemic allyl alcohol in 98% yield.[214] Kovacs and collaborators tried LiTSBBH for this enone reduction at −135 °C, but only a 35% yield was obtained.[215] They found reduction with sodium borohydride at 0 °C gave only a 38% yield.

Latanoprost was successfully prepared in optically active form at gram scale via selective reduction of the carbonyl group of the enone **373** in the presence of a lactone functionality with $(Ipc)_2BCl$ (3.5 equiv) at −25 °C (Scheme 141).[216] The chiral allyl alcohol **374** was obtained in 85% yield with 90% ee.

Scheme 141



Henegar and co-workers also used $(Ipc)_2BCl$ for the 1,2-enone reduction in the preparation of Latanoprost and emphasized workup with water and diethanolamine to precipitate the boron byproducts.[217] However, the examples did not demonstrate the workup or yield via these methods.

During the synthesis of MDL-100240, reduction of 2-chlorocyclohexenone with (*S*)-MeCBS and DMSB was conducted on a multigram scale.[218] Using only a stoichiometric amount of borane reagent averted the over-reduction of the double bond.

The number of steps to prepare Squalamine **375** (Figure 7) was decreased from 16 to 11 by Kinney and co-workers.[219]

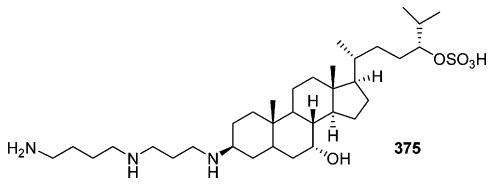
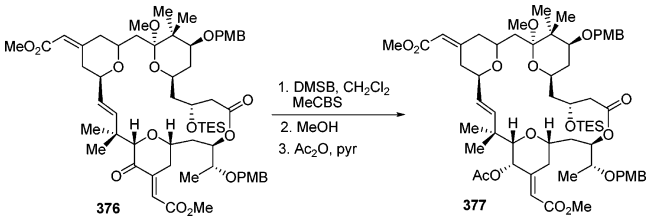


Figure 7.

A key step to set the stereochemistry of the steroidal side chain used (*R*)-MeCBS with BTHF for the reduction of the enone to the allylic alcohol. Unfortunately, experimental examples were not found in the corresponding patent.

Bryostatin 1 is a large macrocycle which required the stereoselective reduction of cyclohexenone **376**. Enantioselective reduction (small scale) with DMSB and MeCBS gave a 91:9 diastereomer ratio of **377** in 89% yield (Scheme 142). A footnote states that MeCBS gave the highest yield and selectivity of all chiral and achiral reducing agents they tested (other reagents tried were not listed).[220]

Scheme 142



The asymmetric reduction of prochiral ketones and enones using chiral borane reagents and catalysts is remarkably effective for the synthesis of chiral alcohols in high enantiomeric excess. The Corey oxazaborolidine catalysts have proven extremely selective in a number of cases and have been used at greater than kilogram scale. This technology has been adopted by process chemists especially for molecules near the final steps to the API and where other

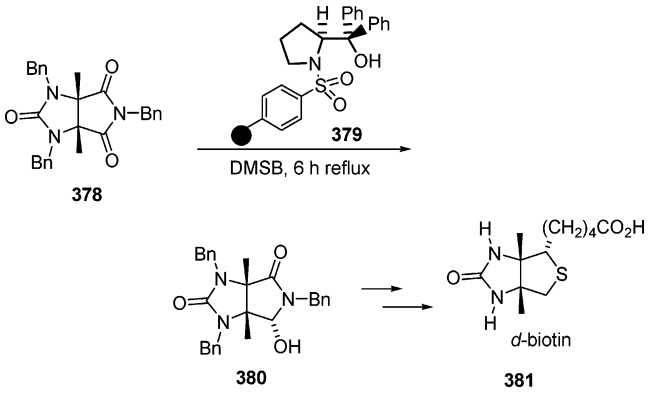
functional groups would be reduced under asymmetric hydrogenation conditions.

5.6. Enantioselective Imide and Imine Reduction

The use of polymer supported oxazaborolidine catalysts holds great promise for the future of this method because of the high yields, selectivity, and ease of product isolation.

An expeditious and enantiocontrolled approach to the total synthesis of *d*-biotin via a polymer supported chiral catalyst and DMSB for the reduction of *meso*-cyclic imide **378** was developed on a small scale (Scheme 143).[221] The *in situ*

Scheme 143



generated catalyst gave the chiral lactam **380** in 91% yield and >98.5% ee. The polymer supported catalyst was recycled five times without a reduction in yield (average yield 95%) or enantioselectivity. This strategy is an economically efficient method for the synthesis of the vitamin *d*-biotin (**381**).

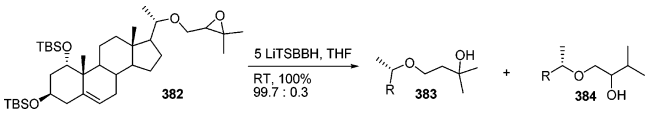
Asymmetric reduction of imines is a method to obtain chiral amines that has not yet reached its potential. One surprising reversal of enantioselectivity has been seen depending on the borane reagent used. MeCBS catalyzed reduction of aromatic imines with CATB gave the opposite selectivity compared to the configuration obtained by using BTHF as the reducing agent. The effect was rationalized by more hindered conformations of the CATB aromatic ring and the imine aromatic ring in the transition state.[222]

6. Reductive Cleavage

Reductive cleavage of functional groups is a diverse reaction sometimes occurring as a side reaction but also useful when the reaction is selective. The Lewis acidic nature of boron compounds has been exploited in a number of ways to assist or participate in cleavage reactions. Selective reductive cleavage of functional groups, such as chiral auxiliaries, halides,[223] tosylates,[224] and other sulfonates,[225] is important for the synthesis of advanced pharmaceutical intermediates. Lithium triethylborohydride (LiTEBH), the strongest of the borohydride reducing agents, has found utility in these types of cleavage reactions but not yet on a large scale.

For the reductive ring opening of epoxide **382**, the related reagent LiTSBBH was used on kilogram scale during the synthesis of Maxacalcitol, an antihyperparathyroidism and antipsoriatic drug.[27] Shimizu and co-workers tested a number of boron and aluminum reducing agents to find that LiTSBBH gave the best selectivity for this cleavage to the tertiary alcohol **383** (Scheme 144). With LiTSBBH, the

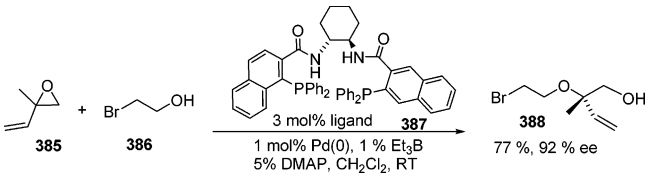
Scheme 144



desired isomer was produced, achieving a 99.7:0.3 ratio of diastereomers in 99% yield as a crystalline solid at a 20 kg scale. Oxidation of the trialkylborane with basic hydrogen peroxide after the epoxide cleavage was essential for production of crystalline product. Apparently, the trialkylborane disturbed the crystallization process.

In a route to Ruboxistaurin mesilate hydrate, condensation of 2-bromoethanol **386** with epoxide **385** in the presence of a chiral palladium catalyst and triethyl borane gave chiral allyl ether **388** with 92% ee (Scheme 145).[226] The tri-

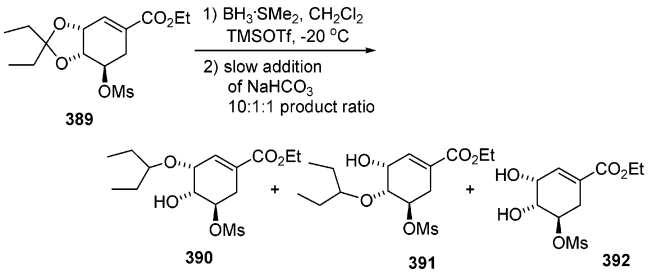
Scheme 145



alkylborane interacts with both the bromo alcohol and the epoxide, presumably forming an "ate" complex. The dialkyldialkoxyborate directs an intramolecular attack of the bromo alcohol on the π-allyl palladium complex giving the high selectivity.[227]

Borane reagents have also been used at kilogram scale for the cleavage of ketals. To make initial kilogram quantities of Oseltamivir for toxicological and clinical studies, Fischer and co-workers used DMSB and trimethylsilyl triflate (TMSOTf) in methylene chloride to carry out the reductive opening of pentylideneketal **389** (Scheme 146).[228] The

Scheme 146



selectivity of the reduction resulted in a 10:1:1 mixture of desired isomer **390** contaminated with the undesired isomer and diol. Interestingly, they found that reductive ketal opening did not take place until they slowly added $NaHCO_3$ to the reaction. Unfortunately, the regioselectivity was prone to deterioration with time. For larger scale production, other reductive conditions were used to cleave the ketal to the desired product.

Couturier and co-workers observed undesired acetonide cleavage (**395**) during the reduction of imide **393** (Scheme 147).[17] Several methods where borane was generated *in situ* gave significant amounts of the acetonide cleavage. Fortunately, use of commercial BTHF minimized this undesired byproduct formation (see Table 3). The hydroboration section also gives several examples of undesired ketal or acetonide cleavage due to borane.

Scheme 147

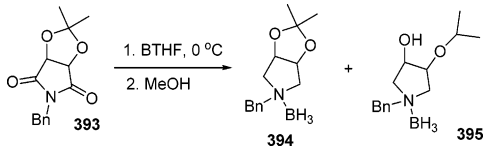


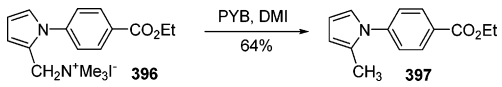
Table 3. Amide Reduction with BTHF

borane method	% isopropyl ether
commercial BTHF	3−5
BTHF generated *in situ*	∼15
in situ BTHF with excess BF_3	19
in situ BTHF with excess $NaBF_4$	∼80

Purification of the acetal amine borane **394** via crystallization effectively removed the isopropyl ether contaminant. The amine borane was then used as an internal hydrogen source for the cleavage of the *N*-benzyl group. In the presence of Pearlman's catalyst [$Pd(OH)_2$/C], the alcohol solvent also acts as the proton donor. Since only one of the three molecules of hydrogen is used for the reductive benzyl cleavage, allyl alcohol acted to scavenge the excess hydrogen and prevent excess pressure in or venting from the reactor. By this method, 194 kg of amine as the hydrotosylate salt was produced.

In the synthesis of a new anti-hypertension drug, FR-143187, Zanka and co-workers needed to cleave an alkyltrimethylammonium iodide.[229] Contrary to literature reports, sodium cyanoborohydride did not accomplish the reduction. Neither sodium triacetoxyborohydride nor dimethylamine borane were effective for the reductive cleavage. However, pyridine borane (PYB) successfully cleaved trimethylamine from the pyrrole adduct **396** to give the desired methyl pyrrole **397** (Scheme 148). The excess pyridine borane

Scheme 148



remaining was washed from the reaction mixture with water and treatment with diluted formalin removed the last traces of PYB. Pyridine borane generated *in situ* was compared to purchased PYB and gave nearly the same yield. The reductive cleavage was conducted on 130 kg of **396** with commercial PYB to obtain a 64% yield of **397**.

As can be seen from the examples, reductive cleavage of functional groups is a diverse topic. In some cases, reductive cleavage is an unproductive impurity generating side reaction. Boron reagents often display high regio- or stereoselectivity toward a desired reductive cleavage.

7. Conclusions

The importance of borane and borohydride reagents in the synthesis of critical drug intermediates has been demonstrated in a vast number of examples. The future of these reagents for use in large scale synthesis is promising due to their excellent selectivity, mild reaction conditions, high yields, and commercial availability.

The broad number of compounds, reactions, and applications using borane chemistry that have been developed at the academic and industrial level in recent years is only the beginning of the development of organoborane chemistry on an industrial scale. Many new and exciting uses of boranes are expected in years to come.

8. List of Abbreviations

Ac	acetyl
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
BOC, Boc	*tert*-butoxycarbonyl
BTHF	borane tetrahydrofuran complex
Bu	butyl
°C	degrees Celsius
CATB	catecholborane
CNS	central nervous system
COD	cyclooctadiene
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DEANB	*N*,*N*-diethylaniline borane
DMA	dimethylamine
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMI	dimethylimidizole
DMS	dimethyl sulfide
DMSB	borane dimethyl sulfide complex
DMSO	dimethyl sulfoxide
DPP	α,α-diphenylpyrrolidinemethanol
dppf	diphenylphosphinoferrocene
ee	enantiomeric excess
Et	ethyl
g	gram(s)
h	hour(s)
$(Ipc)_2BCl$	(+) or (−)-diisopinocampheylchloroborane
k	kilo
KTSBBH	potassium tri-*sec*-butylborohydride
L	liter(s)
LAH	lithium aluminum hydride
LiTEBH	lithium triethylborohydride
LiTSBBH	lithium tri-*sec*-butylborohydride
MBX	trimethylboroxin
Me	methyl
MDEB	methoxydiethylborane
MeCBS	Corey's oxazaborolidine catalyst, (*R*)- or (*S*)-3,3-diphenyl-1-methylpyrrolidine[1,2-*c*]-1,3,2-oxazoborole
MeOH	methanol
mol	mole(s)
MTBE	methyl *tert*-butyl ether
NaTSBBH	sodium tri-*sec*-butylborohydride
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Ph	phenyl
PMBO	*p*-methoxybenzyloxy
Pr	propyl
Py	pyridine
PYB	pyridine borane
RT, rt	room temperature
STAB	sodium triacetoxyborohydride
TBAB	*tert*-butylamine borane
TBDMS	*tert*-butyldimethylsilyl
TEAB	triethylamine borane
TEB	triethylborane
Tf	(trifluoromethyl)sulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMAB	trimethylamine borane
TMS	trimethylsilyl
TMSOTf	trimethylsilyl triflate
TNBB	tri-*n*-butylborane
TPAP	tetrapropylammonium perruthenate

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10. Note Added after ASAP Publication

This paper was published on the Web on March 15, 2006. Corrections were made to the text above Scheme 62 and to Schemes 130 and 136. The paper was reposted on May 23, 2006.

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