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Boronic Esters in Asymmetric Synthesis

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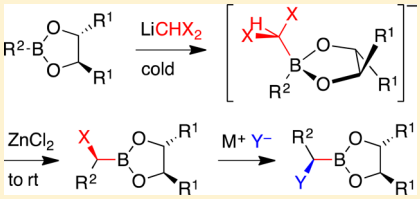
ABSTRACT: The author's work on (α-haloalkyl)boronic esters as reagents for asymmetric synthesis is reviewed. Diastereomeric ratios exceeding 1000 can be achieved with this chemistry, and ratios around 100 are commonplace. The method allows sequential installation of a series of stereocenters and tolerates a wide variety of suitably protected functional substituents. (α-Amidoalkyl)boronic acids include biochemically significant serine protease inhibitors, one of which is the clinically successful proteasome inhibitor bortezomib, used for treatment of multiple myeloma and mantle cell lymphoma.



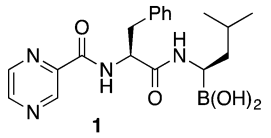
INTRODUCTION

Boronic esters are broadly useful reagents for accomplishing stereocontrolled carbon−carbon and carbon−heteroatom bond formations.[1−4] They are easily prepared and sufficiently resistant to air oxidation to permit convenient handling as ordinary organic reagents. Boric acid from oxidative degradation has only moderate toxicity.

The insertion of a CHCl group from $LiCHCl_2$ into the C−B bond of chiral C_2-symmetrical dioxaborolanes has provided the most stereoselective nonenzymatic route known to secondary alcohols and sequences of adjacent stereocenters.[5] Boronic ester intermediates have also been converted stereospecifically to primary and secondary amines, including pyrrolidines, via alkyltrifluoroborate salts.[6,7]

Compounds having two or more dialkoxyboryl groups on carbon can be deprotonated or deboronated to synthetically useful carbanions.[8,9] Carbanions from α-alkylthio or α-trialkylsilyl boronic esters also have synthetic potential.[10,11] Our research on these compounds was set aside when the asymmetric synthesis with α-halo boronic esters was discovered.[12,13]

Boronic acids are of interest in medicinal chemistry.[1] An α-amido boronic acid, bortezomib (Velcade) (**1**), has been approved by FDA for treatment of multiple myeloma and mantle cell lymphoma. The synthetic route to bortezomib and many other peptidyl boronic acids utilizes my discovery of silylated (α-aminoalkyl)boronic esters (**2**) as the key intermediates.[14] Arbitrarily chosen examples include the potent thrombin inhibitor DuP 714 (**3**),[15] which was unfortunately too toxic and excreted too rapidly to be clinically useful, and peptidyl boronic acid **4**, which we made at the request of virologist William Prusoff and was found to inhibit dimerization of HIV-1 protease, K_i 5 μM.[16] A comprehensive review of boronic acids as enzyme inhibitors has appeared recently,[17] and there are reviews covering peptidyl boronic acids and other proteasome inhibitors as anticancer agents that are under development.[18,19]



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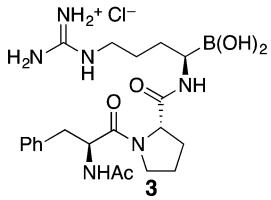

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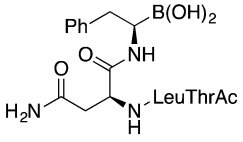

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BASIC PRINCIPLES OF (α-HALOALKYL)BORONIC ESTER HOMOLOGATION

The highly stereoselective (up to 1000:1 dr) homologation of boronic esters of C_2-symmetrical chiral diols to (α-chloroalkyl)-boronic esters and alkylation to *sec*-alkylboronic esters is outlined in Scheme 1. (Dichloromethyl)lithium is either preformed from butyllithium and dichloromethane at −100 °C or generated in situ by addition of LDA to a mixture of the boronic ester substrate **5** and dichloromethane below −30 °C. The adduct **6** rearranges with the aid of zinc chloride on warming toward room temperature. Transition state **7** is in accord with the calculated lowest energy pathway.[20] If the chiral directing group R^0 is secondary alkyl the resulting (α-chloroalkyl)boronic ester **8** is generally formed in ≥99% stereopurity.[5] Separation of **8** from zinc salts and solvent removal constitute the only purification needed before the next step.

Stereoselection does not end with the first step of the sequence. Reaction of **8** with a Grignard reagent leads to borate anion **9**, which has R^1 in the position previously occupied by the remaining Cl of **6** and has that Cl shifted to the vulnerable position for displacement. Transition state **10** has the same relative group sizes as **7** and leads to *sec*-alkylboronic ester **11**. The small amount of minor isomer **12** is alkylated to borate

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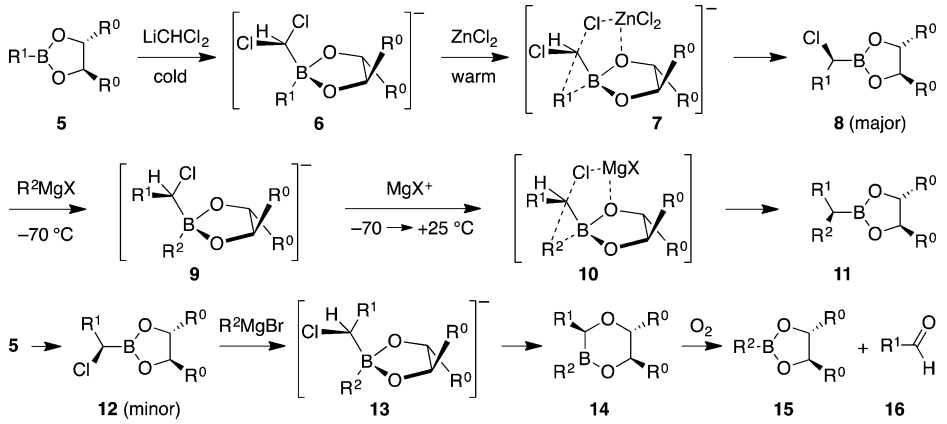
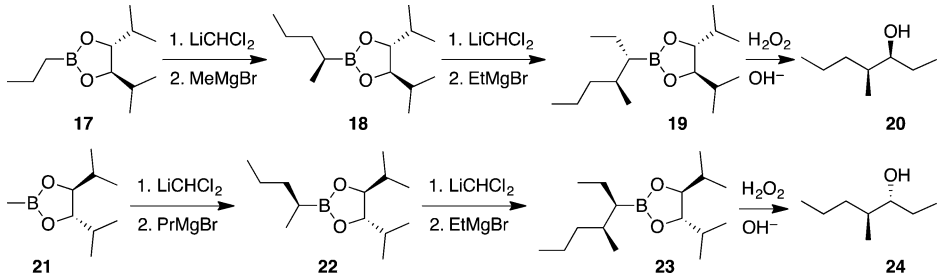
Scheme 1



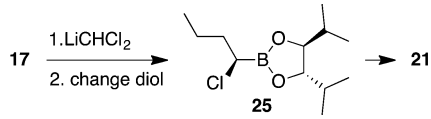
Scheme 2



complex **13**, which has the wrong configuration for migration of the R^2 group, and the dioxaborolane ring oxygen *anti* to the Cl migrates instead to yield ring expanded product **14**. Atmospheric oxygen rapidly oxidizes **14** to boronic ester **15** and aldehyde **16**. The net result is that the major isomer **11** is produced in very high stereopurity, shown experimentally to be ≥99.9% if sufficiently pure **5** having R^0 = *i*-Pr and R^1 = Pr is the starting material.[5]

Insect Pheromone Syntheses. These targets provide good examples of the utility of the fully developed synthetic method. The achievement of such high stereoselection was verified by the synthesis of a pair of diastereomeric insect pheromones. (4*R*,5*R*)-(4,5-Diisopropyl-2-propyl)-1,3,2-dioxaborolane (**17**) was homologated and methylated to **18**, which was homologated and ethylated to **19** (Scheme 2). Peroxidic oxidation yielded **20**, a component of the aggregation pheromone of the elm bark beetle *Scolytus multistriatus*. Homologation of (4*S*,5*S*)-(4,5-diisopropyl-2-methyl)-1,3,2-dioxaborolane (**21**) followed by reaction with propylmagnesium bromide yielded **22**, which has the same (*S*)-configuration in the 2-pentyl group as **18** but the opposite configuration of chiral director. Homologation and ethylation of **22** yielded diastereomer **23**, which was oxidized to (3*R*,4*S*)-4-methyl-3-heptanol (**24**), the trail pheromone of the Southeast Asian ponerine ant *Leptogenys diminuta*. Comparison of ^{13}C NMR spectra of **20** and **24** confirmed that the ratios of **20** to **24** were ~700:1 and 1:500, respectively, in the two samples. Sequential double diastereodifferentiation occurs in each homologation–substitution sequence, and each of these must result in ≥500:1 diastereoselection, with at least one sequence exceeding 1000:1 selection, the selection errors at each sequence being additive.[5]

Further evidence for the high diastereoselection in the pathways to **20** and **24** is provided by the failed experiment that led to its discovery.[5] Boronic ester **17** was homologated and the (*R*,*R*)-diisopropylethanediol was cleaved (by an obsolete method) and replaced with its (*S*,*S*)-enantiomer to form **25** (eq 1). Methylmagnesium bromide with **25** produced **21**



(1)

containing only ~6% of the expected **22**. Disappointment dissipated with the realization that oxygen migration had occurred, that high diastereoselection in the conversion of **17** to **18** would be a consequence, and that **24** could be easily synthesized by starting from **21**. The presence of the very air-sensitive oxygen migration product (**14**, R^0 = *i*-Pr, R^1 = Pr, R^2 = Me) was verified by NMR and mass spectral evidence. The product from oxygen migration is less stable than that from carbon migration by ~30–40 kcal-mol^{-1},[21] and analogous oxygen migration had not been encountered previously.

The high stereoselectivity of the foregoing homologation–alkylation sequence is useful in the preparing certain insect pheromones because separation of stereoisomers by chromatography is not always complete and small amounts of impurities can affect the response of the insects. All four stereoisomers of 4-methyl-3-heptanol were prepared and it was found that *L. diminuta* only responds to the (3*R*,4*S*)-isomer.[22] Later, we synthesized the 4-methyl-3-heptanols with (*R*,*R*)- and (*S*,*S*)-1,2-dicyclohexylethanediol as chiral director. Anderbrant and co-workers found that *Scolytus laevis* is strongly attracted to (3*R*,4*S*)-4-methyl-3-heptanol but that the (3*S*,4*S*)-isomer common to other *Scolytus* species that live in the same area interferes with attractant activity of the (3*R*,4*S*)-isomer.[23] Thus, *S. laevis* can avoid trees infested with species that may be too strong competitors.

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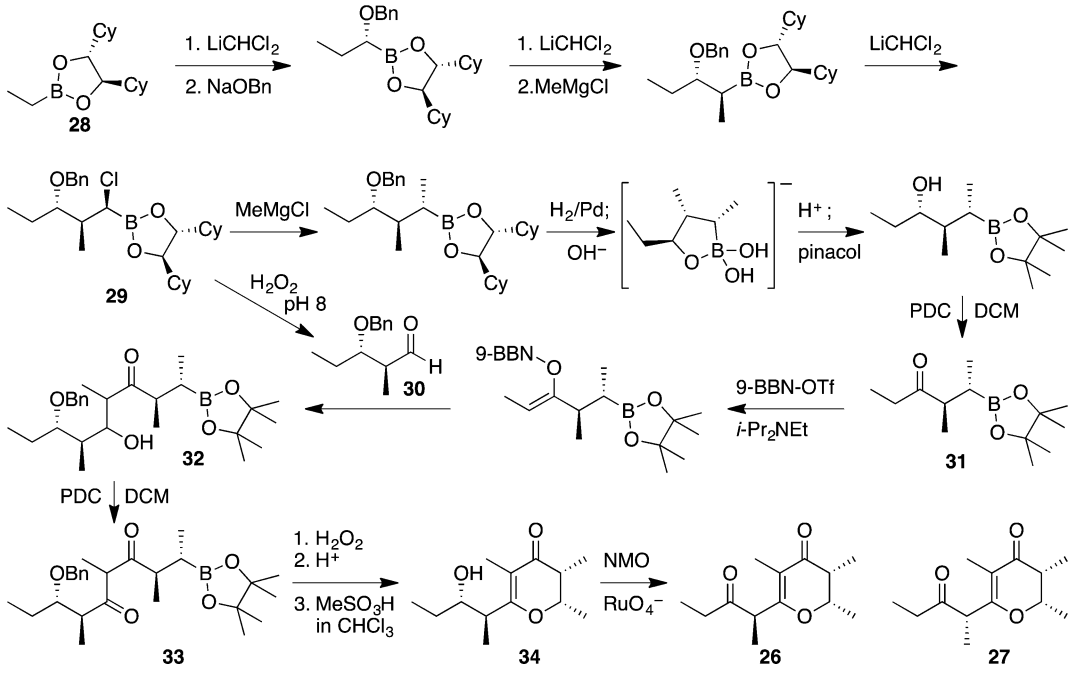
Scheme 3



A synthesis in which the achievement of high stereopurity proved critical is that of stegobinone (**26**) (Scheme 3), the sex pheromone of the drugstore beetle *Stegobium paniceum*[24] and the furniture beetle *Anobium punctatum*.[25] The stereochemistry had been established previously by Hoffmann and co-workers.[26] Their material had only a fraction of the activity of the natural pheromone because the epimer (**27**), which forms as the pheromone ages, is strongly repellent.[26,27] Synthesis via boronic ester homologation provided a stereopure crystalline sample of **26** that was strongly attractive and considerably more stable than the natural pheromone.[28,29]

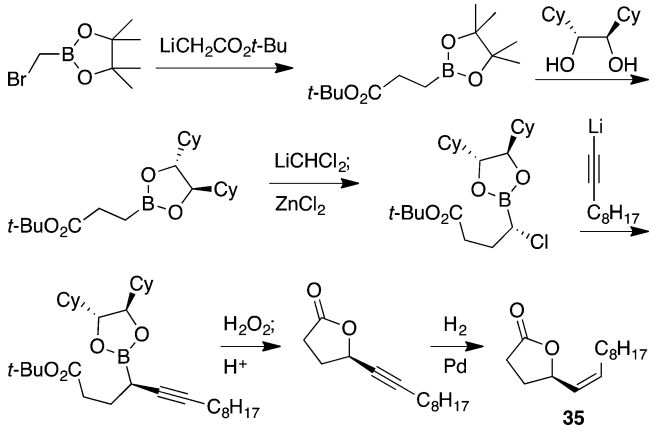
The synthesis began with (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol ethylboronate (**28**) (Scheme 3). A sequence of homologations and substitutions led to (α-chloroalkyl)boronic ester **29**, which was the precursor to both aldehyde **30** and ketone **31**, the two parts assembled in an aldol condensation to make intermediate **32**, which contains the total carbon skeleton of **26**. The replacement of the (*R*,*R*)-diol by pinacol in the route to **31** was done after it was found that the chiral diol was partially destroyed during pyridinium dichromate oxidation. The more recently developed conversion of chiral diol boronic esters to trifluoroborate salts might provide a more efficient way around that problem.[6,7,30] Dichromate oxidation of **32** produced diketone **33**, which was deboronated to the corresponding alcohol with alkaline hydrogen peroxide. The dihydropyranone ring was closed by dilute acid. Debenzylation to stegobiol (**34**) was unexpectedly best accomplished by treatment with ∼25% methanesulfonic acid in chloroform.

Stegobiol (**34**) is stable and easily purified before oxidation to stegobinone (**26**). The natural pheromone contains ∼5% **34**, which when isolated from the natural source was weakly attractive to the insects.[27] Our synthetic material had no attractant activity.[29] It seems probable that chromatographic separation from the natural source was incomplete. It is likely that **34** functions as the natural precursor to **26** and that residual **34** serves the additional function of catalyzing epimerization of **26** at an appropriate rate to make stale trails unattractive to the insects, which live in confined spaces.

The primary utility of the homologation reaction in synthesis is the ability to make pure compounds of predictable stereochemistry for research purposes. More economical syntheses can often be found for industrial production. A chemoenzymatic synthesis of pure **26** and **34**, perhaps useful toward that end, has been reported recently.[31]

Japonilure (**35**), the pheromone of the Japanese beetle *Popillia japonica*, is only attractive to the insects if its enantiopurity is very high. Attempts to homologate an alkynylboronic ester have not been successful, but the less demanding alkynylation of an (α-chloroalkyl)boronic ester provided the key step (Scheme 4). The previously known synthesis involved Midland's asymmetric borane reduction of an alkynyl ketone and required a recrystallization in order to achieve sufficient enantiomeric purity.[32] The boronic ester route is economically competitive with the Midland synthesis and was used for commercial production of **35** by William Hiscox for use in Japanese beetle traps.[33]

Scheme 4



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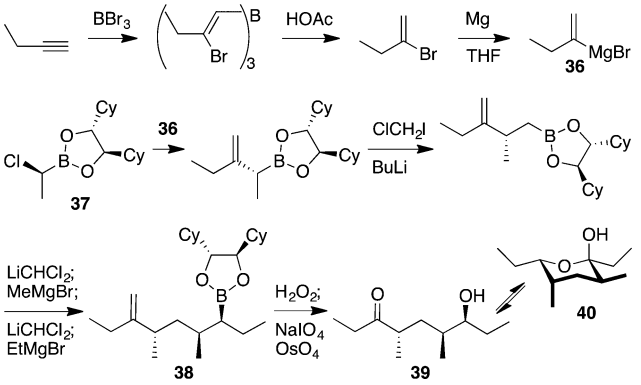
The cigarette beetle, *Lasioderma serricorne*, is a pest of dried foodstuffs and tobacco. The substitution pattern of its pheromone, serricornin (**39**) (Scheme 5), would require a

Scheme 5

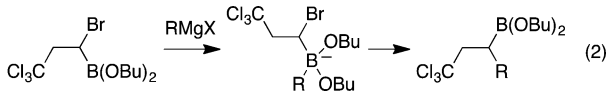


change of chiral directors if the synthesis were begun with the enantiomer of **28**, Scheme 3, and the subsequent two benzyloxy derivatives. Instead, the masked ketone function was provided by an alkene that was subsequently oxidized (Scheme 5).[34] Hydroboration of 3-hexyne with catecholborane yielded a boronic ester that was unexpectedly labile to free radical *Z*/*E* isomerization and thus could not lead to a useful bromoalkene intermediate.[35] Pure 2-bromo-1-butene was obtained via bromoboration of 1-butyne followed by protodeboronation, then converted to the Grignard reagent **36**.[34] Reaction with chloro boronic ester **37** set up the remainder of the synthesis with the correct chiral director. Methylene insertion with (chloromethyl)lithium[36] followed by two more homologation–substitutions led to boronic ester **38**. Deboronation and periodate–osmium tetroxide oxidation yielded serricornin (**39**), which is in equilibrium with its cyclic ketal form **40.** None of the intermediates prior to the deboronation step were purified by chromatography, and the overall yield of pure **39** from boronic ester **37** was 59%.[34] The very high stereoselectivity of the boronic ester homologation exceeds what is needed for production of active pheromone. Several other recent syntheses of **39** have been reported.[37]

■ ANTECEDENTS

The state of the art synthetic method described above was not created from borax in seven days, and without dwelling on obsolete chemistry, it seems appropriate to mention a few high points of its evolution before reviewing the wide variety of applications of (α-haloalkyl)boronic ester chemistry.

The conversion of alkylboronic esters, $RB(OR')_2$, to dialkylborinic esters, R_2BOR', via reaction with organometallic reagents has long been known.[38] After the first (α-haloalkyl)-boronic esters became available via free radical addition to a vinylboronic ester,[39] conversion of one of them to a borinic ester was attempted, but Ray Mah's repeated attempts to get a good analytical sample failed. Elemental analyses fifty years ago did not distinguish chlorine from bromine, lengthening the time it took to deduce, without NMR, what had really happened (eq 2).[21]



(2)

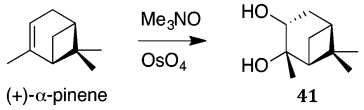
Further work left no doubt about the mechanism,[21] and it was immediately obvious that rearrangement of the intermediate borate had to be a stereospecific process, with inversion of the site of intramolecular nucleophilic displacement and retention of the configuration of the migrating group.

The next major advance came after the work of Köbrich on addition of $LiCHCl_2$ to triarylboranes and rearrangement of the intermediate borate complexes.[40] Rathke reported the alkylation–rearrangement of a (dichloromethyl)boronic ester.[41] Debesh Majumdar had achieved good results in the homologation of boronic esters with lithiated (chloromethyl)-trimethylsilane,[42] and he initiated the productive approach, addition of $LiCHCl_2$ to boronic esters, in spite of my shortsighted advice that −100 °C was not very practical and Rathke's work might have preempted the novelty.[12] Exploration of the scope quickly followed, including bulky group and functional substituent compatibility, known in situ capture of $LiCHCl_2$ by substrates at up to −20 °C,[43,44] and repeated sequential homologation–substitution, using boronic esters of several achiral diols as substrates.[12,45]

Homologation without stereocontrol has limited potential utility, and was used by Brown's group to replace boron by carbon in asymmetric boronic esters derived from hydroboration.[46,47] However, it was immediately apparent that the homologation reaction would be far more useful if its stereochemistry could be controlled. We were incredibly lucky to find that the second chiral director we tried gave very good stereocontrol.[13]

Chiral Directors. We have synthesized a number of other asymmetric targets. Before summarizing these, a consideration of the available choices of chiral directors and advantages of each is appropriate.

Our first successful chiral director was (+)-(1*S*,2*S*,3*R*,5*S*)-pinanediol (**41**) (sign of rotation solvent dependent).[13,48] Either **41** or its enantiomer can be made from α-pinene by osmium tetroxide catalyzed oxidation with trimethylamine *N*-oxide (eq 3).[49,50] The choice of **41** was suggested by the well-



(3)

known success of Brown and Zweifel with a pinene derivative in hydroboration.[51] Rahul Ray tried trimethylamine *N*-oxide in a modified Van Rheenen procedure[52] because it was immediately available in his lab and later found that the usual *N*-methylmorpholine *N*-oxide does not give as good yields. A kinetic study showed that the rate-determining step involves the amine oxide and diol–osmium(VI) complex.[53] Our originally specified solvent, *tert*-butyl alcohol, refluxes above the optimum temperature. The reaction is slower in acetone but yields are nearly quantitative.[54] Neither enantiomer of α-pinene is available in high purity from natural sources, but recrystallization from heptane (or methylcyclohexane) upgrades the enantiomeric purity of pinanediol to practically 100%.[15]

The structure **41** has been written to show its steric relationship to the C_2-symmetrical chiral directors, though pinanediol does not provide sequential double stereodifferentiation. Addition of (dichloromethyl)lithium to a pinanediol boronic ester (**42**) places the dichloromethyl group on the less

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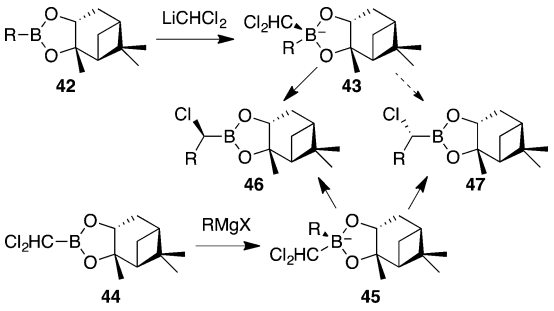
hindered face to produce borate anion **43**. A Grignard reagent similarly attacks the less hindered face of pinanediol (dichloromethyl)boronate (**44**) to form the diastereomeric borate **45** (Scheme 6).[55] Rearrangement of **43** produces (α-

Scheme 6



chloroalkyl)boronic ester **46** in ≥99% diastereomeric purity (except if R = CH_3, 95%) if zinc chloride is used,[56,57] ~90−95% if the only cation is lithium.[13,48] Rearrangement of **45** results in a gross mixture of **46** and its diastereomer **47**, either of which may predominate, and zinc chloride provides only marginal improvement toward **46**.[55]

The use of zinc chloride to catalyze the reaction and improve diastereoselection was discovered after a kinetic study of the conversion of pinanediol phenylboronate (**46**, R = Ph) to its epimer (**47**, R = Ph) in THF indicated that free chloride ion is the active reactant.[58] Epimerization is greatly accelerated by water or DMSO, inhibited by zinc chloride, and minimized at a 1:1 ratio of $LiZnCl_3$ and Li_2ZnCl_4. A rate-law term first-order each in $LiZnCl_3$ and $ZnCl_2$ is small for dilute solutions but extrapolates to large at high concentrations. In practice, high ratios of zinc chloride generally improve yields and stereoselections of sluggish reactions.[59] The possible beneficial effect of zinc chloride was suggested in an NSF renewal proposal, and by the time skeptical referees' faint praise had resulted in denial of funding, Mathew Sadhu had proved that zinc chloride worked even better than hoped for.[56]

The rigid pinanediol structure binds boron without ring strain or loss of rotational freedom and maximizes entropy increase in the ring closure. Consequently, pinanediol esters cannot be hydrolyzed under any practical conditions. This high stability is helpful for purifying and handling the pinanediol esters. Hydrogen peroxide oxidizes pinanediol esters directly to alcohols. However, if isolation of a boronic acid or other derivative is needed, pinanediol esters require special conditions for cleavage. If the boronic acid is water-soluble, it can be separated into the aqueous phase while pinanediol is transferred to phenylboronic acid in an ether phase.[15] Conversion of pinanediol esters to trifluoroborate salts by potassium bifluoride is favorable but incomplete at equilibrium.[6] The cesium salts often precipitate from a two-phase system of cesium fluoride in concentrated hydrofluoric acid and boronic ester in ether, thus considerably improving the conversion.[30] Trifluoroborate salts can be converted to boronic acids or esters via alkylboron difluorides or chlorides.[6,7] Our first method of cleavage, destruction of the pinanediol with boron trichloride,[14,48] is obsolete.

The stereoselection provided by pinanediol boronic esters is sufficient for most practical purposes. If nearly perfect stereocontrol is needed, the sequential double diastereodifferention provided by C_2-symmetrical diols is significant. These diol boronic esters also allow the flexibility of starting a synthesis from a (dichloromethyl)boronic ester. 1,2-Diisopropyl-1,2-ethanediol can be made in 100% diastereomeric purity from either enantiomer of tartaric acid, but the synthesis is laborious.[60] It has excellent properties as a chiral director, including its relatively low molecular weight. 1,2-Dicyclohexyl-1,2-ethanediol was introduced by Hoffmann and co-workers[26] and is considerably easier to prepare.[61] Its greater molecular weight tends to require more dilute solutions for homologations, but its chiral directing properties are equivalent to the diisopropyl analogue. Unfortunately, its easily prepared precursor, 1,2-diphenyl-1,2-ethanediol, is a poor chiral director for homologations.[61,62]

(*R*,*R*)-2,3-Butanediol can be made by fermentation. Observed dr values with its boronic esters were mostly ~20:1.[63] Hydrolysis of the (α-chlorobenzyl)boronic ester to the crystalline boronic acid occurred easily,[63] but a *sec*-alkylboronic ester resisted hydrolysis.[64]

Chiral directors that contain oxygen functionality do not work well. Diacetone mannitol gives slight stereoselection without zinc chloride,[48] ~10:1 dr and destruction of the diacetone mannitol with ~2.7 equiv[65] Dicyclohexanone mannitol works better, dr values mostly ~20 with ~0.7 equiv of zinc chloride, not improved by higher amounts.[66] Attempted homologation of a tartrate ester failed.[48]

Catalytic homologation of pinacol boronic esters with a chiral ligand and ytterbium ion has given an er as high as 15, but a large excess of ligand and 0.3 equiv of ytterbium salt were required.[67] If a good way to remove the chloride ion produced in the reaction could be found, this might become a useful method.

SYNTHETIC APPLICATIONS OF PINANEDIOL BORONIC ESTERS

The preceding section has described how asymmetric synthesis via boronic ester homologation works, high stereocontrol with C_2-symmetrical chiral directors and its utility in certain syntheses, and useful chiral directors. Pinanediol boronic esters were discovered first and used to develop many of the possibilities of this chemistry, which range far beyond what has been described above. The easy accessibility of pinanediol still makes it the lowest cost and most practical chiral director for many applications, and the great stability of pinanediol boronic esters is advantageous for some purposes.

Before the discovery of zinc chloride promotion, (+)-pinanediol phenylboronate (**42**, R = Ph) was used as starting material for both diastereomers of 3-phenyl-2-butanol.[13] These simple targets were chosen because they had already been fully characterized by Cram.[68] The rotations of the products confirmed the direction and degree of stereocontrol and its dependence on the chiral director without significant influence by the B-alkyl group. The possibility of matched/mismatched pairs with more polar B-alkyl substituents such as benzyloxy has not been investigated.

After the beneficial effect of zinc chloride was discovered, several demonstration syntheses were undertaken.[57] The first synthesis of the *S. multistriatus* pheromone **20** was carried out with (+)-pinanediol as chiral director instead of the subsequently discovered 1,2-diisopropyl-1,2-ethanediol shown in Scheme 2. The dioxolane substituted boronic ester of (−)-pinanediol **48** was converted to *exo*-brevicomin (**49**), a component of the pheromone of the pine beetle *Dendroctonus brevicomis*, via two homologations and substitutions followed by

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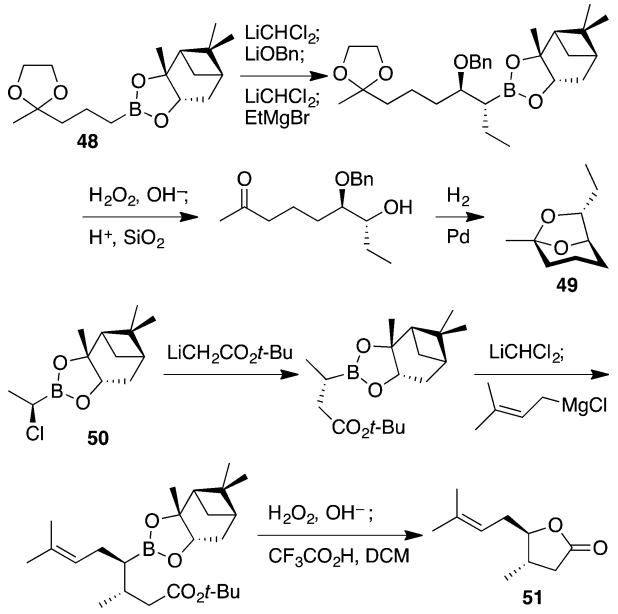
simple conventional transformations (Scheme 7). (−)-Pinanediol methylboronate was homologated to chloro boronic ester

Scheme 7



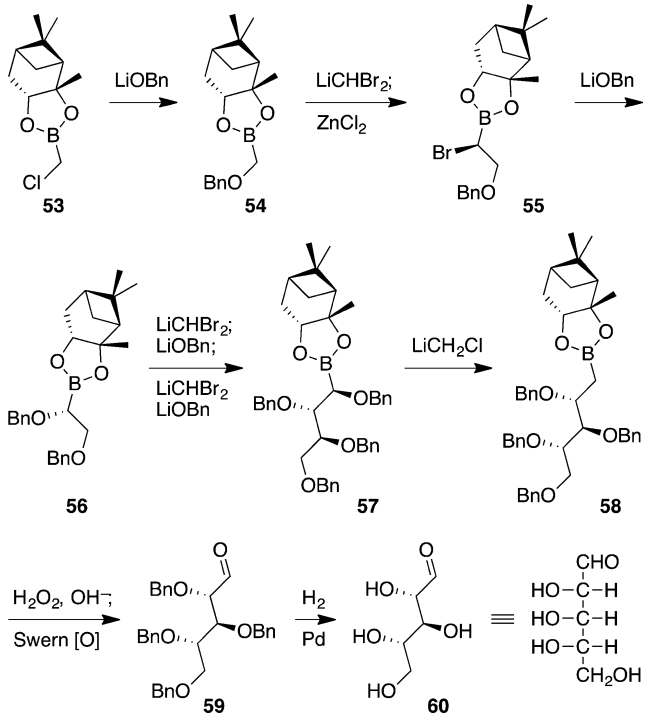
50, dr ∼20:1, then substituted with *t*-butyl lithioacetate and converted via another homologation−substitution to **51**, the wing gland pheromone of the African sugar cane borer *Eldana saccharina* (Scheme 7).

Carbohydrate synthesis presented a more challenging problem. The first step required a source of (halomethyl)-boronic esters. (Chloromethyl)lithium can be preformed at −115 °C,[69,70] but its instability makes it difficult to work with. Mathew Sadhu added butyllithium to a mixture of chloroiodomethane and triisopropyl borate at −78 °C and captured (chloromethyl)lithium in situ with triisopropyl borate. Subsequent acidification produced (chloromethyl)boronic ester **52a** in high yield (eq 4).[36] We had not tried dibromomethane in place of chloroiodomethane because of a previous report of a poor yield in capture by a ketone,[71] but after that report had been forgotten, John Michnick asked why not try it, and the more economical preparation of the (bromomethyl)boronic ester **52b** is now preferred (eq 4).[72]

$$\underset{\text{or } CH_2Br_2}{ClCH_2I} \xrightarrow[-78\ ^\circ C]{BuLi} [XCH_2Li] \xrightarrow[2.\ H^+]{1.\ B(O\text{-}i\text{-}Pr)_3} \underset{\mathbf{52a}\ X = Cl;\ \mathbf{b}\ X = Br}{XCH_2B(O\text{-}i\text{-}Pr)_2} \quad (4)$$

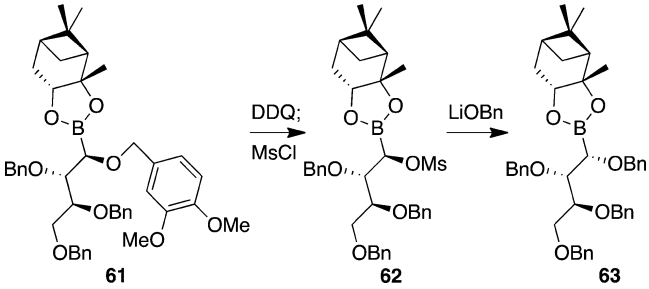
With (chloromethyl)boronic ester **52a** available, the synthesis of L-(+)-ribose (**60**), the enantiomer of natural ribose, was undertaken.[59] Transesterification of **52a** with (+)-pinanediol yielded the (chloromethyl)boronate **53**, which was converted to the benzyloxy derivative **54** by lithium benzyl oxide. Homologation of **54** with (dichloromethyl)lithium and benzyl oxide substitution became progressively less efficient as more carbons were introduced. (Dibromomethyl)lithium generated in situ from dibromomethane and LDA led to intermediates **55** and **56** in good yields. Yields in the pairs of homologation and substitution steps fell to ∼65% by the time intermediate **57** was reached. However, homologation of **57** failed entirely with (dibromomethyl)lithium and was very low with (dichloromethyl)lithium. (Chloromethyl)lithium yielded 36% of homologated product **58**, which was deboronated with hydrogen peroxide. Swern oxidation produced tetrabenzylribose **59**, which was debenzylated to L-(+)-ribose (**60**) (Scheme 8).

Scheme 8



A contemplated though ultimately impractical synthesis of glucose would have required the inversion of the stereocenter at the fourth carbon introduced into **57**. Intermediate **61** was prepared in the same manner as **57** but with lithium 3,4-dimethoxybenzyl oxide used in the last step. Selective deprotection to the hydroxy derivative with DDQ followed by mesylation led to **62**, which with lithium benzyl oxide yielded **63**, a diastereomer of **57** (Scheme 9).[73] As noted in the

Scheme 9



discussion of Schemes 1 and 2, a C_2-symmetrical chiral director would not allow the second inversion,[5] but pinanediol has little steric influence on substitution of an established stereocenter.[55]

A major potential use for a carbohydrate synthesis might be the introduction of stereospecific isotopic labels. This possibility was demonstrated with a synthesis of asymmetrically deuterated glycerol (Scheme 10).[74] Intermediate **55** (from Scheme 8, redrawn inverted) was converted to bromo boronic ester **64a** or its deuterated form **64b**, then reduced with

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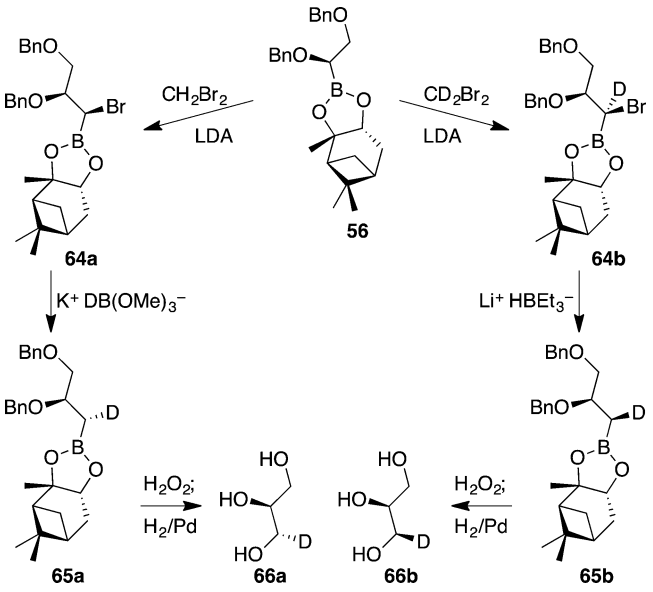
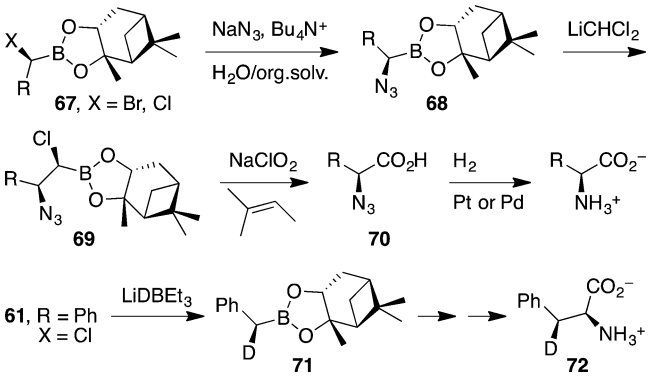
Scheme 10



trialkoxyborodeuteride or triethylborohydride, respectively, to the deuterated diastereomers **65a** and **65b** and finally the deuteroglycerol diastereomers **66a** and **66b**. The CH_2OH groups of glycerol are diastereotopic, and the unlabeled CH_2OH of **66a**/**b** corresponds to the aldehyde carbon of D-glyceraldehyde. A somewhat more elaborate route than that outlined in Scheme 10, beginning with a terminal CH_2OPMB group in place of CH_2OBn, led to asymmetrically deuterated di-O-benzylglyceraldehyde.[74] Debenzylation apparently produced a mixture of oligomeric acetals of glyceraldehyde with itself and some byproduct glycerol, and the NMR spectrum was too complex to interpret.

Amino acid synthesis is another application useful for making labeled compounds (Scheme 11). Displacement of halide from

Scheme 11



67 to form an (α-azidoalkyl)boronic ester (**68**) requires an organic solvent sufficiently polar to extract some azide from water with a phase transfer catalyst and a large excess of sodium azide to minimize epimerization by liberated halide.[57,75] Dichloromethane, the first solvent used, is slowly converted to dangerously explosive diazidomethane, CH_2N_6.[76,77] The recommended alternative is ethyl acetate.[78] The (α-chloroalkyl)boronic esters **69** can be oxidized directly with sodium chlorite to azido carboxylic acids (**70**), then hydrogenated to amino acids.[75] Asymmetrically deuterated benzyl boronic ester **71** has been converted to (2*S*,3*S*)-3-deuterophenylalanine (**72**) (Scheme 11).[79]

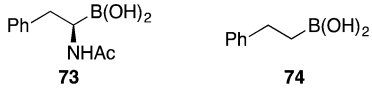
■ (α-AMIDOALKYL)BORONIC ACIDS

The most significant application of (α-haloalkyl)boronic ester chemistry has been the route to (α-amidoalkyl)boronic acids. The successful anticancer drug bortezomib (**1**), mentioned in the Introduction, was found by Julian Adams and associates in a search for effective proteasome inhibitors,[80,81] which required that amido boronic acids be easily synthesized for testing and for industrial production.

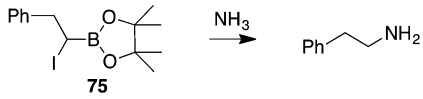
Finding a synthesis was unexpectedly difficult. Dibutyl (iodomethyl)boronate with secondary amines easily yielded (dialkylaminomethyl)boronic acids (eq 5), but attempts to make (aminomethyl)boronic acid inexplicably failed.[82]

$$ICH_2B(OBu)_2 \xrightarrow[H_2O]{R_2NH,\ R \neq H;} R_2NCH_2B(OH)_2 \qquad (5)$$

In 1971, Gustav Lienhard suggested that (1-acetamido-2-phenylethyl)boronic acid (**73**), the boronic acid analogue of *N*-acetylphenylalanine, might be a good chymotrypsin inhibitor,[83] based on the observed activity of (2-phenylethyl)boronic acid (**74**).[84]

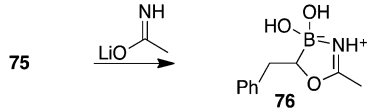


Attempted synthesis of **73** encountered baffling obstacles for several years. After we found a viable general route to (α-iodoalkyl)boronic esters via phenylthio group replacement,[85] rechecking the first attempt confirmed that if any R = H (eq 5) the initial boronic ester product decomposed to amine and trialkoxyborane on distillation.[86] Liquid ammonia at 25 °C converts **75** to 2-phenylethylamine (eq 6).[86]



(6)

Lindquist's report of the synthesis of (benzamidomethyl)-boronic acid from potassiobenzamide and its inhibition of chymotrypsin[87] led us to try lithioacetamide with **75**, but ^{1}H NMR indicated that the slightly soluble product isolated was the O-bonded isomer **76** (eq 7).[88] Later it was found that



(7)

Lindquist's compound was also the O-bonded isomer.[89] It binds to chymotrypsin slightly more strongly than the N-bonded isomer does, but no further report of O-bonded isomers has been found in a literature search. In DMSO N-bonded isomers are produced but side reactions and epimerization occur.[67]

The key insight followed Debesh Majumdar's remark (after his thesis was finished) that he had tried to deprotonate pinacol (α-chlorocyclohexylmethyl)boronate with lithium 2,2,6,6-tetramethylpiperidide, "...but it just gave S_N2 substitution, so I threw it out." What? Would lithiohexamethyldisilazane substitute and form a silylated intermediate that could be acylated in situ to the desired amide? Successful synthesis of **73** followed quickly.

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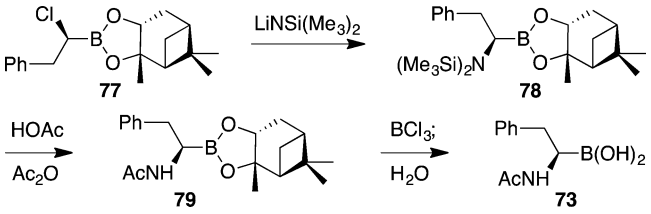
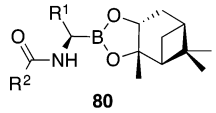
After the stability of the silylated intermediate and its conversion to the acetamido derivative had been confirmed with the ethylene glycol ester, the pinanediol ester **77** was converted to the silylated amino compound **78**, desilylated and acetylated in situ to **79**, and cleaved to **73** by a method that is now obsolete (Scheme 12).[14,88] As expected, amido boronic acid **73** binds chymotrypsin, dissociation constant 2.1×10^{-6} M at pH 7.5, 25 °C.[14]

Scheme 12



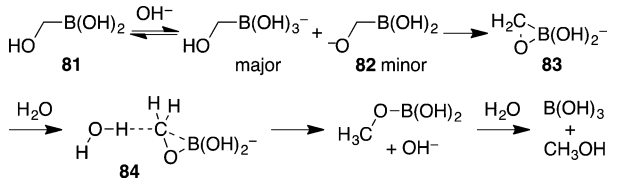
Several other pinanediol (α-acylamidoalkyl)boronic esters (**80**) were made by a similar route.[90,91] With R^1 = $MeSCH_2CH_2$, the homologation was inefficient and instead the vinylboronic ester was homologated and the methylthio group was introduced afterward by radical catalyzed addition. An X-ray structure of the derived ethylene glycol ester indicated coordination of the N-acetyl oxygen to the boron atom.[91] By using dichloromethane-^{13}C, **73** has been made with an α-^{13}C label.[92]



R^1 = Me, Me_2CH, Me_2CHCH_2, $BnOCH_2$, $Br(CH_2)_3$, $BnO(CH_2)_3$, $H_2C{=}CH$, $MeSCH_2CH_2$; R^2 = Me, BnO

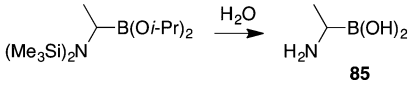
Why are (α-aminoalkyl)boronic acids and esters that contain an NH group unstable, but not their dialkylamino, trialkylammonium, ammonium, or acylated analogues? The behavior of (hydroxymethyl)boronic acid (**81**) provides some clues.[93] In acidic solutions, **81** is stable indefinitely, but at pH ~8 in D_2O, it decomposes to methanol and boric acid on heating a few hours, and the rate is not grossly different in strong base. There is a very strong deuterium isotope effect, H/D rates ~10. These results suggest that the small equilibrium concentration of **82** closes rapidly to 3-membered ring **83**, which is protonated at carbon with carbon−boron bond cleavage in the transition state (**84**) (Scheme 13).

Scheme 13



The deboronation of (α-aminoalkyl)boronic esters and acids presumably follows an analogous pathway, with $C{-}NH_2$ in place of the C−OH of **81**. The reaction would not be as exothermic as the ~40 kcal/mol estimated for (B−C + C−O) to (B−O + C−C) conversion,[21] but would be a considerable fraction of it.

Although the difficulty of isolating amino boronic acids might suggest otherwise, they have lifetimes of a number of hours in water at 37 °C.[94] The alanine analogue **85** was generated in situ from the silylated diisopropyl ester (eq 8) and found to inhibit



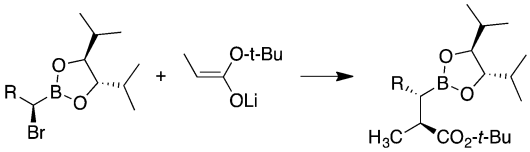
(8)

Salmonella typhimurium D-alanine:D-alanine ligase and *Bacillus stearothermophilus* alanine racemase. The precursor to **85** contained a considerable amount of (α-isopropoxyethyl)-boronic ester impurity as a result of O/N competition in the borate rearrangement, which is not seen with cyclic boronic esters.

We would have made peptidyl boronic acids, but Kettner and Shenvi at du Pont began investigating these with much greater resources immediately after our initial report.[95] The interesting basic synthetic chemistry problem having been solved, NIH was unwilling to support routine extensions of it, even in collaboration with a biochemist who suggested an elastase inhibitor before the du Pont group reported the synthesis of the same class of peptidyl boronic acids and their strong inhibition of elastase.[95,96] Kettner and associates also discovered strong inhibitors of thrombin,[15,97] and their detailed studies of the binding of peptidyl boronic acids to enzymes confirmed the expected binding of boron in place of the natural substrate amide carbonyl group. However, clinically useful activity and specificity have not been achieved.[17] The du Pont group found a good way to transesterify pinanediol esters to water-soluble peptidyl boronic acids, and there are (α-aminoalkyl)boronic acid salts that can be purified as intermediates prior to peptide coupling.[15] In the three decades since our first enabling publication,[14] biochemists have made and tested a wide variety of peptidyl boronic acids and serine proteases. In view of the recent comprehensive review,[17] further discussion of biochemical or medicinal applications in this review of synthetic organoboron chemistry would be superfluous.

SUBSTITUTIONS AND CYCLIZATIONS WITH ESTER ENOLATES AND LITHIONITRILES

tert-Butyl lithioacetate was used in syntheses of **35** (Scheme 4) and **51** (Scheme 7) already described. The reaction of the enolate from *tert*-butyl propionate with (α-bromoalkyl)boronic esters has unexpectedly been found to be highly stereoselective. Pinacol (1-bromopentyl)boronate yielded the racemic *threo* product, and (3*S*,4*S*)-2,5-dimethyl-3,4-hexanediol boronic esters produced *threo*/*erythro* ratios ≥15:1 for R = Bu or *i*-Pr, 10:1 for R = Ph (eq 9).[98]



(9)

Similar *threo* selectivity has been observed in cyclization of (1-chloro-4-cyanobutyl)boronic esters to cyclobutane derivatives.[99] The facile hydroboration of allyl bromide with dichloroborane, generated in situ from boron trichloride and triethylsilane in a noncoordinating solvent,[100] provided precursor **86** (Scheme 14). A series of conventional transformations led to asymmetric intermediate **87**, which is a pair of diastereomers if R ≠ H. Homologation to **88** and deprotonation with LDA presumably resulted in immediate

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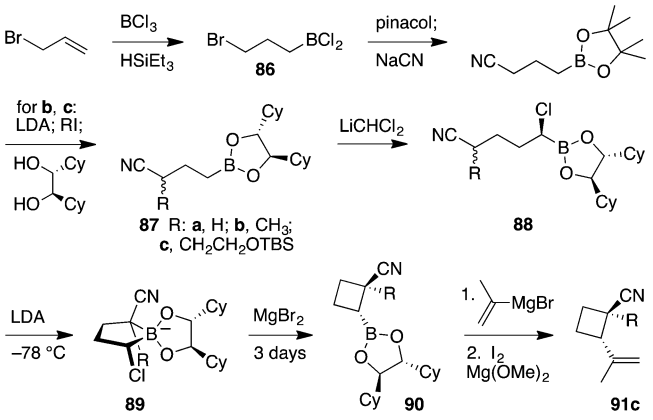
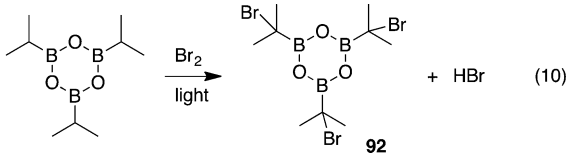
Scheme 14



ring closure to borate anion **89**, but at first yields of rearrangement product **90** varied unpredictably between 60% and zero, and freshly prepared LDA yielded zero, The commercial LDA samples used contained a small amount of magnesium diisopropylamide, which diminished by precipitation as the sample aged. Addition of magnesium bromide to the lithium borate **89** yielded **90** efficiently in high diastereomeric purity. A modified Zweifel alkene synthesis[101] with **90c**, R = CH_2CH_2OTBS, and isopropenylmagnesium bromide yielded **91c**, which has a monoterpenoid carbon skeleton.

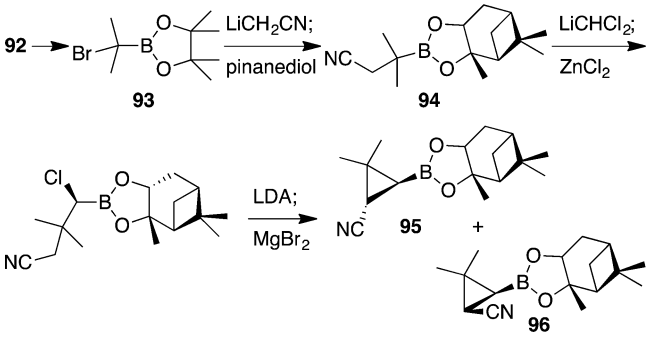
The possibility of stereocontrolled cyclopropane synthesis was investigated briefly with a highly hindered substrate. First, the extremely air sensitive triisopropylboroxine was brominated to **92** under ordinary fluorescent room lighting, a free-radical reaction as fast as a titration (eq 10),[102] much faster than the previously known bromination of *sec*-alkylboronic esters.[103,104]



(10)

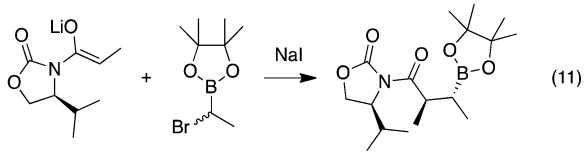
Esterification of **92** with pinacol to **93** followed by substitution with lithioacetonitrile and esterification with pinanediol yielded *tert*-alkylboronic ester **94**, which was homologated with (dichloromethyl)lithium. Cyclization by treatment with LDA followed by magnesium bromide led to a mixture of diastereomeric cyclopropylboronic esters **95** and **96** (Scheme 15). The 1,2-dicyclohexyl-1,2-ethanediol boronic ester analogue of **94** gave a poor yield on homologation.

Scheme 15



Alternatives to **93** gave poor yields of **94** or its analogues with lithioacetonitrile, including the pinanediol, ethylene glycol, and 1,2-dicyclohexyl-1,2-ethanediol esters.[102] The ~2:1 mixture of diastereomers **95** and **96** contrasts with the previous diastereoselection in related reactions.[98,99] The isomer ratios of two batches differed, and epimerization of **95** in the reaction mixture is a possible cause.

The high *threo*-selectivity of the reaction of ester enolates with (α-haloalkyl)boronic esters also prevails with chiral enolates. Reaction of the Evans chiral lithium enolate[105] with racemic pinacol (1-bromoethyl)boronate resulted in dynamic resolution ("retroracemization") of the boronic ester to produce a single substitution product, dr ~55 (eq 11).[106]

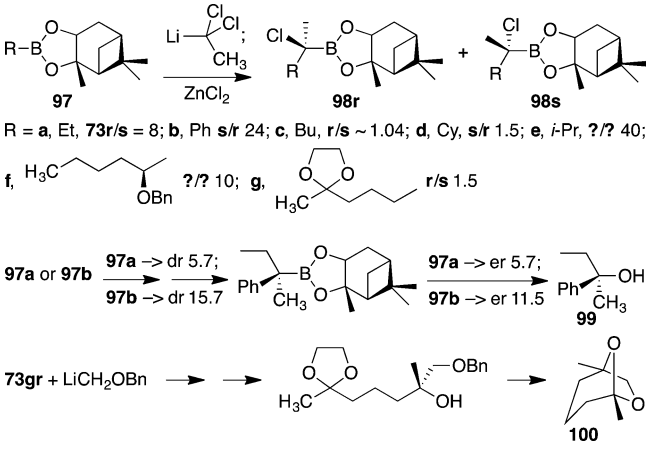


(11)

EXPLORATION OF LIMITS OF BORONIC ESTER SYNTHESIS

Quaternary Stereocenters. The cyclobutane **91c**, Scheme 14, contains a quaternary stereocenter that was generated in high stereopurity. An earlier exploratory investigation of stereocontrolled assembly of pinanediol (α-chloro-*sec*-alkyl)-boronic esters produced unexpected results.[107] Homologation of pinanediol ethylboronate (**97a**) with (1,1-dichloroethyl) lithium followed by substitution with phenylmagnesium bromide produced mainly **98r** but the phenylboronate **97b** produced diastereomer **98s**, resulting in the same major enantiomer of 2-phenyl-2-butanol after introduction of the complementary ethyl or phenyl group and peroxidic oxidation (Scheme 16). There appeared to be some degradation in

Scheme 16



stereopurity as **98s** was converted to **99**. A series of other substituents in **97** produced variable results, a few of them usefully stereoselective. Identification of the predominant isomer was not always achieved. A synthesis of frontalin, a component of a pine beetle pheromone, resulted in a small bias toward its enantiomer (**100**) (Scheme 16).

Alternative Route. For aryl substituted quaternary stereocenters, Aggarwal's α-carbamoyl borate chemistry provides an excellent route.[108−110] Aggarwal's method utilizes the carba-

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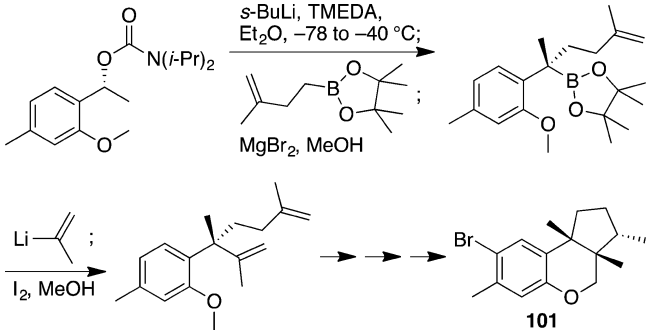
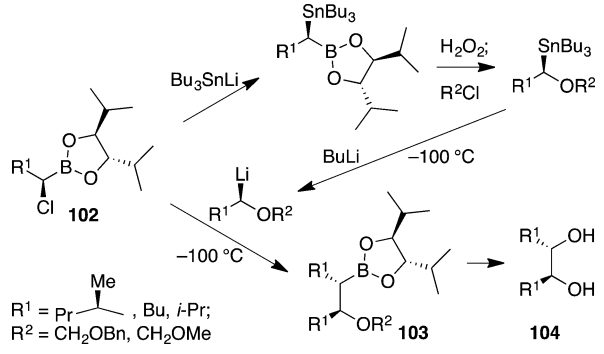
mate ester group, which stabilizes asymmetric organolithium intermediates, in place of halide as the leaving group. Scheme 17 illustrates the boron chemistry that provided the basis for an efficient asymmetric synthesis of aplysin (**101**),[108] a protective antifeedant isolated from sea hares.

Scheme 17



Convergent Coupling of Two Stereocenters. The excellent stereocontrol observed in reactions of (α-haloalkyl)-boronic esters with lithiated esters or nitriles, eqs 9 and 11 and Scheme 14, does not allow choice of diastereomers. (α-Haloalkyl)borate rearrangement retains the configuration of the migrating nucleophilic ligand, so that capture of a stereopure organometallic couples two stereocenters. Enantiomerically pure α-lithio ethers have been coupled with (α-chloroalkyl)-boronic esters.[111] Boronic esters **102** were converted via organotin intermediates to enantiopure (α-alkoxyalkyl)lithiums and coupled to form β-alkoxy boronic esters **103**, which were converted by conventional means to C_2-symmetrical diols **104** (Scheme 18). The *meso* isomer of **104**, R^1 = *i*-Pr, was made by

Scheme 18



coupling two parts of opposite chirality. When R^1 = 2-pentyl, **103** contains four adjacent stereocenters. We used two identical R^1 groups only for convenience in characterization.

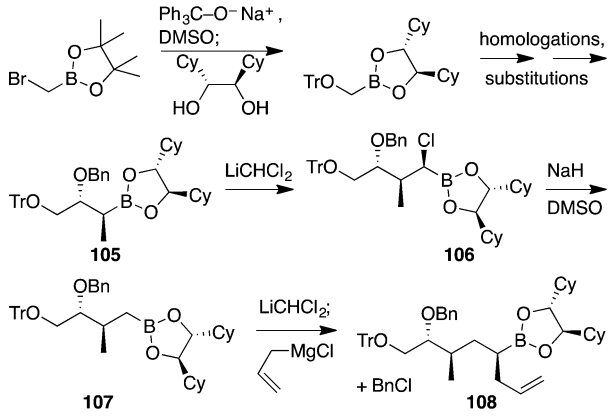
Lithiation of the tin intermediate in Scheme 18 is reversible when R^1 = *sec*-alkyl, and the butyllithium instead of the chiral lithioether reacts with **102** at −78 °C. At −100 °C the lithioether reacts faster with **102** than with tetrabutyltin.

Recent literature suggests possible alternative routes to stereopure organometallic coupling partners. One example is sparteine directed lithiation,[112,113] which provides asymmetric lithium reagents used by Aggarwal in his asymmetric boronic ester synthesis.[114,115] Asymmetric Grignard reagents derived from cleavage of asymmetric sulfoxides provide another possibility.[116] Blakemore's group has made asymmetric (α-chloroalkyl)lithium reagents from stereopure α-chloroalkyl sulfoxides and inserted them into pinacol boronic esters,[117] and insertion into boronic esters of chiral diols would be a small extension. Could chloroalkyl sulfoxides be made from (α-haloalkyl)boronic esters? Thiolate substitution is facile, and chlorination of (α-phenylthio)boronic esters replaces boron with chlorine or alkoxy but a stereospecific mechanism is not likely.[118]

Effects of Alkoxy Groups. Multiple adjacent alkoxy substituents on pinanediol esters directed toward carbohydrate synthesis have been described above, Schemes 8−10. The failure of the sugar synthesis to proceed beyond ribose implies that too many alkoxy groups inhibit homologation. Another possibility is that a chain of four carbons between the boron atom and an alkoxy substituent maximizes B−O interaction and inhibits homologation in an unknown way. Results with some compounds designed as possible intermediates for macrolide synthesis have suggested such interference.

As starting material for these syntheses, (trityloxymethyl)-boronic esters have been found surprisingly easy to make via direct displacement of bromide ion from pinacol (bromomethyl)boronate (Scheme 19).[119] A dipolar aprotic

Scheme 19



solvent, dimethyl sulfoxide, is required. The first two homologation−substitutions then proceeded routinely to **105**.[120] Yields were poor in direct conversion of **105** to **107** with (chloromethyl)lithium,[36] but homologation of **106** and reduction with sodium hydride suspended in DMSO, a reaction discovered by chance in a different context, proved efficient. Homologation−substitution of **107** yielded only 60% of **108**, with benzyl chloride a major side product. (Scheme 19).[120] Two attempts to homologate **108** failed.

The unexpected discovery of benzyl chloride as a major side product in the conversion of **107** to **108** suggests that a 6-membered ring linkage between boron and oxygen may be involved together with zinc chloride in the debenzylation. Steric bulk would prevent such interaction with the trityloxy group in the homologation of **105** to **106**. In support of this hypothesis, in another aspect of this investigation detritylation of **109** with formic acid produced 1,2-oxaborinane **110** (eq 12), which was so stable it was not opened to a 4-(hydroxybutyl)boronic ester by pinanediol.[120]

Other Polar Substituents. Intermediates directed toward a possible synthesis of kainic acid and related compounds became another test of the possibilities and limitations of boronic ester homologation. The route that came the closest began with the

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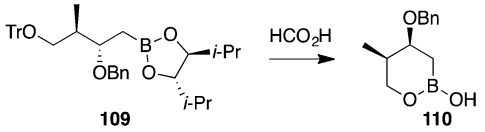
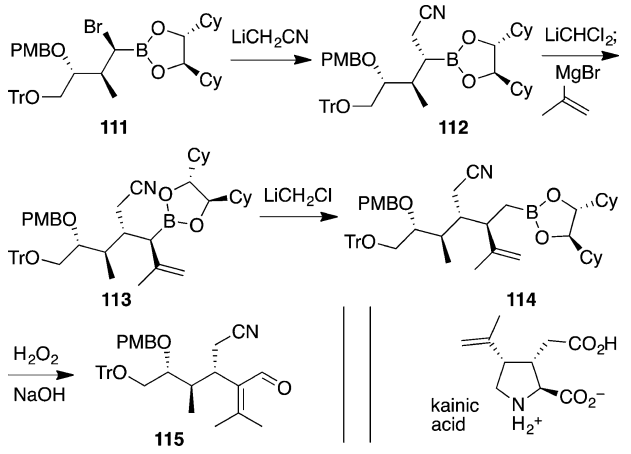


(12)

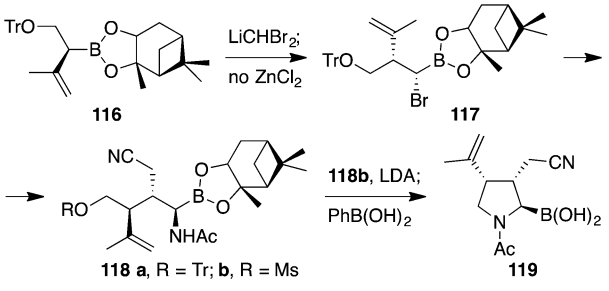
synthesis of (α-bromoalkyl)boronic acid **111**. The bromo intermediate **111** was chosen after the chloro analogue yielded **112** poorly. Conversion of **112** to **113** proceeded without difficulty, as did methylene insertion to **114**. All of the stereocenters and carbon atoms needed for synthesis of the enantiomer of kainic acid were in place, but the conditions chosen for the peroxidic deboronation resulted in overoxidation to aldehyde **115** (Scheme 20). Most of the tritylated intermediates in this sequence were crystalline solids, in contrast to the usual oils encountered in boronic ester chemistry.

Scheme 20



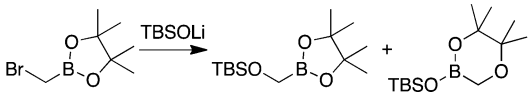
Completion of a kainic acid synthesis from ***ent*-114** would require a number of steps after deboronation. Synthesis from the opposite end of the chain was investigated as an alternative. Synthesis of **116** was routine, but allylic rearrangement occurred if the usual zinc chloride was used in the homologation to **117**, which crystallized from a ~10:1 diastereomer mixture (Scheme 21).[121] Usual homologation–

Scheme 21



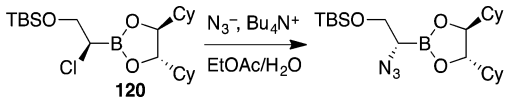
substitutions led to **118**, which was detritylated and mesylated for ring closure. After homologation of the pinanediol ester proved inefficient, it was converted to the boronic acid **119**, but homologation of the ethylene glycol ester of **119** followed by deboronation also produced a poor yield of corresponding aldehyde that could not be purified. An X-ray structure of an (α-aminoalkyl)boronic ester has shown coordination of the amide oxygen to the boron atom,[91] which may be the obstacle to binding the dichloromethyl anion to boron for homologation. The difluoroborane derivative[122] of **119**, which would have stronger B–O binding than the ester, did not capture the dichloromethide anion.[121]

Silyloxy and azido substituents provide relatively nonbasic masked hydroxyl and amino groups, respectively, that are minimally likely to interfere with zinc chloride promoted homologation. Direct substitution of (halomethyl)boronic esters with a silyloxide anion has yielded a mixture with ring expansion product (eq 13).[78] Accordingly, the (hydroxymethyl)boronic esters have been prepared and silylated.[78,93]



(13)

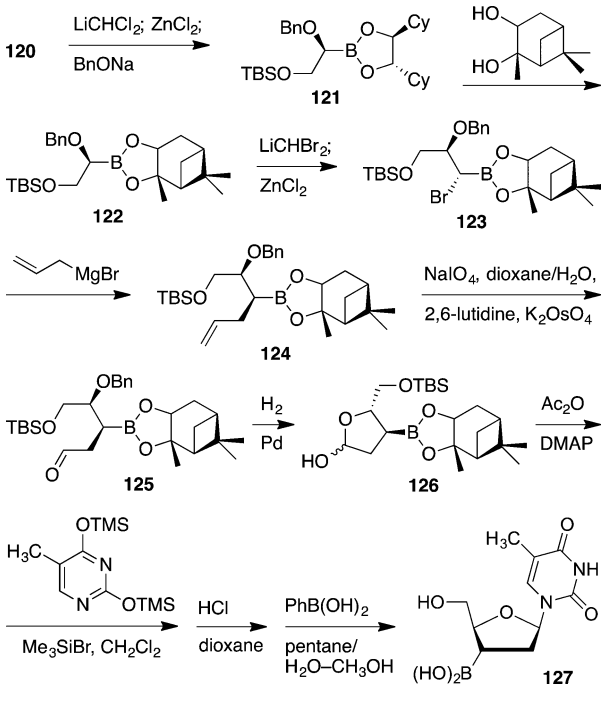
Homologation of (silyloxymethyl)boronic esters was followed by phase-transfer-catalyzed introduction of azide in ethyl acetate or nitromethane and water (eq 14).[78,123]



(14)

tert-Butyldimethylsilyl protection has been used in a recent synthesis of analogues of deoxynucleosides having a boronic acid group in place of the 3′-hydroxyl, which were requested by virologist William Prusoff. Homologation of **120** (eq 14) and substitution provided **121** (Scheme 22).[124] The next stereocenter requires the opposite sense of chiral direction. Pinanediol replaces 1,2-dicyclohexyl-1,2-ethanediol quantitatively to form **122**. The (α-bromoalkyl)boronic ester **123** gave much better results than its chloro analogue in substitution with allylmagnesium bromide to produce **124**. Osmate catalyzed

Scheme 22



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periodate cleavage to aldehyde **125** left the boronic ester function intact. Debenzylation yielded **126**, which after acetylation, treatment with silylated thymidine and trimethylsilyl bromide, acid cleavage of the TBS group, and transesterification of pinanediol yielded one of the target compounds, the thymidine analogue **127** (Scheme 22).[124]

As is usual with deoxyribonucleoside synthesis, **127** is accompanied by the less stable α-anomer. Identification of **127** was confirmed by peroxidic oxidation to thymidine. No antiviral activity of **127** was found. The analogue having 5-fluorouracil in place of thymine had activity that resulted from liberation of 5-fluorouracil over a period of several hours at 37 °C, pH 7.4. A fragmentation involving β-B−O elimination and opening of the deoxyribose ring to an unsaturated aldehyde appeared to be the cause.[124]

A referee criticized the foregoing synthesis as pointless, since it would obviously be possible to hydroborate 2′,3′-didehydro-3′-deoxythymidine and obtain **127** directly. However, that is an experimental question. The presumably easier hydroboration of 5′-vinylnucleosides worked well in some cases and failed in others, with fragmentation of intermediates an apparent problem.[125] Our interest in undertaking this synthesis was to test boronic ester homologation chemistry. Much is still not known about interaction of boron functionality with polar substituents.

TRIFLUOROBORATE DERIVATIVES

The utility of trifluoroborate salts and the ease of their preparation from boronic acids came to our attention from work of Batey[126] and Vedejs.[127] More recently, Molander's work has greatly expanded the field.[128,129] We had discovered a (now obsolete) method of converting C_2-symmetrical diol boronic esters to boronic acids and diol sulfites via treatment with thionyl chloride and imidazole in acetonitrile. This reaction was discovered by William Hiscox, who regularly washed his glassware with alcoholic potassium hydroxide, and was mysteriously irreproducible and could not be scaled up until we found that borosilicate glass surface catalysis was required.[130]

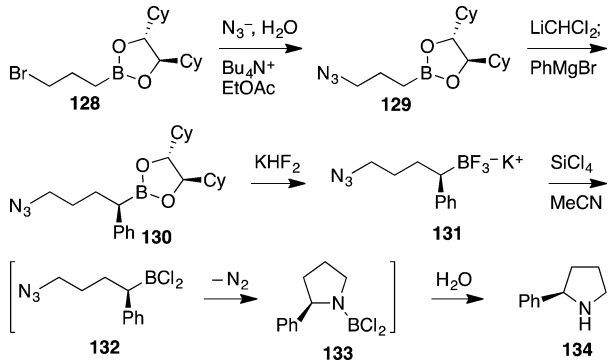
After Gyung-Youn Kim began converting boronic acids to potassium alkyltrifluoroborate derivatives, the question arose whether hydrolytically resistant boronic esters might react directly with potassium trifluoroborate. Pinacol and C_2-symmetrical diol esters do so easily, and the equilibria favor complete conversion to trifluoroborates. Pinanediol esters are incompletely converted, with equilibrium levels of trifluoroborate ~70%.[6] Later it was found that many cesium trifluoroborates can be precipitated in high yield from a solution of pinanediol boronic ester in diethyl ether and cesium fluoride in 2 mol of concentrated aqueous hydrofluoric acid.[30]

Although alkyl azides do not react with boronic esters under any known conditions, the preparation of secondary amines from azides and more reactive boranes, including organoboron dichlorides, is well established.[131] Defluoridation of organotrifluoroborates with TMS chloride[127] or silicon tetrachloride easily generated organodifluoroborane intermediates that led to secondary amines, or with hydrazoic acid to a primary amine (eq 15).[6]

$$R^1\text{-}BF_3^-K^+ + R^2\text{-}N_3 \xrightarrow[H_2O]{SiCl_4,\ MeCN;} \underset{H}{R^1\!\!\overset{N}{}\!\!R^2} \qquad (15)$$

The compatibility of the azido and boronic ester groups allows a straightforward asymmetric pyrrolidine synthesis (Scheme 23). (3-Bromopropyl)dichloroborane (**86**, Scheme 14) was the precursor to boronic ester **128** or the equivalent pinanediol ester. Conversion to the azido derivative **129**, homologation and phenylation to **130**, and conversion to the potassium alkyltrifluoroborate **131** followed established procedures. Treatment with silicon tetrachloride in toluene and some acetonitrile proceeded via postulated intermediates **132** and **133** to (*R*)-2-phenylpyrrolidine (**134**) (Scheme 23).[6] We also made the enantiomer ***ent*-134** and N-methylated it to the phenyl analogue of nicotine, which was then used in a crystallographic study of nicotine binding to cytochrome P450cam.[132]

Scheme 23



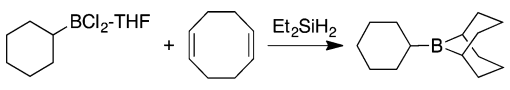
The previously reported synthesis of **134** via Buchwald's asymmetric enamine hydrogenation is shorter but requires a complex chiral titanocene catalyst.[133]

The reactions summarized in eq 15 and Scheme 23 did not reveal whether the active haloborane intermediates were fluorides or chlorides. Tetrachlorosilane produced "faster nitrogen evolution" than TMS chloride in the reactions of alkyltrifluoroborates with azides,[6] but there was an unreported anomaly. Amines were not obtained until the mixture was heated, the immediately evolved gas being tetrafluorosilane, not nitrogen. Byung-Ju Kim's ^{11}B and ^{19}F NMR study revealed that the reaction with TMS chloride stops at alkyldifluoroboranes, but tetrachlorosilane produces alkyldichloroboranes complexed with acetonitrile (eq 16). Complexing of the less acidic

$$R\text{-}BF_3^-K^+ + SiCl_4 \xrightarrow{CH_3CN} R\text{-}\underset{Cl}{\overset{Cl}{B}}\text{-}NCCH_3 + SiF_4 \qquad (16)$$

alkyldifluoroboranes with acetonitrile is weak and only partial. The thermodynamic balance requires release of tetrafluorosilane as well as alkyldichloroborane−solvent complexing in order to favor alkyldichloroboranes, which are the reactive intermediates with alkyl azides.[7]

Alkyldichloroboranes also complex with THF and can be generated in that solvent. Diethylsilane reduction and hydroboration are slowed by the complexing but can be done, as shown by conversion of cyclohexylboron dichloride and 1,5-octadiene to 9-cyclohexyl-9-BBN (eq 17).[7]



(17)

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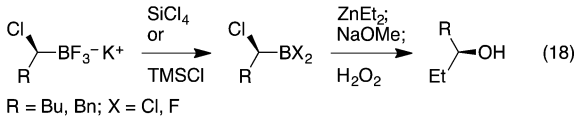
This exploratory work was concluded with a brief investigation of the utility of (α-chloroalkyl)dichloroboranes as synthetic intermediates. Alkyltrifluoroborate formation from pinanediol or 1,2-dicyclohexyl-1,2-ethanediol esters and conversion to alkyldichloroboranes occurs without disturbing the carbon−chlorine link, allowing removal of one chiral director and replacement by its enantiomer. Alkylation of (α-chloroalkyl)dihaloboranes with organometallics less reactive than Grignard reagents should be possible. Diethylzinc followed by rearrangement with base and peroxidic oxidation yielded the expected asymmetric secondary alcohols (eq 18).[7]



(18)

R = Bu, Bn; X = Cl, F

CONCLUDING REMARKS

This Perspective has summarized the use of asymmetric (α-haloalkyl)boronic esters in a variety of highly stereoselective asymmetric syntheses. The most significant features of this synthetic method include the following:

1. Predictable stereochemistry based solely on the diol used as chiral director.
2. Sequential installation of several adjacent stereocenters.
3. ∼99% stereocontrol with the diol easily prepared from either enantiomer of α-pinene.
4. Double diastereoselection with boronic esters of C_2-symmetrical diols with up to 99.9% stereocontrol.
5. Purification of intermediates not required.
6. Functional substituents, including alkoxy, alkenyl, azido, and remote esters and halides.
7. Recovery and recycling of chiral directors.
8. Targets for which the method appears especially useful, including insect pheromones and asymmetrically deuterated compounds.
9. Biochemically interesting and pharmaceutically useful (α-amidoalkyl)boronic acids.
10. Stereoselective reactions of enolates and lithiated nitriles, including cyclizations.
11. Convergent coupling of stereocenters.
12. Conversion of boronic esters to alkyltrifluoroborates and the reaction of the derived alkyldihaloboranes with alkyl azides to form chiral secondary amines, including pyrrolidines.

Some limitations and pitfalls include the following:

1. Nonpolar substrates best with (dihalomethyl)lithium insertion.
2. β-Halogen substituents not tolerated at any point.
3. Inhibition of the rearrangement of (α-haloalkyl)borate anion intermediates by nucleophilic substituents.
4. Easily available oxygen-substituted diols such as tartrate esters or mannitol derivatives not useful as chiral directors.
5. Stoichiometric amount of chiral director required.

Outside the famous hydroboration and trialkylborane chemistry developed by H. C. Brown and the Suzuki−Miyaura coupling process, organoboron chemistry is still an underdeveloped field, though activity has increased greatly in the past decade. Organic chemists may find the reactions unfamiliar, and they are sometimes unpredictable. The author hopes that this Perspective will help current researchers see new opportunities in boronic ester and alkyltrifluoroborate chemistry and that they will exploit the possibilities.

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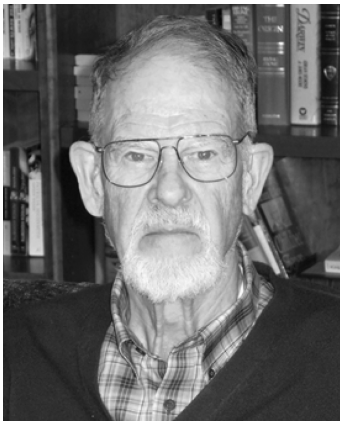
Notes

The authors declare no competing financial interest.

Biography



Donald S. Matteson was born in Kalispell, Montana, in 1932 and was first photographed with Marianna Merritt six weeks later but did not marry her until 1971. He played with now forbidden chemicals at age 12, graduated from U. C. Berkeley in 1954 where he worked with Henry Rapoport, and received his Ph.D. at the University of Illinois in 1957 with Harold R. Snyder. After a year at the du Pont Central Research Department in Wilmington, Delaware, he joined the faculty at Washington State University, Pullman, Washington, in 1958, became Professor Emeritus in 2012, received a Cope Scholar Award in 2013, and still does lab work. Organoboron chemistry was a neglected field in 1958, and early success with it led to his lifelong concentration.

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