α-Halo Boronic Esters: Intermediates for Stereodirected Synthesis

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Contents

Donald S. Matteson was born in Kalispell, MT, in 1932. He received his B.S. in chemistry from the University of California, Berkeley, in 1954, and his Ph.D. from the University of Illinois, Urbana, in 1957. After a year at the Du Pont Central Research Department, he went to Washington State University in 1958 and attained the rank of professor in 1969. His current interests are mainly in the field of organoboron chemistry and associated main-group organometallic chemistry, with emphasis on applications to organic synthesis. He has written a book entitled *Organometallic Reaction Mechanisms* (1974). In addition to α-halo boronic ester chemistry, he has developed a series of boronic esters having two, three, or four boron atoms attached to one carbon atom, has studied boron-substituted carbanions, and has synthesized benzocarborane.

I. Introduction

This review includes all references to compounds that contain the structural unit $XCBO_2$, where X = halogen, as covered by a computer search of *Chemical Abstracts* through the Dec 24, 1988, issue. The BO_2 group may be part of a five- or six-membered ring, with the remaining atoms carbon, or of any acyclic group. No seven-membered ring was found. The reviewer has found a few additional references by other means, especially where the α-halo boronic esters are implicit intermediates not indexed.

α-Halo boronic esters are easily prepared reagents that provide state of the art stereocontrol in asymmetric synthesis as well as in geometry of unsaturated systems. Major emphasis will be on reviewing these applications. However, the basic chemistry was discovered in achiral or racemic model systems before the possibility of easy stereoselective synthesis of α-halo boronic esters was recognized.

α-Halo boronic esters have been reviewed elsewhere either in the context of the author's own work or as part of a much broader coverage of borane and boronic ester chemistry.[1] The present review provides greater depth of coverage of the α-halo boronic esters themselves, but does not include such basic topics as the synthesis and properties of ordinary boronic esters and does not cover trialkylboranes or borinic acids (R_2BOH) except for a few instructive parallels with α-halo boronic esters.

II. Development of α-Halo Boronic Ester Chemistry

A. General Remarks

All of the routes to α-halo boronic esters described before section II.E have been superseded by more convenient and efficient routes. However, the fundamental principles of the chemistry of α-halo boronic esters were discovered as part of this work, most of which was reported during the decade 1959–1968. At that time, it was not apparent how this efficient and mechanistically interesting chemistry could be useful in organic synthesis. When practical general routes to α-halo boronic esters were found later, and especially when excellent chiral control was discovered, these fundamental principles were applied immediately to provide useful synthetic sequences.

It was not until 1966 that the first clear evidence for an (α-haloalkyl)borane intermediate in a hydroboration was reported by Pasto and Snyder[2] and not until 1968 that Brown and co-workers reported the first rear-

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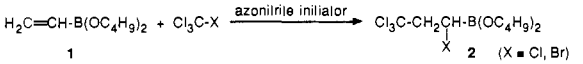
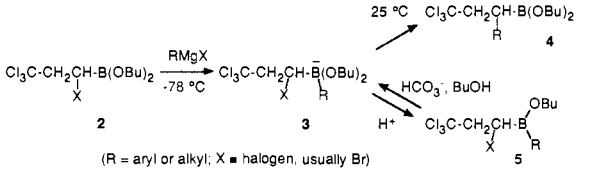
rangement of an (α-haloalkyl)borate derived from a trialkylborane.[3] The trialkylborane chemistry is more widely known than the boronic ester chemistry, but the basic chemistry of α-halo boron compounds was discovered in the boronic ester series first.

B. First Synthesis and Fundamental Chemistry

The first α-haloalkyl boron compound was FCH_2BF_2, prepared from boron trifluoride and diazomethane.[4] It was unstable at 20 °C. The first α-halo boronic esters (2) were prepared 2 years later (1959) via radical-initiated addition of polyhalomethanes to dibutyl vinylboronate (1) and were easily isolated and characterized.[5]



Although the range of structures of accessible α-halo boronic esters was initially highly restricted by the only known mode of synthesis, the novelty of the paired boron and halide neighboring groups prompted investigation of their chemistry. It was soon found that Grignard reagents alkylated the boron to form borate complexes (3), which rearranged via intramolecular S_N2



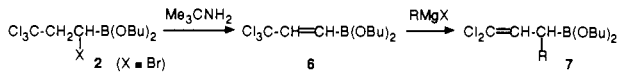
displacement of halide at 25 °C to form *sec*-alkylboronic esters (4).[6,7] Interception of 3 with acid at low temperature led to isolation of α-halo borinic esters (5). Alternative preparation of 5 via radical addition of Cl_3CX to vinylborinic esters, $CH_2{=}CHB(R)OC_4H_9$,[8] followed by treatment of 5 with sodium bicarbonate and butanol also yielded 4.

It is especially important to note that 3 reacts only via alkyl migration, never alkoxy migration. Bond energy estimates for B–O and B–C bonds[9] suggest that 4 is more stable than the isomeric alkoxy migration products (5 (X = OBu)) by as much as 30–40 kcal/mol. The latter isomer (R = ethyl) was synthesized unambiguously[8] and shown not to be present in 4 to the limit of infrared detectability.[6]

These results immediately suggested the synthetic potential of the α-halo boronic esters, if there had only been a general way to obtain them. Obviously, the migration of R and displacement of X^- ought to proceed with stereospecific inversion of the carbon from which X^- was displaced, while retaining the configuration of R. However, it has not been until recently that these expectations could be verified.

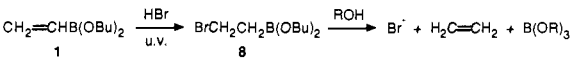
All nucleophilic displacement reactions of 2 appeared to proceed via intermediates analogous to 3, except perhaps when R^- was a very weak base such as halide, though even halide exchanges were clearly accelerated by the boronic ester group.[6] Sodium butanethiolate in butanol readily yielded the analogue of 4 having R = SBu. However, a small amount of byproduct was formed having R = OBu. This result suggested competing intermediates analogous to 3 (R = SBu or OBu).

Sodium butoxide with 2 yielded only displacement product. Elimination of HX from 2 to form 6 was achieved by refluxing in *tert*-butylamine. With Grignard reagents 6 yielded allylic rearrangement product 7, presumably via a borate complex and intramolecular S_N2' displacement.[10]



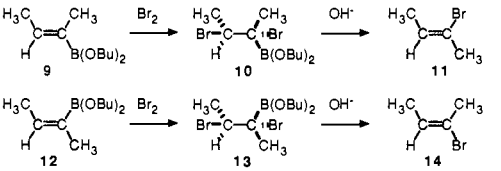
C. β-Halo and α,β-Dihalo Boronic Esters

Dibutyl (2-bromoethyl)boronate (8) was prepared by radical-initiated addition of HBr to 1.[11] In sharp contrast to the α-halo boronic ester series, 8 with any



reagent more basic than sodium iodide failed to undergo nucleophilic substitution and instead yielded elimination products.[11,12] Solvolytic conditions sufficed to cause elimination. Kinetic studies showed that the basicity of the solvent played a major role.[12]

Mikhailov and Aronovich brominated and chlorinated 1 to $XCH_2CHXB(OBu)_2$ and showed that base with the bromo compound caused β-elimination to vinyl bromide.[13] Matteson and Liedtke brominated (*Z*)- and (*E*)-2-butenylboronic esters 9 and 12 to diastereomeric dibromo compounds 10 and 13 and on treatment with base obtained anti elimination products 11 and 14, respectively.[12] The process was stereospecific to the limit of accuracy of the measurements, about ±3%.



The foregoing scheme could have been useful in synthesis if there had been a convenient stereospecific route to 9, 12, and analogous alkenylboronic esters. Such a route was developed many years later, based on hydroboration chemistry, and is discussed in section IV.

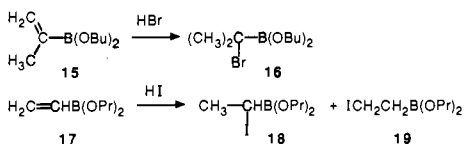
It may be noted in passing that β-elimination in trialkylboranes had been discovered first by Hawthorne and Dupont[14] and has found useful applictions. A notable example is the stereospecific Zweifel alkene synthesis, in which the elimination is normally anti[15] but with special reagents can be made syn.[16] However, this chemistry is outside the scope of this review.

The major significance of β-elimination in the chemistry to be discussed will be the necessity of designing synthetic schemes so as to avoid it.

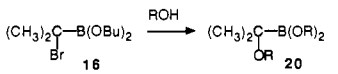
D. α-Halo Boronic Esters via Additions to Alkenes

1. Hydrogen Halide Additions. The synthesis of simple α-halo boronic esters was first accomplished by the ionic addition of hydrogen halides to alkenylboronic esters.[17,18] 2-(1-Alkenyl)boronic esters (15) with liquid hydrogen bromide yielded α-boronic esters (16). Dipropyl vinylboronate (17) with hydrogen iodide gave a 60:40 mixture of α- and β-iodo boronic esters 18 and 19, from which pure 18 was obtained after hydrolytic destruction of the 19.[18]

The foregoing syntheses were the first to provide simple α-halo boronic esters for study of their chemical properties. For example, it was found that 16 solvolyzes

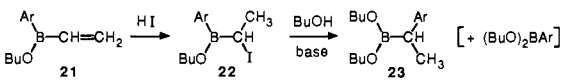


to **20** (R = H) in 50% aqueous ethanol at a rate intermediate between that of *tert*-butyl bromide and isopropyl bromide and that nucleophilic participation by the solvent is more important in the solvolysis of **16** than in that of *tert*-butyl bromide.[18] With sodium

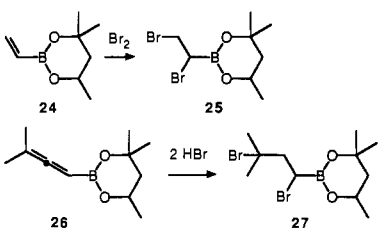


iodide in acetone, **16** reacted 0.4 times as fast as allyl bromide, and dibutyl (1-bromoethyl)boronate reacted 1.5 times faster than allyl bromide. With sodium thiophenolate in butanol, **16** was converted to **20** (R = butyl). Thus, the basicity of butoxide takes precedence over the nucleophilicity of the sulfide anion in the competition, strong evidence that a tetracoordinate borate anion is an intermediate. However, thiourea in acetonitrile converted **16** to the expected *S*-thioureido derivative.[18]

An early synthetic application of the rearrangement of an (α-haloalkyl)borate complex for carbon–carbon bond formation involved the addition of hydrogen iodide to **21** to form **22**, followed by base-induced rearrangement to **23**.[19] Unfortunately, devinylation of **21** led to arylboronic ester as a major byproduct.

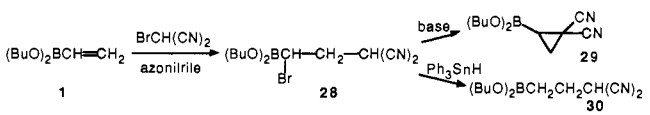


Several of the syntheses described in the foregoing section have later been applied to cyclic boronic esters, often with improved yields and ease of handling. 2-Methyl-2,4-propanediol esters such as **24** are especially resistant to hydrolysis.[20] Bromination of **24** to **25**[20] and dihydrobromination of allenylboronic ester **26** to **27**[21] have been reported.



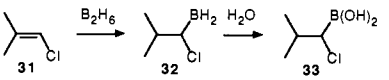
Addition of bromine and hydrogen bromide to various alkenylboronic cyclic esters[22] yields results similar to those reported previously[12,13] for the acyclic esters. Iodination of the catechol ester of (phenylethynyl)boronic acid has yielded a tetraiodo derivative described as $PhCI_2CI_2BO_2C_6H_4$,[23] but the only data, elemental analyses, would seem within experimental error of the more likely $PhC{\equiv}CBO_2C_6I_4$.

2. Radical Reactions. Radical addition of bromomalononitrile to vinylboronic ester **1** efficiently yielded **28**, which with any basic reagent ring closed to the cyclopropane **29** via deprotonation of the malononitrile



unit and intramolecular displacement.[18] Diethyl bromomalonate also added readily to **1**. Anomalously, these reagents failed to add to any other alkenes tested.[18] Triphenyltin hydride reduced **28** to **30**, though this first reduction of an α-halo boronic ester was accompanied by partial reversal of the original radical addition.[24]

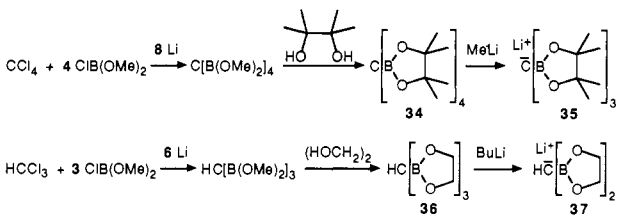
3. Via Hydroboration. Hydroboration of certain chloroalkenes has led to α-chloro boronic esters. The reaction of $(MeO)_2BH$ with (*E*)-1,2-dichloroethene to form $(MeO)_2BCHClCH_2Cl$ has been described in a patent.[25] Hydroboration 1-chloro-2-methylpropene (**31**) with excess diborane followed by prompt hydrolysis yielded (1-chloro-2-methylpropyl)boronic acid (**33**).[26] If the hydroboration mixture was not worked up promptly, the intermediate borane **32** rearranged to isobutylchloroborane.



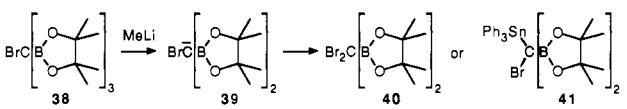
E. α-Halo Boronic Esters via Substitutions

1. Introduction. This section includes some of the more recent general syntheses of α-halo boronic esters. Some are obsolete, but others are the best routes known where control of chirality is not a consideration.

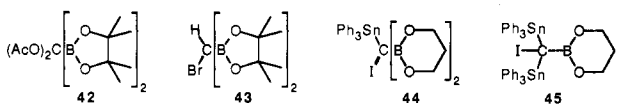
2. From α-Metallo Boronic Esters. The source of α-metallo boronic esters has been the tetraborylmethane **34** and triborylmethane **36** or analogous species, which are converted by butyllithium to carbanionic species such as **35** and **37**.[27-30] The starting materials are a considerable effort to prepare, and not much has been done with the halo boronic esters produced in this manner, but some rather exotic structures have been made.



Bromination of **35** yielded bromo boronic ester **38**, which on treatment with methyllithium did not undergo bromide displacement but deboronation to anion **39**, which with Br_2 yielded **40** or with Ph_3SnCl, **41**.[28] The propanediol ester analogue of **38** was cleanly obtained by bromination of precipitated $LiC[BO_2(CH_2)_3]_3$.[29]



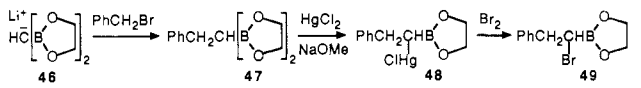
It appears that the reactivity of dibromo diboronic ester **40** toward nucleophiles follows the usual pattern, as treatment with sodium acetate furnished diacetate **42**.[28] Bromo diboronic ester **43** was also obtained from



bromination of the pinacol ester analogue of anion **37**,[28] and iodo tin boronic esters **44** and **45** were obtained

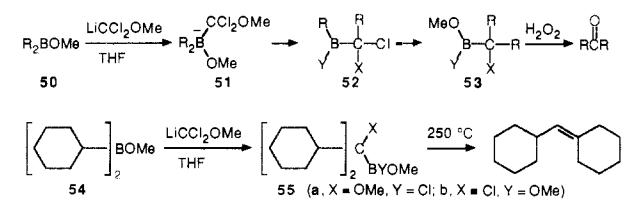
from iodination of the corresponding lithio tin boronic esters.[31] The properties of **43–45** have not been studied. More recently, $H_2C[BO_2(CH_2)_3]_2$ has been lithiated to $LiCH[BO_2(CH_2)_3]_2$,[32] which would provide an easier route to the propanediol ester analogue of **43**, but this has not been tested.

A different kind of bromodemetalation was once used to produce the (1-bromo-2-phenylethyl)boronic ester **49**,



which was at that time inaccessible by other known routes. Lithiodiborylmethane **46** was alkylated with benzyl bromide to form **47**, which was converted to the mercury derivative **48** and then brominated to **49**.[33] The replacement of boron by mercuric chloride had previously been shown to be considerably facilitated by the neighboring boronic ester group.[34]

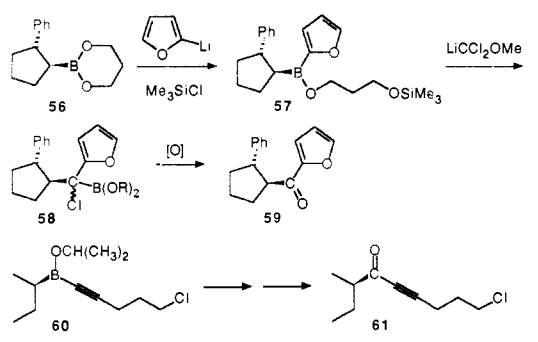
3. Via Insertion Reactions. A series of papers by Brown, Carlson, and Katz described the reaction of borinic esters (**50**, **54**) with $LiCCl_2OMe$, which was



generated in situ from dichloromethyl methyl ether and lithium triethylmethoxide. Appropriate further steps led to ketones,[35–38] alkenes,[39,40] or trialkylcarbinols.[41] α-Chloro boronic esters (**53b**, **55b**) were believed to be intermediates. Only one methoxy peak was observed in the ^1H NMR spectrum of **55**, implying X = Cl, Y = OMe (**55b**) rather than vice versa (**55a**).[40]

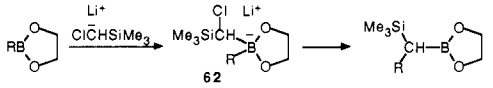
A migrating alkyl group should displace chloride, not methoxide. It therefore seems likely that initially X = OMe and Y = Cl (**52a**, **53a**, **55a**). However, the very acidic BCl unit of series **a** might catalyze interchange of Cl and OMe between boron and carbon to form series **b**, especially after any excess base is consumed in the reaction. Equilibrium may well favor the α-chloro boronic esters (**53b**, **55b**).

Recent developments in hydroboration chemistry have made boronic esters such as **56** available in high enantiomeric and 100% diastereomeric purity. Conversion to borinic esters (for example, **57**) was followed

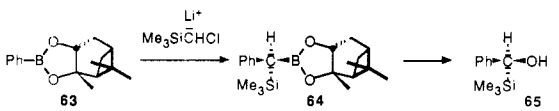


by treatment with dichloromethyl methyl ether and lithium *tert*-butoxide (2 mol), which was found preferable to lithium triethylmethoxide. The resulting presumed α-chloro boronic esters (or α-alkoxy boronic esters?) (**58**) were not isolated but oxidized to ketones (**59**) of high enantiomeric purity. For most of the boronic esters, hydrogen peroxide buffered with phosphate was found to be a satisfactory oxidizing agent, but for particularly hindered examples, trimethylamine *N*-oxide was superior.[42] Acetylenic ketones of high enantiomeric purity (**61**) can be produced from suitable borinates (**60**) but lithium triethylmethoxide is required as the base.[43]

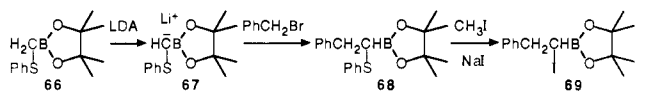
The first insertion into the carbon–boron bond of boronic esters, that of $Me_3SiCHClLi$, is relatively recent.[44] Although α-halo boronic esters are not involved, the reaction proceeds via an α-halo borate intermediate **62**, which is the same intermediate that would be expected from reaction of an alkyllithium with the as yet unknown $Me_3SiCHClBO_2C_2H_4$.



This insertion has been examined briefly to find out if it could provide asymmetric induction. "(*s*)-Pinanediol" phenylboronate (**63**) with $Me_3SiCHClLi$ yielded α-trimethylsilyl boronic ester **64** in 46% de (diastereomeric excess; 46% de = 73:27 diastereomeric ratio) as shown by oxidation to (*S*)-(−)-α-(trimethylsilyl)benzyl alcohol (**65**) of known optical rotation and absolute configurations.[45]



4. From α-Phenylthio Boronic Esters. Conversion of [(phenylthio)methyl]lithium to pinacol [(phenylthio)methyl]boronate (**66**) is straightforward, and lith-



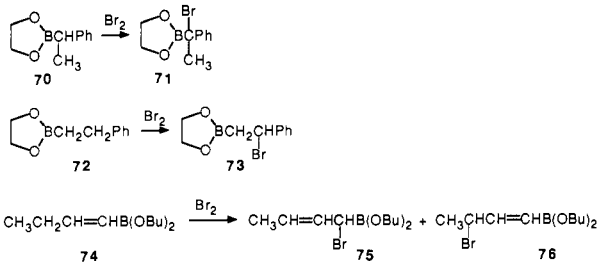
iation of **66** to **67** and alkylation with benzyl bromide to **68** are easy and efficient.[46] The general reaction of alkyl phenyl sulfides with methyl iodide and sodium iodide in dimethylformamide[47] had to be modified by lowering the temperature and lengthening the time in order to avoid dehydrohalogenation to β-styrenyl boronic ester, but then readily yielded the α-iodo boronic ester **69**.[46]

This chemistry apparently provides a general route from primary RX to $RCHIBO_2C_2Me_4$. However, except for the synthesis of (iodomethyl)boronic esters (section III), this route has not been developed further because of the concurrent discovery of the much more general synthesis of α-chloro boronic esters via chain extension of boronic esters with (dichloromethyl)lithium (section V).

5. Radical Halogenations. The first attempt to halogenate a saturated alkylboronic ester was the chlorination of di-*tert*-butyl methylboronate with *tert*-butyl hypochlorite.[48] This was a fiasco for practical purposes, as the rate constant for attack at the *B*-methyl group proved only 1.5 times greater than that for attack on the much more numerous *C*-methyl groups, and the yield of (chloromethyl)boronic ester was only ~10%.

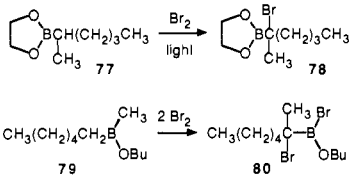
The first successful halogen substitution was bromination of the benzylic boronic ester **70** to **71** by Pasto

and co-workers.[49] However, the directing influence of

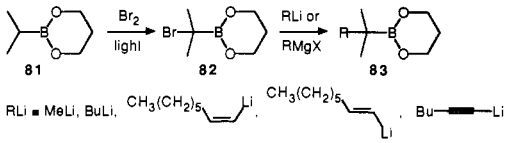


a phenyl group overrules that of a boronic ester, and the (2-phenylethyl)boronic ester **72** yielded only β-bromo boronic ester **73**. At about the same time, Schaumberg and Donovan carried out allylic bromination of dibutyl 1-butenylboronate (**74**), which yielded a 1:1 mixture of allylic isomers **75** and **76**.[50]

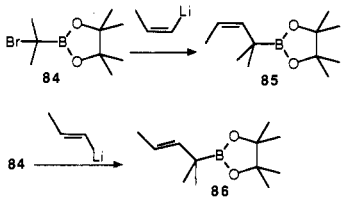
Benzylic and allylic bromination have limited utility, but Pasto and McReynolds went on to show that 2-hexylboronic ester **77** can be brominated efficiently to **78**.[51] Borinic ester **79** underwent bromination and rearrangement to **80**. Lane and Brown had shown that trialkylboranes undergo similar radical bromination.[52]



Improving on Pasto's conditions, Brown, Yamamoto, and co-workers brominated a number of *sec*-alkylboronic esters,[53] for example, **81**, and also studied the reaction of the resulting bromo boronic esters (**82**) with Grignard reagents to form alkylated products (**83**).[54] The limits of sterically hindered groups that could be connected were tested. Isopropylmagnesium halide worked well, but *tert*-butylmagnesium halide gave a low yield.



Hoffmann and Zeiss have utilized this chemistry for a synthesis of (α,α-dimethylcrotyl)boronate **85** for use in diastereoselective synthesis of homoallyl alcohols.[55] Roush and co-workers obtained **85** in 93% isomeric purity and the *E* isomer **86** in 98% purity.[56]



An unsuccessful attempt has been made to replace tin from $Ph_3SnCH(SPh)BO_2C_2Me_4$ by radical chlorination, which resulted instead in complete breakdown to $Ph_3SnCl + Cl_2CHSPh + ClBO_2C_2Me_4$.[57]

F. Fluoro and Perhalo Boronic Esters

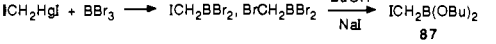
The chemistry of fluorinated boronic esters is almost entirely unknown. There is a report of the synthesis of (perfluorovinyl)boronic esters,[58] and catechol (perfluoropropyl)boronate has been prepared from (perfluoropropyl)lithium and catechol chloroborane.[59] (Fluoromethyl)boron difluoride[4] and (difluoromethyl)boron difluoride[60] have been reported. A Soviet patent has claimed $(Cl_2C{=}CCl)_2B(OH)OMe^-$.[61]

III. (Halomethyl)boronic Esters

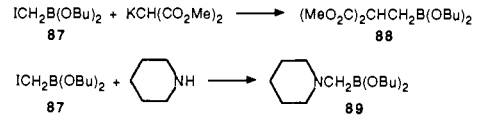
A. From (Iodomethyl)mercuric Iodide

1. Synthesis. It was recognized at an early date that a (halomethyl)boronic ester could have considerable synthetic utility. However, none of the early α-halo boronic ester syntheses were applicable to the (halomethyl)boronic ester problem, and it is only recently that a truly convenient laboratory preparation of these compounds has been found (see section III.D). As noted in section II.E, chlorination of di-*tert*-butyl methylboronate with *tert*-butyl hypochlorite resulted mainly in chlorination of the *tert*-butyl methyl groups.[48] In contrast, the much more reactive trimethylborane has been chlorinated to $ClCH_2B(CH_3)_2$.[62]

The first usable synthesis of a (halomethyl)boronic ester was the reaction of (iodomethyle)mercuric iodide with boron tribromide, which led to **87**.[63,64]

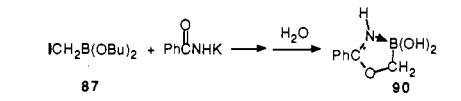


2. Basic Chemistry of $ICH_2B(OR)_2$. With **87** available in reasonable quantities, the range of nucleophiles that would displace the iodide was explored. Anions from malononitrile, dimethyl malonate, diethyl acetamidomalonate, and methyl cyanoacetate were tested successfully, as in the synthesis of **88**, and piperidine yielded **89**.[63,64] Ammonia reacted with **87** but no characterizable product was obtained.



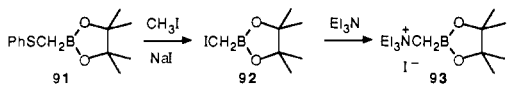
Other nucleophiles such as mercaptides also behaved in the expected manner. However, sodium azide converted **87** to formaldehyde and $B(OR)_3$.[64] This contrasts sharply with the subsequently discovered stability of the α-azido pinanediol boronic esters to be described in section IV, as well as the reported stability of $N_3CH_2BMe_2$.[62]

With potassiobenzamide, **87** formed a derivative that proved to be a good inhibitor of chymotrypsin.[65] Originally believed to be (benzamidomethyl)boronic acid,[65] this compound was subsequently shown to be the *O*-alkylated derivative **90**, which is probably stabilized by chclic coordination as indicated.[66]



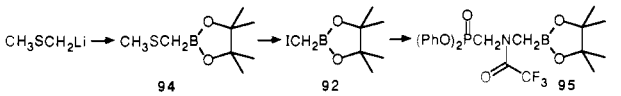
B. Synthesis from Sulfur Compounds

An easier synthesis of **87** utilized the reaction of dibutyl [(phenylthio)methyl]boronate with methyl iodide and sodium iodide in acetonitrile.[67] The analogous pinacol ester **92** was prepared from **91** in the same way. Either **87** or **92** with secondary amines yielded stable



tertiary amine products (see **89**), or with tertiary amines yielded quaternary ammonium salts (**93**). However, the product from **87** and benzylamine disproportionated during distillation to form tributyl borate.[67]

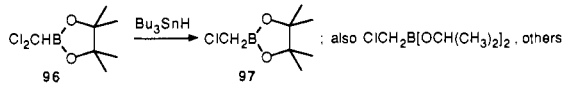
Preparation of **92** from **91** is not the cheapest way for industrial purposes, and a route from lithium dimethyl sulfide via the [(methylthio)methyl]boronic ester **94** has been reported.[68] Reaction of **92** with the appropriate sodio amide has yielded **95**, patented as an inhibitor of smartweed.[69]



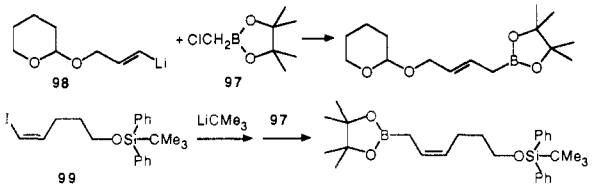
An incidental preparation of catechol (iodomethyl)-boronate has been reported from the reaction of methyl iodide and catechol with $Me_3NBH_2CH_2SMe_2^+I^-$.[70] 5-Heptyl-2-(iodomethyl)-1,3,2-dioxaborinane has been mentioned in a patent on liquid crystals.[71]

C. From Reduction of (Dichloromethyl)boronic Esters

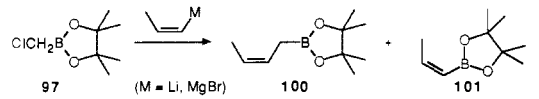
1. The Reduction. Whatever the industrial merits of dimethyl sulfide, from the laboratory worker's point of view the next advance in (halomethyl)boronic ester preparation was Wuts and Thompson's tributyltin hydride reduction[72] of Rathke's (dichloromethyl)boronic (for example, **96**)[73] to (chloromethyl)boronic esters (**97**).



2. Use in Allylboronic Ester Synthesis. Hoffmann's stereoselective homoallylic alcohol synthesis[74] requires allylic boronic esters of defined geometry. One route to these is the reaction of alkenyllithiums such as **98** with (halomethyl)boronic esters such as **97**.[75] A similar reaction of **99** has been used in a synthesis of the antibiotic X-14547A.[76]

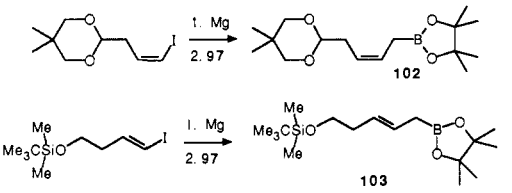


Difficulties have occasionally been encountered in the reactions of **97** with lithium reagents. Roush and coworkers found that reactions of **97** with (*Z*)-1-lithiopropene often gave major amounts of byproduct propenylboronic ester **101**, with variable 0–50% yields of crotylboronic ester **100**.[56]

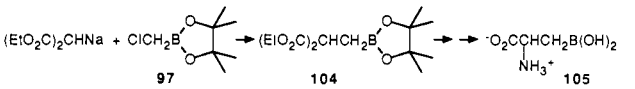


The data presented do not make it entirely clear whether the chloromethyl group is lost from the borate complex prior to aqueous workup. If the alkenyl group migration is slow, it is conceivable that some sort of unknown fragmentation could compete, but protonation of the borate complex during premature workup is perhaps the most common cause of unexpected fragmentations. [(*Z*)-1-Propenyl]magnesium bromide gave better results than the lithium reagent, providing 75–82% of 95% isomerically pure (*Z*)-crotylboronic ester **100**, with <1% **101**. The magnesium cation may well catalyze borate complex rearrangement, as does zinc cation (see section V.B.3). The preferred route to **100** involved reaction of (*Z*)-potassiobutene with FB-$(OMe)_2$.[56]

In recent work, Wuts and Bigelow have used the Grignard route to prepare intermediates **102** and **103** for use in alternative routes to carbomycin C via the Hoffmann homoallylic alcohol synthesis.[77]



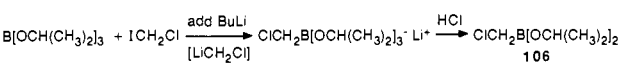
3. Use in Malonic Ester Alkylation. The reaction of dibutyl (iodomethyl)boronate with malonic ester anion and related species has already been noted in section III.A.[64] The reaction of **97** with diethyl sodiomalonate has been used in a synthesis of 2-amino-3-boronopropionic acid (**105**), a boron analogue of aspartic acid.[78] Two moles of **97** was required in order to



achieve good conversion of the malonate to the intermediate **104**, after which 70% of the excess **97** could be recovered and recycled. The requirement for 2 mol of **97** is not understood, though it may be that there is some kind of competition between *O*-bound and *C*-bound borate complexes, only the *C*-bound complex being effective in the displacement process, and that excess boronic ester facilitates equilibration to provide the required species.

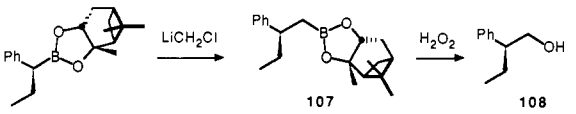
D. From (Chloromethyl)lithium

By far the easiest laboratory preparation of diisopropyl (chloromethyl)boronate (**106**) was discovered after the foregoing chemistry had already been done.

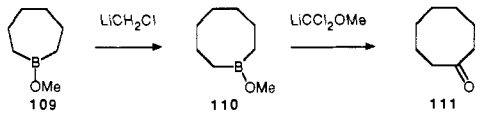


Sadhu and Matteson added butyllithium to a mixture of iodochloromethane and triisopropyl borate in THF at −78 °C and then acidified with ethereal hydrogen chloride, to obtain **106** in 84% yield.[79] The reaction presumably involves the very unstable (chloromethyl)lithium as an intermediate. The choice of triisopropyl borate and the workup conditions were based on the general method for the preparation of boronic esters from lithium reagents developed by Brown and Cole.[80]

(Chloromethyl)lithium also efficiently inserts a methylene group into the carbon–boron bond. Retention of configuration of the migrating alkyl group was demonstrated by the preparation of **107** and its oxidation to the alcohol **108** of known optical rotation and absolute configuration.[79]



Brown and co-workers have investigated several ways of homologating boronic esters and found that (chloromethyl)lithium can be generated from the cheaper bromochloromethane almost as efficiently as from chloroiodomethane.[81] Brown's group has also investigated cyclic borinic esters as substrates for (chloromethyl)lithium and found that ring expansion starting from a readily accessible seven-membered ring **109** can lead to efficient synthesis of the eight-membered ring **110**, the corresponding ketone **111** via the reaction with $LiCCl_2OMe$, and larger medium-sized rings from successive expansions of **110** up to twelve members, with yields ~80% at each ring expansion step.[82]



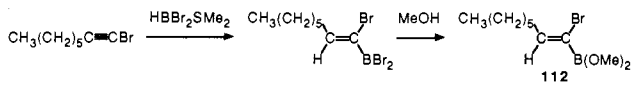
IV. (α-Haloalkenyl)boronic Esters

These constitute a special class of α-halo boronic esters. They are of considerable interest as reagents for preparing alkenyl compounds with almost total control of alkene geometry.

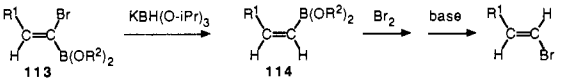
Remarkably, the activating effect of the boronic ester group is sufficient that the vinylic α-halogen can be displaced by suitable nucleophiles. The first observation of this type of displacement was made in the triarylborane series by Köbrich and Merkle,[83] and the first synthetic utility was demonstrated in the trialkylborane series by Negishi and co-workers.[84] Triaryl- and trialkylboranes being generally much more reactive than boronic esters, these precedents were no guarantee that similar behavior would be found in the boronic ester series.

(α-Haloalkenyl)boronic esters were first made by halogenation. Light was required to initiate the bromination of dibutyl ethynylboronate, $HC{\equiv}CB(OBu)_2$, to $BrCH{=}CBrB(OBu)_2$, in contrast to bromination of dibutyl vinylboronate to $BrCH_2CHBrB(OBu)_2$, which was very rapid.[85] The next (α-bromoalkenyl)boronic ester reported was $(CH_3)_2C{=}CBrBO_2C_2H_4$, which resulted when $(CH_3)_2C{=}C(BO_2C_2H_4)_2$ was treated with bromine in carbon tetrachloride at −20 °C.[86] The chemistry of the halogenated product was not investigated.

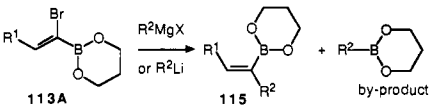
(α-Haloalkenyl)boronic esters of defined geometry were first prepared by Brown and co-workers via hydroboration of 1-haloalkynes with dibromoborane dimethyl sulfide, as in the synthesis of **112**.[87] In this paper there was also the useful observation that dimethyl boronates can be prepared from boronic acids by treatment with methanol in pentane, from which the water produced separates.



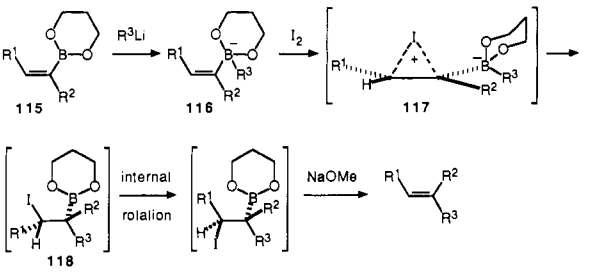
Reduction of (1-bromoalkenyl)boronic esters (**113**) with potassium triisopropoxyborohydride, which was found "far superior" to *tert*-butyllithium or lithium triethylborohydride for this purpose, readily yielded (*Z*)-1-alkenylboronic esters (**114**).[68] Bromination and elimination according to known principles[12] (see section II.C) readily yielded pure (*E*)-1-bromoalkenes.[89]



Replacement of the bromine of **113** by alkyl proved to be a more challenging problem. The best substrates found were 1,3-propanediol esters (1,3,2-dioxaborinanes) **113A**, and diethyl ether worked much better than tetrahydrofuran as solvent.[90] Either Grignard or lithium reagents worked, and addition of methanol (together with sodium methoxide if a Grignard reagent was used) promoted the migration–displacement process to form **115**. A major byproduct if conditions were not right was the alkylboronic ester resulting from cleavage of the alkenyl group.



The bromination and elimination sequence used to convert **114** to primary alkenyl bromides has been similarly used on **115** and related compounds to provide secondary alkenyl bromides of controlled geometry.[91] The alkenyl bromide can in turn be converted via the lithium reagent to the alkenylboronic ester of opposite geometry to **115**. Cyclic boronic esters **115** and their geometric isomers have proved useful in a stereospecific synthesis of trisubstituted olefins,[92] which is an improvement on the Zweifel olefin synthesis[15] as modified by Evans and co-workers,[93] who had used dimethyl alkylboronates and lithioalkenes to assemble an acyclic analogue of the borate complex **116**. The postulated intermediate **117** and the stereospecific migration of the R^3 group make this chemistry closely related to that of α-halo boronic esters, and β-halo boronic esters **118** (see section II.C) are clearly involved.



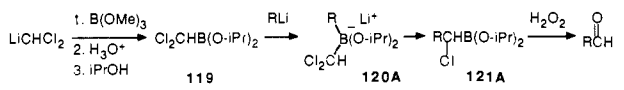
An important application for **114**, **115**, and related alkenylboronic esters is in the Suzuki coupling with alkenyl or aryl halides catalyzed by palladium(0) complexes, which allows construction of dienes and arylalkenes of controlled geometry. Suzuki's group has reported the use of a variety of diisopropyl esters corresponding to **114**[94] and **115**[95] in typical coupling reactions, which are outside the scope of this review.

V. (Dihalomethyl)lithium and Asymmetric Synthesis

A. The Basic Process

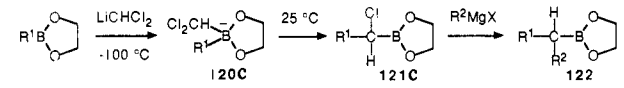
The initial discovery that made this chemistry possible was the preparation of (dichloromethyl)lithium by Köbrich and co-workers,[96] who also demonstrated the

use of this reagent to insert a CHCl group into the carbon–boron bond of a triarylborane.[83] Rathke, Chao, and Wu then used (dichloromethyl)lithium and trimethyl borate followed by further routine manipulations to make diisopropyl (dichloromethyl)boronate (**119**).[73] Alkyllithiums with **119** formed borate com-



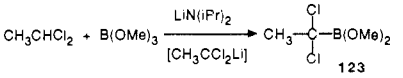
plexes **120A** (see section II.A[6,7]), which rearranged to α-chloro boronic esters **121A**, which were not isolated but oxidized in situ to aldehydes.[73] Yields of aldehydes were available, and it appears that the importance of the discovery was not recognized at the time. Hindsight tells us that the only problem step was the oxidation of α-chloro boronic esters **121A**, which works surprisingly poorly.[97]

Matteson and Majumdar made a few simple modifications of Rathke's chemistry, preparing intermediate cyclic borate complexes **120C** from cyclic boronic esters



and (dichloromethyl)lithium and isolating the resulting α-chloro boronic esters (**121C**).[98,99] Yields of **121C** were generally excellent, and the chlorine was readily replaced by nucleophiles, for example, Grignard reagents to produce **122**, as had been found many years earlier.[6,7] A variety of R^1 groups worked well, including primary and secondary alkyl, *tert*-butyl, aryl, alkenyl, α-alkoxyalkyl, and remote carboxylic ester substituents.[99] Several types of boronic esters and R^2 groups were also examined.

In addition to the prior preparation of (dichloromethyl)lithium from butyllithium and dichloromethane at −100 °C, in situ preparation and capture at −78 °C from lithium diisopropylamide (LDA) and dichloromethane, which had been reported previously for other substrates,[100,101] were carried out successfully.[99] The in situ preparation and capture method also provides the most convenient mole-scale synthesis of diisopropyl (dichloromethyl)boronate (**119**) from triisopropyl borate, dichloromethane, and LDA.[102] This reaction can be carried out at temperatures as high as −5 °C. From trimethyl borate and 1,1-dichloroethane at −78 °C, dimethyl (1,1-dichloroethyl)boronate (**123**) is produced.[102] Preformed (1,1-dichloroethyl)lithium did not work nearly as well.

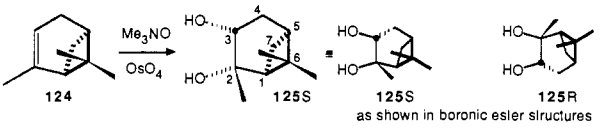


Brown and co-workers have also studied in situ methods for generation of (dichloromethyl)lithium and its capture by boronic esters and have found that *sec*-butyllithium and dichloromethane at −78 °C are effective.[81]

(Dibromomethyl)lithium[103] has been used to prepare pinacol (dibromomethyl)boronate.[104,105] The in situ capture approach[101] is particularly useful for reaction of (dibromomethyl)lithium with boronic esters to make α-bromo boronic esters,[106] which have produced better yields of substitution products in cases where the α-chloro boronic esters reacted sluggishly.[105,106]

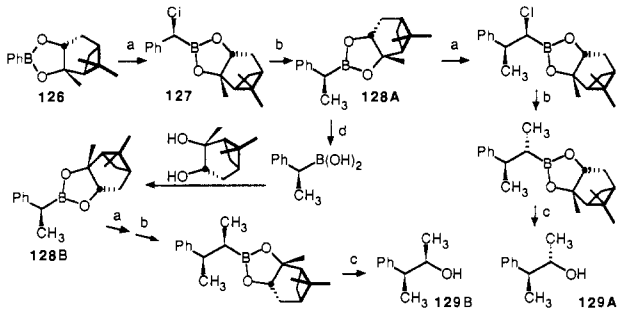
B. Chiral Control

1. The Basic Discovery. "(*s*)-Pinanediol"[107] (**125S**) from the osmium tetraoxide catalyzed oxidation of (+)-α-pinene[108] (**124A**) provided the first successful



chiral control of the insertion of the CHCl group into boronic esters.[109] The choice of this reagent was suggested by the first truly successful directed asymmetric synthesis, hydroboration with boranes derived from α-pinene.[110] The "(*s*)" is a mnemonic that three of the four chiral centers are (*S*),[111,112] including either of those used by *Chemical Abstracts* for indexing,[107] and that this isomer directs formation of (*S*)-α-chloro boronic esters. The first trivial name we use was (+)-pinanediol,[109] but the rotation is solvent dependent, (+) in toluene and (−) in methanol.[111] The enantiomer, "(*r*)-pinanediol" (**125R**), is similarly readily available.

When (*s*)-pinanediol butylboronate reacted with (dichloromethyl)lithium followed by methylmagnesium bromide and the resulting (1-methylpentyl)boronic ester was deboronated with hydrogen peroxide, (*S*)-(+)-2-hexanol was immediately obtained in 80% enantiomeric excess (ee). (Note that ee is defined as $100(x_1 - x_2)$, where x_1 and x_2 are the respective fractions of major and minor enantiomers; 80% ee is a 9:1 isomer ratio.) The first attempt to convert (*s*)-pinanediol phenylboronate (**126**) to the (α-chlorobenzyl)boronate (**127**) led to essentially racemic product. The problem was epimerization of **127** by the chloride ion produced in the reaction, and prompt workup, conversion to **128A**, and oxidation led to (*S*)-(−)-1-phenylethanol, 93–96% ee.[109]



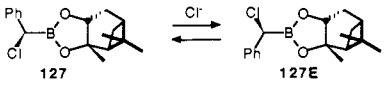
Steps: (a) $LiCHCl_2$; (b) CH_3MgBr; (c) H_2O_2; (d) BCl_3, then H_2O, purified via diethanolamine chelate.

On the basis of the probable mechanism[6,7] as well as stereochemical information available from the trialkylborane series,[112] it was expected that the α-carbon would be inverted as chloride was displaced from it and that the alkyl group would retain its configuration during migration from boron to carbon. The syntheses of two diastereomeric 3-phenyl-2-butanols (**129A** and **129B**), the configurations of which had been established by Cram,[113] demonstrated that these expectations were correct and suggested the synthetic potential of the process. Even without the subsequently discovered improvements, yields and diastereomeric ratios were high. The possibility of assembling several contiguous chiral carbons with free choice of the absolute configuration of each was evident.

In the syntheses just described, for best results the chloroboronic esters were not isolated, but after suffi-

cient time for their formation had elapsed, their solutions were treated directly with the methylmagnesium bromide. It is possible that the magnesium halide played a catalytic role, as yields of the product of one-pot CHCl insertion and alkylation in some instances appeared to be higher than those of the isolated α-chloro boronic esters. However, magnesium halides are clearly not as effective catalysts as zinc chloride, to be discussed in subsection B.3.

2. The Epimerization Problem. Exposure of (*s*)-pinanediol [(*S*)-α-chlorobenzyl]boronate (**127**) to lithium chloride in tetrahydrofuran (THF) leads to equilibration with epimer **127E**. The detailed kinetics have been studied, and the reaction appeared to be first-order in free chloride ion.[114]

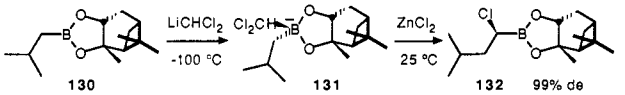


127 127E

With 0.45 M lithium chloride in THF at 25 °C, k_1 = 5.7×10^{-5} s^{-1}, which translates to ~1% randomization in 3 min. With a saturated alkyl instead of phenyl, epimerization is closer to 1% h^{-1}.[114] Since migration of alkyl groups in borate complexes usually requires 10–20 h for completion,[109] these rates account for most if not all of the epimeric α-chloro boronic ester formed in the synthesis process.

The kinetics revealed that small amounts of ionizing solvents such as water or dimethyl sulfoxide greatly accelerated epimerization but, more interestingly, that metal cations capable of complexing with chloride ion greatly retarded epimerization. Zinc chloride led to minimal epimerization rates at the stoichiometry $LiZnCl_3$, and rates remained low throughout the range of $Li_2ZnCl_4/LiZnCl_3$ compositions. Dilute $ZnCl_2$ did not cause epimerization, but mixtures of $ZnCl_2$ and $LiZnCl_3$ led to a term in a rate law that was first-order in each species and that became very rapid as concentrations approached 1 M levels.[114]

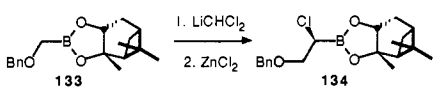
3. Zinc Chloride Catalysis. On the basis of the epimerization data, it appeared worthwhile to test the effect of zinc chloride on the rearrangement of (dichloromethyl)borate complexes. The results exceeded all expectations. The uncatalyzed reaction of the borate **131** derived from pinanediol isobutylboronate (**130**) had



130 131 132 99% de

been very sluggish, with yields 15–33% and the de (diastereomeric excess) of the product **132** ~77%.[115] With 0.7 mol of anhydrous zinc chloride added after formation of the borate complex **131**, the yield rose to 90% and the de to 99%.[111,116,117]

Without zinc chloride, (*s*)-pinanediol [(benzyloxy)-methyl]boronate (**133**) failed to react with (dichloromethyl)lithium. With the catalyst, a good yield of the insertion product **134** was obtained.[115] An extra mole



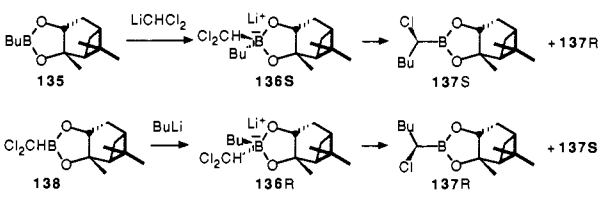
133 134

of zinc chloride was required in order to overcome the effect of complexing by the benzyloxy group of **133**. It was subsequently shown that the diastereoselectivity was relatively poor, ~85% de.[106] Another example of mediocre diastereoselectivity was pinanediol methylboronate, ~91% de. The other de's measured were all in the 97–99% range.[111]

The use of zinc chloride adds some minor inconveniences. It is necessary to dry the zinc chloride rigorously, preferably by stirring the powdered material under vacuum at ~100 °C, in order to achieve consistent results.[111] If LDA is used to generate the (dichloromethyl)lithium, the resulting diisopropylamine must be complexed with an extra mole of zinc chloride.[117] Removal of the zinc salts before proceeding with addition of the nucleophile to the α-chloro boronic ester has not been proved to be necessary in all instances but seems a reasonable precaution.

4. Chiral Directors. Although pinanediol is relatively inexpensive and its boronic esters are very stable and easy to work with, it does have some disadvantages as a chiral director. Its boronic esters are exceedingly difficult to hydrolyze or transesterify,[109] which becomes a problem if some other boronic ester function or a chage of chiral director is needed.

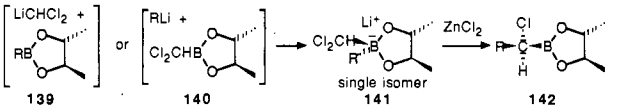
More fundamentally, pinanediol lacks C_2 symmetry, and the two faces of the esterified boron atom behave differently. Nucleophiles attack from the less hindered side, which is the top as illustrated. Thus, addition of (dichlorometyl)lithium to (*s*)-pinanediol butylboronate (**135**) presumably produced borate complex **136S**, which



135 136S 137S
138 136R 137R

has the *S* configuration at boron and which rearranged preferentially to (α*S*)-α-chloro boronic ester **137S** (80% de without zinc chloride).[109] However, addition of butyllithium to (*s*)-pinanediol (dichloromethyl)boronate (**138**) gave diastereomeric borate **136R**, with the *R* configuration at boron, which yielded (α*R*)-α-chloro boronic ester **137R** in only 31% de over **137S**.[118] Several other examples yielded similar results. Zinc chloride catalysis shifted product ratios to favor α*S* isomers but did not give useful diastereoselection.

Common chiral directors having C_2 symmetry, for example, diacetone mannitol and diethyl tartrate, gave poor chiral direction or interfered with the (dichloromethyl)lithium reaction.[109] However, (*R*,*R*)-2,3-butanediol alkylboronates **139** and (*R*,*R*)-2,3-butanediol



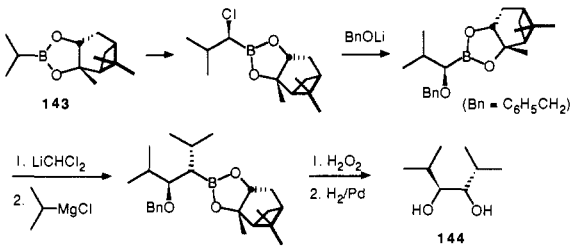
139 140 141 142

(dichloromethyl)boronate (**140**) with alkyllithiums led to the same borate **141**, which independently of the nature of R gave **142** in ~90% de.[119] Ordinarily, lithium and Grignard reagents are interchangeable in these reactions, but where R = vinyl, reaction of RMgBr with **140** yielded **142** in 92% de, and $LiCHCl_2$ with **139** yielded **142** in only 82% de.[120] Perhaps the magnesium ion helps protect the very labile allylic **142** from epimerization.

(*R*,*R*)-2,3-Butanediol is a fermentation product, and the *S*,*S* enantiomer can be made from tartaric acid.

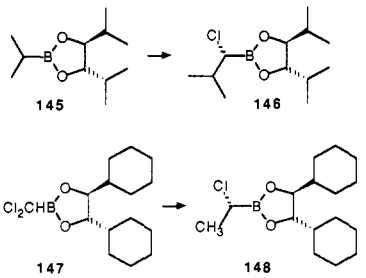
The α-chloro boronic esters hydrolyze rapidly on contact with water,[119] so that derivatives that can be crystallized or converted to an opposite chiral directing group are readily accessible. The major disadvantages of butanediol as a chiral director are that the ease of hydrolysis of butanediol esters makes chromatography difficult or impossible, and the stereoselectivity is not very high.

1,2-Diisopropylethanediol, "DIPED", provides C_2 symmetry, esters stable toward water, and high chiral directing power. The first synthesis of (*S,S*)-DIPED (**144**)[121] started from (*s*)-pinanediol isopropylboronate



(**143**) and was analogous to a previous synthesis of (*S,S*)-5,6-decanediol.[111] The use of **144** as chiral director was at first reported to yield only ~94% de's in the resulting α-chloro boronic esters,[121] but the (*s*)-pinanediol used to make **143** had only ~98% ee, and the DIPED α-chloro boronic esters were transesterified with the same impure pinanediol for the NMR analyses.

More recently, a straightforward synthesis of (*S,S*)-DIPED from natural L-(+)-tartaric acid has been devised.[122] (*S,S*)-DIPED prepared from tartaric acid leads to de's of ~98–99%, as in the conversion of **145** to **146**.[123] Also, (*S,S*)-1,2-dicyclohexylethanediol, readily available from catalytic hydrogenation of resolved 1,2-diphenylethanediol, has given a very high de in the conversion of **147** to **148** by Hoffmann's group.[124] In view of the recent simple preparation of 1,2-diphenylethanediol in high ee by asymmetric osmium tetraoxide catalyzed hydroxylation of *trans*-stilbene by Sharpless' group,[125] dicyclohexylethanediol may well become the chiral director of choice for these syntheses.



C. General Aspects of Synthetic Applications

1. Generality. The reaction of boronic esters with (dichloromethyl)lithium has been shown to provide a very general synthesis of secondary alcohols of high ee, or if two or more chiral carbons are present, high de and ee.[106,109,111] Compatibility with several functional groups has been established, including α-alkoxy,[111] β-alkoxy,[106] β-*tert*-butoxycarbonyl,[111] remote ethylene ketal,[111] β-alkylthio (but not α-phenylthio),[111] and α-azido.[111] Stereospecific displacement of the α-chlorine by a variety of nucleophiles has been demonstrated, including alkyl and aryl,[109,111] alkoxy,[106,111] ester enolate,[111] bis(trimethylsilyl)amino,[115,126,127] azido,[111,128] trialkylstannyl,[123,129] and deuterium from lithium triethylborodeuteride.[130]

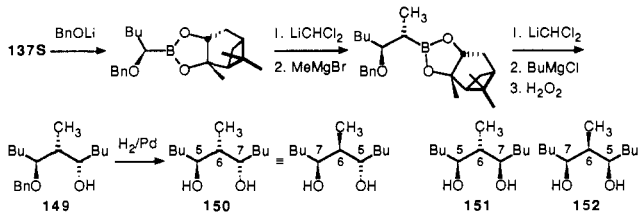
Ordinarily the boronic ester group is oxidatively replaced before other deprotections are undertaken, but it may be noted that hydrogenolysis of benzyl groups or oxidative cleavage of methoxybenzyl groups with dichlorodicyanoquinone[131] can be carried out without disturbing the carbon–boron bond.[132]

2. Replacement of Boron. Replacement of the boronic ester group is usually done stereospecifically with hydrogen peorxide to make an alcohol. However, if an aldehyde function is the ultimate goal, oxidation of the α-chloro boronic ester is inefficient,[97] apparently because of formation of aldehyde peroxide adducts.[106,133] The conversion of $RB(OR')_2$ to RCHO has been carried out via reaction with lithiated methoxy(phenylthio)-methane to form α-methoxy boronic esters, which give good yields of aldehydes on treatment with hydrogen peroxide.[97] For conversion to carboxylic acids, attempts to react $LiCCl_3$ with boronic esters have failed, but thioesters react, permitting conversion of $RB(SR')_2$ to RCO_2H.[134] However, conversion of boronic esters to thioesters is not a trivial problem. Conversion of $RCHClB(OR')_2$ to RCO_2H has been accomplished directly with sodium chlorite ($NaClO_2$).[128]

Stereospecific conversion of chiral $RB(OR')_2$ to RCH_2OH has been described in section III.D. Before the Sadhu–Matteson procedure[79] for generating (chloromethyl)lithium was discovered, Brown and co-workers accomplished the same objective by reacting the boronic ester with (dichloromethyl)lithium and reducing the resulting α-chloro boronic ester with potassium triisopropoxyborohydride, which was found superior to lithium triethylborohydride for this purpose.[135] More recently, a careful comparison of the methods for carrying out this transformation has been carried out by Brown's group.[81]

The rich chemistry of trialkylboranes[2] suggests other possible transformations of boronic esters, and transformation of chiral boranes to a wide variety of chiral derivatives has been reviewed recently by Brown and Singaram.[136] The conversion of $RB(OR')_2$ to RNH_2 is one of the interesting transformations that have been carried out.[137] However, such conversions have not yet been utilized in the context of syntheses based on α-halo boronic ester chemistry.

3. Chirality and Nomenclature. As an adjunct to the syntheses described in section V.D, (*s*)-pinanediol (1*S*)-(1-chlorobutyl)boronate (**137S**) was converted to (5*S*,7*S*)-6-methylundecane-5,7-diol (**150**).[111] The 5-



benzyloxy intermediate **149** represents achievement of the goal of assembling three chiral carbons, but diol **150** has only two because of the overall molecular symmetry. A C_2 rotation at carbon 6 turns the methyl group from back to front but does not otherwise alter the appearance of the structure. However, sites 5 and 7 and their

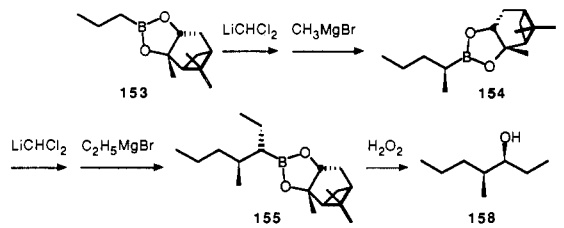
attached groups remain chemically distinct, and, for example, show different NMR absorptions, because of their different relationship (syn/anti) to the central carbon. The two meso isomers **151** and **152**, which were very minor byproducts, have an achiral carbon at the center but clearly differ as geometric isomers.

Mislow and Siegel have suggested terminology based on fundamental topology for describing these and other stereochemical relationships.[138] Chirality is a property of a group, not a point or an atom, and is properly specified only once for a whole molecule. All further stereochemistry is relative (as in *Chemical Abstracts* nomenclature.[107]) The term "stereogenic" describes any site at which there is any pair of ligands that if permuted would result in a stereoisomer of any kind. "Chirotopic" describes *all* sites in a chiral molecule or a chiral portion of a molecule. Carbon 6 in **150** is chirotopic but not stereogenic. Carbon 6 in **151** or **152** is stereogenic but not chirotopic.[138] Terms such as "center of chirality" lack mathematically based definition and may thus contribute to confusion when structures having unusual symmetry such as **150** are encountered.[139]

D. Insect Pheromone Synthesis

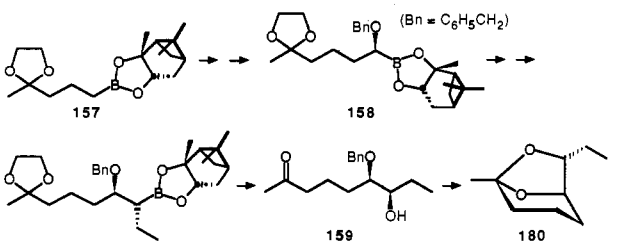
Three examples of insect pheromones have been synthesized from pinanediol boronic esters.[111,116] Each illustrates useful details of the chemistry and synthetic strategy.

(3*S*,4*S*)-4-Methyl-3-heptanol (**156**), a component of the pheromone of the elm bark beetle *Scolytus multistriatus*, was simply prepared from (*s*)-pinanediol propylboronate (**153**).[116] The chiral director was chosen

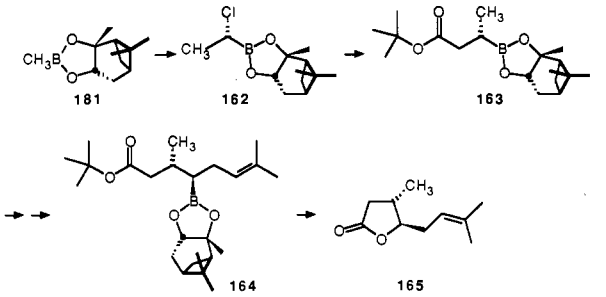


so that **155** would have the correct configuration at the α-carbon, which becomes the alcohol in **156**. The order of connection of the propyl and methyl groups to make precursor **154** was dictated by the choice of chiral director.

exo-Brevicomin (**160**), the aggregation pheromone of the western pine beetle *Dendroctonus brevicomis*, was prepared from (*r*)-pinanediol boronic ester **157**.[111,116] Lithium benzyl oxide was used to install the benzyloxy (BnO) group of **158**, and typical further conversions proceeded without difficulty. Intermediate **160**, reported previously as an oil,[140] crystallized.[116]



Eldanolide (**165**), the wing gland pheromone of the African sugar cane borer *Eldana saccharina*, was prepared starting from (*r*)-pinanediol methylboronate (**161**). Although the (1-chloroethyl)boronic ester **162**



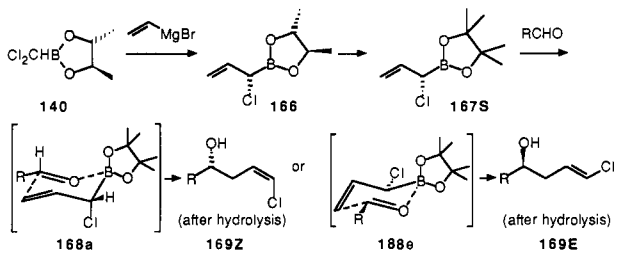
contained 4–5% diastereomeric impurity, the product **163** from reaction with lithium *tert*-butyl acetate was a low-melting solid and was purified to ~98% before proceeding with the synthesis. Introduction of the allylic group of **164** with prenylmagnesium chloride proceeded without detectable allylic rearrangement. The final steps, peroxidic oxidation and acidic lactonization, proceeded routinely.[111]

E. Homoallylic Alcohol Synthesis

The reaction of allylic boronic esters with aldehydes has been noted in sections II.E[55,56] and III.C,[74-77] where α-halo boronic esters were used in the geometrically controlled synthesis of achiral allylic groups. In this section, Hoffmann's use of chiral α-haloallylic boronic esters is discussed briefly.

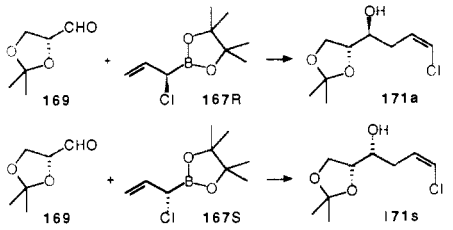
The reaction of pinacol (dichloromethyl)boronate or (dibromomethyl)boronate with vinylmagnesium bromide was used to make model racemic (α-haloallyl)boronic esters, which were found to yield predominantly (*Z*)-halo homoallylic alcohols.[104,105] Attempted conversion of the (α-chloroallyl)boronic ester to the α-methoxy derivative failed for reasons that are not understood. Bromide was displaced by methoxide, and the (α-methoxyallyl)boronate was found to be thermally unstable. [α-(Alkylthio)allyl]boronic esters were also prepared and found to have ordinary stability.[105]

For an enantioselective synthesis, (*R*,*R*)-2,3-butanediol (dichloromethyl)boronate (**140**) reacted with vinylmagnesium bromide to produce the (α*S*)-(α-chloroallyl)boronate **166** in 90–93% de.[105,141] The butanediol

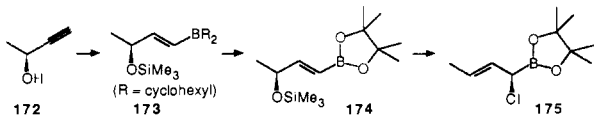


ester failed to yield satisfactory stereoselection in the reaction with aldehydes and was therefore converted to the pinacol ester **167S**. With **167S** and aldehydes the transition state **168A** having the chlorine axial is favored over the alternative **168e** with equatorial chlorine. The major product after hydrolysis of the initially formed borate ester is thus the (*Z*)-chloroalkene **169Z**, which has its absolute configuration as well as its geometry fixed by transition state **168a**. The minor product is the *E* isomer **169E**, which has the opposite absolute configuration.

The Z/E selectivity of this process is insensitive to the R groups, ranging from 93:7 to 96:4 for the series R = CH_3, C_2H_5, C_6H_5, $CH(CH_3)_2$.[141] The directing power of the reaction is sufficient to overcome the influence of chirality already present in the aldehyde. For example, reaction of acetone glyceraldehyde **170** with the enantiomer of **167**, a favorably matched pair, produces anti diastereomer **171a** with a 98.5/1.5 Z/E ratio, and **170** with **167** itself, a mismatched pair, produces syn diastereomer **171s** with an 86/14 Z/E ratio.[120]



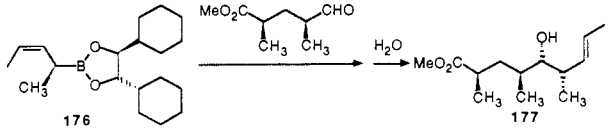
This chemistry has been extended to the (α-chlorocrotyl)boronate **175**, but it has been necessary to prepare **175** in a totally different manner. Attempts to



react propenyl Grignard reagents with (dichloromethyl)boronate **142** resulted in allylic isomerization and epimerization when zinc chloride was used and low chiral induction when it was not. Instead, acetylenic alcohol **172** has been resolved, silylated, and hydroborated with dicyclohexylborane to **173**, oxidized to the alkenylboronic ester with trimethylamine *N*-oxide and transesterified to **174**, and finally treated with thionyl chloride to provide enantiomerically pure **175**.[142-144] Reactions of **175** with aldehydes tend to be highly stereoselective, generally yielding only ~5% E isomer, which is separable by chromatography so that derivatives having high ee and de can be obtained.[144]

(α-Methoxycrotyl)boronic esters have been found to give even higher stereoselectivities in the reaction with aldehydes than does the chloro compound **175**. The methoxy derivative is simply prepared by treating **175** with a suspension of lithium methoxide in THF.[145] This successful displacement contrasts with the failure of the same reaction with pinacol (α-chloroallyl)boronate itself.[105]

For the preparation of an (α-methylcrotyl)boronic ester (**176**) the problem of allylic isomerization and epimerization was circumvented by proceeding via the (1-chloroethyl)boronate (**148**, see section V.B), which was treated with [(*Z*)-1-propenyl]lithium to make **176**, which was converted to >95% diastereomerically pure homoallylic alcohol **177**, a key intermediate in the total synthesis of the macrolide antibiotic mycinolide.[124]

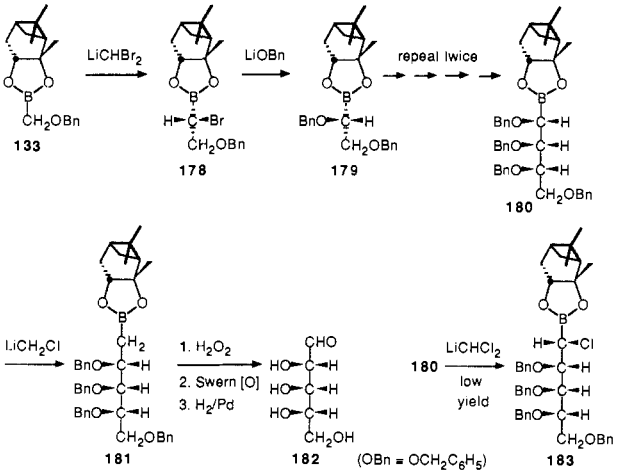


F. Ribose

L-Ribose (**182**) has provided a test of the limits of synthetic applicability of α-halo boronic ester chemistry in a system with a series of oxygen substituents. The synthetic strategy is straightforward, but a number of innovations in practical techniques had to be made in order to carry it out successfully.[106] Some of these have been covered in earlier sections, for example, the preparation of diisopropyl (chloromethyl)boronate (**106**) from (chloromethyl)lithium (section III.D),[79] which served as the practical source of (*s*)-pinanediol [(benzyloxy)methyl]boronate (**133**) (section V.B). The conversion of **133** to the α-chloro boronic ester **134** has already been noted as giving mediocre stereoselection (de 85%), but a worse problem was that the yields of α-chloro boronic esters declined as the chain length increased.

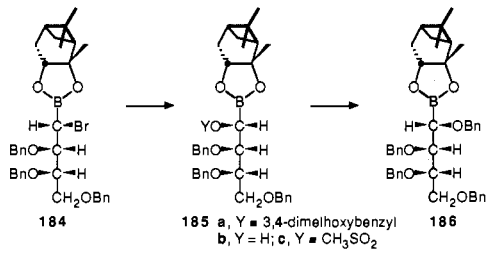
Changing to the α-bromo boronic ester series (**178**) solved the problem. The diastereoselection for **178** was improved somewhat to ~92% de, and the yields in the benzyl oxide displacement steps leading to **179** and its homologues were also improved, so that intermediate **180** could be prepared in 37% yield based on **133**.[106]

An impasse was reached at **180** in that the reaction with (dibromomethyl)lithium failed altogether and that with (dichloromethyl)lithium produced only 14% of intermediate **183**. Thus, the way to hexoses is blocked



until the reasons for the difficulty can be investigated. A makeshift solution to the ribose synthesis was found via the reaction of **180** with (chloromethyl)lithium to form **181** (36%), which was deboronated to the primary alcohol, oxidized to the aldehyde by Swern's method, and deprotected to form L-ribose (**182**) in nearly quantitative yield. No impurity was detectable by 200-MHz ^1H NMR analysis of the ribose obtained.[106]

In order to make any pentose other than ribose by the method just described, it would be necessary to install a carbon with the opposite chirality. Known cleavage of pinanediol esters occurs under conditions incompatible with retention of the benzyloxy protecting groups.[109,115] Therefore, a double inversion sequence was devised, illustrated by the conversion of α-bromo boronic ester **184** to benzyloxy boronic ester **186**, a diastereomer of the ribose intermediate **181**.[132] Reaction with lithium 3,4-dimethoxybenzyl oxide yielded **185a**, which was deprotected [131] to the α-hydroxy boronic ester **185b** and converted to the methanesulfonate **185c**, which was treated with lithium benzyl oxide to form **186**. Comparison of diastereomers **180** and **186** by proton NMR indicated each was free of the other to the limits of detectability.[132]



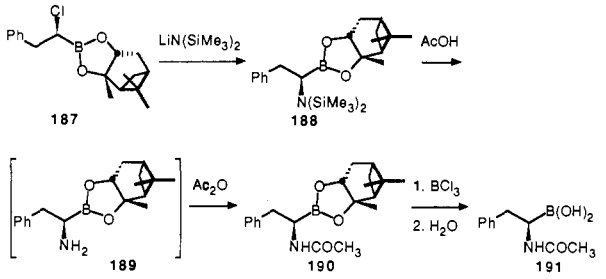
184 185 a, Y = 3,4-dimethoxybenzyl b, Y = H; c, Y = CH_3SO_2 186

G. Amino Boronic Acids

Amino boronic acids and their derivatives have interesting properties as enzyme inhibitors.[126] It was initially expected that reaction of ammonia or an amine with an α-halo boronic ester would form an α-amino boronic ester. This expectation was realized for an *N,N*-dimethylamino boronic ester the first time it was tried (section III.A).[64] However, ammonia did not behave in the same way, and even *N*-metalated amides failed to provide the expected amido boronic esters, yielding *O*-linked derivatives instead.[86]

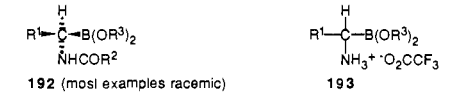
It was not until reaction with a seemingly improbable base, lithiohexamethyldisilazane, was tried that a successful amino boronic ester synthesis was achieved.[126] Even then, amino boronic esters decomposed to amines and esters of boric acid during attempted purification. Prompt acylation yielded stable amido boronic esters that were easily purified, though the first example, ethylene glycol (1-acetamido-2-phenylethyl)boronate, unexpectedly proved so water soluble that it was not extracted into ether from water.[126,127] In view of this extreme water solubility and the fact that the *O*-linked imido boronic ester isomers are insoluble solids isolated in variable yields,[65,127] there is a strong possibility that the amido boronic esters can in fact be major products from the reaction of *N*-lithio amides with α-halo boronic esters, but this question has not been examined.

The first α-amido boronic acid synthesis was that of [(1*R*)-1-acetamido-2-phenylethyl]boronic acid (**191**), the analogue of *N*-acetyl-L-phenylalanine.[126,127] The requisite α-chloro boronic ester **187** with lithiohexamethyldisilazane yielded **188**, which was desilylated to **189** with acetic acid and acetylated in situ with acetic anhydride to form **190**. Cleavage of the pinanediol with boron trichloride[109] followed by hydrolysis yielded the amido boronic acid **191**. As had been anticipated, **191** strongly inhibits chymotrypsin, presumably by stabilizing an enzyme substrate complex resembling the transition state for amide hydrolysis, but with tetracoordinate boron in place of the amide carbon.[126]



187 188 189 190 191

Subsequent to this synthesis, a number of other amido and amino boronic acids summarized by **192** have been prepared by similar routes.[66,115,145-151] Most often, racemic compounds have been used for test purposes.

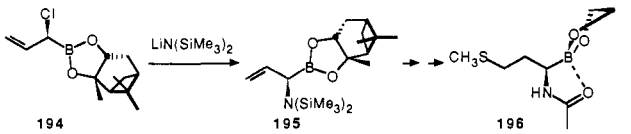


192 (most examples racemic) 193

Kettner and Shenvi have synthesized **192** having R^1 = CH_3, $(CH_3)_2CH$, or $PhCH_2$, R^2 = MeOSucc-Ala-Ala-Pro-, and R^3 = H.[145] These proved to be excellent inhibitors of leucocyte elastase and pancreatic elastase, with dissociation constants in the nanomolar range, as well as cathepsin G and chymotrypsin. Simpler **192** (R^1 = (*S*)-EtMeCH, other alkyl, or phenyl; R^2 = CH_3; R^3 = H) have been prepared by Kinder and Katzenellenbogen and have also been found to inhibit elastase and chymotrypsin.[146] It was also found that α-amido boronic acids are converted by aqueous hydrofluoric acid to stable, crystalline BF_2 derivatives.[146] Shenvi has shown that free α-amino acids or esters can be isolated as stable trifluoroacetate salts (**193**) and that purified free amino boronic acids can survive several days in water at pH 7 with negligible loss.[147]

Syntheses of **192** with R^1 = alkyl or benzyl have been largely routine, but some more complicated structures have required a bit of new boron chemistry for their syntheses. For R^1 = $Br(CH_2)_3$, allyl bromide was hydroborated with catecholborane, and the resulting (3-bromopropyl)boronic ester was transesterified with pinanediol and converted to the α-chloro boronic ester.[115] The remote bromine does not compete with the α-chlorine in the displacement with lithiohexamethyldisilazane.

The *N*-acetylmethionine analogue, **192** with R^1 = $CH_3SCH_2CH_2$, R^2 = CH_3, and R^3 = H, required testing of several routes in order to complete the synthesis.[149] Attempted reaction of (dichloromethyl)lithium with $CH_3SCH_2CH_2B(OR)_2$ failed or gave poor yields,[149] in contrast to the successful reaction with the [2-(hexylthio)ethyl]boronic ester.[111] However, reaction of pinanediol (α-chloroallyl)boronate (**194**) with lithiohexamethyldisilazane proceeded normally to provide **195**,[149] in contrast to the reported failure of alkoxide to yield displacement product with (α-chloroallyl)boronic esters (section V.E),[105] a failure that has been repeated in our laboratory. Conversion of **195** to the acetamido derivative was followed by radical addition of methanethiol to the vinyl group and cleavage of the pinanediol with boron trichloride to produce the boronic acid analogue of *N*-acetylmethionine, which was difficult to purify but yielded a crystalline ester **196** with ethylene glycol.



194 195 196

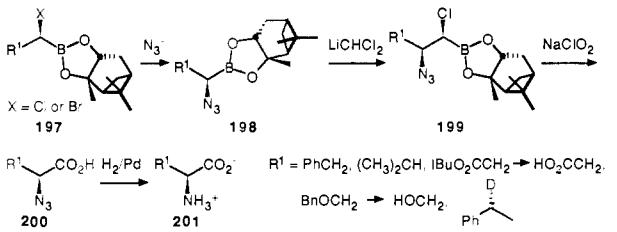
An X-ray structure of **196** revealed two principal features of interest, internal coordination of the amide oxygen to the weakly acidic boron atom and a chiral twist in the 1,3,2-dioxaborolane ring.[149] The O–C–C–O dihedral angle is 17°, which is exaggerated for clarity in the drawing. The internal coordination provides a rationale for the high water solubility of α-amido boronic acids[127] as well as the stability of the BF_2 derivatives.[146] The chiral twist would be enhanced and directed by chiral substituents and provides a basis for the chiral inductions that have been observed.

Several other enzyme inhibition studies have been reported. The enantiomer of **192** (R^1 = $(CH_3)_2CHCH_2$;

R^2 = CH_3; $(OR^3)_2$ = pinanediol (the analogue of D-leucine))[115] was a more active inhibitor of *Bacillus cereus* β-lactamase than **192** itself.[150] The enzyme study was conducted in an aqueous borate buffer, in which the pinanediol transesterifies to boric acid and generates free **192** (R^3 = H). The racemic alanine analogue $CH_3CH(NH_2)B(OH)_2$ has been prepared as the hydrolytically labile *N*-bis(trimethylsilyl) diisopropyl ester derivative and has been found to inhibit *Bacillus stearothermophilus* alanine racemase and *Salmonella typhimurium* D-alanine:D-alanine ligase.[151] Preparation of **192** with R^1 = $Br(CH_2)_3$ and R^2 = an appropriate polypeptide followed by conversion of R^1 to the methoxy derivative has yielded a potent thrombin inhibitor.[152] Peptide derivatives prepared by Kettner and Shenvi have been found effective against elastase-induced emphysema in hamsters,[153] and the kinetics and mode of their binding to enzymes have been studied.[154]

H. Amino Acid Synthesis

An asymmetric amino acid synthesis has been carried out as summarized by the conversion of **197** to **201**.[128,130]



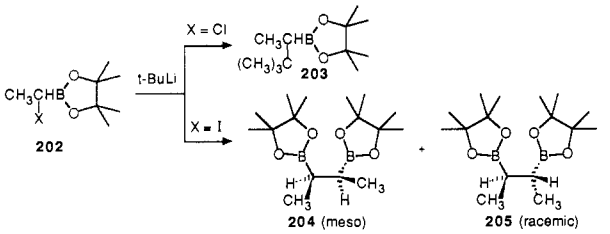
The conversion of α-halo boronic esters **197** to α-azido boronic esters **198** was carried out with a large excess of azide and a phase-transfer catalyst in dichloromethane and water in order to suppress competing epimerization of the α-halo boronic ester by the halide liberated in the reaction.[111] Except where R^1 = benzyl, the reaction of α-chloro boronic esters proved to be so sluggish that there was danger of generating diazidomethane, and α-bromo boronic esters were used. Conversion of **198** to **199** was carried out as described previously.[111] Attempted oxidation of **199** with hydrogen peroxide yielded what appeared to be a peroxide adduct of the aldehyde, as has been observed previously,[106] and attempted further oxidation failed. However, sodium chlorite, which has been used previously to oxidize aldehydes to carboxylic acids,[155] directly converted **199** to the α-azido acids **200**, which were conventionally reduced to the amino acids **201** and deprotected if necessary.[128] The enantiomeric purity of the amino acids was shown to be 92–96%.

Chirally deuterated phenylalanine was prepared via reduction of (*s*)-pinanediol (α-chlorobenzyl)boronate (**127**, section V.C) with lithium triethylborodeuteride.[130] The chiral selectivity was verified by oxidizing the deuterated benzylboronic ester to asymmetrically deuterated benzyl alcohol.

I. Convergent Coupling of Two Chiral Segments

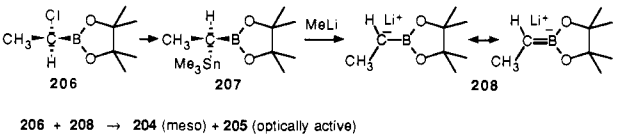
1. An α-Lithio Boronic Ester. A limitation of the synthesis with boronic esters and (dichloromethyl)lithium is that repetition in order to assemble a sequence of chiral carbons ultimately leads to diminishing yields. If larger molecules are to be constructed by this technique, a means of converting an α-halo boronic ester to a carbanion so that it can be joined to another α-halo boronic ester is needed. The first exploration in this direction was the synthesis of an α-lithio boronic ester.

Reaction of pinacol (1-chloroethyl)boronate (**202** (X = Cl)) with *tert*-butyllithium yielded the expected alkyl substitution product **203**, but pinacol (1-iodoethyl)-



boronate (**202** (X = I)) under the same conditions yielded the diastereomeric coupling products **204** and **205**, presumably via an α-lithio boronic ester.[129] However, no conditions tested allowed generation of the α-lithio boronic ester from **202** without simultaneously coupling it to **202**.

An α-trimethylstannyl boronic ester (**207**) was found to be a satisfactory source of the α-lithio ester (**208**). Transesterification of the (*R*,*R*)-2,3-butanediol ester with pinacol yielded optically active **206**, which with



206 + 208 → 204 (meso) + 205 (optically active)

(trimethylstannyl)lithium yielded **207**. Methyllithium converted **207** to tetramethyltin and the α-lithio boronic ester **208**, which with **207** yielded an optically active version of the same mixture of diastereomers **204** and **205** obtained from the coupling of **202** (X = I) with *tert*-butyllithium. Since it is improbable that **206** would racemize under the reaction conditions used, this result indicates that the lithio boronic ester **208** does not retain its configuration, as if it is the planar carbanion indicated.[129] Although the boron-stabilized carbanion is interesting from a theoretical point of view, it has limited synthetic utility.

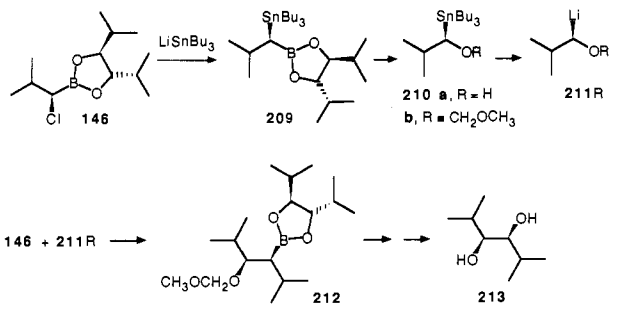
It was also shown that α-lithio boronic ester **208** reacts with a different α-halo boronic ester and with an aldehyde to form the expected products.[129]

2. Stereospecific Coupling of Chiral Carbons. For purposes of stereocontrolled coupling, α-chloro boronic esters have been converted to α-hydroxy tin compounds, one of which had been resolved previously by Still and Sreekumar and shown to be convertible to an α-lithio ether ith full retention of configuration.[156] Conversion of α-tributylstannyl boronic ester **209** to the corresponding α-hydroxy tin compound **210** and on to (*R*)-α-lithio ether **211R** has recently been accomplished.[123] Several problems had to be soleved in order to make **211R** efficiently and couple it to an α-chloro boronic ester.

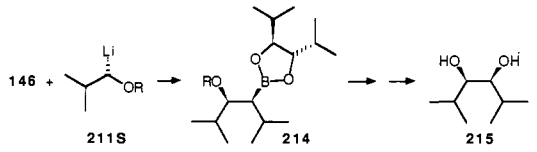
It was found that pinanediol esters are too hindered to serve as sources of α-hydroxy tin compounds, the peroxidic deboronation being very sluggish, but that "DIPED" esters work very well. Coupling of an α-lithiobutyl ether with an (α-chlorobutyl)boronic ester proceeded easily, but the same reaction gave low yields when first tested with branched reactants **146** and **211**,

and much tributylstannyl ether **210b** was recovered. It was finally discovered that the reaction of butyllithium with **210b** is reversible, and the sterically hindered boronic ester **146** reacts faster with the small equilibrium concentration of butyllithium than with **211R** at −78 °C, but by mixing the reactants at −100 °C this problem can be overcome.

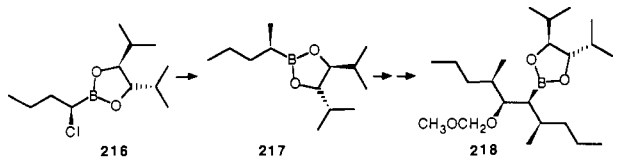
Coupling of **211R** with **146** yields **212** in high diastereomeric purity. Peroxidic deboronation and hydrolysis of the methoxymethyl ether yielded **213**, the same "(*S,S*)-DIPED" used as the chiral director, chosen as an initial target because it would be easy to identify unequivocally.[123]



In order to confirm the diastereomeric purity (and consequently the enantiomeric purity) of **212** and **213**, the lithio ether **211S** (enantiomer of **211R**) was coupled with **146** to make diastereomer **214** and *meso*-DIPED (**215**).



Finally, to demonstrate that more than two chiral carbons could be assembled in this manner, DIPED (1-chlorobutyl)boronate (**216**) was elaborated via **217** and additional manipulations to provide the coupled product **218** containing four chiral centers.[123]



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(107) The *Chemical Abstracts* name for "(*s*)-pinanediol" is [1*S*-(1α,2β,3β,5α)]-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol. A trivial name such as [1*S*-(1α,2β,3β,5α)]-pinanediol, (1*S*,2*S*,3*R*,5*S*)-pinanediol, or (*S*)-$\alpha\beta\beta\alpha$-2,3-pinanediol could distinguish this from isomers. However, the pinanediol moiety is completely renamed by *Chemical Abstracts* when it is esterified with a boronic acid. For example, (*s*)-pinanediol (*S*)-(chlorophenylmethyl)boronate (**127**) is named [3a*S*-[2(*R**),3aα,4β,6β,7aα]]-2-(chlorophenylmethyl)hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole. The permuted numbering makes the ring chiral centers (3a*S*,4*S*,6*S*,7*R*), but *Chemical Abstracts* nomenclature chooses a single chiral center to specify absolute configuration and defines all the rest in a relative sense by descriptors α and β for rings and *R** and *S** for open chains. The designation of the side-chain chirality as "2(*R**)" means that if this were the enantiomer in which index carbon 3a is *R*, the 2-(chlorophenylmethyl) substituent would also be *R*, but in this case carbon 3a is *S*; therefore the side chain at position 2 is *S*. What the foregoing discussion probably clarifies best is the reason for using trivial names backed by structure drawings.
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(139) A referee has suggested that the term "chiral center" should be replaced by "stereogenic center" in the light of the philosophical comment by Mislow and Siegel,[138] "...it is advisable to abandon expressions such as 'center of chirality'...". However, "stereogenic" also refers to geometric isomers, for example, the CHCl groups of 1,2-dichloroethene.[138] Thus, "stereogenic center" is insufficient to specify a tetrahedral carbon bearing four different ligands. "Chiral[ly stereogenic] center" is definitive, but the syllables in brackets in no way alter what is included in the set of items referred to. All tetrahedral stereogenic centers are chiral,[138] and in the ordinary context of organic synthesis there is no ambiguity in the terms "chiral center" or "chiral carbon". This terminology may well have descended via the illegitimate branch of etymology, but these useful, succinct, well-established terms have been used in this review with the expectation that all readers know what they mean.
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