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Boronic Esters in Stereodirected Synthesis

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1. INTRODUCTION

The chemical stability of boronic acids [$R^1B(OH)_2$] and their esters [$R^1B(OR^2)_2$], and the favorable steric properties of the latter, make them outstanding reagents for asymmetric synthesis as well as for geometrically controlled olefin synthesis. Boronic acid analogues of natural substrates can function as enzyme inhibitors, and stereoselective syntheses of some examples will also be described briefly in this review.

The useful properties of boron derive from its close relationship to carbon, from which it differs by lack of one nuclear charge. Boron can fit into organic compounds as a heteroatom as easily as can nitrogen or oxygen, and the first compounds containing carbon boron bonds date from 1860.[1] These included triethylborane [$(C_2H_5)_3B$], a spontaneously flammable liquid, and ethylboronic acid [$C_2H_5B(OH)_2$], an air stable solid having a sweet taste. Several syntheses of boronic acids were reported in the subsequent century.[2] The best were based on the reaction of trialkyl borates [$B(OR)_3$] with Grignard reagents.[3,4]

Boronic acids remained laboratory curiosities until the recent development of synthetic organoborane chemistry, perhaps because there are no known natural products which contain a boron-carbon bond. Biological reduction of borates would require an excessively large energy input. The boron-oxygen bond is 30-40 kcal/mol (125-165 kJ/mol) stronger than the boron-carbon bond.[5] Boron does occur chelated solely by oxygen in the antibiotics boromycin[6] and aplasmomycin,[7] and boric acid is an essential micronutrient for plants.[8]

Boronic acids and esters are convenient laboratory reagents, generally stable in air, easy to manipulate, and not particularly toxic. Reversible exchange between $RB(OR^1)_2$ and R^2OH to form $RB(OR^2)_2$ and R^1OH is usually very rapid, and acyclic boronic esters must be protected from moisture. However, sterically hindered cyclic boronic esters, the most useful synthetic intermediates, are not easily hydrolyzed and can be chromatographed, extracted, or distilled in the manner of typical organic compounds. The general properties of boronic esters have been reviewed in more detail elsewhere.[2]

Much boronic ester chemistry has antecedents or analogues in trialkylborane chemistry, which will not be reviewed here. Those reactions of trialkylboranes which cannot utilize all three alkyl groups are inapplicable to boronic esters, which are generally less reactive. Otherwise, an advantage of boronic esters or acids is that the single organic group is totally differentiated chemically from the alkoxy ligands, so that the carbon-boron linkage can be utilized very efficiently. In addition, their stability generally allows rigorous purification.

2. SYNTHESIS OF BORONIC ACIDS AND ESTERS

2.1. From Grignard or Lithium Reagents. The classical synthesis of boronic acids (**1**) from Grignard reagents and trialkyl borates[2-4] has been updated to an efficient Organic Syntheses preparation of phenylboronic acid.[9] This procedure is applicable to making a wide variety of boronic acids in mol and larger quantities.

$$RMgX + B(OCH_3)_3 \longrightarrow RB(OCH_3)_3^- \xrightarrow{H_3O^+} \underset{\mathbf{1}}{RB(OH)_2}$$

A recent useful variant of the classical approach utilizes an organolithium reagent and triisopropyl borate, followed by acidification with anhydrous hydrogen chloride to form the diisopropyl organylboronate (**2**) directly.[10] Triisopropyl borate was shown to be the best of the available alkyl borates for this purpose. Yields are often 90%.

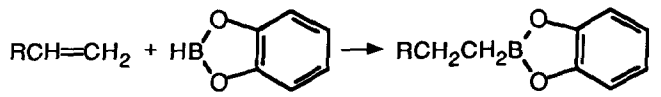
$$RLi + B(O\text{-}iPr)_3 \longrightarrow RB(O\text{-}iPr)_3^- Li^+ \xrightarrow{HCl} \underset{\mathbf{2}}{RB(O\text{-}iPr)_2} + iPrOH \qquad [iPr = CH(CH_3)_2]$$

Aryl Grignard reagents formed in the presence of borane-THF at 0-25 °C yield $ArBH_3^-$, which with acid yields $ArB(OH)_2$.[11] Sonication allows this process to be carried out even in the presence of a free amino substituent.[12]

Lithium reagents are presumably intermediates in the synthesis of tetrakis(dimethoxyboryl)methane (**3**) and related compounds.[13]

3

2.2. Via Hydroboration. Hydroboration with excess diborane followed by alcoholysis of the BH_2 group can yield boronic esters,[14,15] but the preferable approach is to use a borane that is already in the right oxidation state. Catecholborane (**4**),[16] dithiaborolane (**5**),[17] and dibromoborane-dimethyl sulfide (**6**)[18] are particularly effective reagents.



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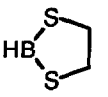

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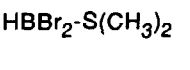
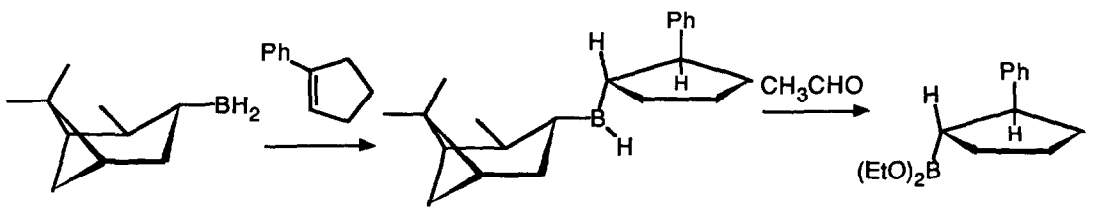


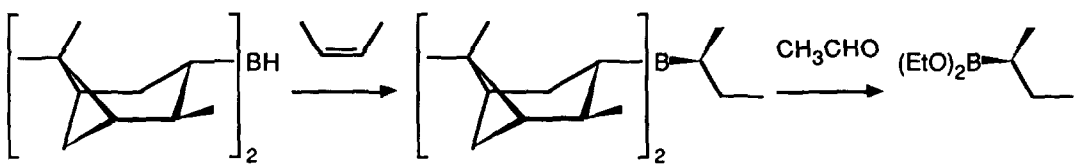
6

A recent discovery of considerable potential is hydroboration with catecholborane at 25 °C in the presence of Wilkinson's catalyst.[19] Hydroboration with catecholborane catalyzed by $Rh(PPh_3)_3Cl$ and related species differs significantly from conventional hydroboration in regio- and stereoselectivity.[20] These reactions have been carried out in the context of hydroboration/oxidation and the presumed boronic ester intermediates have not been isolated.

Chiral organoboranes (**8** or **11**) derived from hydroboration with isopinocampheylborane (**7**) or diisopinocampheylborane (**10**) react with acetaldehyde to form chiral diethyl alkylboronates (**9** or **12**).[21] Crystallization of the borane intermediates can often lead to boronic esters having very high enantiomeric purity.[22,23,24]



7 **8** **9**



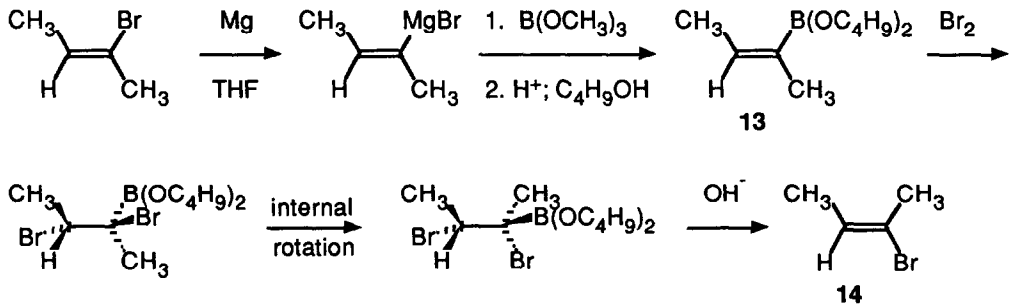
10 **11** **12**

This quick summary of syntheses of boronic esters and acids leaves out several other routes which may be useful for specialized purposes and are reviewed elsewhere.[2]

3. ALKENYLBORONIC ESTERS

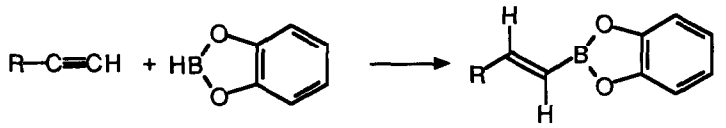
3.1. Preparation and Haloalkenes. Haloalkenes serve as one of several sources of alkenylboronic esters, or an alkenylboronic ester can be converted stereospecifically to a haloalkene of either geometry.

The first stereocontrolled synthesis of alkenylboronic esters involved the reaction of a (*Z*)- or (*E*)-alkenylmetallic with trimethyl borate, as in the synthesis of dibutyl (*E*)-(1-methyl-1-propenyl)boronate (**13**), which had to be fractionated to remove small amounts of the opposite isomer.[25] Bromination followed by treatment with base led to the (*E*)-bromoalkene (**14**), which has inverted carbon skeleton geometry.



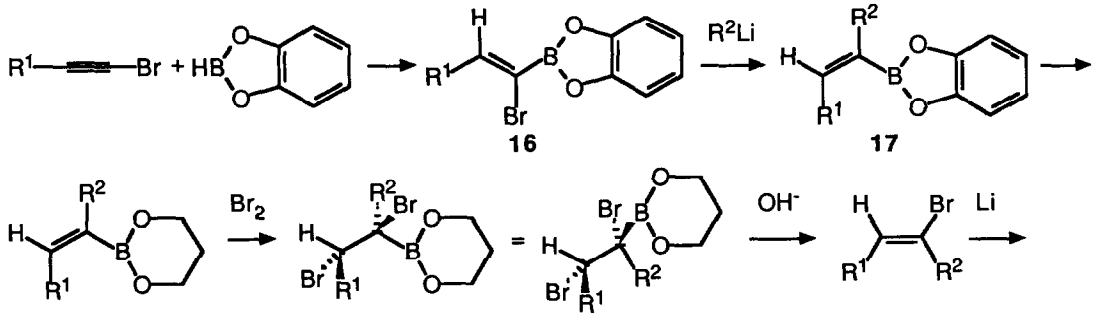
13 **14**

More sophisticated organoborane chemistry can be used to provide any desired pure alkenylboronic ester. The ancestral reaction is hydroboration of an alkyne with catecholborane (**4**), which stereospecifically yields an (*E*)-alkenylboronic ester (**15**).[26] This reaction works best with terminal alkynes as illustrated. It can be used with symmetrical alkynes (RC≡CR), but gives regioisomer mixtures if the R groups differ.

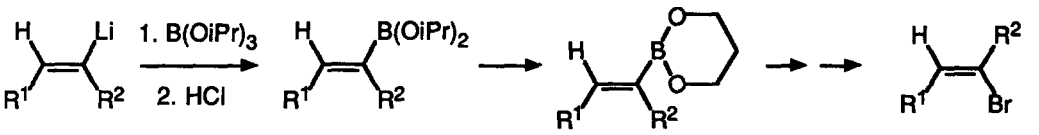


4 **15**

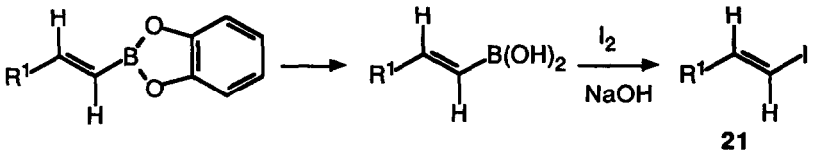
Nonterminal alkenylboronic esters can be made by beginning with hydroboration of a 1-bromo–alkyne to the (*Z*)-(bromoalkenyl)boronic ester **16**.[27] Stereospecific displacement of the α-bromide then inverts the carbon to provide the (*E*)-alkenylboronic ester **17** having arbitrarily chosen R^1 and R^2.[28] Transesterification followed by *anti*-bromination and *anti*-deboronobromination[25] then yields the (*E*)-bromoalkene **18**, which can be converted to the (*E*)-boronic ester **19**.[29] The (*E*)-boronic ester can in turn serve as a source of the pure (*Z*)-bromoalkene (**20**).



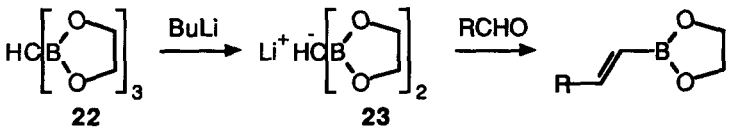
16 **17** **18**

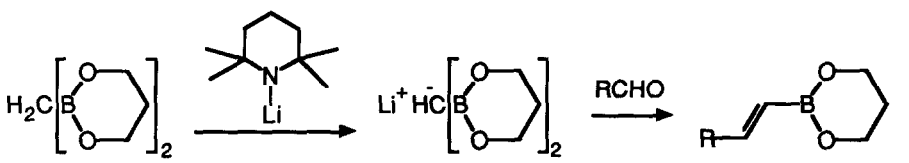


Iodination of (*E*)-alkenylboronic acids in the presence of sodium hydroxide[30] or with chloramine-T/NaI[31] leads to (*E*)-1-iodoalkenes (**21**), opposite the stereochemical result from bromination and base treatment.

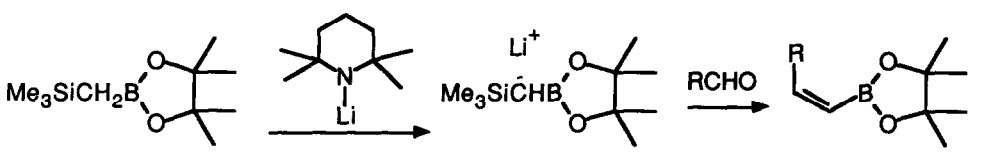


An alternative route to (*E*)-1-alkenylboronic esters is the efficient reaction of aldehydes with lithiodiboryl–methanes (**23** or **25**), which can be made either by deboronation of triborylmethanes[32,33] (**22**) or deprotonation of diborylmethanes[34] (**24**). The (*E*)/(*Z*) isomer ratio is ~20:1. Ketones yield mixtures of isomers.

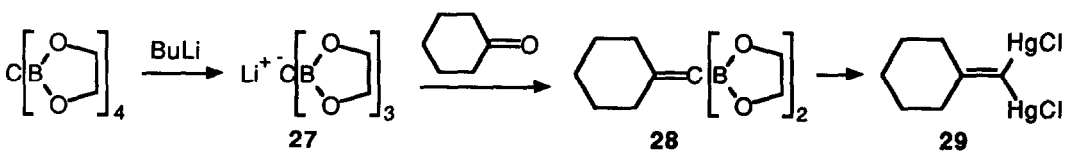




Lithiation of a [(trimethylsilyl)methyl]boronic ester (**26**) results in a reagent which yields predominantly (*Z*)-1-alkenylboronic esters with aldehydes, though the isomer ratio was only ~70/30.[35] The possibility of improving the isomer ratio by changing the boronic ester group or the alkyl groups on silicon was not explored.

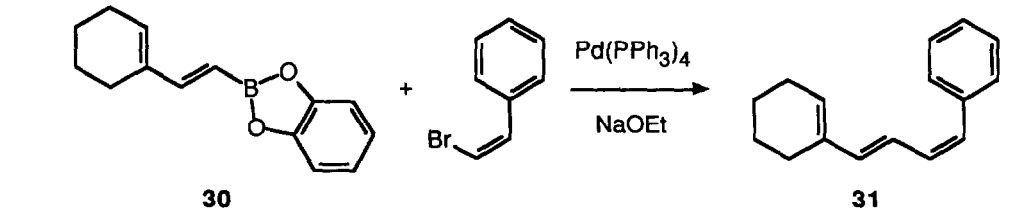


Lithiotriborylmethanes (**27**) with aldehydes or ketones yield 1,1-alkenyldiboronic esters (**28**),[36,37] which have been used as sources of 1,1-bis(chloromercuri)alkenes (**29**).[38]

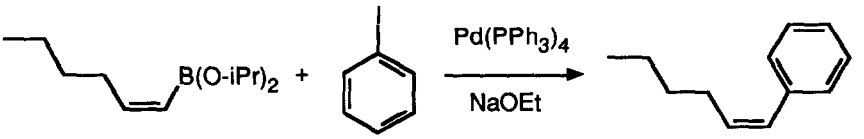


3.2. Diene Synthesis. Palladium(0) catalyzed coupling of alkenylaluminums with aryl or alkenyl halides was first reported by Negishi and Baba, but under the conditions originally used, alkenylboranes failed to react.[39,40] Suzuki, Miyaura, and coworkers have found that alkenylboranes couple stereospecifically with aryl, alkenyl, or allyl halides in the presence of sodium ethoxide and a catalytic amount of tetrakis(triphenylphosphine)-palladium.[41] Only those couplings which have been carried out with boronic esters will be reviewed here. Omitted substrates include allylic halides, which coupled with alkenyldisiamylboranes but gave poor results with catechol boronic esters, apparently for the trivial reason that the catechol ring was allylated in competition with coupling.[42]

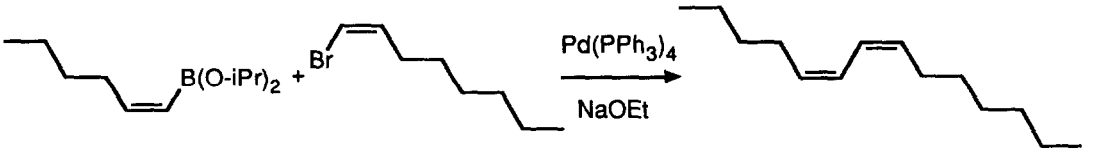
At first, only the (*E*)-alkenylboranes directly available from hydroboration of alkynes were used.[43,44] Alkenylboronic ester **30** with (*Z*)-β-styryl bromide, a typical example, yields 87% of the coupling product **31** in 98% isomeric purity.[45] (*Z*)-Alkenylboronic esters such as **32** have been tested more recently, for example in the synthesis of (*Z*)-alkenylbenzenes (**33**), (*Z*,*Z*)-dienes (**34**), and (*E*,*Z*)-dienes, including the silkworm moth pheromone bombykol (**35**), and have yielded excellent results.[46]



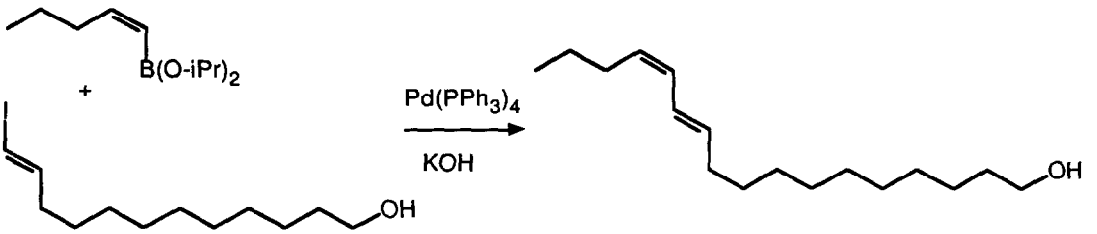
30 **31**



32 **33**



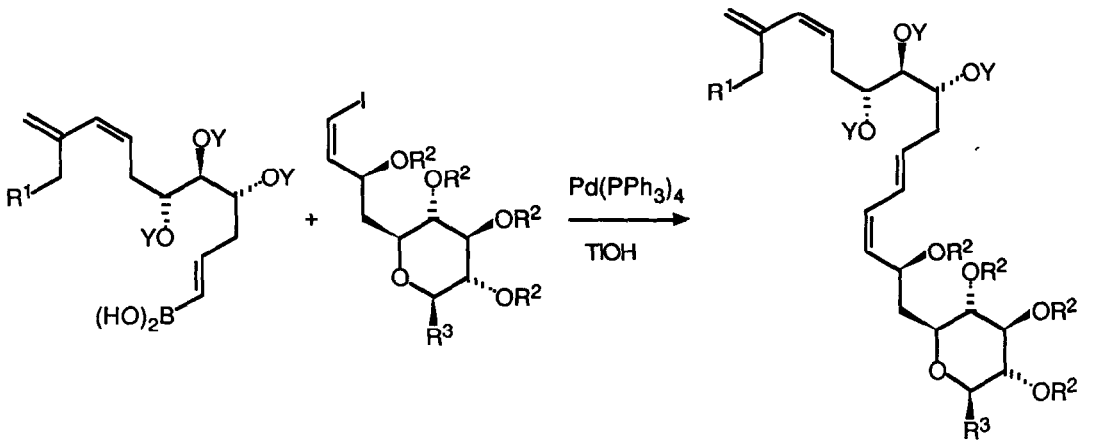
32 **34**



35

Earlier syntheses of bombykol (**35**) and its three geometric isomers had utilized only (*E*)-alkenylboronic esters available from hydroboration of 1-alkynes, and the necessary (*E*)- or (*Z*)-1-haloalkenes were also made from (*E*)-alkenylboronic esters.[47,48]

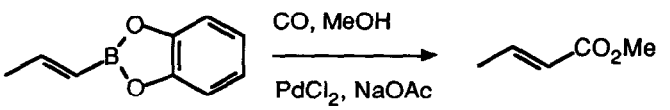
Kishi and coworkers have found that the mechanism of the coupling reaction involves reaction of the haloalkene with the catalyst to form an alkenylpalladium complex, which then reacts with the borane in the rate-determining coupling step. Reaction in the presence of thallium hydroxide is 1000 times faster than with potassium hydroxide, and boronic acids give cleaner results than catechol esters or disiamylalkenylboranes. For model studies, hydroborations of 1-alkynes provided (*E*)-1-alkenylboronic esters, but in order to avoid problems with other alkenyl groups, it was necessary to use the reaction of a lithiodiborylmethane with an aldehyde to prepare the intermediate partially illustrated by **36**. Although the model aldehyde reactions were 90-95% selective as discussed in section 3.1, in this actual application the unwanted (*Z*)-isomer amounted to 15%. The **36** was then coupled with **37** to provide the intermediate **38** containing carbons 52-115 of the carbon skeleton of the marine natural product palytoxin.[49]



36 **37** **38**

(where R^1 is a 29-carbon chain with substituents, R^2 is *p*-methoxybenzyl, R^3 is a 15-carbon chain with substituents, Y is *tert*-butyldimethylsilyl)

3.3. Alkenecarboxylic Esters. In addition to diene couplings, Suzuki and coworkers have shown that carbonylation of alkenylboronic esters can be carried out to make carboxylic esters (**39** and **40**).[50,51] The geometry of the original boronic ester is retained.



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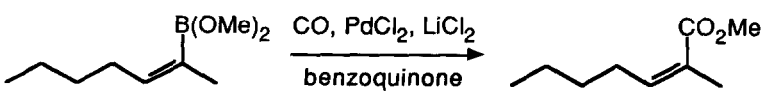

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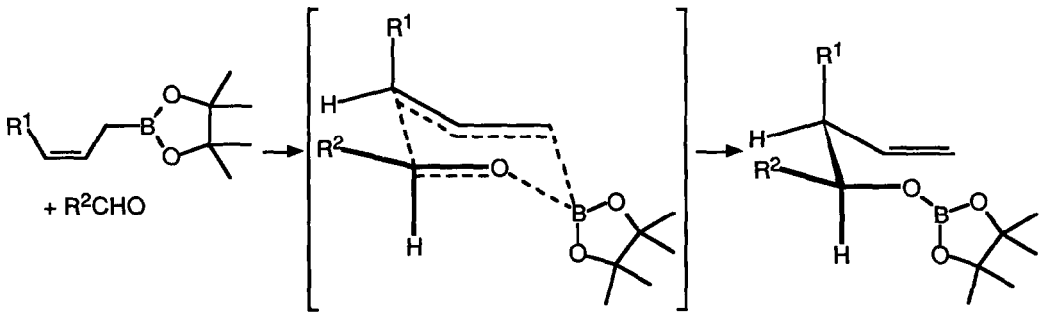
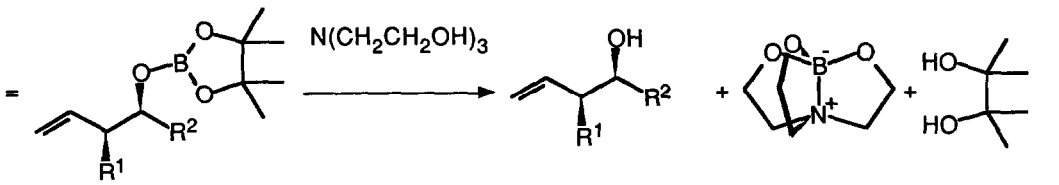
4. ALLYLBORONIC ESTERS WITH ALDEHYDES

4.1. Racemic Model Systems and Diene Synthesis. The first example of allylic rearrangement in the reaction of a crotylborane with an aldehyde was reported by Mikhailov and Pozdnev,[52] but the rapid allylic isomerization of the borane itself, observed by Kramer and Brown,[53] had masked the subsequently discovered fact that the only pathway for reactions of allylic boranes with aldehydes involves allylic rearrangement.[54,55] At low temperatures, allylic isomerization of the borane is frozen out and chiral allylboranes can be useful in chiral synthesis.[56,57]

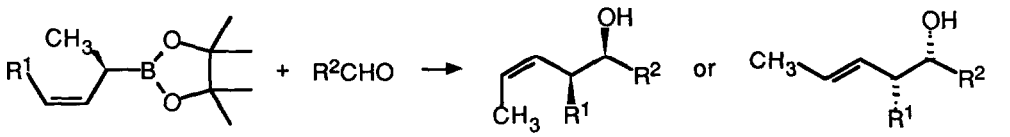
Allylic boronic esters react readily with aldehydes,[58] but are relatively inert toward isomerization. Hoffmann has developed the allylic boronic esters into important synthetic reagents, and has reviewed his work.[59] The mechanism of the reaction with aldehydes may be described as a hetero-Cope rearrangement, illustrated by transition state **41** from a (*Z*)-substituted allylboronic ester. The initially formed borate esters (**42**) are cleaved with triethanolamine to *syn*-homoallylic alcohols (**43**). The *syn/anti* diastereomer ratios range from 80/20 to 95/5, and the ratio is improved by bulky alkyl groups R^2.





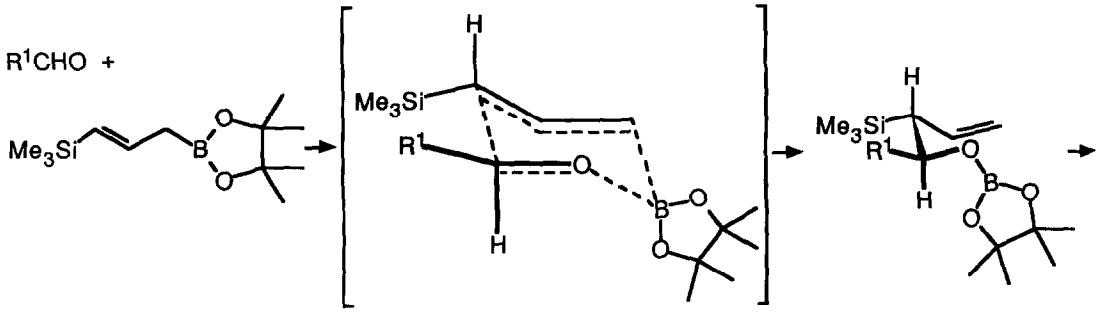
42 **43** (racemic) $R^1 = CH_3$,[60] RO,[61,62] CH_3S[63]

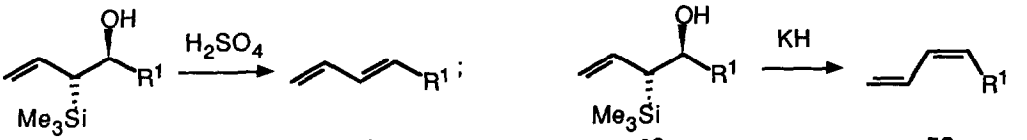
A limitation of Hoffmann's reaction is that an α-substituent on the allylic group as in **44** results in (*Z*)/(*E*)-mixtures (**45** and **46**), with isomer ratios often as unselective as 3:1.[64] For a given chirality of starting material **44**, opposite chiralities of **49** and **50** result as indicated. The mechanism will be discussed in section 4.3 in connection with a homochiral example.



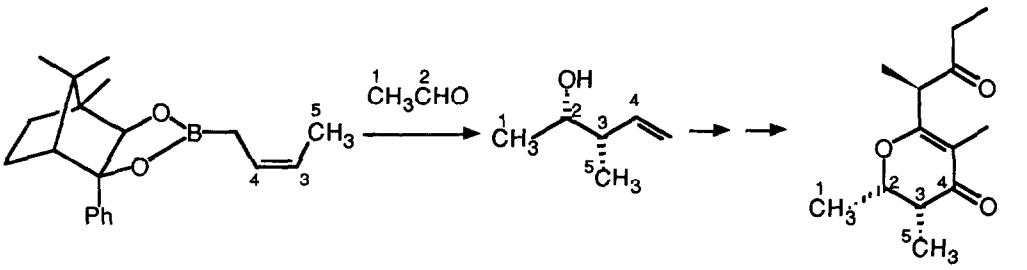
44 **45** **46**

This synthesis is not restricted to (*Z*)-substituted allylic groups. High diastereoselectivity was obtained in the reaction of the (*E*)-[(trimethylsilyl)allyl]boronic ester **47** with aldehydes, and the resulting *anti*-[(trimethylsilyl)-allyl]carbinols (**48**) have been converted to (*E*)-dienes (**49**) or (*Z*)-dienes (**50**) in ≥98% purity.[65]

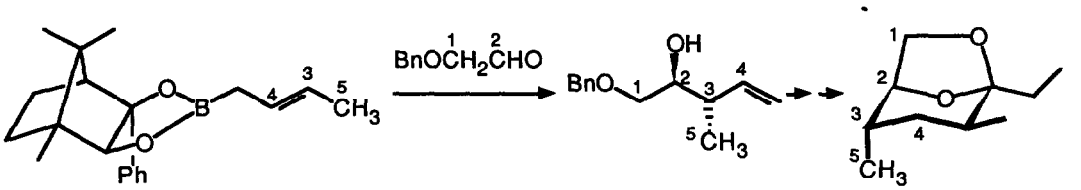




4.2. Chiral Direction with Boronic Esters. Boronic esters of chiral diols such as ester **51** of (+)-phenylbornanediol can lead to substantial enantiomeric excesses (ee's) in the homoallylic alcohol product. For example, intermediate **52** was obtained as 95% of the diastereomer mixture in 70% ee and used in the synthesis of the pheromone of the drugstore beetle, *Stegobium panaceum* (**53**).[66] Crystallization was used in order to obtain enantiomerically pure product, which was 1000 times more active biologically than the racemate.

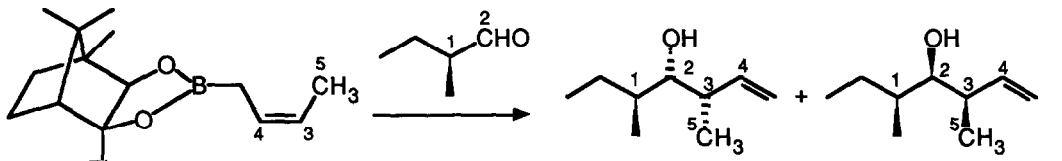


The opposite absolute configuration and the opposite diastereomeric relationship are illustrated by boronic ester **54**, which was converted to intermediate **55** in 95% diastereomeric purity but only 52% ee, then to the multistriatin (**56**), the major component of the aggregation pheromone of the elm bark beetle, *Scolytus multistriatus*.

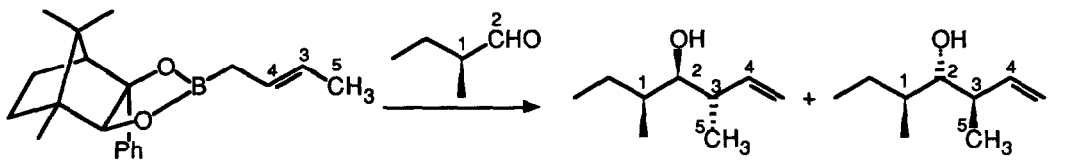


54 (Bn = $C_6H_5CH_2$) **55** **56**

If the chiral boronic ester is paired with a properly matched homochiral aldehyde to take advantage of double stereodifferentiation effects, high diastereomeric ratios of homochiral products result.[67] Examples of matched pairs include the reaction of **51** with aldehyde **57** to form a 95:5 mixture of **58** and **59**, and the reaction of **54** with **57** to produce a 92:8 mixture of **60** and **61**.

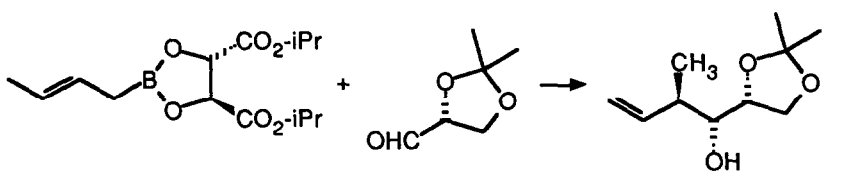


51 **57** **58** (95%) **59** (5%)

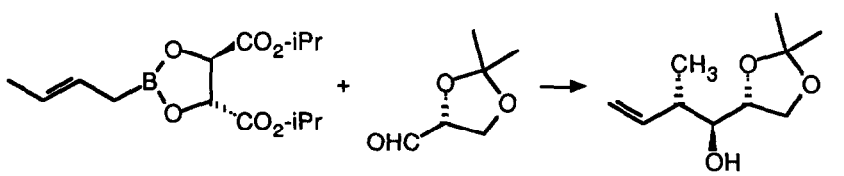


54 **57** **60** (92%) **61** (8%)

Roush and coworkers have found that boronic esters of diisopropyl tartrate (**62** and **65**) yield high diastereoselectivity with chiral aldehydes.[68,69]



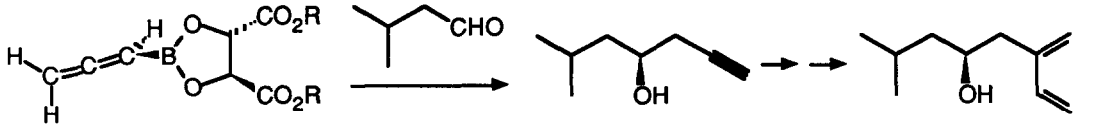
62 **63** **64** (96% of product)



65 **63** **66** (87% of product)

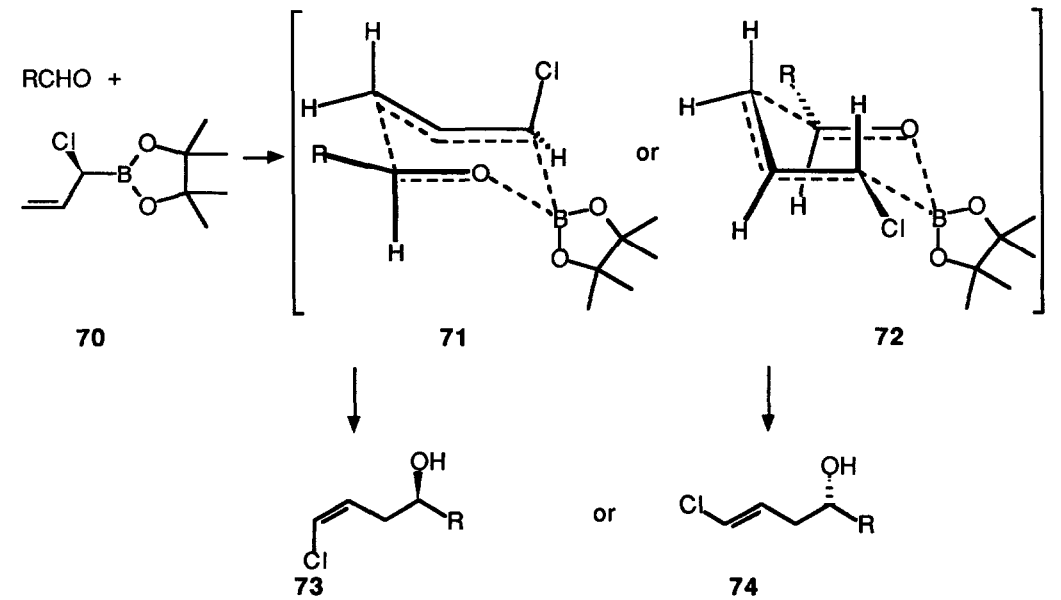
With matched pairs such as **62** and **63**, the diastereomer ratios (96:4 in favor of **64**) are comparable to those obtained by Hoffmann's group with phenylbornanediol esters,[70] and diisopropyl tartrate is a much cheaper reagent. With mismatched pairs such as **65** and **63**, the isomer ratios (87:13 for **66**) are much better than the mixtures obtained from phenylbornanediol derivatives.

Yamamoto's group have found that hindered tartrate esters of allenylboronic acid, a special class of allylboronic esters, can yield very high enantiomeric excesses in reactions with aldehydes.[71,72] For example, **67** with 2-methylbutanal yielded intermediate **68** in 99.6% ee, which was converted to the pheromone (-)-ipsenol (**69**).



67 R = CH[CH(CH3)2]2 **68** **69**

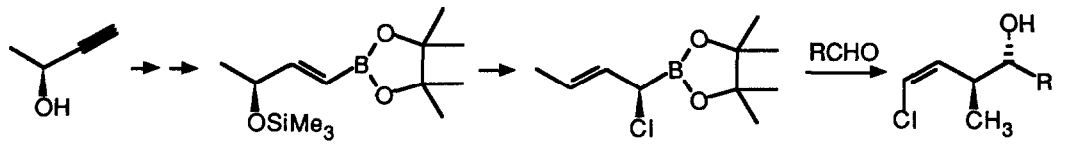
4.3. Homochiral Boronic Esters. Hoffmann's allylboronate reactions have been further improved by the use of homochiral boronic esters. For example, pinacol (1*S*)-1-chloroallylboronate (**70**) was prepared in 92% ee via the chiral CHCl insertion method discussed in section 5. The major pathway (93-96%) leads to (*Z*)-homoallylic alcohols **73**, presumably via transition state **71** with the chlorine axial, with essentially complete chirality transfer.[73] The (*E*)-homoallylic alcohol byproduct **74** presumably arises from transition state **72** with the chlorine equatorial, which leads to the opposite absolute configuration. The diastereomers are separated in order to provide maximum chirality control.



70 **71** **72**

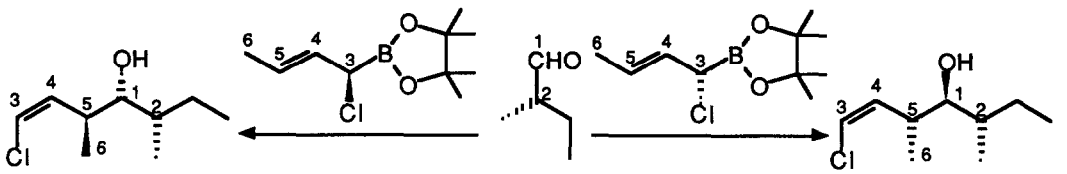
73 **74**

The (1*S*)-1-chlorocrotylboronic ester **76** could not be obtained in good enantiomeric excess from a chiral dichloromethylboronate and (*E*)-1-propenyllithium because of allylic isomerization, and was made instead by a more roundabout route. The homochiral acetylenic alcohol **75** was made by reduction of the corresponding ketone with isopinocampheyl-9-borabicyclononane (Midland's reagent[74]). Silylation and hydroboration of **75** led to **76**, which with thionyl chloride yielded **77**. Achiral aldehydes with **77** yielded (*Z*)-*anti* homoallylic alcohols **78**, 92-96% ee, >95% diastereomeric purity.



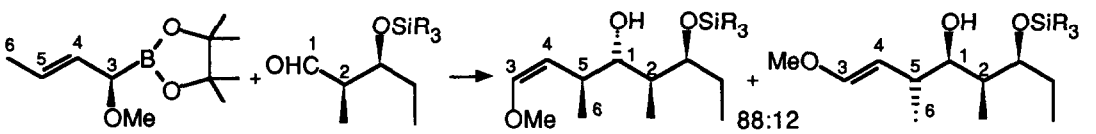
75 76 77 78

With (*S*)-2-methylbutanal (**57**), matched boronic ester **77** yielded diastereomer **79** in 98% purity, and mismatched boronic ester **80** yielded diastereomer **81** in 90% purity.[75]



79 77 57 80 81

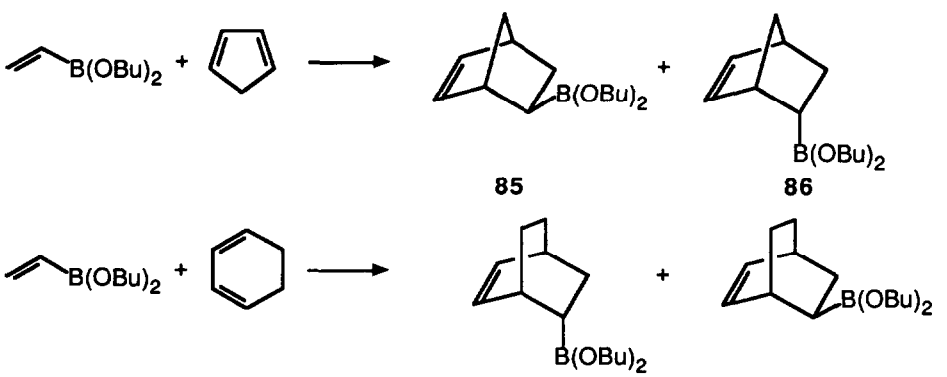
The chloro boronic esters are not selective enough with mismatched chiral aldehydes and yield too much (*E*)-byproduct for synthetic purposes. Displacement of the chloride from **80** with methoxide leads to methoxy boronic ester **81**, which with mismatched aldehydes such as **82** yields useful (*Z*/*E*)-ratios of products such as **83** and **84**.[76] The more selective reagent reacts very slowly, and high pressure (4 kbar) was required for reasonable conversions.



81 82 83 84

5. DIELS-ALDER REACTIONS

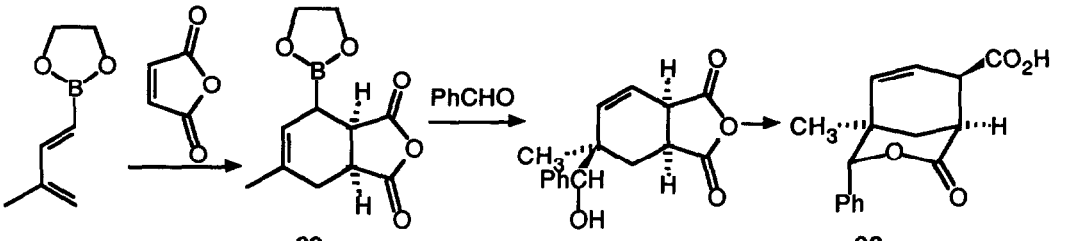
Further work will be required before Diels-Alder reactions of boronic esters will be useful in stereodirected synthesis, but the field is ripe for investigation. Dibutyl vinylboronate with cyclopentadiene yielded 83% of a 61:39 ratio of *exo* product (**85**) to *endo* (**86**), and use of the di-*tert*-butyl boronic ester increased the proportion of *exo* isomer modestly to 73%.[77] With cyclohexadiene, the product was 80% *endo* isomer (**87**) and 20% *exo* (**88**).[78]



85 86

87 88

More recently, the Diels-Alder reaction of maleic anhydride with a butadienylboronic ester has been reported to produce the adduct **89**, which with benzaldehyde yields the transformation product **90** diastereoselectively.[79]



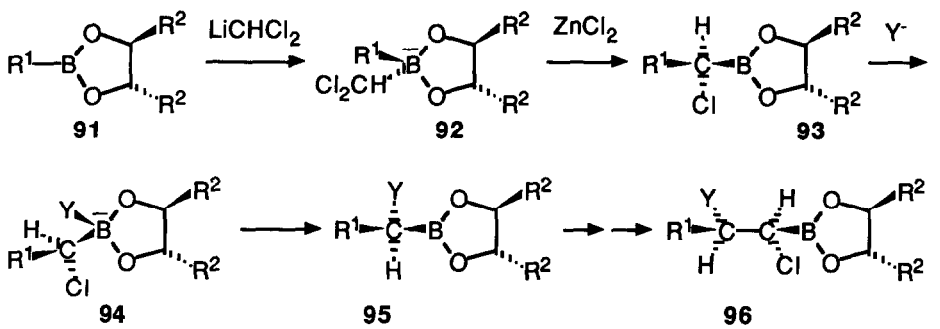
89 **90**

Products **85-90** are all necessarily racemic. The possibility of enantioselective Diels-Alder reactions of boronic esters remains to be explored.

6. α-HALO BORONIC ESTERS

6.1. Chiral CHCl Insertion. The reaction of $LiCHCl_2$ with boronic esters inserts the CHCl group into the carbon-boron bond in excellent yields, and can be chirally controlled to provide one of the most stereoselective syntheses known.[80] Further transformations of the resulting α-chloro boronic esters provide a broad generality of synthetic targets, and a strong case can be made that this is the most generally applicable method of directed chiral synthesis discovered to date.

A generalized example is illustrated by the conversion of chiral boronic ester **91** to the borate salt **92**, which on warming to 0-25 °C in the presence of zinc chloride yields the chiral α-chloro boronic ester **93**. If R^2 in the chiral director is properly chosen, the diastereomeric excess at the newly formed chiral center in **93** is generally 98-99% or better, regardless of R^1. Treatment of **93** with various nucleophiles Y^- leads via borate complex **94** to the α-substituted boronic ester **95**. Since **95** is merely a special case of **91**, provided the Y group is reasonably inert, the process can be repeated to introduce additional chiral centers, as illustrated by **96**.



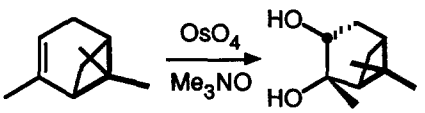
91 **92** **93**

94 **95** **96**

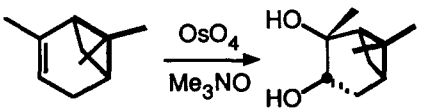
As illustrated, (*S,S*)-diol directing groups always yield (α*R*)-α-chloro boronic esters.

6.2. Pinanediol Esters. Our first results were obtained with a more complex diol, (*s*)-pinanediol (**97**), which was prepared by osmium tetraoxide catalyzed oxidation[81] of (+)-α-pinene.[82,83] The enantiomer, (*r*)-pinanediol (**98**), is also readily available. The signs of rotations of the pinanediols are solvent dependent, and

the (*r*) and (*s*) are mnemonics for the production of (α*R*)- and (α*S*)-α-chloro boronic esters, respectively. As implied by the structure drawings, (*s*)-pinanediol mimics an open chain (*R*,*R*)-diol as a chiral director.

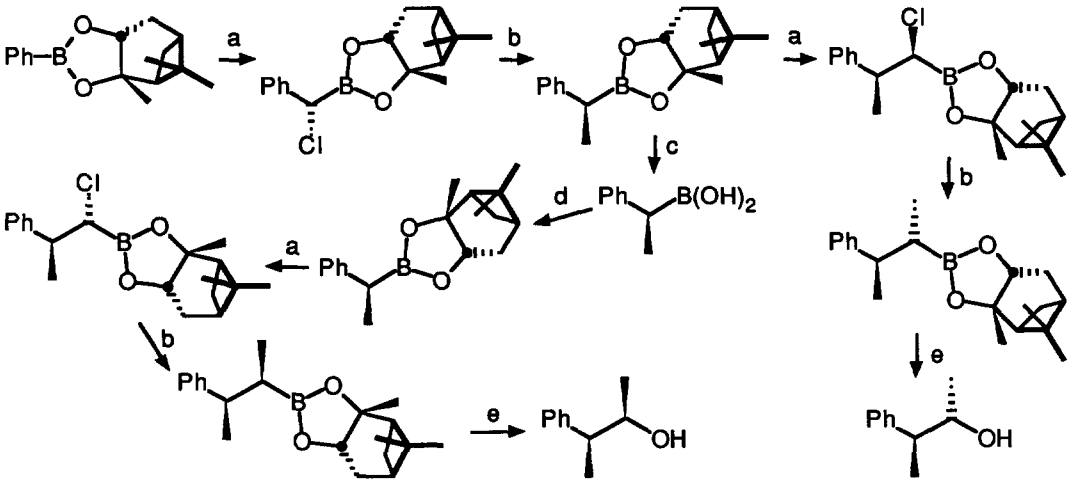


97



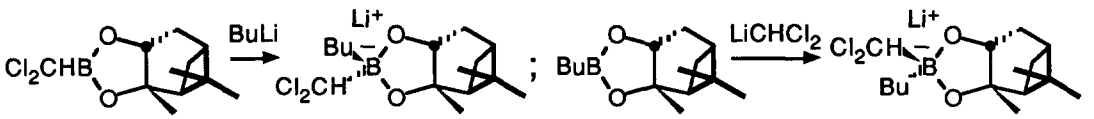
98

An early synthetic application of pinanediol esters was the synthesis of the two diastereomers of 3-phenyl-2-butanol (**99** and **100**),[84,85] chosen as demonstration targets because they had been characterized previously by Cram.[86] The details are obsolete, but the strategic concept of changing the chiral director if needed is illustrated.



99 **100** (a) $LiCHCl_2$; (b) CH_3MgBr; (c) BCl_3, then $(HOCH_2CH_2)_2NH$, then H_3O^+; (d) (*r*)-pinanediol; (e) H_2O_2

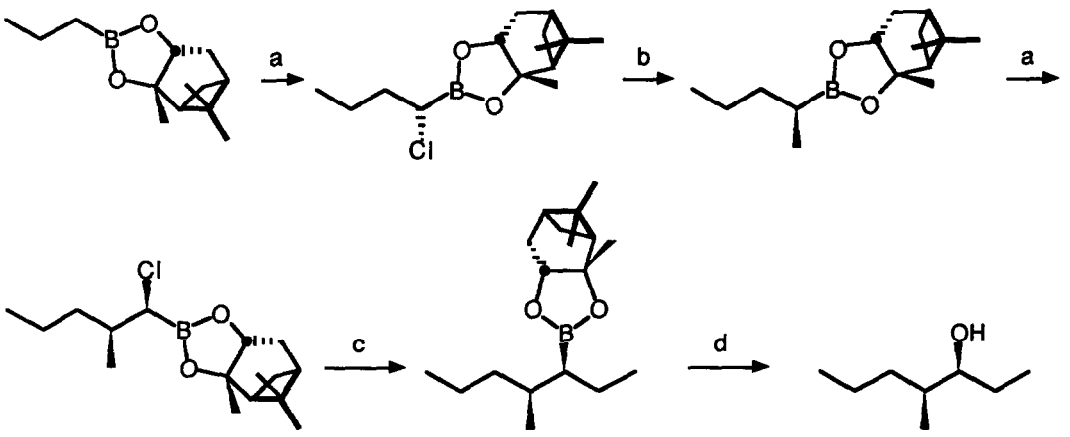
Although pinanediol esters have good chiral directing properties, they do have two general limitations. One is the difficulty of cleavage, implicit in the use of BCl_3 in step (c) on the route to **99**. The other is that the pinanediol unit lacks C_2 symmetry, and reaction of pinanediol (dichloromethyl)boronate (**101**) with butyllithium yields a borate complex **102** which is a diastereomer of the borate complex **104** formed from pinanediol butylboronate (**103**) and (dichloromethyl)lithium.[87] Unfortunately, rearrangement of diastereomer **102** does not yield the high diastereomeric ratios found with **104**.



101 **102** **103** **104**

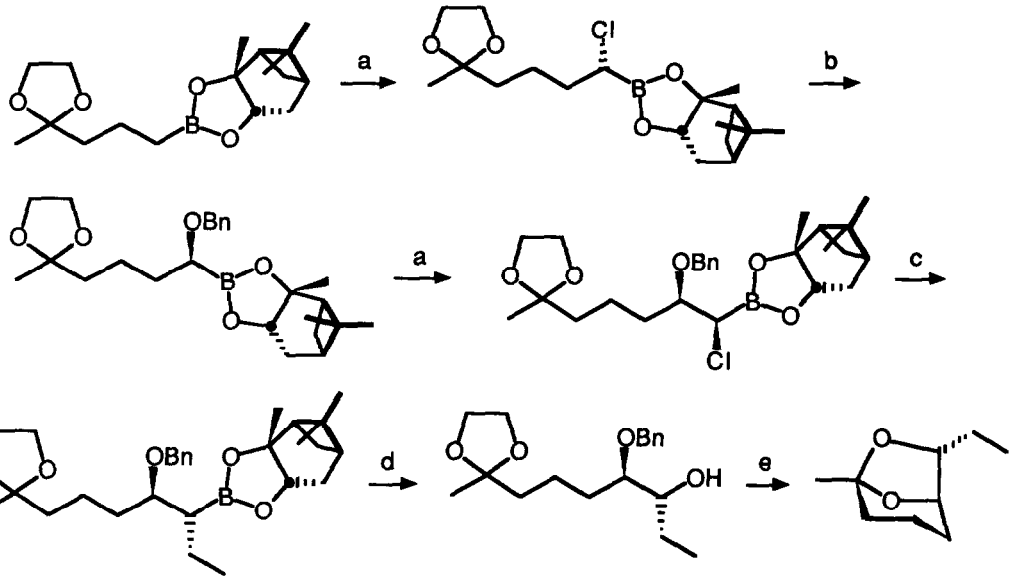
6.3. Pheromone Syntheses. If there are only two chiral centers, it is often possible to select the chiral director and the order of introduction of the alkyl groups to provide the desired isomer. This strategy was used in the syntheses of the minor component of the pheromone of the elm bark beetle, *Scolytus multistriatus*, (**105**) (major component: see **56**, part **4.2**), and also *exo*-brevicomin (**106**), the pheromone of the western pine bark

beetle, *Dendroctonus brevicomis*. The synthesis of the wing gland pheromone eldanolide (**108**) of the African sugar cane borer, *Eldana saccharina*, did not allow such a free choice of isomers, but the natural isomer fortuitously has the combination of chiral centers allowed by the synthesis. These syntheses of **105-108** were among the first in which zinc chloride catalysis was used to provide 97% or greater diastereomeric excesses (de's) at each step. The intermediate **107** was formed only in ~90% de, but was recrystallized to 96% de before proceeding.[88,89]



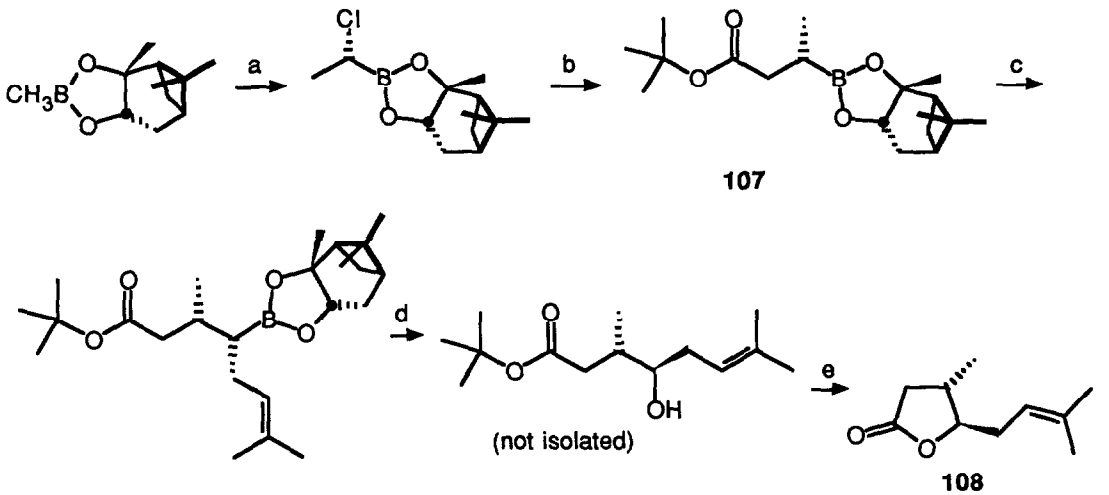
105

(a) 1. $LiCHCl_2$, -100 °C; 2. $ZnCl_2$, 20 °C; (b) CH_3MgBr; (c) C_2H_5MgBr; (d) H_2O_2



106

(a) 1. $LiCHCl_2$, -100 °C; 2. $ZnCl_2$, 20 °C; (b) $C_6H_5CH_2OLi$; (c) C_2H_5MgBr; (d) H_2O_2; (e) H_2/Pd; H^+

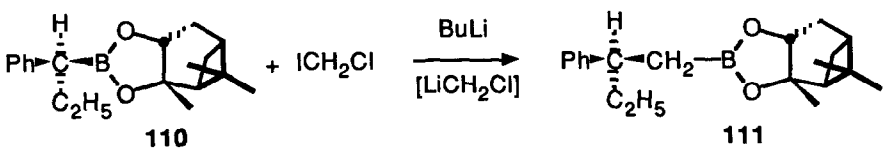


(a) 1. $LiCHCl_2$, -100 °C; 2. $ZnCl_2$, 20 °C; (b) $LiCH_2CO_2C(CH_3)_3$ (c) (a), then $(CH_3)_2C{=}CHCH_2MgCl$; (d) H_2O_2; (e) H^+

6.4. L-Ribose Synthesis. Application of the pinanediol boronic ester chemistry to the synthesis of ribose required several innovations. An efficient synthesis of diisopropyl (chloromethyl)boronate (**109**) involved the in situ generation of unstable (chloromethyl)lithium from butyllithium and iodochloromethane in the presence of triisopropyl borate.[90] This chemistry can also be used to insert a methylene group into the carbon-boron bond of a boronic ester, as in the conversion of **110** to **111**.

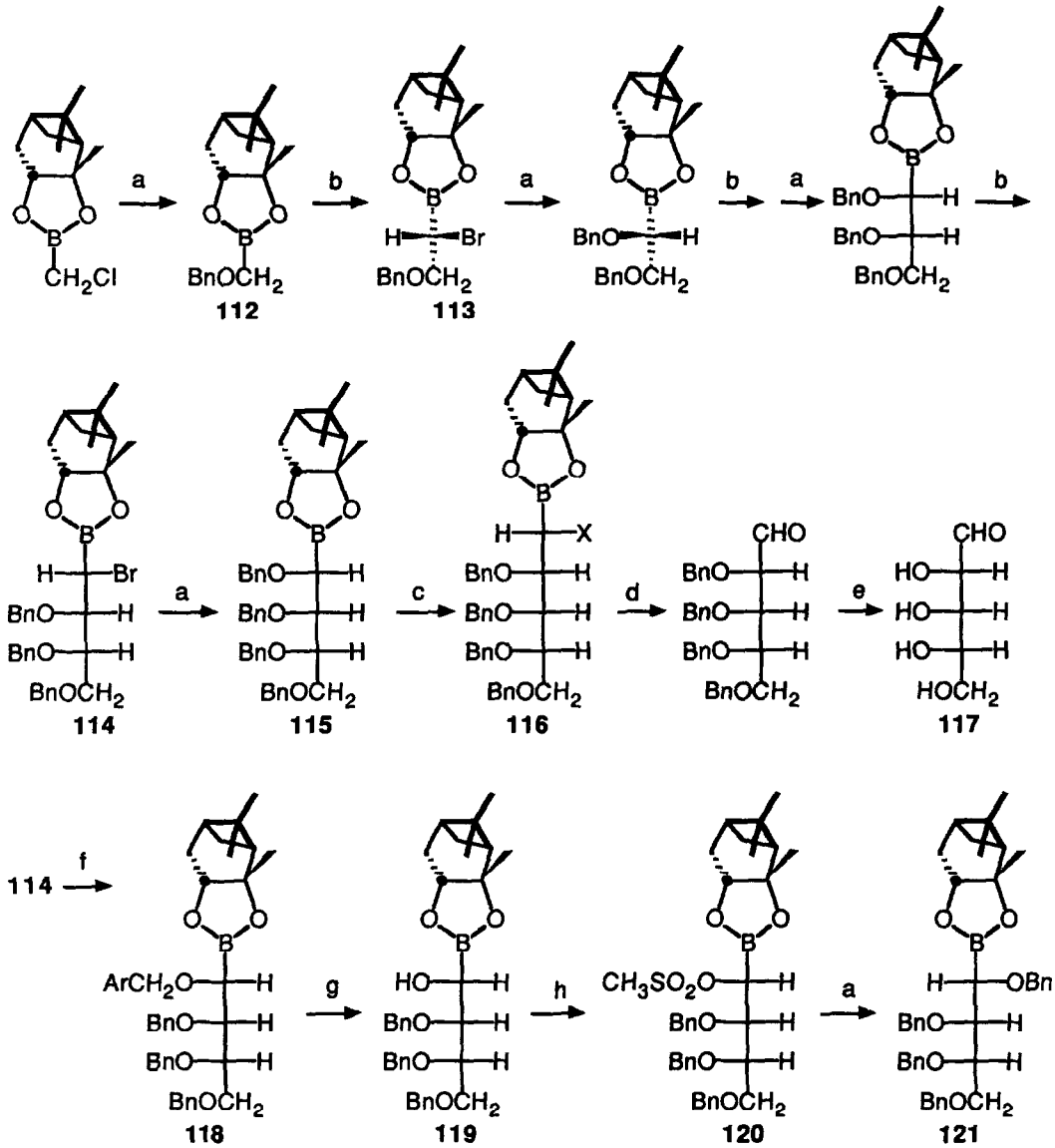
$$B[OCH(CH_3)_2]_3 + ICH_2Cl \xrightarrow[[LiCH_2Cl]]{BuLi} ClCH_2B[OCH(CH_3)_2]_3^- \xrightarrow{HCl} ClCH_2B[OCH(CH_3)_2]_2$$

109



110 **111**

The second innovation was the use of (dibromomethyl)lithium in place of the chloro compound in the chain extension process. Because (dibromomethyl)lithium is much less stable than the chloro analogue, it was generated from dibromomethane and lithium diisopropylamide in the presence of the boronic ester substrate. This led to improved chiral control in the conversion of **112** to **113** and improved yields in all steps through the preparation of **114** and **115**. Although intermediate **115** was obtained in 36% overall yield from **112**, the fifth carbon of **116** was inserted only with difficulty. (Dichloromethyl)lithium yielded only 14%, (chloromethyl)lithium 35%, though either intermediate was then easily converted to L-ribose (**117**) nearly quantitatively.[91]

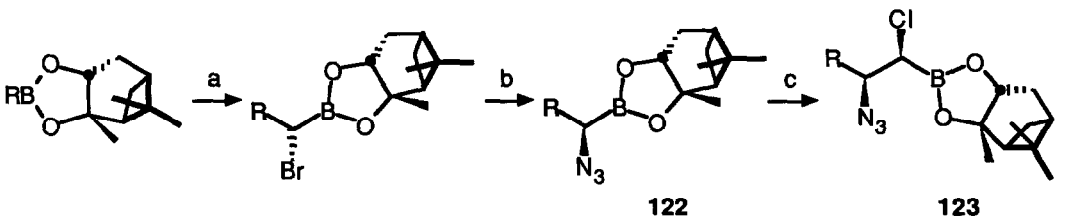


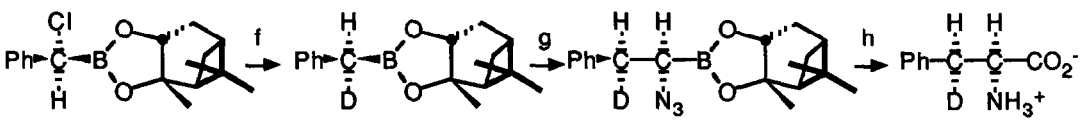
(a) $LiOCH_2C_6H_5$; (b) $LiN[CH(CH_3)_2]_2$ + CH_2Br_2, -78 °C, then $ZnCl_2$, 20 °C; (c) LiCHXCl, X = Cl or H; (d) if X = Cl, H_2O_2, or if X = H, Swern oxidation; (e) H_2/Pd; (f) 3,4-$(CH_3O)_2C_6H_3CH_2OLi$; (g) DDQ; (h) CH_3SO_2Cl, $(C_2H_5)_3N$.

Instead of changing the chiral director, double inversion at a chiral center was carried out by conversion of the bromo compound **114** to the 3,4-dimethoxybenzyl ether[92] **118**, which with dichlorodicyanoquinone (DDQ) yielded the α-hydroxy boronic ester **119**. Then conversion to the methanesulfonate **120** followed by treatment with lithium benzyl oxide yielded boronic ester **121**, the diastereomer of **115**. Because of the difficulties encountered with further carbon insertion, no further work was done with **121**, except to note that **121** and **115**

were clearly different compounds, and neither contained a detectable amount of the other by 200 MHz NMR analysis.[93]

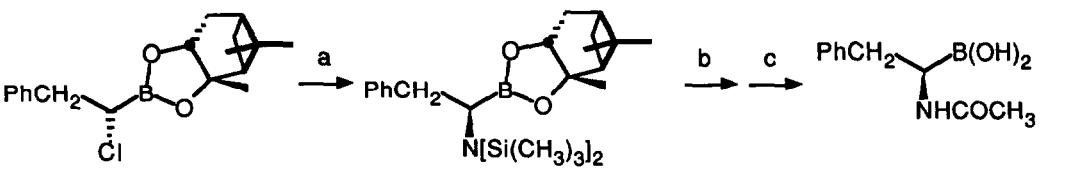
6.5. Amino Acid Synthesis. Conversion of an α-bromo boronic ester to an α-azido boronic ester **122** followed by a second homologation to the β-azido-α-chloro boronic ester **123** and oxidation with sodium chlorite yields the α-azido acid **124**, which is readily reduced, and deprotected if necessary, to the amino acid **125**.[94] This procedure is readily adaptable to the preparation of amino acids bearing chiral deuterium labels, as in the preparation of deuterated intermediate **126** and its conversion to chirally deuterated phenylalanine (**127**).[95]





(a) $LiCHBr_2$ (if R = $PhCH_2$, Cl analogue used); $ZnCl_2$; (b) large excess of NaN_3, $CHCl_2/H_2O$, phase transfer cat.; (c) $LiCHCl_2$; $ZnCl_2$; (d) $NaClO_2$; (e) H_2/Pd or Pt; (f) $LiDB(C_2H_5)_3$; (g) a, b; (h) c-e.

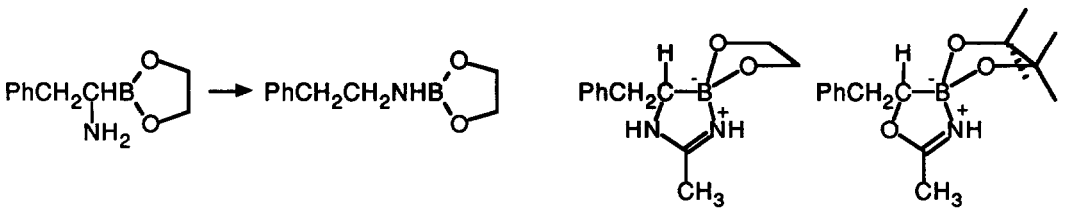
6.6. α-Amido Boronic Acids. α-Amino boronic acids or esters deboronate surprisingly easily to amines but can be made in silyl protected form, for example **128**, and acylated to stable derivatives. These often show competitive inhibition of serine proteases and related enzymes. For example, (1*R*)-1-acetamido-2-phenylethylboronic acid (**129**), the analogue of *N*-acetyl-L-phenylalanine, is a good inhibitor of chymotrypsin, with a dissociation constant of 2.1 X 10^{-6} M at pH 7.5, 25 °C.[96]



(a) $LiN[Si(CH_3)_3]_2$; (b) CH_3CO_2H, $(CH_3CO)_2O$; (c) BCl_3, then H_2O.

In a detailed study of the synthesis of **129**,[97] the free amino boronic ester **130** was isolated in impure form but rearranged to **131** on heating, and the free amino boronic acid survived in water at pH 7 at 0 °C with a half-life

>0.5 hour, perhaps much longer. The amidino boronic ester **132** was also synthesized and found to be stable, and it was concluded that the insoluble product from the reaction of lithioacetamide with the corresponding α-chloro phenylethylboronic ester was probably the *O*-alkylation product **133.**

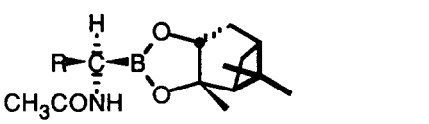


130 **131** **132** **133**

More recently, Shenvi has isolated several free amino boronic esters as their trifluoroacetate salts and found them to be stable.[98] A buffered solution of pinacol 1-amino-2-phenylethylboronate (analogous to **130**) was <10% converted to phenylethylamine in 3 days at room temperature. The amino boronic acids were aminopeptidase inhibitors at submicromolar concentrations.

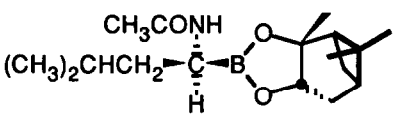
(Benzamidomethyl)boronic acid, $PhCONHCH_2B(OH)_2$, is also a chymotrypsin inhibitor, $K_i = 8.1 \times 10^{-6}$ M at pH 7.5.[99] The *O*-linked isomer $PhC(=NH)O\text{-}CH_2B(OH)_2$ (analogous to **133**), which had been obtained earlier and was originally believed to be the amido boronic acid, was a somewhat stronger inhibitor of chymotrypsin.[100]

Several other α-amido boronic esters (**134-137**) have been prepared.[101] Hydrolysis of **135** in an aqueous borate buffer produced a solution of the boronic acid analogue of *N*-acetyl-D-leucine, which inhibits *Bacillus cereus* β-lactamase, $K_i = 44 \times 10^{-6}$ M.[102] Kinder and Katzenellenbogen have also synthesized several amido boronic esters and acids, including the isoleucine analogue (**134**, R = (*S*)-$C_2H_5(CH_3)CH$-), and shown that boronic acids derived from **134** are elastase inhibitors.[103]

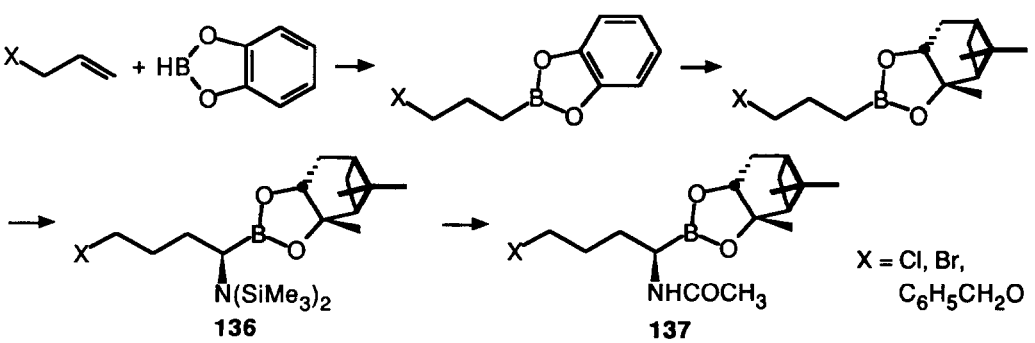


R = CH_3, $(CH_3)_2CH$, or $(CH_3)_2CHCH_2$

134



135



136 **137**

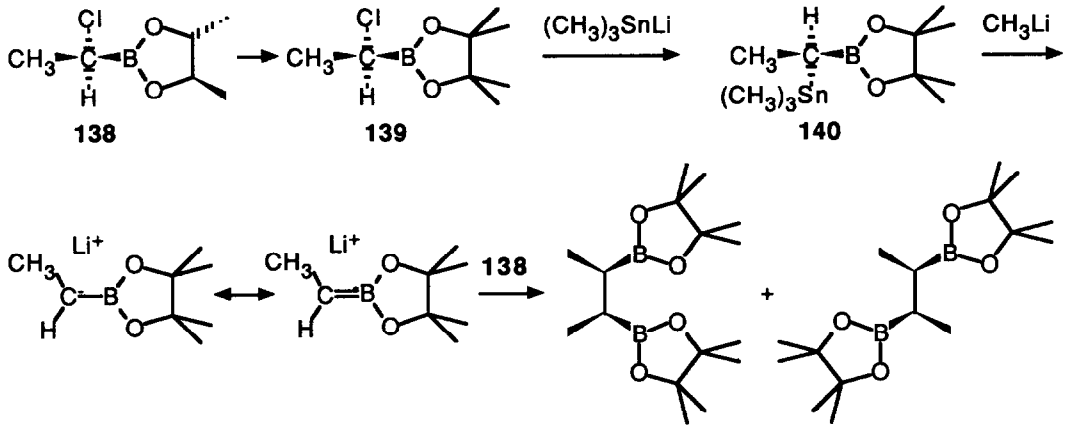
X = Cl, Br, $C_6H_5CH_2O$

Although not of biochemical interest in themselves, the structures represented by **136** and **137** are potential precursors to arginine or proline analogues. Suitable acylation of **136** (X = Br) and replacement of bromide by a guanidino group has yielded "Z-D-Phe-Pro-boroArg," an excellent inhibitor of thrombin, $K_i = 8 \times 10^{-9}$ M.[104]

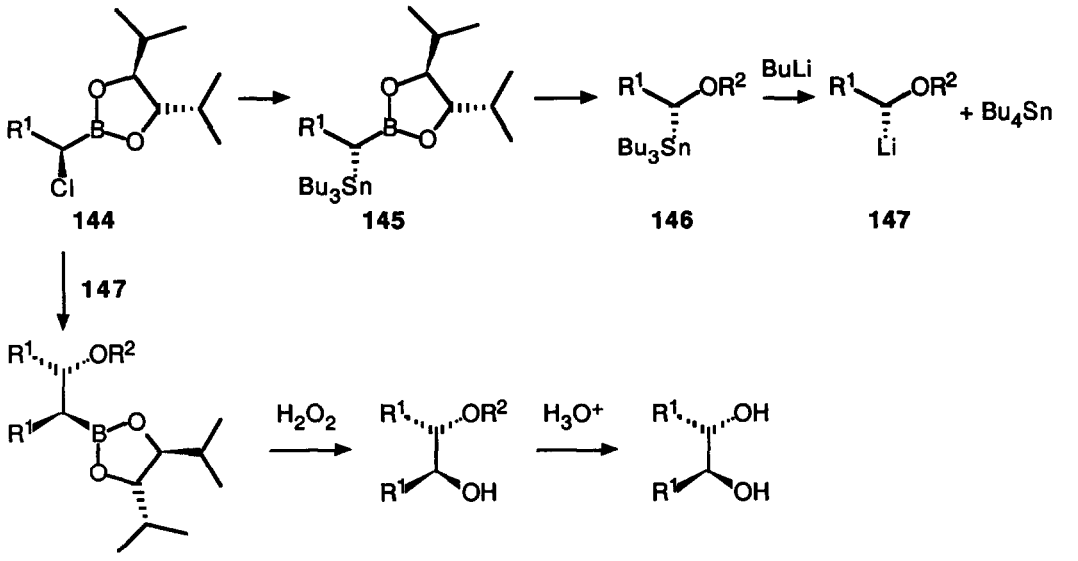
A series of peptide analogues $R^1NHCH(R^2)B(OH)_2$, where R^1 = methoxysuccinyl-Ala-Ala-Pro- and R^2 = CH_3, $CH(CH_3)_2$, or $CH_2C_6H_5$, has been synthesized by Kettner and Shenvi and shown to inhibit chymotrypsin, cathepsin G, and leucocyte and pancreatic elastase with K_i's in the nanomolar range.[105] The most active of these, $R^2 = CH(CH_3)_2$ ["MeOSuc-Ala-Ala-Pro-boroValOH"], has been shown to be effective against elastase-induced emphysema in hamsters.[106] The kinetics of binding of this peptide analogue and several related compounds to α-lytic protease from Lysobacter enzymogenes (an enzyme similar to elastase) have been studied,[107] and the binding site of the boronic acid to serine has been found to involve an interaction with histidine as well by ^{15}N NMR studies.[108]

6.7. Coupling of Chiral Centers. Up to this point, all of the constructions of more than one chiral center with α-chloro boronic esters have involved a linear sequence of assembly. Although yields are high in each step, the repetitive losses inherent in linear sequences ultimately limit the practical number of steps that can be carried out. A convergent connection of chiral centers was desired in order to overcome this limitation.

The first attempt at convergent connection involved an α-lithio boronic ester (**140**).[109] The butanediol ester **138** was converted to the pinacol ester **139** so that there would be only one chiral center undergoing transformation and the result would be unambiguous if any chiral selectivity were found. Conversion of **139** to the tin derivative **140** was straightforward, and reaction with methyllithium readily yielded the α-lithio boronic ester **141** and tetramethyltin. Coupling of **139** with **141** yielded a mixture of diastereomers **142** and **143**, which was optically active because of the stereospecific displacement of chloride from **139**. An identical proportion of racemic diastereomers **142** and **143** was obtained from the reaction of racemic $CH_3CHIBO_2C_2(CH_3)_4$ with *tert*-butyllithium.



Still and Sreekumar have reported that α-lithio ethers retain their configuration.[110] Conversion of α-chloro boronic esters **144** to α-tributylstannyl boronic esters **145** followed by peroxidic deboronation and alkylation has yielded the homochiral α-tributylstannyl ethers **146** used as precursors to homochiral α-lithio ethers **147**.[111]



R^1 = *n*-butyl, isopropyl, (*R*)-$CH_3CH_2CH_2CH(CH_3)$-; R^2 = $CH_2OCH_2C_6H_5$, CH_2OCH_3

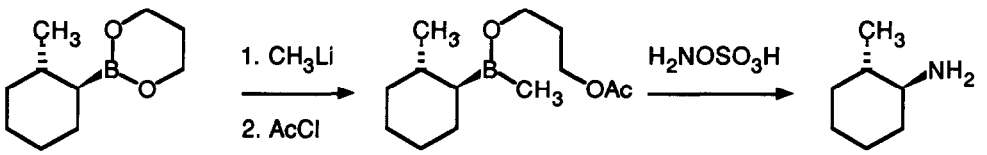
When R^1 was chosen as *n*-butyl, coupling of **144** with **147** proceeded smoothly to yield **148**, which was deboronated and hydrolyzed to yield the known (*S*,*S*)-5,6-decanediol in ~96% de. However, when R^1 was isopropyl, the yield of **148** under the previously established coupling conditions, mixing the reactants at -78 °C and allowing rearrangement of the resulting borate complex to occur at 20 °C, was only 20%. It turned out that the formation of **147** is reversible, so that the sterically hindered **147** with R^1 = isopropyl reacts with the tetrabutyltin to regenerate a trace of butyllithium, which is captured by **144**. Formation of **147** is evidently exothermic, as merely reducing the initial coupling temperature to -100 °C produced satisfactory results.[112] The diastereomer of **148** was generated from **144** with the enantiomer of **147**, R^1 = isopropyl, and the de of the **148** was shown to be 98% by NMR analysis. These results indicate that the formation of the tin and lithio intermediates **146** and **147** and the coupling process are stereospecific, the slight diastereomeric impurity being present in the α-chloro boronic ester **144**.

7. CONVERSION OF CHIRAL BORONIC ESTERS TO ALKYLBORANES.

Boronic esters do not react in several of the well known transformations of trialkylboranes, and it therefore can be useful to convert homochiral boronic esters to borinic esters or trialkylboranes. This chemistry has been reviewed recently by Brown,[113] and the description here will be kept brief. The conversion of alkyl(isopinocampheyl)boranes to boronic esters of high enantiomeric purity by treatment with acetaldehyde has been noted in part 2.2, and this route has been the source of the homochiral boronic esters used in Brown's studies. While it may seem roundabout to go from a trialkylborane to a boronic ester and back to a trialkylborane, crystalline diethanolamine chelates of boronic acids provide an additional opportunity to refine an intermediate to very high enantiomeric purity.[114]

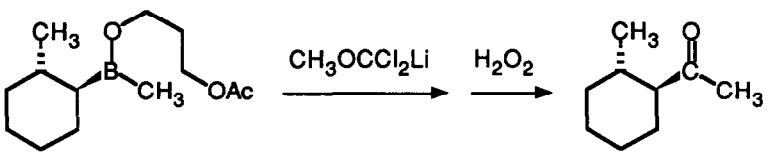
Homochiral boronic esters are potentially available in much wider diversity via the α-chloro boronic ester chemistry described in section 6, and this area appears ripe for immediate further development.

As examples for demonstration purposes, several enantiomerically pure boronic esters such as **150** were prepared via chiral hydroboration with isopinocampheylborane, purification of the borane intermediate, removal of the isopinocampheyl group with acetaldehyde, and transesterification with a diol (see also part 2.2, structure **9**). Treatment with methyllithium followed by acetylation yielded the borinic ester intermediate **151**, which with the aminating agent hydroxylamine-*O*-sulfonic acid resulted in preferential migration of the secondary alkyl group to nitrogen to yield the primary amine **152** in high enantiomeric purity.[115]



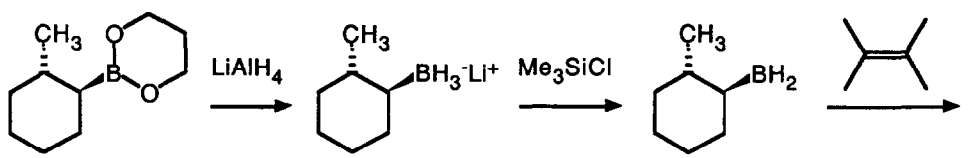
150 **151** **152**

Treatment with CH_3OCCl_2Li converts **151** and similar borinic esters to ketones such as **153** having >99% ee.[116] Although only one example is illustrated here, an extensive series of ketones was synthesized. Homochiral alkyl alkynyl ketones have been prepared by a similar route.[117]

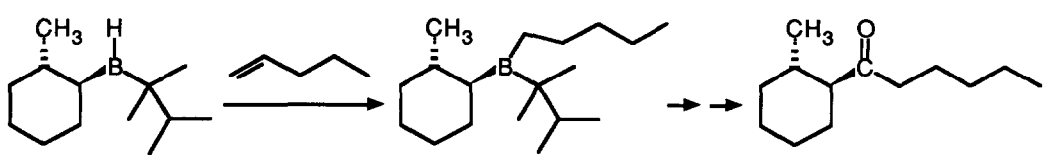


151 **153**

Alternatively, boronic ester **150** has been converted to the borane (**154**) and thexylborane (**155**), which was used to hydroborate an alkene and converted via the dialkylthexylborane **156** to the homochiral ketone **157** by Brown's previously established chemistry.[118] Again, a number of related examples were provided, and other previously known transformations of **156** were described in the new context of synthesis of pure enantiomers.

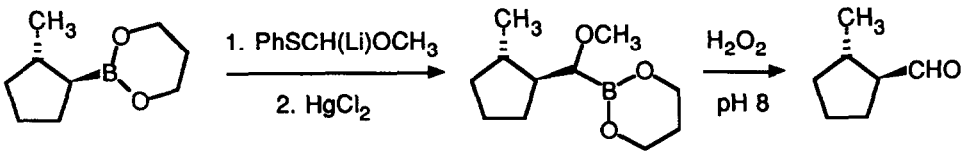


150 **154**



155 **156** **157**

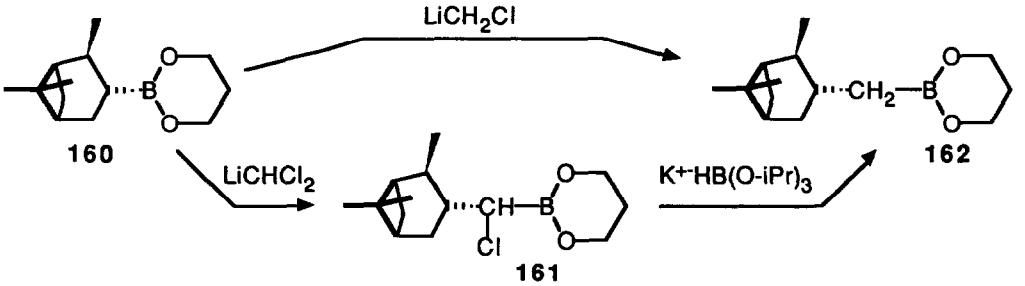
The reaction of $PhSCHLiOCH_3$ with homochiral boronic esters (**158**) has been used to synthesize aldehydes (**159**), which have been converted to homochiral acids and alcohols.[119]



158 **159**

Application of the reagents $LiCHCl_2$ and $LiCH_2Cl$, described in section 6, to chiral boronic esters derived from hydroboration has considerable synthetic potential. Homochiral cycloalkylboron compounds and certain boron substituted heterocycles are readily accessible via hydroboration but not from the α-chloro boronic ester synthesis (section 6), which instead provides a wide variety of chiral acyclic compounds and the opportunity to construct a series of adjacent chiral centers. Conversely, acyclic chiral compounds are inaccessible by hydroboration except where special circumstances of symmetry or substitution permit, and hydroboration does not provide any general construction of more than two adjacent chiral centers. Thus, the two methods complement each other.

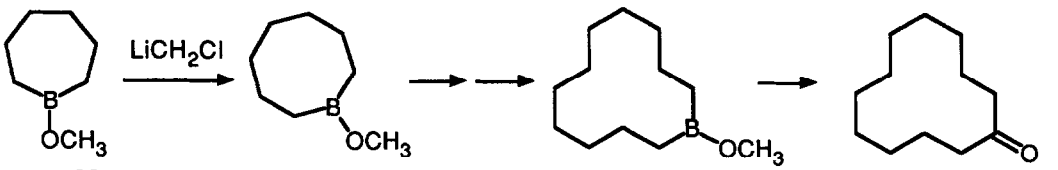
The only combination of the two methods in synthesis to date has involved the insertion of a simple methylene group into the carbon-boron bond. Brown's group has investigated several experimental procedures for accomplishing this conversion. First, the reaction of the boronic esters with (dichloromethyl)lithium was carried out by either of the procedures described by Matteson and Majumdar,[120] that is, the reagent was preformed at -100 °C[121,122] or generated from dichloromethane and lithium diisopropylamide at -78 °C in the presence of the boronic ester substrate,[123] and the α-chloro boronic ester was then reduced with potassium tri(isopropoxy)borohydride. Alternatively, the (dichloromethyl)lithium was generated in situ from *sec*-butyllithium and dichloromethane and the α-chloro boronic ester was reduced as before, or the Sadhu-Matteson procedure for generating (chloromethyl)-lithium (part 6.4) was used, with the less expensive bromochloromethane in place of the slightly more efficient iodochloromethane.[124] An illustration of the type of conversion achieved is illustrated by the routes from **160** to **162**, either directly or via **161**.



160 **161** **162**

A final application of this methylene insertion chemistry has not yet been put into the context of chiral synthesis, but has interesting possibilities. The ring of borepane **163**, easily derived from 1,5-hexadiene via hydroboration, has been enlarged by reaction with (chloromethyl)lithium to form borocane **164**. Repetition of the ring enlargement

was carried out all the way to the twelve-membered ring **165**. These compounds can be converted to carbocycles by standard methods of alkylborane chemistry, for example, the ketone **166**.[125]



163 **164** **165** **166**

The significance of the foregoing example can be appreciated when the difficulty of direct synthesis of medium sized carbocyclic rings is considered. Organic chemists in general have been slow to utilize boron chemistry because of its unfamiliarity and the consequent risk that unanticipated results may derail a planned synthesis. The reviewer hopes that the recent developments summarized in this article will prove sufficiently enticing that many more organic chemists will undertake applications of boronic ester chemistry, and that boron will take its rightful place alongside silicon as the most useful of metalloidal elements for carrying out organic synthesis.

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