Pergamon

Tetrahedron 54 (1998) 10555–10607

TETRAHEDRON

Tetrahedron report number 463

α-Halo Boronic Esters in Asymmetric Synthesis

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Received 5 March 1998

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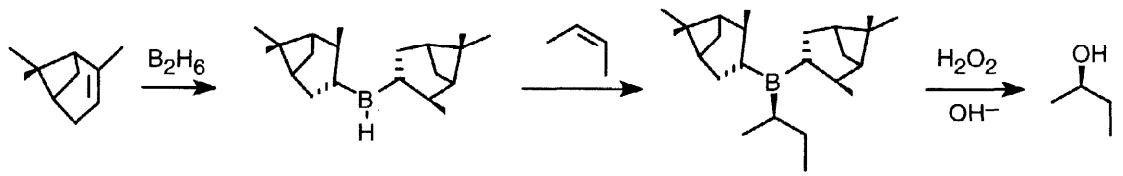
PII: S0040-4020(98)00321-4

INTRODUCTION

The major focus of this review will be the α-chloroalkylboronic ester chemistry first reported by Matteson, Majumdar, and Ray in 1980,[1,2] with emphasis on developments since our previous Tetrahedron Report.[3] This chemistry consistently provides exceptionally high diastereomeric and enantiomeric excesses, and is readily adaptable to a very wide variety of synthetic targets. Only a few of the many promising applications have been tested to date.

It is appropriate to begin with Brown and Zweifel's hydroboration of *cis*-2-butene with (–)-diisopinocampheylborane (**2**) derived from (+)-α-pinene (**1**) to form the intermediate trialkylborane **3**, which was oxidized with alkaline hydrogen peroxide to (*R*)-(–)-2-butanol (**4**).[4,5] This is generally acknowledged to be the first nonenzymatic asymmetric synthesis that led to a truly high enantiomeric excess in the product, and it preceded other asymmetric syntheses by a number of years. When **2** of high enantiomeric purity[6] is used and the procedure is optimized, this process yields 98% enantiomeric excess (ee) in the final product, (*R*)-(–)-2-butanol (**4**).[7] Since (–)-α-pinene is also readily available, it is equally easy to prepare (*S*)-(+)-2-butanol by this route.



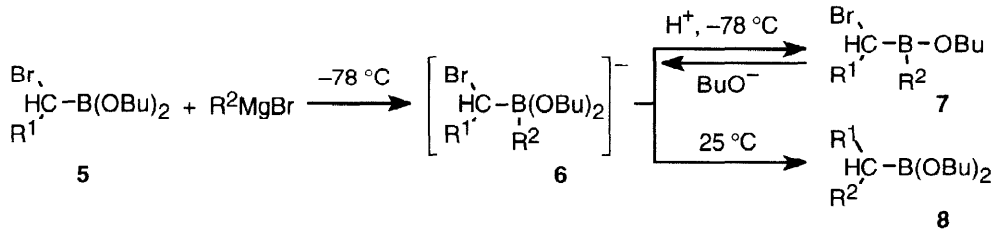
1 2 3 4

The success of the Brown–Zweifel synthesis results from the favorable properties of the boron atom, which include small size for maximum steric interactions and stable, stereospecifically replaceable bonds to carbon. The choice of the abundant, inexpensive pinyl group as stereodirector was also highly significant. A severe limitation on the generality of this synthesis is that most 1,2-disubstituted ethylenes yield regioisomers on hydroboration, but those boranes that are accessible via this chemistry are not easily made via other routes and constitute a valuable resource for asymmetric synthesis.

FUNDAMENTALS OF α-HALO BORONIC ESTER CHEMISTRY

Mechanism of halide displacement

α-Halo boronic esters date from 1959, when they were first made via radical additions to a vinylboronic ester.[8] Their reactions with nucleophiles followed shortly, and the results are summarized in the illustrated reaction of a boronic ester (**5**) with a Grignard reagent to form a borate complex (**6**), which yielded a borinic ester (**7**) if acidified cold but underwent alkyl or aryl migration with halide displacement to form new boronic ester (**8**) if warmed to 25 °C, or if the borinic ester (**7**) was treated with mild base and butanol.[9,10]



Several important points were established in this early work:

(1) The scheme illustrated with Grignard reagents is very general for basic nucleophiles. Nucleophiles that are not basic enough to form borate complexes nevertheless displace the α-halide relatively rapidly, evidently via a nucleophilic displacement mechanism that is facilitated by weak coordination to the boron atom.[9,10]

(2) Nucleophilic displacement of halide is strongly favored over competing elimination, to the point that hydrogen halide elimination was hard to achieve even with a system that is particularly prone to elimination.[11] Even "tertiary" halides such as 2-bromopropyl-2-boronic esters preferentially undergo nucleophilic displacement.[12]

(3) Alkoxide does not normally compete with alkyl or aryl as the migrating group to any detectable extent. This is related to the very strong thermodynamic bias in favor of boronic esters [$R^1R^2CHB(OBu)_2$] over their borinic ester isomers [$R^1CH(OBu)BR^2(OBu)$].[9]

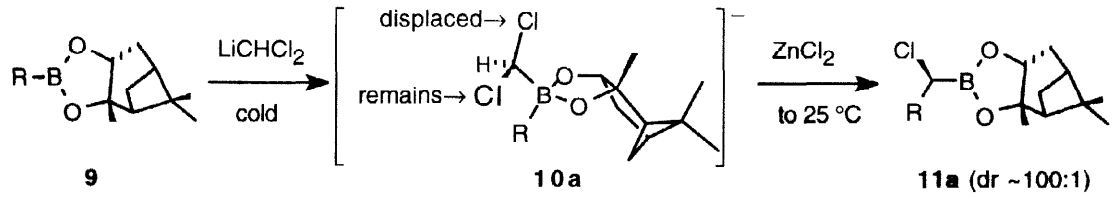
Limited exceptions to rules (2) and (3) have been discovered only recently and will be discussed later.

The general mechanism of reaction of Grignard reagents with α-halo boronic esters clearly requires that the halide be displaced with inversion of the carbon atom, and that the migrating alkyl group retain its configuration. Although the potential utility of this borate rearrangement for synthetic purposes was immediately apparent, only a minor and inefficient synthetic application was found at that time.[13] There was no general route to α-halo boronic esters, and the base sensitivity of these compounds discouraged any attempt at resolution with bisdemethylbrucine, the only method then known for resolution of a boronic acid.[14]

(Dihalomethyl)borate rearrangement

Rathke, Chao, and Wu made a (dichloromethyl)boronic ester and reacted it with alkyllithiums to form (α-chloroalkyl)boronic esters, which were not isolated but oxidized to aldehydes.[15] Their yields were variable and the aldehyde synthesis did not appear promising. In the light of hindsight, the problem probably was that the oxidation of α-chloro boronic esters to aldehydes is often complicated by aldol condensations at high pH.

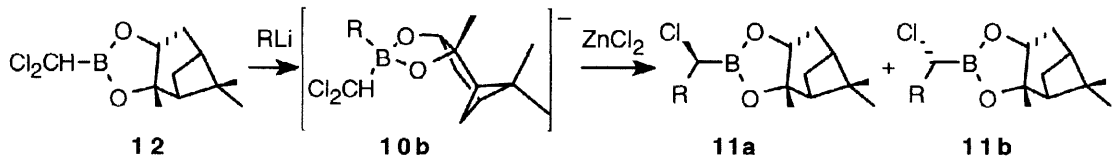
A few years later, we consistently isolated (α-chloroalkyl)boronic esters in high yields from alkylboronic esters and (dichloromethyl)lithium,[1,16] then achieved 10:1 to 20:1 diastereomeric ratios (dr's) with pinanediol boronic esters (**9**).[2,17] The use of zinc chloride as a catalyst and chloride ion scavenger for the rearrangement of the borate intermediate (**10a**) improved the dr's in the (α-chloroalkyl)boronic ester product (**11a**) to ~100:1.[18] This process has been described as "homologation", though it is more accurately "chain extension" inasmuch as **11a** are not true homologues of **9**.



9 **10a** **11a** (dr ~100:1)

Most of our work has been done with preformed (dichloromethyl)lithium, which is made from butyllithium and dichloromethane at −100 °C. However, addition of LDA to dichloromethane generates (dichloromethyl)lithium in the presence of the boronic ester at temperatures up to −20 °C.[18] This in situ method generates diisopropylamine as a byproduct, and requires an additional mole of zinc chloride to compensate for amine—zinc complexation, but is more practical for large scale preparations.

It is important to note that what might seem at first glance to be an equivalent process, starting from pinanediol (dichloromethyl)boronate (**12**) and an organolithium reagent, is in fact different and synthetically useless, because the kinetically formed borate complex postulated to have structure **10b** is a diastereomer of **10a** and rearranges with very little diastereoselection to a gross mixture of diastereomeric α-chloro boronic esters **11a** and **11b**.[19]

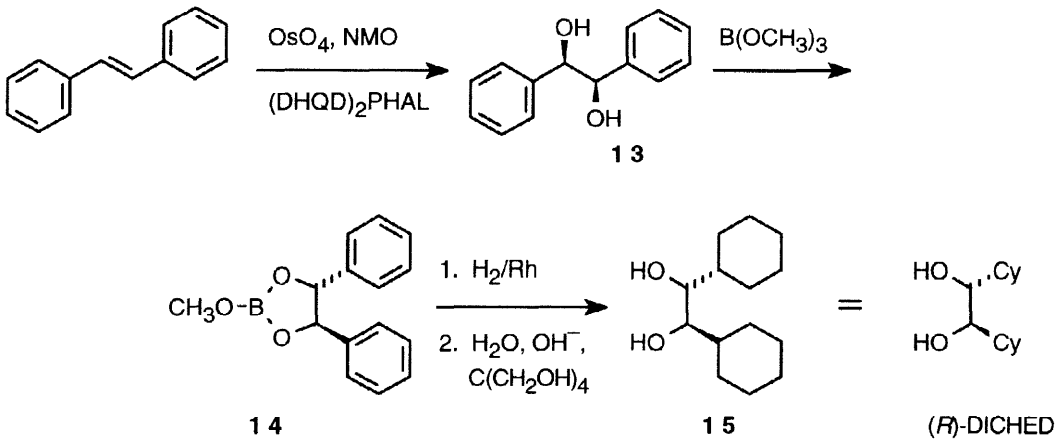


12 **10b** **11a** **11b**

This pinanediol boronic ester chemistry has been reviewed in detail in an earlier Tetrahedron Report[3] and elsewhere.[20-22] Pinanediol is easy to make and effective enough for most purposes, but has been supplanted by (*R*)- or (*S*)-(*R**,*R**)-1,2-dicyclohexyl-1,2-ethanediol, which we abbreviate as (*R*)- or (*S*)-DICHED, in most of our recent work. DICHED is easily prepared and leads to higher stereoselection than pinanediol.

Chiral directors of C_2-symmetry

DICHED was introduced by Hoffmann and coworkers,[23] and is now readily available in large quantities via Sharpless dihydroxylation of *trans*-stilbene to (*R*)-(*R**,*R**)-1,2-diphenylethane-1,2-diol (**13**) or its (*S*)-enantiomer.[24] A slight modification of the Wang-Sharpless procedure overcomes solubility problems with potassium osmate, and a revised hydrogenation process avoids problems with commercial rhodium on alumina catalysts, which vary greatly in activity and tend to cause hydrogenolysis of the benzylic hydroxyl groups.[25] The diol (**13**) is converted to a borate ester (**14**) before hydrogenation over rhodium trichloride and alumina, which generates highly active catalyst in situ when hydrogen is introduced. Rhodium is recyclable as the trichloride. The resulting borate ester is finally hydrolyzed to DICHED, illustrated here by the (*R*)-isomer (**15**).[25]



Naturally, 1,2-diphenyl-1,2-ethanediol was tested as a chiral director, but failed to yield satisfactory diastereoselection.[23] (*R*,*R*)-2,3-Butanediol boronic esters had generally yielded ~20:1 dr's on chain extension,[26] and prompted exploration of other 1,2-diols having C_2-symmetry. The first preparation of 1,2-diisopropyl-1,2-ethanediol, "DIPED", was carried out via pinanediol boronic esters.[27] These DIPED boronic esters uniformly yielded diastereomeric ratios on chain extension that measured a strikingly uniform 30:1 after transesterification with pinanediol and 200-MHz NMR analysis. When the ee of the pinanediol used for the preparation as well as the analysis

of these samples was taken into account, the results suggested that the real dr's of the DIPED (α-chloroalkyl)boronates might exceed 100:1. This has never been verified directly, but no evidence to the contrary has been observed. Subsequent samples of DIPED were prepared in high enantiomeric purity from tartaric acid.[28]

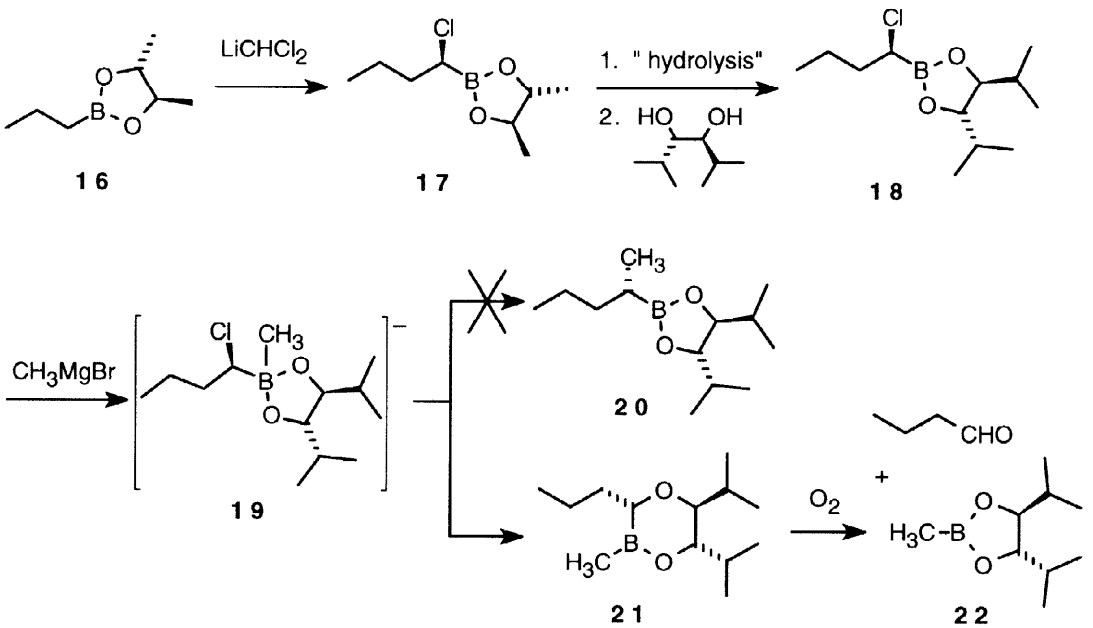
It may be noted in passing that readily available diols bearing polar substituents are unsatisfactory as chiral directors. Tartrate boronic esters did not yield α-chloro boronic esters with (dichloromethyl)lithium,[17] and boronic esters of 2,5-dimethyl-2,5-dimethoxy-3,4-hexanediol, prepared from tartaric acid in fewer steps than DIPED, yielded mediocre dr's.[29]

Ultrahigh diastereoselection

A very important factor in support of our choice of DICHED was the discovery that a closely similar diol, (*S*)-(*R**,*R**)-2,5-dimethyl-3,4-hexanediol (diisopropylethanediol, "DIPED"), can provide >1000:1 diastereoselection in the sequence from alkylboronic ester to α-chloro boronic ester to *sec*-alkylboronic ester.[30] Enantiomerically pure DIPED is accessible from tartaric acid in several steps. DICHED, like DIPED, has C_2-symmetry, but is now considerably easier to make. Although extreme diastereoselection has not been rigorously proved with DICHED, Hoffmann and coworkers found that it gives excellent stereocontrol,[23] and in our own experience this has held true.

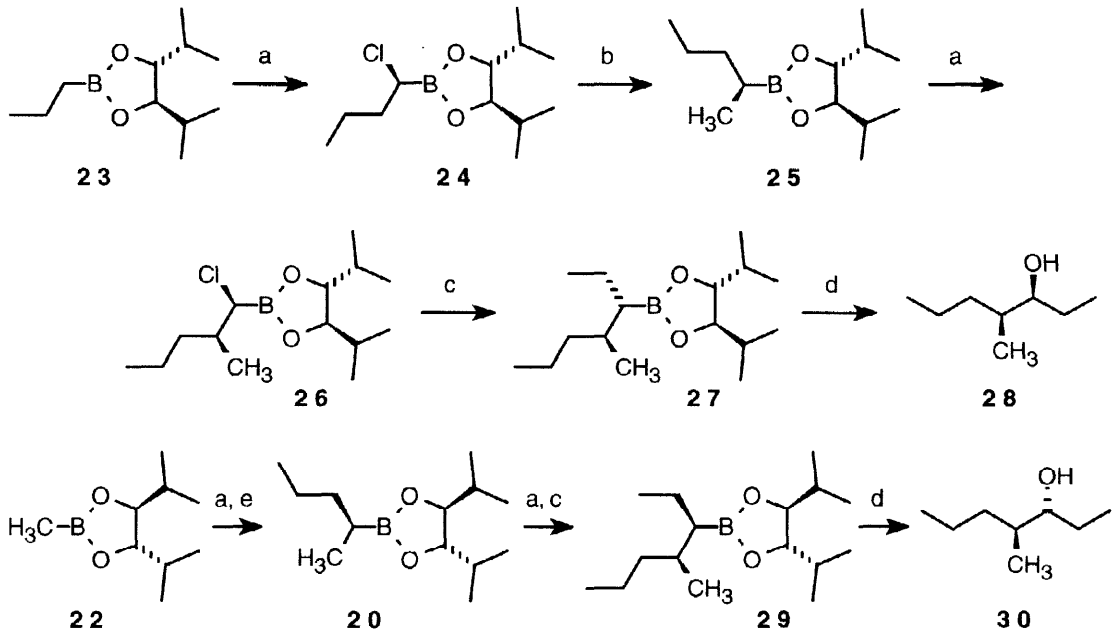
The evidence for extreme diastereoselection with DIPED is of two types. The first type of evidence was found serendipitously during an attempted synthesis of (*R*)-(*R**,*S**)-4-methyl-3-heptanol (**30**),[30] the trail pheromone of a southeast Asian ponerine ant, *Leptogenys diminuta*.[31] The diastereomeric (*S*)-(*R**,*R**)-4-methyl-3-heptanol (**28**), a component of the aggregation pheromone of the elm bark beetle, *Scolytus multistriatus*, had been synthesized earlier with pinanediol as chiral director.[32] It seemed a simple and worthwhile exercise to repeat the synthesis of **28** with the new chiral director, and then to change chiral directors in the middle of the synthesis to produce **30**.

First, the kinetically disfavored diastereomer (*S*)-DIPED (*S*)-1-chlorobutylboronate (**18**) was synthesized from (*R*,*R*)-2,3-butanediol propylboronate via chain extension to the (*S*)-1-chlorobutyl boronic ester **17** followed by cleavage of the diol by transesterification with diethanolamine, acid hydrolysis, and esterification with (*S*)-DIPED. Treatment of **18** with methylmagnesium bromide did not yield the expected 1-methylbutylboronic ester (**20**) but an air sensitive borinic ester (**21**), which oxidized rapidly to butyraldehyde and (*S*)-DIPED methylboronate (**22**).[30] The thermodynamically disfavored rearrangement of intermediate borate **19** to the borinic ester **21** must be kinetically compelled by strong steric interactions.



Methylation of a 1:1 mixture of (*S*)-DIPED (*R*)- and (*S*)-(1-chloro-2-phenylethyl)boronates led to >95% ee (*R*)-1-phenyl-2-propanol plus phenylacetaldehyde and (*S*)-DIPED methylboronate from destruction of the (*S*)-(α-chloroalkyl)boronate, reinforcing the foregoing evidence that what is normally the minor diastereomer of the (α-chloroalkyl)boronic ester is largely diverted to an entirely different product from that of the major diastereomer in the usual synthetic route.[30]

The other line of evidence was obtained by careful measurement of the dr's of the diastereomeric 4-methyl-3-heptanols. (*R*)-DIPED propylboronate (**23**) was converted to chloro boronic ester **24** and (*R*)-DIPED (*S*)-(1-methylbutyl)boronate (**25**), which on further chain extension with (dichloromethyl)lithium to **26**, ethylation to **27**, and peroxidic oxidation yielded (*S*)-(*R**,*R**)-4-methyl-3-heptanol (**28**) having a dr to its (*R**,*S**)-diastereomer of ~700:1 as measured by 75 MHz ^{13}C-NMR (comparing the weak diastereomer peaks to the 0.55% ^{13}C-^{13}C satellites of the major isomer) and confirmed by gas chromatography. (*R*)-(*R**,*S**)-4-Methyl-3-heptanol (**30**) in 500:1 dr to its (*R**,*R**)-diastereomer was similarly obtained from (*S*)-DIPED methylboronate (**22**) via chain extension and reaction with propylmagnesium chloride to produce (*S*)-DIPED (*S*)-(1-methylbutyl)boronate (**20**), the diastereomer of **25** that could not be obtained from (*S*)-DIPED (*S*)-(1-chlorobutyl)boronate (**18**) and methylmagnesium bromide.



a, $LiCHCl_2$; $ZnCl_2$; b, CH_3MgBr; c, C_2H_5MgBr; d, H_2O_2, OH^-; e, $CH_3CH_2CH_2MgCl$.

In order to achieve 500:1 dr's in **28** and **30**, the average diastereoselection has to be 1000:1 per stereocenter, >500:1 at the poorer site and >1000:1 at the other to meet the average. There

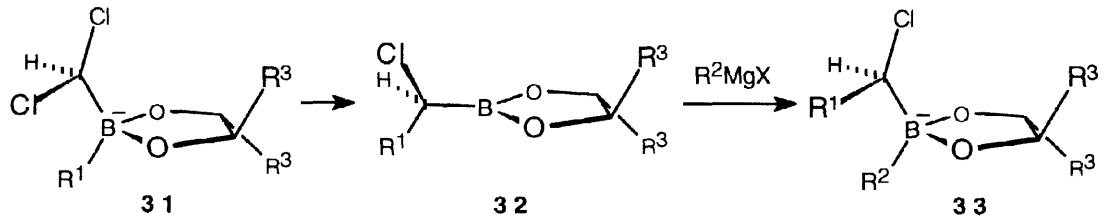
must be less than one part per million of the enantiomers of **28** or **30** from random double chirality errors. However, it is probable that most of the ~0.2% of diastereomeric impurity arises not from lack of stereoselectivity in the main process, but from an achiral boronic ester impurity in the DIPED boronic ester used as starting material. Another of our samples, the (*S*)-(*R**,*R**)-isomer, contained a readily detectable 0.5% diastereomeric impurity, which in view of the higher purity obtained with its enantiomer can only be attributed to impure starting material. Organic chemists are not normally concerned with producing liquid reagents in 99.9% purity and analyzing for 0.1% contaminants.

What real use can such precise stereocontrol have? An immediate example of scientific utility was provided by Bestmann's group, who showed that **30** is highly active as the ant trail pheromone, but that **28** and the enantiomers of **28** and **30** had only ~0.2% as much activity as **30**, in rough proportion to the amount of **30** present as an impurity.[31] Chromatographic purification of these compounds from a mixture of isomers would have been difficult at best.

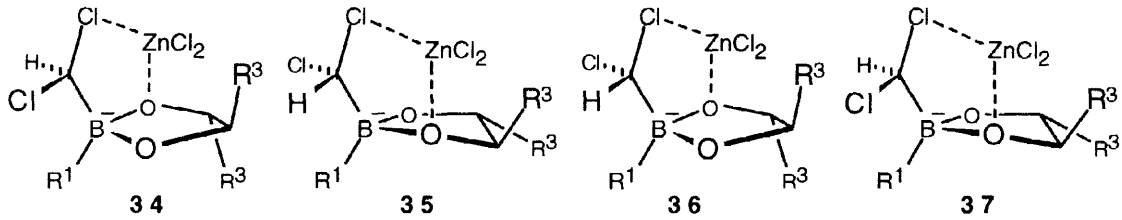
Mechanism

It should first be noted that the mechanism does not involve any sort of enantioface selection, in contrast to the great majority of asymmetric syntheses. The initial establishment of the asymmetric center involves selective nucleophilic displacement of one of two diastereotopic halides during an intramolecular rearrangement process.

The sequential double diastereoselection seen with DIPED boronic esters, and presumably all other boronic esters of C_2-symmetry, depends on the inversion of the carbon atom when the alkyl group migrates to displace one chloride ion from the dimethylborate complex **31** to form the (α-chloroalkyl)boronic ester **32**. Inversion places the remaining chloride of **32** in the vulnerable position for displacement in the subsequent borate complex **33**. The C_2-symmetry makes both faces of the boron atom equivalent in boronic ester intermediates such as **32**, which contrasts with the nonequivalence of the boron atom faces noted for pinanediol esters.



The strong effect of zinc chloride in promoting and directing the migration of R^1 in anion **31** suggests that the zinc cation might complex with one of the boronic ester oxygens while assisting the chloride ion to depart. The author attempted to use MMX calculations to explore possible transition state energies and, although the results were inconclusive, rashly drew some structures to illustrate the concept, and chose **37** as leading to the observed product in preference to **35**.[22] The major virtue of this choice, which never did really look right, was that it stimulated Corey and coworkers to write the most reasonable transition state structure, **34**, based on analogies and qualitative arguments[33] and, independently, Midland to carry out a set of Gaussian calculations.[34] Using a model in which Mg replaces Zn and R^3 is CH_3, Midland found **34** to be 4.7 kcal/mol below **35** at the RHF/6-31G* level, and 12.6 and 16.9 kcal/mol, respectively, below **36** and **37** at the RHF/3-21G level.



These drawings may exaggerate the extent to which the five-membered 1,3,2-dioxaborolane (diol boronic ester) ring flexes so that the R^3 groups are pseudoaxial (**34**, **36**) or pseudoequatorial (**35**, **37**), but in any event the ring is not planar and eclipsing strain between R^3 and H on the adjacent carbon is avoided. 1,3,2-Dioxaborolanes containing trigonal boron [e.g. **32**] do have very nearly planar rings in spite of the eclipsing strain, presumably as a result of strong B—O π-

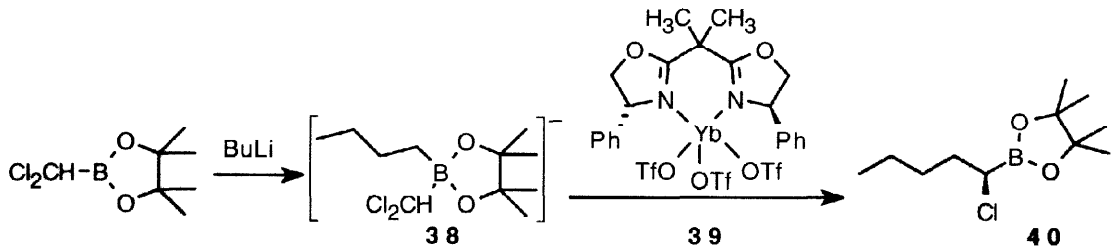
bonding,[35] but even weak coordination of a fourth ligand to the boron atom is enough to make the ring nonplanar.[36]

MMX calculations strongly favor the pseudoequatorial ligand orientation for borate complexes and will not minimize for the pseudoaxial orientation, but this is misleading when the metal ion is introduced into the system. It appears from Midland's results that the most important repulsion is between the ligands on the metal cation and a *syn*-oriented chlorine in the $CHCl_2$ group, and the second most important repulsion is between the metal with its ligands and the nearest alkyl substituent derived from the diol making up the dioxaborolane ring, and any preference for pseudoequatorial ligands is irrelevant to the transition state for chloride displacement.

The transition state **34** provides not only a satisfying explanation of why the observed (α-chloroalkyl)boronic ester isomer **32** is favored, but serves equally well to explain why intermediate **33** undergoes alkyl (R^2) migration easily while its diastereomer (e.g. **19**) does not. A different orientation of the metal cation, closer to the plane of the 1,3,2-dioxaborolane ring and outside it, has to be invoked to account for the displacement by oxygen and concomitant ring expansion when the kinetically disfavored (α-chloroalkyl)boronic ester (e.g. **18**) is treated with an organometallic reagent.[22]

Chiral catalysis

The use of chiral Lewis acids to catalyze the rearrangement of an achiral (dichloromethyl)borate anion (**38**) to an asymmetric (α-chloroalkyl)boronic ester (**40**) has been reported recently by Jadhav and Man.[37] The best catalyst found was a complex (**39**) formed in situ from a bisoxazoline and ytterbium triflate, and it was necessary to use a nonpolar, noncomplexing solvent.



This catalytic system will require more development work before it can provide a truly practical synthetic method. As it is, best results were obtained with 0.3 mole of ytterbium triflate and 5 moles of (*R*)-ligand, which yielded (*R*)-(1-chloropentyl)boronic ester **40** in 88% ee. Competition for the ligand by lithium ion present in the reaction mixture was postulated as a likely problem. Other metal triflates tested included $Zn(OTf)_2$, $Cu(OTf)_2$, and $Lu(OTf)_3$. Under conditions where $Yb(OTf)_3$ with the optimal ligand produced **40** in 71% ee, these other triflates led to 45%, 45%, and 60% ee, respectively.

SYNTHESIS WITH DICHED BORONIC ESTERS

General considerations

The efficient asymmetric synthesis of (*R*)- and (*S*)-(*R**,*R**)-1,2-dicyclohexyl-1,2-ethanediol ("DICHED")[23-25] has been outlined in a preceding section, "Chiral directors of C_2-symmetry".

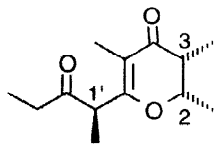
The chain extension and substitution reactions work best with nonpolar substituents. Much effort has been expended in attempts to incorporate common functional substituents into substrates for the boronic ester chain extension. The pattern that has emerged is that substituents of relatively low polarity work best. After hydrocarbons, ethers are the most compatible substrates, though there has been an unexpected benzylic ether cleavage in a compound where the boronic ester group and the ether oxygen can form a six-membered ring. Highly polar functions such as *N*,*N*-dialkylamides appear to be incompatible with the chain extension reaction.

The most successful total syntheses have been those of insect pheromones. The simple synthesis of the isomerically pure 4-methyl-3-heptanols has been described above under "Ultrahigh diastereoselection". What follows begins with our most complex successful synthesis, that of stegobinone, and the two sections immediately following describe results obtained while searching for a feasible route to stegobinone. The use of ester enolates as anions for halide displacements is included here, and involves a different mechanism for stereoselection at a second chiral center. This stereoselection is in turn related to what must prevail in the reaction of an allylic Grignard reagent with a chiral ester of boric acid, and to products useful in Hoffmann's reactions of asymmetric allylic boronic esters with aldehydes. Finally, investigations into the compatibility of DICHED boronic esters with multiple alkoxy and other polar substituents are described.

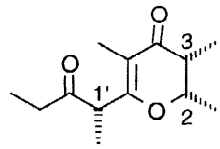
Stegobinone and stegobiol

Stegobinone (**41**) is the pheromone of the Anobiid beetle *Stegobium paniceum*, a pest of stored dried spices and other foodstuffs,[38] and also the furniture beetle, *Anobium punctatum*.[39] Stegobinone epimerizes readily on a time scale of hours or days to 1′-epistegobinone (**42**), which is repellent to the insects. The presence of ~3% **42** effectively neutralizes the attractive effect of **41**. A plausible hypothesis to account for the natural selection of such a pheromone system is that these insects typically live in confined spaces where evaporation would be ineffective at removing obsolete pheromone trails. This epimerization to a repellent serves that purpose.

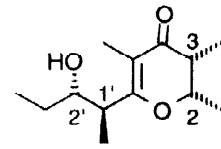
The challenge to the chemist is to make and purify stegobinone fast enough to obtain the compound free from its 1′-epimer **42**. Syntheses by Hoffmann and coworkers[40] and by Mori and Ebata[41] provided impure stegobinone having <1% of the natural activity, just enough activity to indicate clearly that **41** is the attractive isomer. Natural stegobinone contains 5% of stegobiol (**43**), a likely biogenetic precursor, and there was evidence that suggested that stegobiol was part of the attractant system. Since a standard secondary alcohol oxidation was expected to convert stegobiol to stegobinone, stegobiol was chosen as the initial target.



41 stegobinone



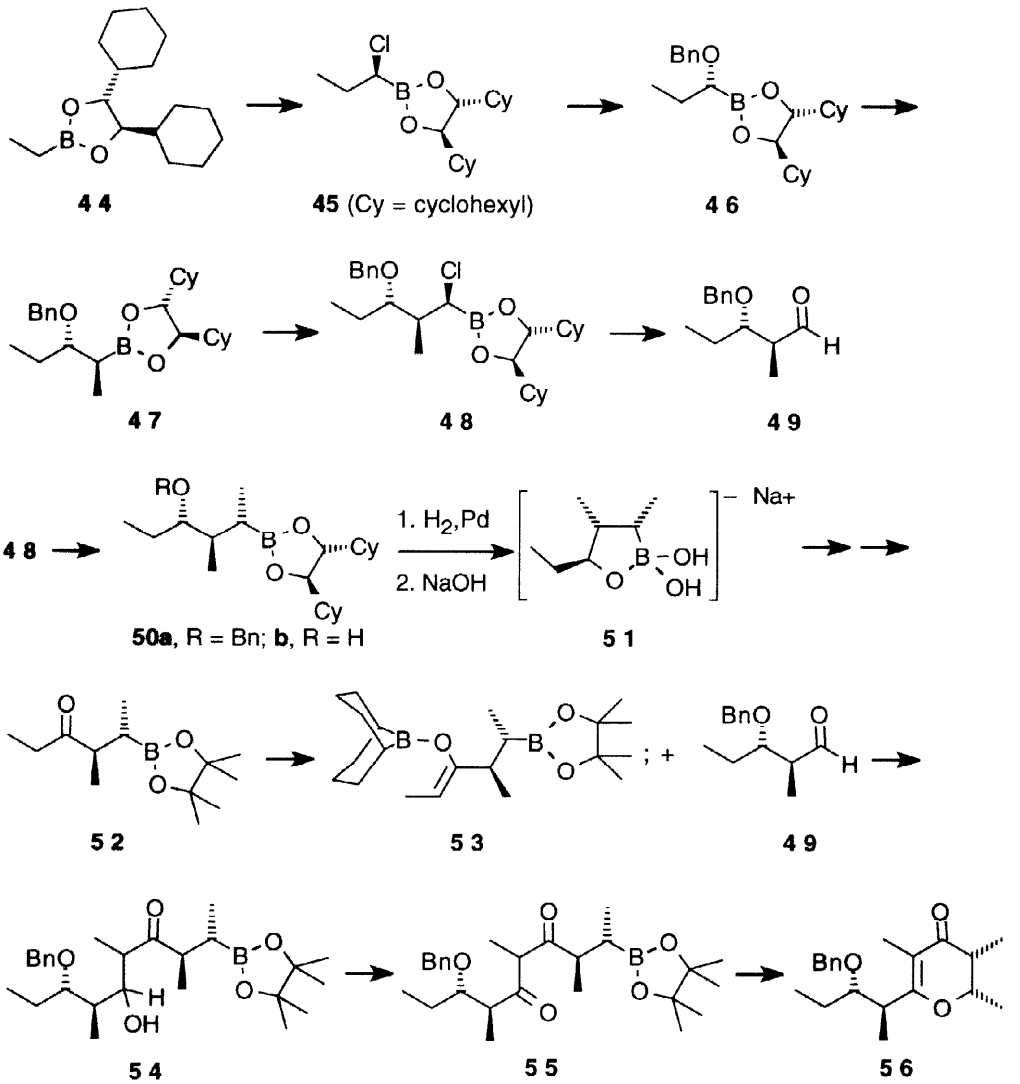
42 epistegobinone



43 stegobiol

The synthesis as it was finally worked out utilizes a common intermediate (**48**) for both chiral segments of stegobiol.[42] Esters of ethylboronic acid are easily made via the conventional route from the ethyl Grignard reagent[22] or, alternatively, by hydroboration of ethylene with boron trichloride and triethylsilane,[43] and transesterification leads to (*R*)-DICHED ethylboronate (**44**), more formally described as [4*R*-(4α,5β)]-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane. The reaction with (dichloromethyl)lithium followed by treatment with zinc chloride was used for three chain extensions, **44** to **45**, **46** to an intermediate not illustrated, and **47** to key intermediate **48**. (These reactions were successful with (dichloromethyl)lithium generated in situ as well as preformed.) Nucleophilic displacement with lithium benzyl oxide converted **45** to **46**. Reactions with methylmagnesium chloride produced **47** from its chloro precursor, and converted **48** to **50a**. Peroxidic oxidation of **48** at pH 8-9 yielded **49** (55-65% from **44**). Although **49** epimerized if subjected to chromatography, it was easily obtained in high enantiomeric and diastereomeric purity (~99%) by distillation.

The other half of the stegobinone molecule was derived from the ketone **52**, which was obtained in ~39% yield from **44**. Debenzylation of **50a** was straightforward, but prior attempts to oxidize **50b** directly had resulted in partial cleavage and oxidation of the DICHED. Base hydrolysis of **50b** proved feasible because the resulting boronic acid cyclized to water-soluble salt **51**, from which the DICHED could be removed by ethereal extraction. The pinacol ester derived from **51** was oxidized efficiently to **52**.



The enolate **53** made from 9-BBN triflate proved better than other boron enolates tested for aldol condensation with aldehyde **49**. The only other enolate tested was the lithium enolate, which also worked. Intermediate **54** was not isolated but oxidized with chromium(VI) directly to **55**, which on peroxidic deboronation yielded easily purifiable *O*-benzylstegobiol (**56**).

Debenzylation of **56** to stegobiol (**43**) by hydrogenolysis resulted in some hydrogenation of the double bond, but it was accidentally discovered that methanesulfonic acid in chloroform provides a more selective process. Stegobiol (**43**) had been reported previously as an oil which

was weakly attractive to,[44] but the pure sample crystallized and was found to have no attractant properties.[42,45] Oxidation of stegobiol was readily accomplished with perruthenate and amine oxide, and the resulting stegobinone (**41**) was readily crystallized, stable for months, and very highly attractive to *S. paniceum*.[42,45]

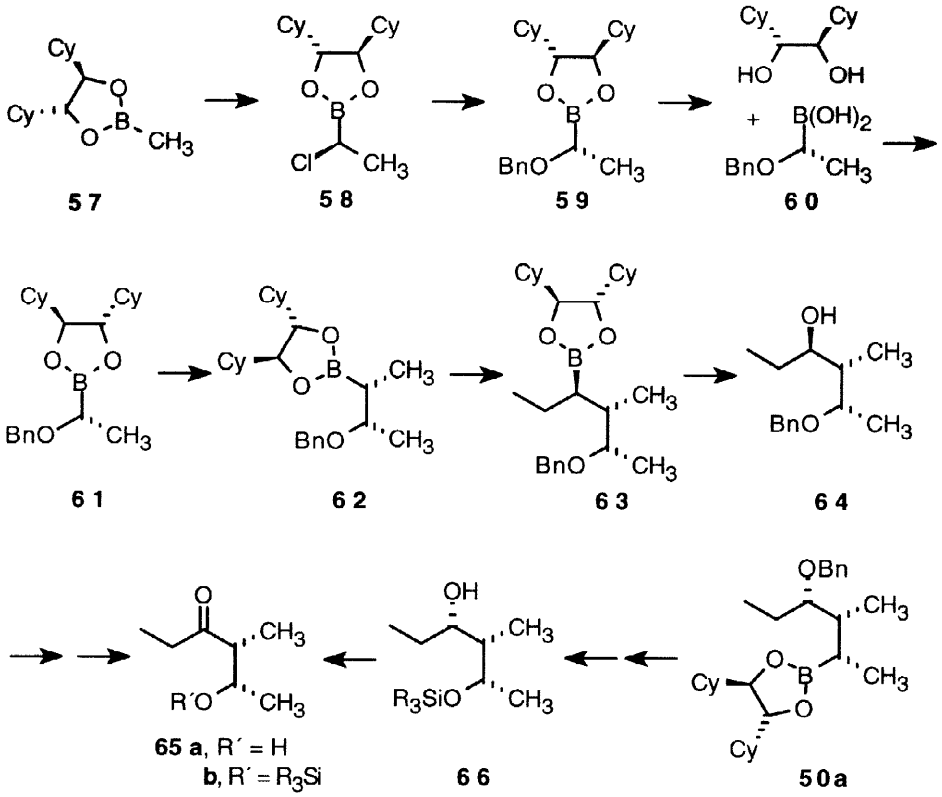
Chiral director removal/replacement

Prior to the discovery of the route to stegobinone described above, a different strategy was tested, which was based on the ester cyclization route reported by Mori and Ebata.[41] For the right hand side of stegobinone (**41**), the route chosen required the use of (*R*)-DICHED to guide construction of the first asymmetric center at C(2), followed by its removal and replacement with the enantiomeric (*S*)-DICHED for construction of the second asymmetric center at C(3).

Hydrolysis of chiral 1,2-diol boronic esters (1,3,2-dioxaborolanes) of C_2-symmetry is contrathermodynamic because of the unfavorable entropy of converting three molecules (boronic ester + 2 H_2O) to two (boronic acid + diol) plus the relative stability of the 4,5-*trans*-disubstituted dioxaborolane ring. Under basic conditions, nothing changes except that the boron atom forms a hydroxylated, tetracoordinate anion in both the boronic ester and the boronic acid. This problem was overcome by treating the [1-(benzyloxy)ethyl]boronic ester **59** with aqueous base and TAPS {3-[tris(hydroxymethyl)methylamino]propanesulfonic acid} or pentaerythritol in the presence of ether, which extracted the liberated DICHED.[46] Although NMR evidence indicated that only two hydroxyl groups of the triol were ligated to boron, the water solubility of these polyols and their borate esters appeared to be a factor in the success of the separation.

Preparation of **59** from **57** was carried out via the usual chain extension with (dichloromethyl)lithium to **58** followed by treatment with lithium benzyl oxide. Boronic acid **60** separated from (*R*)-DICHED was esterified with (*S*)-DICHED to form **61**, which was converted to **62** via chain extension and methylation and on to **63** via chain extension and ethylation.

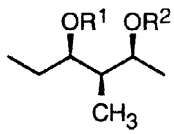
Deboronation with hydrogen peroxide yielded **64**. For purposes of the stegobinone synthesis, **65** was derived from **64** via oxidation to the ketone, debenzylation, and silyl protection.



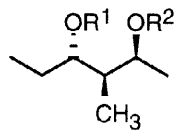
This rather convoluted synthesis of **65** had evolved from a failed attempt to use the Mori-Ebata model[41] for our synthesis, for which a carboxylate ester of **65a** rather than the silyl derivative **65b** was needed (see below). After carrying out our first successful synthesis of stegobinone via a variant of the route already outlined, using **65** in place of **52** for the aldol condensation with aldehyde **49**, it became apparent that it might be easier to make **66** via **50a**, which proved true.

The diastereomeric difference between **64** and **66** is irrelevant to the stegobinone synthesis. The synthetic significance of this change of chiral directors is that it provides a rational general stereoselective route to differentially protected 1,3-diols having the relative stereochemistry of **64**, the *syn,syn* isomer when rewritten as **67**(**64′**). This diastereomer is not accessible via boronic

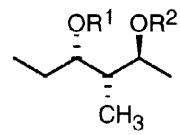
ester chemistry without a change of chiral directors. The *anti,syn* relationship of **68(66′)** was achieved with a single chiral director, and it would be a trivial exercise in starting from the other end of the chain to reach its *syn,anti* inverse **69**. The *anti,anti* relationship of **70** is what will result if boronic ester chain extension is continued to a fourth carbon. There is no good direct way to replace boron by hydrogen, though conversion of the boron to hydroxyl might be followed by conventional reduction of an alcohol sulfonate to the hydrocarbon.



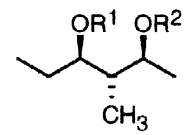
67 (64′)



68 (66′)



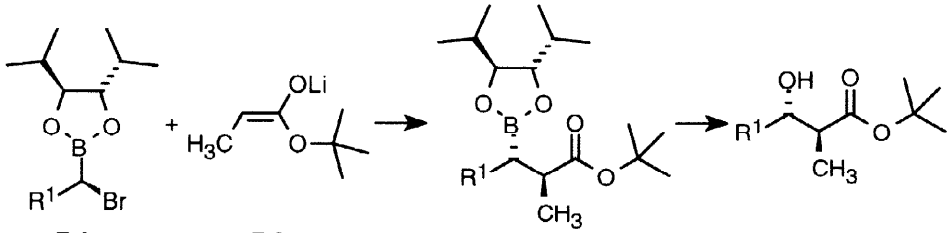
69



70

Enolates, α-bromo boronic esters, and retroracemization

The left hand side of the stegobiol molecule corresponds to a β-hydroxy acid if the Mori-Ebata route[41] is followed. Reaction of several α-bromo boronic esters (**71**) with *t*-butyl lithiopropionate (**72**), a *trans*-enolate, yielded *anti*-boronic esters (**73**) in 94-98% diastereomeric purity, as indicated by peroxidic deboronation to *anti* -α-methyl-β-hydroxy carboxylic esters (**74**).[47]

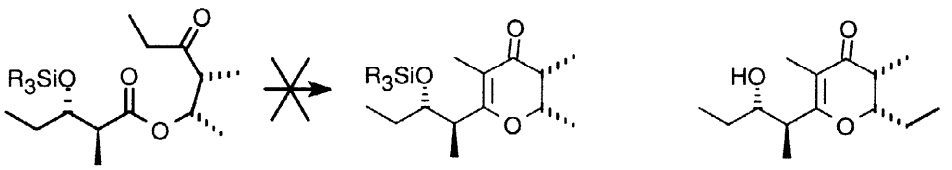


71 **72** **73** **74**

It appeared that this route would easily provide the left-hand portion, C(1′)-C(5′), of stegobiol, and it did, though later observations imply that the enantiomeric purity of **74** might not always have turned out as high as the diastereomeric purity (see below). It also seemed plausible that a *cis*-enolate such as those derived from oxazolidinones ought to yield the *syn*-α-methyl-β-hydroxy ester, corresponding to C(1)-C(4) of stegobiol, but this proved to be a wrong guess. Instead, oxazolidinone enolates also yielded the *anti*-product almost exclusively.[48]

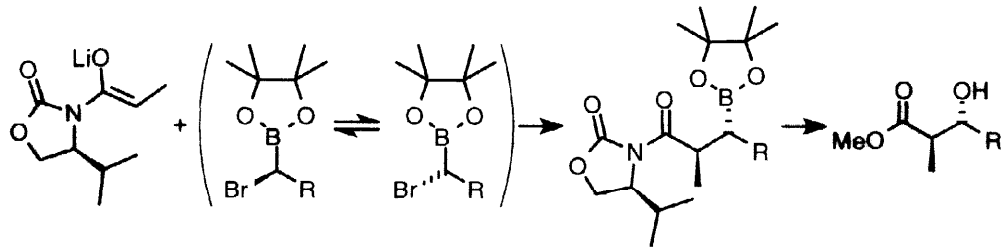
The possibility of using the α-bromo boronic ester to set one asymmetric center and the Evans chiral oxazolidinone enolate[49] to control the other was then tested as a means of forcing *syn*-diastereomer formation. The result was a gross mixture in which the *anti*-isomer predominated.

The only plausible explanation for this result was that the α-bromo boronic ester was epimerizing under the reaction conditions. Furthermore, the strong bias against simple displacement of halide from the nonkinetic diastereomer of the α-bromo boronic ester by simple alkyl groups must be diminished for enolates. This route was accordingly abandoned for the right-hand portion of stegobiol, which was instead made via **64**. Esterification of the hydroxy ketone **65a** with the silylated acid derived from **74** (R^1 = Et) led to **75**, a variant of the Mori-Ebata intermediate,[41] but attempted ring closure to **76** failed.[50] Subsequently, a different method for closing an ester to serricorone (**77**) was described by Oppolzer and Rodriguez.[51]



75 **76** **77**

As part of the foregoing investigation, the reaction of the Evans enolate (**78**) with racemic pinacol boronic esters **79** was found to provide the single diastereomer **80** in high diastereomeric purity, confirmed by conversion to the known series of hydroxy esters **81**.[48] With R = CH_3, the yield of **80** was higher than half of the racemate of **79**, and by adding sodium iodide to accelerate racemization, **80** was obtained in high yield from a 1:1 ratio of enolate **78** to racemate (*RS*)-**79**. It is apparent that the enolate **78** reacts much more rapidly with ***S*-79** than with ***R*-79**, allowing time for continuous enantiomeric equilibration. Larger R groups (butyl, isopropyl) resulted in good stereocontrol but not as good yields, apparently because of decomposition of the enolate **78** during longer reaction times.



78 S-79 R-79 80 81

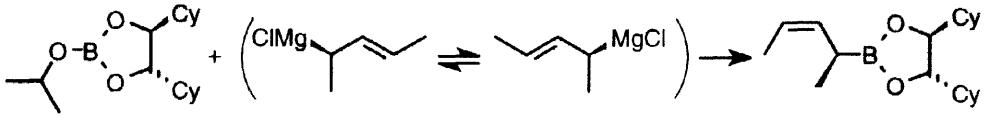
We described this process as "enantioselective capture with retroracemization" or just "retroracemization", since the net result is to run racemization backwards.[48] Other examples of similar phenomena have been described as "dynamic kinetic resolution",[52] "enantiomerization",[53] "retroracemization",[54] or just "racemization" with a description of the context.[55-57]

A disturbing observation during the foregoing investigation was that DICHED α-bromo boronic esters epimerize fairly rapidly during reactions with enolates, and that the epimer that fails to yield internal nucleophilic displacement products with alkyl groups derived from Grignard reagents reacts readily enough with enolates to produce substantial percentages of the undesired diastereomer. Thus, the reaction of ester enolates with α-bromo boronic esters[47] does not provide a reliable route to enantiomerically pure α-methyl-β-hydroxy carboxylic esters,[48] though 300-MHz NMR is apparently adequate to detect any substantial amounts of unwanted diastereomers in the DICHED boronic ester intermediates.

Retroracemization in a boronic ester synthesis

Reaction of (*S*)-DICHED isopropyl borate (**82**) with 2-pentenyl-4-magnesium chloride (**83**) results in enantioselective capture and retroracemization of **83**.[57] This reaction produces the same product, (*S*)-DICHED (*S*)-(*Z*)-1-methyl-2-butenylboronate (**84**), that can be obtained from (*S*)-DICHED (*R*)-(1-chloroethyl)boronate and (*Z*)-1-propenyllithium.[23] The mechanism and stereoselectivity are unrelated to (α-haloalkyl)boronic ester formation, but might be related in some way to the reaction of enolates with α-bromo boronic esters. The 97% diastereomeric purity of **84** from retroracemization is not quite as high as the 99.5% purity obtained from the (α-

chloroethyl)boronic ester route,[23] but it is high enough to be useful, and the simplicity of the process is highly significant.



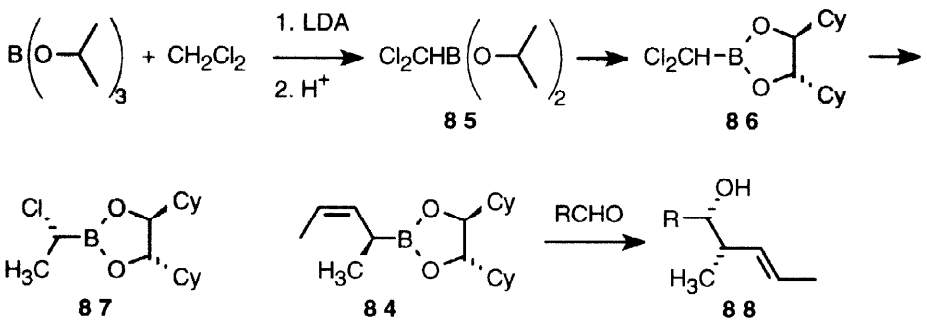
82 ***R*-83** ***S*-83** **84**

Because the magnesium cation is probably displaced in an S_E2' reaction with allylic rearrangement, it is not obvious which enantiomer of **83** reacts with the chiral borate ester **82**, or what factors might most influence enantioface selection as the boron attacks the allylic carbon. If boron attacks *syn* to the departing magnesium cation, there may be a cyclic transition state in which magnesium cation is transferred from carbon to an oxygen atom in the dioxaborolane ring.

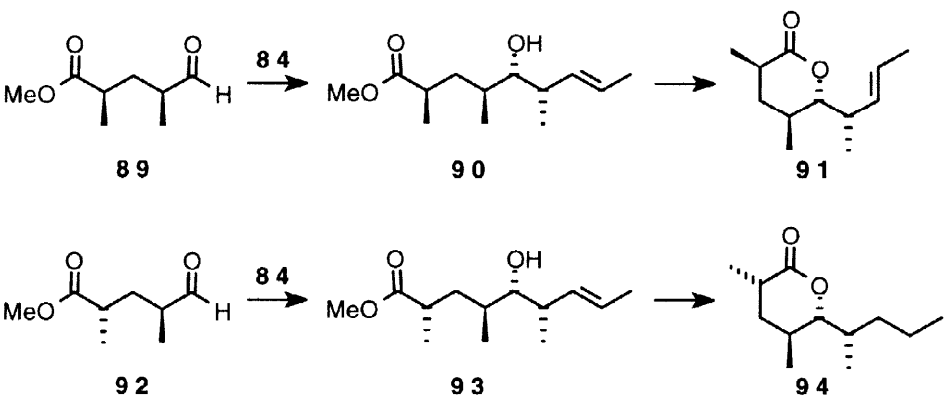
The reaction of propionate enolates with α-bromo boronic esters involves enantioface selection on the enolate, and the transition state may have a structure related to that for the enantioface selection in the allylic Grignard reagent **83**. Another example of enantioface selection involves reaction of chiral boronic esters with α-chloro carbanions, discussed under "α-Chloro boronic esters from α-chlorobenzyl anions" near the end of this article.

Asymmetric allylic boronic esters: mycinolide V, invictolide

The allylic boronic ester **84** has been used as a key reagent in natural product synthesis via Hoffmann's asymmetric allylboration of an aldehyde.[23,60] Diisopropyl (dichloromethyl)boronate (**85**) has been prepared from preformed (dichloromethyl)lithium[58] or, more efficiently, by addition of lithium diisopropylamide to a mixture of triisopropyl borate and dichloromethane in THF.[59] The (*S*)-DICHED ester was prepared by transesterification and was methylated in the usual manner to provide **87**. (*Z*)-1-Propenyllithium converted **87** to **84** in very high purity, and the reaction of **84** with aldehydes provided a general route to chiral homoallylic alcohols **88**.[23]



With aldehyde **89**, **84** was converted to homoallylic alcohol **90**, which cyclized to lactone **91**, the key intermediate in the first mycinolide V synthesis. Similarly, the diastereomeric series with **92** yielded **93**, which was converted to the natural product invictolide (**94**) by lactonization and hydrogenation.[23,60]

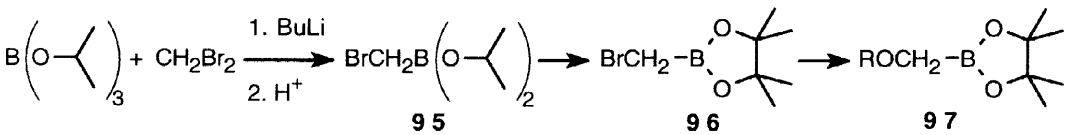


The allylic asymmetric center immediately adjacent to the boron atom provides the chirality control for these syntheses. It should be noted that the synthesis of **84** involves propenylation of an (α-chloroethyl)boronic ester, not methylation of an (α-chlorocrotyl)boronic ester, because the latter have proved extremely labile to epimerization and allylic rearrangement. (α-Methoxycrotyl)boronic esters are valuable reagents for asymmetric reactions with aldehydes, but frustration in attempts to make these compounds directly via (α-chlorocrotyl)boronic esters has led to adoption of a roundabout route to these compounds.[61]

Other chiral allylic boronic esters have also been used extensively in place of enolates in asymmetric synthesis,[62] generally with chirality control provided by the diol with which the boron is esterified. Boronic esters of dialkyl tartrates are easily prepared and among the most useful of these. However, this very extensive chemistry is outside the scope of this review.

Exploratory studies with alkoxy substituents

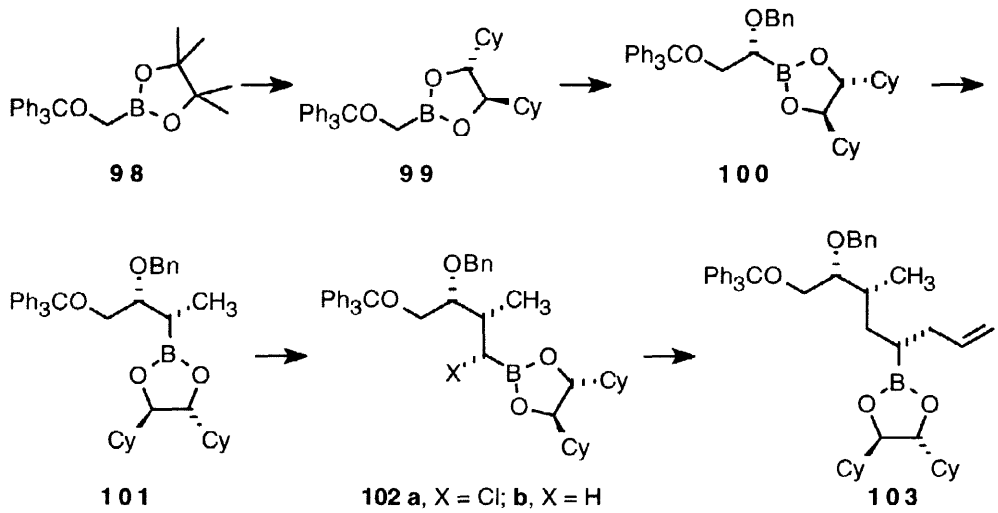
This section is primarily concerned with syntheses based on (alkoxymethyl)boronic esters, which in turn are derived from diisopropyl (chloromethyl)boronate[63] or, preferably, (bromomethyl)boronate (**95**).[64] Addition of butyllithium to dibromomethane in the presence of triisopropyl borate generates unstable (bromomethyl)lithium, which is captured by triisopropyl borate. Addition of an alkoxide to the isopropyl ester **95** would result in competition between isopropoxy and the added alkoxy group for displacement of the bromide, and **95** is therefore converted to the pinacol ester (**96**), postponing the introduction and possible partial loss of the chiral director until chirality is relevant to the synthesis.



The group R was initially chosen as benzyl or, for differentiation from benzyloxy groups to be introduced later, *p*-methoxybenzyl, and several intermediates designed to be useful in an attempted synthesis of the macrolide aglycone leuconolide were prepared.[65] However, after the discovery that sodium trityl oxide in dimethyl sulfoxide displaces bromide from **96** to produce the (trityloxymethyl)boronic ester **98** efficiently, it was found that **98** has a number of good synthetic properties, including the fact that it and several of the simpler (ω-trityloxyalkyl)boronic esters are crystalline solids.[35]

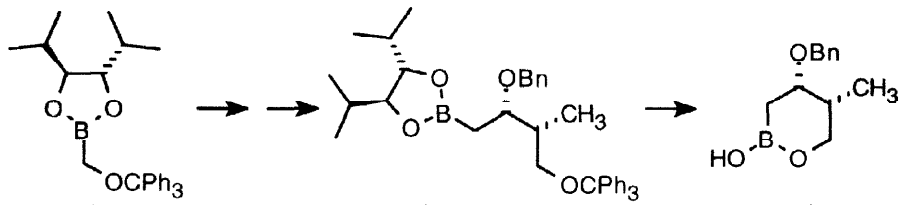
The synthesis of leuconolide was not feasible with the available resources via this chemistry, but (*R*)-DICHED ester **99** was the starting point for the approach that proceeded the farthest.

Chain extensions and substitutions with the appropriate nucleophiles led to intermediates **100** and **101**. Attempts to insert a methylene group into **101** with (chloromethyl)lithium[63] failed, and it appeared that the problem was elimination of the boron and the β-benzyloxide. However, (dichloromethyl)lithium inserted normally into **101** to form **102a**. Reduction of the CHCl group of **102a** to the CH_2 group of **102b** was accomplished with sodium hydride in dimethyl sulfoxide, a new reagent for carrying out this type of reduction. This reagent had been discovered serendipitously when excess sodium hydride was used to prepare sodium benzyl oxide, and hydride substitution was observed to compete with benzyloxy substitution.[65] Chain extension of **102b** and reaction of the chloro intermediate with allylmagnesium chloride led to **103**.



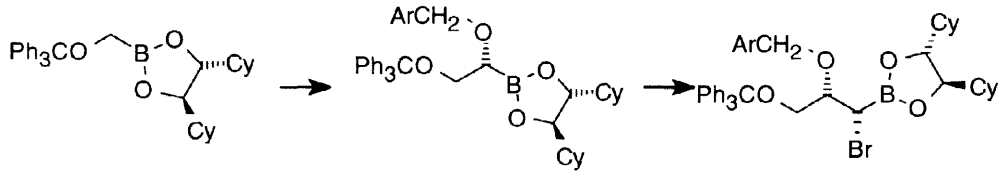
Yields were in the usual 80-90% range for each carbon insertion and substitution up through the preparation of **102b**, but the yield of **103** was only ~60%, and benzyl chloride was obtained as a major byproduct during the preparation of the chloro precursor to **103**. It was surmised that a six-membered ring could be formed by linkage of the benzyloxy oxygen atom to the boron atom, and that zinc chloride perhaps catalyzed the transfer of the benzyl group to chloride ion. The net result would be a borate complex which would liberate DICHED on hydrolysis, leaving a polar *B*-hydroxy-1,2-oxaborin that would be tightly bound to a silica column and lost during workup.

Although the postulated *B*-hydroxyoxaborin byproduct was not retrieved from the preparation of **103**, a compound of this class (**106**) was observed when the (*S*)-(*R**,*R**)-1,2-diisopropylethane-1,2-diol ["(*S*)-DIPED"] ester **105** was detritylated with formic acid and produced **106** instead of the expected DIPED boronate. The conversion of DIPED (trityloxymethyl)borate (**104**) to intermediate **105** involved a typical series of reactions with (dichloromethyl)lithium and nucleophilic displacement. In this case, the final methylene group was successfully introduced with (chloromethyl)lithium.[65]

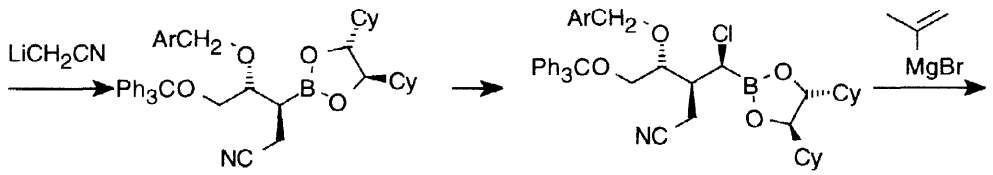


104 **105** **106**

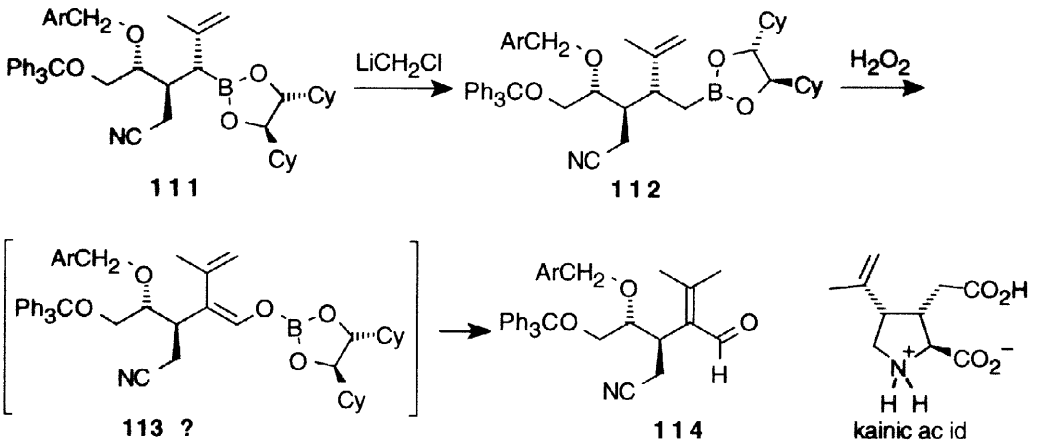
Another sequence involving DICHED (trityloxymethyl)boronate was undertaken with the carbon skeleton of kainic acid in mind.[66] This involves no new principles, and the entire sequence proceeded very smoothly, up until it crashed unexpectedly at the peroxidic deboronation step.



99 **107** (Ar = *p*-$MeOC_6H_4$) **108**



109 **110**

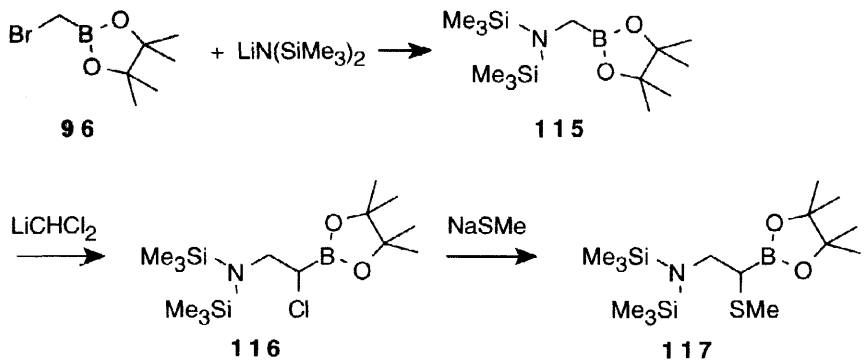


Conversion of (*R*)-DICHED (trityloxymethyl)boronate to the chain extended *p*-methoxybenzyl derivative **107** was carried out in the usual way, via treatment with (dichloromethyl)lithium and zinc chloride followed by lithium *p*-methoxybenzyl oxide. (Dibromomethyl)lithium converted **107** to **108**, which reacted with lithioacetonitrile to form **109**. (The chloro analog of **108** had proved unreactive.) (Dichloromethyl)lithium converted **109** to **110**, which reacted readily with isopropenylmagnesium bromide to produce **111**, and chain extension to **112** with (chloromethyl)lithium proved routine. Hydrogen peroxide unexpectedly converted **112** to aldehyde **114**, presumably via enolate **113**.[66]

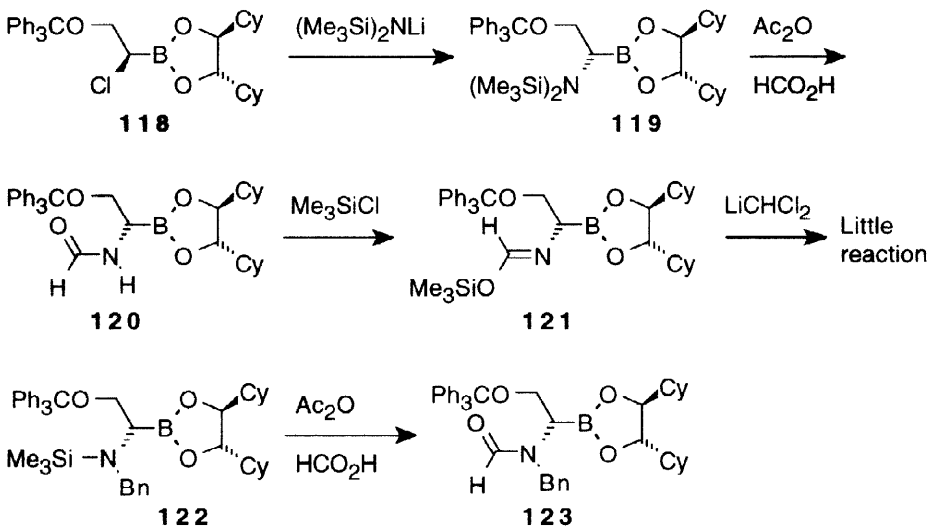
The amount of base used may have been insufficient to suppress radical reactions, and there may be a way to deboronate this material to the alcohol without rearrangement, but these questions were not pursued. Kainic acid corresponds to the enantiomeric series, which was completed as far as ***ent*-112**.[66] Kainic acid would have a carboxyl group in place of the trityloxymethyl as well as the cyano group. The *p*-methoxybenzyloxy group would have to be replaced by nitrogen with retention, or the amino acid epimerized, and appropriate pyrrolidine ring closure would have to be accomplished at the right point. It did not appear practical to pursue this route further.

Exploratory studies with amide substituents

It was of interest to pursue the synthesis and chain extension of masked amino boronic esters as possible precursors to kainic acid and other compounds of biological significance. It was found straightforward to carry out a chain extension on a simple achiral silylated (aminomethyl)boronic ester (**115**) to form the racemic α-chloro boronic ester (**116**).[67] However, **116** was resistant to substitution with lithium benzyl oxide, and required a better nucleophile such as sodium methyl mercaptide, which yielded **117**. Thus, it appeared that the silylated amino group strongly deactivates α-halo boronic esters toward nucleophilic substitution.

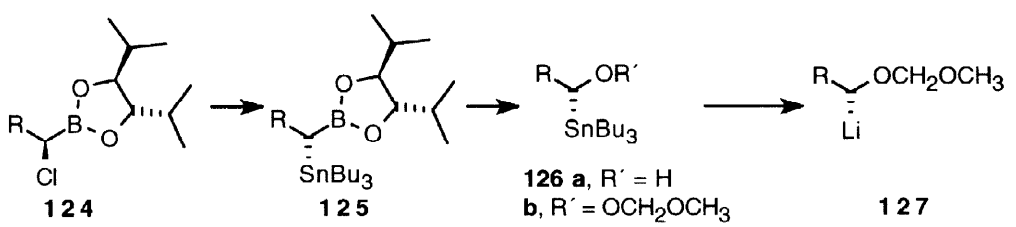


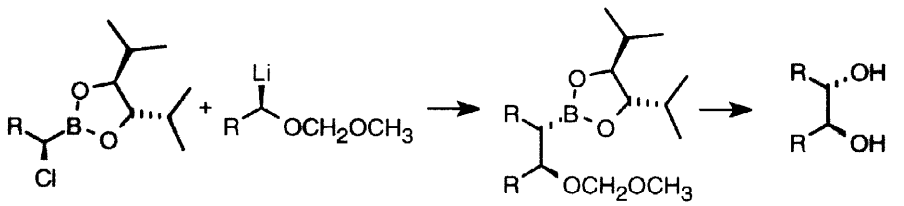
With more complex structures, attempted chain extension of several types of blocked amino functions failed almost completely.[67] Conversion of chloro boronic ester **118** (derived from ***ent*-99**) to the bis(trimethylsilyl)amino derivative **119** was routine, but unlike **115**, **119** proved inert toward attempted insertion of a chloromethyl group. Formylation of **119** to **120**, a simple extension of known chemistry,[68] was followed by silylation in the hope of obtaining a compound that would undergo chain extension, but **121** also proved inert, as did the *N*-benzyl compounds **122** and **123**.[67] Evidently the boronic ester group in these compounds captures (dichloromethyl)lithium in the usual manner, as indicated by the failure of the reaction mixture to darken as would have occurred if the unstable carbanion had persisted in the reaction mixture until warmed, but rearrangement of the borate complex is very slow.



Coupling with α-lithio ethers

The mechanism of the displacement of halide from α-halo boronic esters requires not only inversion of the configuration of the carbon from which halide is displaced, but also retention of configuration of the carbon atom that migrates from boron to carbon. Most carbanions cannot be made in enantiomerically pure form, but α-lithio ethers can be made in high enantiomeric purity from organotin compounds.[69] Conversion of (*S*)-DIPED (α-chloroalkyl)boronates (**124**) to the corresponding tributyltin derivatives **125** followed by peroxidic deboronation to α-tributylstannyl alcohols **126a** was followed by conversion to the α-tributylstannyl ethers **126b**, which were converted by *n*-butyllithium to the α-lithio ethers **127**. Reaction of **124** with **127** at –78 °C resulted in the expected coupling to **128** when R was *n*-butyl, and chiral 5,6-decanediol (**129**, R = C_4H_9) was obtained in >98% diastereomeric purity.[70]





124 **127** **128** **129**

When R was isopropyl and **124** was added to **127** at –78 °C, the major product was from the reaction of **124** with the *n*-butyllithium used to generate **127** from **126b**. This unexpected problem was circumvented by cooling the reaction mixture to –100 °C. It was postulated that the tin/lithium exchange reaction must have a higher heat of activation, hence a higher temperature coefficient, than the reactions of the organolithiums with borate esters, so that at –100 °C the more stable α-lithio ether **127** is not converted at a competitive rate to the more reactive *n*-butyllithium. At –78 °C this conversion coupled with rapid butylation of the boron atom of **124** is faster than entropically unfavorable alkylation of **124** by the sterically hindered α-lithio ether **127**. There is of course no need for the two R groups to be the same, but for purposes of proving the diastereomeric purity, >98%, it is convenient to have a symmetrical diol as product.[70]

The enantiomerically pure tin compounds **126** are valuable synthetic reagents in other contexts[71] and can be made in other ways,[69,72] though the synthesis from boronic esters is potentially a useful route for making multigram quantities.

SYNTHESIS WITH PINANEDIOL BORONIC ESTERS

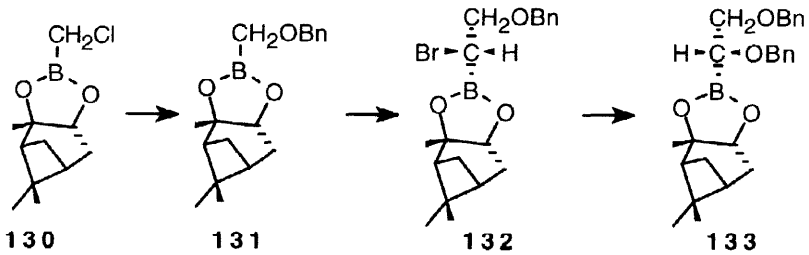
General comments

Pinanediol remains a useful chiral director, even though it does not give quite as precise stereocontrol as DICHED or other diols of C_2-symmetry. Either enantiomer of pinanediol can be produced easily in substantial quantities,[73] and pinanediol boronic esters are especially resistant to hydrolysis. Because pinanediol was the first chiral director used successfully with α-halo boronic esters, it has a longer history and is more widely known than DICHED, and has had several types

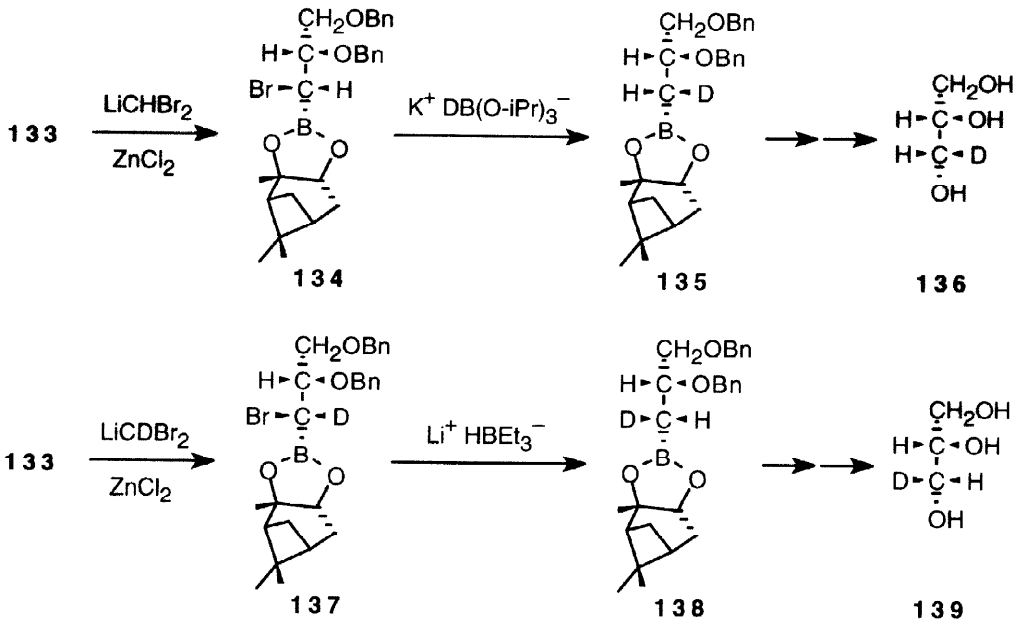
of applications that have not yet been tested with DICHED boronic esters. There are a few instances in which pinanediol esters are clearly superior to esters of C_2-symmetrical diols as synthetic intermediates.

Isotopic labels

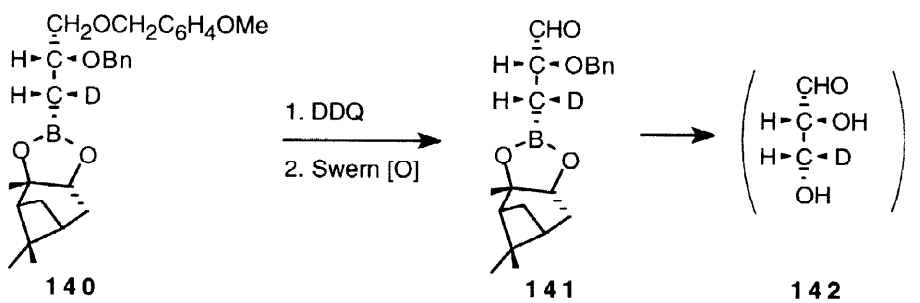
Pinanediol esters have been used to synthesize glycerol with a stereoselectively placed deuterium label at either of two diastereotopically related positions.[74] The carbon to which the labels were attached is the one that becomes the terminal CH_2OH group of glucose via the normal enzymatic synthesis, the only site in glucose that has a diastereotopic pair of hydrogens. The synthesis began with (*S*)-pinanediol (chloromethyl)boronate (**130**), which was converted to the benzyloxy derivative **131**. Chain extension with (dibromomethyl)lithium to **132** and treatment with lithium benzyl oxide to produce **133** essentially repeat part of the earlier L-ribose synthesis.[75]



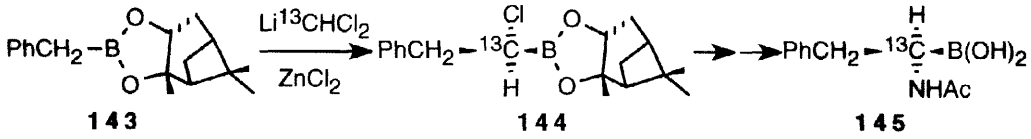
One of the label positions was reached by chain extension of **133** to **134** with (dibromomethyl)lithium, followed by reaction with potassium borodeuteride to form **135**, which was deboronated with hydrogen peroxide and debenzylated to yield the deuteriated glycerol **136**. The complementary label pattern was obtained by generating (deuteriodibromomethyl)lithium from dideuteriodibromomethane to form **137**, which with lithium triethylborohydride yielded **138**, the precursor to deuteriated glycerol **139**. NMR analysis indicated that each isomer was obtained in ~96% diastereomeric purity.[74]



The original goal of this project was to prepare stereoselectively labeled D-glyceraldehyde (**142**). Toward that end, the *p*-methoxybenzyloxy boronic ester **140** was synthesized, starting from **130**, and the protecting group was cleaved with dichlorodicyanoquinone (DDQ). Swern oxidation then yielded aldehyde **141**. Peroxidic deboronation and debenzylation with hydrogen and palladium yielded what appeared to be **142** containing glycerol as an impurity. However, glyceraldehyde exists as a gross mixture of oligomeric hemiacetals and acetals, and the exceedingly complex NMR spectrum did not provide a satisfactory way to compare the product with authentic glyceraldehyde. Since glycerol can be converted to glyceraldehyde phosphate enzymatically, there seemed no point in further pursuit of **142**.[74]



A ^{13}C label has been incorporated into the boronic acid analog of *N*-acetylphenylalanine (**145**). The synthesis was begun from pinanediol benzylboronate (**143**), and the preparation of (dichloromethyl)lithium-^{13}C was optimized with respect to consumption of dichloromethane-^{13}C for the preparation of intermediate chloro boronic ester **144**.[76]

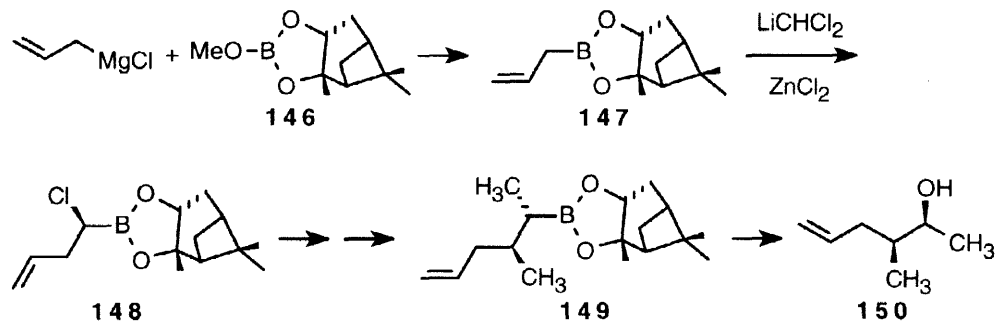


143 **144** **145**

Reaction of pinanediol phenylboronate with (dichloromethyl)lithium followed by reduction with lithium triethylborodeuteride has led to pinanediol benzylboronate (**143**) with a deuterium label placed diastereoselectively in the CH_2 group. The position of the label was verified by peroxidic oxidation to deuteriated benzyl alcohol, and the labeled **143** was converted to labeled phenylalanine via further chain extensions.[77]

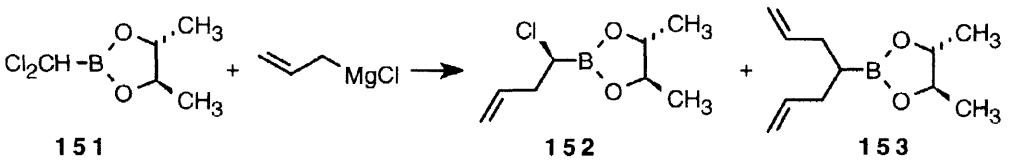
An allylic boronic ester chain extension

Allylic boronic esters have provided an example in which the pinanediol ester is superior to esters of C_2-symmetry for synthetic purposes. (*S*)-Pinanediol allylboronate (**147**), which is most easily prepared by allylation of pinanediol methoxyboronate (**146**), underwent normal chain extension with (dichloromethyl)lithium to form the α-chloro boronic ester **148**. Further substitution and chain extension led to **149** and deboronation to (2*S*,3*S*)-3-methyl-5-hepten-2-ol (**150**).[78]



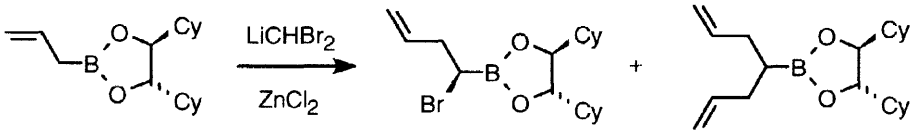
146 **147** **148** **149** **150**

(*R*,*R*)-Butanediol (dichloromethyl)boronate (**151**) with allylmagnesium chloride was tested as an alternative source of a 1-chloro-3-butenylboronic ester (**152**), but major amounts of the (diallylmethyl)boronate **153** were formed as a byproduct under a variety of conditions.[78] The evidence appeared to indicate that the allylborate anion formed from allylmagnesium bromide and **151** could transfer an allyl anion to the product **152** under the reaction conditions, though the possibility of an error in interpretation or experimental technique could not be ruled out unequivocally.



151 **152** **153**

In a subsequent study, it was found that treatment of DICHED allylboronate (**154**) with (dibromomethyl)lithium produced a mediocre yield of the expected chain extension product **155** together with substantial amounts of DICHED (diallylmethyl)boronate (**156**).[65] Thus, the diallylated product can only arise via allyl anion transfer from the allylborate anion, composed of **154** plus $CHBr_2^-$, to the free α-bromo boronic ester **155**, as there is no other source of allyl anion in the reaction mixture.



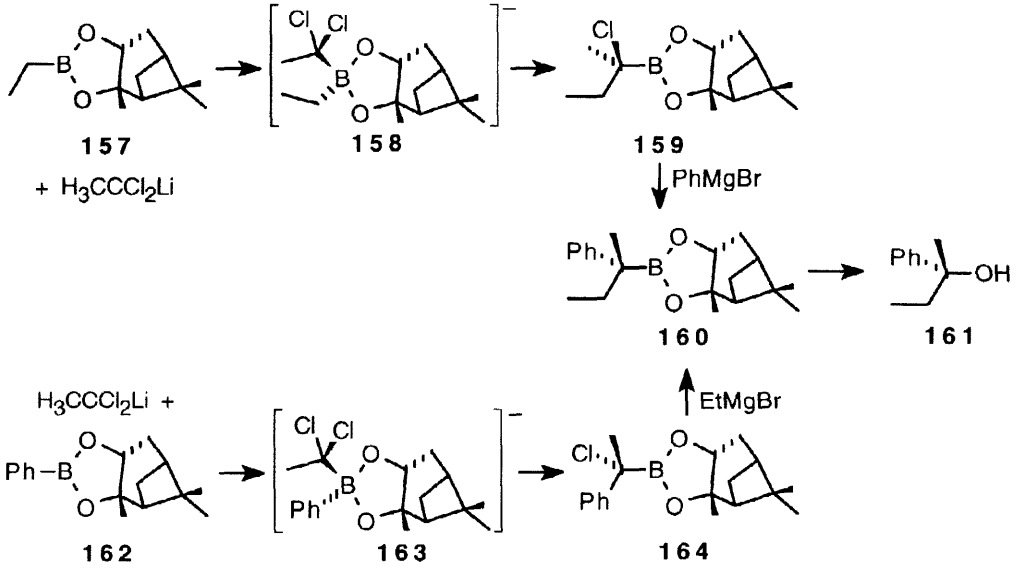
154 **155** **156**

Asymmetric tertiary alcohol synthesis

Treatment of 1,1-dichloroethane with LDA in the presence of a boronic ester results in generation and capture of (1,1-dichloroethyl)lithium. Reaction of (*S*)-pinanediol ethylboronate (**157**) with (1,1-dichloroethyl)lithium presumably results in formation of the borate complex **158**, which rearranges to the (*R*)-(1-chloro-1-methylpropyl)boronate **159**. Phenylmagnesium bromide

in diethyl ether converts **159** to (*S*)-pinanediol (*S*)-(1-methyl-1-phenyl)boronate (**160**), as indicated by conversion to (*R*)-2-phenyl-2-butanol (**161**) in 76% ee, a value consistent with the diastereomeric composition of **159** and **160** estimated from ^{1}H-NMR spectra. When the reaction of **159** with phenylmagnesium bromide was carried out in THF, there was some loss of configuration, and the ee of the derived **161** fell to 70%.[79]

Unexpectedly, the reaction of (1,1-dichloroethyl)lithium with (*S*)-pinanediol phenylboronate (**162**) led to the (*S*)-(1-chloro-1-phenylethyl)boronate **164**, as shown by treatment with ethylmagnesium bromide, which yielded the same **160** and **161** as those obtained from **157**. The diastereomeric ratio of **164** was 25:1 (92% de), but this fell to 88% de for **160** and 84% ee for **161**. Thus, the stereochemical preference in the rearrangement of borate anion **163** is opposite that for all other known examples of this type of reaction.[79]

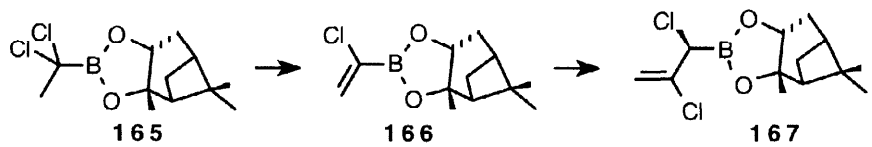


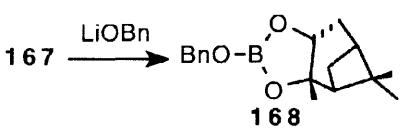
Insertion of (1,1-dichloroethyl)lithium into other pinanediol boronic esters did not yield useful results. Stereoselection was very low with *n*-alkylboronic esters. An α-branch appeared to help initial diastereoselection, but there was a strong tendency toward epimerization and elimination of hydrogen halide from intermediates.[79]

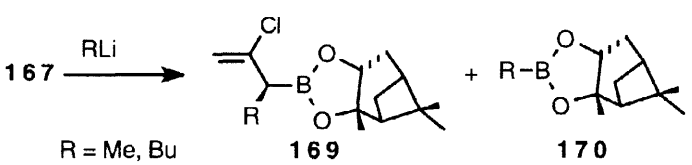
A (chlorovinyl)boronic ester

This work began with the synthesis of pinanediol (1-methoxyvinyl)boronate, with the hope that the 1-methoxyvinyl group might serve as an acetyl synthon. The carbon-boron bond was generated from (1-methoxyvinyl)lithium and the diisopropyl ester was transesterified with pinanediol. However, attempts to achieve chain extension with (dichloromethyl)lithium failed, and no useful stereoselective reactions of this compound were observed in a brief investigation.

The in situ generation of (1,1-dichloroethyl)lithium in the presence of trimethyl borate[59] followed by transesterification yielded (*S*)-pinanediol (1,1-dichloroethyl)boronate (**165**), which was dehydrochlorinated to the (1-chlorovinyl)boronate (**166**) with lithium chloride in dimethylformamide.[80] The reaction with (dichloromethyl)lithium and zinc chloride proceeded normally to produce pinanediol (1,2-dichloroallyl)boronate (**167**). Lithium benzyl oxide converted **167** to pinanediol benzyl borate (**168**). With methylmagnesium bromide or butylmagnesium chloride, **167** was converted to a mixture of the (1-alkyl-2-chloroallyl)boronic ester **169** (the halide displacement product) and the alkylboronic ester **170** (replacement of the entire dichloroallyl group) in ~3:1 ratio. The 1-bromo analog of **167** was also prepared but epimerized to a considerable extent and yielded mainly **170** with butylmagnesium chloride.

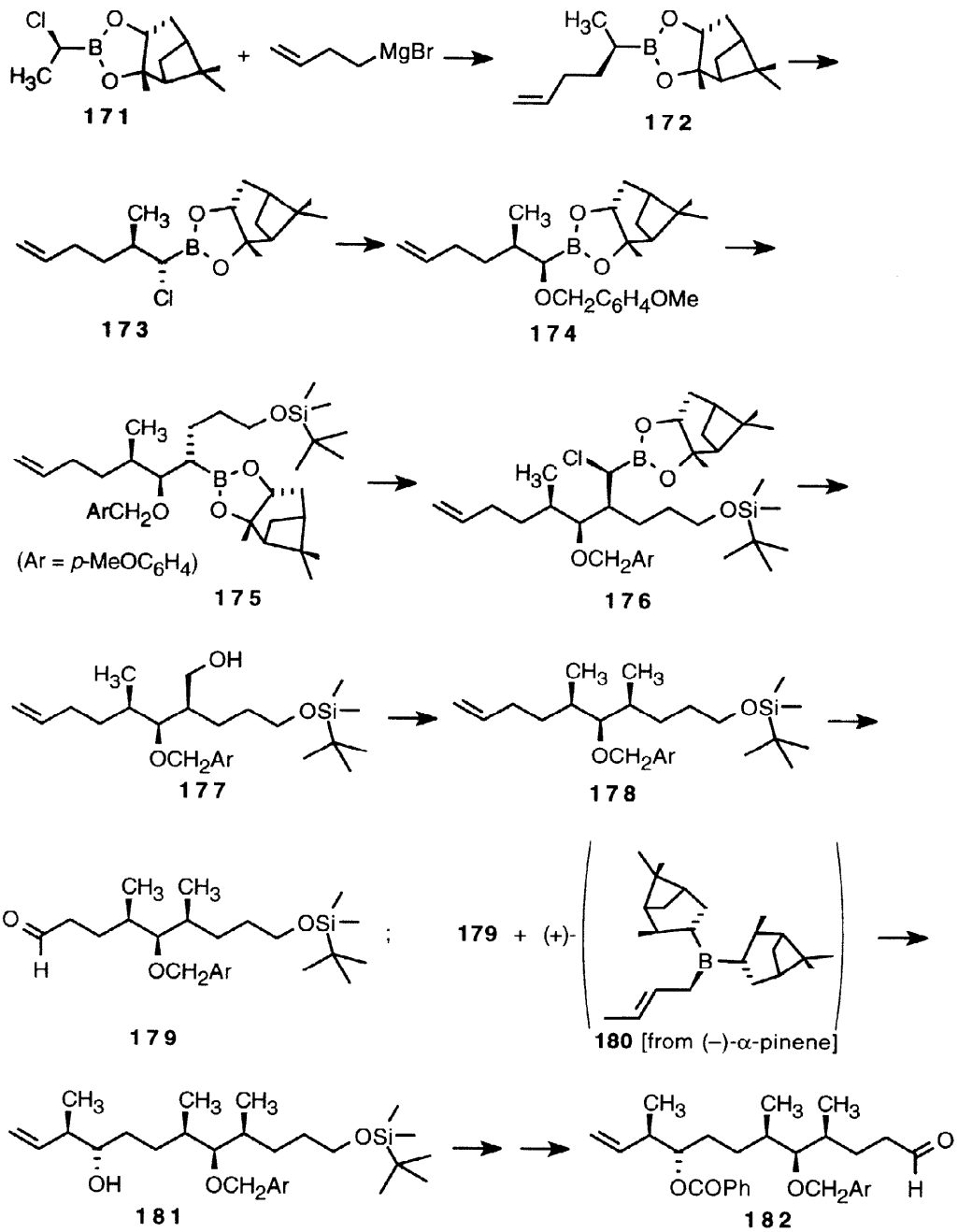






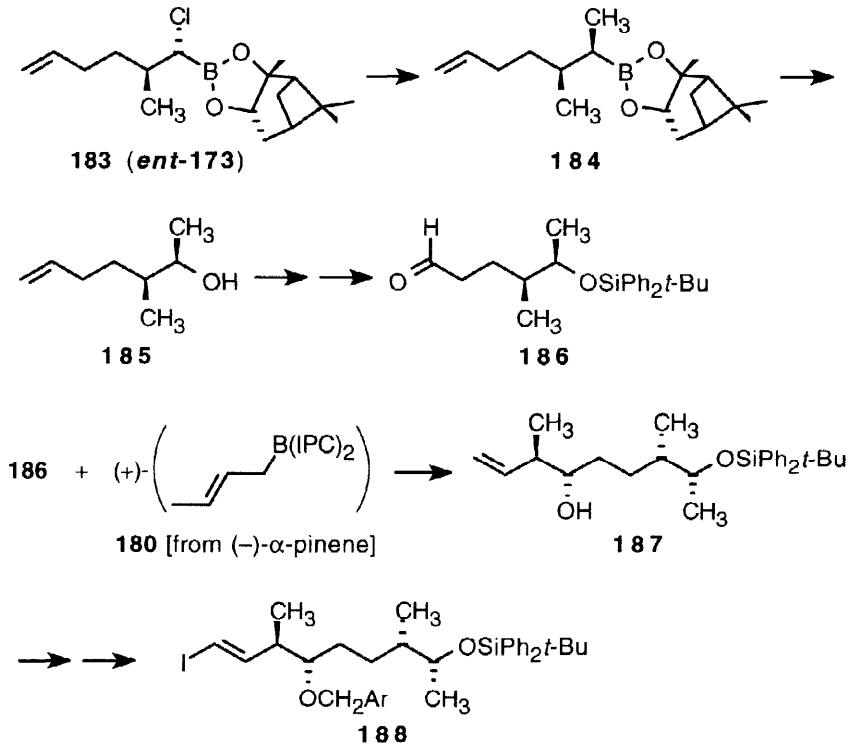
Synthesis of a tautomycin fragment

Maurer and Armstrong have used both pinanediol boronic esters and chiral crotylborane chemistry in the synthesis of the C1-C21 fragment of the serine/threonine phosphatase inhibitor tautomycin.[81] (*S*)-Pinanediol (1-chloroethyl)boronate (**171**)[32] with the homoallylic Grignard reagent yielded **172**. Chain extension to **173** and substitution with *p*-methoxybenzyl oxide yielded **174**. Another chain extension and alkylation yielded **175**, and a fourth reaction with (dichloromethyl)lithium furnished **176** in mediocre yield, accompanied by β-elimination of the boryl and *p*-methoxybenzyloxy groups. The objective here was to convert the last carbon inserted to a methyl group, and the chloride was reduced with trimethoxyborohydride. Direct insertion of a methylene group with (chloromethyl)lithium, which has given better results in one case[75] and worse in another,[65] was apparently not tested here. Unfortunately, there is no known way to replace boron by hydrogen under mild conditions, and this had to be done via oxidative deboronation to **177**, conversion to a methanesulfonate, and reduction to **178**. Ozonolysis to aldehyde **179** was followed by allylboration with (+)-crotyldiisopinocampheylborane (**180**) to form **181**, which was subjected to further transformations to make intermediate **182**.[81]

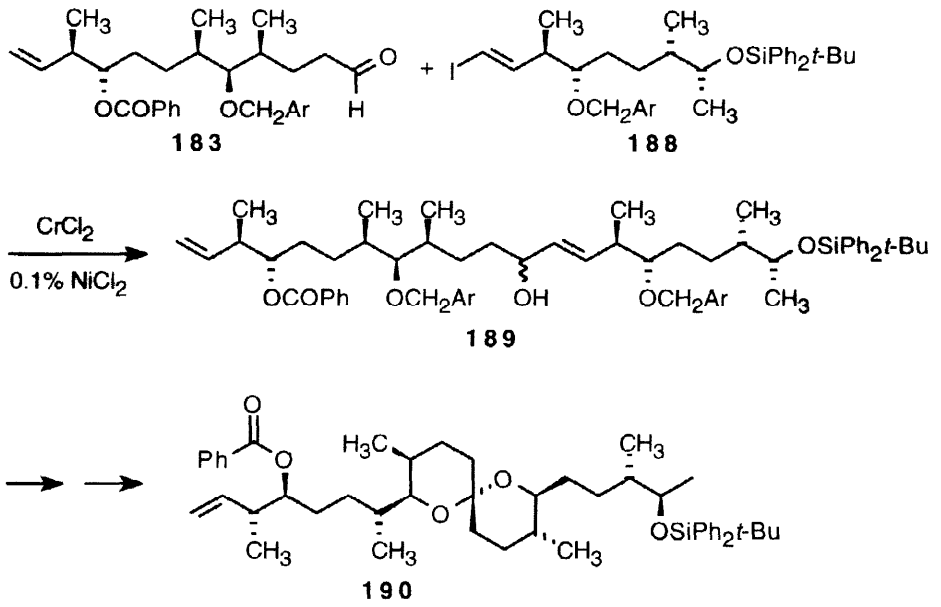


The second fragment was constructed from **183**, the enantiomer of **173**.[81] Methylation to **184** and peroxidic deboronation to **185** were followed by conventional steps to **186**, which with

(+)-crotyldiisopinocampheylborane underwent allylboration to **187**, which was converted in several more steps to unsaturated iodo derivative **188**.[81]



The final carbon-carbon connection of fragments **183** and **188** to **189** was carried out via a nickel chloride catalyzed reductive coupling with chromous chloride. Several more conventional steps, including oxidation of the secondary alcohol present in **189** to the ketone that is central to the spiroacetal structure, led to **190**, a major fragment of the tautomycin structure. It was noted that this synthetic route could be useful for providing ^{13}C labeled material for NMR studies of binding to the phosphatase enzyme.[81]



RELATED ASYMMETRIC BORONIC ESTER CHEMISTRY

General remarks

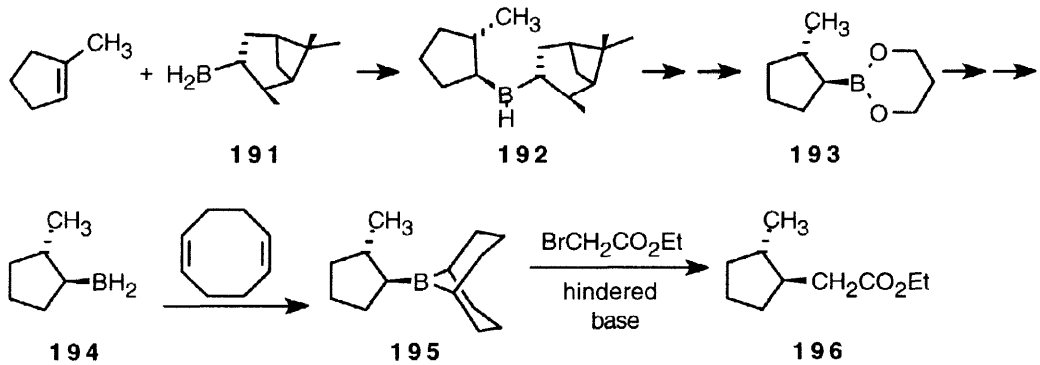
Although most asymmetric boronic esters have been made via α-halo boronic esters, a few have been made by other routes. The synthesis of an asymmetric allylic boronic ester **84** via a retroracemization process[57] has been described above. A roundabout route to α-chloro- and α-methoxycrotyl boronic esters[82] has been reviewed previously.[3,20]

Asymmetric hydroboration of cycloalkenes with diisopinocampheylborane or monoisopinocampheylborane followed by conversion to boronic esters[3,83] provides some (cycloalkyl)boronic esters that cannot be prepared easily from α-halo boronic esters. Transformations of these compounds into more reactive types of organoboranes have been developed with boronic esters made via this route and have been reviewed previously.[3] Recent additions to this chemistry are described below. Chain extensions similar to those described in the preceding sections have also been carried out with these compounds.

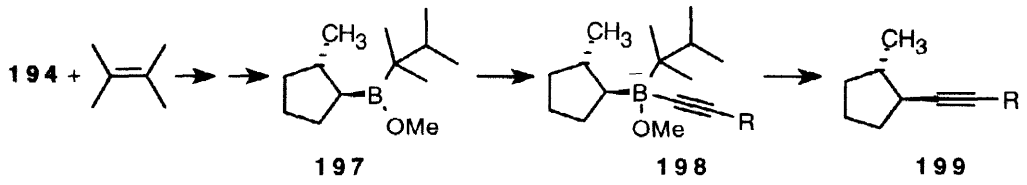
Finally, hydrozirconation provides an interesting alternative approach to the preparation of asymmetric boronic esters. Not enough is known about this chemistry to predict its future potential at this time.

Alkylboranes from boronic esters

Reaction of certain cycloalkenes or heterocycloalkenes with diisopinocampheylborane or monoisopinocampheylborane (**191**) results in highly diastereoselective hydroboration, as illustrated by the preparation of the *trans*-2-methylcyclopentylborane **192**. Oxidation of **192** with an aldehyde followed by suitable esterification yields asymmetric boronic ester **193**, which has been reduced with lithium aluminum hydride to the corresponding alkylborohydride and acidified to form the monoalkylborane **194**.[84] The 9-borabicyclo[3.3.1]nonane (9-BBN) derivative **195** can be made by reaction of **194** with 1,5-cyclooctadiene, and further reaction with ethyl bromoacetate and potassium 2,6-di-*tert*-butylphenoxide has yielded **196**, the product from addition of the bromoacetate enolate to boron and migration of the methylcyclopentyl group from boron to the α-carbon of the enolate with displacement of bromide.[84] This reaction is mechanistically similar to rearrangements of α-haloalkylborates derived from α-halo boronic esters, but boronic esters are apparently not acidic enough toward ethyl bromoacetate enolate to form the requisite intermediate. Nitriles and ketones were made in an analogous manner.[84]

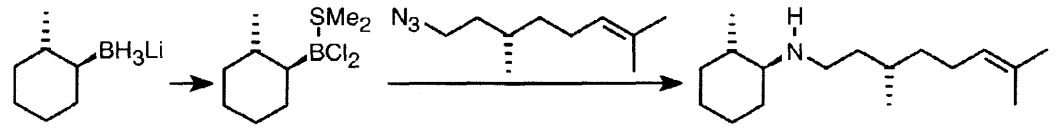


Boranes derived from enantiomerically pure boronic esters have been used to make a series of enantiomerically pure acetylenes. For example, hydroboration of 2,3-dimethyl-2-butene with **194** followed by treatment with methanol has yielded borinic ester **197**, which with acetylide ions yielded a borate complex **198**. Treatment with iodine yielded acetylenes **199** in high enantiomeric purity.[85]



197 **198** **199**

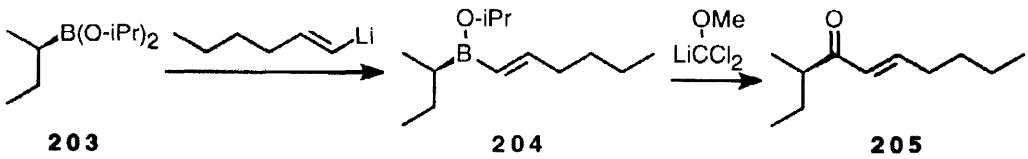
The borohydrides from lithium aluminum hydride reduction of enantiomerically pure boronic esters, for example **200**, are converted by three moles of anhydrous hydrogen chloride in dimethyl sulfide to dimethyl sulfide complexes of alkyldichloroboranes such as **201**, which are a useful class of reagents. For example, **201** with an alkyl azide has yielded the chiral secondary amine **202** in high enantiomeric purity.[86]



200 **201** **202**

Enantiomeric enrichment of boranes

Asymmetric boronic esters prepared via hydroboration and cleavage of the pinyl groups have been used to prepare conjugated acyclic α-chiral (*E*)-alkenones, as outlined in the conversion of diisopropyl (*R*)-2-butylboronate (**203**) to the borinic ester **204**, which was carbonylated with (dichloromethyl)methyl ether and lithium triethylcarboxide to form the ketone **205** in high enantiomeric purity.[87]



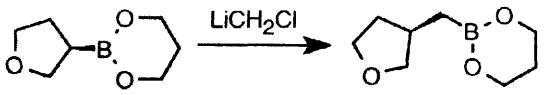
203 **204** **205**

Hydroboration with diisopinocampheylborane[4,5] yields different amounts of the minor diastereomer with different substrates. It has been found that the reaction of the minor isomers with benzaldehyde to cleave the pinyl groups is generally slower than reaction of the major isomers, so that kinetic resolution can enhance the enantiomeric purity of the isolated boronic ester to >99%.[88] Kinetic resolution is achieved very simply by using slightly less than two equivalents of aldehyde. The cleavage of the second pinyl group is the step where differentiation occurs.

It should be noted that kinetic resolution works only for diisopinocampheylborane derivatives (for example **3**, the precursor to **203**) and not monoisopinocampheylborane derivatives such as **192**. Monoisopinocampheylborane hydroborates double bonds on the opposite enantioface to that selected by diisopinocampheylborane. As a consequence, a borinic ester derived from **192** will react more slowly with aldehydes than its minor diastereomer, and if the cleavage of pinene is incomplete, the boronic ester **193** will have its enantiomeric purity slightly diminished. Purification of monoisopinocampheylborane derivatives such as **192** can often be accomplished by recrystallization.[89]

Chain extension of asymmetric boronic esters

Diisopinocampheylborane hydroborates heterocycles such as 2,3- or 2,5-dihydrofuran to form asymmetric boranes, which serve as sources of asymmetric boronic esters. These boronic esters can undergo the usual chain extension with (chloromethyl)lithium, which was generated from bromochloromethane and butyllithium. The homologation of boronic ester **206** to **207** is illustrative.[90]



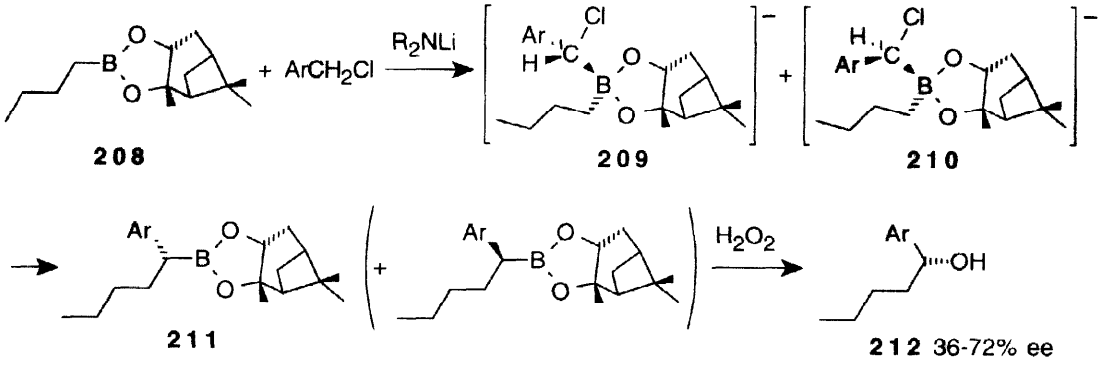
206 207

A comparative study of $LiCH_2Cl$,[63] $LiCH_2Br$,[29] and $LiCH_2I$[91] for chain extension of unfunctionalized $RB(OR')_2$ to $RCH_2B(OR')_2$ has been reported.[92] The general conclusion was that $LiCH_2Br$ is usually the best of these unless the boronic ester is fairly sterically hindered, in which case $LiCH_2Cl$ is usually a little better.[92] However, the gross effect of alkoxy substituents, which apparently inhibit reactions of $LiCH_2Br$ but allow those of $LiCH_2Cl$,[29] was not examined further in this investigation.

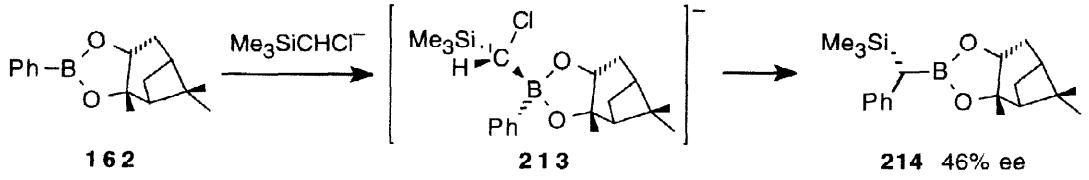
Various boronic esters prepared via hydroboration have been converted to (*R*,*R*)-2,3-butanediol esters. These were converted by (dichloromethyl)lithium to chain-extended α-chloro boronic esters, which with methylmagnesium chloride yielded various α-methyl boronic esters. A number of illustrative examples were provided of conversions of these boronic esters to asymmetric derivatives, including $R^*B(OR')_2$ to R^*CHO to R^*CO_2H and $R^*B(OR')_2$ via α-methylborinic esters to R^*NH_2 or R^*COR'.[93]

α-Chloro boronic esters from α-chlorobenzyl anions

Kabalka and coworkers have recently reported that α-chlorobenzyl anions generated in situ via deprotonation of benzylic chlorides or reductive metallation of benzylic dichlorides in the presence of trialkylboranes lead to (α-chlorobenzyl)borate anions, which rearrange to benzylboranes.[94] With (*S*)-pinanediol butylboronate (**208**) as substrate, enantioface selection occurs on the benzylic anion, favoring **209** over **210**.[95] Rearrangement to boronic esters **211** followed by peroxidic oxidation has led to the (*R*)-1-aryl-1-pentanols **212** in 36-72% ee in a series of ten examples. (*R*)-DICHED butylboronate was similarly converted to (*R*)-1-phenyl-1-pentanol in 70% ee.[95]



It may be noted that these recent results of Kabalka's group remarkably parallel an earlier observation on the conversion of (*S*)-pinanediol phenylboronate (**162**) and [(trimethylsilyl)(chloro)methyl]lithium to borate anion **213** and boronic ester **214** in 46% ee.[96]

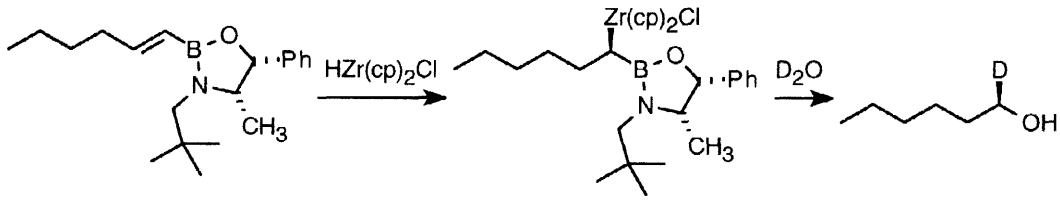


Although the stereoselectivity of these reactions is disappointing, the results do illuminate some of the fundamental mechanistic characteristics of α-chloro boronic ester chemistry. The intermediate anions **209** and **213** as well as the analogous anion derived from (*R*)-DICHED phenylboronate all belong to the class in which displacement of the chloride ion is sterically disfavored (see "Mechanism" and "Ultrahigh diastereoselection" above). In the analogous anions derived from (dichloromethyl)lithium and boronic esters, it is the chlorine in the position of the aryl group of **209** or the silyl group of **213** that is preferentially displaced. That these reactions proceed efficiently may be attributed to the high reactivity of benzylic or silyl substituted halides, as well as the high migratory aptitude of the phenyl group in the case of **213**. However, in view of the observations that the enantioface selection during the first step yields borate intermediates **209** or **213** that require the next step to be the rearrangement/displacement that is strongly disfavored

sterically, it is difficult to imagine how this type of pathway could be modified to make it efficient and highly stereoselective.

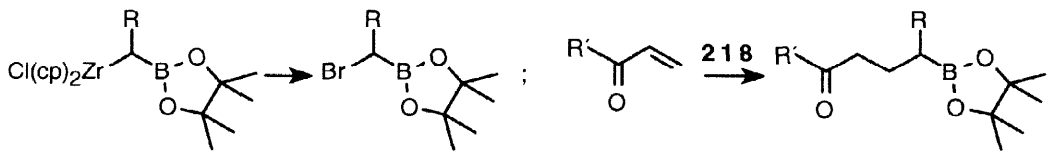
Hydrozirconation

(*E*)-1-Hexenylboronic esters are easily prepared via hydroboration of 1-hexyne. The chiral ester **215** underwent hydrozirconation to provide **216**, which with deuterium oxide yielded asymmetrically labeled (*R*)-1-deuterio-1-hexanol (**217**) in 80% ee.[97] Several other deuteriated alcohols were made in 82-93% ee.



215 **216** **217**

Another reaction of α-zirconio boronic esters is replacement of zirconium by halogen, best accomplished with *N*-halosuccinimides, as illustrated by the conversion of **218** to **219**.[98] The zirconium of **218** is also replaced by various Michael acceptors, represented by the conversion to **220**.[99] At the time of this review, it has not been reported whether these zirconium replacements are stereospecific, and the possibility of using such reactions for asymmetric synthesis remains an intriguing question.



218 **219** **220**

Acknowledgment. Our work has been supported by the National Science Foundation, most recent grants numbered CHE8922672, CHE9303074 and CHE9613857, and the National Institutes of Health, grants GM39063, GM44995, and GM50298.

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Biographical sketch

Donald S. Matteson

Donald S. Matteson was born in Kalispell, Montana in 1932, where his hobbies of hiking, photography, music, and mixing strange chemicals originated. His family moved to California in 1947. He received his B. S. degree in chemistry at the University of California, Berkeley, in 1954, where he did undergraduate research with Henry Rapoport. His Ph. D. was obtained with Harold Snyder at the University of Illinois, Urbana, in 1957, with a thesis on heterocycles. However, Snyder's work on organoboron chemistry brought that field to his attention, and it has been his principal interest ever since. After a year at the du Pont Central Research Department, Wilmington, Delaware, he moved to Washington State University as an instructor in 1958, reaching the rank of professor in 1969. His earlier organoboron work emphasized reaction mechanisms, and his interests have gradually evolved to asymmetric synthesis. He has written two books, "Organometallic Reaction Mechanisms" (Academic Press, 1974) and "Stereodirected Synthesis with Organoboranes" (Springer, 1995), and has 180 other technical publications.