Asymmetric Synthesis with Boronic Esters

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Received October 8, 1987 (Revised Manuscript Received February 25, 1988)

Boron was the key element in the first nonenzymatic asymmetric synthesis to achieve high enantioselectivity. Brown and Zweifel found that the dialkylborane from hydroboration of (+)-α-pinene hydroborated *cis*-2-butene and that subsequent oxidation with alkaline hydrogen peroxide yielded (−)-(*R*)-2-butanol in up to 98.4% enantiomeric excess (ee).[1] Since then, Brown and co-workers have developed asymmetric hydroboration and subsequent organoborane transformations to provide a wide variety of useful highly enantioselective syntheses, which are reviewed in the preceding Account.[2]

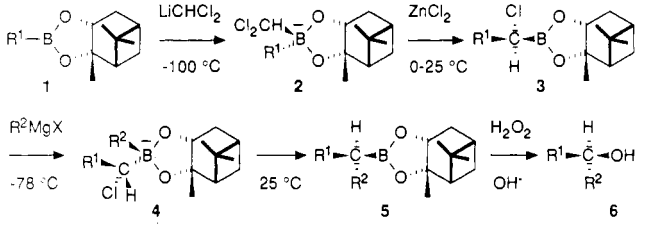
Our work utilizes boron in asymmetric synthesis in a new and fundamentally different way: The overall process inserts a new asymmetric carbon into an existing boron–carbon bond. Diastereoselectivities are routinely in the 100:1 range, and yields are high. The product still has a boron–carbon bond, and the insertion may be repeated to assemble several adjacent chiral centers. We have used such repetitive sequences to synthesize natural products ranging from insect pheromones to L-ribose to chirally deuteriated phenylalanine, and the possibilities are far from exhausted.

The boronic esters [$R^1B(OR^2)_2$] used as starting materials for our process are easily prepared on a large scale from Grignard reagents[3–5] or organolithium compounds[6] with borate esters. Brown's asymmetric hydroboration[2] provides a route to several boronic esters of potential interest that we have not yet exploited as starting materials. Simple boronic esters are easily transesterified with chiral diols.[7–9] The resulting cyclic chiral boronic esters (e.g., **1**) are generally air-stable compounds that can be handled as ordinary organic reagents. Their reactions with carbanionic reagents require the usual inert-atmosphere techniques familiar to organic chemists, and the usual functional blocking groups are compatible. Nucleophiles initiate reaction by attack at the boron atom, which is often about as reactive as an aldehyde carbon. No special hazards are involved.[5]

The Chiral Process

Our process begins with addition of (dichloromethyl)lithium[10–12] to the boron atom of a chiral boronic ester (**1**) to form a borate complex (**2**). Stereoselection occurs during the migration of the alkyl or aryl group R^1 from boron to the dihalomethyl carbon, from which chloride ion is displaced nucleophilically to form the chiral α-chloro boronic ester product (**3**).[7,13–15] Zinc chloride catalyzes this migration step and is required in order to achieve 98.5–99.5% diastereomeric purity (97–99% diastereomeric excess (de))[16] of **3**.[14,15]

An α-halo boronic ester (**3**) can react with a wide variety of nucleophiles. With a Grignard reagent, a borate complex (**4**) is formed at low temperatures[17,18] and rearranges on warming to form a new boronic ester (**5**). Our first use for **5** was peroxidic oxidation to the optically active secondary alcohol (**6**).[7,13] This is the most general chiral synthesis of acyclic secondary alcohols known. The group R^1 may contain any functional substituents compatible with lithium or Grignard reagents or with hydroboration, and R^2 may be derived from any lithium or Grignard reagent or from an enolate. The opposite enantiomer of the chiral director depicted is readily available.



More interesting than the simple secondary alcohol synthesis just described is the possibility of subjecting **5** to a second cycle of chain extension via **7** and **8** to install a second chiral center before carrying out the

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(1) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486–487.
(2) Brown, H. C. *Acc. Chem. Res.*, preceding paper in this issue.
(3) Snyder, H. R.; Kuck, J. A.; Johnson, J. R. *J. Am. Chem. Soc.* **1938**, *60*, 105–111.
(4) Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, pp 68–72.
(5) Reviews: (a) Matteson, D. S. In *The Chemistry of the Metal–Carbon Bond. The Use of Organometallic Compounds in Organic Synthesis*; Hartley, F. R., Ed.; Wiley: New York, 1987; Vol. 4, pp 307–409. (b) Matteson, D. S. *Synthesis* **1986**, 973–985.
(6) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316–1319.
(7) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.
(8) Sadhu, K. M.; Matteson, D. S.; Hurst, G. D.; Kurosky, J. M. *Organometallics* **1984**, *3*, 804–806.
(9) Matteson, D. S.; Kandil, A. A. *Tetrahedron Lett.* **1986**, *27*, 3831–3834.
(10) (a) Köbrich, G.; Flory, K.; Drischel, W. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 513. (b) Köbrich, G.; Merkle, H. R. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 74.
(11) Rathke, M. W.; Chao, E.; Wu, G. *J. Organomet. Chem.* **1976**, *122*, 145–149.
(12) (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588–7590. (b) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529–1535.
(13) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536–1543.
(14) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078; correction, 6195.
(15) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819.
(16) Diastereomeric excess (de) and enantiomeric excess (ee) are defined in the same way, $2(x - 50)$, where x is the percent of the major isomer in the mixture.
(17) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599–2603.
(18) Matteson, D. S. *Acc. Chem. Res.* **1970**, *3*, 186–193.

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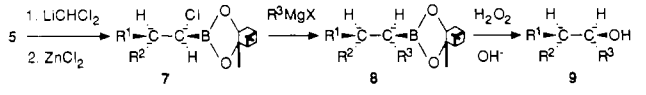
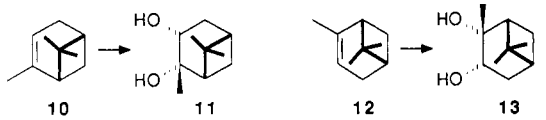
peroxidic oxidation to produce a secondary alcohol (**9**) having two chiral centers.[7,13,15] This scheme with minor variations summarizes all of our insect pheromone syntheses.[14,15] Before we review these in detail, a fuller description of the synthetic method will be useful.



7 8 9

Pinanediol. The high chiral selectivities reported in hydroborations with pinene derivatives[1] led to our intuitive choice of boronic esters **1** made from "(*s*)-pinanediol" (**11**) as starting materials. We found that (+)-α-pinene (**10**) is easily converted to **11** in 2-mol lots by osmium tetraoxide catalyzed oxidation with trimethylamine *N*-oxide.[19] Both **10** and **11** of 98% ee, as well as the enantiomer "(*r*)-pinanediol" (**13**) made from (−)-α-pinene (**12**), have recently become commercially available.[20] The rotation of **11** is (+) in toluene but (−) in methanol, and the "(*s*)" is a mnemonic that **11** directs the formation of (αS)-α-chloro boronic esters.[15]

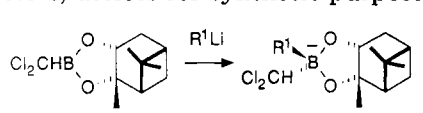


10 11 12 13

(*s*)-Pinanediol led to several (αS)-α-chloro boronic esters in 80–90% de[16] even before the discovery of zinc chloride catalysis, which increased the de's to 97–99% with few exceptions. Pinanediol esters are formed on mixing almost any other type of boronic ester with pinanediol in ether solution. Their stability toward air and water makes them easy to handle and to purify, and side reactions during their use as synthetic intermediates tend to be minimal. Their ultimate deboronation with hydrogen peroxide leads to recovery of potassium bis(pinanediol) borate, which is readily recyclable to pinanediol boronic esters.

Pinanediol boronic esters resist hydrolysis. Degradative cleavage to boronic acids has been accomplished with boron trichloride[13,21] under conditions incompatible with retention of benzyl protecting groups.[22]

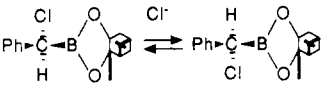
The boron atom of a pinanediol ester has two diastereotopic faces for nucleophilic attack.[23] Attack of a lithium or Grignard reagent on the less hindered face of (*s*)-pinanediol (dichloromethyl)boronate (**14**) should yield an intermediate borate (**15**) diastereomeric to **2** derived from an alkylboronic ester (**1**) and (dichloromethyl)lithium. The difference between **15** and **2** was plainly evident when it was found that **15** yielded a gross mixture of diastereomeric (*R*)- and (*S*)-α-chloro boronic esters, useless for synthetic purposes.



14 15 (isomer of 2)

(19) (a) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, 449–450. (b) Ray, R.; Matteson, D. S. *J. Indian Chem. Soc.* **1982**, *59*, 119–123.
(20) Aldrich Chemical Co., Milwaukee, WI.
(21) (a) Matteson, D. S.; Sadhu, K. M.; Lienhard, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 5241–5242. (b) Matteson, D. S.; Sadhu, K. M. *Organometallics* **1984**, *3*, 614–618.
(22) Matteson, D. S.; Jesthi, P. K.; Sadhu, K. M. *Organometallics* **1984**, *3*, 1284–1288.
(23) Tsai, D. J. S.; Jesthi, P. K.; Matteson, D. S. *Organometallics* **1983**, *2*, 1543–1545.

Epimerization. Lithium chloride is produced during rearrangement of **2** to **3** and caused equilibration of our first batch of (*s*)-pinanediol (αS)-(α-chlorobenzyl)boronate (**16**) with its (αR) epimer (**17**) within a few hours at 25 °C.[7,13]



16 17

A kinetic study showed 1% epimerization of **16** to **17** in only 3 min in tetrahydrofuran (THF) nearly saturated with lithium chloride (0.45 M) at 25 °C.[24] With (*s*)-pinanediol (1*S*)-(1-chloropentyl)boronate (**3**, R^1 = butyl), 1% epimerization took an hour, but the preparative rearrangement of **2** to **3** in this system required 10 h.[13] Epimerization was strongly inhibited by zinc chloride or mercuric chloride.[24] The mechanism of epimerization appears to be S_N2 displacement of chloride ion by chloride ion.[24]

Zinc Chloride Catalysis. From the foregoing studies, it was anticipated that zinc chloride might prove a useful epimerization inhibitor, but the big surprise was its improvement of the sluggish conversion of (*s*)-pinanediol isobutylboronate (**1**, R^1 = isobutyl) to chloro boronic ester **3**, in which yields had been only 15–33% and the de only 77%.[14] Addition of 0.6 mol of zinc chloride to the borate complex (**2**, R^1 = isobutyl) increased the yield to 90% and the de[16] to 99%.[14,15]

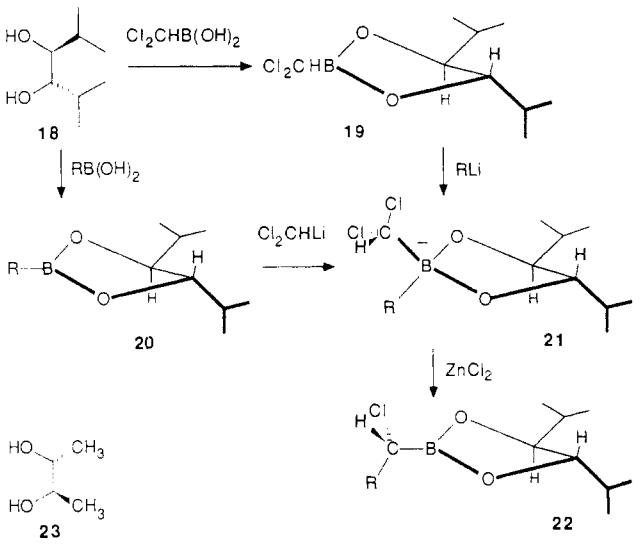
With zinc chloride catalysis, all (*s*)-pinanediol boronates (**1**) yielded (1*S*)-(1-chloroalkyl)boronates in 97–99% de, with two major exceptions, $R^1 = CH_3$ (91% de)[15] and $R^1 = PhCH_2OCH_2$ (80% de).[25] The latter had failed to react altogether in the absence of zinc chloride. With R^1 = Ph (**16**) the de remained at 94–96%, but the purity was otherwise improved so that the material crystallized and was easily purified.[24]

The catalysis does not merely retard epimerization but alters the ratio of products, as shown unequivocally with the gross mixtures obtained by starting from the (dichloromethyl)boronate **14**.[23] Lewis acids other than zinc chloride have been explored only briefly, with ferric chloride showing some beneficial effect in a single experiment.[15]

Alternative Chiral Directors. Two limitations of pinanediol esters that have already been mentioned include the difficulty of hydrolysis to boronic acids and the absence of C_2 symmetry, resulting in two diastereotopic faces at the boron atom. The most obvious diols having C_2 symmetry, tartrate esters and diacetone mannitol, have not yielded useful results.[13]

(*S,S*)-Diisopropylethanediol (DIPED) (**18**)[9] and (*R,R*)-2,3-butanediol (**23**)[8] now appear to be promising as chiral directors. Illustrating with derivatives of **18**, the C_2 symmetry leads to the same chiral borate intermediate **21** and (αR)-α-chloro boronic ester product **22** regardless of whether the starting materials are a (dichloromethyl)boronate (**19**) and an alkyllithium or an alkylboronate (**20**) and (dichloromethyl)lithium. The enantiomers of **18** and **23** are also available at somewhat greater cost.

(24) Matteson, D. S.; Erdik, E. *Organometallics* **1983**, *2*, 1083–1088.
(25) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116–5121.



Diisopropyl (dichloromethyl)boronate, $Cl_2CHB[OCH(CH_3)_2]_2$, the other precursor to **19**, is easily prepared by addition of LDA to a mixture of dichloromethane and triisopropyl borate in THF at −5 °C or below.[26]

The reported de's for the DIPED (1*R*)-(1-chloroalkyl)boronates **22** were generally 92–94%,[9] but this estimate is almost certainly too low. (+)-α-Pinene of 98% ee[20] was the source of the pinanediol used both to direct the synthesis of the DIPED and to transesterify the products for NMR measurements. The analytical scheme makes the effects of the impurities additive, so that the highest possible apparent de would have been 96%, assuming no further lowering by undetected meso impurity in the DIPED. More recently, we have developed an efficient synthesis of DIPED from tartaric acid,[27] and preliminary results with DIPED from this source have indicated undetectably low amounts of diastereomer.[28] Also, Hoffmann and co-workers have used a diol of very similar steric requirements, dicyclohexylethanediol, and reported 99% de for the product.[29]

2,3-Butanediol (**23**) only yielded 90% de's of (1*S*)-(1-chloroalkyl)boronic esters,[8] though the purity of the butanediol was not verified. Butanediol is of interest as a chiral directing group because it is a fermentation product which might be made in large quantities. Butanediol boronic esters are easily hydrolyzed to boronic acids in case a change of chiral direction is needed in a synthetic scheme.

Comments on the Mechanism. The chiral selection process in the conversion of (dihalomethyl)borates **2** to α-chloro boronic esters **3** is mechanistically unique. One of the two diastereotopic halogen atoms is selected for nucleophilic displacement. The only possibly analogous system we are aware of is the Lewis acid catalyzed opening of chiral 2,3-butanediol ketals,[30] and the analogy even there is not at all clear. All other introductions of chirality, including biochemical processes, involve enantioface selection at sp^2 carbon.

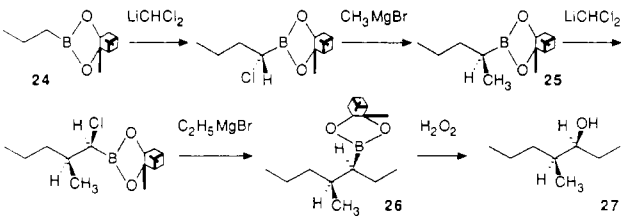
We cannot explain the high chiral selectivity. A crystal structure of an ethylene glycol α-amido boronate has revealed a slightly nonplanar five-membered ring having a dihedral angle of 16° along the C–C axis of the ethylene glycol unit.[31] DIPED boronate **21** should be more nonplanar (exaggerated for clarity in the drawing) so that the nonbonded electron pairs of the oxygen atoms with any attached cations are syn to the isopropyl substituents. (*r*)-Pinanediol boronates may be distorted from planarity in the same direction as **21**. We have not found any simple transition state model that predicts the correct product, but we do not know the state of aggregation of the salt. All that can be said at present is that the immediate environment of the boron atom is evidently strongly chirally biased, and all boronic esters having the same chiral twist in the ring lead to the same preferred chirality of α-chloro boronic ester product.

Synthetic Applications

Our new method has been used for the synthesis of insect pheromones,[15] L-ribose,[25] and amino acids.[32] The introduction of a specific chiral deuterium label has been demonstrated with benzyl alcohol and phenylalanine.[33] The introduction of chiral ^{13}C atoms would only require the use of labeled dichloromethane or dibromomethane. Hoffmann and co-workers have used this chemistry in a different context to produce a chiral intermediate for the synthesis of mycinolide V.[29]

Insect Pheromones. Two adjacent chiral centers are present in each of the three examples chosen for synthesis. Each compound has been assembled with high efficiency by choosing the correct enantiomer of pinanediol (**11** or **13**) and the correct order of introduction of substituent groups.

(3*S*,4*S*)-4-Methyl-3-heptanol (**27**), a component of the aggregation pheromone of the elm bark beetle, *Scolytus multistriatus*, is the simplest example of the series.[14,15] The synthesis began from (*s*)-pinanediol propylboronate (**24**), introduced the methyl group in the correct position in **25**, connected the ethyl group to make **26**, and finished with deboronation to the alcohol (**27**). Only the numbered intermediates were purified. The measured de of **25** was 98%, the presumed 1–2% diastereomer content of **27** was not detected, and the yield of **27** based on **24** was 58–63%,[14] or an average of nearly 80% for each carbon introduced.

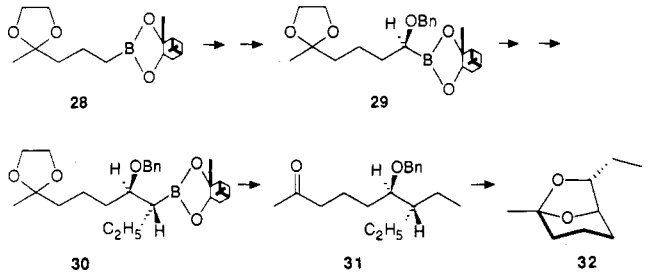


Although we did not do so, it would clearly be possible to make the (3*S*,4*R*) diastereomer of **27** by starting from (*s*)-pinanediol methylboronate and then introducing the propyl group to make the (1*R*) diastereomer of **25**.

(26) Matteson, D. S.; Hurst, G. D. *Organometallics* **1986**, *5*, 1465–1467.
(27) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5034–5036.
(28) Matteson, D. S.; Sarkar, A.; Sadhu, K. M.; Tripathy, P. B., to be published.
(29) Ditrich, K.; Bube, T.; Stürmer, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1028–1030.
(30) Johnson, W. S.; Harbert, C. .; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279–5280.
(31) Matteson, D. S.; Michnick, T. J.; Willett, R. D.; Patterson, C. D. *Organometallics*, submitted for publication.
(32) Matteson, D. S.; Beedle, E. C. *Tetrahedron Lett.* **1987**, *28*, 4499–4502.
(33) Matteson, D. S.; Beedle, E. C.; Christenson, E.; Dewey, M. A.; Peterson, M. L. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 675–683.

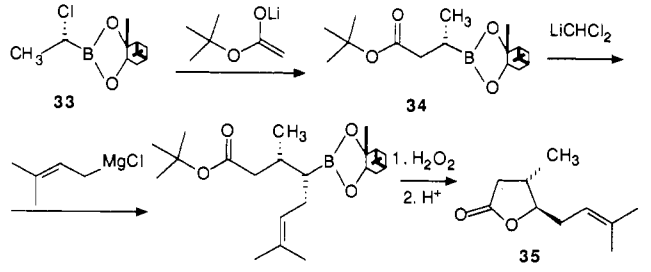
A significant feature of these sequential assemblies of paired chiral centers is that the amount of opposite enantiomer produced is vanishingly small. If the 99:1 diastereomer ratio measured for **25** is repeated in the formation of **26** and the isomer distribution is statistical, then the ratios of isomers of **27** will be (3*S*,4*S*), 98; (3*S*,4*R*), 1; (3*R*,4*S*), 1; enantiomer (3*R*,4*R*), 0.01. In much of our work, minor diastereomeric byproducts have been at levels too low for us to detect.

exo-Brevicomin (**32**), an aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*, was synthesized starting from the ethylene ketal of 5-chloro-2-pentanone, which was converted to the Grignard reagent and then boronic ester **28**. Our route intersects a previous synthesis by Sherk and Fraser-Reid[34] at intermediate **31**, which was previously reported as an oil but proved to be a low-melting crystalline solid when prepared in high purity by our route. We showed that **31** could be purified by recrystallization, though our actual brevicomin sample was prepared from crude **31** and shown to be 97–98% *exo*-brevicomin and the remainder *endo*-brevicomin by NMR and GC analysis.[15]



The α- and β-alkoxy boronic ester intermediates **29** and **30** were not initially expected to be routine intermediates. β-Halo boronic esters undergo B–X elimination extremely readily.[18,35] It has turned out that our synthetic procedures generally tolerate α- and β-alkoxy groups without difficulty.[15]

Eldanolide (**35**), the wing gland pheromone of the African sugar cane borer, *Eldana saccharina*, was synthesized in a straightforward manner from (*r*)-pinanediol (1*R*)-(1-chloroethyl)boronate (**33**).[15] The diastereomeric purity of **33** was 95%, but that of **34** was upgraded to 98% by recrystallization. Introduction of the second chiral center produced <0.5% of minor isomer.

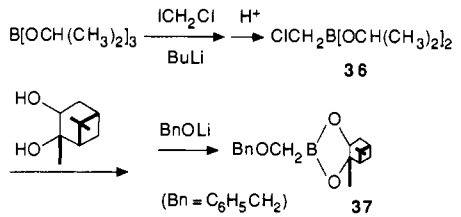


It would not be possible to obtain the diastereomers of **32** and **35** merely by altering the order of introduction of substituents. In order to make the diastereomer of **32**, an alkoxy group would have to be used in place of the initial boron-bound alkyl group, which is impractical. The diastereomer of **35** would require starting from t-$BuO_2CCH_2B(OR)_2$, which is evidently unstable.[36]

In such instances, it is possible in principle to reach the second diastereomer by removing the chiral director used to install the first chiral center and then replacing it with its enantiomer for introduction of the second chiral center. This strategy has been demonstrated in our synthesis of (2*R*,3*S*)-3-phenyl-2-butanol,[13] chosen as an early target because it and its diastereomer had been well characterized by Cram.[37] The pinanediol ester proved so resistant to hydrolysis that we resorted to degradative cleavage with boron trichloride. This synthesis is now obsolete in several details and will not be reviewed further here. Butanediol esters are readily hydrolyzable[8] but have not yet been tested in a synthetic sequence of this type.

L-(+)-Ribose. It might seem superfluous to synthesize a simple sugar after the elegant Masamune–Sharpless synthesis,[38] but a major practical reason for synthesizing these ubiquitous and abundant natural products is to obtain samples bearing isotopic labels in specific positions. For that purpose it is an advantage to introduce each carbon independently, and our approach is promising.

The synthesis of L-ribose (**42**)[25] required several innovations before it could be completed. Progress was greatly aided by the discovery of a simple and efficient route to diisopropyl (chloromethyl)boronate (**36**). Addition of an alkyllithium to a mixture of chloroiodomethane and triisopropyl borate at −78 °C generated unstable (chloromethyl)lithium, which was captured efficiently by the borate ester.[39] Workup with anhydrous hydrogen chloride[6] provided **36**, and conversion to the (*s*)-pinanediol ester followed by treatment with lithium benzyl oxide yielded (*s*)-pinanediol ((benzyloxy)methyl)boronate (**37**).

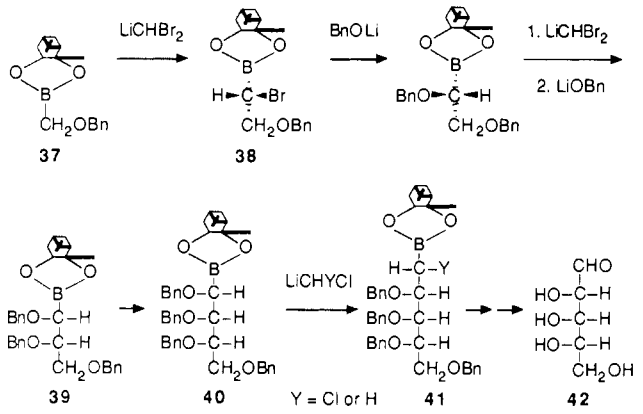


With **37** readily available, the synthesis of ribose (**42**) via successive insertion of carbon with (dichloromethyl)lithium and displacement of chloride by benzyl oxide appeared straightforward. However, several further complications intervened. It appeared that the benzyloxy groups retard the reaction by complexing with the zinc chloride catalyst, and this effect was only partially remedied by addition of an extra mole of catalyst for each benzyloxy group present. The isomer ratio produced in the first reaction with (dichloromethyl)lithium was a poor 9:1. Finally, this particular route was defeated by low yields, which multiplied out to 10% by the time three-carbon intermediate **39** was assembled.[25]

The problems were largely overcome by the use of (dibromomethyl)lithium, which yielded **38** in 94% de.

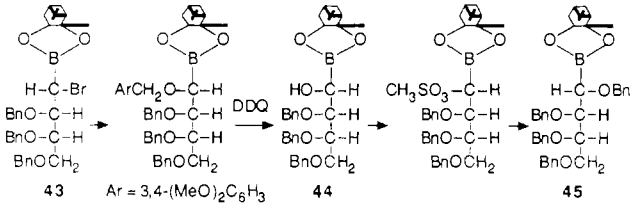
(34) Sherk, A. E.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 932–935.
(35) Matteson, D. S.; Liedtke, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 1526–1531.
(36) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20–28.
(37) (a) Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863–3870. (b) Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2149–2151.
(38) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949–951.
(39) (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687–1689. (b) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795–798.

Although (dibromomethyl)lithium is unstable, it is easily generated in situ from dibromomethane and lithium diisopropylamide. Conversion of **37** to the four-carbon intermediate **40** was accomplished in an overall yield of 36%. However, connection of the fifth carbon of **41** failed with (dibromomethyl)lithium and succeeded in low yield with (dichloromethyl)lithium. (Chloromethyl)lithium proved 3 times better, but still not efficient (36%), though the subsequent deboronation, Swern oxidation, and debenzylation to ribose (**42**) were essentially quantitative.[25]



37 **38** **39** **40** **41** **42**

Although the efficient conversion of **40** to L-ribose (**42**) seems strong evidence for its isomeric purity, we have also prepared the isomer **45** from intermediate **43** by a double-inversion route.[40] The contrasting NMR spectra of **40** and **45** indicated that each did not contain any of the other at the detection threshold limit, 1–2%.



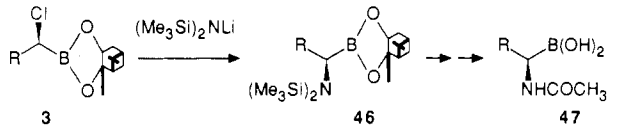
43 **44** **45**

The use of the 3,4-dimethoxybenzyl blocking group[41] and its removal with dichlorodicyanoquinone (DDQ) might appear to be an unnecessary detour. However, in a model study treatment of an α-halo boronic ester with sodium hydroxide did not yield the α-hydroxy boronic ester but apparent products of migration of the pinanediol ligand oxygens.

We have recently used the *p*-methoxybenzyl group[41] to provide differential protection for the eventual aldehyde carbon in a synthesis of asymmetrically deuteriated D-glyceraldehyde, HOCHDCHOHCHO.[42] Work on this synthesis appears promising but is not yet complete.

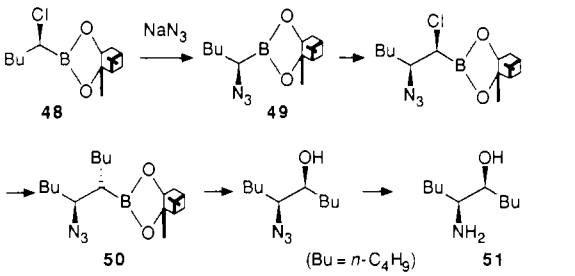
Amino Acids. We have recently developed a general synthesis of L-α-amino acids (**56**),[32] which appears promising for introducing chiral deuterium labels.[33] Azido boronic esters (**53**) are the key intermediates.

Antecedents to the amino acid synthesis include an α-amido boronic acid (**47**) synthesis via silylated intermediates **46**. Free amino boronic esters turned out to be surprisingly unstable toward deboronation, though they survived long enough to allow acylation in situ to the stable amide derivatives. Some of the amido boronic acids have interesting properties as serine protease inhibitors.[21,22,43-45]



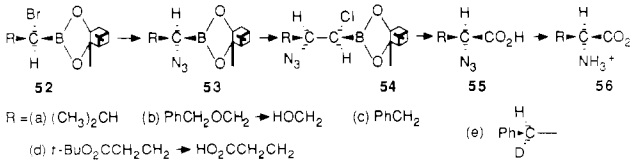
3 **46** **47**

Attempts to use **46** as a precursor to amino acids via insertion of (dichloromethyl)lithium into the carbon–boron bond yielded intermediates that could not be definitively purified and characterized. We then turned to azido boronic esters. We had previously prepared the β-azido boronic ester **50** and converted it to chiral amino alcohol **51**.[15] The reaction of α-chloro boronic ester **48** (de[16] 97% by NMR measurements) with azide ion had to be carried out in a phase-transfer system in order to avoid epimerization prior to formation of the α-azide **49**, and several refinements of the general procedure had to be developed along the way in order to avoid β-elimination of boron and the azide up through intermediate **50**, but once these details were taken care of, **51** was obtained in 96% de, with the 2% of diastereomer positively identified through a separate synthesis of its racemic form.



48 **49** **50** **51**

In most of the cases of interest for amino acid synthesis, except R = benzyl, α-chloro boronic esters react too slowly with sodium azide, and it is necessary to use the α-bromo compounds **52** instead. Some epimerization inevitably occurred during the reaction with azide, and de's of **53** were generally 92–96%. Chain extension of **53** to **54** in the usual manner generated a superfluous chiral center, which was lost during oxidation with sodium chlorite[46] to form the α-azido acid **55**. Catalytic hydrogenation readily yielded the amino acids (**56**).[32]



52 **53** **54** **55** **56**

For the functionalized amino acids serine (R = $HOCH_2$) and glutamic acid (R = $HO_2CCH_2CH_2$) it was

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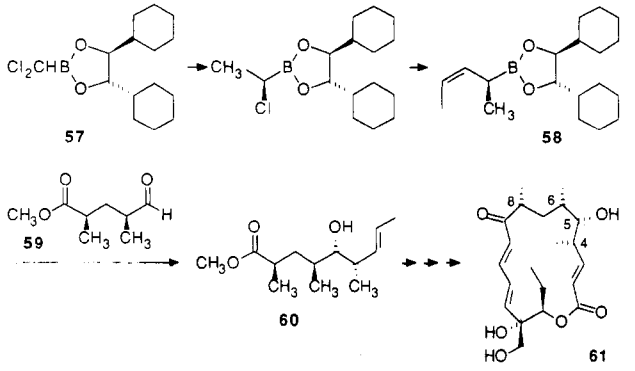
(46) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890. (b) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096. (c) Krause, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 1175–1176.

necessary to use protected functionality during the course of the synthesis and remove it in conventional ways.[32] For the chirally labeled benzyl group, (*s*)-pinanediol (*S*)-(chlorophenylmethyl)boronate (**18**) was reduced with lithium triethylborodeuteride to form the (*S*)-(deuteriophenylmethyl)boronate, and it was shown that the de of the chiral label was at least 96%.[33]

A Macrolide Synthesis. A different kind of application of our chiral synthesis has been reported by Hoffmann and co-workers in their synthesis of mycinolide V (**61**), the aglycone of the macrolide antibiotic mycinomycin.[29] The key intermediate **60** was synthesized starting from (*S,S*)-1,2-dicyclohexylethanediol (dichloromethyl)boronate (**57**), which was treated successively with methyllithium, zinc chloride, and ((*Z*)-1-propenyl)lithium to provide the (1*S*)((*Z*)-1-methyl-2-butenyl)boronate **58** in 99% de and 76% yield. Diastereoselective condensation of **58** with chiral aldehyde **59** according to the procedure developed previously by Hoffmann[47] yielded the intermediate **60**, which was further transformed and incorporated into the mycinolide structure (**61**). In **61** the chiral center constructed by α-chloro boronic ester chemistry is at C-4; the other chiral centers derived from **60** are at C-5 to C-8.

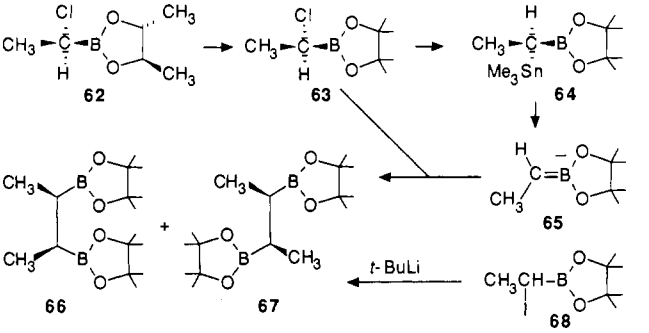


Carbanions from α-Halo Boronic Esters

The synthetic operations described up to this point utilize α-halo boronic esters to extend the chain one chiral carbon at a time an indefinite number of times. However, for synthetic efficiency a convergent approach is needed. One possibility is to join the α-halo boronic ester to an organometallic reagent containing a number of carbon atoms. Indeed, this has already been demonstrated in several instances where the organometallic did not contain chiral centers, but our ultimate objective is to convert an α-halo boronic ester to a nucleophile, so that a second series of chiral centers can be built and then joined to the first in a convergent manner.

An α-Boryl Carbanion. Indirect conversion of an α-halo boronic ester to an α-boryl carbanion provides a suitable nucleophile for reaction with another α-halo boronic ester, but unfortunately with loss of the chirality at the carbanionic carbon.

The critical series of experiments involved conversion of (*R,R*)-2,3-butanediol (1*S*)-(1-chloroethyl)boronate (**62**) to the pinacol ester (**63**), which was converted to the trimethyltin derivative (**64**).[48] Treatment with methyllithium at −100 °C formed the α-boryl carbanion **65**, which reacted with optically active **63** to form an optically active mixture of diastereomeric 2,3-diborylbutanes **66** and **67** in roughly equal amounts. Thus, it appears that the carbanion **65** does not retain its configuration, in accord with its expected carbon–boron double-bond character. Diboryl carbanions have been reported previously and appear to be substantially stabilized by carbon–boron π-bonding.[36]



An identical mixture of **66** and **67** (except that the chiral isomer **67** was racemic) was obtained from the reaction of racemic pinacol (1-iodoethyl)boronate (**68**) with *tert*-butyllithium. When **65** was prepared in this way, only the coupling products **66** and **67** could be obtained, evidently because **65** reacts rapidly with **68**. Preparation of carbanion **65** from the tin compound **64** allowed selection of a chloro boronic ester or carbonyl compound as substrate. Methyl iodide failed to react before **65** decomposed.

Though of theoretical interest, the loss of chirality of α-boryl carbanion **65** is disappointing for synthetic purposes. It might be possible to influence the diastereomer ratio in the coupling by choice of chiral esterifying groups on boron, but this possibility has not yet been explored.

α-Lithio Ethers. Still and Sreekumar have reported that α-lithio ethers prepared from α-trialkylstannyl ethers retain their configuration.[49] A suitable tin precursor was resolved into enantiomers on a small scale to provide an example.

The straightforward preparation of α-trimethylstannyl boronic ester **64** suggested a new route to α-trialkylstannyl ethers. (*R,R*)-2,3-Butanediol (1*S*)-(1-chloropentyl)boronate (**69**) (88% de) was converted to the tributylstannyl derivative **70**, which with hydrogen peroxide yielded the α-tributylstannyl alcohol **71**.[28,50] From **71** to the α-lithio ether **72** was mere duplication of the route of Still and Sreekumar.[49] Then **72** was treated with (*s*)-pinanediol (1*S*)-(1-chloropentyl)boronate (**48**) (96% de) to form the coupling product **73**, which was deboronated with hydrogen peroxide and hydrolyzed with acid to yield (5*R*,6*R*)-5,6-decanediol (**74**) (84% de), the enantiomer of which had been prepared previously.[15] The sum of the diastereomeric impurities in the two halves **69** and **48** matches the total diastereomeric impurity in the product **74** within experimental error, which indicates that all of the inter-

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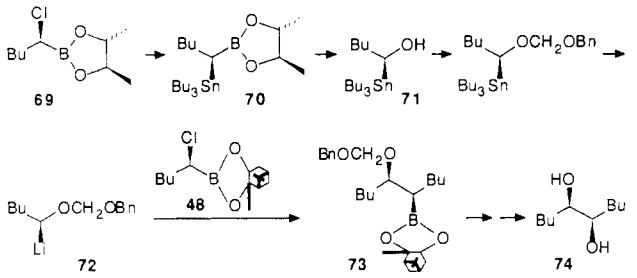
vening steps are stereospecific.



The reason the 2,3-butanediol ester **69** was used for the preparation of the tin compound **70** was that the pinanediol ester **48** proved unsuitable, apparently because of steric hindrance. The reaction of **48** with (tributylstannyl)lithium yielded a mixture of products, and attempted deboronation of the impure intermediate to the α-tributylstannyl alcohol **70** failed.

In recent work, we have repeated the foregoing scheme with DIPED esters throughout. The (*S,S*) enantiomer of **73** was obtained without any evidence of meso diastereomer at the ~1% detection threshold.[28]

Concluding Remarks

Our new highly stereoselective method of chiral synthesis is clearly powerful and wide ranging. In terms of the variety of groups permitted on the chiral carbon and the combinations of functionality that can be assembled easily on adjacent chiral carbons, it is the most general directed asymmetric synthesis known.

The cost of generality is that each chiral carbon has to be introduced separately. However, alternative chiral syntheses require approximately the same number of steps. The Masamune–Sharpless sugar synthesis[38] and the chiral aldol condensation[51,52] each introduce two chiral centers in one operation, but that has to be preceded by an operation to produce an olefin of controlled geometry. The total number of steps required in order to produce a finished pair of chiral centers is about the same with our method as with each of the others, and which method is most efficient in a given situation depends on the details of the target structure and available starting materials.

The organolithium and magnesium reagents used in our syntheses are inherently costly, and requirements for low temperatures add an additional cost. However, we have generated (dihalomethyl)lithiums from LDA and dihalomethane with in situ capture by borate or boronate esters at temperatures up to −5 °C.[26,53] Borate esters are inexpensive.

We look forward to future applications of this chemistry to syntheses of greater complexity.

The work described has been supported by National Science Foundation Grant No. CHE8400715 and National Institutes of Health Grant No. GM33801.

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Photochemistry and Photophysics within Cyclodextrin Cavities

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Received January 19, 1988 (Revised Manuscript Received June 1, 1988)

Cyclodextrins (CDs) are cyclic oligosaccharides that possess internal cavities capable of complexing hydrophobic organic and organometallic molecules in aqueous solution. The physical chemistry of complexation by CDs has been extensively studied.[1] Three distinct CDs are commonly available, each having a slightly different cavity diameter: α-CD (cyclohexaamylose), with a 6.5-Å cavity; β-CD (cycloheptaamylose), with 7.5-Å cavity; and γ-CD (cyclooctaamylose), with a 9.0-Å cavity. These molecules are shaped like truncated cones, with a smaller and a larger diameter opening at, respectively, the primary hydroxyl and the secondary hydroxyl faces of the cyclic sugar network. The interior of the cavities is lined with ether oxygens and presents a relatively hydrophobic surface to an incoming guest. The guest is stabilized within the cavity of all the CDs primarily by hydrophobic forces. The variable cavity diameter of the CDs has been used advantageously to sequester guests based on their size: e.g., simple benzene derivatives fit easily within α-CD, while larger aromatics can be accommodated within β-CD (e.g., naphthalene) or γ-CD (pyrene).

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