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DIRECTED ASYMMETRIC SYNTHESIS WITH BORONIC ESTERS *

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Summary

Our recent work on asymmetric synthesis is reviewed. Boronic esters with (dichloromethyl)lithium at −100°C form borate complexes which rearrange at 0–25°C, preferably in the presence of zinc chloride, to form α-chloro boronic esters. (+)-Pinanediol boronic esters routinely yield (α*S*)-α-chloro boronic esters which are > 99% this single diastereomer, and which readily undergo displacement of the chloride by nucleophilic reagents such as Grignard reagents or alkoxides to yield chiral boronic esters. The sequence may be repeated to install adjacent chiral centers. Since (−)-pinanediol is also readily available, this process provides a useful method for absolute control of stereochemistry. An alternative chiral directing group, (*R*,*R*)2,3-butanediol, yields 95% (α*S*)-α-chloro boronic esters and is useful for several practical purposes. Our ultimate products have been chiral alcohols formed from peroxidic cleavage of the boronic ester group, including examples of insect pheromones containing paired chiral centers. We have also prepared several α-acetamido boronic esters, which are inhibitors of serine protease enzymes.

Introduction

Trialkylboranes are well known to undergo a variety of reactions which result in insertion of an additional carbon atom into the boron–carbon bond [1–6]. This type of process is generally referred to as "homologation," a term which in its original sense would have referred to the conversion of $R-BX_2$ to $R-CH_2-BX_2$, but which is used loosely to describe the insertion of a functionalized carbon as well. Boronic esters fail to react with most of the reagents that have been found useful for this purpose with trialkylboranes [7–10]. Rathke and coworkers showed that dichloro-

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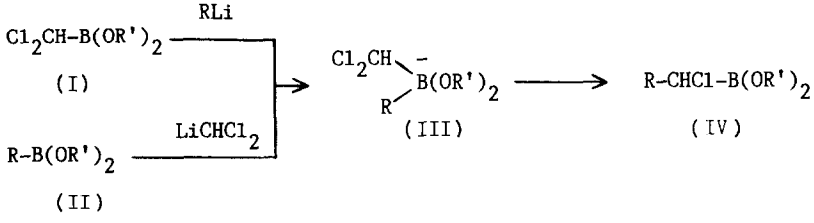
methaneboronic esters (I) (Scheme 1) could be used to homologate organolithium compounds, the products after oxidation being aldehydes [11]. Because the intermediate borate complex (III) in this process would have been the same if formed from (dichloromethyl)lithium and a boronic ester (II), Rathke's work amounted to a virtual demonstration of the feasibility of synthesizing α-chloro boronic esters (IV) from boronic esters (II), even though his group did not isolate IV.

Our first successful boronic ester homologation utilized (trimethylsilyl)chloromethyllithium, a reagent described by Magnus and coworkers [12]. Similar reagents had been used by Larson's group to homologate trialkylboranes [13,14], and we found that we could homologate boronic esters to α-trimethylsilyl boronic esters (V) in high yields [7,8]. Unfortunately, these silyl boronic esters proved to have limited synthetic utility.

Our attention then turned to α-chloro boronic esters (IV). We had found two decades earlier that α-halo boronic esters undergo facile nucleophilic displacements by a mechanism which involves bonding of the nucleophile to the boron atom followed by rearrangement of the resulting borate complex with expulsion of the halide [15]. This mechanism allows Grignard or lithium reagents to serve as the nucleophiles, and our earlier results suggested that α-halo boronic esters would be highly useful synthetic reagents if there were any good way to make them [15,16]. Rathke's work [11] left no doubt that homologation of boronic esters with (dichloromethyl)lithium would be successful, but we did not anticipate just how fortunate this choice of reactions to study would prove to be.

Homologation with (dichloromethyl)lithium

Majumdar then decided to investigate homologation of boronic esters with (dichloromethyl)lithium and obtained generally excellent yields [17]. The reaction tolerated the presence of essential functional substituents in the boronic ester, including ketals and carboxylic esters. The α-chloro substituent proved as readily replaceable, even in sterically hindered systems, as the α-bromo substituents [15,18] had previously. The products after displacement being boronic esters, it was apparent that the homologation process could be repeated, and that complex structures could be assembled efficiently. What was missing at that point was a way to control the chirality of the carbon atoms introduced in the homologation process.



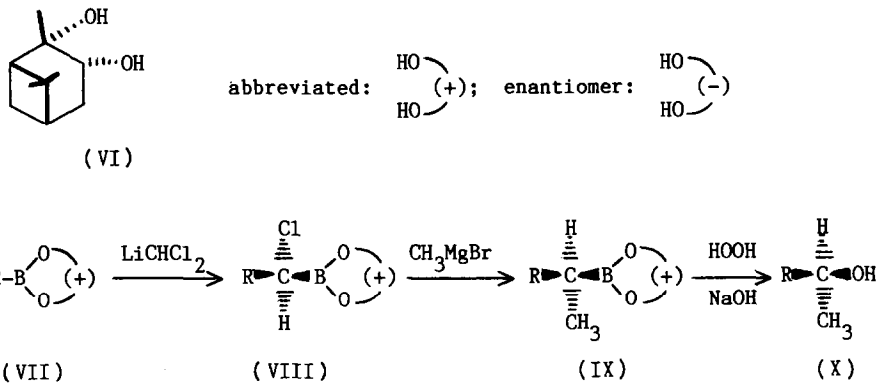
SCHEME 1

Chiral directing groups

A quick test reaction, homologation of diacetonemannitol benzylboronate, showed that some degree of chiral induction was possible, though the diasteromer ratio in this first case was only about 60/40. A more hindered chiral directing group was desired. The very high degree of chiral induction achieved in hydroborations with diisopinocampheylborane [19], derived from α-pinene, suggested to us that a diol derived from α-pinene might prove to be a superior chiral directing group when incorporated into boronic esters. Though pinanediol (VI) (Scheme 2) was known from oxidation of α-pinene with osmium tetraoxide [20], the quantities of material we would need required that this process be done catalytically. Highly hindered trisubstituted olefins react sluggishly and overoxidize readily to α-keto alcohols, and not even the recently developed catalytic methods [21,22] proved satisfactory, but Ray persisted and chose a combination of trimethylamine oxide and pyridine that promoted very clean osmium tetraoxide catalyzed dihydroxylation of α-pinene, nopol ethers, and other hindered olefins [23,24]. Both (+)- and (−)-α-pinene are readily available, though not in 100% enantiomeric purity. Enantiomerically pure pinanediols have been obtained in the form of their sodium or potassium borate complexes by recrystallization [25–27].

(+)-Pinanediol butaneboronate (VIIa) was homologated with (dichloromethyl)-lithium to yield (+)-pinanediol (*S*)-1-chloropentane-1-boronate (VIIIa), which was treated with methylmagnesium bromide to form the (*S*)-2-hexaneboronic ester (IXa) [25,26]. Oxidation with hydrogen peroxide then yielded (*S*)-2-hexanol (Xa) having approximately 80% enantiomeric excess (ee) by optical rotation.

Our first homologation of (+)-pinanediol benzeneboronate (VIIb) carried through a similar series of following steps led to (*R*)-1-phenylethanol, the "wrong" isomer, in only 8% ee. It was soon recognized that the α-chloro boronic ester might be epimerized by contact with the chloride ion formed in the reaction, and that the benzylic chloride VIIIb would epimerize much more readily than a typical saturated α-chloro boronic ester such as VIIIa. We had been allowing the rearrangement of the borate complex intermediates III to proceed overnight at 25°C to insure completion. Fortunately, the phenyl group migrates faster than alkyl groups, and one hour at



(VI)

(VII) (VIII) (IX) (X)

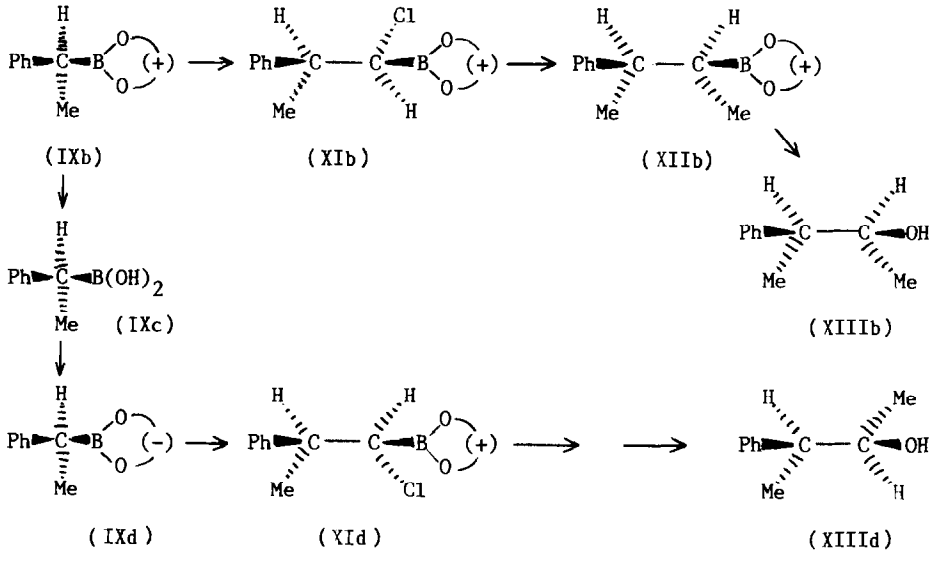
(a: R = n-C_4H_9; b: R = C_6H_5)

SCHEME 2

0°C proved sufficient for the rearrangement to proceed in high yield. This revised set of conditions led to the preparation of (*S*)-1-phenylethanol (Xb) in 94% ee.

To demonstrate the potential of the synthetic method, we homologated the 1-phenylethaneboronic ester (IXb) (Scheme 3) to introduce a second chiral center, treated the resulting α-chloro boronic ester (XIb) with methylmagnesium bromide to form the 3-phenylbutane-2-boronic ester (XIIb), and oxidized with hydrogen peroxide to form (2*S*,3*S*)-3-phenyl-2-butanol (XIIIb) in a diastereomeric purity of 94% and an overall yield from VIIb of 67%. To make the other diastereomer, (2*R*,3*S*)-3-phenyl-2-butanol, IXb was cleaved with boron trichloride (attempted hydrolysis of the pinanediol ester having failed) and converted via the crystalline diethanolamine ester to optically pure (*S*)-1-phenylethaneboronic acid IXc, which was esterified with (−)-pinanediol to form IXd and then homologated, methylated, and deboronated to form the alcohol XIIId in 96% diastereomeric purity, 45% overall yield from VIIb [25,26]. Our original choice of these alcohols as synthetic targets was based on the fact that their relative and absolute configurations and physical properties had been well established by Cram for use in his classical studies of nonclassical ions [28].

The phenyl and benzylic boronic esters turned out to have been exceptionally fortunate choices for demonstrating the synthetic method, which gave merely good yields with the butaneboronic ester VIIa or cyclohexaneboronic ester, miserable yields with (+)-pinanediol isobutylboronate (XIV) (Scheme 4) and no homologation at all with pinanediol benzyloxymethaneboronate. Frustration with the low yields of (+)-pinanediol (*S*)-1-chloro-3-methylbutane-1-boronate (XVIa) led to attempts to improve the yield by starting from pinanediol dichloromethaneboronate (XVII) and isobutylmagnesium bromide, but this route yields a different tetrahedral borate intermediate (XVb) from that formed from the isobutylboronic ester and (dichloromethyl)lithium (XVa), and the rearrangement product was formed in good yield but contained about 30% XVIa and 70% α(*R*)-epimer XVIb [29].



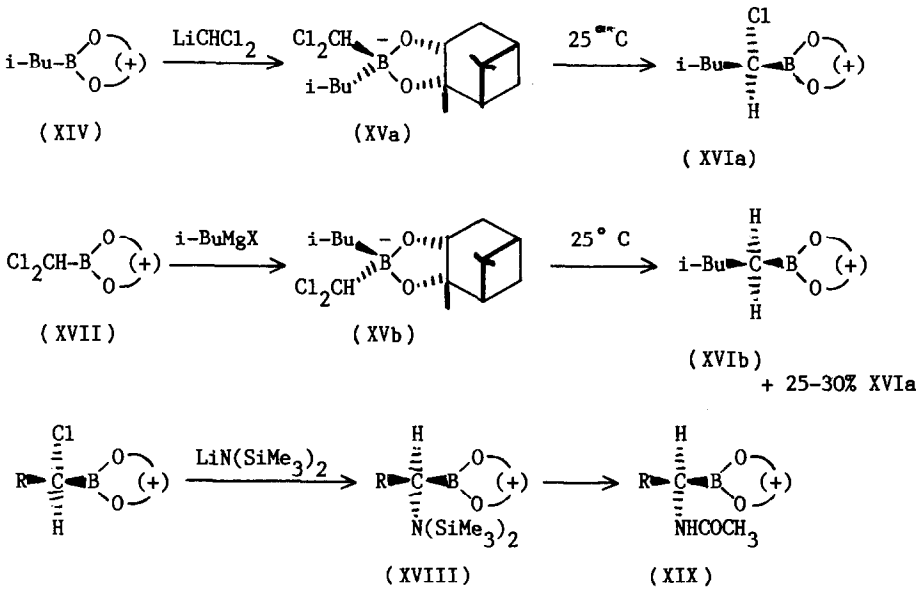
SCHEME 3

Catalyzed homologation

The other approach to the problem was attempted catalysis of the rearrangement of XVa (Scheme 4). Several metal salts failed, until Sadhu tried anhydrous zinc chloride and chose the correct stoichiometry, which turned out to be between one half and one mole of zinc chloride per mole of boronic ester. The yield of XVIa immediately rose to 90%, but what was more surprising, the diasteromer ratio of XVIa/XVIb measured by 200 MHz NMR was 200/1 [30]. Furthermore, homologation of a series of pinanediol boronic esters (including n-butyl, n-propyl, (*S*)-2-pentyl, benzyl, and some containing ether functions) routinely yielded diasteromeric purities near or beyond the detection limits of the NMR spectra, generally 99.5%. The major exception encountered was the methaneboronic ester, which yielded 95% diastereoselectivity. The easily epimerizable α-chlorobenzylboronic ester VIIIb was obtained only in 96% diastereomeric purity, but was now found to be a recrystallizable solid, easily freed from its diastereomer.

Epimerization

We have studied the kinetics of the epimerization process in some detail [31]. The reaction is first-order in α-chloro boronic ester (VIIIb) (Scheme 2) and approximately three–fourths order in lithium chloride. The pseudo-first-order rate constant at 0.45 *M* LiCl in THF (nearly saturated) is 5.7×10^{-5} s^{-1} at 25°C. A typical saturated α-chloro boronic ester (VIIIa) epimerizes 1/20 as fast. In the presence of zinc chloride, the epimerization rate is greatly reduced, the minimum rates being at the composition $LiZnCl_3$. However, excess zinc chloride catalyzes epimerization in a process that is first-order in zinc chloride and first-order in trichlorozincate, and the



(R: a, $PhCH_2$; b, i-Bu; c, i-Pr; d, CH_3)

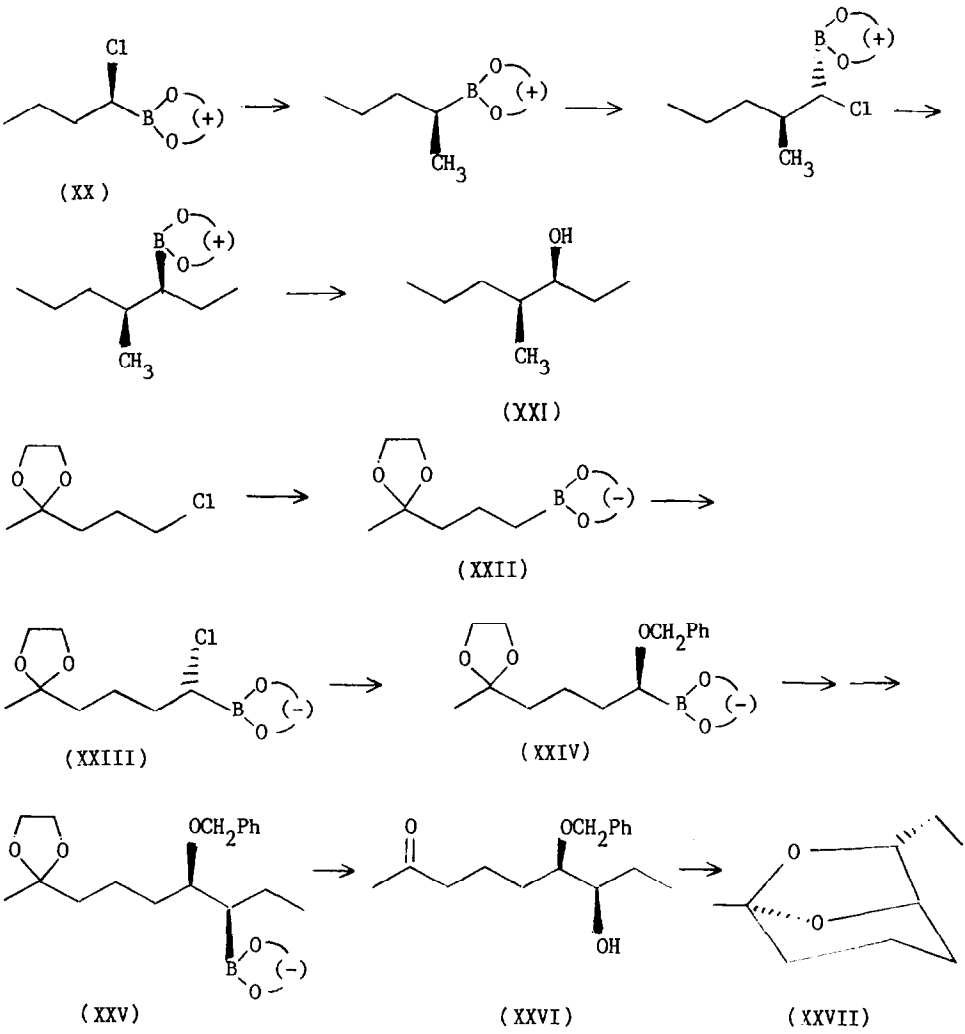
SCHEME 4

optimum stoichiometry for synthetic purposes is a final composition corresponding to a mixture of $LiZnCl_3$ and Li_2ZnCl_4. The epimerization rate is low, 1/3 to 1/10 that without the zinc chloride, and not very sensitive to the salt composition in this range.

The observed rates of epimerization are sufficient to account for most if not all of the observed deviation from stereospecificity of the uncatalyzed homologation of pinanediol boronic esters.

Synthetic applications

This new approach to chiral synthesis should have a wide variety of useful applications, which we have only begun to explore. A simple example is the conversion of (*S*)-α-chloro boronic esters to (*R*)-α-bis(trimethylsilyl)amino boronic esters XVIII and then to (*R*)-α-acetamido boronic esters XIX (Scheme 4) [27,32,33].



SCHEME 5

The boronic acids derived from XIX correspond to the natural L-amino acids and show interesting properties as competitive inhibitors of serine protease enzymes. For example, (*R*)-1-acetamido-2-phenylethane-1-boronic acid, the derivative of XIXa corresponding to *N*-acetyl L-phenylalanine, was bound strongly to chymotrypsin with a dissociation constant of 2.1×10^{-6} *M* at 25°C and pH 7. The enantiomer, analogous to *N*-acetyl D-phenylalanine, showed only 1/20 the chymotrypsin inhibiting capability of the L-isomer.

More interesting possibilities involve the controlled assembly of adjacent chiral centers. Our first example was the straightforward synthesis of the elm bark beetle pheromone component XXI by a straightforward route from (+)-pinanediol 1(*S*)-1-chlorobutane-1-boronate (XX) (Scheme 5) [30].

The synthesis of *exo*-brevicomin (XXVII) (Scheme 5), an aggregation pheromone of the western pine beetle, provided a somewhat more complex test of our synthetic capabilities. (−)-Pinanediol had to be used in order to obtain the natural enantiomer. We started from the ketal boronic ester XXII in order to test the compatibility of the homologation process with the ketal function and also because this route led to the same intermediate XXVI previously prepared by Sherk and Fraser-Reid in a glucose-based synthesis of brevicomin [34]. The ketal did not interfere, except that workup without exposure to acid was required, and the α-chloro boronic ester XXIII was 99.5% diastereomerically pure by 200 MHz NMR analysis. The product from treatment with lithium benzyloxide, (XXIV), showed about 2% diastereomeric impurity, as if some epimerization had taken place during the displacement process. Homologation of the α-benzyloxy boronic ester XXIV followed by reaction with ethylmagnesium bromide to form XXV proceeded normally, and peroxidic deboronation followed by cleavage of the ketal with acid yielded the Fraser-Reid intermediate (XXVI), which was previously reported as an oil [34] but crystallized in our laboratory. Hydrogenolysis of the crude XXVI yielded 97–98% pure *exo*-brevicomin (XXVII) by GLC and NMR analysis. We showed that the precursor XXVI could be freed from the 2–3% diastereomer by recrystallization from ether/pentane, although we have not actually used the purified XXVI to make a pure sample of *exo*-brevicomin.

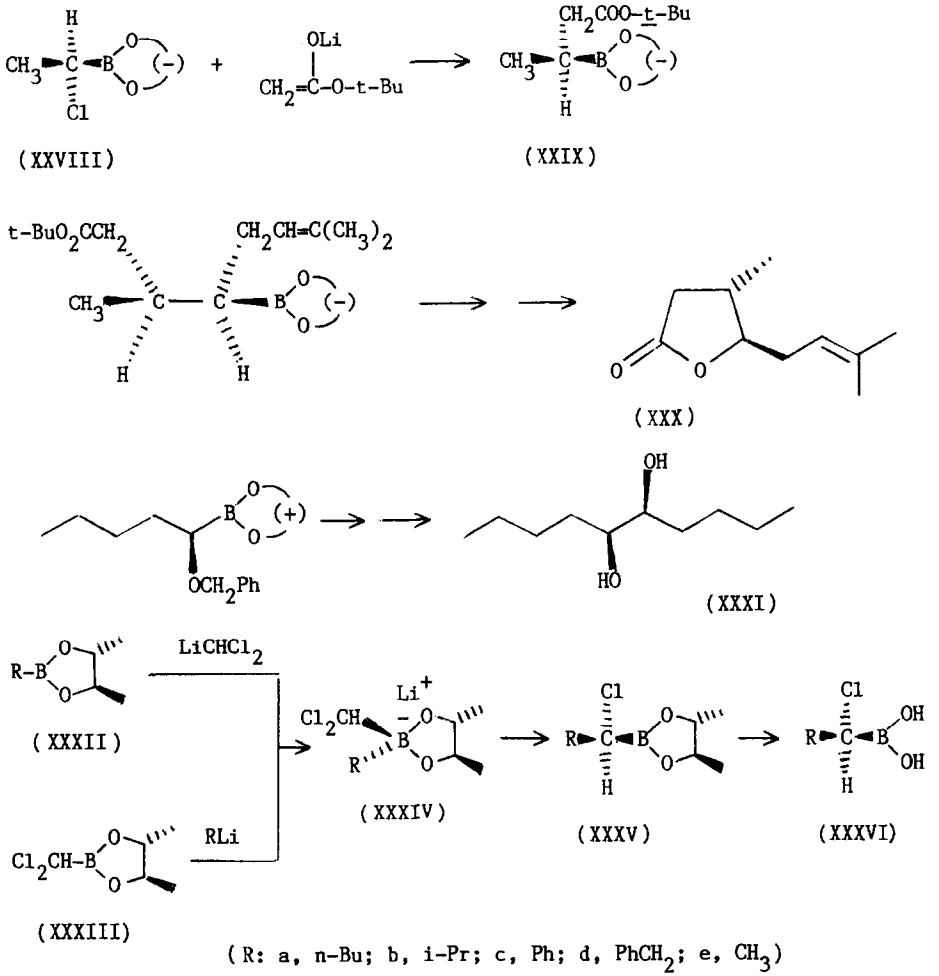
Eldanolide (XXX) (Scheme 6), the wing gland pheromone of the African sugar cane borer moth, has been synthesized from (−)-pinanediol 1(*R*)-1-chloroethaneboronate (XXVIII) in a straightforward manner [35]. Although the diastereomeric purity of XXVIII is only 95%, the intermediate XXIX has been found to be a low-melting solid that can be purified readily by recrystallization.

(*S*,*S*)-Decane-5,6-diol (XXXI) (Scheme 6) was synthesized in a model study prior to the brevicomin synthesis [36]. Refinement of our techniques has resulted in the preparation of crude XXXI in 98.5% diastereomeric purity, the 1.5% *meso*-isomer being detectable by ^{13}C NMR. This provides additional confirmation that our homologations are better than 99% diastereoselective at each step. It may be noted that the theoretical amount of the enantiomer, (*R*,*R*)-decane-5,6-diol, is below 0.01: as a result of the double homologation, provided that the pinanediol is enantiomerically pure. A single recrystallization of XXXI removed all detectable amounts of the *meso*-diastereomer.

Butanediol dichloromethaneboronate

In early work with the zinc chloride catalysis, Sadhu tested (*R*,*R*)-2,3-butanediol

butane-1-boronate (XXXIIa) (Scheme 6) as a substrate for homologation with (dichloromethyl)lithium and found that the homologation product was 2,3-butanediol 1(*S*)-1-chloropentane-1-boronate (XXXVa) with a diastereomeric purity of 95%. At first, this result seemed less exciting than the 99.5% diastereoselections being obtained with pinanediol esters, but (*R*,*R*)-2,3-butanediol offers some significant advantages for certain purposes. Not the least of these is its commercial availability in enantiomerically pure form from a fermentation process. (Its enantiomer is potentially available by synthesis from diethyl tartrate.) The C_2 symmetry of the butanediol makes it possible to generate the same borate intermediates (XXXIV) either from boronic esters (XXXII) and (dichloromethyl)lithium or from butanediol dichloromethaneboronate (XXXIII) and lithium or Grignard reagents. Although moisture sensitive, XXXIII is otherwise stable on storage and can be used as an off the shelf reagent for converting commonplace organometallics to α-chloro boronic



SCHEME 6

esters (XXXV) that are useful starting points for a wide variety of chiral syntheses. Surprisingly, the diastereoselectivity turned out to be insensitive to the migrating group R, and was uniformly 95–96% in all experiments where proper precautions to purify starting materials XXXII or XXXIII were taken, even when $R = CH_3$. Finally, the butanediol esters are very easily hydrolyzed on contact with water, and we have shown in two examples to date that the resulting (*S*)-α-chloro boronic acids (XXXVI) can be recrystallized to high enantiomeric purity [37].

It may be concluded that the zinc chloride catalyzed homologation of chiral boronic esters with (dichloromethyl)lithium and related auxiliary chemistry provides an exceedingly powerful new approach to the control of absolute configuration in synthesis.

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