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## **Boron Tethered Radical Cyclizations**

by

David V. Smil

A thesis submitted in conformity with the requirements for the degree of Master of Science Graduate Department of Chemistry University of Toronto Toronto, Ontario, Canada

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### Abstract

The hydroboration of a variety of alkynes with either dibromoborane-dimethyl sulfide complex, catechol borane, or dicyclohexyl borane was closely examined, and the high yield preparation of numerous boronic acids was established. Two facile protocols were devised for the formation of haloalkyl boronates, one relying on the simple condensation of the free boronic acids with haloalcohols, the other proceeding from a dibromoalkenyl borane hydroboration intermediate and involving the Lewis acid mediated ring opening of cyclic ethers/epoxides. The boronates were screened under radical conditions involving catalytic tributyltin hydride, and the majority of those examined were found to cyclize in an exclusive 5-, 6-, or 7-*exo* manner to afford 1,3-, 1,4-, and 1,5-diols in high yield following oxidative cleavage of the C-B bond.

An attempted investigation into the stereoselectivity of such processes resulted in the discovery of a ring strain facilitated intramolecular homolytic substitution ( $S_{Hi}$ ) reaction at boron, the first example of such a transformation. The resultant 1,4-diols were shown by X-ray crystallographic analysis to have originated from an intermediate *cis* fused [4,3,0]-nonane ring system, but otherwise showed little diastereoselectivity.

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# Abbreviations

AIBN	azobisisobutyronitrile
Bn	benzyl
Bu	butyl
cat.	catalytic
CB	catecholborane
Chx	cyclohexyl
d	doublet
DAIB	dimethyl-2,2'-azobisisobutyrate
EI	electron impact
Eq.	equation
equiv.	equivalent
Et	ethyl
Ether	diethyl ether
EtOAc	ethyl acetate
Fig.	figure
h	hours
HB	hydroboration
In.	initiator
<i>i</i> Pr	isopropyl
IR	infra-red
m	multiplet
М	molar
Me	methyl
min	minutes
μL	micro-liter
mp	melting point
MS	molecular sieves or mass spectrometry, depending on context
NMR	nuclear magnetic resonance
ON	over night
р	pentet
Ph	phenyl
[O]	unspecified oxidation reaction

q	quartet
quant	quantitative yield
R	alkyl group
rt	room temperature
S	singlet
t	triplet
tBu	tertbutyl
TBDMS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TTMSS	tris(trimethylsilyl)silane
х	generic halide

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Chapter I:

Introduction

### **I.1 Intramolecular Radical Cyclizations**

#### I.1.1 Introduction

Over the last 15 years the importance of radical cyclizations has grown considerably, and such processes are now invaluable tools for the construction of numerous synthetic and natural products.<sup>1</sup> Studied initially as basic research on radicals, these intramolecular radical additions to multiple bonds soon became popular mechanistic probes as both qualitative and quantitative understanding grew.<sup>2</sup> It is these physical organic studies that led to subsequent interest by organic chemists, and today, the chemo-, regio-, and stereoselectivities of many classes of radical cyclizations are well established. Conceptual and practical advances continue to be reported in this evolving field, and further growth is stimulated not only by necessity, but also by the elegance and effectiveness of many radical cyclization processes.

#### I.1.2 General Aspects

The success and utility of radical cyclizations in organic synthesis is rooted in several advantages intrinsic to these processes. In general, high functional group tolerance and mild reaction conditions are amongst the principle benefits, making radical cyclizations suitable for the elaboration of potentially sensitive substrates.<sup>3</sup> Furthermore, the presence of both the radical site and radical acceptor within the same molecule confers a sizable rate enhancement to the overall reaction. Aside from lowering reaction times, such rate accelerations also serve to make reactions cleaner by reducing the formation of undesired side products. Favorable enthalpic and entropic effects of ring size and geometry also play a role in facilitating many of these cyclizations. Although these advantages make radical cyclizations attractive options for use in synthesis, it is the often high degree of regio- and stereoselectivity evident in these processes which ultimately gives them their utility.

Regioselectivity is a fundamental concern because it has direct bearing on the ring size of the product formed, and the distribution of possible products. In principle, two competing pathways are possible in a radical cyclization: attack of the radical at the terminal end of the multiple bond (*endo* cyclization) or attack at the "internal" atom (*exo* cyclization).<sup>4</sup> Usually the highly regioselective nature of these processes dictates that *exo* cyclization and formation of the smaller ring is often strongly favored over endo cyclization. While formation of the larger ring is usually precluded, the evolution of radical cyclization methodology has seen the development of protocols capable of reversing this bias, allowing access to the "disfavored" ring systems.

Of equal importance are the high levels of stereoselectivity observed in radical cyclizations. Intensive theoretical and empirical studies have led to the construction of guidelines for the rationalization and prediction of stereochemistry at newly formed stereogenic centers, and the interplay and influence of conformational and electronic effects on the outcome of cyclizations is well understood. Such effects, often subtle, are numerous and varied, and defy any simple, concise treatment. Consequently, examination of some general principles and a cross-section of examples is best to address some of the more interesting trends in stereoselection.

#### I.1.3 Major Classes of Stereoselective Radical Cyclizations

Nearly all known stereoselective radical cyclizations are under substrate control given their early transition states, and those in which one or more new stereocenters are formed can be divided into four broad classes (Figure I.1.3.1).<sup>2</sup>



Class 1 encompasses cyclization of perhaps the simplest substrates, achiral radicals bearing both prostereogenic radical and alkene centers. Cyclizations of this form can occur with simple diastereoselection, also referred to as mutual face selection, and there is potential for the formation of two racemic products. Cyclization of chiral radicals bearing prostereogenic radical or alkene atoms, class 2 and class 3, can occur with relative asymmetric induction if either the alkene or radical is prostereogenic, and if both are prostereogenic, then cyclization proceeds with both relative asymmetric induction and simple diastereoselection. All three classes of cyclization convert an sp<sup>2</sup> center (or centers) to a stereogenic sp<sup>3</sup> center (or centers) through a face selective reaction. In the majority of cases involving relative asymmetric induction, the existing stereocenter is located in the forming ring between the radical and the alkene. Only a few examples are known of substrate control where the existing stereocenter is outside the forming ring. Radical cyclizations involving chiral auxiliaries are conceptually related to the other classes of cyclizations, but are treated separately.

#### I.1.4 Addressing Basic Stereochemical Concerns

The ubiquitous stereoselective 5-*exo* cyclization of substituted hexenyl radicals and their analogs represents the largest body of stereoselective radical reactions. Consequently, analysis of such systems is most suited for demonstrating some fundamental, underlying factors that determine observed stereoselection.

Because radical reactions have early transition states, the interpretation of selectivity usually focuses on the conformational bias of the radical and not on steric interactions in the final product. At present, the simplest depiction of influential conformational factors can be found in the Beckwith-Houk transition state model<sup>5</sup> which serves as the basis for predicting and rationalizing the stereoselectivity of 5-*exo* hexenyl radical cyclizations (Figure I.1.4.1).<sup>2</sup>





chair-equatorial (major product)

boat-equatorial (minor product)





chair-axial (minor product)

boat-axial (major product)

Figure I.1.4.1

The preference of the radical to approach the alkene in a tetrahedral-like manner can be best accommodated through the folding of the hexenyl radical into either of the four pictured conformations, allowing one to predict the stereochemistry in cyclizations of C2, C3, or C4-substituted radicals. For mono-substituted systems, the major product usually arises from the chair-equatorial transition structure. The doubly disfavored boat-axial transition state structure provides the same product, but is thought to be too high in energy to be a significant contributor. Minor products can often be observed, resulting typically from both the chair-axial and boat equatorial transition states. With higher degrees of substitution, one must evaluate the effects of the substituents on the relative energies of the other three principle transition state structures.

#### I.1.5 Known Tethers

To this point, no mention has been made about the nature of the tether linking the two reactive sites. While all carbon chains dominated as connectors in early work involving radical cyclizations, the library of linkers has been extended to include chains containing heteroatoms. Although ether linkages are the most widely used heteroatomic tethers, the use of amines and sulfides has also been reported. Such tethers have been used successfully in the synthesis of products not requiring excision of the tethering moiety following cyclization - that is, incorporation of the tethering chain into the target structure.

A substantial conceptual leap with regard to the development of radical cyclizations occurred when it was proposed that tethers did not have to be permanent fixtures in the product skeletons, but could rather act only as temporary connections. In this way, one could fully exploit the advantages of a tethered process, but remove the the tethering group from the cyclized product in order to access simpler products, and release functionality capable of undergoing further transformations. The use of esters and amides as linkers addresses this issue to some degree, but connections of this type can undergo only a limited number of transformations following cyclization. Only with the advent of silicon tethered radical chemistry was a truly versatile, temporary connection found. The development of silicon tethered radical cyclizations is appraised in a later section, while some examples of more traditional radical cyclizations are outlined below.

#### I.1.6 Methods to Conduct Radical Cyclizations

While a variety of transformations can be accomplished through the use of radical species, relatively few methods exist to conduct such radical processes. Of these few methods, even fewer are truly practical, with others involving more exotic radical precursors and agents to both trigger and sustain chain reaction. Methods of generating radicals applicable to both inter- and intramolecular processes, principally metal hydride based protocols, are briefly summarized below.

#### I.1.6.1 Metal Hydride Methods

Tributylstannane and tris(trimethylsilyl)silane are the two most popular compounds in an increasing collection of reagents for carrying out reactions by the "metal hydride" method.<sup>3</sup> This method, the most general and frequently used protocol for conducting radical cyclizations, involves the use of metal hydrides as precursors and/or promoters of radical chain reactions.

Equation I.1.6.1.1 shows the chain for tributyltin hydride (Bu<sub>3</sub>SnH). An analogous chain can be written for tris(trimethylsilyl)silane ((TMS)<sub>3</sub>SiH or TTMS).<sup>2</sup>

Initiation In• + Bu<sub>3</sub>SnH  $\longrightarrow$  InH + Bu<sub>3</sub>Sn• Propagation A-X + Bu<sub>3</sub>Sn•  $\longrightarrow$  A• + Bu<sub>3</sub>SnX A•  $\longrightarrow$  B• Termination B• + Bu<sub>3</sub>SnH  $\longrightarrow$  B-H + Bu<sub>3</sub>Sn• Equation I.1.6.1.1

Abstraction of a hydrogen atom by an initiator radical results in a tributyltin radical, which then proceeds to abstract a suitable radical precursor X (typically a Br or I) on substrate A-X to generate the reactive radical A•. This radical species then undergoes a transformation (or series of transformations), giving rise to a new radical, B•, which is trapped by a hydrogen atom from the metal hydride to give the final product B-H, and regenerate the tributyltiun radical capable of continuing the chain. Competitive trapping of A• with a hydrogen atom can be reduced or even entirely eliminated by employing low concentrations of the metal hydride reagent. If this direct reduction is a major concern, TTMS is used given its poorer hydrogen donor abilities. The overriding problems with the use of stoichiometric amounts of tributyltin hydride are the high toxicity of the reagent, and the substantial difficulty encountered in removing the tin residues from the final product(s). To avoid these non-trivial concerns, tributyltin hydride can be used in a catalytic fashion via the introduction of a co-reductant into the reaction mixture. This co-reductant, typically sodium cyanoborohydride (NaBH<sub>3</sub>CN), serves to regenerate the active tributyltin hydride reagent by reduction of the the tributyltin halide salt (Bu<sub>3</sub>SnX).<sup>6</sup>

#### I.1.6.2 Other Methods

Alternate methods useful for generating radical species and conducting radical reactions include the allyltributylstannane based "fragmentation method", atom and group transfer reactions,

the "thiohydroxamate method", and a variety of non-chain methods involving radical/radical coupling promoted by organocobalt(III) complexes, oxidative processes facilitated by manganese (III) salts, and reductive protocols relying on samarium(II) iodide.<sup>3</sup> While useful in highly tailored or difficult radical processes, these methods are not nearly as popular as metal hydride based protocols, and will not be discussed further.

#### I.1.7 An Overview of Selected Radical Cyclizations

A vast number of effective intramolecular radical cyclizations have been reported in the literature, and a comprehensive summary exploring the many subtleties and flexibility of such processes is difficult to compile. Consequently, only a rudimentary overview is in order to demonstrate the significance of these processes to organic chemistry.

#### I.1.7.1. Formation of 5-Membered Rings

The formation of carbocycles from sugars with preservation of stereochemistry is a challenging problem in organic synthesis, and one which has been successfully addressed with the use of intramolecular radical cyclizations. For example, tin hydride mediated cyclization of **1** provides a 91:9 ratio of  $2\alpha / 2\beta$  in 89% isolated yield (Scheme I.1.7.1).<sup>7</sup>



Construction of fused rings via hexenyl radical cyclization is also a particularly useful process. *Cis* ring fusion invariably predominates when fused 6,5- or 5,5-rings are constructed. An illustrative example is shown in Scheme I.1.7.2, involving the tin hydride promoted cyclization of 3 in 89% yield to produce a mixture of 4, 5 $\alpha$ , and 5 $\beta$ , all of which show *cis* ring fusion.<sup>8</sup>





This propensity for the formation of *cis* fused ring junctions was elegantly exploited in Curran's synthesis of hirsutene **6** (Scheme I.1.7.1.3). Here, a domino radical cyclization is employed to construct a tricyclic skeleton showing exclusive *cis-anti-cis* fusion.<sup>9</sup>



Scheme I.1.7.1.3

Radical cyclization also provides a convenient option for the often difficult task of forming C-C bonds at bridgehead centers. Cyclization of bromide 7 to the tricycle 8 (Scheme I.1.7.4) is one such known transformation,<sup>10</sup> and successful transannular cyclizations to form bridgehead rings have also been reported.<sup>11</sup>



Scheme I.1.7.1.4

Heterocycles can also be readily accessed via radical cyclization, and the development of a general route to  $\gamma$ -lactones **10** utilizing an ether linkage was an early success in the use of heteroatomic tethers (Scheme I.1.7.5).<sup>12</sup>



Initially, 9 is formed as a mixture of anomers, and subsequent Jones oxidation to lactone 10 showed the final product to be 98% *trans* isomer. The location of the oxygen atom in the chain,  $\beta$  to the radical center, is of importance since it significantly accelerates the 5-*exo* cyclization. The

formation of pyrrolidines using related nitrogen-substituted systems was demonstrated by Padwa (Scheme I.1.7.6).<sup>13</sup>



#### I.1.7.2 Formation of 3- And 4-Membered Rings

While the formation of five-membered rings via radical cyclization is routine, preparation of three- and four-membered rings is considerably more challenging. For both the cyclization of butenyl and pentenyl radicals, the equilibrium lies heavily in favor of the ring open form, so 3-*exo* and 4-*exo* cyclizations give rise to stable products in rare cases. For example, the 3-*exo* -trig closure of ether **11** follows a standard 5-*exo* -trig cyclization to afford **12**, a reaction driven by conversion of an alkyl radical to a more stable silylallyl radical (Scheme I.1.7.2.1).<sup>14</sup>



The stereoelectronically preferred 4-exo cyclization pathway of pentenyl radicals can be rapid enough to be useful if appropriate substituents are present. A number of highly stereoselective 4-exo cyclizations of heteroatom containing pentenyl radicals have been reported, and in all cases, *trans*-disubstituted heterocycles are formed, even though the substitution patterns vary considerably. For example, the construction of *trans*-disubstituted  $\beta$ -lactams such as 14 can be achieved via 4-exo cyclization of bromoacyl enamides such as 13 (Scheme I.1.7.2.2).<sup>15</sup>





While 4-*exo* cyclizations do have a limited scope, the high selectivity is an attractive feature, and since new substrates that undergo 4-*exo* cyclizations have recently been discovered, more systematic stereoselectivity studies can be conducted. *Bona fide* examples of 5-*endo* cyclizations<sup>16</sup>, the competitive pathway for pentenyl radicals, are even rarer than their 4-*exo* counterparts and have found little application.

#### I.1.7.3 Formation of 6-Membered And Larger Rings

While the formation of three- and four-membered rings via radical cyclization is hindered by intrinsic difficulties, preparation of six-membered rings is also hampered by two distinct factors. Firstly, 6-*exo* closure of heptenyl radicals is more than an order of magnitude slower than the analogous hexenyl radical cyclization<sup>17</sup>, so its more difficult to conduct cyclizations using the tin hydride method due to increased interception of the intermediate radical. Secondly, the abstraction of allylic hydrogens through a six-membered ring transition state becomes an important, or even dominant competing reaction. While these problems do not altogether preclude the use of radical cyclization procedures for the preparation of six-membered rings, cyclization precursors must be appropriately designed to suppress the competing pathways.

One tactic is to remove all allylic hydrogens capable of undergoing abstraction, a measure taken in the cyclization of dieneone **15** (Scheme I.1.7.3.1).<sup>18</sup>



Scheme I.1.7.3.1

While effective at eliminating the hydrogen abstraction pathway, this practice severely limits the scope of the cyclizations that can be conducted. If the presence of allylic hydrogens is unavoidable or desired, then introduction of an activating group on the alkene acceptor is imperative in order to significantly increase the rate of cyclization over that of hydrogen abstraction. The comparison studies depicted in Scheme I.1.7.3.2 testify to the importance of this activating effect.<sup>19</sup>



Scheme I.1.7.3.2

A less efficient and more difficult entry into six-membered ring systems can be achieved through the use of 6-endo cyclizations, which usually occur by default in systems which particularly disfavor 5-exo modes of closure. Although the introduction of internal alkene substituents provides increased amounts of 6-endo products, the most popular way to favor this mode of closure has been through the exploitation of ring strain in polycyclic systems. Substrates bearing  $\beta$ -lactams are amongst those that most effectively translate ring strain into high selectivities, as shown in Scheme I.1.7.3.3.<sup>20</sup>



The intermediate chair-axial transition state serves to minimize A-strain between the amide carbonyl and the ester, giving rise to only the product pictured.

Intriguing examples of 8-endo,<sup>21</sup> 9-endo,<sup>22</sup> and even 10-endo <sup>23</sup> cyclizations occurring with excellent stereoselectivity do exist, although yields are often low or modest, and general models do not yet exist.

### **I.2 Silicon Tethered Radical Cyclizations**

#### I.2.1 Introduction

Intramolecular radical cyclizations have been at the forefront of silicon tethered chemistry since their viability was first demonstrated in the mid-1980s. To date, such reactions represent approximately half of all publications in the field of silicon tethered processes,<sup>24</sup> and numerous groups continue to advance synthetic strategies for a variety of products based on this concept.

The utility of the "Temporary Silicon Connection", a term coined by Stork,<sup>25</sup> lies in the consistently high degree of regio- and stereocontrol observed at the reacting centers, particularly in the case of small ring formation. The cyclization of a radical center generated on one of the silicon ligands onto a proximal radical acceptor on a second ligand to form such rings can be classified according to the type of closure performed. 5-Exo and 6-endo cyclizations, carried out from a common precursor, represent the bulk of silicon tethered radical chemistry, while some 6-exo examples, alongside more impressive 7-,8-, and 9 membered ring formations, are also known.

#### I.2.2 Origins

In 1984, Nishiyama reported the stereoselective synthesis of 1,3-diols via a silicon-tethered radical cyclization strategy.<sup>26</sup> Although seminal work with simple alkyl silane systems demonstrating the increased rates and reversed regioselectivities possible in such cyclizations had been performed by Wilt several years earlier,<sup>27</sup> this formal "hydro-hydroxymethylation" of allylic alcohols stands as the first true application of silicon tethered chemistry. In a representative example, cinnamyl alcohol is first silylated with (bromomethyl)dimethylchlorosilane to produce the starting silyl ether **16**. This material, treated under standard radical cyclization conditions (tributyltin hydride, AIBN in refluxing benzene), affords the cyclic product **17**, which is readily transformed in high yield to the 1,3-diol **18** by Tamao-Fleming oxidation (Scheme I.2.2.1).



Scheme I.2.2.1

The 5-exo mode of cyclization predominates, but the 6-endo mode of cyclization leading to 1,4-diols can also be observed in systems without terminal alkene substitution (this pathway can be quite competitive, potentially accounting for as much as 40% of cyclized material). In order to rationalize the predominant syn-selectivity in the cyclization of substrates such as silyl ether **19**, a chair-like transition state can be invoked (Scheme I.2.2.2).



**Scheme I.2.2.2** 

Following Nishiyama's lead, Stork demonstrated that this hydroxymethylation protocol could be used to provide control of adjacent ring juncture stereochemistry. For example, radical cyclization of a precursors such as **20** and **21** proceed smoothly, yielding only a single diastereomer in each case (Scheme I.2.2.3).<sup>28</sup>



Scheme I.2.2.3

In all reactions of this nature, the newly formed *cis*-fused 5-membered ring impose a cup shape on the radical intermediate, and because the stannane can then only approach from the convex side, the radical is trapped with the hydrogen atom *anti* to the controlling allylic hydroxyl.

#### I.2.3 5-Exo and 6-Endo Cyclizations

Numerous applications of the silicon-directed radical cyclization have been reported for the synthesis of natural products, including steroid side chains and sugar chemistry. Crimmins described the total synthesis of (-)-talaromycin A 23, which relies on a hydroxymethylation sequence to transform penultimate allylic alcohol 22 into the natural product (Scheme I.2.3.1).<sup>29</sup>



Scheme I.2.3.1

Majetich employed the same process in the elaboration of allylic alcohol 24 in the total synthesis of  $(\pm)$ -14-deoxyisoamijiol 25, a member of the marine diterpenes dolastanes with a linearly fused 5-7-6 tricyclic framework (Scheme I.2.3.2).<sup>30</sup>



Scheme I.2.3.2

An elegant example developed by Fraser-Reid involves a serial 5-exo / 6-exo radical cyclization onto the hexopyranose 26 to afford the bicycle 27 following oxidation (Scheme I.2.3.3).<sup>31</sup> This system also demonstrates the possibility of using a trialkyl stannane radical chain carrier in a catalytic fashion.



Scheme I.2.3.3

A notable application of the preference for 6-endo-cyclization is the synthesis of physiologically significant 22-hydroxylated steroids investigated extensively by Koreeda. Complete stereochemical control was induced for the two newly formed stereocenters at C-17 and C-20 of 29 and 31, derived from the cyclization of silylated E-allylic alcohols 28 and 30 Scheme I.2.3.4).<sup>32</sup>



Scheme I.2.3.4

The observed mode of cyclization could result from conformational rigidity and a lower degree of substitution at C-20 versus C-17. Subsequent model studies also revealed that the C-18 methyl group has on important steric effect on precluding 5-exo cyclization. In contrast, the Z precursors failed to cyclize in either fashion, and its speculated that 6-*endo* cyclization is disfavored largely due to the steric bulk of the C-21 methyl group.

Replacement of (bromomethyl)silyl ethers with  $\alpha$ -bromovinylsilyl ethers provides a route to the regio- and stereoselective hydroacylation or -vinylation of allylic alcohols. In the cyclization of **32**, the 5-membered siloxane ring **33** was the major product, although some of the 6-membered compound was also isolated (Scheme I.2.3.5).<sup>33</sup>



There is speculation, however, that the latter product may not have originated directly from a 6-*endo* cyclization pathway, but rather via a secondary rearrangement involving a cyclopropane intermediate of the tertiary radical formed after 5-*exo* cyclization.

The vinyl halo-silane described above hints at the possibility of employing the silyl ether derivative as a radical acceptor rather than as a donor (as in all cases dealt with to this point). For example, a known route to the natural product statine utilizes a 5-*exo* cyclization of ether **34** to furnish the bicycle **35** as a 3:2 epimeric mixture (Scheme I.2.3.6).<sup>34</sup> Protodesilylation and subsequent transformations gave the desired  $\beta$ -hydroxy- $\delta$ -amino acid.



The scope of (bromomethyl)dimethylsilyl radical cyclizations was further expanded by the work of Malacria and co-workers who first explored the use of propargylic ethers in an analogous role. Interestingly, cyclizations of substrates of the general form **36** gave only cyclized products in the 5-*exo*-mode (Scheme I.2.3.7).<sup>35</sup>



Scheme I.2.3.7

The presence of a highly reactive and configurationally labile intermediate vinylic radical allows for the formation of either a *cis* or *trans* substituted alkene whose configuration depends on the substitution pattern of the parent propargylic alcohol. When  $R^3 = alkyl$ , *E* alkenes predominate, while substrates with  $R^3 = Ph$  or SiMe<sub>3</sub> reverses this selectivity.

Fascinating radical cascade reactions have also been reported using these propargylic silyl ether systems, and have given a great deal of insight into the competitive addition of  $\alpha$ -silylmetyhyl radicals to either a double or triple bond. Surprisingly, 5-exo-dig cyclization predominates, a striking result given that a 5-hexenyl radical normally has a faster cyclization rate than the corresponding 5-hexynyl radical. This silicon facilitated preference is exploited in the formation of carbocyclic systems such as **38**, arrived at via sequential cyclization of precursor **37** (Scheme I.2.3.8).<sup>36</sup>



Scheme I.2.3.8

Once again, reversing the role of the silicon tether as a radical acceptor rather than a donor was applied successfully to the stereocontrolled synthesis of C-glycosides, this time by Stork.<sup>37</sup> Radicals generated from selenosugars like **39** were found to cyclize with an ethynyl group tethered by an  $\alpha$ -OH to form the corresponding  $\alpha$ -C-glycoside **40** following desilylation (Scheme I.2.3.9). In general, very good E selectivity was obtained for the for the styryl moiety.



Scheme 1.2.3.9

Skrydstrup and Beau subsequently extended the scope of this reaction by carrying out the process via a reductive desulfonylation of glycosyl pyridinyl sulfones induced by samarium(II) diiodide.<sup>38</sup>

#### I.2.4 6-Exo Cyclizations and Larger Ring Formations

In Stork's investigations of C-glycoside construction, it was also discovered that radical cyclization with a silicon connector on either the 3- or 6-hydroxyl group of the phenylselenoglycosides gave good yields of the corresponding  $\beta$ -C-glycosides, exclusively (Scheme I.2.4.1).<sup>37</sup>



Scheme I.2.4.1

These processes constitute a 6-exo- and 7-exo-dig-ring closure respectively, and are remarkably efficient considering the nature of the cyclization, and the conformational adjustment required in the pyranose ring such that the hydroxyl or hydroxymethyl group resides in an axial orientation.

Exclusive 7-endo-trig-cyclization has been reported in the stereocontrolled synthesis of 2' and 3' C-branched nucleosides. A vicinal radical at the 2' or 3' center underwent cyclization to yield 1,5-diols following standard Tamao oxidation (Scheme I.2.4.2).<sup>39</sup>



Scheme I.2.4.2

In a subsequent report, Chattopadadhyaya found that alkynylsilyl ethers, capable or undergoing 5-*exo-dig* cyclization, could also be attached to a nucleoside scaffold, and underwent the desired cyclizations in yields often greater than 90%.

Only in the study of mixed silaketals have cyclizations forming 8 and 9 membered rings been reported. These substrates exhibit a largely *endo-trig* cyclization tendency, presumably due to the relatively long Si-O bonds, and large O-Si-O bond angles. Furthermore, the presence of two oxygen atoms serves to reduce transannular interactions, favoring the formation of medium-sized silacycles. For example, bromide **41** was found to undergo an impressive 8-*endo-trig* cyclization to form **42**, although 7-*exo-trig* selectivity can be re-induced by using an electron-withdrawing group on the radical acceptor (Scheme I.2.4.3).<sup>40</sup>



Application of 9-*endo-trig* cyclization was reported in the construction of *C*-disaccharides using a temporary dimethyl silaketal connection. Standard stannane reduction of **43** (or treatment of an analogous sulfone precursor with samarium(II) diiodide) induces a clean 9-*endo-trig* cyclization to yields disacchardide **44** in reasonable overall yield (Scheme I.2.4.4).<sup>41</sup>



#### **I.3 Temporary Boron Connections**

Although silicon has found tremendous success as a tethering medium for radical cyclization processes, it remains the only element demonstrated to be capable of forming a truly versatile, easily removable, *temporary* connection between the reactive sites. Given the benefits inherent in this type of temporary tether, finding alternate linkers with the same degree of effectiveness is an attractive goal.

As a suitable silicon substitute, boron, a related metalloid, holds similar potential. Although the use of boron in any radical tethering capacity has never been reported, nothing in related intermolecular radical work involving organoboron compounds suggests that intramolecular processes involving the element as a linker should fail. While fundamental differences between the two metalloids do exist - boron's sp<sup>2</sup> based planar triangular geometry and empty valence versus silicon's sp<sup>3</sup> supported tetrahedral geometry - boron is not excluded as a potential alternate.

# Chapter II:

**Results & Discussion** 

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### **II.1 Boron Tethered Radical Cyclizations**

#### **II.1.1 Objectives**

The goal of this project was to demonstrate the viability of boron tethered radical cyclizations by developing and optimizing a general method for such transformations. An efficient, four step sequence comprised of (i) a terminal alkyne hydroboration, (ii) boronic ester formation, (iii) radical cyclization, (iv) and C-B bond transformation was proposed for this purpose (Scheme II.1.1.1).



Hydroboration of an alkyne 45 generates an E-vinyl boronic acid 46 upon suitable workup, which readily undergoes esterification with a haloalcohol. Under radical conditions, the resultant E-vinyl boronic ester (boronate) 47 is then potentially capable of an intramolecular cyclization to yield an intermediate boracycle 48. Subsequent functionalization of the C-B bond, most readily achieved via a simple oxidative cleavage, liberates a diol product 49. The process in its entirety constitutes a formal hydroxyalkylation of an E-enol if the C-B bond of the starting acid is treated as a "masked" alcohol.

At the outset of this project, there were no examples of boron tethered radical cyclizations reported in the literature, and efforts were primarily directed at developing a protocol to carry out such reactions. The facile and versatile preparation, handling, and storage of organoboron compounds was one of the principle motivations for initiating our research in this area, and the high degree of synthetic flexibility exhibited by the C-B bond<sup>42</sup> was also an attractive feature given the potential for considerably expanding the scope and utility of radical cyclization methodology. If proven viable, it was hoped that the yields of these processes could be optimized to rival the results obtained in previously reported silicon tethered radical cyclization work.

#### **II.1.2 Preparation of Substrates**

All of the substrates screened in the radical cyclization process were prepared via an efficient, high yielding two step hydroboration-esterification pathway. In total, nineteen cyclization precursors were prepared in this manner and with relative ease based largely on reliable and proven protocols reported in the literature. Furthermore, all the preparations furnished substrates requiring no extensive purification following isolation, an attractive aspect of the envisaged strategy.

#### **II.1.2.1** Synthesis of (E)-Vinyl Boronic Acids

All (*E*)-vinyl boronic acids were accessed via hydroboration of the corresponding alkyne. Several hydroborating agents were considered for this purpose, and dibromoborane-dimethyl sulfide complex was chosen for the hydroboration of simple alkyl alkynes such as 1-hexyne **45b**.<sup>43</sup> Commercially available and easy to use, this reagent works quickly under mild conditions, leaving no alkyl residues to be removed from the final product. Aqueous treatment of the dibromo-alkenyl borane **50** intermediate affords the free (*E*)-1-hexenyl boronic acid **46b** in high yield (Scheme II.1.2.1.1).



Several (*E*)-vinyl alkyl boronic acids were prepared in this manner, and consistently high yields were observed with a variety of alkyl substituents (Table II.1.2.1.2).

Table II.1.2.1.2

Acids prepared using this method were isolated as highly crystalline solids, although prolonged periods in dehydrating environments (i.e. vacuum line) were found to facilitate the formation of a trimeric anhydride species. Present as viscous oils, the anhydrides are manifested in <sup>1</sup>H NMR spectra as downfield shifted  $\alpha$ -vinyl proton signals, and detected amounts can vary from sample to sample (see Experimental, Chapter III).

Although effective at hydroborating terminal alkynes in a regioselective manner (with greater than 95:5 selectivity for the terminal position), the hydroboration of an internal alkyne, 3-hexyne **51**, with dibromoborane produced an inseparable mixture of products. Aside from the desired (E)-1-ethyl-1-butenyl boronic acid **52**, a substantial amount of (Z)-1-propyl-1-propenyl boronic acid **53** was also observed (Scheme II.1.2.1.3). This isomeric material is most likely a result of acid promoted double bond migration facilitated by the presence of HBr in the reaction mixture during work-up, and cannot be removed by selective recrystallization from the product mixture.



Attempts at extending the use of the dibromoborane-dimethyl sulfide complex to the hydroboration of aryl alkynes met with little success. While some reaction was evident by NMR, the observed rates were to slow too be synthetically useful on these electron deficient substrates. Consequently, another commercially available reagent, catecholborane (CB),<sup>44</sup> was considered for the hydroboration of aryl alkynes such a phenyl acetylene **45f**. CB did react to give the desired aryl vinyl boronic acid **46f** following hydrolytic cleavage of the catechol moiety from the catechol-alkenyl borane intermediate **54** (Scheme II.1.2.1.4)



Scheme II.1.2.1.4

Three readily available aryl alkynes were hydroborated in modest to high yields using this reagent (Table II.1.2.1.5).

R <sup>1</sup>	CB R1	46 B(OH)2
Compound	R <sup>1</sup>	Yield (%)
46f		76
46g	-	40
46h	MeO-	66
		_

Table II.1.2.1.5

A significant problem with this protocol was the hydrolytic cleavage and subsequent removal of residual catechol from the final product which was often difficult and time-consuming. Only by repeated re-crystallization from a mixture of THF-hexanes could all traces of catechol be eliminated.

It was initially conceived that catecholborane would also be an effective reagent for the preparation of functionalized vinyl boronic acids. The first attempt at synthesizing such a product began with investigations into the hydroboration of benzyl propargyl ether **45i**. The known Lewis acidity and consequent sensitivity of the dibromoborane-dimethyl sulfide reagent to heteroatoms immediately precluded its use on any functionalized substrates, so CB was the next obvious choice. While hydroboration itself was found to proceed to completion as supported by NMR data, hydrolytic removal of the catechol moiety proved to be impossible. Varying the acidity, basicity, temperature, and duration of the hydrolysis step was either ineffectual, or encouraged full decomposition of the hydroborating reagents had to be considered which would offer more readily transformable intermediates (attempted hydroboration of substrates such as trimethylsilyl acetylene, propargyl bromide, and 3-(*t*-butyldimethylsiloxy)-1-propyne were plagued with the same problem, in addition to general unreactivity or promoted substrate degradation or deprotection).

Selected was dicyclohexyl borane, Chx<sub>2</sub>BH,<sup>45</sup> a hydroborating agent requiring *in situ* preparation. Upon treatment with this reagent, the benzyl propargyl ether **45i** readily underwent hydroboration, and subsequent oxidation of the two C-B bonds binding the cyclohexyl moieties
resulted in the formation of a boronate 55 that underwent facile hydrolytic cleavage to afford the free acid 46i (Scheme II.1.2.1.6). The free acid of a TBDMS protected analog (46j) was also successfully prepared in comparable yield.



Careful column chromatography on silica gel was conducted in order to separate the desired free acid from the substantial amount of cyclohexanol present in the reaction mixture. Interestingly, the acids are isolated almost entirely in their anhydride form following this chromatography.

#### II.1.2.2 Synthesis of (E)-Vinyl Boronic Esters

Following isolation of the crystalline (E)-vinyl boronic acids, a radical precursor was introduced into the target substrates via a facile esterification with one of three selected haloalcohols: 2-bromoethanol, 2-iodoethanol, or 3-bromopropanol. Generally, treatment of any free boronic acid **46** with 2.5 equivalents of the haloalcohol in either THF or ether and in the presence of 4 Å molecular sieves resulted in formation of the bis protected product **47** (Scheme II.1.2.2.1).



Scheme II.1.2.2.1

The bulk of the cyclization precursors to be screened were prepared in this manner, and high yields were observed in all cases (Table II.1.2.2.2)

	•	ſ		X I
R <sup>1</sup> B(O <b>46</b>	H) <sub>2</sub> <u>x H</u> n	H	R <sup>1</sup>	(1)n $B^{-0}$ (1)n $B^{-0}$ (1)n (1)n
Compound	R <sup>1</sup>	n	х	Yield (%)
47a	Pr	1	Br	97
47b	Pr	1	1	57
47c	Pr	2	Br	83
47d	Bu	1	Br	91
47e	<i>i</i> Pr	1	Br	88
47f	<i>t</i> Bu	1	Br	91
47g	Chx	1	Br	89
<b>47</b> h	Ph	1	Br	85
47i	Ph ~	1	1	83
47j	Ph	2	Br	85
47k	<i>p</i> -tolyl	1	Br	83
471	<i>p</i> -MeO-Ph	1	Br	70
47m	BnOCH <sub>2</sub>	1	Br	68
47n	TBDMSOCH <sub>2</sub>	1	Br	70

Table II.1.2.2.2

All boronates were isolated as viscous, colorless oils, and unreacted acid was removed from the product by filtration through a pad of celite, a measure also required for the removal of sieve residues. Molecular sieves are essential to the preparation, driving the process to completion and producing higher yields of adduct. No further purification of the esters was required other than removing excess haloalcohol under reduced pressure. Distillation of the esters themselves under reduced pressure was found to result in rapid decomposition, and column chromatography on silica gel was never explored given the possibility of hydrolysis (evident in TLC analysis). Because of the tendency towards heat promoted decomposition, the thermal stability of the esters in solution was tested by refluxing the material in THF for a period of 24 h. During this time, only a minor degree of hydrolysis was observed, and no decomposition was otherwise evident. Similarly, it was also determined that while some minimal hydrolysis does take place if the boronate is stored for a prolonged period of time (more than 2 weeks) at room temperature, no such degradation is evident even after several months if the ester is stored under refrigeration.

In order to generate an aryl radical precursor, the esterification of (E)-1-hexenyl boronic acid **46b** was also attempted with 2-bromophenol, but no boronate could be isolated. Reaction of

the same acid with 2-bromobenzyl alcohol, however, proved possible, cleanly giving the bisprotected ester in high yield (> 80%).

Spurred by the desire to produce 4-bromobutanol and 5-bromobutanol protected boronates and the commercial unavailability of these particular haloalcohols, a one pot hydroborationesterification procedure was sought that would rely on the Lewis acid promoted ring opening of a cyclic ether by an intermediate alkenyl-dibromo borane species to install the haloalcohol moiety onto the substrate. In a manner similar to the tribromoborane promoted ring opening of cyclic ethers and epoxides,<sup>46</sup> it was found that (E)-1-hexenyl-dibromo borane **56**, derived from the hydroboration of 1-hexyne **45b** with dibromoborane-methyl sulfide complex, quantitatively opened THF (**57a**) and THP (**57b**) (Scheme II.1.2.2.3).



Cyclohexene oxide was also readily opened at room temperature, resulting in a quantitative yield of the bis protected boronate (58). All products generated by this method required no further purification.

Given that the mentioned esterification protocols do not allow for the synthesis of monoprotected boronates (a statistical mixture of mono-, di-, and unprotected material is produced when esterification is attempted with one equivalent of haloalcohol), diisopropyl esters of (E)-1-pentenyl (**59a**) and 2-phenyl-(E)-1-ethenyl (**59b**) boronic acid were prepared to act as intermediates for the *in situ* preparation of these mono-protected species. It was anticipated that reaction of these diisopropyl esters under the radical conditions in the presence of one equivalent of a haloalcohol would result in the exchange of one isopropyl moiety for one haloalcohol molecule. The resultant mono-haloalkylated species should then cyclize to the desired intermediate boracyle.

Synthesis of the diisopropyl esters is also trivial, although somewhat more time consuming. Preparation requires stirring of the free boronic acid in a 1:1 mixture of isopropanol

and toluene for one week at 80 °C. Subsequent removal of residual solvents under reduced pressure affords the bis protected material in > 95% purity.

#### **II.1.3 Preliminary Considerations for Radical Cyclization**

In order to carry out the desired intramolecular radical cyclizations, a method capable of generating radical species from the halide functionality found within the substrates had to be selected. Based on this consideration, it was decided that the use of a tin hydride promoted chain reaction would be the most effective way of achieving the intended transformation. An added attraction was the capacity to make this process catalytic in the chosen tin hydride by means of a previously established protocol.<sup>47</sup> The catalytic nature of the chain carrier potentially eliminates unwanted side reactions, lowers the overall toxicity of the entire process, and makes product isolation and purification far simpler.

#### II.1.3.1 Selection of a Tin Hydride Method

The selection of tributyltin hydride as the radical chain promoter and carrier was influenced by its status as the reagent of choice for such transformations, its relatively low cost, and the ease of its preparation. The decision to attempt the envisaged cyclizations by using this reagent in a catalytic fashion was based on the aforementioned benefits of such a process. Efforts were then made to optimize this catalytic tributyltin hydride system for efficiency and yield.

### II.1.3.1.1 Preparation of Tributyltin Hydride

Commercial tributyltin hydride has a limited shelf life, and its quality is suspect if the reagent is not frequently redistilled to ensure purity. Given the high toxicity of organotin compounds, the repeated exposures entailed in these purifications are best avoided. Consequently, tributyltin hydride was freshly prepared in our laboratory by the method of Kuivila (Scheme II.1.3.1.1).<sup>48</sup>

4 Bu<sub>3</sub>SnCl 
$$\frac{\text{LiAlH}_4}{\text{Et}_2\text{O}, 0 \,^{\circ}\text{C} \text{ to r.t.}}$$
 4 Bu<sub>3</sub>SnH + LiAlCl<sub>4</sub>

#### Equation II.1.3.1.1.1

Commercially available tributyltin chloride is readily reduced within several hours by lithium aluminum hydride suspended in ether. Following an aqueous quench, the tributyltin hydride is localized in the organic solvent, which is removed under reduced pressure to afford the crude tin hydride. Very rapid distillation under the best vacuum achievable yields a clear, colorless liquid which can remain unchanged for up to a year if stored and handled properly. Commercial tribuyltin hydride, on the other hand, was found to show a fine white precipitate indicative of decomposition within days of initial use.

#### **II.1.3.2** Selection of Initiators

In order to trigger the tributyltin hydride supported radical chain reaction, a suitable initiator had to selected. The widely used nitrile based initiator, AIBN, was an obvious choice for use in the 60-70 °C range initially planned for executing the cyclizations. The initiator dimethyl-2,2'- azobisisobutyrate (DAB), which shows an almost identical half-life profile to AIBN,<sup>49</sup> was also considered given its ready availability.

#### **II.1.3.3** Selection of Solvent

The catalytic variant of a tin hydride process demands that a solvent be employed with a high enough dielectric constant to adequately solvate the required co-reductant. The co-reductant called for in use with tributyltin hydride is sodium cyanoborohydride, a commercially available, mild reducing agent. The extremely low solubility of this salt in benzene precluded the use of this classic solvent for the proposed cyclizations, and the standard solvent employed in conjunction with NaBH<sub>3</sub>CN, *t*-butanol, was also rejected. The principle concern was that the *t*-butanol could undergo transesterification with the haloalcohol protected boronates **47** to yield an unreactive species incapable of cyclization (Scheme II.1.3.2.1).



After considering several solvents with dielectric constants approaching that of *t*-butanol (12.47), THF, with a dielectric constant of 7.58, was found to be well suited for the reaction system. Like benzene and *t*-butanol, THF can be heated to a relatively high temperature should the reaction call for such conditions, and NaBH<sub>3</sub>CN, appraised as a 0.25M solution, was found to be entirely soluble in THF above 35 °C.

#### **II.1.3.4** Oxidation of Boracycles

Oxidation methods were sought for the conversion of the intermediate boracycles to the corresponding alcohols. Aside from the traditional method of C-B bond oxidation, treatment with alkaline peroxide,<sup>50</sup> the use of a milder oxidant was also considered. Trimethylamine-N-oxide

(TMANO)<sup>51</sup> is known to oxidize trialkylboranes under neutral conditions, as is sodium perborate (NaBO<sub>3</sub>),<sup>52</sup> and both were to be explored as an alternative to the peroxide protocol.

# **II.1.4 Initial Cyclizations Attempts**

Given the entirely novel nature of the cyclizations to be attempted, no real rational planning of reaction conditions could be attempted, nor could any potential problems aside from direct reduction of the radical precursor be anticipated. Consequently, a set of reasonable conditions was adapted from related work involving the intamolecular additions of  $\alpha$ -boryl radicals<sup>53</sup> to serve as a starting point for subsequent development.

<u>Initial</u>	Conditions for Cyclization:	HSnBu <sub>3</sub> , 0.01 equiv.	
		NaBH <sub>3</sub> CN, 2.5 equiv.	
		DAB, 0.1 equiv.	
		Alkenyl boronic ester, 1.0 equiv.	
		THF, 0.1 M solution	
		Refluxed at 70 °C under nitrogen, 5 h.	

Initial Conditions for Oxidation: TMANO, 5.0 equiv. Boracycle, 1.0 equiv. Benzene, 0.05 M solution

The first attempted cyclizations were conducted on an alkyl derived boronic ester, di(2bromoethyl)-(E)-1-hexenyl boronate **47d**, and an aryl derived boronic ester, di(2-bromoethyl)-2phenyl-(E)-ethenyl boronate **47h**, employing the conditions outlined above. These initial attempts proved quite encouraging, furnishing the two expected 5-exo-trig cyclization products, 1,3octanediol **49b** and 4-phenyl-1,3-butanediol **49c**, in modest yields following oxidation and hydrolytic cleavage (Scheme II.1.4.1).



#### **II.1.5** Optimization of Cyclization Conditions

While the initial attempts described above demonstrated that the envisaged cyclizations were in fact possible, it was evident that the conditions employed were not ideally suited for the transformation. Although the general protocol was adequate, its components required optimization.

Reviewing the data accumulated in these initial trials, it was apparent that direct ionic reduction of the radical precursors (halides) in the presence of the NaBH<sub>3</sub>CN co-reductant was a significant problem, and needed to be overcome in order to raise the yields of the isolated diols. From <sup>1</sup>H NMR spectra of the crude reaction mixtures immediately following cyclization, one could ascertain that the reactions had not gone to completion given the presence of diagnostic vinylic proton signals. Also evident were signals suggesting the formation of halide reduction products, formed via an undesired, competitive pathway in significant amounts.

#### **II.1.5.1** Establishing the Degree of Direct Halide Reduction

In order to critically evaluate the extent of ionic reduction occurring during the cyclization reactions, it was proposed that this reaction pathway be studied independently of the cyclization process. This was done simply by eliminating the initiator and tributyl tin hydride from the reaction mixture, thereby making a radical process impossible. All other reaction mixture components were maintained as they were in the initial trials.

It was felt that the reaction temperature had a direct bearing on the degree of ionic reduction observed, so this was the principle factor to be varied in the reduction studies. Examining temperature effects was achieved by stirring di(2-bromoethyl)-(E)-1-hexenyl boronate **47d** in the presence of 2.5 equivalents of NaBH<sub>3</sub>CN, in THF at different temperatures for 24 h (Scheme II.1.5.1.1).



Scheme II.1.5.1.1

The transformation of the methylene carbons bearing the halides to methyl groups by the direct reduction of the halides can be measured by <sup>1</sup>H NMR. The shifts of the protons on those carbon atoms are substantially different before and after reduction, and quantification on the basis of the spectral data is trivial. The direct reduction was studied between 40 °C and 70 °C, the upper temperature limit at which the initial trials were conducted. A direct reduction profile could then be assembled based on the NMR measurements (Graph II.1.5.1.2).

It is clear that the amount of non-reduced, halogenated moieties decreases exponentially as the temperature is increased within the stated range. In other words, higher temperatures facilitate direct ionic reduction, a pathway competitive with and detrimental to the radical process being conducted.



### **II.1.5.2** Cyclization Trials at Lower Temperatures

The cyclizations described for the initial trials were attempted again, beginning with runs conducted at 40 °C. Although this temperature maximizes the number of available halide precursors, there is an unfortunate corresponding decrease in the rate of initiation. After a 24 h period, little reduction in the number of vinylic protons was observed by NMR, and almost all the halide precursors seemed intact. In order to make the reactions proceed at a synthetically useful rate, the temperature would have to be increased somewhat. Consequently, further trials were conducted at 50 °C and 55 °C, and although it was found that initiation was still exceedingly slow at 50 °C, the reaction was proceeding quite well at 55 °C. Anticipating that the radical chain could collapse at this lower temperature, more initiator (an additional 0.3 equivalents) was introduced into the reaction, and the cyclization allowed to run for an additional 24 h. In subsequent analysis of the crude reaction mixtures, the <sup>1</sup>H NMR spectra were found to be entirely free of vinylic proton signals, suggesting complete reaction by the desired radical pathway.

Treatment of these crude mixtures with the TMANO oxidant and work-up as described for the initial trials resulted in higher observed yields for both of the diol products (Scheme II.1.5.2.1).



This positive result was fully anticipated in light of the fact that by lowering the reaction temperature from 70 °C to 55 °C, the amount of direct reduction is essentially cut in half (see Graph II.1.5.1.2).

Several replicate runs using the above conditions were conducted in order to gauge the reproducibility of the process, and to establish if higher yields were obtained in a consistent manner. Interestingly, one of these runs employed a graphite bath as the heat source for the reaction, a replacement for the oil baths used in all the previous runs, and after work-up of the

reaction, it was discovered that all of the starting material was still present. This anomalous result occurred because the heat transfer from the graphite bath to the reaction vessel was not as efficient as that from an oil bath, so the internal temperature of the reaction mixture was not a constant 55 °C. What this result did reveal was the effective operational threshold for the initiator in the reactions being conducted. Consequently, it is absolutely critical that the temperature of the reactants be no lower than 55 °C during the entire course of the reaction.

# II.1.5.3 Evaluation of the Co-Reductant

Given the demonstrated negative effect of the co-reductant on the substrate, increasing the relative concentration of this reagent in solution was never a question. Although more efficient recycling of the tributyltin halide salt could potentially be achieved in this manner, it was felt that the change would be more harmful than helpful. What was investigated was decreasing the concentration of this co-reductant to further stem the direct reduction of the halides. While previous trials employed a slight excess of NaBH<sub>3</sub>CN (in relation to the moles of halide), a run was conducted on the hexenyl substrate with exactly two equivalents of the salt. Curiously, while there should have been enough of this reductant to fully recycle all of the tin present, the reaction was found not to have gone to completion. Presumably, the radical chain collapsed at some point because the regeneration of the tin hydride wasn't being performed as effectively as in the previous trials. Consequently, all cyclizations that followed during the course of this work were conducted with 2.5 equivalents of the co-reductant.

# II.1.5.4 Tributyltin Hydride Effects

The effect of variable amounts of tin hydride in the reaction mixture was also examined. Addition of more than 1 mol % tin hydride was never considered given the drawbacks of the reagent, and only one trial was conducted to establish if the cyclization of di(2-bromoethyl)-(E)-1-hexenyl boronate 47d could be carried out with 0.5 mol % of tributyltin hydride. This trial, like the one with a reduced amount of co-reductant, showed substantial amounts of starting material upon termination. It was apparent that the radical chain couldn't be supported effectively with such a low tin concentration, so all subsequent efforts were conducted with the initially chosen mole percentage.

# **II.1.5.5** Substrate Concentration Effects

Running the cyclizations under more dilute conditions than then the 0.1 M concentration used for the initial trials had no beneficial effects on yield or rate of cyclization, and was avoided simply because of the greater solvent demands. More concentrated solutions, however, were clearly detrimental as the solubility of the coreductant became a problem at the relatively low reaction temperature being employed. The initially employed concentration was selected as ideal for these reasons.

#### II.1.5.6 Effectiveness of C-B Bond Oxidants

While TMANO was employed effectively to oxidize the C-B bond in all the cyclization attempts to this point, the possibility was entertained that yields might be even higher if the oxidation was carried out using either the basic peroxide system, or sodium perborate. In order to more closely gauge the effectiveness of each individual oxidant, a cyclization trial was once again carried out on the di(2-bromoethyl)-(E)-1-hexenyl boronate system **47d**, using the now improved conditions, and the intermediate boracycle was partitioned three ways. The three portions were then oxidized separately, each by only one of the proposed oxidative methods. After isolation and purification of the resulting 1,3-octanediol **49b**, it was noted that the yield obtained from the TMANO oxidation was approximately 15% higher than for both of the alternate methods. On the basis of this result, it was decided that the use of TMANO was indeed ideal for oxidative functionalization of the intermediate boracycles.

It should also be noted that when isolating the final products following oxidation, any solutions of the diols in organic solvents should be dried with anhydrous sodium sulfate  $(Na_2SO_4)$ , rather than with anhydrous magnesium sulfate  $(MgSO_4)$ . The later is more Lewis acidic, and is known to effectively coordinate diols, thus lowering the isolated yields.

#### **II.1.6** Establishing the Necessity of Tethering

Prior to proceeding with the cyclization of numerous substrates, it was deemed necessary to unequivocally establish the tethered nature of the reaction. One can imagine that the products of 5-*exo* or 6-*endo* cyclization could also be obtained via an intermolecular pathway, so to rule out this possibility, a pair of control experiments were performed. In the first, 2-hex-1-enyl-[1,3,2]-dioxaborlolane **60** was subjected to the radical conditions in the presence of 2-bromoethanol, while in the second, the free hexenyl boronic acid **46b** was reacted in the presence of 1-bromo-2-(t-butyldimethylsiloxy)-ethane (Scheme II.1.6.1).



In both reactions, no change in the vinylic proton signals was observed by <sup>1</sup>H NMR, and only disappearance of the halide radical precursor could be seen. It was clear that since tethering of the reactive partners was precluded, the reaction couldn't proceed intermolecularly.

## **II.1.7** Overview and Analysis of Attempted Cyclizations

After establishing a simple, effective, and efficient protocol for carrying out the desired boron tethered radical cyclizations (see conditions outlined below), all that remained was screening a variety of substrates to establish full proof of concept. Numerous cyclization precursors were synthesized by the methods outlined earlier, and each was subjected to the reaction conditions listed below. The results from the 5- and 6-*exo* cyclization trials are summarized in Table II.1.7.1, while more significant work is reported later.

<b>Optimized</b> Conditions for Cyclization:	HSnBu <sub>3</sub> , 0.01 equiv.
	NaBH <sub>3</sub> CN, 2.5 equiv.
	DAB, 0.4 equiv.
	Alkenyl boronic ester, 1.0 equiv.
	0.1 M solution
	Refluxed at 55 °C under nitrogen, 48 h.
<b>Optimized Conditions for Oxidation:</b>	TMANO, 5.0 equiv.
	Boracycle, 1.0 equiv.
	Benzene, 0.05 M solution

R <sup>1</sup>		(1) <i>cat.</i> (2) [O]	Bu₃Sn⊦		он он 49 <sup>or</sup> он 0н 61
Entry	R <sup>1</sup>	n	х	Product	Yield(%)
47a	Pr	Br	1	49a	81
47d	Bu	Br	1	<b>49b</b>	77
47e	<i>i</i> Pr	Br	1	61a	83
47f	<i>t</i> Bu	Br	1	61b	67
47g	Chx	Br	1	61c	77
47h	Ph	Br	1	49c	ස
47k	<i>p</i> -tolyl	Br	1	49d	65
47c	Pr	Br	2	49e	85
47j	Ph	Br	2	49f	75
47Ъ	Pr	I	1	49a	73
47i	Ph	1	1	49c	68

Tabl	e I	I.1.	7.1

# II.1.7.1 5-Exo-Trig Cyclizations

As anticipated from the initial trials involving di(2-bromoethyl)-(E)-1-hexenyl boronate **47d** and di(2-bromoethyl)-2-phenyl-(E)-ethenyl boronate **47h**, substrates **47a,b,i,k** (see Table II.1.7.1) also cyclized in a 5-*exo*-trig fashion to afford 1,3 diols **49a-d** in high yields following oxidation and hydrolytic cleavage. A classical Beckwith-Houk transition state model can be invoked to rationalize this observed cyclization tendency (Figure II.1.7.1.1).



Free rotation around the C-B bond allows for attack by the radical on both the re and si faces of the olefin, and the absence of any effects encouraging enantioselectivity results in a racemic mixture of products. All the substrates screened showed an overwhelming 5-exo-trig cyclization preference, an effect observed in the majority of radical process with potential for the formation of both 5 and 6 membered rings.

In order to gauge the level of regioselectivity, an authentic sample of 2-Butyl-butane-1,4diol 62, the potential 6-endo product for the cyclization of 47d, was synthesized by an alternate strategy (Scheme II.1.7.1.2. For preparation see Experimental, Chapter III).



The <sup>1</sup>H and <sup>13</sup>C spectra of this material were then compared to those of the crude reaction mixture following oxidation, and no signals corresponding to the 6-endo product were evident. Based on this result and with the limit of detection of NMR in mind, the exo cyclization selectivity for these tethered cyclizations is greater than 95 : 5. It should also be noted that an authentic sample of 1,3-octanediol 49b was prepared via another route to unambiguously confirm the identity of the boron tethered cyclization product (Scheme II.1.7.1.3. For preparation see Experimental, Chapter III).



The degree of regioselectivity, like the overall yield and rate of the reactions, appears to be independent of the alkyl or aryl substituent placed at the  $\beta$  vinylic position. Cyclization is compatible with a wide range of substituents, and conceivably any such group can be installed at the  $\beta$  vinylic position via the aforementioned hydroboration strategies. However, when cyclization was attempted with 3-(benzyloxy) (47m) or 3-(t-butyldimethylsiloxy)-(E)-1-propenyl (47n) boronates, no desired products were evident as a result of some competitive decomposition pathway, perhaps accelerated by the  $\gamma$  oxygen.

Investigation of iodides (47b and 47i) as radical precursors proved successful as well, although yields from these more reactive species were not any higher than those obtained from brominated starting materials. Presumably, more ready direct reduction parallels the greater ease of radical generation from an iodide precursor.

Realizing that it would be desirable to carry out these cyclization using only one equivalent of the reacting haloalcohol, and given the absence of methodology to prepare mono protected boronates, the in situ generation of these mono-protected species from diisopropyl boronates was investigated. Reaction of diisopropyl boronates **59a** and **59b** under the stipulated radical conditions and in the presence of only one equivalent of haloalcohol did result in the formation of cyclized materials **49a** and **49f**, but yields of isolated diols were found to be substantially lower than those obtained from substrates with two haloalcohol moieties already installed (39% and 43% respectively).

### II.1.7.2 5-Exo-Trig Cyclization / SHi Sequences

Cyclization of substrates **47e-g** was expected to produce 1,3-diols via the 5-*exo*-trig cyclization pathway observed for the primary alkyl and aryl  $\beta$  substituted substrates. Surprisingly, only 1,4-diols **61a-c** were isolated. These results suggest that following the 5-*exo*-trig cyclization, the boracyclic radical intermediate **63** rearranges to radical **64** prior to undergoing H-atom trapping from the tributylstannane (Scheme II.1.7.2.1).



Although 1,4-diols can potentially be formed via a 6-endo-trig cyclization pathway, they would be of different structure than those isolated from the cyclization and subsequent rearrangement of these secondary or tertiary  $\beta$  substituted boronates. An authentic sample of 5,5-dimethyl-1,4-hexanediol **61b** was prepared independently to make certain the identity of the diol product from the boron tethered radical cyclization-rearrangement pathway was as assigned (Scheme II.1.7.2.2. For preparation, see Experimental, Chapter III).



The high selectivity for the formation of either **49** or **61**, depending on the substituents, is particularly noteworthy. Although the origin of this effect is not clear, presumably the extra steric bulk of  $R^1 = iPr$ , *t*Bu or Chx lowers the rate of H-atom trapping in the corresponding radical **63**, and facilitates the intramolecular homolytic substitution ( $S_{Hi}$ )<sup>54,55</sup> reaction at boron. The rearrangement is not observed in substrates with a primary alkyl or aryl group  $\alpha$  to the intermediate radical. Primary alkyl substituents allow for more rapid H-atom trapping because of lower steric hindrance, while aryl substituents stabilize the intermediate radical at the  $\alpha$  position. Similar S<sub>H</sub>i reactions at silicon or tin have not been observed, perhaps due to competing  $\beta$ -scission. Intermolecular S<sub>H</sub>i reactions at boron by carbon-centered radicals have been observed in the gasphase,<sup>56</sup> but to our knowledge this is the first example of an intramolecular S<sub>H</sub>i reaction at boron and the first example at a boronic ester.

#### II.1.7.3 6-Exo-Trig Cyclizations

Attempted 6-exo cyclizations, conducted with substrates 47c and 47j also proved possible, giving rise to 1,4-diols 49e and 49f. Much like their 5-exo counterparts, these reactions were very clean, and once again, the exo mode of cyclization prevailed. 7-endo products were not isolated, and yields were on par with previous cyclizations. A standard sample of 1,4-octanediol 49e, the product from the cyclization of 47c, was synthesized separately for comparison with the cyclization product (Scheme II.1.7.3.1. For preparation, see Experimental, Chapter III).



Based on the comparison of the spectral data, it was determined that these cyclizations were indeed proceeding in a 6-*exo*-trig fashion to produce 1,4-diols.

### II.1.7.4 7- And 8-Exo-Trig Cyclizations

The previously described preparation of substrates **57a** and **57b** made it possible to attempt difficult 7-*exo* and even rarer 8-*exo* cyclizations respectively. Employing the optimized conditions, **57a** cyclized successfully in an exclusive 7-*exo* fashion, producing 1,5-diol **65** in high yield (Scheme II.1.7.4.1). Attempted 8-*exo* cyclization of **57b** failed to yield any desired product.



#### **II.1.7.5** Stereoselectivity

Cyclization of substrate **58** was chosen to serve as an initial attempt in elucidating the stereoselectivity of a radical cyclization employing a boron tether. With the anticipated 5-exo product containing three stereocentres and resulting from oxidation of a [4,3,0]-nonane fused ring system, both the nature of the intermediate ring fusion and alkene facial selectivity, if any, could be determined. With eight possible diastereomers arising from the cyclization, it was hoped that the intermediate ring system would show exclusively *cis* fusion. Indeed, this outcome was anticipated based on the overwhelming number of literature precedents with a wide variety of tethered substrates. Should the reaction proceed as expected, the processes would be of greater utility than one showing a mixture of *cis* and *trans* products.

Rather surprisingly, the cyclization of **58** proved far more interesting than originally anticipated. Instead of the expected 1:1 mixture of diastereomeric 1,3-diols, a 1.3:1 mixture of diastereomeric 1,4-diols **66a** and **66b** was isolated in very high yield (Scheme II.1.7.5.1).



While <sup>13</sup>C NMR of the original diol mixture showed the products to be present in a ratio of approximately 1.3:1 (consistent over several cyclization trials), isolation and characterization of the individual diastereomers was impossible given that they could not be separated by column chromatography. In an attempt to render the diols separable, the mixture was subjected to acetalization with dimethoxypropane in order to yield two distinct acetonides. However, both diols didn't undergo protection under these conditions, and it was subsequently possible to separate the one acetonide **67** that did form from the other diateroemer present as the free alcohol **66a**. Cleavage of the acetonide **67** then liberated the other free diol **66b**, and charaterization of both was then possible (Scheme II.1.7.5.2).



Scheme II.1.7.5.2

While <sup>1</sup>H and <sup>13</sup>C NMR data is significantly different for both products, it offers no discernible information on the stereochemistry of either compound. To this end, it was desirable to obtain X-ray crystallographic data on both structures, and this was achieved via formation and crystallization of their *p*-nitrobenzoate derivatives **68a** and **68b**.

From the ORTEP projections of **68a** and **68b** (Figure II.1.7.5.3), it is evident that substituents on the ring are oriented in *cis* fashion, suggesting an intermediate *cis* fused [4,3]-nonane system. However, it is impossible to evaluate the degree of facial selectivity observed during the attack of the radical on the  $\alpha$  vinylic carbon given the subsequent rearrangement.



Figure II.1.7.5.3

Molecular orbital calculations suggest that the intermediate *cis* fused bicyclic [4,3]-nonane system (calculated with methyl instead of butyl substitution) is 9 kcal/mol higher in energy than the corresponding *cis* fused [4,4]-decane system **70**, a factor presumably responsible for driving the observed intramolecular homolytic substitution ( $S_{Hi}$ ) reaction at boron. Expansion of the 5-membered ring can be readily accommodated from the transient exocyclic secondary alkyl radical **69** to yield a less strained 6-membered ring **70**. The resultant secondary alkyl radical is then trapped to yield the final bicycle (Scheme II.1.7.5.4).



Scheme II.1.7.5.4

#### **II.1.8** Conclusions

Like their silicon tethered counterparts, boron tethered intramolecular radical cyclizations have the potential to be a viable tool for the construction of acyclic molecules by exploiting the intrinsic regio-and stereoselective nature of intramolecular cyclization processes. Catalytic tin hydride mediated cyclization of stable alkenyl boronic esters (boronates), readily prepared via versatile hydroboration and esterification strategies, offers access to intermediate boracycles with the capacity for numerous C-B bond transformations. Facile oxidation of these intermediates with TMANO gives rise to 1,3-, 1,4-, and even 1,5- diols depending on the mode of cyclization. Substrates capable of undergoing 5-, 6-, and 7-*exo* cyclization do so in an exclusive manner, and in high yield.

An interesting intramolecular homolytic substitution (S<sub>H</sub>i) reaction at boron is observed in the cyclization of substrates substituted with a secondary or tertiary alkyl centre at the  $\beta$ -vinylic position, or those leading to an intermediate *cis* fused[4,3,0]-nonane system, a relatively high energy structure encouraging the 1,2-boron migration. X-ray crystallographic analysis of a pair of 1,4-diols unexpectedly produced by this type of 5-*exo* cyclization-S<sub>H</sub>i sequence involving a cyclohexyl haloalcohol reveals definite *cis* disposition of substituents on the cyclohexyl ring, with no diastereoselectivity apparent at the third stereocenter.

With the foundation established, future efforts will be directed at expanding the scope of boron tethered radical cyclizations. Examinations into the cyclization of stabilized  $\alpha$ -boryl radicals have already been initiated, and additional work will include investigations into other S<sub>H</sub>i reactions at boron.

Chapter III:

Experimental

# **III.1 General Experimental**

All <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a 400 / 100 MHz Varian Unity spectrometer in CDCl<sub>3</sub> (referenced at  $\delta$  7.24 and 77.00 ppm for <sup>1</sup>H and <sup>13</sup>C, respectively) or C<sub>6</sub>D<sub>6</sub> (referenced at  $\delta$  7.15 and 127.00 ppm for <sup>1</sup>H and <sup>13</sup>C, respectively). Features of peaks in the <sup>1</sup>H NMR spectra are labelled in brackets after each chemical shift in the following order: integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet), and coupling constant. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as neat films on NaCl plates. Low resolution mass spectra were recorded on a Bell and Howell 21-490 spectrometer, and high resolution spectra were recorded on an AEI MS3074 spectrometer.

Reaction solvents were distilled prior to use, under inert atmosphere unless otherwise stated. Diethyl ether (ether), THF, and benzene were distilled from sodium wire / benzophenone. Dichloromethane was distilled from CaH<sub>2</sub>. 2-Bromoethanol and 2-iodoethanol were distilled and stored over 4 Å sieves. All reagents, unless otherwise noted, were purchased from Aldrich Chemical Company, Fisher Scientific Limited or BDH.

Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Whatman Company) was performed with distilled hexanes and distilled ethyl acetate. Analytical thin-layer chromatography (TLC), was performed on pre-coated silica gel plates, (Alugram SIL G/UV<sub>254</sub> purchased from Rose Scientific Limited), visualized with a UV<sub>254</sub> lamp (Spectroline, Longlife Filter) and stained with 20% phosphomolybdic acid in ethanol (commercially available), ceric molybdate (17.3 g MoO<sub>3</sub>, 14.4 mL concentrated NH<sub>4</sub>OH in 48 mL H<sub>2</sub>O, slowly added to 7.6 g of (NH<sub>4</sub>)<sub>2</sub>Ce(SO<sub>4</sub>)<sub>4</sub>·2H<sub>2</sub>O, in 100 mL of 50% H<sub>2</sub>SO<sub>4</sub>, then diluted to 500 mL with H<sub>2</sub>O) or iodine. Solvent systems associated with  $R_f$  values and chromatography are reported as volumetric ratios.

# **III.2 General Synthetic Procedures**

#### Cyclization of Di(Haloalkyl) Alkenyl Boronates 47a-n, 57a-b, 58

Sodium cyanoborohydride (942 mg, 15.0 mmol), initiator (DAB) (552 mg, 2.40 mmol), and tributyl stannane (16  $\mu$ L, 0.06 mmol) were added to a 0.1 M solution of the di(haloalkyl) alkenyl boronate (6.00 mmol) in THF at room temperature. The reaction mixture was stirred vigorously and heated to 55 °C for 48 h, during the course of which a fine white precipitate formed. The mixture was then cooled to room temperature and the solvent removed under reduced pressure. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and filtered to remove the white precipitate, followed by concentration of the filtrate *in vacuo*. The residual oil was taken on without further purification.

# Cyclization From Di(Isopropyl) Alkenyl Boronates Using 1:1 Ratio of Bromo-Alcohol to Boronic Ester 59a-b

To a 0.1 M solution of the di(isopropyl) alkenyl boronate (6.00 mmol) in THF at room temperature was added the bromo-alcohol (6.00 mmol). The resulting solution was stirred for 3 h prior to the addition of sodium cyanoborohydride (942 mg, 15.0 mmol), initiator (DAB) (552 mg, 2.40 mmol), and tributyl stannane (16  $\mu$ L, 0.06 mmol). The reaction mixture was then stirred vigorously and then heated to 55 °C for 48 h, during the course of which a fine white precipitate formed. The mixture was then cooled to room temperature and the solvent removed under reduced pressure. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and filtered to remove the white precipitate, followed by concentration of the filtrate *in vacuo*. The residual oil was taken on without further purification.

#### **Oxidation of Cyclization Products and Liberation of Diols**

To a 0.05 M solution of the cyclized material (6.00 mmol) in benzene was added trimethylamine-*N*-oxide dihydrate (TMANO; 3.33 g, 30.0 mmol). The clear reaction mixture was then stirred vigorously, and heated to reflux for 24 h, after which H<sub>2</sub>O (20 mL) was added. The resulting bi-phasic system was stirred an additional 24 h at 85°C. After cooling to room temperature, the aqueous and organic layers were separated, and the aqueous layer extracted with  $CH_2Cl_2$  (5 x 15 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, EtOAc/hexanes) afforded the desired diol.

#### Preparation of Di(Haloethyl) or Di(Halopropyl) Alkenyl Boronates 47a-n

To a 0.2 M solution of alkenyl boronic acid (18.0 mmol) in ether (or THF, for less soluble aryl alkenyl boronic acids) were added the halo-alcohol (45.0 mmol) and 4 Å molecular sieves (20 g). The resulting mixture was protected from light, and stirred for 1 day prior to vacuum filtration through a layer of celite. The solvent was then removed *in vacuo*, and the excess halo-alcohol removed in 8 h under high vacuum (1 mm Hg) to yield the desired boronate. The material was stored at 5 °C under nitrogen.

# Preparation of Di(Bromocyclohexyl), Di(Bromobutyl), and Di-(Bromopentyl) Alkenyl Boronates 57a-b, 58

To a 1.0 M solution of alkyne (28.0 mmol) in  $CH_2Cl_2$  was added dibromoborane-methyl sulfide complex (1.0 M solution in  $CH_2Cl_2$ , 28.8 mmol), dropwise at 0 °C. The resulting solution was then allowed to warm gradually to room temperature. Subsequently, an excess of THF was added dropwise at 0 °C, and the solution then warmed gradually to room temperature before being refluxed for 3 h. Full decolorization of the solution was observed during heating. Solvents were then removed *in vacuo* to yield the desired boronate. The material was stored at 5 °C under nitrogen.

#### Preparation of Di(Isopropyl) Alkenyl Boronates 59a-b

A solution of alkenyl boronic acid (35.0 mmol) in isopropanol (120 mL) and toluene (100 mL) was heated to reflux with a Dean-Stark apparatus for 1 week. The solvents were then removed *in vacuo*, and the residual oil distilled under reduced pressure to afford the desired boronate.

#### Preparation of Alkyl Alkenyl Boronic Acids 46a-e (J. Org. Chem. 1980, 45, 389-395)

To a 1.0 M solution of alkyne (28.0 mmol) in  $CH_2Cl_2$  was added dibromoborane-methyl sulfide complex (1.0 M solution in  $CH_2Cl_2$ , 28.8 mmol), dropwise at 0 °C. The resulting solution was then allowed to warm gradually to room temperature, and stirred overnight. The solvent was then removed *in vacuo* and the residue dissolved in ether (40 mL). The solution was then cooled to 0 °C, and sodium hydroxide (3.0 M in H<sub>2</sub>O, 57.0 mmol) added dropwise. Stirring of the biphasic system for 3 h was followed by separation of the aqueous and organic layers, and extraction of the aqueous layer with ether (5 x 25 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the desired acid.

# Preparation of Aryl Alkenyl Boronic Acids 46f-h (J. Am. Chem. Soc. 1974, 96, 5249-5255)

The aryl acetylene (41.7 mmol) was added dropwise to neat catecholborane (5.00 g, 41.7 mmol) at 5 °C. The reaction mixture was then stirred vigorously at 80 °C for 3 h prior to cooling and the addition of  $H_2O$  (20 ml) at room temperature. The resulting mixture was reheated to 80 °C, and stirred for 1 hour. A white precipitate formed upon cooling, and was collected by filtration. Recrystallization of this solid from THF-hexanes gave the desired acid.

#### Preparation of Functionalized Alkenyl Boronic Acids 46i-j (Synthesis 1988, 103-106)

To a 0.5 M solution of borane-methyl sulfide complex (7.00 mmol) in DME at 0 °C was added cyclohexene (14.00 mmol). The solution was stirred for 15 m at 0 °C, warmed to room temperature, and stirred an additional hour at which point a thick, white precipitate of dicyclohexylborane was observed. The mixture was cooled to 0 °C, the alkyne (7.00 mmol) added, and the solution then allowed to warm to room temperature. The dicyclohexylborane reacted to yield a clear, colorless solution, which was then stirred for 1 h prior to the addition of trimethylamine-*N*-oxide dihydrate (TMANO; 1.56g, 14.00 mmol). The solution warmed briefly to relux, and was stirred for 1 h prior to filtration and removal of the DME under reduced pressure. The residue was then stirred with 10 mL of H<sub>2</sub>O for 24 h prior to extraction of the aqueous layer with ether (4 x 25 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography (silica, EtOAc/hexanes) to afford the desired acid.

# **III.3** Synthetic Preparations

(E)-Pentenylboronic Acid (46a) (J. Am. Chem. Soc. 1975, 97, 5608-5609)



Obtained in 76% yield; white crystalline solid; mp = 80 °C (lit. mp = 79-81 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.94 (1H, dt, J = 17.6, 6.6 Hz, H<sub>4</sub>), 5.51 (1H, dt, J = 17.6, 1.4 Hz, H<sub>5</sub>), 2.17 (2H, m, H<sub>3</sub>), 1.46 (2H, m, H<sub>2</sub>), 0.91 (3H, t, J = 7.4 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.59, 122.0 (br), 37.69, 21.35, 13.69.

(E)-Hexenylboronic Acid (46b) (J. Org. Chem. 1975, 40, 1083-1090)



Obtained in 94% yield; white crystalline solid; mp = 61 °C (lit. mp = 61-62 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.96 (1H, dt, J = 17.5, 6.6 Hz, H<sub>5</sub>), 5.52 (1H, dt, J = 17.6, 1.4 Hz, H<sub>6</sub>), 2.20 (2H, m, H<sub>4</sub>), 1.36 (4 H, m, H<sub>2</sub>, H<sub>3</sub>), 0.90 (3H, t, J = 7.4 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.92, 35.44, 30.46, 22.36, 13.99 (one signal absent).

(E)-3-Methyl-1-butenylboronic Acid (46c) (J. Org. Chem. 1979, 44, 3374-3382)



Obtained in 79% yield; white crystalline solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.93 (1H, dd, J = 17.8, 6.2 Hz, H<sub>4</sub>), 5.47 (1H, dd, J = 17.7, 1.4 Hz, H<sub>5</sub>), 2.38 (1H, m, H<sub>2</sub>), 1.00 (6H, 2d, J = 6.7 Hz, H<sub>1</sub>, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.73, 119.72, 22.26, 22.15 (one signal absent).

(E)-3,3-Dimethyl-1-butenylboronic Acid (46d) (J. Org. Chem. 1989, 54, 6075-6079)



Obtained in 83% yield; white crystalline solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.95 (1H, d, J = 18.0 Hz, H<sub>5</sub>), 5.45 (1H, d, J = 18 Hz, H<sub>6</sub>), 1.02 (9H, 2s, H<sub>1</sub>, H<sub>3</sub>, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.46, 35.05, 28.79, 28.755 (one signal absent).

(E)-2-Cyclohexyl-1-ethenylboronic Acid (46e) (J. Am. Chem. Soc. 1975, 40, 5249-5255)



Obtained in 96% yield; white crystalline solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.88 (1H, dd, J = 17.9, 6.2 Hz, H<sub>7</sub>), 5.46 (1H, dd, J = 17.9, 1.5 Hz, H<sub>8</sub>), 1.0-2.2 (11H, m, H<sub>5</sub>, H<sub>4</sub>, H<sub>3</sub>, H<sub>2</sub>, H<sub>1</sub>, H<sub>6</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.77, 158.15, 43.16, 31.90, 25.92 (one signal absent).

(E)-2-Phenyl-1-ethenylboronic Acid (46f) (J. Am. Chem. Soc. 1975, 40, 5249-5255)



Obtained in 76% yield; white crystalline solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (1H, d, J = 18.2 Hz, H<sub>7</sub>), 7.25-7.65 (5H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>6</sub>), 6.34 (1H, d, J = 18.1 Hz, H<sub>8</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  152.45, 129.61, 128.84, 127.71, 127.22 (one signal absent).

(E)-2-(4-Methylphenyl)-1-ethenylboronic Acid (46g) (J. Organomet. Chem. 1979, 179, C7-C8)



Obtained in 40% yield; white crystalline solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (1H, d, J = 18.2 Hz, H<sub>8</sub>), 7.10-7.60 (4H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 6.29 (1H, d, J = 18.2 Hz, H<sub>9</sub>), 2.39 (3H, s, H<sub>3</sub>); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>)  $\delta$  152.13, 139.62, 129.40, 127.52, 127.02, 21.40 (one signal absent).

(E)-2-(4-Methoxyphenyl)-1-ethenylboronic Acid (46h) (J. Organomet. Chem. 1979, 179, C7-C8)



Obtained in 66% yield; white crystalline solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (1H, d, J = 18.1 Hz, H<sub>8</sub>), 7.56 (2H, d, J = 8.8 Hz, H<sub>2</sub>, H<sub>5</sub>), 6.92 (2H, d, J = 8.6 Hz, H<sub>1</sub>, H<sub>6</sub>), 6.15 (1H, d, J = 18.1 Hz, H<sub>9</sub>), 3.84 (3H, s, H<sub>3</sub>); <sup>13</sup>C NMR (100MHz), CDCl<sub>3</sub>)  $\delta$  160.72, 151.63, 129.02, 128.47, 114.08, 55.35 (one signal absent).

(E)-3-Benzyloxy-1-propenylboronic Acid (46i)



Obtained in 26% yield; colorless crystalline solid; mp = 58 °C;  $R_f = 0.4$  (10:1 CH<sub>2</sub>Cl<sub>2</sub> / Methanol); IR  $\upsilon$  3225, 1636, 1354, 1108, 1020, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.33 (5H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>), 6.55 (1H, dt, J = 18.1, 4.6 Hz, H<sub>9</sub>), 6.71 (1H, dt, J = 18.1, 1.6 Hz, H<sub>10</sub>), 4.53 (2H, s, H<sub>7</sub>), 4.10 (2H, dd, J = 4.6, 1.9 Hz, H<sub>8</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  146.74, 137.73, 128.40, 127.78, 123.0 (br), 72.46, 71.59 (one signal absent); MS (EI) *m/e* (rel intensity) 131 (13), 105 (10), 92 (30), 91 (100), 79 (10); HRMS (EI) *m/e* calcd (M<sup>+</sup>) 431.2023, found 431.2009.

#### (E)-3-t-Butyldimethylsilyloxy-1-propenylboronic Acid (46j)



Obtained in 15% yield as the trimeric anhydride; colorless oil;  $R_f = 0.8$  (10:1 CH<sub>2</sub>Cl<sub>2</sub> / Methanol); IR; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.99 (1H, dt, J = 17.6, 3.5 Hz, H<sub>3</sub>), 5.82 (1H, dt, J = 17.7, 2.0 Hz, H<sub>4</sub>), 4.30 (2H, s, H<sub>2</sub>), 0.91 (9H, s, t-butyl of TBDMS), 0.07 (6H, s, methyl of TBDMS); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.34, 64.61, 25.93, 18.43, -5.35; MS (EI) *m/e* (rel intensity) 537 (74), 497 (26), 381 (69), 339 (100), 299 (56), 175 (49), 133 (28); HRMS (EI) *m/e* calcd 594.3742, found 594.3761.

#### Di(2-bromoethyl)-(E)-1-pentenyl Boronate (47a)



Obtained in 97% yield; pale yellow oil; IR (neat)  $\upsilon$  3440, 2960, 1632, 1464, 1327, 1114, 1072, 996, 943, 795 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.65 (1H, dt, J = 17.2, 6.6 Hz, H<sub>4</sub>), 5.47 (1H, dt, J = 17.6, 1.5 Hz, H<sub>5</sub>), 4.18 (4H, t, J = 6.2 Hz, H<sub>1</sub>'), 3.47 (4H, t, J = 6.3 Hz, H<sub>2</sub>'), 2.13 (2H, m, H<sub>3</sub>), 1.44 (2H, m, H<sub>2</sub>), 0.90 (3H, t, J = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.33, 63.65, 37.97, 32.24, 21.56, 13.75.

Di(2-iodoethyl)-(E)-1-pentenyl Boronate (47b)



Obtained in 57% yield; yellow oil; IR (neat)  $\upsilon$  3456, 2957, 1631, 1463, 1311, 993, 795 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.64 (1H, dt, J = 17.5, 6.6 Hz, H<sub>4</sub>), 5.44 (1H, dt, J = 17.6, 1.4 Hz, H<sub>5</sub>), 4.10 (4H, t, J = 6.6 Hz, H<sub>1</sub>'), 3.26 (4H, t, J = 6.6 Hz, H<sub>2</sub>'), 2.12 (2H, m, H<sub>3</sub>), 1.43 (2H, m, H<sub>2</sub>), 0.89 (3H, t, J = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHZ, CDCl<sub>3</sub>)  $\delta$  154.38, 64.32, 37.95, 21.56, 13.75, 5.52; MS (EI) *m/e* (rel intensity) 353 (15), 251 (19), 239 (28), 199 (14), 155 (100); HRMS (EI) *m/e* calcd (M<sup>+</sup>) 421.9411, found 421.9431.

#### Di(3-bromopropyl)-(E)-1-pentenyl Boronate (47c)



Obtained in 83% yield; yellow oil; IR (neat) v 3432, 2900, 1632, 1478, 1334, 995, 793 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.58 (1H, dt, J = 17.5, 5.7 Hz, H<sub>4</sub>), 5.51 (1H, dd, J = 17.4, 1.3 Hz, H<sub>5</sub>), 3.99 (4H, td, J = 5.9, 1.1 Hz, H<sub>1</sub>'), 3.49 (4H, dt, J = 6.6, 1.3 Hz, H<sub>3</sub>'), 2.09 (6H, m, H<sub>2</sub>', H<sub>3</sub>), 1.42 (2H, m, H<sub>2</sub>), 0.89 (3H, dt, J = 7.3, 1.1 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  153.27, 61.15, 37.95, 34.51, 30.26, 21.61, 13.76; MS (EI) *m/e* (rel intensity) 356 (12), 287 (42), 229 (67), 218 (100), 165 (45), 123 (83), 97 (86), 69 (71); HRMS (EI) *m/e* calcd 355.9981, found 355.9990.

Di-isopropyl-(E)-1-pentenyl Boronate (59a)



Obtained in 90% yield; colorless oil; IR (neat)  $\upsilon$  2971, 1633, 1376, 1122, 995, 948, 835, 729, 630 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, benzene-D<sub>6</sub>)  $\delta$  6.95 (1H, dt, J = 17.2, 6.6 Hz, H<sub>4</sub>), 5.68 (1H, dt, J = 17.2, 1.5 Hz, H<sub>5</sub>), 4.52 (2H, m, J = 5.9 Hz, H<sub>2</sub>'), 2.10 (2H, m, H<sub>3</sub>), 1.37 (2H, m, J = 7.7 Hz, H<sub>2</sub>), 1.17 (12H, d, J = 6.2 Hz, H<sub>1</sub>', H<sub>3</sub>'), 0.84 (3H, t, J = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, benzene-D<sub>6</sub>)  $\delta$  152.47, 65.25, 38.38, 24.83, 22.14, 13.92; MS (EI) *m/e* (rel intensity) 183

(31), 139 (17), 129 (46), 112 (27), 97 (100), 87 (72), 69 (37), 59 (46); HRMS (EI) *m/e* calcd (M+) 198.1791, found 198.1781.

Di(2-bromoethyl)-(E)-1-hexenyl Boronate (47d)



Obtained in 91% yield; pale yellow oil; IR (neat) v 3439, 2958, 1635, 1465, 1346, 998, 943, 772 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.65 (1H, dt, J = 17.6, 6.4 Hz, H<sub>5</sub>), 5.46 (IH, dt, J = 17.4, 1.6 Hz, H<sub>6</sub>), 4.17 (4H, t, J = 6.4 Hz, H<sub>1</sub>'), 3.46 (4H, t, J = 6.4 Hz, H<sub>2</sub>'), 2.14 (2H, m, H<sub>4</sub>), 1.34 (4H, m, H<sub>2</sub>, H<sub>3</sub>), 0.88 (3H, t, J = 7.1 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCL<sub>3</sub>)  $\delta$  154.60, 63.65, 35.57, 32.21, 30.51, 22.27, 13.88; MS (EI) *m/e* (rel intensity) 259 (77), 215 (60), 151 (60), 109 (98), 107 (100); HRMS (EI) *m/e* calcd (M<sup>+</sup>) 341.9824, found 341.9843.

Di(4-bromobutyl)-(E)-1-hexenyl Boronate (57a)



Obtained in 100% yield; pale yellow oil; IR (neat)  $\upsilon$  3232, 2956, 1633, 1409, 1342, 1250, 1059, 998, 748, 645 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.55 (1H, dt, J = 17.6, 6.6 Hz, H<sub>5</sub>), 5.47 (1H, dt, J = 17.2, 1.5 Hz, H<sub>6</sub>), 3.88 (4H, t, J = 6.2 Hz, H<sub>1</sub>'), 3.43 (4H, t, J = 7.0 Hz, H<sub>4</sub>'), 2.20-1.20 (14H, m, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>2</sub>', H<sub>3</sub>'), 0.87 (3H, t, J = 7.3 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  153.08, 62.48, 62.27, 35.54, 33.61, 30.60, 30.11, 29.95, 29.40, 22.27, 13.88.

#### Di(5-bromopentyl)-(E)-1-hexenyl Boronate (57b)



Obtained in 100% yield; pale yellow oil; IR (neat)  $\upsilon$  3303, 2940, 1632, 1343, 1239, 1053, 994, 736, 645 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.55 (1H, dt, J = 17.6, 6.6 Hz, H<sub>5</sub>, 5.48 (1H, dt, J = 17.5 Hz, 1.5 Hz, H<sub>6</sub>), 3.85 (4H, t, J = 6.3 Hz, H<sub>1</sub>'), 3.39 (4H, t, J = 7.0 Hz, H<sub>5</sub>'), 2.20-1.20 (18H, m, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>2</sub>', H<sub>3</sub>', H<sub>4</sub>'), 0.87 (3H, t, J = 5.5 Hz, H<sub>1</sub>), <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  152.73, 63.13, 62.84, 35.56, 33.69, 32.52, 32.48, 30.74, 30.66, 30.56, 24.59, 24.54, 22.30, 13.91.

# Di(2-bromoethyl)-3-methyl-(E)-1-butenyl Boronate (47e)



Obtained in 88% yield; pale yellow oil; IR (neat)  $\upsilon$  3583, 2961, 1631, 1465, 1317, 1214, 997, 941, 831, 773, 637 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.62 (1H, dd, J = 17.5, 6.4 Hz, H<sub>4</sub>), 5.41 (1H, dd, J = 17.6, 0.7 Hz, H<sub>5</sub>), 4.18 (4H, td, J = 5.7, 0.7 Hz, H<sub>1</sub>'), 3.47 (4H, td, J = 5.5, 0.8 Hz, H<sub>2</sub>'), 2.34 (1H, m, H<sub>2</sub>), 1.01 (3H, d, J = 0.8 Hz, H<sub>1</sub>), 1.00 (3H, d, J = 0.7 Hz, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  160.95, 63.79, 33.85, 32.41, 21.7.

### Di(2-bromoethyl)-3,3-dimethyl-(E)-1-butenyl Boronate (47f)



Obtained in 91% yield; pale yellow oil; IR (neat)  $\upsilon$  3472, 2960, 1623, 1476, 1316, 1215, 999, 938, 833, 773, 637 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.65 (1H, d, J = 18 Hz, H<sub>5</sub>), 5.36 (1H, d, J = 17.9 Hz, H<sub>6</sub>), 4.18 (4H, t, J = 6.4 Hz, H<sub>1</sub>'), 3.47 (4H, t, J = 6.4 Hz, H<sub>2</sub>'), 1.01 (9H, s, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.30, 63.64, 34.97, 32.22, 28.85.

Di(2-bromoethyl)-2-cyclohexyl-(E)-1-ethenyl Boronate (47g)



Obtained in 89% yield; yellow oil; IR (neat) v 3216, 2919, 1634, 1446, 1350, 1151, 994, 825 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.56 (1H, dd, J = 17.5, 6.3 Hz, H<sub>8</sub>), 5.38 (1H, dd, J = 17.8, 1.2 Hz, H<sub>7</sub>), 4.14 (4H, t, J = 6.3 Hz, H<sub>1</sub>'), 3.43 (4H, t, J = 6.4 Hz, H<sub>2</sub>'), 1.0-2.1 (11H, m, H<sub>6</sub>, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.69, 63.59, 43.39, 32.25, 32.02, 31.84, 26.09, 25.89.

Di(2-bromoethyl)-2-phenyl-(E)-1-ethenyl Boronate (47h)



Obtained in 85% yield; yellow oil; IR (neat)  $\upsilon$  3418, 3058, 3023, 2964, 1617, 1576, 1494, 1338, 1213, 1074, 996, 942, 846, 749, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.40 (6H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>7</sub>), 6.22 (1H, d, J = 18.2 Hz, H<sub>8</sub>), 4.27 (4H, t, J = 6.2 Hz, H<sub>1</sub>'), 3.52 (4H, t, J = 6.3 Hz, H<sub>2</sub>'); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  149.41, 137.41, 128.96, 128.56, 127.11, 127.01, 63.78, 32.28; MS (EI) *m/e* (rel intensity) 362 (25), 259 (39), 179 (49), 131 (100), 109 (78), 77 (45); HRMS (EI) *m/e* calcd (M<sup>+</sup>) 361.9524, found 361.9511.

#### Di(2-iodoethyl)-2-phenyl-(E)-1-ethenyl Boronate (47i)



Obtained in 83% yield; colorless oil; IR (neat) v 3363, 3024, 1616, 1575, 1494, 1342, 1188, 1074, 991, 839, 745, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.30-7.40 and 7.50-7.55 (5H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>), 7.46 (1H, d, J = 18.1 Hz, H<sub>7</sub>), 6.21 (1H, d, J = 18.0 Hz, H<sub>8</sub>), 4.23 (4H, t, J = 6.6 Hz, H<sub>1</sub>'), 3.34 (4H, t, J = 6.8 Hz, H<sub>2</sub>'); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  149.51, 137.45, 128.97, 128.57, 127.14, 127.04, 64.48, 5.44; MS (EI) *m/e* (rel intensity) 456 (21), 329 (14), 225 (39), 155 (100), 131 (41), 77 (20); HRMS (EI) *m/e* calcd (M<sup>+</sup>) 455.9255, found 455.9243.

# Di(3-bromopropyl)-2-phenyl-(E)-1-ethenyl Boronate (47j)



Obtained in 85% yield; colorless oil; IR (neat)  $\upsilon$  3383, 3023, 1616, 1576, 1494, 1334, 1036, 912, 750, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25–7.55 (6H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>7</sub>), 6.27 (1H, d, J = 18.1 Hz, H<sub>8</sub>), 4.09 (4H, t, J = 5.8 Hz, H<sub>1</sub>'), 3.54 (4H, t, J = 6.6 Hz, H<sub>3</sub>'), 2.15 (4H, p, J = 6.4 Hz, H<sub>2</sub>'); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  148.61, 137.63, 128.80, 128.55, 127.06, 61.33, 34.47, 30.23; MS (EI) *m/e* (rel intensity) 390 (13), 281 (17), 205 (53), 131 (100), 117 (61), 104 (52), 58 (46); HRMS (EI) *m/e* calcd (M<sup>+</sup>) 389.9824, found 389.9824.

### Di-isopropyl-2-phenyl-(E)-1-ethenyl Boronate (59b)



Obtained in 92% yield; colorless oil; IR (neat)  $\upsilon$  3583, 2872, 1618, 1369, 944, 750, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, benzene-D<sub>6</sub>)  $\delta$  7.82 (1H, d, J = 17.6 Hz, H<sub>7</sub>), 7.00-7.45 (5H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>); 6.40 (1H, d, J = 17.9 Hz, H<sub>8</sub>); 4.58 (2H, m, J = 6.2 Hz, H<sub>2</sub>·); 1.20 (12H, d, J = 5.6 Hz, H<sub>1</sub>·, H<sub>3</sub>·); <sup>13</sup>C NMR (100 MHz, benzene-D<sub>6</sub>)  $\delta$  148.54, 138.64, 128.80, 128.69, 127.34, 65.54, 24.83; MS (EI) *m/e* (rel intensity) 232 (37), 175 (13), 146 (47), 132 (100), 105 (34), 59 (43); HRMS (EI) *m/e* calcd (M<sup>+</sup>) 232.1635, found 232.1641.

#### Di(2-bromoethyl)-2-(p-methyl-phenyl)-(E)-1-ethenyl Boronate (47k)



Obtained in 66% yield; yellow oil; IR (neat)  $\upsilon$  3396, 3020, 2965, 2879, 1619, 1569, 1512, 1411, 1340, 1219, 1073, 996, 944, 801, 668, 626 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.45–7.10 (5H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>, H<sub>8</sub>), 6.15 (1H, d, J = 18.1 Hz, H<sub>9</sub>), 4.26 (4H, t, J = 6.4 Hz, H<sub>1</sub>'), 3.52 (4H, t, J = 6.2 Hz, H<sub>2</sub>'), 2.34 (3H, s, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  149.41, 139.07, 134.72, 129.28, 127.08, 63.76, 32.27, 21.30; MS (EI) *m/e* (rel intensity) 376 (35), 259 (55), 236 (76), 177(69), 145 (98), 107 (100), 71 (52); HRMS (EI) *m/e*calcd (M<sup>+</sup>) 375.9668, found 375.9671.

Di(2-bromoethyl)-2-(p-methoxy-phenyl)-(E)-1-ethenyl Boronate (471)



Obtained in 70% yield; yellow oil; IR (neat)  $\upsilon$  3406, 2962, 1575, 1254, 1033, 816, 719, 668 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 (2H, d, J = 9.0 Hz, H<sub>2</sub>, H<sub>5</sub>), 7.39 (1H, d, J = 17.7 Hz, H<sub>8</sub>), 6.87 (2H, d, J = 8.7 Hz, H<sub>1</sub>, H<sub>6</sub>), 6.05 (1H, d, J = 18.0 Hz, H<sub>9</sub>), 4.26 (4H, t, J = 6.4 Hz, H<sub>1</sub>'), 3.82 (3H, s, H<sub>3</sub>), 3.52 (4H, t, J = 6.3 Hz, H<sub>2</sub>'); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  160.35, 149.05, 128.55, 113.96, 63.75, 62.78, 55.28, 35.96, 32.27; MS (EI) *m/e* (rel intensity) 392 (21), 277 (53), 252 (100), 161 (77), 109 (63); HRMS (EI) *m/z* calcd (M<sup>+</sup>) 389.9649, found 389.9637.

#### Di(2-bromoethyl)-3-(benzyloxy)-(E)-1-propenyl Boronate (47m)



Obtained in 68% yield; yellow oil; IR (neat)  $\upsilon$  3397, 2854, 1640, 1352, 1111, 809, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.22–7.36 (5H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>), 6.70 (1H, dt, J = 17.8, 4.4 Hz, H<sub>9</sub>), 5.82 (1H, dt, J = 17.7, 1.8 Hz, H<sub>10</sub>), 4.54 (2H, s, H<sub>7</sub>), 4.20 (4H, t, J = 6.3 Hz, H<sub>1</sub>'), 4.11 (2H, dd, J = 4.4, 1.8 Hz, H<sub>8</sub>), 3.47 (4H, t, J = 6.0 Hz, H<sub>2</sub>'); <sup>13</sup>C NMR (100 MHZ, CDCl<sub>3</sub>)  $\delta$  148.86, 138.09, 128.38, 127.67, 127.65, 72.55, 71.58, 63.72, 62.76, 32.28.

#### Di(2-bromoethyl)-3-(t-butyl-dimethylsilyloxy)-(E)-1-propenyl Boronate (47n)


Obtained in 70% yield; colorless oil; IR (neat)  $\upsilon$  3218, 2929, 1639, 1350, 1129, 836 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.71 (1H, dt, J = 17.4, 3.5 Hz, H<sub>3</sub>), 5.82 (1H, dt, J = 17.6, 1.1 Hz, H<sub>4</sub>), 4.25 (2H, 2d, J = 2.2 Hz, H<sub>2</sub>), 4.09-4.21 (4H, 2t, J = 6.2 Hz, H<sub>1</sub>·), 3.47 (4H, t, J = 6.2 Hz, H<sub>2</sub>·); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ 

1,3-Heptanediol (49a) (J. Org. Chem. 1992, 57, 5990-5994)



Obtained in 81% yield from 47a, 73% yield from 47b, 39% from 59a; colorless oil;  $R_f = 0.35$  (10:1 CH<sub>2</sub>Cl<sub>2</sub> / methanol); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.70–3.56 (3H, m, H<sub>5</sub>, H<sub>7</sub>), 3.06 (2H, broad s, 2 x -OH), 1.72-1.57 (3H, m, H<sub>4</sub>, H<sub>6</sub>), 1.50-1.28 (5H, m, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>), 0.90 (3H, t, J = 7.1 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  71.50, 62.86, 39.70, 34.42, 29.08, 18.89, 14.07.



Obtained in 85% yield; colorless oil;  $R_f = 0.70 (10:1 \text{ CH}_2\text{Cl}_2 / \text{methanol})$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.71-3.58 (3H, m, H<sub>5</sub>, H<sub>8</sub>), 2.40 (2H, broad s, 2 x -OH), 1.71-1.58 (3H, m, H<sub>4</sub>, H<sub>6</sub>), 1.50-1.25 (7H, m, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>7</sub>), 0.88 (3H, t, J = 6.8 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  71.39, 62.38, 36.98, 34.14, 28.83, 27.75, 22.53, 13.84.

**1,3-Octanediol** (49b) (J. Am. Chem. Soc. 1984, 106, 8193-8197)



Obtained in 77% yield; colorless oil;  $R_f = 0.40 (10:1 \text{ CH}_2\text{Cl}_2 / \text{methanol})$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.68–3.54 (3H, m, H<sub>6</sub>, H<sub>8</sub>), 3.38 (2H, broad s, 2 x -OH), 1.69-1.55 (3H, m, H<sub>5</sub>, H<sub>7</sub>), 1.47-1.37 (3H, m, H<sub>4</sub>, H<sub>5</sub>), 1.36-1.20 (4H, m, H<sub>2</sub>, H<sub>3</sub>), 0.87 (3H, t, J = 6.8 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  71.83, 62.72, 37.20, 34.08, 28.86, 27.89, 22.68, 14.03.

1,5-Decanediol (65)



Obtained in 68% yield; colorless oil;  $R_f = 0.20$  (7:3 EtOAc / hexanes); IR (neat)  $\upsilon$  3390, 2930, 2418, 1655, 1466, 1253, 1141, 1055, 664 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.62 (2H, t, J = 6.2 Hz, H<sub>10</sub>), 3.64-3.59 (1H, m, H<sub>6</sub>), 1.90 (2H, broad s, 2 x -OH), 1.60-1.20 (14H, m, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>7</sub>, H<sub>8</sub>, H<sub>9</sub>), 0.86 (3H, t, J = 6.9 Hz, H<sub>1</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  71.80,

62.66, 37.48, 36.94, 32.57, 31.86, 25.30, 22.60, 21.78, 13.99; MS (EI) *m/e* (rel intensity) 175 (2, MH<sup>+</sup>) 157 (7), 131 (11), 101 (40), 85 (100), 67 (33), 57 (65); HRMS (EI) *m/e* calcd (MH<sup>+</sup>) 175.1698, found 175.1705.

(1S,2R)-2-((2R)-2-(Hydroxy-hexyl)-cyclohexanol (66a)



Obtained together with **58e** in 80% yield; colorless oil;  $R_f = 0.70$  (7:3 EtOAc / hexanes); IR  $\upsilon$  3345, 2929, 2857, 1448, 976 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.90-3.80 (1H, m, H<sub>6</sub>, H<sub>8</sub>), 3.30 (2H, broad s, 2 x -OH), 1.80-1.10 (17H, m, H<sub>1-5</sub>, H<sub>7</sub>, H<sub>9-11</sub>), 0.86 (3H, t, J = 6.3 Hz, H<sub>12</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  70.67, 69.81, 39.87, 38.88, 38.17, 32.93, 28.57, 27.80, 25.28, 23.81, 21.71, 13.99; MS (CI) *m/e* (rel intensity) 201 (35), 183 (53), 165 (100), 125 (60), 98 (100), 81 (98); HRMS (CI) *m/e* calcd (MH<sup>+</sup>) 201.1855, found 201.1860.

#### 1S,2R)-2-((2S)-2-(Hydroxy-hexyl)-cyclohexanol (66b)



Obtained together with **58d** in 80% yield; colorless oil;  $R_f = 0.70$  (7:3 EtOAc / hexanes); IR  $\upsilon$  3345, 2929, 2857, 1448, 976 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.73-3.54 (1H, m, H<sub>6</sub>, H<sub>8</sub>), 3.30 (2H, broad s, 2 x -OH), 1.80-1.10 (17H, m, H<sub>1-5</sub>, H<sub>7</sub>, H<sub>9-11</sub>), 0.86 (3H, t, J = 6.3 Hz, H<sub>12</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  69.19, 68.56, 39.05, 38.29, 37.52, 32.08, 27.98, 27.00, 24.78, 22.69, 20.55, 13.99; MS (CI) *m/e* (rel intensity) 201 (35), 183 (53), 165 (100), 125 (60), 98 (100), 81 (98); HRMS (CI) *m/e* calcd (MH<sup>+</sup>) 201.1855, found 201.1859.



Obtained in 83% yield; colorless oil;  $R_f = 0.46$  (10:1 CH<sub>2</sub>Cl<sub>2</sub> / methanol); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.61 (3H, m, H<sub>5</sub>, H<sub>7</sub>), 3.32 (1H, m, -OH), 3.15 (1H, broad s, -OH), 1.61 (4H, m, H<sub>4</sub>, H<sub>6</sub>), 1.39 (1H, m, H<sub>2</sub>), 0.87 (6H, 2d, J = 3.5 Hz, H<sub>1</sub>, H<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  76.68, 62.79, 33.70, 31.01, 29.46, 18.66, 17.50.

5,5-Dimethyl-1,3-hexanediol (61b) (J. Org. Chem. 1992, 57, 1412-1421)



Obtained in 67% yield; colorless oil;  $R_f = 0.34$  (10:1 CH<sub>2</sub>Cl<sub>2</sub> / methanol); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.65 (2H, m, H<sub>8</sub>), 3.18 (1H, dd, J = 10.4, 1.3 Hz, H<sub>6</sub>), 1.68 (3H, m, H<sub>5</sub>, H<sub>7</sub>), 1.29 (1H, m, H<sub>5</sub>), 0.87 (9H, s, H<sub>1</sub>, H<sub>3</sub>, H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  80.07, 62.94, 34.96, 30.40, 28.44, 25.68.

4-Cyclohexyl-1,3-butanediol (61c)



Obtained in 77% yield; white crystalline solid; mp = 43°C;  $R_f = 0.20$  (7:3 EtOAc / hexanes); IR (neat)  $\upsilon$  3330, 2851, 1450, 1057, 976, 892, 668 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.62 (2H, dp, H<sub>10</sub>), 3.33 (1H, m, H<sub>8</sub>), 0.80-1.80 (15H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>, H<sub>7</sub>, H<sub>9</sub>); <sup>13</sup>C NMR

(100 MHz, CDCl<sub>3</sub>) δ 76.09, 62.86, 43.72, 31.08, 29.38, 29.10, 28.03, 26.48, 26.27, 26.14; MS (EI) *m/e* (rel intensity) 173 (2, MH<sup>+</sup>), 113 (12), 95 (45), 89 (52), 71 (100), 55 (32); HRMS (EI) *m/e* calcd (MH<sup>+</sup>) 173.1542, found 173.1539.

4-Phenyl-1,3-butanediol (49c) (J. Org. Chem. 1982, 47, 1378-1380)



Obtained in 63% yield from **47h**, 68% from **47i**, 43% from **59b** colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 (5H, 2m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>6</sub>), 4.07 (1H, m, H<sub>8</sub>), 3.82 (2H, m, H<sub>10</sub>), 2.77 (2H, m, H<sub>7</sub>), 2.60 (2H, broad s, 2 x -OH), 1.75 (2H, m, H<sub>9</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  138.03, 129.37, 128.56, 126.53, 72.91, 61.59, 44.30, 37.74.

5-Phenyl-pentane-1,4-diol (49f) (Bull. Chem. Soc. Jpn. 1994, 67, 1694-1700)



Obtained in 75% yield; colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 (5H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>), 3.84 (1H, m, H<sub>8</sub>), 3.66 (2H, m, H<sub>11</sub>), 2.80 (1H, dd, J = 13.5, 4.5 Hz, H<sub>7</sub>), 2.70 (1H, dd, J = 13.5, 8.4 Hz, H<sub>7</sub>), 1.71 (3H, m, H<sub>9</sub>, H<sub>10</sub>), 1.54 (1H, m, H<sub>10</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  138.41, 129.39, 128.60, 126.53, 72.66, 62.94, 44.19, 33.76, 29.25.

## 4-(4-Methylphenyl)-1,3-butanediol (49d)



Obtained in 65% yield; colorless oil;  $R_f = 0.50 (10:1 \text{ CH}_2\text{Cl}_2 / \text{methanol})$ ; IR (neat)  $\upsilon$  3356, 2922, 1515, 1438, 1054, 809 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.09 (4H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 4.03 (1H, m, H<sub>9</sub>), 3.81 (2H, m, H<sub>11</sub>), 2.73 (2H, m, H<sub>8</sub>), 2.61 (1H, broad s, -OH), 2.45 (1H, broad s, -OH), 2.31 (3H, s, H<sub>3</sub>), 1.74 (2H, m, H<sub>10</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  136.13, 134.83, 129.29, 129.26, 73.01, 61.66, 43.87, 37.76, 20.99; HRMS (EI) *m/e* calcd (M<sup>+</sup>) 180.1159, found 180.1150.

## **III.4 X-Ray Crystal Preparation**

#### Separation of mixture of 66a / 66b.

To a solution of the 66a / 66b mixture (300 mg, 1.50 mmol) in dry acetone (7.5 mL) was added dimethoxypropane (1.47 mL, 12.0 mmol) and CSA (37 mg, 0.15 mmol). After stirring at room temperature for 3 h, the mixture was quenched with triethylamine (0.4 mL) and extracted with ether (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residual oil by column chromatography (silica, EtOAc/hexanes) afforded the acetonide **67** and the diol **66a**.

The acetonide 67 (60 mg, 0.25 mmol) was stirred at room temperature with acetic acid (5 mL, 80% in H<sub>2</sub>O). After 2 h, the solution was neutralized with sodium bicarbonate (saturated aqueous solution), and extracted with ether (3 x 15 mL). The combined oragnic layers were dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residual oil by column chromatography (silica, EtOAc/hexanes) afforded diol **66b**.

#### Preparing p-Nitrobenzoic Acid Derivatives 68a and 68b.

Diol **66a** or **66b** (75 mg, 0.37 mmol) were dissolved in dichloromethane (11mL), followed by addition of DCC (309 mg, 1.50 mmol), DMAP (23 mg, 0.19 mmol), and *p*nitrobenzoic acid (313 mg, 1.87 mmol). The resulting solution was stirred at room temperature for 1 day, prior to removal of the solvent *in vacuo*. The residual solid was then purified by column chromatography (silica, EtOAc/hexanes) to afford the crystalline bis-*p*-nitrobenzoate diol derivative. Crystals suitable for X-ray analysis were prepared via slow crystallization from a mixture of EtOAc / hexanes.

## **III.5** Synthesis of Standards

#### 1,3-Octanediol (49b)

To a solution of hexanal (2.38 g, 23.8 mmol) in ether (75 mL) at -78 °C was added allylmagnesium bromide (1.0 M in ether, 25.00 mmol) dropwise over 10 min. The resulting solution was stirred for 5 h while warming to room temperature, and then quenched with aqueous ammonium chloride. Extraction of the aqueous layer with ether (5 x 20 ml), and concentration of the combined organic layers *in vacuo* afforded 4-hydroxy-nonene in 97% yield. This material was taken on without further purification.

A solution of 4-hydroxy-nonene (1.50 g, 10.6 mmol) in 3:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH (29 mL) was ozonolyzed at -78 °C. Subsequently, the solution was warmed to 0 °C, and sodium borohydride (798 mg, 21.1 mmol) added. After stirring for 5 h while warming to room temperature, the solution was quenched with aqueous ammonium chloride (20 mL), and the aqueous layer extracted with ether (4 x 20 mL). Concentration of the combined organic layers *in vacuo* and purification of the resulting oil by column chromatography (silica, EtOAc/hexanes) afforded the title compound in 5% yield. This material was found to be spectroscopically identical to that obtained via the boron tethered radical cyclization of 47d.

#### 2-Butyl-butane-1,4-diol (62) J. Med. Chem. 1985, 28, 36-40

To a slurry of lithium hydride (812 mg, 102 mmol) in pentane (20 mL) was added allyl alcohol (5.00 g, 86.1 mmol) at room temperature. The mixture was stirred until hydrogen evolution ceased, and cooled in an ice bath prior to the addition of TMEDA (10.00 g, 86.05 mmol) and *n*-butyllithium (1.6 M in hexanes, 84.0 mmol). The reaction mixture was stirred at room temperature for 2 h prior to quenching by the addition of an excess of freshly crushed dry ice. The mixture was subsequently stirred for 30 min, acidified with 1 *N* HCl, and stirred for an additional 3 h. The layers were then separated, and the aqueous layer extracted with pentane (4 x 50 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. Distillation of the residual oil at 85-90 °C (5 mm) afforded 4-butyl-dihydro-furan-2-one<sup>57</sup> in 30% yield.

To a slurry of lithium aluminum hydride (1.13 g, 29.8 mmol) in ether (60 mL) at 0 °C was added 4-butyl-dihydro-furan-2-one (3.53 g, 24.8 mmol) in ether (5 mL). The resulting solution was stirred for 15 min prior to being warmed to room temperature, and subsequently refluxed overnight. After cooling in an ice bath, the mixture was quenched with water (10 mL), and enough 2 M HCl added to dissolve the precipitate formed. The aqueous layer was then extracted with ether (5 x 50 mL), and the combined organic layers dried, filtered, and concentrated *in vacuo* to afford the title compound in 20% yield following column chromatography (silica, EtOAc/hexanes).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.90-3.80 (2H, broad s), 3.80-70 (1H, m), 3.70-3.55 (2H, m), 3.50-3.39 (1H, m), 1.75-1.50 (3H, m), 1.40-1.18 (6H, m), 0.90 (3H, t, *J* = 6.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  66.25, 61.02, 39.37, 35.81, 31.44, 29.26, 22.91, 13.99.

#### 1,4-Octanediol (49e)

To a solution of  $\gamma$ -butyrolactone (1.00 g, 11.6 mmol) in toluene (25 mL) at -78 °C was added DIBAL (1.0 M in hexanes, 12.8 mmol). The resulting solution was allowed to stir for 3 h prior to the dropwise addition of *n*-butyllithium (1.6 M in hexanes, 17.4 mmol). After warming to room temperature overnight, the reaction was quenched with water (20 mL), and the aqueous layer extracted with ether (5 x 20 mL). Concentration of the combined organic layers *in vacuo* and purification of the resulting oil by column chromatography (silica, EtOAc/hexanes) afforded the title compound in 42% yield. This material was found to be spectroscopically identical to that obtained via the boron tethered radical cyclization of **47c**.

#### 5,5-Dimethyl-1,4-hexanediol (61b)

To pivalaldehyde (2.50 g, 29.1 mmol) in ether (90 mL) at -78 °C was added allylmagnesium bromide (1.0 M in ether, 30.5 mmol) dropwise over 10 min. The resulting solution was stirred for 5 h while warming to room temperature, and then quenched with aqueous ammonium chloride. Extraction of the aqueous layer with ether (4 x 25 mL), and concentration of the combined organic layers *in vacuo* afforded 2,2-dimethyl-hex-5-en-3-ol in 76% yield. This material was taken on without further purification.

To a solution of 2,2-dimethyl-hex-5-en-3-ol (500.0 mg, 3.90 mmol) in THF (78 mL) at 0 °C was added borane-dimethylsulfide complex (1.48 g, 19.5 mmol).<sup>58</sup> The resulting solution was warmed to room temperature over 4 h, and then quenched with water (20 mL) at 0 °C. The THF was removed *in vacuo*, the aqueous layer cooled to 0 °C, and hydrogen peroxide (50% in water, 398 mg, 11.7 mmol) added. Sodium hydroxide (470 mg, 11.7 mmol in 5 mL of water) was then added, followed by stirring at room temperature for 1 h prior to neutralization with 2 M HCl, and extraction of the aqueous layer with ether (3 x 30 mL). Concentration of the combined organic extracts *in vacuo* and purification of the resulting oil by column chromatography (silica, EtOAc/hexanes) afforded the title compound in 95% yield. This material was found to be spectroscopically identical to that obtained via the boron tethered radical cyclization of **47f**.

# Appendix A: Submitted Articles

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## First Examples of Boron Tethered Radical Cyclizations and Intramolecular Homolytic Substitutions at Boron<sup>\*\*</sup>

Robert A. Batey\* and David V. Smil

Silicon tethered radical cyclizations, first reported by Nishiyama<sup>[1]</sup> and Stork,<sup>[2]</sup> are a useful strategy for the construction of C-C bonds. Numerous syntheses have incorporated these processes, accounting for approximately half of the publications in the field of silicon tethered chemistry.<sup>[3]</sup> The success of temporary silicon connections in radical chemistry, coupled with our ongoing interest in developing new reactions involving organoboron compounds,<sup>[4]</sup> led us to consider employing boron in an analogous tethering role. We now report the first examples of *boron tethered radical cyclizations*, for the synthesis of 1,3-, 1,4-, and 1,5-diols. The general strategy followed in this initial study employs the covalent C-B-O linkage of boronic esters as a tether (Scheme 1). We envisaged that the ease of synthesis of the precursor boronic acids 1 and esters 2, and the synthetic versatility of the C-B bond<sup>[5]</sup> in the cyclized products 3 would significantly expand the scope of tethered radical processes.

Scheme 1. General strategy for boron tethered radical cyclizations of alkenyl boronic esters 2.



The requisite (*E*)-alkenyl boronic acids 1 were obtained in good yields via hydroboration of the corresponding alkynes using either dibromoborane-methyl sulfide complex<sup>[6]</sup> when R<sup>1</sup> = alkyl, or catecholborane<sup>[7]</sup> for R<sup>1</sup> = aryl. Treatment of 1 with 2-bromoethanol, 2-iodoethanol, or 3-bromopropanol in THF, in the presence of 4 Å molecular sieves, at room temperature over 24 hours, readily afforded the (*E*)-alkenyl boronic esters 2. The precursors 2 were then subjected to free-radical conditions using Corey's catalytic tributylstannane method.<sup>[8]</sup> Thus, heating 2a-f (substrates with *n*-alkyl or aryl substituents at the  $\beta$  alkenyl position) at 55 °C in THF for 48 hours, in the presence of DAB<sup>[9]</sup> as a radical initiator, afforded the corresponding products 3. Immediate oxidation of 3 with trimethylamine-*N*-oxide (TMANO)<sup>[10]</sup> afforded 1,3- or 1,4-diols 4a-f (Table 1), resulting from 5- or 6-*exo*-trig radical cyclization respectively (> 95 : 5).<sup>[11]</sup>

R <sup>1</sup> 2a-k	B₂(Ơ⌒ᠭ)	$\frac{(1) cat}{(2) [0]}$	E Bu <sub>3</sub> SnH <sup>(a)</sup> (⊎)		
Substrate	R <sub>1</sub>	x	<u>n</u>	Product	Yield [%][c]
2a	Pr	Br	I	4a	81
2 Ь	Bu	Br	1	4 b	77
2 c	Ph	Br	1	4 c	63
2d	<i>p-</i> tolyl	Br	1	<b>4d</b>	65
2e	Pr	Br	2	4e	85
2f	Ph	Br	2	<b>4 f</b>	75
2 g	Pr	Ι	1	<b>4</b> a	73
2 h	Ph	Ι	1	4 c	68
2 i	<i>i</i> Pr	Br	1	5a	83
2j	<i>t</i> Bu	Br	1	5 b	67
2 k	Chx	Br	1	5 c	77

Table 1. Intramolecular cyclization of boronic esters 2 to diols 4 or 5.

011011

[a] Substrate 2 in THF (0.1 M),  $Bu_3SnH$  (0.01 equiv.),  $NaBH_3CN$  (2.5 equiv.), DAB (0.4 equiv.), 55 °C, 48 h. [b] Cyclization product in benzene (0.05 M), TMANO (5.0 equiv.), 80 °C, 24 h;  $H_2O$ , 80 °C, 24 h. [c] Isolated yields following column chromatography.

Initial attempts to perform these cyclizations in refluxing THF gave lower yields (10-40% below those for the optimized conditions) due to competing direct reduction of the C-Br bond of 2. Ionic reduction of 2 by the sodium cyanoborohydride co-reductant, in the absence of radical initiator, was demonstrated to be increasingly competitive with increasing temperature. An optimal reaction temperature of 55 °C, the operational threshold of the radical initiator, effectively lowers the formation of direct reduction products. Cyclizations can also be conducted using stoichiometric tributylstannane with high dilution to minimize direct reduction, but the catalytic tributylstannane method is more convenient due to the greater ease of product purification. Comparable results were obtained with iodides 2g and 2h as the radical precursors. The tethered nature of the radical process was unambiguously established by attempting to cyclize 2-hex-1-enyl-[1,3,2]-dioxaborolane in the presence of 2-bromoethanol, and (*E*)-hexenyl boronic acid in the presence of

1-bromo-2-(*t*-butyldimethylsiloxy)-ethane. In both cases, tethering of the two reactive species as boronate esters is precluded, and cyclization products were not observed. A preliminary attempt at using less than 2 equivalents of the bromoethanol per boronic acid was also made. However, treatment of the diisopropyl esters<sup>[12]</sup> of alkenyl boronic acids with 1 equivalent of bromoethanol, and subsequent free-radical cyclization and oxidation, resulted in 20 - 40% lower yields of the 1,3-diols.

For the substates 2i - 2k, containing *s*-alkyl or *t*-alkyl substituents at the  $\beta$  alkenyl position, we were surprised to isolate 1,4-diols **5**, rather than the expected 1,3-diols  $4!^{[13]}$  These results suggest that following 5-*exo*-trig cyclization of **6**, the boracyclic radical intermediate **7** rearranges to radical **8**, before undergoing H-atom trapping from tributylstannane (Scheme 2). Although the origin of this effect is not clear, presumably for 2i - 2k, the extra steric bulk of R<sup>1</sup> lowers the rate of H-atom trapping in the corresponding radicals **7** facilitating the intramolecular homolytic substitution (S<sub>H</sub>i)<sup>[14,15]</sup> reaction at boron.<sup>[16,17]</sup> Intermolecular S<sub>H</sub>i reactions at boron by carbon-centered radicals have been observed in the gas-phase,<sup>[18]</sup> but to our knowledge this is the first reported example of an intramolecular S<sub>H</sub>i reaction at boron.

Scheme 2. Radical cyclization and  $S_Hi$  pathway leading to 1,4-diols 5 for  $R^1 = iPr$ , *t*Bu, Chx.



Ring opening of THF with an alkenyldibromoborane provides ready access to the 4bromobutyl boronates 9, without the necessity of proceeding via boronic acid intermediates (Scheme 3).<sup>[19]</sup> Efficient cyclization of boronate 9 occurs under our standard conditions providing access to 1,5-diol 10. This is a rare example of a 7-*exo*-trig radical cyclization.<sup>[20]</sup> A preliminary attempt to elucidate the diastereoselectivity of a boron tethered cyclization was conducted using boronate 11, prepared in an analagous manner to 9 by ring-opening of cyclohexene oxide (2 equiv.) at 0 °C with (*E*)-hexenyldibromoborane. Treatment of 11 according to the standard protocol formed an inseparable 1.3:1 mixture of the diastereomeric *1,4-diols* 12, again resulting from a tandem cyclization - S<sub>H</sub>i mechanism (Scheme 3).<sup>[21]</sup>



Scheme 3. Syntheses of **10** and **12**. a) HBBr<sub>2</sub>.SMe<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, r.t.; b) THF, r.t.; c) Bu<sub>3</sub>SnH (*cat.*), NaCNBH<sub>3</sub>, DAB (*cat.*), THF, 55 °C; d) TMANO, 80 °C; H<sub>2</sub>O, 80 °C.

We have demonstrated the first examples of boron tethered free-radical reactions and shown that they are a useful alternative to the widely used silicon tethered radical processes. In some cases rearranged products are observed, resulting from an additional intramolecular  $S_{\rm Hi}$  reaction at boron. Further studies and applications of both boron-tethered free-radical cyclizations and  $S_{\rm Hi}$  reactions at boron will be reported in due course.

#### Experimental Section

Radical cyclization of 2a: To a 0.1 M solution of 2a (1.96 g, 6.00 mmol) in THF was added NaBH<sub>3</sub>CN (942 mg, 15.0 mmol), initiator (DAB) (552 mg, 2.40 mmol), and Bu<sub>3</sub>SnH (16  $\mu$ L, 0.06 mmol) at room temperature under nitrogen. The reaction mixture was stirred vigorously and heated to 55 °C for 48 h, during the course of which a fine precipitate formed. After cooling to room temperature, the solvent was removed *in vacuo*. The residue was then taken up in dichloromethane (20 mL), filtered, and the solvent removed *in vacuo*. The residual oil was then taken up in benzene (120 ml), and TMANO (3.33 g, 30.0 mmol) was added. The light yellow solution was stirred vigorously, and heated at reflux for 24 h. H<sub>2</sub>O (20 mL) was then added, and the resulting biphasic system stirred for an additional 24 h at 85 °C. After cooling to room temperature, the layers were separated, and the aqueous layer extracted with dichloromethane (5 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification of the residual oil by column chromatography on silica gel (20% ethyl acetate/hexanes as eluant) afforded diol 4a<sup>[22]</sup> (642 mg, 4.86 mmol) as a clear, colorless oil (81% yield): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  3.62 (3H, m), 3.06 (2H, broad s), 1.64 (3H, m), 1.42 (5H, m), 0.90 (3H, t, *J* = 7.1 Hz).

Keywords: boronic esters · boron tethers · cyclizations · homolytic substitution ··radicals

[\*] Prof. R. A. Batey, D. V. Smil
Department of Chemistry, Lash Miller Laboratories,
80 St. George Street, University of Toronto,
Toronto, Ontario, M5S 3H6 (Canada)
Phone/Fax: (+1)416-978-5059
E-mail: rbatey@alchemy.chem.utoronto.ca
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[12] Diisopropyl boronates were formed by refluxing the corresponding boronic acids in a 1:1 mixture of isopropanol and toluene for 1 week.

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[16] This example must proceed via a 3-membered transition state or intermediate. Similar  $S_{Hi}$  reactions at silicon or tin are unlikely to have been observed due to competing  $\beta$ -scission.

[17] Preliminary *ab initio* calculations (UHF/3-21G<sup>\*</sup>, MacSpartan Plus, Version 1.1.7) suggest that 7 ( $R^1 = Me$ ,  $R^2 = H$ ) is approximately 8 kcal mol<sup>-1</sup> higher in energy than 8 ( $R^1 = Me$ ,  $R^2 = H$ ).

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## Appendix B:

## X-Ray Crystal Structure Data

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Table 1. Crystal data and structure refinement fo	r k98143.			
Identification code	k98143			
Empirical formula	C29 H37 N2 O8 (includes 0.5 hexane)			
Formula weight	541.61			
Temperature	150.0(1) K			
Wavelength	0.71073 Å			
Crystal system	Triclinic			
Space group	P-1			
Unit cell dimensions	a = 11.5529(9)  Å	$\alpha = 72.274(4)^{\circ}.$		
	$b = 12.1338(10) \text{ \AA}$	$\beta = 76.376(6)^{\circ}$ .		
	$c = 12.3742(9) \text{ \AA}$	$\gamma = 63.574(5)^{\circ}$ .		
Volume	1469.4(2) Å <sup>3</sup>			
Z	2			
Density (calculated)	1.224 Mg/m <sup>3</sup>			
Absorption coefficient	0.089 mm <sup>-1</sup>			
F(000)	578			
Crystal size	0.42 x 0.34 x 0.28 mm <sup>3</sup>			
Theta range for data collection	4.12 to 25.00°.			
Index ranges	0 < =h < =13, -12 < =k < =1	4, -14 < =1 < =14		
Reflections collected	14015			
Independent reflections	5047 [R(int) = 0.053]			
Completeness to theta = $25.00^{\circ}$	97.6 %			
Absorption correction	Denzo-SMN			
Refinement method	Full-matrix least-squares on F	2		
Data / restraints / parameters	5047 / 0 / 354			
Goodness-of-fit on F <sup>2</sup>	1.043			
Final R indices [I>2sigma(I)]	R1 = 0.0526, $wR2 = 0.1410$			
R indices (all data)	R1 = 0.0932, $wR2 = 0.1564$			
Extinction coefficient	0.005(3)			
Largest diff. peak and hole	0.288 and -0.206 e.Å <sup>-3</sup>			

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Table 1. Crystal data and structure refinement for 1.

Identification code k98121a Empirical formula  $C_{26}H_{30}N_{2}O_{8}$ 498.52 Formula weight 150.0(1) K Temperature 0.71073 Å Wavelength Crystal system Orthorhombic Space group Pna2, a = 23.1990(4) Å alpha = 90<sup>o</sup> Unit cell dimensions b = 7.5063(2) Å beta = 90<sup>°</sup> c = 28.6312(9) Å gamma = 90<sup>o</sup> 4985.8(2) Å<sup>3</sup>, 8 Volume, Z Density (calculated) 1.328 Mg/m<sup>3</sup> Absorption coefficient 0.099 mm<sup>-1</sup> F(000) 2112 0.36 x 0.34 x 0.29 mm Crystal size θ range for data collection 4.11 to 26.36<sup>0</sup> Limiting indices  $-28 \le h \le 28$ ,  $-9 \le k \le 9$ ,  $-35 \le 1 \le 35$ Reflections collected 37193 Independent reflections 9623 (R = 0.086) Absorption correction Scalepack Full-matrix least-squares on F<sup>4</sup> Refinement method Data / restraints / parameters 9623 / 1 / 653 Goodness-of-fit on  $F^2$ 1.015 Final R indices  $[I>2\sigma(I)]$  R1 = 0.0691, wR2 = 0.1640 R indices (all data) R1 = 0.0941, wR2 = 0.1854Absolute structure parameter 0.5(11) Extinction coefficient 0.0044(14) Largest diff. peak and hole 0.710 and -0.263 eÅ<sup>-3</sup>

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