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UMI
Boron Tethered Radical Cyclizations and Potassium Organotrifluoroborates in Organic Synthesis

By

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Boron Tethered Radical Cyclizations and Potassium

Organotrifluoroborates in Organic Synthesis

Ph.D. (2001)

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Abstract

This thesis is a summary of work conducted between September 1996 and April 2001 under the guidance of Dr. Robert Batey at the University of Toronto.

Investigations into the use of temporary boron connections for facilitating radical cyclization processes produced a viable alternative to previously reported silicon tethered radical cyclization methodology. It was shown that a covalent C-B-O linkage could serve as a removable tether for the catalytic tributyltin hydride (Bu3SnH) and stoichiometric tris(trimethylsilyl)silane [(Me3Si)3SiH] mediated radical cyclization of di(haloalkyl)(E)/(Z)-alkenylboronates and diallyl/dipropargyl (α-haloalkyl)boronates respectively. Following exclusive 5-, 6-, and 7-exo-trig/dig closures, trimethylamine N-oxide or basic hydrogen peroxide oxidation of the C-B bond resulted in a variety of 1,3-, 1,4-, and 1,5-diols respectively in high yields. In certain instances of di(haloalkyl) (E)/(Z)-alkenylboronate cyclization, a novel intramolecular homolytic substitution (S_{Hi}) reaction at boron was observed. Stereoselectivities were comparable to those observed for analogous silicon (or otherwise) tethered systems in all cases involving the generation of chiral diol products.
Potassium allyl-, (E)/(Z)-crotyl-, vinyl- and aryltrifluoroborates were synthesized from the corresponding boronic acids with the intent to develop air and moisture stable organoboron allylating, crotylating, vinylating, and arylating agents. In a process promoted equally well by catalytic and stoichiometric quantities of boron trifluoride-diethyl etherate (BF$_3$-OEt$_2$), potassium allyltrifluoroborate was found to add efficiently to a variety of aldehydes at low and room temperature, producing homoallyl alcohols in high yield. Potassium (E)/(Z)-crotyltrifluoroborates reacted with similar efficiency, and with high stereoselectivity. Mechanistically, the intermediacy of a highly reactive allyl- or crotylboron difluoride species is proposed. Catalysis of these additions with stoichiometric quantities of aqueous hydrochloric acid (HCl) was also possible.

In addition, potassium vinyl- and aryltrifluoroborates showed high reactivity in Rh(acac)(CO)$_2$/dppb and Rh(acac)(CO)$_2$/dppf catalyzed additions to both enones and aldehydes at elevated temperatures, producing β-functionalized ketones and allyl/benzyl alcohols in high yields. Similarly, potassium vinyl- and aryltrifluoroborates were added to enones and aldehydes at room temperature under Rh(acac)(CO)$_2$/tBu$_3$P catalysis. However, only potassium aryltrifluoroborates were found to be reactive in additions to aldehydes at room temperature under catalysis with (activated) zinc dust, a process further facilitated by a number of Lewis acids. A distinct procedural advantage intrinsic to all the addition processes involving potassium vinyl- and aryltrifluoroborates is the option of using water as the exclusive reaction solvent.
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Abbreviations

Ac  acetyl
acac  acetylacetonate
AIBN  \(\alpha,\alpha'-\text{azobisisobutyronitrile}\)
Ar  aryl
9-BBN  9-borabicyclo[3.3.1]nonane
binap  \(2,2'-\text{bis(diphenylphosphino)}-1,1'\text{-binaphthyl}\)
Bn  benzyl
Bu  butyl
cat.  catalytic
Chx  cyclohexyl
CI  chemical ionization
coe  cyclooctene
CSA  camphorsulfonic acid
d  doublet
DAB  dimethyl 2,2'-azobisisobutyrate
DAST  \((N\text{-ethylethanaminato})\text{trifluorosulfur}\)
DCC  dicyclohexylcarbodiimide
d.e.  diastereomeric excess
diop  \(2,3'-\text{O-isopropylidene-2,3-hydroxy-1,4-bis(diphenylphosphanyl)butane}\)
DMAP  4-(dimethylamino)pyridine
dppb  1,4-bis(diphenylphosphino)butane
dppe  1,2-bis(diphenylphosphino)ethane
dppf  1,1'-bis(diphenylphosphino)ferrocene
d.r.  diastereomeric ratio
e.e.  enantiomeric excess
EI  electron impact
equiv.  equivalent
ESR  electron spin resonance
Et  ethyl
EtOAc  ethyl acetate
EWG  electron withdrawing group
GC  gas chromatography
h  hours
In  initiator
Ipc  isopinocampheyl
iPr  isopropyl
IR  infra-red
LUMO  lowest unoccupied molecular orbital
m  multiplet
M  molar
Me  methyl
MeO-MOP  2-(diphenylphosphany1)-2'-methoxy-1,1'-binaphthyl
min  minute
μL  micro-liter
mp  melting point
MS  mass spectrometry
MVK  methyl vinyl ketone
NMR  nuclear magnetic resonance
p  pentet
Ph  phenyl
pm  picometer ($10^{-12}$ m)
Pr  propyl
Py  pyridine
q  quartet
quant.  quantitative
R  unspecified alkyl group
rt  room temperature
s  singlet
SOMO  singly occupied molecular orbital
t  triplet
iBu  tert-butyl
TBDMS  tert-butyldimethylsilyl
THF  tetrahydrofuran
THP  tetrahydropyran
TLC  thin-layer chromatography
TMANO  trimethylamine N-oxide
TMEDA  tetramethylethylenediamine
TMS  trimethylsilyl
TTMSS  tris(trimethylsilyl)silane
X  unspecified halide
Section A - Boron Tethered Radical Cyclizations
Chapter AI - Introduction
AI.1 Intramolecular Radical Cyclizations

AI.1.1 Introduction

Over the last 20 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. Initially studied as basic research on radicals, intramolecular radical additions to multiple bonds soon became popular mechanistic tools as both qualitative and quantitative understanding grew, eventually capturing the interest of synthetic organic chemists. Today, the chemo-, regio-, and stereoselectivities of many classes of radical cyclizations are well established, and their synthetic utility is unquestionable. 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.

AI.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, radical processes exhibit high functional group selectivity and tolerance, eliminating the need for elaborate protection schemes often essential in synthetic sequences, and because reaction conditions are mild, radical cyclizations are suitable for the elaboration of potentially sensitive substrates. Furthermore, the presence of both the radical site and radical acceptor within the same molecule confers an appreciable rate enhancement on the overall addition process, with synthetically useful radical cyclizations having rate constants on the order of $k = 10^5$ s$^{-1}$ or greater. 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 great synthetic 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” (proximal) atom (exo cyclization). Usually, the highly regioselective nature of radical cyclization 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 and efforts are typically focused on minimizing the amount of this product, the evolution of radical cyclization methodology has seen the development of protocols capable of reversing this bias, allowing access to the disfavored ring systems.

Also of importance are the high levels of stereoselectivity observed in radical cyclizations, an effect stemming from a reduction in the degrees of freedom of the unimolecular transition state. 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 radical cyclizations is now well understood. Such effects, often subtle, are numerous and varied, and defy any simple, concise treatment. Consequently, only a brief examination of some general principles and a cross-section of examples is presented to best address some of the more interesting trends in stereoselection.

**AI.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 three broad classes (Figure AI.1.3.1). Class 1 encompasses cyclization of 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 either a prostereogenic radical or alkene center (Class 2 and Class 3) can occur with relative asymmetric induction, while if
both the radical and alkene are proterogenetic, then cyclization proceeds with relative asymmetric induction and simple diastereoselection.

![Diagram of cyclization classes]

Class 1 - Simple Diastereoselection

Class 2 - Relative Asymmetric Induction (Proterogenetic Alkene)

Class 3 - Relative Asymmetric Induction (Proterogenetic Radical and Alkene)

Figure AL1.3.1 - Major Classes of Stereoselective Radical Cyclizations

All three classes of cyclization convert an sp² center (or centers) to a stereogenic sp³ center (or centers) through a face selective addition. In the majority of cases involving relative asymmetric induction, the existing stereocenter is located in the ring forming between the radical and the alkene. Only a few examples of substrate control are known where the existing stereocenter is outside of the forming ring.

AL1.4 Addressing Basic Stereochemical Concerns

The ubiquitous stereoselective 5-exo cyclization of substituted 5-hexenyl radicals and their analogs represents the largest body of known stereoselective radical reactions. Consequently, an understanding of the underlying factors that determine the observed
stereoselection in such systems is essential for application of these processes within a synthetic strategy.

Cyclization of 5-hexenyl radicals to give the thermodynamically disfavored exo product is both exothermic and irreversible. Because these processes have early transition states, the interpretation of regio- and stereoselectivity 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 adaptable Beckwith-Houk transition state model, which serves as the basis for unambiguously predicting and rationalizing the stereoselectivity of 5-exo hexenyl radical cyclizations (Figure Al.1.4.1).

![Figure Al.1.4.1 - Beckwith-Houk Transition State Model](image)

The preference of the radical to approach the alkene in a tetrahedral-like manner, thereby optimizing the overlap of the radical SOMO and alkene LUMO, is best accommodated through the folding of the 5-hexenyl radical into any of the four pictured conformations, allowing one to predict the stereochemistry in the cyclization of C-2-, C-3-, or C-4-substituted radicals. For monosubstituted 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 principal transition state structures. In several such cases, there is excellent evidence for the importance of boat transition structures.

The corresponding 6-endo transition state is higher in energy because of the poorer overlap of the radical SOMO and alkene LUMO orbitals, and the higher degree of ring strain. Consequently, this mode of cyclization occurs to a lesser extent, resulting in minor, although at times not unsubstantial, amounts of 6-endo cyclization derived products. Although 5-hexenyl radicals have an intrinsic preference for exo ring closure, the regioselectivity can be altered or even reversed by the character of the radical (alkyl, vinyl, aryl), the substituents on the radical, or the nature of the radical acceptor (e.g. double or triple bond).

AI.1.5 Radical and Acceptor Tethering

Intramolecular radical cyclizations by definition require the connection of the radical to the acceptor, and a variety of tethers is available for this purpose. While all carbon chains dominated as connectors in early work involving radical cyclizations, the selection of linkers was quickly extended to include chains containing heteroatoms. Ethers have established themselves as the most widely exploited heteroatomic connectors, proving effective for a variety of radical cyclizations such as the interesting 5-exo-trig/3-exo-trig sequence demonstrated by Luh (Scheme AI.1.5.1).

![Scheme AI.1.5.1](image)

Amines, sulfides, amides, acetals, and esters have also been extensively investigated, and such tethers have been used successfully in the synthesis of products not requiring excision of the tethering moiety following cyclization. Products derived from
cyclizations employing these tethers almost always incorporate elements of the tethering chain into their final structure.

A substantial conceptual leap with regard to the development of radical cyclization methodology occurred when it was proposed that tethers did not have to be permanent fixtures in the product skeletons, but could instead be employed only as temporary connections. This would allow one to fully exploit the inherent advantages of a tethered process, but removal of the tethering unit from the cyclized product would give rise to simpler products, or release functionality potentially capable of undergoing further transformations. The use of esters and amides as linkers presents this possibility, but connections of that type can undergo only a limited number of transformations, and their removal can be problematic. Only with the advent of silicon tethered radical cyclization chemistry was a truly versatile, temporary connection found.

**AI.2 Silicon Tethered Radical Cyclizations**

**AI.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, and a number of groups continue to advance synthetic methodology and strategies for the synthesis of complex products based on this concept.

The utility of the “temporary silicon connection”, a term coined by Stork, 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. Cyclizations of the 5-exo and 6-endo type, 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.
**AL2.2 Pioneering Work**

In 1984, Nishiyama reported the stereoselective synthesis of 1,3-diols via a silicon tethered radical cyclization strategy. Although seminal work with simple alkyl silane systems demonstrating the increased rates and reversed regioselectivities possible in such cyclizations had been performed by Wilt one year earlier, this formal hydro-hydroxymethylation of allylic alcohols stands as the first true application not only of silicon tethered radical chemistry, but of silicon tethered chemistry in general. In a representative example, cinnamyl alcohol is first silylated with (bromomethyl)-dimethylchlorosilane to produce the starting silyl ether [1]. This material, when treated under standard radical cyclization conditions (tributyltin hydride, Bu$_3$SnH, and catalytic AIBN in refluxing benzene), affords the cyclic product [2], which is readily transformed in high yield to the corresponding 1,3-diol [3] by Tamao-Fleming oxidation (Scheme AL2.2.1).

![Scheme AL2.2.1](image)

The 5-exo-trig mode of cyclization predominates, but the 6-endo-trig 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 the cyclized material. In order to rationalize the predominant syn selectivity in the cyclization of substrates such as silyl ether [4], a chair-like transition state can be invoked (Scheme AL2.2.2).
Following Nishiyama's lead, Stork demonstrated that this hydro-hydroxymethylation protocol could be used to provide control of adjacent ring juncture stereochemistry. For example, radical cyclization of substrate [5] proceeds smoothly, yielding only a single diastereomer of the resultant 1,3-diol [6] (Scheme AL2.2.3).  

In all reactions of this nature, the newly formed cis fused 5-membered ring imposes a cup shape on the radical intermediate, and consequently, the stannane can only approach from the convex side, trapping the radical with a hydrogen atom anti to the controlling allylic hydroxyl.
AL2.3 5-Exo and 6-Endo Silicon Tethered Radical Cyclizations

Numerous applications of the silicon directed radical cyclization strategy relying on either 5-exo or 6-endo closures have been reported for the synthesis of natural products, the construction of steroid side chains and in sugar chemistry. Crimmins described the total synthesis of (-)-talaromycin A, which relies on a hydro-hydroxymethylation sequence to transform penultimate allylic alcohol [7] into the natural product (Scheme AL2.3.1).\textsuperscript{12}

![Scheme AL2.3.1](image)

Majetich employed the same process in the elaboration of allylic alcohol [8] during the total synthesis of (±)-14-deoxyisoamijiol, a member of the marine diterpene dolastanes with a linearly fused 5-7-6 tricyclic framework (Scheme AL2.3.2).\textsuperscript{13}

![Scheme AL2.3.2](image)

Vinyl silanes present the possibility of employing the silyl ether derivative as a radical acceptor rather than as a donor. For example, a known route to the natural product
statine utilizes a 5-exo-trig cyclization of ether [9] to furnish the bicycle [10] as a 3:2 epimeric mixture (Scheme AI.2.3.3). Protodesilylation and subsequent transformations gave the desired β-hydroxy-γ-amino acid, statine.

![Scheme AI.2.3.3](image)

A notable application of 6-endo-trig 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 [12], derived from the cyclization of silylated (E)-allylic alcohol [11] (Scheme AI.2.3.4).

![Scheme AI.2.3.4](image)

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 an important steric effect that helps to preclude 5-exo-trig cyclization. In contrast, the (Z)-allylic alcohol analogue of the precursor failed to cyclize in either fashion, and it is speculated that the 6-endo-trig cyclization is disfavored largely due to the steric bulk of the C-21 methyl group.
An elegant example put forward by Fraser-Reid involves a serial 5-exo-trig / 6-exo-trig radical cyclization onto the hexapyranose [13] to afford the bicyclic product [14] following oxidation (Scheme AI.2.3.5). This system also demonstrates the possibility of using a trialkylstannane radical chain carrier in a catalytic fashion.

Scheme AI.2.3.5

Once again, reversing the role of the silicon tether to act as a radical acceptor rather than as a donor was applied successfully to the stereocontrolled synthesis of C-glycosides, this time by Stork. Radicals generated from selenosugars like [15] were found to cyclize onto an ethynyl group tethered via an α-hydroxyl to form the corresponding α-C-glycoside [16] following desilylation (Scheme AI.2.3.6). In general, very good trans selectivity was obtained for the resultant styryl moiety.

Scheme AI.2.3.6

The scope of (bromomethyl)dimethylsilyl radical cyclizations was further expanded by Malacria and co-workers who first explored the use of propargylic ethers acting as radical traps in a manner similar to that demonstrated in Scheme AI.2.3.6. Interestingly, cyclization of substrates having the general form [17] gave only products derived from the 5-exo-dig mode of cyclization [18] (Scheme AI.2.3.7).
The presence of a highly reactive and configurationally labile intermediate vinylic radical allows for the formation of either the trans [18a] or cis substituted alkene [18b], whose configuration depends on the substitution pattern of the parent propargylic alcohol. When R = alkyl, the (E)-alkenes [18a] predominate, while substrates with R = Ph or SiMe₃ reverse this selectivity, favouring [18b].

Fascinating radical cascade reactions have also been reported using these propargylic silyl ether systems, and have yielded a great deal of insight into the competitive addition of α-silylmethyl radicals to double and triple bonds. Surprisingly, 5-exo-dig cyclization predominates, a striking result given that a 5-hexenyl radical normally exhibits a faster cyclization rate than the corresponding 5-hexynyl radical. This silicon facilitated preference is exploited in the formation of carbocyclic products such as [20] from [19] (Scheme AI.2.3.8).¹⁹
AL2.4 6-Exo and Larger Silicon Tethered Radical Cyclizations

Applications of 6-exo closures and the formation of larger rings via silicon tethered radical cyclization methodology are less frequent. 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 [21] gave exclusively the corresponding β-C-glycosides [22] in good yields following desilylation (Scheme AL2.4.1).

These processes constitute a 6-exo-dig and 7-exo-dig ring closures 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 [23] at the 2' or 3' center underwent stereocontrolled cyclization to yield 1,5-diols [24] following standard Tamao oxidation (Scheme AL2.4.2). Remarkably, no 6-exo-trig or directly reduced product was detected.
Only in the study of mixed silaketals have cyclizations forming 8- and 9-membered rings been reported. These substrates exhibit a large endo 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 within the substrates serves to reduce transannular interactions, favoring the formation of medium sized silacycles. For example, bromide [25] was found to undergo an impressive 8-endo-trig cyclization to form [26], although 7-exo-trig selectivity can be re-induced by using an electron-withdrawing group on the radical acceptor (Scheme AL2.4.3).

Application of 9-endo-trig cyclization was reported in the construction of C-disaccharides using a temporary dimethyl silaketal connection. Standard stannane reduction of [27] (or treatment of an analogous sulfone precursor with samarium(II)
diiodide] induces a clean cyclization to yield disaccharide [28] in reasonable overall yield (Scheme AI.2.4.4).22

![Scheme AI.2.4.4](image)

Ring sizes larger than that attainable through this 9-endo-trig closure have not been reported with the use of silicon tethered radical cyclization methodology.

### AI.3 Temporary Boron Connections

#### AI.3.1 Reported Uses of Temporary Boron Connections

While the use of silicon as a temporary connection for radical and Diels-Alder processes (amongst others) has been widely reported, analogous uses of temporary boron connections have remained virtually unexplored. Although no boron tethered radical process had been disclosed prior to the work described here, several boron tethered protocols were known for other classes of reactions.

In 1991, Narasaka demonstrated the use of phenylboronic acid as a template for Diels-Alder reactions, employing a temporary O-B-O connection to bring together the diene, anthrone, and the dienophile, 4-hydroxy-2-butoate (Scheme AI.3.1.1).23a The analogous tethering of α-hydroxy-o-quinodimethanes to 4-hydroxy-2-butoate, followed by Diels-Alder addition, was reported soon after.23b In both instances, the reactions proceed in an intramolecular manner via the mixed boronates consisting of the diene and dienophile components, and the corresponding cycloadducts were formed with
high regio- and stereoselectivity. In the absence of phenylboronic acid, no addition products were observed under otherwise identical reaction conditions.

![Reaction Scheme](image)

**Scheme AI.3.1.1**

A similar strategy was later used by Nicolaou in an effort directed towards the construction of the Taxol® ABC ring system, clearly establishing the utility of this approach within the context of total synthesis.24

Soon after, intramolecular C-H insertion reactions of boroxy Fischer carbene complexes [29] were reported by Barluenga for the regio- and diastereoselective modification of terpenes (Scheme AI.3.1.2).25
A number of similar in situ generated dialkylboroxy and diaminoboroxy Fischer carbene complexes were later used for the preparation of 1,3-diols and 1,2-amino alcohol derivatives via an analogous C-H insertion strategy.\textsuperscript{25b}

While use of the C-Si-O linkage for Diels-Alder processes has been widely exploited,\textsuperscript{7} analogous use of the C-B-O temporary connection remained unexplored until Batey's initial work involving alkenylboronate [30] tethered intramolecular Diels-Alder reactions for the construction of substituted cyclohexenols [31] (Scheme AL3.1.3).\textsuperscript{26a}

The concept was subsequently extended to the Diels-Alder addition of dienylboron compounds with unactivated dienophiles. In an efficient boron tethered process, 1,3-dienylboronates [32] underwent intramolecular Diels-Alder reaction with various allyl and homoallyl alcohols under thermal conditions to provide substituted cyclohexenols [33] following oxidative removal of the boron (Scheme AL3.1.4).\textsuperscript{26b}
More recently, use of a C-B-N linkage had been reported for the construction of aromatic 5- and 6-membered B-N heterocycles via ring closing metathesis (Scheme AL.3.1.5). Although the boron connector ultimately gets incorporated into the product, the process does represent the ingenious use of a boron tethering strategy.

Ring closing metathesis of the appropriate vinyl aminoborane [34] and allyl aminoborane [37] first gives the azaboracycloalkenes [35], which are subsequently converted to the 1,2-azaborolide [36] and 1,2-azaborine [38].

Aside from these isolated examples, boron tethered methodology has found no wide synthetic applicability. While the existence of diverse silicon tethered methodology has undoubtedly prevented the development of boron tethered reactions, the utility of boron as a connecting element has certainly not been exhausted.
AI.3.2 Use of Temporary Boron Connections for Radical Reactions

Although silicon has found tremendous success as a tethering medium for radical cyclizations, it remained the only element demonstrated to be capable of forming a truly versatile, easily removable, temporary connection between the reactive sites in such processes. Given the effectiveness and versatility of silicon tethered radical cyclizations, finding an alternate linker capable of further extending the scope of temporarily tethered radical cyclization methodology stood as an attractive goal.

Boron was considered as a suitable alternative to silicon in temporarily tethered radical cyclization processes because of several benefits commonly associated with the use of organoboron compounds. Firstly, a wide range of protocols has been reported for the preparation of organoboron compounds, so a great deal of flexibility exists for the synthesis of boron tethered cyclization precursors. Secondly, organoboron compounds tend to exhibit greater stability in the presence of air and moisture than their organosilicon counterparts, making them much easier to store and handle. Perhaps most importantly, however, the greater synthetic flexibility of the C-B bond, when compared to that of the C-Si bond, opens up the possibility for a wider variety of post-cyclization transformations designed to remove the temporary tether (Figure AI.3.2.1).

![Diagram of Synthetic Flexibility of the C-B Bond](Figure AI.3.2.1 - Synthetic Flexibility of the C-B Bond)
While boron and silicon are chemically related metalloids, some fundamental differences do exist between the atoms. Boron's sp$^2$ based planar triangular geometry (C-B-O = 120°) and shorter M-C [B(sp$^2$)-C(sp$^2$) = 153-161 pm] and M-O [B(sp$^3$)-O = 137-139 pm] bonds differ appreciably from silicon's sp$^3$ supported tetrahedral geometry (C-Si-O = 109.5°) and longer M-C [Si(sp$^3$)-C(sp$^3$) = 194 pm] and M-O [Si(sp$^3$)-O = 183 pm] bonds, and these differences may allow for the development of novel, synthetically useful tethered radical cyclization processes.
Chapter AII - Results and Discussion
AII.1 Cyclizations of Di(haloalkyl) Alkenylboronates

AII.1.1 Introduction

At the outset of the research program, the goal was to demonstrate the viability of boron tethered radical cyclizations by developing and optimizing a general method for such transformations. Related radical cyclization protocols already known in the literature proved to be invaluable for the development of this general method.

Carboni had recently reported both intermolecular radical additions and radical cyclizations using haloalkenylboronates [39] (Scheme AII.1.1.1).

Given Carboni's success with these substrates, related alkenylboronates were initially considered as suitable radical traps and boron scaffolds to which the radical precursor could be appended. The general strategy envisaged employs the covalent C-B-O linkage of the boronic esters as a tether, and is comprised of a four step sequence involving (1) terminal alkyne hydroboration, (2) boronic ester formation, (3) radical cyclization, and (4) C-B bond transformation (Scheme AII.1.1.2).
The overall approach relies on the relative simplicity of each constituent step. Hydroboration of a terminal alkyne [40] presents itself as the most flexible, facile method of building a suitable (E)-alkenylboronic acid [41], which can then be readily converted to the requisite (E)-alkenylboronic ester (boronate) [42] via a straightforward esterification processes involving a haloalcohol of choice. It was anticipated that conventional tributyltin hydride (Bu$_3$SnH) radical cyclization methodology could then be employed for ring closure to produce an intermediate boracycle [43], followed by trivial oxidative cleavage of the C-B bond allowing access to the expected diol products. Overall, the process can be viewed as a formal hydroxyalkylation of an (E)-enol if the C-B bond of the starting acid is treated as a "masked" alcohol.

**AII.1.2 Preparation of Cyclization Precursors**

All of the substrates to be employed in the radical cyclization process were prepared with relative ease via an efficient, high yielding, two step hydroboration-esterification pathway based largely on reliable and proven protocols reported in the literature. An attractive, and to some extent unforeseen, aspect of all the preparations was that they did not necessitate further purification of the isolated materials.
AII.1.2.1 Synthesis of \((E)\)- and \((Z)\)-Alkenylboronic Acids

All required \((E)\)-alkenylboronic acids [41] were prepared in high yield via hydroboration of the corresponding terminal alkyne [40] (Table AII.1.2.1.1). Largely for reasons of convenience, dibromoborane-dimethyl sulfide complex (HBB\(_2\)-SMe\(_2\)) was chosen for the hydroboration of alkynes [40] where \(R^1 = \text{alkyl}\). Commercially available and easy to use, this reagent reacts rapidly under mild conditions, leaving no residues to be removed from the final product following basic hydrolysis of the intermediate \((E)\)-alkenyl dibromoborane. Unfortunately, use of HBB\(_2\)-SMe\(_2\) cannot be extended to the hydroboration of alkynes [40] where \(R^1 = \text{aryl}\) because the rate of reaction is too slow with these relatively electron deficient substrates to make the reaction synthetically useful. To carry out these hydroborations, another commercially available reagent, catecholborane, was used. Although catecholborane reacts as efficiently as the HBB\(_2\)-SMe\(_2\), hydrolytic cleavage of the intermediate \((E)\)-catechol alkenylboronate leaves trace catechol residues in the isolated product necessitating recrystallization of the \((E)\)-alkenylboronic acid [41].

\[
\begin{align*}
\text{R}^1 & \xrightarrow{[40]} \text{1) HBB\(_2\)-SMe\(_2\), CH\(_2\)Cl\(_2\), 0 \degree C \text{ to rt} \\
& \quad \text{2) 3M NaOH, Et\(_2\)O, 0 \degree C \text{ to rt} } \\
& \quad \text{1) Catecholborane, 80 \degree C } \\
& \quad \text{2) H\(_2\)O, 80 \degree C } \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>((E))-Alkenylboronic Acid [41]</th>
<th>(R^1)</th>
<th>Hydroborating Reagent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (\text{Pr})</td>
<td></td>
<td>HBB(_2)-SMe(_2)</td>
<td>84</td>
</tr>
<tr>
<td>b (\text{Bu})</td>
<td></td>
<td>HBB(_2)-SMe(_2)</td>
<td>94</td>
</tr>
<tr>
<td>c (\text{iPr})</td>
<td></td>
<td>HBB(_2)-SMe(_2)</td>
<td>81</td>
</tr>
<tr>
<td>d (\text{tBu})</td>
<td></td>
<td>HBB(_2)-SMe(_2)</td>
<td>92</td>
</tr>
<tr>
<td>e (\text{Chx})</td>
<td></td>
<td>HBB(_2)-SMe(_2)</td>
<td>96</td>
</tr>
<tr>
<td>f (\text{Ph})</td>
<td></td>
<td>Catecholborane</td>
<td>76</td>
</tr>
<tr>
<td>g (p)-Tolyl</td>
<td></td>
<td>Catecholborane</td>
<td>71</td>
</tr>
</tbody>
</table>

Table AII.1.2.1.1 - \((E)\)-Alkenylboronic Acids
While these hydroboration protocols were suitable for the preparation of (E)-alkenylboronic acids [41], an alternate approach had to be used to access (Z)-alkenylboronic acid [46] analogues. (Z)-Hexenylboronic acid [46a] and (Z)-2-phenylethenylboronic acid [46b] were obtained from the corresponding (Z)-1-iodoalk-1-enes [45] according to a protocol reported by Heck (Scheme AII.1.2.2).32

\[
\begin{align*}
R^1 & \equiv \quad 1) \text{ nBuLi, THF, -78 °C} \quad R^1 \equiv \quad 1) \text{ Chx}_2\text{BH, THF, 0 °C to rt} \\
[40] & \quad 2) \text{ I}_2, \text{ THF, -78 °C to rt} \quad >90 \%
\end{align*}
\]

\[
\begin{align*}
R^1 & \equiv \quad 1) \text{ nBuLi, Et}_2\text{O, -78 °C} \\
[44] & \quad 2) \text{ B(OMe)}_3, \text{ -78 °C to rt} \\
& \quad 3) \text{ 2M HCl}
\end{align*}
\]

\[
\begin{align*}
R^1 &= \text{ Bu, 76% [46a]} \\
R^1 &= \text{ Ph, 70% [46b]}
\end{align*}
\]

Scheme AII.1.2.2

The required terminal iodoalkynes [44] are first prepared by trapping of the corresponding acetylide anions with iodine, and subsequently hydroborated with dicyclohexylborane (Chx2BH). Protodeboronation with acetic acid liberates the desired (Z)-1-iodoalk-1-ene [45], and lithium-halogen exchange followed by addition to trimethyl borate and hydrolysis finally gives the target (Z)-alkenylboronic acid [46] in reasonably high yield.

Both the (E)- [41] and (Z)-alkenylboronic acids [46] were all isolated as highly crystalline solids, although prolonged periods in a dehydrating environment such as a vacuum chamber were found to facilitate the formation of trimeric anhydride species. Present as viscous oils, the anhydrides are evident in $^1$H NMR spectra of the alkenylboronic acids as a downfield shift in the $\alpha$-vinyl proton signals. Detected amounts vary from sample to sample, and the presence of the anhydrides is not detrimental to subsequent synthetic steps.
AII.1.2.2 Synthesis of (E)- and (Z)-Alkenylboronic Esters

Esterification of the (E)-[41] and (Z)-alkenylboronic acids [46] with haloalcohols was considered to be the most efficient and flexible protocol for the introduction of the radical precursor into the target substrate. Initially, esterification with 2-bromoethanol, 2-iodoethanol, and 3-bromo-1-propanol was performed in order to generate cyclization precursors capable of providing information on the efficiency of cyclization from two different halide precursors, and to gauge the effects of tether length on the mode of addition. By treating the free (E)- [41] or (Z)-alkenylboronic acids [46] with 2.5 equivalents of the haloalcohols in THF at room temperature and in the presence of 4 Å molecular sieves, it was possible to obtain the desired (E)- [42] and (Z)-alkenylboronic esters [47] (boronates) in high yields (Table AII.1.2.2.1).

All (E)- [42] and (Z)-alkenylboronates [47] were isolated as viscous oils, and required no additional purification following filtration through a plug of celite and the removal of excess haloalcohol under reduced pressure. The cleanliness of these reactions is fortuitous given that distillation of the (E)- [42] and (Z)-alkenylboronates [47] under reduced pressure was found to result in rapid decomposition, and column chromatography on silica gel encourages substantial hydrolysis. Because of the aforementioned tendency towards heat promoted decomposition, the thermal stability of the (E)- [42] and (Z)-alkenylboronates [47] in solution was tested by refluxing [42a] 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 determined that while some minimal hydrolysis does take place if the (E)- [42] and (Z)-alkenylboronates [47] are stored for a prolonged period of time (more than 2 weeks) at room temperature, no such degradation takes place if the material is stored under refrigeration (5 °C).
Because both 4-bromo-1-butanol and 5-bromo-1-pentanol are not commercially available, an alternative method of preparing boronates with these alcohols had to be devised. To this end, a one pot hydroboration-esterification procedure involving the Lewis acid promoted ring opening of a cyclic ether by an intermediate (E)-alkenyl dibromoborane was proposed as being most efficient. In a manner analogous to the tribromoborane promoted ring opening of cyclic ethers and epoxides, it was found that (E)-1-hexenyl dibromoborane [48], generated by the hydroboration of 1-hexyne with

Table AII.1.2.2.1 - (E)/(Z)-Alkenylboronic Esters

<table>
<thead>
<tr>
<th>(E)- or (Z)-Alkenylboronate</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>n</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42a</td>
<td>Pr</td>
<td>1</td>
<td>Br</td>
<td>97</td>
</tr>
<tr>
<td>42b</td>
<td>Pr</td>
<td>1</td>
<td>I</td>
<td>87</td>
</tr>
<tr>
<td>42c</td>
<td>Pr</td>
<td>2</td>
<td>Br</td>
<td>83</td>
</tr>
<tr>
<td>42d</td>
<td>Bu</td>
<td>1</td>
<td>Br</td>
<td>91</td>
</tr>
<tr>
<td>42e</td>
<td>iPr</td>
<td>1</td>
<td>Br</td>
<td>88</td>
</tr>
<tr>
<td>42f</td>
<td>iBu</td>
<td>1</td>
<td>Br</td>
<td>98</td>
</tr>
<tr>
<td>42g</td>
<td>iBu</td>
<td>2</td>
<td>Br</td>
<td>86</td>
</tr>
<tr>
<td>42h</td>
<td>Chx</td>
<td>1</td>
<td>Br</td>
<td>89</td>
</tr>
<tr>
<td>42i</td>
<td>Ph</td>
<td>1</td>
<td>Br</td>
<td>90</td>
</tr>
<tr>
<td>42j</td>
<td>Ph</td>
<td>1</td>
<td>I</td>
<td>86</td>
</tr>
<tr>
<td>42k</td>
<td>Ph</td>
<td>2</td>
<td>Br</td>
<td>87</td>
</tr>
<tr>
<td>42l</td>
<td>p-Tolyl</td>
<td>1</td>
<td>Br</td>
<td>94</td>
</tr>
<tr>
<td>47a</td>
<td>Bu</td>
<td>1</td>
<td>Br</td>
<td>90</td>
</tr>
<tr>
<td>47b</td>
<td>Ph</td>
<td>1</td>
<td>Br</td>
<td>89</td>
</tr>
</tbody>
</table>
HBBBr$_2$-SMe$_2$, could rapidly and quantitatively open 2 equivalents of THF or THP at room temperature to produce the corresponding boronates [42m] and [42n] respectively (Scheme AII.1.2.2.2). Cyclohexene oxide was also opened under these conditions to produce boronate [42o].

![Scheme AII.1.2.2.2](image_url)

A definite limitation of these esterification protocols is that they do not allow for the inclusion of just one haloalcohol moiety into the substrate, something which may become of greater importance as the cost of the haloalcohol increases, or availability decreases. Attempts at using only 1 equivalent of the desired haloalcohol or cyclic ether for esterification resulted in a statistical mixture of mono-, di-, and unesterified material, a problem potentially resolved through the use of (E)- or (Z)-alkenyl-diisopropyl boronates. It was anticipated that reaction of the (E)- and (Z)-alkenyl-diisopropyl boronates with only 1 equivalent of a haloalcohol would result in the exchange of one isopropyl moiety for one haloalcohol unit. Unfortunately, there is no reliable method available to evaluate accurately if this actually occurs in solution. However, a couple of (E)-alkenyl-diisopropyl boronates [49] were prepared to see if they could be used for in situ tethering with 1 equivalent of a haloalcohol during the course of an attempted radical cyclization (Scheme AII.1.2.2.3).
The substrates diisopropyl (E)-1-pentenylboronate [49a] and diisopropyl 2-phenyl-(E)-ethenylboronate [49b] were generated by refluxing the corresponding (E)-alkenylboronic acids [41b] and [41f] in a 1:1 mixture of isopropyl alcohol and toluene for one week, followed by the subsequent removal of residual solvents under reduced pressure, and distillation of the residual material.

AII1.3 Radical Cyclization and Boron Tether Removal Methods

In order to carry out the desired boron tethered radical cyclizations, an initial set of conditions compatible with the (E)- [42] and (Z)-alkenylboronates [47] and suitable for efficiently promoting their intramolecular closures had to be selected. Several separate elements constitute the initial protocol, and it was anticipated that each could be independently manipulated if required in order to refine the overall approach.

AII1.3.1 Radical Chain Method and Mechanism

It was anticipated in the planning stages of this project that use of a tributyltin hydride mediated radical chain method would be suitable for effecting the desired intramolecular closures. The use of Bu$_3$SnH methods for performing radical reactions has dominated past work in the field, and the relative ease of their execution has traditionally been an attractive feature.³ Radicals can be conveniently generated from simple halide precursors such as alkyl or aryl bromides and iodides, and tributyltin hydride itself is commercially available at relatively low cost. Although the high toxicity of Bu$_3$SnH is a concern, a catalytic variant of the Bu$_3$SnH method has been reported by Corey.³⁴ Use of this catalytic version is particularly attractive not only for reducing the overall toxicity of the process, but also for potentially lowering or eliminating unwanted side reactions, and facilitating product isolation and purification by reducing organotin residues.
The catalytic cycle and radical chain process operating during a boron tethered radical cyclization involving \((E)\)-[42] and \((Z)\)-alkenylboronates [47], and conducted using the catalytic tributyltin hydride method is straightforward (Scheme AII.1.3.1.1).

![Chemical Reaction Diagram](image)

**Scheme AII.1.3.1.1**

The initiator, dimethyl 2,2'-azobisisobutyrate (DAB), which has a similar half-life profile to \(\alpha,\alpha'\)-azobisisobutyronitrile (AIBN) \((t_{1/2} = 10\) h at 66 °C)\(^{35}\) and was selected for reasons of availability, undergoes thermal homolytic cleavage in the manner shown. The two alkyl radicals generated from this cleavage subsequently abstract a hydrogen atom from tributyltin hydride to form a tributyltin radical, the chain promoter and carrier. The tributyltin radical promoted homolytic cleavage of the C-X bond in the substrate then generates the alkyl radical required for the intramolecular ring closure, and the tributyltin
halide formed in this step is recycled to tributyltin hydride by *in situ* reduction with sodium cyanoborohydride (NaCNBH₃), a mild, commercially available reducing agent. The intermediate radical obtained following cyclization is trapped by reaction with tributyltin hydride, a process which also serves to regenerate the essential tributyltin radical required to propagate the subsequent cycle.

This catalytic variant of the tributyltin hydride process dictates that a solvent be employed with a high enough dielectric constant to adequately solvate the required co-reductant, NaCNBH₃. However, the tert-butanol typically used for this purpose is best avoided in reactions involving any type of boronate given the capacity for transesterification. After considering several solvents with dielectric constants approaching that of tert-butanol (12.47), THF, with a dielectric constant of 7.58, was selected as a solvent. Like tert-butanol, THF can be heated to a relatively high temperature should the reaction call for such conditions, and NaCNBH₃, evaluated as a 0.25 M solution, was found to be entirely soluble in THF above 35 °C.

**AII.1.3.2 Removal of the Temporary Boron Connection**

In order to effectively evaluate the results of the anticipated cyclizations, it was decided that the temporary boron tether should be removed in order to access products more readily isolated and purified than the intermediate boracycles. Oxidative cleavage of the C-B bond followed by hydrolysis appeared satisfactory for this purpose given the facile protocols reported in the literature for such a transformation.

Alkaline hydrogen peroxide, the most convenient and frequently used reagent for oxidizing C-B bonds, was not considered for our purposes given the potential for generating lethal hydrogen cyanide (HCN) during the work-up step of the oxidation protocol. Work-up requires bringing the solution to neutral pH with hydrochloric acid, a measure which could result in the formation of HCN from reaction of the hydrochloric acid with sodium cyanoborohydride residues in the reaction mixture. Trimethylamine *N*-oxide (TMANO), a milder and more selective oxidizing agent known to oxidize trialkylboranes under neutral conditions, was considered as an ideal alternative. The only anticipated drawbacks to using TMANO were the longer reaction times and elevated temperatures required for the oxidative step.
AII.1.4 Initial Boron Tethered Radical Cyclization Efforts

Having chosen Corey's catalytic Bu$_3$SnH method for carrying out the boron tethered radical cyclizations and TMANO for the subsequent oxidative removal of the temporary boron connection, a base set of conditions was selected for both steps. Cyclization: 0.01 equivalents of Bu$_3$SnH, 2.5 equivalents of NaCNBH$_3$, 0.1 equivalents of DAB, and 1 equivalent of (E)- [42] or (Z)-alkenylboronic ester [47] (as a 0.1 M solution in THF) would be refluxed at 70 °C under nitrogen. Oxidation: 5 equivalents of TMANO and 1 equivalent of the boracycle (as a 0.05 M solution in benzene) would be refluxed at 80 °C, followed by hydrolysis at 80 °C in water. The conditions were rationally modeled on those reported by Corey$^{34}$ and Kabalka$^{37}$ respectively, and were designed to serve as a reasonable starting point for subsequent optimization.

The first attempted cyclizations employing these conditions were conducted on di(2-bromoethyl) (E)-1-hexenylboronate [42d] and di(2-bromoethyl) 2-phenyl-(E)-ethenyl boronate [42i], a representative alkyl and aryl substituted (E)-alkenylboronate [42] respectively (Scheme AII.1.4.1).

![Scheme AII.1.4.1](image)

These initial cyclization attempts proved to be quite encouraging, producing the anticipated 1,3-diols [50a] and [50b] through 5-exo-trig ring closure. By monitoring the disappearance of diagnostic vinylic proton signals in the $^1$H NMR spectra of solution aliquots taken during the course of the reaction, it was possible to establish that nearly full conversion of the (E)-alkenylboronates [42d] and [42i] to cyclized material was achieved after only 5 h. The degree of conversion assessed by this method, however, was not fully reliable given the complexity of the $^1$H NMR spectra. The yields, determined for
the overall two step cyclization-oxidation process, were modest following purification of the 1,3-diols [50a] and [50b] by chromatography on silica gel.

AIL1.5 Optimization of Reaction Conditions

While the initial cyclization attempts demonstrated that the envisaged ring closures were in fact possible, it was evident that the conditions employed were not ideally suited for the transformation, a fact reflected in the modest yields. With a careful review of the $^1$H NMR data obtained during the initial trials, it was possible to ascertain that the reactions had not actually gone to completion, and that direct ionic reduction of the halides (radical precursors) by the NaCNBH$_3$ co-reductant appeared to be a significant, competitive pathway. In order to gauge the impact of this ionic reduction on the overall cyclization process, a means of assessing and quantifying the detrimental effect had to be devised. For this purpose, it was proposed that the ionic reduction pathway be studied independently of the radical cyclization process.

AIL1.5.1 Establishing the Degree of Ionic Halide Reduction

It was felt at the outset that the reaction temperature had the greatest impact on the degree of ionic halide reduction observed, so this was the principle factor varied in the ionic reduction model study. All other constituents of the reaction system, aside from the initiator, DAB, and Bu$_3$SnH which were eliminated in order to shut down the radical pathway, were maintained in their original trial amounts.

The ionic reduction model system, consisting of di(2-bromoethyl) (E)-1-hexenyl boronate [42d] and 2.5 equivalents of sodium cyanoborohydride as a 0.1 M solution in THF, was heated to 40 °C, 50 °C, 60 °C, and 70 °C in four separate runs (Scheme AII1.5.1.1).
The transformation of the methylene carbons bearing the halides to methyl groups by ionic halide reduction was clearly evident in the $^1$H NMR spectra obtained from the temperature trials. The shifts of the protons on the methylene and methyl carbons are substantially different, so quantifying the degree of reduction was trivial. A reduction profile based on the $^1$H NMR data was assembled for the trials conducted between 40 °C and 70 °C (Figure AII.1.5.1.2).

![Reduction Profile](image)

**Figure AII.1.5.1.2 - Effect of Temperature on Direct Halide Reduction**

It is clear that the amount of non-reduced halide bearing moieties decreases exponentially as a function of temperature within the studied range. Not only do higher temperatures facilitate the ionic reduction pathway, but the effect is quite pronounced. Based on this data, lowering the reaction temperature could potentially lead to an increase in the degree of conversion and yield of the reactions by indirectly increasing the number of radicals capable of undergoing cyclization.
AII.1.5.2 Cyclization Trials at Lower Temperatures

The cyclizations described in Scheme AII.1.4.1 were attempted again, beginning with runs conducted at 40 °C and 50 °C. Although these temperatures maximize the number of available halide radical precursors, there is a corresponding decrease in the rate of initiation. Consequently, even after 24 h, little or no change was observed in the vinylic proton \(^1H\) NMR signals, and almost all halide radical precursors appeared intact, indicating that no reaction had taken place.

Trials conducted at 55 °C, however, proved more rewarding. After 24 h, the observed vinylic proton \(^1H\) NMR signals had decreased substantially, indicating that the reactions were in fact proceeding, albeit at a slower rate. In order to attain full conversion and ensure that the radical chain would not collapse at this lower temperature, an additional 0.3 equivalents of DAB were added, and the reactions run for a further 24 h. Subsequent \(^1H\) NMR analysis revealed quantitative disappearance of the vinylic proton signals, suggesting that the reactions had gone to completion. Oxidation of the crude reaction mixtures and purification by chromatography on silica gel once again gave the expected 1,3-diols \([50a]\) and \([50b]\), now in higher yields (Scheme AII.1.5.2.1).

![Scheme AII.1.5.2.1](image)

This increase in yield is not altogether surprising given that lowering the reaction temperature from 70 °C to 55 °C essentially cuts in half the amount of ionic halide reduction taking place. The higher yields obtained at 55 °C also bear out the initial hypothesis that ionic halide reduction was the primary contributor to yield erosion.

Several replicate runs were conducted using the lower temperature conditions in order to gauge the reproducibility of the process, and the yields of the 1,3-diols \([50a]\) and
obtained varied by no more than ± 5%. Care must be taken, however, to ensure that the reaction mixture stays at a constant 55 °C as this temperature constitutes the effective operational threshold of the initiator. Any cooling of the system threatens to collapse the radical chain, and terminate cyclization.

AIL1.5.3 Alternative Cyclization Methods

In light of the detrimental effect that NaCNBH₃ has on the efficiency of cyclization at higher temperatures, alternate radical cyclization methods were considered in order to eliminate the undesired ionic halide reduction pathway. Carrying out the cyclizations with stoichiometric Bu₃SnH (1.1 equivalents) in benzene (0.1 M) at 80 °C over 48 h resulted in lower isolated yields of the 1,3-diols [50a] and [50b] (40-50%), and purification by chromatography on silica gel was decidedly more tedious due to the greater amount of organotin residues in the crude products. Employing the catalytic tributyltin hydride method in THF at room temperature with triethyl borane[38] initiation failed to yield any product, as did room temperature cyclization in THF promoted by samarium(II) iodide.[39]

AIL1.6 Establishing the Necessity of Tethering

Before proceeding with the cyclization of all available substrates, the necessity of tethering the radical and trap together by means of a temporary boron connection was unambiguously established. The product 1,3-diols resulting from 5-exo-trig cyclization can also potentially be obtained via an intermolecular addition pathway, so to rule out this possibility, a pair of control experiments was performed. In the first, 2-(E)-hex-1- enyl-[1,3,2]-dioxaborolane [51] was prepared by esterification of (E)-hex-1-enylboronic acid [41b] with ethylene glycol, and then subjected to the optimized cyclization conditions in the presence of 2 equivalents of 2-bromoethanol, while the second involved attempted addition of 2 equivalents of 1-bromo-2-(tert-butyldimethylsiloxy)ethane to (E)-hex-1-enylboronic acid [41b] under the same conditions (Scheme AII.1.6.1).
In both cases, tethering of the reacting partners is precluded, and as anticipated, no addition products were observed. The vinylic proton $^1$H NMR signals were unchanged, and column chromatography on silica gel of the oxidized reaction mixtures failed to yield any diol products.

AII.1.7 Overview and Analysis of Cyclizations

Having established a simple and relatively efficient protocol for carrying out some rudimentary boron tethered radical cyclizations, a systematic study of cyclization modes was initiated using the variety of available $(E)$-[42] and $(Z)$-alkenylboronates [47] (see AII.1.2.2). Each substrate was subjected to the identical, optimized catalytic Bu$_3$SnH cyclization conditions, and the temporary boron tether was removed oxidatively using TMANO according to the initially outlined protocol. Cyclization: 0.01 equivalents of Bu$_3$SnH, 2.5 equivalents of NaCNBH$_3$, 0.1 equivalents of DAB, and 1 equivalent of $(E)$-[42] or $(Z)$-alkenylboronic ester [47] (as a 0.1 M solution in THF) are refluxed at 55 °C under nitrogen for 48 h. Oxidation: 5 equivalents of TMANO and 1 equivalent of the boracycle (as a 0.05 M solution in benzene) are refluxed at 80 °C for 24 h, followed by hydrolysis at 80 °C in water for 12 h.

AII.1.7.1 5-Exo-Trig Cyclizations

As anticipated from the initial cyclization trials involving di(2-bromoethyl) $(E)$-1-hexenylboronate [42d] and di(2-bromoethyl) 2-phenyl-$(E)$-ethenylboronate [42i], all other substrates with $n$-alkyl or aryl substituents at the $\beta$-alkenyl position cyclized
efficiently in 5-exo-trig fashion under the optimized conditions to give 1,3-diols [50] in high isolated yields following oxidation of the C-B bond (Table AII.1.7.1.1).

\[
\begin{align*}
R^1 & \quad X \quad 1,3\text{-Diol} \quad \text{Yield (\%)} \\
[42] \text{ or } [47] & \\
[42a] & \text{Pr} \quad \text{Br} \quad \text{c} \quad 81 \\
[42b] & \text{Pr} \quad \text{I} \quad \text{c} \quad 73 \\
[42d] & \text{Bu} \quad \text{Br} \quad \text{a} \quad 77 \\
[42i] & \text{Ph} \quad \text{Br} \quad \text{b} \quad 63 \\
[42j] & \text{Ph} \quad \text{I} \quad \text{b} \quad 68 \\
[42l] & \text{p-Tolyl} \quad \text{Br} \quad \text{d} \quad 65 \\
[47a] & \text{Bu} \quad \text{Br} \quad \text{a} \quad 72 \\
[47b] & \text{Ph} \quad \text{Br} \quad \text{b} \quad 60 \\
\end{align*}
\]

Table AII.1.7.1.1 - 5-Exo-Trig Cyclizations of (E)/(Z)-Alkenylboronic Esters

It is clear from the isolated yields of the 1,3-diols that comparable results are obtained when using iodide radical precursors [42b] and [42j], despite the expected higher reactivity of these substrates. Alkene geometry also has no effect on the nature of the cyclization as illustrated by the closure of (Z)-alkenylboronic esters [47a] and [47b] to give 1,3-diols [50a] and [50b], the same 1,3-diols as those obtained from cyclization of the corresponding (E)-alkenylboronate analogues [42d] and [42i].

In order to accurately gauge the level of regioselectivity in these cyclizations, an authentic sample of 2-butyl-1,4-butanediol, the diol attainable from 6-endo-trig cyclization of (E)-alkenylboronate [42d], was prepared by lithium aluminum hydride (LiAlH\(_4\)) reduction of 4-butyldihydrofuran-2-one.\(^{40}\) The \(^1\)H and \(^{13}\)C NMR spectra of this
pure material were then compared to those of the crude reaction mixture following cyclization and oxidation of \((E)\)-alkenylboronate [42d], at which point it became clear that no signals corresponding to the 6-endo-trig cyclization product were present. Based on this result, and taking into account the NMR limit of detection, the 5-exo-trig closure selectivity for the cyclization of \((E)\)-alkenylboronate [42d] was determined to be greater than 95:5. To confirm this result, an authentic sample of \(1,3\)-octanediol [50a], the product of observed 5-exo-trig closure, was also prepared via ozonolysis of \(4\)-hydroxy-non-1-ene.\(^{41}\) Subsequent GC analysis of this pure material and the crude reaction mixture showed the two to have major peaks with identical retention times. The 6-endo-trig cyclization product, 2-butyl-1,4-butanediol was not apparent in the trace of the crude reaction mixture.

A preliminary attempt at using less than 2 equivalents of haloalcohol per \((E)\)-\([41]\) or \((Z)\)-alkenylboronic acid \([46]\) was also conducted through the intermediacy of diisopropyl \((E)\)-alkenylboronates \([49]\). Unfortunately, the treatment of diisopropyl \((E)\)-1-pentenylboronate \([49a]\) and diisopropyl 2-phenyl-\((E)\)-ethenylboronate \([49b]\) with 1 equivalent of 2-bromoethanol, followed by radical cyclization and oxidation under the optimized conditions, resulted in only a 39% yield of \(1,3\)-diol \([50a]\), and a 43% yield of \(1,3\)-diol \([50b]\).

AII.1.7.2 5-Exo-Trig Cyclization and \(S_{N}I\) Sequences

Substrates with sec- or tert-alkyl substituents at the \(\beta\)-alkenyl position were also expected to produce 1,3-diols upon cyclization and subsequent C-B bond oxidation, but surprisingly, only 1,4-diols \([52]\) were isolated in all cases (Table AII.1.7.2.1).
These results suggest that following 5-exo-trig cyclization of the (E)-alkenylboronates [42], the boracyclic radical intermediate [53] first rearranges to another boracyclic radical intermediate [54] prior to trapping with an H atom from the Bu3SnH (Scheme AII.1.7.2.2).

Table AII.1.7.2.1 - 5-Exo-Trig Cyclization and S\textsubscript{Hi} Sequences

<table>
<thead>
<tr>
<th>(E)-Alkenylboronate [42]</th>
<th>R\textsuperscript{1}</th>
<th>X</th>
<th>1,4-Diol [52]</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>e</td>
<td>iPr</td>
<td>Br</td>
<td>a</td>
<td>83</td>
</tr>
<tr>
<td>f</td>
<td>iBu</td>
<td>Br</td>
<td>b</td>
<td>67</td>
</tr>
<tr>
<td>h</td>
<td>Chx</td>
<td>Br</td>
<td>c</td>
<td>77</td>
</tr>
</tbody>
</table>

The high selectivity for the formation of either a 1,3- [50] or 1,4-diol [52] depending on the nature of the β-alkenyl position substituent is particularly noteworthy. Although the origin of the effect is not clear, presumably the extra steric bulk when R\textsuperscript{1} is a sec- or tert-alkyl substituent serves to lower the rate of H atom trapping by the corresponding intermediate radical [53], and facilitates an intramolecular homolytic substitution (S\textsubscript{Hi})\textsuperscript{42} at boron.\textsuperscript{43} While similar S\textsubscript{Hi} reactions were recently proposed for β-silyl radicals,\textsuperscript{44} and intermolecular S\textsubscript{Hi} reactions of carbon centered radicals at boron centers have been observed in the gas phase,\textsuperscript{45} these processes constitute the first
examples of solution phase intramolecular $S_{11}$ reactions at boron, and the first to involve a boronic ester.

Thermodynamically, the driving force for the $S_{11}$ reaction appears to be the release of ring strain associated with the transition from 5-membered boracyclic radical intermediate [53] to 6-membered boracyclic radical intermediate [54]. Molecular orbital calculations on a model system with $R^1 = \text{Me}$, and $R^2 = \text{H}$ showed radical intermediate [53] to be approximately 8 kcal mol$^{-1}$ higher in energy than radical intermediate [54].

An alternative mechanism for the observed transformations involving $\beta$-scission to give an (RO)$_2$B$^\cdot$ radical was also eliminated based on calculated thermodynamic data. The energy barriers for the degenerate $S_{11}$ rearrangement and the $\beta$-scission reaction of a model (HO)$_2$BCH$_2$CH$_2^\cdot$ radical were found to be 11.7 and 47.6 kcal mol$^{-1}$ respectively (Figure AII.7.2.3). The highly endothermic nature of the $\beta$-scission pathway was subsequently confirmed by Carboni, who calculated the energy barrier for the process to be 30.8 kcal mol$^{-1}$ in an analogous glycol boronate system.

\[
\begin{align*}
S_{11} \text{ Transition State} & \quad \beta-\text{Scission Transition State} \\
\begin{array}{c}
\text{HO}_2\text{OH} \\
\begin{array}{c} \text{B} \end{array}
\end{array} & \quad \begin{array}{c}
\text{HO}_2\text{OH} \\
\begin{array}{c} \text{B} \end{array}
\end{array} \\
\begin{array}{c}
\text{B-C} = 1.734 \text{ Å}
\end{array} & \quad \begin{array}{c}
\text{B-C} = 2.440 \text{ Å}
\end{array} \\
\begin{array}{c}
\text{B-O} = 1.382 \text{ Å}
\end{array} & \quad \begin{array}{c}
\text{B-O} = 1.350 \text{ Å}
\end{array} \\
\begin{array}{c}
\text{C-C} = 1.437 \text{ Å}
\end{array} & \quad \begin{array}{c}
\text{C-C} = 1.370 \text{ Å}
\end{array} \\
\text{Relative Energy} = +11.4 \text{ kcal mol$^{-1}$} & \quad \text{Relative Energy} = +48.5 \text{ kcal mol$^{-1}$}
\end{align*}
\]

Figure AII.7.2.3 - Parameters for $S_{11}$ and $\beta$-Scission Transition States

Indeed, such an unprecedented $\beta$-scission is unlikely simply because the (RO)$_2$B$^\cdot$ radical formally has five electrons in the valence shell of boron. A significant bridging interaction may also exist between the boron and the $\beta$-boryl radical (as suggested in Scheme AII.7.2.2) which may provide impetus for the $S_{11}$ pathway, or assist it in some manner. Both kinetic studies and molecular orbital calculations suggest that such an effect exists in $\beta$-silyl radical rearrangements.
Interestingly, cyclization of (E)-alkenylboronate [42h] with stoichiometric Bu$_3$SnH (1.1 equivalents) in benzene at 55 °C over 48 h resulted in an inseparable mixture of the 1,4-diol [52c] and 1,3-diol [50e], the latter material originating from 5-exo-trig closure not followed by S$_{Hi}$ rearrangement (Scheme AI.7.2.4).

\[
\begin{align*}
\text{[42h]} & \quad \begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O} \\
\text{Br}
\end{array} \\
\text{1} & \quad \text{Bu$_3$SnH, DAB (cat.),} \\
& \quad \text{THF, 55 °C, 48 h} \\
\text{2} & \quad \text{TMANO, C$_6$H$_5$, 80 °C, 24 h} \\
\text{3} & \quad \text{H$_2$O, 80 °C, 12 h} \\
\text{Chx} & \quad \begin{array}{c}
\text{OH} \\
\text{OH} \\
\text{OH}
\end{array} \\
\text{[52c]} & \quad \begin{array}{c}
\text{Chx} \\
\text{OH} \\
\text{OH} \\
\text{OH}
\end{array} \\
\text{24-52\%} & \quad \frac{[\text{Bu$_3$SnH}]}{[\text{52c}]} : [\text{50e}] \\
0.10 \text{ M} & \quad 7.9 \\
0.25 \text{ M} & \quad 4.8 \\
0.50 \text{ M} & \quad 3.3 \\
0.75 \text{ M} & \quad 2.6
\end{align*}
\]

Scheme AI.7.2.4

The product ratio of 1,4-diol [52c] to 1,3-diol [50e] decreased steadily with increasing Bu$_3$SnH concentration; 7.9:1 (0.1 M), 4.8:1 (0.25 M), 3.3:1 (0.5 M), to 2.6:1 (0.75 M), as the efficiency of H atom trapping with the tributyltin hydride increases relative to the S$_{Hi}$ rearrangement. Since this increase in stoichiometric Bu$_3$SnH concentration effectively traps more unrearranged material in systems showing a tendency for the S$_{Hi}$ process, it was reasoned that a decrease in catalytic tributyltin hydride concentration might encourage an S$_{Hi}$ reaction in systems which have not shown such any propensity for rearrangement thus far.

This hypothesis was tested in the cyclization of (E)-alkenylboronate [42d] under the optimized catalytic tributyltin hydride conditions, at different Bu$_3$SnH concentrations (Scheme AI.7.2.5).
Subsequent GC analysis of the crude reaction mixtures revealed that the product ratio of 1,3-diol [50a] to 1,4-diol [52d] decreased slightly with decreasing Bu₃SnH concentration; 100:0 (0.1 M), 95:5 (0.05 M), to 91:9 (0.01 M), as the efficiency of H atom trapping with the Bu₃SnH also decreases.

Confirmation that the S_Hi rearrangement was indeed a radical process came from the reaction of (E)-alkenylboronate [42f] in the presence of a stoichiometric amount of tributyltin deuteride (Bu₃SnD) (1.1 equivalents) in benzene (0.1 M) at 55 °C over 48 h (Scheme AL.7.2.6).

The cyclization produced a separable 8.2:1 mixture of 1,4-diol [55a] and 1,3-diol [55b], the product of 5-exo-trig closure not followed by S_Hi rearrangement. The 1,4-diol [55a] was isolated showing deuterium atom incorporation at the 3-position, possible only via trapping of intermediate radical [54].
Another unexpected and somewhat different 5-exo-trig cyclization-S_{Hi} sequence was observed during the cyclization of (E)-alkenylboronate [42a], a substrate initially prepared to help elucidate the stereoselectivity of a boron tethered radical cyclization. Instead of obtaining a mixture of diastereomeric 1,3-diols, an inseparable 1.3:1 mixture of diastereomeric 1,4-diols [56a] and [56b] was isolated in high yield (Scheme AII.1.7.2.7).

![Scheme AII.1.7.2.7](image)

Unfortunately, the observed diastereomeric 1,4-diol ratio provides no information on the stereoselectivity of the initial tethered cyclization because it only reflects the product distribution originating from the subsequent S_{Hi} rearrangement. While the 1.3:1 diastereomeric ratio was determined via $^1$H and $^{13}$C NMR spectroscopy of the crude reaction mixture, it was not possible to accurately establish the stereochemistry of the individual diastereomers via this method. To do so, separation of the mixture and subsequent X-ray crystallographic analysis appeared ideal.

In an attempt to render the 1,4-diols [56a] and [56b] separable, the mixture was first treated with 2,2'-dimethoxypropane in order to yield two distinct 7-membered ketals (Scheme AII.1.7.2.8). Unexpectedly, only one of the 1,4-diols underwent ketalization, allowing for facile separation from the other free 1,4-diol by chromatography on silica gel. Subsequent cleavage of the ketal, followed by formation of the crystalline bis-p-nitrobenzoate derivatives of both 1,4-diols, [57a] and [57b], provided material suitable for X-ray crystallographic analysis.
From the resulting ORTEP projections of [57a] and [57b] (see Appendix B), it was possible to confirm the expected cis disposition of the substituents on the core cyclohexane ring of both 1,4-diols, suggesting the intermediacy of a cis fused [4.3.0]-nonane boracyclic radical intermediate immediately following 5-exo-trig cyclization. The absolute configuration of the hydroxyl bearing carbons was also unambiguously established.

Mechanistically, the radical process begins with the expected 5-exo-trig closure, followed by an intramolecular $S_{H,i}$ reaction at boron (Scheme AII.1.7.2.9).

Scheme AII.1.7.2.9
Molecular orbital calculations suggest that the cis fused [4.3.0]-nonane boracyclic radical intermediate \([58]\) is 9 kcal mol\(^{-1}\) higher in energy (when calculated with methyl instead of butyl substitution) than the corresponding cis fused [4.4.0]-decane boracyclic radical intermediate \([59]\). Presumably, this energy difference is the driving force behind the \(S_{\text{Hi}}\) rearrangement, which serves to release the ring strain associated with the cis fused [4.3.0]-nonane boracyclic radical intermediate \([58]\).

**AII.1.7.3 6-Exo-Trig Cyclizations**

Using the established catalytic \(\text{Bu}_3\text{SnH}\) conditions, it was also possible to efficiently carry out high yielding 6-exo-trig closures of (E)-alkenylboronates \([42]\) with \(n\)-alkyl, \(\text{tert-alkyl}\), and aryl substituents at the \(\beta\)-alkenyl position (Table AII.1.7.3.1).

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>(E)-Alkenylboronate ([42])</th>
<th>(R^1)</th>
<th>(X)</th>
<th>1,4-Diol ([52])</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>Pr</td>
<td>Br</td>
<td>d</td>
<td>85</td>
</tr>
<tr>
<td>g</td>
<td>(\text{tBu})</td>
<td>Br</td>
<td>e</td>
<td>81</td>
</tr>
<tr>
<td>k</td>
<td>Ph</td>
<td>Br</td>
<td>f</td>
<td>75</td>
</tr>
</tbody>
</table>

**Table AII.1.7.3.1 - 6-Exo-Trig Cyclizations of (E)-Alkenylboronic Esters**

Significantly, no 1,5-diols arising from potential 7-endo-trig cyclization were isolated, or evident in the crude reaction mixtures by \(^1\)H and \(^13\)C NMR spectroscopy. GC analyses of each mixture also showed only one major peak corresponding to the 1,4-diols \([52d]-[52f]\). Furthermore, no \(S_{\text{Hi}}\) rearrangement was observed following 6-exo-trig cyclization of \(\text{tert-alkyl}\) substituted (E)-alkenylboronate \([42g]\). Presumably, there is no driving force to expand the unstrained 6-membered boracyclic radical intermediate.
resulting from the initial closure, and H atom trapping of this species gives rise to the observed 1,4-diol [52e].

AIL1.7.4 7- And 8-Exo-Trig Cyclizations

The previously described preparation of (E)-alkenylboronates [42m] and [42n] made it possible to attempt ambitious 7-exo-trig and 8-exo-trig cyclizations respectively. Surprisingly, it was possible to effect exclusive 7-exo-trig closure of (E)-alkenylboronate [42m] under the catalytic Bu3SnH conditions, leading to the isolation of a single product, 1,5-diol [60], in high yield (Scheme AII.1.7.4.1).

![Scheme AII.1.7.4.1](image)

This extremely clean and rare process showed no 1,6-diol arising from a corresponding 8-endo-trig cyclization pathway as determined by 1H and 13C NMR spectroscopy of the crude reaction mixture. Confirmation of the high selectivity was again established via GC analysis which showed a solitary major peak.

Attempted 8-exo-trig cyclization of (E)-alkenylboronate [42n] failed to yield any 1,6-diol product. Not unexpectedly, direct H atom trapping of the alkyl radicals in this system occurs at a faster rate than the sluggish 8-exo-trig closure.

AIL1.8 Conclusion

The boron tethered radical cyclizations reported here constitute the first such known group of reactions. Like their silicon tethered counterparts, they are a viable tool for the construction of acyclic molecules via a highly regioselective cyclization strategy employing a temporary connection. The convenience and flexibility of the silicon
tethered radical cyclization processes, however, is superseded by that of the boron tethered methodology given the greater inherent stability and ease of preparation of the required organoboron substrates, and the increased synthetic flexibility of the C-B bond.
AII.2 Cyclizations of Diallyl (α-Haloalkyl)boronates

AII.2.1 Introduction

In contrast to α-silyl radical reactions, processes involving α-boryl radicals have only recently received attention from synthetic chemists like Carboni, who reported the first known cyclizations of (α-haloalkyl)boronates [61] in 1995 (Scheme AII.2.1.1).[29]

\[
\begin{align*}
\text{B(OR)}_2 + \text{Bu}_3\text{SnH, AIBN (cat.)} & \rightarrow \text{B(OR)}_2 + \text{B(OR)}_2 + \text{B(OR)}_2 \\
\text{C}_6\text{H}_6, \Delta \text{ or h} & \rightarrow \text{Me} \quad 38\% \\
\text{Me} & \quad 38\% \\
\text{Me} & \quad 11\%
\end{align*}
\]

Scheme AII.2.1.1

Shortly thereafter, Batey demonstrated the intermolecular additions of α-boryl radicals [62] to electron deficient and electron rich alkenes (α,β-unsaturated esters and ethers) (Scheme AII.2.1.2), as well as their addition to allylstannanes.[31]

\[
\begin{align*}
\text{B(OR)}_2 + \text{OBu} & \rightarrow \text{B(OR)}_2 \\
\text{Bu}_3\text{SnH, AIBN (cat.)}, & \text{C}_6\text{H}_6, \Delta \\
\text{Me} & 71\%
\end{align*}
\]

Scheme AII.2.1.2

Takai later extended this methodology, reporting further intermolecular additions to a variety of α,β-unsaturated esters, nitriles, and sulfones.[32] In contrast, attempts made by Batey to add α-boryl radicals intermolecularly to more sterically demanding cis and trans disubstituted and trisubstituted alkene traps resulted in unsatisfactory yields of the desired adducts.

In order to overcome the difficulties associated with these intermolecular additions, it was envisaged that the α-boryl radicals could be tethered to the chosen
alkene traps. The general strategy envisaged once again employs the covalent C-B-O linkage of boronic esters as a tether, and is comprised of a three step sequence involving (1) boronic ester formation via transesterification, (2) radical cyclization, and (3) C-B bond transformation (Scheme AII.2.1.3).

![Scheme AII.2.1.3](image)

Preparation of the requisite (haloalkyl)boronate [64] is readily achieved via transesterification of the corresponding diisopropyl (haloalkyl)boronate [63] with the allyl (or propargyl) alcohol of choice. Radical cyclization subsequently gives rise to intermediate boracycle [65], which is then transformed to 1,3-diol following oxidative cleavage of the C-B bond. Overall, the process can be viewed as a formal hydroxymethylation of an allylic or propargylic alcohol if the C-B bond of the starting diisopropyl (haloalkyl)boronate [63] is treated as a "masked" alcohol.

Given that this overall strategy is analogous to that employed for the majority of reported silicon tethered radical cyclizations, particular interest lies in being able to directly compare the boron tethered radical cyclization results with those obtained from the silicon tethered approach. It was anticipated that both the shorter C-B [B(sp²)-C(sp³) = 153-161 pm] versus C-Si [Si(sp³)-C(sp³) = 194 pm] bond lengths and the tricoordinate boron (C-B-O = 120°) versus tetracoordinate silicon (C-Si-O = 109.5°) geometry
would affect the 5-exo-trig and 6-endo-trig transition states for the cyclization, and hence the observed product distributions.

AII.2.2 Preparation of Cyclization Precursors

All of the substrates to be employed in the radical cyclization process were prepared with relative ease via a convenient and efficient in situ ditransesterification pathway. Employing this method, a single diisopropyl (α-haloalkyl)boronate \[63\] can serve as a common precursor for the synthesis of differently functionalized (α-haloalkyl)boronates \[64\].

AII.2.2.1 Synthesis of Diisopropyl (α-Haloalkyl)boronates

Diisopropyl (bromomethyl)boronate \[63a\] was prepared following a protocol reported by Matteson (Scheme AII.2.2.1.1).\(^5\)

\[
\begin{align*}
\text{CH}_2X_2 + \text{B(OLiPr)}_3 & \xrightarrow{n\text{BuLi, THF, -78 °C}} \left[ \begin{array}{c}
\text{iPrO} \\
\text{X} \\
\text{B} \\
\text{O} \\
\text{L} \\
\text{O} \\
\text{Pr}
\end{array} \right]^{\text{Li}^+} \\
& \xrightarrow{\text{MeSO}_3\text{H}, -78 °C \text{ to r.t.}} \left[ \begin{array}{c}
\text{iPrO} \\
\text{X} \\
\text{B} \\
\text{O} \\
\text{L} \\
\text{O} \\
\text{Pr}
\end{array} \right] \xrightarrow{X = \text{Br}, 89\% \ [63a]} X = \text{I}, 85\% \ [63b]
\end{align*}
\]

Scheme AII.2.2.1.1

Low temperature lithium-halogen exchange with dibromomethane initially generates (bromomethyl)lithium, which subsequently adds to triisopropyl borate [B(OLiPr)\(_3\)], producing tetracoordinate borate [66]. Treatment of this intermediate with anhydrous methanesulfonic acid then gives rise to diisopropyl (bromomethyl)boronate [63a]. An analogous procedure reported by Wallace involving the addition of (iodomethyl)lithium to triisopropyl borate was suitable for the preparation of (iodomethyl)boronate [63b].\(^5\)
Similarly, synthesis of diisopropyl (1-iodopentyl)boronate [63c] required the preparation of diisopropyl butylboronate [67] followed by a (chloromethyl)lithium based one carbon homologation to diisopropyl (1-chloropentyl)boronate [68] and subsequent halogen exchange (Finkelstein reaction) to the iodide (Scheme AII.2.2.1.2).

\[
\begin{align*}
\text{B(OiPr)}_3 & \xrightarrow{(1) nBuLi, THF, -78 \, ^\circ\mathrm{C} \text{ to rt}} \text{B(OiPr)}_2 \\
& \xrightarrow{(2) \text{HCl/\text{Et}_2\text{O}, 0 \, ^\circ\mathrm{C}} \text{ to rt}} \text{B(OiPr)}_2 \\
& \xrightarrow{\text{CH}_2\text{Cl}_2, nBuLi, THF, -100 \, ^\circ\mathrm{C}} \text{B(OiPr)}_2 \\
\text{B(OiPr)}_2 & \xrightarrow{\text{[63c]}} \text{B(OiPr)}_2 \\
& \xrightarrow{\text{Nal, acetone, rt}} \text{B(OiPr)}_2 \\
& \xrightarrow{95\%} \text{[68]}
\end{align*}
\]

Scheme AII.2.2.1.2

Low temperature deprotonation of dichloromethane initially provides the highly unstable (dichloromethyl)lithium anion, which then adds readily to the diisopropyl butylboronate [67]. Subsequent butyl group migration produces the diisopropyl (1-chloropentyl)boronate [68], which is then treated with sodium iodide in acetone to ensure near quantitative halogen exchange.

All of the isolated and purified diisopropyl (α-haloalkyl)boronates [63] were obtained as clear, pale yellow oils which were best stored under refrigeration (5 °C) in order to minimize the amount of hydrolysis.

AII.2.2.2 Synthesis of Diallyl and Dipropargyl (α-Haloalkyl)boronates

Conversion of the diisopropyl (α-haloalkyl)boronates [63] to suitably functionalized radical cyclization precursors was achieved via ditransesterification with an allyl or propargyl alcohol of choice. In order to carry out this transformation, the diisopropyl (α-haloalkyl)boronate [63] was stirred with 2 equivalents of the allyl or propargyl alcohol at room temperature in dry hexanes for 16 h, followed by the removal of all solvents in vacuo (Scheme AII.2.2.2.1).
The limitation of this esterification protocol is the inability to introduce just one allyl or propargyl alcohol ligand onto the diisopropyl (α-haloalkyl)boronate [63], something which may become of greater importance as the cost of the alcohol increases, or availability decreases. Unfortunately, attempts at using only 1 equivalent of a desired allyl or propargyl alcohol with a diisopropyl (α-haloalkyl)boronate [63] resulted in a statistical mixture of mono- and di-transesterified material, so the original 2 equivalent transesterification protocol was kept as the standard substrate preparation method. It was expected, however, that the unreacted allyl or propargyl alcohol ligands could be reisolated following reaction and purification by chromatography on silica gel.

Evaluation of the crude reaction products by $^1$H NMR spectroscopy showed the ditransesterification to be quantitative, and the resulting diallyl [64] and dipropargyl (α-haloalkyl)boronates [69] to be extremely pure. Because none of the diallyl [64] or dipropargyl (α-haloalkyl)boronates [69] required further purification, they were taken on directly into the radical cyclization step, making it possible to conduct the entire tethering-cyclization-oxidation sequence in one pot simply by changing solvents. The nature of the various substituents on the allyl and propargyl units, along with their impact on the radical cyclization process, is described below.

AIL2.3 Radical Cyclization and Boron Tether Removal Methods

In order to carry out the desired boron tethered radical cyclizations, a set of conditions compatible with the diallyl [64] and dipropargyl (α-haloalkyl)boronates [69]
and suitable for efficiently promoting their intramolecular closures had to be selected. A convenient method for removing the boron tether also had to be considered.

AII.2.3.1 Radical Chain Method and Mechanism

Earlier work concerning stoichiometric and catalytic Bu$_3$SnH mediated radical processes involving (α-haloalkyl)boronates [62] had demonstrated a marked tendency for these substrates to undergo direct halide reduction under those conditions. It was anticipated that this direct halide reduction would be a significant impediment to the efficient execution of the boron tethered α-boryl radical cyclizations, so a method capable of addressing this problem was sought during the planning stage of the project. Use of an organosilane reagent, tris(trimethylsilyl)silane (TTMSS), appeared to be ideally suited for this purpose.

While Bu$_3$SnH traps alkyl radicals with rates on the order of $k = 10^6$ M$^{-1}$ s$^{-1}$, TTMSS is a less reactive hydrogen atom donor ($k = 10^3$ M$^{-1}$ s$^{-1}$), presumably because the Si-H bond (79 kcal mol$^{-1}$) is 5 kcal mol$^{-1}$ stronger than the Sn-H bond (74 kcal mol$^{-1}$). Consequently, it is expected that direct reduction of the α-boryl radical will be reduced if TTMSS is used as a reaction mediator as opposed to tributyltin hydride.

TTMSS is also used to conveniently generate radicals from simple precursors such as alkyl or aryl bromides and iodides, but the reagent's practical advantages extend beyond those of Bu$_3$SnH. It is generally easier to remove TTMSS residues from reaction products than it is to remove tributyltin hydride residues, and the lower toxicity of the reagent makes the overall process less hazardous. Unfortunately, TTMSS ($16/g$) is available commercially at a higher cost than Bu$_3$SnH ($3/g$), and is typically used in a stoichiometric fashion.

The radical chain process operating during a boron tethered radical cyclization conducted using TTMSS is straightforward (Scheme AII.2.3.1.1).
The initiator, α,α’-azobisisobutyronitrile (AIBN), was selected for reasons of availability, and undergoes thermal homolytic cleavage in the manner shown. The two alkyl radicals generated from this cleavage subsequently abstract a hydrogen atom from TTMSS to form a tris(trimethylsilyl)silyl radical, the chain promoter and carrier. The tris(trimethylsilyl)silyl radical promoted homolytic cleavage of the C-X bond in the substrate then generates the α-boryl radical required for the intramolecular ring closure, along with tris(trimethylsilyl)silyl halide.

In the same way that boron participates strongly in π-bonding in vinylboranes, the α-boryl radical is stabilized by electron delocalization into the empty 2p-orbital of boron (Figure AII.2.3.1.2).
Analysis by electron spin resonance (ESR) spectroscopy not only confirms this delocalization, but also suggests the possibility of further, minor electron delocalization into the oxygen p-orbitals.\textsuperscript{48} Overall, the magnitude of the delocalization energy is reported to be in the range of 8-20 kcal mol\textsuperscript{-1},\textsuperscript{59} a stabilization energy comparable to that evident in benzyl-type radicals.

While tributyltin radicals add reversibly to both alkenes and alkynes, the danger exists here that the tris(trimethylsilyl)silyl radicals can potentially add to the substrate's allyl or propargyl moieties, a process known to be irreversible. Fortunately, the rate of these addition processes ($k = 10^7$ M\textsuperscript{-1} s\textsuperscript{-1}) is significantly slower than the competitive reaction of tris(trimethylsilyl)silyl radicals with the organic halide ($k = 10^8$-10\textsuperscript{9} M\textsuperscript{-1} s\textsuperscript{-1}).

The intermediate radical obtained following cyclization is trapped by reaction with TTMSS ($k = 10^5$ M\textsuperscript{-1} s\textsuperscript{-1}), a process which also serves to regenerate the essential tris(trimethylsilyl)silyl radical required to propagate another cycle.

With only the solubility of the substrate, TTMSS, and the initiator to consider, a wider variety of solvents can be considered than in catalytic systems requiring a co-reductant. Most radical processes, including those mediated by TTMSS, are typically conducted in benzene, a solvent entirely suited for the boron tethered cyclizations to be attempted.

\textbf{AIL2.3.2 Removal of the Temporary Boron Connection}

In order to effectively evaluate the results of the anticipated cyclizations, it was decided that the temporary boron tether should be removed in order to access products that are easier to isolate and purify than the intermediate boracycles. Oxidative cleavage of the C-B bond followed by hydrolysis appeared satisfactory for this purpose.

Unlike previous work involving catalytic \textit{Bu}_3SnH mediated cyclization of (E)-[42] and (Z)-alkenylboronates [47], the possibility did not exist of producing HCN at the
oxidative stage of the process. Consequently, alkaline hydrogen peroxide was selected as the best possible oxidant for cleavage of the C-B bond in the intermediate boracycles. Unlike trimethylamine N-oxide (TMANO), alkaline hydrogen peroxide is effective at room temperature, and can achieve full C-B bond oxidation within minutes, increasing the overall convenience of this step.

**AIL.2.4 Initial Boron Tethered Radical Cyclization Efforts**

Having chosen TTMSS for carrying out the boron tethered radical cyclizations, and alkaline hydrogen peroxide for the subsequent oxidative removal of the temporary boron connection, a base set of conditions was selected for both transformations. Cyclization: 1.2 equivalents of TTMSS (as a 0.1 M solution in benzene), 0.4 equivalents of AIBN, and 1 equivalent of the diallyl [64] or dipropargyl (haloalkyl)boronate [69] would be refluxed at 80 °C under nitrogen. Oxidation; 5 equivalents of H₂O₂, 5 equivalents of NaOH, and 1 equivalent of the boracyle (as a 0.2 M solution in THF/H₂O) would be stirred at room temperature. The conditions were rationally modeled on those reported by Chatgilialoglu and Kuivila respectively, and were designed to serve as a reasonable starting point for subsequent optimization.

The first attempted cyclizations employing these conditions were conducted on dicinnamyl (bromomethyl)boronate [64a] (Scheme AIL.2.4.1).

![Scheme AIL.2.4.1](image)

This initial cyclization attempt proved to be extremely successful, producing the anticipated 1,3-diol [70a] in high yield through 5-exo-trig ring closure. By monitoring the reduction of diagnostic vinylic proton signals and disappearance of bromomethyl group proton signals in the ¹H NMR spectra of solution aliquots taken during the course of the
reaction, it was possible to establish that nearly full conversion of the dicinnamyl (bromomethyl)boronate [64a] to cyclized material was achieved after 20 h.

Cyclization of dicinnamyl (bromomethyl)boronate [64a] was also attempted using catalytic $\text{Bu}_3\text{SnH}^{34}$ (0.01 equivalents) in THF (0.1 M) at 55 °C for 48 h. As anticipated, direct ionic reduction of the halide by the sodium cyanoborohydride co-reductant was overwhelming, allowing for the formation of only a trace amount of the 5-exo-trig cyclization product, 1,3-diol [70a]. Consequently, the use of stoichiometric tributyltin hydride (1.1 equivalents) in benzene (0.1 M) at 80 °C for 20 h was also examined. Although the yield of isolated 1,3-diol [70a] increased to about 31%, direct reduction, now presumably via a radical pathway, was still significant. In light of these results, TTMSS appears to be the ideal reagent for carrying out these transformations.

AII.2.5 Establishing the Necessity of Tethering

Before proceeding with the cyclization of all available substrates, the necessity of tethering the radical and trap together by means of a temporary boron connection was unambiguously established. The product 1,3-diols resulting from 5-exo-trig cyclization can also potentially be obtained via an intermolecular addition pathway, so to rule out this possibility, a pair of control experiments was performed. In the first study, 2-bromomethyl-[1,3,2]-dioxaborolane [71] was first prepared by transesterification of diisopropyl (bromomethyl)boronate [63a] with ethylene glycol, and then subjected to the cyclization conditions in the presence of 2 equivalents of cinnamyl alcohol, while the second study involved the attempted addition of 2 equivalents of 1-phenyl-3-(tert-butyldimethylsiloxy)-1-propene to diisopropyl (bromomethyl)boronate [63a] under the same conditions (Scheme AII.2.5.1).
In both cases, tethering of the reacting partners is precluded, and as anticipated, no addition products were observed. The vinylic proton \(^1\)H NMR signals were unchanged, and column chromatography on silica gel of the oxidized reaction mixtures failed to yield any diol products.

**AIL2.6 Overview and Analysis of Cyclizations**

Having established a simple and efficient protocol for carrying out the boron tethered cyclization of \(\alpha\)-boryl radicals, a systematic study of cyclization modes was initiated using a variety of diallyl [64] and dipropargyl (\(\alpha\)-haloalkyl)boronates [69] (see AII.2.2.2). Each substrate was subjected to the identical TTMSS cyclization conditions, and the temporary boron tether was removed oxidatively using alkaline hydrogen peroxide according to the initially outlined protocol. Cyclization; 1.2 equivalents of TTMSS (as a 0.1 M solution in benzene), 0.4 equivalents of AIBN, and 1 equivalent of the diallyl [64] or dipropargyl (\(\alpha\)-haloalkyl)boronate [69] are refluxed at 80 °C under nitrogen for 20 h. Oxidation; 5 equivalents of H₂O₂, 5 equivalents of NaOH, and 1 equivalent of the boracycle (as a 0.2 M solution in THF/H₂O) are stirred at room temperature for 2h.

**AIL2.6.1 Cyclization of Diallyl (Halomethyl)boronates**

As anticipated from the initial cyclization trials involving dicinnamyl (bromomethyl)boronate [64a], all other diallyl (halomethyl)boronates [64] unsubstituted at the proximal alkene carbon cyclized efficiently in 5-exo-trig fashion under the
optimized conditions to give 1,3-diols [70] in high yields following oxidation of the C-B bond (Table AII.2.6.1.1).

![Chemical Structure]

<table>
<thead>
<tr>
<th>Diallyl (halomethyl)boronate</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>1,3-Diol</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[64]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Ph</td>
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<tr>
<td>g</td>
<td>Me</td>
<td>Me</td>
<td>Br</td>
<td>e</td>
<td>71</td>
</tr>
</tbody>
</table>

**Table AII.2.6.1.1 - 5-Exo-Trig Cyclizations of Proximally Unsubstituted Diallyl (Halomethyl)boronates**

It is clear from the isolated yields of the 1,3-diols [70] that comparable results are obtained when using iodide radical precursors [64a] and [64f], despite the expected higher reactivity of these substrates. Terminal mono- and di-<i>n</i>-alkyl substitution produced similar results, as did terminal aryl substitution.

In order to accurately gauge the level of regioselectivity in these cyclizations, the crude reaction mixtures were subjected to <sup>13</sup>C NMR and GC analysis. In each case, following the removal of silane and allyl alcohol residues by column chromatography on silica gel, the <sup>13</sup>C NMR spectrum showed only one -CH<sub>2</sub>OH signal, and only one peak was observed in the GC trace. For the cyclization of diallyl (bromomethyl)boronate [64c], an authentic sample of 2-methyl-1,3-propanediol [70b] was also subjected to <sup>13</sup>C
NMR and GC analysis for comparison, confirming the product to be that formed from 5-exo-trig closure, and not 6-endo-trig addition. Based on the $^{13}$C NMR and GC results, and taking into account the limit of detection for each instrumental technique, the 5-exo-trig closure selectivity for the cyclization of the various diallyl (halomethyl)boronates [64] was determined to be greater than 95:5.

Cyclization attempts using isopropyl allyl (halomethyl)boronates, generated in situ by mixing only 1 equivalent of an allyl alcohol with a diisopropyl (halomethyl)boronate [63], unfortunately resulted in decreased yields of the isolated 1,3-diols [70]. For example, the cyclization of isopropyl cinnamyl (bromomethyl)boronate only gave a 62% yield of the 1,3-diol [70a], a full 20% lower than that observed in cyclization of dicinnamyl (bromomethyl)boronate [64a].

A substantial erosion in yield was also observed in the cyclization of diallyl (halomethyl)boronates [64] bearing a proximal methyl group on the alkene, presumably because of the greater steric hindrance at the tertiary olefinic carbon (Table AII.2.6.1.2).

\[
\begin{align*}
\text{X} & \quad \text{O} \quad \text{B} & \quad R' \\
\text{[64]} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \Quad
In these cases, 5-exo-trig cyclization is definitely slower than for proximally unsubstituted alkenes, and more dilute reaction conditions are required to minimize the increasingly competitive direct reduction of the α-boryl radical. Only with a TTMSS concentration of 0.01 M do the reported, synthetically useful yields become possible, with the standard 0.1 M reaction conditions returning only a trace of the cyclized products. Interestingly, no 6-endo-trig cyclization was evident with these systems despite the more favorable steric aspects of the alkene terminus. Such results are sharply in contrast with observations for the analogous substrates employing a silicon tether where 6-endo-trig cyclization was found to predominate.9

AII.2.6.2 Cyclization of Dipropargyl (Halomethyl)boronates

Like alkenes, it was expected that alkynes would act as efficient radical traps, so boron tethered radical cyclizations were attempted using several dipropargyl (halomethyl)boronates [69]. The ensuing 5-exo-dig closures gave access to unsaturated 1,3-diols [72] in modest yields following oxidation of the C-B bond (Table AII.2.6.2.1).

![Cyclization reaction scheme](image)

<table>
<thead>
<tr>
<th>Dipropargyl (halomethyl)boronate</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>1,3-Diol</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[69]</td>
<td></td>
<td></td>
<td></td>
<td>[72]</td>
<td></td>
</tr>
<tr>
<td>a</td>
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<td>H</td>
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<td>Me</td>
<td>H</td>
<td>Br</td>
<td>c</td>
<td>62</td>
</tr>
</tbody>
</table>

Table AII.2.6.2.1 - 5-Exo-Dig Cyclizations of Dipropargyl (Halomethyl)boronates
Comparable yields were once again obtained on transition from dipropargyl (bromomethyl)boronate [69b] to dipropargyl (iodomethyl)boronate [69c], although the yields overall were a little lower than those reported for the diallyl (halomethyl)boronate [64] cyclizations.

As before, analysis by both $^{13}$C NMR and GC was conducted to establish the level of cyclization regioselectivity. Following the removal of silane and unreacted propargyl alcohol residues by column chromatography on silica gel, the $^{13}$C NMR spectrum of crude 1,3-diols [72a] and [72b] showed only one $\text{-CH}_2\text{OH}$ signal, while that for 1,3-diol [72c] showed only the expected two. In all cases, only one peak was observed in the GC trace. For the cyclization of dipropargyl (bromomethyl)boronate [69a], an authentic sample of 2-methylene-1,3-propanediol [72a] was also subjected to $^{13}$C NMR and GC analysis for comparison, confirming the product to be that formed from 5-exo-dig closure, and not 6-endo-dig addition. Based on the $^{13}$C NMR and GC results, and taking into account the limit of detection for each instrumental technique, the 5-exo-dig closure selectivity for the cyclization of the selected dipropargyl (halomethyl)boronates [69] was determined to be greater than 95:5.

AII.2.6.3 Stereoselectivity in $\alpha$-Boryl Radical Cyclizations

Some select investigations into the stereoselectivity of $\alpha$-boryl radical cyclizations were conducted using a set of racemic substrates. In each case, tethering of the radical trap was conducted in the aforementioned manner, and the standard cyclization conditions were once again employed.

Cyclization using dicycloclyx-2-enyl (bromomethyl)boronate [64i] produced the anticipated cis 1,3-diol [70h] in high yield, and as the sole product via the intermediacy of a cis fused oxaborolane (Scheme AII.2.6.3.1).
Closure of the 4-substituted hexenyl radicals generated from diallyl (bromomethyl)boronates [64m] and [64n] resulted in high yields of the expected 1,3-diols [70I] and [70j], although substantially different selectivities were observed for the two cases (Scheme AII.2.6.3.2).

Cyclization of diallyl (bromomethyl)boronate [64m] gave a 68:32 mixture of 1,3-diols [70i]-anti and [70i]-syn as determined by $^{13}$C NMR analysis of the crude product. Establishing the relative stereochemistry of both the major and minor diastereomer was accomplished by comparison of the $^{13}$C NMR shifts with literature values reported for the separate compounds. The observed major anti diastereomer originates through the pseudoequatorial disposition of both methyl substituents in the Beckwith-Houk transition state,² a biasing effect made stronger by substitution of a more sterically demanding group at the 4-position. Cyclization of diallyl (bromomethyl)boronate [64n] makes use of this effect to achieve a greater than 98:2 selectivity for the anti diastereomer of 1,3-diol
[70j]. These selectivities are comparable to those reported for analogous substrates employing a silicon tether, with the exception that no products originating from 6-endo-trig cyclization are observed.9

An initial attempt at the cyclization of a 1-substituted hexenyl radical, a transformation very rarely accomplished by means of a silicon tether,60 was conducted using diallyl (1-iodopentyl)boronate [63c] (Scheme AII.2.6.3.3).

\[
\text{Bu}_3\text{B} \text{O-CH} \text{CH} \text{-CHCH} \text{-CH} \text{-CH} \text{CH} \text{-CH} \text{-CH} \text{CH} \text{-CH}-\text{Bu} \quad 1) \text{TTMSS (slow add'n) [0.10 M], AIBN (cat.), C}_6\text{H}_6, 80 \degree \text{C}, 20 \text{ h} \\
\text{Bu}_3\text{B} \text{O-CH} \text{CH} \text{-CHCH} \text{-CH} \text{-CH} \text{CH} \text{-CH} \text{-CH}-\text{Bu} \quad 2) \text{H}_2\text{O}, \text{NaOH, THF/H}_2\text{O, rt, 2 h} \\
\]

Scheme AII.2.6.3.3

As expected from a Beckwith-Houk transition state, the syn diastereomer of the product 1,3-diol [70k] now predominates.2 However, cyclization of diallyl (1-iodopentyl)boronate [63c] is more difficult, presumably for steric reasons, and shows a lower yield attainable only via slow addition of the TTMSS.

AII.2.7 Conclusion

The intramolecular α-boryl radical cyclizations reported here constitute an important extension of boron tethered radical cyclization methodology. Like their silicon tethered counterparts, they are a viable tool for the construction of acyclic molecules via a highly regioselective cyclization strategy employing a temporary connection. The convenience and flexibility of the silicon tethered radical cyclization processes, however, is superseded by that of the boron tethered methodology given the greater inherent stability and ease of preparation of the required organoboron substrates, and the increased synthetic flexibility of the C-B bond. Furthermore, undesirable side-products resulting from 6-endo-trig cyclization are avoided, a trend presumably reflecting the shorter C-B bond length and the tricoordinate geometry of the boronates.
Chapter AIII - Experimental
AIII.1 General Experimental

Reagents, unless otherwise noted, were purchased from the Aldrich Chemical Company or Fisher Scientific Ltd., and used as received. Reaction solvents were distilled under an argon atmosphere prior to use unless otherwise stated. Diethyl ether (Et₂O), THF, and benzene were distilled from Na metal and benzophenone ketyl, while dichloromethane (CH₂Cl₂) was distilled from calcium hydride (CaH₂). All other solvents used were reagent grade.

All manipulations were carried out under a nitrogen atmosphere in either flame-dried or oven-dried glassware. Column chromatography on silica gel (60 Å, 230-400 mesh, Whatman Company or Toronto Research Chemicals, Inc.) was performed with hexanes and ethyl acetate (EtOAc). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (Alugram SIL G/UV254, Rose Scientific Ltd.), visualized with a UV254 lamp (Spectroline Longlife filter), and stained with 20% phosphomolybdic acid in ethanol (Aldrich Chemical Company). Solvent systems associated with Rf-values and chromatography are reported as volumetric ratios.

All ¹H and ¹³C NMR spectra were obtained on a 400 MHz Varian Unity spectrometer in CDCl₃ (referenced to the residual solvent signals at δ 7.24 and 77.00 ppm for ¹H and ¹³C respectively) or C₆D₆ (referenced to the residual solvent signals at δ 7.15 and 127.00 ppm for ¹H and ¹³C respectively). Features of peaks in the ¹H NMR spectra are labeled in brackets after each chemical shift in the following order: integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = 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 mass spectra were recorded on an AEI MS3074 spectrometer. Gas chromatography analyses were performed on a Perkin-Elmer AutoSystem XL instrument equipped with a 30.0 m cross-linked 35% Ph ME silicone capillary column (0.25 mm x 0.25 μm film thickness).

References following compound names indicate where previously reported literature ¹H and ¹³C NMR spectroscopic data may be found. If no reference is present,
$^1$H and $^{13}$C NMR spectroscopic data for that compound had not been reported in the literature at the time of writing.

AIII.2 Synthetic Methods and Compound Data

**Di(haloalkyl) Alkenylboronates**

**Preparation of $\beta$-Alkyl-(E)-Alkenylboronic Acids [41a]-[41e]$^{30}$**

To a 1.0 M solution of the requisite alkyl acetylene (28.0 mmol) in CH$_2$Cl$_2$ was added BBr$_2$·SMe$_2$ (1.0 M solution in CH$_2$Cl$_2$, 28.8 mmol) dropwise at 0 °C. The resulting solution was then allowed to warm gradually to room temperature, and stirred for 16 h. The solvent was subsequently removed *in vacuo*, and the residue dissolved in Et$_2$O (40 mL). The solution was then cooled to 0 °C, and NaOH (3.0 M in H$_2$O, 57.0 mmol) added dropwise. Stirring of the biphasic mixture for 3 h was followed by separation of the aqueous and organic layers, and extraction of the aqueous layer with Et$_2$O (5 x 25 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated *in vacuo* to afford the $\beta$-alkyl-(E)-alkenylboronic acid.

**Preparation of $\beta$-Aryl-(E)-Alkenylboronic Acids [41f] and [41g]$^{31}$**

The requisite arylacetylene (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$_2$O (20 mL) at room temperature. The resulting mixture was heated to 80 °C, and stirred for 1 h. A white precipitate formed upon cooling, and was collected by filtration. Recrystallization of this solid from THF/hexanes gave the $\beta$-aryl-(E)-alkenylboronic acid.
Preparation of β-Alkyl- and Aryl-(Z)-Alkenylboronic Acids [46a] and [46b]\\(^2\)

(1) Formation of 1-Iodo-1-alkynes [44]

A solution of alkyne (0.122 mol) in THF (30 mL) was cooled to -78 °C. \( n \)-BuLi (1.6 M in hexanes, 0.122 mol) was added dropwise, and the solution allowed to stir for 2 h prior to the addition of iodine (30.9 g, 0.122 mol) in THF (40 mL) dropwise over 1 h. After warming to room temperature, the solution was diluted with pentane (100 mL), and washed with brine (3 x 30 mL). The organic layer was dried (MgSO\(_4\)), filtered, and concentrated \textit{in vacuo}. Residual material was distilled under reduced pressure to afford the 1-iodo-1-alkyne.

(2) Formation of \((Z)\)-1-Iodo-1-alkenes [45]

BH\(_3\)·SMe\(_2\) (1.60 mL, 16.8 mmol) was added to THF (45 mL) at 0 °C, followed by the dropwise addition of cyclohexene (3.41 mL, 33.7 mmol). The solution was stirred at 0 °C for 1 h, warmed to room temperature, stirred for 1 h, and then re-cooled to 0 °C. 1-Iodo-1-alkyne (16.8 mmol) was added, and the solution warmed to room temperature. After stirring for 1 h, the reaction was quenched with glacial acetic acid (20 mL). The material was subsequently taken up in pentane (100 mL), and washed with brine (3 x 25 mL). The organic layer was dried (MgSO\(_4\)), filtered, concentrated \textit{in vacuo}, and distilled under reduced pressure to afford the \((Z)\)-1-iodo-1-alkene.

(3) Formation of \((Z)\)-1-Alkenylboronic Acids [46]

To a solution of 1-iodo-1-alkene (7.14 mmol) in Et\(_2\)O (47 mL) at -78 °C was added \( n \)-BuLi (1.6 M in hexanes, 8.57 mmol). The solution was then stirred for 1 h prior to the addition of triisopropyl borate (1.98 mL, 8.57 mmol), allowed to warm to room temperature, and stirred for an additional 16 h. The reaction was subsequently quenched with HCl (2.0 M in H\(_2\)O, 4.3 mL), and stirred for 1 h prior to extraction with Et\(_2\)O (4 x 50 mL). The organic layer was dried with (MgSO\(_4\)), filtered, and concentrated \textit{in vacuo} to give the \((Z)\)-1-alkenylboronic acid.
Preparation of (E)-Alkenylboronates [42a]-[42l] and (Z)-Alkenylboronates [47a] and [47b]

To a 0.2 M solution of the (E)/(Z)-alkenylboronic acid (18.0 mmol) in THF was added the haloalcohol (45.0 mmol) and 4 Å molecular sieves (10 g). The resulting mixture was protected from light, and stirred for 24 h prior to vacuum filtration through a pad of celite. The solvent was then removed in vacuo, and the excess haloalcohol removed in 8 h under high vacuum (1 mm Hg) to afford the di(haloethyl) or di(halopropyl) (E)/(Z)-alkenylboronate. This material was stored at 5 °C under nitrogen.

Preparation of (E)-Alkenylboronates [42m]-[42o]

To a 1.0 M solution of 1-alkyne (28.0 mmol) in CH₂Cl₂ was added Br₂-SMe₂ (1.0 M solution in CH₂Cl₂, 28.8 mmol) dropwise at 0 °C. The resulting solution was then allowed to warm gradually to room temperature, and stirred for 16 h. Subsequently, the cyclic ether (56.0 mmol) of choice was added dropwise, and the solution stirred for 3 h. The solvent was then removed in vacuo to afford the (E)-alkenylboronate. The material was stored at 5 °C under nitrogen.

Preparation of Diisopropyl (E)-Alkenylboronates [49]

A solution of (E)-alkenylboronic acid (35.0 mmol) in isopropanol (120 mL) and toluene (100 mL) was heated to reflux with a Dean-Stark trap for 1 week. The solvents were then removed in vacuo, and the residual oil distilled under reduced pressure to afford the diisopropyl (E)-alkenylboronate. The material was stored at 5 °C under nitrogen.

Preparation of (E)-Hex-1-enyl-[1,3,2]-dioxaborolane [51]

(E)-Hexenylboronic acid (2.54 g, 20.0 mmol) and ethylene glycol (1.24 g, 20.0 mmol) were dissolved in benzene (200 mL) and heated to reflux for 2 h. The water/benzene azeotrope was subsequently removed by slow distillation at atmospheric pressure, and the residual oil purified by distillation under reduced pressure (bp = 53 °C at 6 mm Hg) to afford the title compound.
Cyclization of Di(haloalkyl) \( (E)/(Z) \)-Alkenylboronates (Catalytic Tributyltin Hydride)\(^3\)

\( \text{NaCNBH}_3 \) (942 mg, 15.0 mmol), initiator (DAB) (552 mg, 2.40 mmol), and \( \text{Bu}_3\text{SnH} \) (16 \( \mu \text{L}, 0.06 \text{ mmol}) were added to a 0.1 M solution of the di(haloalkyl) \( (E)/(Z) \)-alkenylboronate (6.00 mmol) in THF at room temperature. The reaction mixture was then stirred vigorously, and heated to 55 °C for 48 h prior to cooling, and removal of the solvent \textit{in vacuo}. The residue was taken up in \( \text{CH}_2\text{Cl}_2 \) (20 mL) and filtered to remove any precipitate, followed by concentration of the filtrate \textit{in vacuo}. The residual oil was taken on to the oxidation stage without further purification.

Cyclization With Diisopropyl \( (E) \)-Alkenylboronates (Catalytic Tributyltin Hydride)\(^3\)

To a 0.1 M solution of the diisopropyl \( (E) \)-alkenylboronate (6.00 mmol) in THF at room temperature was added the haloalcohol (6.00 mmol). The resulting solution was stirred for 3 h prior to the addition of \( \text{NaCNBH}_3 \) (942 mg, 15.0 mmol), initiator (DAB) (552 mg, 2.40 mmol), and \( \text{Bu}_3\text{SnH} \) (16 \( \mu \text{L}, 0.06 \text{ mmol}). The reaction mixture was then stirred vigorously and heated to 55 °C for 48 h prior to cooling, and removal of the solvent \textit{in vacuo}. The residue was taken up in \( \text{CH}_2\text{Cl}_2 \) (20 mL) and filtered to remove any precipitate, followed by concentration of the filtrate \textit{in vacuo}. The residual oil was taken on to the oxidation stage without further purification.

Cyclization of Di(haloalkyl) \( (E)/(Z) \)-Alkenylboronates (Stoichiometric Tributyltin Hydride or Tributyltin Deuteride)\(^3\)

To a solution of the di(haloalkyl) \( (E)/(Z) \)-alkenylboronate (1.3 mmol) in benzene (13 mL) was added \( \text{Bu}_3\text{SnH} \) or \( \text{Bu}_3\text{SnD} \) (1.4 mmol) and initiator (DAB) (120 mg, 0.50 mmol). The reaction mixture was then stirred vigorously and heated to 55 °C for 48 h. After cooling to room temperature, the solvent was removed \textit{in vacuo}, and the residual oil taken on to the oxidation stage without further purification.
**C-B Bond Oxidation**

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 solution was then stirred vigorously and heated to 80 °C for 24 h, after which H₂O (20 mL) was added. The resulting biphasic mixture was stirred an additional 24 h at 80 °C. After cooling to room temperature, the aqueous and organic layers were separated, and the aqueous layer extracted with CH₂Cl₂ (5 x 15 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. Purification by column chromatography (silica, EtOAc/hexanes) afforded the desired diol.

**Preparation of 1,3-Octanediol [50a]**

1. **Formation of 4-Hydroxy-1-nonene**

To a solution of hexanal (2.38 g, 23.8 mmol) in Et₂O (75 mL) at -78 °C was added allylmagnesium bromide (1.0 M in Et₂O, 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 saturated NH₄Cl. Extraction of the aqueous layer with Et₂O (5 x 20 mL), and concentration of the combined organic layers in vacuo afforded 4-hydroxy-1-nonene in 97% yield. This material was taken on to the ozonolysis stage without further purification.

2. **Formation of 1,3-Octanediol**

A solution of 4-hydroxy-1-nonene (1.50 g, 10.6 mmol) in 3:1 CH₂Cl₂/MeOH (29 mL) was ozonolyzed at -78 °C. Subsequently, the solution was warmed to 0 °C, and NaBH₄ (798 mg, 21.1 mmol) added. After stirring for 5 h while warming to room temperature, the solution was quenched with saturated aqueous NH₄Cl (20 mL), and the aqueous layer extracted with Et₂O (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.
Preparation of 2-Butyl-1,4-butanediol

(1) Formation of 4-Butyldihydrofuran-2-one

To a slurry of LiH (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-BuLi (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 (MgSO4), filtered, and concentrated in vacuo. Distillation of the residual oil at 85-90 °C (5 mm) afforded 4-butyldihydrofuran-2-one in 30% yield.

(2) Formation of 2-Butyl-1,4-butanediol

To a slurry of LiAlH4 (1.13 g, 29.8 mmol) in Et2O (60 mL) at 0 °C was added 4-butyldihydrofuran-2-one (3.53 g, 24.8 mmol) in Et2O (5 mL). The resulting solution was stirred for 15 min prior to being warmed to room temperature, and subsequently refluxed for 16 h. After cooling in an ice bath, the mixture was quenched with H2O (10 mL), and enough 2 M HCl added to dissolve the precipitate that had formed. The aqueous layer was then extracted with Et2O (5 x 50 mL), and the combined organic layers dried (MgSO4), filtered, and concentrated in vacuo to afford the title compound in 20% yield following column chromatography (silica, EtOAc/hexanes). 1H NMR (400 MHz, CDCl3) δ 3.90-3.80 (2H, broad s), 3.80-7.0 (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); 13C NMR (100 MHz, CDCl3) δ 66.25, 61.02, 39.37, 35.81, 31.44, 29.26, 22.91, 13.99.
Separation of 1,4-Diols [56a] and [56b]

(1) Acetonide Formation

To a solution of the [56a] and [56b] mixture (300 mg, 1.50 mmol) in dry acetone (7.5 mL) was added 2,2’-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 NEt₃ (0.4 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification of the residual oil by column chromatography (silica, EtOAc/hexanes) afforded the diol [56a] and the acetonide of diol [56b].

(2) Acetonide Cleavage

The acetonide of diol [56b] (60 mg, 0.25 mmol) was stirred at room temperature with acetic acid (5 mL, 80% in H₂O). After 2 h, the solution was neutralized with saturated NaHCO₃, and extracted with Et₂O (3 x 15 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residual oil by column chromatography (silica, EtOAc/hexanes) afforded diol [56b].

Preparation of p-Nitrobenzoic Acid Derivatives [57a] and [57b]

Diols [56a] and [56b] (75 mg, 0.37 mmol) were dissolved separately in CH₂Cl₂ (11 mL), 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.
(E)-1-Pentenylboronic Acid [41a] (J. Am. Chem. Soc. 1975, 97, 5608)

\[
\begin{align*}
&\text{B(OH)}_2
\end{align*}
\]

Obtained in 76% yield; white crystalline solid; mp = 80 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.94 \text{ (1H, dt, } J = 17.6, 6.6 \text{ Hz)}, 5.51 \text{ (1H, dt, } J = 17.6, 1.4 \text{ Hz)}, 2.17 \text{ (2H, m)}, 1.46 \text{ (2H, m)}, 0.91 \text{ (3H, t, } J = 7.4 \text{ Hz}); ^{13}\text{C NMR (100 MHz, CDCl}}_3 \delta 157.59, 122.0 \text{ (br), 37.69, 21.35, 13.69.}

(E)-1-Hexenylboronic Acid [41b] (J. Org. Chem. 1975, 40, 1083)

\[
\begin{align*}
&\text{B(OH)}_2
\end{align*}
\]

Obtained in 94% yield; white crystalline solid; mp = 61 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.96 \text{ (1H, dt, } J = 17.5, 6.6 \text{ Hz)}, 5.52 \text{ (1H, dt, } J = 17.6, 1.4 \text{ Hz)}, 2.20 \text{ (2H, m)}, 1.36 \text{ (4H, m)}, 0.90 \text{ (3H, t, } J = 7.4 \text{ Hz}); ^{13}\text{C NMR (100 MHz, CDCl}_3 \delta 157.92, 35.44, 30.46, 22.36, 13.99 \text{ (one signal absent).}

(E)-3-Methyl-1-butenyliaboronic Acid [41c] (J. Org. Chem. 1979, 44, 3374)

\[
\begin{align*}
&\text{B(OH)}_2
\end{align*}
\]

Obtained in 79% yield; white crystalline solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.93 \text{ (1H, dd, } J = 17.8, 6.2 \text{ Hz)}, 5.47 \text{ (1H, dd, } J = 17.7, 1.4 \text{ Hz)}, 2.38 \text{ (1H, m)}, 1.00 \text{ (6H, 2d, } J = 6.7 \text{ Hz}); ^{13}\text{C NMR (100 MHz, CDCl}_3 \delta 164.73, 119.72, 22.26, 22.15 \text{ (one signal absent).}

![Structure](image)

Obtained in 83% yield; white crystalline solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.95 (1H, d, $J = 18.0$ Hz), 5.45 (1H, d, $J = 18$ Hz), 1.02 (9H, 2s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.46, 35.05, 28.79, 28.755 (one signal absent).


![Structure](image)

Obtained in 96% yield; white crystalline solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.88 (1H, dd, $J = 17.9, 6.2$ Hz), 5.46 (1H, dd, $J = 17.9, 1.5$ Hz), 1.0-2.2 (11H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 162.77, 158.15, 43.16, 31.90, 25.92 (one signal absent).


![Structure](image)

Obtained in 76% yield; white crystalline solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77 (1H, d, $J = 18.2$ Hz), 7.25-7.65 (5H, m), 6.34 (1H, d, $J = 18.1$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 152.45, 129.61, 128.84, 127.71, 127.22 (one signal absent).
(E)-2-(4-Methylphenyl)-1-ethenylboronic Acid [41g] (J. Organomet. Chem. 1979, 179, C7)

Obtained in 40% yield; white crystalline solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.75 (1H, d, J = 18.2 Hz), 7.10-7.60 (4H, m), 6.29 (1H, d, J = 18.2 Hz), 2.39 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.13, 139.62, 129.40, 127.52, 127.02, 21.40 (one signal absent).

Di(2-bromoethyl) (E)-1-pentenylboronate [42a]

Obtained in 97% yield; yellow oil; IR (NaCl, thin film) ν 3440, 2960, 1632, 1327, 1114, 1072, 996, 943, 795 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.65 (1H, dt, J = 17.2, 6.6 Hz), 5.47 (1H, dt, J = 17.6, 1.5 Hz), 4.18 (4H, t, J = 6.2 Hz), 3.47 (4H, t, J = 6.3 Hz), 2.13 (2H, m), 1.44 (2H, m), 0.90 (3H, t, J = 7.3 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.33, 63.65, 37.97, 32.24, 21.56, 13.75 (one signal absent).
Di(2-iodoethyl) (E)-1-pentenylboronate [42b]

Obtained in 57% yield; yellow oil; IR (NaCl, thin film) ν 3456, 2957, 1631, 1463, 1311, 993, 795 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.64 (1H, dt, J = 17.5, 6.6 Hz), 5.44 (1H, dt, J = 17.6, 1.4 Hz), 4.10 (4H, t, J = 6.6 Hz), 3.26 (4H, t, J = 6.6 Hz), 2.12 (2H, m), 1.43 (2H, m), 0.89 (3H, t, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 154.38, 64.32, 37.95, 21.56, 13.75, 5.52 (one signal absent); MS (EI) m/z (rel intensity) 353 (15), 251 (19), 239 (28), 199 (14), 155 (100); HRMS (EI) m/z calcd (M⁺) 421.9411, found 421.9431.

Di(3-bromopropyl) (E)-1-pentenylboronate [42c]

Obtained in 83% yield; yellow oil; IR (NaCl, thin film) ν 3432, 2900, 1632, 1478, 1334, 995, 793 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.58 (1H, dt, J = 17.5, 5.7 Hz), 5.51 (1H, dd, J = 17.4, 1.3 Hz), 3.99 (4H, td, J = 5.9, 1.1 Hz), 3.49 (4H, dt, J = 6.6, 1.3 Hz), 2.09 (6H, m), 1.42 (2H, m), 0.89 (3H, dt, J = 7.3, 1.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 153.27, 61.15, 37.95, 34.51, 30.26, 21.61, 13.76 (one signal absent); MS (EI) m/z (rel intensity) 356 (12), 287 (42), 229 (67), 218 (100), 165 (45), 123 (83), 97 (86), 69 (71); HRMS (EI) m/z calcd 355.9981, found 355.9990.
Di(2-bromoethyl) (E)-1-hexenylboronate [42d]

![Chemical Structure]

Obtained in 91% yield; yellow oil; IR (NaCl, thin film) ν 3429, 2958, 1635, 1465, 998, 943, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.65 (1H, dt, J = 17.6, 6.4 Hz), 5.46 (1H, dt, J = 17.4, 1.6 Hz), 4.17 (4H, t, J = 6.4 Hz), 3.46 (4H, t, J = 6.4 Hz), 2.14 (2H, m), 1.34 (4H, m), 0.88 (3H, t, J = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 154.60, 63.65, 35.57, 32.21, 30.51, 22.27, 13.88 (one signal absent); MS (EI) m/z (rel intensity) 259 (77), 215 (60), 151 (60), 109 (98), 107 (100); HRMS (EI) m/z calcld (M⁺) 341.9824, found 341.9843.

Di(2-bromoethyl) 3-methyl-(E)-1-butenyIboronate [42e]

![Chemical Structure]

Obtained in 88% yield; yellow oil; IR (NaCl, thin film) ν 3583, 2961, 1631, 1465, 1317, 1214, 997, 941, 831, 773, 637 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.62 (1H, dd, J = 17.5, 6.4 Hz), 5.41 (1H, dd, J = 17.6, 0.7 Hz), 4.18 (4H, td, J = 5.7, 0.7 Hz), 3.47 (4H, td, J = 5.5, 0.8 Hz), 2.34 (1H, m), 1.01 (3H, d, J = 0.8 Hz), 1.00 (3H, d, J = 0.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 160.95, 63.79, 33.85, 32.41, 21.7 (one signal absent).
**Di(2-bromoethyl) 3,3-dimethyl-(E)-1-butenylboronate [42f]**

![Structure of Di(2-bromoethyl) 3,3-dimethyl-(E)-1-butenylboronate]

Obtained in 91% yield; yellow oil; IR (NaCl, thin film) v 3472, 2960, 1623, 1476, 1316, 1215, 999, 938, 833, 773, 637 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 6.65 (1H, d, \(J = 18\) Hz), 5.36 (1H, d, \(J = 17.9\) Hz), 4.18 (4H, t, \(J = 6.4\) Hz), 3.47 (4H, t, \(J = 6.4\) Hz), 1.01 (9H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 164.30, 63.64, 34.97, 32.22, 28.85 (one signal absent).

**Di(2-bromoethyl) 2-cyclohexyl-(E)-1-ethenylboronate [42h]**

![Structure of Di(2-bromoethyl) 2-cyclohexyl-(E)-1-ethenylboronate]

Obtained in 89% yield; yellow oil; IR (NaCl, thin film) v 3216, 2919, 1634, 1446, 1350, 994, 825 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 6.56 (1H, dd, \(J = 17.5, 6.3\) Hz), 5.38 (1H, dd, \(J = 17.8, 1.2\) Hz), 4.14 (4H, t, \(J = 6.3\) Hz), 3.43 (4H, t, \(J = 6.4\) Hz), 1.0-2.1 (11H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 159.69, 63.59, 43.39, 32.25, 31.84, 26.09, 25.89 (one signal absent).
Di(2-bromoethyl) 2-phenyl-(E)-1-ethenylboronate [42i]

Obtained in 85% yield; yellow oil; IR (NaCl, thin film) ν 3418, 3058, 3023, 2964, 1617, 1576, 1494, 1338, 1213, 1074, 996, 942, 846, 749, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (6H, m), 6.22 (1H, d, J = 18.2 Hz), 4.27 (4H, t, J = 6.2 Hz), 3.52 (4H, t, J = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 149.41, 137.41, 128.96, 128.56, 127.11, 127.01, 63.78, 32.28; MS (EI) m/z (rel intensity) 362 (25), 259 (39), 179 (49), 131 (100), 109 (78), 77 (45); HRMS (EI) m/z calcd (M⁺) 361.9524, found 361.9511.

Di(2-iodoethyl) 2-phenyl-(E)-1-ethenylboronate [42j]

Obtained in 83% yield; colorless oil; IR (NaCl, thin film) ν 3363, 3024, 1616, 1575, 1494, 1342, 1188, 1074, 991, 839, 745, 692 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.40 and 7.50-7.55 (5H, m), 7.46 (1H, d, J = 18.1 Hz), 6.21 (1H, d, J = 18.0 Hz), 4.23 (4H, t, J = 6.6 Hz), 3.34 (4H, t, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 149.51, 137.45, 128.97, 128.57, 127.14, 127.04, 64.48, 5.44; MS (EI) m/z (rel intensity) 456 (21), 329 (14), 225 (39), 155 (100), 131 (41), 77 (20); HRMS (EI) m/z calcd (M⁺) 455.9255, found 455.9243.
**Di(3-bromopropyl) 2-phenyl-(E)-1-ethenylboronate [42k]**

Obtained in 85% yield; colorless oil; IR (NaCl, thin film) v 3383, 3023, 1616, 1576, 1494, 1334, 1036, 912, 750, 693 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.25-7.55 (6H, m), 6.27 (1H, d, \(J = 18.1\) Hz), 4.09 (4H, t, \(J = 5.8\) Hz), 3.54 (4H, t, \(J = 6.6\) Hz), 2.15 (4H, p, \(J = 6.4\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.61, 137.63, 128.80, 128.55, 127.06, 61.33, 34.47, 30.23 (one signal absent); MS (EI) \(m/z\) (rel intensity) 390 (13), 281 (17), 205 (53), 131 (100), 117 (61), 104 (52), 58 (46); HRMS (EI) \(m/z\) calcld (M\(^+\)) 389.9824, found 389.9824.

**Di(2-bromoethyl) 2-(p-methyl-phenyl)-(E)-1-ethenylboronate [42l]**

Obtained in 66% yield; yellow oil; IR (NaCl, thin film) v 3396, 3020, 2965, 2879, 1619, 1569, 1512, 1411, 1340, 1219, 1073, 996, 944, 801, 668, 626 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45-7.10 (m, 6.15 (1H, d, \(J = 18.1\) Hz), 4.26 (4H, t, \(J = 6.4\) Hz), 3.52 (4H, t, \(J = 6.2\) Hz), 2.34 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.41, 139.07, 134.72, 129.28, 127.08, 63.76, 32.27, 21.30 (one signal absent); MS (EI) \(m/z\) (rel intensity) 376 (35), 259 (55), 235 (76), 177(69), 145 (98), 107 (100), 71 (52); HRMS (EI) \(m/z\) calcld (M\(^+\)) 375.9668, found 375.9665.
Di(4-bromobutyl) (E)-1-hexenylboronate [42m]

```
\begin{center}
\includegraphics[width=0.2\textwidth]{di_4_bromobutyl_1_hexenylboronate}
\end{center}
```

Obtained in 100% yield; yellow oil; IR (NaCl, thin film) \( \nu \) 3232, 2956, 1633, 1409, 1342, 1250, 1059, 998, 748, 645 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.55 (1H, dt, \( J = 17.6, 6.6 \) Hz), 5.47 (1H, dt, \( J = 17.2, 1.5 \) Hz), 3.88 (4H, t, \( J = 6.2 \) Hz), 3.43 (4H, t, \( J = 7.0 \) Hz), 2.20-1.20 (14H, m), 0.87 (3H, t, \( J = 7.3 \) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 153.08, 62.48, 35.54, 33.61, 30.60, 30.11, 29.95, 22.27, 13.88 (one signal absent).

Di(5-bromopentyl) (E)-1-hexenylboronate [42n]

```
\begin{center}
\includegraphics[width=0.2\textwidth]{di_5_bromopentyl_1_hexenylboronate}
\end{center}
```

Obtained in 100% yield; yellow oil; IR (NaCl, thin film) \( \nu \) 3303, 2940, 1632, 1343, 1239, 1053, 994, 736, 645 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.55 (1H, dt, \( J = 17.6, 6.6 \) Hz), 5.48 (1H, dt, \( J = 17.5 \) Hz, 1.5 Hz), 3.85 (4H, t, \( J = 6.3 \) Hz), 3.39 (4H, t, \( J = 7.0 \) Hz), 2.20-1.20 (18H, m), 0.87 (3H, t, \( J = 5.5 \) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 152.73, 63.13, 35.56, 33.69, 32.52, 30.74, 30.66, 24.59, 22.30, 13.91 (one signal absent).
(Z)-Hexenylboronic Acid [46a] (J. Org. Chem. 1975, 40, 1083)

Obtained in 76% yield; white crystalline solid; mp = 80 °C; 

$^1$H NMR (400 MHz, CDCl$_3$) 

$\delta$ 6.90 (1H, dt, $J = 17.6, 6.6$ Hz), 5.49 (1H, dt, $J = 17.6, 1.4$ Hz), 2.10 (2H, m), 1.41 (2H, m), 0.90 (3H, t, $J = 7.3$ Hz); 

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.12, 36.52, 21.90, 13.74 (one signal absent).

(Z)-2-Phenyl-1-ethenylboronic Acid [46b] (J. Am. Chem. Soc. 1975, 97, 5608)

Obtained in 70% yield; white crystalline solid; 

$^1$H NMR (400 MHz, CDCl$_3$) 

$\delta$ 7.69 (1H, d, $J = 18.2$ Hz), 7.63-7.20 (5H, m), 6.30 (1H, d, $J = 18.1$ Hz); 

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 151.90, 129.72, 127.87, 127.93, 126.98 (one signal absent).

Di(2-bromoethyl) (Z)-1-hexenylboronate [47a]

Obtained in 90% yield; yellow oil; 

IR (NaCl, thin film) $\nu$ 3431, 2955, 1636, 1462, 996, 945, 771 cm$^{-1}$; 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.64 (1H, dt, $J = 17.6, 6.4$ Hz), 5.43 (1H, dt, $J = 17.4, 1.5$ Hz), 4.15 (4H, t, $J = 6.3$ Hz), 3.47 (4H, t, $J = 6.4$ Hz), 2.14 (2H, m), 1.33 (4H, m), 0.88 (3H, t, $J = 7.2$ Hz); 

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.10, 63.55, 35.24, 32.72, 30.21, 21.98, 13.85 (one signal absent); 

MS (EI) $m/z$ (rel intensity) 259 (77), 215
(60), 151 (60), 109 (98), 107 (100); HRMS (EI) m/z calcd (M⁺) 341.9824, found 341.9836.

**Di(2-bromoethyl) 2-phenyl-(Z)-1-ethenylboronate [47b]**

![Image](attachment:image.png)

Obtained in 89% yield; yellow oil; IR (NaCl, thin film) v 3415, 3060, 3019, 2963, 1619, 1573, 1498, 1338, 1211, 1071, 993, 947, 845, 745 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39 (6H, m), 6.31 (1H, d, J = 17.9 Hz), 4.25 (4H, t, J = 6.1 Hz), 3.51 (4H, t, J = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 149.83, 137.22, 129.24, 128.72, 126.98, 127.13, 63.89, 32.19; MS (EI) m/z (rel intensity) 362 (25), 259 (39), 179 (49), 131 (100), 109 (78), 77 (45); HRMS (EI) m/z calcd (M⁺) 361.9524, found 361.9511.

**Diisopropyl (E)-1-pentenylboronate [49a]**

![Image](attachment:image.png)

Obtained in 90% yield; colorless oil; IR (NaCl, thin film) v 2971, 1633, 1376, 1122, 995, 948, 835, 729, 630 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 6.95 (1H, dt, J = 17.2, 6.6 Hz), 5.68 (1H, dt, J = 17.2, 1.5 Hz), 4.52 (2H, m, J = 5.9 Hz), 2.10 (2H, m), 1.37 (2H, m, J = 7.7 Hz), 1.17 (12H, d, J = 6.2 Hz), 0.84 (3H, t, J = 7.3 Hz); ¹³C NMR (100 MHz, C₆D₆) δ 152.47, 65.25, 38.38, 24.83, 22.14, 13.92 (one signal absent); MS (EI) m/z (rel intensity) 183 (31), 139 (17), 129 (46), 112 (27), 97 (100), 87 (72), 69 (37), 59 (46); HRMS (EI) m/z calcd (M⁺) 198.1791, found 198.1781.
Diisopropyl 2-phenyl-(E)-1-ethenylboronate [49b]

![Structural formula of Diisopropyl 2-phenyl-(E)-1-ethenylboronate]

Obtained in 92% yield; colorless oil; IR (NaCl, thin film) u 3583, 2872, 1618, 1369, 944, 750, 692 cm⁻¹; ¹H NMR (400 MHz, CD₆D₆) δ 7.82 (1H, d, J = 17.6 Hz), 7.00-7.45 (5H, m); 6.40 (1H, d, J = 17.9 Hz); 4.58 (2H, m, J = 6.2 Hz); 1.20 (12H, d, J = 5.6 Hz); ¹³C NMR (100 MHz, CD₆D₆) δ 148.54, 138.64, 128.80, 128.69, 127.34, 65.54, 24.83 (one signal absent); MS (EI) m/z (rel intensity) 232 (37), 175 (13), 146 (47), 132 (100), 105 (34), 59 (43); HRMS (EI) m/z calcd (M⁺) 232.1635, found 232.1641.

1,3-Octanediol [50a] (J. Am. Chem. Soc. 1984, 106, 8193)

![Structural formula of 1,3-Octanediol]

Obtained in 77% yield from [42d] and 72% from [47a]; colorless oil; Rᵢ = 0.40 (10:1 CH₂Cl₂/methanol); ¹H NMR (400 MHz, CDCl₃) δ 3.68-3.54 (3H, m), 3.38 (2H, broad s), 1.69-1.55 (3H, m), 1.47-1.37 (3H, m), 1.36-1.20 (4H, m), 0.87 (3H, t, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 71.83, 62.72, 37.20, 34.08, 28.86, 27.89, 22.68, 14.03.

4-Phenyl-1,3-butanediol [50b] (J. Org. Chem. 1982, 47, 1378)

![Structural formula of 4-Phenyl-1,3-butanediol]

Obtained in 63% yield from [42i], 68% from [42j], and 60% from [47b]; colorless oil; Rᵢ = 0.40 (7:3 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.25 (5H, 2m), 4.07 (1H, m), 3.82 (2H, m), 2.77 (2H, m), 2.60 (2H, broad s), 1.75 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 138.03, 129.37, 128.56, 126.53, 72.91, 61.59, 44.30, 37.74.
1,3-Heptanediol [50c] (J. Org. Chem. 1992, 57, 5990)

![Structure of 1,3-Heptanediol]

Obtained in 81% yield from [42a], 73% yield from [42b]; colorless oil; Rf = 0.35 (10:1 CH2Cl2/methanol); 1H NMR (400 MHz, CDCl3) δ 3.70-3.56 (3H, m), 3.06 (2H, broad s), 1.72-1.57 (3H, m), 1.50-1.28 (5H, m), 0.90 (3H, t, J = 7.1 Hz); 13C NMR (100 MHz, CDCl3) δ 71.50, 62.86, 39.70, 34.42, 29.08, 18.89, 14.07.

4-(4-Methylphenyl)-1,3-butanediol [50d]

![Structure of 4-(4-Methylphenyl)-1,3-butanediol]

Obtained in 65% yield; colorless oil; Rf = 0.50 (10:1 CH2Cl2/methanol); IR (NaCl, thin film) ν 3356, 2922, 1515, 1438, 1054, 809 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.09 (4H, m), 4.03 (1H, m), 3.81 (2H, m), 2.73 (2H, m), 2.61 (1H, broad s), 2.45 (1H, broad s), 2.31 (3H, s), 1.74 (2H, m); 13C NMR (100 MHz, CDCl3) δ 136.13, 134.83, 129.29, 129.26, 73.01, 61.66, 43.87, 37.76, 20.99; HRMS (EI) m/z calcd (M⁺) 180.1159, found 180.1150.

2-(E)-Hex-1-enyl-[1,3,2]-dioxaborolane [51]

![Structure of 2-(E)-Hex-1-enyl-[1,3,2]-dioxaborolane]

Obtained in 97% yield; colorless oil; IR (NaCl, thin film) ν 2964, 1639, 1368, 1120, 995, 839, 727, 622 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 6.93 (1H, dt, J = 17.4, 6.7 Hz), 5.50 (1H, dt, J = 17.5, 1.4 Hz), 4.19 (4H, t, J = 6.0 Hz), 2.23 (2H, m), 1.32 (4H, m), 0.91 (3H, t, J = 7.3 Hz); 13C NMR (100 MHz, CDCl3) δ 157.92, 68.13, 35.44, 30.46, 22.36, 13.99
(one signal absent); MS (EI) m/z (rel intensity) 154 (23), 109 (98), 107 (100), 79 (65); HRMS (EI) m/z calcd (M⁺) 154.0137, found 154.0129.

5-Methyl-1,4-hexanediol [52a] (Tetrahedron 1978, 34, 897)

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Obtained in 83% yield; colorless oil; R_f = 0.46 (10:1 CH₂Cl₂/methanol); \(^1\)H NMR (400 MHz, CDCl₃) δ 3.61 (3H, m), 3.32 (1H, m), 3.15 (1H, broad s), 1.61 (4H, m), 1.39 (1H, m), 0.87 (6H, 2d, J = 3.5 Hz); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 76.68, 62.79, 33.70, 31.01, 29.46, 18.66, 17.50.

5,5-Dimethyl-1,4-hexanediol [52b] (Can. J. Chem. 1972, 50, 1502)

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Obtained in 67% yield; colorless oil; R_f = 0.34 (10:1 CH₂Cl₂/methanol); \(^1\)H NMR (400 MHz, CDCl₃) δ 3.65 (2H, m), 3.18 (1H, dd, J = 10.4, 1.3 Hz), 1.68 (3H, m), 1.29 (1H, m), 0.87 (9H, s); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 80.07, 62.94, 34.96, 30.40, 28.44, 25.68.

4-Cyclohexyl-1,4-butanediol [52c] (Tetrahedron Lett. 1987, 28, 2599)

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Obtained in 77% yield; white crystalline solid; mp = 43 °C; R_f = 0.20 (7:3 EtOAc/hexanes); IR (NaCl, thin film) v 3330, 2851, 1450, 1057, 976, 892, 668 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 3.62 (2H, dp), 3.33 (1H, m), 0.80-1.80 (15H, m); \(^1^3\)C NMR
(100 MHz, CDCl₃) δ 76.09, 62.86, 43.72, 31.08, 29.38, 29.10, 28.03, 26.48, 26.27, 26.14; MS (EI) m/z (rel intensity) 173 (2, MH⁺), 113 (12), 95 (45), 89 (52), 71 (100), 55 (32); HRMS (EI) m/z calcd (MH⁺) 173.1542, found 173.1539.

1,4-Octanediol [52d] (Tetrahedron 1977, 33, 1945)

\[
\text{CH}_2\text{CH}_2\text{OH} \quad \text{CH}_2\text{CH}_2\text{OH}
\]

Obtained in 85% yield; colorless oil; Rₚ = 0.70 (10:1 CH₂Cl₂/methanol); ¹H NMR (400 MHz, CDCl₃) δ 3.71-3.58 (3H, m), 2.40 (2H, broad s), 1.71-1.58 (3H, m), 1.50-1.25 (7H, m), 0.88 (3H, t, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 71.39, 62.38, 36.98, 34.14, 28.83, 27.75, 22.53, 13.84.

6,6-Dimethyl-1,4-heptanediol [52e] (Bull. Chem. Soc. Jpn. 1995, 68, 250)

\[
\text{CH}_2\text{CH}_{2}\text{OH} \quad \text{CH}_2\text{CH}_{2}\text{OH}
\]

Obtained in 81% yield; colorless oil; Rₚ = 0.30 (7:3 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 1.63 (1H, m), 3.50 (2H, m), 2.90 (1H, br s), 1.54 (2H, m), 1.40 (2H, m), 1.25 (2H, m), 0.83 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ 69.25, 62.63, 51.11, 36.57, 30.19, 30.06, 28.90.


\[
\text{Ph} \quad \text{CH}_2\text{CH}_2\text{OH} \quad \text{CH}_2\text{CH}_2\text{OH}
\]

Obtained in 75% yield; colorless oil; Rₚ = 0.45 (7:3 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.25 (5H, m), 3.84 (1H, m), 3.66 (2H, m), 2.80 (1H, dd, J = 13.5, 4.5
Hz), 2.70 (1H, dd, J = 13.5, 8.4 Hz), 1.71 (3H, m), 1.54 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.41, 129.39, 128.60, 126.53, 72.66, 62.94, 44.19, 33.76, 29.25.

5,5-Dimethyl-3-deutero-1,4-hexanediol [55a]

\[
\begin{array}{c}
\text{OH} \\
\text{D} \\
\text{OH}
\end{array}
\]

Obtained in 45% yield together with [55b]; colorless oil; $R_f = 0.40$ (7:3 EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.70 (1H, m), 3.61 (1H, m), 3.18 (1H, d, J = 10.2 Hz), 2.90 (2H br s), 1.68 (2H, m), 1.25 (1H, m), 0.88 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 80.04, 62.91, 34.95, 30.31, 28.31, 28.13, 29.94, 25.68; MS (EI) m/z (rel intensity) 148 (5, MH$^+$), 130 (25), 112 (16), 90 (25), 72 (100), 57 (36); HRMS (EI) m/z calc'd (M$^+$) 147.1374, found 147.1374.

5,5-Dimethyl-4-deutero-1,3-hexanediol [55b]

\[
\begin{array}{c}
\text{OH} \\
\text{D} \\
\text{OH}
\end{array}
\]

Obtained in 45% yield together with [55a]; colorless oil; $R_f = 0.45$ (7:3 EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.96 (1H, m), 3.78 (2H, m), 2.60 (2H, br s), 1.61 (2H, m), 1.37 (1H, dt, J = 8.1, 2.0 Hz), 0.89 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 69.97, 61.76, 40.29, 30.15, 30.06, 51.38, 51.19, 51.01; MS (EI) m/z (rel intensity) 148 (14, MH$^+$), 130 (53), 112 (34), 75 (62), 57 (100); HRMS (Cl, OH$^+$) m/z calc'd (MH$^+$) 148.1439, found 148.1439.

92
Obtained as a mixture in 80% yield; colorless oil; Rf = 0.70 (7:3 EtOAc/hexanes); IR (NaCl, thin film) ν 3345, 2929, 2857, 1448, 976 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.90-3.80 (1H, m), 3.73-3.54 (1H, m), 3.30 (2H, broad s), 1.80-1.10 (17H, m), 0.86 (3H, t, J = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 70.67, 69.81, 69.19, 68.56, 39.87, 39.05, 38.88, 38.29, 38.17, 37.52, 32.93, 32.08, 28.57, 27.98, 27.80, 27.00, 25.28, 24.78, 23.81, 22.69, 21.71, 20.55, 13.99; MS (Cl) m/z (rel. intensity) 201 (35), 183 (53), 165 (100), 125 (60), 98 (100), 81 (98); HRMS (Cl) m/z calcd (MH⁺) 201.1855, found 201.1859.

1,5-Decanediol [60] (J. Chem. Soc. Perkin Trans. 1 2000, 211)

Obtained in 68% yield; colorless oil; Rf = 0.20 (7:3 EtOAc/hexanes); IR (NaCl, thin film) ν 3390, 2930, 2418, 1655, 1466, 1253, 1141, 1055, 664 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.62 (2H, t, J = 6.2 Hz), 3.64-3.59 (1H, m), 1.90 (2H, broad s), 1.60-1.20 (14H, m), 0.86 (3H, t, J = 6.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 71.80, 62.66, 37.48, 36.94, 32.57, 31.86, 25.30, 22.60, 21.78, 13.99; MS (EI) m/z (rel. intensity) 175 (2, MH⁺) 157 (7), 131 (11), 101 (40), 85 (100), 67 (33), 57 (65); HRMS (EI) m/z calcd (MH⁺) 175.1698, found 175.1705.
AIII.3 Synthetic Methods and Compound Data

_Diallyl (α-Haloalkyl)boronates_

**Preparation of Diisopropyl (bromomethyl)boronate [63a]**

A solution of CH₂Br₂ (2.09 g, 12.0 mmol) and triisopropyl borate (1.98 g, 15.0 mmol) in THF (15 mL) was cooled to -78 °C. The solution was stirred vigorously during the addition of n-BuLi (10.0 mmol, 1.6 M in hexanes) via syringe, down the side of the flask, over 0.5 h. Methanesulfonic acid (0.96 g, 10.00 mmol) was then added dropwise over 5 mins, and the solution allowed to warm to room temperature over 20 h. The solvents were then removed by distillation at atmospheric pressure, followed by distillation of the product from the fine lithium methanesulfonate precipitate under reduced pressure (bp = 55 °C at 6 mm Hg).

**Preparation of Diisopropyl (iodomethyl)boronate [63b]**

A solution of CH₂I₂ (3.21 g, 12.0 mmol) and triisopropyl borate (1.98 g, 15.0 mmol) in THF (15 mL) was cooled to -78 °C. The solution was stirred vigorously during the addition of n-BuLi (10.0 mmol, 1.6 M in hexanes) via syringe, down the side of the flask, over 0.5 h. Methanesulfonic acid (0.96 g, 10.00 mmol) was then added dropwise over 5 mins, and the solution allowed to warm to room temperature over 20 h. The solvents were then removed by distillation at atmospheric pressure, followed by distillation of the product from the fine lithium methanesulfonate precipitate under reduced pressure (bp = 55 °C at 6 mm Hg).

**Preparation of Diisopropyl (1-iodopentyl)boronate [63c]**

(1) **Formation of Diisopropyl butylboronate [67]**

To a stirred solution of triisopropyl borate (8.60 mL, 37.3 mmol) in THF (150 mL) at -78 °C was added n-BuLi (40.0 mmol, 2.5 M in hexanes) over a 2 h period using a syringe pump. The mixture was subsequently allowed to warm to rt over 16 h, and then cooled to 0 °C, at which point anhydrous HCl (40.0 mmol, 1.0 M in Et₂O) was added via syringe. After stirring for 30 min, the Et₂O solution was canulated off the LiCl
precipitate, and the organic layer concentrated in vacuo. The residual material was distilled under reduced pressure (bp = 45 °C at 4 mm Hg) to afford the title compound in 80% yield as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.33 (2H, septet, $J = 6.0$ Hz), 1.33-1.20 (4H, m), 1.12 (12H, d, $J = 6.0$ Hz), 0.85 (3H, t, $J = 7.5$ Hz), 0.69 (2H, t, $J = 7.5$ Hz).

(2) Formation of Diisopropyl (1-chloropentyl)boronate [68]$^{31}$

A solution of CH$_2$Cl$_2$ (3.0 mL, 46.6 mmol) in THF (70 mL) was cooled to -100 °C. The solution was stirred vigorously during the addition of n-BuLi (35.5 mmol, 1.6 M in hexanes) via syringe, down the side of the flask, over 0.5 h. Diisopropyl butylboronate [67] (6.00 g, 32.2 mmol) in THF (20 mL) at -78 °C was then added via cannula over 15 mins, and the solution allowed to warm to room temperature over 20 h. The solvents were then removed by distillation at atmospheric pressure, followed by distillation of the residual oil under reduced pressure (bp = 58 °C at 2 mm Hg) to afford the title compound in 76% yield as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.46 (2H, septet, $J = 6.0$ Hz), 3.32 (1H, t, $J = 8.0$ Hz), 1.83-1.72 (2H, m), 1.40-1.22 (4H, m), 1.19-1.10 (12H, 2 d), 0.94-0.85 (3H, t, $J = 7.5$ Hz).

(3) Formation of Diisopropyl (1-iodopentyl)boronate [63c]$^{32}$

The diisopropyl (1-chloropentyl)boronate [68] (2.50 g, 10.7 mmol) was then dissolved in acetone (20 mL), and NaI (4.79 g, 32.0 mmol) added to the solution. Stirring of the resultant mixture at room temperature for 20 h was followed by filtration to remove the NaCl precipitate, and removal of the solvent in vacuo. The residual oil was distilled under reduced pressure (bp 74 °C at 2 mm Hg) to afford the title compound.

Preparation of 2-Bromomethyl-[1,3,2]-dioxaborolane [71]

Diisopropyl (bromomethyl)boronate [63a] (4.44 g, 20.0 mmol) and ethylene glycol (1.24 g, 20.0 mmol) were dissolved in benzene (200 mL) and heated to reflux for 2 h. The isopropanol/benzene azeotrope was subsequently removed by slow distillation at atmospheric pressure, and the residual oil purified by distillation under reduced pressure (bp = 46 °C at 6 mm Hg) to afford the title compound.
Allyl or Propargyl Alcohol Tethering and Subsequent Radical Cyclization

To a solution of diisopropyl (bromomethyl)boronate [63a] (1.00 g, 4.48 mmol) in dry hexanes (45 mL) was added the allyl or propargyl alcohol (8.96 mmol), and the reaction mixture stirred at room temperature for 16 h. The solvent was then removed in vacuo to afford a colorless oil, to which was immediately added benzene (45 mL), TTMSS (1.66 mL, 5.38 mmol), and AIBN (295 mg, 1.79 mmol). The resulting solution was subsequently heated to reflux for 20 h, and after cooling to room temperature, the solvent was removed in vacuo to afford a yellow oil which was taken on to the oxidation stage without further purification.

C-B Bond Oxidation

The crude cyclization product was taken up in a 1:1 mixture of THF/H₂O (20 mL). NaOH (894 mg, 22.4 mmol) was added, followed by the dropwise addition of H₂O₂ (50% w/w in H₂O, 1.52 mL, 22.4 mmol). The reaction mixture was then stirred for 2 h at room temperature, before acidification to ca. pH 7 with 5 N HCl and dilution with CH₂Cl₂ (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to a yellow oil. The pure 1,3-diol was isolated following column chromatography (silica, EtOAc/hexanes).

Diisopropyl (bromomethyl)boronate [63a] (Synlett 1991, 631)

```
\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\text{O}i\text{Pr}};
\node (B) at (-1,0) {\text{Br}};
\node (C) at (0,-0.5) {\text{B}};
\node (D) at (1,-0.5) {\text{O}i\text{Pr}};
\draw (A) -- (B);
\draw (B) -- (C);
\draw (C) -- (D);
\end{tikzpicture}
\end{center}
```

Obtained in 89% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 4.45-4.35 (2H, m), 2.50 (2H, s), 1.19-1.15 (12H, d, J = 6.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 66.21, 24.37 (one signal absent).
Diisopropyl (iodomethyl)boronate [63b] (Tetrahedron Lett. 1997, 38, 765)

Obtained in 85% yield; yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.40-4.35 (2H, m), 2.60 (2H, s), 1.20-1.10 (12H, d, $J$ = 6.1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 66.06, 24.17 (one signal absent).

Diisopropyl (1-iodopentyl)boronate [63c] (J. Org. Chem. 1987, 52, 5116)

Obtained in 95% yield; yellow oil; IR (NaCl, thin film) $\nu$ 3271, 2957, 2823, 2867, 2361, 1699, 1456, 1381, 1106 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.42-4.29 (2H, septet, $J$ = 6.0 Hz), 3.15 (1H, t, $J$ = 7.9 Hz), 1.86-1.76 (2H, m), 1.53-1.21 (4H, m), 1.17-1.11 (12H, 2 d), 0.94-0.84 (3H, t, $J$ = 7.4 Hz).

2-Benzyl-1,3-propanediol [70a] (J. Org. Chem. 1990, 55, 6107)

Obtained in 82% yield; colorless oil; $R_f = 0.30$ (7:3 EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.12 (5H, m), 3.75-3.70 (2H, dd, $J$ = 10.8, 3.9 Hz), 3.64-3.56 (2H, dd, $J$ = 10.7, 3.7 Hz), 3.40-3.20 (2H, br s), 2.59-2.54 (2H, d, $J$ = 7.5 Hz), 2.06-1.96 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.79, 128.91, 128.35, 126.04, 64.88, 43.77, 34.16.
2-Methyl-1,3-propanediol [70b] (*Tetrahedron* 1992, 48, 3827)

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Obtained in 68% yield; colorless oil; \( R_f = 0.30 \) (7:3 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.70-3.50 (4H, m), 2.0-1.8 (1H, m), 0.84-0.80 (3H, d, \( J = 6.9 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 67.12, 37.03, 13.07.


\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Obtained in 70% yield; colorless oil; \( R_f = 0.35 \) (7:3 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.83-3.76 (2H, dd, \( J = 10.9, 3.8 \) Hz), 3.66-3.59 (2H, dd, \( J = 10.6, 7.9 \) Hz), 1.82-1.72 (1H, m), 1.36-1.14 (4H, m), 0.91-0.87 (3H, t, \( J = 7.3 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 66.74, 41.64, 29.88, 20.32, 14.29.


\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Obtained in 75% yield; colorless oil; \( R_f = 0.35 \) (7:3 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.80-3.69 (2H, m), 3.64-3.51 (2H, m), 1.75-1.64 (1H, m), 1.30-1.15 (6H, m), 0.90-0.82 (3H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 66.41, 65.63, 41.83, 29.35, 27.38, 22.89, 13.95.
2-(1-Methylethyl)-1,3-propanediol [70e] (J. Org. Chem. 1991, 56, 6458)

Obtained in 71% yield; colorless oil; R<sub>f</sub> = 0.35 (7:3 EtOAc/hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.10-4.00 (1H, m), 3.80-3.65 (3H, m), 1.78-1.40 (2H, m), 0.92-0.89 (6H, d, J = 6.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 65.94, 42.60, 26.76, 20.30.

2,2-Dimethyl-1,3-propanediol [70f] (J. Org. Chem. 1982, 47, 4702)

Obtained in 43% yield; colorless oil; R<sub>f</sub> = 0.35 (7:3 EtOAc/hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.46 (4H, d, J = 5.3 Hz), 2.93 (2H, br s), 0.87 (6H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 71.34, 36.33, 21.21.

2-Benzyl-2-methyl-1,3-propanediol [70g] (Tetrahedron 1995, 51, 11445)

Obtained in 46% yield; colorless oil; R<sub>f</sub> = 0.40 (7:3 EtOAc/hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.30-7.18 (5H, m), 3.53 (4H, d, J = 3.5 Hz), 2.95 (2H, br s), 2.67 (2H, s) 0.74 (3H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 137.72, 130.54, 127.95, 126.09, 69.83, 40.00, 39.75, 18.48.
(1S*, 2S*)-2-Hydroxymethylcyclohexan-1-ol [70h] (J. Am. Chem. Soc. 1993, 115, 5254)

\[
\begin{align*}
\text{Obtained in 74\% yield; colorless oil; } R_f &= 0.30 \text{ (7:3 EtOAc/hexanes); } \\
^1\text{H NMR (400 MHz, } \text{CDCl}_3) \delta &= 4.15-4.05 \text{ (1H, m), 3.75-3.65 (2H, m), 3.00-2.40 (2H, br s), 1.80-1.20 (9H, m); } \\
^{13}\text{C NMR (100 MHz, } \text{CDCl}_3) \delta &= 69.77, 66.12, 42.31, 32.84, 24.90, 23.49, 20.41.
\end{align*}
\]

(2R*,3S*)-2-Methyl-1,3-butanediol [70i]-anti (J. Org. Chem. 1988, 52, 5909)

\[
\begin{align*}
\text{Obtained in 76\% yield together with [70i]-syn; colorless oil; } R_f &= 0.40 \text{ (7:3 EtOAc/hexanes); } \\
^1\text{H NMR (400 MHz, } \text{CDCl}_3) \delta &= 4.10 \text{ (1H, br s), 4.00-3.90 (1H, m), 3.75 (1H, br s), 3.70-3.44 (2H, m), 1.77-1.68 (1H, m), 1.11 (3H, d, } J = 6.4 \text{ Hz), 0.81 (3H, d, } J = 7.0 \text{ Hz); } \\
^{13}\text{C NMR (100 MHz, } \text{CDCl}_3) \delta &= 73.54, 67.98, 41.60, 21.81, 13.55.
\end{align*}
\]


\[
\begin{align*}
\text{Obtained in 76\% yield together with [70i]-anti; colorless oil; } R_f &= 0.40 \text{ (7:3 EtOAc/hexanes); } \\
^1\text{H NMR (400 MHz, } \text{CDCl}_3) \delta &= 4.10 \text{ (1H, br s), 3.70-3.44 (3H, m), 1.63-1.52 (1H, m), 1.14 (3H, d, } J = 6.2 \text{ Hz), 0.76 (3H, d, } J = 7.0 \text{ Hz); } \\
^{13}\text{C NMR (100 MHz, } \text{CDCl}_3) \delta &= 70.53, 66.34, 40.01, 19.36, 10.70.
\end{align*}
\]
(2R*,3S*)-2,4-Dimethyl-1,3-pentanediol [70j]-anti (Helv. Chim. Acta 1990, 659)

Obtained in 78% yield together with [70j]-syn; colorless oil; \( R_f = 0.40 \) (7:3 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 6 3.67 (2H, m), 3.37 (1H, m), 2.20 (2H, br s), 1.72-1.58 (5H, m), 0.90 (6H, d, J = 6.6 Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) 6 76.83, 63.07, 33.77, 31.05, 29.56, 18.71, 17.37.

(2R*,3S*)-2-Methyl-1,3-heptanediol [70k]-anti (J. Org. Chem. 1991, 55, 1020)

Obtained in 52% yield together with [79k]-syn; colorless oil; \( R_f = 0.40 \) (7:3 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 6 3.75 (1H, m), 3.62 (2H, d, J = 5.5 Hz), 3.10 (2H, br s), 1.78-1.68 (1H, m), 1.50-1.18 (6H, m), 0.88-0.82 (6H, 2t, J = 7.0 and 7.1 Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) 6 75.79, 68.34, 39.27, 33.92, 28.69, 22.99, 14.09, 10.09.

(2S*,3S*)-2-Methyl-1,3-heptanediol [70k]-syn (J. Org. Chem. 1991, 55, 1020)

Obtained in 52% yield together with [70k]-anti; colorless oil; \( R_f = 0.40 \) (7:3 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 6 3.75 (1H, m), 3.62 (2H, d, J = 5.9 Hz), 3.30 (1H, br s), 3.00 (1H, br s), 1.77-1.67 (1H, m), 1.50-1.20 (6H, m), 0.88-0.82 (6H, 2t, 101
$J = 7.3 \text{ Hz and } 7.3 \text{ Hz}$; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 74.18, 66.80, 38.93, 33.58, 28.34, 22.64, 13.97, 9.96.

2-(Bromomethyl)-[1,3,2]-dioxaborolane [71] (Synlett 1991, 631)

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O}
\end{array}
\]

Obtained in 94% yield; colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.22 (4H, t, $J = 6.1$ Hz), 2.47 (2H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 68.07 (one signal absent).


\[
\begin{array}{c}
\text{CH} \\
\text{OH}
\end{array}
\]

Obtained in 62% yield; colorless oil; $R_f = 0.35$ (7:3 EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.12 (2H, t, $J = 1.1$ Hz), 4.22 (4H, s), 1.95 (2H, br s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 147.41, 112.36, 64.76.

2-Ethylidene-1,3-propanediol [72b] (Tetrahedron Lett. 1986, 27, 993)

\[
\begin{array}{c}
\text{CH} \\
\text{OH}
\end{array}
\]

Obtained in 65% yield; colorless oil; $R_f = 0.35$ (7:3 EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.66-5.59 (1H, m), 4.32-4.30 (2H, s), 4.20-4.16 (2H, s), 2.30 (2H, br s), 1.69-1.66 (3H, d, $J = 7.0$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.62, 125.63, 67.65, 59.76, 13.04.

Obtained in 62% yield; colorless oil; R<sub>f</sub> = 0.35 (7:3 EtOAc/hexanes); \( ^1H \) NMR (400 MHz, CDCl<sub>3</sub>) \( \delta \) 5.06 (2H, d, \( J = 8.8 \) Hz), 4.39 (1H, q, \( J = 6.6 \) Hz), 4.25 (1H, d, \( J = 13.2 \) Hz), 4.13 (1H, d, \( J = 13.2 \) Hz), 1.31 (3H, d, \( J = 6.6 \) Hz); \( ^13C \) NMR (100 MHz, CDCl<sub>3</sub>) \( \delta \) 151.04, 111.52, 69.76, 64.00, 22.11.
References (Section A)

(1) For a general review of radical additions, including radical cyclizations, see D.P. Curran, *Synthesis* 1988, 417-439 and 489-513.


(22) A. Chénédé, E. Perrin, E.D. Rekai, P. Sinay, *Synlett* 1994, 420-422.


(47) MP2/6-31G*/UHF/6-31G*. Calculations were performed on a Silicon Graphics Octane with Spartan Version 5.0.3 (Wavefunction Inc., Irvine, CA, 1997). The transition state located for the $\text{S}_\text{H}i$ reaction (B-C-C 65.5°; B-C 1.734, C-C 1.437 Å) shows a single imaginary frequency (688 cm$^{-1}$).


Section B - Potassium Allyl-, Crotyl-, Alkenyl-, and Aryltriﬂuoroborates
Chapter BI - Introduction
BL.1 Allyl- and Crotylboron Additions to Aldehydes

BL.1.1 Introduction

The reaction of triallylborane with aldehydes to form boronic esters of homoallylic alcohols was discovered by Mikhailov and Bubnov in 1964, and the addition of tricrotylborane to formaldehyde was reported soon after. Today, the allylation and crotylation of aldehydes is widely employed in organic synthesis to prepare synthetically versatile homoallylic alcohols. A variety of different allyl- and crotylmetallic compounds have been used for these transformations, including those derived from Li, B, Mg, Al, Si, Ti, Cr, Zn, Zr, In, and Sn, among others. The importance of allyl- and crotylboron compounds in acyclic stereoselection was demonstrated in the mid 1980s, and these reagents are particularly useful because of the high yields and excellent levels of stereocontrol they provide. Conceptual and practical advances relating to the preparation and use of allyl- and crotylboron compounds continue to be reported, attesting to the significant role these reagents play in modern organic synthesis.

BL.1.2 Preparation and General Aspects

Two main classes of allyl- and crotylboron reagents, allyl/crotyl dialkylboranes and allyl/crotyl boronates, have found the widest application in organic synthesis. Both types of reagents are generally prepared by routes involving the reaction of an allylic organometallic species with an electrophilic borylating agent.

Allyldialkylboranes, such as 9-(2-propenyl)-9-borabicyclo[3.3.1]nonane [1], are typically prepared by treating a methoxydialkylborane with allylmagnesium bromide or an allylaluminum reagent (Scheme BL.1.2.1).
Allylboronates such as 2-(2-propenyl)1,3,2-dioxaborolane-4,5-dicarboxylate [2], the tartrate ester of allylboronic acid, are prepared in a similar fashion through the use of allylmagnesium bromide (Scheme BI.1.2.2).§

\[
\begin{align*}
\text{MgBr} & \quad 1) \text{B(OiPr)}_3, \text{Et}_2\text{O}, -78 \degree \text{C} \\
& \quad 2) \text{H}_2\text{O}^+, \text{rt} \\
& \quad 3) \text{DIPT}, \text{rt} 75-85% \\
& \quad \text{COOCH(CH}_3\text{)}_2 \\
& \quad \text{COOCH(CH}_3\text{)}_2 \quad \text{[2]}
\end{align*}
\]

Scheme BI.1.2.2

Unfortunately, like most 2-butenylorganometallics, 2-butenyl(dialkyl)boranes are sensitive to sequential, rapid, and reversible 1,3-boron shifts (1,3-borotropic rearrangements) that result in (E)- to (Z)-olefin isomerization via the 1-methyl-2-propenylboron isomer (Scheme BI.1.2.3).\(^*\)

\[
\begin{align*}
\text{BR}_2 & \quad \text{R}_2\text{B} \\
& \quad \leftrightarrow \text{BR}_2 \quad \leftrightarrow \text{BR}_2
\end{align*}
\]

Scheme BI.1.2.3

From a synthetic standpoint, the major consideration is that this isomerization process, measurable on the NMR time scale, is practically instantaneous on the synthetic operations time scale at temperatures above 25 °C. Consequently, these reagents must generally be prepared and used at temperatures of -78 °C or below in order for this isomerization processes to be suppressed, and even then, many 2-butenyl(dialkyl)boranes are configurationally unstable. Interestingly, the 1,3-borotropic shift is sensitive to steric factors, and configurationally defined 2-butenyl(dialkyl)boranes such as (E)- and (Z)-2-butenyl(diisopinocampheyl)boranes [3] can be prepared at -78 °C. The process initially involves preparation of the required (E)- or (Z)-2-butenylpotassium species, available through metalation of either cis- or trans-2-butene with butyllithium in the presence of.
potassium tert-butoxide, and subsequent attack on methoxy-(diisopinocampheyl)borane (Scheme BI.1.2.4).10

\[
\begin{align*}
\text{R}^1 & = \text{Me}, \text{R}^2 = \text{H} \\
\text{R}^1 & = \text{H}, \text{R}^2 = \text{Me}
\end{align*}
\]

Scheme BI.1.2.4

Unlike 2-butenyl(dialkyl)boranes, 2-butenylboronates have much greater configurational stability as a result of the alkoxy groups, which stabilize the boron atom by resonance, and reduce its' Lewis acidity.11 This stability has allowed for the purification of many 2-butenylboronates by distillation, and analysis of their isomeric purity by capillary GC analysis.

The addition of \((E)\)- and \((Z)\)-2-butenylpotassium species to triisopropyl borate, followed by hydrolysis to the corresponding \((E)\)- or \((Z)\)-2-butenylboronic acid and subsequent treatment with a diol, is the general strategy employed for the synthesis of configurationally defined \((E)\)- and \((Z)\)-2-butenylboronates such as the diisopropyl 2-crotyl-1,3,2-dioxaborolane-4,5-dicarboxylates [4] (Scheme BI.1.2.5).9a

\[
\begin{align*}
\text{R}^1 & = \text{Me}, \text{R}^2 = \text{H} \\
\text{R}^1 & = \text{H}, \text{R}^2 = \text{Me}
\end{align*}
\]

Scheme BI.1.2.5

While simple dimethyl and diisopropyl allyl- and crotylboronates are hydrolytically unstable and undergo protonolysis of the allyl or crotyl moiety very easily,6b they can be converted to more stable, but less reactive boronic esters, such as
pinacol allyl- and crotylboronates. Most of these reagents can be purified by distillation, and stored without substantial degradation for prolonged periods of time under refrigeration and with the exclusion of moisture. They are generally well-behaved synthetic intermediates, and tend to be the allyl/crotylboron reagents used in the majority of synthetic applications.

**BL1.3 Reactivity and Simple Diastereoselectivity**

Allylboron compounds readily undergo addition to aldehydes upon mixing of the two components in an inert solvent. Of the allylboron reagents employed in such processes, allyldialkylboranes have proven to be the most reactive, with addition occurring instantaneously at -78 °C. Allylboronates are generally less reactive, with reactivity dependant on the nature of the diol unit bound to boron. Allylboronates prepared from simple diols show relatively high reactivity, while cyclic boronates prepared from 1,2- or 1,3-diols, such as the commonly employed pinacol allylboronates, are far less reactive. While the pinacol allylboronates are the least reactive members of this class, tartrate ester modified allylboronates show outstanding reactivity at -78 °C.

The increased reactivity of these species is most likely due to the increased electrophilicity of the boron, a phenomenon evident in the relatively deshielded $^{11}$B chemical shifts in these reagents, which fall around $\delta = 37$ ppm. The $^{11}$B chemical shifts for less reactive allylboronates prepared from cyclic diols typically fall around $\delta = 33$ ppm. Steric effects also play a role in influencing the reactivity of diverse species such as pinacol and ethylene glycol allylboronates.

While 2-butenyl(dialkyl)boranes are amongst the most reactive species in the crotylboron reagent family, they do show configurational instability. This phenomenon makes simple 2-butenyl(dialkyl)boranes such as 9-(2-butenyl)-9-borabicyclo[3.3.1]-nonane poorly suited for application in stereoselective reactions with aldehydes since mixtures of anti- and syn- homoallyl alcohols, enriched in the anti-isomer, are usually obtained. The $(E)/(Z)$ isomerization of the 2-butenyl(dialkyl)boranes is, however, suppressed by steric factors as evident in the highly diastereoselective reaction of $(E)$- and $(Z)$-2-butenyl(diisopinocampheyl)boranes [3] with aldehydes at -78 °C. In contrast to the 2-butenyl(dialkyl)boranes, 2-butenylboronates have found widespread
application in acyclic diastereoselective synthesis given the ease of their preparation, configurational stability, and highly stereoselective reactions with aldehydes.\(^5\)

The diastereoselectivity of achiral crotyl(dialkyl)borane and crotylboronate additions to achiral aldehydes is closely dependent on the isomeric purity of the reagent, further emphasizing the need for reagent synthesis to be highly stereoselective. Addition proceeds by way of a chair-like, 6-membered cyclic transition state with predictable transfer of olefinic stereochemistry to \textit{anti} [from \((E)\)-crotylboronates] or \textit{syn} [from \((Z)\)-crotylboronates] relationships about the newly formed C-C bond in the racemic homoallyl alcohol product (Scheme BI.1.3.1).\(^6\)

\[\text{\begin{tikzpicture}[baseline=-0.5ex]
  \node at (0,0) {$\text{B(OR)}_2 + \text{R}^1\text{CHO} \rightarrow \begin{array}{c}
  \text{Me} \\
  \text{H} \\
  \text{OR} \\
  \text{H} \\
  \text{R} \\
  \text{B-OR}
  \end{array}$ \hspace{1cm} \rightarrow \begin{array}{c}
  \text{R}^1 \\
  \text{OH} \\
  \text{anti}
  \end{array}$}
\end{tikzpicture}}\]

\[\text{\begin{tikzpicture}[baseline=-0.5ex]
  \node at (0,0) {$\text{\begin{array}{c}
  \text{H} \\
  \text{OR} \\
  \text{B-OR}
  \end{array}} \hspace{1cm} \rightarrow \begin{array}{c}
  \text{Me} \\
  \text{R} \\
  \text{OH} \\
  \text{syn}
  \end{array}$}
\end{tikzpicture}}\]

\textbf{Scheme BI.1.3.1}

The formation of \textit{syn}-diastereomers from \((E)\)-crotylboronates and \textit{anti}-diastereomers from \((Z)\)-crotylboronates is precluded by the substantially higher energy of the required twist-boat-like transition state, with calculations by Houk showing the chair conformation to be 34 kJ mol\(^{-1}\) more stable.\(^6\) Consequently, only in rare cases does product isomeric purity deviate markedly from reagent isomeric purity.

Several studies have shown that \((E)\)-crotylboronates are generally more reactive than \((Z)\)-crotylboronates.\(^{11,16}\) As a result, kinetic enhancement of reaction diastereoselectivity can be achieved in many cases through the use of the \((E)\)-crotylboronate as the excess reagent. Similarly, it was reported by Schlosser that the diastereoselectivity of \((Z)\)-crotylboronate reactions can be enhanced by first treating the
reagent with 0.05-0.1 equivalents of acetaldehyde in order to consume any contaminating (E)-crotylboronate isomer.\(^\text{17}\)

**BL1.4 Single Asymmetric Induction**

The first chiral allylmetal compounds to be studied were the 4-allyl- and 4-crotyl-1,10,10-trimethyl-6-phenyl-3,5-dioxa-4-boratricyclo[5.2.1.0]decanes developed by Hoffmann (Scheme BL1.4.1).\(^\text{18}\) While the selectivity of 4-allyl-1,10,10-trimethyl-6-phenyl-3,5-dioxa-4-boratricyclo[5.2.1.0]decane [5] with most aldehydes falls in the range of 36-72% e.e. for reactions at -40 °C, the related 4-allyl-3-oxa-5-aza-4-boratricyclo-[5.2.1.0]decane [6] gives substantially better selectivities in the range of 88-96% e.e. at -78 °C.\(^\text{19}\) As important as these chiral directors were to the historical development of this methodology, they are now obsolete for most purposes.\(^\text{6b}\)

\[
\begin{align*}
\text{[5]} & \quad \text{or} \quad \text{[6]} \\
\text{Allyl(diisopinocamphey1)borene [7] consistently gives excellent stereo-} & \text{selectivities falling in the range of 83-96% e.e. when reacted with aldehydes at -78 °C (Scheme BL1.4.2).} & \text{7b,10 At -100 °C, enantioselectivity is further improved to 96-99% e.e.} & \text{20} \\
\text{The homoallyl alcohols obtained from these additions have an (R) absolute configuration} & \text{at the carbinol center if the diisopinocamphey1borene unit is derived from (+)-\alpha-pinene.}
\end{align*}
\]

\[\text{36-72% e.e. [5]} \quad \text{88-96% e.e. [6]}\]
Diisopropyl 2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylate [2] is in the best cases as enantioselective as allyl(diisopinocampheyl)borane [7], showing stereoselectivities in the range of 82-88% e.e. with unhindered aliphatic aldehydes. Unfortunately, in additions to hindered aliphatic, aromatic, and α,β-unsaturated aldehydes, the selectivity falls to 55-75% e.e. (Scheme BL.1.4.3). The reaction is often run in the presence of 4 Å molecular sieves to remove traces of water, which reduces the e.e.’s by hydrolyzing the tartrate boronic ester to give the achiral allyl- or crotylboronic acid. The selectivity in additions to aryl and acetylenic aldehydes can be improved via conversion of the aldehydes to their chromium carbonyl or cobalt carbonyl complexes, respectively.

The enantioselectivity of 2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylate [2] has been rationalized in terms of the lone pair repulsions between the carbonyl oxygens of the tartrate ester and the aldehyde substrate, but such a proposal remains tentative until appropriate calculations are performed.

The use of 2-allyl- and (E)-2-crotyl-4,5-trans-diphenyl-1,3-bis(4-methylphenylsulfonyl)-1,3,2-diazaborolidines has also been reported. In reactions with aldehydes,
extremely high selectivities in the range of 95-97% ee are obtained with 2-allyl-4,5-trans-diphenyl-1,3-bis(4-methylphenylsulfonyl)-1,3,2-diazaborolidine [8] (Scheme BL1.4.4).

![Chemical Structure](image)

Scheme BL1.4.4

The chiral director is an arenesulfonyl derivative of (R,R)-1,2-diphenylethane-1,2-diamine, and can be easily prepared and resolved. With the amine groups sulfonated, the 1,3,2-diazaborolidine derivatives behave much like boronic esters, but have one considerable advantage as chiral directors in the sense that the arenesulfonyl groups are forced into conformations pointing away from the phenyls.

### BL2 Alkenyl- and Arylboron Additions to Enones and Aldehydes

#### BL2.1 Introduction

The use of organometallics as nucleophilic reagents for the construction of C-C bonds is prevalent in synthetic organic chemistry. While the addition of organolithium and organomagnesium reagents to carbonyl groups is a method widely employed for the construction of alcohols, organocopper and organozinc reagents have been extensively investigated in conjugate additions to α,β-unsaturated carbonyl compounds. Although these classes of organometallics have proven indispensable for these transformations, the corresponding reactions of organoboron compounds had not been well developed until recently, when the stability of these reagents and the mild conditions under which they react became attractive features.
BL2.2 Conjugate Additions of Alkenyl- and Arylboron Compounds

The development of alkenyl- and arylboron conjugate additions to a variety of substrates has been marked by the advent of both uncatalyzed and catalyzed process. Indeed, most alkenyl- and all arylboron species lack the necessary reactivity to undergo addition in the absence of a promoter.

BL2.2.1 Uncatalyzed 1,4-Addition Processes

In order to overcome the difficulties associated with the conjugate addition of organocopper derivatives to easily polymerizable \( \alpha,\beta \)-unsaturated ketones, Brown developed the conjugate addition of trialkylboranes to methyl vinyl ketone (MVK), and later extended the scope of this reaction by demonstrating conjugate additions of alkenylboron species to this substrate. \( B \)-Alkenyl-9-borabicyclo[3.3.1]nonanes \([9a]\), readily prepared by hydroboration of acetylenes with 9-borabicyclo[3.3.1]nonane (9-BBN), were shown to undergo 1,4-addition to MVK and related \( \alpha,\beta \)-unsaturated ketones, providing the corresponding \( \gamma,\delta \)-unsaturated ketones following hydrolysis of the initially formed enol borinate intermediate (Scheme BL2.2.1.1). An analogous reaction of \( B \)-alkenyl-9-borabicyclo[3.3.1]nonanes \([9b]\) with 4-methoxy-3-buten-2-one proceeded via a 1,4-addition-elimination pathway to provide conjugated trans, trans-dienones.

\[
\begin{align*}
R^1 & \quad \text{alkyl} \\
R^2 & \quad \text{alkyl, aryl}
\end{align*}
\]

Scheme BL2.2.1.1
Only s-cis enones were found to be reactive in these processes, while s-trans enones such as 2-cyclohexenone and 2-cyclopentenone returned complex mixtures of unidentifiable products. This observation is consistent with a reaction that proceeds via a cyclic 6-membered transition state involving chelation between the boron center of the B-alkenyl-9-borabicyclo[3.3.1]nonane [9] and the oxygen of the ketone carbonyl group (Figure BI.2.2.1.2).

![Figure BI.2.2.1.2 - Transition State for Addition of Alkenylboranes and Alkenylboronates to s-cis α,β-Unsaturated Ketones](image)

Transfer of the vinyl group from boron to carbon occurs in a regio- and stereospecific manner. Consequently, preparation of the B-alkenyl-9-borabicyclo[3.3.1]nonane [9] from a terminal acetylene (R^2 = H) ultimately results in formation of the trans-γ,δ-unsaturated ketone product.

**BI.2.2.2 Catalyzed 1,4-Addition Processes**

The mechanism proposed for the reaction of B-alkenyl-9-borabicyclo[3.3.1]-nonanes [9] with MVK and related α,β-unsaturated ketones was also postulated to occur for the related conjugate addition of alkenylboronic acids [10] and diisopropyl alkenylboronates [11] to α,β-unsaturated ketones reported by Suzuki. Since both alkenylboronic acids [10] and diisopropyl alkenylboronates [11] are less reactive than the corresponding B-alkenyl-9-borabicyclo[3.3.1]nonanes [9], catalysis with boron trifluoride etherate (BF$_3$·OEt$_2$) was required (Scheme BI.2.2.2.1).[^32]
The BF$_3$·OEt$_2$ activates the diisopropyl alkenylboronate [11] (and similarly, the alkenylboronic acid [10]) by fluoride displacement of one alkoxy group from the boron to form an intermediate alkenylfluoroborinate, which then reacts with the $\alpha$, $\beta$-unsaturated ketone via the proposed cyclic 6-membered transition state (see Figure BL2.2.1.2). The use of BF$_3$·OEt$_2$ for the activation of the diisopropyl alkenylboronates [11] does prevent the introduction of Lewis acid-sensitive functionality into the $\alpha$, $\beta$-unsaturated ketone substrate, so a number of other protocols utilizing alternative fluorinating agents such as (N-ethylethanaminato)trifluorosulfur (DAST), NaF, NaBF$_4$, and cyanuric fluoride have been developed to overcome this limitation.$^{33}$

This protocol constitutes an important improvement on the $B$-alkenyl-9-borabicyclo[3.3.1]nonane [9] methodology given that the regio- and stereoselective synthesis of $B$-(1,2- or 2,2-disubstituted-1-alkenyl)-9-borabicyclo[3.3.1]nonanes [9] is generally quite difficult. The corresponding diisopropyl (1,2- or 2,2-disubstituted-1-alkenyl)boronates [11] can be prepared regio- and stereoselectively via either a hydroboration-alkylation sequence with 1-bromo-1-alkynes,$^{34}$ or a haloboration-alkylation sequence with 1-alkynes$^{35}$ respectively. Furthermore, both the alkenylboronic acids [10] and diisopropyl alkenylboronates [11] offer the additional advantage of being more stable than the $B$-alkenyl-9-borabicyclo[3.3.1]nonanes [9].

The lack of $s$-trans $\alpha$, $\beta$-unsaturated ketone reactivity was subsequently addressed by Miyaura with the introduction of nickel(II) acetylacetone [Ni(acac)$_2$] catalyzed alkenyl(disiamyl)borane [12] conjugate additions to $\alpha$, $\beta$-unsaturated ketones and esters (Scheme BL2.2.2.2).$^{36}$
Both $s$-cis and $s$-trans $\alpha,\beta$-unsaturated ketones afforded $\gamma,\delta$-unsaturated ketones in good yields, and with complete retention of alkenyl(disiamyl)borane [12] stereochemistry. As a result, reaction involving a cyclic 6-membered transition state was ruled out, and although the exact course of the addition process remains to be clarified, preliminary studies indicated that the reaction did not involve the formation of a 1-alkenylnickel(II) species and its addition to the $\alpha,\beta$-unsaturated ketone. The mechanism that was proposed involves the oxidative addition of the enone to a nickel(I) species, providing an allylnickel(III) intermediate, followed by transmetallation with the alkenyl-(disiamyl)borane [12] and subsequent reductive elimination from the boron enolate (Scheme BL2.2.2.3).

Scheme BL2.2.2.3

Unlike the conjugate addition of alkenylboron species, the conjugate addition of arylboron derivatives remained entirely unexplored until Uemura’s pioneering report dealing with the palladium(0) catalyzed addition of sodium tetraphenylborate (NaBPh₄) to $\alpha,\beta$-unsaturated ketones and aldehydes. In initial trials with NaBPh₄, it was discovered that a phenyl moiety could be transferred to an $\alpha,\beta$-unsaturated ketone or aldehyde in the
presence of catalytic palladium(II) acetate [Pd(OAc)$_2$] and antimony(III) chloride (SbCl$_3$) (Scheme BI.2.2.2.4).$^{37}$

$$
\begin{align*}
R^1, R^2, R^3 = & \text{H, alkyl, aryl} \\
R^4 = & \text{H, alkyl}
\end{align*}
$$

**Scheme BI.2.2.4**

The conjugate addition was applicable to a variety of $\alpha,\beta$-unsaturated ketones and aldehydes, but the product yield was found to be very dependent on the nature of the substrate as reflected in the wide range of yields obtained.

Since it is known that NaBP$_4$ reacts with acetic acid to give triphenylboron (Ph$_3$B), benzene, and sodium acetate, it was speculated that Ph$_3$B was actually the primary phenylating species in this reaction. Based on this premise, a plausible reaction pathway was proposed (Scheme BI.2.2.2.5).

$$
\begin{align*}
\text{Ph}_3\text{B} & \xrightarrow{\text{Pd(0)}} [\text{PhPdBP}_4] \\
\text{SbCl}_3 & \rightarrow \text{PhPdBP}_4 \\
\text{AcOH} & \rightarrow \text{PhPdBP}_4
\end{align*}
$$

**Scheme BI.2.2.5**

122
Phenylpalladium borane (Ph₂PdBPh₃), initially formed \textit{in situ} by oxidative addition of a C-B bond to palladium(0), adds to the enone to produce an arylpalladium(II) intermediate. Antimony(III) chloride, as a weak Lewis acid, may coordinate to the carbonyl oxygen of this species, and concerted elimination of Ph₂BPDCl can then occur to give an antimony(III) enolate. Protonolysis of the enolate subsequently leads to the β-arylated ketone. The palladium(0) required to propagate the cycle may be regenerated by reductive elimination of Ph₂BCl from Ph₂BPdCl.

Under the same conditions, arylboronic acids [13] can be used as an alternative to NaBPh₄, significantly expanding the scope of these reactions. Although the process is more substrate selective, a wide variety of arylboronic acids [13] is tolerated (Scheme B.2.2.2.6). The reaction is presumed to proceed via a path analogous to that proposed for the tetraphenylborate anion reactions (see Scheme B.2.2.2.5).

![Scheme B.2.2.6](image)

Scheme B.2.2.6

While palladium(0) catalysis opened up the possibility of adding arylboronic acids [13] conjugatively to α,β-unsaturated ketones, the introduction of rhodium(I) catalysis for this purpose dramatically expanded the scope of the reaction. Miyaura was first to report this advance, showing that both alkenyl- [10] and arylboronic acids [13] could be efficiently added to a variety of α,β-unsaturated ketones and aldehydes in the presence of (acetylacetonate)(dicarbonyl)rhodium(I) [Rh(acac)(CO)₂] and 1,4-bis(diphenylphosphino)butane (dppb) (Scheme B.2.2.2.7).
Various arylboronic acids [13] having ortho- and para-substituents smoothly underwent addition, and no appreciable difference was noted between electron-withdrawing and electron-donating group substitution.

These additions were carried out based on previous observations that the organic groups on the boron atom readily displace the RO-Pd bond (RO = acac, AcO, or MeO) in RO-Pd-X under neutral conditions, while the Pd-X bond remains quite inert to such transmetallation with organoboronic acids. The overall transformation was thought to proceed via a catalytic cycle involving transmetallation between a rhodium(I) enolate and the alkenyl- [10] or arylboronic acid [13] to give an alkenyl- or arylrhodium(I) species, followed by insertion of the enone into the alkenyl- or aryl-Rh bond (Scheme BL2.2.2.8).

The direct hydrolysis of the rhodium(I) enolate with water to give a hydroxyrhodium(I) species, and its subsequent transmetallation with the alkenyl- [10] or arylboronic acid [13] is another probable process capable of producing the alkenyl- or arylrhodium(I) intermediate. The overall reaction is sensitive to the steric effect of
substituents at the β-position of the enone (R²), presumably due to the steric hindrance encountered in the coordination and insertion of the enone.

Following the initial report detailing the conjugate addition of alkenyl- [10] and arylboronic acids [13] to α,β-unsaturated ketones and aldehydes, an asymmetric variant of the reaction was also reported by Miyaura. Use of Rh(acac)(CO)₂ with a variety of chiral phosphine ligands resulted in only trace amounts of the desired adducts, but catalysis with a rhodium(I) complex generated in situ by mixing (acetylacetonate)bis-(ethylene)rhodium(I) [Rh(acac)(C₂H₄)₂] and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(S)-binap] in an aqueous solvent proved highly effective (Scheme BI.2.2.2.9).³⁹

\[
\begin{align*}
R'^1B(OH)_2 + R'^2\text{C} = \text{O} + \text{Rh(acac)(C}_2\text{H}_4)_2\text{ (cat.), (S)-binap} & \rightarrow R^1\text{C} = \text{O} + \text{R}^2 \text{ (91-99% e.e.)}
\end{align*}
\]

\[\begin{array}{c}
R'^1 = \text{alkenyl [10] } \\
R'^1 = \text{aryl [13]} \\
R'^2, R'^3 = H, \text{ alkyl, aryl}
\end{array}\]

Scheme BI.2.2.2.9

The scope of the catalytic asymmetric addition is broad, although the yields are variable. Arylboronic acids [13] bearing either electron-withdrawing or electron-donating groups reacted equally well, as did alkenylboronic acids [10].

It was proposed that insertion of the enone's C-C double bond into the alkenyl- or aryl-Rh bond is a key step in the catalytic cycle of this process. In the highly skewed structure known for transition-metal complexes coordinated with a binap ligand, the initial rhodium-(S)-binap intermediate has an open space at the lower part of the vacant coordination site, the upper part being blocked by one of the phenyl rings of the binap ligand (Scheme BI.2.2.2.10).
The olefinic double bond of the enone coordinates to rhodium with its \textit{si} face, and subsequent migratory insertion forms a stereogenic carbon whose absolute configuration is \((S)\). All of the products formed had this absolute configuration resulting from attack on the \textit{si} face of the enone substrates.

Although considerable efforts have been made to develop efficient chiral catalytic systems for asymmetric 1,4-additions, successful examples are rare in terms of enantioselectivity, catalytic activity, and generality,\(^{40}\) making the utility of these facile, asymmetric, rhodium(I)-catalyzed processes so much greater. Furthermore, the alkenyl-\([10]\) and arylboronic acids [13] used are much less reactive towards enones in the absence of a rhodium catalyst than other organometallics used for these transformations such as organomagnesium or organolithium reagents. Consequently, no 1,2-addition to the enones takes place in the presence or absence of the catalyst, making the process entirely chemoselective.

Maintaining that the preparation, isolation, and purification of the organoboronic acids used for asymmetric conjugate additions is not always easy, Hayashi promptly demonstrated the use of alkenylboronates for these processes. He reported that 2-alkenyl-
1,3,2-benzodioxaboroles [14], readily accessible by hydroboration of alkynes with catecholborane, can be also be used successfully in asymmetric 1,4-additions under rhodium(I) catalysis in the presence of binap (Scheme BL2.2.2.11).41

\[
\begin{array}{c}
\text{R}^1, \text{R}^2 = \text{alkyl, aryl} \\
\text{R}^3, \text{R}^4 = \text{alkyl} \\
[14]
\end{array}
\]

Scheme BL2.2.2.11

The presence of a base was necessitated by the decomposition of the 2-alkenyl-1,3,2-benzodioxaboroles [14], which liberates the corresponding alkenylboronic acid and catechol, making the reaction medium acidic. In the absence of a base, selectivity is still high, but yields are substantially eroded.

More recently, analogous asymmetric conjugate additions of arylboronic acids and arylboronates to \(\alpha,\beta\)-unsaturated esters,42 \(\alpha\)-alkenylphosphonates43 and nitroalkenes44 proceeding under similar conditions have been reported.

**BL2.3 Alkenyl- and Arylboron Additions to Carbonyl Compounds**

While the conjugate addition of alkenyl- and arylboron species to a variety of \(\alpha,\beta\)-unsaturated compounds has been reported, comparatively little work has been done regarding their addition to carbonyl groups. Organolithium and organomagnesium compounds have traditionally been the nucleophiles of choice for such transformations, and only recently was the scope of reagents extended to include organoboron compounds.

One of the few reports involving the addition of an alkenylboron species to a carbonyl group was presented by Brown in the late 1970s when he described the addition of \(B\)-alkenyl-9-borabicyclo[3.3.1]nonanes [9b] to aldehydes (Scheme BL2.3.1).45
Yields for the process are extremely variable, and applications of this protocol are rare.\textsuperscript{45b} Considerably more effort has been directed at investigating the addition of arylboron species to carbonyl groups.

Following his pioneering work on the rhodium(I)-catalyzed 1,4-addition of alkenyl- \textsuperscript{[10]} and arylboronic acids \textsuperscript{[13]} to \(\alpha,\beta\)-unsaturated ketones and aldehydes,\textsuperscript{38} Miyaura adapted the reaction conditions for the first rhodium(I)-catalyzed addition of alkenyl- \textsuperscript{[10]} and arylboronic acids \textsuperscript{[13]} to aldehydes. In the presence of \(\text{Rh(acac)}(\text{CO})_2\) and 1,1'-bis(diphenylphosphino)ferrocene (dppf), the alkenyl- \textsuperscript{[10]} and arylboronic acids \textsuperscript{[13]} underwent smooth addition to a variety of aldehydes (Scheme BL2.3.2).\textsuperscript{46}

\begin{equation}
\begin{array}{c}
\text{R}^1\text{B(OH)}_2 + \text{R}^2\text{CHO} \xrightarrow{\text{Rh(acac)}(\text{CO})_2/dppf (cat.)} \text{R}^1\text{OH} \\
\text{R}^1 = \text{alkenyl} \; \text{[10]} \\
\text{R}^1 = \text{aryl} \; \text{[13]} \\
\text{R}^2 = \text{alkyl, aryl}
\end{array}
\end{equation}

Scheme BL2.3.2

The asymmetric version of this protocol employing the monodentate ligand 2-(diphenylphosphanyl)-2'-methoxy-1,1'-binaphthyl [(S)-MeO-MOP] and phenylboronic acid gave rise to moderate asymmetric induction, with \((R)-(+)-(1\text{-naphthyl})\)-(phenyl)methanol formed preferentially from the attack of phenylboronic acid on 1-naphthaldehyde (Scheme BL2.3.3). Chiral bidentate ligands such as 2,3-o-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphanyl)butane (diop) and binap only produced racemic alcohols when tested in the same reaction.
The general reaction was found to be sensitive to electronic effects both in the aldehyde and the boronic acid, suggesting that the mechanism involves the nucleophilic attack of the alkenyl or aryl group on the aldehyde carbonyl. The reaction was facilitated by the presence of an electron-withdrawing group on the aromatic aldehydes, and an electron-donating group on the aryloboronic acids [13]. Only in the exceptional case of 4-nitrobenzaldehyde did the substrate remain entirely unreactive. Additions to aliphatic aldehydes were generally the slowest as their electrophilicity is lower than that of aromatic aldehydes.

It was proposed that the reaction involved transmetallation between the alkenyl-[10] or aryloboronic acid [13] and the RO-Rh species (RO = acac or OH) to give an alkenyl- or aryl-Rh complex, followed by insertion of the aldehyde into the alkenyl- or aryl-Rh bond (Scheme BL2.3.4).
It was also clear from the screening of several phosphine ligands, that the reaction was induced by rhodium-phosphine complexes having a large P-Rh-P angle, which was thought to affect the rate of carbonyl insertion into the Rh-C bond. Monodentate phosphines such as triphenylphosphine (Ph₃P) and tricyclohexylphosphine (Ch₃₃P), along with 1,2-bis(diphenylphosphanyl)ethane (dppe) were totally ineffective ligands, but complexes derived from dppb, diop, and especially dppf exhibited high catalytic activity. A later study of the same reaction encompassing a wider variety of phosphine ligands came to the same conclusions, but a couple of new activity correlations were also discovered. It was found that catalyst activity was also highly dependent on both the basicity and stoichiometry of the phosphine ligands employed.

While the effect of bidentate phosphine ligands was the same as that observed previously, the reaction was also remarkably accelerated by bulky and donating trialkylphosphines such as tri(isopropyl)phosphine (tPr₃P) and tri(tert-butyl)phosphine (tBu₃P) when using 1 equivalent of the phosphine to the rhodium metal. The use of tBu₃P with (acetylaceionate)bis(cyclooctene)rhodium(1) [Rh(acac)(coe)₂] allowed for quantitative conversion even at room temperature (Scheme BL2.3.5), although the addition of excess tBu₃P dropped the yields considerably.

\[
\text{ArB(OH)₂ + R'CHO} \xrightarrow{\text{Rh(acac)(coe)₂/tBu₃P (cat.)}} \text{ArOH} \quad \text{R'} = \text{alkyl, aryl} \quad \text{DME/H₂O, rt} \quad 28-96\%
\]

Scheme BL2.3.5

In contrast to the reactions catalyzed by Rh(acac)(CO)₂/dppf at 80 °C, which were highly sensitive to electronic effects in the aldehydes and the aryloboronic acids [13], Rh(acac)(coe)₂/tBu₃P quantitatively catalyzed the reaction of all representative aldehydes, including previously unreactive nitrobenzaldehydes. Addition to aliphatic aldehydes did remain very slow.

Interestingly, the Rh(acac)(coe)₂/tBu₃P catalytic system yielded the 1,2-addition product in preference to that arising from 1,4-addition when tested in the reaction of phenylboronic acid with cinnamaldehyde (Scheme BL2.3.6).
More recently, Miyaura extended the scope of these rhodium(I)-catalyzed alkenyl- [10] and arylboronic acid [13] additions by conducting analogous reactions with imines. It was shown that $N$-arylsulfonyl aldimines could be readily phenylated with sodium tetraphenylborate under rhodium(I) catalysis,48a while arylboronic acids [13] were added to $N$-sulfonyl aldimines under similar conditions.48b

BL.3 Potassium Organotrifluoroborate Salts

BL.3.1 Introduction

Organotrifluoroborate salts ($\text{RBF}_3\text{M}$, $\text{M} =$ alkali metal), and more generally, compounds having the formula $[\text{R}_n\text{BF}_{n+1}]^-(n \leq 3)$, have been prepared and used sporadically in synthesis throughout the last 60 years. Only recently have extended efforts been made to find novel applications for these underutilized and versatile species.

BL.3.2 Background

In 1940, Fowler reported the preparation of tetraalkylammonium triphenylfluoroborates $(\text{CH}_3)_4\text{NBPh}_3\text{F}$ and $(\text{C}_4\text{H}_9)_4\text{NBPh}_3\text{F}$ by reaction of the triphenylborane-ammonia complex with one equivalent of tetraalkylammonium fluoride, but no yields for the process were given.49 Salts such as these, particularly those having potassium as the counterion, interested researchers in the 1960s during the quest to prepare stable perfluoroalkylated boron derivatives. The first potassium organotrifluoroborate salt to be reported, potassium trifluoromethyltrifluoroborate (CF$_3$BF$_3$K), was prepared by Chambers from trifluoromethyltrimethylstannane and boron trifluoride (Scheme BL.3.2.1, $R =$ CF$_3$).30
Unlike trivalent boron compounds bearing a fluorine atom at the α or β position which have proven to be very unstable as a result of fluorine migration from carbon to boron, \( \text{CF}_3\text{BF}_3\text{K} \) proved to be entirely stable. The stability of the \((\text{CF}_3\text{BF}_3)^-\) ion is attributed to the saturation of the acceptor tendencies of the boron atom, and delocalization of the charge on the ion.

Following this initial report, other potassium organotrifluoroborate salts were synthesized from the corresponding organostannanes; potassium vinyltrifluoroborate and methyltrifluoroborate,\(^{52a}\) potassium pentafluorophenyltrifluoroborate,\(^{52bc}\) potassium (2-trifluoromethylphenyl)trifluoroborate,\(^{52d}\) and potassium (1S)-isopinocampheyltrifluoroborate\(^{52e}\) (see Scheme BL3.2.1). All of these salts were described as being very stable, even at elevated temperatures.

The drawback to this early method of preparing potassium organotrifluoroborate salts was that it necessitated the formation of intermediate organodifluoroboranes. Following preliminary efforts by Thierig and Umland,\(^{53}\) Vedejs reported a significant advance in the direct preparation of preparing potassium organotrifluoroborate salts by showing that the hydroxyl ligands of aryloboronic acids [13] could be displaced with potassium hydrogen difluoride (\(\text{KHF}_2\)) (Scheme BL3.2.2).\(^{54}\)

\[
\text{ArB(OH)}_2 + \text{KHF}_2 \text{ (excess)} \rightarrow \text{KHF}_2 \text{MeOH/H}_2\text{O, rt} \rightarrow \text{ArBF}_3\text{K} \quad \text{[13]} \\
\text{[17]}
\]

Scheme BL3.2.2

The resulting potassium aryltrifluoroborate salts [17] were readily purified by subsequent recrystallization from acetonitrile.
BL3.3 Applications of Potassium Organotrifluoroborate Salts

Until the 1990s, the potassium organotrifluoroborate salts which had been prepared received little attention with regard to their application in organic synthesis. Following his detailed preparation of numerous potassium aryltrifluoroborates [17], Vedejs demonstrated their application as useful precursors for the formation of arylboron difluoride (ArBF₂) Lewis acids. When treated with chlorotrimethylsilane (TMSCI) in acetonitrile, the ArBF₃K salts [17] were found to generate ArBF₂ species, as supported by ¹¹B and ¹⁹F NMR shifts. When the reaction of the ArBF₃K salts [17] and TMSCl was performed in the presence of potential Lewis bases such as amino acid derived amidine carboxylates, the trivalent ArBF₂ Lewis acids were intercepted to form the corresponding oxazaborolidinones (Scheme BL3.3.1). Analogous complexes derived from 1,3-diketones were also easily prepared.

Scheme BL3.3.1

In later work, enolates derived from the oxazaborolidinones were stereoselectively alkylated with methyl iodide, allyl bromide, and benzyl bromide. Such alkylations were possible because the derived enolates maintained asymmetric memory as a result of the stereogenic boron atom’s resistance to equilibration with achiral, trivalent boron species on the enolate alkylaition time scale.

More recently, Petasis showed that fluoroalkenes can be prepared via the electrophilic fluorination of potassium alkenyltrifluoroborates [16]. Reaction of the potassium alkenyltrifluoroborates [16] with one equivalent of Selectfluor™ was found to produce the corresponding alkenyl fluorides as (E)/(Z) mixtures (Scheme BL3.3.2).
Having described the coupling of arenediazonium tetrafluoroborates with sterically unhindered alkenyl- [10] and arylboronic acids [13] under mild conditions, Genêt sought to increase the nucleophilicity of the organoborane moiety in the transmetallation step. It was thought that this could be accomplished through the use of potassium alkenyl- [16] and aryltrifluoroborates [17], and subsequent experimentation confirmed it to be so. Not only were potassium alkenyl- [16] and aryltrifluoroborates [17] found to be suitable nucleophiles in palladium-catalyzed cross-coupling with arenediazonium tetrafluoroborates, but they are actually much more efficient than the corresponding organoboronic acids (Scheme BL3.3.3).  

\[
\text{ArN}_2\text{BF}_4 + \text{RBF}_3\text{K} \xrightarrow{\text{Pd(OAc)}_2\text{(cat.)}} \text{Ar-R}
\]

\[
\begin{align*}
\text{R} & = \text{alkenyl [16],} \\
& \text{aryl [17]} \\
\end{align*}
\]

The higher reactivity of the RBF₃K species, when compared to the corresponding RB(OH)₂, is probably due to the higher nucleophilicity of the organic group on the boron atom. Indeed, fluoride-mediated Suzuki cross-coupling reactions have been reported by Wright, who speculates that the species actually undergoing transmetallation in the reaction is the aryltrifluoroborate anion ArBF₃⁻, and that this transmetallation does occur more readily than transmetallation from fluoroxyboronates such as ArBF₂OH and/or ArBF(OH)₂⁻. Other authors have also confirmed the higher reactivity of potassium

Following introduction and development of the boronic (acid) Mannich reaction by Petasis, Hansen further extended the scope of this protocol by exploiting the higher reactivity of potassium alkenyltrifluoroborate salts [16]. It was shown that upon treatment with trimethylsilyl chloride, potassium alkenyltrifluoroborates [16] such as potassium (E)-2-phenyl-1-ethenyl-trifluoroborate [16a] are easily converted in situ to the corresponding tricoordinate difluoroboranes, which then react efficiently with imines (Scheme BI.3.3.4). These three-component couplings constitute the first known boronic Mannich reactions involving heterocyclic aldehydes, and although the yields are quite low, they do represent an improvement over the yields obtained by Petasis in attempts made with similar substrates.

While potassium alkenyl- [16] and aryltrifluoroborates [17] have now found extensive use in cross-coupling reactions, the synthetic potential of potassium alkyltrifluoroborates [15] has remained almost entirely unexplored. Work by Molander involving the palladium-catalyzed coupling of potassium alkyltrifluoroborates [15] with alkenyl- and aryltosylates stands as the only known example of their application (Scheme BI.3.3.5).
No report on the preparation and/or application of a potassium allyl- [18] or crotyltrifluoroborate salt [19] (Figure BL3.3.6) was known in the literature prior to publication of the work detailed in this thesis.

Figure BL3.3.6 - Potassium Allyl- and Crotyltrifluoroborates

BL4 Potassium Allyl-, Crotyl-, Alkenyl-, and Aryltrifluoroborates

The extension of potassium organotrifluoroborate methodology into the area of organoboron nucleophilic additions is attractive for a number of reasons. Increased practicality and reactivity are amongst the potential benefits.

While the allyl- and crotylboron compounds presently employed for the allylation and crotylation of aldehydes are varied and highly efficient, all are fundamentally unstable. The same can be said of the alkenyl- and arylboron species being used for 1,4-additions to α,β-unsaturated carbonyl compounds, and direct nucleophilic additions to aldehyde carbonyl groups. All of these organoboron reagents, which are either boranes, boronic acids, or boronic esters, vary in their stability, but are ultimately degraded by air and/or moisture. As a result, there is a degree of inconvenience associated with their handling and storage. Indeed, many of the reagents, particularly the oxygen sensitive organoboranes, often require isolated preparations immediately prior to use, precluding the accumulation of any substantial stores.

In addition to handling and storage issues, many of the reagents are often difficult to isolate and purify following preparation. The isolation of boronic acids can be
problematic given their tendency to form trimeric anhydride species and propensity for protodeboronation, while other factors, such as the thermal instability of many boronic esters, prevent purification by distillation.

The use of potassium alkenyl-[16], aryl-[17], allyl-[18], and crotyl-trifluoroborates [19] potentially eliminates all of the isolation, purification, handling, and storage problems encountered with the other classes of organoboron reagents. The potassium organotrifluoroborate salts are highly crystalline solids which precipitate from the reaction medium almost immediately after formation, and their purification by recrystallization is highly effective and trivial to perform. Furthermore, no special precautions such as an inert atmosphere or rigorously dry conditions are required for their handling, given their stability to air and moisture. Storage is also facile, as potassium organotrifluoroborates have shelf-lives on the order of months to years. With these benefits in mind, investigations into the preparation and reaction of potassium alkenyl-[16], aryl-[17], allyl-[18], and crotyltrifluoroborates [19] were initiated.
Chapter BII - Results and Discussion
BII.1 Potassium Allyl- and Crotyltrifluoroborates

BII.1.1 Introduction

Synthetically versatile homoallylic alcohols are typically prepared by the allylation and crotylation of aldehydes.\textsuperscript{3,4} A variety of organometallic reagents has been used for these transformations, but allyl- and crotylboron compounds are particularly useful because of the high yields and excellent levels of stereocontrol they provide (Scheme BII.1.1.1).\textsuperscript{6}

\begin{equation}
\begin{array}{c}
\text{R}^1\text{R}^2\text{B}X_2 \quad \text{R}^3\text{CHO} \quad \text{R}^2\text{OH} \\
\text{[A]} \quad \text{R}^1\text{R}^2\text{BR}_2 \\
\text{R}^1\text{R}^2\text{BF}_3\text{K} \\
\end{array}
\end{equation}

Scheme BII.1.1.1

Of the two main classes of allyl- and crotylboron compounds, allyl/crotyl dialkylboranes [A] and allyl/crotyl boronates [B], only one reagent, allyl pinacol boronate, is commercially available at the present time.\textsuperscript{16a} Other allyl- and crotylboron compounds are usually prepared immediately prior to use due to their sensitivity to air and/or moisture, and the difficulties involved in their subsequent storage and handling.

It has been shown that potassium organotrifluoroborate salts (RBF\textsubscript{3}K), aside from being more readily isolated than the corresponding boronic acids, are also air and water stable.\textsuperscript{50,52,53} Consequently, it was anticipated that the preparation of potassium allyl- [18] and crotyltrifluoroborate salts [19] from allyl- and crotylboron compounds would confer a high degree of air and water stability on these reagents, making their use in synthetic
processes more convenient. Furthermore, because Vedejs had shown that potassium aryltrifluoroborates [17] are useful precursors for the preparation of arylboron difluoride Lewis acids,\textsuperscript{54,55} it was expected that potassium allyl- [18] and crotyltrifluoroborates [19] would be convenient precursors for the \textit{in situ} formation of highly reactive allyl- [21] and crotylboron difluoride [22] species (Figure BII.1.1.2).\textsuperscript{65}

\[ \text{R}^1 = \text{H}, \text{R}^2 = \text{H} \; [21] \]
\[ \text{R}^1 = \text{H}, \text{R}^2 = \text{Me} \; [22a] \]
\[ \text{R}^1 = \text{Me}, \text{R}^2 = \text{H} \; [22b] \]
\[ \text{R}^1 = \text{Me}, \text{R}^2 = \text{Me} \; [23] \]

\textbf{Figure BII.1.1.2 - Allyl- and Crotylboron Difluoride}

While independently prepared 2-propenyldifluoroborane [21] was reported as being entirely unreactive in the attempted allylation of benzaldehyde,\textsuperscript{65b} more recent theoretical calculational data challenge this result,\textsuperscript{65a} as do experimental findings from the research described here.

\textbf{BII.1.2 Allylboron Difluoride}

In 1998, Fujimoto reported a systematic theoretical study on the effects of structure and substituents on reactivity in allylboration processes, and amongst the allylboron reagents examined was allylboron difluoride [21].\textsuperscript{65a} The structure of the complex formed between allylboron difluoride [21] and formaldehyde was calculated at the MP2/6-31G** level of theory (Figure BII.1.2.1).
Interestingly, the activation energy for the reaction of allylboron difluoride [21] with formaldehyde was calculated to be a mere 0.67 kcal mol\(^{-1}\), and as a result, it was speculated that reaction in such a system should take place spontaneously, and instantaneously. When compared to the complex formed between \(B\)-allyl-1,3,2-dioxaborolane and formaldehyde, it also became apparent that the B-O bond distance is much shorter in the allylboron difluoride [21]-formaldehyde complex (1.771 Å versus 2.724 Å). This observation was attributed to boron’s greater electrophilicity arising from the large difference in electronegativity between boron and fluorine, which serves to activate the boron by suppressing electron delocalization from the fluorine atoms to the boron center. As a result, the unoccupied, reactive \(p\)-orbital is effectively localized on the boron, allowing for greater interaction with a potential electron-donor. This phenomenon is similarly exploited in the use of boron trifluoride (BF\(_3\)) as an efficient Lewis acid in organic synthesis.

**BIL1.3 Preparation of Potassium Allyl- and Crotyltrifluoroborates**

The preparation of potassium allyl- [18] and crotyltrifluoroborates [19] was achieved via the corresponding boronic acids in a manner analogous to that used for the synthesis of other potassium trifluoroborate salts. The addition of either allylmagnesium bromide\(^{12}\) or crotylpotassium\(^9\) to trimethyl borate or triisopropyl borate respectively,
followed by acidic hydrolysis, was used to prepare the requisite intermediate allyl- and crotylboronic acids (Scheme BII.1.3.1). Particular care is required to avoid isomerization of \((E)\)-crotyl potassium during the preparation of \((E)\)-crotylboronic acid.

```
\begin{align*}
\text{MgBr} & \quad \text{\textit{BF}_3\text{K}} \\
\text{1) B(O\text{Me})_3, THF, -78 \degree C} \\
\text{2) H}_3\text{O}^+, 0 \degree C} \\
\text{3) KHF}_2, \text{H}_2\text{O, rt, 30 min} \\
\text{\textit{BF}_3\text{K}} & \quad 76\% [18]
\end{align*}
```

\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{1) nBuLi, KOtBu, THF, -78 \degree C} \\
\text{2) B(O\text{Pr})_3, -78 \degree C} \\
\text{3) H}_3\text{O}^+, \text{rt} \\
\text{4) KHF}_2, \text{H}_2\text{O, rt, 30 min} \\
\text{\textit{BF}_3\text{K}} & \quad R^1 = H, R^2 = Me, 70\% [19a] \\
& \quad R^1 = Me, R^2 = H, 71\% [19b] \\
& \quad R^1 = Me, R^2 = Me, 73\% [20]
\end{align*}

Scheme BII.1.3.1

Subsequent conversion of the allyl- and crotylboronic acids to the potassium allyl- [18] and crotyltrifluoroborates [19] was achieved by treatment with aqueous potassium hydrogen fluoride (KHF₂), followed by recrystallization of the resulting precipitate from acetonitrile. Potassium 3-methyl-2-butene-1-trifluoroborate [20] was prepared in an analogous manner. If required, formation of the potassium allyl- [18] and crotyltrifluoroborates [19] (or any other class of potassium organotrifluoroborate salt) can also be achieved by treatment of a corresponding boronate or diazaborane with KHF₂.

The isolated potassium allyl- [18] and crotyltrifluoroborate salts [19] were found to be highly air and water stable solids which could be stored at room temperature in plastic bottles for months without any degradation. In the case of the potassium crotyltrifluoroborates [19], no loss of isomeric purity was observed after prolonged storage.

BII.1.4 Additions of Potassium Allyltrifluoroborate to 4-Nitrobenzaldehyde

In order to generate the highly reactive allyl- [21] and crotylboron difluoride [22] species, a fluorine atom must be stripped from the potassium allyl- [18] or crotyltrifluoroborate [19]. Vedejs reported that this is possible through the use of a weak
Lewis acid such as chlorotrimethylsilane (TMSCI), which he used to generate aryloboron difluoride species from potassium aryltrifluoroborates. Consequently, a number of Lewis acids were screened to evaluate their effectiveness at catalyzing the addition of potassium allyltrifluoroborate (2 equivalents) to 4-nitrobenzaldehyde (Table BII.1.4.1).

\[
\begin{align*}
\text{4-Nitrobenzaldehyde} + \text{Potassium Allyltrifluoroborate} & \xrightarrow{\text{Lewis acid}} \text{Homoallyl Alcohol} \\
\text{CHO} & \xrightarrow{[18]} \text{OH}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(OMe)(_3)</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>AlCl(_3)</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Ti((\text{OPr}))(_4)</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>TMSCI</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>SnCl(_4)</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>BF(_3)OEt(_2)</td>
<td>100</td>
<td>96</td>
</tr>
</tbody>
</table>

Table BII.1.4.1 - Effect of Lewis Acids on the Allylation of 4-Nitrobenzaldehyde With Potassium Allyltrifluoroborate

By conducting the allylation at -78 °C in dichloromethane, it was determined that with 2 equivalents of BF\(_3\)OEt\(_2\), full conversion was achieved within 15 minutes, and the isolated product yield of homoallyl alcohol [24a] was 96%. Other Lewis acids also promoted the reaction, but showed lower degrees of conversion under the same reaction conditions. The fluoride abstraction is presumably an equilibrium process requiring a strong Lewis acid to produce an appreciable concentration of the allyloboron difluoride [21] species, which then attacks the aldehyde carbonyl. Reaction of the potassium allyltrifluoroborate [18] does not occur within 15 minutes (or any length of time) in the absence of a Lewis acid, even at temperature at or above 0 °C.
Interestingly, trace amounts of allylation product [24a] could, however, be detected in the absence of a Lewis acid catalyst following prolonged reaction at room temperature in a Pyrex® glass vessel. Presumably, the vessel’s borosilicate glass acts as a very weak Lewis acid, bringing about the slow reaction. Indeed, use of the potassium allyl- [18] and crotyltrifluoroborate salts [19] in borosilicate glassware results in a permanent etching of the glass surface following irreversible deposition of fluoride ions onto the glass matrix.

In general, the need for the introduction of an external Lewis acid into the reaction mixture distinguishes the reactivity of the potassium allyl- [18] and crotyltrifluoroborate salts [19] from that of most allyl- and crotylboron compounds, which do not require activation in order to undergo addition in organic solvents.

Having established BF$_3$·OEt$_2$ as the most efficient promoter for the allylation process, the catalytic use of this Lewis acid was investigated. Use of catalytic BF$_3$·OEt$_2$ (5 mol%) at -78 °C in dichloromethane produced only trace amounts of the addition product [24a], but reaction at room temperature did proceed with full conversion after 3 h. The 95% isolated yield of homoallyl alcohol [24a] was comparable to that obtained through the use of stoichiometric BF$_3$·OEt$_2$ at -78 °C. Use of stoichiometric BF$_3$·OEt$_2$ at room temperature proved detrimental, seemingly facilitating the decomposition of the product homoallyl alcohol [24a].

**BII.1.5 Additions of Potassium Allyltrifluoroborate to Aldehydes**

Using the two available allylation protocols, stoichiometric BF$_3$·OEt$_2$ (2 equivalents) at -78 °C in dichloromethane over 15 mins (Method A) and catalytic BF$_3$·OEt$_2$ (5 mol%) at room temperature in dichloromethane over 3-6 h (Method B), a variety of substituted and unsubstituted aromatic and aliphatic aldehydes were allylated with potassium allyltrifluoroborate [18] (2 equivalents) to give the homoallylic alcohols [24] in high yields (Table BII.1.5.1). The isolated product yields were uniformly high for both protocols, and all functional groups on the aldehydes were tolerated equally well.
Table BIL.1.5.1 - BF₃·OEt₂ Catalyzed Allylation of Aldehydes With Potassium Allyltrifluoroborate

Analogous additions of both potassium allyltrifluoroborate [18] and the potassium crotyltrifluoroborates [19] to a variety of substituted and unsubstituted aryl and alkyl ketones were also carried out using Method B. While Method A seemingly led to rapid decomposition of the tertiary alcohol products, Method B allowed for their isolation in consistently high yields. Extensive findings from these studies are reported elsewhere.[57]

BIL.1.6 Addition of Potassium 3-Methyl-2-butenyltrifluoroborate to Aldehydes

The addition of potassium 3-methyl-2-butenyltrifluoroborate [20] to a variety of substituted and unsubstituted aryl and alkyl aldehydes using both Method A and Method B was similarly successful (Table BII.1.6.1).
\[
\begin{align*}
R^1 \text{CHO} + & \quad \text{Method A or B} \\
[20] & \quad \text{BF}_3 \text{OEt}_2 \\
[25] & \quad \text{OH} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>R^1</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n-\text{C}<em>7\text{H}</em>{15})</td>
<td>25a</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>Ph</td>
<td>25b</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>4-MeOC_6H_4</td>
<td>25c</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>4-NO_2C_6H_4</td>
<td>25d</td>
<td>90</td>
<td>89</td>
</tr>
</tbody>
</table>

\(^a\text{BF}_3\text{OEt}_2\) (2.0 equiv.), [20] (2.0 equiv.), \(\text{CH}_2\text{Cl}_2\), \(-78^\circ\text{C}\), 15 mins.  
\(^b\text{BF}_3\text{OEt}_2\) (0.05 equiv.), [20] (2.0 equiv.), \(\text{CH}_2\text{Cl}_2\), rt, 3-6 h.

Table BIL1.6.1 - BF\(_3\)OEt\(_2\) Catalyzed Allylation of Aldehydes With Potassium 3-Methyl-2-butenyltrifluoroborate

Yields of the homoallyl alcohols [25] were comparable to those obtained from the corresponding potassium allyltrifluoroborate [18] reactions, and uniformly high irrespective of whether Method A or Method B was used.

**BIL1.7 Additions of Potassium Crotyltrifluoroborates to Aldehydes**

Crotylation of substituted and unsubstituted aryl and alkyl aldehydes using potassium crotyltrifluoroborates [19] was also highly efficient using both Method A and Method B (Table BIL1.7.1). Homoallyl alcohols [26] were obtained with excellent levels of stereocontrol, and in uniformly high yields.
Table BII.1.7.1 - Crotylation of Aldehydes With Potassium Crotyltrifluoroborates

The potassium (Z)-crotyltrifluoroborate [19a] consistently gave rise to the syn diastereomer, while the potassium (E)-crotyltrifluoroborate [19b] gave the expected anti product in all cases. Both of these observations are consistent with the addition of a crotylboron difluoride [22] (tricoordinate boron species) to the aldehyde via a Zimmerman-Traxler-like (closed) transition state (Scheme BII.1.7.2). It is not clear why the reaction of both potassium crotyltrifluoroborates [19] with p-anisaldehyde resulted in marginally lower diastereomeric ratios when compared to the reaction of these reagents with the other substrates.
While it was not possible to observe the proposed crotylboron difluoride intermediates [22] directly by $^{11}$B NMR spectroscopy of the reaction mixture, it was possible to independently generate (Z)-crotylboron difluoride [22a] by the addition of BF$_3$·OEt$_2$ (1 equivalent) to potassium (Z)-crotyl trifluoroborate [19a] in deuterated acetonitrile (CD$_3$CN) at room temperature. The observed $^{11}$B NMR resonance of this solution (Z)-crotylboron difluoride species [22a] (CD$_3$CN, broad singlet, $\delta = 24.6$ ppm) was comparable to that reported for pure (Z)-crotylboron difluoride [22a] (CDCl$_3$, triplet, $\delta = 27.7$ ppm, $J = 80.6$ Hz). The collapse of the $^{11}$B-$^{19}$F splitting evident in $^{11}$B NMR of the solution (Z)-crotylboron difluoride species [22a] is attributable to the species' rapid exchange of fluoride with the (Z)-crotyl trifluoroborate anion also present in solution. This process, initially observed by Vedejs in work with aryloboron difluoride species, serves to average the fluorine environment and the $^{11}$B chemical shifts.

**BII.1.8 Acid Catalyzed Addition of Potassium Allyltrifluoroborate to Aldehydes**

Remarkably, the addition of potassium allyltrifluoroborate [18] to a variety of aldehydes is also catalyzed by stoichiometric amounts of aqueous hydrochloric acid (HCl) in methanol solution. While reaction with 1 equivalent of HCl fails to give full conversion (only about 28-55% in selected trials) to the product homoallyl alcohol [24] after 1 h, the use of 2 equivalents results in quantitative conversion of the starting aldehyde in the same time period (Table BII.1.8.1).
The isolated homoallyl alcohol [24] yields were found to be consistently high, and comparable to yields obtained from both the stoichiometric and catalytic BF$_3$OEt$_2$ mediated processes. Use of the HCl catalysis protocol also provides a viable alternative for the allylation and crotylation of potentially Lewis acid sensitive substrates with potassium allyl- [18] and crotyl trifluoroborates [19].

It is suspected that in the HCl catalyzed process, the potassium allyl trifluoroborate [18] is acting as a precursor for the *in situ* generation of dimethyl allyl boronate [27] in the methanolic solvent, which then reacts rapidly with the aldehyde (Scheme BII.1.8.2).

Dimethyl allyl boronate [27] is observable by $^{11}$B NMR spectroscopy if potassium allyl trifluoroborate [18] is stirred in methanol with 2 equivalents of aqueous HCl for 0.5 h. In addition to dimethyl allyl boronate [27] ($\delta = 30.50$ ppm), potassium
allyltrifluoroborate [18] (δ = 4.61 ppm) is also visible, as is a trace amount of B(OMe)_3 (δ = 18.81 ppm) which presumably originates from protodeboronation of the potassium allyltrifluoroborate [18] reagent. The ratio of dimethyl allylboronate [27] to potassium allyltrifluoroborate [18] at this stage is approximately 6:1, as judged by the relative heights of the respective ¹¹B NMR peaks. If the solution is stirred for 1.5 h, the potassium allyltrifluoroborate [18] is converted fully to dimethyl allylboronate [27], and a significant increase in the amount of B(OMe)_3 is also observed such that the dimethyl allylboronate [27] to B(OMe)_3 ratio is now approximately 5:1. After 4 h, the dimethyl allylboronate [27] to B(OMe)_3 ratio becomes 3:1 as more of the dimethyl allylboronate [27] is protodeboronated. The mechanism by which HCl facilitates the conversion of potassium allyltrifluoroborate [18] to dimethyl allylboronate [27] is unclear, although the H_3O^+ facilitated removal of F^- from potassium allyltrifluoroborate [18] is highly suspected.

BII.1.9 Applications of Potassium Allyl- and Crotyltrifluoroborates

While the allylation and crotylation of simple alkyl and aryl aldehydes with potassium allyl- [18] and crotyltrifluoroborates [19] has been exhaustively demonstrated under both Lewis acid and aqueous acid catalysis, reaction of these reagents with other suitable electrophiles (such as imines) and the development of alternative catalytic protocols stand as attractive goals for future investigations. Development of a protocol for the asymmetric addition of the potassium allyl- [18] and crotyltrifluoroborates [19] to aldehydes is also highly desirable, and the established HCl catalysis protocol may provide a foundation for such development by illustrating the potential for in situ installation of a chiral director onto the boron reagent. To this point, only very limited steps have been taken towards these goals, and the results of those experiments are not reported here for lack of real developments. To date, only one alternative application of the potassium allyl- [18] and crotyltrifluoroborate reagents [19] has been reported.

Following publication of the potassium allyl- [18] and crotyltrifluoroborate [19] methodology (see Appendix D), Lautens demonstrated the addition of these salts to a variety of 2-vinyloxiranes (Scheme BII.1.9.1).
This protocol ingeniously utilizes the BF$_3$·OEt$_2$ required for catalysis of the allylation process for initial rearrangement of the 2-vinylxirane to the corresponding terminal aldehyde, which is subsequently attacked by the potassium allyl- [18] or crotyltrifluoroborate [19].
BII.2 Potassium Alkenyl- and Aryltrifluoroborates

BII.2.1 Introduction

Following recent reports by Miyaura and Hayashi detailing the rhodium(I)-catalyzed nucleophilic addition of alkenyl- and arylboronic acids to a variety of unsaturated substrates, it was anticipated that the corresponding potassium alkenyl- [16] and aryltrifluoroborates [17] would serve as more reactive boron reagents in these transformations. When compared to the boronic acids, additional advantages of these reagents such as their greater stability to air and water, ease of isolation, and the avoidance of trimeric anhydride formation made their potential use even more attractive.

Application of potassium alkenyl- [16] and aryltrifluoroborates [17] as nucleophiles in rhodium(I)-catalyzed processes was first considered for additions to enones and aldehydes as a strategy for extending the scope of these transformations (Scheme BII.2.1.1).

![Scheme BII.2.1.1](image)

Based on literature protocol, formation of the requisite potassium alkenyl- [16] and aryltrifluoroborates [17] was expected to be trivial. Furthermore, the previously reported rhodium(I)-catalyzed additions of alkenyl- [10] and arylboronic acids [13] to enones and aldehydes would serve as both a useful guide for the development of conditions, and a standard by which to gauge the comparative reactivity of the potassium alkenyl- [16] and aryltrifluoroborates [17] in these processes.
BII.2.2 Preparation of Potassium Alkenyl- and Aryltrifluoroborates

All of the potassium alkenyl- [16] and aryltrifluoroborate reagents [17] employed in the rhodium(I)-catalyzed addition processes were prepared with relative ease and efficiency from the corresponding alkenyl- [10] and arylboronic acids [13].

The requisite \((E)\)-alkenylboronic acids [10] were prepared in high yield via hydroboration of the corresponding terminal alkyne (Scheme BII.2.2.1). Dibromoborane-dimethyl sulfide complex \((\text{HBB}_2\text{SMe}_2)^{69}\) was chosen for the hydroboration of 1-hexyne, while catecholborane\(^{70}\) was used for the hydroboration of phenylacetylene.

Conversion of the \((E)\)-alkenylboronic acids [10] to the desired potassium \((E)\)
alkenyltrifluoroborates [16] was then accomplished by treatment with aqueous \(\text{KHF}_2\) as first described by Vedejs.\(^{54,55}\) Subsequent refrigeration of the reaction mixture to ensure near quantitative precipitation of the crystalline products was followed by recrystallization of the crude salts from acetonitrile, providing pure quantities of the potassium \((E)\)-alkenyltrifluoroborates [16] in high yield.

The commercial availability of several requisite arylboronic acids [13] precluded the need for their independent synthesis. Following treatment of the purchased arylboronic acids [13] with aqueous \(\text{KHF}_2\), refrigeration, and recrystallization from acetonitrile, a variety of the corresponding potassium aryltrifluoroborates [17] was obtained in yields ranging from modest to quantitative (Table BII.2.2.2).
\[
\begin{array}{ccc}
\text{ArB(OH)}_2 & \xrightarrow{\text{H}_2\text{O}, \text{rt.}} & \text{KHF}_2 \\
[13] & & 30 \text{ min} \\
& & \xrightarrow{\text{ArBF}_3\text{K}} \\
[17]
\end{array}
\]

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td>Ph</td>
<td>quant.</td>
</tr>
<tr>
<td>17b</td>
<td>3-NO\text{C}_6\text{H}_4</td>
<td>85</td>
</tr>
<tr>
<td>17c</td>
<td>4-Ac\text{C}_6\text{H}_4</td>
<td>32</td>
</tr>
<tr>
<td>17d</td>
<td>4-MeOC\text{C}_6\text{H}_4</td>
<td>71</td>
</tr>
<tr>
<td>17e</td>
<td>3-Thiophene</td>
<td>quant.</td>
</tr>
</tbody>
</table>

Table BIL2.2.2 - Potassium Aryltrifluoroborates

The potassium alkenyl- [16] and aryltrifluoroborates [17] were stored with no special precautions in plastic containers at room temperature for prolonged periods of time. Even after months of storage, no degradation was observable by \(^1\text{H}, \text{\textsuperscript{13}C,}\) and \(^{11}\text{B}\) NMR analysis of the reagents.

**BIL2.3 Rhodium(I)-Catalyzed Additions to Enones**

**BIL2.3.1 Initial Rhodium(I)-Catalyzed Additions to MVK**

In order to focus on the effect of the potassium alkenyl- [16] and aryltrifluorobororate reagents [17] on the conjugate addition to enones, the same catalyst and reaction conditions as those reported by Miyaura for the conjugate addition of alkenyl- [10] and arylboronic acids [13] to enones were selected for initial studies. Potassium phenyltrifluoroborate [17a] and methyl vinyl ketone (MVK) were chosen as representative substrates.

By using 2 equivalents of potassium phenyltrifluoroborate [17a] in the presence of Rh(acac)(CO)\(_2\) (3 mol %) and 1,4-bis(diphenylphosphino)-butane (dppb) (3 mol %), conjugate addition to MVK proceeded with full conversion after 16 h in MeOH/water (6:1) at 50 °C. The relative rate of reaction for potassium phenyltrifluoroborate [17a] was greater than that for phenylboronic acid under otherwise identical conditions, as
determined by quench of the reaction and isolation of the ketone [28a] at 1, 4, 8, and 16 h (Table BII.2.3.1.1).

Table BII.2.3.1.1 - Rhodium(I)-Catalyzed Additions of Potassium Phenyltrifluoroborate and Phenylboronic Acid to MVK

<table>
<thead>
<tr>
<th>t (h)</th>
<th>Yield (%) of [28a]a</th>
<th>PhBF₃K [17a]</th>
<th>PhB(OH)₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>79</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>91</td>
<td>82b</td>
<td></td>
</tr>
</tbody>
</table>

a Isolated yields. b 99% GC yield reported in reference (38).

This comparative study demonstrates the greater reactivity of the potassium phenyltrifluoroborate salt [17a], and provided the impetus for further investigations into the general reactivity of other potassium alkenyl- [16] and aryltrifluoroborates [17].

BII.2.3.2 Optimization of Reaction Conditions

Following the successful conjugate addition of potassium phenyltrifluoroborate [17a] to MVK, the effect of reaction parameters on the overall process was systematically examined in order to optimize the reaction conditions.

Reducing the amount of potassium phenyltrifluoroborate [17a] to 1.1 equivalents proved detrimental, producing a modest drop in the isolated yield of ketone [28a] to 82% after 16 h. Reaction using a less expensive, commercially available rhodium(I) source such as Wilkinson's catalyst [Rh(PPh₃)₂Cl], 3 mol % resulted in only a 42% isolated yield of [28a] after 16 h, while use of a cheaper, monodentate phosphine ligand, triphenylphosphine (PPh₃, 2 equivalents), dropped the isolated yield of [28a] slightly to
84% after 16 h. Reaction did not proceed at all in the absence of a phosphine ligand. A decrease in catalyst loading was also found to have little impact on the process, with 1 mol% Rh(acac)(CO)₂ returning an 89% yield of [28a].

When the reaction was conducted in dry MeOH or with 10 equivalents of water, the reaction was slower, with product [28a] to starting material ratios at 16 h of 25:75 and 80:20, respectively. Significantly, when conducted in water, addition proceeded as efficiently as in the DME/water solvent system, providing [28a] in 90% yield. It was also possible to carry out the reaction in a THF/water solvent system, but the observed degree of conversion after 16 h was only 65%.

BII.2.3.3 Overview and Analysis of Conjugate Additions to Enones

A variety of potassium alkenyl- [16] and aryltrifluoroborates [17] were found to react efficiently with MVK using the standard protocol, giving comparable isolated yields of the ketone products [28] (Table BII.2.3.3.1). Particularly noteworthy is the addition of electron-deficient potassium 3-nitrophenyltrifluoroborate [17b] to MVK given that the corresponding 3-nitrophenylboronic acid does not add under otherwise identical conditions. This observation further demonstrates the greater reactivity of the tetracoordinate trifluoroborate salts in these conjugate additions.
<table>
<thead>
<tr>
<th>Reagent</th>
<th>R¹</th>
<th>Ketone</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td>Ph</td>
<td>28a</td>
<td>91</td>
</tr>
<tr>
<td>17b</td>
<td>3-NO₂C₆H₄</td>
<td>28b</td>
<td>59</td>
</tr>
<tr>
<td>17c</td>
<td>3-AcC₆H₄</td>
<td>28c</td>
<td>98</td>
</tr>
<tr>
<td>17e</td>
<td>3-Thiophene</td>
<td>28d</td>
<td>quant.</td>
</tr>
<tr>
<td>16a</td>
<td>(E)-2-Phenylethenyl</td>
<td>28e</td>
<td>quant.</td>
</tr>
<tr>
<td>16b</td>
<td>(E)-Hexenyl</td>
<td>28f</td>
<td>90</td>
</tr>
</tbody>
</table>

Table BII.2.3.3.1 - Rhodium(I)-Catalyzed Additions of Potassium Alkenyl- and Aryltrifluoroborates to MVK

Having established the feasibility of rhodium(I)-catalyzed addition of potassium alkenyl- [16] and aryltrifluoroborates [17] to MVK, the scope of the processes was briefly studied with terminally monosubstituted and cyclic enone substrates. Under the optimized conditions, cyclohexenone and (E)-4-phenyl-3-buten-2-one reacted with potassium 3-thiophenetrifluoroborate [17e] and potassium phenyltrifluoroborate [17a], respectively, to furnish the substituted ketones [28g] and [28h] in high yields (Scheme BII.2.3.3.2).

![Scheme BII.2.3.3.2]
Given the effectiveness of this addition protocol with enones, conjugate additions to other \( \alpha,\beta \)-unsaturated substrates were considered. While the addition of potassium phenyltrifluoroborate [17a] to methyl acrylate failed under the optimized conditions, addition to acrolein was found to proceed in high yield (Scheme BII.2.3.3.3).

![Scheme BII.2.3.3.3](image)

**BII.2.3.4 Room Temperature Conjugate Additions**

Although it was not possible to conduct the conjugate addition of potassium alkenyl-or aryltrifluoroborates [17] to enones at room temperature using the Rh(acac)(CO)\(_2\)/dppb catalytic system, use of a Rh(acac)(CO)\(_2\)/tBu\(_3\)P catalytic system did drive the reaction. While Miyaura demonstrated the effectiveness of the Rh(acac)(coe)\(_2\)/tBu\(_3\)P system for the addition of alkenyl- [10] and arylboronic acids [13] to aldehydes at room temperature,\(^{47}\) use of these conditions was never extended to the conjugate addition of alkenyl- [10] and arylboronic acids [13] to enones. Indeed, when the addition of phenylboronic acid to MVK and \((E)-4\)-phenyl-3-buten-2-one was attempted using Rh(acac)(CO)\(_2\)/tBu\(_3\)P, only a small amount of the ketones [28a] and [28h] was obtained (Scheme BII.2.3.4.1). Use of potassium phenyltrifluoroborate [17a], however, afforded ketones [28a] and [28h] in yields comparable to those obtained under the high temperature conditions.
The Rh(acac)(CO)$_2$/tBu$_3$P catalyzed room temperature conjugate addition of potassium phenyltrifluoroborate [17a] to MVK and (E)-4-phenyl-3-buten-2-one was equally effective with water as the exclusive solvent.

**BII.2.3.5 Mechanism of Conjugate Additions to Enones**

A mechanism totally analogous to that reported by Miyaura for the rhodium(I)-catalyzed addition of alkenyl- [10] and arylboronic acids [13] to enones$^{38,39}$ cannot be assumed for the potassium alkenyl- [16] and aryltrifluoroborate [17] conjugate additions given the critical role of water in these later processes. While Miyaura suggests that transmetallation takes place between a rhodium(I) enolate and the alkenyl- [10] or arylboronic acid [13] involved to give an alkenyl- or arylrhodium(I) species, the transmetallation of a rhodium(I) enolate with a potassium alkenyl- [16] or aryltrifluoroborate [17] cannot possibly be operating in the potassium alkenyl- [16] and aryltrifluoroborate [17] conjugate additions. If such a transmetallation were taking place, water would not be required to promote the reaction. Consequently, it is more plausible to speculate that the rhodium(I) enolate is directly hydrolyzed by water to give a hydroxyrhodium(I) species, which subsequently undergoes transmetallation with the potassium alkenyl- [16] or aryltrifluoroborate [17] to provide an alkenyl- or arylrhodium(I) intermediate. This is followed by insertion of the enone into the alkenyl-Rh or aryl-Rh bond (Scheme BII.2.3.5.1).
BIL2.3.6 Attempted Asymmetric Conjugate Addition

Efforts at adding potassium alkenyl- [16] and aryltrifluoroborate salts [17] conjugatively to enones in an asymmetric fashion met with no success (Scheme BIL2.3.6.1), and further investigations were not pursued.

![Diagram](image)

**Scheme BIL2.3.6.1**

Direct use of Miyaura's conditions for the asymmetric conjugate addition of alkenyl- [10] and arylboronic acids [13] to enones provided no reaction in the addition of potassium phenyltrifluoroborate [17a] to cyclohexenone.

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BII.2.4 Rhodium(I)-Catalyzed Additions to Aldehydes

BII.2.4.1 Initial Rhodium(I)-Catalyzed Additions to Benzaldehyde

For initial studies into the rhodium(I)-catalyzed addition of potassium alkenyl- [16] and aryltrifluoroborates [17] to aldehydes, the same catalyst and reaction conditions as those reported by Miyaura for the rhodium(I)-catalyzed addition of alkenyl- [10] and arylboronic acids [13] to aldehydes were selected. Potassium phenyltrifluoroborate [17a] and benzaldehyde were chosen as representative substrates.

Reaction of benzaldehyde with 2 equivalents of potassium phenyltrifluoroborate [17a] in the presence of Rh(acac)(CO)2 (3 mol %) and 1,1'-bis(diphenylphosphino)ferrocene (dpff) (3 mol %) resulted in the formation of benzylic alcohol [30a] in high yield, with the reaction proceeding to full conversion after 16 h in DME/water (1:1) at 80 °C (Table BII.2.4.1.1). Potassium phenyltrifluoroborate [17a] is again more reactive than the corresponding phenylboronic acid. When potassium phenyltrifluoroborate [17a] was used, conversion was almost complete after 8 h, whereas less than half of the aldehyde had undergone reaction with the phenylboronic acid.

\[
\text{PhCHO} \xrightarrow{[17a] \text{or PhB(OH)}_2 \text{ (2 eq.), \ Rh(acac)(CO)}_2 \text{ (3 mol%), dpff (3 mol%), DME/H}_2\text{O, 80 °C, 16 h}} \xrightarrow{} \text{PhCH(OH)CH}_2\text{Ph} \text{ [30a]}
\]

<table>
<thead>
<tr>
<th>(t) (h)</th>
<th>(\text{PhBF}_3\text{K [17a]})</th>
<th>(\text{PhB(OH)}_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>16</td>
<td>&gt;99</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

\(a\) Determined by \(^1\text{H NMR of the crude reaction mixture.}\)

Table BII.2.4.1.1 - Rhodium(I) Catalyzed Additions of Potassium Phenyltrifluoroborate and Phenylboronic Acid to Benzaldehyde
BIL.2.4.2 Optimization of Reaction Conditions

Following the successful addition of potassium phenyltrifluoroborate [17a] to benzaldehyde, the effect of reaction parameters on the overall process was systematically examined in order to optimize the reaction conditions.

The use of 2 equivalents of the potassium alkenyl- [16] or aryltrifluoroborate reagent [17] was once again found to be optimal, with the isolated yields of benzylic alcohol [30a] dropping to 69% and 28% with 1.5 and 1.1 equivalents of potassium phenyltrifluoroborate [17a] respectively. Significantly, in the reaction of potassium phenyltrifluoroborate [17a] with 4-nitrobenzaldehyde, the ligands dppb (1 equivalent) and triphenylphosphine (2 equivalents) were found to be effective, with yields dropping only slightly from 85% with dppf to 83% with PPh3 and 76% with dppb. This is in sharp contrast to the results obtained in the addition of phenylboronic acid to aldehydes in which no reaction occurs with PPh3 as a ligand.46 This suggests that the P-Rh-P angle does not significantly affect catalyst activity under the conditions used, an observation which may be useful in the design of more active or asymmetric catalysts for the reaction.

Reaction did not proceed at all in the absence of a phosphine ligand. A decrease in catalyst loading was also found to have no measurable impact on the processes, with 1 mol % Rh(acac)(CO)2 returning an 81% yield of benzylic alcohol [30a].

When the reaction of potassium phenyltrifluoroborate [17a] with 4-nitrobenzaldehyde was conducted in dry DME or with just 10 equivalents of water, the reaction was slower, with product to starting material ratios at 16 h of 23:77 and 80:20, respectively. When conducted in water with no co-solvent, addition over 16 h proceeded with a yield nearly identical to that obtained from reaction in the DME/water solvent system, providing benzylic alcohol [30b] in 84% yield. It was possible to carry out the reaction in a THF/water solvent system, but the observed degree of conversion after 16 h was only 73%.

In the reaction of potassium phenyltrifluoroborate [17a] with 4-nitrobenzaldehyde, the degree of conversion observed after 16 h of reaction was found to drop sharply with decreasing temperature. At 70 °C, only 27% of the aldehyde underwent arylation, while reactions at 60 °C and 40 °C lead to 18% and 5% conversion respectively. No reaction was observed at room temperature.
BIL.2.4.3 Overview and Analysis of Additions to Aldehydes

A variety of potassium alkenyl- [16] and aryltrifluoroborates [17] were found to react efficiently with a range of alkyl and aryl aldehydes using the standard protocol, giving high isolated yields of the alcohol products [30] (Table BIL.2.4.3.1).

\[
\text{R}^2\text{CHO} \xrightarrow{[16] \text{ or } [17]} \text{R}^1\text{BF}_3\text{K}, \text{ Rh(acac)}(\text{CO})_2 \text{ (3 mol%)}, \text{ dpdf (3 mol%), DME/H}_2\text{O, 80 °C, 16 h} \rightarrow \text{OH}
\]

<table>
<thead>
<tr>
<th>R'BF₃K</th>
<th>R²</th>
<th>Alcohol</th>
<th>Yield (%)</th>
</tr>
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<tbody>
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<td>79</td>
</tr>
<tr>
<td>17a</td>
<td>4-NO₂C₆H₄</td>
<td>30b</td>
<td>85</td>
</tr>
<tr>
<td>17d</td>
<td>4-NO₂C₆H₄</td>
<td>30c</td>
<td>92</td>
</tr>
<tr>
<td>16a</td>
<td>4-NO₂C₆H₄</td>
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<td>2-Naphthyl</td>
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<tr>
<td>17a</td>
<td>C₆H₁₁</td>
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<td>86</td>
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</table>

Table BIL.2.4.3.1 - Rhodium(I)-Catalyzed Additions of Potassium Alkenyl- and Aryltrifluoroborates to Aldehydes
Significantly, nitro-substituted aldehydes that reacted efficiently with potassium alkenyl- [16] and aryltrifluoroborates [17] in these studies were found to be unreactive when the corresponding boronic acids were used under otherwise identical conditions. Addition of potassium phenyltrifluoroborate [17a] to 4-hydroxybenzaldehyde was found to fail entirely, and it is presumed that arylation of this substrate with phenylboronic acid was not reported by Miyaura for the same reason.46,47

BII.2.4.4 Room Temperature Additions to Aldehydes

While it was not possible to add potassium alkenyl- [16] and aryltrifluoroborates [17] to aldehydes at room temperature using the Rh(acac)(CO)2/dppf catalytic system, use of Rh(acac)(CO)2/tBu3P did give rise to addition products (Scheme BII.2.4.4.1). Indeed, this was anticipated given Miyaura's success in adding alkenyl- [10] and arylboronic acids [13] to aldehydes at room temperature using the similar Rh(acac)(coe)2/tBu3P system.47

![Chemical Reaction Diagram](image_url)

<table>
<thead>
<tr>
<th>R1</th>
<th>Alcohol</th>
<th>Yield (%)</th>
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<tr>
<td>Ph</td>
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<tr>
<td>4-NO2C6H4</td>
<td>30b</td>
<td>83</td>
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<tr>
<td>4-MeOC6H4</td>
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<td>84</td>
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</table>

Table BII.2.4.4.1 - Rhodium(I)-Catalyzed Additions of Potassium Aryltrifluoroborates to Aldehydes at Room Temperature

The Rh(acac)(CO)2/tBu3P catalyzed, room temperature addition of potassium phenyltrifluoroborate [17a] to the aldehyde substrates was equally effective with water as the exclusive solvent.
**BII.2.4.5 Mechanism of Additions to Aldehydes**

As in Miyaura's work involving the rhodium(I)-catalyzed addition of alkenyl-[10] and arylboronic acids [13] to aldehydes,\(^{46,47}\) reaction presumably proceeds via transmetallation between the potassium alkenyl- [16] or aryltrifluoroborate salt [17] and the RO-Rh species (RO = acac or OH) to give an alkenyl- or aryl-Rh complex. This is followed by insertion of the aldehyde into the alkenyl- or aryl-Rh bond, and subsequent hydrolysis of the resulting rhodium(I) species (Scheme BII.2.4.5.1).

![Scheme BII.2.4.5.1](image)

**BII.2.4.6 Attempted Asymmetric Addition to Aldehydes**

The reaction of potassium phenyltrifluoroborate [17a] with 4-nitrobenzaldehyde was run under a variety of conditions in the presence of several different chiral ligands such as binap, diop, and (2S,3S)-(−)-bis(diphenylphosphinophino)butane (S,S-chiraphos). Unfortunately, the pairing of each ligand with Rh(acac)(CO)\(_2\) or Rh(acac)(C\(_2\)H\(_4\))\(_2\) in DME/water at 80 °C and dioxane/water at 100 °C failed, in all cases, to produce any e.e. in the product alcohol [30b]. Indeed, when Rh(acac)(CO)\(_2\) was used with each of the chiral ligands, the reaction altogether failed to produce any product, racemic or otherwise, while use of Rh(acac)(C\(_2\)H\(_4\))\(_2\) resulted in only modest degrees of conversion (Scheme BII.2.4.6.1).
BII.2.5 Zinc(0)-Catalyzed Additions to Aldehydes

**BII.2.5.1 Introduction**

While the rhodium(I)-catalyzed additions of potassium alkenyl- [16] and aryltrifluoroborates [17] to enones and aldehydes proceed efficiently under the developed conditions, there is a relatively high cost associated with these transformations given that the rhodium(I) catalysts tend to be very expensive [Rh(acac)(CO)₂ = $222/g, Rh(acac)(C₂H₄)₂ = $330/g]. Consequently, it was hoped that a cheaper, alternate transition metal could be found which catalyzes the addition processes as effectively.

Screening for such a catalyst was performed using the addition of potassium alkenyl- [16] and aryltrifluoroborates [17] to aldehydes as the test reaction.

**BII.2.5.2 Initial Screening Process**

At the outset, the possibility that a palladium(II) based catalytic system might show some reactivity under the standard conditions employed with the Rh(acac)(CO)₂/dppf catalytic system was explored. Unfortunately, neither PdCl₂/dppf (5 mol%) or Pd(OAc)₂/dppf (5 mol%) showed any catalytic activity in the addition of potassium phenyltrifluoroborate [17a] to 4-nitrobenzaldehyde in DME/water at 80 °C after 16 h. The same was true for the processes carried out at room temperature using PdCl₂/tBu₃P (5 mol%) and Pd(OAc)₂/tBu₃P (5 mol%). After these preliminary and unsuccessful efforts, transmetallation of the potassium alkenyl- [16] and aryltrifluoroborates [17] with zinc to form reactive alkenyl and aryl zinc species was considered as a viable alternative.
The transmetallation of alkenyl- and arylboron species with zinc is a relatively recent phenomenon. In the 1980s, Molander first showed that tetracoordinate alkenylboronate complexes [31] can undergo transmetallation with zinc(II) chloride (ZnCl₂) to give the corresponding alkenylzincs,⁷¹ while analogous transmetallations of (Z)-tri-1-alkenylboranes⁷² [32] and (E)-1-alkenylboranes⁷³ [33] with dialkylzincs was demonstrated in the 1990s (Scheme BII.2.5.2.1). Migration of the alkenyl groups from boron to zinc was found to take place with retention of olefin geometry.

\[
\begin{align*}
\text{R}^1\text{C} = \text{B} & \quad + \quad \text{ZnCl}_2 \quad \text{THF} \quad \rightarrow \quad \text{R}^1\text{C} = \text{ZnCl} + \\
\text{OMe Na}^+ & \quad + \quad \text{NaCl} \\
\text{[31]} & \quad \text{[31]} \\
\text{R}^1\text{C} = \text{B} & \quad \text{Et}_2\text{Zn} \quad \text{hexanes, } 0 ^\circ \text{C} \quad \text{5 min} \quad \rightarrow \quad \text{R}^1\text{C} = \text{ZnEt}_{2-n} \\
\text{[32]} & \quad \text{n = 1, 2} \\
\text{R}^1\text{C} = \text{B(CH}_3\text{)}_2 & \quad \text{R}_2\text{Zn} \quad \text{hexanes, } -78 ^\circ \text{C to } 0 ^\circ \text{C} \quad \text{10 min} \quad \rightarrow \quad \text{R}^1\text{C} = \text{ZnR} \\
\text{[33]} & \quad \text{[33]} \\
\end{align*}
\]

Scheme BII.2.5.2.1

In light of the facile transmetallation observed by Molander using a tetracoordinate alkenylboronate complex [31] and ZnCl₂, it was anticipated that potassium alkenyl- [16] and aryltrifluoroborates [17] could be similarly transmetallated. To ascertain whether such a transmetallation was in fact possible, benzaldehyde and 4-bromobenzaldehyde were reacted with potassium phenyltrifluoroborate [17a] (2 equivalents) in the presence of several zinc sources (1 equivalent) in DME/water for 16 h at room temperature. While the inclusion of zinc(II) sulfate (ZnSO₄), ZnCl₂, or granular Zn (30 mesh) failed to produce any arylation of the aldehydes, Zn dust (325 mesh) did show 24% and 67% conversion of benzaldehyde and 4-bromobenzaldehyde to the alcohols [30a] and [30b] respectively (Scheme BII.2.5.2.2). Reaction in the absence of a Zn source did not proceed at all.
Zn (30 mesh), ZnSO₄, ZnCl₂ gave no reaction.
Zn dust gave 24% conversion to [30a] \((R¹ = H)\), 67% conversion to [30p] \((R¹ = Br)\).

Scheme B11.2.5.2.2

No direct zinc mediated reduction of the aldehydes to the corresponding benzylic alcohols was observed under these conditions, and the process appeared to be extremely clean with no side products or decomposition evident in the \(^1\)H and \(^13\)C NMR spectra of the crude reaction mixtures.

Preliminary efforts at transmetallating to a metal other than Zn were conducted under the same conditions using granular Sn (30 mesh), tin(IV) chloride (SnCl₄), Cu powder, and copper(II) bromide (CuBr₂), but no reaction was observed in any of the trials. The encouraging Zn transmetallation results, however, prompted further refinement of the zinc(0) catalysis conditions.

B11.2.5.3 Optimization of Reaction Conditions

In order to encourage full conversion of the benzaldehyde and 4-bromobenzaldehyde to alcohols [30a] and [30p], the reaction was repeated under the same conditions, but allowed to run for 64 h. While this was sufficient to fully convert the more electrophilic 4-bromobenzaldehyde to [30p], benzaldehyde underwent only 62% conversion to [30a]. Consequently, prolonging the reaction time was not satisfactory both from the standpoint of reactivity, and practicality. Reaction of both aldehydes at higher temperature \((80 ^\circ C)\) for 16 h to encourage full conversion within that time frame proved highly detrimental. While \(^1\)H and \(^13\)C NMR spectroscopy showed both of the aldehydes to be fully consumed, substantial amounts of direct aldehyde reduction were also observed. In the case of 4-bromobenzaldehyde, the ratio of desired product alcohol [30p] to 4-bromobenzyl alcohol appeared to be on the order of 1.6:1.

It was eventually proposed that increasing the equivalents of Zn dust could drive the reactions to completion at room temperature within 16 h. When 4-
bromobenzaldehyde was reacted in the presence of 5 equivalents of Zn dust, this did in fact prove to be the case, and a 77% yield of alcohol [30p] was isolated following purification by column chromatography on silica gel. Less electrophilic benzaldehyde, however, only reacted to 26% conversion under the same conditions. Only with 10 equivalents of Zn dust did benzaldehyde undergo full conversion under the prevailing conditions to give alcohol [30a] in 71% isolated yield. Despite the increased amounts of Zn dust in the system, no direct aldehyde reduction was observed in either case.

Although full conversion within 16 h at room temperature in DME/water was now possible, it was desirable to reduce the number of Zn dust equivalents being used for the process. Activation of the Zn dust and the resulting increase in reactivity was seen as a potential answer. Consequently, a sample of activated Zn dust (designated Zn* dust) was produced by the facile activation of Zn dust with 1,2-dibromoethane and TMSCl in THF (Scheme BII.2.5.3.1).

\[
\text{Zn}\text{dust} \xrightarrow{1,2\text{-dibromoethane}, \text{TMSCl, THF,} \quad 80^\circ \text{C to rt}} \text{Zn}^*\text{dust}
\]

**Scheme BII.2.5.3.1**

When benzaldehyde and 4-bromobenzaldehyde were subsequently reacted with potassium phenyltrifluoroborate [17a] and 1 equivalent of Zn* dust, the expected increase in reactivity was observed. The 1 equivalent of Zn* dust was sufficient to fully convert 4-bromobenzaldehyde and give rise to alcohol [30p] in 82% yield, but benzaldehyde once again showed only 75% conversion. While this is a substantial improvement over the 24% conversion observed with 1 equivalent of Zn dust, full conversion of benzaldehyde would eventually require 2 equivalents of Zn* dust, and alcohol [30a] isolated from this reaction was obtained in 79% yield.

When the arylation of 4-bromobenzaldehyde was attempted with 1 equivalent of Zn* dust and only 1 equivalent of potassium phenyltrifluoroborate [17a], the reaction did not proceed to completion, showing a conversion of 89%. As a result, all subsequent arylation processes were conducted using 2 equivalents of potassium phenyltrifluoroborate [17a]. No reaction with 4-bromobenzaldehyde was observed when 2
equivalents of phenylboronic acid were used with 1 equivalent of Zn* dust, but it was possible to efficiently generate and react potassium phenyltrifluoroborate [17a] \textit{in situ} by using 2 equivalents of phenylboronic acid in conjunction with 6 equivalents of aqueous KHF$_2$ in the reaction mixture (Scheme BII.2.5.3.2).

\[
\begin{array}{c}
\text{Br} \quad \text{CHO} \\
\xrightarrow{\text{PhB(OH)$_2$, KHF$_2$, Zn* (dust), DME/H$_2$O, rf, 16 h}} \\
\text{Br} \quad \text{OH}
\end{array}
\]

\textbf{Scheme BII.2.5.3.2}

The arylation of both benzaldehyde and 4-bromobenzaldehyde with potassium phenyltrifluoroborate [17a] and Zn or Zn* dust did not proceed in dry organic solvents such as DME, THF, or CH$_2$Cl$_2$.

\textbf{BII.2.5.4 Overview and Analysis of Additions to Aldehydes}

Potassium phenyltrifluoroborate [17a] was reacted efficiently with several aryl aldehydes using Zn or Zn* dust under the optimized conditions to give high isolated yields of the corresponding alcohols [30] (Table BII.2.5.4.1). Comparatively electron deficient aldehydes such as 4-bromo- and 4-cyano benzaldehyde required fewer equivalents of both Zn and Zn* dust in order to react fully, as opposed to benzaldehyde and naphthaldehyde.
The reaction of nitro-substituted aldehydes in these zinc(0)-catalyzed arylation processes was avoided given the rapid reduction of this functionality under such conditions. Inexplicably, the attempted arylation of 4-methoxy- and 4-hydroxy-benzaldehyde with potassium phenyltrifluoroborate [17a] under these conditions also failed, with the Zn and Zn* dust agglomerating almost immediately upon introduction into the reaction mixture. Only trace amounts (<6%) of the desired product alcohols were formed.

Somewhat unexpectedly, the attempted arylation of aliphatic aldehydes, such as octanal, also failed to produce any appreciable amount of addition product (<10%), as did attempts at adding both potassium (E)-hexenyltrifluoroborate [16b] and potassium benzylltrifluoroborate to 4-bromobenzaldehyde. In all cases, some of the aldehyde and potassium trifluoroborate salt could be re-isolated following column chromatography of the crude reaction mixture. The reason(s) for the apparent lack of reactivity shown by the aliphatic aldehydes and potassium alkenyl- [16] and benzylltrifluoroborate salts is not understood at this point.

---

Table BII.2.5.4.1 - Zinc(0)-Catalyzed Additions of Potassium Phenyltrifluoroborate to Aldehydes

<table>
<thead>
<tr>
<th>R¹</th>
<th>Alcohol</th>
<th>Yield (%) [Zn]</th>
<th>Yield (%) [Zn*]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph¹</td>
<td>30a</td>
<td>71</td>
<td>79</td>
</tr>
<tr>
<td>4-CNC₆H₄ᵇ</td>
<td>30i</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>4-BrC₆H₄ᵇ</td>
<td>30p</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td>2-Naphthylᶜ</td>
<td>30q</td>
<td>74</td>
<td>76</td>
</tr>
</tbody>
</table>

ᵃ 10.0 equiv. Zn dust and 2.0 equiv. Zn* dust.
ᵇ 5.0 equiv. Zn dust and 1.0 equiv. Zn* dust.
**BII.2.5.5 Mechanism of Zinc(0)-Catalyzed Additions to Aldehydes**

The zinc(0)-catalyzed arylation of aldehydes presumably proceeds via transmetallation between the potassium phenyltrifluoroborate [17a] and Zn dust. The zinc undergoes oxidative insertion into the Ar-B bond to give an Ar-Zn complex. This is followed by insertion of the aldehyde into the Ar-Zn bond, and subsequent hydrolysis of the resulting zinc(II) species (Scheme BII.2.5.5.1).

\[ \text{Zn(0) + PhBF}_3\text{K} \rightarrow \text{PhZn(II)}L_n \rightarrow \text{Ph}R^1\text{CHO} \rightarrow \text{Ph}R^1\text{OH} \]

Scheme BII.2.5.5.1

It is difficult to speculate as to the nature of the groups or ligands occupying zinc’s coordination sphere at any given time, but insertion of the zinc(0) into two Ar-B bonds to form a diarylzinc(II) species (L_n = Ar) has not been ruled out.

**BII.2.5.6 Lewis Acid Catalyzed Additions to Aldehydes**

In order to make the zinc(0)-catalyzed arylation process possible in dry organic solvents, it was proposed that a Lewis acid be added to activate the aldehyde carbonyl group, and make it more susceptible to nucleophilic attack. Interestingly, a number of the Lewis acids (1 equivalent) screened in the reaction of potassium phenyltrifluoroborate [17a] (2 equivalents) with 4-bromobenzaldehyde did in fact induce reactivity when the addition process was performed with Zn* dust (1 equivalent) in dry DME for 16 h (Table BII.2.5.6.1).
Lewis Acid Conversion

\[
\begin{array}{lll}
\text{Lewis Acid} & \text{Conversion (\%)} & \text{Yield (\%)} \\
\text{B(OMe)_3} & - & - \\
\text{Ti(OiPr)_4} & - & - \\
\text{CuBr_2} & 56 & - \\
\text{TMSCl} & 95 & 80 \\
\text{MgBr_2} & 100 & 84 \\
\text{AlCl_3} & 100 & 87 \\
\text{BF_3\cdot OEt_2} & 100 & 86 \\
\end{array}
\]

Table BIL2.5.6.1 - Zinc(0)-Catalyzed, Lewis Acid Promoted Additions of Potassium Phenyltrifluoroborate to Aldehydes

Attempts at using the effective Lewis acids in a catalytic fashion (10 mol\%) proved unsuccessful, with no or little (<30\%) conversion being observed. When the effective Lewis acids were employed in the absence of Zn\(^{+}\) dust in dry DME, no reaction took place.

BIL2.5.7 Future Extensions of Zinc(0)-Catalyzed Methodology

While the arylation processes described here constitute a foundation for zinc(0)-catalyzed addition processes using potassium aryltrifluoroborates [17], the methodology can potentially be extended to include the addition of potassium alkenyltrifluoroborates [16] to aldehydes, and the addition of potassium alkenyl- [16] and aryltrifluoroborates [17] conjugatively to enones. Also highly desirable is the ability to perform all of these zinc(0)-catalyzed addition process in an asymmetric fashion.

Catalytic enantioselective additions of diorganozincs to aldehydes and enones have been made possible through the use of either chiral Lewis acids or Lewis bases as chiral catalysts.\(^7\) It may therefore be possible to employ one or both of these approaches
to effect chiral transformations using the organozinc species derived from a potassium alkenyl- [16] or aryltrifluoroborate salt [17].
Chapter BIII - Experimental
BIII.1 General Experimental

Reagents, unless otherwise noted, were purchased from the Aldrich Chemical Company or Fisher Scientific Ltd., and used as received. Reaction solvents were distilled under an argon atmosphere prior to use unless otherwise stated. Diethyl ether (Et₂O), THF, and benzene were distilled from Na metal and benzophenone ketyl, and dichloromethane (CH₂Cl₂) was distilled from calcium hydride (CaH₂). All other solvents used were reagent grade.

All manipulations were carried out under a nitrogen atmosphere in either flame-dried or oven-dried glassware. Column chromatography on silica gel (60 Å, 230-400 mesh, Whatman Company or Toronto Research Chemicals, Inc.) was performed with hexanes and ethyl acetate (EtOAc). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (Alugram SIL G/UV₂₅₄, Rose Scientific Ltd.), visualized with a UV₂₅₄ lamp (Spectroline Longlife filter), and stained with 20% phosphomolybdic acid in ethanol (Aldrich Chemical Company). Solvent systems associated with Rf values and chromatography are reported as volumetric ratios.

All ¹H, ¹³C, ¹¹B, and ¹⁹F NMR spectra were obtained on a 400 MHz Varian Unity spectrometer in CDCl₃ (referenced to the residual solvent signals at δ 7.24 and 77.00 ppm for ¹H and ¹³C respectively), C₆D₆ (referenced to the residual solvent signals at δ 7.15 and 127.00 ppm for ¹H and ¹³C respectively) or CD₃CN (referenced to the residual solvent signals at δ 1.94 and δ 1.32 ppm for ¹H and ¹³C respectively). Boron chemical shifts were externally referenced to BF₃·OEt₂ (δ 0.00 ppm). Fluorine chemical shifts were externally referenced to CFCl₃ (δ 0.00 ppm). Features of peaks in the ¹H NMR spectra are labeled in brackets after each chemical shift in the following order; integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = 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 mass spectra were recorded on an AEI MS3074 spectrometer. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, BC.
References following compound names indicate where previously reported literature $^1$H and $^{13}$C NMR spectroscopic data may be found. If no reference is present, $^1$H and $^{13}$C NMR spectroscopic data for that compound had not been reported in the literature at the time of writing.

BIII.2 Synthetic Methods and Compound Data

Potassium Allyl- and Crotyltrifluoroborates

Preparation of Potassium Allyltrifluoroborate [18]

To a solution of trimethyl borate (22.7 mL, 0.200 mol) in Et$_2$O (300 mL) cooled to -78 °C was added allylmagnesium bromide (1.0 M in Et$_2$O, 200 mL, 0.200 mol) slowly over ca. 30 min. The reaction mixture was stirred for 2 h at -78 °C, and then poured immediately into an Erlenmeyer flask containing 2 N HCl (300 mL). The resulting biphasic solution was vigorously stirred for 30 min, after which the layers were separated and the aqueous layer extracted with Et$_2$O (3 x 75 mL). The combined organic extracts were concentrated in vacuo to afford a pale yellow oil. KHF$_2$ (3.5 M in H$_2$O, 156 mL, 0.700 mol) was then added, the reaction mixture stirred for 30 min at rt, and subsequently stored at 4 °C for 12 h. The white precipitate was then filtered off and recrystallized from acetonitrile to afford [18].

Preparation of Potassium (Z)-2-Butenyltrifluoroborrate [19a]

To a solution of cis-2-butene (23.0 mL, 0.225 mol) in THF (150 mL) at -78 °C was added potassium tert-butoxide (22.4 g, 0.200 mol). n-BuLi (2.5 M in hexanes, 80.0 mL, 0.200 mol) was then added at a rate such that the internal temperature did not exceed -50 °C. After the addition was complete, the internal temperature of the reaction mixture was allowed to rise to -20 °C for 45 min prior to being recooled to -78 °C. Triisopropyl borate (37.6 g, 0.200 mol) was then added at a rate such that the internal temperature did not rise above -50 °C. The reaction mixture was subsequently stirred for an additional 45 min, and then rapidly poured into a separatory funnel containing 1 N HCl (400 mL) saturated with NaCl. The layers were separated and the aqueous layer extracted with Et$_2$O
(4 x 100 mL). The combined organic extracts were concentrated in vacuo to afford a clear, colorless oil which was redissolved in MeOH (25 mL). KHF₂ (3.5 M in H₂O, 156 mL, 0.700 mol) was then added, the reaction mixture stirred for 30 min at rt, and subsequently stored at 4 °C for 12 h. The white precipitate was then filtered off and recrystallized from acetonitrile to afford [19a].

Preparation of Potassium (E)-2-Butenytrifluoroborate [19b]

To a solution of trans-2-butene (23.0 mL, 0.225 mol) in THF (150 mL) at -78 °C was added potassium tert-butoxide (22.4 g, 0.200 mol). n-BuLi (2.5 M in hexanes, 80.0 mL, 0.200 mol) was then added at a rate such that the internal temperature did not exceed -60 °C. After the addition was complete, the internal temperature of the reaction mixture was allowed to rise to -50 °C. The reaction mixture was stirred for 15 min at this temperature prior to being recooled to -78 °C. Triisopropyl borate (37.6 g, 0.200 mol) was then added at a rate such that the internal temperature did not rise above -60 °C. The reaction mixture was subsequently stirred for an additional 45 min, and then rapidly poured into a separatory funnel containing 1 N HCl (400 mL) saturated with NaCl. The layers were separated and the aqueous layer extracted with Et₂O (4 x 100 mL). The combined organic extracts were concentrated in vacuo to afford a clear, colorless oil which was redissolved in MeOH (25 mL). KHF₂ (3.5 M in H₂O, 156 mL, 0.700 mol) was then added, the reaction mixture stirred for 30 min at rt, and subsequently stored at 4 °C for 12 h. The white precipitate was then filtered off and recrystallized from acetonitrile to afford [19b].

Preparation of Potassium 3-Methyl-2-butenytrifluoroborate [20]

To a solution of 3-methyl-2-butene (25.2 mL, 0.225 mol) in THF (150 mL) at -78 °C was added potassium tert-butoxide (22.4 g, 0.200 mol). n-BuLi (2.5 M in hexanes, 80.0 mL, 0.200 mol) was then added at a rate such that the internal temperature did not exceed -60 °C. After the addition was complete, the internal temperature of the reaction mixture was allowed to rise to -50 °C. The reaction mixture was stirred for 15 min at this temperature prior to being recooled to -78 °C. Triisopropyl borate (37.6 g, 0.200 mol) was then added at a rate such that the internal temperature did not rise above -60 °C. The
reaction mixture was subsequently stirred for an additional 45 min, and then rapidly poured into a separatory funnel containing 1 N HCl (400 mL) saturated with NaCl. The layers were separated and the aqueous layer extracted with Et₂O (4 x 100 mL). The combined organic extracts were concentrated in vacuo to afford a clear, colorless oil which was redissolved in MeOH (25 mL). KHF₂ (3.5 M in H₂O, 156 mL, 0.700 mol) was then added, the reaction mixture stirred for 30 min at rt, and subsequently stored at 4 °C for 12 h. The white precipitate was then filtered off and recrystallized from acetonitrile to afford [20].

Procedures for Allylation and Crotylation

Method A (Stoichiometric BF₃·OEt₂)

To a suspension of the aldehyde (1.00 mmol) and potassium allyl- [18] or crotyltrifluoroborate [19] (296 mg, 2.00 mmol) in CH₂Cl₂ (10 mL) at -78 °C was added BF₃·OEt₂ (0.25 mL, 1.97 mmol). The reaction mixture was stirred for 15 min at -78 °C and then quenched with saturated aqueous NaHCO₃ (10 mL). The reaction mixture was subsequently allowed to warm to rt. The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to afford a clear, colorless oil. The homoallylic alcohol was then purified by column chromatography (silica, EtOAc/hexanes).

Method B (Catalytic BF₃·OEt₂)

To a suspension of the aldehyde (1.00 mmol) and potassium allyl- [18] or crotyltrifluoroborate [19] (296 mg, 2.00 mmol) in CH₂Cl₂ (10 mL) at rt was added BF₃·OEt₂ (60 μL, 0.05 mmol). The reaction mixture was stirred for 3-6 h prior to separation of the layers and extraction of the aqueous layer with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to afford a clear, colorless oil. The homoallylic alcohol was then purified by column chromatography (silica, EtOAc/hexanes).
**Method C (Stoichiometric HCl)**

To a suspension of the aldehyde (1.00 mmol) and potassium allyl- [18] crotyltrifluoroborate [19] (296 mg, 2.00 mmol) in MeOH (5 mL) at rt was added HCl (1.0 M in H$_2$O, 2.00 mL, 2.00 mmol). The reaction mixture was stirred for 1 h prior to separation of the layers and extraction of the aqueous layer with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated *in vacuo* to afford a clear, colorless oil. The homoallylic alcohol was then purified by column chromatography (silica, EtOAc/hexanes).

**Potassium Allyltrifluoroborate [18]**

\[
\text{BF}_3^\cdot \text{K}^+ 
\]

Obtained in 76% yield; white crystalline solid; $^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 6.00-5.89 (1H, m), 4.75 (1H, d, $J$ = 17.0 Hz), 4.66 (1H, d, $J$ = 10.0 Hz), 1.12 (2H, br s); $^{13}$C NMR (125 MHz, CD$_3$CN) $\delta$ 142.82, 111.12, 27.20 (br); $^{11}$B NMR (160 MHz, CD$_3$CN) $\delta$ 4.98 (q, $J$ = 58.6 Hz); $^{19}$F NMR (376 MHz, CD$_3$CN) $\delta$ -140.6 (q, $J$ = 58.6 Hz); MS (FAB) $m/z$ (rel intensity) 257 (53), 256 (27), 109 (100); HRMS (FAB) $m/z$ calcd for (C$_3$H$_4$BF$_3$)$^-$ 109.0436, found 109.0436; Anal calcd for C$_3$H$_4$BF$_3$K 24.35 (C), 3.41 (H), found 24.26 (C), 3.42 (H).

**Potassium (Z)-2-Butenyltrifluoroborate [19a]**

\[
\text{BF}_3^\cdot \text{K}^+ 
\]

Obtained in 70% yield; white crystalline solid; $^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 5.62-5.49 (1H, m), 5.23-5.11 (1H, m), 1.56 (3H, dd, $J$ = 6.5, 1.0 Hz), 1.01 (2H, br s); $^{13}$C NMR (125 MHz, CD$_3$CN) $\delta$ 133.67, 120.16, 19.5 (br), 12.88; $^{11}$B NMR (160 MHz, CD$_3$CN) $\delta$ 4.98 (q, $J$ = 58.6 Hz); $^{19}$F NMR (376 MHz, CD$_3$CN) $\delta$ -140.4 (q, $J$ = 58.6 Hz); MS (FAB) $m/z$ (rel intensity) 287 (23), 286 (16), 285 (37), 269 (24), 125 (28), 124 (13), 123
(100), 122 (29); HRMS (FAB) m/z calcd for \((\text{C}_4\text{H}_7\text{BF}_3)^+\) 123.0592, found 123.0587; Anal calcd for \(\text{C}_4\text{H}_7\text{BF}_3\text{K}\) 29.66 (C), 4.36 (H), found 29.23 (C), 4.61 (H).

**Potassium \((E)\)-2-Butenyltrifluoroborate [19b]**

\[\begin{array}{c}
\text{BF}_3^- \text{K}^+
\end{array}\]

Obtained in 71% yield; white crystalline solid; \(^1\text{H NMR (500 MHz, CD}_3\text{CN)} \delta 5.56-5.44 (1H, m), 5.16-5.04 (1H, m), 1.56 (3H, dq, \(J = 6.5, 1.5 \text{ Hz})\), 0.97 (2H, br s); \(^{13}\text{C NMR (125 MHz, CD}_3\text{CN)} \delta 133.67, 120.16, 19.8 (br), 12.88; \(^{11}\text{B NMR (160 MHz, CD}_3\text{CN)} \delta 4.93 (q, \(J = 58.6 \text{ Hz})\); \(^{19}\text{F NMR (376 MHz, CD}_3\text{CN)} \delta -140.9 (q, \(J = 58.6 \text{ Hz})\); MS (FAB) m/z (rel intensity) 287 (13), 286 (11), 285 (52), 284 (29), 283 (14), 123 (100), 122 (30); HRMS (FAB) m/z calcd for \((\text{C}_4\text{H}_7\text{BF}_3)^+\) 123.0592, found 123.0576.

**Potassium 3-Methyl-2-butene(trifluoroborate [20]**

\[\begin{array}{c}
\text{BF}_3^- \text{K}^+
\end{array}\]

Obtained in 73% yield; white crystalline solid; \(^1\text{H NMR (500 MHz, CD}_3\text{CN)} \delta 5.31-5.17 (1H, br s), 1.63 (3H, s), 1.54 (3H, s), 1.35-1.10 (2H, br s); \(^{13}\text{C NMR (125 MHz, CD}_3\text{CN)} \delta 128.02, 118.94, 17.98, 14.85; \(^{11}\text{B NMR (160 MHz, CD}_3\text{CN)} \delta 4.91 (q, \(J = 56.7 \text{ Hz})\); \(^{19}\text{F NMR (376 MHz, CD}_3\text{CN)} \delta -138.03 (q, \(J = 56.7 \text{ Hz})\); MS (ES) m/z (rel intensity) 137 (100, M-K\(^+\)), 117 (75), 97 (72), 87 (61).
1-(4-Nitrophenyl)but-3-en-1-ol [24a] (Synthesis 2000, 959)

\[
\text{OH} \\
\text{O}_2\text{N}
\]

Obtained in 96% yield (Method A), 95% yield (Method B) and 90% yield (Method C); yellow oil; \( R_f = 0.32 \) (1:4 EtOAc/hexanes); IR (NaCl, thin film) \( \nu \) 3418, 3120, 2980, 2910, 1665, 1605, 1520, 1348, 1058, 754, 700 cm\(^{-1}\); \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.17 (2H, d, \( J = 8.5 \) Hz), 7.51 (2H, d, \( J = 8.5 \) Hz), 5.83-5.71 (1H, m), 5.20-5.12 (2H, m), 4.88-4.82 (1H, m), 2.58-2.50 (1H, m), 2.48-2.39 (2H, m); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 151.11, 147.11, 133.15, 126.50, 123.54, 119.50, 72.11, 43.80; MS (EI) \( m/z \) (rel intensity) 194 (MH\(^+\), 6), 153 (16), 152 (100), 122 (13), 106 (21), 105 (16), 94 (16), 78 (19), 77 (19); HRMS (EI) \( m/z \) calcd for C\(_{10}\)H\(_{12}\)NO\(_3\) 194.0817, found 194.0816.

1-(4-Methoxyphenyl)but-3-en-1-ol [24b] (Chem. Ber. 1990, 123, 1357)

\[
\text{OH} \\
\text{MeO}
\]

Obtained in 95% yield (Method A), 89% yield (Method B) and 89% yield (Method C); yellow oil; \( R_f = 0.36 \) (1:4 EtOAc/hexanes); \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.27 (2H, d, \( J = 8.5 \) Hz), 6.87 (2H, d, \( J = 9.0 \) Hz), 5.82-5.73 (1H, m), 5.18-5.09 (2H, m), 4.67 (1H, t, \( J = 6.5 \) Hz), 3.79 (3H, s), 2.48 (2H, t, \( J = 7.0 \) Hz), 2.04 (1H, br s); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 158.96, 136.00, 134.58, 127.04, 118.21, 113.74, 72.93, 55.24, 43.73.
1-(4-Methylsulfanylphenyl)but-3-en-1-ol [24c]

Obtained in 90% yield (Method A), 93% yield (Method B) and 88% yield (Method C); yellow oil; 
\( R_f = 0.40 \) (1:4 EtOAc/hexanes); IR (NaCl, thin film) \( \nu = 3390, 3080, 2985, 2905, 1660, 1599, 1495, 1048, 915, 820 \) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.26-7.18 \) (4H, m), 5.81-5.70 (1H, m), 5.16-5.08 (2H, m), 4.64 (1H, t, \( J = 6.5 \) Hz), 2.48-2.42 (5H, m), 2.35 (1H, br s); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 140.70, 137.29, 134.22, 126.47, 126.28, 118.26, 72.78, 43.57, 15.78 \); MS (EI) \( m/z \) (rel intensity) 194 (M\(^+\), 14), 154 (15), 153 (100), 110 (20), 79 (19), 78 (30), 77 (45); HRMS (EI) \( m/z \) calcd for C\(_{11}\)H\(_{14}\)OS 194.0765, found 194.0775.

4-(1-Hydroxybut-3-enyl)benzonitrile [24d] (J. Org. Chem. 1990, 55, 2415)

Obtained in 95% yield (Method A), 95% yield (Method B) and 87% yield (Method C); yellow oil; 
\( R_f = 0.39 \) (1:4 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.58 \) (2H, d, \( J = 8.5 \) Hz), 7.43 (2H, d, \( J = 8.0 \) Hz), 5.79-5.68 (1H, m), 5.14-5.08 (2H, m), 4.76 (1H, dd, \( J = 7.5, 5.0 \) Hz), 2.73 (1H, br s), 2.52-2.36 (2H, m); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 149.22, 133.27, 132, 126.39, 119.01, 118.72, 110.72, 72.24, 43.57. \)
1-(3,4-Dichlorophenyl)but-3-en-1-ol [24e] (Tetrahedron Lett. 1996, 37, 9253)

\[
\text{\includegraphics[width=0.2\textwidth]{image.png}}
\]

Obtained in 85% yield (Method A), 86% yield (Method B) and 85% yield (Method C); yellow oil; \( R_f = 0.37 \) (1:4 EtOAc/hexanes); \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.42 (1H, d, \( J = 2.0 \) Hz), 7.38 (1H, d, \( J = 8.0 \) Hz), 7.13 (1H, dd, \( J = 8.0, 2.0 \) Hz), 5.79-5.67 (1H, m), 5.16-5.10 (2H, m), 4.64 (1H, dd, \( J = 7.5, 5.0 \) Hz), 2.57 (1H, br s), 2.50-2.34 (2H, m); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 143.94, 133.41, 132.30, 131.10, 130.20, 127.73, 125.09, 119.09, 71.87, 43.61.


\[
\text{\includegraphics[width=0.2\textwidth]{image.png}}
\]

Obtained in 84% (Method A) and 85% yield (Method B); yellow oil; \( R_f = 0.30 \) (1:4 EtOAc/hexanes); IR (NaCl, thin film) \( \nu \) 3422, 2936, 1640, 1604, 1517, 1465, 1431, 1374, 1270, 1235, 1153, 1124, 1034, 916, 858, 820 cm\(^{-1}\); \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.87 (1H, d, \( J = 2.0 \) Hz), 6.83 (1H, d, \( J = 8.0 \) Hz), 6.77 (1H, dd, \( J = 8.0, 2.0 \) Hz), 5.83-5.71 (2H, m), 5.15-5.07 (2H, m), 4.61 (1H, t, \( J = 6.5 \) Hz), 3.83 (3H, s), 2.46 (2H, t, \( J = 7.0 \) Hz), 2.33 (1H, br s); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 146.53, 144.90, 135.89, 134.57, 118.74, 118.07, 114.10, 108.32, 73.23, 55.77, 43.66; MS (EI) \( m/z \) 194 (M\(^+\), 4), 154 (14), 153 (100), 151 (8), 125 (30), 123 (5), 110 (12), 94 (8), 93 (72), 65 (38); HRMS (CI) \( m/z \) calcd for C\(_{11}\)H\(_{13}\)O\(_3\) (MH\(^+\)) 193.0865, found 193.0853.
1-Phenylbut-3-en-1-ol [24g] (J. Org. Chem. 1999, 64, 186)

Obtained in 93% yield (Method A), 91% yield (Method B) and 90% yield (Method C); yellow oil; R_ƒ = 0.35 (1:4 EtOAc/hexanes); ^1H NMR (400 MHz, CDCl₃) δ 7.42-7.25 (5H, m), 5.90-5.75 (1H, m), 5.17 (1H, d, J = 18.0 Hz), 5.15 (1H, d, J = 10.0 Hz), 4.73 (1H, t, J = 6.5 Hz), 2.58-2.45 (2H, m), 2.29 (1H, br s); ¹³C NMR (100 MHz, CDCl₃) δ 143.80, 134.39, 128.31, 127.44, 125.74, 118.26, 73.23, 43.72.


Obtained in 82% yield (Method A), 84% yield (Method B) and 78% yield (Method C); yellow oil; R_ƒ = 0.60 (1:9 EtOAc/hexanes); ^1H NMR (400 MHz, CDCl₃) δ 5.88-5.75 (1H, m), 5.15-5.08 (2H, m), 3.65-3.57 (1H, m), 2.32-2.24 (1H, m), 2.15-2.07 (1H, m), 1.60 (1H, br s), 1.48-1.18 (12H, m), 0.86 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 134.92, 118.03, 70.66, 41.92, 36.80, 31.80, 29.60, 29.26, 25.66, 22.64, 14.08.


Obtained in 89% yield (Method A) and 91% yield (Method B); yellow oil; R_ƒ = 0.48 (1:4 EtOAc/hexanes); ^1H NMR (400 MHz, CDCl₃) δ 7.41-7.36 (2H, m), 7.31 (2H, t, J = 7.5 Hz), 7.27-7.21 (1H, m), 6.60 (1H, d, J = 16.0 Hz), 6.24 (1H, dd, J = 16.0, 6.5 Hz), 5.93-
5.80 (1H, m), 5.23-5.16 (2H, m), 4.35 (1H, q, J = 6.5 Hz), 2.48-2.34 (2H, m), 2.03 (1H, s); ^13C NMR (100 MHz, CDCl₃) δ 136.57, 133.98, 131.49, 130.24, 128.49, 127.57, 126.41, 118.38, 71.64, 41.92.


![Structure of 3,3-Dimethylundec-1-en-4-ol](image)

Obtained in 84% yield (Method A) and 85% yield (Method B); yellow oil; R_f = 0.65 (1:9 EtOAc/hexanes); ^1H NMR (400 MHz, CDCl₃) δ 5.79 (1H, dd, J = 17.5, 11.0 Hz), 5.08-4.95 (2H, td, J = 16.7, 0.9 Hz); 3.21 (1H, d, J = 10.2 Hz); 1.54-1.42 (2H, m), 1.34-1.14 (12H, m), 0.98 (3H, s), 0.97 (3H, s), 0.86 (3H, t, J = 7.0 Hz); ^13C NMR (100 MHz, CDCl₃) δ 145.54, 113.20, 78.26, 41.64, 31.85, 31.39, 29.66, 29.31, 27.07, 23.09, 22.63, 21.98, 14.07.


![Structure of 2,2-Dimethyl-1-phenylbut-3-en-1-ol](image)

Obtained in 88% yield (Method A) and 86% yield (Method B); yellow oil; R_f = 0.40 (1:4 EtOAc/hexanes); ^1H NMR (400 MHz, CDCl₃) δ 7.35-7.25 (5H, m), 5.92 (1H, dd, J = 17.5, 11.0 Hz), 5.15 (2H, dd, J = 10.8, 1.5 Hz), 5.09 (1H, dd, J = 17.5, 1.5 Hz), 4.43 (1H, s), 2.10 (1H, br s), 1.03 (3H, s), 0.97 (3H, s); ^13C NMR (100 MHz, CDCl₃) δ 145.06, 140.77, 127.76, 127.44, 127.35, 113.77, 80.60, 42.20, 24.41, 21.05.

![Structure](image)

Obtained in 90% yield (Method A) and 92% yield (Method B); yellow oil; R_f = 0.41 (1:4 EtOAc/hexanes); ^1^H NMR (400 MHz, CDCl_3) δ 7.19 (2H, d, J = 8.6 Hz), 6.82 (2H, d, J = 8.6 Hz), 5.90 (1H, dd, J = 17.5, 10.8 Hz), 5.11 (1H, dd, J = 11.0, 1.5 Hz), 5.05 (1H, dd, J = 17.5, 1.5 Hz), 4.37 (1H, d, J = 2.5 Hz), 3.78 (3H, s), 1.98 (1H, d, J = 2.7 Hz), 0.98 (3H, s); ^13^C NMR (100 MHz, CDCl_3) δ 158.90, 145.21, 132.97, 128.80, 113.67, 112.87, 80.28, 55.18, 42.31, 24.48, 20.98.

1-(4-Nitrophenyl)-2,2-dimethylbut-3-en-1-ol [25d]

![Structure](image)

Obtained in 90% yield (Method A) and 89% yield (Method B); yellow crystalline solid; mp = 55-56 °C; R_f = 0.34 (1:4 EtOAc/hexanes); IR (NaCl, thin film) ν 3450, 2971, 1542, 1348, 1031, 972, 9111, 794, 735 cm^-1; ^1^H NMR (400 MHz, CDCl_3) δ 8.10 (2H, d, J = 8.8 Hz), 7.42 (2H, d, J = 8.7 Hz), 5.84 (1H, dd, J = 17.5, 10.5 Hz), 5.12 (1H, dd, J = 9.7, 1.2 Hz), 5.02 (1H, dd, J = 17.5, 1.2 Hz), 4.48 (1H, d, J = 1.5 Hz) 2.47 (1H, d, J = 2.6 Hz), 0.98 (3H, s), 0.92 (3H, s); ^13^C NMR (100 MHz, CDCl_3) δ 148.28, 147.05, 143.93, 128.49, 122.43, 114.56, 79.57, 42.21, 23.86, 21.04; MS (El) m/z (rel intensity) 153 (61), 152 (47), 136 (34), 106 (29), 77 (24), 70 (100), 69 (78), 55 (31); HRMS (El) m/z calcd for C_{12}H_{13}NO_3 222.1133, found 222.1130.

\[
\begin{align*}
\text{OH} & & \text{CH}_2 \\
\end{align*}
\]

Obtained in 84% yield (Method A) and 85% yield (Method B); yellow oil; Rₓ = 0.60 (1:9 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl₃) δ 5.74 (1H, ddd, J = 16.5, 12.0, 8.0 Hz), 5.12-5.08 (2H, m), 3.41-3.34 (1H, m), 2.19 (1H, sextet, J = 7.0 Hz), 1.63 (1H, br s), 1.53-1.43 (2H, m), 1.40-1.22 (10H, m), 1.02 (3H, d, J = 7.0 Hz), 0.87 (3H, t, J = 7.0 Hz); \(^{13}\)C NMR (100 MHz, CDCl₃) δ 140.34, 116.14, 74.65, 44.07, 34.20, 31.82, 29.67, 29.28, 25.72, 22.63, 16.25, 14.07.


\[
\begin{align*}
\text{OH} & & \text{CH}_2 \\
\end{align*}
\]

Obtained in 74% yield (Method A) and 76% yield (Method B); yellow oil; Rₓ = 0.60 (1:9 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl₃) δ 5.83-5.73 (1H, m), 5.12-5.03 (2H, m), 3.50-3.44 (1H, m), 2.31-2.21 (1H, m), 1.51 (1H, br s), 1.50-1.44 (2H, m), 1.39-1.22 (10H, m), 1.01 (3H, d, J = 7.0 Hz), 0.87 (3H, t, J = 6.5 Hz); \(^{13}\)C NMR (100 MHz, CDCl₃) δ 141.10, 115.11, 74.65, 43.36, 33.96, 31.81, 29.63, 29.28, 26.07, 22.63, 14.07, 13.95.
(1S*,2S*)-2-Methyl-1-phenylbut-3-en-1-ol [26c] (J. Am. Chem. Soc. 1996, 118, 12349)

Obtained in 94% yield (Method A) and 93% yield (Method B); yellow oil; R_f = 0.37 (1:4 EtOAc/hexanes); 'H NMR (400 MHz, CDCl_3) δ 7.37 - 7.24 (5H, m), 5.81 (1H, ddd, J = 17.0, 10.5, 8.0 Hz), 5.23-5.16 (2H, m), 4.34 (1H, d, J = 8.0 Hz), 2.48 (1H, sextet, J = 7.0 Hz), 2.29 (1H, br s), 0.87 (3H, d, J = 7.0 Hz); 13C NMR (100 MHz, CDCl_3) δ 142.36, 140.57, 128.14, 127.54, 126.78, 116.69, 77.74, 46.18, 16.43.


Obtained in 91% yield (Method A) and 92% yield (Method B); yellow oil; R_f = 0.37 (1:4 EtOAc/hexanes); 'H NMR (400 MHz, CDCl_3) δ 7.37-7.26 (5H, m), 5.81-5.71 (1H, m), 5.07-5.00 (2H, m), 4.58 (1H, dd, J = 5.5, 3.0 Hz), 2.63-2.53 (1H, m), 2.20 (1H, d, J = 3.0 Hz), 1.01 (3H, d, J = 7.0 Hz); 13C NMR (100 MHz, CDCl_3) δ 142.50, 140.21, 127.95, 127.23, 126.45, 115.40, 77.19, 44.54, 14.03.
(1S*,2S*)-1-(4-Methoxyphenyl)-2-methylbut-3-en-1-ol [26e] (Chem. Ber. 1990, 123, 1357)

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{OH} & \quad \text{MeO}
\end{align*}
\]

Obtained in 91% yield (Method A) and 95% yield (Method B); yellow oil; \( R_f = 0.38 \) (1:4 EtOAc/hexanes); \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.25 (2H, d, \( J = 9.0 \) Hz), 6.88 (2H, d, \( J = 9.0 \) Hz), 5.81 (1H, ddd, \( J = 17.0, 10.5, 8.0 \) Hz), 5.24-5.15 (2H, m), 4.29 (1H, d, \( J = 8.0 \) Hz), 3.80 (3H, s), 2.45 (1H, sextet, \( J = 7.0 \) Hz), 2.29 (1H, br s), 0.83 (3H, d, \( J = 7.0 \) Hz); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 159.04, 140.89, 134.58, 127.92, 116.53, 113.57, 77.43, 55.18, 46.28, 16.50.

(1S*,2R*)-1-(4-Methoxyphenyl)-2-methylbut-3-en-1-ol [26f] (Synlett 1998, 8, 903)

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{OH} & \quad \text{MeO}
\end{align*}
\]

Obtained in 91% yield (Method A) and 93% yield (Method B); yellow oil; \( R_f = 0.38 \) (1:4 EtOAc/hexanes); \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.21 (2H, d, \( J = 8.5 \) Hz), 6.86 (2H, d, \( J = 9.0 \) Hz), 5.76-5.66 (1H, m), 5.07-5.03 (1H, m), 5.02-4.98 (1H, m), 4.52 (1H, d, \( J = 6.0 \) Hz), 3.79 (3H, s), 2.61-2.48 (1H, m), 2.14 (1H, br s), 1.02 (3H, d, \( J = 7.0 \) Hz); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 158.78, 140.28, 134.73, 127.6, 115.35, 113.36, 76.98, 55.18, 44.62, 14.39.

![Chemical Structure]

Obtained in 96% yield (Method A) and 94% yield (Method B); yellow oil; Rf = 0.34 (1:4 EtOAc/hexanes); IR (NaCl, thin film) ν 3419, 3120, 2988, 2910, 1665, 1609, 1520, 1350, 1059, 922, 855, 754, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (2H, d, J = 9.0 Hz), 7.48 (2H, d, J = 8.5 Hz), 5.72 (1H, ddd, J = 17.0, 10.5, 8.0 Hz), 5.20-5.12 (2H, m), 4.51 (1H, d, J = 7.0 Hz), 2.49 (1H, br s), 2.44 (1H, sextet, J = 7.0 Hz), 0.91 (3H, d, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 149.83, 147.20, 139.08, 127.50, 123.27, 117.74, 76.66, 46.21, 16.17; MS (EI) m/z (rel intensity) 207 (M⁺, 1), 153 (25), 152 (100), 122 (15), 106 (24), 105 (17), 94 (17); HRMS (EI) m/z calcd for C₁₁H₁₃NO₂ 207.0895, found 207.0887.

(1S*,2R*)-2-Methyl-1-(4-nitrophenyl)but-3-en-1-ol [26h] (Synth. Commun. 1999, 29, 1287)

![Chemical Structure]

Obtained in 95% yield (Method A) and 94% yield (Method B); yellow oil; Rf = 0.34 (1:4 EtOAc/hexanes); IR (NaCl, thin film) ν 3420, 3120, 2988, 2910, 1665, 1608, 1521, 1349, 1060, 922, 855, 754, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (2H, d, J = 9.0 Hz), 7.45 (2H, d, J = 8.5 Hz), 5.74 (1H, ddd, J = 17.0, 10.5, 7.0 Hz), 5.07 (1H, dt, J = 10.5, 1.5 Hz), 5.03 (1H, dt, J = 17.0, 1.5 Hz), 4.73 (1H, d, J = 5.0 Hz), 2.61-2.51 (1H, m), 2.47 (1H, br s), 0.94 (3H, d, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 149.99, 146.91, 139.25, 127.15, 123.11, 116.39, 75.97, 44.51, 13.34; MS (EI) m/z 207 (M⁺, 1), 153 (20),
152 (100), 122 (20), 106 (30), 105 (24), 94 (30); HRMS (EI) m/z calcd for C_{11}H_{13}NO_{3} 207.0895, found 207.0882.

**BIII.3 Synthetic Methods and Compound Data**

*Potassium Alkenyl- and Aryl trifluoroborates*

**General Procedure for the Preparation of Potassium Trifluoroborate Salts [16] and [17]**

To a solution of the boronic acid (1.0 equiv.) in a minimal amount of MeOH was added KHF_{2} (4.5 M in H_{2}O, 3.5 equiv.). Almost instantaneously, a thick white precipitate was formed. The reaction mixture was stirred for 15 min at rt. The white precipitate was subsequently filtered off and recrystallized from acetonitrile to afford a white, crystalline solid.

**General Procedure for the Rhodium(I)-Catalyzed Addition of Potassium Alkenyl-[16] and Aryl trifluoroborates [17] to Enones (MVK) at High Temperature (Method A1)**

A suspension of the potassium alkenyl- [16] or aryl trifluoroborate [17] (2.00 mmol), Rh(acac)(CO)_{2} (8 mg, 0.03 mmol) and dpff (17 mg, 0.03 mmol) in MeOH (6 mL) was stirred under a nitrogen atmosphere for 15 min at rt. Methyl vinyl ketone (84 µL, 1.00 mmol) and water (1 mL) were then added, and the reaction mixture stirred at 50 °C for 16 h. After cooling to rt, the reaction mixture was diluted with water (5 mL) and CH_{2}Cl_{2} (20 mL). The layers were separated and the aqueous layer extracted with CH_{2}Cl_{2} (3 x 5 mL). The combined organic extracts were dried (MgSO_{4}), filtered and concentrated *in vacuo* to afford crude material which was subsequently purified by column chromatography (silica, EtOAc/Hexanes).
General Procedure for the Rhodium(I)-Catalyzed Addition of Potassium Alkenyl-[16] and Aryltrifluoroborates [17] to Enones (MVK) at Room Temperature (Method A2)

A suspension of the potassium alkenyl- [16] or aryltrifluoroborate [17] (2.00 mmol), Rh(acac)(CO)₂ (8 mg, 0.03 mmol) and tri-tert-butylphosphine (12 mg, 0.06 mmol) in MeOH (6 mL) was stirred under a nitrogen atmosphere for 15 min at rt. Methyl vinyl ketone (84 µL, 1.00 mmol) and water (1 mL) were then added, and the reaction mixture stirred at rt for 16 h. The reaction mixture was subsequently diluted with water (5 mL) and CH₂Cl₂ (20 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to afford crude material which was subsequently purified by column chromatography (silica, EtOAc/Hexanes).

General Procedure for the Rhodium(I)-Catalyzed Addition of Potassium Alkenyl-[16] and Aryltrifluoroborates [17] to Aldehydes at High Temperature (Method B1)

A suspension of the aldehyde (1.00 mmol), the potassium alkenyl- [16] or aryltrifluoroborate [17] (2.00 mmol), Rh(acac)(CO)₂ (8 mg, 0.03 mmol) and dppf (17 mg, 0.03 mmol) in a 1:1 mixture of DME/H₂O (6 mL) was stirred under a nitrogen atmosphere at 80 °C for 16 h. The reaction mixture was then cooled to rt and diluted with CH₂Cl₂ (20 mL). The layers were separated, and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to afford crude material which was subsequently purified by column chromatography (silica, EtOAc/Hexanes).

General Procedure for the Rhodium(I)-Catalyzed Addition of Potassium Alkenyl-[16] and Aryltrifluoroborates [17] to Aldehydes at Room Temperature (Method B2)

A suspension of the aldehyde (1.00 mmol), the potassium alkenyl- [16] or aryltrifluoroborate [17] (2.00 mmol), Rh(acac)(CO)₂ (8 mg, 0.03 mmol) and tri-tert-butylphosphine (12 mg, 0.06 mmol) in a 1:1 mixture of DME/H₂O (6 mL) was stirred at rt for 16 h. The reaction mixture was then diluted with CH₂Cl₂ (20 mL). The layers were separated, and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined
organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to afford crude material which was subsequently purified by column chromatography (silica, EtOAc/Hexanes).

**General Procedure for the Activation of Zinc Dust**

Zinc dust (3.27 g, 50.0 mmol) and 1,2-dibromoethane (0.47 g, 0.22 mL, 2.5 mmol) in THF (20 mL) were heated to reflux, and then allowed to cool to room temperature. The heat and cool cycle is repeated 4 more times prior to the introduction of TMSCl (0.05 g, 0.06 mL, 0.5 mmol) and stirring of the solution for 15 mins at room temperature. The solvent was subsequently removed in vacuo, and the resulting activated zinc dust dried under reduced pressure for 1 h.

**General Procedure for the Zinc(0)-Catalyzed Addition of Potassium Aryltrifluoroborates [17] to Aldehydes at Room Temperature (Method B3)**

A suspension of the aldehyde (1.00 mmol), the potassium aryltrifluoroborate [17] (2.00 mmol), and activated zinc dust (65 mg, 1.00 mmol or 130 mg, 2.00 mmol) in a 1:1 mixture of DME/H₂O (6 mL) was stirred at rt for 16 h. The reaction mixture was then diluted with CH₂Cl₂ (20 mL). The layers were separated, and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to afford crude material which was then purified by column chromatography (silica, EtOAc/hexanes).

**General Procedure for the Zinc(0)-Catalyzed Addition of Arylboronic Acids [13] to Aldehydes at Room Temperature - In Situ Formation of Potassium Aryltrifluoroborates [17] (Method B4)**

A suspension of the aldehyde (1.00 mmol), the arylboronic acid [13] (2.00 mmol), activated zinc dust (65 mg, 1.00 mmol), and KHF₂ (4.5 M in H₂O, 6.00 mmol) in a 1:1 mixture of DME/H₂O (6 mL) was stirred at room temperature for 16 h prior to being diluted with CH₂Cl₂ (20 mL). The layers were separated, and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and
concentrated in vacuo to afford crude material which was then purified by column chromatography (silica, EtOAc/hexanes).

General Procedure for the Zinc(0)-Catalyzed Addition of Potassium Aryltrifluoroborates [17] to Aldehydes at Room Temperature in a Dry Organic Solvent (DME)

A suspension of the aldehyde (1.00 mmol), the potassium aryltrifluoroborate [17] (2.00 mmol), activated zinc dust (65 mg, 1.00 mmol), and Lewis acid (1.00 mmol) in dry DME (6 mL) was stirred at room temperature for 16 h prior to being diluted with CH₂Cl₂ (20 mL). The layers were separated, and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated in vacuo to afford crude material which was then purified by column chromatography (silica, EtOAc/hexanes).


\[
\text{\begin{tikzpicture}
\draw (0,0) -- (1,0) -- (1.5,0.5) -- (0.5,0.5) -- cycle;
\end{tikzpicture}} \text{BF}_3^-\text{K}^+
\]

Obtained in 89% yield; white crystalline solid; mp = >260 °C; ¹H NMR (200 MHz, [D₆]acetone) δ 7.79 (1H, d, J = 18.1 Hz), 7.30-7.63 (5H, m), 6.38 (1H, d, J = 18.0 Hz); ¹³C (50 MHz, [D₆]acetone) δ 151.32, 130.66, 127.45, 127.70, 127.48 (one signal absent); ¹¹B NMR (80 MHz, [D₆]acetone) δ 3.80 (d, J = 46 Hz); ¹⁹F NMR (235 MHz, [D₆]acetone) δ 10.47 (d, J = 49 Hz).

\[ \text{BF}_3^-\text{K}^+ \]

Obtained in 92% yield; white crystalline solid; mp = >260 °C; $^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 5.74-5.64 (1H, m), 5.37-5.28 (1H, m), 2.03-1.94 (2H, m), 1.39-1.29 (4H, m), 0.90 (3H, t, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CD$_3$CN, 70 °C) $\delta$ 137.56, 36.92, 33.56, 23.89, 14.97 (one signal absent); $^{11}$B NMR (160 MHz, CD$_3$CN) $\delta$ -0.70 (d, $J = 51$ Hz); $^{19}$F NMR (376 MHz, CD$_3$CN) $\delta$ 11.32 (d, $J = 63$ Hz); MS (FAB) m/z (rel intensity) 151 (100, M$^+$), 91 (23); HRMS (FAB) m/z calcld (M$^+$) 151.0906, found 151.0908.


\[ \text{Ph} \text{BF}_3^-\text{K}^+ \]

Obtained in 89% yield; white crystalline solid; mp = >260 °C; $^1$H NMR (200 MHz, [D$_6$]acetone) $\delta$ 7.59 (1H, s), 7.44 (2H, m), 7.25 (2H, m); $^{13}$C NMR (50 MHz, [D$_6$]acetone) $\delta$ 138.20, 130.43, 110.62 (one signal absent); $^{11}$B NMR (80 MHz, [D$_6$]acetone) $\delta$ 4.42 (d, $J = 54$ Hz); $^{19}$F NMR (235 MHz, [D$_6$]acetone) $\delta$ 9.50 (d, $J = 53$ Hz).


\[ \text{BF}_3^-\text{K}^+ \]

Obtained in 85% yield; white crystalline solid; mp = 258-261 °C; $^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 8.25 (1H, s), 7.98 (1H, dd, $J = 8.0$, 2.0 Hz), 7.85 (1H, d, $J = 7.5$ Hz), 7.41 (1H, t, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CD$_3$CN, 70 °C) $\delta$ 139.31, 129.12, 126.84, 122.00
(one signal absent); $^{11}$B NMR (160 MHz, CD$_3$CN) δ -0.77 (d, $J = 44$ Hz); $^{19}$F NMR (376 MHz, CD$_3$CN) δ 8.71 (d, $J = 53$ Hz); MS (FAB) m/z (rel intensity) 190 (100, M$^+$), 174 (20); HRMS (FAB) m/z calcd (M$^+$) 190.0287, found 190.0284; Anal calcd for C$_8$H$_4$O$_2$BF$_3$K 31.47 (C), 1.76 (H), found 31.53 (C), 1.66 (H).

**Potassium 4-Acetylphenyltrifluoroborate [17c]**

![Bond formula of potassium 4-acetylphenyltrifluoroborate]

Obtained in 32% yield; white crystalline solid; mp = 260 °C; $^1$H NMR (400 MHz, CD$_3$CN) δ 7.77 (2H, d, $J = 8.0$ Hz), 7.55 (2H, d, $J = 8.0$ Hz), 2.52 (3H, s); $^{13}$C NMR (125 MHz, CD$_3$CN, 70 °C) δ 137.05, 133.34, 128.22, 27.43 (two signals absent); $^{11}$B NMR (160 MHz, CD$_3$CN) δ -0.63 (d, $J = 44$ Hz); $^{19}$F NMR (376 MHz, CD$_3$CN) δ 9.19 (d, $J = 40$ Hz); MS (FAB) m/z (rel intensity) 187 (88, M$^+$), 183 (54), 91 (100), 59 (29); HRMS (FAB) m/z calcd (M$^+$) 187.0542, found 187.0541; Anal calcd for C$_9$H$_7$OBF$_3$K 42.51 (C), 3.12 (H), found 42.71 (C), 3.30 (H).


![Bond formula of potassium 4-methoxyphenyltrifluoroborate]

Obtained in 71% yield; white crystalline solid; mp = >260 °C; $^1$H NMR (200 MHz, [D$_6$]acetone) δ 7.38 (2H, d, $J = 8.5$ Hz), 6.68 (2H, d, $J = 8.5$ Hz), 3.70 (3H, s); $^{13}$C NMR (50 MHz, [D$_6$]acetone) δ 158.20, 133.42, 112.68, 54.95 (one signal absent); $^{11}$B NMR (80 MHz, [D$_6$]acetone) δ 4.39 (br q, $J = 53$ Hz); $^{19}$F NMR (235 MHz, [D$_6$]acetone) δ 8.05 (br q, $J = 50$ Hz).

![Structure of Potassium 3-Thiopenetrifluoroborate]

Obtained in quantitative yield; white crystalline solid; mp = 250-256 °C; \(^1\)H NMR (400 MHz, CD\(_2\)CN) \(\delta\) 7.23-7.18 (2H, m), 7.15-7.11 (1H, m); \(^13\)C NMR (125 MHz, CD\(_2\)CN, 70 °C) \(\delta\) 152-149 (br), 133.30, 127.52, 125.06; \(^19\)F NMR (376 MHz, CD\(_2\)CN) \(\delta\) 13.35 (br s); MS (FAB) \(m/z\) (rel intensity) 151 (100, \(M^+\)); HRMS (FAB) \(m/z\) calcd (\(M^+\)) 151.0018, found 151.0014.

4-Phenylbutan-2-one [28a] (J. Org. Chem. 1996, 61, 1493)

![Structure of 4-Phenylbutan-2-one]

Obtained in 91% yield (Method A1), 87% yield (Method A2); colorless oil; \(R_f = 0.43\) (3:7 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.26 (2H, m), 7.23-7.17 (3H, m), 2.90 (2H, t, \(J = 7.5\) Hz), 2.76 (2H, t, \(J = 8.0\) Hz), 2.14 (3H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 207.71, 140.86, 128.35, 128.15, 125.96, 44.97, 29.88, 29.58.


![Structure of 4-(3-Nitrophenyl)butan-2-one]

Obtained in 59% yield (Method A1); colorless oil; \(R_f = 0.35\) (3:7 EtOAc/hexanes); IR (NaCl, thin film) \(\nu\) 3110, 2978, 1720, 1411, 1054, 951, 840, 735, 701, 688 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.08-8.03 (2H, m), 7.56-7.40 (2H, m), 3.00 (2H, t, \(J = 7.5\) Hz), 2.83
(2H, t, $J = 7.5$ Hz), 2.17 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.71, 143.05, 134.84, 129.34, 123.13, 121.34, 44.29, 30.04, 29.06; MS (EI) $m/z$ (rel intensity) 193 (1, M$^+$), 176 (11), 150 (17), 134 (36), 133 (100), 104 (28), 103 (48); HRMS (EI) $m/z$ calcd (M$^+$) 193.1739, found 193.0734.

4-(4-Acetylphenyl)butan-2-one [28c]

Obtained in 98% yield (Method A1); colorless oil; $R_f = 0.50$ (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 3115, 2986, 1715, 1695, 1439, 1188, 1082, 967, 740, 720 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (2H, d, $J = 8.0$ Hz), 7.23 (2H, d, $J = 8.0$ Hz), 2.90 (2H, t, $J = 7.5$ Hz), 2.75 (2H, d, $J = 7.5$ Hz), 2.52 (3H, s), 2.10 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 207.05, 197.55, 146.67, 135.11, 128.46, 128.40, 44.27, 29.39, 26.37; MS (EI) $m/z$ (rel intensity) 190 (1, M$^+$), 175 (100), 147 (26), 105 (29), 77 (17); HRMS (EI) $m/z$ calcd (M$^+$) 190.0994, found 190.0991; Anal calcd for C$_{12}$H$_{14}$O$_2$ 75.77 (C), 7.42 (H), found 76.08 (C), 6.95 (H).

4-Thiophen-3-yl-butan-2-one [28d] (Tetrahedron, 1979, 35, 329)

Obtained in quantitative yield (Method A1); colorless oil; $R_f = 0.22$ (1:9 EtOAc/hexanes); IR (NaCl, thin film) ν 3102, 2923, 1717, 1410, 1361, 1162, 844, 775, 684, 632 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.22 (1H, dd, $J = 3.0$ Hz), 6.94-6.89 (2H, m), 2.89 (2H, t, $J = 8.0$ Hz), 2.73 (2H, t, $J = 8.0$ Hz), 2.12 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 207.53,
140.99, 127.84, 125.35, 120.21, 44.00, 29.75, 23.96; MS (EI) m/z (rel intensity) 154 (37, M\(^+\)), 111 (100), 97 (38); HRMS (EI) m/z calcld (M\(^+\)) 154.0452, found 154.0449.


\[
\text{\includegraphics{phenylhexen2one.png}}
\]

Obtained in quantitative yield (Method A1); colorless oil; R\(_f\) = 0.44 (1:4 EtOAc/hexanes); IR (NaCl, thin film) \(\nu\) 3120, 2998, 1720, 1662, 1473, 1275, 922, 802, 745, 703, 674 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.26 (4H, m), 7.20 (1H, t, \(J = 7.0, 1.5\) Hz), 6.40 (1H, d, \(J = 16.0\) Hz), 6.19 (1H, dt, \(J = 16.0, 7.0\) Hz), 2.57 (2H, t, \(J = 7.0\) Hz), 2.46 (2H, q, \(J = 7.0\) Hz), 2.13 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 207.61, 137.16, 130.44, 128.60, 128.25, 126.82, 125.75, 42.78, 29.67, 26.82; MS (EI) m/z (rel intensity) 174 (90, M\(^+\)), 131 (55), 117 (67), 115 (63), 104 (31), 91 (100); HRMS (EI) m/z calcld (M\(^+\)) 174.1045, found 174.1040.


\[
\text{\includegraphics{decen2one.png}}
\]

Obtained in 90% yield (Method A1); colorless oil; R\(_f\) = 0.19 (1:19 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.42-5.27 (2H, m), 2.42 (2H, t, \(J = 7.5\) Hz), 2.19 (2H, q, \(J = 7.0\) Hz), 2.07 (3H, s), 1.94-1.87 (2H, m), 1.30-1.18 (4H, m), 0.82 (3H, t, \(J = 7.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 208.23, 131.40, 128.04, 43.43, 32.02, 31.49, 29.73, 26.72, 22.00, 13.75.
3-Thiophen-3-yl-cyclohexanone [28g]

Obtained in 76% yield (Method A1); colorless oil; \( R_f = 0.19 \) (1:4 EtOAc/hexanes); IR (NaCl, thin film) \( \nu \) 3402, 2938, 1711, 1419, 1350, 1317, 1260, 1223, 1096, 939, 846, 779, 650 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.29 (1H, dd, \( J = 4.0 \) Hz), 6.99 (2H, d, \( J = 4.5 \) Hz), 3.22-3.10 (1H, m), 2.74-2.64 (1H, m), 2.56-2.30 (3H, m), 2.22-2.05 (2H, m), 1.90-1.72 (2H, m); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 210.76, 145.33, 126.38, 125.88, 119.44, 48.44, 41.19, 39.77, 32.32, 24.97; MS (EI) \( m/z \) (rel intensity) 180 (100, \( M^+ \)), 137 (41), 124 (30), 123 (91), 110 (74); HRMS (EI) \( m/z \) calcd (\( M^+ \)) 180.0609, found 180.0605.


Obtained in 82% yield (Method A1), 80% yield (Method A2); colorless oil; \( R_f = 0.29 \) (3:7 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38-7.20 (10H, m), 4.65 (1H, t, \( J = 7.5 \) Hz), 3.22 (2H, d, \( J = 7.5 \) Hz), 2.11 (3H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 206.67, 143.77, 128.48, 127.60, 127.57, 127.54, 126.34, 49.55, 45.95, 30.50.

![3-Phenylpropanal](image)

Obtained in 77% yield (Method A1); colorless oil; \( R_f = 0.20 \) (3:7 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.82 (1H, s), 7.33-7.19 (5H, m), 3.00-2.94 (2H, t, \( J = 7.5 \) Hz), 2.81-2.77 (2H, td, \( J = 7.9, 0.7 \) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 201.49, 140.29, 128.56, 128.25, 126.26, 45.22, 28.07.

Diphenylmethanol (Benzhydrol) [30a] (Tetrahedron 1994, 50, 3447)

![Diphenylmethanol](image)

Obtained in 79% yield (Method B1), 77 % yield (Method B2), 79% yield (Method B3); colorless crystalline solid; mp = 65-66 °C; \( R_f = 0.50 \) (3:7 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.42-7.24 (10H, m), 5.85 (1H, s), 2.22 (1H, br s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 143.78, 128.49, 127.57, 126.53, 76.26.

(4-Nitrophenyl)phenylmethanol [30b] (Tetrahedron 1994, 50, 217)

![4-Nitrophenyl)phenylmethanol](image)

Obtained in 85% yield (Method B1), 83% yield (Method B2); yellow crystalline solid; mp = 78 °C; \( R_f = 0.40 \) (1:4 EtOAc/hexanes); IR (NaCl, thin film) \( \nu \) 3400, 2998, 1518, 1452, 1345, 1184, 1008, 962, 857, 731 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.11 (2H, d, \( J = 8.0 \) Hz), 7.51 (2H, d, \( J = 8.0 \) Hz), 7.35-7.25 (5H, m), 5.82 (1H, s), 2.98 (1H, s); \(^13\)C
NMR (100 MHz, CDCl₃) δ 150.77, 146.93, 142.55, 128.77, 128.20, 126.94, 126.57, 123.50. 75.30; MS (EI) m/z (rel intensity) 229 (13, M⁺), 228 (51), 212 (11), 182 (15), 165 (25, 151 (26), 150 (38), 107 (52), 105 (100); HRMS (EI) m/z calcd (M⁺) 229.0739, found 229.0743; Anal calcd for C₁₁H₁₀N 68.12 (C), 4.84 (H), 6.11 (N), found 67.92 (C), 4.60 (H), 6.09 (N).

(4-Methoxyphenyl)-(4-nitrophenyl)methanol [30c] (J. Org. Chem. 1978, 43, 1509)

\[
\text{O}_2\text{N} \quad \text{OH} \quad \text{OMe}
\]

Obtained in 92% yield (Method B1); yellow crystalline solid; mp = 96 °C; Rf = 0.35 (1:4 EtOAc/hexanes); IR (NaCl, thin film) ν 3412, 2978, 1499, 1341, 1142, 1019, 956, 862, 719 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.14 (2H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.8 Hz), 6.85 (2H, d, J = 8.8 Hz), 5.83 (1H, s), 3.77 (3H, s), 2.43 (1H, br s); ¹³C NMR (100 MHz, CDCl₃) δ 159.47, 151.08, 134.94, 128.04, 126.87, 123.51, 114.18, 74.96, 55.23.


\[
\text{O}_2\text{N} \quad \text{OH} \quad \text{O}
\]

Obtained in 82% yield (Method B1); colorless oil; Rf = 0.30 (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 3423, 2996, 1518, 1479, 1346, 1244, 1147, 1093, 912, 841, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.21 (a, J = 9.0 Hz), 7.60 (2H, d, J = 9.0 Hz), 7.40-7.25 (5H, m), 6.72 (1H, d, J = 16.0 Hz), 6.29 (1H, dd, J = 16.0, 7.0 Hz), 5.48 (1H, d, J = 7.0 Hz), 2.42 (1H, br s); ¹³C NMR (100 MHz, CDCl₃) δ 149.77, 147.30, 135.80, 132.20,
130.04, 128.66, 128.29, 126.93, 126.65, 123.74, 74.34; MS (Cl) m/z (rel intensity) 256 (27, MH), 255 (100, M), 253 (44); HRMS (Cl) m/z calcd (M) 255.0895, found 255.0883.

(E)-1-(4-Nitrophenyl)hept-2-en-1-ol [30e]

![Chemical structure]

Obtained in 85% yield (Method B1); colorless oil; R_f = 0.30 (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 2928, 1700, 1528, 1347, 1248, 1158, 1099, 971, 856, 784, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (2H, d, J = 9.1 Hz), 7.48 (2H, d, J = 8.3 Hz), 5.81-5.77 (1H, m), 5.52 (1H, ddt, J = 15.1, 7.4, 1.5 Hz), 5.22 (1H, d, J = 7.5 Hz), 2.40 (1H, br s), 2.10 (2H, q, J = 6.9 Hz), 1.38-1.25 (4H, m), 0.85 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 150.56, 138.16, 133.67, 129.72, 128.48, 124.47, 124.39, 69.96, 31.86, 31.06, 22.14, 13.84; MS (EI) m/z (rel intensity) 234 (5, M⁺), 174 (100), 77 (85); HRMS (EI) m/z calcd (M⁺) 234.1128, found 234.1130.

(3-Nitrophenyl)phenylmethanol [30f] (Chem. Pharm. Bull. 1989, 37, 615)

![Chemical structure]

Obtained in 88% yield (Method B1); yellow oil; R_f = 0.60 (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 3406, 3056, 1528, 1430, 1351, 1191, 1028, 736, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (1H, m), 8.12-8.08 (1H, m), 7.70 (1H, d, J = 7.5 Hz), 7.48 (1H, t, J = 8.0 Hz), 7.37-7.28 (5H, m), 5.91 (1H, s), 2.52 (1H, br s); ¹³C NMR (100 MHz, CDCl₃) δ 145.74, 142.71, 132.42, 129.31, 128.89, 128.31, 126.59, 122.36, 121.25, 75.31; MS (Cl) m/z (rel intensity) 230 (24, MH), 229 (100, M⁺); HRMS (Cl) m/z calcd (M⁺) 229.0739, found 229.0734.
(2-Nitrophenyl)phenylmethanol [30g] *(Chem. Ber. 1985, 118, 3673)*

![Chemical structure](image)

Obtained in 85% yield (Method B1); yellow oil; R<sub>f</sub> = 0.60 (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 3396, 3032, 1526, 1429, 1302, 1179, 1019, 744, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl₃) δ 7.83 (1H, d, J = 8.0 Hz), 7.68 (1H, d, J = 8.0 Hz), 7.54 (1H, t, J = 8.0 Hz), 7.36 (1H, t, J = 8.0 Hz), 7.28-7.18 (5H, m), 6.32 (1H, s), 3.16 (1H, br s); <sup>13</sup>C NMR (100 MHz, CDCl₃) δ 141.44, 138.36, 133.31, 129.19, 128.43, 128.33, 127.88, 126.84, 124.54, 71.25. MS (Cl) m/z (rel intensity) 230 (100, M<sup>+</sup>), 229 (M<sup>+</sup>), 181 (11), 153 (7); HRMS (Cl) m/z calcd (M<sup>+</sup>) 229.0739, found 229.0749.

*(E)-1-(2-Nitrophenyl)hept-2-en-1-ol [30h]*

![Chemical structure](image)

Obtained in 88% yield (Method B1); clear, colorless oil; R<sub>f</sub> = 0.70 (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 3406, 2929, 1708, 1605, 1522, 1347, 1198, 971, 855, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl₃) δ 8.15 (2H, d, J = 9.0 Hz), 7.51 (2H, d, J = 8.5 Hz), 5.84-5.75 (1H, m), 5.56 (1H, ddt, J = 15.0, 7.5, 1.5 Hz), 5.24 (1H, d, J = 7.5 Hz), 2.45 (1H, br s), 2.04 (2H, q, J = 7.0 Hz), 1.38-1.23 (4H, m), 0.86 (3H, t, J = 7.0 Hz); <sup>13</sup>C NMR (100 MHz, CDCl₃) δ 150.56, 134.49, 131.14, 130.41, 126.73, 124.19, 123.49, 74.33, 31.72, 30.95, 22.10, 13.76; MS (Cl) m/z (rel intensity) 236 (15, M<sup>+</sup>), 235 (100, M<sup>+</sup>), 151 (28); HRMS (Cl) m/z calcd (M<sup>+</sup>) 235.1208, found 235.1199.
4-(Hydroxyphenylmethyl)benzonitrile [30i] (J. Am. Chem. Soc. 1978, 100, 7920)

\[
\begin{align*}
\text{ Obtained in 87\% yield (Method B1), 80\% yield (Method B3); colorless oil; } & \text{ \(R_f = 0.30\) (3:7 EtOAc/hexanes); } \\
\text{ 1H NMR (400 MHz, CDCl}_3\text{) } & \text{\(\delta 7.56 (2H, \text{ dt, } J = 8.5, 2.0 \text{ Hz}), 7.48 (2H, \text{ dt, } J = 8.0, 1.0 \text{ Hz}), 7.37-7.27 (5H, m), 5.80 (1H, d, J = 3.5 \text{ Hz}), 2.97 (1H, d, J = 3.5 \text{ Hz}); } \\
\text{ 13C NMR (100 MHz, CDCl}_3\text{) } & \text{\(\delta 148.92, 142.71, 132.10, 128.69, 128.07, 126.91, 126.56, \)} \text{ } \\
& \text{118.72, 110.78, 75.37.} \\
\end{align*}
\]

(4-Hydroxythiophen-3-yl-methyl)benzonitrile [30j]

\[
\begin{align*}
\text{ Obtained in 80\% yield (Method B1); colorless oil; } & \text{ \(R_f = 0.27\) (3:7 EtOAc/hexanes); } \\
\text{ IR (NaCl, thin film) } & \nu 3418, 2229, 1608, 1412, 1149, 1037, 790, 750, 549 \text{ cm}^{-1}; \text{ 1H NMR (400 MHz, CDCl}_3\text{) } \delta 7.61 (2H, d, J = 8.0 \text{ Hz}), 7.50 (2H, d, J = 8.0 \text{ Hz}), 7.29 (1H, dd, J = 5.0, 3.0 \text{ Hz}), 7.18 (1H, d, J = 3.0 \text{ Hz}), 6.95 (1H, dd, J = 5.0, 1.0 \text{ Hz}). 5.91 (1H, s), 2.81 (1H, br s); \text{ 13C NMR (100 MHz, CDCl}_3\text{) } \delta 148.42, 144.02, 132.21, 126.92, 126.82, \text{ } \\
& 125.93, 122.30, 118.70, 111.12, 71.67; \text{ MS (EI) } m/z \text{ (rel intensity) } 215 (42, M^+), 182 (16), \text{ } \\
& 131 (18), 130 (42), 113 (24), 111 (49), 104 (36), 91 (61), 85 (100); \text{ HRMS (EI) } m/z \text{ calcd (M^+)} 215.0405, \text{ found 215.0404.} \\
\end{align*}
\]
(E)-4-(1-Hydroxyhept-2-ene)benzonitrile [30k]

Obtained in 85% yield (Method B1); colorless oil; Rf = 0.40 (1:4 EtOAc/hexanes); IR (NaCl, thin film) ν 3425, 2928, 2229, 1608, 1406, 970, 831 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (2H, d, J = 8.5 Hz), 7.45 (2H, d, J = 8.5 Hz), 5.79-5.72 (1H, m), 5.54 (1H, dd, 16.0, 7.0 Hz), 5.17 (1H, d, J = 7.0 Hz), 2.31 (1H, br s), 2.02 (2H, q, J = 7.0 Hz), 1.37-1.23 (4H, m), 0.85 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 148.61, 142.22, 134.28, 132.82, 132.12, 131.29, 126.69, 110.88; MS (EI) m/z (rel intensity) 215 (8, M⁺), 214 (17), 158 (100), 145 (59), 130 (47); HRMS (EI) m/z calcd (M⁺) 215.1310, found 215.1311.


Obtained in 71% yield (Method B1); colorless crystalline solid; mp = 68 °C; Rf = 0.40 (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 3432, 2997, 1720, 1436, 1283, 1114, 1017, 911, 838, 709 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (2H, d, J = 8.5 Hz), 7.44 (2H, d, J = 8.0 Hz), 7.36-7.24 (5H, m), 5.84 (1H, s), 3.88 (3H, s), 2.74 (1H, br s); ¹³C NMR (100 MHz, CDCl₃) δ 166.92, 148.73, 143.23, 129.72, 129.11, 128.62, 127.86, 126.60, 126.28, 75.81, 52.05; MS (EI) m/z (rel intensity) 242 (20, M⁺), 137 (60), 105 (64), 86 (67), 84 (100); HRMS (EI) m/z calcd (M⁺) 242.0943, found 242.0935.
(E)-Methyl 4-(1-hydroxy-3-phenylallyl)benzoate [30m]

![Chemical Structure]

Obtained in 71% yield (Method B1); colorless oil; Rf = 0.33 (3:7 EtOAc/hexanes); IR (NaCl, thin film) ν 3480, 2019, 1714, 1471, 1295, 1104, 970, 842, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.5 Hz), 7.37 (2H, d, J = 7.5 Hz), 7.31 (2H, t, J = 7.0 Hz), 7.24-7.22 (1H, m), 6.68 (1H, d, J = 16.0 Hz), 6.33 (1H, dd, J = 16.0, 7.0 Hz), 5.43 (1H, d, J = 7.0 Hz), 3.91 (3H, s), 2.40 (1H, br s); ¹³C NMR (100 MHz, CDCl₃) δ 166.91, 147.71, 136.19, 131.35, 130.78, 129.88, 129.40, 128.59, 127.99, 126.62, 126.16, 74.73, 52.08; MS (El) m/z (rel intensity) 268 (57, M⁺), 253 (25), 209 (46), 193 (22), 164 (23), 163 (100), 131 (26), 105 (55); HRMS (El) m/z calcd (M⁺) 268.1099, found 268.1112.

(4-Methoxyphenyl)phenylmethanol [30n] (Tetrahedron 2000, 56, 1135)

![Chemical Structure]

Obtained in 90% yield (Method B1), 84% yield (Method B2); white crystalline solid; mp = 65 °C; Rf = 0.45 (1:4 EtOAc/hexanes); IR (NaCl, thin film) ν 3998, 2923, 1478, 1327, 1023, 961, 880, 712, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.27 (7H, m), 6.87 (2H, d, J = 8.6 Hz), 3.79 (3H, s), 2.42 (1H, br s); ¹³C NMR (100 MHz, CDCl₃) δ 158.94, 143.97, 136.14, 128.36, 127.85, 127.34, 126.35, 113.79, 75.70, 55.20.
Di(4-methoxyphenyl)methanol [30o] (J. Am. Chem. Soc. 1988, 110, 1862)

Obtained in 83% yield (Method B1); colorless oil; \( R_f = 0.35 \) (3:7 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.28 (4H, d, \( J = 8.8 \) Hz), 6.87 (4H, d, \( J = 8.8 \) Hz), 5.78 (1H, s), 3.79 (6H, s), 2.39 (1H, br s); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 158.96, 136.36, 127.73, 113.81, 75.37, 55.27.


Obtained in 85% yield (Method B1), 82% yield (Method B3), 83% yield (Method B4); colorless oil; \( R_f = 0.20 \) (1:4 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.50-7.22 (9H, m), 5.78 (1H, s), 2.32 (1H, br s); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 143.32, 142.68, 131.52, 128.63, 128.18, 127.85, 126.50, 121.38, 75.62.


Obtained in 98% yield (Method B1), 76% yield (Method B3); white crystalline solid; mp = 85 °C; \( R_f = 0.60 \) (3:7 EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.92-7.80 (5H, m), 7.54-7.31 (7H, m), 5.97 (1H, s), 2.20 (1H, br s); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \)

\[
\begin{align*}
\text{Obtained in 86\% yield (Method B1); colorless oil; } R_f & = 0.45 \text{ (1:4 EtOAc/hexanes); }^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.38-7.24 \text{ (5H, m), 4.38 (1H, d, } J = 7.0 \text{ Hz), 2.02-1.92 (1H, m), 1.85-1.72 (2H, m), 1.71-1.56 (3H, m), 1.43-1.34 (1H, m), 1.31-0.67 (5H, m); }^1\text{C NMR (100 MHz, CDCl}_3) \delta 142.24, 128.17, 127.40, 126.62, 79.39, 44.95, 29.30, 28.81, 26.41, 26.08, 26.00.}
\end{align*}
\]
References (Section B)


Appendix A - Selected NMR Spectra (Section A)
Appendix B - X-Ray Crystal Structure Data (Section A)
Table 2. Atomic coordinates \( x \times 10^4 \) and equivalent isotropic displacement parameters \( \AA^2 \times 10^3 \) for k98143. \( U(\text{eq}) \) is defined as one third of the trace of the orthogonalized \( U^{ij} \) tensor.

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Symmetry transformations used to generate equivalent atoms:

#1 -x + 3, -y + 1, -z
Table 4. Anisotropic displacement parameters ($\AA^2 \times 10^3$) for k98143. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^*u^{11} + \ldots + 2hka^*b^*u^{12}]$

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters \([\AA^2 \times 10^3]\) for \(l\).

The anisotropic displacement factor exponent takes the form:

\[-2\pi^2 \left[ (h\alpha)^2 u_{11} + \ldots + 2hka b^* u_{12} \right] \]

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Appendix C - Selected NMR Spectra (Section B)
[28c]