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Reactions of Diisopropylaminoborane and Metal Dialkylaminoborohydrides

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2015

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REATIONS OF DIISOPROPYLAMINOBORANE AND METAL DIALKYLAMINOBOROHYDRIDES

A dissertation submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

by

Christopher L. Bailey

June 2015

The Dissertation of Christopher L. Bailey is approved:

Professor Bakthan Singaram, Advisor

Professor Pradip Mascharak, Chair

Professor Rebecca Braslau

Tyus Miller
Vice Provost and Dean of Graduate Studies
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2015
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Abstract

REACTIONS OF DIISOPROPYLAMINOBORANE AND METAL DIALKYLAMINOBOROHYDRIDES

by

CHRISTOPHER L. BAILEY

Diisopropylaminoborane (H₂B-N(iPr)₂) is prepared as a monomer from the reaction of lithium diisopropylaminoborohydride with trimethylsilyl chloride at ambient conditions. Monomeric aminoboranes, such as H₂B-N(iPr)₂, can reduce nitriles and esters in the presence of catalytic amounts of LiBH₄. Diisopropylaminoborane serves as an inexpensive boron source in the palladium-catalyzed borylation of aryl bromides, iodides, and triflates, affording the corresponding boronic acid upon work-up. From aryl bromides and iodides, the borylation reaction affords the boronic acids in moderate to good yields. Borylation of aryl triflates affords the corresponding boronic acids in high yields.

Boronic acids can be synthesized upon reaction of H₂B-N(iPr)₂ with Grignard reagents at ambient conditions. Aliphatic, aromatic, and heteroaromatic (diisopropylamino)boranes are readily synthesized at ambient temperature by the reaction of Grignard reagents with H₂B-N(iPr)₂. This borylation reaction can be carried out under Barbier conditions, where H₂B-N(iPr)₂ traps the in situ formed Grignard reagent from the corresponding organic halide and magnesium metal. Simple acid hydrolysis of the product organo(diisopropylamino)borane leads to the corresponding boronic acid in good to excellent yield.
Reaction of H₂B-N(iPr)₂ with two equivalents of Grignard reagents results in the formation of B,B-dialkyl(diisopropylamino)borane within one hour at room temperature. This has allowed for the preparation of a series of symmetrical and unsymmetrical aminoboranes. Unsymmetrical B,B-dialkyl(diisopropylamino)boranes are prepared by reaction of H₂B-N(iPr)₂ with a sterically demanding Grignard reagent, followed by a less hindered one, or by reaction with dialkylzinc followed by subsequent reaction with a Grignard or organolithium reagent. Furthermore, H₂B-N(iPr)₂ reacts only once with the mild dialkylzinc reagents, affording the boronic acid upon aqueous work-up.

Magnesium aminoborohydride, a by-product of the reaction of Grignard reagents with H₂B-N(iPr)₂, is an unknown class of borohydride. Chloromagnesium dimethylaminoborohydride (ClMg⁺[H₃B-NMe₂]⁻, MgAB) is an analogue of the versatile lithium dialkylaminoborohydrides (LAB reagents), prepared by the reaction of dimethylamine-borane with methylmagnesium chloride. MgAB can reduce amides to alcohols or aldehydes under ambient conditions and is complementary to the commonly utilized lithium aluminum hydride (LiAlH₄) and diisobutylaluminum hydride (DIBAL) reagents, though it exhibits enhanced chemoselectivity. MgAB can reduce amides in the presence of esters, nitriles, and units of unsaturation. MgAB has also been shown to reduce lactams to the corresponding amines.
Dedication

To my family,

for your love and support.

To Dr. Bakthan Singaram,

for taking me into your lab

To Dr. Andrew Bockus,

for your advice, collaboration, laughter, and friendship

And to my husband, Dr. Ryan Shelby,

I love you with all my heart.

Chemicals! But what are they?
Acknowledgements

The work presented in this thesis could not have been done without the support of faculty, coworkers, family, and friends. I would like to start by expressing gratitude for my advisor, Dr. Bakthan Singaram. I will be eternally thankful for the guidance, advice, and generosity he has provided throughout my time as his student. I learned so much about organic synthesis from his lecture and personal discussion. Bakthan has a sincere enthusiasm for chemistry, science, education, and mentoring that has been an inspiration to me. Prior to joining his group, I was hesitant to speak in public, let alone speak about science. Bakthan has taught me how to think critically about chemistry, how to talk, and how to write about chemistry. Bakthan teaches his students to value the importance of effective communication skills. Through his guidance and practice, I have not only overcome a fear of speaking, but I speak loudly and confidently about chemistry. Bakthan, you are wise, you are weird, and I have enjoyed my time as your student. I only hope that I will be able to inspire students as you have.

I would also like to thank the members of my research committee for their valuable guidance. I thank Dr. Pradip Mascharak for serving as the chair of my committee. An accomplished chemist, Pradip taught me the value of a well-thought explanation, and that I should never suffer a fool. To Dr. Rebecca Braslau, I owe a debt of gratitude. Beyond her masterful skills as a teacher, Rebecca is a keen editor. Under her instruction, I have learned how to sharpen my writing skills, as well as how
correctly to use an adverb. Thank you both. I also thank Eric Stangeland for sitting as the outside committee member on my qualifying exam.

I would like to thank Professor Daniel Palleros. He is an excellent teacher one of the most passionate educators I have ever met. Working with him, I learned how to teach, and how to love teaching.

I would like to thank my fellow members of the Singaram Group, past and present. To Dr. Dustin Haddenham, thank you for helping me get a start in a research lab. That simple act of kindness launched my career in chemistry. Thank you for being patient and training me in all aspects of the work with LAB reagents and diisopropylaminoborane. To think that neither one of us thought triflates would be reactive with the aminoborane. To Dr. Scott Eagon, thank you for the advice and encouragement. And most of all, thank you for your humor. To Dr. Jake Clary, I say enough with Rush Limbaugh. To Dr. Jaime Saavedra, may your documents always be foxy. To Angel Resendez, ¡esparamé!

Outside of the group, I have to give many thanks to all my fellow graduate students at UCSC for helping make the graduate experience a pleasurable one. Kenji Kurita and Andrew Bockus were two of my best friends in graduate school. Their moral support throughout the years has been invaluable. Nathaniel Zuckerman, Stephanie Curzon, Jake Haecikl, Christopher Warner, and Walter Bray always gave good advice about research or life. I have always been impressed by their consideration for others, and their scientific intelligence. I would like to thank the
members of the Linington, Lokey, and Mascharak, research group for general suggestions about chemistry and support of chemicals and instrumentation.

If no man is an island, so too is no chemist. I would like to thank staff members of the Department of Chemistry and Biochemistry. My graduate studies would not have been as smooth without them: Karen Fry, Janet Jones, Leslie-Reid Harrison, Karen Meece, and Patti Schell. I am grateful for the endless help from Jack (Hsiau-Wei) Lee regarding nuclear magnetic resonance, and MestReNova support.

Lastly, I need to say a special thanks to the wonderful undergraduate students I have had the pleasure of working with: Brian Crowder, Lucas Klabunde, Alex Joh, Chris Anderson, Alex Lill, Zefan Hurley, Kara Nguyen, and John Balderrama. I never would have been able to finish the work without your help, your questions, and your advice. More importantly, I am glad that after working together we became friends. I am proud of all of you.
The text of this dissertation includes portions of the following previously published material:

1. “Lithium Aminoborohydrides 17. Palladium Catalyzed Borylation of Aryl Iodides, Bromides, and Triflates with Diisopropylaminoborane Prepared from Lithium Diisopropylaminoborohydride”
   Dustin Haddenham, Christopher L. Bailey, Chau Vu, Gabby Nepomuceno, Scott Eagon, Lubov Pasumansky, Bakthan Singaram

   Christopher L. Bailey, Chris L. Murphy, Jacob W. Clary, Scott Eagon, Naomi Gould, Bakthan Singaram

3. “Reduction of Weinreb Amides to Aldehydes Under Ambient Conditions with Magnesium Borohydride Reagents”
   Christopher L. Bailey, Jacob W. Clary, Chittreeya Tansakul, Lucas Klabunde, Christopher L. Anderson, Alexander Y. Joh, Alexander T. Lill, Natalie Peer, Rebecca Braslau, Bakthan Singaram

Professor Bakthan Singaram directed and supervised all of the research described in these papers.
CHAPTER 1

Introduction and Background of Lithium Aminoborohydrides, Diisopropylaminoborane, and Boronic Acids
1.1 Introduction

Introduction of chemoselective hydride reagents has changed the way chemists tackle regiochemical challenges. Prior to the advent of metal hydride reagents, the reductions of aldehydes or ketones were accomplished through non-hydridic methods; often involving the reaction of the starting compound with a metal in solution.\(^1\) For example, benzophenone was reduced to benzhydrol by zinc and sodium hydroxide (Eq. 1).\(^2\)

\[
\begin{align*}
\text{O} & \quad \text{Zn/NaOH, EtOH} & \quad \text{OH} \\
\text{\text{[benzophenone]}} & \quad 2-3 \text{~h, 70 °C} & \quad \text{[benzhydrol]}
\end{align*}
\]

(1)

A simple aliphatic aldehyde was reduced to the corresponding primary alcohol by treating it with iron in acetic acid (Eq. 2).\(^3\)

\[
\begin{align*}
\text{O} & \quad \text{Fe}\text{O}^0, \text{HOAc} \\
\text{\text{[aldehyde]}} & \quad 6-7 \text{~h, 100 °C} & \quad \text{\text{[alcohol]}}
\end{align*}
\]

(2)

These methods have some serious drawbacks, including the production of large quantities of metal by-products, the requirement for long reactions times and high temperatures, and modest yields of the desired products. Consequently, these once standard methods are seldom utilized in modern organic chemistry. Despite the drawbacks, non-hydric methods for reduction remain in use today. The Meerwien-Ponndorf-Verley reduction is still being used for the reduction of ketones.\(^4\) The use of isopropanol as both a solvent and a hydride source in this reaction ensures a mild and safe reduction (Eq. 3).\(^5\)
Additionally, these methods suffer from poor yields and a lack of general applicability to a variety of carbonyl groups. Thus, a demand for general, efficient, and mild methods for the reduction of various organic functionalities persists.

1.2 Metal Hydride Reagents

Metal hydride reagents were first realized as useful reagents when Schlesinger and Brown discovered that diborane could reduce aldehydes and ketones to their corresponding alcohols at low temperatures.\(^1\text{a,6}\) Unfortunately, the method for production of diborane proved inefficient and limiting.\(^1\text{a,7}\) The subsequent discovery that diborane could be generated by the reaction of boron trifluoride etherate (\(\text{BF}_3\):\(\text{OEt}_2\)) with lithium hydride (\(\text{LiH}\)) allowed for further study (Scheme 1.1).\(^8\)

\[
6 \text{LiH} + 8 \text{BF}_3\text{OEt}_2 \xrightarrow{\text{Et}_2\text{O}} \text{LiBH}_4 + 6 \text{LiBF}_4
\]

\[
\text{LiH} + \frac{1}{2} (\text{BH}_3)_2 \xrightarrow{\text{Et}_2\text{O}} \text{LiBH}_4
\]

**Scheme 1.1.** Preparation of Lithium Borohydride from Lithium Hydride

The corresponding reaction with the more abundant sodium hydride proceeded in tetrahydrofuran (THF) to yield sodium borohydride (\(\text{NaBH}_4\)).\(^9\) Furthermore, it was shown that allowing sodium hydride to react with trimethylborate at high temperatures produced sodium borohydride (Eq. 4).\(^10\)
This safe reducing agent has been popular for over sixty years, and is still widely used as a mild reducing agent, capable of reducing both ketones and aldehydes.\textsuperscript{11}

The mild reducing power that makes sodium borohydride such a popular reagent also limits it use. While NaBH\textsubscript{4} allows for selective reductions of aldehydes or ketones, less reactive functional groups remain untouched. A more powerful reducing agent is needed for other functional groups such as carboxylic acids or nitriles. In addition, sodium borohydride is water soluble, limiting its use with organic solvents other than alcohols and polyethers. These drawbacks led to the search for more powerful metal hydride reagents.

Schlesinger reported the preparation of lithium aluminum hydride (LiAlH\textsubscript{4}) upon reaction of lithium hydride with aluminum trichloride in ether (Eq. 5).\textsuperscript{12}

$$4 \text{LiH} + \text{AlCl}_3 \xrightarrow{\text{Et}_2\text{O}} 4 \text{LiAlH}_4 + 3 \text{LiCl} \quad (5)$$

LiAlH\textsubscript{4} was found to be quite a powerful reducing agent, capable of reducing many different organic functional groups, including functionalities shown to be inert to NaBH\textsubscript{4}.\textsuperscript{13} Beyond its powerful reducing capabilities, LiAlH\textsubscript{4} has many other attractive features: its ease of preparation and commercial availability; it is indefinitely stable at room temperature under an inert atmosphere; and is soluble in ethereal solvents, allowing for ease of isolation of products.\textsuperscript{14} Because of these properties, LiAlH\textsubscript{4} remains one of the most popular powerful reducing reagents in modern organic chemistry.
Despite its broad use, LiAlH$_4$ does suffer some drawbacks. The powerful reducing properties of LiAlH$_4$ preclude its use in multifunctional compounds where selective reduction is desired. Aside from its reducing capabilities, the reagent itself has proved difficult to handle. As a pyrophoric reagent, extreme care must be taken to exclude air and moisture while handling LiAlH$_4$. In addition, simple aqueous quench and work-up procedures are problematic for reactions involving LiAlH$_4$. Instead of resolving into a separation of layers, the formation of aluminum alkoxide emulsions occur, leading to difficulty in recovering the desired product.$^{14}$

The discovery of NaBH$_4$ and LiAlH$_4$ changed the manner in which the reduction of functional groups is carried out in organic synthesis.$^{15}$ Sodium borohydride is mild and selective, capable of reducing aldehydes and ketones with ease. Conversely, LiAlH$_4$ is much more powerful, reducing nearly all functional groups. These two reagents represent the two extremes of a broad spectrum of reducing agents. Ever since the discovery of LiAlH$_4$, there have been efforts in the development of safe and accessible alternatives to this powerful reducing reagent.$^{16}$ This has been achieved in many different ways by either increasing the reactivity of NaBH$_4$ or decreasing the reactivity of LiAlH$_4$. One manner of controlling the reducing power of complex metal hydrides is through the replacement of one of the hydrogen atoms with another substituent or substituents in the complex ion.$^{17}$ The replacement of a hydride with an alkyl substituent modulates the reducing power by exerting a steric and/or electronic influence.
Preparation of substituted derivatives increase the stability of new hydride reagents, but are often accompanied by a decrease in reactivity. For example, introduction of alkoxy groups to LiAlH₄ produce stable, yet mild and selective reducing agents, such as lithium trimethoxyaluminohydride (LTMA)¹⁸ and lithium tris-tert-butoxyaluminohydride (LTBA).¹⁹ These types of reagents are prepared by the reaction of LiAlH₄ with an alcohol. The desired product precipitates from diethyl ether and can be taken up in THF or diglyme (Scheme 1.2).²⁰

\[
\begin{align*}
\text{LiAlH}_4 + 3 \text{MeOH} & \xrightarrow{\text{Et}_2\text{O}, 25 \degree C} \text{Li(MeO)}_3\text{AlH}_6 + 3 \text{H}_2 \\
\text{LiAlH}_4 + 3 \text{fBuOH} & \xrightarrow{\text{Et}_2\text{O}, 25 \degree C} \text{Li(fBuO)}_3\text{AlH}_6 + 3 \text{H}_2
\end{align*}
\]

**Scheme 1.2. Preparation of Lithium Alkoxyaluminohydrides**

LTBA can reduce aldehydes and ketones to their corresponding alcohols and acid chlorides to the corresponding aldehydes, while the less sterically hindered LTMA reduces aromatic and aliphatic nitriles to the corresponding aldehydes.²¹ These lithium alkoxyaluminohydride reagents have analogous reactivity and stability to the mild reducing agent NaBH₄, but still possess the problems of LiAlH₄ such as the formation of gels during work-up. Consequently, no real synthetic advantages are gained by the use of these modified LiAlH₄ alternatives.

**1.3. Alkali Metal Alkylborohydrides**

Attempts to prepare stable derivatives of LiAlH₄ resulted in reagents that are less reactive, but also difficult to handle. In contrast, preparation of alkyl-substituted borohydrides led to more powerful reagents. Alkylborohydrides are useful reducing
agents and as such their syntheses are important.\textsuperscript{22} Brown demonstrated that metal hydrides add to borane under ambient conditions to form borohydrides. For example, potassium hydride adds to borane to form potassium borohydride (Eq. 6).\textsuperscript{23}

\[
H_3B\cdot\text{THF} + KH \xrightarrow{\text{THF, 25 }{\circ}\text{C}} \text{KBH}_4
\]  

(6)

In the preparation of alkylborohydrides from metal hydrides, potassium hydride adds to borane quickly, followed in reaction rate by sodium hydride, and then lithium hydride. The rate of addition of metal hydride is related to the corresponding crystal lattice energy.\textsuperscript{24} Lithium hydride has the greatest lattice energy and thus reacts slower with borane, compared to potassium hydride and sodium hydride. In contrast with the slow reactivity with borane, lithium hydride reacts with unhindered trialkylboranes, such as trimethylborane (Eq. 7).\textsuperscript{25}

\[
\text{LiH} + \text{Me}_3B \xrightarrow{\text{THF, 65 }{\circ}\text{C, 0.5 h}} \text{Me}_3B\text{H Li}
\]  

(7)

Although direct addition of lithium hydride is possible with unhindered trialkylboranes, lithium hydride does not react with hindered trialkylboranes. The reaction of lithium hydride with tributylborane is sluggish, giving low yields even after prolonged reaction times.\textsuperscript{23}

Dialkylborohydrides are useful as reducing agents: the direct addition of metal hydrides to dialkylboranes has been demonstrated.\textsuperscript{26} Brown reported that sodium hydride reacts with 9-borabicyclo[3.3.1]nonane (9-BBN) to afford the sodium borohydride of 9-BBN under ambient conditions (Eq. 8).\textsuperscript{27}
Similarly, the potassium borohydride of 9-BBN is obtained upon reaction of potassium hydride with 9-BBN. At room temperature, lithium hydride does not add to 9-BBN, but the lithium borohydride of 9-BBN forms under reflux (Eq. 9).

\[
\text{BH} + \text{LiH} \xrightarrow{\text{THF} \ 65 \ ^\circ \text{C}, \ 2 \ h} \text{BH}_2\text{Li}
\]  

(9)

To probe the generality of the addition of lithium hydride to dialkylboranes, Brown explored the reaction of lithium hydride with diisopinocampheylborane. Unfortunately, after two hours at reflux, a complex distribution of products is obtained. Under ambient conditions, dicyclohexylborane and disiamylborane proved unreactive to lithium hydride. Upon heating, each borane gives a mixture of products. Contrary to the poor reactivity of lithium hydride with diisopinocampheylborane, potassium hydride reacts to afford potassium borohydride (Eq. 10).  

\[
\text{BH} + \text{LiH} \xrightarrow{\text{THF} \ 65 \ ^\circ \text{C}, \ 2 \ h} \text{BH}_2\text{K}
\]  

(10)

Another alternative to LiAlH₄ are alkali metal trialkylborohydrides, which can be synthesized by the reaction of alkali metal hydrides with trialkylboranes. Potassium derivatives of these metal hydride reagents are the simplest to synthesize via this route, but are the least reactive among the alkali metal trialkylborohydrides. Conversely, lithium trialkylborohydrides are powerful reducing agents, although the preparation is accomplished through indirect methods. As lithium hydride proves
unable to add to dialkylboranes or hindered trialkylboranes, an alternative method is needed to prepare lithium di- and trialkylborohydrides. Corey reported a procedure where tert-butyllithium was allowed to react with hindered tri-\(n\)-butylborane under cryogenic conditions to afford the lithium tributylborohydride (Eq. 11).\(^{31}\)

\[
\begin{align*}
\text{Li} + n\text{-Bu}_3\text{B} & \overset{\text{THF}}{\underset{-78 ^\circ \text{C}, 0.5 \text{ h}}{\rightarrow}} n\text{-Bu}_3\text{BHLi} + \\
\end{align*}
\]

The reaction is general and works for various trialkylboranes. The isobutene side-product volatilizes when the reaction mixture is warmed to room temperature, allowing for isolation of the pure trialkylborohydride. Despite the direct preparation of trialkylborohydrides by this method, the requirement for cryogenic conditions, along with the reactivity of tert-butyllithium limits large-scale utilization.\(^{32}\) Brown also demonstrated that reaction of lithium aluminum hydride with 9-BBN affords the lithium boroxydride of 9-BBN (Eq. 12).\(^ {33}\)

\[
\begin{align*}
\text{BH} & + \text{LiAlH}_4 \overset{\text{Et}_2\text{O}}{\underset{0 ^\circ \text{C}, 0.5 \text{ h}}{\rightarrow}} \text{BH}_2\text{Li} + \text{AlH}_3 \\
\end{align*}
\]

To test the generality of this reaction, lithium aluminum hydride was allowed to react with mono-, di-, and trialkylboranes. In each instance, the corresponding mono-, di-, and trialkylborohydrides were produced quantitatively (Scheme 1.3).
Scheme 1.3. Preparation of Mono-, Di-, and Trialkylborohydrides from LiAlH₄

The unwanted alane is removed by precipitation with 1,4-diazabicyclo[2.2.2]octane (DABCO), allows for isolation of the desired borohydride. Later, Brown developed a procedure to generate borohydrides by reaction of lithium trimethoxyaluminoxyhydride (LTMAH) with hindered trialkylboranes (Eq. 13).³⁴

Unfortunately, the reaction with LTMAH results in the formation of an aluminum oxide gel, restricting isolation of the product borohydride. This complication can be alleviated by allowing potassium triisopropoxyborohydride to react with the alkylboranes in lieu of LTMAH.³⁵ The resulting borohydrides are easily isolated from the solution.

Lithium trialkylborohydrides are some of the most powerful nucleophilic reducing agents known, but suffer from many of the same problems as LiAlH₄. These problems arise from their extreme pyrophoric nature and lack of chemoselectivity. One of the more popular trialkylborohydrides is lithium triethylborohydride...
Lithium triethylborohydride (LiEt$_3$BH), referred to as “Super-Hydride.” Lithium triethylborohydride is prepared by the reaction of lithium hydride and triethylborane at ambient temperature (Eq. 14).

$$\text{LiH} + \text{BEt}_3 \xrightarrow{\text{THF, 25} \, ^\circ \text{C}} \text{LiEt}_3\text{BH} \quad (14)$$

As the name suggests, Super-Hydride is a powerful reducing agent, exceeding the power of LiAlH$_4$. This is exemplified by the rate of reduction of $n$-octyl chloride. In this reaction, LiEt$_3$BH produces $n$-octane in only 4 hours at room temperature, whereas LiAlH$_4$ requires 24 hours to perform the same transformation. As can be expected from such a powerful reducing agent, LiEt$_3$BH is capable of reducing most carbonyl functional groups.

Hydride reagents produced since the 1940s fall into two dominant classes representing their extreme difference in reactivity. The first includes LiAlH$_4$ and lithium trialkylborohydrides: powerful reducing reagents capable of reducing most carbonyl functional groups, while the second includes trialkoxyborohydrides and sodium borohydride: mild, chemoselective reducing agents.

Research has been conducted into modulating the power of these reducing agents, whether aluminum or boron-based, through the introduction of amino groups in place of alkyl or alkoxy groups. Nitrogen is less electronegative than oxygen: the nitrogen groups should be more effective at donating their lone pair of electrons to the metal center. Consequently, aminoborohydride compounds are hypothesized to have enhanced hydride-delivering abilities compared to borohydride or trialkoxy
derivatives. Hutchins demonstrated this reactivity in the synthesis and reactivity of sodium aminoborohydrides (Eq. 15).\(^\text{37}\)

\[
\text{H}_3\text{B}:\text{NHMe}_2 + \text{NaH} \xrightarrow{\text{THF, } 25 \degree \text{C, } 1 \text{ h}} \text{Na}^+ [\text{H}_3\text{B-\text{NMe}_2}]^- \quad (15)
\]

Sodium dimethylaminoborohydride shows enhanced reductive capability; reducing aldehydes, ketones, and esters to their corresponding alcohols. Unfortunately, these reductions require long reaction times and elevated temperatures, precluding their utility and advancement of this methodology. Furthermore, reactivity towards amides has proven unreliable. For example, reduction of \(N,N\)-diethylcyclohexane carboxamide with sodium dimethylaminoborohydride affords a mixture of the corresponding alcohol and amine products (Eq. 16).

\[
\begin{align*}
\text{O} & \xrightarrow{\text{Na}^+ [\text{H}_3\text{B-\text{NMe}_2}]^- \text{THF, } 65 \degree \text{C, } 24 \text{ h}} \quad \text{15\%} \\
\text{N} & \quad \text{85\%}
\end{align*}
\]

These drawbacks may be due to the small size of the sodium cation, as small cations have more Lewis acidic character. Other borohydride reagents have also shown this trend of decreased reactivity with smaller cations. For instance, the reactivity of lithium, sodium, and potassium borohydrides decreases in the series \(\text{LiBH}_4 > \text{NaBH}_4 > \text{KBH}_4\).\(^\text{6}\) No further work has appeared in the literature on the use of sodium aminoborohydride reducing agents; the goal of preparing powerful, air-stable reducing agents seemed to be as elusive as ever. The discovery and subsequent characterization of the reducing properties of lithium aminoborohydrides (LAB reagents) by the Singaram group was a breakthrough.\(^\text{38}\)
1.4 Lithium Aminoborohydrides

Lithium aminoborohydride reagents were first reported by Singaram while investigating the hydroboration of $\beta,\beta$-disubstituted enamines with borane dimethylsulphide (BMS). In this reaction, morpholinoborane was formed as a byproduct (Eq. 17).$^{39a,b}$

\[
\text{H}_3\text{B}\cdot\text{SMe}_2, 25^\circ\text{C} \quad \rightarrow \quad \text{BH}_2 + \text{H}_2\text{B}-\text{N} \quad \text{(17)}
\]

To verify this observation, authentic samples of these aminoboranes were needed. Consequently, several methods for their production were explored and a new method for the synthesis of aminoboranes was developed (Eq. 18).$^{39}$

\[
\text{H}_3\text{B}:\text{HN} \quad \rightarrow \quad \text{nBuLi, 0 }^\circ\text{C} \quad \rightarrow \quad \text{LiH}_3\text{B} - \text{N} \quad \rightarrow \quad \text{H}_2\text{B}-\text{N} \quad + \quad \text{CH}_4 \quad \text{(18)}
\]

Reaction of $n$-butyllithium or methyllithium with an amine-borane ($\text{H}_3\text{B}:\text{NHR}_2$) in THF affords the corresponding LAB reagents in quantitative yields. When the LAB reagents were quenched with methyl iodide at $0^\circ\text{C}$, a violent exothermic reaction ensued. The corresponding aminoboranes were isolated in high purity as determined by $^{11}\text{B}$-NMR. Methyl iodide is known to react in a similarly vigorous fashion with LiAlH$_4$ and LiEt$_3$BH, suggesting that LAB reagents are powerful reducing agents.$^{1a}$

1.4.1 Characterization of LAB reagents

The method used for synthesizing LAB reagents is general, and a wide variety of amino groups are accommodated. Following this procedure, several representative LAB reagents have been prepared (Figure 1.1).
The identity of LAB reagents can be assayed using two diagnostic criteria: \( ^{11}\text{B}-\text{NMR} \) coupling constants and the exothermic reaction of LAB reagents with methyl iodide. LAB reagents and their amine-borane precursors both appear as sharp quartets with identical chemical shifts in \( ^{11}\text{B}-\text{NMR} \) spectra, with the difference being their B-H coupling constants. LAB reagents exhibit \( ^{11}\text{B}-\text{NMR} \) coupling constants between 82 and 87 Hz, while amine-borane coupling constants range from 95–98 Hz. The identity of LAB reagents can also be assayed by their vigorous reaction with methyl iodide, which liberates methane and the corresponding aminoborane, while amine-borane complexes are unreactive towards methyl iodide.

LAB reagents are prepared as standard solutions in THF and can be stored for prolonged periods of time in a moisture-free environment without decomposition or loss of reactivity. In addition, LAB reagents can be prepared in solid form by removing the solvent under high vacuum. Unlike LiAlH\(_4\), LAB reagents did not react violently or liberate hydrogen upon contact with water, but rather are converted to the
corresponding amine-boranes. LAB reagents are also non-pyrophoric; they liberate hydrogen slowly with protic solvents. Aqueous quench of the reaction allows for easy phase separation and simple work-up.

1.4.2 Reducing Properties of LAB Reagents

During various studies with LAB reagents, a variety of functionalities are reduced, requiring simple acidic work-up to isolate the desired product. Unlike other powerful reducing reagents, once the LAB is generated, reductions are performed without any precautions to exclude air. In order to maximize yields with LAB reagents requiring reflux or long reaction times, moisture must be excluded. Thus, it is ideal to carry out these reactions in THF under inert atmosphere. Solid LAB reagents are stable enough to be handled in dry air with the same ease as sodium borohydride, providing a safe and stable alternative to LiAlH₄.

1.4.2.1 Reduction of Aldehydes and Ketones

The reduction of aliphatic aldehydes and ketones is completed using LAB reagents in 15-30 minutes at 0 °C.⁴¹ The reduction of 2-methylcyclohexanone with lithium (di-n-propylamino)borohydride (LiH₃B-N(nPr)₂) gives a 2:3 ratio of cis- to trans-2-methylcyclohexanol in 95% yield (Eq. 19).

\[
\text{Eq. 19}
\]
Aromatic ketones can be reduced just as easily. Whether aliphatic or aromatic, the reductions of both aldehydes and ketones requires one equivalent of the LAB reagent for complete reduction to occur.

The stereoselective reductions of 4-substituted cyclohexanones signify that LAB reagents behave like unhindered hydride reagents, regardless of the size of the amine moiety. For instance, the reduction of 4-tert-butylcyclohexanone using LiH₃B-N(nPr)₂ gave 99% trans-4-tert-butylcyclohexanol in 95% yield (Eq. 20).⁴¹d,⁴⁰

\[
\text{Reduction of the same substrate by a less hindered LAB reagent, lithium dimethylaminoborohydride, provided the same product in comparable yield, attesting to the reactive nature of LAB reagents in general. Additionally, the reduction of 3-methylcyclohexanone by lithium pyrrolidinoborohydride (LiPyrrBH₃) provided } \text{cis-3-methylcyclohexanol as the major product (Eq. 21).}
\]

\[
\text{Taken together, these observations indicate that LAB reagents prefer axial attack in the reduction of cyclic ketones, similar to other small reducing agents. The simple preparation and mild reaction conditions of LAB reagents prompted several researchers to use these reagents in their work. Sessler utilized LiPyrrBH₃ in the synthesis of dipyrrrolylquinoxaline analogues (Eq. 22).}^{4¹}
\]
Interestingly, the reduction of α,β-unsaturated aldehydes and ketones provides the corresponding allylic alcohols with amazing regioselectivity. The exclusive 1,2-reduction of both α,β-unsaturated aldehydes and ketones by LAB reagents is seldom seen with other reagents. Thus, these results demonstrate that LAB reagents complement the reactivity of LiAlH₄. For example, LiAlH₄ reduction of cinnamaldehyde gives the corresponding saturated alcohol exclusively. In contrast, LiPyrBH₃ reduce trans-cinnamaldehyde exclusively to the 1,2-reduction product trans-cinnamyl alcohol in 95% yield (Eq. 23).

\[
\text{Cinnamaldehyde} \xrightarrow{\text{LiH}_3B-N} \text{trans-Cinnamyl alcohol} \quad (23)
\]

The α,β-unsaturated ketone (R)-(-)-carvone is similarly reduced to the corresponding 1,2-reduction product in 96% yield (Eq. 24).

\[
\text{(R)-(-)-Carvone} \xrightarrow{\text{LiH}_3B-N} \text{1,2-reduction product} \quad (24)
\]

The chemoselectivity of LAB reagents can be demonstrated through the reduction of Hagemann's ester. Using one equivalent of LiPyrBH₃, the more reactive α,β-unsaturated ketone is reduced, leaving the ester untouched (Eq. 25).
1.4.2 Reduction of Esters

Although several reducing agents will reduce esters to alcohols, all practical methodologies require rigorous exclusion of air.\textsuperscript{43} In contrast, LAB reagents can reduce both aliphatic and aromatic esters without the need to exclude air.\textsuperscript{42d} For instance, ethyl benzoate is reduced to benzyl alcohol in 30 min at 0 °C in 95% yield (Eq. 26).

\[
\begin{align*}
\text{O} & \quad \text{LiH}_3\text{B} - \text{N} \quad \text{OH} \\
\text{CO}_2\text{Et} & \quad \text{THF, 25 °C, 3h} \quad 94\% \\
\text{CO}_2\text{Et} & \quad \text{OH}
\end{align*}
\]

(25)

Reduction of the α,β-unsaturated ester, ethyl cinnamate, affords the 1,2-reduction product, cinnamyl alcohol, in 95% yield (Eq. 27).

\[
\begin{align*}
\text{O} & \quad \text{LiH}_3\text{B} - \text{N} \quad \text{OH} \\
\text{OEt} & \quad \text{THF, 0 °C, 30 min} \quad 95\% \\
\text{OH} & \quad \text{C}_{12}H_{11}
\end{align*}
\]

(26)

The mild reaction conditions, short reaction times, and chemoselectivity of the reductions of aliphatic and aromatic esters by LAB reagents make them excellent alternatives to the other available methods.\textsuperscript{42d,44}

1.4.2.3 Reduction of Amides

Current methods for the reductions of tertiary amides require rigorous exclusion of air.\textsuperscript{42} Primary and secondary amides are not reduced by LAB reagents
even under reflux. A variety of aromatic and aliphatic tertiary amides are reduced, with the isolation of the corresponding products in excellent yields.\textsuperscript{42c,d} Interestingly, reduction of unhindered tertiary amides, such as \(N,N\)-dimethylbenzamide, provide benzyl alcohol regardless of the LAB reagent used. When reducing more sterically demanding tertiary amides, selective C-O or C-N bond cleavage can be achieved through variation of the steric environment on the amine moiety of the LAB reagent.\textsuperscript{45} For example, reduction of 1-pyrrolidinoctanamide with LiPyrrBH\textsubscript{3} provides 1-octanol in 77\% yield, while the same reduction with the more sterically crowded lithium diisopropylaminoborohydride (LiH\textsubscript{3}B-N(iPr)\textsubscript{2}), provides 1-octylpyrrolidine in 95\% yield (Scheme 1.4).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme1.png}
\end{center}

**Scheme 1.4.** Chemoselective Reduction of Tertiary Amides with LAB reagents

The selectivity of this reduction appears to involve a common intermediate, 1, the initial reduction product of the amide (Figure 1.2).\textsuperscript{42d,45k}
Figure 1.2. Mechanism of the Reduction of Tertiary Amides

From this intermediate there are two possible routes to the corresponding amine or alcohol. In Path A, the iminium species 3 is formed by the expulsion of the lithium dihydridoaminoborinate 2 by the nitrogen lone pair. This iminium is then reduced to the corresponding amine 4 by remaining LAB reagent. In Path B, the complexation of an aminoborane to the nitrogen of 1 converts the amine to the ammonium moiety 5, making it a better leaving group. Cleavage of the B-O bond and subsequent expulsion of the diaminodihydridoborohydride moiety produces aldehyde 6, which can be rapidly reduced to the corresponding alcohol 7. During this study, the sterics of the amide as well as the LAB reagent were found to dictate the route of the reaction. As the amino groups in the LAB reagent become more sterically demanding, the formation of the amine product through C-O bond cleavage is favored. It has been thought that unfavorable steric interactions between the LAB reagent and the amide nitrogen are responsible for this trend. In contrast, reductions performed using LiAlH₄ predominantly form the amine product through C-O bond cleavage, while those carried out using LiEt₃BH⁴⁺ produce the alcohol product through C-N bond cleavage. While previous methods have required the use of two different reagents to afforded
selective C-O or C-N bond cleavage, LAB reagents can accomplish this simply by chemists altering the steric environment of the amine moiety.

A widely used pseudoephedrine-based chiral auxiliary for the synthesis of chiral alcohols has been described by Myers. Upon reaction with lithium diisopropylamide (LDA), the amide can be deprotonated and then alkylated with an alkyl halide to give the substituted amide in 95-99% de. Subsequent removal of the pseudoephedrine chiral auxiliary can be accomplished by reducing the amide with lithium pyrrolidinoborohydride (Eq. 28) or lithium amidoborohydride (LiH3B-NH2), providing the desired chiral alcohol in high yield and greater than 90-95% ee.

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \quad \text{R} \\
\text{OH} & \quad 1. \text{LDA, LiCl, } -78 \degree C \\
& \quad 2. \text{R'-X} \\
\text{OH} & \quad \text{N} \quad \text{O} \quad \text{R'} \\
\text{95-99% de} & \quad \text{LiH}_3\text{B-N} \quad \text{THF, 3 h} \\
& \quad \text{OH} \quad \text{R'} \\
& \quad 90-95\% \text{ ee}
\end{align*}
\]

The removal of Myers' chiral auxiliary by LAB reagents is so mild that this method has become widely used. Theodorakis successfully employed lithium amidoborohydride for the removal of the Myers' chiral auxiliary in this synthesis of borelledin, an anti-tumor agent (Eq. 29).

\[
\begin{align*}
\text{OH} & \quad \text{N} \quad \text{O} \quad \text{OBn} \\
& \quad \text{Li}^+ [\text{H}_3\text{BNH}_2]^\cdot 4 \text{ equiv} \\
& \quad -78 \degree C \text{ to } 0 \degree C, 3 \text{ h} \\
& \quad \text{HO} \quad \text{OBn} \\
& \quad 90\% 
\end{align*}
\]

1.4.2.4 Reduction of Lactams

Lactam reductions are of great interest to organic chemistry in natural products and synthetic organic chemistry. Typically these reductions are completed using LiAlH4 with more chemoselective methods using diisobutylaluminum hydride
(DIBAL),\textsuperscript{50} borane,\textsuperscript{51} sodium borohydride,\textsuperscript{52} and rhodium-catalyzed hydrosilation.\textsuperscript{53} All of these methods require rigorous exclusion of air, creating a need for a more easily handled reducing reagent. LAB reagents reduce various $N$-alkyl lactams to the corresponding cyclic amines.\textsuperscript{54} These reductions are complete after two hours in refluxing THF, with isolation of the cyclic amine products using an easy aqueous work-up. For example, 1-cyclohexyl-2-pyrrolidinone is reduced to the corresponding amine in 80\% yield (Eq. 30).\textsuperscript{51}

![Chemical structure of lactam reduction](image)

$$\text{O} \quad \text{Li}^+ [\text{H}_3\text{BNNMe}_2]^{-} \quad 1.5 \text{ equiv}$$

$$\text{THF, 65 °C, 2 h} \quad \text{80\%}$$

This method is generalizable to six-membered lactams, leading to applications in alkaloid chemistry.

**1.4.2.5 Reduction of Alkyl Halides**

During recent work with LAB reagents, Singaram discovered that the stoichiometry of $n$-butyllithium is important for the reduction of alkyl halides.\textsuperscript{55} If this reduction is completed using a LAB reagent that had been synthesized using a stoichiometric amount of $n$-butyllithium, the expected reduction products are not seen. Instead, the reaction yields a mixture of an alkylated amine-borane along with the desired aminoborane (Scheme 1.5). When the same reaction is completed using a LAB reagent synthesized with a slight excess of $n$-butyllithium, the expected reaction product is observed.
Scheme 1.5. Reaction Products Obtained from LAB Reagents Synthesized with Different Amounts of \( n \)-Butyllithium

This difference in reactivity might be the result of mixed aggregate formation, Lewis acid effects from excess \( n \)-butyllithium, or a combination of the two. The reduction properties of LAB reagents are dependent upon the stoichiometry of the \( n \)-butyllithium used in their production.

1.5 Aminoboranes

Aminoboranes (\( \text{R}_2\text{B-NR}'_2 \)) have been used as precursors of boron nitride based ceramics in materials science.\(^{56} \) Dihydridoaminoboranes (\( \text{H}_2\text{B-NR}^1\text{R}^2 \)) have been known since the discovery of the hydroboration reaction, but were found to be unreactive as hydroborating reagents.\(^{57} \) In addition, dihydridoaminoboranes readily form mixtures of cyclic and linear oligomers, preventing purification.\(^{58} \) Consequently, they have been scarcely studied as useful tools for synthetic organic chemistry even though they have potential as mild hydride transfer reagents.
It has been postulated that the B-N bond in aminoboranes exists as a quasi-double bond due to participation of the nitrogen lone pair donating into the empty p-orbital of the boron atom.\textsuperscript{59} In order for the nitrogen lone pair to participate in the B-N, the three bonds to boron must be planar (the B sp\textsuperscript{2} hybridized) as demonstrated by Goubeau and Becher.\textsuperscript{60} Calculations of the force constants of the B-N bond in aminoboranes indicate a bond order of 1.8 at room temperature, making this B-N bond the only combination of boron with another element that can reach such a high bond order.\textsuperscript{61} Dipole measurements of the B-N bond show that this bond can be in two different resonance forms according to Pauling’s electron theory.\textsuperscript{62} Since the bond moments of some methylated aminoboranes are almost zero, it was postulated that resonance between these two forms occurs (Figure 1.3).

\[ \overset{\cdot}\cdot\cdot \text{N} = \text{BH}_2 \quad \iff \quad \overset{\cdot}\cdot\cdot \text{N} = \text{BH}_2 \]

**Figure 1.3.** Resonance Structures of the B-N Bond in Aminoboranes

In agreement with this, calculation of the charge distribution between the boron and nitrogen by the LCAO-molecular orbital method indicates that simple aminoboranes have charge transfer from boron to nitrogen.\textsuperscript{63}

Another result of the molecular orbital calculations was the discovery that rotation about the B-N bond is restricted. Ryschkewitsch demonstrated this through NMR investigations of aminoboranes.\textsuperscript{64} As observed in the \textsuperscript{1}H-NMR, the two methyl groups of the unsymmetrically substituted (methylphenylamino)dimethylborane appear to be non-equivalent, implying restricted rotation. The methyl groups present separate signals with different chemical shifts. As the temperature of the sample was
increased, the peaks for the two methyl groups underwent broadening, eventually merging into one peak at 100 °C. Based on these observations, the energy of activation for rotation of the B-N bond was calculated from the temperature dependence of the chemical shift, showing the hindered rotation of the B-N bond to be on the order of 10-15 kcal/mol. Additionally, aminoboranes have been shown to be nearly unreactive. The low reactivity and bond order of these compounds led to the idea that aminoboranes exist as cyclic structures held together by coordination of the free lone pair of nitrogen with the boron of another aminoborane (Figure 1.4).

\[
2 \text{Me}_2\text{NBH}_2 \rightleftharpoons \text{H}_2\text{B} \equiv \text{NMe}_2 \\
\text{Me}_2\text{N} \equiv \text{BH}_2
\]

**Figure 1.4.** Monomeric and Dimeric Forms of Aminoboranes

Dimeric aminoboranes are usually formed if one or more of the substituents on the boron or nitrogen are a hydrogen or halogen. Aminodihalogenboranes containing amines with small alkyl groups dimerize due absence of steric bulk on the amine.\textsuperscript{65,66} Higher polymeric aminoboranes are also known but are seldom used outside of material science because of their general lack of reactivity as synthetic reagents in organic chemistry.

### 1.6 Synthesis of Dialkylaminoboranes

Recently, monomeric (dialkylamino)boranes (H\textsubscript{2}B–NR\textsubscript{1}R\textsubscript{2}, with R\textsubscript{1} and R\textsubscript{2} being sterically demanding alkyl groups) have found use in palladium-catalyzed synthesis of boronic acids from the corresponding aryl and alkenyl halides.\textsuperscript{67} In addition, the requirement for efficient and safe methods for hydrogen storage has
renewed interest in the synthesis of aminoboranes as possible hydrogen storage materials.\textsuperscript{68,69} Renewed interest in the reactivity of these aminoboranes sparked research into the synthesis of aminoboranes.

1.6.1 Reduction of (Amino)dihaloboranes

Dialkylaminoboranes can be synthesized from the corresponding (amino)dihaloboranes by reduction with LiAlH\textsubscript{4} in toluene (Eq. 31).\textsuperscript{70}

\[
\text{N-BCl}_2 + \text{LiAlH}_4 \xrightarrow{\text{toluene}} \text{N-BH}_2
\]  

(31)

The products of this reduction are dependent on the substituents of the amine in the (amino)dihaloborane species. When secondary (amino)dihalogenoboranes with bulky amino substituents are reduced by LiAlH\textsubscript{4}, the corresponding monomeric aminoboranes are formed as the sole products. Conversely, when the amino substituents of the (amino)dihalogenoboranes are small, several other byproducts are formed, along with the expected monomeric aminoborane. There are no further reports on this synthetic route to aminoboranes since other methods are much more practical.

1.6.2 Thermal Dehydrogenation of Amine-Boranes

Amine-borane compounds undergo thermally induced dehydrogenation at elevated temperature, affording mixtures of cyclic aminoboranes and borazines. For instance, dimethylamine-borane eliminated hydrogen at 130 °C to quantitatively yield a cyclic dimer (Eq. 32).\textsuperscript{71}
These dialkylaminoboranes have been known to form mixtures of cyclic and linear oligomers, preventing purification.\(^{58}\) If the nitrogen atom of the aminoborane is sterically hindered, oligomerization is prevented. Thus, isolation of monomeric aminoboranes is possible.\(^{72}\)

Baker and Dixon conducted a study on the thermal dehydrogenation of amine-boranes using varying degrees of steric hindrance to monitor the ratios of monomer to dimer of the final aminoborane.\(^{70}\) The monomeric aminoboranes were isolated in high yields on a multigram scale as distillable and non-pyrophoric liquids. For example, diisopropylamine-borane was converted to diisopropylaminoborane in 85% yield (Eq. 33).

\[
\begin{align*}
\text{H}_3\text{B}:\text{NH}_2\text{Pr}_2 & \xrightleftharpoons[^{160-200 \ ^\circ \text{C}}_{85\%}]^{\text{neat}} \text{H}_2\text{B}-\text{NPr}_2 \ + \ \text{H}_2 \\
\end{align*}
\]

This synthetic route is amenable for the synthesis of a chiral version of a dialkylaminoborane. Monomeric aminoboranes display triplets in the deshielded range of \(\delta +34–37\) ppm in their \(^{11}\text{B}\)-NMR spectra, whereas the amine-boranes display quartets at \(\delta -14–20\) ppm.

### 1.6.3 Metal-Catalyzed Dehydrogenation of Amine-Boranes

Amine-borane complexes undergo dehydrogenation at elevated temperatures to produce a mixture of monomeric and dimeric aminoboranes.\(^{70,74}\) The same dehydrogenation reaction of amine-boranes proceeds at substantially lower
temperatures in the presence of a transition metal catalyst.\textsuperscript{61} For example, a solution of dimethylamine-borane in the presence of 0.5 mol\% [Rh(1,5-cod)(\(\mu\)-Cl)]\(_2\) (1,5-cod = 1,5-cyclooctadiene) or RhCl\(_3\)\(\cdot\)3H\(_2\)O provides the cyclic dimethylaminoboranes in 40-60 hours at room temperature (Eq. 34).

\[
2 \text{Me}_2\text{HN:BH}_3 \xrightarrow{5 \text{ mol} \% \text{Rh(I) or Rh(III)}} \text{25 - 45 °C} \quad \text{H}_2\text{B} \equiv \text{NMe}_2 \\ \text{Me}_2\text{N} \equiv \text{BH}_2 + 2 \text{H}_2 \quad (34)
\]

This has been demonstrated with the iridium complex [Ir(1,5-cod)(\(\mu\)-Cl)]\(_2\), which requires 72 hours at 45 °C for complete dehydrogenation to occur.\textsuperscript{61} When neat dimethylamine-borane is heated to 45 °C for 7 days in the absence of a catalyst, the starting amine-borane can be recovered quantitatively.

Catalytic dehydrogenation has been applied to other secondary amine-boranes such as pyrrolidinoborane,\textsuperscript{73} and has also been utilized for the formation of monomeric dialkylaminoboranes. For instance, when diisopropylamine-borane is treated with a Rh catalyst, the corresponding monomeric diisoproplaminoborane is produced with the evolution of hydrogen gas (Eq. 35).

\[
\text{H}_3\text{B:NH} \equiv \text{iPr}_2 \xrightarrow{5 \text{ mol} \% \text{Rh(I) or Rh(III)}} \text{25 - 45 °C} \quad \text{H}_2\text{B} \equiv \text{NPr}_2 + \text{H}_2 \\ (35)
\]

The formation of monomeric diisopropylaminoborane is due to the steric bulk of the nitrogen substituent. Primary amine-borane complexes such as H\(_3\)B:NH\(_3\) can also undergo catalytic dehydrogenation. Unfortunately, the product isolated is not an aminoborane species, but rather a borazine derivative (Eq. 36).\textsuperscript{73c}
The production of aminoboranes has been of great significance in the areas of hydrogen storage,\textsuperscript{74} transfer hydrogenation reactions\textsuperscript{75} and inorganic polymers.\textsuperscript{76} With the increased need for alternative sources of energy, these reactions have garnered interest as possible hydrogen storage materials.\textsuperscript{77}

The high cost of precious metals warrants the search for alternative inexpensive base metal catalysts. Baker found that $N$-heterocyclic carbene nickel complexes exhibited long catalyst lifetimes and high levels of hydrogen release in the dehydrogenation of amine-borane complexes.\textsuperscript{78} Manners described the dehydrogenation of amine-boranes using 2 mol\% of Cp$_2$TiCl$_2$ activated by two equivalents of $n$-butyllithium at 20 $^\circ$C (Eq. 37).\textsuperscript{79}

\[
2 \text{Me}_2\text{HN:BH}_3 \xrightarrow{2 \text{ mol\% } [\text{Cp}_2\text{Ti}]} \text{toluene, 20 $^\circ$C, 5 h} \quad \begin{array}{c}
\text{H}_2\text{B} \quad \text{NMe}_2 \\
\text{Me}_2\text{N} \quad \text{BH}_2
\end{array} + 2 \text{H}_2 \quad (37)
\]

In a separate report, Manners investigated the use of photoactivated iron complexes in the dehydrogenation of dimethylamine-borane.\textsuperscript{80} In the presence of light, the reaction affords the aminoborane dimer in high yield (Eq. 38)

\[
2 \text{Me}_2\text{HN:BH}_3 \xrightarrow{[\text{CpFe(CO)}_2]_2 ~ 5 \text{ mol\%}} \text{THF, 20 $^\circ$C, 4 h, h} \nu \quad \begin{array}{c}
\text{H}_2\text{B} \quad \text{NMe}_2 \\
\text{Me}_2\text{N} \quad \text{BH}_2
\end{array} + 2 \text{H}_2 \quad (38)
\]

Finally, Chirik reported that a bis(cyclopentadienyl)titanium and bis(indenyl)zirconium catalysts can be used for the dehydrogenation of amine-boranes at room temperatures.\textsuperscript{81} This work has broadened the applicability of these
methods of synthesis for aminoboranes by decreasing the cost of the catalyst and the temperatures required. Unfortunately, there is still a need for a safe and mild route to the synthesis of these aminoboranes.

1.6.4 In Situ Deprotonation of Amine-Boranes

Vaultier reported the palladium-catalyzed borylation of iodides and bromides using dialkylaminoboranes as a boron source. The dialkylaminoboranes appear to be efficient reagents in borylation reactions. Noting the drawbacks of thermally induced or metal-catalyzed dehydrogenation, Vaultier sought to generate the aminoboranes to generate the boryldiisopropylammonium salt from the corresponding amine–borane complex (Scheme 1.6). Upon addition of a base, the aminoborane was generated.

\[
\begin{align*}
H_3B:NM/iPr_2 + HCl &\quad \xrightarrow{\text{Et}_2O, 0^\circ C, 30 \text{ min}} H_2ClB:NM/iPr_2 + H_2 \\
H_3B:NM/iPr_2 + HN/iPr_2 &\quad \xrightarrow{\text{Et}_2O, 0^\circ C, 30 \text{ min}} H_2B-N/iPr_2 + [H_2N/iPr_2]^+Cl^-
\end{align*}
\]

Scheme 1.6. Generation of Diisopropylaminoborane Under Acidic Conditions

1.6.5 Reduction of Alkyl Halides with Lithium Aminoborohydrides

During the initial work with LAB reagents by Singaram, it was observed that the reaction of LAB with methyl iodide was exothermic. Analysis of this reaction using $^{11}$B-NMR spectroscopy showed the formation of the corresponding aminoboranes in high purity (Eq. 39).
With renewed interest in aminoboranes, this method of preparation was investigated further. Given that most current synthetic procedures of aminoboranes require harsh conditions, transition metal catalysts, and the evolution of hydrogen, the production of aminoboranes from LAB reagents appeared to be a viable alternative. The reaction of methyl iodide with LAB reagents is sensitive to temperature. Even at 0 °C, this reaction produces a mixture of amine-borane along with the desired aminoboranes.\(^{55}\) The reaction of LAB reagents with methyl iodide in the presence of a catalytic amount of triethylborane produces aminoboranes exclusively.\(^{84}\) Addition of a catalytic amount of triethylborane to LAB reagents generates catalytic amounts of LiEt\(_3\)BH and aminoborane.\(^{85,86}\) LiEt\(_3\)BH is known to reduce methyl iodide, regenerating triethylborane, which in turn reacts with more LAB, to generate LiEt\(_3\)BH and aminoborane (Figure 1.5). While this method of generating aminoborane is interesting, it requires the use of pyrophoric triethylborane.

**Figure 1.5.** Catalytic Cycle in the Reaction of Et\(_3\)B with LAB and Methyl Iodide

To explore formation of aminoboranes further, Singaram investigated the reaction of different LAB reagents and other alkyl halides. The reaction of a LAB reagent with
trimethylsilyl chloride (TMS-Cl) affords the corresponding aminoboranes (H₂B-NR₂) (Eq. 40).

\[
\text{LiH}_2\text{B-NR}_2 + \text{TMS-Cl} \xrightarrow{\text{THF, 25 °C}} \text{H}_2\text{B-NR}_2 + \text{TMS-H} + \text{LiCl} \tag{40}
\]

The general nature of the reaction of LAB reagents with TMS-Cl allows for the preparation of a variety of aminoboranes (Table 1.1).

**Table 1.1.** Aminoboranes Synthesized from LAB Reagents and TMS-Cl

<table>
<thead>
<tr>
<th>Entry</th>
<th>H₂B-NR₂</th>
<th>Monomer</th>
<th>Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>None formed</td>
<td>100% δ +3 t, J_{BH} = 113 Hz</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>None formed</td>
<td>100% δ +2 t, J_{BH} = 107 Hz</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>1% δ +36 t, J_{BH} = 113 Hz</td>
<td>99% δ +2 t, J_{BH} = 111 Hz</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>40% δ +37 t, J_{BH} = 125 Hz</td>
<td>60% δ +2 t, J_{BH} = 110 Hz</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>100% δ +35 t, J_{BH} = 125 Hz</td>
<td>None formed</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image" /></td>
<td>100% δ +35 t, J_{BH} = 125 Hz</td>
<td>None formed</td>
</tr>
</tbody>
</table>

*The ratio of aminoboranes were determined by \(^{11}\text{B}-\text{NMR spectroscopy}*. }
Aminoboranes with sterically nondemanding substituents, such as pyrrolidinoborane, exist as dimers (Table 1.1, Entry 1). As steric demand around the nitrogen atom increases, the aminoborane exists as a mixture of the monomer and dimer. Sterically hindered aminoboranes, such as diisopropylaminoborane (Table 1.1, Entry 5) and dicyclohexylaminoborane (Table 1.1, Entry 6), exist exclusively as monomers.

Heterocyclic LAB reagents, such as pyrazolyl-LAB and imidazolyl-LAB, do not afford the corresponding aminoboranes when mixed with TMS-Cl. Instead, these LAB reagents are prepared from the corresponding heterocyclic-borane complex and n-butyllithium. Consequently, pyrrolylborane is synthesized by the direct reaction of pyrrole with borane tetrahydrofuran (H\textsubscript{3}B:THF) (Eq. 41).

\[
\begin{align*}
\text{NH} + \text{H}_3\text{B:THF} & \xrightarrow{\text{THF, 25 °C, 4 h}} \text{N-BH}_2 + \text{H}_2
\end{align*}
\]  
(Eq. 41)

Pyrazole and imidazole also produce the corresponding pyrazoloborane (Eq. 42) and imidazoloborane (Eq. 43) with BH\textsubscript{3}:THF at 65 °C.

\[
\begin{align*}
\text{N} + \text{H}_3\text{B:THF} & \xrightarrow{\text{THF, 65 °C, 4 h}} \text{N-BH}_2 + \text{H}_2 \\
\text{NN} + \text{H}_3\text{B:THF} & \xrightarrow{\text{THF, 65 °C, 4 h}} \text{N-BH}_2 + \text{H}_2
\end{align*}
\]

(Eq. 42) 
(Eq. 43)

The heterocyclic LAB reagents do not afford the aminoboranes as monomers. Pyrrole and pyrazole form dimeric aminoboranes whereas imidazole generates polymeric aminoboranes. Pyrazoloaminoborane forms a six-membered dimer through boron-nitrogen coordination, whereas pyrroloborane forms a four-membered dimer through boron-hydrogen coordination (Figure 1.6).
Figure 1.6. Dimers of Pyrazoloborane and Pyrroloborane

1.7 Reactions of Monomeric Diisopropylaminoborane

Singaram investigated aminoboranes as potential hydroborating agents for alkenes and alkynes. A series of hydroboration reactions were attempted utilizing different aminoboranes and either 1-hexene or 1-hexyne. With the exception of pyrroloborane, none of the aminoboranes exhibited hydroboration properties. Additionally, Wrackmeyer demonstrated that pyrroloborane hydroborates two equivalents of alkyne to give $B$-pyrrolyl-dialkenylborane. Singaram has demonstrated the hydroboration of styrene with pyrroloborane at room temperature produced 2-phenylethylboronic acid in 50% yield following basic hydrolysis (Eq. 44).

$$\begin{align*}
\text{N-BH}_2 + \text{C}_6\text{H}_5\text{CH} = \text{CH}_2 & \xrightarrow{1. \text{THF, } 25^\circ\text{C}} \text{C}_6\text{H}_5\text{CH} = \text{CHB(OH)}_2 \\
\text{N-BH}_2 & \xrightarrow{2. \text{Basic work-up}} \text{C}_6\text{H}_5\text{CH} = \text{CHB(OH)}_2 \\
\end{align*}$$

(44)

Similar reaction of phenylacetylene affords the corresponding ($E$)-styrylboronic acid acid in 40% yield (Eq. 45).

$$\begin{align*}
\text{N-BH}_2 + \text{C}_6\text{H}_5\text{C} = \text{C}_2 & \xrightarrow{1. \text{THF, } 25^\circ\text{C}} \text{C}_6\text{H}_5\text{C} = \text{C}_2\text{B(OH)}_2 \\
\text{N-BH}_2 & \xrightarrow{2. \text{Basic work-up}} \text{C}_6\text{H}_5\text{C} = \text{C}_2\text{B(OH)}_2 \\
\end{align*}$$

(45)

Unfortunately, attempts to utilize monomeric diisopropylaminoborane as a hydroboration reagent have been unsuccessful.
1.7.1 Reduction of Nitriles and Esters

During the investigation of reactivity of diisopropylaminoborane (H₂B-N(iPr)₂), it was discovered that nitriles are reduced at room temperature in the presence of catalytic amount of LiBH₄. Reaction of 4-bromo-2-fluorobenzonitrile with H₂B-N(iPr)₂ affords the product in 90% yield following work-up (Eq. 46).

\[
\begin{align*}
\text{CN} & \quad + \quad \text{H}_2\text{B} \quad \text{N} \quad \text{NH}_2 \\
\text{Br} & \quad \text{F} & \quad \text{LiBH}_4 \text{ cat.} & \quad \text{THF}, \text{25 °C}, \text{5 h} & \quad \text{90%} \\
\end{align*}
\]

This reaction is noteworthy, as it does not require the use of any transition metal catalyst. Established methods of nitrile reduction utilize a variety of hydride reducing agents and often require transition metal salts as catalysts. The presence of a catalytic amount of LiBH₄ is essential for this reduction to occur. In the absence of LiBH₄, H₂B-N(iPr)₂ proves inert towards nitriles, and LiBH₄ alone does not reduce nitriles, even under refluxing condition. Examination of the preparation of H₂B-N(iPr)₂ has provided insight into this reducing capability. Aminoboranes prepared from the reaction of LAB reagents with methyl iodide contain trace amounts of LiBH₄ as a by-product (Scheme 1.7). Conversely, solutions of aminoboranes prepared with TMS-Cl contain no LiBH₄.
Scheme 1.7. Differences in the Impurities of Aminoboranes

This reducing system allows for the successful reduction of various nitriles to the corresponding amines in good to excellent yields (Eq. 47).

\[
\begin{align*}
\text{LiH}_{3}\text{B} + \text{H}_{3}\text{C-I} & \xrightarrow{\text{THF, 25 }^\circ\text{C, 1 h}} \text{H}_{2}\text{B} + \text{LiBH}_4 \text{ cat.} \\
\text{made with} & \text{1.1 equiv. } \text{nBuLi} \\
\text{LiH}_{3}\text{B} + \text{TMS-Cl} & \xrightarrow{\text{THF, 25 }^\circ\text{C, 1 h}} \text{H}_{2}\text{B} + \text{no LiBH}_4 \\
\text{made with} & \text{1 equiv. } \text{nBuLi}
\end{align*}
\]

Aromatic nitriles bearing electron-withdrawing groups give significant yield of the amine. For example, 4-bromo-2-chlorobenzonitrile is reduced to 4-bromo-2-chlorobenzylamine in almost quantitative yield (Eq. 48).

\[
\begin{align*}
\text{R-CN} + \text{H}_{2}\text{B} \xrightarrow{\text{LiBH}_4 \text{ cat.}} \text{R-NH}_2 \\
\text{THF, 25 }^\circ\text{C, 5 h} & \quad \text{(47)}
\end{align*}
\]

Substrates with steric crowding of the nitrile require elevated temperatures for the reaction to reach completion, as with the reduction of 2-chloro-5-fluorobenzonitrile (Eq. 49).
The reactions of ortho fluorine substituted benzonitriles are of particular note. Reaction of 6-fluorobenzonitrile with \( \text{H}_2\text{B-N(iPr)}_2 \) affords the corresponding benzylamine. LAB reagents react with fluorine-containing nitriles via a tandem displacement/reduction reaction, affording the corresponding 2-(dialkylamino)benzylamine. For example, reaction of 2-fluorobenzonitrile with lithium dimethylaminoborohydride (LiH\(_3\)B-NMe\(_2\)) affords 2-(aminomethyl)-N,N-dimethylaniline in 80% yield (Eq. 50).\(^{93}\)

Thus, the \( \text{H}_2\text{B-N(iPr)}_2/\text{LiBH}_4 \) reduction methodology complements the LAB tandem reaction methodology (Scheme 1.8).

Scheme 1.8. Reduction or Tandem Amination/Reduction of 4-Fluorobenzonitrile

Aldehydes and ketones are reduced selectively by \( \text{H}_2\text{B-N(iPr)}_2/\text{LiBH}_4 \). In a competitive reduction of 4-bromo-2-fluorobenzonitrile and benzaldehyde, the
aldehyde is reduced to benzyl alcohol in 30 min, leaving 4-bromo-2-fluorobenzonitrile intact (Eq. 51).

\[
\begin{align*}
\text{F} & \quad \text{CN} & + & \quad \text{H}_2\text{B-N(iPr)}_2, \text{LiBH}_4\text{cat.} \\
\text{Br} & & & \quad \text{THF, 25 °C, 30 min} \\
\text{F} & \quad \text{CN} & + & \quad \text{PhCH}_2\text{OH}
\end{align*}
\]

(51)

Conversely, pure H₂B-N(iPr)₂ does not react with aldehydes, ketones, or nitriles, even with extended reflux; the unchanged starting materials are recovered from the reaction mixture.

The H₂B-N(iPr)₂/LiBH₄ system proves to be a general reducing agent that can reduce other functional groups. This system reduces aldehydes and ketones at room temperature. When mixed with esters at room temperature, no reduction is observed. Methyl benzoate is reduced to benzyl alcohol in 95 % yield after 2 hours at 65 °C (Eq. 52).

\[
\begin{align*}
\text{PhCO}_2\text{Me} & + \quad \text{H}_2\text{B-N(iPr)}_2, \text{LiBH}_4\text{cat.} \\
\text{THF, 65 °C, 2 h} & & \quad \text{98%} \\
\text{PhCH}_2\text{OH}
\end{align*}
\]

(52)

The H₂B-N(iPr)₂/cat. LiBH₄ system reduces methyl octanoate to octanol in 98% yield after 2 hours at 65 °C (Eq. 53).

\[
\begin{align*}
\text{C}_8\text{H}_{17}\text{CO}_2\text{Me} & + \quad \text{H}_2\text{B-N(iPr)}_2, \text{LiBH}_4\text{cat.} \\
\text{THF, 65 °C, 2 h} & & \quad \text{98%} \\
\text{C}_8\text{H}_{17}\text{CH}_2\text{OH}
\end{align*}
\]

(53)

**1.7.2 Borylation of Aryl Halides**

In 2003, Alcaraz and Vaultier reported a palladium-catalyzed borylation of various halides using monomeric dialkylaminoboranes, including H₂B-N(iPr)₂. The
aminoboranes were prepared by thermal dehydrogentation of the precursor amine-
boranes. The resulting (dialkylamino)boranes were evaluated in a palladium-
catalyzed coupling process in dioxane at 80 °C for 15 h in the presence of 4-
iodoanisole and triethylamine (Scheme 1.9).

Scheme 1.9. Borylation of 4-Iodoanisole with Hindered (Dialkylamino)boranes

The hindered (dialkylamino)boranes led to the corresponding
aryl(dialkylamino)monohydridoboranes in good yields. The outcome of the
borylation of 4-iodoanisole appears to be dependent on the steric bulk of the amino
moiety of the aminoboranes. Borylation was performed in 99% yield with the less
hindered H₂B-N(iPr)₂, compared to 51% yield when the crowded 2,2,6,6-
tetramethylpiperidinoborane was used. The resulting organo(dialkylamino)boranes
were hydrolyzed to afford the corresponding boronic acids in moderate yields.
1.8 Boronic Acids

Boronic acids are trivalent organic compounds containing one carbon-based substituent. Over the last thirty years, researchers have found a broad range of applications for these versatile compounds. Beyond their ubiquity in synthetic organic applications, boronic acids have found broad use in medical research as pharmaceutical agents for the development of enzyme inhibitors,\textsuperscript{95} boron neutron capture therapy agents,\textsuperscript{96} feedback-controlled drug delivery polymers,\textsuperscript{97,98} and saccharide sensors.\textsuperscript{99}

1.8.1 Applications of Boronic Acids in Organic Chemistry

The Suzuki–Miyaura reaction is one of the most common palladium-catalyzed cross-coupling reactions used in modern organic synthesis for carbon–carbon bond formation. It employs a wide range of organoboronic acids, boronates, and potassium trifluoroborates. Boronic acids have gained prominence following the discovery by Suzuki and Miyaura that arylboronic acids are efficient coupling partners with aryl bromides in the synthesis of substituted biaryl compounds (Scheme 1.10).\textsuperscript{100}

\[
\begin{align*}
\text{Scheme 1.10. Suzuki-Miyaura Cross-Coupling} \\
\text{Since the initial report, the Suzuki-Miyaura reaction has become one of the most powerful and effective methods for carbon-carbon bond formations in modern chemistry.}\textsuperscript{101} \text{ The Suzuki–Miyaura reaction has evolved into the most common cross-coupling reaction in both academia and industry. This utility stems from the many}
\end{align*}
\]
attractive attributes of boronic acids: their stability in air, thermal stability, functional group tolerance, and negligible toxicity. There is a wide range of aryl- and 1-alkenylboron reagents that undergo palladium-catalyzed couplings with alkyl, allylic, aryl, and 1-alkynyl substrates. Allylic halides react with aryl- and 1-alkenylboron reagents, but alkyl- and allylboron reagents fail to give the corresponding coupling products. This is most possibly caused by the slow reductive elimination from α-alkyl-1-allyl- or diallyl palladium(II) complexes, preventing an efficient catalytic cycle.\textsuperscript{102} Fuse et al. reported the coupling of 2-thiopheneboronic acid with an alkenyl iodide in 84\% yield (Eq. 54).\textsuperscript{103}

\begin{equation}
\begin{array}{c}
\text{Scheme 1.11. Selected Suzuki Reactions}
\end{array}
\end{equation}

Boronic acids also participate in many other C-C bond formation reactions,\textsuperscript{104} including coupling with vinyl halides (Scheme 1.11).\textsuperscript{105}
boronic acids in other reactions. While the use of boronic acids in carbon-carbon bond formation is well established, the corresponding carbon-heteroatom bond formation through cross-coupling is less so. Works by Chan, Evans, and Lam report the development of copper-promoted oxygen- and nitrogen-alkylation with boronic acids, which serve as a breakthrough in the realm of C-heteroatom bond formation (Scheme 1.12).

\[
\text{Scheme 1.12. Chan-Evans-Lam Cross-Coupling}
\]

Using this methodology, a host of phenols, amides, amines, sulfonamides, and N-heterocycles undergo alkylation with ease. Cross-coupling via the Chan-Evans-Lam reaction has gained popularity due to its mild conditions and high yields.

Beyond their ubiquity in cross-coupling reactions, boronic acids have other uses in organic chemistry. Hall reported the use of arylboronic acids as catalytic activators in the Diels-Alder cycloaddition reactions of propiolic acid with various dienes. The boronic acid-catalyzed cycloaddition of 2,3-dimethylbuta-1,3-diene with the dieneophile proceeds at room temperature to afford the corresponding adduct in 83% yield (Eq. 55).
The catalysis of these Diels-Alder reactions most likely proceeds through lowering the LUMO of the dieneophile by the formation of a covalent adduct between the boronic acid and the carboxylic acid. In the absence of boronic acid, only trace amounts of the desired products are isolated.

Boronic acids are efficient catalysts for the amidation of carboxylic acids, through formation of an activated acylboronate complex. Takemoto has expanded on the catalytic use of boronic acids to promote the intramolecular hetero-Michael reaction of α,β-unsaturated acids. The combination of catalytic amounts of an aminoboronic acid and a chiral aminothiourea allows the aza- and oxo-reactions to proceed in high yields. This methodology was applied to the asymmetric synthesis of (+)-Erythrococccamide B. The intermediate was isolated in 94% yield and in 92% ee (Scheme 1.13).


Takemoto envisioned that the boron species formed an acylboronate complex bearing the carboxylic acid moiety of substrate. The subsequent C–heteroatom bond-forming step proceeds through the cyclization of the complex.
Boronic acids are used in the synthesis of functionalized amines. One example of an organoboron-based method for nucleophilic addition to unsaturated C-N bonds is the Petasis reaction.\textsuperscript{112} The Petasis reaction is a multicomponent reaction between a boronic acid, an aldehyde, and an amine, wherein the amine and aldehyde first react to form an imine or iminium ion. An alkyl group is transferred from the boronic acid to the imine carbon, affording the corresponding amine (Scheme 1.14).

\[ \text{Scheme 1.14. The Petasis Reaction} \]

This reaction can be carried out with secondary amines, sterically hindered primary amines, hydrazines or anilines.\textsuperscript{113} Pyne utilized the Petasis reaction in the synthesis of various alkaloids.\textsuperscript{114}

1.8.2 Applications of Boronic Acids in Chemical Biology and Medicinal Chemistry

The use of boronic acids as pharmaceutical agents is a direct result of the unique electronic and physiochemical properties of boron.\textsuperscript{115} Boron contains an empty p orbital, which makes it a Lewis acid and a strong electrophile. This allows boron to make co-ordinate, or dative bonds with nucleophiles, transforming boron from a neutral trigonal planar structure to an anionic tetrahedral structure (Scheme 1.15).

\[ \text{Scheme 1.15. Example of Conversion of Neutral Boron to Anionic Boron} \]
Boronic acids are useful for biomedical applications due in part to this facile conversion, as well as the strong complex formation with diols, and the Lewis acidity of the boron atom.

The effective use of boron compounds in medicinal chemistry as enzyme inhibitors is in large part due to their ability to trap nucleophiles. Compounds containing boronic acids have been used for the development of enzyme inhibitors of arginase, nitric oxide synthase (NOS), peptidases/proteases, as well as transpeptidases.116

α-Aminoboronic acid derivatives act as inhibitors of serine proteases.117 Serine proteases are a diverse group of proteolytic enzymes that play a role in numerous physiological functions including apoptosis, cell differentiation, digestion, and growth.118 Proteases are vital in many metabolic processes throughout the body; a considerable amount of research has focused on compounds with potential activity against proteases.119 A prominent boron-containing therapeutic agent is bortezomib®, a modified dipeptide bearing a C-terminal boronic acid in place of a carboxylic acid (Figure 1.7).

![Figure 1.7. Protease Inhibitor Bortezomib®](image)

In 2003, the U.S. Food and Drug Administration (FDA) granted accelerated approval
to bortezomib® as a single agent in treating multiple myeloma; a rare bone marrow cancer.\textsuperscript{120} Bortezomib® is the first FDA-approved boronic acid agent for clinical use, selectively inhibiting the 26S proteasome over more common serine proteases.\textsuperscript{121} The boron atom in bortezomib binds to a threonine residue in the catalytic site of the 26S proteasome with high affinity and specificity.\textsuperscript{122} In normal cells, the proteasome regulates the level of proteins in cells through degradation of ubiquitin-tagged proteins. The 26S proteasome directly impacts cellular transcription regulation, cell-cycle progression, and apoptosis, since the turnover of the vast majority of intracellular proteins is regulated through this ubiquitin–proteasome pathway. Bortezomib® has since been approved for the treatment of mantle cell lymphoma and it is under investigation in clinical studies for a variety of other malignancies.\textsuperscript{123}

One significant area of development in boron-based biologically active compounds is the discovery of new antifungal agents from derivatives of boronic acids: benzoxaboroles. The benzoxaborole motif was first synthesized and characterized by Torssell\textsuperscript{124} and was determined to be a hydrolytically stable, water-soluble boronic acid (Figure 1.8).\textsuperscript{125}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{benzoxaborole.png}
\caption{The General Structure of a Benzoxaborole, and Tavaborole®}
\end{figure}

Benzoxaboroles as a class of compounds are known to be stable to strong acids and bases. Tavaborole®, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, is a clinical
drug candidate with potent antifungal activities against the major dermatophytes responsible for onychomycosis, \(^{126}\) a fungal infection in fingernails and toenails common among older people.\(^ {127}\)

Currently in Phase III trials, tavaborole\(^ {®}\) has been shown to perforate into the nail plate, the deepest site of infection and a highly resistant barrier that prevents the passage of most antifungal drugs. Studies have demonstrated tavaborole\(^ {®}\) has better penetration compared to ciclopirox\(^ {®}\), a clinically approved antifungal drug.\(^ {25}\) Tavaborole\(^ {®}\) has also shown in vitro efficacy against a broad range of fungi, such as *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*.\(^ {24}\)

In terms of its mechanism of action, tavaborole\(^ {®}\) inhibits yeast leucyl-tRNA synthetase, an aminoacyl-transfer RNA synthetase. The inhibitory complex was crystallized and found to involve an adduct in which two B–O bonds are formed between the benzoxyborole boron atom and the 2'- and 3'-hydroxyls of the terminal ribose in the repair site of the leucyl-tRNA synthetase complex.\(^ {128}\) The formation of this stable adduct inhibits the synthesis of leucyl-tRNA\(^ {\text{Leu}}\), blocking protein synthesis.

Boronic acids bind reversibly 1,2- and 1,3-diols under aqueous conditions (Scheme 1.16).\(^ {129}\) Stemming from this behavior, boronic acids are used as glucose sensors. Appended to a fluorophore, either covalently or electrostatically, boronic acid molecules modulate fluorescence as a function of saccharide concentration.\(^ {130}\)

This property has been investigated in the development of carbohydrate sensors for the management of diabetes mellitus.
Diabetes occurs when the body fails to produce or properly use insulin. Produced in the pancreas, insulin is a hormone needed for the conversion of sugar and starches into metabolic energy. Diabetes affects more than 387 million people globally. To control the disease, especially in severe forms, it is vital that blood sugar levels are consistently and regularly monitored. Given the urgency of this need, there is great interest in developing a glucose sensor that can assist in the management of diabetes.

Singaram has prepared a boronic acid-based optical glucose sensor utilizing fluorescence as a detection method. The sensor operates under physiological conditions and gives a reproducible signal in vitro. Previously, the synthesis of thin
film polymers containing the sensing components was investigated with the goal of preparing an implantable sensor with selectivity for glucose. Current research is directed towards the application of this sensor in detecting various metabolic saccharide biomarkers as a way to probe intestinal permeability.¹³²

1.9 Conclusion

Lithium aminoborohydrides are powerful, non-pyrophoric reducing agents that have been shown to reduce virtually all of the functionalities for which lithium aluminum hydride is now used (Figure 1.9).

![Figure 1.9. Reductions with LAB Reagents](image_url)
The reactivity of LAB reagents is comparable to LiAlH₄. LAB reagents are air-stable, non-pyrophoric, thermally stable, and liberate hydrogen slowly with protic solvents above pH 4. LAB reagents, whether solid or as THF solutions, retain their chemical activity for at least 6 months when stored under nitrogen at 25 °C. LAB reagents can be synthesized from any primary or secondary amine, thus allowing precise control of the steric and electronic environment of these reagents.

The spectrum of reactions of lithium aminoborohydrides is not limited to their reduction properties. Interestingly, both a hydride and amine can be transferred in tandem amination/reduction reactions of halobenzonitriles. Also, the amination or reduction properties of LAB reagents can be fine-tuned to control their reactivity. The work covered in this thesis is targeted to promote new LAB-mediated reactions that are complementary to existing synthetic methods and that are important in realizing the true potential of these synthetically useful reagents.

Several mild and convenient methods for the preparation of aminoboranes in solution have been developed. Diisopropylaminoborane can be synthesized from the corresponding LAB reagent and methyl iodide in the presence of catalytic triethylborane. Aminoboranes are prepared from LAB reagents by reaction with TMS-Cl. Both heterocyclic and secondary amines are used for the synthesis of aminoboranes. Depending on the steric hindrance around the amine, aminoboranes can exist as monomers, dimers, or mixtures. Aminoboranes derived from heterocyclic amines, such as pyrrole, pyrazole, and imidazole, can be prepared by the direct reaction of borane-tetrahydrofuran. Pyrrole and pyrazole form dimeric aminoboranes,
whereas imidazole forms polymeric aminoboranes. Pyrazole derived aminoborane forms a six-membered dimer through boron-nitrogen coordination. Ordinarily, aminoboranes are not hydroborating reagents, however pyrrolylborane hydroborates both styrene and alkynes at ambient temperatures. In addition, monomeric aminoboranes, such as \( \text{H}_2\text{B-N(iPr)}_2 \), can reduce aldehydes, ketones, esters, and nitriles in the presence of catalytic amounts of \( \text{LiBH}_4 \).

The following chapters of this dissertation describe advances in probing the reactivity profile of diisopropylaminoborane derived from lithium diisopropylaminoborohydride. The second chapter describes the synthesis of boronic acids and esters from the palladium-catalyzed borylation of aryl iodides, bromides, and triflates using diisopropylaminoborane. Aryl boronic acids comprise an important class of compounds with established utility in synthetic organic chemistry, as well as many biomedical applications. This borylation methodology for synthesis of boronic acids is complementary to existing synthetic methods.

The third chapter discusses the reactions of diisopropylaminoborane with various organometallic reagents, including organolithium, organozinc, and Grignard reagents. The results obtained from the optimized borylation of alkyl and aryl bromides under Grignard and modified-Barbier conditions using diisopropylaminoborane are reported.

The fourth chapter discusses the reactions of diisopropylaminoborane with multiple equivalents of organometallic reagents. The preparation of symmetrical and unsymmetrical diorgano(diispropyl)aminoboranes are described. Efforts to prepare,
isolate and characterize these intermediates, as well as exploring additional reactivity are reported.

The fifth and final chapter details the discovery of a new class of aminoborohydrides, halomagnesium dimethylaminoborohydrides. Chloromagnesium dimethylaminoborohydride (ClMg⁺ [H₃B-NMe₂]⁻, MgAB) is an analogue of the versatile LAB reagents, prepared by the reaction of dimethylamine-borane with methylmagnesium chloride. Discovered as a byproduct of the reaction of aminoboranes with Grignard reagents, MgAB is investigated for the controlled reduction of amides to aldehydes under ambient conditions. This reactivity is complementary to LiAlH₄ and diisobutylaluminum hydride (DIBAL) reagents, while exhibiting enhanced chemoselectivity.
1.10 References


Dimethylaminoborane was synthesized from the corresponding LAB, methyl iodide and 1 equivalent of triethylborane. This showed the dimethylaminoborane to be 100% dimer by $^{11}$B-NMR ($\delta = +3.3, J_{BH} = 98$ Hz).

These LAB reagents were prepared from corresponding heterocyclic borane complex and nBuLi.


94 These alcohols are contaminated with a small amount of butylboronic esters.


CHAPTER 2

The Palladium-Catalyzed Borylation of Aryl Bromides, Iodides, and Triflates with Diisopropylaminoborane
2.1 Introduction

Boronic acids are trivalent organic compounds containing one carbon-based substituent, which have become an important class of compounds used in organic chemistry. Over the last thirty years, researchers have found a broad range of applications for these versatile compounds. Beyond their ubiquity in synthetic organic applications, boronic acids have found broad use in medical research as pharmaceutical agents for the development of enzyme inhibitors,\(^1\) boron neutron capture therapy agents,\(^2\) feedback-controlled drug delivery polymers,\(^3,4\) and saccharide sensors.\(^5\)

2.2 Preparation of Aryl Boronic Acids and Esters

Historically, the synthesis of aryl boronic acids is essentially limited to the reaction of aryl Grignard or lithium reagents\(^6\) with trialkyl borates at low temperatures. Variable yields of arylboronic acids are obtained and the pre-formation of the Grignard or aryl lithium species is required. Additionally, a restricted number of functional groups are tolerated by these organometallic reagents due to the basic and nucleophilic reaction conditions, limiting the chemical diversity available. Furthermore, the preparation of the ArMgX or ArLi reagents from aryl chloride derivatives is often difficult, necessitating the use of the less readily available aryl bromides or iodides.

2.2.1 Transition Metal Catalyzed Borylation of Aryl Halides

Arylboronic esters can also be synthesized by a transition metal catalyzed borylation of aryl halides. The cross-coupling between an aryl halide and an
(alkoxy)diboron species directly produces aryl boronic esters without the problems associated with Grignard and organolithium reagents. Consequently, this route has also been found to be compatible with diverse functionalities not possible with Grignard or organolithium reagents, such as esters, nitriles, nitros, and acyl groups. For example, Ishiyama et al. reported the palladium-catalyzed coupling reactions of bis(pinacolato)diboron (B₂Pin₂) with aryl halides, representing a one-step procedure for the preparation of arylboronic esters from aryl halides. The aryl halide and B₂Pin₂ were heated to 80 °C in DMSO in the presence of a palladium catalyst and a base. The reaction proceeded to completion in 2 to 24 hours, depending on the aryl halide, with good to excellent yields. Electron-donating groups present on the aromatic ring are detrimental, slowing down the reaction. For example, the formation of p-methoxyphenylboronic ester from the corresponding aryl bromide proceeds in 24 h with an 80% yield, whereas the same reaction of 4-bromobenzonitrile provides 76% yield of the corresponding boronic ester in just one hour (Eq. 1 & 2).

\[
\text{MeO} \begin{array}{cccc}
\text{Br} & \text{O} & \text{B} & \text{O} \\
\end{array}
\quad \text{PdCl₂(dppf), KOAc} \\
\text{DMSO, 80 °C, 24 h} \\
\text{80%}
\]

\[
\text{MeO} \begin{array}{cccc}
\text{B} & \text{O} & \text{O} & \text{O} \\
\end{array}
\quad \text{Br} \\
\]

(1)

\[
\text{NC} \begin{array}{cccc}
\text{Br} & \text{O} & \text{B} & \text{O} \\
\end{array}
\quad \text{PdCl₂(dppf), KOAc} \\
\text{DMSO, 80 °C, 1 h} \\
\text{76%}
\]

(2)

When product yields are based on the boron atom, they are divided in half because only one of the pinacol molecules is incorporated into the final product. The lack of
atom economy in this reaction is made up for by the reaction tolerance of many different functional groups, so it is still highly used today.

The nickel catalyst (1,3-bis-(diphenylphosphino)propane)nickel(II) chloride (NiCl$_2$(dppf)) was used by Tour to facilitate cross coupling between pinacolborane and aryl bromides.$^8$ Percec expanded this methodology to access boronic esters from aryl chlorides, bromides, and iodides using an inexpensive boron source, 5,5-dimethyl-1,3,2-dioxaborinane (neopentylglycolborane). A mixed ligand catalyst NiCl$_2$(dpdp)/dppf system was employed, accelerating the reaction in the presence of zinc metal. Using that methodology, Percec was able to access a wide range of boronic esters, including o-methoxyphenylboronic ester, isolated from the corresponding bromide in 95% after 1 h of reflux (Eq. 3).$^9,10$

\[
\begin{align*}
\text{Br} & \quad + \quad \text{NiCl}_2(\text{dpdp}), \text{dppf} \\
\text{OMe} & \quad \xrightarrow{\text{Zn}^0, \text{Et}_3\text{N}, \text{toluene}, 100 \, ^\circ\text{C}, 1 \, \text{h}} \quad \text{OMe}
\end{align*}
\]  

(Eq. 3)

Borylation reactions are not limited to only aryl halides, but can be expanded to include pseudohalogens such as mesylates, tosylates, and triflates. Using the mixed-ligand methodology, Percec reported on the use of several aryl mesylates.$^{11}$ 4-Cyanophenyl mesylate is converted to the corresponding boronic ester in 83% yield (Eq. 4). Kwong reported a procedure to access borylation products of aryl tosylates using an exotic phosphine ligand in refluxing t-butanol, with B$_2$Pin$_2$ as the boron source.$^{12}$ Indol-5-yl tosylate is converted to the boronic esters in 73% yield (Eq. 5).
Aryl triflate compounds can also be utilized in palladium-catalyzed borylation. 4-Formylphenyl triflate is converted to the corresponding boronic ester in 91% yield from $\text{B}_2\text{Pin}_2$ and a palladium catalyst (Eq. 6). 8-Quinolineboronic ester is also obtained from the corresponding aryl triflate in 65% yield through a similar reaction (Eq. 7).

Boronic esters can also be synthesized from other boron sources, such as pinacolborane. The synthesis of boronic esters from aryl halides and pinacolborane usually produce high yields while tolerating a diverse set of functionality. For example, ethyl 4-iodobenzoate is converted to the corresponding boronic ester in 74% yield when pinacolborane and a palladium catalyst are used (Eq. 8). Likewise, 4-
iodonitrobenzene yields 84% of the corresponding boronic ester using the same reaction conditions (Eq. 9).

\[
\text{OEt} \quad \text{I} \quad \text{O}
\text{Et} \quad \text{PdCl}_2(\text{dppf}), \text{Et}_3\text{N}
\text{1,4-dioxane, 80 °C, 2 h}
\text{74%}
\]

\[
\text{O}^+ \quad \text{N}^+ \quad \text{O}
\text{O} \quad \text{PdCl}_2(\text{dppf}), \text{Et}_3\text{N}
\text{1,4-dioxane, 80 °C, 5 h}
\text{84%}
\]

Unfortunately, as pinacolborane is a hydroboration reagent, it is not compatible with compounds containing alkenes or alkynes. Thus, products from the borylation of compounds containing alkenes or alkynes by pinacolborane will most likely contain side products from the hydroboration of these functionalities. The heavy metal catalyst plays an important role in the synthesis of boronic acids from aryl and alkenyl halides and triflates. Other catalysts have also been developed for the synthesis of boronic acids from benzene and other non-halogenated aromatics.

**2.2.2 Transition Metal Catalyzed Borylation of Aromatic C-H Bonds**

The development of iridium and rhodium catalysts has made it possible for the direct functionalization of aromatic C-H bonds in the synthesis of boronic esters. These borylation reactions occur at room temperature requiring a 1:1 molar ratio of arene to boron reagent with or without an inert alkane solvent. The starting material can be both arene or heteroarene compounds (Eq. 10 & 11).
The regioselectivity of this reaction depends on the starting material used. For instance, when arenes are used, the borylation is controlled by steric effects. Conversely, the borylation occurs at the C-H bond $\alpha$ to the heteroatom on heteroarenes, unless there is a large group present on the heteroatom.

### 2.2.3 Aminoborane for the Synthesis of Boronic Acid Intermediates

In addition to trialkylborates, HBPin and B$_2$Pin$_2$, other boron sources have been used to synthesis boronic acids. Vaultier reported a palladium-catalyzed borylation of various halides using monomeric dialkylaminoboranes, such as diisopropylaminoborane (Scheme 2.1).$^{18}$

![Scheme 2.1. Synthesis of Boronic Acid Intermediates from H$_2$B-N(iPr)$_2$](image)

The yields of the boronic acids synthesized under this methodology were varied from 20 to as high as 95%. Furthermore, Vaultier demonstrated the borylation of various alkenyl halides.$^{36b}$ This methodology was adapted to include the borylation of aryl
chlorides,\textsuperscript{19} and aryl diazonium salts.\textsuperscript{20} Vaultier also reported the synthesis of unsymmetrical biaryl compounds by the sequential borylation of an aryl iodide using diisopropylaminoborane, followed by a Suzuki–Miyaura cross coupling of second aryl iodide.\textsuperscript{21} Using this procedure, 4-methoxy-4'-methyl-1,1'-biphenyl was prepared from 4-iodoanisole and 4-iodotoluene in 75\% yield (Eq. 12).

\[
\begin{align*}
\text{MeO} & \quad \text{I} \quad + \quad \text{H}_2\text{B} - \text{N} \quad \xrightarrow{1. \text{PdCl}_2(\text{dppp}), \text{Et}_3\text{N} \quad \text{toluene, 100 °C, 1h}} \quad \text{MeO} \\
& \quad \quad \quad \quad \text{1. PdCl}_2(\text{dppp}), \text{Et}_3\text{N} \quad \text{toluene, 100 °C, 1h} \quad \quad \quad 1 \quad \text{PdCl}_2(\text{dppp}), \text{Et}_3\text{N} \quad \text{toluene, 100 °C, 1h} \quad \quad \quad 1 \quad \text{PdCl}_2(\text{dppp}), \text{Et}_3\text{N} \quad \text{toluene, 100 °C, 1h} \\
& \quad \quad \quad \quad \quad \quad \quad \quad \text{MeO} \\
& \quad \quad \quad \quad \quad \quad \quad \quad \text{MeO} \\
& \quad \quad \quad \quad \quad \quad \quad \quad \text{MeO} \\
& \quad \quad \quad \quad \quad \quad \quad \quad \text{MeO} \\
\end{align*}
\]

The aminoboranes used in the Vaultier borylation methodology were synthesized by thermal decomposition of the precursor amine-boranes at high temperatures. This produced the desired aminoborane, along with concomitant evolution of hydrogen gas (Eq. 13).

\[
\begin{align*}
\text{H}_3\text{B} : \text{HN} \quad & \quad \xrightarrow{200 °C} \quad \text{H}_2\text{B} - \text{N} \quad + \quad \text{H}_2 \\
& \quad \quad \quad \quad \text{H}_2\text{B} - \text{N} \quad + \quad \text{H}_2 \\
& \quad \quad \quad \quad \text{H}_2\text{B} - \text{N} \quad + \quad \text{H}_2 \\
& \quad \quad \quad \quad \text{H}_2\text{B} - \text{N} \quad + \quad \text{H}_2 \\
\end{align*}
\]

Aminoboranes have been known since the discovery of the hydroboration reaction in 1956.\textsuperscript{22} Their reactivity has been scarcely studied as useful tools for synthetic organic chemistry. Currently, methods for the syntheses of aminoboranes are limited to thermally-induced dehydrogenation,\textsuperscript{40,23} or metal-catalyzed dehydrogenation of the corresponding amine-borane adducts (R\textsubscript{1}R\textsubscript{2}HN:BH\textsubscript{3}) (Scheme 2.2).\textsuperscript{24} Aminoboranes are known to easily form mixtures of dimers and oligomers, preventing further purification.\textsuperscript{25} If the steric hindrance around the nitrogen is large enough, the aminoborane exists as a monomer and is thus highly reactive.
Scheme 2.2. Existing Methods to Synthesize Aminoboranes

Aminoboranes can also be synthesized from LAB reagents by reaction with an alkyl halide (Eq. 14).²⁶

\[
\begin{align*}
\text{H}_3\text{B} : \text{HN} & \quad \xrightarrow{160 - 200 \, ^\circ\text{C}} \quad \text{H}_2\text{B} : \text{N} + \text{H}_2 \\
\text{H}_3\text{B} : \text{HN} & \quad \xrightarrow{[\text{Rh}(1,5\text{-cod})(\mu\text{-Cl})]_2} \quad \text{H}_2\text{B} : \text{N}
\end{align*}
\]

This reaction occurs when a hydride from the LAB reagent attacks the alkyl halide in an S\text{N}_2 fashion, producing the corresponding aminoborane. When this reaction was first discovered in 1992, the reactivity of the aminoboranes towards various functionalities was investigated. Based on the reactions of a pyrrolidinoborane, it was concluded that aminoboranes are inert towards most functionalities.

As previously mentioned, diisopropylaminoborane can serve as a boron source for the synthesis of boronic acids in Vaultier’s borylation reaction.⁴⁰ Unfortunately, the synthesis of diisopropylaminoborane used in this borylation reaction required high temperatures and evolved hydrogen. Diisopropylaminoborane can also be synthesized from the corresponding LAB reagent without the evolution of hydrogen or high temperatures, providing a milder route to these aminoboranes.²⁷ When the generality of the aminoborane borylation reaction was probed with
diisopropylaminoborane, it was observed that the yield of boronic acid varied depending on the synthetic route used to prepare the diisopropylaminoborane. A systematic study revealed the cause of the variable yields of boronic acid obtained in this reaction, allowing the scope of this reaction to be expanded to include aryl triflates. This chapter discusses the results from the optimized borylation of aryl iodides, bromides and triflates using diisopropylaminoborane prepared from lithium diisopropylaminoborohydride.

2.3 Results and Discussion

2.3.1 Synthesis of Boronic Acids from Diisopropylaminoborane

Aminoboranes are typically prepared in situ in tetrahydrofuran (THF) from LAB reagents and used without further purification. To explore whether the diisopropylaminoborane prepared from LAB reagents could be used in Vaultier’s borylation, the reaction of diisopropylaminoborane 1 with p-iodoanisol 2a was carried out in THF in the presence of a palladium catalyst (Scheme 2.3). The formation of aryl(diisopropylamino)borane 3 was followed by $^{11}$B-NMR spectroscopy on reaction aliquots. Gratifyingly, after 12 hours at reflux, the formation of 3 was confirmed by $^{11}$B-NMR spectroscopy of the reaction mixture. However, a simple acid/base work-up provided the corresponding boronic acid 4a in only 50% yield (Table 2.1, Entry 1). Additionally, this result could not be reproduced reliably and varied from reaction to reaction, warranting further optimization.
Scheme 2.3. Synthesis of \( p \)-Methoxyphenylboronic Acid from \( \text{H}_2\text{B-N(iPr)}_2 \)

Closer examination of the procedure for the preparation of aminoboranes revealed that products from reaction of a LAB reagent and methyl iodide contained a trace amount of lithium borohydride (LiBH₄), while aminoboranes prepared from LAB and trimethylsilyl chloride (TMS-Cl) were essentially pure.²⁹ Thus the borylation reaction using pure 1 prepared from LAB and TMS-Cl was pursued (Table 2.1, Entries 1-2). The use of 1 contaminated with LiBH₄ causes a black precipitate of palladium metal to form. Gratifyingly, the reaction of 1 prepared from LAB and TMS-Cl with \( p \)-iodoanisol 2a resulted in a significantly higher and reproducible yield of 4a (Table 2.1, Entry 2), and no black palladium precipitate was observed.³⁰

Another concern in using methyl iodide is that the LiBH₄ may reduce the aryl halide to the corresponding hydrocarbon by palladium-catalyzed proto-dehalogenation. Lipshutz reported reduction in for the palladium-catalyzed reaction of aryl triflates by amine-boranes.³¹
Table 2.1. Aminoborane Optimization Study

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X</th>
<th>Additive</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃I</td>
<td>None</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>TMSCl</td>
<td>None</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl</td>
<td>LiBH₄ᵇ</td>
<td>45</td>
</tr>
</tbody>
</table>

ᵇReactions were carried out on a 2.5 mmol scale with 1 equiv. aryl iodide, 2 equiv. H₂B-N(iPr)₂, 5 equiv. of triethylamine, and 5 mol % palladium catalyst. 20 mol % LiBH₄ was added to the reaction after addition of the H₂B-N(iPr)₂.

In an effort to confirm the role of LiBH₄, pure 1 was spiked with 20 mol % LiBH₄ and used in the borylation reaction (Table 2.1, Entry 3). The addition of LiBH₄ caused the visible precipitation of black palladium, and resulted in a significantly reduced yield of 4a consistent with the earlier results. These results strongly support the detrimental presence of LiBH₄ in this borylation reaction. Consequently, the optimization studies were carried out using pure 1 prepared from LAB and TMS-Cl.

Attention was next turned to optimize the stoichiometry of this borylation reaction. Previous studies used two equivalents of 1 for complete borylation of aryl and alkenyl halides. To confirm the need for this stoichiometry, a solution of two equivalents of 1 was added to one equivalent of triethylamine and heated to reflux. After 15 hours, an aliquot was analyzed via ¹¹B-NMR spectroscopy, revealing a disproportionation of aminoborane 1, as evidenced by two additional signals in the ¹¹B-NMR spectrum. From the chemical shift and multiplicity of the signals, these
peaks were assigned to triethylamine-borane and \(N,N,N',N'\)-tetraisopropylboranediadamine (Eq. 15).

\[
\begin{align*}
\text{H}_2\text{B}:\text{NEt}_3 + \text{Et}_3\text{N} \rightarrow \text{H}_2\text{B} \quad + \quad \text{R}_2\text{N} \quad + \quad \text{H}_3\text{B}:\text{NEt}_3 \\
\text{1} \quad \text{Et}_3\text{N} \quad \text{THF, 65 °C} \quad \text{15}
\end{align*}
\]

Since these disproportionation products are inactive boron donors, the borylation reaction requires an excess of 1 for complete borylation of the aryl or alkenyl halide. Consequently, two equivalents of aminoborane 1 were routinely used in the optimized borylation reactions.

Next, various palladium catalysts were screened in the reaction of 1 with 2a (Table 2.2). The previously used bis(triphenylphosphine)palladium(II) chloride catalyst afforded only a moderate yield of 4a (Table 2.2, Entry 1).

**Table 2.2.** Palladium Catalyst Optimization for the Reaction of H\(_2\)B-N(iPr)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Source</th>
<th>Additive</th>
<th>% Yield</th>
<th>Pd Cost (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl(_2)(PPh(_3))(_2)</td>
<td>None</td>
<td>76</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>PdCl(_2)</td>
<td>20 mol% PPh(_3)</td>
<td>89</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)(_2)</td>
<td>20 mol% PPh(_3)</td>
<td>85</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Pd(_2)db(_3)CHCl(_3)</td>
<td>20 mol% PPh(_3)</td>
<td>87</td>
<td>13(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl iodide, 2 equiv. H\(_2\)B-N(iPr)\(_2\), 5 equiv. triethylamine, and 5 mol % of palladium catalyst. \(^b\)Dollars per mmole; prices taken from Sigma-Aldrich in January 2015. \(^c\)Price to synthesize in-house following the procedure in reference 6.
This palladium catalyst is more expensive and air sensitive when compared to other palladium catalyst used in the present study. On the other hand, the relatively inexpensive and stable palladium dichloride (PdCl$_2$) catalyst provided the highest yield of 4a (Table 2.2, Entry 2). PdCl$_2$ not only improved the isolated yield of 4a but also lowered the overall cost of this borylation reaction, making it the best choice. The generality and scope of this reaction was investigated using a series of aryl iodides 2a-h with 1. The results are summarized in Table 2.3.

**Table 2.3.** Boronic Acid Synthesis from Aryl Iodides$^a$

<table>
<thead>
<tr>
<th>Aryl Iodide</th>
<th>Boronic Acid</th>
<th>% Yield</th>
<th>Aryl Iodide</th>
<th>Boronic Acid</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO-I$_2$</td>
<td>MeO-B(OH)$_2$</td>
<td>89</td>
<td>F-I$_2$</td>
<td>F-B(OH)$_2$</td>
<td>57</td>
</tr>
<tr>
<td>2a</td>
<td>4a</td>
<td></td>
<td>2e</td>
<td>4e</td>
<td></td>
</tr>
<tr>
<td>F-I$_2$</td>
<td>F-B(OH)$_2$</td>
<td>57</td>
<td>F-I$_2$</td>
<td>F-B(OH)$_2$</td>
<td>50</td>
</tr>
<tr>
<td>2b</td>
<td>4b</td>
<td>84</td>
<td>2f</td>
<td>4f</td>
<td>50</td>
</tr>
<tr>
<td>F-I$_2$</td>
<td>F-B(OH)$_2$</td>
<td>50</td>
<td>NC-I$_2$</td>
<td>NC-B(OH)$_2$</td>
<td>20</td>
</tr>
<tr>
<td>2c</td>
<td>4c</td>
<td>73</td>
<td>2g</td>
<td>4g</td>
<td>20</td>
</tr>
<tr>
<td>F-I$_2$</td>
<td>F-B(OH)$_2$</td>
<td>50</td>
<td>S-I$_2$</td>
<td>S-B(OH)$_2$</td>
<td>99</td>
</tr>
<tr>
<td>2d</td>
<td>4d</td>
<td>80</td>
<td>2h</td>
<td>4h</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl iodide, 2 equiv. H$_2$B-N(iPr)$_2$, 5 equiv. triethylamine, 5 mol % palladium catalyst, and 20 mol % triphenylphosphine.
The reaction of aryl iodides with 1 in the presence of PdCl₂ resulted in isolation of the corresponding boronic acids in poor to excellent yields (Table 2.3). Aryl iodides bearing an electron-donating group (EDG), such as methoxy or methyl, afforded the corresponding boronic acids in high yields. For example, p-methoxyphenylboronic acid 4a was obtained in 89% isolated yield from 2a. Conversely, substrates containing an electron-withdrawing group (EWG) afforded the corresponding boronic acid in diminished yields. For instance, 3-cyanophenylboronic acid 4g was obtained in only 20% isolated yield from 2g, while 4-fluorophenylboronic acid 4f was isolated in 57% yield from 2a. In both cases unreacted starting material was recovered from the reaction mixture. Unfortunately, aryl iodides containing chloro substituents only resulted in recovery of the starting material with no formation of the desired boronic acid products. Aryl iodides bearing ortho-substituents produced the corresponding boronic acids in lower yields compared to analogous meta- and para-substituted compounds. These diminished yields are likely due to steric retardation at the oxidative insertion step. For example, o-methylphenylboronic acid 4c was obtained in 73% isolated yield from 2c. The highest yield was obtained from 2-iodothiophene 2h providing the corresponding boronic acid 4h in 99% isolated yield. Unfortunately, N-heterocycles, such as iodopyridine, iodoquinoline, and iodopyrazole did not undergo this borylation reaction; only starting material was recovered. The optimized conditions were then applied to the synthesis of boronic acids from aryl bromides. The results are summarized in Table 2.4
Table 2.4. Palladium Catalyst Optimization for the Reaction of H₂B-N(iPr)₂ and p-Bromoanisol

![Chemical structure](image)

1. Pd, Et₃N
   THF, 65°C, 16 h
2. Aq. work up

| Entry | Pd Source                  | Additive      | % Yield | Pd Cost
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(PPh3)₂</td>
<td>None</td>
<td>64</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂</td>
<td>20 mol% PPh₃</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>20 mol% PPh₃</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Pd₂dba₃•CHCl₃</td>
<td>20 mol% PPh₃</td>
<td>85</td>
<td>13</td>
</tr>
</tbody>
</table>

Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl iodide, 2 equiv. H₂B-N(iPr)₂, 5 equiv. triethylamine, and 5 mol % of palladium catalyst. Dollars per mmole; prices taken from Sigma-Aldrich in January 2015. Price to synthesize in-house following the procedure in reference 6.

As shown in Table 2.4, the reaction conditions optimized for aryl iodide 2a did not yield similar conversions for aryl bromide substrates 5a (Table 2.4, Entry 2). This difference in reactivity between aryl iodides and bromides may be due to the difference in the activation barrier of the oxidative insertion step. In an effort to optimize the yield of 6a from 5a, various palladium catalysts were screened (Table 2.4). It was found that tris(dibenzylideneacetone)dipalladium(chloroform) complex (Pd₂dba₃•CHCl₃) produced the highest yield of 6a from the reaction of 5a with 1 (Table 2.4, Entry 4). With the optimized borylation of aryl bromides in hand, various aryl bromides 5a-h were allowed to react with 1 in the presence of catalytic Pd₂dba₃•CHCl₃ to check the generality of this reaction. These results are summarized in Table 2.5.
Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl bromide, 2 equiv. H$_2$B-N(iPr)$_2$, 5 equiv. triethylamine, 5 mol % palladium catalyst and 20 mol % triphenylphosphine.

The reaction of 1 with various aryl bromides in the presence of Pd$_2$dba$_3$•CHCl$_3$, PPh$_3$, Et$_3$N, THF, 65 °C, 16 h produced the corresponding boronic acids in moderate to excellent yields (Table 2.5). However, yields were slightly lower than previously obtained with analogous aryl iodides, which can be attributed to the lower reactivity of the carbon-bromide bond. Additionally, reactivity trends that were previously observed with aryl iodides containing EWG and EDG substituents are also applicable to aryl bromides (Table 2.5, Entries 1-5). For example, p-bromoanisol 5a produced 6a in an excellent 85% isolated yield, while 1-bromo-4-fluorobenzene 5e was converted to 6e in a moderate 40% isolated yield. Additionally, aryl bromides containing chloride or nitrile groups

# Table 2.5. Boronic Acid Synthesis from Aryl Bromides

<table>
<thead>
<tr>
<th>Aryl Bromide</th>
<th>Boronic Acid</th>
<th>% Yield</th>
<th>Aryl Bromide</th>
<th>Boronic Acid</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO-Br</td>
<td>MeO-B(OH)$_2$</td>
<td>85</td>
<td>F-Br</td>
<td>F-B(OH)$_2$</td>
<td>40</td>
</tr>
<tr>
<td>5a</td>
<td>6a</td>
<td></td>
<td>5e</td>
<td>6e</td>
<td></td>
</tr>
<tr>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>80</td>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>51</td>
</tr>
<tr>
<td>5b</td>
<td>6b</td>
<td></td>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>87</td>
</tr>
<tr>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>35</td>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>72</td>
</tr>
<tr>
<td>5c</td>
<td>6c</td>
<td></td>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td></td>
</tr>
<tr>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>34</td>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td></td>
</tr>
<tr>
<td>5d</td>
<td>6d</td>
<td></td>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td></td>
</tr>
<tr>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>51</td>
<td>-Br</td>
<td>B(OH)$_2$</td>
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<td>6f</td>
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<td>-Br</td>
<td>B(OH)$_2$</td>
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<tr>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td>72</td>
<td>-Br</td>
<td>B(OH)$_2$</td>
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<tr>
<td>5h</td>
<td>6h</td>
<td></td>
<td>-Br</td>
<td>B(OH)$_2$</td>
<td></td>
</tr>
</tbody>
</table>

*Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl bromide, 2 equiv. H$_2$B-N(iPr)$_2$, 5 equiv. triethylamine, 5 mol % palladium catalyst and 20 mol % triphenylphosphine.
produced little to no yields of the corresponding boronic acids, with recovery of the starting material from the reaction mixture. Heterocyclic bromides, such as 2-bromothiophene 5g and 3-bromothiophene 5h, provided the corresponding boronic acids 6g and 6h in 87% and 72% isolated yield respectively. As observed previously with N-heterocycles, such as bromopyridine, bromoquinoline, and N,N-dimethylaniline, were unreactive in this borylation reaction. Finally, the 1-alkenylboronic acid (E)-styrylboronic acid 6f was obtained from the corresponding alkenylbromide 5f in 51% isolated yield. The moderate yield obtained in this reaction is likely due to proto-deborylation of the vinyl boronic acid during the acid/base work-up.

The scope of this borylation reaction was extended to include aryl mesylates, tosylates, and triflates using the optimized procedures developed above for aryl iodides and bromides. The results are summarized below (Table 2.6).
Table 2.6. Palladium Catalyst Optimization for the Reaction of H$_2$B-N(iPr)$_2$ and p-Methoxyphenyl Triflate$^a$

\[
\begin{array}{cccc}
\text{Entry} & \text{Pd Source} & \text{Additive} & \% \text{ Yield} \\
1 & \text{PdCl}_2(P\text{Ph}_3)_2 & \text{None} & 0 \\
2 & \text{PdCl}_2 & 20 \text{ mol}\% \text{ PPh}_3 & 0 \\
3 & \text{Pd(OAc)}_2 & 20 \text{ mol}\% \text{ PPh}_3 & 0 \\
4 & \text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3 & 20 \text{ mol}\% \text{ PPh}_3 & 87 \\
\end{array}
\]

$^a$Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl iodide, 2 equiv. H$_2$B-N(iPr)$_2$, 5 equiv. triethylamine, and 5 mol % of palladium catalyst. $^b$Dollars per mmole; prices taken from Sigma-Aldrich in January 2015. $^c$Price to synthesize in-house following the procedure in reference 6.

When aryl mesylates or tosylates were allowed to react with 1 under these optimized reaction conditions, only starting material was recovered. Intermediate 3 was not formed in the reaction, as evidenced by $^{11}$B-NMR analysis of the reaction. Gratifyingly, the reaction of the $p$-methoxyphenyl triflate$^5$ 7a with 1 in the presence Pd$_2$dba$_3$·CHCl$_3$ afforded the corresponding boronic acid in good yield (Table 2.6, Entry 4). With the discovery that boronic acids could be synthesized from aryl triflate 7a and 1, the scope was probed to determine the generality of this new reaction (Table 2.7).
Table 2.7. Boronic Acid Synthesis from Aryl Triflates

![Chemical reaction diagram]

Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl triflate, 2 equiv. H$_2$B-N(iPr)$_2$, 5 equiv. triethylamine, 5 mol % palladium catalyst and 20 mol % triphenylphosphine.

The reaction of various aryl triflates with 1 in the presence of catalytic Pd$_2$dba$_3$•CHCl$_3$ produced the corresponding boronic acids in higher yields than analogous aryl iodide and bromide compounds (Table 2.7). These increased yields are likely due to the much higher reactivity of the aryl triflate bond for palladium oxidative insertion.$^{43}$ Even aryl triflates containing EWG substituents afforded the corresponding boronic acid in good to excellent yields. For example, $p$-chlorophenylboronic acid 8f was obtained in 97% yield from 7f while both aryl
iodide and bromide compounds containing the same functionality failed to produce any product whatsoever. $p$-Fluorophenyl triflate 7g also gave the corresponding boronic acid 8g in 81% yield, much higher than that realized with analogous aryl iodide 2e and bromide 5e. Additionally, $p$-cyanophenylboronic acid 9h was isolated in 70% yield from 7h. The analogous aryl iodide or bromide gave poor yields in this reaction, with recovery of the unreacted starting material. Naphthyl triflate 7i was also found to be an excellent substrate for this borylation reaction, affording 1-naphthylboronic acid 8i in 82% isolated yield. On the other hand, only starting material was recovered from the analogues naphthyl iodo- and bromo-compounds. As observed before, nitrogen-containing triflates did not produce the corresponding boronic acids and only starting material was recovered from the reactions. Overall, aryl triflates performed better than the analogous iodo- and bromo-compounds and a variety of functional groups were tolerated in this borylation reaction.

2.3.2 Synthesis of Aryl Boronic Esters

Over time, boronic acids undergo dehydration, forming the boronic acid anhydride, a boroxine.\textsuperscript{52} Conversely, boronic esters do not undergo such dehydration, and are thus more air-stable than the analogous boronic acids.\textsuperscript{36,37} As a consequence, boronic esters have gained favor in organic synthesis as replacements for the corresponding boronic acids. Thus, isolation of the aryl boronic esters directly from the borylation reaction of $p$-idoanisol 9a was pursued. Gratifyingly, upon quenching the reaction mixture with neopentyl glycol, the corresponding aryl boronic ester was observed by $^{11}$B NMR analysis: the borylation intermediate 3, seen as a doublet at $\delta+$
39 ppm, was replaced with a broad singlet at $\delta + 28$ ppm, indicating successful formation of the ester 10a (Scheme 2.4). Upon work-up, the boronic ester 10a was obtained in 99% yield (Table 2.8, Entry 1).

**Scheme 2.4. Boronic Ester Synthesis from H$_2$B-N(iPr)$_2$ and p-Iodoanisol**

Using this technique to quench the borylation reaction, several aryl iodides and bromides were converted to the corresponding aryl boronic esters with comparable or superior yields than in the formation of the analogous boronic acids (Table 2.8).

**Table 2.8. Boronic Ester Synthesis from H$_2$B-N(iPr)$_2$, Aryl Iodides, and Bromides$^a$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl Halide</th>
<th>Boronic Ester</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO-I</td>
<td>MeO-B</td>
<td>99$^b$</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>10b</td>
<td>90$^c$</td>
</tr>
<tr>
<td>3</td>
<td>S-Br</td>
<td>10c</td>
<td>89$^c$</td>
</tr>
</tbody>
</table>

$^a$Reactions were carried out on a 2.5 mmol scale with 1 equiv. aryl halide, 2 equiv. H$_2$B-N(iPr)$_2$, 5 equiv. triethylamine, 5 mol% palladium catalyst and 20 mol% triphenylphosphene. $^b$PdCl$_2$ catalyst used. $^c$Pd$_2$dba$_3$•CHCl$_3$ catalyst used.
The higher yields obtained for these products can be attributed to the increased stability of the boronic esters and the ease of their isolation. Isolation of pure boronic esters from this reaction requires a simple quench of the reaction with neopentyl glycol, filtration to remove spent palladium, and subsequent extraction. Conversely, isolation of pure boronic acids requires multiple steps and acidification to lower the pH to obtain a pure product. The conditions required for the isolation of boronic acids can promote protodeboronation of the product, lowering the isolated yields. Thus, isolation of the boronic ester from the reaction mixture is ideal for sensitive boronic acid derivatives.

2.4 Conclusion

The reactivity of diisopropylaminoborane 1 was evaluated in the palladium-catalyzed Vaultier borylation of aryl iodides, bromides, and triflates. It was found that use of 1 prepared in situ from the corresponding LAB reagent with TMS-Cl and resulted in the highest yields of the corresponding boronic acids. However, the presence of a small amount of LiBH₄ side product in this borylation reaction causes precipitation of palladium, lowering yields of the desired products. After screening various palladium catalysts, palladium dichloride was found to be the most effective catalyst with aryl iodides. Conversely, Pd₂dba₃•CHCl₃ worked the best for aryl bromides and triflates. Upon treatment of the reaction mixture with an aqueous work-up, the corresponding boronic acid compounds are formed. Isolation of boronic acid compounds from the reaction of 1 with aryl iodide- and bromide- compounds resulted in moderate to excellent yields. Unfortunately, aryl iodides and bromides were found
to be intolerant of many functional groups. However, many of the functional groups not compatible with aryl iodides and bromides worked exceptionally when the halide was replaced by a triflate. Overall, a wide variety of boronic acids have been synthesized from the corresponding aryl iodides, bromides, and triflates in moderate to excellent yields using easily accessible diisopropylaminoborane and a relatively inexpensive palladium catalyst.

2.5 Experimental Section

General Methods. All reactions were performed in oven-dried, argon-cooled glassware. All air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. Diisopropylamine was distilled over CaH₂ prior to use. Anhydrous tetrahydrofuran (THF) was freshly obtained from a solvent purification system (Pure Solv MD, Innovative Technology Inc.). Aminoboranes were not isolated but were characterized and used in solutions. NMR spectra were recorded at 500 MHz (¹H), 125 MHz (¹³C), and 160.4 MHz (¹¹B). All ¹H NMR and ¹³C NMR chemical shifts are reported in δ units relative to the respective solvent of the NMR sample. ¹¹B NMR samples are reported relative to the external standard BF₃·Et₂O (δB = 0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration.

General Procedure for the Preparation of Diisopropylaminoborane 1 M Solution in THF. To an oven dried and argon cooled 100-mL round-bottomed flask equipped with a stir bar was added diisopropylamine (5.00 g, 7 mL, 50 mmol) followed by
THF (18 mL). The solution was cooled to 0 °C (ice bath) and borane dimethylsulfide (5 mL, 10 M, 50 mmol) was added dropwise via syringe. After 1 h of stirring at 0 °C, an aliquot was removed for analysis by $^{11}$B-NMR. The analysis showed the solution to be diisopropylamine-borane complex ($\delta_B$ -21, q, $J_{BH} = 95$ Hz). To the stirring solution, $n$-butyllithium (20 mL, 2.5 M, 50 mmol) was added dropwise via cannula needle. After 1 h of stirring at 0 °C, an aliquot was removed for analysis by $^{11}$B-NMR, which showed the solution to be lithium diisopropaminoborohydride ($\delta_B$ -23, q, $J_{BH} = 83$ Hz). Trimethylsilyl chloride (3.20 mL, 25 mmol) was added dropwise over 5 min via syringe while stirring at 0 °C. After 1 h of stirring at 25 °C, an aliquot was taken and analyzed via $^{11}$B-NMR, which showed the solution to be monomeric diisopropaminoborane ($\delta_B$ +35, t, $J_{BH} = 125$ Hz). The solution was transferred to an oven-dried, argon-cooled ampoule via a cannula needle.

**General Procedure for the Synthesis of Boronic Acids from Aryl Iodides, Bromides, or Triflates.** The following procedure for the synthesis of $p$-methoxyphenylboronic acid from $p$-iodoanisol, $\text{H}_2\text{B-N(iPr)}_2$, and $\text{PdCl}_2$ is representative. To an oven-dried and argon cooled 50-mL round-bottomed flask equipped with a sidearm, condenser, and stir bar was added triphenylphosphine (0.131 g, 0.5 mmol, 20 mol %), $p$-iodoanisol (0.585 g, 2.5 mmol), and triethylamine (1.78 mL, 12.5 mmol). This solution was then degassed by alternating vacuum and argon three times. Palladium dichloride (0.023 g, 0.13 mmol, 5 mol %) was then added under positive argon pressure. After stirring at room temperature for 15 min, diisopropaminoborane (5 mL, 1M solution in THF, 5 mmol) was added and the
reaction mixture was degassed again by alternating vacuum and argon three times. The reaction solution was then heated to reflux. After 12-20 h of reflux the reaction was cooled to 0 °C and 6 mL of methanol was added through the condenser slowly (Caution: exothermic and hydrogen evolution). After 15 min of stirring all the solvent was removed under reduced pressure to yield a black solid. This solid was dissolved with sodium hydroxide (3M, 8 mL) and subsequently washed with hexanes (3 x 10 mL). The aqueous layer was then cooled to 0 °C (ice bath) and acidified to pH ≤ 1 with concentrated HCl, with the boronic acid usually precipitating out as a white solid. The aqueous fraction was then extracted with Et₂O (3 x 10 mL). The organic fractions were combined, dried over MgSO₄, concentrated under reduced pressure to yield a white solid (0.338 g, 89% yield).

4-Methoxyphenylboronic acid (4a). Off-white solid, 89% Yield, ¹H-NMR (500 MHz, MeOH-d4) δ 3.74 (s, 1H), 6.84 (d, 2H, J = 8.5 Hz), 7.64 (d, 2H, J = 8.0 Hz); ¹³C-NMR (125 MHz, MeOH-d4) δ 53.9, 112.7, 135.2, 161.5; ¹¹B-NMR (160 MHz, MeOH) δB +28.7. EM (ESI): m/z (M+) calcd. for C₉H₁₄BO₃ 181.10260, found 181.10305.

4-Tolylboronic acid (4b). Off-white solid, 84% Yield, ¹H-NMR (500 MHz, CDCl₃) δ 2.45 (s, 3H), 7.33 (d, 2H, J = 8.0 Hz), 8.14 (d, 2H, J = 8.0 Hz); ¹³C-NMR (125
MHz, CDCl$_3$) $\delta$ 21.9, 128.9, 133.7, 135.9, 143.1; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B$ +29.1. EM (ESI): $m/z$ (M+) calcd. for C$_9$H$_{14}$BO$_2$ 165.11054, found 165.10814.

2-Tolylboronic acid (4c). Off-white solid, 73% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.86 (s, 3H), 7.31 (d, 1H, $J = 8.0$ Hz), 7.35 (t, 1H, $J = 7.5$ Hz), 7.49 (t, 1H, $J = 7.5$ Hz), 8.26 (d, 1H, $J = 7$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 23.3, 125.4, 130.8, 132.4, 137.5, 146.5; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B$ +28.5.

Phenylboronic acid (4d). Off-white solid, 80% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.54 (t, 2H, $J = 7.5$ Hz), 7.62 (t, 1H, $J = 7.5$ Hz), 8.27 (d, 2H, $J = 7.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 128.1, 132.9, 135.8; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B$ +28.5. EM (ESI): $m/z$ (M+) calcd. for C$_8$H$_{12}$BO$_2$ 151.08092, found 151.09249.

4-Fluorophenylboronic acid (4e). Off-white solid, 57% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.21 (t, 2H, $J = 9.0$ Hz), 8.24 (t, 2H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, MeOD) $\delta$ 112.2 (d, $J_F = 20$ Hz), 134.0 (d, $J_F = 8.0$ Hz) 162.7 (d, $J_F = 246$ Hz); $^{11}$B-NMR (160 MHz, MeOD) $\delta_B$ +28.5. EM (ESI): $m/z$ (M+) calcd. for C$_8$H$_{11}$BO$_2$F 169.08972, found 169.08307.
3-Fluoro-4-methylphenylboronic acid (4f). Off-white solid, 50% Yield, $^1$H-NMR (500 MHz, MeOH-d4) δ 2.21 (s, 3H), 7.13 (t, 1H, $J = 7.0$ Hz), 7.29 (s, 1H), 7.35 (s, 1H); $^{13}$C-NMR (125 MHz, MeOH-d4) δ 14.7, 120.7, 120.8, 130.6, 132.1, 162.6 (d, $J_F = 242$ Hz); $^{11}$B-NMR (160 MHz, MeOH-d4) δ$_B$ +28.8; EM (ESI): $m/z$ (M+) calcd. for C$_9$H$_{13}$BFO$_2$ 183.10495, found 183.09872.

3-Cyanophenylboronic acid (4g). Off-white solid, 20% Yield, $^1$H-NMR (500 MHz, MeOH-d4) δ 7.45 (t, 1H, $J = 8.0$ Hz), 7.67 (d, 1H, $J = 8.0$ Hz) 7.96 (m, 1H); $^{13}$C-NMR (125 MHz, MeOH-d4) δ 111.2, 118.7, 128.1, 133.0, 137.1, 137.9; $^{11}$B-NMR (160 MHz, MeOH-d4) δ$_B$ +27.6

Thiopen-2-ylboronic acid (4h). Off-white solid, 99% Yield, $^1$H-NMR (500 MHz, MeOH-d4) δ 4.79 (s, 3H), 7.13 (s, 1H), 7.59 (s, 2H); $^{13}$C-NMR (125 MHz, MeOH-d4) 127.4, 130.9; $^{11}$B-NMR (160 MHz, MeOH-d4) δ$_B$ +26.8; EM (ESI): $m/z$ (M+) calcd. for C$_4$H$_3$BO$_2$S 157.05865, found 157.04891.
4-Methoxyphenylboronic acid (6a). Off-white solid, 85% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 3.89 (s, 3H), 7.02 (d, 2H, $J = 8.0$ Hz), 8.17 (d, 2H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 55.2, 113.6, 137.6, 163.4; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B +28.0$. EM (ESI): $m/z$ (M$^+$) calcd. for C$_7$H$_{10}$BO$_3$ 153.05946, found 153.07175.

4-Tolylboronic acid (6b). Off-white solid, 80% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.45 (s, 3H), 7.32 (d, 2H, $J = 7.0$ Hz), 8.14 (d, 2H, $J = 6.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 21.9, 128.1, 128.9, 135.8, 135.9, 143.1; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B +29.2$; EM (ESI): $m/z$ (M$^+$) calcd. for C$_9$H$_{13}$BNaO$_2$ 187.09163, found 187.09008.

2-Tolylboronic acid (6c). Off-white solid, 35% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.87 (s, 3H), 7.32 (d, 1H, $J = 8.0$ Hz), 7.36 (t, 1H, $J = 7.5$ Hz), 7.50 (t, 1H, $J = 7.5$ Hz), 8.27 (d, 1H, $J = 7.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 23.2, 125.4, 130.8, 132.4, 137.5, 146.5; $^{11}$B-NMR (160 MHz, MeOH-d$_4$) $\delta_B +30.9$; EM (ESI): $m/z$ (M$^+$) calcd. for C$_9$H$_{13}$BNaO$_2$ 187.08632, found 187.09008.

Phenylboronic acid (6d). Off-white solid, 83% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.54 (t, 2H, $J = 7.0$ Hz), 7.61 (t, 1H, $J = 7.0$ Hz), 8.27 (d, 2H, $J = 6.5$ Hz); $^{13}$C-NMR
(125 MHz, CDCl₃) δ 128.1, 132.8, 135.8; ¹¹B-NMR (160 MHz, MeOH) δ_B +29.3; EM (ESI): m/z (M+) calcd. for C₇H₁₁BNaO₂ 173.08423, found 173.07443.

4-Fluorophenylboronic acid (6e). Off-white solid, 40% Yield, ¹H-NMR (500 MHz, CDCl₃) δ 7.20 (t, 2H, J = 9.0 Hz), 8.23 (t, 2H, J = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃) δ 115.4 (d, J_F = 20 Hz), 138.2 (d, J_F = 9.8 Hz), 166.3 (d, J_F = 253Hz); ¹¹B-NMR (160 MHz, MeOH) δ_B +28.9; EM (ESI): m/z (M+) calcd. for C₈H₁₃BNaO₂ 141.04730, found 141.05176.

(E)-Styrylboronic acid (6f). Off-white solid, 51% Yield, ¹H-NMR (500 MHz, MeOH-d₄) δ 6.18 (d, 1H), 7-7.3 (m, 5H) 7.42 (d, 1H, J = 7.0 Hz); ¹³C-NMR (125 MHz, MeOH-d₄) δ 126.6, 127.6, 127.9, 128.3, 137.8, 146.9; ¹¹B-NMR (160 MHz, MeOH-d₄) δ_B +32.4; EM (ESI): m/z (M+) calcd. for C₉H₉BNaO₂ 171.05905, found 171.05878.

Thiophen-2-ylboronic acid (6g). Off-white solid, 87% Yield, ¹H-NMR (500 MHz, MeOH-d₄) δ 7.08 (s, 1H), 7.53 (s, 1H), 7.57 (s, 1H); ¹³C-NMR (125 MHz, MeOH-d₄) δ 127.6, 130.9, 135.3; ¹¹B-NMR (160 MHz, MeOH-d₄) δ_B +26.7; EM (ESI): m/z (M+) calcd. for C₆H₉BNaO₂S 179.02403, found 179.03085.
Thiophen-3-ylboronic acid (6h). Off-white solid, 72% Yield, $^1$H-NMR (500 MHz, MeOH-d4) δ 7.28 (s, 1H) 7.36 (s, 1H) 7.84 (s, 1H); $^{13}$C-NMR (125 MHz, MeOH-d4) δ 124.6, 127.3, 131.6, 134.3; $^{11}$B-NMR (160 MHz, MeOH-d4) δ$_B$ +27.0.

4-Methoxyphenylboronic acid (8a). Off-white solid, 87% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) δ 3.89 (s, 3H), 7.02 (d, 2H, $J = 8.0$ Hz), 8.17 (d, 2H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 55.2, 113.6, 137.6, 163.4; $^{11}$B-NMR (160 MHz, MeOH) δ$_B$ +29.1; EM (ESI): m/z (M+) calcd. for C$_{13}$H$_{14}$B 181.11073, found 181.11831.

4-Tolylboronic acid (8b). Off-white solid, 86% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) δ 2.45 (s, 3H), 7.32 (d, 2H, $J = 7.0$ Hz), 8.13 (d, 2H, $J = 5.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 21.9, 128.9, 130.8, 143.1; $^{11}$B-NMR (160 MHz, MeOH) δ$_B$ +29.3; EM (ESI): m/z (M+) calcd. for C$_9$H$_{13}$BNaO$_2$ 187.09835, found 187.09008.

2-Tolylboronic acid (8c). Off-white solid, 78% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) δ 2.85 (s, 3H), 7.30 (d, 1H, $J = 8.0$ Hz), 7.34 (t, 1H, $J = 7.5$ Hz), 7.48 (t, 1H, $J = 7.5$ Hz) 8.25 (d, 1H, $J = 7.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 23.2, 125.4, 130.8,
132.4, 137.5, 146.5; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B$ +30; EM (ESI): m/z (M+) calcd. for C$_7$H$_9$BNaO$_2$ 173.07764, found 173.07443.

**3,4-Dimethylboronic acid (8d).** Off-white solid, 85% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.61 (s, 3H), 2.65 (s, 3H), 7.54 (s, 1H), 8.24 (s, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 20.0, 20.5, 128.2, 129.7, 133.7, 136.3, 137.0, 141.8; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B$ +29.3; EM (ESI): m/z (M+) calcd. for C$_8$H$_{11}$BNaO$_2$ 187.10383, found 187.09008.

**Phenylboronic acid (8e).** Off-white solid, 74% Yield, $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.53 (t, 2H, $J = 8.0$ Hz), 7.62 (t, 1H, $J = 7.5$ Hz), 8.26 (d, 2H, $J = 6.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 128.1, 132.9, 135.8; $^{11}$B-NMR (160 MHz, MeOH) $\delta_B$ +29.2; EM (ESI): m/z (M+) calcd. for C$_6$H$_{15}$O$_4$ 151.09629, found 151.09649.

**4-Chlorophenylboronic acid (8f).** Off-white solid, 97% Yield, $^1$H-NMR (500 MHz, MeOD) $\delta$ 5.70 (d, 2H, $J = 7.0$ Hz), 6.04 (d, 2H, $J = 6.5$ Hz); $^{13}$C-NMR (125 MHz, MeOD) $\delta$ 125.7, 133.4; $^{11}$B-NMR (160 MHz, MeOD) $\delta_B$ +30.4; EM (ESI): m/z (M+) calcd. for C$_6$H$_{11}$BClO$_2$ 185.04943, found 185.05351.
4-Fluorphenylboronic acid (8g). Off-white solid, 81% Yield, $^1$H-NMR (500 MHz, MeOH-d4) δ 7.01 (t, 2H, $J = 8.5$ Hz), 7.70 (s, 2H); $^{13}$C-NMR (125 MHz, MeOH-d4) δ 113.9 (d, $J_F = 20$ Hz), 135.7 (d, $J_F = 8$ Hz), 164.3 (d, $J_F = 244$ Hz); $^{11}$B-NMR (160 MHz, MeOH-d4) δ$_B$ +28.7; EM (ESI): $m/z$ (M+) calcd. for C$_6$H$_7$BFO$_2$ 141.05107, found 141.05176.

4-Cyanophenylboronic acid (8h). Off-white solid, 70% Yield, $^1$H-NMR (500 MHz, MeOD) δ 6.04 (d, 2H, $J = 8.0$ Hz), 6.23 (d, 2H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, MeOD) δ 116.8, 129.0, 132.4; $^{11}$B-NMR (160 MHz, MeOD) δ$_B$ +28.3 EM (ESI): $m/z$ (M+) calcd. for C$_9$H$_{11}$BNO$_2$ 176.09440, found 176.08774.

Naphthalen-2-ylboronic acid (8i). Off-white solid, 82% Yield, $^1$H-NMR (500 MHz, MeOH-d4) δ 5.86 (p, 2H, $J = 6.5$ Hz), 6.26-6.39 (m, 4H), 6.74 (t, 1H); $^{13}$C-NMR (125 MHz, MeOH-d4) δ 126.8, 127.7, 128.7, 129.6, 131.4, 135.7; $^{11}$B-NMR (160 MHz, MeOH-d4) δ$_B$ +29.3; EM (ESI): $m/z$ (M+) calcd. for C$_{12}$H$_{13}$BNaO$_2$ 223.09631, found 223.09008.

General Procedure for the Synthesis of Aryl Boronic Esters from Aryl Halides.

The following procedure for the synthesis of 2-(4-methoxyphenyl)-5,5-dimethyl-
1,3,2-dioxaborinane from \textit{p}-iodoanisol, H$_2$B-N(iPr)$_2$, and PdCl$_2$ is representative. To an oven-dried and argon-cooled 50-mL round-bottomed flask equipped with a sidearm, condenser, and stir bar was added triphenylphosphine (0.131 g, 0.5 mmol, 20 mol%), \textit{p}-iodoanisol (0.585 g, 2.5 mmol), and triethylamine (1.78 mL, 12.5 mmol). This solution was then degassed by alternating vacuum and argon three times. Palladium dichloride (0.023 g, 0.13 mmol, 5 mol%) was then added under positive argon pressure. After stirring at room temperature for 15 min diisopropylaminoborane (5 mL, 1M, 5 mmol) was added and the reaction mixture was degassed again by alternating vacuum and argon three times. The reaction solution was then heated to reflux. After 12-20 h of reflux the reaction was cooled to 0 °C and neopentyl glycol (6 mL, 1 M solution in THF, 6.0 mmol) was slowly added through the condenser and the solution was allowed to warm to 25 °C. After 15 min of stirring at 25 °C, 1M HCl (6 mL) was added and the mixture was filtered through a pad of celite. The mixture was then extracted with Et$_2$O (3 x 10 mL). The organic fractions were combined, washed with brine (2 x 10 mL), dried over MgSO$_4$, and concentrated under reduced pressure to yield a yellow oil (0.545g, 99% yield).

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {MeO} ;
\node (b) at (1,-1) {B} ;
\node (c) at (2,-1) {O} ;
\node (d) at (3,0) {O} ;
\node (e) at (4,-1) {\text{\textbullet\text{-}}} ;

\draw (a) -- (b) -- (c) -- (d) -- (e) ;
\end{tikzpicture}
\end{center}

\textbf{2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (10a).} Yellow Oil, 99% yield. $^1$H-NMR (500 MHz, CDCl$_3$) δ 1.02 (s, 6H), 3.76 (s, 4H), 3.80 (s, 3H), 6.92 (d, $J = 8.5$ Hz, 2H), 7.83 (d, $J = 9.0$ Hz, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 22.0, 32.0,
55.1, 72.4, 113.4, 128.9, 132.4, 135.9, 162.1; $^{11}$B-NMR (160 MHz, CDCl$_3$) $\delta_B +27.0$. EM (ESI): $m/z$ (M+) calcd. for C$_{12}$H$_{18}$BO$_3$ 221.12795, found 221.13435.

\[ \text{Yellow Oil, 90% yield.} \]

\[ \text{1H-NMR (500 MHz, CDCl$_3$) $\delta$ 1.10 (s, 6H), 2.41 (s, 3H), 3.80 (s, 4H), 7.23 (d, $J = 7.5$ Hz, 2H), 7.78 (d, $J = 5.0$ Hz, 2H); } \]

\[ \text{13C-NMR (125 MHz, CDCl$_3$) $\delta$ 21.7, 22.0, 31.9, 72.4, 128.5, 134.1, 140.8; } \]

\[ \text{11B-NMR (160 MHz, CDCl$_3$) $\delta_B +27.1$. EM (ESI): } \]

\[ m/z \text{ (M+) calcd. for C$_{12}$H$_{18}$BO$_2$ 205.14448, found 205.13944.} \]

\[ \text{Yellow Oil, 89% yield.} \]

\[ \text{1H-NMR (500 MHz, CDCl$_3$) $\delta$ 1.04 (s, 6H), 3.77 (s, 4H), 7.20 (s, 1H), 7.58 (s, 1H), 7.63 (s, 1H); } \]

\[ \text{13C-NMR (125 MHz, CDCl$_3$) $\delta$ 21.9, 72.5, 128.2, 131.5, 135.8; } \]

\[ \text{11B-NMR (160 MHz, CDCl$_3$) $\delta_B +25.5$. EM (ESI): } m/z \text{ (M+) calcd. for C$_9$H$_{14}$BO$_2$S 197.08817, found 197.0821.} \]
2.6 References


30 The irreproducibility of the reactions containing LiBH$_4$ is probably due to the varying amounts of LiBH$_4$ present in each batch of aminoborane.


34 The use of commercially available Pd$_2$dba$_3$•CHCl$_3$ does not lower the overall cost of this reaction, but when synthesized its cost is comparable to PdCl$_2$(PPh$_3$)$_2$. Moreover, Pd$_2$dba$_3$•CHCl$_3$ is stable and can be stored on the bench for long periods of time with no deposition, unlike PdCl$_2$(PPh$_3$)$_2$.


CHAPTER 3
Reaction of Grignard Reagents with Diisopropylaminoborane.
Synthesis of Alkyl, Aryl and Heteroaryl Boronic Acids From Organo(diisopropyl)aminoborane by a Simple Hydrolysis
3.1 Introduction

Boronic acids and their derivatives are very important compounds in organic chemistry, as chemical intermediates or building blocks. Their use in transition metal-catalyzed cross-coupling reactions can lead to carbon–carbon and carbon–heteroatom bond formation. Beyond their use in the ubiquitous Suzuki–Miyaura coupling reaction,\(^1\) synthetic applications for boronic acids include use in Diels–Alder reactions,\(^2\) as chiral auxiliaries\(^3\) in the separation of cyclic cis- and trans-1,2-diols,\(^4\) as protecting groups,\(^5\) and as precursors to boron enolates.\(^6\) Thus, the demand for organoboron compounds has been growing concurrently.

Classical routes for the preparation of boronic acids involve the utilization of Grignard or lithium reagents with trialkoxyboranes.\(^7\) In many cases the Grignard reagents are preferred due to their availability, stability, and general lower cost. In contrast, organolithium reagents can provide access to unique organoboronic acids, which cannot be accessed via the Grignard route. Traditionally, boronic acids and boronate esters are obtained from organohalides (I, Br) after metal-halogen exchange with lithium or magnesium and subsequent reaction with trialkoxyboranes. Although efficient at generating boronic acids, such conditions are not compatible with many functional groups such as reactive carbonyls or nitriles, requiring tedious additional protection–deprotection steps. Since the late 1990s, a considerable number of transition metal-catalyzed borylation reactions have been developed. Direct CH borylation of aromatics have been reported.\(^8\) However these methods require expensive borylating agents and toxic rare earth metal catalysts.
3.2 Preparation of Boronic Acids from Grignard and Organolithium Reagents

The traditional route to form aryl- and 1-alkenylboronic acids and esters is from the reactions of Grignard reagents with trialkylborates. This is an efficient method for the preparation of relatively simple boron compounds in large quantities. It is used in industry to prepare aromatic (Eq. 1) and vinylic boronic acids (Eq. 2).⁹

\[
\begin{align*}
\text{Ar-MgX} & \quad + \quad \text{B(OMe)₃} \quad \xrightarrow{\text{Et₂O, Aq. work-up}} \quad \text{Ar-B(OH)}_2 \\
\text{MgBr} & \quad + \quad \text{B(OMe)₃} \quad \xrightarrow{\text{Et₂O, Aq. work-up}} \quad \text{B(OH)}_3
\end{align*}
\]

Matteson reported that the synthesis of stereospecific alkenylboronic acids or esters requires the reaction of a (Z)- or (E)-2-butene-1-ylmagnesium bromide with trimethylborate (Eq. 3).¹⁰

\[
\begin{align*}
\text{Br-CH₂-CH=CH₂} & \quad \xrightarrow{\text{1. Mg⁰, Et₂O}} \quad \text{Br-CH₂-CH=CH₂} \quad \xrightarrow{\text{2. B(OMe)₃}} \quad \text{Br-CH₂-CH=CH₂} \quad \xrightarrow{\text{3. Aq. work-up}} \quad \text{Br-CH₂-CH=CH₂-B(OH)₂}
\end{align*}
\]

Unfortunately, application of these classical procedures on the synthesis of boronic acids or esters usually suffers from bis-alkylation leading to unwanted borinic acid derivatives along with the formation of trialkylboranes. Khotinsky reported in 1909 that reaction of a methylborate solution with phenylmagnesium bromide produced a mixture of phenyboronic and phenylborinic acids (Eq. 4).¹¹

\[
\begin{align*}
\text{MgBr} & \quad + \quad \text{B(OMe)₃} \quad \xrightarrow{\text{Et₂O}} \quad \text{PhB(OH)₂} \quad + \quad \text{PhB(OH)₂}
\end{align*}
\]
Johnson reported that reversing the order of addition and running the reaction at low temperature (-12 °C) produced phenylboronic acid in approximately 30% yield\textsuperscript{12}. A systematic study between phenylmagnesium bromide and trimethylborate in diethyl ether confirmed the low temperature requirement (generally below -50 °C) for increased yields of boronic acid (Eq. 5)\textsuperscript{12}.

\[
\text{ArMgBr} \quad \xrightarrow{\text{B(OMe)}_3 3 \text{ equiv}} \quad \text{ArB(OH)}_2 \quad \text{Et}_2\text{O}, -50 ^\circ\text{C}
\] \hspace{1cm} (5)

As reaction conditions approach ambient temperatures, increasing amounts of diphenylborinic ester were formed by the second addition of Grignard reagent to the intermediate dimethylbenzene boronate\textsuperscript{13}. Utilization of this method for larger scale industrial production was limited due to the low temperature requirements. This problem was alleviated by using excess amounts of trialkylborate. With increased reaction temperatures, organomagnesium halide reagents reacted with more electrophilic functional groups. The incompatibility of Grignard reagents with many functional groups was the major limitation of this methodology.

In order to circumvent the drawbacks of using Grignard reagents in the synthesis of boronic acids, organolithium reagents were employed. An improved method for producing arylboronic acids was reported by Brown and Cole\textsuperscript{14}. This method utilized the transmetallation of aryllithium reagents with an excess of trialkylborate such as trimethyl-, triethyl-, or triisopropylborate, followed by acid hydrolysis (Eq. 6).
Reaction of an organolithium reagent with triisopropyl borate, followed by acidification with HCl led directly to boronic esters in high yields without the problem of unwanted side products. Using this procedure, Brown was able to synthesize a diverse range of compounds, including alkynyl boronic acids and esters.\(^\text{15}\) For example, reaction of ethynylcyclopentane with triisopropylborate followed by acidic work-up afforded the boronic acid in 88\% yield (Eq. 7).

\[
\text{R-Li} + \text{B(O\text{Pr})}_3 \overset{1. \text{Et}_2\text{O}, -78 ^\circ\text{C}}{\longrightarrow} \overset{2. \text{HCl, Et}_2\text{O}}{\longrightarrow} \text{R-B-OH} \quad (6)
\]

A modification of this reaction also allowed for the synthesis of \(\alpha\)-haloboronic esters. Preparation of boronic acids by reaction with organolithium reagents is amenable to new continuous flow methodologies.\(^\text{16}\) Due to the reactivity of lithium reagents, the reaction must be carried out at -78 °C to avoid multiple additions. The need for cryogenic conditions makes these processes less economically feasible, especially on larger scales. Attention has turned to the production of boronic acids and esters under safer, and milder conditions.

The use of cyclic dioxaborolanes such as isopropoxypinacolborane have reduced the formation of borinic acid side products.\(^\text{17,18}\) Walsh reported the synthesis of various boronates using novel derivatives of glycol borates.\(^\text{19}\) The glycol borates reacted efficiently with Grignard reagents at room temperature to yield their corresponding boronates in high yields. The reaction of phenylmagnesium bromide
with isopropyl glycol borate afforded the boronic ester in 98% yield (Eq. 8).

\[
\begin{align*}
\text{MgBr} & \quad + \quad \text{B(OMe)}_3 \\
1. \text{THF, rt, 2 h} & \quad \rightarrow \quad \text{B} \quad \text{OH} \\
2. \text{Aq. work-up} & \quad \rightarrow \quad \text{98%}
\end{align*}
\]

The researchers also reported that glycol borates were amenable to reactions with organolithium reagents at -20 °C. Similar reactivity was reported by Stoltz in the synthesis of Dragamididin D.\textsuperscript{20}

Colobert reported a one-pot procedure to synthesize arylboronic acids without the need for cryogenic conditions.\textsuperscript{21} Electrophilic borylation was accomplished employing the direct insertion of magnesium by a magnesium/bromide exchange with \(i\text{PrMgCl\cdotLiCl}\) complex, a procedure first reported by Knochel.\textsuperscript{22} Their methodology proved tolerant towards many functional groups; aryl moieties with electron-donating and electron-withdrawing substituents gave the boronic acids in excellent yields. Even an aryl bromide bearing a sensitive nitrile was converted into the corresponding boronic acid in good yield (Eq. 9).

\[
\begin{align*}
\text{NC} & \quad \text{Br} & \quad \text{NC} & \quad \text{MgBr\cdotLiCl} & \quad \text{OH} \\
\text{THF, 25 °C} & \quad \rightarrow \quad \text{NC} & \quad \text{MgBr\cdotLiCl} & \quad \text{B(OMe)}_3 & \quad \text{72%} \\
0 \degree C, 2 h & \quad \rightarrow \quad \text{NC} & \quad \text{B} & \quad \text{OH} \\
\end{align*}
\]

3.3 Borylation Using Diisopropylaminoborane

Aminoboranes have been known since the discovery of the hydroboration reaction in 1956.\textsuperscript{23} Their reactivity as useful tools for synthetic organic chemistry has been scarcely studied. Currently, methods for the syntheses of aminoboranes are limited to thermally-induced dehydrogenation,\textsuperscript{24} or metal-catalyzed dehydrogenation
of the corresponding amine-borane adducts ($R_1R_2HN:BH_3$).\textsuperscript{25} Aminoboranes can also be synthesized from LAB reagents by reaction with trimethylsilyl chloride.\textsuperscript{26} Aminoboranes are known to easily form mixtures of dimers and oligomers, preventing purification.\textsuperscript{27} If the steric hindrance around the nitrogen is large enough, the aminoborane exists as a monomer and is highly reactive.

As previously mentioned, diisopropylaminoborane can serve as a boron source for the synthesis of boronic acids in Vaultier’s borylation reaction.\textsuperscript{40} During the investigation into the properties of aminoboranes, it was found that aminoborane dimers are inert as hydride donors both in hydroboration and reduction reactions. Consequently, the study of the reactivity of aminoboranes has focused on the reactions of monomeric aminoboranes, such as diisopropylaminoborane. Initially, diisopropylaminoborane ($H_2B-N(iPr)_2$ 1) was examined as a potential boron source for the synthesis of boronic acids. The palladium catalyzed borylation of aryl bromides with $H_2B-N(iPr)_2$ was attempted under Vaultier conditions:\textsuperscript{29} phenylboronic acid and 4-methoxyphenylboronic acid are successfully synthesized from the corresponding aryl bromides (Scheme 3.1).

![Scheme 3.1. Palladium-Catalyzed Synthesis of Boronic Acids from $H_2B-N(iPr)_2$](image_url)
This reaction is compatible with various electron-withdrawing and electron-donating aryl substituents, even heteroaryl halides (Chapter 2).\textsuperscript{28} Aryl bromides containing nitriles behave differently, and led to the discovery that $\text{H}_2\text{B-}\text{N}((\text{iPr})_2$ can reduce nitriles in the presence of a catalytic amount of $\text{LiBH}_4$.\textsuperscript{29}

Singaram reported on the reactivity of Grignard reagents with organoboranes, such as 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBPin).\textsuperscript{30} Under ambient temperatures, alkyl, aryl, heteroaryl, vinylic, and allylic Grignard reagents reacted with HBPin to afford the corresponding pinacolboronates in high yields. The initially formed alkyl(dialkoxy)borohydride intermediate quickly eliminated hydridomagnesium bromide (HMgBr) and afforded the product boronic ester. This methodology was used to prepare a host of boronate esters, including 2-thiophenylpinacolboronic ester isolated in 92\% yield (Eq. 10)

\[ \text{S} \text{Br} + \text{HB} \xrightarrow{\text{Mg}^+, \text{THF}, 25 \, ^\circ \text{C}, 3 \, \text{h}} \text{B} \xrightarrow{92\%} \]

With the reactivity of Grignard reagents and organoboranes established, the reactivity of Grignard reagents with diisopropylaminoborane was probed. This chapter discusses the results of the reaction of diisopropylaminoborane with various organometallic reagents. The results obtained from the optimized borylation of alkyl and aryl bromides under Grignard and modified-Barbier conditions using diisopropylaminoborane prepared from lithium diisopropylaminoborohydride are reported.
3.4 Results and Discussion

Aminoboranes are typically prepared in situ in tetrahydrofuran (THF) from LAB reagents and used without further purification.\textsuperscript{31} Exploration of the literature revealed no studies detailing the reaction of diisopropylaminoborane with organometallic reagents. Consequently, the reactivity of diisopropylaminoborane prepared from the corresponding LAB reagent with various organometallic reagents including alkyllithium, alkylzinc bromide, and alkylmagnesium bromide was explored.

3.4.1 Reaction of Diisopropylaminoborane with Lithium and Zinc Reagents

The reaction of diisopropylaminoborane 1 with phenyl lithium was carried out in THF at 0 °C. The reaction progress was monitored by $^{11}$B-NMR spectroscopy of reaction aliquots. After one hour, the $^{11}$B-NMR spectrum showed a wide distribution of products. When the reaction was repeated at -78 °C, the same distribution of products was observed, although the aliquots had warmed to room temperature in the NMR tube in the short time between taking the sample and acquiring the $^{11}$B-NMR spectrum (Figure 3.1).
As seen by $^{11}$B-NMR, the initial addition intermediate is the boronate complex 2, seen as a triplet at $\delta_B$ -13 ppm ($J_{BH} = 78$ Hz). This boronate species decomposes by transfer of a hydride to afford the desired borylation product 3, as well as products lithium diisopropylaminoborohydride 4, and lithium borohydride 5. The inability to control nucleophilic addition of phenyllithium to the boron atom of 1 even under cryogenic conditions precluded further investigation into the reaction of organolithium reagents.

To probe the reactivity of organozinc reagents, the reaction of 1 with one equivalent $p$-cyanophenyl zinc bromide was carried out in THF at 0 °C, monitoring by $^{11}$B-NMR spectroscopy of reaction aliquots. Disappointingly, after one hour, the $^{11}$B-NMR spectrum also showed a distribution of products. Contrary to the observed
reactivity of phenyllithium, the aryl zinc bromide added to the boron atom multiple times. Upon aqueous quench, $^{11}$B-NMR analysis revealed a mixture of the corresponding boronic acid ($\delta_B +35, s$), as well as the corresponding borinic acid ($\delta_B +53, s$). These observations prompted an evaluation of the reactions of 1 with less reactive organometallic species.

The reaction of 1 with one equivalent of the mild reagent diethylzinc was carried out in THF at room temperature. Within ten minutes of the addition of diethylzinc, a bluish-gray precipitate formed, coating the interior of the reaction flask. The reaction progress was monitored by $^{11}$B-NMR spectroscopy of reaction aliquots. After one hour, analysis by $^{11}$B-NMR revealed the absence of 1 ($\delta_B +35, t, J_{BH} = 125$ Hz) and the appearance of one intermediate, corresponding to ethyl(diispropylamino)borane ($\delta_B +42, d, J_{BH} = 112$ Hz) (Eq. 11).

$$\text{Zn} + \text{H}_2\text{B} + 35, t, J_{BH} = 125 \text{ Hz} \xrightarrow{\text{THF, 1 h, rt}} \text{H} \text{N} \text{B} + 42, d, J_{BH} = 112 \text{ Hz} \xrightarrow{\text{Aq. work-up}} \text{OH} \text{B} + 33, s \text{ 70% yield}$$

Upon aqueous quench, $^{11}$B-NMR analysis showed the addition product had been converted to the corresponding boronic acid ($\delta_B +33, s$), which was isolated in 70% yield. This observation indicates that dialkylzinc reagents are reactive enough to transfer an alkyl group to the boron atom. The generality of this reaction was probed further by varying the stoichiometric equivalents of the diethylzinc. Even in the presence of 50% excess, only one ethyl group is transferred to the boron atom. Analysis of the solid precipitate by powder X-ray diffraction (PXRD) showed that the
sample was crystalline zinc metal with no impurities or amorphous phases. The subsequent reaction of 1 with dimethylzinc followed by aqueous work-up, afforded the corresponding methylboronic acid in 50% yield. Although the reaction of 1 with dialkylzinc reagents is a direct method for synthesizing boronic acids, this methodology is limited by the sparse commercial availability of those reagents. Consequently, the reactivity of 1 with Grignard reagents was explored.

3.4.2 Reaction of Diisopropylaminoborane with Grignard Reagents

Diisopropylaminoborane 1 was allowed to react with one equivalent of p-tolylmagnesium bromide at 25 °C in THF, and the reaction progress was followed by \(^{11}\text{B}-\text{NMR}\) spectroscopy of reaction aliquots (Figure 3.2).

\[
\begin{align*}
\text{Ar-MgBr} & \quad \overset{\text{THF, 1 h, rt}}{\longrightarrow} & \quad \text{H}_{3}\text{B-N(Et)_{2}} \\
1 & \quad 3 & \quad 6 & \quad 7 \\
\text{Ar-B-N(Et)_{2}} & \quad \text{H}_{3}\text{B-N(Et)_{2}}
\end{align*}
\]

\[
\begin{align*}
\delta & \quad 35, \text{t} \quad J_{BH} = 125 \text{ Hz} \\
\delta & \quad 10, \text{t} \quad J_{BH} = 73 \text{ Hz} \\
\delta & \quad 42, \text{d} \quad J_{BH} = 112 \text{ Hz} \\
\delta & \quad 22, \text{q} \quad J_{BH} = 88 \text{ Hz}
\end{align*}
\]

**Figure 3.2.** Top: Reaction of H\(_{2}\)B-N(iPr)\(_{2}\) with p-Tolylmagnesium Bromide. Bottom: \(^{11}\text{B}-\text{NMR}\) Spectrum of Reaction Mixture.

After 30 minutes, \(^{11}\text{B}-\text{NMR}\) analysis revealed the absence of 1 (\(\delta_{B} \ = \ 35, \text{t}, J_{BH} = 125 \text{ Hz}\)) and the appearance of the single addition product aryl(diisopropylamino)borane 6 (\(\delta_{B} \ = \ 42, \text{d}, J_{BH} = 112 \text{ Hz}\)) and what appeared to be the magnesium analogue of a LAB
reagent, bromomagnesium aminoborohydride 7 (BrMg⁺·H₂B-N(iPr)₂, δB -22, q, J_{BH} = 88 Hz).³³ The ¹¹B-NMR spectrum also showed small amounts of the initially formed boronate adduct 3 (δB -12, t, J_{BH} = 75 Hz). Similar results were obtained when p-tolylmagnesium chloride was used.

The mechanism of borylation involves an initial nucleophilic attack by the p-tolylmagnesium bromide on the boron atom of 1, forming the bromomagnesium tolylaminoborohydride adduct 3. Once intermediate 3 is formed, the next step in the reaction pathway is its subsequent decomposition (Scheme 3.2). This decomposition proceeds via either a hydride transfer to magnesium bromide, forming 6 and hydridomagnesium bromide (pathway A), or though a hydride transfer to starting material 1, forming 6 and 7 concurrently (pathway B).

Scheme 3.2. Proposed Pathways of the Reaction of Grignard Reagents with H₂B-N(iPr)₂

Hydridomagnesium halides (HMgX, where X = Cl, Br) are known compounds. HMgBr does not undergo reductive elimination, but rather disproportionate to MgBr₂ and MgH₂ in THF.³⁴,³⁵ Compared to HMgBr, HMgCl does not disproportionate to MgCl₂ and MgH₂.³⁵ MgH₂ and HMgCl are both mild reducing agents soluble in
THF.\textsuperscript{35,36} HMgCl is prepared quantitatively by reacting isopropylmagnesium chloride with pinacolborane in THF.\textsuperscript{35}

To determine which reaction pathway is preferred, HMgCl was generated in situ and allowed to react with 1 (Scheme 3.3). If Pathway A is favored, HMgCl should be capable of transferring a hydride to the boron atom of 1, forming a mixture of 1 and 7.

\[
\text{MgCl} + \text{H-BO}_2 \xrightarrow{\text{THF, 1 h, rt}} \text{HMgCl} + \text{BO}_2
\]

\[
\text{HMgCl} + \text{H}_2\text{BN(iPr)}_2 \xrightarrow{\text{THF, 1 h, rt}} \text{No Reaction}
\]

Scheme 3.3. Testing the Ability of HMgCl to Transfer Hydride to H$_2$B-N(iPr)$_2$

Analysis of the reaction mixture by $^{11}$B-NMR spectroscopy showed the absence of a signal corresponding to chloromagnesium diisopropylaminoborohydride. This observation indicates that HMgCl is incapable of transferring a hydride to 1 and that Pathway A is not favored. Because there is an inherent difference in reactivity between HMgCl and HMgBr, this experiment does not conclusively rule out Pathway A. It does provide strong evidence that the observed bromomagnesium diisopropylaminoborohydride 7 is the result of hydride transfer from intermediate 3 to 1 (Pathway B).

Furthermore, it was found that 1.2 equivalents of 1 were required for greater than 95% conversion to the boronic acid. This result indicates that the reaction pathway does not exclusively proceed through Pathway B, as two equivalents of 1
would be required to account for quantitative conversion. Although the reaction mechanism is not fully understood, it is possible that the reaction proceeds concomitantly through both Pathways A, and B.

### 3.4.3 Synthesis of Chloromagnesium Dimethylaminoborohydride

To confirm the identity and characterize 7 (chemical shift and coupling constant), synthesis of authentic halomagnesium diisopropylaminoborohydride was attempted from diisopropylamine-borane and methylmagnesium chloride in THF. Analysis by $^{11}$B-NMR spectroscopy of the reaction mixture showed a small amount of the chloromagnesium diisopropylaminoborohydride ($\delta_B$ -17, $J_{BH} = 83$ Hz) and a number of disproportionation products. When the less sterically hindered dimethylamine-borane was allowed to react with an equivalent of methylmagnesium chloride, chloromagnesium dimethylaminoborohydride ($\delta_B$ -16, $q$, $J_{BH} = 83$ Hz) was produced quantitatively (Eq. 12).

$$\text{H}_3\text{B} : \text{NHMe}_2 + \text{H}_3\text{OMgCl} \xrightarrow{\text{THF, 0 °C, 1h}} \text{ClMg}^+ [\text{H}_3\text{B-NMe}_2]^+ + \text{CH}_4$$

(12)

### 3.4.4 Synthesis of Boronic Acids

The generality of reaction of Grignard reagents with H$_2$B-N(iPr)$_2$ was investigated by using commercially available Grignard reagents, which were titrated to accurately determine their concentration prior to use. The boronic acids were isolated from the magnesium hydride and aminoborohydride by-products by
quenching the reaction mixture with hydrochloric acid (3M) followed by extraction (Scheme 3.4).

Scheme 3.4. Synthesis of Boronic Acids from H₂B-N(iPr)₂

This methodology was applied to a variety of aryl and alkyl Grignard reagents, affording the corresponding boronic acids often in quantitative yields (Table 3.1). With commercially available Grignard reagents, the reaction was carried out at 0 °C for one hour.
Table 3.1. Synthesis of Boronic Acids from Commercial Grignard Reagents

| Entry | Grignard | Product | % Yield
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgBr</td>
<td>[(\text{C}_6\text{H}_5\text{B} \cdot \text{OH})]</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>MgCl</td>
<td>[(\text{C}_6\text{H}_5\text{B} \cdot \text{OH})]</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>MgBr</td>
<td>[(\text{C}_6\text{H}_5\text{B} \cdot \text{OH})]</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>MgCl</td>
<td>[(\text{C}_6\text{H}_5\text{B} \cdot \text{OH})]</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>MgCl</td>
<td>[(\text{C}_6\text{H}_5\text{B} \cdot \text{OH})]</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>MgBr</td>
<td>[(\text{C}<em>{10}\text{H}</em>{11}\text{B} \cdot \text{OH})]</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>MgBr</td>
<td>[(\text{C}<em>{10}\text{H}</em>{11}\text{B} \cdot \text{OH})]</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>MgBr</td>
<td>[(\text{C}_6\text{H}_5\text{B} \cdot \text{OH})]</td>
<td>90\textsuperscript{c,d}</td>
</tr>
<tr>
<td>9</td>
<td>MgBr</td>
<td>[(\text{C}_6\text{H}_5\text{B} \cdot \text{OH})]</td>
<td>95\textsuperscript{e,d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions were carried out on a 2.4 mmol scale with 1 equiv. Grignard reagent, 1.2 equiv. \(\text{H}_2\text{B-N(\text{\textit{i}}\text{Pr})}_2\), 0 \(^\circ\)C, one hour. \textsuperscript{b}Isolated yield after acidic aqueous work-up. \textsuperscript{c}Reaction temp. -45 \(^\circ\)C, \textsuperscript{d}crude yield, \textsuperscript{e}Reaction temp. -78 \(^\circ\)C
Both organomagnesium bromide and organomagnesium chloride Grignard reagents (Table 3.1, Entries 1 and 2) are compatible with H$_2$B-N(iPr)$_2$. The borylation reaction was amendable to primary (Table 3.1, Entries 6 and 7), secondary (Table 3.1, Entry 5), or tertiary (Table 3.1, Entry 4) Grignard reagents. It was interesting to find that phenylmagnesium bromide was smoothly converted to the boronic acid in less than 30 minutes at -45 °C (Table 3.1, Entry 8). This result implied that one hour of reaction time is not required at the reaction temperature of 0 °C. When the reaction was carried out at -78 °C, the reaction mixture froze and magnetic stirring stopped. In this case, the reaction flask was removed from the cryogenic bath, allowed to warm until the magnetic stir bar was free turning and returned to the -78 °C conditions (Table 3.1, Entry 9). Though the isotherm was not maintained at a constant temperature, the isolated yield of boronic acid was greater than 90%. Unfortunately, the solution of phenylmagnesium bromide was old and $^1$H NMR showed signs of degradation. Therefore, these results are not reported, though $^{11}$B-NMR analysis showed only formation of the monoaddition product.

3.4.5 Reaction of Diisopropylaminoborane with Alkyl Bromides and Magnesium Under Barbier Conditions

The reaction of Grignard reagents with trimethylborate is always the first method considered for the synthesis of simple boronic acids.\textsuperscript{38} This reaction is generally a good method for effecting this transformation. The formation of Grignard reagents is always theoretically accompanied by competing Wurtz coupling of the
halide. The competitive Wurtz coupling is problematic only when dealing with reactive halides such as allyl, benzyl, and primary halides (Eq. 13).

\[
\text{Br} \quad \xrightarrow{\text{Mg}^0, \text{Et}_2\text{O}} \quad \text{Br}
\]  

(13)

For compounds such as aryl halides or alkenyl halides, Wurtz coupling is not an issue.

The synthesis of reactive species such as allylmagnesium bromide is performed at low temperature and under conditions of low concentration to avoid the formation of 1,5-hexadiene as the major, or even sole product of the reaction.\(^{39,40}\) The Barbier reaction was developed for the synthesis of alcohols from carbonyl compounds and organomagnesium reagents. The method entails heating a mixture of the alkyl halide and carbonyl compound together with magnesium under an inert atmosphere. It was found that with reactive halides, Wurtz coupling was greatly reduced, since having the carbonyl compound (the electrophile) present during the formation of allylmagnesium bromide (the nucleophile), the organometallic nucleophile will attack the harder of the two electrophiles, giving the alcohol rather than 1,5-hexadiene.

In addition to allowing for the synthesis of Grignard reagents from reactive halides, the experimental set-up for Barbier reaction is much simpler than the classic Grignard reaction. Under Barbier conditions, essentially all of the reagents are added at one time, avoiding the more labor-intensive stepwise addition of reagents. After the compatibility of H\(_2\)B-N(iPr)\(_2\) with Grignard reagents was established, simplification
of the procedure was examined by employing a modified Barbier system. In this case, the organic halide is added to a mixture of magnesium turnings and $\text{H}_2\text{B}-\text{N}(\text{iPr})_2$ at 65 °C. Under these Barbier-type conditions, a number of aryl halides underwent smooth conversion to the corresponding boronic acids in fair to good isolated yields (Table 3.2).

**Table 3.2. Synthesis of Boronic Acids Under Modified Barbier Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromide</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="" alt="Bromide 1" /></td>
<td><img src="" alt="Product 1" /></td>
<td>79&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="Bromide 2" /></td>
<td><img src="" alt="Product 2" /></td>
<td>67&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="" alt="Bromide 3" /></td>
<td><img src="" alt="Product 3" /></td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="" alt="Bromide 4" /></td>
<td><img src="" alt="Product 4" /></td>
<td>&lt;50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="" alt="Bromide 5" /></td>
<td><img src="" alt="Product 5" /></td>
<td>&lt;50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions were carried out on a 2 mmol scale with 1 equiv. Mg$^0$, 1 equiv. bromide, 1.2 equiv. $\text{H}_2\text{B}-\text{N}(\text{iPr})_2$, 65 °C, 2-3 h. <sup>b</sup>Isolated yield after acidic aqueous workup. <sup>c</sup>Conversion based on $^{11}$B-NMR integration relative to $\text{H}_2\text{B}-\text{N}(\text{iPr})_2$.

The synthesis of boronic acids under the modified Barbier conditions was amenable to a number of aryl bromides. 1-Bromonapthalene underwent borylation to yield the
boronic acid in 79% (Table 3.2, Entry 1), while the electron-rich 4-methoxyphenylboronic acid was isolated in 67% from 4-bromoanisol (Table 3.2, Entry 2). The heteroaromatic substrate 2-bromothiophene afforded the thiophenylboronic acid in 74% yield (Table 3.2, Entry 3). Non-aryl substrates, including α-bromostyrene and 9-bromoanthracene, were not compatible with the Barbier conditions. When allylic and benzylic halides were subjected to the modified Barbier conditions, rapid consumption of the magnesium metal was observed. Subsequent $^{11}$B-NMR analysis showed an approximate 1:1 mixture of the corresponding allyl(diisopropyl)aminoborane and unreacted 1 (Table 3.2, Entries 4 and 5). This observation is explained by the reactivity of allyl- and benzylbromide reagents towards homocoupling and reduction. Overall, the reaction of alkyl, aryl, and heteroaryl bromides with 1 under Grignard and Barbier conditions is expedient, safe, and mild.

3.5 Conclusion

In summary, the reactivity of diisopropylaminoborane 1 was evaluated in the borylation of alkyl, aryl, and heteroaryl bromides. Diisopropylaminoborane is prepared from the reaction of lithium diisopropylaminoborohydride with TMS-Cl. Use of 1 resulted in high yields of the corresponding boronic acids. Diisopropylaminoborane is stable in solution for long periods of time, upwards of one year. Organolithium reagents were found to be highly reactive with diisopropylaminoborane, giving multiple products, even under cryogenic conditions. Organozinc bromide reagents are similarly reactive, giving a mixture of boronic and
borinic acids. Dialkylzinc reagents react with 1 to afford the corresponding boronic acids. A simple and mild borylation of aryl and alkyl halides with 1 under mild Grignard and Barbier conditions has been described. Performing the borylation reaction under Barbier conditions allows the use of a simple one-pot procedure, and avoids the use of low temperatures and expensive transition metal catalysts. The reaction proceeds in excellent yields, affords a single addition product under mild conditions, and does not require a huge excess of the boron donor. The organo(diisopropylamino)borane product is easily hydrolyzed to the corresponding boronic acid. Although the borylation mechanism is not fully understood, evidence is provided that the reaction mechanism is distributed between two reaction pathways. In either pathway, a hydride is transferred from the organo(diisopropylamino)borohydride to MgBr to form HMgBr (Pathway A), or to the starting material 1, to form bromomagnesium diisopropylaminoborohydride (Pathway B). Evidence suggests that the reaction proceeds mainly through Pathway A, as only 1.2 equivalents of 1 is required for greater than 95% conversion to the organo(diisopropylamino)borane. During the mechanistic investigation, halomagnesium diisopropylaminoborohydride was identified as a byproduct and an analogue was subsequently synthesized from dimethylamine-borane and methylmagnesium chloride.
3.6 Experimental Section

**General Methods.** All reactions were performed in oven-dried, argon-cooled glassware. Diisopropylamine was distilled over CaH₂ prior to use. The dimethylamine-borane was used as received from Callery Chemical Company. The diisopropylaminoborane was used as synthesized; it was stored under argon at room temperature. All Grignard reagents were used as received from Aldrich and were stored in the bottle received and kept in the refrigerator held at 4 °C. The concentrations of the Grignard reagents were monitored using the titration method described by Knochel.⁴¹ Magnesium metal was used as received from Aldrich. All air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. Tetrahydrofuran (THF) was freshly obtained from a solvent purification system (Pure Solv MD, Innovative Technology inc.). NMR spectra were recorded at 500 MHz (¹H), 125 MHz (¹³C), and 160.4 MHz (¹¹B). All ¹H NMR and ¹³C NMR chemical shifts are reported in δ units relative to the respective solvent of the NMR sample. ¹¹B NMR samples are reported relative to the external standard BF₃:Et₂O (δ_B = 0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration.

**General Procedure for the Titration of Grignard Reagents.** To an oven-dried and argon-cooled 40-mL centrifuge tube was added iodine (0.254 g, 1 mmol). The saturated solution of LiCl in THF (3 mL) was added and stirring was started. After the iodine was completely dissolved, the resulting brown solution was cooled to 0 °C.
(ice bath). To the stirring solution the Grignard reagent was added dropwise via a 1.00-mL syringe (0.01-mL graduations) until the brown color disappeared. The amount consumed contains 1 equivalent of the organometallic reagent relative to iodine in the case of Grignard reagents. Average of three trials for each Grignard tested.

**General Procedure for the Preparation of Saturated Solution of LiCl.** To an oven-dried and argon-cooled 250-mL round bottom flask equipped with a stir bar was added anhydrous LiCl (42.39 g, 100 mmol). Anhydrous THF (200 mL) was added and the mixture was stirred for 24 h at room temperature until the LiCl was completely dissolved, resulting in the formation of a 0.5 M solution of LiCl. Solution was transferred to an oven-dried and argon-cooled 125-mL ampoule via cannula for storage.

**General Procedure for the Preparation of Diisopropylaminoborane 1 M Solution in THF.** To an oven-dried and argon-cooled 100-mL round-bottom flask equipped with a stir bar was added diisopropylamine (5.00 g, 7 mL, 50 mmol) followed by THF (18 mL). The solution was cooled to 0 °C (ice bath) and borane dimethylsulfide (5 mL, 10 M, 50 mmol) was added dropwise via syringe. After one hour of stirring at 0 °C, an aliquot was removed for analysis by $^{11}$B-NMR. The analysis showed the solution to be diisopropylamine-borane complex ($\delta_B -21, q, J_{BH} = 95$ Hz). To the stirring solution, n-butyllithium (20 mL, 2.5 M, 50 mmol) was added dropwise via cannula needle. After one hour of stirring at 0 °C, an aliquot was removed for analysis by $^{11}$B-NMR, which showed the solution to be lithium diisopropylaminoborohydride.
(δ_B -23, q, J_{BH} = 83 Hz). Trimethylsilyl chloride (3.20 mL, 25 mmol) was added dropwise over 5 min via syringe while stirring at 0 °C. After one hour of stirring at 25 °C, an aliquot was taken and analyzed via $^{11}$B-NMR, which showed the solution to be monomeric diisopropylaminoborane (δ_B +35, t, J_{BH} = 125 Hz). The solution was transferred to an oven-dried, argon-cooled ampoule via a cannula needle. Note that, although the chemical shift of the corresponding amine-borane complex is virtually identical to that of LAB reagents, the J-values of the amine-borane complex is different and range from 95-98 Hz.

**General Procedure for the Preparation of Chloromagnesium Dimethylaminoborohydride.** To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a stir bar was added methylmagnesium chloride (0.83 mL, 2.4 M solution in THF, 2.0 mmol) and was cooled to 0 °C (ice bath). In a separate oven-dried and argon-cooled 15-mL round-bottom flask equipped with a stir bar was added dimethylamine-borane (0.118 g, 2.0 mmol) followed by anhydrous THF (2.0 mL). The dimethylamine-borane solution was added dropwise over 10 min via syringe to the solution of methylmagnesium chloride. After 0.5 h of stirring at 0 °C, an aliquot was taken and analyzed via $^{11}$B-NMR, which showed the solution to be chloromagnesium dimethylaminoborohydride (δ_B -16, q, J_{BH} = 83 Hz).

**General Procedure for the Preparation of Aryl Boronic Acids from Dialkylzinc Reagents.** The following procedure for the preparation of ethylboronic acid is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a stir bar was added H$_2$B-N(iPr)$_2$ (2 mL, 2 mmol). To the stirring
solution was added diethylzinc (2 mL, 1M, 2 mmol) dropwise via syringe. After one hour of stirring, 3M HCl (5 mL) was added dropwise over 5 min and allowed to stir for 30 min. The reaction mixture was then refluxed for 15 min. Following reflux, the solution was transferred to a separatory funnel and extracted with Et₂O (2 x 15 mL). The organic layers were combined and washed with 1M HCl (4 x 15mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford ethylboronic acid as a white powder.

![Ethylboronic acid structure](image)

**Ethylboronic acid.** White powder. (0.171 g, 70%). $^{11}$B-NMR (160.4 MHz, CDCl₃): δ +32.

**General Procedure for the isolation of Solid Zinc Metal from the Reaction of Diisopropylaminoborane with Diethylzinc.** To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a stir bar was added H₂B-(iPr)₂ (2 mL, 1M, 2 mmol). To the stirring solution was added diethylzinc (2 mL, 1M, 2 mmol) dropwise via syringe. After one hour of stirring, the grey solid was isolated by vacuum filtration, washed with Et₂O (2 x 10 mL), hexanes (2 x 10 mL) and dried in vacuo to yield a grey powder (0.124 g, 95% yield). Analysis of the solid precipitate by powder X-ray diffraction (PXRD) showed that the sample was crystalline zinc metal with no impurities or amorphous phases (Figure 3.3).
General Procedure for the Preparation of Aryl Boronic Acids from Grignard Reagents. The following procedure for the preparation of $p$-tolylboronic acid is representative. To an oven-dried and argon-cooled 50-mL round-bottom flask equipped with a stir bar was added $\text{H}_2\text{B-N(iPr)}_2$ (2.4 mL, 1M, 2.4 mmol) and was cooled to 0 °C (ice bath). To the stirring solution was added $p$-tolylimagnesium bromide (2 mL, 1M, 2 mmol) dropwise over 5 min via syringe. After one hour, with the reaction still on ice, 3M HCl (5 mL) was added dropwise over 5 min and the reaction was allowed to stir for 30 min. The reaction mixture was then refluxed for 15 min. Following reflux, the solution was transferred to a separatory funnel and extracted with Et$_2$O (2 x 15 mL). The organic layers were combined and washed with 1M HCl (4 x 15 mL), dried over anhydrous MgSO$_4$, and concentrated under reduced
pressure to afford \( p \)-tolylboronic acid as a white powder. For other boronic acids prepared by this method see Table 3.4. Because of their facile dehydration, boronic acids tend to provide inconsistent melting points. Therefore, the melting points for boronic acids were not taken.\(^{42}\)

\[
\text{\begin{tikzpicture}
\draw[thick] (-0.5,0) -- (0.5,0) -- (0.5,0.5) -- (-0.5,0.5) -- cycle;
\draw[thick] (-0.5,0.5) -- (-0.5,1.5);
\draw[thick] (0.5,0.5) -- (0.5,1.5);
\draw[thick] (-0.5,1.5) -- (0.5,1.5);
\draw[thick] (0,0) -- (0,0.5);
\node [align=center] at (0,0.75) {B(OH)\(_2\)};
\end{tikzpicture}}
\]

**Phenylboronic acid (Table 3.4, Entry 1, 8, 9).**\(^{16}\) White powder; (0.234 g, 95%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.52 (t, \( J = 6 \) Hz, 2H), 7.61 (t, \( J = 7 \) Hz, 1H), 8.26 (d, \( J = 5.5 \) Hz, 2H); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)): \( \delta \) 128.0, 132.7, 135.7; \(^{11}\)B-NMR (160.4 MHz, CDCl\(_3\)): \( \delta \)B +30.7.

\[
\text{\begin{tikzpicture}
\draw[thick] (-0.5,0) -- (0.5,0) -- (0.5,0.5) -- (-0.5,0.5) -- cycle;
\draw[thick] (-0.5,0.5) -- (-0.5,1.5);
\draw[thick] (0.5,0.5) -- (0.5,1.5);
\draw[thick] (-0.5,1.5) -- (0.5,1.5);
\draw[thick] (0,0) -- (0,0.5);
\node [align=center] at (0,0.75) {B(OH)\(_2\)};
\end{tikzpicture}}
\]

**\( o \)-Tolylboronic acid (Table 3.4, Entry 2).**\(^{16}\) White powder; (0.226 g, 88%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 2.82, 7.27 (m, 2H), 7.459 (dt, \( J = 1.5 \), 7 Hz, 1H), 8.22 (dd, \( J = 7 \) Hz, 1H); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)): \( \delta \) 23.1, 125.3, 130.7, 132.3, 137.4, 146.4; \(^{11}\)B-NMR (160.4 MHz, CDCl\(_3\)): \( \delta \)B +31.9.

\[
\text{\begin{tikzpicture}
\draw[thick] (-0.5,0) -- (0.5,0) -- (0.5,0.5) -- (-0.5,0.5) -- cycle;
\draw[thick] (-0.5,0.5) -- (-0.5,1.5);
\draw[thick] (0.5,0.5) -- (0.5,1.5);
\draw[thick] (-0.5,1.5) -- (0.5,1.5);
\draw[thick] (0,0) -- (0,0.5);
\node [align=center] at (0,0.75) {B(OH)\(_2\)};
\end{tikzpicture}}
\]

**\( p \)-Tolylboronic acid (Table 3.4, Entry 3).**\(^{16}\) White powder; (0.345 g, 95%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 2.44 (s, 3H), 7.32 (d, \( J = 7.5 \) Hz, 1H), 8.13 (d, \( J = 7.5 \) Hz, 1H); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)): \( \delta \) 21.9, 128.9, 133.7, 135.9, 143.1; \(^{11}\)B-NMR (160.4 MHz, CDCl\(_3\)): \( \delta \)B +30.4.
**t-Butylboronic acid (Table 3.4, Entry 4).** White powder; (0.481 g, 94%). $^{13}$C NMR (125.7 MHz, CDCl$_3$): $\delta$ 27.8; $^{11}$B-NMR (160.4 MHz, CDCl$_3$): $\delta_B$ +32.7.

$\text{B(OH)}_2$

**Cyclohexylboronic acid (Table 3.4, Entry 5).** White powder; (0.497 g, 97%). $^{13}$C NMR (125.7 MHz, CDCl$_3$): $\delta$ 27.3, 27.5, 28.3; $^{11}$B-NMR (160.4 MHz, CDCl$_3$): $\delta_B$ +33.5.

$\text{C}_6\text{H}_{11}\text{B(OH)}_2$

**n-Hexylboronic acid (Table 3.4, Entry 6).** White powder; (0.404 g, 95%). $^{13}$C NMR (125.7 MHz, CDCl$_3$): $\delta$ 14.7, 23.4, 24.2, 25.0, 32.5, 32.8; $^{11}$B-NMR (160.4 MHz, CDCl$_3$): $\delta_B$ +34.4.

$\text{C}_6\text{H}_{13}\text{B(OH)}_2$

**n-Decylboronic acid (Table 3.4, Entry 7).** White powder; (0.888 g, 95%). $^{13}$C NMR (125.7 MHz, CDCl$_3$): $\delta$ 14.1, 22.7, 23.4, 24.4, 29.4, 29.5, 29.7, 31.9, 32.4; $^{11}$B-NMR (160.4 MHz, CDCl$_3$): $\delta_B$ +33.9.

**General Procedure for the Preparation of Aryl Boronic Acids Under Barbier-type Conditions.** The following procedure for the preparation of 1-naphthylboronic acid is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a condenser and stir bar was added magnesium turnings (0.058 g, 2.4 mmol) and was activated by addition of iodine crystals and warming until the iodine
sublimed. The flask was cooled to 25 °C and was purged with Ar. To the reaction flask was added H$_2$B-N(iPr)$_2$ (2.4 mL, 1M, 2.4 mmol) and the flask was brought to reflux. 1-Bromonapthalene (0.3 mL, 2.0 mmol) was then added dropwise with constant stirring at 65 °C. The reaction was complete after 4 h as evidenced by the disappearance of H$_2$B-N(iPr)$_2$ starting material (δ +35, t, $J_{BH} = 125$ Hz), and the appearance of the borylation intermediate (δ +38, d, $J_{BH} = 112$ Hz) with the corresponding bromomagnesium aminoborohydride signal (MgBr$^+$ H$_3$B-NiPr$_2$, δ -28, q, $J_{BH} = 88$ Hz). The reaction was then cooled to 25 °C and acidified with 3M HCl (3mL) (CAUTION: hydrogen evolution). After 10 min of stirring, the reaction mixture was warmed to 65 °C and stirred for an additional 15 min. The reaction mixture was then transferred to a separatory funnel and extracted with Et$_2$O (3 x 15 mL). The combined organic layers were dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure to afford 1-napthylboronic acid as a white solid. The results for the other boronic acids prepared by this method are summarized in Table 2.5. For copies of the $^1$H, $^{13}$C and $^{11}$B-NMR spectrum see Appendix B. Because of their facile dehydration, boronic acids tend to provide inconsistent melting points. Therefore, the melting points for boronic acids were not taken.$^{45}$

\[ \text{1-Naphthylboronic acid (Table 3.5, Entry 1).}^{16} \text{ White powder; (0.253g, 79%). } ^1\text{H NMR (500 MHz, DMSO-d$_6$): } \delta 3.44 (\text{brs, 1H}), 7.50 (\text{m, 3H}), 7.78 (\text{d, } J = 5 \text{ Hz, 1H}), 7.91 (\text{t, } J = 9.5 \text{ Hz, 2H}), 8.36 (\text{brs, OH}), 8.42 (\text{dd, } J = 8 \text{ Hz, 1 Hz, 1H}); ^{13}\text{C NMR} \]
(125.7 MHz, DMSO-d$_6$): δ 128.2, 128.8, 129.1, 132.0, 132.9, 135.7; $^{11}$B-NMR (160.4 MHz, DMSO-d$_6$): δ$_B$ +30.2.

4-Methoxyphenylboronic acid (Table 3.5, Entry 2). White powder; (0.196g, 67%). $^1$H NMR (500 MHz, CDCl$_3$): δ 3.89 (s, 3H), 7.03 (d, $J$ = 8.5 Hz, 2H), 8.17 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR (125.7 MHz, CDCl$_3$): δ 55.3, 113.7, 137.7, 163.4; $^{11}$B-NMR (160.4 MHz, CDCl$_3$): δ$_B$ +29.1.

2-Thiopheneboronic acid (Table 3.5, Entry 3). White powder; (0.221g, 74%). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.33 (dd, $J$ = 3.5, 4.5 Hz, 1H), 7.83 (d, $J$ = 4.5 Hz, 1H), 8.06 (d, $J$ = 4 Hz, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$): δ 128.9, 135.1, 139.8; $^{11}$B-NMR (160.4 MHz, CDCl$_3$): δ$_B$ +27.0.

Allylboronic acid (Table 3.5, Entry 4). $^{46}$ $^{11}$B-NMR (160.4 MHz, CDCl$_3$): δ$_B$ +42.1 (d, $J_{BH} = 147$ Hz), +36.6 (t, $J_{BH} = 129$ Hz).

1-Phenylethylboronic acid (Table 3.5, Entry 5). $^{47}$ $^{11}$B-NMR (160.4 MHz, CDCl$_3$): δ$_B$ +42.1 (d, $J_{BH} = 147$ Hz), +36.6 (t, $J_{BH} = 123$ Hz).
3.7 References


CHAPTER 4

Investigation of the Reaction of Diisopropylaminoborane with Organometallic Reagents. Synthesis of Symmetrical and Unsymmetrical Diorgano(diisopropylamo)boranes
4.1 Introduction

Borinic acids and their derivatives are lesser-known compounds in organic chemistry, used primarily as synthetic building blocks. Their use in transition metal-catalyzed cross-coupling reactions can lead to atom-economical carbon–carbon bond formation.¹ Synthetic applications for borinic acid esters include the synthesis of ketones² and trialkylboranes, the recognition of diols,³ as well as inhibitors of bacterial cell growth.⁴ Classical routes for the preparation of borinic acids and esters involve the utilization of Grignard or lithium reagents with trialkylborates.⁵ In many cases the Grignard reagents are preferred due to their availability, stability, safer handling in land, and general lower cost.

4.1.1 Preparation of Borinic Acids and Esters from Organometallic Reagents

Borinic acids were first prepared in 1894 by Michaelis who hydrolyzed diphenylchloroborane to diphenylborinic acid.⁶ The development of the chemistry of the borinic acids has been hampered by the lack of adequate methods for their isolation and characterization. Borinic acids have diminished longevity, forming anhydrides. Letsinger reported the synthesis and isolation of borinic acids as their corresponding aminoethylenes.⁷ The dialkylborinic acids were trapped upon reaction with ethanolamine, which precipitated the borinates as stable solids (Eq. 1).⁸

\[
2 \text{RMgBr} + \text{BOR}_3 \xrightarrow{1. \text{THF, } 25 \degree \text{C}} \xrightarrow{2. \text{ethanolamine}} \text{H}_2\text{N} \downarrow \text{R} \downarrow \text{B-O} \uparrow \text{R} \uparrow
\]

(1)

Letsinger also prepared unsymmetrical borniates by this method.⁹ Reaction of naphthylmagnesium bromide with di-\textit{n}-butylphenylboronate followed by aqueous
quench and treatment with ethanolamine affords the unsymmetrical aminoethyl borinic ester (Eq. 2).

\[
\text{MgBr} + (n\text{BuO}_2)\text{BPh} \xrightarrow{1. \text{Et}_2\text{O}, -60 \degree \text{C}, 12 \text{ h}} \xrightarrow{2. \text{HCl, ethanolamine}} \text{H}_2\text{N} \quad \text{Ar} \quad \text{B} - \text{O}
\]

(2)

Lippincot reported the synthesis of borinic acids from the reactions of an excess of aryl Grignard reagents with trimethoxyboroxine (Eq. 3).\(^{10}\)

\[
6 \text{ArMgBr} + \begin{array}{c}
\text{OMe} \\
\text{MeO} \\
\text{B} \\
\text{O} \\
\text{B} \\
\text{OMe}
\end{array} \xrightarrow{1. \text{THF}, -60 \degree \text{C}, 2 \text{ h}} \xrightarrow{2. \text{HCl}} 3 \text{Ar}_2\text{BOH}
\]

(3)

While this is a direct method for preparing borinic esters, these reactions are limited by the requirement for low reaction temperatures, coupled with poor yields.\(^{11}\) Coates and Livingstone described a procedure to produce borinic acids from the aminodichloroboranes.\(^{12}\) This procedure was more economical than that reported by Lippincot, as it requires only a slight excess of Grignard. Brown and Cole reported an improved method for the preparation of borinic acids using organolithium reagents.\(^{13}\) Cole has also shown that symmetrical borinic esters can be synthesized by allowing a Grignard reagent to react with an excess of trialkyborate.\(^{14}\) For example, when triisopropylborate is allowed to react with two equivalents of ethylmagnesium bromide at -78 \degree \text{C}, the symmetrical diethyl(isopropyl)borate is isolated in 93\% yield (Eq. 4).

\[
2 \text{EtMgBr} + \text{B(OiPr)}_3 \xrightarrow{1. \text{THF}, -78 \degree \text{C}, 2 \text{ h}} \xrightarrow{2. \text{HCl/} \text{Et}_2\text{O}} \text{B-OiPr}
\]

(4)
Another route to accessing borinic esters involves the reaction of triethylborane. Upon reaction with methanol, triethylborane reacts to afford the borinic acid. Shapiro demonstrated the in situ generation of diethyl(methyl)borate by allowing triethylborane to react with methanol in THF at -78 °C (Eq. 5).\(^{15}\)

\[
\text{Et}_3\text{B} + \text{HOMe} \xrightarrow{\text{THF, -78 °C, 30 min}} \text{B} - \text{OMe}
\]

This technique is less than ideal due to the pyrophoric nature of the starting material and the limitation in that only symmetrical borinic acids can be formed.

### 4.1.2 Applications of Borinic Acids and Esters

While not as extensively used as boronic acids, borinic acids are valued for their bioactivity as well as their synthetic applications. In 2005 Benkovic and coworkers demonstrated that diphenylborinic acid is an effective inhibitor of trypsin, a serine protease. Borinic esters have been researched as possible bacterial growth inhibitors, due to their ability to inhibit menaquinone methytransferase, a bacterial enzyme.\(^4\)

Borinic acids also have use in Suzuki-Miyaura cross-coupling reactions in industry. Winkle demonstrated that bis(3,5-dimethylphenyl)borinic acid is an inexpensive alternative to the analogous boronic acid.\(^{16}\) The methodology requires one-half equivalent of the borinic acid to form product. The diaryl borinic acid is allowed to react with a vinyl triflate in the presence of palladium catalyst, which affords the coupling product in 91% yield (Eq. 6).
Zou and coworkers also reported a cross-coupling methodology between diarylborinic acids and tosyl hydrazones, resulting in high yields of product.\(^{17}\)

Borinic esters are of synthetic interest due to their ability to be converted to ketones using \(\alpha,\alpha\)-dichloromethyl methyl ether (DCME) in the presence of a hindered base, such as lithium tert-butoxide or lithium triethylmethoxide (Eq. 7).\(^{18}\)

\[
\begin{align*}
R_1^1 \text{B}-\text{OR}_2^2 &+ \text{Cl}_2\text{HCOMe} \quad \xrightarrow{1. \text{LiO}^+\text{Bu}, 1 \text{h}, 0 \degree \text{C}} \quad \text{R}_1^1\text{R}_2^2 \text{O} \\
&\xrightarrow{2. \text{H}_2\text{O}_2, \text{NaOH}} \text{R}_1^1\text{R}_2^2 \text{Cl} \\
\end{align*}
\]

This reaction occurs through the deprotonation of DCME followed by addition of the carbanion to the boron atom, forming boronate species \(1\) (Scheme 4.1).\(^{19}\)

**Scheme 4.1.** Mechanism of the DCME Reaction to Produce Ketones

Following formation of \(1\), a subsequent series of 1,2-migrations from boron to carbon
produce boronic ester 2. Alkaline oxidation of 2 yields the desired ketone. The DCME reaction is also used for the preparation of tertiary alcohols from trialkylboranes.\textsuperscript{20} Brown and Srebnik demonstrated the ease with which symmetrical, unsymmetrical, even chiral borinic esters are converted to the corresponding ketones.\textsuperscript{21} When subjected to DCME conditions, the chiral methyl([1S,2S]-exo-2-norbornyl)isopropylborate is converted to the methyl ketone in 68% yield in 86% ee (Eq. 8).\textsuperscript{22}

\[
\begin{array}{c}
\text{B}^{\text{OiPr}} \quad \text{Cl}_2\text{HCOMe} \\
\end{array}
\begin{array}{c}
\text{1.LiOtfBu, 1 h, 0 }^\circ\text{C} \\
\text{2. H}_2\text{O}_2, \text{NaOH} \quad 68\%, 86\% \text{ ee} \\
\end{array}
\]

Soderquist reported the use of DCME chemistry to access carboxylic acids from B-alkoxy-9-BBN derivatives.\textsuperscript{23}

\subsection*{4.2 Diisopropylaminoborane as a Nitrogen-Based Boron Donor}

Aminoboranes (H\textsubscript{2}B-NR\textsubscript{2}) have been known since the discovery of the hydroboration reaction in 1956.\textsuperscript{24} Their reactivity as useful tools for synthetic organic chemistry has been scarcely studied. These compounds are prepared from the corresponding amine-borane adducts.

Amine-boranes are of interest to the materials science and energy production industries. They have been shown to be a potential avenue of hydrogen storage, as they can contain a high density of hydrogen gas, and are safe to handle. Boron nitride (B-N) ceramics are valued for their excellent thermal characteristics: thermal shock resistance and conductivity. In addition to their applications in the materials and
energy industries, amine-boranes are useful synthetic precursors for aminoboranes.

Dehydrogenation of the an amine-borane adduct affords the corresponding aminoborane. Diisopropylamine-borane is dehydrogenated thermally produce diisopropylaminoborane and hydrogen gas.\(^{25}\) Alternatively, amine-borane adducts are dehydrogenated in the presence of a transition metal catalyst.\(^{26}\) Although this method alleviates the need for high temperatures, the expensive metal catalysts are toxic and difficult to remove. Dimers and other oligomers of aminoboranes form when there is low steric demand around the nitrogen, preventing purification.\(^{27}\) As steric demand around the nitrogen increases, the aminoborane exists as a monomer and is reactive.

Singaram reported the synthesis of aminoboranes from lithium aminoborohydrides (LAB reagents).\(^{28}\) LAB reagents react with trimethylsilyl chloride (TMS-Cl) in THF to give the corresponding aminoborane.\(^{29}\) This technique allows for the synthesis of aminoboranes without the use of expensive metal catalysts, extreme reaction temperatures, or the generation of hydrogen gas. Lithium diisopropylaminoborane reacts with TMS-Cl at 0 °C to afford monomeric diisopropylaminoborane (H\(_2\)B-N(iPr)\(_2\)) (Eq. 9).\(^{30}\)

\[
\begin{align*}
\text{LiH}_2\text{B} - \text{N} & \xrightarrow{T\text{MS-Cl}} \text{THF, 0 °C} \rightarrow \text{H}_2\text{B} - \text{N} \\
\end{align*}
\]

The reaction is complete within an hour and provides pure product in a safe manner.

### 4.2.1 Reaction of Diisopropylaminoborane with Grignard Reagents

Singaram reported on the reactivity of organoboranes with Grignard reagents.\(^{31}\) When H\(_2\)B-N(iPr)\(_2\) is allowed to react with \(p\)-tolylmagnesium bromide at 0 °C in
THF, $^{11}$B-NMR analysis reveals the formation of the borylation product, $p$-tolyl(diisopropylamino)borane ($\delta_B +42$, d, $J_{BH} = 112$ Hz) as well as the side-product bromomagnesium diisopropylaminoborohydride (Eq. 10).

Upon acidic quench and work-up, the aryl(diisopropylamino)borane intermediate is quantitatively converted to the corresponding boronic acid.$^{31b}$ This methodology was used to prepare multiple boronic acids (Chapter 3). Due to the increased steric environment around the boron atom, it was assumed that a second equivalent of Grignard would not be able to react. To verify this hypothesis, $H_2B-N(iPr)_2$ was allowed to react with two equivalents of ethylmagnesium bromide in THF at 25 ºC (Eq. 11).

Surprisingly, $^{11}$B-NMR analysis of the reaction mixture revealed a single intermediate: a sharp singlet at $\delta_B +47$, indicating that the Grignard reagent had indeed added twice to the boron atom to afford diethyl(diisopropylamino)borane. This reaction is noteworthy in that organometallic addition was complete within 30 minutes at room temperature. This result indicates that reaction of $H_2B-N(iPr)_2$ with an excess of Grignard has the potential to access borinates without the need for
cryogenic reaction conditions. This chapter discusses the results of the reaction of H$_2$B-N(iPr)$_2$ with multiple equivalents of organometallic reagents. The results and observations obtained from the reaction of Grignard and dialkylzinc reagents with H$_2$B-N(iPr)$_2$ prepared from lithium diisopropylaminoborohydride are reported.

4.3. Results and Discussion

Aminoboranes are typically prepared in situ in tetrahydrofuran (THF) from LAB reagents and used without further purification. Exploration of the literature reveals no studies detailing the preparation of borinic acids or esters at room temperature. Consequently, the reactivity of diisopropylaminoborane prepared from the corresponding LAB reagent with multiple equivalents of Grignard reagents was explored.

4.3.1 Reactions of Diisopropylaminoborane with Multiple Equivalents of Grignard Reagent

The reaction of diisopropylaminoborane with a stoichiometric excess of ethylmagnesium bromide was investigated as a model reaction. Two equivalents of ethylmagnesium bromide were allowed to react with H$_2$B-N(iPr)$_2$ (Eq. 12).

Reaction progress was monitored by $^{11}$B-NMR of reaction aliquots (Figure 4.1).
Upon addition of one equivalent of the ethylmagnesium bromide, a mixture of products is observed. The addition of the Grignard to the boron atom of \( \text{H}_2\text{B-N(iPr)}_2 \) forms the expected boronate complex 3, \( (d_B \text{ -13, } t, J_{BH} = 78 \text{ Hz}) \) (Figure 4.1, A). This boronate intermediate can transfer a hydride to \( \text{H}_2\text{B-N(iPr)}_2 \) to form \( B- \)
ethyl(diisopropyl)aminoborane 4 (δ_B +42, d, J_{BH} = 84 Hz) and bromomagnesium diisopropylaminoborohydride 5 (d_B -24, q, J_{BH} = 84 Hz). Of particular interest is the appearance of the double addition product, B,B-diethyl(diisopropylamino)borane 6 (δ_B +47, s). Upon addition of a second equivalent of ethylmagnesium bromide, all intermediates converged to the double addition product 6 (Figure 4.1, B). The disappearance of all other intermediates, giving 6 as the sole product indicates that double addition of a Grignard reagent to the boron atom is not only possible, but also facile. Upon quenching the reaction mixture with 1M HCl, diethylborinic acid 7 (δ_B +55) is the primary product (Figure 4.1, C).

To evaluate the generality of this double addition, H_2B-N(iPr)_2 was allowed to react with two equivalents of p-tolylmagnesium bromide (Eq. 13).

![Reaction Equation](image)

Analysis of the reaction mixture by ¹¹B-NMR reveals a single peak at δ_B +45, corresponding to B,B-di-p-tolyl(diisopropylamino)borane. The generality of this method allows for the preparation of multiple symmetrical B,B-diorgano(diisopropylamino)boranes from the reaction of H_2B-N(iPr)_2 with different Grignard reagents (Table 4.1).
Table 4.1. Preparation of Symmetrical $B, B$-Diorgano(diisopropylamino)boranes with Two Equivalents of Grignard Reagents\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Grignard</th>
<th>Product</th>
<th>$^{11}$B Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgCl</td>
<td><img src="image" alt="Product 1" /></td>
<td>$\delta +46$</td>
</tr>
<tr>
<td>2</td>
<td>MgBr</td>
<td><img src="image" alt="Product 2" /></td>
<td>$\delta +47$</td>
</tr>
<tr>
<td>3</td>
<td>MgBr</td>
<td><img src="image" alt="Product 3" /></td>
<td>$\delta +43$</td>
</tr>
<tr>
<td>4</td>
<td>MgBr</td>
<td><img src="image" alt="Product 4" /></td>
<td>$\delta +45$</td>
</tr>
<tr>
<td>5</td>
<td>MgCl</td>
<td><img src="image" alt="Product 5" /></td>
<td>$\delta +43$</td>
</tr>
<tr>
<td>6</td>
<td>MgCl</td>
<td><img src="image" alt="Product 6" /></td>
<td>$\delta +47^b$</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions were carried out on a 2 mmol scale with 2 equiv. Grignard reagent, 1 equiv. $\text{H}_2\text{B-N(iPr)}_2$, 25 °C, 30 min. \textsuperscript{b}65 °C

The reaction of $\text{H}_2\text{B-N(iPr)}_2$ with two equivalents of a Grignard reagent appears to be general, affording the double addition product at room temperature. The rate of reaction of the Grignard reagents with $\text{H}_2\text{B-N(iPr)}_2$ is dependent on the steric nature...
of the Grignard. Sterically unhindered Grignard reagents such as methylmagnesium chloride (Table 4.1, Entry 1) and ethylmagnesium bromide (Table 4.1, Entry 2) react within 30 minutes to afford the double addition product. Aromatic Grignard reagents, such as phenylmagnesium bromide (Table 4.1, Entry 3) and p-tolylmagnesium bromide (Table 4.1, Entry 4) require one hour to react to completion. Of particular note is the reaction of branched aliphatic Grignard reagents. Isopropylmagnesium chloride (Table 4.1, Entry 5) was slow to react with H$_2$BN(iPr)$_2$. Analysis of the reaction mixture by $^{11}$B-NMR confirmed that the single addition product ($\delta_B +42$, d, $J_{BH} = 120$ Hz) was formed within an hour, however the second addition required an additional two hours at room temperature. Similar results were observed with the reaction of tert-butylmagnesium chloride with H$_2$BN(iPr)$_2$ (Table 4.1, Entry 6). Double addition of the hindered tert-butyl Grignard was sluggish, requiring refluxing conditions to reach completion.

Based on these observations, it was theorized that allowing H$_2$BN(iPr)$_2$ to react with three equivalents of Grignard might afford access to trialkylboranes. To test this hypothesis, H$_2$BN(iPr)$_2$ was allowed to react with three equivalents of phenylmagnesium bromide in THF at room temperature. Analysis of the reaction mixture by $^{11}$B-NMR revealed a singlet at $\delta_B +43$, indicating that reaction had halted at the double addition product: $B,B$-diphenyl(diisopropylamino)borane. To verify these results, H$_2$BN(iPr)$_2$ was allowed to react with three equivalents of ethylmagnesium bromide in THF at room temperature. Similar to the observed results with phenylmagnesium bromide, $^{11}$B-NMR analysis of the reaction mixture revealed the
$B,B$-diethyl(diisopropylamino)borane. These observations indicate that the B-N bond is resistant to subsequent attack by a third equivalent of Grignard reagent.

### 4.3.2 Preparation of Unsymmetrical $B,B$-Diorgano(diisopropylamino)boranes from Diisopropylaminoborane and Grignard Reagents

The sluggish reaction of $\text{H}_2\text{B-N(iPr)}_2$ with hindered Grignard reagents suggests a method of controlling addition of Grignard reagents to the boron atom. As hindered Grignard reagents are slow to add to the boron atom a second time, it was envisioned that unsymmetrical $B,B$-diorgano(diisopropylamino)boranes could be formed from reaction of a hindered Grignard reagent, followed by subsequent reaction with an unhindered reagent. Thus the preparation of unsymmetrical $B,B$-diorgano(diisopropylamino)boranes from Grignard reagents was explored.

The sequential reaction of $\text{H}_2\text{B-N(iPr)}_2$ with a cyclohexylmagnesium chloride followed by phenylmagnesium bromide was investigated as a model reaction, and could be easily monitored using $^{11}\text{B}$-NMR analysis. In the case of the formation of $B$-cyclohexyl-$B$-phenyl(diisopropylamino)borane, one equivalent of cyclohexylmagnesium chloride was allowed to react with $\text{H}_2\text{B-N(iPr)}_2$ (Eq. 14).

\[ \begin{array}{c}
\text{MgCl} & \to & \text{THF, 25 °C} & \text{MgCl} & \to & \text{THF, 25 °C} \\
\text{+ H}_2\text{B-N(iPr)}_2 & \to & \text{+ H}_2\text{B-N(iPr)}_2 & \to & \text{+ H}_2\text{B-N(iPr)}_2 & \to \\
\text{Cyclohexyl} & \text{MgBr} & \text{Ph-MgBr} & \text{8} & \text{9} \\
+35, t & +42, d & +45, s
\end{array} \]

Reaction progress was monitored by $^{11}\text{B}$-NMR of reaction aliquots (Figure 4.2). After one hour of reaction, the cyclohexyl(diisopropylamino)borane 8 is present ($\delta_8 +42, d$, $J_{\text{BH}} = 121 \text{ Hz}$). The characteristic coupling constant and peak shift indicates the initial
addition was complete (Figure 4.2, A).

A: Addition of Cyclohexylmagnesium Chloride

B: Addition of Phenylmagnesium Bromide

Figure 4.2. Preparation of an Unsymmetrical $B,B$-Diorgano(diisopropylamino)borane from $\text{H}_2\text{B-N(iPr)}_2$, Cyclohexylmagnesium Chloride, and Phenylmagnesium Bromide

One equivalent of phenylmagnesium bromide was added to the reaction mixture and was allowed to react for an additional hour. Analysis of the reaction mixture by $^{11}\text{B}$-NMR revealed the emergence of the unsymmetrical $B$-cyclohexyl-$B$-phenyl(diisopropylamino)borane 9 ($\delta_B +45$, s), along with a substantial amount of 8, indicating incomplete reaction (Figure 4.2, B). Heating the reaction to 40 °C for three hours facilitated the second addition.

The controlled sequential addition of Grignard reagents was further probed by the preparation of $B$-isopropyl-$B$-methyl(diisopropylamino)borane. This unsymmetrical aminoborane was prepared through two routes. In the first route, $\text{H}_2\text{B-N(iPr)}_2$ was allowed to react with an equivalent of the hindered isopropylmagnesium
chloride, followed by an equivalent of methylmagnesium chloride (Figure 4.3).

\[
\begin{align*}
\text{H}_2\text{B} & \quad \xrightarrow{\text{iPrMgCl, THF, 25 °C}} \quad \text{H} \quad \xrightarrow{\text{MeMgCl}} \\
\text{+ 35, t} & \quad J_{\text{BH}} = 125 \text{ Hz} & \quad \text{10} & \quad J_{\text{BH}} = 117 \text{ Hz} & \quad \text{11} \quad +47, \text{s}
\end{align*}
\]

A: Addition of Isopropylmagnesium Chloride

B: Addition of Methylmagnesium Chloride

Figure 4.3. Preparation of B-Isopropyl-B-methyl(diisopropylamino)borane from H₂B·N(iPr)₂, via Sequential Addition of iPrMgCl and MeMgCl

Analysis by \(^{11}\)B-NMR showed only formation of the B-isopropyl(diisopropylamino)borane 10 (δB \(+43, d, J_{\text{BH}} = 117 \text{ Hz}\)). Upon addition of an equivalent of methylmagnesium chloride, B-isopropyl-B-methyl(diisopropylamino)borane 11 is formed as the sole product.

The second route to prepare B-isopropyl-B-methyl(diisopropylamino)borane involved reversing the order of addition, allowing the less hindered methylmagnesium chloride to react with H₂B·N(iPr)₂, followed by reaction of the
hindered isopropylmagnesium chloride. Thus, $\text{H}_2\text{B-N(iPr)}_2$ was allowed to react with one equivalent of methylmagnesium chloride at room temperature. After 30 minutes, analysis by $^{11}$B-NMR showed a distribution of multiple products (Figure 4.4).

![Figure 4.4. Reaction of $\text{H}_2\text{B-N(iPr)}_2$ with One Equivalent of Methylmagnesium Chloride](image)

As observed in the $^{11}$B-NMR spectrum, the primary intermediates included the single addition intermediate $B$-methyl(diisopropylamino)borane 12 ($\delta_B +40$, d, $J_{BH} = 120$ Hz) as well as $B,B$-dimethyl(diisopropylamino)borane 13 ($\delta_B +45$). This distribution of products was consistent with observations of the reactions of unhindered Grignard reagents with $\text{H}_2\text{B-N(iPr)}_2$. Upon addition of an equivalent of isopropylmagnesium chloride to the reaction mixture, analysis by $^{11}$B-NMR again showed a mixture of products (Figure 4.5).
Figure 4.5. Reaction of H$_3$B-N(iPr)$_2$ with Methylmagnesium Chloride Followed by Isopropylmagnesium Chloride

As observed in the $^{11}$B-NMR spectrum, in addition to $B,B$-dimethyl(diisopropylamino)borane 13, intermediate 12 reacted with isopropylmagnesium chloride to afford $B$-isopropyl-$B$-methyl(diisopropylamino)borane 14 ($\delta_B$ +47). This observation confirms the mode of controlled sequential addition of Grignard reagents: addition of the sterically hindered reagent followed by reaction of a less hindered reagent allows for the preparation of unsymmetrical $B,B$-diorgano(diisopropylamino)boranes. The generality of this method of controlled addition allows for the preparation of multiple unsymmetrical $B,B$-diorgano(diisopropylamino)boranes (Table 4.2).
Table 4.2. Preparation of Unsymmetrical B,B-Diorgano(diisopropylamino)boranes from Grignard Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$MgX</th>
<th>$R_2$MgX</th>
<th>Product</th>
<th>$^{11}$B Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgCl</td>
<td>MgCl</td>
<td><img src="image" alt="Product 1" /></td>
<td>$\delta +47$</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexylMgCl</td>
<td>MgCl</td>
<td><img src="image" alt="Product 2" /></td>
<td>$\delta +46$</td>
</tr>
<tr>
<td>6</td>
<td>phenylMgBr</td>
<td>MgBr</td>
<td><img src="image" alt="Product 3" /></td>
<td>$\delta +45$</td>
</tr>
</tbody>
</table>

$^a$Reactions were carried out on a 2 mmol scale with 1 equiv. $R_1$MgX and 1 equiv. $H_2B-N(iPr)_2$, 25 $^\circ$C, 30 min, followed by 1 equiv. $R_2$MgX.

Gratifyingly, the unsymmetrical aminoboranes were formed as the sole products of the sequential addition procedure.

4.3.3 Reactions of Diisopropylaminoborane with Diethylzinc and Grignard Reagents

The reaction of $H_2B-N(iPr)_2$ with one equivalent of diethylzinc was carried out in THF at room temperature. After one hour, analysis by $^{11}$B-NMR revealed the absence of $H_2B-N(iPr)_2$ and the appearance of ethyl(diisopropylamino)borane ($\delta_B +42$, d, $J_{BH} = 112$ Hz). Upon quench and work up, ethylboronic acid was isolated in 70% yield (Chapter 3, Eq. 15).
This observation was noteworthy in that mild diethylzinc added only once, even when used in stoichiometric excess. This reaction suggests another method of controlling addition of organometallic reagents to the boron atom. It was envisioned that unsymmetrical $B,B$-diorgano(diisopropylamino)boranes could be formed upon reaction of dialkylzinc, followed by subsequent reaction with a Grignard reagent. Thus the preparation of unsymmetrical $B,B$-diorgano(diisopropylamino)boranes from dialkylzincs followed by addition of Grignard reagents was explored.

The sequential reaction of $H_2B-N(iPr)_2$ with a diethylzinc and phenylmagnesium bromide was investigated as a model reaction. In the formation of $B$-ethyl-$B$-phenyl(diisopropylamino)borane, one equivalent of diethylzinc was allowed to react with $H_2B-N(iPr)_2$ at 25 ºC. After 30 minutes, an equivalent of phenylmagnesium bromide was added to the mixture (Eq. 16).

Gratifyingly, the sequential addition afforded only one product in the $^{11}$B-NMR spectra: a singlet at $\delta_{B} +46$, indicating formation of $B$-ethyl-$B$-phenyl(diisopropylamino)borane. Similar results were observed in the sequential reaction of $H_2B-N(iPr)_2$ with diethylzinc, followed by addition of phenyllithium (Eq.
Furthermore, when \( \text{H}_2\text{B-N(iPr)}_2 \) was allowed to react with diethylzinc, followed by reaction with cyclohexylmagnesium chloride, \( \text{B-cyclohexyl-B-ethyl(diisopropylamino)borane} \) was formed as the sole product (Eq. 18).

Indeed, the sequential addition of diethylzinc followed by addition of an organometallic reagent to the boron atom of \( \text{H}_2\text{B-N(iPr)}_2 \) appears general.

### 4.3.4 Quenching \( \text{B,B-Diorgano(diisopropylamino)borane} \) to form the Corresponding Borinic Ester

As reaction of \( \text{H}_2\text{B-N(iPr)}_2 \) with three equivalents of Grignard reagent did not afford the trialkylborane, it was surmised that the stability of the B-N bond prohibits subsequent organometallic attack. To test this hypothesis, \( \text{B,B-diphenyl(diisopropylamino)borane} \) was subjected to DCME conditions. Thus \( \text{B,B-diphenyl(diisopropylamino)borane} \) was mixed with DCME in the presence of lithium \( \text{tert-butoxide} \) at 0 °C (Eq. 19).
Disappointingly, analysis by $^{11}$B-NMR revealed no reaction, even after extended reaction times. This observation was confirmed by subjecting $B$-ethyl-$B$-phenyl(diisopropylamino)borane to the same reaction conditions: no reaction was observed after extended reaction time. Thus attention was turned to hydrolyzing the B-N bond to form the corresponding borinate ester.

$B,B$-diethyl(diisopropylamino)borane was hydrolyzed to diethylborinic acid upon treatment with 1M HCl. When quenching diorgano(diisopropylamino)borane, aqueous hydrochloric acid was used to form the corresponding borinic acid. $B,B$-diorgano(diisopropylamino)borane products that bearing aliphatic groups were generally hydrolyzed to the respective borinic acid by adding 1M HCl. Double addition products bearing even one aromatic group were resistant to hydrolysis at room temperature, due to the conjugated stability of the B-N bond. For example, $B,B$-diphenyl(diisopropylamino)borane did not hydrolyze to the borinic acid, even in an excess of 1M HCl. $B$-cyclohexyl-$B$-ethyl(diisopropylamino)borane was quantitatively converted to the $B$-cyclohexyl-$B$-ethyl(methyl)borate upon treatment with 1M HCl in methanol (Eq. 20).
This stability of aromatic $B,B$-diorhano(diisopropylamino)boranes allows for their isolation. $B,B$-diphenyl(diisopropylamino)borane and $B$-isopropyl-$B$-phenyl(diisopropylamino)borane were isolated by simple filtration followed by concentration in vacuo. Analysis by $^{11}$B-NMR shows that $B,B$-diphenyl(diisopropylamino)borane is stable in air for three months.

4.4. Conclusion

In summary, the reactivity of diisopropylaminoborane $\text{H}_2\text{B-N(iPr)}_2$ was investigated in the preparation of symmetrical and unsymmetrical $B,B$-diorhano(diisopropylamino)boranes by reaction of organometallic reagents. Diisopropylaminoborane is prepared from the reaction of lithium diisopropylaminoborohydride with TMS-Cl. Diisopropylaminoborane is stable in solution indefinitely. Grignard reagents react twice to form symmetrical $B,B$-diorhano(diisopropylamino)boranes. Sterically hindered Grignard reagents are slow to add a second time to the boron atom. This allows for the preparation of unsymmetrical $B,B$-diorhano(diisopropylamino)boranes by the sequential reaction of a hindered Grignard followed by an unhindered Grignard. Dialkylzinc reagents react only once with $\text{H}_2\text{B-N(iPr)}_2$. This allows for an alternate route to prepare unsymmetrical $B,B$-diorhano(diisopropylamino)boranes by the sequential reaction of diethylzinc followed by subsequent reaction with a Grignard reagent. The boron atom
of H₂B-N(𝑖Pr)₂ was found to be resistant to a third attack of an organometallic reagent, preventing access to trialkylboranes. The B,B-diorgano(diisopropylamino)boranes were also resistant to further attack, but can be converted to the borinate esters. B,B-diorgano(diisopropylamino)boranes bearing aliphatic groups are readily converted to the corresponding borinate esters, while B,B-diorgano(diisopropylamino)boranes bearing aromatic groups are stable.

4.5. Experimental

General Methods. All reactions were performed in oven-dried, argon-cooled glassware. Diisopropylamine was distilled over CaH₂ prior to use. All Grignard reagents were used as received from Aldrich and were stored at room temperature. All air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. The concentrations of the Grignard reagents were monitored using the titration method described by Knochel.\textsuperscript{34} Tetrahydrofuran (THF) was freshly obtained from a solvent purification system (Pure Solv MD, Innovative Technology Inc.). NMR spectra were recorded at 500 MHz (\(\textsuperscript{1}H\)), 125 MHz (\(\textsuperscript{13}C\)), and 160.4 MHz (\(\textsuperscript{11}B\)). All \(\textsuperscript{1}H\) NMR and \(\textsuperscript{13}C\) NMR chemical shifts are reported in \(\delta\) units relative to the respective solvent of the NMR sample. \(\textsuperscript{11}B\)-NMR samples are reported relative to the external standard BF₃:Et₂O (\(\delta_B = 0\)). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration.

General Procedure for the Titration of Organometallic Reagents. To an oven-dried and argon-cooled 40-mL centrifuge tube equipped with a stir bar was added
iodine (0.254 g, 1 mmol) followed by a saturated solution of LiCl in THF (3 mL). After the iodine was completely dissolved, the resulting brown solution was cooled to 0 °C (ice bath). To the stirring solution was added methylmagnesium chloride dropwise via a 1.00-mL syringe (0.01-mL graduations) until the brown color disappeared. The amount consumed contains 1 equivalent of the organometallic reagent relative to iodine in the case of Grignard reagents and 0.5 equivalents for dialkylzinc reagents. Average of three trials for each reagent tested.

**General Procedure for the Preparation of Saturated Solution of LiCl.** To an oven-dried and argon-cooled 250-mL round bottom flask equipped with a stir bar was added anhydrous LiCl (42.39 g, 100 mmol). Anhydrous THF (200 mL) was added and the mixture was stirred for 24 h at room temperature until the LiCl was completely dissolved, resulting in the formation of a 0.5 M solution of LiCl. Solution was transferred to an oven-dried and argon-cooled 125-mL ampoule via cannula for storage.

**General Procedure for the Preparation of Diisopropylaminoborane 1 M Solution in THF.** To an oven-dried and argon-cooled 100-mL round-bottomed flask equipped with a stir bar was added diisopropylamine (5.00 g, 7 mL, 50 mmol) followed by THF (18 mL). The solution was cooled to 0 °C (ice bath) and borane dimethylsulfide (5 mL, 10 M, 50 mmol) was added dropwise via syringe. After 1 h of stirring at 0 °C, an aliquot was removed for analysis by $^{11}$B-NMR. The analysis showed the solution to be diisopropylamine-borane complex ($\delta_B$ -21, q, $J_{BH} = 95$ Hz). To the stirring solution, $n$-butyllithium (20 mL, 2.5 M, 50 mmol) was added dropwise via cannula
After 1 h of stirring at 0 °C, an aliquot was removed for analysis by \(^{11}\text{B}\)-NMR, which showed the solution to be lithium diisopropaminoborohydride (\(\delta_B\) -23, q, \(J_{\text{BH}} = 83 \text{ Hz}\)). Trimethylsilyl chloride (3.20 mL, 25 mmol) was added dropwise over 5 min via syringe while stirring at 0 °C. After 1 h of stirring at 25 °C, an aliquot was taken and analyzed via \(^{11}\text{B}\)-NMR, which showed the solution to be monomeric diisopropylaminoborane (\(\delta_B +35, \text{ t, } J_{\text{BH}} = 125 \text{ Hz}\)). The solution was transferred to an oven-dried, argon-cooled ampoule via a cannula needle.

**General Procedure for Preparation of Symmetrical \(B,B\)-Diorgano(diisopropylamino)borane From Two Equivalents of Grignard Reagent and Diisopropylaminoborane.** The preparation \(B,B\)-diethyl(diisopropylamino)borane is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a magnetic stir bar rubber septum was added diisopropylaminoborane (2.0 mL, 1M/THF, 2.0 mmol). To the solution was added ethylmagnesium bromide (2.0 mL, 2M, 4.0 mmol) drop-wise with constant stirring at 25 °C. After the reaction was allowed to stir for 60 min, an aliquot was removed for analysis by \(^{11}\text{B}\)-NMR, which showed the solution to be \(B,B\)-diethyl(diisopropylamino)borane (\(\delta_B +47\)).

\[
\text{B,B-Diethyl(diisopropylamino)borane. } \quad ^{11}\text{B-NMR } (160.4 \text{ MHz, THF): } \delta_B +47.
\]

\[
\text{B,B-Dimethyl(diisopropylamino)borane. } \quad ^{11}\text{B-NMR } (160.4 \text{ MHz, THF): } \delta_B +46.
\]
**B,B-Diphenyl(diisopropylamino)borane.** $^{11}$B-NMR (160.4 MHz, THF): $\delta_B +43$.

**B,B-Di-p-tolyl(diisopropylamino)borane.** $^{11}$B-NMR (160.4 MHz, THF): $\delta_B +45$.

**B,B-Diisopropyl(diisopropylamino)borane.** $^{11}$B-NMR (160.4 MHz, THF): $\delta_B +43$.

**B,B-Di-tert-butyl(diisopropylamino)borane.** $^{11}$B-NMR (160.4 MHz, THF): $\delta_B +47$.

**General Procedure for Preparation of Unsymmetrical B,B-Diorgano(diisopropylamino)borane From Two Equivalents of Grignard Reagent and Diisopropylaminoborane.** The preparation of $B$-isopropyl-$B$-methyl(diisopropylamino)borane is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a magnetic stir bar rubber septum was added diisopropylaminoborane (2.0 mL, 1M/THF, 2.0 mmol). To the solution was added isopropylmagnesium chloride (1.0 mL, 1M, 1.0 mmol) drop-wise with constant stirring at 25 °C. After 30 minutes of stirring, methylmagnesium chloride
(1.0 mL, 1M, 1.0 mmol) was added drop-wise. After stirring for 60 min, an aliquot was removed for analysis by \(^{11}\text{B-NMR}\), which showed the solution to be \(B\)-isopropyl-\(\text{B-methyl(diisopropylamino)borane}\) (\(\delta_\text{B} +47\)).

\[\text{B-Isopropyl-B-methyl(diisopropylamino)borane.}\] \(^{11}\text{B-NMR (160.4 MHz, THF): } \delta_\text{B} +47.\]

\[\text{B-Cyclohexyl-B-methyl(diisopropylamino)borane.}\] \(^{11}\text{B-NMR (160.4 MHz, THF): } \delta_\text{B} +46.\]

\[\text{B-Ethyl-B-phenyl(diisopropylamino)borane.}\] \(^{11}\text{B-NMR (160.4 MHz, THF): } \delta_\text{B} +45.\]

**General Procedure for Preparation of Unsymmetrical \(B,\text{B-Diorgano(diisopropylamino)borane From One Equivalent of Diethylzinc, One Equivalent Grignard Reagent, and Diisopropylaminoborane.}\)** The preparation \(\text{B-ethyl-B-phenyl(diisopropylamino)borane}\) is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a magnetic stir bar rubber septum was added diisopropylaminoborane (2.0 mL, 1M/THF, 2.0 mmol). To the solution was added diethylzinc (1.0 mL, 1M, 1.0 mmol) drop-wise with constant stirring at 25°C. After 30 minutes of stirring, phenylmagnesium bromide (1.0 mL, 1M, 1.0 mmol) was added drop-wise. After stirring for 60 min, an aliquot was removed for analysis by \(^{11}\text{B-NMR}\), which showed the solution to be \(\text{B-ethyl-B-}\)
phenyl(diisopropylamino)borane ($\delta_B +47$).

$B$-Ethyl-$B$-phenyl(diisopropylamino)borane. $^{11}$B-NMR (160.4 MHz, THF): $\delta_B +45$.

$B$-Cyclohexyl-$B$-ethyl(diisopropylamino)borane. $^{11}$B-NMR (160.4 MHz, THF): $\delta_B +45$.

General Procedure for Preparation of Unsymmetrical Borinic Esters From One Equivalent of Diethylzinc, One Equivalent Grignard Reagent, and Diisopropylaminoborane. The preparation $B$-cyclohexyl-$B$-ethyl(methyl)borate is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a magnetic stir bar rubber septum was added diisopropylaminoborane (2.0 mL, 1M/THF, 2.0 mmol). To the solution was added diethylzinc (1.0 mL, 1M, 1.0 mmol) drop-wise with constant stirring at 25 °C. After 30 minutes of stirring, phenylmagnesium bromide (1.0 mL, 1M, 1.0 mmol) was added drop-wise. After stirring for 60 min, the reaction was quenched by the addition of a solution of 1M HCl in methanol (2mL). An aliquot was removed for analysis by $^{11}$B-NMR, which showed the solution to be $B$-cyclohexyl-$B$-ethyl(methyl)borate ($\delta_B +54$).

$B$-Cyclohexyl-$B$-ethyl(methyl)borate. $^{11}$B-NMR (160.4 MHz, THF): $\delta_B +54$. 

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General Procedure for Isolation of \(\textit{B,B-Diorgano(diisopropylamino)boranes}\) From Two Equivalents of Grignard Reagent and Diisopropylaminoborane. The preparation \(\textit{B,B-diphenyl(diisopropylamino)borane}\) is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a magnetic stir bar rubber septum was added diisopropylaminoborane (2.0 mL, 1M/THF, 2.0 mmol). To the solution was added phenylmagnesium bromide (2.0 mL, 2M, 4.0 mmol) drop-wise with constant stirring at 25 °C. After the reaction was allowed to stir for 60 min, the solution was concentrated under reduced pressure and dissolved in pentane (10 mL). Solid precipitate was removed by vacuum filtration. The organic layer was concentrated under reduced pressure to yield the product was a white solid.

**\(\textit{B,B-Diphenyl(diisopropylamine)borane}\)**. White solid; (0.234 g, 95%). \(\textsuperscript{1}\text{H}\) NMR (500 MHz, CDCl\(_3\)): \(\delta\ 7.23\) (d, \(J = 7.8\) Hz, 4H), \(7.15\) (t, \(J = 7.2\) Hz, 4H), \(7.11 \text{–} 7.05\) (m, 2H), \(3.67\) (dd, \(J = 14.0, 7.4\) Hz, 2H), \(1.09\) (d, \(J = 6.6\) Hz, 12H); \(\textsuperscript{13}\text{C}\) NMR (125.7 MHz, CDCl\(_3\)): \(\delta\ 130.7, 128.9, 127.4, 126.4, 49.1, 24.5\); \(\textsuperscript{11}\text{B}\)-NMR (160.4 MHz, CDCl\(_3\)): \(\delta_{\text{B}} +43\).

**\(\textit{B-Ethyl-B-phenyl(diisopropylamine)borane}\)**. Yellow solid; (0.370 g, 80%). \(\textsuperscript{1}\text{H}\) NMR (500 MHz, CDCl\(_3\)): \(\delta\ 7.33 \text{–} 7.30\) (m, 3H), \(7.26 \text{–} 7.22\) (m, 1H), \(7.18 \text{–} 7.14\) (m, 1H), \(3.76\) (p, \(J = 6.8\) Hz, 2H), \(3.35\) (p, \(J = 6.6\) Hz, 2H), \(1.44\) (d, \(J = 6.5\) Hz, 6H), \(1.18\) (d, \(J = 6.7\) Hz, 12H); \(\textsuperscript{13}\text{C}\) NMR (125.7 MHz, CDCl\(_3\)): \(\delta\ 134.9, 130.7, 127.3, 126.3, 49.1, 47.7, 24.5, 19.6\); \(\textsuperscript{11}\text{B}\)-NMR (160.4 MHz, CDCl\(_3\)): \(\delta_{\text{B}} +43\).

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4.6. References


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CHAPTER 5

Controlled Reduction of Tertiary Amides to Alcohols, Aldehydes, or Amines Using Chloromagnesium Hydride and Metal Dimethylaminoborohydride Reagents
5.1 Introduction

Functional group transformations remain vital tools in organic synthesis; the development of new methods to carry out delicate transformations is essential. Reduction of amides with metal hydride reagents to the corresponding alcohols or amines is known. Sodium borohydride (NaBH₄) reduces amides to alcohols at elevated temperatures. In the preparation of syn-β-hydroxy-α-amino acids from pseudoephenamine glycinamide, Myers reported that an excess of NaBH₄ affords reduction of an amide to an alcohol at elevated temperatures (Scheme 5.1).

Scheme 5.1. Reduction of a Pseudoephenamine Amide with NaBH₄

The reduction of amides to the corresponding aldehydes represents a challenge: several methods are available. Controlling the partial reduction of amides to aldehydes often relies on substrate-specific conditions to achieve a high yield of the aldehyde. In these instances, the outcome of the reaction is dependent upon the nature of the substituent on the amide nitrogen atom, with bulkier substituents affording higher yields of aldehydes. In most cases, this transformation is carried out with lithium aluminum hydride (LiAlH₄), diisobutylaluminum hydride (DIBAL), and their derivatives. Generally, the reduction of amides to aldehydes with commercially available metal hydride sources results in poor yields of the aldehydes. These methods suffer from serious drawbacks: exothermic work-up and
require cryogenic reaction conditions. Current methods lead to over-reduction to amines or alcohols. Borohydrides reduce tertiary amides, but are not as reactive as aluminum hydrides.\textsuperscript{11}

One synthetic strategy to prevent over-reduction employs specialized amide derivatives: \(N\)-acylcarbazoles\textsuperscript{12} (acylimidazoles\textsuperscript{13} and acylaziridines\textsuperscript{14}), and morpholine amides.\textsuperscript{15} Of particular note are \(N\)-methoxy-\(N\)-methylamides (Weinreb amides).\textsuperscript{4} First described by Weinreb in 1981, these amides undergo a unique interaction with organometallics. Where other carbonyl groups react to form alcohols, Weinreb amides yield the corresponding ketones or aldehydes when allowed to react with Grignard reagents and metal hydrides, respectively. The presence of the methoxy group on the \(N\)-atom allows for the formation of stable chelates of the tetrahedral intermediate following addition of one equivalent of organometallic nucleophile. The formation of this stable tetrahedral intermediate prevents further nucleophilic addition (Scheme 5.2).

\[ \text{Scheme 5.2. Weinreb Amide Chelation Following Addition of an Organometallic Reagent} \]

Weinreb amides are prepared easily from carboxylic acids\textsuperscript{16} and their derivatives: acid chlorides,\textsuperscript{4} esters,\textsuperscript{17} lactones, and anhydrides.\textsuperscript{14} Since their discovery, these amides have been utilized extensively as acylating agents in synthesis.\textsuperscript{14,18} The reaction of Weinreb amides with Grignard and organolithium reagents is one of the best ways to
generate ketones. Controlled reduction of amides, including Weinreb amides, to aldehydes typically uses strong reducing agents, such as DIBAL or LiAlH₄, and cryogenic reaction conditions.¹⁹ DIBAL is capable of reducing amides to aldehydes at -78 °C with little over-reduction arising from β-hydride elimination. A literature search revealed no reported reductions of Weinreb amides to aldehydes using DIBAL at 25 °C, as this presumably gives a mixture of products, including alcohols, amines, and aminals.²⁰

The literature contains examples in which Weinreb amides are reduced to aldehydes via LiAlH₄, DIBAL, or Red-Al. While morpholine amides offered reactivity comparable to that of Weinreb amides without the exotic dimethylhydroxylamine, large-scale additions to morpholine amides typically involved carbon nucleophiles. Carey demonstrated the large-scale preparation of 2-methyloxazole-4-carboxaldehyde by the reduction of the precursor Weinreb amide.²¹ Only 0.34 equivalents of LiAlH₄ was required to reduce the amide in tetrahydrofuran (THF) at -35 °C, with no evidence of over-reduction (Eq. 1).

\[
\text{N} = \text{O} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{N}\end{array}
\xrightarrow{1. \text{ 0.34 equiv. LiAlH}_4} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{N}\end{array}
\xrightarrow{2. \text{ AcOH/THF, -30 °C}} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{N}\end{array}
\xrightarrow{3. \text{ Rochelle salt, -15 to 20 °C \ 50\%}} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{N}\end{array}
\]

(1)

Despite the ease of reduction, the work-up procedure proved cumbersome. The reaction mixture was quenched with acetic acid and treated with aqueous potassium sodium tartrate (Rochelle salt) solution to dissolve the aluminum salts. The acetic acid quench was optimized to provide an overall neutral pH solution, as the aldehyde
decomposes under strongly acidic or basic conditions. A morpholine analogue of the Weinreb amide was explored as an alternative, but similar reducing conditions provided lower yields of aldehyde and more of the alcohol by-product. In the synthesis of 24(S)-hydroxyvitamin D$_2$, Meckler described a procedure to access a key aldehyde intermediate from the reduction of the Weinreb amide with DIBAL at -60 °C for 3 hours. The reduction required two equivalents of DIBAL to consume the amide. The aluminum salts were removed by treatment of the reaction mixture with potassium tartrate, followed by filtration over Celite to afford the desired aldehyde in 74% yield (Eq. 2).\(^{22}\)

\[
\text{2 equiv. DIBAL} \quad \text{THF, -60 °C, 3 h} \quad \text{74%}
\]

Mickel used Red-Al conditions to reduce a Weinreb amide to the aldehyde in the scale-up synthesis of discodermolide, a potent inhibitor of tumor cell growth.\(^{23}\) A previous synthesis by Smith reduced the amide using DIBAL at -78 °C for 3 hours;\(^{24}\) such cryogenic conditions were difficult to achieve on industrial scale. Instead, Mickel employed a solution of the Weinreb amide with Red-Al at -20 °C. Upon quench with aqueous citric acid, work-up, and chromatography, the aldehyde was isolated in 68% yield (Scheme 5.3).
Scheme 5.3. Red-Al Reduction of a Weinreb Amide in the Synthesis of Discodermolide

Recent work on the partial reduction of amides uses titanium and zirconium hydrides.\textsuperscript{25} Buchwald reported that the combination of titanium(IV) isopropoxide and diphenylsilane reduces $N,N$-disubstituted amides to aldehydes.\textsuperscript{26} Using this method, 6-((\textit{tert}-butyldimethylsilyl)oxy)-$N,N$-diethylhexanamide is reduced to afford the aldehyde in 87\% yield (Eq. 3)

\[
\text{TBSO} \begin{array}{c} \text{NET}_2 \end{array} \xrightarrow{1. \text{Ti(OiPr)}_4, \text{Ph}_2\text{SiH}_2 \atop 25^\circ \text{C}, 2 \text{ h}} \text{TBSO} \begin{array}{c} \text{O} \end{array}
\]

(3)

As this reaction proceeds though an enamine intermediate, the method is limited to $\alpha$-enolizable substrates. Aromatic amides and amides bearing $\alpha$-stereocenters are not tolerated. Lemaire reported a variation of this method, using tetramethyldisiloxane in lieu of diphenylsilane.\textsuperscript{27}

Georg reported a promising reduction of tertiary amides, including Weinreb amides, to aldehydes using $\text{Cp}_2\text{Zr(H)Cl}$ (the Schwartz reagent).\textsuperscript{28} First reported in 1969, the Schwartz reagent became reliably used for hydrozirconation and
reduction. The reduction methodology reported by Georg requires an excess of the reagent, proceeds through an imine intermediate. The methodology is noteworthy in that the reductions are carried out at room temperature, affording the product within 30 minutes. Georg reduced a series of amides with this methodology. For example, N,N-diethyl-4-nitrobenzamide is reduced to 4-nitrobenzaldehyde in 81% yield (Eq. 4).

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O}_2\text{N} & \quad \text{H}
\end{align*}
\]

1. Cp₂Zr(H)Cl, 25 °C, 30 min  2. Short path silica filtration  81%

Reductions proceed regardless of the steric nature of the amide nitrogen. The sterically crowded N,N-diisopropyl-4-methoxybenzamide is reduced to 4-methoxybenzaldehyde in 75% yield (Eq. 5).

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

1. Cp₂Zr(H)Cl, 25 °C, 15 min  2. Short path silica filtration  75%

Ganem demonstrated a procedure to reduce amides and lactams to the corresponding imines using two equivalents of Cp₂Zr(H)Cl, followed by anhydrous work-up. Although the Schwartz reagent is commercially available, it is expensive and problematic for long-term storage due to its sensitivity to air, light, and moisture. Moreover, this reagent has poor solubility in common organic solvents. The sensitivity of this zirconium reagent requires that it be prepared immediately prior to use, limiting its synthetic application. These drawbacks lower the effective use of the Schwartz reagent. Thus, it was desirable to develop a stable reducing agent based
on readily available metals, capable of controlled room temperature reduction of amides.

Singaram reported the reduction of amides with various lithium aminoborohydrides (LAB reagents); reducing both aliphatic and aromatic amides. The product of the reduction is dependent on the steric environment of the amino group of the LAB reagent (Scheme 5.4).\(^{32}\)

**Scheme 5.4.** Chemoselective Reduction of 1-Pyrrolidinoctanamide with LAB Reagents

Reduction of 1-pyrrolidinoctanamide with lithium pyrrolidinoborohydride gives 1-octanol as the sole product in 77% yield. Reduction of the same substrate with the sterically demanding lithium diisopropylaminoborohydride affords \(N\)-octylpyrrolidine in 95% yield. Controlled reduction of Weinreb amides using either LAB reagents or 9-borabicyclo3.3.1nonane (9-BBN) was not investigated.\(^{33}\)

Braslau and Tansakul observed that the addition of commercial vinylmagnesium bromide to THP-protected Weinreb amide 1 gave a mixture of the desired vinyl ketone 2 and aldehyde 3 (Eq. 6).\(^{34}\)
Using freshly prepared vinylmagnesium bromide, only the desired α,β-unsaturated ketone 2 was formed, indicating the presence of a hydride reducing agent contaminant in the commercial sample of Grignard reagent. To verify this hypothesis, the older commercial vinylmagnesium bromide was allowed to react with benzaldehyde. \(^1\)H-NMR analysis of the product revealed a 2:1 mixture of the expected allylic alcohol, 1-phenyl-2-propen-1-ol, and benzyl alcohol (Eq. 7).

\[ \text{PhMgCl, THF, 0 °C, 1 h} \rightarrow \text{PhOH} + \text{PhCHO} \]  

A similar observation of reduction products from Grignard reactions with Weinreb amides was reported. In the synthesis of unsymmetrical ketones, Williams found that in the reaction of phenylmagnesium chloride with Weinreb amide 4, the desired ketone 5 was isolated in 87% yield along with 2% of the corresponding aldehyde 6 (Scheme 5.5).\(^{15}\)

**Scheme 5.5. Reaction of Weinreb Amide 4 with Phenylmagnesium Chloride**

These observations warranted an investigation into the reduction of Weinreb amides
using magnesium-based hydrides.

5.2. Magnesium Hydrides

Hydridomagnesium halides (HMgX, X = Cl or Br) have been investigated since the 1950s.\(^{35}\) Wiber and Strebel reported the synthesis of HMgCl and HMgBr via the reaction of Grignard reagents with diborane. Firestone reported on the synthesis of HMgBr. Firestone obtained grey soot upon the pyrolysis of ethylmagnesium bromide in vacuo at high temperatures for 4 hours (Eq. 8).\(^{36}\)

\[
\text{MgBr} \xrightarrow{\text{vacuum, 220 °C, 4 h}} \text{HMgBr} \tag{8}
\]

This soot was reportedly capable of reducing esters implying it contained HMgBr. Firestone used this material to prepare pyridoxine from diethyl 5-hydroxy-6-methylpyridine-3,4-dicarboxylate. Stirring the dicarboxylate with the grey HMgBr powder overnight afforded pyridoxine in 30% yield (Eq. 9).

\[
\text{HO-} \begin{array}{c} \text{CO}_2\text{Et} \\ \text{CO}_2\text{Et} \end{array} \xrightarrow{\text{HMgBr}} \begin{array}{c} \text{HO-} \\ \text{N} \end{array} \begin{array}{c} \text{OH} \\ \text{OH} \end{array} \\
\text{Et}_2\text{O, 25 °C, 12 h} \quad 30\% \tag{9}
\]

However, Firestone was unable to prepare authentic samples of HMgBr for analysis.

Ashby reported extensively on the synthesis of HMgX compounds by the reaction of magnesium halides with an active form of MgH\(_2\).\(^{37}\) Preparation of the active form of MgH\(_2\) was achieved using Ph\(_2\)Mg or Et\(_2\)Mg and equimolar amounts of LiAlH\(_4\) in diethyl ether (Eq. 10).
The resulting MgH₂ was insoluble in diethyl ether and was isolated by filtration. When the solid MgH₂ was allowed to react with a solution of MgX₂ (X = Cl and Br) in THF at 25 °C, 2 equivalents of HMgX were formed (Eq. 11).

\[
\text{MgH}_2 + \text{MgX}_2 \xrightarrow{\text{THF, 25 °C}} 2 \text{HMgX}
\]

This reaction was exothermic and resulted in a clear solution, indicating that reaction between MgH₂ and MgX₂ had occurred. HMgX compounds were insoluble in diethyl ether, yet both HMgBr and HMgCl were soluble in THF. Ashby confirmed the formation of HMgX compounds by infrared spectroscopy. The infrared spectra of both HMgCl and HMgBr present an absorption band at 1280 cm⁻¹, not present in the spectra of MgCl₂ or MgBr₂. The identity of the Mg–H stretching band in HMgBr and HMgCl was confirmed by preparing DMgBr and DMgCl from LiAlD₄ and comparing the IR spectra of HMgX to DMgX. Bands at 1260 and 1290 cm⁻¹ correspond to HMgBr and HMgCl, respectively. Ashby conducted molecular weight studies on HMgBr and HMgCl, which indicate the compounds to be dimeric in dilute solutions (Figure 5.1).

![Diagram](image.png)

**Figure 5.1.** Proposed Structure of Dimeric HMgX
Singaram reported the formation of magnesium-based hydrides as by-products of the reaction of Grignard reagents with organoboranes. In the investigation of the synthesis of pincaolboronate esters, HMgX was prepared from the reaction of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBPin) with an equivalent of a Grignard reagent (Eq. 12).39

\[ \text{RMgX} + \text{H-B} \stackrel{\text{THF, 25 °C, 1 h}}{\rightarrow} \text{R-B} + \text{HMgX} \]  

(12)

In a separate study, Singaram reported the formation of halomagnesium dialkylaminoborohydrides as a by-product of the reaction of Grignard reagents with diisopropylaminoborane (H₂B-N(iPr)₂, Chapter 3) (Eq. 13).40

\[ \text{RMgX} + \text{H₂B-N(iPr)₂} \stackrel{\text{THF, 25 °C, 1 h}}{\rightarrow} \text{H} \text{B} \text{NiPr₂} + \text{H₃B-N(iPr)₂} \]  

(13)

With these methods in hand to prepare magnesium hydrides from organoboranes, the reducing capability of the resulting hydride reagents was explored. This chapter discusses the results from the optimized reduction reactions of aliphatic, aromatic, and heteroaromatic amides, including Weinreb amides, using HMgCl prepared from HBPin, and chloromagnesium dimethylaminoborohydride prepared from dimethylamine-borane.

5.3. Results and Discussion

5.3.1. Synthesis of HMgX from Grignard Reagents and HBPin

As reported by Clary and Singaram, \( \rho \)-tolylmagnesium bromide was allowed to react with HBPin in THF at 25 °C. After one hour, an aliquot of the reaction
mixture was analyzed by $^{11}$B-NMR spectroscopy: $p$-tolylpinacolboronate was formed quantitatively (Scheme 5.6).

![Scheme 5.6. Formation of $p$-Tolylboronic Ester and HMgBr](image)

Dialkoxyalkylborohydride species display a broad singlet in the region of $\delta$ 0 to +10 in the $^{11}$B-NMR spectrum. Analysis of the reaction mixture showed no evidence of the borohydride adduct. Based on the reaction stoichiometry, it was concluded that 1 equivalent of HMgBr had formed. HMgBr is insoluble in THF, undergoing Schlenk equilibrium to MgH$_2$ and MgBr$_2$. HMgCl, prepared from isopropylmagnesium chloride and HBPin, was more stable in THF than HMgBr (Eq. 14).

$$ \text{HMgCl formation was confirmed through IR analysis. An absorption band at 1292 cm}^{-1} \text{ corresponds to H-MgCl stretching. The concentration of HMgCl was evaluated by gas evolution analysis (Table 5.1).} $$
Table 5.1 Analysis of HMgCl Concentration by Gas Evolution Analysis\(^a\)

<table>
<thead>
<tr>
<th>Run</th>
<th>(V_{\text{injected}}, \text{mL})</th>
<th>(V_{\text{displaced}}, \text{mL})</th>
<th>mmol H(_2)</th>
<th>mmol HMgCl(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>12</td>
<td>0.48</td>
<td>0.48</td>
</tr>
<tr>
<td>2</td>
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<td>12.4</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>11.2</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>12.4</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>12.6</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>12.6</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>12.4</td>
<td>0.50</td>
<td>0.50</td>
</tr>
</tbody>
</table>

\(^a\)Reactions were carried out on a 2.0 mmol scale with 1 equiv. HBPin, 1 equiv. isopropylmagnesium chloride, anhydrous THF (2.0 mL), argon, 25 °C, 1 hour. Aliquots from the supernatant (0.5 mL) were injected into the modified Hempel gas-measuring device containing a 1:1 quenching solution of H\(_2\)O/MeOH \(^b\)Theoretical molarity of HMgCl = 0.50

The data demonstrate that the measured moles of hydrogen gas evolved are equivalent to the moles of arylboronate substrate. Ruling out the formation of precipitate, the data indicate a 1:1 stoichiometry between alkylboronate and HMgCl. Using gas evolution analysis to measure the molarity of HMgCl,\(^{39}\) this procedure was used to consistently produce 0.5 M solutions of HMgCl in THF. Solutions of HMgCl were not amenable to long-term storage. As the solution aged, a light grey precipitate formed, turning the solution cloudy. This cloudy HMgCl solution demonstrated no gas evolution upon injection into a gas-measuring device. Stored solutions of HMgCl were unreactive within one week of preparation. Thus freshly prepared HMgCl solutions were utilized in the subsequent studies.
5.3.2 Synthesis of MgAB Reagent from the Reaction of Grignard Reagents and Amine-Borane

As reported by Singaram, the reaction of Grignard reagents with H$_2$B-N(iPr)$_2$ afford halomagnesium diisopropylaminoborohydride.$^{39}$ Attempts were made to prepare an authentic sample of the borohydride from diisopropylamine-borane and methylmagnesium chloride in THF. Analysis by $^{11}$B-NMR spectroscopy of the reaction mixture showed a small amount of the chloromagnesium diisopropylaminoborohydride ($\delta_B$ -17, $J_{BH} = 83$ Hz) as well as a number of disproportionation products. When the less sterically hindered dimethylamine-borane was allowed to react with an equivalent of methylmagnesium chloride, chloromagnesium dimethylaminoborohydride (MgAB) was produced quantitatively (Eq. 15).$^{40}$

\[
\begin{align*}
H_3B:NMMe_2 &+ H_3CMgCl &\xrightarrow{\text{THF, 0 °C, 1 h}} &\text{ClMg}^+ [H_3B-NMMe_2]^- &+ CH_4 \\
\delta_B &=-14 &\delta_B &=-16 &J_{BH} &= 98 \text{ Hz, q} &J_{BH} &= 83 \text{ Hz, q}
\end{align*}
\]

In the $^{11}$B-NMR spectrum in THF, the MgAB species appears as a quartet at $\delta_B$ -16 ppm, while the starting amine-borane has a chemical shift of $\delta_B$ -14 ppm. The starting material and the product are further distinguished by their coupling constants; dimethylamine-borane exhibits a quartet with $J_{BH} = 98$ Hz, while the product chloromagnesium dimethylaminoborohydride has $J_{BH} = 83$ Hz (Figure 5.2).
When synthesizing MgAB, chloride-based Grignard reagents give complete conversion. Bromide-based Grignard reagents afford mixtures due to Schlenk disproportionation. Solutions of MgAB can be stored under inert atmosphere at room temperature for at least three months without any disproportionation, as monitored by $^{11}$B-NMR. An investigation into the partial reduction of amides using HMgCl and MgAB was carried out.

### 5.3.3 Controlled Reduction of Weinreb Amides Using HMgCl and MgAB

The reduction of $N$-methoxy-$N$-methylbenzamide to benzaldehyde was investigated as a model substrate. An equimolar mixture of HMgCl and the amide was stirred at 25 °C for 3 hours. TLC analysis showed the formation of benzaldehyde as the only product, along with traces of unreacted amide starting material. A slight stoichiometric excess of HMgCl (1.2 equivalents) was required to push the reaction to completion. Upon acidic work-up, $^1$H-NMR analysis of the crude mixture showed
benzyl alcohol in addition to benzaldehyde. Apparently, the reduction of benzaldehyde occurs during the acidic aqueous quench. While this reaction was of interest, the instability of HMgCl limited practical exploration.

Attention was turned to exploring the use of the more stable MgAB reagent. Thus, reduction of N-methoxy-N-methylbenzamide to benzaldehyde using MgAB was investigated. One equivalent of MgAB reduced N-methoxy-N-methylbenzamide to benzaldehyde in 30 minutes at 25 °C, as evidenced by TLC. After acidic quench and aqueous work-up, ¹H-NMR of the crude mixture revealed the presence of benzyl alcohol in addition to benzaldehyde. It was speculated that an inexpensive sacrificial electrophile such as acetaldehyde could be used as a hydride scavenger during the quench. Indeed, dropwise transfer of the reduction mixture to a pentane solution of acetaldehyde and acetic acid prevented the over-reduction, but contamination was observed. Attempted purification of the crude benzaldehyde by silica gel column chromatography resulted in the isolation of essentially pure benzyl alcohol. Dimethylaminoborane (H₂B-NMe₂), the by-product from MgAB, exists as a stable dimer and is usually unreactive to aldehydes.⁴⁴ Curran reported a similar observation in the silica gel-promoted reduction by N-heterocyclic carbene (NHC) boranes.⁴⁵ In the presence of silica gel, 3-phenylpropanal was reduced by the NHC-borane to 3-phenylpropanol in 95% yield in 15 min at room temperature (Eq. 16).

\[
\text{PhCH} = \text{H} + \text{NHC-BH₃} \xrightarrow{\text{silica gel, EtOAc, 25 °C, 15 min}} \text{PhCH₂OH} \quad \text{(16)}
\]
In the absence of silica gel, the NHC-borane was inert to aldehydes and ketones. Evidently, activation of the aldehyde carbonyl by silica gel results in the reduction of to the alcohol by the H$_2$B-NMe$_2$ dimer.

Even though MgAB is an excellent reducing agent to achieve the controlled reduction of Weinreb amides to aldehydes, convenient isolation of pure aldehyde products proved challenging. Purification of aldehydes by addition of bisulfite is a well-established procedure. Treatment of ketones and aldehydes with aqueous sodium bisulfite form insoluble solid bisulfite adducts (Eq. 17).$^{46}$

\[
\begin{align*}
\text{RCHO} & \quad \text{HO\textsubscript{SO\textsubscript{3}}ONa} \\
& \quad \text{OH} \quad \text{ONa} \\
& \quad \text{bisulfite adduct} \\
& \quad \text{Aq. acid or base} \\
\end{align*}
\]

The bisulfite adducts are insoluble in most organic solvents, allowing for isolation by filtration. Separating bisulfite adducts from the crude reaction mixture, followed by the regeneration of the aldehyde, proved to be convenient and practical. The aldehydes were readily regenerated by treatment with aqueous acid,$^{47}$ base,$^{48}$ or formaldehyde, allowing for the isolation of various aldehydes (Table 5.2).$^{49}$

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Table 5.2. Reduction of Weinreb Amides to Aldehydes with MgAB$^a$

![Reduction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Product</th>
<th>% Yield$^b$</th>
<th>Entry</th>
<th>Amide</th>
<th>Product</th>
<th>% Yield$^b$</th>
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$^a$Reactions conducted on a 2 mmol scale with 1 equiv. Weinreb amide and 1 equiv. MgAB. $^b$Isolated yield of aldehyde after liberation from bisulfite adduct.

Weinreb amide substrates of varying steric and electronic nature were reduced under these mild conditions. Aromatic substrates bearing electron-donating (Table 5.2, Entries 2–4) or electron-withdrawing (Table 5.2, Entries 6–9) groups were amenable to reduction without complication. Reduction was even observed for substrates with increased steric demand (Table 5.2, Entries 2 and 7). Furthermore, the cinnamic amide was reduced without over-reduction to cinnamyl alcohol as a side
product (Table 5.2, Entry 5). The previously reported reduction of \( N \)-methoxy-\( N \)-methylcinnamamide with \( \text{Cp}_2\text{Zr(H)Cl} \) affords significant amounts of the cinnamyl alcohol (Scheme 5.7).\(^{28a,b}\)

![Scheme 5.7. Reduction of \( N \)-Methoxy-\( N \)-methylcinnamamide with \( \text{Cp}_2\text{Zr(H)Cl} \)](https://example.com/scheme.png)

Aliphatic amides are also amenable to reduction with this methodology (Table 5.2, Entry 10). Of particular interest is the chemoselective reduction of the substituted amides by MgAB. The reduction of the cinnamic amide demonstrated 1,2−reduction in the absence of 1,4−reduction (Table 5.2, Entry 5). The chemoselectivity was further explored by examining the room temperature reaction of methyl 4-(methoxy(methyl)carbamoyl)benzoate with MgAB, affording methyl 4-formylbenzoate in 70% yield (Table 5.2, Entry 11). Gratifyingly, a similar result was obtained in the reaction of MgAB with \( N \)-methoxy-\( N \)-methyl-4-nitrobenzamide, which afforded 4-nitrobenzaldehyde in 89% yield (Table 5.2, Entry 12). Lastly, reaction of 4-cyano-\( N \)-methoxy-\( N \)-methylbenzamide with MgAB led to conversion to 4-cyanobenzaldehyde in 74% yield (Table 5.2, Entry 13). The reduction of Weinreb amides in the presence of a nitro group, a nitrile, an ester, and conjugated olefin functionalities indicates a unique chemoselectivity profile for MgAB.

The bisulfite adducts of aldehydes formed in the work-up protocol are stable crystalline solids, amenable to long term storage or use in situ.\(^{50}\) Vounatsos demonstrated the use of bisulfite adducts of aldehydes in reductive amination.
reactions. Using this method, Vounatsos performed the reductive amination of low molecular weight aldehydes trapped as the corresponding bisulfite adducts. The amination of the bisulfite adduct of acetaldehyde with benzylamine afforded the \(N\)-benzylethanamine in 60% yield (Eq. 18)

\[
\text{OH} \quad \text{SO}_3\text{Na} + \quad \text{H}_2\text{N} - \text{C}_6\text{H}_4\text{CH}_2\ \text{2-picoline borane} \quad \text{MeOH, 30 °C, 12 h} \quad \text{N} - \text{benzylethanamine} \quad \text{60% yield} \ (18)
\]

Thus reduction of Weinreb amides to aldehydes with a work-up to directly provide the robust bisulfite adducts directly was explored. Isolation of the bisulfite adducts in lieu of liberating the free aldehyde allowed expansion of the study to include adducts of water-soluble aldehydes. For example, heteroaromatic amides were amenable to the reduction procedure, however the corresponding aldehydes are water soluble, hindering isolation of the free aldehyde (Table 5.3).

**Table 5.3. Reduction of Weinreb Amides to Aldehydes Isolated as Bisulfite Adducts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{N} = \text{O})</td>
<td>(\text{N} \quad \text{SO}_3\text{Na})</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Br} = \text{N})</td>
<td>(\text{Br} \quad \text{SO}_3\text{Na})</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>(\text{S} = \text{N})</td>
<td>(\text{S} \quad \text{SO}_3\text{Na})</td>
<td>67</td>
</tr>
</tbody>
</table>

\(^a\)Reactions conducted on a 2 mmol scale with 1 equiv. Weinreb amides and 1 equiv. MgAB. \(^b\)Isolated yield of solid bisulfite adduct
5.3.4 Elaboration of the Reductive Scope of MgAB

After the successful reduction of Weinreb amides, the general reactivity of MgAB with other amides was probed. Using the optimized procedure from the Weinreb amide reduction study, benzamide was allowed to react with MgAB at room temperature. The reaction was exothermic: gas was evolved, followed by the immediate formation of a white precipitate. Analysis by $^{11}$B-NMR showed the appearance of the dimethylamine-borane ($\delta_{B}$ -14, $q$, $J_{BH} = 98$ Hz). Evidently, the amide proton is acidic enough to quench MgAB to form the amine-borane, releasing gas and forming a precipitate. Similar results were observed upon reaction of MgAB with N-methylbenzamide: an exothermic evolution of gas was observed accompanied by simultaneous precipitation. These observations indicate that primary and secondary amides are not amenable to reduction with MgAB. Thus, attention was turned to tertiary amides.

Amides of morpholine have been shown to be equally reactive as Weinreb amides.\textsuperscript{15} Martinez demonstrated that reduction with LiAlH$_4$ of N-protected $\alpha$-amino aldehyde from the precursor morpholine amide is an inexpensive alternative to the Weinreb amide. The Boc-protected aldehyde of alanine was prepared in 75% yield from the Boc-protected morpholine amide (Eq. 19).

\begin{equation}
\text{BocHN}_\text{5} \xrightarrow[1. \text{LiAlH}_4, \text{THF}, 0^\circ\text{C}]{2. \text{Aq. work-up} \text{75%}} \text{BocHN}_\text{2.}
\end{equation}

Similar to reactivity with Weinreb amides, very little alcohol formation resulted from the reaction of the morpholine amides. Martinez postulated that a strong stable metal-
Chelated tetrahedral intermediate is formed. Thus, the acyl morpholine morpholino(phenyl)methanone was allowed to react with MgAB at room temperature; reaction progress was monitored by TLC (Eq. 20).

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O}
\end{array}
\quad \xrightarrow{\text{ClMg}^+ [\text{H}_3\text{B-NMe}_2]^+} 
\begin{array}{c}
\text{O} \\
\end{array}
\]

\[\text{THF, 25 °C}\]

(20)

The acyl morpholine was consumed, affording benzaldehyde within three hours. As with Weinreb amides, reverse quench of the reaction mixture by addition to a pentane solution of acetaldehyde and acetic acid prevented the over-reduction of the resulting benzaldehyde to benzyl alcohol. Similar results were observed upon reaction of MgAB with the acyl pyrrolidine phenyl(pyrrolidin-1-yl)methanone, which afforded benzaldehyde after 4 hours (Eq. 21).

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O}
\end{array}
\quad 1. \text{ClMg}^+ [\text{H}_3\text{B-NMe}_2]^+ 
\begin{array}{c}
\text{THF, 25 °C, 4 h} \\
2. \text{MeCHO/AcOH} \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\]

72%

(21)

Lastly, reaction of \(N,N\)-dimethylbenzamide with MgAB, followed by the same reverse quench, afforded benzaldehyde after 5 hours of reaction at 25 °C (Eq. 22).

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O}
\end{array}
\quad 1. \text{ClMg}^+ [\text{H}_3\text{B-NMe}_2]^+ 
\begin{array}{c}
\text{THF, 25 °C, 5 h} \\
2. \text{MeCHO/AcOH} \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\]

74%

(22)

Attempts to reduce amides with more sterically demanding substitution on nitrogen with MgAB resulted in no reaction. \(N,N\)-Diethylbenzamide and \(N,N\)-diisopropylbenzamide were unreactive with MgAB even after extended reaction
times. Reverse quench of the reaction solutions, followed by aqueous work-up afforded the starting materials.

Having demonstrated the ability of MgAB to reduce some tertiary amides to aldehydes, attention was turned to the isolation procedure with the goal of streamlining the process. Short-path column chromatography can be utilized with the use of aluminum oxide (basic alumina) instead of silica gel. Basic alumina is a common solid-phase for various chromatographic procedures. Contrary to observations with silica gel, basic alumina does not activate the aldehyde carbonyl, preventing further reduction. Reaction of N-methoxy-N-methylbenzamide with MgAB, followed by reverse quench and alumina column chromatography affords benzaldehyde in 74% yield (Eq. 23).

\[
\text{O} \quad \text{ClMg}^+ \left[ \text{H}_3\text{B-NMe}_2 \right]^- \quad \text{THF, 25 °C, 30 min} \\
\text{O} \quad \text{MeCHO/AcOH} \\
\text{O} \quad \text{Alumina column} \\
\text{H} \quad \text{74%}
\]

Purification of the crude aldehyde by basic alumina chromatography was found to be simpler and faster than the formation, isolation, and liberation of bisulfite adducts. Use of this procedure allows for the reduction of various tertiary amides. A variety of substrates that vary in electronic and steric properties were investigated (Table 5.4).
### Table 5.4. Reduction of Tertiary Amides to Aldehydes with MgAB

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Product</th>
<th>% Yield$^b$</th>
<th>Entry</th>
<th>Amide</th>
<th>Product</th>
<th>% Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>74$^c$</td>
<td>7</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>53$^e$</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>65$^c$</td>
<td>8</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>65$^g$</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>63$^d$</td>
<td>9</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>60$^g$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>70$^d$</td>
<td>10</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>74$^f$</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>92$^d$</td>
<td>11</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>70$^f$</td>
</tr>
<tr>
<td>6</td>
<td><img src="image1.png" alt="Amide" /></td>
<td><img src="image1.png" alt="Product" /></td>
<td>74$^d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Reactions conducted on a 2 mmol scale with 1 equiv. amide and 1 equiv. MgAB.  
$^b$Isolated yield of aldehyde after column chromatography.  
$^c$30 min.  $^d$3 h.  $^e$4 h.  $^f$5 h

Aromatic and aliphatic amides are reduced to the aldehydes in good yields. Substitution of the aromatic substrates with electron-donating (Table 5.4, Entries 6 & 8) or electron-withdrawing groups (Table 5.4, Entries 5, 7, 11) do not significantly alter the reaction course. Aliphatic amides are viable substrates (Table 5.4, Entries 2 & 4), highlighting the generality of this reduction. One equivalent of MgAB is required for aldehyde formation from aliphatic and aromatic amides. The rate of reduction of amides indicates a preference for substrates in which the lone pair of the nitrogen is electron donating and thus more delocalized across the amide bond by
resonance. This trend accounts for the observed reaction time of dimethyl amides (5 hours) versus morpholine amides (3 hours), as well as Weinreb amides (30 minutes).

**5.3.5 Reduction of Amides to Alcohols with MgAB**

Earlier work with sodium aminoborohydrides established the reduction of amides to alcohols. Unfortunately, mixtures of products were often obtained and the steric environment of both the amide and the sodium aminoborohydride requires careful balancing to achieve the desired products. LAB reagents prove more reliable alternatives, reducing amides with no by-product.\(^5\) Reports on the reactivity of LAB reagents indicate that the reduction of tertiary amides to the alcohol is a general method and represent a substantial improvement over other reducing agents. Aqueous acidic quench and work-up of \(N\)-methoxy-\(N\)-methylbenzamide reactions mediated by MgAB afforded benzyl alcohol. Evidently, interaction of the aqueous acid with dimethylaminoborane liberates additional hydride, resulting in reduction to the alcohol, even at stoichiometric equivalence of the original MgAB reagent. Singaram reported similar reactivity in the reactions or esters with LAB reagents.\(^5\) One equivalent of LAB reagent was sufficient to reduce esters to alcohols. Thus, the reduction of amides to alcohols by reaction with MgAB was explored.

Consistent with past observations, the reactions of sterically demanding \(N,N\)-diethylbenzamide and \(N,N\)-diisopropylbenzamide resulted in no reduction even under prolonged reaction times at room temperature. Reaction with less sterically demanding amides resulted in conversion to alcohols (Table 5.5).
The reaction of amides with 1.25 equivalents of MgAB, followed by acidic quench and work-up, afford the desired alcohols in good yields. The reductions were general, reducing pyrrolidine amides (Table 5.5, Entry 1), Weinreb amides (Table 5.5, Entries 2 and 3), and morpholine amides (Table 5.5, Entries 4 and 5). Reductions of aromatic amides progress regardless of the electronic nature of the aromatic ring. Of particular note is the chemoselectivity of the reductions. The Weinreb amide is selectively reduced in the presence of either an ester (Table 5.5, Entry 2), or a nitrile (Table 5.5, Entry 3).

**Table 5.5. Reduction of Amides to Alcohols with MgAB\(^a\)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Product</th>
<th>% Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="amide1" /></td>
<td><img src="image2" alt="alcohol1" /></td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="amide2" /></td>
<td><img src="image4" alt="alcohol2" /></td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="amide3" /></td>
<td><img src="image6" alt="alcohol3" /></td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="amide4" /></td>
<td><img src="image8" alt="alcohol4" /></td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="amide5" /></td>
<td><img src="image10" alt="alcohol5" /></td>
<td>75</td>
</tr>
</tbody>
</table>

\(^a\)Reactions conducted on a 2 mmol scale with 1 equiv. amide and 1.25 equiv. MgAB, followed by aqueous acidic work-up. \(^b\)Isolated yield
5.3.6. Reduction of Lactams to Amines with MgAB

The reduction of lactams to amines is an important transformation in the synthesis of biologically active pharmaceutical compounds. This reduction has been reported with many reagents including DIBAL, alane, sodium bis(2-methoxyethoxy)aluminum hydride, NaBH₄, LiAlH₄, and borane-tetrahydrofuran (H₃B-THF). Of these reagents, LiAlH₄ and H₃B-THF have been two of the most commonly used reagents. Singaram reported the reduction of various N-alkyl lactams to the cyclic amines using lithium dimethylaminoborohydride. Reductions are complete after refluxing in THF for 2 hours. The cyclic amine products are isolated after an aqueous work-up in very good to excellent yields. For example, 1-decyl-2-pyrrolidinone is reduced to N-decylpyrrolidine in 96% yield (Eq. 24).

\[
\text{N-O} \quad 1.5 \text{ equiv. LiH}_{3}B\text{-NMe}_{2} \quad \text{THF, 65 °C, 2 h} \quad 96\% \\
\]

To further probe the reactivity of MgAB, the reduction of lactams was explored. Following the same reaction conditions, 4-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one was allowed to react with an excess of MgAB in refluxing THF (Eq. 25).

\[
\text{N-O} \quad 1.5 \text{ equiv. ClMg}^{+} \text{[H}_{3}B\text{-NMe}_{2}]^{-} \quad \text{THF, 65 °C, 2 h} \quad 80\% \\
\]

Gratifyingly, upon acidic quench and work-up, the cyclic amine is isolated in 80% yield. This methodology allows for the reduction of several other lactams (Table 5.6).
Table 5.6. Reduction of Lactams to Amines with MgAB

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactam</th>
<th>Amine</th>
<th>% Yield(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Lactam 1" /></td>
<td><img src="image2" alt="Amine 1" /></td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Lactam 2" /></td>
<td><img src="image4" alt="Amine 2" /></td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Lactam 3" /></td>
<td><img src="image6" alt="Amine 3" /></td>
<td>80</td>
</tr>
</tbody>
</table>

\(^{a}\)Reactions conducted on a 5 mmol scale with 1 equiv. lactam and 1.5 equiv. MgAB, THF, 65 °C. \(^{b}\)Isolated yield.

### 5.3.7 Reduction of Amides to Aldehydes with LAB Reagents

The controlled reduction of amides to aldehydes with MgAB expands the versatility of amide reduction by aminoborohydrides (Scheme 5.8).

![Scheme 5.8. Reduction of Amides with Aminoborohydride Reagents](image7)

LAB reagents have been used to reduce amides to give either the corresponding alcohols or amines.\(^{26b}\) Reduction of amides with lithium pyrrolidinoborohydride

200
yields alcohols, whereas reaction with the sterically crowded lithium diisopropylaminoborohydride yields amines. The reduction of amides to aldehydes with MgAB prompted a reevaluation of the reactivity of lithium dimethylaminoborohydride (Me-LAB). It was reasoned that if the reduction of an amide with Me-LAB afforded alcohols, then the reaction was likely proceeding through an aldehyde intermediate. Past reduction studies with LAB reagents never explored the possibility of isolating aldehydes from the reaction mixture. Thus the reduction of amides to aldehydes with Me-LAB was explored. Using the optimized procedure from the controlled reduction study of Weinreb amides to aldehydes, the reaction of \(N\)-methoxy-\(N\)-methylbenzamide with Me-LAB was carried out at room temperature (Eq. 27).

\[
\text{O} \quad \underset{\text{THF, 25°C}}{\text{LiH}_3\text{B-NMe}_2} \quad \text{O} \\
\text{N} \quad \text{H} \\
\text{O} 
\]

As evidenced by TLC analysis, the amide was reduced within 30 minutes to afford benzaldehyde as the only observable intermediate. Following the reverse quench and bisulfite purification protocol, benzaldehyde was isolate in 77% yield. Consequently, the reduction of morpholino(phenyl)methanone, followed by reverse quench and bisulfite purification gave benzaldehyde in 74% (Eq. 28)

\[
\text{O} \quad \underset{\text{THF, 25°C, 2 h}}{\text{1. LiH}_3\text{B-NMe}_2} \quad \text{O} \\
\text{N} \quad \text{H} \\
\text{O} \\
\text{1. LiH}_3\text{B-NMe}_2} \quad \text{THF, 25°C, 2 h} \\
\text{2. MeCHO/AcOH} \\
\text{3. Aq. NaHSO}_3 \\
\text{4. Aq. H}_2\text{C}=\text{O} \\
\text{74%} 
\]

(27)
The reduction of the morpholine amide with Me-LAB was complete within 2 hours, as contrasted with 3 hours required for reduction with MgAB. Lastly, reduction of the aliphatic amide N-methoxy-N-methylcyclohexanecarboxamide with Me-LAB, followed by reverse quench and bisulfite purification afforded cyclohexanecarboxaldehyde in 80% yield (Eq. 29).

Reaction of amides with the sterically unencumbered Me-LAB, followed by reverse quench and isolation, afforded the corresponding aldehydes. These reductions suggest a broader applicability of LAB reagents in the reduction of amides.

5.4. Conclusion

In summary, a mild and simple method for the reduction of amides to aldehydes under ambient conditions has been developed. Two magnesium hydride reagents were prepared and investigated. HMgCl was prepared by the reaction of HBPin with an aliphatic Grignard reagent. HMgCl was shown to reduce Weinreb amides to aldehydes within three hours. This reagent is not amenable to long term storage, and must be prepared prior to use. Chloromagnesium dimethylaminoborohydride (MgAB) was prepared by the reaction of methylmagnesium chloride with dimethylamine-borane at 0 °C. Reduction of amides with MgAB, followed by acidic aqueous work-up affords the corresponding alcohols. Reverse quench of the reaction mixture
utilizing a sacrificial electrophile affords the crude aldehyde. MgAB was shown to reduce a series of tertiary amides to aldehydes, but was unreactive to sterically demanding amides. The aldehyde product can be effectively isolated as the corresponding bisulfite adduct, which can be stored, or unveiled to provide pure aldehyde. Conversely, the aldehydes were isolated using alumina column chromatography of the crude reaction material. MgAB exhibits a unique chemoselective profile, capable of reducing amides in the presence of a nitro group, a nitrile, an ester, and a conjugated double bond. MgAB is milder, safer, and complementary to reducing agents typically used to convert Weinreb amides to aldehydes. Contrary to HMgCl, solutions of MgAB are amenable to long-term storage under argon. Similar to the analogous LAB reagent, MgAB reduces N-alkyl lactams to the cyclic amine. The results of the amide reduction study with MgAB prompted an investigation into the reaction of lithium dimethylaminoborohydride with amides. Me-LAB also effects the reduction of amides to aldehydes. This work demonstrates the broad reactivity of metal dimethylaminoborohydride reagents.

5.5. Experimental Section

**General Methods.** All reactions were performed in oven-dried, argon-cooled glassware. The dimethylamine-borane was used as received from Callery Chemical Company. The pinacolborane was used as received from Aldrich, stored under argon in a refrigerator held at 5 °C. All Grignard reagents were used as received from Aldrich and were stored at room temperature. All air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum.
Pinacolborane was added via syringe, with the dispensed amounts measured by mass difference of the syringe before and after addition. The concentrations of the Grignard reagents were monitored using the titration method described by Knochel. Tetrahydrofuran (THF) was freshly obtained from a solvent purification system (Pure Solv MD, Innovative Technology Inc.). NMR spectra were recorded at 500 MHz (\(^1\)H), 125 MHz (\(^{13}\)C), and 160.4 MHz (\(^{11}\)B). All \(^1\)H-NMR and \(^{13}\)C NMR chemical shifts are reported in \(\delta\) units relative to the respective solvent of the NMR sample. \(^{11}\)B-NMR samples are reported relative to the external standard BF\(_3\)::Et\(_2\)O (\(\delta_B = 0\)). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration.

**General Procedure for the Titration of Grignard Reagents.** To an oven-dried and argon-cooled 40-mL centrifuge tube equipped with a stir bar was added iodine (0.254 g, 1 mmol) followed by a saturated solution of LiCl in THF (3 mL). After the iodine was completely dissolved, the resulting brown solution was cooled to 0 °C (ice bath). To the stirring solution was added methylmagnesium chloride dropwise via a 1.00-mL syringe (0.01-mL graduations) until the brown color disappeared. The amount consumed contains 1 equivalent of the organometallic reagent relative to iodine in the case of Grignard reagents. Average of three trials for each Grignard tested.

**General Procedure for the Preparation of Saturated Solution of LiCl.** To an oven-dried and argon-cooled 250-mL round bottom flask equipped with a stir bar was added anhydrous LiCl (42.39 g, 100 mmol). Anhydrous THF (200 mL) was added and the mixture was stirred for 24 h at room temperature until the LiCl was
completely dissolved, resulting in the formation of a 0.5 M solution of LiCl. Solution was transferred to an oven-dried and argon-cooled 125-mL ampoule via cannula for storage.

**General Procedure for the Synthesis of Weinreb Amides From Carboxylic Acids.** The procedure for the preparation of \( N \)-methoxy-\( N \)-methylbenzamide is representative. To a 50-mL RBF equipped with a stir bar was added benzoic acid (1.83 g, 15 mmol) followed by DCM (25 mL). To the stirring solution was added carbonyldiimidazole (2.67 g, 16.5 mmol) and the reaction was allowed to stir. After 20 min of stirring, \( N,O \)-dimethylhydroxylamine hydrochloride (1.76 g, 18 mmol) was added followed by pyridine (3.1 mL, 45 mmol). The reaction was allowed to stir and was monitored by TLC. Upon completion, the reaction was quenched with 3M HCl (30 mL). The organic layer was washed with 3M HCl (4 x 15 mL) and saturated NaHCO\(_3\) (4 x 15 mL), dried over magnesium sulfate, and concentrated under reduced pressure to yield the product as a pale oil.

![Chemical Structure](image)

**\( N \)-methoxy-\( N \)-methylbenzamide.** Clear oil (1.37 g, 83% yield). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 7.65 – 7.59 (m, 2H), 7.43 – 7.36 (m, 1H), 7.38 – 7.31 (m, 2H), 3.50 (s, 3H), 3.30 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 169.9, 134.1, 130.5, 128.1, 127.9, 60.9, 33.7.
**N-Methoxy-N,2-dimethylbenzamide.** Clear oil (1.52 g, 85% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.29 – 7.21 (m, 2H), 7.17 (d, $J = 7.4$ Hz, 2H), 3.45 (s, 5H), 3.34 – 3.21 (m, 4H), 2.31 (s, 3H). $^{13}$C NMR (CDCl$_3$): $\delta$ 135.2, 134.7, 130.1, 129.1, 126.1, 125.4, 61.0, 19.1.

**N-Methoxy-N,3,5-trimethylbenzamide.** Clear oil (1.52 g, 53% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.19 (s, 2H), 7.02 (s, 1H), 3.51 (s, 3H), 3.27 (s, 3H), 2.28 (s, 6H). $^{13}$C NMR (CDCl$_3$): $\delta$ 170.3, 137.4, 134.1, 132.0, 125.5, 60.8, 33.9, 21.1.

**N,4-Dimethoxy-N-methylbenzamide.** Yellow oil (2.26 g, 77% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.69 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 3.80 (s, 3H), 3.52 (s, 3H), 3.31 (s, 3H). $^{13}$C NMR (CDCl$_3$): $\delta$ 169.4, 161.5, 130.5, 126.0, 113.2, 60.9, 55.3, 33.9.
3-Bromo-N-methoxy-N,4-dimethylbenzamide. Orange oil (2.53 g, 62% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.91 – 7.85 (m, 1H), 7.57 – 7.52 (m, 2H), 7.28 – 7.22 (m, 2H), 3.55 (s, 3H), 3.34 (s, 3H), 2.42 (s, 3H). $^{13}$C NMR (CDCl$_3$): $\delta$ 167.61, 140.3, 131.8, 130.0, 126.9, 123.9, 121.6, 60.7, 33.2, 22.5.

4-Chloro-N-methoxy-N-methylbenzamide. Yellow oil (2.08 g, 70% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.62 – 7.55 (m, 2H), 7.32 – 7.27 (m, 2H), 3.45 (s, 2H), 3.27 (s, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ 168.5, 136.5, 132.2, 129.7, 128.1, 61.0, 33.4.

N-Methoxy-N-methyl-4-(trifluoromethyl)benzamide. Orange oil (3.50 g, 98% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.76 (d, $J$ = 8.0 Hz, 2H), 7.64 (d, $J$ = 8.0 Hz, 2H), 3.50 (s, 3H), 3.35 (s, 3H).
**N-Methoxy-N-methyl-4-nitrobenzamide.** Yellow oil (2.76 g, 87% yield). $^1$H NMR  
(CDCl$_3$): $\delta$ 8.27 (d, $J = 8.9$ Hz, 1H), 7.84 (d, $J = 8.9$ Hz, 1H), 3.53 (s, 3H), 3.40 (s, 3H).

**4-Cyano-N-methoxy-N-methylbenzamide.** Clear oil (1.31 g, 98% yield). $^1$H NMR  
(CDCl$_3$): $\delta$ 7.72 (d, $J = 8.3$ Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 3.48 (s, 3H), 3.32 (s, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 167.9, 138.3, 131.8, 128.8, 118.1, 114.1, 61.3, 33.2.

**Methyl 4-(methoxy(methyl)carbamoyl)benzoate.** White solid (0.777 g, 58% yield).  
$^1$H NMR (CDCl$_3$): $\delta$ $\delta$ 8.07 (d, $J = 8.3$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 3.94 (s, 2H), 3.53 (s, 3H), 3.37 (s, 3H).
N-Methoxy-N-methyloctanamide. Clear oil (0.47 g, 78% yield). $^1$H NMR (CDCl$_3$): δ 3.62 (s, 3H), 3.12 (s, 3H), 2.35 (t, $J$ = 7.6 Hz, 2H), 1.56 (p, 2H), 1.33 – 1.17 (m, 8H), 0.87 – 0.79 (m, 3H). $^{13}$C NMR (CDCl$_3$): δ 174.9, 61.2, 31.9, 31.7, 29.4, 29.1, 24.7, 22.6, 14.1.

5-Bromo-N-methoxy-N-methylnicotinamide. Yellow oil (1.63 g, 45% yield). $^1$H NMR (CDCl$_3$): δ 8.82 (d, $J$ = 1.8 Hz, 1H), 8.70 (d, $J$ = 2.3 Hz, 1H), 8.13 (t, $J$ = 2.1 Hz, 1H), 3.53 (s, 3H), 3.34 (s, 3H). $^{13}$C NMR (CDCl$_3$): δ 165.7, 152.5, 147.4, 138.7, 131.1, 120.2, 61.5, 33.1.

N-Methoxy-N-methylpicolinamide. Clear oil (1.12 g, 55% yield). $^1$H NMR (CDCl$_3$): δ 8.82 (d, $J$ = 4.1 Hz, 1H), 7.99 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.91 – 7.82 (m, 1H), 7.57 (dd, $J$ = 7.8, 4.9 Hz, 1H), 3.94 (s, 3H), 3.61 (s, 3H).
**N-Methoxy-N-methylthiophene-2-carboxamide.** Yellow oil (1.88 g, 73% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.89 (dd, $J = 3.8, 1.3$ Hz, 1H), 7.48 (dd, $J = 5.0, 1.3$ Hz, 1H), 7.02 (dd, $J = 5.0, 3.8$ Hz, 1H), 3.69 (s, 3H), 3.29 (s, 3H). $^{13}$C NMR (CDCl$_3$): $\delta$ 162.1, 134.2, 133.2, 132.2, 126.7, 61.4, 32.9.

**N-Methoxy-N-methylcyclohexanecarboxamide.** Clear oil (2.55 g, 88% yield). $^1$H NMR (CDCl$_3$): $\delta$ 3.65 (s, 3H), 3.13 (s, 3H), 2.64 (t, 1H), 1.79 – 1.68 (m, 4H), 1.68 – 1.59 (m, 1H), 1.49 – 1.39 (m, 2H), 1.32 – 1.15 (m, 3H). $^{13}$C NMR (CDCl$_3$): $\delta$ 61.7, 53.7, 40.2, 32.4, 29.2, 26.0.

**General Procedure for the Synthesis of Tertiary Amides From Carboxylic Acids.**

The procedure for the preparation of morpholino(phenyl)methanone is representative. To a 50-mL RBF equipped with a stir bar was added benzoic acid (1.83 g, 15 mmol) followed by DCM (25 mL). To the stirring solution was added carbonyldiimidazole (2.67 g, 16.5 mmol) and the reaction was allowed to stir. After 20 min of stirring, morpholine (1.55 mL, 18 mmol) was added. The reaction was allowed to stir and was monitored by TLC. Upon completion, the reaction was quenched with 3M HCl (30 mL). The organic layer was washed with 3M HCl (4 x 15 mL) and saturated NaHCO$_3$
(4 x 15 mL), dried over magnesium sulfate, and concentrated under reduced pressure to yield the product as a pale oil.

Morpholino(phenyl)methanone. White solid (1.51 g, 79% yield). $^1$H NMR (CDCl$_3$): δ 7.37 (s, 5H), 3.65 (br s, 4H), 3.40 (br s, 4H). $^{13}$C NMR (CDCl$_3$): δ 170.5, 135.4, 129.9, 128.6, 128.3, 127.2, 66.9, 48.3, 42.7.

1-Morpholino-4-phenylbutan-1-one. Clear oil (2.22 g, 96% yield). $^1$H NMR (CDCl$_3$): δ 7.27 (t, $J = 7.5$ Hz, 2H), 7.20 – 7.15 (m, 3H), 3.60 (br s, 4H), 3.34 (br s, 4H), 2.67 (t, $J = 7.5$ Hz, 2H), 2.29 (t, $J = 7.5$ Hz, 2H), 1.97 (p, $J = 7.5$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): δ 171.4, 141.6, 128.5, 128.4, 126.0, 66.9, 66.6, 45.9, 41.9, 35.3, 32.1, 26.6.

4-Benzylphenyl(morpholino)methanone. White solid (2.65 g, 94% yield). $^1$H NMR (CDCl$_3$): δ 7.48 – 7.43 (m, 2H), 7.28 (dd, $J = 8.2$, 6.8 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.19 – 7.15 (m, 2H), 3.99 (s, 2H), 3.53 (br s, 4H), 1.89 (t, $J = 6.9$ Hz, 4H). $^{13}$C NMR (CDCl$_3$): δ 170.6, 143.4, 140.5, 133.2, 129.2, 129.1, 128.7, 127.5, 126.5, 94.9, 67.0, 41.9.
4-Chlorophenyl(morpholino)methanone. Amber solid (3.22 g, 96% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.35 (dd, 4H), 3.66 (br s, 4H), 3.43 (br s, 4H). $^{13}$C NMR (CDCl$_3$): $\delta$ 169.4, 136.0, 133.7, 128.9, 128.7, 66.9, 48.4, 42.7.

4-Chloromethylphenyl(pyrrolidin-1-yl)methanone. White solid (2.54 g, 76% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.51 (d, $J = 8.2$ Hz, 2H), 7.41 (d, $J = 8.2$ Hz, 2H), 4.58 (s, 2H), 3.64 (t, $J = 7.0$ Hz, 2H), 3.41 (t, $J = 6.6$ Hz, 2H), 1.95 (p, $J = 6.9$ Hz, 2H), 1.87 (q, $J = 6.4$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 169.2, 139.1, 137.4, 128.6, 127.7, 49.7, 46.3, 45.8, 26.5, 24.6.

3-Bromo-4-methylphenyl(pyrrolidin-1-yl)methanone. Brown solid (3.99 g, 98% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.67 (d, $J = 1.7$ Hz, 1H), 7.33 (dd, $J = 7.8$, 1.7 Hz, 1H), 7.22 (d, $J = 7.8$ Hz, 1H), 3.59 (t, $J = 7.0$ Hz, 2H), 3.40 (t, $J = 6.6$ Hz, 2H), 2.37 (s, 3H), 1.92 (p, $J = 6.8$ Hz, 2H), 1.84 (p, $J = 6.6$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 168.1, 139.8, 136.3, 131.1, 130.6, 126.1, 124.7, 49.7, 46.4, 26.4, 24.5, 22.9.
**Pyrrolidin-1-yl(4-(trifluoromethyl)phenyl)methanone.** Yellow solid (1.19 g, 97% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.66 (d, $J = 8.2$ Hz, 2H), 7.61 (d, $J = 8.1$ Hz, 2H), 3.64 (s, 2H), 3.39 (s, 2H), 1.93 (s, 4H).

**4-Methoxyphenyl(pyrrolidin-1-yl)methanone.** White solid (1.98 g, 96% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.52 (d, $J = 8.9$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 3.83 (s, 4H), 3.63 – 3.52 (m, 3H), 1.99 – 1.84 (m, 3H).

**N,N-dimethyl-4-nitrobenzamide.** Yellow solid (1.79 g, 92% yield). $^1$H NMR (CDCl$_3$): $\delta$ 8.21 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 3.08 (s, 10H), 2.92 (s, 10H). $^{13}$C NMR (CDCl$_3$): $\delta$ 169.2, 148.2, 142.5, 128.1, 123.7, 39.3, 35.3.

**General Procedure for the Preparation of HMgCl from Grignard Reagents and Pinacolborane.** To an oven-dried and Ar cooled 25-mL round-bottom flask equipped with a magnetic stir bar and fitted with rubber septum was added anhydrous THF (4.0 mL) followed by pinacolborane (0.57g, 4.5 mmol). Isopropylmagnesium chloride (4.5 mL, 1M, 4.5 mmol) was added dropwise over 5 min at 25 °C with constant stirring.
The reaction was complete after one hour as evidenced by the disappearance of pinacolborane starting material ($\delta_B +28, d, J_{BH} = 174 \text{ Hz}$), and the appearance of a singlet at $\delta_B +31 \text{ ppm}$ via $^{11}\text{B-}\text{NMR}$. Note that no precipitate is formed in this reaction.

**General Procedure for Analysis of Hydridomagnesium Chloride Concentration by Gas Evolution Analysis.** A 50-mL round-bottom flask equipped with a magnetic stir bar and fitted with rubber septum was charged with anhydrous THF (3.45 mL) followed by pinacolborane (0.441 g, 0.5 mL, 3.45 mmol). To the solution was added isopropylmagnesium chloride (3.45 mmol, 1M/THF) dropwise over 5 min at 25 °C. The reaction was complete after 1 hour as evidenced by $^{11}\text{B-}\text{NMR}$ analysis. Aliquots from the supernatant (0.5 mL) were injected into the modified Hempel gas measuring device with a 1:1 quenching solution of H$_2$O/MeOH with constant stirring. The volume displaced by hydrogen gas was measured and converted to moles of hydrogen gas according to the ideal gas law (PV=nRT). The process was repeated eight times (Table 5.1).

**General Procedure for Reduction of Using HMgCl.** The following procedure for the preparation of benzyl alcohol is representative. To a 15-mL round-bottom flask equipped with a stir bar was added benzaldehyde (0.20 mL, 2 mmol) followed by THF (2 mL). To the stirred solution was added HMgCl (4 mL, 0.5M, 2 mmol). The reaction was allowed to stir and was monitored by TLC. The reaction was quenched with 1M HCl (4 mL). The aqueous phase was extracted with Et$_2$O (3 x 10 mL). The combined organic layers were dried over anhydrous MgSO$_4$, filtered, and
concentrated under reduced pressure to afford a mixture of benzyl alcohol and \(i\text{PrBPin.}\)

**General Procedure for the Preparation of Chloromagnesium Dimethylaminoborohydride, 1 M Solution in THF.** An oven-dried, argon-cooled 50-mL round-bottom flask equipped with a stir bar and septa was charged with an ethereal solution of MeMgCl (10.35 mL, 2.9M, 30 mmol) and cooled to 0 °C (ice bath). A 1.5M solution of dimethylamine-borane in THF (20 mL, 30 mmol) was added with stirring over a period of 40 min. After one hour of stirring, a 0.4 mL aliquot was taken for \(^{11}\text{B-NMR} \text{ analysis. The } ^{11}\text{B-NMR spectrum indicated formation of the chloromagnesium aminoborohydride product (} \delta_B \text{ -16, q, } J_{BH} = 83 \text{ Hz). The MgAB solution was then transferred to an oven-dried, argon-cooled ampoule via a cannula for storage. Note that, although the chemical shift of the corresponding amine-borane complex is close to that of the MgAB, the } J_{BH} \text{ values of dimethylamine-borane are 98 Hz.}**

**General Procedure for the Reduction of Weinreb Amides to Aldehydes with MgAB Purified by Bisulftite Adduct Formation.** The following procedure for the reduction of \(N\)-methoxy-\(N\)-methylbenzamide by MgAB is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a stir bar and septa was added \(N\)-methoxy-\(N\)-methylbenzamide (0.305 mL, 2 mmol) followed by THF (1.7 mL). Chloromagnesium dimethylaminoborohydride (MgAB, 2 mL, 1M, 2 mmol) was then added dropwise via a syringe. The reaction was monitored by TLC (Hex/EtOAc, 1:1). After 30 min, the reaction solution was added dropwise to a
solution of acetaldehyde (2 mmol) and acetic acid (2 mmol) in pentane (10 mL). After 15 min, saturated aqueous NH₄Cl (2 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et₂O (2 x 10 mL). The combined organic layers was washed with 1M HCl (10 mL), dried with magnesium sulfate, and concentrated under reduced pressure to yield crude aldehyde as an orange oil. The crude aldehyde (2 mmol) was transferred to a round-bottom flask equipped with a magnetic stir bar followed by EtOH (3 mL) and EtOAc (5 mL) and cooled with an ice bath. A saturated aqueous solution of NaHSO₃ (1 mL) was added with stirring. After 4 h, the solid bisulfite adduct was isolated by vacuum filtration, washed with Et₂O (3 x 5 mL) and dried under vacuum to yield a white solid. The bisulfite adduct was then added to a round-bottom flask dissolved in H₂O (10 mL) and a 37% formalin solution (2 mL) was added followed by Et₂O (20 mL). The biphasic solution was stirred for 1 h. The aqueous layer was separated and extracted with a 1:1 mixture of THF/Et₂O (3 x 10 mL). The combined organic layers was dried over magnesium sulfate, and concentrated under reduced pressure to give the aldehyde as a pale yellow oil (0.160 g, 75% yield). For other aldehydes prepared by this method see Table 5.2.

Benzaldehyde. Pale yellow oil (0.160 g, 75% yield). ¹H NMR (CDCl₃): δ 7.48–7.51 (m, 2H), 7.59–7.61 (m, 1H), 7.84–7.86 (m, 2H), 9.97 (s, 1H). ¹³C NMR (CDCl₃): δ 128.5, 129.0, 130.1, 134.5, 136.4, 192.4 ppm.
o-Tolualdehyde. Pale yellow oil (0.178 g, 74% yield). $^1$H NMR (CDCl$_3$): $\delta$ 2.68 (s, 3H), 7.24–7.26 (m, 1H), 7.33–7.36 (m, 1H), 7.44–7.48 (m, 1H), 7.77–7.79 (m, 1H), 10.25 (s, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ 19.7, 126.4, 131.8, 132.1, 133.7, 134.2, 140.7, 192.9 ppm.

3,5-Dimethylbenzaldehyde. Pale yellow oil (0.217 g, 81% yield). $^1$H NMR (CDCl$_3$): $\delta$ 2.39 (s, 6H), 7.26–7.27 (m, 1H), 7.48–7.50 (m, 2H), 9.95 (s, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ 21.1, 127.6, 136.3, 136.7, 138.8, 192.7 ppm.

p-Methoxybenzaldehyde. Yellow oil (0.223 g, 82% yield). $^1$H NMR (CDCl$_3$): $\delta$ 3.83 (s, 3H), 6.94–6.96 (d, $J = 8.8$ Hz, 2H), 7.78–7.79 (d, $J = 6.9$ Hz, 2H), 9.83 (s, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ 55.6, 114.3, 129.9, 132.0, 164.6, 190.8 ppm.

trans-Cinnamaldehyde. Yellow oil (0.185 g, 70% yield). $^1$H NMR (CDCl$_3$): $\delta$ 6.66–6.71 (dd, $J = 15.9$, 7.6 Hz, 1H), 7.39–7.42 (m, 3H), 7.46 (d, $J = 15.9$ Hz, 1H),
7.52–7.54 (m, 2H), 9.67 (d, J = 7.6 Hz, 1H). $^{13}$C NMR (CDCl$_3$): δ 128.5, 129.1, 131.3, 134.0, 152.9, 193.8 ppm.

3-Bromo-4-methylbenzaldehyde.$^{56}$ White solid (0.322 g, 81% yield). $^1$H NMR (CDCl$_3$): δ 2.44 (s, 3H), 7.35–7.37 (d, J = 7.7 Hz, 1H), 7.66–7.69 (d, J = 7.7 Hz, 1H), 7.99, (s, 1H), 9.87 (s, 1H). $^{13}$C NMR (CDCl$_3$): δ 23.5, 125.7, 128.5, 131.4, 133.5, 135.9, 145.2, 190.7 ppm.

o-Bromobenzaldehyde.$^{57}$ Pale yellow oil (0.274 g, 74% yield). $^1$H NMR (CDCl$_3$): δ 7.40–7.47 (m, 2H), 7.64 (m, 1H), 7.89–7.91 (m, 1H), 10.35 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ 122.5, 127.2, 128.0, 129.9, 133.5, 134.8, 192.0 ppm.

p-Chlorobenzaldehyde.$^{41}$ White solid (0.197 g, 70% yield). $^1$H NMR (CDCl$_3$): δ 7.49–7.51 (d, J = 8.4 Hz, 2H), 7.80–7.82 (d, J = 8.4 Hz, 2H), 9.97 (s, 1H); $^{13}$C NMR (CDCl$_3$) δ 129.6, 131.0, 134.8, 141.0, 190.9 ppm.
**p-Trifluoromethylbenzaldehyde.**\(^{41}\) Pale yellow oil (0.261 g, 75% yield). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.79–7.81 (d, \(J = 7.8\) Hz, 2H), 7.99–8.01 (d, \(J = 7.8\) Hz, 2H), 10.1 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 66.0, 126.2, 130.1, 138.8, 191.3 ppm.

![p-Trifluoromethylbenzaldehyde](image)

**Octanal.**\(^{41}\) Pale yellow oil (0.205 g, 80% yield). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.82–0.85 (t, \(J = 7.0\) Hz, 3H), 1.20–1.29 (m, 6H), 1.55–1.60 (m, 4H), 2.36–2.39 (t, \(J = 7.0\) Hz, 2H), 9.72 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 14.1, 22.2, 22.6, 29.1, 29.2, 31.7, 44.0, 202.9 ppm.

![Octanal](image)

**p-Cyanobenzaldehyde.**\(^{37}\) White solid (0.194 g, 74% yield). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.85 (d, \(J = 8.3\) Hz, 2H), 8.00 (d, \(J = 8.3\) Hz, 1H), 10.10 (s, 1H) ppm; \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 117.9, 130.1, 130.9, 132.6, 133.1, 190.9 ppm.

![p-Cyanobenzaldehyde](image)

**Methyl 4-formylbenzoate.**\(^{23}\) White solid (0.230 g, 70% yield). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.96 (s, 3H), 7.95 (d, \(J = 8.4\) Hz, 2H), 8.19 (d, \(J = 8.3\) Hz, 2H), 10.10 (s, 1H) ppm; \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 52.8, 129.7, 130.4, 135.3, 139.3 166.4, 191.8 ppm.
\[ \text{p-Nitrobenzaldehyde} \] Yellow solid (0.269 g, 89% yield). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 8.06–8.08 (d, \( J = 8.0 \) Hz, 2H), 8.36–8.38 (d, \( J = 8.8 \) Hz, 2H), 10.1 (s, 1H); \(^13\)C NMR (CDCl\(_3\)) \( \delta \) 124.4, 130.6, 140.1, 151.2, 190.5 ppm.

**General Procedure for the Reduction of Weinreb Amides to Aldehydes with MgAB, Isolated as Bisulfite Adducts.** The following procedure for the formation of the bisulfite adduct of 5-bromonicotinaldehyde is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a stir bar and septa was added 5-bromo-N-methoxy-N-methylnicotinamide (0.490 g, 2 mmol) followed by THF (1.7 mL). Chloromagnesium dimethylaminoborohydride (MgAB, 2 mL, 1 M, 2 mmol) was then added dropwise via a syringe. The reaction was monitored by TLC (Hex/EtOAc, 1:1). After 30 min, the reaction solution was added dropwise to a solution of acetaldehyde (2 mmol) and acetic acid (2 mmol) in pentane (10 mL). After 15 min, saturated aqueous NH\(_4\)Cl (2 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et\(_2\)O (2 × 10 mL). The combined organic layers was washed with 1M HCl (10 mL), dried with magnesium sulfate, and concentrated under reduced pressure to yield orange oil. To a round-bottom flask equipped with a magnetic stir bar was charged the crude aldehyde (2 mmol) followed by EtOH (3 mL) and EtOAc (5 mL) and cooled with an ice bath. A saturated aqueous solution of NaHSO\(_3\) (1 mL) was added with stirring. After 4 h, the solid bisulfite adduct was isolated by vacuum filtration, washed with Et\(_2\)O (3 × 5 mL) and dried.
under vacuum to yield a white solid (0.407 g, 70%). Thermal decomposition of the compounds prohibited melting point measurement, and elemental analysis gave unreliable results, as is typical of bisulfite adducts. For other adducts prepared by this method see Table 5.3.

**Sodium hydroxy(pyridin-2-yl)methanesulfonate.** White solid (0.296 g, 70% yield); mp 150 °C (dec). $^1$H NMR (D$_2$O): $\delta$ 5.66 (br s, 1H), 7.56 (t, $J$ = 6.6 Hz, 1H), 7.76 (d, $J$ = 8.0 Hz, 1H), 8.04 (m, 1H), 8.54 (d, $J$ = 5.2 Hz, 1H); $^{13}$C NMR (D$_2$O): $\delta$ 81.4, 121.4, 122.8, 138.3, 143.3 ppm; MS (ESI): m/z (M$^+$) calcd. for C$_6$H$_6$NNaO$_4$S 210.9915; peak not seen due to ion suppression.

**Sodium (5-bromopyridin-3-yl)(hydroxy)methanesulfonate.** White solid (0.407 g, 70% yield); mp 140 °C (dec). $^1$H NMR (D$_2$O): $\delta$ 5.73 (br s, 1H), 8.47 (t, $J$ = 2.0 Hz, 1H), 8.76 (d, $J$ = 1.9 Hz, 1H), 8.82 (d, $J$ = 2.2 Hz, 1H); $^{13}$C NMR (D$_2$O): $\delta$ 83.7, 121.8, 135.9, 141.5, 146.6, 150.4 ppm; MS (ESI): m/z (M$^+$) calcd. for C$_6$H$_6$BrNNaO$_4$S 288.9020; peak not seen due to ion suppression.
**Sodium hydroxy(thiophen-2-yl)methanesulfonate.** White solid (0.290 g, 67% yield); mp 155 °C (dec). $^1$H NMR (D$_2$O): $\delta$ 5.79 (br s, 1H), 7.67–7.77 (m, 1H), 7.90 (d, $J$ = 8.0 Hz, 1H), 8.19 (t, $J$ = 8.0 Hz, 1H). $^{13}$C NMR (D$_2$O): $\delta$ 102.0, 126.0, 127.0, 127.4, 146.8 ppm; MS (ESI): $m/z$ (M+) calcd. for C$_5$H$_5$NaO$_4$S 215.9527; peak not seen due to ion suppression. C$_5$H$_5$NaO$_4$S: C 27.78, H 2.33, S 29.66; found C 21.99, H 1.18, S 20.94.

**General Procedure for the Reduction of Amides to Aldehydes with MgAB, Purified by Alumina Column Chromatography.** The following procedure for the reduction of N-methoxy-N-methylbenzamide by MgAB is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a stir bar and septa was added N-methoxy-N-methylbenzamide (0.305 mL, 2 mmol) followed by THF (1.7 mL). Chloromagnesium dimethylaminoborohydride (MgAB, 2 mL, 1M, 2 mmol) was then added dropwise via a syringe. The reaction was monitored by TLC (Hex/EtOAc, 1:1). After 30 min, the reaction solution was added dropwise to a solution of acetaldehyde (2 mmol) and acetic acid (2 mmol) in pentane (10 mL). After 15 min, saturated aqueous NH$_4$Cl (2 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et$_2$O (2 x 10 mL). The combined organic layers was washed with 1M HCl (10 mL), dried with magnesium sulfate, and concentrated under reduced pressure to yield crude aldehyde as an orange oil. To a fritted column was added 25 g of aluminum oxide (basic alumina) in hexane slurry.
and covered by a thin layer of sand. The system was flushed with a 1:1 mixture of hexanes:ethyl acetate (solvent). The crude aldehyde was carefully applied to the sand and more solvent was dispensed. Fractions of 1-2 mL were analyzed via TLC. All relevant fractions were collected and dried over magnesium sulfate, and concentrated under reduced pressure to yield yellow oil. The combined organic layers was dried over magnesium sulfate, and concentrated under reduced pressure to give the aldehyde as a pale yellow oil (0.160 g, 75% yield). For other aldehydes prepared by this method see Table 5.4.

\[
\text{Benzaldehyde. Pale yellow oil (0.160 g, 75\% yield).}  
\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}): } \delta 7.48-7.51 \text{ (m, 2H), 7.59-7.61 (m, 1H), 7.84-7.86 (m, 2H), 9.97 (s, 1H).} \text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}): } \delta 128.5, 129.0, 130.1, 134.5, 136.4, 192.4 \text{ ppm.}
\]

\[
\text{Cyclohexanecarboxaldehyde. Clear oil (0.146 g, 65\% yield).}  
\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}): } \delta 9.55 \text{ (s, 1H), 2.17 (td, } J = 10.2, 4.2 \text{ Hz, 1H), 1.87 – 1.78 (m, 2H), 1.67 (dq, } J = 11.4, 3.8 \text{ Hz, 2H), 1.61 – 1.54 (m, 3H), 1.35 – 1.10 (m, 6H).} \text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}): } \delta 204.9, 50.0, 26.0, 25.0.
\]
**4-Phenylbutanal.** Clear oil (0.207 g, 70% yield). $^1$H NMR (CDCl$_3$): $\delta$ 9.76 (t, $J = 1.7$ Hz, 1H), 7.30 (t, $J = 7.4$ Hz, 2H), 7.20 (dd, $J = 16.2$, 7.1 Hz, 3H), 2.67 (t, $J = 7.6$ Hz, 2H), 2.46 (td, $J = 7.3$, 1.6 Hz, 2H), 1.97 (p, $J = 7.4$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 202.4, 141.3, 128.5, 126.2, 43.2, 35.1, 23.7.

**p-Chlorobenzaldehyde.** White solid (0.259 g, 92% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.49–7.51 (d, $J = 8.4$ Hz, 2H), 7.80–7.82 (d, $J = 8.4$ Hz, 2H), 9.97 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 129.6, 131.0, 134.8, 141.0, 190.9 ppm.

**4-Benzylbenzaldehyde.** Clear oil (0.290 g, 74% yield). $^1$H NMR (CDCl$_3$): $\delta$ 9.98 (s, 1H), 7.84 – 7.79 (m, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.34 – 7.30 (m, 2H), 7.26 – 7.22 (m, 1H), 7.21 – 7.18 (m, 2H), 4.07 (s, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 192.1, 148.6, 139.9, 134.8, 130.6, 130.2, 129.7, 129.2, 129.1, 128.8, 126.6, 42.2.
3-Bromo-4-methylbenzaldehyde. White solid (0.212 g, 53% yield). $^1$H NMR (CDCl$_3$): $\delta$ 2.44 (s, 3H), 7.35–7.37 (d, $J = 7.7$ Hz, 1H), 7.66–7.69 (d, $J = 7.7$ Hz, 1H), 7.99, (s, 1H), 9.87 (s, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ 23.5, 125.7, 128.5, 131.4, 133.5, 135.9, 145.2, 190.7 ppm.

$p$-Methoxybenzaldehyde. Yellow oil (0.164 g, 60% yield). $^1$H NMR (CDCl$_3$): $\delta$ 3.83 (s, 3H), 6.94–6.96 (d, $J = 8.8$ Hz, 2H), 7.78–7.79 (d, $J = 6.9$ Hz, 2H), 9.83 (s, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ 55.6, 114.3, 129.9, 132.0, 164.6, 190.8 ppm.

4-Chloromethylbenzaldehyde. White solid (0.175 g, 60% yield). $^1$H NMR (CDCl$_3$): $\delta$ 10.02 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 2H), 7.56 (d, $J = 7.8$ Hz, 2H), 4.63 (s, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 191.8, 144.0, 136.3, 130.3, 129.3, 45.5.
\( p\)-Nitrobenzaldehyde.\(^{37}\) Yellow solid (0.212 g, 70% yield). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 8.06–8.08 (d, \( J = 8.0 \) Hz, 2H), 8.36–8.38 (d, \( J = 8.8 \) Hz, 2H), 10.1 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 124.4, 130.6, 140.1, 151.2, 190.5 ppm.

**General Procedure for the Reduction of Amides to Alcohols with MgAB.** The following procedure for the reduction of phenyl(pyrrrolidin-1-yl)methanone is representative. To an oven-dried and argon-cooled 50-mL round-bottom flask equipped with a magnetic stirring bar and fitted with a rubber septum was added charged with phenyl(pyrrrolidin-1-yl)methanone (0.350 g, 2 mmol) followed by anhydrous THF (1.6 mL). To the stirred solution was added MgAB (2.5 mL, 1M, 2.5 mmol). After 3 hours of stirring, the reaction mixture was cooled to 0 °C and quenched by the slow addition of 3M HC1 (4 mL, 12 mmol) [Caution: Hydrogen evolution!]. The aqueous and organic fractions were separated and the aqueous fraction extracted with Et\(_2\)O (3 x 10 mL). The combined ethereal fractions were washed with 3M NaOH (3 x 10 mL), dried over MgSO\(_4\), and concentrated under reduced pressure to yield benzyl alcohol as a clear oil (0.180 g, 83%). For other alcohols prepared by this method see Table 5.5.
Benzyl alcohol. Clear oil (0.180 g, 83% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.26 – 7.13 (m, 5H), 4.43 (s, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 140.9, 128.4, 127.4, 126.9, 64.8.

Methyl 4-(hydroxymethyl)benzoate. Clear oil (0.306 g, 92% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.93 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.7$ Hz, 2H), 4.68 (s, 2H), 3.84 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.2, 146.2, 129.9, 129.9, 129.3, 126.6, 64.7, 52.2.

4-(Hydroxymethyl)benzonitrile. Clear oil (0.197 g, 74% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.57 (d, $J = 8.1$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 4.70 (s, 2H), 3.09 (s, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 146.6, 127.0, 118.9, 110.7, 63.9.

1-Octanol. Clear oil (0.211 g, 81% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.58 (q, $J = 6.2$ Hz, 2H), 2.14 (t, $J = 5.1$ Hz, 1H), 1.53 (p, $J = 6.8$ Hz, 2H), 1.37 – 1.17 (m, 10H), 0.85 (t, $J = 6.7$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 62.9, 32.9, 31.9, 29.5, 29.4, 25.9, 22.8, 14.2.
4-(Trifluoromethyl)phenylmethanol. Yellow oil (0.264 g, 75% yield). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.58 (d, $J = 8.3$ Hz, 1H), 7.42 (d, $J = 7.9$ Hz, 1H), 4.70 (s, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 144.8, 130, 126.9, 125.5, 123.2, 64.4.

**General Procedure for the Reduction of Lactams to Amines with MgAB.** The following procedure for the reduction of 4-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one is representative. To an oven-dried and argon-cooled 50-mL round-bottom flask equipped with a sidearm, stir bar, and condenser was added chloromagnesium dimethylaminoborohydride (MgAB, 7.5 mL, 1M, 7.5 mmol). To the solution, 4-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (0.816 g, 5 mmol) was added neat via syringe. The reaction mixture heated to reflux. After 2 h, the reaction was cooled to 0 °C (ice bath) and quenched by the slow addition of 3 M HCl (12 mL). (Caution! Hydrogen evolution!) The aqueous layer was then extracted with Et$_2$O (4 x 20 mL) and cooled to 0 °C (ice bath). To the aqueous, solid NaOH was added until basic to litmus, and the aqueous layer was extracted with Et$_2$O (4 x 20 mL). The organic fractions were combined, dried over MgSO$_4$, and concentrated under reduced pressure to give 4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine as a brown oil (0.599 g, 80% yield). For other amines prepared by this method see Table 5.6.
4-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine. Brown oil (0.599 g, 80% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.81 (t, $J = 7.7$ Hz, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 6.64 (d, $J = 7.1$ Hz, 2H), 4.22 (t, $J = 5.0$ Hz, 2H), 3.15 (t, $J = 5.0$ Hz, 2H), 2.80 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.3, 136.6, 121.4, 118.2, 115.9, 112.6, 49.1, 38.7.

$N$-Octyloxazoline. Clear oil (0.664 g, 72% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.51 – 2.43 (m, 2H), 2.43 – 2.35 (m, 2H), 1.80 – 1.73 (m, $J = 3.9$, 3.5 Hz, 5H), 1.49 (p, $J = 7.6$, 7.0 Hz, 3H), 1.33 – 1.19 (m, 16H), 0.86 (t, $J = 6.7$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 56.6, 54.1, 31.7, 29.5, 29.1, 28.9, 27.6, 22.5, 13.9.

$N$-Benzylpyrrolidine. Yellow oil (0.577 g, 72% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.34 – 7.26 (m, 3H), 7.24 – 7.19 (m, 2H), 3.59 (s, 2H), 2.52 – 2.45 (m, 4H), 1.76 (p, $J = 3.1$ Hz, 4H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 139.4, 128.9, 128.2, 126.9, 60.8, 54.2, 23.4.

General Procedure for the Preparation of Lithium Dimethylaminoborohydride, 1 M Solution in THF. To an oven-dried, argon-cooled 100-mL round-bottom flask equipped with a stir bar and septa was added dimethylamine-borane (2.95 g, 50 mmol), followed by anhydrous THF (27 mL) and cooled to 0 °C (ice bath). To the solution was added $n$-butyllithium (20 mL, 2.5 M, 50 mmol) dropwise via cannula
needle (**CAUTION**: gas evolution). After stirring at 0 °C for 1 hour, an aliquot was taken and analyzed by $^{11}$B-NMR which showed the solution to be lithium dimethylaminoborohydride ($\delta_B$ -16, q, $J_{BH} = 83$ Hz). The LAB reagent was transferred to an oven-dried, argon-cooled ampoule via a cannula needle. Note that, although the chemical shift of the corresponding amine-borane complex is close to that of the MgAB, the $J_{BH}$ values of dimethylamine-borane are 98 Hz.

**General Procedure for the Reduction of Amides to Aldehydes with Me-LAB, Purified by Bisulfite Adduct Formation.** The following procedure for the reduction of N-methoxy-N-methylbenzamide by Me-LAB is representative. To an oven-dried and argon-cooled 25-mL round-bottom flask equipped with a stir bar and septa was added N-methoxy-N-methylbenzamide (0.305 mL, 2 mmol) followed by THF (1.7 mL). Chloromagnesium dimethylaminoborohydride (Me-LAB, 2 mL, 1M, 2 mmol) was then added dropwise via a syringe. The reaction was monitored by TLC (Hex/EtOAc, 1:1). Upon completion, the reaction solution was added dropwise to a solution of acetaldehyde (2 mmol) and acetic acid (2 mmol) in pentane (10 mL). After 15 min, saturated aqueous NH$_4$Cl (2 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et$_2$O (2 x 10 mL). The combined organic layers was washed with 1M HCl (10 mL), dried with magnesium sulfate, and concentrated under reduced pressure to yield crude aldehyde as an orange oil. The crude aldehyde (2 mmol) was transferred to a round-bottom flask equipped with a magnetic stir bar followed by EtOH (3 mL) and EtOAc (5 mL) and cooled with an ice bath. A saturated aqueous solution of NaHSO$_3$ (1 mL) was added with stirring. After
4 h, the solid bisulfite adduct was isolated by vacuum filtration, washed with Et₂O (3 × 5 mL) and dried under vacuum to yield a white solid. The bisulfite adduct was then added to a round-bottom flask dissolved in H₂O (10 mL) and a 37% formalin solution (2 mL) was added followed by Et₂O (20 mL). The biphasic solution was stirred for 1 h. The aqueous layer was separated and extracted with a 1:1 mixture of THF/Et₂O (3 x 10 mL). The combined organic layers was dried over magnesium sulfate, and concentrated under reduced pressure to give the aldehyde as a pale yellow oil (0.160 g, 75% yield).

![Benzaldehyde](image)

**Benzaldehyde.** Pale yellow oil (0.160 g, 75% yield). $^1$H NMR (CDCl₃): δ 7.48–7.51 (m, 2H), 7.59–7.61 (m, 1H), 7.84–7.86 (m, 2H), 9.97 (s, 1H). $^{13}$C NMR (CDCl₃): δ 128.5, 129.0, 130.1, 134.5, 136.4, 192.4 ppm.

![Cyclohexanecarboxaldehyde](image)

**Cyclohexanecarboxaldehyde.** Clear oil (0.179 g, 80% yield). $^1$H NMR (CDCl₃): δ 9.55 (s, 1H), 2.17 (td, $J = 10.2, 4.2$ Hz, 1H), 1.87 – 1.78 (m, 2H), 1.67 (dq, $J = 11.4, 3.8$ Hz, 2H), 1.61–1.54 (m, 3H), 1.35–1.10 (m, 6H). $^{13}$C NMR (CDCl₃): δ 204.9, 50.0, 26.0, 25.0.
5.6 References


Unreported results. The amount of isolated aldehyde was not quantified.

Unreported results. The amount of isolated aldehyde was not quantified.


Molecular weight was determined through Ebulloscopic studies in THF.


Conclusion

Lithium aminoborohydrides (LAB reagents) are powerful, non-pyrophoric reducing agents that can reduce virtually all of the functional groups for which LiAlH₄ is now used. LAB reagents are safe and convenient reagents, and have been utilized in modern synthesis as chemoselective reducing agents. During investigations to probe the reactive properties of LAB reagents, it was discovered that dialkylaminoboranes were formed when LAB reagents are reacted with methyl iodide or trimethylsilyl chloride (TMS-Cl). Diisopropylaminoborane (H₂B-N(iPr)₂) is prepared as a monomer from the reaction of lithium diisopropylaminoborohydride with trimethylsilyl chloride at ambient conditions. Diisopropylaminoborane is stable in solution for long periods of time, upwards of one year. Monomeric aminoboranes, such as H₂B-N(iPr)₂, can reduce nitriles and esters in the presence of catalytic amounts of LiBH₄.

Chapter 2 described the reactivity of H₂B-N(iPr)₂ in the palladium-catalyzed borylation of aryl iodides, bromides and triflates. It was found that use of H₂B-N(iPr)₂ prepared in situ from lithium diisopropylaminoborohydride and TMS-Cl resulted in the highest yields of boronic acids. Diisopropylaminoborane served as an inexpensive boron source in the borylation reaction, affording the corresponding boronic acid upon work-up. Presence of LiBH₄ in the reaction caused precipitation of palladium metal, lowering yields of the desired products. After screening various palladium catalysts, palladium dichloride was found to be the most effective catalyst for the borylation of aryl iodides. Conversely, Pd₂dba₃CHCl₃ served as the best catalyst for
the borylation of aryl bromides and triflates. It was also discovered that the isolated product could be modulated depending on the work-up used. When the reaction is treated with an acid/base work-up, the corresponding boronic acid was isolated; while boronic esters were formed when the reaction mixture was quenched with neopentyl glycol. Isolation of the boronic acids from the reaction of $\text{H}_2\text{B-N(iPr)}_2$ with aryl iodides and bromides was accomplished in moderate to excellent yields. Unfortunately, aryl iodides and bromides were found to be intolerant of electron-withdrawing groups. Many of the functional groups not compatible with aryl iodides and bromides worked exceptionally well for the corresponding aryl triflate. Borylation of aryl triflates affords the corresponding boronic acids in high yields. Overall, a wide variety of boronic acids and esters have been synthesized from the corresponding aryl iodides, bromides, and triflates with moderate to excellent yields using $\text{H}_2\text{B-N(iPr)}_2$ and a palladium catalyst.

Chapter 3 described the reactivity of $\text{H}_2\text{B-N(iPr)}_2$ with various organometallic reagents. Reaction of $\text{H}_2\text{B-N(iPr)}_2$ with Grignard reagents resulted in the borylation of alkyl, aryl, and heteroaryl bromides. Use of $\text{H}_2\text{B-N(iPr)}_2$ resulted in high yields of the corresponding boronic acids. Organolithium reagents were found to be highly reactive with $\text{H}_2\text{B-N(iPr)}_2$, giving multiple products even under cryogenic conditions. Organozinc bromide reagents are similarly reactive, giving a mixture of boronic and borinic acids. Dialkylzinc reagents reacted with $\text{H}_2\text{B-N(iPr)}_2$ to afford the corresponding boronic acids upon work-up. A simple and mild borylation of aryl and alkyl halides with $\text{H}_2\text{B-N(iPr)}_2$ under mild Grignard and Barbier conditions has been
described. This borylation reaction can be carried out under Barbier conditions, where \( \text{H}_2\text{B-}N(i\text{Pr})_2 \) traps the in situ formed Grignard reagent from the corresponding organic halide and magnesium metal. Performing the borylation reaction under Barbier conditions allows the use of a simple one-pot procedure, and avoids the use of low temperatures and expensive transition metal catalysts. The reaction proceeded in excellent yields, affording a single addition product under mild conditions, and did not require an excess of the boron donor. The organo(diisopropylamino)borane product was easily hydrolyzed to the corresponding boronic acid. Although the borylation mechanism is not fully understood, evidence was provided that the reaction mechanism proceeds through two possible reaction pathways. In either pathway, a hydride is transferred from the organo(diisopropylamino)borohydride to \( ^{\dagger}\text{MgBr} \) to form \( \text{HMgBr} \) (Pathway A), or to the starting material \( \text{H}_2\text{B-}N(i\text{Pr})_2 \), to form bromomagnesium diisopropylaminoborohydride (Pathway B). Evidence suggests that the reaction proceeds mainly through Pathway A, as only 1.2 equivalents of \( \text{H}_2\text{B-}N(i\text{Pr})_2 \) is required for greater than 95% conversion to the organo(diisopropylamino)borane. During the mechanistic investigation, halomagnesium diisopropylaminoborohydride was identified as a byproduct and an analogue was subsequently synthesized from dimethylamine-borane and methylmagnesium chloride.

Chapter 4 described the reaction of \( \text{H}_2\text{B-}N(i\text{Pr})_2 \) in the preparation of symmetrical and unsymmetrical \( B,B \)-diorgano(diisopropylamino)boranes from reaction of organometallic reagents. Grignard reagents react twice to form symmetrical \( B,B \)-
diorgano(diisopropylamino)boranes. It was discovered that sterically hindered Grignard reagents are slow to add twice to the boron atom of H₂B-N(iPr)₂. This allowed for the preparation of unsymmetrical B,B-diorgano(diisopropylamino)boranes by the sequential reaction of a hindered Grignard reagent followed by subsequent reaction with an unhindered Grignard. Dialkylzinc reagents react only once with H₂B-N(iPr)₂. This allowed for an alternate route to prepare unsymmetrical B,B-diorgano(diisopropylamino)boranes by the sequential reaction of diethylzinc followed by subsequent reaction with a Grignard reagent. The boron atom of H₂B-N(iPr)₂ was found to be resistant to a third attack of an organometallic reagent, preventing access to trialkylboranes. The B,B-diorgano(diisopropylamino)boranes prepared were also resistant to further attack, necessitating conversion to the corresponding borinate ester. B,B-diorgano(diisopropylamino)boranes bearing aliphatic groups were readily converted to the corresponding borinate esters, whereas B,B-diorgano(diisopropylamino)boranes bearing aromatic groups are stable.

The fifth and final chapter described the synthesis and investigation of chloromagnesium dimethylaminoborohydride (ClMg⁺ [H₃B-NMe₂]⁻, MgAB) an analogue of the versatile LAB reagents, prepared by the reaction of dimethylamineborane with methylmagnesium chloride. Two magnesium hydride reagents were prepared and investigated for their reactive potential. HMgCl was prepared by the reaction of pinacolborane with isopropylmagnesium chloride. HMgCl was also shown to reduce Weinreb amides to aldehydes within three hours. This reagent was not
amenable to long term storage, and must be prepared prior to use. Reduction of amides with MgAB, followed by acidic aqueous work-up affords the corresponding alcohol. Reverse quench of the reaction mixture utilizing a sacrificial electrophile affords the crude aldehyde. MgAB was shown to reduce a series of tertiary amides to aldehydes, but was unreactive to sterically demanding amides. The aldehyde product was effectively isolated as the corresponding bisulfite adducts, which were stored, or unveiled to provide pure aldehydes. Conversely, the aldehydes were isolated through alumina column chromatography of the crude reaction material. MgAB exhibited a unique chemoselective profile, capable of reducing amides in the presence of a nitro group, a nitrile, an ester, and a conjugated double bond. MgAB is mild, safe, and complementary to reducing agents typically used to convert Weinreb amides to aldehydes. Contrary to HMgCl, solutions of MgAB were amenable to long-term storage under inert atmosphere. Similar to the analogous LAB reagent, MgAB was also shown to reduce N-alkyl lactams to the cyclic amine. The results of the amide reduction study with MgAB prompted an investigation into the reaction of lithium dimethylaminoborohydride with amides. Following the optimized protocol with Me-LAB allowed for the reduction of amides to aldehydes. This work demonstrates the broad reactivity of metal dimethylaminoborohydride reagents.
Appendix A
Spectra for Compounds in Chapter 2
MeO-\text{B(OH)}_2
B(OH)$_2$
B(OH)$_2$
B(OH)$_2$
$\text{C}_{6}\text{H}_{5}\text{B(OH)}_{2}$
$\text{B(OH)}_2$
F – B(OH)$_2$
F-B(OH)₂
3-Fluoro-4-ethylphenylboronic acid
made from 4-Iodo-2-fluoro-toluene
169.4 MHz MeOH-d4
Pulse Sequence: preset
B(OH)$_2$

NC

-40 ppm

Pulse sequence: great.
3-Cyanophenylboronic acid
made from 3-Iodobenzonitrile
125.7 MHz MeOH-d4
Pulse Sequence: s2pul
$\text{S} - \text{B(OH)}_2$
$\text{S} - \text{B(OH)}_2$
MeO-\[\text{phenyl}\]-B(OH)\(_2\)
MeO−B(OH)₂
MeO–B(OH)$_2$
B(OH)$_2$
$\text{B(OH)}_2$
Phenylboronic acid
B(OH)$_2$
\( \text{S} \rightarrow \text{B(OH)}_2 \)
MeO—C6H5—B(OH)2
MeO—B(OH)_2
MeO-$\textbf{C}_6\textbf{H}_4$-$\text{B(OH)}_2$
B(OH)$_2$
$\text{B(OH)}_2$
B(OH)$_2$
B(OH)$_2$
B(OH)$_2$
$\text{B(OH)}_2$
$\text{C}_6\text{H}_5\text{B(OH)}_2$
Cl-\[\text{B(OH)}_2\]
$\text{F} - \text{C}_6\text{H}_4 - \text{B(OH)}_2$
F\text{-}[\text{B(OH)}_2]
NC—C_B(OH)_2
p-cyanophenylboronic acid
made from p-cyanophenyl triflate
500 MHz MeOD
Pulse Sequence: presat
NC—\( \text{B(OH)}_2 \)
$\text{B(OH)}_2$
$\text{B(OH)}_2$
$\text{B(OH)}_2$
$\text{B(OH)}_2$
B(OH)$_2$
MeO

B

O
MeO–[B–O]–MeO
Appendix B
Spectra for Compounds in Chapter 3
\[ \text{H}_3\text{B} - \text{NMe}_2 + \text{MgCl} \]

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Appendix C
Spectra for Compounds in Chapter 4
Appendix D

Spectra for Compounds in Chapter 5
Bibliography


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