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Copper-catalyzed diboration of ketones: facile synthesis of tertiary α -Hydroxyboronate esters

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**Copper-Catalyzed Diboration of
Ketones: Facile Synthesis of
Tertiary α -Hydroxyboronate Esters**

By

Melissa McIntosh

Accepted in Partial Completion for the
Degree Master of Science

Moheb A. Ghali, Dean of the Graduate School

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MASTER'S THESIS

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Melissa McIntosh

February 19, 2010

**Copper-Catalyzed Diboration of
Ketones: Facile Synthesis of
Tertiary α -Hydroxyboronate Esters**

A Thesis

Presented to

The Faculty of

Western Washington University

In Partial Fulfillment

Of the Requirements for the Degree

Master of Science

By

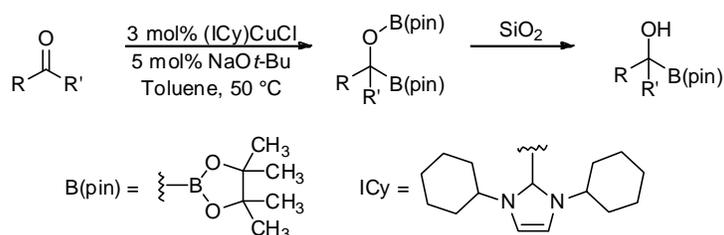
Melissa McIntosh

February 2010

Abstract

The versatility of the C–B bond in organic synthesis has led to extensive development of new methods for the selective incorporation of boron into organic substrates. The incorporation of boron substituents alpha to heteroatoms provides direct entry into substrates analogous to those formed and utilized in the Matteson homologation reaction. Our group has explored the diboration of various ketones using the (ICy)CuOt-Bu catalyst developed by Sadighi and co-workers. We found that (ICy)CuOt-Bu could be generated *in situ* using 3 mol % (ICy)CuCl and 5 mol% NaOt-Bu (Scheme 1). This catalyst system was shown to cleanly afford the diboration of various ketones in toluene at 50 °C over 2–22 hours. Treatment of the resulting products with SiO₂ provides the corresponding α -hydroxyboronate esters. Products derived from aryl ketones are prone to decomposition during isolation via silica gel chromatography. Protection of alcohols has been achieved in a two step one flask procedure using TBSOTf. Matteson homologation products have been obtained in low yields by homologation of TBS-protected alcohols.

Scheme 1



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Table of Contents

Abstract	iv
Acknowledgements	v
List of Figures and Tables	viii
List of Abbreviations	ix
Chapter 1. Diboration of Carbon Heteroatom Double Bonds	
1.1 Introduction	1
1.2 Diboration of Aldimines and Thiocarbonyls	3
1.3 Reduction of Carbon Dioxide, Leading to the Diboration of Aldehydes	6
1.4 Asymmetric Synthesis of α -Aminoboronate Esters	8
1.5 Summary and Conclusions	9
1.6 References	10
Chapter 2. Copper-Catalyzed Diboration of Ketones: Facile Synthesis of α -Heteroatom-Substituted Boronate Esters	
2.1 Introduction	13
2.2 Background	14
2.3 Results and Discussion	16
2.3.1 Synthesis of (IPr)CuOt-Bu (9a)	17
2.3.2 Synthesis of (ICy)CuOt-Bu (9b)	18
2.3.3 Synthesis of (IiPr)CuOt-Bu (9c)	19
2.3.4 NMR Scale Reactions	20
2.3.5 Isolation of Diboration Products	25
2.3.6 Protection of Alcohols	32
2.3.7 Matteson-Type Homologation Reactions	34

2.4	Summary and Conclusions	35
2.5	Experimental	36
2.5.1	Synthesis of (NHC)CuCl (8) and (NHC)CuO <i>t</i> -Bu (9)	37
2.5.2	Synthesis of Ketones	42
2.5.3	Diboration of Ketones monitored by ¹ H NMR Spectroscopy	42
2.5.4	Diboration of Ketones with <i>In Situ</i> Generated Catalyst	43
2.5.5	Isolation of Ketone Diboration Products	48
2.5.6	Vinyl Boronate Ester Synthesis	54
2.5.7	TBS Protection of Alcohols	55
2.5.8	Matteson Homologation Reactions	56
2.5.9	Hydrosilylation of Ketones	57
2.5.10	Reduction of Hydrosilylated Ketone	58
2.6	References	59

List of Figures

Figure 1.1	Suzuki Cross-Coupling Catalytic Cycle	1
Figure 1.2	Examples of α -Aminoboronate Esters and Boronic Acids	3
Figure 1.3	Proposed Mechanism for the Platinum-Catalyzed Diboration of Aldimines	5
Figure 1.4	DFT-Calculated Catalytic Cycle	7
Figure 2.1	<i>N</i> -Heterocyclic Carbene-Metal Complex	13
Figure 2.2	NHC Copper-Catalyst	16
Figure 2.3	Assignment of Stereochemistry	27
Figure 2.4	Conformational Isomers of 12d	28

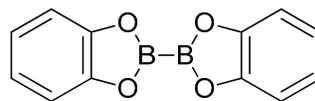
List of Tables

Table 1.1	Pt(cod)Cl ₂ -Catalyzed Diboration of Aldimines	4
Table 1.2	Copper-Catalyzed Diboration of Aldehydes	6
Table 1.3	Synthesis of Functionalized α -Aminoboronate Esters	8
Table 2.1	Determination of the Reactivity of Various Catalysts in Carbonyl Diboration	17
Table 2.2	Copper-Catalyzed Diboration of Ketones Monitored by ¹ H NMR Spectroscopy (eq 2.7)	21
Table 2.3	Examination of the Effects of Additives on the Diboration of Acetophenone	21
Table 2.4	Diboration Reactions Monitored by ¹ H NMR Spectroscopy	23
Table 2.5	Synthesis and Isolation of α -Hydroxyboronate Esters	26
Table 2.6	O–B Bond Cleavage Attempts	30

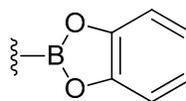
List of Abbreviations

Anal calcd	Analysis calculated
Bn	Benzyl
Boc	<i>t</i> -Butyloxycarbonyl
cod	Cyclooctadiene
CSA	Camphorsulfonic Acid
DHP	Dihydropyran
dr	Diastereomeric ratio
Et	Ethyl
GCMS	Gas chromatograph mass spectroscopy
HRMS	High resolution mass spectroscopy
Hz	Hertz
IR	Infrared
Me	Methyl
MHz	Mega hertz
MOM	Methoxymethyl
MP	Melting point
Ms	Methanesulfonyl (Mesyl)
n-BuLi	Normal butyllithium
NHC	<i>N</i> -Heterocyclic carbene
NMR	Nuclear magnetic resonance
Ph	Phenyl
Phe	Phenylalanine

TBS	<i>t</i> -Butyldimethylsilyl (also TBDMS)
TBSOTf	<i>tert</i> -Butyldimethylsilyltrifluoromethylsulfonate
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TES	Triethylsilyl
Tf	Trifluoromethylsulfonate
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMS	Tetramethylsilane
Ts	<i>p</i> -Toluenesulfonyl
B ₂ cat ₂	Bis(catecholato)diboron

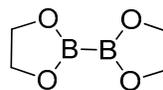


Bcat



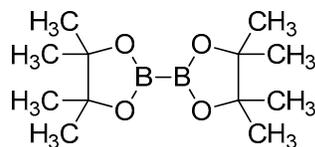
B₂eg₂

Bis(ethyleneglycolato)diboron

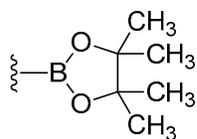


B₂pin₂

Bis(pinacolato)diboron

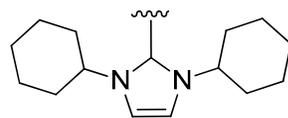


Bpin



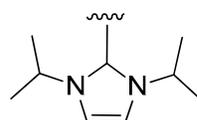
ICy

1,3-Dicyclohexylimidazol



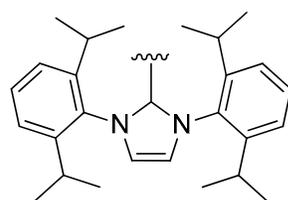
i-Pr

1,3-Diisopropylimidazol



IPr

1,3-Bis(2,6-diisopropylphenyl)imidazol



Chapter One

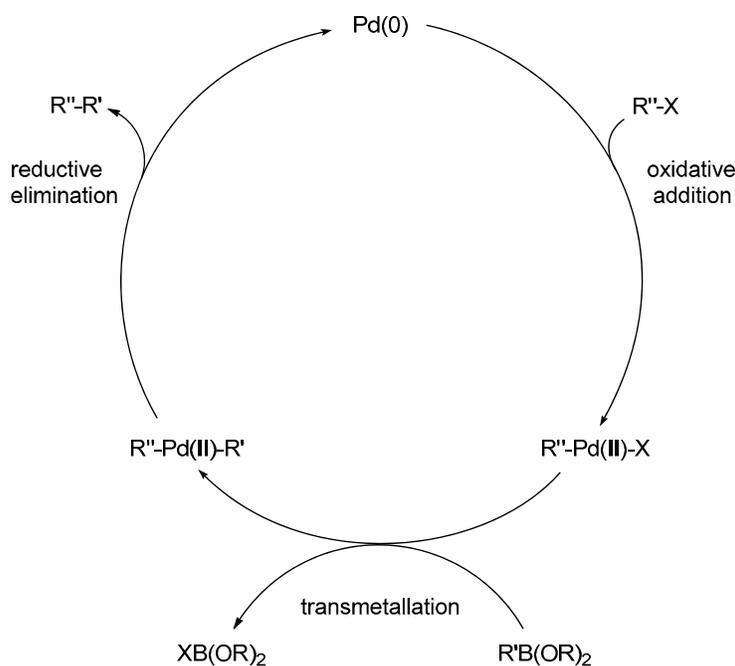
Diboration of carbon heteroatom double bonds

1.1. Introduction

The synthetic versatility of the carbon–boron bond makes organoboron complexes valuable reagents in organic synthesis.^{1–7} The most commonly utilized transformations of these bonds include oxidation to alcohols and the Suzuki-Miyaura coupling reaction (eq 1.1).¹ The Suzuki coupling involves an organohalide or pseudohalide being coupled with an organoboronate ester or boronic acid. The reaction mechanism is analogous to typical organometallic coupling reactions, involving oxidative addition, transmetalation, and reductive elimination (Figure 1.1).



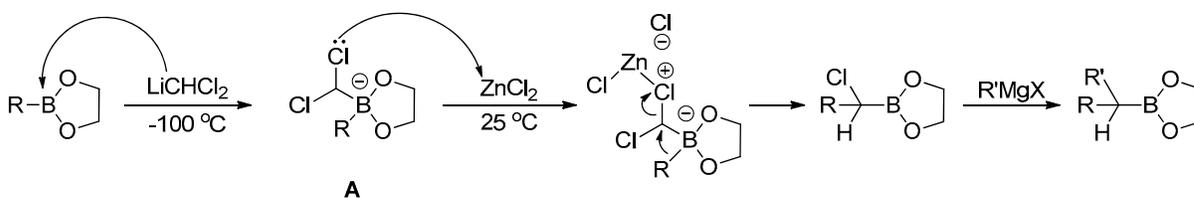
Figure 1.1. Suzuki Cross-Coupling Catalytic Cycle



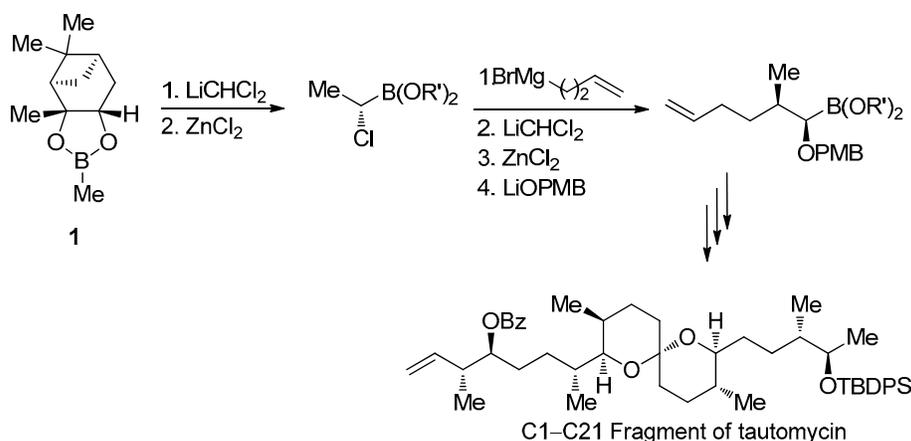
The Matteson homologation reaction is another synthetically useful tool that utilizes the carbon–boron bond (Scheme 1.1).^{2–5} Through these homologations the carbon–boron bond is transformed into a carbon–carbon bond, iteratively elongating the

carbon backbone of a molecule. The reaction proceeds by the addition of lithiated methylene chloride to the organoboronate ester to form intermediate **A**. A Lewis acid can then coordinate to a chlorine atom. Upon warming to room temperature the carbon–boron bond migrates, displacing the chloride to form a new carbon–carbon bond. The remaining isolable α -chloroboronate ester can then undergo nucleophilic displacement to form a second carbon–carbon bond. The Matteson homologation reaction can also use chiral boronate esters for asymmetric synthesis, including the synthesis of natural products.⁶ The C1–C21 fragment of tautomycin was synthesized, in part, by using several Matteson homologation sequences beginning with chiral pinanediol boronate ester **1** (Scheme 1.2).⁸ Tautomycin has pharmacological applications as an inhibitor of protein phosphatases.

Scheme 1.1. Matteson Homologation



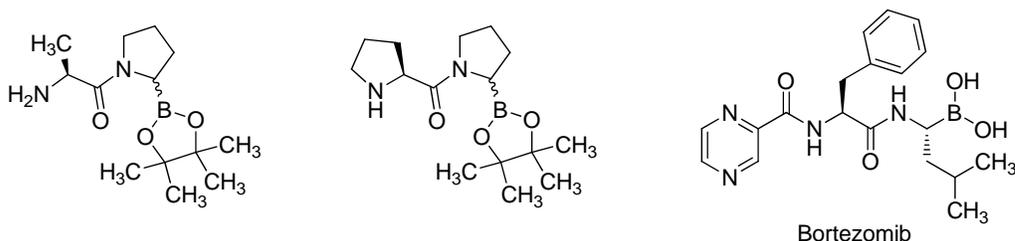
Scheme 1.2. Asymmetric Synthesis of Tautomycin



In addition to the synthetic utility of organoboronate esters, some boronic acids and boronate esters have biological activity and pharmaceutical applications.⁹⁻¹¹ Bortezomib, commercially known as Velcade[®], contains an α -amino boronic acid and is the first proteasome inhibitor to be tested in humans and approved by the FDA for the

treatment of two types of cancer (relapsed multiple myeloma and mantle cell lymphoma).¹⁰⁻¹¹ Boronic acids and boronate esters also have applications as immunosuppressants (Figure 1.2).⁹

Figure 1.2. Examples of α -Aminoboronate Esters and Boronic Acids



The preparation of boronic acids and boronate esters with control of regio-, diastereo-, and enantioselectivity has become possible via metal-catalyzed hydroboration and diboration of unsaturated substrates.¹²⁻¹³ This chapter discusses the various metal-catalyzed diborations of polarized double bonds performed prior to the work discussed in this thesis.

1.2. Diboration of Aldimines and Thiocarbonyls

Different types of metal catalysts can be used in the diboration of polarized double bonds. These reactions yield diborated products which can be isolated as synthetically useful α -heteroatom-substituted boronate esters. Aldimines, aldehydes and α,β -unsaturated ketones are a few examples of substrates that participate in metal-catalyzed diboration reactions.

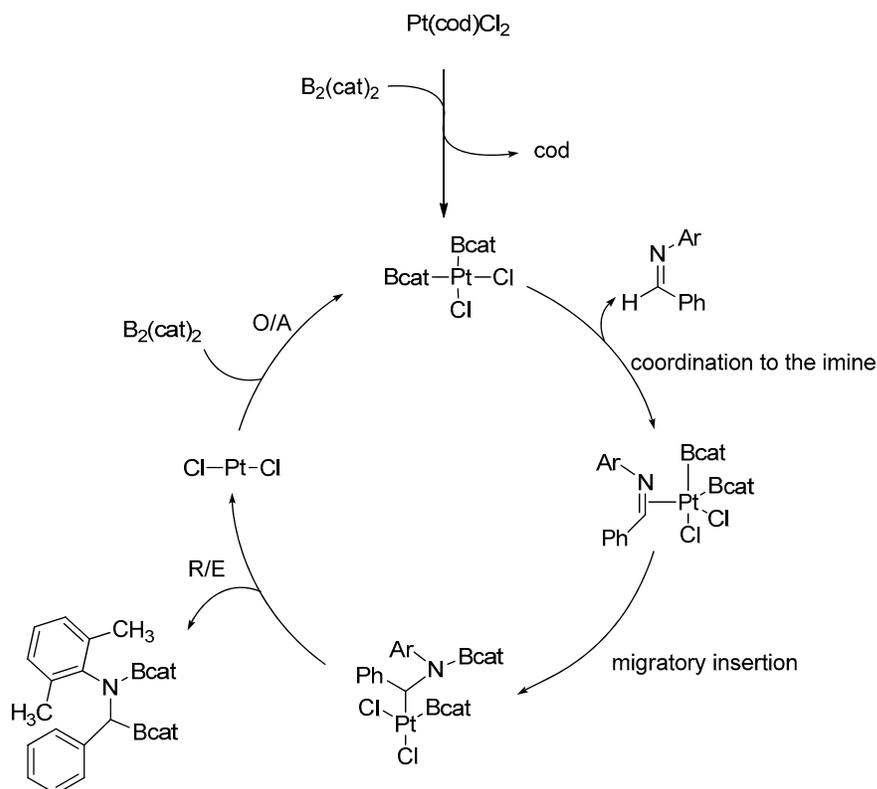
Baker et al. used commercially available $\text{Pt}(\text{cod})\text{Cl}_2$ as a precatalyst in the diboration of alkenes, alkynes, vinyl arenes, and aldimines. The diborated aldimine provided the first direct route to α -aminoboronate esters.¹² During optimization of the reaction, Baker and co-workers found that the catalyst effectiveness depended on the Pd-bound halide ligand, the diene, and the diboron reagent. The $\text{Pt}(\text{cod})\text{Cl}_2$ precatalyst and bis(catecholato)diboron provided the most general reaction scope, and aromatic substrates provided good to moderate yields (Table 1.1). Simple aliphatic aldimines, however, did not produce significant yields of the diborated product.

Table 1.1. Pt(cod)Cl₂-Catalyzed Diboration of Aldimines

substrate	product	% yield
		78
		95
		66

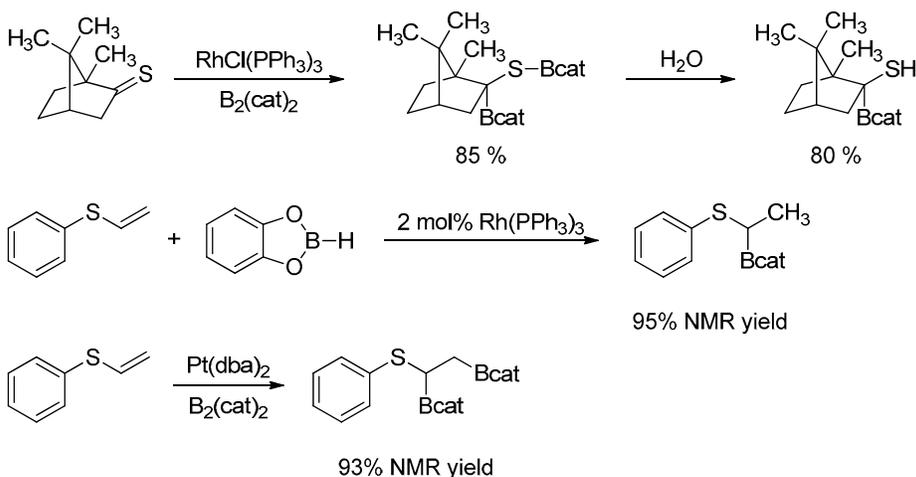
A mechanism for the platinum-catalyzed diboration of aldimines was proposed by Baker et al. (Figure 1.3). The mechanism involves oxidative addition of bis(catecholato)diboron to Pt(cod)Cl₂ to enter into the catalytic cycle. The imine then coordinates to the active catalyst species and undergoes migratory insertion. Reductive elimination then provides the desired aldimine and PtCl₂. A second equivalent of bis(catecholato)diboron can then add to the PtCl₂, regenerating the active catalyst.

Figure 1.3. Proposed Mechanism for the Platinum-Catalyzed Diboration of Aldimines



Baker and co-workers then used a rhodium catalyst in the diboration of thiocarbonyls (Scheme 1.3).¹³ Thiocarbonyls are much more reactive than carbonyls because of poor C=S orbital overlap, resulting in a weaker π bond. Baker developed three direct routes for the synthesis of α -thioboronate esters using hydroboration and diboration. Baker's group also used a platinum catalyst in the diboration of vinyl sulfides.

Scheme 1.3. Metal-Catalyzed Diboration and Hydroboration of Thiocarbonyl and Vinyl Sulfides



1.3. Reduction of Carbon Dioxide, Leading to the Diboration of Aldehydes

More recently, Sadighi and coworkers developed organocopper(I) complexes supported by *N*-heterocyclic carbene (NHC) ligands as pre-catalysts for copper(I) boryl complexes.¹⁴ They used [1,3-bis (2,6-di-isopropylphenyl) imidazol-2-ylidene]copper *tert*-butoxide (IPrCuOt-Bu) and bis(pinacolato) diboron in the reduction of CO₂ to CO and pinBOBpin under mild reaction conditions. The group then moved on to a less sterically hindered NHC (1,3-dicyclohexylimidazol-2-ylidene) copper complex (ICyCuOt-Bu) and achieved greater catalytic turnover.

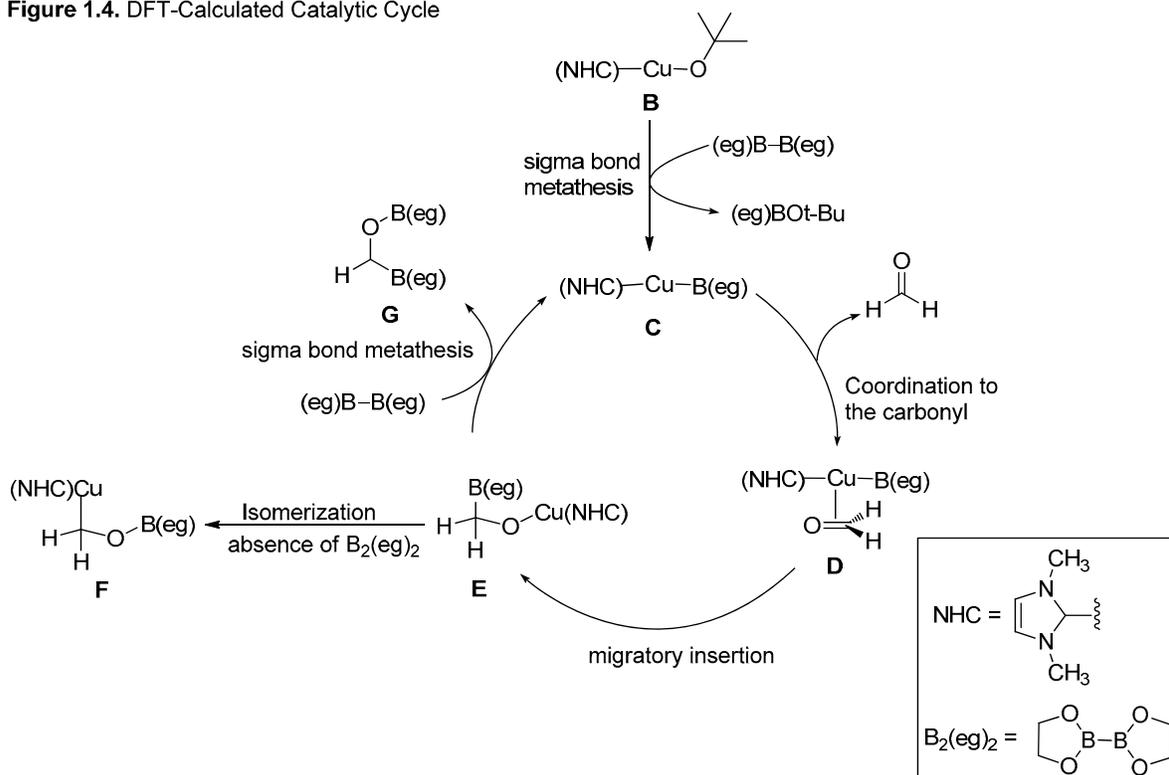
Sadighi also found the (ICy)CuOt-Bu was an active precatalyst for the diboration of aldehydes by a mechanism involving insertion into the copper–boron bond (Table 1.2).¹⁵ The reaction scope was found to be general, providing moderate to high yields with aryl, heteroaryl and alkyl aldehydes.

Table 1.2. Copper-Catalyzed Diboration of Aldehydes

pinB–Bpin + R-CHO		1 mol% (ICy)CuOt-Bu		R-CH(OBpin)-Bpin	
		C ₆ H ₆ , 22h, 22 °C			
entry	R =	% yield	entry	R =	% yield
1	C ₆ H ₅	88	8	2,4,6-Me ₃ C ₆ H ₂	73
2	4-MeOC ₆ H ₄	86	9	<i>n</i> -butyl	94
3	4-MeC ₆ H ₄	94	10	<i>iso</i> -butyl	95
4	4-BrC ₆ H ₄	80	11	<i>tert</i> -butyl	71
5	4-ClC ₆ H ₄	81	12	cyclohexyl	97
6	4-CF ₃ C ₆ H ₄	87	13	3-pyridyl	66
7	2-MeOC ₆ H ₄	91	14	2-thienyl	95

The catalytic cycle of copper-catalyzed diboration was studied by Zhao using DFT calculations (Figure 1.4).¹⁶ The precatalyst (NHC)CuOt-Bu (**B**) undergoes sigma bond metathesis with bis(ethyleneglycolato)diboron to produce the active catalyst species (**C**). The copper boryl complex will coordinate to the carbonyl to form **D** and undergo β -migratory insertion forming a copper–oxygen bond and a carbon–boron bond (**E**). A second diboron reagent can then react with the compound through sigma bond metathesis to generate the diborated product **G** and regenerate the active catalytic species **C**. The mechanism reported by Zhao is similar to what Sadighi had proposed, with one exception. After the migratory insertion step Sadighi was able to isolate a thermodynamically stable intermediate **F**. Zhao and co-workers found that **F** did not take part in the catalytic cycle and was obtained by an isomerization that occurs in the absence of the diboron reagent. When the diboron is present, as it is during catalytic conditions, **E** does not isomerize and remains in the catalytic cycle.

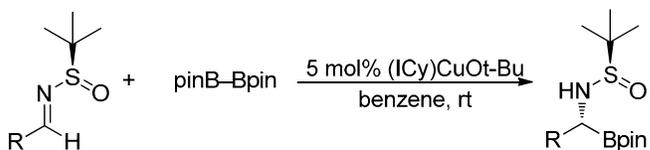
Figure 1.4. DFT-Calculated Catalytic Cycle



1.4. Asymmetric Synthesis of α -Aminoboronate Esters

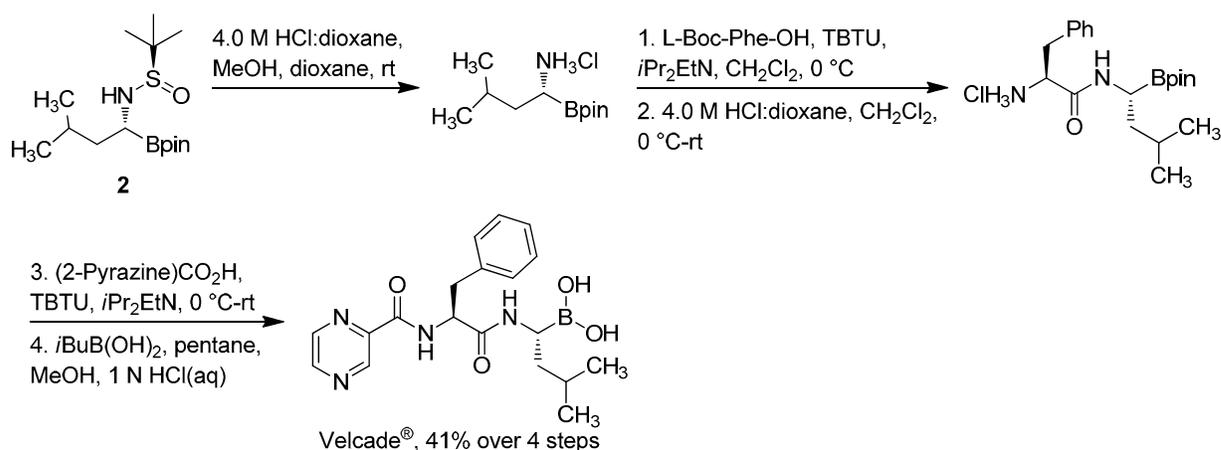
Beenen and Ellman developed the first asymmetric addition of diboron to a carbon–heteroatom double bond using Sadighi’s catalyst (Table 1.3).¹⁷ The group first attempted the diboration of *tert*-butanesulfinyl aldimines using the platinum catalyst reported by Baker. The low yields and selectivity led to the application of Sadighi’s catalyst to these chiral imines. Under these reactions conditions, moderate to high yields and good diastereoselectivity (Table 1.3) were obtained. The reaction was not sensitive to sterics or electronics and addition to aromatic aldimines could be achieved at 0 °C with higher catalyst loading. α -Aminoboronate ester **2** (entry 1, Table 1.3) was used in the asymmetric synthesis of Velcade[®] (Bortezomib), providing this valuable pharmaceutical agent in 41% yield over 4 steps from **2** (Scheme 1.4).

Table 1.3. Synthesis of Functionalized α -Aminoboronate Esters



entry	R	% yield	dr
1	(CH ₃) ₂ CHCH ₂ -	74	> 98:2
2	PhCH ₂ -	59	> 98:2
3	PhCH ₂ CH ₂ -	70	99:1
4	(CH ₃) ₂ CH-	88	> 98:2
5	cyclohexyl-	81	97:3
6	(CH ₃) ₃ C-	75	96:4
7	Ph-	54	99:1
8	4-methoxyphenyl-	57	> 98:2
9	4-chlorophenyl-	61	99:1
10	2-chlorophenyl-	52	> 97:3
11	4-(CF ₃)-phenyl-	66	95:5
12	TBDPSOCH ₂ -	75	> 99:1

Scheme 1.4. Asymmetric Synthesis of Velcade®



1.5. Summary and Conclusions

Complexes containing boronic acids and boronate esters are important intermediates in organometallic and organic syntheses, and can also have important biological applications. These acids and esters have been used in Matteson homologation and Suzuki coupling reactions to form new carbon–carbon bonds. Chiral boronate esters can be utilized in the asymmetric synthesis of natural products such as in the synthesis of the C1–C21 fragment of tautomycin (Scheme 1.2). Bortezomib (Figure 1.2) is an example of a boron-containing molecule that is currently used in cancer treatment.

The discovery of new α -heteroatom-substituted boronate esters is limited by the number of methods that are currently known for their synthesis. The method used by Sadighi and co-workers can be utilized in the diboration of other polarized double bonds to provide α -heteroatom-substituted boronate esters. The synthetic utility of these diborated products in Matteson homologation has not yet been explored.

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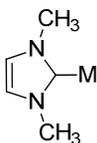
Chapter Two

Copper-Catalyzed Diboration of Ketones: Facile Synthesis of α -Heteroatom-Substituted Boronate Esters

2.1. Introduction

Over the past 3 decades *N*-heterocyclic carbenes (NHC) have emerged as valuable ligands in organometallic chemistry and are heavily utilized due to their unique stability (Figure 2.1).¹⁻⁴ These carbene compounds have two types of electronic stabilization. The nitrogens can donate electron density through resonance into the empty p orbital of the carbene carbon, resulting in a nucleophilic carbene. Alternatively, the nitrogens can withdraw electron density, through inductive effects, from the carbene carbon, making the carbene electrophilic.¹

Figure 2.1. *N*-Heterocyclic Carbene-Metal Complex



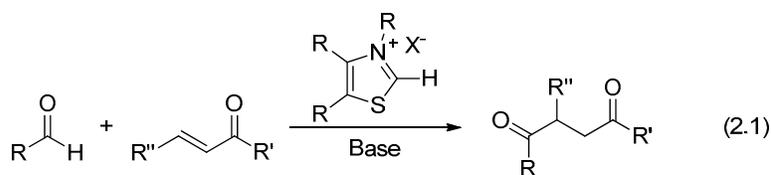
In addition to the electronic stabilization from the nitrogen atoms their stability has been postulated to originate from steric effects, kinetic effects, π interactions, the large triplet to singlet gap (~ 80 kcal/mol) in imidazol-2-ylidenes, and other electronic effects.¹⁻⁵ The ability to synthesize thiazol-2-ylidenes shows that nitrogen can be replaced with other heteroatoms and still produce stable carbenes.⁵ Unsaturated NHC complexes have also been formed, demonstrating that the π interactions from the imidazole are not vital for carbene stabilization.⁴ The production and isolation of stable

unencumbered imidazol-2-ylidenes show that steric effects are not necessary for the production of stable NHC's. Nitrogen-bound bulky substituents, however, do increase the stability of these NHC's which has resulted in numerous examples of potential NHC's to use as either ligands or catalysts.

2.2. Background

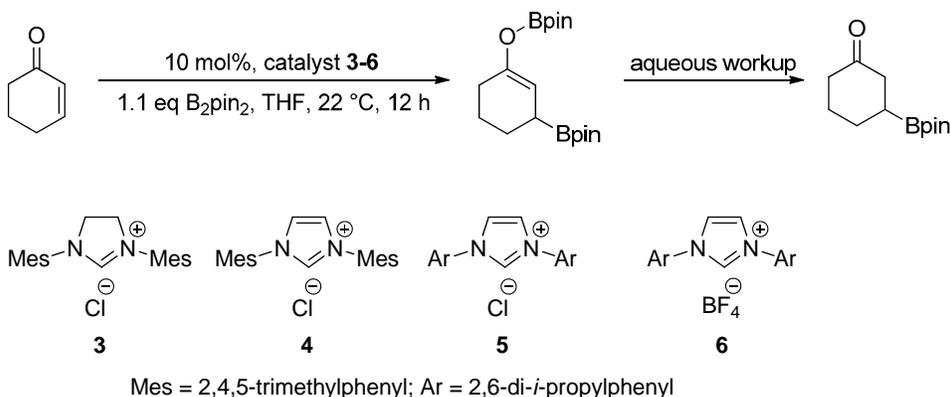
The ability for NHC's to act as organocatalysts or ligands in organometallic catalysis, make these molecules useful tools in organic synthesis. As organocatalysts, NHC's are strong nucleophiles and can promote unique organic transformations. In organometallic catalysis, NHC's serve as good sigma donors which results in unique reactivity for the attached electron rich metal.

Thiazolium based carbenes can be used as organocatalysts in the addition of aldehydes to activated double bonds (eq 2.1).⁵ A quaternary thiazolium salt in the presence of a base forms an ylide which can activate the aldehyde to nucleophilically add to enones. Thiazolium salts can be employed as catalysts for addition of aliphatic, aromatic, and heterocyclic aldehydes to α,β -unsaturated ketones, esters, nitriles, and phenyl vinyl sulfones. The resulting products include γ -diketones, 4-oxocarboxylic esters, and 4-oxonitriles respectively. *N*-benzylated thiazolium salts work best for aliphatic aldehydes, whereas *N*-alkylated thiazolium salts are ideal for aromatic aldehydes. Both types of catalyst are adequate for heterocyclic aldehydes. Triethylamine and sodium acetate were the most suitable bases for these types of reactions. Similar catalytic activity was seen with other azolium salts such as benzimidazolium salts and benzo and naphtho [2,1-d]thiazolium salts.



Hoveyda and coworkers found that a simple NHC could be used as an effective catalyst for the conjugate addition of bis(pinacolato)diboron to α,β -unsaturated carbonyl complexes (Scheme 2.1).⁶ Cyclic and acyclic α,β -unsaturated ketones or esters underwent the conjugate addition reaction with 2.5–10 mol% of the NHC catalyst. This process was also explored using a copper variant of the catalyst supported by NHC ligands. The copper-catalyzed reactions also afforded the boron enolate products, but showed less functional group tolerance and site-selectivity than the NHC-catalyzed reactions.

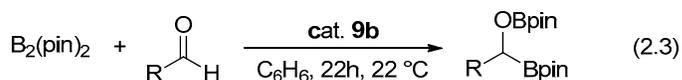
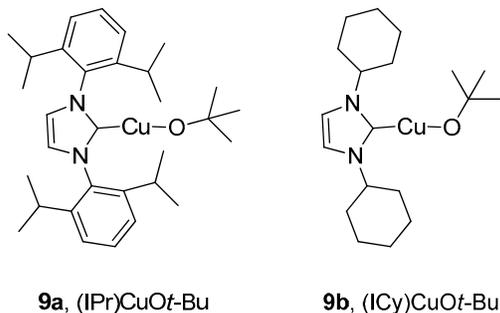
Scheme 2.1. Conjugate Addition of B_2pin_2 to α,β -Unsaturated Carbonyl Compounds



N-Heterocyclic carbenes have proven to be efficient ligands in metal and non metal-mediated reactions. One example of an NHC-bound catalyst was reported by Sadighi and coworkers, in which bulky, electron rich NHC's were used to synthesize copper catalyst **9a** and **9b** (Figure 2.2).⁷⁻⁸ The NHC complex containing the larger substituents (**9a**) proved to be more stable. The increased stability of **9a** decreased the

reactivity of the complex toward the diboration of aldehydes, so **9b** was used to obtain efficient catalysis. The development of **9b** for the diboration of aldehydes provided the general reaction conditions of 22 hours at 22 °C (eq 2.3).

Figure 2.2. NHC Copper-Catalyst



This chapter discusses the copper-catalyzed diboration of ketones using Sadighi's *N*-heterocyclic carbene catalyst.⁷ The diboration of ketones was accomplished using the well-defined catalyst and an *in situ*-formed catalyst; increased reaction rates and conversion to products was observed with the *in situ*-formed catalyst.⁹

2.3. Results and Discussion

Copper-catalysts supported by *N*-heterocyclic carbene ligands are necessary to perform the diboration reactions discussed in this thesis. These catalysts are not commercially available, requiring their synthesis. [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper *tert*-butoxide {(IPr)CuOt-Bu, **9a**}, [1,3-dicyclohexylimidazol-2-ylidene]copper *tert*-butoxide {(ICy)CuOt-Bu, **9b**}, and [1,3-diisopropylimidazol-2-ylidene]copper *tert*-butoxide {(IiPr)CuOt-Bu, **9c**} were

synthesized from their corresponding imidazolium salts following the general procedure provided by Sadighi et al.⁷

2.3.1. Synthesis of (IPr)CuOt-Bu (**9a**)

The first NHC-copper complex synthesized in this study was (IPr)CuOt-Bu (eq 2.4).⁷ The synthesis was a two-step process starting from the imidazolium salt. A ¹H NMR spectra of **9a** matched the reported spectral data. The known diboration of *p*-tolualdehyde was performed using (IPr)CuOt-Bu showing 80% conversion after about two days (Table 2.1, entry 1). (IPr)CuOt-Bu was shown to be less reactive than (ICy)CuOt-Bu in the diboration of aldehydes reported by Sadighi,⁸ so the synthesis of (ICy)CuOt-Bu was pursued.

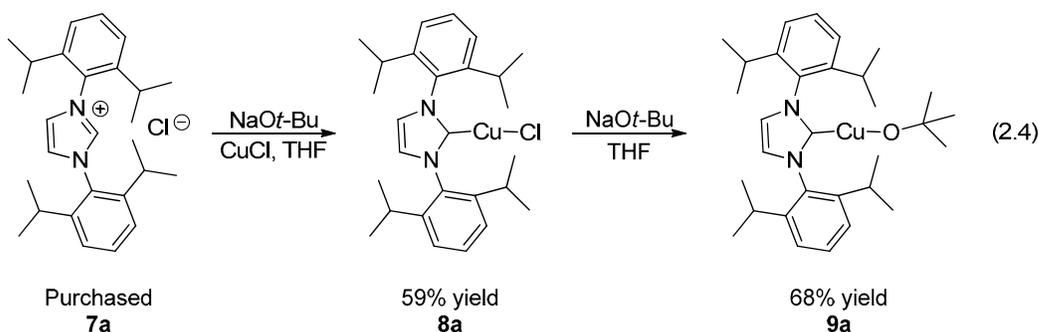


Table 2.1. Determination of the Reactivity of Various Copper Catalysts in Carbonyl Diboration

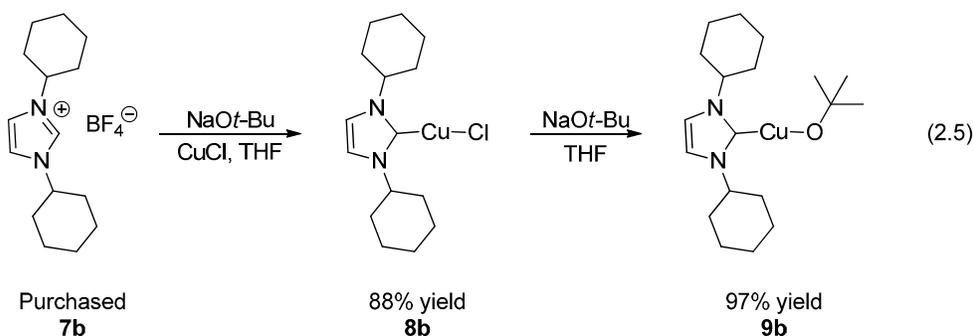
Entry	Catalyst	mol %	Substrate	Parameters	Conversion
1	(IPr)CuOt-Bu (9a)	1	<i>p</i> -tolualdehyde	18.5 h 22 °C, 24.5 h 50 °C	80%
2	(ICy)CuOt-Bu (9b)	1	<i>p</i> -tolualdehyde	2 h 22 °C	100%
3	(<i>li</i> -Pr)CuOt-Bu ^a (9c)	1	<i>p</i> -tolualdehyde	2 h 22 °C, 19 h 50 °C	41%
4	(<i>li</i> -Pr)CuOt-Bu ^a (9c)	2.3	Acetophenone	20 h 50 °C, 24 h 80 °C	0
5	(ICy)CuOt-Bu (9b)	2.3	Acetophenone	70 h 70 °C	90%
6	(ICy)CuOt-Bu (9b)	1	Acetophenone	24 h 70 °C ^b	< 10%

^a Pure catalyst could not be obtained. ^bReaction was run with double the concentration of each reagent.

2.3.2. Synthesis of (ICy)CuOt-Bu (**9b**)

1,3-dicyclohexylimidazolium chloride (**7d**) was not commercially available, so the compound was synthesized. Synthesizing this imidazolium salt proved difficult, and the method used by Herrmann et al.¹⁰ was modified to get a clean imidazolium salt. The imidazolium salt was very hygroscopic and would turn into a honey-like substance when in contact with filter paper. Because of the hygroscopic nature of the salt, much of the product was lost during attempts to recrystallize it. To obtain a dry salt, the product was left on high-vacuum overnight and then transferred into the glovebox. Addition of the imidazolium salt to copper (I) chloride (eq 2.5) resulted in irreproducible product formation, which was indicated by the different colors of products (red, green, yellow) that were isolated. Regardless of the color, ¹H NMR spectra of **8b** suggested the product was pure. These results indicate the presence of a highly colored impurity that is not active in ¹H NMR spectroscopy. When the next step was attempted, the highly colored sources of **8b** resulted in **9b**, which was plagued by numerous impurities (Table 2.1, entry 4). Around this time, 1,3-dicyclohexylimidazolium tetrafluoroborate (**7b**) became commercially available and was obtained for the synthesis of the copper chloride complex. The copper chloride species was synthesized from the clean, dry imidazolium salt using a modified procedure developed by Ellman and Beenen.¹¹ A clean light yellow copper chloride complex was acquired. The final step in synthesizing **9b** (addition of NaOt-Bu) with this lightly colored copper chloride species worked well and was reproducible (eq 2.5). A small amount of impurities were seen in the product by ¹H NMR spectroscopy, but the known diboration of *p*-tolualdehyde with the newly made (ICy)CuOt-Bu proceeded to completion in 2 hours at room temperature (Table 2.1, entry

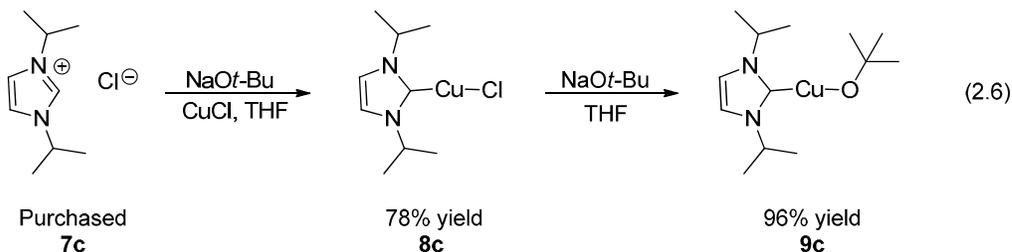
2). The diboration of acetophenone was also examined using this catalyst, providing 90% completion after 70 hours at 70 °C (Table 2.1, entry 6). Even though the catalyst was stored in the freezer at -30 °C, it showed clear signs of degradation after about a month with almost complete loss of catalytic activity. A ^1H NMR spectra was taken of the catalyst, and compared to the original ^1H NMR spectra, which showed that degradation had occurred. Entries 7 and 8 in Table 2.1 show the lack of activity of (ICy)CuOt-Bu (**9b**) after it had degraded.



2.3.3. Synthesis of (IiPr)CuOt-Bu (**9c**)

1,3-di-isopropyl imidazolium chloride (**7c**) is commercially available, but could prove more cost-effective to synthesize. The synthesis, however proved difficult, exhibiting many of the same problems encountered during the synthesis of 1,3-dicyclohexylimidazolium chloride (**7d**). After failing to synthesize a clean imidazolium salt with various trials using different methods, the imidazolium salt was purchased. The purchased imidazolium salt was then used following equation 2.6 to produce an impure catalyst as shown by ^1H NMR spectroscopy. The known diboration of *p*-tolualdehyde was then attempted giving only 41% conversion after 21 hours (Table 2.1, entry 3). The related saturated isopropyl complex is thermally unstable, so it is assumed that the

unsaturated species is thermally unstable as well, resulting in catalyst degradation under the reaction conditions. No further attempts were made to purify this catalyst to determine if increased catalytic activity could be achieved.



2.3.4. NMR Scale Reactions

The well-defined copper catalyst (**9b**) described by Sadighi⁷ was used in the diboration of ketones (eq 2.7). These NMR reactions were run using 1–2.3 mol% catalyst in deuterated benzene and monitored by ¹H NMR spectroscopy. The diboration of acetophenone was performed by analogy to the conditions developed by Sadighi with aldehydes. After 70 hours at 70 °C, 90% conversion of acetophenone to diboration product was observed (Table 2.2). Increased reaction temperatures resulted in decreased conversion, presumably due to catalyst decomposition. The diboration of 3-pentanone was also examined, but no reaction was observed at 70 °C.

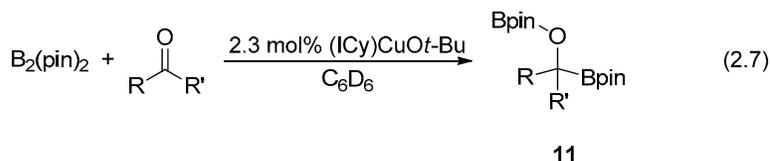
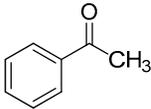
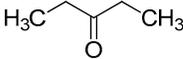
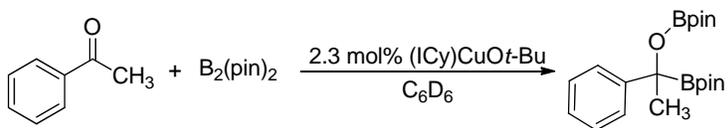


Table 2.2. Copper-Catalyzed Diboration of Ketones Monitored by ^1H NMR Spectroscopy (eq 2.7)

Ketone	Parameters	% Conversion
	70 h, 70 °C	90
	2.5 h, 70 °C	0

The diboration of acetophenone using **9b** was optimized using various additives. Because the catalyst is highly sensitive to water, we postulated that adventitious water may cause the loss of catalyst activity. Addition of common drying agents (entries 3–6, Table 2.3) did not improve the catalyst turnover, and in the case of mol sieves and MgSO_4 , shut down the reaction completely. The use of basic additives in the reaction proved to be the most effective at improving the reaction rate. Sodium bicarbonate provided the highest conversion (85%) after 68 hours at 50 °C, but addition of other amphiphilic bases did not improve conversion (Table 2.3).

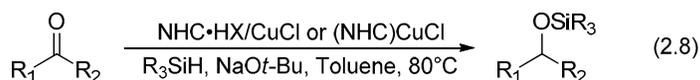
Table 2.3. Examination of the Effects of Additives on the Diboration of Acetophenone



11a

Entry	Additive	Parameters	% Conversion
1	None	70 h 70 °C	90
2	None	68 h 50 °C	71
3	Crushed 3 Å mol sieves	17 h 70 °C	0
4	MgSO_4	20 h 50 °C	0
5	Na_2SO_4	22 h 70 °C, 68 h 50 °C	19
6	K_2CO_3	68 h 50 °C	59
7	NaO_2CCH_3	68 h 50 °C	46
8	NaHCO_3	68 h 50 °C	85
9	KHP	6 d 70 °C, 7 d 50 °C	53
10	$\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$	22 h 70 °C	0

The diboration of ketones using **9b** proved difficult. While researching options for improving the catalytic system, literature on the *in situ* formation of the copper catalyst was found.¹² Nolan and coworkers were able to use *in situ*-formed catalyst, analogous to Sadighi's, in the hydrosilylation of ketones (eq 2.8). The catalyst could be formed *in situ* from the combination of the corresponding imidazolium salt, copper chloride, and sodium *tert*-butoxide in the reaction flask. Alternatively, the active catalyst could be generated starting with the (NHC)CuCl species in the presence of sodium *tert*-butoxide. Nolan et al. performed these reactions at elevated temperatures using 3 mol % catalyst loading {NHC•HX/CuCl or (NHC)CuCl} and 20 mol % NaO*t*-Bu. The reactions provided moderate to high yields (66–99%) of the corresponding siloxanes.



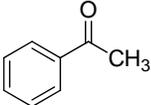
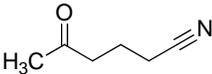
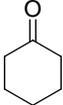
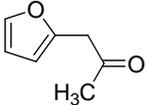
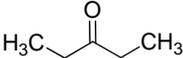
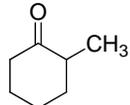
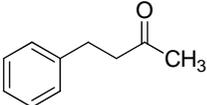
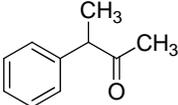
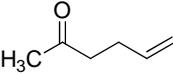
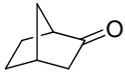
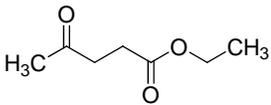
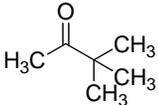
The diboration of various ketones was accomplished through the *in situ* formation of the NHC copper-catalyst using 3 mol % (ICy)CuCl (**8b**) and 20 mol% NaO*t*-Bu, in benzene-*d*₆ (Table 2.4). The reaction progress was monitored by ¹H NMR spectroscopy. Under these conditions, excess NaO*t*-Bu was necessary because of the inability to accurately measure out less than one milligram of material in the glovebox. Formation of a dilute solution of sodium *tert*-butoxide was attempted, however, the substance would not dissolve completely. The *in situ* formation of the catalyst starting from the imidazolium salt was attempted (ICy•HCl/CuCl, NaO*t*-Bu), but not successful in the diboration of aldehydes. The diboration of ketones was performed using the *in situ* catalyst formation (**8b**, NaO*t*-Bu) at 50 °C over 2–22 hours, resulting in 100% conversion to the corresponding diboration product (Table 2.4). It is interesting to note that the

diboration of 2-methylcyclohexanone proceeded significantly faster than cyclohexanone, proceeding to completion in 1.5 hours as opposed to 20 hours. It is possible that there is a small amount of impurity (that could not be removed by distillation) present in cyclohexanone that is retarding the catalyst activity.

Table 2.4. Diboration Reactions Monitored by ^1H NMR Spectroscopy

$$\text{B}_2\text{pin}_2 + \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}' \xrightarrow[20 \text{ mol\% NaOt-Bu, C}_6\text{D}_6]{3 \text{ mol\% (ICy)CuCl}} \text{R}-\overset{\text{Bpin}}{\underset{\text{R}'}{\text{C}}}-\text{Bpin}$$

11

Entry	Ketone	Conditions	% Conv.	Entry	Ketone	Conditions	% Conv.
1		22 h, 50 °C	100	7		4.5 h, 50 °C	100
2		20 h, 50 °C	100	8		1.5 h, 50 °C	100
3		20 h, 50 °C	100	9		1.5 h, 50 °C	100 >97:3 dr
4		2.5 h, 50 °C	100	10		20.5 h, 50 °C	100 11:1 dr
5		4.5 h, 50 °C	100	11		93 h, 50 °C	95
6		2 h, 50 °C	100	12		96 h, 90 °C	0

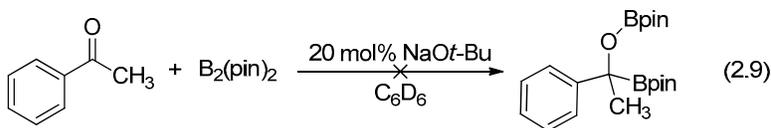
The diboration of ketones using the optimized reaction conditions tolerated a variety of functional groups. Aryl, cyclic, and dialkyl ketones provided 100% conversion

at 50 °C over 2.5–20 hours (entries 1–4, Table 2.4). The more functionalized ketones that were tolerated contained alkenyl, ester, nitrile, and furyl groups (entries 5–8, Table 2.4). These functionalized ketones proceeded to 100% conversion at 50 °C over 1.5–4.5 hours. Entries 9–10 of table 2.4 show that chiral ketones can be diborated with high diastereoselectivity.

The diboration of norcamphor, pinacolone, and 2,3-butanedione proved problematic. The bicyclic ketone, norcamphor showed 95% conversion after 93 hours at 50 °C. At increased temperature (70 °C) only 54% conversion occurred after 22 hours. Higher catalyst loading, up to 6 mol %, did not improve the conversion to the diborated product. We believe that steric effects hinder norcamphor from going to complete conversion due to the difficulty of the copper complex coordinating to the carbonyl. The slow rate of coordination likely results in alternative catalyst decomposition pathways. When using the standard reaction conditions, no conversion was observed with pinacolone. Increasing the temperature or catalyst loading did not promote the diboration of this sterically hindered ketone. The steric hindrance of pinacolone is thought to impede either coordination to the copper-catalyst or migratory insertion. The diboration of 2,3-butanedione only proceeded to 50% conversion (of possible product) after 69 hours at 50 °C. It is speculated that the diketone can chelate to the copper catalyst and generate an inactive catalyst species.

The addition of bases to the diboration reaction using **9b** caused a faster reaction rate and better conversion. It was speculated that the basic sodium *tert*-butoxide complexes with the diboron reagent acting as the catalyst instead of the copper-boryl species proposed by Sadighi.⁷ A control experiment was done, excluding the copper

catalyst, using 20 mol % sodium *tert*-butoxide, and a stoichiometric amount of bis(pinacolato)diboron and acetophenone in benzene-*d*₆ (eq 2.9). The reaction was run under typical conditions of 15 hours at 50 °C. The control experiment showed no conversion to products.



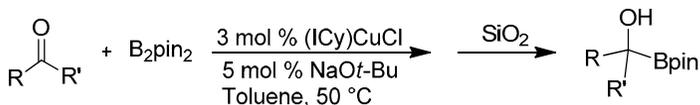
2.3.5. Isolation of Diboration Products

Direct isolation of the diborated products was attempted using Sadighi's method⁸ which consisted of filtering the concentrated diboration product through Celite with pentane. Filtration of the diborated ketones through Celite did not provide clean product in contrast to what was observed with aldehydes.⁸ Direct isolation of the diborated products was then attempted using Davisil[®] grade silica gel. Davisil[®] is silanized silica gel, which often results in a decreased propensity to decomposition with acid-sensitive compounds.¹³ Unfortunately, a small amount of hydrolysis occurred and a mixture of the diborated product and the α -hydroxyboronate ester was observed. No further attempts were made to isolate the diboration products of these ketones.

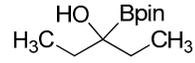
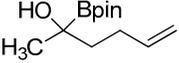
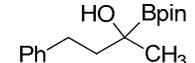
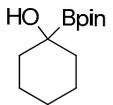
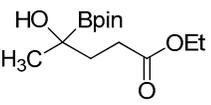
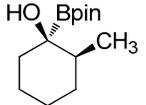
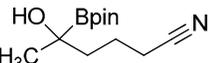
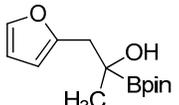
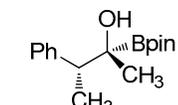
The *in situ* diboration conditions were used to form isolable tertiary α -hydroxyboronate esters (Table 2.5). Diboration reactions were run using 1–3 mmols of ketone, 3 mol % (ICy)CuCl (**8b**) and 5 mol % NaOt-Bu in toluene at 50 °C for 3–17 hours. Selective hydrolysis of the O–B bond in the presence of the C–B bond was achieved during purification by chromatography on silica gel. All simple and functionalized alkyl ketones tolerated purification by chromatography except

norcamphor. Although 95% conversion to products could be achieved for the diboration of norcamphor at 50 °C over 93 hours, isolation proved problematic. Reversion to starting materials occurred during isolation attempts of this substrate using silica gel chromatography.

Table 2.5. Synthesis and Isolation of α -Hydroxyboronate Esters



12

Entry	Product	Time	Yield	Entry	Product	Time	Yield
1		17 h	52 %	6		6 h	70 %
2		3 h	81 %	7		22 h	74%
3		2.5 h	55 %	8		2.5 h	83 % >97:3 dr
4		5 h	55 %	9		2 h	87 %
5		24 h	83 % 11:1 dr				

The diboration of chiral ketones provides diastereomers. Determination of the relative configuration of these diastereomers can be done using a variety of methods. The relative stereochemistry of **12j** is being probed by recrystallization to form single crystals for X-ray diffraction. The hydrosilylation¹² of **10** and reduction to known alcohol **17** (eq 2.10) was also performed to provide further incite into the relative stereochemistry of **12j**. The hydrosilylation reaction uses the same *in situ* developed catalyst and is presumed to proceed by the same mechanism providing similar selectivity. Desilylation

of **16** provided a mixture of alcohols **17a** and **17b** in a 2:1 ratio of diastereomers. Both diastereomers were matched to known literature spectral data, indicating **17a** as the major product. By analogy, the major diastereomer for **12j** is then determined to be (2R*, 3S*)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ol (Figure 2.3).

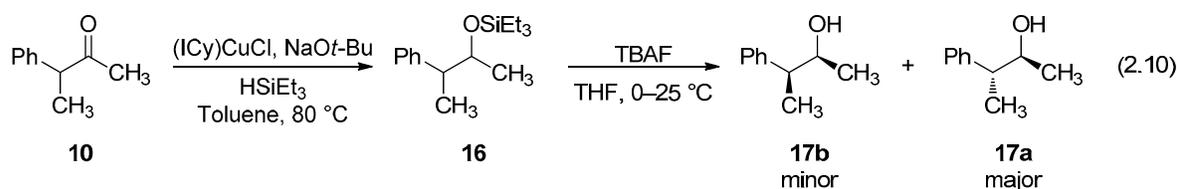
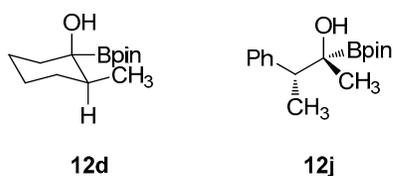


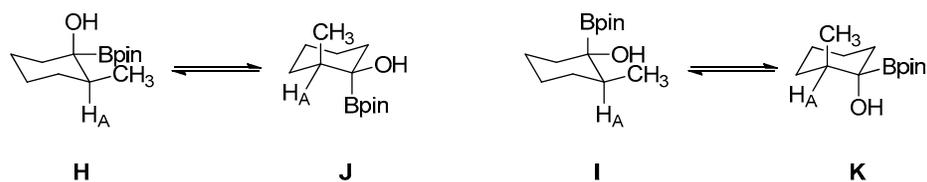
Figure 2.3. Assignment of Stereochemistry



The α -hydroxyboronate ester (**12d**) produced from 2-methylcyclohexanone provided an 83% yield with >97:3 diastereomeric ratio. The relative stereochemistry of **12d**, shown in Figure 2.3, was determined using conformational analysis, 2-dimensional gradient COSY NMR spectroscopy, and coupling constant analysis. The 2D COSY was used to assign each hydrogen in the ^1H NMR spectrum. H_A was found to be adjacent to the methyl substituent and was a key hydrogen to determine the relative stereochemistry. The coupling constants for the quartet of triplets assigned to H_A were determined to be 13.0, 6.6, and 3.2 Hz. The quartet results from the adjacent methyl substituent ($J = 6.6$ Hz) and matches the J -value of the methyl doublet ($J = 6.5$ Hz). The remaining two J -values result from an axial-axial coupling ($J = 13.0$ Hz) and an axial-equatorial coupling ($J = 3.2$ Hz). H_A must be axial to have the large axial-axial coupling that is observed ruling out conformers **J** and **K** (Figure 2.4). This leaves two possible diastereomers that are consistent with these J -values, diastereomers **H** and **I**. Diastereomer **H** results from

addition of the boron (as copper boryl) *anti* to the equatorial methyl substituent. Isomer **I** results from addition *syn* to the methyl substituent. Diastereomer **I** requires an axial Bpin substituent, rather than the axial methyl substituent which would result from the chair-flip conformer **K**. Based on the steric bulk of Bpin as compared to CH₃, isomer **I** was ruled out and the relative stereochemistry is assigned as isomer **H**.

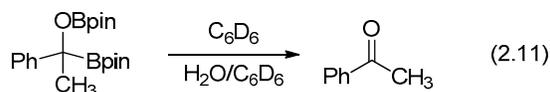
Figure 2.4. Conformational Isomers of **12d**



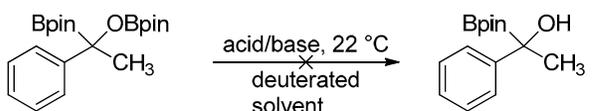
In contrast to the dialkyl ketone derived α -hydroxyboronate esters reported in Table 2.5, attempts to obtain the α -hydroxyboronate ester resulting from acetophenone (**11a**) were unsuccessful. Filtration through a silica gel plug with diethyl ether resulted in reversion of **11a** back to acetophenone. Alternative work-up protocols were explored, including filtration through alumina and Florisil. The alumina plug filtered out the desired product and provided only impurities. The Florisil filtration produced a complex mixture of products.

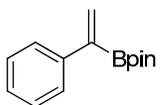
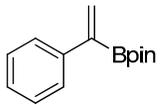
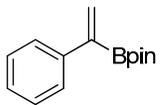
Exposing **11a** to air also adversely affected the product, causing it to decompose. At this point it was unclear if oxygen was the source of the decomposition or if moisture was responsible. To clarify the source of decomposition, the acetophenone diboration was run under the usual NMR scale conditions and after showing normal conversion, degassed benzene-*d*₆ saturated with H₂O, was added. A ¹H NMR spectra was then taken showing complete reversion to acetophenone indicating that water is responsible for the decomposition (eq 2.11). Because normal filtration techniques were unsuccessful, a

Kugelrohr distillation was used to isolate diborated acetophenone. The Kugelrohr distillation results were promising, providing the diboration product in moderate yield with increased purity. This technique was not optimized, however, due to the expectation that other isolation techniques would prove more general.

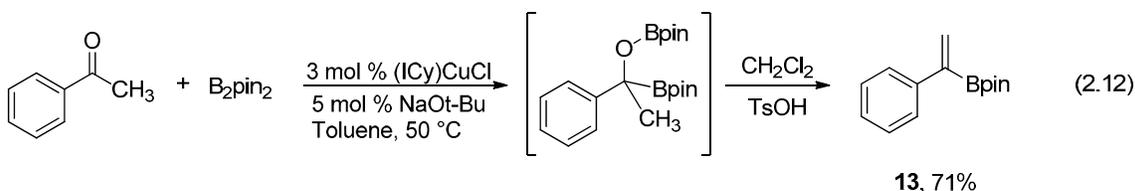


Continued attempts to isolate the α -hydroxyboronate ester **12a** proved to be difficult. Knowing that diborated acetophenone would revert back to starting material in the presence of water led to the exploration of organic acids and bases for selective cleavage of the O–B bond. Crude diboronate **11a** was treated with various additives in deuterated solvent at 22–50 °C and the progress was monitored by ^1H NMR spectroscopy. In all reactions no alcohol formation was observed (Table 2.6). Addition of various bases and Lewis acids led to decomposition into unidentifiable products. Reactions involving camphorsulfonic acid (CSA), HCl/dioxane and *p*-toluenesulfonic acid (TsOH), however, all provided conversion to the synthetically useful branched vinyl boronate ester **13**. TsOH provided the cleanest formation of **13**.

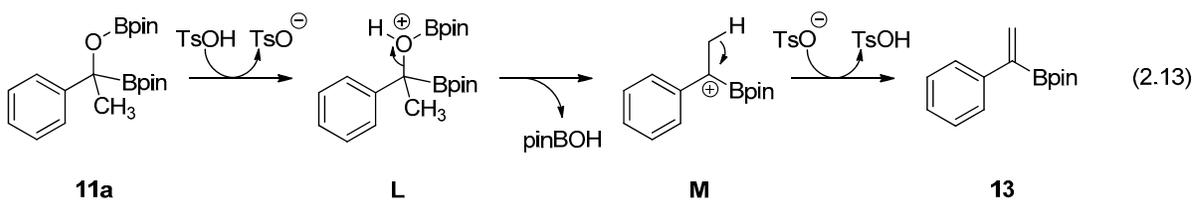
Table 2.6. O–B Bond Cleavage Attempts


Solvent	acid/base	Conditions	Result
C ₆ D ₆	NaOt-Bu	16.5 h	decomposition side products
C ₆ D ₆	NaOt-Bu/ <i>t</i> -BuOH	5 h	decomposition side products
C ₆ D ₆	BF ₃ ·OEt ₂	4 h	decomposition side products
CDCl ₃	AcOH/NaOAc	2.5 h, 22 °C 17.5 h, 50 °C	decomposition side products
CDCl ₃	CSA	3 h	 after 4 d 13
CDCl ₃	HCl/dioxane	21 h	 2 h 13
CDCl ₃	TsOH	4 h	 13

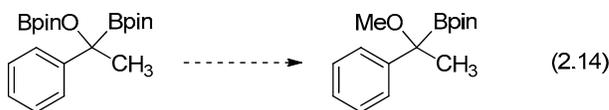
Vinyl boronate ester **13** was formed through a two-step reaction. The two-step procedure for the formation of vinyl boronate ester **13** included the standard diboration of acetophenone, followed by addition of a stoichiometric amount of *p*-toluenesulfonic acid. After 3 hours the solvent was removed by vacuum. The resulting black oil was filtered through Celite with pentane to remove the copper salts. Using this procedure vinyl boronate ester **13** was isolated in 53% yield. Upon reaction optimization, methylene chloride was found to be a better solvent in the second step, providing vinyl boronate ester **13** in 71% yield (eq 2.12).¹⁴



The formation of vinyl boronate ester **13** is believed to proceed by an E1 type reaction mechanism (eq 2.13). TsOH protonates the oxygen, to form **L**, which is ionized to form **M** and pinB–OH. The carbocation that is formed is stabilized by the neighboring aromatic ring. *p*-Toluenesulfonic acid is then reformed by the deprotonation of the adjacent hydrogen, providing branched vinyl boronate ester **13**. Examination of the reaction scope and functional group compatibility of vinyl boronate ester formation is currently being pursued.



With the obstacles encountered in the formation/isolation of the α -hydroxyboronate ester derived from acetophenone, the direct formation of alkoxy-protected alcohols was examined. Formation of the α -methoxy-substituted boronate esters were expected to be less prone to decomposition. One methylation reaction was attempted using camphorsulfonic acid and methyl iodide, in deuterated chloroform; no conversion was observed at room temperature. Methylations attempted with trimethyloxonium tetrafluoroborate in deuterated chloroform also provided none of the desired product, even at elevated reaction temperatures.



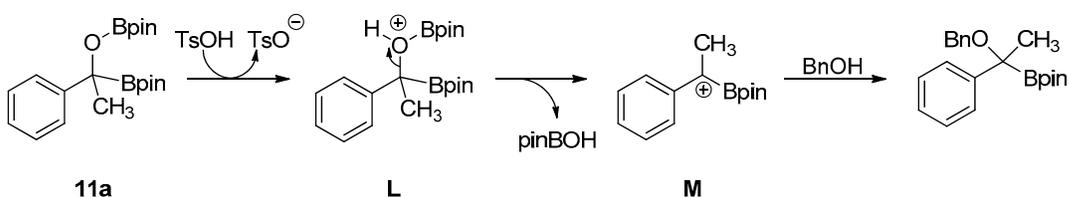
2.3.6. Protection of Alcohols

The isolation and characterization of tertiary α -hydroxyboronate esters was previously unknown. Demonstrating the synthetic utility of these tertiary α -hydroxyboronate esters is an important aspect of this research. In order to demonstrate the synthetic utility the development of Matteson homologation reactions was desired to utilize the newly formed C–B bond. Typical homologation reactions involve alkoxy-protected alcohols, so conditions to protect these alcohols were desired.

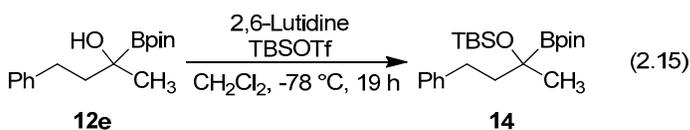
Various protecting groups were examined to allow the formation of α -alkoxyboronate esters that are analogous to those typically used in the Matteson homologation reaction. Methoxymethyl (MOM) protection was attempted using MOMCl, sodium iodide, and diisopropyl ethylamine in DME resulting in decomposition products.¹⁵ Benzyl protections were also explored. Benzyl protection of **12g** with benzylbromide and sodium hydride in THF failed to provide the desired benzyl ether. An alternative route to Bn-protected alcohols was reported by Matteson for less-substituted hydroxyl boronate esters. Under these conditions a benzyl ether was formed through an α -mesylate intermediate.¹⁶ Accordingly, the mesylate was prepared using **12e**, mesylchloride and triethylamine in methylene chloride. The crude mesylate was used immediately, treating this reaction intermediate with lithium benzyl oxide (BuLi and BnOH). Unfortunately, the two-step benzyl protection did not produce the desired product. A third and final attempt to add the benzyl protecting group to the substrate

included the addition of benzyl alcohol and *p*-toluenesulfonic acid to **11a**. Under these reaction conditions, formation of carbocation **M** was expected (Scheme 2.2), followed by trapping of the carbocation with benzyl alcohol. This reaction method did not produce the desired protected product. Dihydropyran (DHP) protection of the alcohol was also attempted, by the addition of DHP and *p*-toluenesulfonic acid to **12e** in methylene chloride, but production of the desired protected alcohol was not obtained.¹⁷ Thus far the TBS protection of **12e** has been the only successful transformation involving these products.

Scheme 2.2. Attempted Benzyl Protection of **11a**

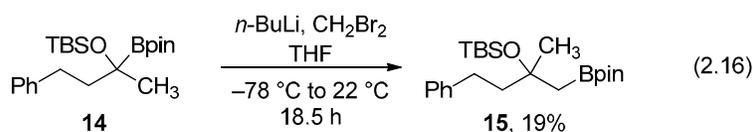


The TBS protection of **12e** was optimized to provide the desired silyl ether in moderate yield (eq 2.15). The optimized reaction conditions required 3 equivalents of 2,6-lutidine and 1.5 equivalents *tert*-butyldimethylsilyltrifluoromethylsulfonate (TBSOTf) at -78 to 22 °C over 19 hours.¹⁸ The reagents used in this protection were distilled and stored in a dessicator to provide optimal yield. The compatibility of these reaction conditions with other alcohols will be examined to determine the generality of this method.



2.3.7. Matteson-Type Homologation Reactions

The homologation of **14** was completed using 1 equivalent of protected alcohol, 1.5 equivalents of dibromomethane, and 1.5 equivalents butyllithium in THF.¹⁹ Clean product was obtained in low yield (eq 2.16). Optimization of this reaction is currently underway. An alternative homologation reaction was explored using bromochloromethane and zinc chloride in THF at $-100\text{ }^{\circ}\text{C}$. The ^1H NMR spectra of the crude material showed minimal homologation product.



A 2-step diboration/homologation reaction sequence was attempted. Concurrent work done by Cameron Moore in our research group showed that direct homologation of diborated aldehydes was possible. The general diboration procedure for each substrate was followed. Upon removal of the copper salts, the crude materials were subjected to typical homologation procedures, except the use of 2.5 equivalents of BuLi and CH_2Br_2 . The first equivalent of BuLi and CH_2Br_2 is believed to displace the oxygen-bound boron substituent and allow homologation of the carbon-bound boronate ester. The diboration/homologation of 3-pentanone, cyclohexanone and 2-methylcyclohexanone were performed using bromochloromethane and butyl lithium in THF at $-100\text{ }^{\circ}\text{C}$. The desired homologation products were not observed, but the reaction commonly resulted in cleavage of the O-B bond, providing the corresponding α -hydroxyboronate ester as the major product. The steric congestion surrounding the C-bound boronate ester is believed

to be responsible for the inability to achieve homologation under these reaction conditions.

2.4. Summary and Conclusions

N-Heterocyclic carbenes have proven to be efficient catalysts, ligands, and reactants in a multitude of transformations. Sadighi and coworkers showed a copper complex supported by NHC ligands to be an effective catalyst in the diboration of aldehydes. Sadighi's procedure was used to synthesize (NHC)CuO*t*-Bu (**9a–c**) which were used in the copper-catalyzed diboration of ketones. (ICy)CuO*t*-Bu (**9b**) proved to be the most useful complex for the copper-catalyzed diboration of ketones.

Optimization of the reaction conditions revealed the *in situ* formation of the catalyst to be the most effective method to obtain the diboration of ketones. Isolation via silica gel chromatography provided moderate to high yields of the corresponding α -hydroxyboronate esters. Previous methods using the well-defined catalyst system showed clean isolation of diborated aldehydes by filtration through Celite.⁸ This method was not applicable to the *in situ* diboration of ketones due to the reduced purity of diboration products that result from ketones. The TBS protection of one α -hydroxyboronate ester was accomplished and examined in the Matteson homologation reaction, providing preliminary support for the ability to homologate these highly substituted intermediates. The optimization of homologation reactions is currently being explored.

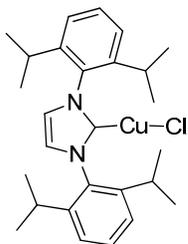
2.5. Experimental

General Techniques: Oxygen-sensitive, moisture-sensitive or hygroscopic materials were handled under purified nitrogen in a MBraun glovebox or by standard Schlenk line techniques. All reactions involving air-sensitive materials were carried out in oven-dried glassware under a nitrogen atmosphere. All solvents were dried and degassed by standard procedures unless used for extractions or isolations. TLC analysis used 500 μ m, 60 Å silica layer fluorescence UV plates. Flash Chromatography was carried out on hand-packed columns of silica gel or Davisil[®]. NMR spectra were collected on UNITY[®]Inova and Mercury_{plus} spectrometers at 500 MHz and 300 MHz for ¹H NMR, 125 and 75.5 MHz for ¹³C NMR, and 160 MHz for ¹¹B NMR. ¹H NMR spectra are referenced to C₆D₆ at 7.16 ppm, to CD₂Cl₂ at 5.32 ppm, to acetone-*d*₆ at 2.05 ppm, to CDCl₃ at 7.26 ppm or to an internal tetramethylsilane (TMS) standard at 0.00 ppm. The ¹H NMR data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sep = septet, m = multiplet), coupling constants (Hz), and integration. ¹³C NMR spectra are referenced to benzene-*d*₆ at 125.39 ppm, to CD₂Cl₂ at 54.0 ppm, to acetone-*d*₆ at 206.7 ppm, or to CDCl₃ at 77.23 ppm. ¹¹B NMR spectra were referenced by an external trifluoroborate sample. IR spectra were collected on NICOLET iS10 spectrometer and absorptions reported in cm⁻¹. Elemental analyses were performed by Guelph Chemical Laboratories LTD, Guelph, ON, Canada. Elemental analysis data are reported as follows: empirical formula; calculated percent carbon, calculated percent hydrogen, calculated percent nitrogen; observed percent carbon, observed percent hydrogen, observed percent nitrogen. High Resolution Mass Spectrometry (HRMS) was

performed by the University of California, Irvine Mass Spectrometry Facility, Irvine, CA.

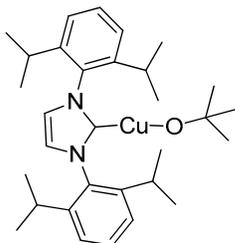
HRMS data are reported as follows: calculated exact mass; found exact mass.

2.5.1. Synthesis of (NHC)CuCl (**8**) and (NHC)CuOt-Bu (**9**)



8a

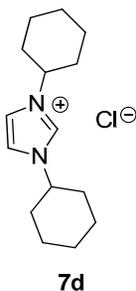
[1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidene]copper(I) chloride (8a**).**²⁰ NaOt-Bu (102 mg, 1.06 mmol) was added to a flame dried Schlenk flask equipped with a stirbar. CuCl (105 mg, 1.06 mmol) was then added to the flask, followed by 1,3-bis(2,6-di-isopropylphenyl)imidazolium chloride (45 mg, 1.06 mmol). THF (5.3 mL) was added, and the reaction mixture was stirred for 4 hours. The resulting solution was filtered over Celite, rinsed with THF, and concentrated *in vacuo* producing **8a** as a gray solid (305 mg, 59%). ¹H NMR (500 MHz, acetone-*d*₆): δ = 7.71 (s, 2H), 7.54 (t, *J* = 7.8, 2H), 7.41 (d, *J* = 7.8, 4H), 2.66 (sep, *J* = 6.8, 4H), 1.30 (d, *J* = 6.8, 12H), 1.25 (d, *J* = 6.8, 12H). ¹³C NMR (125 MHz, acetone-*d*₆): δ = 147.1, 136.3, 131.8, 125.5, 125.4, 30.0, 25.5, 24.5.



9a

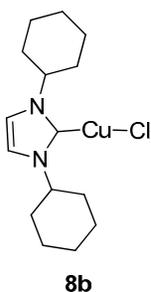
[1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidene]copper(1) *tert*-butoxide (9a).²¹

NaO*t*-Bu (60 mg, 626 μ mol) was added to a flame dried Schlenk flask equipped with a stirbar. **8a** (305 mg, 625 μ mol) was then added to the flask, followed by THF (2.9 mL). The reaction mixture was stirred for 1.5 hours. The resulting solution was filtered over Celite, rinsed with THF, and concentrated *in vacuo* to produce **9a** as a light brown solid (225 mg, 68%). ¹H NMR (500 MHz, benzene-*d*₆): δ = 7.22 (t, *J* = 7.8, 2H), 7.07 (d, *J* = 7.8, 4H), 6.28 (s, 2H), 2.60 (sep, *J* = 6.8, 4H), 1.41 (d, *J* = 6.3, 12H), 1.32 (s, 9H), 1.08 (d, *J* = 6.8, 12H).



1,3-dicyclohexylimidazolium chloride (7d).¹⁰ Toluene (50 mL) was added to a flame-dried 250 mL round bottom flask equipped with a stirbar. Cyclohexylamine (5.7 mL, 50 mmol) was then added, followed by paraformaldehyde (1.5g, 50mmol) with rapid stirring. After 30 minutes at room temperature the flask was cooled to 0 °C and another equivalent of cyclohexylamine (5.7 mL, 50 mmol) was added. After 10 minutes at 0 °C, 3.3 M aqueous HCl (15 mL, 50 mmol) was added dropwise over 30 minutes to the cooled mixture. The solution was allowed to warm to room temperature and 40% aqueous glyoxal (5.7 mL, 50 mmol) was added dropwise over 30 minutes. The resulting cloudy mixture was stirred for 16 hours at 50 °C. After the mixture had cooled, 50 mL of ether and 25 mL of aqueous saturated Na₂CO₃ were added, and the layers were separated. The

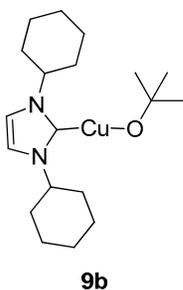
aqueous layer was extracted with ether (3×50 mL). The volatiles were removed *in vacuo*, and the residue was extracted with 75 mL of methylene chloride, dried over MgSO_4 , and filtered. After removal of the volatiles *in vacuo*, the solid residue was broken down into a beige hygroscopic solid by treatment with ether. Due to the small amount obtained, the aqueous layer was re-extracted with CH_2Cl_2 (3×50 mL). The resulting residue was dissolved in 75 mL of CH_2Cl_2 , dried over MgSO_4 , and subsequently filtered. The removal of the solvents by vacuum resulted in a cream colored solid. The product was left under high-vacuum overnight providing **7d** as a beige colored solid (2.185 g, 16%). ^1H NMR (300 MHz, CDCl_3): $\delta = 11.12$ (s, 1H), 7.26 (m, 2H), 4.58 (m, 2H), 2.12–1.00 (overlapping multiplets, 20H).



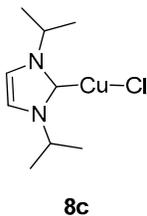
[1,3-dicyclohexylimidazol-2-ylidene]copper(I) chloride (8b).⁸ An oven dried 25 ml round bottom flask equipped with a stirbar was charged with 1,3-dicyclohexylimidazolium tetrafluoroborate (500 mg, 1.56 mmol) followed by NaOt-Bu (158 mg, 1.6 mmol), CuCl (173 mg, 1.7 mmol), and THF (10 mL). The reaction mixture was stirred for 1.5 h resulting in a cloudy yellow reaction mixture, which was filtered through Celite, rinsed with THF and concentrated *in vacuo*. The resulting yellow foam was broken down in ether and triturated with small amounts of THF. The triturant was collected and concentrated, affording **8b** as a pale yellow solid (455 mg, 88%). ^1H NMR

(500 MHz, CD₂Cl₂): δ = 6.95 (s, 2H), 4.28 (tt, J = 12.2, 3.9, 2H), 2.06 (m, 4H), 1.89 (m, 4H), 1.77-1.61 (m, qd, J = 12.7, 3.7, 6H), 1.46 (qt, J = 13.2, 3.4, 4H), 1.25 (qt, J = 13.2, 3.9, 2H).

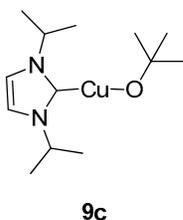
The desired compound was also synthesized using **7d** following the same procedure, but producing only a 23% yield of a pale yellow foam.



[1,3-dicyclohexylimidazol-2-ylidene]copper(I) *tert*-butoxide (9b).⁸ A round bottom flask equipped with a stirbar containing **8b** (880 mg, 2.65 mmol) was charged with NaOt-Bu (255 mg, 2.65 mmol) and THF (7 mL). The reaction mixture was stirred for 1 hour, followed by filtration through Celite and rinsing with THF. Upon concentration, **9b** was isolated as a light peach foam (953 mg, 97%). ¹H NMR (500 MHz, benzene-*d*₆): δ = 6.23 (br s, 2H), 4.33 (br s, 2H), 2.0–0.9 (overlapping multiplets, 29H).

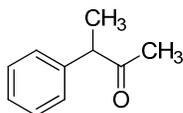


(1,3-di-isopropylimidazol-2-ylidene)copper(I) chloride (8c): An oven dried round bottom flask equipped with a stirbar was charged with CuCl (584 mg, 5.9 mmol) followed by NaOt-Bu (548 mg, 5.7 mmol), THF (14.5 mL), and 1,3-di-isopropylimidazolium chloride (1.0 g, 5.3 mmol). The reaction mixture was stirred for 1.5 hours. The resulting suspension was then filtered through Celite, rinsed with THF, and concentrated *in vacuo*. The yellow solid was taken up in ether and triturated with THF. The volatiles were removed *in vacuo* affording **8c** as a white solid (1.04 g, 78%). ¹H NMR (300 MHz, CD₂Cl₂): δ = 6.98 (s, 2H), 4.74 (sep, *J* = 6.7, 2H), 1.48 (d, *J* = 7.0, 12H).



(1,3-di-isopropylimidazol-2-ylidene)copper(I) tert-butoxide (9c): To a scintillation vial equipped with a stirbar containing **8c** (1.039g, 4.14 mmol) was added THF (11 mL) followed by NaOt-Bu (398 mg, 4.14 mmol). The reaction mixture was stirred for 1 hour and the resulting solution was filtered through Celite, rinsed with THF, and concentrated *in vacuo*. Upon concentration, **9c** was isolated as a brown paste (1.16 g, 96%). ¹H NMR (300 MHz, benzene-*d*₆): δ = 6.24 (s, 2H), 4.66 (br s, 2H), 1.50 (s, 9H), 1.02 (d, *J* = 7.0, 12H).

2.5.2. Synthesis of Ketones



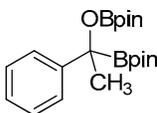
10

3-phenylbutan-2-one (10): An oven dried 100 mL round bottom flask was charged with 60% dispersion of NaH in mineral oil (900 mg, 22.5 mmol), THF (30 mL), phenyl acetone (2 mL, 15 mmol), and methyl iodide (1.9 mL, 30 mmol). The reaction mixture was refluxed at 80 °C overnight. No starting material remained after reflux as shown by TLC analysis. The mixture was washed with 1 M HCl (20 mL) followed by saturated NaHCO₃ (20 mL), and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by silica gel chromatography (1:9 Et₂O:C₆H₁₄) provided **10** as a dark yellow liquid (1.85g, 83%). **IR** (neat) 2976, 1711, 1493, 1354, 1164, 699 cm⁻¹. **¹H NMR** (C₆D₆): δ = 7.07 (m, 2H), 7.00 (m, 3H), 3.24 (q, *J* = 6.83, 1H), 1.65 (s, 3H), 1.28 (d, *J* = 6.83, 3H). **¹³C NMR** (C₆D₆): δ = 206.8, 141.7, 129.5, 128.4, 127.6, 54.0, 28.3, 17.9. **HRMS** (CAB) calcd for (C₁₀H₁₂O+Na)⁺ 171.0786, found 171.0783.

2.5.3. Diboration of Ketones Monitored by ¹H NMR Spectroscopy

General procedure A for the diboration of ketones:⁸ In a glovebox, an oven dried J-Young NMR tube was charged with bis(pinacolato)diboron (13 mg, 0.050 mmol), and benzene-*d*₆ (0.150 mL), followed by the ketone (0.050 mmol). A solution of (ICy)CuOt-Bu (0.425 mL, 2.7 mM (ICy)CuOt-Bu solution in benzene-*d*₆) was then added and the reaction mixture was removed from the glovebox and heated in an oil bath.

For reactions requiring 1 mol% (ICy)CuOt-Bu (9b): A solution of (ICy)CuOt-Bu (0.0050 mmol, 0.185 mL, 2.7 mM (ICy)CuOt-Bu solution in benzene-*d*₆) was added to the J-Young NMR tube containing bis(pinacolato)diboron, the ketone, and benzene-*d*₆ (0.40 mL).

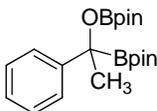


11a

***α*-methyl [(Pinacol)boroxy]benzyl(pinacol)boronate (11a).** General procedure A was followed using 2.4 mol% (ICy)CuOt-Bu to give 90% conversion by ¹H NMR spectroscopy. ¹H NMR (500 MHz, benzene-*d*₆): δ = 7.83 (d, *J* = 7.3, 2H), 7.22 (t, *J* = 7.8, 2H), 7.05 (t, *J* = 7.3, 1H), 1.97 (s, 3H), 1.13 (s, 6H), 1.11 (s, 6H), 1.04 (s, 6H), 1.00 (s, 6H).

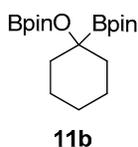
2.5.4. Diboration of Ketones with *In Situ* Generated Catalyst

General procedure B for the *in situ* diboration of ketones:⁹ In a glovebox, an oven dried J-Young NMR tube was charged with sodium *tert*-butoxide (1 mg, 0.010 mmol), a solution of (ICy)CuCl (0.300 mL, 5.0 mM solution of (ICy)CuCl in benzene-*d*₆), bis(pinacolato)diboron (13 mg, 0.050 mmol), 0.20 mL benzene-*d*₆, and the ketone (0.050 mmol). The reaction mixture was removed from the glovebox and placed in a 50 °C oil bath for 2–22 hours.

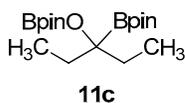


11a

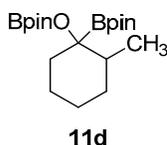
***α*-methyl [(pinacol)boroxy]benzyl(pinacol)boronate (11a).** General procedure B was followed with acetophenone (0.0060 mL, 0.050 mmol) and heated to 50 °C resulting in 100% conversion after 22 hours. ¹H NMR (500 MHz, benzene-*d*₆): δ = 7.83 (d, *J* = 7.3, 2H), 7.22 (t, *J* = 7.8, 2H), 7.05 (t, *J* = 7.3, 1H), 1.97 (s, 3H), 1.13 (s, 6H), 1.11 (s, 6H), 1.04 (s, 6H), 1.00 (s, 6H).



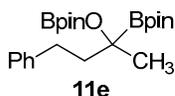
4,4,5,5-tetramethyl-2-((1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexyl)oxy)-1,3,2-dioxaborolane (11b). General procedure B was followed with cyclohexanone (0.0050 mL, 0.050 mmol) and heated to 50 °C resulting in 100% conversion after 22 hours. ¹H NMR (500 MHz, benzene-*d*₆): δ = 2.06 (m, 2H), 1.92 (m, 4H), 1.52 (m, 3H), 1.34 (m, 1H), 1.12 (s, 12H), 1.10 (s, 12H).



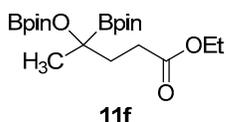
4,4,5,5-tetramethyl-2-(3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)pentan-3-yl)-1,3,2-dioxaborolane (11c). General procedure B was followed with 3-pentanone (0.0053 mL, 0.050 mmol) and heated to 50 °C resulting in 100% conversion after 20 hours. ¹H NMR (500 MHz, benzene-*d*₆): δ = 1.97 (q, *J* = 7.1, 4H), 1.12 (s, 12H), 1.10 (s, 12H), 1.09 (t, *J* = 7.3, 6H).



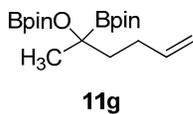
4,4,5,5-tetramethyl-2-(2-methyl-1-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)cyclohexyl)-1,3,2-dioxaborolane (11d). General procedure B was followed with 2-methylcyclohexanone (0.0060 mL, 0.050 mmol) using 0.060 mmol B₂(pin)₂ and heated to 50 °C resulting in 100% conversion after 1.5 hours. ¹H NMR (500 MHz, benzene-*d*₆): δ = 2.62 (m, 1H), 1.86–1.64 (overlapping multiplets, 6H), 1.46 (m, 2H), 1.20 (d, *J* = 6.3, 3H), 1.12 (s, 24H).



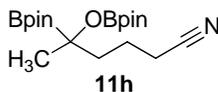
4,4,5,5-tetramethyl-2-(4-phenyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)butan-2-yl)-1,3,2-dioxaborolane (11e). General procedure B was followed with benzyl acetone (0.0075 mL, 0.050 mmol) and heated to 50 °C resulting in 100% conversion after 2.5 hours. ¹H NMR (500 MHz, benzene-*d*₆): δ = 7.16 (m, 4H), 7.05 (m, 1H), 3.20 (td, *J* = 12.7, 4.8, 1H), 2.90 (td, *J* = 12.7, 4.8, 1H), 2.20 (td, *J* = 13.7, 4.8, 1H), 2.11 (td, *J* = 12.7, 4.8, 1H), 1.62 (s, 3H), 1.12 (s, 24H).



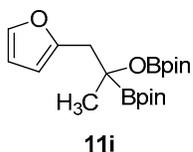
ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)pentanoate (11f). General procedure B was followed with ethyl levulinate (0.0070 mL, 0.050 mmol) using 0.060 mmol B₂(pin)₂ and heated to 50 °C resulting in 100% conversion after 2 hours. ¹H NMR (500 MHz, benzene-*d*₆): δ = 3.91 (q, *J* = 6.8, 2H), 2.25 (m, 1H), 2.12 (m, 1H), 1.96 (m, 1H), 1.11 (t, *J* = 6.8, 3H), 1.05 (s, 15H), 0.94 (s, 12H).



4,4,5,5-tetramethyl-2-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-2-yl)oxy)-1,3,2-dioxaborolane (11g). General procedure B was followed with 5-hexen-2-one (0.0060 mL, 0.050 mmol) using 0.060 mmol $B_2(\text{pin})_2$ and heated to 50 °C resulting in 100% conversion after 4.5 hours. ^1H NMR (500 MHz, benzene- d_6): δ = 5.91 (m, 1H), 5.11 (d, J = 17.1, 1H), 4.97 (d, J = 10.0, 1H), 2.42 (m, 2H), 1.93 (m, 2H), 1.57 (s, 3H), 1.10 (s, 24H).

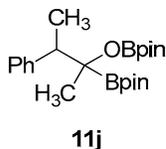


5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)hexanenitrile (11h). General procedure B was followed with 5-oxohexanenitrile (0.0056 mL, 0.050 mmol) using 0.060 mmol $B_2(\text{pin})_2$ and heated to 50 °C resulting in 100% conversion after 4.5 hours. ^1H NMR (500 MHz, benzene- d_6): δ = 1.69 (m, 1H), 1.64–1.40 (overlapping multiplets, 5H; s, 3H), 1.09 (s, 24H).

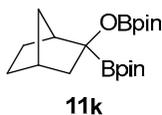


2-(1-(furan-2-yl)-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11i). General procedure B was followed with 2-furyl acetone (0.0058 mL, 0.050 mmol) using 0.060 mmol $B_2(\text{pin})_2$ and heated to 50 °C resulting in 100% conversion after 1.5 hours. ^1H NMR (500 MHz, benzene- d_6): δ = 7.11

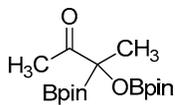
(dd, $J = 1.95, 0.97$, 1H), 6.21 (m, 1H), 6.11 (m, 1H), 3.32 (d, $J = 15.1$, 1H), 3.18 (d, $J = 14.6$, 1H), 1.59 (s, 3H), 1.09 (s, 24H).



4,4,5,5-tetramethyl-2-(3-phenyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)butan-2-yl)-1,3,2-dioxaborolane (11j). General procedure B was followed with 3-phenylbutan-2-one (0.350 mL, 0.143 M solution of ketone in benzene- d_6) using 0.060 mmol $B_2(\text{pin})_2$ and heated to 50 °C resulting in 100% conversion after 20.5 hours in an 11:1 diastereomeric ratio. ^1H NMR (500 MHz, benzene- d_6): $\delta = 7.46$ (d, $J = 8.1$, 2H), 7.15 (m, 2H), 7.06 (m, 1H), 3.02 (q, $J = 7.3$, 1H), 1.62 (d, $J = 7.3$, 3H), 1.52 (s, 3H), 1.13 (s, 6H), 1.11 (s, 6 H), 1.08 (s, 6H), 1.07 (s, 6H).



4,4,5,5-tetramethyl-2-(((1S,2S,4R)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[2.2.1]heptan-2-yl)oxy)-1,3,2-dioxaborolane (11k). General procedure B was followed with norcamphor (5.5 mg, 0.050 mmol) using 0.060 mmol $B_2(\text{pin})_2$ and heated to 50 °C resulting in 100% conversion after 93 hours. ^1H NMR (500 MHz, benzene- d_6): $\delta = 2.75$ (d, $J = 3.9$, 1H), 2.35 (m, 2H), 2.16 (t, $J = 4.4$, 1H), 1.93 (dt, $J = 9.8, 1.9$, 1H), 1.60–1.00 (overlapping multiplets, 29H).

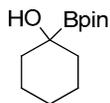


11I

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy)butan-2-one (11I). General procedure B was followed with 2,3-butanedione (0.0060 mL, 0.050 mmol) using 0.060 mmol $B_2(\text{pin})_2$ and heated to 50 °C resulting in 50% conversion after 69 hours. ^1H NMR (500 MHz, benzene- d_6): δ = 1.63 (s, 3H), 1.17 (s, 27H).

2.5.5. Isolation of Ketone Diboration Products

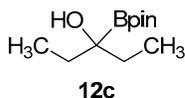
General procedure C for the *in situ* diboration of ketones: In a glovebox, an oven dried resealable solvent flask equipped with stirbar, was charged with bis(pinacolato)diboron (0.305 g, 1.2 mmol), NaOt-Bu (0.00500 g, 0.050 mmol), (ICy)CuCl (0.0100 g, 0.030 mmol), and toluene (12 mL), followed by the ketone (1.0 mmol). The flask was sealed and removed from the glovebox and heated to 50 °C for 5–17 h. The reaction mixture was then filtered through a silica plug, rinsed with ether and concentrated *in vacuo*. The corresponding α -hydroxyboronate ester was purified by silica gel chromatography.



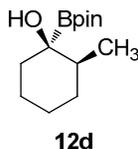
12b

1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanol (12b). General procedure C was followed using 1.2 mmol diboron (0.305 g), 0.050 mmol NaOt-Bu (0.00500 g),

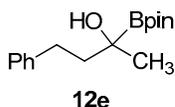
0.030 mmol (ICy)CuCl (0.0100 g), 12 mL toluene, and 1.0 mmol cyclohexanone (0.110 mL), and reacted for 22 hours. Purification by column chromatography (10:90 Et₂O:CH₂Cl₂) provided **12 b** as a yellow oil (0.168 g, 74%). ¹H NMR (500 MHz, benzene-*d*₆): δ = 2.02 (m, 2H), 1.84 (m, 2H), 1.59 (m, 2H), 1.50 (m, 3H), 1.39 (m, 2H), 1.01 (s, 12H). ¹³C NMR (125 MHz, benzene-*d*₆): δ = 84.0, 36.9, 26.7, 25.0, 23.3. ¹¹B NMR (160 MHz, benzene-*d*₆): δ = 32.4. IR (neat) 3410, 2930, 1371, 1319, 1135, 968, 951, 856, 689 cm⁻¹. HRMS (CAB) calcd for (C₁₂H₂₃BO₃+NH₄)⁺ 244.2086, found 244.2082 Anal Calcd for C₁₂H₂₃BO₃: C, 63.74; H, 10.25. Found: C, 63.62; H, 10.16.



3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-ol (12c). General procedure C was followed using 3.3 mmol diboron (0.841 g), 0.15 mmol NaO*t*-Bu (0.0140 g), 0.090 mmol (ICy)CuCl (0.0300 g), 36 mL toluene, and 3.0 mmol 3-pentanone (0.320 mL), and reacted for 17 hours. Purification by column chromatography (8:92 Et₂O:CH₂Cl₂) provided **12 c** as a clear light brown oil (0.311 g, 52%). ¹H NMR (500 MHz, benzene-*d*₆): δ = 1.86 (s, 1H), 1.76 (m, 2H), 1.64 (m, 2H), 1.11 (t, *J* = 7.3, 6H), 1.00 (s, 12H). ¹³C NMR (125 MHz, benzene-*d*₆): δ = 84.5, 33.4, 25.2, 10.3. ¹¹B NMR (160 MHz, benzene-*d*₆): δ = 33.3. IR (neat) 3500, 2977, 1318, 1260, 1133, 968, 853, 686 cm⁻¹. HRMS (CAB) calcd for (C₁₁H₂₃BO₃+NH₄)⁺ 232.2086, found 232.2078.

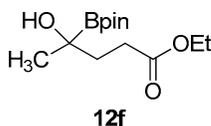


(1R*, 2S*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanol (12d). General procedure C was followed using 2.4 mmol diboron (0.612 g), 0.10 mmol NaOt-Bu (0.0100 g), 0.060 mmol (ICy)CuCl (0.0200 g), 24 mL toluene, and 2.0 mmol methylcyclohexanone (0.240 mL), and reacted for 2.5 hours. Purification by column chromatography (1:9 Et₂O:CH₂Cl₂) provided **12d** as a colorless oil (0.392 g, 83%) in >97:3 dr by ¹H NMR spectroscopic analysis. ¹H NMR (500 MHz, benzene-*d*₆): δ = 1.95 (qt, *J* = 13.2, 3.9, 1H), 1.87 (m, 1H), 1.79 (dq, *J* = 13.0, 6.6, 3.2, 1H), 1.75–1.70 (om, 3H), 1.65 (td, *J* = 3.9, 13.2, 1H), 1.45 (m, 1H), 1.42–1.27 (m, 1H; qt, *J* = 13.0, 3.9, 1H), 1.10 (d, *J* = 6.5, 3H), 1.00 (s, 12H). ¹³C NMR (125 MHz, benzene-*d*₆): δ = 84.4, 37.8, 36.0, 29.2, 27.1, 25.1, 25.0, 20.2, 19.4. ¹¹B NMR (160 MHz, benzene-*d*₆): δ = 33.1. IR (neat) 2926, 1372, 1315, 1136, 964, 853, 674 cm⁻¹. HRMS (CAB) calcd for (C₁₃H₂₅BO₃+NH₄)⁺ 258.2243, found 258.2242. Anal Calcd for C₁₃H₂₅BO₃: C, 65.02; H, 10.49. Found: C, 65.30; H, 10.69.



4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ol (12e). General procedure C was followed using 3.3 mmol diboron (0.841 g), 0.15 mmol NaOt-Bu (0.0140 g), 0.090 mmol (ICy)CuCl (0.0300 g), 36 mL toluene, and 3.0 mmol benzyl acetone (0.450 mL), and reacted for 3 hours. Purification column chromatography (1:9 Et₂O:CH₂Cl₂) provided **12e** as a colorless oil (0.672 g, 81%). ¹H NMR (500 MHz, benzene-*d*₆): δ = 7.20 (m, 4H), 7.07 (m, 1H), 3.30 (td, *J* = 13.2, 4.9, 1H), 2.76 (td, *J* = 12.7, 4.9, 1H), 2.05 (td, *J* = 12.7, 4.5, 1H), 1.92 (td, *J* = 12.7, 4.9, 1H), 1.73 (s, 1H), 1.39 (s, 3H), 0.99 (s, 12H). ¹³C NMR (125 MHz, benzene-*d*₆): δ = 143.0, 128.4, 128.3,

125.6, 83.8, 46.7, 32.1, 26.1, 24.6, 24.4, 24.3. ^{11}B NMR (160 MHz, benzene- d_6): δ = 33.1. **IR** (neat) 3375, 3050, 1372, 1322, 1141, 1105, 853, 699 cm^{-1} . **HRMS** (CAB) calcd for $(\text{C}_{16}\text{H}_{25}\text{BO}_3+\text{NH}_4)^+$ 294.2244, found 294.2245. **Anal** Calcd for $\text{C}_{16}\text{H}_{25}\text{BO}_3$: C, 69.58; H, 9.12. Found: C, 69.54; H, 9.46.



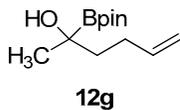
Ethyl-4-hydroxy-4(4,4,5,5-tetramethyl-3,2,1-dioxaborolan-2-yl)pentanoate (12f).

General procedure C was followed using 2.4 mmol diboron (0.612 g), 0.10 mmol NaOt-Bu (0.0100 g), 0.060 mmol (ICy)CuCl (0.0200 g), 24 mL toluene, and 2.0 mmol ethyl levulinate (0.285 mL), and reacted for 2.5 hours. Purification by column chromatography (using Davisil[®], 1:4 Et₂O:CH₂Cl₂) provided **12f** as a clear pale yellow oil (0.255, 55%).

^1H NMR (500 MHz, benzene- d_6): δ = 3.96 (q, J = 6.8, 2H), 2.69 (m, 1H), 2.57 (m, 1H), 2.13 (m, 1H), 2.04 (m, 1H), 1.72 (s, 1H), 1.31 (s, 3H), 0.96 (s, 12H), 0.95 (t, J = 6.8, 3H).

^{13}C NMR (125 MHz, benzene- d_6): δ = 174.1, 84.5, 60.4, 36.6, 30.9, 26.6, 25.0, 25.0,

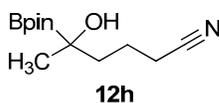
14.6. ^{11}B NMR (160 MHz, benzene- d_6): δ = 32.8. **IR** (neat) 2977, 1735, 1372, 1324, 1143, 1108, 851 cm^{-1} . **HRMS** (CAB) calcd for $(\text{C}_{16}\text{H}_{25}\text{BO}_3+\text{H})^+$ 273.1876, found 273.1881.



2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-2-ol (12g).

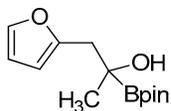
General procedure C was followed using 1.2 mmol diboron (0.305 g), 0.050 mmol NaOt-Bu (0.0500 g), 0.030 mmol (ICy)CuCl (0.0100 g), 12 mL toluene, and 1.0 mmol 1-hexen-2-

one (0.116 mL), and reacted for 6 hours. Purification by column chromatography (8:92 Et₂O:CH₂Cl₂) provided **12g** as a colorless oil (0.159 g, 70%). **¹H NMR** (500 MHz, benzene-*d*₆): δ = 5.91 (dddd, *J* = 16.6, 9.8, 6.3, 1H), 5.11 (dq, *J* = 17.1, 1.9, 1H), 4.97 (dq, *J* = 10.2, 1.9, 1H), 2.47 (m, 1H), 2.24 (m, 1H), 1.84 (m, 2H), 1.73 (m, 1H), 1.36 (s, 3H), 0.99 (s, 12H). **¹³C NMR** (125 MHz, benzene-*d*₆): δ = 134.0, 114.8, 84.4, 41.4, 30.8, 26.9, 25.1, 25.0. **¹¹B NMR** (160 MHz, benzene-*d*₆): δ = 33.0. **IR** (neat) 3470, 2977, 1610, 1372, 1360, 1321, 1137, 853 cm⁻¹. **HRMS** (CAB) calcd for (C₁₂H₂₃BO₃+NH₄)⁺ 244.2086, found 244.2086. **Anal** Calcd for C₁₂H₂₃BO₃: C, 63.74; H, 10.25. Found: C, 63.66; H, 10.40.



5-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanenitrile (12h).

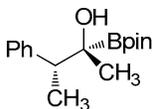
General procedure C was followed using 2.4 mmol diboron (0.610 g), 0.10 mmol NaO*t*-Bu (0.0100 g), 0.060 mmol (ICy)CuCl (0.0200 g), 24 mL toluene, and 2.0 mmol 5-oxohexane-nitrile (0.230 mL), and reacted for 6 hours. Purification by column chromatography (using Davisil[®], 1:4 Et₂O:CH₂Cl₂) provided **12h** as a clear yellow oil (0.260 g, 55%). **MP** 38.7-41.3 °C. **¹H NMR** (500 MHz, benzene-*d*₆): δ = 1.64–1.30 (m, 7H), 1.22 (s, 3H), 0.97 (s, 12H). **¹³C NMR** (125 MHz, benzene-*d*₆): δ = 120.0, 84.6, 40.3, 26.7, 25.0, 24.9, 22.4, 17.5. **¹¹B NMR** (160 MHz, benzene-*d*₆): δ = 33.2. **IR** (neat) 3496, 2976, 2243, 1479. 1372, 1319, 1144, 1102, 856, 694 cm⁻¹. **HRMS** (CAB) calcd for (C₁₂H₂₂BNO₃+NH₄)⁺ 257.2039, found 257.2036. **Anal** Calcd for C₁₂H₂₂BNO₃: C, 60.27; H, 9.27; N, 5.86. Found: C, 59.94; H, 8.98; N, 5.81.



12i

1-(furan-2-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-ol (12i).

General procedure C was followed using 1.2 mmol diboron (0.305 g), 0.050 mmol NaO*t*-Bu (0.00500 g), 0.030 mmol (ICy)CuCl (0.0100 g), 12 mL toluene, and 1.0 mmol 2-furyl acetone (0.120 mL), and reacted for 2 hours. Purification by column chromatography (using Davisil[®], 5:95 Et₂O:CH₂Cl₂) provided **12i** as a yellow oil (0.220 g, 87%). ¹H NMR (500 MHz, benzene-*d*₆): δ = 7.08 (t, *J* = 1.5, 1H), 6.10 (d, *J* = 1.5, 2H), 3.00 (d, *J* = 14.6, 1H), 2.88 (d, *J* = 14.6, 1H), 2.02 (s, 1H), 1.42 (s, 3H), 1.00 (d, *J* = 8.3, 12H). ¹³C NMR (125 MHz, benzene-*d*₆): δ = 154.5, 141.4, 110.9, 107.8, 84.5, 40.6, 26.3, 25.1, 25.0. ¹¹B NMR (160 MHz, benzene-*d*₆): δ = 33.1. IR (neat) 3453, 2977, 1460, 1372, 1325, 1141, 851, 724 cm⁻¹. HRMS (CAB) calcd for (C₁₃H₂₁BO₄+Na)⁺ 275.1433, found 275.1436. Anal Calcd for C₁₃H₂₁BO₄: C, 61.93; H, 8.40. Found: C, 61.58; H, 8.65.



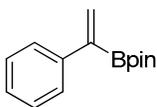
12j

(2R*, 3S*)-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ol (12j).

General procedure C was followed using 1.2 mmol diboron (0.305 g), 0.050 mmol NaO*t*-Bu (0.00500 g), 0.030 mmol (ICy)CuCl (0.0100 g), 12 mL toluene, and 1.0 mmol 3-phenylbutan-2-one (0.148 g), and reacted for 24 hours. Purification by column chromatography (3:97 Et₂O:CH₂Cl₂) provided **12j** as a colorless solid (0.228 g, 83%) in 11:1 dr by ¹H NMR spectroscopic analysis. **mixture**: MP 46.5-49.6 °C. IR (neat) 3481,

2974, 1452, 1318, 1141, 1095, 851 cm^{-1} . **HRMS** (CAB) calcd for $(\text{C}_{16}\text{H}_{25}\text{BO}_3+\text{Na})^+$ 299.1797, found 299.1802. **Anal** Calcd for $\text{C}_{16}\text{H}_{25}\text{BO}_3$: C, 68.58; H, 9.12. Found: C, 69.30; H, 9.34. **major diastereomer:** ^1H NMR (500 MHz, benzene- d_6): δ = 7.43 (d, J = 7.3, 2H), 7.20 (t, J = 7.3, 2H), 7.11 (t, J = 7.3, 1H), 3.00 (q, J = 7.3, 1H), 1.77 (s, 1H), 1.51 (d, J = 7.3, 3H), 1.27 (s, 3H), 0.99 (s, 6H), 0.982 (s, 6H). ^{13}C NMR (125 MHz, benzene- d_6): δ = 144.4, 130.0, 128.5, 126.8, 84.5, 48.6, 25.4, 25.1, 25.0, 18.7. ^{11}B NMR (160 MHz, benzene- d_6): δ = 32.8. **minor diastereomer:** ^1H NMR (500 MHz, benzene- d_6): δ = 7.48 (d, J = 7.3, 2H), 2.92 (q, J = 7.3, 1H), 1.88 (s, 1H), 1.46 (d, J = 6.8, 3H), 1.42 (s, 3H), 0.89 (s, 6H), 0.80 (s, 6H).

2.5.6. Vinyl Boronate Ester Synthesis

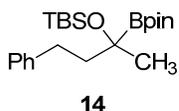


13

4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (13). General procedure C was followed using 2.2 mmol diboron (0.560 g), 0.10 mmol NaOt-Bu (0.0100 g), 0.060 mmol (ICy)CuCl (0.0200 g), 24 mL toluene, and 2.0 mmol acetophenone (0.240 mL), and reacted for 16 hours. Upon concentration the reaction mixture was taken up in pentane, filtered through Celite and concentrated *in vacuo*. To a flask containing crude diboronate **11a**, 2.4 mmol *p*-toluenesulfonic acid (0.456 g) was added, followed by 24 mL CH_2Cl_2 . The reaction was stirred at 22 $^\circ\text{C}$ for 3.5 hours and concentrated *in vacuo*. Purification by column chromatography (2:98 ethyl acetate:hexanes) provided **13** as a

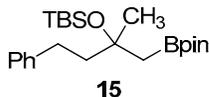
white solid (0.326 g, 71%). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 7.48 (d, J = 7.3, 2H), 7.31 (t, J = 7.5, 2H), 7.25 (m, 1H), 6.06 (m, 2H), 1.32 (s, 12H).

2.5.7. TBS Protection of Alcohols



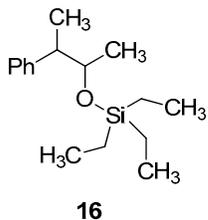
***tert*-butyldimethyl((4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)oxy)silane (14).** An oven-dried round bottom flask equipped with a stirbar was charged with **12e** (0.276 g, 1 mmol), and CH_2Cl_2 (3.7 mL), followed by 2,6-lutidine (0.350 mL, 3 mmol). The reaction flask was cooled to $-78\text{ }^\circ\text{C}$ by dry ice/isopropanol bath under a nitrogen atmosphere, upon which *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.350 mL, 1.5 mmol) was added. The reaction mixture was slowly warmed to room temperature overnight. After 17 h saturated aqueous NH_4Cl was added (10 mL) and the aqueous layer was extracted with ethyl acetate (4×10 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by column chromatography (7:3 hexanes: CH_2Cl_2) provided **14** as a colorless oil (0.218 g, 56%). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 2.77 (td, J = 4.9, 13.2, 1H), 2.58 (td, J = 4.4, 12.7, 1H), 1.83 (td, J = 4.9, 13.2, 1H), 1.72 (td, J = 12.7, 4.4, 1H), 1.26 (s, 15H), 0.897 (s, 9H), 0.110 (s, 3H), 0.0820 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 143.7, 128.7, 128.4, 125.6, 83.8, 45.0, 31.7, 26.3, 26.2, 25.1, 25.1, 18.6, -1.9, -2.4. $^{11}\text{B NMR}$ (160 MHz, CDCl_3): δ = 32.8. **IR** (neat) 2927, 1460, 1372, 1321, 1112, 833, 772, 698 cm^{-1} . **HRMS** (CAB) calcd for $(\text{C}_{22}\text{H}_{39}\text{BO}_3+\text{H})^+$ 391.2844, found 391.2846. **Anal** Calcd for $\text{C}_{22}\text{H}_{39}\text{BO}_3\text{Si}$: C, 67.68; H 10.07. Found: C, 67.42; H, 10.20.

2.5.8. Matteson Homologation Reactions



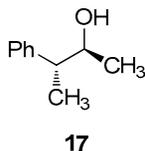
tert-butyl dimethyl((2-methyl-4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)oxy)silane (15). An oven-dried round bottom flask equipped with a stirbar was charged with **14** (0.0600 g, 0.159 mmol), THF (1 mL), and dibromomethane (0.0160 mL, 0.231 mmol). The reaction flask was cooled to $-78\text{ }^{\circ}\text{C}$, upon which *n*-butyllithium (0.145 mL, 0.231 mmol, 1.6 M solution *n*-BuLi in hexanes) was added dropwise over 10 minutes. The reaction flask was allowed to warm to room temperature overnight. After 18.5 h saturated aqueous ammonium chloride (10 mL) was added to the reaction mixture and the aqueous layer was extracted with pentane ($4 \times 10\text{ mL}$). The organic layers were combined and dried with magnesium sulfate, filtered, and concentrated *in vacuo*. Products were isolated by silica gel chromatography. Purification by chromatography (7:3 hexanes: CH_2Cl_2) provided **15** as a colorless oil (0.0121 g, 19%). **$^1\text{H NMR}$** (500 MHz, CDCl_3): $\delta = 7.27$ (t, $J = 7.6$, 2H), 7.18 (m, 3H), 2.71 (m, 2H), 1.81 (m, 2H), 1.34 (s, 3H), 1.24 (s, 12H), 0.891 (s, 9H), 0.107 (s, 3H), 0.099 (s, 3H). **$^{13}\text{C NMR}$** (125 MHz, CDCl_3): $\delta = 143.7$, 128.4, 128.2, 125.4, 82.9, 75.0, 46.6, 30.8, 30.1, 25.9, 24.9, 24.8, 18.2, -2.0.

2.5.9. Hydrosilylation of Ketones¹²



Triethyl((3-phenylbutan-2-yl)oxy)silane (16). An oven-dried resealable solvent flask equipped with a stirbar was charged with (ICy)CuCl (0.010 g, 0.030 mmol), NaOt-Bu (0.019 g, 0.20 mmol), **10** (0.148 g, 1.0 mmol), and 4 mL toluene. The flask was sealed and removed from the glovebox. Degassed triethylsilane (0.800 ml, 5 mmol) was then added to the reaction and the flask was resealed and heated to 80 °C for 19.5 h. The reaction mixture was allowed to cool to room temperature. Activated carbon was added and the mixture was filtered through Celite, rinsed with ethyl acetate and concentrated *in vacuo* affording a yellow oil. The product was used in the next step without further purification. **major diastereomer:** ¹H NMR (500 MHz, CDCl₃): δ = 7.26 (m, 2H), 7.24–7.14 (m, 3H), 3.91 (qn, *J* = 6.1 1H), 2.74 (qn, *J* = 6.7, 1H), 1.25 (d, *J* = 6.8, 3H), 1.05 (d, *J* = 6.3, 3H), 0.88 (t, *J* = 7.8, 9H), 0.48 (m, 6H). **minor diastereomer:** ¹H NMR (500 MHz, CDCl₃): δ = 7.26 (m, 2H), 7.24–7.14 (m, 3H), 3.84 (qn, *J* = 6.3, 1H), 2.65 (qn, *J* = 7.1, 1H), 1.29 (d, *J* = 6.8, 3H), 0.99 (d, *J* = 5.9, 3H), 0.95 (t, *J* = 7.8, 9H), 0.58 (m, 6H).

2.5.10. Reduction of Hydrosilylated Ketone



(2R*, 3S*)-3-phenylbutan-2-ol (17). A flame-dried round bottom flask equipped with a stirbar was charged with **16** (0.295 g, 1.12 mmol), 8 mL of THF and *tert*-butylammonium fluoride (2.24 mL, 2.24 mmol, 1 M solution TBAF in THF) at 0 °C. The reaction was stirred at 0 °C for 5 min and then at 22 °C for 1 h. Deionized water (25 mL) was added and the aqueous layer was extracted with methyl *tert*-butyl ether (3 × 25 mL). The organic layers were combined and rinsed with DI water (3 × 25 mL), dried with sodium sulfate, and concentrated *in vacuo*. Purification by silica gel chromatography (3:7 Et₂O:hexanes) provided **17** as a colorless liquid (0.129 g, 77%) as a 2.5:1 mixture of diastereomers. The product was compared to the literature and the major diastereomer was found to be (2R*, 3S*)-3-phenyl-2-butanol.²² **major diastereomer:** ¹H NMR (500 MHz, CDCl₃): δ = 7.35–7.30 (m, 2H), 7.25–7.18 (m, 3H), 3.84 (m, 1H), 2.67 (qn, *J* = 7.3, 1H), 1.40 (s, 1H), 1.26 (d, *J* = 7.3, 3H), 1.22 (d, *J* = 6.3, 3H). **minor diastereomer:** ¹H NMR (500 MHz, CDCl₃): δ = 7.35–7.30 (m, 2H), 7.25–7.18 (m, 3H), 3.84 (m, 1H), 2.73 (qn, *J* = 6.8, 1H), 1.40 (s, 1H), 1.33 (d, *J* = 6.8, 3H), 1.09 (d, *J* = 6.3, 3H).

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