New Synthetic Applications of Boronic Acid Catalysis for Alcohol Activation

by

Joshua Yakiwchuk

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry

University of Alberta

Abstract

Organic chemistry has its foundations in the 19th century; since, it has grown into a number of industries affecting our daily lives such as the manufacture of goods and life saving pharmaceuticals. The need for new and increasingly efficient synthetic methods has grown in response to the consumerism and industry of the 20th century. Some of the existing methods in synthetic organic chemistry are inefficient processes despite the explosive development over the last 60 years. Currently, there is a search for new, mild and efficient methods to produce common chemical functionality found in many of the goods and drugs used by people every day.

Arylboronic acids are a modular and stable class of compounds and may provide an answer to the replacement of some classical synthetic protocols. Boronic acids in general have an affinity for oxygen acting as Lewis acids through alcohol activation. This thesis investigates boronic acids as viable alternatives to classical catalysts and reagents using alcohols, a ubiquitous functional group, as substrates.

Elimination of alcohols has been a difficult task in organic chemistry for nearly a century requiring harsh conditions and stoichiometric activating agents. Transformation of an inexpensive alcohol, especially a primary alcohol, to an alkene in a mild and catalytic manner would simplify synthetic chemistry providing an alternative to what are harsh and toxic stoichiometric reactions. Chapter 2 will discuss investigations into the dehydrative elimination of alcohols.

Amide bonds are a stable linkage found in all biological systems. Interest in their formation is founded in researching the effect of new peptides and various pharmaceuticals. It is useful to form these linkages in a mild and catalytic manner. Currently, amides are predominately formed by coupling a carboxylic acid with an amine using various coupling reagents and a few catalytic methods; an alternate disconnection such as an alcohol and a nitrile could provide an alternate pathway to synthesize this functionality. The Ritter reaction, an amide formed from an alcohol and a nitrile, lacks wide-spread adoption due to the lack of mild, efficient and general methods. Chapter 3 will discuss an attempt to develop a mild boronic acid catalyzed Ritter reaction.

The Friedel-Crafts alkylation is one of the oldest ways of making bonds with aryl compounds but still enjoys widespread use to this day. Unfortunately, despite the advancement over the last decade, the Friedel-Crafts reaction is still plagued by high temperatures, low functional group tolerance and excessive substrate waste. Chapter 4 will discuss the activation of free benzyl alcohols for the formation of diarylmethanes using Friedel-Crafts chemistry and a novel boronic acid catalyst.

Preface

Some of the research conducted in this thesis forms part of a collaboration as detailed below.

Chapter 2 of this thesis was original research where I conducted all the mentioned research. Hall, D.G. was involved with project conception and initiation.

Chapter 3 of this thesis forms part of a collaboration with an undergraduate research assistant Sun, Y.; I was a supervisor and mentor for this undergraduate research project. I conducted assay and reaction planning, half of the targeted reactions, product characterization and verification. The assay and half of the remaining reactions in Chapter 3 were completed by Sun, Y. Hall, D.G. was involved with project conception and initiation.

Chapter 4 of this thesis has been published as Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703. My role in this broad project consisted of identifying the boundaries of suitable substrates, in particular, deactivated benzylic alcohols, neutral arenes and an application through the synthesis of a small pharmaceutical compound, beclobrate. I also aided in writing and preparing the supporting information. Dansereau, J. performed initial catalyst optimization and substrate scope using *meta*-xylenes as a nucleophile (his contributions to reaction scope are not displayed in this thesis). Mo, X. worked on control experiments, mechanistic study using a deuterated benzyl alcohol, completed various reactions to test the scope of benzylic alcohols and neutral arenes (his contributions to reaction scope are not displayed in this thesis), and was the lead for writing and preparation of the supporting material. Hall, D.G. was the supervisory author and along with McCubbin, J.A. bother were involved with project conception, initiation, troubleshooting and writing of the manuscript.

Acknowledgements

My time at the University of Alberta has allowed me to meet many fabulous individuals. First and foremost, I must extend my gratitude to Dr. Dennis G. Hall who has guided my graduate studies through mentoring and his encouragement to grow by setting challenges which only research can provide. This was a fantastic opportunity working with you and the Hall Research Group.

I would like to extend my appreciation to my Supervisory and Master's Examination Committee: Dr. Todd Lowary, Dr. Charles Lucy and Dr. Frederick West. Thank you for guidance and feedback throughout my research studies at the University of Alberta.

Next I would like to thank Mark Miskolzie, Wayne Moffatt, Randy Whittal and Jason Dibbs for their technical expertise and guidance throughout my research. I greatly appreciated the help of Anita Weiler whom we all know has kept all graduate students in check and provided a cheery environment to all who visit.

Without the support of the Hall Research Group, I'm not sure if any of this would be possible. Thank you for being there through classes, research and all the fun times. Thank you to Xiaobin whom was the first person I met once I moved for graduate studies, we have been through a lot buddy, now on to the next adventure. Thank you Hall Group, I'll miss you guys!

Good times and troubled times have come and gone during my graduate studies but my friendship with You-Ri will remain long after I am gone. Thank you You-Ri for the great friendship we share. I would also like to thank my family: my mom, dad, sister and grandparents; you supported me on dark days and celebrated with me during

Last but definitely not least, I am grateful for my girlfriend Jade who has shouldered my burdens at my side each day; this would have been much more difficult without you.

Finally, thank you to the Department of Chemistry who made this all possible.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

ºC	Degrees Centigrade or degrees Celsius
ΔG^o	Standard Gibbs Free Energy
ACS	American Chemical Society
Aq	Aqueous (as a solution in water)
Ar	Arene (represents a general arene moiety)
BAC(s)	Boronic acid Catalyst(s)
BDE	Bond Dissociation Energy
Cat	Catalyst
CBS	Corey-Bakshi-Shibata
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEE	Diethyl Ether
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DNBSA	2,4-Dinitrobenzenesulfonic acid
E_a	Energy of Activation or Activation Energy
E_i	Elimination inter/intramolecular
EDG	Electron Withdrawing Group
Equiv.	Equivalents
EWG	Electron Drawing Group
FBAHA	Ferroceniumboronic acid hexafluoroantimonate
FGI	Functional Group Inter-conversion
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
L, **L_n**	Ligand(s)
LG	Leaving group
M	Metal atom
M.S.	Molecular sieves
***m*CPBA**	*meta*-Chloroperoxybenzoic acid
MEK	Methyl Ethyl Ketone

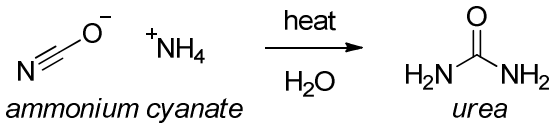
MIBA	5-Methoxy-2-iodophenylboronic acid
mmol	Millimole
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
o/m/p	*Ortho/meta/para*
PCC	Pyridinium Chlorochromate
PFBA	2,3,4,5,6-Pentafluorophenylboronic acid
pKa	pKa = $-\log_{10}$ of the acid dissociation constant for a given compound
PTC	Phase-Transfer Catalysis
Pyr	Pyridine
R, $\mathbf{R^1}$, $\mathbf{R^2}$…$\mathbf{R^n}$	Represent a general alkyl moiety or various other moieties as specified
RT	Room Temperature (25º C)
TFBA	2,3,4,5-Tetrafluorophenylboronic acid
TLC	Thin-Layer Chromatography
Tol	Toluene
Ts	Tosyl

1 Introduction: Investigations into Catalysis Involving Boronic Acids and Derivatives

1.1 The Catalytic Advantage

1.1.1 Origins of Organic Synthesis

Organic synthesis has its foundation in Germany, 1828, with the discovery of a simple reaction converting ammonium cyanate into urea, also known as the Wöhler synthesis (**Scheme 1-1**).[1]



Scheme 1-1: Wöhler synthesis.

This work is cited as one of the first known syntheses of an organic compound.[2] Although simplistic in nature, the idea of forming organic material from inorganic material would proceed to spawn further investigations disproving the common 19th century idea of Vitalism: the belief in an extra, vital force which was thought to be required for all organic syntheses.[3] Wöhler laid the groundwork for Adolf von Baeyer to advance industrial chemistry due to his efforts in the synthesis of various organic dyes including indigo, which was a relatively unknown concept in the 19th century.[4]

A number of years later, a young employee of the Friedrich Bayer & Company, a chemist by the name of Felix Hoffman sought to find a method of producing a less irritating salicylate. Following the previous work of chemists such as von Glim, and Kraut, Hoffman managed to improve the production of acetylsalicylic acid using a combination of the Kolbe Synthesis followed by refluxing salicylic acid with acetic anhydride. This work was a remarkable achievement for the year 1897 as it is commonly noted as one of the first industrial syntheses for

pharmaceutical purposes.[5] Once acetylsalicylic acid was marketed as Aspirin, its effectiveness, improved tolerability and reliable synthesis drove it to become a landmark drug. The advent of the pharmaceutical industry provided a reason for scientists to study the synthesis of organic compounds.[6] Industrial and commercial synthesis became an additional drive for this new research which advanced organic synthesis to new heights.

Nearing the mid 20th century, larger synthetic targets were tackled, but without much success, with the exception being Paul Rabe's synthesis of quinine in 1918.[7] Synthesis of increasingly complex molecules followed over the next few decades, when a prodigy emerged: Robert Woodward, Nobel Laureate in 1965. His life was dedicated to solving problems such as designing synthetic routes to many molecules considered complex or previously unobtainable due to a lack of strategy.[8]

The synthesis of strychnine was important due to its impact on the development of synthetic chemistry as a tool which facilitated organic structure determination at the time.[9] On the other hand, reserpine was the most complex synthesis of that era, with seven asymmetric stereocentres, a remarkable advancement from the few years prior.[10] Using his knowledge of physical organic chemistry, Woodward was the first chemist to inductively predict chemical reactivity and product outcome in the synthesis of a complex target, in many cases a natural product, with great success.[11] Such conceptual advancement led to great organic syntheses like the synthesis of morphine,[12] chlorophyll[13] and vitamin B_{12},[14] followed by numerous other achievements by many chemists which are still grand achievements to this day (**Figure 1-1**).

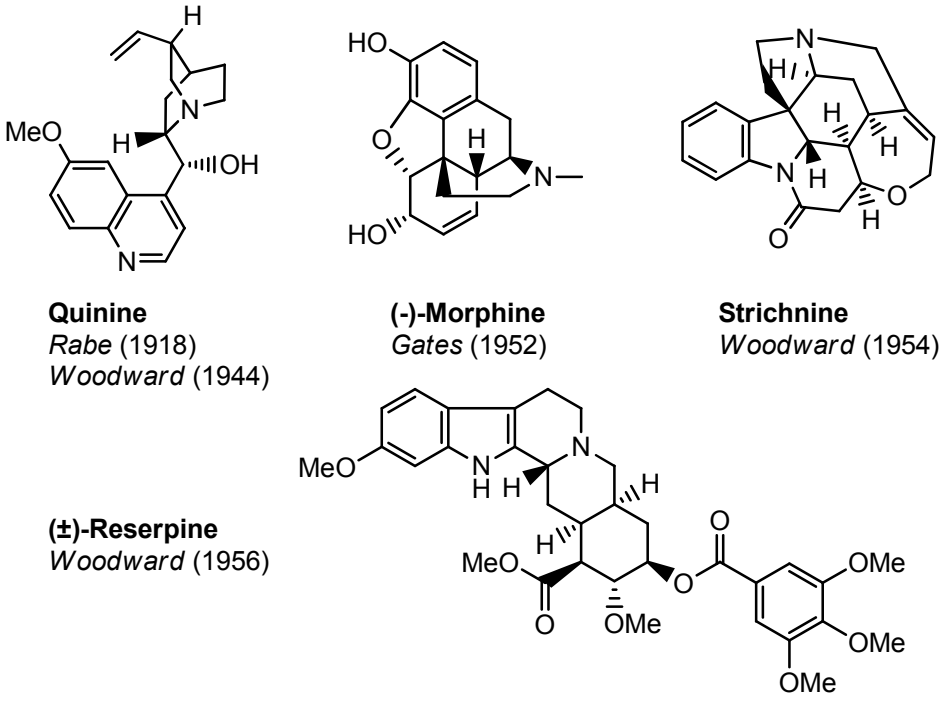


Figure 1-1: Early synthetic targets of the 20th century.

Synthesis of many biologically active targets allowed both chemists and biologists to gain an understanding of their effects on humans and inspired the scientific community to produce new and interesting molecules such as cephalosporin[15], which improved upon the antibacterial capabilities of the biologically obtained penicillin V. Syntheses became targeted as in the case of Chlorthiazide, which originated from a search for an effective antihypertensive agent.[16] The post-war consumerism pushed science to the edge of innovation and led to investigation into the synthesis of many pharmaceuticals and material products (**Figure 1-2**).

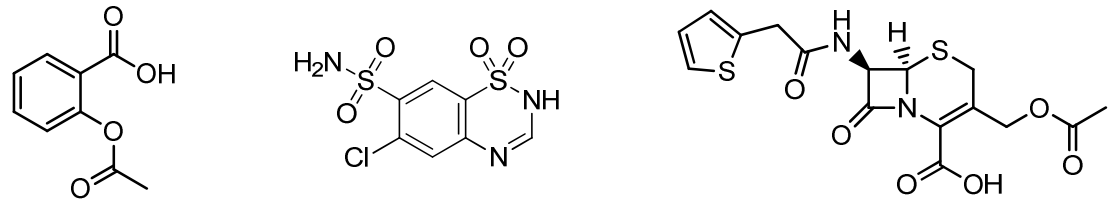
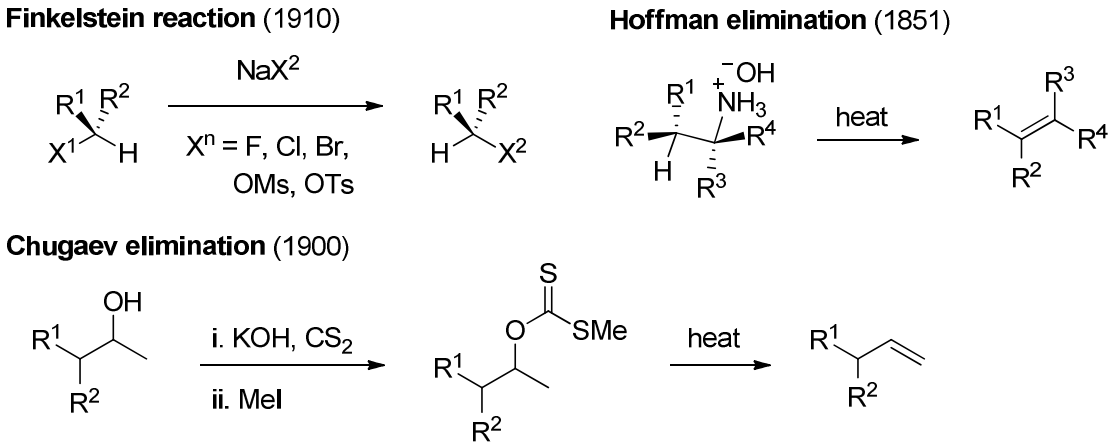


Figure 1-2: Early synthetic pharmaceuticals.

1.1.2 Stoichiometric Synthesis

Increased demand for useful chemical and pharmaceutical compounds during World War I accelerated the need for new chemical reactions. Until this point, the vast majority of chemical reactions had been stoichiometric, meaning: an equal molar amount of reagent was used for a particular chemical transformation of a substrate, but in many cases an excess of reagent was added to push the reaction to consume all of the starting material (**Scheme 1-2**). Stoichiometric reactions may be broken down into a few different classes but two of the most basic transformations are those that provoke functional group inter-conversion and more importantly, coupling-type reactions that combine two molecular fragments into a larger molecule.

Early efforts at functional group inter-conversion (FGI) included reactions such as the Finkelstein reaction for inter-conversion of various halides,[17] Chugaev elimination as a method of dehydration,[18] and transformations such as the Hoffmann elimination transforming a secondary amine into an olefin.[19] The products of the aforementioned reactions could undergo further functionalization toward the desired synthetic target.

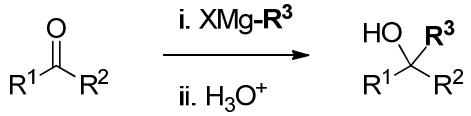


Scheme 1-2: Early methods of functional group inter-conversion.

Converting a chemical functionality to another is important to enable access to a diverse set of chemical moieties. Although, when it comes to increasing the complexity of a molecule, carbon-carbon/carbon-heteroatom bond forming reactions are far more prevalent.

Some of the early carbon-carbon bond forming reactions resulted in symmetric products by using sodium coupling, which was displayed by exploratory chemistry of Wurtz[20] and Fittig[21] who found that mixing sodium metal with either alkyl iodide or aryl bromide led to dimerized products. Following this discovery, many decades would pass until the emergence of a method for production of more useful asymmetric adducts.

The Grignard reaction is a landmark carbon-carbon bond formation whereby a halo-alkyl magnesium salt is reacted with a carbonyl resulting in formation of an adduct combining the two organic moieties (**Scheme 1-3**).[22] This reaction was a notable achievement since it expanded the functionality of carbonyls and increased chemists' ability to create complex structures.[23]



Scheme 1-3: Grignard reaction.

Expanding molecular complexity is also commonly achieved through the formation of amides. Amide formation is commonly found in the synthesis of biologically active molecules such penicillin V.[24] A classical method of synthesizing amide moieties is the Schotten–Baumann reaction, which involves use of a reactive acid chloride and a primary or secondary amine (**Scheme 1-4**).[25] This reaction has an advantage of combining two different moieties, although at the cost of producing one equivalent of acid, which reduces overall efficiency.

Scheme 1-4: Schotten-Baumann reaction (1884).

Despite their utility, the aforementioned reactions all have one common drawback: they are all stoichiometric.

1.1.3 Transitioning to Catalysis

Many stoichiometric reactions have yet to be replaced by general catalytic alternatives, although some chemical reactions already have a catalytic variant. Catalytic reactions can often be defined as having a sub-stoichiometric amount of a chemical compound, the catalyst, which increases the rate of the reaction by lowering the energy of activation without influencing the reaction equilibrium.[26] The advantages of catalytic systems have become increasingly apparent over the years especially in the context of large scale industrial and pharmaceutical syntheses. Catalysts allow reactions to proceed that would not be otherwise possible (**Figure 1-3**).[27] The recent field of Green Chemistry pushes for overall waste reduction; catalysis is but one method of pursuing this goal.[28]

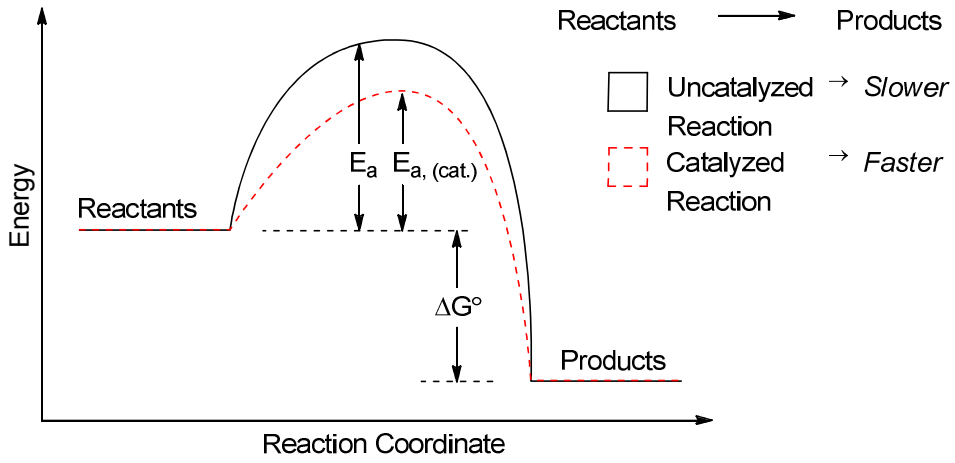


Figure 1-3: Catalysis – Energetics and rates.

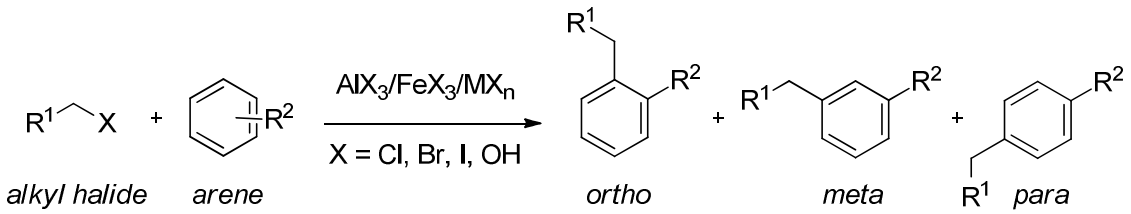
Green Chemistry traditionally consists of twelve principles that can be simplified as the reduction of: waste, risk, impact and cost (**Figure 1-4**).[29] Catalysis, one of the twelve principles of green chemistry, has a great opportunity to abide by many if not nearly all the other principles, if implemented in an appropriate manner. This ideal requires the development of catalysts for high-impact chemical reactions and transformations.

12 Principles of Green Chemistry

1) Safety Control
2) Atom Economy
3) Reduced Toxicity
4) Safer Chemical Reagents
5) Safer Solvents/Auxiliaries
6) Energy Effeciency
7) Renewable Feedstock
8) Shorter Synthesis
9) Catalysis
10) Design for Degradation
11) Pollution Prevention
12) Accident Prevention

Figure 1-4: Twelve principles of Green Chemistry.

An early example of a carbon-carbon bond forming reaction is known as the Friedel-Crafts reaction. Since its discovery in 1877, the Friedel-Crafts reaction has enabled numerous examples of alkylation and acylation of various aromatic compounds, traditionally using alkyl and acyl halides and harsh Lewis acids (aluminum trichloride and iron trichloride).[30] Although Friedel-Crafts reactions can function catalytically, in many cases a super-stoichiometric amount of Lewis acid is used to enhance reaction yield (**Scheme 1-5**).[31] Furthermore, the Friedel-Crafts reaction does suffer from a few issues: use of toxic alkyl and acyl halides, various reaction side products, over-alkylation of the initial arene product, and many structural isomers due to issues with positional selectivity (*ortho*, *meta* and *para*).[32] Finding a suitable catalytic variant can help old chemistry to abide by the principles of Green Chemistry. The Friedel-Crafts reaction can be scaled-up easily but is somewhat limited in application. Continued research and will lead to more active and tolerant transition-metal chemistry, a new field closely linked with many of the catalytic reactions used by chemists to this day.

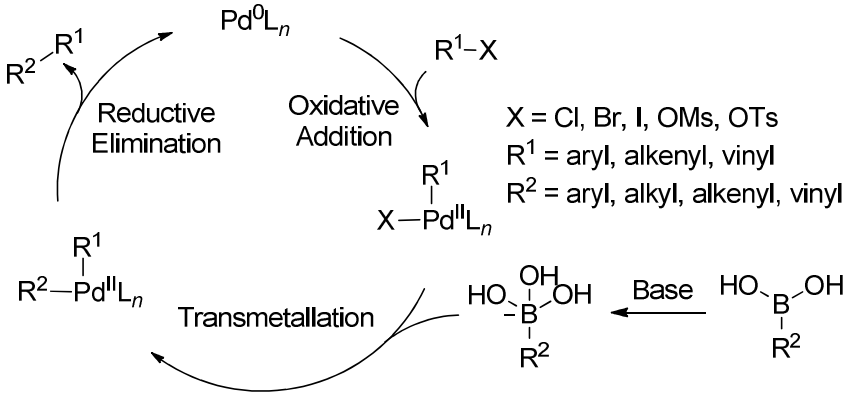


NOTE: Positional selectivity on arene is influenced by R^2: if R^2 is an EDG, then *ortho*/*para* selectivity is expected but if R^2 is an EWG then *meta* substitution is expected.

Scheme 1-5: Friedel-Crafts alkylation (1877).

Catalytic cross-coupling with transition metals emerged due to the development of palladium chemistry in the mid-late 20th century. The first examples of catalytic coupling were observed by Meerwein (1939)[33] and Kharasch (1941/1943)[34] who were able to provide the first asymmetric sp^2-sp^2 cross-coupling reactions with the use of a deactivated sp^2 centre which was reacted with nucleophilic diazonium salts or an aryl Grignard reagent. The significance of the studies by Meerwein and Kharasch is that transition metals could possibly promote the formation of carbon-carbon bonds, but are only required in a sub-stoichiometric amount.

The arrival of palladium-based cross-coupling chemistry gave rise to what is the most widely used and popularized class of reactions: Mizoroki-Heck, Negishi, and Suzuki-Miyaura reactions, amongst others. The Nobel Prize for 2010 was awarded to Richard Heck, Ei-ichi Negishi and Akira Suzuki for these practical methods of carbon-carbon bond formation. While the Heck, Negishi and Suzuki-Miyaura reactions all occur in a similar manner, it was the latter that became most prevalent due to the nature of its starting materials (**Scheme 1-6**). The Suzuki-Miyaura cross-coupling consists of a palladium catalyst, an aryl halide, an aryl or alkyl boronate and a base.[35] Suzuki-Miyaura cross coupling has been extended to include alkyl boronates following the development of various ligands which modulate the catalyst's activity.[35]



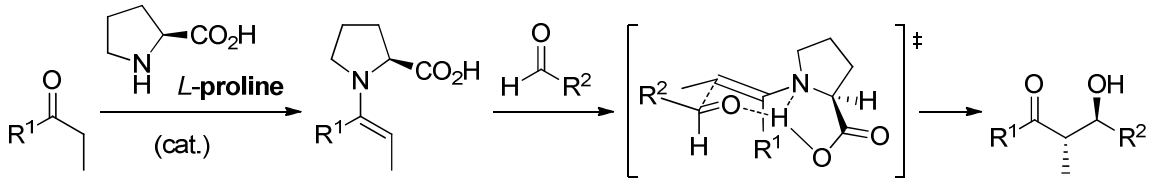
Scheme 1-6: The Suzuki-Miyaura cross-coupling reaction.

Transition metal catalysts can produce some remarkable transformations, many of which are catalytic but are plagued with high cost and various levels of toxicity. Indeed, a large number of catalytic reactions used today by the chemical industry involve transition metal catalysts, but there is an increasing drive toward replacements that do not require their use.[36] The push for an alternative to transition metals is driven by attempts to reduce cost while improving efficiency, and to reducing the environmental impact of reactions. One of the many methods of addressing these concerns comes in the form of organocatalysis.

1.1.4 Organocatalysis

Transition metals have been firmly rooted as efficient catalytic systems for decades, in many cases producing optically enriched products.[37] The most widely accepted alternative to transition metals is organocatalysis. Organocatalytic reactions generally are performed using small, abundantly available or derived organic molecules.[38] Organocatalysis generally proceeds through a few main mechanistic pathways: formation of temporary covalent bonds, acid/base catalysis and phase-transfer catalysis.

One of the most commonly cited examples of organocatalysis is that of enamine catalysis (**Scheme 1-7**). Enamine catalysis usually enlists a proline derivative to form a temporary covalent bond via condensation with a carbonyl group as a way of priming a substrate to be the nucleophilic component of an aldol reaction.[39] The temporary chiral amine moiety can subsequently transmit its stereochemical information through a Zimmerman-Traxler type transition-state thereby resulting in a chiral cross-aldol product.[40] The mechanistic proposal is also supported by various computational theories supporting the observed product.[41]

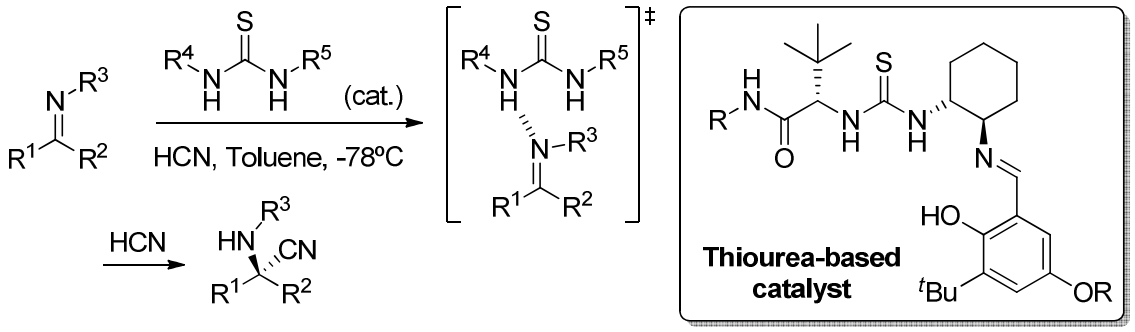


Scheme 1-7: Covalent organocatalysis – Enamine catalysis of an aldol reaction.

Organocatalysis is also encountered in the form of acid/base catalysis which may commonly be categorized as such:

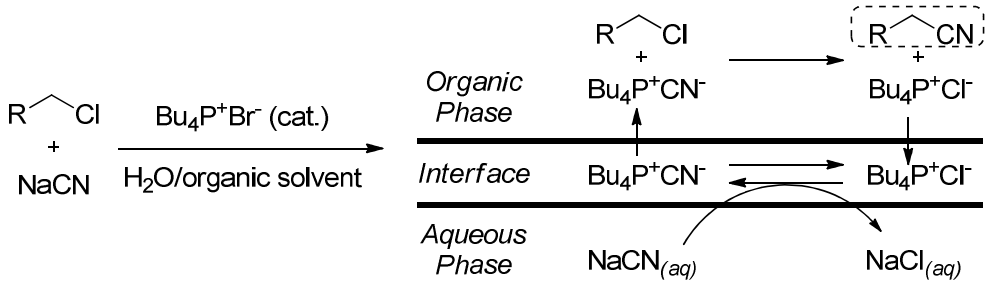
1. **Specific catalysis** – where the reaction rate is accelerated due to the aid of a specific acid in a pre-equilibrium step, usually a protonated form of the solvent.
2. **General catalysis** – where an acid is directly involved in the rate determining step of a reaction as is the case with other catalytic reactions.[42]

One famous example of an organic Brønsted acid is the thiourea-derived catalyst.[43] One of the first uses of the organocatalytic thiourea-derivative was observed in the Strecker reaction, an addition of hydrocyanide to an imine yielding a chiral amine (**Scheme 1-8**).[44] Thiourea catalysts owe their activity to hydrogen bonding with the imine or carbonyl substrate, which activates the substrate for nucleophilic attack. Including an appropriate chiral scaffold allowed additions to thiourea-activated imines and carbonyls to become highly enantioselective, a significant achievement considering the absence of any metal catalyst.[45]



Scheme 1-8: Non-covalent catalysis – Thiourea catalyzed Strecker reaction.

Phase-transfer catalysis (PTC) is a method that can enable a reaction between two substrates with vastly different polarities.[46] One example of PTC is using non-polar alkyl halides, as substrates which could be subjected to a displacement reaction by use of a polar inorganic salt.[46] The PTC reaction involves counter-ion exchange between the salt and a catalytic amount of a phase-transfer agent; this strategy circumvents many solubility issues through use of this biphasic, aqueous-organic system. The phase-transfer agent facilitates movement of the nucleophilic anion from the aqueous phase into the organic phase where the reaction occurs.[47] Traditionally, large alkyl ammonium or phosphonium cations are employed to make anionic species soluble in organic solvent; therefore, these nucleophilic anions are allowed to interact with the halide electrophile in non-polar organic solutions under mild conditions.[48] It is not unusual for PTC to enable reactions that may not ordinarily occur under a given set of conditions, as is the case with cyanation of an alkyl halide using sodium cyanide.[49] Even in the cases where the reaction is normally possible, PTC conditions sometimes enable higher yielding, milder and safer reaction conditions. Further application includes choosing a chiral, optically pure ammonium or phosphonium counter-ion, and subsequently, these reactions can yield enantiomerically enriched products increasing their utility.[50] An alternative yet similar strategy to PTC is use of crown ethers, which can effectively render an anion hydrophobic, and therefore soluble in organic media allowing for reactivity with other organic compounds.[51]



Scheme 1-9: Phase-transfer catalysis –Tetrabutylammonium catalyzed cyanation.

It is clear that organocatalysis has become a powerful and effective synthetic tool for organic chemists. Currently, catalytic organic molecules have shown that despite their promising uses, they haven not yet become replacements for transition metals. The determination of researchers is leading them to pursue increasingly benign but effective catalytic reactions; one area of this research has led to investigzation of boron as a pseudo-metal surrogate with unique properties.

1.2 Properties of Boronic Acids and Esters

Boron is known as a relatively benign, non-metallic element.[52] Clever exploitation of the vacant *p*-orbital present in boron has allowed boron-containing molecules to be capable of gaining some of the reactivity of transition-metals.[53] The Lewis acidity of some boron compounds has a profound effect on its reactivity, in some cases allowing them to perform chemistry ordinarily observed via transition metal species.[54] Although boron may exist in many forms, some of the most common are boranes, boronic acids and boronate esters. Their structure can be varied to moderate their Lewis acidity and even affect their stability.

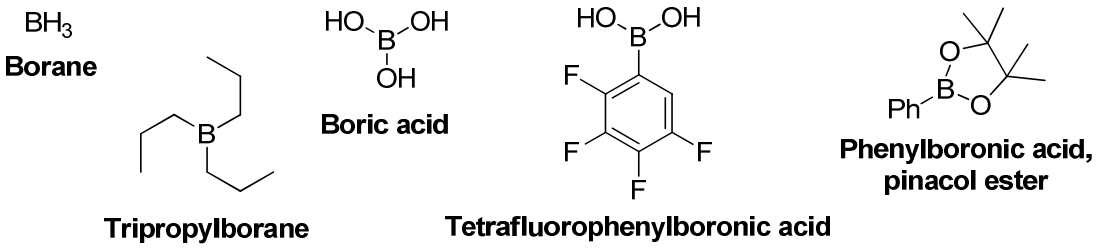


Figure 1-5: Common boranes, boronic acids, and boronic esters.

The stability of various boron species is a major reason for their popularity with modern chemists. In general, boranes and borinic acids are readily oxidized, which lead to one of the more stable classes of boron compounds, boronic acids.[55] Boronic acids and esters are extremely useful, appearing in many synthetic transformations, the most famous of which is the Suzuki-Miyaura cross-coupling reaction.[56]

As the utility of boronic acids increased, some researchers have initiated investigations into how their activity can be adjusted and controlled (**Figure 1-6**). The attractiveness of boronic acids in any role lies in their modularity, particularly the aryl derivatives.[57] There are a number of sites that can be adjusted to affect the Lewis acidity of aryl boronic acids and they include:

- Functional groups on the arene: particularity the electronic nature of any functional group on said arene, EWG or EDG may influence the acidity of boron through resonance or induction.[58]
- The *ortho*-group of the arene: this has a cooperative effect with substrate binding and activation.[55]
- The ester derivative of the boronic acid: this unit can affect the electronics of the boronic acid as well; in general the pKa of the boronic ester is lower than pKa of the boronic acid.[59]

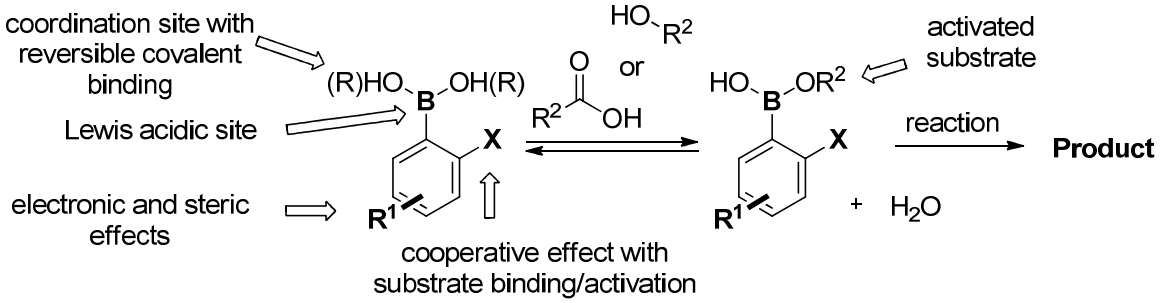


Figure 1-6: Reactivity of arylboronic acids.

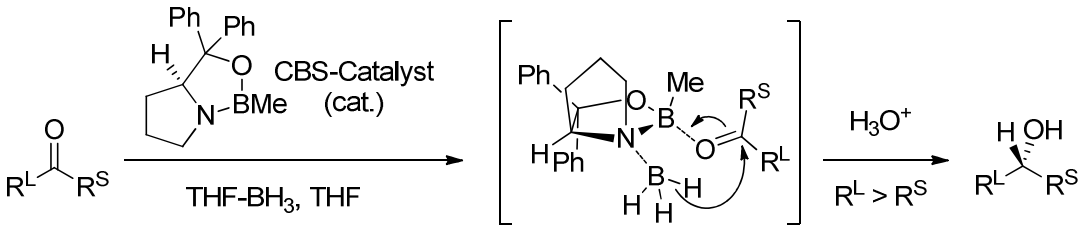
Boron chemistry relies upon the vacant or occasionally filled *p*-orbital to allow a ligand exchange and activation of a newly bound substrate; this allows the activated species to become susceptible to further reactivity. The degree to which this will occur depends upon the Lewis acidity of the boron species, the steric properties of the molecule and the nature of nucleophile complexed with boron. Some of these properties of boron can be observed in the Matteson homologation,[60] allylboration reactions,[61] and some Friedel-Crafts reactions.[57]

As chemists studied boronic acids, in many cases a clear trend emerged, the affinity of boron with oxygen. The reversibility of this boron-oxygen bond is an important virtue of boronic acids such that this unique element can exploit available oxygen atoms and activate them to undergo various synthetic transformations.

1.3 Boronic Acid Catalysis

The relationship between boron and oxygen blossomed into various catalytic reactions where boron-containing compounds are used in stoichiometric and eventually catalytic application.

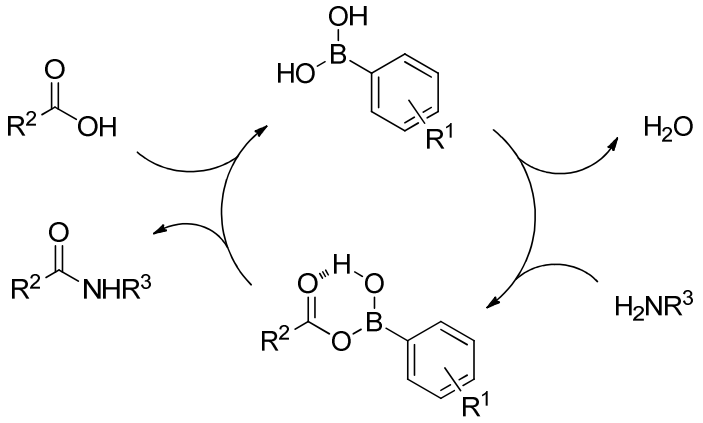
One of the first noted examples of a catalytic boron compound is in the Corey-Bakshi-Shibata (CBS) reduction, which affords a chiral alcohol in high enantioselectivity when reduced from its ketone counterpart (**Scheme 1-10**).[62] A CBS reduction was groundbreaking at the time due to it functioning without harsh reducing agents such as lithium aluminum hydride;[63] only the ketone substrate, CBS reagent and borane are required for asymmetric reduction.[64] Here boron acts as a Lewis acid aiding in the activation of the ketone and priming it for a subsequent reduction.



Scheme 1-10: Generalized CBS-reduction.

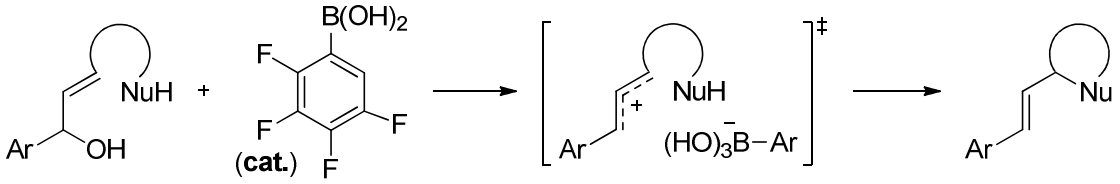
This robust CBS catalyst has seen use in the synthesis of many natural products and was incorporated in large scale production of pharmaceuticals.[65] Effective catalysts in the pharmaceutical industry are considered to be safe and capable of efficiently producing large quantities of useful synthetic products.[66]

The unique properties of mild boron-containing molecules allow for many organocatalytic reactions and replacement of some reagents with associated toxicity or low atom-economy. Transformations resulting in formation of amide functionality are a great example. Amide bond formation is prominent in synthesis and the pharmaceutical industry.[67] Amide formation is a transformation which in some cases is still catalyzed via toxic metal catalysts[68] but the main issue is the use of toxic and stoichiometric peptide coupling reagents.[69] Many boronic acids such as 3,4,5-trifluorophenylboronic acid,[70] bifunctional derivatives like) 2-(dimethylamino methylphenylboronic acid,[71] and even 2-iodo-5-methoxyphenylboronic acid[72] can catalyze amide formation directly from a carboxylic acid and an amine in a mild and efficient manner with minimal generation of waste (**Scheme 1-11**).

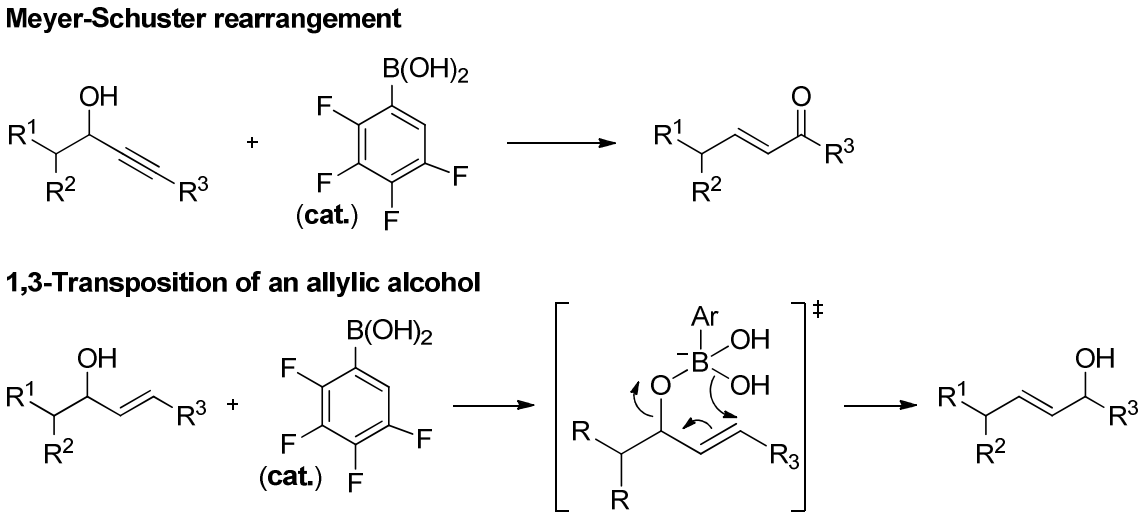


Scheme 1-11: Boronic acid catalyzed amide bond formation.

Boronic acid catalysis is also a simple yet effective form of alcohol activation to provoke what is traditionally mediated by metal and harsh stoichiometric reactions. One example of boronic acid catalyzed alcohol activation can be observed in the direct carbo- and heterocyclizations of allylic alcohols (**Scheme 1-12**).[73] The Meyer-Schuster rearrangement and the 1,3-transposition of allylic alcohols constitute other examples of reactions that may be catalyzed by boronic acids (**Scheme 1-13**).[74] Reactions involving the activation of allylic alcohols were previously predominated by strong acids and transition metals such as rhenium. These have now become accessible via organocatalysis following the discovery of tetrafluorophenylboronic acid.



Scheme 1-12: Boronic acid catalyzed carbo- and heterocyclizations.



Scheme 1-13: Boronic acid catalyzed migration of activated alcohols.

Advancements such as these aid synthetic efforts by providing mild alternatives that are more tolerant of various functional groups and can avoid many of the safety concerns associated with some older chemistry. As will be discussed in this thesis, it is important to note, that arylboronic acids are not simple Lewis acids; their activity is not always explainable by conventional methods.

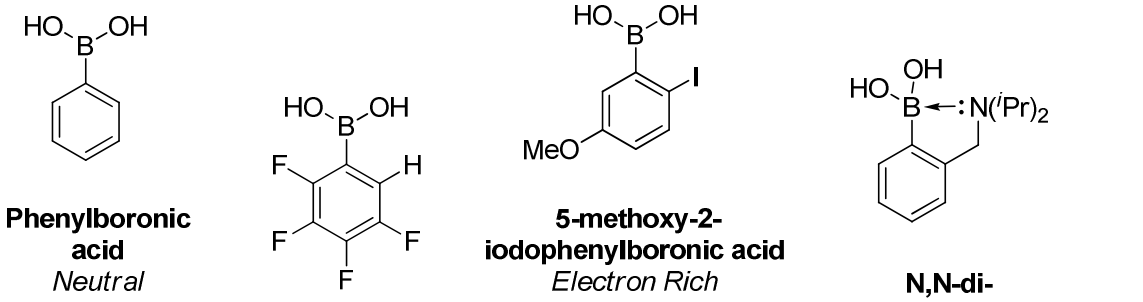


Figure 1-7: Various arylboronic acid catalysts.

Increasingly, it is clear that the *ortho*-substituent of arylboronic acids plays a role in not only the Lewis acidity of this species but with its reactivity as well. More complex catalysts such as bifunctional boronic acid derivatives have been observed, one of which was N,N-di-isopropylbenzylamineboronic acid also used in amide coupling[71] and another variant bifunctional

catalyst that is capable of catalyzing the condensation of carboxylic acids.[75] These examples provide an obvious example that the optimized catalysts where several modes of activation are possible. The aforementioned observations warrant investigation into the activity of arylboronic acids in various catalytic reactions.

1.4 Thesis Objective

Uncovering the catalytic activity of arylboronic acids is a step in advancing organocatalysis and avoiding harsher conditions involving transition metals. The ability to fine-tune the reactivity of the *pseudo*-metallic arylboronic acid is paramount in achieving mild yet catalytic processes. Investigation of new catalytic transformations involving arylboronic acids has the potential to find intriguing and informative chemical reactivity of these recently discovered organocatalysts. Thus, the overall goal of this thesis is to further expand the available portfolio of transformations which can be catalyzed by boronic acids.

Looking through classical literature and textbooks, it is clear that some of the most difficult chemical transformations are sometimes the simplest. One example is the elimination of a primary aliphatic alcohol. Although there are exceptional circumstances in which elimination of an alcohol can be achieved, all current methods employ either harsh conditions, or a two-step method involving a functional group interconversion of the alcohol followed by subsequent elimination. Existing methods often use toxic reagents and/or lack atom-economy. Chapter 2 discusses the search for an oxophilic boronic acid to catalytically eliminate a primary alcohol leaving only an alkene in its place.

Amides, ubiquitous in modern pharmaceuticals are a desirable linkage; and most catalytic amide forming reactions involve the condensation between an amine and a carboxylic acid. Alternative disconnections would allow further masking of the amide functionality and new synthetic routes to target molecules; this suggests new catalytic reactions to form amides would be useful to synthetic chemists. The Ritter reaction is one such alternative disconnection, facilitating the coupling of an alcohol and a nitrile with subsequent hydrolysis into an amide. Chapter 3 will discuss modifications to the Ritter reaction in an attempt at finding a catalytic variant.

Friedel-Crafts reactions have enjoyed widespread use since their discovery in 1877. The search for a modern catalytic Friedel-Crafts reaction has seen much success although with a few major drawbacks: the inclusion of transition metals as the active catalyst and harsh reaction conditions. Chapter 4 will discuss a new Friedel-Crafts alkylation protocol involving a *tetra*-ionic arylboronic acid catalyst with alcohols as substrates as one method of providing mild and functional-group tolerant reaction conditions.

Although arylboronic acids have been well known as coupling partners in the Suzuki-Miyaura reaction for nearly half a century, it is clear that their potential catalytic activity have left much to be discovered. Probing for new and interesting reactions involving arylboronic acids is just one method of understanding a little more about this unique and emerging class of catalysts.

1.5 References

1 Wöhler, F. Annalen der Physik und Chemie **1828**, 88, 253–256.

2 Cohen, P.S.; Cohen, S.M. *J. Chem. Ed.* **1996**, *73*, 883-886.

3 Minden, H. T. *Physics Today* **1994**, *47*, 124–125.; Cohen, P.S.; Cohen, S.M *J. Chem. Ed.* **1996**, *73*, 883-886.

4 De Meijere, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7836–7840.

5 Ugurlucan, M.; Caglar, I.M.; Caglar, F.N.T.; Ziyade, S.; Karatepe, O.; Yildiz, Y.; Zencirci, E.; Ugurlucan, F.G.; Arslan, A.H.; Korkmaz, S.; Filizcan, U.; Cicek, S. *Recent Patents on Cardiovascular Drug Discovery* **2012**, *7*, 71-76.

6 Stone, E. Philosophical Transactions of the Royal Society of London **1763**, 53, 195-200.

7 Rabe, P. and Kindler, K. *Chem. Ber.* **1918**, *51*, 466-467.

8 Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; John Wiley & Sons: New York, 1996.

9 (a) Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751. (b) Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247-288.

10 (a) Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. *J. Am. Chem. Soc.* **1956**, *78*, 2023–2025. (b) Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. *J. Am. Chem. Soc.* **1956**, *78*, 2657-2657. (c) Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. *Tetrahedron* **1958**, *2*, 1-57.

11 Craig, G.W. *Helv. Chim. Acta.* **2011**, *94*, 923-946.

12 Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380–1393.

13 Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P. *et al*. *J. Am. Chem. Soc.* **1960**, *82*, 3800–3802.

14 Woodward, R.B. *Pure Appl. Chem.* **1961**, *2*, 383-404.; Woodward, R.B. *Pure Appl. Chem.* **1973**, *33*, 145-178.

15 Synthesis of Cephalosporin C1: Woodward, R.B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852–853.

16 (a) Novello, F.C.; Sprague, J.M. *J. Am Chem Soc.* **1957**, *79*, 2028-2029. (b) Beyer, K.H.; Baer, J.E.; Russo, H.F.; Haimbach, A.S. *Fed Proc.* **1957**, *16*, 282.

17 Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528–1532.

18 Tschugaeff, L. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3118–3126.

19 von Hofmann, A.W. *Justus Liebigs Ann. Chem.* **1851**, *78*, 253–286.

20 Wurtz, A. *Ann. Chim. Phys.* **1855**, *44*, 275–312. Wurtz, A. *Ann. Chem. Pharm.* **1855**, *96*, 364–375.

21 (a) Fittig, R. *Justus Liebigs Ann. Chem.* **1862**, *121*, 361–365. (b) Verified by Tollens: Tollens, B.; Fittig, R. *Justus Liebigs Ann. Chem.* **1864**, *131*, 303–323. (c) Tollens, B.; Fittig, R. *Justus Liebigs Ann. Chem.* **1864**, *129*, 369–370.

22 (a) Grignard, M.V.; Moissan, M.H. *Compt. Rend.* **1900**, *130*, 1322-1324. (b) Ashby, E.C. *Q. Rev. Chem. Soc.* **1967**, *21*, 259-285.; Ashby, E.C.; Lammele, J. (c) Neumann, H.M. *Acc. Chem. Res.* **1974**, *7*, 272–280.

23 Shirley, D. A. *Org. React.* **1954**, *8*, 28–58.

24 Synthesis of Penicillin V by Sheehan, with a variation of the Schotten-Baumann reaction: Sheehan, J.C.; Henry-Logan, K.R. *J. Am. Chem. Soc.* **1957**, *79*, 1262–1263.

25 (a) Schotten, C. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2544–2547. (b) Baumann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 3218–3222.

26 IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). XML on-line corrected version: http://goldbook.iupac.org (2006) created by M. Nic, J. Jirat, B. Kosata; updates compiled by A. Jenkins. http://goldbook.iupac.org/C00876.html (accessed June 18th, 2015).

27 Anastas, P.T. *Aldrichchimica Acta* **2015**, *48*, 3-4.

28 (a) Wilson, M.P.; Schwarzman, M.R. *Environ Health Perspect.* **2009**, *117*, 1202–1209. (b) Taylor, D.A. *Environ Health Perspect.* **2010**, *118*, A254–A257.

29 Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, U.K.; 1998.

30 Friedel, C.; Crafts, J.-M. *Compt. Rend.* **1877**, *84*, 1392- 1395.

31 Rueping, M.; Nachtsheim, B.J. *Beilstein Journal of Organic Chemistry* **2010**, *6* (6), 1-24.

32 (a) Calloway, N.O. *Chem. Rev.* **1935**, *17*, 327–392. (b) Rueping, M.; Nachtsheim, B.J. *Beilstein Journal of Organic Chemistry* **2010**, *6* (6), 1-24.

33 Meerwein, H.; Buchner, E.; van Emster, K. *J. Prakt. Chem.* **1939**, *152*, 237–266.

34 (a) Kharasch, M.S.; Fields, E.K. *J. Am. Chem. Soc.* **1941**, *63*, 2316–2320. (b) Kharasch, M.S.; Fuchs, C.F. *J. Am. Chem. Soc.* **1943**, *65*, 504–507.

35 Johansson Seechurn, C.C.C.; Kitching, M.O.; Colacot, T.J. Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.

36 Chorkendorff, I.; Niemantsverdriet, J. W. *Introduction to Catalysis, in Concepts of Modern Catalysis and Kinetics*; Wiley-VCH: Weinheim, 2003.

37 Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis*. Wiley-VCH: Weinheim, 1996.

38 List, B.; Yang, J.W. *Science* **2006**, *313*, 1584-1586.

39 Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.

40 List, B.; Lerner, R.A.; Barbas III, C.F.B. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

41 (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911-12912. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273-11283.

42 Jencks, W.P. *Acc. Chem. Res.* **1980**, *13*, 161-169.

43 Taylor, M.S.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543.

44 Vachal, P.; Jacobsen, E.N. J. Am. Chem. Soc. 2002, 124, 10012-10014.

45 Brak, K.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.

46 Maruoka, K. *Asymmetric Phase Transfer Catalysis*. Wiley-VCH: Weinheim, 2008.

47 Starks, C.M. *J. Am. Chem. Soc.* **1971**, *93*, 195-199.

48 Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4226.

49 Starks, C.M.; Owens, R.M. *J. Am. Chem. Soc.* **1973**, *95*, 3613-3617.

50 Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348.

51 Pedersen, C.J. *Angew. Chem. Int. Ed.* **1988**, *27*, 1021-1027.

52 (a) Nielsen, F.H. *Plant and Soil* **1997**, *2*, 199-208. (b) Howe, P.D. *Biol. Trace Elem. Res.* **1998**, *66*, 153-166.

53 (a) Toporcer, L.H.; Dessy, R.E.; Green, I.E. *Inorg. Chem.* **1965**, *4*, 1649-1655. (b) Fehlner, T.P. The Metallic Face of Boron. In *Advancesin Inorganic Chemistry*; Skyes, A.G., Ed.; Academic Press: Orlando, 1990; Vol. 35; p 199-233. (c) Hermann, A.; McSorley, A.; Ashcroft. N.W.; Hoffmann, R. *J. Am. Chem. Soc.* **2012**, *134*, 18606-18618.

54 Houghton, R.P. *Metal Complexes in Organic Chemistry*; Cambridge University Press: Cambridge, 1979.

55 Hall, D.G. Strucuture, Properties, and Preparation of Boronic Acid Derivatives. Overview of their Reactions and Applications. Chapter 1 in *Boronic Acids*, Ed.: D.G. Hall, Wiley-VCH: Weinheim, 2011, pp 1-135.

56 Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

57 McCubbin, J. A.; Hosseini, H.; Krokhin, O. V. *J. Org. Chem.* **2010**, *75*, 959-962.

58 Yan, J.; Springsteen, G.; Deeter, S.; Wang, B. *Tetrahedron* **2004**, *60*, 11205-11209.

59 Yasuda, M.; Yoshika, S.; Yamasaki, S.; Somyo, T.; :Chiba, K.; Baba, A. *Org. Lett.* **2006**, *8*, 761-764.

60 Matteson, D.S.; Sadhu, K.M.; Peterson, M.L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819.

61 Touré, B.B.; Hall, D.G. *Chem. Rev.* **1994**, *94*, 4439-4486.

62 (a) Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553. (b) DFT calculations: Nevalainen, V. *Tetrahedron: Asymmetry* **1992**, *3*, 1441.

63 Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH: New York, 1999, p 1077.

64 Corey, E.J.; Helal, C.J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012.

65 (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763-784. (b) Cho, B.T. *Tetrahedron* **2006**, *62*, 7621-7643.

66 Gadamasetti, K.G. Process Chemistry in the Pharmaceutical Industry: An Overview. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K.G., Ed.; Marcel Dekker: New York, 1999; p 3-17.

67 Lanigan, R.M.; Sheppard, T.D. *Eur. J. Org. Chem.* **2013**, 7453-7465.

68 (a) Allen, C.L.; Williams, J.M.J. *Chem. Soc. Rev.* **2011**, *40*, 3405-3415. (b) Lundberg H.; Tinnis F.; Adolfsson H. *Synlett* **2012**, *23*, 2201–2204. (c) Allen C. L.; Chhatwal A. R.; Williams J. M. J. *Chem. Commun.* **2012**, *48*, 666–668. (d) Lundberg H.; Tinnis F.; Adolfsson H. *Chem. Eur. J.* **2012**, *18*, 3822–3826.

69 (a) Valeur, E.; Bradely, M. *Chem. Rev. Soc.* **2009**, *38*, 606-631. (b) Eh-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557-6602.

70 (a) Maki T.; Ishihara K.; Yamamoto H. *Tetrahedron* **2007**, *63*, 8645–8657. (b) Ishihara K.; Ohara S.; Yamamoto H. *J. Org. Chem.* **1996**, *61*, 4196–4197.

71 (a) Arnold K.; Davies B.; Giles R. L.; Grosjean C.; Smith G. E.; Whiting A. *Adv. Synth. Catal.* **2006**, *348*, 813–820. (b) Arnold K.; Batsanov A. S.; Davies B.; Whiting A. *Green Chem.* **2008**, *10*, 124–134.

72 (a) Al-Zoubi R. M.; Marion O.; Hall D. G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879. (b) Gernigon N.; Al-Zoubi R. M.; Hall D. G. *J. Org. Chem.* **2012**, *77*, 8386–8400. (c) Fatemi, S.; Gernigon, N.; Hall, D.G. *Green Chemistry* **2015**, 4016-4028.

73 Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D.G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187-6190.

74 Zheng, H.; Lejkowski, M.; Hall, D.G. *Chem. Sci.* **2011**, *2*, 1305-1310.

75 Sakakura, A.; Ohkubo, T.; Yamashita, R.; Akakura, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 892-895.

2 Investigations into the Dehydrative Elimination of Alcohols

2.1 Introduction & Objective

Alcohols are ubiquitous chemical precursors to a large number of synthetic targets in organic synthesis. This stems from the abundance of alcohol containing molecules used as raw materials, many of which usually derived from easily obtainable starting materials or a myriad of natural sources including: petroleum, sugars,[1] biomass,[2] and fermentation products.

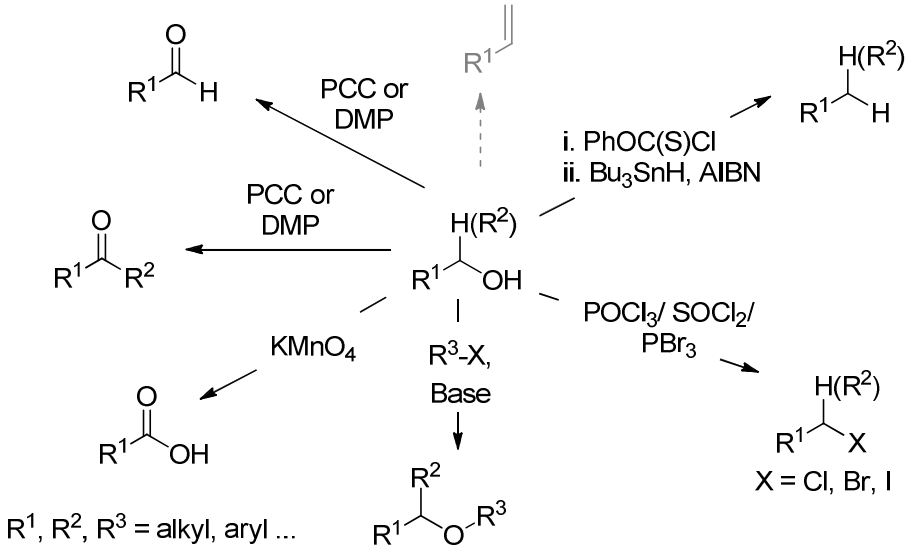


Figure 2-1: Potential transformations of an alcohol.

The presence of an alcohol is often a prelude to a number of other chemical transformations (**Figure 2-1**). The oxidation of alcohols is common where they are converted to their corresponding aldehyde or ketone using pyridinium chlorochromate (PCC)[3] but this has largely been replaced by more modern equivalents such as the Swern oxidation,[4] and the Dess-Martin periodinane (DMP) reagent.[5] It is also possible to completely oxidize the alcohol to the carboxylic acid using potassium permanganate.[6] Asymmetric coupling is also possible by using the Williamson ether synthesis.[7] A number of functional group interconversions (FGIs) are possible subsequently converting the alcohol into either a halide[8] or pseudo-halide, useful for

further cross-coupling or alternative transformations. Also, it is possible to reduce the alcohol to its alkane equivalent by use of the Barton-McCombie reaction.[9] One other transformation of an alcohol is its elimination into an alkene. Alkene chemistry is well-developed and there are a myriad of reactions which alkenes may undergo making them a versatile functional group (**Figure 2-2**).

Alkenes may yield a variety of oxidized products such as alcohols using hydroboration[10] and oxymercuration,[11] and vicinal diols using osmium tetroxide.[12] Alkenes are susceptible to oxidative fragmentation, when desired, using ozonolysis[13] and potassium permanganate[14] giving fragments in various forms including aldehydes, ketones and carboxylic acids. Some interesting reactions exclusive to alkenes such as epoxidation[15] and cyclopropanation[16] may also be achieved using these precursors. Classic hydrogenation[17] and hydro-halogenation reactions[18] are also possible. Alkenes are also an entry route to direct Heck coupling products[19], cross-metathesis reactions[20] and allow introduction of a boronic ester handle for Suzuki-Miyaura cross-coupling.[21]

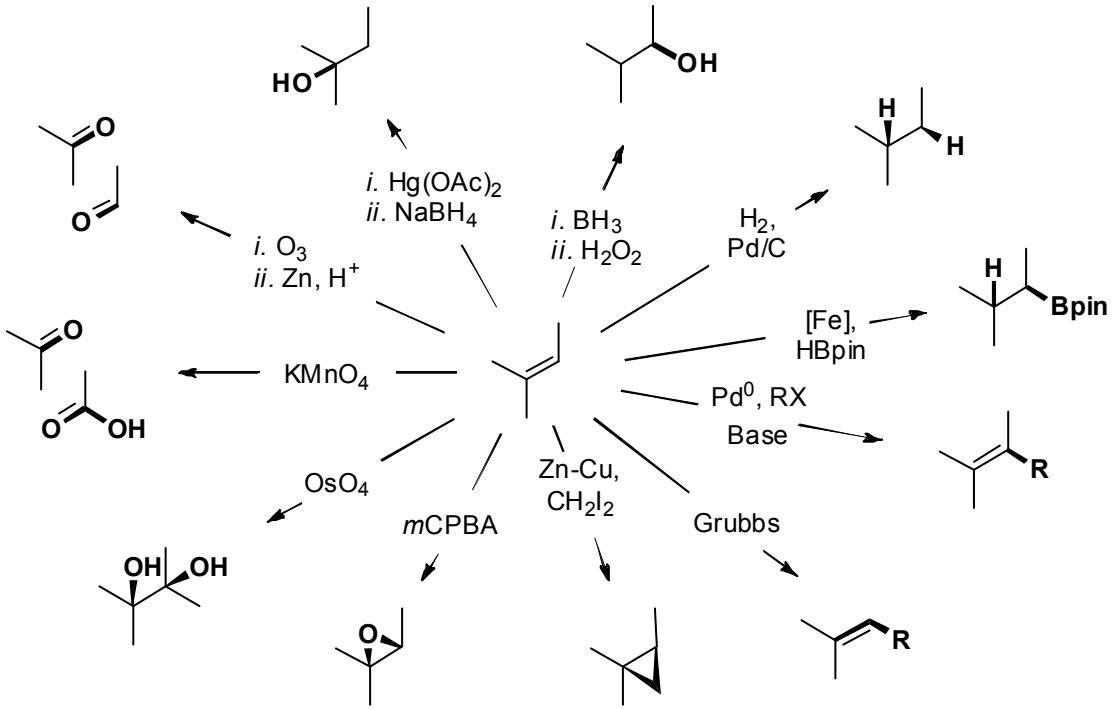
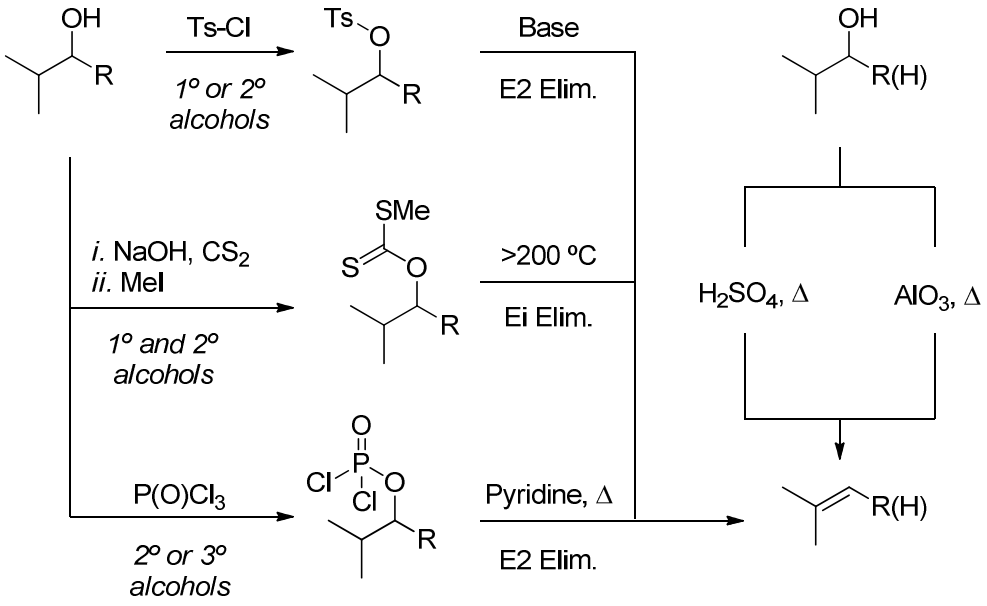


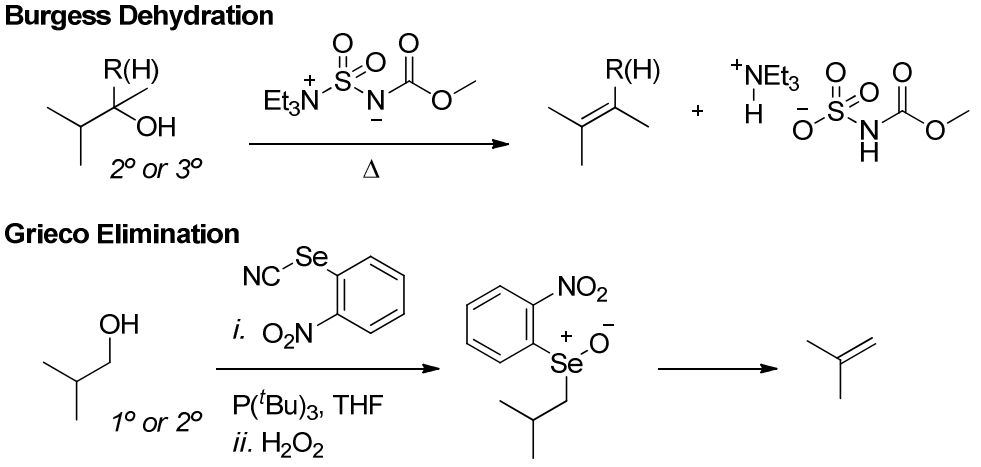
Figure 2-2: Reactions and transformations involving an alkene precursor.

Masking an alkene as an alcohol would allow for some advantageous reactivity. Unfortunately, methods for conversion of an alcohol directly into an alkene are rather limited (**Scheme 2-1**). Classical one-step transformations include use of concentrated sulphuric acid[22] or aluminum oxide[23] but these methods are quite harsh due to high temperatures and extremely acidic conditions. A milder and more useful method is dehydration by use of phosphoryl chloride; [24] unfortunately, it requires a toxic phosphorus-containing compound.[25] Some two-step dehydration reactions include the elimination of a tosylate,[26] which may lengthen syntheses unless previously installed as a protecting group and the Chugaev reaction which uses harsh reagents such as sodium hydroxide, and sensitive reagents such as carbon disulfide and iodomethane for preparation.[27]



Scheme 2-1: Alkene formation through known elimination reactions.

The Burgess reagent is a more interesting and purely organic derivative which results in a milder reaction, but it is applicable only to secondary or tertiary alcohols.[28] The Grieco elimination is one of the better reactions for the elimination of alcohols;[29] it is good for eliminating difficult primary alcohols but requires the use of a toxic selenium species.[30]



Scheme 2-2: Elimination of alcohols using Grieco and Burgess reactions.

These more advanced dehydration reactions are synthetically useful given their tolerance to other functional groups, but they are not perfect (**Scheme 2-2**). Despite their milder reactivity, the

Burgess and Grieco eliminations are not catalytic, provide poor atom economy and lack generality.

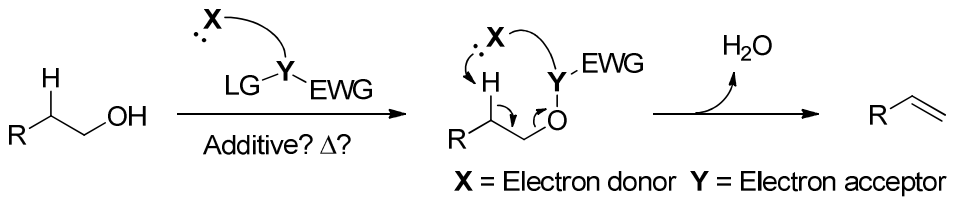
It is desirable to have a clean and efficient route to alkenes from the ubiquitous alcohol, preferably with the following attributes:

- Mild conditions
- Single-step, direct without intermediary leaving group
- Good functional group tolerance
- Catalytic reaction protocol

Harsh, multi-step and multi-component reactions have become the norm when it comes to dehydration reactions. Due to the sheer diversity of reactions that may be used to transform an alkene, it is worth investigating new and more efficient methods for their synthesis.

2.2 Design and Strategy

Design of a new reaction for the dehydration of alcohols must take into account both the acidity of the β-hydrogen as well as the electronic nature of the alcohol and therefore its ability to be a good leaving group. Unfortunately, alcohols tend to have a strong bond with carbon, which is evident by their bond dissociation energy (BDE) of 391 kJ mol^{-1}; in an alkane, a carbon-carbon BDE is approximately 357 kJ mol^{-1} and a carbon-hydrogen BDE is 384 kJ mol^{-1}.[31] Additionally, a good proportion of the existing methods for eliminating alcohols occur through intramolecular *syn* elimination (E_i) (**Scheme 2-3**).

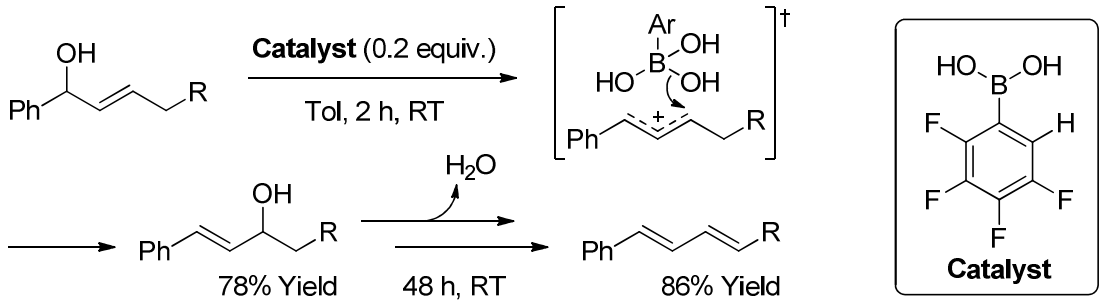


Scheme 2-3: E_i mechanism of common dehydration reactions.

Taking the existing dehydration reactions and relevant bond strengths into account, it is obvious that there are two main requirements for a new reaction to induce the elimination of alcohols: pre-activation of the alcohol and pre-organization of the activated substrate. Pre-activation of the alcohol is necessary as alcohols are naturally a terrible leaving group unless subjected to strong acids and high temperatures. Pre-organization of the activated substrate is important as it enables the breaking of many strong bonds in a rapid manner while avoiding long-lived charges.

The activating agent ideally should have a vacant orbital or exchangeable group to accept the alcohol and able to be made sufficiently electron poor such that it activates the alcohol. As a secondary measure, either an internal or external base should be available to remove the β-hydrogen thereby inducing the elimination of the activated alcohol

Recently, there has been a report defining the activity of tetrafluorophenylboronic acid (TFBA) as the active catalyst in the 1,3-transposition of allylic alcohols and the Meyer-Schuster rearrangement of propargylic alcohols.[32] This also included an interesting report of elimination of an allylic alcohol from the substrate (**Scheme 2-4**).



Scheme 2-4: Elimination of an allylic alcohol using TFBA.

Another study has found that TFBA (pKa 6.0) has an increased ability to activate alcohols over Lewis acids of a lower pKa such as pentafluorophenylboronic acid (pKa 3.5).[33] Secondary effects from the *ortho* substituents on the catalyst provide enhanced reactivity such that it is more active over what is seemingly a much stronger catalyst, based on expected Lewis acid strength (**Figure 1-7**; **Figure 4-1**). TFBA provides many of the characteristics desired for an ideal reaction to eliminate alcohols and appears to be an excellent initial catalyst for this transformation.

The purpose of this investigation is to evaluate potential boron-based catalysts to afford an elimination product from an alcohol under mild reaction conditions. A primary alcohol is the ideal model substrate and is very desirable for dehydration, and unfortunately the most difficult. As described above, current state-of-the-art methodologies display poor atom-economy. If elimination can occur on a primary alcohol then the possibility of dehydrating a more stabilized alcohol would be much more likely. Good selectivity should be achievable by using an oxophilic boron activator but is desired in a catalytic quantity. The primary goal of this investigation is to afford the elimination of an alcohol would be catalyzed at mild temperatures using a boronic acid.

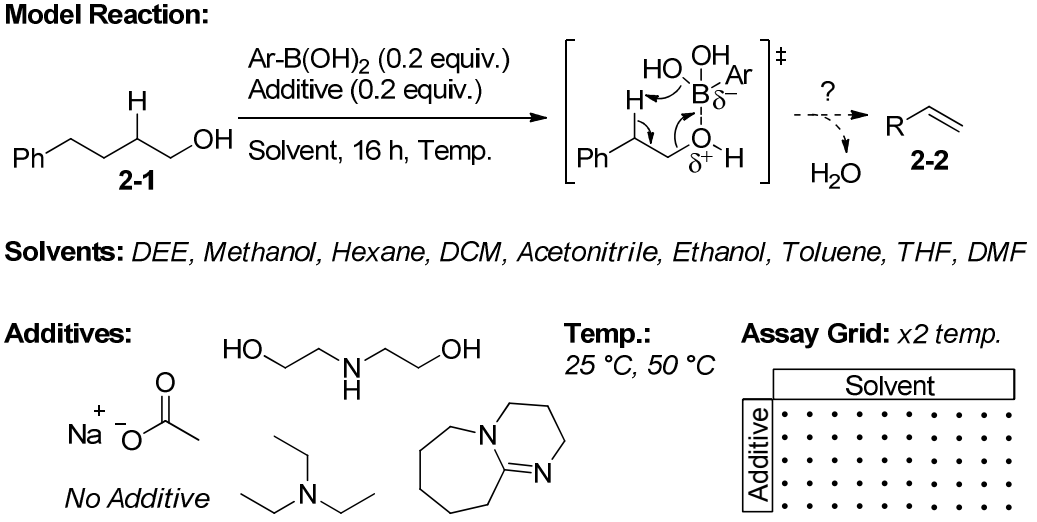
2.2.1 High-Throughput Screening of Fluorinated Arylboronic Acids

The initial search for a boronic acid catalyst (BAC) that could afford the elimination product from an alcohol would be ideally served by high-throughput screening (HTS) of catalysts similar to TFBA. Each assay would test one catalyst in a variety of conditions and incorporate a number of different solvents, additives and temperatures (**Scheme 2-5**). Each assay assessed a chosen activator and took place in a grid of 10 solvents by four additives with a control. They were run in duplicate at two temperatures: room temperature (25 ºC) and an elevated temperature (50ºC) using teflon-lined screw-top vials (100 reactions per activator). Solvents of varying polarities were used including: diethyl ether (DEE), methanol, hexane, dichloromethane (DCM), acetonitrile, ethanol, toluene (Tol), tetrahydrofuran (THF) and dimethylformamide (DMF). The amount of activator was designated to be 0.2 equivalents such that if the dehydration were to occur, there would be enough of the boronic acid to produce a detectable quantity of product.

There is a possibility that it is too difficult to deprotonate the β-hydrogen from an unactivated alcohol therefore, it is reasonable to propose inclusion of a base to assist in the elimination of an alcohol. Chosen bases provided a wide range in strength including: diethanolamine, triethylamine, sodium acetate and 1,8-diazabicycloundec-7-ene (DBU). A control without base was included in each trial to ensure the base was not the activating species.

Finally, the model alcohol was selected such that it did not have any activating or stabilizing properties yet both model reactant (**2-1**) and product (**2-2**) are both easily visible by thin-layer chromatography (TLC). If any elimination were to occur, it would likely proceed through some variation of a step-wise sigmatropic rearrangement, based on avoidance of charge build up.

Analysis of crude product was completed with thin-layer chromatography (TLC) and compared with standards of the alcohol starting material (**2-1**), alkene product (**2-2**) and activator for each assay. Only the appearance of new spots warranted purification and analysis by nuclear magnetic resonance (NMR) spectroscopy.



Scheme 2-5: Proposed HTS for elimination of alcohols using BACs.

Building upon the success of TFBA activation of allylic alcohols, fluorine based boronic acids were amongst the first activators tested in this assay (**Figure 2-3**) with approximately 1,100 reactions. Sadly, no elimination product was observed with any of the electron deficient fluorinated aryl boronic acids (**2-3a** – **2-3k**). Despite the great activity of TFBA (**2-3c**) and its more potent derivative (**2-3d**) toward π-activated alcohols, its activity toward an unactivated alcohol was not significant.

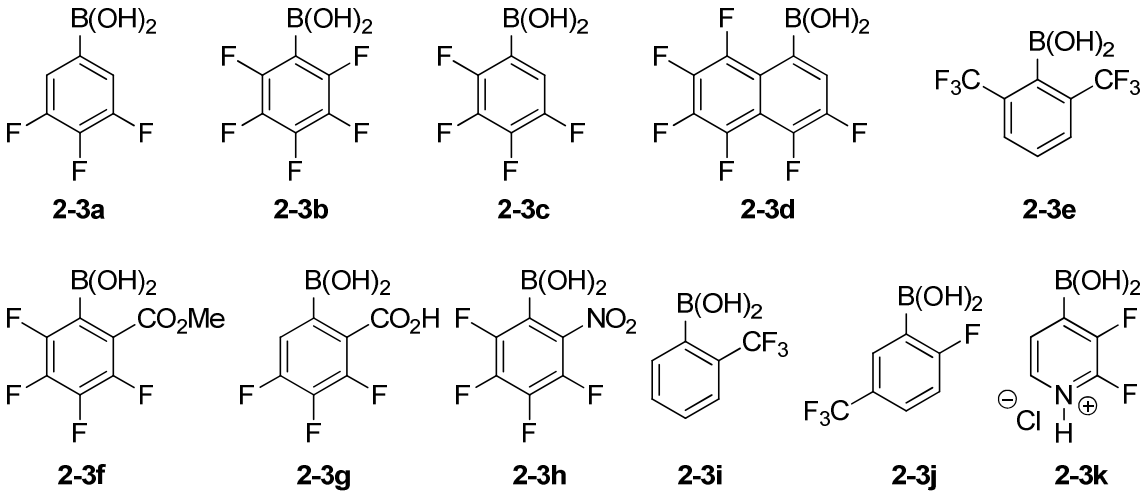
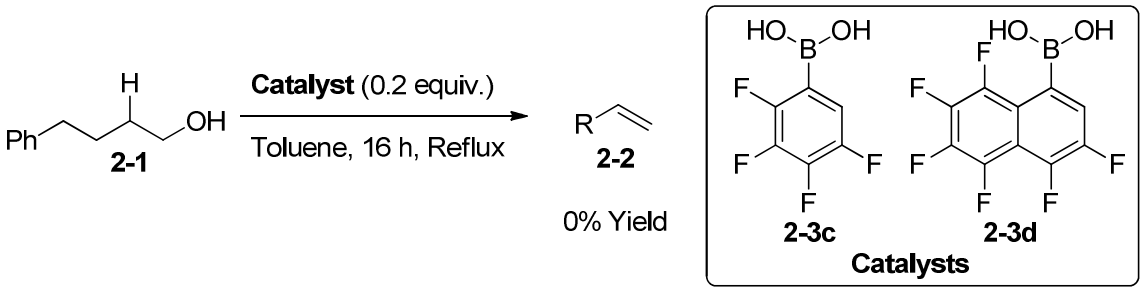


Figure 2-3: HTS for elimination of alcohols using fluorinated BACs.

Since the aforementioned polyfluorinated catalysts did not yield any product, a few tests were conducted with the most promising conditions matching the reported elimination of an allylic alcohol (**Scheme 2-6**). Despite high temperature conditions with the use of a Dean-Stark apparatus for azeotropic removal of water from the reaction mixture, TFBA (**4-3c**) and 3,4,5,6,7,8-hexafluoronapthylboronic acid (**4-3d**) still did not give the desired product.

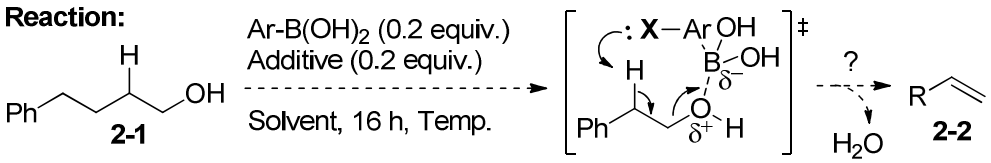


Scheme 2-6: Azeotropic test reaction for BA catalyzed dehydration.

2.2.2 Screening of Bifunctional Boronic Acids

Adjusting the HTS on the assumption that a base may assist the elimination of an alcohol, it was reasonable to propose that the increased proximity of an intramolecular base could be more likely to induce a reaction (**Scheme 2-7**). The assay for each bifunctional activator followed as

before in duplicate at two temperatures with 10 solvents by four additives and one control (100 reactions per activator).



Scheme 2-7: Refined HTS for elimination of alcohols using bifunctional BACs.

The next set of chosen catalysts had some form of bifunctionality associated with them including *ortho* substituents (**Figure 2-4**). These potential catalysts contained either oxygen (**2-4a** – **2-4h**) or a counter ion (**2-4i**)[34] which could possibly assist in deprotonation and/or development of carbocation character for the dehydration through donation of electron density. Unfortunately, no alcohol elimination was observed.

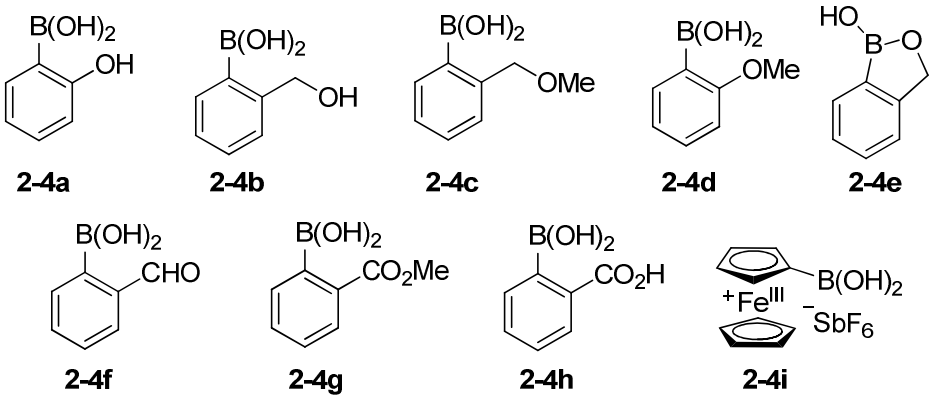


Figure 2-4: HTS for elimination of alcohols using salt and oxygen-containing BACs.

Assuming that a stronger intramolecular base was required, another screening using the aforementioned assay conditions (100 reactions per activator) was performed using various nitrogen- and sulphur containing arylboronic acids (**Figure 2-5**). Once again, there was no alkene formation despite the increased basicity of these alternative arylboronic acids (**2-5a** – **2-5g**).

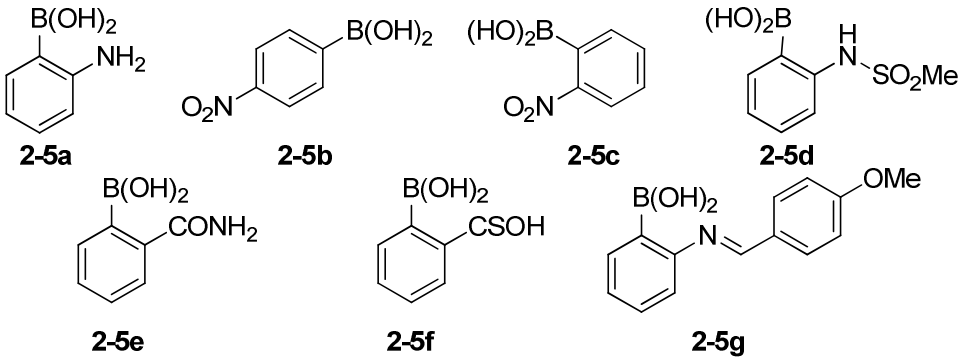
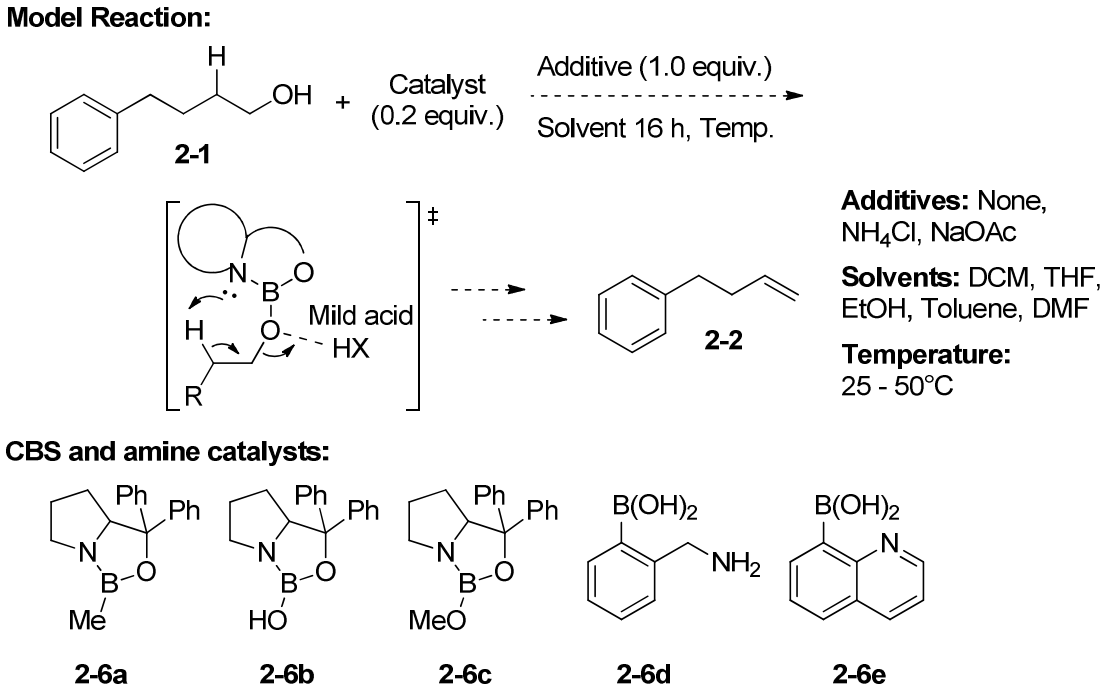


Figure 2-5: HTS for elimination of alcohols using heteroatom-containing BACs.

The lack of activity from the aforementioned boronic acids and HTS method implies that another approach must be taken. The rationale behind using activators with direct boron-nitrogen bond was to allow for the possibility of a six-membered transition state, which can potentially favour the elimination product. Therefore, building upon the idea of an intramolecular-assisted dehydration, repurposing existing bifunctional boronic acids was an intriguing method (**Scheme 2-8**). This truncated assay consisted of five solvents (DCM, THF, EtOH, Toluene and DMF), two additives (ammonium chloride and sodium acetate) with a control. Each activator was assayed in duplicate at 25 and 50 ºC for a total of 30 reactions each. The change from stronger bases to a weak acid and weak base was due to the hypothesis of a proton shuttle aiding in the reaction to hopefully make the newly formed boron-oxygen bond a better leaving group.

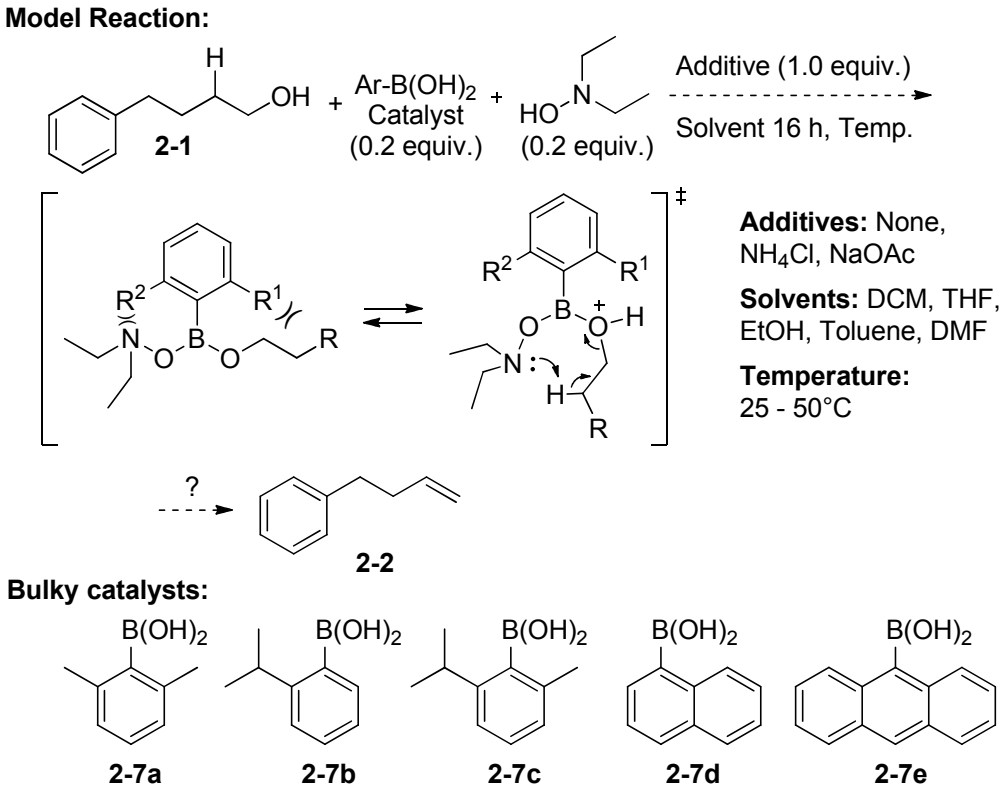
This smaller assay involved use of a commercially available Corey-Bakshi-Shibata catalyst (**2-6a**) and various derivatives (**2-6b** – **2-6c**) which are used in the enantioselective reduction of ketones.[35] Allowing for the possibility of a more flexible transition state, some boronic acids were tested where the basic site is located a few carbons away from the Lewis acidic site. The Whiting catalyst used in dehydration of a carboxylic acid resulting in amide formation (**2-6d**)[36]

and a derivative (**2-6e**) were tested as well. Again, none of the mentioned conditions gave any alkene product.



Scheme 2-8: HTS for elimination of alcohols using CBS and Whiting-type BACs.

Further derivatization of this bifunctional approach can take advantage of both boron-oxygen bonds and may allow a more flexible system for elimination. This design involved an intermediate catalyst formed *in situ* by combination of a hydroxylamine with the boronic acid yielding a bifunctional site directly bound to boron as opposed to being bound to the arene (**Scheme 2-9**). Again, this assay involved 30 different reaction conditions for each potential catalyst. This should allow the proposed transition state to assume a number of conformations such that the optimal attack angle for dehydration may be adopted. A number of large and bulky arylboronic acids (**2-7a** – **2-7e**) were used to effectively push the hydroxylamine arm toward the active site of the alcohol and perhaps facilitate the elimination reaction.



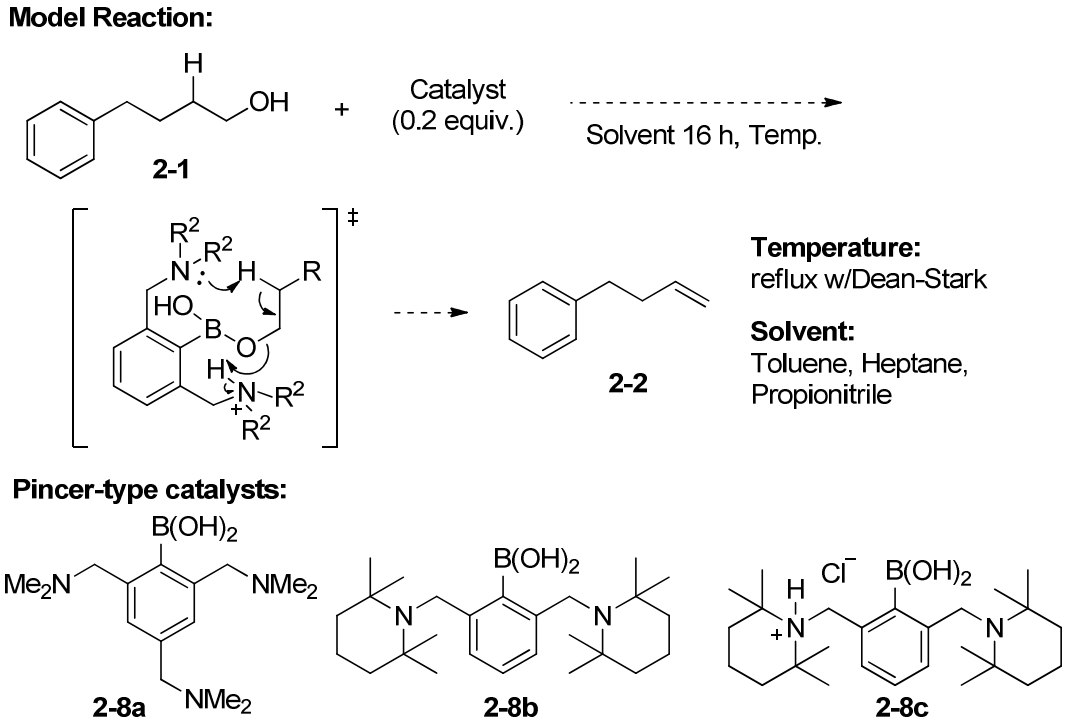
Scheme 2-9: HTS for elimination of alcohols using bulky BACs with hydroxylamine.

Unfortunately, this broad screening assay of bifunctional boronic acids and derivatives did not manage to find a catalyst that was able to dehydrate alcohol **2-1** and therefore alkene **2-2** was not observed.

2.2.3 Pincer-Type Boronic Acids

The next strategy aimed for a more organized transition state using a pincer-type catalyst. The premise of this approach was to simultaneously protonate the oxygen bound to boron making it a better leaving group and induce the elimination using a second functional arm (**Scheme 2-10**). The first pincer-type BAC came from 2,4,6-tris[(N,N-diethylamino)methyl]phenylboronic acid (**2-8a**) but yielded no alkene product.[37] One pincer-type catalyst containing both a Lewis acid and Brønsted base moieties was used in the dehydrative intramolecular condensation of dicarboxylic acids was also tested (**2-8b**).[38] Catalyst **2-8b** was protonated to form a Lewis acid

with a pre-activated amine moiety to act as a Brønsted acid (**2-8c**). Despite the high temperature and azeotropic removal of water, in addition to the increased proximity of two different catalytic active sites, these complex hypotheses appeared insufficient to predict the required reactivity to afford the desired elimination product.

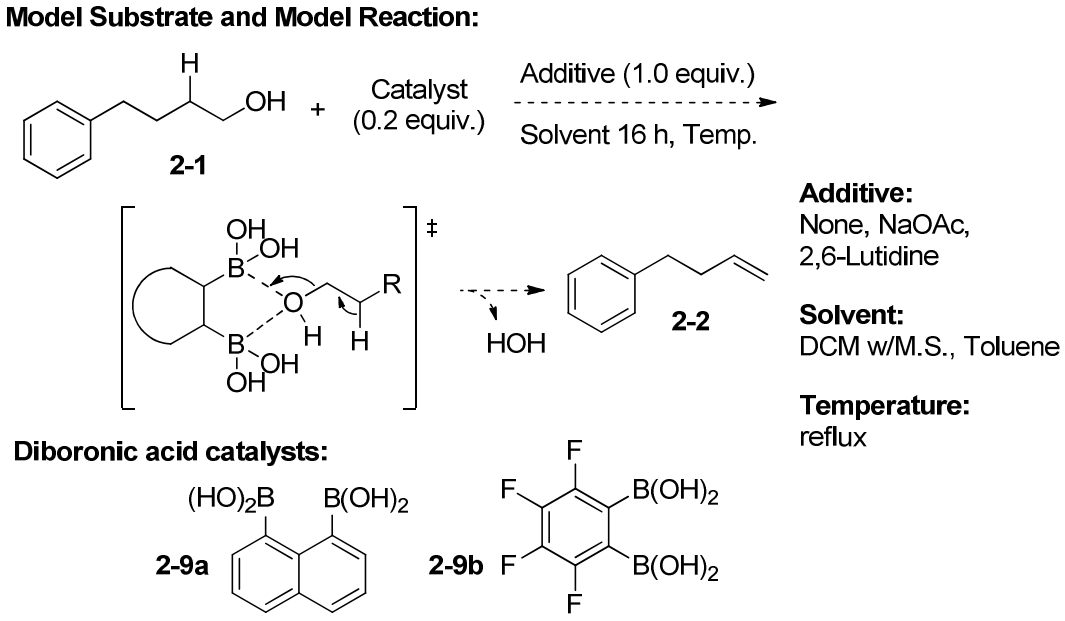


Scheme 2-10: Proposed reactions for elimination of alcohols using pincer-type BACs.

2.2.4 Azeotropic Elimination

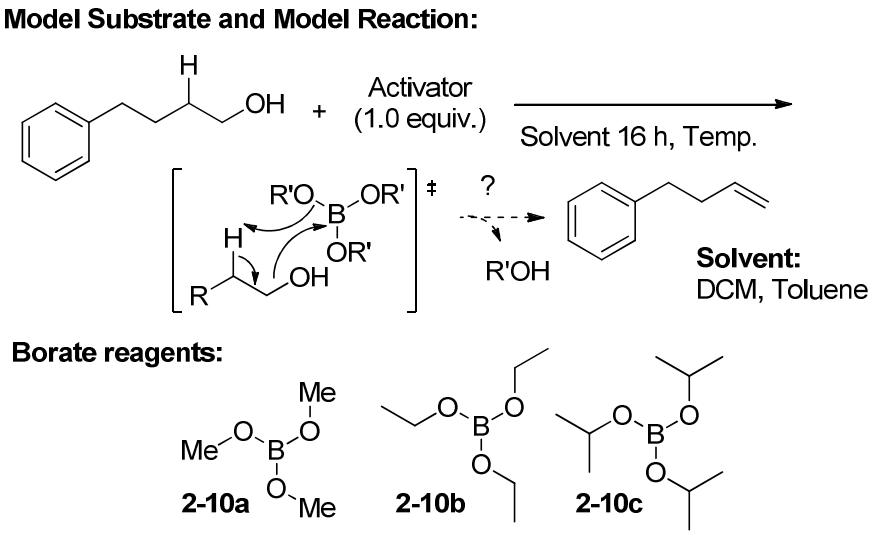
Forgoing the constraint of mild temperature, a number of catalysts were examined for dehydration activity under conditions for azeotropic removal of water (**Scheme 2-11**). The use of diboronic acids came as an answer to a super activated alcohol that could possibly be eliminated under thermal conditions. This truncated assay once again made use of proton shuttles and a control reaction in only two different solvents leading to six reactions per catalyst. This involved a diboronic acid catalyst (**2-9a**[39] – **2-9b**[40]), which should activate an alcohol subsequently provoking elimination. This screening was performed with sodium acetate and 2,6-lutidine;

Here, lutidine was used as a proton shuttles to assist in the elimination, of course a control was also run but all to no avail, there was no reaction.



Scheme 2-11: Proposed reactions for elimination of alcohols using aryl diboronic acids.

The final attempt at elimination of an alcohol was by use of a known dehydrating agent, trimethyl borate (**2-10a**) and derivatives (**2-10b** – **2-10c**).[41] After much effort, even at elevated temperature, azeotropic removal of water did not lead to the observation of an alkene as expected (**Scheme 2-12**).



Scheme 2-12: Proposed reactions for elimination of alcohols using borate compounds.

2.3 Discussion and Future Directions

Despite the large number of approaches toward the proposed elimination of a primary alcohol, none have yielded the desired unsaturation. Why might this be the case? A brief analysis of the various bond energies may reveal some information as to why this transformation is so very difficult (**Table 2-1**).[42] The carbon-hydroxy bond has dissociation energy of 391 kJ mol^{-1}; therefore, without proper activation this bond is not likely to break. Neutral boron has a high boron-oxygen bond energy of 806 kJ mol^{-1} suggesting that its formation is favourable; and indeed, formation of a boronic ester does occur and is readily visible by NMR spectroscopy. This implies that if a boron-oxygen bond with an alcohol can be formed either partially (through Lewis acid activation) or completely (via deprotonation to form a boronic ester species) then it may be possible to make the carbon-oxygen bond electron deficient, enough that it would be possible to break this bond. One must also take into account the relatively strong carbon-hydrogen bond of 384 kJ mol^{-1}. This implies that the best way to eliminate an alcohol using temporary boron-oxygen bonds is by transforming the hydroxyl group into a good leaving group.

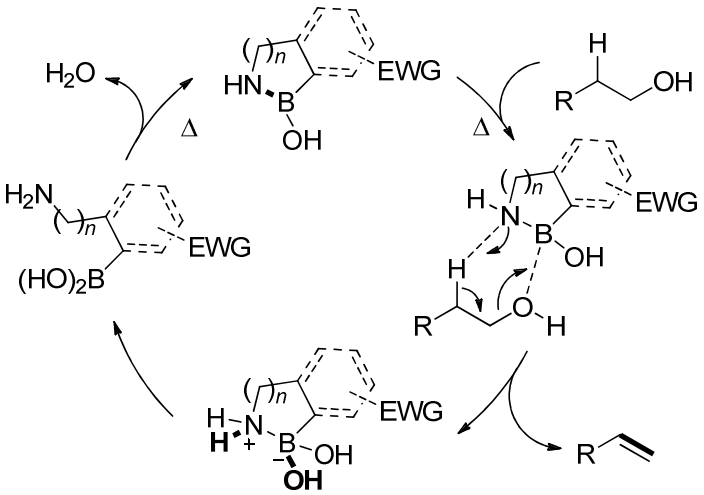
If this elimination reaction can be achieved then two obstacles exist. The largest obstacle is breaking the β-hydrogen-carbon bond; therefore there is a requirement for a basic site or additive to deprotonate the thus initiating the dehydration. Although, the this could be avoided if the elimination system was provided more energy; this could be provided by either an extremely Lewis acidic boronic acid with a balanced amount of activating energy in the form of heat.

Table 2-1: Selected BDEs of carbon, nitrogen and boron compounds.

Bond	BDE (KJ/mol)	Bond	BDE (KJ/mol)
$H_3CC\mathbf{H_2}CH_2OH$	384	B-O	519
$H_3C\mathbf{C}H_2$-CH_2OH	357	B-C	448
$HC_3CH_2CH_2$-**OH**	391	B-N	378
$H_3CCH_2CH_2$-$\mathbf{NH_2}$	356		

Luo, Y.R., *Comprehensive Handbook of Chemical Bond Energies*. Boca Raton: CRC Press, 2007.
Benson, S.W. *J. Chem. Educ.* **1965**, *42*, 502.
Kerr, J.A. *Chem. Rev.* **1966**, *66*, 465.

This then beckons a few approaches to achieve this transformation. Since this reaction requires the breaking of a number of bonds, taking an existing catalyst increasing the energy available to it by using higher temperature may make the reaction more favourable. Another option is to design a reagent with more internal energy that can be released. This could appear in a reagent designed to contain energy much like a compressed spring. This reagent may contain a ring with a boron-nitrogen bond such that the size of the ring can be correlated to the amount of energy embedded in the molecule;[43] this energy could be released upon binding an alcohol substrate with a β-hydrogen (**Scheme 2-13**). Furthermore, such an activator could be regenerated by expelling water.



Scheme 2-13: Proposed activator and its reactivity toward the elimination of alcohols.

One final possibility is by using a catalytic leaving group like an embedded tosylate (**Figure 2-6**). This system could form an unstable boronate species which could potentially undergo a boron-to-sulphur transfer leading to the desired activated alcohol. Elimination of an alcohol could possibly yield the desired alkene using a simple base as with commonly employed elimination of sulphonate.[26]

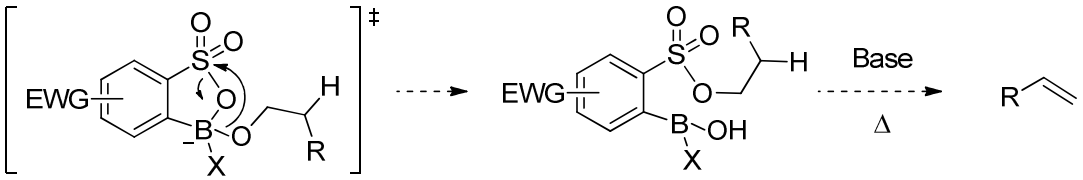
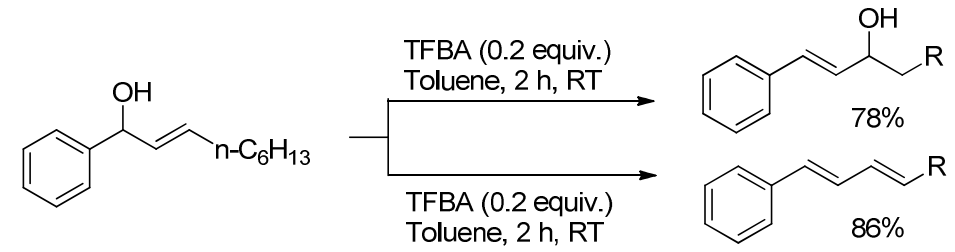


Figure 2-6: Possible catalytic leaving group based on a boronic acid scaffold.

2.4 Conclusions

Investigating a difficult transformation such as the dehydration of a primary alcohol does have its risk. The initial requirements for mild reaction conditions may have imposed too many restrictions far too early in development; it would be more beneficial to approach from a less desirable transformation and build upon its reactivity.

Perhaps this could be addressed by backtracking and optimizing the initial literature findings for the elimination of a conjugated alcohol first (**Scheme 2-14**), followed by re-investigation of this reaction for more difficult substrates.[32]



Zheng, H.; Lejkowski, M.; Hall, D.G. *Chem. Sci*. **2011**, *2*, 1305-1310.

Scheme 2-14: BAC induced alcohol elimination reaction.

Increasing our understanding of the elimination of an activated alcohol using a BAC can be augmented by using targeted experiments and computation. The final frontier would be to apply the literature dehydration toward the dehydration of neutral or deactivated alcohols.

2.5 Experimental

General Methods

The following materials include representative experimental procedures and details for the synthesis and isolation of compounds. Unless otherwise stated, all reactions were performed in capped vials and glassware with no further precautions. Tetrahydrofuran (THF), dichloromethane (DCM), methanol, dimethylformamide (DMF) and toluene (Tol) were purified using a double cartridge solvent purification system prior to use. All other solvents were purchased as ACS reagents and used without further purification. Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes and ethyl acetate as eluents. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light and with $KMnO_4$ or phosphomolybdic acid (PMA) stains. Commercial 4-phenylbutanol and 4-phenylbutene were used as standards in all observations. ^{1}H NMR spectra were recorded on 400 MHz or 500 MHz instruments. The residual solvent protons (^{1}H/$CHCl_3$) or the solvent carbon (^{13}C) were used as internal references. ^{1}H NMR data is presented as follows: chemical shifts in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sept, septet; dd, doublet of doublets; m, multiplet. The error of coupling constants from ^{1}H NMR spectra is estimated to be 0.3 Hz.

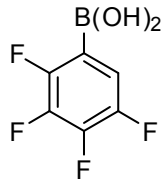
General Assay Procedure

Into 2 mL screw top vials was placed 0.2 mmol of a corresponding boronic acid catalyst, 1.0 mmol of additive, 1 mL of solvent, 1.0 mmol of 4-phenylbutanol and sealed. The reaction was reacted at 25 ºC in an agitator for 16 hours, or with 10 minutes of agitation followed by heating in a calibrated aluminum block at 50 ºC for 16 hours. No precaution was made to exclude moisture or oxygen from the reaction mixture. The reaction mixtures were visualized for the appearance of 4-phenyl butane (**2-2**) and co-spotted with the catalyst, 4-phenylbutanol (**2-1**) then checked using TLC and stained with either $KMnO_4$ or PMA. If there was any observed reaction, the corresponding reaction mixture was concentrated under reduced pressure, then purified via silica plug using hexanes and further analyzed by ^{1}H and ^{11}B NMR spectroscopy.

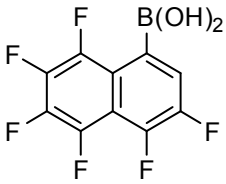
Standard Azeotropic Procedure

Into a 5 mL round bottom flask was placed 0.2 mmol of a corresponding boronic acid catalyst, 1.0 mmol of additive, 1 mL of high boiling point solvent, 1.0 mmol of 4-phenylbutanol and connected . The reaction was heated in an oil bath while connected to a Dean-Stark apparatus filled with a corresponding solvent for 16 hours. The reaction mixtures were visualized for the appearance of 4-phenyl butane (**2-2**) and co-spotted with the catalyst, 4-phenylbutanol (**2-1**) then checked using TLC and stained with either $KMnO_4$ or PMA. If there was any observed reaction, the corresponding reaction mixture was concentrated under reduced pressure, purified via silica plug using hexanes and further analyzed by ^{1}H and ^{11}B NMR spectroscopy.

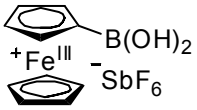
Synthesized Catalysts



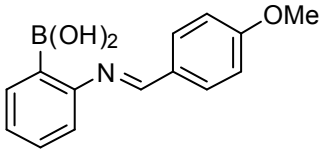
2,3,4,5-Tetrafluorophenylboronic acid (2-3c): This compound was synthesized as per a previous report in 76% yield.[32]



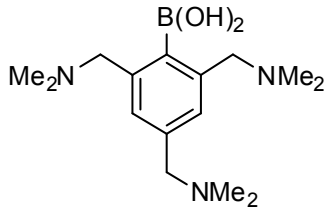
3,4,5,6,7,8-Hexafluoronapthylboronic acid (2-3d): This was synthesized as per a previous report in 43% overall yield.[32]



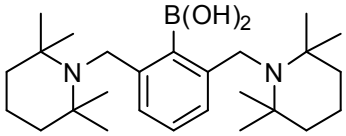
Ferroceniumboronic acid hexafluoroantimonate salt (2-4i): This compound was synthesized as per a previous report in 72% yield.



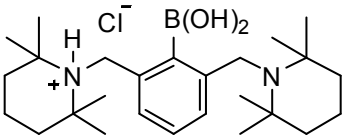
(*E*)-(2-((4-Methoxybenzylidene)amino)phenyl)boronic acid (2-5g): This compound was synthesized *in situ*, by pre-mixing 0.2 mmol of 2-aminophenylboronic acid with 0.2 mmol of 4-methoxybenzaldehyde in the appropriate assay solvent.



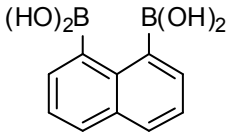
2,4,6-Tris[(N,N-diethylamino)methyl]phenylboronic acid (2-8a): 2,4,6-Tris[(N,N-dimethylamino)methyl]benzene was prepared according to the literature in 82% yield.[37] To a flame dried flask under nitrogen was added 1.0 mmol of 2,4,6-tris[(N,N-dimethylamino)methyl]benzene and 5 mL of dry THF using anhydrous technique. The reagent was stirred and allowed to homogenize then cooled to 78°C using a dry-ice/acetone bath. To the mixture was added 1.1 mmol of *tert*-butyl lithium in pentanes (1.7 M) in a dropwise manner and it was stirred at 78°C for 1 hour. Then 3.0 mmol of distilled trimethyl borate was added and allowed to stir for an additional hour before being allowed to warm to room temperature overnight while stirring under a nitrogen atmosphere. This reaction was quenched using 10 mL of 1M HCl and extracted using ethyl acetate (2 x 20mL) concentrated under a reduced atmosphere. This crude mixture was purified on silica gel using hexanes:ethyl acetate (4:1) and gave **2-8a** in 72% yield.



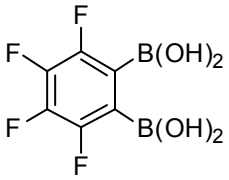
2,6-Bis[(N,N-diisopropylamino)methyl]phenylboronic Acid (2-8b): This was synthesized as per a previous report in 30% overall yield.[38]



2-(N-Diisopropylamino)methyl-6-[(N,N'-diisopropylaminohydrochloride)methyl] phenylboronic Acid (2-8c): This was synthesized *in situ* using 0.1 mmol of **2-8b** and 0.1 mL of 1.0 M hydrogen chloride in dry diethyl ether into the assay flask and mixing in the appropriate assay solvent.



Naphalene-1,8-diboronic acid (2-9a): This compound was synthesized as per a previous report.[39]



3,4,5,6-Tetrafluorophenyl-1,2-diboronic acid (2-9b): This compound was synthesized as per a previous report.[40]

2.6 References

1 Matthews, C.E.; van Holde, K.E.; Ahern, K.G. *Biochemistry.* Benjamin Cummings: New York, 1999.

2 Detroy, R.W.; St. Julian, G. *Crit. Rev. Microbiol.* **1983**, *10*, 203-28.

3 Corey, E.J.; Suggs, W. *Tetrahedron Lett.* **1975**, *16*, 2647-2650.

4 (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482. (c) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148–4150.

5 (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Meyer, S.D.; Schreiber, S.L. *J. Org. Chem.* **1994**, *59*, 7549.

6 Rankin, K.N.; Liu, Q.; Hendry, J.; Yee, H.; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* **1998**, *39*, 1095.

7 (a) Williamson, A. *Philosophical Magazine* **1850**, *37*, 350-356. (b) Williamson, W. *Liebigs Ann. Chem.* **1851**, *77*, 37. (c) Williamson, W. *J. Chem. Soc.* **1852**, *106*, 229. (d) Dermer, O.C. *Chem. Rev.* **1934**, *14*, 385.

8 (a) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528. (b) Bordwell, F. G.; Brannen, W. T. *J. Am. Chem. Soc.* **1964**, *86*, 4645-4650. (c) Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845. (d) Streitwieser, A. *Chem. Rev.* **1956**, *56*, 571-752.

9 (a) Barton, D.H.R.; McCombie, S. W. J. Chem. Soc., Perkin Trans. 1 **1975**, 1574-1585. (b) McCombie, S.W.; Motherwell, W.B.; Tozer, M. *Org. React.* **2011**, *77*, 161. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413-1432.

10 (a) Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 247. (b) Brown, H.C. *Tetrahedron*, **1961**, *12*, 117. (c) Allred, E.L.; Sonnenberg, J.; Winstein S. *J. Org. Chem.* **1960**, *25*, 25. (d) Brown, C.A.; Coleman, R.A. *J. Org. Chem.* **1979**, *44*, 2328.

11 (a) Bordwell, F.G.; Douglass, M.L. *J. Am Chem. Soc.* **1966**, *88*, 993-999. (b) Whitesides, G.M.; San Filippo, J. Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611-6624. (c) Pasto, D.J.; Gontarz, J.A. *J. Am. Chem. Soc.* **1971**, *93*, 6902-6908.

12 (a) Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965-3968. (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059-1070.

13 (a) Criegee, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 745-752. (b) Veysoglu, T.; Mitscher, L.A.; Swayze, J.K. *Synthesis* **1980**, 807-810. (c) Cremer, D.; Crehuet, R.; Anglada, J. *J. Am. Chem. Soc.* **2001**, *123*, 6127-6141.

14 Lee, D.G.; Lamb, S.E.; Chang, V.S. *Org. Synth. Coll.* **1990**, *7*, 397.

15 (a) Swern, D. Organic Peroxides; Wiley Interscience: New York, 1971; Vol 2. (b) Kim, C.; Traylor, T.G.; Perrin, C.L. *J. Am. Chem. Soc.* **1998**, *120*, 9513-9516. (c) Johnson, R.A.; Sharpless, K.B. *Comp. Org. Syn.* **1991**, *7*, 389-436.

16 Wittig, G.; Wingler, F. *Chemische Berichte* **1964**, *97*, 2146-2164.

17 (a) Baltzly, R. *J. Am. Chem. Soc.* **1952**, *74*, 4586. (b) Horner, L.; Reuter, H.; Herrmann, E. *Justus Liebigs Ann. Chem.* **1962**, *660*, 1. (c) Baltzly, R. *J. Org. Chem.* **1976**, *41*, 928. (d) Mori, A.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Sajiki, H. *Org. Lett.* **2006**, *8*, 3279-3281.

18 Kropp, P.J.; Dans, K.A.; Crawford, S.D.; Tubergen, M.W.; Kepler, K.D.; Craig, S.L. Wilson, V.P. *J. Am. Chem. Soc.* **1990**, *112*, 7433-7434.

19 (a) Heck, R.F.; Nolley, Jr., J.P. *J. Org. Chem.* **1972**, *37*, 2320-2322. (b) de Meijere, A.; Meyer, Jr., F.E.; *Angew. Chem. Int. Ed.* **1994**, *33*, 2379–2411. (c) Beletskaya, I.P.; Cheprakov, A.V. *Chem. Rev.* **2000**, *100*, 3009-3066. (d) McCartney, D.; Guiry, P.J. *Chemical Society Reviews* **2011**, *40*, 5122-5150.

20 (a) Calderon, N; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* **1967**, *8*, 3327-3329. (b) Nguyen, S.T.; Johnson, L.K.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975. (c) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039-2041. (d) Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.

21 Greenhalgh, M.D.; Thomas, S.P. *Chem. Commun.* **2013**, *49*, 11230-11232.

22 (a) Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* **1990**, *59*, 60. (b) Saunders Jr., W.H.; Cockerill, A.F. Ref. 3, pp. 221, 317; Knözinger, H. in *The Chemistry of the Hydroxyl Group*, pt. 2; Wiley: New York, 1971, p. 641.

23 Mattern, R.-H. *Tetrahedron Lett.* **1996**, *37*, 291.

24 (a) Mehta, G.; Murthy, A.N.; Reddy, D.S.; Reddy, A.V. *J. Am. Chem. Soc.* **1986**, *108*, 3443. (b) Giner, J.-L.; Margot, C.; Djerassi, C. *J. Org. Chem.* **1989**, *54*, 369.

25 (a) Rosenthal, T.; Baum, G.L.; Frand, U.; Molho, M. *Chest* **1978**, *73*, 623-626. (b) Quistad, G.B.; Zhang, N.; Sparks, S.E.; Casida, J.E. *Chem. Res. Toxicol.* **2000**, *13*, 652-657.

26 (a) Corey, E.J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111. (b) Corey, e.J.; Posner, G.H..; Atkinson, R.F.; Wingard, A.K.; Halloran, D.J.; Radzik, D.M.; Nash, J.J. *J. Org Chem.* **1989**, *54*, 389.

27 (a) Tschugaeff, L. *Berichte der deutschen chemischen Gesellschaft* **1900**, *33*, 3118-3126. (b) Bader, R.F.W.; Bourns, A.N. *Can. J. Chem.* **1961**, *39*, 348. (c) DePuy, C.H.; King, R.W. Ref. 138, p. 444; Nace, H.R., Ed. *Org. React.* **1962**, 12, 57. (d) Lee, A.W.M.; Chan, W.H.; Wong, H.C.; Wong, M.S. *Synth. Commun.* **1989**, *19*, 547.

28 Burgess, E.M., Penton, H.R., Jr.; Taylor, E.A. *J. Am. Chem. Soc.* **1970**, *92*, 5224-5226.

29 Grieco, P.A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486.

30 (a) Gasmi, A., Garnier, R.; Galliot-Guilley, M.; Gaudillat, C.; Quartenoud, B.; Buisine, A.; Djebbar, D. *Vet. Hum. Toxicol.* **1997**, *39*, 304-308. (b) Nuttall, K.L. *Ann. Clin. Lab. Sci.* **2006**, *36*, 409-420.

31 Blanksby, S.J.; Ellison, G.B. *Acc. Chem. Res.* **2003**, *36*, 255-263.

32 Zheng, H.; Lejkowski, M.; Hall, D.G. *Chem. Sci.* **2011**, *2*, 1305-1310.

33 Ricardo, C.L.; Mo, X.; McCubbin, J.A.; Hall, D.G. *Chem. Eur. J.* **2015**, *21*, 4218-4223.

34 Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9695-9703.

35 (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *Chemical Communications* **1981**, *7*, 315. (b) Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Corey, E.J.; Bakshi, R. K.; Shibata, S.; Chen, C.P.; Singh, V.K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

36 (a) Arnold, K.; Batsanov, A.S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124-134. (b) Georgiou, I.; Ilyashenko, G.; Whiting, A. *Acc. Chem. Res.* **2009**, *42*, 756-768.

37 Mercer, S.M.; Robert, T.; Dixon, D.V.; Chen, C.-S.; Ghoshouni, Z.; Harjani, J.R.; Jahangiri, S.; Peslherbe, G.H.; Jessop, P.G. *Green Chem.* **2012**, *14*, 832-839.

38 Sakakura, A.; Ohkubo, T.; Yamashita, R.; Akakura, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 892-895.

39 Prabhakaran, P.; Puranik, V.G.; Chandran, J.N.; Rajamohanan, P.R.; Hofmann, H.-J.; Sanjayan, G. *J. Chemical Communications* **2009**, *23*, 3446-3448.

40 (a) Chase, P.A.; Henderson, L.D.; Piers, W.E.; Parvez, M.; Clegg, W.; Elsegood, M.R.J. *Organometallics* **2006**, *25*, 349-357. (b) Durka, K.f; Lulinski, S.; Serwatowski, J.; Wozniak, K. *Organometallics* **2014**, *33*, 1608-1616.

41 Lewis, R..J, Sr.; *Hawley's Condensed Chemical Dictionary*. 13th ed. NY: John Wiley & Sons, Inc., 1997, p. 1136.

42 (a) Benson, S.W. *J. Chem. Educ.* **1965**, *42*, 502. (b) Kerr, J.A. *Chem. Rev.* **1966**, *66*, 465. (c) Luo, Y.R., *Comprehensive Handbook of Chemical Bond Energies*. Boca Raton: CRC Press, 2007.

43 Vshyvenko, S.; Suzuki, I.; Clapson, M.; Hall, D.G. University of Alberta, unpublished results.

3 An Attempt to Develop a Mild Boronic Acid Catalyzed Ritter Reaction

3.1 Introduction & Objective

Amides are ubiquitous throughout nature; they are the foundation of life being present as key components of proteins. The inherent stability of amides can justify their incorporation in biological systems. As a result, *in vivo* environments react to a myriad of amide-containing molecules; this is made apparent by the large portion of currently available herbicides, pesticides and pharmaceuticals containing the amide functional group (**Figure 3-1**).[1]

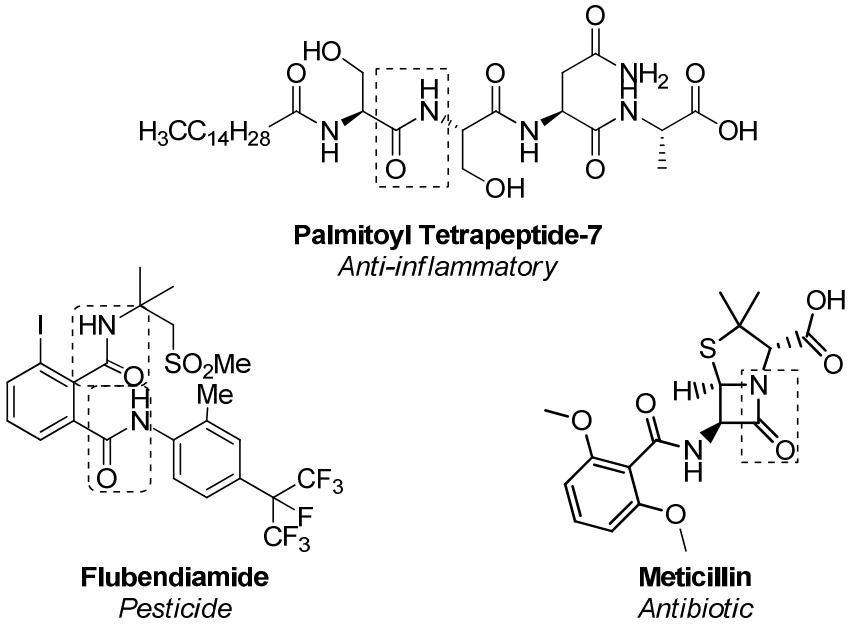
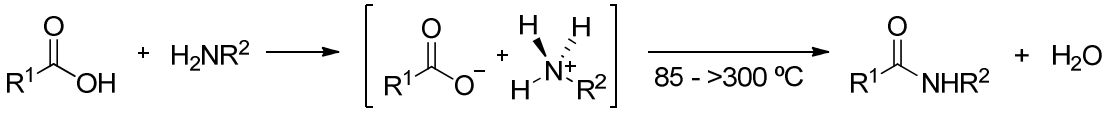


Figure 3-1: Some commercial amide-containing compounds.

Accordingly, synthetic routes to amide moieties are continually being pursued for the synthesis of peptides and other amide-containing organic molecules. The most obvious and simplest amide disconnection sought is that of an amine and a carboxylic acid.

Thermal dehydration is one of the simplest and oldest synthetic methods for production of amides (**Scheme 3-1**). The advantage is that no other activating reagents are necessary but after

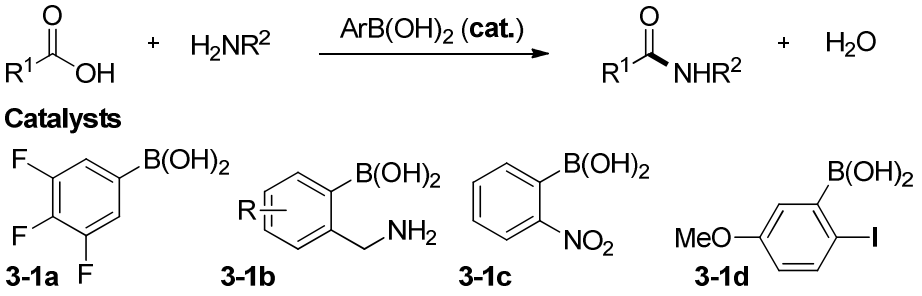
proceeding through the initial ammonium carboxylate salt, high temperatures are necessary to dehydrate the resulting species to form an amide.[2] Such harsh conditions are far from ideal and in some cases may cause decomposition of the product.



Scheme 3-1: Amide formation through condensation of a carboxylic acid and amine.

Modern alternatives have been developed involving activation by use of various reagents allowing milder reaction conditions. However, since some of these reagents such as carbodiimides, and uranium or phosphonium salts are toxic and generate excessive waste; finding safer and more efficient alternatives should be a priority. [3] A number of researchers have begun to investigate catalytic methods for production of amides.

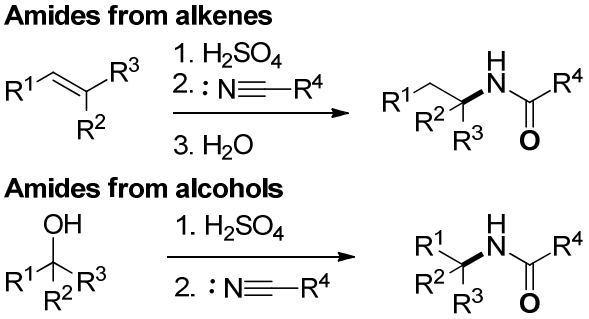
Catalytic methods help to ensure mild and clean formation of amides. It is methods such as these which coincide with the views and priorities of the *ACS Green Chemistry Institute Roundtable* (**Scheme 3-2**).[4] Notably, boronic acids play a crucial role in these reactions using various classes such as electron deficient and bifunctional derivatives (**3-1a**[5], **3-1b**[6], **3-1c**[7] and **3-1d**[8]). Until the appearance of 5-methoxy-2-iodophenylboronic acid (MIBA), boronic acids for the catalytic synthesis of amides have only been active at temperatures of 80 ºC or higher. On the other hand, for many substrates MIBA is active at mild, ambient temperatures.[8]



Scheme 3-2: Direct amide formation using catalytic boronic acids.

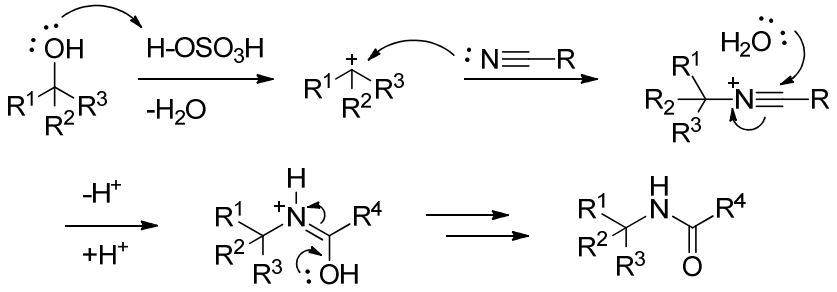
Although the disconnection of amides through carboxylic acid and amine building blocks are most common in the formation of amides, alternate disconnections are useful as they expand the possible synthetic routes toward a specific amide product. An alternative pathway which is less obvious than the traditional carboxylic acid and amine condensation to make an amide bond is by use of the Ritter reaction.

The Ritter reaction produces amides using a slightly different approach, primarily by combining an alkene or alcohol with a nitrile, which subsequently undergoes hydrolysis (**Scheme 3-3**).[9]



Scheme 3-3: Classical Ritter reaction of alkenes and alcohols to form amides.

This reaction proceeds first through formation of a carbocation by use of sulphuric acid, followed by nucleophilic addition of a nitrile and subsequent hydrolysis of the nitrilium intermediate to produce the desired amide (**Scheme 3-4**).



Scheme 3-4: Reaction mechanism of the Ritter reaction from an alcohol substrate.

Ritter reactions have been modified such that sulphuric acid could be replaced by other, more accessible and catalytic acid sources (**Figure 3-2**). Ritter reactions between acetonitrile and secondary benzylic alcohols were achieved with catalytic amounts of Brønsted acids such as 2,4-dinitrobenzenesulfonic acid (DNBSA)[10]; although, *o*-benzenedisulfonimide; has shown that it is more general allowing formation of alkyl-alkyl amides.[11]

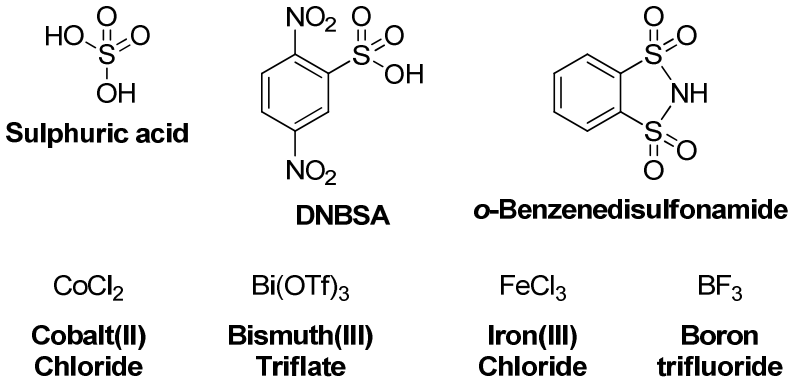
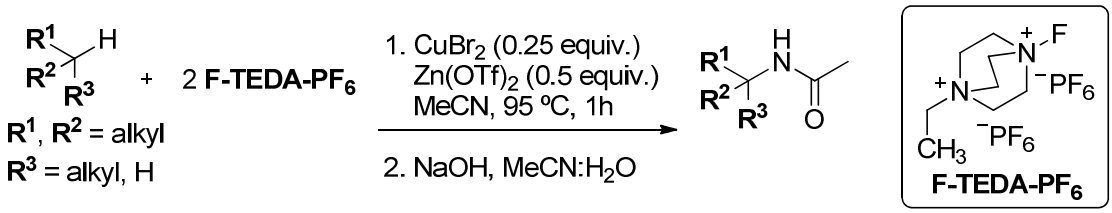


Figure 3-2: Common activators and catalysts used in the Ritter reaction.

The Ritter reaction is not limited simply by one class of acids but rather, are also able to be effectively catalyzed using many metal-based Lewis acids such as cobalt dichloride,[12] cobalt(III),[13] bismuth triflate,[14] iron trichloride[15] and boron trifluoride.[16]

The Ritter reaction has also been expanded to involve tertiary alkanes as electrophiles allowing direct C-N bond formation using copper-based C-H activation (**Scheme 3-5**).[17] Other variations

have appeared including alternative reaction conditions which allow Ritter-type substitution reactions[18] and even photo-Ritter variants.[19]

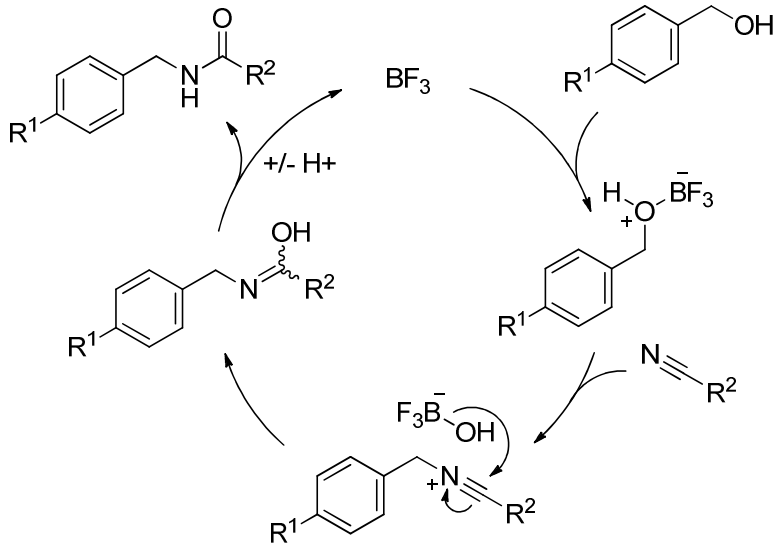


Scheme 3-5: Intermolecular Ritter-type C−H amination of unactivated sp^3 carbons.

Indeed, amide formation through the Ritter reaction has evolved since its infancy replacing activation by use of sulphuric acid with various catalysts and more general reaction conditions.[20] Many modified Ritter reactions rely upon metal-based Lewis acids for their activity, suitable replacements would be desirable. Although the appearance of DNBSA, *o*-benzenedisulfonimide and boron trifluoride do provide organocatalytic alternatives, they all have inherently low pKa and high reaction temperatures which suggest that development of more benign conditions would be a useful endeavour.

3.2 General Design and Methods

The novelty of the Ritter reaction is clear in its use of a non-obvious amide disconnection such as an alcohol and a nitrile compound. This is advantageous within synthetic organic chemistry and can aid in the masking and production of amides containing compounds. The goal of this research is to investigate the possibility of a mild and boronic acid catalyzed version of the Ritter reaction using alcohols as common, inexpensive and non-toxic substrates.

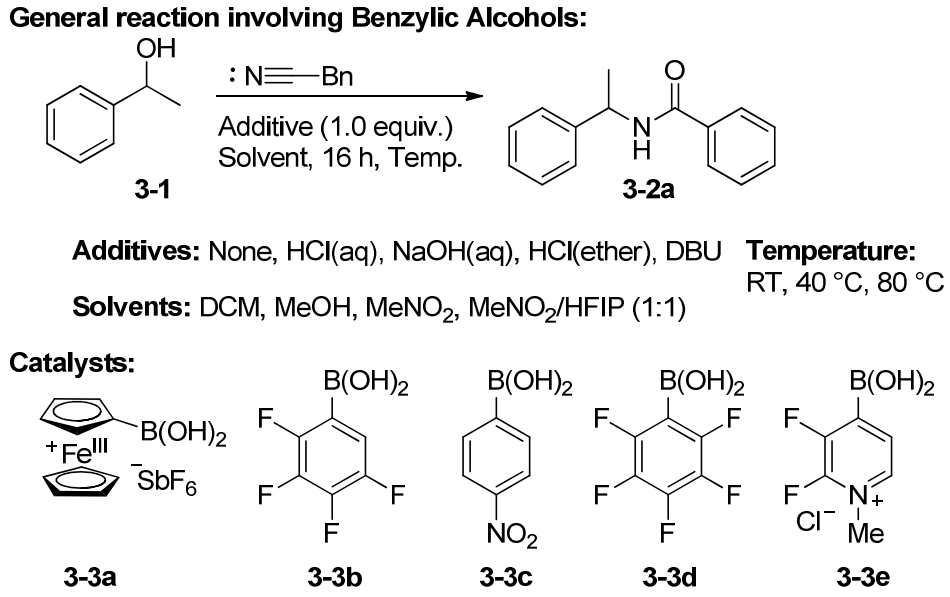


Scheme 3-6: Mechanism of the boron trifluoride catalyzed Ritter reaction.

Understanding the elucidated mechanistic cycle of an analogous Lewis acid such as boron trifluoride should allow prediction of how a boronic acid would also behave under similar Ritter reaction conditions (**Scheme 3-6**).[16]. Since the reaction using boron trifluoride was found to function best in refluxing 1,2-dichloroethane (DCE), a number of alterations enabling use of milder catalysts such as boronic acids or replacement of chlorinated solvents was desired.

Following boron trifluoride catalyzed Ritter reaction as a model reaction, a benzyl alcohol and a nitrile were used to yield a standard product (**Scheme 3-7**). It is desirable to replace DCE with a solvent that is more able to stabilize intermediate cationic species; so, a number of alternatives were proposed such as dichloromethane (DCM), methanol, nitromethane and a nitromethane-hexafluoroisopropanol mixture similar to previously developed reactions using boronic acid catalysts.[21,22] Temperature was to be kept mild and ideally at ambient temperature but not to exceed 80 ºC. Additives were also included to shuttle protons around the solvent to possibly reduce the reaction's energy barrier. Finally, potential boronic acid activators were tested for catalytic activity. As with previously developed reactions, the array of boronic acids tested were

electron poor such that they can reasonably activate an alcohol for substitution by the nitrile when subjected to Ritter reaction conditions in small screw-top vials. The crude reaction was analyzed by thin-layer chromatography (TLC) and compared with reference standards or the starting material (**3-1**), product (**3-2a)**, and catalyst.



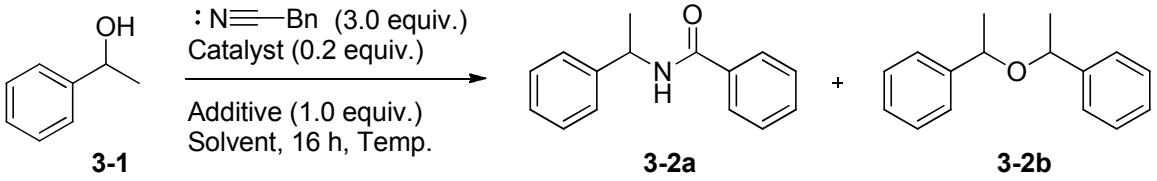
Scheme 3-7: Assay screening for a boronic acid catalyzed Ritter reaction.

3.3 Results and Discussion

This investigation proceeded through collaboration with an undergraduate research assistant named Yibai Sun who was involved in all facets of this research but primarily running the high-throughput screening (HTS) and targeted assay (**Scheme 3-7**; **Table 3-1**). Traditional high-throughput screening (**Scheme 3-7**) did not yield any desired product so a more targeted approach was taken. This targeted screening involved the two boronic acids which have the best ability to catalyze reactions with π-activated alcohols, namely ferroceniumboronic acid hexafluoroantimonate salt (FBAHA; **3-3a**) and tetrafluorophenylboronic acid (TFBA; **3-3b**).[21] This revised screen also eliminated any additive and restricted the solvents to nitromethane or a

nitromethane-hexafluoroisopropanol mixture (**Table 3-1**), the solvents where the aforementioned catalysts were most active in previous works on alcohol activation.[21,22]

Table 3-1: Probing for a catalytic Ritter reaction using electron deficient boronic acids.



3-1 **3-2a** **3-2b**

Entry	Catalyst	Conditions	Solvent	Temp (ºC)	Products[†]
1	**3-3a**	---	$MeNO_2$	40	**3-2a** (<5%), **3-2b** (34%)
2	**3-3a**	---	$MeNO_2$:HFIP (1:1)	40	**3-2a** (<5%), **3-2b** (20%) + other
3	**3-3a**	---	$MeNO_2$	80	**3-2a** (<5%)
4	**3-3a**	---	$MeNO_2$:HFIP (1:1)	80	**3-2a** (<5%)
5	**3-3b**	---	$MeNO_2$	40	**3-2a** (<5%)
6	**3-3b**	---	$MeNO_2$:HFIP (1:1)	40	**3-2a** (<5%), **3-2b** (<5%)
7	**3-3b**	---	$MeNO_2$	80	**3-2a** (<5%), **3-1** (0%)
8	**3-3b**	---	$MeNO_2$:HFIP (1:1)	80	**3-2a** (<5%), **3-1** (52%)
9	**3-3a**	INV	$MeNO_2$	reflux	**3-2a** (<5%), styrene, other
10	**3-3a**	H_2O (3 equiv.); INV	$MeNO_2$	reflux	**3-2a** (<5%), other
11	**3-3b**	INV	$MeNO_2$	reflux	**3-2b** (37%), **3-1** (63%)
12	**3-3b**	H_2O (3 equiv.); INV	$MeNO_2$	reflux	**3-2b** (53%), **3-1** (46%), other
13	**3-3b**	INV	$MeNO_2$:HFIP (1:1)	reflux	**3-2a** (21%), **3-2b** (77%), other
14	**3-3b**	H_2O (3 equiv.); INV	$MeNO_2$:HFIP (1:1)	reflux	**3-2a** (<5%), **3-2b** (<5%), **3-1** (90%)
15	BF_3	*Ref. 16*	DCE	reflux	**3-2a** (85%)
16	BF_3	---	$MeNO_2$:HFIP (1:1)	80	**3-2a** (<5%)
17	**3-3b**	---	DCE	reflux	**3-2a** (<5%)

Note: **3-1** = Starting Material, **3-2a** = Amide Product, **3-2b** = Homo-Coupling Product
INV = Procedure performed by inverse addition of the alcohol over 2 hours
[†] Trace amounts are <5% as determined using an NMR internal standard (trichloroethylene)

The first few tests (entries 1-8) used the most active catalysts (**3-3a** and **3-3b**) under standard one-pot conditions but to only a trace amount of the desired amide (**3-2a**) or a homo-coupling product (**3-2b**). It is obvious that activation of the alcohol did occur due to formation of the benzyl ether (**3-3b**). The actual appearance of this homo-coupling product (**3-2b**) does suggest that the benzyl alcohol (**3-1**) is the best available nucleophile, not the desired nitrile, since the homo-coupling product is formed faster than the amide (**3-2a**).

Reducing the severity of this homo-coupling issue was achieved by slowly adding the benzylic alcohol (**3-1**) into the reaction mixture; these conditions discourage a high concentration of activated substrate in the reaction mixture but also keeps the concentration of free alcohol low and diminishes the chance of self-condensation (entries 9-15). Water was added to various trials (entries 10, 12 and 14) to retard the reaction and hopefully reduce the amount of homo-coupling, unfortunately to no effect. These later trials actually managed to increase the homo-coupling product dramatically in yields of 5-77%, a result opposite to what was desired.

It is interesting to note that a single test reaction conducted at reflux using nitromethane-hexafluoroisopropanol as solvent and inverse addition (entry 13) does give the amide product (**3-2a**) in 21% yield but with a large proportion of the homo-coupling product. Reproducing the literature reaction was possible using boron trifluoride giving the desired amide product in 85% yield (entries 14 and 15).[16] Although in the initial assay screen, boronic acids were not active in DCM, the higher boiling point allowed by DCE may permit a boronic acid to catalyze the Ritter reaction based on the example with boron trifluoride.

3.4 Conclusions

Thus far, this investigation suggests that the formation of an amide from an alcohol and nitrile using a boronic acid can indeed form the desired product but not yet in an efficient manner. The main issue encountered with a boronic acid catalyzed Ritter reaction is the low nitrile nucleophilicity, which is not enough to give a decent yield of the desired amide product (**3-2a**). Unfortunately, this issue became increasingly apparent when the more nucleophilic alcohol (**3-1**) favourably forms a homo-coupling product (**3-2b**) despite a competing substrate, the nitrile. Slowing the alcohol addition would decrease its concentration in solution; theoretically, this

could allow the nitrile more time to react with the activated species but without competition from other potential substrates. There is also a possibility that the formation of the nitrilium species is reversible, and in order to facilitate amide formation, hydrolysis must be fast enough to occur in the lifetime of the intermediate nitrilium species.

Currently, arylboronic acids are not suitable candidates to replace current catalytic Ritter reaction protocols. With additional research on boronic acid catalysis and reaction optimization, a viable catalytic alternative may eventually be found to afford a milder Ritter reaction.

3.5 Experimental

The following materials include representative experimental procedures and details for the synthesis and isolation of compounds. Unless otherwise stated, all reactions were performed in capped regular glassware with no further precautions. Dichloromethane (DCM), and methanol were purified using a cartridge solvent purification system prior to use. All other solvents were purchased as ACS reagents and used without further purification. Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes and ethyl acetate as eluents. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light and with $KMnO_4$ or phosphomolybdic acid (PMA) stains. Commercial dichloroethane (DCE) were used as standards in all observations. ^1H NMR spectra were recorded on 400 MHz or 500 MHz instruments. The residual solvent protons ($^1H/CHCl_3$) were used as internal references. ^1H NMR data is presented as follows: chemical shifts in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d,

doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sept, septet; dd, doublet of doublets; m, multiplet. The error of coupling constants from ^{1}H NMR spectra is estimated to be 0.3 Hz. The amide product, 1-phenylethyl benzamide (**3-2a**) was categorized by comparison with its ^{1}H NMR spectrum as previously reported. [23]

General Assay Procedure

The general assay procedure follows conditions described in **Scheme 3-7**. To a srew-top vial, a mixture of 1-phenylethanol (0.25 mmol; 31 mg) and benzonitrile (0.75 mmol; 77 mg) was added. The mixture was diluted in 1.0 mL of solvent ($MeNO_2$, $MeNO_2$:HFIP (1:1), DCM, or MeOH). As required, the following additives were added: hydrogen chloride (0.25 mmol, 0.25 mL of a 1 M solution), sodium hydroxide (0.25 mmol, 9.7 mg in 0.25 mL of water), hydrogen chloride (0.25 mmol; 0.25 mL of a 1 M ether solution) and DBU (0.25 mmol; 38 mg). Finally the catalyst (**3-3a** – **3-3e**; 0.05 mmol) was added, and the mixtures were reacted at ambient temperature. The vial was capped and no precautions were taken to exclude oxygen or moisture. After reacting for 16 hours with stirring at the appropriate temperature, TLC analysis of crude products was compared with standardized products then the mixture was concentrated under reduced pressure. The crude products were then diluted in DCM (5 mL) and washed with water twice (10 mL) then with brine (10 mL) and concentrated. Finally, the products were purified on silica gel using 1:1 of DCM:hexane with 2% triethylamine and observed by ^{1}H NMR to show product distribution as described.

Targeted Reaction Procedure

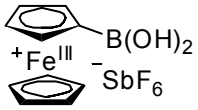
This targeted reaction procedure follows the reactions outlined in **Table 3-1**.To a dried 25 mL round bottom flasks was added a mixture of 1-phenylethanol (1.0 mmol; 120 mg), benzonitrile (3.0 mmol; 230 mg) and catalyst **3-3a** or **3-3b** (0.1 mmol) in 4 mL of solvent ($MeNO_2$:HFIP (1:1) and $MeNO_2$). Water (3.0 mmol; 21 mg) was added as required. The reaction vessel was equipped with a condenser and the mixture was stirred for 16 hours at the designated temperature. The mixture was concentrated under reduced pressure. The crude products were then diluted in DCM (5 mL) and washed with water twice (10 mL) then with brine (10 mL) and concentrated. Finally, the products were purified on silica gel chromatography using DCM:hexane (1:1) with 2% triethylamine and compounds were characterized by ^{1}H NMR spectroscopy to show product distribution as described.

Targeted Reaction Procedure (with inverse addition)

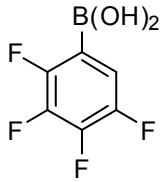
This targeted reaction procedure follows the reactions outlined in **Table 3-1**. To a dried 25 mL round bottom flask was added a mixture of benzonitrile (3.0 mmol; 230 mg) and catalyst **3-3a** or **3-3b** (0.1 mmol) in $MeNO_2$:HFIP (1:1) or $MeNO_2$ (3.0 mL). Water (3.0 mmol; 54 mg) was added as required. The reaction vessel was equipped with a condenser and by syringe pump 1-phenylethanol (1.0 mmol; 120 mg) in matching solvent (1.0 mL) was added over 2 hours during which time the mixture was stirred and allowed to react for a further 14 hours at the designated temperature. The mixture was concentrated under reduced pressure. The crude products were then diluted in DCM (5 mL) and washed with water twice (10 mL) then with brine (10 mL) and concentrated. Finally, the products were purified on silica gel using DCM:hexane (1:1) with 2%

triethylamine and compounds were characterized by ^{1}H NMR spectroscopy to show product distribution as described.

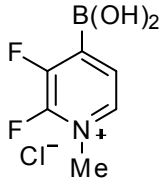
Synthesized Catalysts



Ferroceniumboronic acid hexafluoroantimonate salt (3-3a): This compound was prepared as per a previous report.[22]



2,3,4,5-Tetrafluorophenylboronic acid (3-3b): This compound was prepared as per a previous report.[24]



2,3-Difluoro-4-methylpyridiniumboronic acid (3-3e): This compound was prepared as per a previous report.[24]

3.6 References

1 (a) Ghose, A.K.; Viswanadhan, V.N.; Wendoloski, J.J. *J. Comb. Chem.* **1999**, *1*, 55–68. (b) Roughley, S.D.; Jordan, A.M. *J. Med. Chem.* **2011**, *54*, 3451–3479.

2 (a) Arnold, K.; Davies, B.; Giles, R.L.; Grojean, C.; Smith, G.E.; Whiting, A. *Adv. Synth. Catal.* **2006**, *348*, 813-820. (b) Charville, H.; Jackson, D.A.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010**, *46*, 1813-1823.

3 (a) Montalbetti, C.A.G.N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827-10852. (b) Carey, J.S.; Laffan, D.; Thomson, C.; Williams, M.T. *Org. Biomol. Chem.* **2006**, *4*, 2337-2347.

4 Constable, D.J.C.; Dunn, P.J.; Hayler, J.D.; Humphrey, G.R.; Leazer, J.L.; Linderman, R.J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T.Y. *Green Chem.* **2007**, *9*, 411−420.

5 (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196-4197. (b) Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron*, **2007**, *63*, 8645-8657.

6 Arnold, K.; Batsanov, A.S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124-134.

7 Liu, S.; Yang, Y.; Liu, X.; Ferdousi, F.K.; Batsanov, A.S.; Whiting, A. *Eur. J. Org. Chem.* **2013**, *5692*.

8 (a) Al-Zoubi, R.; Marion, O.; Hall, D.G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879. (b) Gernigon, N.; Al-Zoubi, R.M.; Hall, D.G. *J. Org. Chem.* **2012**, *77*, 8386. (c) Fatemi, S.; Gernigon, N.; Hall, D.G. *Green Chem.* **2015**, *17*, 4016-4028.

9 Ritter, J.J.; Kalish, J.A. *J. Am. Chem. Soc.* **1948**, *70*, 4048-4050.

10 Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Guitiérrez, J.M.; Rodríguez, F. *Eur. J. Org. Chem.* **2007**, 4642-4645.

11 Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Eur. J. Org. Chem.* **2009**, 430-436.

12 Mukhopadhyay, M.; Reddy, M.M.; Maikap, G.C.; Iqbal, J. *J. Org. Chem.* **1995**, *60*, 2670-2676.

13 Mukhopadhyay, M.; Iqbal, J. *J. Org. Chem.* **1997**, *62*, 1843-1845.

14 Callens, D.; Burton, A.J.; Barrett, A.G.M. *Tetrahedron Lett.* **2006**, *47*, 8699-8701.

15 Anxionnat, B.; Guérinot, A.; Reymond, S.; Cossy, J. *Tetrahedron Lett.* **2009**, *50*, 3470-3473.

16 Firouzabadi, H.; Sardarian, A.R.; Badparva, H. *Synth. Commun.* **1994**, *24*, 601-607.

17 Michaudel, Q.; Thevenet, D.; Baran, P.S. *J. Am. Chem. Soc.* **2012**, *134*, 2547-2550.

18 Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Tetrahedron* **1994**, *50*, 8997-9008.

19 Passananti, M.; Cermola, F.; DellaGreca, M.; Iesce, M. R.; Previtera, L.; Sferruzza, R.; Temussi, F. *Int. J. Photoenergy* **2014**, *2014*, 1-6.

20 Guérinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 19-28.

21 Ricardo, C.L.; Mo, X.; McCubbin, J.A.; Hall, D.G. *Chem. Eur. J.* **2015**, *21*, 4218-4223.

22 Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

23 Yadav, J.S.; Reddy, B.V.S.; Pandurangam, T.; Reddy, Y.J.; Gupta, M.K. *Catalysis Communications* **2008**, *9*, 1297-1301.

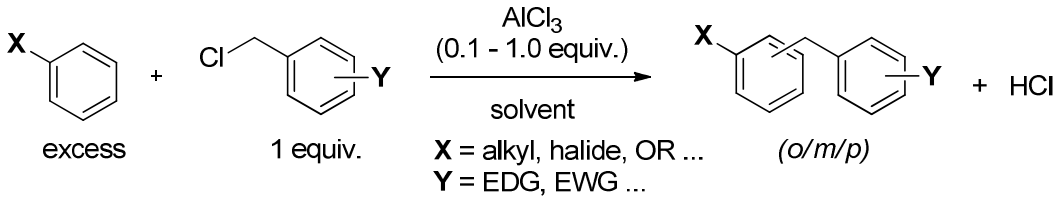
24 Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D.G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187-6190.

4 Activation of Benzylic Alcohols for the Formation of Diarylmethanes using Friedel-Crafts Chemistry

4.1 Introduction & Objective

The Friedel-Crafts alkylation is a versatile method of carbon-carbon bond formation, dating back to 1877.[1] Despite its age, this reaction is still relevant today due to its relatively broad scope and application in the synthesis of many aryl-alkyl containing compounds. Unfortunately, to this day the Friedel-Crafts alkylation still suffers from a few disadvantages.

Traditional Friedel-Crafts alkylations (**Scheme 4-1**) tend to require a stoichiometric amount of a harsh activating agent such as aluminum trichloride.[2] Unfortunately, toxic benzyl halides are required for this classic reaction yielding the expected product with a harmful and corrosive haloacid by-product.[3]

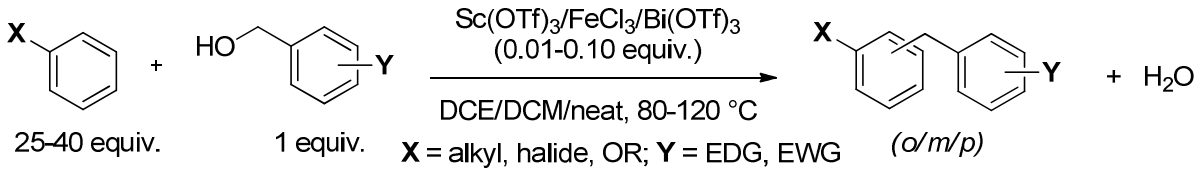


Scheme 4-1: Classical Friedel-Crafts alkylation.

Recently, due to its importance in industry, the Friedel-Crafts reaction has been noted as a top priority in synthetic methodology by the *ACS Green Chemistry Institute Roundtable*.[4]

The drawbacks of classical Friedel-Crafts reactions have not gone unnoticed.[5] Efforts toward catalytic variants have been pursued using alternative Lewis acids such as scandium triflate,[6] iron(III) chloride,[5,7] and bismuth triflate.[8] Elimination of the halide starting material has the consequent effect of preventing haloacid formation. In the case of benzylation, this was

accomplished through investigation of alcohol-based electrophiles to supplant the more harmful and less environmentally friendly benzylic halides. In this manner, the only by-product produced is water. Use of these carefully chosen transition-metal activators allowed the development of reliable catalytic Friedel-Crafts variations for the benzylation of arenes (**Scheme 4-2**).



Scheme 4-2: Catalytic Friedel-Crafts of benzyl alcohols using transition metals.

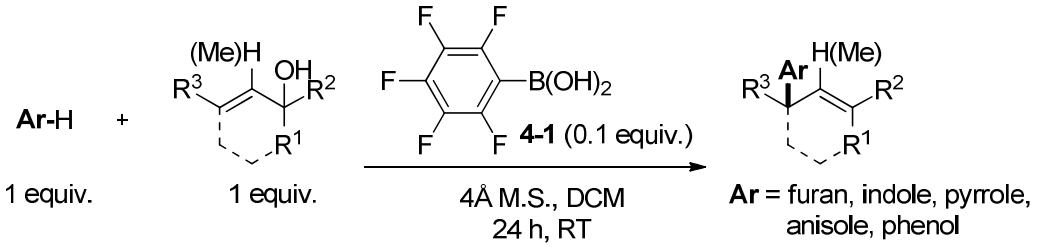
Despite these recent improvements to the Friedel-Crafts alkylation, there are some remaining weaknesses to the new protocols:

- A large excess of an arene nucleophile is required, usually as a co-solvent
- High reaction temperatures
- Somewhat limited substrate scope, typically only with electron-rich arenes

The idea of boronic acid catalysis involving alcohols has emerged due to their oxophilic nature but is also supported by the mild and modular properties of many arylboronic acids. Arylboronic acids have now become entrenched in the activation of allylic and benzyl alcohols to promote various transformations.[9]

One ground-breaking transformation utilizing boronic acid catalysis was a variation of the Friedel-Crafts reaction with allylic alcohols using the electron deficient 2,3,4,5,6-pentafluorophenylboronic acid (PFBA; **4-1**) in a catalytic quantity (**Scheme 4-3**).[10] This reaction afforded arene-heterocycle adducts at room temperature, which is strikingly milder than previously reported variants (80-120 ºC). This relatively benign catalyst is a good alternative to the previous Brønsted and Lewis acids with the additional benefit of avoiding transition metals.

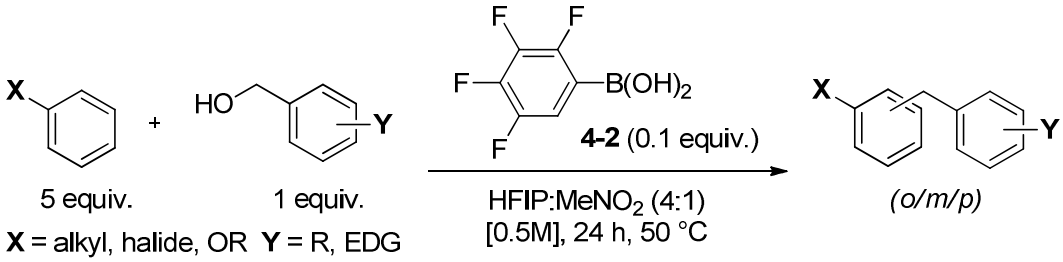
Despite the advantages, the substrate scope of PFBA in Friedel-Crafts reactions is limited to stabilized secondary and tertiary allylic alcohols as well as very electron rich arene nucleophiles.



Scheme 4-3: Pentafluorophenylboronic acid catalyzed Friedel-Crafts alkylation.

Building upon the discovery of pentafluorophenylboronic acid,[10] 2,3,4,5-tetrafluorophenylboronic acid (TFBA; **4-2**) was subsequently discovered to be superior in a number of reactions involving activation of an allylic or benzylic alcohol. It is surprising that the removal of a single *ortho* fluoride from PFBA (pKa 3.5) can afford a more active catalyst; this is counter-intuitive due to the decreased pKa of TFBA (pKa 6.0).[11]

Development of the TFBA catalyst (**4-2**) began with allylic and propargylic alcohol activation subsequently resulting in the formation of transposed products.[12] The discovery of this altered catalyst marked new organocatalytic activity previously unobtainable by use of pentafluorophenylboronic acid. This advancement suggested that improvement of boronic acid catalyzed Friedel-Crafts reaction was possible, if somewhat unpredictable (**Scheme 4-4**).[11]



Scheme 4-4: Tetrafluorophenylboronic acid catalyzed Friedel-Crafts alkylation.

Thus far, boronic acid catalyzed Friedel-Crafts alkylation has improved to the point of requiring only a small amount of the arene nucleophile, reduced reaction temperature and removing the need for a transition metal catalyst. Progress toward a general organocatalytic Friedel-Crafts reaction requires further optimization of the catalyst enabling improvement of the substrate scope as the final stride.

4.2 Experimental Design & Methods

Surveying the current boronic acids used in the Friedel-Crafts alkylation, it is clear that to improve the catalytic reactivity and substrate scope while maintaining a mild Lewis acid catalyst, other structural aspects of the arylboronic acid scaffold must be taken into consideration (**Figure 4-1**).[9] Since the Friedel-Crafts reaction is reliant upon formation of a carbocation, this variation requires a catalyst with a greater ability to ionize a benzyl alcohol. The obvious method of increasing the reactivity of the arylboronic acid would be to follow the trend of decreasing catalyst pKa;[13] unfortunately, aforementioned research has also uncovered that increased catalytic activity was not dependant on pKa alone.[11] Comparison of PFBA and TFBA led to the consideration of a unique ionic boronic acid: ferroceniumboronic acid hexafluoroantimonate salt, with potential as an air- and moisture-tolerant catalyst for Friedel-Crafts alkylations.

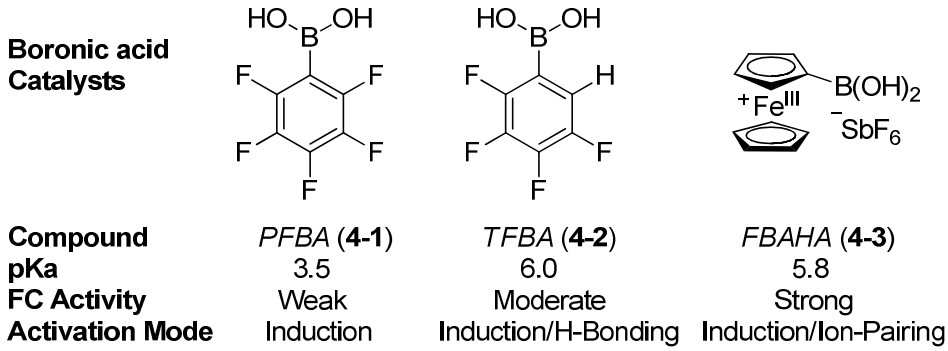
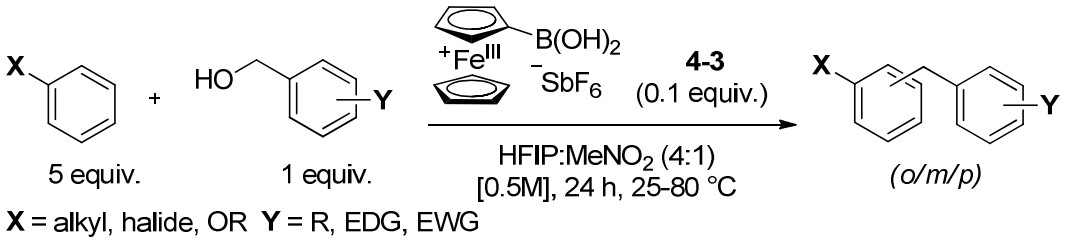


Figure 4-1: Current boronic acid catalysts for use in the Friedel-Crafts reaction.

The proposed catalyst, ferroceniumboronic acid hexafluoroantimonate (FBAHA), offers a decreased pKa of 5.8 over its ferroceneboronic acid precursor with a pKa of 10.8 (**Scheme 4-5**).[14] The main purpose of searching for a new catalyst is to increase the scope of boronic acid catalyzed Friedel-Crafts alkylations.



Scheme 4-5: Friedel-Crafts alkylation using ferroceniumboronic acid.

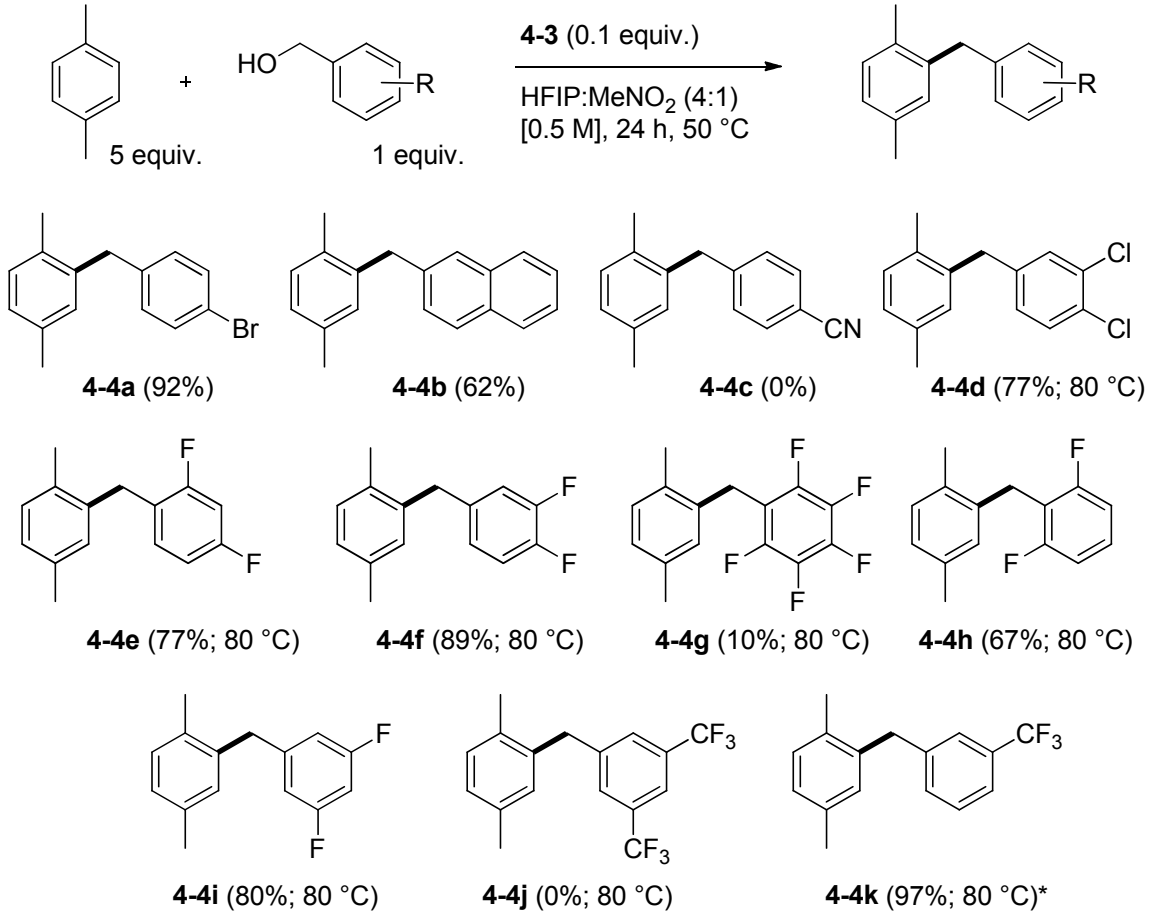
The reactivity of FBAHA was probed using increasingly electron deficient substrates to push the boundaries of boronic acid catalyzed Friedel-Crafts alkylations. The optimized reaction conditions were previously determined by a former lab mate, Julien Dansereau.[15] The optimized solvent was an unusual mixture of 1,1,1,3,3,3-hexafluoroisopronol with nitromethane in a 4:1 ratio, which was previously found to be the highest yielding solvent with TFBA, the predecessor of FBAHA.[11] A current lab mate, Xiaobin Mo, has researched possible mechanistic explanations for the improved reactivity of FBAHA over its predecessor, TFBA.[16] My role in this broad project consisted of identifying the boundaries of suitable substrates, in particular, deactivated benzylic alcohols, neutral arenes and the synthesis of a small pharmaceutical compound, beclobrate.

4.3 Results and Discussion

4.3.1 Reactivity of Primary Alcohols

The FBAHA based Friedel-Crafts alkylations of primary alcohols are higher yielding than those catalyzed by TFBA (**Figure 4-2**). Particularity, FBAHA reacted with electron deficient primary

benzylic alcohols (**4-4d** – **4-4i**) where TFBA was restricted to neutral or slightly activated alcohols.[11]



* Reverse reaction with α,α,α-trifluorotoluene and 2,5-dimethylbenzyl alcohol gives 0% at 80 °C.

Figure 4-2: Scope of primary alcohols in the Friedel-Crafts alkylation using FBAHA.

Slightly deactivated substrates such as of 4-bromobenzyl alcohol (**4-4a**) proceed to form the Friedel-Crafts product in excellent yield, while the yield of a neutral substrate such as 2-hydroxymethylnaphthalene (**4-4b**) was moderate, due to solubility issues. Unfortunately, extremely electron deficient substrates such as 4-cyanobenzyl alcohol (**4-4c**) gave no detectable product as the resulting primary carbocation would be too unstable.

Improved catalyst reactivity of boronic acid **4-3** has provided the means to activate the hydroxyl group of some highly electron deficient species including polychlorinated and polyfluorinated benzyl alcohols toward Friedel-Crafts alkylations (**4-4d** – **4-4i**). An expected trend was revealed such that as the number of fluorine atoms increase, and subsequently the electron deficiency of the arene, the propensity of the benzylic alcohol to ionize decreases. It is important to compare the 3,5-difluorobenzyl alcohol (**4-4i**) where the lone-pair provided by fluorine atoms in the conjugated arene compensates for the negative inductive effect and likely accounts for the drastically improved reactivity over the latter, 3,5-bis(trifluoromethyl)benzyl alcohol (**4-4j**), which has no such electronic stabilization. Fortunately, when a single trifluoromethyl substituent is removed (**4-4k**), the desired reactivity is restored.

4.3.2 Reactivity of Secondary Alcohols

The expected increased reactivity of secondary alcohol substrates is immediately noticeable for this Friedel-Crafts reaction. Reaction with much more electron deficient substrates is possible with greater ease than with the primary alcohols (**Figure 4-3**). This observation is not surprising considering the known stabilizing effect enabled by secondary and tertiary carbocation centres, which results in a lower energy transition state when compared to their primary counterparts.[17]

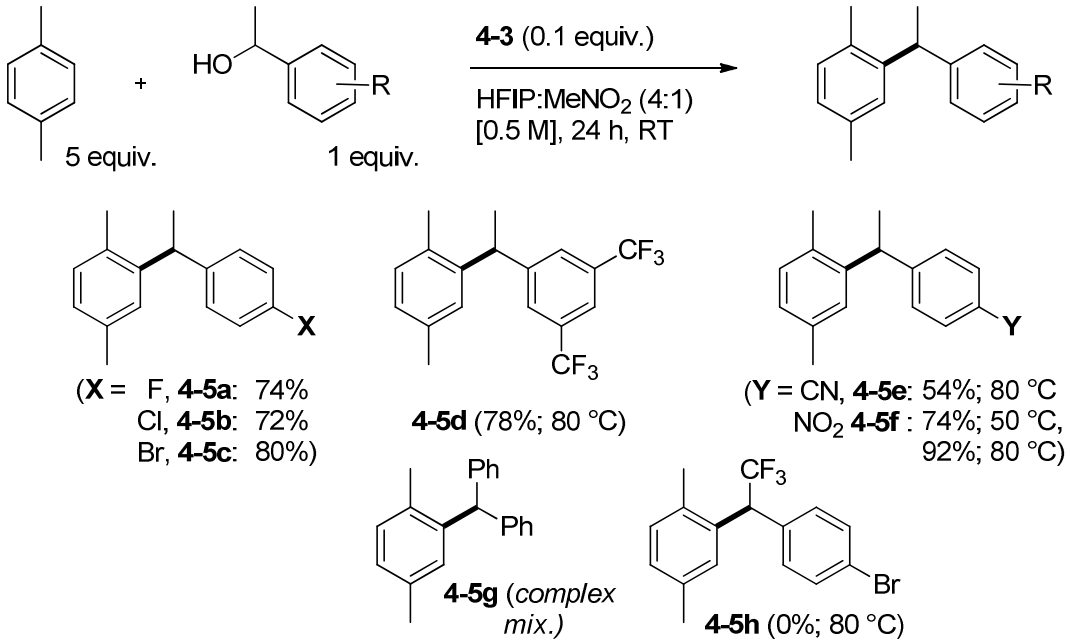
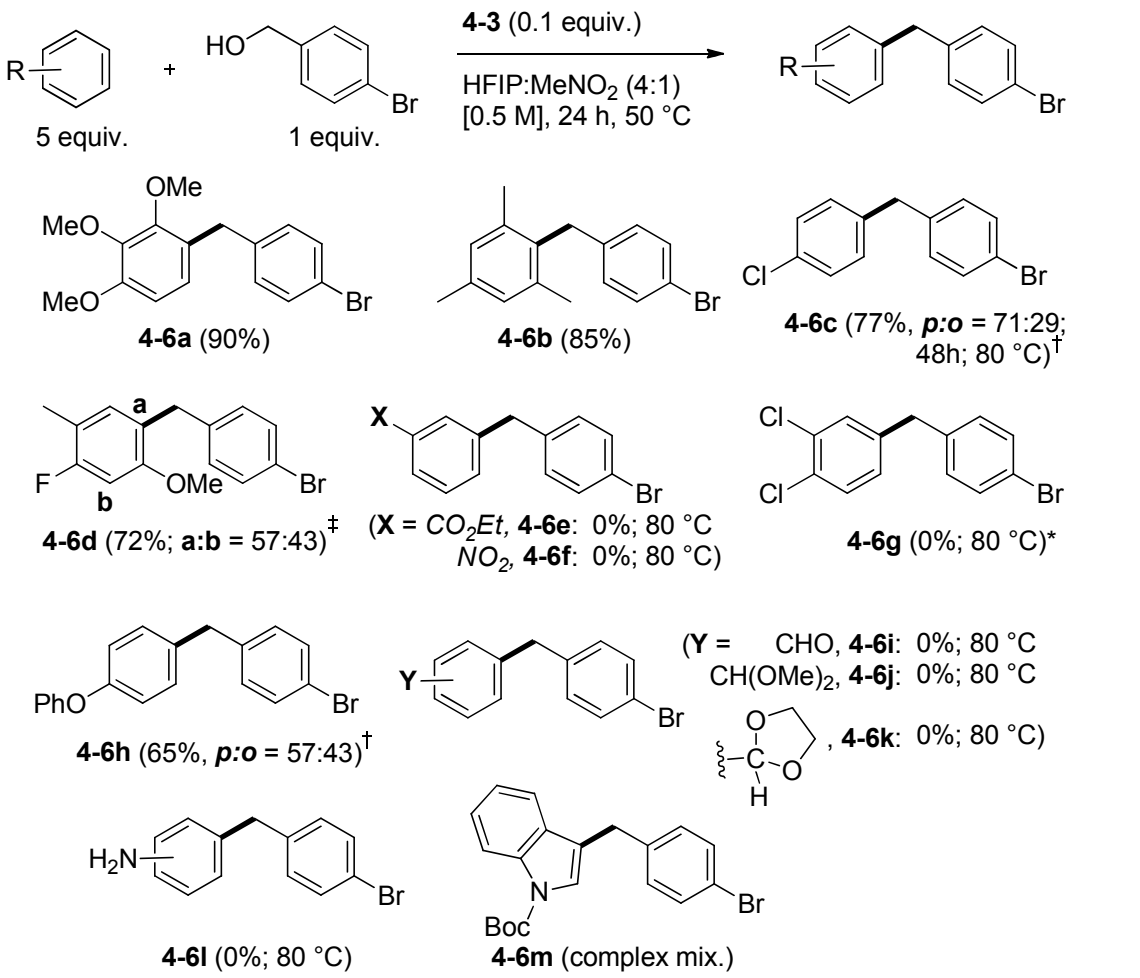


Figure 4-3: Scope of secondary alcohols in the Friedel-Crafts alkylation using FBAHA.

The Friedel-Crafts reaction of secondary benzyl alcohols substituted with various halides (**4-5a** – **4-5c**) has lead to good yields. Moving from a primary alcohol to a secondary alcohol allows reaction of the bis(trifluoromethyl) benzylic alcohol to give product **4-5d.** This result is not surprising due to the greater carbocation stabilization provided by this secondary alcohol and subsequently afforded a greater yield. Following this expected trend, more electron deficient benzylic alcohols involving cyano (**4-5e**) and nitro groups (**4-5f**) also proceeded with moderate to excellent yields. Not all attempts were successful such as the creation of a triarylmethane (**4-5g**), which yields a complex mixture of inseparable products. Attempted destabilization of the secondary benzyl alcohol with a trifluoromethyl substituent (**4-5h**) resulted in no reaction; this result lends evidence to an S_N1-type mechanism.

4.3.3 Reactivity of Arenes

The resulting Friedel-Crafts reaction of various arenes gave results much like that of the benzyl alcohol where the electron rich arenes gave better reactivity than their deficient counterparts (**Figure 4-4**).



* Reverse reaction with bromobenzene and 3,4-dichlorobenzyl alcohol gives 73%, ***p:o*** = 58:42.†

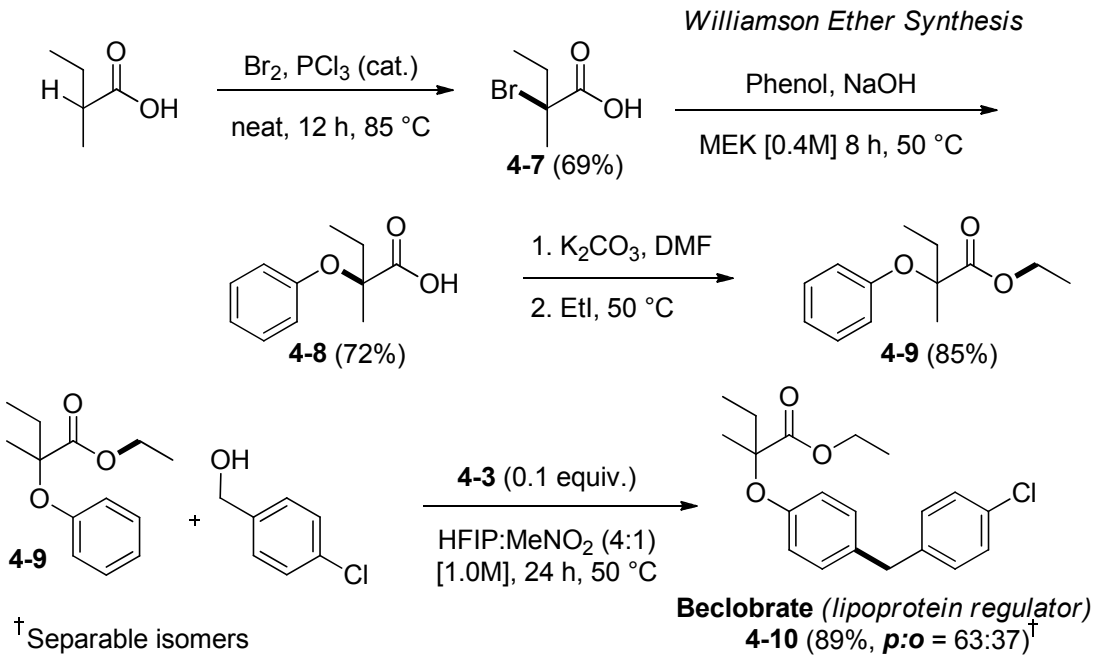
† Separable isomers

‡ Isomers not separable, ratio determined by ^{1}H NMR spectroscopy

Figure 4-4: Scope of arenes in the Friedel-Crafts alkylation using FBAHA.

4.3.4 Synthesis of Beclobrate

As mentioned before, several pharmaceutical drugs and natural products contain the diarylmethane framework. As an application of the FBAHA-based Friedel-Crafts alkylation, beclobrate, a lipoprotein regulator, was synthesized under the standard reaction conditions.



Scheme 4-6: Synthesis of Beclobrate.

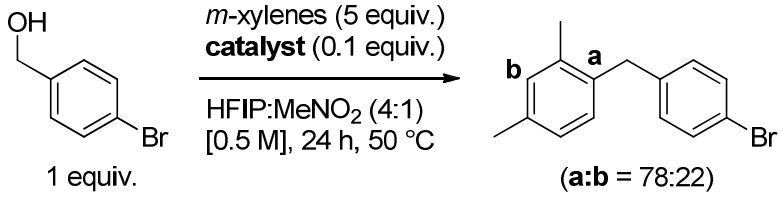
Beclobrate was synthesized using simple methods and basic starting materials. First, 2-methylbutanoic acid was subjected to the Hell-Volhard-Zelinsky reaction giving the brominated product **4-7**.[18] A subsequent Williamson ether synthesis (**4-8**) followed by protection of the carboxylic acid gave the beclobrate precursor **4-9**.[19] When **4-9** was finally subjected to the new Friedel-Crafts alkylation protocol, beclobrate (**4-10**) was successfully synthesized in 89% yield (*p:o* 63:37) without decomposition and with successful separation of the two isomers by column chromatography.

4.4 Proposed Mechanism

The mechanistic proposal was established based upon a number of observations. It has already been established that boronic acid catalysts activate allylic and benzylic alcohols by generating transient carbocations that can undergo the Friedel-Crafts alkylation.[10] The ferroceniumboronic acid hexafluoroantimonate is a more complex variation of many other arylboronic acids; fortunately, a number of controls performed by collaborators have confirmed that the boronic acid is indeed the active site of this catalyst where the ferrocenium moiety simply modulates the pKa of the boronic acid (**Table 4-1**).[16,20]

Table 4-1: Control experiments examining the role of the boronyl unit.

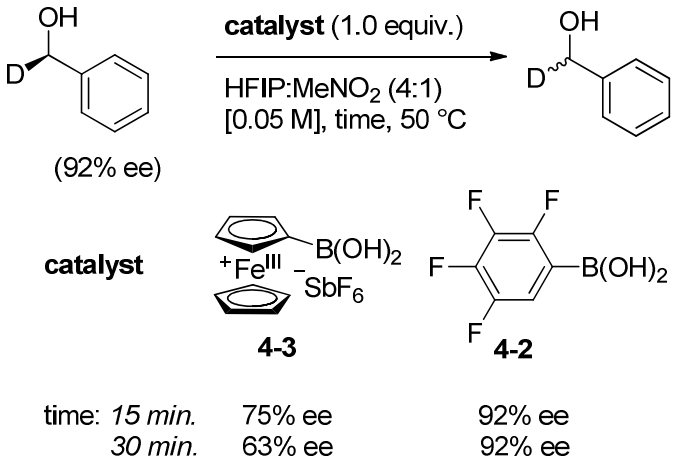
*This work was the result of a collaboration with Xiaobin Mo and Julien Dansereau.[20]



Catalyst	*Yield*
$[CpFe(III)CpB(OH)_2]^+ SbF_6^-$ (**4-3**)	87%
$[CpFe(III)Cp]^+ SbF_6^-$	15%
$[CpFe(III)CpBpin]^+ SbF_6^-$	45%
$[CpFe(III)CpBpin]^+ SbF_6^-$ + 4A m.s.	27%
$Ag^+ SbF_6^-$	0%
CF_3CO_2H	Trace

As previously discussed, the reactivity of the various trifluoromethane-containing species (**4-4j**, **4-4k**, and **4-5g**) suggests a S_N1-type mechanism. Scission of the carbon-oxygen bond becomes increasingly difficult as the number of trifluoromethyl moieties increase along with their proximity to the carbocation site. Collaborative work by Xiaobin Mo has also shown that unlike TFBA, FBAHA will racemize a chiral deuterated primary alcohol suggesting complete ionization of the benzylic alcohol (**Scheme 4-7**).[21] This information allows a collective proposal

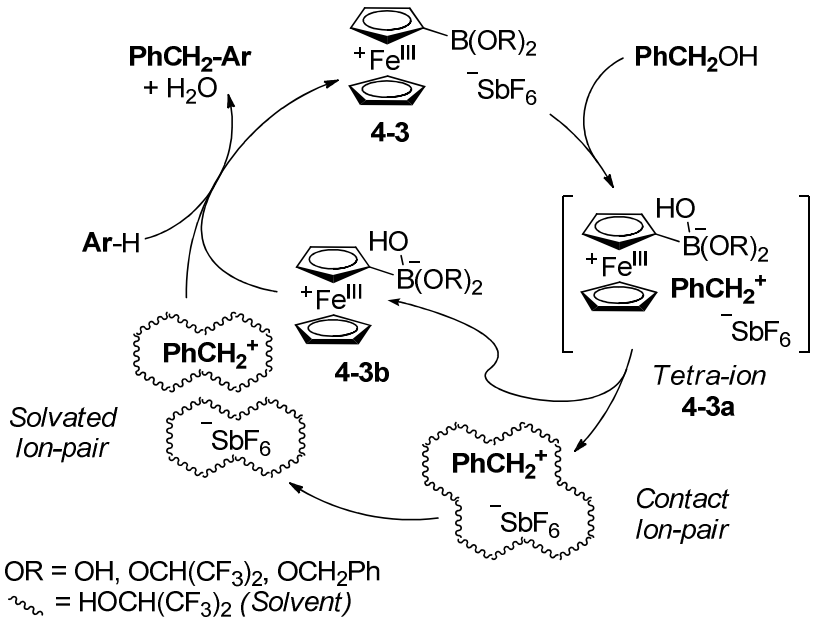
for a plausible catalytic cycle for this FBAHA Friedel-Crafts alkylation to be collectively proposed with all the contributors to this research (**Scheme 4-8**).[22]



Scheme 4-7: Ionization of optically enriched, deuterated alcohol.

*This work was the result of a collaboration with Xiaobin Mo.[21]

The FBAHA catalyzed Friedel-Crafts reaction likely begins with alcohol activation to form a tetra-ion species (**4-3a**) and a benzylic carbocation. It is not unreasonable to suggest that there is formation of a contact ion-pair followed by dissociation with the anionic boronate species (**4-3b**). The concept of ion-pairing in catalysis is not new, it is reasonable to propose something of that effect in this process.[23] Given that antimony hexafluoride is a non-coordinating counter-ion,[24] it is likely that there is a further dissociation of the ion-pair into a solvated anion thereby exposing the carbocation and allowing it to be more reactive in the context of a Friedel-Crafts alkylation. Finally, it is proposed that the arene can nucleophilically attack the carbocation with subsequent elimination of water and recycling of the FBAHA catalyst.



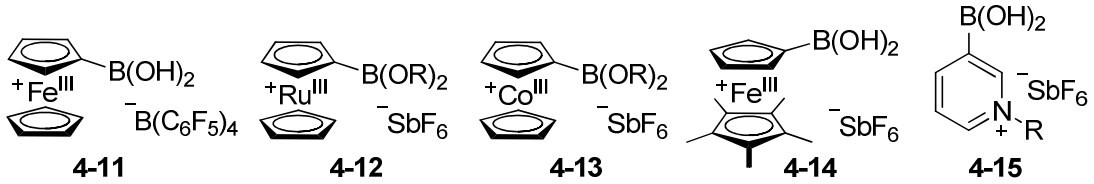
Scheme 4-8: Mechanistic proposal of FBAHA based Friedel-Crafts alkylation.

Taking the stated substrate scope into account, arene nucleophilicity is consistent with electrophilic substitution as the rate-determining step. The next step to solidifying this mechanism is isolation of an intermediate species. Although difficult, the strongest evidence can come from isolating a crystal structure of the tetra-ion species (**4-3a**), this would the proposed activity of FBAHA.

4.5 Summary

The FBAHA based Friedel-Crafts alkylation has two major avenues for improvement. The first target for improvement is to reduce reliance upon hexafluoroisopropanol as the solvent. Although hexafluoroisopropanol is useful for stabilizing the ionic species in this reaction, it is rather expensive when the reaction is conducted on a large scale. The second target is creating a more active catalyst (**Figure 4-5**). Moving to bulkier counter-ions such as tetrakis(pentafluorophenyl)borate may further expose the carbocation leading to a more reactive complex (**4-11**). On the other hand, more stable complexes may be synthesized by using

ruthenium (**4-12**) or cobalt (**4-13**) in the metallocene, which have a lower redox potential and therefore different reactivity by being less susceptible to coordination and subsequently, deactivation.[25] Another improvement may result by use of pentamethylcyclopentadiene to effectively force the counter-ion closer to the boronic acid, and therefore possibly promote a faster or more effective ion-pair disproportionation (**4-14**). There is also a possibility that addition of more electron withdrawing groups such as a pyridinium salt (**4-15**) could also afford a more active catalyst, and one less susceptible to deactivation which plagues the ferrocenium scaffold.



4-11 **4-12** **4-13** **4-14** **4-15**

Figure 4-5: Potentially active FBAHA derivatives.

Herein lies a new boronic acid, ferroceniumboronic acid hexafluoroantimonate salt, with distinguished potential as an air- and moisture-tolerant catalyst for Friedel-Crafts alkylations of neutral to slightly activated arenes and remarkable compatibility with a wide range of benzylic alcohols.

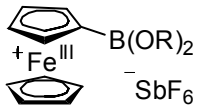
4.6 Experimental

General Methods

The following materials include representative experimental procedures and details for the synthesis and isolation of compounds. Full characterisation of all new compounds and partial characterisation of known compounds presented in this thesis are described. Acetone was dried with magnesium sulfate before use. Unless otherwise stated, all reactions were performed in capped regular glassware with no further precautions. Dichloromethane (DCM) and

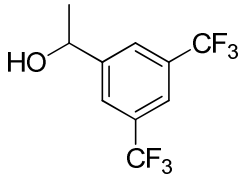
tetrahydrofuran (THF) were purified using a double cartridge solvent purification system prior to use. All other solvents were purchased as ACS reagents and used without further purification. Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes, ethyl acetate, dichloromethane, diethyl ether and toluene as eluents. Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 F 254 plates. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes and ethyl acetate as eluents. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light and with $KMnO_4$ or phosphomolybdic acid (PMA) stains. ^1H NMR spectra were recorded on 400 MHz or 500 MHz instruments. The residual solvent protons ($^1H/CHCl_3$) or the solvent carbon (^{13}C) were used as internal references. ^1H NMR, ^{13}C NMR, and ^{19}F NMR data is presented as follows: chemical shifts in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sept, septet; dd, doublet of doublets; m, multiplet. The error of coupling constants from ^1H NMR spectra is estimated to be 0.3 Hz. The error of coupling constants from ^1H NMR spectra is estimated to be 0.3 Hz. High-resolution mass spectra were recorded on an oaTOF analyzer. Infrared (IR) spectra were obtained using cast-film technique with frequencies expressed in cm^{-1}; the intensity of the band is indicated as s (strong), m (medium) and w (weak). The resolution of the IR instrument is 4 wavenumbers. Melting points (m. p.) were measured on a melting point apparatus and uncorrected.

General Procedure for the Synthesis of Ferroceniumboronic Acid Hexafluoroantimonate salt (4-3).



Synthesis for this compound was synthesized as per a previous report.[26]

General Procedure for the Synthesis of Benzylic Alcohols



1-(3,5-Bis(trifluoromethyl)phenyl)ethan-1-ol (4-5d'): Prepared by dissolving 3',5'-Bis(trifluoromethyl)acetophenone (786 mg, 3.00 mmol) in 12 mL of THF:MeOH (1:1) then cooling to 0 °C. While stirring, sodium borohydride (150 mg, 4.00 mmol) was added in portions and the solution reacted for 1 h. The crude mixture was concentrated under reduced pressure then diluted in ethyl acetate (20 mL) and water (20 mL). The organic layer was washed with water (20 mL × 2) then brine (20 mL × 1). The organic layer was dried over anhydrous magnesium sulphate then filtered. The organic layer was concentrated under reduced pressure and the product isolated as a white solid (243 mg, 94%; M.p. 67.8-68.2 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (s, 2H), 7.82 (s, 1H), 5.07 (qd, *J* = 6.5, 3.8 Hz, 1H), 2.0 (d, *J* = 3.8 Hz, 1H), 1.58 (d, J = 6.5 Hz, 1H).

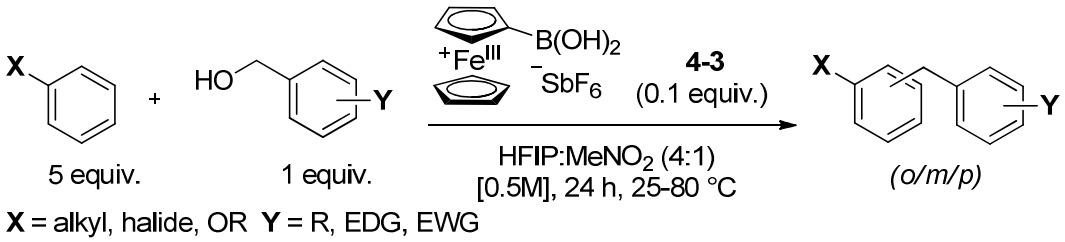
^{13}C NMR ($CDCl_3$, 125 MHz): δ148.2, 131.8 (q, *J* = 33.3 Hz), 125.6, 124.4, 121.3, 69.2, 25.6.

^{19}F NMR ($CDCl_3$, 476 MHz): δ -62.2 (s, 6F).

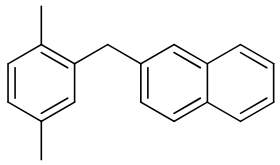
IR (Microscope, cm^{-1}): 3238.11 (br s), 2978.93 (m), 2937.07 (m), 2899.97 (m), 1818.85 (w), 1802.39 (w), 1623.49 (w), 1456.61 (m), 1434.74 (m), 1383.68 (s), 1383.68 (m),1373.88 (w), 1339.31 (w), 1320.43 (s), 1295.78 (s), 1279.12 (s), 1115.04 (s), 1024.95 (m), 922.91 (w), 896.02 (s), 842.07 (m), 725.25 (w), 705.02 (s), 683.88 (s).

HRMS (EI) for $C_{10}H_8F_6O$: Predicted: 258.0479; Found: 258.0483.

General Procedure for Friedel-Crafts Benzylations



To a vial equipped with a stir bar, containing the benzyl alcohol and the arene in a solvent mixture of 4:1 hexafluoroisopropanol and nitromethane, was added the ferrocenium boronic acid catalyst. The vial was capped and stirred at the stated temperature for the indicated time. Upon completion as monitored by TLC, the crude reaction mixture was concentrated under reduced pressure and subjected to flash column chromatography using ethyl acetate/hexane as the eluent to afford the product. Only the structures of the major products are shown. The ratio of regioisomer mixtures (where present) was assigned by ^{1}H NMR spectroscopic analysis of crude reaction mixtures. Only the major products are characterized for mixtures where the regioisomeric ratios are > 90:10. For product mixtures that contain regioisomers, assignment of the peaks corresponding to the major products in the ^{13}C NMR spectra was performed by comparison with those from existing literature reports. No assignment was made if neither the major nor the minor products have been previously reported.



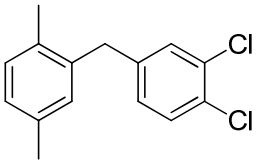
2-(2,5-Dimethylbenzyl)naphthalene (4-4b): Prepared using 2-napthylmethyl alcohol (79 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a yellow oil (76 mg, 62%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.75 (t, *J* = 8.6 Hz, 2H), 7.53 (s, 1H), 7.43 (m, 2H), 7.30 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.97 (s, 1H), 4.12 (s, 2H), 2.30 (s, 3H), 2.24 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.5, 138.1, 135.4, 133.6, 133.5, 132.0, 130.8, 130.2, 127.9, 127.6, 127.5, 127.5, 127.2, 126.8, 125.9, 125.2, 39.6, 21.0, 19.2.

IR (Microscope, cm^{-1}): 3050.92 (m), 3016.29 (w), 2921.14 (m), 2859.66 (w), 1632.73 (w), 1600.80 (m), 1505.55 (s), 1442.88 (m), 1377.88 (m), 1269.74 (w), 1154.50 (w), 1154.50 (w), 1124.06 (w), 958.70 (w), 886.36 (w), 852.04 (m), 811.21 (s), 777.78 (s), 739.18 (m).

HRMS (EI) for $C_{19}H_{18}$: Predicted: 246.1409; Found: 246.1409.



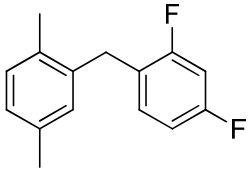
1,2-Dichloro-4-(2,5-dimethylbenzyl)benzene (4-4d): Prepared from 3,4-dichlorobenzyl alcohol (89 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a colorless oil (102 mg, 77%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2.1 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.89 (s, 1H), 3.89 (s, 2H), 2.30 (s, 3H), 2.17 (s, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.9, 137.3, 135.7, 133.3, 132.3, 130.7, 130.5, 130.4, 130.2, 129.9, 128.1, 127.6, 38.6, 21.0, 19.2.

IR (Microscope, cm^{-1}): 2999.73 (w), 2921.07 (m), 2863.23 (w), 1561.92 (w), 1503.91 (m), 1469.76 (s), 1131.13 (m), 1030.99 (m), 810.56 (m).

HRMS (EI) for $C_{15}H_{14}Cl_2$: Predicted: 264.0472; Found: 264.0472.



2-(2,4-Difluorobenzyl)-1,4-dimethylbenzene (4-4e): Prepared from from 2,4-difluorobenzyl alcohol (72 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a colorless oil (78 mg, 67%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.92 (td, *J* = 8.6, 1.9 Hz, 1H), 6.91 (s, 1H), 6.83 (tdt, *J* = 9.1, 2.6, 0.9 Hz, 1H), 6.78 (ddd, *J* = 8.5, 2.6, 0.9, 1H), 3.92 (s, 2H), 2.31 (s, 3H), 2.23 (s, 3H).

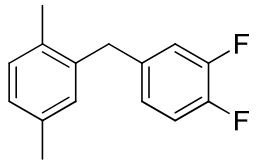
^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.5 (dd, *J* = 244.8, 10.2 Hz), 160.7 (dd, *J* = 248.0, 12.0 Hz), 137.0, 135.5, 133.3, 131.0 (dd, *J* = 9.3, 6.2 Hz), 130.5, 130.3, 127.4, 123.3 (dd, *J* = 16.1, 3.8 Hz), 111.0 (dd, *J* = 20.8, 3.7 Hz), 103.5 (t, *J* = 25.8 Hz), 31.4, 20.9, 18.9.

^{19}F NMR ($CDCl_3$, 476 MHz): δ -114.4 (q, *J* = 8.3 Hz, 1F), -114.6 (app. Quin., *J* = 7.4 Hz, 1F).

IR (Microscope, cm^{-1}): 3077.08 (w), 3044.83 (w), 3002.64 (w), 2923.45 (m), 2864.22 (w), 1620.13 (s), 1602.94 (s), 1503.13 (s), 1439.21 (m), 1427.56 (m), 1379.91 (w), 1280.97 (m),

1263.84 (m), 1165.87 (w), 1136.59 (s), 1086.35 (s), 966.45 (s), 849.25 (s), 809.24 (m) 727.33 (w).

HRMS (EI) for $C_{15}H_{14}F_2$: Predicted: 232.1064; Found: 232.1064.



2-(3,4-Difluorobenzyl)-1,4-dimethylbenzene (4-4f): Prepared from 3,4-difluorobenzyl alcohol (72 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column

chromatography (hexane) and isolated as a colorless oil (103 mg, 89%).

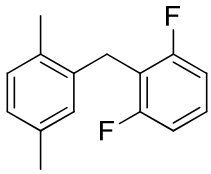
^{1}NMR ($CDCl_3$, 500 MHz): δ 7.08 (t, *J* = 8.1 Hz, 2H), 7.03 (t, *J* = 10.0 Hz, 1H), 6.93 (s, 1H), 6.90 (d, *J* = 9.2 Hz, 1H), 6.87-6.84 (m, 1H), 3.92 (s, 2H), 2.33 (s, 3H), 2.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.5 (dd, *J* = 190.0, 12.7 Hz), 148.6 (dd, *J* = 188.2, 12.7 Hz), 137.7, 137.6, 135.6, 133.3, 130.7, 130.4, 127.5, 124.3, 117.4 (d, *J* = 17.1 Hz), 117.0 (d, *J* = 17.0 Hz), 38.6, 20.9, 19.1.

^{19}F NMR ($CDCl_3$, 476 MHz): δ -138.2 (ddd, *J* = 20.6, 11.2, 8.8 Hz, 1F), -142.1 (m, 1F).

IR (Microscope, cm^{-1}): 3042.57 (w), 3001.05 (w), 2923.62 (m), 2864.85 (w), 1607.81 (m), 1517.17 (s), 1432.79 (m), 1380.05 (w), 1283.54 (m), 1208.45 (m), 1115.36 (m), 955.31 (w), 864.73 (w), 811.35 (m), 763.83 (m), 750.94 (w).

HRMS (EI) for $C_{15}H_{14}F_2$: Predicted: 232.1064; Found: 232.1067.



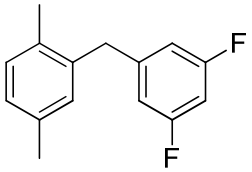
2-(2,5-Dimethylbenzyl)-1,3-difluorobenzene (4-4h): Prepared from 2,6-difluorobenzyl alcohol (72 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a white solid (78 mg, 67%). M.p. 51.2-52.3 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (tt, *J* = 8.3, 6.5 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.96-6.90 (m, 3H), 6.79 (s, 1H), 3.98 (s, 2H), 2.38 (s, 3H), 2.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.7 (dd, *J* = 247.3, 8.7 Hz), 136.8, 135.4, 132.9, 130.0, 128.9, 127.9, 127.0, 116.2 (t, *J* = 20.1 Hz), 111.2 (dd, *J* = 20.3, 6.1 Hz), 25.5, 21.0, 19.2; **^{19}F NMR** ($CDCl_3$, 476 MHz): δ -114.1 (t, *J* = 6.5 Hz, 2F).

IR (Microscope, cm^{-1}): 3004.97 (w), 2924.52 (m), 2864.13 (w), 1624.80 (s), 1592.29 (m), 1502.2 (m), 1469.43 (s), 1379.92 (w), 1266.61 (m), 1237.58 (m), 1206.15 (w), 1155.51 (w), 1105.72 (w), 1062.59 (w), 1012.29 (s), 808.66 (m), 790.01 (m), 770.44 (m), 726.00 (w), 706.06 (w), 682.98 (w).

HRMS (EI) for $C_{15}H_{14}F_2$: Predicted: 232.1064; Found: 232.1064.



2-(3,5-Difluorobenzyl)-1,4-dimethylbenzene (4-4i): Prepared from 3,5-difluorobenzyl alcohol (72 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a colorless oil (93 mg, 80%).

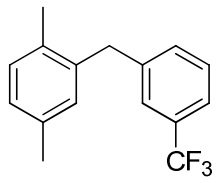
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.94 (s, 1H), 6.67-6.64 (m, 3H), 2.34 (s, 3H), 2.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.1 (dd, *J* = 260.8, 12.9 Hz), 144.7, 137.0, 135.6, 133.3, 130.8, 130.5, 127.7, 111.4 (dd, *J* = 19.2, 5.7 Hz), 101.4 (t, *J* = 25.4 Hz), 39.1, 20.9, 19.1.

^{19}F NMR ($CDCl_3$, 476 MHz): δ -110.6 (t, *J* = 9.7 Hz, 2F).

IR (Microscope, cm^{-1}): 3084.97 (w), 3002.31 (w), 2923.25 (m), 2861.94 (w), 1624.86 (s), 1594.80 (s), 1504.46 (m), 1458.85 (s), 1441.29 (m), 1379.84 (w), 1321.81 (m), 1155.66 (w), 1117.81 (s), 991.19 (s), 969.42 (w), 921.98 (w), 846.79 (s), 811.52 (m), 765.33 (w), 676.70 (w), 651.82 (w).

HRMS (EI) for $C_{15}H_{14}F_2$: Predicted: 232.1064; Found: 232.1065.



1,4-Dimethyl-2-(3-(trifluoromethyl)benzyl)benzene (4-4k): Prepared from 3-(trifluoromethyl) benzyl alcohol using 3-trifluoromethylbenzyl alcohol (88 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a yellow oil (128 mg, 97%).

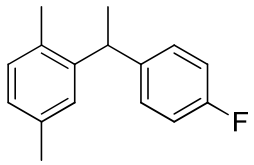
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (d, *J* = 7.7 Hz, 1H), 7.41 (s, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.91 (s, 1H), 4.00 (s, 2H), 2.30 (s, 3H), 2.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.5, 137.5, 135.6, 133.3, 132.0, 130.8, 130.7, 130.5, 130.4, 128.7, 127.5, 124.1 (dq, J = 319.4, 3.7 Hz), 123.1, 39.2, 20.9, 19.1.

^{19}F NMR ($CDCl_3$, 476 MHz): δ -62.9 (s, 3F).

IR (Microscope, cm^{-1}): 3042.57 (w), 3001.22 (w), 2924.02 (w), 2865.54 (w), 1614.20 (w), 1596.79 (w), 1504.08 (m), 1448.13 (m), 1332.43 (s), 1261.43 (w), 1163.85 (s), 1125.64 (s), 1093.74 (m), 1074.52 (s), 995.20 (w), 811.34 (m), 762.64 (w), 729.69 (m), 664.77 (w).

HRMS (EI) for $C_{16}H_{15}F_3$: Predicted: 264.1126; Found: 268.1125.



2-(1-(4-Fluorophenyl)ethyl)-1,4-dimethylbenzene (4-5a): Prepared from 1-(4-fluorophenyl) ethan-1-ol (70 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a pale yellow solid (84 mg, 74%). M.p. 52.6-53.8 °C.

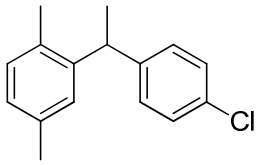
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.14-7.11 (m, 2H), 7.06 (s, 1H), 7.05 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 6.97 Hz, 1H), 6.98-6.94 (m, 2H), 4.29 (q, J = 7.2 Hz, 1H), 2.34 (s, 3H), 2.19 (s, 3H), 1.60 (d, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.0, 160.1, 143.5, 141.9, 135.4, 132.8, 130.3, 129.0, 127.3, 126.8, 115.0, 114.9, 40.2, 22.2, 21.2, 19.2.

^{19}F NMR ($CDCl_3$, 476 MHz): δ -117.85.

IR (Microscope, cm^{-1}): 2967.64 (m), 2926.37 (m), 2873.70 (w), 1602.58 (w), 1507.95 (s), 1457.33 (m), 1373.54 (w), 1222.00 (s), 1158.04 (m), 1096.13 (w), 1050.86 (w), 1015.03 (w), 834.85 (s), 810.94 (m), 762.85 (w), 731.18 (w).

HRMS (EI) for $C_{16}H_{17}F$: Predicted: 228.1314; Found: 228.1315.



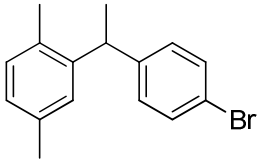
2-(1-(4-Chlorophenyl)ethyl)-1,4-dimethylbenzene (4-5b): Prepared from 1-(4-chlorophenyl) ethan-1-ol (78 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as an off-white solid (88 mg, 72%). M.p. 70.4-71.7 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23-7.21 (m, 1H), 7.09-7.07 (m, 2H), 7.02 (d, *J* = 7.39 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 1H), 2.32 (s, 3H), 2.17 (s, 3H), 1.57 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.8, 143.1, 135.4, 132.8, 131.4, 130.4, 129.0, 128.3, 127.3, 126.9, 40.3, 22.0, 21.2, 19.2.

IR (Microscope, cm^{-1}): 3086.56 (w), 2065.04 (w), 3049.06 (w), 2964.43 (s), 2927.11 (m), 2871.13 (m), 1901.64 (w), 1783.49 (w), 1610.28 (w), 1495.35 (s), 1486.46 (s), 1454.77 (s), 1379.27 (m), 1370.69 (w), 1091.19 (m), 1049.48 (w), 1013.84 (m), 997.95 (w), 892.48 (w), 831.65 (s), 824.08 (s), 789.33 (m), 718.20 (w).

HRMS (EI) for $C_{16}H_{17}{}^{35}Cl$: Predicted: 244.1019; Found: 244.1021.



2-(1-(4-Bromophenyl)ethyl)-1,4-dimethylbenzene (4-5c): Prepared using 1-(4-bromophenyl) ethan-1-ol (100 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified

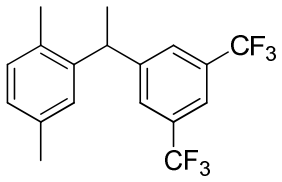
by flash column chromatography (hexane) and isolated as isolated as an off-white solid (116 mg, 80%). M.p. 59.4-60.5 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.38 (m, 2H), 7.06-7.04 (m, 4H), 4.26 (q, *J* = 7.18, 1H), 2.34 (s, 3H), 2.19 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.4, 143.0, 135.4, 132.8, 131.3, 130.4, 129.4, 127.3, 126.9, 119.5, 40.4, 21.9, 21.2, 19.2.

IR (Microscope, cm^{-1}): 3040.98 (w), 3018.47 (w), 2967.77 (s), 2922.36 (m), 2873.58 (w), 1896.21 (w), 1613.08 (w), 1590.01 (w), 1498.85 (s), 1486.31 (s), 1453.74 (m), 1401.50 (w), 1373.51 (w), 1325.22 (w), 1291.24 (w), 1181.28 (w), 1157.34 (w), 1074.10 (m), 1049.02 (w), 1010.30 (s), 884.50 (w), 824.35 (m), 811.16 (m), 786.05 (w), 737.82 (w).

HRMS (EI) for $C_{16}H_{17}Br$: Predicted: 290.0493; Found: 290.0499.



2-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)-1,4-dimethylbenzene (4-5d): Prepared using 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol (129 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a yellow oil (135 mg, 78%).

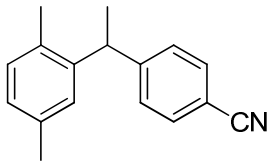
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (s, 1H), 7.62 (s, 2H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.01 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 1.67 (d, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.9, 141.6, 135.9, 132.6, 131.5 (q, *J* = 33.0 Hz), 130.7, 127.5, 127.3, 124.5, 122.3, 120.0, 40.8, 21.8, 21.2, 19.2.

^{19}F NMR ($CDCl_3$, 476 MHz): δ -62.3 (s, 6F).

IR (Microscope, cm^{-1}): 2973.66 (w), 2928.64 (w), 2878.03 (w), 1622.11 (w), 1502.23 (w), 1465.54 (w), 1370.36 (m), 12779.22 (s), 1173.54 (s), 1134.72 (s), 1051.97 (w), 979.04 (w), 896.49 (m), 865.52 (w), 844.96 (w), 812.30 (w), 726.89 (w), 706.98 (m), 682.89 (m).

HRMS (EI) for $C_{18}H_{16}F_6$: Predicted: 346.1156; Found: 346.1154.



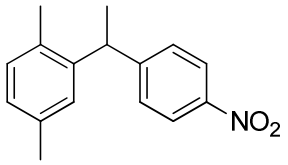
4-(1-(2,5-Dimethylphenyl)ethyl)benzonitrile (4-5e): Prepared using 1-(4-cyanophenyl)ethan-1-ol (74 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane:ethyl acetate, 90:10) and isolated as a dark yellow solid (64 mg, 54%). M.p. 89.3-90.0 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55-7.54 (m, 2H), 7.25-7.24 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 7.8 Hz, 1H), 4.33 (q, J = 7.2 Hz, 1H), 2.32 (s, 3H), 2.14 (s, 3H), 1.60 (d, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.0, 142.1, 135.6, 132.8, 132.2, 130.5, 128.4, 127.3, 127.3, 119.0, 109.7, 41.1, 21.7, 19.2.

IR (Microscope, cm^{-1}): 3018.47 (w), 2968.60 (s), 2926.40 (s), 2873.33 (m), 2227.38 (s), 1719.16 (w), 1605.75 (s), 1500.84 (s), 1454.88 (s), 1410.51 (m), 1377.92 (w), 1270.52 (w), 1157.46 (w), 1111.20 (w), 1060.53 (w), 1019.20 (w), 1000.27 (w), 884.86 (w), 839.58 (s), 810.77 (s), 761.76 (w), 733.1 (w).

HRMS (EI) for $C_{17}H_{17}N$: Predicted: 235.1361; Found 235.1363.



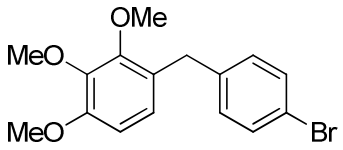
1,4-Dimethyl-2-(1-(4-nitrophenyl)ethyl)benzene (4-5f): Prepared from 1-(4-nitrophenyl)ethan-1-ol (84 mg, 0.50 mmol) and p-xylene (265 mg, 2.50 mmol) at 80 °C. Crude product was purified by flash column chromatography (hexane:ethyl acetate, 90:10) and isolated as a yellow solid (117.36 mg, 92%). M.p. 105.4-106.2 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.15-8.14 (m, 2H), 7.34-7.32 (m, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 1H), 2.35 (s, 3H), 2.18 (s, 3H), 1.66 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.2, 146.2, 142.0, 135.7, 132.7, 130.6, 128.4, 127.4, 127.3, 123.6, 41.0, 21.7, 21.2, 19.2.

IR (Microscope, cm^{-1}): 2970.27 (m), 2931.75 (w), 2873.75 (w), 1602.90 (m), 1519.17 (s), 1453.94 (m), 1346.05 (s), 1182.90 (w), 1157.56 (w), 1110.02 (w), 1049.03 (w), 1014.22 (w), 855.57 (s), 813.24 (m), 784.69 (w), 734.60 (w), 698.20 (m).

HRMS (EI) for $C_{16}H_{17}NO_2$: Predicted: 255.1259; Found: 255.1261.

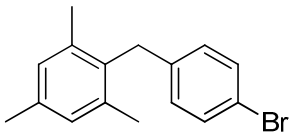


1-(4-Bromobenzyl)-2,3,4-trimethoxybenzene (4-6a): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and 1,2,3-trimethoxybenzene (420 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane:ethyl acetate, 90:10) and isolated as colorless oil (152 mg, 90%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.40 (m, 2H), 7.10-7.08 (m, 2H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 2H), 2.87 (s, 3H), 3.76 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.5, 151.8, 142.4, 140.5, 131.3, 130.5, 126.6, 124.4, 119.6, 107.1, 60.7, 60.7, 56.0, 35.3.

HRMS (ESI) for $C_{16}H_{17}BrO_3$ $[M+Na]^+$: Predicted: 359.0253; Found: 359.0253



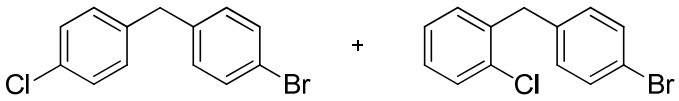
2-(4-Bromobenzyl)-1,3,5-trimethylbenzene (4-6b): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and 1,3,5-trimethylbenzene (300 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a white solid (89 mg, 85%). M.p. 72.6-73.9 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.33 (m, 2H), 6.89 (s, 2H), 6.89-6.87 (m, 2H), 3.95 (s, 2H), 2.29 (s, 3H), 2.18 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.1, 136.9, 135.9, 133.1, 131.3, 129.5, 128.9, 119.4, 34.1, 20.9, 20.0.

IR (Microscope, cm^{-1}): 2972.36 (m), 2930.50 (m), 1899.65 (w), 1612.63 (w), 1577.41 (w), 1486.04 (s), 1447.34 (m), 1401.33 (w), 1373.20 (w), 1265.16 (w), 1177.54 (w), 1071.26 (w), 1010.56 (m), 877.61 (w), 859.26 (w), 813.17 (m), 800.78 (m), 784.79 (s), 740 .35 (m), 721.47 (w).

HRMS (EI) for $C_{16}H_{17}Br$: Predicted: 290.0493; Found: 290.0499.



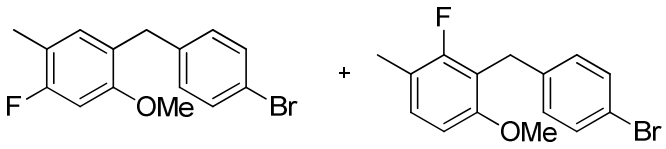
1-Bromo-4-(4-chlorobenzyl)benzene (4-6c): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and chlorobenzene (306 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and isolated as a colorless oil (112 mg, 77%, 58:42 mixture of regioisomers).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.42 (m, 1.91H), 7.41-7.39 (m, 0.41H), 7.29-7.27 (m, 1.24H), 7.23-7.20 (m, 0.88H), 7.17-7.15 (m, 0.42H), 7.11-7.04 (m, 3.11H), 4.08 (s, 0.83H, minor), 3.92 (s, 1.17H, major).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.5, 138.9, 138.5, 138.0, 134.2, 132.2, 131.7, 131.6, 131.0, 130.7, 130.6, 130.2, 129.7, 128.7, 128.0, 127.0, 120.2, 120.1, 40.6, 38.7.

IR (Microscope, cm^{-1}): 3024.81 (w), 2912.27 (w), 2844.18 (w), 1594.19 (w), 1572.27 (w), 1487.73 (s), 1442.86 (m), 1403.87 (m), 1071.27 (m), 1012.14 (m), 783.31 (m), 751.01 (m).

HRMS (EI) for $C_{13}H_{10}BrCl$: Predicted: 279.9655; Found: 279.9658.



1-(4-Bromobenzyl)-4-fluoro-2-methoxy-5-methylbenzene (4-6d): Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and 3-fluoro-4-methylanisole (350 mg, 2.50 mmol) and isolated as a colorless oil (111 mg, 72%, 57:43 mixtures of regioisomers).

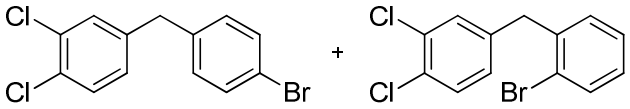
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.30 (m, 1.62H), 7.11-7.09 (m, 0.51H), 7.03-7.00 (m, 1.23H), 6.81-6.79 (m, 0.57H), 6.57-6.51 (m, 1.11H), 3.79 (s, 1.17H), 3.76 (s, 0.75H), 3.74 (s, 0.48H), 3.72 (s, 1.68H), 2.16 (d, *J* = 2.3 Hz, 1.26 H), 2.12 (d, *J* = 1.9 Hz, 1.71H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.3, 160.6, 159.3, 158.7, 156.4, 156.4, 156.1, 156.1, 140.1, 139.7, 132.3, 132.3, 131.3, 131.2, 130.5, 130.3, 128.9, 128.8, 124.1, 124.1, 119.6, 119.5, 117.0, 116.8, 116.2, 116.0, 115.7, 115.5, 105.9, 105.9, 98.9, 98.7, 55.8, 55.6, 34.7, 29.7, 28.0, 28.0, 14.1, 14.1, 13.6, 13.6.

19F NMR ($CDCl_3$, 476 MHz): δ -117.5 (t, 0.57F, J = 10.6 Hz), -120.0 (d, 0.43F, J = 8.7 Hz).

IR (Microscope, cm^{-1}): 3001.90 (w), 2927.92 (m), 2854.18 (m), 1732.20 (w), 1626.70 (m), 1595.98 (m), 1508.68 (s), 1487.90 (s), 1465.42 (m), 1444.74 (m), 1326.35 (m), 1265.21 (m), 1193.55 (m), 1101.96 (s), 1071.58 (m), 1012.54 (s), 892.55 (w), 832.77 (w), 795.04 (m), 724.21 (w).

HRMS (EI) for $C_{15}H_{14}BrFO$: Predicted: 308.0212; Found: 308.0210.



4-6g-*para* **4-6g**-*ortho*

Prepared from 3,4-dichlorobenzyl alcohol (89 mg, 0.50 mmol) and bromobenzene (392 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) as a colorless oil (115 mg, 73%, 1.4:1 mixtures of regioisomers).

4-(4-Bromobenzyl)-1,2-dichlorobenzene (4-6g-para):

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.44 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.06-7.04 (m, 2H), 7.01 (dd, *J* = 8.2, 1.9 Hz, 1H), 3.90 (s, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.6, 138.7, 132.5, 131.8, 130.7, 130.5, 130.4, 130.4, 128.2, 120.5, 40.9.

IR (Microscope, cm^{-1}): 3060.58 (w), 3023.33 (w), 2924.02 (s), 2851.34 (m), 1897.97 (w), 1731.67 (w), 1688.84 (w), 1593.21 (w), 1562.58 (w), 1487.69 (s), 1470.51 (s), 1433.67 (w), 1397.33 (w), 1236.94 (w), 1132.17 (m), 1071.84 (m), 1031.81 (m), 1012.16 (m), 925.50 (w) 875.12 (w), 840.85 (w), 809.13 (m) 792.35 (m), 729.47 (w), 685.56 (w).

HRMS (EI) for $C_{13}H_9BrCl_2$: Predicted: 313.9265; Found: 313.9261.

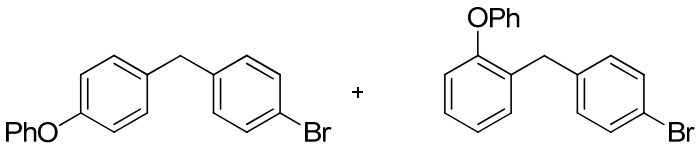
4-(2-Bromobenzyl)-1,2-dichlorobenzene (4-6g-*ortho*):

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.01 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.18 (d, J = 7.3 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.2 Hz), 1H, 4.10 (s, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.7, 139.0, 133.1, 132.4, 131.0, 130.7, 130.3, 130.3, 128.4, 128.3, 127.7, 124.8, 40.9.

IR (Microscope, cm - 1): 3056.87 (w), 2924.83 (w), 2852.16 (w), 1589.72 (w), 1567.57 (w), 1470.12 (s), 1439.70 (m), 1397.14 (m), 1193.57 (w), 1132.53 (m), 1029.53 (s), 948.91 (w), 924.19 (w), 880.78 (w), 830.05 (w), 803.12 (m), 756.00 (m), 734.27 (m), 685.03 (w).

HRMS (EI) for $C_{13}H_9BrCl_2$: Predicted: 313.9266; Found: 313.9266.



4-6h-*para* **4-6h**-*ortho*

Prepared from 4-bromobenzyl alcohol (94 mg, 0.50 mmol) and diphenylether (436 mg, 2.50 mmol). Crude product was purified by flash column chromatography (hexane) and Isolated as a colorless oil (110 mg, 65%, 57:43 mixtures of regioisomers).

1-Bromo-4-(4-phenoxybenzyl)benzene (4-6-h-*para*): isolated as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.41 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.13-7.11 (m, 2H), 7.08 (t, *J* = 5.5 Hz, 3H), 7.01-6.59 (m, 2H), 6.95-6.94 (m, 2H), 3.91 (s, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.3, 155.6, 140.1, 135.3, 131.5, 130.6, 130.0, 129.7, 123.1, 120.0, 119.0, 118.7, 40.6.

IR (Microscope, cm $^{-1}$): 3037.62 (m), 2919.75 (m), 1730.33 (w), 1590.09 (s), 1505.41 (s), 1487.23 (s), 1166.42 (m), 1102.85 (w), 1071.48 (m), 10112.00 (s), 871.35 (m), 794.41 (m), 748.20 (m), 691.52 (s).

HRMS (EI) for $C_{19}H_{15}OBr$: Predicted: 338.0306; Found: 338.0309.

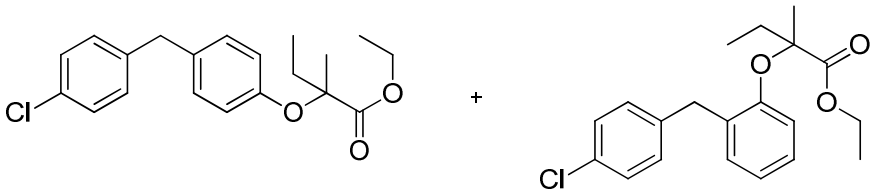
1-(4-Bromobenzyl)-2-phenoxybenzene (4-6h-*ortho*): isolated as an off-white solid. M.p. 71.4-71.9 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.35 (m, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.18 (dd, *J* = 9.3, 6.4 Hz, 1H), 7.19 (dd, *J* = 10.8, 4.9 Hz, 1H), 7.08 (s, 1H), 7.08-7.07 (m, 2H), 7.06 (m, 1H), 6.89-6.86 (m, 3H), 3.94 (s, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.5, 154.5, 139.5, 132.1, 131.3, 130.9, 130.7, 129.7, 127.9, 123.9, 122.8, 119.8, 119.4, 117.9, 35.5.

IR (Microscope, cm^{-1}): 3084.84 (w), 3041.33 (w), 3027.49 (w), 2921.61 (w), 2852.13 (w), 1951.97 (w), 1905.24 (w), 1581.41 (w), 1581.12 (m), 1482.92 (s), 1451.61 (m), 1439.42 (w), 1331.11 (w), 1291.46 (w), 1233.50 (s), 1206.40 (m), 1170.01 (w), 1113.94 (w), 1091.11 (w), 1010.02 (w), 917.54 (w), 878.93 (w), 787.50 (m), 758.36 (s), 720.16 (w), 689.09 (m).

HRMS (EI) for $C_{19}H_{15}OBr$: Predicted: 338.0306; Found 338.0304.



4-10-*para* **4-10**-*ortho*

Ethyl 2-(4-(4-chlorobenzyl)phenoxy)-2-methylbutanoate (Beclobrate; 4-10): Prepared from 4-chlorobenzyl alcohol (71 mg, 0.5 mmol) and ethyl 2-phenoxy-2-methylbutanoate (556 mg, 2.5 mmol). Product was obtained with yield of 89% (63:37 mixtures of regioisomers). Characterization matches that from a previous report as per Beller et al.[27]

4.7 References

1 Friedel, C.; Crafts, J.-M. *Compt. Rend.* **1877**, *84*, 1392- 1395.

2 (a) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1962**, *84*, 1688-1695. (b) Olah, G. A.; Kobayash.S; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448-7461.

3 Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 1-24.

4 Constable, D.J.C.; Dunn, P.J.; Hayler, J.D.; Humphrey, G.R.; Leazer, J.J.L.; Linderman, R.J.; Lorenz, K.; Manley, J.; Pearlman, B.A.; Wells, A.; Zaks, A.; Zhang, T.Y. *Green Chem.* **2007**, *9*, 411-420.

5 Mertins, K.; Iovel, I.; Kischel, J.;Zapf, A.;Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 238-242.

6 Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S. *J. Org. Chem.* **1997**, *62*, 6997-7005.

7 Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913-3917.

8 Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033-1037.

9 Zheng, H.; D.G. Hall, D.G. *Aldrichimica Acta* **2014**, *47*, 41-51.

10 McCubbin, J.A.; Hosseini, H.; Krokhin, O.V. *J. Org. Chem.* **2010**, *75*, 959-962.

11 Ricardo, C.L.; Mo, X.; McCubbin, J.A.; Hall, D.G. *Chem. Eur. J.* **2015**, *21*, 4218-4223.

12 Zheng, H.; Lejkowski, M.; Hall, D.G. *Chem. Sci.* **2011**, *2*, 1305-1310.

13 Zheng, H.; McDonald, R.; Hall, D. G. *Chem. Eur. J.* **2010**, *16*, 5454-5460.

14 Moore, A.N.J.; Wayner, D.D.M. *Can. J. Chem.* **1999**, *77*, 681-686.

15 Reaction optimization accomplished by Julien Dansereau, see Table 1 regarding Optimization of Friedel−Crafts Benzylation: Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

16 Mechanistic studies accomplished by Xiaobin Mo, see Scheme 1 regarding control experiments examining the importance and the role of the boronyl unit of FBAHA: Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

17 Olah, G.A.; Westerman, P.W.; Nishimura, J. *J. Am. Chem. Soc.* **1974**, *96*, 3548–3559.

18 Johansson, L.; Fotsch, C.; Bartberger, M.D.; Castro, V.M.; Chen, M.; Emery, M.; Gustafsson, S.; Hale, C.; Hickman, D.; Homan, E.; Jordan, S.R.; Komorowski, R.; Li, A.; McRae, K.; Moniz, G.; Matsumoto, G.; Orihuela, C.; Palm, G.; Veniant, M.; Wang, M.; Williams, M.; Zhang, J. *J. Med. Chem.* **2008**, *51*, 2933-2943.

19 Oh, L.M.; Wang, H.; Shilcrat, S.C.; Herrmann, R.E.; Patience, D.B.; Spoors, P.G.; Sisko, J. *Org. Process Res. Dev.* **2007**, *11*, 1032-1042.

20 See Scheme 1 regarding Control Experiments Examining the Importance and the Role of the Boronyl Unit: Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

21 See Scheme 2 regarding Ionization of optically enriched, deuterated alcohol: Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

22 See Scheme 3 regarding the proposed catalytic cycle and mode of activation for FBAHA: Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

23 Maruoka, K. *Asymmetric Phase Transfer Catalysis*. Wiley-VCH: Weinheim, 2008.

24 Honeychuck, R.V.; Hersh, W.H. *Inorg. Chem.* **1989**, *28*, 2869-2886.

25 Elschenbroich, C. *Organometallics*, 3e; Wiley-VCH: Weinheim, 2006.

26 Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

27 2-phenoxy-2-methylbutanoate prepared as per Beller et al. (2006). Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691-695.

5 Conclusions and Future Perspectives

These last few years have been an exciting time for boronic acids as they begin to display more activity than they was previously thought to be possible. Boronic acids are most well known as stoichiometric reagents in reactions such as the Suzuki-Miyaura cross-coupling but increasingly their versatility as catalysts is coming to light.

Chapter 2 discussed investigations toward boronic acid catalyzed dehydration reactions with the goal of replacing current state-of-the-art transformations, such as the Grieco and Burgess eliminations, which lack atom economy and use harsh conditions. It was previously found that tetrafluoroboronic acid (TFBA) could easily eliminate an activated allylic alcohol under ambient conditions. Extending this activation to discover if there could be any activity with non-allylic alcohols did not yield any successful dehydration. Despite a large number of conditions and potential boronic acid activators with a number of different properties, it is clear that elimination of an alcohol is a very difficult process. Indeed, a brief analysis of the corresponding bond strengths in a substrate such as a primary alcohol shows that transformation of an alcohol into an alkene is thermodynamically unfavourable. There is still a need for catalytic reactions to fill this void, and efforts are ongoing. Analysis of various bond dissociation energies within a model primary alcohol has lead to a theoretical reagent with built in energy primed for a six-membered E_i-type dehydration (**Scheme 2-13**). Currently, the most obvious approach is currently backtracking to known literature dehydrations and finding new ways of increasing their reactivity in alcohols of moderate difficulty such as isolated allylic systems before attempting more challenging substrates like primary non-allylic alcohols. Hopefully, there is a boronic acid

with a specific set of conditions such that it will one day serve as an activator or possibly a catalyst in a general reaction for the elimination of alcohols.

Chapter 3 described the first stages of finding milder Ritter reaction conditions to form an amide bond. Initial results were not as successful as desired but this prompted a more direct evaluation of highly activated boronic acid catalysts: TFBA and ferroceniumboronic acid hexafluoroantimonate salt (FBAHA). Isolated results have determined that activation by boronic acids could potentially provide an alternative to much harsher acids traditionally required for the Ritter reaction. Unfortunately, research has also revealed that under the vast majority of conditions, the alcohol is more nucleophilic than the nitrile complicating the observed product distribution. Much work remains to be done to elucidate optimal conditions to enable a mild boronic acid catalyzed Ritter reaction to be viable alternative to other well-established methods of amide bond formation.

Finally, the research of Chapter 4 has shown that boronic acids can be general catalysts for the Friedel-Crafts reaction. FBAHA has enabled activation of benzylic alcohols under mild conditions enabling the Friedel-Crafts reaction to occur catalytically and more efficiently than previously possible. This Friedel-Crafts variation has been able to catalyze alkylation of neutral to slightly deactivated arenes and show compatibility with a wide variety of benzylic alcohols. The appearance of FBAHA and other bifunctional boronic acids have solidified secondary effects as a viable research branch in the area of boronic acid catalysis. Perhaps this research could provide new insight and enable new, useful and unusual transformations.

Arylboronic acids have shown remarkable activity being able to induce a wide variety of transformations through their activation of alcohols. As a result, boronic acids, esters and derivatives are now appearing at the forefront of innovation. Current challenges are to increase boronic acid catalyzed reaction scope and decrease loadings with a more active boronic acid catalyst. Only time will show how this class of compounds can contribute to synthetic methods for industrial and academic settings alike.

Bibliography

Allen C.L.; Chhatwal A. R.; Williams J.M.J. *Chem. Commun.* **2012**, *48*, 666–668.

Allen, C.L.; Williams, J.M.J. *Chem. Soc. Rev.* **2011**, *40*, 3405-3415.

Allred, E.L.; Sonnenbcrg, J.; Winstcin S. *J. Org. Chem.* **1960**, *25*, 25.

Al-Zoubi, R.; Marion, O.; Hall, D.G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879.

Anastas, P.T. *Aldrichchimica Acta* **2015**, *48*, 3-4.

Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, U.K.; 1998.

Anxionnat, B.; Guérinot, A.; Reymond, S.; Cossy, J. *Tetrahedron Lett.* **2009**, *50*, 3470-3473.

Arnold K.; Davies B.; Giles R. L.; Grosjean C.; Smith G. E.; Whiting A. *Adv. Synth. Catal.* **2006**, *348*, 813–820.

Arnold, K.; Batsanov, A.S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124-134.

Arnold, K.; Davies, B.; Giles, R.L.; Grojean, C.; Smith, G.E.; Whiting, A. *Adv. Synth. Catal.* **2006**, *348*, 813-820.

Ashby, E.C. *Q. Rev. Chem. Soc.* **1967**, *21*, 259-285.

Ashby, E.C.; Lammele, J.; Neumann, H.M. *Acc. Chem. Res.* **1974**, *7*, 272–280.

Bader, R.F.W.; Bourns, A.N. *Can. J. Chem.* **1961**, *39*, 348.

Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273-11283.

Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911-12912.

Baltzly, R. *J. Am. Chem. Soc.* **1952**, *74*, 4586. (b) Horner, L.; Reuter, H.; Herrmann, E. *Justus Liebigs Ann. Chem.* **1962**, *660*, 1. (c) Baltzly, R. *J. Org. Chem.* **1976**, *41*, 928.

Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Eur. J. Org. Chem.* **2009**, 430-436.

Barton, D.H.R.; McCombie, S. W. J. Chem. Soc., Perkin Trans. 1 **1975**, 1574-1585.

Baumann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 3218–3222.

Beletskaya, I.P.; Cheprakov, A.V. *Chem. Rev.* **2000**, *100*, 3009-3066.

Benson, S.W. *J. Chem. Educ.* **1965**, *42*, 502.

Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059-1070.

Beyer, K.H.; Baer, J.E.; Russo, H.F.; Haimbach, A.S. *Fed Proc.* **1957**, *16*, 282.

Blanksby, S.J.; Ellison, G.B. *Acc. Chem. Res.* **2003**, *36*, 255-263.

Bordwell, F. G.; Brannen, W. T. *J. Am. Chem. Soc.* **1964**, *86*, 4645-4650.

Bordwell, F.G.; Douglass, M.L. *J. Am Chem. Soc.* **1966**, *88*, 993-999.

Brak, K.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.

Brown, C.A.; Coleman, R.A. *J. Org. Chem.* **1979**, *44*, 2328.

Brown, H.C. *Tetrahedron*, **1961**, *12*, 117.

Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 247.

Burgess, E.M., Penton, H.R., Jr.; Taylor, E.A. *J. Am. Chem. Soc.* **1970**, *92*, 5224-5226.

Calderon, N; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* **1967**, *8*, 3327-3329.

Callens, D.; Burton, A.J.; Barrett, A.G.M. *Tetrahedron Lett.* **2006**, *47*, 8699-8701.

Calloway, N.O. *Chem. Rev.* **1935**, *17*, 327–392.

Carey, J.S.; Laffan, D.; Thomson, C.; Williams, M.T. *Org. Biomol. Chem.* **2006**, *4*, 2337-2347.

Charville, H.; Jackson, D.A.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010**, *46*, 1813-1823.

Chase, P.A.; Henderson, L.D.; Piers, W.E.; Parvez, M.; Clegg, W.; Elsegood, M.R.J. *Organometallics* **2006**, *25*, 349-357.

Chorkendorff, I.; Niemantsverdriet, J. W. Introduction to Catalysis, in Concepts of Modern Catalysis and Kinetics; Wiley-VCH: Weinheim, 2003.

Cohen, P.S.; Cohen, S.M *J. Chem. Ed.* **1996**, *73*, 883-886.

Constable, D.J.C.; Dunn, P.J.; Hayler, J.D.; Humphrey, G.R.; Leazer, J.J.L.; Linderman, R.J.; Lorenz, K.; Manley, J.; Pearlman, B.A.; Wells, A.; Zaks, A.; Zhang, T.Y. *Green Chem.* **2007**, *9*, 411-420.

Corey, E.J.; Bakshi, R. K.; Shibata, S.; Chen, C.P.; Singh, V.K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

Corey, E.J.; Helal, C.J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012.

Corey, e.J.; Posner, G.H..; Atkinson, R.F.; Wingard, A.K.; Halloran, d.J.; Radzik, D.M.; Nash, J.J. *J. Org Chem.* **1989**, *54*, 389.

Corey, E.J.; Suggs, W. *Tetrahedron Lett.* **1975**, *16*, 2647-2650.

Corey, E.J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111.

Craig, G.W. *Helv. Chim. Acta.* **2011**, *94*, 923-946.

Cremer, D.; Crehuet, R.; Anglada, J. *J. Am. Chem. Soc.* **2001**, *123*, 6127-6141.

Crich, D.; Quintero, L. *Chem. Rev*. **1989**, *89*, 1413-1432.

Criegee, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 745-752.

de Meijere, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7836–7840.

de Meijere, A.; Meyer, Jr., F.E.; *Angew. Chem. Int. Ed.* **1994**, *33*, 2379–2411.

Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763-784.; Cho, B.T. *Tetrahedron* **2006**, *62*, 7621-7643.

DePuy, C.H.; King, R.W. Ref. 138, p. 444; Nace, H.R., Ed. *Org. React.* **1962**, 12, 57.

Dermer, O.C. *Chem. Rev.* **1934**, *14*, 385.

Detroy, R.W.; St. Julian, G. *Crit. Rev. Microbiol.* **1983**, *10*, 203-28.

Durka, K.f; Lulinski, S.; Serwatowski, J.; Wozniak, K. *Organometallics* **2014**, *33*, 1608-1616.

Eh-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557-6602.

Elschenbroich, C. *Organometallics*, 3e; Wiley-VCH: Weinheim, 2006.

Fatemi, S.; Gernigon, N.; Hall, D.G. *Green Chem.* **2015**, *17*, 4016-4028.

Fehlner, T.P. The Metallic Face of Boron. In *Advancesin Inorganic Chemistry*; Skyes, A.G., Ed.; Academic Press: Orlando, 1990; Vol. 35; p 199-233.

Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528–1532.

Firouzabadi, H.; Sardarian, A.R.; Badparva, H. *Synth. Commun.* **1994**, *24*, 601-607.

Fittig, R. *Justus Liebigs Ann. Chem.* **1862**, *121*, 361-365.

Friedel, C.; Crafts, J.-M. *Compt. Rend.* **1877**, *84*, 1392-1395.

Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

Gadamasetti, K.G. Process Chemistry in the Pharmaceutical Industry: An Overview. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K.G., Ed.; Marcel Dekker: New York, 1999; p 3-17.

Gasmi, A., Garnier, R.; Galliot-Guilley, M.; Gaudillat, C.; Quartenoud, B.; Buisine, A.; Djebbar, D. *Vet. Hum. Toxicol.* **1997**, *39*, 304-308.

Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380–1393.

Georgiou, I.; Ilyashenko, G.; Whiting, A. *Acc. Chem. Res.* **2009**, *42*, 756-768.

Gernigon N.; Al-Zoubi R. M.; Hall D. G. *J. Org. Chem.* **2012**, *77*, 8386–8400.

Ghose, A.K.; Viswanadhan, V.N.; Wendoloski, J.J. *J. Comb. Chem.* **1999**, *1*, 55–68.

Giner, J.-L.; Margot, C.; Djerassi, C. *J. Org. Chem.* **1989**, *54*, 369.

Gispert, J.R. *Coordination Chemistry*. Wiley-VCH: Weinheim, 2008.

Greenhalgh, M.D.; Thomas, S.P. *Chem. Commun.* **2013**, *49*, 11230-11232.

Grieco, P.A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486.

Grignard, M.V.; Moissan, M.H. *Compt. Rend.* **1900**, *130*, 1322-1324.

Guérinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 19-28.

Hall, D.G. Strucuture, Properties, and Preparation of Boronic Acid Derivatives. Overview of their Reactions and Applications. Chapter 1 in *Boronic Acids*, Ed.: D.G. Hall, Wiley-VCH: Weinheim, 2011, pp 1-135.

Heck, R.F.; Nolley, Jr., J.P. *J. Org. Chem.* **1972**, *37*, 2320-2322.

Hermann, A.; McSorley, A.; Ashcroft. N.W.; Hoffmann, R. *J. Am. Chem. Soc.* **2012**, *134*, 18606-18618.

Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *Chemical Communications* **1981**, *7*, 315.

Honeychuck, R.V.; Hersh, W.H. *Inorg. Chem.* **1989**, *28*, 2869-2886.

Houghton, R.P. *Metal Complexes in Organic Chemistry*; Cambridge University Press: Cambridge, 1979.

Howe, P.D. *Biol. Trace Elem. Res.* **1998**, *66*, 153-166.

Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913-3917.

Ishihara K.; Ohara S.; Yamamoto H. *J. Org. Chem.* **1996**, *61*, 4196–4197.

Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196-4197.

Jencks, W.P. *Acc. Chem. Res.* **1980**, *13*, 161-169.

Johansson Seechurn, C.C.C.; Kitching, M.O.; Colacot, T.J. Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.

Johansson, L.; Fotsch, C.; Bartberger, M.D.; Castro, V.M.; Chen, M.; Emery, M.; Gustafsson, S.; Hale, C.; Hickman, D.; Homan, E.; Jordan, S.R.; Komorowski, R.; Li, A.; McRae, K.; Moniz, G.; Matsumoto, G.; Orihuela, C.; Palm, G.; Veniant, M.; Wang, M.; Williams, M.; Zhang, J. *J. Med. Chem.* **2008**, *51*, 2933-2943.

Johnson, R.A.; Sharpless, K.B. *Comp. Org. Syn.* **1991**, *7*, 389-436.

Kerr, J.A. *Chem. Rev.* **1966**, *66*, 465.

Kharasch, M.S.; Fields, E.K. *J. Am. Chem. Soc.* **1941**, *63*, 2316–2320.

Kharasch, M.S.; Fuchs, C.F. *J. Am. Chem. Soc.* **1943**, *65*, 504–507.

Kim, C.; Traylor, T.G.; Perrin, C.L. *J. Am. Chem. Soc.* **1998**, *120*, 9513-9516.

Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.

Kropp, P.J.; Dans, K.A.; Crawford, S.D.; Tubergen, M.W.; Kepler, K.D.; Craig, S.L. Wilson, V.P. *J. Am. Chem. Soc.* **1990**, *112*, 7433-7434.

Lanigan, R.M.; Sheppard, T.D. *Eur. J. Org. Chem.* **2013**, 7453-7465.

Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH: New York, 1999, p 1077.

Lee, A.W.M.; Chan, W.H.; Wong, H.C.; Wong, M.S. *Synth. Commun.* **1989**, *19*, 547.

Lee, D.G.; Lamb, S.E.; Chang, V.S. *Org. Synth. Coll.* **1990**, *7*, 397.

Lewis, R..J, Sr.; *Hawley's Condensed Chemical Dictionary*. 13th ed. NY: John Wiley & Sons, Inc., 1997, p. 1136.

List, B.; Lerner, R.A.; Barbas III, C.F.B. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

List, B.; Yang, J.W. *Science* **2006**, *313*, 1584-1586.

Liu, S.; Yang, Y.; Liu, X.; Ferdousi, F.K.; Batsanov, A.S.; Whiting, A. *Eur. J. Org. Chem.* **2013**, *5692*.

Lundberg H.; Tinnis F.; Adolfsson H. *Chem. Eur. J.* **2012**, *18*, 3822–3826.

Lundberg H.; Tinnis F.; Adolfsson H. *Synlett* **2012**, *23*, 2201–2204.

Luo, Y.R., Comprehensive Handbook of Chemical Bond Energies. Boca Raton: CRC Press, 2007.

Maki T.; Ishihara K.; Yamamoto H. *Tetrahedron* **2007**, *63*, 8645–8657.

Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron*, **2007**, *63*, 8645-8657.

Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148–4150.

Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.

Maruoka, K. *Asymmetric Phase Transfer Catalysis*. Wiley-VCH: Weinheim, 2008.

Mattern, R.-H. *Tetrahedron Lett.* **1996**, *37*, 291.

Matteson, D.S.; Sadhu, K.M.; Peterson, M.L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819.

Matthews, C.E.; van Holde, K.E.; Ahern, K.G. *Biochemistry.* Benjamin Cummings: New York , 1999.

McCartney, D.; Guiry, P.J. *Chemical Society Reviews* **2011**, *40*, 5122-5150.

McCombie, S.W.; Motherwell, W.B.; Tozer, M. *Org. React.* **2011**, *77*, 161.

McCubbin, J.A.; Hosseini, H.; Krokhin, O.V. *J. Org. Chem.* **2010**, *75*, 959-962.

Meerwein, H.; Buchner, E.; van Emster, K. *J. Prakt. Chem.* **1939**, *152*, 237–266.

Mehta, G.; Murthy, A.N.; Reddy, D.S.; Reddy, A.V. *J. Am. Chem. Soc.* **1986**, *108*, 3443.

Mercer, S.M.; Robert, T.; Dixon, D.V.; Chen, C.-S.; Ghoshouni, Z.; Harjani, J.R.; Jahangiri, S.; Peslherbe, G.H.; Jessop, P.G. *Green Chem.* **2012**, *14*, 832-839.

Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691-695.

Mertins, K.; Iovel, I.; Kischel, J.;Zapf, A.;Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 238-242.

Meyer, S.D.; Schreiber, S.L. *J. Org. Chem.* **1994**, *59*, 7549.

Michaudel, Q.; Thevenet, D.; Baran, P.S. *J. Am. Chem. Soc.* **2012**, *134*, 2547-2550.

Minden, H. T. *Physics Today* **1994**, *47*, 124–125.

Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J.A.; Hall, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 9694-9703.

Montalbetti, C.A.G.N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827-10852.

Moore, A.N.J.; Wayner, D.D.M. *Can. J. Chem.* **1999**, *77*, 681-686.

Mori, A.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Sajiki, H. *Org. Lett.* **2006**, *8*, 3279-3281.

Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.

Mukhopadhyay, M.; Iqbal, J. *J. Org. Chem.* **1997**, *62*, 1843-1845.

Mukhopadhyay, M.; Reddy, M.M.; Maikap, G.C.; Iqbal, J. *J. Org. Chem.* **1995**, *60*, 2670-2676.

Nevalainen, V. *Tetrahedron: Asymmetry* **1992**, *3*, 1441.

Nguyen, S.T.; Johnson, L.K.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975.

Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; John Wiley & Sons: New York, 1996.

Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis*. Wiley-VCH: Weinheim, 1996.

Nielsen, F.H. *Plant and Soil* **1997**, *2*, 199-208.

Novello, F.C.; Sprague, J.M. *J. Am Chem Soc.* **1957**, *79*, 2028-2029.

Nuttall, K.L. *Ann. Clin. Lab. Sci.* **2006**, *36*, 409-420.

Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965-3968.

Oh, L.M.; Wang, H.; Shilcrat, S.C.; Herrmann, R.E.; Patience, D.B.; Spoors, P.G.; Sisko, J. *Org. Process Res. Dev.* **2007**, *11*, 1032-1042.

Olah, G. A.; Kobayash.S; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448-7461.

Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1962**, *84*, 1688-1695.

Olah, G.A.; Westerman, P.W.; Nishimura, J. *J. Am. Chem. Soc.* **1974**, *96*, 3548–3559.

Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4226.

Passananti, M.; Cermola, F.; DellaGreca, M.; Iesce, M. R.; Previtera, L.; Sferruzza, R.; Temussi, F. *Int. J. Photoenergy* **2014**, *2014*, 1-6.

Pasto, D.J.; Gontarz, J.A. *J. Am. Chem. Soc.* **1971**, *93*, 6902-6908.

Pedersen, C.J. *Angew. Chem. Int. Ed.* **1988**, *27*, 1021-1027.

Prabhakaran, P.; Puranik, V.G.; Chandran, J.N.; Rajamohanan, P.R.; Hofmann, H.-J.; Sanjayan, G. *J. Chemical Communications* **2009**, *23*, 3446-3448.

Quistad, G.B.; Zhang, N.; Sparks, S.E.; Casida, J.E. *Chem. Res. Toxicol.* **2000**, *13*, 652-657.

Rabe, P. and Kindler, K. *Chem. Ber.* **1918**, *51*, 466-467.

Rankin, K.N.; Liu, Q.; Hendry, J.; Yee, H.; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* **1998**, *39*, 1095.

Ricardo, C.L.; Mo, X.; McCubbin, J.A.; Hall, D.G. *Chem. Eur. J.* **2015**, *21*, 4218-4223.

Ritter, J.J.; Kalish, J.A. *J. Am. Chem. Soc.* **1948**, *70*, 4048-4050.

Rosenthal, T.; Baum, G.L.; Frand, U.; Molho, M. *Chest* **1978**, *73*, 623-626.

Roughley, S.D.; Jordan, A.M. *J. Med. Chem.* **2011**, *54*, 3451–3479.

Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 1-24.

Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033-1037.

Sakakura, A.; Ohkubo, T.; Yamashita, R.; Akakura, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 892-895.

Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Guitiérrez, J.M.; Rodríguez, F. *Eur. J. Org. Chem.* **2007**, 4642-4645.

Saunders Jr., W.H.; Cockerill, A.F. Ref. 3, pp. 221, 317; Knözinger, H. in *The Chemistry of the Hydroxyl Group*, pt. 2; Wiley: New York, 1971, p. 641.

Schotten, C. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2544–2547.

Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039-2041.

Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.

Sheehan, J.C.; Henry-Logan, K.R. *J. Am. Chem. Soc.* **1957**, *79*, 1262–1263.

Sheehan, J.C.; Henry-Logan, K.R. Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348.

Shirley, D. A. *Org. React.* **1954**, *8*, 28–58.

Starks, C.M. *J. Am. Chem. Soc.* **1971**, *93*, 195-199.

Starks, C.M.; Owens, R.M. *J. Am. Chem. Soc.* **1973**, *95*, 3613-3617.

Stone, E. Philosophical Transactions of the Royal Society of London **1763**, 53, 195-200.

Streitwieser, A. *Chem. Rev.* **1956**, *56*, 571-752.

Swern, D. Organic Peroxides; Wiley Interscience: New York, 1971; Vol 2.

Taylor, D.A. *Environ Health Perspect.* **2010**, *118*, A254–A257.

Taylor, M.S.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543.

Tollens, B.; Fittig, R. *Justus Liebigs Ann. Chem.* **1864**, *131*, 303–323.

Toporcer, L.H.; Dessy, R.E.; Green, I.E. *Inorg. Chem.* **1965**, *4*, 1649-1655.

Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Tetrahedron* **1994**, *50*, 8997-9008.

Touré, B.B.; Hall, D.G. *Chem. Rev.* **1994**, *94*, 4439-4486.

Tschugaeff, L. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3118–3126.

Tschugaeff, L. Berichte der deutschen chemischen Gesellschaft **1900**, 33, 3118-3126.

Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S. *J. Org. Chem.* **1997**, *62*, 6997-7005.

Ugurlucan, M.; Caglar, I.M.; Caglar, F.N.T.; Ziyade, S.; Karatepe, O.; Yildiz, Y.; Zencirci, E.; Ugurlucan, F.G.; Arslan, A.H.; Korkmaz, S.; Filizcan, U.; Cicek, S. *Recent Patents on Cardiovascular Drug Discovery* **2012**, *7*, 71-76.

Vachal, P.; Jacobsen, E.N. J. Am. Chem. Soc. 2002, 124, 10012-10014.

Valeur, E.; Bradely, M. *Chem. Rev. Soc.* **2009**, *38*, 606-631.

Veysoglu, T.; Mitscher, L.A.; Swayze, J.K. *Synthesis* **1980**, 807-810.

Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* **1990**, *59*, 60.

von Hofmann, A.W. *Justus Liebigs Ann. Chem.* **1851**, *78*, 253–286.

Whitesides, G.M.; San Filippo, J. Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611-6624.

Williamson, A. *Philosophical Magazine* **1850**, *37*, 350-356.

Williamson, W. *J. Chem. Soc.* **1852**, *106*, 229.

Williamson, W. *Liebigs Ann. Chem.* **1851**, *77*, 37.

Wilson, M.P.; Schwarzman, M.R. *Environ Health Perspect.* **2009**, *117*, 1202–1209.

Wittig, G.; Wingler, F. *Chemische Berichte* **1964**, *97*, 2146-2164.

Wöhler, F. Annalen der Physik und Chemie **1828**, 88, 253–256.

Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P. *et al*. *J. Am. Chem. Soc.* **1960**, *82*, 3800–3802.

Woodward, R.B. *Pure Appl. Chem.* **1961**, *2*, 383-404.

Woodward, R.B. *Pure Appl. Chem.* **1973**, *33*, 145-178.

Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. *J. Am. Chem. Soc.* **1956**, *78*, 2023–2025.

Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. *J. Am. Chem. Soc.* **1956**, *78*, 2657-2657.

Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. *Tetrahedron* **1958**, *2*, 1-57.

Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751.

Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247-288.

Woodward, R.B.; Doering, W.E. *J. Am. Chem. Soc.* **1944**, *66*, 849–849.

Woodward, R.B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852–853.

Woodward, RB.; Doering, W.E. *J. Am. Chem. Soc.* **1945**, *67*, 860–874.

Wurtz, A. *Ann. Chem. Pharm.* **1855**, *96*, 364–375.

Wurtz, A. *Ann. Chim. Phys.* **1855**, *44*, 275–312.

Yadav, G.D.; Sengupta, S. *Org. Proc. Res. Dev.* **2002**, *6*, 256-262.

Yadav, J.S.; Reddy, B.V.S.; Pandurangam, T.; Reddy, Y.J.; Gupta, M.K. *Catalysis Communications* **2008**, *9*, 1297-1301.

Yan, J.; Springsteen, G.; Deeter, S.; Wang, B. *Tetrahedron* **2004**, *60*, 11205-11209.

Yasuda, M.; Yoshika, S.; Yamasaki, S.; Somyo, T.; :Chiba, K.; Baba, A. *Org. Lett.* **2006**, *8*, 761-764.

Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D.G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187-6190.

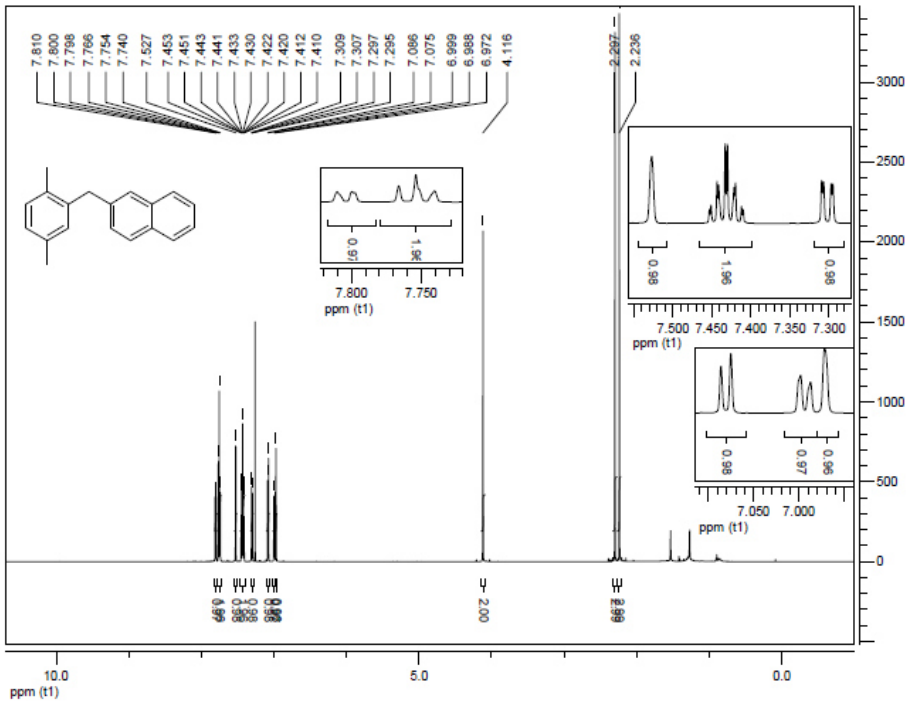
Zheng, H.; Lejkowski, M.; Hall, D.G. *Chem. Sci.* **2011**, *2*, 1305-1310.

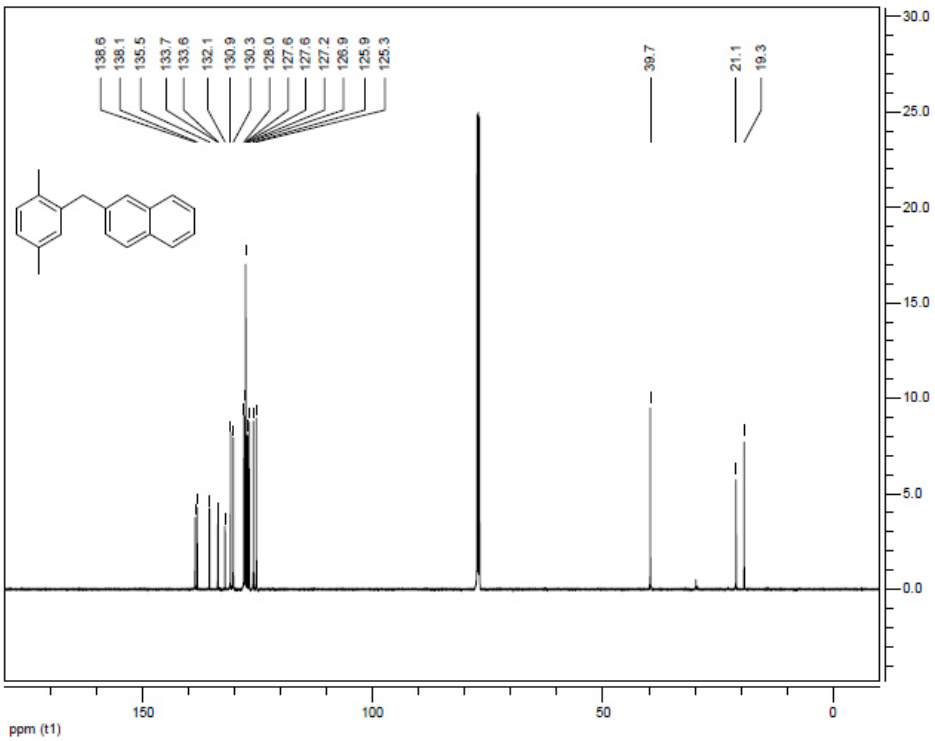
Zheng, H.; McDonald, R.; Hall, D. G. *Chem. Eur. J.* **2010**, *16*, 5454-5460.

Appendix – Selected NMR Spectra

NMR spectroscopic analysis of 2-(2,5-Dimethylbenzyl)naphthalene.

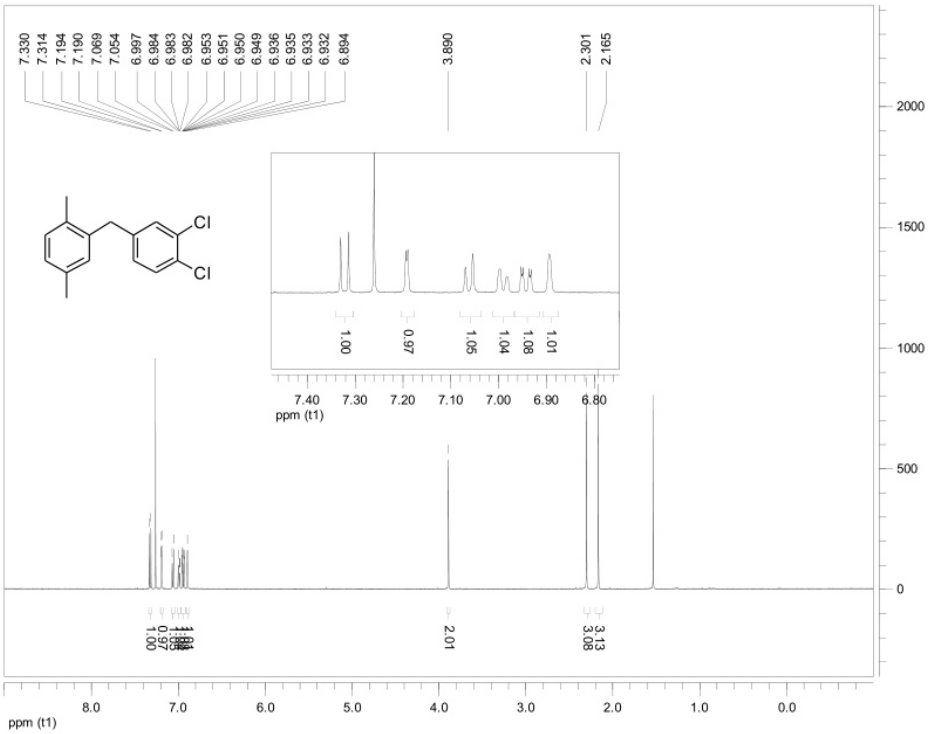
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

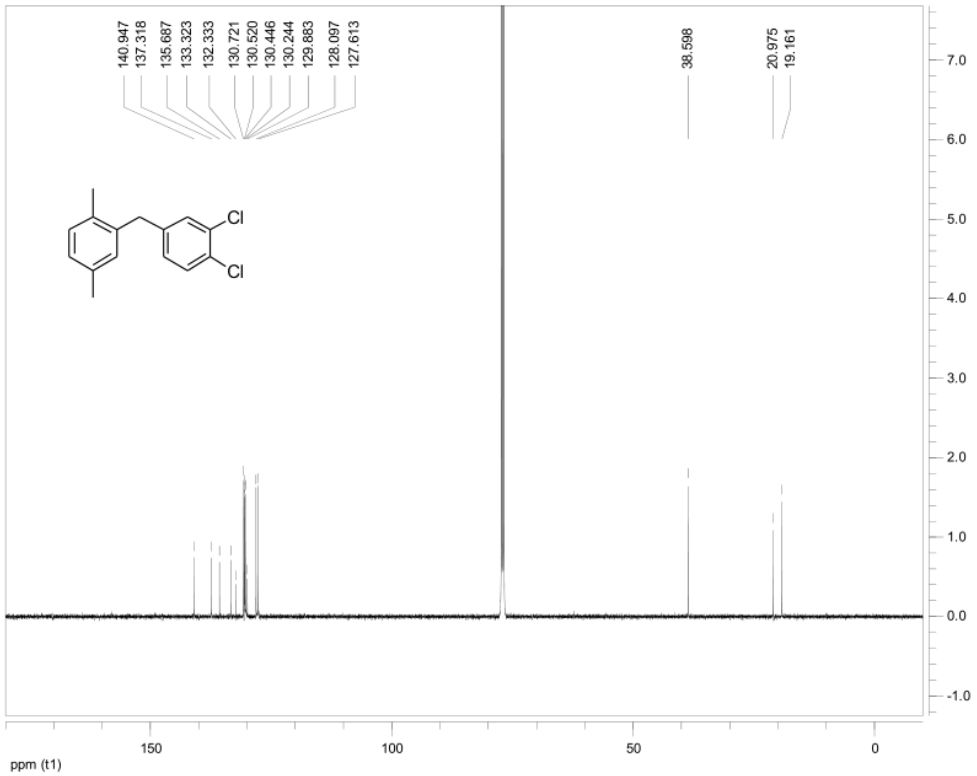




NMR spectroscopic analysis of 1,2-Dichloro-4-(2,5-dimethylbenzyl)benzene.

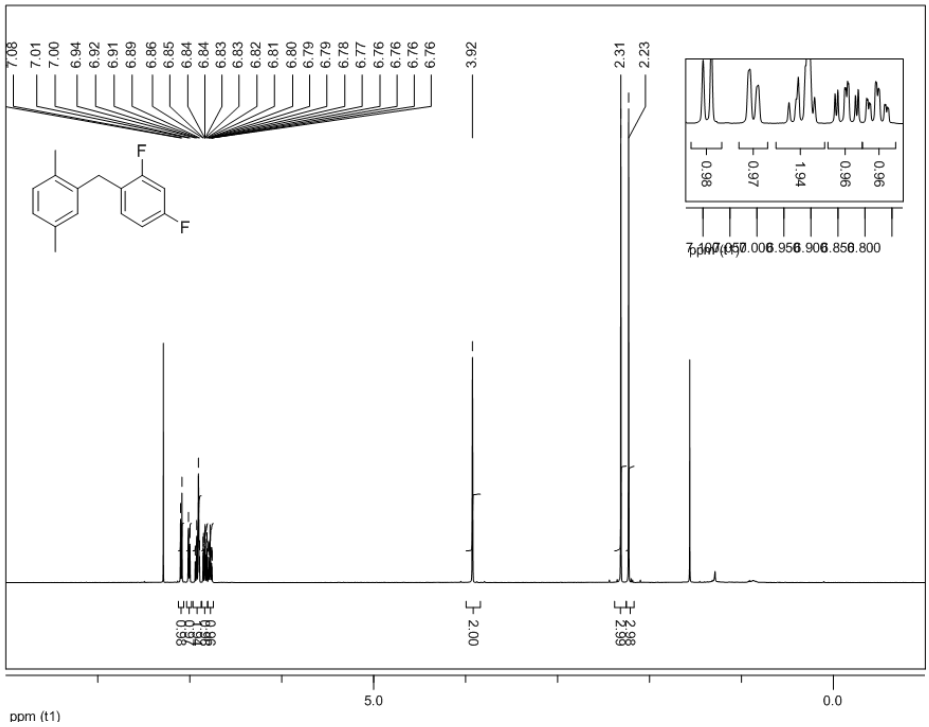
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

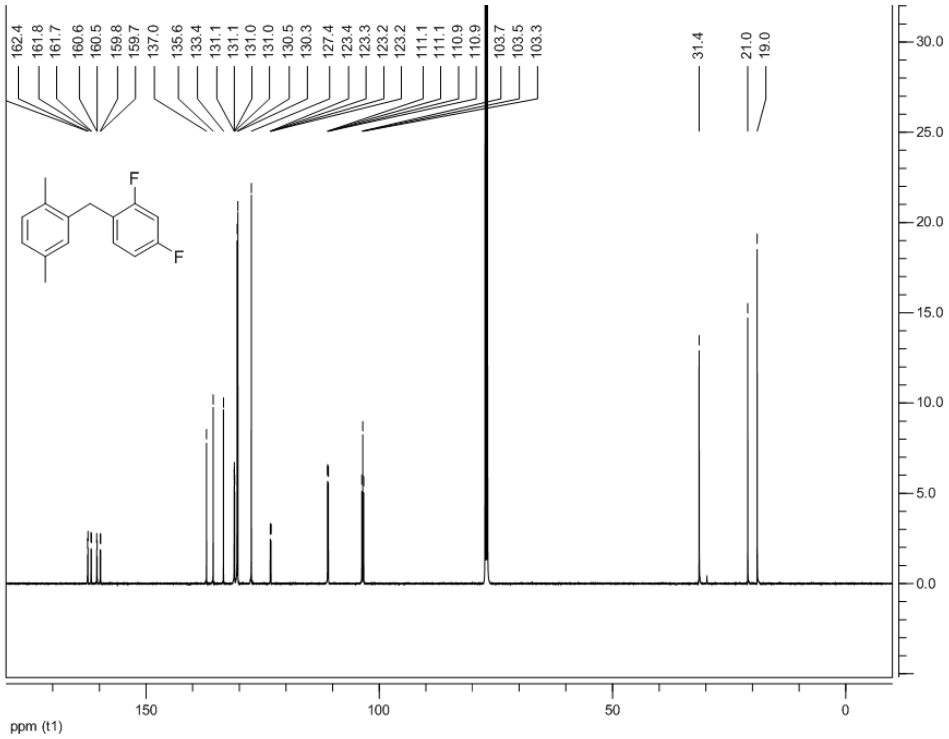




NMR spectroscopic analysis of 2-(2,4-Difluorobenzyl)-1,4-dimethylbenzene.

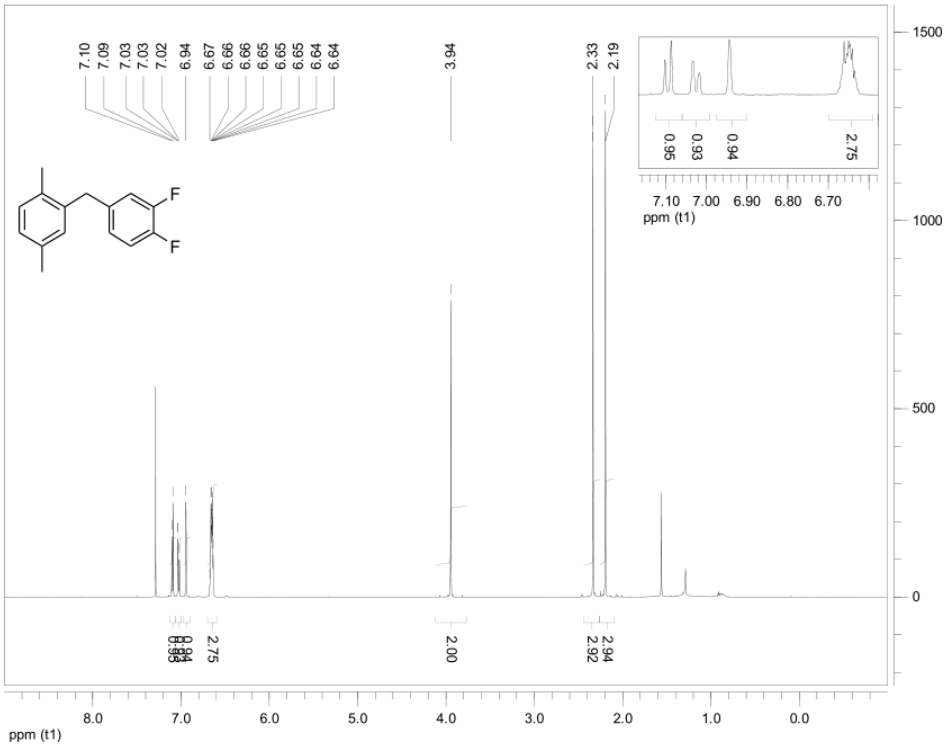
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

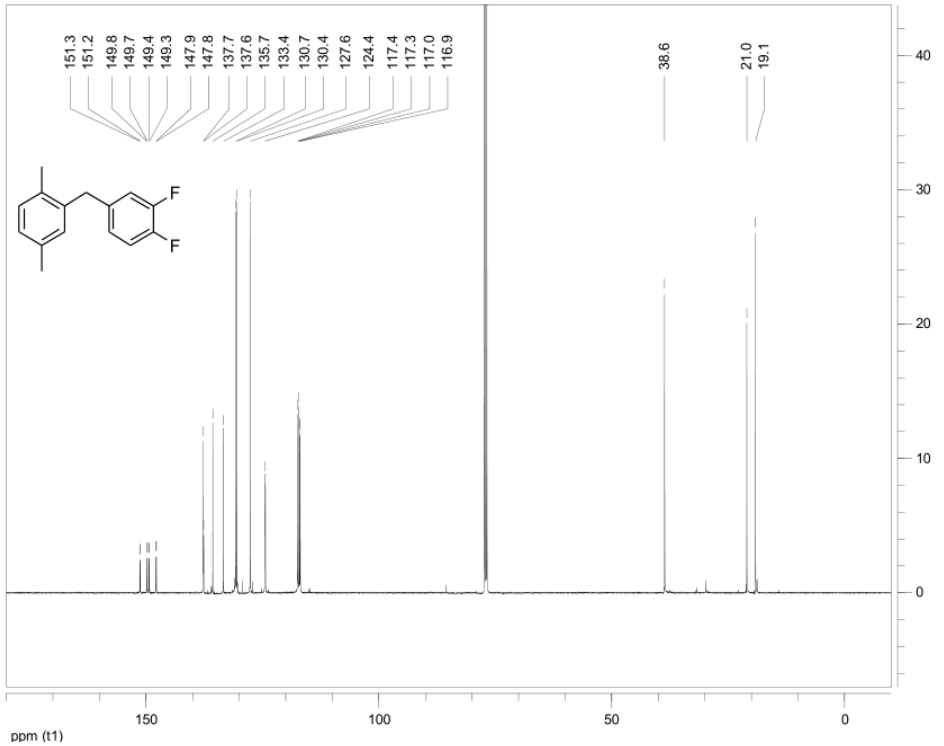




NMR spectroscopic analysis of 2-(3,4-Difluorobenzyl)-1,4-dimethylbenzene.

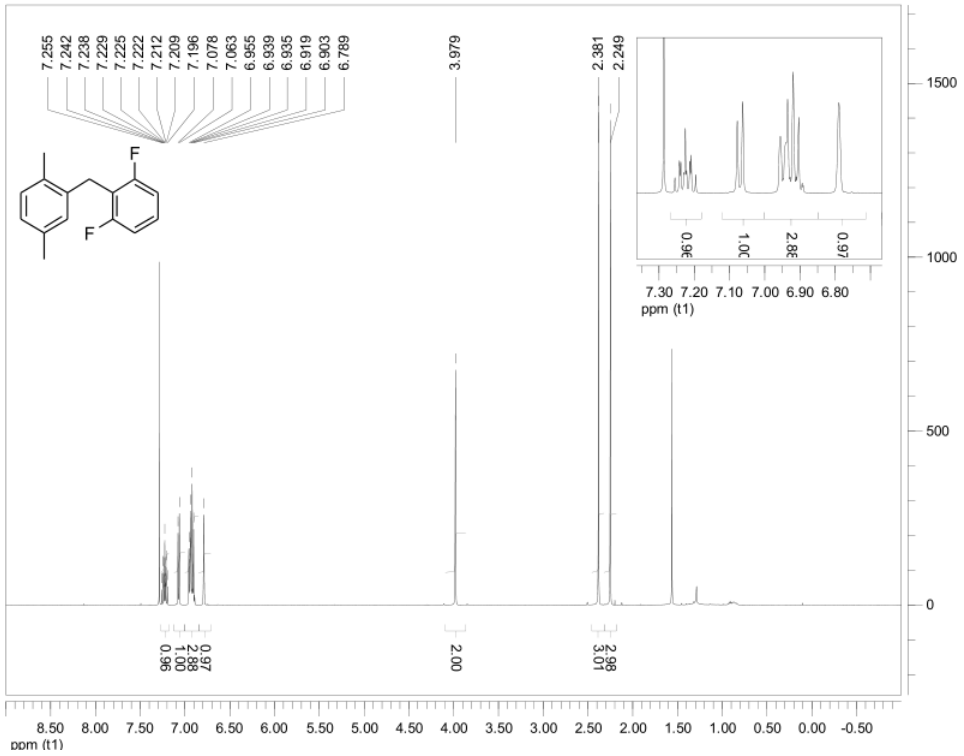
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

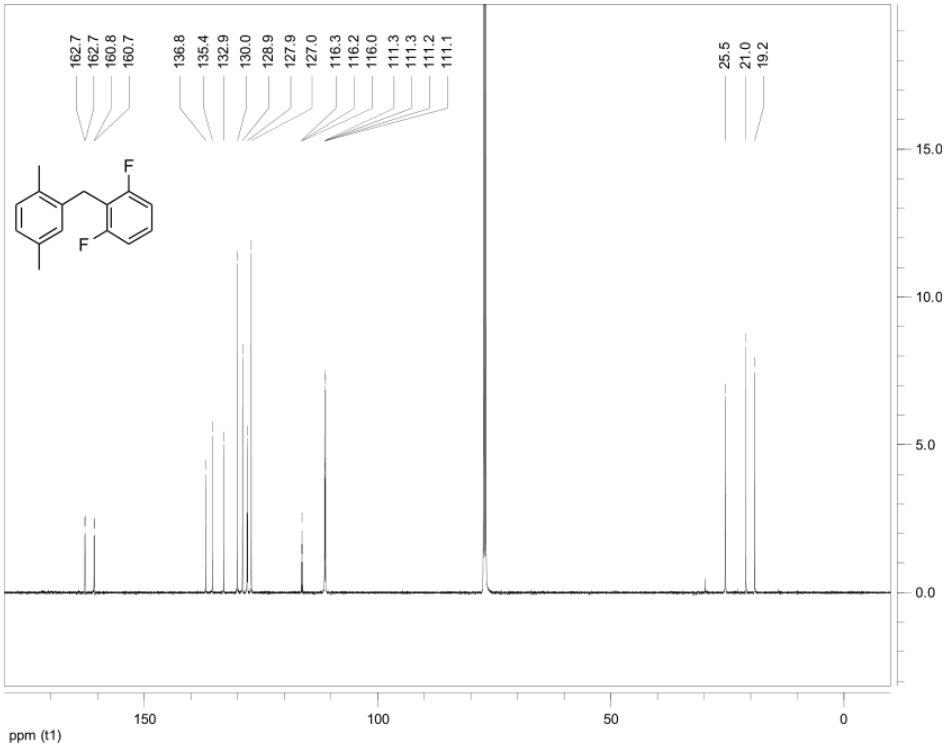




NMR spectroscopic analysis of 2-(2,5-Dimethylbenzyl)-1,3-difluorobenzene.

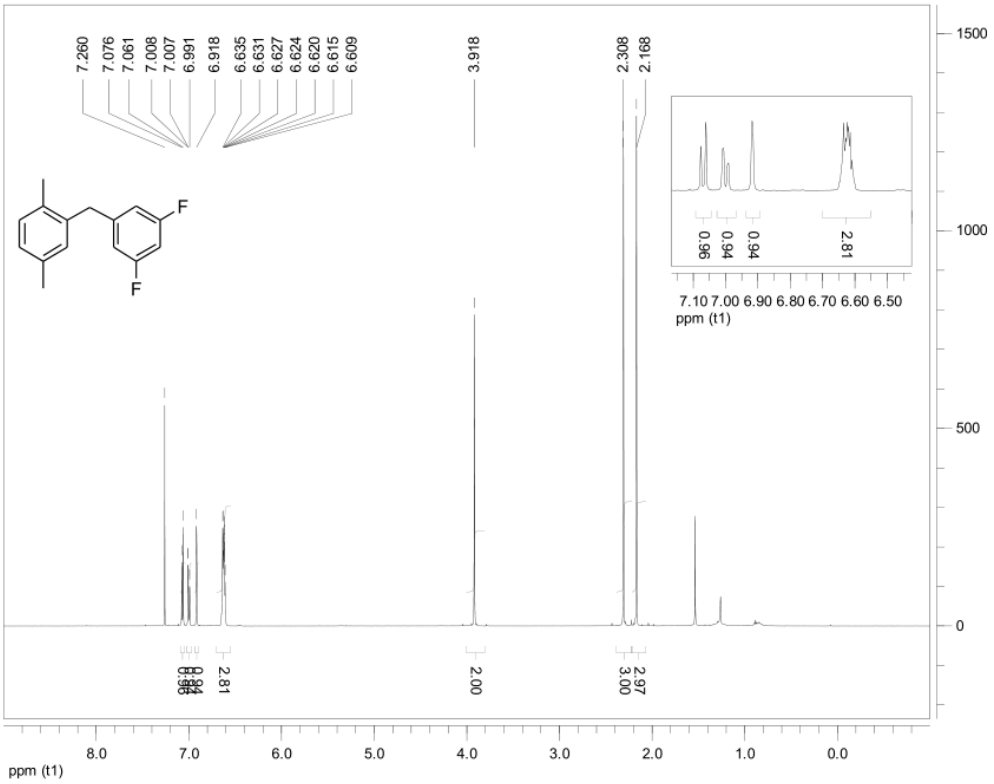
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

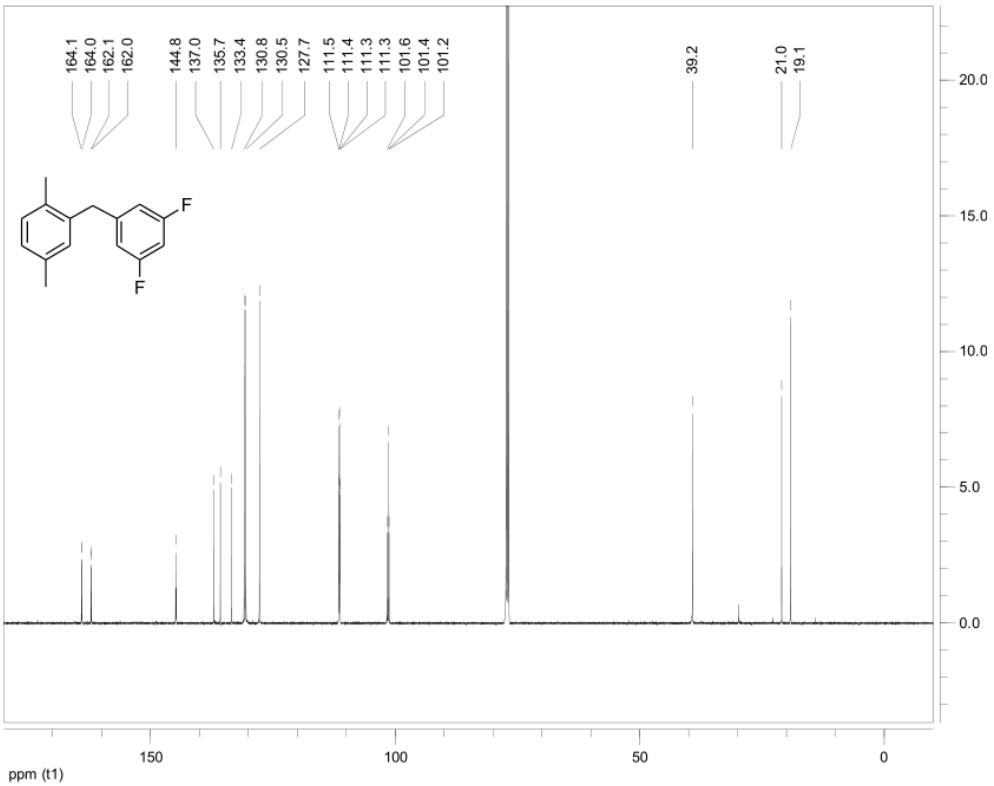




NMR spectroscopic analysis of 2-(3,5-Difluorobenzyl)-1,4-dimethylbenzene.

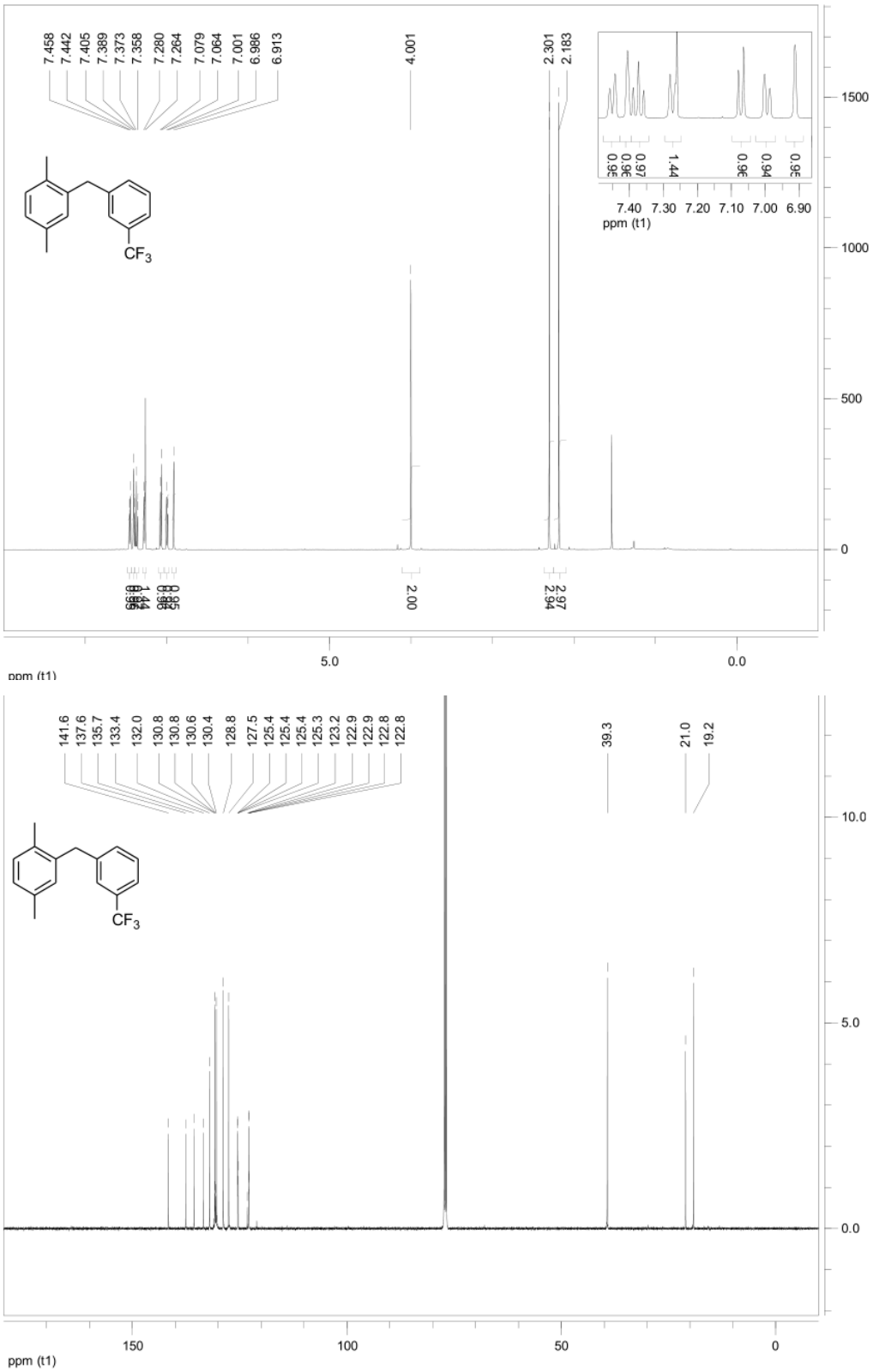
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).





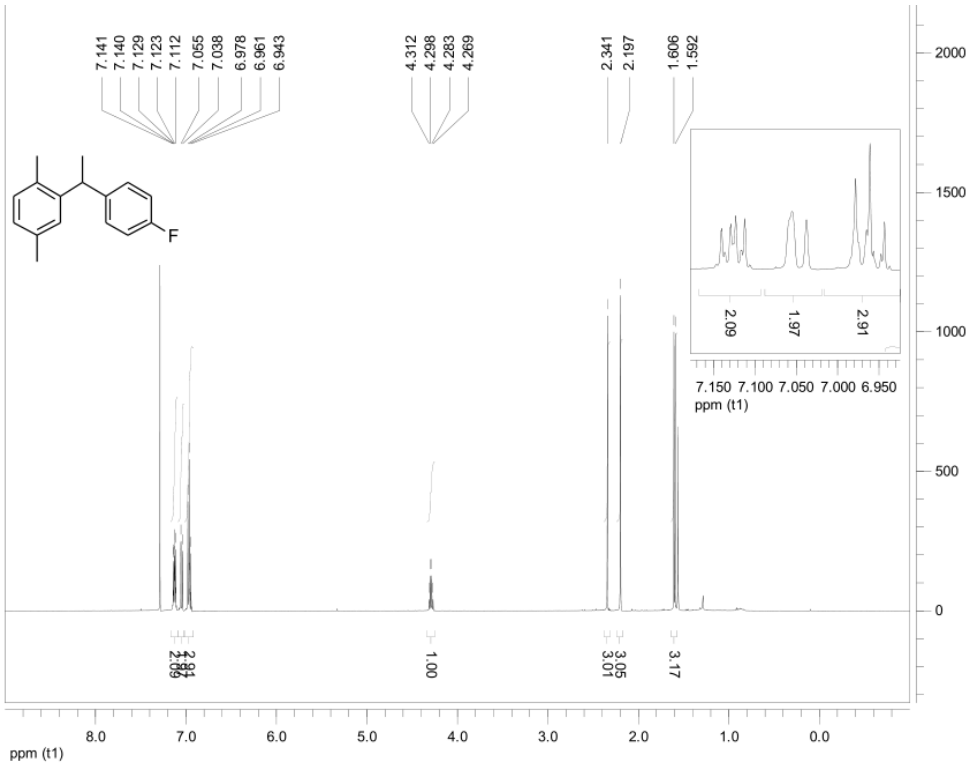
NMR spectroscopic analysis of 1,4-Dimethyl-2-(3-(trifluoromethyl)benzyl)benzene.

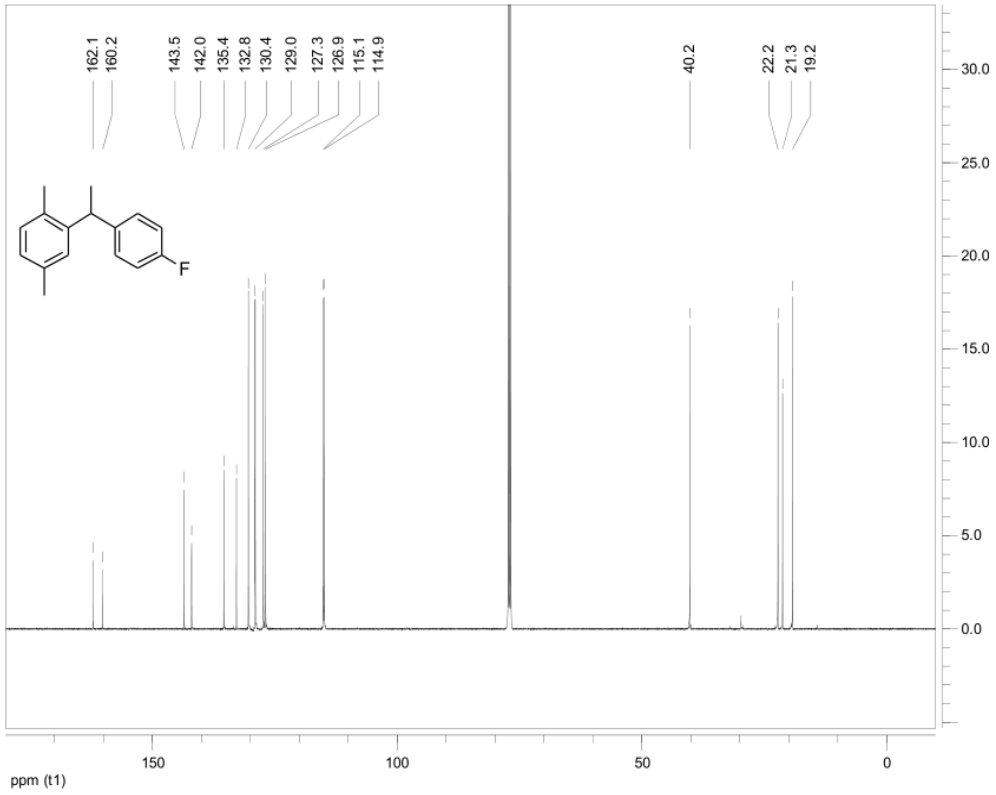
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).



NMR spectroscopic analysis of 2-(1-(4-Fluorophenyl)ethyl)-1,4-dimethylbenzene.

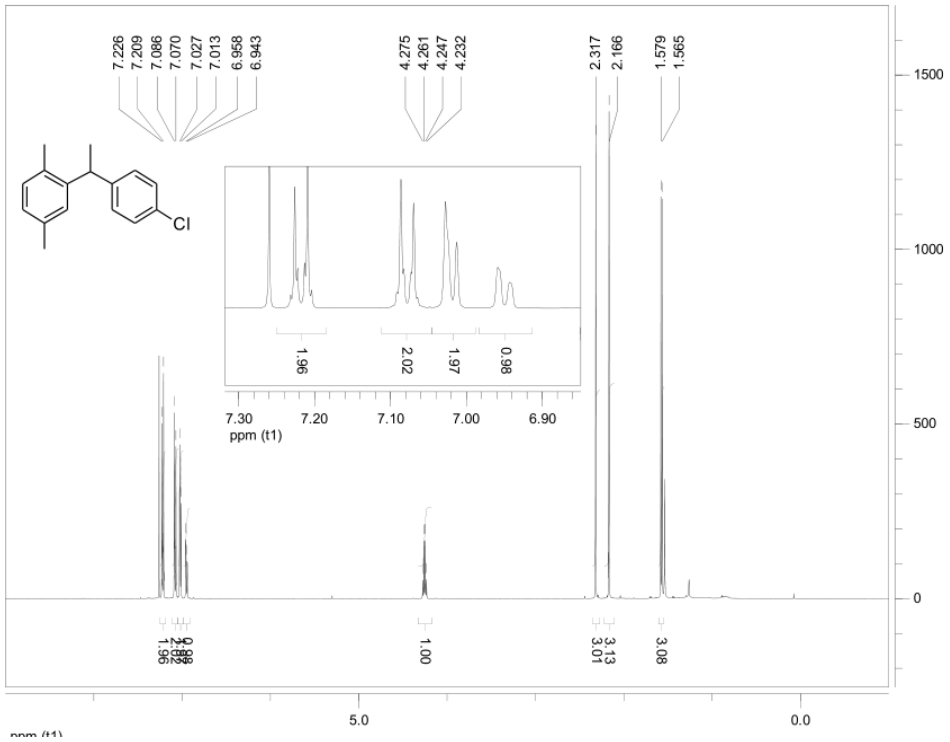
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

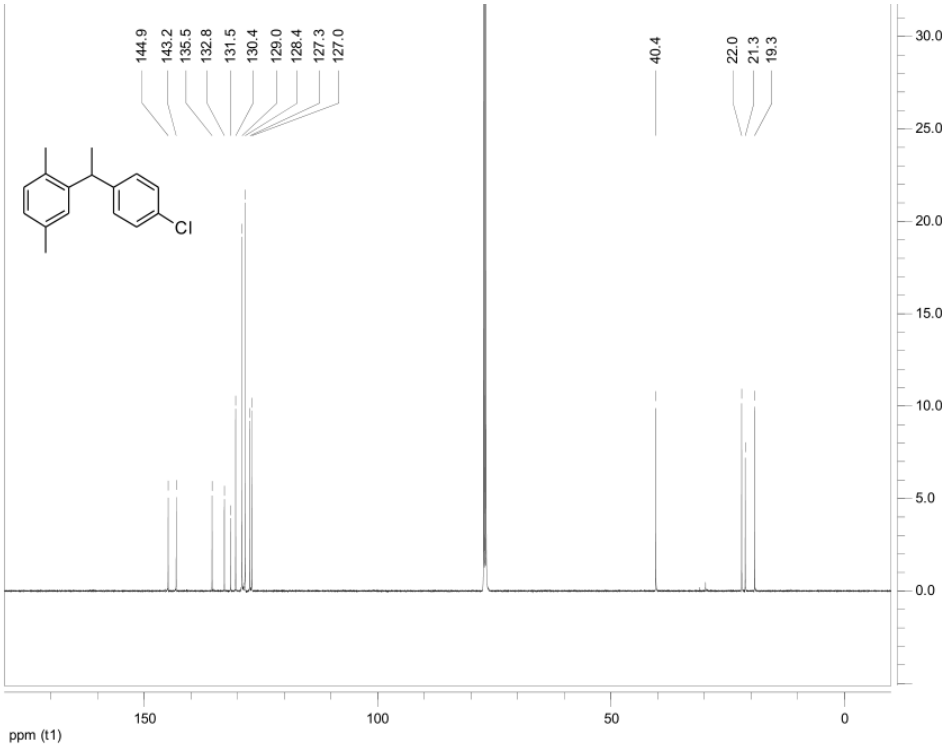




NMR spectroscopic analysis of 2-(1-(4-Chlorophenyl)ethyl)-1,4-dimethylbenzene.

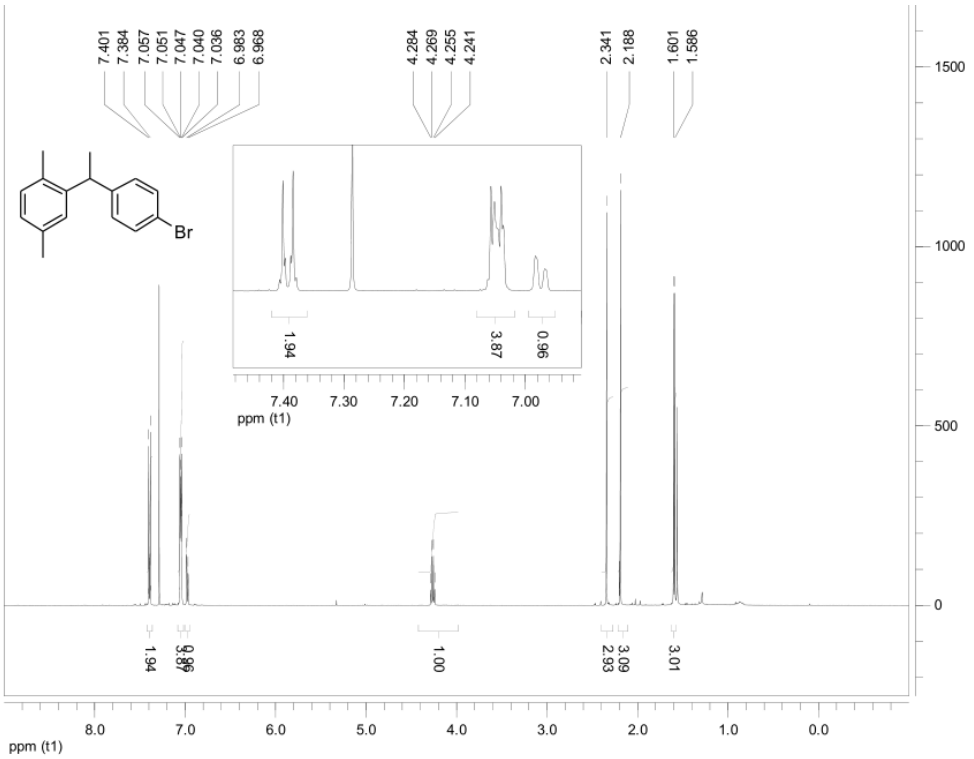
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

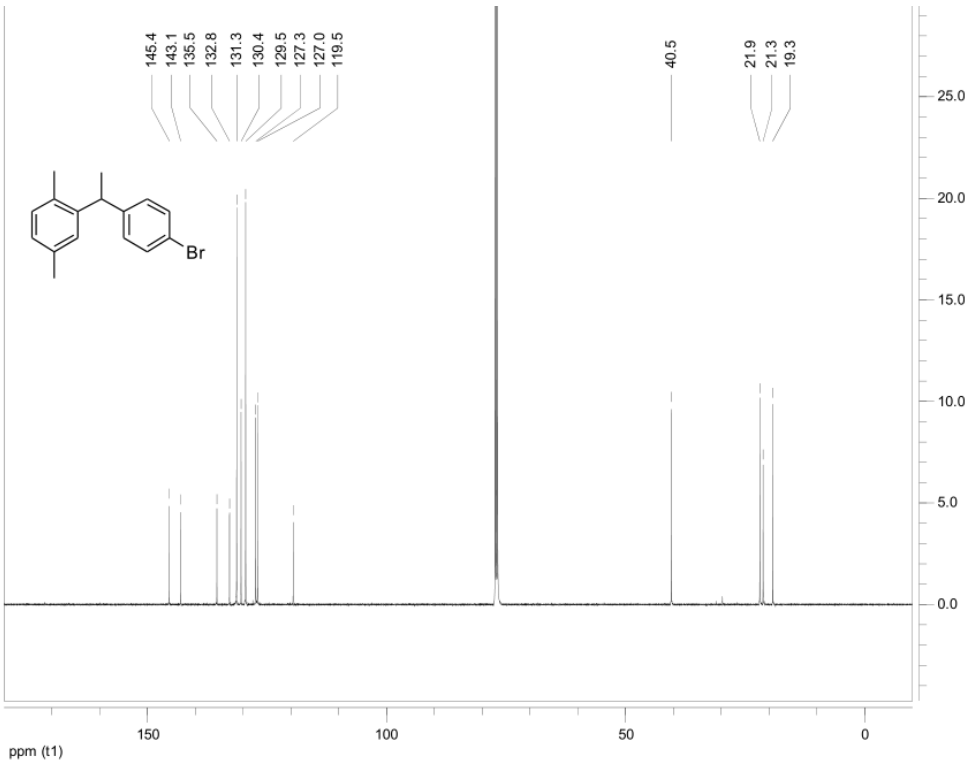




NMR spectroscopic analysis of 2-(1-(4-Bromophenyl)ethyl)-1,4-dimethylbenzene.

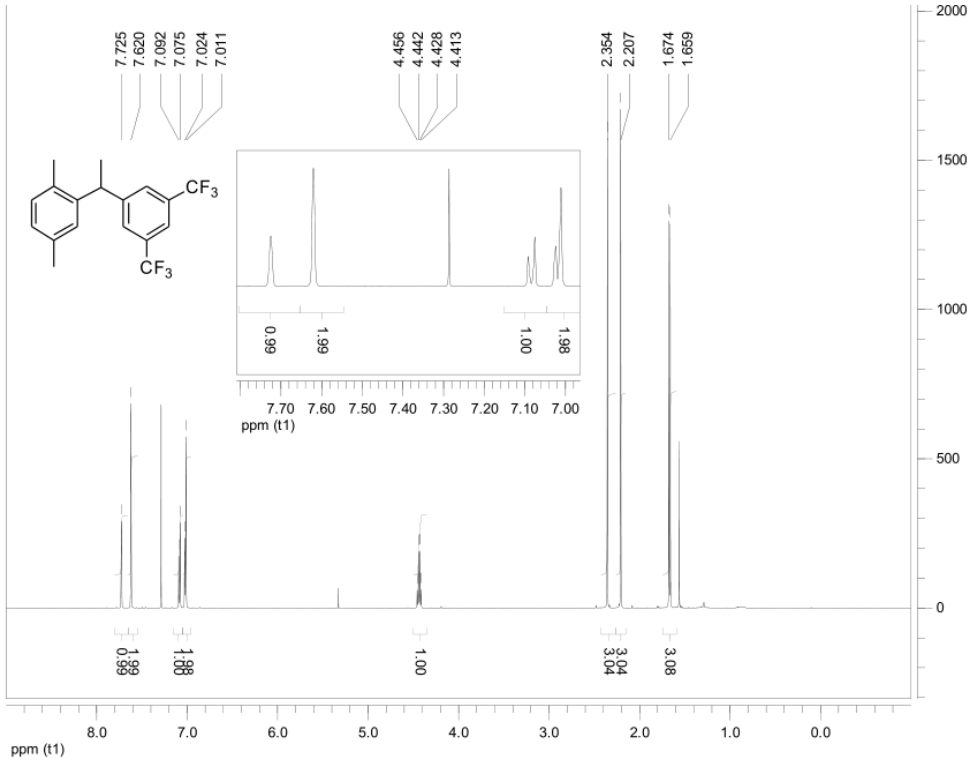
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

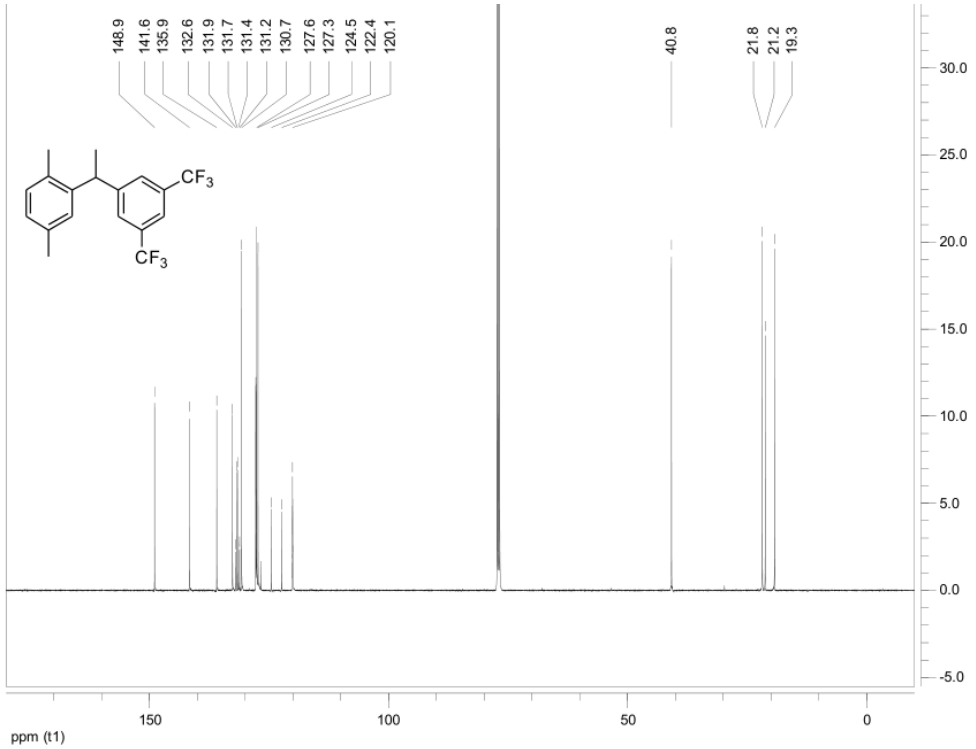




NMR spectroscopic analysis of 2-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)-1,4-dimethylbenzene.

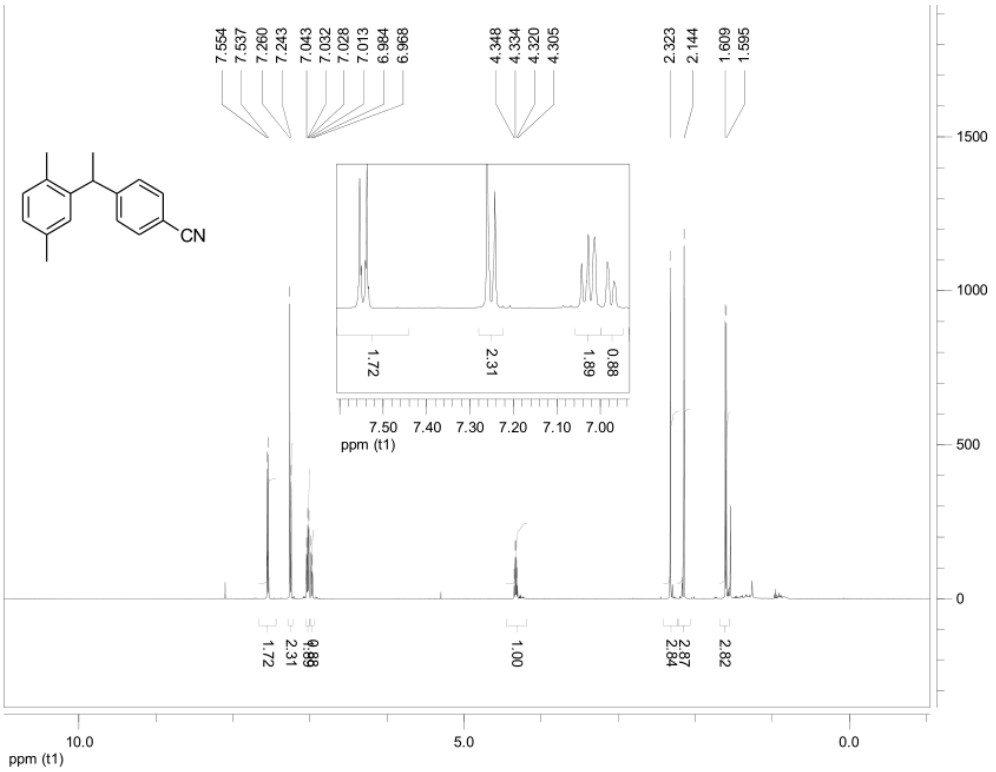
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

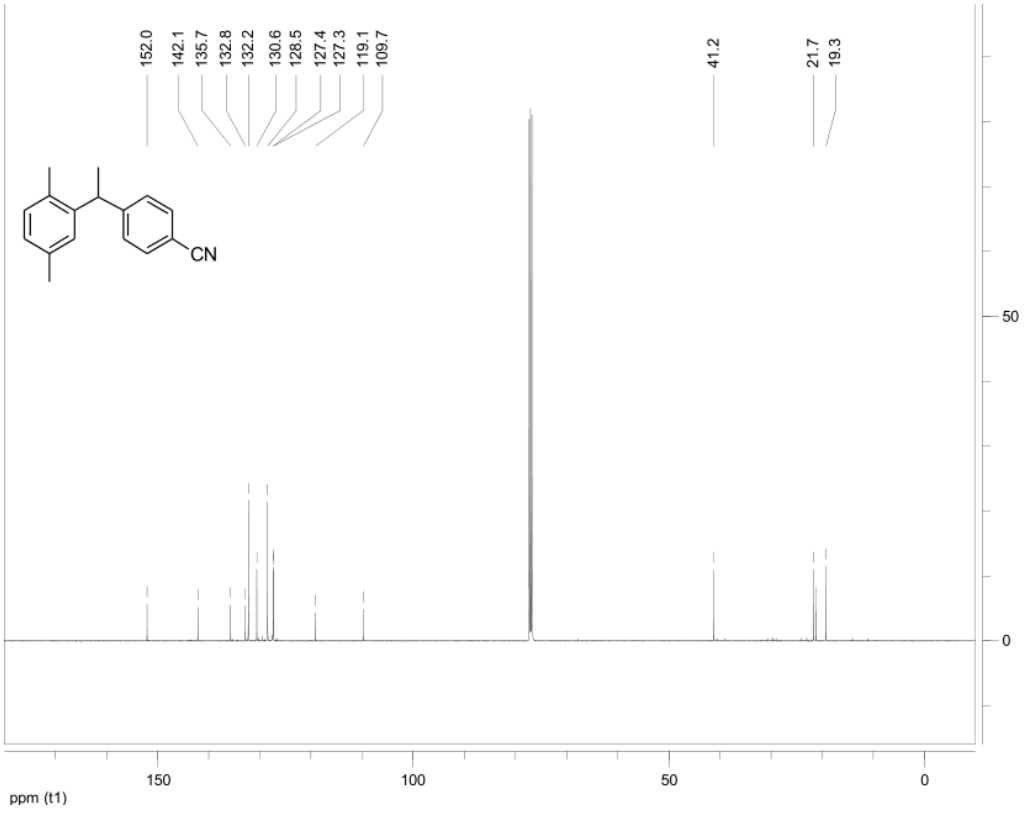




NMR spectroscopic analysis of 4-(1-(2,5-Dimethylphenyl)ethyl)benzonitrile.

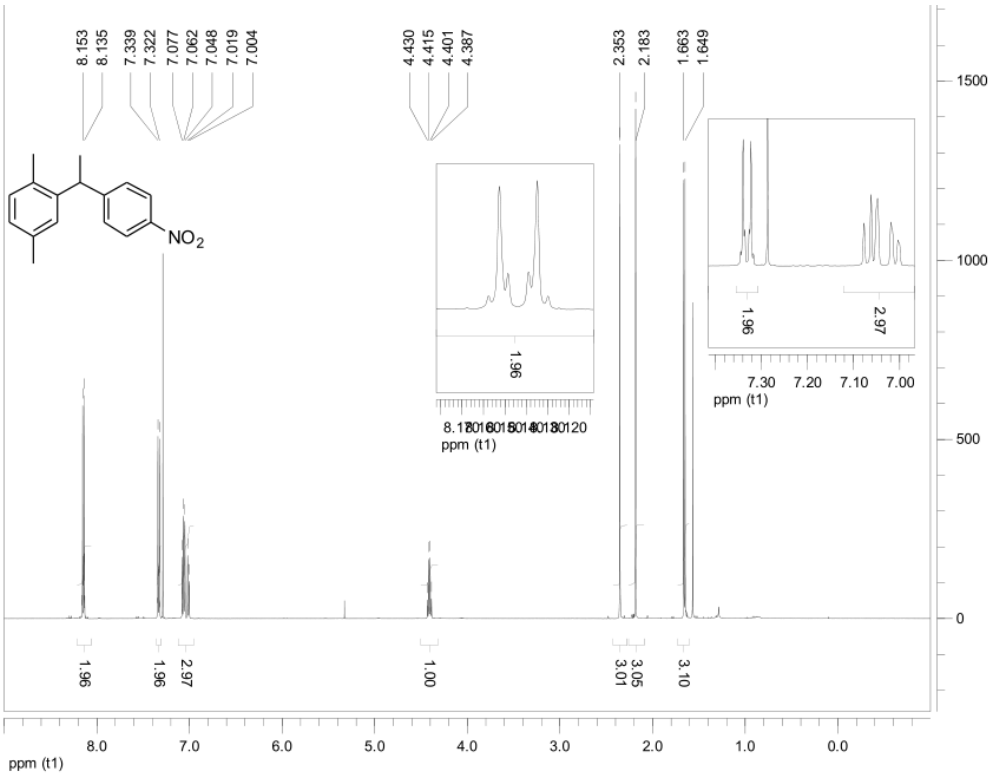
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

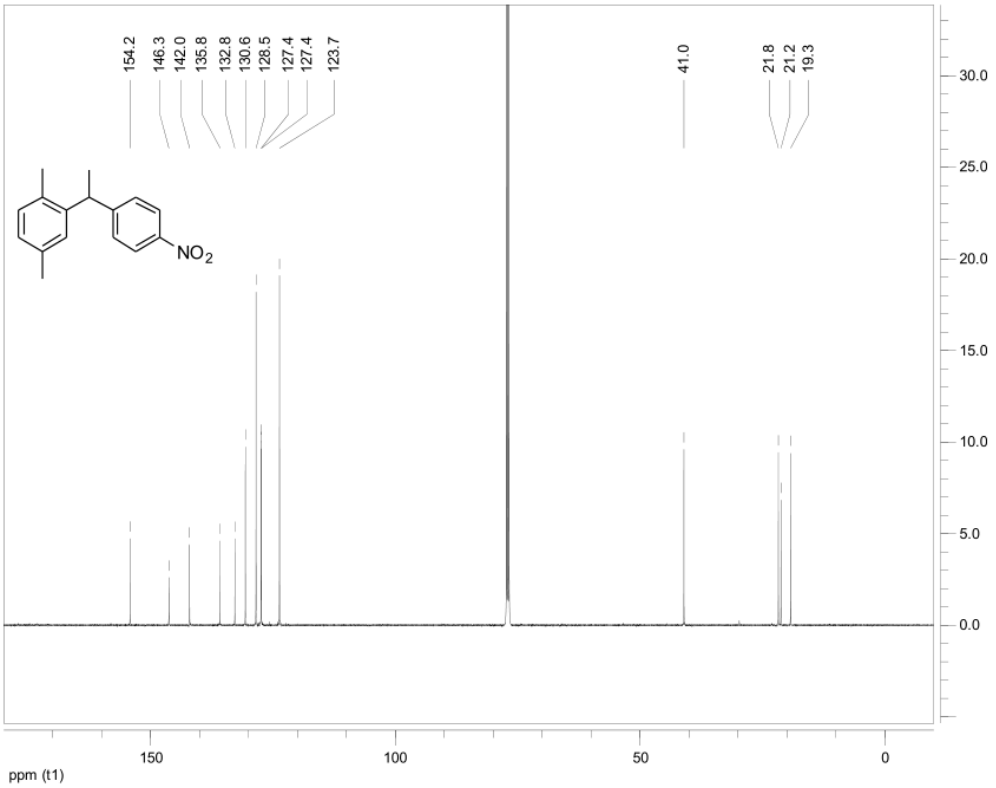




NMR spectroscopic analysis of 1,4-Dimethyl-2-(1-(4-nitrophenyl)ethyl)benzene.

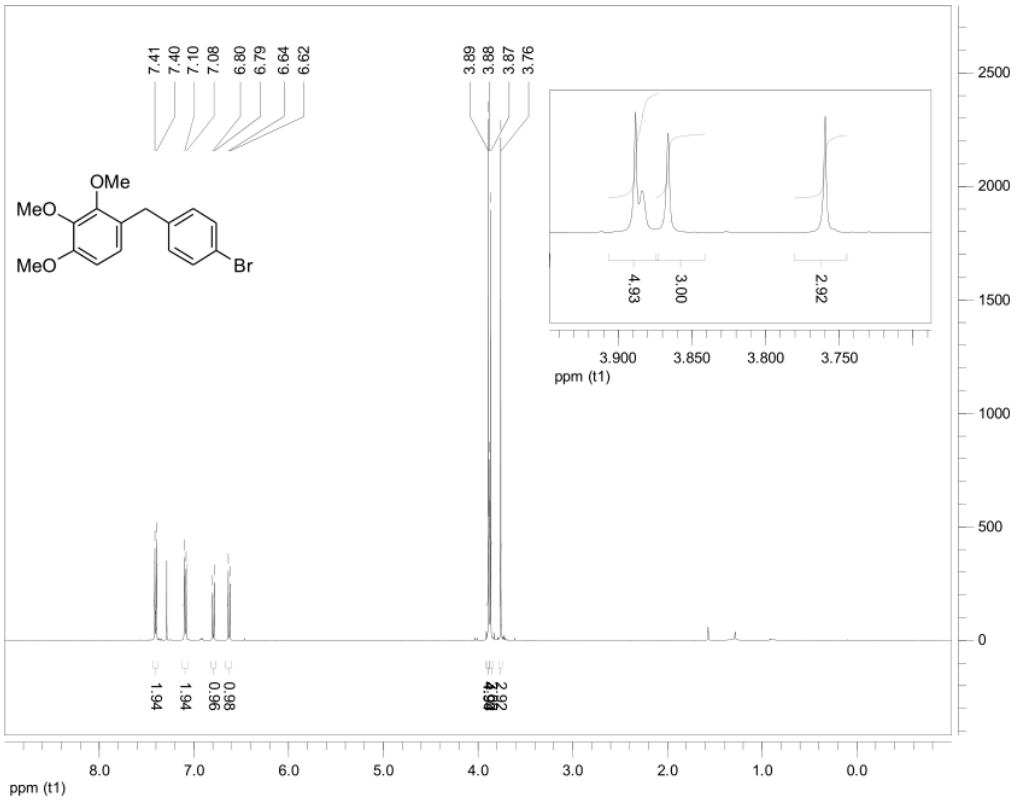
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

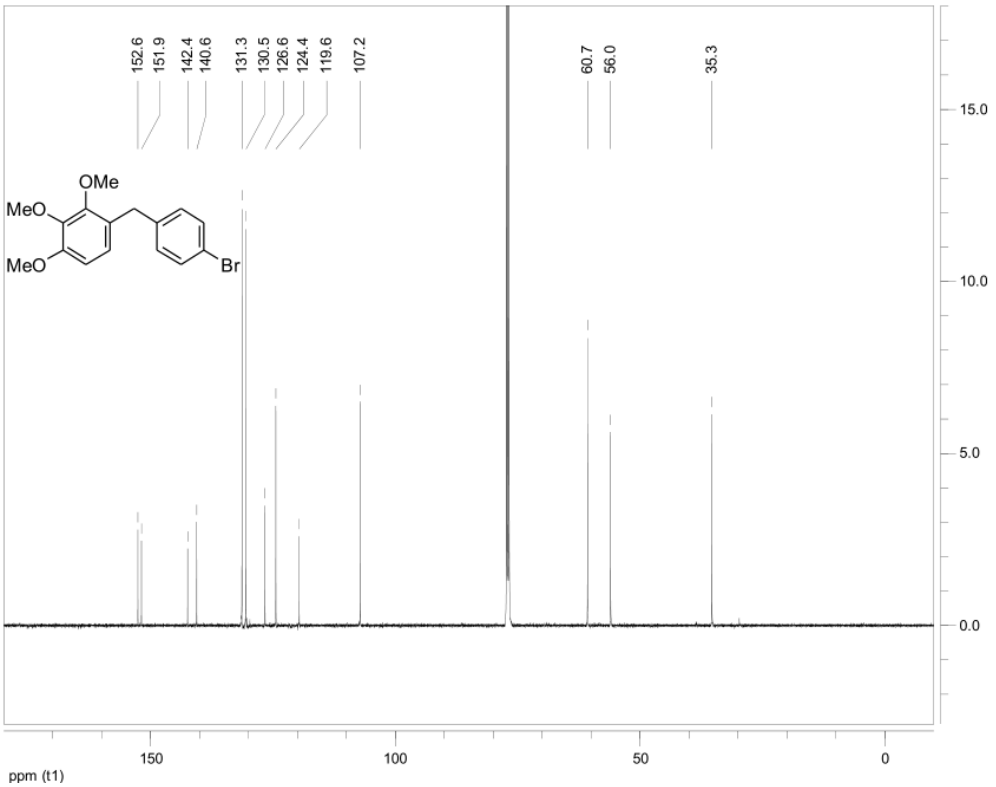




NMR spectroscopic analysis of 1-(4-Bromobenzyl)-2,3,4-trimethoxybenzene.

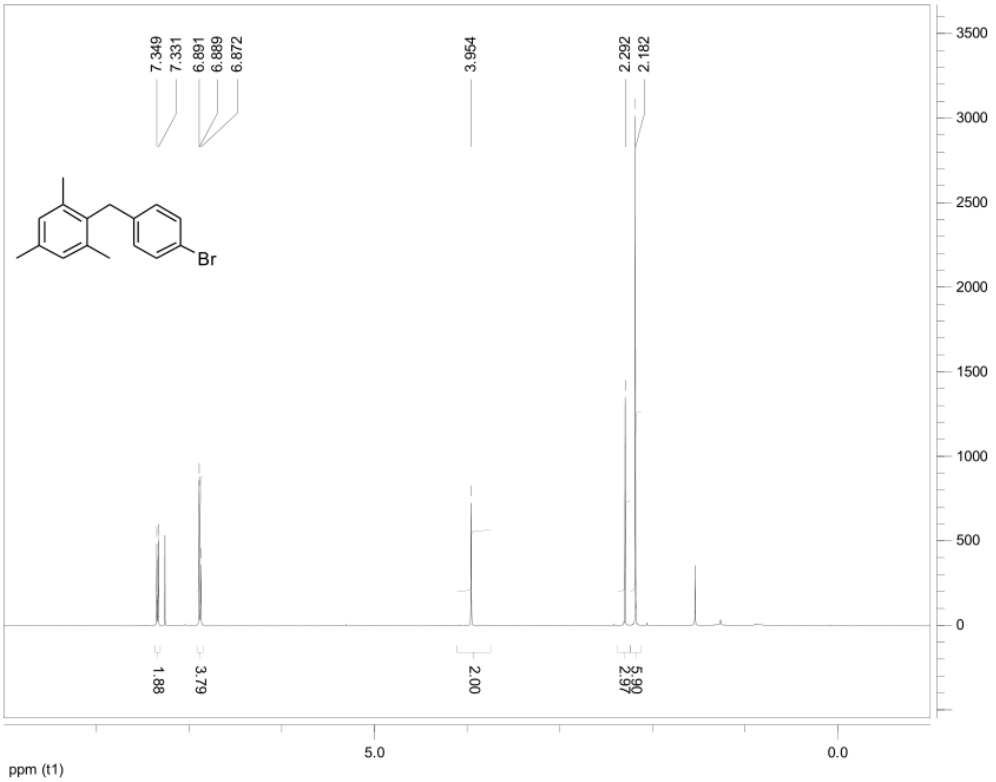
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

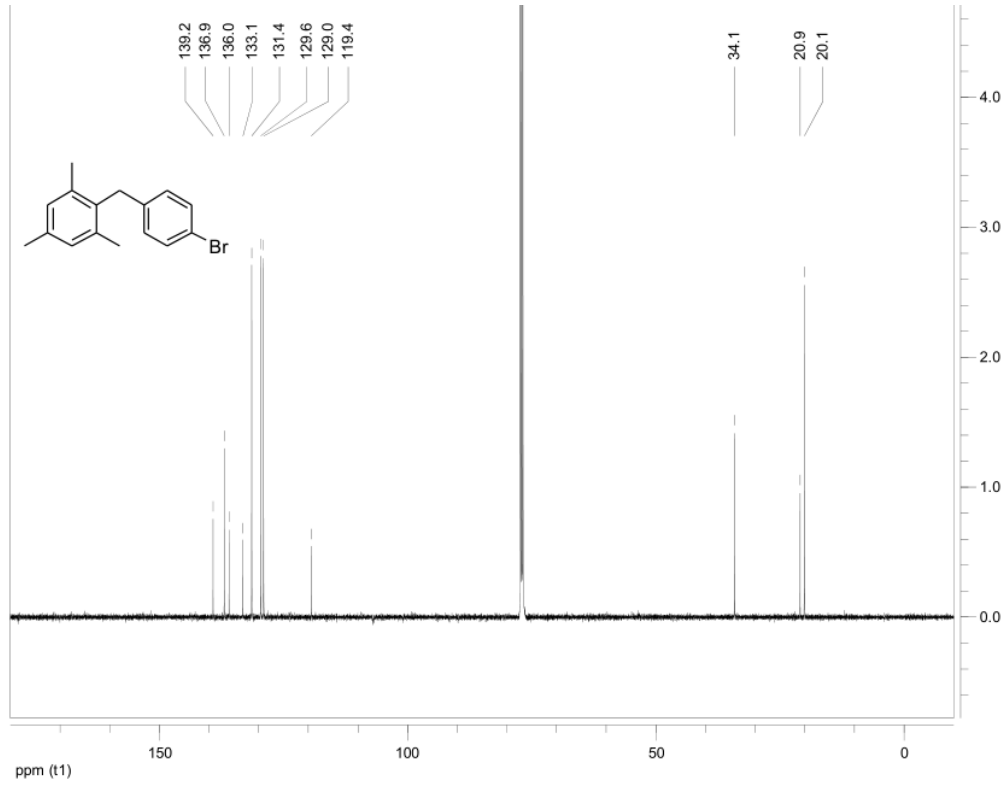




NMR spectroscopic analysis of 2-(4-Bromobenzyl)-1,3,5-trimethylbenzene.

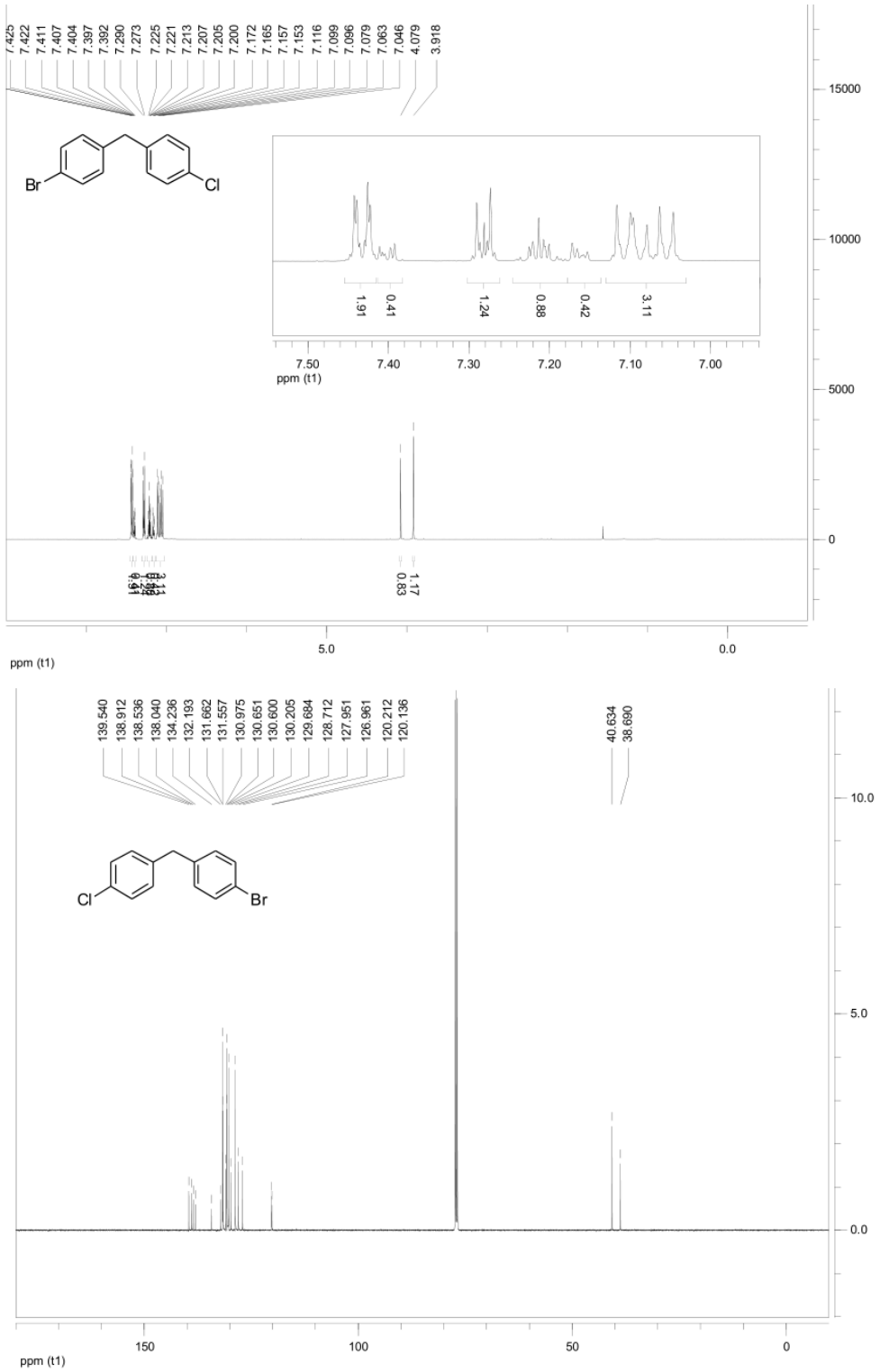
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).





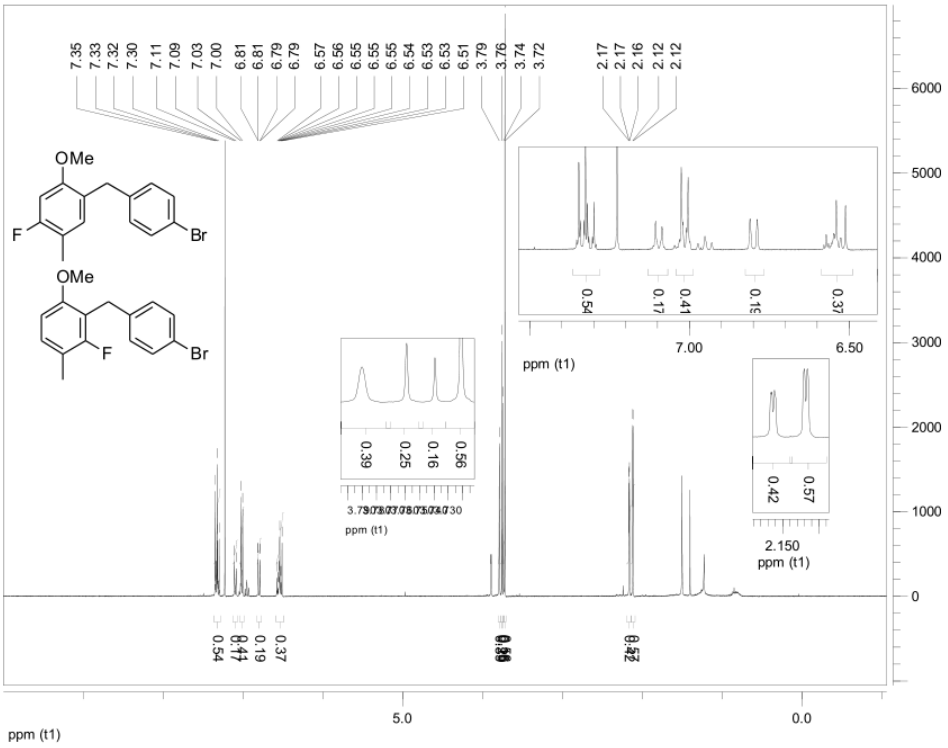
NMR spectroscopic analysis of 1-Bromo-4-(4-chlorobenzyl)benzene and 1-Bromo-4-(2-chlorobenzyl)benzene.

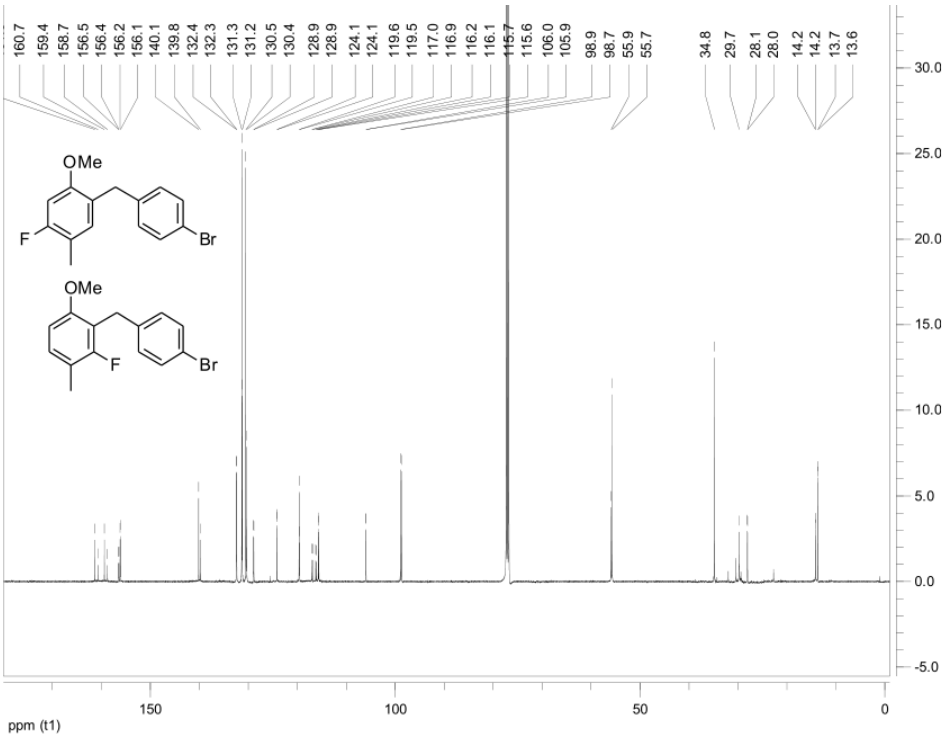
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).



NMR spectroscopic analysis of 1-(4-Bromobenzyl)-4-fluoro-2-methoxy-5-methylbenzene and 1-(4-Bromobenzyl)-6-fluoro-2-methoxy-4-methylbenzene.

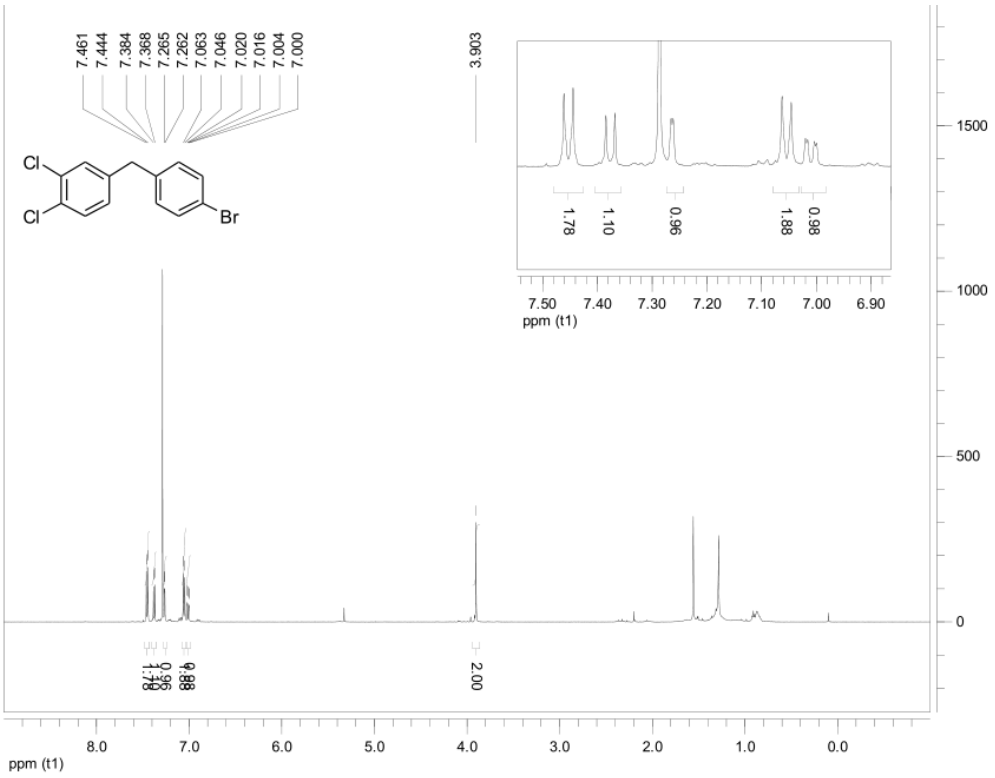
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

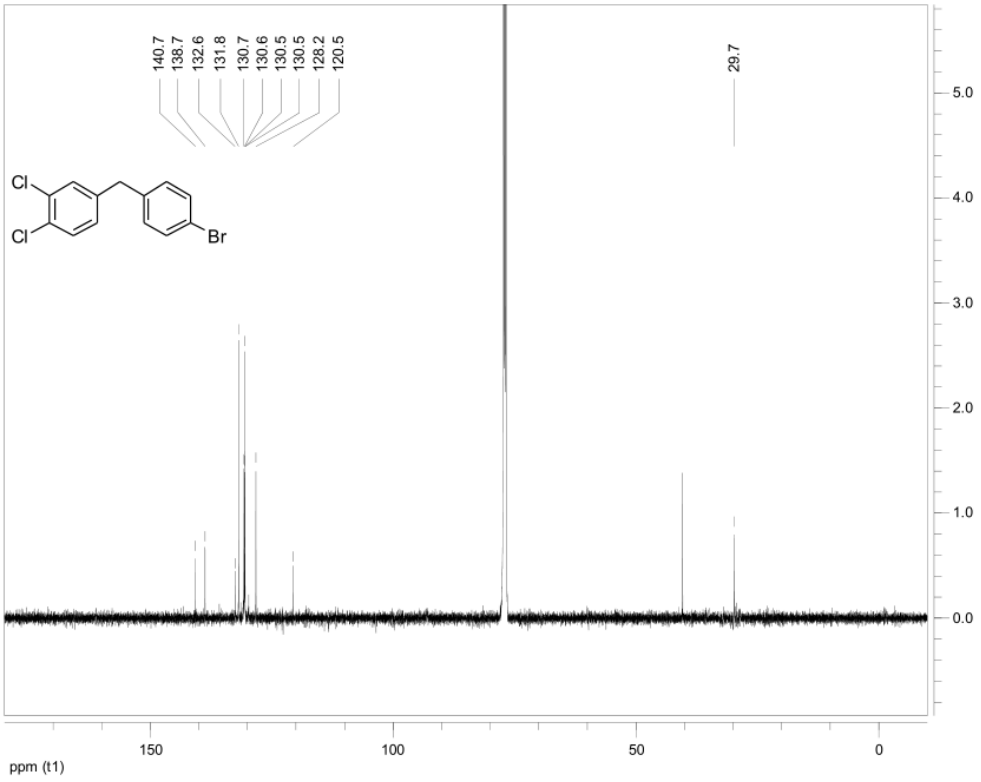




NMR spectroscopic analysis of 4-(4-Bromobenzyl)-1,2-dichlorobenzene.

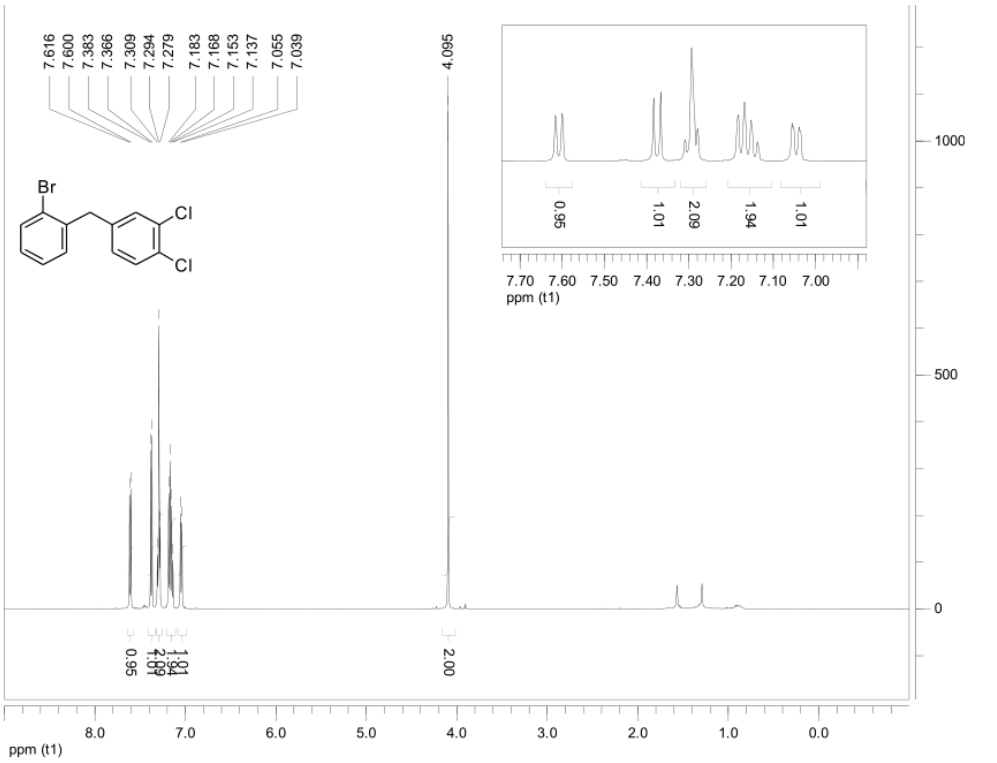
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

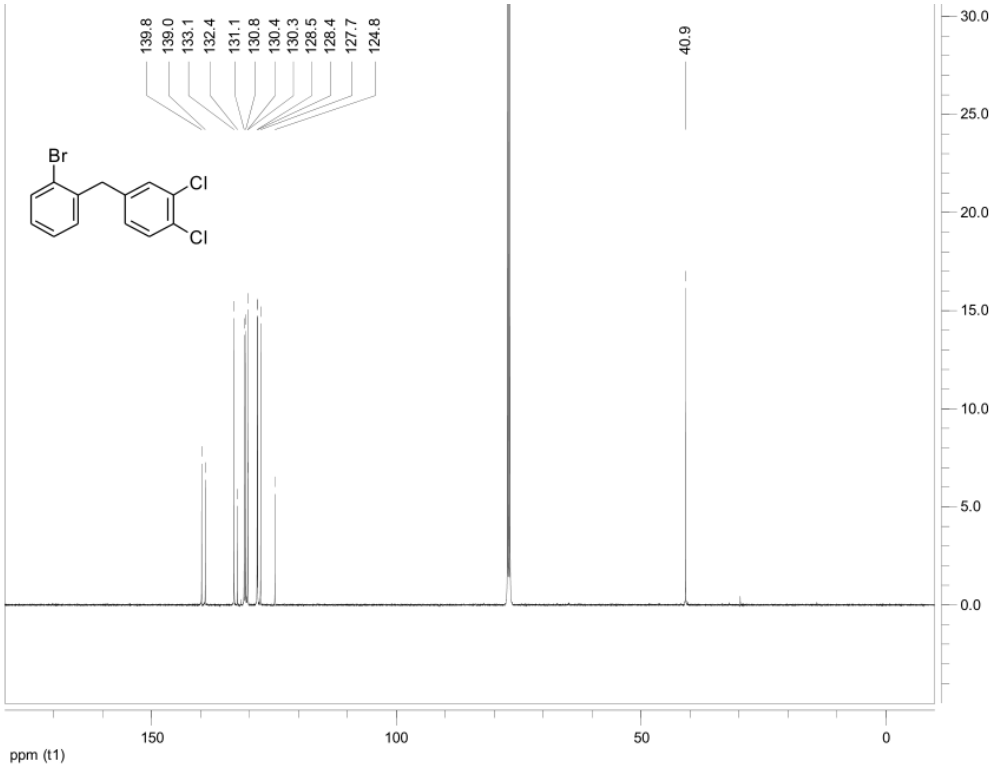




NMR spectroscopic analysis of 4-(2-Bromobenzyl)-1,2-dichlorobenzene.

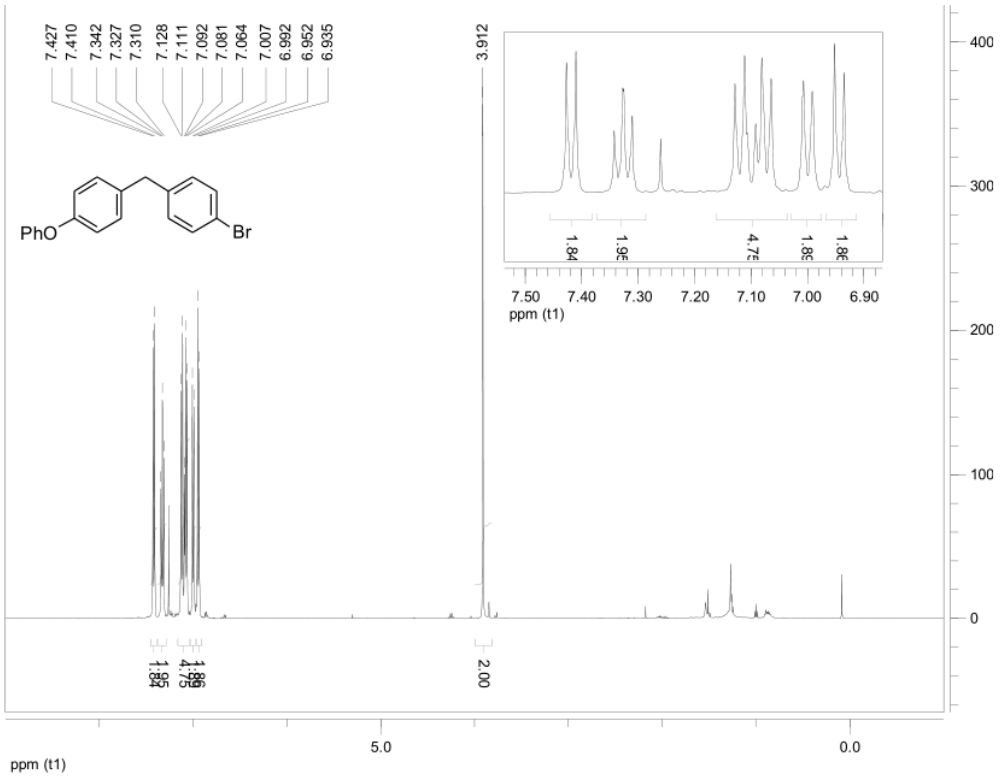
Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).

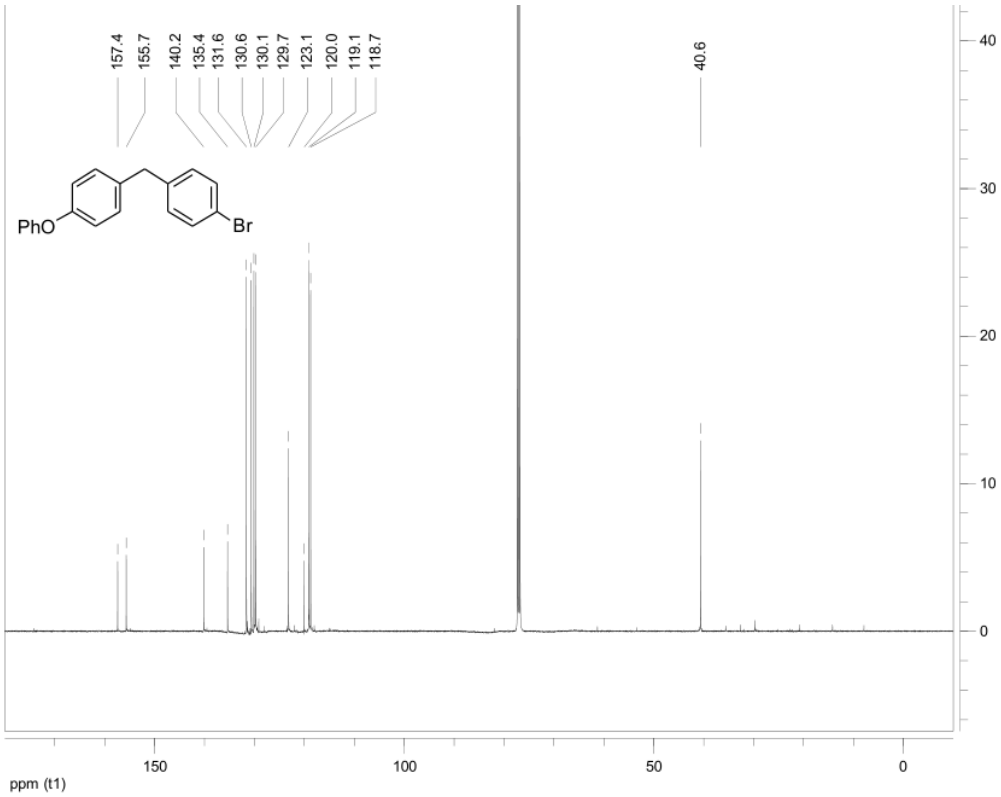




NMR spectroscopic analysis of 1-Bromo-4-(4-phenoxybenzyl)benzene.

Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).





NMR spectroscopic analysis of 1-(4-Bromobenzyl)-2-phenoxybenzene.

Top: ^{1}H NMR spectra ($CDCl_3$, 500 MHz). Bottom: ^{13}C NMR spectra ($CDCl_3$, 125 MHz).