Boron-Mediated Methodologies for Carbon-Oxygen, Carbon-Hydrogen Bond Breaking and Carbon-Nitrogen, Carbon-Carbon Bond Formation

by

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Abstract

Boron Lewis acids are a class of reagent that has been widely studied and utilized in organic chemistry for over sixty years. The popularity of these reagents comes from their diverse reactivity, functional group tolerance, and non-toxic nature. For these reasons, the continued development of chemistries involving boron reagents still receives much attention. This thesis examines the development of new methodologies for the functionalization of organic molecules based on boron reagents.

Chapter 1 briefly describes general methodologies to synthesize azide compounds. Later, the mechanisms of photochemical decomposition of various azides will be discussed.

Borontribromide-mediated dissociation of carbon-oxygen bonds has been extensively used to cleave aryl ethers. However, the regioselectivity is low when applying this method to unsymmetrical dialkyl ethers. The second chapter of this thesis describes the cleavage of unsymmetrical dialkyl ethers employing mixed boron trihalides. The selectivity profile of this new methodology is evaluated on various ether substrates, including benzyl, allyl, and propargyl ethers.

Nitrenes are a high energy, reactive specie generated from thermolysis or photolysis of an azide precursor. Recently, it has been demonstrated that boryl nitrenes can insert into C−H bonds of unreactive substrates such as alkanes. The third chapter describes a one-pot three-step procedure to generate amino alcohols from simple or complex alcohols utilizing a boryl azide precursor. Using mixed boron halides, as described in chapter 2, many dialkoxyboryl chlorides were prepared and subsequently converted to the dialkoxyboryl azide. Chapter 3 describes the investigation of the photochemical decomposition of these azides.

The Suzuki-Miyaura reaction is a versatile and powerful synthetic method to construct C−C bonds using aryl boronic acids. However, the application of this method in modification of biomolecule substrates is limited due to the instability of many biological molecules such as proteins in the presence of bases and high temperature. Chapter 4 will discuss the synthesis of new N-heterocyclic carbenes ligands to facilitate the Suzuki cross-coupling reaction in aqueous media in the absence of bases and elevated temperature.

Preface

The work in Chapter 2 of this thesis has been published as Atienza, B. J. P; **Truong, N.**; Williams, F. J *Org. Lett.*, **2018**, 20 (20), 6332–6335. As co-first author, I was involved in developing the chemistry for every part of this paper, including preparing the ether substrates, repeating the cleavage reaction experiments as well as conducting functional group tolerance test. I also aided in writing and preparing the supporting information.

Acknowledgements

First and foremost, I would like to extend my gratitude to my supervisor, Professor Florence Williams for her guidance, training, and education during the time I was in her group. I have learned a lot of theoretical knowledge and practical skills in organic chemistry from her.

I also thank all of the other members of Williams lab past and present for their invaluable discussions and suggestions during my research, and, more importantly, the good times we have shared together.

I would also like to extend thanks to my Supervisory and Master's Examination Committee: Prof. Steven Bergens, Prof. Todd Lowary and Prof. Rylan Lundgren for their valuable feedback throughout my research studies at the Department of Chemistry, University of Alberta.

Last but definitely not least, I am grateful for my wife, Lan Anh, for her love, support, and encouragement; my graduate school life would have been much more difficult without you.

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List of Symbols and Abbreviations

ºC	Degrees Centigrade or degrees Celcius
Δ	Heat
Ac	Acetyl
All	Allyl
Aq	Aqueous
Ar	Arene (represents a general arene moiety)
Bn	Benzyl
Boc	Tert-butoxycarbonyl
Calcd	Calculated
DCC	N, N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMEU	Dimethylethyleneurea
DMF	Dimethylformamide
DMPU	N, N′-Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPA	Diphenylphosphoryl azide

ee	Enantiomeric excess
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	Electron Ionization
ESI	Electrospray Ionization
Et	Ethyl
Equiv.	Equivalent
FDA	Food and Drug Administration
Fmoc	Fluorenylmethyloxycarbonyl
Hex	Hexane (mixture of isomers)
HIV	Human immunodeficiency viruses
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilaside
Me	Methyl
MHz	Megahertz
mL	Millilitre(s)
mmol	Millimole
MS	Mass Spectrometry
NHS	N-Hydroxysuccinimide
NMR	Nuclear Magnetic Resonance
PMHS	Polymethylhydrosiloxane
OAc	Acetate

OEt	Ethoxy
OMe	Methoxy
Pd	Palladium
Ph	Phenyl
PNB	para-Nitrobenzoate
***i*Pr**	Isopropyl
R	Generalized alkyl group of substituent
rt	Room temperature
***t*-Bu**	Tert-butyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	Tosyl
wkp	Workup

Chapter 1: Introduction to Nitrenes and Theirs Properties under Photochemical Conditions

Overview of Chapters 1-3

A main goal of this thesis is to develop a one-pot process to install nitrogen into organic molecules via boryl azides. The first chapter discusses known approaches to installing azides and their photochemical decomposition pathways, including decomposition to nitrene intermediates. Chapter two describes a method to access boryl chlorides via the cleavage of unsymmetrical dialkyl ethers. These boryl chlorides are an important intermediate necessary to access to boryl azides. Finally, chapter three outlines the the transformation of boryl chlorides to boryl azides and the investigation of their photochemical decomposition, which results in the amination of alkyl chains.

1.1 Introduction

Organic molecules can be viewed as carbon-hydrogen frameworks decorated with heteroatoms such as nitrogen, oxygen, halogens, sulfur, and phosphorus. From this list, nitrogen-containing fragments are particularly important as they are found in DNA, proteins, and metal porphyrins, which possess fundamental roles in living system.[1] Moreover, among U.S FDA approved pharmaceuticals in 2012, 84% of drugs contain at least one nitrogen atom, whereas those containing at least one nitrogen heterocycle represent 59%.[2] Due to the paramount importance of nitrogen in biologically active organic compounds, the development of new C–N bond forming reactions remains a highly investigated area in both academia and industry (**Figure 1-1**),[3,4,5] particularly for late stage incorporation. Recently, the use of nitrene precursors to introduce nitrogen containing functionality into an organic framework has received much attention.

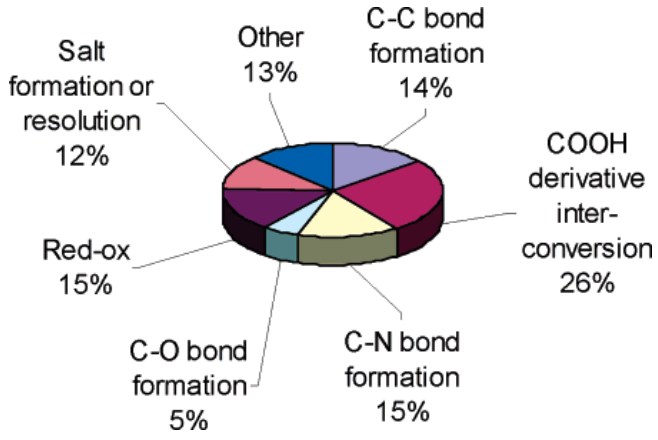


Figure 1-1: Distribution of reaction conducted at Pfizer from 1985 to 2002

Nitrenes are species containing neutral, monovalent nitrogen atoms. Nitrenes exist in two forms: either a singlet or a triplet state, which can be interconverted through intersystem crossing. A singlet nitrene has its electrons arranged as two lone pairs, leaving one empty p orbital. The electrons of a triplet state are divided across three orbitals, one filled and two half-filled. Since nitrenes have an incomplete octet, they typically exhibit short lifetimes and high reactivity toward a variety of organic substrates.[6]

Traditional approaches for nitrogen introduction such as reductive carbonyl amination or imine alkylation often require protecting groups to avoid side reactions.[7] Many modern methods have been developed such as Buchwald-Hartwig coupling, allylic amination, and hydroamination of alkenes.[7] However, these methods require specific functionality in order to introduce nitrogen atom. The use of a reactive high-energy nitrene species can allow nitrogen incorporation across unactivated C–H bonds rather than requiring a more reactive functional group in the substrate of interest, and hence many advances have been made in this area.[7]

1.2 The Preparation of Azide Precursors

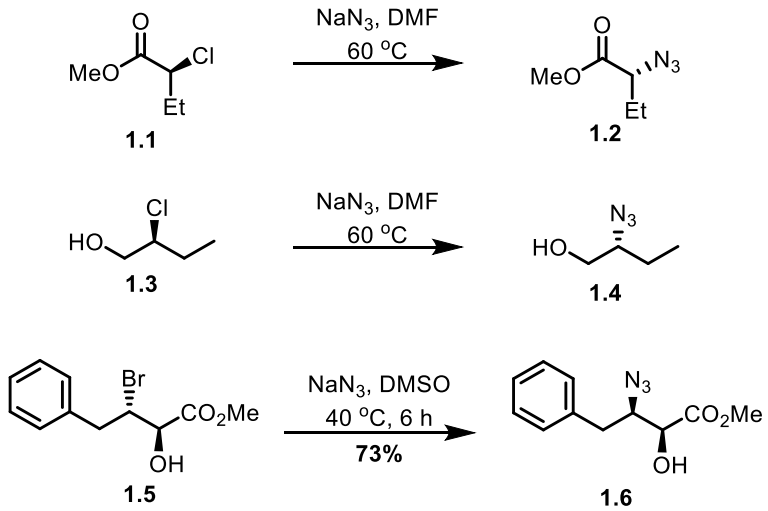
The first organic azide investigated was the preparation of phenyl azide in 1864, reported by Peter Griess.[8] This chemistry was further developed by the discovery of hydrogen azide, and

azides became more highly used after the discovery of the Curtius rearrangement of acyl azides to yield isocyanates in 1890.[9] Since 1950, these compounds have been receiving considerable attention, as they can be used as precursors for nitrogen-rich compounds such as azirines, aziridines, triazolines, and triazoles. The development of "Click Chemistry" using a Huisgen cycloaddition with azide compounds resulted in a dramatic increase in the use of organic azides.[10,11,12] Hence, numerous synthetic approaches for the synthesis of organic azides have been developed focusing on alkyl, aryl, and acyl azides. These methods will be outlined in the following sections.

1.2.1 The Synthesis of Alkyl Azides

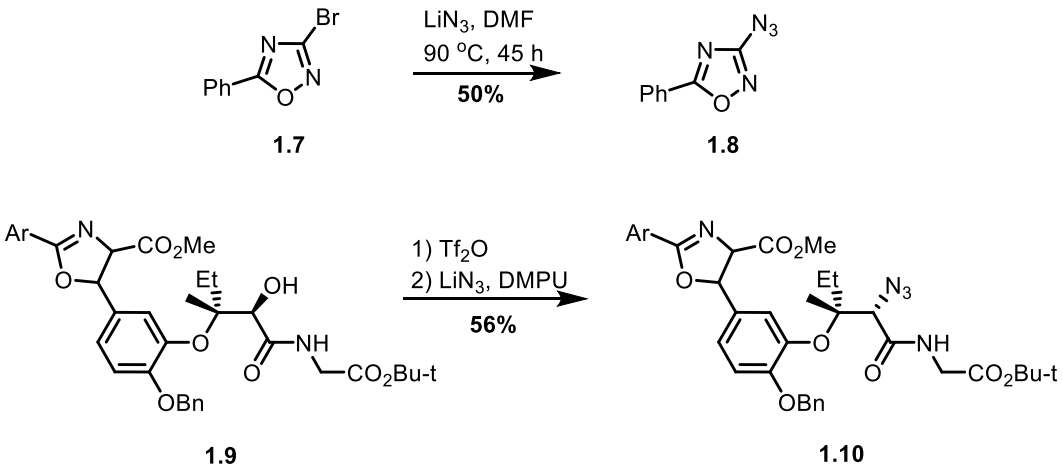
1.2.1.1 Azide Formation via Nucleophilic Substitutions

Among the most common strategies to prepare alkyl azides, a conventional halide displacement is often the method of choice. Sodium azide has sufficient nucleophilicity for nucleophilic displacement, and low Brönsted basicity, minimizing undesired elimination reactions (**Scheme 1-1**).[13,14]



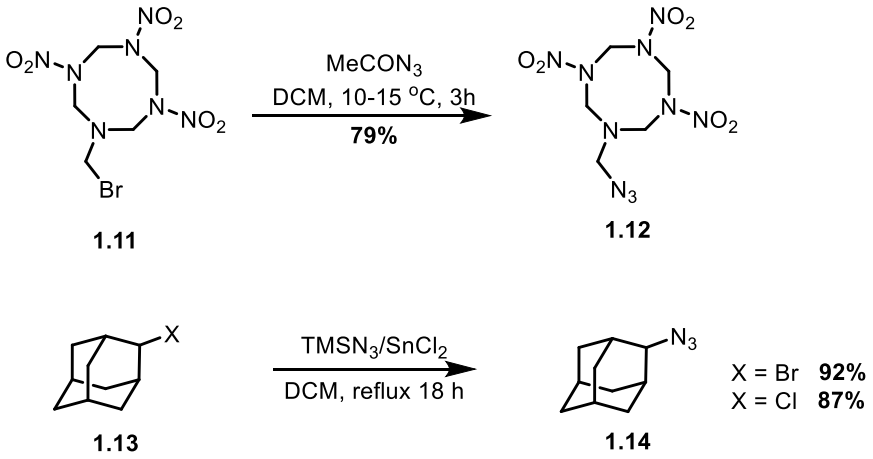
Scheme 1-1: Synthesis of alkyl azides from halides-employed sodium azide[15,16]

Generally, nucleophilic displacement with alkali metal azide to synthesize alkyl azides is carried out in polar solvents such as DMSO or DMF to solubilize the azide salts. Even though good yields can be generally achieved in such solvents, difficulties sometimes arise related to alkyl azide isolation as well as incomplete azide salt solubility. In this regard, lithium azide, which has higher solubility in these solvents, is employed to enhance the reaction rate and efficiency (**Scheme 1-2**).[13]



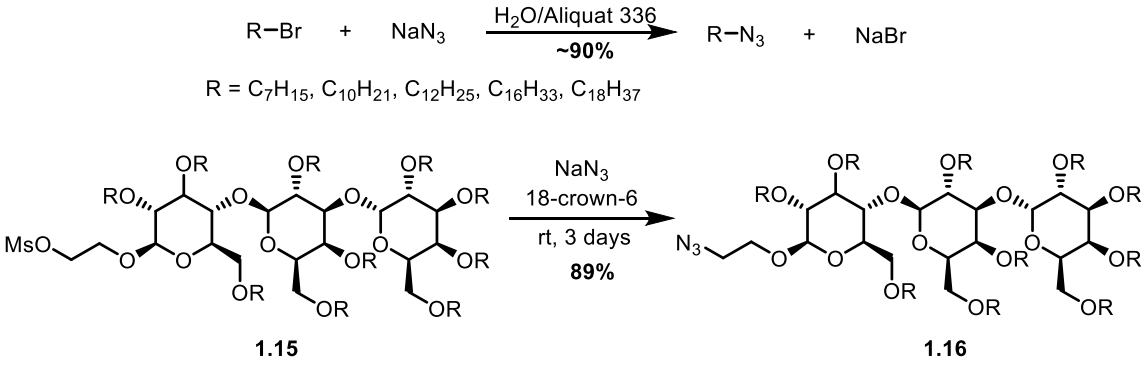
Scheme 1-2: Synthesis of alkyl azides from halides-employed lithium azide[17,18]

Besides lithium azide, other azide sources such as acetyl azide or trimethylsilyl azide can be used as an alternate azide source. These organic azide transfer agents are soluble in organic solvent, and also permit synthesis under non-basic conditions.[19,20] Activated primary alkyl halides (e.g. benzyl halides, allyl bromide, chloroacetonitrile) typically react with trimethylsilyl azide ($TMSN_3$) to give alkyl azides in good yield.[13,21] Meanwhile, cyclic secondary and tertiary substrates react with $TMSN_3$ in the presence of stannic chloride.[20]



Scheme 1-3: Synthesis of alkyl azides using different azide sources[19,20]

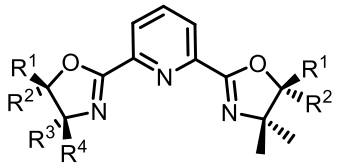
Another widely used approach is to use a phase transfer catalyst. The main advantage of a phase transfer catalyst is to expand the range of usable solvents.[22-24] Various alkyl bromides which are not normally reactive in aqueous environments due to poor solubility were converted to the corresponding alkyl azides in high yields in the presence of Aliquat 336 (**Scheme 1-4**).[25] Recently, crown ethers (e.g. 18-crown-6 ether) were utilized in the synthesis of azide substituted glycosides by mesylate displacement with sodium azide (**Scheme 1-4**).[26]



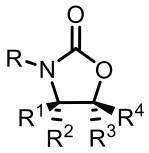
Scheme 1-4: Synthesis of alkyl azides employing phase transfer catalyst

1.2.1.2 Azide Formation via Ring Opening of Epoxides and Aziridines

Another route to access to azide compounds is the ring opening of epoxides or aziridines (**Scheme 1-5**). Interestingly, the azide products of this transformation, β-azido alcohols and β-azido amines, are valuable intermediates for further functionalization. These intermediates can be converted easily to β-amino alcohols and 1,2-diamines, respectively. β-amino alcohol moieties presented widely in β-adrenergic blockers are used in the treatment of cardiovascular disorders,[27] hypertension,[28] and other disorders.[29,30] They are also the intermediates for the synthesis of novel anti-HIV agents,[31] protein kinase C inhibitor balanol,[32] liposidomycin B class of antibiotics[33] or unnatural amino acids.[34,35] In asymmetric synthesis, β-amino alcohol derivatives are used as chiral ligands and chiral auxiliaries[36,37] such as Pyridine-2,6-bis(oxazolines) (PYBOX)[38] or Evans' Oxazolidinone (**Figure 1-1**).[39,40]



Pyridine-2,6-bis(oxazolines)



Evans' Oxazolidinone

Figure 1-2: β-amino alcohol-containing chiral ligands and auxiliaries

Meanwhile, the 1,2-diamine unit can be found in nature in the structure of vitamin H (or biotin), penicillins or cephalosporins (**Figure 1-2**). In organic synthesis, compounds equipped with 1,2-diamino functionality are valuable synthetic intermediates for the synthesis of nitrogen-containing macrocycles,[41-43] heterocycles[44] or chiral ligands.[45,46]

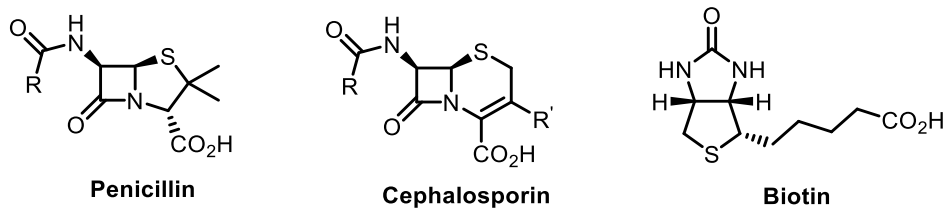
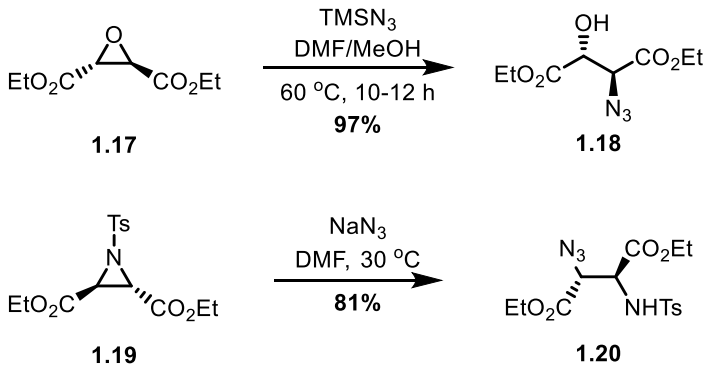


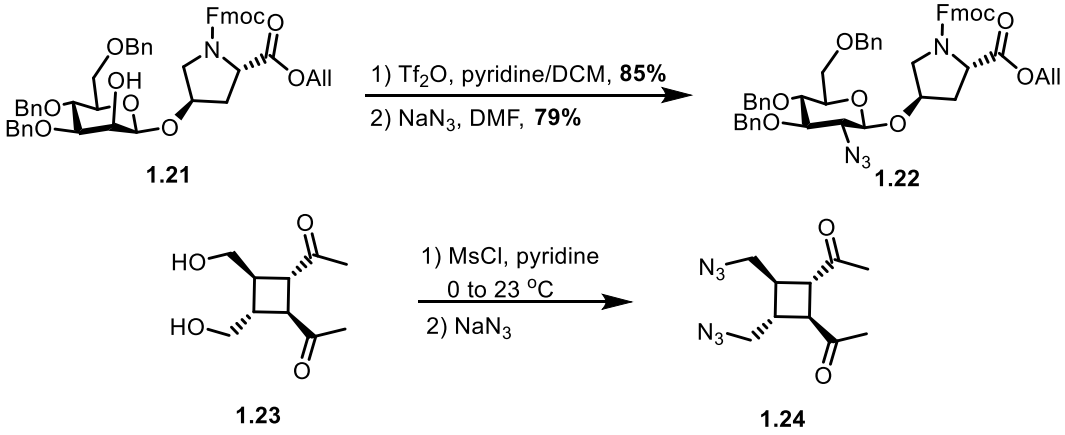
Figure 1-3: 1,2-diamino moieties in nature



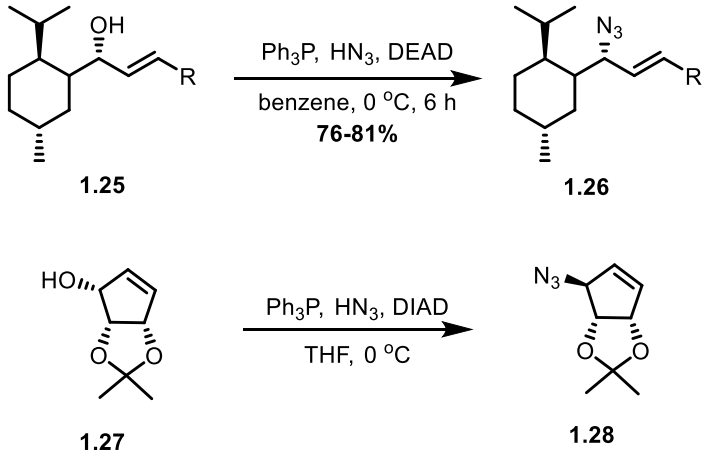
Scheme 1-5: The synthesis of azides by ring opening of epoxides and aziridines[47,48]

1.2.1.3 Azide Formation from Alcohols

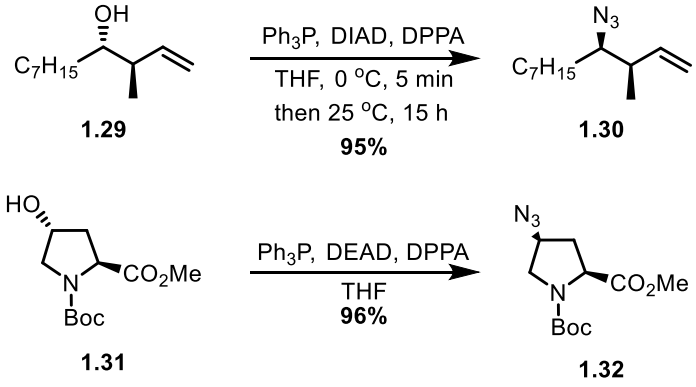
Alcohols can be converted to azides in a two-step process involving the activation of a hydroxyl group and subsequent azide substitution. This is generally achieved by the conversion of an alcohol to a sulfonate followed by the addition of an azide ion (**Scheme 1-6**).[49,50] A more direct route to access azides from alcohols is to employ the Mitsunobu reaction. In these reactions, primary and secondary alcohols are treated with hydrogen azide in the presence of triphenylphosphane and diethyl azodicarboxylate (DEAD)[51] or diisopropyl azodicarboxylate (DIAD)[52] to give the corresponding azides with inversed configuration (**Scheme 1-7**). Recently, a safer azide source, diphenylphosphoryl azide (DPPA), has been utilized to replace the explosive and dangerous reagent hydrogen azide (**Scheme 1-8**).[53,54]



Scheme 1-6: Indirect pathway to azides from alcohols



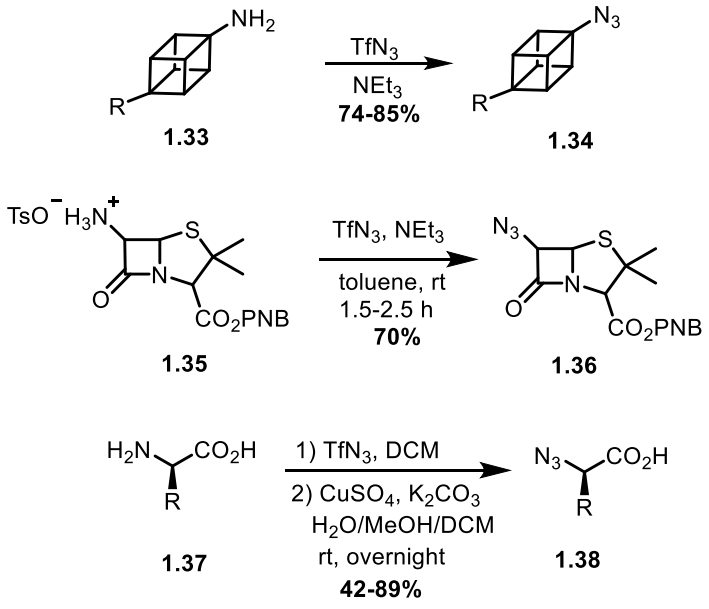
Scheme 1-7: The synthesis of azides via Mitsunobu reaction



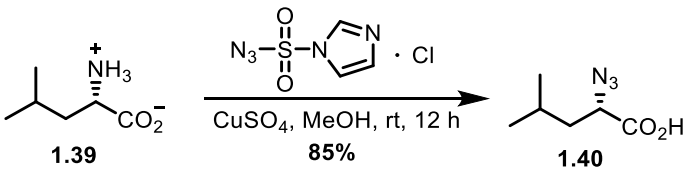
Scheme 1-8: Direct synthesis to azides from alcohols employing DPPA

1.2.1.4 Azide Formation from Amines

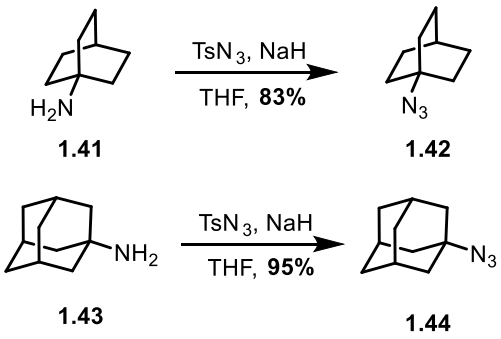
The introduction of N_3 to a carbon skeleton can also be achieved by employing an existing amine in the substrate. When an aliphatic amine is treated with trifluoromethanesulfonyl azide (Triflyl azide, TfN_3), the amine functional group is transformed into an azide group via the diazo transfer reaction (**Scheme 1-9**).[55-58] Due to the potential explosive nature and instability of neat triflic azide, its formation is usually formed in-situ prior to the addition of amine. The crystalline, shelf-stable imidazole-1-sulfonyl azide hydrochloride has been recently used as an alternative for the conversion of primary alkyl and aryl amines into azides (**Scheme 1-10**).[59] An alternative route to obtain alkyl azides from amines is to react amine substrates with toluenesulfonyl azide (TsN_3 and sodium hydride) (**Scheme 1-11**).[60,61]



Scheme 1-9: The synthesis azides via diazo transfer reaction utilizing triflyl azide



Scheme 1-10: The synthesis of azides via diazo transfer reaction employing imidazole-1-sulfonyl azide hydrochloride

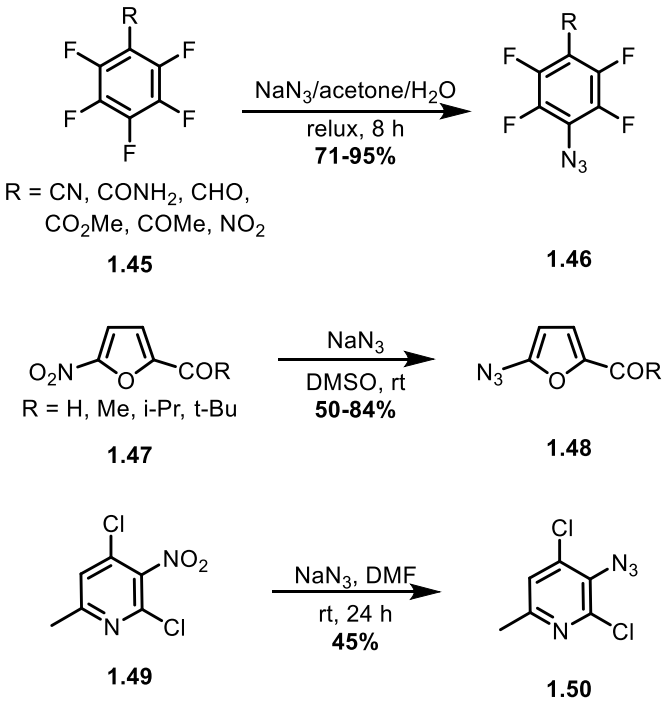


Scheme 1-11: The synthesis of azides via diazo transfer reaction using tosyl azide

1.2.2 The Synthesis of Aryl Azides

1.2.2.1 Azide Formation via Nucleophilic Substitutions

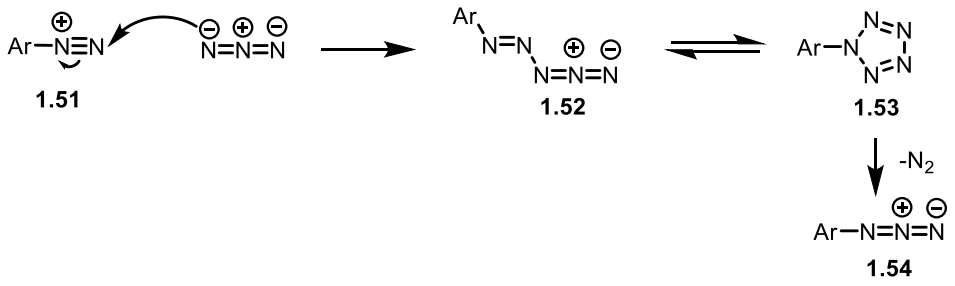
Nucleophilic substitution with azides is also a useful synthetic route to prepare aryl azides. The S_NAr is effective only in electron poor aromatic systems, particularly those containing electron withdrawing groups in ortho and/or para positions relative to the leaving group (**Scheme 1-12**).[62] The replacement of a leaving group in activated substrates also works well for heteroaryl compounds (**Scheme 1-12**).[63,64]



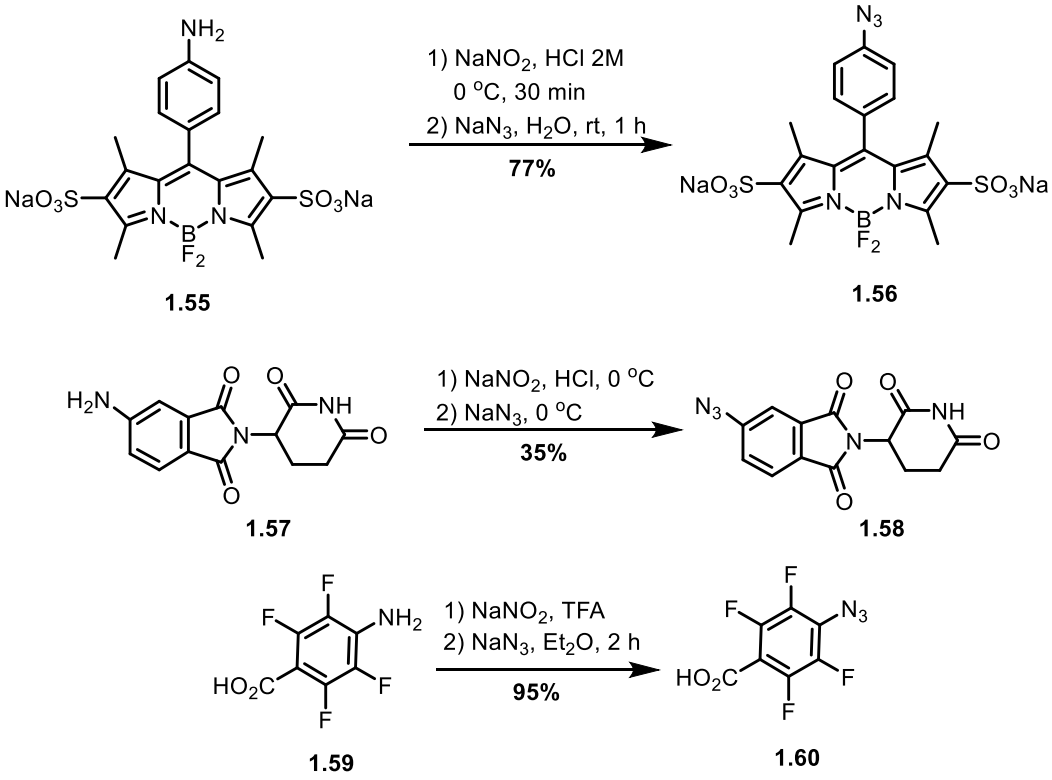
Scheme 1-12: The synthesis of azides via nucleophilic aromatic substitution reaction

1.2.2.2 Azide Formation via Diazonium Intermediates

The conversion of aromatic and heteroaromatic amines to diazonium compounds followed by the addition of sodium azide has been frequently employed for the synthesis of aryl azides (**Scheme 1-14**). The mechanism of this reaction does not involve the displacement of a diazonium group with azide ion by nucleophilic substitution. Instead, there is an addition reaction between **1.51** with azide ion to form an open pentazene **1.52** or a cyclic pentazole **1.53** followed by the decomposition of this intermediate to give aryl azide **1.54** (**Scheme 1-13**).[65]



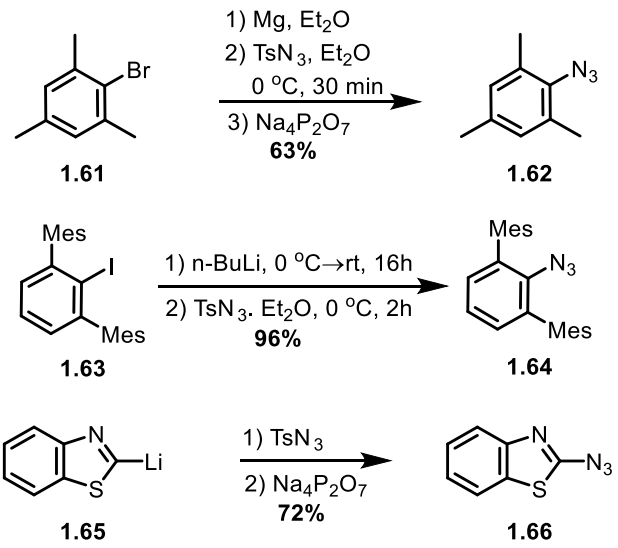
Scheme 1-13: Mechanism of azide formation via diazonium intermediates



Scheme 1-14: The synthesis of azides via diazonium intermediates[66-68]

1.2.2.3 Azides Formation from Organometallic Reagents

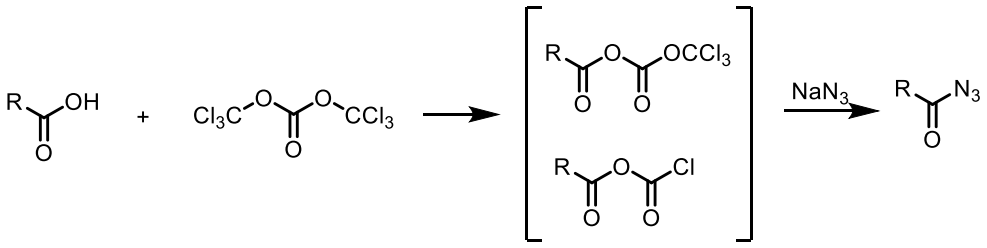
An indirect route to introduce azides into electron rich aromatic rings, or into aromatic substrates with functional groups not otherwise tolerated is to convert aryl halides to a Grignard or lithium reagent followed by reaction with tosyl azide.



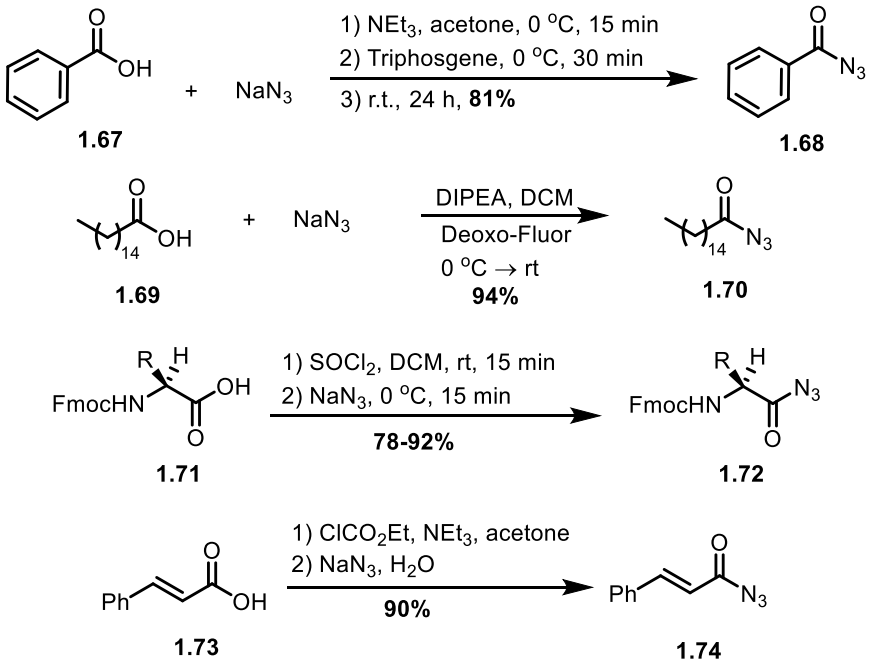
Scheme 1-15: The synthesis of azides from organometallic reagents[69-71]

1.2.3 The Synthesis of Acyl Azides

Acyl azides can be obtained in a one pot procedure by treating a carboxylic acid with sodium azide and triphosgene (**Scheme 1-17**).[72] Triphosgene is known to generate acid chlorides or anhydrides upon reaction with acid carboxylics.[73] These intermediates are formed in-situ and quickly convert to azide products upon the addition of azide sources (**Scheme 1-16**). Instead of triphosgene, Deoxo-fluor can be used to activate acid functionality. Deoxo-fluor is a fluorination agent which convert carboxylic acids to acid fluorides before nucleophilic substitution of the azide ion.[74,75] An alternative strategy is to convert the carboxylic acid to an acid chloride with thionyl chloride before adding sodium azide to afford the final acyl azide (**Scheme 1-17**).[76] Similar results are observed when carboxylic acids are transformed to anhydrides by ethyl chloroformate (**Scheme 1-17**).[77]



Scheme 1-16: The activation of carboxylic acids by triphosgene



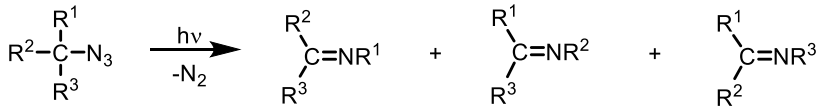
Scheme 1-17: The synthesis of azides from carboxylic acids

1.3 Photochemistry of Azides – The Formation of Nitrenes

1.3.1 Photochemistry of Alkyl Azides

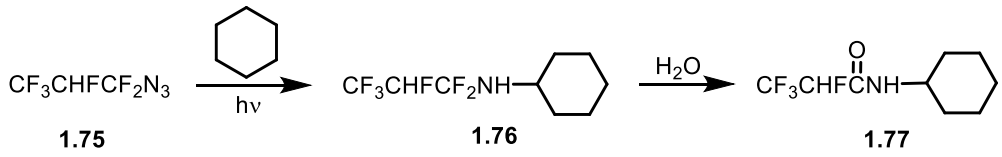
Generally, the photodecomposition of alkyl azides at room temperature leads to imines as the major product via a rearrangement which avoids the production of alkyl nitrenes (**Scheme 1-18**).[78-81] The imine products arise from the migration of hydrogen, an alkyl or aryl group to the nitrogen center. Nitrogen gas is released in the process.[79] Hydrogen atoms and aryl

groups migrate more readily than an n-alkyl group.[79] For phenyl methyl azide, the phenyl/hydrogen migration ratio is equal.[79]



Scheme 1-18: The rearrangement of alkyl azides under photolysis

There are few exceptions in which the photolysis of alkyl azides results in products other than imines. Highly fluorinated azide **1.75** underwent light induced decomposition in cyclohexane to give amide **1.77** in 18% yield after workup. This observation indicated a relatively long lifetime for this type of nitrene in order to allow for an intermolecular C-H insertion process.[82]

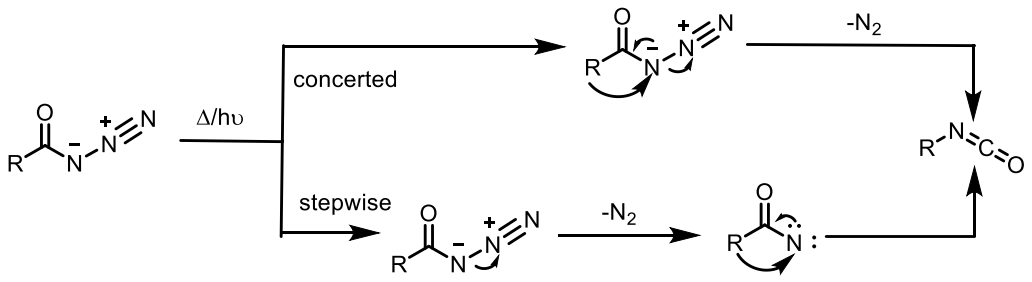


Scheme 1-19: Photodecomposition of fluorinated azide

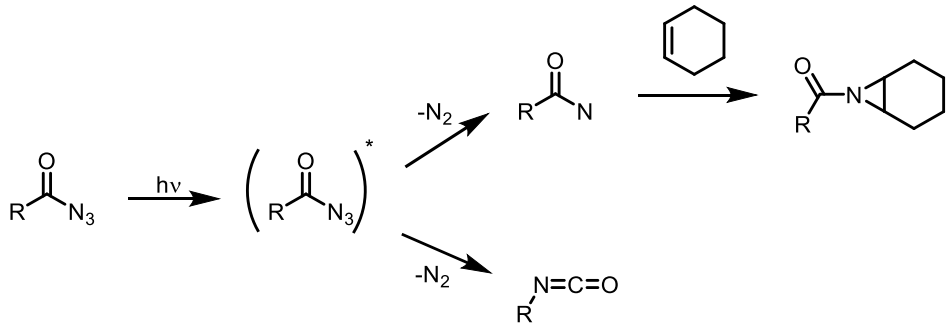
1.3.2 Photochemistry of Acyl Azides

The rearrangement of carbonyl azides under conditions to furnish isocyanates has been well studied over the years and is known as a Curtius rearrangement.[83,84] Thermally, acyl azides reliably produce isocyanates through a concerted process (**Scheme 1-20**).[81,85,86] In contrast, the mechanism of light-induced Curtius rearrangement is still a controversial topic. Early reports successfully trapped a nitrene intermediate upon photolysis-induced decomposition of carbonyl azide.[86-88] These results indicate that the photochemical Curtius rearrangement

is stepwise. However, whether the isocyanate is generated from singlet or triplet nitrene or not, is still a debate.[89]



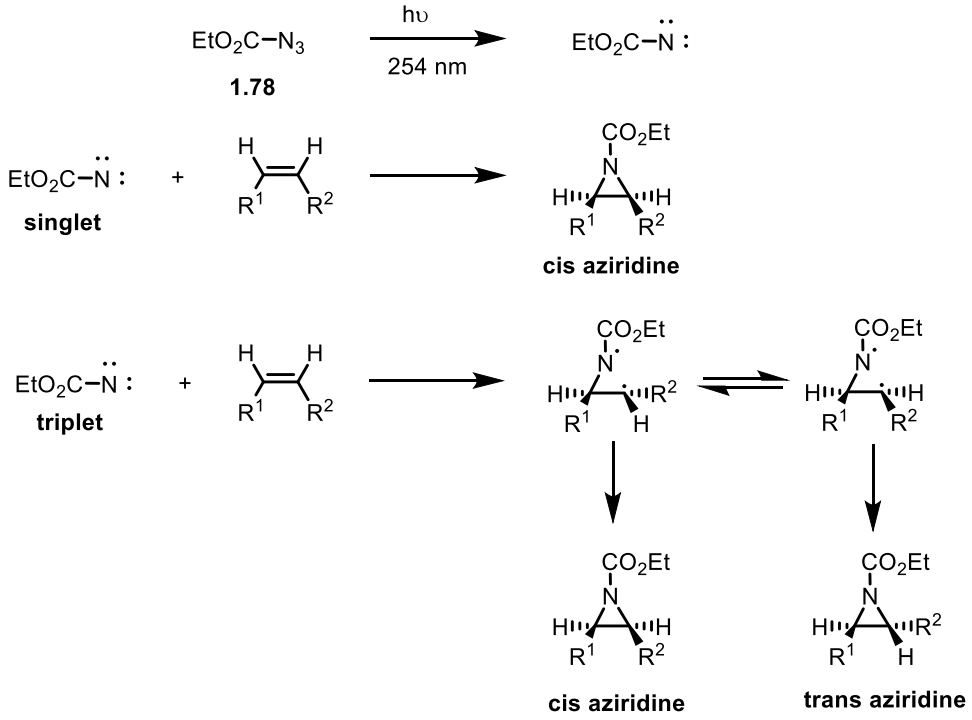
Scheme 1-20: Two known mechanisms of Curtius rearrangement



Scheme 1-21: Photodecomposition of carbonyl azide

In contrast to carbonyl azide, azidoformates (RO-CO-N_3) do not give rise to the formation of isocyanates and instead generate acyl nitrenes that are readily trapped by nitrene trapping agents upon irradiation.[90-93] For example, irradiation of carbethoxy azide **1.78** in the presence of different alkenes leads to the generation of various aziridines.[93,94] Aziridinations offer a hint at the singlet/triplet character of the intermediate nitrene. In the case of a reactive singlet nitrene, the stereochemistry (cis versus trans) of aziridination is determined by the stereochemistry of the starting alkene; however, complete stereospecificity is typically lost in the case of reactive triplet nitrenes.[93] This can be explained by the formation of a diradical intermediate being generated after the initial addition of the triplet nitrene to the alkene.[93] Rotation around the carbon-carbon bond of the aziridine precursor prior to ring closure provides access to both cis and trans isomers.[93] Therefore, triplet nitrenes should show no

cis/trans specificity unless the lifetime of the diradical intermediate is less than the time needed for carbon-carbon bond rotation.[93]

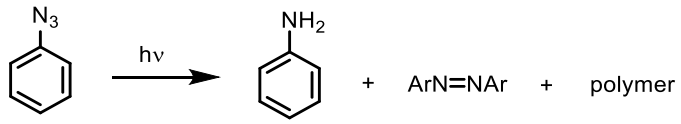


Scheme 1-22: Photodecomposition of carbethoxy azide in the presence of alkene

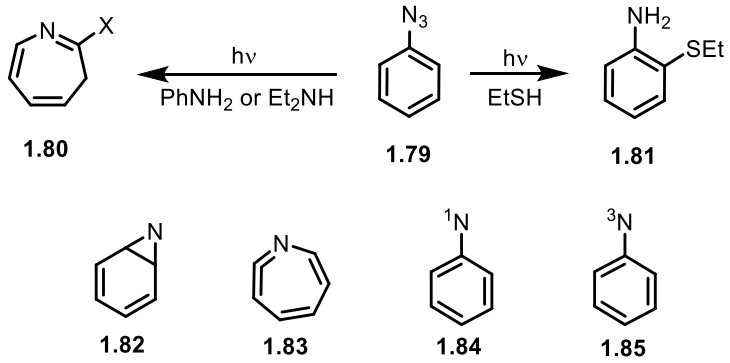
1.3.3 Photochemistry of Aryl Azides

Phenyl azide and most of its derivatives decompose photochemically in hydrocarbon solvents to give rise to a mixture of aniline, azo-benzene and polymeric tars instead of expected insertion products or aziridines (**Scheme 1-23**).[95] The yield of polymeric products increases when the time of irradiation is long.[95] There are a few exceptions when the irradiation leads to insertion products. During the photolysis of phenyl azide **1.79** in diethyl amine, azepine **1.80** is found in high yield (**Scheme 1-24**).[96] Beside azepines, ortho-substituted aniline **1.81** is detected upon photolysis of **1.79** in ethanethiol (**Scheme 1-24**).[97] The results can be explained by the formation of azirine **1.82** and/or ketenimine **1.83**

intermediates upon photolysis of **1.79** in solution (**Scheme 1-24**).[95-97] When the solution is diluted, the azo-benzene forms instead of polymer, indicating these intermediate **1.82** and **1.83** serve as a reservoir for triple nitrene **1.85**, which then dimerize or react with azide **1.79** to form azobenzene.[95-97]

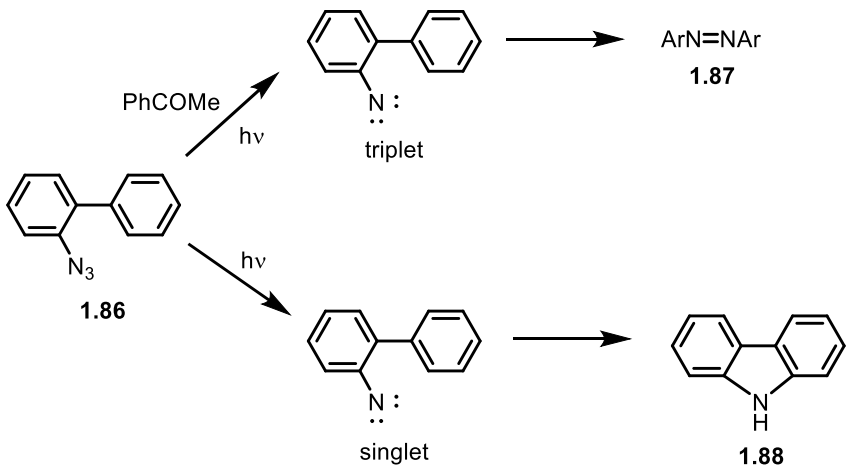


Scheme 1-23: Photolysis of aryl azide



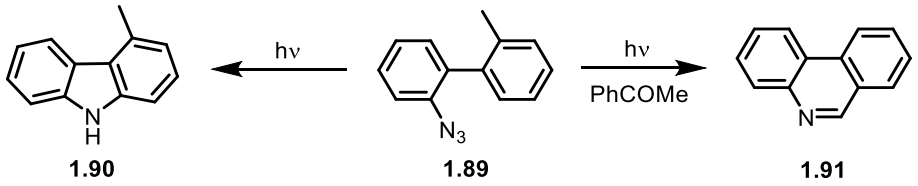
Scheme 1-24: Photochemical decomposition of phenyl azide in various solvents

On the other hand, *o*-azidobiphenyl **1.86** and its derivatives undergo photochemical decomposition to give identifiable products. The photolysis of *o*-azidobiphenyl lead to the formation of carbazole **1.88** in good yield (71%) along with a small amount of 2,2-azobiphenyl **1.87** (9-12%).[98] In the presence of acetophenone or acetone as solvent, the yield of carbazole decreases significantly.[98] As the ketones are known to serve as triplet sensitizers in photolytic conditions, these triplet intermediates will give rise to the formation of triplet nitrene.[98] The results indicate that the singlet nitrene lead to carbazole **1.88** whereas the azo compound is formed from triplet nitrene.[98]



Scheme 1-25: Photolysis of o-azidobiphenyl

Further evidence for the difference in reactivity preferences for singlet and triple nitrenes is found from the photolysis of 2-azido-2'methylbiphenyl **1.89**. The decomposition of **1.89** under irradiation gives mostly carbazole **1.91** along with small amount of phenanthridine **1.90**.[99] The yield of carbazole **1.90** drops sharply accompanied by the increase of **1.91**.[99] These observations support that carbazole is produced solely from singlet nitrene.[99]

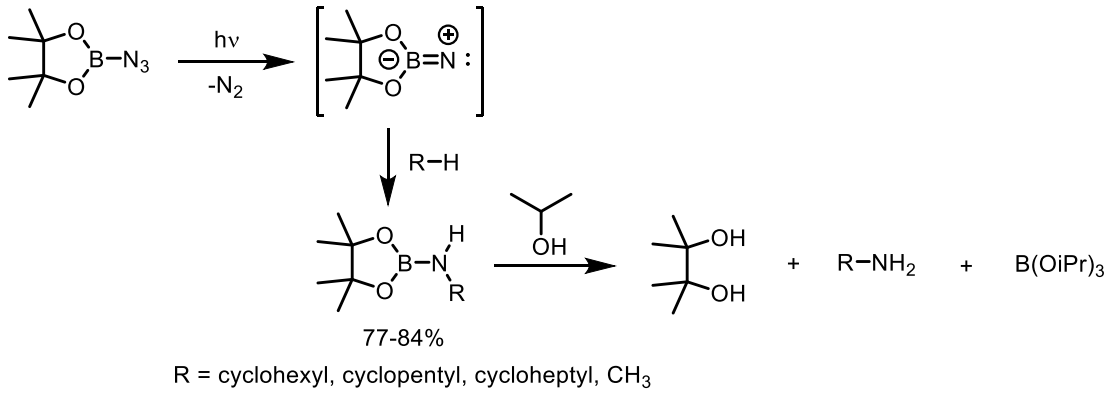


Scheme 1-26: Photolysis of 2-azido-2'methylbiphenyl

1.4 Introduction to Borylnitrene

Borylnitrenes are the isoelectronic and isosteric substitution of a CC unit of vinylidene by a BN unit. These species were successfully generated by Paetzold and coworkers from the boryl azides in 1981 and characterized in 2006 and 2009.[100-102] The introduction of O substituents to the boron center disfavors rearrangement to the iminoborane as well as

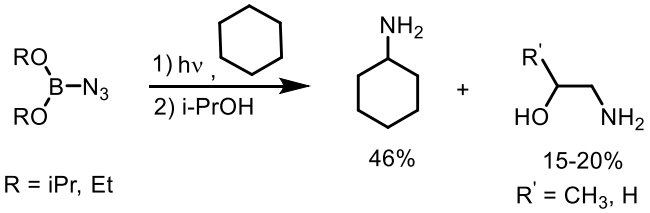
increasing the gap between the ground state and the excited state, which increases the lifetime of the nitrene intermediate.[101,103] Bettinger and co-workers later demonstrated that borylnitrenes are able to undergo efficient intermolecular C–H insertion with unactivated C–H bonds from simple alkanes upon photolysis of boryl azide precursors when the alkane was the solvent (**Scheme 1-27**).[104]



Scheme 1- 27: C-H insertion of borylnitrene

1.5 Thesis Objective

Even though the photochemical decomposition of azides to nitrenes has been investigated for over half a century, the synthetic utility of this transformation is limited to very specific substrate classes due to the challenges in controlling the chemoselectivity of nitrene reactivity. For example, C–H amination is a well-studied reaction for nitrenes; however, efficient C–H insertion reactions are only observed with highly electrophilic nitrenes such as fluorinated phenyl, cyano, carbonyl, and oxycarbonylnitrenes.[81,95] Many of these groups are also difficult to remove after the insertion reaction. Hence, the general use of photolysis of azides in organic chemistry as an amination strategy has been limited.



Scheme 1-28: Inter- and intramolecular insertion of borylnitrene

Although the use of UV irradiation to facilitate C−H insertion of nitrenes in solution is rare in the literature, it is clear that their application has left much to be discovered. Bettinger's results shows the potential to use borylnitrenes to perform intramolecular C−H insertion, which can lead to valuable amino alcohol products and avoids amine protecting groups that can be challenging to remove (**Scheme 1-28**).[105] Even though the authors observed intramolecular products, the intermolecular process is still dominant. Therefore, this thesis examines the irradiation within the conditions that favor the intramolecular pathways as well as expand the substrate scope beyond *i*-propyl and ethyl alcohols.

Prior to a systematic exploration of the photochemical decomposition of borylazides and subsequent amination chemistry, a general method for the generation of borylazide precursors in an efficient and clean fashion must be developed. Access to dialkoxyboryl chlorides will facilitate azide installation to provide dialkoxyboryl azides, as described by Bettinger and coworkers.[101,104,105] However, controlled introduction of nucleophiles such as alcohols to partially displace halides on boron halides in order to access these dialkoxyboryl chlorides, unlike carbon-based counterparts, are scarce in the literature. Ethers, which are known to be easily cleaved by BBr_3, can predictably furnished mono- or dialkoxyboron bromide, but in an unselective manner for unsymmetrical alkyl ethers. The next chapter of this thesis outlines a detailed study of boron-mediated ether cleavage to access to dialkoboryl chlorides by combining boron halide mixtures to cleave dialkyl ethers in a regioselective fashion.

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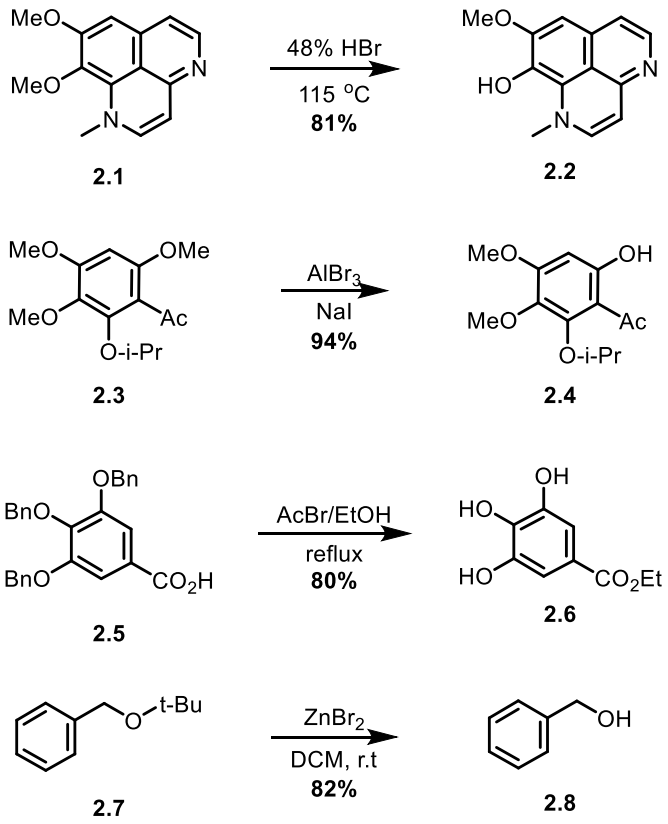
Chapter 2: Predictable Cleavage of Unsymmetrical Dialkyl Ethers with Boron Trihalides

2.1 Introduction

The cleavage of C−O linkages is an important reaction in organic synthesis, especially in the degradation and transformation of natural compounds, in which alcohols and ethers are the most common functionality.[1] More importantly, the interconversion between alcohols and ethers via the formation and disconnection of C−O is widely utilized in the protection of hydroxy groups.[2,3] As a result, a number of tactics for this transformation have been reported involving the use of acids, bases or transition metals.

2.1.1 Acid-mediated Ether Cleavage

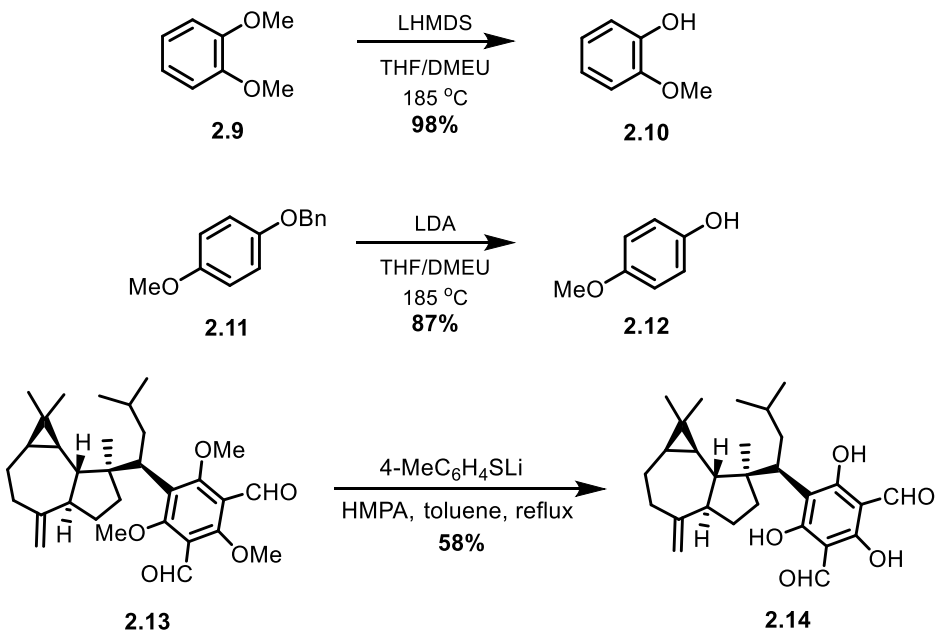
The use of Brønsted acid such as hydroiodic or hydrobromic acid to hydrolyze ethers appeared firstly in 1861.[4,5,6] Ethers are converted to the desired alcohols in the presence of a large excess of concentrated acid, often at reflux (**2.1, 2.5, Scheme 2-1**).[4] The efficiency of this method was recently enhanced by the addition of phase transfer catalysts.[7] Other acidic reagents such as diluted sulfuric acid, trifluoroacetic acid or pyridinium salts can also be employed for this cleavage.[8,9,10,11] The drawbacks of these Brønsted acid strategies are the harsh reaction conditions, which limit applications. To avoid the need of elevated temperature and high acid concentrations, Lewis acids can be used as a replacement.[4,12,13] Lewis acid-mediated ether cleavage often proceed at lower temperatures compared to Brønsted acids (**2.3, 2.7, Scheme 2-1**).[4,12,13] Boron-mediated ether cleavage will be discussed in a separate section below (**2.1.4**), as it is the foundation for the work in this chapter.



Scheme 2-1: Acid-mediated ether cleavage[14,15,16,17]

2.1.2 Base-mediated Ether Cleavage

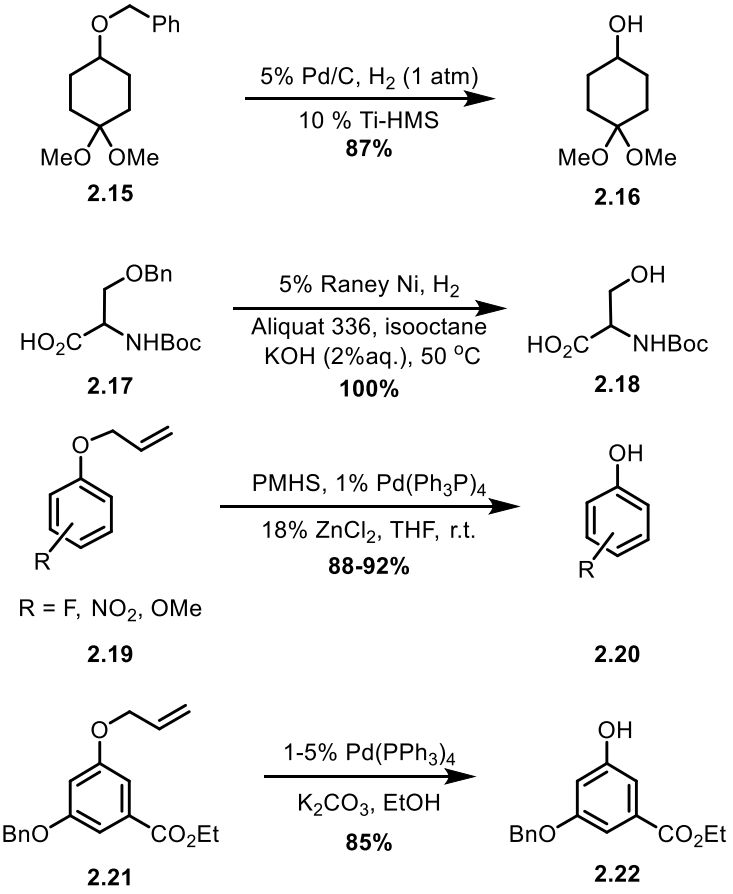
In comparison with its acid counterpart, the use of base in the cleavage of C–O linkages is not common. Bases which have been shown to cleave ethers tend to have very specific and limited substrate scope, which also limits the generality of such a strategy.[8,12,13] Hindered amine bases (**2.9, 2.11, Scheme 2-2**) and thiolates (**2.13, Scheme 2-2)** are two well-studied classes of basic reagents applied to ether cleavage.[8,12,13] Specifically, base-mediated ether cleavage tends to proceed well for substrates with an aryloxide leaving group.



Scheme 2-2: Base-mediated ether cleavage[18,19]

2.1.3 Metal-catalyzed Ether Cleavage

Ever since Heck first introduced palladium cross-coupling as a new C−C bond forming strategy in the late 1960s, the use of palladium and other precious metal catalyzed coupling reactions has significantly expanded the organic chemistry toolbox.[20-24] Metal catalysts have also attracted attention in the area of ether cleavage thanks to their catalytic nature and mild reaction conditions. Palladium-based reagents (**2.15, 2.19, 2.21, Scheme 2-3**), platinum, and Raney nickel (**2.17, Scheme 2-3**) are some examples of useful catalysts that are successfully applied to cleave allyl, benzyl, benzhydryl, and trityl ethers, sometimes with the aid of catalytic acid.[8,12,13]

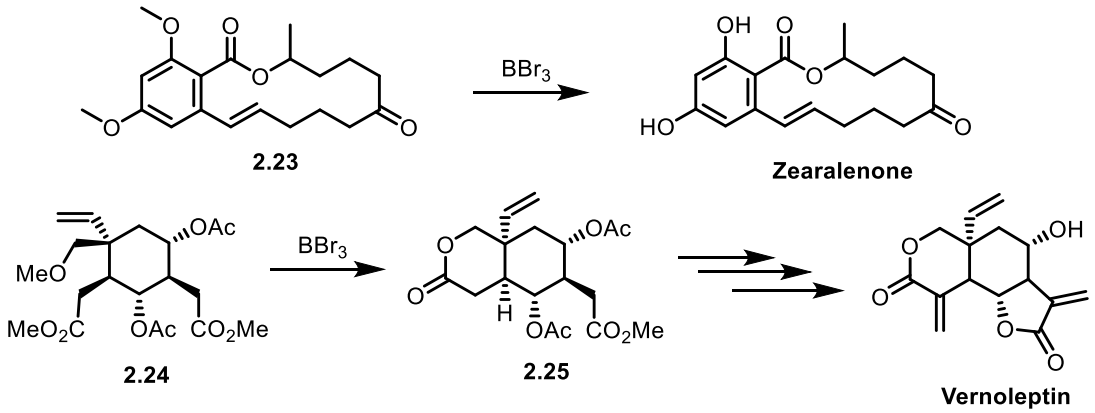


Scheme 2-3: Metal catalyzed C−O bond dissociation[25,26,27,28]

2.1.4 The Use of BBr_3 for Ether Cleavage

When it comes to the cleavage of aryl methyl ethers, boron tribromide is a reagent of choice.[4,12,13] The application of BBr_3 for ether cleavage was first discovered by Benton and Dillon in 1942.[29] Its usefulness was later reviewed by McOmie and co-workers.[30] The obvious advantage of boron tribromide is that the ether linkage disconnection is affected under moderately mild conditions. The reaction is conveniently performed in various solvents such as dichloromethane, pentane or benzene at −78 °C to room temperature. The desired product is achieved via aqueous work-up to cleave the intermediate boryl ester product. Furthermore, BBr_3 mediated ether cleavage has been successfully exploited in the

syntheses of a variety of complex natural products and biologically active compounds (**Scheme 2-4**).[4,12,13]

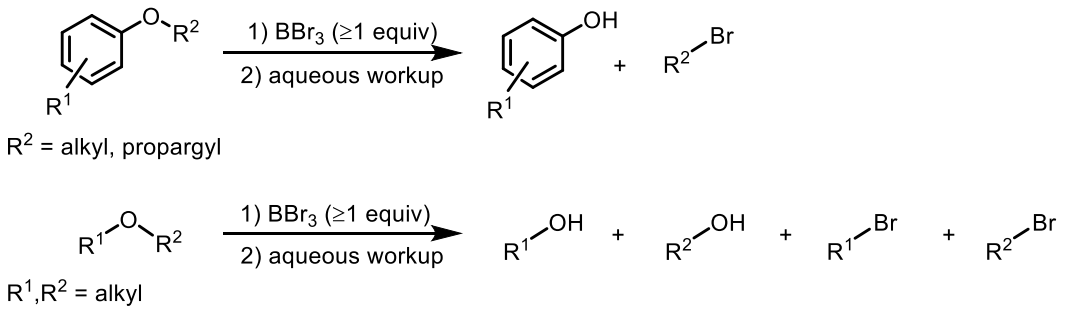


Scheme 2-4: Synthetic application of BBr_3 in total synthesis[31-36]

2.2 Research Objective

Even though the synthetic utility of boron tribromide reagents with aryl alkyl ethers has been expended in numerous synthetic endeavors and used in challenging natural product syntheses, this reagent has surprising limitations in the cleavage of unsymmetrical alkyl ethers due to moderately poor regioselectivity, and in several cases poor yields of the desired alcohol (**Scheme2-5**).[8,12,13,37] One cause of this is the propensity of intermediate boron esters $(RO)_xBBr_{3-x}$ to decompose to alkyl bromides.[38,39] Additionally, the effectiveness of ether cleavage reactions are typically reliant on a stoichiometric amount of boron tribromide. To the best of our knowledge, though there have been sporadic reports on the occasional application of BBr_3 in dialkyl ether cleavage, there has been no systematic study on the selectivity of BBr_3 for ether cleavage of unsymmetrical alkyl ethers. As such, the objective of this project is to perform a systematic study on the selectivity of cleavage of

unsymmetrical alkyl ethers by employing a combination of BBr_3 with BCl_3 to affect a mild and predictable cleavage of unsymmetrical alkyl ethers.

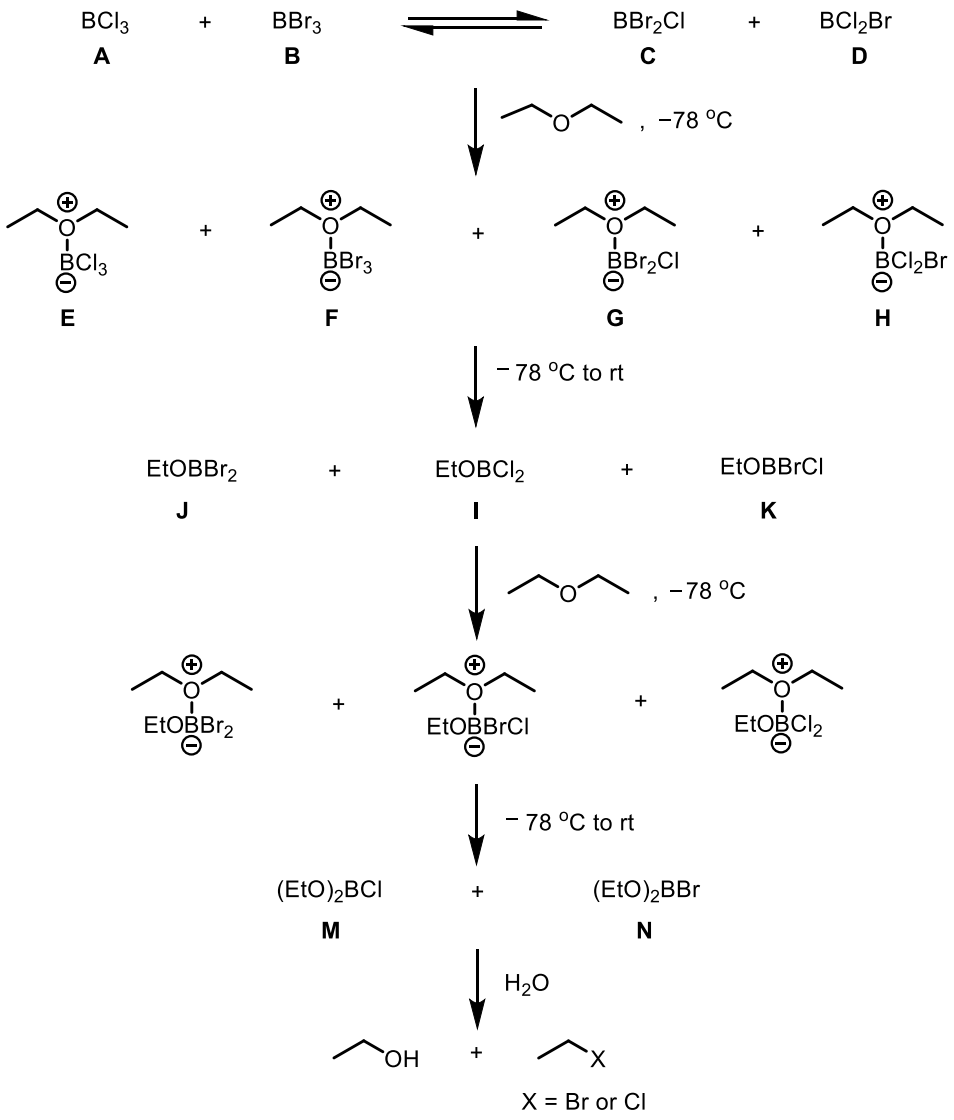


Scheme 2-5: Chemoselectivity of borontribromide-mediated ether cleavage

2.3 Rationale for Experimental Plan

The reactivity of ethers toward homoleptic boron halides has been well-studied and generally obey the following trend: $BI_3>BBr_3>BCl_3>BF_3$.[40,41] Therefore, BCl_3, unlike its counterpart BBr_3, generally does not trigger cleavage of unactivated ether substrates at room temperature.[8] Instead, it often forms stable coordination complexes. Mixtures of homoleptic boron halides are known to redistribute, forming mixtures of heteroleptic boron halides.[42] Even though the reactivity and selectivity of ethers towards heteroleptic boron halides has not been well-studied, other boron halide variants such as phenyl boryl chloride or dimethylbromo borane (Guindon's reagent) have proven effective to cleave C−O bonds generally.[43,44,45] Therefore, we speculated that heteroleptic boron halides would possess a mix of character between the boron trichloride and boron tribromide species. Our reaction design was to employ the heteroleptic boron halides generated from the equilibrium between BBr_3 and BCl_3. In practice, to this boron trihalide mixture was added one equivalent (relative to total moles of boron reagents) of diethyl ether at −78 °C, at which temperature the boron-ether complexes can be observed ((**Scheme 2-6**). The formation of ethoxyboron

dihalide intermediates can be observed upon warming to room temperature, and the entire process can be repeated to generate diethoxyboryl chloride (**M**) and diethoxyboryl bromide (**N**). These intermediates produce the desired alcohol upon aqueous workup. Interestingly, the reaction strongly favored the formation of diethoxyboryl chloride **M** over diethoxyboryl bromide **N**. These observations started the following investigation of substrate scope,[77] and lead to the further expansion of investigations in chapters 3 involving intermediate **M**.



Scheme 2-6: Proposed reaction plan

2.4 Results and Discussion

2.4.1 Optimization of Reaction Conditions

We began by examining the disproportionation of BBr_3 and BCl_3 at different ratios when mixing them in dichloromethane at room temperature. It was found that when equal amounts of BCl_3 and BBr_3 (1:1) were added to dichloromethane, a mixture of trihaloboranes (BCl_3, BCl_2Br, BBr_2Cl, BBr_3) was rapidly generated and observed via ^{11}B NMR (**Figure 2-1**). The furthest peak (**A**) was assigned to BCl_3 based on the literature while the most deshielded peak (**B**) among trihaloboranes mixture was assigned to BBr_3, also matching literature values. Similarly, the two major peaks were appointed to BBr_2Cl (**C**) and $BBrCl_2$ (**D**).

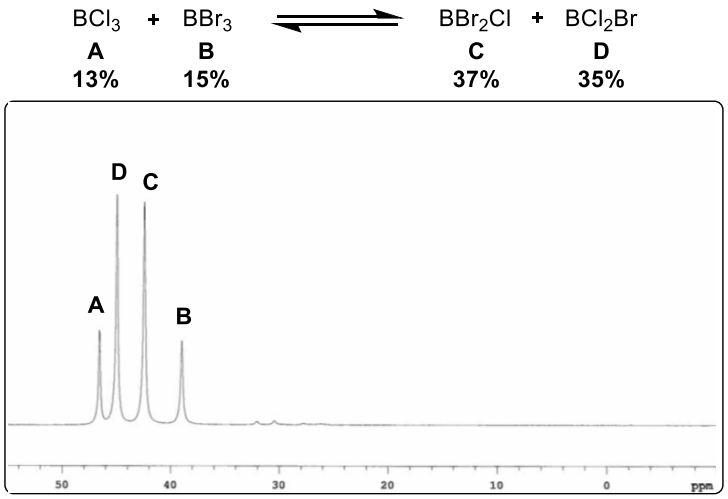


Figure 2-1: ^{11}B NMR spectra of boron heteroleptic mixture

It can be seen from the ^{11}B NMR that the trihaloboranes generated from the mixture of BCl_3 and BBr_3 (1:1) favored the formation of heteroleptic complexes (**Figure 2-1**). The ratios of these signals do not substantially change over a wide range of temperatures (−78 °C – rt). Addition of one equivalent (based on total moles of boron) of diethyl ether at –78 °C, generated four new boron signals assigned as the ether complexes of the various boron species (**Figure 2-2**). Interestingly, these ratios are nearly identical to the ratios observed in the absence of ether.

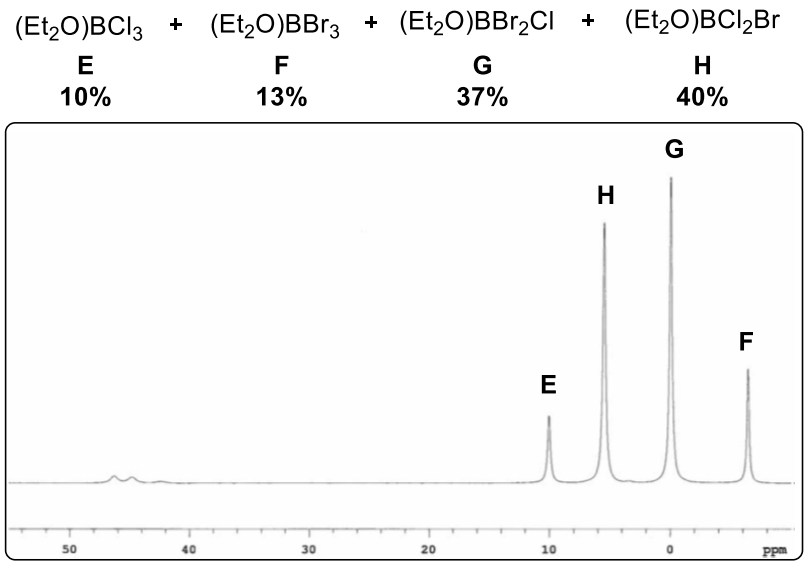


Figure 2-2: ^{11}B NMR spectra after first addition at – 78 ^{o}C

On warming at room temperature overnight, these four boron signals merge to three more shielded boron signals assigned as a mixture of $EtOBX_2$ compounds, where X = Cl or Br (**Figure 2-3**). Analysis of ^{1}H NMR of the mixture revealed that ethyl bromide was formed predominantly over ethyl chloride (>10:1). This suggests a strong kinetic preference for bromide to react in nucleophilic displacement of the C−O bond rather than the chloride.

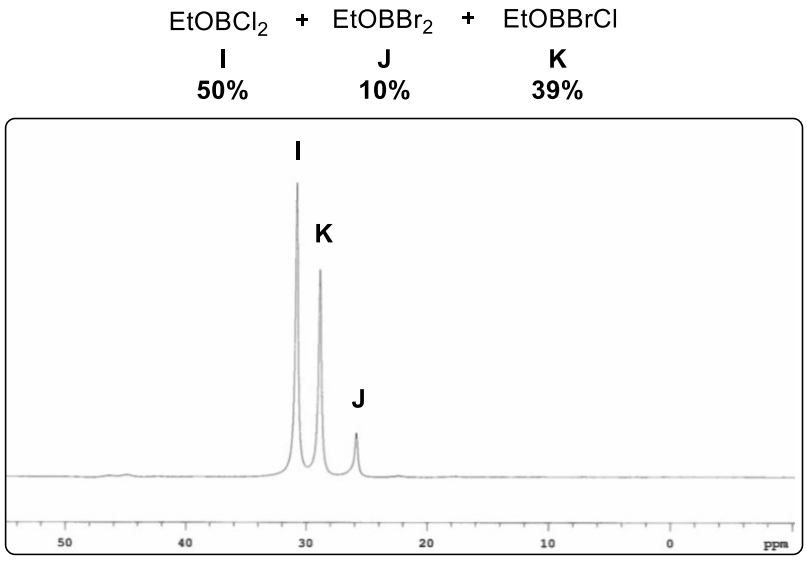


Figure 2-3: ^{11}B NMR spectra of reaction after 16 hours of warming to rt

The $(EtO)_2BX$ reaction mixture was then exposed to a second equivalent of diethyl ether at –78 °C. Upon warming to room temperature, the three boron signals further coalesced into two new peaks at >10:1 ratio, and were assigned as $(EtO)_2BCl$ (**M**) and $(EtO)_2BBr$ (**N**), respectively (**Figure 2-4**). Triethoxy borate was also observed. Finally, simple hydrolysis of the diethoxyboryl halides with aqueous workup produced ethanol along with the ethyl halide products.

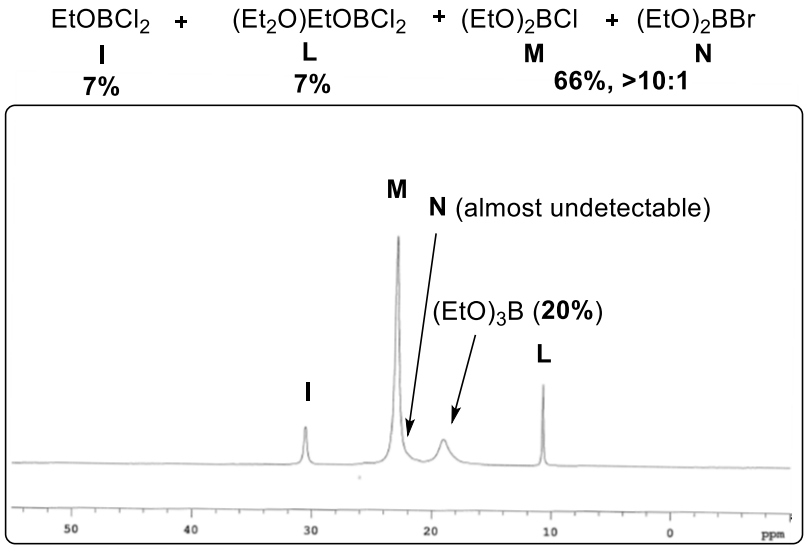


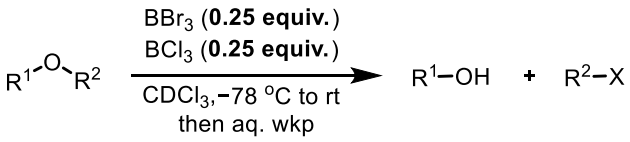
Figure 2-4: ^{11}B NMR spectra of final solution

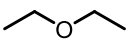
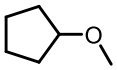
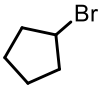
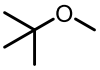
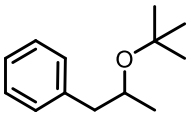
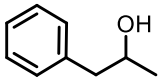
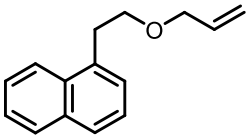
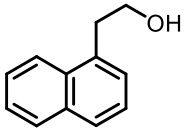
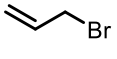
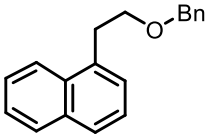
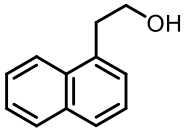
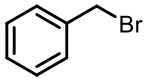
To compare the efficiency of this protocol with ether cleavage with BBr_3 alone, we treated diethyl ether with 0.5 mole equivalent of BCl_3 or BBr_3 alone in separate NMR tubes and analyzed the decomposition of each of the ether complexes. The ether complex of BCl_3, $(Et_2O)BCl_3$, was relatively stable at −78 °C to ca. 70°C (heated for 1 h, in deuterated benzene), while the ether complex of BBr_3, $(Et_2O)BBr_3$, can only be observed within 1 h at room temperature, as conversion to afford $EtOBBr_2$ was kinetically fast. After addition of another one mole equivalent of diethyl ether to $EtOBBr_2$, the ether complex immediately converts to the desired $(EtO)_2BBr$ along with a new peak, which was assumed to be B_2O_3. After three to five days of aging at room temperature, this $(EtO)_2BBr$ and B_2O_3 mixture

coalesced to B_2O_3 alone, and only traces of $(EtO)_2BBr$ could be observed suggesting instability of $(EtO)_2BBr$. Concurrently, ethyl bromide could be observed to form by following the ^1H NMR. Bringing these pieces of information together, we conclude that the presence of BCl_3 modulates the reactivity of BBr_3 Lewis acid, but BCl_3 alone displays insufficient reactivity, making the two Lewis acids together better than one.

2.4.2 Examination of Selectivity Profile

Table 2-1: Selectivity profile of mixture boron halides on various alkyl substrates



Entry	Substrate	Compound Number	Major Alcohol Product[a]	Major Halide Product[b]
1		**2.26**	 N.D.	 71%
2		**2.27**	 N.D.	 71%
3		**2.28**	 N.D.	 74%
4		**2.29**	 61%	 63%
5		**2.30**	 90%	 70%
6		**2.31**	 93%	 73%

[a]Isolated yields. [b]NMR yields. N.D. = Not determined.

Satisfied, we next investigated the regioselectivity of this method. To determine the selectivity of cleavage in unsymmetrical ethers, we subjected a variety of ether substrates to a 1:1 molar ratio of BCl_3 to BBr_3 at –78 °C followed by warming to room temperature (Table 2-1). In all cases, the formation of dialkoxyboryl halides followed the same model as

described above, at >10:1 ratio of chloride to bromide. Comparison of 1°, 2°, and 3° alkyl groups in the ether substrate table verified that the alkyl group which is most capable of stabilizing positive charge is inevitably the group which is converted to the alkyl halide.

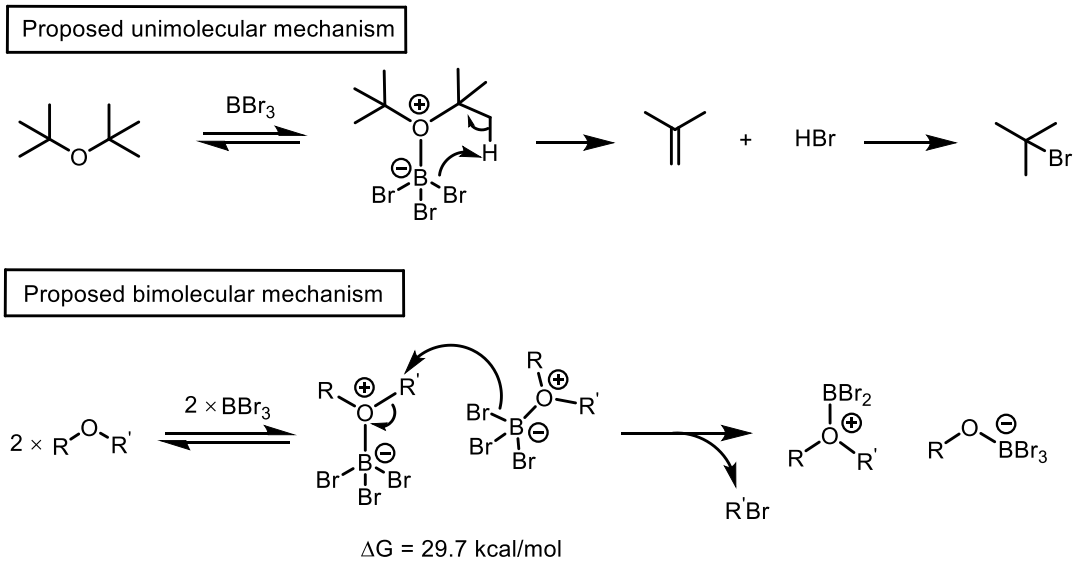


Figure 2-5: Proposed mechanism of BBr_3-mediated ether cleavage by Sousa et al

Although BBr_3 has been historically used for heterolytic cleavage of C−O linkages, the exact mechanism of this transformation has only recently been further elaborated. In 2014, Sousa and coworkers proposed two possible pathways of BBr_3-mediated cleavage of ethers: a unimolecular and bimolecular mechanism (**Figure 2-5**).[46] Based on the computational methods, they suggested that unimolecular process is the most favored mechanism for the cleavage of ethers containing highly branched alkyl groups (secondary or tertiary). Meanwhile, mixed ethers of primary alkyl groups are likely to undergo a bimolecular pathway. This conclusion was re-investigated by Lord et. al. While they agreed that two possible mechanisms exist for ether cleavage depending on the identity of the ethers involved, they argued that the proposed complexes involved in the bimolecular proposal were incorrect.[47] Instead, they suggested an alternative mechanism involving attack of $diether_n$-BX_n adducts by boron tetrabromide (**Figure 2-6**).

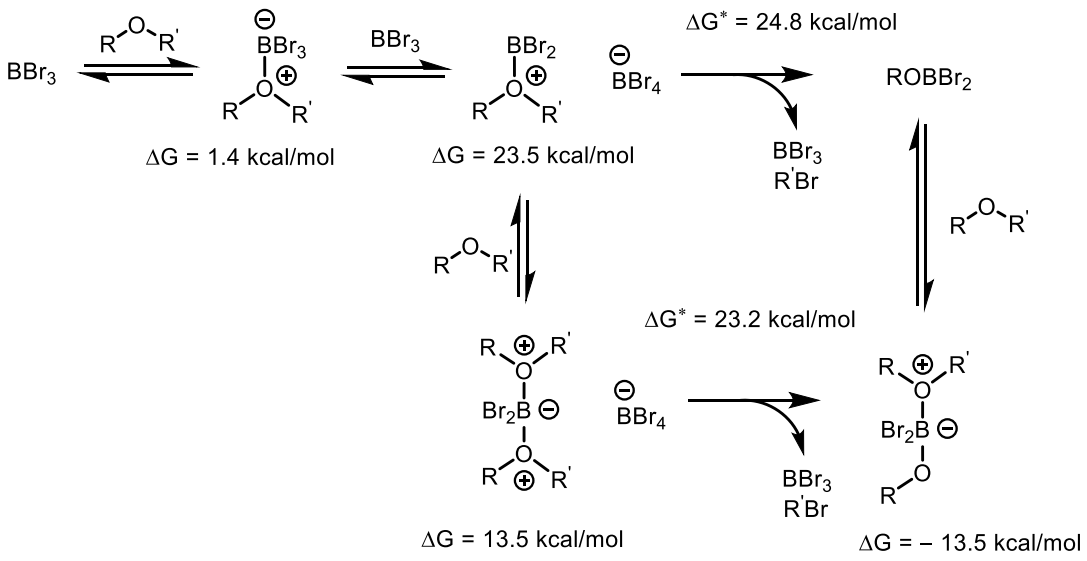
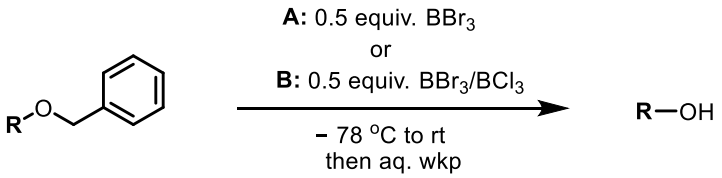


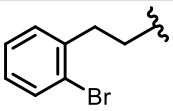
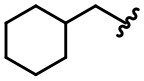
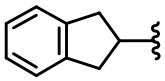
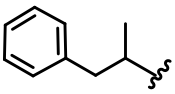
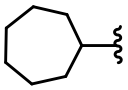
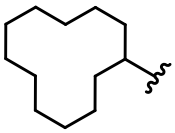
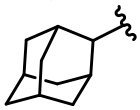
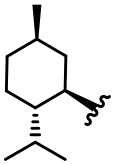
Figure 2-6: Proposed mechanism of BBr_3-mediated ether cleavage by Lord et al

It is at this point unclear if the same mechanistic conclusions would apply to our system. In a bimolecular mechanism, with different boron centers involved in either activating the ether for attack or supplying the nucleophilic halide, as proposed by Lord and coworkers, the distribution of the two different halides may significantly change the barriers of these processes and related undesired pathways.

2.4.3 Examination of Benzyl Ethers

Table 2-2: Screen of benzyl ethers



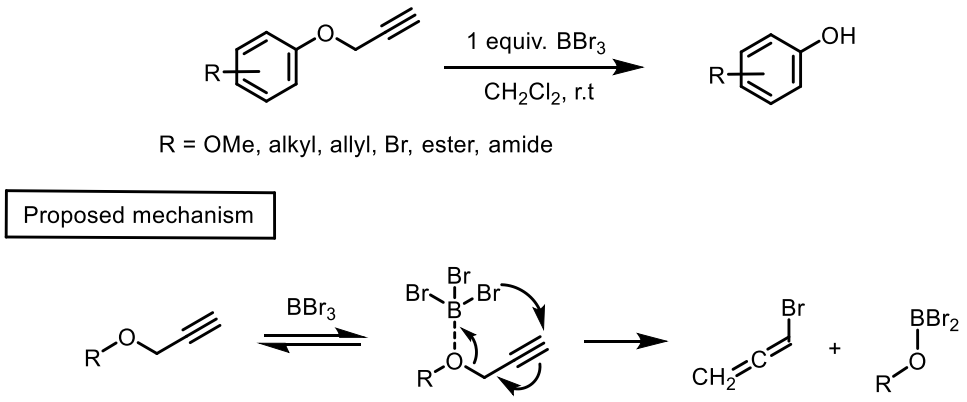
Entry	R^1	Compound Number	Method	Isolated Yield
1		**2.32**	**A** **B**	72% 90%
2		**2.33**	**A** **B**	68% 93%
3		**2.34**	**A** **B**	30% 67%
4		**2.35**	**A** **B**	34% 72%
5		**2.36**	**A** **B**	32% 61%
6		**2.37**	**A** **B**	38% 64%
7		**2.38**	**A** **B**	42% 67%
8		**2.39**	**A** **B**	33% 72%

Encouraged by the result of benzyl ether example in Table **2-1** (entry 6), a wide range of alkyl benzyl ethers was investigated (**Table 2-2**). Acyclic and cyclic primary alkyl benzyl ethers both underwent smooth reaction to give the corresponding alcohol in excellent yields. The reaction efficiencies decreased when performing the same reaction on secondary alkyl ethers. In such cases, secondary bromides were formed in minor amounts, though benzyl

alcohol was never observed. It may therefore be the case that the secondary alkoxyboryl halide intermediates are simply less stable. In addition to benzyl halides, the only byproducts generated through reactions with secondary ethers secondary halides and a precipitate we presume to be B_2O_3.

Importantly, in comparison with BBr_3, the mixture of BBr_3 and BCl_3 cleaved alkyl benzyl ethers to furnish the corresponding alcohols in excellent yield and high regioselectivity. Moreover, the dialkoxyboryl chloride intermediates were dominant in all cases (>10:1). The alkyl halide products were formed in reverse ratio (more bromide than chloride). Interestingly, the stereochemical integrity of chiral ethers (**2.39**) was retained during the transformation, provided the chiral center was not at the site of halogenation.

2.4.4 Examination of Propargyl Ethers

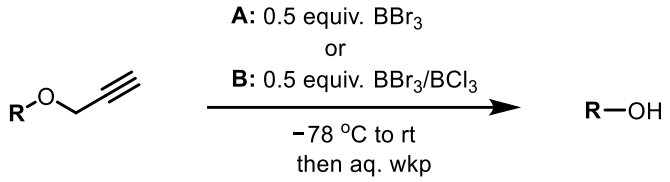


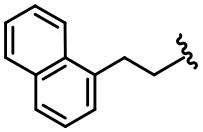
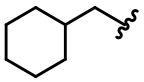
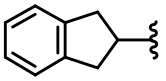
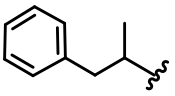
Scheme 2-7: The deprotection of propargyl aryl ether by BBr3

In 2004, Finn and coworkers published a study on the propargyl group as a protecting group for the ArOH and $ArCO_2H$ functional groups (**Scheme 2-7**).[48] In this study, a propargyloxy unit, which is less commonly used in protecting group strategies than the allyl group, was selectively cleaved to give the desired alcohols by employing stoichiometric amounts of boron tribromide. A wide range of aryl propargyl ethers formed the desired alcohols in good to excellent yield. Finn suggested a unimolecular mechanism for this transformation, with

regards to the observation of allenyl bromide byproducts. The ether first coordinates to boron tribromide before the intramolecular transfer of bromide to the terminal position of the alkyne.

Table 2-3: Screen for propargyl ethers

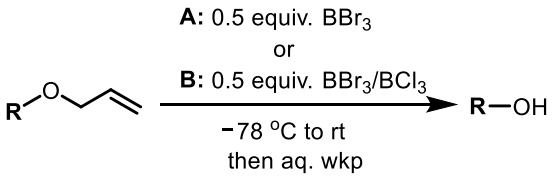


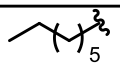
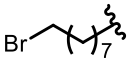
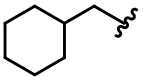
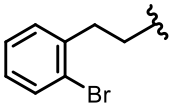
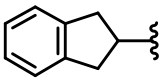
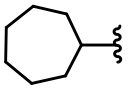
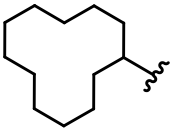
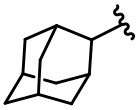
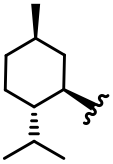
Entry	R^1	Compound Number	Method	Isolated Yield
1		**2.40**	**A** **B**	20% 37%
2		**2.41**	**A** **B**	23% 36%
3		**2.42**	**A** **B**	16% 31%
4		**2.43**	**A** **B**	13% 29%

Encouraged by Finn's results, we further applied our optimal conditions to various alkyl propargyl ethers (**Table 2-3**). Both primary and secondary alkyl propargyl ethers were evaluated for this cleavage. Even though there were improvements when the mixture of boron trihalides was employed, the yields were low compared to benzyl ethers. Analysis of ^{11}B NMR spectra of the crude reaction material showed the generation of borylation byproducts. Further, we did not observe intact propargyl functional groups in the ^{1}H NMR spectra. Based on these observations, Finn's unimolecular depropargylation mechanism was likely not operative in our system, and an aromatic ether may be required for efficient deprotection.

2.4.5 Examination of Allyl Ethers

Table 2-4: Screen for allyl ethers



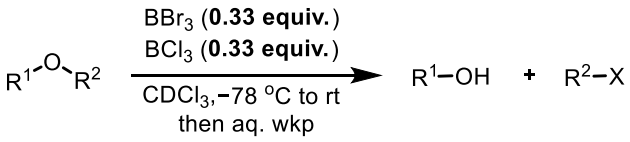
Entry	R^1	Compound Number	Method	Isolated Yield
1		**2.44**	**A** **B**	68% 88%
2		**2.45**	**A** **B**	78% 87%
4		**2.46**	**A** **B**	71% 87%
5		**2.47**	**A** **B**	74% 86%
6		**2.48**	**A** **B**	32% 73%
7		**2.49**	**A** **B**	30% 63%
8		**2.50**	**A** **B**	40% 61%
9		**2.51**	**A** **B**	39% 59%
10		**2.52**	**A** **B**	32% 57%
11		**2.53**	**A** **B**	36% 72%

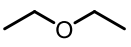
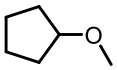
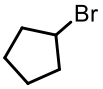
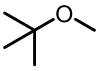
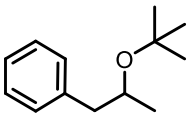
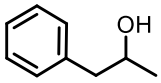
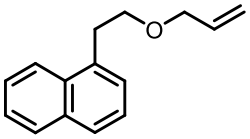
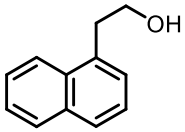
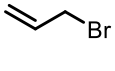
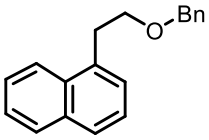
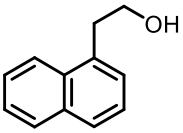
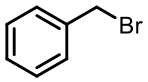
Having established the optimized cleavage conditions for benzyl ethers, we expanded our substrate scope with respect to allyl ethers (**Table 2-4**). As showed in table 2-1 above, the treatment of substrate **2.30** bearing the allyl group with a mixture of boron halides resulted

in the formation of the corresponding alcohol in excellent yield. The use of allyl groups instead of benzyl can provide additional value, as the allyl bromide byproduct can be easily removed under high vacuum upon completion of the reaction. This also allows for the clean generation of dialkoxyboryl choloride intermediates, which will be expanded upon in chapter 3. A screen of numerous allyl ethers was carried out to delineate scope as shown in table 2-4. Primary substrates were prone to cleavage, resulting in good yields, whereas the reaction was less effective for secondary substrates. Similar to the benzyl ether case, secondary halides were observed, but not allyl alcohol. Overall, the combination of BBr_3 and BCl_3 enhanced the regioselectivity and yield for both primary and secondary allyl ethers as compared to BBr_3 alone. In all cases, dialkoxyboryl chloride was the major intermediate.

2.4.6 Evaluation of Boron Halide Equivalents

Table 2-5: Selectivity data of substoichiometric boron halides



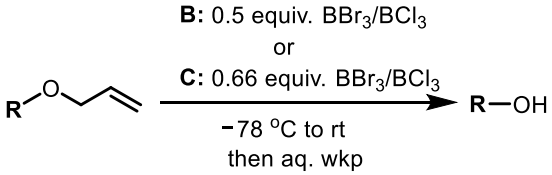
Entry	Substrate	Compound Number	Major Alcohol Product[a]	Major Halide Product[b]
1		**2.26**	 N.D.	 85%
2		**2.27**	 N.D.	 83%
3		**2.28**	 N.D.	 92%
4		**2.29**	 70%	 71%
5		**2.30**	 99%	 92%
6		**2.31**	 99%	 93%

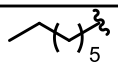
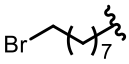
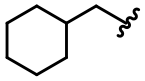
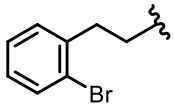
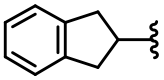
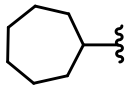
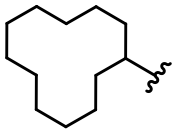
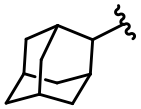
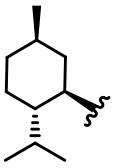
[a]Isolated yields. [b]NMR yields. N.D. = Not determined.

In our design, one equivalent of total boron halides can react with two equivalents of ether to furnish dialkoxyboryl halides, which will give rise to alcohols upon hydrolysis, and alkyl halide byproducts. Our observations were that the dominant intermediate was dialkoxy boron chloride and alkyl bromide. These combined results indicate a faster attack of activated ether

complexes by bromide as compared to chloride. Taking these pieces of information together, we assumed that increasing the total bromide equivalents to be stoichiometric with the starting ether could improve reaction yields for secondary ethers. Therefore, we sought to evaluate if the 0.66 equivalent of total boron halides (0.33 equivalents of BBr_3) would lead to improved results. Table 2-5 and 2-6 illustrated that such a predicted improvement was achieved when higher amounts of boron halides were applied.

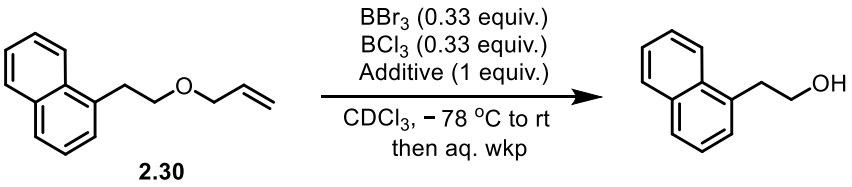
Table 2-6: Comparison of boron halides equivalents



Entry	R^1	Compound Number	Method	Isolated Yield
1		**2.44**	**B** **C**	88% 99%
2		**2.45**	**B** **C**	87% 97%
4		**2.46**	**B** **C**	87% 97%
5		**2.47**	**B** **C**	86% 98%
6		**2.48**	**B** **C**	73% 82%
7		**2.49**	**B** **C**	63% 71%
8		**2.50**	**B** **C**	61% 70%
9		**2.51**	**B** **C**	59% 68%
10		**2.52**	**B** **C**	57% 64%
11		**2.53**	**B** **C**	72% 79%

2.4.6 Evaluation of Functional Group Tolerance

Table 2-7: Functional group tolerance screening



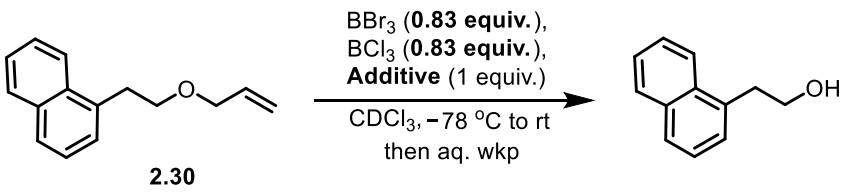
2.30

Entry	Additive	Yield
1	Ethyl Acetate	92%
2	Cyclohexene	99%
3	Dibutyl sulfide	20%
4	Acetonitrile	19%
5	Methanol	17%
6	Triethylamine	16%
7	Pyridine	20%

Yields were determined by NMR with internal standard

The functional group tolerance of this protocol was studied by performing the reaction in the presence of additives containing various functional groups. (**Table 2-7**) The removal of an allyl group in substrate **2.30** proceeded smoothly to form the corresponding product in excellent yield in the presence of either ethyl acetate or cyclohexene. Entries 3-7, however, showed a significant decrease in yield when dibutyl sulfide, acetonitrile, methanol, triethyl amine or pyridine was present. We reasoned that this could be explained by complexation of the boron halide reagents with these additives.

Table 2-8: Functional group tolerance test with additional equivalent of boron halides



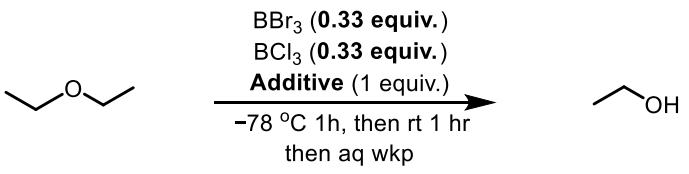
2.30

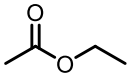
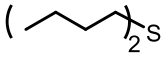
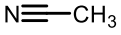
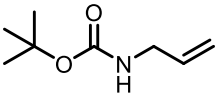
Entry	Additive	Yield
1	Dibutyl sulfide	95%
2	Acetonitrile	91%
3	Methanol	32%
4	Triethylamine	93%
5	Pyridine	96%

Yield were determined by NMR with internal standard

We hypothesized that adding an excess of boron halides to account for the formation of boron complexes with the additives would address this problem. As a result, an extra equivalent of total boron halides (equal to the equivalent of additive) was added to the reaction. Table 2-8 shows the results of this investigation. The desired product was achieved in high yield in the presence of additional equivalent of both BBr_3 and BCl_3 in all entries except entry 3. The additives were themselves also not degraded by the boron trihalides, other than a minor amount of borane addition to cyclohexene, as observed by ^1H NMR. The poor reactivity of the ether cleavage in the presence of alcohol could be explained by the production of protic acid which then protonates the ether starting materials, preventing boron complexation.

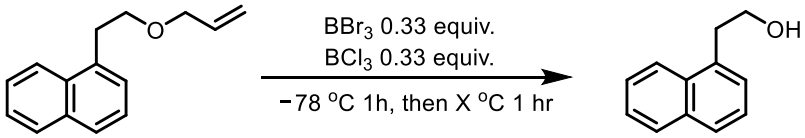
Table 2-9: Degradation of additives under reaction conditions



Entry	Additive	% Additive remaining	Degredation product
1		94	ND
2		84	ND
3		quant	ND
4		quant	ND
5		<5	allylamine

Yields were determined by NMR with internal standard. quant = quantitative conversion. ND = not determined

2.4.7 Evaluation of Temperature Effects on Reaction Rate



Entry	Temperature (°C)	Yield
1	– 78	9
2	– 50	28
3	– 30	75
4	– 10	89
5	10	96

Yields were determined by NMR with mesitylene internal standard

Scheme 2-8: Effect of temperature on reaction rate

In our design for the cleavage protocol, the reaction was left at −78 °C and allowed to reach to room temperature overnight without monitoring. Uncontrolled warming does not inform at what temperature the reaction initiates and what time the reaction completes. This information is important and necessary when scaling up the process. The influence of temperature was evaluated by performing the addition of ether at −78 °C, and then bringing to a specific constant temperature for one hour. Although it is likely that different substrates react at different rates, substrate **2.30** was chosen as a representative model for this evaluation. As can be seen from the graph, conversion of the ether was almost completed at 10 °C. Additionally, in the range from −50 to −30, there was a rapid jump in conversion.

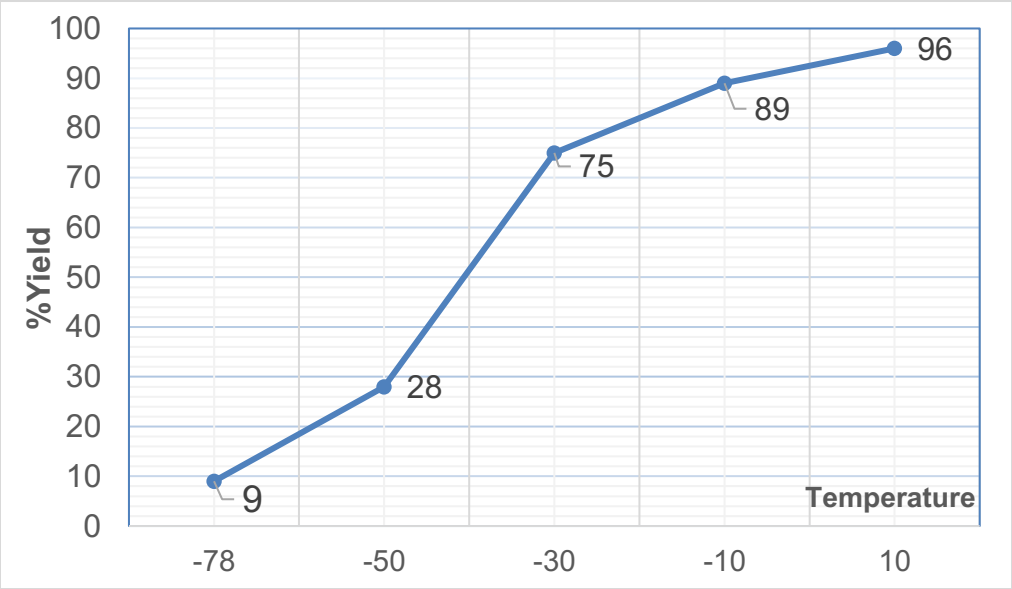


Figure 2-7: The effect of temperature on reaction rate

2.4.8 Evaluation of Large-scale Reaction

To prove the further synthetic application of this cleavage reaction, a 255 milligram scale reaction was carried out using **2.30** as a representative substrate (previous reactions

were performed at 0.40 mmol scale, which corresponds to 85 mg **2.30**). Under the optimal conditions, scale-up gave high reproducibility and yield (89%).

2.5 Conclusion

We have introduced a systematic study on the regioselectivity of unsymmetrical alkyl ether cleavage. This transformation is achieved via the combination of BBr_3 and BCl_3. The ligand exchange equilibrium between BBr_3 and BCl_3 favors the formation of heteroleptic complexes which are presumed to be active in the cleavage of C−O linkages. This study also expands the classic BBr_3 Lewis acid-mediated cleavage of ethers to unsymmetrical alkyl ethers. More importantly, it addresses the traditional challenge of BBr_3 with dialkyl substrates: poor regioselectivity and low yield. In all of the trials, the use of heteroleptic boron halides exhibited improved reactivity profiles (regioselectivity, yield, and functional group tolerance) as compared to BBr_3 alone.

Interestingly, the dialkoxyboryl chloride intermediates, $(RO)_2BCl$, are notable as these type of boron complexes have been used by Bettinger and coworkers to study the reactivity of open-shell nitrene intermediates. Only a limited number of dialkoxyboryl chloride complexes have been reported in the literature, however, suggesting that this reaction may open a new opportunity for discovery.

2.6 Experimental

General information: Reactions were carried out in oven-dried (> 130 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous reagents was accomplished with oven-dried syringes or cannulae. Dichloromethane (DCM), ethyl acetate (EA), and tetrahydrofuran (THF) were purified using a double cartridge solvent purification system prior to use. All other solvents were purchased,

vacuum-distilled (twice) and stored under nitrogen over oven-dried (> 200 °C) molecular sieves (3Å or 4Å). Deuterated dichloromethane (d_2-DCM) and deuterated chloroform ($CDCl_3$) were stored in a container with oven-dried (> 200 °C) molecular sieves (3Å or 4Å). Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm silica gel with a fluorescent indicator UV_{254} (EMD Millipore), which were visualized under UV light and with a $KMnO_4$ stain. Flash chromatography columns were packed with 230-400 mesh silica gel (Silacycle). All reagents were purchased from commercial suppliers: Sigma Aldrich, AK Scientific, and Acros, at purity greater than (95%), unless otherwise specified. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 or 500 MHz, and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 or 125 MHz. Proton decoupled boron nuclear magnetic resonance spectra (^{11}B{^{1}H} NMR) were recorded at 160 MHz, usually using a quartz NMR tube to avoid background signals (*vide infra*). The chemical shifts were reported on the δ scale (ppm) and referenced to the residual protonated solvent (^{1}H) or to the deuterated solvent (^{13}C) peaks: $CDCl_3$ (7.26 ppm, ^{1}H; 77.06 ppm, ^{13}C), and CD_2Cl_2 (5.32 ppm, ^{1}H; 53.5 ppm, ^{13}C). The following abbreviations are used in reporting NMR data: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sept, septet; dd, doublet of doublets; m, multiplet. Unless otherwise stated, Boron (^{11}B NMR) nuclear magnetic resonance spectra were recorded without any chemical shift adjustment. In cases where the NMR tube used in the measurement of ^{11}B NMR nuclear magnetic resonance spectra was not made of quartz, spectral adjustment (backward linear prediction) was done to subtract the contribution of borosilicates from the measurements.

2.6.1 Preparation of Control Solutions for in-situ Intermediate Comparison

BCl_3 in CD_2Cl_2:

Under an atmosphere of nitrogen at room temperature, a solution of BCl_3 (100 μL, 1.00 M CH_2Cl_2, 0.10 mmol) was added to a flame-dried NMR tube containing 0.40 mL CD_2Cl_2. The solution was vortexed for 1 min at room temperature, and the ^{11}B NMR spectrum was acquired for BCl_3: ^{11}B NMR (128 MHz, CD_2Cl_2) δ 47.7. The spectral data was in agreement with that previously reported.[49]

BBr_3 in CD_2Cl_2:

Under an atmosphere of nitrogen at room temperature, a solution of BBr_3 (100 μL, 1.00 M CH_2Cl_2, 0.10 mmol) was added to a flame-dried NMR tube containing 0.40 mL CD_2Cl_2. The solution was vortexed for 1 min at room temperature, and the ^{11}B NMR spectrum was acquired for BBr_3: ^{11}B NMR (128 MHz, CD_2Cl_2) δ 40.0. The spectral data was in agreement with that previously reported.[49]

2.6.2 Titration of BCl_3 with Et_2O, Formation $(Et_2O)BCl_3$ Coordination Complex

Under an atmosphere of nitrogen at room temperature, a solution of BCl_3 (100 μL, 1.00 M CH_2Cl_2, 0.10 mmol) was added to a flame-dried NMR tube containing 0.40 mL CD_2Cl_2. The solution was vortexed for 1 min at room temperature, and Et_2O (11.0 μL, 0.10 mmol) was added to the reaction mixture and again vortexed for 1 min at room temperature.

$(Et_2O)BCl_3$: ^1H NMR (400 MHz, CD_2Cl_2) δ 3.70 (brs, 4H), 1.25 (brs, 6H); ^{13}C NMR (125 MHz, CDCl3) δ 54.2, 15.1; ^{11}B NMR (160 MHz, CD_2Cl_2) δ 10.8.[49] This complex is stable at

–78 to 70 °C. No substantial decomposition of the complex was observed at 70 °C, unless the reaction was heated to reflux in PhMe (110 °C).

2.6.3 Titration of BBr_3 with Et_2O, Formation $(Et_2O)BBr_3$ Coordination Complex

Under an atmosphere of nitrogen at room temperature, a solution of BBr_3 (100 μL, 1.00 M CH_2Cl_2, 0.10 mmol) was added to a flame-dried NMR tube containing 0.4 mL CD_2Cl_2. The solution was vortexed for 1 min at room temperature, the solution temperature was cooled to –78 °C and Et_2O (11.0 μL 0.10 mmol) was added dropwise, the ether was allowed to diffuse in the solution for ca. 10 min. The spectra of the complex were obtained within 5 mins at room temperature. $(Et_2O)BBr_3$: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.70 (brs, 4H), 1.25 (brs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.2, 15.1; ^{11}B NMR (160 MHz, CD_2Cl_2) δ -6.1.

The Et_2OBBr_3 complex decomposed rapidly at room temperature within 2 hours to furnish $EtOBBr_2$: ^{11}B NMR (160 MHz, CD_2Cl_2) δ 25.9. Addition of second molar equivalent of Et_2O to $EtOBBr_2$ furnished a new complex, assigned as $(Et_2O)B(OEt)Br_2$: ^{11}B NMR (160 MHz, CD_2Cl_2) δ -6.0. The $(Et_2O)B(OEt)Br_2$ complex decomposed rapidly at room temperature within 1 hour to furnish two new boron peaks assigned as $(EtO)_2BBr$: ^{11}B NMR (160 MHz, CD_2Cl_2) δ 22.3.

2.6.4 Titration of Diethyl Ether with BCl_3/BBr_3

Under an atmosphere of nitrogen at room temperature, a solution of BCl_3 (100 μL, 1.00 M CH_2Cl_2, 0.10 mmol, 0.25 equiv.), and BBr_3 (100 μL, 1.00 M CH_2Cl_2, 0.10 mmol, 0.25 equiv.) was added to a flame-dried NMR tube containing 0.4 mL CD_2Cl_2. The solution was vortexed for 1 min at room temperature and analyzed by ^{11}B NMR: ^{11}B NMR (128 MHz, CD_2Cl_2) δ

46.6.[21] (BCl_3, integration: 0.6), 45.0 (integration: 1.9), 42.4 (integration: 2.2), 39.0 (BBr_3 integration: 1.0).[21] The peak at 45.0 was assigned to BCl_2Br, and the peak at 42.4 was assigned to $BClBr_2$ based on literature trends.[49]

The resulting solution was then cooled to –78 °C, followed by the addition of Et_2O (21.0 μL, 0.20 mmol, 0.50 equiv.) to afford four ether complexes: ^{11}B NMR (128 MHz, CD_2Cl_2) δ 10.0 [$(Et_2O)BCl_3$],[21] 5.5 [$(Et_2O)BCl_2Br$], −0.1 [[$(Et_2O)BClBr_2$], −6.4 [$(Et_2O)BBr_3$]. The relative ratio of these ether complexes was in good agreement with the ratio of the starting Lewis acids. These complexes decomposed within 8 hours upon warming to room temperature, affording three new boron peaks. These peaks were assigned as follows: ^{11}B NMR (128 MHz, CD_2Cl_2) δ 30.8 [$B(OEt)Cl_2$],[49] 28.9 [B(OEt)BrCl], and 25.9 [$B(OEt)Br_2$].

The solution containing these three boron intermediates was then cooled to –78 °C, and a second addition of Et_2O (21.0 μL, 0.20 mmol, 0.50 equiv.) was added to afford three ether complexes. These decomposed upon warming at room temperature to 4 boron peaks assigned as: ^{11}B NMR (128 MHz, CD_2Cl_2) δ 30.6 [$B(OEt)Cl_2$], 23.0 [$B(OEt)_2Cl$],[49] 19.0 [$B(OEt)_3$], and 10.8 [$(OEt_2)B(OEt)Cl_2$]. There was also indication of very minor amounts of [$B(OEt)_2Br$] which were nearly undetectable. Therefore, the final ratio of [$B(OEt)_2Cl$] and [$B(OEt)_2Br$] was assigned to be > 10:1.

2.6.5 Examination of Selectivity Profile

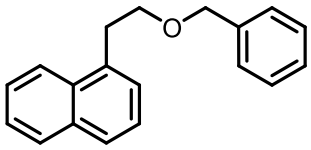
Under an atmosphere of nitrogen at room temperature, a solution of BCl_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol) was mixed with BBr_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol) in a flame-dried NMR tube containing 0.20 mL of CD_2Cl_2 or $CDCl_3$. After 5 minutes, with occasional stirring using a vortex mixer (1 min, 2-3x), the solution was placed in a –78 °C cooling bath, and the desired ether (0.40 mmol, 2.00 equiv. relative to the total boron halides,

dissolved in 0.20 mL of CH_2Cl_2) was added dropwise over 5 min. The solution was maintained at –78 °C and allowed to reach 10–20 °C overnight (*vide infra,* ~16h). Upon completion of the reaction, mesitylene (42 μL, 0.30 mmol, 1.0 equiv.) was added dropwise, then the reaction was analyzed by ^{1}H NMR to determine the yield of products by integrating relative to mesitylene.

2.6.6 The Syntheses of Benzyl Ethers

Under an atmosphere of nitrogen at room temperature, the starting alcohol (1.00 g, 1.00 equiv.) was dissolved in 20 mL THF in a 1-necked, flame-dried, round bottom flask. To this solution sodium hydride (60% dispersed in mineral oil, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, benzyl bromide (1.20 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. After cooling to room temperature, 30 mL of water was added to quench the reaction followed by the addition of diethyl ether (30 mL). The organic layer was separated and washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1% to 5% EtOAc in hexane) on silica gel to afford the desired product.

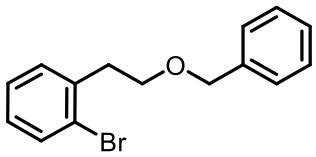
1-(2-(benzyloxy)ethyl)naphthalene (2.31)



Synthesized according to the general procedure using 1.00 g 2-(1-naphthyl)ethanol (5.81 mmol, 1.00 equiv.), 0.46 g NaH (11.6 mmol, 2.00 equiv.), and 0.83 mL benzyl bromide (6.97 mmol, 1.20 equiv.). The product was isolated as a colorless oil (93%) after purification by

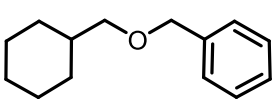
column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.05 (m, 2H), 7.88−7.85 (m, 1H), 7.76−7.74 (m, 1H), 7.54-7.47 (m, 2H), 7.44−7.37 (m, 5H), 4.57 (s, 2H), 3.88−3.83 (m, 2H), 3.47−3.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 134.8, 133.9, 132.1, 128.8, 128.4, 127.7, 127.6, 127.1, 126.8, 125.9, 125.5, 125.5, 123.7, 73.1, 70.6, 34.5. Spectroscopic data were in good agreement with those previously reported.[50]

1-bromo-2-(2-phenoxyethyl)benzene (2.32)



Synthesized according to the general procedure using 1.00 g 2-bromophenethyl alcohol (4.97 mmol, 1.00 equiv.), 0.40 g NaH (9.94 mmol, 2.00 equiv.), and 1.00 mL benzyl bromide (11.6 mmol, 1.20 equiv.). The product was isolated as a colorless oil (81%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 5.2, 0.8 Hz, 1H), 7.37−7.22 (m, 7H), 7.08 (td, J = 5.2, 1.2 Hz, 1H), 4.55 (s, 2H), 3.73−3.71 (m, 2H), 3.09 (t, J = 4.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.2, 132.8, 131.2, 128.4, 128.0, 127.6, 127.6, 127.4, 124.7, 73.0, 69.4, 36.6; HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{15}OBr$ 290.0306; Found 290.0305.

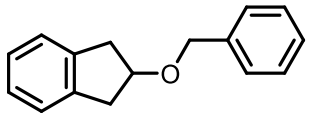
((Cyclohexylmethoxy)methyl)benzene (2.33)



Synthesized according to the general procedure using 1.00 g cyclohexanemethanol (8.76 mmol, 1.00 equiv.), 0.70 g NaH (17.5 mmol, 2.00 equiv.), and 1.25 mL benzyl bromide (10.5

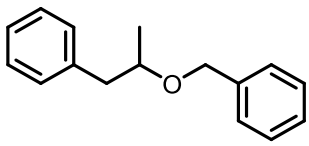
mmol, 1.20 equiv.). The product was isolated as a colorless oil (73%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.34 (m, 4H), 7.28−7.27 (m, 1H), 4.50 (s, 2H), 3.28 (d, *J* = 6.5 Hz, 2H), 1.81−1.78 (m, 2H), 1.73−1.63 (m, 4H), 1.28−1.18 (m, 3H), 0.99−0.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 128.3, 127.6, 127.4, 76.4, 73.0, 38.2, 30.2, 26.7, 26.0; Spectroscopic data were in good agreement with those previously reported.[51]

2-(Benzyloxy)-2,3-dihydro-1H-indene (2.34)



Synthesized according to the general procedure using 1.00 g 2-indanol (7.45 mmol, 1.00 equiv.), 0.60 g NaH (14.9 mmol, 2.00 equiv.), and 1.06 mL benzyl bromide (8.94 mmol, 1.20 equiv.). The product was isolated as a colorless oil (85%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.34 (m, 4H), 7.30−7.29 (m, 1H), 7.23−7.20 (m, 2H), 4.60 (s, 2H), 4.47−4.45 (m, 1H), 3.20 (dd, *J* = 12.8, 5.6 Hz, 2H), 3.07 (dd, *J* = 12.8, 4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ140.9, 138.6, 128.4, 127.7, 127.6, 126.5, 124.7, 79.9, 71.1, 39.4. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{16}O$ 224.1201; Found 224.1200.

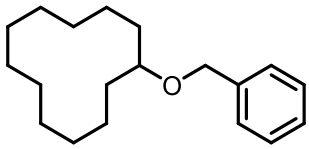
(2-(Benzyloxy)propyl)benzene (2.35)



Synthesized according to the general procedure using 1.00 g 1-phenyl-2-propanol (7.34 mmol, 1.00 equiv.), 0.59 g NaH (14.7 mmol, 2.00 equiv.), and 1.05 mL benzyl bromide (8.81

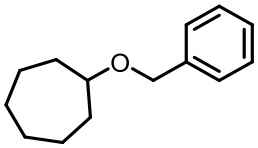
mmol, 1.20 equiv.). Product was isolated as a colorless oil (79%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (m, 10H), 4.60 (dd, *J* = 11.6, 6.4 Hz, 1H), 4.51 (dd, *J* = 12, 6.4 Hz, 1H), 3.82−3.75 (m, 2H), 3.05−2.96 (m, 1H), 2.78−2.72 (m, 1H), 1.26−1.23 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 138.9, 129.5, 128.3, 128.2, 127.5, 127.4, 126.1, 76.2, 70.6, 43.2, 19.6. Spectroscopic data were in good agreement with those previously reported.[52]

(Benzyloxy)cyclododecane (2.36)



Synthesized according to the general procedure using 1.00 g cyclododecanol (5.42 mmol, 1.00 equiv.), 0.43 g NaH (10.8 mmol, 2.00 equiv.), and 0.77 mL benzyl bromide (6.50 mmol, 1.20 equiv.). The product was isolated as a colorless oil (64%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.28−7.26 (m, 1H), 4.52 (s, 2H), 3.55-3.51 (m, 1H), 1.71−1.64 (m, 2H), 1.57−1.51 (m, 2H), 1.47−1.30 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 128.3, 127.8, 127.4, 76.3, 70.3, 28.9, 24.7, 24.2, 23.3, 23.2, 20.8. Spectroscopic data were in good agreement with those previously reported.[53]

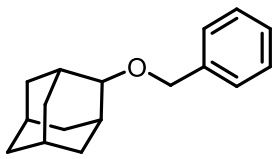
(Allyloxy)cycloheptane (2.37)



Synthesized according to the general procedure using 1.00 g cycloheptanol (8.76 mmol, 1 equiv.), 0.70 g NaH (17.5 mmol, 2.00 equiv.), and 1.25 mL benzyl bromide (10.5 mmol, 1.20

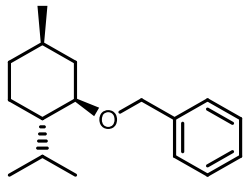
equiv.). The product was isolated as a colorless oil (76%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.33 (m, 4H), 7.32−7.26 (m, 1H), 4.54 (s, 2H), 3.59−3.53 (m, 1H), 1.99−1.92 (m, 2H), 1.76−1.67 (m, 4H), 1.61−1.53 (m, 4H), 1.44−1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 128.3, 127.5, 127.3, 79.4, 70.1, 33.9, 28.5, 23.0. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{20}O$ 204.1514; Found 204.1512.

2-(Allyloxy)adamantane (2.38)



Synthesized according to the general procedure using 1.00 g 2-adamantanol (6.57 mmol, 1.00 equiv.), 0.52 g NaH (13.1 mmol, 2.00 equiv.), and 0.94 mL benzyl bromide (7.88 mmol, 1.20 equiv.). The product was isolated as a colorless oil (68%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.34 (m, 4H), 7.29−7.26 (m, 1H), 4.56 (s, 1H), 3.57−3.56 (m, 1H), 2.16 (d, J = 12 Hz, 2H), 2.11−2.10 (m, 2H), 1.89−1.83 (m, 4H), 1.74 (s, 2H), 1.67 (d, J = 9.2 Hz, 2H), 1.54−1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 128.3, 127.3, 127.2, 81.2, 69.3, 37.7, 36.6, 31.8, 31.7, 27.6. Spectroscopic data were in good agreement with those previously reported.[54]

(1S,2R,4R)-2-(Allyloxy)-1-isopropyl-4-methylcyclohexane (2.39)



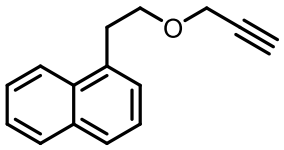
Synthesized according to the general procedure using 1.00 g menthol (6.40 mmol, 1.00 equiv.), 0.51 g NaH (12.8 mmol, 2.00 equiv.), and 0.91 mL benzyl bromide (7.68 mmol, 1.20 equiv.). The product was isolated as a colorless oil (78%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.32 (m, 4H), 7.28−7.25 (m, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.18 (dt, *J* = 10.5, 4.5 Hz, 1H), 2.34−2.28 (m, 1H), 2.22−2.18 (m, 1H), 1.69−1.61 (m, 2H), 1.41−1.27 (m, 2H), 1.02−0.83 (m, 9H), 0.72 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 128.3, 127.9, 127.4, 78.8, 70.5, 48.4, 40.4, 34.6, 31.6, 25.6, 23.3, 22.4, 21.1, 16.1. Spectroscopic data were in good agreement with those previously reported.[55]

2.6.7 The Syntheses of Propargyl Ethers

A 1-necked, oven-dried, round bottom flask containing a stir bar was charged with the alcohol substrate (1.00 g, 1.00 equiv.) and 20 mL THF. To this solution, sodium hydride (60% dispersed in mineral oil, 1.50 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, propargyl bromide (1.20 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. Afterward, the reaction was allowed to cool to room temperature. The reaction was subsequently diluted with 30 mL H_2O and 30 mL diethyl ether, and the layers were separated. The organic layer was washed with water (3x30 mL), dried over $MgSO_4$, filtered, and

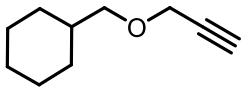
concentrated *in vacuo*. The residue was then purified by flash column chromatography (1% to 5% EtOAc in hexane) on silica gel to afford desired product.

1-(2-(Prop-2-yn-1-yloxy)ethyl)naphthalene (2.40)



Synthesized according to the general procedure using 1.00 g 2-(1-naphthyl)ethanol (5.81 mmol, 1.00 equiv.), 0.35 g NaH (8.72 mmol, 1.50 equiv.), and 0.62 mL propargyl bromide (6.97 mmol, 1.20 equiv.). The product was isolated as a colorless oil (76%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (m, 1H), 7.88−7.85 (m, 1H), 7.76−7.74 (m, 1H), 7.55−7.47 (m, 2H), 7.44−7.38 (m, 2H), 4.19 (d, *J* = 2.4 Hz, 2H), 3.89 (t, *J* = 7.2 Hz, 2H), 3.42 (t, *J* = 7.2 Hz, 2H), 2.43 (t, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 133.9, 132.1, 128.8, 127.2, 126.8, 126.0, 125.5, 125.5, 123.6, 79.8, 74.4, 70.3, 58.2, 33.1. Spectroscopic data were in good agreement with those previously reported.[56]

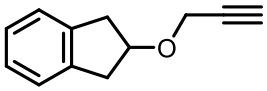
((Prop-2-yn-1-yloxy)methyl)cyclohexane (2.41)



Synthesized according to the general procedure using 1.00 g cyclohexanemethanol (8.76 mmol, 1.00 equiv.), 0.52 g NaH (13.1 mmol, 1.50 equiv.), and 0.94 mL propargyl bromide (10.5 mmol, 1.20 equiv.). The product was isolated as a colorless oil (84%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (d, *J* = 2.4 Hz, 1H), 3.31 (d, *J* = 6.4 Hz, 1H), 2.40 (t, *J* = 2.4 Hz, 1H), 1.78−1.55 (m,

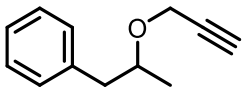
6H) 1.29−1.14 (m, 3H), 0.99−0.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.2, 76.1, 74.0, 58.2, 37.9, 30.1, 26.6, 25.9; HRMS (EI) m/z: $[M-H]^+$ Calcd for $C_{10}H_{15}O$ 151.1122; Found 151.1121.

2-(Prop-2-yn-1-yloxy)-2,3-dihydro-1H-indene (2.42)



Synthesized according to the general procedure using 1.00 g 2-indanol (7.45 mmol, 1.00 equiv.), 0.45 g NaH (11.2 mmol, 1.50 equiv.), and 0.80 mL propargyl bromide (8.94 mmol, 1.20 equiv.). The product was isolated as a colorless oil (73%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.21 (m, 2H), 7.18−7.15 (m, 2H), 4.62−4.56 (m, 1H), 4.23−4.22 (m, 2H), 3.20 (dd, *J* = 16, 6.4 Hz, 2H), 3.03 (dd, *J* = 16, 4.8 Hz, 2H), 2.45−2.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 126.6, 124.7, 80.0, 79.6, 74.2, 56.3, 39.1. Spectroscopic data were in good agreement with those previously reported.[57]

(2-(Prop-2-yn-1-yloxy)propyl)benzene (2.43)

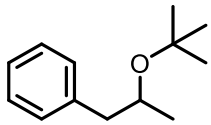


Synthesized according to the general procedure using 1.00 g 1-phenyl-2-propanol (7.34 mmol, 1.00 equiv.), 0.44 g NaH (11.0 mmol, 1.50 equiv.), and 0.78 mL propargyl bromide (8.81 mmol, 1.20 equiv.). The product was isolated as a colorless oil (80%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2H), 7.23−7.20 (m, 3H), 4.15 (d, *J* = 2.4 Hz, 2H), 3.91-3.83 (m, 1H), 2.96 (dd, *J* = 13.6, 6 Hz, 1H), 2.66 (dd, *J* = 13.6, 7.2 Hz, 2H), 2.38 (t, *J* = 2.4 Hz, 1H), 1.16 (d, *J*

= 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 129.5, 128.3, 126.2, 80.3, 75.9, 73.8, 55.9, 42.9, 19.3. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{14}O$ 174.1044; Found 174.4043.

2.6.8 The synthesis of *t*-butyl ether

(2-(Tert-butoxy)propyl)benzene (adapted from a procedure by McClure[58]) (4.29)

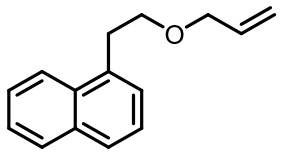


To a rapidly stirring suspension of anhydrous magnesium sulfate (4.81 g, 40.0 mmol) in 30 mL of CH_2Cl_2, concentrated sulfuric acid (0.55 mL, 10.0 mmol) was added dropwise. After stirring for 15 minutes, a mixture of t-butanol (4.78 mL, 50.0 mmol) and 1-phenyl-2-propanol (1.40 mL, 10.0 mmol) dissolved in 10 mL of CH_2Cl_2 was added and the reaction was allowed to stir at room temperature. The progress of the reaction was monitored by TLC. Upon completion of the reaction by TLC analysis, the reaction was quenched by the addition of 75 mL of 5% sodium bicarbonate solution and stirred until all magnesium sulfate had dissolved. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (1% to 5% EtOAc in Hexane) on silica gel to afford the desired ether as a colorless oil (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.26 (m, 2H), 7.20−7.18 (m, 3H), 3.802−3.75 (m, 1H), 2.61 (dd, J = 8.8, 4.4 Hz, 1H), 2.62 (dd, J = 8.8, 4.4 Hz, 1H), 1.12 (d, J = 4 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 129.7, 128.1, 126.0, 73.5, 68.9, 45.7, 28.4, 22.8 Spectroscopic data were in good agreement with those previously reported.[59]

2.6.9 The Syntheses of Allyl Ethers

A 1-necked, flame-dried, round bottomed flask containing a stir bar was charged with the alcohol substrate (1.00 g, 1.00 equiv.) and 20 mL THF. To this solution, sodium hydride (60% dispersed in mineral oil, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, allyl bromide (2.00 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. Afterward, the reaction was allowed to cool to room temperature. The reaction was subsequently diluted with 30 mL H_2O and 30 mL diethyl ether, and the layers were separated. The organic layer was washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified by flash column chromatography 1% to 5% EtOAc in Hexane) on silica gel to afford pure ether.

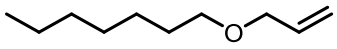
1-(2-(Allyloxy)ethyl)naphthalene (2.30)



Synthesized according to the general procedure using 1.00 g 2-(1-naphthyl)ethanol (5.81 mmol, 1.00 equiv.), 0.46 g NaH (11.6 mmol, 2.00 equiv.), and 1.00 mL allyl bromide (11.6 mmol, 2.00 equiv.). The product was isolated as a colorless oil (86%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 1H), 7.87−7.85 (m, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.54−7.51 (m, 1H), 7.50−7.47 (m, 1H), 7.43−7.38 (m, 2H), 5.98−5.90 (m, 1H), 5.30−5.26 (m, 1H), 5.20−5.17 (m, 1H), 4.03 (dt, J = 5.5, 1.5 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8, 133.8, 132.1, 128.8, 127.0, 126.8, 125.9, 125.5, 125.4,

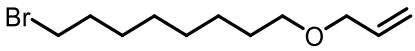
123.7, 117.0, 72.0, 70.6, 33.4. Spectroscopic data were in good agreement with those previously reported.[60]

1-(Allyloxy)heptane (2.44)



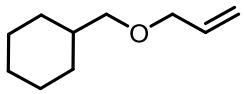
Synthesized according to the general procedure using 1.00 g 1-heptanol (8.60 mmol, 1 equiv.), 0.69 g NaH (17.2 mmol, 2.00 equiv.), and 1.49 mL allyl bromide (17.2 mmol, 2.00 equiv.). The product was isolated as a colorless oil (49%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97−5.87 (m, 1H), 5.29−5.24 (m, 1H), 5.18−5.14 (m, 1H), 3.96 (dt, J = 5.6, 1.4 Hz, 2H), 3.42 (t, J = 6.7 Hz, 2H), 1.62−1.55 (m, 2H), 1.36−1.28 (m, 8H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 116.7, 71.8, 70.6, 31.9, 29.8, 29.2, 26.2, 22.7, 14.1. HRMS (EI) m/z: [M−H] Calcd for $C_{10}H_{19}O$ 155.1436; Found 155.1435.

1-(Allyloxy)-8-bromooctane (2.45)



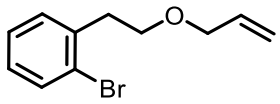
Synthesized according to the general procedure using 1.00 g 8-bromo-1-octanol (4.78 mmol, 1 equiv.), 0.38 g NaH (9.56 mmol, 2.00 equiv.), and 0.83 mL allyl bromide (9.56 mmol, 2.00 equiv.). The product was isolated as a colorless oil (43%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95−5.88 (m, 1H), 5.28−5.24 (m, 1H), 5.18−5.15 (m, 1H), 3.97−3.95 (m, 2H), 3.43−3.38 (m, 4H), 1.88−1.82 (m, 2H), 1.61−1.55 (m, 2H), 1.45−1.40 (m, 2H), 1.37−1.30 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 116.7, 71.8, 70.4, 34.0, 32.8, 29.7, 29.3, 28.7, 28.1, 26.1; HRMS (EI) m/z: [M−C_2H_5] Calcd for $C_9H_{16}OBr$ 219.0384; Found 219.0384.

((Allyloxy)methyl)cyclohexane (2.46)



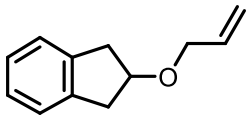
Synthesized according to the general procedure using 1.00 g cyclohexanemethanol (8.76 mmol, 1.00 equiv.), 0.70 g NaH (17.5 mmol, 2.00 equiv.), and 1.51 mL allyl bromide (17.5 mmol, 2.00 equiv.). The product was isolated as a colorless oil (58%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96−5.86 (m, 1H), 5.29−5.23 (m, 1H), 5.17-5.14 (m, 1H), 3.95 (dt, *J* = 5.6, 1.4 Hz, 2H) 3.23 (d, *J* = 6.4 Hz, 2H), 1.78−1.53 (m, 6H), 1.30−1.10 (m, 3H), 0.98−0.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 116.5, 76.4, 72.0, 38.2, 30.2, 26.7, 25.9; HRMS (EI) m/z: [M−H] Calcd for $C_{10}H_{17}O$ 153.1279; Found 153.1280.

1-(2-(Allyloxy)ethyl)-2-bromobenzene (2.47)



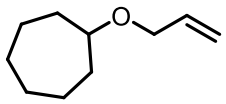
Synthesized according to the general procedure using 1.00 g 2-bromophenethyl alcohol (4.97 mmol, 1.00 equiv.), 0.40 g NaH (9.94 mmol, 2.00 equiv.), and 0.86 mL allyl bromide (9.94 mmol, 2.00 equiv.). The product was isolated as a colorless oil (51%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8 Hz, 1H), 7.31−7.23 (m, 2H), 7.11−7.07 (m, 1H), 5.96−5.88 (m, 1H), 5.31−5.26 (m, 1H), 5.20−5.18 (m, 1H), 4.03−4.01 (m, 2H), 3.71−3.67 (m, 2H), 3.09-3.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 135.0, 132.8, 131.2, 128.0, 127.4, 124.6, 116.9, 71.8, 69.4, 36.5. Spectroscopic data were in good agreement with those previously reported.[61]

2-(Allyloxy)-2,3-dihydro-1H-indene (2.48)



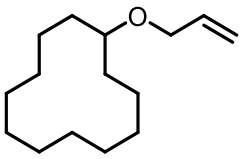
Synthesized according to the general procedure using 1.00 g 2-indanol (7.45 mmol, 1.00 equiv.), 0.60 g NaH (14.9 mmol, 2.00 equiv.), and 1.29 mL allyl bromide (14.9 mmol, 2 equiv.). The product was isolated as a colorless oil (91%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.22 (m, 2H), 7.20−7.17 (m, 1H), 6.03−5.93 (m, 1H), 5.36−5.30 (m, 1H), 5.23−5.19 (m, 1H), 4.46−4.40 (m, 1H), 4.10−4.07 (m, 2H), 3.23−3.18 (m, 2H), 3.06−3.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 135.0, 126.5, 124.7, 116.8, 79.9, 70.1, 39.3. Spectroscopic data were in good agreement with those previously reported.[62]

(Allyloxy)cycloheptane (2.49)



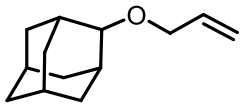
Synthesized according to the general procedure using 1.00 g cycloheptanol (8.76 mmol, 1.00 equiv.), 0.70 g NaH (17.5 mmol, 2.00 equiv.), and 1.52 mL allyl bromide (17.5 mmol, 2.00 equiv.). The product was isolated as a colorless oil (54%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94−5.88 (m, 1H), 5.28−5.24 (m, 1H), 5.14−5.12 (m, 1H), 3.97−3.95 (m, 2H), 3.49−3.44 (m, 1H), 1.92−1.86 (m, 2H), 1.69−1.50 (m, 8H), 1.41−1.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 116.2, 79.5, 69.2, 33.9, 28.5, 23.0. Spectroscopic data were in good agreement with those previously reported.[63]

(Allyloxy)cyclododecane (2.50)



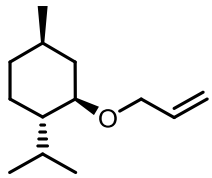
Synthesized according to the general procedure using 1.00 g cyclododecanol (5.42 mmol, 1.00 equiv.), 0.43 g NaH (10.8 mmol, 2.00 equiv.), and 0.94 mL allyl bromide (10.8 mmol, 2.00 equiv.). The product was isolated as a colorless oil (91%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96−5.88 (m, 1H), 5.29−5.24 (m, 1H), 5.16−5.13 (m, 1H), 3.98 (dt, J = 5.5, 1.5 Hz, 2H), 3.48−3.45 (m, 1H), 1.64−1.59 (m, 2H), 1.50−1.45 (m, 2H), 1.42−1.31 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 116.4, 76.4, 69.4, 29.0, 24.7, 24.3, 23.3, 23.2, 20.8. Spectroscopic data were in good agreement with those previously reported.[64]

2-(Allyloxy)adamantane (2.51)



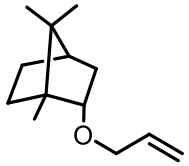
Synthesized according to the general procedure using 1.00 g 2-adamantanol (6.57 mmol, 1.00 equiv.), 0.52 g NaH (13.1 mmol, 2.00 equiv.), and 1.14 mL allyl bromide (13.1 mmol, 2.00 equiv.). The product was isolated as a colorless oil (88%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01−5.91 (m, 1H), 5.32−5.26 (m, 1H), 5.16−5.12 (m, 1H), 4.01−3.99 (m, 1H), 3.48 (t, J = 3.2 Hz, 2H), 2.08−2.01 (m, 4H), 1.87−1.77 (m, 4H), 1.71−1.63 (m, 4H), 1.50−1.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 115.9, 81.1, 68.4, 37.7, 36.6, 31.8, 31.6, 27.5. Spectroscopic data were in good agreement with those previously reported.[65]

(1S,2R,4R)-2-(Allyloxy)-1-isopropyl-4-methylcyclohexane (2.52)



Synthesized according to the general procedure using 1.00 g menthol (6.40 mmol, 1.00 equiv.), 0.51 g NaH (12.8 mmol, 2.00 equiv.), and 1.11 mL allyl bromide (12.8 mmol, 2.00 equiv.). The product was isolated as a colorless oil (92%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98−5.88 (m, 1H), 5.29−5.23 (m, 1H), 5.15−5.12 (m, 1H), 4.14−4.09 (m, 1H), 3.91−3.86 (m, 2H), 3.07 (td, *J* = 10.8, 4.4 Hz, 1H), 2.25−2.21 (m, 2H), 2.12−2.06 (m, 1H), 1.67−1.59 (m, 2H), 1.36−1.30 (m, 1H), 1.28−1.20 (m, 1H), 0.92−0.88 (m, 6H), 0.77 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 116.3, 78.8, 69.6, 48.3, 40.6, 34.6, 31.6, 25.6, 23.4, 22.4, 21.0, 16.3. Spectroscopic data were in good agreement with those previously reported.[63]

(1S,2S,4R)-2-(Allyloxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (2.53)



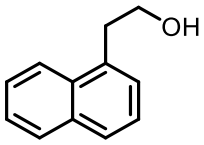
Synthesized according to the general procedure using 1.00 g borneol (6.48 mmol, 1.00 equiv.), 0.52 g NaH (13.0 mmol, 2.00 equiv.), and 1.12 mL allyl bromide (13.0 mmol, 2.00 equiv.). The product was isolated as a colorless oil (53%) after purification by column chromatography (1% to 5% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93−5.84 (m, 1H), 5.28−5.22 (m, 1H), 5.12−5.08 (m, 1H), 4.01−3.95 (m, 1H), 3.88−3.82 (m, 1H), 3.25 (dd, *J* = 3.6, 7.6 Hz, 2H), 1.80−1.74 (m, 1H), 1.69−1.46 (m, 4H), 1.00 (s, 6H), 0.91 (s, 3H),

0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 115.2, 86.6, 69.9, 49.2, 46.5, 45.1, 38.7, 34.5, 27.3, 20.3, 20.2, 11.9. Spectroscopic data were in good agreement with those previously reported.[63]

2.6.10 The Cleavage Reaction with Mixed BBr_3/BCl_3

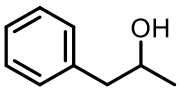
An oven-dried NMR tube containing 0.20 mL of CD_2Cl_2 or $CDCl_3$ was charged with a solution of BCl_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.50 equiv.) and BBr_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.50 equiv.). After 5 minutes, with occasional stirring using a vortex mixer (1 min, 2-3x), the solution was placed under N_2 atmosphere and cooled to –78 °C in an acetone bath. Next, the desired ether (0.40 mmol, 2.00 equiv. relative to the total boron halides, dissolved in 0.20 mL of CH_2Cl_2) was added dropwise over 5 min. The solution was maintained at –78 °C and allowed to reach 10–20 °C overnight (*vide infra,* ~16h). After completion, the reaction was quenched and washed with water (3x10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (5% to 30% EtOAc in Hexane) on silica gel to afford the pure alcohol.

1-Naphthaleneethanol



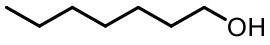
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.0 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.56−7.49 (m, 2H), 7.43 (app t, *J* = 7.0 Hz, 1H), 7.39 (d, *J* = 6.5 Hz, 1H), 3.97 (q, J = 6.5 Hz, 2H), 3.35 (t, J = 6.5 Hz, 2H), 1.69 (t, J = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 134.0, 132.1, 128.8, 127.3, 127.1, 126.0, 125.6, 125.5, 123.6, 63.0, 36.2. Spectral data were in complete agreement with reported values.[66]

3-Phenyl-2-propanol



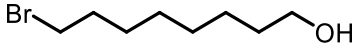
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H) 7.27−7.19 (m, 3H), 4.05−3.95 (m, 1H), 2.80 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.69 (dd, *J* = 13.4, 7.8 Hz, 1H), 1.54 (brs, 1H), 1.25 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 129.4, 128.5, 126.5, 68.9, 45.8, 22.8 Spectral data were in complete agreement with reported values.[67]

1-Heptanol



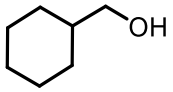
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 2H), 1.59−1.53 (m, 2H), 1.39−1.25 (m, 9H), 0.88 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.1, 32.8, 31.8, 29.1, 25.7, 22.6, 14.1. Spectral data were in complete agreement with reported values.[68]

8-Bromo-1-octanol



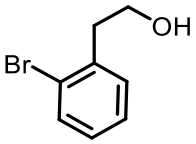
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.4 Hz, 2H), 3.40 (t, *J* = 7.2 Hz, 2H), 1.89−1.81 (m, 2H), 1.60-1.53 (m, 2H), 1.47−1.26 (m, 10H), 1.62−1.55 (m, 2H), 1.36−1.28 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.0, 34.0, 32.8, 32.8, 29.2, 28.7, 28.1, 25.7. Spectral data were in complete agreement with reported values.[69]

Cyclohexanemethanol



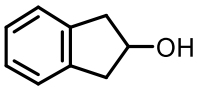
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (d, *J* = 6.4 Hz, 2H), 2.26 (brs, 1H), 1.73−1.61 (m, 5H), 1.48−1.38 (m, 1H), 1.27−1.07 (m, 3H), 0.93−0.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.5, 40.4, 29.6, 26.6, 25.8. Spectral data were in complete agreement with reported values.[70]

2-(2-Bromophenyl)ethanol



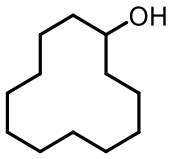
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.28−7.23 (m, 2H), 7.11−7.06 (m, 1H), 3.86 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.16 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 132.9, 131.2, 128.1, 127.4, 124.6, 61.9, 39.2. Spectral data were in complete agreement with reported values.[71]

2-Indanol



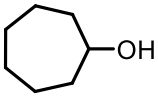
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.31 (m, 2H), 7.26−7.24 (m, 2H), 4.76−4.73 (m, 1H), 3.27 (dd, *J* = 16.5, 6.0 Hz, 2H), 2.97 (dd, *J* = 16.5, 3.0 Hz, 2H), 1.97 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 126.7, 125.0, 73.2, 42.6. Spectral data were in complete agreement with reported values.[72]

Cyclododecanol



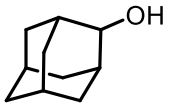
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84-3.82 (m, 1H), 1.67−1.62 (m, 2H), 1.46−1.36 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.2, 32.5, 24.2, 23.9, 23.4, 23.3, 21.0. Spectral data were in complete agreement with reported values.[73]

Cycloheptanol



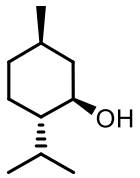
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75−3.72 (m, 1H), 2.52 (brs, 1H), 1.87−1.80 (m, 2H), 1.60−1.41 (m, 8H), 1.36−1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.5, 37.4, 28.1, 22.6. Spectral data were in complete agreement with reported values.[74]

2-Adamantanol



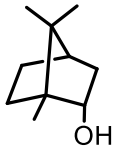
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (brs, 1H), 2.08 (d, J = 12.8 Hz, 2H), 1.87−1.79 (m, 6H), 1.70−1.68 (m, 5H), 1.52 (d, J = 12.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.6, 37.6, 36.6, 34.6, 31.0, 27.6, 27.1. Spectral data were in complete agreement with reported values.[75]

Menthol



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (ddd, *J* = 10.4, 10.4, 4.0 Hz, 1H), 2.18 (septd, *J* = 6.8, 2.8 Hz, 1H), 1.96-1.91 (m, 1H), 1.65−1.57 (m, 3H), 1.44−1.12 (m, 1H), 1.12−0.99 (m, 1H), 0.97−0.83 (m, 3H), 0.90 (d (overlapping with multiplet), *J* = 6.8 Hz, 3H), 0.89 (d (overlapping with multiplet), *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.5, 50.1, 45.1, 34.6, 31.7, 25.8, 23.2, 22.2, 21.0, 16.1. Spectral data were in complete agreement with reported values.[76]

Borneol



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99−3.97 (m, 1H), 2.25 (dddd, *J* = 10.0, 8.4, 4.8, 3.6 Hz, 1H), 1.92−1.84 (m, 1H), 1.75−1.67 (m, 2H), 1.60 (app t, *J* = 4.4 Hz, 1H), 1.26−1.18 (m, 2H), 0.92 (dd, *J* = 13.6, 3.6 Hz, 1H), 0.85 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.3, 49.5, 48.0, 45.1, 39.0, 28.3, 25.9, 20.2, 18.7, 13.3. Borneol is commercially available, and the spectral data match the authentic sample from the commercial supplier.

2.6.11 Evaluation of Temperature Effects on Reaction Rate

A solution of BCl_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.33 equiv.) was mixed with BBr_3 (100 μL, 1.0 M in CH_2Cl_2, 0.10 mmol, 0.33 equiv.) in an NMR tube containing 0.2 mL of CD_2Cl_2 or $CDCl_3$. After 5 minutes, with occasional stirring using a vortex mixer (1 min,

2-3x), the solution was placed in a –78 °C cooling bath. Mesitylene (42 μL, 0.30 mmol, 1.00 equiv.) was added dropwise followed by **2.30** (64.0 mg, 0.30 mmol, 1.00 equiv., dissolved in 0.2 mL CH_2Cl_2). The solution was maintained at –78 °C for one hour, then removed from the bath and placed in a cooling bath of designated temperature. After one hour, the reaction was analyzed by ^{11}B NMR, ^{1}H NMR, and ^{13}C NMR to determine the yield of the desired product by integrating relative to mesitylene.

2.6.12 Evaluation of Functional Group Tolerance

Under an atmosphere of nitrogen at room temperature, a solution of BCl_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.33 equiv.) was mixed with BBr_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.33 equiv.) in a flame-dried NMR tube containing 0.2 mL of CD_2Cl_2 or $CDCl_3$. After 5 minutes, with occasional stirring using a vortex mixer (1 min, 2-3x), the solution was placed in a –78 °C cooling bath, and the ether **2.30** (0.30 mmol, 1 equiv. relative to the total boron halides, dissolved in 0.20 mL of CH_2Cl_2) and the addictive (0.30 mmol, 1.00 equiv.) was added dropwise over 5 min. The solution was maintained at –78 °C and allowed to reach 10–20 °C overnight (*vide infra,* ~16h). Upon completion of the reaction, mesitylene (42.0 μL, 0.30 mmol, 1.00 equiv.) was added dropwise, then the reaction was analyzed by ^{1}H NMR to determine the yield of products by integrating relative to mesitylene.

2.6.13 Evaluation of Degradation of Additives under Reaction Conditions

Under an atmosphere of nitrogen at room temperature, a solution of BCl_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.33 equiv.) was mixed with BBr_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.33 equiv.) in an NMR tube containing 0.20 mL of CD_2Cl_2 or $CDCl_3$. After 5 minutes, with occasional stirring using a vortex mixer (1 min, 2-3x), the solution was placed in a –78 °C cooling bath. Mesitylene (42.0 μL, 0.30 mmol, 1.00 equiv.) and the additive

(0.30 mmol, 1.00 equiv.) was added dropwise followed by the diethyl ether (31.0 μL, 0.30 mmol, 1.00 equiv.). The solution was maintained at –78 °C for one hour, then removed from the bath allowed to reach room temperature. After one hour, the reaction was analyzed by ^{11}B NMR, ^{1}H NMR, and ^{13}C NMR to determine the extent of additive degradation by integrating relative to mesitylene.

2.6.14 Scaled Up Ether Cleavage Reaction

A solution of BCl_3 (400 μL, 1.00 M in CH_2Cl_2, 0.40 mmol, 0.33 equiv.) was mixed with BBr_3 (400 μL, 1.00 M in CH_2Cl_2, 0.40 mmol, 0.33 equiv.) in a 25 mL, 1-necked, flame-dried, round bottomed flask containing 0.8 mL of CH_2Cl_2. After 5 minutes stirring using a stir bar, the flask was placed in a –78 °C cooling bath, and ether **2.30** (1.20 mmol, 1.00 equiv.), dissolved in an additional 0.8 mL of CH_2Cl_2, was added dropwise over 5 min to the boron reagents. The solution was maintained at –78 °C and allowed to reach 10–20 °C overnight (*vide infra*, ~16 h). After completion, the reaction was quenched and washed with water (3x15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (5-20% EA in Hex) on silica gel to afford the desired product as a white solid (0.186 g, 89%).

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Chapter 3: Amino Alcohol Formation through Photochemical Decomposition of Borylazides

3.1 Introduction

Nitrogen is found in many natural products such as alkaloids, peptides, or nucleosides.[1,2] Due to the paramount importance of nitrogen, a large number of methodologies have been developed for the preparation of amino compounds: reductive amination of carbonyl compounds,[3] Buchwald-Hartwig amination,[4] hydroamination or aminohydroxylation of olefins,[5] to name but a few.[6] Methods often require the presence of specific functionality (e.g., carbonyl or double bond) prior to the introduction of the nitrogen atom. An emerging approach to nitrogen introduction is through C−H functionalization, typically using a reactive high-energy nitrene species. Although nitrenes have long been regarded as highly reactive but poorly selective species, many advances have been made in this area by employing metal catalysts (**Figure 3-1**).[7-10]

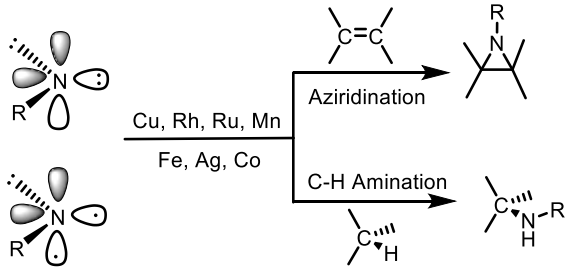
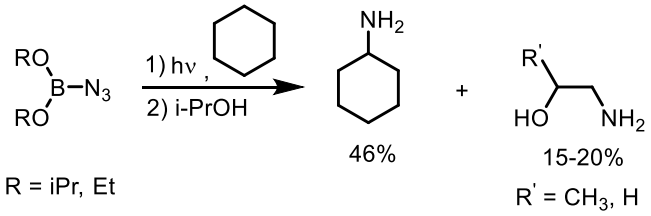


Figure 3-1: Classical reaction of nitrenes

The synthetic utility of boryl azide in the functionalization of organic compounds has been previously investigated by the Bettinger group.[11-15] Bettinger and coworkers developed new methods to functionalize alkanes with boryl nitrenes, resulting in the formation of alkyl amines. They achieved these transformations by irradiating dialkkoxyboryl azides in alkane solvents.[12] They explained this observation by the intermolecular C−H insertion of the

intermediate nitrene, which is generated under photochemical decomposition of the azide precursor. While Bettinger's investigations focused on intermolecular C–H insertions, in one instance they observed an undesired amino alcohol formed from an intramolecular reaction with the isopropyl ligand on the boron center (**Scheme 3-1**).[16] This intramolecular reactivity was not further pursued. However, their observation provides a potential new route to access amino alcohols from simple alcohol starting materials. This method would avoid the use of a metal catalyst and would provide a free amine product instead of a protected amine (typical nitrene-mediated amination methods require sulfonyl or carbonyl groups on the introduced nitrogen center).[17-19]

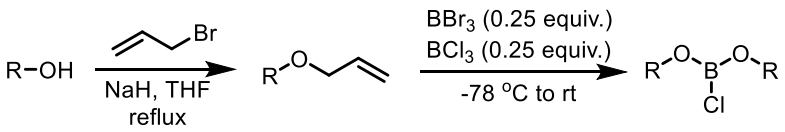


Scheme 3-1: C−H insertion observed by the Bettinger group

3.2 General Design and Methods

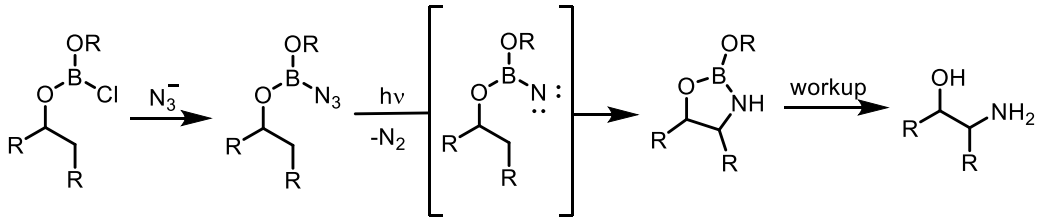
Bettinger and coworkers generate their dialkoxyboryl azides from the corresponding dialkoxyboryl chloride precursor, making the generation of dialkoxyboryl chlorides a key step of our strategy. Dialkoxyboryl chlorides have historically been accessed by disproportionation of trialkyl borates and BCl_3.[20] However, this method works best for small trialkyl borates due to challenges associated with the preparation of large, bulky trialkyl borates. Our group has concentrated on the in-situ selective preparation of mono- and dialkoxyboryl chlorides from alcohols and boron trichloride directly. During the course of our investigations, we had discovered that alcohols, metal alkoxides, and silyl-protected

alcohols are either ineffective or inefficient for this purpose, providing a mixture of trialkyl borates, dialkoxyboryl chloride, and monoalkoxyboryl chloride. However, as described in chapter 2, ethers can be used to predictably furnished mono- or dialkoxyboryl chloride with high efficiency and selectivity (**Scheme 3-2**). The allyl halide byproduct in this reaction is removed under vacuum.



Scheme 3-2: Mixture of boron halides mediated dialkoxychloroborane formation

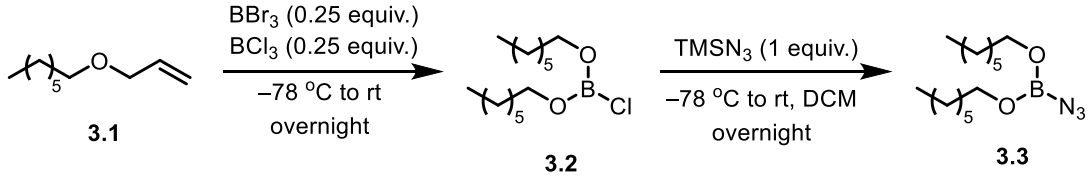
Starting from a target substrate containing an alcohol, Bettinger had shown that quantitative conversion from the dialkoxyboryl chloride to the dialkoxyboryl azide occurs upon addition of trimethylsilyl azide. Exposure to light at the appropriate wavelength would then generate the reactive nitrene species via dinitrogen extrusion. Calculations predict that boryl nitrenes are more stable than carbon-based nitrenes due to an empty p-orbital on the boron center which accepts electron density from an adjacent nitrene lone pair.[11] This electron delocalization stabilizes the nitrene and attenuates the poor chemoselectivity that is often associated with high energy nitrenes. Intramolecular insertion into a neighbouring sp^3 C–H bond leads to an amino alcohol upon aqueous workup due to the lability of B–N and B–O bonds in protic alcohol and water environments.



Scheme 3-3: Outline of proposed strategy for intramolecular nitrogen delivery

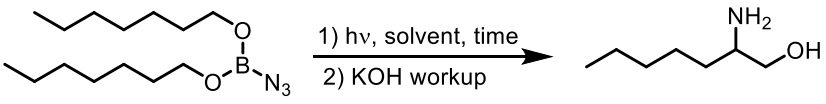
3.3 Result and Discussion

3.3.1 Optimization of Reaction Conditions



1-(Allyloxy)heptane (**3.1**) was chosen as a model for this transformation. 1-(Allyloxy)heptane is a primary alkyl allyl ether, which gives rise to diheptoxyboryl chloride intermediate (**3.2**) in high yield upon boron trihalide ether cleavage. This substrate was chosen for its functional group simplicity. Diheptoxyboryl chloride intermediate (**3.2**) was converted to the azide precursor by treatment with trimethylsilyl azide ($TMSN_3$). The reaction proceeded smoothly to give diheptoxyboryl azide (**3.3**) from the chloride intermediate in quantitative yield. TMSCl was removed under vacuum and the reaction residue was resuspended in the chosen solvent. This procedure was used to evaluate several solvents for the amination of the heptoxy side chain upon irradiation (**Table 3-1**).

Table 3-1: Screen for reaction conditions



3.3

Entry	Time	Solvent	Concentration	Yield
1	16	$CDCl_3$	0.33	ND
2	16	$CDCl_3$	0.25	ND
3	16	$CDCl_3$	0.20	ND
4	16	CD_3NO_2	0.20	ND
5	16	C_6H_6	0.20	ND
6	9	$CDCl_3$	0.20	ND
7	16	$CDCl_3$	0.20	ND*

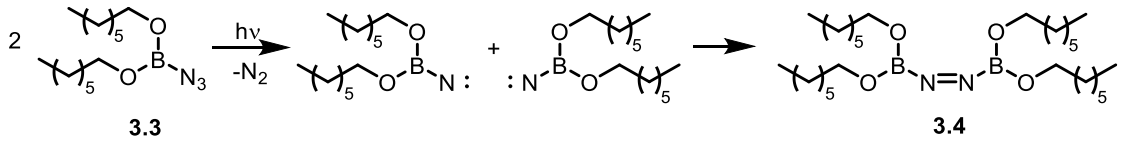
ND = not determined by LC-MS

* reaction was performed at 40 ^oC without UV irradiation

The mixture was irradiated under UV light and monitored by ^{11}B NMR until the starting material peak was gone. Unfortunately, across different solvents and different concentrations, no amination products were observed by ^1H NMR and LC-MS data upon hydrolysis (entry 1). The product of the reaction was simply the heptyl alcohol that one would obtain upon hydrolysis of the starting dialkoxy boron species. A test reaction was also performed in the absence of irradiation. The solution was left at 40 ^oC (the same at the internal temperature of the photo reactor) for 16 hours. It was shown that the boron-azide peak remained unchanged in the ^{11}B NMR, indicating that irradiation is responsible for altering the boron complex in some manner.

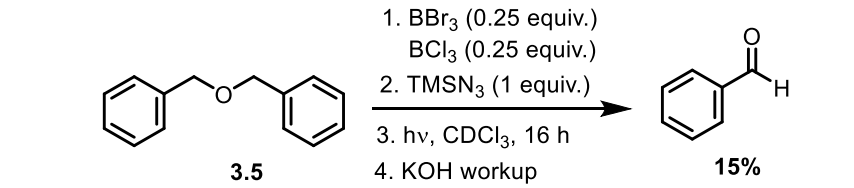
UV light may be inducing the photochemical decomposition of an azide to a nitrene intermediate. However, the insertion step was not effective. One possible explanation is that the intermediate nitrene may be combining with another azide or second nitrene equivalent to make diazo species in situ (**Scheme 3-4**). Alternatively, the nitrene may be reacting with

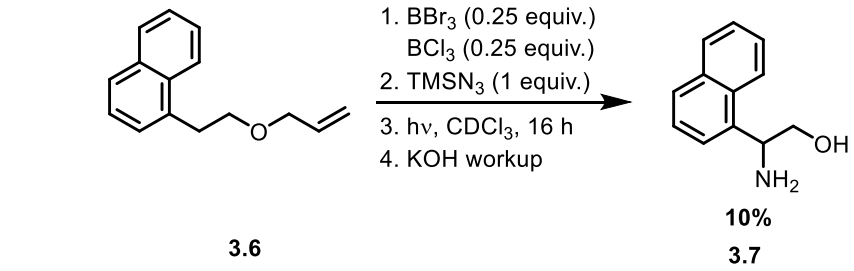
solvent, though it should be noted that no byproducts have thus far been observed that could correspond with solvent reactivity.



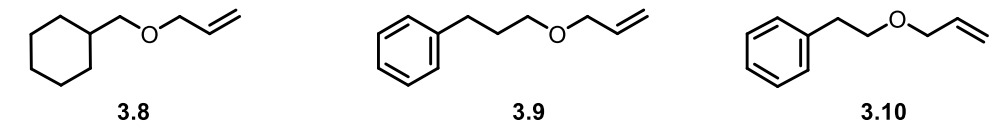
Scheme 3-4: Proposed side reaction

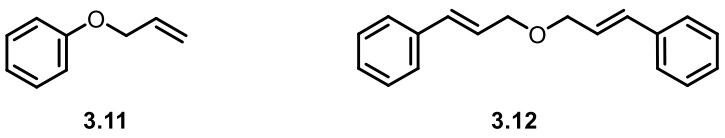
3.3.2 Examination of Various Alkyl Groups





Other substrates examined





Scheme 3-5: Screening of various substrates

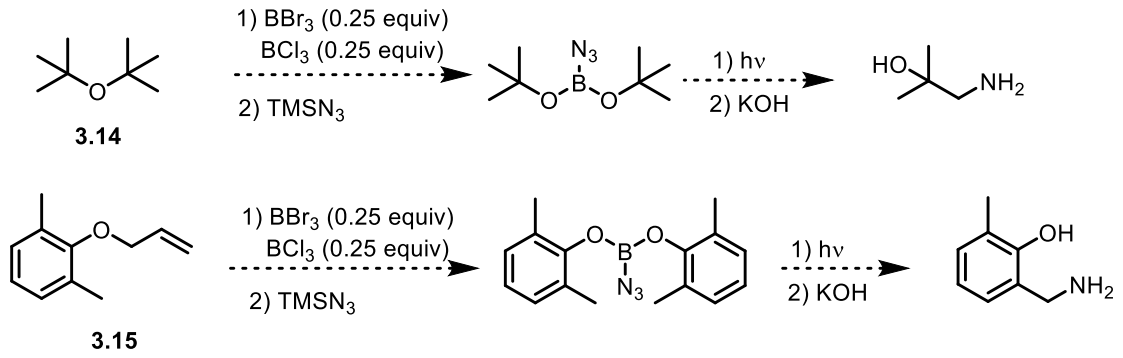
Based on the analysis above, a variety of primary alkyl allyl ethers containing different types of C−H bonds was screened. Substrate **3.5** containing benzylic C−H bonds, which is more reactive than primary alkyl C−H bonds, was examined for this reaction. Unfortunately, instead of giving desired product, **3.5** was successfully converted to benzaldehyde, which is presumed to proceed through an aminal intermediate. Substrate **3.6**, which has an extended aromatic system also produced amino alcohol product in modest yield. In contrast, substrate **3.8** containing a tertiary C−H bond failed to yield the desired amino alcohol product. Similarly, the same results were observed for substrates **3.7** and **3.8** bearing benzylic C−H bonds beside primary and secondary C−H bonds.

3.4 Conclusions and future works

Thus far, the initial results suggest that the formation of an amino alcohol from a simple ether by employing a borylnitrene intermediate can indeed form the desired product but not yet in an efficient manner. The main issue often encountered with nitrenes is the short lifetime and high reactivity. Therefore, nitrene intermediates can decompose or perform other reactions rather than in the expected route. Looking back to Bettinger's results, the nitrene preferred intermolecular insertion to intramolecular insertion under their examined conditions. The experiment where the intramolecular insertion was observed as a minor product was the irradiation of acyclic diisopropoxyboryl azide. Since this involves a secondary alkyl side chain, we believe steric hindrance of the alkyl group may play an important role. In order to achieve the insertion of nitrenes to C–H positions, the nitrene must be formed at a suitable distance from the desired reactive group.

Future work includes screening different substrates in order to understand which functional groups result in an intramolecular insertion reaction (**Scheme 3-6**). Wavelength, solvent and

concentration are also variables to explore further for this transformation. Finally, the use of photocatalyst to initiate the decomposition of azide will be considered.



Scheme 3-6: Future directions

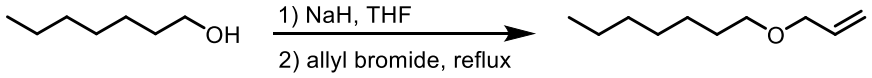
3.5 Experimental

General information: Reactions were carried out in oven-dried (> 130 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous reagents was accomplished with oven-dried syringes or cannulae. Dichloromethane (DCM), ethyl acetate (EA), and tetrahydrofuran (THF) were purified using a double cartridge solvent purification system prior to use. All other solvents were purchased, vacuum-distilled (twice) and stored under nitrogen over oven-dried (> 200 °C) molecular sieves (3Å or 4Å). Deuterated dichloromethane (d^2-DCM) and deuterated chloroform ($CDCl_3$) were stored in a container with oven-dried (> 200 °C) molecular sieves (3Å or 4Å). Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm silica gel with a fluorescent indicator UV_{254} (EMD Millipore), which were visualized under UV light and with a $KMnO_4$ stain. Flash chromatography columns were packed with 230-400 mesh silica gel (Silacycle). All reagents were purchased from commercial suppliers: Sigma Aldrich, AK Scientific, and Acros, at purity greater than (95%), unless otherwise specified.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 or 500 MHz, and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 or 125 MHz. Proton decoupled boron nuclear magnetic resonance spectra (^{11}B{^{1}H} NMR) were recorded at 160 MHz, usually using a quartz NMR tube to avoid background signals (*vide infra*). The chemical shifts were reported on the δ scale (ppm) and referenced to the residual protonated solvent (^{1}H) or to the deuterated solvent (^{13}C) peaks: $CDCl_3$ (7.26 ppm, ^{1}H; 77.06 ppm, ^{13}C), and CD_2Cl_2 (5.32 ppm, ^{1}H; 53.5 ppm, ^{13}C). 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. Unless otherwise stated, Boron (^{11}B NMR) nuclear magnetic resonance spectra were recorded without any chemical shift adjustment. In cases where the NMR tube used in the measurement of ^{11}B NMR nuclear magnetic resonance spectra was not made of quartz, spectral adjustment (backward linear prediction) was done to subtract the contribution of borosilicates from the measurements.

3.5.1 The Synthesis of Ether Substrates

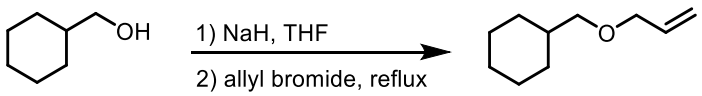
1-(Allyloxy)heptane (3.1)



To a round bottom flask containing heptanol (1.00 g, 8.60 mmol, 1.00 equiv.) in 30 mL THF, sodium hydride (60% dispersed in mineral oil, 0.69 g, 17.2 mmol, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, allyl bromide (2.08 g, 17.2 mmol, 2.00 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. Afterwards, the reaction was allowed to cool to room temperature. The reaction was subsequently diluted with 30 mL H_2O and 30 mL

diethyl ether, and the layers were separated. The organic layer was washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (5% ethyl acetate in hexane) on silica gel to afford pure product as a colorless oil (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97−5.87 (m, 1H), 5.29−5.24 (m, 1H), 5.18−5.14 (m, 1H), 3.96 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 1.62−1.55 (m, 2H), 1.36−1.28 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 116.7, 71.8, 70.6, 31.9, 29.8, 29.2, 26.2, 22.7, 14.1. HRMS (EI) m/z: [M−H] Calcd for $C_{10}H_{19}O$ 155.1436; Found 155.1435.

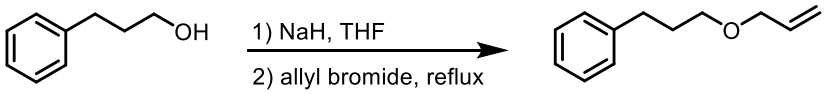
((Allyloxy)methyl)cyclohexane (3.8)



To a round bottomed flask containing cyclohexanemethanol (1.00 g, 8.76 mmol, 1.00 equiv.) in 30 mL THF, sodium hydride (60% dispersed in mineral oil, 0.70 g, 17.5 mmol, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, allyl bromide (2.12 g, 17.5 mmol, 2.00 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. Afterward, the reaction was allowed to cool to room temperature. The reaction was subsequently diluted with 30 mL H_2O and 30 mL diethyl ether, and the layers were separated. The organic layer was washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (5% ethyl acetate in hexane) on silica gel to afford pure product as a colorless oil (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96−5.86 (m, 1H), 5.29−5.23 (m, 1H), 5.17-5.14 (m, 1H), 3.95 (dt, *J* = 5.6, 1.4 Hz, 2H) 3.23 (d, *J* = 6.4 Hz, 2H), 1.78−1.53 (m, 6H), 1.30−1.10 (m, 3H), 0.98−0.88 (m, 2H); ^{13}C NMR (125 MHz,

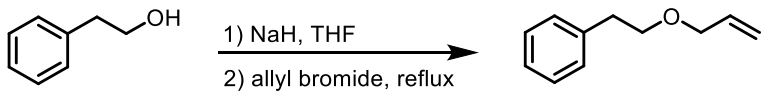
$CDCl_3$) δ 135.3, 116.5, 76.4, 72.0, 38.2, 30.2, 26.7, 25.9; HRMS (EI) m/z: [M−H] Calcd for $C_{10}H_{17}O$ 153.1279; Found 153.1280.

(3-(Allyloxy)propyl)benzene (3.9)



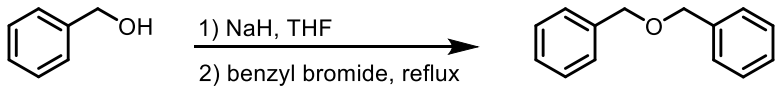
To a round bottomed flask containing 3-phenyl-1-propanol (1.00 g, 7.34 mmol, 1.00 equiv.) in 30 mL THF, sodium hydride (60% dispersed in mineral oil, 0.59 g, 14.7 mmol, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, allyl bromide (1.78 g, 14.7 mmol, 2.00 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. Afterward, the reaction was allowed to cool to room temperature. The reaction was subsequently diluted with 30 mL H_2O and 30 mL diethyl ether, and the layers were separated. The organic layer was washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (5% ethyl acetate in hexane) on silica gel to afford pure product as a colorless oil (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.21−7.18 (m, 3H), 5.98−5.90 (m, 1H), 5.31−5.27 (m, 1H), 5.20−5.17 (m, 1H), 3.98 (dt, J = 6.5, 1.5 Hz, 2H), 3.46 (t, J = 6.5 Hz, 2H), 2.72 (t, J = 8.0 Hz, 2H), 1.96−1.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 135.0, 128.5, 128.3, 125.8, 116.8, 71.9, 69.5, 32.4, 31.4. Spectroscopic data were in good agreement with those previously reported.[21]

(2-(Allyloxy)ethyl)benzene (3.10)



To a round bottomed flask containing 2-phenylethanol (1.00 g, 8.20 mmol, 1.00 equiv.) in 30 mL THF, sodium hydride (60% dispersed in mineral oil, 0.65 g, 16.4 mmol, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, allyl bromide (1.98 g, 16.4 mmol, 2.00 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. Afterward, the reaction was allowed to cool to room temperature. The reaction was subsequently diluted with 30 mL H_2O and 30 mL diethyl ether, and the layers were separated. The organic layer was washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (5% ethyl acetate in hexane) on silica gel to afford pure product as a colorless oil (73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.28 (m, 2H), 7.24−7.20 (m, 3H), 5.94−5.88 (m, 1H), 5.28−5.25 (m, 1H), 5.18−5.16 (m, 1H), 4.01−3.99 (m, 2H), 3.66 (t, J = 7.0 Hz, 2H), 2.91 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 134.9, 128.9, 128.4, 126.2, 116.9, 71.9, 71.3, 36.4. Spectroscopic data were in good agreement with those previously reported.[22]

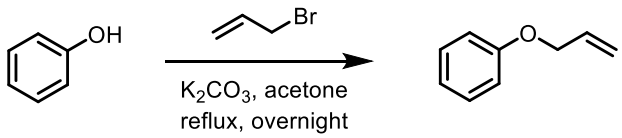
Dibenzyl ether (3.5)



A 1-necked round bottomed flask was flame-dried and cooled under a stream of nitrogen gas. The flask was charged with benzyl alcohol (1.00 g, 9.25 mmol, 1.00 equiv.) in 30 mL THF. To this solution, sodium hydride (60% dispersed in mineral oil, 0.74 g, 18.5 mmol,

2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, benzyl bromide (1.32 mL, 11.1 mmol, 1.20 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. After cooling to room temperature, 30 mL of water was added to quench the reaction followed by the addition of diethyl ether (30 mL). The organic layer was separated and washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) on silica gel to afford the desired product as a colorless oil (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 10H), 4.58 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 128.4, 127.8, 127.6, 72.1. Spectroscopic data were in good agreement with those previously reported.[23]

(Allyloxy)benzene (adapted from a procedure by Brimble[27]) (3.11)

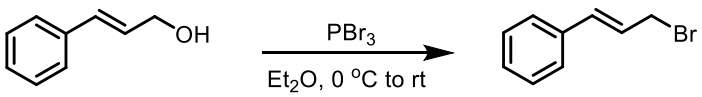


Under an atmosphere of nitrogen at room temperature, phenol (0.50 g, 5.31 mmol, 1.00 equiv.) potassium carbonate (1.47 g, 10.6 mmol, 2.00 equiv.) were dissolved in 30 mL acetone in a 1-necked, flame-dried, round bottomed flask. To this solution, allyl bromide (0.96g, 7.96 mmol, 1.50 equiv) was added and allowed to stir for a few minutes at room temperature before heating to reflux overnight. The flask was then cooled to room temperature and the reaction mixture was filtered through a pad of celite. The residue was concentrated *in vacuo* and purified by flash column chromatography (3% ethyl acetate in hexane) on silica gel to afford the desired product as a colorless oil (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2H), 6.98−6.93 (m, 3H), 6.11−6.06 (m, 1H), 5.46−5.42 (m, 1H), 5.32−5.29 (m, 1H), 4.56 (d, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6,

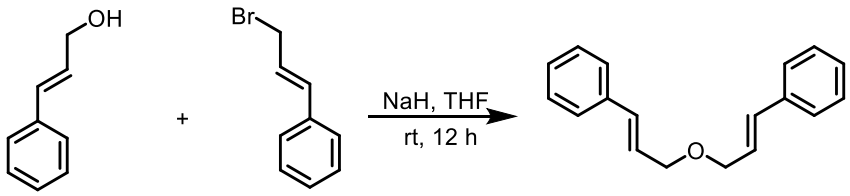
133.4, 129.4, 120.8, 117.6, 114.8, 68.7. Spectroscopic data were in good agreement with those previously reported.[24]

(E,E')-Dicinnamyl ether (adapted from a procedure by Strohmann[25] and Yoon[26])

(3.12)



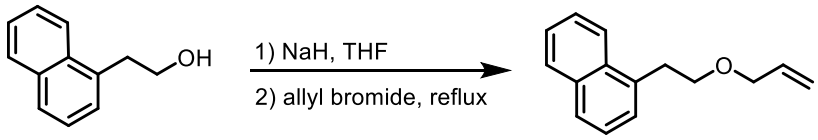
Phosphorus tribromide (0.82 mL, 8.65 mmol, 1.50 equiv.) was added to a solution of cinnamyl alcohol (2.32 g, 17.3 mmol, 1.00 equiv.) in diethylether (25 mL) at 0 °C. The solution was allowed to warm to room temperature and stired for 24 h. Then, a saturated solution of ammoniumchloride was added to quench the reaction. The phases were separated, and the aqueous phase was extracted with diethylether (3×20 mL). The combined organic phases were washed with brine, dried over MgSO4, filtered, and concentrated in vacuo to yield pure product as a yellow oil (87%). ^{1}H NMR (400 MHz, CDCl3) δ 7.41−7.38 (m, 2H), 7.35−7.32 (m, 2H), 7.29−7.27 (m, 1H), 6.66 (d, *J* = 15.5 Hz, 1H), 6.44−6.38 (m, 1H), 4.17 (dd, *J* = 8, 1 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 135.8, 134.6, 128.7, 128.4, 126.8, 125.2, 33.4. Spectroscopic data were in good agreement with those previously reported.[25]



A flame-dried round bottom flask equipped with a stir bar was charged with (*E*)-cinnamyl alcohol (1.34 g, 10.0 mmol, 1.00 equiv.) in 20 mL dry THF. To this solution, sodium hydride (60% dispersed in mineral oil, 2.00 equiv.) was added and allowed to stir for 30 minutes at

room temperature under inert atmosphere. Then, (*E*)-cinnamyl bromide (2.17 g, 11.0 mmol, 1.10 equiv.) dissolved in 12 mL THF was added to the flask at 0 °C. The mixture was allowed to warm slowly to room temperature and stir for 12 h. Upon completion, the reaction was quenched by slow addition of saturated NH_4Cl. The aqueous layer was extracted with Et_2O (2×20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was purified by flash column chromatography (3% ethyl acetate in hexane) on silica gel to afford the desired product as a colorless oil (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.39 (m, 4H), 7.33−7.30 (m, 4H), 7.25−7.23 (m, 2H), 6.64 (d, *J* = 15.4 Hz, 2H), 6.33 (dt, *J* = 16.1, 6.3 Hz, 2H), 4.21 (dd, *J* = 6.3, 1.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 132.6, 128.6, 127.7, 126.5, 126.0, 70.8. Spectroscopic data were in good agreement with those previously reported.[26]

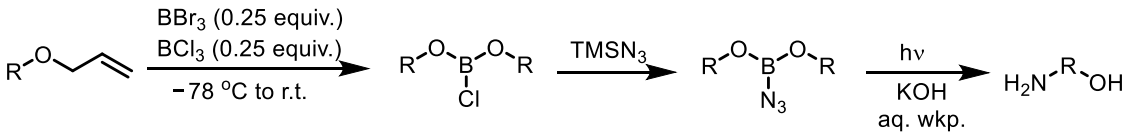
1-(2-(Allyloxy)ethyl)naphthalene (3.6)



To a round bottomed flask containing 2-phenylethanol (1.00 g, 5.81 mmol, 1.00 equiv.) in 30 mL THF, sodium hydride (60% dispersed in mineral oil, 0.46 g, 11.6 mmol, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, allyl bromide (1.00 mL, 11.6 mmol, 2.00 equiv.) was added and the reaction mixture was stirred at room temperature for 10 minutes before heating to reflux overnight. Afterward, the reaction was allowed to cool to room temperature. The reaction was subsequently diluted with 30 mL H_2O and 30 mL diethyl ether, and the layers were separated. The organic layer was washed with water (3x30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (5% ethyl acetate in hexane) on silica gel to

afford pure product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97-5.87 (m, 1H), 5.29−5.24 (m, 1H), 5.18−5.14 (m, 1H), 3.96 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 1.62−1.55 (m, 2H), 1.36−1.28 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 116.7, 71.8, 70.6, 31.9, 29.8, 29.2, 26.2, 22.6, 14.1. Spectroscopic data were in good agreement with those previously reported.[22]

3.5.2 Generation of Dialkoxyboryl azides and subsequent irradiation



An oven-, or flame-dried quartz NMR tube containing 0.20 mL of CD_2Cl_2 or $CDCl_3$ was charged with a solution of BCl_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.50 equiv.) and BBr_3 (100 μL, 1.00 M in CH_2Cl_2, 0.10 mmol, 0.50 equiv.). After 5 minutes, with occasional vortexing (1 min, 2-3x), the solution was placed under an N_2 atmosphere and cooled to –78 °C in a dry ice/acetone bath. Next, the desired ether (0.40 mmol, 2.00 equiv. relative to the total boron halides, dissolved in 0.20 mL of $CDCl_3$) was added dropwise over 5 min. The solution was maintained at –78 °C and allowed to reach 10–20 °C overnight. The progress of the reaction was monitored by 11B NMR spectroscopy. Typically, the reaction proceeds to complete conversion after 16 h (some substrates may need additional time). Then, the reaction was cooled to –78 °C, and $TMSN_3$ (26.5 μL, 0.20 mmol, 1.00 equiv.) was added by syringe and allowed to slowly diffuse in the cold solution. After slow warming to room temperature overnight, the reaction was placed under vacuum, and the TMSCl by-product was significantly reduced (>80%) or completely evaporated based on ^{1}H NMR. If any of the volatiles (TMSCl, CD_2Cl_2 and dichloromethane) were still present based on ^{1}H NMR, then 0.4 mL $CDCl_3$ was added and evaporation was repeated. Afterward, the appropriate

deuterated solvent (exact volume depends on the target concentration) was added to the residue remaining in the NMR tube. The solution was then irradiated inside a Rayonet photoreactor, equipped with eight low-pressure mercury lamps (λ_{max} = 254 nm), arranged in circular fashion, and a fan, for an appropriate time. The internal photoreactor temperature was maintained roughly at 35-40 ^{o}C, by using a fan in the photoreactor. Finally, the solution was put under a positive pressure of dry nitrogen gas before and during the irradiation. Once completed, the reaction was slowly quenched by dropwise addition of concentrated KOH solution (6 M, 0.50 mL) and transferred to a flask. The reaction vessel was washed with CH_2Cl_2 (minimum 3x, ca. 3 mL) and concentrated KOH solution (6 M, minimum 3x, 3 mL) and stirred for 2 hours. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo* before submitting to NMR analysis. An aliquot of this solution was analyzed by Liquid Chromatography/Mass Spectrometry.

3.6 References

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Chapter 4: Synthesis of N-Heterocyclic Carbene Ligands to Facilitate Suzuki-Miyaura Coupling Reactions in Aqueous Media

4.1 Introduction

4.1.1 Introduction Transition Metal-catalyzed Carbon Cross-coupling Reactions

Carbon-carbon bond formation is the key step in the preparation of complex molecules from simple starting materials. Aldol reactions, Grignard reactions, and the Diels-Alder reactions are a few examples of impactful methods to construct complex carbon frameworks. In the last few decades, metal-catalyzed cross-coupling has emerged for construction of aryl carbon-carbon bonds.[1-5] Coupling reactions have become a strategy of choice in industry and academia alike.[6,7,8,9] Because of the impact of the discovery of these reactions, the 2010 Nobel Prize in Chemistry was awarded to Richard Heck, Ei-ichi Negishi and Akira Suzuki.[10,11]

Carbon-carbon bond forming processes involve the treatment of halides or triflates with organometallic reagents in the presence of transition metal complexes generally based on nickel, palladium or platinum. Palladium is widely used for this reaction due to its effectiveness and substrate scope tolerance.[6,7,8] The generally accepted mechanism for this transformation is represented in **Figure 4-1**. The first step is oxidative addition of halides (or pseudohalides) to the active Pd(0) species. The reaction then progresses by transmetallation of an organometallic species to form a Pd(II) intermediate. The transmetallation is followed by reductive elimination to lead to C-C bond formation with the regeneration of the Pd(0) species.[5]

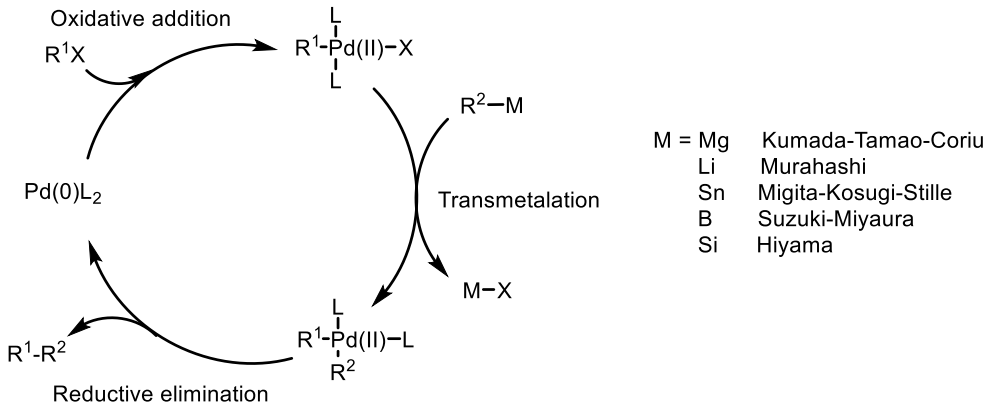


Figure 4-1: General catalytic cycles of cross coupling reaction

4.1.2 Suzuki-Miyaura Coupling

Among many different cross-coupling reactions listed, Suzuki-Miyaura coupling is the most widely exploited cross-coupling reaction protocol (**Figure 4-2**).[2,11-14] Organoboron compounds are employed as the transmetallation partner. Organoboranes enjoy significant attention due to the mild experimental conditions allowed and high stability of the organoboron substrates towards oxygen and moisture as compared to other transmetallation partners.[15-18]

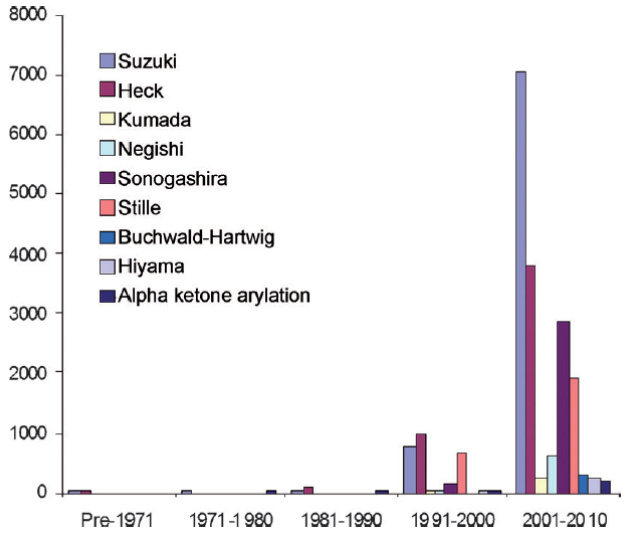


Figure 4-2: Number of publications and patents on metal-catalyzed cross coupling reactions 1971-2010[5]

4.1.3 Cross Coupling Reactions in Aqueous Environments

Out of all metals employed for cross coupling reactions, much work has been done to perform palladium catalysis in water for biological systems.[19-21] The Davis group has developed biomolecular compatible Pd-complexes to tag and modify peptides, sugars,[22] proteins,[23,24] and DNA.[25] This cross-coupling strategy was successfully applied to the cell-surface labelling of *Escherichia coli*.[26] The 4-iodo-phenylalanine was incorporated into the bacterial surface protein and subsequently reacted with fluorescent boronic acid in the presence of $Pd(OAc)_2(ADHP)_2$ (2-amino-4,6-dihydroxypyrimidine) as a catalyst.[26] The reaction proceeded well at 37 ºC for 1 h with less than 3% cell death.[26] By applying 2-dimethylamino-4,6-dihydroxypyrimidine (DMADPH), dimethylguanidine (DMG) and tetramethylguanidine (TMG) as ligands, they further expanded the application of this system to radiobiology by allowing the labelling of peptides and proteins with a fluorine-18 isotope.[24] Chen and coworkers demonstrated N-heterocyclic carbene ligands containing hydrophilic quaternary ammonium groups can facilitate Pd-mediated Suzuki-Miyaura coupling reaction of many unnatural amino acids and proteins.[27] This catalyst system was also utilized to label proteins on the surface of mammalian cells.[27] Recently, the Pentelute group reported the use of (RuPhos)Pd complexes for selective cysteine conjugation reactions under biocompatible reaction conditions. Fluorescent tags, affinity tag, bioconjugation handles, and drug molecules were successfully attached to proteins and peptides by this palladium-based reagent.[47]

Even though there are many efforts to perform Suzuki-Miyaura reactions without base or high temperature, for most applications Suzuki-Miyaura reactions still require elevated temperature and/or the addition of base or mixed organic solvent in order to achieve appropriate catalytic efficiency. This can be problematic for the modification of

biomolecules, especially for protein modifications. The examples by the Davis, Chen and Pentalute demonstrate the potential for Suzuki-Miyaura catalysis to be performed on a wider range of substrates and in greener conditions, however no single catalytic design has been optimized to a sufficient degree as to be useful across a variety of substrates under neutral, protic, room temperature conditions.

4.1.4 Introduction to N-Heterocyclic Carbene ligand

Besides phosphorous-containing ligands, N-heterocyclic carbenes (NHCs) are a highly effective ligand type for cross coupling reactions.[28-31] Since the first stable NHC was isolated by Arduengo in 1991,[32] NHCs have become ubiquitous in the literature, especially in the field of organometallic chemistry. Compared to phosphines, NHC ligands are less toxic and show higher thermal stability.[28] Furthermore, metal complexes of NHCs are typically stable in water and resistant to oxidation by air, which makes these ligands well-suited for cross coupling reactions in water and alcohol solvents (**Figure 4-3**) (sometimes considered the natural enemy of organometallic species).[28,33]

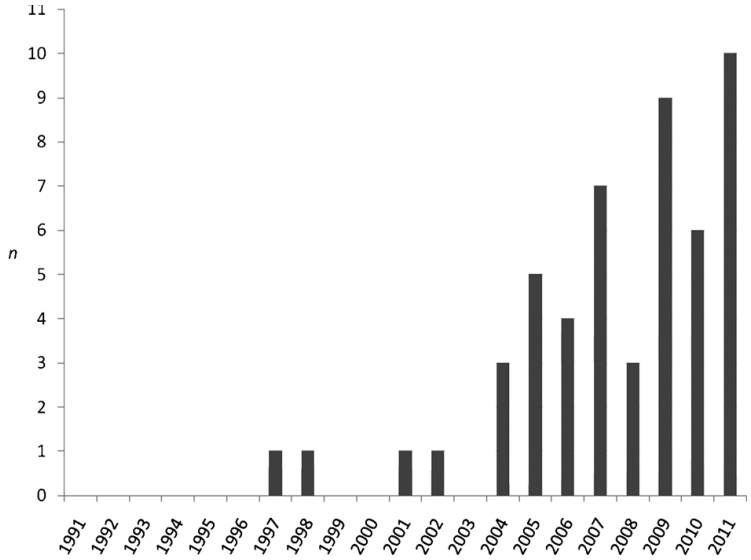


Figure 4-3: Number of publications dealing with water-soluble NHCs 1991-2011[33]

In 2013, the Cardierno group reported the first air-stable Au(III) complexes containing water-soluble sulfonated NHC ligands.[34] These complexes were accessed easily by oxidation of Au(I) precursor complexes. The authors successfully applied the Au(III)-NHC complex to the synthesis of enol lactones from γ-alkynoic acids in water-toluene mixtures. Remarkably, the catalyst could be isolated after the reaction and recycled up to 10 times without loss of catalytic activity or selectivity. This catalytic robustness is common in *N*-heterocyclic carbenes based on the Arduengo (imidazolium) scaffold.

4.2 General Design and methods

In the Suzuki-Miyaura reaction, base is often necessary in order to promote transmetallation.[12,18] There are two known mechanisms of transmetallation in the presence of base (**Figure 4-4**).[35] In the first mechanism, a hydroxide or alkoxide moiety coordinates to the boron center of the boronic acid, weakening and activating the B−C bond for exchange with the palladium center. In the second, more commonly referenced mechanism, hydroxide or alkoxide first performs a ligand exchange on the palladium center before coordinating to the boron species and facilitating the subsequent transmetallation. In a neutral protic environment, however, the concentrations of hydroxide or alkoxide in solution are quite low, which should result in significant reductions in reaction rate provided that transmetallation is the rate determining step in such scenarios.

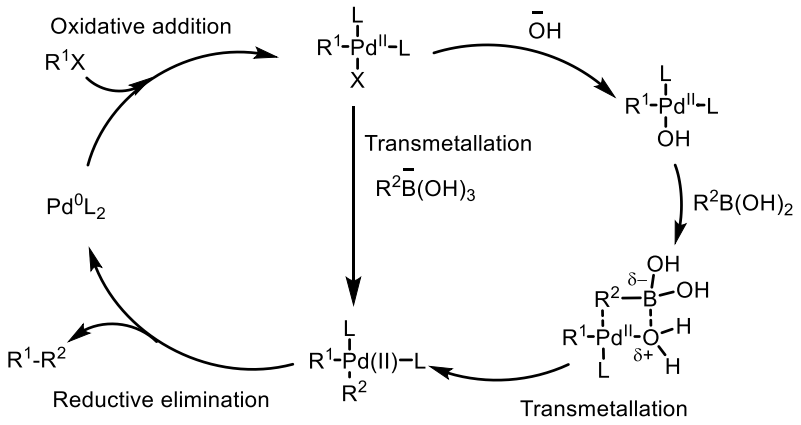


Figure 4-4: Two known mechanism of Suzuki-Miyaura reaction

In order to overcome the need for exogenous base, we sought to design a ligand containing heteroatoms on the side chains. These heteroatoms will coordinate with an approaching organoboron compound, creating partial negative charge character on the boron center, which then would promote transmetallation. These side chains would also increase the water-solubility of the Pd catalyst due to the polarity of the heteroatom functional groups. Ideally, the ligand should be a bidentate ligand to strongly bind to metal to minimize free metal. The proposal structure is represented in **Figure 4-5**.

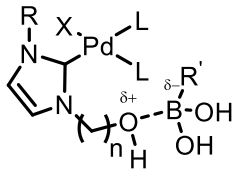


Figure 4-5: The proposal structure of desired catalyst

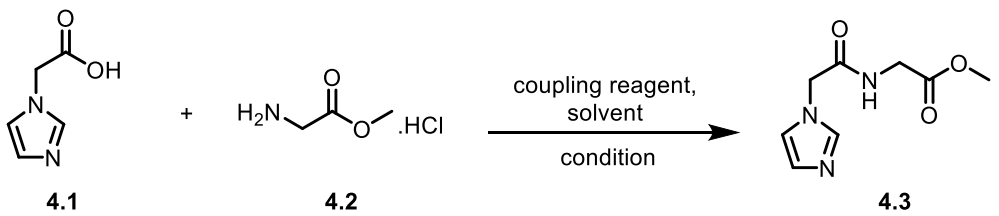
4.3 Result and Discussion

4.3.1 Ligand synthesized from imidazole-1-acetic acid

Starting from imidazole-1-acetic acid (**4.1**), an amidation reaction was performed to convert the acid group to an amide derivative. Generally, the acid group is activated to a more reactive functional group such as an acid chloride/bromide or anhydride before treating with an amine nucleophile. There is also a one-pot approach which employs coupling reagents that convert the acid to a more reactive intermediate in situ in the presence of the amine nucleophile. These coupling reagents (DCC, EDC, HBTU, etc) are widely used in the preparation of amide bonds.

Imidazole-1-acetic acid **4.1** was treated with glycine methyl ester in the presence of N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), Hexafluorophosphate Benzotriazole Tetramethyl Uronium (HBTU) or boric acid ($B(OH)_3$) (**Table 4-1**). Carbodiimide-based methods are the most common methods for the synthesis of esters and amides from carboxylic acids.[36-39] It is typically used with an additive such as hydroxybenzotriazole (HOBt) or 4-(dimethylamino)pyridine (DMAP) to prevent side reactions and to accelerate the coupling process.[37] Even though EDC is a more powerful coupling reagent compared to DCC, DCC is still one of the reagents of choice due to the low solubility of the DCU by-product. More recently, boron-based compounds have been used as a general method to promote direct amidation reactions.[40-42] The use of boron catalysis is considered to be greener as the reaction releases less wasteful byproducts and maximizes atom economy.[43]

Table 4-1: Screening of conditions to amidate 4.1



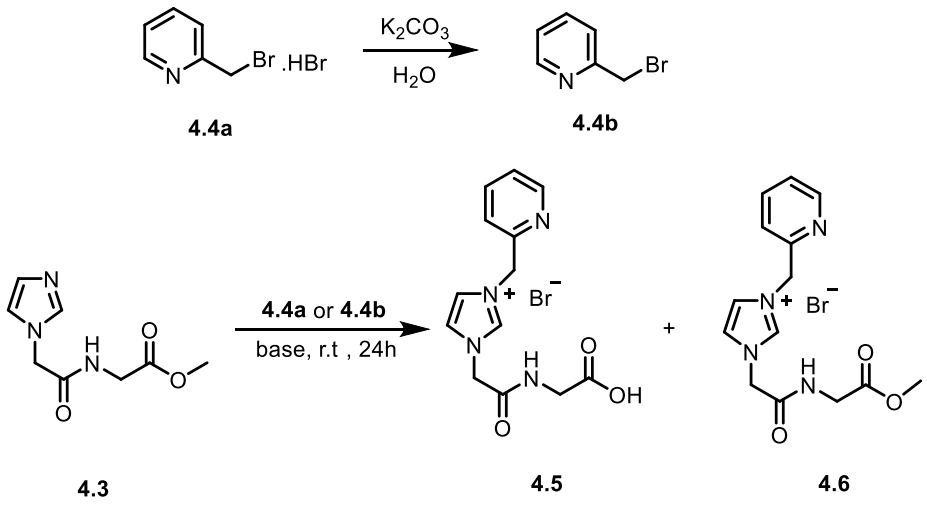
4.1 4.2 4.3

Entry	Coupling Reagent	Equivalent	Solvent	Condition	Yield[a]
1	DCC	1.5	DCM-ACN	DMAP (0.1 equiv.) 0 ^{o}C to rt, 24 h	23%
2	EDC	1.5	DCM-ACN	DMAP (0.1 equiv.) 0 ^{o}C to rt, 24 h	32%
3	EDC	1.5	DCM-ACN	DIEPA (2 equiv.) DMAP (0.1 equiv) 0 ^{o}C to rt, 24 h	71%
4[b]	EDC	1.5	ACN	NHS (1.5 equiv.) rt, 16 h	ND
5	H_3BO_3	0.5	Toluene	DIPEA (1.3 equiv.) M.S., 130 ^{o}C, 24 h	ND
6	H_3BO_3	0.5	Mesitylene	DIPEA (1.3 equiv.) M.S., 140 ^{o}C, 24 h	ND
7[c]	H_3BO_3	0.5	Mesitylene	DIPEA (1.3 equiv.) M.S., 140 ^{o}C, 24 h	ND
8	H_3BO_3	0.5	Mesitylene	M.S,140 ^{o}C, 24 h	ND

ND = not determined by LC-MS
M.S. = molecular sieves
a: isolated yield
b: NHS was form in-situ prior to the addition of EDC
c: the amount of molecular sieves was double

After screening the reaction in the presence of four different coupling reagents, the LC-MS results showed the desired product in entries 1-3. The boric acid additive/catalyst (entry 5-8) was not successful at facilitating this amide formation in our hands even at high temperature and extended time. The number of molecular sieves increased from entry 6 to 7, but this did not appear to impact the reaction. The yield was overall higher when using EDC in comparison with DCC. In entry 3, diisopropylethylamine (DIPEA) was added to neutralize

the amine in the reaction mixture and this appeared to significantly improve conversion to the desired product.



Entry	Reactant	Base	Product[a]
1	4.4a	K_2CO_3	**4.5** (42%), **4.6** (ND)
2	4.4a	DIPEA	**4.5** (40%), **4.6** (6%)
3	4.4b	none	**4.5** (10%), **4.6** (26%)

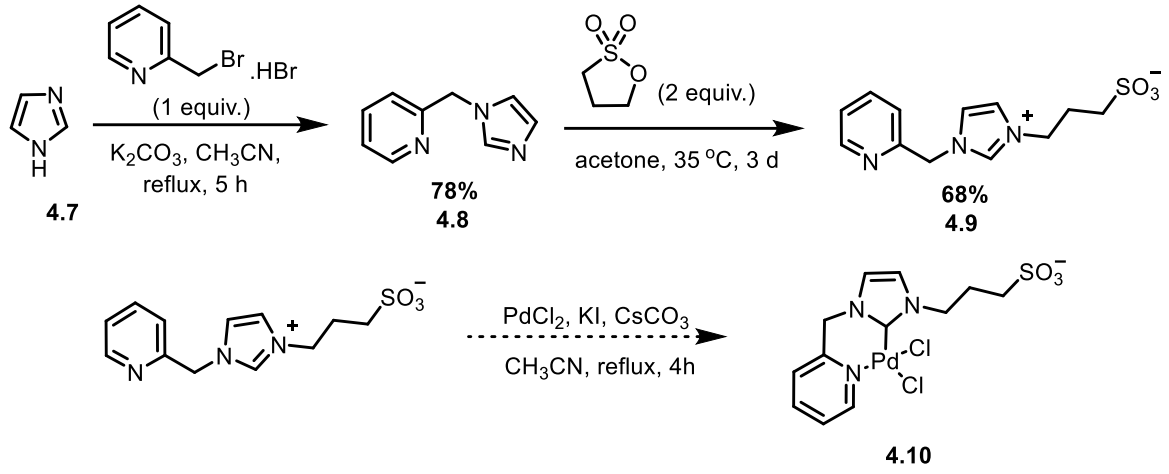
a: isolated yield, ratio was determined by NMR

Scheme 4-1: The insertion of picolyl to 4.3

The picolyl group was attached to substrate **4.3** by treatment of amide substrate **4.3** with picolyl bromide **4.4** (**Scheme 4-1**) under mildly basic conditions. The reaction was performed in aqueous media in the presence of base. Unfortunately, the ester group on the side chain was completely hydrolyzed during this process. The mixture was unable to be separated by HPLC.

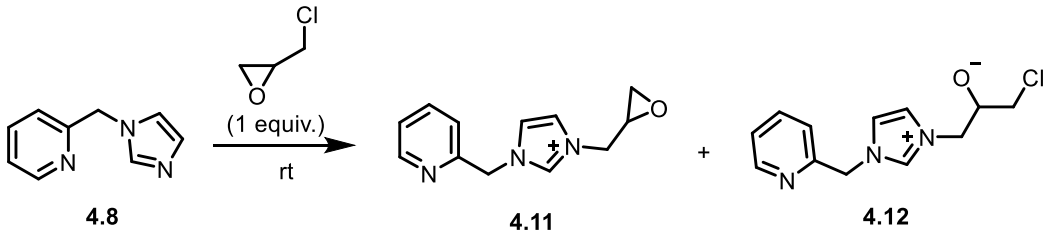
4.3.2 Ligand Synthesized from Imidazole

Ligand **4.9** was prepared by following literature procedure and provided good yield (68%). To generate the Pd complex, palladium (II) chloride and Palladium (II) acetate was employed in the presence of base ($CsCO_3$). We observed the formation of palladium-bound carbene when using $PdCl_2$ only. The optimal conditions are under investigation.



Scheme 4-2: The preparation of ligand 4.9

Another ligand designed related to compound **4.9** was also investigated by reacting compound **4.8** with epichlorohydrin. Besides desired product **4.11**, there is a possible product **4.12** which could be generated. Efforts to separate the mixture failed to give the desired product or compound **4.12** cleanly.



Scheme 4-3: Nucleophilic substitution of epichlohydrin by 4.8 to form 4.11

4.4 Conclusions and Future Works

Thus far, we have made several ligands for palladium catalysis investigations. The first class of ligands starting from imidazole-1-acetic acid were successfully synthesized and simply have to undergo metalation to generate the desired palladium complex. Both the ester and acid forms of this ligand design provide interesting functional groups for Suzuki-Miyaura

reaction acceleration testing in neutral protic media. Ligand **4.9** was also prepared in good yield and will soon be converted into the palladium complex for testing.

Further investigations will include generating additional amides on the imidazolium ligand design. The amide is stable to hydrolysis and there might be a robust group for catalytic activity and boron-activation.

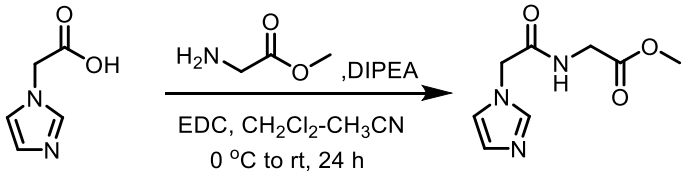
At this point, while we will continue to build our ligand library to examine optimal designs for Suzuki-Miyaura catalysis, work is now focused on moderately high throughput screening for palladium complex activity using HPLC. The ligands described here, along with related NHC ligands, will be tested for activity upon metallation. Various reaction partners, including unnatural amino acids and heteroatom rich boronic acids, will be used to evaluate the catalytic potential of these palladium complexes in a near-neutral ($NaHCO_3$) aqueous and alcohol environment.

4.5 Experimental

General information: Reactions were carried out in oven-dried (> 130 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous reagents was accomplished with oven-dried syringes or cannulae. Dichloromethane (DCM), ethyl acetate (EA), tetrahydrofuran (THF), dimethylformamide (DMF), and acetonitrile (ACN) were purified using a double cartridge solvent purification system prior to use. All other solvents were purchased, vacuum-distilled (twice) and stored under nitrogen over oven-dried (> 200 °C) molecular sieves (3Å or 4Å). Deuterated dichloromethane (d^2-DCM) and deuterated chloroform ($CDCl_3$) were stored in a container with oven-dried (> 200 °C) molecular sieves (3Å or 4Å). Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm silica gel with a fluorescent indicator

UV_{254} (EMD Millipore), which were visualized under UV light and with $KMnO_4$ stain. Flash chromatography columns were packed with 230-400 mesh silica gel (Silacycle). All reagents were purchased from commercial suppliers: Sigma Aldrich, AK Scientific, and Acros, at purity greater than (95%), unless otherwise specified. Reverse phase HPLC was perform on an Agilent Technologies 1260 Infinity instrument (C8, 150×4.6 mm, 20 mL/min) Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 or 500 MHz, and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 or 125 MHz. The chemical shifts were reported on the δ scale (ppm) and referenced to the residual protonated solvent (^{1}H) or to the deuterated solvent (^{13}C) peaks: $CDCl_3$ (7.26 ppm, ^{1}H; 77.06 ppm, ^{13}C), and CD_2Cl_2 (5.32 ppm, ^{1}H; 53.5 ppm, ^{13}C). 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.

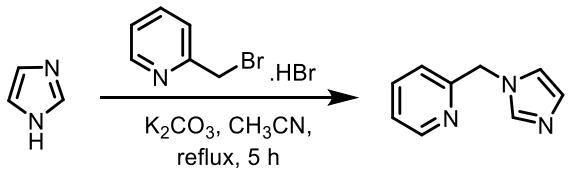
(2-(allyloxy)ethyl)benzene (4.3)



To a round bottom flask containing glycine methyl ester hydrochloride (0.25 g, 2.00 mmol, 2.00 equiv.) in 4 mL dicholoromethane-acetonitrile (1:1), diisopropylethylamine (0.35 mL, 2.00 mmol, 2.00 equiv.) was added and allowed to stir for 30 minutes at room temperature. Then, imidazole-1-acetic acid (0.12 g, 1.00 mmol, 1.00 equiv.) followed by 4-(dimethylamino)pyridine (0.012 g, 0.10 mmol, 0.10 equiv.) was added and the reaction mixture was cooled to 0 °C in an ice bath. Next, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.14 g, 0.75 mmol, 0.75 equiv.) was add and the

reaction was maintained at 0 °C. After 1 hour, the same amount of 3-(3-dimethylaminopropyl) carbodiimide was added to the flask and the ice bath was removed. The reaction was allowed to warm to room temperature and stirred for 24 hours. Upon completion, solvent was removed in vacuo. The residue was then diluted in 3 mL H_2O to produce a homogeneous solution. Reverse phase preparative HPLC was used to provide the desired product (71%). HPLC conditions (C8, 20 mL/min; solvent A = acetonitrile, solvent B = water): 0-2 min: 0% A; 2-17 min:0-20% A gradient. Compound **4.3** R_t = 8.5-9.5 min. ^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (s, 1H), 7.12 (s, 1H), 6.99 (s, 1H), 3.98 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.6, 169.9, 139.5, 129.0, 121.8, 52.7, 50.0, 41.9; HRMS (ESI) m/z: [M+H] Calcd for $C_8H_{12}N_3O_3$ 198.0873; Found 198.0874.

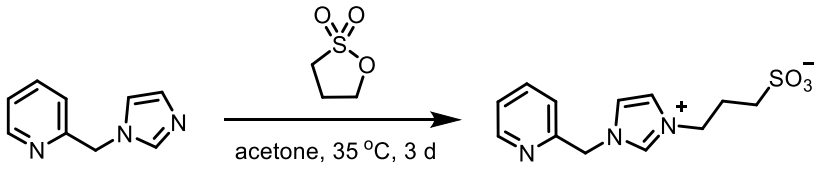
2-(1H-Imidazol-1-ylmethyl)pyridine (4.8) (adapted from a procedure by Lee[45] and Hwang[46])



To a round bottom flask containing imidazole (0.11 g, 1.52 mmol, 1.00 equiv.) in 5 mL acetonitrile, 2-picolyl bromide hydrobromide (0.38 g, 1.52 mmol, 1.00 equiv.) was added followed by potassium carbonate (0.84 g, 6.10 mmol), and the mixture was heated to reflux for 5 hours. The solvent was then removed under reduced pressure. The residue was subsequently diluted with 5 mL H_2O and 5 mL dichloromethane, and the layers were separated. The organic layer was washed with 5 mL water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an orange liquid which did not require further purification (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74−8.73 (m, 1H), 7.82−7.78 (m, 1H), 7.75 (s, 1H), 7.40 (s, 1H), 7.39−7.36 (m, 1H), 7.14−7.13 (m, 1H), 7.09−7.08 (m, 1H), 5.39 (s, 2H). ^{13}C

NMR (125 MHz, $CDCl_3$) δ 156.0, 149.5, 137.5, 137.2, 129.8, 122.9, 121.1, 119.4, 52.4. Spectroscopic data were in good agreement with those previously reported.[45]

1-(2-picolyl)-3-(3-sulfonatopropyl)imidazolium (4.9) (adapted from a procedure by Cardierno)[44]



To a round bottom flask containing 2-(1H-imidazol-1-ylmethyl)pyridine (0.24 g, 1.50 mmol, 1.00 equiv.) in dry acetone (4.0 mL), 1,3-propanesultone (0.37 g, 3.00 mmol, 2.00 equiv.) was added and allowed to stir for 4 days at room temperature under a nitrogen atmosphere. Then, the mixture was filtered to collect the brown solid precipitate. The solid was washed several times with acetone and dried in vacuo to yield a white solid as the final product, which required no further purification (68%). ^{1}H NMR (400 MHz, D_2O) δ 8.91 (s, 1H), 8.49 (d, J = 3.2 Hz, 1H), 7.91−7.88 (m, 1H), 7.56 (s, 1H), 7.49−7.42 (s, 3H), 5.50 (s, 2H), 4.36 (t, J = 4.8 Hz, 2H), 2.89 (t, J = 4.8 Hz, 2H), 2.32−2.27 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ 153.0, 150.4, 139.9, 137.2, 125.5, 124.6, 124.0, 123.7, 54.6, 49.0, 48.2, 26.0. Spectroscopic data were in good agreement with those previously reported.[44]

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Chapter 5: Conclusions and Future Perspectives

Boron compounds have displayed diverse reactivity profiles in many organic reactions. However, there is still room for the discovery of new reactions and the optimization of existing methodologies based on boron reagents. This research has expanded knowledge concerning the use of boron chemistry to facilitate C−O and C−H bond breaking and C−N and C−C bond forming reactions.

Chapter 2 discussed the systematic study toward the cleavage of unsymmetrical dialkyl ethers by boron tribromide. The classic BBr_3 Lewis acid-mediated cleavage of ethers was re-investigated and expanded to unsymmetrical alkyl ether substrates. During the course of our investigation, we delineated an efficient protocol to disassociate C−O linkages in ether by the combination of equal amounts of two different triboron halides, namely boron tribromide and boron trichloride. The heteroleptic boron halides generated from the mixture of BBr_3 and BCl_3 can trigger the disassociation of C−O bonds in high selectivity. By employing a mixture of trihaloboranes, the poor regioselectivity and low yield, which are disadvantages of BBr_3 toward unsymmetrical ethers, have been addressed. In all of our experiments, the use of mixed boron halides exhibits an improvement in reactivity profiles (regioselectivity and yield) when compared to BBr_3 alone. Additionally, the clean conversion of ethers to alcohols and halide products is achieved with substoichiometric amounts of boron halide reagents. Interestingly, our methods also provide an alternate route to access to [*B-Cl*]-dialkyl boronate esters. Such acyclic dialkoxy boryl chlorides are synthetically challenging to get access through other methods.

Chapter 3 described the first stages of developing a new direct and selective C−N bond formation utilizing nitrene intermediates. Taking advantage of BBr_3 and BCl_3 together, we have successfully synthesized various dialkoxychloroborane derivatives, which allows

access to the preparation of various boryl azide complexes to serve as nitrene precursors. Initial results have determined that C−H bonds in benzylic positions are more likely to be amenable to C–H functionalization by the borylnitrene species. However, there are many questions which need to be answered. Did we really generate the nitrene in an efficient way? If the nitrene did form during the irradiation, how do we direct the nitrene to react with the desired C–H bond? Even though the Bettinger group observed both intramolecular and intermolecular C−H insertion, their examples included only ethyl and isopropyl boryl azide. To answer the first question, we need to re-investigate our substrate scope in the same optimal conditions. Nitrenes are well-known for their high a reactivity and often suffer from poor chemoselectivity. However; in most of our trials, alcohol is the major product after workup, indicating no reaction with the alkoxy chain (**Scheme 3-4**). In order to perform insertion, the nitrene intermediate has to be in a suitable distance and geometry. This may be the current limitation on the substrates examined (which were mostly lacking steric bulk). Therefore, substrates containing bulky alkyl groups will be examined in future studies (**Scheme 3-6**).

Finally, the research of chapter 4 is to synthesize new N-heterocyclic carbene ligands to support Suzuki-Miyaura coupling reactions in aqueous media. Currently, a few NHC ligands have been made from our lab. Various palladium sources will be examined to generate pallidum complexes from the ligands described in this chapter. The ester group of **4.6** has a tendency to hydrolyze under mild basic condition. This would be problematic for attachment to palladium as the use of base is inevitable and will likely catalyze hydrolysis to the acid. Hence, the ester group should be replaced by another functionality such as an amide.

In conclusion, boron reagents have shown impressive activity being able to trigger the disassociation of C−O and C−H bonds for further functionalization of organic molecules.

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Chapter 1:

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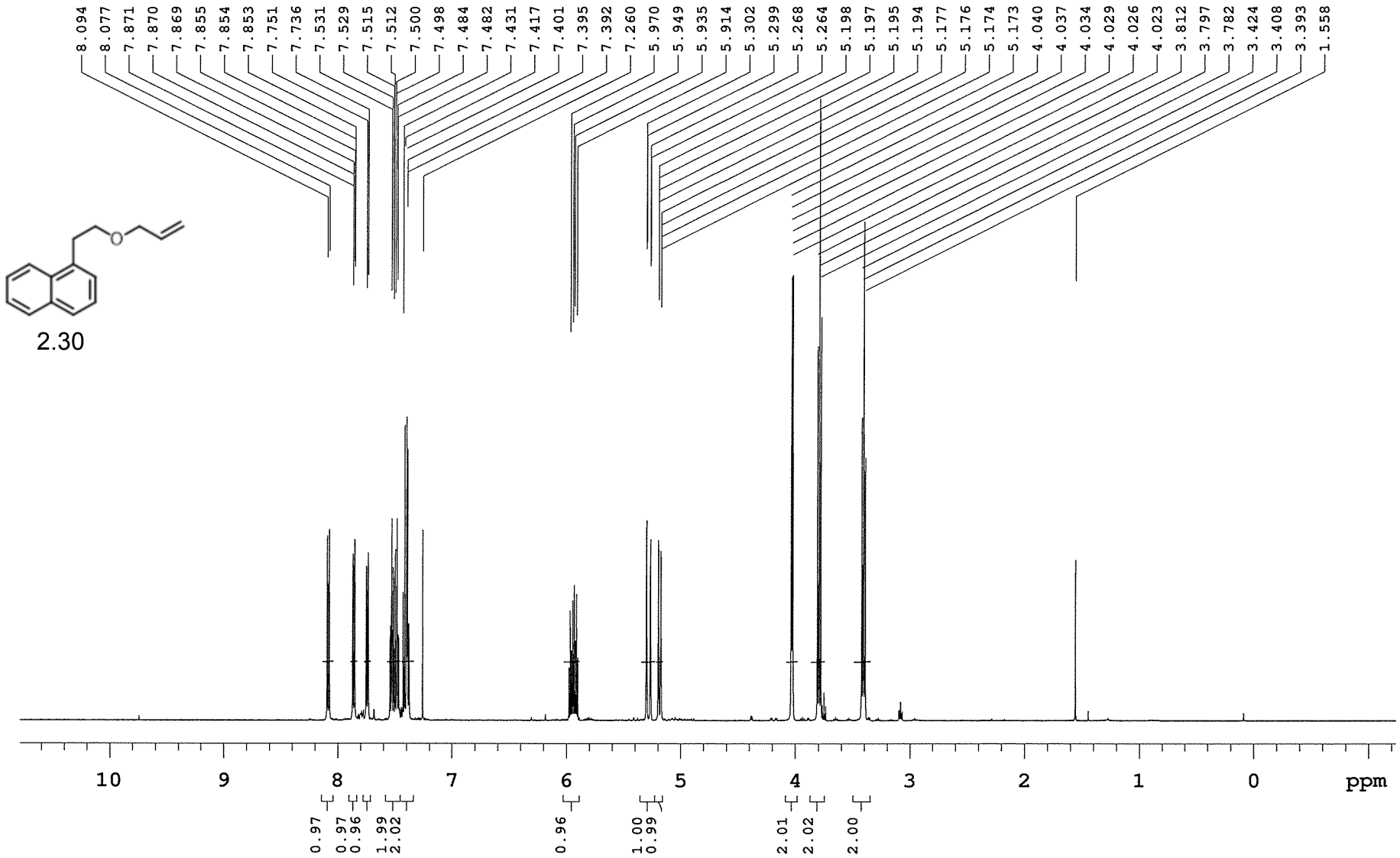
Appendix: Selected NMR Spectra

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: u500, Jan 6 2018	Sweep Width(Hz): 6009.62	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT	Digital Res.(Hz/pt): 0.09	Hz per mm(Hz/mm): 25.04	Completed Scans 32

Nam, NT-1-naphthaleneethanol_allyl_ether_after_column
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



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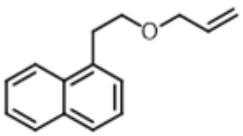
Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Jan 6 2018	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 228

Nam, NT-1-naphthaleneethanol_allyl_ether_after_column
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



2.30

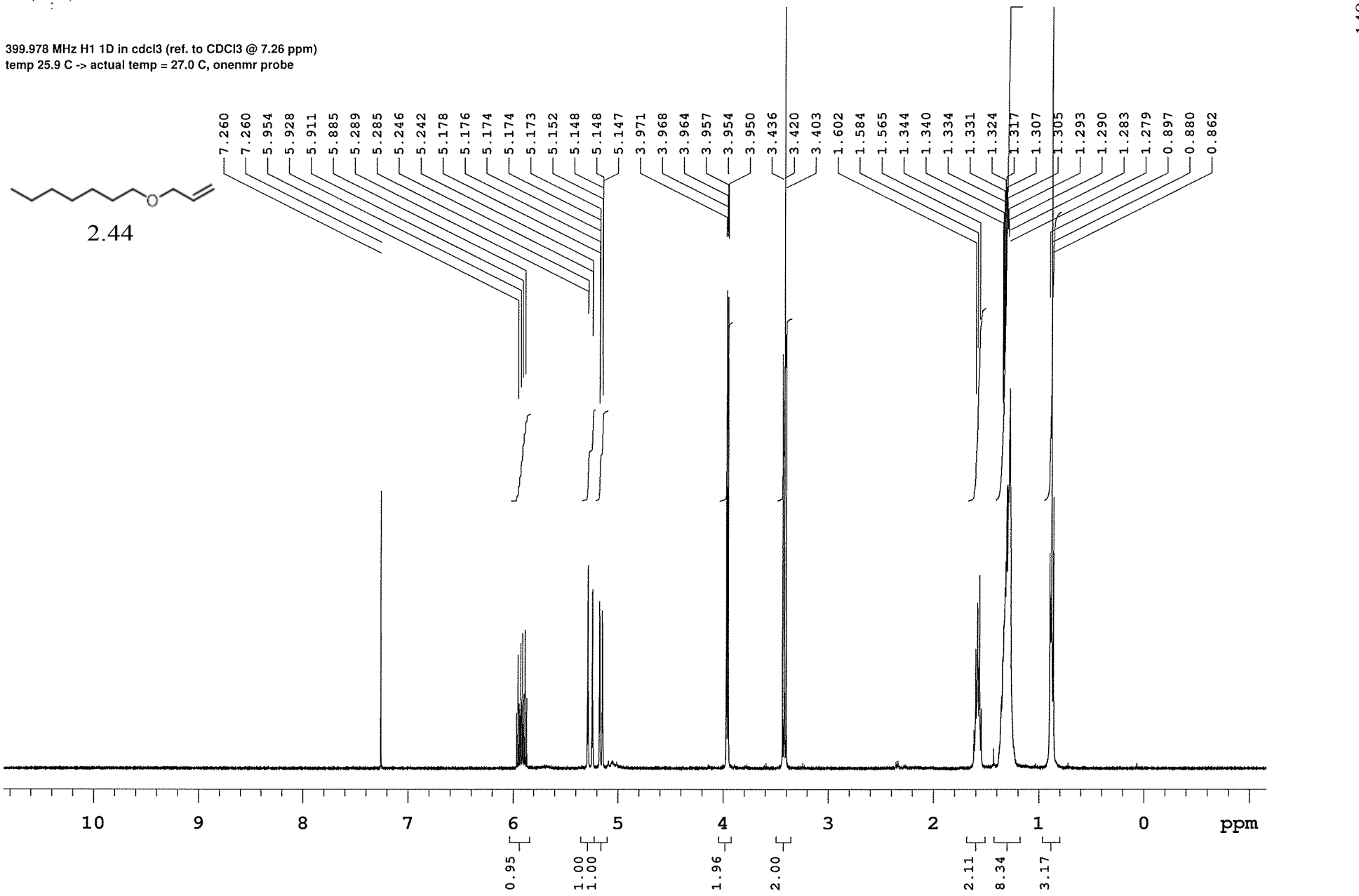
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.01/2018.01.06.u5_NT-1-naphthaleneethanol_allyl_ether_after_column_loc2_10.40_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: mr400, Feb 13 2018 | Sweep Width(Hz): 4807.69 | Acquisiton Time(s): 5 | Relaxation Delay(s): 0.1
Pulse Sequence: s2pul | Digital Res.(Hz/pt): 0.07 | Hz per mm(Hz/mm): 20.03 | Completed Scans 16

399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2018.02.13.mr4_NT-HEPTANOL_ALLYL_ETHER_COUMN_WITH_TEA_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Feb 13 2018	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 188

Nam, NT-heptanol_allyl_ether_column_with_tea
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

2.44

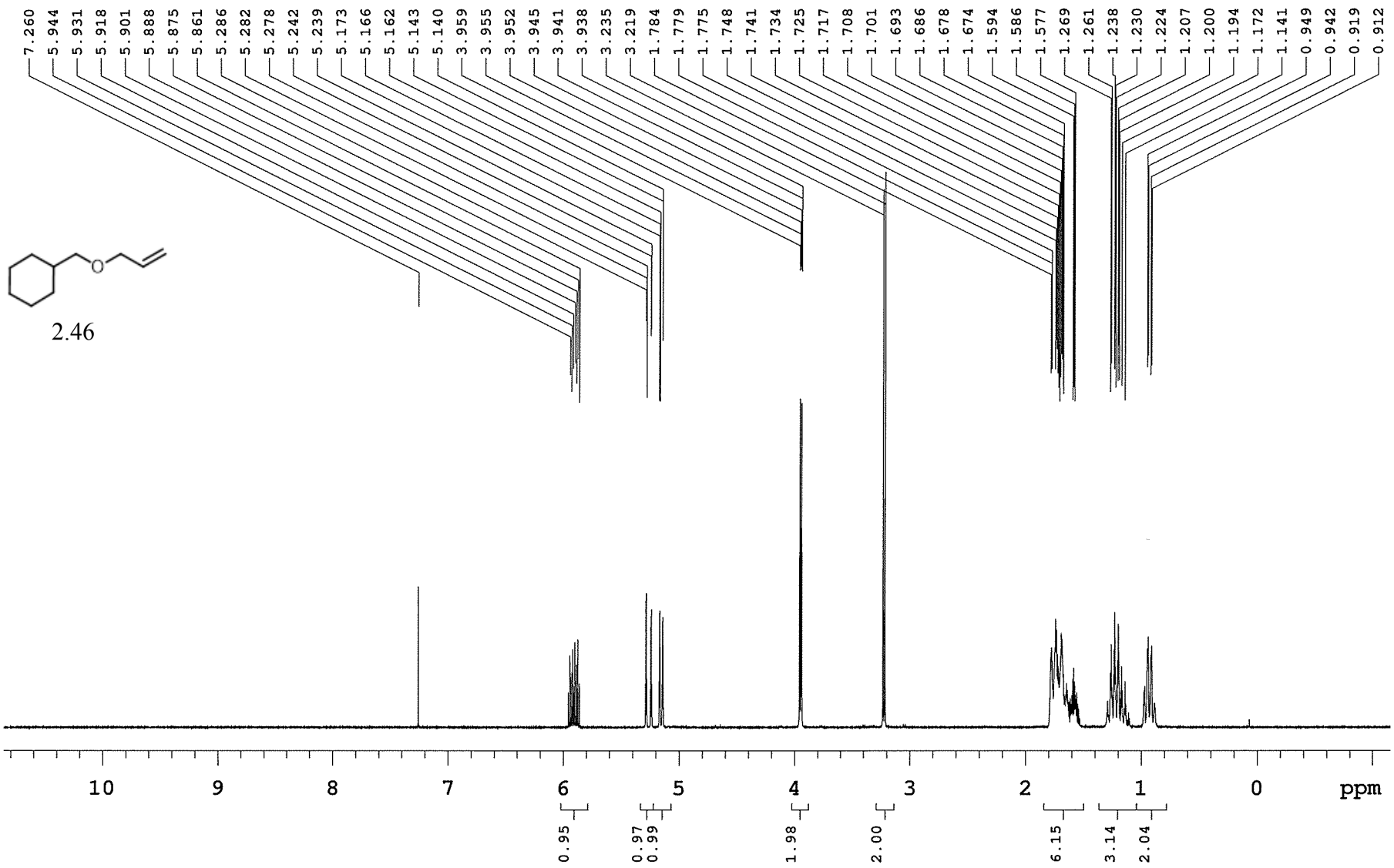
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.02/2018.02.13.u5_NT-heptanol_allyl_ether_column_with_tea_loc1_18.27_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: i400, Feb 6 2018	Sweep Width(Hz): 4801.92	Acquisiton Time(s): 4.998	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.07	Hz per mm(Hz/mm): 20.01	Completed Scans 32

399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe



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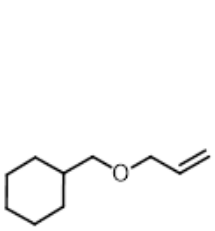
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: u500, Dec 28 2017	Sweep Width(Hz): 33783.8	Acquisition Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 48

Nam, NT-cyclohexanemethanol_allyl_ether_after_column
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



2.46

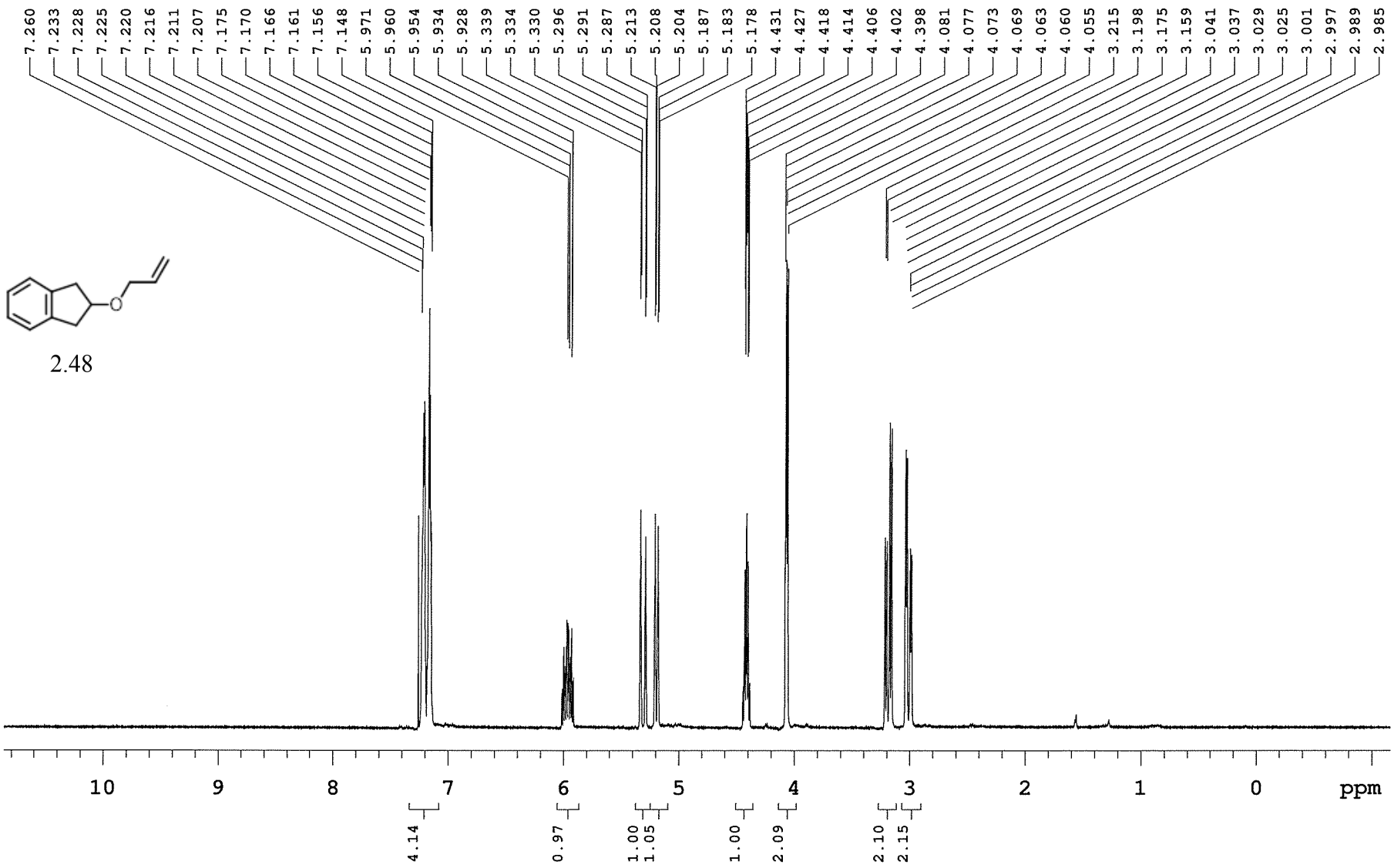
File: /mnt/d600/home15/ljwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2017.12/2017.12.28.u5_NT-cyclohexanemethanol_allyl_ether_after_column_loc1_13.48_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: mr400, Feb 12 2018	Sweep Width(Hz): 4807.69	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.07	Hz per mm(Hz/mm): 20.03	Completed Scans 16

399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



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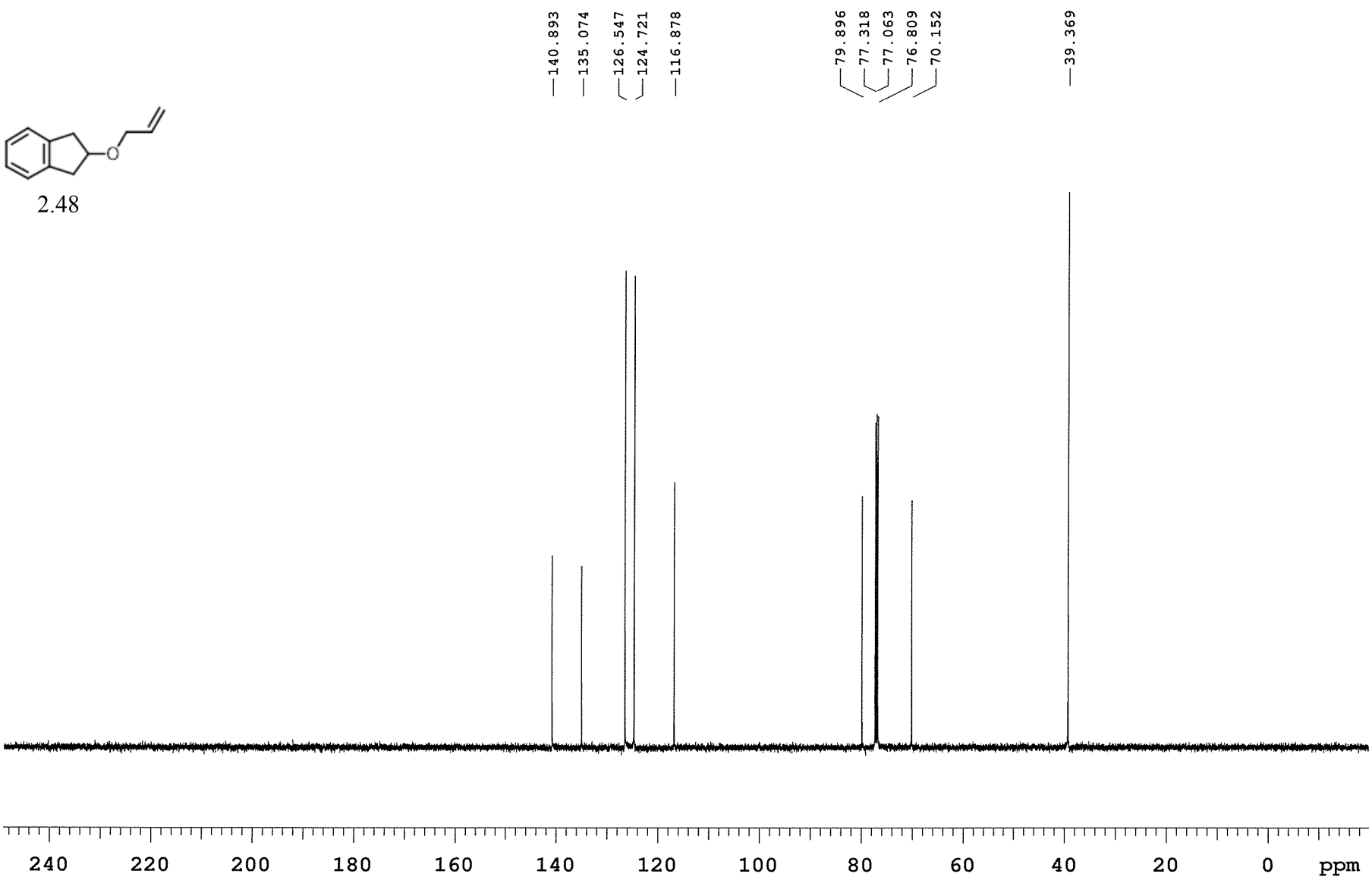
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: u500, Feb 12 2018	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 12

Nam, nt-2-indanol_allyl_ether_coulmn_with_tea
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



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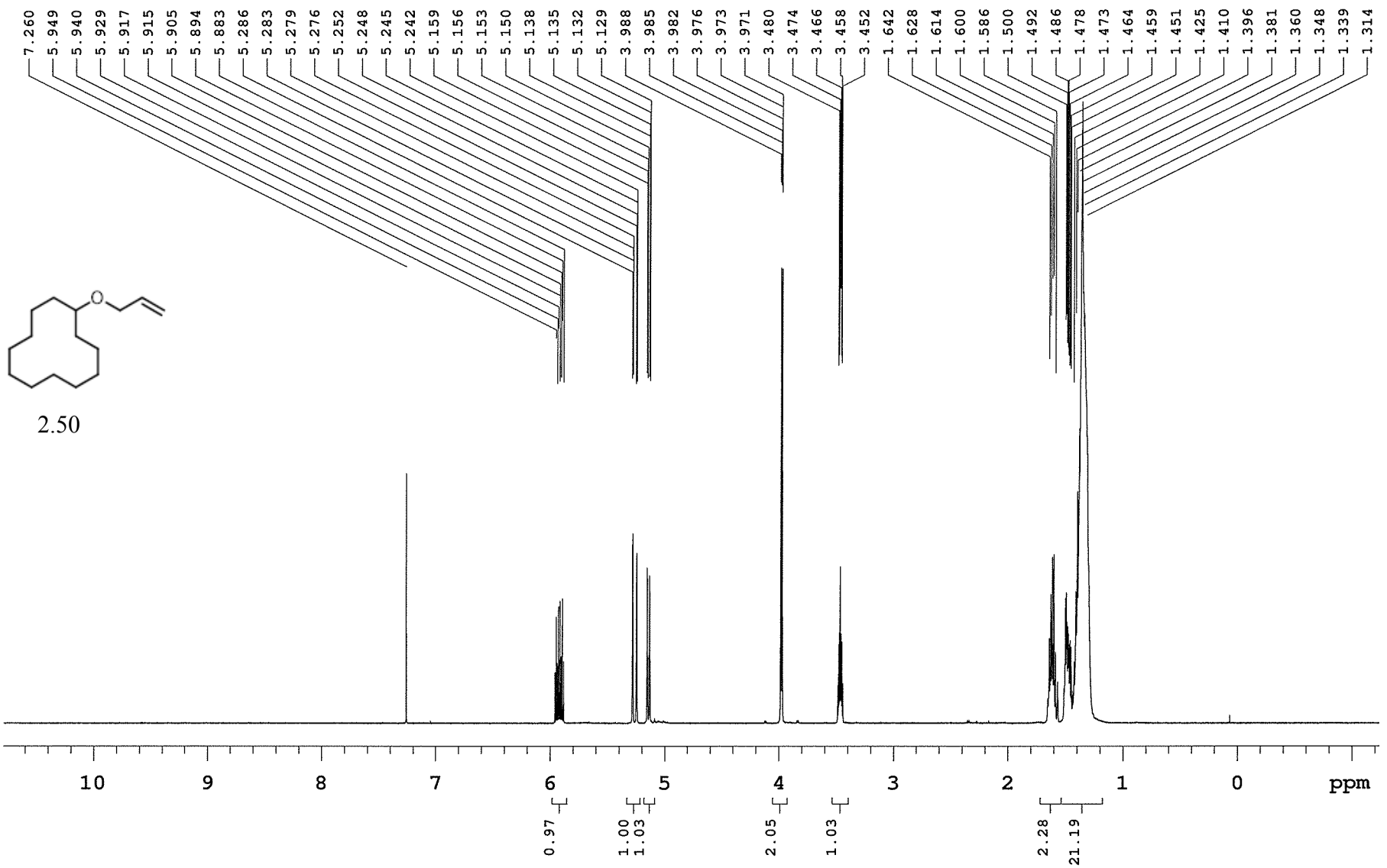
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	u500, Dec 28 2017	Sweep Width(Hz):	6009.62	Acquisiton Time(s):	5	Relaxation Delay(s):	0.1
Pulse Sequence:	PRESAT	Digital Res.(Hz/pt):	0.09	Hz per mm(Hz/mm):	25.04	Completed Scans	16

Nam, NT-cyclododecanol_allyl_ether_after_column
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



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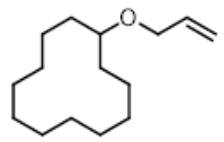
Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Dec 28 2017	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 372

Nam, NT-cyclododecanol_allyl_ether_after_column
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



2.50

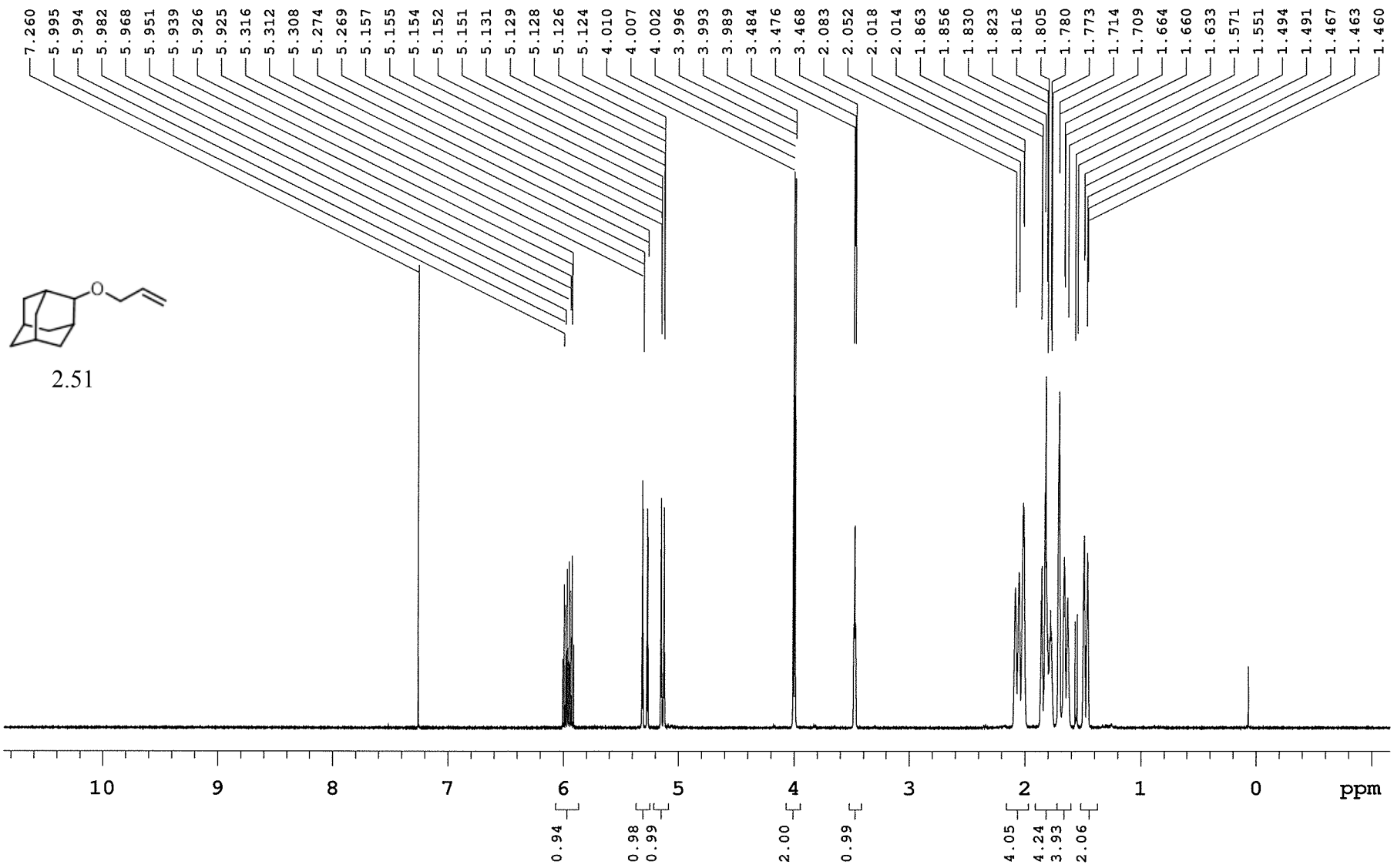
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2017.12/2017.12.28.u5_NT-cyclododecanol_allyl_ether_after_column_loc2_13.54_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: mr400, Jan 10 2018	Sweep Width(Hz): 4807.69	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.07	Hz per mm(Hz/mm): 20.03	Completed Scans 32

399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



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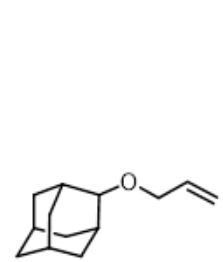
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: u500, Jan 10 2018	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 68

Nam, NT-2-adamantanol_allyl_ether_after_column
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



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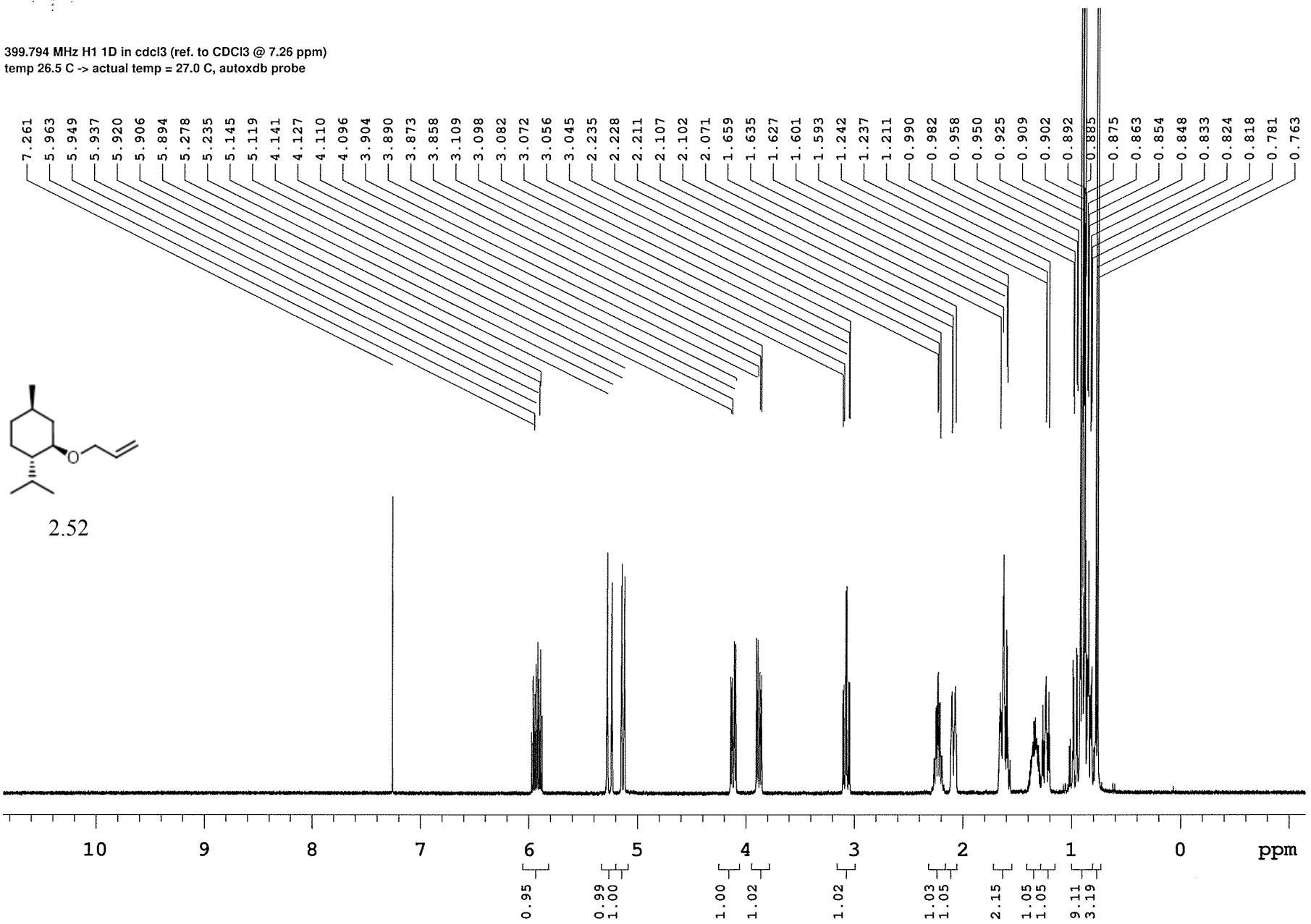
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: i400, Feb 15 2018	Sweep Width(Hz): 4801.92	Acquisiton Time(s): 4.998	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.07	Hz per mm(Hz/mm): 20.01	Completed Scans 16

399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe



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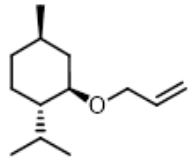
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: u500, Feb 15 2018 | Sweep Width(Hz): 33783.8 | Acquisiton Time(s): 1 | Relaxation Delay(s): 1
Pulse Sequence: s2pul | Digital Res.(Hz/pt): 0.26 | Hz per mm(Hz/mm): 140.76 | Completed Scans 88

Nam, NT-menthol_allyl_ether_column_with_tea
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



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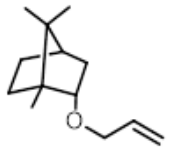
Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: i400, Feb 5 2018 | Sweep Width(Hz): 4801.92 | Acquisiton Time(s): 4.998 | Relaxation Delay(s): 0.1
Pulse Sequence: s2pul | Digital Res.(Hz/pt): 0.07 | Hz per mm(Hz/mm): 20.01 | Completed Scans: 16

399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe



2.53

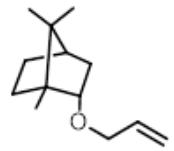
File: /mnt/d600/home15/jwnmr/nmrdata/Nam/2018.02.15.i4_NT-isobenecol_allyl_ether_column_with_tea_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Feb 15 2018 | Sweep Width(Hz): 33783.8 | Acquisiton Time(s): 1 | Relaxation Delay(s): 1
Pulse Sequence: s2pul | Digital Res.(Hz/pt): 0.26 | Hz per mm(Hz/mm): 140.76 | Completed Scans 116

Nam, NT-isobenerol_allyl_ether_column_with_tea
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



2.53

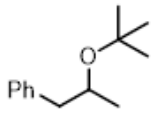
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.02/2018.02.15.u5_NT-isobenerol_allyl_ether_column_with_tea_loc7_20.03_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: i600, Jun 8 2018	Sweep Width(Hz): 7183.91	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.11	Hz per mm(Hz/mm): 29.93	Completed Scans 16

599.926 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.2 C -> actual temp = 27.0 C, autoxid probe



2.29

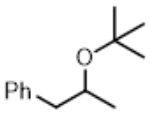
File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2018.06.08.i6_NT-1-phenyl_prop-2-ol_t-butyl_ether_after_column_cyclohexane_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Jun 8 2018 | Sweep Width(Hz): 33783.8 | Acquisiton Time(s): 1 | Relaxation Delay(s): 1
Pulse Sequence: s2pul | Digital Res.(Hz/pt): 0.26 | Hz per mm(Hz/mm): 140.76 | Completed Scans 40

Nam, NT-1-phenyl_prop-2-ol_t-butyl_ether_after_column
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



2.29

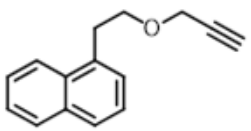
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.06/2018.06.08.u5_NT-1-phenyl_prop-2-ol_t-butyl_ether_after_column_loc1_18.08_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: mr400, Apr 24 2018	Sweep Width(Hz): 4807.69	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.07	Hz per mm(Hz/mm): 20.03	Completed Scans 16

399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



2.40

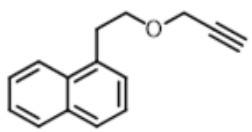
File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2018.04.24.mr4_NT-1-naphthalene_ethanol_propargyl_ether_after_column_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Apr 24 2018 | Sweep Width(Hz): 33783.8 | Acquisiton Time(s): 1 | Relaxation Delay(s): 1
Pulse Sequence: s2pul | Digital Res.(Hz/pt): 0.26 | Hz per mm(Hz/mm): 140.76 | Completed Scans 128

Nam, NT-1-naphthalene_ethanol_propargyl_ether_after_column
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



2.40

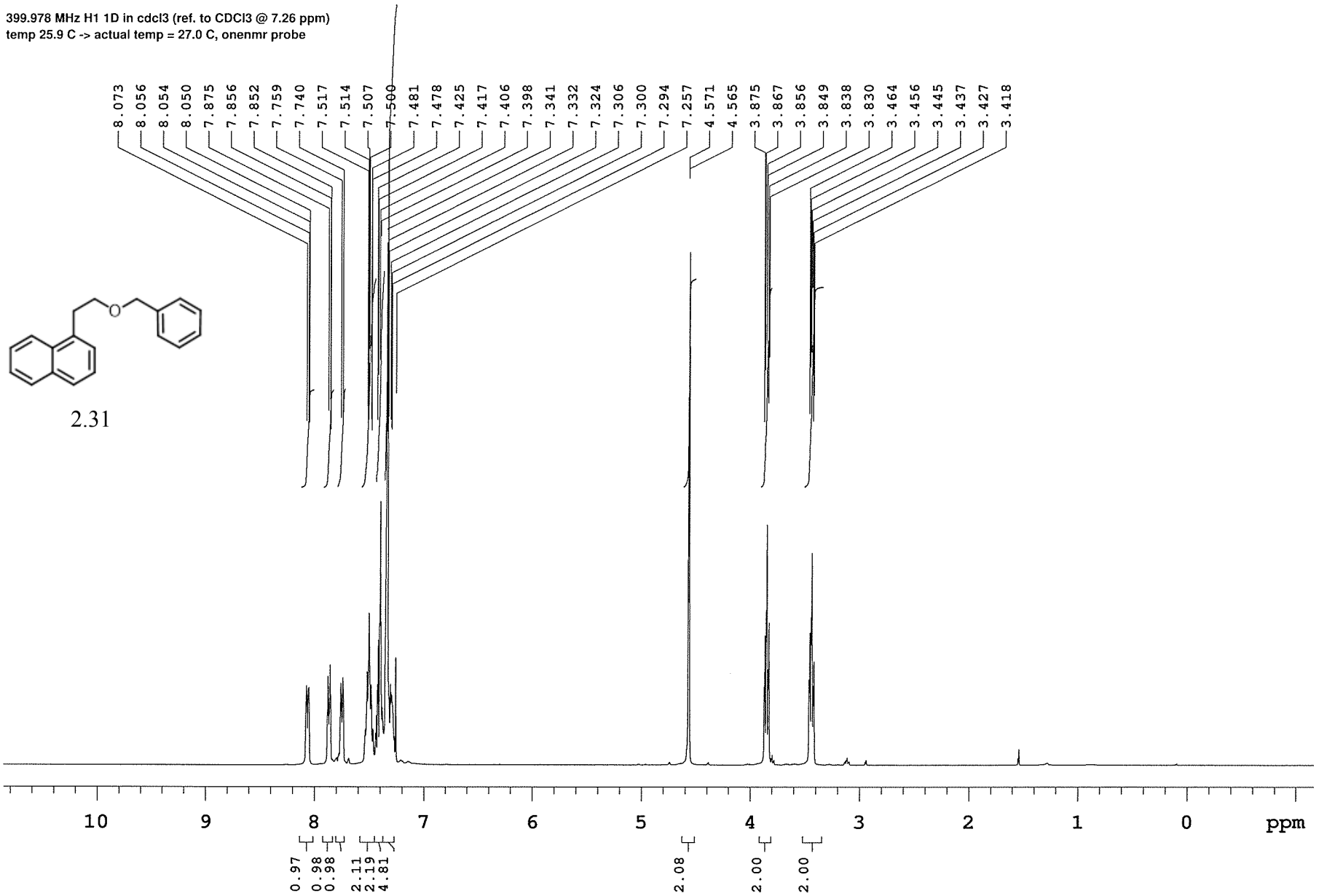
File: /mnt/d600/home15/jwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.04/2018.04.24.u5_NT-1-naphthalene_ethanol_propargyl_ether_after_column_loc7_19.15_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: mr400, Apr 16 2018	Sweep Width(Hz): 4807.69	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.07	Hz per mm(Hz/mm): 20.03	Completed Scans 16

399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



2.31

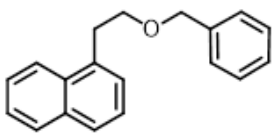
File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2018.04.16.mr4_NT-1_naphthalene_ethanol_benzyl_ether_after_column_H1_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Apr 17 2018	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 84

Nam, NT-1-naphthalene_ethanol_benzyl_ether_after_column
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



2.31

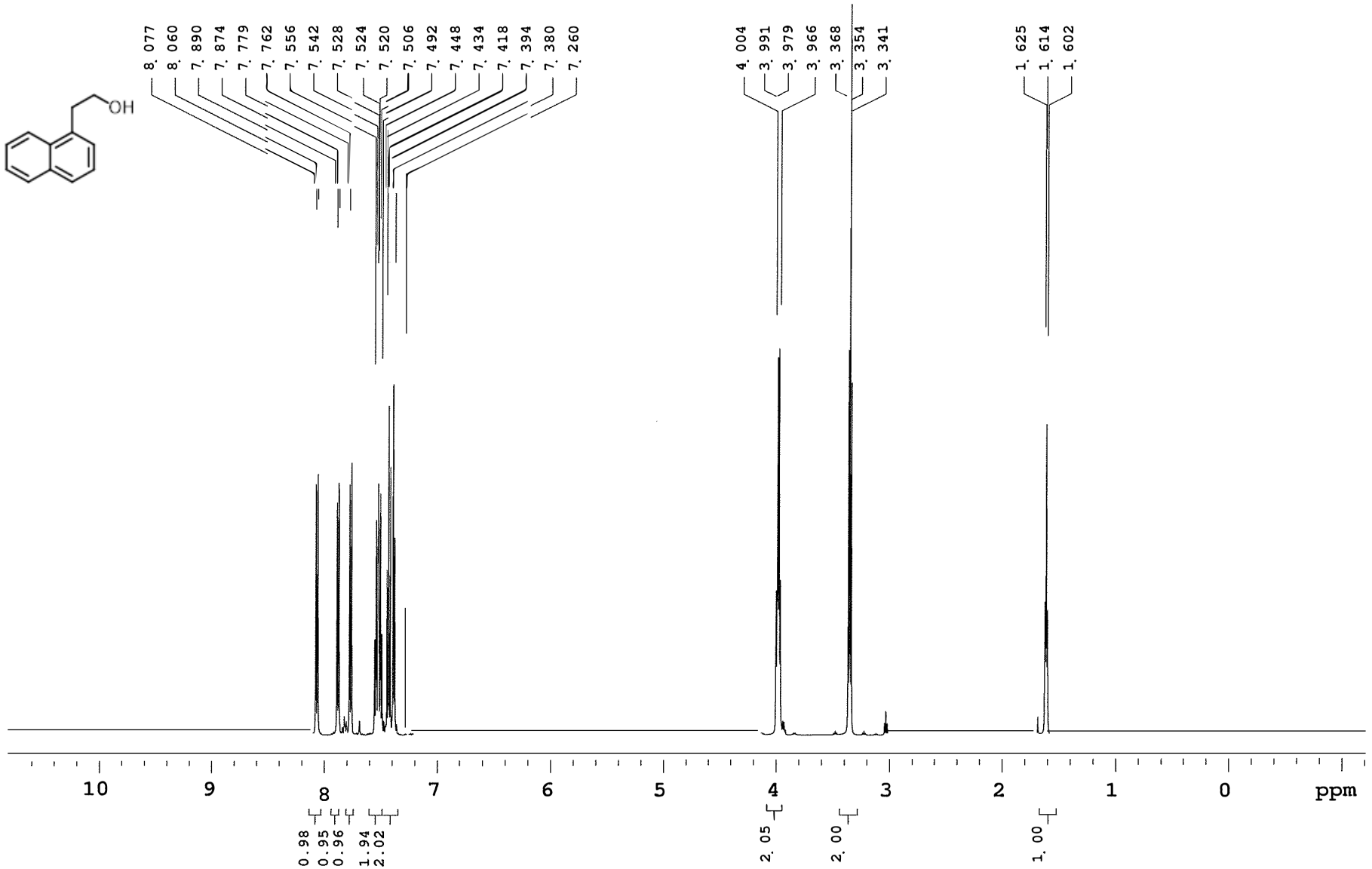
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.04/2018.04.17.u5_NT-1-naphthalene_ethanol_benzyl_ether_after_column_loc10_03.40_C13_1D

Department of Chemistry, University of Alberta

Agilent Technologies

Recorded on: u500, Jun 17 2018	Sweep Width(Hz): 6009.62	Acquisiton Time(s): 5	Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT	Digital Res.(Hz/pt): 0.09	Hz per mm(Hz/mm): 25.04	Completed Scans 8

Nam, NT-naphthalene_ethanol_from_BCl3_alone
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



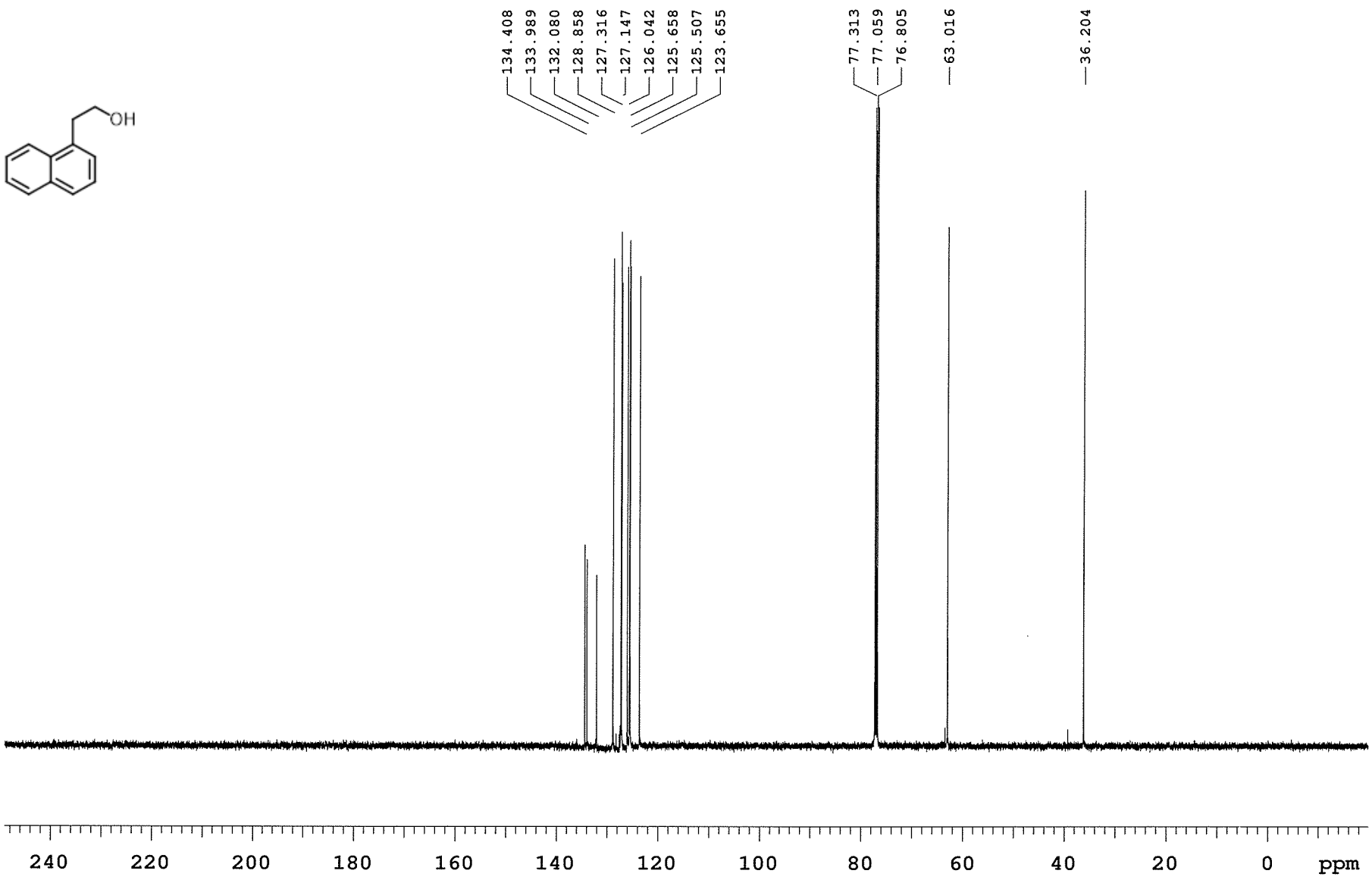
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.06/2018.06.17.u5_NT-naphthalene_ethanol_from_BCl3_alone_ioc7_22.07_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: u500, Jun 17 2018	Sweep Width(Hz): 33783.8	Acquisiton Time(s): 1	Relaxation Delay(s): 1
Pulse Sequence: s2pul	Digital Res.(Hz/pt): 0.26	Hz per mm(Hz/mm): 140.76	Completed Scans 24

Nam, NT-naphthalene_ethanol_from_BCl3_alone
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



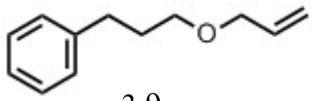
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.06/2018.06.17.u5_NT-naphthalene_ethanol_from_BCl3_alone_loc7_22.08_C13_1D

Agilent Technologies

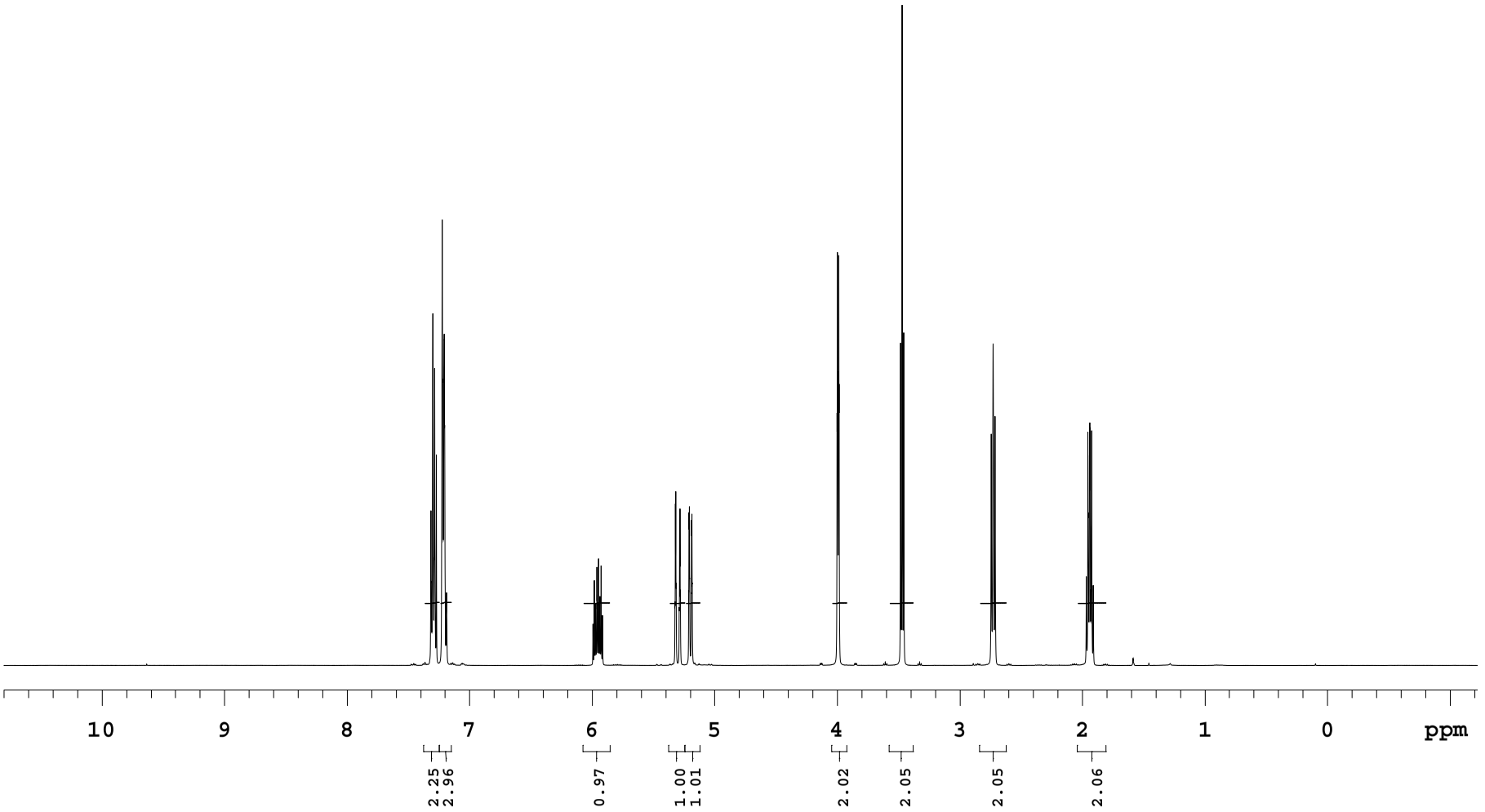
Department of Chemistry, University of Alberta

Recorded on: **u500, Oct 17 2018**	Sweep Width(Hz): **6009.62**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25.04**	Completed Scans **8**

Nam, NT-3phenyl-1propanol_allyl_ether
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



3.9



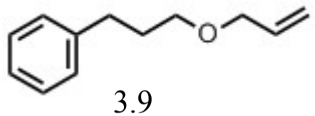
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.10/2018.10.17.u5_NT-3phenyl-1propanol_allyl_ether_loc1_12.47_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	u500, Oct 17 2018	Sweep Width(Hz):	33783.8	Acquisiton Time(s):	1	Relaxation Delay(s):	1
Pulse Sequence:	s2pul	Digital Res.(Hz/pt):	0.26	Hz per mm(Hz/mm):	140.76	Completed Scans	36

Nam, NT-3phenyl-1propanol_allyl_ether
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



3.9

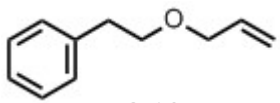
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.10/2018.10.17.u5_NT-3phenyl-1propanol_allyl_ether_loc1_12.48_C13_1D

Agilent Technologies

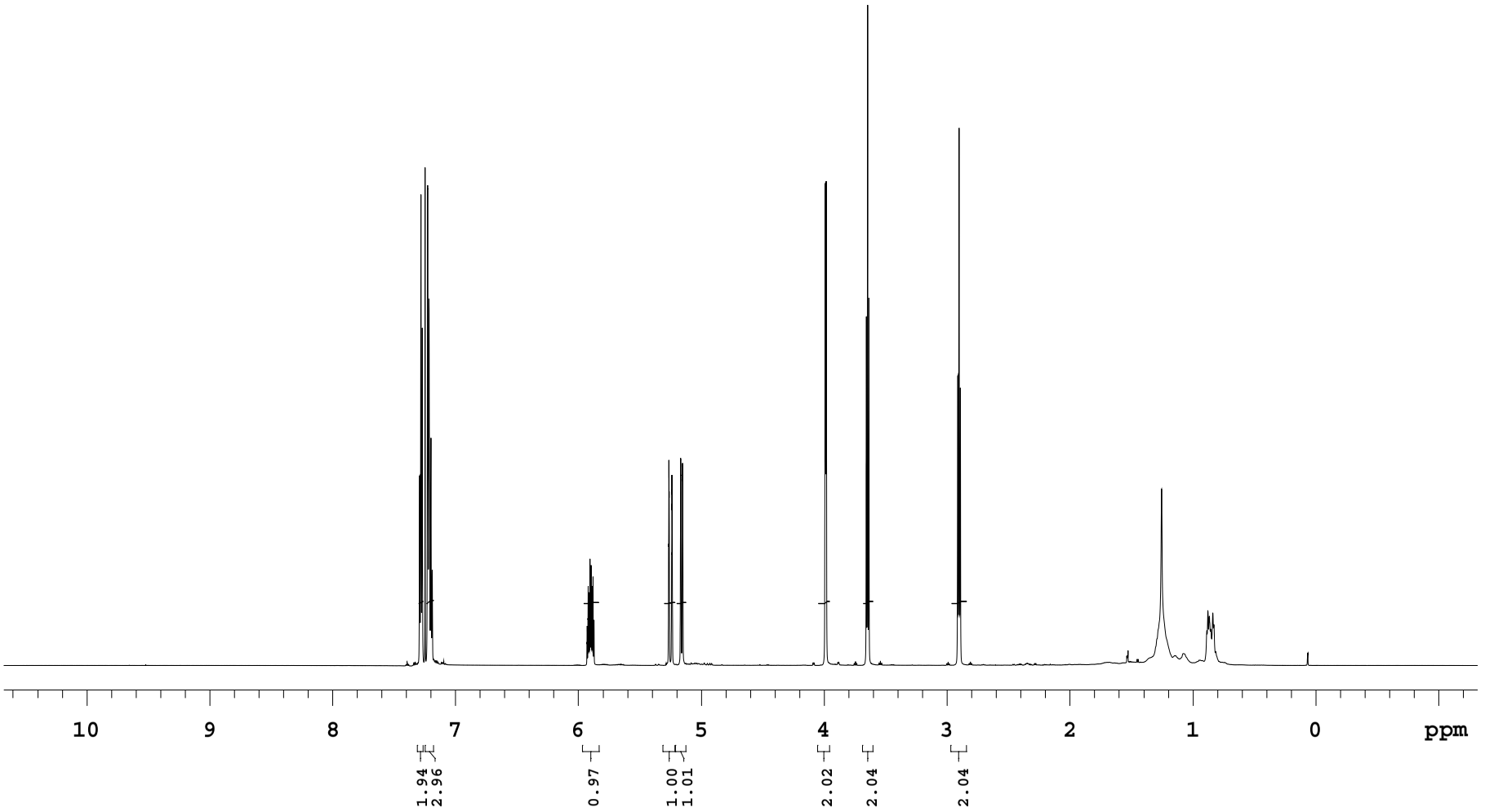
Department of Chemistry, University of Alberta

Recorded on:	v700, Nov 20 2018	Sweep Width(Hz):	8389.26	Acquisiton Time(s):	5	Relaxation Delay(s):	0.1
Pulse Sequence:	PRESAT	Digital Res.(Hz/pt):	0.13	Hz per mm(Hz/mm):	34.95	Completed Scans	8

Nam, NT-2-phenyl_ethanol_allyl_ether
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



3.10



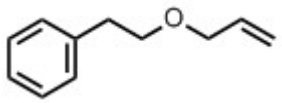
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.11/2018.11.20.v7_NT-2-phenyl_ethanol_allyl_ether_loc64_14.15_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	v700, Nov 20 2018	Sweep Width(Hz):	48076.9	Acquisiton Time(s):	1	Relaxation Delay(s):	1
Pulse Sequence:	s2pul	Digital Res.(Hz/pt):	0.37	Hz per mm(Hz/mm):	200.32	Completed Scans	128

Nam, NT-2-phenyl_ethanol_allyl_ether
175.975 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



3.10

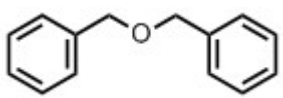
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.11/2018.11.20.v7_NT-2-phenyl_ethanol_allyl_ether_loc64_14.16_C13_1D

Agilent Technologies

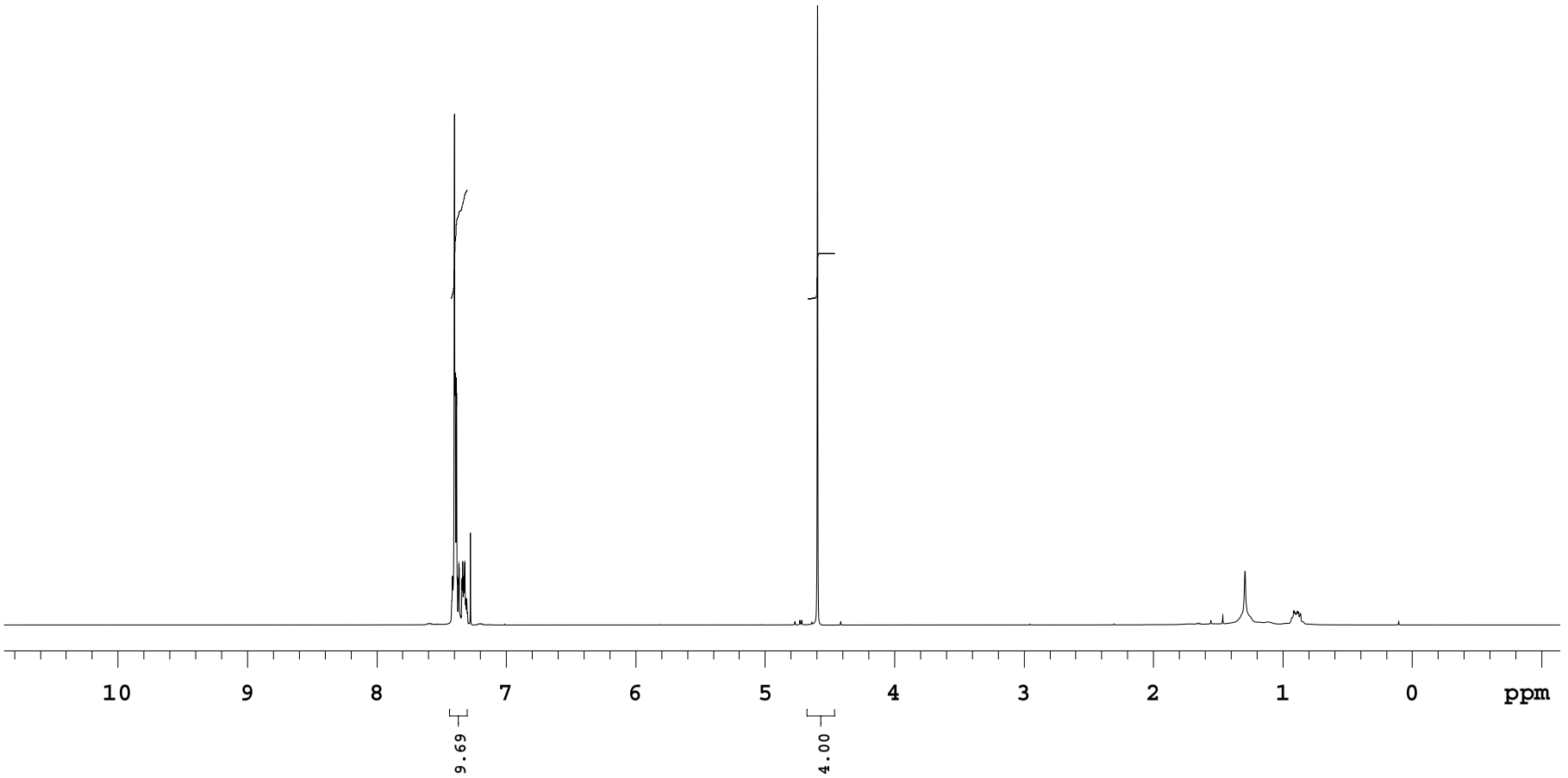
Department of Chemistry, University of Alberta

Recorded on: **mr400, Nov 10 2018**	Sweep Width(Hz): **4807.69**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.07**	Hz per mm(Hz/mm): **20.03**	Completed Scans **16**

399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



3.5



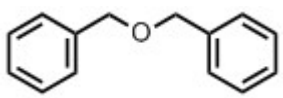
File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2018.11.10.mr4_NT-dibenzyl_ether_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **mr400, Feb 5 2019**	Sweep Width(Hz): **27173.9**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.21**	Hz per mm(Hz/mm): **113.22**	Completed Scans **176**

100.586 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



3.5

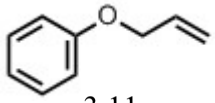
File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2019.02.05.mr4_NT-dibenzyl_ether_carbon_C13_1D

Agilent Technologies

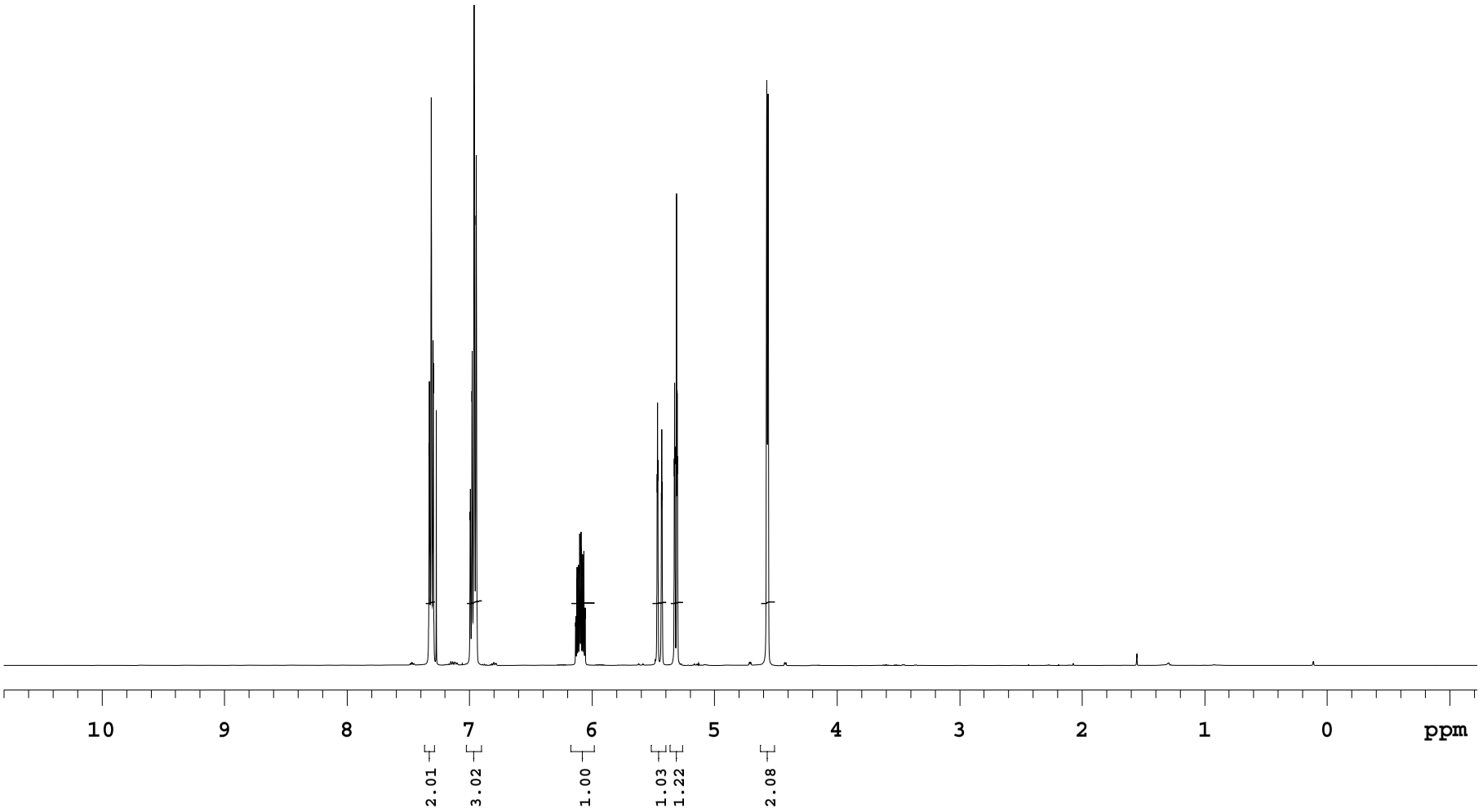
Department of Chemistry, University of Alberta

Recorded on: **u500, Oct 11 2018**	Sweep Width(Hz): **6009.62**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25.04**	Completed Scans **16**

Nam, NT-phneyl_allyl_ether
499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



3.11



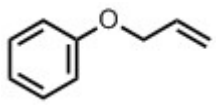
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.10/2018.10.11.u5_NT-phneyl_allyl_ether_loc1_13.00_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **u500, Oct 11 2018**	Sweep Width(Hz): **33783.8**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.26**	Hz per mm(Hz/mm): **140.76**	Completed Scans **12**

Nam, NT-phneyl_allyl_ether
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



3.11

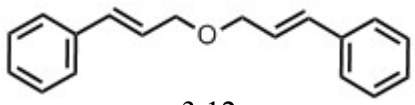
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.10/2018.10.11.u5_NT-phneyl_allyl_ether_loc1_13.02_C13_1D

Agilent Technologies

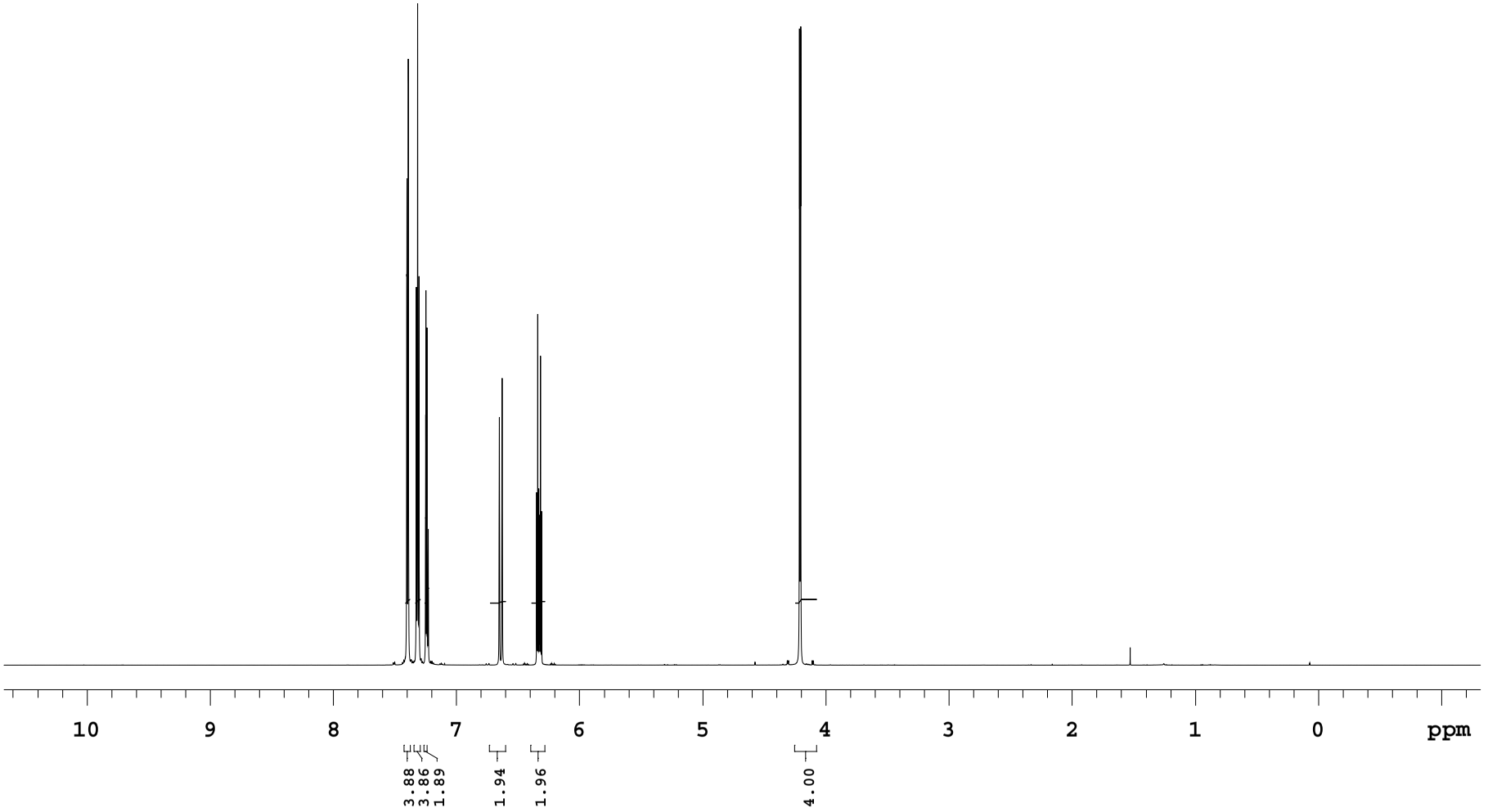
Department of Chemistry, University of Alberta

Recorded on: **v700, Nov 7 2018**	Sweep Width(Hz): **8389.26**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.13**	Hz per mm(Hz/mm): **34.95**	Completed Scans **8**

Nam, NT-dicinnamyl_ether
699.762 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



3.12



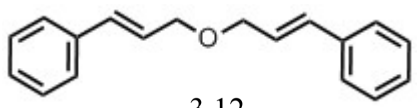
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.11/2018.11.07.v7_NT-dicinnamyl_ether_loc57_15.15_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **v700, Nov 7 2018**	Sweep Width(Hz): **48076.9**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.37**	Hz per mm(Hz/mm): **200.32**	Completed Scans **52**

Nam, NT-dicinnamyl_ether
175.975 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.5 C -> actual temp = 27.0 C, coldid probe



3.12

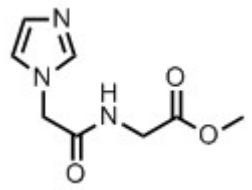
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.11/2018.11.07.v7_NT-dicinnamyl_ether_loc57_15.12_C13_1D

Agilent Technologies

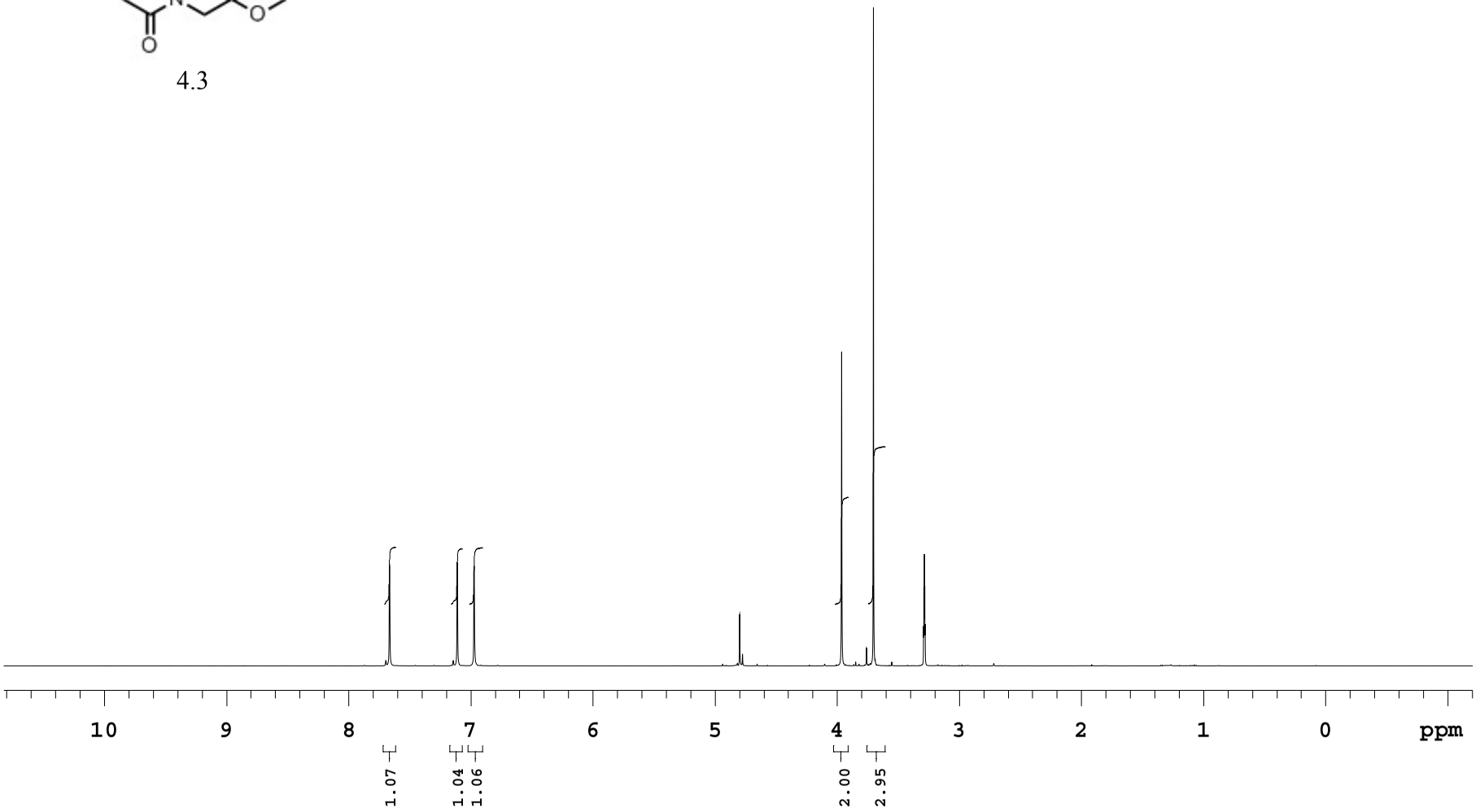
Department of Chemistry, University of Alberta

Recorded on: **u500, Oct 25 2018**	Sweep Width(Hz): **6009.62**	Acquisiton Time(s): **3**	Relaxation Delay(s): **2**
Pulse Sequence: **PRESAT**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25.04**	Completed Scans **8**

Nam, NT-imidazole_amide_repeat
499.799 MHz H1 1D in cd3od (ref. to CD3OD @ 3.30 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



4.3



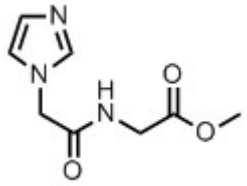
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.10/2018.10.25.u5_NT-imidazole_amide_repeat_loc6_13.13_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	u500, Oct 25 2018	Sweep Width(Hz):	33783.8	Acquisiton Time(s):	1	Relaxation Delay(s):	1
Pulse Sequence:	s2pul	Digital Res.(Hz/pt):	0.26	Hz per mm(Hz/mm):	140.76	Completed Scans	256

Nam, NT-imidazole_amide_repeat
125.688 MHz C13{H1} 1D in cd3od (ref. to CD3OD @ 49.0 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



4.3

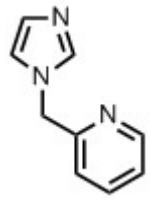
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.10/2018.10.25.u5_NT-imidazole_amide_repeat_loc6_13.14_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **ibd5, Sep 27 2018**	Sweep Width(Hz): **6000.6**	Acquisiton Time(s): **5**	Relaxation Delay(s): **0.1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.09**	Hz per mm(Hz/mm): **25**	Completed Scans **16**

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



4.8

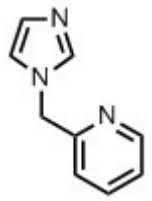
File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2018.09.27.i5_NT-_picolyl-imidazole_H1_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on: **u500, Sep 28 2018**	Sweep Width(Hz): **33783.8**	Acquisiton Time(s): **1**	Relaxation Delay(s): **1**
Pulse Sequence: **s2pul**	Digital Res.(Hz/pt): **0.26**	Hz per mm(Hz/mm): **140.76**	Completed Scans **512**

Nam, -imidazole-picolyl
125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



4.8

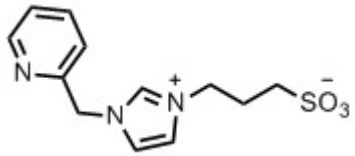
File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2018.09/2018.09.28.u5_-imidazole-picolyl_loc6_07.23_C13_1D

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	i600, Aug 26 2017	Sweep Width(Hz):	7183.91	Acquisiton Time(s):	3	Relaxation Delay(s):	2
Pulse Sequence:	presat	Digital Res.(Hz/pt):	0.11	Hz per mm(Hz/mm):	29.93	Completed Scans	16

599.927 MHz H1 1D in d2o (ref. to external acetone @ 2.225 ppm)
temp 25.8 C -> actual temp = 27.0 C, autoxid probe



4.9

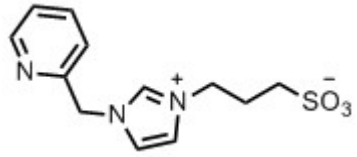
File: /mnt/d600/home15/fjwnmr/nmrdata/Nam/2017.08.26.i6_imidazole+picolyl+sulfonal_H1_presat

Agilent Technologies

Department of Chemistry, University of Alberta

Recorded on:	u500, Aug 26 2017	Sweep Width(Hz):	33783.8	Acquisiton Time(s):	1	Relaxation Delay(s):	1
Pulse Sequence:	s2pul	Digital Res.(Hz/pt):	0.26	Hz per mm(Hz/mm):	140.76	Completed Scans	156

Nam, imi-picol-sulfo
125.688 MHz C13{H1} 1D in d2o (ref. to external acetone @ 31.07 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



4.9

File: /mnt/d600/home15/fjwnmr/nmrdata/DATA_FROM_NMRSERVICE/Nam/2017.08/2017.08.26.u5_imi-picol-sulfo_loc1_20.04_C13_1D