Boronic Acid Catalysis: A Mild Approach to Hydroxyl Group Activation for Carbon-Carbon and Carbon-Nitrogen Bond Formation

By

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Abstract

Environmental concerns and a rising focus on sustainability are of increasing importance in society. As these concerns begin to impose limitations on synthetic chemistry and industrially relevant processes, more efficient alternatives to facilitate the synthesis of organic compounds must be developed. As one of the *Twelve Principles of Green Chemistry*, catalysis will be a vital technology to both society and the chemical industry. The use of cooperative catalysts, activation by light (photocatalysis), and electrical current (electrochemistry) has led to new processes of chemical bond formation, as well as expansion of the scope of previously explored methodologies. However, even with these new catalytic strategies, the use of the common hydroxyl functional remains under-explored. In this regard, boronic acids have recently emerged as catalysts for their mild and selective activation. Herein, the development of three boronic acid catalysed methodologies will be discussed.

Chapter two will focus on the development of a boronic acid catalysed coupling of π-activated alcohols with borate and silane nucleophiles. In a direct comparison between potassium trifluoroborates and organosilane nucleophiles, organosilanes lead to higher reaction yields, a wider substrate scope, and proceed with high *E/Z* selectivity when alkenyl silanes are employed as substrates. Furthermore, the reaction proceeds under mild conditions with up to near quantitative. This method complements existing methodologies as a unifying strategy for deoxygenative coupling reactions of alcohols with pseudo-organometallic reagents.

Given the well explored reactivity and value azides and nitriles possess as precursors to a variety of nitrogenous compounds, the *ACS Green Institute Pharmaceutical Roundtable* has ranked their preparation, without the use of metal salts, as a critical area of research. Chapter three will discuss

the preparation of azides and nitriles using bench-stable azidotrimethylsilane and trimethylsilyl cyanide. Azidotrimethylsilane and trimethylsilyl cyanide are silane-bound, nucleophilic reagents capable of intercepting a presumed generated carbocation. A variety of diarylaceto nitriles, diarylmethyleneazides, and otherwise difficult to prepare allylic azides, are reported in modest to near quantitative yields.

Due to the importance that α-functionalized saturated *N*- and *O*- heterocycles have in medicinal chemistry, novel strategies for their preparation are of high value. Chapter 4 will discuss the initial results of a boronic acid catalysed coupling of cyclic hemiaminals and cyclic hemiacetals with silane nucleophiles. Previous studies have highlighted various Lewis and Brønsted acids that are capable of catalytically activating cyclic hemiacetals for nucleophilic substitution. However, this is the first report on the use of cyclic hemiaminals as substrates. Initial results suggest compatibility of a diverse scope of organosilane nucleophiles and *N*-protecting groups. Moreover, the optimized methodology proceeds under mild conditions, while producing only environmentally benign by-products.

Acknowledgements

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Statement of Co-Authorship and Originality

The work presented in this thesis was conducted by the author under the supervision of Professor J. Adam McCubbin in the Department of Chemistry at the University of Winnipeg. Molecular Modelling and DFT calculations were preformed by Professor Josh W. Hollett at the University of Winnipeg.

Table of Contents

List of Schemes

List of Tables

List of Figures

Abbreviations

°C	Degrees Celsius
APIs	Active Pharmaceutical Ingredients
Aq	Aqueous (as a solution in water)
Ar	Arene (represents a general arene moiety)
BAC	Boronic acid catalysis
Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
***n*-Bu**	Butyl
***sec*-Bu**	*Sec*-Butyl
t-Bu	*tert*-Butyl
Calcd	Calculated
cat.	Catalytic
cm^{-1}	wavenumbers
Cy	Cyclohexane
d	Doublet
dd	Double-doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIBAL	Diisobutylaluminium hydride
DMF	Dimethylformamide
E	Electrophile
EDG	Electron donating group
Equiv.	Equivalents
EWG	Electron withdrawing group
Et	Ethyl
FGIs	Functional group interconversion

h	Hour
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
LG	Leaving group
m	multiplet
M	Metal atom
Me	Methyl
MeCN	Acetonitrile
mol	Mole
M.S.	Molecular sieves
mCPBA	*meta*-Chloroperoxybenzoic acid
MIBA	5-Methoxy-2-iodophenylboronic acid
mmol	Millimole
NMR	Nuclear magnetic resonance
Nu	Nucleophile
***o*-QMs**	*ortho*-Quinone methides
o/m/p	*Ortho/meta/para*
Ph	Phenyl
pin	Pinacolato
pK_a	$pK_a = -\log_{10}$ of the acid dissociation constant for a given species
Pyr	Pyridine
R, R^1,…, R^n	Representation of various moieties as specified in text
RT	Room Temperature (25 ˚C)
temp	Temperature
THF	Tetrahydrofuran
TIPS	Triisopropylsilane
TLC	Thin-layer chromatography
TM	Transition metal
TMS	Trimethylsilane

Tol	Toluene
Ts	*para*-Toluenesulfonyl
T.S.	Transition state

CHAPTER 1 - Introduction

1.1 Boronic Acids

1.1.1 Structure and Reactivity

Boronic acids, popularized by the Nobel Prize-winning Suzuki-Miyaura cross-coupling reaction, are widely commercially available with significant structural diversity. They are an attractive class of organic compounds, due to their low toxicity, stability, and the ease with which they are handled.[1] Upon eventual decomposition, boronic acids degrade into boric acid (environmentally benign), and can therefore be classified as "green" compounds.[2] They consist structurally of a central tri-valent boron atom with one carbon-based substituent and two hydroxyl groups, which allow for, among other effects, hydrogen bond donation.[3] Boronic acids, in their neutral form, are electron-deficient, with the boron atom having six valence electrons. Consequently, the sp^2-hybridized boron atom has a vacant p-orbital orthogonal to the substituents, resulting in a trigonal planar geometry and Lewis acidic character.[4]

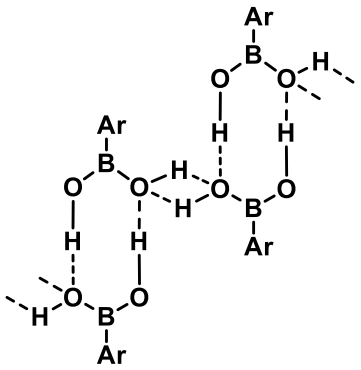


Figure 1-1. Extended hydrogen-bond network of arylboronic acid in the crystalline state

X-Ray crystallography has been used to elucidate the structure and geometry of many boronic acid derivatives. Rettig and Trotter first reported that crystalline phenylboronic acid consists of two distinct molecules, associated by a pair of O-H-O hydrogen bonds.[5] It was further shown that each dimer then hydrogen bonds to four nearby units to form an effectively infinite array of layers (**Figure 1-1**).[5] Analysis of other arylboronic acid species has been completed and reveals that a co-planarity CBO_2 unit does not always occur. When an arylboronic acid bears a *para*-substituent (**Figure 1-2(a), Figure 1-2(c)**), the CBO_2 unit is co-planar with the ring itself, whereas *ortho*-substituents (*e.g.* a nitro group) causes the CBO_2 plane to orthogonalize (**Figure 1-2(b)**).[4] Rotation of the CBO_2 plane is likely due to a combination of increased steric strain from the *ortho*-nitro group, and possible interactions between an oxygen atom on the nitro group and the adjacent boron atom.[4]

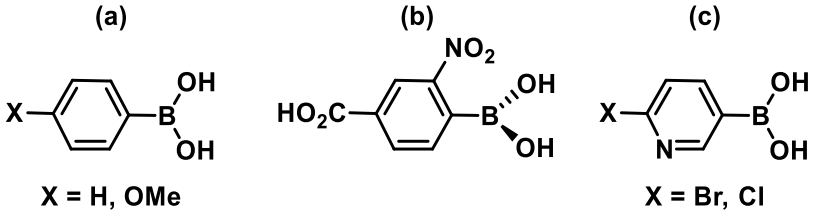
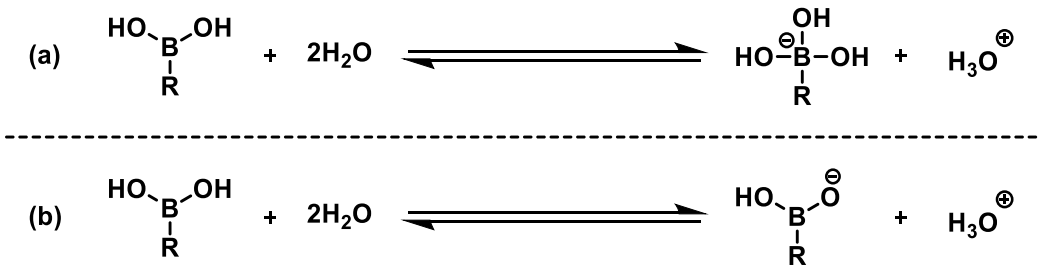


Figure 1-2. Arylboronic acid derivatives displaying co-planar geometry **(a)** & **(c)** and orthogonal geometry **(b)** of the CBO_2 plane

Due to the Lewis acid character that boronic acids possess, Lewis basic molecules are able to coordinate to the central boron atom. When coordination occurs, the central boron atom adopts a carbon-like tetrahedral geometry.[4] Upon coordination to anionic ligands, the negative charge is formally represented on the boron atom. However, the charge is evenly distributed amongst the heteroatoms. In 1958, Lorand and Edwards demonstrated that an equilibrium of a hydrated anionic tetrahedral species and a trivalent neutral species was present (**Scheme 1-1(a)**), rather than an

equilibrium with a trivalent ion (**Scheme 1-1(b)**).[6] This demonstration explains why the acidic character of most boronic acids is that of a Lewis acid and not a Brønsted acid.



Scheme 1-1: Boronic acids as **(a)** Lewis acids and **(b)** Brønsted acids

The reactivity of various boronic acids is determined primarily by the nature of the carbon-based substituent; this allows for the direct electronic tuning of the Lewis acidic boron atom. As such, general trends of pK_a can be observed for specific substituents. Arylboronic acids with electron-withdrawing substituents are the most acidic, arylboronic acids without electron-withdrawing substituents follow, and alkylboronic acids are the least acidic. The most acidic of all known boronic acid species, 3-pyridylboronic acid (**Figure 1-3**), has a pK_a of approximately 4.0.[4,7] This value is drastically different than that of the least acidic boronic acid, methylboronic acid, which has a pK_a of approximately 10.4 (**Figure 1-3**).[4,7]

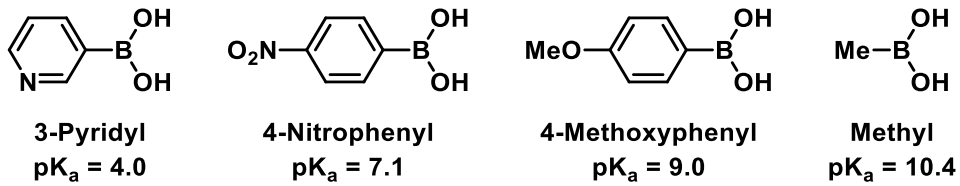
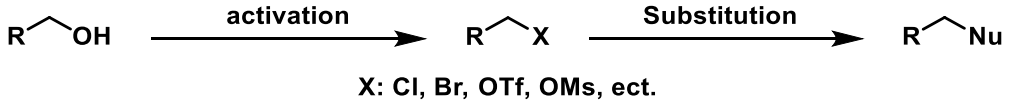


Figure 1-3. pK_a values of selected boronic acids

1.2 Hydroxyl Functional Groups in Organic Synthesis

1.2.1 Conventional Methods for Alcohol Activation

With approximately two thirds of biologically active natural products containing at least one, hydroxyl groups are ubiquitous in nature and important functional groups for organic synthesis.[8] The manipulation of hydroxyl functional groups and C-O bonds in general, is important for the synthesis of complex molecules. Conventionally for alcohols, the hydroxyl functional group is converted to an activated species (tosylate, halide, sulfonate, etc.) before subsequent functionalization is carried out (**Scheme 1-2**). This general strategy includes well-known reactions like the Mitsunobu reaction and the Appel reaction.[9,10] An analysis of industrial process chemistry shows that approximately 22% of functional group interconversions (FGIs) preformed in the preparation of active pharmaceutical ingredients involves substitution of hydroxyl groups for halides.[11] While these classical manipulations are extremely powerful and have diverse applications, they are undesirable at the industrial level, due to the large amounts of halogenated waste they generate. Thus, the ACS Green Chemistry Institute Pharmaceutical Roundtable ranks catalytic hydroxyl group activation as a critical area of research.[12]



Scheme 1-2: Classical approach to the stoichiometric activation of alcohols

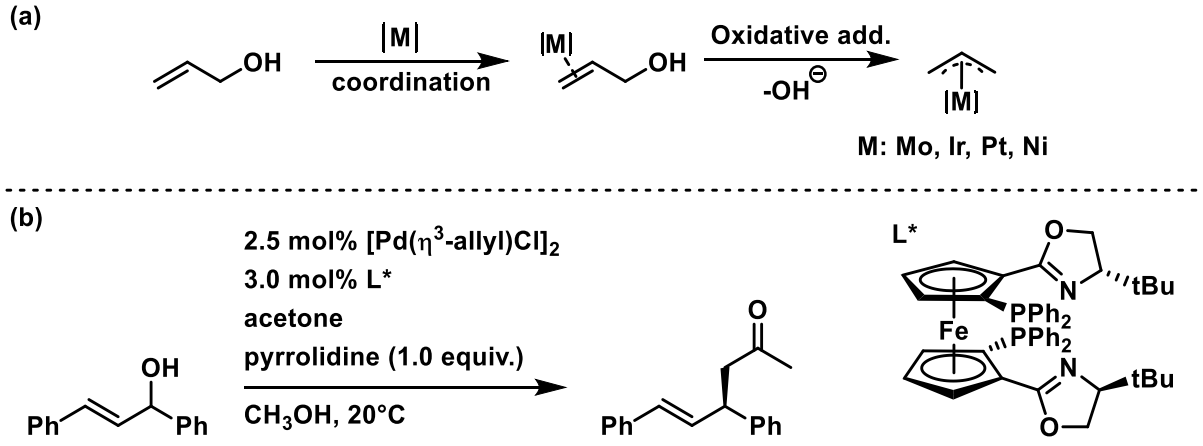
1.2.2 Catalytic Methods for Alcohol Activation

Environmental concerns and a rising focus on sustainability are of increasing importance in society. As these concerns begin to impose limitations on synthetic chemistry and industrially relevant processes, more efficient alternatives to facilitate the synthesis of organic compounds must be developed. As one of the Twelve Principles of Green Chemistry,[13] catalysis will be a vital technology to both society and the chemical industry. The use of cooperative catalysis,[14] activation by light (photocatalysis),[15] and electrical current (electrochemistry)[16] has led to new processes for chemical bond formation, as well as expansion of the scope of previously explored methodologies.

1.2.2.1 Transition Metal Catalysed Activation of Allylic Alcohols

Transition metal catalysed allylic substitution reactions have received significant attention since their initial report in 1970. The seminal work of Tsuji involved the substitution allylic chlorides with a series of carbanions *via* the formation of π-allylpalladium intermediates.[17] Development of this type of chemistry since the initial report has been focused on leaving group variation, which has led to the inclusion of unactivated allylic alcohols as substrates, and asymmetric variants. While many transition metals (Mo, Ir, Pt, Ni) have been reported to catalyse the substitution of allylic alcohols, they are all thought to proceed by the same π-allyl intermediate species (**Scheme 1-3(a)**).[18–21] Modern approaches to allylic substitution feature large, complex, chiral ligands capable of inducing enantioinduction. An interesting example involves a ferrocene based phosphinooxazoline ligand for the asymmetric allylation of acetone (**Scheme 1-3(b)**).[21] While this

strategy has powerful applications in the synthesis of important biologically active molecules, it is limited to the use of allylic substrates.

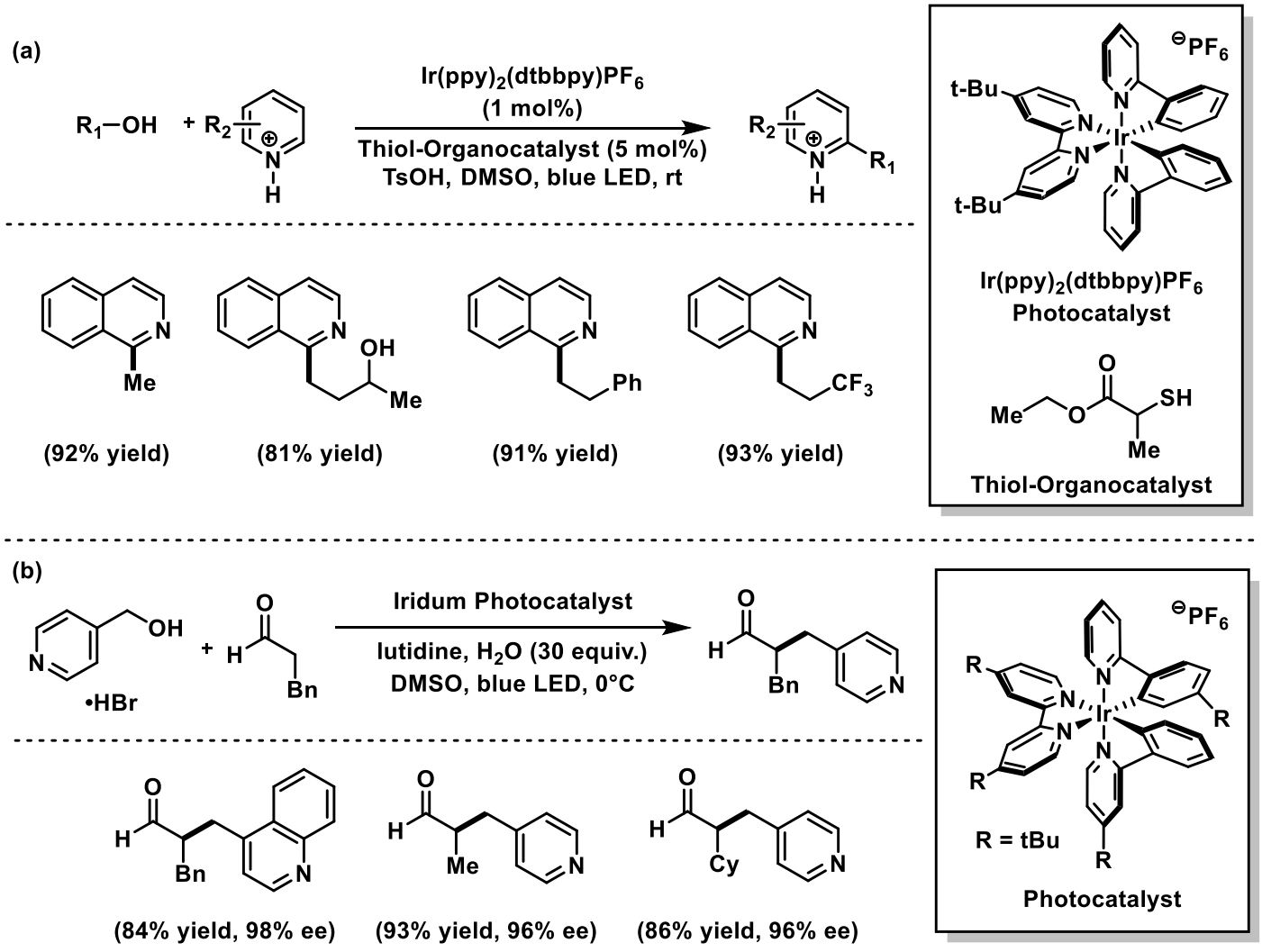


Scheme 1-3: (a) Transition metal catalysed activation of allylic alcohols *via* π-allyl intermediates **(b)** asymmetric allylation of acetone *via* a π-allyl intermediate

1.2.2.2 Photoredox Activation of Alcohols – A Radical Approach

Photoredox catalysis has begun to emerge as a powerful tool that allows for the development of novel modes of reactivity. Through these new strategies, several unique approaches for the activation of the hydroxyl functional group in alcohols have been reported in recent years. The first account of photochemical activation of alcohols was reported by MacMillan and co-workers, which employed the use of a complex dual thiol/photocatalytic system that mimics deoxyribonucleotide synthesis.[22] An α-oxy radical is generated from an alcohol substrate *via* a thiol and photocatalyst; the α-oxy radical then adds to a pyridinium ion by Minisci-type chemistry, affording an α-amino radical. The α-amino radical then undergoes a spin-centred shift elimination of water to afford the product upon protonation (**Scheme 1-4(a)**).[22] The utility of this "spin-

centered shift" system has also been extended to the enantioselective α-benzylation of aldehydes using alcohols as substrates.[23] Using an iridium photocatalyst, heterobenzylic alcohols (*e.g.* 4-(hydroxymethyl)pyridine) undergo a single electron transfer and protonation to generate α-amino radical species; the α-amino radical then undergoes the key spin-centred shift generating a benzyl radical. When introduced to an *in-situ* generated chiral enamine, the desired products are afforded in excellent yield with high enantioselectivity (up to 98% ee) (**Scheme 1-4(b)**).[23]



Scheme 1-4: (a) MacMillan's strategy for dual photoredox catalysed/organocatalysed activation of alcohols **(b)** Spin-centered shift approach for the α-benzylation of aldehydes

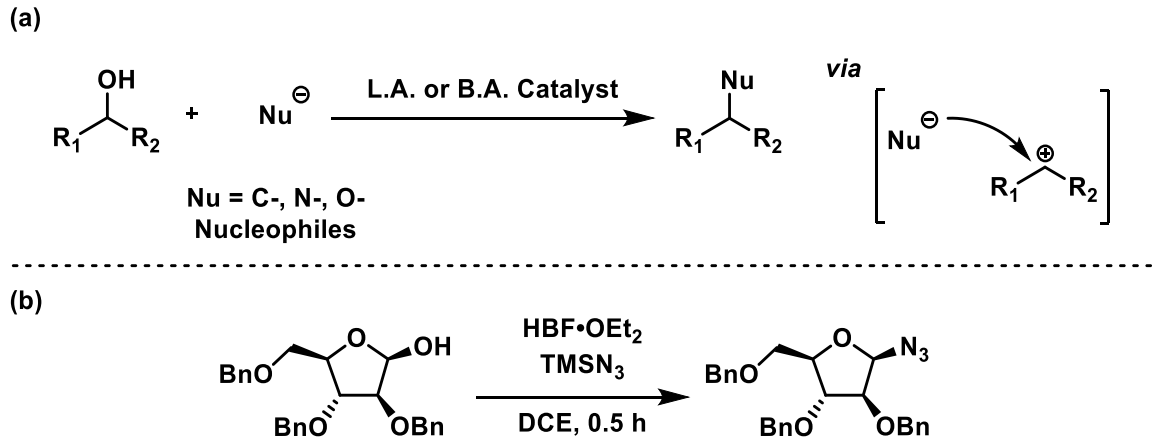
1.2.2.3 Lewis and Brønsted Acids as Catalysts for Alcohol Activation

The use of Lewis and Brønsted acid catalysis for the activation of alcohols remains the most popular method for their functionalization. This normally requires the use of π-activated alcohols as substrates.[24] The activation process involves coordination or protonation of the hydroxyl group in order to polarize the C-O bond, followed by the introduction of a nucleophile (**Scheme 1-5(a)**). In this regard, the Friedel-Crafts alkylation of benzylic alcohols has received significant attention in recent years. Several different catalytic systems such as $FeCl_3$,[25] $Bi(OTf)_3$,[26] $InCl_3$,[27–29] $HBF_3{\bullet}OEt_2$,[30–32] and $Ca(NTf_2)_2$[33,34] have provided insight towards the use of an expanded scope of nucleophiles, since different catalytic systems are optimal for C-, N-, and O-based nucleophiles.[35]

In a series of reports by Baba and co-workers, the first direct coupling of organosilane nucleophiles with benzylic, allylic, and propagylic alcohols is described.[27–29] Mediated by $InCl_3$ a variety of alcohols are activated electrophilically as coupling partners with allylic, vinyl, and alkynyl silanes. A similar process was reported by Niggemann *et. al.* using $Ca(NTf_2)_2$.[33] However, this system is limited to allyl and vinyl silanes as nucleophiles. Gandon and co-workers report the direct coupling of alcohols with vinyl boronic acids using the same $Ca(NTf_2)_2$ catalyst.[34] Through the use of additives such as $n Bu_4NBF_4$ and KPF_6, the reaction was accelerated. This effect was attributed to the formation of a heteroleptic complex between the additives and the catalyst, which served to increase Lewis acidity.[34] Several other organoboron nucleophiles (*e.g.* R-BF_3K, R-BPIN) were investigated, however, their use resulted in no reaction or complex mixtures of products.[34]

The use of $HBF_3{\bullet}OEt_2$ as a Brønsted acid catalyst for the activation of benzylic and benzhydryl alcohols was reported by Bolshan and co-workers. This system allows for the use of a diverse scope of nucleophilic coupling partners including allylic silanes,[31] vinyl and alkynyl

trifluoroborates,[30] as well as silylazides. The most noteable example of this work is in the formation of N-gylcosidic linkages when protected carbohydrates and azidotrimethylsilane are used as reactants (**Scheme 1-5(b)**).[32]



Scheme 1-5: (a) The general process for Lewis and Brønsted acid activation of alcohols **(b)** Formation of N-glycosidic linkages mediated by Brønsted Acid catalysis

1.2.2.4 Catalytic Strategies for Mitsunobu and Appel Reactions

Due to the importance that the Mitsunobu and Appel reactions hold in organic synthesis, a significant amount of effort has been focused on the development of catalytic alternatives. The conventional methodologies generate stoichiometric waste in the form of phosphine oxide and azocarboxylate reagent biproducts. In recent years several advancements towards a catalytic method have been made by Toy,[36] Taniguchi,[37,38] O'Brien and Aldrich,[39] and Denton.[40–42]

In 2006, Toy and co-workers reported the first account of a Mitsunobu reaction proceeding with a sub-stoichiometric amount of azocarboxylate reagent. The strategy was developed from the

previously reported oxidation of azocarboxylate species using hypervalent iodine reagents. Using di(acetoxy)iodobenzene as a stoichiometric oxidant, acetic acid was generated as waste, replacing the usual toxic hydrazine.[36] Inspired by the work of Toy, Tamiguchi *et. al.* began to investigate the use of other oxidants for azodicaroxylate recycling. By using arylazodicarboxylate species, an iron phthalocyanine co-catalyst, and oxygen as the oxidant, efficient recycling of the azo- species as achieved.[38] In this system, the only by-product generated is water.

With the recycling of toxic azocarbloxylate species addressed, attention then turned to the undesired generation of phosphine oxide waste. First reported for use in the Wittig reaction, O'Brien and co-workers implemented a phosphorous(V)-mediated transformation using hydrosilanes as reductants.[43] When this strategy was applied to the Mitsunobu reaction, esterification was achieved, but racemization of the product was observed.[43] Aldrich *et. al.* envisioned a system that involves both the azo-recycling ability of Taniguchi's method and the phosphine-recycling ability of the O'Brien method. Through optimization of reaction conditions, this was achieved. However, the reaction scope was limited, and lacked any significant inversion of the stereocentre.[39]

While the advancements discussed have made significant progress toward a truly catalytic Mitsunobu reaction, they all require the addition of a stoichiometric additive, and are therefore not truly catalytic. In 2019, Denton and co-workers reported on the first truly catalytic Mitsunobu reaction. Denton's strategy involves a redox-neutral dehydration using a phosphorus-based organocatalyst (**Figure 1-4**)[42] Beyond the catalytic and waste-free nature of this method, several functional groups that may interfere with esterification reactions including esters, amides, phthalimides, and nitriles showed excellent tolerance under these conditions.[42]

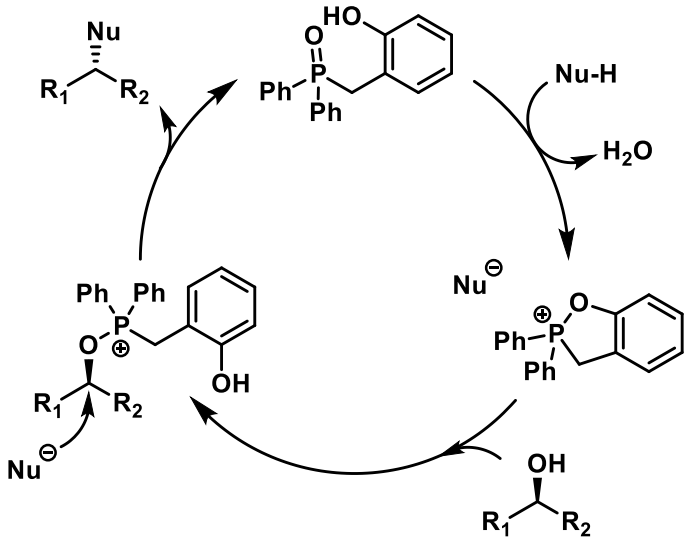


Figure 1-4: A proposed catalytic cycle for the fully catalytic Mitsunobu reaction

1.3 Boronic Acid Catalysis (BAC)

1.3.2 Overview

Due to the utility of boronic acids as reagents, they have become important building blocks in organic synthesis. Boronic acids act as a key component in many significant transformations such as the Nobel Prize-winning Suzuki-Miyaura cross-coupling,[44,45] Chan-Lam coupling,[46,47] and Petasis reaction,[48–50] among many others. However, the ability of boronic acids to act as catalysts has only recently emerged as an area of interest and remains largely under-explored.[51]

The Lewis acidic character of boronic acids allows for the reversible formation of covalent bonds with a variety of hydroxyl group-containing molecules. In this context, the covalent complexes formed from carboxylic acids, carbonyl species, and alcohols are activated as electrophiles, making them susceptible to nucleophilic substitution or addition (**Figure 1-5**).[4,51]

Basic conditions normally promote the formation of tetravalent, anionic boronate species.[4] This mode of activation promotes the enolization of carbonyl species, increasing their nucleophilicity towards a diverse scope of electrophiles.[4] Furthermore, *ortho*-substituents can be introduced to provide secondary effects such as reagent binding, and transition state stabilization.

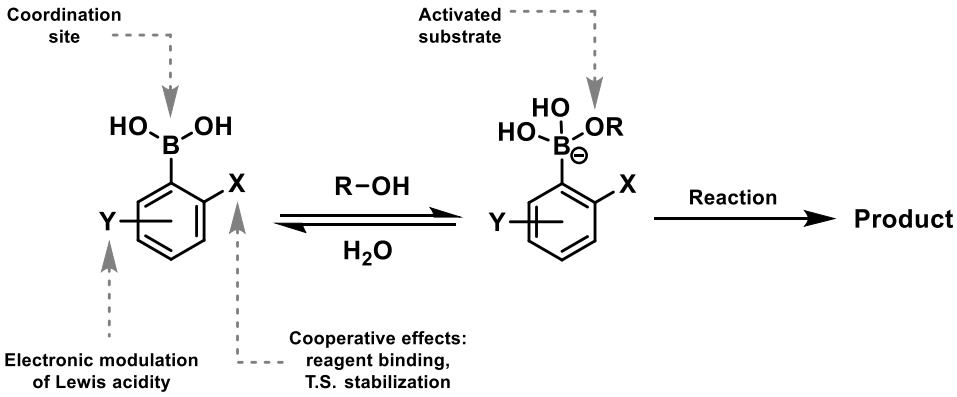


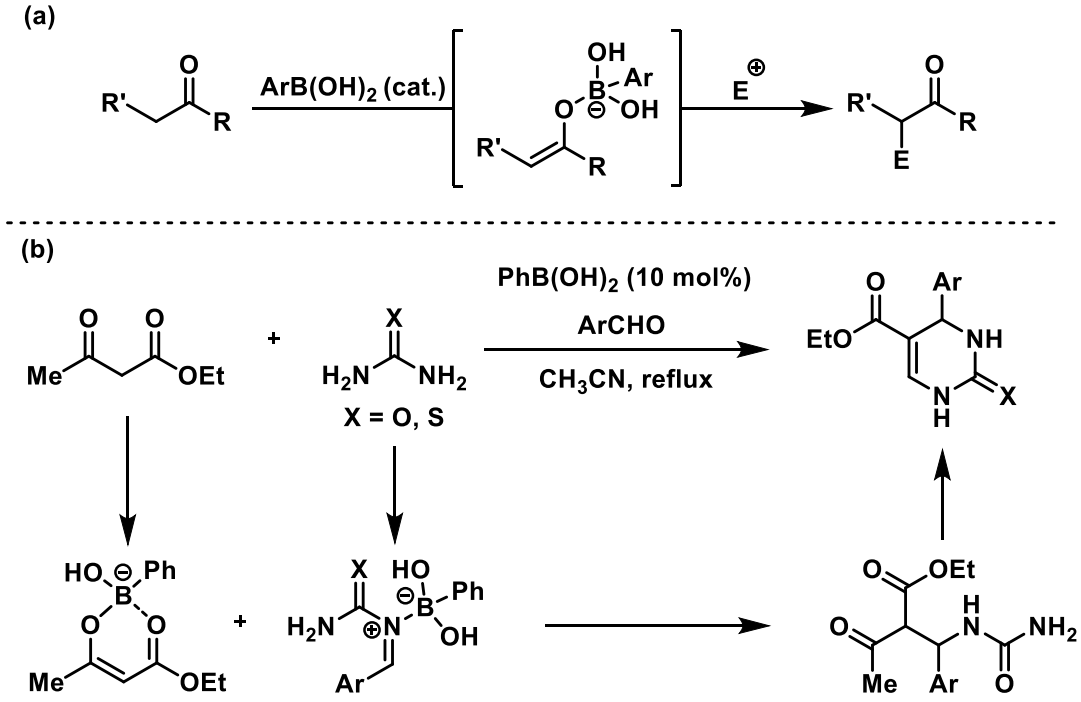
Figure 1-5: The Concept of Boronic Acid Catalysis (BAC)

1.3.3 Nucleophilic Activation *via* Boronic Acid Catalysis

1.3.3.1 Carbonyl Group Activation

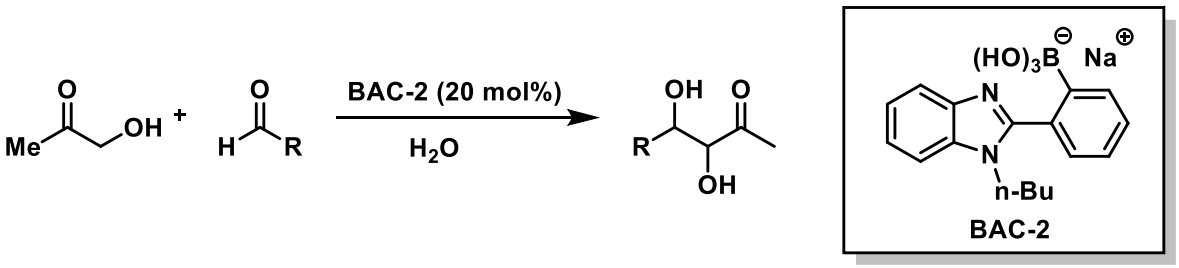
Conventionally, Lewis acids activate carbonyl species by increasing the electrophilicity of the carbonyl carbon atom. However, boronic acids are able to activate carbonyl species as nucleophiles through the formation of a tetravalent, anionic boronate species (**Scheme 1-6(a)**). In 2006, Carboni and co-workers identified phenylboronic acid (**BAC-1**) as an efficient catalyst for the Biginelli reaction.[52] In their report, they suggest a mechanism in which phenylboronic acid not only forms

a boron enolate with ethyl aceto-acetate, but also activates the acylimine intermediate *via* boron-nitrogen coordination (**Scheme 1-6(b)**)



Scheme 1-6: (a) Boronic acid catalysed activation of carbonyl species *via* boron enolate formation; **(b)** Boronic acid catalysed Biginelli reaction

In 2008 Whiting and co-workers reported that the *N*-butyl-1-benzimidazole-2-phenylboronic acid hydroxide complex (**BAC-2**) was able to catalyse the Aldol condensation of α-hydroxy ketones and aldehydes (**Scheme 1-7**).[53] Similar to that of the Bignelli reaction, they report dual catalytic activation where the imidazole facilitates boron enolate formation, and holds the aldehyde in position for nucleophilic attack through hydrogen bonding.[53]

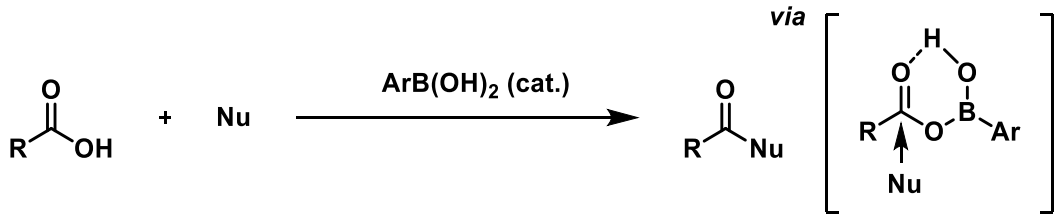


Scheme 1-7: Boronic acid catalysed Aldol condensation

1.3.4 Electrophilic Activation *via* Boronic Acid Catalysis

1.3.4.1 Carboxylic Acid Activation

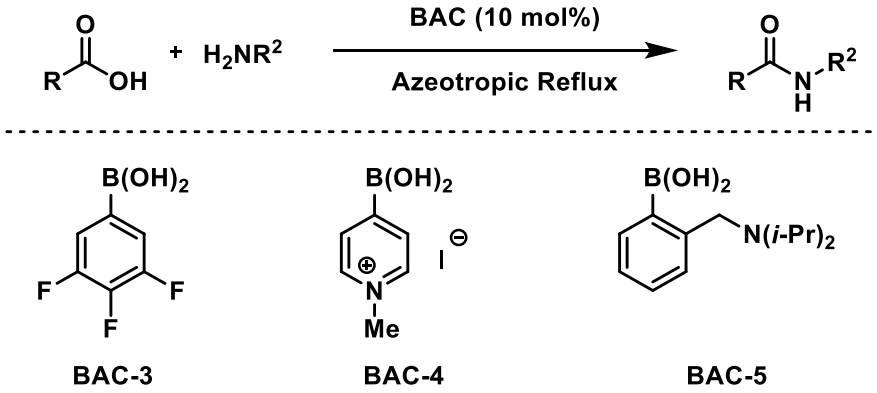
It is proposed that when a boronic acid activates a carboxylic acid, a mono-acyl boronic ester is formed upon condensation. This mono-acyl boronic ester is then activated for nucleophilic displacement (**Scheme 1-8**).[51]



Scheme 1-8: Boronic acid catalysed activation of carboxylic acids for nucleophilic displacement

The formation of amide bonds is one of the most widely studied and important reactions in organic synthesis, with almost half of synthetic drugs containing at least one such bond.[8] As such, a large library of coupling reagents have been developed such as carbodiimides, and those that generate

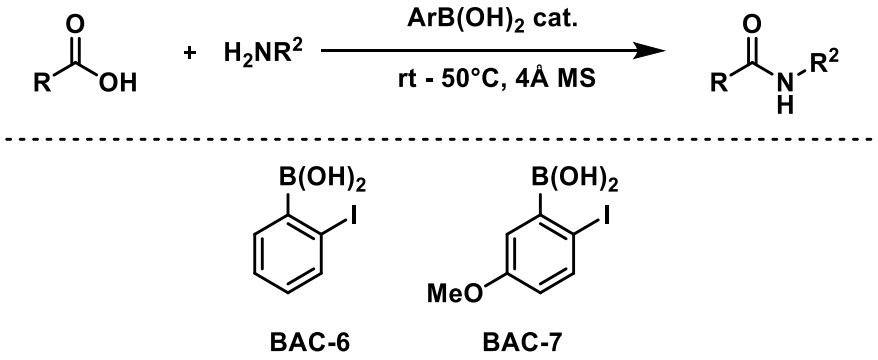
acyl chlorides. However, these reagents are often costly, and their reactions suffer from poor atom economy, generating significant amounts of stoichiometric waste.[54] The use of arylboronic acids as catalysts for direct amidation was first reported in 1996 by Yamamoto and co-workers, where they used 3,4,5-trifluorophenylboronic acid (**BAC**-3) in non-polar solvents.[55] Later, they also identified pyridiniumboronic acid (**BAC-4**) as an effective catalyst for the reaction in polar solvents.[56] However, the reaction conditions are harsh, requiring temperatures above 100°C and azeotropic reflux (**Scheme 1-9**). Since these initial reports, several other arylboronic acids have been reported for the direct amidation of carboxylic acids. In 2006, Whiting and co-workers identified 2-(diisopropyl-aminomethyl)-4-trifluoromethylphenylboronic acid (**BAC-5**) as an effective catalyst (**Scheme 1-9**).[57] While this system does not require temperatures above 100°C, 85°C and azeotropic reflux are still required.



Scheme 1-9: Yamamoto's and Whiting's Boronic acid catalysts for direct amidation of carboxylic acids

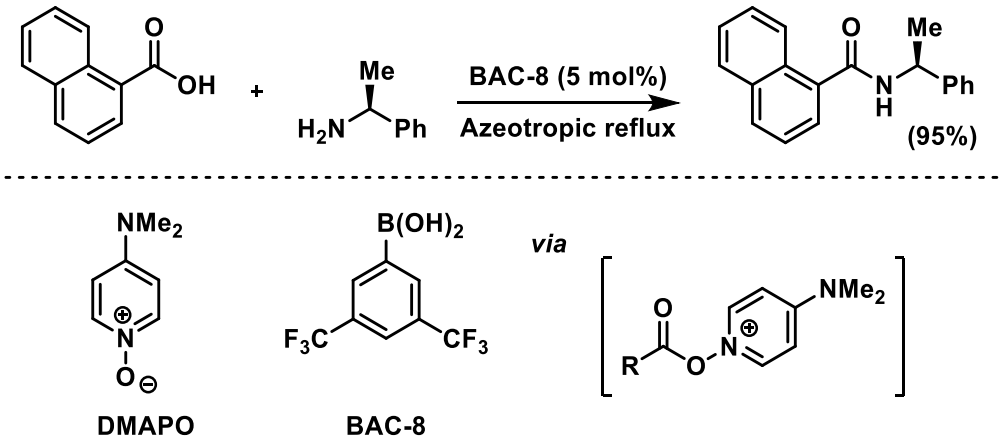
In 2008, Hall *et. al.* identified *ortho*-iodophenylboronic acid (**BAC-6**) as an effective catalyst for direct amidation at room temperature in the presence of 4Å molecular sieves (**Scheme 1-10**). It is particularly interesting that the *ortho*-iodo catalyst out-preforms both the analogous ortho-bromo

and *ortho*-chloro species, demonstrating the subtle, yet important secondary substituent effects in boronic acid catalysts.[54,58] Through further optimization, they identified 5-Methoxy-2-iodophenylboronic acid (MIBA) (**BAC-7**) as a second generation amidation catalyst (**Scheme 1-10**).[51] Using this system, the direct and catalytic amidation of aliphatic carboxylic acids and amines was achieved at room temperature.



Scheme 1-10: Hall's boronic acid catalysts for direct amidation of carboxylic acids

In 2015, a cooperative catalyst system including 2,5-bis(trifluromethyl)phenylboronic acid (**BAC-8**) and 4-(N,N-dimethylamino)pyridine N-oxide (DMAPO) that operates at ambient temperatures was identified by Ishihara and co-workers (**Scheme 1-11**).[57,59] The reports suggest that DMAPO takes part in the formation of an activated acyl N-oxide, which is then displaced by an amine nucleophile, generating the desired products. This system is particularly effective for the amidation of sterically hindered α-branched and α-arylated carboxylic acids.[59]



Scheme 1-11: Ishihara's cooperative catalytic system between 4-(*N*,*N*-dimethylamino)pyridine *N*-oxide and bis-3,5-trifluoromethylphenylboronic acid

The concept of boronic acid catalysis has also been employed in a diverse array of cycloaddition reactions involving α,β-unsaturated carboxylic acids. The boronic acid catalysed Diels-Alder and [3+2] cycloadditions are reactions that illustrate the unique secondary substituent effects of boronic acid catalysts. Electron-poor boronic acids have been shown to activate unsaturated carboxylic acids sufficiently, *via* lowering of their *LUMO* energy, so that they can participate as dienophiles in cycloaddition reactions.[60] The *LUMO* energy is lowered through a dehydrative reaction between the carboxylic acid and boronic acid, generating a monoacylborate species.[60] Following the formation of the desired cycloadduct, the water produced through the initial dehydration reaction then assists with the regeneration of the boronic acid catalyst.[2,60,61] Using boronic acids, efficient, atom-economical cycloaddition reactions involving acrylic and propiolic acid derivatives with azides, 1,3-dienes, nitrones, and nitrile oxides have been developed.[2,58,60] The presence of a boronic acid catalyst was shown to dramatically improve the yield and reaction rate.[58,60]

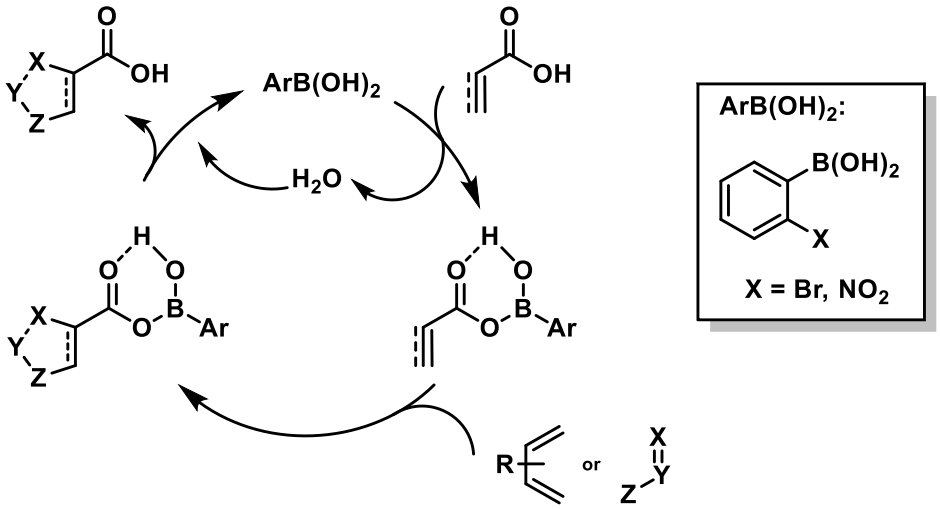
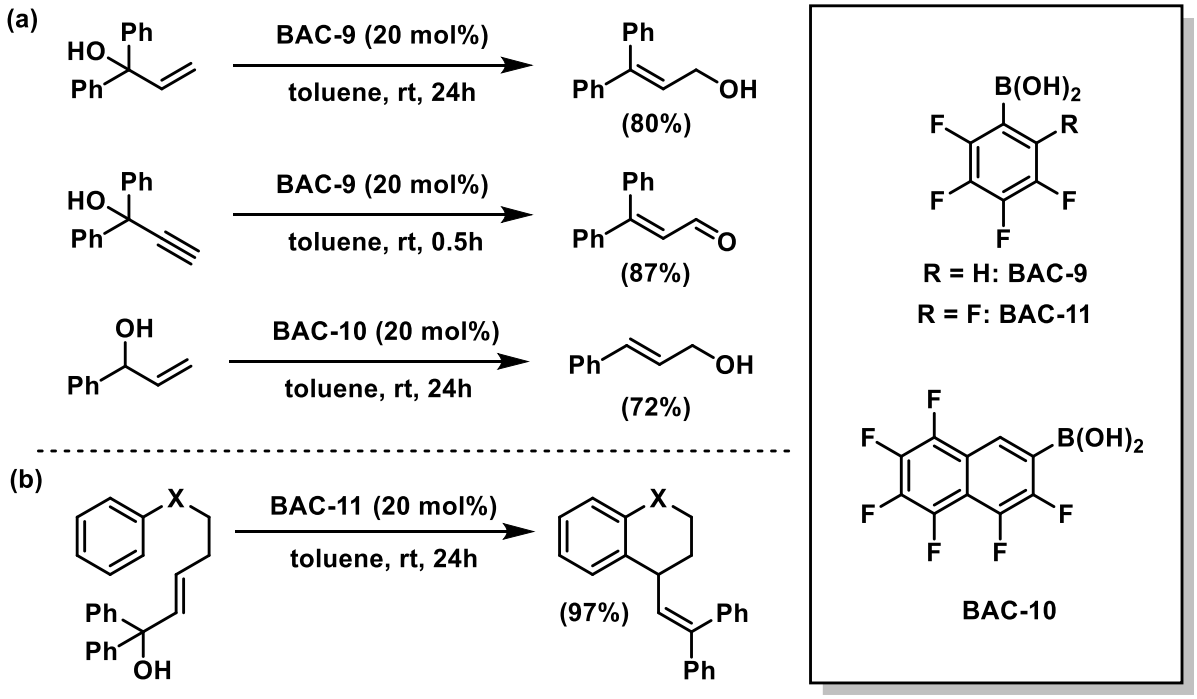


Figure 1-6: A proposed catalytic cycle for BAC Diels-Alder and dipolar cycloaddition reactions

1.3.4.2 Alcohol Activation

The hydroxyl functional group of alcohol molecules can also be activated directly and catalytically by arylboronic acids. Generally, electron-poor boronic acids are more effective at coordinating to the oxygen atom of the hydroxyl group. The oxygen coordinating ability of electron-poor boronic acids, in conjunction with the reactivity of π-activated alcohols, can result in various degrees of ionization. Developed by Hall and co-workers, the boronic acid catalysed 1,3-transposition of allylic alcohols and the related Meyer-Schuster rearrangement of propargylic alcohols, is an efficient strategy for otherwise difficult-to-prepare allylic alcohols and α,β-unsaturated carbonyl species (**Scheme 1-12a**). Readily ionized alcohol substrates participate in the rearrangement when tetrafluorophenyl boronic acid (**BAC-9**) is employed as a catalyst.[62] For less readily ionized species, hexafluoronapthalene boronic acid (**BAC-10**) was used.[62] Using similar conditions, Hall and co-workers extended this strategy to proceed sequentially through rearrangement and intramolecular nucleophilic attack.[63] A library of allylic alcohols containing pendant C-, N-, and

O- based nucleophiles was prepared. When treated with tetrafluorophenyl boronic acid (**BAC-9**), the synthesis of diverse carbo- and heterocyclic products was achieved (**Scheme 1-12b**).[63]

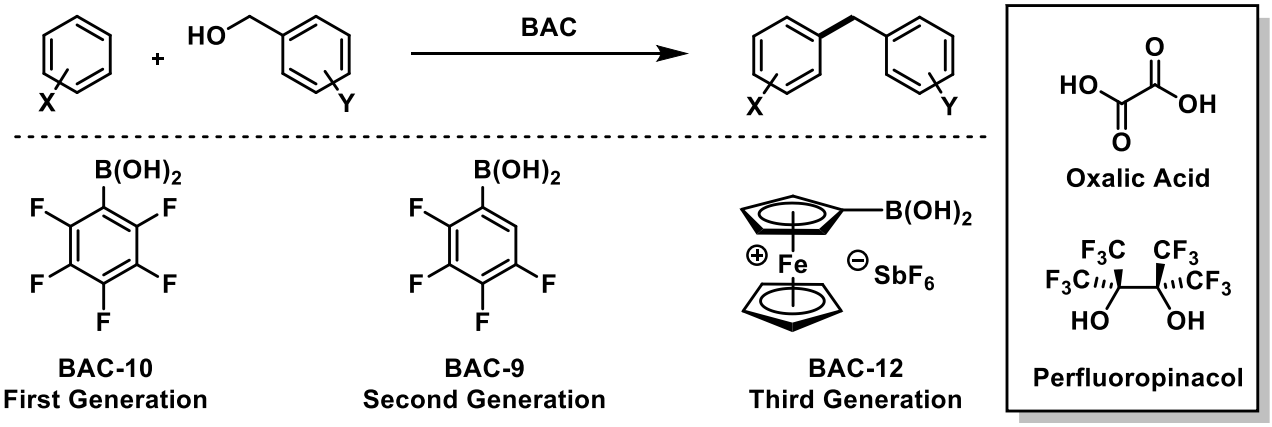


Scheme 1-12: (a) Boronic acid catalysed activation of allylic and propargylic alcohols for the 1,3-transposition, and **(b)** intramolecular cyclization of allylic alcohols *via* pendant nucleophiles

Boronic acids have also been developed as efficient catalysts for intermolecular Friedel-Crafts reactions. In 2010, McCubbin *et. al.* reported that pentafluorophenyl boronic acid (**BAC-11**) is highly Lewis acidic, displays excellent catalytic activity, and allows for the use of mild reaction conditions in the direct arylation of allylic alcohols.[64] When compared to more conventional protic (*e.g. p*-TsOH) and Lewis acid catalysts (*e.g.*$FeCl_3$), significantly higher yields and purity were obtained.[64] The use of pentafluorophenylboronic acid (**BAC-11**) limited the substrate scope to readily ionized alcohols and electron-rich arene nucleophiles such as furan, indole, and pyrrole.[64] The formation of an allylic carbocation during C-O bond activation is suggested, with the

regioselectivity controlled by steric effects.[61,64] It was later determined by Hall and co-workers that tetrafluorophenylboronic acid (**BAC-9**) and a nitromethane/hexafluoroisopropanol (HFIP) solvent mixture provided improved conditions, leading to expansion of the substrate scope.[62] Due to the pharmaceutical relevance of diarylmethane scaffolds and their ease of preparation by direct arylation of benzylic alcohols, McCubbin and Hall screened new boronic acid catalysts for the reaction. Ferroceniumboronic acid hexafluoroantimonate salt (**BAC-12**) was identified to have increased activity.[65] Using a 4:1 nitromethane/HFIP solvent mixture, a broad substrate scope was observed including previously unreactive benzylic alcohols containing destabilizing electron-withdrawing substituents (*e.g.* nitro).[65]

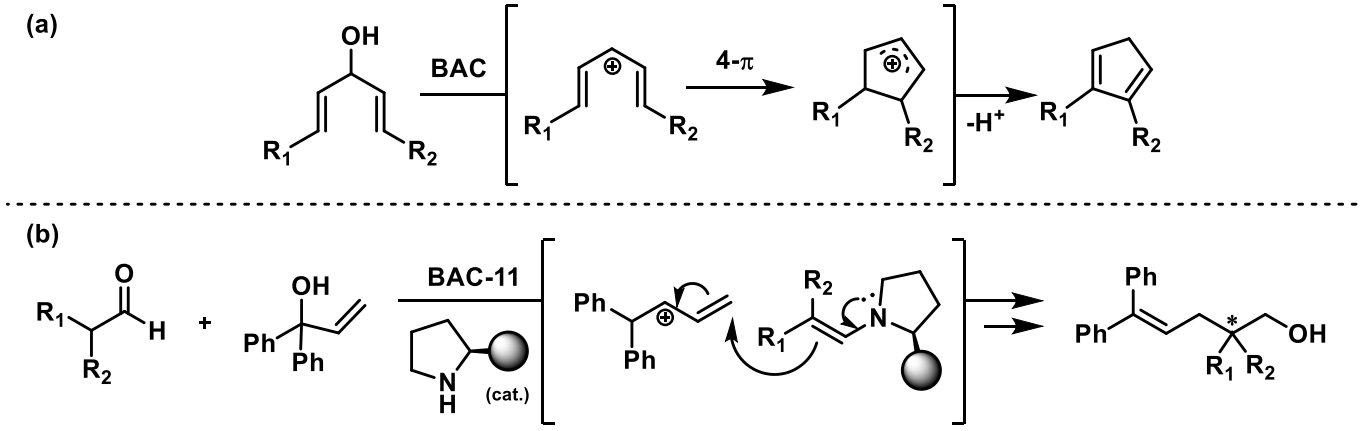
Through the development of iterative deconvolution catalyst screening, Moran and co-workers identified that mixtures of the appropriate boronic acid and dihydroxy ligands lead to increased catalytic activity.[66] Using previously developed reaction conditions for boronic acid catalysed Friedel-Crafts reactions, this iterative deconvolution strategy revealed that the previously substrate limited catalyst (**BAC-11**) displayed activity comparable to that of the ferroceniumboronic acid hexafluoroantimonate salt when oxalic acid was used as a co-catalyst.[66] Inspired by the work of Moran, Hall and co-workers revisited the boronic acid catalysed Friedel-Crafts reaction in search of new sub-stoichiometric additives to address the limited reactivity of very challenging electrophilic substrates (*e.g. p*-nitrobenzyl alcohol). It was found that perfluoropinacol synergistically activates ferroceniumboronic acid hexafluoroanimonate allowing *p*-nitrobenzyl alcohols to participate in Friedel-Crafts chemistry.[67] It should be noted that no other diols were successful at activating the ferroceniumboronic acid sufficiently to produce the desired product, even at elevated temperatures.[67]



Scheme 1-13: Boronic Acid Catalysts for Friedel-Crafts Reactions

Novel boronic acid catalysed methodologies that employ tandem/multi-catalysts and co-catalysts have begun to emerge as useful strategies for the preparation of complex molecular scaffolds. In a similar fashion to that of allylic alcohols, bis-allylic alcohols ionize, resulting in the formation of pentadienyl cations. These pentadienyl cations then undergo a 4π electrocyclic ring closure to yield substituted cyclopentadienes. This is formally known as the Nazarov cyclization (**Scheme 1-14(a)**). While only sporadic examples of alcohol participation are found in the literature, the boronic acid catalysed reaction proceeds in excellent yield. To increase the diversity of products obtained, the resulting cyclopentadiene products were subjected to the boronic acid catalysed Diels-Alder conditions, leading to the formation of highly functionalized bicyclic species.[68] Hall and co-workers also arrived at the realization that many of the products obtained from boronic acid catalysis are structurally related to starting materials of other boronic acid catalysed methodologies. This led to the development of several other one-pot strategies. Products obtained from 1,3-tranposition of alcohols can be dehydrated to obtain dienes, which can then be subject to boronic acid catalysed Diels-Alder cycloaddition employing acrylic acid as a dienophile. The resulting product may then be subjected to boronic acid catalysed amidation to form products containing exocyclic amide units.[60,62] Stereogenic carbon centres have also been prepared by

employment of a chiral enamine co-catalyst. Allylic alcohols are activated by ferroceniumboronic acid hexafluoroantimonate in one catalytic cycle and met by an *in-situ,* catalytically generated, nucleophilic chiral enamine.[69] This method affords the desired products with high yields and enantioselectivities (up to 90%, 97% *ee*) (**Scheme 1-14(b)**).[69]



Scheme 1-14: (a) Boronic acid catalysed Nazarov cyclization **(b)** Boronic acid catalysed alkylation of branched aldehydes with allylic alcohols

1.4 Thesis Objective

The ready availability and structural diversity of hydroxyl functional group-containing molecules and their biological relevance makes them an attractive class of substrates for organic synthesis. Despite these attributes, mild conditions for their reactions remain under-developed. It is therefore an important goal, not only for organic synthesis, but in the interest of environmental sustainability to investigate new catalytic strategies involving boronic acids. In this context, BAC has proven to be effective for the direct activation of alcohols.

With inspiration drawn from the ferroceniumboronic acid catalysed Friedel-Crafts reaction, this work focuses on expanding the scope of products obtained by introducing a diverse array of

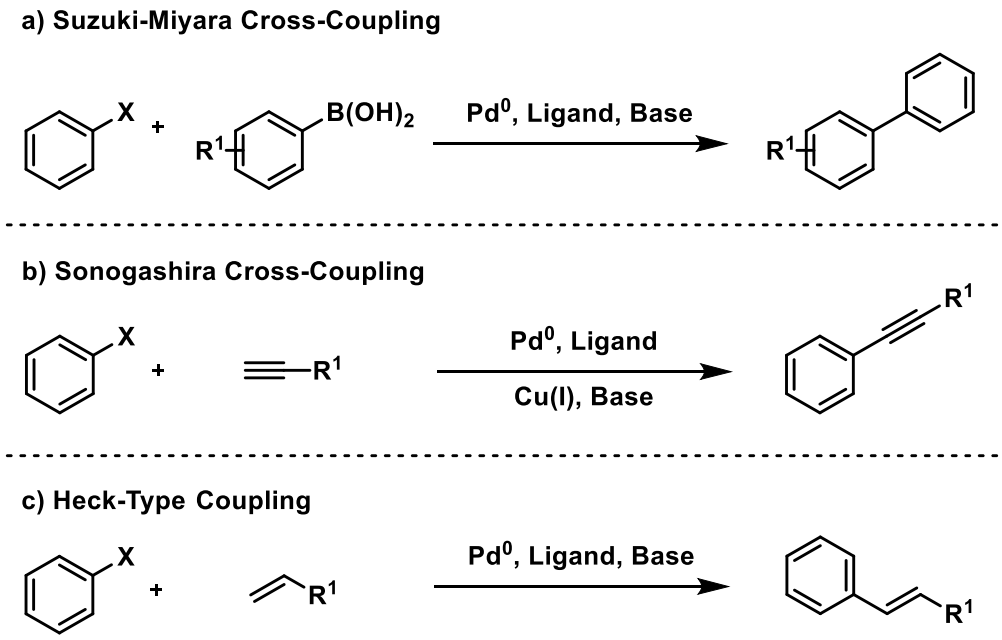
nucleophiles to “trap” the presumed carbocation intermediates. Chapter 2 will present the results from our carbon-carbon bond forming methodology. The introduction of organoborate and organosilane nucleophiles allows for the allylation, vinylation, and alkynylation of various allylic, propargylic, and benzylic alcohols. Chapter 3 will focus on the results of our BAC preparation of organoazides and nitriles.

To further explore the scope of hydroxyl functional groups activated by BAC, the concept is expanded to the direct activation of “lone-pair” activated alcohols. Chapter 4 will introduce our preliminary results for the activation and substitution of protected cyclic aminals and cyclic acetals. Initial results suggest a broad scope of silane-based nucleophiles are suitable coupling partners under ambient conditions.

CHAPTER 2 – Boronic Acid Catalysed C-C Coupling of Alcohols with Borate and Silane Nucleophiles

2.1 Introduction

Palladium catalysed cross-coupling reactions allow for the rapid assembly of complex molecular structures. They are readily employed in the synthesis of important biologically active molecules and in the industrial scale synthesis of pharmaceuticals. While conventional methods like the Suzuki,[44] Sonogashira,[70] and Heck-type[71] coupling reactions are extremely powerful, the significant amounts of potentially toxic, transition-metal and halogenated waste they produce are not sustainable. As such, the development of novel methodologies capable of introducing structural motifs containing unsaturated carbon-carbon bonds is of significant value for organic synthesis. Not only is the formation of a carbon-carbon bonds important, but unsaturated structural motifs may be easily manipulated to produce other relevant or sensitive functional groups. Moreover, the identification of cross-coupling reactants that can reduce the formation of potentially hazardous bi-products is also an important goal. In this regard, the activation of hydroxyl functional groups has been ranked as a critical area of research by the *ACS Green Chemistry Institute Pharmaceutical Roundtable*.[12]



Scheme 2-1: Conventional methods for palladium catalysed cross-coupling reactions

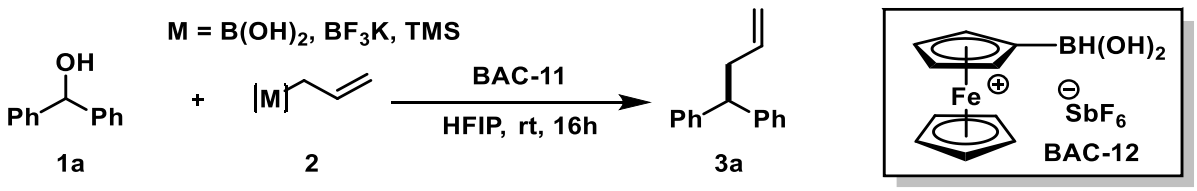
2.2 Objective

Interested in expanding the utility of the McCubbin and Hall's ferroceniumboronic acid hexafluoroantimonate salt catalysed Friedel-Crafts reaction,[65] we believed that by using pseudo-organometallic species as nucleophiles, important structural motifs could be introduced. This chapter will focus on our efforts to introduce new pseudo-organometallic reagents as coupling partners with alcohols activated as electrophiles by boronic acid catalysis. Through collaboration with Professor J. Hollett, computational mechanistic studies were also performed to investigate the stereospecific addition of vinyl silanes to the presumed carbocation. These mechanistic investigations provide insight toward the stereospecific addition, and catalyst regeneration.

2.3 Results and Discussion

2.3.1 Optimization of Reaction Conditions

Based on the previously discussed boronic acid catalysed Friedel-Crafts reactions of McCubbin and Hall,[65] we evaluated the same reaction conditions for the deoxygenative allylation of benzhydryl alcohol (**1a**) with either allyl boronic acid (**2a**), allyl potassium trifluoroborate (**2b**), or allyltrimethylsilane (**2c**) at 70°C. The free boronic acid was unsuccessful in producing the desired product. However, the trifluoroborate salt produced the desired product **3a** in 55% yield; the use of the allyltrimethylsilane resulted in 93% yield. A series of solvents were also investigated; however, it was determined that hexafluoroisopropanol (HFIP) was the optimal due to its ability to stabilize carbocation intermediates. No significant differences in yield were observed at elevated temperature, therefore ambient temperature was taken to be optimal. Other boronic acids that have been shown to effectively activate allylic and benzylic alcohols proved to be ineffective for this allylation reaction.[72,73] It has been reported that HFIP alone is capable of activating alcohols to participate in various coupling reactions.[74] A control experiment with no catalyst added was preformed at ambient temperature. The desired product was obtained in only 15% yield**.**



Scheme 2-2: Optimized reaction conditions for the direct coupling of alcohols with borate and silane nucleophiles

Table 2-1: Optimization of reaction conditions for the boronic acid catalysed coupling of alcohols with borate and silane nucleophiles

Entry	Catalyst	Solvent	[M]	Temp (◦C)	Yield (%)
1	**BAC-12**	HFIP	$B(OH)_2$	70	n.r.
2	**BAC-12**	HFIP	BF_3K	70	55%
3	**BAC-12**	HFIP	TMS	70	93%
4	**BAC-12**	CH_3CN	TMS	70	n.r.
5	**BAC-12**	DCE	TMS	70	n.r.
6	**BAC-12**	DCM	TMS	70	n.r.
7	**BAC-12**	Toluene	TMS	70	n.r.
8	**BAC-12**	HFIP	TMS	rt	91%
9	**BAC-9**	HFIP	TMS	rt	n.r.
10	**BAC-11**	HFIP	TMS	rt	n.r.
11	-	HFIP	TMS	rt	15%

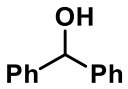
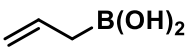
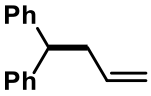
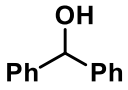
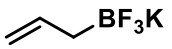
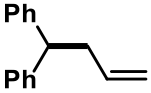
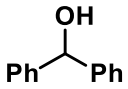
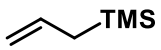
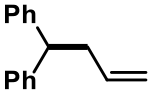
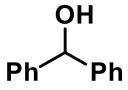
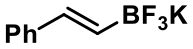
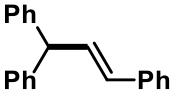
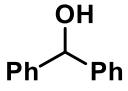
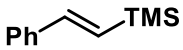
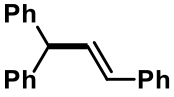
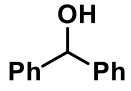
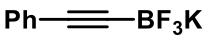
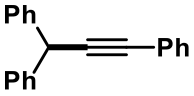
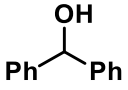
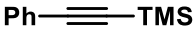
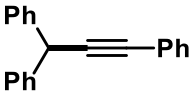
[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [c]A complex mixture of products was obtained as evidence by ^{1}H NMR spectrum of the crude material; [d]No reaction.

2.3.2 Scope of Borate and Silane Nucleophiles

With the optimized reaction conditions in hand, the scope and limitations of the methodology were investigated by exposing benzhydryl alcohol (**1a**) to various potassium trifluoroborates and organosilane nucleophiles (**Table 2-1**). In general, the nucleophilic addition of organosilane species out-performs the nucleophilic addition of organoborate species. This trend can be observed by comparing entries 1-3, 4-5, and 6-7. Entries 1-3 are the prototypical allylation reaction conditions, all of which were expected to result in the formation of product **3a**; entries 4-5 resulted in the formation of the vinylated product **3b**; and entries 6-7 resulting in the formation of the alkynyl product **3c**. The yields obtained from these reactions can be explained by the nature of each nucleophile. The boronic acid species used in entry 1 bears a neutral central boron atom, which results in a reduced nucleophilic character in comparison to that of a negatively charged tetravalent trifluoroborate species used for entry 2. For entry 3, a highly nucleophilic allyl trimethylsilane (**2c**) was used, resulting in the formation of the desired product in excellent yield.

Furthermore, the intermediate species is stabilized by the formation of a β-silyl cation, which is hypothesized to lead to higher yields.[75]

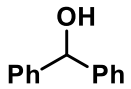
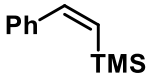
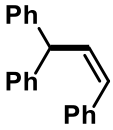
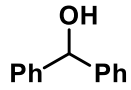
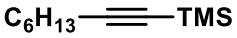
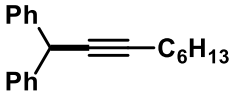
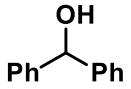
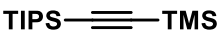
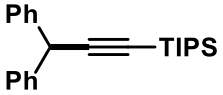
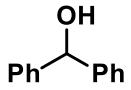
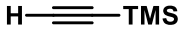
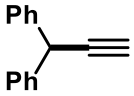
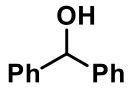
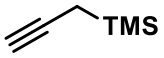
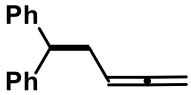
Table 2-2: A direct comparison between the BAC addition of organosilane and organoboron nucleophiles to alcohols

Entry	Alcohol (**1**)	R^3–M (**2**)	Product (**3**)[a]	Yield (**%**)[b]
1	 **1a**	 **2a**	 **3a**	0%
2	 **1a**	 **2b**	 **3a**	55%
3	 **1a**	 **2c**	 **3a**	91%
4	 **1a**	 **2d**	 **3b**	76%
5	 **1a**	 **2e**	 **3b**	78%
6	 **1a**	 **2f**	 **3c**	29%
7	 **1a**	 **2g**	 **3c**	94%

[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [c]A complex mixture of products was obtained as evidence by ^{1}H NMR spectrum of the crude material; [d]No reaction.

Displayed in **Table 2-2** is the extended scope of organosilane coupling partners. The nucleophilic addition of *cis*-2-phenyl-vinylsilane resulted in the formation of product **3d** in a stereospecific manner, with good yield (**Table 2-2, entry 1**). Further diversification was achieved by varying the substituent on alkynyl silane species. Use of trimethylsilyloctyne resulted in the formation of product **3e** in a modest yield of 56%. Use of a Triisopropylsilane substituent resulted in only a trace amount of product **3f**. The terminal alkynyl silane **2k** was an unsuccessful at generating product 3g, which would proceed through an unstable primary vinyl cation intermediate. Displaying similar reactivity to allyl trimethylsilane, the use of propargyl trimethylsilane affords allene product **3h** in good yield.

Table 2-3: Extended organosilane substrate scope

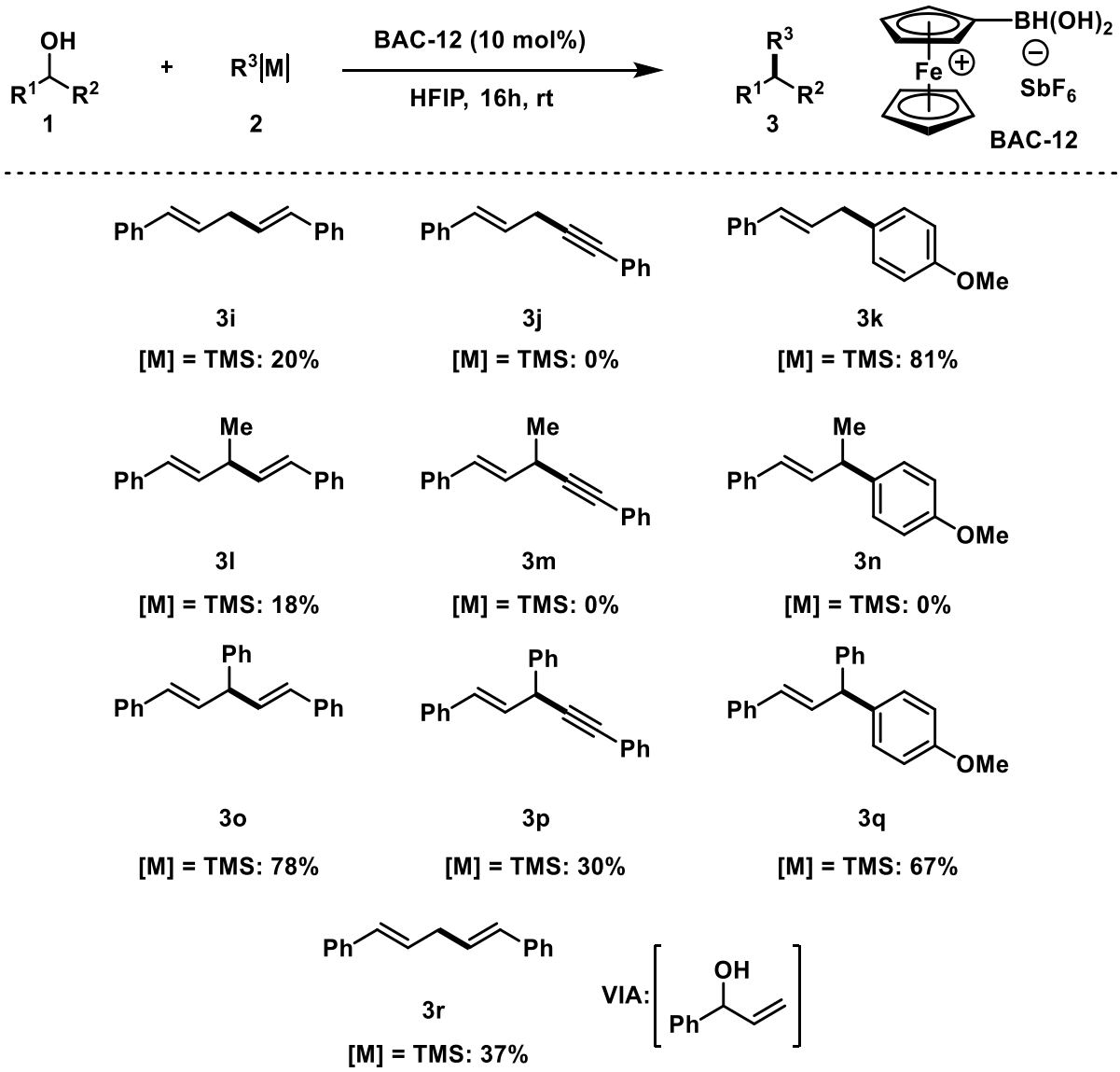
Entry	Alcohol (**1**)	R^3[M](**2**)	Product (**3**)[a]	Yield (%)[b]
1	 **1a**	 **2h**	 **3d**	70%
2	 **1a**	 **2i**	 **3e**	56%
3	 **1a**	 **2j**	 **3f**	<5%
4	 **1a**	 **2k**	 **3g**	0%[d]
5	 **1a**	 **2l**	 **3h**	80%

[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [d]No reaction.

2.3.3 Scope of Allylic, Benzylic, and Propargylic Alcohols

To further examine the scope of the alcohol substrates, a series of allylic alcohols were subjected to the optimized reaction conditions with a variety of organosilane nucleophiles (**Scheme 2-3**). To our satisfaction, cinammyl alcohol proved to be a suitable electrophile. When used with *trans*-2-phenylvinylsilane product, **3i** was obtained in low yield of 20%. Surprisingly, **3j** was not obtained when trimethylsilylphenylacetylene is used. However, **3k** is obtained in high yield of 81% when

4-trimethylsilylanisole is used. The addition of substituents to the carbocation bearing carbon atom should result in increased stability and allow for less nucleophilic organosilanes to be used as coupling partners. However, addition of a methyl substituent to this carbon atom results in a decreased yield in the analogous vinyl product **3l**, and no formation of the arylated product **3n**. Addition of a phenyl substituent to the carbocation bearing carbon atom results in increased yield of the vinyl product **3o** (78%). Inclusion of alkynyl silanes resulted in formation of product **3p**, albeit in a low yield of 30%, and a moderate yield of 67% for the analogous arylated product **3q**. While the phenyl substituent may greatly stabilize the presumed carbocation that is generated, allowing for expansion of the nucleophile scope, it also introduces a more crowded steric environment reducing the ability of bulky nucleophiles to attack. It is known that some allylic alcohols undergo a 1,3-transposition under boronic acid catalysed conditions.[62] Product **3r** was obtained in low yield, from a secondary allylic alcohol after either a 1,3-transposition or direct conjugate addition occurred.

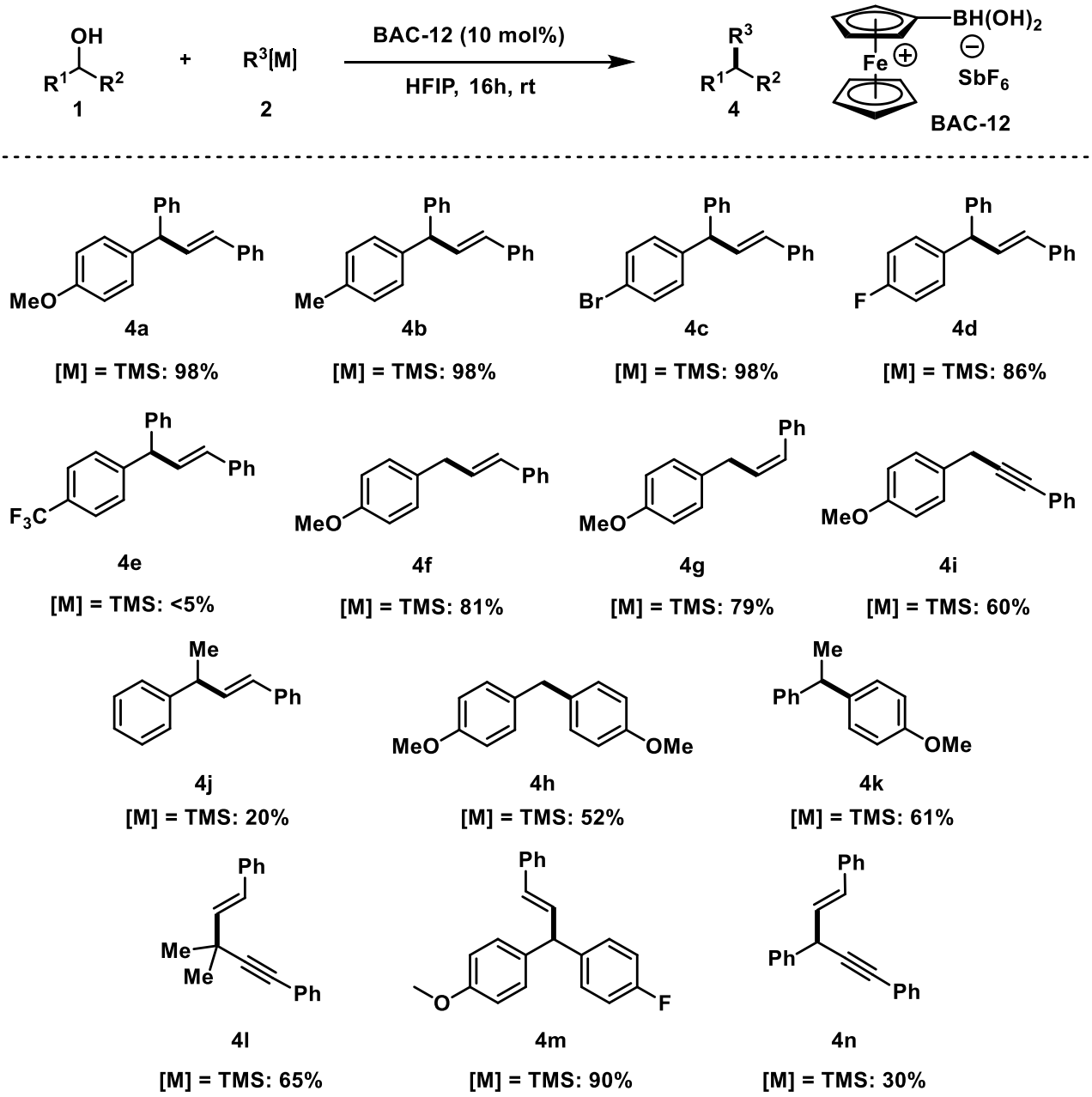


[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [d]No reaction.

Scheme 2-3: Scope of allylic alcohols with various organosilanes as nucleophiles

In order to further explore how electronics affect the generation of the presumed carbocation, several substituted benzhydryl alcohols were prepared. Unsurprisingly, activated electron-rich species afford the desired products in excellent yield (**4a-4d, Scheme 2-4**), while benzhydryl

alcohols with strong electron-withdrawing groups performed poorly, affording the product **4e** in only trace amounts. Primary benzylic alcohols are only tolerated when strongly electron-donating substituents are located at the *para*- position **4f-4i**. Similarly, electron-rich, 4-Methoxybenzyl alcohol is a suitable electrophile for arylation reactions, providing product **4h** in moderate yield. The alcohol prepared from the reduction of acetophenone is also capable of sufficiently stabilizing a carbocation intermediate, where product **4j** was obtained in low yield of 20%, and product **4k** in a moderate yield of 61%. The Meyer-Scheuster rearrangement of propargylic alcohols has been shown to be catalysed by boronic acids.[62] Nucleophilic silanes are capable of intercepting the carbocation intermediate before rearrangement occurs. Product **4l** was obtained in moderate yield of 65% when a tertiary propargylic alcohol was used, and **4n** was obtained in a low yield of 30% when a secondary propargylic alcohol was used.



[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields

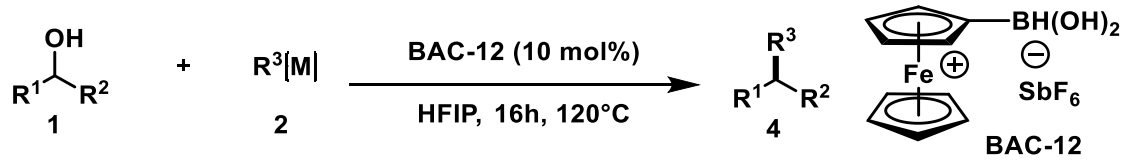
Scheme 2-4: Scope of benzylic and propargylic alcohols with a variety of organosilane nucleophiles

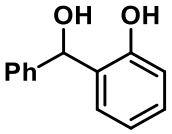
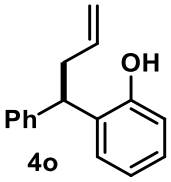
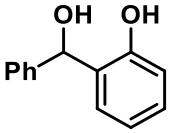
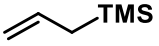
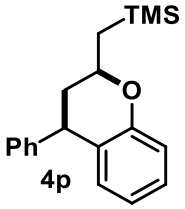
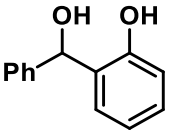
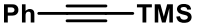
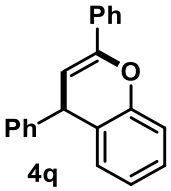
2.3.4 Boronic Acid Catalysed Generation of *ortho*-Quinone Methides

Ortho-Quinone methides (*o*-QMs) are reactive cross-conjugated species commonly found in nature. Vascular plants use quinone methides for the preparation of complex lignin polymers.[76] Furthermore, it is believed that quinone methides are the ultimate cytotoxic species responsible for the reactivity of various biologically active molecules. *o*-QMs are generated synthetically using a variety of methods including thermolysis,[77] oxidation,[78] acid promoted β-elimination,[79–81] base promoted β-elimination,[82] and addition of alkyl magnesium and alkyl lithium species.[83] Of these strategies, acid promoted β-elimination serves to be the most powerful, as a diverse scope of nucleophiles can be used. However, this strategy offers low functional group tolerance and requires the lengthy preparation of precursors. It should be stated, that while these strategies for the generation of *o*-QMs are powerful, they have a distinct reactivity difference from that discussed in this thesis and will therefore not be explored in extended detail.

Use of *ortho*-hydroxy benzhydryl alcohols under BAC conditions allows for the *in-situ* generation of *o*-QMs. Initially, allylic potassium trifluoroborate was used as a nucleophile and a single direct coupling product was obtained in low yield (**Table 2-3, entry 1**). However, when the experiment was repeated with allyl trimethylsilane as a nucleophile, a 2,4-substituted benzochroman product was obtained in high yield (**Table 2-3, entry 2**). Interestingly, the trimethylsilyl functional group is retained in the product. It is likely that the organosilane nucleophile undergoes direct addition to an *in-situ* generated *o*-QM resulting in the formation of a β-silyl cation intermediate species, which is then intercepted by the *ortho* oxygen atom. Use of phenyl alkynyl trimethylsilane also affords a 2,4-substituted dihydro benzochroman product (**Table 2-3, entry 3**). In this case de-silation occurs, which is most likely due to the the increased stability of the conjugated product.

Table 2-4: Prepared *O*-Heterocycles *via* boronic acid catalysed formation of *ortho*-quinone methides



Entry	Alcohol (**1**)	R^3-M (**2**)	Product (**4**)[a]	Yield (**%**)[b]
1			 **4o**	36%
2			 **4p**	80%
3			 **4q**	82%

[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [d]No reaction.

2.3.5 Computational Studies for the Stereospecific Coupling of Vinyl Silanes

In order to gain insight towards the stereospecific addition of vinyl silanes to the presumed *in-situ* generated carbocation, we initiated a collaboration with Professor J. Hollett at the University of Winnipeg. It has previously been proposed that addition of vinyl silanes to *in-situ* generated carbocations is due to the formation of a stabilized β-silyl cation intermediate. Rotation of the C-C single bond is then restricted, as the increased stabilization is only achieved when the

carbocation bearing carbon atom and silicon atom are coplanar.[84] The studies performed by Professor Hollett determined that this did not fully explain the retention of the C-C double bond geometry. He conducted computational studies on nucleophilic addition process employing the method B3LYP/6-31G(d,p) with the SMD solvation model for DCM. All energies are calculated relative to the initial state of the reactants (0 kJ/mol). It was found that after addition of a vinyl silane nucleophile to a diphenyl cation, desilyation in both the *cis*- and *trans*- pathways is barrierless and happens instantaneously as the zwitterionic borate catalyst approaches the intermediate species. Whereas, rotation of the C-C bond requires 40.1 kJ/mol for *cis* to *trans* isomerization (Figure 2-1) and 81.2 kJ/mol for *trans* to *cis* isomerization (Figure 2-2). Further studies are currently being carried out using ωB79x-d in order to obtain more accurate results that include dispersion correction.

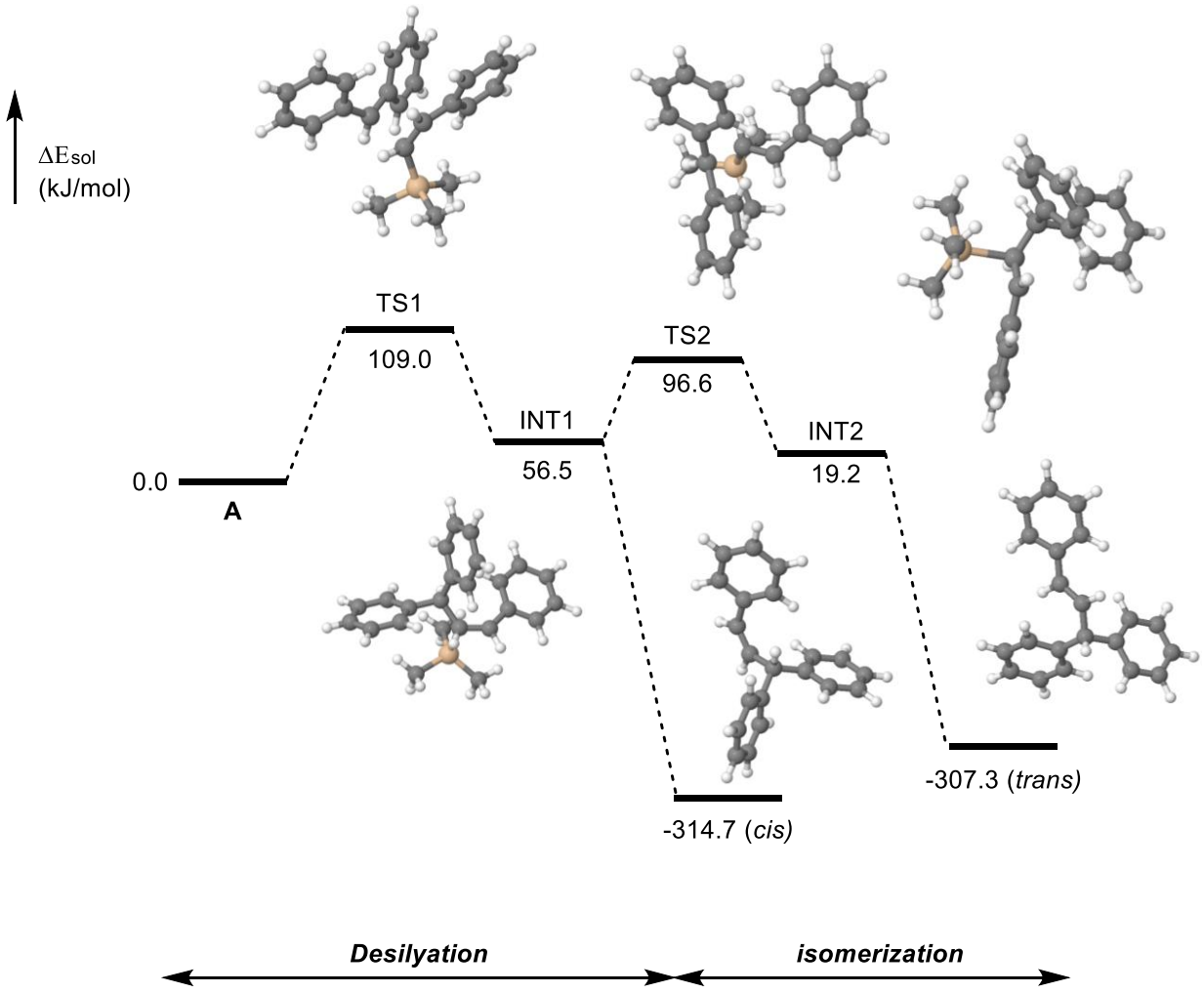


Figure 2-1: Solvated model reaction pathway for the stereospecific addition of *cis*-2-phenylvinylsilane to diphenylmethanol. Calculations completed by J. W. Hollett

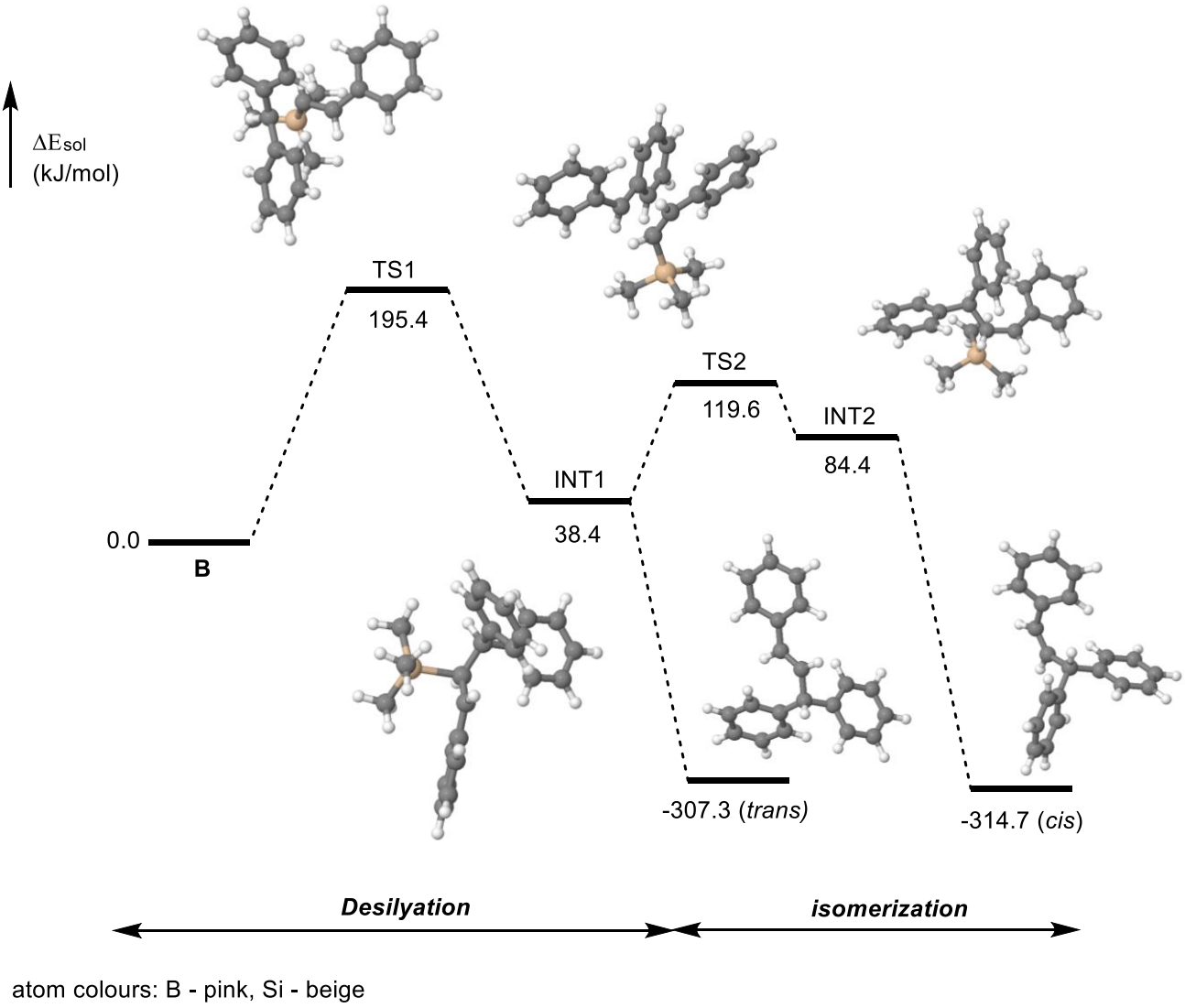
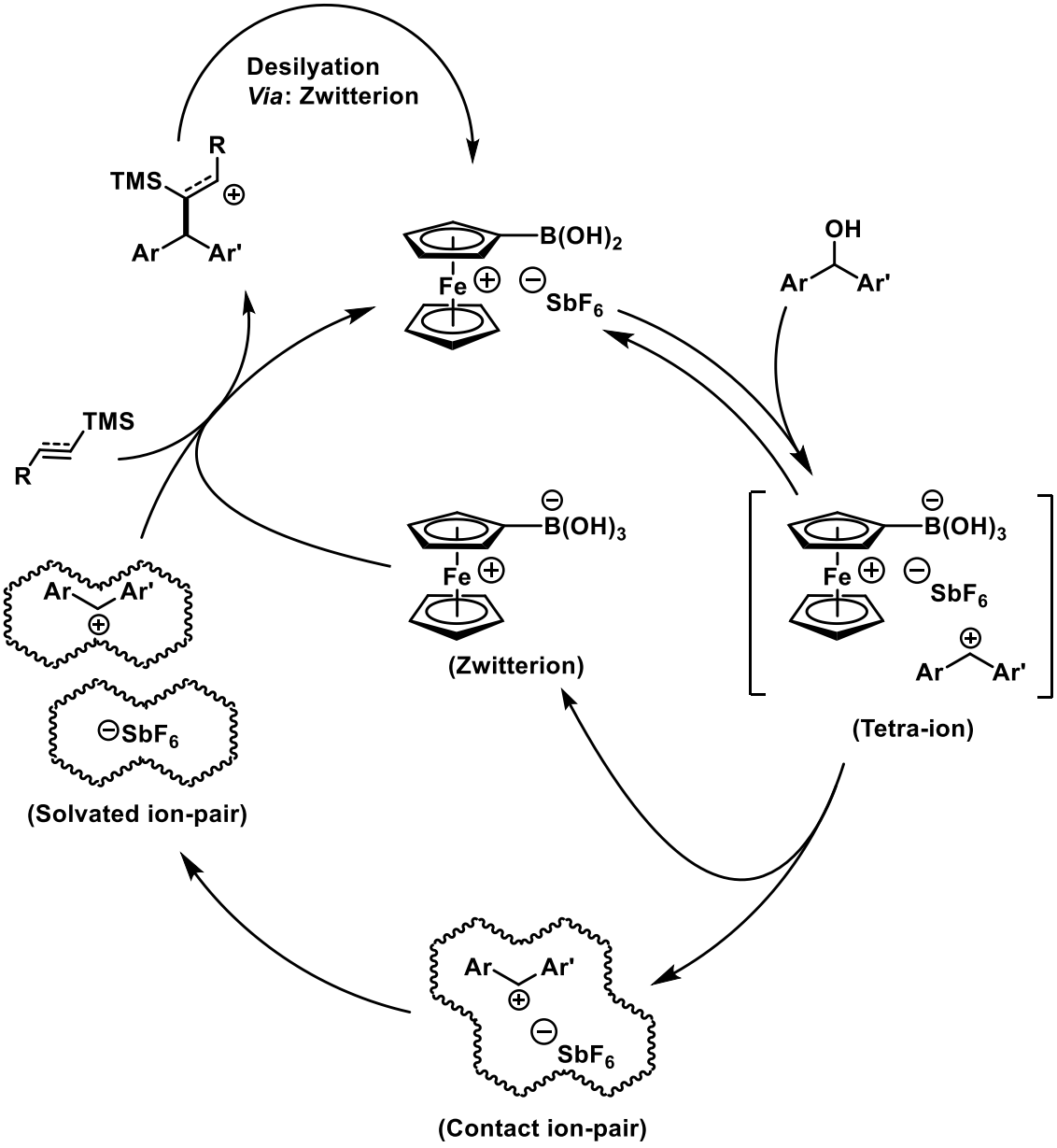


Figure 2-2: Solvated model reaction pathway for the stereospecific addition of *trans*-2-phenylvinylsilane to diphenylmethanol. Calculations completed by J. W. Hollett

2.3.6 Proposed Mechanism

Based on previous studies by McCubbin and Hall,[65,67] and the results from our computational study, the following catalytic cycle can be proposed (**Scheme 2-5**). The alcohol substrate is fully ionized by ferroceniumboronic acid hexafluoroantimonate (**BAC-12**), resulting in the formation of a tetra-ion species. This tetra-ion then undergoes decomposition to form a zwitterionic borate

and a contact ion-pair. The formation of the contact ion-pair is thought to occur due to the cationic nature of the ferroceniumboronic acid. Due to the lack of coordination between the hexafluoroanitomate anion and the carbocation, the contact ion-pair is prone to dissociate and forms a solvated ion-pair. This not only sterically exposes the generated carbocation, but the non-coordinating ability of the antimonate anion increases the energy of the carbocation. As a consequence, the carbocations electrophilicity is drastically increased and is therefore more susceptible to nucleophilic attack. When organosilane nucleophiles are used, a β-silyl cation intermediate is formed, which is then immediately desilyated *via* nucleophilic attack of the zwitterionic borate species, generating the unsaturation in the product while regenerating the active catalyst.



Scheme 2-5: A proposed catalytic cycle for the BAC coupling of alcohols with organosilane nucleophiles

2.4 Summary

This chapter reports a study that was focused on expanding the utility of ferroceniumboronic acid hexafluoroantimonate (**BAC-12**). Attention was focused on the expansion of both the nucleophile and electrophile substrate scope, allowing for the direct substitution of hydroxyl functional groups for a diverse array of unsaturated carbon-based motifs. In a direct comparison of organoboron and organosilane nucleophiles, organosilane nucleophiles allow for not only higher yields, but a significant expansion of the nucleophilic substrate scope. When *trans*- and *cis*-2-phenylvinyl silane are used the reaction proceeds in a stereospecific manner. Our computational results suggest that the stabilized β-silyl cation formation restricts rotation of the adjacent carbon-carbon bond. Furthermore, the barriers for conversion from *cis*- to *trans*- and *trans*- to *cis*- are significant in comparison to desilyation.

Future effort should be directed at the development of an asymmetric variation of this reaction. Bulky chiral boronic acid derivatives are commercially available, and their structural similarity to chiral phosphoric acids suggest that enantioinduction may be possible. Several modifications to the ferroceniumboronic acid salt scaffold can therefore be envisioned. Planar chiral ferrocene units can be prepared *via* Directed-*ortho* Metalation in enantiomerically pure form.[85]

2.5 Experimental

2.5.1 General Methods

The following includes representative experimental procedures and details for isolation of compounds. Full characterization of all novel, and partial characterisation of known compounds presented in the report are described along with associated intermediates involved in their synthesis.

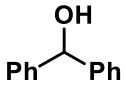
^{1}H and ^{13}C NMR were recorded using a Bruker Ultrashield^{TM} 400 Spectrometer at 400 and 100 MHz, respectively. NMR shifts are reported in δ (ppm) relative to a TMS or $CDCl_3$ internal standard. Coupling patterns are reported using the following scheme; (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet), coupling constants (*J*) in Hz, and proton integration. Thin layer chromatography (TLC) was performed on plastic backed TLC plates from EMD Millipore Corporation^{TM} (200 μm, indicator $KMNO_4$), and flash chromatography employed silica gel from SiliCycle Inc^{TM} (40-63 μm, 230-400 mesh).

Unless otherwise noted, all solvents were purchased as ACS reagents and are used without further purification. Trifluoroborates were prepared directly from commercially available boronic acids. Details for the preparation of these, as well as silane and alcohol substrates are discussed below. All other reagents were purchased from Aldrich^{TM} or Alfa Aesar^{TM} and used as received.

***General Procedure A* for the preparation of Ferroceniumboronic Acid Hexafluoroantimonate Salt:** Ferroceniumboronic acid hexafluoroantimonate was prepared according to a literature prodecure.[65] Ferrocene boronic acid (2.30g, 10.0 mmol) was dissolved in 20.0 mL of acetone. The mixture was stirred at room temperature for 15 minutes. To the mixture was added Silver hexafluoroantimonate(V) (3.40g, 10.0 mmol) resulting in an imidiate colour change to a dark blue solution. The mixture was stirred at room temperature for 30 minutes and then filtered through Celite. The resulting dark blue solution was collected and concentrated *en vacuo* overnight. The product **Ferreceniumboronic acid hexafluoroantimonate** was collected as a dark blue, crystalline solid (3.20g, 76%). ^{1}H and ^{13}C spectra were not obtained in high quality due to the paramagnetic nature of iron (III).

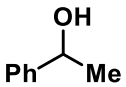
***General Procedure B* for the Preparation of Allylic and Benzylic Alcohols by $NaBH_4$ Reduction**: To a round-bottom flask containing the ketone substrate (10.0 mmol) in MeOH (50.0 mL) was added the $NaBH_4$ (15.0 mmol), slowly, in several portions. The resulting solution was allowed to stir for 3 hours at room temperature, and to it was added saturated $NH_4Cl(aq)$ solution (20.0 mL) and the solvent removed *in vacuo*. The residue was partitioned between water (50.0 mL) and EtOAc (50.0 mL). The organic fraction was washed with water (1 x 50.0 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

(1a): Diphenylmethanol[30]



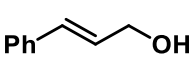
Prepared according to *General Procedure* ***B*** with Benzophenone (1.82g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**1a**) as a white crystalline solid (1.77g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (d, *J* = 6.8 Hz, 4H), 7.36 – 7.31 (t, *J* = 7.2 Hz, 4H), 7.29 – 7.24 (t, *J* = 7.3 Hz, 2H), 5.86 – 5.84 (d, *J* = 3.7 Hz, 1H), 2.18 – 2.17 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 128.5, 127.5, 126.5, 76.2.

(1b): α-Methyl-benzenemethanol[28]



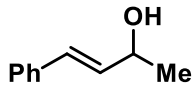
Prepared according to *General Procedure* ***B*** with Acetophenone (3.00g, 25.0 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**1b**) as a colourless oil (3.00g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.16 (m, 5H), 4.76 – 4.68 (q, *J* = 6.48 Hz, 1H), 3.26 – 3.20 (s, 1H), 1.40 – 1.34 (d, *J* = 6.60, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 128.2, 127.0, 125.2, 69.8, 24.8.

(1c): 3-Phenyl-2-propen-1-ol[34]



Prepared according to *General Procedure* ***B*** with *trans*-2-Cinnamaldehyde (1.34g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (1% EtOAc/Hex) afforded the desired product (**1c**) as a white crystalline solid (1.22g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (d, *J* = 7.2Hz, 2H), 7.32 – 7.27 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.20 (t, *J* = 7.21 Hz, 1H), 6.62 – 6.56 (d, *J* = 15.9 Hz, 1H), 6.38 – 6.30 (dt, J_1 = 5.75 Hz, J_2 = 15.9 Hz, 1H), 4.31 – 4.27 (d, *J* = 5.75 Hz, 1H), 1.96 – 1.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 131.0, 128.5, 128.5, 127.6, 126.4, 63.6.

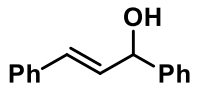
(1d): 4-Phenyl-3-buten-2-ol[33]



Prepared according to General Procedure ***B*** with *trans*-4-Phenyl-3-buten-2-one (1.46g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**1d**) as a colourless oil (1.38g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (d, *J* = 8.78 Hz, 2H), 7.38 – 7.32 (t, *J* = 7.78 Hz, 2H), 7.31 – 7.25 (t, *J* = 7.03 Hz, 1H), 6.62 – 6.56 (d, *J* = 16.06 Hz, 1H), 6.33 – 6.26 (dd, *J* = 15.81 Hz, 1H), 4.55 – 4.47 (m, 1H), 2.50 – 2.40 (s, 1H), 1.42 – 1.39 (d, *J* = 6.53 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 133.5, 129.1, 128.44, 127.47, 126.3, 68.6, 23.3.

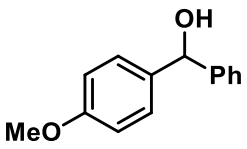
***General Procedure C* for the Preparation of Benzylic Alcohols by Addition of Phenyl Lithium:** To an oven-dried flask, cooled to room temperature under Ar, was added bromobenzene (10.0 mmol) and freshly dried and degassed THF (20.0 mL). The resulting solution was cooled to -78°C and to it was added a solution of *n*-BuLi (12.0 mmol, 7.50 mL, 1.60M in hexanes) dropwise *via* syringe. The mixture was allowed to stir for 30 minutes -78°C, then to it was added the electrophile (Substituted benzaldehyde, 15.0 mmol). The bath was removed, and the mixture allowed to warm to room temperature. The reaction was quenched by the addition of saturated NH_4Cl(*aq*) solution (20.0 mL), diluted with EtOAc (30.0 mL), and washed with water (2 x 30.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

(1e): α-(2-Phenylethenyl)-benzenemethanol[33]



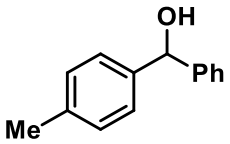
Prepared according to General Procedure ***C*** with cinnamaldehyde (2.10g, 10.0 mmol) and bromobenzene (1.59g, 12.0 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**1e**) as a colourless oil (1.99g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (d, *J* = 6.96 Hz, 2H), 7.31 – 7.26 (t, *J* = 6.96 Hz, 4H), 7.26 – 7.21 (t, *J* = 6.96 Hz, 3H), 7.19 – 7.15 (t, *J* = 7.09 Hz, 1H), 6.60 – 6.54 (d, *J* = 15.65 Hz, 1H), 6.32 – 6.26 (dd, *J* = 15.9 Hz, 1H), 5.26 – 5.23 (d, *J* = 6.48 Hz, 1H), 2.83 – 2.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 136.4, 131.5, 130.3, 128.4, 127.5, 126.4, 126.2, 74.8.

(1f): (4-Methoxyphenyl)(phenyl)methanol[30]



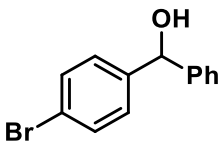
Prepared according to General Procedure ***C*** with 4-methoxybenzadlehyde (1.35g, 10.0 mmol) and bromobenzene (1.55g, 1.05 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**1f**) as a white crystalline solid (1.97g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 7H), 6.89 – 6.82 (d, *J* = 8.80 Hz, 2H), 5.80 – 5.77 (s, 1H), 3.78 – 3.75 (s, 3H), 2.26 – 2.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 144.0, 136.1, 128.3, 127.8, 127.3, 126.3, 113.8, 75.7, 55.2.

(1g): (4-Methylphenyl)(phenyl)methanol[30]



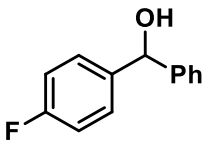
Prepared according to General Procedure ***C*** with 4-methylbenzaldehyde (1.20g, 10.0 mmol) and bromobenzene (1.55g, 1.05 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**1g**) as a colourless crystalline solid (1.80g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H), 7.25 – 7.20 (m ,3H), 7.14 – 7.10 (d, *J* = 7.83 Hz, 2H), 5.76 – 5.74 (s, 1H), 2.32 – 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 140.9, 137.8, 129.1, 128.3, 127.3, 126.4, 126.4, 76.0, 21.0.

(1h): (4-Bromophenyl)(phenyl)methanol[86]



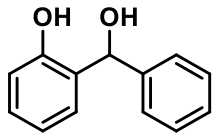
Prepared according to General Procedure ***C*** with 4-bromobenzaldehyde (1.85g, 10.0 mmol) and bromobenzene (1.55g, 1.05 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**1h**) as a white crystalline solid (2.39g, 91%). NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (d, *J* = 8.56 Hz, 2H), 7.35 – 7.32 (d, *J* = 4.40 Hz, 4H), 7.30 – 7.23 (m, 3H), 5.80 – 5.78 (s, 1H), 2.25 – 2.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 142.7, 131.5, 128.6, 128.2, 127.8, 126.5, 121.4, 75.6.

(1i): (4-Fluorophenyl)(phenyl)methanol[87]



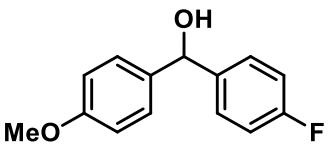
Prepared according to General Procedure ***C*** with 4-fluorobenzaldehyde (1.24 g, 10.0 mmol) and bromobenzene (1.55g, 1.05 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**1i**) as a colourless oil (1.84g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 7H), 6.98 – 6.92 (t, *J* = 8.80 Hz, 2H), 5.69 – 5.66 (s, 1H), 2.75 – 2.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 160.8, 143.5, 139.4, 128.4, 128.2, 128.1, 127.6, 126. 4, 115.2, 115.0, 75.4.

(1j): 2-(Hydroxy(phenyl)methyl)phenol[88]



Prepared according to General Procedure ***C*** with 2-hydroxybenzaldehyde (1.22 g, 1.06 mL, 10.0 mmol) and bromobenzene (3.14 g, 2.10 mL, 20.0 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**1j**) as a colourless crystalline solid (1.04 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.83 (s, 1H), 7.40 – 7.28 (m, 5H), 7.21 – 7.28 (m, 5H), 7.21 – 7.15 (t, *J* = 7.03 Hz, 1H), 6.91 – 6.78 (m, 3H), 6.01 – 5.97 (s, 1H), 2.95 – 2.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 141.8, 129.2, 128.7, 128.24, 128.22, 126.8, 126.5, 119.9, 117.2, 77.0.

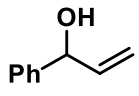
(1k): (4-Fluorophenyl)(4-Methoxyphenyl)methanol[89]



Prepared according to General Procedure ***C*** with 4-fluorobenzaldehyde (1.24g, 10.0 mmol) and 4-methoxybromobenzene (1.87g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**1k**) as a colourless oil (2.11g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (dd, *J* = 8.43 Hz, 2H), 7.23 – 7.19 (d, *J* = 8.43 Hz, 2H), 7.01 – 6.95 (t, *J* = 8.80 Hz, 2H), 6.86 – 6.82 (d, *J* = 8.68 Hz, 2H), 5.72 – 5.70 (s, 1H), 3.77 – 3.74 (s, 3H), 2.51 – 2.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 160.7, 159.0, 139.7, 135.9, 128.0, 127.9, 127.2, 115.2, 114.9, 113.8, 75.0, 55.1.

***General Procedure D* for the Preparation of Allylic Alcohols by Addition of Vinylmagnesium bromide:** To an oven-dried flask, cooled to room temperature under Ar, was added the vinylmagnesium bromide (12.0 mmol, 12.0 mL) and freshly dried and degassed THF (20.0 mL). The solution was cooled to 0°C in an ice water bath and to it was added bezaldehyde (10.0 mmol, 1.01 mL). The mixture was warmed to room temperature and allowed to stir for one hour. The reaction was quenched by the addition of saturated NH_4Cl(*aq*) solution (20.0 mL), diluted with EtOAc (30.0 mL), and washed with water (2 x 30.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

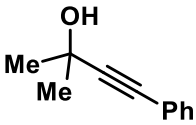
(1l): α-Ethenylbenzenemethanol[90]



Prepared according to General Procedure ***D*** with benzaldehyde (1.06g, 1.01 mL, 10.0 mmol) and vinylmagnesium bromide (1.00 M, 12.0 mL, 12.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**1l**) as a colourless oil (1.27g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 6.05 – 5.95 (m, 1H), 5.33 – 5.26 (m, *J* = 17.12 Hz, 1H), 5.18 – 5.11 (m, 2H), 2.44 – 2.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.1, 128.4, 127.6, 126.2, 114.9, 75.1.

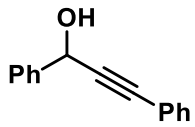
***General Procedure E* for the Preparation of Alkynyl Substrates**: To an oven-dried flask, cooled to room temperature under Ar, was added the alkyne (10.0 mmol) and freshly dried and degassed THF (20.0 mL). The resulting solution was cooled to -78°C in a dry-ice/acetone bath and to it was added a solution of BuLi (12.0 mmol, 7.50 mL, 1.60M in hexanes) dropwise *via* syringe. The mixture was allowed to stir for 30 minutes at -78°C, then to it was added the electrophile (acetophenone, benzaldehyde, TMS-Cl, or TIPS-Cl, 15.0 mmol). The bath was removed, and the mixture allowed to warm to room temperature. The reaction was quenched by the addition of saturated $NH_4Cl(aq)$ solution (20.0 mL), diluted with EtOAc (30.0 mL), and washed with water (2 x 30.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

(1m): 1,1-Dimethyl-3-phenyl-2-propyn-1-ol[33]



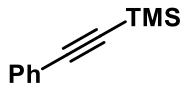
Prepared according to General Procedure ***E*** with acetone (1.64g, 2.10 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**1m**) as a white crystalline solid (1.49 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H), 7.32 – 7.28 (m, 3H), 1.63 – 1.61 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 128.1, 128.0, 122.7, 93.9, 81.9, 65.4, 31.3.

(1n): 1,3-Diphenylpropargyl alcohol[34]



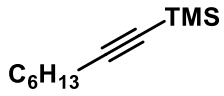
Prepared according to General Procedure ***E*** with benzaldehyde (1.06 g, 1.01 mL, 10.0 mmol) and phenylacetylene (1.02 g, 1.05 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**1n**) as a colourless oil (1.94 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.57 (d, *J* = 7.09, 2H), 7.47 – 7.43 (m, 2H), 7.40 – 7.35 (t, *J* = 6.96 Hz, 2H), 7.34 – 7.25 (m, 4H), 5.67 – 5.64 (d, *J* = 5.99 Hz, 1H), 2.63 – 2.60 (d, *J* = 6.11 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 131.6, 128.57, 128.51, 128.3, 128.2, 126.6, 122.3, 88.7, 86.5, 64.9.

(2g): Trimethylsilylphenylacetylene[28]



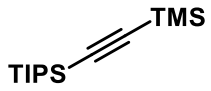
Prepared according to *General Procedure* ***E*** with phenylacetylene (1.02 g, 10.0 mmol) and trimethylsilyl chloride (1.08g, 1.27 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**2g**) as a colourless oil (0.892 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.32 – 7.26 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9, 128.4, 128.1, 123.2, 105.1, 94.1, -0.04.

(2i): 1-Octynyltrimethylsilane[91]



Prepared according to *General Procedure **E*** with 1-octyne (1.02g, 10.0 mmol) and trimethylsilyl chloride (1.08g, 1.27 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**2i**) as a colourless oil (0.892 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 – 2.21 (t, *J* = 7.09 Hz, 2H), 1.58 – 1.47 (m, *J* = 7.58 Hz, 2H), 1.45 – 1.25 (m, 6H), 0.94 – 0.89 (t, *J* = 6.72 Hz, 3H), 0.18 – 0.16 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) due to COVID-19 no spectra was collected.

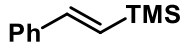
(2j): (Trimethylsilyl)(triisopropylsilyl)acetylene[91]



Prepared according to *General Procedure **E*** with trimethylsilylacetylene (1.02g, 10.0 mmol) and triisopropyl chloride (1.93g, 2.13 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**2j**) as a colourless oil (0.892 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 – 1.09 (d, *J* = 4.01 Hz, 21H), 0.21 – 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) due to COVID-19 no spectra was collected.

***General Procedure F* for the preparation of *Trans*-2-phenylvinyl-trimethylsilane:** To an oven-dried flask charged with a stirbar was added the trimethylsilylphenylacetylene (**2g**) (1.74g, 10.0 mmol) and dry ether (30.0 mL). To the mixture was added DIBAL-H (46.0 mL, 46.0 mmol, 1.00 M, 1.40 mol equiv.) over 10 minutes. The reaction mixture was stirred for 21 hours at room-temperature and carefully quenched with ice-cold 10% *aq* H_2SO_4 (250 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 x 50.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated in *vacuo.* The residue was purified by flash chromatography to afford the product.

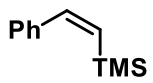
(2e): *Trans*-2-phenylvinyl-trimethylsilane[92]



Prepared according to General Procedure ***F*** with trimethylsilylphenylacetylene (1.74g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**2e**) as a colourless oil (1.65 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (d, *J* = 7.09 Hz, 2H), 7.27 – 7.22 (t, *J* = 7.70 Hz, 2H), 7.19 – 7.14 (t, *J* = 7.21 Hz, 1H), 6.85 – 6.79 (d, *J* = 19.19, 1H), 6.45 – 6.39 (d, *J* = 19.19, 1H), 0.12 – 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 138.3, 129.4, 128.4, 127.9, 126.3, -1.2.

***General Procedure G* for the preparation of *Cis*-2-phenylvinyl-trimethylsilane:** To an oven-dried flask charged with a stirbar was added the trimethylsilylphenylacetylene (**2g**) (1.74g, 10.0 mmol) and dry henxanes (5.00 mL). To the mixture was added DIBAL-H (26.5 mL, 26.5 mmol, 1.00M, 1.15 mol equiv.) over 5 minutes. The reaction mixture was stirred for 21 hours at room-temperature and carefully quenched with ice-cold 5% *aq* H_2SO_4 (250 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 x 50.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated in *vacuo.* The residue was purified by flash chromatography to afford the product.

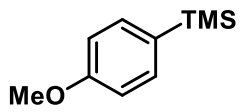
(2h): *Cis*-2-phenylvinyl-trimethylsilane[92]



Prepared according to General Procedure ***G*** with trimethylsilylphenylacetylene (1.74g, 10 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**2h**) as a colourless oil (1.61 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (d, J = 15.04 Hz, 1H), 7.42 – 7.31 (m, 5H), 5.95 – 5.91 (d, J = 15.15 Hz, 1H), 0.17 – 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 140.1, 132.8, 128.1, 127.8, 127.2, 0.1.

***General Procedure H* for the Preparation of Aryltrimethylsilanes:** To an oven-dried flask, cooled to room temperature under Ar, was added the substituted bromobenzene (10.0 mmol, 1.26 mL) and freshly dried and degassed THF (20 mL). In a dry-ice/acetone bath and to it was added a solution of n-BuLi (12.0 mmol, 7.50 mL, 1.60M in hexanes) dropwise *via* syringe. The mixture was allowed to stir for 30 minutes at -78°C, then to it was added the TMS-Cl (12.0 mmol, 1.52 mL). The bath was removed, and the mixture allowed to warm to room temperature. The reaction was quenched by the addition of saturated $NH_4Cl(aq)$ solution (20.0 mL), diluted with EtOAc (30.0 mL), and washed with water (2 x 30.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography to afford the product.

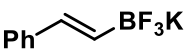
(2m): 4-trimethylsilylanisole[93]



Prepared according to General Procedure ***H*** with 4-methoxybromobenzene (1.87g, 10.0 mmol) and trimethylsilyl chloride (1.30g, 1.52 ml, 12.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**2m**) as a white crystalline solid (1.71g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.42 (d, *J* = 8.86 Hz, 2H), 6.92 – 6.89 (d, *J* = 8.68 Hz, 2H), 3.80 – 3.79 (s, 3H), 0.25 – 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 134.6, 132.2, 131.3, 115.7, 113.5, 54.9, -0.9.

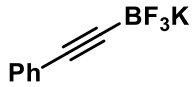
***General Procedure I* for the Preparation of Trifluoroborates:** To a 20 mL reaction vial was added the boronic acid substrate (10.0 mmol) and 2.00 mL of methanol. The resulting solution was allowed to stir for 5 minutes, then to it was added an aqueous solution of KHF_2 (6.00 mmol, 9.00 mL, 4.50M). The reaction mixture was allowed to stir for 30 minutes. The mixture was filtered by suction, washed with ethyl acetate (2 x 30.0 mL) and allowed to dry overnight to afford the desired product.

(2d): *Trans*-2-phenylvinyl potassium trifluoroborate[30]



Prepared according to *General Procedure* ***I*** with Phenyl-vinylboronic acid (1.48g, 10.0 mmol) to afford the desired product (**2d**) as a white crystalline solid (1.036 g, 70%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.24 – 7.21 (d, *J* = 7.2 Hz, 2H), 7.13 – 7.08 (t, *J* = 7.6 Hz, 2H), 6.99 – 6.94 (t, *J* = 7.3 Hz, 1H), 6.56 – 6.50 (d, *J* = 18.2 Hz, 1H), 6.26 – 6.18 (m, 1H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 146.6, 144.1, 129.6, 120.6, 119.6.

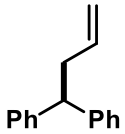
(2f): Phenylacetylene potassium trifluoroborate[30]



Prepared according to General Procedure ***I*** with Phenyl-acetyleneboronic acid (1.46g, 10.0 mmol) to afford the desired product (**2f**) as a white crystalline solid (1.18g, 81%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.20 – 7.16 (m, 2H), 7.12 – 7.05 (m, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 132.6, 129.5, 128.3, 126.8, 91.3.

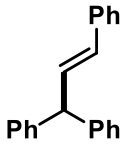
***General Procedure J* for the Coupling of Trifluoroborates with Activated Alcohols:** To a 10.0 mL vial, equipped with a stir bar, was added the trifluoroborate substrate (0.5 mmol), alcohol substrate (0.5 mmol) and 3.00 mL of hexafluoroisopropyl alcohol (HFIPA). The solution was allowed to stir at room temperature for 5 minutes. To the resulting solution feroceniumboronic acid (0.05 mmol, 0.023 g), the reaction mixture was allowed to stir overnight at room temperature. The mixture was transferred to a separatory funnel. With water (20.0 mL) and ethyl acetate (20.0 mL), the organic layer was collected, and dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by flash chromatography (EtOAc/Hexanes).

(3a): 4,4-Diphenyl-but-1-ene[28]



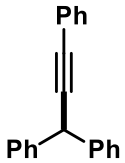
Prepared according to General Procedure ***J*** with diphenylmethanol (0.184g, 0.5 mmol) and potassium allyltrifluoroborate (0.073g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**3a**) as a colourless oil (0.057g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 10H), 5.78 – 5.64 (m, 1H), 5.07 – 4.92 (dd, *J* = 15.7 Hz, 1H), 4.02 – 3.96 (dd, *J* = 15.7 Hz, 1H), 2.84 – 2.78 (t, *J* = 7.0, 2H); *^{13}C* NMR (100 MHz, $CDCl_3$) δ 144.5, 136.8, 128.4, 127.9, 126.1, 116.2, 51.2, 39.9.

(3b): 1,3,3-Triphenylpropene[33]



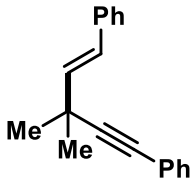
Prepared according to General Procedure ***J*** with diphenylmethanol (0.184g, 0.5 mmol) and *trans*-2-phenylvinyl potassium trifluoroborate (0.126g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**3b**) as a white crystalline solid (0.102g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (d, *J* = 7.09 Hz, 2H), 7.31 – 7.14 (m, 13H), 6.69 – 6.62 (dd, *J* = 15.89 Hz, 1H), 6.37 – 6.30 (d, *J* = 15.77 Hz, 1H), 4.89 – 4.85 (d, *J* = 7.45 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.2, 132.5, 131.4, 128.6, 128.4, 128.4, 127.2, 126.4, 126.2, 54.1.

(3c): 1,3,3-Triphenyl-propyne[30]



Prepared according to General Procedure ***J*** with diphenylmethanol (0.184g, 0.5 mmol) and phenylacetylene potassium trifluoroborate (0.124g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**3c**) as an orange crystalline solid (0.053g, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.41 (m, 6H), 7.33 – 7.25 (m, 7H), 7.24 – 7.18 (m, 2H), 5.21 – 5.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 131.7, 128.6, 128.2, 127.94, 127.89, 126.9, 123.5, 90.2, 84.9, 43.7.

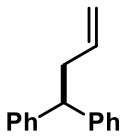
(4t): 1,5-Diphenyl-3,3-dimethyl-pent-1-en-4-yne



Prepared according to General Procedure ***J*** with 4-dimethyl-4-phenyl-3-butyn-2-ol (0.160g, 0.5 mmol) and *trans*-2-phenylvinyl potassium trifluoroborate (0.174g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**4t**) as a yellow oil (0.104g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 7H), 7.24 – 7.16 (m, 3H), 6.77 – 6.72 (d, *J* = 15.7 Hz, 1H), 6.26 – 6.20 (d, *J* = 15.9 Hz, 1H), 1.50 – 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 136.4, 131.6, 128.5, 128.2, 127.7, 127.3, 127.2, 126.4, 123.8, 95.0, 82.4, 34.3, 30.0.

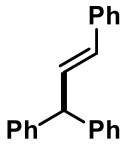
***General Procedure K* for the Coupling of Organosilanes with Activated Alcohols:** To a 10.0 mL vial, equipped with a stir bar, was added the organosilane substrate (0.6 mmol), alcohol substrate (0.5 mmol), and 2.00 mL of hexafluoroisopropyl alcohol (HFIP). The solution was allowed to stir at room temperature for 5 minutes. To the resulting solution ferroceniumboronic acid (0.05 mmol, 0.023g), the reaction mixture was allowed to stir overnight at room temperature. The mixture was was filtered over a silica plug. With ethyl acetate (4 x 10.0 mL) the filtrate was collected, and concetraed in *vacuo.* The residue was purified by flash chromatography (EtOAc/Hexanes).

(3a): 4,4-Diphenyl-but-1-ene[28]



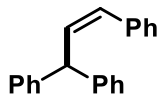
Prepared according to General Procedure ***K*** with diphenylmethanol (0.184g, 0.5 mmol) and allylic trimethylsilane (0.068g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**3a**) as a colourless oil (0.094g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 10H), 5.78 – 5.64 (m, 1H), 5.07 – 4.92 (dd, *J* = 15.7 Hz, 1H), 4.02 – 3.96 (dd, *J* = 15.7 Hz, 1H), 2.84 – 2.78 (t, *J* = 7.0, 2H); *^{13}C* NMR (100 MHz, $CDCl_3$) δ 144.5, 136.8, 128.4, 127.9, 126.1, 116.2, 51.2, 39.9.

(3b): 1,3,3-Triphenylpropene[33]



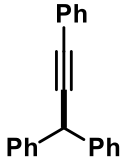
Prepared according to General Procedure ***K*** with diphenylmethanol (0.184g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**3b**) as a white crystalline solid (0.102g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (d, *J* = 7.1 Hz, 5H), 7.62 – 7.44 (m, 10H), 6.72 – 6.62 (dd, *J* = 15.7 Hz, 1H), 6.38 – 6.32 (d, *J* = 15.7 Hz, 1H), 4.91 – 4.86 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.6, 132.5, 131.4, 128.6, 128.4, 128.3, 127.3, 126.3, 126.2, 54.2.

(3d): 1,3,3-Triphenylpropene[33]



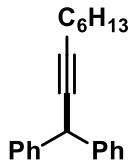
Prepared according to General Procedure ***K*** with diphenylmethanol (0.09 g, 0.5 mmol) and *cis*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**3d**) as a colourless oil (0.094 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.53 (m, 15H), 6.66 – 6.63 (d, *J* = 11.37 Hz, 1H), 6.14 – 6.06 (t, *J* = 10.51 Hz, 1H), 5.22 – 5.18 (d, *J* 10.51 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ was not collected due to COVID-19.

(3c): 1,3,3-Triphenylpropyne[30]



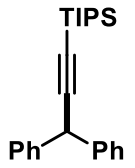
Prepared according to General Procedure ***K*** with diphenylmethanol (0.184g, 0.5 mmol) and trimethylsilylphenylacetylene (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**3c**) as an orange crystalline solid (0.126 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.41 (m, 6H), 7.33 – 7.25 (m, 7H), 7.24 – 7.18 (m, 2H), 5.21 – 5.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 131.7, 128.6, 128.2, 127.94, 127.89, 126.9, 123.5, 90.2, 84.9, 43.7.

(3e): 1,1-Diphenyloctyne[30]



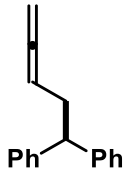
Prepared according to General Procedure ***K*** with diphenylmethanol (0.184g, 0.5 mmol) and 1-octynyltrimethylsilane (0.109g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**3e**) as an orange oil (0.077g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (d, *J* = 7.7 Hz, 4H), 7.29 – 7.24 (t, *J* = 7.7 Hz, 4H), 7.21 – 7.15 (t, *J* = 7.21 Hz, 2H), 4.97 – 4.95 (s, 1H), 2.49 – 2.40 (t, *J* = 6.96 Hz, 2H), 1.59 – 1.51 (m, *J* = 7.21 Hz, 2H), 1.46 – 1.37 (m, 2H), 1.33 – 1.24 (m, 4H), 0.91 – 0.86 (t, *J* = 6.96 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 128.4, 127.8, 126.6, 85.2, 80.6, 43.3, 31.3, 28.9, 28.6, 22.5, 18.9, 14.0.

(3f): 1,1-Diphenyl-3-triisopropylsilane[94]



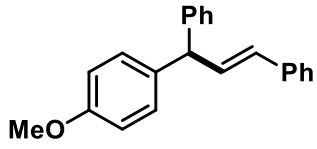
Prepared according to General Procedure ***K*** with diphenylmethanol (0.184g, 0.5 mmol) and (trimethylsilyl)(triisopropylsilyl)acetylene (0.152g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**3f**) as a colourless oil (0.008g, <5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.17 (m, 10H), 1.10 – 1.07 (s, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 138.8, 128.6, 128.5, 128.4, 127.8, 127.5, 126.7, 108.4, 85.5, 85.4, 44.3, 18.6, 11.3.

(3h): 1,1'-(3,4-Pentadienylidene)bis-benzene[28]



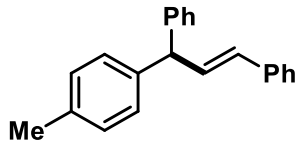
Prepared according to General Procedure ***K*** with diphenylmethanol (0.184g, 0.5 mmol) and propargyl trimethylsilane (0.056g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**3h**) as a colourless oil (0.088g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 10H), 5.72 -5.65 (q, *J* = 14.18, 1H), 4.84 – 4.79 (d, *J* = 7.70, 1H), 4.78 – 4.74 (q, *J* = 6.48, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 143.4, 128.3, 126.4, 93.9, 76.3, 50.7.

(4a): 1-[(2E)-1,3-Diphenyl-2-propen-1-yl]-4-methoxybenzene[30]



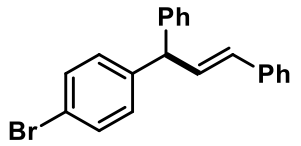
Prepared according to General Procedure ***K*** with (4-methoxyphenyl)(phenyl)methanol (0.107g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4a**) as a colourless oil (0.147g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (d, *J* = 7.28 Hz, 2H), 7.29 – 7.14 (m , 8H), 7.13 – 7.10 (d, *J* = 8.78 Hz, 2H), 6.48 – 6.79 (d, *J* = 8.87, 2H), 6.67 – 6.59 (dd, *J* = 15.81, 1H), 6.33 – 6.27 (d, *J* = 15.81 Hz, 1H), 4.83 – 4.79 (d, *J* = 7.27 Hz, 1H), 3.71 – 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 143.7, 137.2, 135.5, 132.8, 131.1, 129.5, 128.5, 128.4, 127.1, 126.28, 126.22, 113.8, 55.7, 53.2.

(4b): 1-[(2E)-1,3-Diphenyl-2-propen-1-yl]-4-methylbenzene[95]



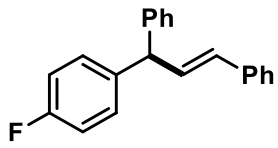
Prepared according to General Procedure ***K*** with (4-methylphenyl)(phenyl)methanol (0.099g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4b**) as a colourless oil (0.139g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.46 (d, *J* = 7.37 Hz, 2H), 7.45 – 7.28 (m, 8H), 7.27 – 7.21 (m, 4H), 6.82 – 6.75 (dd, *J* = 15.77 Hz, 1H), 6.49 – 6.46 (d, *J* = 15.89 ,1H), 4.99 – 4.96 (d, *J* = 7.58, 1H), 2.45 – 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.5, 137.3, 135.9, 132.7, 131.2, 129.5, 128.59, 128.50, 128.45, 128.41, 127.2, 126.3, 126.2, 53.7, 20.9.

(4c): 1-[(2E)-1,3-Diphenyl-2-propen-1-yl]-4-bromobenzene[95]



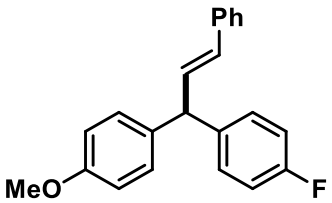
Prepared according to General Procedure ***K*** with (4-bromophenyl)(phenyl)methanol (0.131g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4c**) as a colourless solid (0.171g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (d, *J* = 8.44 Hz, 2H), 7.35 – 7.15 (m, 10H), 7.09 – 7.05 (d, *J* = 8.13 Hz, 2H), 6.62 – 6.55 (dd, *J* = 15.77 Hz, 1H), 6.34 – 6.28 (d, *J* = 15.77 Hz, 1H), 4.83 – 4.79 (d, *J* = 7.46 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 142.5, 136.9, 131.8, 131.5, 130.3, 128.56, 128.52, 128.50, 127.5, 126.6, 126.2, 120.3, 53.5.

(4d): 1-[(2E)-1,3-Diphenyl-2-propen-1-yl]-4-fluorobenzene[95]



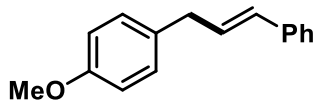
Prepared according to General Procedure ***K*** with (4-fluorophenyl)(phenyl)methanol (0.104g, 0.6 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4d**) as a colourless oil (0.123g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (t, *J* = 7.21 Hz, 2H), 7.32 – 7.26 (t, *J* = 7.70, 4H(, 7.25 – 7.16 (m, 6H), 7.01 – 6.96 (t, *J* = 8.80 Hz, 2H), 6.68 – 6.59 (dd, *J* = 15.89, 1H), 6.35 – 6.29 (d, *J* = 15.04 Hz, 1H), 4.89 – 4.85 (d, *J* = 7.46 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 160.3, 143.3, 139.1, 137.1, 132.3, 131.5, 130.1, 130.0, 128.5, 127.4, 126.5, 126.3, 115.3, 115.1, 53.3.

(4m): (4-Fluorophenyl)(4-methoxyphenyl)methanol



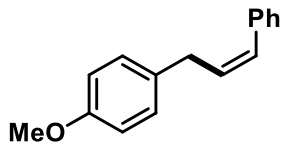
Prepared according to General Procedure ***K*** with (4-Fluorophenyl)(4-Methoxyphenyl)methanol (0.116g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4m**) as a colourless oil (0.143g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (d, *J* = 7.58 Hz, 2H), 7.30 – 7.25 (t, *J* = 7.33 Hz, 2H), 7.22 – 7.14 (m, 3H), 7.13 – 7.10 (d, *J* = 8.80 Hz, 2H), 7.00 – 6.95 (t, *J* = 8.68 Hz, 2H), 6.87 – 6.83 (d, *J* = 8.68 Hz, 2H), 6.64 – 6.56 (dd, *J* = 15.89 Hz, 1H), 6.32 – 6.26 (d, *J* = 15.89 Hz, 1H), 4.83 – 4.79 (d, *J* = 7.34 Hz, 1H), 3.78 – 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.2, 158.2, 139.4, 137.1, 135.3, 132.6, 131.3, 130.0, 129.9, 129.5, 128.5, 127.3, 126.2, 115.2, 115.0, 113.9, 55.2, 52.5.

(4f): (E)-3-(4-Methoxyphenyl)-1-phenylpropene[34]



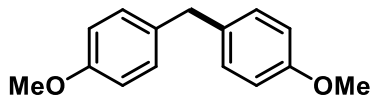
Prepared according to General Procedure ***K*** with 4-methoxybenzyl alcohol (0.069g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4f**) as a colourless oil (0.091g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (d, *J* = 7.21 Hz, 2H), 7.30 – 7.13 (m, 5H), 6.87 – 6.83 (d, *J* = 8.68 Hz, 2H), 6.51 – 6.44 (d, *J* = 15.89 Hz , 1H), 6.42 – 6.34 (dt, *J* = 15.77 Hz, 1H), 3.79 – 3.77 (s, 3H), 3.49 – 3.46 (d, *J* = 6.60 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 137.5, 132.2, 130.7, 129.7, 129.6, 128.5, 127.0, 126.1, 113.9, 55.2, 38.4.

(4g): (Z)-3-(4-Methoxyphenyl)-1-phenylpropene



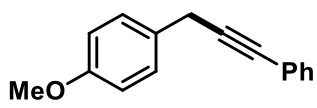
Prepared according to General Procedure ***K*** with 4-methoxybenzyl alcohol (0.069g, 0.5 mmol) and *cis*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4g**) as a colourless oil (0.089g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 5H), 7.15 – 7.12 (d, *J* = 8.80 Hz, 2H), 6.86 – 6.82 (d, *J* = 8.70 Hz, 2H), 6.59 – 6.54 (d, *J* = 11.50 Hz, 1H), 5.87 – 5.79 (m, *J* = 7.40 Hz, 1H), 3.80 – 3.77 (s, 3H), 3.64 – 3.59 (d, *J* = 7.40 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 137.3, 138.3, 131.1, 129.7, 129.2, 128.7, 128.2, 126.8, 113.9, 55.3, 33.7.

(4h): 4,4'-Dimethoxydiphenylmethane[96]



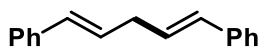
Prepared according to General Procedure ***K*** with 4-methoxybenzyl alcohol (0.069g, 0.5 mmol) and 4-trimethylsilylanisole (0.108g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**4h**) as a colourless crystalline solid (0.059 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 – 7.05 (d, 4H), 6.83 – 6.78 (d, 4H), 3.85 – 3.84 (s, 2H), 3.75 – 3.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 ,133.6, 129.6, 113.8, 55.2, 40.1.

(4i): 1-Methoxy-4-(3-phenyl-2-propyn-1-yl)benzene[97]



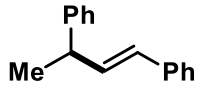
Prepared according to General Procedure ***K*** with 4-methoxybenzyl alcohol (0.069g, 0.5 mmol) and trimethylsilylphenylacetylene (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4i**) as a red solid (0.066g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.62 – 7.55 (m, 5H), 7.18 – 7.14 (d, *J* = 8.68 Hz, 2H), 4.09 – 4.08 (s, 3H), 4.06 – 4.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 131.6, 130.1, 128.9, 128.8, 128.2, 127.7, 123.7, 113.9, 87.9, 82.4, 55.3, 24.8.

(3i): (E,E)-1,5-Diphenyl-1,4-pentadiene[34]



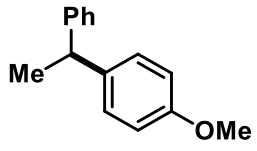
Prepared according to General Procedure ***K*** with 3-phenyl-2-propen-1-ol (0.067 g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**3i**) as a colourless oil (0.022g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.38 (d, *J* = 7.53 Hz, 4H), 7.35 – 7.30 (t, *J* = 7.28 Hz, 4H), 7.25 – 7.20 (t, *J* = 7.28 Hz, 2H), 6.52 – 6.46 (d, *J* = 15.81 Hz, 2H), 6.36 – 6.27 (dt, *J* = 15.81 Hz, 2H), 3.17 – 3.12 (t, *J* = 6.77 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 131.0, 128.5, 128.2, 127.0, 126.0, 36.1.

(4j): Trans-1,3-Diphenyl-1-butene[34]



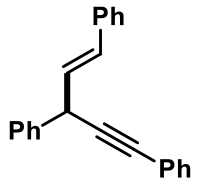
Prepared according to General Procedure ***K*** with α-methyl-benzenemethanol (0.061g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4j**) as a colourless oil (0.021g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 8H), 7.24 – 7.15 (m, 2H), 6.41 – 6.39 (s, 2H), 3.68 – 3.59 (m, 1H), 1.48 – 1.44 (d. 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 137.5, 135.2, 128.5, 128.4, 127.2, 127.0, 126.19, 126.13, 42.5, 21.2.

(4k): 1-Phenyl-1-(4-methoxyphenyl)ethane[98]



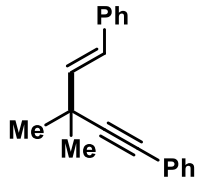
Prepared according to General Procedure ***K*** with α-methyl-benzenemethanol (0.061g, 0.5 mmol) and 4-trimethylsilylanisole (0.108g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4k**) as a colourless oil (0.065 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (t, J = 6.96 Hz, 3H), 7.22 – 7.16 (t, J = 6.96 Hz, 2H), 7.15 – 7.12 (d, J = 8.86 Hz, 2H), 4.12 – 4.06 (m, J = 7.21 Hz, 1H), 3.78 – 3.76 (s, 3H), 1.63 – 1.59 (d, J = 7.21 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 137.7, 128.5, 128.3, 127.5, 125.9, 113.7, 55.2, 43.9, 29.7, 22.0.

(4n): 1,1',1''-(1E)-1-Penten-4-yne-1,3,5-triyltris-benzene[34]



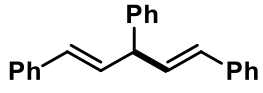
Prepared according to General Procedure ***K*** with 1,3-Diphenylpropargyl alcohol (0.104g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4n**) as a white crystalline solid (0.044 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.18 (m, 15H), 6.79 – 6.74 (d, *J* = 15.81 Hz, 1H), 6.36 – 6.30 (dd, 15.56 Hz, 1H), 4.76 – 4.72 (d, *J* = 6.52 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 136.8, 131.6, 130.4, 129.6, 128.6, 128.5, 128.2, 127.9, 127.7, 127.5, 127.0, 126.5, 123.4, 88.8, 85.4, 41.2.

(4l): 1,1'-[(1E)-3,3-Dimethyl-5-phenyl-1-penten-4-yne-1,5-diyl]bis-benzene



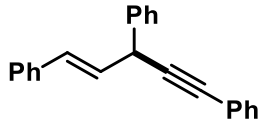
Prepared according to General Procedure ***K*** with 4-dimethyl-4-phenyl-3-butyn-2-ol (0.080g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**4l**) as a white crystalline solid (0.01 g, 7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 7H), 7.24 – 7.16 (m, 3H), 6.77 – 6.72 (d, *J* = 15.7 Hz, 1H), 6.26 – 6.20 (d, *J* = 15.9 Hz, 1H), 1.50 – 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 136.4, 131.6, 128.5, 128.2, 127.7, 127.3, 127.2, 126.4, 123.8, 95.0, 82.4, 34.3, 30.0.

(3o): 1,1',1''-(1E,4E)-1,4-Pentadiene-1,3,5-triyltris-benzene[34]



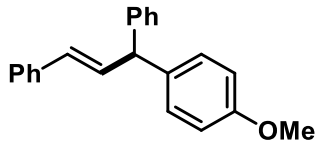
Prepared according to General Procedure ***K*** with α-(2-Phenylethenyl)-benzenemethanol (0.105g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**3o**) as a colourless crystalline solid (0.115g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 740 – 7.34 (d, *J* = 7.21 Hz, 4H), 7.33 – 7.30 (t, *J* = 3.42 Hz, 4H), 7.29 – 7.21 (m, 6H), 7.20 – 7.15 (t, *J* = 7.33 Hz, 3H), 6.47 – 6.45 (d, *J* = 2.56 Hz, 4H), 4.38 – 4.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 137.3, 131.8, 130.8, 128.6, 128.5, 128.1, 127.3, 126.6, 126.2, 51.6.

(3p): 1,1',1''-(1-Penten-4-yne-1,3,5-triyl)tris-benzene[34]



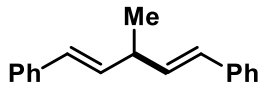
Prepared according to General Procedure ***K*** with α-(2-Phenylethenyl)-benzenemethanol (0.105g, 0.5 mmol) and trimethylsilylphenylacetylene (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**3p**) as an orange solid (0.088g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (d, *J* = 6.60 Hz, 4H), 7.85 – 7.76 (m, 4H), 7.77 – 7.66 (m, 7H), 7.24 – 7.16 (d, *J* = 15.65 Hz, 1H), 6.81 – 6.73 (dd, *J* = 15.60 Hz, 1H), 5.21 – 5.17 (d, *J* = 6.35 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 136.8, 131.7, 130.5, 129.6, 128.7, 128.5, 128.2, 120.0, 127.7, 127.5, 127.1, 126.5, 123.5, 88.8, 85.4, 41.2.

(3q): 1-[(2E)-1,3-Diphenyl-2-propen-1-yl]-4-methoxy-benzene[30]



Prepared according to General Procedure ***K*** with α-(2-Phenylethenyl)-benzenemethanol (0.105g, 0.5 mmol) and 4-trimethylsilylanisole (0.108g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**3q**) as a colourless oil (0.100 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 15H), 6.86 – 6.82 (d, *J* = 7.95 Hz, 2H), 6.68 – 6.60 (dd, *J* = 15.90 Hz, 1H), 6.35 – 6.29 (d, *J* = 15.90 Hz, 1H), 4.85 – 4.81 (d, *J* = 7.34 Hz, 1H), 3.76 – 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 143.8, 137.3, 135.6, 132.9, 131.1, 129.6, 128.6, 128.5, 128.4, 127.2, 126.3, 126.2, 113.8, 55.2, 53.3.

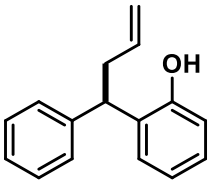
(3l): 1,1'-[(1E,4E)-3-Methyl-1,4-pentadiene-1,5-diyl]bis-benzene[34]



Prepared according to General Procedure ***K*** with 4-Phenyl-3-buten-2-ol (0.074g, 0.5 mmol) and *trans*-2-phenylvinylsilane (0.104g, 0.6 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**3l**) as a colourless oil (0.042 g, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (d, *J* = 7.27 Hz, 4H), 7.30 – 7.22 (t, *J* = 7.27 Hz, 4H), 7.20 – 7.17 (t, *J* = 7.27 Hz, 2H), 6.42 – 6.39 (d, *J* = 16.31. 2H), 6.26 – 6.19 (dd, *J* = 15.81 Hz, 2H), 3.24 – 3.14 (m, *J* = 13.80 Hz, 1H), 1.30 – 1.27 (d, *J* = 6.77 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 134.2, 128.8, 128.4, 127.0, 126.1, 40.0, 20.2.

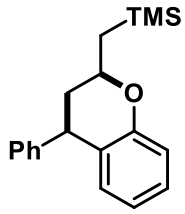
***General Procedure L* for the Coupling of Organosilanes with *ortho*-Substituted Benzhydryl Alcohols:** To a 10.0 mL vial, equipped with a stir bar, was added the organosilane substrate (0.6 mmol), alcohol substrate (0.5 mmol), and 2.00 mL of hexafluoroisopropyl alcohol (HFIP). The solution was allowed to stir at room temperature for 5 minutes. To the resulting solution ferroceniumboronic acid haxafluoroantiomnate salt (0.05 mmol, 0.023g), the reaction mixture was allowed to stir overnight at 120°C temperature. The mixture was cooled to room-temperature and filtered over a silica plug. With ethyl acetate (4 x 10.0 mL) the filtrate was collected, and concetraed in *vacuo.* The residue was purified by flash chromatography (EtOAc/Hexanes).

(4o): 2-(1-Phenyl-3-buten-1-yl)phenol[99]



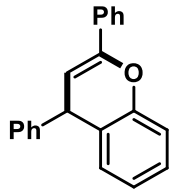
Prepared according to General Procedure ***L*** with 2-(Hydroxy(phenyl)methyl)phenol (0.100 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**4o**) as a brown oil (0.043 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 5H), 7.27 – 7.21 (m, 1H), 7.17 – 7.11 (t, *J* = 7.70 Hz, 1H), 7.01 – 6.95 (t, *J* = 7.58, 1H), 6.78 – 6.76 (d, *J* = 7.94 Hz, 1H),5.81 – 5.69 (m, 1H), 5.07 – 5.00 (dq, *J* = 17.11 Hz, 1H), 4.79 – 4.93 (dq, *J* = 10.14 Hz, 1H), 4.77 – 4.75 (s, 1H), 4.34 – 4.29 (t, *J* = 7.83 Hz, 1H), 2.89 – 2.73 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 143.6, 136.7, 130.5, 128.4, 128.2, 128.0, 127.4, 126.3, 120.8, 116.3, 115.9, 44.2, 38.9.

(4p) 3,4-Dihydro-4-phenyl-2-[(trimethylsilyl)methyl]-2H-1-benzopyran[99]



Prepared according to General Procedure ***L*** with 2-(Hydroxy(phenyl)methyl)phenol (0.100 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**4p**) as a purple oil (0.119 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.14 (m, 6H), 7.04 – 7.01 (dd, *J* = 20.8 Hz, 1H), 6.94 – 6.88 (t, *J* = 7.21 Hz, 1H), 6.84 – 6.77 (m, 1H), 4.44 – 4.23 (m, 2H), 2.32 – 2.00 (m, 2H), 1.30 – 1.18 (m, 1H), 1.10 – 0.95 (m, 1H), 0.23 – 0.09 (d, *J* = 48.8 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) was not collected due to COVID-19.

(4q): 2,4-Diphenyl-4H-1-benzopyran[99]



Prepared according to General Procedure ***L*** with 2-(Hydroxy(phenyl)methyl)phenol (0.100 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**4q**) as an orange solid (0.117 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (d, *J* = 6.69Hz, 2H), 7.44 – 7.26 (m, 8H), 7.25 – 7.10 (m, 4H), 6.98 – 6.91 (m, 2H), 5.62 – 5.57 (d, *J* = 4.16 Hz, 1H), 4.86 – 4.82 (d, *J* = 4.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 147.8, 146.6, 134.2, 129.7, 128.6, 128.4, 128.3, 128.2, 127.67, 126.66, 124.7, 123.4, 116.6, 100.8, 41.1, 29.6.

2.5.4 Computational Details

All computational experiments described in this chapter were conducted by Prof. Josh W. Hollett.

General Computational Details:

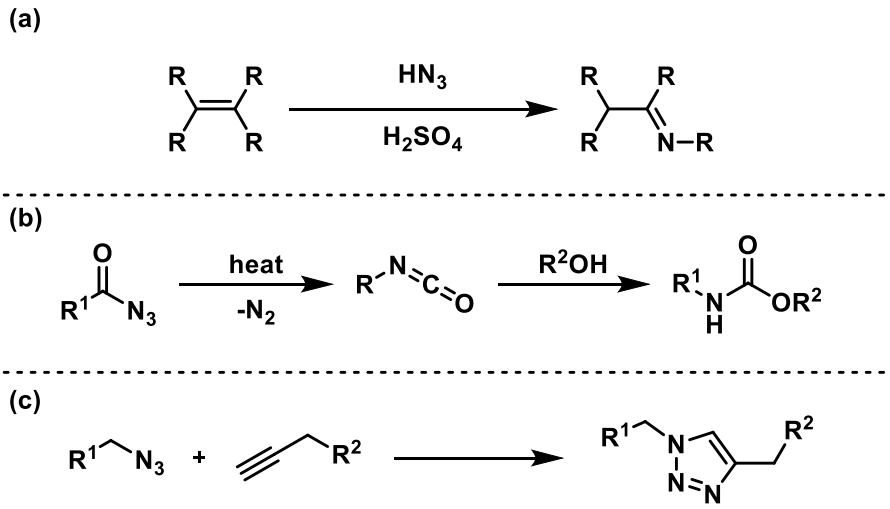
All structures and energies reported were determined at the B3LYP/6-31G(d,p) level of theory with SMD DMC solvation using GAMESS [20 April 2017(R1)]. Cartesian coordinates are given in Angstrom and can be found in Appendix B.

CHAPTER 3 – Boronic Acid Catalysed Preparation of Azides and Nitriles

3.1 Introduction

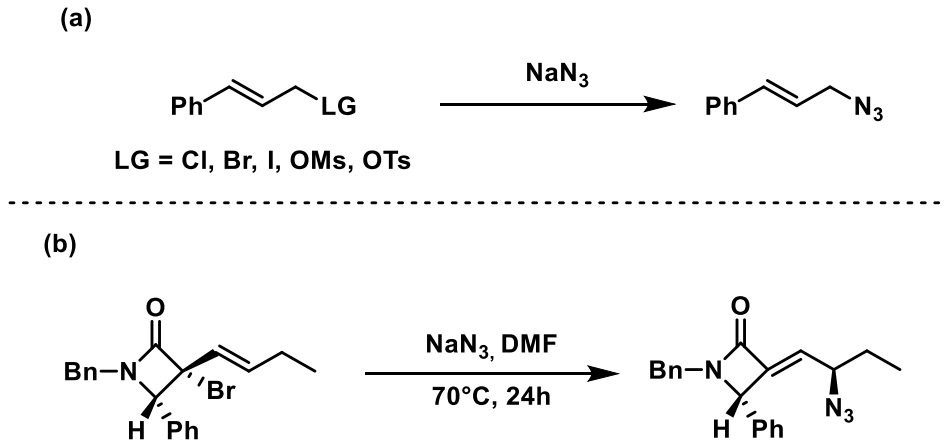
Nitrogen atoms play an essential role in the biological activity of agro-chemicals, natural products, pharmaceuticals, and other important biologically relevant molecules.[100] Similarly, the common hydroxyl functional group is ubiquitous in nature, and is readily accessible in alcohols as a feedstock chemical. Approximately 23% of functional group interconversions that are during the preparation of active pharmaceutical ingredients involve the direct substitution of a hydroxyl functional groups for a halide,[10] tosylate,[101] or mesylate,[102] followed by a subsequent manipulation.[103] Unfortunately, these conventional methods often require harsh conditions, while also generating stoichiometric amounts of potentially toxic waste. As such, synthetic organic chemists have long been interested in a mild, effective, and catalytic method to achieve a "hydroxyl to amine" functional group interconversion.

Organic azides are valuable precursors in organic synthesis. Their use has been extensively explored and their unique reactivity has been used in a variety of important reactions including the Schmidt reaction,[104] the Curtius rearrangement,[105] and 1,3-dipolar cycloadditions.[106] Furthermore, azides are often recognized as primary amine equivalents. In this regard, several strategies have been developed for the preparation of organic azides using alcohols as starting materials.



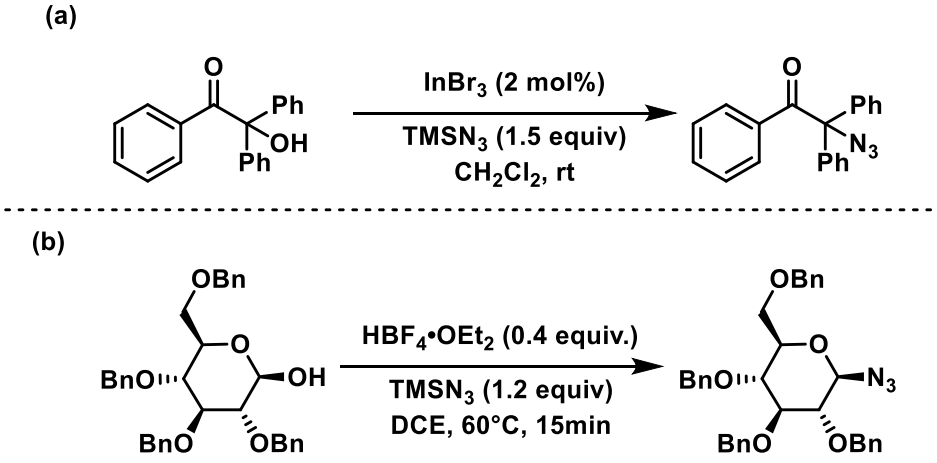
Scheme 3-1: (a) The Schmidt reaction, **(b)** the Curtius rearrangement, and **(c)** 1,3-dipolar cycloaddition

The most well-developed approach for the preparation of allylic and benzylic azides is nucleophilic substitution (**Scheme 3-2(a)**). Due to the significant attention this strategy has received, a diverse scope of electrophiles has been investigated for the incorporation of sodium azide. Mechanistically, this approach proceeds through an S_N2 or S_N2'-type pathway, resulting in inversion of stereochemistry. For example this strategy has been exploited by Tolomelli and co-workers in the diastereoselective synthesis of 3(2'-amino)-β-lactams (**Scheme 3-2(b)**).[107]



Scheme 3-2: (a) General scheme for the preparation of allylic azides *via* nucleophilic substitution **(b)** Tolomelli's strategy for the diastereoselective synthesis of 3(2'-amino)-β-lactams

Due to safety concerns regarding the use of sodium azide, its application to large-scale synthesis is limited. In this regard, many new strategies to circumvent its use have been explored. Several Lewis and Brønsted acids including (but not limited to) $Cu(OTf)_2$,[108] AgOTf,[19] $FeCl_3$,[109] $InBr_3$,[110] and $BF_3{\cdot}OEt_2$[32] have been employed as catalysts for the direct substitution of various electrophiles using azidotrimethylsilane ($TMSN_3$). Venugopalan and co-workers reported access to a variety of 2-Azido-1,2,2-triarylethanones through the azidation of α-hydroxy ketones, employing $TMSN_3$ and $InBr_3$ as a catalyst (**Scheme 3-3(a)**).[110] Through the use of $BF_3{\cdot}OEt_2$, Bolshan and co-workers report the direct substitution of benzhydryl alcohols using azidotrimethylsilane.[32] Interestingly, Bolshan's methodology allows for the preparation of azide substituted carbohydrates (**Scheme 3-3(b)**).[32] Strategies developed previous to this rely on harsh conditions and employ hydrazoic acid or sodium azide as reagents.



Scheme 3-3: (a) Venugopalan's strategy for the preparation of Azido-1,2,2-triarylethanones **(b)** Bolshan's strategy for the Brønsted acid catalysed formation of *N*-glycosidic linkages

3.2 Objective

Due to the prevalence of nitrogen atoms in important biologically active molecules, a simple and mild method for the direct substitution of a hydroxyl functional group for a nitrogen-based nucleophile would be of high value for organic synthesis. Furthermore, nitrogen containing nucleophiles that may be directly interconverted to a variety of functional groups would be particularly useful in medical chemistry. Conventional methods to achieve this type of transformation often involve metal azides and nitriles. However, these species are problematic and cannot be used on the industrial scale due to their potential to explode and toxicity, respectively.

This chapter will focus on the development of a boronic acid catalysed substitution of hydroxyl groups for azide and nitrile nucleophiles. Use of silane bound species allows for improved safety, while affording the desired products in moderate to near quantitative yield.

3.3 Results and Discussion

3.3.1 Optimization of Reaction Conditions

In order to determined if *in situ* generated azide and nitrile nucleophiles were capable of intercepting the presumed carbocation under BAC conditions, a series of reaction parameters were screened (**Table 3-1**). Initially, the conditions for our previously discussed direct carbon-carbon coupling of alcohols with borate and silane nucleophiles were used. Benzhydryl alcohol (**1a**) was used as an electrophile, and the conventional metal salt species, sodium azide and potassium cyanide, were used as nucleophiles. At room temperature, a trace amount of the desired azide

product was isolated (**Table 3-1, entry 1**). Whereas, with the use of KCN none of the desired nitrile product was observed (**Table 3-1, entry 3**). Elevated temperatures were then investigated, and it was determined that 70˚C was optimal (**Table 3-1, entry 2**). To further improve the safety and potential for scalability of the reaction, silane bound nucleophiles were investigated (**Table 3-1, entries 5 - 10**). It was determined that azidotrimethylsilane and trimethylsilyl cyanide, perform similar to that of the metal salts, while decreasing toxicity concerns and potential for explosion (**Table 3-1, entries 1 - 4**).

Table 3-1: Optimization of reaction conditions for the boronic acid catalysed preparation of azides and nitriles

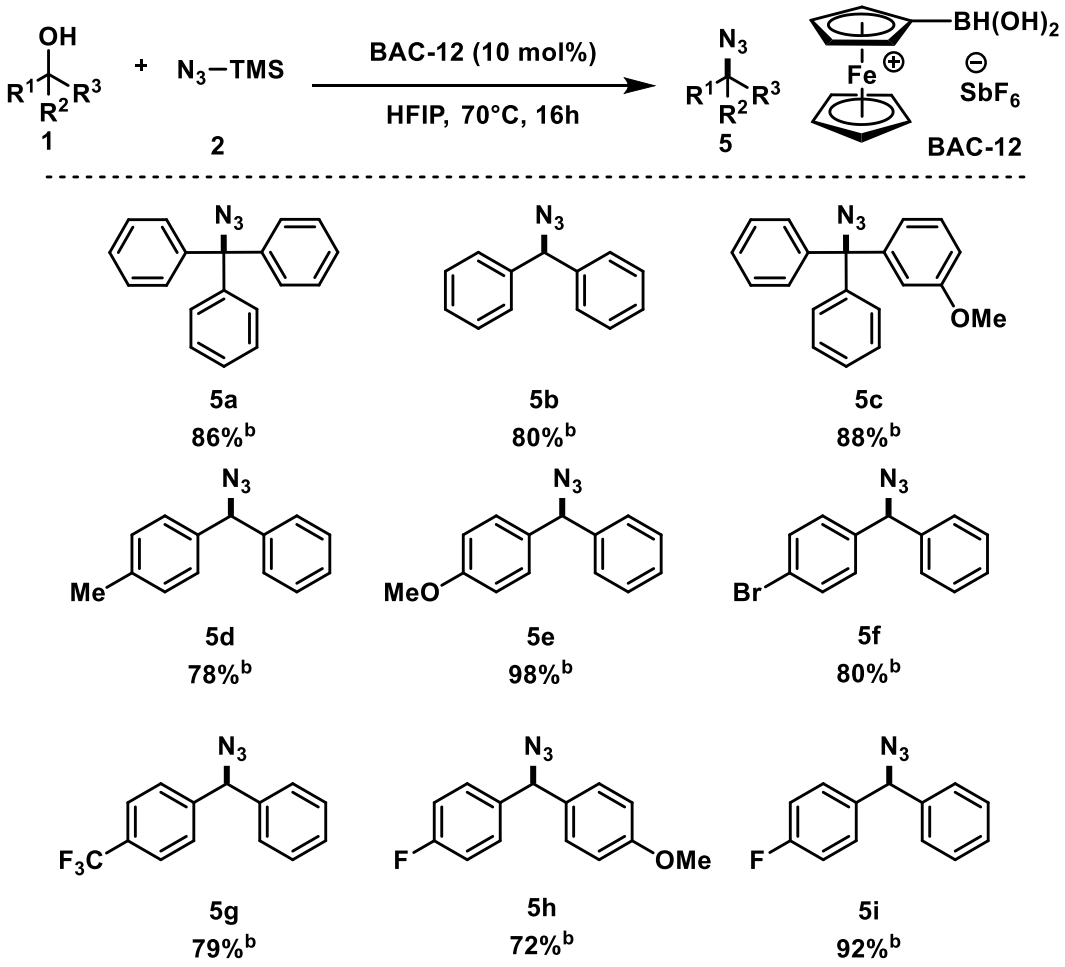
Entry	Catalyst	Solvent	Nucleophile	Temp (˚C)	Yield (%)
1	Fc B.A. SbF_6	HFIP	NaN_3	rt	trace[a]
2	Fc B.A. SbF_6	HFIP	NaN_3	70˚C	84%[b]
3	Fc B.A. SbF_6	HFIP	KCN	rt	trace[a]
4	Fc B.A. SbF_6	HFIP	KCN	70˚C	60%[b]
5	Fc B.A. SbF_6	HFIP	$TMSN_3$	rt	0%[d]
6	Fc B.A. SbF_6	HFIP	$TMSN_3$	70˚C	80%[b]
7	Fc B.A. SbF_6	HFIP	$TMSN_3$	120˚C	81%[b]
8	Fc B.A. SbF_6	HFIP	TMSCN	rt	0%[d]
9	Fc B.A. SbF_6	HFIP	TMSCN	70˚C	52%[b]
10	Fc B.A. SbF_6	HFIP	TMSCN	120˚C	0%[d]

[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [c]A complex mixture of products was obtained as evidence by ^{1}H NMR spectrum of the crude material; [d]No reaction.

3.3.1 Scope of Benzylic Alcohols

Once the optimal reaction conditions were determined, the diversity of electrophile structure was investigated (**Scheme 3-4**). Tertiary benzylic alcohols afforded the desired products **5a** and **5c** in excellent yields of 86% and 88%, respectively. A variety of substituted benzhydryl alcohols were prepared and subject to the boronic acid catalysed reaction conditions. Benzhydryl alcohols with

electron-donating substituents and electron-withdrawing substituents are well tolerated, affording the desired products (**5d-5f**) in good to excellent yield.

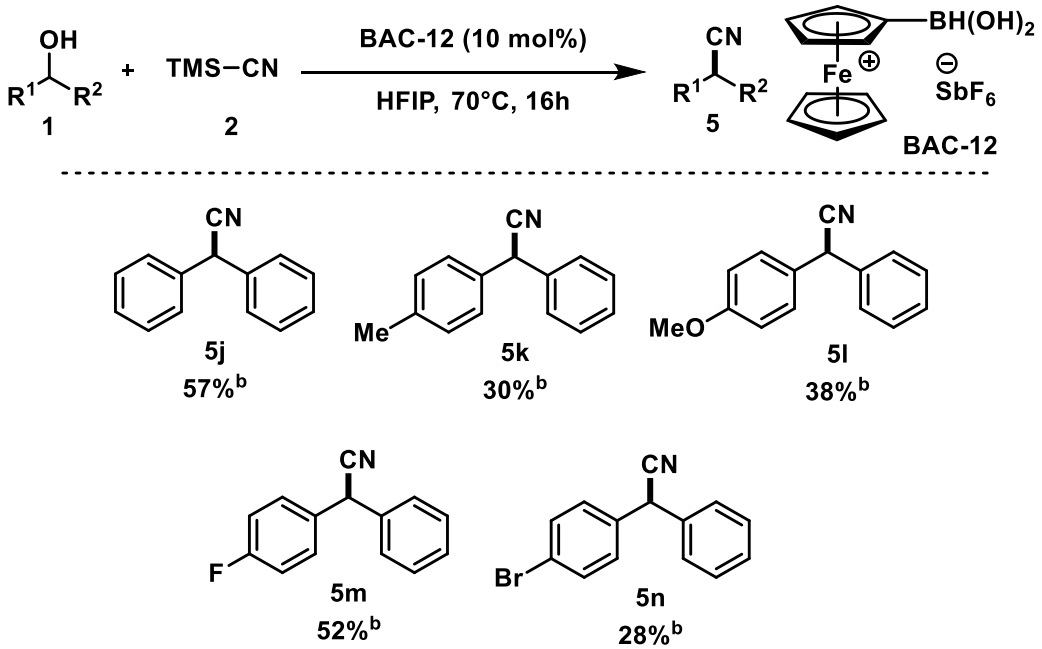


[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields

Scheme 3-4: Scope of Benzylic alcohols with azidotrimethylsilane as a nucleophile

Similar to the scope of prepared azides, a variety of benzhydryl nitriles were prepared in low to moderate yield (**Scheme 3-5**). However, only benzhydryl alcohols with relatively neutral or electron-donating substituents afford the desired products. unfortunately, all other sub-classes of

π-activated alcohols (*e.g.* allylic and propargylic) are not suitable as electrophiles when trimethylsilyl cyanide is used as a nucleophile.



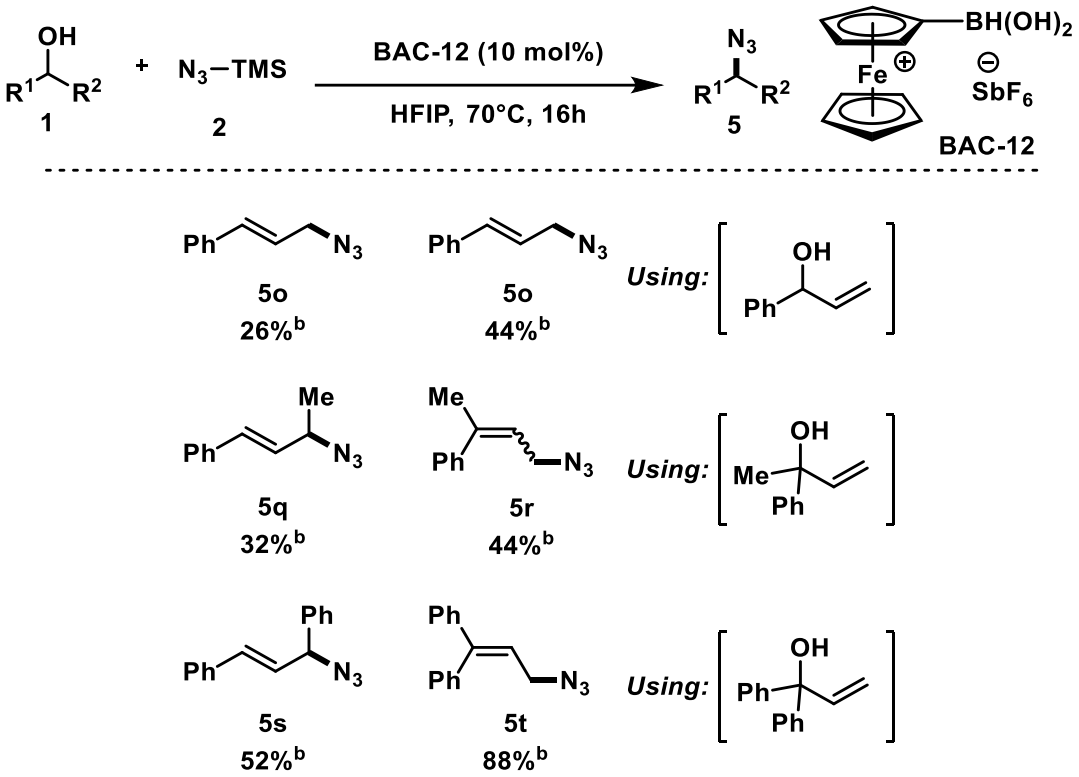
[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields;

Scheme 3-5: Scope of benzylic alcohols with trimethylsilyl cyanide as a nucleophile

3.3.2 Scope of Allylic Alcohols

We next investigated allylic and propargylic alcohols as substrates for our C-N coupling methodology. The primary allylic alcohol prepared from cinnamaldehyde was a suitable coupling partner, affording product **5o** in a low yield of only 25%. The addition of substituents at the carbon atom bearing the presumed carbocation results in increased yield of the desired products.

Secondary azide **5q** was obtained in an increased yield of 32%, and benzylic azide **5s** was obtained in a modest yield of 52%. When secondary allylic alcohols are employed, difficult to prepare allylic azides are obtained. Product **5o** is obtained in an increased yield of 44%, relative to when the primary allylic alcohol is employed. Addition of a methyl substituent has no significant effect on the yield obtained for product **5r**, which was obtained in a yield of 44% with a 1:2 ratio between E/Z isomers. Product **5t** was obtained in an excellent yield of 88%. Secondary allylic alcohols may undergo activation in two different distinct ways. It is proposed that a boronic acid catalysed 1,3-transoposition of the allylic alcohol occurs, followed by electrophilic activation of the resulting allylic alcohol and subsequent substitution.[62] Alternatively, the secondary allylic alcohol could be electrophilically activated and undergo direct S_N2' substitution. Based on the increased yield when secondary allylic alcohols are employed, it is most likely the latter pathway is operating. Unfortunately, secondary and tertiary propargylic alcohols are not suitable substrates for our direct C-N coupling methodology. The corresponding Meyer-Scheuster rearrangement products are obtained in near quantitative yield when secondary and tertiary propargylic alcohols are employed as substates.[62] We propose that azidotrimethylsilane is not sufficiently nucleophilic to compete with the rearrangement pathway, resulting in the formation of no desired azide products.



[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [c]A complex mixture of products was obtained as evidence by ^{1}H NMR spectrum of the crude material; [d]No reaction.

Scheme 3-6: Scope of allylic alcohols with azidotrimethylsilane as a nucleophile

3.4 Summary

In summary, the direct substitution of hydroxyl groups for azides is achieved under mild boronic acid catalysed conditions. The developed methodology is practical, efficient, and does not employ the potentially explosive conventional metal salts. Use of secondary allylic alcohols allows for the preparation of otherwise difficult to obtain allylic azides. In order to further display to the utility of this methodology, diversification experiments display the value of azides as precursors in

organic synthesis. Additionally, diarylaceto nitriles may also be prepared under the same conditions when trimethylsilyl cyanide is employed as a nucleophile.

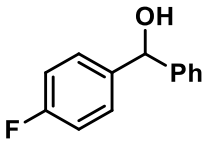
To further develop the utility of this methodology, investigation of other nucleophilic cyanide reagents may provide access to the desired. However, the value of the desired products must be weighed against use of potentially toxic reagents.

3.5 Experimental

3.5.2 Procedures and Characterization Data for Starting Materials

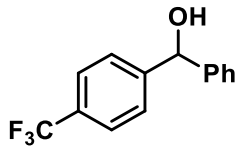
***General Procedure C* for the Prepartion of Benzylic Alcohols by Addition of Phenyl Lithium:** To an oven-dried flask, cooled to room temperature under Ar, was added bromobenzene (10.0 mmol) and recently dried and degassed THF (20 mL). The resulting solution was cooled to -78°C and to it was added a solution of *n*-BuLi (12.0 mmol, 7.50 mL, 1.60M in hexanes) dropwise *via* syringe. The mixture was allowed to stir for 30 minutes -78°C, then to it was added the electrophile (Substituted benzaldehyde, 15.0 mmol). The bath was removed, and the mixture allowed to warm to room temperature. The reaction was quenched by the addition of saturated NH_4Cl(*aq*) solution (20.0 mL), diluted with EtOAc (30.0 mL), and washed with water (2 x 30.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

(1i): (4-Fluorophenyl)(phenyl)methanol[87]



Prepared according to *General Procedure* ***C*** with 4-fluorobenzaldehyde (1.24g, 10 mmol) and bromobenzene (1.55g, 1.05 mL, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (Hex) afforded the desired product (**1i**) as a colourless oil (1.84g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 7H), 6.98 – 6.92 (t, *J* = 8.80 Hz, 2H), 5.69 – 5.66 (s, 1H), 2.75 – 2.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 160.8, 143.5, 139.4, 128.4, 128.2, 128.1, 127.6, 126. 4, 115.2, 115.0, 75.4.

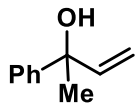
(1o): (4-trifluoromethyl)-benzenemethanol[111]



Prepared according to *General Procedure* ***C*** with 4-trifluoromethylbromobenzene (2.25g, 10.0 mmol) and benzaldehyde (7.50 mL, 12.0 mmol). Purification of the crude reaction mixture by flash chromatography (10 % EtOAc/Hex) afforded the desired product (**1o**) as a colourless oil (1.51g, 60%). R_f = 0.30 (10 % EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (d, *J* = 8.18 Hz, 2H), 7.48 – 7.44 (d, *J* = 8.43 Hz, 2H), 7.35 – 7.24 (m, 5H), 5.81 – 5.79 (s, 1H), 2.70 – 2.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 143.1, 129.7, 128.7, 128.0, 126.64, 126.60, 125.4, 122.7, 75.6.

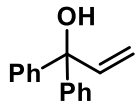
***General Procedure D* for the Preparation of Allylic Alcohols by Addition of Vinylmagnesium bromide:** To an oven-dried flask, cooled to room temperature under Ar, was added the vinylmagnesium bromide (12.0 mmol, 12.0 mL) and freshly dried and degassed THF (20.0 mL). The solution was cooled to 0°C in an ice water bath and to it was added bezaldehyde (10.0 mmol, 1.01 mL). The mixture was warmed to room temperature and allowed to stir for one hour. The reaction was quenched by the addition of saturated NH_4Cl(*aq*) solution (20.0 mL), diluted with EtOAc (30.0 mL), and washed with water (2 x 30.0 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

(1p): α-ethenyl-α-methyl-benzenemethanol[90]



Prepared according to *General Procedure **D*** with acetophenone (1.2g, 1.17 mL, 10.0 mmol) and vinylmagnesium bromide (1.00M, 12.0 mL, 12.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**1p**) as a colourless oil (1.20g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (d, *J* = 7.21 Hz, 2H), 7.34 – 7.28 (t, *J* = 7.33 Hz, 2H), 7.24 – 7.19 (t, *J* = 7.33 Hz, 1H), 6.18 – 6.10 (dd, *J* = 17.23 Hz, 1H), 5.29 – 5.26 (d, *J* = 17.23 Hz, 1H), 5.14 – 5.09 (d, *J* = 10.15 Hz, 1H), 2.22 – 2.21 (s, 1H), 1.63 – 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 144.8, 128.0, 126.8, 125.1, 124.2, 112.1, 29.1.

(1q): α-ethenyl-α-phenyl-benzenemethanol[90]

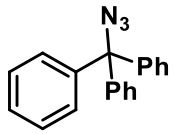


Prepared according to *General Procedure* ***D*** with benzophenone (1.80g, 10.0 mmol) and vinylmagnesium bromide (1.00 M, 12.0 mL, 12.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**1q**) as a colourless oil (1.60g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (d, *J* = 6.96 Hz, 4H), 7.29 – 7.25 (t, *J* = 6.96 Hz, 4H), 7.23 – 7.18 (t, *J* = 7.21, 2H), 6.49 – 6.41 (dd, *J* = 10.14 Hz, 1H), 5.29 – 5.26 (d, *J* = 5.25 Hz, 1H), 5.25 – 5.24 (s, 1H), 2.36 – 2.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 143.4, 128.0, 127.1, 126.8, 113.9, 79.3.

3.5.3 Characterization Data for Products

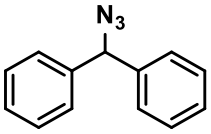
***General Procedure M* for the preparation of Azides:** To a 10.0 mL vial, equipped with a stir bar, was added the azidotrimethylsilane (0.6 mmol), alcohol substrate (0.5 mmol), and 2.00 mL of hexafluoroisopropyl alcohol (HFIP). The solution was allowed to stir at room temperature for 5 minutes. To the resulting solution was added ferroceniumboronic acid (0.05 mmol, 0.023g), the reaction mixture was allowed to stir overnight at 70°C. After cooling to room temperature, the mixture was concentrated in *vacuo*. The residue was purified by flash chromatography (EtOAc/Hexanes).

(5a): (Azidomethanetriyl)tribenzene[32]



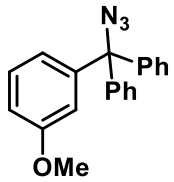
Prepared according to *General Procedure **M*** with triphenylmethanol (0.130 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (100% Hex) afforded the desired product (**5a**) as a white colourless oil (0.112 g, 86%). R_f = 0.25 (100% Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 128.4, 128.1, 127.6.

(5b): 1,1'-(azidomethylene)bis-benzene[112]



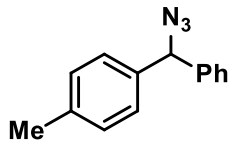
Prepared according to *General Procedure **M*** with diphenylmethanol (0.092 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (100% Hex) afforded the desired product (**5b**) as a white crystalline solid (0.084 g, 80%). R_f = 0.15 (100% Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 10H), 5.70 – 5.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 128.6, 127.9, 127.3, 68.4.

(5c): 1-(azidodiphenylmethyl)-4-methoxy-benzene[113]



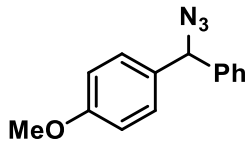
Prepared according to *General Procedure* ***M*** with ## (0.145 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**5c**) as a white oil (0.138 g, 87.5%). R_f = ## (##% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 11H), 6.89 – 6.78 (m, 3H), 3.69 – 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.6, 142.9, 129.0, 128.3, 128.0, 127.6, 120.9, 114.6, 112.6, 55.0.

(5d): 1-(Azido(Phenyl)methyl)-4-methylbenzene[32]



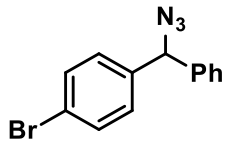
Prepared according to *General Procedure* ***M*** with (4-methylphenyl)(phenyl)methanol (0.099 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (3% EtOAc/Hex) afforded the desired product (**5d**) as white crystalline solid (0.087 g, 78%). R_f = 0.64 (3% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H), 7.20 – 7.12 (q, J = 8.13 Hz, 4H), 5.66 – 5.65 (s, 1H), 2.32 – 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.7, 136.5, 129.3, 128.5, 127.8, 127.3, 127.2, 68.2, 21.0.

(5e): 1-(azidophenylmethyl)-4-methoxy-benzene[32]



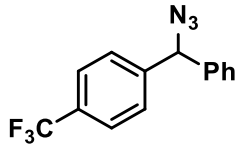
Prepared according to *General Procedure* ***M*** with (4-methoxyphenyl)(phenyl)methanol (0.107g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (3% EtOAc/Hex) afforded the desired product (**5e**) as a white crystalline solid (0.101g, 98%). R_f = 0.29 (3% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 7.21 – 7.18 (d, *J* = 8.53 Hz, 2H), 6.87 – 6.83 (d, *J* = 8.78 Hz, 2H), 5.65 – 5.63 (s, 1H), 3.75 – 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 139.7, 131.6, 128.6, 128.5, 127.7, 127.1, 113.9, 67.9, 55.1.

(5f): 1-(azidophenylmethyl)-4-bromo-benzene



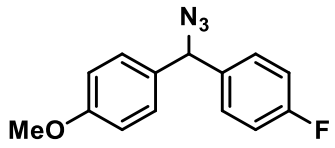
Prepared according to *General Procedure* ***M*** with (4-bromophenyl)(phenyl)methanol (0.132 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (3% EtOAc/Hex) afforded the desired product (**5f**) as white crystalline solid (0.115g, 80%). R_f = 0.31 (3% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.52 (d, *J* = 8.28 Hz, 2H), 7.45 – 7.32 (m, 5H), 7.27 – 7.23 (d, *J* = 8.28 Hz, 2H), 5.73 – 5.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 131.7, 128.9, 128.7, 128.2, 127.3, 121.9, 67.7.

(5g): 1-(azidophenylmethyl)-4-trifluoromethyl-benzene



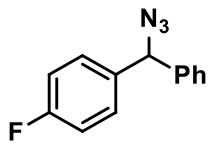
Prepared according to *General Procedure* ***M*** with (4-trifluoromethylphenyl)(phenyl)methanol (0.126 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**5g**) as white crystalline solid (0.110 g, 79%). R_f = 0.24 (5% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.56 (d, *J* = 8.19 Hz, 2H), 7.46 – 7.40 (d, *J* = 8.56 Hz, 2H), 7.39 – 7.25 (m, 5H), 5.74 – 5.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 138.7, 130.3, 130.0, 128.9, 128.5, 127.5, 127.4, 125.3, 122.6, 67.9.

(5h): 1-(Azido(4-methoxyphenyl)methyl)-4-fluorobenzene



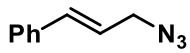
Prepared according to *General Procedure* ***M*** with (4-fluorophenyl)(4-methoxyphenyl)methanol (0.116g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**5h**) as a white crystalline solid (0.093g, 72%). R_f = 0.33 (5% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (t, *J* = 5.87 Hz, 2H), 7.20 – 7.17 (d, *J* = 8.31 Hz, 2H), 7.05 – 6.99 (t, *J* = 8.61 Hz, 2H), 6.89 – 6.86 (d, *J* = 8.80 Hz, 2H), 5.56 – 5.62 (s, 1H), 3.79 – 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 161.0, 159.4, 135.7, 131.4, 128.9, 128.8, 128.6, 115.5, 115.3, 114.1, 67.3, 55.2.

(5i): 1-(azidophenylmethyl)-4-fluoro-benzene



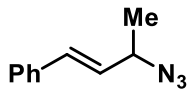
Prepared according to *General Procedure* ***M*** with (4-fluorophenyl)(phenyl)methanol (0.101g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (3% EtOAc/Hex) afforded the desired product (**5i**) as white crystalline solid (0.104g, 92%). R_f = 0.35 (3% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m ,7H), 7.04 – 6.98 (t, *J* = 8.68 Hz, 2H), 5.69 – 5.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) Due to COVID-19 no ^{13}C was obtained.

(5o): (3-azido-1-propen-1-yl)-benzene[114]



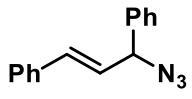
Prepared according to *General Procedure* ***M*** with 3-phenyl-2-propen-1-ol (0.067 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (1% EtOAc/Hex) afforded the desired product (**5o**) as an orange oil (0.023g, 28%). R_f = 0.22 (1% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (d, *J* = 7.09 Hz, 2H), 7.36 – 7.31 (t, *J* = 7.09 Hz, 2H), 7.29 – 7.25 (t, *J* = 7.09 Hz, 1H), 6.67 – 6.61 (d, *J* = 15.77 Hz, 1H), 6.28 – 6.19 (dd, *J* = 15.77 Hz, 1H), 3.95 – 3.91 (d, *J* = 6.60 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 134.5, 128.6, 128.1, 126.5, 122.3, 52.9.

(5q): (3-azido-1-buten-1-yl)-benzene[115]



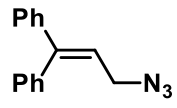
Prepared according to *General Procedure **M*** with 4-phenyl-3-buten-2-ol (0.074 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (1% EtOAc/Hex) afforded the desired product (**5q**) as an orange oil (## g, ##%). R_f = 0.21 (1% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (d, *J* = 6.96 Hz, 2H), 7.36 – 7.31 (t, *J* = 7.70 Hz, 2H), 7.29 – 7.24 (m, 1H), 6.63 – 6.57 (d, *J* = 15.77 Hz, 1H), 6.18 – 6.11 (dd, *J* = 15.77 Hz, 1H), 4.21 – 4.13 (m, *J* = 6.60 Hz, 1H), 1.39 – 1.36 (d, *J* = 6.60 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 132.1, 128.6, 128.3, 128.0, 126.6, 59.6, 20.2.

(5s): 1,1'-[(1E)-3-azido-1-propene-1,3-diyl]bis-benzene[116]



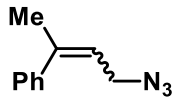
Prepared according to *General Procedure **M*** with α-(2-phenylethenyl)-benzenemethanol (0.118 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (1% EtOAc/Hex) afforded the desired product (**5s**) as a colourless oil (0.061g, 52%). R_f = 0.22 (1% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 10H), 6.74 – 6.68 (d, *J* = 15.65 Hz, 1H), 6.32 – 6.25 (dd, *J* = 15.77 Hz, 1H), 5.22 – 5.18 (d, *J* = 7.21 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 135.9, 132.9, 128.8, 128.6, 128.2, 128.1, 127.0, 126.9, 126.7, 68.6, 67.2, 29.6.

(5t): (3-azidoprop-1-ene-1,1-diyl)dibenzene[19]



Prepared according to *General Procedure* ***M*** with α-ethenyl-α-phenyl-benzenemethanol (0.106g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**5t**) as colourless oil (0.103g, 88%). R_f = 0.40 (5% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (d, *J* = 7.09 Hz, 2H), 7.36 – 7.31 (t, *J* = 7.09 Hz, 2H), 7.29 – 7.25 (t, *J* = 7.09 Hz, 1H), 6.67 – 6.61 (d, *J* = 15.77 Hz, 1H), 6.28 – 6.19 (dd, *J* = 15.77 Hz, 1H), 3.95 – 3.91 (d, *J* = 6.60 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 134.5, 128.6, 128.1, 126.5, 122.3, 52.9.

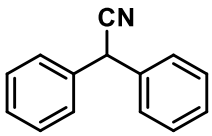
(5r): (E)-(4-azidobut-2-en-2-yl)benzene[19]



Prepared according to *General Procedure* ***M*** with α-ethenyl-α-methyl-benzenemethanol (0.075g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**5r**) as colourless oil (0.038g, 44%). R_f = 0.48 (5% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (d, *J* = 8.07 Hz, 2H), 7.44 – 7.31 (m, 4H), 7.22 – 7.19 (d, *J* = 6.97 Hz, 1H), 5.96 – 5.90 (t, *J* = 7.45 Hz, 1H), 4.05 – 4.00 (d, *J* = 7.33 Hz, 2H), 3.76 – 3.72 (d, *J* = 7.33 Hz, 1H), 2.18 – 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.3, 141.3, 140.2, 128.3, 127.7, 127.6, 127.3, 125.8, 120.1, 119.1, 49.2, 48.4, 25.5, 16.2.

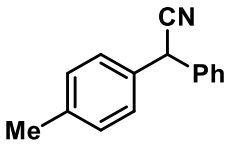
***General Procedure N* for the preparation of nitriles:** To a 10 mL vial, equipped with a stir bar, was added the trimethylsilyl cyanide (0.6mml), alcohol substrate (0.5mmol), and 2 mL of hexafluoroisopropyl alcohol (HFIP). The solution was allowed to stir at room temperature for 5 minutes. To the resulting solution was added ferroceniumboronic acid (0.05 mmol, 0.023g), the reaction mixture was allowed to stir overnight at 70°C. After cooling to room temperature, the mixture was concentrated in *vacuo*. The residue was purified by flash chromatography (EtOAc/Hexanes).

(5j): α-phenyl-Benzeneacetonitrile[117]



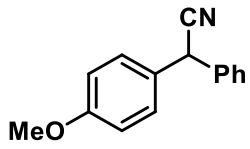
Prepared according to *General Procedure **N*** with diphenylmethanol (0.092 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**5j**) as orange crystalline solid (0.050 g, 52%). R_f = 0.40 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 10H), 5.15 – 5.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.78, 129.18, 128.23, 127.71, 42.60.

(5k): 4-methyl-α-phenyl-benzeneacetonitrile[118]



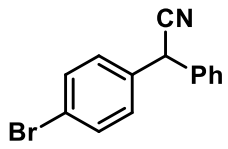
Prepared according to *General Procedure* ***N*** with (4-methylphenyl)(phenyl)methanol (0.099 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**5k**) as an orange crystalline solid (0.031g, 30%). R_f = 0.38 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 7.24 – 7.20 (d, *J* = 8.03 Hz, 2H), 7.19 – 7.13 (d, *J* = 8.03 Hz, 2H), 5.11 – 5.09 (s, 1H), 2.33 – 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 126.1, 132.9, 129.8, 129.1, 128.1, 127.6, 127.5, 119.7, 42.2, 21.0.

(5l): 4-methoxy-α-phenyl-benzeneacetonitrile[119]



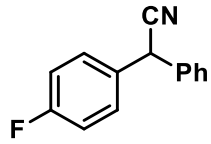
Prepared according to *General Procedure* ***N*** with (4-methoxyphenyl)(phenyl)methanol (0.107g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**5l**) as an orange crystalline solid (0.034g, 30%). R_f = 0.44 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 7.26 – 7.22 (d, *J* = 8.53 Hz, 2H), 6.89 – 6.86 (d, *J* = 8.78 Hz, 2H), 5.09 – 5.08 (s, 1H), 3.79 – 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 136.2, 129.1, 128.8, 128.1, 127.9, 127.5, 119.8, 114.5, 55.2, 41.7.

(5n): 4-bromo-α-phenyl-benzeneacetonitrile[119]



Prepared according to *General Procedure* ***N*** with (4-bromophenyl)(phenyl)methanol (0.132g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**5n**) as an orange crystalline solid (0.038g, 28%). R_f = 0.35 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (d, *J* = 8.53 Hz, 2H), 7.44 – 7.33 (m, 5H), 7.27 – 7.23 (d, *J* = 8.53 Hz, 2H), 5.14 – 5.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 134.9, 132.2, 129.3, 128.4, 127.6, 122.3, 119.1, 42.0.

(5m): 4-methoxy-α-phenyl-benzeneacetonitrile[119]



Prepared according to *General Procedure* ***N*** with (4-fluorophenyl)(phenyl)methanol (0.101 g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**5m**) as an orange oil (0.053 g, 52%). R_f = 0.38 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 7H), 7.07 – 7.02 (t, *J* = 8.53 Hz, 2H), 5.81 – 5.79 (s, 1H), 4.19 – 4.10 (m, *J* = 5.77 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.5, 138.5, 134.8, 129.3, 129.2, 128.7, 127.6, 115.7, 115.5, 85.0, 72.5.

CHAPTER 4 – Boronic Acid Catalysed Preparation of α-Substituted Saturated *N*- and *O*- Heterocycles

4.1 Introduction

Heterocycles have a diverse range of applications, from ligands in catalysis, integral components of functional materials, and their particular importance in medicinal chemistry. In an analysis of FDA approved Pharmaceuticals completed by Njardarson and co-workers, they determined that 59% of small molecule therapeutics contain a nitrogen heterocycle,[103] while 27% contain at least one oxygen heterocycle.[120] While the occurrence of saturated nitrogen heterocycles is well represented by a variety of molecular species,[103] the frequency of oxygen heterocycles is primarily represented by carbohydrates.[120]

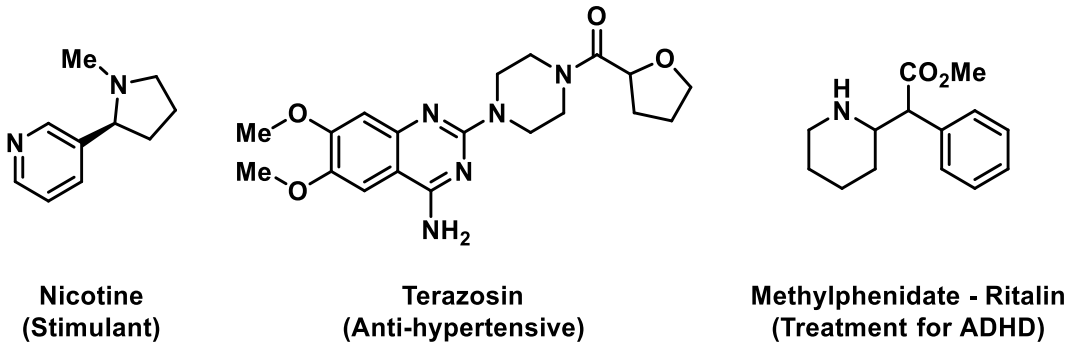
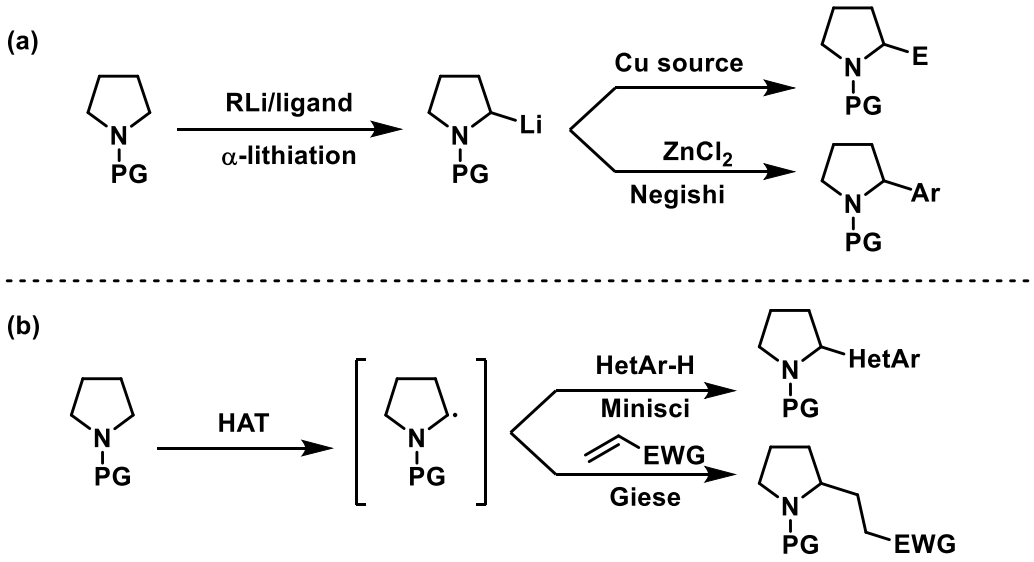


Figure 4-1: Select examples of important biologically active molecule containing α-substituted saturated *N*- and *O*- Heterocycles

Nitrogen heterocycles are of the most prominent subunits in FDA approved drugs.[103] Among them, piperidine is the most prevalent, followed by piperazine and pyrrolidine.[103] In this regard, methodologies that allow for the direct substitution of saturated *N*-heterocycles are highly sought after. One conventional approach for the installation of α-substitutents is dependant on transmetallation of an organolithium species, generated through Beak-type directed lithiation

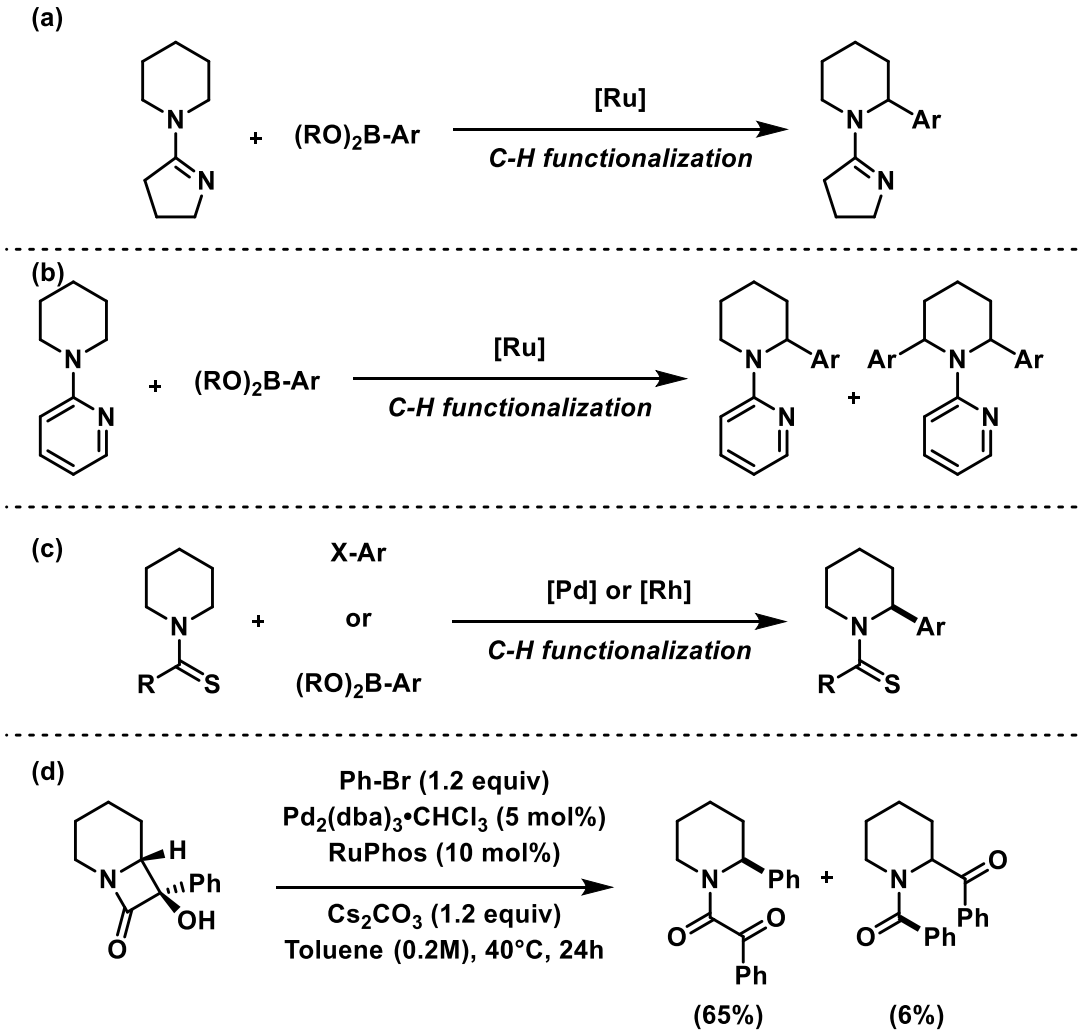
conditions, with a cuprate or zincate. The resulting transmetalated species may then participate in various cross-coupling reactions (*e.g.* Negishi cross-coupling) (**Scheme 4-1(a)**). Baudoin and co-workers have extended this approach to β-selective substitution using ligand control.[121] Using a similar pre-activation strategy, α-radical species may be generated through hydrogen-atom transfer (HAT) or photoredox activation. Once the α-radical has been generated it is free to participate in a variety of radical centred chemistry including Minisci-type reactions (**Scheme 4-1(b)**) or the Giese addition (**Scheme 4-1(b)**).



Scheme 4-1: Strategies to prepare α-substituted *N*- and *O*- saturated heterocycles using **(a)** lithiation/transmetallation **(b)** pre-generation of an α-radical species

Recently, a significant amount of attention has been directed at the development of strategies that exploit C-H activation to achieve α-functionalization of *N*-heterocycles. Sames and co-workers reported the use of ruthenium catalysis and an amidine directing group for the preparation of α-arylated products in low to moderate yields (**Scheme 4-2(a)**).[122] In a similar fashion, Maes co-workers sought to expand this strategy for use with pyridyl directing groups. However, both mono- and bis- arylated products were obtained (**Scheme 4-2(b)**).[123] More recently, several recent studies

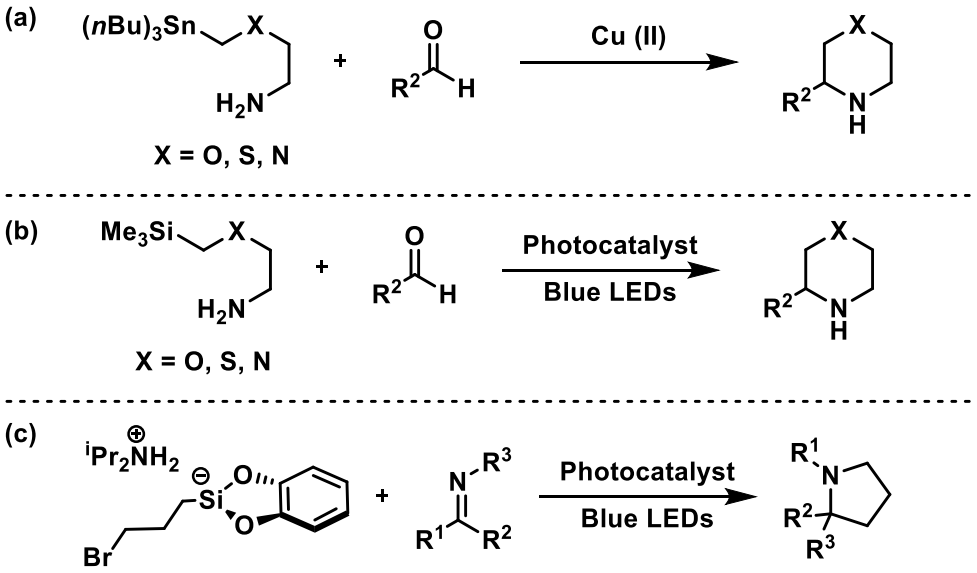
report on the use thioamide directing groups that allow access to enantioselective α-substitution (**Scheme 4-2(c)**).[124–126] Moreover, Sarpong and co-workers have reported the formation of α-functionalized piperidines by a "stain-release" approach (**Scheme 4-2(d)**).



Scheme 4-2: (a) Sames's amidine directing group strategy for α-functionalization **(b)** Maes's pyridyl directing group strategy for α-functionalization **(c)** Enantioselective α-functionalization

In a series of reports by Bode and co-workers, they highlight the utility of a copper catalysed annulation reaction using SnAP reagents (**Scheme 4-3(a)**).[127,128] The key intermediate, an

aldimine, is generated through the condensation of an organotin-tethered amine and an aldehyde.[127,128] They have since developed a silicon-based annulation variants (SLAP) that are compatible with continuous flow (**Scheme 4-3(b)**).[129–131] Inspired by the acyclic starting material approach used by Bode, Molander and co-works recently reported a photoredox-mediated radical/polar crossover strategy for the synthesis of saturated N-heterocycles (**Scheme 4-3(c)**).[132] This strategy allows for the preparation of α-functionalized piperidines and pyrrolidines with crowded quaternary centres, when ketimines are employed as starting materials.[132]



Scheme 4-3: (a) Bode's SnAP annulation strategy **(b)** Bode's SLAP annulation strategy **(c)** Molander's photoredox-mediated/polar crossover annulation strategy

While significant effort has been directed at the preparation of α-functionalized *N*-heterocycles, the analogous saturated *O*-heterocycles have received little attention. In 1994 Trost and co-workers reported the 1,3-bis(diphenylphosphino)propane catalysed cyclization of hydroxyl-2-alkynoates, resulting in the formation of α-functionalized tetrahydrofurans and tetrahydropyrans.[133] An

asymmetric variatint of Trost's phosphine-catalysed strategy was later developed by Fu and co-workers.[134]

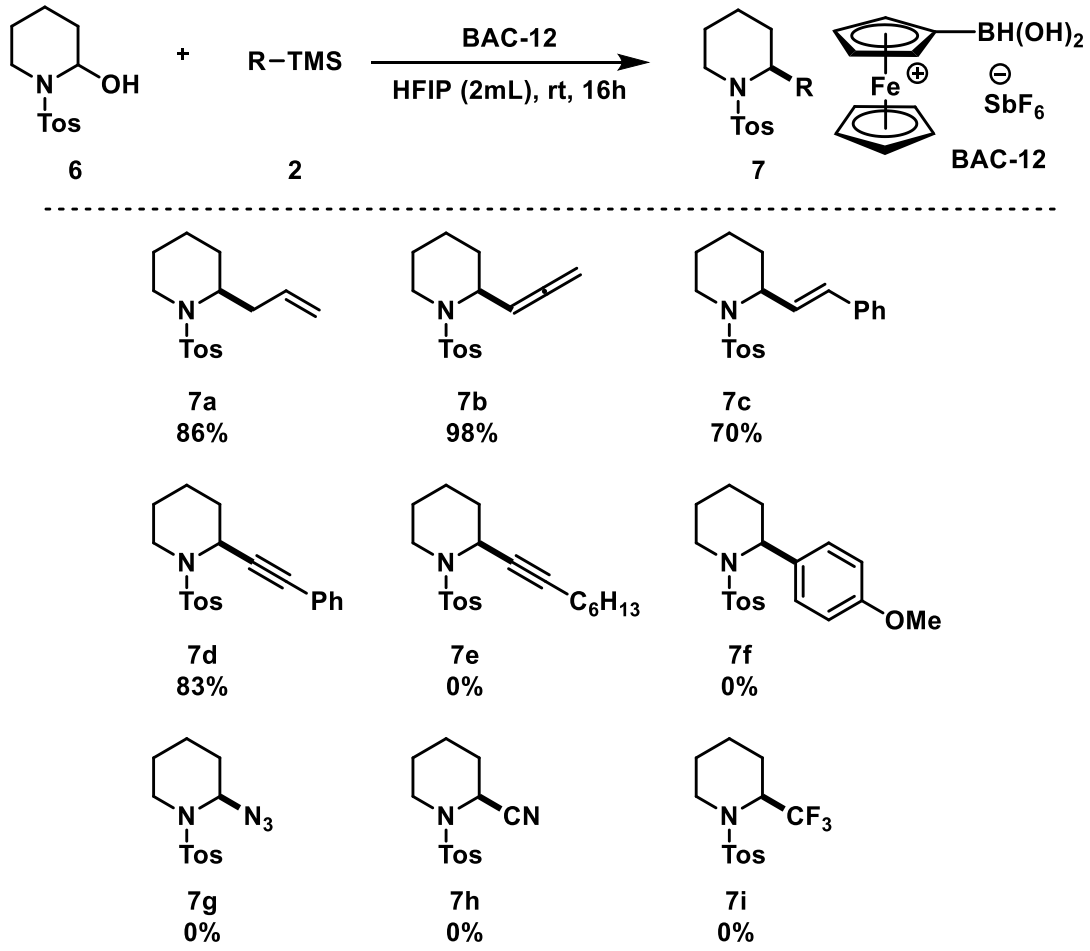
4.3 Results and Discussion

Due to the importance that α-functionalized saturated *N*- and *O*-heterocycles have in medicinal chemistry, the development of new methodologies to prepare them is an important goal. Lewis and Brønsted acids have been shown to be effective catalysts for the electrophilic activation of cyclic and non-cyclic hemi-acetals.[32] However, the catalytic activation of cyclic hemi-aminals has yet to be reported, even though they are easily accessed by the reduction of protected lactams. Herein, we report on the initial results of a boronic acid catalysed coupling of cyclic hemi-acetals and hemi-aminals with silane nucleophiles.

4.3.1 Scope of the prepared N- and O- Heterocycles

Using the previously discussed optimized reaction conditions for the boronic acid catalysed coupling of alcohols with borate and silane nucleophiles, we began to investigate the use of cyclic hemi-aminals as electrophiles. The study was initiated by first examining the allylation of tosyl protected-2-Piperidinol. To our satisfaction, the use of allyl trimethylsilane and 1-(4-methylphenyl)sulfonyl-2-Piperidinol resulted in the formation of product **7a** in excellent yield. Suspected to have a similar reactivity to that of allyl trimethylsilane, the use of propargyl trimethyl silane lead to the production of the allene product **7b** in a near quantitative. Other organosilane

nucleophiles also resulted in the formation of the corresponding desired products **7c** and **7d** in yields of 70% and 83%, respectively.

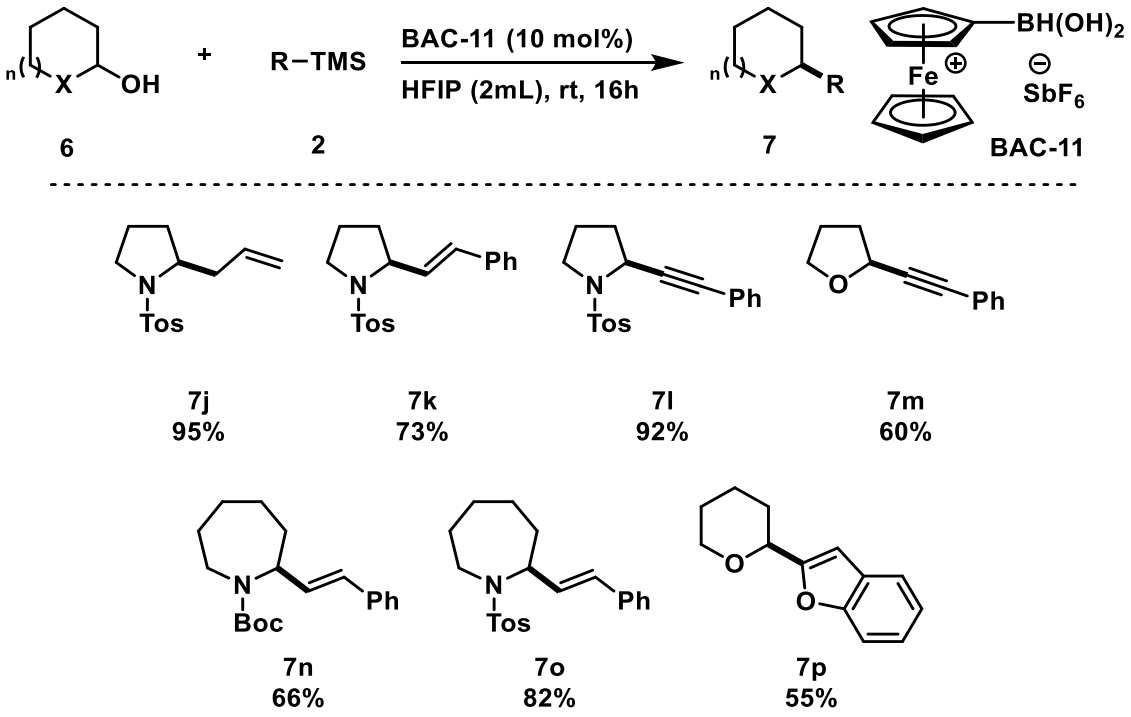


[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [c]A complex mixture of products was obtained as evidence by ^{1}H NMR spectrum of the crude material; [d]No reaction.

Scheme 4-4: Scope of organosilane nucleophiles

Cyclic hemi-acetals are also well tolerated as substrates, producing substituted furan **7m** and pyran **7p** products in modest yields. The reaction to produce **7p** not only highlights the use of cyclic hemi-acetals as substrates, but the silane unit on the 2-trimethylsilyl benzofuran controls the

regiochemistry in which nucleophilic attack occurs. substitution is only observed at the C2 position, rather than the normally observed C3 position. Both 6- and 7-membered cyclic hemi-aminals result in the formation of α-functionalized pyrrolidines **7j-7l** and azepanes **7n** and **7o** in good yields. Furthermore, the BOC protecting group employed is example **6n** is retained in the product, providing potential access to unprotected α-functionalized saturated *N*-heterocycles.



[a]Reaction conditions: to a vial containing **1** (0.5 mmol) and **2** (0.6 mmol) in HFIP (2 mL) was added the catalyst **BAC-11** (0.5 mmol). The mixture was allowed to stir for 16 hours at room temperature, then filtered through a plug of silica gel (EtOAc) and concentrated *in vacuo*. The residue was purified by flash chromatography; see Experimental Section for details; [b]Isolated yields; [c]A complex mixture of products was obtained as evidence by ^{1}H NMR spectrum of the crude material; [d]No reaction.

Scheme 4-5: Scope of cyclic hemiaminal and hemiacetal electrophiles

4.4 Summary

The initial results reported provide evidence that the boronic acid catalysed electrophilic activation of cyclic hemi-acetals and hemi-aminals provides an efficient route to α-functionalized saturated

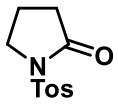
O- and *N*-heterocycles. Furthermore, this preliminary study is the first report of Lewis or Brønsted acid catalysed activation of cyclic hemi-aminals. The "lone-pair" activated cyclic hemi-aminals are prepared in a two-step fashion: protection of the lactam pre-cursor, followed by reduction of the carbonyl C-O double bond. A variety of organosilane nucleophiles can be introduced generating high value coupledproducts and structural motifs that can be further manipulated.

4.5 Experimental

4.5.2 Procedures and Characterization Data for Starting Materials

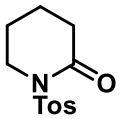
***General Procedure P* for the Protection of Lactams:** To an oven-dried flask, cooled to room-temperature under argon, was added the lactam (20.0 mmol) and THF (30.0 mL). The resulting solution was cooled to -78°C in a dry-ice/acetone bath and to it was added a solution of *n*-BuLi (24.0 mmol, 15.0 mL, 1.60M in hexanes) dropwise *via* syringe. The mixture was allowed to stir for 30 minutes at -78°C, then to it was added tosyl chloride (20.0 mmol, 3.81 g) or BOC_2O (20.0 mmol, 4.40 g). The bath was removed, and the mixture was allowed to warm to room temperature. The reaction was quenched by the addition of saturated $NH_4Cl(aq)$ solution (20.0 mL), diluted with EtOAc (50.0 mL), and washed with water (2 x 50.0 mL). the organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

(6a): 1-(Tosyl)-pyrrolidin-2-one[135]



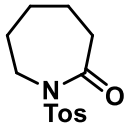
Prepared according to *General Procedure* ***P*** with 2-pyrrolidinone (1.70g, 20.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6a**) as a colourless solid (1.68g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.31(d, *J* = 8.5 Hz, 2H), 3.92 – 3.87 (t, *J* = 7.0 Hz, 2H), 2.47 – 2.43 (m, 5H), 2.13 – 2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 145.2, 135.2, 129.7, 128.1, 47.3, 32.2, 21.7, 18.2.

(6b): 1-(4-methylphenyl)sulfonyl- 2-Piperidinone[135]



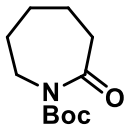
Prepared according to *General Procedure* ***P*** with δ-valerolactam (2.53g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6b**) as a colourless solid (2.41g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (d, *J* = 7.58 hz, 2H), 7.35 – 7.32 (d, *J* = 7.95 Hz, 2H), 3.95 – 3.91 (t, *J* = 5.99 Hz, 2H), 2.45 – 2.44 (s, 5H), 2.47 – 1.99 (m, 2H), 1.84 – 1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 144.7, 136.1, 129.3, 128.7, 46.9, 34.1, 23.2, 21.6, 20.4.

(6c): 1-(Tosyl)-azepan-2-one[135]



Prepared according to *General Procedure* ***P*** with ε-caprolactam (2.26g, 20.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6c**) as a colourless oil (2.24g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.85 (d, *J* = 8.31 Hz, 2H), 7.33 – 7.28 (d, *J* = 8.07 Hz, 2H), 4.04 – 4.00 (t, *J* = 4.77 Hz, 2H), 2.55 – 2.41 (s, 3H), 1.86 – 1.80 (m ,2H), 1.76 – 1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 144.4, 136.6, 129.2, 128.5, 46.4, 38.7, 29.3, 29.1, 22.9, 21.6.

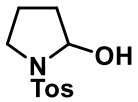
(6d): N-Boc-ε-Caprolactam



Prepared according to *General Procedure* ***P*** with ε -caprolactam (2.83g, 25.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6d**) as a colourless solid (2.80g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 – 3.80 (m, 2H), 2.70 – 2.62 (m, 2H), 1.85 – 1.70 (m, 6H), 1.52 (s, 9H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 153.2, 83.0, 46.5, 39.8, 29.5, 29.0, 28.3, 23.9.

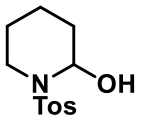
***General Procedure Q* for the Preparation of Cyclic Aminals:** To an oven-dried flask, cooled to room-temperature under Ar, was added the Boc- or Tosyl- protected lactam (10.0 mmol) and CH_2Cl_2 (30.0 mL). The resulting solution was cooled to -78°C in a dry-ice/acetone bath and to it was added a solution of DIBAL-H (16.7 mmol, 16.7 mL, 1.00M in PhMe) dropwise *via* syringe. The mixture was allowed to stir for 60 minutes at -78°C, then to it was added MeOH (10.0 mL) and a saturated solution of Rochelle's salt (10.0 mL). The bath was removed, and the mixture was allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 (20.0 mL) and washed with water (2 x 40.0 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

(6e): 1-(Tosyl)-pyrrolidin-2-ol[136]



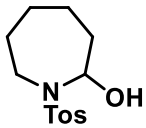
Prepared according to *General Procedure* ***Q*** with 1-(Tosyl)-pyrrolidin-2-one (2.56 g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6e**) as a colourless solid (2.18 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.72 (dd, *J* = 29.5 Hz, 2H), 7.34 – 7.30 (d, *J* = 7.9 Hz, 2H), 5.44 – 5.40 (m, 1H), 3.60 – 3.47 (m, 1H), 3.20 – 3.00 (m, 1H), 2.45 – 2.41 (s, 3H), 2.16 – 1.88 (m, 2H), 1.82 – 1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 129.8, 127.1, 83.9, 47.5, 33.8, 22.9, 21.5.

(6f): 1-(4-methylphenyl)sulfonyl-2-Piperidinol



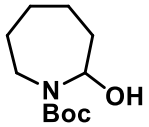
Prepared according to *General Procedure* ***Q*** with 1-(4-methylphenyl)sulfonyl- 2-Piperidinone (2.53 g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6f**) as a colourless solid (2.30g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.28 (d, *J* = 7.9 Hz, 2H), 5.56 – 5.50 (d, *J* = 2.7 Hz, 1H), 3.62 – 3.54 (d, *J* = 11.9 Hz, 1H), 3.18 – 3.08 (t, *J* = 12.1 Hz, 1H), 2.43 – 2.40 (s, 3H), 2.30 – 2.24 (s, 1H), 1.75 – 1.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) was not obtained due to COVID-19.

(6g): 1-Tosyl-azepan-2-ol



Prepared according to *General Procedure* ***Q*** with1-(Tosyl)-azepan-2-one (2.68g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6g**) as a yellow oil (2.17 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.72 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.28 (d, *J* = 7.9 Hz, 2H), 4.82 – 4.45 (m, 1H), 2.97 – 2.89 (m, 2H), 2.44 – 2.41 (s, 3H), 2.40 – 2.37 (dd, *J* = 1.6 Hz, 1H), 1.64 – 1.53 (m, 2H), 1.52 – 1.42 (m, 2H), 1.38 – 1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 136.9, 129.6, 127.0, 101.2, 42.8, 33.4, 29.2, 25.9, 23.9, 21.4.

(6h): 2-Hydroxy-azepane-1-carboxylic acid tert-butyl ester



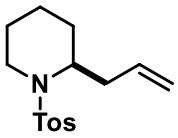
Prepared according to *General Procedure* ***Q*** with N-Boc-ε-Caprolactam (2.14g, 10.0 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**6h**) as a colourless oil (1.35g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 – 4.48 (s, 1H), 3.16 – 3.04 (d, *J* = 6.1 Hz, 2H), 2.46 – 2.32 (m, 2H), 1.70 – 1.61 (m, 3H), 1.46 – 1.42 (s, 9H), 1.40 – 1.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 79.8, 43.7, 33.7, 29.8, 28.4, 26.2, 21.6.

***General Procedure R* for the Preparation of Cyclic Acetals:** To an oven-dried flask, cooled to room-temperature under argon, was added unsaturated oxygen heterocycle (10.0 mmol) and MeOH (30.0 mL). The resulting solution was cooled to 0°C in a ice bath and to it was added HCl (30.0 mL, 1.00M) dropwise *via* syringe. The mixture was allowed to stir for 2 hours at room temperature. The mixture was diluted with MeOH (20.0 mL) and washed with water (2 x 40.0 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the product.

4.5.3 Characterization Data for Products

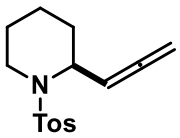
***General Procedure S* for the Coupling of Organosilanes with cyclic hemi-aminals and hemi-acetals:** To a 10.0 mL vial, equipped with a stir bar, was added the organosilane substrate (0.60 mmol), alcohol substrate (0.5 mmol), and 2.00 mL of hexafluoroisopropyl alcohol (HFIP). The solution was allowed to stir at room temperature for 5 minutes. To the resulting solution ferroceniumboronic acid haxafluoroantiomnate salt (0.05 mmol, 0.023g), the reaction mixture was allowed to stir overnight at 120°C temperature. The mixture was cooled to room-temperature and filtered over a silica plug. With ethyl acetate (4 x 10.0 mL) the filtrate was collected, and concetraed in *vacuo.* The residue was purified by flash chromatography (EtOAc/Hexanes).

(7a): 1-(4-methylphenyl)sulfonyl-2-(2-propen-1-yl)-piperidine



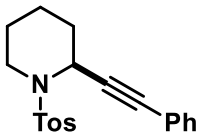
Prepared according to *General Procedure* ***S*** with 1-(4-methylphenyl)sulfonyl-2-Piperidinol (0.120g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**7a**) as a colourless oil (0.120g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 6.69 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.26 (d, *J* = 8.1 Hz, 2H), 5.75 – 5.63 (m, 1H), 5.06 – 4.99 (t, *J* = 9.2 Hz, 2H), 4.14 – 4.06 (m, 1H), 3.79 – 3.72 (d, *J* = 14.3 Hz, 1H), 3.02 – 2.91 (t, *J* = 13.3 Hz, 1H), 2.43 – 2.39 (s, 3H), 2.32 – 2.24 (t, *J* = 7.2 Hz, 2H), 1.60 – 1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 138.6, 134.8, 129.4, 126.8, 116.9, 52.3, 40.5, 33.8, 26.4, 24.4, 21.3, 17.9.

(7b): 1-[(4-methylphenyl)sulfonyl]-2-(2-allenyl)-piperidine



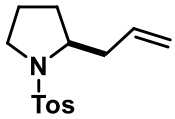
Prepared according to *General Procedure* ***S*** with 1-(4-methylphenyl)sulfonyl-2-Piperidinol (0.120g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**7b**) as a colourless oil (0.136g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.68 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.26 (d, *J* = 7.9 Hz, 2H), 4.96 – 4.90 (m, 1H), 4.75 – 4.60 (m, 3H), 3.88 – 3.68 (d, *J* = 12.9 Hz, 1H), 3.00 – 2.90 (t, *J* = 12.5 Hz, 1H), 2.42 – 2.40 (s, 3H), 1.78 – 1.38 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 142.8, 137.7, 129.3, 127.0, 88.8, 76.8, 51.3, 41.4, 28.8, 25.1, 21.3, 18.7.

(7d): 1-[(4-methylphenyl)sulfonyl]-2-(2-phenylethynyl)-piperidine[138]



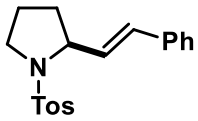
Prepared according to *General Procedure* ***S*** with 1-(4-methylphenyl)sulfonyl-2-Piperidinol (0.120g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (5% EtOAc/Hex) afforded the desired product (**7d**) as a white solid (0.140g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.71 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.14 (m, 5H), 6.99 – 6.96 (d, *J* = 8.2 Hz, 2H), 5.07 – 5.04 (t, *J* = 3.2 Hz, 1H), 3.79 – 3.72 (d, *J* = 11.7 Hz, 1H), 2.92 – 2.84 (t, *J* = 11.9 Hz, 1H), 2.30 – 2.24 (s, 3H), 1.94 – 1.82 (m, 2H), 1.88 – 1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 134.9, 131.4, 129.2, 128.1, 128.0, 127.9 122.3, 86.8, 84.2, 46.8, 42.2, 31.5, 25.2, 21.3, 19.3.

(7j): 2-Allyl-1-(tosyl)-pyrrolidine



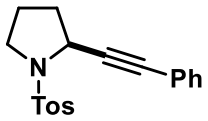
Prepared according to *General Procedure* ***S*** with 1-(Tosyl)-pyrrolidin-2-ol (0.260g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (25% EtOAc/Hex) afforded the desired product (**7j**) as a colourless crystalline solid (.242g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.29 (d, *J* = 7.9 Hz, 2H), 5.85 – 5.73 (m, 1H), 5.12 – 5.04 (m, 2H), 3.71 – 3.63 (m, 1H), 3.21 – 3.14 (m, 1H), 2.44 – 2.42 (s, 3H), 2.35 – 2.26 (m, 1H), 1.85 – 1.72 (m, 1H), 1.69 – 1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 135.0, 134.6, 129.6, 127.5, 117.6, 59.7, 49.1, 40.8, 30.1, 23.9, 21.5.

(7k): 2-Styryl-1-(tosyl)-pyrrolidine[139]



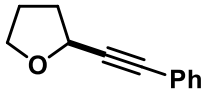
Prepared according to *General Procedure* ***S*** with 1-(Tosyl)-pyrrolidin-2-ol (0.260g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (20% EtOAc/Hex) afforded the desired product (**7k**) as a brown solid (0.130g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 7H), 6.57 – 6.51 (d, *J* = 15.7 Hz, 1H), 6.08 – 6.01 (dd, *J* =15.7 Hz, 1H), 4.37 – 4.30 (q, *J* = 4.3 Hz, 1H), 3.52 – 3.30 (m, 2H), 2.39 – 2.34 (s, 3H), 1.90 – 1.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 136.5, 135.6, 130.5, 129.9, 129.4, 128.3, 127.5, 127.4, 126.4, 61.6, 48.5, 32.7, 23.8, 21.3.

(7l): 2-Phenylethynyl-1-(tosyl)-azepane[138]



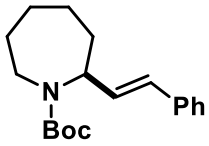
Prepared according to *General Procedure* ***S*** with 1-(Tosyl)-pyrrolidin-2-ol (0.300g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (50% EtOAc/Hex) afforded the desired product (**7l**) as a colourless crystalline solid (0.230g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.18 (m, 7H), 4.78 – 4.74 (m, 1H), 3.50 – 3.34 (m, 2H), 2.34 – 2.30 (s, 3H), 2.26 – 2.00 (m, 3H), 1.94 – 1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 135.5, 131.4, 129.2, 128.1, 127.9, 127.5, 122.4, 87.5, 83.9, 50.8, 47.0, 33.9, 24.1, 21.2.

(7m): Tetrahydro-2-(2-phenylethynyl)-furan[140]



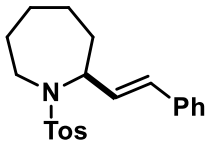
Prepared according to *General Procedure* ***S*** with Tetrahydro-2-furanol (0.044g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**7m**) as a colourless oil (0.051g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.41 (m, 2H), 7.31 – 7.26 (m, 3H), 4.83 – 4.78 (m, *J* = 5.13 Hz, 1H), 4.05 – 3.97 (m, *J* = 7.33 Hz, 1H), 3.89 – 3.82 (m, *J* = 7.70 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.13 – 2.07 (m, 2H), 2.00 – 1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 128.1, 122.8, 89.0, 84.4, 68.5, 67.8, 33.3, 25.4.

(7n): 2-Styryl-azepane-1-carboxylic acid tert-butyl ester



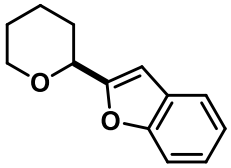
Prepared according to *General Procedure* ***S*** with 2-hydroxy-azepane-1-carboxylic acid tert-butyl ester (0.220g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**7n**) as a colourless oil (0.141g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 5H), 6.42 – 6.02 (m, 2H), 4.83 – 4.50 (d, 1H), 3.96 – 3.68 (dd, *J* = 15.7 Hz, 1H), 2.82 – 2.70 (t, *J* 13.0 Hz, 1H), 2.24 – 2.02 (m, 1H), 1.90 – 1.74 (d, *J* = 10.1 Hz, 2H), 1.51 – 1.42 (d, *J* 14.3 Hz, 9H), 0.90 – 0.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 137.2, 130.9, 128.9, 128.7, 126.4, 79.6, 53.4, 40.0, 29.7, 28.6, 25.7, 19.8.

(7o): 2-Stryl-1-(tosyl)-azepane



Prepared according to *General Procedure* ***S*** with 1-Tosyl-azepan-2-ol (0.230g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**7o**) as a colourless oil (0.220g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.16 (m, 7H), 6.40 (dd, *J* = 16.1 Hz, 1H), 5.99 (dd, *J* = 15.9 Hz, 1H), 4.76 – 4.72 (m, 2H), 3.78 – 3.73 (m, 2H), 3.06 – 2.98 (m, 2H), 2.35 (s, 3H), 1.80 – 1.76 (s, 3H), 1.65 – 1.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 138.6, 136.6, 130.5, 129.3, 128.5, 128.4, 127.5, 127.4, 126.3, 58.9, 43.8, 35.4, 30.3, 29.5, 24.3, 21.3.

(7p): 2-(tetrahydro-2H-pyran-2-yl)-benzofuran[141]



Prepared according to *General Procedure* ***S*** with tetrahydro-2H-pyran-2-ol (0.051g, 0.5 mmol). Purification of the crude reaction mixture by flash chromatography (10% EtOAc/Hex) afforded the desired product (**7p**) as a colourless oil (0.056g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.51 (d, *J* = 7.45 Hz, 1H), 7.48 – 7.45 (d, *J* = 7.21 Hz, 1H), 7.27 – 7.17 (m, 2H), 6.62 – 6.61 (s, 1H), 4.57 – 4.53 (d, 1H), 4.15 – 4.09 (m, 1H), 3.70 – 3.62 (t, *J* = 11.3 Hz, 1H), 2.02 – 1.84 (m, 3H), 1.78 – 1.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.7, 128.1, 123.9, 122.6, 120.9, 111.3, 102.7, 73.4, 68.7, 29.9, 25.7, 23.0.

CHAPTER 5 – Conclusions and Future Work

In conclusion, three novel boronic acid catalysed methodologies have been developed. We have successfully extended the utility of ferrocenium boronic acid hexafluoroantimonate as a catalyst by expanding the electrophilic substrate scope. Furthermore, we have also demonstrated the ability of pseudo-organometallic reagents to intercept the presumed generated carbocation. To this extent, a diverse scope of products containing high value C-C and C-N bonds, under mild conditions have been prepared.

Chapter 2 focused on our efforts to expand the utility of the ferrocenium boronic acid hexafluoroantimonate beyond its reported use in Friedel-Crafts arylation reactions.[65] we successfully expanded the electrophilic substrate scope to include allylic and propargylic alcohols, while still employing the reported benzylic alcohols as substrates. Initially, we investigated free boronic acids and boronic acid derivatives as nucleophiles. It was determined that these substrates were either not nucleophilic enough to participate or provided a limited scope when they did. Our attention then turned to the use of organosilanes as nucleophiles. Use of organosilanes as nucleophiles resulting in the formation of desired products in increased yields and expansion of the substrate scope.

The *ACS Green Institute Pharmaceutical Roundtable* highlights several areas of research that require immediate attention due to safety and environmental concerns. Catalytic hydroxyl group activation and preparation of azides without employed of metal salt species belong to this list. With the completion of our boronic acid catalysed C-C bond forming method, we envisioned a similar method that employed azidotrimethylsilane and trimethylsilyl cyanide as nucleophiles. With slightly elevated temperatures, various triaryl, diaryl, and allylic azides may be prepared. However,

when trimethylsilyl cyanide is used as a nucleophile only benzhydryl alcohols are suitable coupling partners.

Given the prevalence of α-functionalized saturated heterocycles in pharmaceuticals, novel methodologies for their preparation are an important goal. With inspiration drawn from Bolshan and co-workers Brønsted acid catalysed azidization of carbohydrates; we envisioned an analogues reaction using cyclic hemiaminals as "lone-pair" activated alcohols, a mode a reactivity previously unreported.[32] A series of α-functionalized saturated *N*-heterocycles have been prepared under mild conditions using a variety of organosilane nucleophiles. Furthermore, the cyclic hemiacetals are also tolerated providing access to α-functionalized saturated *O*-heterocycles.

Current evidence suggests that our methodology proceeds through an S_N1-type mechanism. The development of an enantioselective variant would be a powerful method to access a diverse pool of chiral products. Future work should be directed at the development of a chiral ferroceniumboronic acid salt derivative. Modification of the ferrocene scaffold, use of a chiral counter-ion, or addition of hydrogen-bond donating additives may prove successful at introducing asymmetry.

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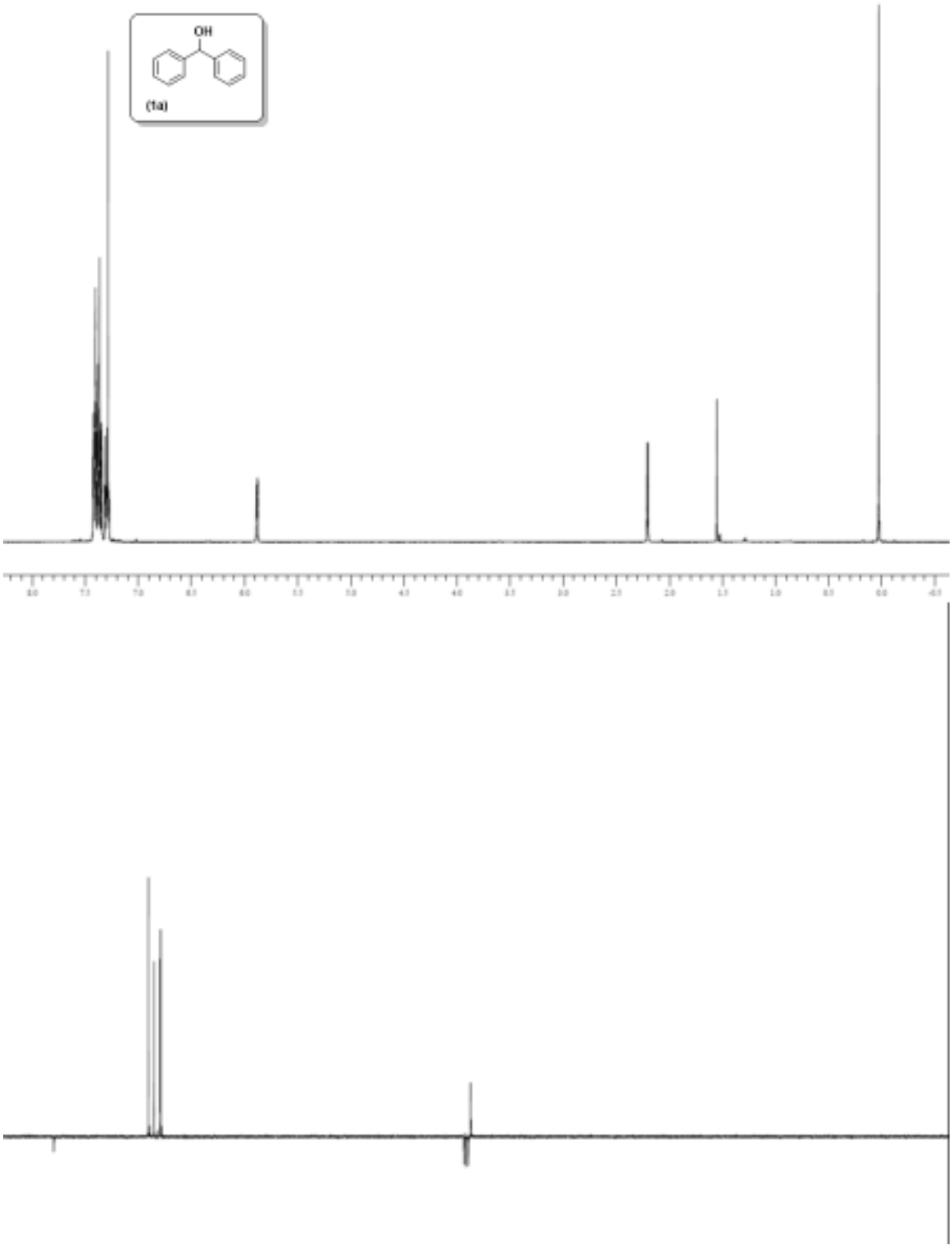
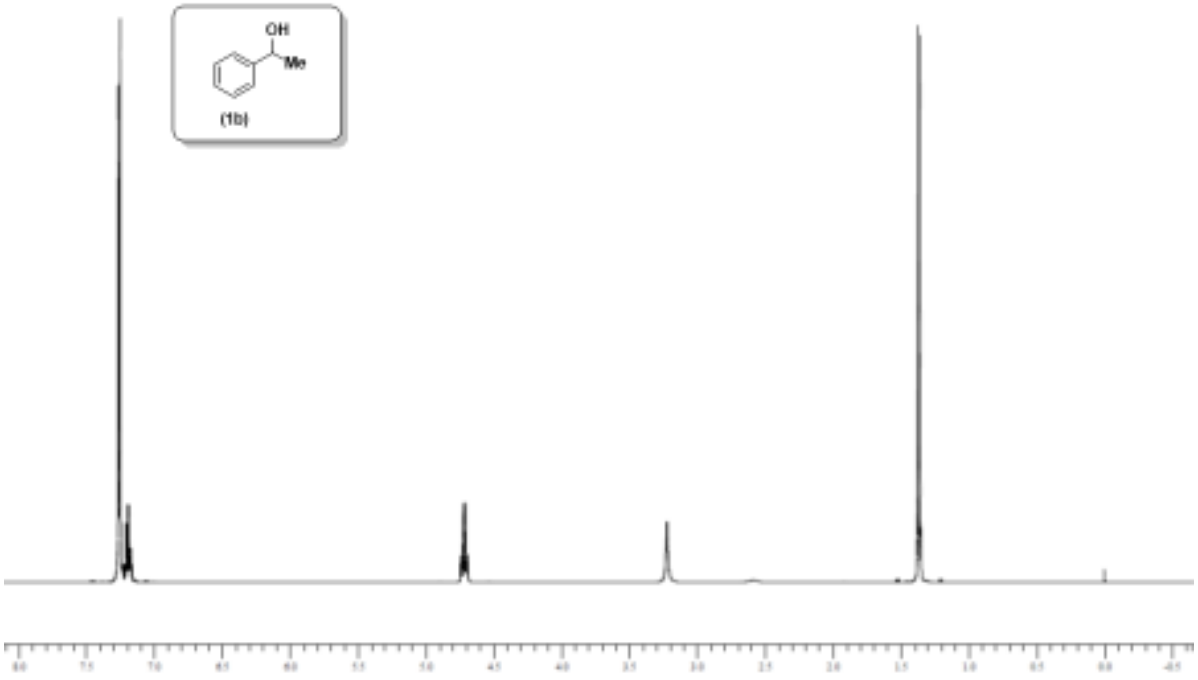
Appendix A – NMR Spectra

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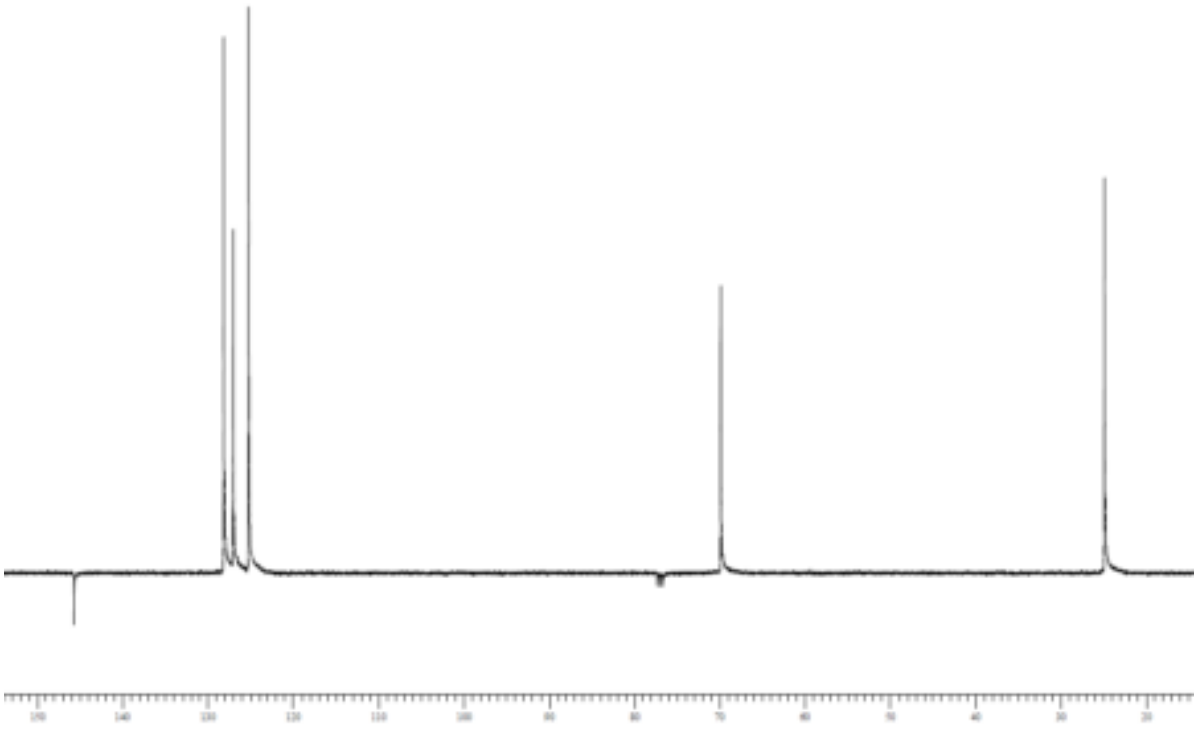

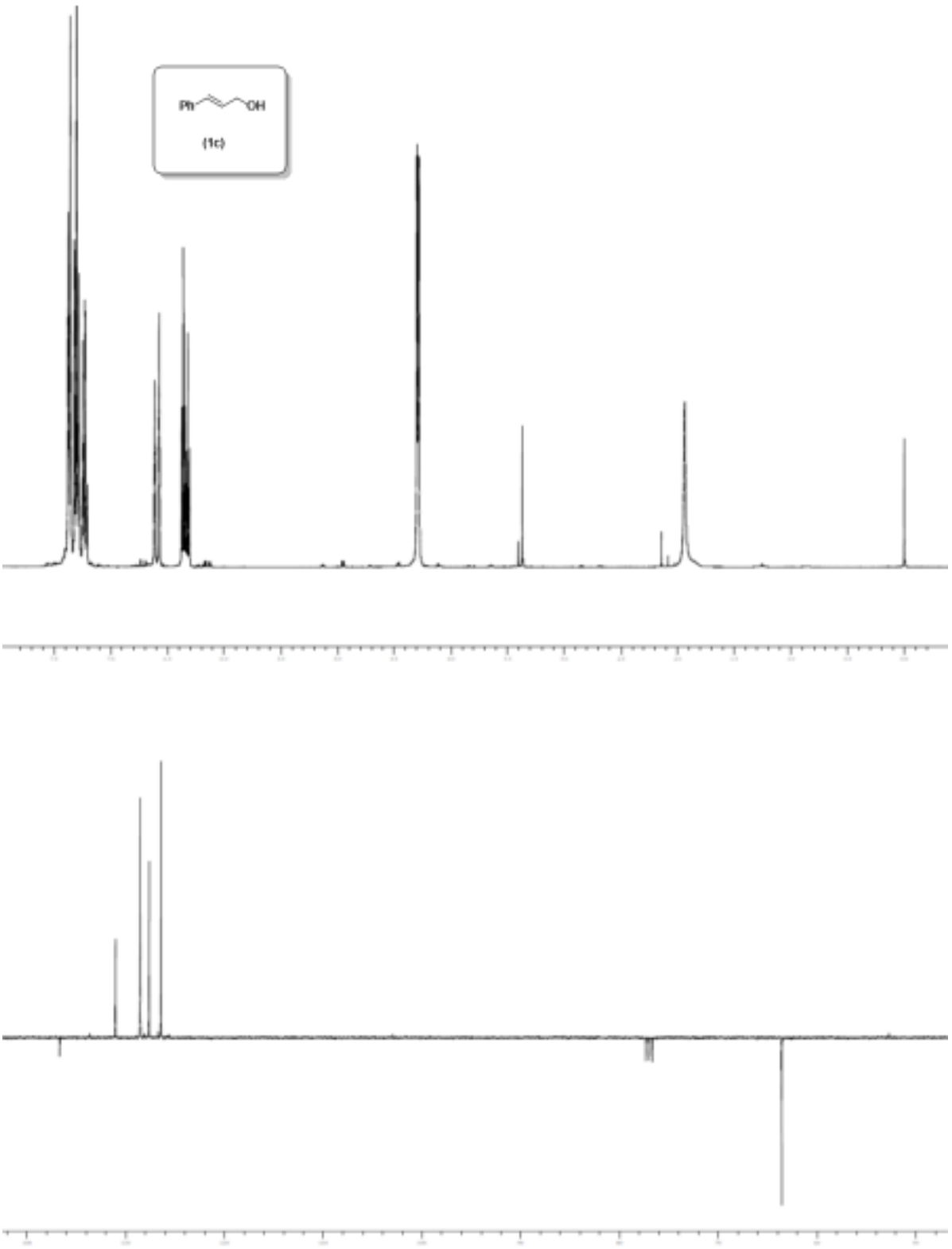
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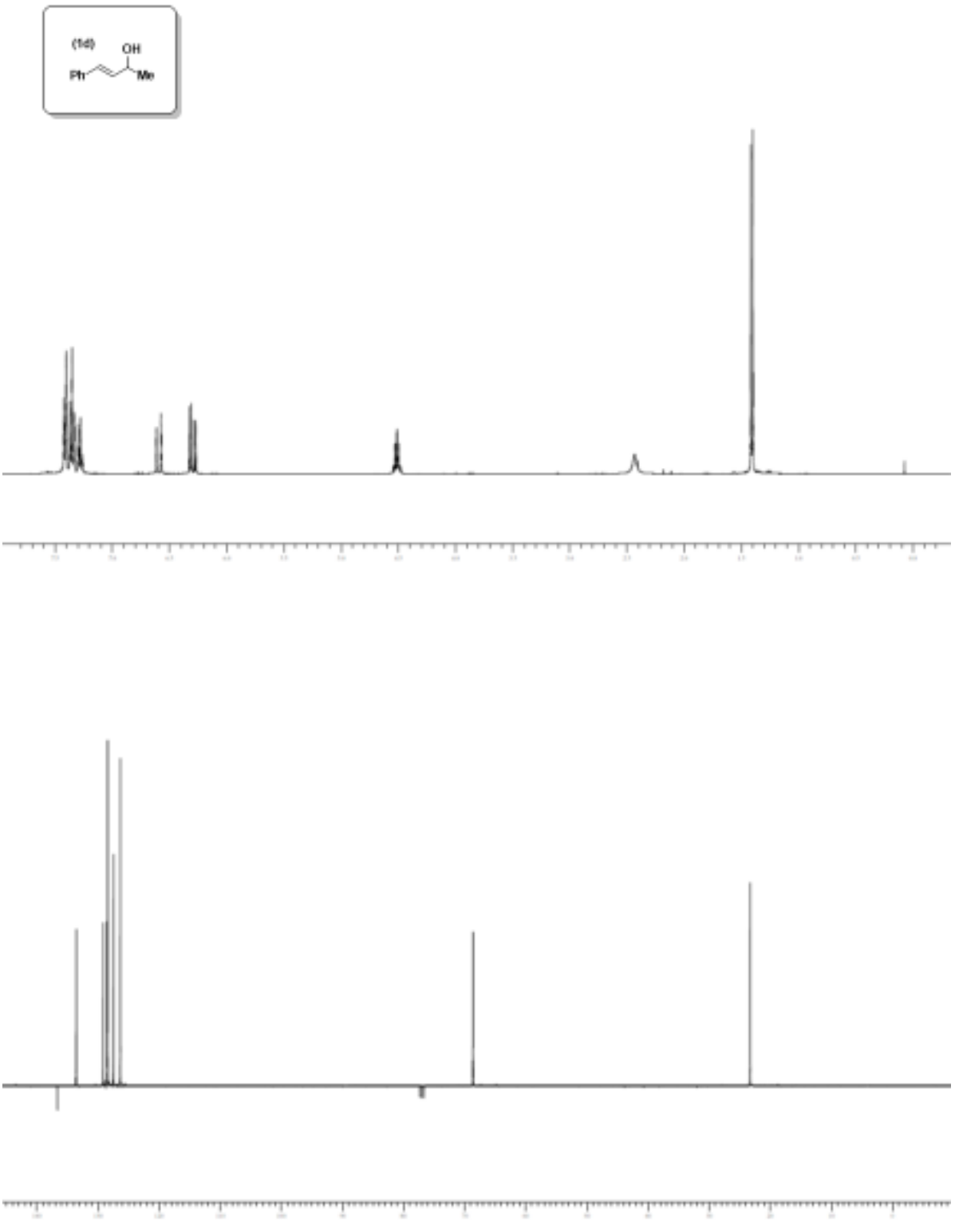
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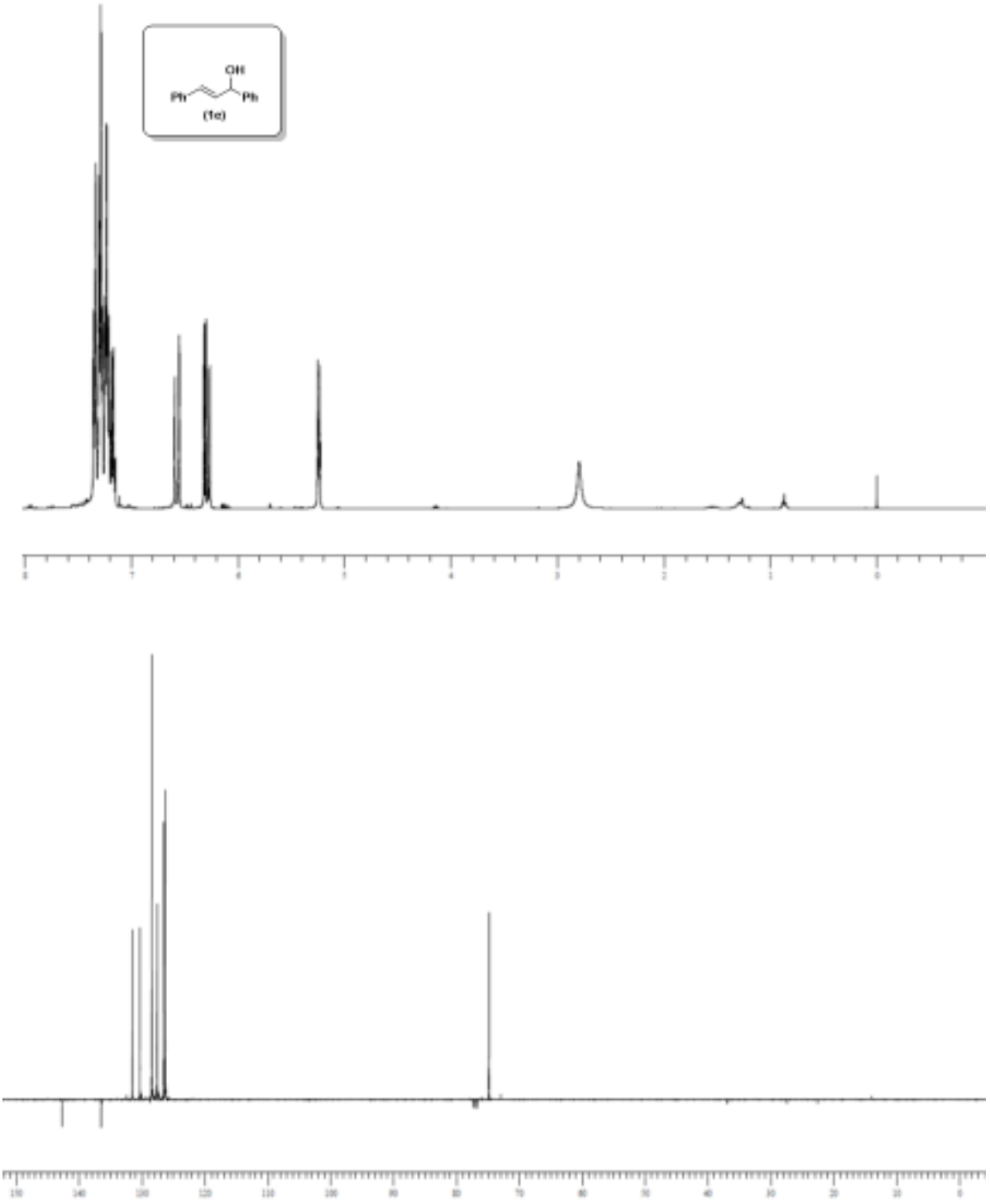
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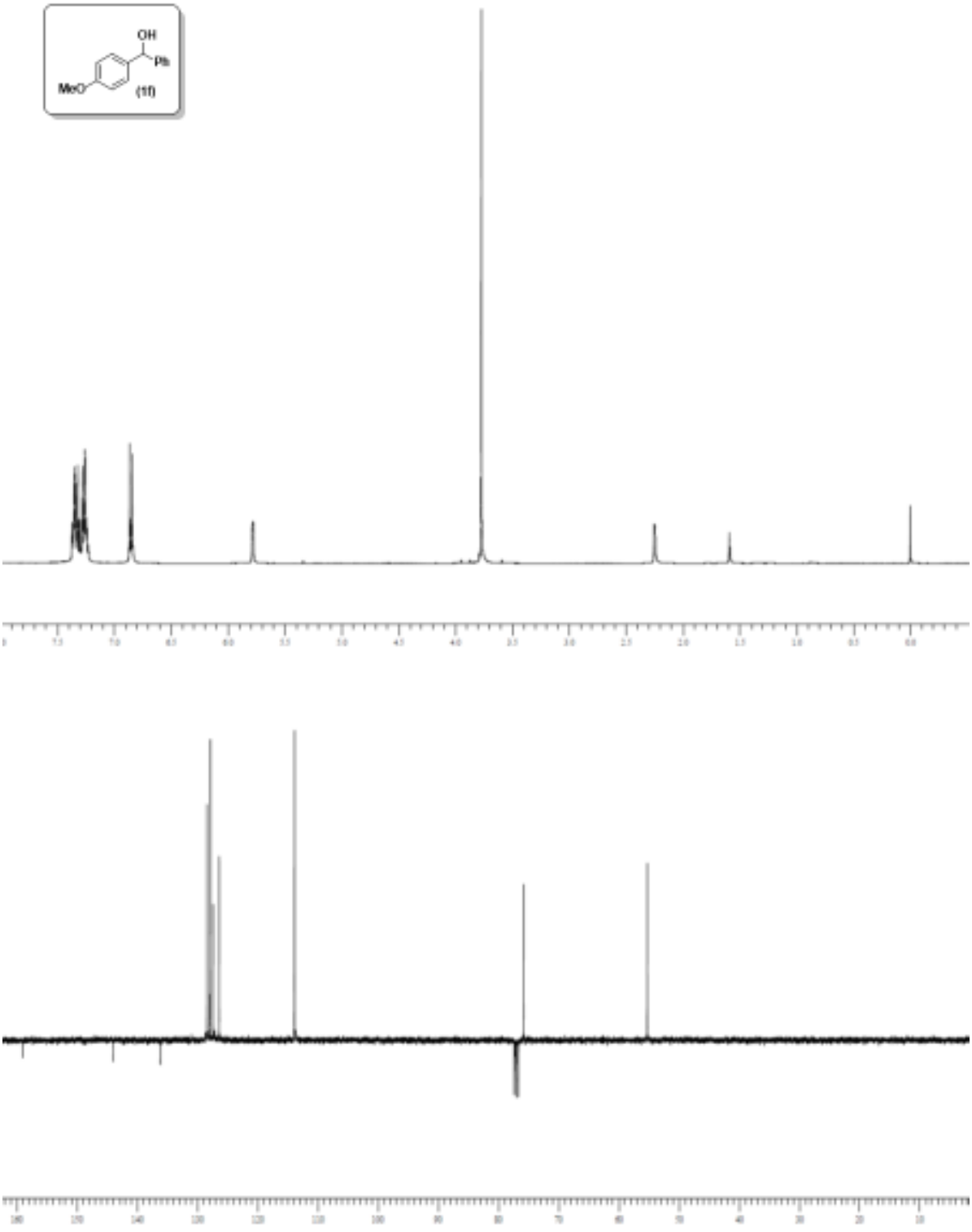
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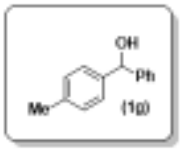
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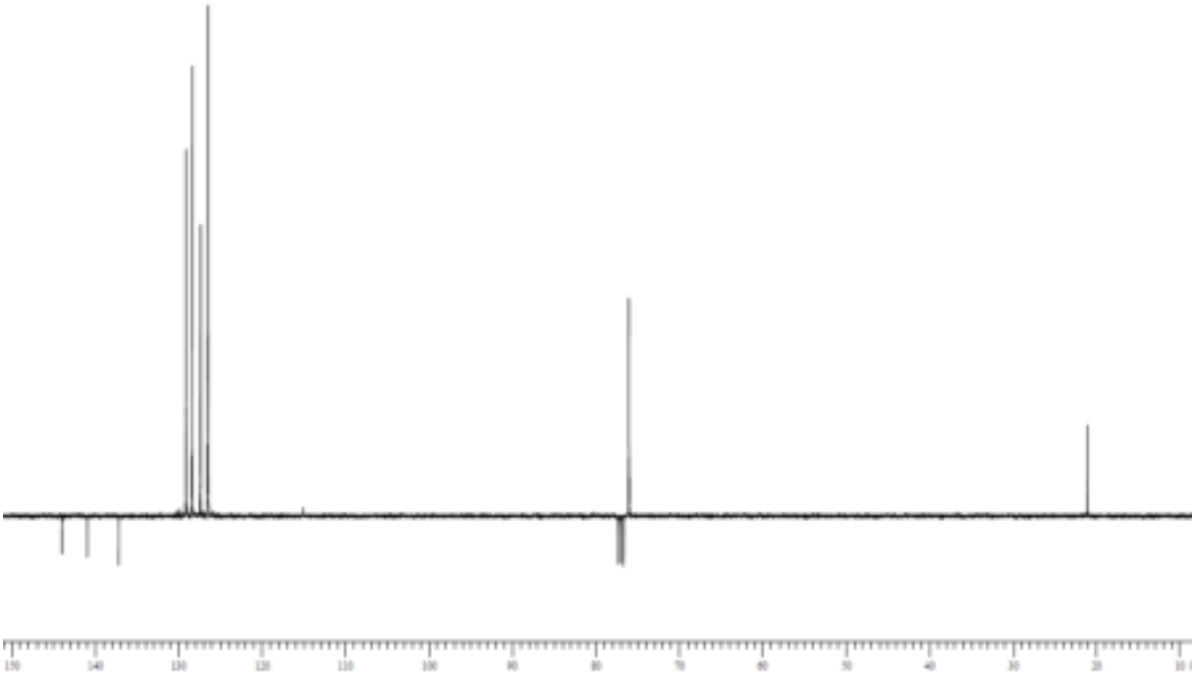

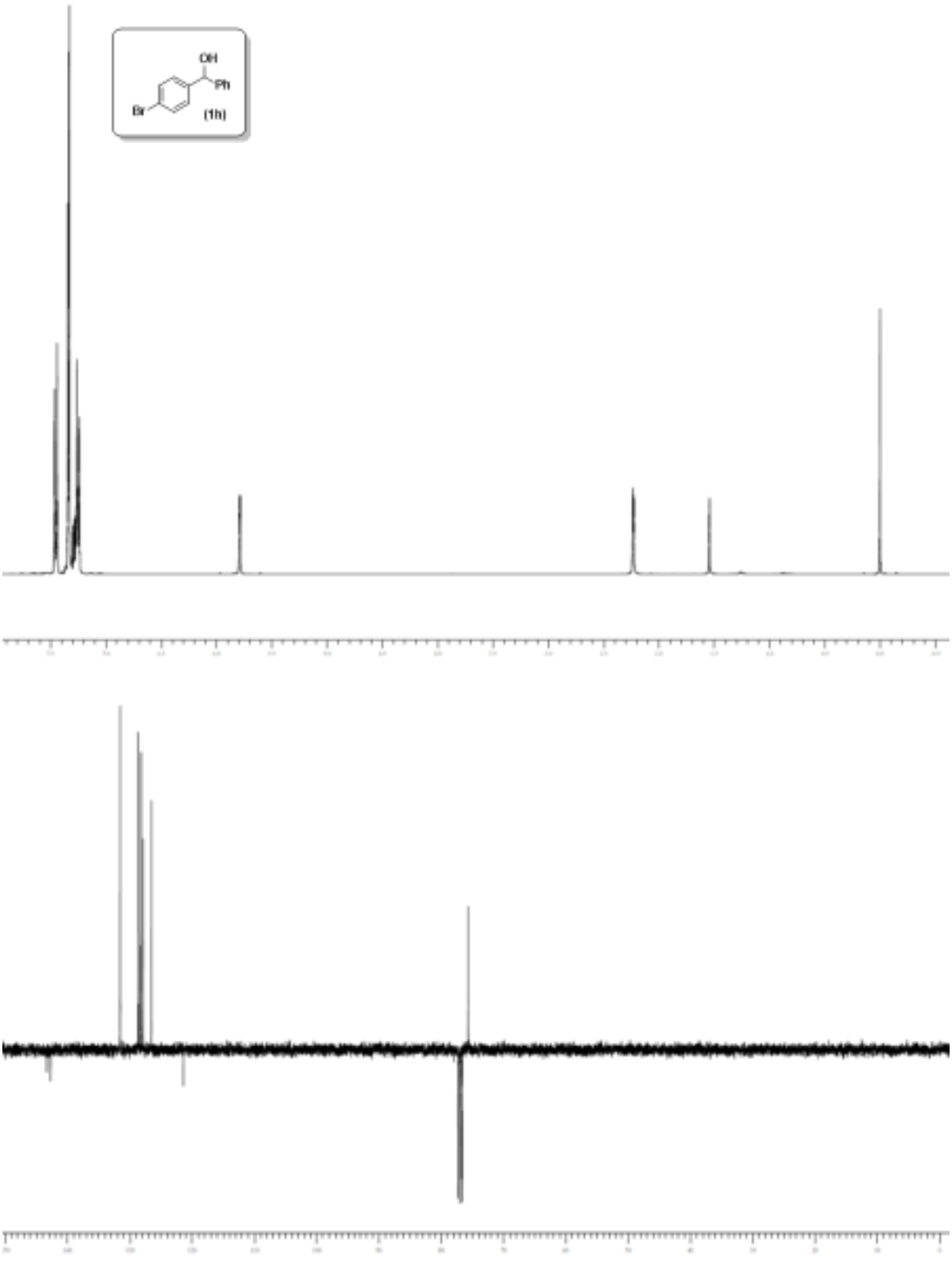
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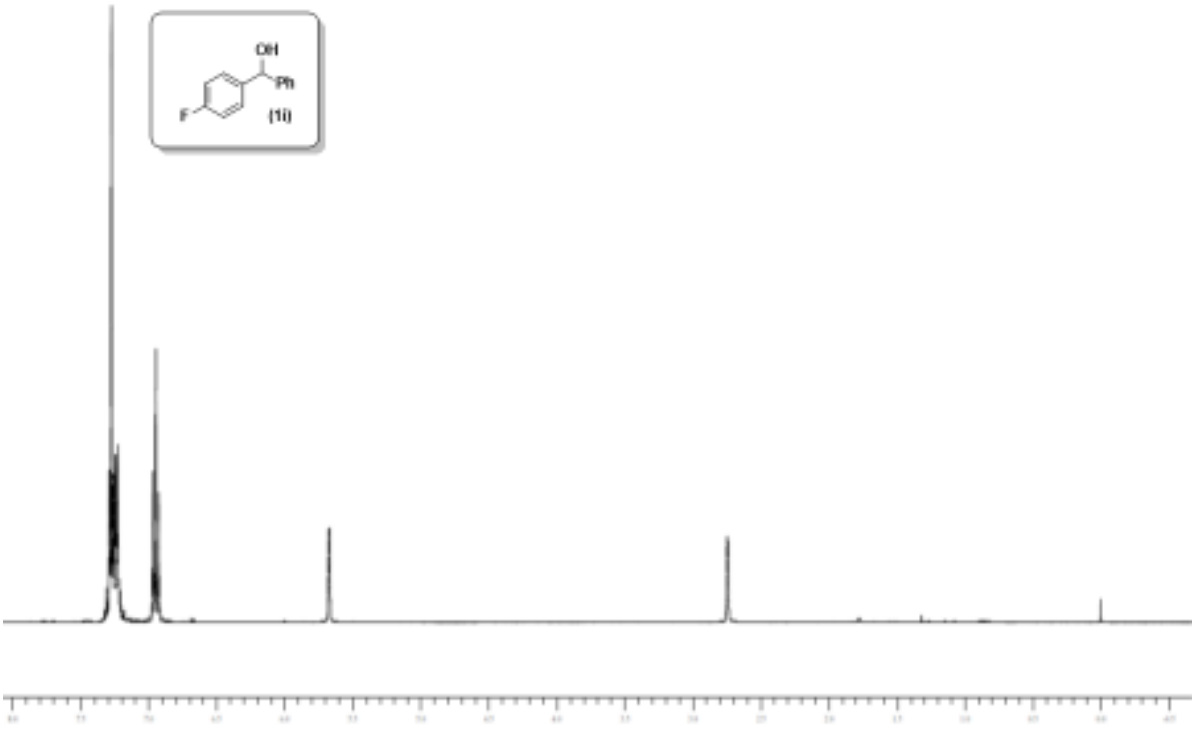
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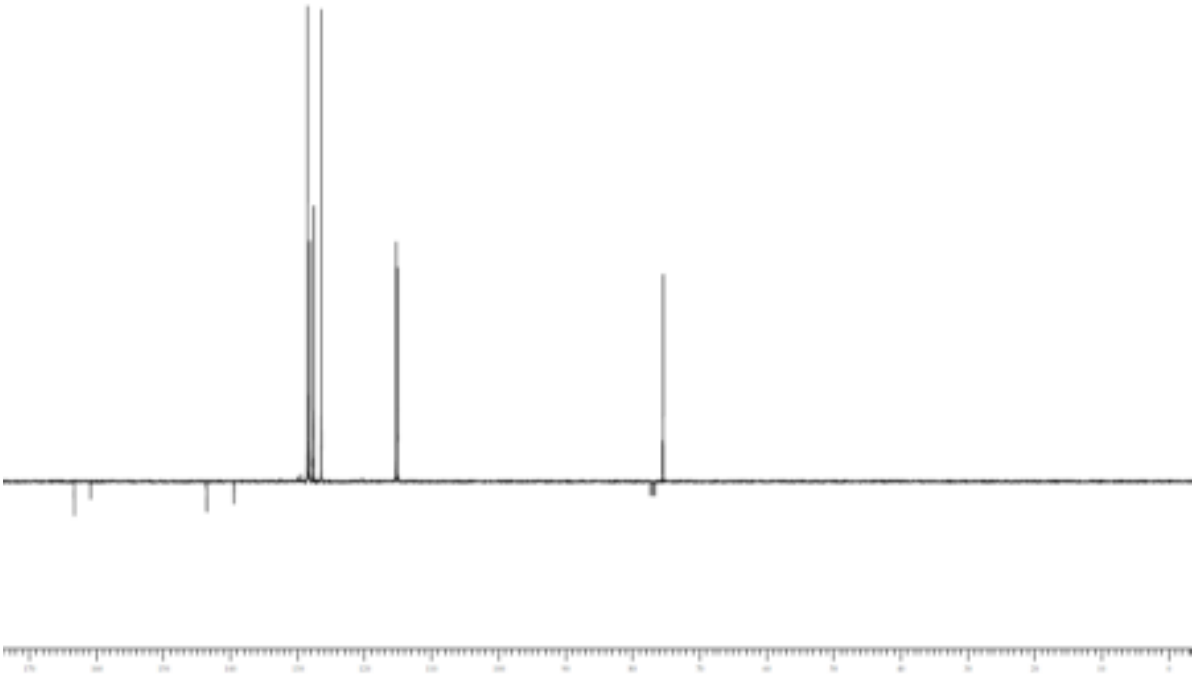

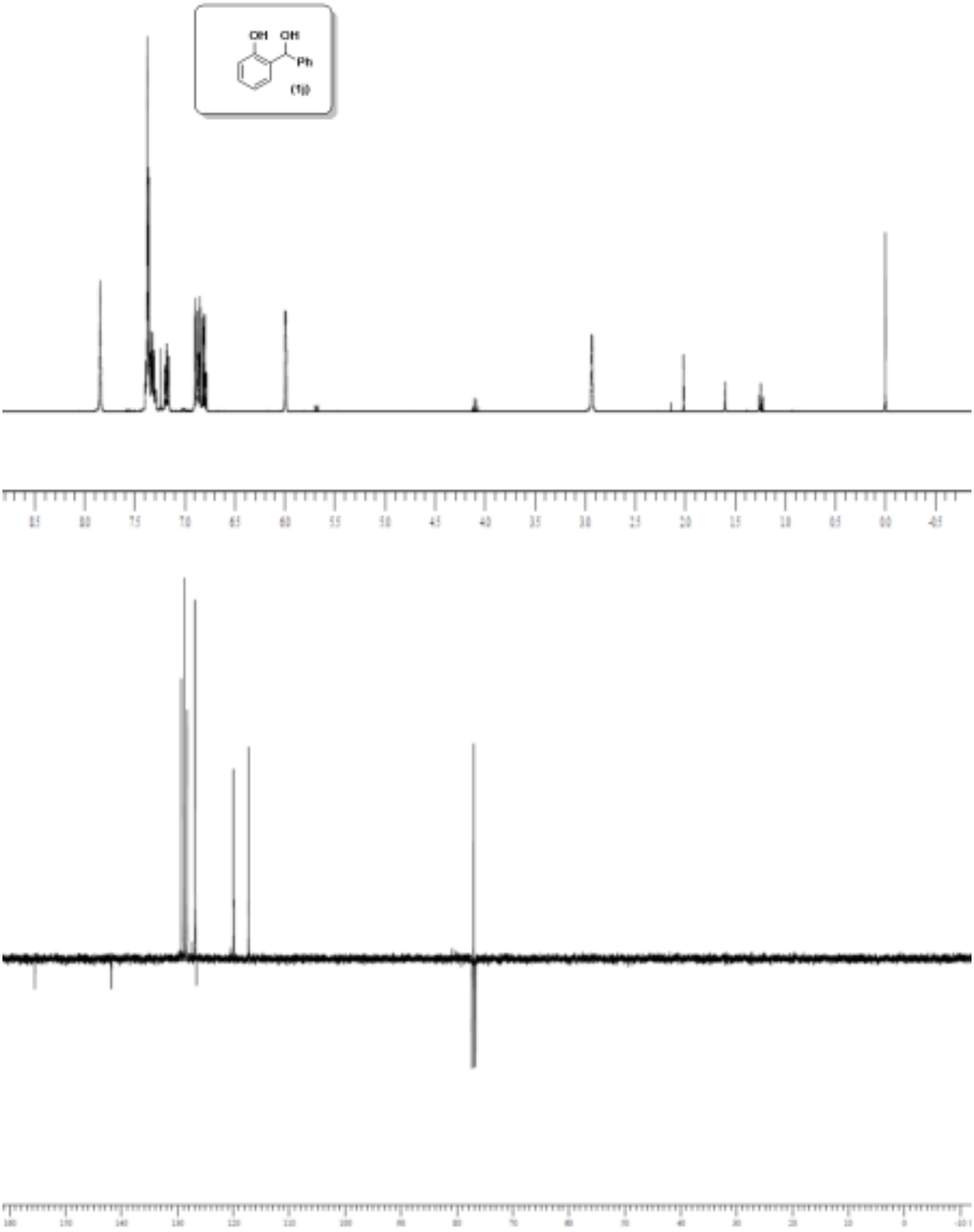
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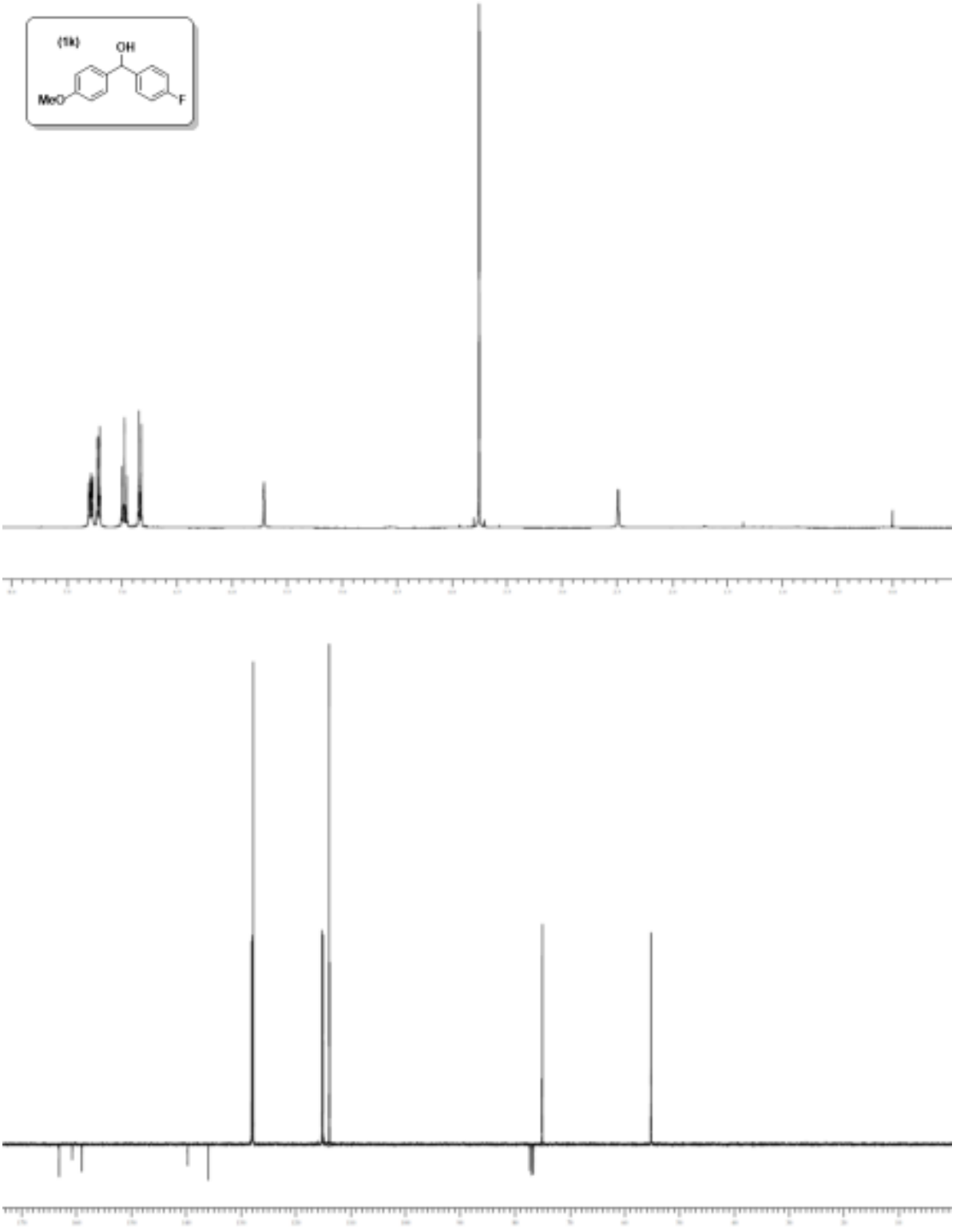
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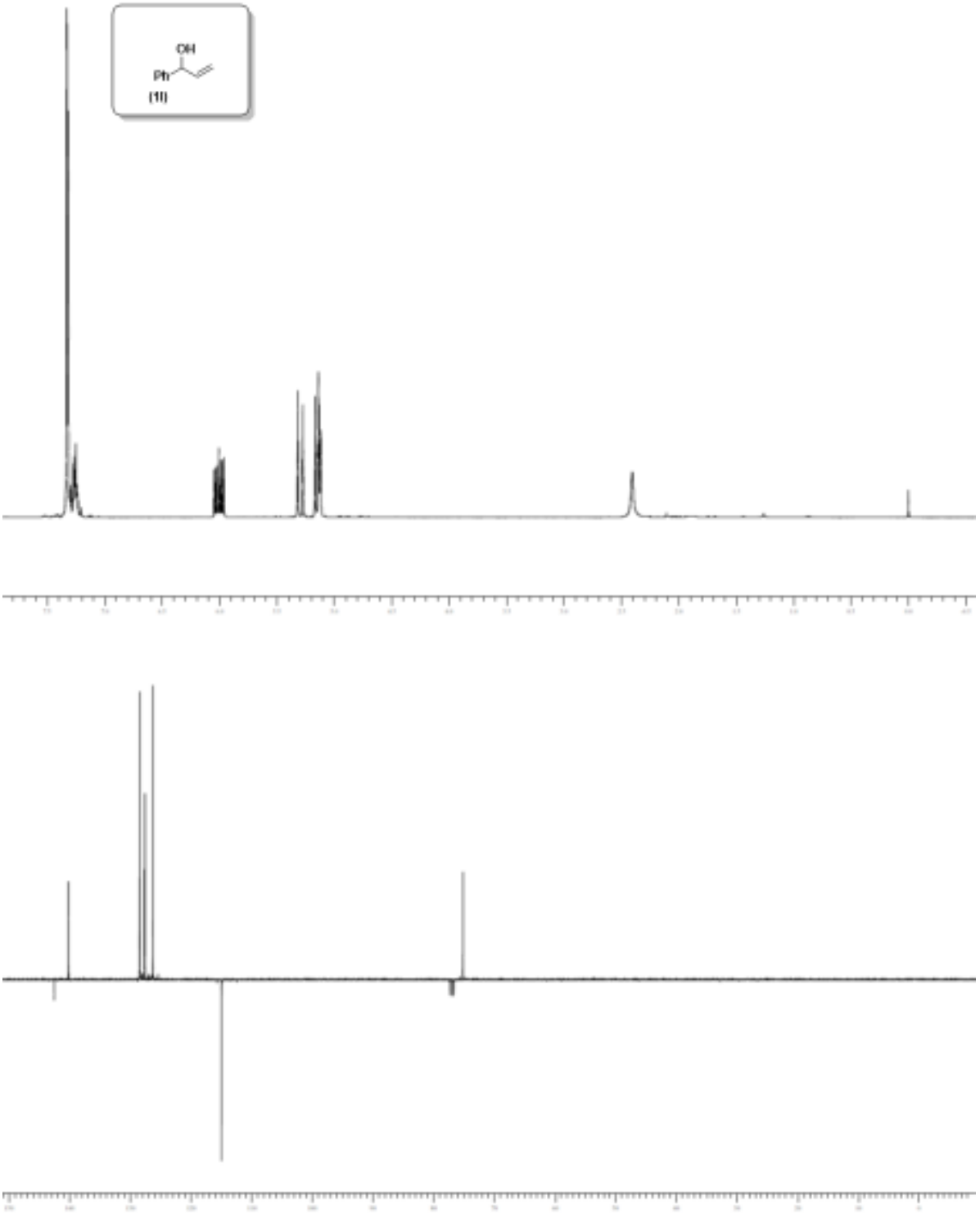
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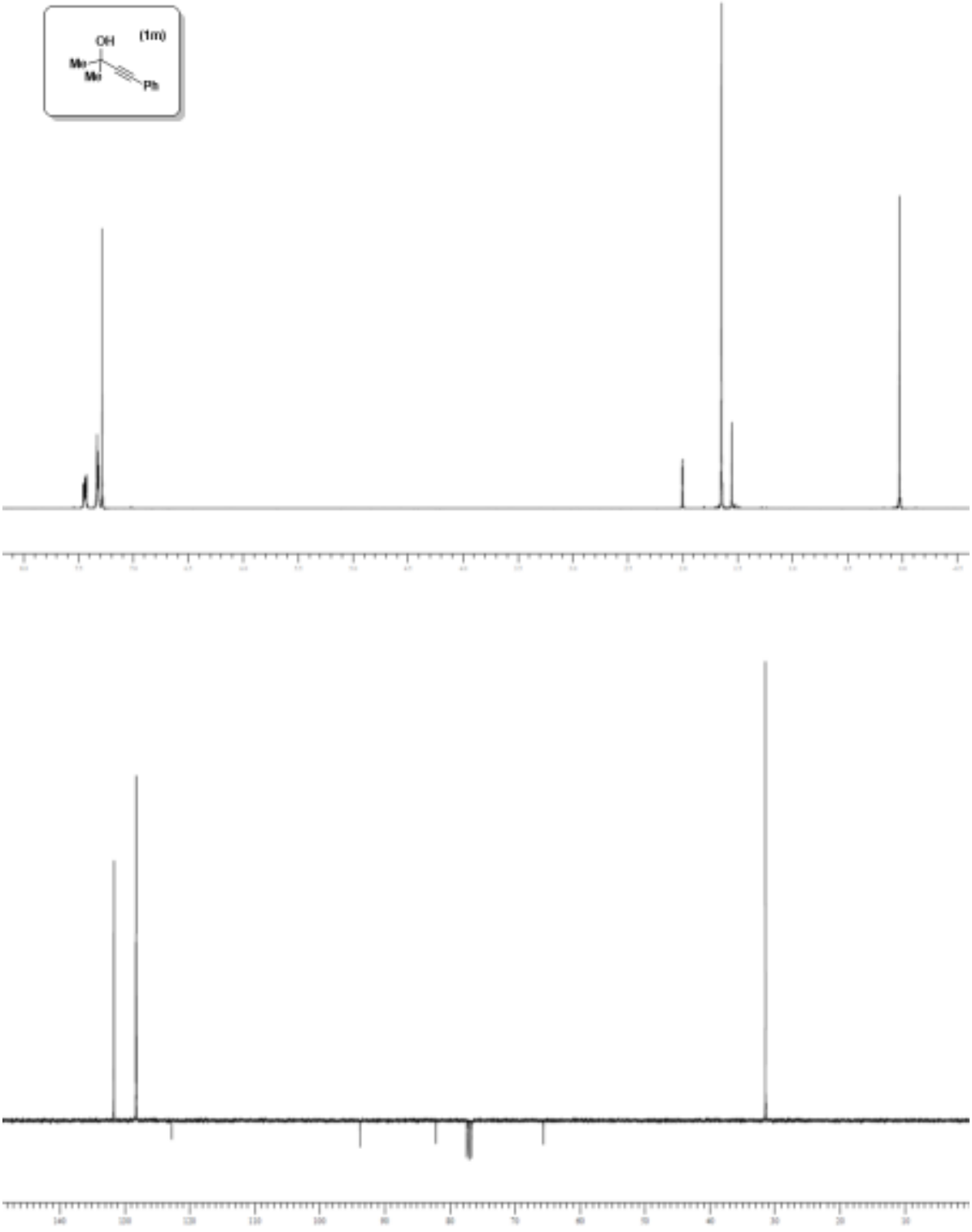
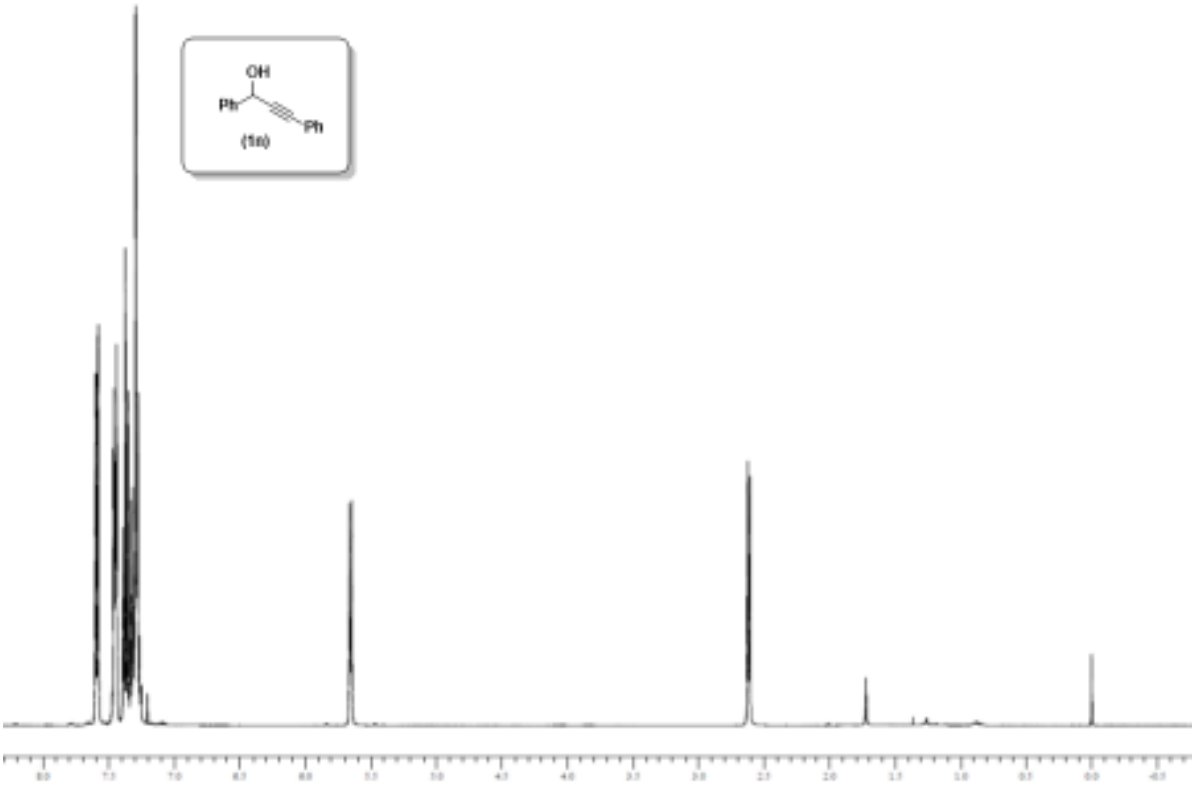
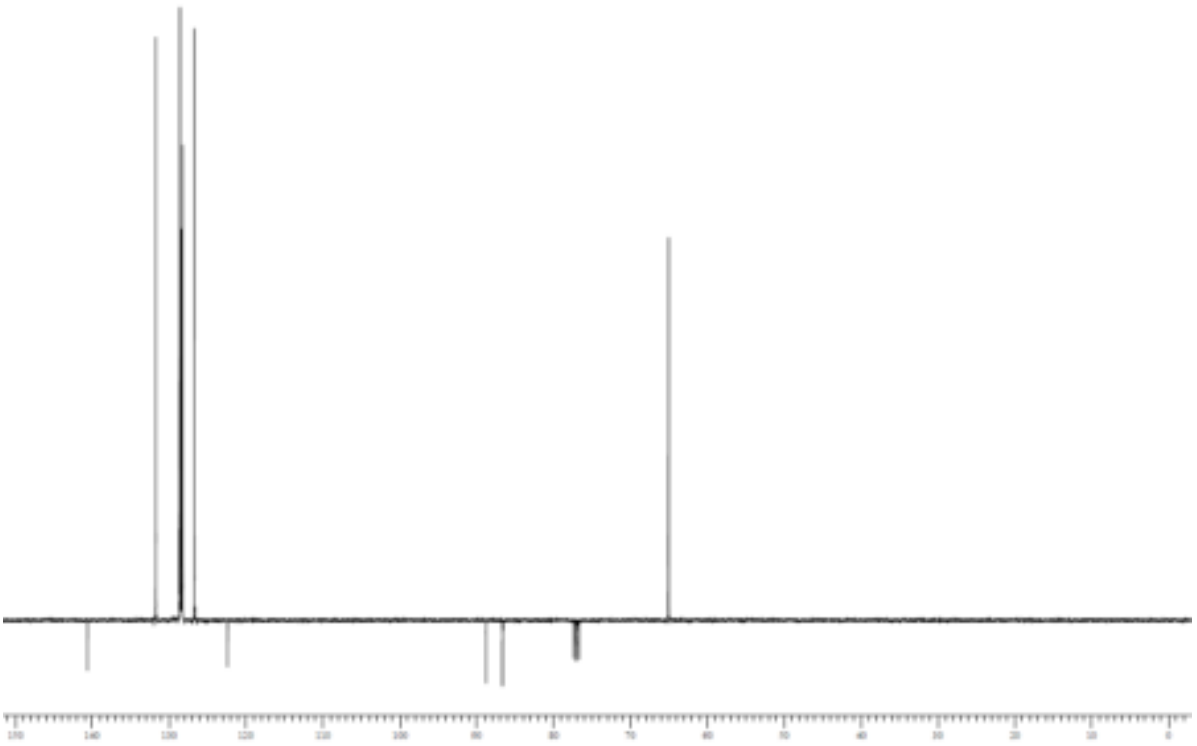
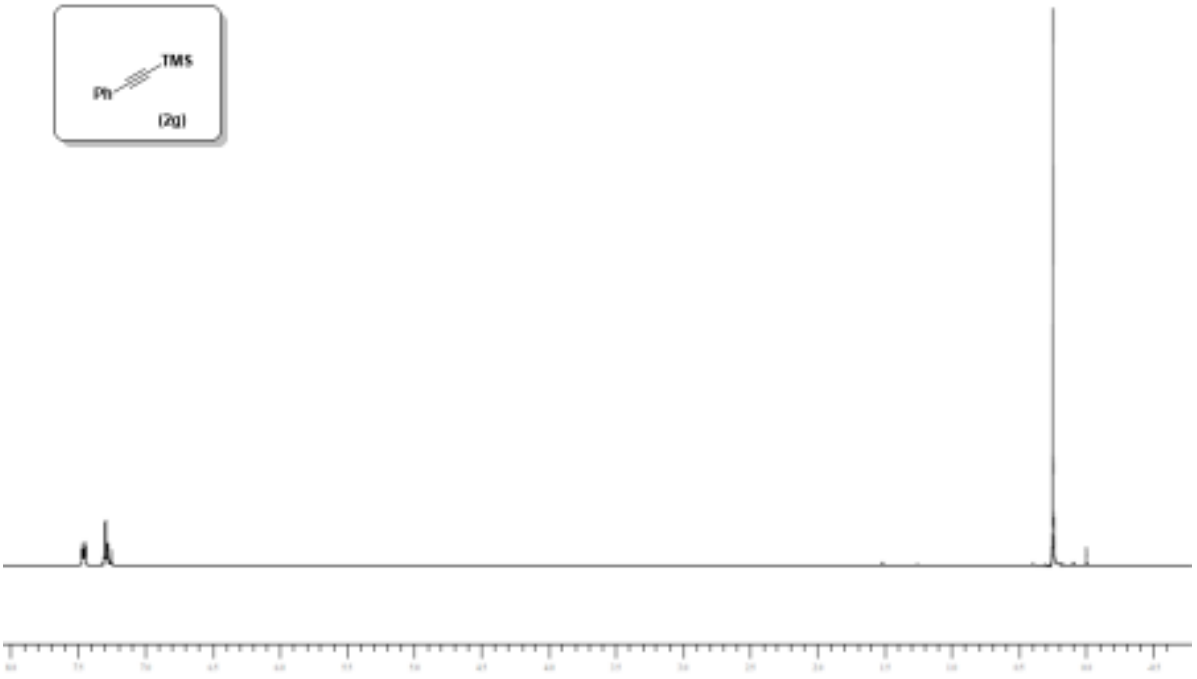
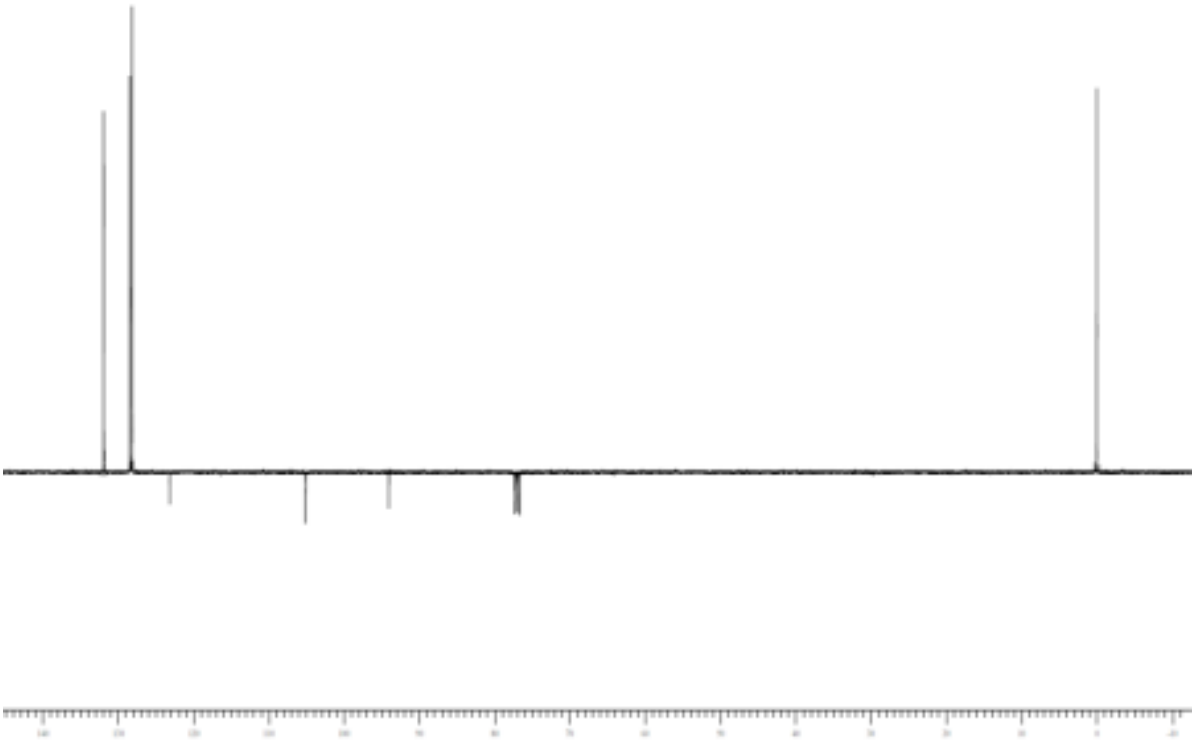
Ph
(1l)

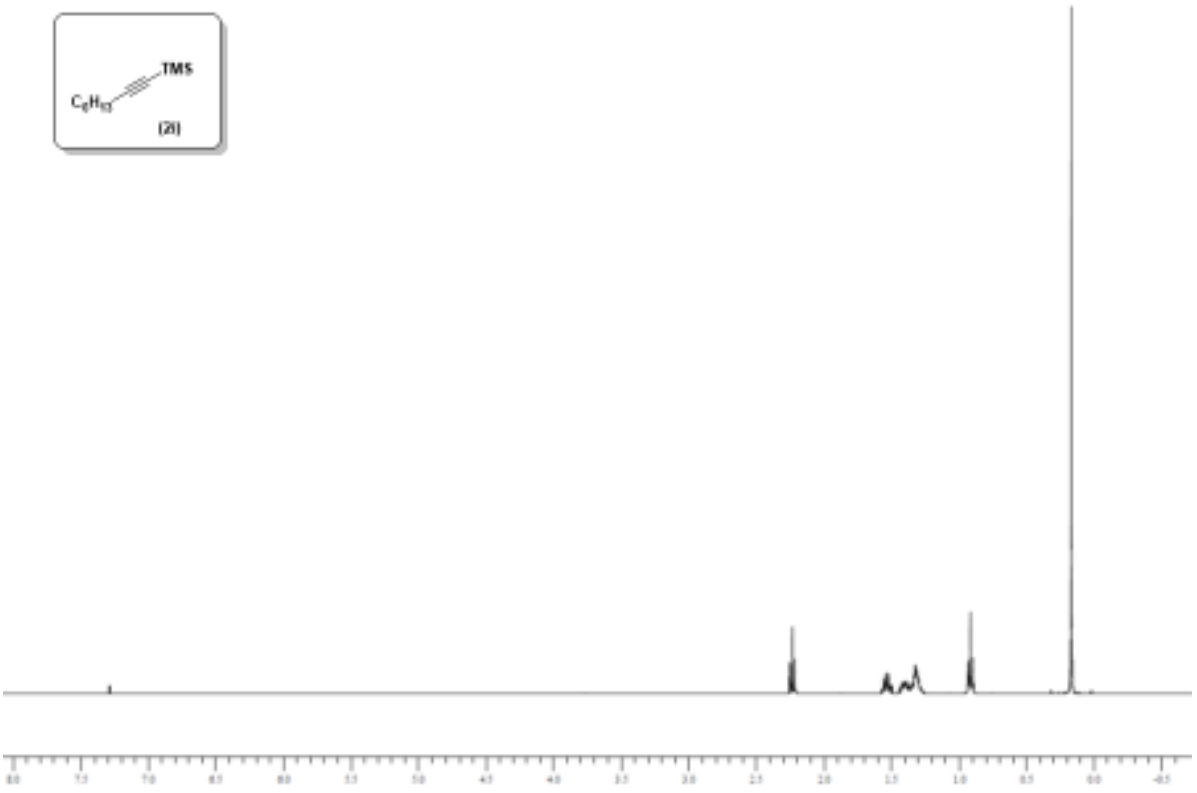

(1m)
OH
Me
Me
Ph

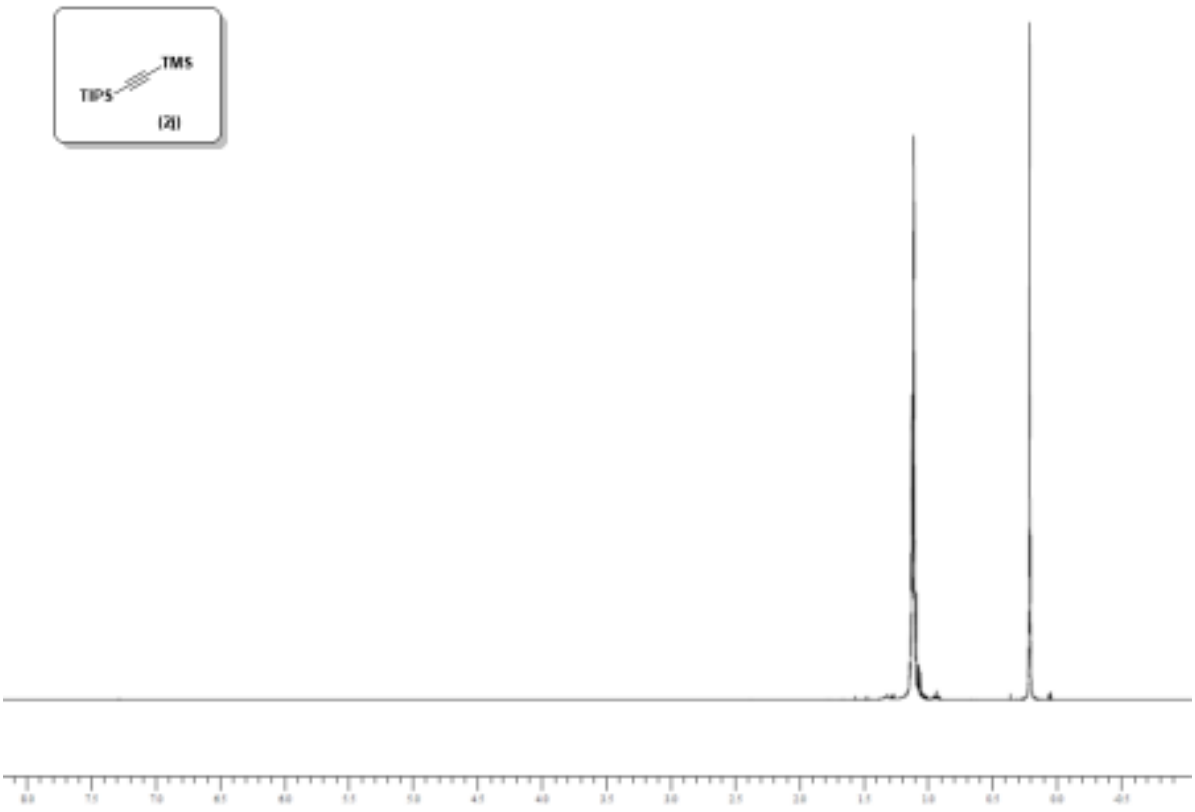

OH
Ph
Ph
(1n)

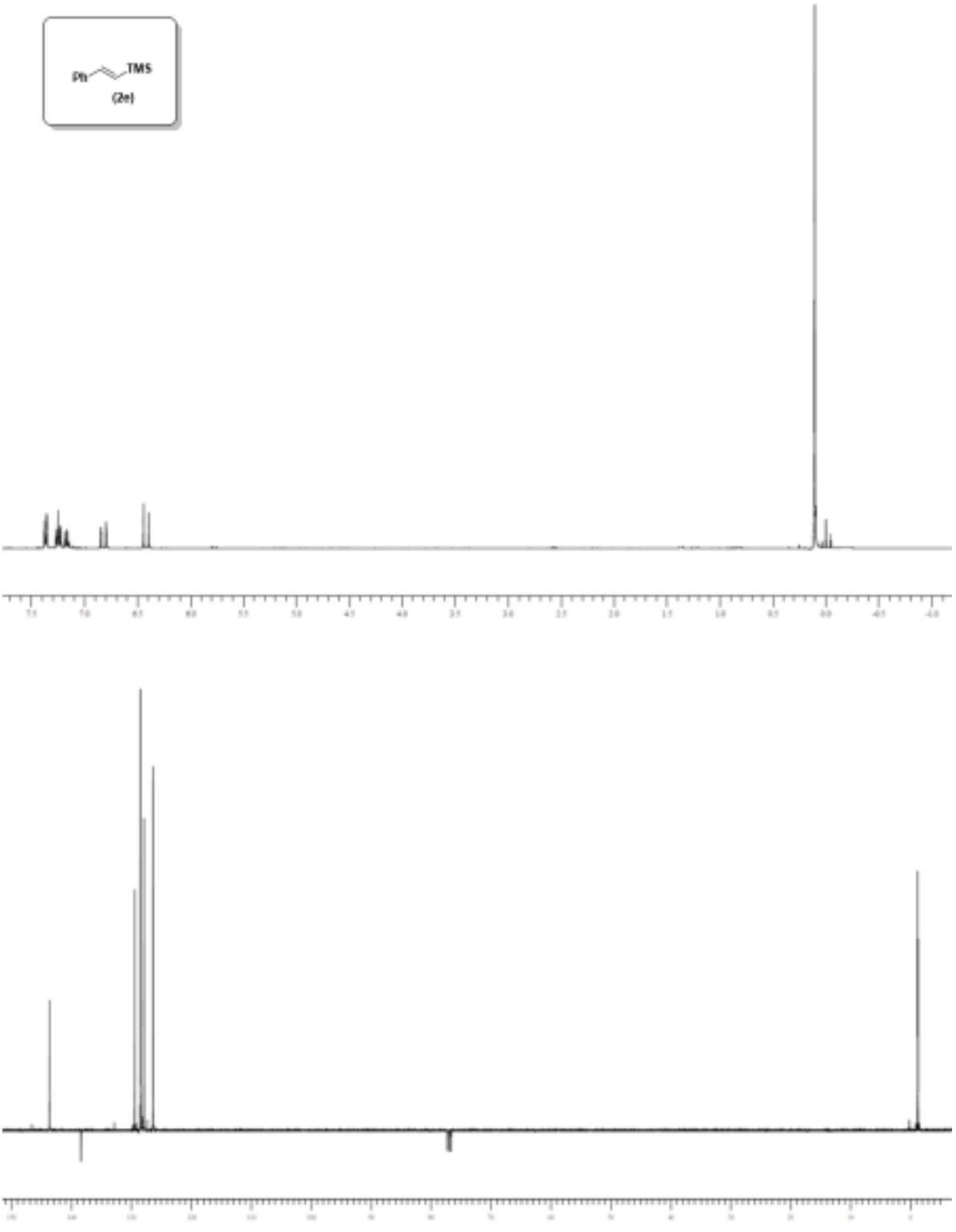


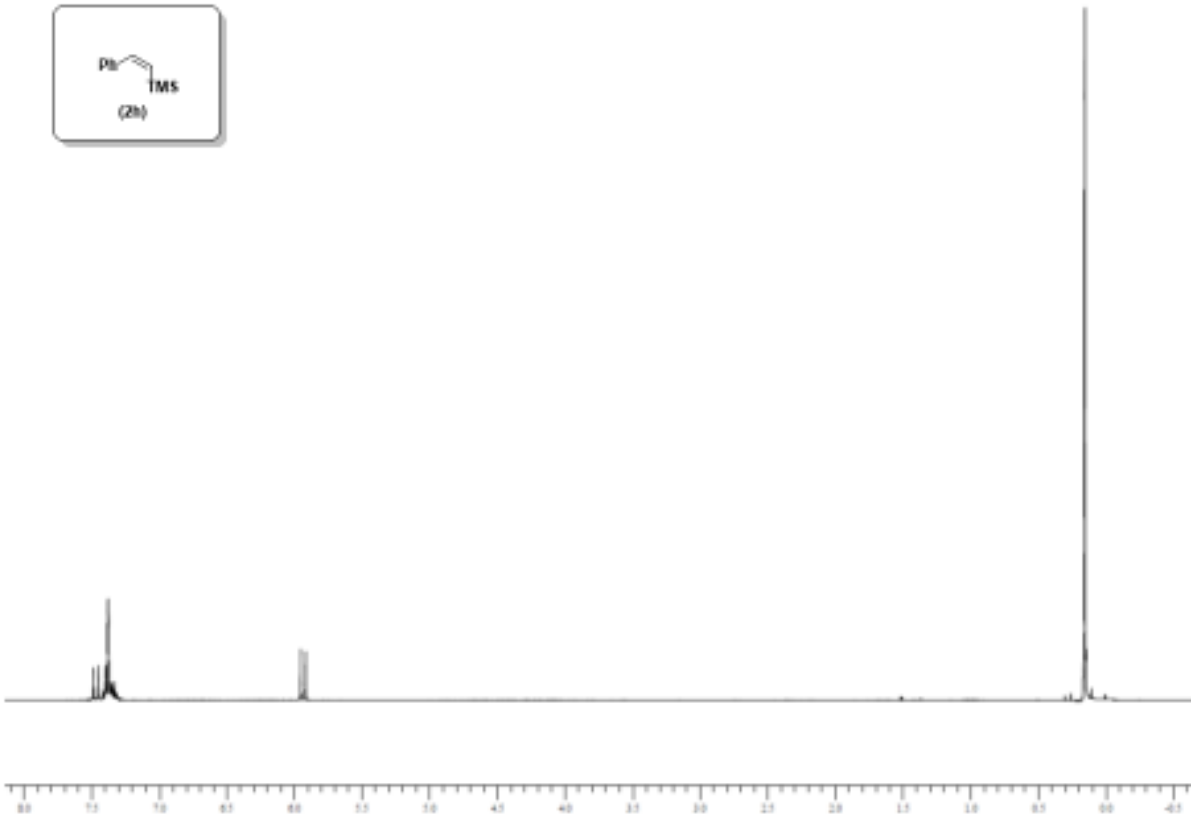

TMS
Ph
(2g)




TMS
C_6H_{13}
(2i)


TMS
TIPS
(2)


Ph
TMS
(2e)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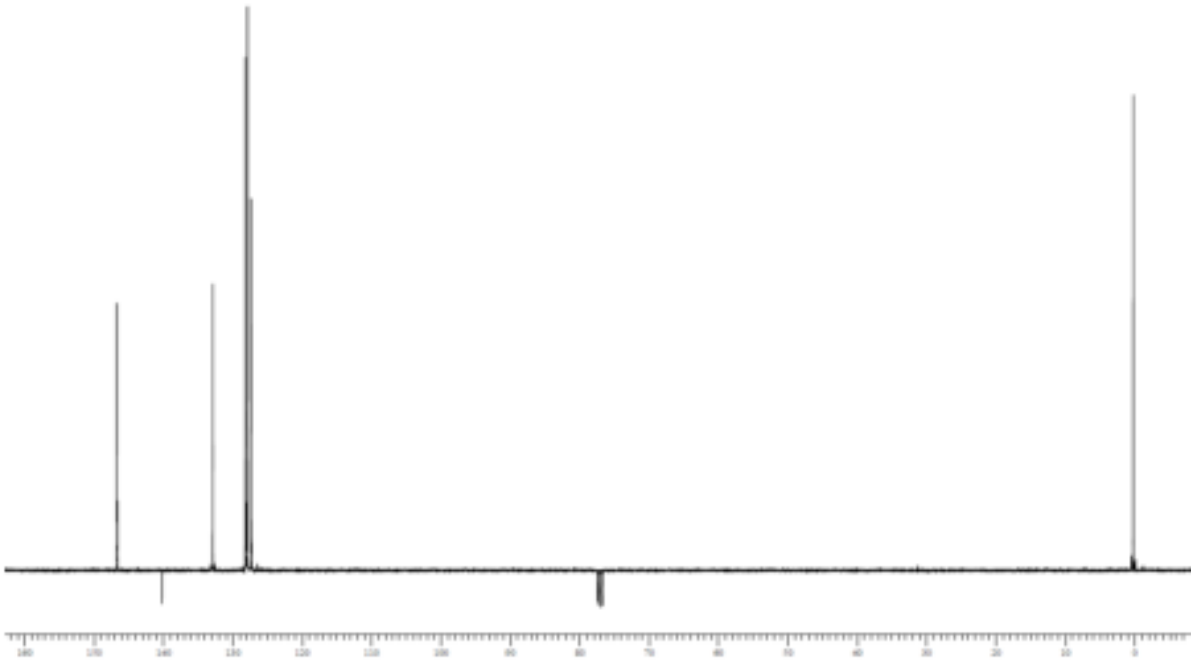
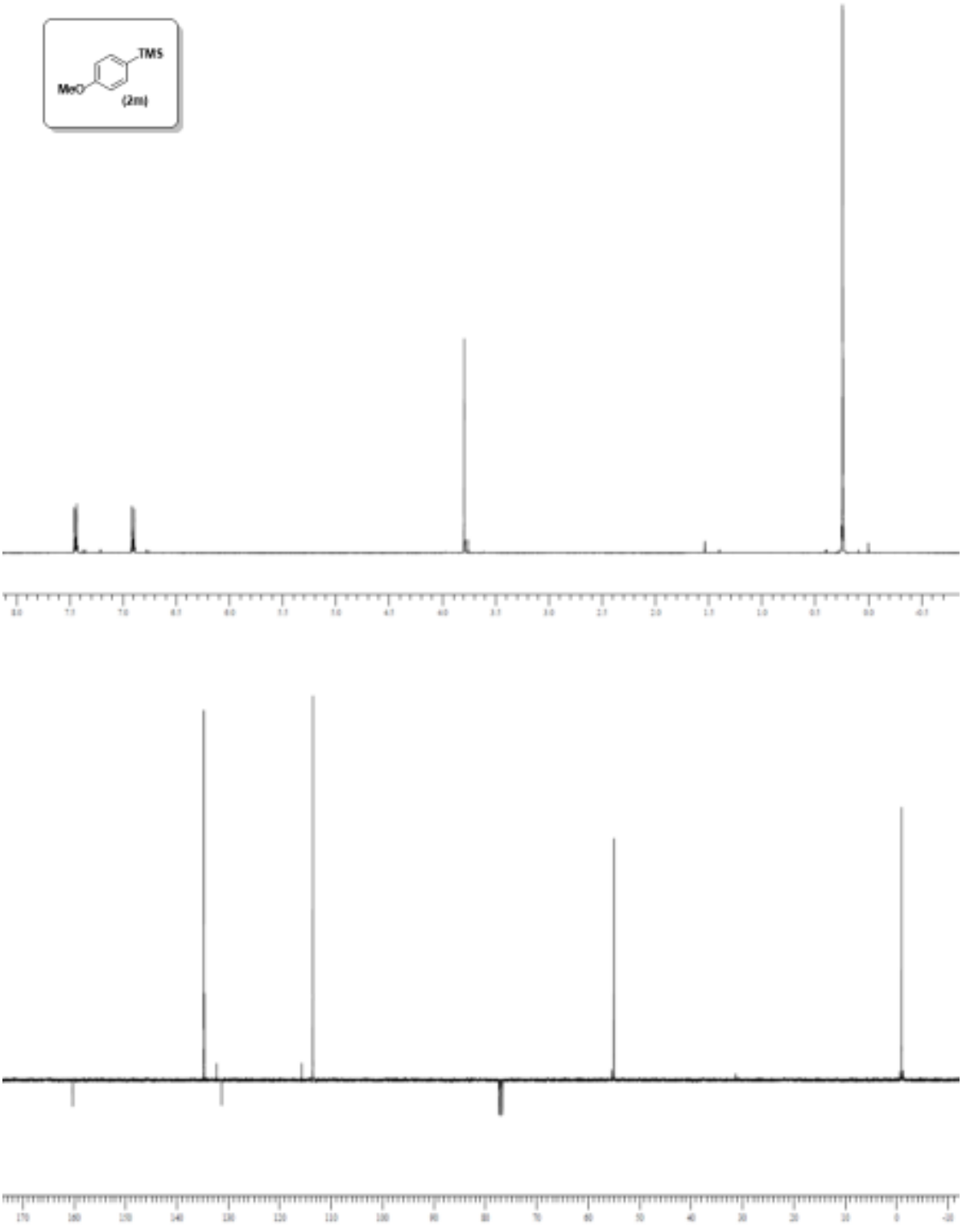
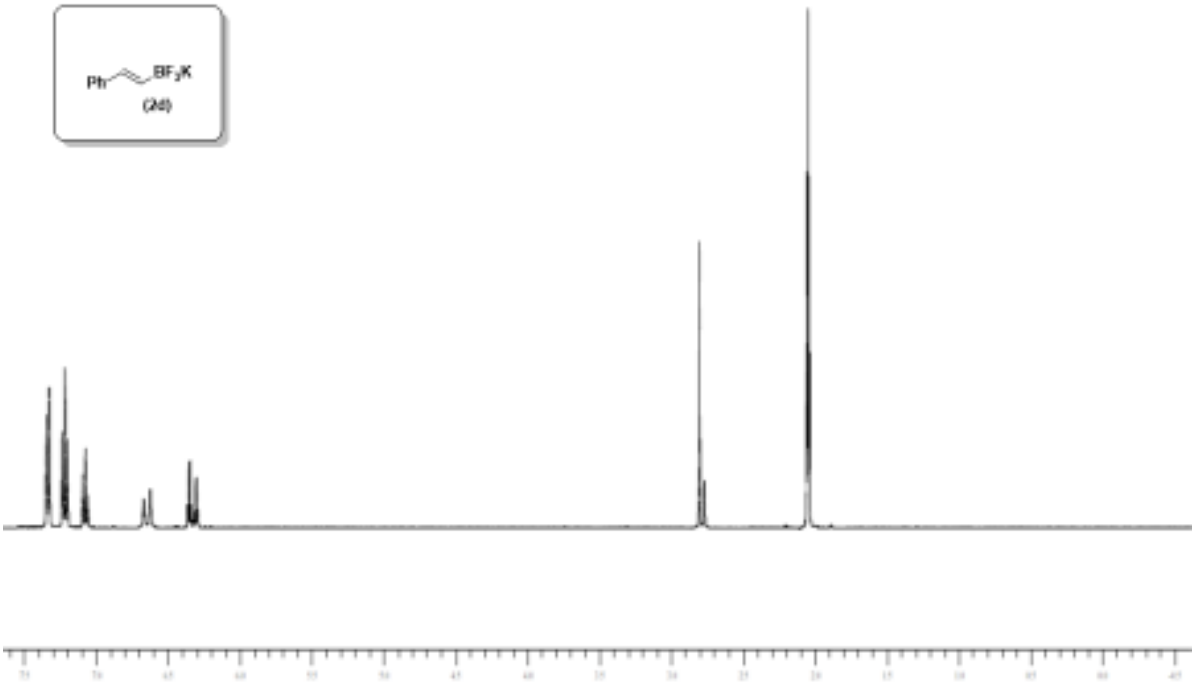
TMS
(2h)




TMS
MeO
(2m)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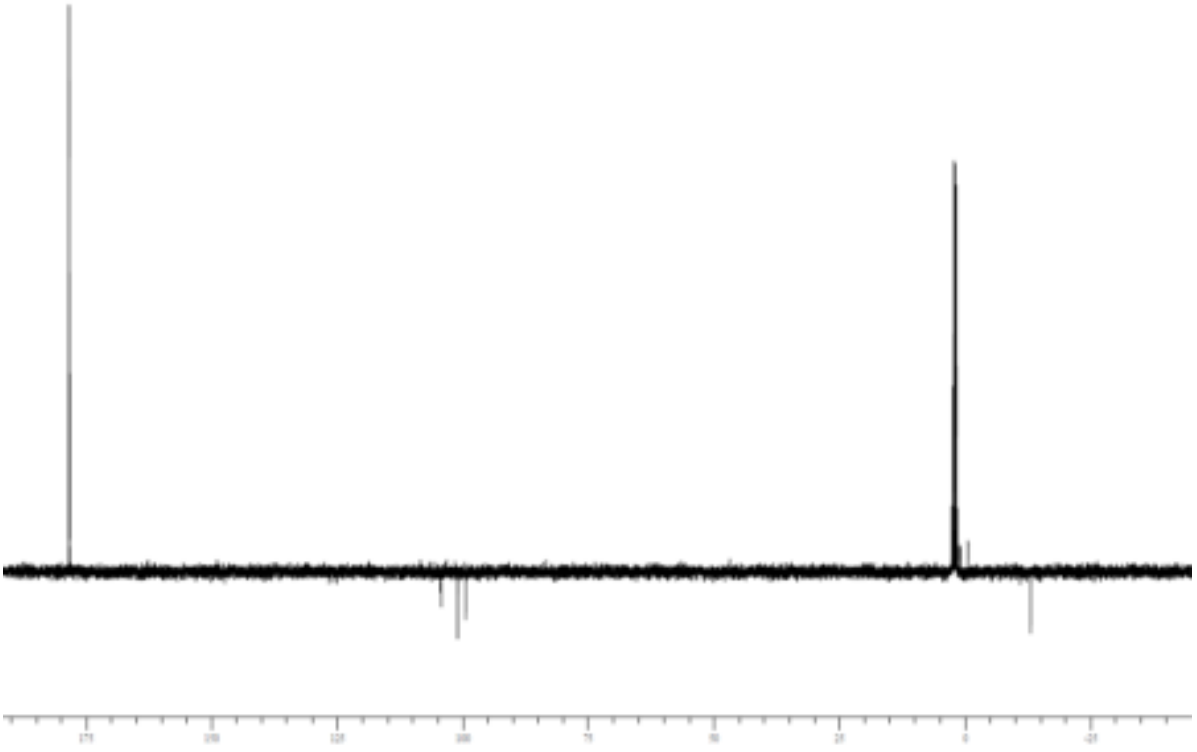
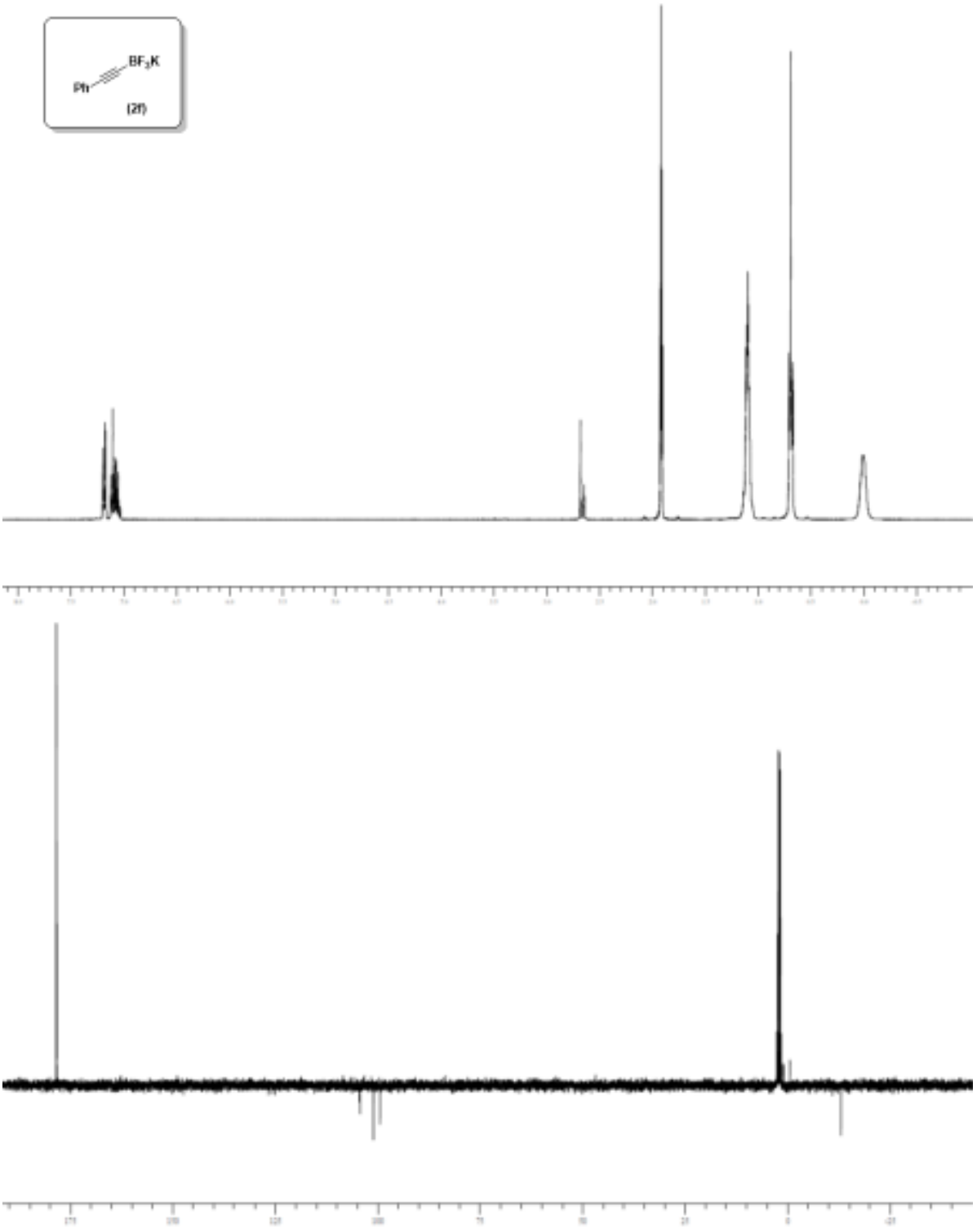
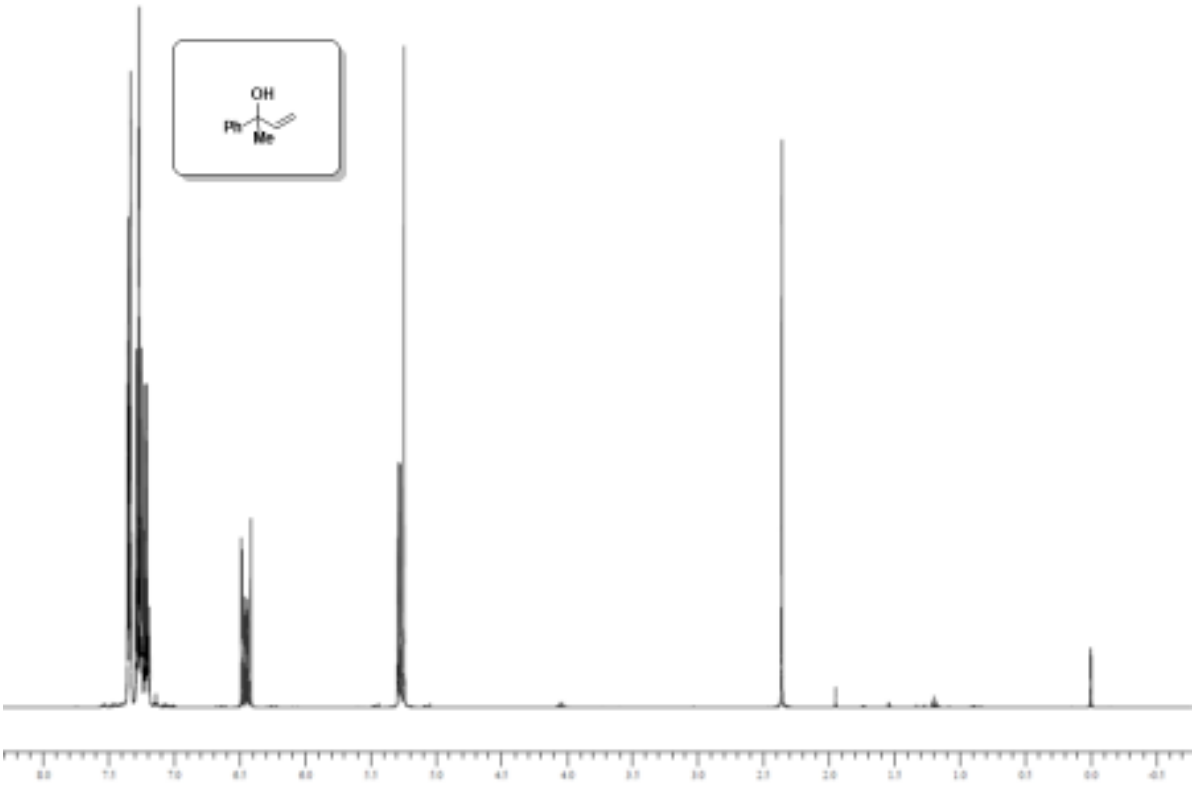
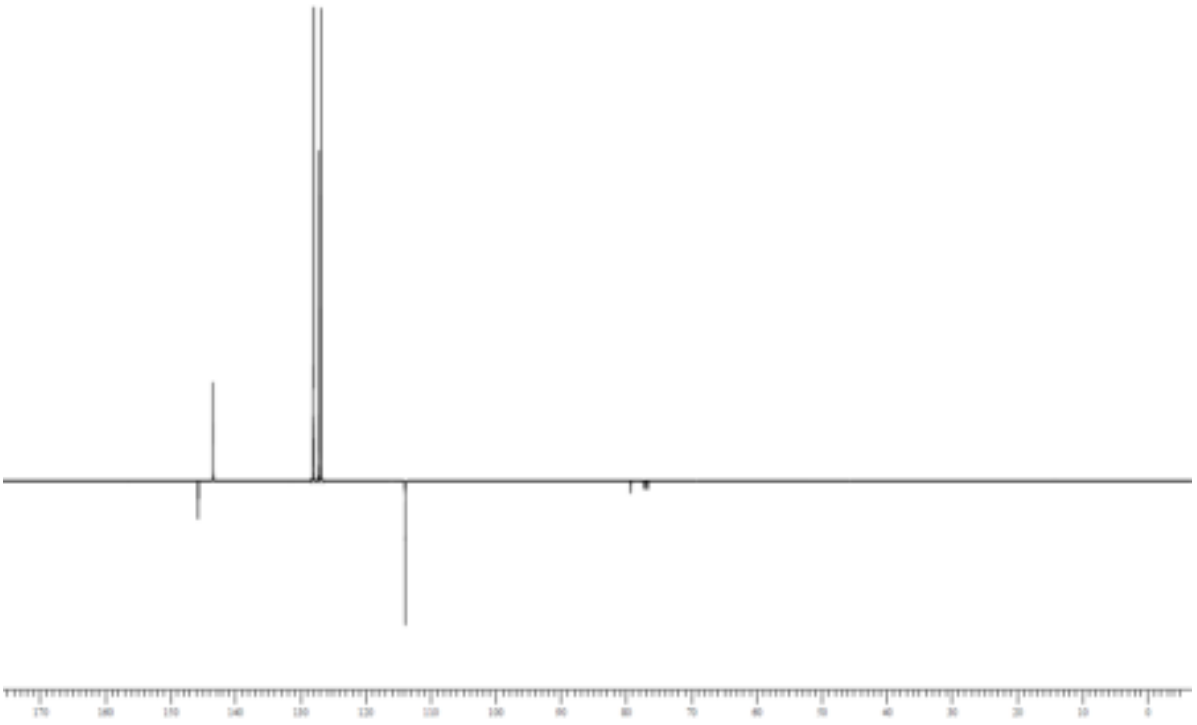
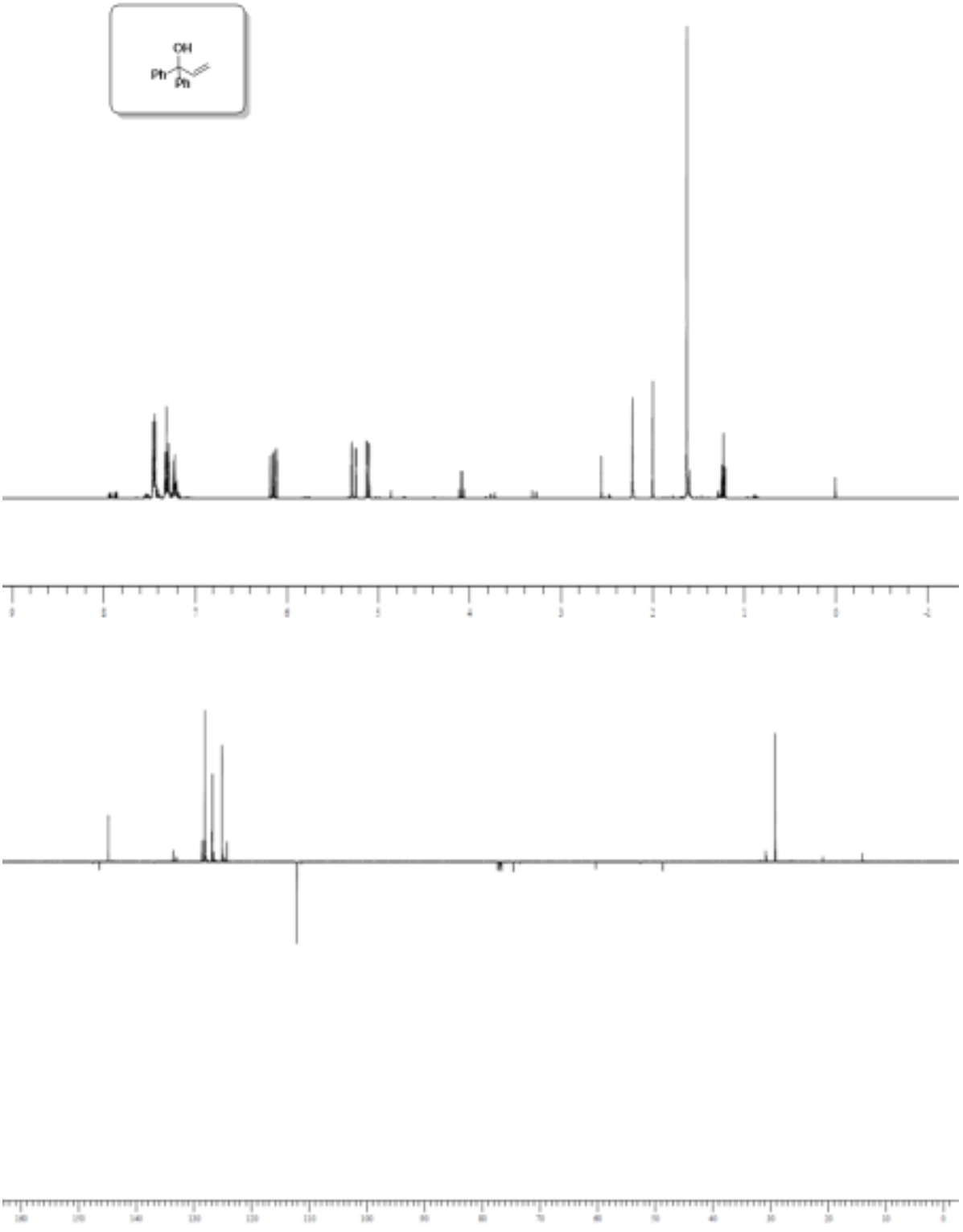
BF3K
(24)

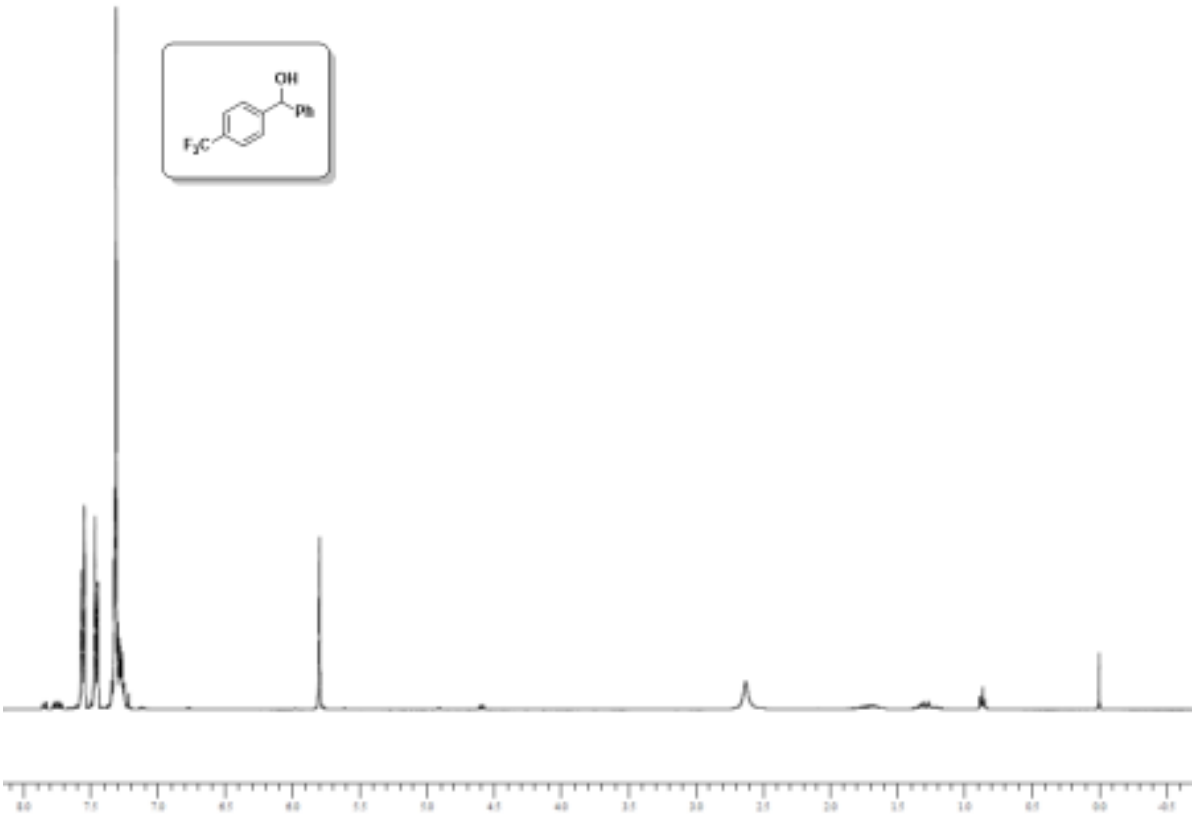


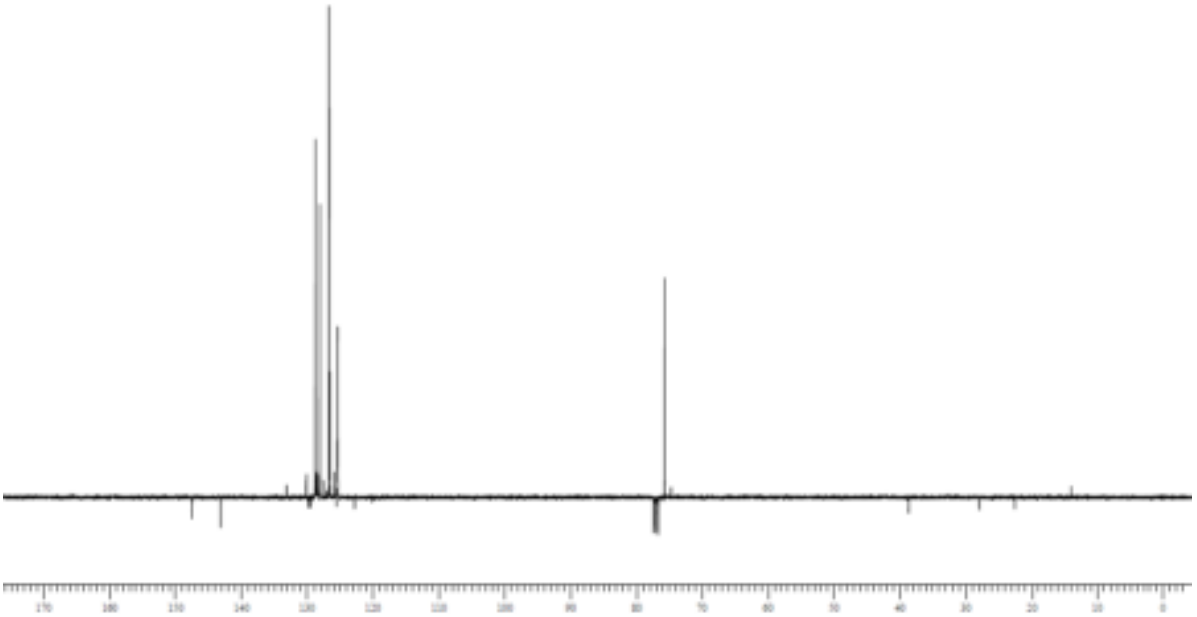

Ph
BF3K
(2f)

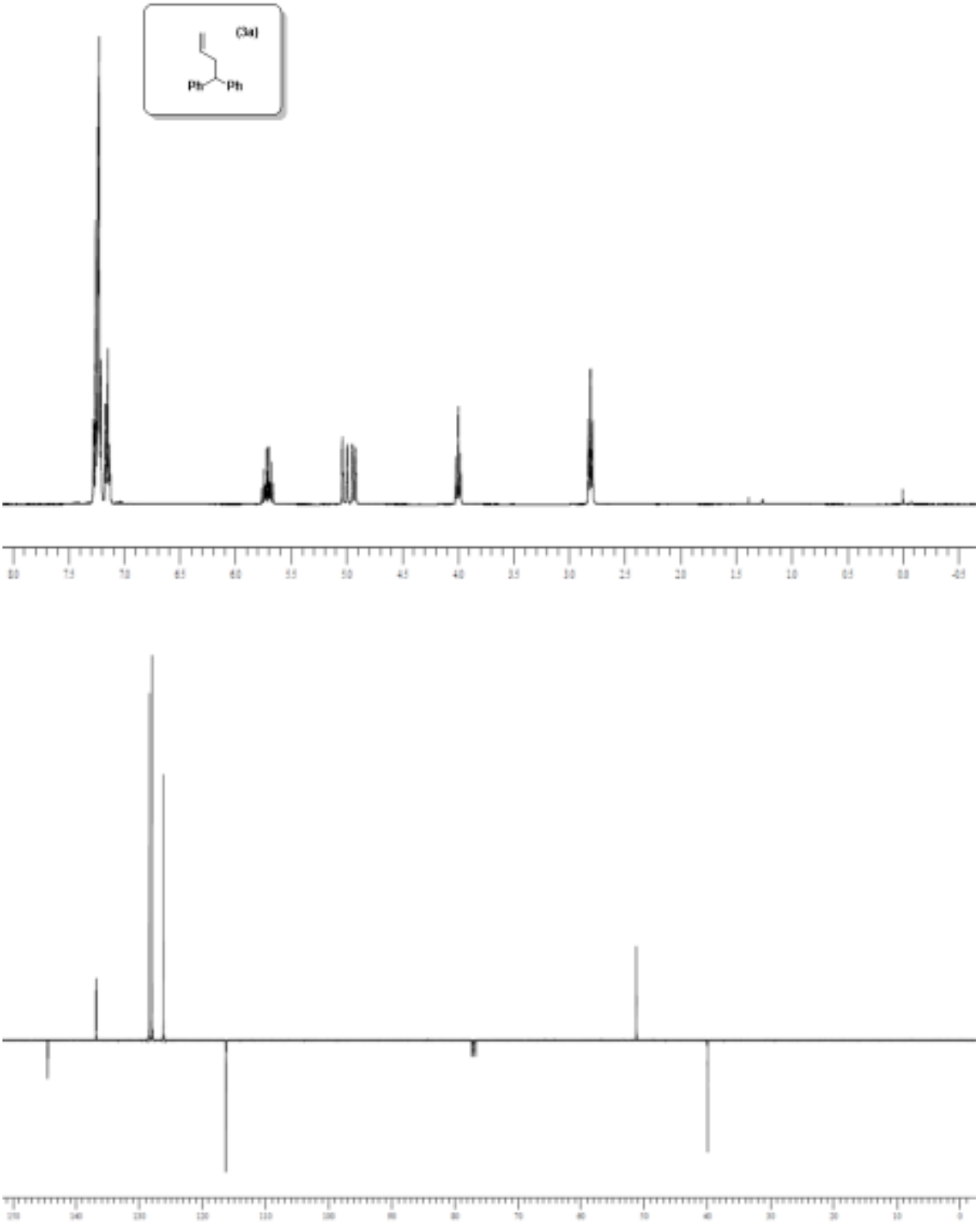

OH
Ph
Me

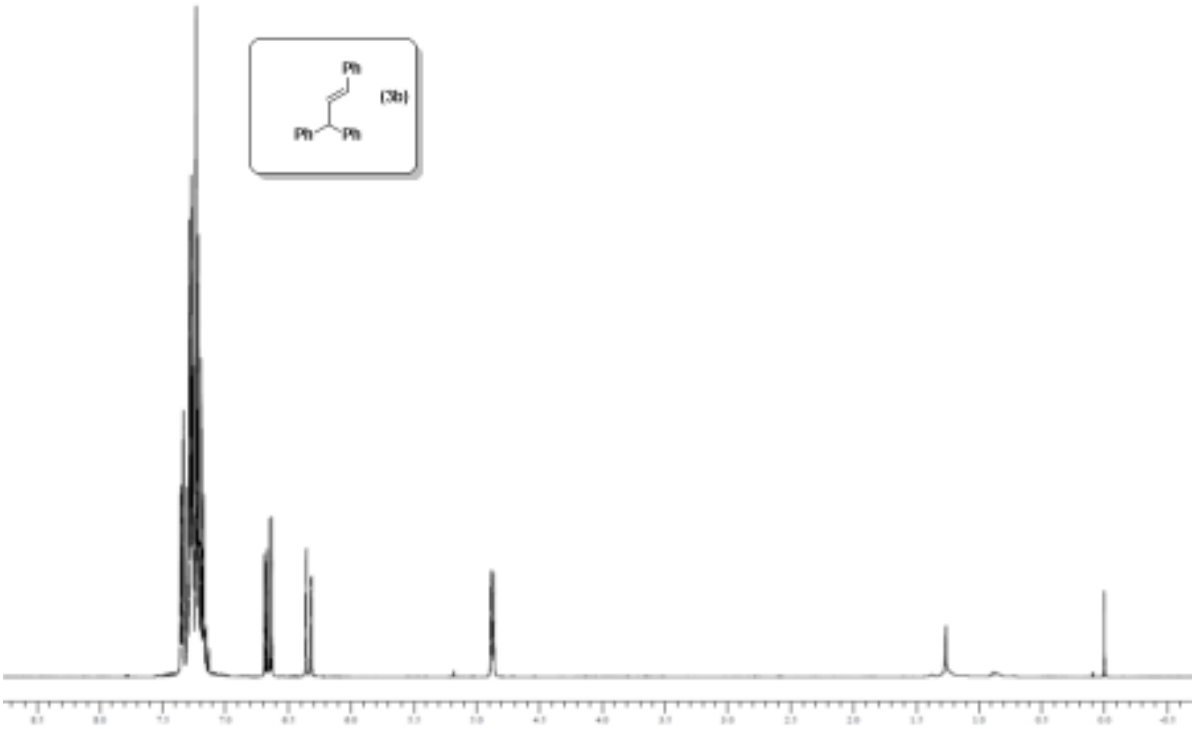


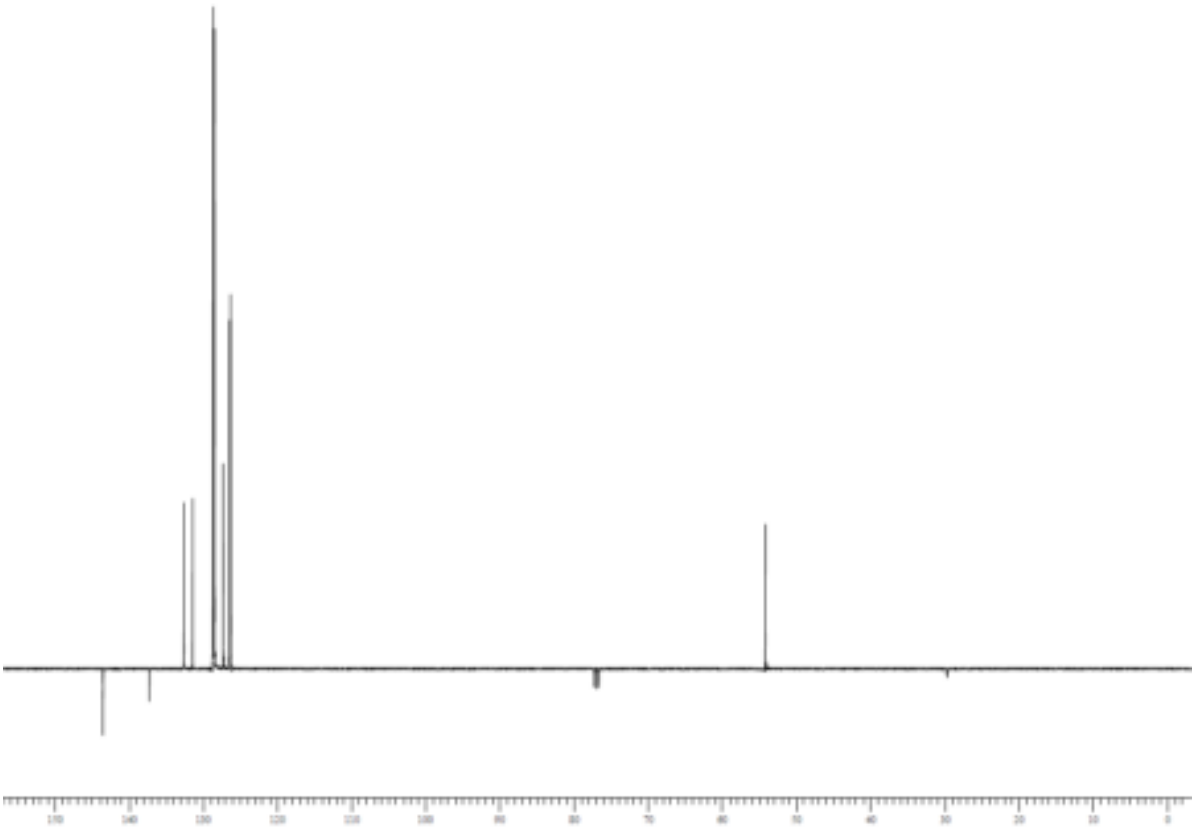

OH
Ph
Ph

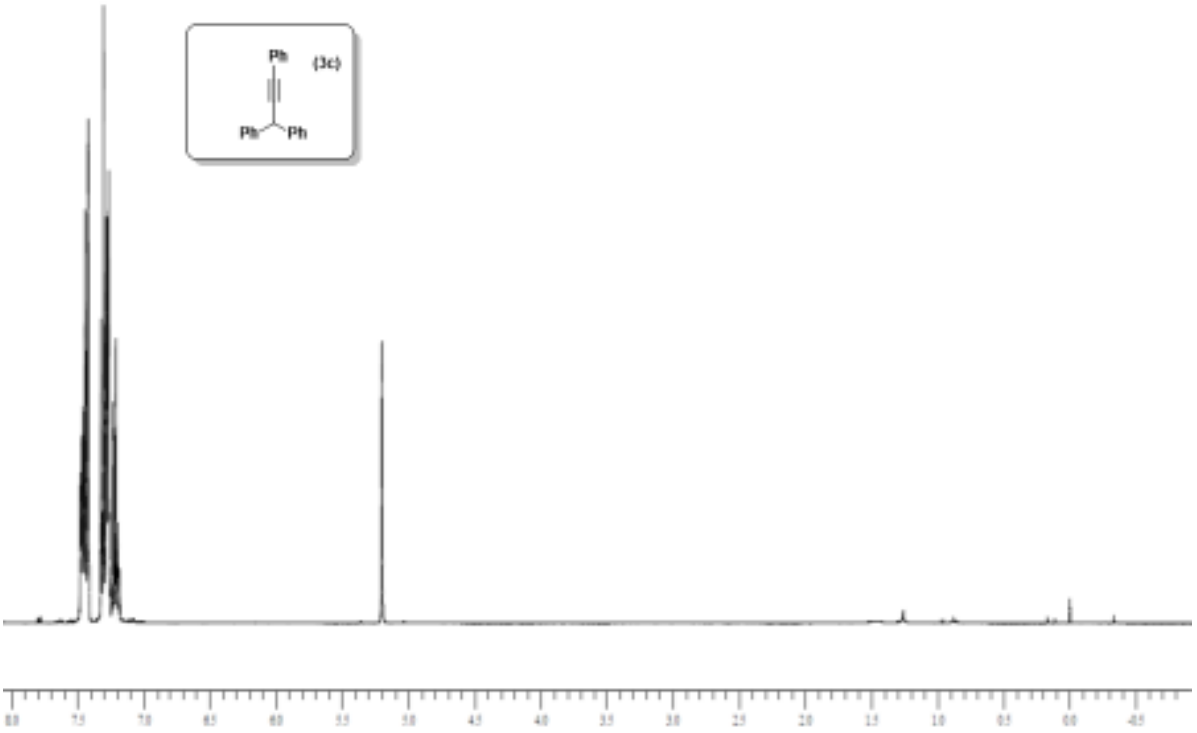

OH
Ph
F3C

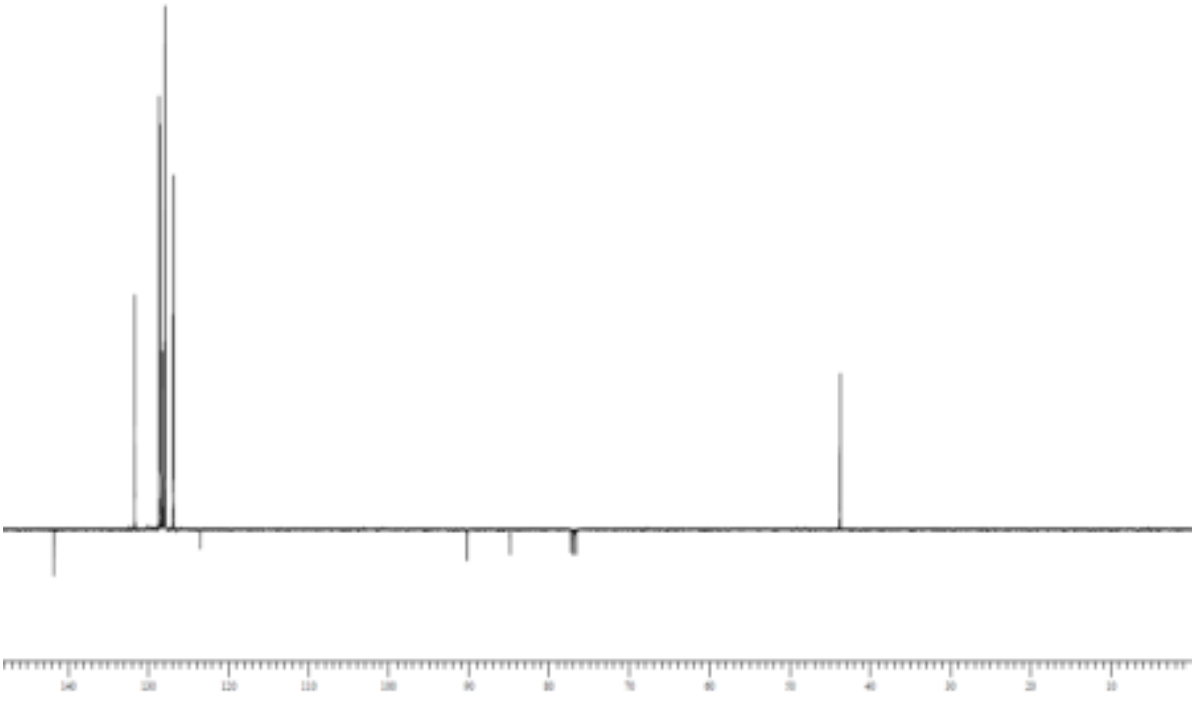


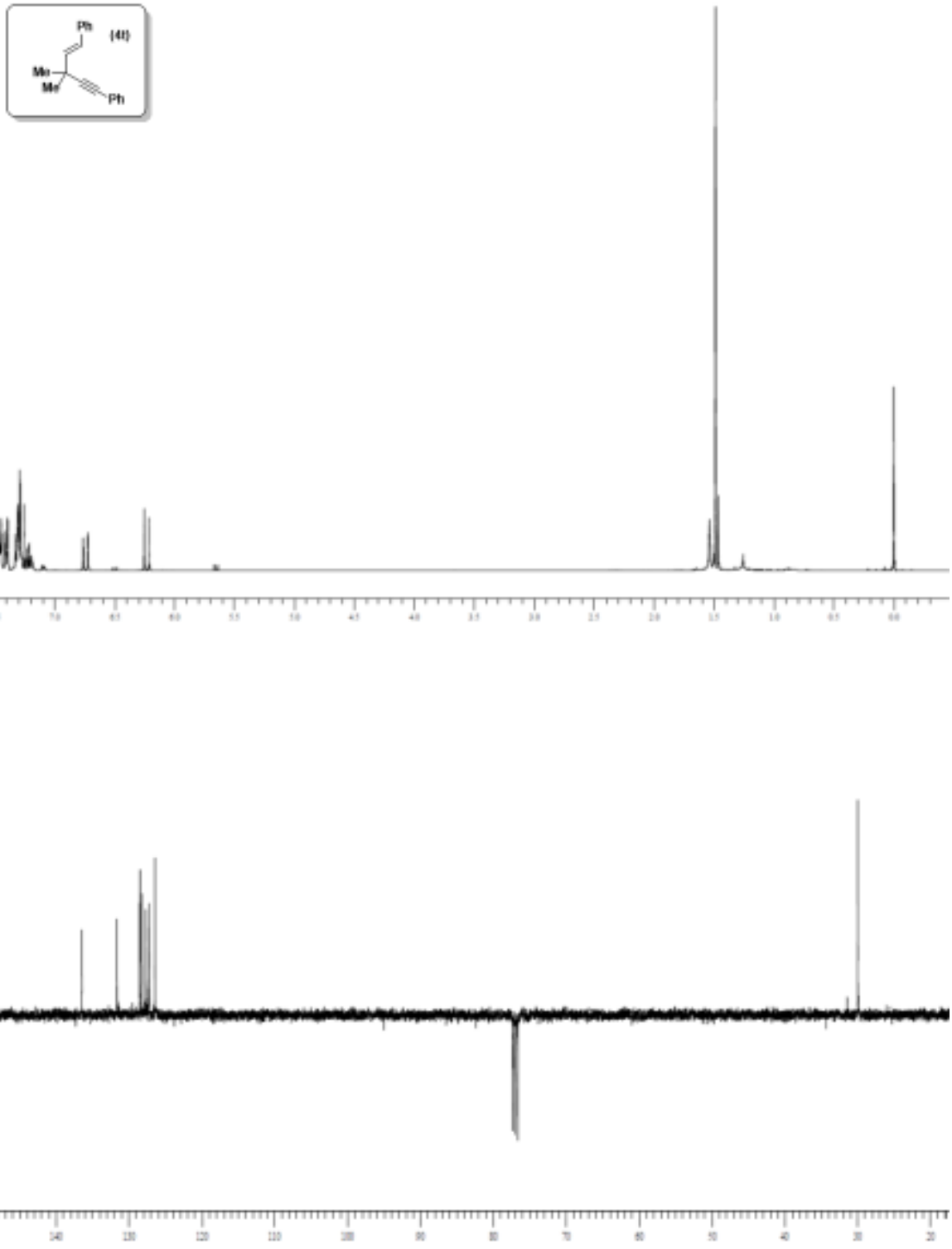

(3a)
Ph
Ph

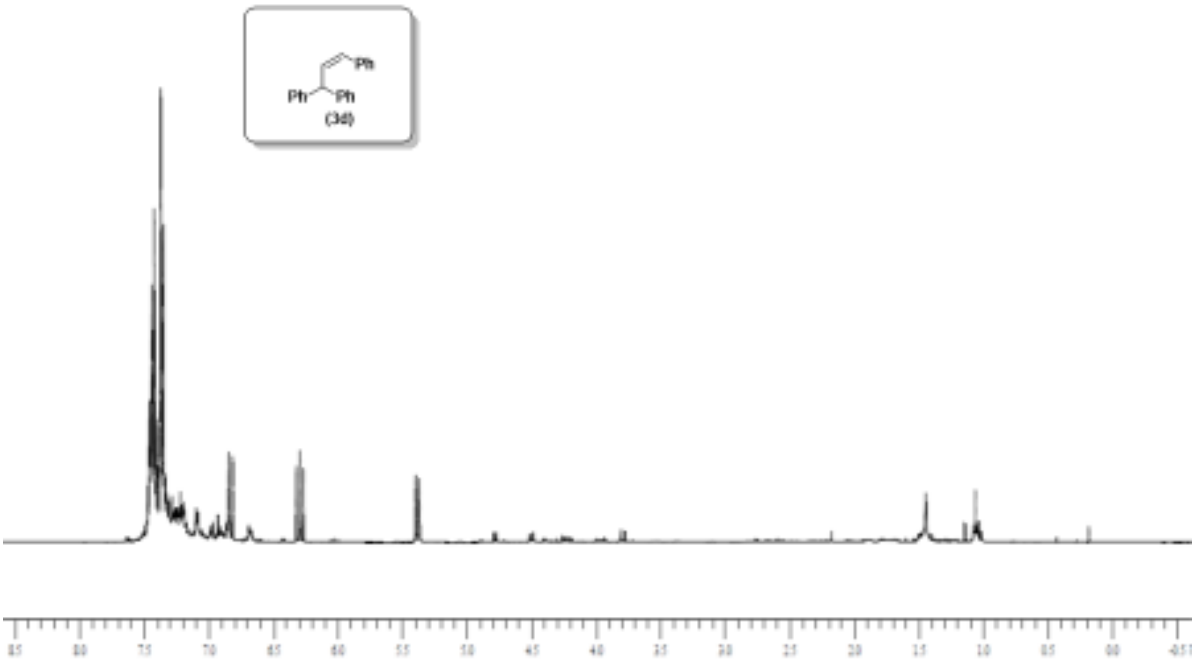

Ph
Ph
Ph
(3b)

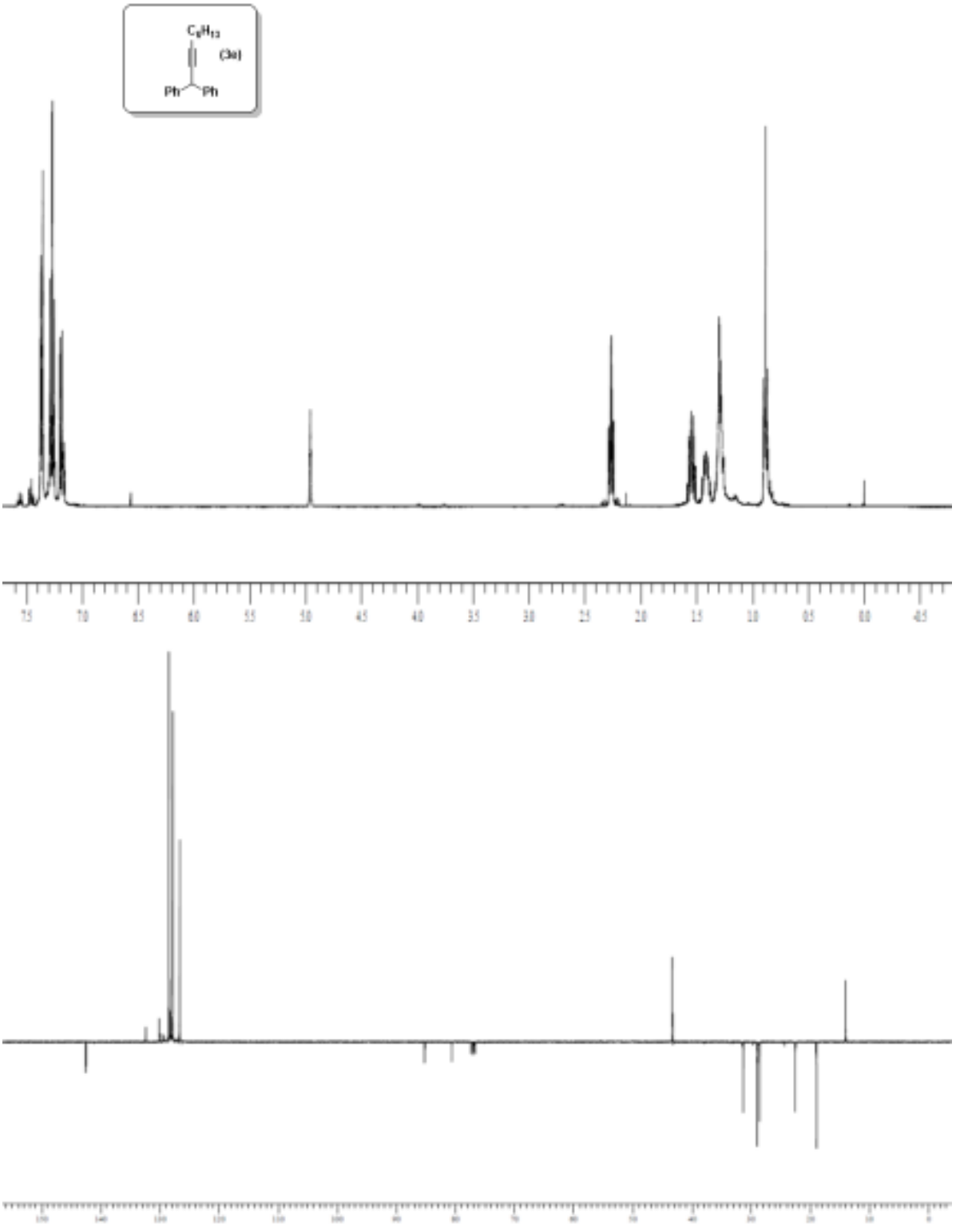


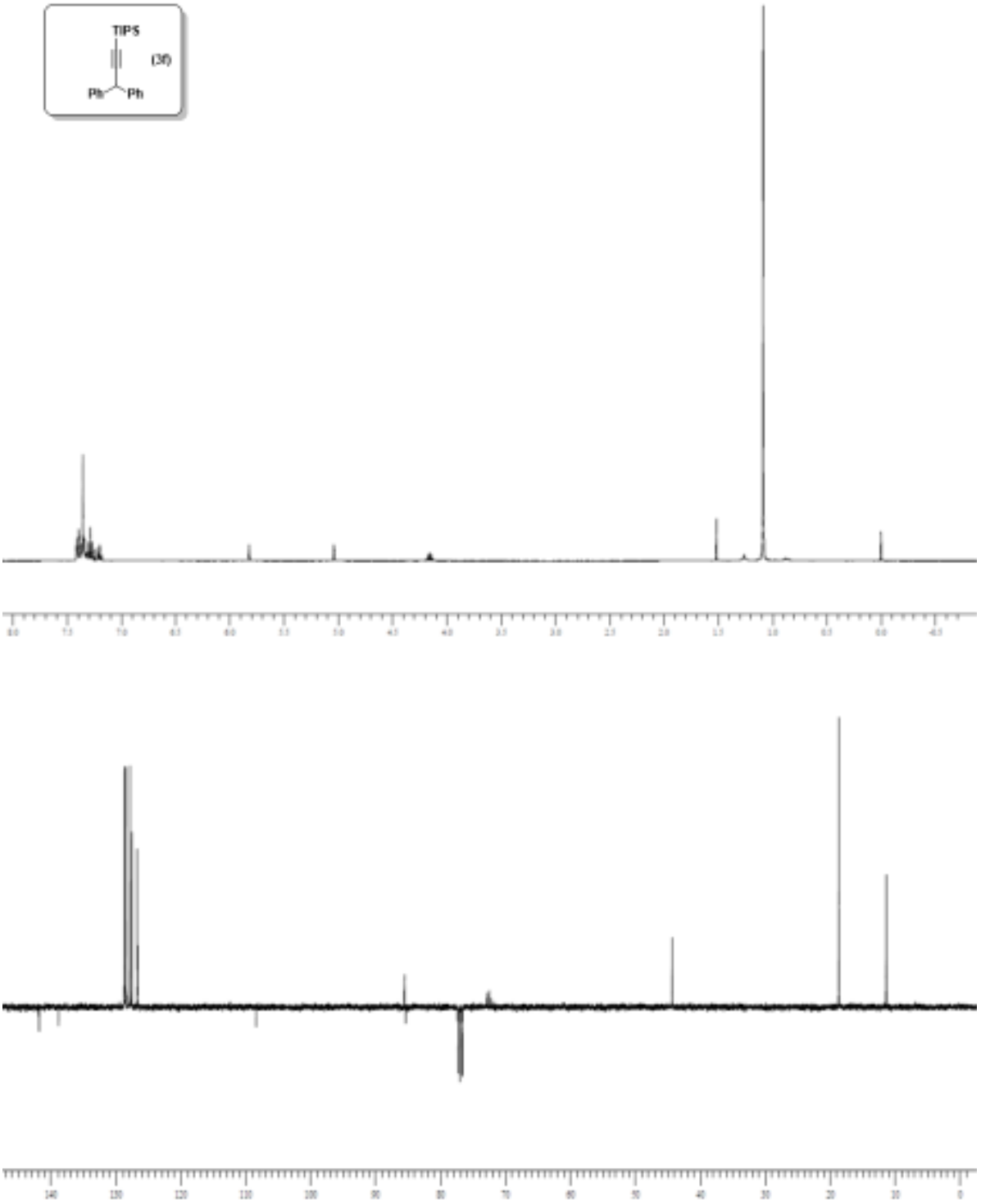

Ph
(3c)
Ph
Ph

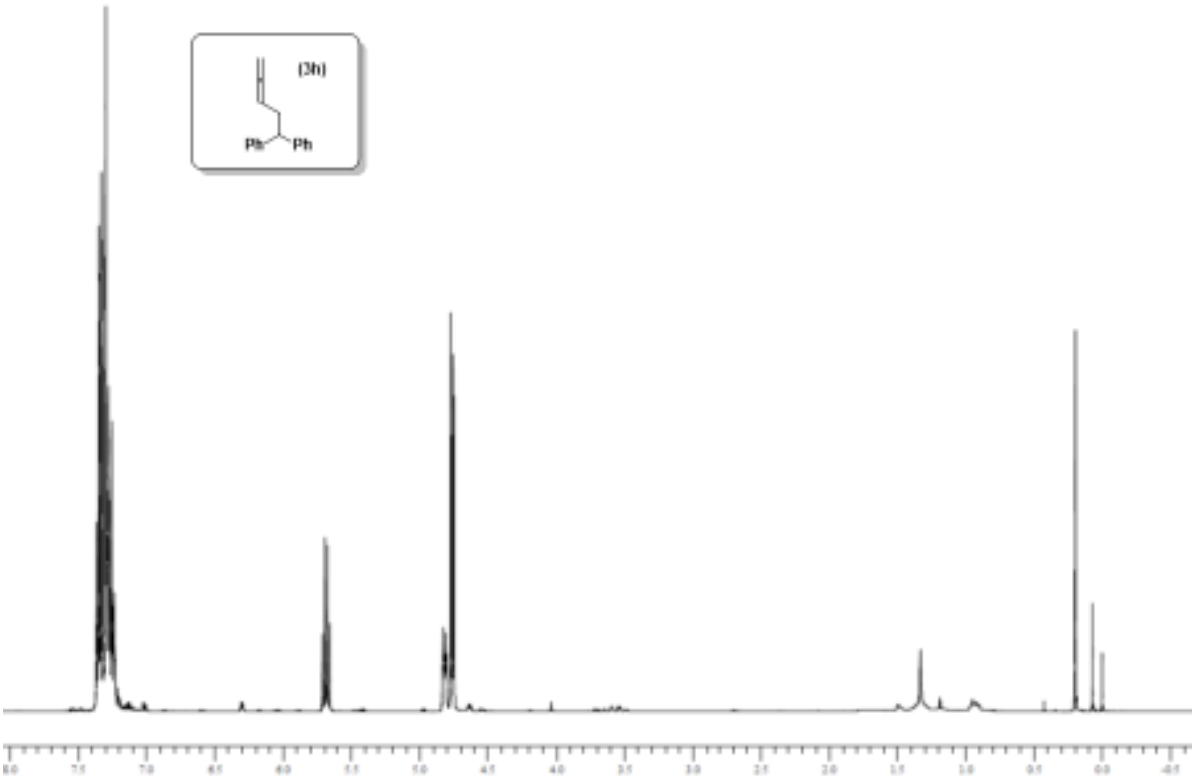



Ph
(4l)
Me
Me
Ph


Ph
Ph
Ph
(34)


C6H13
(3a)
Ph
Ph


TIPS
(3f)
Ph
Ph


(3h)
Ph
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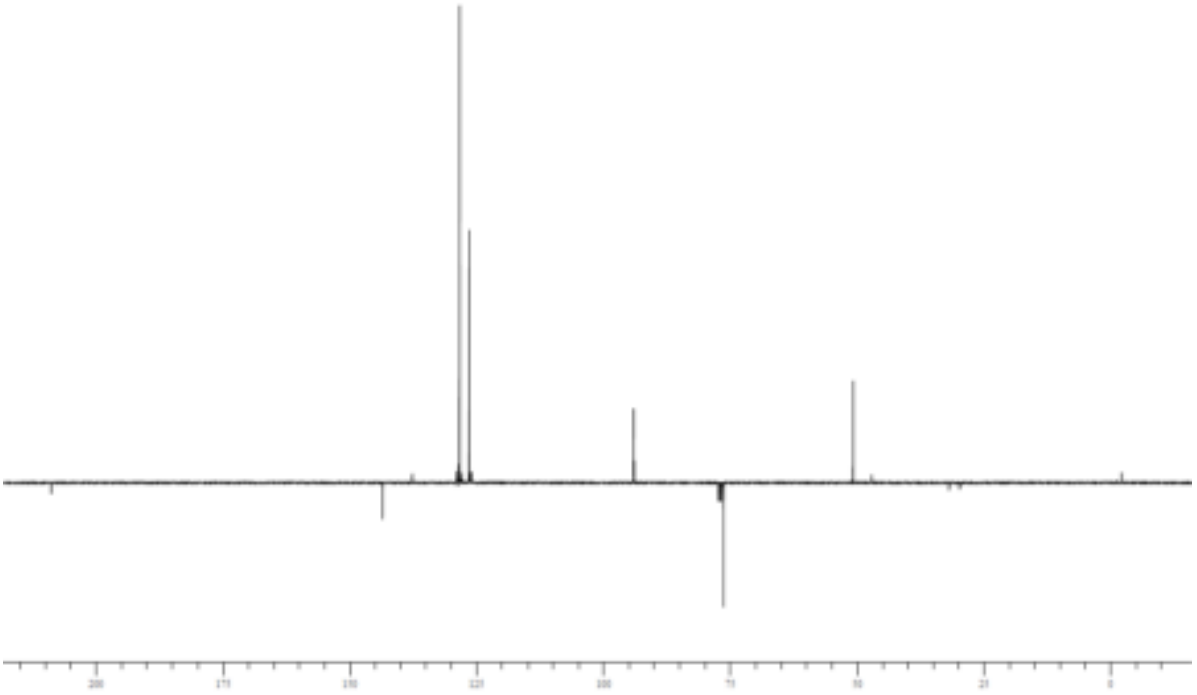
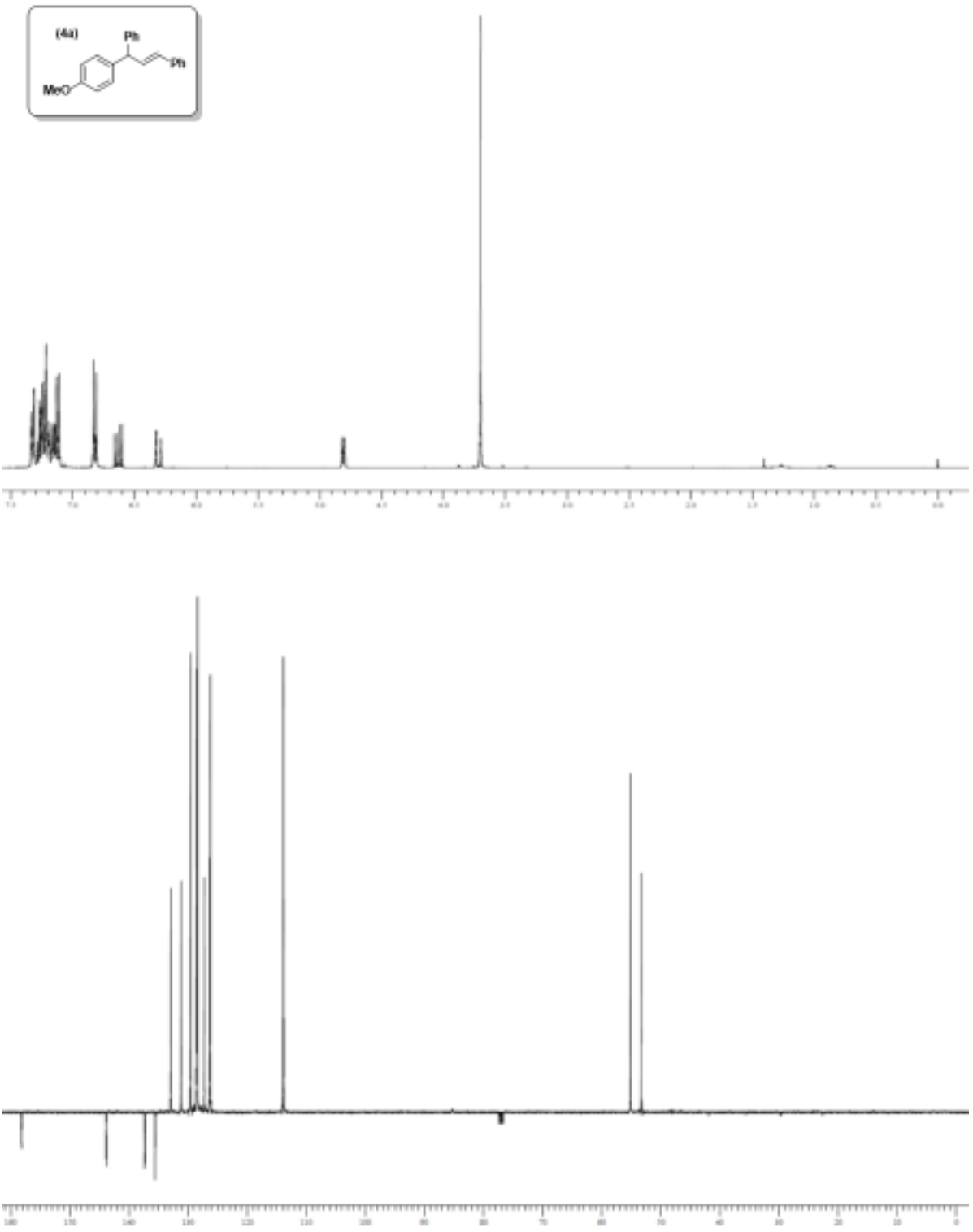
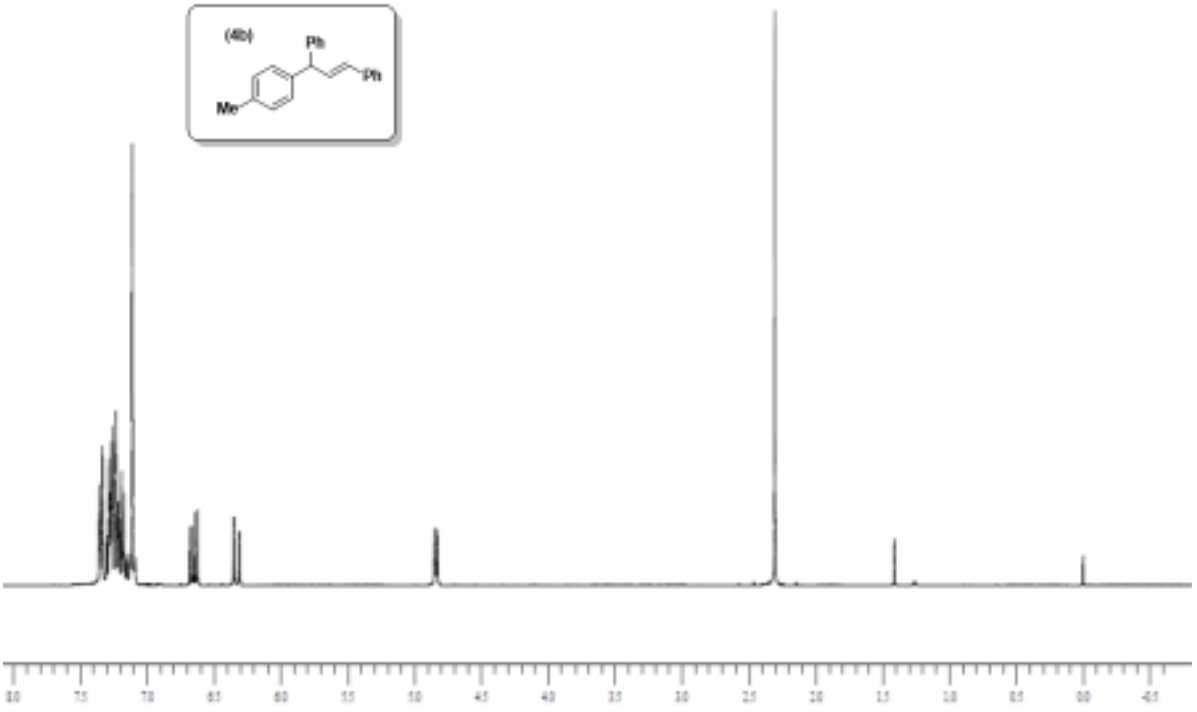
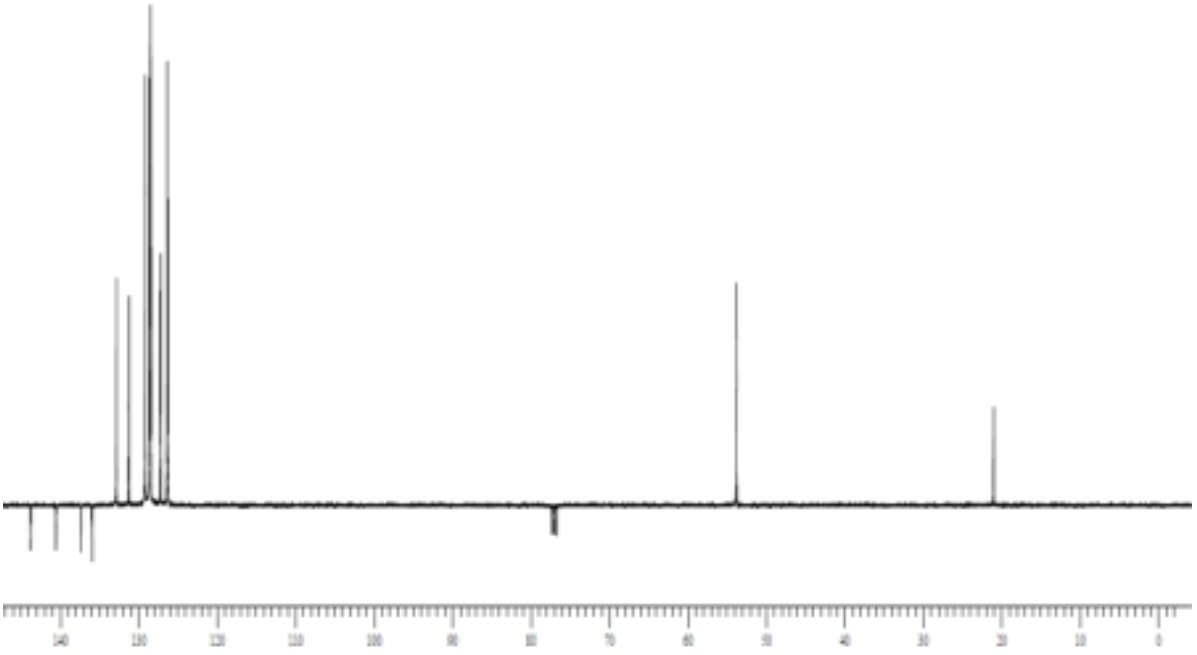
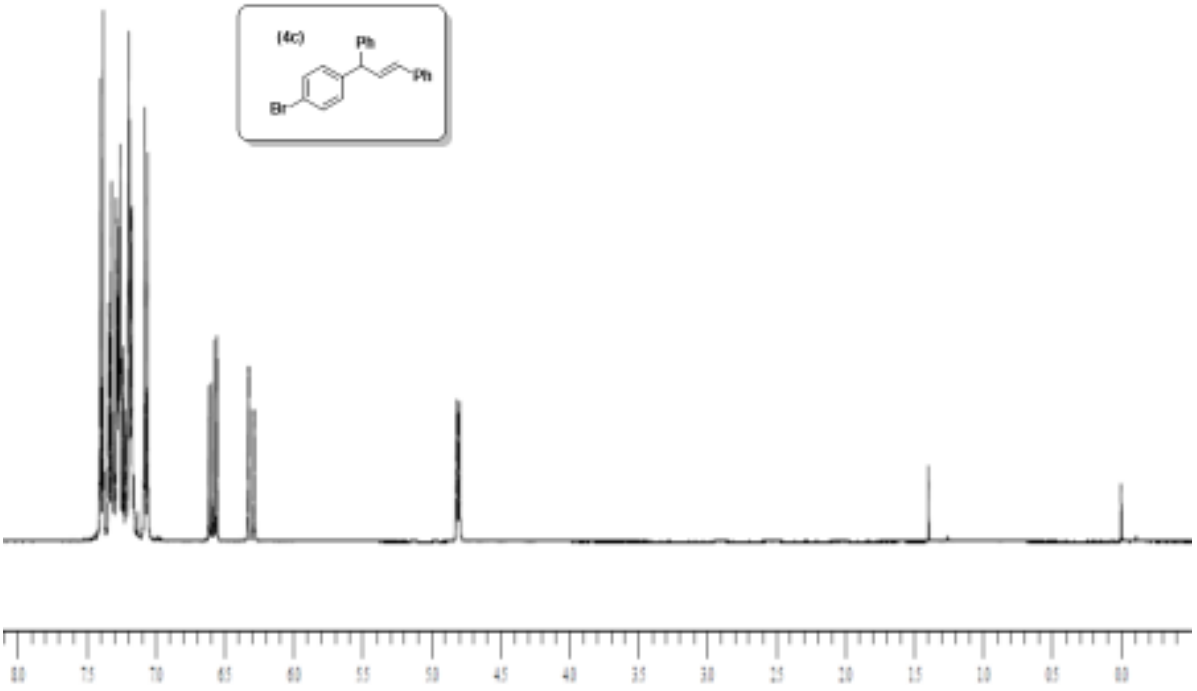
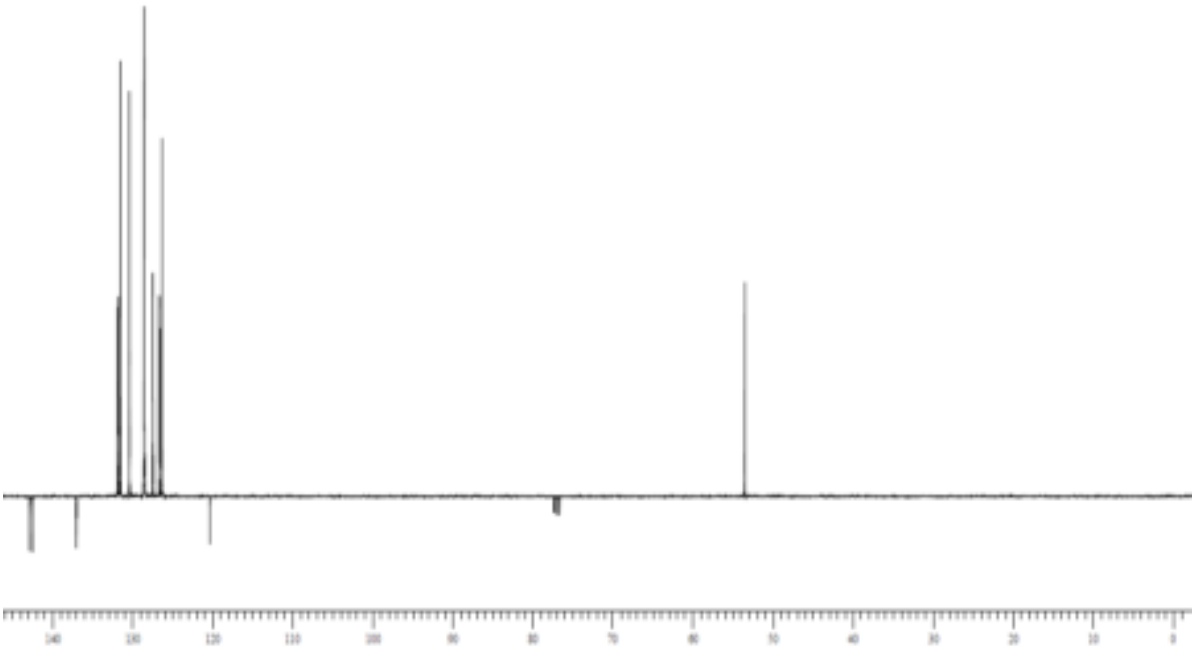


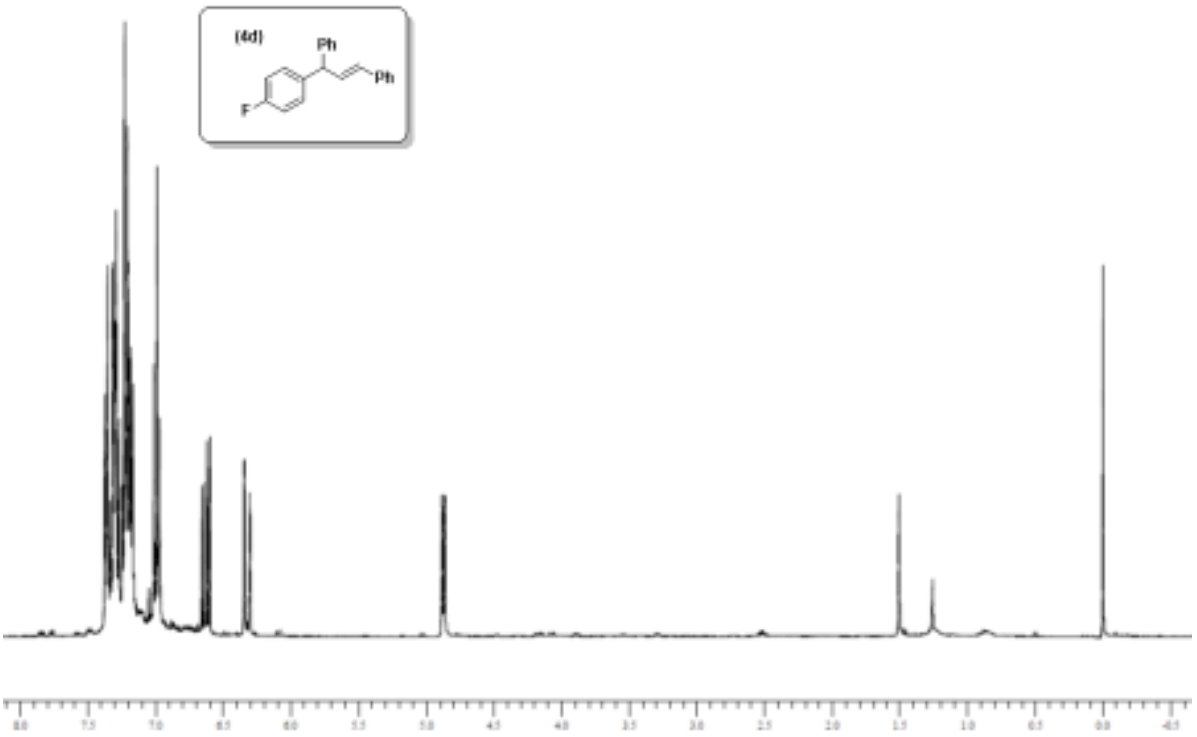

(4a)
Ph
Ph
MeO

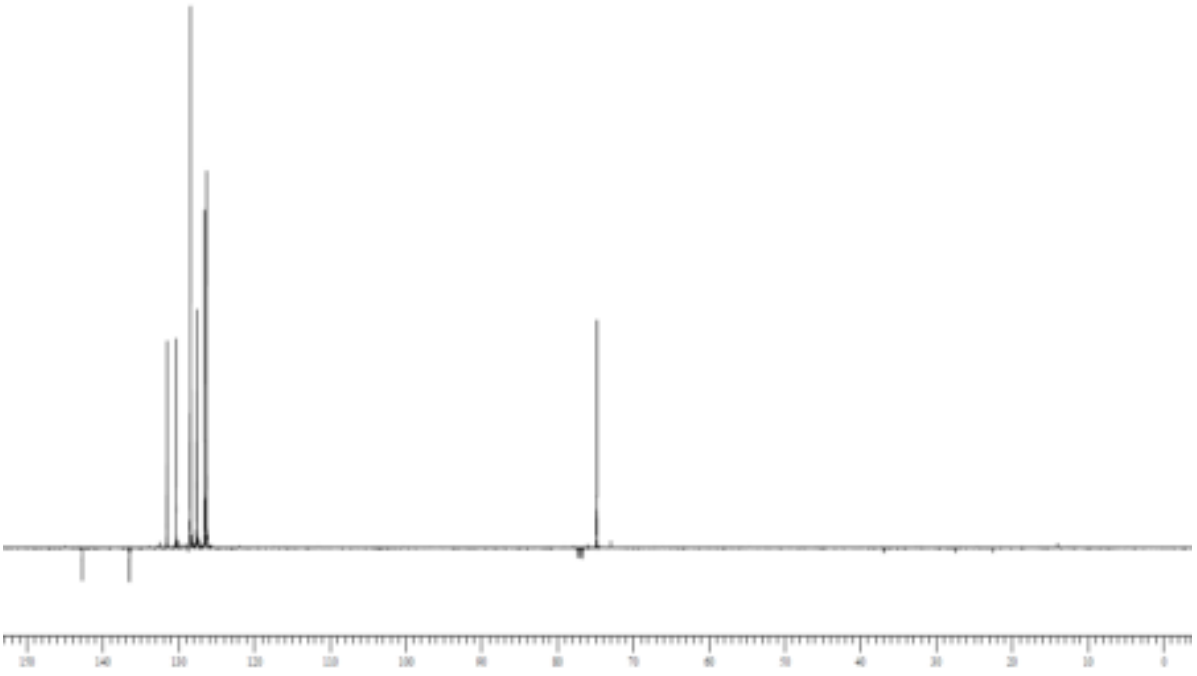

(4b)
Ph
Ph
Me

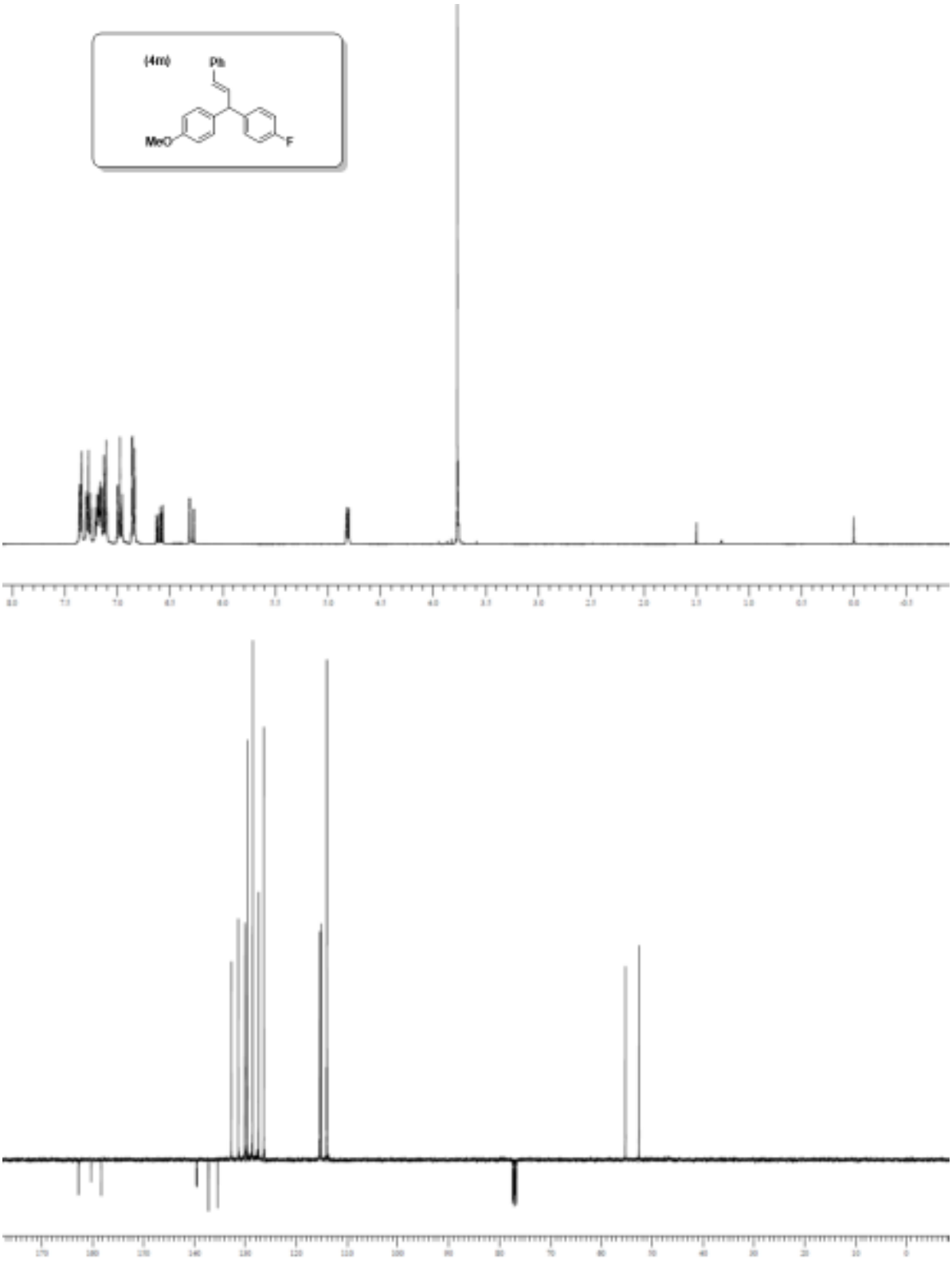


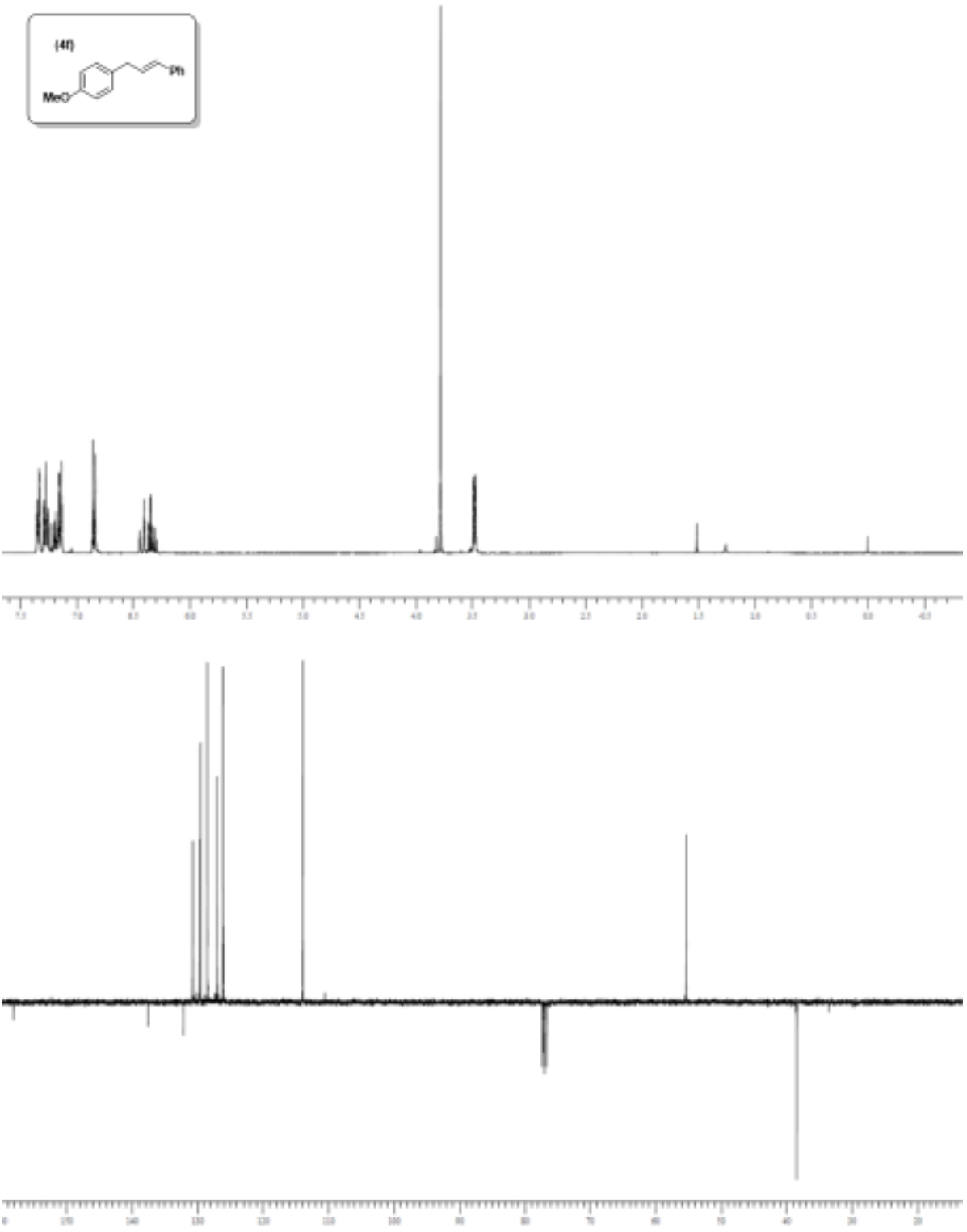

(4c)
Ph
Ph
Br




(4d)
Ph
Ph
F




(4m)
Ph
MeO
F


(4f)
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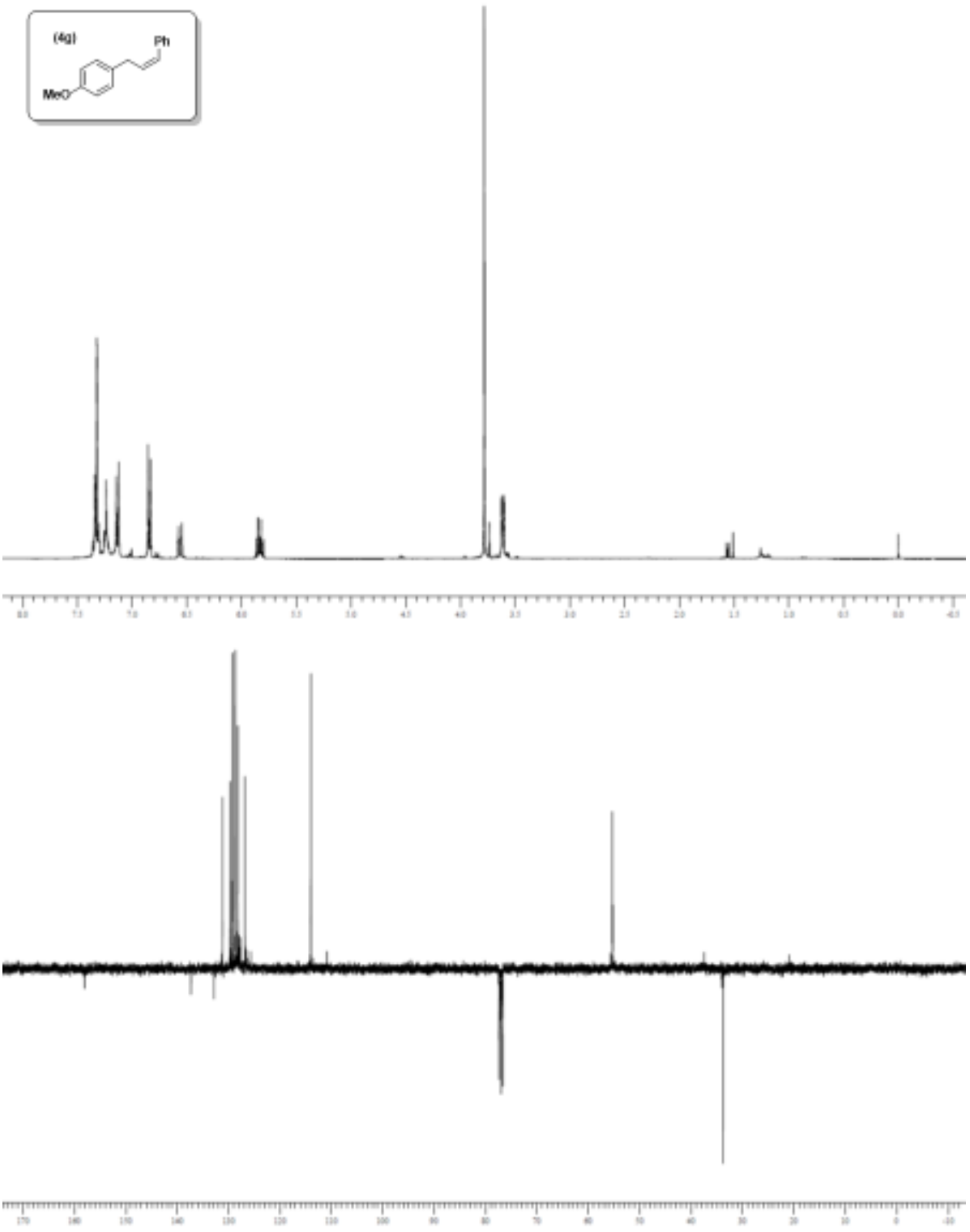
(4g)
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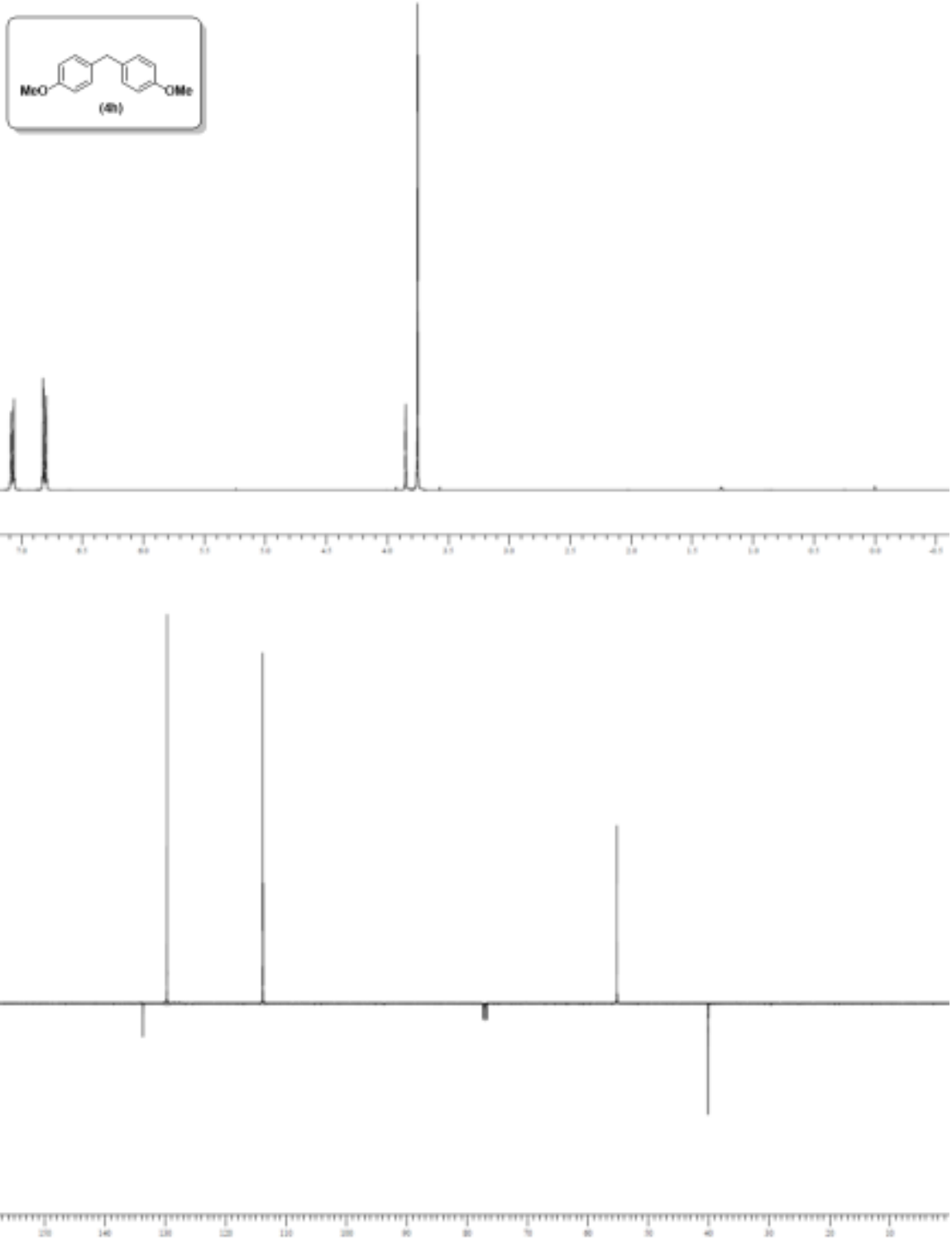
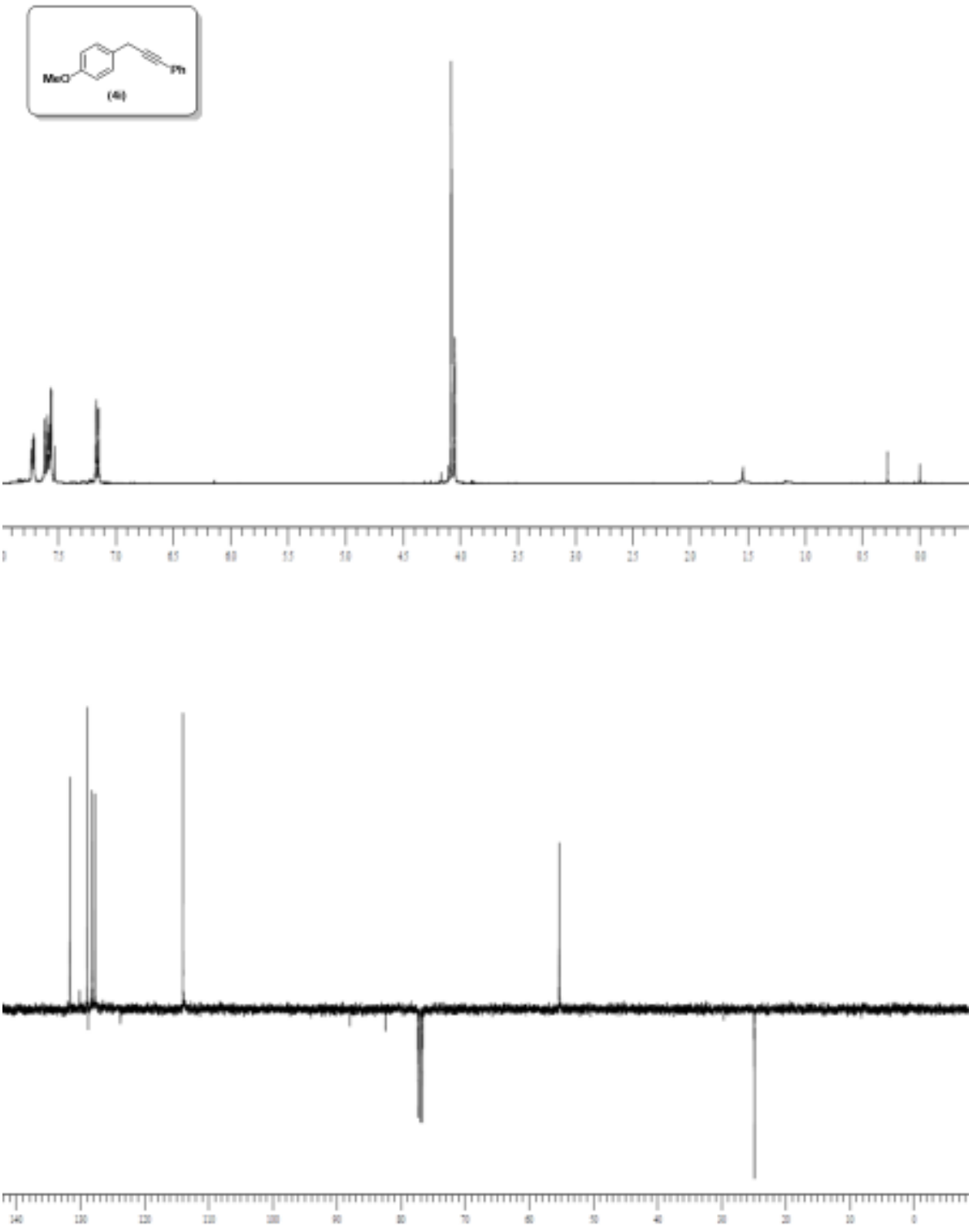
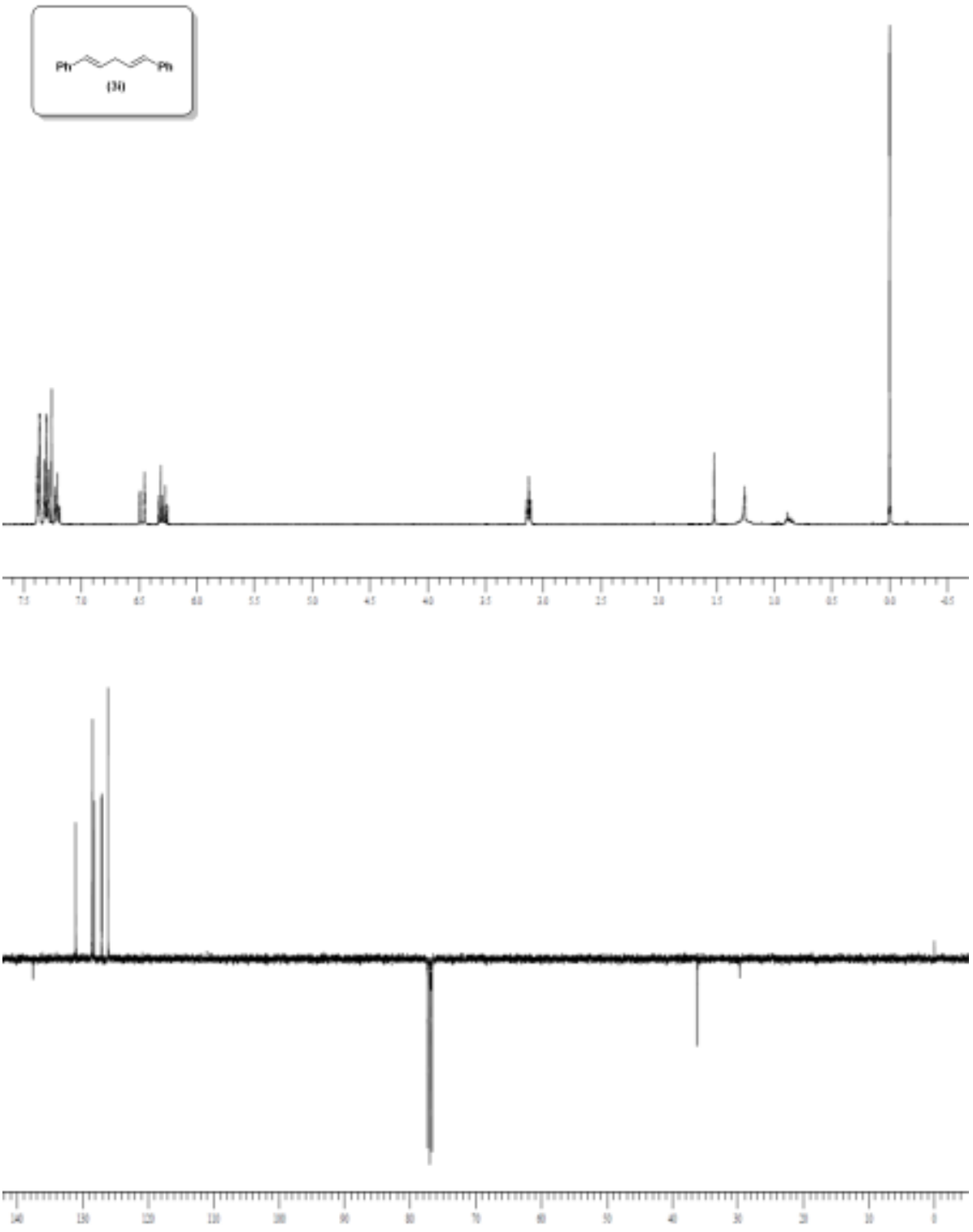
MeO


MeO
OMe
(4h)


MeO
Ph
(4i)


Ph
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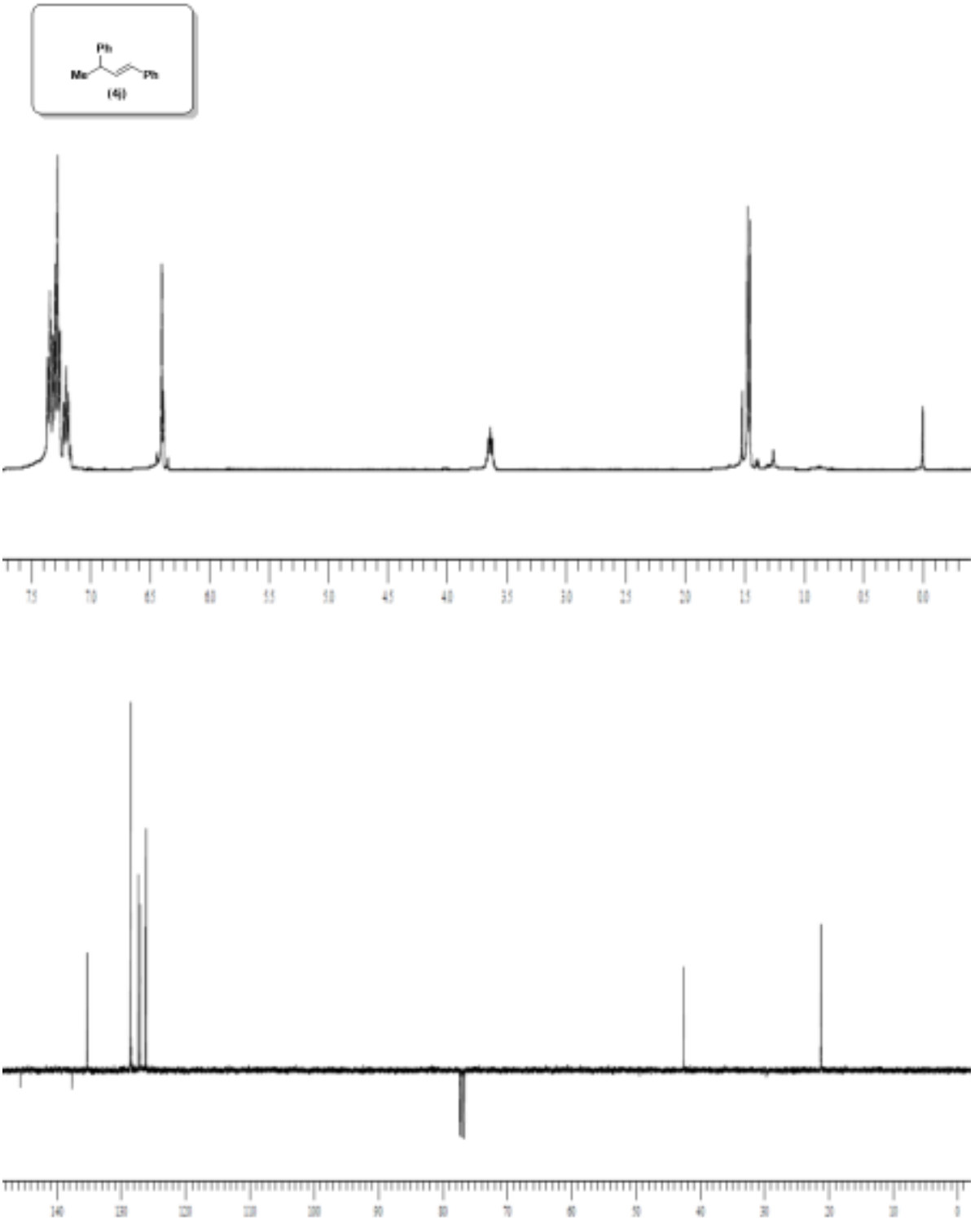
(3i)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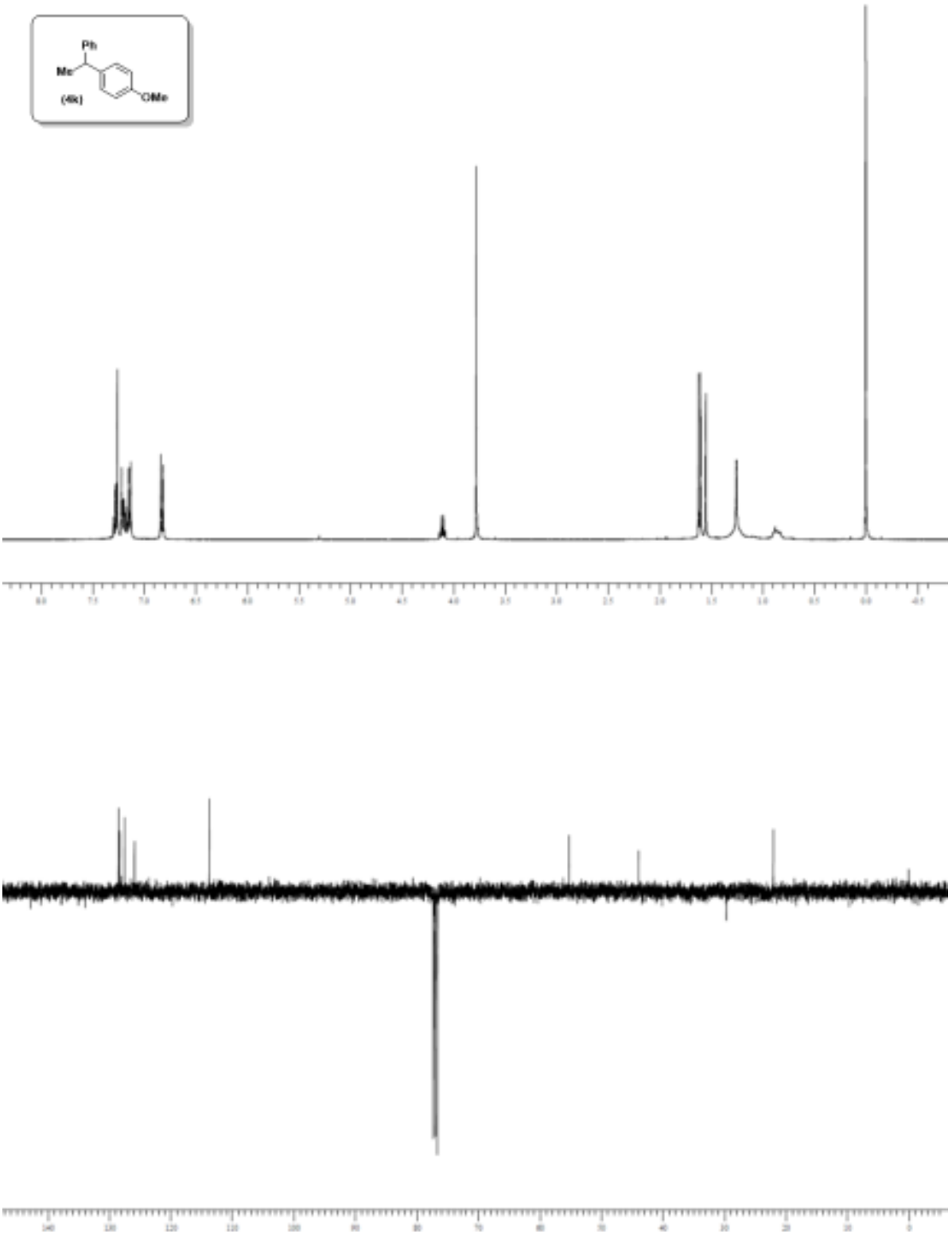
Me
Ph
(4j)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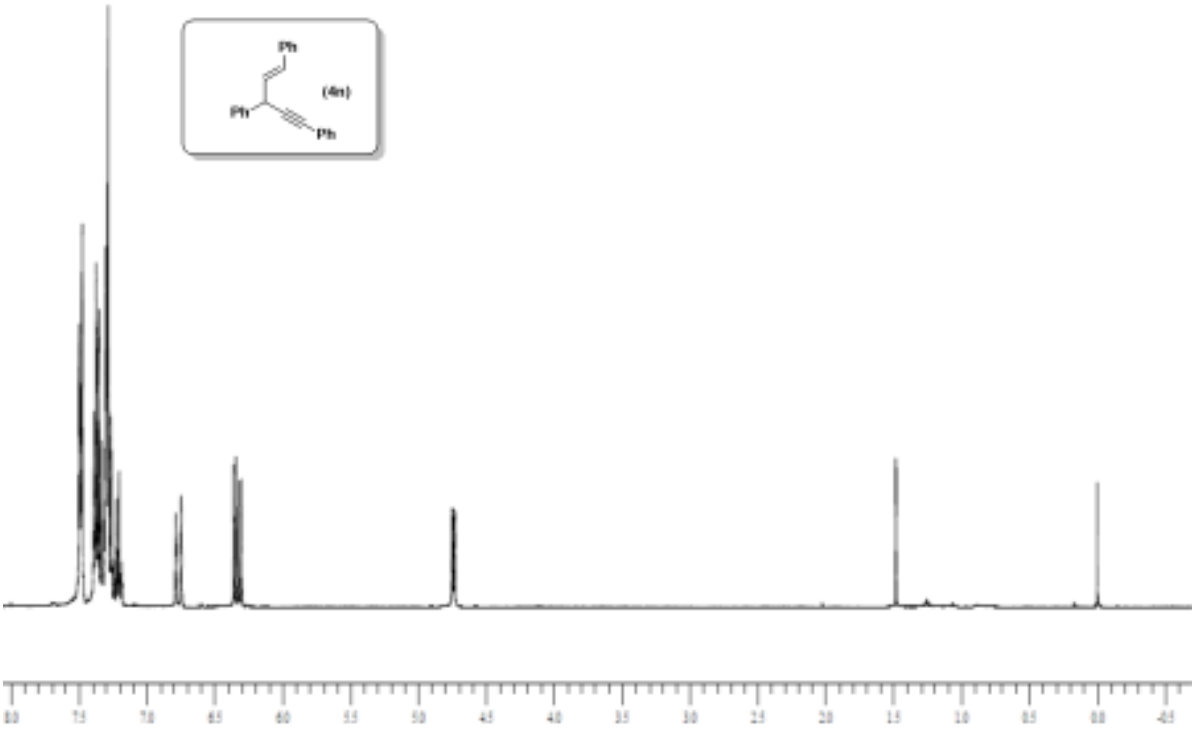
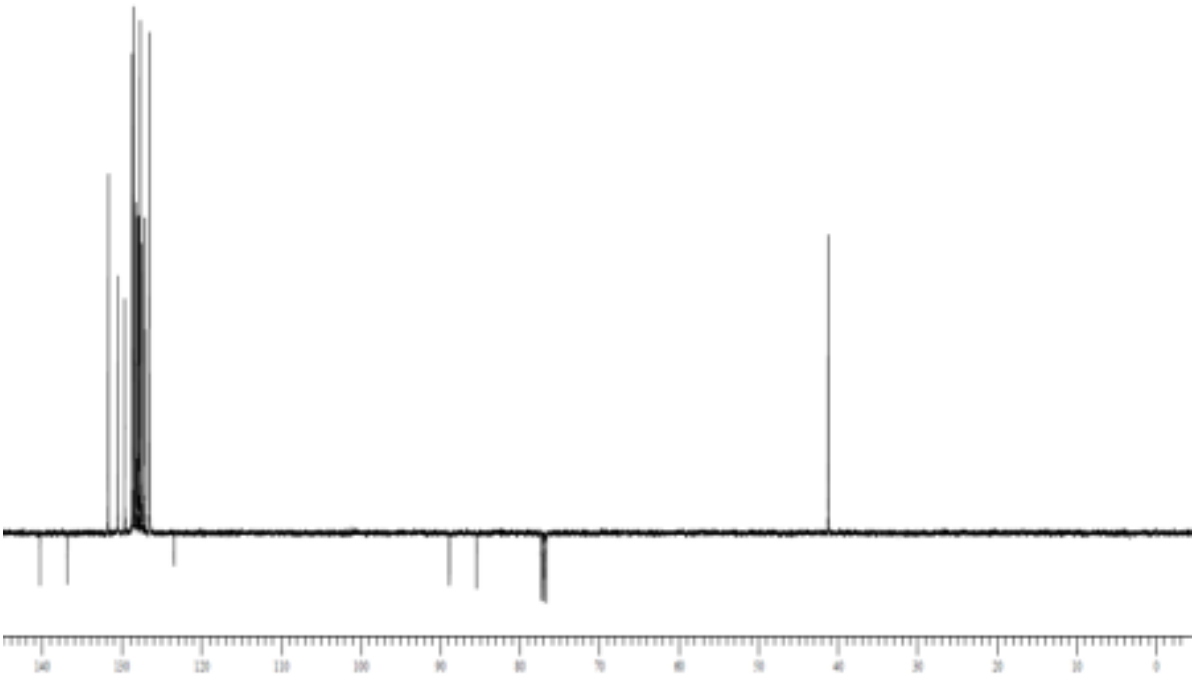
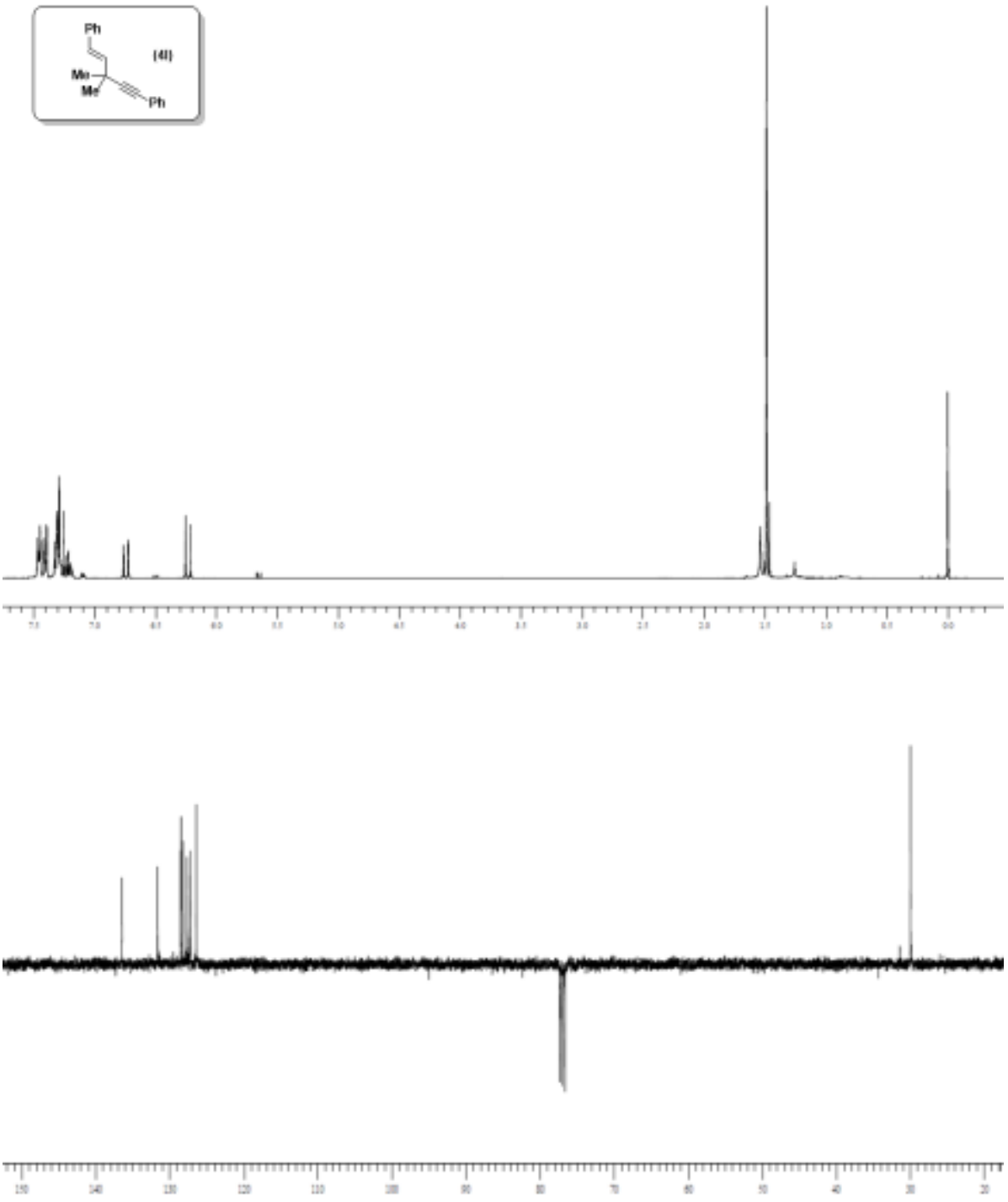
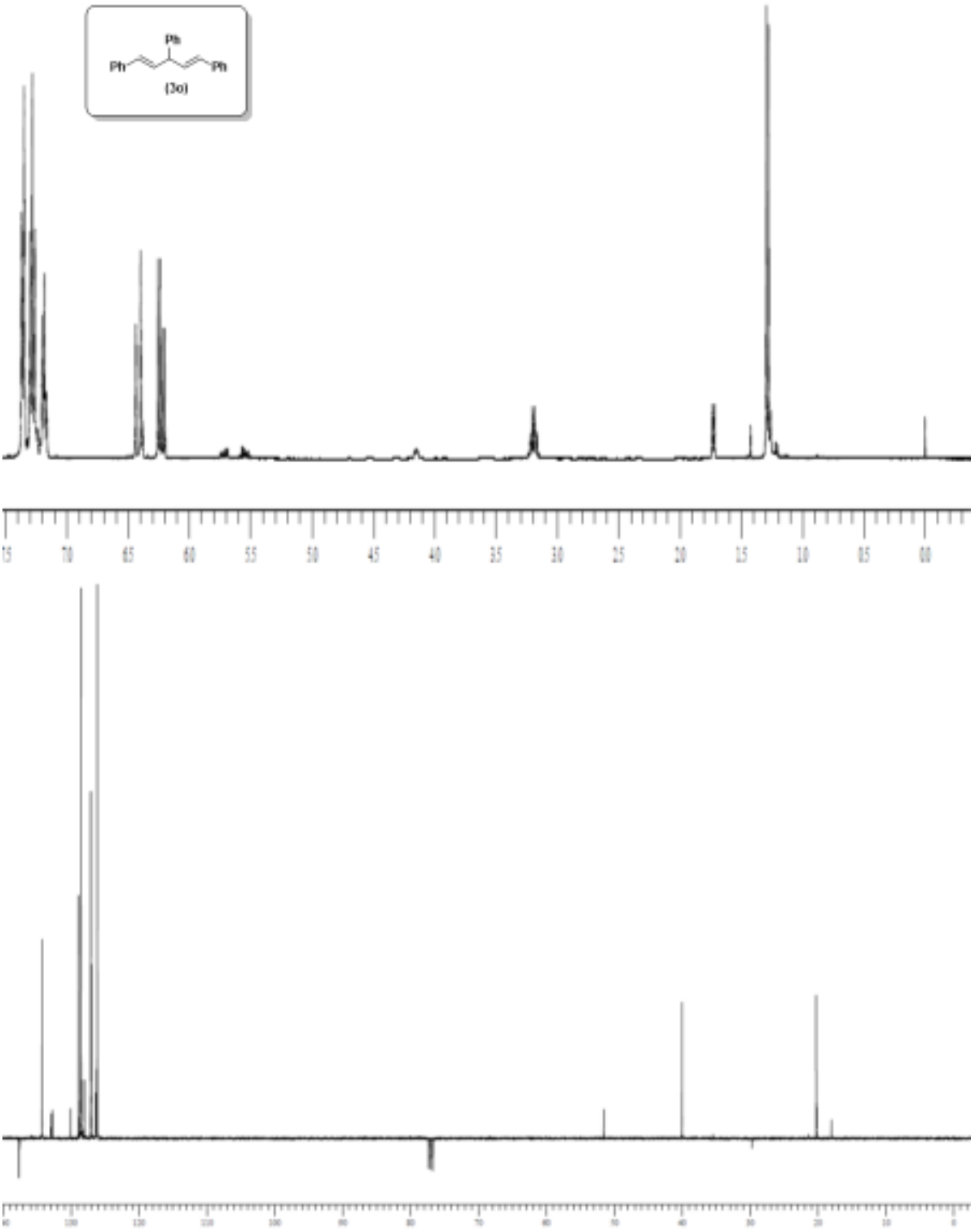
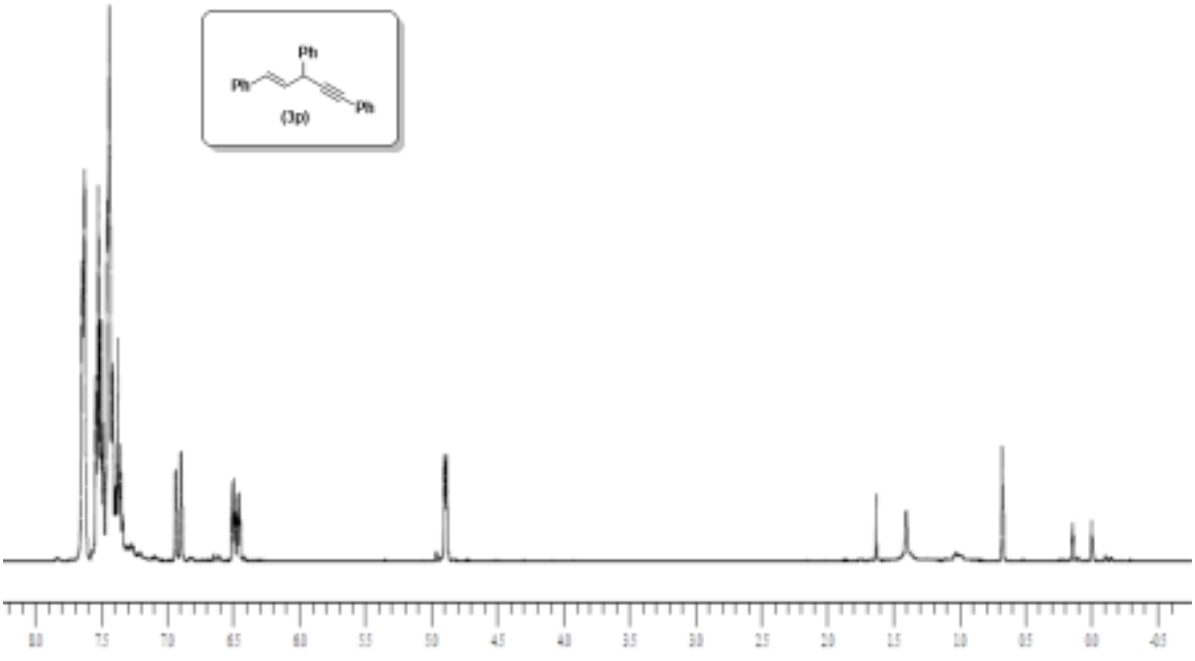
OMe
(4k)

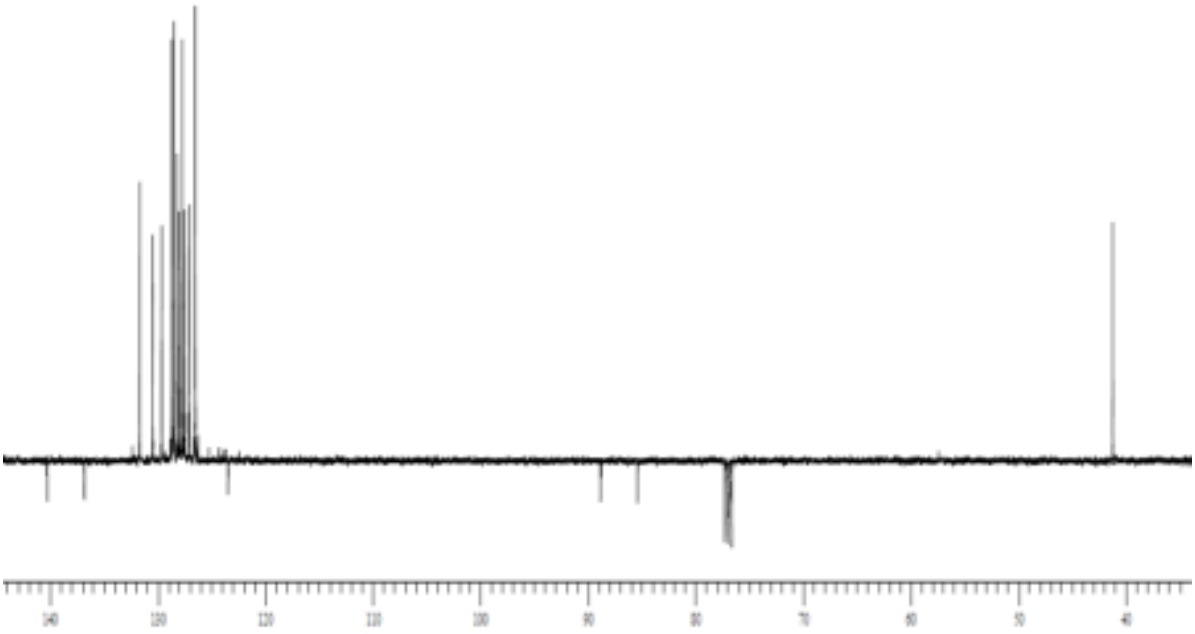

Ph
(4n)
Ph
Ph

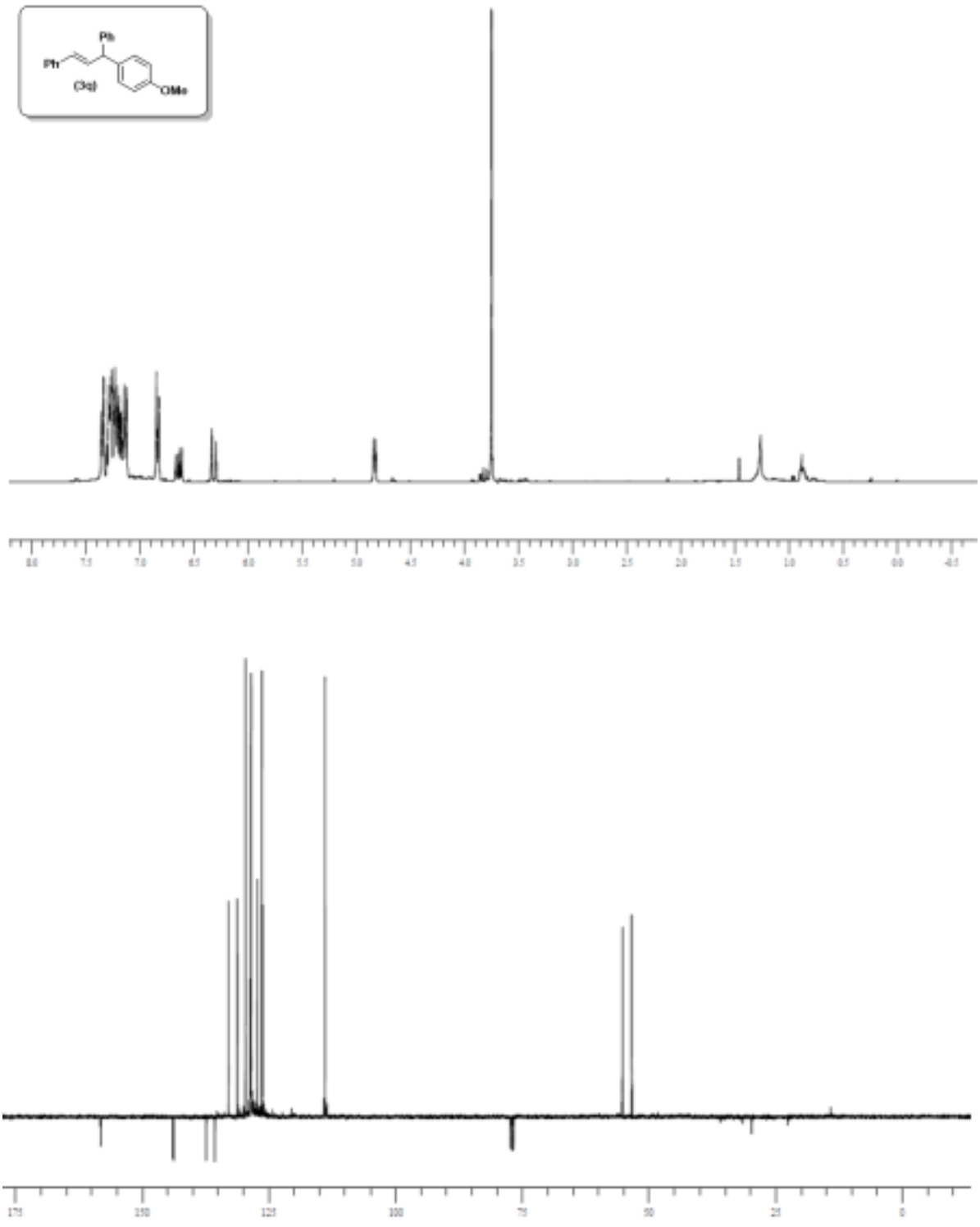


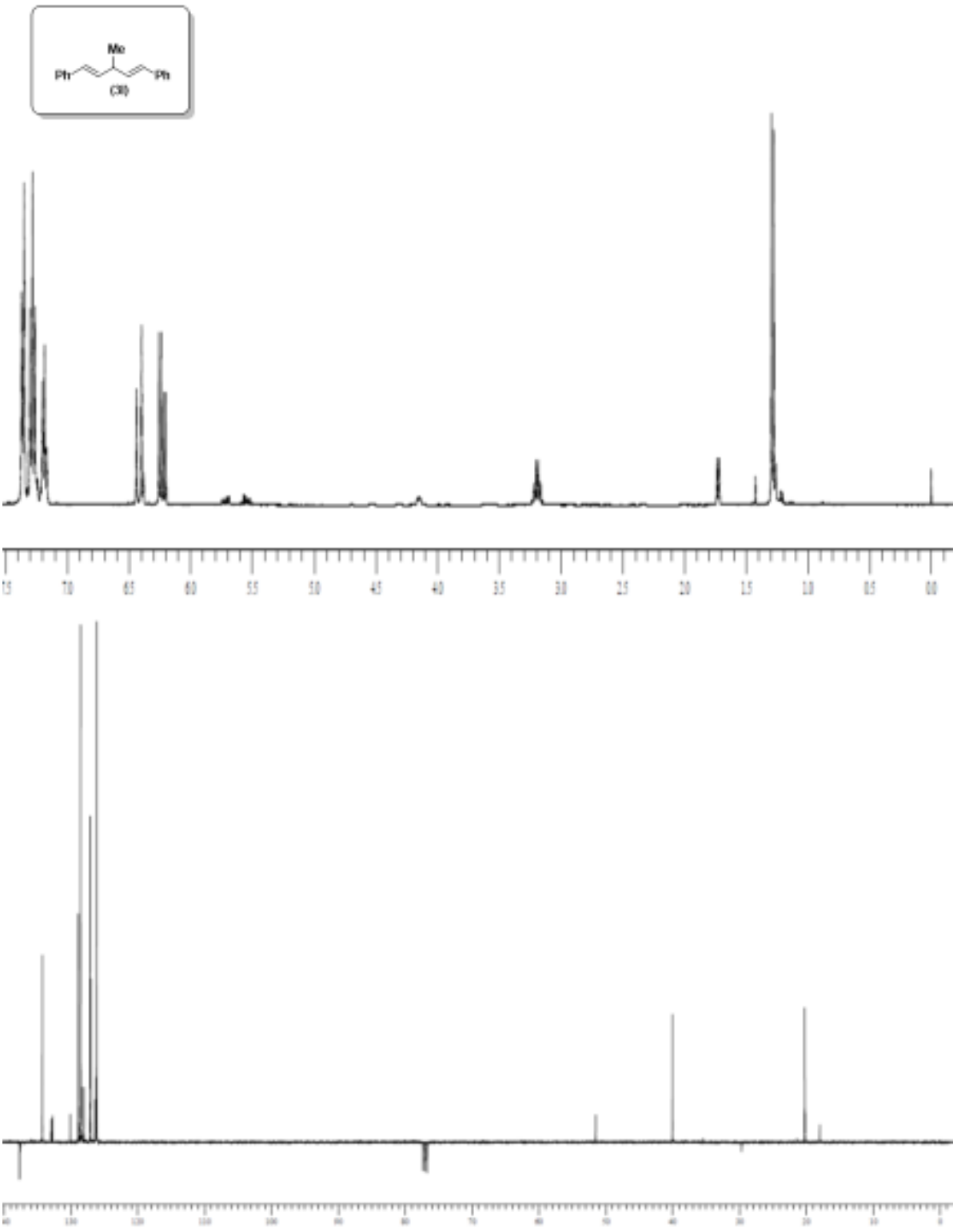

Ph
(4l)
Me
Me
Ph

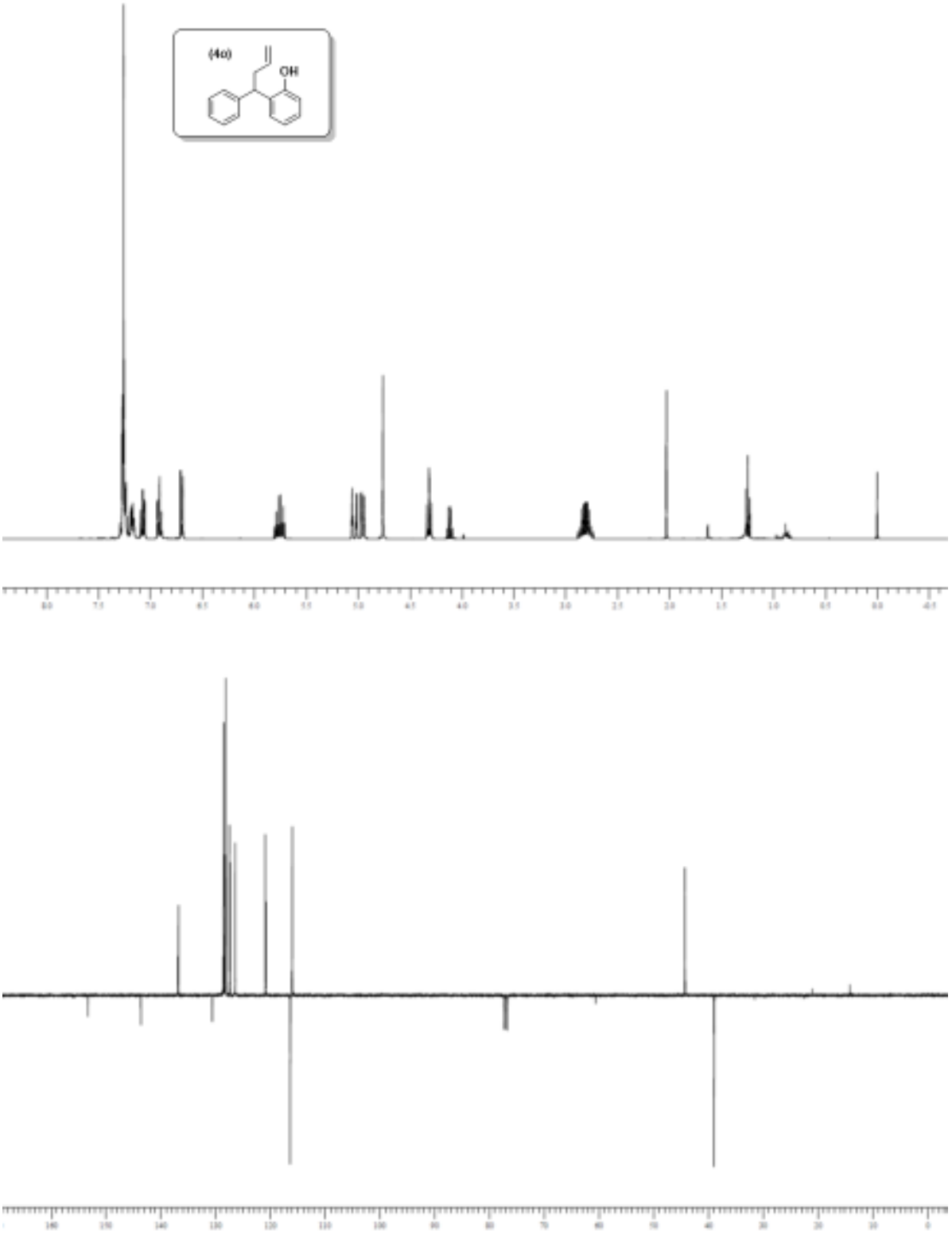

Ph
Ph
Ph
(3o)


Ph
Ph
Ph
(3p)




Ph
Ph
(3q)
OMe


Me
Ph
Ph
CH3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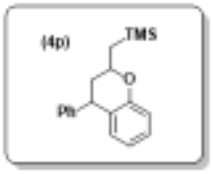
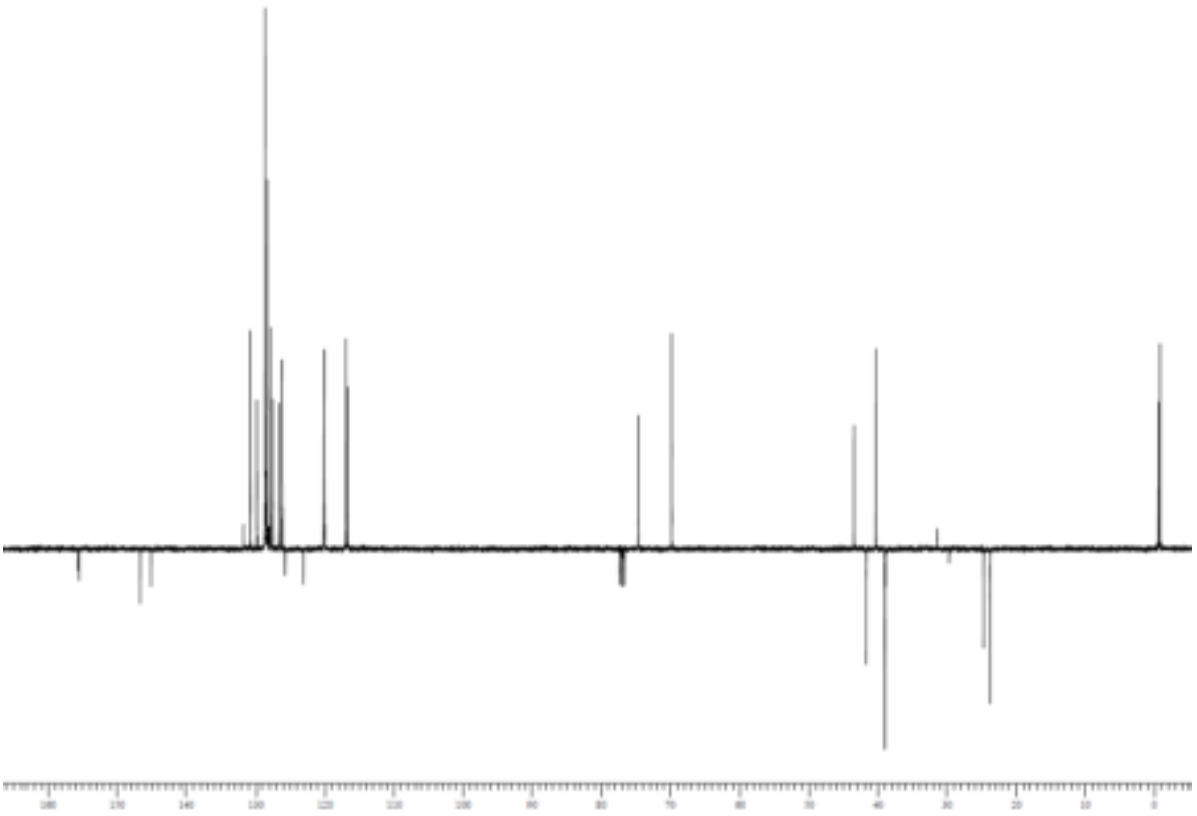
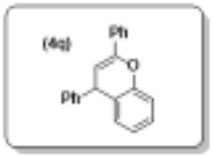
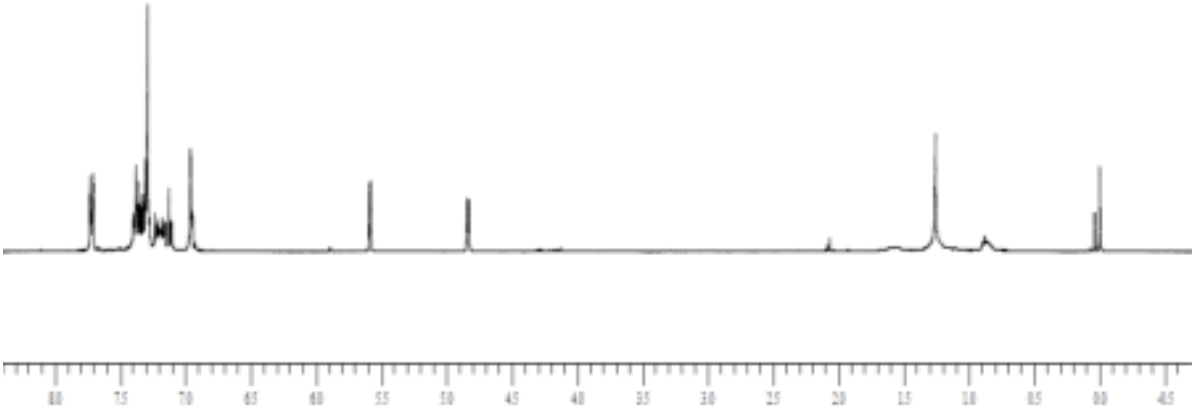
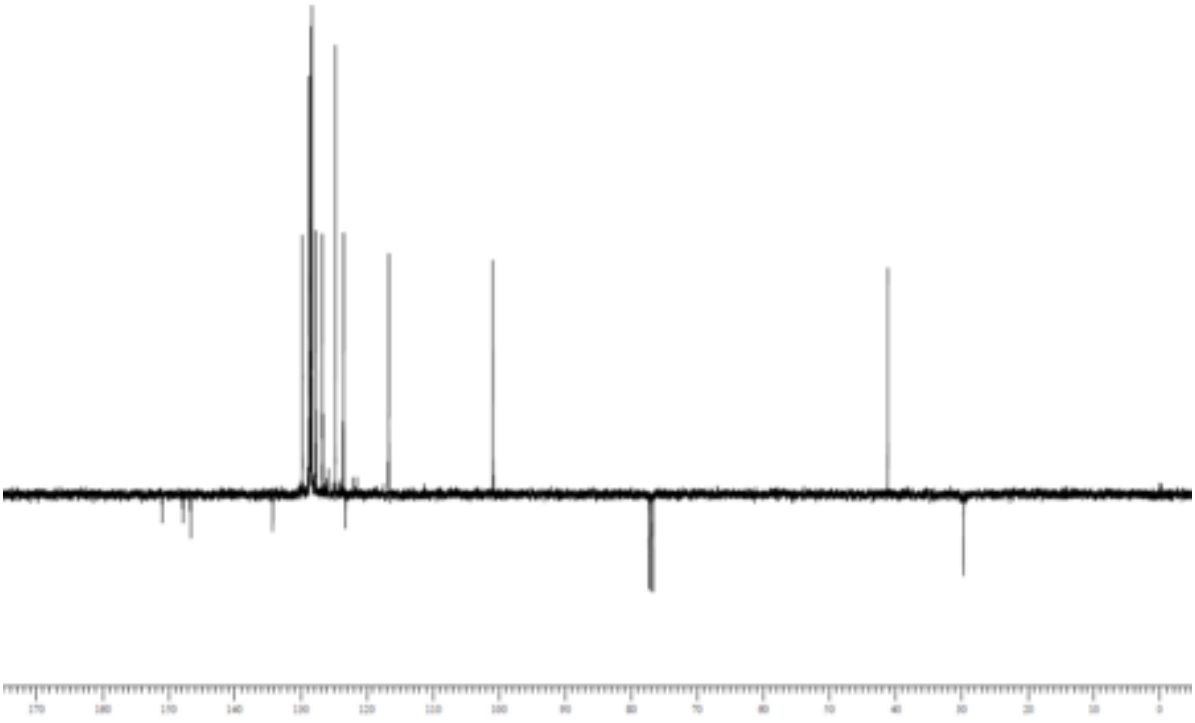
OH

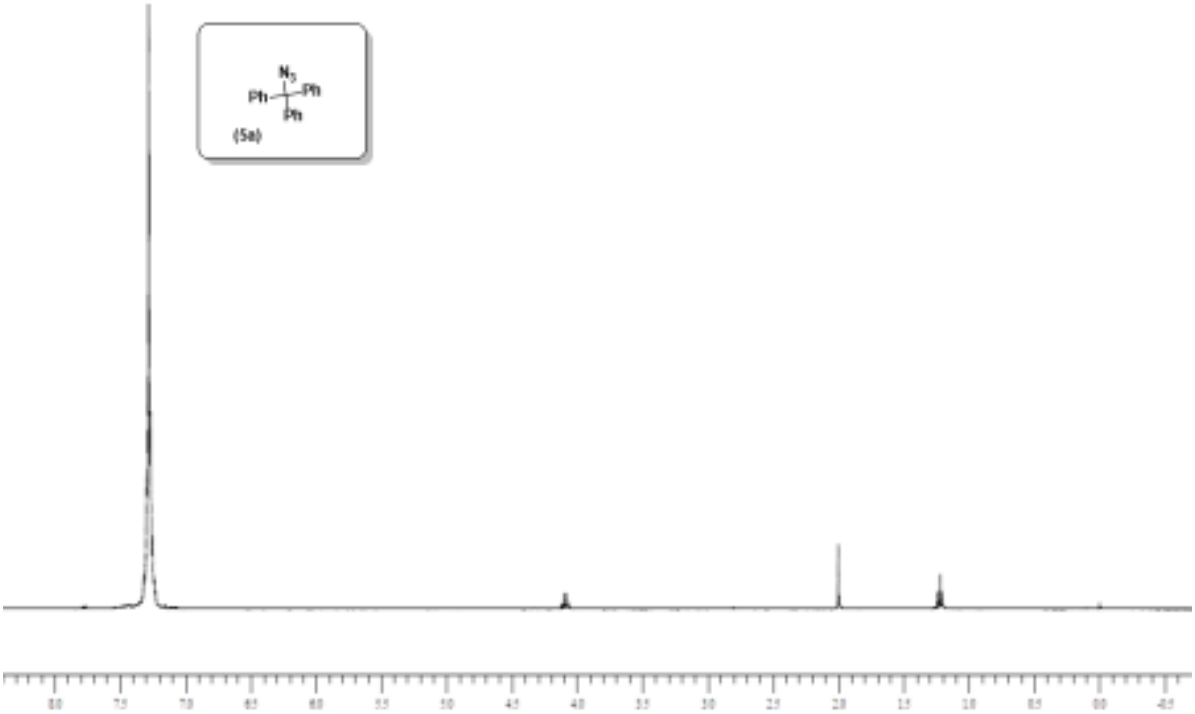

(4p)
TMS
O
Ph

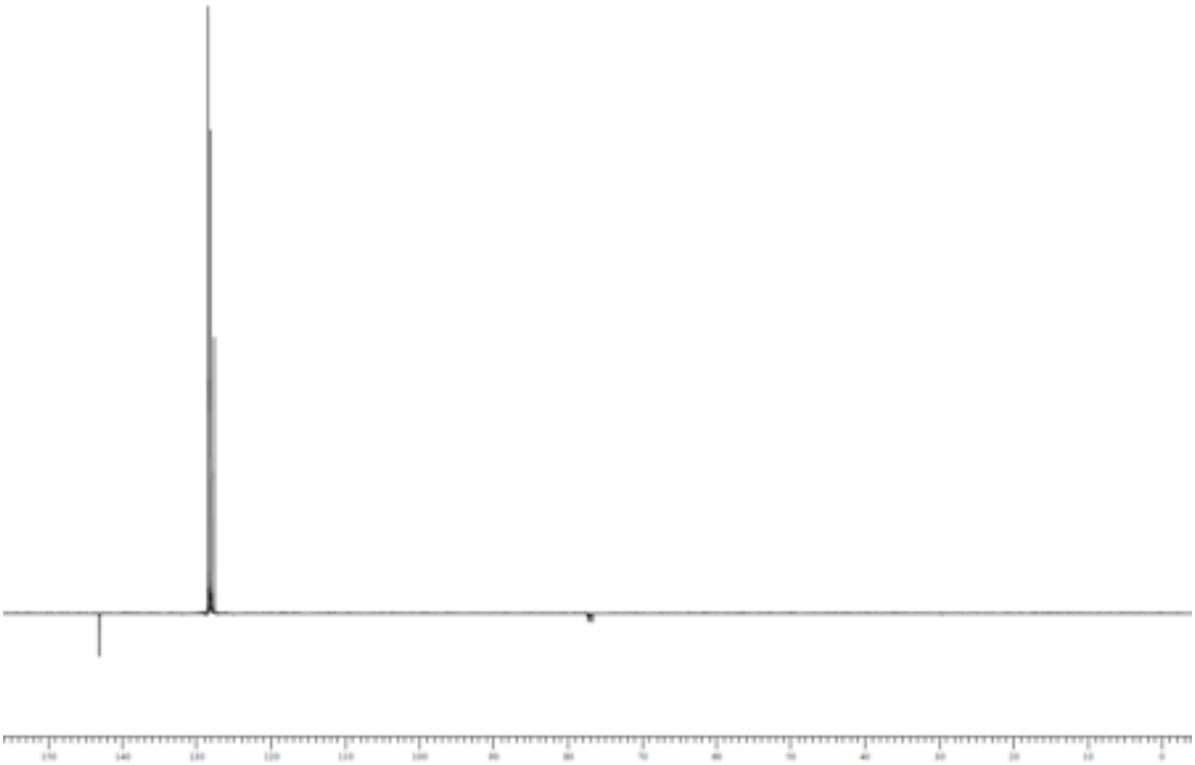


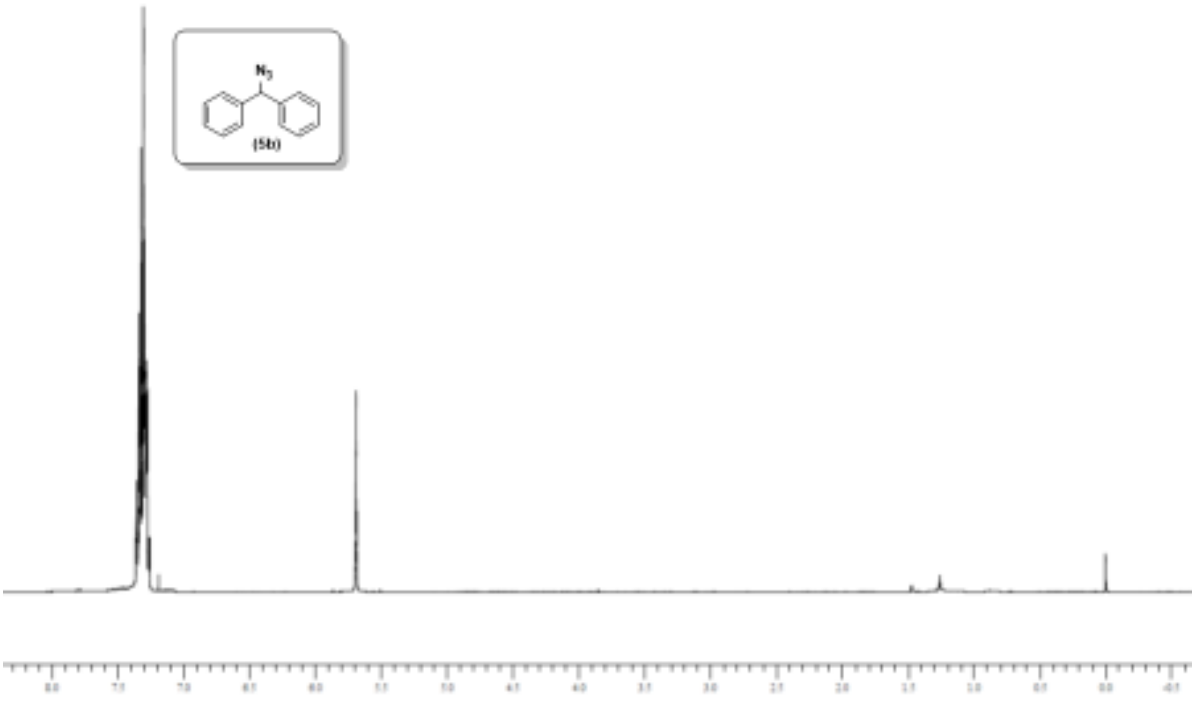

(4q)
Ph
O
Ph

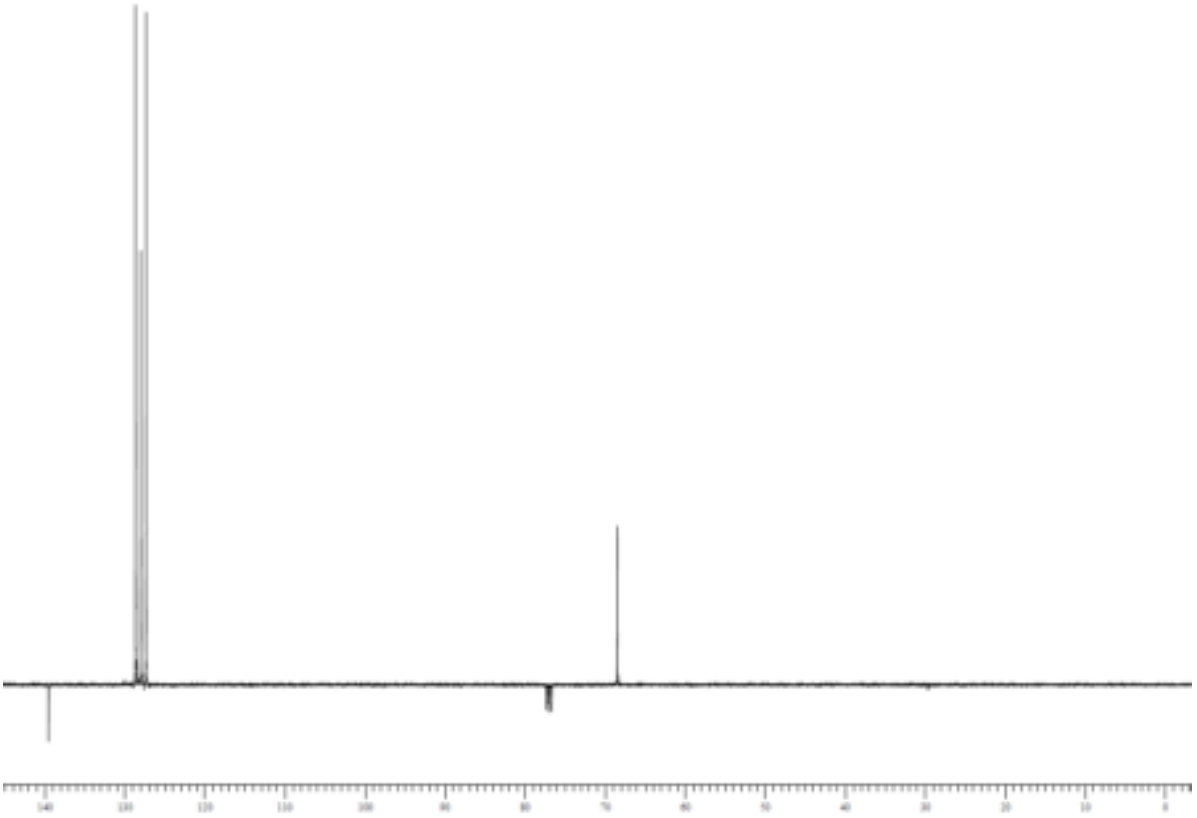


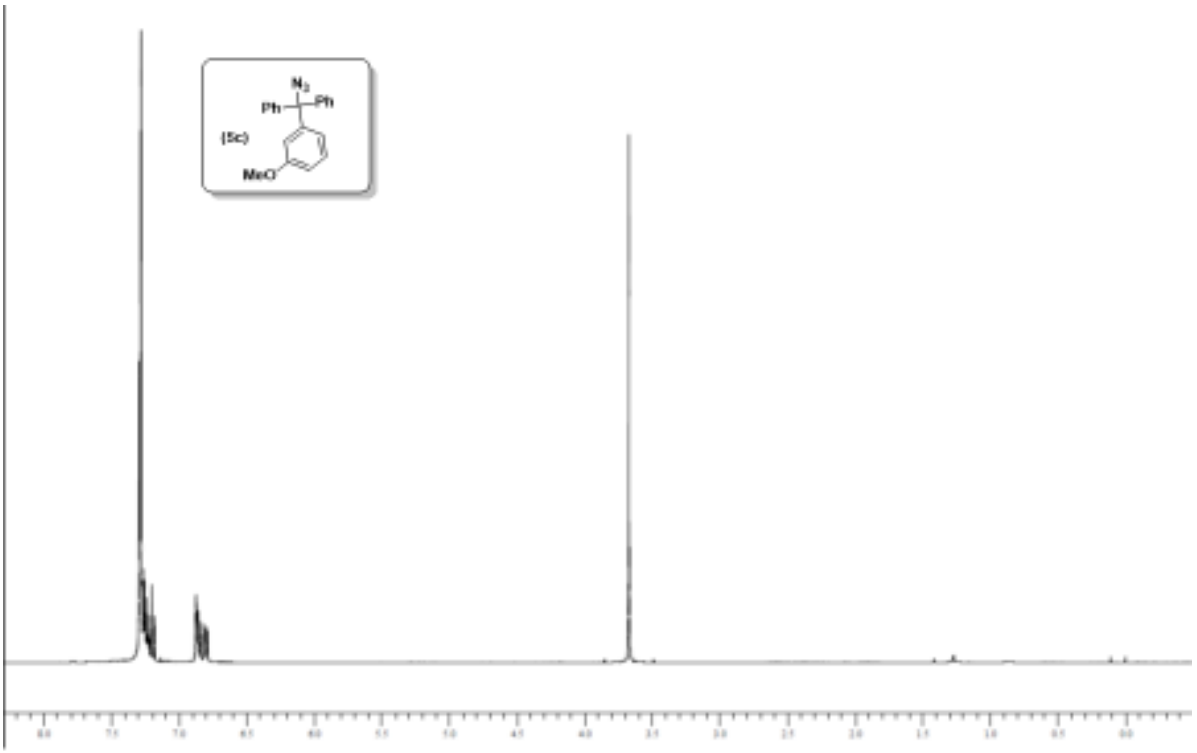


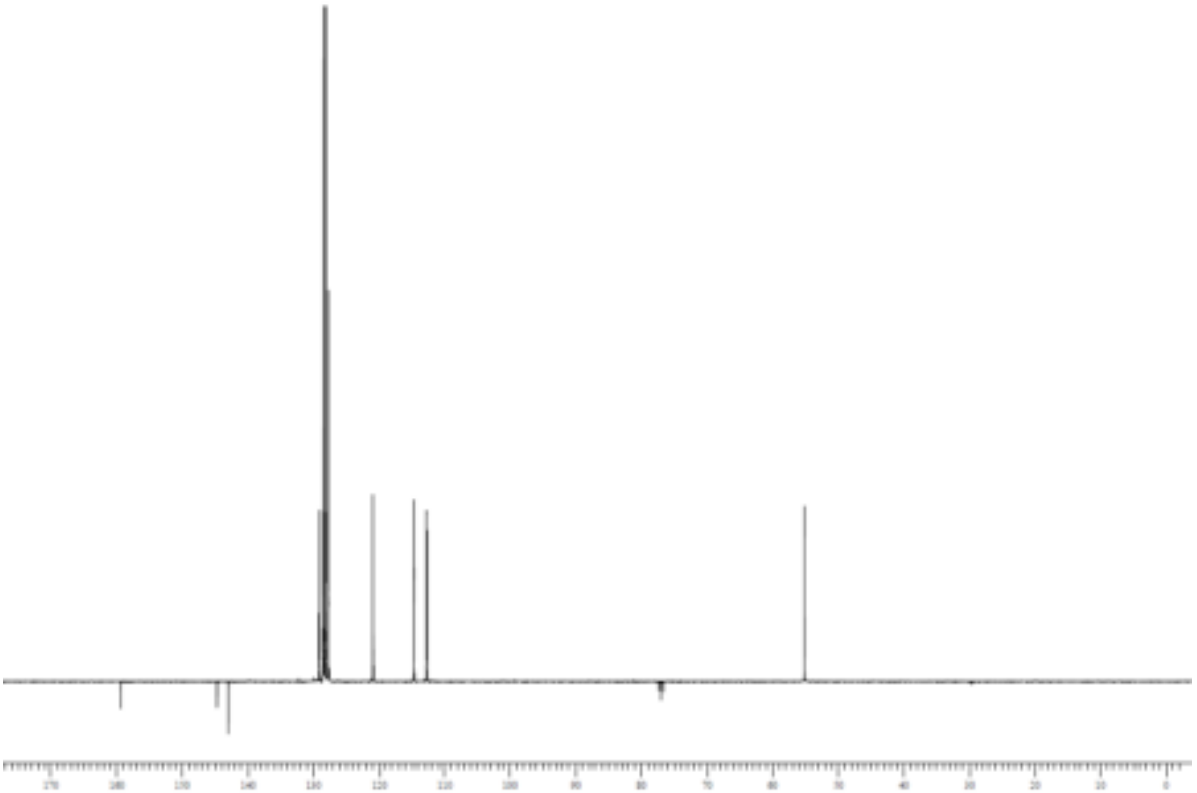

Ph
Ph
Ph
(5a)

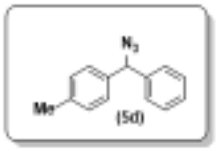


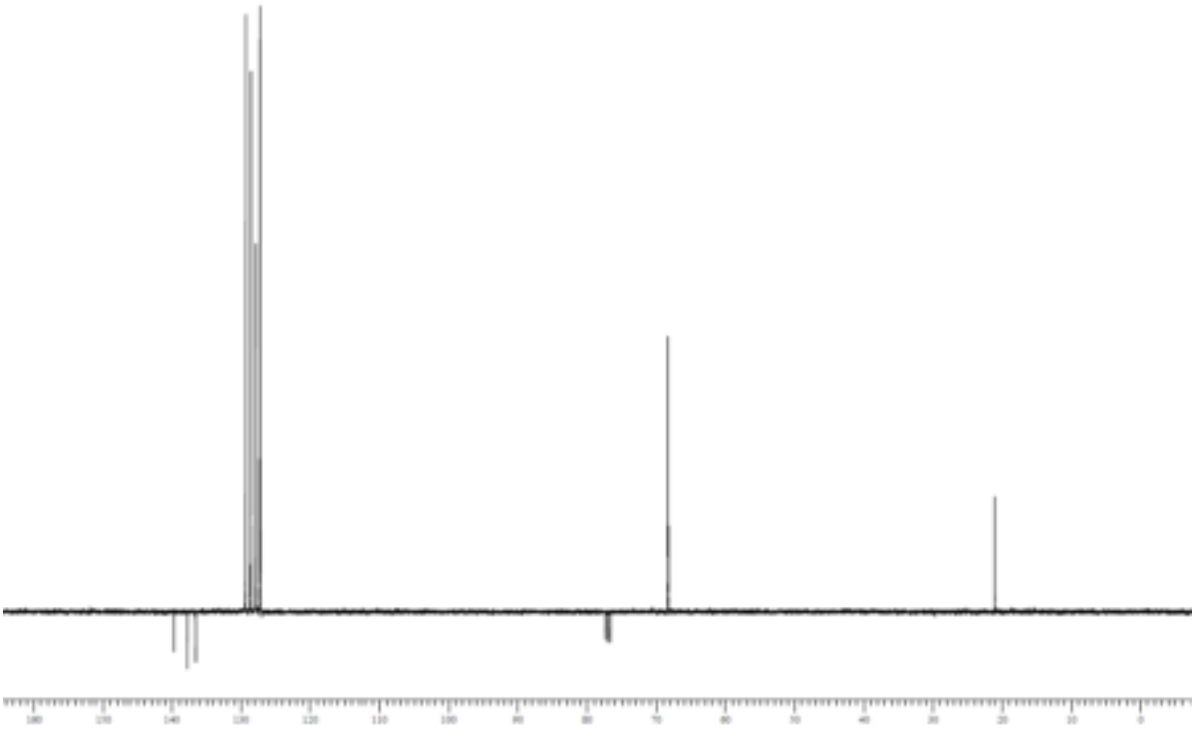

N3
(5b)

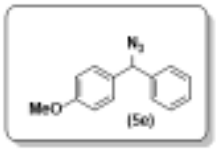


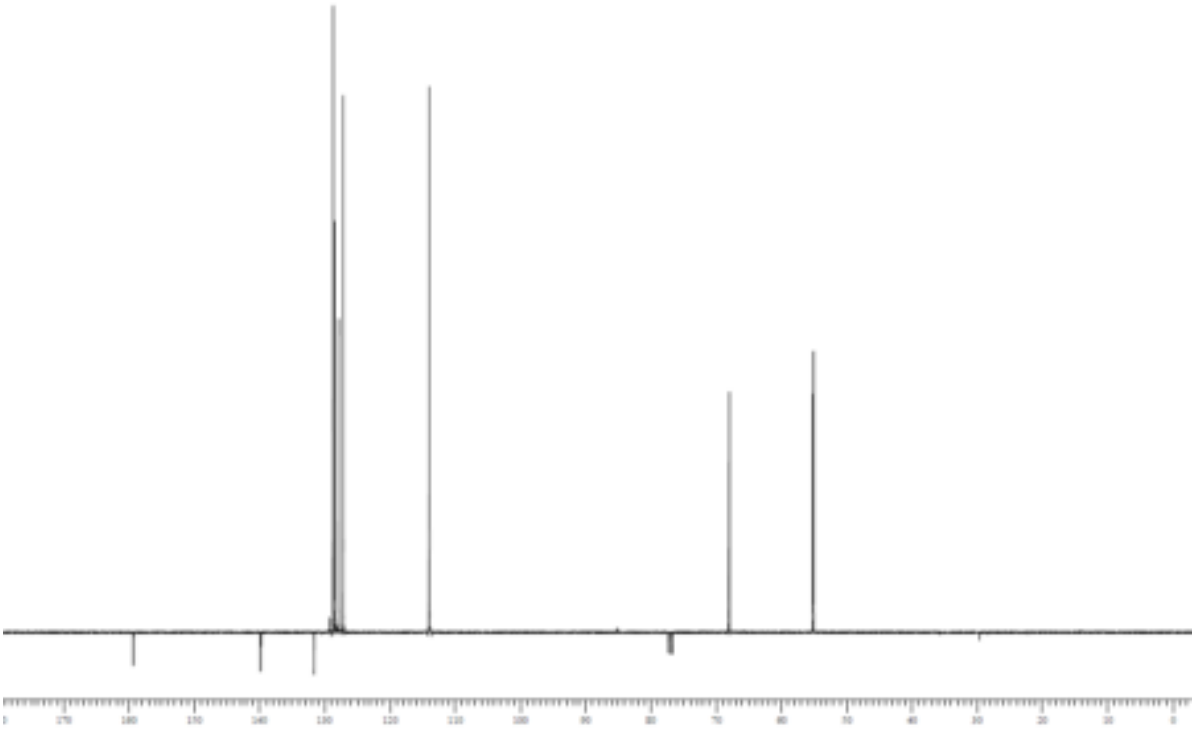

N2
Ph
Ph
(5c)
MeO

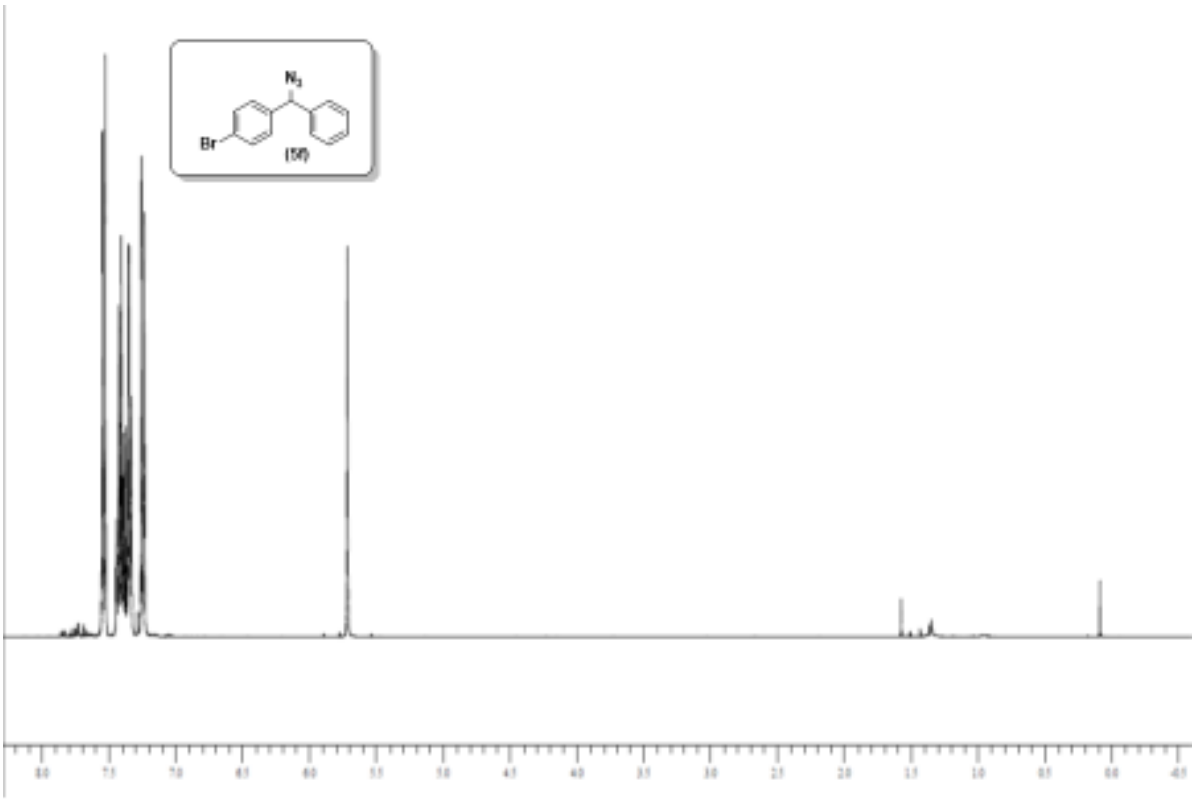


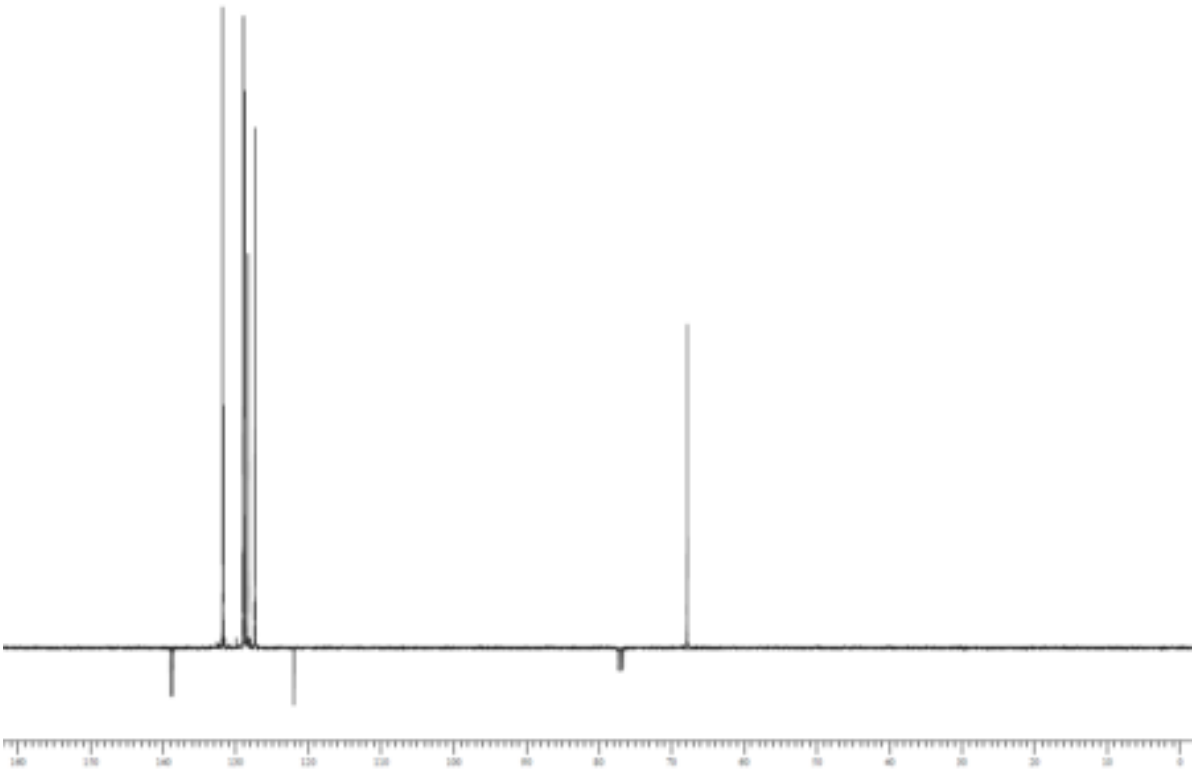

N3
Me
(5d)

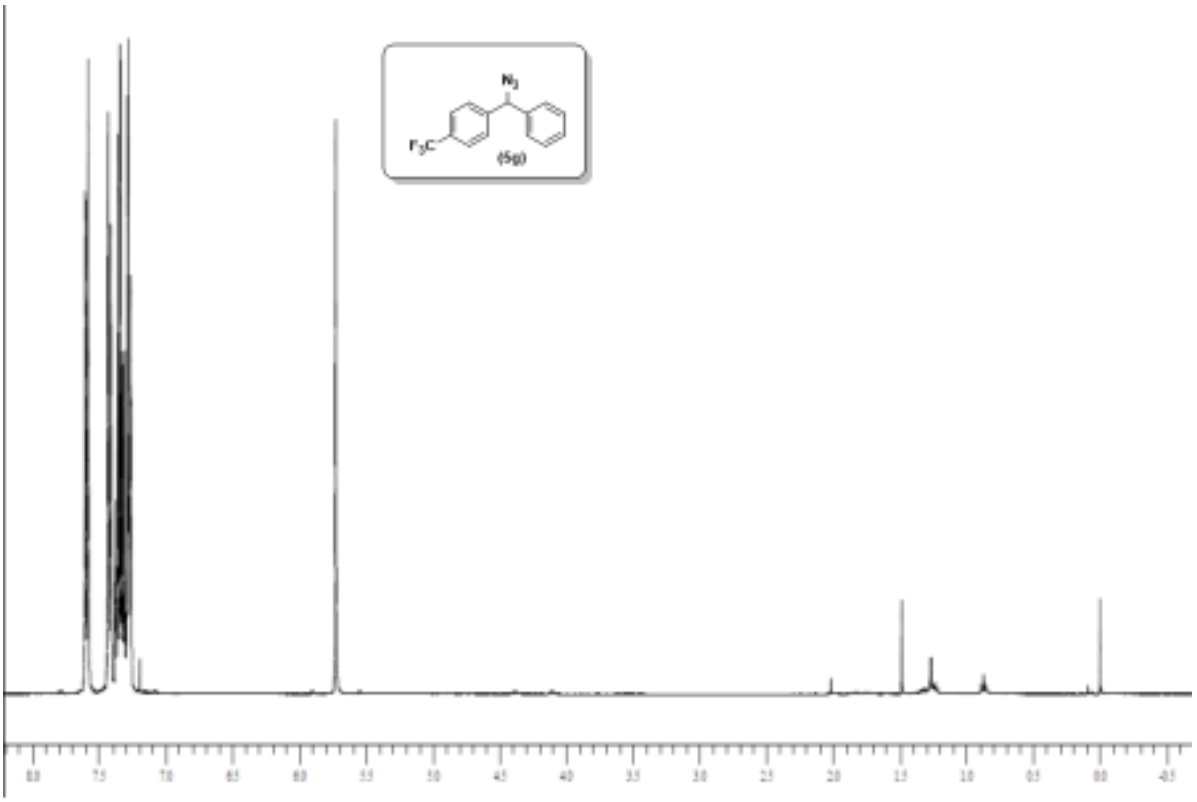


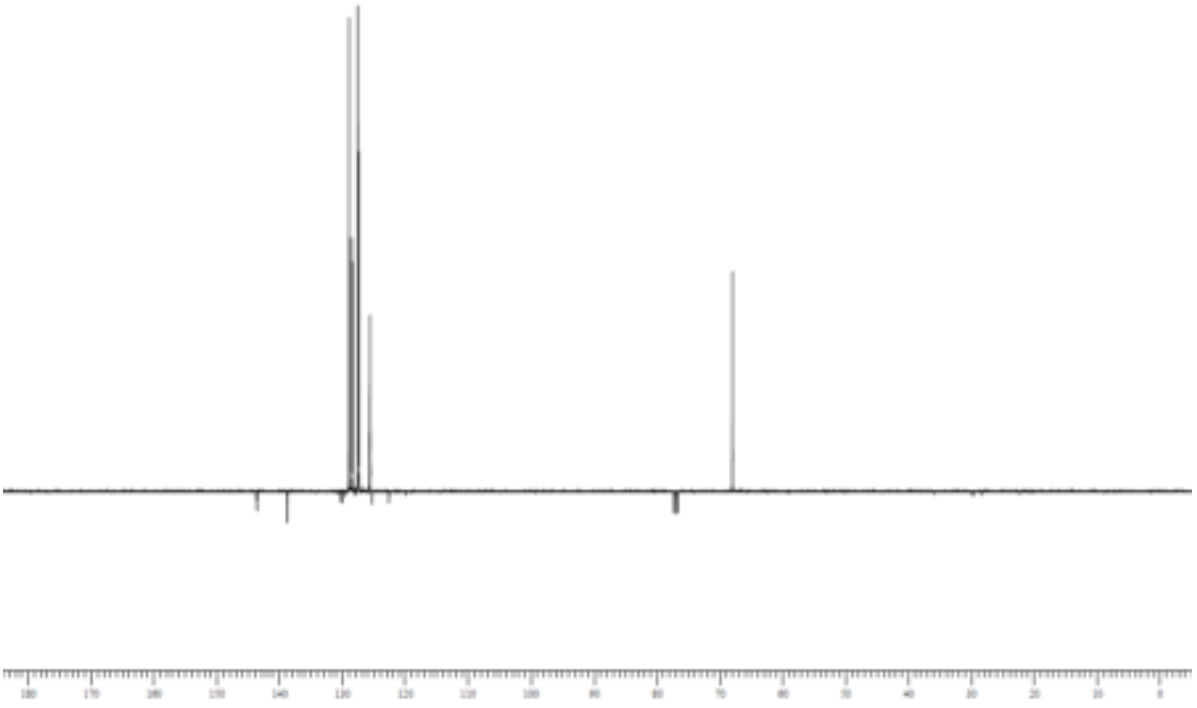

N3
MeO
(5o)

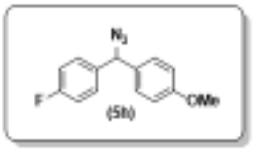


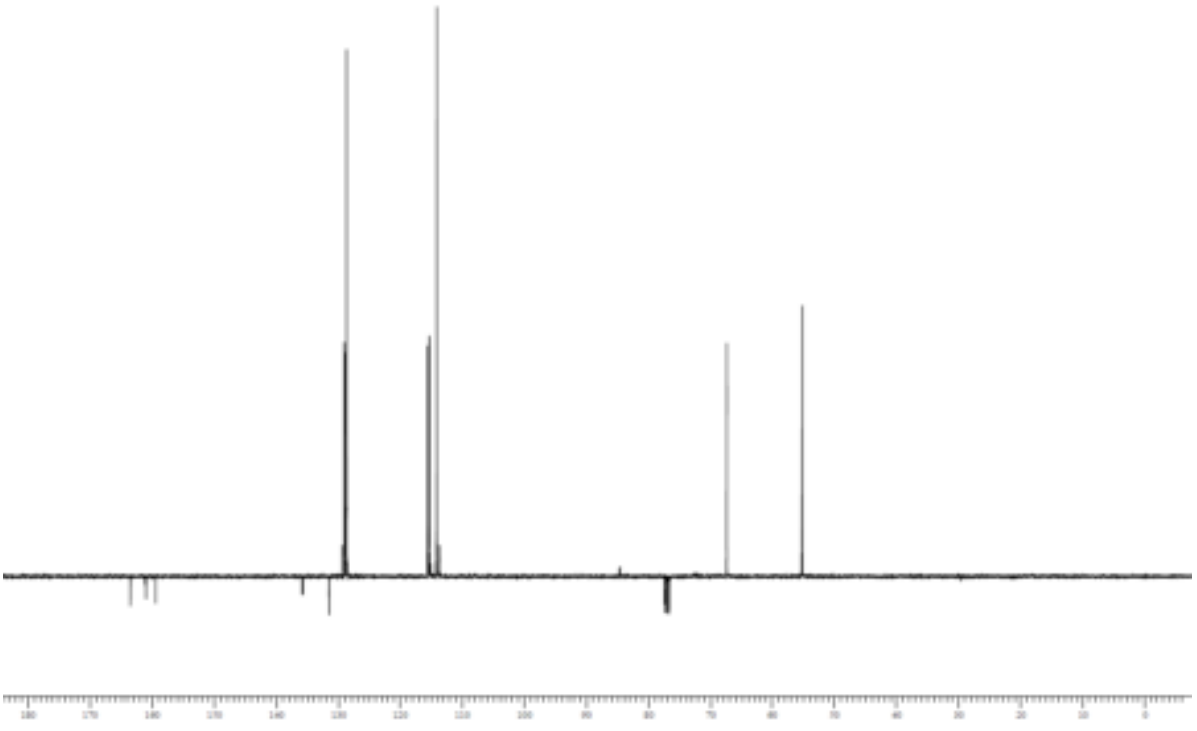

N3
Br
(5f)

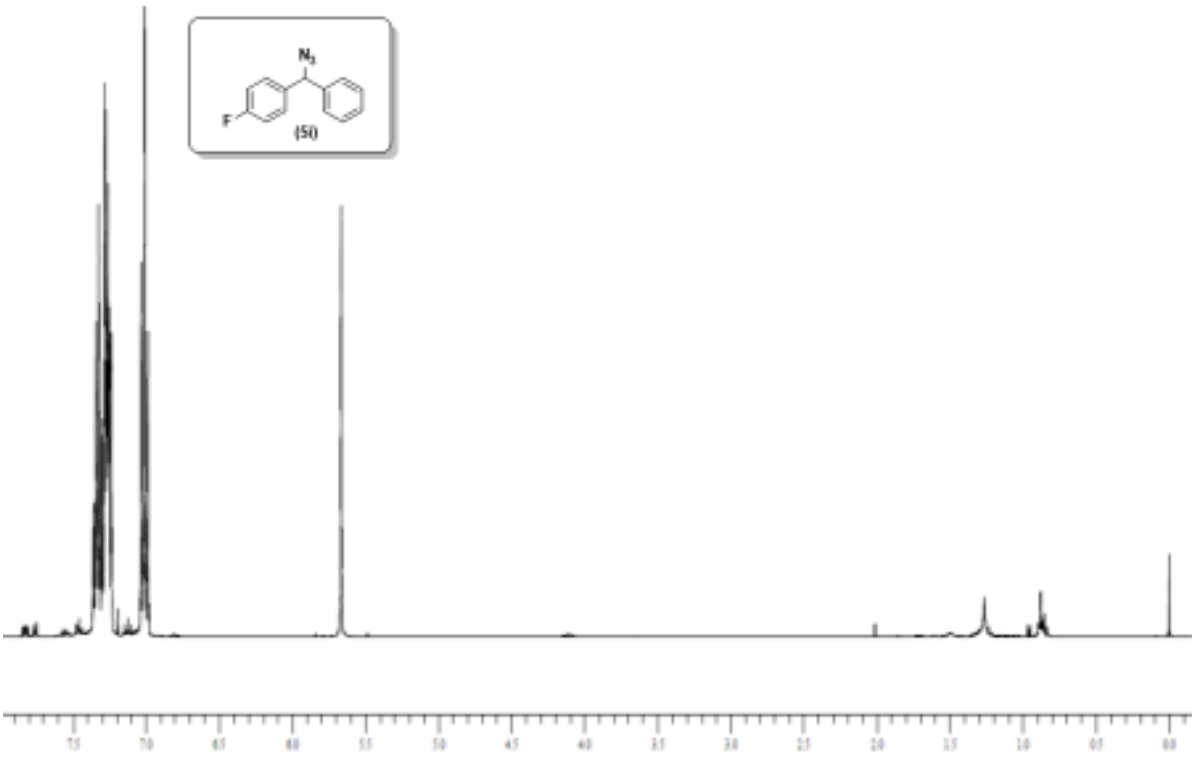


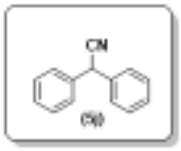

N3
F3C
(5g)

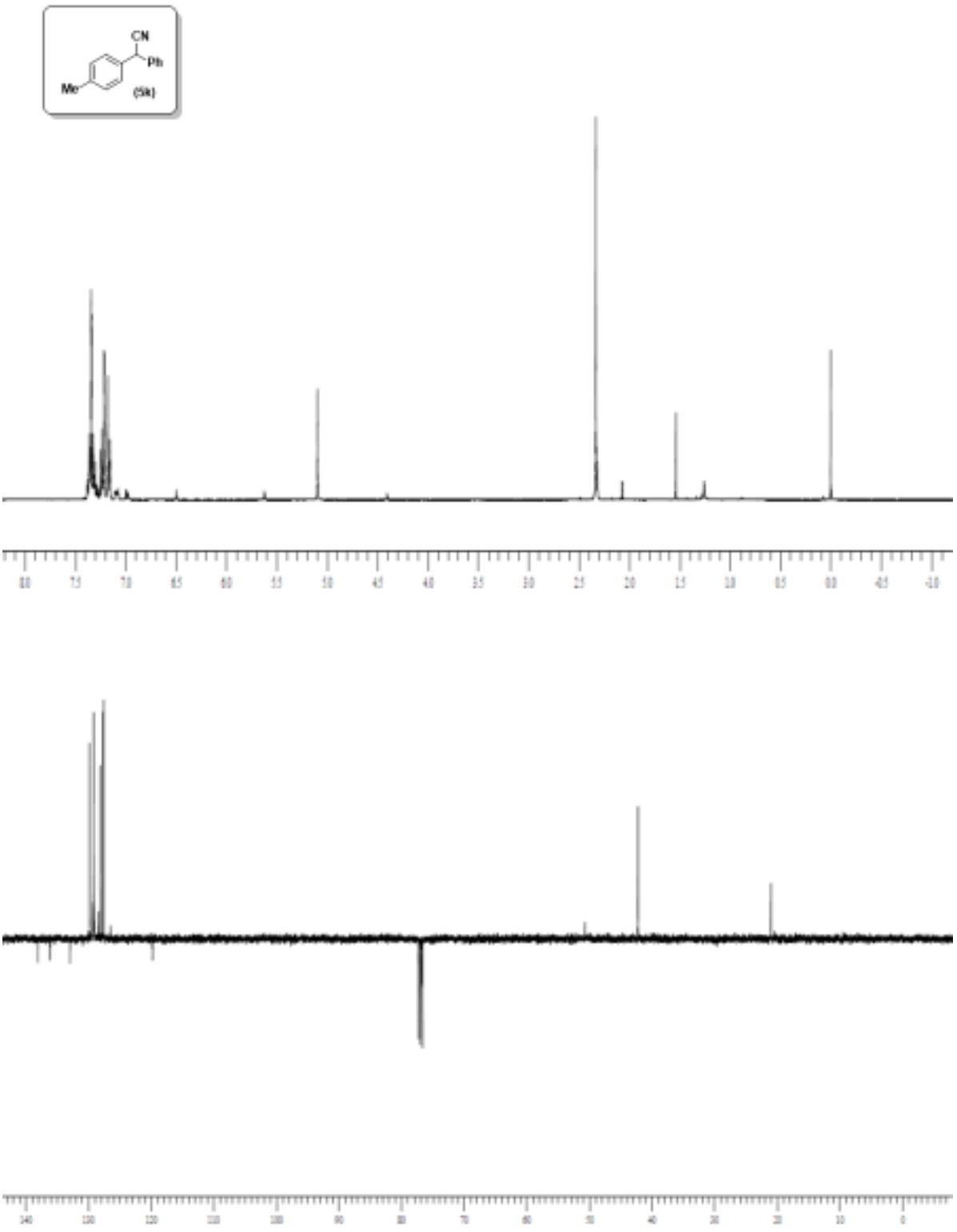


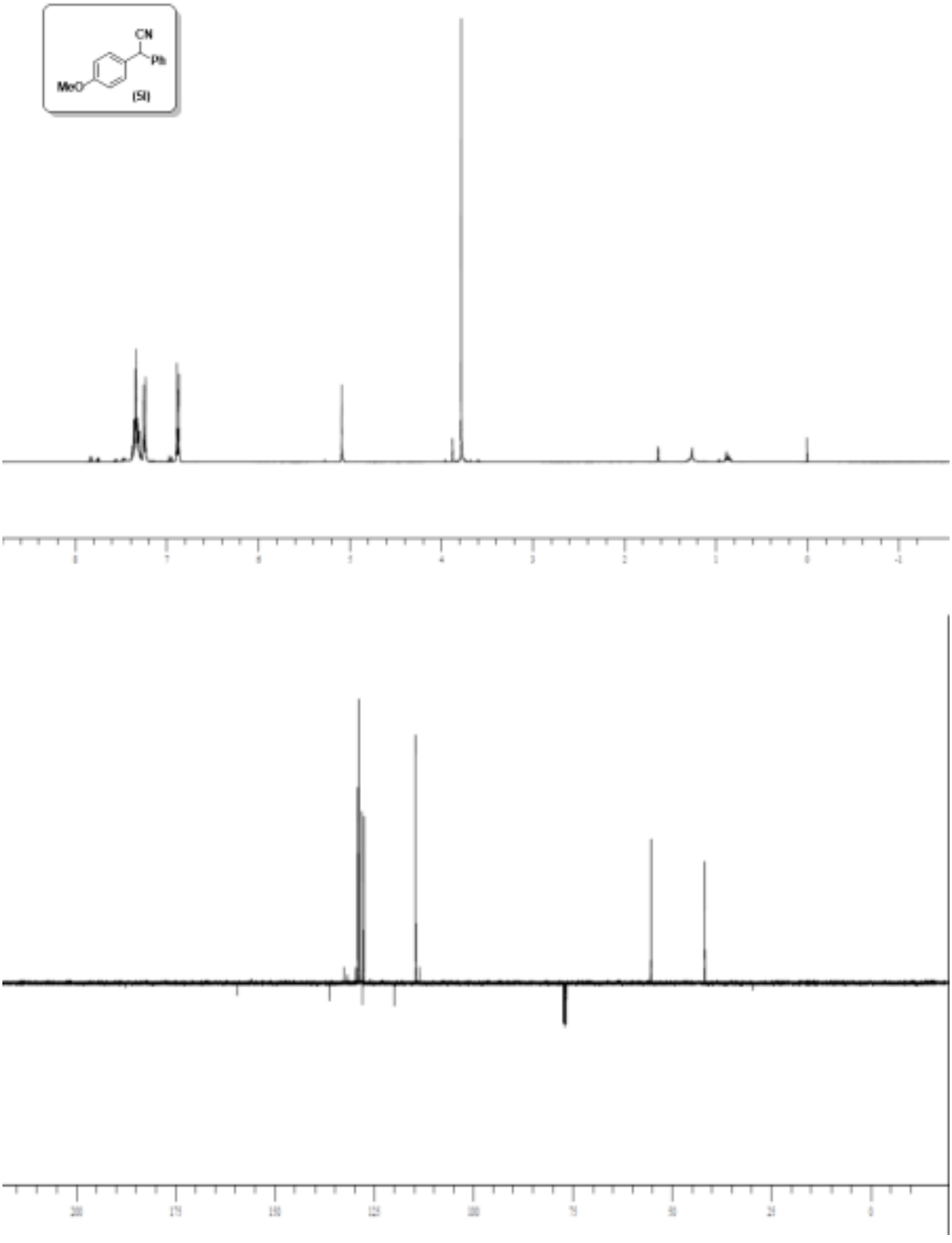

N3
F
OMe
(5h)

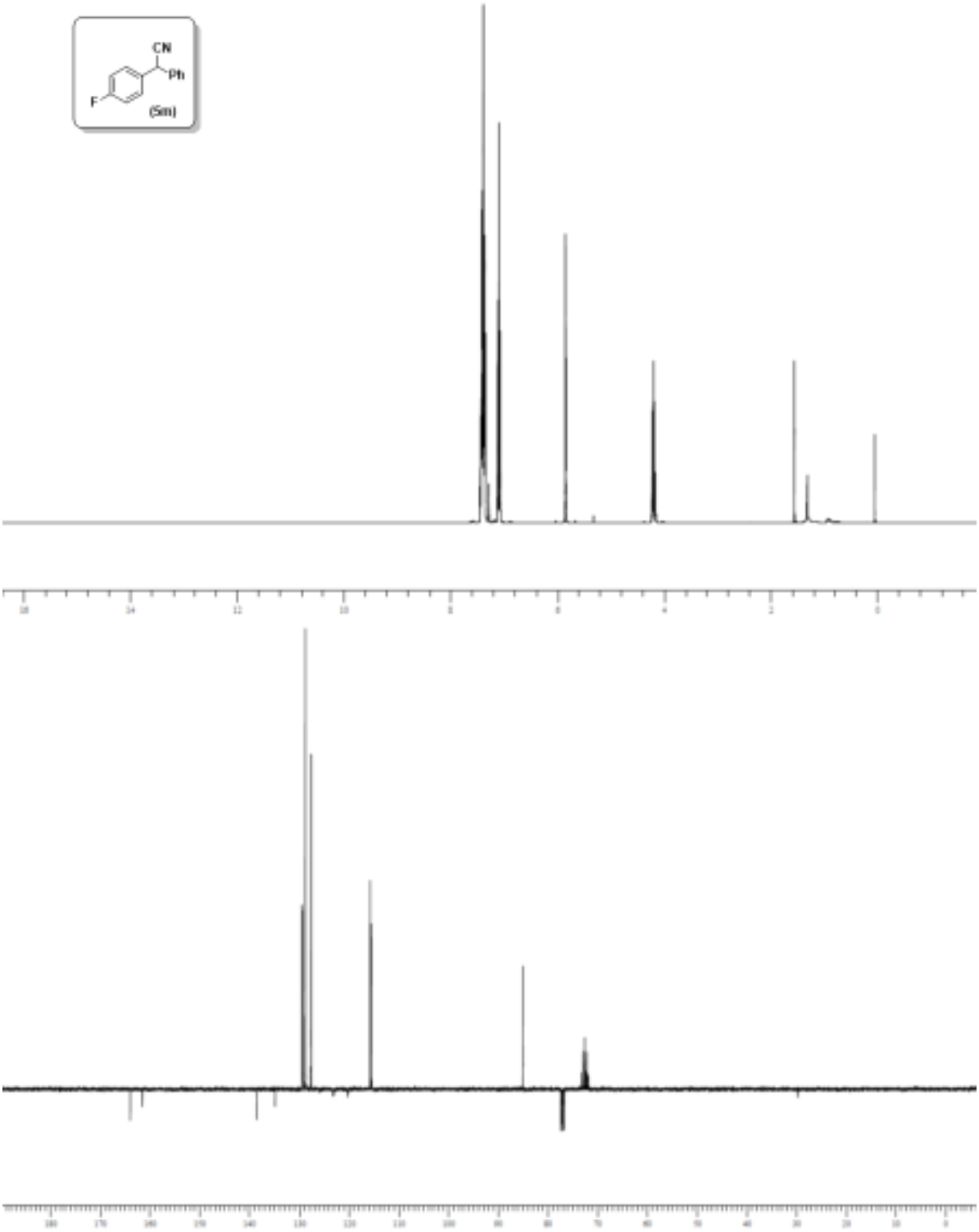


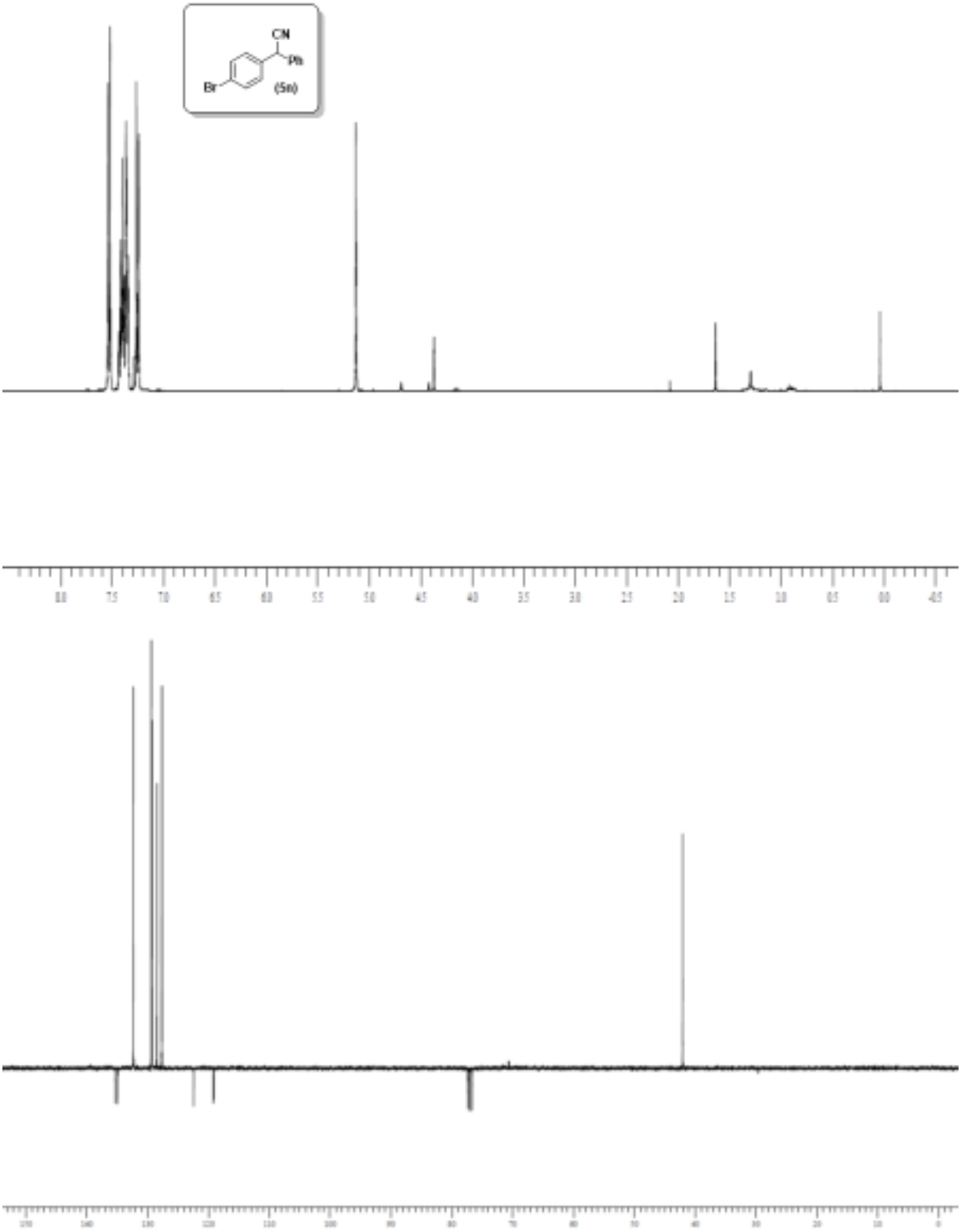

N3
F
(50)

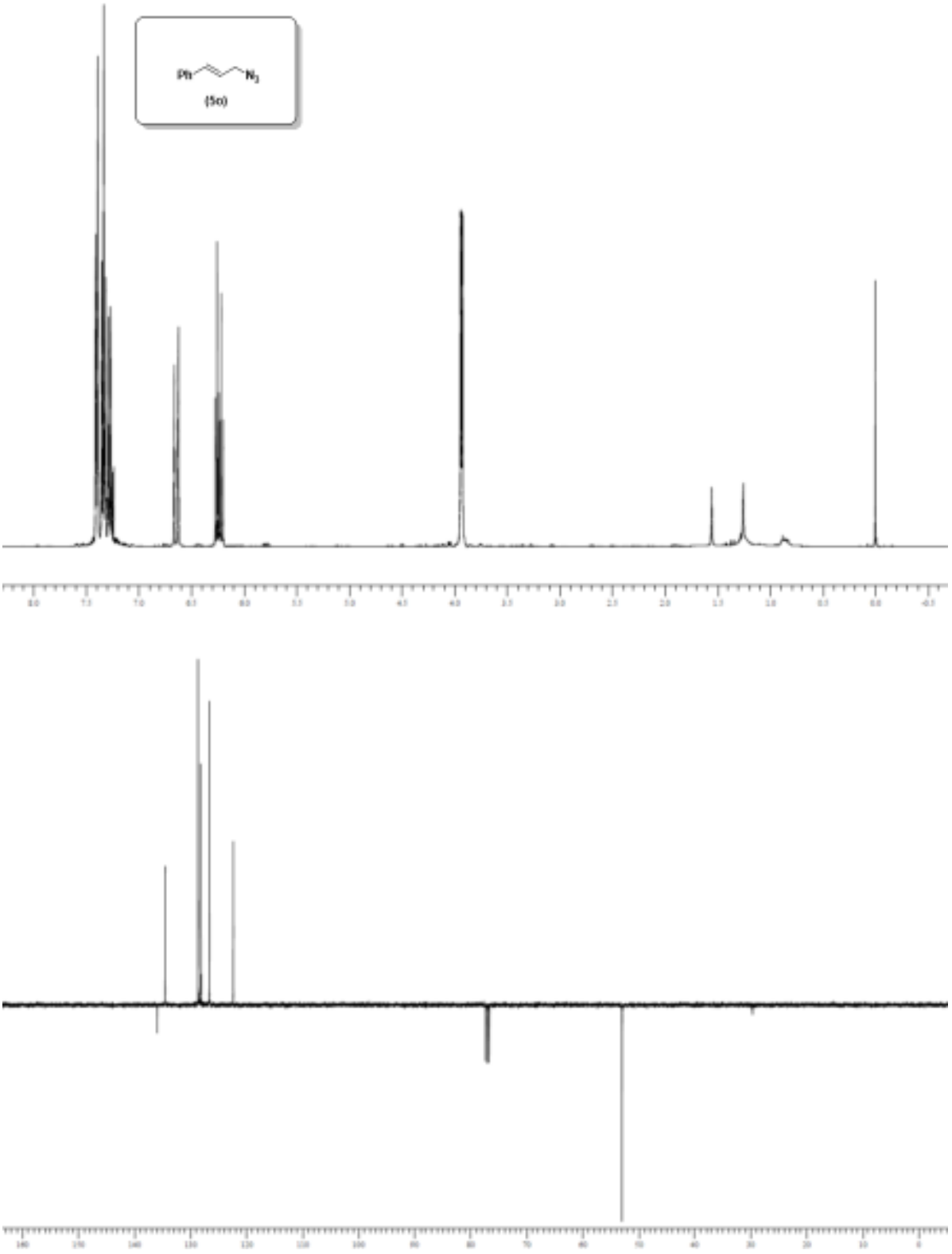

CN
(76)

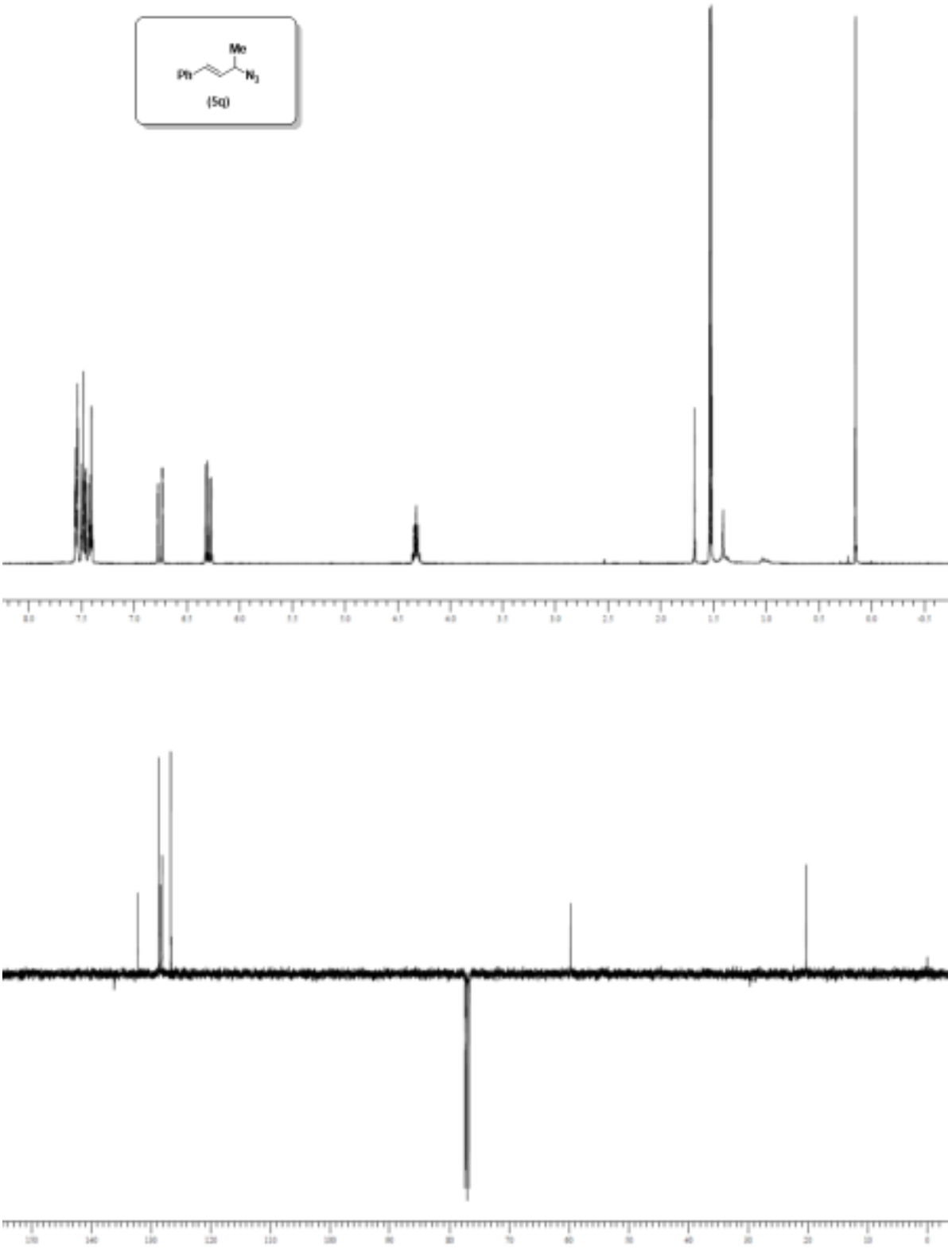

CN
Ph
Me
(5k)

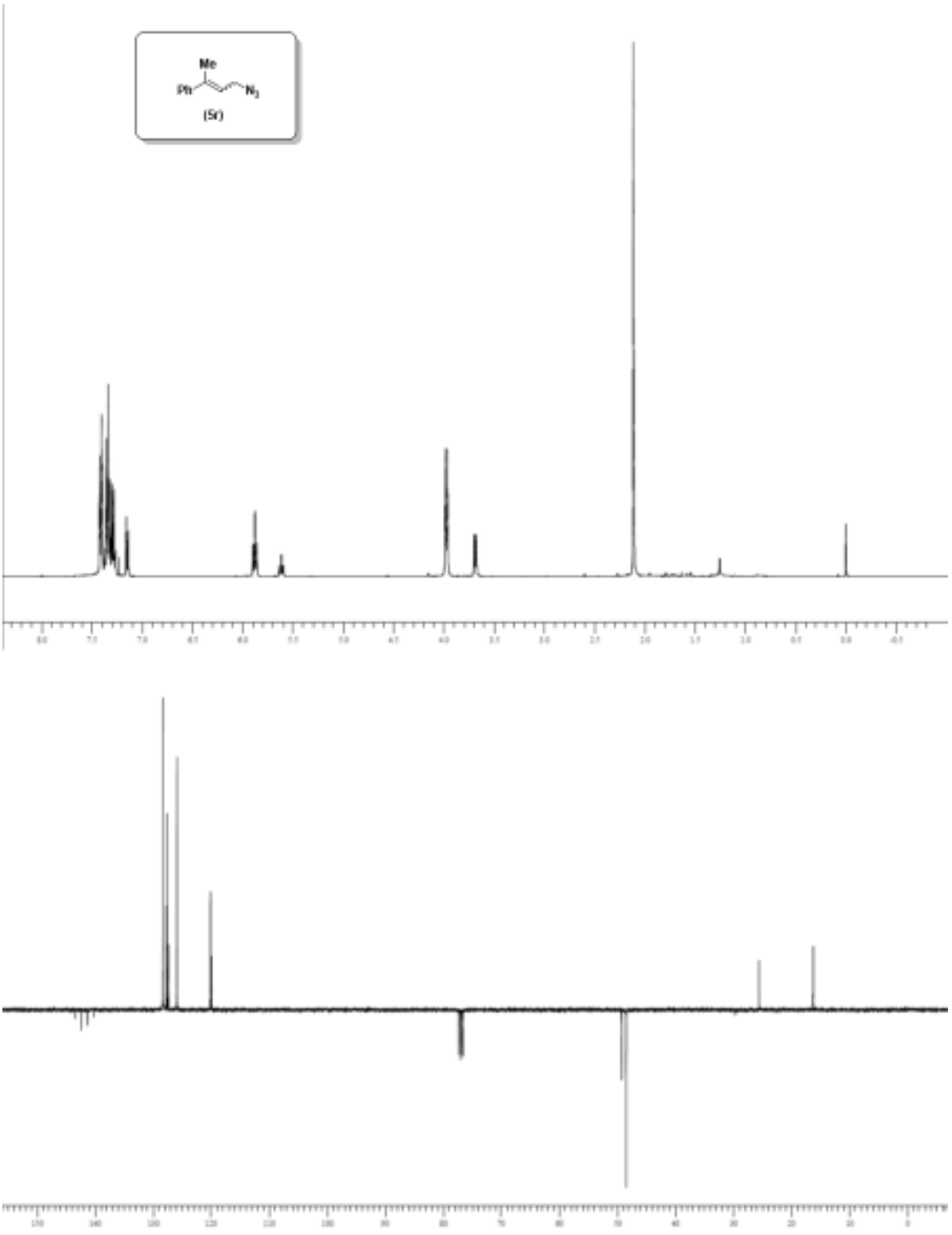

CN
Ph
MeO
(5l)

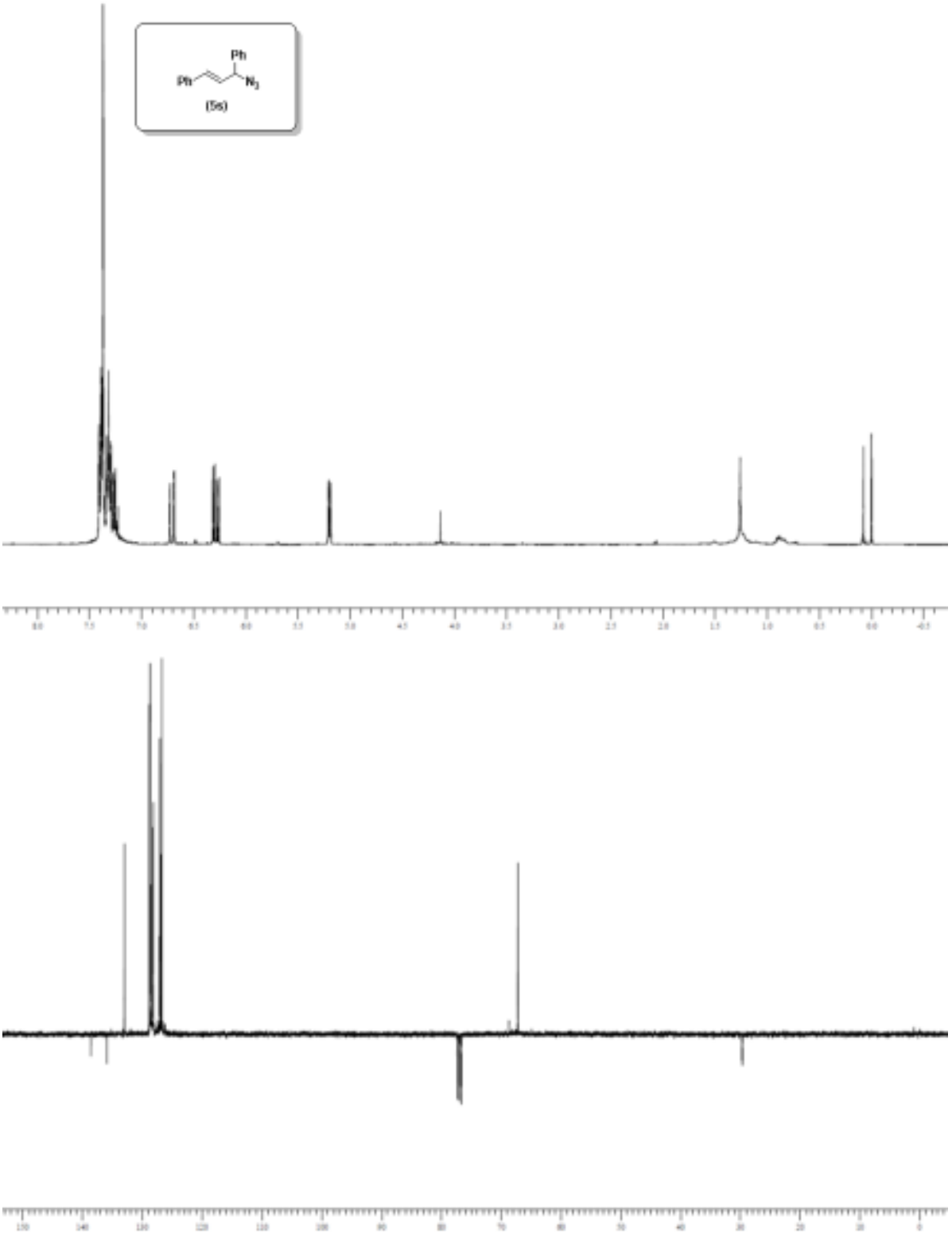

CN
Ph
F
(5m)

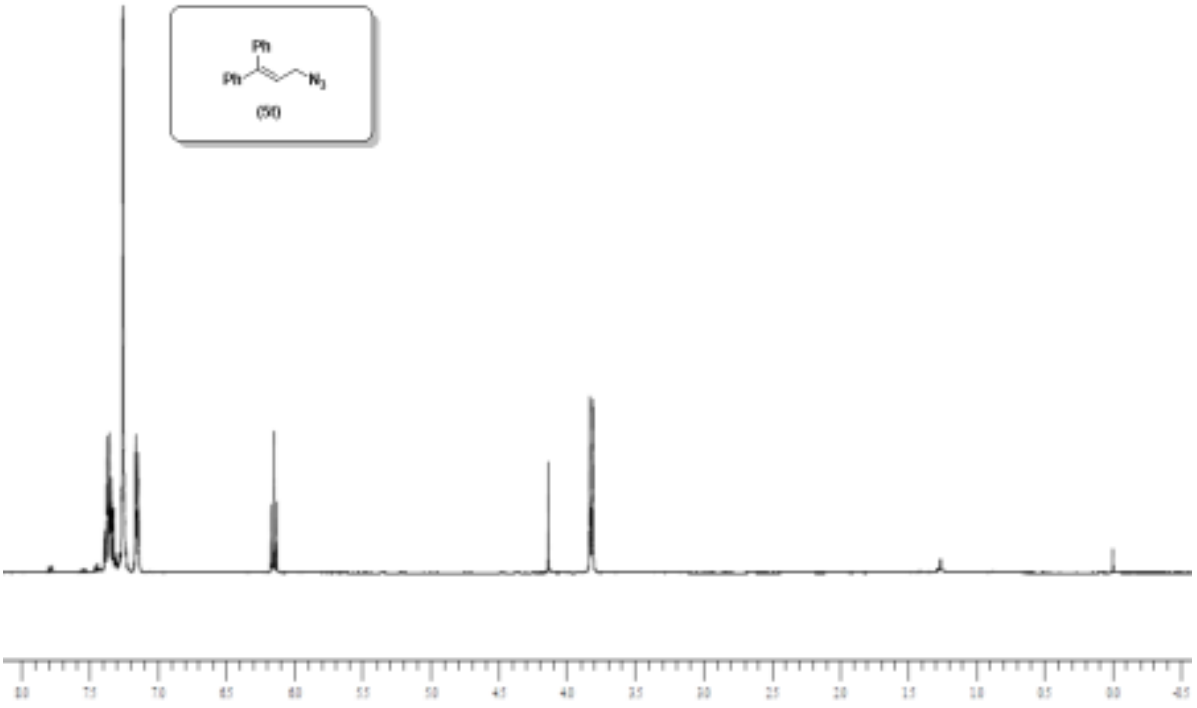

CN
Ph
Br
(5n)

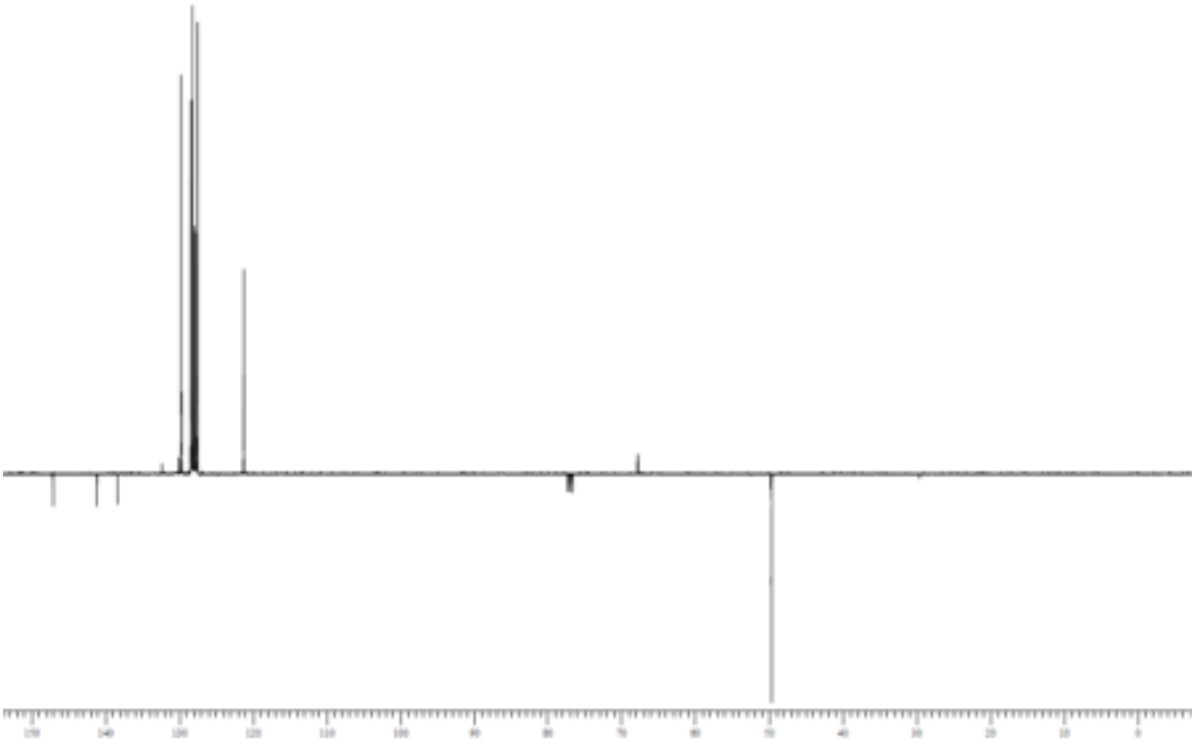

Ph
N3
(5o)

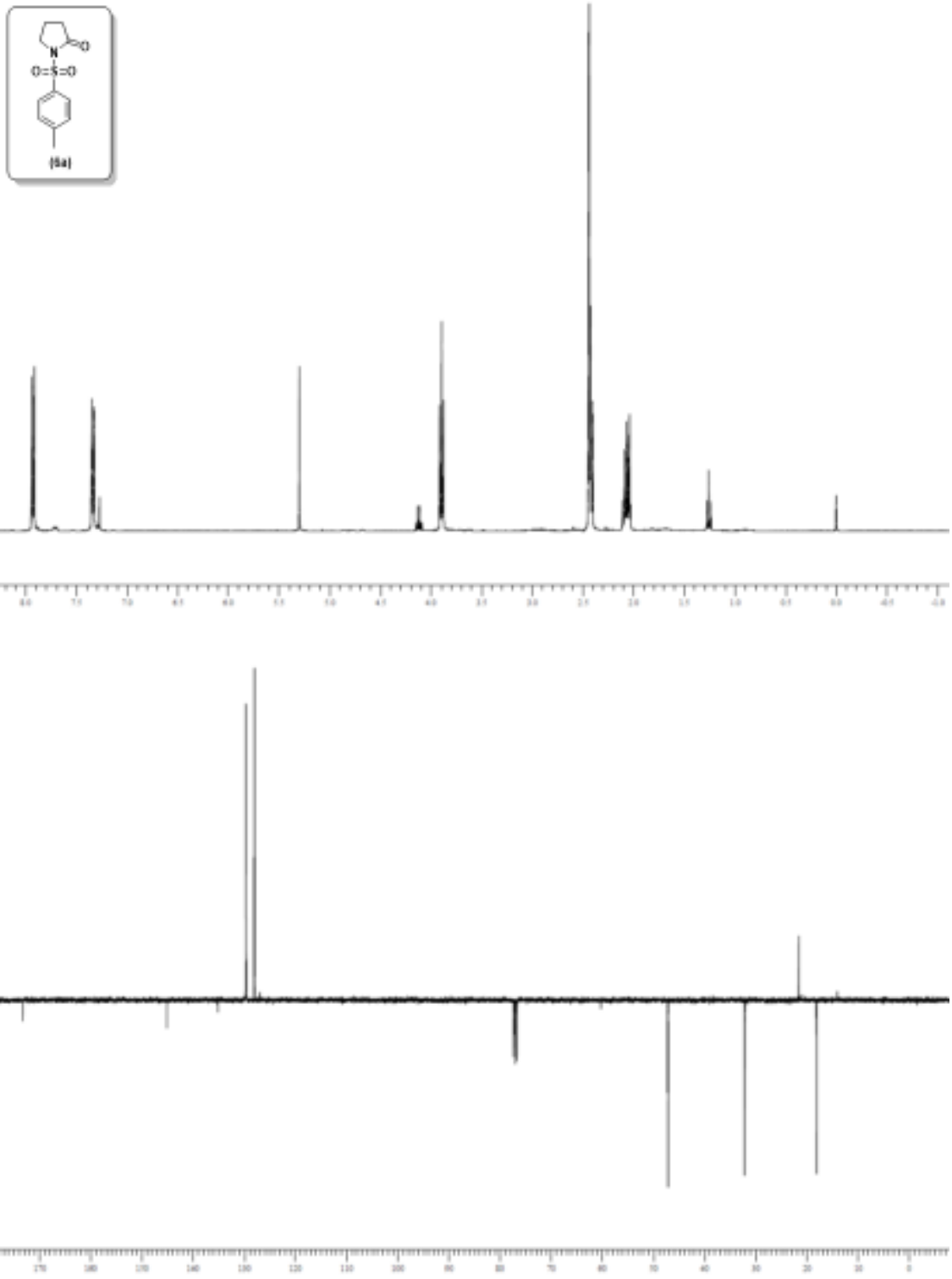

Me
Ph
N3
(5q)

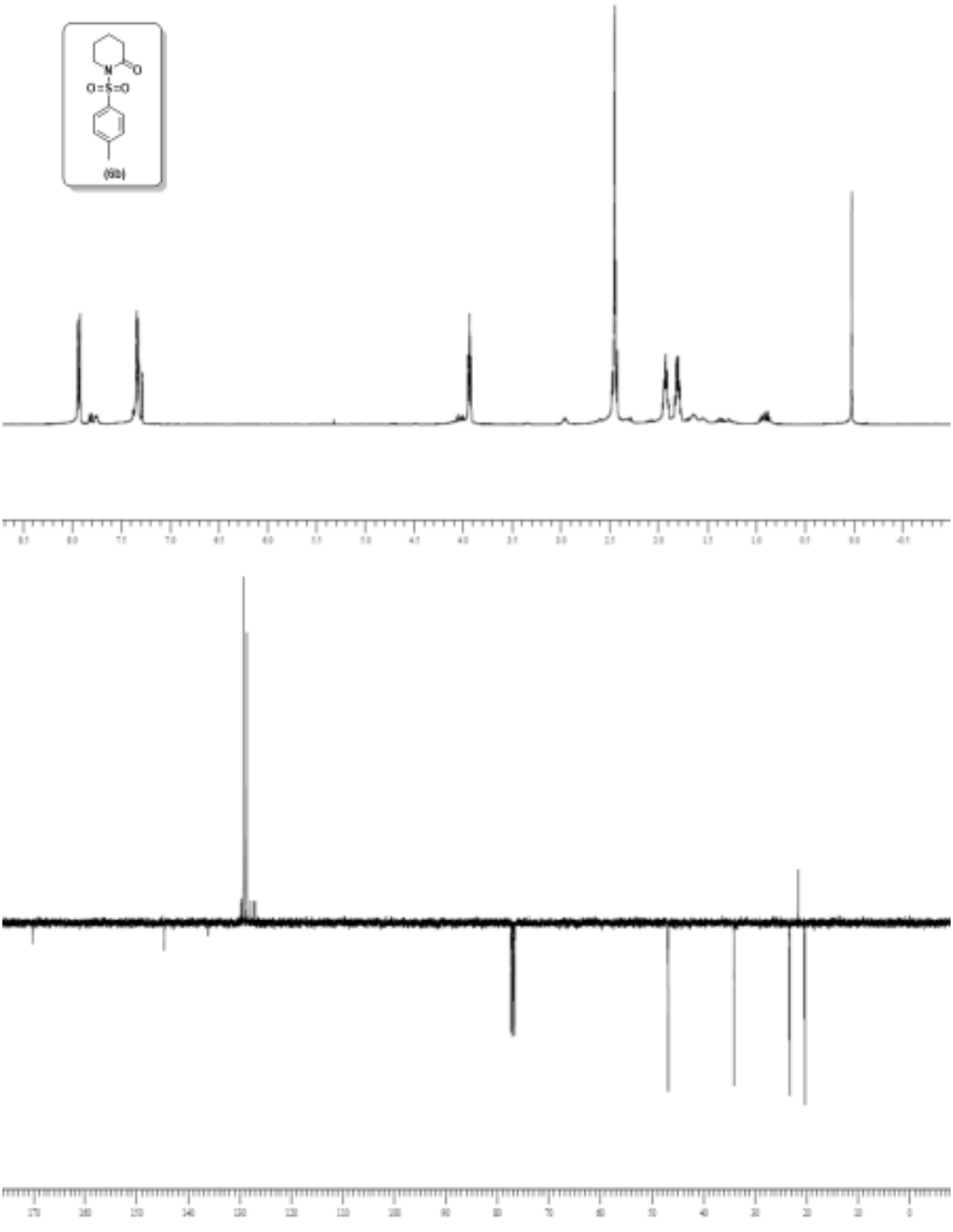

Me
Ph
N3
(Sr)

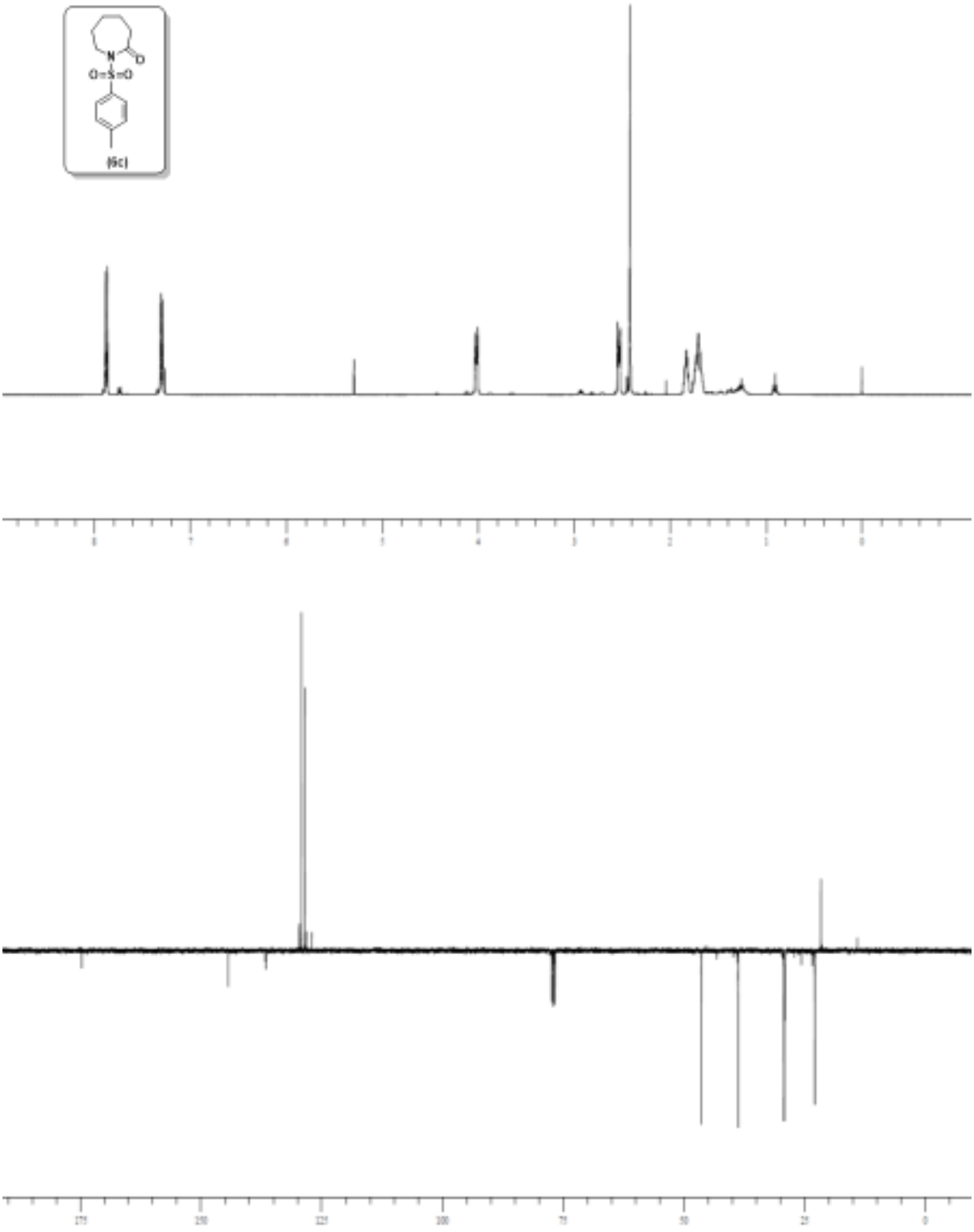

Ph
Ph
N3
(5s)

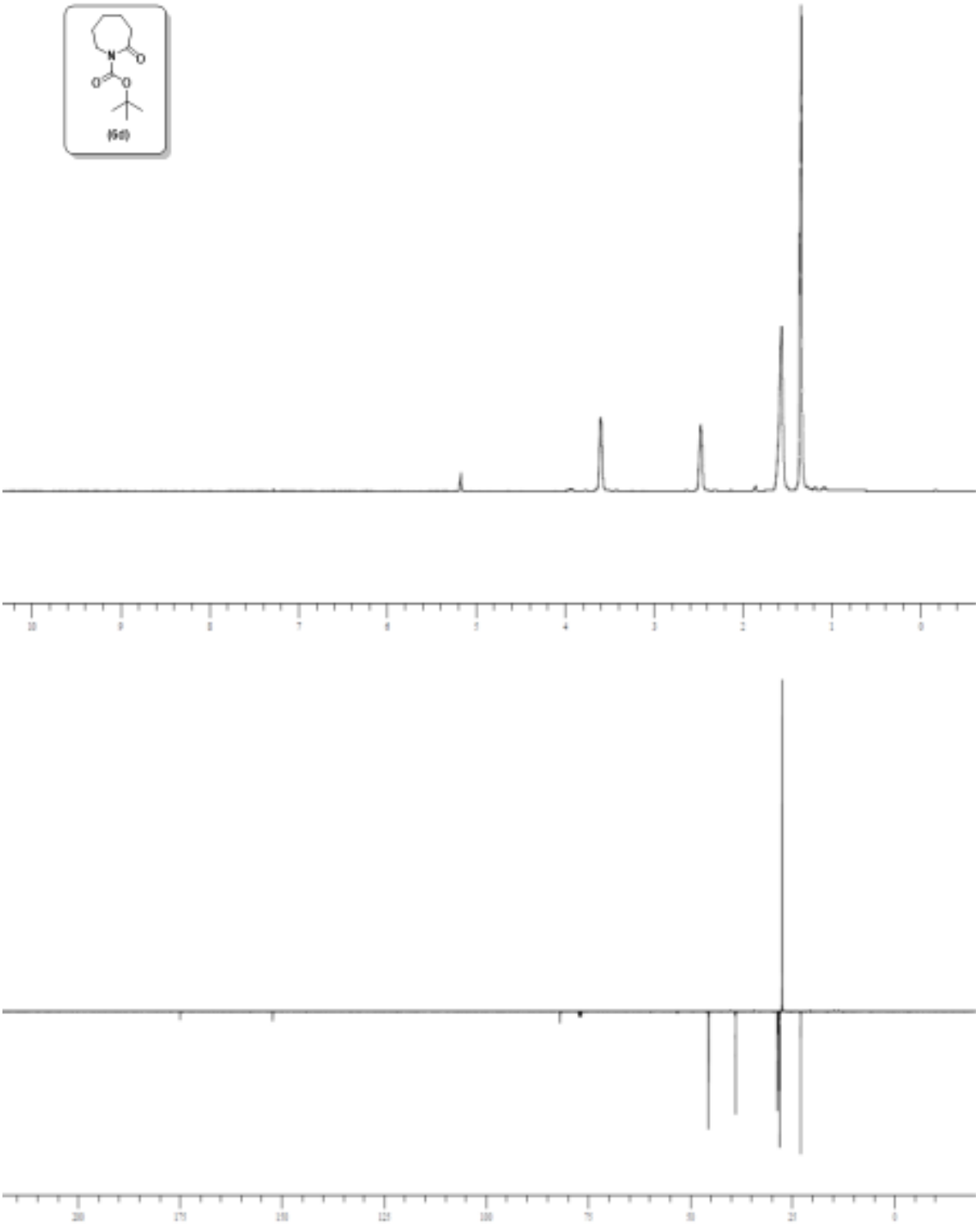

Ph
Ph
N3
(9l)

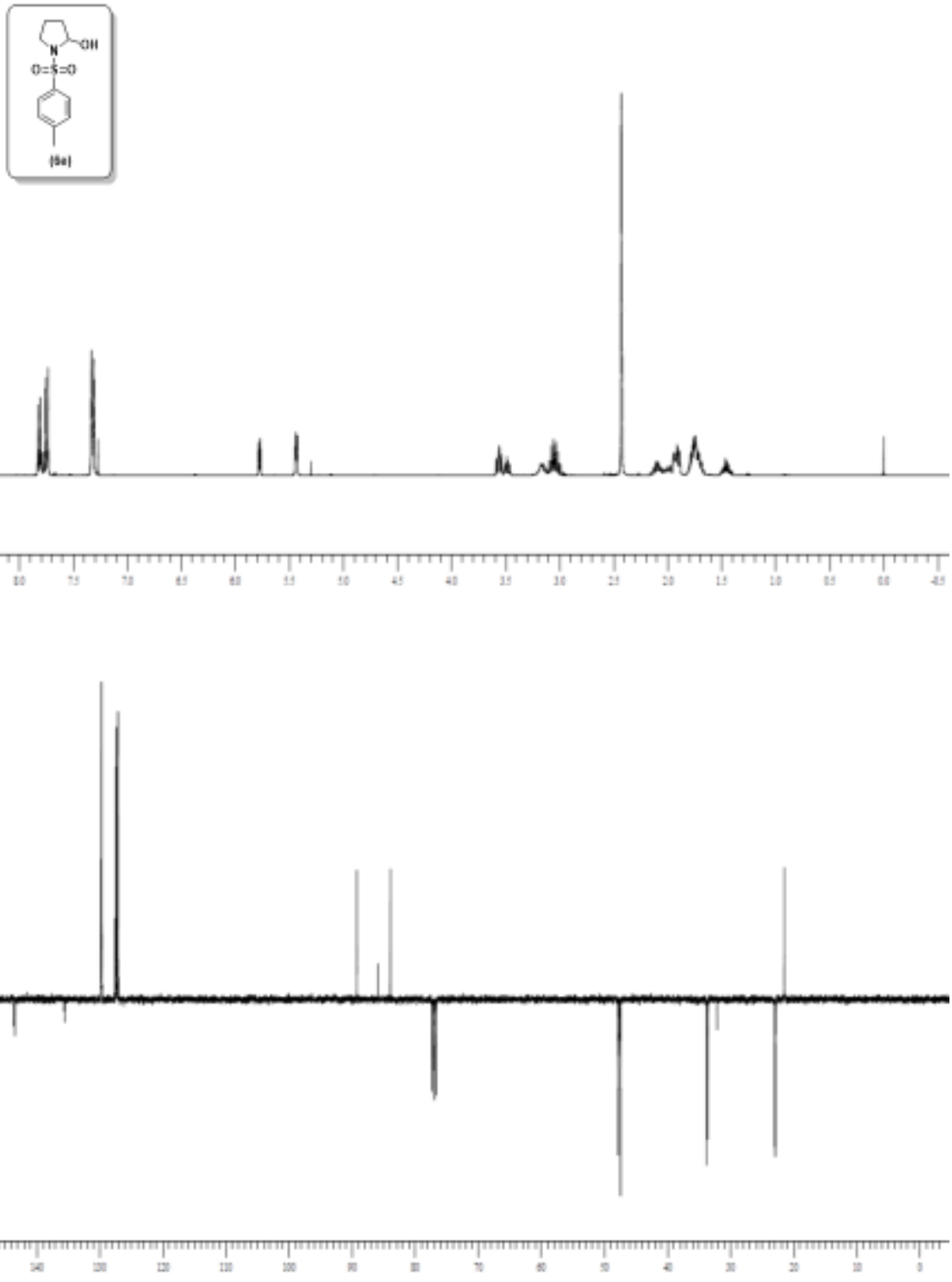


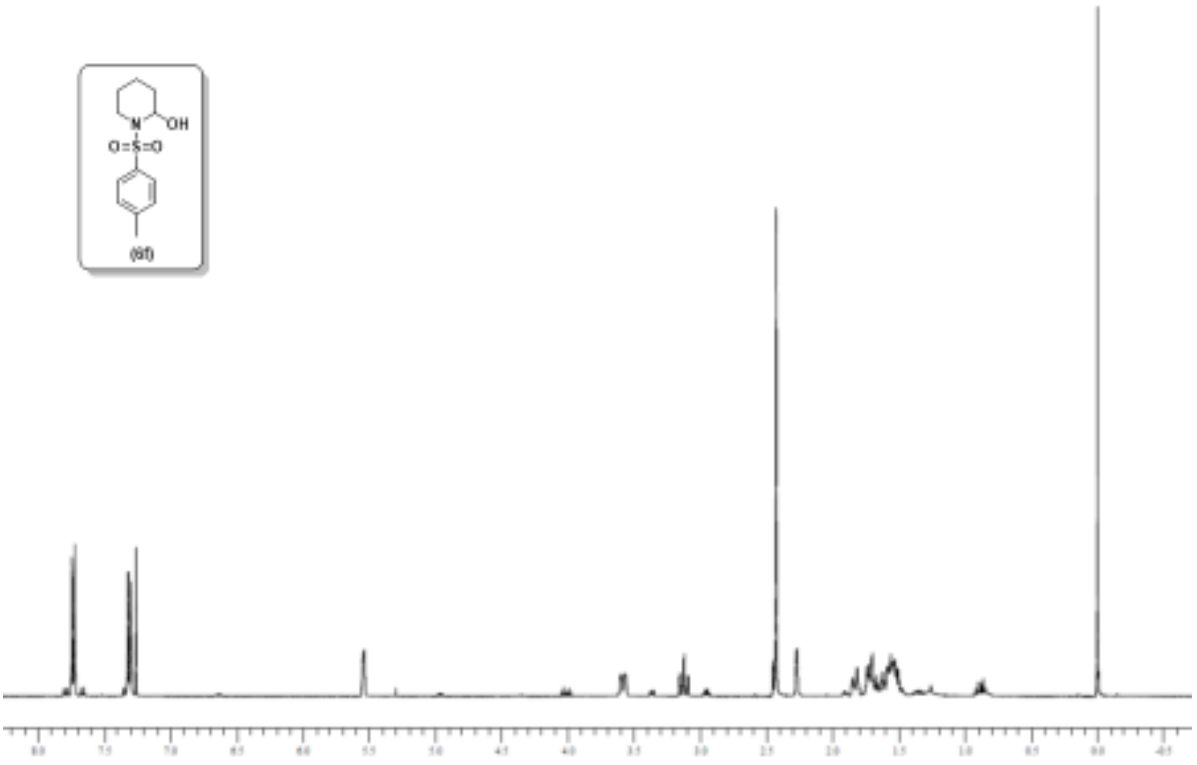

(5a)

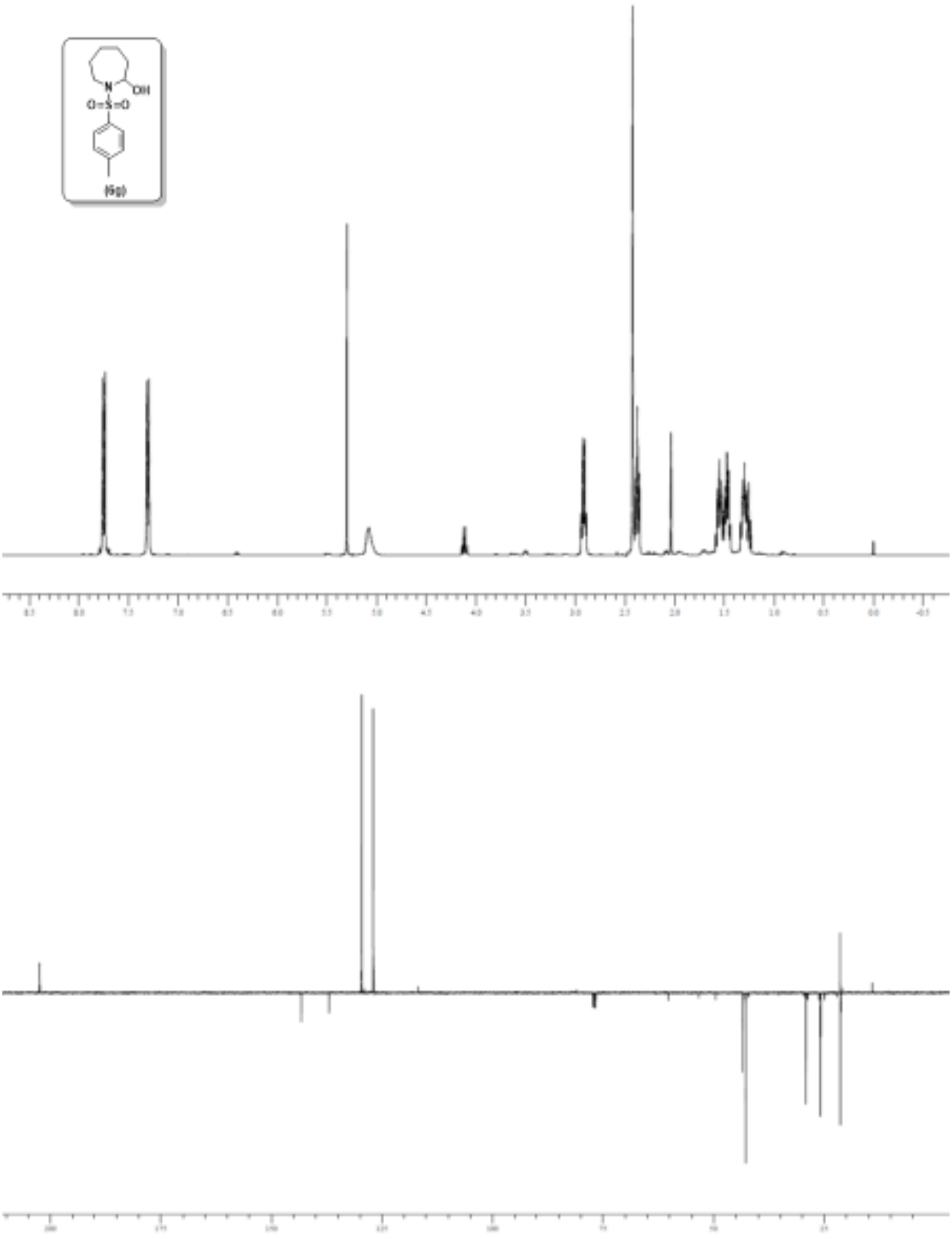


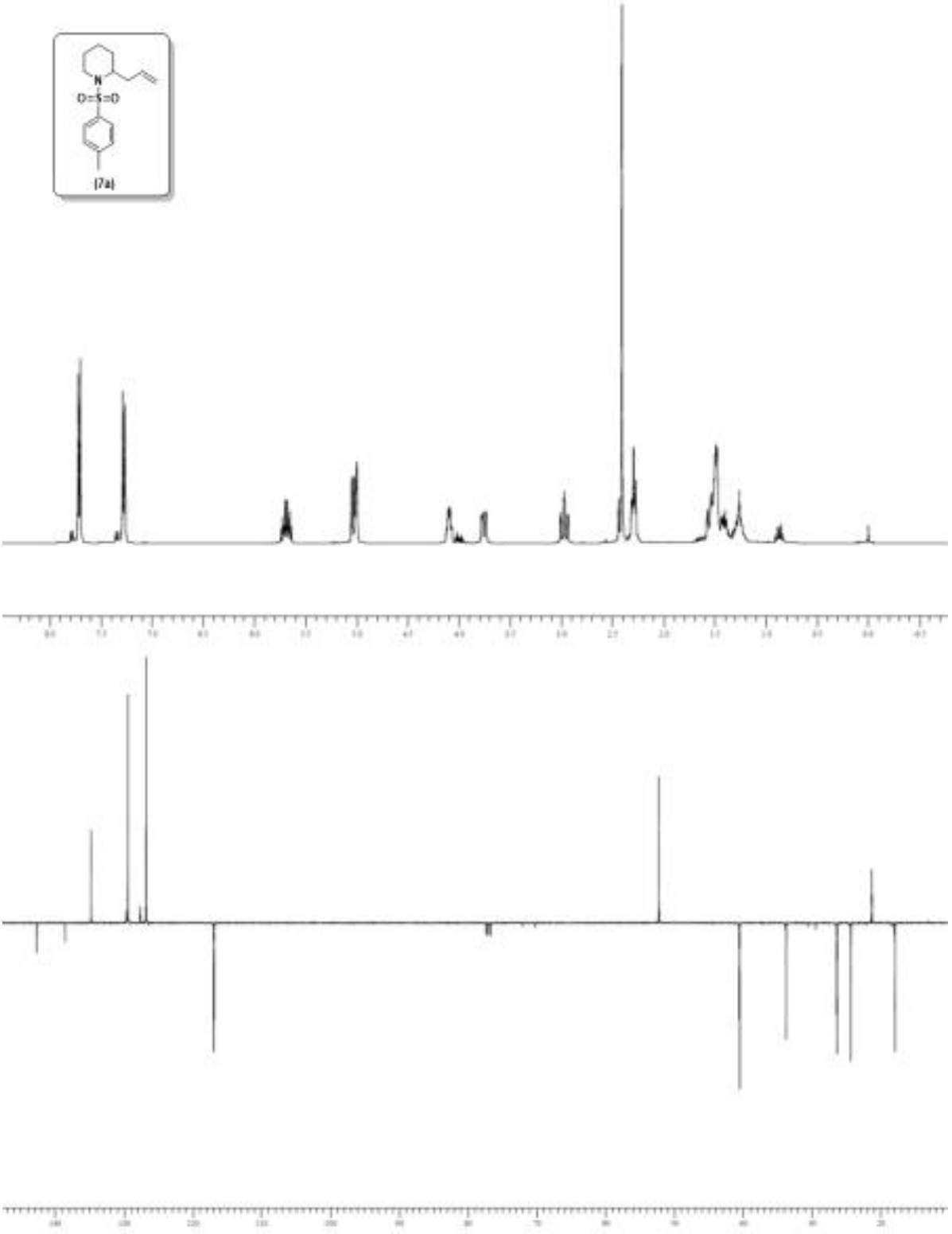

(9c)

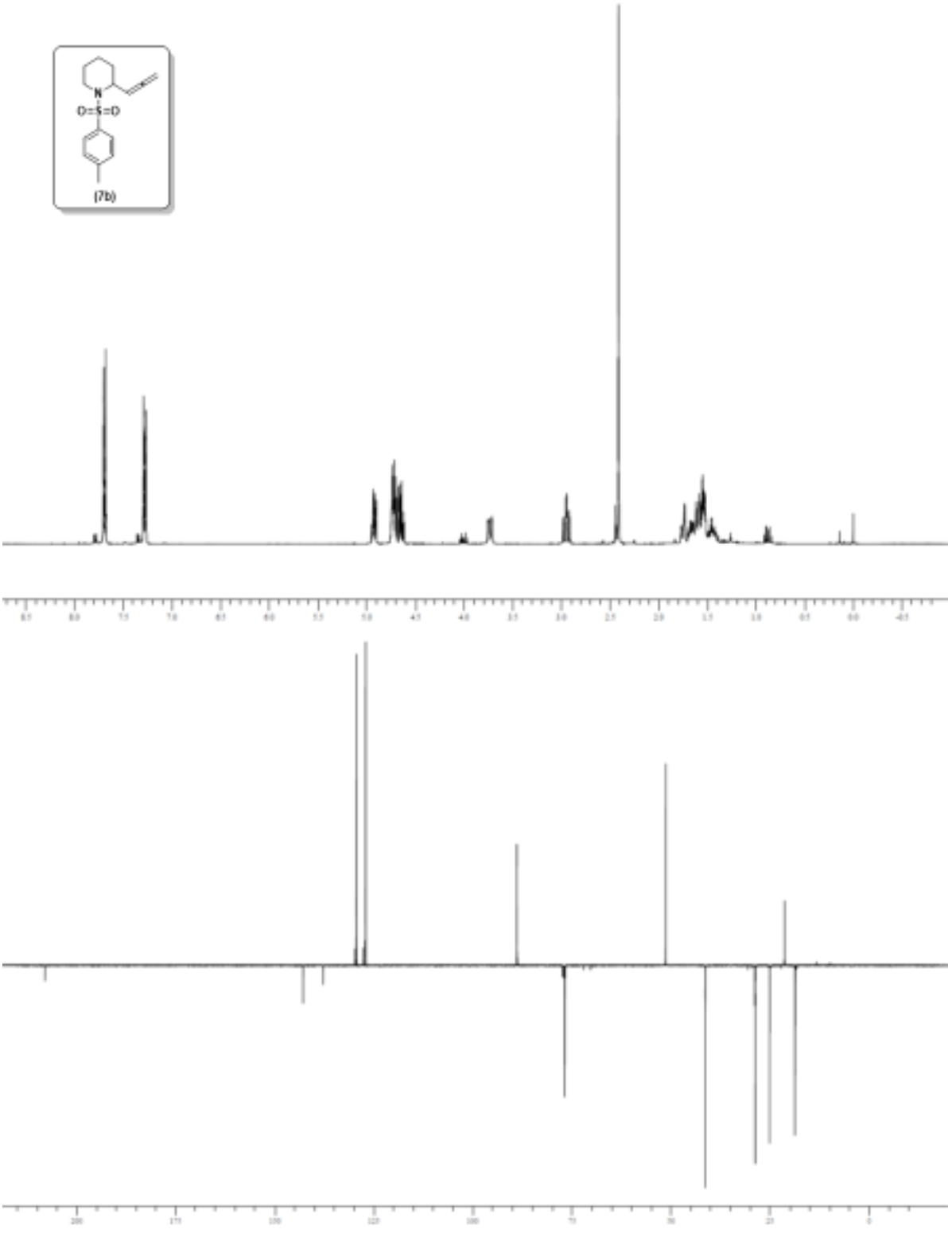

(6d)

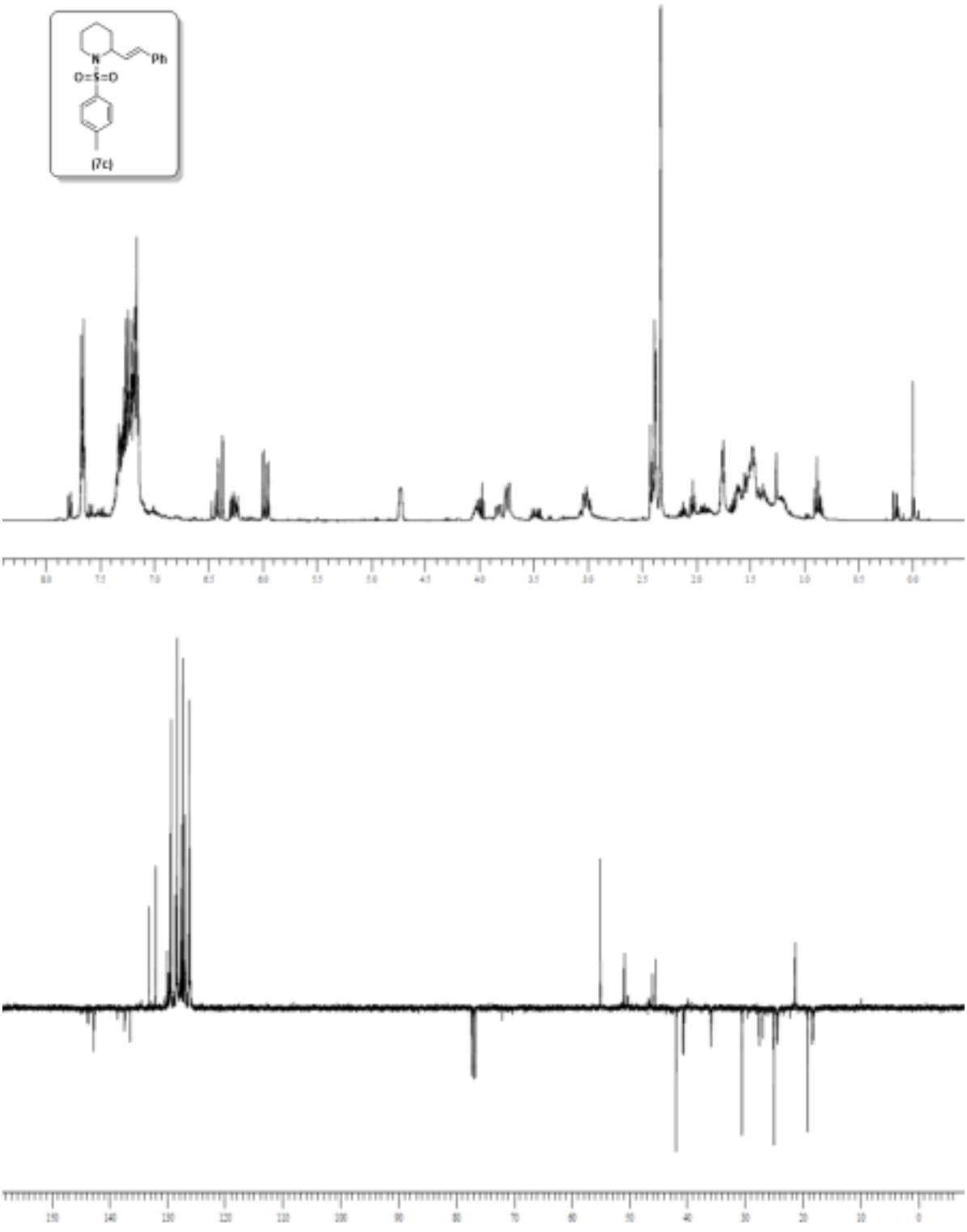

OH
N
O=S=O
(5e)

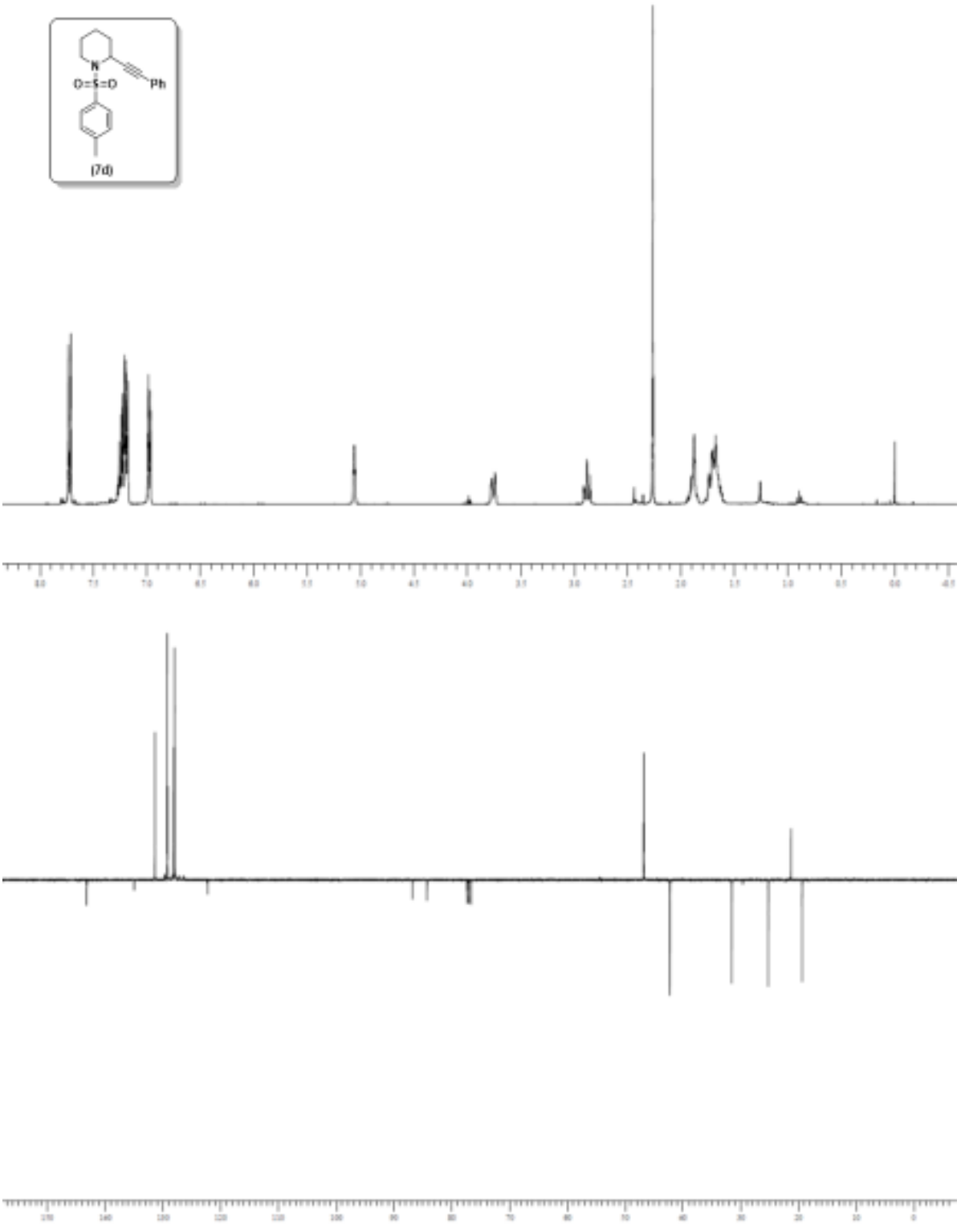

OH
O=S=O
(6f)

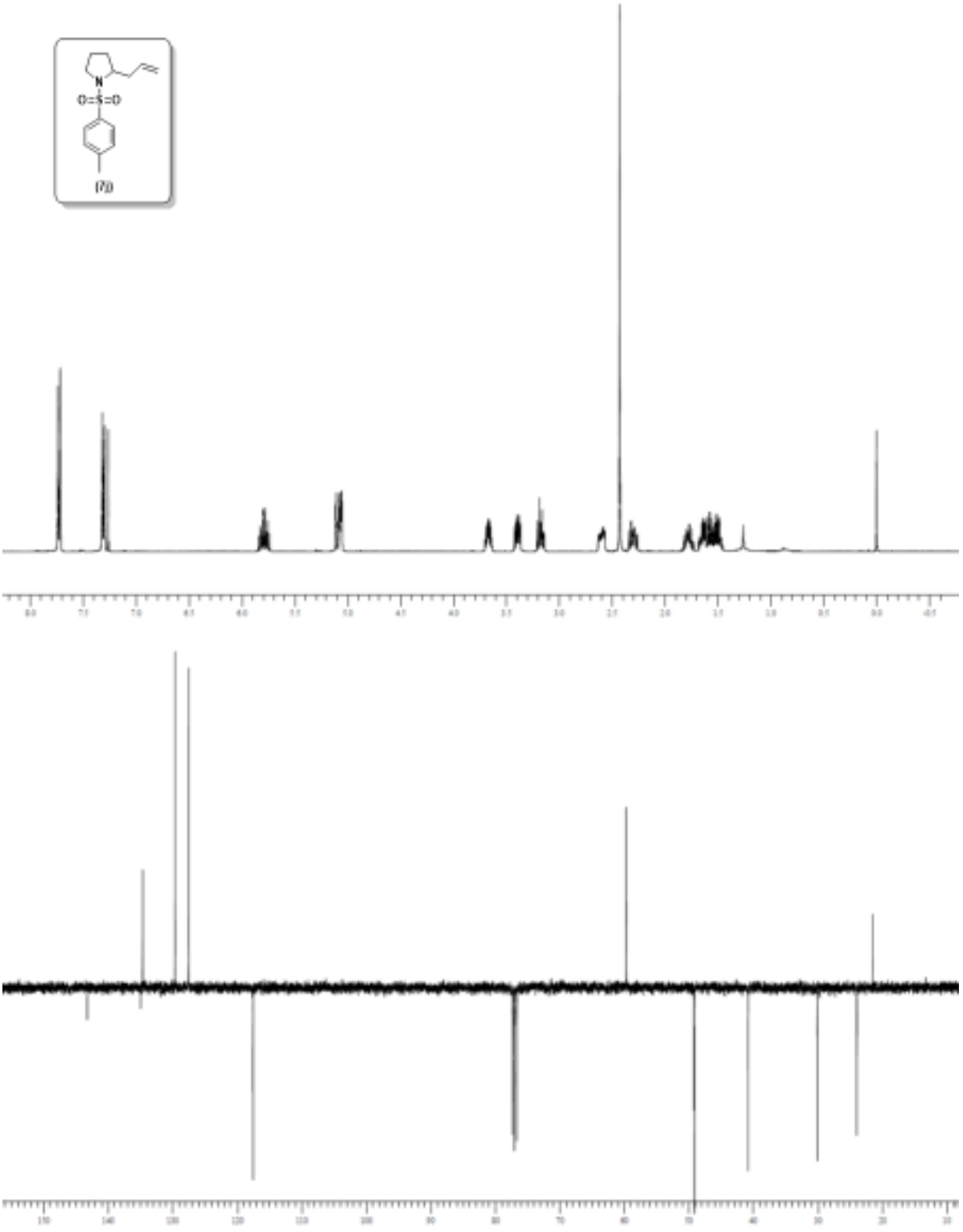

OH
O=S=O
(5g)

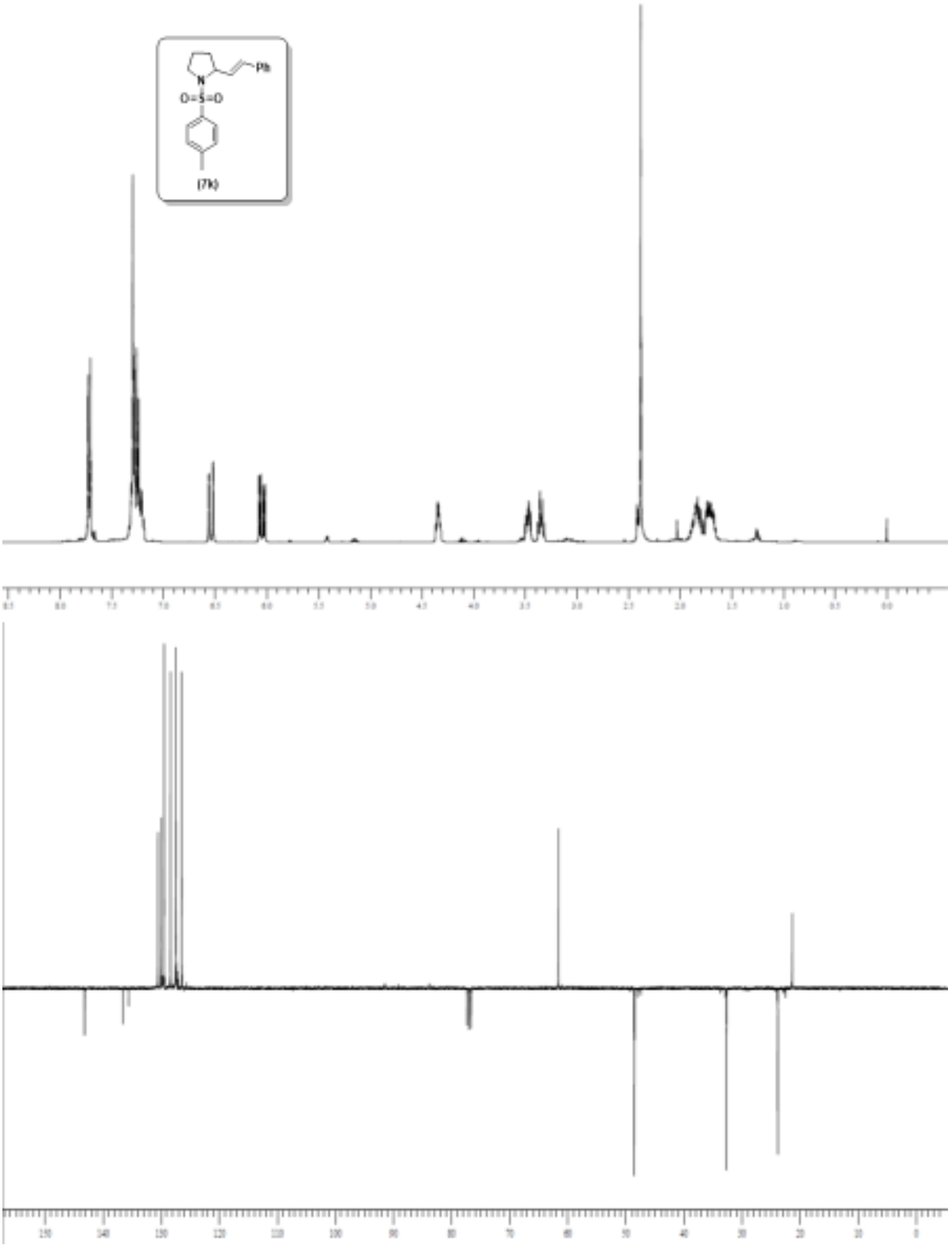

(7a)

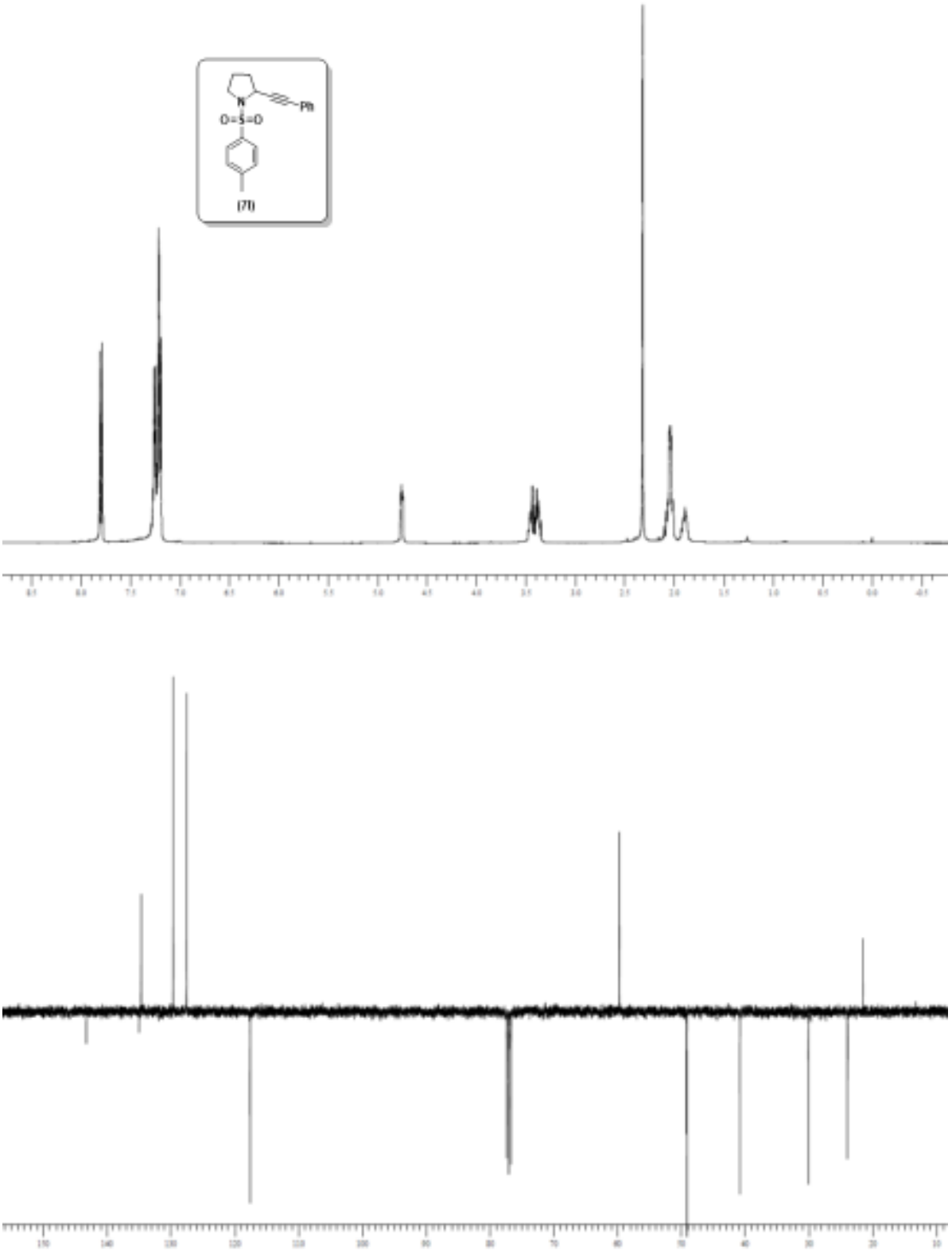

N
O=S=O
(7b)

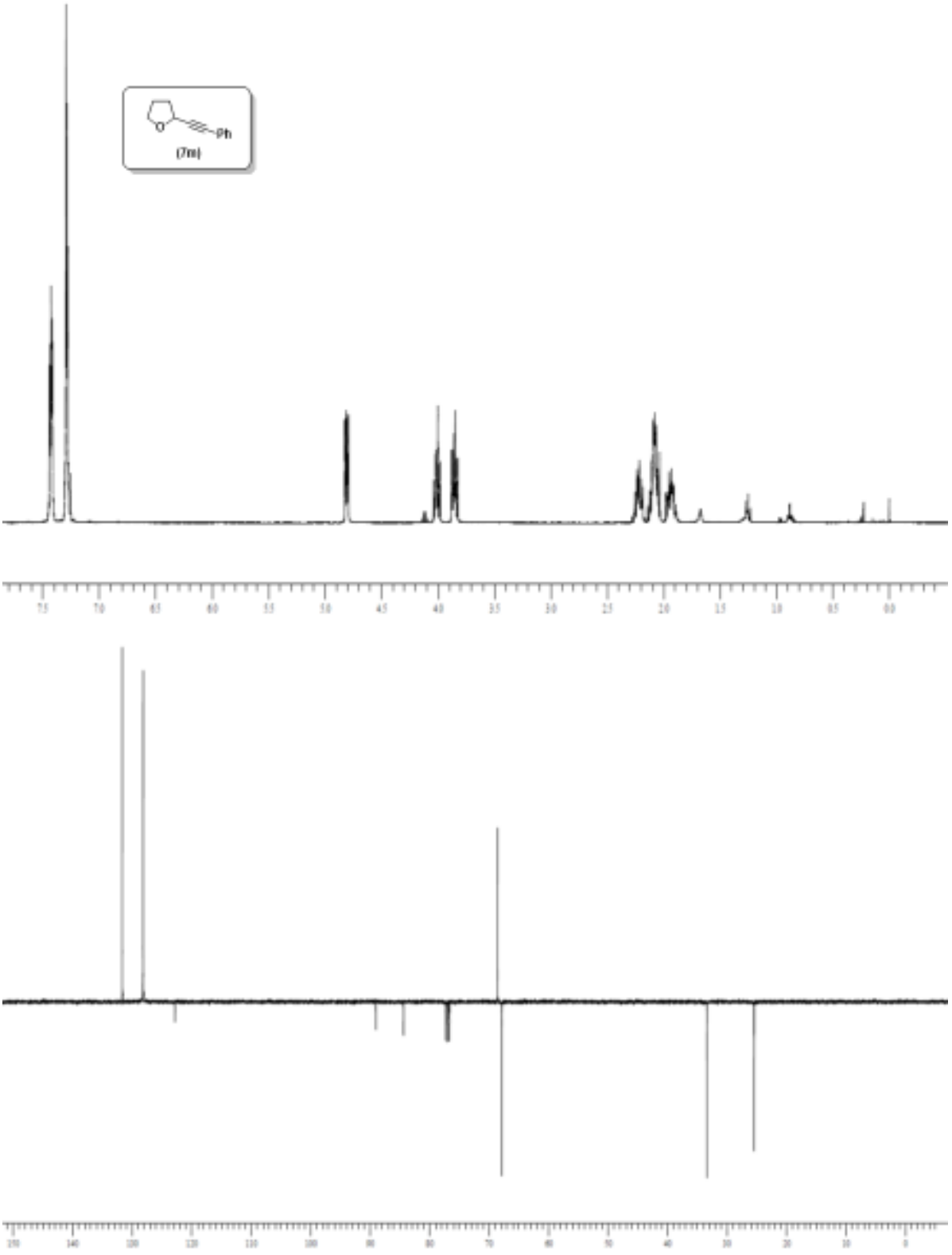

N
Ph
O=S=O
(7c)

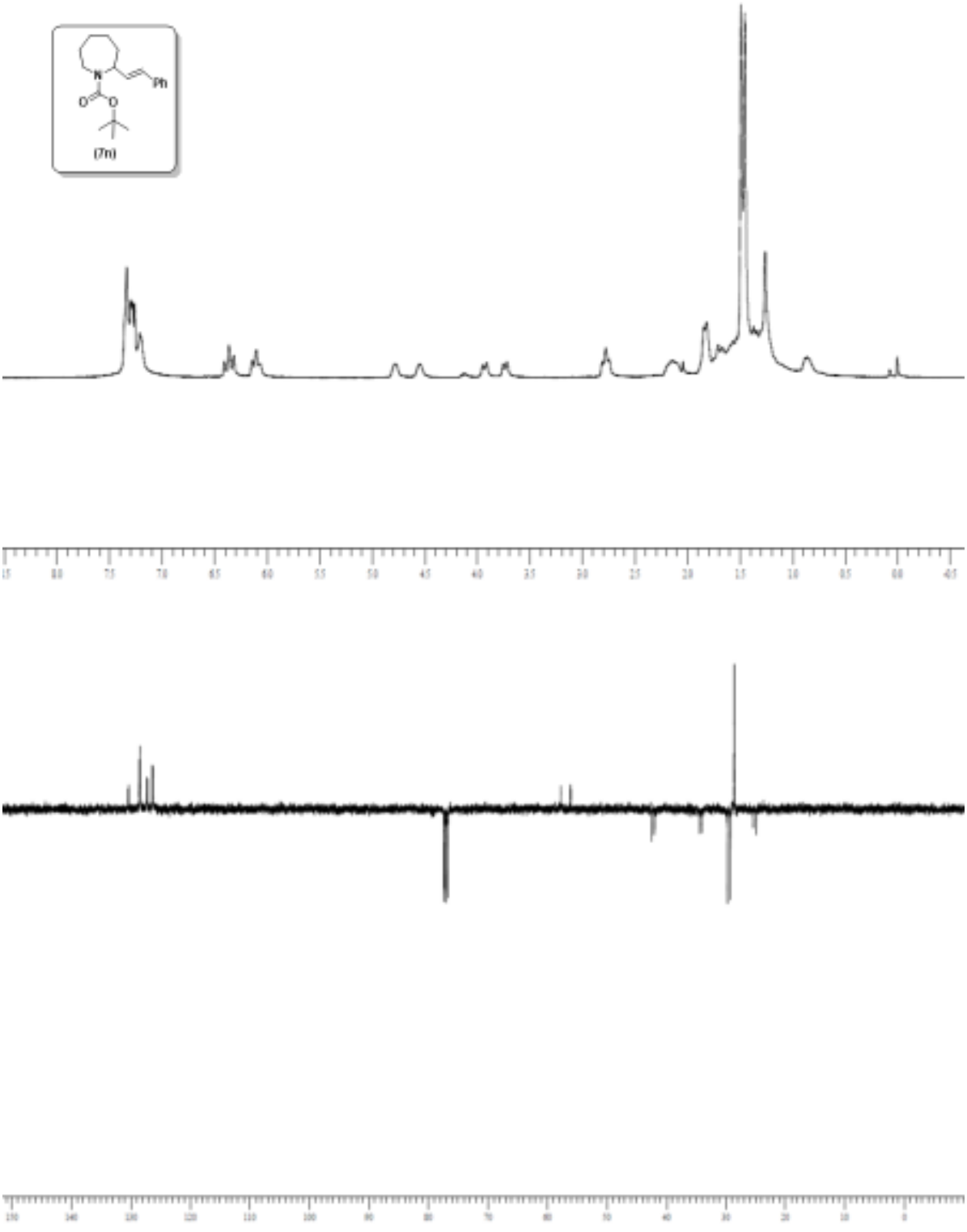

N
O=S=O
Ph
(7d)

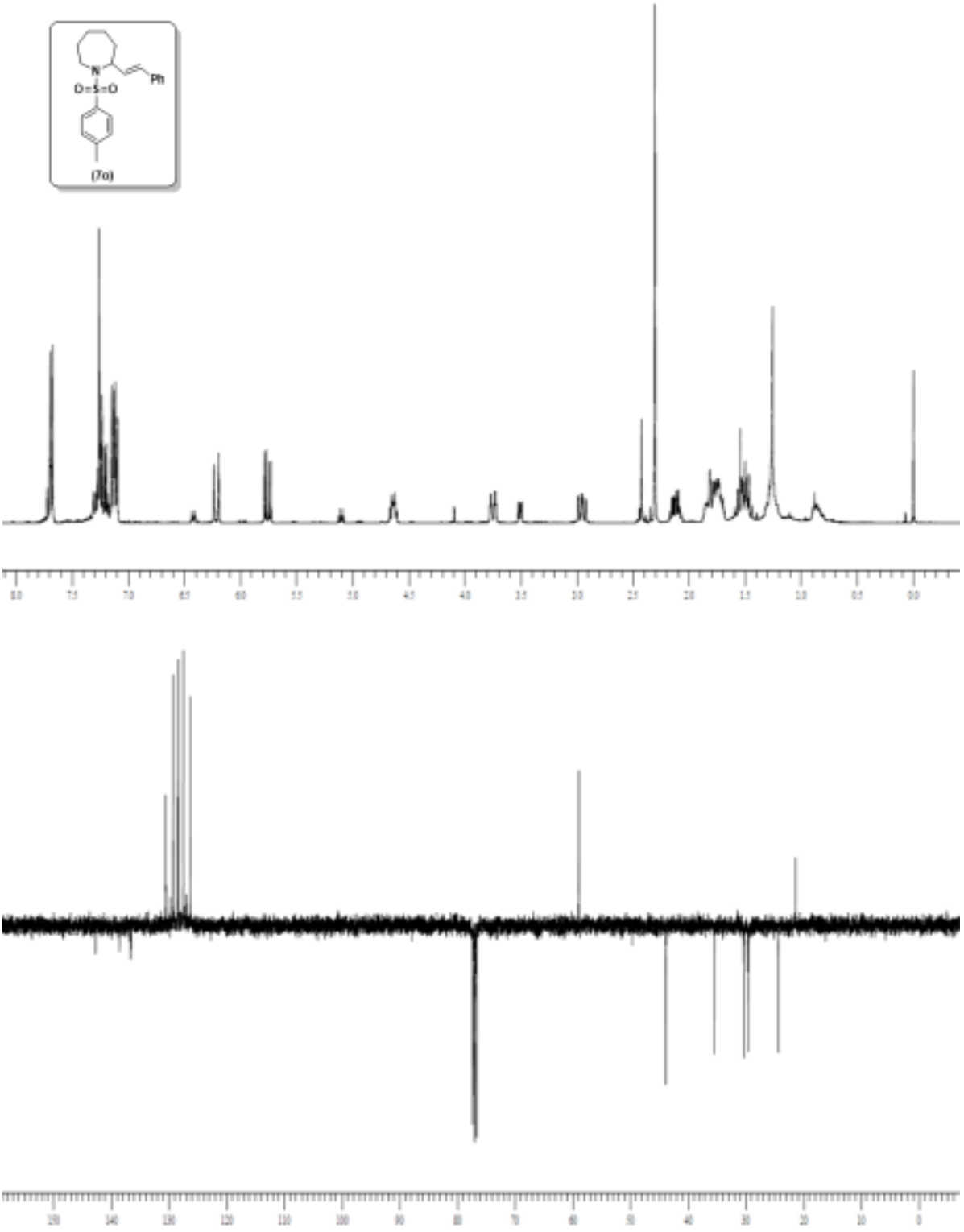

N
O=S=O
(7j)

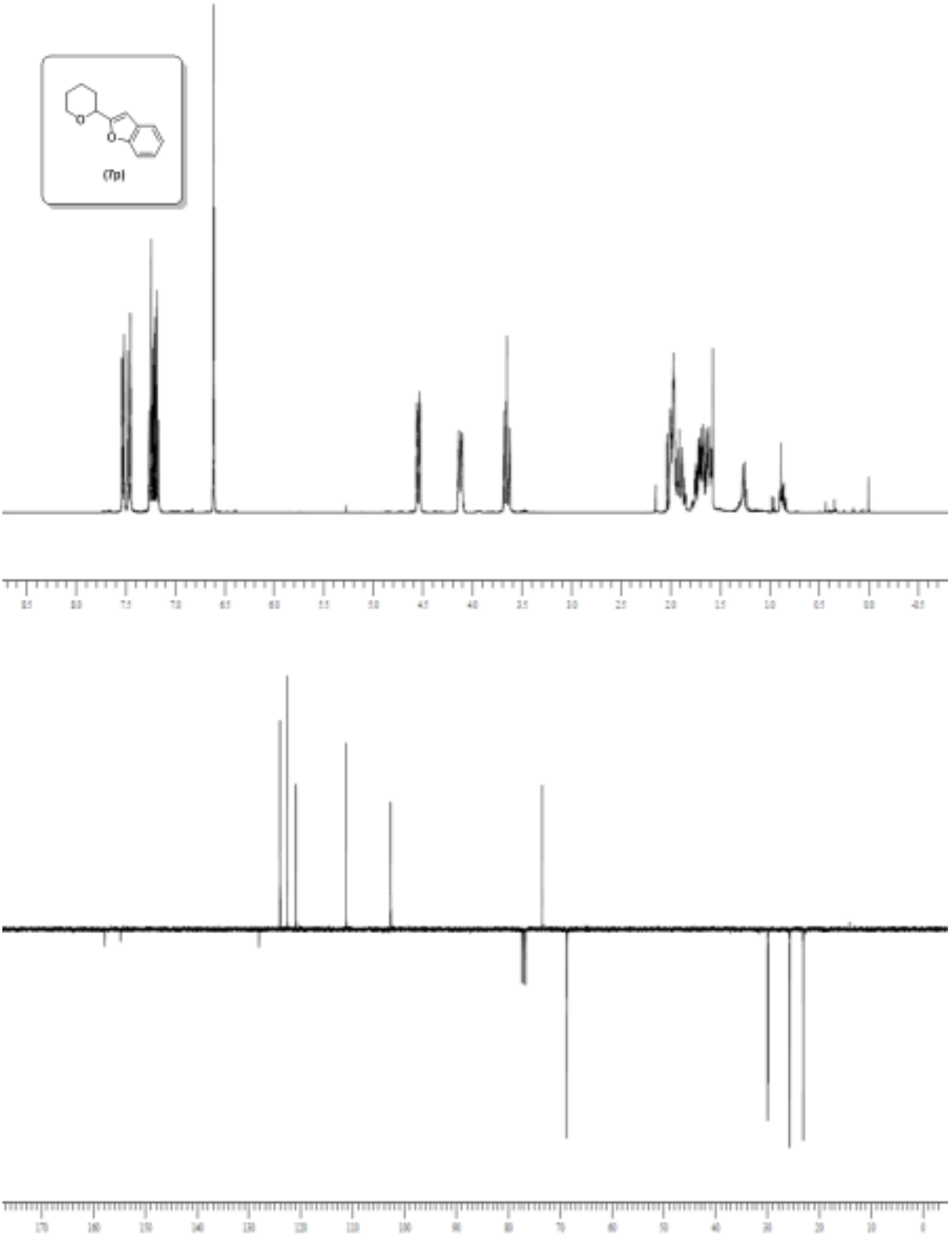

Ph
N
O=S=O
(7k)


Ph
O=S=O
(7l)


Ph
(7m)


N
O
O
Ph
(7n)


N
O=S=O
Ph
(7o)


(7p)

Appendix B – Computational Coordinates

All coordinates are reported in Angstrom.

Stereospecific addition of *cis*-2-phenylvinylsilane (Figure 2-1)

TS1

Energy: -3201804.362 kJ mol^{-1}
Gibbs free energy: -3200801.495 kJ mol^{-1}

C	-0.229602	-2.747334	1.010560
C	-2.438064	0.018116	-1.170937
C	-0.826298	2.003418	-2.207039
C	-0.524696	4.429319	-1.131261
C	0.934226	6.253748	-2.335264
C	2.122038	5.716923	-4.634542
C	1.835052	3.335391	-5.743224
C	0.387443	1.504303	-4.539037
C	-4.685305	0.402036	0.430923
C	-6.922395	-0.808335	-0.369419
C	-9.187438	-0.465731	0.929465
C	-9.249637	1.046081	3.089460
C	-7.032803	2.207643	3.946832
C	-4.775999	1.893258	2.636785
C	0.927377	-1.141193	2.756089
C	3.227499	0.291894	2.623115
C	3.940040	1.718141	4.781441
C	6.128980	3.162511	4.770072
C	7.639275	3.246790	2.598234
C	6.956250	1.877483	0.438338
C	4.781647	0.411328	0.448670
Si	1.048289	-5.430309	-1.119316
C	1.890182	-7.967519	1.254560
C	3.870526	-4.851667	-3.225148
C	-1.712384	-6.535668	-3.102862
H	8.126515	1.958257	-1.244911
H	9.347218	4.386101	2.586647
H	6.660708	4.230718	6.439107
H	2.757472	1.665388	6.460364

H	4.257512	-0.628911	-1.226035
H	-6.891199	-1.988880	-2.049422
H	-10.893753	-1.390563	0.262906
H	-11.005205	1.296755	4.122390
H	-7.061528	3.348768	5.652209
H	-3.071173	2.749201	3.383946
H	2.725319	2.917782	-7.544240
H	3.249927	7.157945	-5.564135
H	1.131725	8.112205	-1.488155
H	-1.480339	4.922001	0.607586
H	0.126179	-0.324355	-5.434378
H	-2.735631	-1.491888	-2.527112
H	-0.112276	-0.826739	4.509528
H	-1.958383	-3.539690	1.819277
H	3.658391	-3.282710	-4.556332
H	4.123844	-6.565691	-4.366406
H	5.624071	-4.578341	-2.162835
H	-2.207232	-5.264054	-4.661659
H	-3.414717	-6.848843	-1.964259
H	-1.224788	-8.356979	-3.965653
H	3.481822	-7.391553	2.447986
H	2.439906	-9.707214	0.270443
H	0.300131	-8.428467	2.498655

INT1

Energy: -3201869.749 kJ mol^{-1}
Gibbs free energy: -3200853.955 kJ mol^{-1}

C	-0.546711	-2.222934	0.876807
C	-2.126922	-0.553252	-1.002766
C	-0.879695	1.695804	-2.313993
C	-0.638189	4.068352	-1.154260
C	0.491768	6.082743	-2.428249
C	1.392359	5.768107	-4.889366
C	1.121864	3.431136	-6.084227
C	-0.020236	1.421817	-4.808697
C	-4.596740	0.189352	0.335098
C	-6.879438	-0.021902	-0.996622
C	-9.165460	0.666310	0.125575
C	-9.206491	1.581377	2.600735
C	-6.947330	1.792506	3.947629
C	-4.663365	1.092433	2.825045

C	1.406821	-1.531467	2.583561
C	3.528817	0.139969	2.540797
C	4.769008	0.506473	4.901904
C	6.816060	2.126128	5.108281
C	7.741544	3.337012	2.945097
C	6.612402	2.932240	0.584032
C	4.515312	1.374874	0.370402
Si	1.077369	-5.424161	-0.813533
C	2.045317	-7.605160	1.816525
C	3.810335	-4.529810	-2.882743
C	-1.663440	-6.778539	-2.637813
H	7.376106	3.838126	-1.089397
H	9.369623	4.579224	3.094310
H	7.715643	2.424413	6.927140
H	4.068197	-0.467450	6.567704
H	3.674555	1.055092	-1.462378
H	-6.873852	-0.729890	-2.926460
H	-10.913410	0.482090	-0.936629
H	-10.985112	2.111267	3.478376
H	-6.956272	2.489934	5.878805
H	-2.934305	1.234590	3.925450
H	1.777766	3.174770	-8.012738
H	2.273992	7.337233	-5.876983
H	0.666443	7.902862	-1.494377
H	-1.349989	4.360154	0.746190
H	-0.271689	-0.371537	-5.779237
H	-2.699625	-1.833682	-2.518350
H	1.332796	-2.625781	4.330485
H	-1.918274	-3.376631	1.918496
H	3.320353	-3.169719	-4.360305
H	4.450252	-6.261330	-3.831334
H	5.418136	-3.792870	-1.811830
H	-2.122331	-5.726017	-4.357740
H	-3.378281	-6.955943	-1.492795
H	-1.114340	-8.691832	-3.222149
H	3.700621	-6.937544	2.864615
H	2.551752	-9.433589	0.978568
H	0.516631	-7.964150	3.167758

TS2

Energy: -3201831.937 kJ mol^{-1}
Gibbs free energy: -3200740.982 kJ mol^{-1}

C	-0.302049	-1.267096	1.646649
C	2.461341	1.192655	0.873627
C	1.200012	3.684165	1.268531
C	-0.762250	4.630295	-0.258720
C	-1.787030	7.013690	0.185415
C	-0.894494	8.495436	2.181600
C	1.017646	7.566614	3.744916
C	2.039732	5.177596	3.304650
C	3.822494	0.543976	-1.510477
C	6.046282	-0.905462	-1.304807
C	7.458779	-1.559457	-3.430382
C	6.673512	-0.773933	-5.822711
C	4.486470	0.687758	-6.062201
C	3.079160	1.347521	-3.934786
C	-1.597911	-1.808728	-0.605316
C	-4.210099	-1.458938	-1.181809
C	-5.962425	-0.432067	0.576194
C	-8.473037	-0.124639	-0.093691
C	-9.293382	-0.831899	-2.514698
C	-7.600612	-1.851563	-4.275728
C	-5.082140	-2.168639	-3.622488
Si	1.175850	-4.244698	3.323553
C	3.601198	-3.192752	5.714357
C	2.516038	-6.521596	0.942588
C	-1.612009	-5.676259	5.029112
H	-8.258695	-2.394967	-6.141070
H	-11.265671	-0.584701	-3.028441
H	-9.807909	0.661984	1.250141
H	-5.340383	0.128062	2.447008
H	-3.755310	-2.963371	-4.973313
H	6.699993	-1.496448	0.549978
H	9.172330	-2.668316	-3.212839
H	7.762853	-1.279639	-7.487453
H	3.878451	1.333180	-7.913774
H	1.422239	2.523377	-4.183337
H	1.706465	8.695628	5.314792
H	-1.701198	10.350452	2.530627
H	-3.301096	7.704204	-1.016676
H	-1.543450	3.488013	-1.769288

H	3.528915	4.473051	4.531755
H	3.644726	0.745555	2.491826
H	-0.470794	-2.604816	-2.138233
H	-1.394679	-0.237184	3.061810
H	-3.097142	-6.287192	3.721970
H	-2.452928	-4.353960	6.383172
H	-0.994828	-7.343614	6.096073
H	5.397503	-2.576144	4.893516
H	4.029101	-4.810942	6.939130
H	2.891720	-1.677225	6.935271
H	1.042585	-7.345164	-0.257040
H	3.427388	-8.087465	1.950448
H	3.940048	-5.664571	-0.287330

INT2

Energy: -3201903.329 kJ mol^{-1}
Gibbs free energy: -3200891.293 kJ mol^{-1}

C	-0.294935	-0.481616	1.275713
C	2.363950	0.830806	0.982226
C	1.876615	3.690570	1.162684
C	1.593708	5.275482	-0.938100
C	1.076431	7.842560	-0.621551
C	0.819976	8.868879	1.794672
C	1.107179	7.312085	3.903333
C	1.631657	4.748824	3.583791
C	4.028280	-0.074477	-1.187355
C	6.421595	-1.053531	-0.586178
C	8.068136	-1.914645	-2.456879
C	7.356450	-1.811250	-4.993388
C	4.998525	-0.822452	-5.634729
C	3.356114	0.038160	-3.757540
C	-1.896161	-0.919318	-0.796877
C	-4.595412	-0.797232	-0.895587
C	-6.077117	0.304175	1.050555
C	-8.680685	0.436566	0.807577
C	-9.860847	-0.521299	-1.364736
C	-8.434714	-1.602389	-3.312547
C	-5.825630	-1.729718	-3.088764
Si	0.115580	-4.288883	2.409200
C	2.541908	-4.076423	5.004504
C	1.184862	-6.307104	-0.304565

C	-3.026629	-5.283092	3.733149
H	-9.363512	-2.323358	-4.992030
H	-11.901651	-0.402286	-1.544685
H	-9.807661	1.301722	2.285917
H	-5.172117	1.104889	2.706432
H	-4.700902	-2.550819	-4.597854
H	7.021843	-1.111881	1.377650
H	9.907648	-2.654687	-1.929312
H	8.630753	-2.477162	-6.456378
H	4.432934	-0.704867	-7.603935
H	1.562078	0.840613	-4.342696
H	0.946234	8.091681	5.794615
H	0.420758	10.867262	2.030580
H	0.892335	9.045147	-2.274245
H	1.836072	4.546229	-2.835311
H	1.879048	3.560832	5.244429
H	3.380607	0.351753	2.713726
H	-0.983405	-1.499140	-2.546487
H	-1.258557	0.256849	2.949448
H	-4.515588	-5.406146	2.307711
H	-3.668873	-4.024596	5.244468
H	-2.803598	-7.168508	4.564284
H	4.445344	-3.715772	4.292739
H	2.568611	-5.918910	5.955537
H	2.076011	-2.653862	6.431045
H	-0.299867	-6.585898	-1.716834
H	1.690964	-8.176276	0.433533
H	2.853637	-5.528571	-1.239674

Cis product

Energy: -2128182.584 kJ mol^{-1}
Gibbs free energy: -2127448.445 kJ mol^{-1}

C	6.675304	0.565250	-2.118748
C	5.546698	2.845667	-2.076406
C	6.201240	5.109557	-0.578278
C	4.234812	6.651025	0.338288
C	4.748660	8.822250	1.739566
C	7.247536	9.517104	2.240339
C	9.221807	8.033955	1.307157
C	8.707023	5.854878	-0.088362
C	8.807109	-0.397892	-0.477672

C	11.304603	-0.787558	-1.906328
C	11.634831	0.003340	-4.410520
C	13.954534	-0.315702	-5.639841
C	15.987798	-1.419090	-4.377528
C	15.684765	-2.208347	-1.872907
C	13.369367	-1.893969	-0.655094
C	7.892636	-2.794502	0.874105
C	7.078359	-2.663336	3.390895
C	6.139361	-4.800153	4.624752
C	5.993227	-7.105772	3.351331
C	6.798107	-7.259003	0.839748
C	7.739358	-5.122078	-0.386653
H	11.171368	8.580665	1.651875
H	7.651945	11.214418	3.323078
H	3.197404	9.972947	2.438127
H	2.286062	6.126058	-0.050080
H	10.261761	4.766485	-0.867117
H	7.172918	-0.871983	4.394487
H	5.523320	-4.658632	6.579194
H	5.261469	-8.770532	4.305459
H	6.694887	-9.046674	-0.167047
H	8.372592	-5.270041	-2.335101
H	17.255801	-3.066194	-0.864991
H	17.790637	-1.667087	-5.329217
H	14.162263	0.307689	-7.586177
H	10.073184	0.879602	-5.412787
H	13.159733	-2.520571	1.289813
H	9.173780	1.011785	0.994789
H	3.882140	3.072286	-3.270297
H	5.863741	-0.840871	-3.391654

Trans product

Energy: -2128192.956
Gibbs free energy: -2127466.970

C	6.808260	0.932967	0.719353
C	6.008751	2.580290	-1.038406
C	5.188957	5.206710	-0.606576
C	5.496762	6.477509	1.713854
C	4.655581	8.952007	2.022375
C	3.494165	10.232583	0.022499
C	3.191619	9.009795	-2.296418

C	4.035488	6.531096	-2.603904
C	7.574504	-1.798089	0.309428
C	10.181786	-2.347338	1.452557
C	12.129037	-0.552034	1.426143
C	14.492295	-1.107208	2.467315
C	14.944346	-3.468052	3.552835
C	13.014634	-5.271211	3.595335
C	10.659664	-4.713265	2.548634
C	7.331460	-2.713162	-2.422808
C	5.192310	-4.098299	-3.148672
C	4.899538	-4.949582	-5.629664
C	6.751134	-4.424633	-7.433783
C	8.886337	-3.034729	-6.738291
C	9.174302	-2.190700	-4.254622
H	2.300506	9.984512	-3.869631
H	2.842774	12.164189	0.269618
H	4.916260	9.890035	3.831146
H	6.416665	5.535813	3.288990
H	3.790188	5.594888	-4.417284
H	3.739302	-4.515317	-1.755492
H	3.230060	-6.029151	-6.146810
H	6.533915	-5.090516	-9.364597
H	10.339354	-2.617653	-8.129106
H	10.856502	-1.134572	-3.735660
H	13.342423	-7.111980	4.446129
H	16.778751	-3.898659	4.369318
H	15.977173	0.311989	2.432664
H	11.787962	1.301836	0.611469
H	9.168708	-6.128371	2.592647
H	6.229927	-2.930538	1.419589
H	5.908339	1.952931	-2.994923
H	6.874486	1.509315	2.694594

Stereospecific addition of *trans*-2-phenylvinylsilane (Figure 2-2)

TS1

Energy: -3201831.937 kJ mol^{-1}
Gibbs free energy: -3200740.982 kJ mol^{-1}

C	-0.302049	-1.267096	1.646649
C	2.461341	1.192655	0.873627
C	1.200012	3.684165	1.268531

C	-0.762250	4.630295	-0.258720
C	-1.787030	7.013690	0.185415
C	-0.894494	8.495436	2.181600
C	1.017646	7.566614	3.744916
C	2.039732	5.177596	3.304650
C	3.822494	0.543976	-1.510477
C	6.046282	-0.905462	-1.304807
C	7.458779	-1.559457	-3.430382
C	6.673512	-0.773933	-5.822711
C	4.486470	0.687758	-6.062201
C	3.079160	1.347521	-3.934786
C	-1.597911	-1.808728	-0.605316
C	-4.210099	-1.458938	-1.181809
C	-5.962425	-0.432067	0.576194
C	-8.473037	-0.124639	-0.093691
C	-9.293382	-0.831899	-2.514698
C	-7.600612	-1.851563	-4.275728
C	-5.082140	-2.168639	-3.622488
Si	1.175850	-4.244698	3.323553
C	3.601198	-3.192752	5.714357
C	2.516038	-6.521596	0.942588
C	-1.612009	-5.676259	5.029112
H	-8.258695	-2.394967	-6.141070
H	-11.265671	-0.584701	-3.028441
H	-9.807909	0.661984	1.250141
H	-5.340383	0.128062	2.447008
H	-3.755310	-2.963371	-4.973313
H	6.699993	-1.496448	0.549978
H	9.172330	-2.668316	-3.212839
H	7.762853	-1.279639	-7.487453
H	3.878451	1.333180	-7.913774
H	1.422239	2.523377	-4.183337
H	1.706465	8.695628	5.314792
H	-1.701198	10.350452	2.530627
H	-3.301096	7.704204	-1.016676
H	-1.543450	3.488013	-1.769288
H	3.528915	4.473051	4.531755
H	3.644726	0.745555	2.491826
H	-0.470794	-2.604816	-2.138233
H	-1.394679	-0.237184	3.061810
H	-3.097142	-6.287192	3.721970
H	-2.452928	-4.353960	6.383172
H	-0.994828	-7.343614	6.096073
H	5.397503	-2.576144	4.893516
H	4.029101	-4.810942	6.939130
H	2.891720	-1.677225	6.935271

H	1.042585	-7.345164	-0.257040
H	3.427388	-8.087465	1.950448
H	3.940048	-5.664571	-0.287330

INT1

Energy: -3201903.329 kJ mol^{-1}
Gibbs free energy: -3200891.293 kJ mol^{-1}

C	-0.294935	-0.481616	1.275713
C	2.363950	0.830806	0.982226
C	1.876615	3.690570	1.162684
C	1.593708	5.275482	-0.938100
C	1.076431	7.842560	-0.621551
C	0.819976	8.868879	1.794672
C	1.107179	7.312085	3.903333
C	1.631657	4.748824	3.583791
C	4.028280	-0.074477	-1.187355
C	6.421595	-1.053531	-0.586178
C	8.068136	-1.914645	-2.456879
C	7.356450	-1.811250	-4.993388
C	4.998525	-0.822452	-5.634729
C	3.356114	0.038160	-3.757540
C	-1.896161	-0.919318	-0.796877
C	-4.595412	-0.797232	-0.895587
C	-6.077117	0.304175	1.050555
C	-8.680685	0.436566	0.807577
C	-9.860847	-0.521299	-1.364736
C	-8.434714	-1.602389	-3.312547
C	-5.825630	-1.729718	-3.088764
Si	0.115580	-4.288883	2.409200
C	2.541908	-4.076423	5.004504
C	1.184862	-6.307104	-0.304565
C	-3.026629	-5.283092	3.733149
H	-9.363512	-2.323358	-4.992030
H	-11.901651	-0.402286	-1.544685
H	-9.807661	1.301722	2.285917
H	-5.172117	1.104889	2.706432
H	-4.700902	-2.550819	-4.597854
H	7.021843	-1.111881	1.377650
H	9.907648	-2.654687	-1.929312
H	8.630753	-2.477162	-6.456378
H	4.432934	-0.704867	-7.603935

H	1.562078	0.840613	-4.342696
H	0.946234	8.091681	5.794615
H	0.420758	10.867262	2.030580
H	0.892335	9.045147	-2.274245
H	1.836072	4.546229	-2.835311
H	1.879048	3.560832	5.244429
H	3.380607	0.351753	2.713726
H	-0.983405	-1.499140	-2.546487
H	-1.258557	0.256849	2.949448
H	-4.515588	-5.406146	2.307711
H	-3.668873	-4.024596	5.244468
H	-2.803598	-7.168508	4.564284
H	4.445344	-3.715772	4.292739
H	2.568611	-5.918910	5.955537
H	2.076011	-2.653862	6.431045
H	-0.299867	-6.585898	-1.716834
H	1.690964	-8.176276	0.433533
H	2.853637	-5.528571	-1.239674

TS2

Energy: -3201804.362 kJ mol^{-1}
Gibbs free energy: -3200801.495 kJ mol^{-1}

C	-0.229602	-2.747334	1.010560
C	-2.438064	0.018116	-1.170937
C	-0.826298	2.003418	-2.207039
C	-0.524696	4.429319	-1.131261
C	0.934226	6.253748	-2.335264
C	2.122038	5.716923	-4.634542
C	1.835052	3.335391	-5.743224
C	0.387443	1.504303	-4.539037
C	-4.685305	0.402036	0.430923
C	-6.922395	-0.808335	-0.369419
C	-9.187438	-0.465731	0.929465
C	-9.249637	1.046081	3.089460
C	-7.032803	2.207643	3.946832
C	-4.775999	1.893258	2.636785
C	0.927377	-1.141193	2.756089
C	3.227499	0.291894	2.623115
C	3.940040	1.718141	4.781441
C	6.128980	3.162511	4.770072
C	7.639275	3.246790	2.598234

C	6.956250	1.877483	0.438338
C	4.781647	0.411328	0.448670
Si	1.048289	-5.430309	-1.119316
C	1.890182	-7.967519	1.254560
C	3.870526	-4.851667	-3.225148
C	-1.712384	-6.535668	-3.102862
H	8.126515	1.958257	-1.244911
H	9.347218	4.386101	2.586647
H	6.660708	4.230718	6.439107
H	2.757472	1.665388	6.460364
H	4.257512	-0.628911	-1.226035
H	-6.891199	-1.988880	-2.049422
H	-10.893753	-1.390563	0.262906
H	-11.005205	1.296755	4.122390
H	-7.061528	3.348768	5.652209
H	-3.071173	2.749201	3.383946
H	2.725319	2.917782	-7.544240
H	3.249927	7.157945	-5.564135
H	1.131725	8.112205	-1.488155
H	-1.480339	4.922001	0.607586
H	0.126179	-0.324355	-5.434378
H	-2.735631	-1.491888	-2.527112
H	-0.112276	-0.826739	4.509528
H	-1.958383	-3.539690	1.819277
H	3.658391	-3.282710	-4.556332
H	4.123844	-6.565691	-4.366406
H	5.624071	-4.578341	-2.162835
H	-2.207232	-5.264054	-4.661659
H	-3.414717	-6.848843	-1.964259
H	-1.224788	-8.356979	-3.965653
H	3.481822	-7.391553	2.447986
H	2.439906	-9.707214	0.270443
H	0.300131	-8.428467	2.498655

INT2

Energy: -3201869.749 kJ mol^{-1}
Gibbs free energy: -3200853.955 kJ mol^{-1}

C	-0.546711	-2.222934	0.876807
C	-2.126922	-0.553252	-1.002766
C	-0.879695	1.695804	-2.313993
C	-0.638189	4.068352	-1.154260
C	0.491768	6.082743	-2.428249

C	1.392359	5.768107	-4.889366
C	1.121864	3.431136	-6.084227
C	-0.020236	1.421817	-4.808697
C	-4.596740	0.189352	0.335098
C	-6.879438	-0.021902	-0.996622
C	-9.165460	0.666310	0.125575
C	-9.206491	1.581377	2.600735
C	-6.947330	1.792506	3.947629
C	-4.663365	1.092433	2.825045
C	1.406821	-1.531467	2.583561
C	3.528817	0.139969	2.540797
C	4.769008	0.506473	4.901904
C	6.816060	2.126128	5.108281
C	7.741544	3.337012	2.945097
C	6.612402	2.932240	0.584032
C	4.515312	1.374874	0.370402
Si	1.077369	-5.424161	-0.813533
C	2.045317	-7.605160	1.816525
C	3.810335	-4.529810	-2.882743
C	-1.663440	-6.778539	-2.637813
H	7.376106	3.838126	-1.089397
H	9.369623	4.579224	3.094310
H	7.715643	2.424413	6.927140
H	4.068197	-0.467450	6.567704
H	3.674555	1.055092	-1.462378
H	-6.873852	-0.729890	-2.926460
H	-10.913410	0.482090	-0.936629
H	-10.985112	2.111267	3.478376
H	-6.956272	2.489934	5.878805
H	-2.934305	1.234590	3.925450
H	1.777766	3.174770	-8.012738
H	2.273992	7.337233	-5.876983
H	0.666443	7.902862	-1.494377
H	-1.349989	4.360154	0.746190
H	-0.271689	-0.371537	-5.779237
H	-2.699625	-1.833682	-2.518350
H	1.332796	-2.625781	4.330485
H	-1.918274	-3.376631	1.918496
H	3.320353	-3.169719	-4.360305
H	4.450252	-6.261330	-3.831334
H	5.418136	-3.792870	-1.811830
H	-2.122331	-5.726017	-4.357740
H	-3.378281	-6.955943	-1.492795
H	-1.114340	-8.691832	-3.222149
H	3.700621	-6.937544	2.864615
H	2.551752	-9.433589	0.978568

H	0.516631	-7.964150	3.167758

Cis product

Energy: -2128182.584 kJ mol^{-1}
Gibbs free energy: -2127448.445 kJ mol^{-1}

C	6.675304	0.565250	-2.118748
C	5.546698	2.845667	-2.076406
C	6.201240	5.109557	-0.578278
C	4.234812	6.651025	0.338288
C	4.748660	8.822250	1.739566
C	7.247536	9.517104	2.240339
C	9.221807	8.033955	1.307157
C	8.707023	5.854878	-0.088362
C	8.807109	-0.397892	-0.477672
C	11.304603	-0.787558	-1.906328
C	11.634831	0.003340	-4.410520
C	13.954534	-0.315702	-5.639841
C	15.987798	-1.419090	-4.377528
C	15.684765	-2.208347	-1.872907
C	13.369367	-1.893969	-0.655094
C	7.892636	-2.794502	0.874105
C	7.078359	-2.663336	3.390895
C	6.139361	-4.800153	4.624752
C	5.993227	-7.105772	3.351331
C	6.798107	-7.259003	0.839748
C	7.739358	-5.122078	-0.386653
H	11.171368	8.580665	1.651875
H	7.651945	11.214418	3.323078
H	3.197404	9.972947	2.438127
H	2.286062	6.126058	-0.050080
H	10.261761	4.766485	-0.867117
H	7.172918	-0.871983	4.394487
H	5.523320	-4.658632	6.579194
H	5.261469	-8.770532	4.305459
H	6.694887	-9.046674	-0.167047
H	8.372592	-5.270041	-2.335101
H	17.255801	-3.066194	-0.864991
H	17.790637	-1.667087	-5.329217
H	14.162263	0.307689	-7.586177
H	10.073184	0.879602	-5.412787
H	13.159733	-2.520571	1.289813

H	9.173780	1.011785	0.994789
H	3.882140	3.072286	-3.270297
H	5.863741	-0.840871	-3.391654

Trans product

Energy: -2128192.956
Gibbs free energy: -2127466.970

C	6.808260	0.932967	0.719353
C	6.008751	2.580290	-1.038406
C	5.188957	5.206710	-0.606576
C	5.496762	6.477509	1.713854
C	4.655581	8.952007	2.022375
C	3.494165	10.232583	0.022499
C	3.191619	9.009795	-2.296418
C	4.035488	6.531096	-2.603904
C	7.574504	-1.798089	0.309428
C	10.181786	-2.347338	1.452557
C	12.129037	-0.552034	1.426143
C	14.492295	-1.107208	2.467315
C	14.944346	-3.468052	3.552835
C	13.014634	-5.271211	3.595335
C	10.659664	-4.713265	2.548634
C	7.331460	-2.713162	-2.422808
C	5.192310	-4.098299	-3.148672
C	4.899538	-4.949582	-5.629664
C	6.751134	-4.424633	-7.433783
C	8.886337	-3.034729	-6.738291
C	9.174302	-2.190700	-4.254622
H	2.300506	9.984512	-3.869631
H	2.842774	12.164189	0.269618
H	4.916260	9.890035	3.831146
H	6.416665	5.535813	3.288990
H	3.790188	5.594888	-4.417284
H	3.739302	-4.515317	-1.755492
H	3.230060	-6.029151	-6.146810
H	6.533915	-5.090516	-9.364597
H	10.339354	-2.617653	-8.129106
H	10.856502	-1.134572	-3.735660
H	13.342423	-7.111980	4.446129
H	16.778751	-3.898659	4.369318
H	15.977173	0.311989	2.432664

H	11.787962	1.301836	0.611469
H	9.168708	-6.128371	2.592647
H	6.229927	-2.930538	1.419589
H	5.908339	1.952931	-2.994923
H	6.874486	1.509315	2.694594