Brønsted Acid-Catalyzed Reactions of Vinylboronic Acids and Benzhydryl Alcohols

by

Renata Olivia Barichello

A thesis submitted to the

School of Graduate and Postdoctoral Studies in partial

fulfillment of the requirements for the degree of

Master of Science in Applied Bioscience

Faculty of Science

University of Ontario Institute of Technology

(Ontario Tech University)

Oshawa, Ontario, Canada

April 2020

THESIS EXAMINATION INFORMATION

Submitted by: **Renata O. Barichello**

Master of Science in **Applied Bioscience**

Thesis title: Brønsted Acid-Catalyzed Reactions of Vinylboronic Acids and Benzhydryl Alcohols

An oral defense of this thesis took place on April 21, 2020 in front of the following examining committee:

Examining Committee:

Chair of Examining Committee	Dr. Janice Strap
Research Supervisor	Dr. Yuri Bolshan
Examining Committee Member	Dr. Jean-Paul Desaulniers
Thesis Examiner	Dr. Marc J. Adler, Ryerson University

The above committee determined that the thesis is acceptable in form and content and that a satisfactory knowledge of the field covered by the thesis was demonstrated by the candidate during an oral examination. A signed copy of the Certificate of Approval is available from the School of Graduate and Postdoctoral Studies.

Abstract

The functionalization of benzhydryl alcohols is an approach to form important building blocks in organic synthesis. More specifically, the derivatization of benzhydryl alcohols to afford an alkene is a desired approach due to the wide variety of derivatizations applicable to 1,3,3-triphenylpropene derivatives. However, many approaches towards functionalization rely on harsh reaction conditions or the use of Lewis acid catalysts, which leads to low functional group tolerance. Herein, a methodology for the formation of 1,3,3-triphenylpropene derivatives through a Brønsted acid-catalyzed reaction of styrylboronic acids and benzhydryl alcohols is reported. The use of tetrafluoroboric acid diethyl ether complex ($HBF_4 \cdot OEt_2$) in substoichiometric amounts is desirable as it allows for the introduction of the desired alkene structural motif under less harsh conditions than the previously reported methodologies. Using milder reaction conditions results in a broader scope of benzhydryl alcohols and styrylboronic acids as starting materials.

Keywords: Styrylboronic Acid; Benzhydryl Alcohol; Brønsted Acid; Catalysis; Alkenylation

Author's Declaration

I hereby declare that this thesis consists of original work of which I have authored. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I authorize the University of Ontario Institute of Technology to lend this thesis to other institutions or individuals for the purpose of scholarly research. I further authorize University of Ontario Institute of Technology to reproduce this thesis by photocopying or by other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research. I understand that my thesis will be made electronically available to the public.

Renata O. Barichello

Statement of Contributions

I hereby certify that I am the sole author of this thesis and that no part of this thesis has been published or submitted for publication. I have used standard referencing practices to acknowledge ideas, research techniques, or other materials that belong to others. Furthermore, I hereby certify that I am the sole source of the creative works and/or inventive knowledge described in this thesis.

For my grandmother, Maria Barichello, who was not able to receive an education.

May the sacrifice you made for your family always be remembered.

Acknowledgements

I'd like to start by thanking my supervisor, Prof. Yuri Bolshan, for giving me the opportunity to join his group. Since joining the Bolshan group in 2017, I have acquired a tremendous amount of theoretical and practical knowledge in the field of synthetic organic chemistry. In addition, I would like to thank Prof. Bolshan for providing me with guidance and support during this project.

Thank you to all of my colleagues in the Bolshan group, both those who have graduated and those still completing their degrees. You have all impacted my time in our group in so many positive ways. Thank you for making our lab a space where everyone feels comfortable and appreciated.

To my committee member, Prof. Jean-Paul Desaulniers, thank you for offering your guidance throughout this project and for taking the time to review this work. In addition, I would like to thank Dr. Marc J. Adler for acting as my external examiner and for reviewing this dissertation.

I would like to thank Ontario Tech University for providing the research facility and equipment as well as the funding for this project. In addition, I'd like to thank the Ontario Ministry of Research Innovation and Science for providing funding through the Early Research Award, and NSERC for additional funding.

To the Falzon family, whom I have lived with since 2014, thank you for acting as my second family for all of these years. Marla, thank you for helping me find a smile on the stressful days and for laughing with me on the best days.

To my family, thank you all for supporting me throughout this experience. Aunt Suzanne and Uncle Steven, thank you for encouraging me to follow in your footsteps and pursue a graduate degree. Zia Vali and Nonna thank you for stepping in to help my father raise my sister and me. The sacrifices you have both made gave us the opportunity to become who we are today. To my sister, Julia, thank you for being my best friend and my rock. You've inspired me to follow my dreams and to never let the opinions of others dictate who I want to be.

Last but not least, I would like to thank my father, Roy. Dad, you raised me to be my own advocate and to believe in myself no matter what challenge was put before me. Thank you for teaching me I can do anything I set my mind to no matter how difficult it may seem. Thank you for showing me the value of hard work and for always reminding me to never give up. Finally, thank you for supporting me both emotionally and financially throughout my education; without you this degree would not have been possible.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations and Symbols

THF	Tetrahydrofuran
eq.	Equivalents
°C	Degrees Celsius
H_2O	Water
KHF_2	Potassium bifluoride
HF	Hydrogen fluoride
BF_3	Boron trifluoride
KF	Potassium Fluoride
$Pd(PPh_3)_4$	Palladium-tetrakis(triphenylphosphine)
EtONa	Sodium ethoxide
EtOH	Ethanol
h	Hour(s)
$(CH_2O)_n$	Paraformaldehyde
min	Minute(s)
$HBF_4 \cdot OEt_2$	Tetrafluoroboric acid diethyl ether complex
CH_3CN	Acetonitrile
rt	Room temperature
$SiMe_3$	Trimethylsilyl
DCE	Dichloroethane
BQ	Benzoquinone
mCPBA	*meta*-Chloroperbenzoic acid

DCM	Dichloromethane
$Bi(OTf)_3$	Bismuth tris(trifluoromethanesulfonate)
PhI	Phenyliodide
HFIP	Hexafluoroisopropanol
$Pd(OAc)_2$	Palladium(II) acetate
PPh_3	Triphenylphosphine
DMF	Dimethylformamide
KO^tBu	Potassium *tert*-butoxide
DMSO	Dimethyl sulfoxide
n-BuLi	*n*-Butyllithium
$Ca(NTf_2)_2$	Calcium(II) bis(trifluoromethanesulfonimide)
nBu_4NPF_6	Tetrabutylammonium hexafluorophosphate
TfOH	Trifluoromethane sulfonic acid
DBE	1,2-Dibromoethane
temp / Temp.	Temperature
$RB(OH)_2$	Boronic acid
µl	Microliters
BF_4^-	Tetrafluoroborate
^{1}H-NMR	Proton nuclear magnetic resonance spectroscopy
ppm	Parts per million
$CDCl_3$	Deuterated chloroform
HBF_4	Tetrafluoroboric acid
TFA	Trifluoroacetic acid

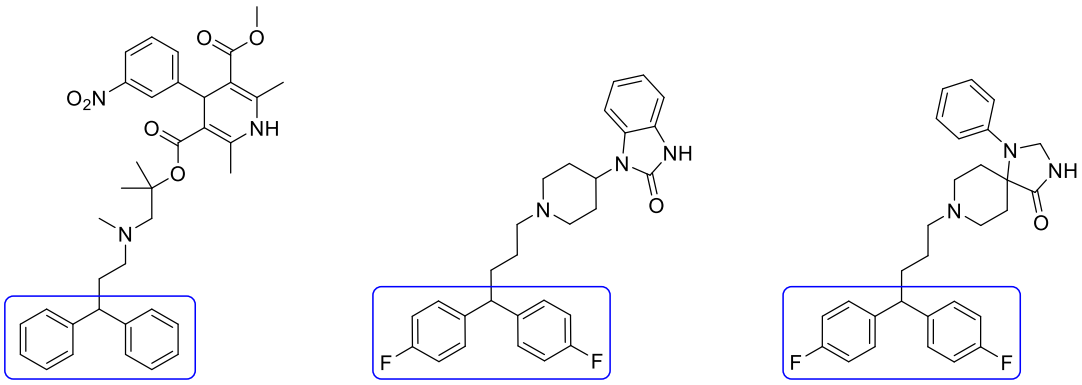
H_2SO_4	Sulfuric acid
aq	Aqueous
C-C	Carbon-carbon
$B(OH)_3$	Boric acid
TLC	Thin-layer chromatography
NMR	Nuclear magnetic resonance spectroscopy
OMe	Methoxy
OEt_2	Diethyl ether
M	Molarity
Pd^0	Palladium(0)
Me	Methyl
Boc	*tert*-Butoxycarbonyl
EWG	Electron withdrawing group
Cp	Cyclopentadienyl
BINAP	2,2'-Bis(diphenylphosphaneyl)-1,1'-binaphthalene
K_2CO_3	Potassium carbonate
$^{13}C\{^1H\}$-NMR	Carbon proton decoupled nuclear magnetic resonance spectroscopy
MHz	Megahertz
TMS	Tetramethylsilane
HRMS	High resolution mass spectroscopy
DART	Direct analysis in real time
FT-IR	Fourier-transform infrared spectroscopy
ATR	Attenuated total reflectance

Å	Angstrom
nm	Nanometer
ml	Milliliters
HCl	Hydrochloric acid
EtOAc	Ethyl acetate
$MgSO_4$	Magnesium sulfate
$NaHCO_3$	Sodium bicarbonate
mmol	Millimole
mg	Milligram

Chapter 1: Introduction and Significance

1.1 Benzhydryl Motif

The benzhydryl moiety is a structural motif present in a variety of pharmaceutical compounds. The use of this structural motif in pharmaceuticals has shown a wide variety of applications including but not limited to hypolipidemics, anti-allergics, anti-Parkinson agents, opioid agonists, and anticoagulants.[1] A substructure search of the benzhydryl motif bound to an sp^3 carbon revealed over 40 FDA approved drugs with the desired structural motif. Some notable examples of medicinally relevant compounds containing the benzhydryl motif are Lercanidipine **1**, an antihypertensive, as well as antipsychotics, Pimozide **2**, and Fluspirilene **3** (Figure 1).[2-4]



Lercanidipine **1** Pimozide **2** Fluspirilene **3**

Figure 1: Pharmaceutical compounds containing the benzhydryl motif with varying biological activity

In addition to the pharmaceutically relevant molecules containing the benzhydryl motif, natural products have been isolated containing this moiety. Specifically, natural products have been isolated possessing a benzhydryl alkene moiety. Some of these natural products include calyxin H **4**, and blepharocalyxin A **5** (Figure 2).[5,6]

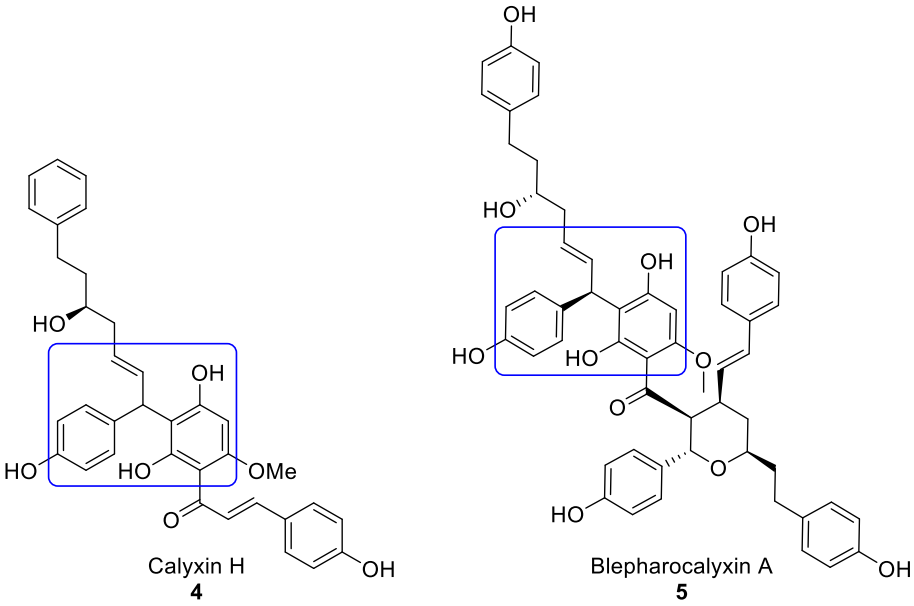
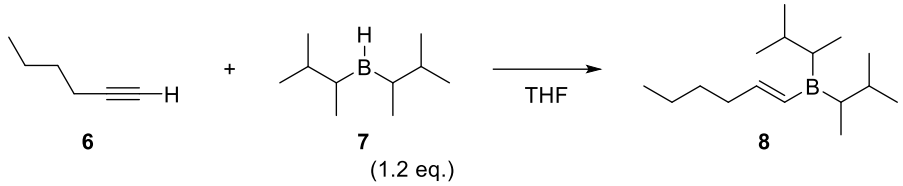


Figure 2: Natural products containing the benzhydryl motif adjacent to an alkene

Due to the diverse range of pharmacological properties small molecules containing the benzhydryl motif possess, it is an important basis for methodology development in order to allow access to novel compounds containing this desired structure.

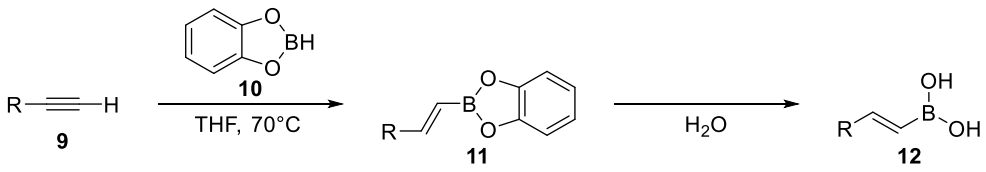
1.2 Organoborane Compounds

Organoboranes have shown a wide variety of synthetic utility since the first isolation of a boronic acid in 1860 by Frankland.[7] However, the synthesis of vinyl organoboranes was not achieved until the early 1960s.[8] Brown and Zweifel determined that the treatment of 1-hexyne **6** with disiamylborane **7** resulted in the quantitative formation of monohydroboration product **8** (Scheme 1).[8]



Scheme 1: Synthesis of monohydroboration products from terminal alkynes and disiamylborane

Although this report did not outline the direct synthesis of vinylboronic acids, it was realized that bulky hydroborating agents facilitate the formation of monohydroboration products.[8] Brown later determined that catecholborane **10** could act as a hydroboration reagent for terminal alkynes **9** in order to form only the monohydroborated product.[9] The use of catecholborane allows for the formation of a vinylboronic acid catechol ester **11** which can then be saponified to form a vinylboronic acid **12** (Scheme 2).[9]



Scheme 2: Synthesis of vinylboronic acids from terminal alkynes

Over the years, since the discovery of boronic acids **13**, a number of organoboranes have been developed for use in organic synthesis (Figure 3). Boronic esters **14** are derivatives of boronic acids, in which the hydroxyl groups are replaced with alkoxy or aryloxy groups.[7] This modification allows for the formation of a less polar substrate

through removal of the hydrogen bond donating capability that boronic acids possess.[7] In addition, trifluorinated crystalline derivatives of boronic acids are called potassium trifluoroborate salts **15**. Modification of the boronic acids to potassium trifluoroborate salts allows for the formation of shelf stable molecules, which can be employed in a similar fashion as boronic acids and beyond.[7]

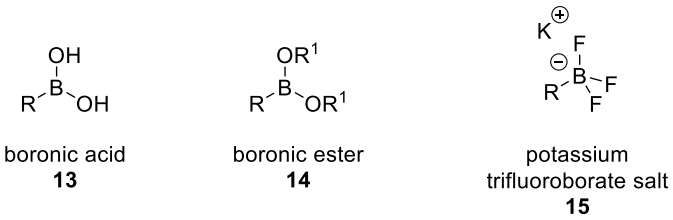


Figure 3: Common organoborane reagents

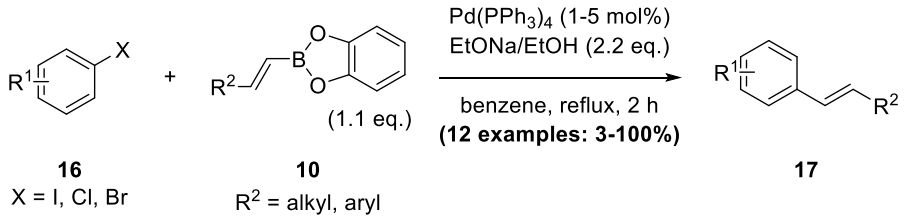
Although boronic esters and potassium trifluoroborate salts are stable alternatives of boronic acids, there are drawbacks associated with both substrates. Boronic esters have proven to be less reactive than boronic acids,[10] requiring the use of more harsh reaction conditions. In addition, formation of boronic esters from boronic acids generally requires the use of dehydrating conditions and excess amount of alcohol or diol.[7] Commonly, the synthesis of alkenyl potassium trifluoroborate salts requires the addition of KHF_2 as a fluorinating agent.[10] Although KHF_2 is utilized as a safer alternative to HF and BF_3, it causes etching of glassware.[11] A safer alternative has been recently developed which allows for the formation of potassium trifluoroborate salts from boronic acids. This method utilizes KF and tartaric acid in the presence of arylboronic acids and styrylboronic acids to form the desired potassium trifluoroborate salt under non-etching conditions.[11]

Boronic acids are of particular interest as a reagent due to their stability at ambient and high temperatures,[7] degradation into environmentally benign boric acid,[7] and

the low toxicity that these compounds possess.[7] Due to the beneficial aspects of boronic acids as reagents, and the limitations associated with boronic acid derivatives, boronic acids continue to be considered a practical reagent in organic synthesis.

1.2.1 Organoboranes in Synthetic Methodology

Organoboranes have shown a wide range of synthetic utility, in particular their use in cross-coupling reactions is commonly reported. Organoboranes were first noted to be able to transmetallate with palladium (II) acetate and subsequently add to methyl acrylate by Heck.[12,13] Miyaura and Suzuki subsequently reported the synthesis of arylated alkenes **17** utilizing vinylboronic acid catechol esters **10** (Scheme 3). They noted the addition of a base to the system allowed the reaction to proceed in high yields.[14] This methodology was subsequently expanded to include the use of arylboronic acids, heteroarylboronic acids, and alkenylboronic acids in addition to the previously reported alkenylboronic esters.[7,15]

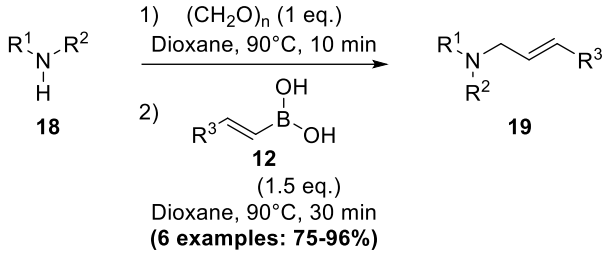


Scheme 3: Palladium-catalyzed cross-coupling of vinylboronic acid catechol esters and arylhalides

Since the discovery that boronic acids could be used in Suzuki-Miyara palladium-catalyzed cross-coupling reactions, the use of boronic acids in metal-catalyzed methodologies has become more prevalent.[7] Chan, Evans and Lam independently determined that copper diacetate can also be used as a catalyst to couple arylboronic acids and aryl or heteroaryl halides.[16-18] Notably, the Chan-Lam reaction has been used to couple organic moieties to nitrogen and oxygen nucleophiles including phenols,

heterocycles, amines, and amides.[7] This method has since been expanded to include the use of vinylboronic acids, and continues to be investigated for the vinylation of nitrogen nucleophiles in the presence of catalytic amounts of copper.[19]

Inspired by the works presented by Suzuki, Petasis envisioned that vinylboronic acids **12** could be used as a stable vinyl nucleophile in Mannich type reactions.[20] The use of vinylboronic acids in multicomponent reactions was first reported by Petasis for the synthesis of allylamines **19** (Scheme 4).[20] In addition, the method was expanded to the use of arylboronic acids for the formation of α-arylglycines,[21] and to different carbonyl derivatives for the formation of α-amino acids,[22] and *anti-β*-amino alcohols.[23]



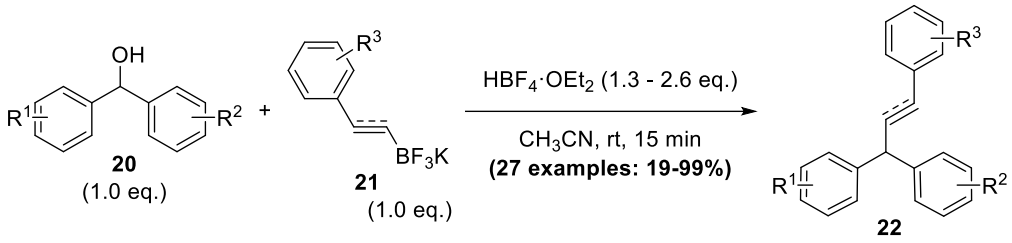
Scheme 4: Synthesis of allylamines through a multicomponent reaction of secondary amines, paraformaldehyde, and vinylboronic acids

In addition to their uses in metal-catalyzed cross-coupling reactions and multicomponent synthesis, vinylboronic acids have been utilized in a number of metal-free methodologies. Notably, base-catalyzed substitutions of secondary bromides,[24] benzylic mesylates,[24] and allylic bromides.[25]

1.3 Derivatization of Benzhydryl Alcohols

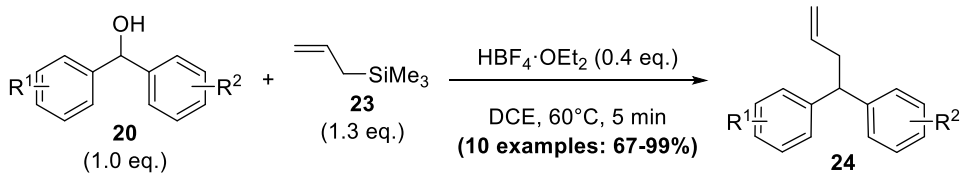
The development of methods for the derivatization of benzhydryl alcohols **20** allows for the practical synthesis of compounds possessing the desirable benzhydryl motif. Benzhydryl alcohols are of particular interest as a starting material due to their commercial availability, stability, and ease of preparation.[26] However, many industrially useful Brønsted acid-catalyzed substitution reactions rely on the use of an activated alcohol as opposed to a direct substitution of an unprotected alcohol.[27] This approach of utilizing an activated alcohol as a leaving group is common due to hydroxyl groups being poor leaving groups.[28] The drawback to these methods is that an additional reaction is required to prepare the starting material, thus compromising the overall yield of the synthetic pathway and producing unnecessary waste products.[27] On the contrary, the use of substrates bearing unprotected alcohols is desirable as the byproduct formed is water. Moreover, it does not require additional reactions to form an appropriate leaving group.[27] As such a number of methods have been developed for the derivatization of benzhydryl alcohols, in order to overcome these drawbacks. Of particular interest are Brønsted acid-catalyzed derivatizations of benzhydryl alcohols.

A Brønsted acid-catalyzed method for the alkenylation and alkynylation of benzhydryl alcohols **20** with potassium trifluoroborate salts **21** was developed by Fisher and Bolshan in 2015 (Scheme 5).[26] The method highlights the efficacy of $HBF_4 \cdot OEt_2$ for the activation of benzhydryl alcohols in order to undergo substitution reactions.



Scheme 5: $HBF_4 \cdot OEt_2$ catalyzed alkenylation and alkynylation of benzhydryl alcohols with potassium trifluoroborate salts

Unlike precedent literature, this method allowed for the formation of a benzhydrylium carbocation without initial activation of the secondary alcohol. Due to the success of the alkynylation reaction, the allylation of benzhydryl alcohols was tried in the presence of substoichiometric amounts of $HBF_4 \cdot OEt_2$ (Scheme 6).[29]



Scheme 6: $HBF_4 \cdot OEt_2$ catalyzed allylation of benzhydryl alcohols with allyltrimethylsilane

This method further demonstrated the utility of $HBF_4 \cdot OEt_2$ to facilitate S_N1 reactions of benzhydryl alcohols due to its use in catalytic amounts resulting in high yields of the desired products.[29] Finally the azidation of benzhydryl alcohols was reported by Regier, Maillet, and Bolshan further justifying the use of $HBF_4 \cdot OEt_2$ for the derivatization of benzhydryl alcohols.[30] In similar fashion to the allylation of benzhydryl alcohols, the azidation of benzhydryl alcohols proceeded in the presence of substoichiometric amounts of $HBF_4 \cdot OEt_2$ and showed a wide range of functional group tolerance.[30] In addition, this methodology allowed for the derivatization of tertiary benzylic alcohols, and carbohydrates unlike previously reported methods.[30]

1.4 Applications and Synthesis of 1,3,3-Triphenylpropene Derivatives

Methodology development for the alkenylation of benzhydryl alcohols **1** is of particular interest due to the synthetic utility of alkenes. More specifically, the synthesis of 1,3,3-triphenylpropene derivatives **37** can be achieved. These derivatives **25**-**28** have been shown to act as synthetic precursors for biologically active structural motifs including substituted benzofurans **29**, indenes **30**, indolines **31**, indoles **32**, and quinolines **33** (Figure 4).[31-35]

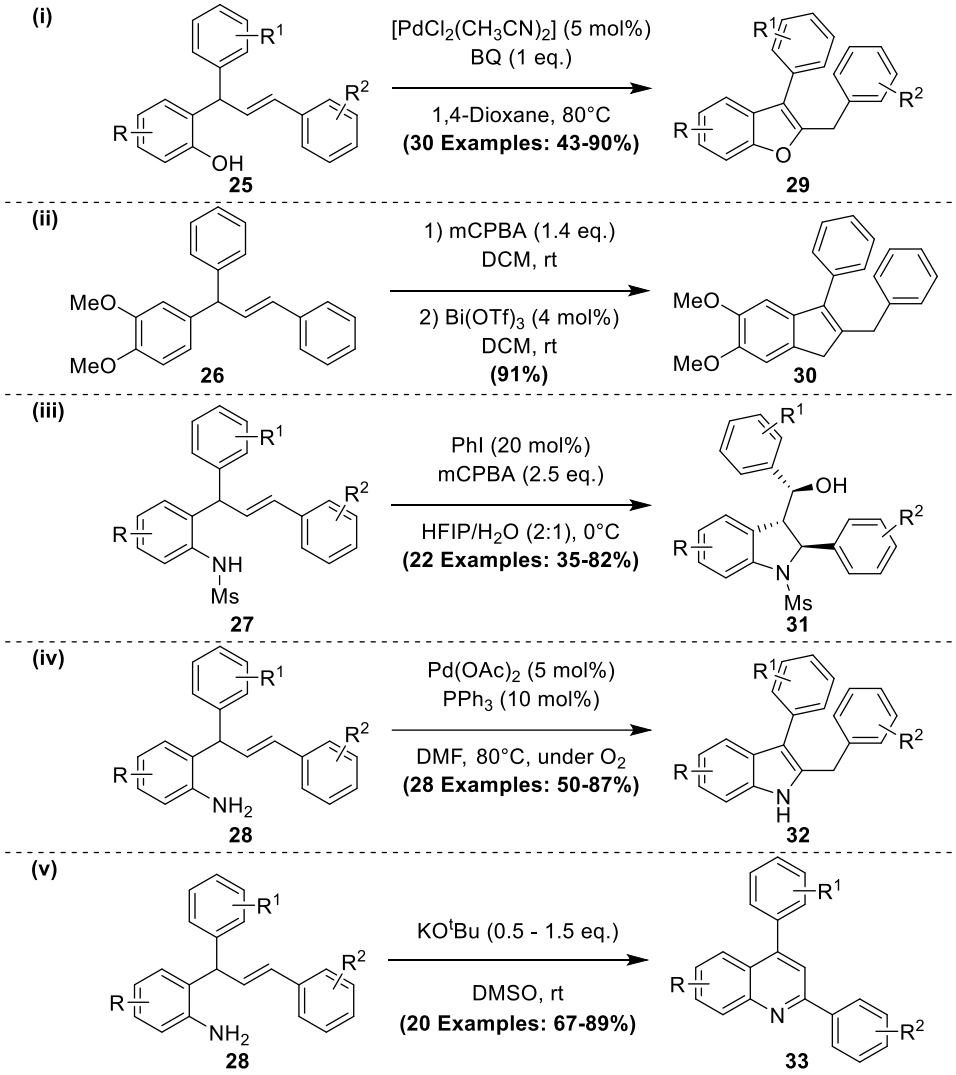
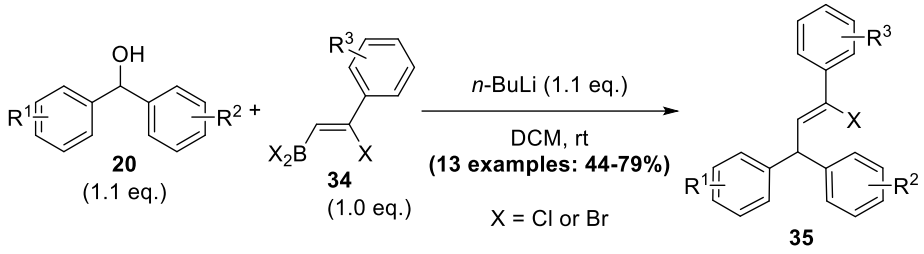


Figure 4: Synthetic utility of 1,3,3-triphenylpropene derivatives for the formation of substituted (i) benzofurans, (ii) indenes, (iii) indolines, (iv) indoles, and (v) quinolines

1.4.1 Base-Catalyzed Synthesis of 1,3,3-Triphenylpropene Derivatives

The alkenylation of benzhydryl alcohols for the formation of halogenated 1,3,3-triphenylpropene derivatives **35** was first achieved by Kabalka et al. in 2005 (Scheme 7).

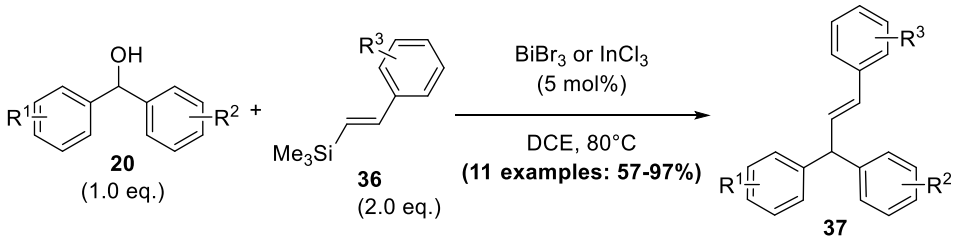


Scheme 7*: n*-BuLi catalyzed alkenylation of benzhydryl alcohols with vinylboron dihalides

This method allows for the introduction of a vinyl moiety to an unprotected alcohol, improving upon precedent literature limited to the installation of an allyl group.[28] Despite the utility of this methodology there are a number of drawbacks including the use of stoichiometric amounts of *n*-BuLi, preformation of unstable haloborane intermediates **34**, long reaction times, limited scope, and the use of chlorinated solvent in order to proceed.

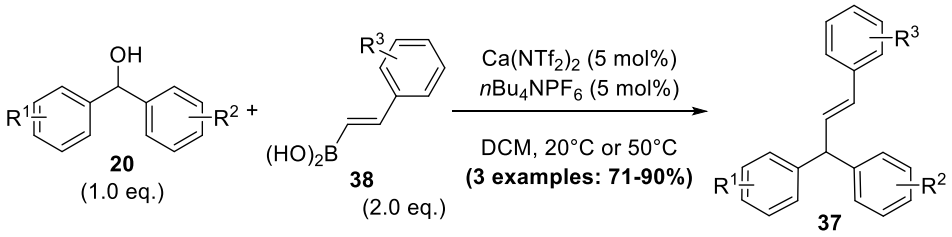
1.4.2 Lewis Acid-Catalyzed Synthesis of 1,3,3-Triphenylpropene Derivatives

In order to overcome the limitations associated with the base-catalyzed method, Baba et al. reported the coupling of alcohols with alkenylsilanes **36** (Scheme 8).



Scheme 8: Lewis acid-catalyzed alkenylation of benzhydryl alcohols with alkenylsilanes

As an improvement upon the method developed by Kabalka et al. bismuth or indium halides were used as Lewis acid catalysts in substoichiometric amounts to alleviate the necessity of *n*-BuLi for the transformation.[36] Although the method improved upon the previous literature, the use of large equivalents of alkenylsilanes is unfavourable due to the fact that they are not commercially available substrates. Similarly, this method also relied on the use of chlorinated solvents and showed low functional group tolerance. Gandon at al. reported an additional calcium (II) catalyzed alkenylation reaction of alcohols with vinylboronic acids **38** (Scheme 9).[37]



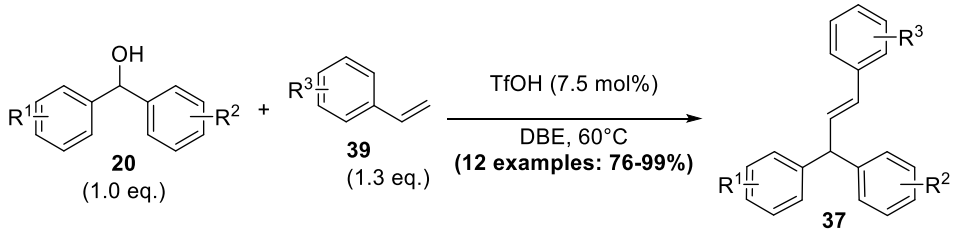
Scheme 9: Lewis acid-catalyzed alkenylation of benzhydryl alcohols with vinylboronic acids

The use of vinylboronic acids as starting materials is beneficial due to their commercial availability, low toxicity, stability, and degradation to environmentally friendly boric acid.[7] However, $Ca(NTf_2)_2$ is an expensive reagent (Sigma Aldrich; $129 US per gram) even when used in catalytic amounts. In addition, the reported methodology displays low functional group tolerance, utilized a chlorinated solvent, and required large amounts of vinylboronic acid starting materials.

1.4.3 Brønsted Acid-Catalyzed Synthesis of 1,3,3-Triphenylpropene Derivatives

The first Brønsted acid-catalyzed formation of 1,3,3-triphenylpropene derivatives **37** from benzhydryl alcohols was reported by Ji et al. in 2011 (Scheme 10). This method

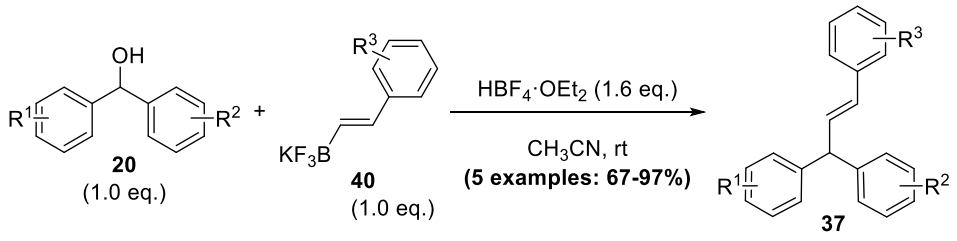
utilized TfOH in catalytic amounts in the presence of styrene derivatives **39** in order to form the desired motif.[38]



Scheme 10: Brønsted acid-catalyzed alkenylation of benzhydryl alcohols with styrene derivatives

Although the use of a Brønsted acid catalyst eliminated the need for an inert atmosphere, low functional group tolerance was reported for the benzhydryl substrates **20**. In addition, long reaction times were required in order to force the formation of the desired product due to the formation of a dimeric ether intermediate.[38]

As previously stated the alkenylation and alkynylation of benzhydryl alcohols **20** with potassium trifluoroborate salts was achieved by Fisher and Bolshan in the presence of $HBF_4{\cdot}OEt_2$ (Scheme 11).[26]



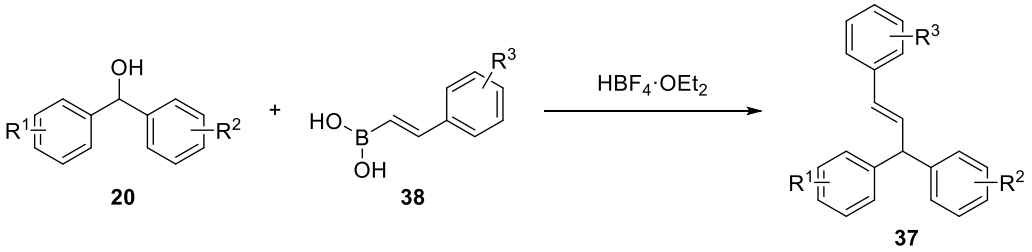
Scheme 11: Brønsted acid-catalyzed alkenylation of benzhydryl alcohols with potassium trifluoroborate salts

Although this method was successful for the alkynylation of benzhydryl alcohols there are a number of drawbacks associated with it. The substrates tolerated by the method for the alkenylation of benzhydryl alcohols was limited to benzhydryl alcohols possessing electron-donating substituents. In addition to a minimal number of successful examples reported, in order to facilitate the transformation 1.6 eq. of $HBF_4{\cdot}OEt_2$ was required.

Finally, potassium trifluoroborate salts were required as coupling partners, which are formed from boronic acid precursors under non-etching conditions.

1.5 Research Objective

We had set out to develop a methodology for a Brønsted acid-catalyzed alkenylation of benzhydryl alcohols **20** for the synthesis of 1,3,3-triphenylpropene derivatives **37** (Scheme 12). Inspired by the works of Gandon et al. (Section 1.4.2) we sought to utilize vinylboronic acids **38** as stable, environmentally benign nucleophiles. In addition, the works of Fisher and Bolshan (Section 1.4.3) inspired the use of substoichiometric amounts of $HBF_4 \cdot OEt_2$ as a Brønsted acid to facilitate the desired transformation. Utilizing this approach, we sought to develop a methodology which did not require an inert atmosphere, utilized catalytic amounts of Brønsted acid, and allowed for wider scope than previously reported methods.



Scheme 12: Proposed approach for the $HBF_4 \cdot OEt_2$ catalyzed reaction of vinylboronic acids and benzhydryl alcohols for the synthesis of 1,3,3-triphenylpropene derivatives

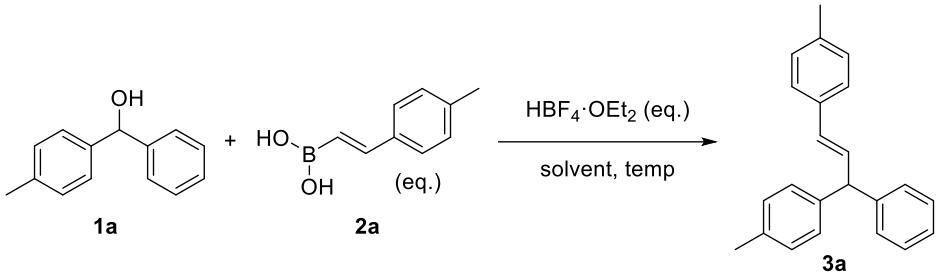
Chapter 2: Results and Discussion

2.1 Optimization of the Brønsted acid-catalyzed Alkenylation of Benzhydryl Alcohols and Styrylboronic Acids

Optimization of the alkenylation of benzhydryl alcohols was conducted using *trans*-2-(4-methylphenyl)vinylboronic acid **2a** and 4-methylbenzhydrol **1a** as test substrates in the presence of $HBF_4 \cdot OEt_2$ (Table 1). $HBF_4 \cdot OEt_2$ was chosen as the Brønsted acid due to its high acidity with a pKa ~0.5 in water,[26] its proven ability to form benzhydryl cations,[26] and the non-nucleophilic character of its conjugate base (BF_4^-).[26] An initial solvent screening was performed with 1,4-dioxane (entry 1) and toluene (entry 2). These solvents were investigated due to their high boiling points of 101°C and 111°C respectively,[39] which would allow for a greater range of temperatures to be investigated during optimization. The desired product **3a** was isolated in 9% and 73% yield in 1,4-dioxane and toluene respectively.

It was hypothesized that the alkenylation of benzhydryl alcohols with vinylboronic acids occurred via an S_N1 mechanism (Section 2.2). Through an S_N1 process, the formation of a benzhydryl carbocation would occur in the presence of $HBF_4 \cdot OEt_2$. 1,4-Dioxane as a polar aprotic solvent is able to stabilize this intermediate. The ability of 1,4-dioxane to strongly stabilize the electrophilic intermediate is suspected to impede addition of the desired alkenyl nucleophile to the benzhydryl cation. On the contrary, toluene does not solvate the benzhydryl cation as strongly as 1,4-dioxane. Therefore, it was hypothesized that toluene does not have the ability to stabilize the carbocation, therefore, making it more reactive.

Table 1: Optimization of the alkenylation reaction of 4-methylbenzhydrol and *trans*-2-(4-methylphenyl)vinylboronic acid



1a **2a** **3a**

Entry	Solvent	$RB(OH)_2$ (eq.)	$HBF_4 \cdot OEt_2$ (eq.)	Temp. (°C)	Time (min)	Yield **3a**
1	1,4-dioxane	1.3	0.40	80	20	9%
2	Toluene	1.3	0.40	80	20	73%
3	Toluene	1.5	0.40	80	15	76%
4	Toluene	1.1	0.40	80	25	59%
5	Toluene	1.5	0.30	80	15	77%
6[a]	Toluene	1.5	0.30	80	25	67%
7	Acetonitrile	1.3	0.40	80	20	75%
8	Acetonitrile	1.5	0.40	80	15	85%
9	Acetonitrile	1.5	0.30	80	15	85%
10	Acetonitrile	1.5	0.25	80	15	85%
11	Acetonitrile	1.5	0.20	80	15	82%
12	Acetonitrile	1.5	0.25	90	15	81%
13	Acetonitrile	1.5	0.25	70	15	98%
14	Acetonitrile	1.5	0.25	60	25	82%
15	Acetonitrile	1.5	0.20	70	25	91%
16[b]	Acetonitrile	1.5	0.25	70	15	87%

[a] Addition of 5 µl of water
[b] New aliquot of acid used

Since the use of toluene resulted in a higher isolated yield optimization was continued with this solvent and the boronic acid loading was increased to 1.5 eq. (entry 3). This resulted in an increased yield of 76%, while decreasing the loading to 1.1 eq. (entry 4) resulted in an 18% decrease in isolated yield to 59%. Due to the high cost of

styrylboronic acids, other variables were investigated in lieu of further increasing the boronic acid loading. The amount of $HBF_4 \cdot OEt_2$ was reduced to 0.3 eq. (entry 5), which resulted in a minimal increase in the isolated yield to 77%. It was hypothesized that the boronic acid could be partially present in its dehydrated form boroxine.[7] Although boroxines have appeared in literature for vinylation and arylation reactions,[40] it was unclear if they would be able to act as a nucleophile in this system. In order to determine if boroxine was interfering with the reaction, 5 μl of water was added in order to hydrate any boroxine in the mixture prior to reaction with the benzhydryl alcohol (entry 6). This addition of water resulted in a decreased isolated yield, leading to the hypothesis that an excess amount of water is detrimental to the synthesis.

Although the addition of water was attempted in order to hydrate any boroxine present in the reaction mixture, water can cause a variety of effects on organic reactions. Particularly, the use of water in an S_N1 reaction can act as a competing nucleophile thus inhibiting the desired transformation. As such, a sample of **2a** was analyzed by ^{1}H-NMR to determine the ratio of boroxine to boronic acid in the starting material (Figure 5). Consistent with literature values, three of the boroxine (i) alkenyl protons produce a signal at 6.29 ppm with an integration of 3.[40] Shifted upfield, one of the alkenyl protons on the boronic acid (ii) produces a signal at 6.08 ppm with an integration of 1 (Figure 5A). In addition, six of the aromatic protons on boroxine produce a signal at 7.52 ppm with an integration of 6 which is consistent with literature values.[40] Shifted upfield, two of the aromatic protons on the boronic acid produce a signal at 7.39 ppm with an integration of 2 (Figure 5B).

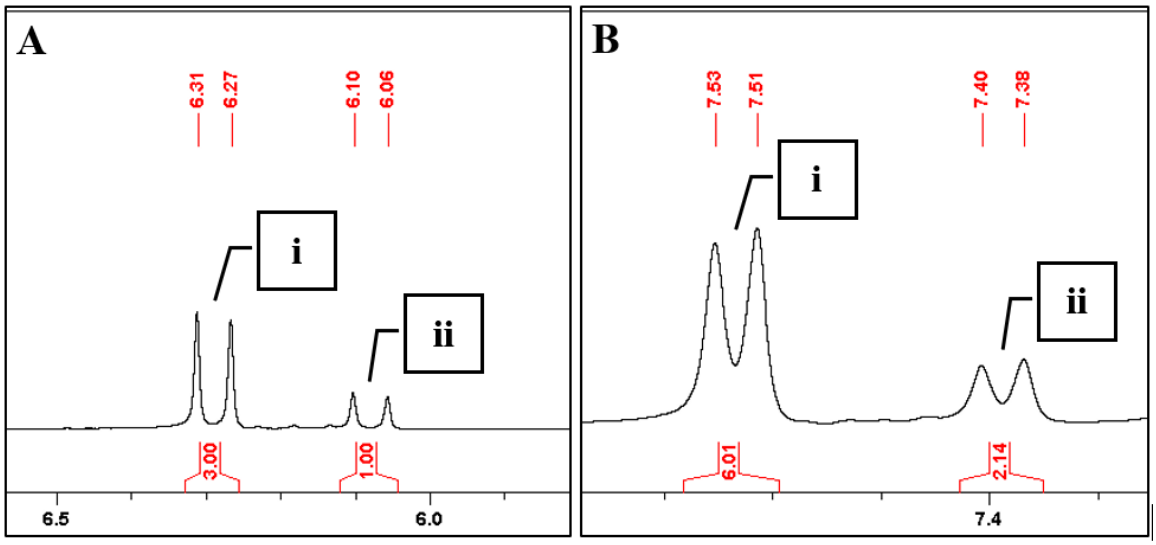


Figure 5: ^{1}H-NMR of *trans*-2-(4-methylphenyl)vinylboronic acid in $CDCl_3$ used to determine the ratio of (i) boroxine to (ii) boronic acid

Comparing the structures of boronic acid and boroxine, it is expected that boroxine signals would appear further downfield due to the cyclic structure of boroxine. The conjugation between the empty p-orbitals of boron and the lone pairs on oxygen results in greater shielding of the protons. Based on the integration patterns displayed, the boronic acid and boroxine are present in a 1:1 ratio in the starting material. Applying this ratio when utilizing 1.5 eq. of boronic acid, if boroxine was unable to participate in the transformation the maximum isolated yield of **3a** would be 75%. Entry 5, utilizing 1.5 eq. of boronic acid, the desired product was isolated with a yield of 77%. This result implies that it is possible for the boroxine to participate in the desired transformation, and further optimization was continued in order to determine if this hypothesis was valid.

Although toluene was successful in the initial screening of reaction conditions, S_N1 reactions are known to occur more rapidly in polar solvents. As such a new solvent, acetonitrile, was considered due to its polar aprotic nature, and fairly high boiling point of 82°C.[39] Acetonitrile did facilitate the transformation with the product **3a** isolated in 75%

yield in the presence of 1.3 eq. of boronic acid **2a** and 0.4 eq. of $HBF_4 \cdot OEt_2$ (entry 7). Similarity to the investigation of reaction conditions with toluene as a solvent the loading of styrylboronic acid was varied. An increase of **2a** to 1.5 eq. resulted in a 10% increase of the isolated yield (85%, entry 8). Due to the results obtained while investigating toluene as the reaction solvent, reduction of the boronic acid loading was not tried. Increasing the loading of **2a** to 1.5 eq. in both toluene and acetonitrile proved to be beneficial. However, the isolated yield was greater in acetonitrile (85%, entry 8) compared to toluene (76%, entry 3). In a similar fashion to 1,4-dioxane, acetonitrile has the ability to stabilize the benzhydrylium ion through the lone pairs on nitrogen. The notable difference between 1,4-dioxane and acetonitrile is their polarity. Acetonitrile and 1,4-dioxane have dielectric constants of 36.64[41] and 2.22[41] respectively, meaning that acetonitrile is a polar solvent. Mechanistically, the use of a polar solvent in an S_N1 reaction facilitates the formation of a carbocation. This is due to the nature of polar solvents possessing partial positive and partial negative character, which is able to stabilize a charged species better than non-polar solvents. In addition, the increased isolated yield to 85% further supports the hypothesis that boroxines are able to participate in the desired transformation.

As a result, acetonitrile was chosen as the optimal solvent and further optimization was conducted. The reduction of $HBF_4 \cdot OEt_2$ was attempted, which revealed that the loading could be lowered to 0.25 eq. without adverse effects on the isolated yield of **3a** (entries 8-10). Further reduction of the Brønsted acid loading to 0.20 eq. resulted in a decrease in isolated yield (82%, entry 11). Lastly, the reaction temperature was varied. The reaction was tried at an external temperature of 90°C, in order to observe the desired

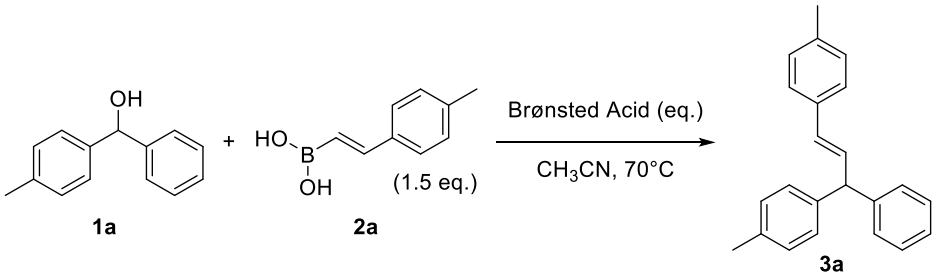
transformation at the boiling point of the reaction mixture (81%, entry 12). It was found that by decreasing the temperature to 70°C, 98% yield of product **3a** was obtained (entry 13). Due to the minimal difference in isolated yield between 0.25 eq. and 0.20 eq. of $HBF_4 \cdot OEt_2$ at 80°C, the lower Brønsted acid loading was also investigated at the optimal temperature of 70°C, which resulted in a 7% decrease in yield (entry 15).

It has been suspected by the Bolshan group that $HBF_4 \cdot OEt_2$ may absorb water over time and this may impact the performance of the acid. Based on unpublished results, the impact of water absorption varies between the developed methodologies. Prior to investigating the functionalities tolerated in this transformation it was noted that the $HBF_4 \cdot OEt_2$ being used to conduct the reactions had been stored in a separate vial for over a year. Due to the unknown impact of water absorption by the acid on this method, an aliquot of $HBF_4 \cdot OEt_2$ from the original bottle was investigated under the optimized conditions (Table 1, entry 16). The use of the new aliquot of acid resulted in a decreased yield of **3a** to 87%, and optimization with various Brønsted acids was continued (Table 2).

Further screening of Brønsted acids began with the investigation of $HBF_{4(aq)}$ and a similar yield of 83% of **3a** was obtained; however, the reaction required double the time to proceed to completion (entry 2). Trifluoroacetic acid (entry 3) and sulfuric acid (entry 4) were also investigated and resulted in decreased isolated yields of 52% and 38%, respectively. Once it had been established that $HBF_{4(aq)}$ and $HBF_4 \cdot OEt_2$ were the most suitable acids for this system, the equivalents of each acid was varied from 0.30 eq. to 0.10 eq. loading to probe the impact on the yield. With regards to the $HBF_{4(aq)}$ 0.3 eq.

loading resulted in a decreased isolated yield further supporting the hypothesis that excess water was detrimental to the method.

Table 2: Investigation of Brønsted acids



Entry	Brønsted Acid	Acid (eq.)	Time (min)	Yield **3a**
1[a]	$HBF_4{\cdot}OEt_2$	0.25	15	87%
2	HBF_4 (48% in H_2O)	0.25	30	83%
3	TFA	0.25	75	52%
4	H_2SO_4	0.25	25	38%
5	$HBF_4{\cdot}OEt_2$	0.30	15	89%
6	$HBF_4{\cdot}OEt_2$	0.20	15	84%
7	$HBF_4{\cdot}OEt_2$	0.15	15	85%
8	$HBF_4{\cdot}OEt_2$	0.10	15	85%
9	HBF_4 (48% in H_2O)	0.30	25	79%
10	HBF_4 (48% in H_2O)	0.20	25	81%
11	HBF_4 (48% in H_2O)	0.15	20	85%
12	HBF_4 (48% in H_2O)	0.10	20	84%
13	$HBF_4{\cdot}OEt_2$	0.35	15	89%
14[b]	$HBF_4{\cdot}OEt_2$	0.25	15	72%

[a] New aliquot of acid used
[b] 1.7 eq. of *trans*-2-(4-methylphenyl)vinylboronic acid (**2a**)

An $HBF_{4(aq)}$ loading of 0.15 eq. afforded the desired product in optimal yield of 85% (entry 11); however, the use of $HBF_4{\cdot}OEt_2$ in 0.25 eq. (entry 1) was still favourable as it was hypothesized that 4-methylbenzhydrol **1a** would be one of the higher yielding benzhydrol substrates. As seen in previous Brønsted acid-catalyzed methodologies using

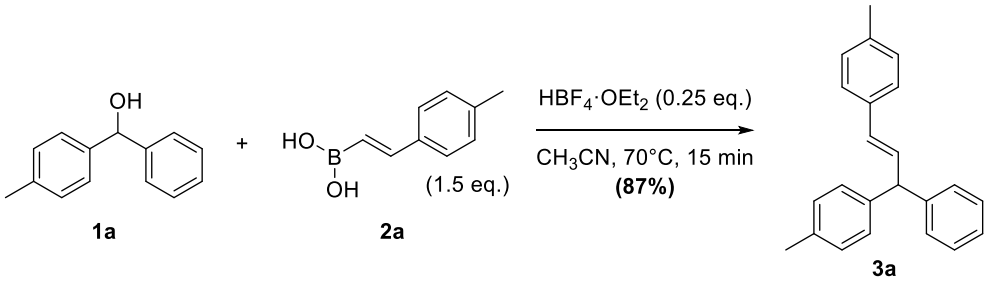
benzhydrols developed by the Bolshan group, the use of **1a** tends to give high yields and can be considered an ideal substrate.[26,29,30] The methyl group on **1a** acts as an electron-donating substituent. Through hyperconjugation, this electron-donating group stabilizes the carbocation intermediate formed in an S_N1 reaction. Since the formation of the carbocation could be considered as the rate determining step, stabilization of the intermediate allows for the substitution reaction to occur more easily. Based on the hypothesis that the alkenylation of benzhydryl alcohols is occurring via an S_N1 mechanism, it is hypothesized that electron-donating substrates would be better suited to this transformation. Moreover, the methodology developed by Fisher and Bolshan for the alkenylation of benzhydrols displayed poor tolerance to electron-withdrawing substrates[26] further supporting this hypothesis.

Due to the hypothesis that **1a** would likely be one of the best benzhydrols for this methodology, reducing the acid loading in order to use $HBF_{4(aq)}$ was thought to be potentially detrimental during the scope investigation. Although the use of $HBF_4{\cdot}OEt_2$ in 0.30 eq. did result in a slightly higher yield, it was not significant enough to justify increasing the acid loading above 0.25 eq. (entry 5). An $HBF_4{\cdot}OEt_2$ loading of 0.35 eq. was also tried, resulting in an isolated yield of 89% which was not a statistically significant increase (entry 13).

An additional experiment was conducted using 1.7 eq. of boronic acid in the presence of 0.25 eq. of $HBF_4{\cdot}OEt_2$ (72%, entry 14). This experiment was performed in order to further investigate the effect of boroxine on the formation of **3a**. Due to the 1:1 ratio of boroxine to boronic acid in the starting material, increasing the loading of boronic acid above 1.5 eq. was considered. It was hypothesized that if boroxine was not

participating in the transformation, increasing the boronic acid loading would subsequently increase the isolated yield of the desired product. However, increasing the boronic acid loading resulted in a decreased isolated yield of **3a**, leading to the conclusion that a boronic acid loading of 1.5 eq. is optimal for this transformation.

The optimized conditions for the alkenylation of benzhydryl alcohols were established using 4-methylbenzhydrol **1a**, with 1.5 eq. of *trans*-2-(4-methylphenyl)vinylboronic acid **2a**, and 0.25 eq. $HBF_4 \cdot OEt_2$ as a catalyst in acetonitrile at 70°C (Scheme 13).



Scheme 13: Optimized conditions for the $HBF_4 \cdot OEt_2$ catalyzed reaction of *trans*-2-(4-methylphenyl)vinyl boronic acid and 4-methylbenzhydrol

2.2 Mechanistic Considerations

Based on the effects of solvents noted through optimization of the reaction conditions presented in Section 2.1 and previous work by the Bolshan group, it was hypothesized that the transformation occurred through an S_N1 mechanism. In addition, mechanistic investigation performed by Regier, Maillet, and Bolshan, also showed that the $HBF_4{\cdot}OEt_2$ catalyzed derivatization of benzhydryl alcohols occurs through an S_N1 type mechanism.[30] Additional studies have shown that under acidic conditions benzhydryl alcohols are protonated, and water is eliminated to form a benzhydryl cation, which further supports the proposed S_N1 mechanism.[42]

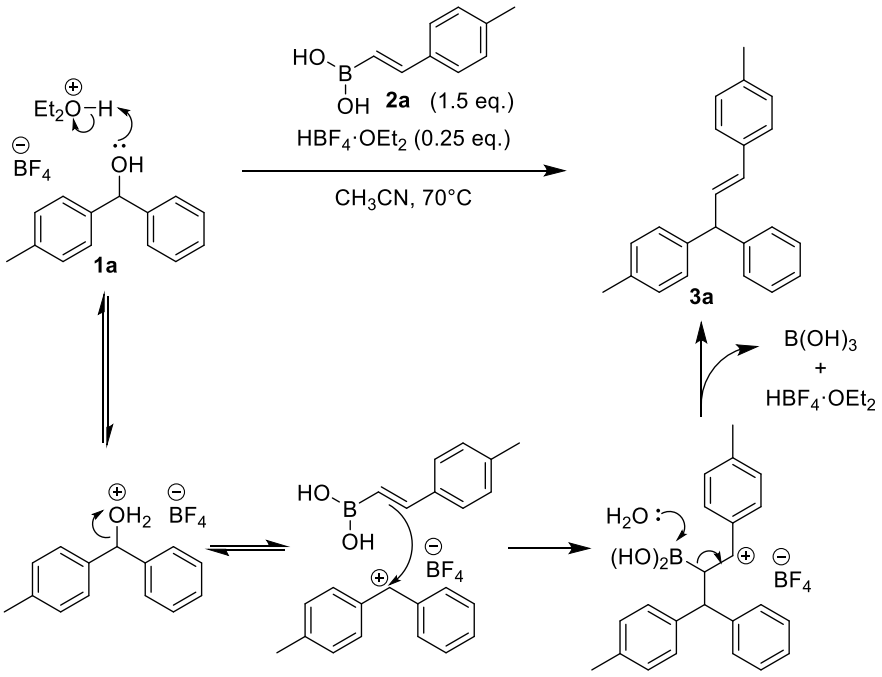
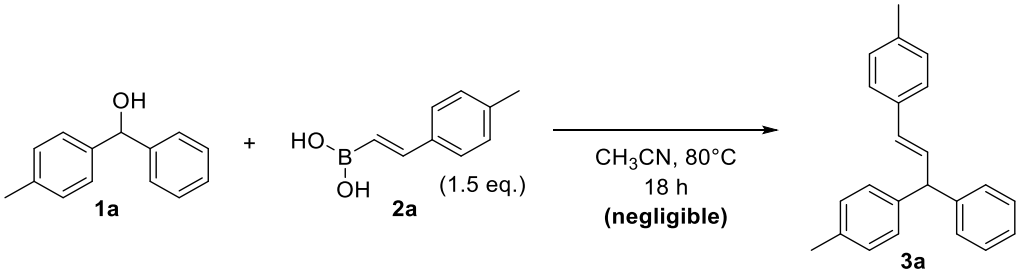


Figure 6: Mechanism for the alkenylation of benzhydryl alcohols with styrylboronic acids in the presence of $HBF_4{\cdot}OEt_2$

The proposed mechanism follows literature, with a benzhydryl cation forming in the presence of catalytic amounts of $HBF_4{\cdot}OEt_2$. The alkene functionality of the styrylboronic acid then acts as a nucleophile to form a C-C bond with the benzhydrylium

ion. Water then facilitates the removal of boric acid, regeneration of $HBF_4{\cdot}OEt_2$, and the formation of the desired product (Figure 6). It is hypothesized that there is an equilibrium between the benzhydryl alcohol and benzhydrylium ion. As noted previously, the addition of water to the system resulted in a decreased yield of **3a** due to the potential of water to act as a competing nucleophile (Section 2.1). Considering the proposed equilibrium, formation of the benzhydrylium ion is not the rate determining step in this process. Further supporting this hypothesis is the observation that decreasing the nucleophilicity of the vinylboronic acid coupling partner resulted in increased reaction times for the transformation (Section 2.3).

In order to further verify the mechanism, the reaction was attempted with the exclusion of $HBF_4{\cdot}OEt_2$ (Scheme 14). The formation of the desired product **3a** was not observed via TLC after 15 minutes, implying that the transformation is dependent on carbocation formation facilitated by a Brønsted acid. The mixture was left overnight and a work-up NMR was performed, which showed complete consumption of the starting benzhydrol **1a** and the appearance of the desired product **3a** was negligible.

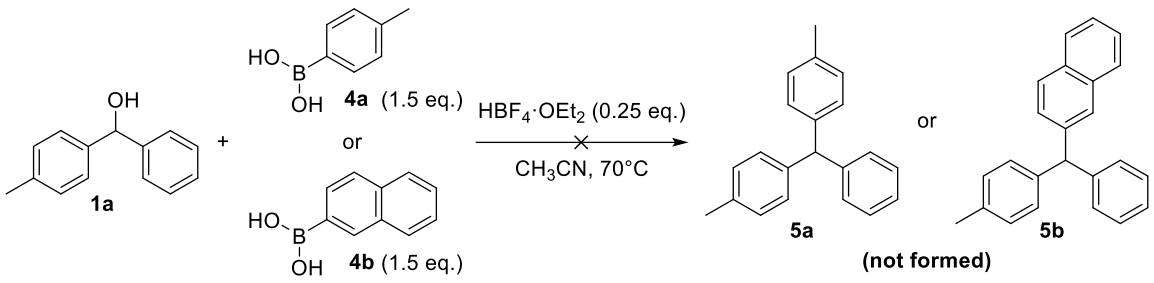


Scheme 14: Mechanistic verification of the alkenylation of benzhydryl alcohols via the exclusion of $HBF_4{\cdot}OEt_2$

Although negligible, the formation of the desired product after an extended period of time implies that the Lewis acidity of the boronic acid **2a** could act to facilitate the transformation. Boronic acids are understood to act as mild Lewis acids due to the empty

p-orbital boron possesses.[7] Thus under harsher conditions it is possible that this transformation could proceed without the addition of a Brønsted acid. However, due to the fact that no desired product was observed after 15 minutes utilizing the optimized conditions, it is unlikely that the transformation is promoted by the Lewis acidity of the boronic acid.

In addition, the reaction was tried with derivatives of phenylboronic acid **4a**, **4b** (Scheme 15). TLC of these reaction mixtures did not show consumption of the benzhydryl alcohol **1a**, leading to the hypothesis that the nucleophilic attack at the carbocation occurs through the conjugated alkene of the styrylboronic acid.



Scheme 15: Mechanistic verification of the alkenylation of benzhydryl alcohols via the addition of phenylboronic acid derivatives

2.3 Evaluation of the Functional Group Tolerance of the Brønsted Acid-Catalyzed Alkenylation of Benzhydryl Alcohols and Styrylboronic Acids

With the optimized conditions in hand, the functional group tolerance on the benzhydryl alcohol was investigated (Figure 7).

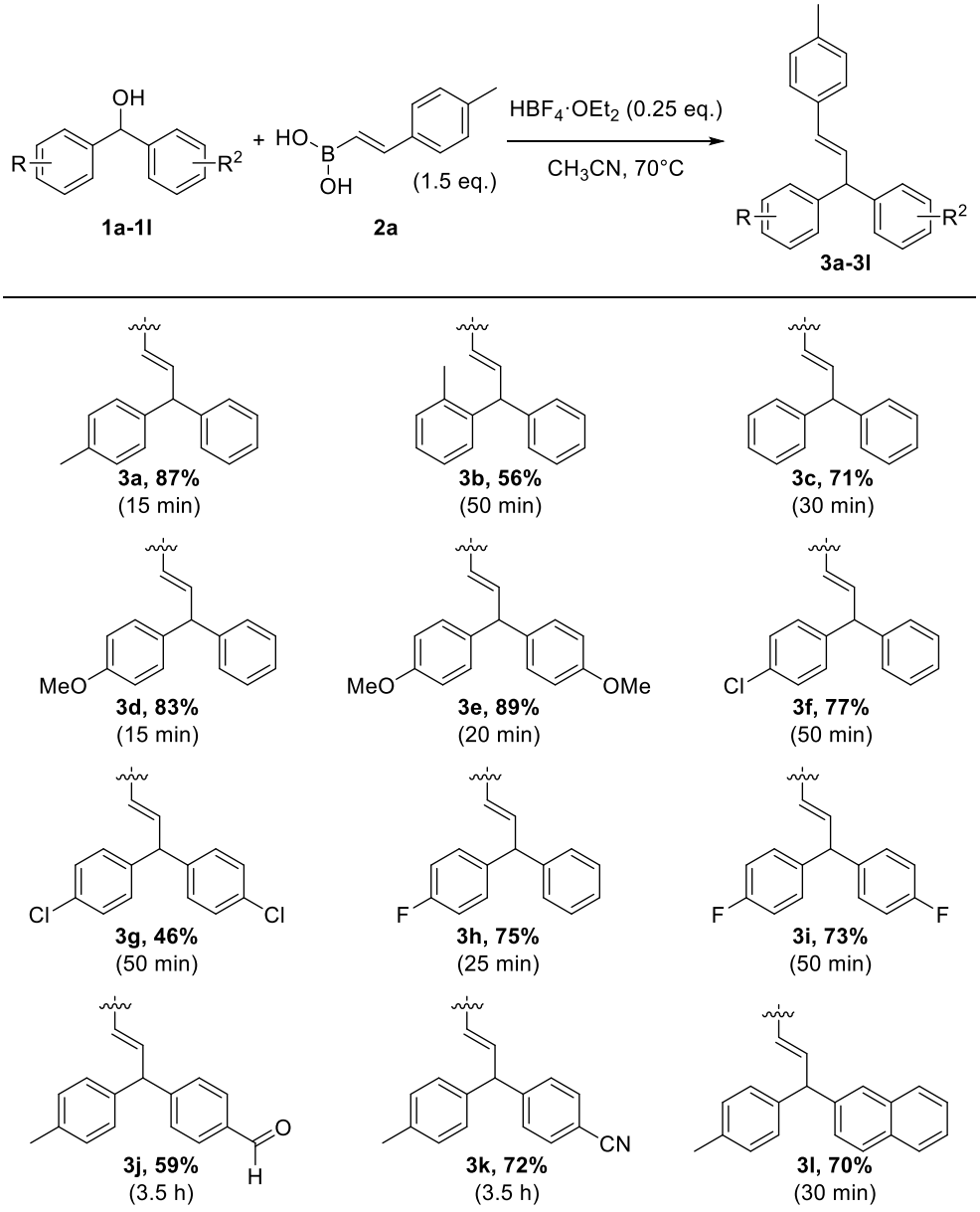


Figure 7: Reactions of *trans*-2-(4-methylpheny)vinylboronic acid with various benzhydryl alcohols

In order to evaluate steric effect on the transformation, 2-methylbenzhydrol **1b** was tested resulting in an isolated yield of 56% of the product **3b**. This decrease in yield suggests that the methodology is sensitive to steric hinderance. The use of diphenylmethanol **1c** as a neutral substrate resulted in 71% of the product **3c**, implying the presence of electron-donating substituents would be better suited for this transformation. Additional electron-donating substituents were then investigated using 4-methoxybenzhydrol **1d** and 4,4'-dimethoxybenzhydrol **1e**, which gave high yields of 83% of **3d** and 89% of **3e**, respectively. Although the use of diphenylmethanol **1c** resulted in a reduced yield in the case of **3c**, the effect of electron-withdrawing substituents was investigated next. To this end, 4-chlorobenzhydrol **1f** and 4,4'-dichlorobenzhydrol **1g** resulted in reduced yields of 77% of **3f** and 46% of **3g**, respectively. In addition, the reaction time had to be increased to 50 minutes. The use of 4-fluorobenzhydrol **1h** and 4,4'-difluorobenzhydrol **1i** resulted in good yields of 75% of **3h** and 73% of **3i**, respectively. The presence of an aldehyde **1j** and nitrile **1k** group at the 4' position of 4-methylbenzhydrol resulted in yields of 59% and 72% over 3.5 hours for **3j** and **3k**, respectively. The use of naphthalen-2-yl(p-tolyl)methanol **1l** was also attempted to give the yield of 70% of **3l**.

As stated previously, electron-donating substituents aid in the stabilization of the benzhydryl cation intermediate formed through an S_N1 reaction. In a similar fashion to 4-methylbenzhydrol **1a**, the presence of electron-donating methoxy substituents stabilizes the carbocation intermediate. On the contrary, electron-withdrawing substituents destabilize the intermediate. The results of this transformation listed above highlight that the presence of electron-donating substituents such as methyl and methoxy groups aid in

the formation of the desired product showing increased yield compared to the neutral substrate. While the presence of electron-withdrawing substituents such as the unprotected aldehyde and nitrile hinder the formation of the desired product showing decreased yields compared to the electron-donating substrates. The use of benzhydryl alcohols with halide substituents gave mixed results. Halides are able to act as electron-withdrawing groups due to their high electronegativity, thus inductively pulling electron density away from the neighbouring aromatic ring. However, they are also able to act as mild electron-donating groups through the mesomeric effect due to the number of lone pairs they possess. The use of 4,4'-dichlorobenzhydrol **1g** highlights the strong inductive effect of chlorine, resulting in an isolated yield lower than the neutral substrate. On the contrary, the use of 4,4'-difluorobenzhydrol **1i** resulted in a similar isolated yield to the neutral substrate. This result leads to the hypothesis that the inductive effect of fluorine on the benzhydryl alcohol is negated by the mesomeric effect. In addition, the reactions with electron-donating substrates proceeded faster than the neutral benzhydryl alcohol, while the substrates with electron-withdrawing substrates proceeded slower. These results are consistent with the proposed S_N1 mechanism because electron-donating groups will better stabilize the carbocation, increasing the rate at which it forms.

Functional group tolerance of the styryl boronic acid was subsequently investigated with 4-methylbenzhydrol (Figure 8). Overall, modification of the boronic acid resulted in reduced yields in all cases. The use of *trans*-2-phenylvinylboronic acid **2b** resulted in a low yield of **3m**, this substrate was then tried with 0.15 eq. of $HBF_4{\cdot}OEt_2$ resulting in an isolated yield of 34%. The use of *trans*-2-(4-biphenyl)vinylboronic acid **2c** yielded 60% of **3n**. Electron-withdrawing substituents in the *para*-position resulted in

yields of 62%, 77% and 18% for products **3o**, **3p**, and **3q**, respectively. Synthesis of **3o** was tried with both 0.15 eq. and 0.35 eq. of $HBF_4 \cdot OEt_2$ resulting in yields of 51% and 67% respectively. Similarly, a 0.15 eq. loading was tried for the synthesis of **3p** resulting in a reduced yield of 65%. Finally, the use of a fluoride substituent in the *meta*-position **2g** resulted in a yield of 38% for product **3r**. This substrate was also tried with an $HBF_4 \cdot OEt_2$ loading of 0.35 eq. resulting in a similar isolated yield of 39%. The reduction of $HBF_4 \cdot OEt_2$ loading for the synthesis of products **3o**, and **3p** showed a greater than 10% reduction in isolated yields further supporting the hypothesis that the reduction of acid loading is detrimental. However, increasing $HBF_4 \cdot OEt_2$ loading to 0.35 eq. for the synthesis of **3o**, and **3r** did not prove beneficial to the methodology showing a maximum yield increase of 5%.

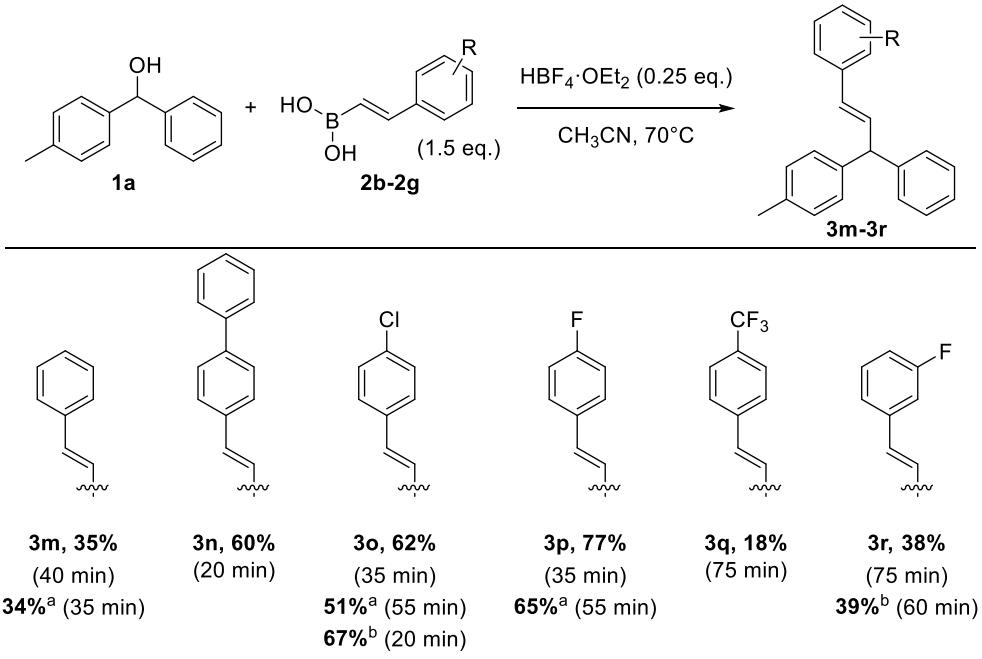


Figure 8: Reactions of 4-methylbenzhydrol with styrylboronic acids. [a] 0.15 eq. of $HBF_4 \cdot OEt_2$, [b] 0.35 eq. of $HBF_4 \cdot OEt_2$

Modification of the boronic acids speak to the importance of the nucleophilicity of the boronic acid coupling partner. As shown through mechanistic considerations, the

addition of the boronic acid to the benzhydryl cation is proposed to occur through the conjugated alkene (Section 2.2). Utilizing *trans*-2-phenylvinylboronic acid **2b**, resulted in a decreased yield when compared to *trans*-2-(4-methylphenyl)vinylboronic acid **2a**. Due to the electron-donating nature of methyl substituents, it is hypothesized that the addition of electron density to the aromatic ring increases the nucleophilicity of the alkene. This is further highlighted when comparing the isolated yields of products **3m** and **3q**. The presence of a strongly electron-withdrawing trifluoromethyl substituent resulted in much lower yields compared to the neutral substrate. Electron-withdrawing substituents are thought to decrease the nucleophilicity of the boronic acid coupling partner by pulling electron density away from the aromatic ring and consequently the alkene. Interestingly, the halide substituents chlorine and fluorine have an effect similar to the electron-donating substituents. As stated previously, halides have greater electronegativity values compared to carbon, thus they inductively pull electron density away from the aromatic ring. However, halides are also able to donate electron density into the aromatic ring via the mesomeric effect. It is hypothesized that the mesomeric effect of halides on the boronic acid is much stronger than the inductive effect due to the increased nucleophilicity in comparison to the neutral substrate. Comparing the results of *trans*-2-(3-fluorophenyl)vinylboronic acid (**3r**, 38%) and *trans*-2-(4-fluorophenyl)vinylboronic acid (**3p**, 77%), it is apparent that the location of the aromatic substituent is an important factor in this transformation. Fluorine substituents are able to donate electron density towards the *ortho*- and *para*-positions on an aromatic ring. The decreased isolated yield of **3r** is expected since the fluorine is in *meta*-position with respect to the vinylic carbon, and is unable to donate electron density to the alkene.

Additional reactions were conducted in order to determine the effects of various functional groups on both the benzhydryl alcohol and the boronic acid (Figure 9).

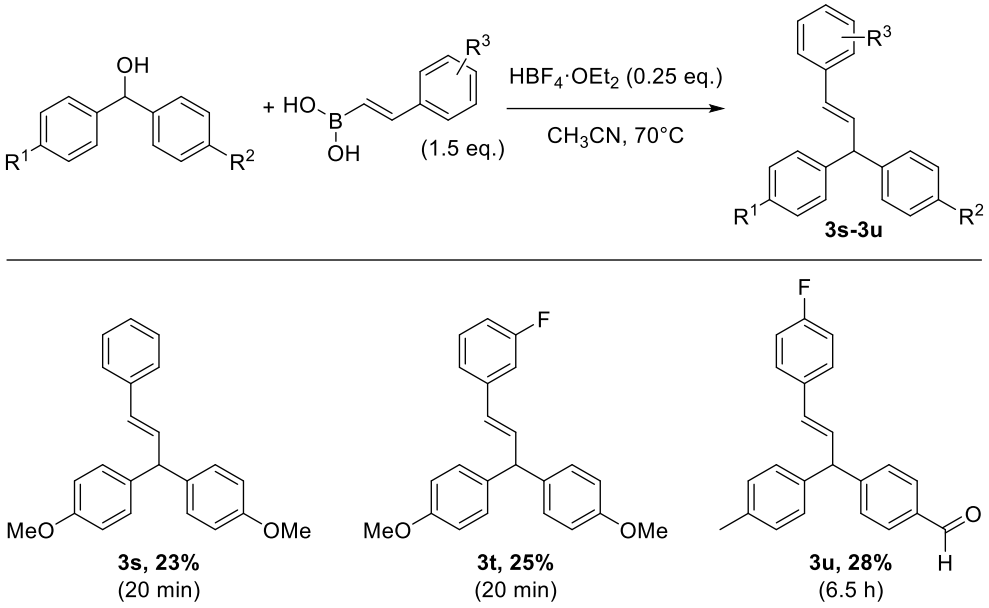


Figure 9: Reactions conducted with various functional groups on the benzhydryl alcohol and styrylboronic acid

4,4'-Dimethoxybenzhydrol **1e** was used in combination with *trans*-2-phenylvinylboronic acid **2b** and *trans*-2-(3-fluorophenyl)vinylboronic acid **2e** resulting in isolated yields of 23% and 25% for products **3s**, and **3t** respectively. Since the use of these boronic acids resulted in low isolated yields with 4-methylbenzhydrol **1a**, they were reacted with 4,4'-dimethoxybenzhydrol **1e**. 4,4'-Dimethoxybenzhydrol **1e** had shown greater isolated yields when reacted with *trans*-2-(4-methylphenyl)vinylboronic acid **2a** compared to 4-methylbenzhydrol **1a**. Although it was anticipated that the isolated yields would increase when modifying the benzhydryl alcohol, the opposite effect was observed.

Previously, the Bolshan group has observed that in the presence of $HBF_4{\cdot}OEt_2$ benzhydryl alcohols may undergo a disproportionation reaction. The disproportionation reaction between two molecules of **1e** can occur in the presence of catalytic amounts of

$HBF_4 \cdot OEt_2$ forming a bis(4-methoxyphenyl)methane **6**, and 4,4'-dimethoxybenzophenone **7** (Figure 10).

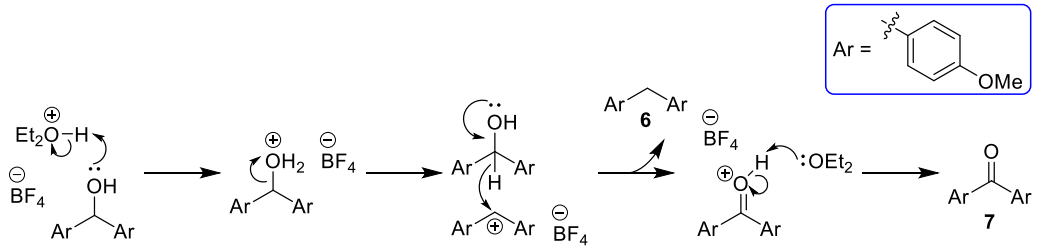
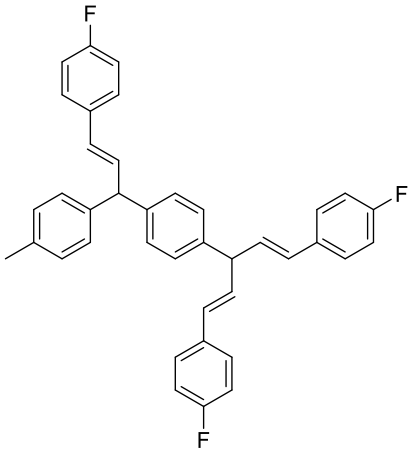


Figure 10: Disproportionation of 4,4'-dimethoxybenzhydrol in the presence of $HBF_4 \cdot OEt_2$

After isolating both **3s** and **3t** it was noted that bis(4-methoxyphenyl)methane **6**, a diarylmethane derivative, was isolated in yields of 16% and 27% respectively. Due to the methoxy substituents on 4,4'-dimethoxybenzhydrol **1e**, the carbocation is highly stabilized decreasing the reactivity of the benzhydrylium ion. The decreased reactivity of the benzhydrylium ion was thought to limit byproduct formation in the desired transformation consequently improving the yield. The presence of bis(4-methoxyphenyl)methane **6** indicates that in the presence of *trans*-2-phenylvinylboronic acid **2b**, and *trans*-2-(3-fluorophenyl)vinylboronic acid **2e** the disproportionation reaction is occurring more rapidly than the desired transformation. The nucleophilicity of both the aforementioned boronic acids is hypothesized to be low in order for this to occur.

4-(Hydroxy(*p*-tolyl)methyl)benzaldehyde **1j** was investigated in combination with *trans*-2-(4-fluorophenyl)vinylboronic acid **2g** and product **3u** was obtained in 28% yield. Unpublished results have suggested that the dialkenylation of an aldehyde occurs between salicylaldehyde and vinylboronic acids in the presence of $HBF_4 \cdot OEt_2$. Upon further investigation into the byproducts formed during the synthesis of **3u**, it was apparent that dialkenylation was occurring at the unprotected aldehyde after the desired transformation occurred (Figure 11).



8

Figure 11: Byproduct of the reaction of *trans*-2-(4-fluorophenyl)vinyl boronic acid and 4-(hydroxy(*p*-tolyl)methyl)benzaldehyde

Although it was formed in small amounts, this byproduct formation explains the low isolated yield, 28% of product **3u,** since 3.0 eq. of boronic acid are required to form the byproduct **8**. In addition, the formation of this product could give rise to new avenues for a Brønsted acid-catalyzed dialkenylation reaction of benzaldehydes.

2.4 Challenging Cases of Benzhydryl Alcohols and Boronic Acids

The reaction did not afford the desired products when other benzhydryl alcohols were tried in the presence of *trans*-2-(4-methylphenyl)vinylboronic acid (Figure 12). While 4-hydroxybenzhydrol **1m** and 4-acetamidobenzhydrol **1n** resulted in the formation of the desired product, all attempts to remove solvents from the isolated product were unsuccessful. This result was unexpected due to results obtained in previously reported methodologies,[26] in addition the high polarity of these desired products would suggest that low polarity solvents should be easily removed. The isolated products were left to concentrate *in vacuo* for four days; however, the solvent was still present. Reactions of xanthydrol **1o** and 4-dimethylaminobenzhydrol **1p** resulted in complex mixtures of products containing byproducts of similar polarity that could not be removed from the desired product.

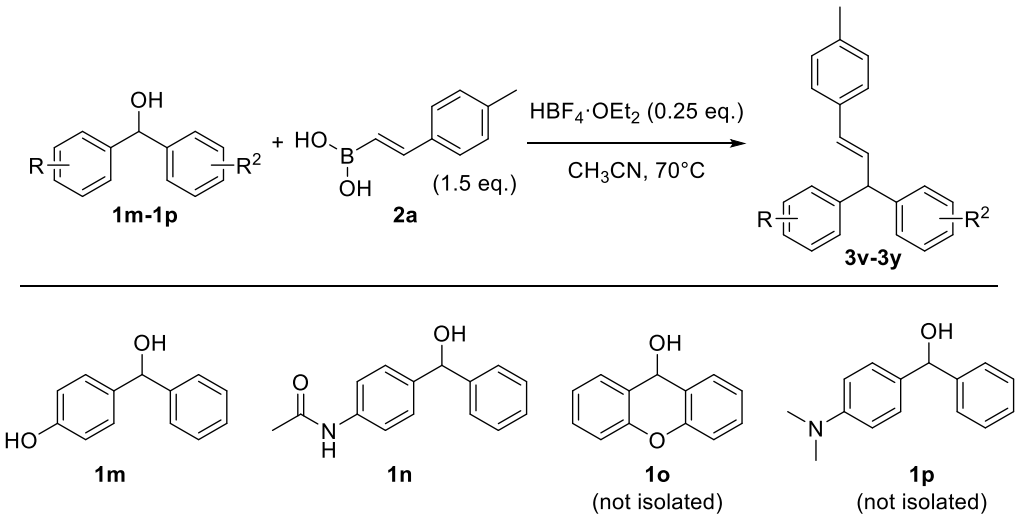


Figure 12: Unsuccessful reactions of *trans*-2-(4-methylpheny)vinylboronic acid with benzhydryl alcohols

Additional reactions with vinylboronic acids were conducted in the presence of 4-methylbenzhydrol **1a**, which resulted in complex mixtures of products from which the desired product was not isolated (Figure 13). *Trans*-2-(4-methoxyphenyl)vinylboronic

acid **2h** was used in order to evaluate the effect of strongly electron-donating substituents on the synthesis. It is hypothesized that the strongly electron-donating nature of the methoxy substituent increases the reactivity of the boronic acid, promoting a variety of side reactions which compete with the desired transformation. As previously noted, boronic acids which have electron-donating substituents on the aromatic ring showed increased nucleophilicity compared to unsubstituted aromatics and electron-withdrawing substituents. *Trans*-2-(4-methoxyphenyl)vinylboronic acid **2h** was subjected to the reaction conditions excluding 4-methylbenzhydrol **1a** in order to determine if decomposition of the boronic acid was occurring. Visualization by TLC showed the boronic acid had formed decomposition products after 5 minutes. It is unclear if these decomposition products are able to act as nucleophiles which result in the complex mixture of products observed.

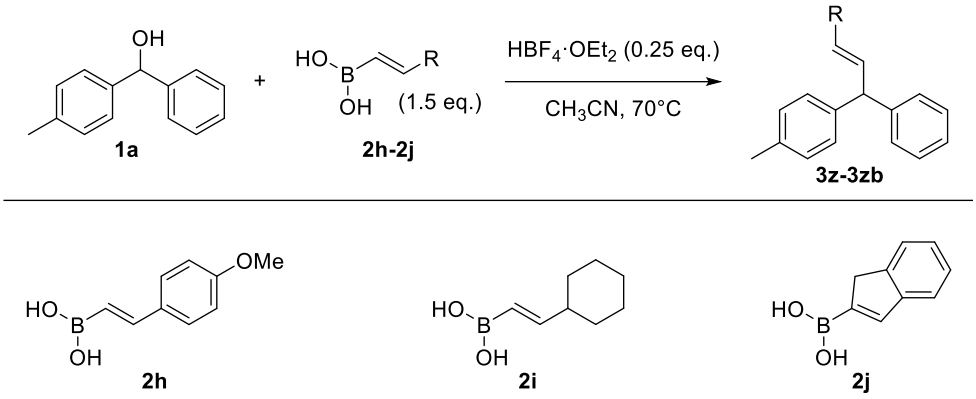


Figure 13: Unsuccessful reactions of 4-methylbenzhydrol with vinylboronic acids

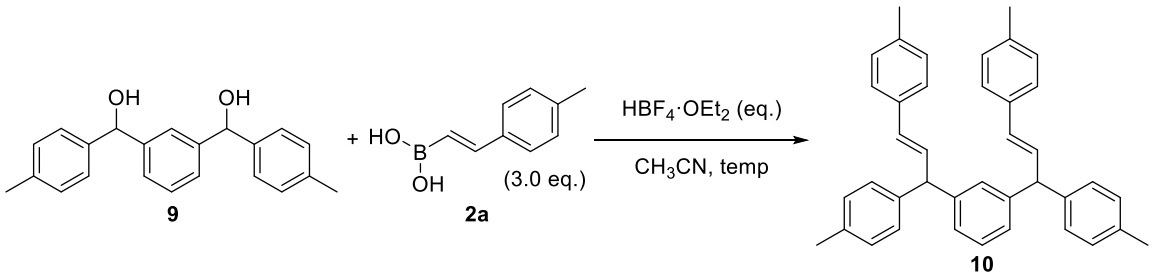
When *trans*-2-cyclohexylvinylboronic acid **2i** was tried, no evidence of the desired product **3za** formation through work-up NMR was detected. This result suggests that nucleophilic addition of an alkene to the benzhydryl cation is only applicable when the alkene is conjugated to an aromatic ring. Finally, 1H-indene-2-boronic acid **2j** was

submitted to the reaction conditions resulting in the formation of an inseparable mixture of the desired product **3zb** and a byproduct.

2.5 Expansion of the Methodology to Bisbenzhydryl Alcohols

Initial investigation for the expansion of the methodology to include bisbenzhydryl alcohols has been tried. 1,3-phenylenebis(*p*-tolylmethanol) **9** was chosen as a starting material due to its similarities with 4-methylbenzhydrol **1a** with regards to electronics (Table 3). Initial investigation began with the optimized conditions for the alkenylation of benzhydryl alcohols; however, the loading of both $HBF_4{\cdot}OEt_2$ and *trans*-2-(4-methylphenyl)vinylboronic acid **2a** were doubled in order to facilitate the addition of both alkenes (entry 1).

Table 3: Optimization of the dialkenylation reaction of trans-2-(4-methylphenyl)vinylboronic acid and 1,3-phenylenebis(*p*-tolylmethanol)



Entry	Concentration (M)	$HBF_4{\cdot}OEt_2$ (eq.)	Temp. (°C)	Time (min)	Yield **10**
1	0.2	0.50	70	30	40%
2	0.1	0.50	70	15	54%
3	0.1	0.50	60	15	47%
4	0.1	0.50	80	15	52%
5	0.1	0.40	70	35	50%

Utilizing these conditions, the desired product **10** was isolated with a 40% yield. The amount of acetonitrile added to the reaction was varied in order to see the effect of concentration on the desired transformation. Upon decreasing the concentration to 0.1M (entry 2), the desired product was isolated in 54% yield. Variation of temperature

was then tried (entries 3-4), neither increasing nor decreasing the temperature proved to better facilitate the formation of the desired product. With the optimal temperature determined to be 70°C, the loading of $HBF_4 \cdot OEt_2$ was varied. Decreasing the acid loading to 0.4 eq. (entry 5) resulted in an isolated yield of 50% of **10**.

Broadening the scope of the methodology to these types of substrates provides access to a class of molecules, which are scarcely studied. Although these molecules are similar to the benzhydryl alcohols studied in the reported methodology, the steric effects during the first and second addition of the alkenes is different. The addition of the two alkenes is hypothesized to occur via a stepwise S_N1 process, where substitution of one of the alcohols occurs prior to substitution of the second alcohol (Figure 14).

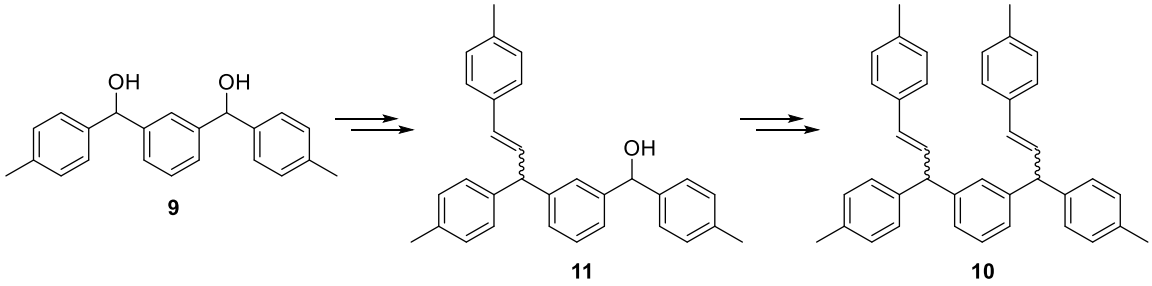


Figure 14: Proposed stepwise substitution of trans-2-(4-methylphenyl)vinylboronic acid to 1,3-phenylenebis(*p*-tolylmethanol)

Based on the proposed process, the addition of the first alkene will occur in a similar fashion to the reported methodology. However, due to the large size of the alkenyl moiety it is hypothesized that the second substitution reaction will be impacted by steric hinderance. Results obtained during the investigation of steric effect on the transformation (Section 2.3) suggested steric hinderance reduces the effectiveness of nucleophilic addition to the benzhydrylium ion. As such, steric hinderance from the alkenyl moiety is hypothesized to reduce the yield of the second substitution reaction and consequently the yield of **10**. Although the optimal isolated yield of product **10** was 54%

during this initial investigation, it was considered to be fairly reasonable due to the stepwise addition of alkenes. Assuming the additions occur with the same effectiveness, in order to obtain an isolated yield of the desired product in 54% each addition would have occurred in 73% yield similar to the other substrates reported throughout.

Chapter 3: Conclusions and Future Work

3.1 Future Work

Although a variety of methods have been developed for the Brønsted acid-catalyzed transformation of benzhydryl alcohols, there still exists an issue with regards to enantioselectivity. In order for these methods to be industrially relevant, the compounds formed should ideally be optically pure,[43] thus, there is a need to further develop the aforementioned methodology in an enantioselective fashion.

Transition metals offer a variety of oxidation states, and coordination modes, which can be utilized to induce stereo-, chemo-, and regioselectivity in desired transformations.[44] A variety of transition metals have been used to catalyze the reaction of η^3-benzylic complexes with nucleophiles, the most common being palladium.[45] Utilization of η^3-benzylpalladium complexes with a benzhydryl alcohol type system has been investigated, with the focus primarily on the addition of heteroatoms. Hirano and Miura have published works with evidence that suggest an η^3-benzylic intermediate has facilitated the addition of methylene compounds **2** to an activated benzhydrol derivatives **1** in an enantioselective fashion (Figure 15).[46]

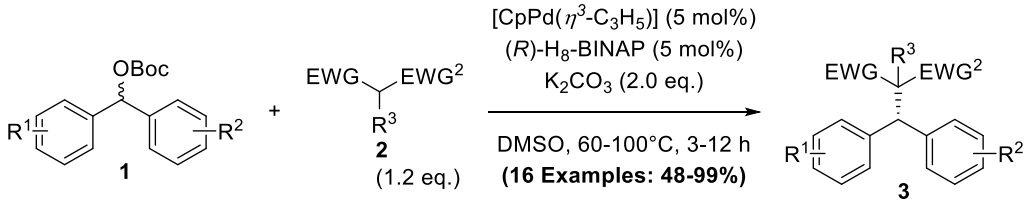


Figure 15: Reaction of activated benzhydrol derivatives with methylene compounds published by Hirano and Miura.

Additional methods utilizing phosphonates,[47] nitrogen and oxygen nucleophiles,[48] and sulfones[49] were also achieved. Although the methods proved to be quite successful,

the formation of C-C bonds was limited to the use of methylene compounds. In addition, the use of an unprotected alcohol was not supported under the developed conditions.[49]

Based on the methods of Hirano and Miura, we believe that it is possible to modify the proposed method to utilize an η^3-benzylic intermediate. By adding an acid such as trifluoroacetic acid in catalytic amounts to eliminate water, a Pd^0 catalyst such as $CpPd(\eta^3\text{-}C_3H_5)$, and a chiral ligand we believe that it is possible to develop an enantioselective alkenylation of 2-naphthyl(phenyl)methanol with styrylboronic acids.

3.2 Conclusion

A method for the Brønsted acid-catalyzed alkenylation of benzhydryl alcohols with styrylboronic acids has been established and is described. The developed method improves upon the works of Fisher and Bolshan (Section 1.4.2) as the alkenylation of benzhydryl alcohols occurs in substoichiometric amounts of $HBF_4 \cdot OEt_2$. In addition, the developed method occurs in the presence of styrylboronic acid, eliminating the need to form potassium trifluoroborate salt coupling partners. Finally, the developed method tolerates benzhydryl alcohols with electron-withdrawing substituents in addition to electron-donating substituents. The developed method allows for greater derivatization of the benzhydryl moiety, which may allow for further investigation into this biologically relevant motif.

Chapter 4: Experimental Methods

4.1 General Synthetic Information

Solvents and reagents were purchased from Sigma Aldrich and used without further purification. Deuterated solvent ($CDCl_3$) was purchased from Cambridge Isotope Laboratories, Inc. and was used for ^{1}H-NMR and $^{13}C\{^{1}H\}$-NMR characterization. NMR spectra were recorded at 25˚C on a Bruker Ascend™ 400 NMR. ^{1}H and $^{13}C\{^{1}H\}$-NMR spectra were recorded at 400 MHz and 100 MHz respectively. All chemical shifts were recorded in ppm values, referenced externally to TMS. High Resolution Mass Spectrometry (HRMS) data was recorded using a JMS T100-LC AccuTOF with a direct analysis real time (DART) ion source. FT- IR spectra were recorded on a Bruker ALPHA-P spectrometer using a Platinum ATR with a diamond ATR crystal. Automated flash column chromatography was performed using Biotage purification system. Low acidity 60 Å silica from Silicycle and ACS grade solvents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel (60 Å) with visualization using ultraviolet light (254 nm) and by staining with potassium permanganate or phosphomolybdic acid.

4.2 Synthesis of Benzhydryl Alcohols

Procedure A:

All reactions were conducted in a 50 ml round bottom flask equipped with a magnetic stir bar, which were oven dried overnight. To the flask at room temperature benzaldehyde (1.0 eq.) was added. The flask was purged with argon, and anhydrous THF (0.3 M) was added. The flask was immersed in an ice bath and stirred during the dropwise addition of Grignard reagent (3.0 eq.). The reaction was stirred for 10 minutes subsequently, it was removed from the ice bath and was stirred at room temperature until benzaldehyde could no longer be visualized by TLC. The reaction was quenched with 1M HCl, diluted with 20 ml of water and extracted with 20 ml of EtOAc. The organic layer was washed with water (3 x 20 ml), and brine (1 x 15 ml) then dried over $MgSO_4$ and concentrated *in vacuo*. Unless otherwise stated the crude reaction mixture was purified by column chromatography using silica gel and hexanes/ethyl acetate mobile phase. The fractions containing the desired product were concentrated *in vacuo* and the product was then dried under vacuum for 16 h.

Procedure B:

All reactions were conducted in a 50 ml round bottom flask equipped with a magnetic stir bar, which were oven dried overnight. To the flask at room temperature benzaldehyde (1.0 eq.) was added. The flask was purged with argon, and anhydrous THF (0.3 M) was added. The flask was immersed in an ice bath and stirred during the dropwise addition of Grignard reagent (3.0 eq.). The reaction was stirred for 10 minutes subsequently, it was removed from the ice bath and was stirred at room temperature until benzaldehyde could no longer be visualized by TLC. The reaction was acidified with 7.5

ml 1M HCl, and stirred at room temperature for 1 hour. The reaction was quenched with saturated $NaHCO_3$, diluted with 30 ml water and extracted with 30 ml EtOAc. The organic layer was washed with water (3 x 30 ml), and brine (1 x 20 ml) then dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography using silica gel and hexanes/ethyl acetate mobile phase. The fractions containing the desired product were concentrated *in vacuo* the product was then dried under vacuum for 16 h.

4.3 Synthesis of 1,3,3-Triphenylpropene Derivatives

All reactions were conducted in a 5 ml round bottom flask equipped with a magnetic stir bar. To the flask at room temperature benzhydryl alcohol (1.0 eq.), boronic acid (1.5 eq.), and anhydrous acetonitrile (0.2 M) were added. The flask was covered with a septum fitted with an exit needle, immersed in an oil bath at 70˚C and stirred for 1 minute. $HBF_4 \cdot Et_2O$ (0.25 eq.) was added, and the reaction was stirred at 70˚C until the benzhydryl alcohol could no longer be visualized by TLC. The reaction was quenched with saturated $NaHCO_3$ (3 ml), diluted with ethyl acetate (20 ml), and water (20 ml). The organic layer was washed with water (3x20 ml), and brine (1x15 ml) then dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography using silica gel and hexanes/ethyl acetate mobile phase. The product was dissolved in acetonitrile (3 ml), followed by the addition of hexanes (1.5 ml) in a 20 ml scintillation vial. The mixture was agitated for 30 seconds, and allowed to settle for 4 minutes. The acetonitrile layer was concentrated *in vacuo*, and the vial containing the product was then placed under vacuum overnight.

References:

(1) Taylor, S. J.; Netherton, M. R. *J. Org. Chem.* **2006**, *71*, 397-400.

(2) Freeman, H. *Br. J. Psych.* **1979**, *135*, 82-83.

(3) Rimoldi, E.; Lumina, C.; Giunta, L.; Moscatelli, P.; Gatto, E. *Cur. Ther. Res.* **1993**, *54*, 248-253.

(4) Wang, S.-J.; Lu, K.-T.; Gean, P.-W. *Br. J. Pharmacol.* **1997**, *120*, 1114-1118.

(5) Kadota, S.; Prasain, J. K.; Li, J. X.; Basnet, P.; Dong, H.; Tani, T.; Namba, T. *Tetrahedron Lett.* **1996**, *37*, 7283-7286.

(6) Panda, N. R.; Bhoi, S. R.; Rawal, R. M.; Raval, M. K. *Pharm. Biol. Eval.* **2017**, *4*, 148-154.

(7) Hall, D. G. In *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Wiley: 2005, p 1-99.

(8) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 3834-3840.

(9) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371.

(10) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, *2003*, 4313-4327.

(11) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 9385-9388.

(12) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083-1090.

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

(14) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866-867.

(15) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513-519.

(16) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933-2936.

(17) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937-2940.

(18) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944.

(19) Motornov, V.; Latyshev, G. V.; Kotovshchikov, Y. N.; Lukashev, N. V.; Beletskaya, I. P. *Adv. Synth. Catal.* **2019**, *361*, 3306-3311.

(20) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583-586.

(21) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463-16470.

(22) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445-446.

(23) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798-11799.

(24) Li, C.; Zhang, Y.; Sun, Q.; Gu, T.; Peng, H.; Tang, W. *J. Am. Chem. Soc.* **2016**, *138*, 10774-10777.

(25) Ueda, M.; Nishimura, K.; Kashima, R.; Ryu, I. *Synlett* **2012**, *23*, 1085-1089.

(26) Fisher, K. M.; Bolshan, Y. *J. Org. Chem.* **2015**, *80*, 12676-12685.

(27) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, *2011*, 647-666.

(28) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.-Z. *Org. Lett.* **2005**, *7*, 2865-2867.

(29) Orizu, I.; Bolshan, Y. *Tetrahedron Lett.* **2016**, *57*, 5798-5800.

(30) Regier, J.; Maillet, R.; Bolshan, Y. *Eur. J. Org. Chem.* **2019**, *2019*, 2390-2396.

(31) Chan, C.-K.; Tsai, Y.-L.; Chang, M.-Y. *Tetrahedron* **2017**, *73*, 3368-3376.

(32) Nallagonda, R.; Rehan, M.; Ghorai, P. *Org. Lett.* **2014**, *16*, 4786-4789.

(33) Rehan, M.; Hazra, G.; Ghorai, P. *Org. Lett.* **2015**, *17*, 1668-1671.

(34) Rehan, M.; Nallagonda, R.; Das, B. G.; Meena, T.; Ghorai, P. *J. Org. Chem.* **2017**, *82*, 3411-3424.

(35) Wang, S.-E.; He, Q.; Fan, R. *Org. Lett.* **2017**, *19*, 6478-6481.

(36) Nishimoto, Y.; Kajioka, M.; Saito, T.; Yasuda, M.; Baba, A. *Chem. Comm.* **2008**, 6396-6398.

(37) Leboeuf, D.; Presset, M.; Michelet, B.; Bour, C.; Bezzenine-Lafollee, S.; Gandon, V. *Chem. Eur. J.* **2015**, *21*, 11001-11005.

(38) Yue, H.-L.; Wei, W.; Li, M.-M.; Yang, Y.-R.; Ji, J.-X. *Adv. Synth. Catal.* **2011**, *353*, 3139-3145.

(39) Lide, D. R. In *CRC Handbook of Chemistry and Physics, 84th Edition*; Taylor & Francis: 2003, p 15-14 - 15-18.

(40) Peng, C.; Zhang, W.; Yan, G.; Wang, J. *Org. Lett.* **2009**, *11*, 1667-1670.

(41) Lide, D. R. In *CRC Handbook of Chemistry and Physics, 84th Edition*; Taylor & Francis: 2003, p 6-155 - 6-177.

(42) Costa, P.; Fernandez-Oliva, M.; Sanchez-Garcia, E.; Sander, W. *J. Am. Chem. Soc.* **2014**, *136*, 15625-15630.

(43) Bolshan, Y.; Chen, C.-y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111-114.

(44) Trost, B. M.; Czabaniuk, L. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 2826-2851.

(45) Le Bras, J.; Muzart, J. *Eur. J. Org. Chem.* **2016**, *2016*, 2565-2593.

(46) Tabuchi, S.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6973-6977.

(47) Matsude, A.; Hirano, K.; Miura, M. *Org. Lett.* **2018**, *20*, 3553-3556.

(48) Najib, A.; Hirano, K.; Miura, M. *Org. Lett.* **2017**, *19*, 2438-2441.

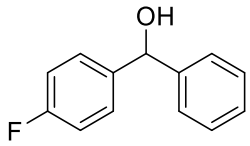
(49) Najib, A.; Hirano, K.; Miura, M. *Chem. Eur. J.* **2018**, *24*, 6525-6529.

Appendices

Appendix A: Compound Characterization

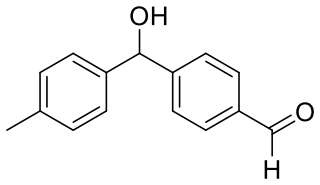
A1: Characterization of Benzhydryl Alcohols

4-fluorobenzhydrol (1h)



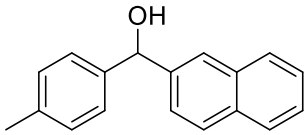
The title compound was synthesized from 4-fluorobenzaldehyde (0.2 ml, 1.86 mmol, 1.0 eq.), phenylmagnesium bromide (5.6 ml, 5.60 mmol, 3.0 eq., 1M in THF) in THF (6.2 ml, 0.3M) at room temperature for 1 hour following procedure 4.2A. Purification by silica gel chromatography using hexanes/EtOAc (18:7) afforded product **1h** (377.0 mg, quantitative yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.36 (m, 7H), 6.99-7.04 (m, 2H), 5.83 (s, 1H), 2.20 (s, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 163.38, 160.93, 143.64, 139.56, 139.53, 128.58, 128.26, 128.18, 127.73, 126.46, 115.39, 115.18, 75.59.

4-(hydroxy(*p*-tolyl)methyl)benzaldehyde (1j)



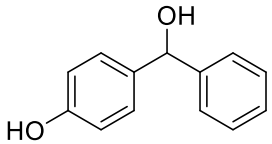
The title compound was synthesized from 4-(diethoxymethyl)benzaldehyde (0.5 ml, 2.51 mmol, 1.0 eq.), *p*-tolylmagnesium bromide (7.5 ml, 7.50 mmol, 3.0 eq., 1M in THF) in THF (8.4 ml, 0.3M) at room temperature for 1 hour following procedure 4.2B. Purification by silica gel chromatography using hexanes/EtOAc (3:2) afforded product **1j** (406.7 mg, 71% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.81-7.84 (m, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 5.85 (s, 1H), 2.44 (s, 1H), 2.33 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 192.00, 150.61, 140.23, 137.95, 135.49, 129.93, 129.47, 126.82, 126.66, 75.74, 21.12; FT-IR ν 3381.63, 2843.44, 1679.38, 1604.89, 1213.37, 1053.05, 877.93, 767.05, 538.23 cm^{-1}. HRMS ($M+H^{+}$) calc'd 227.10666; found 227.10672.

naphthalen-2-yl(*p*-tolyl)methanol (1l)



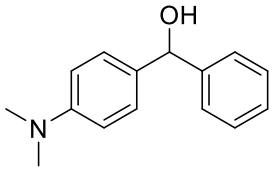
The title compound was synthesized from 2-naphthaldehyde (100 mg, 0.64 mmol, 1.0 eq.), *p*-tolylmagnesium bromide (2.1 ml, 2.1 mmol, 3.3 eq., 1M in THF) in THF (2.5 ml, 0.3M) at room temperature in a 25 ml round bottom flask for 3.5 hours following procedure 4.2A. Purification by two-solvent recrystallization using EtOAc/hexanes afforded product **1l** (60.4 mg, 38% yield) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76-7.88 (m, 4H), 7.39-7.49 (m, 3H), 7.29 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 5.95 (d, J = 2.6 Hz, 1H), 2.32 (s, 1H), 2.29 (d, J = 3.3 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 141.26, 140.78, 137.40, 133.25, 132.83, 129.23, 129.12, 128.25, 128.05, 127.64, 126.69, 126.42, 126.12, 125.88, 124.85, 124.76, 76.19, 21.11.

4-hydroxybenzhydrol (1m)



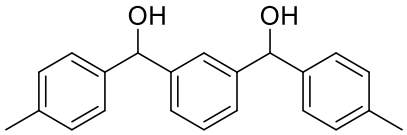
The title compound was synthesized from 4-hydroxybenzaldehyde (301.3 mg, 2.47 mmol, 1.0 eq.), phenylmagnesium bromide (7.4 ml, 7.40 mmol, 3.0 eq., 1M in THF) in THF (6.2 ml, 0.3M) at room temperature for 1.5 hours following procedure 4.2A. Purification by two-solvent recrystallization using EtOAc/hexanes afforded product **1m** (435.3 mg, 88%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.26-7.35 (m, 4H), 7.12-7.20 (m, 3H), 6.66-6.70 (m, 2H), 5.67 (d, J = 3.9 Hz, 1H), 5.59 (d, J = 3.4 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6) δ 156.13, 146.18, 136.16, 127.94, 127.48, 126.44, 126.10, 114.74, 73.97.

4-dimethylaminobenzhydrol (1p)



The title compound was synthesized from 4-(dimethylamino)benzaldehyde (213.5 mg, 1.43 mmol, 1.0 eq.), phenylmagnesium bromide (4.3 ml, 4.30 mmol, 3.0 eq., 1M in THF) in THF (4.8 ml, 0.3M) at room temperature for 2 hours following procedure 4.2A. Purification by silica gel chromatography using hexanes/EtOAc (11:14) afforded product **1p** (315.1 mg, 98%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.39 (m, 4H), 7.19-7.24 (m, 3H), 6.69 (d, J = 8.5 Hz, 2H), 5.77 (s, 1H), 2.92 (s, 6H), 2.13 (d, J = 3.1 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 150.16, 144.26, 131.98, 129.60, 128.29, 127.74, 127.13, 126.34, 115.28, 112.48, 75.96, 40.59.

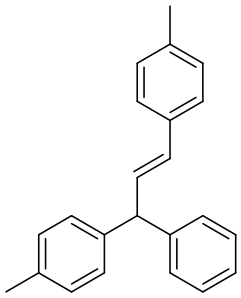
1,3-phenylenebis(*p*-tolylmethanol) (9)



The title compound was synthesized from isophthaldehyde (100 mg, 0.75 mmol, 1.0 eq.), *p*-tolylmagnesium bromide (3.8 ml, 7.50 mmol, 5.1 eq., 1M in THF) in THF (2.8 ml, 0.3M) at room temperature for 3.5 hours following procedure 4.2A. Purification by two-solvent recrystallization using EtOAc/hexanes afforded product **9** (143.2 mg, 60% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.07-7.23 (m, 11H), 5.76 (d, J = 4.0 Hz, 2H), 5.61 (d, J = 3.9 Hz, 2H), 2.25 (s, 6H); ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6) δ 145.61, 142.75, 135.62, 128.53, 127.63, 126.20, 124.55, 124.02, 74.17, 20.64; FT-IR ν 3281.62, 2916.51, 1602.82, 1510.87, 1440.25, 1215.14, 1016.43, 752.64, 570.77 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 336.19581; found 336.19668.

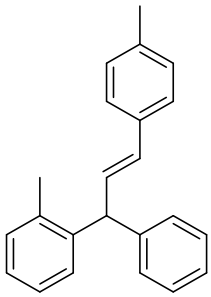
A2: Characterization of 1,3,3-Triphenylpropene Derivatives

(*E*)-4,4'-(3-phenylprop-1-ene-1,3-diyl)bis(methylbenzene) (3a)



The title compound was synthesized from 4-methylbenzhydrol (45.9 mg, 0.23 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (56.3 mg, 0.35 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (7.9 µl, 0.060 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 15 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3a** (60.2 mg, 87% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16-7.31 (m, 7H), 7.06-7.14 (m, 6H), 6.59 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 4.83 (d, *J* = 7.5 Hz, 1H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 143.87, 140.67, 136.98, 135.88, 134.54, 131.76, 131.06, 129.17, 129.14, 128.61, 128.52, 128.41, 126.29, 126.18, 53.79, 21.14, 21.00; FT-IR ν 2919.86, 1604.28, 1510.41, 1492.03, 969.58, 809.18, 697.98 cm^{-1}. HRMS (M-H$^+$) calc'd 297.16378; found 297.16379.

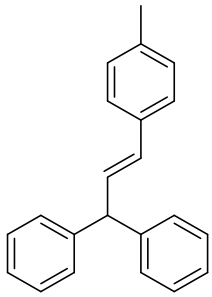
(*E*)-1-methyl-2-(1-phenyl-3-(*p*-tolyl)allyl)benzene (3b)



The title compound was synthesized from 2-methylbenzhydrol (28.9 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.4 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 50 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (99:1) afforded product **3b** (24.5 mg, 56% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15-7.30 (m, 11H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.60 (dd, *J* = 15.8, 6.9 Hz, 1H), 6.18 (d, *J* = 15.9 Hz, 1H), 5.05 (d, *J* = 6.9 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 142.96, 141.72, 137.06, 136.43, 134.60, 131.56, 131.19, 130.56, 129.23, 128.95, 128.61, 128.39, 126.49, 126.31, 126.21, 126.04,

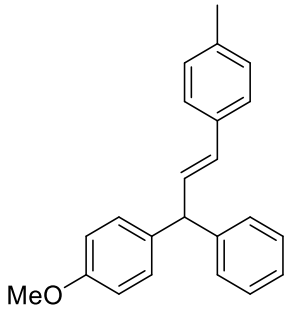
50.42, 21.19, 19.81; FT-IR ν 2919.88, 1510.11, 1487.70, 1449.86, 971.89, 744.39, 697.39, 504.72 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 316.20598; found 316.20589.

(*E*)-(3-(*p*-tolyl)prop-2-ene-1,1-diyl)dibenzene (3c)



The title compound was synthesized from diphenylmethanol (27.1 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.7 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 30 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3c** (29.6 mg, 71% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19-7.32 (m, 13H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.61 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.31 (d, *J* = 15.9 Hz, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ 143.72, 137.12, 134.54, 131.61, 131.31, 129.24, 128.71, 128.49, 126.43, 126.25, 54.23, 21.21.

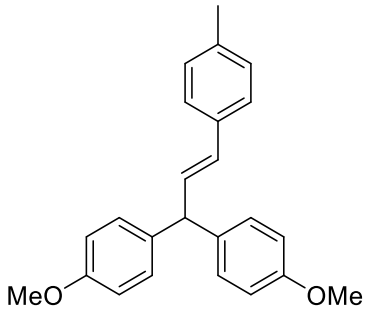
(*E*)-1-methoxy-4-(1-phenyl-3-(*p*-tolyl)allyl)benzene (3d)



The title compound was synthesized from 4-methoxybenzhydrol (31.5 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.7 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 15 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (47:3) afforded product **3d** (38.2 mg, 83% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18-7.31 (m, 7H), 7.11 (dd, *J* = 20.4, 8.2 Hz, 4H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.58 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 4.82 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ 158.17, 144.02, 137.06, 135.84, 134.59, 131.94, 131.06, 129.66, 129.24, 128.65, 128.47, 126.36, 126.23, 113.88, 55.29, 53.39, 21.21; FT-IR ν 2926.23, 1608.37, 1507.69, 1450.77, 1244.53,

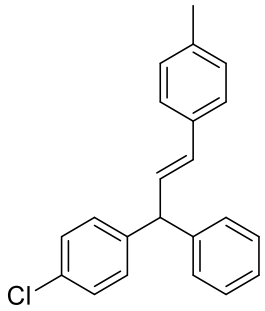
1175.19, 1032.29, 968.41, 831.37, 773.28, 697.99, 503.90 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 332.20089; found 332.20140.

(*E*)-4,4'-(3-(*p*-tolyl)prop-2-ene-1,1-diyl)bis(methoxybenzene) (3e)



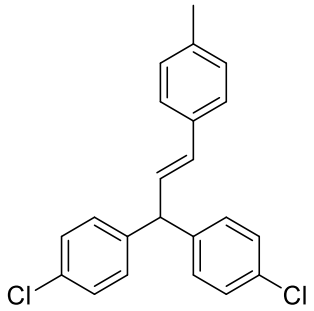
The title compound was synthesized from 4,4'-dimethoxybenzhydrol (35.8 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (34.7 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 20 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (9:1) afforded product **3e** (44.8 mg, 89% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.1 Hz, 2H), 7.07-7.14 (m, 6H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.56 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 4.78 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 6H), 2.31 (s, 3H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ 158.12, 137.00, 136.13, 134.64, 132.26, 130.80, 129.77, 129.58, 129.23, 126.22, 113.85, 55.29, 52.54, 21.20; FT-IR ν 2932.35, 1608.27, 1505.30, 1460.31, 1244.83, 1109.27, 1028.15, 973.80, 826.64, 757.07, 508.00 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 362.21146; found 362.21204.

(*E*)-1-chloro-4-(1-phenyl-3-(*p*-tolyl)allyl)benzene (3f)



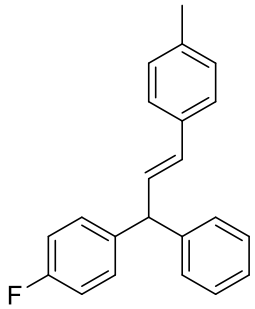
The title compound was synthesized from 4-chlorobenzhydrol (31.6 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.2 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 50 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (24:1) afforded product **3f** (35.7 mg, 77% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09-7.32 (m, 14H), 6.55 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 4.84 (d, *J* = 7.4 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ 143.20, 142.22, 137.32, 134.30, 132.24, 131.68, 131.00, 130.07, 129.39, 129.29, 129.22, 128.62, 126.65, 126.26, 126.10, 53.55, 21.21.

(*E*)-4,4'-(3-(*p*-tolyl)prop-2-ene-1,1-diyl)bis(chlorobenzene) (3g)



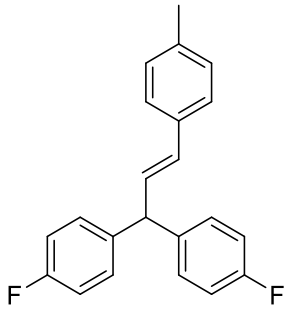
The title compound was synthesized from 4,4'-dichlorobenzhydrol (37.2 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.6 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 50 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3g** (23.7 mg, 46% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24-7.29 (m, 6H), 7.10-7.14 (m, 6H), 6.50 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.27 (d, *J* = 15.8 Hz, 1H), 4.81 (d, *J* = 7.3 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 141.67, 137.51, 134.04, 132.48, 132.03, 130.37, 129.96, 129.32, 128.72, 126.26, 52.86, 21.20; FT-IR ν 2919.89, 1487.83, 1403.55, 1088.76, 1013.23, 967.91, 819.01, 797.01, 527.25 cm^{-1}. HRMS (M^+) calc'd 352.07801; found 352.07610.

(*E*)-1-fluoro-4-(1-phenyl-3-(*p*-tolyl)allyl)benzene (3h)



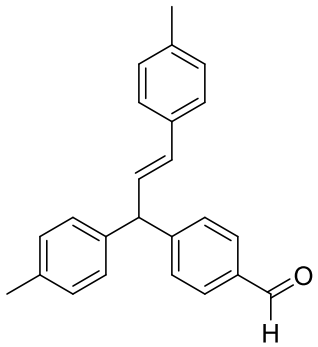
The title compound was synthesized from 4-fluorobenzhydrol (29.3 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.1 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 25 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (49:1) afforded product **3h** (33.0 mg, 75% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16-7.33 (m, 9H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.98 (t, *J* = 8.4 Hz, 2H), 6.57 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 7.4 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 162.61, 160.18, 143.36, 139.26, 139.23, 137.11, 134.22, 131.32, 131.23, 130.02, 129.94, 129.13, 128.48, 128.43, 126.43, 126.10, 115.21, 115.00, 53.27, 21.06; FT-IR ν 2921.09, 1601.37, 1504.80, 1450.68, 1220.93, 1156.97, 968.29, 836.92, 778.92, 697.63, 498.39 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 320.18090; found 320.18144.

(*E*)-4,4'-(3-(*p*-tolyl)prop-2-ene-1,1-diyl)bis(fluorobenzene) (3i)



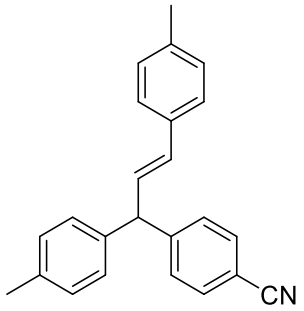
The title compound was synthesized from 4,4'-difluorobenzhydrol (32.7 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.7 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 50 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3i** (34.3 mg, 73% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.8 Hz, 2H), 7.09-7.17 (m, 6H), 6.99 (t, *J* = 8.5 Hz, 4H), 6.52 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 4.83 (d, *J* = 7.3 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 162.81, 160.38, 139.19, 139.16, 137.40, 134.19, 131.62, 131.12, 130.09, 130.01, 129.31, 126.25, 115.45, 115.24, 52.60, 21.20;

(*E*)-4-(1,3-di-*p*-tolylallyl)benzaldehyde (3j)



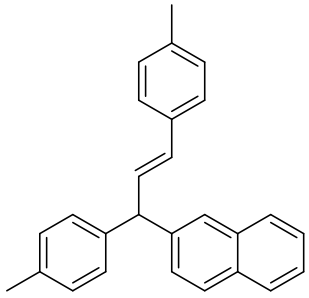
The title compound was synthesized from 4-(hydroxy(*p*-tolyl)methyl)benzaldehyde (32.9 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.4 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 3.5 h following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (43:7) afforded product **3j** (27.8 mg, 59% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 3H), 7.06-7.15 (m, 7H), 6.57 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.32 (d, *J* = 15.8 Hz, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 2.32 (m, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 191.84, 151.05, 139.50, 137.28, 136.32, 134.69, 134.05, 131.81, 130.35, 129.87, 129.27, 129.19, 129.15, 129.08, 128.35, 126.13, 53.83, 21.06, 20.92; FT-IR ν 2919.82, 1698.08, 1602.46, 1573.97, 1510.02, 1210.20, 968.33, 801.65, 525.17 cm^{-1}. HRMS ($M+H^+$) calc'd 327.17434; found 327.17450.

(*E*)-4-(1,3-di-*p*-tolylallyl)benzonitrile (3k)



The title compound was synthesized from 4-(hydroxy(*p*-tolyl)methyl)benzonitrile (32.8 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (36.0 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 3.5 h following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (21:4) afforded product **3k** (34.0 mg, 72% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.03-7.14 (m, 8H), 6.52 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 2.32 (m, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 149.40, 139.12, 137.41, 136.50, 133.89, 132.23, 132.16, 132.06, 129.95, 129.40, 129.35, 129.30, 129.18, 129.10, 128.32, 126.14, 118.87, 110.12, 53.68, 21.07, 20.92; FT-IR ν 2919.84, 2226.09, 1604.86, 1510.28, 968.25, 800.18, 571.10 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 341.20123; found 341.20138.

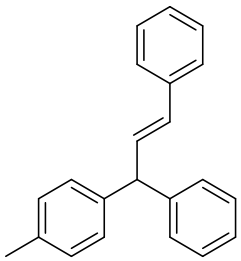
(*E*)-2-(1,3-di-*p*-tolylallyl)naphthalene (3l)



The title compound was synthesized from naphthalen-2-yl(*p*-tolyl)methanol (36.2 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.4 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 30 min following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (49:1) afforded product **3l** (35.8 mg, 70% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74-7.80 (m, 3H), 7.68 (d, *J* = 0.7 Hz, 1H), 7.39-7.46 (m, 2H), 7.34 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.07-7.21 (m, 7H), 6.68 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.00 (d, *J* = 7.4 Hz, 1H), 2.32 (d, *J* = 4.0 Hz, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 141.43, 140.55, 137.13, 136.07, 134.60, 133.58, 132.28, 131.64, 131.41, 129.26, 129.18, 128.72, 128.54, 128.08, 127.86, 127.64, 127.45, 126.83, 126.29, 126.02, 125.58, 53.93, 21.22, 21.09; FT-IR ν 2918.65, 1599.54, 1509.67,

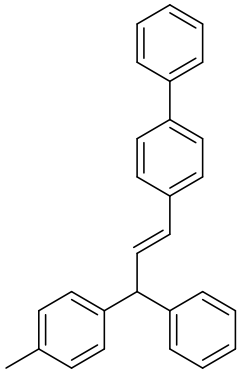
967.67, 798.63, 732.05, 498.86 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 366.22163; found 366.22140.

(*E*)-(3-(*p*-tolyl)prop-1-ene-1,3-diyl)dibenzene (3m)



The title compound was synthesized from 4-methylbenzhydrol (28.7 mg, 0.15 mmol, 1.0 eq.), *trans*-2-phenylvinylboronic acid (32.1 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 40 min following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3m** (14.2 mg, 35% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.38 (m, 2H), 7.18-7.32 (m, 9H), 7.12 (s, 3H), 6.66 (dd, *J* = 15.8, 7.6 Hz, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 7.5 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 143.73, 140.52, 137.33, 135.97, 132.78, 131.22, 129.17, 128.61, 128.51, 128.48, 128.44, 127.24, 126.35, 126.29, 53.80, 21.01.

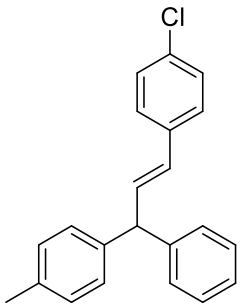
(*E*)-4-(3-phenyl-3-(*p*-tolyl)prop-1-en-1-yl)-1,1'-biphenyl (3n)



The title compound was synthesized from 4-methylbenzhydrol (29.0 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-biphenyl)vinylboronic acid (49.9 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 20 min following procedure A. Purification by silica gel chromatography using hexanes/EtOAc (49:1) afforded product **3n** (31.8 mg, 60% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52-7.59 (m, 4H), 7.39-7.44 (m, 4H), 7.29-7.34 (m, 3H), 7.19-7.25 (m, 3H), 7.11-7.15 (m, 4H), 6.70 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.37 (d, *J* = 15.7 Hz, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 2.33 (m, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 143.69, 140.73, 140.48, 139.99, 136.37, 135.98, 132.94, 130.75, 129.18, 128.89, 128.73, 128.61, 128.52, 128.45, 127.20, 127.16, 127.10, 127.03, 126.88, 126.69, 126.37, 53.84, 21.01; FT-IR ν 2920.06, 1597.48,

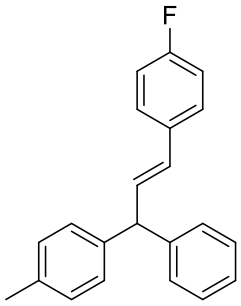
1486.66, 971.08, 755.57, 688.96, 480.68 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 378.22163; found 378.22190.

(*E*)-1-chloro-4-(3-phenyl-3-(*p*-tolyl)prop-1-en-1-yl)benzene (3o)



The title compound was synthesized from 4-methylbenzhydrol (28.8 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-chlorophenyl)vinylboronic acid (39.7 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 35 min following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3o** (28.5 mg, 62% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19-7.32 (m, 10H), 7.09-7.14 (m, 3H), 6.63 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.28 (dd, *J* = 15.8, 1.0 Hz, 1H), 4.84 (d, *J* = 7.5 Hz, 1H), 2.32 (m, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 143.47, 140.26, 136.09, 135.82, 133.51, 132.81, 130.03, 129.22, 128.61, 128.57, 128.49, 128.48, 127.49, 126.45, 53.77, 21.01; FT-IR ν 2920.78, 1598.83, 1489.01, 1449.85, 1091.84, 1011.63, 967.36, 807.54, 697.38, 497.81 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 336.15135; found 336.15200.

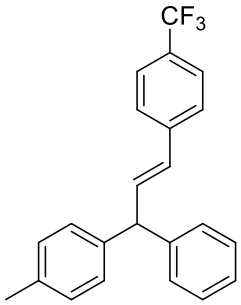
(*E*)-1-fluoro-4-(3-phenyl-3-(*p*-tolyl)prop-1-en-1-yl)benzene (3p)



The title compound was synthesized from 4-methylbenzhydrol (28.9 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-fluorophenyl)vinylboronic acid (36.3 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 35 min following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (49:1) afforded product **3p** (34.0 mg, 77% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.33 (m, 4H), 7.19-7.23 (m, 3H), 7.12 (s, 4H), 6.94-6.99 (m, 2H), 6.57 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 4.84 (d, *J* = 7.5 Hz, 1H), 2.32 (m, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 163.33, 160.89, 143.62, 140.41, 136.03, 133.49, 133.45, 132.56, 132.54, 130.03, 129.20, 128.56, 128.47, 127.77, 127.69,

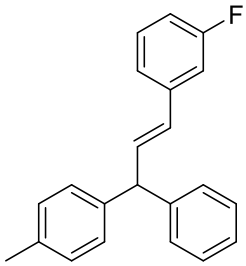
126.40, 115.44, 115.23, 53.75, 21.00; FT-IR ν 3024.65, 1599.93, 1506.27, 1449.74, 1225.41, 1156.67, 967.17, 810.28, 697.73, 508.58 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 320.18090; found 320.18131.

(*E*)-1-methyl-4-(1-phenyl-3-(4-(trifluoromethyl)phenyl)allyl)benzene (3q)



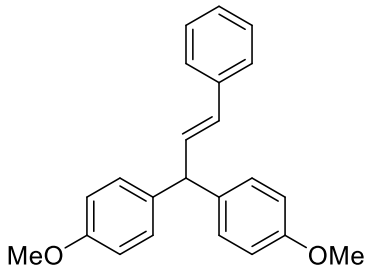
The title compound was synthesized from 4-methylbenzhydrol (29.0 mg, 0.15 mmol, 1.0 eq.), *trans*-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (47.4 mg, 0.22 mmol, 1.5 eq.), $HBF_4 \cdot Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 75 min following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3q** (9.5 mg, 18% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 34.2, 8.3 Hz, 4H), 7.22-7.34 (m, 6H), 7.10-7.15 (m, 4H), 6.76 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 4.88 (d, *J* = 7.5 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 143.20, 140.80, 139.98, 136.24, 135.58, 130.01, 129.29, 128.58, 128.57, 128.49, 126.57, 126.43, 125.51, 125.47, 125.43, 125.39, 53.81, 21.03.

(*E*)-1-fluoro-3-(3-phenyl-3-(*p*-tolyl)prop-1-en-1-yl)benzene (3r)



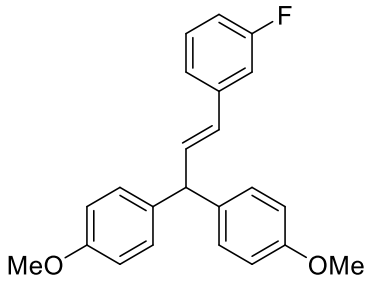
The title compound was synthesized from 4-methylbenzhydrol (28.9 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(3-fluorophenyl)vinylboronic acid (36.3 mg, 0.22 mmol, 1.5 eq.), $HBF_4 \cdot Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 75 min following procedure 4.3. Purification by silica gel chromatography using hexanes afforded product **3r** (16.9 mg, 38% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.33 (m, 2H), 7.20-7.24 (m, 4H), 7.10-7.14 (m, 5H), 7.05-7.08 (m, 1H), 6.86-6.91 (m, 1 H), 6.67 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 7.5 Hz, 1H), 2.32 (m, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 164.31, 161.88, 143.40, 140.19, 139.75, 139.67, 136.13, 134.24, 130.21, 130.19, 129.93, 129.85, 129.24, 128.58, 128.51, 128.49, 126.48, 122.19, 122.16, 114.12, 113.91, 112.84, 112.62, 53.72, 21.02.

(*E*)-4,4'-(3-phenylprop-2-ene-1,1-diyl)bis(methoxybenzene) (3s)



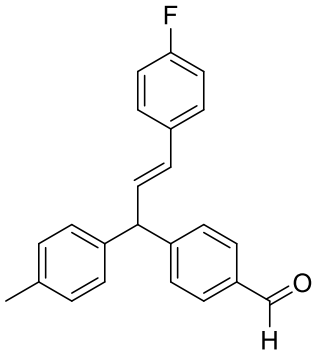
The title compound was synthesized from 4,4'-dimethoxybenzhydrol (35.7 mg, 0.15 mmol, 1.0 eq.), *trans*-2-phenylvinylboronic acid (32.4 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 20 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (9:1) afforded product **3s** (11.3 mg, 23% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.37 (m, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.12-7.21 (m, 5H), 6.83-6.87 (m, 4H), 6.62 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 4.80 (d, *J* = 7.4 Hz, 1H), 3.79 (s, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 158.11, 137.38, 135.93, 133.22, 130.91, 129.54, 128.49, 127.21, 126.28, 113.84, 55.26, 52.50.

(*E*)-4,4'-(3-(3-fluorophenyl)prop-2-ene-1,1-diyl)bis(methoxybenzene) (3t)



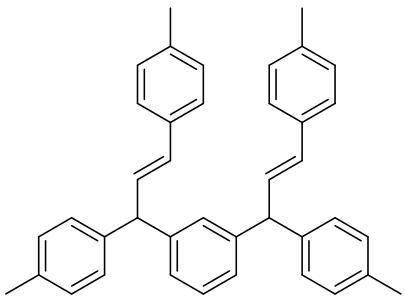
The title compound was synthesized from 4,4'-dimethoxybenzhydrol (35.5 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(3-fluorophenyl)vinylboronic acid (12.5 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 20 minutes following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (9:1) afforded product **3t** (12.5 mg, 25% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21-7.25 (m, 1H), 7.05-7.14 (m, 6H), 6.83-6.91 (m, 5H), 6.64 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 4.80 (d, *J* = 7.4 Hz, 1H), 3.79 (s, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 164.30, 161.87, 158.18, 139.78, 139.71, 135.56, 134.66, 129.92, 129.88, 129.86, 129.84, 129.50, 122.16, 122.13, 11406, 113.88, 112.79, 112.58, 55.25, 52.41.

(*E*)-4-(3-(4-fluorophenyl)-1-(*p*-tolyl)allyl)benzaldehyde (3u)



The title compound was synthesized from 4-(hydroxy(*p*-tolyl)methyl)benzaldehyde (32.8 mg, 0.15 mmol, 1.0 eq.), *trans*-2-(4-fluorophenyl)vinylboronic acid (36.0 mg, 0.22 mmol, 1.5 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.25 eq.) in acetonitrile (0.7 ml, 0.2M) at 70˚C for 6.5 h following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (47:3) afforded product **3u** (13.4 mg, 28% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.81-7.83 (m, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.31-7.34 (m, 2H), 7.09-7.15 (m, 4H), 6.96-7.01 (m, 2H), 6.55 (dd, *J* = 15.8, 7.5 Hz, 1H), 6.31 (d, *J* = 15.8 Hz, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 2.33 (m, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 191.91, 163.50, 161.04, 150.85, 139.35, 136.56, 134.86, 133.10, 133.06, 131.26, 131.24, 130.88, 130.00, 129.43, 129.25, 128.41, 127.86, 127.78, 115.56, 115.35, 53.88, 21.02.

1,3-bis((*E*)-1,3-di-*p*-tolylallyl)benzene (10)

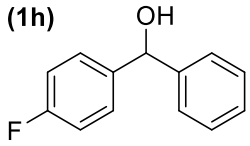


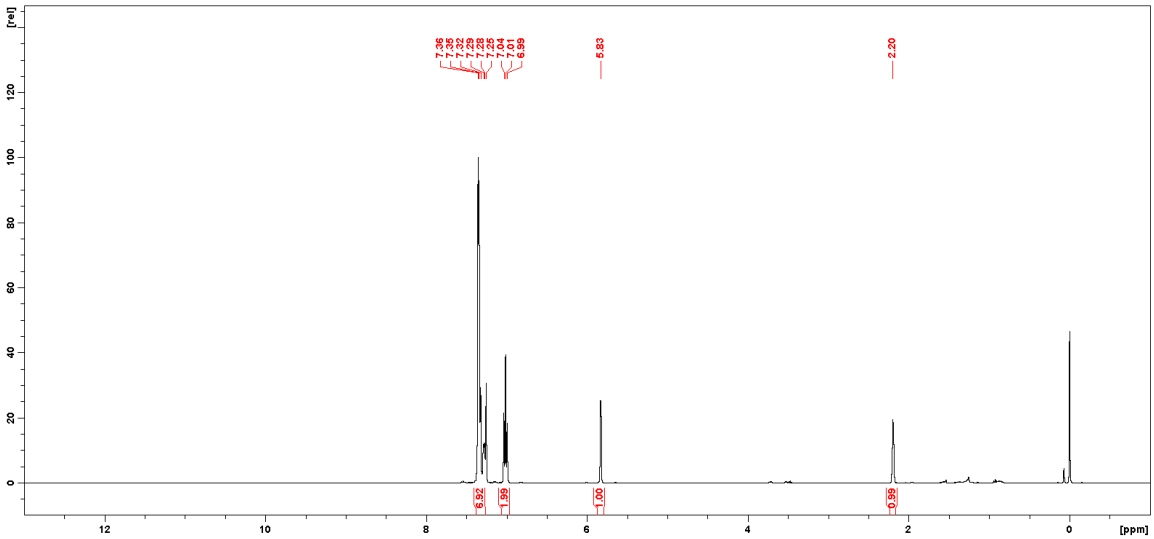
The title compound was synthesized from 1,3-phenylenebis(*p*-tolylmethanol) (23.4 mg, 0.07 mmol, 1.0 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (35.7 mg, 0.22 mmol, 3.0 eq.), $HBF_4{\cdot}Et_2O$ (5.0 µl, 0.036 mmol, 0.5 eq.) in acetonitrile (0.7 ml, 0.1M) at 70˚C for 15 min following procedure 4.3. Purification by silica gel chromatography using hexanes/EtOAc (24:1) afforded product **10** (20.7 mg, 54% yield) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20-7.22 (m, 5H), 7.14-7.15 (m, 1H), 7.04-7.10 (m, 14H), 6.56 (dd, *J* = 15.8, 7.5 Hz, 2H), 6.27 (d, *J* = 15.8 Hz, 2H), 4.80 (d, *J* = 7.4 Hz, 2H), 2.31 (m, 12H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ 143.86, 140.65, 140.62, 136.88, 135.78, 134.58, 131.85, 131.84, 130.97, 129.20, 129.16, 129.11, 129.06, 128.49, 128.46, 126.55, 126.53, 126.17, 53.70, 21.13, 20.99; FT-IR ν 2918.62, 1599.63, 1509.74, 967.66, 797.57, 731.47, 514.51 cm^{-1}. HRMS ($M+NH_4^+$) calc'd 536.33118; found 536.33106.

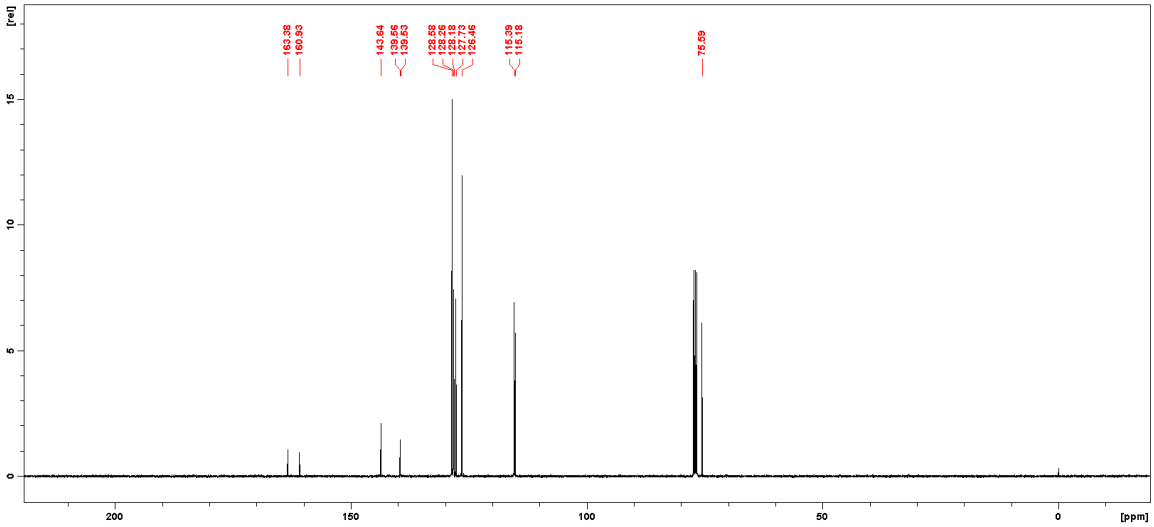
Appendix B: NMR Spectra

B1: Benzhydryl Alcohols

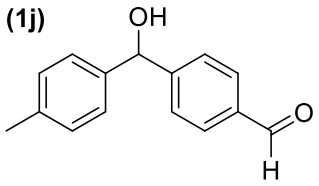
(1h)

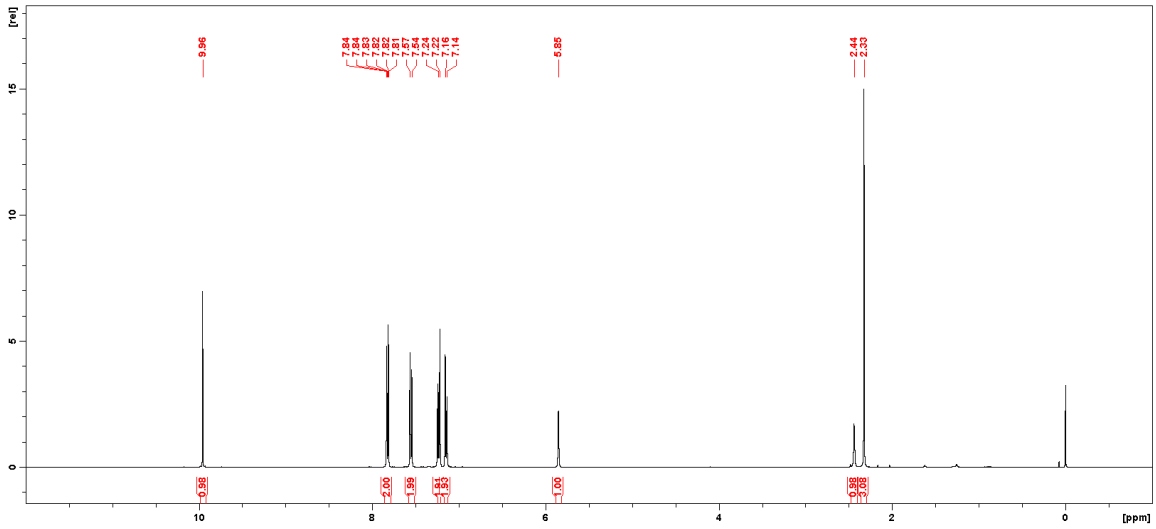


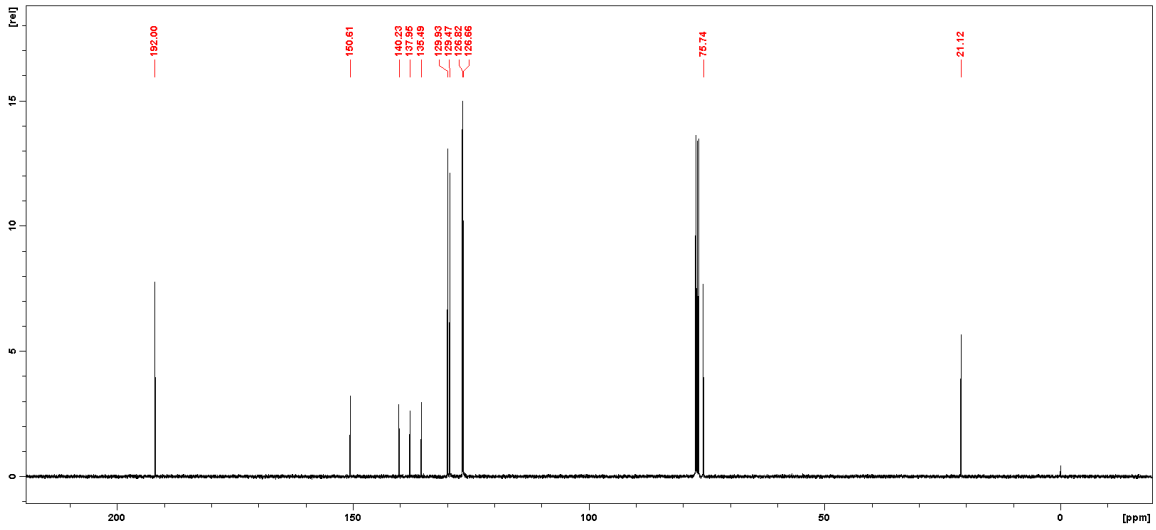




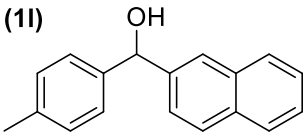
(1j)

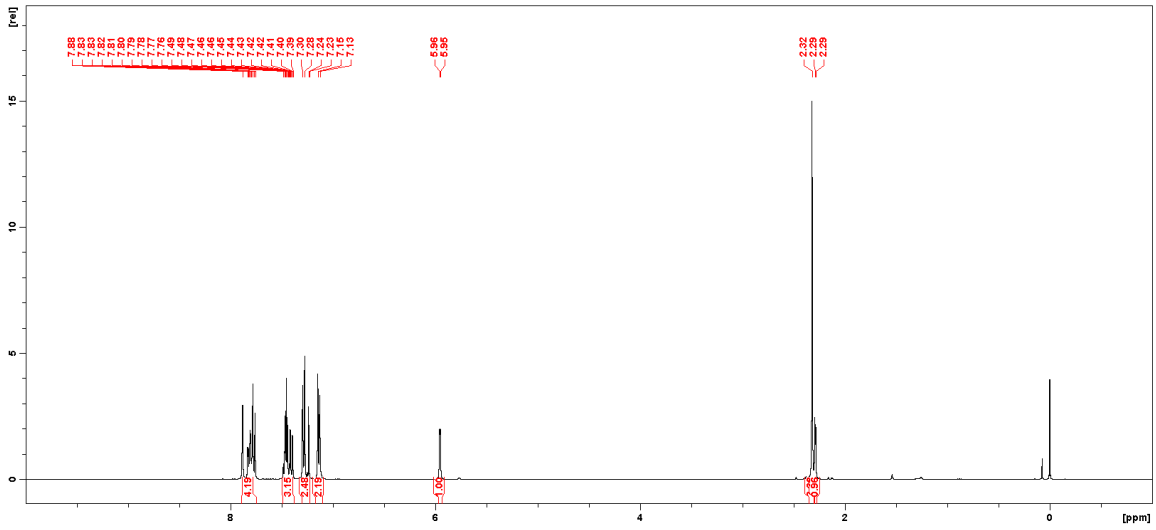

OH
O
H

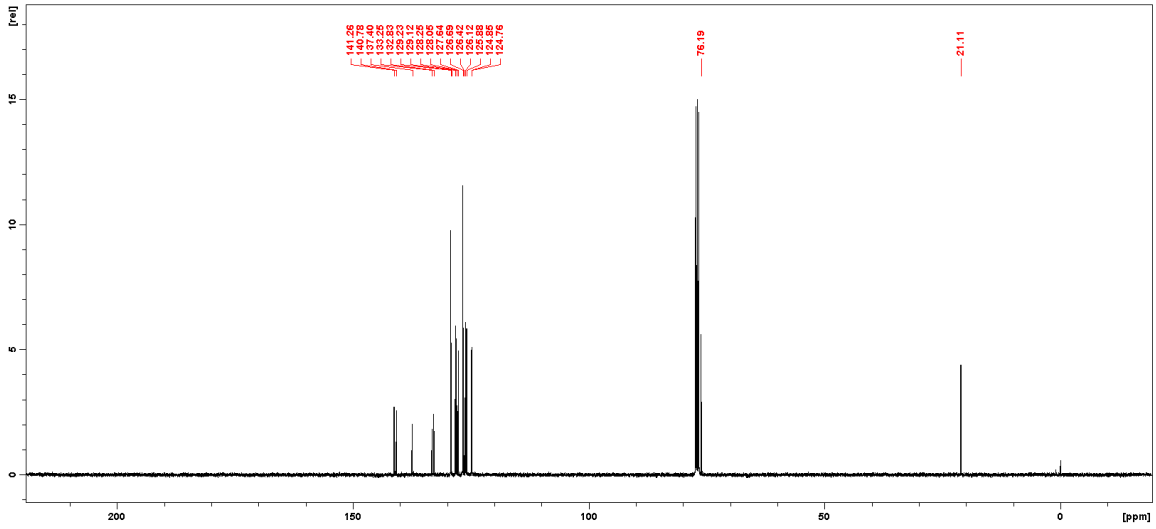

[rel]
9.96
7.84
7.84
7.83
7.82
7.82
7.82
7.81
7.57
7.54
7.24
7.22
7.16
7.15
7.14
6.85
2.44
2.33
0.98
2.00
1.99
1.91
1.93
1.00
0.98
3.08
[ppm]


[rel]
192.00
150.61
140.23
137.95
136.49
129.93
129.47
128.82
128.82
128.68
76.74
21.12
[ppm]

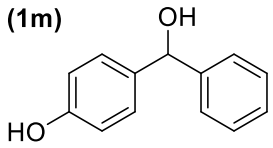
(1l)

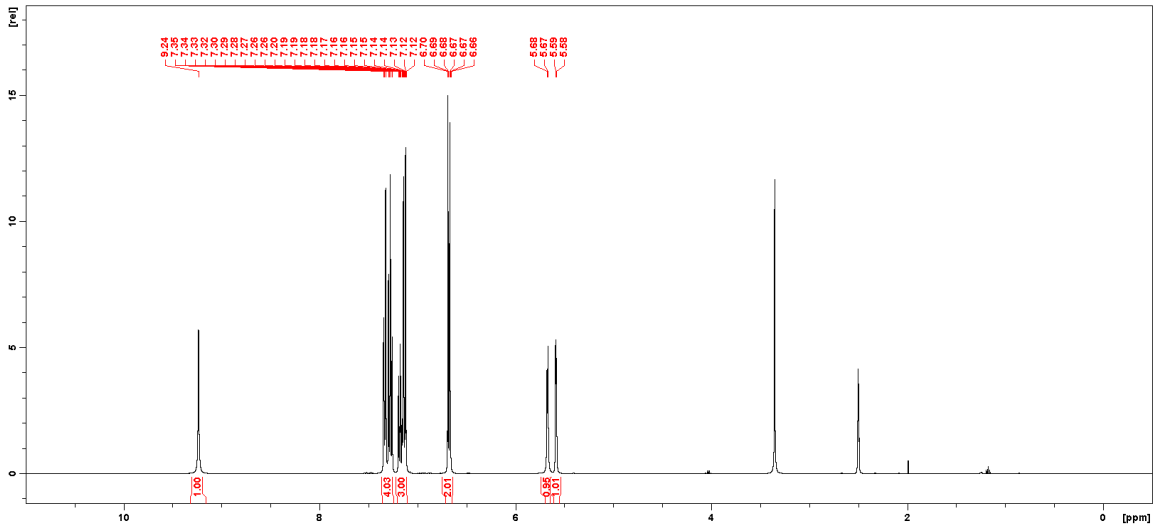

OH

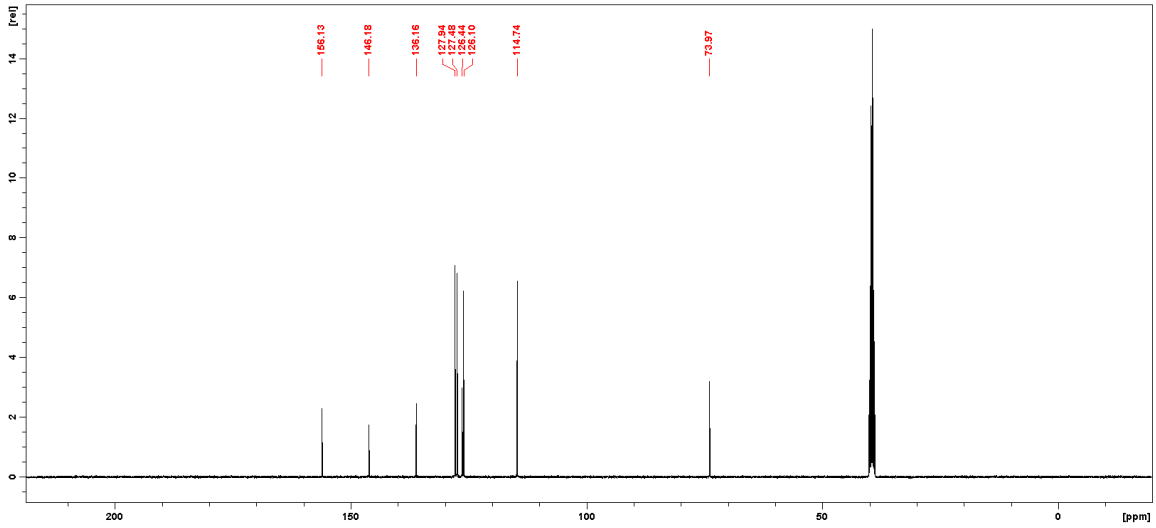

[rel]
7.88
7.83
7.82
7.81
7.80
7.79
7.78
7.77
7.76
7.49
7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.42
7.42
7.41
7.40
7.39
7.30
7.28
7.24
7.23
7.15
7.13
5.96
5.95
2.32
2.29
2.29
4.19
3.15
2.45
2.19
1.00
0.95
0.87
[ppm]


[rel]
141.26
140.78
137.49
133.25
132.83
129.83
129.12
128.25
127.64
126.69
126.42
125.12
125.88
124.85
124.76
76.19
21.11
[ppm]

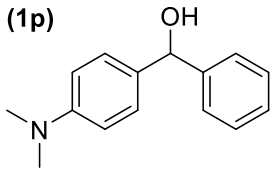
(1m)

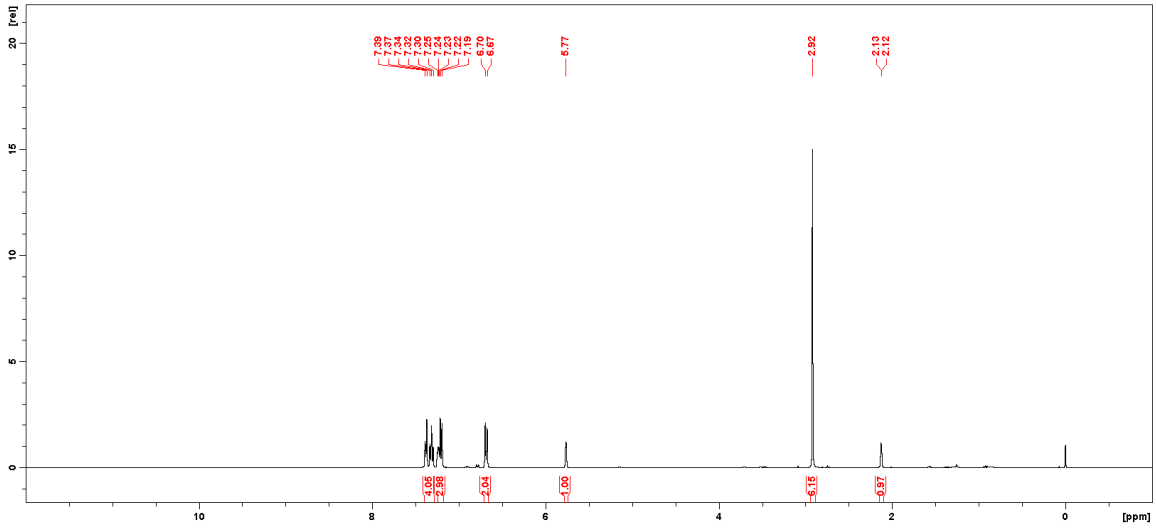

OH
HO

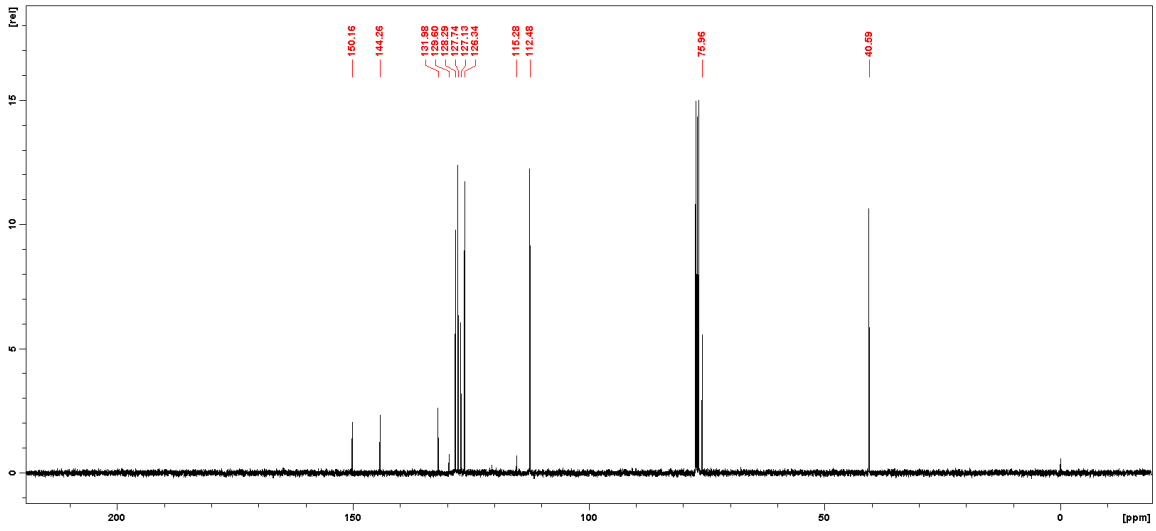

[rel]
9.24
9.23
7.34
7.33
7.32
7.30
7.29
7.28
7.27
7.26
7.25
7.20
7.19
7.19
7.18
7.18
7.17
7.17
7.16
7.16
7.15
7.15
7.14
7.14
7.13
7.12
7.12
6.70
6.69
6.68
6.67
6.67
6.66
5.68
5.67
5.59
5.58
1.00
4.03
3.00
2.01
0.95
1.01
10
8
6
4
2
0
[ppm]


[rel]
156.13
146.18
136.16
127.94
127.48
126.44
126.10
114.74
70.97
200
150
100
50
0
[ppm]

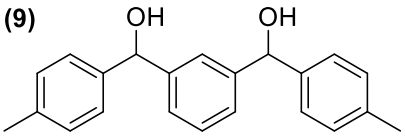
(1p)

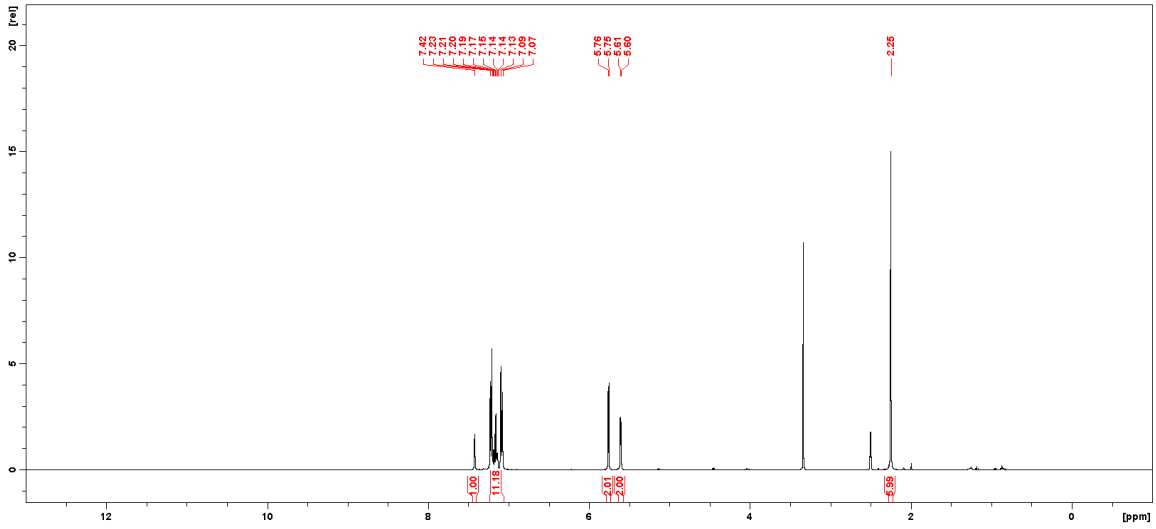

OH
N

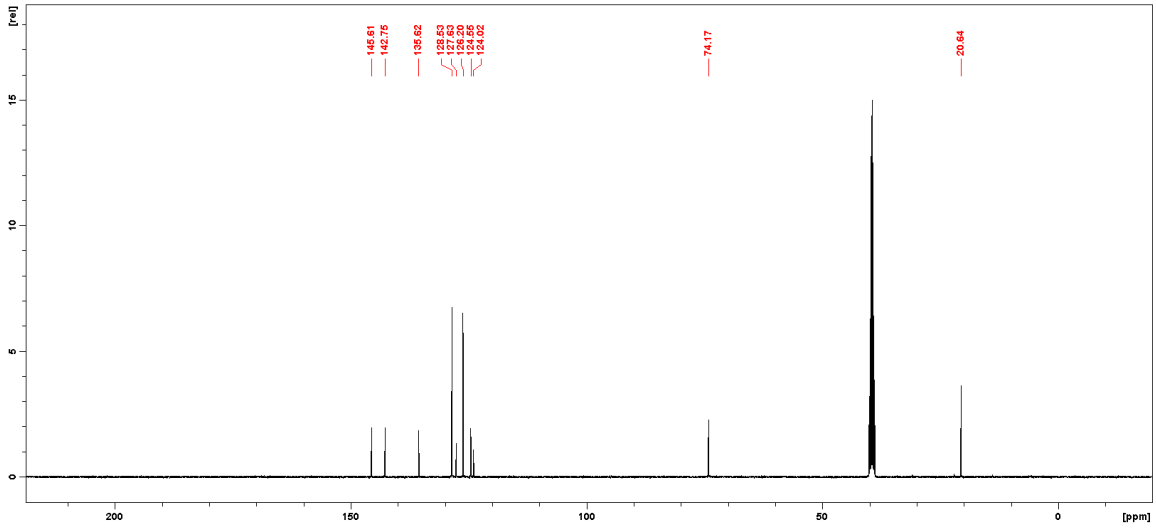

[rel]
7.39
7.37
7.34
7.32
7.30
7.26
7.24
7.23
7.22
7.19
6.70
6.67
5.77
2.92
2.13
2.12
4.06
2.96
2.04
1.00
5.15
0.97
[ppm]


[rel]
150.16
144.26
131.98
129.60
129.29
127.74
127.13
126.34
118.28
112.48
76.96
40.59
[ppm]

(9)

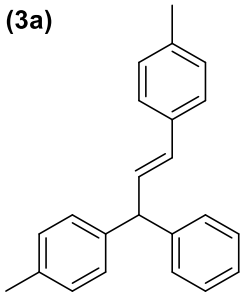

OH
OH

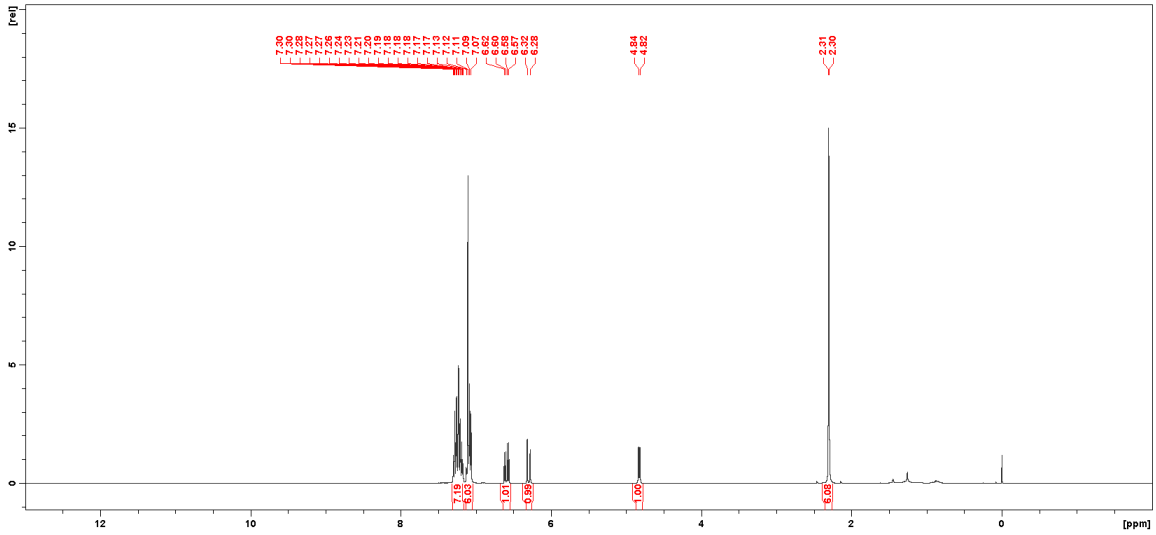

[rel]
7.42
7.23
7.21
7.20
7.19
7.17
7.15
7.14
7.13
7.09
7.07
5.76
5.75
5.61
5.60
2.25
1.00
11.18
2.01
2.00
5.99
[ppm]

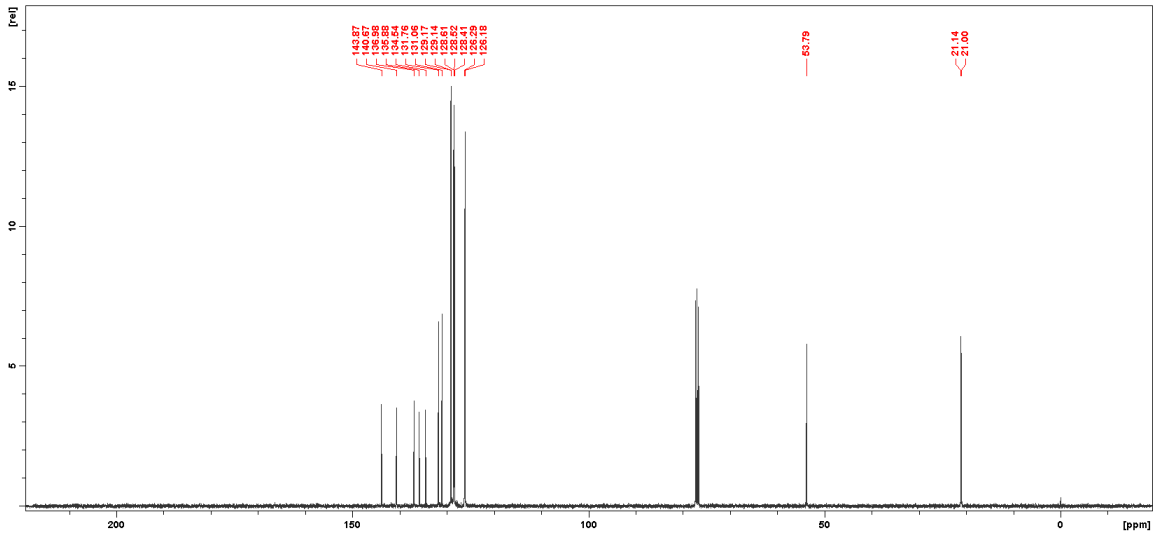

[rel]
145.61
142.75
135.62
128.53
127.63
126.20
124.65
124.02
74.17
20.64
[ppm]

B2: 1,3,3-Triphenylpropene Derivatives

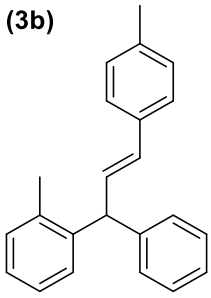
(3a)

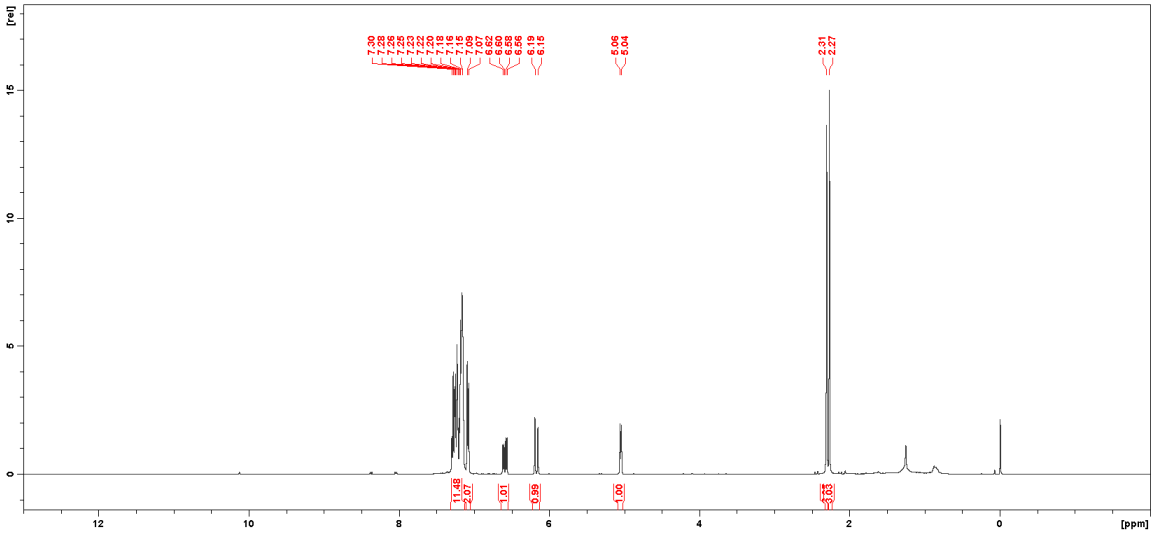


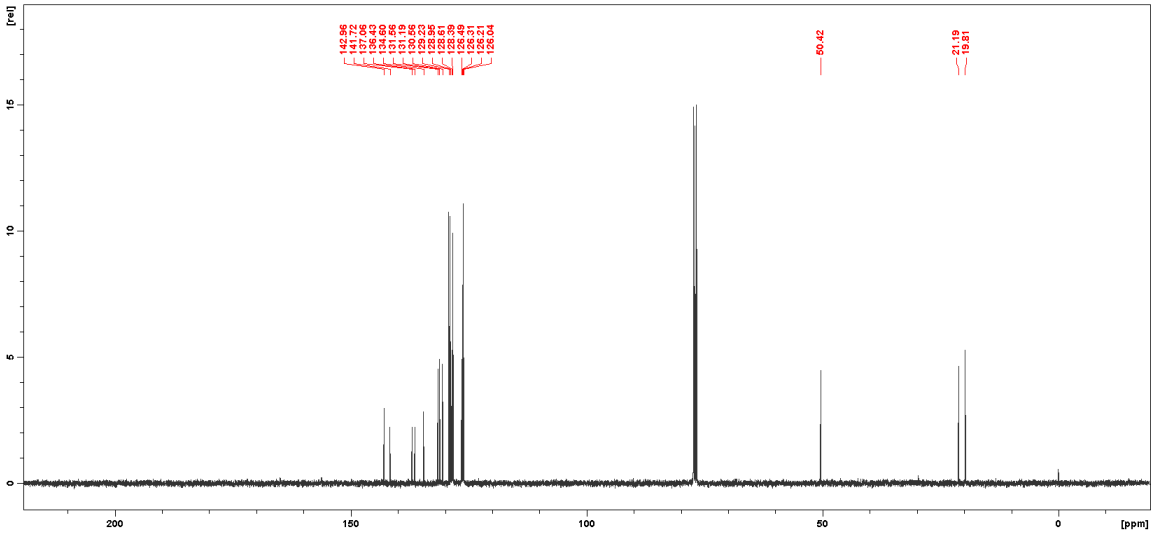




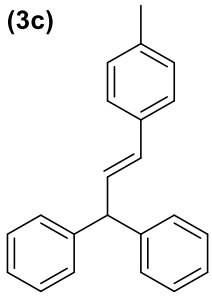
(3b)

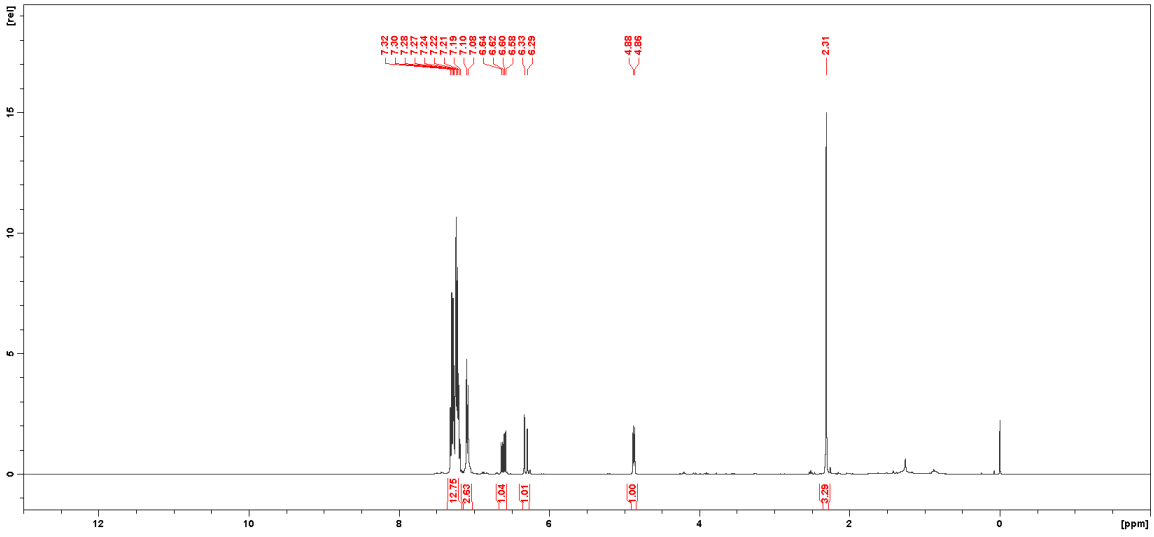


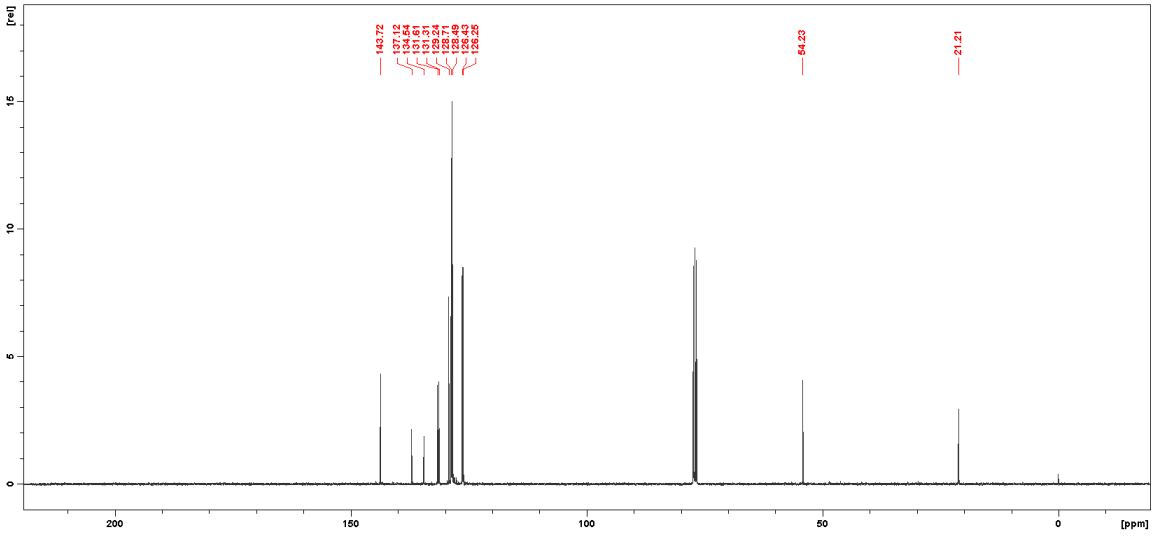

[rel]
7.30
7.28
7.26
7.25
7.23
7.22
7.20
7.18
7.16
7.15
7.09
7.07
6.62
6.60
6.58
6.56
6.19
6.15
5.06
5.04
2.31
2.27
11.48
2.07
1.01
0.99
1.00
3.03
[ppm]


[rel]
142.56
141.72
137.06
136.43
134.60
131.56
131.19
130.55
129.23
128.95
128.61
128.39
128.49
126.31
126.21
126.04
50.42
21.19
19.81
[ppm]

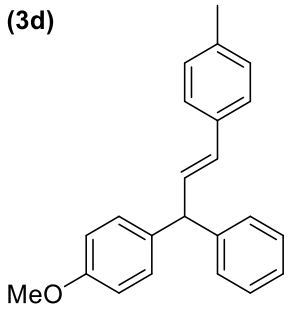
(3c)

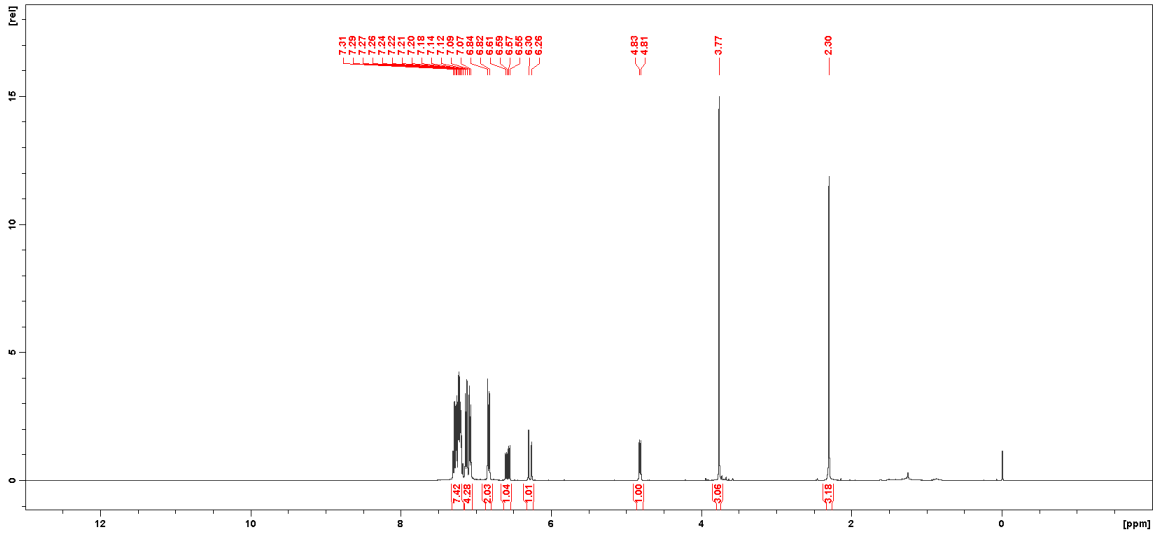


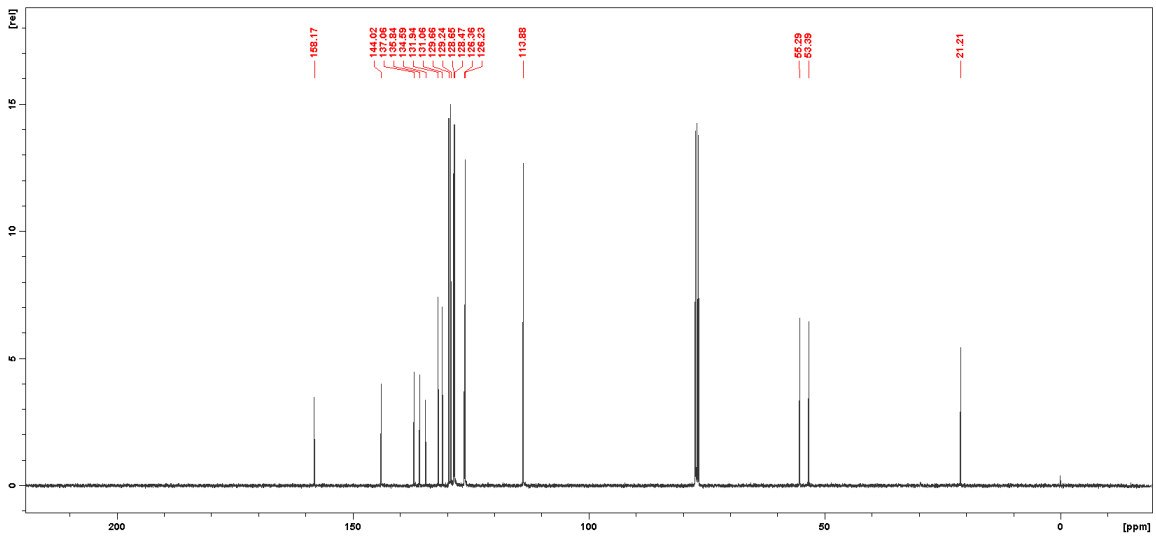

[rel]
7.32
7.30
7.28
7.27
7.24
7.22
7.21
7.19
7.10
7.08
6.64
6.62
6.60
6.58
6.33
6.29
4.88
4.86
2.31
12.76
2.65
1.04
1.01
1.00
3.29
[ppm]


[rel]
143.72
137.12
134.64
131.61
131.31
129.24
128.71
128.49
126.43
126.25
54.23
21.21
[ppm]

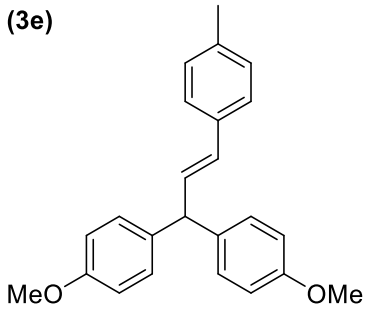
(3d)

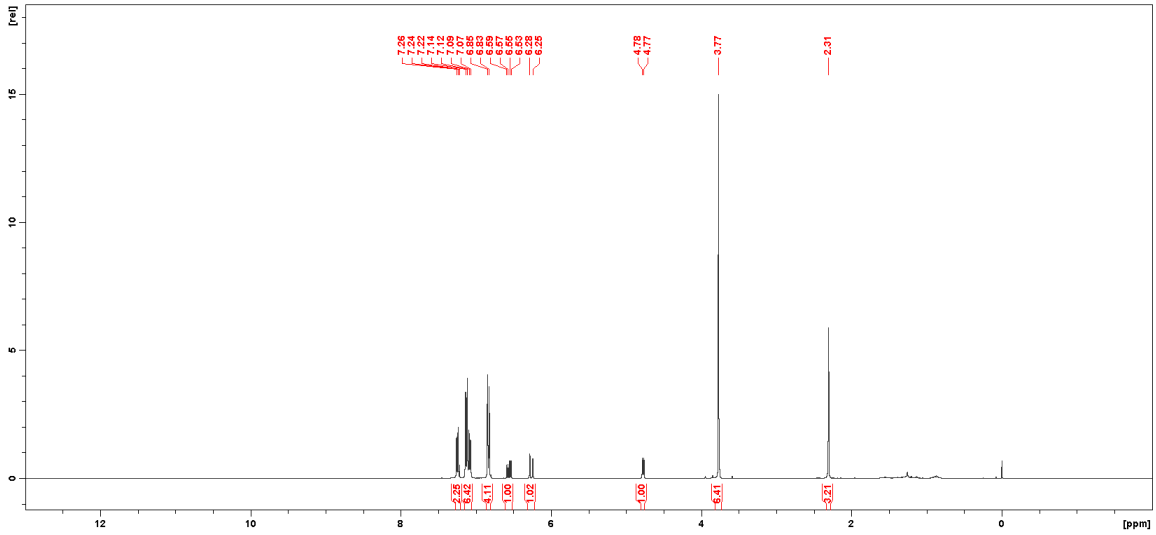

MeO

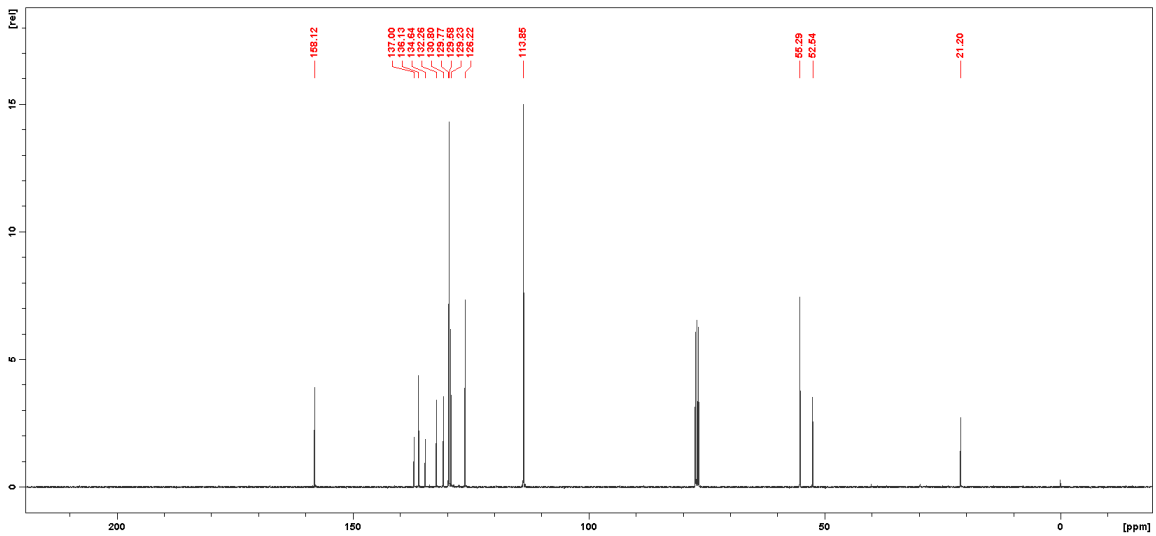

[rel]
7.31
7.29
7.27
7.26
7.24
7.22
7.21
7.20
7.18
7.14
7.12
7.09
7.07
6.84
6.82
6.61
6.59
6.57
6.55
6.30
6.28
4.83
4.81
3.77
2.30
7.42
4.28
2.03
1.04
1.01
1.00
3.06
3.18
[ppm]


[rel]
158.17
144.02
137.06
135.84
134.59
131.34
131.06
129.66
129.24
128.65
128.47
126.95
126.23
113.88
55.29
53.39
21.21
[ppm]

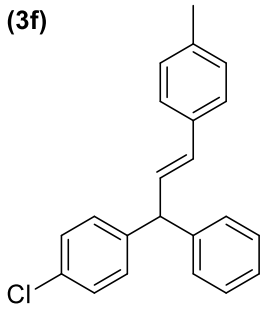
(3e)

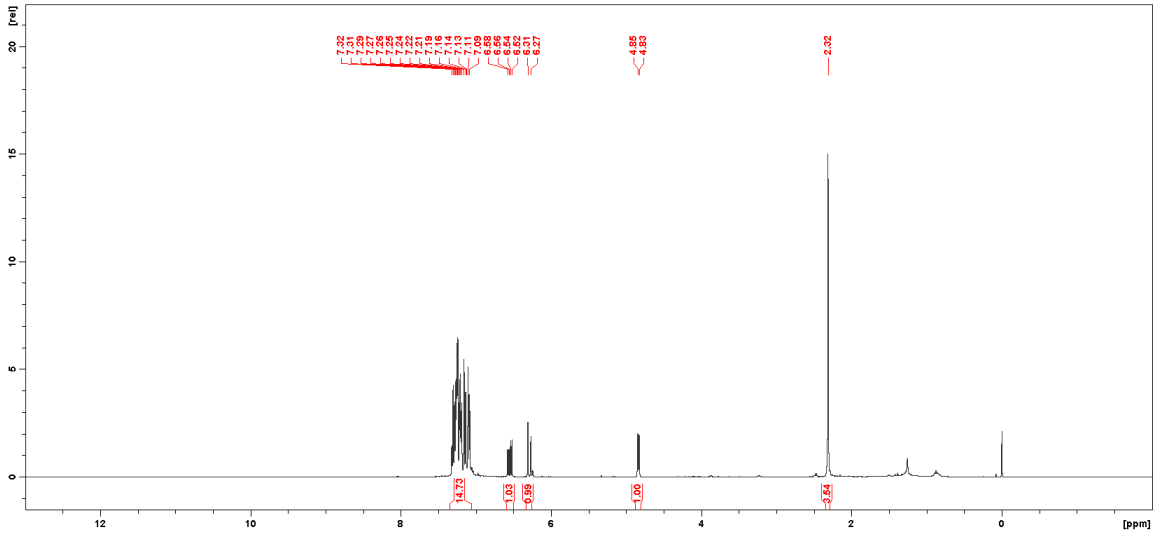

MeO
OMe

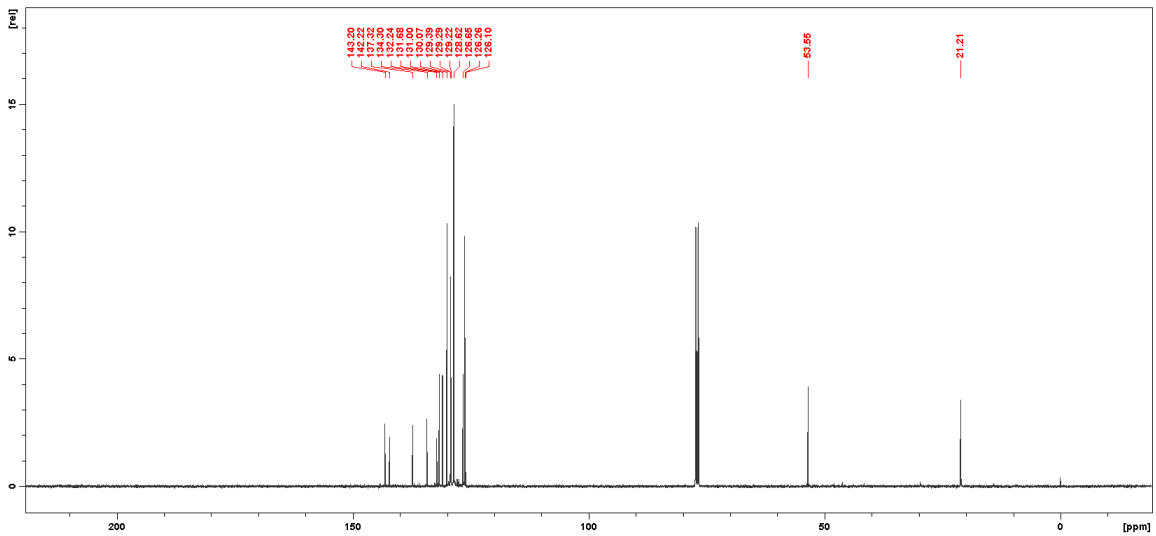

[rel]
7.26
7.24
7.22
7.14
7.12
7.09
7.07
6.85
6.83
6.69
6.67
6.65
6.53
6.28
6.26
4.78
4.77
3.77
2.31
2.26
6.42
6.11
1.00
1.02
1.00
6.41
3.21
[ppm]


[rel]
158.12
137.00
136.13
134.64
132.26
130.90
130.37
129.58
129.23
126.22
113.85
55.29
52.64
21.20
[ppm]

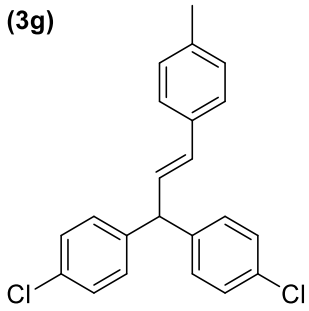
(3f)

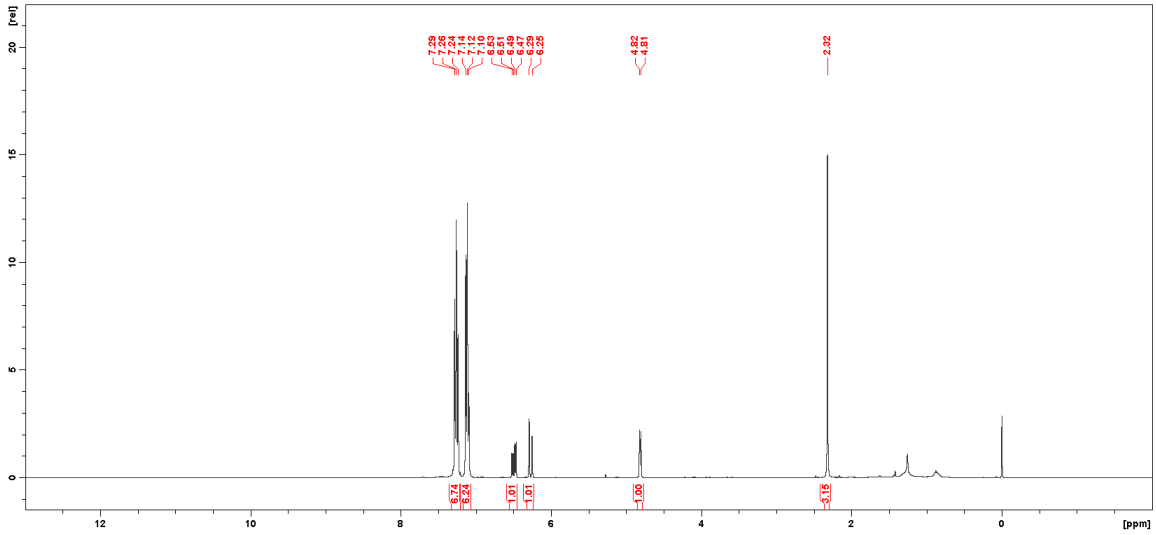

Cl

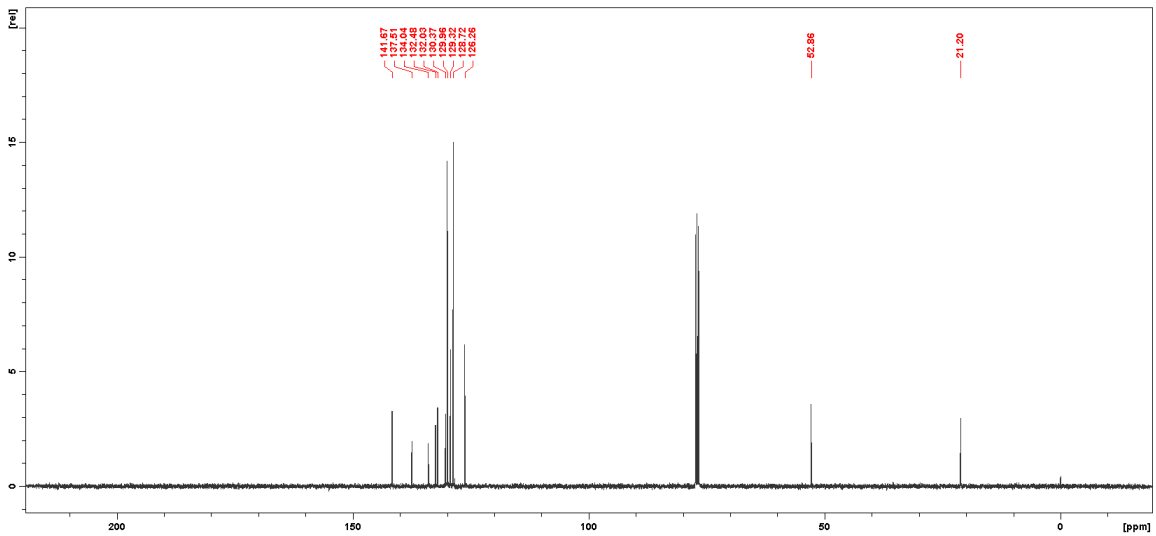

[rel]
7.32
7.31
7.29
7.27
7.26
7.25
7.24
7.22
7.21
7.19
7.18
7.14
7.13
7.11
7.09
6.58
6.56
6.54
6.52
6.31
6.27
4.85
4.83
2.32
14.73
1.03
0.99
1.00
3.64
[ppm]


[rel]
143.20
142.22
137.22
134.30
132.24
131.66
131.06
130.07
129.29
129.22
128.62
128.52
126.26
126.10
53.55
21.21
[ppm]

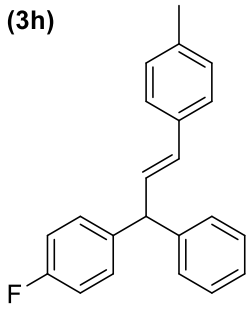
(3g)

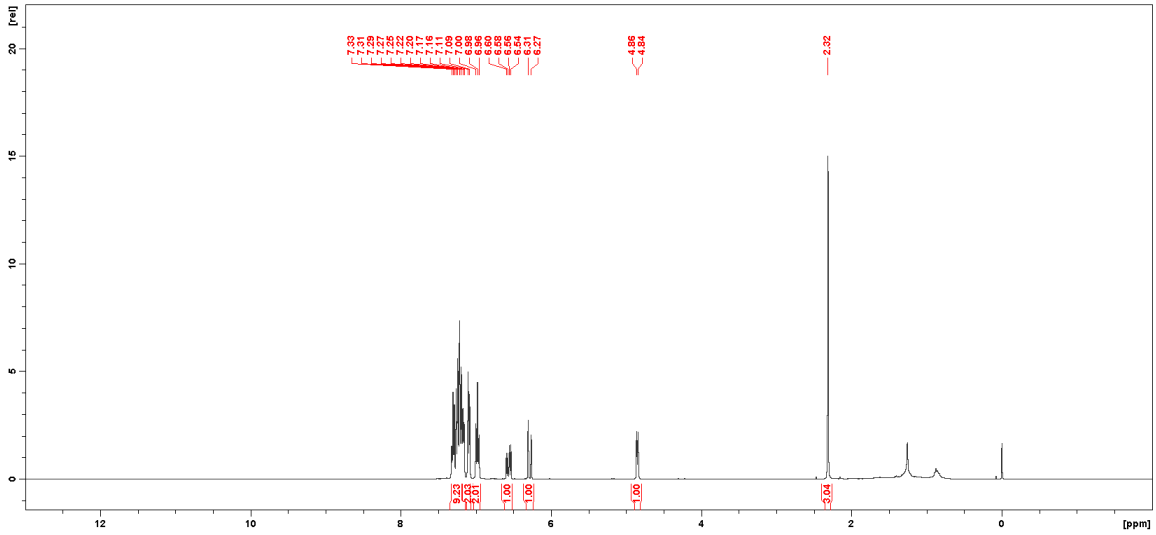

Cl
Cl

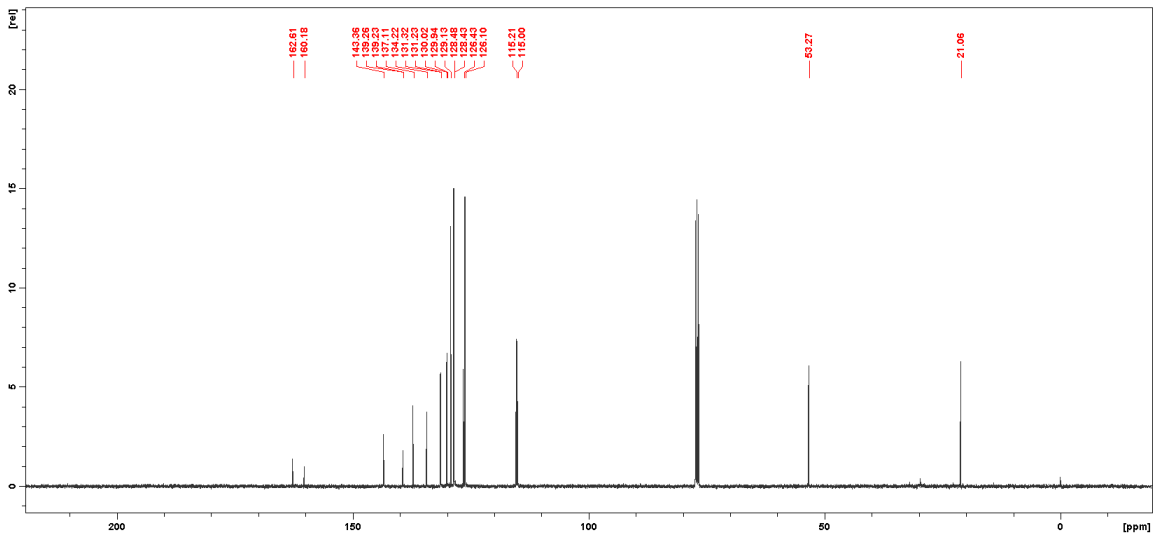

[rel]
7.29
7.26
7.24
7.14
7.12
7.10
6.53
6.51
6.49
6.47
6.29
6.25
4.82
4.81
2.32
6.74
6.24
1.01
1.01
1.00
3.15
[ppm]


[rel]
141.67
137.51
134.04
133.48
132.03
130.37
129.66
129.32
128.72
126.26
62.86
21.20
[ppm]

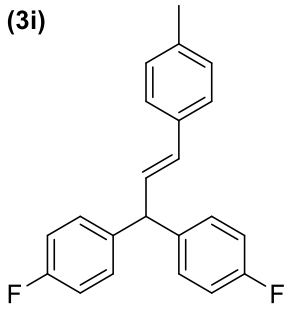
(3h)

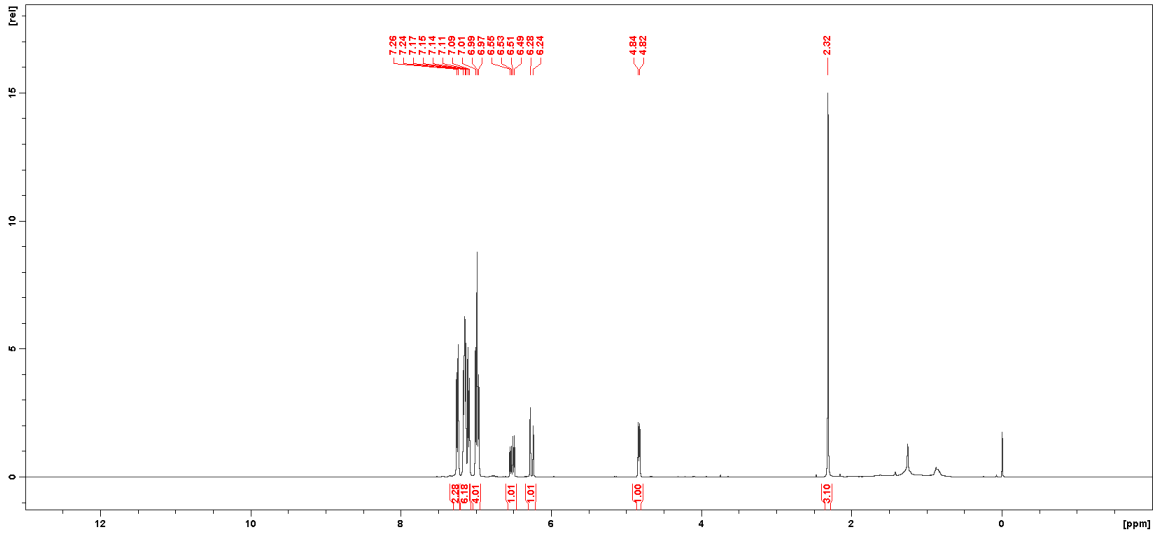

F

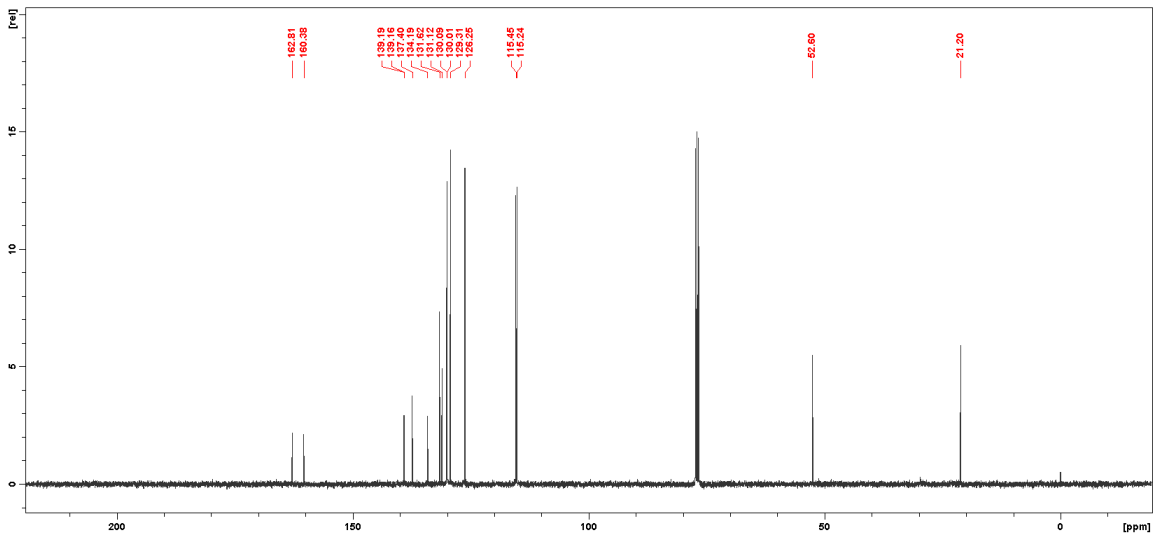

[rel]
7.33
7.31
7.29
7.27
7.25
7.22
7.20
7.17
7.16
7.11
7.09
7.00
6.98
6.96
6.69
6.68
6.66
6.64
6.61
6.27
4.86
4.84
2.32
9.23
2.03
2.01
1.00
1.00
1.00
3.04
[ppm]


[rel]
162.61
160.18
143.36
139.26
139.23
137.11
134.22
131.32
131.22
130.02
129.94
129.48
128.48
128.43
126.43
126.10
115.21
115.00
53.27
21.06
[ppm]

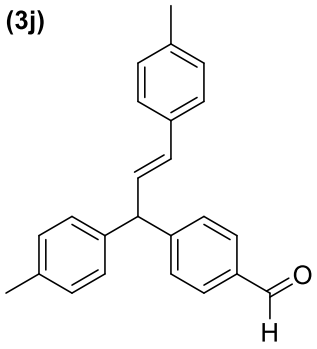
(3i)

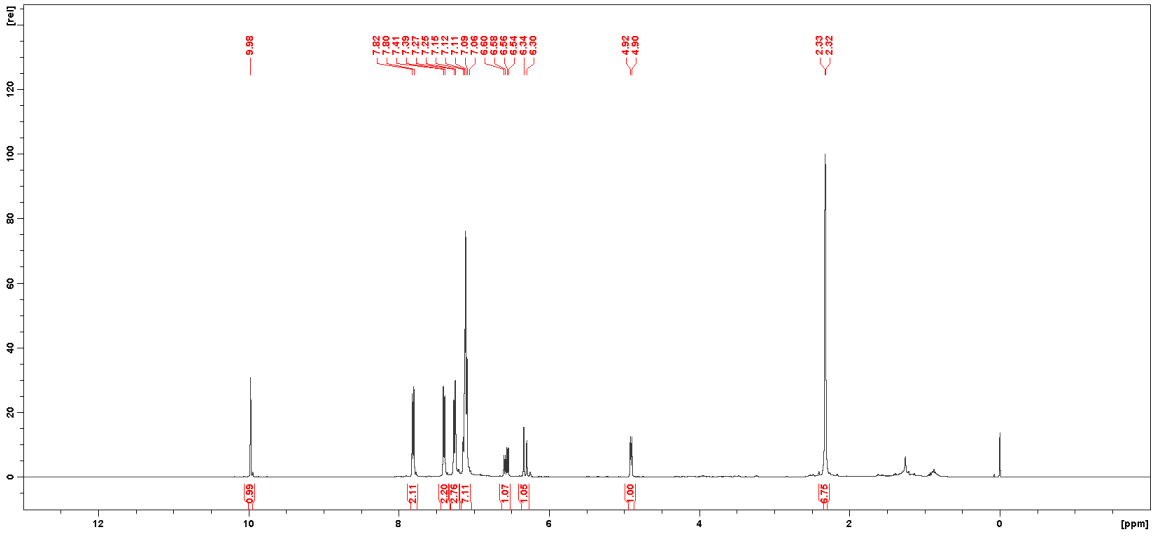

F
F

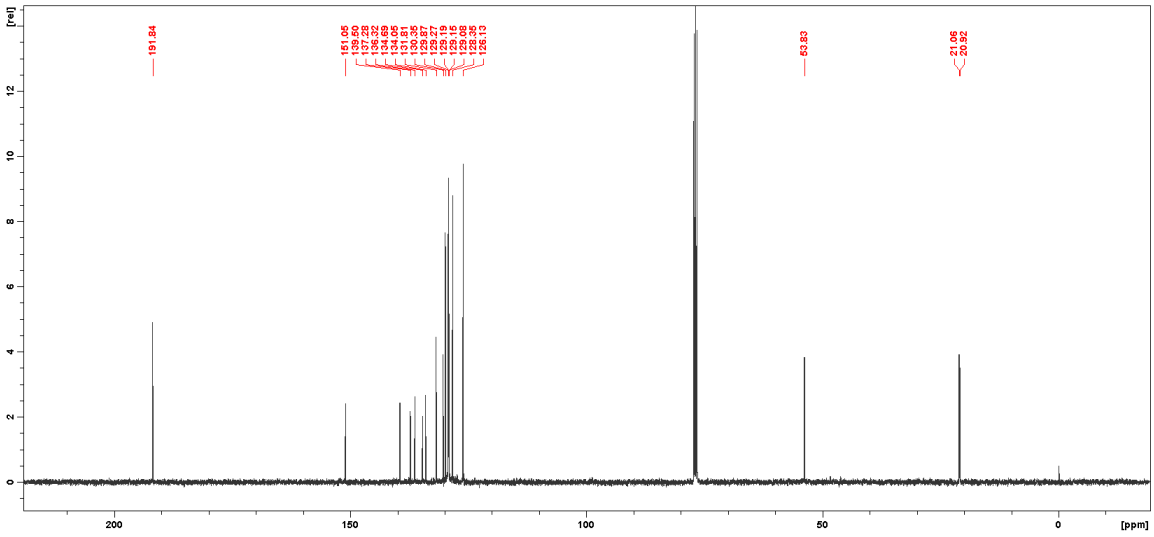

[rel]
7.26
7.24
7.17
7.15
7.14
7.11
7.09
7.01
6.99
6.97
6.55
6.53
6.51
6.49
6.28
6.24
4.84
4.82
2.32
2.28
6.18
4.01
1.01
1.01
1.00
3.10
[ppm]


[rel]
162.81
160.38
139.19
139.16
137.40
134.19
131.62
131.12
130.09
130.01
129.31
129.25
115.45
115.24
62.60
21.20
[ppm]

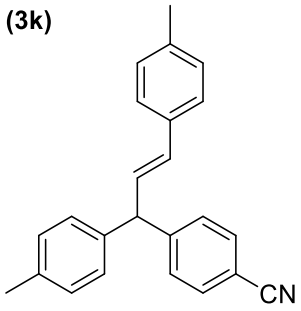
(3j)

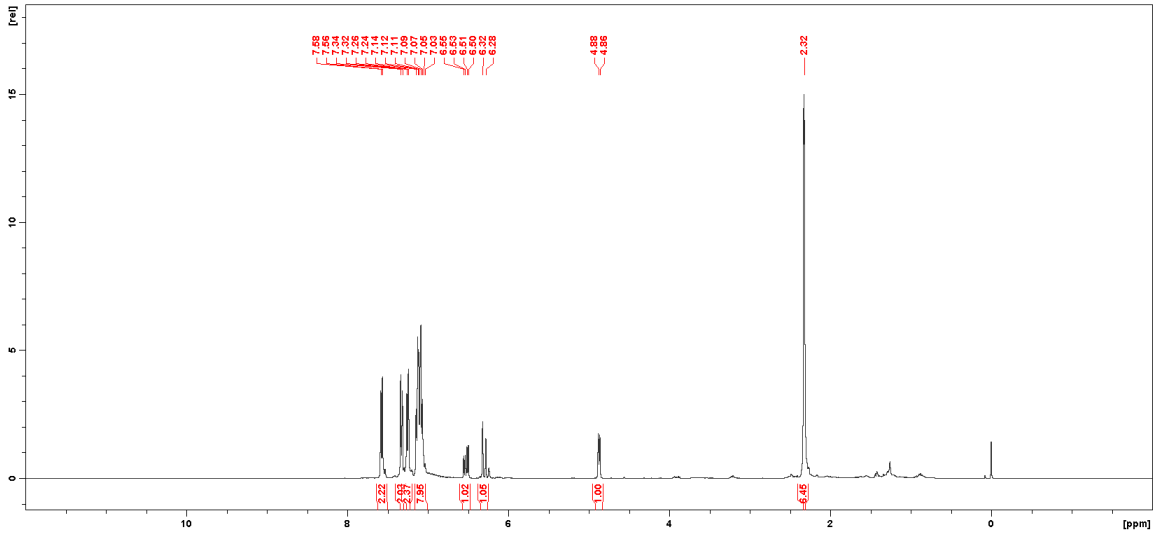

O
H

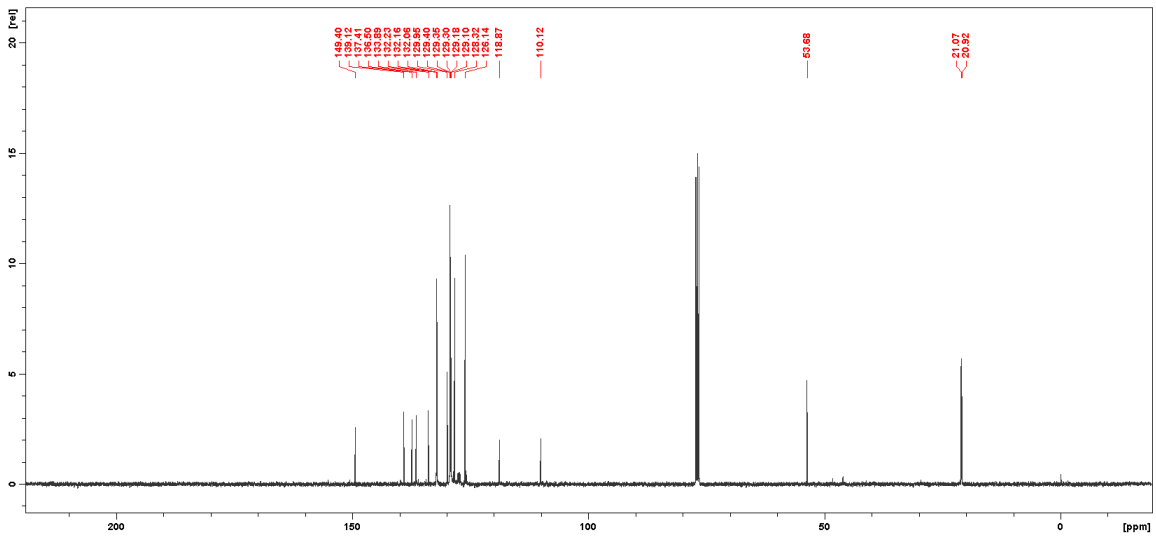

[rel]
9.98
7.82
7.80
7.41
7.39
7.27
7.25
7.15
7.12
7.11
7.09
7.06
6.69
6.68
6.56
6.54
6.54
6.30
4.92
4.90
2.33
2.32
0.99
2.11
2.20
2.20
2.11
1.07
1.06
1.00
6.75
[ppm]


[rel]
191.84
151.05
139.80
137.28
134.32
134.08
134.05
131.81
129.95
129.27
129.19
129.15
129.08
128.35
126.10
53.83
21.06
20.92
[ppm]

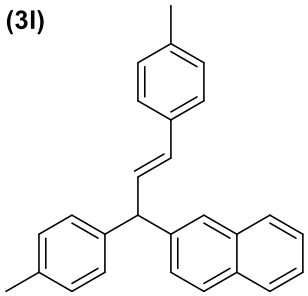
(3k)

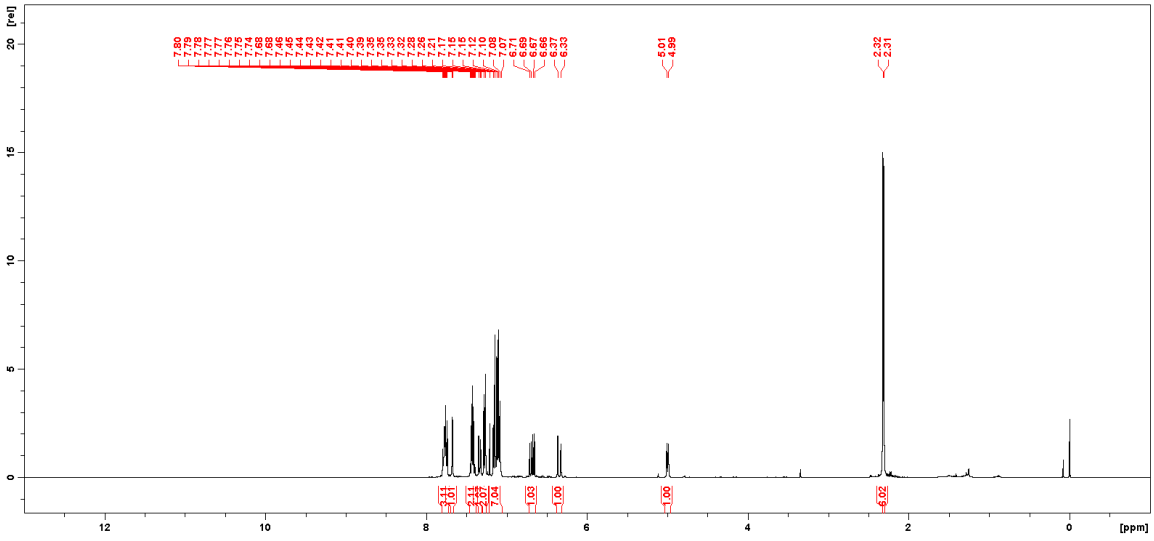

CN

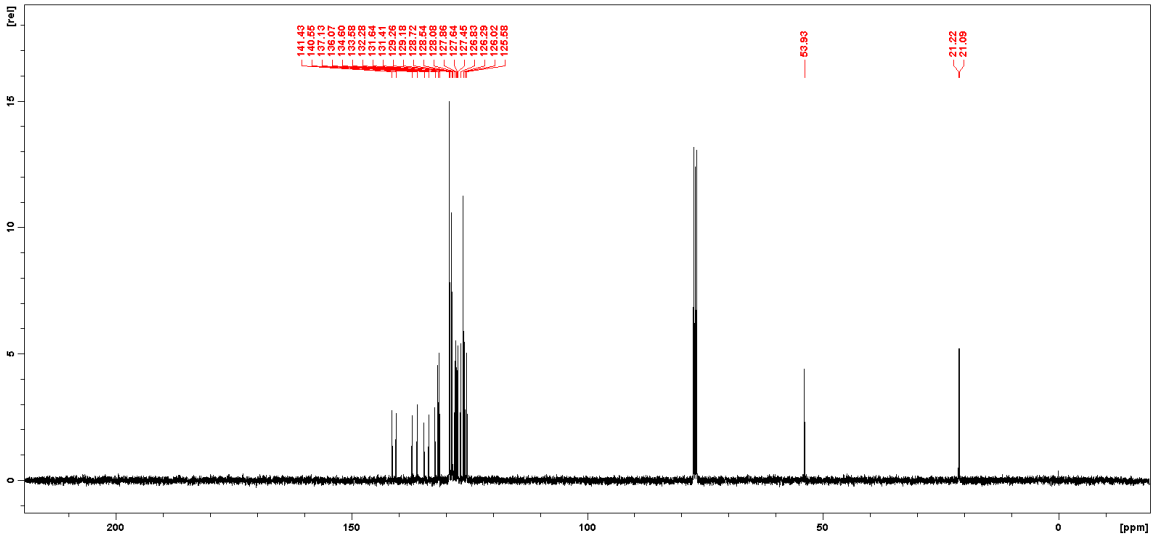

[rel]
7.58
7.56
7.34
7.32
7.26
7.24
7.14
7.12
7.11
7.09
7.07
7.07
7.05
7.03
6.55
6.53
6.51
6.50
6.32
6.32
6.28
4.88
4.86
2.32
2.22
6.03
2.37
7.95
1.02
1.05
1.00
6.45
[ppm]


[rel]
149.40
139.12
137.41
136.50
133.89
132.23
132.16
132.06
129.95
129.40
129.35
129.30
129.15
129.10
128.32
126.14
118.87
110.12
53.68
21.07
20.92
[ppm]

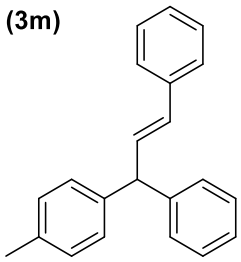
(3l)

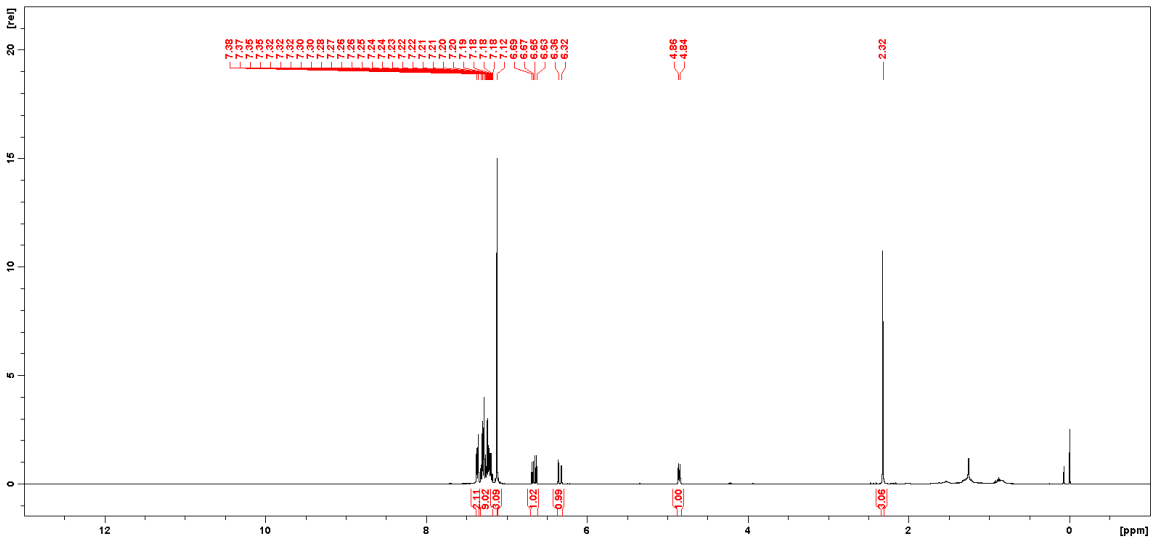


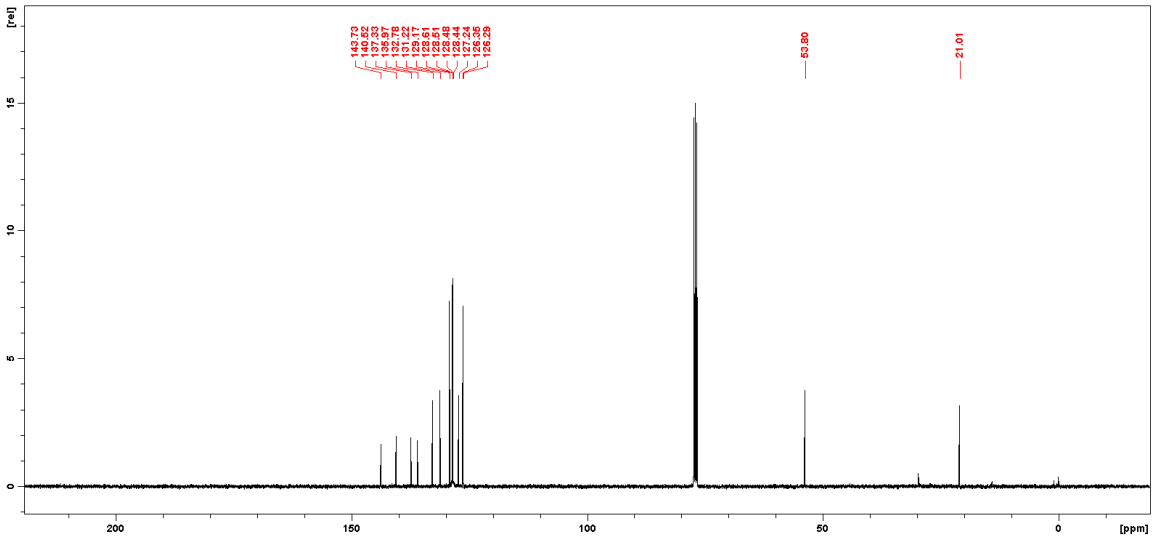

[rel]
20
15
10
5
0
7.80
7.79
7.78
7.77
7.77
7.76
7.75
7.74
7.68
7.68
7.46
7.45
7.44
7.43
7.42
7.41
7.41
7.40
7.39
7.36
7.35
7.33
7.32
7.28
7.26
7.21
7.17
7.15
7.15
7.12
7.10
7.08
7.07
6.71
6.69
6.67
6.66
6.37
6.33
5.01
4.99
2.32
2.31
1.01
3.01
2.13
2.07
2.04
1.03
1.00
1.00
6.02
12
10
8
6
4
2
0
[ppm]


[rel]
15
10
5
0
141.43
140.55
137.13
136.07
134.60
133.58
132.28
131.64
131.41
129.26
129.18
128.72
128.54
128.08
127.86
127.74
127.45
126.83
126.29
126.02
125.68
53.93
21.22
21.09
200
150
100
50
0
[ppm]

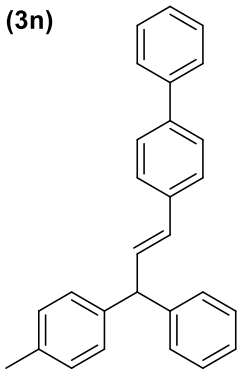
(3m)

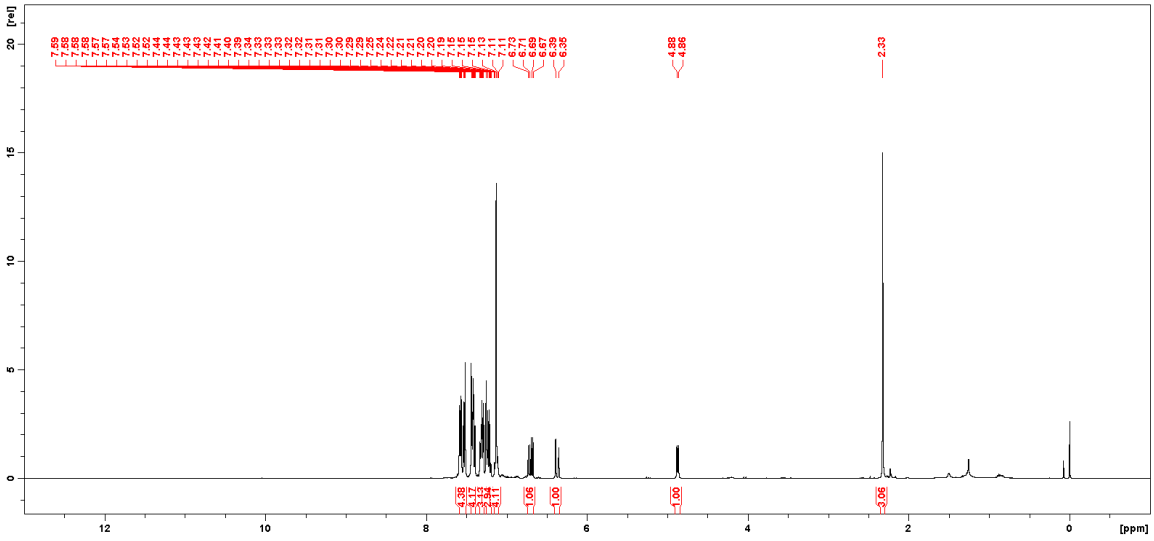


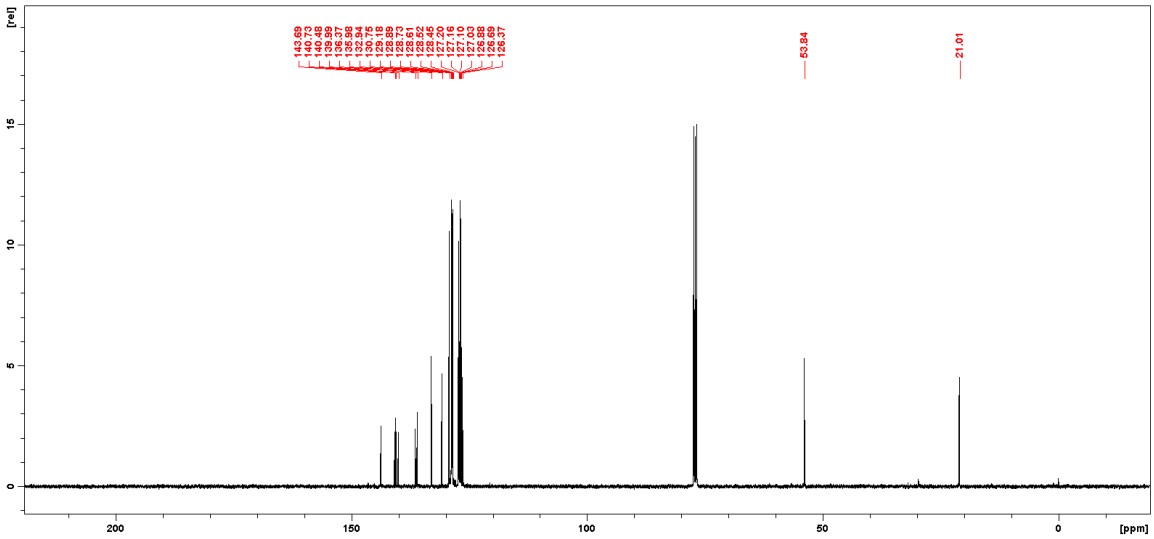

[rel]
7.38
7.37
7.35
7.35
7.33
7.32
7.32
7.30
7.30
7.28
7.27
7.27
7.26
7.25
7.24
7.24
7.23
7.22
7.22
7.21
7.21
7.20
7.20
7.19
7.18
7.18
7.18
7.12
6.69
6.67
6.65
6.63
6.38
6.32
4.86
4.84
2.32
2.11
5.02
0.99
1.02
0.59
1.00
3.06
[ppm]


[rel]
143.73
140.52
137.33
136.57
132.78
131.22
129.17
128.61
128.51
128.48
127.44
127.24
126.35
126.29
53.80
21.01
[ppm]

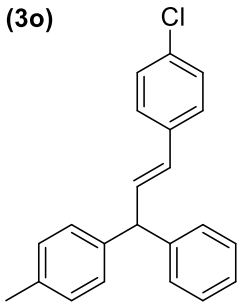
(3n)

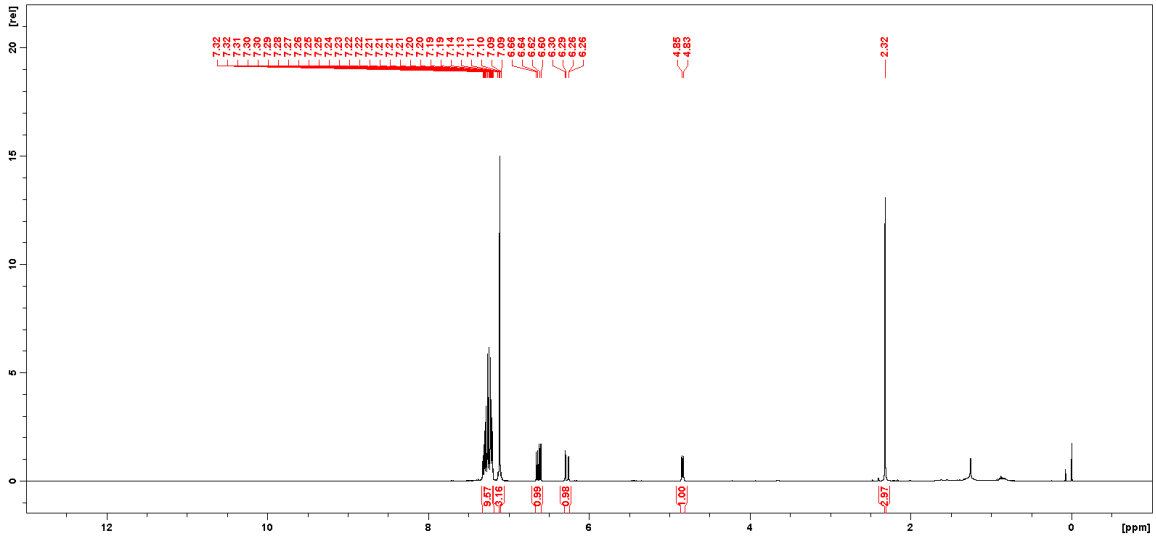


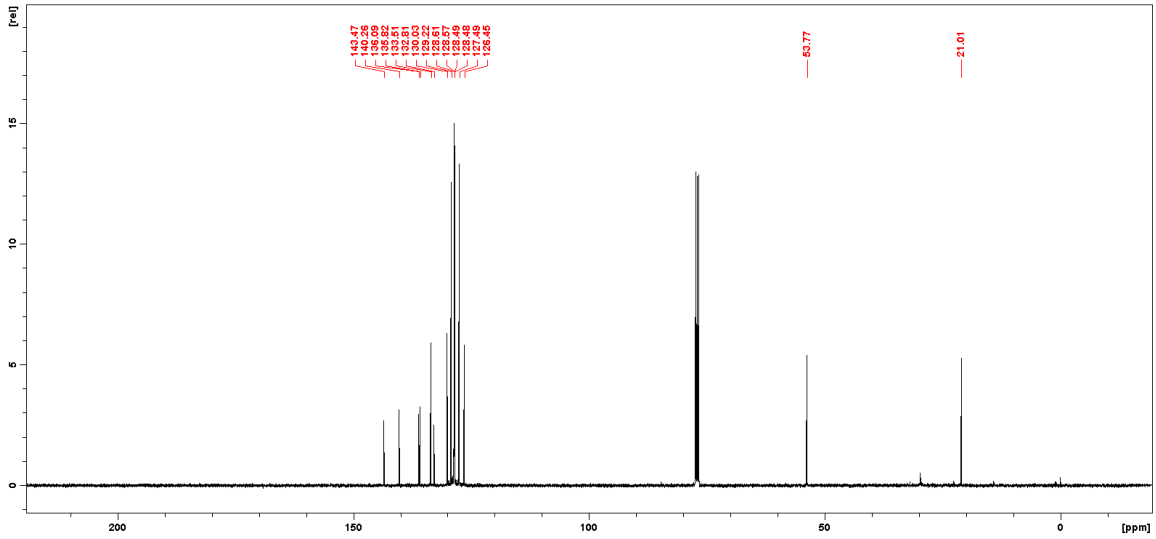

[rel]
20
15
10
5
0
12
10
8
6
4
2
0
[ppm]
4.88
4.86
2.33
4.38
4.12
3.13
3.04
3.11
1.06
1.00
1.00
3.06


[rel]
15
10
5
0
200
150
100
50
0
[ppm]
143.69
140.73
140.48
139.99
136.37
136.98
132.94
130.75
129.18
128.89
128.73
128.61
128.52
128.45
128.20
127.16
127.10
126.93
126.88
126.69
126.37
53.84
21.01

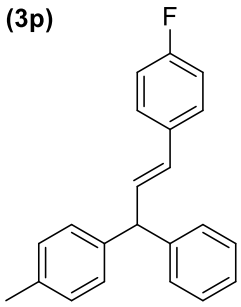
(3o)

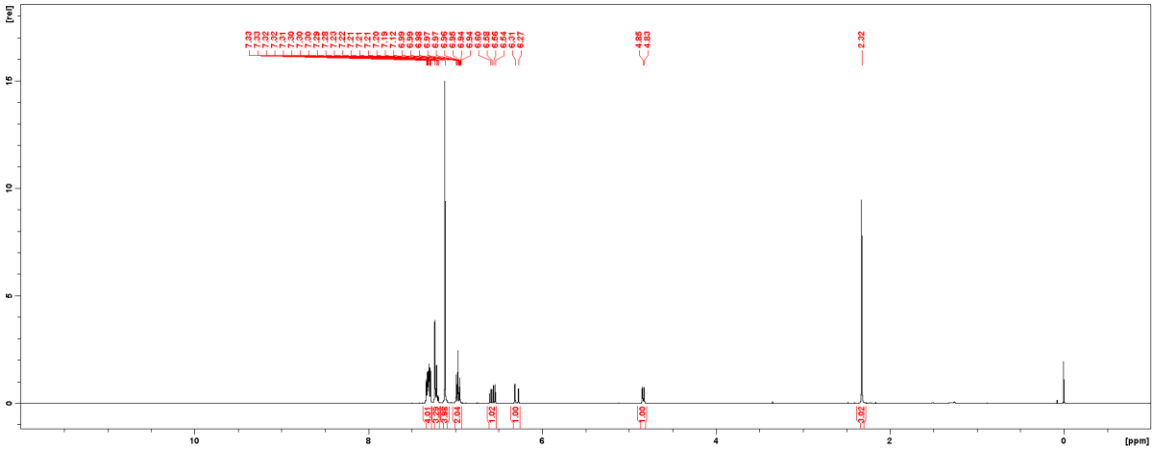

Cl

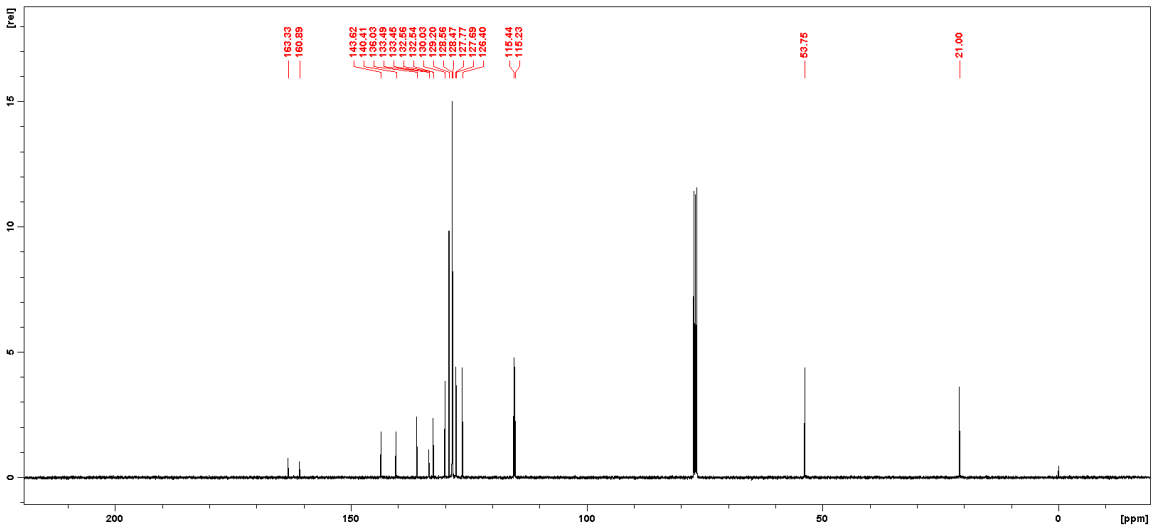

[rel]
7.32
7.32
7.31
7.30
7.30
7.29
7.28
7.27
7.27
7.26
7.25
7.25
7.24
7.23
7.22
7.22
7.21
7.21
7.21
7.21
7.20
7.20
7.19
7.19
7.14
7.13
7.11
7.10
7.09
7.09
6.66
6.64
6.62
6.60
6.30
6.29
6.26
6.25
4.85
4.83
2.32
9.57
0.16
0.99
0.98
1.00
2.97
[ppm]


[rel]
143.47
140.26
136.69
136.62
133.51
132.81
130.03
129.22
128.61
128.57
128.49
128.48
127.49
126.46
53.77
21.01
[ppm]

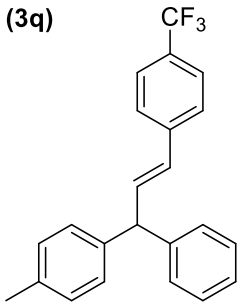
(3p)

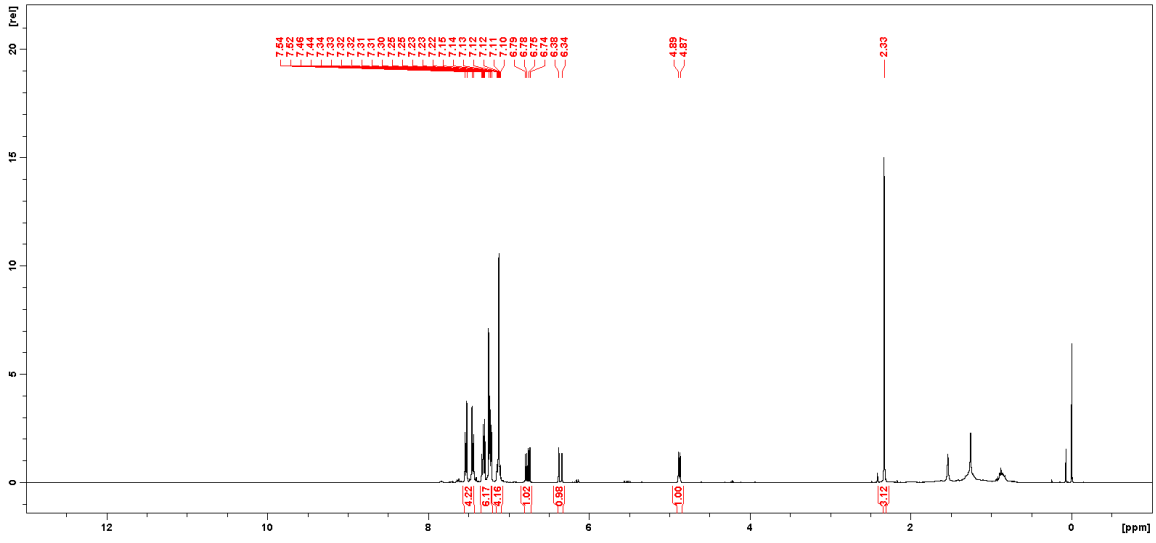

F

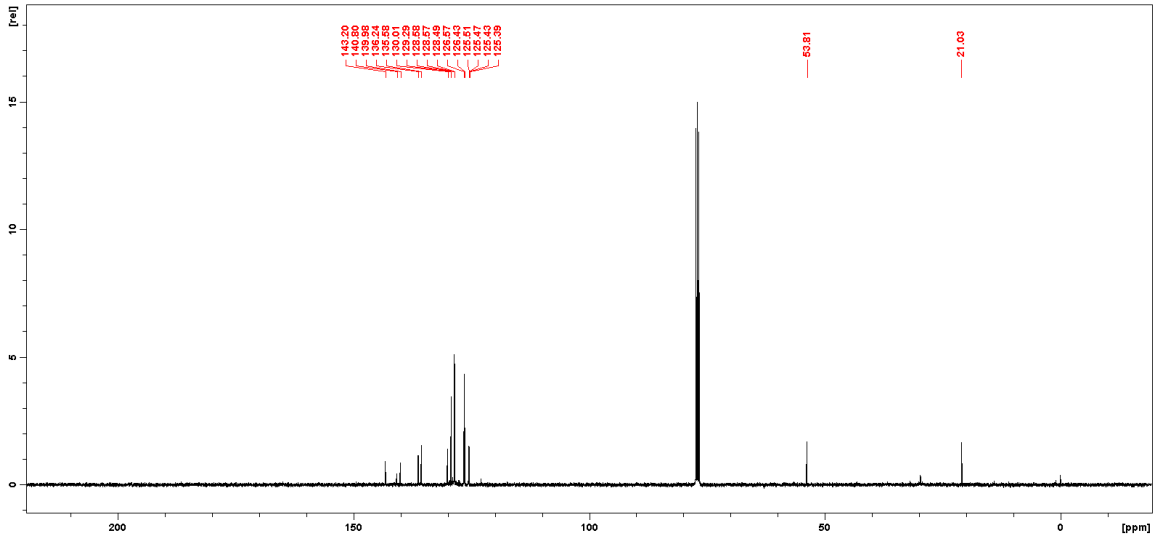

[rel]
[ppm]
2.32


[rel]
[ppm]
163.33
160.89
143.62
140.41
138.03
133.46
133.45
132.56
132.54
130.03
129.20
128.56
128.47
127.77
127.69
126.40
115.44
115.23
53.75
21.00

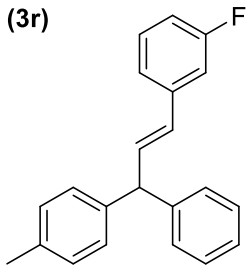
(3q)

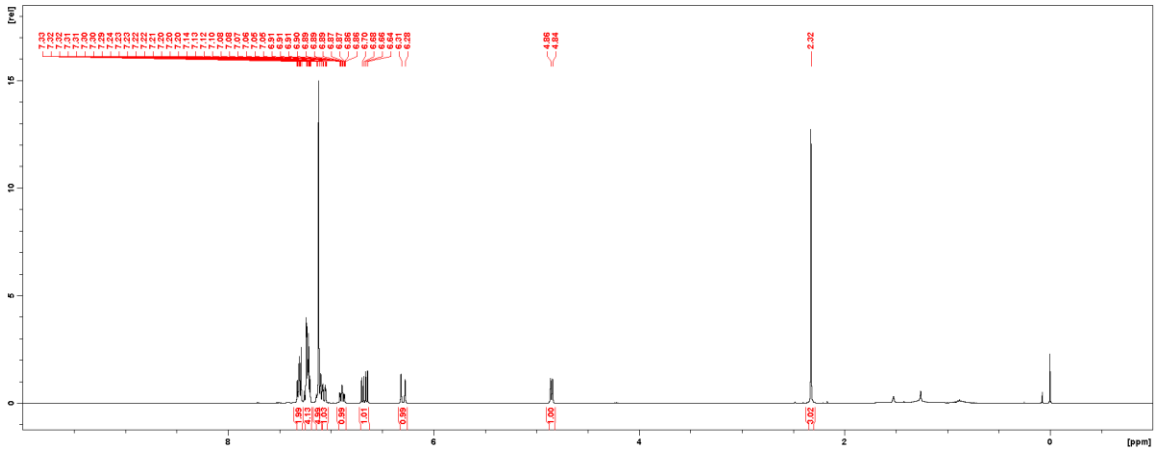

CF3

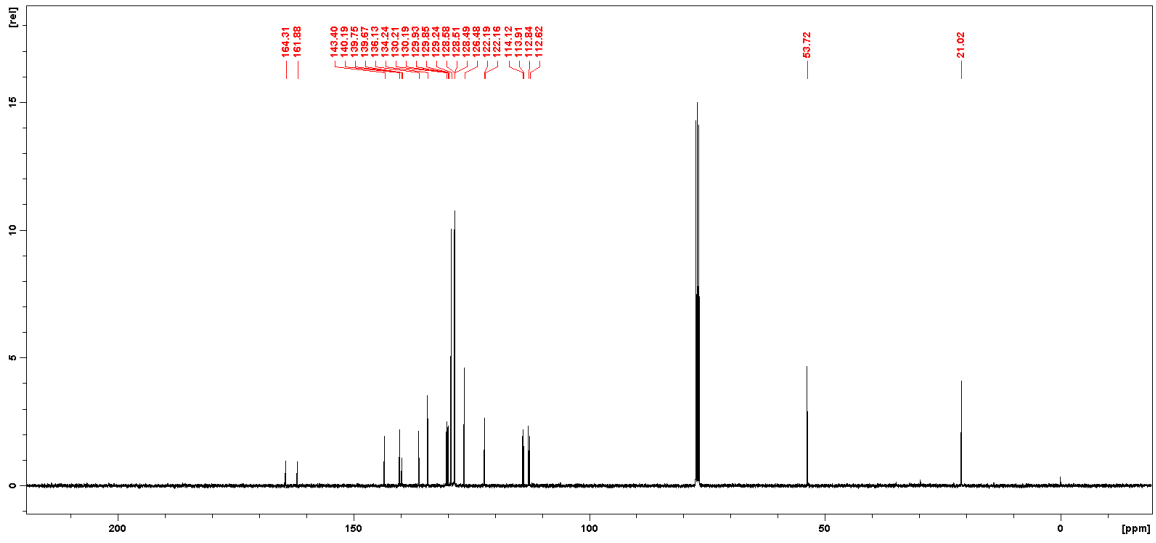

7.64
7.62
7.46
7.45
7.44
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.26
7.25
7.23
7.23
7.22
7.15
7.14
7.13
7.12
7.12
7.11
7.10
6.79
6.78
6.75
6.74
6.38
6.34
4.89
4.87
2.33
4.22
6.17
6.16
1.02
0.98
1.00
3.12
[rel]
[ppm]


143.20
140.80
139.98
136.24
135.68
130.01
129.29
128.69
128.57
128.49
126.67
126.43
125.51
125.47
125.43
125.39
53.81
21.03
[rel]
[ppm]

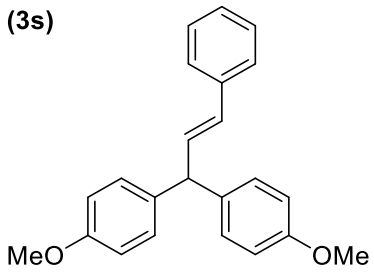
(3r)

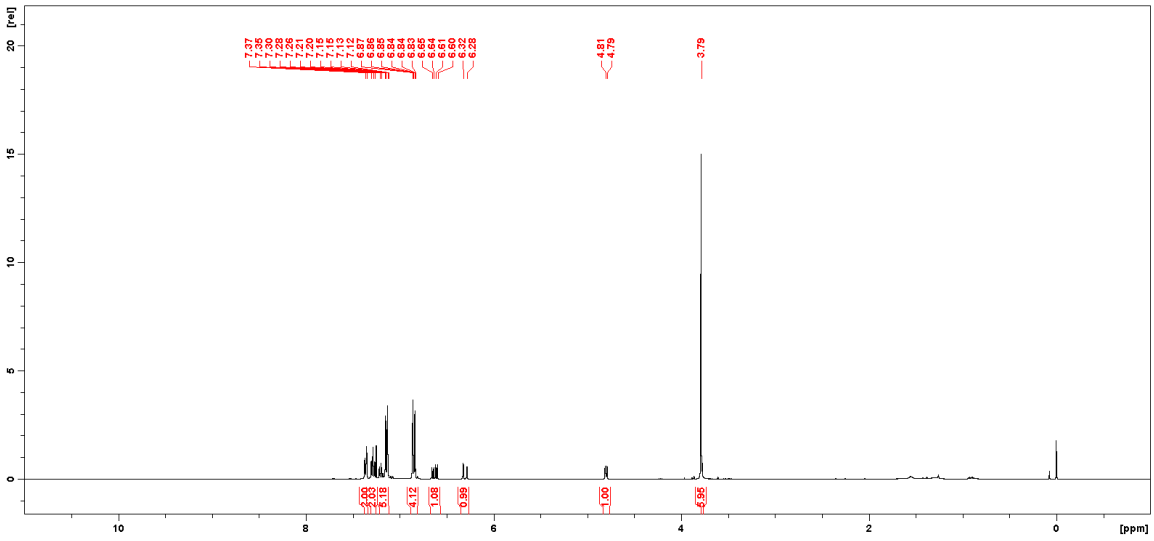

F

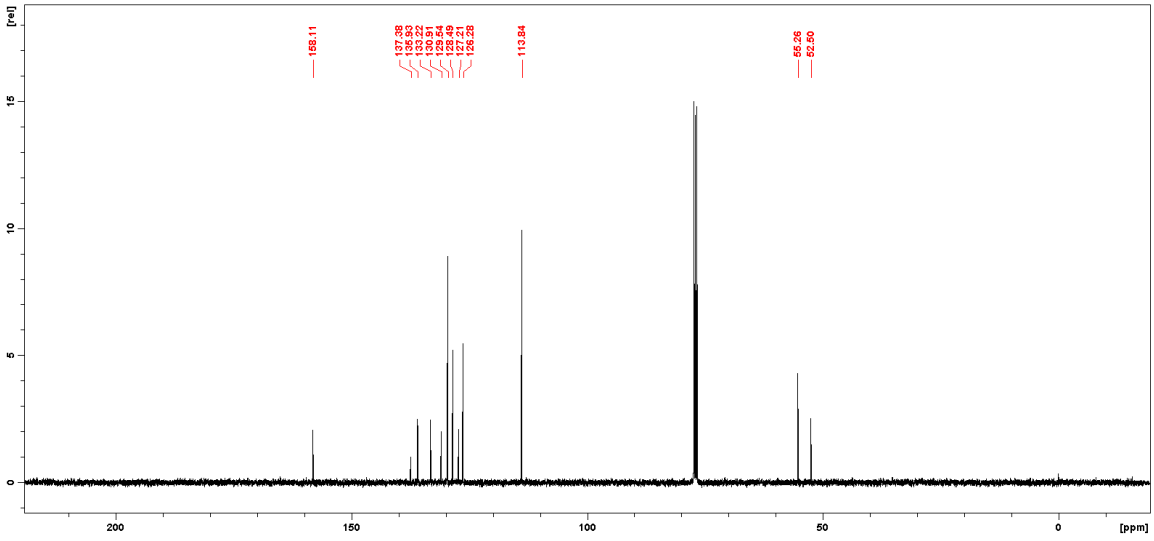

[rel]
[ppm]
2.32


[rel]
[ppm]
164.31
161.88
143.40
140.19
139.75
139.67
136.13
134.24
130.21
130.19
129.53
129.24
128.89
128.61
128.49
126.48
122.19
122.15
114.12
113.91
112.84
112.62
53.72
21.02

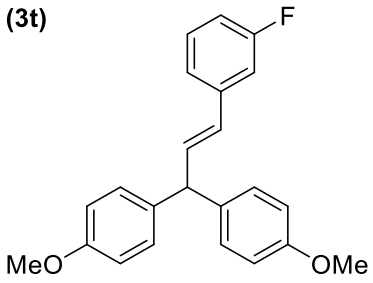
(3s)

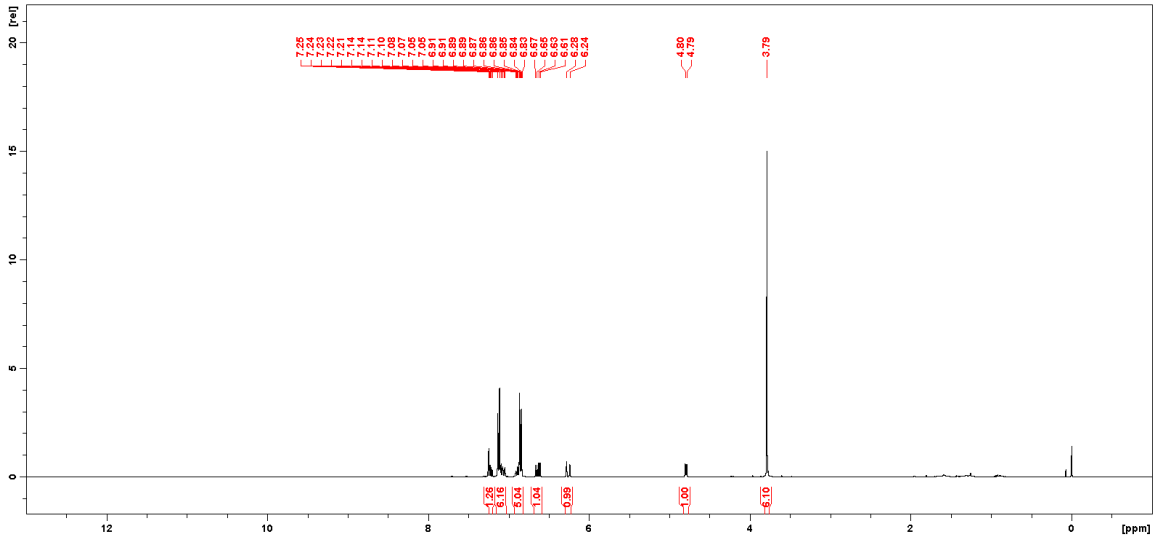

MeO
OMe

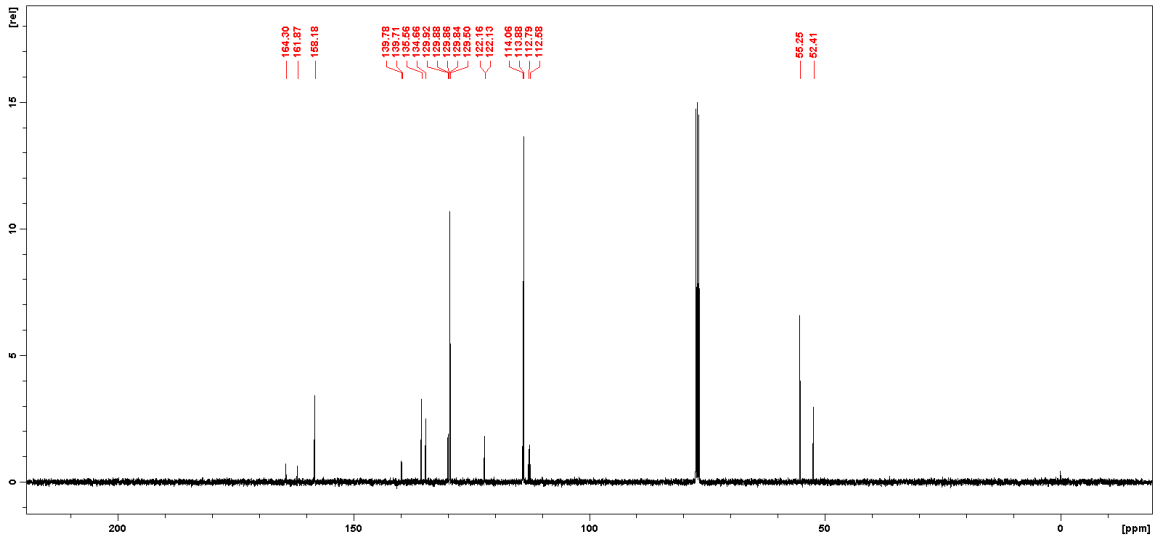

[rel]
7.37
7.35
7.30
7.28
7.26
7.21
7.20
7.15
7.15
7.13
7.12
6.87
6.86
6.86
6.84
6.84
6.83
6.65
6.64
6.61
6.60
6.32
6.28
4.81
4.79
3.79
2.00
2.10
3.19
4.12
1.08
0.99
1.00
6.55
[ppm]


[rel]
158.11
137.38
135.93
133.22
130.51
129.54
128.49
127.21
126.28
113.84
55.26
52.50
[ppm]

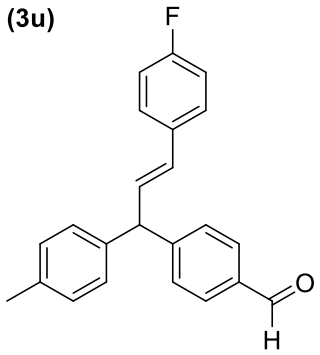
(3t)

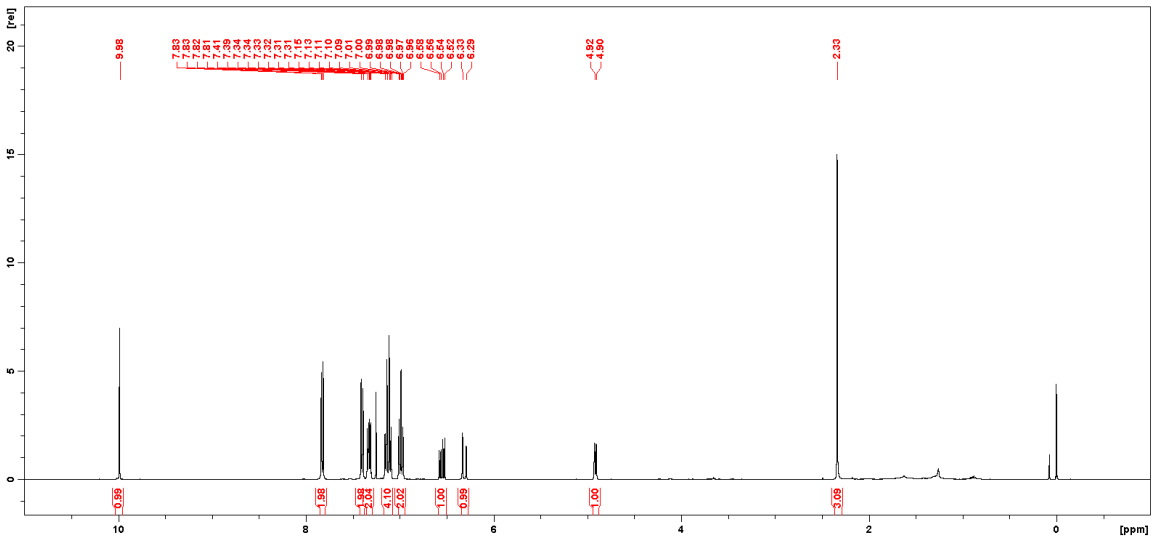

F
MeO
OMe

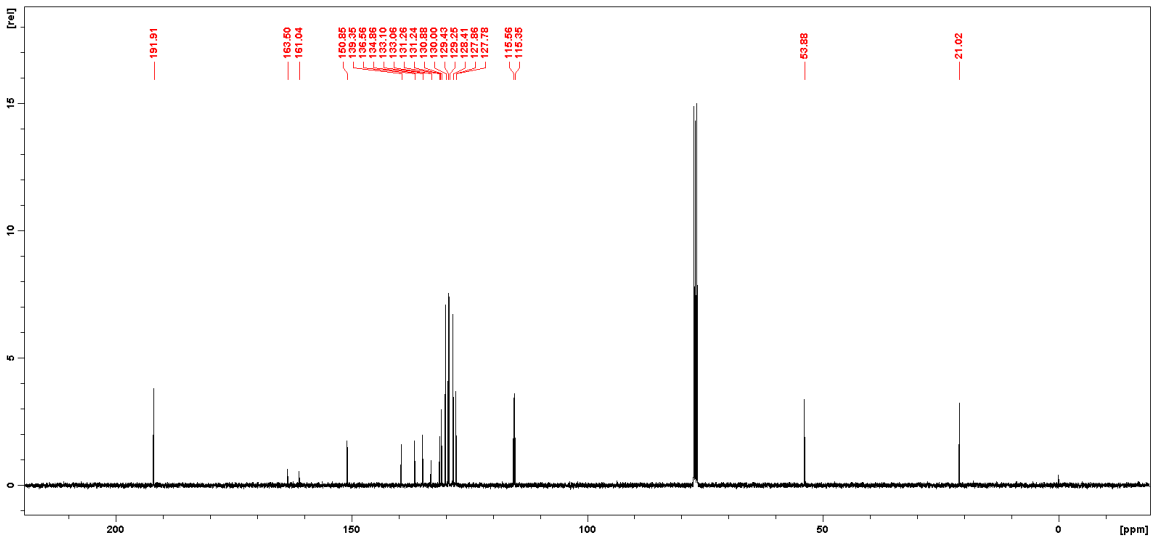

[rel]
20
15
10
5
0
7.25
7.24
7.23
7.22
7.21
7.14
7.11
7.10
7.08
7.07
7.06
7.05
6.91
6.91
6.89
6.89
6.87
6.86
6.86
6.85
6.84
6.83
6.67
6.65
6.63
6.61
6.23
6.24
4.80
4.79
3.79
1.28
6.16
5.04
1.04
0.99
1.00
6.10
12
10
8
6
4
2
0
[ppm]


[rel]
15
10
5
0
164.30
161.87
158.18
139.78
139.71
135.56
134.66
134.62
129.88
129.86
129.84
129.50
122.16
122.13
114.06
113.88
112.79
112.68
55.25
52.41
200
150
100
50
0
[ppm]

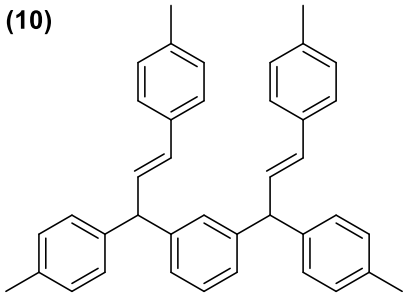
(3u)

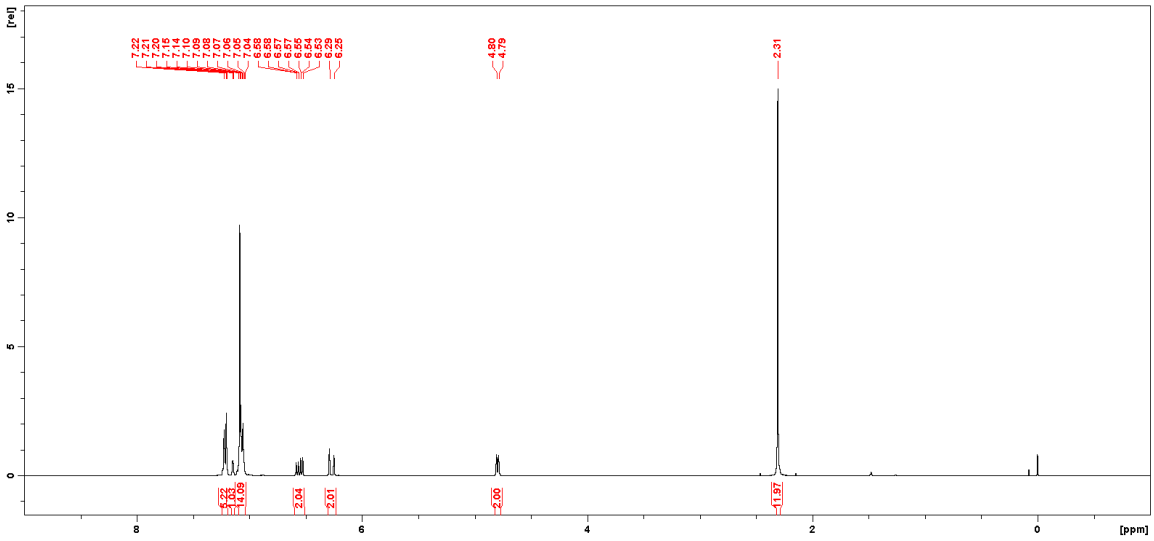

F
O
H

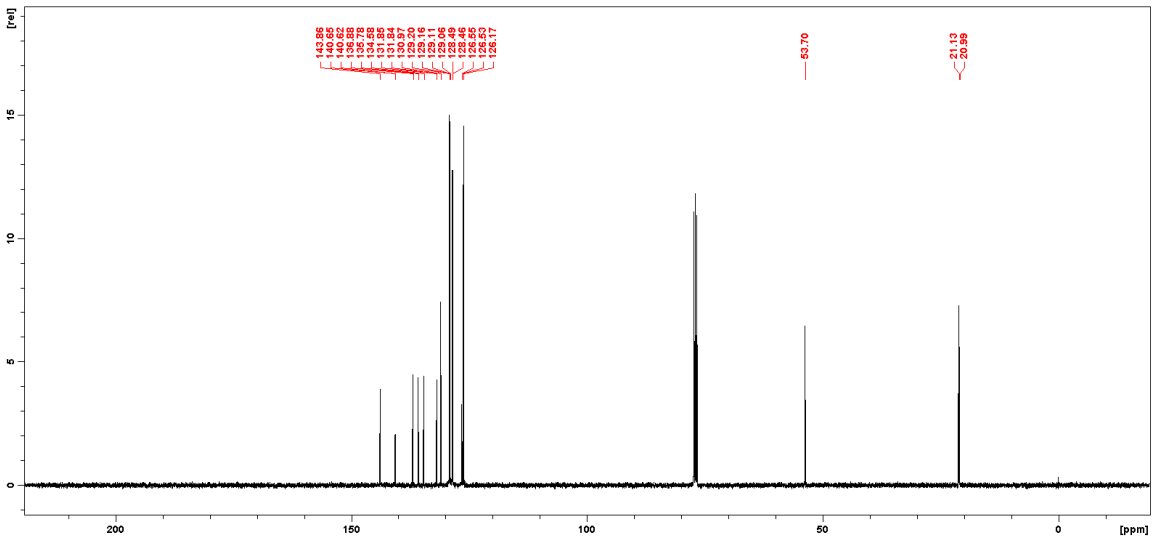

[rel]
9.98
7.83
7.83
7.82
7.81
7.41
7.39
7.34
7.34
7.33
7.32
7.31
7.31
7.15
7.13
7.11
7.10
7.09
7.01
7.00
6.99
6.98
6.97
6.96
6.56
6.56
6.54
6.52
6.33
6.29
4.92
4.90
2.33
0.99
1.98
1.04
1.04
4.16
2.02
1.00
0.99
1.00
3.09
[ppm]


[rel]
191.91
163.50
161.04
160.95
139.35
136.56
134.86
134.10
133.06
131.26
131.24
130.88
130.00
129.43
128.25
128.41
127.96
127.78
115.56
115.35
53.88
21.02
[ppm]

(10)




[rel]
7.22
7.21
7.20
7.15
7.14
7.10
7.09
7.08
7.07
7.06
7.05
7.04
6.69
6.68
6.67
6.67
6.65
6.54
6.53
6.53
6.29
6.25
4.80
4.79
2.31
4.22
4.09
2.04
2.01
2.00
11.97
[ppm]


[rel]
143.86
140.65
140.42
136.88
135.78
134.68
131.95
131.84
130.97
129.30
129.16
129.11
128.96
128.49
128.46
126.65
126.63
126.17
53.70
21.13
20.99
[ppm]