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Development of Novel Synthetic Methods Utilizing Group III and IV Reagents

Gang Dong
University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a dissertation written by Gang Dong entitled "Development of Novel Synthetic Methods Utilizing Group III and IV Reagents." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

George W. Kabalka, Major Professor

We have read this dissertation and recommend its acceptance:

Richard M. Pagni, Ziling (Ben) Xue, Engin Serpersu

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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Anne Mayhew
Vice Chancellor and
Dean of Graduate Studies

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Development of Novel Synthetic Methods Utilizing Group III and IV Reagents

A Dissertation
Presented for the
Doctor of Philosophy
Degree

The University of Tennessee, Knoxville

Gang Dong
May 2005

DEDICATION

This dissertation is dedicated to my beloved wife Chunlan Chen for her constant support and endless love; to my son Ziqing Dong for his infinite curiosity that inspires me to keep studying and the happiness he brings to my life; to my respected parents Guangju Dong and Mincai Li for their understanding and patience; and my parent-in-laws Haozhou Chen and Aizhen Zhou for their encouragement and support.

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Most importantly, I would like to thank my wife, Chunlan Chen, for her love, support, patience and encouragement. I would also like to thank my sister-in-law and brother-in-law for their constant support and understanding.

ABSTRACT

This dissertation summarizes the development of novel synthetic methods involving Group III & IV reagents. These newly discovered reactions include the rhodium-catalyzed direct cross-coupling of allylic alcohols with aryl- and vinylboronic acids; palladium-catalyzed coupling reaction of Baylis-Hillman acetate adducts with both potassium organotrifluoroborate reagents and organosiloxanes; efficient syntheses of functionalized allylmetals such as allylboranes, allylsilanes, and allylgermanes; application of allylboranes to the synthesis of homoallylic alcohols; syntheses of 4-(1-alkynyl)-2(5H)-furanones and coumarins; utilization of potassium alkynyltrifluoroborates in the synthesis of conjugated enediynes; and application of potassium alkynyltrifluoroborates as reagents in the Petasis reaction.

The new synthetic methodologies involving Group III & IV reagents developed in this dissertation are important transformations in modern organic synthesis. Mild reaction conditions and a tolerance for various organic functional groups are advantages of these methodologies. The ability to recycle the catalytic system in some cases is another attractive feature for ionic liquids-involved methods.

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LISTS OF SYMBOLS AND ABBREVIATIONS

AcOH	Acetic acid
$AlCl_3$	Aluminum chloride
aq	Aqueous
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
BF_3	Boron trifluoride
BF_3K	Potassium trifluoroborate
B-H	Baylis-Hillman adduct
$BmimBF_4$	1-Butyl-3-methylimidazolium tetrafluoroborate
BmimBr	1-Butyl-3-methylimidazolium bromide
$BmimPF_6$	1-Butyl-3-methylimidazolium hexafluorophosphate
brs	Broad peaks
Bu	Butyl
n-BuBr	*n*-Butyl bromide
n-BuLi	*n*-Butyl lithium
n-Bu_4NF	Tetrabutylammonium fluoride
n-Bu_4NI	Tetrabutylammonium iodide
t-Bu	*tert*-Butyl
^oC	Degree Celsius
^{13}C nmr	Carbon-13 nuclear magnetic resonance
$CDCl_3$	Chloroform-*d*
CH_2Cl_2	Methylene chloride

CN	Nitrile group
Cs_2CO_3	Cesium carbonate
CuI	Cuprous iodide
$Cu(OAc)_2$	Copper(II) acetate
d	Doublet
DABCO	1,4-Diazabicyclo[2,2,2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
δ	Symbol of chemical shift
DMF	Dimethyl formide
d_6 DMSO	Deuterized dimethylsulfoxide
dppf	Diphenylphosphinoferrocene
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
^{19}F nmr	Fluorine-19 nuclear magnetic resonance
g	Gram
GC	Gas Chromatography
^{1}H nmr	Proton nuclear magnetic resonance
Hg	Mercury
H_2O	Water
h	Hour
Hz	Hertz
J	Proton-proton coupling constant

K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KHF_2	Potassium hydrogenfluoride
m	Multiplet
Me	Methyl
MeOH	Methanol
Me_3Si	Trimethylsilyl
mg	milligram
Mg	Magnesium
$MgSO_4$	Magnesium sulfate
min	Minutes
ml	Mililiter
mmol	Milimole
MMP	Matrix metalloproteinase
mp	Melting point
MS	Mass Spectroscopy
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
NLO	Non-Linear Optics
NMR	Nuclear magnetic resonance spectroscopy
[O]	Oxidation
OAc	Acetoxy
PAHs	Polycyclic aromatic hydrocarbons

$P(t\text{-}Bu)_3$	Tri-*tert*-butylphosphine
Pd	Palladium
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(OAc)_2$	Palladium acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphino)dichloropalladium(II)
PEG	Polyethlene glycol
Ph	Phenyl
PPh_3	Triphenylphosphine
R	Alkyl
$RhCl_3$	Rhodium chloride
rt	Room temperature
s	Singlet
$Sc(OTf)_3$	Scandium triflate
Si	Silicon
SiO_2	Silica gel
Sn	Tin
t	Triplet
TBAF	Tetrabutylammonium fluoride
tol	*p*-tolyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography

TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
UV	Ultraviolet Spectroscopy

Part I. Reactions of Allylic Reagents

Chapter 1

Introduction

1.1.1 Allylation Reaction

Transition metal complexes, particularly Pd(0) complexes, are important in organic syntheses.[1] Reactions involving π-allylpalladium complexes are particularly important and their synthetic applications are the subject of Part I of this dissertation.

1.1.1.1 Allylation of Nucleophiles

Formation of π-allylpalladium complexes by oxidative addition of various allylic compounds to Pd(0) and subsequent reaction of these complexes with soft carbon nucleophiles are the basis of catalytic allylation. After a reaction involving π-allylpalladium complex, Pd(0) is regenerated, which then undergoes an oxidative addition to another allylic compound. Consequently the reaction is catalytic (Figure 1-1-1). Similarly, hard carbon nucleophiles in organometallic compounds of main group metals are allylated with π-allylpalladium intermediates. The reaction proceeds via transmetallation.

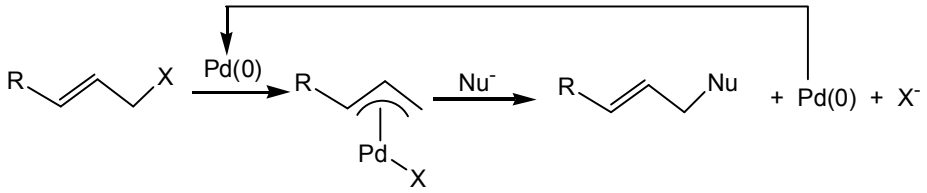


Figure 1-1-1: Catalytic cycle.

The efficient catalytic cycle is ascribed to the fact that Pd(0) is more stable than Pd(II). In addition to palladium, other transition metal complexes, such as those of molybdenum[2], rhodium[3] and other metals, are used for catalytic allylation. Several other catalytic transformations of allylic compounds utilizing π-allylpalladium intermediates are possible and they are summarized in Figure 1-1-2.

A number of allylic leaving groups shown in Figure 1-1-3 are cleaved by Pd catalysts. Generally, allylic esters are used most frequently as substrates for the catalytic reactions.

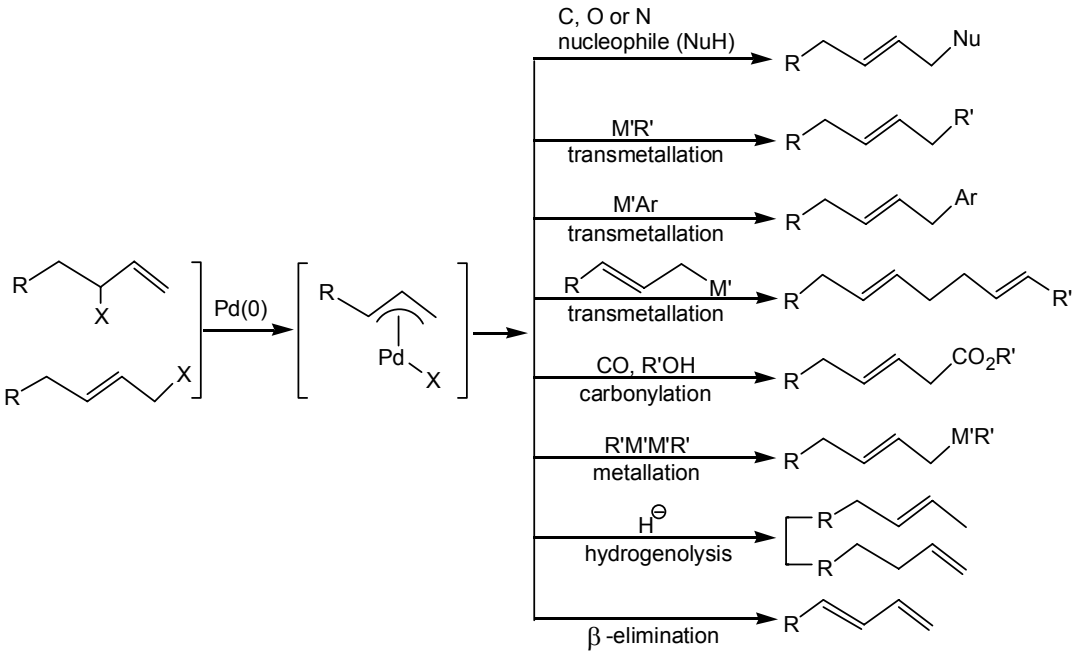


Figure 1-1-2: Pd-catalyzed reactions of allylic compounds.

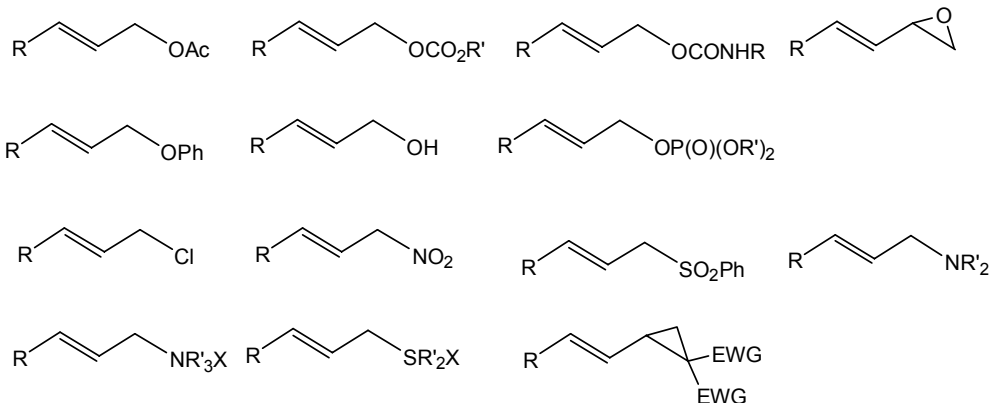


Figure 1-1-3: Allylic compounds used for Pd-catalyzed reactions

1.1.1.2 Stereochemistry of Pd-Mediated Allylation Reaction

The stereochemistry of the Pd-mediated, or catalyzed, allylation of nucleophiles has been studied extensively.[4-6] In the first step, formation of the π-allylpalladium complex by the attack of Pd(0) on an allylic acetate proceeds by inversion (*anti* attack). Subsequent reaction of soft carbon nucleophiles such as nitrogen and oxygen nucleophiles gives product by inversion. Thus overall retention is observed. However, transmetallation of π-allylpalladium with hard carbon nucleophiles such as organometallic compounds afford configuration-retained intermediates, and the final products are obtained by reductive elimination, which involves retention. Thus an overall inversion is observed in these cases (Figure 1-1-4).[7, 8]

Pd-catalyzed reactions of nucleophiles with substituted π-allyl systems usually occur at the less substituted side with high regioselectivity, although some exceptions are known. For example, using a modified Wilkinson complex, the quaternary substituted product is obtained as a main product from a tertiary allylic carbonate (Figure 1-1-5).[9]

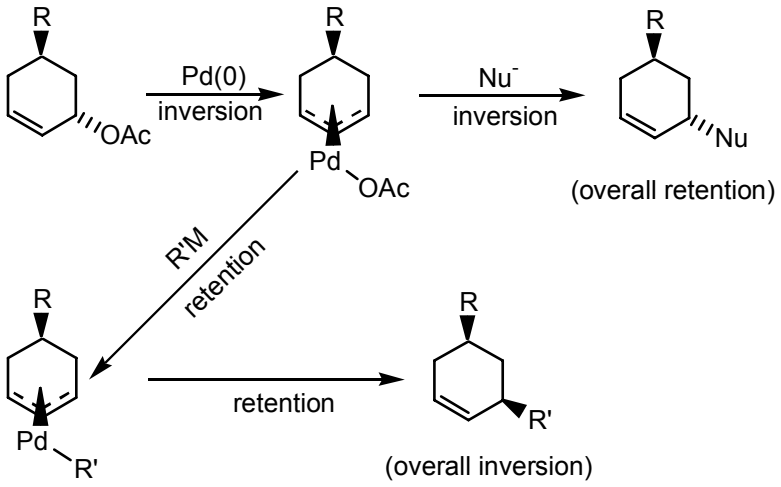


Figure 1-1-4: Stereochemistry of allylation reaction.

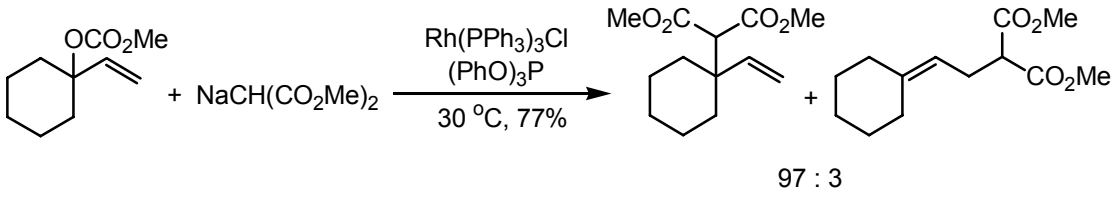


Figure 1-1-5: Formation of a quaternary carbon.

1.1.1.3 Allylation *via* Transmetallation

Cross-coupling of allylic compounds can also occur by transmetallation between π-allyl intermediates and organometallic compounds of Mg, Zn, B, Al, Si and Sn followed by reductive elimination of the metal.

Reactions of an allylic dithioacetal with MeMgBr in the presence of a Ni catalyst affords alkenes bearing a *tert*-butyl group.[10] In this reaction, generation of the π-allylnickel intermediate by oxidative addition and subsequent transmetallation with MeMgBr affords **A** (Figure 1-1-6)**.** Then the methylated product **B** is formed by reductive elimination, and finally the dimethylated product **C** is formed by a sequence of similar reactions.

Coupling of allyl bromide with tolylboronic acid proceeds smoothly with a ligandless Pd catalyst (Figure 1-1-7).[11] The reaction of an allylic carbonate with vinylstannane in aqueous DMF at room temperature with ligandless Pd catalyst gives the 1,4-diene in high yield (Figure 1-1-8).[12] Also, the reaction of PhZnCl with an allylic lactone produces 3-phenylcyclohexene with inversion, as expected (Figure 1-1-9).[7]

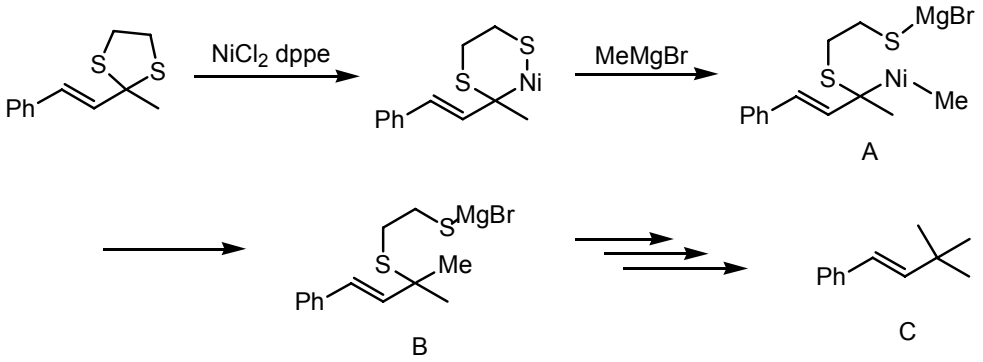


Figure 1-1-6: Ni-catalyzed allylation reaction of Grignard reagent.

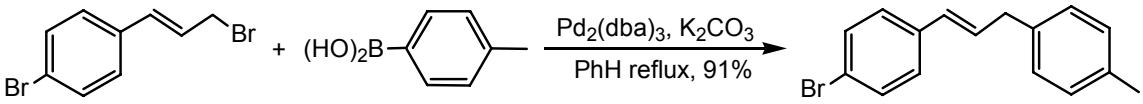


Figure 1-1-7: Pd-catalyzed allylation reaction of boron reagent.

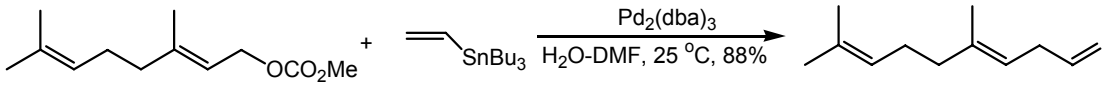


Figure 1-1-8: Pd-catalyzed allylation reaction of tin reagent.

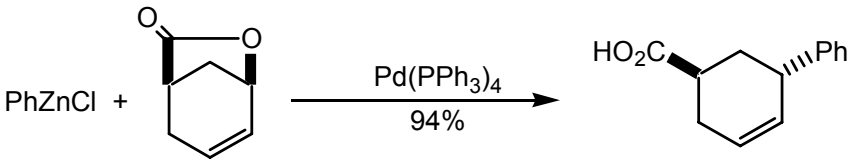


Figure 1-1-9: Pd-catalyzed allylation reaction of zinc reagent.

1.1.2 Boronic Esters or Acids in Transition-Metal Catalyzed Reactions

Cross-coupling reactions, now accessible via a variety of organometallic reagents, provide fundamental synthetic methods (Figure1-1-10). In 1972, Kumada and Tamao[13] and Corriu[14] independently reported that the reaction of organomagnesium reagents with alkenyl or aryl halides is catalyzed by Ni(II) complex. Kochi[15] reported that Fe(III) could be used for cross-coupling Grignard reagents with 1-halo-1-alkenes and that Li_2CuCl_4 catalyzed the coupling of haloalkanes. The palladium catalyzed reaction of Grignard reagents was first reported by Murahashi[16], the synthetic utility of which was then demonstrated by Negishi[17] using the reactions of organic derivatives of aluminum, zinc, and zirconium. After these discoveries, many other organometallic reagents have proven to be highly useful as nucleophiles for cross-coupling reactions, e.g., organolithium by Murahashi,[18] organostannane by Migita[19] and Stille,[20] 1-alkenylcopper(I) by Normant,[21] organosilicon by Hiyama.[22]

Organoboron compounds are highly electrophilic but the organic groups on boron are weakly nucleophilic which limits the use of organoboron reagents in ionic reactions. The coordination of a negatively charged base to the boron atom is an efficient method for increasing nucleophilicity of the remaining organic group on boron.[23] However, intermolecular transfer reactions analogous to the Grignard-like reaction are relatively rare. Fortunately, organoboron compounds, even organoboronic acids and esters, have

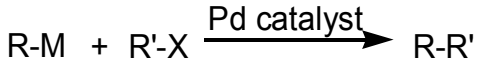


Figure 1-1-10: Cross-coupling of organometallic reagents.

sufficient reactivity for transmetallation to other metals. Transmetallations to silver(I),[24] magnesium(II),[25] zinc(II),[26] aluminum(II),[27] tin(IV),[28] copper(I),[29] and mercury(II)[30] halides have been extensively studied. In 1978, Negishi reported that iodobenzene selectively couples with the 1-alkynyl group on lithium l-hexynyl(tributy1)borate through a palladium-catalyzed addition-elimination sequence (Heck-type process).[17i] The cross-coupling of organoboron compounds, which involving transmetallation to palladium(II) halides as a key step, was found to proceed smoothly only when activated by base. This reaction has proven to be quite general for a wide range of selective carbon-carbon bond forming reactions[31]

Although a variety of organometallic reagents undergo cross-coupling reactions, much attention has been focused on the use of organoboronic acids for coupling since they are generally thermally stable and inert to both water and oxygen, thus they can be handled without special precautions.

Over the past twenty years, the palladium-catalyzed coupling of aryl-, vinyl-, alkyl-, and alkynylboron reagents (including boranes, boronic esters and boronic acids) with aryl, alkyl and vinyl bromides, iodides and triflates has been studied extensively.[32] Rather surprisingly, few studies[33] on the use of organoboron reagents as nucleophiles in palladium-catalyzed allylic reactions have been reported. In 1982, Suzuki reported the coupling of alkenylboranes with 3,4-epoxy-1-butene.[34] In 1984, his group applied an intramolecular coupling reaction of allyl halides with an alkenylborane as the key step to successfully synthesize humulene.[35] Allyl phenoxides,[33a] allyl acetates,[36] allyl carbonates,[37] and allyl phosphates[38] have also been utilized in the coupling reaction with organoborane reagents. Two recent articles initiated a breakthrough in this field. The first

one[33b] reported the coupling of arylboronic acids with allyl bromides under basic conditions in refluxing benzene (58 - 91% yield), while the second one[33c] described the reaction of phenylboronic acid with allylic acetates under basic conditions in water at room temperature using a resin-supported palladium catalyst (45-99% yield). Later, Balme extended the reaction utilizing various Pd catalytic systems and solvents.[39]

1.1.3 Potassium Organotrifluoroborates

Many of the recent studies on the Suzuki coupling reaction have focused on metal ligand systems that facilitate cross coupling and expand its scope.[40, 41] Much less effort has been concentrated on expanding the range of the organoboron coupling partner, which should be an equally rewarding endeavor.

1.1.3.1 Preparation of Potassium Organotrifluoroborates

Organotrifluoroborate salts or, more generally, compounds of formula $[R_nBF_{4-n}]^-$ ($n \leq 3$), have been mere laboratory curiosities until recently in 1940, when Fowler and Kraus[42] described the preparation of tetraalkylammonium triphenylfluoroborates by reaction of the triphenylborane-ammonia complex with one equivalent of tetraalkylammonium fluoride. Trifluoroborate salts, particularly those having potassium as the counterion, were studied in the early 1960s. Interest in these systems was motivated by the formation of stable perfluoroalkylated boron derivatives. Trivalent boron compounds bearing a fluorine atom at an α or β position proved to be very unstable (migration of the fluorine from carbon to boron occurs), which is not the case with

potassium organotrifluoroborates. The first such salt, potassium trifluoromethyltrifluoroborate, was prepared by Chambers *et al*.[43] from trifluoromethyltrimethylstannane (Figure 1-1-11-i, R = CF_3).

Following the preliminary results obtained by Thierig and Um-land,[44] Vedejs *et al*.[45] showed that hydroxyl ligands of arylboronic acids could be displaced with potassium hydrogen difluoride (KHF_2), thereby leading to potassium aryltrifluoroborates (Figure 1-1-11-ii). However, treatment of arylboronic acids with aqueous KHF_2 resulted in the instantaneous deposition of a voluminous precipitate of the potassium aryltrifluoroborate. A slight modification of the original procedure[45] allowed the synthesis of potassium aryltrifluoroborates in almost quantitative yields and in analytically pure form (Figure 1-1-12). After the addition of KHF_2, the solvents were removed in vacuo and the remaining solid was extracted with acetone. KHF_2 and other salts (KBF_4, KF, etc.) are insoluble in acetone; hence, on removal of the solvent from the extracts, very pure compounds were obtained. Where necessary, the product could be purified by re-precipitation from an acetone/diethyl ether mixture. This procedure proved to be very general and was used for the isolation and purification of all potassium organotrifluoroborates described in this thesis.[46]

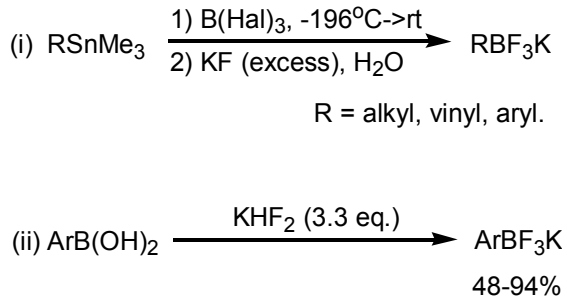


Figure 1-1-11: Preparation of potassium organotrifluoroborates.

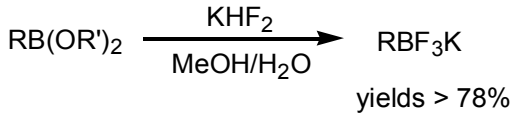


Figure 1-1-12: Modified method.

Potassium aryltrifluoroborates can also be prepared directly from aryl bromides by a sequence of classical bromine-lithium exchange, boronation, and *in situ* treatment with aqueous KHF_2 (Figure 1-1-13), without having to isolate the intermediate boronic acid derivative.

In the same way, treatment of readily available alkenylboronic acids or esters[47] with KHF_2 affords the corresponding potassium alkenyltrifluoroborates in high yields. Potassium hydrogen difluoride is sufficiently reactive to cleave the boron-oxygen bonds in boronic esters. Potassium alkenyltrifluoroborates can also be prepared directly from alkynes through hydroboration followed by oxidation with acetaldehyde and *in situ* treatment with KHF_2.

1.1.3.2 Application of Potassium Organotrifluoroborates in Transition Metal-Catalyzed Cross-Coupling Reactions

In addition to their air stability, the greater nucleophilicity[48] of the organic moiety in the potassium trifluoroborates compounds compared to the corresponding organoboranes and organoboronic acid derivatives makes the fluoroborates potentially valuable starting materials for palladium-catalyzed cross coupling reactions.

In 1997, Genêt *et al* first reported the cross-coupling reaction of potassium organotrifluoroborates with arenedizaonium salts in the presence of a palladium

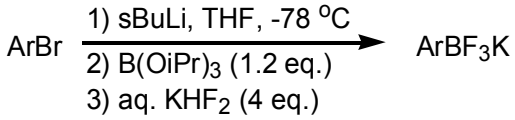


Figure 1-1-13: Preparation from arylbromides.

catalyst.[46] This demonstrated that potassium organotirfluoroborates were suitable substrates in palladium-catalyzed reactions. The coupling of potassium organotrifluoroborates with diaryliodonium salts was later discovered by Chen.[49] It is noteworthy that base was not required in either of these reactions.

Although Fu reported that potassium aryltrifluoroborates are reluctant to couple to aryl halides,[50] Molander has successfully demonstrated that aryl-, alken-1-yl-, alkyl-, and alkyn-1-yltrifluoroborates all participate efficiently in palladium-catalyzed cross-coupling reactions with aryl halides and triflates.[51]

Transition metal-catalyzed formation of carbon heteroatom bonds has emerged as a powerful tool in organic synthesis.[52] It was simultaneously shown by Chan and Evans that cross-coupling between arylboronic acids and phenols was efficiently mediated by copper salts.[53] In this reaction, stoichiometric amounts of base and $Cu(OAc)_2$ are necessary in order to achieve high yields of biaryl ethers. Very recently, Batey has described a procedure for copper(II)-catalyzed etherification with potassium organotrifluoroborates as coupling partners.[54]

1.1.4 Ionic Liquids

Environmentally cleaner technologies have become a major area of interest throughout both industry and academia. The search for alternatives to hazadous solvents has become a high priority. Recently ionic liquids have been proposed as promising solvents for "clean process" and "green chemistry".[55, 56] These two catchwords reflect current efforts to drastically reduce the amounts of solvent and catalyst consumption in chemical processes. The use of ionic liquids could make a contribution in this area, particularly with regard to solvent and catalyst usage.

1.1.4.1 History of Ionic Liquids

Ionic liquids are not new; they have been known for many years. For example, $[EtNH_3][NO_3]$, which has a melting point of 12 °C, was first described in 1914.[57] However, initial attempts describing transition-metal compounds as biphasic catalysis in quaternary ammonium ionic liquids were reported by Parshall in 1972.[58] In 1981, it was reported that ruthenium compounds in ionic liquids based on the tetrabutylphosphonium cation were able of catalyzing the hydrogenation of carbon monoxide to ethylene glycol at 220 °C.[59] At the beginning of the 1990s Chauvin showed that the oligomerization of olefins can be performed by nickel complexes in organoaluminate ionic liquids.[60-62] This Ziegler-Natta type reaction occurs in a typical biphasic catalytic system where the products are easily separated from the reaction mixture by simple decantation and the recovered catalyst solution can be reused several times without any significant changes in catalytic performance.

The advent of ambient-temperature, air- and water stable 1-butyl-3-methylimidazolium tetrafluoroborate and hexafluorophosphate ionic liquids, independently reported by Dupont[63] and Chauvin's group,[64] provided new impetus for the use of these materials as solvents for transition-metal catalyst precursors.

1.1.4.2 Ambient-temperature Air, and Water Stable Ionic Liquids

Simple quaternary ammonium and phosphonium halides, such as tetrabutylammonium bromide (mp 102-104 °C) and tetrabutylphosphonium bromide (mp 100-103 °C), can be used for dissolving transition-metal catalyst precursors. These ionic liquids are particularly suitable for reactions that operate at relatively high temperatures. Moreover, the use of these relatively high melting point ionic liquids allows one to pour off organic products from the catalyst medium at room temperature. However, since a great number of reactions involving transition metals occur under mild conditions, the use of ambient-temperature, air- and water-stable ionic liquids is preferred. Ambient-temperature, air- and water-stable ionic liquids can be obtained by the substitution of the halide anion of the 1,3-dialkylimidazolium cation by other "weakly" coordinating anions (Table 1-1-1).[65] Among the various ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate (bmimBF_4) and bmimPF_6 are the most popular and were used in the studies summarized in this thesis.[65d]

These ionic liquids have limited miscibility with various polar and nonpolar organic substrates and solvents, but they dissolve organometallic precursors based on rhodium, ruthenium, palladium, nickel, cobalt, and iron complexes. Moreover, due to their inherent ionic nature, ionic liquids can effectively stabilize cationic transition metal

Table 1-1-1: Melting point of room-temperature ionic liquids based on the 1-alkyl-3-methylimidazolium cation

R	X	M.P. (^{o}C)
Et	BF_4	15
n-Bu	BF_4	-81
Et	PF_6	60
n-Bu	PF_6	10
Et	$AlCl_4$	-80
n-Bu	$AlCl_4$	-88

species that are known to be more active than their neutral analogues.[66] Indeed, it was recently observed that Ni(I)[67] species or highvalent manganese-oxo compounds are easily stabilized in these media.

1.1.4.3 Synthesis of Room Temperature Ionic Liquids

Room temperature ionic liquids are easy accessible by the alkylation of commercially available methylimidazole with *n*-butylbromide which produces the corresponding 1-butyl- 3-methylimidazolium bromide; this is then followed by anion metathesis, as shown for bmimPF_6 in Figure 1-1-14. A microwave-assisted method can be used for a solventless synthesis of imidazolium ionic liquids.[68] Moreover, many ionic liquids are now commercially available and general procedures for their preparation can be found in the literature.

Alternatively, the one-pot reaction of formaldehyde, methylamine, glyoxal, tetrafluoroboric acid, and *n*-butylamine can be used to obtain a mixture of tetrafluoroborate compounds containing the 1,3-dibutylimidazolium (41%), 1-butyl-3-methylimidazolium (50%), and 1,3-dimethylimidazolium (9%) cations Figure 1-1-15.[69, 70]

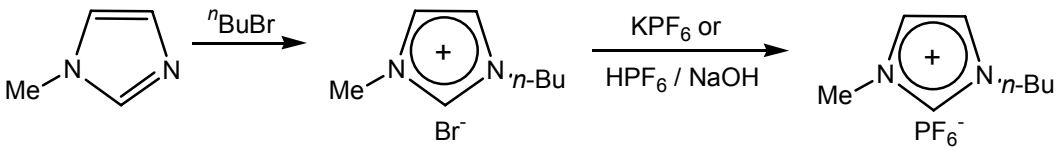


Figure 1-1-14: Preparation of bmimPF_6.

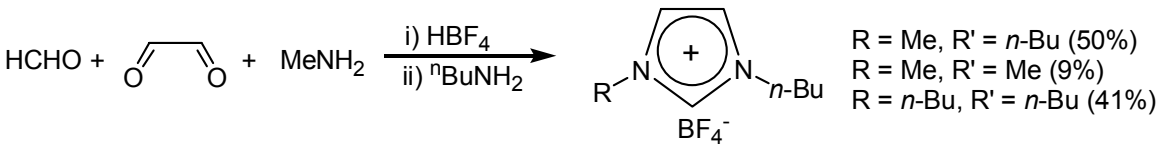


Figure 1-1-15: One-pot synthesis of bmimBF_4.

1.1.5 Scope of Part I

Part I of this dissertation is focused on newly discovered allylation reactions involving organometallic catalysts and reagents. These reactions include: (a) rhodium-catalyzed direct coupling of allylic alcohols with boronic acids; (b) palladium-catalyzed coupling of functionalized allylic acetates, Baylis-Hillman acetate adducts, with potassium organotrifluoroborates; (c) palladium-catalyzed coupling of Baylis-Hillman acetate adducts with organosiloxanes; (d) palladium-catalyzed syntheses of functionalized allylboranes and potassium allyltrifluoroborates and their application in the synthesis of homoallylic alcohols; and (e) efficient synthesis of functionalized allylsilanes and allylgermanes. A brief description of allylation reactions, organoboron reagents in organic synthesis and allylation reaction, synthesis and development of potassium organotrifluoroborates, and ionic liquids has been presented in this chapter because they are fundamental in the new chemistry discussed in this part.

Chapter 2

Rhodium-Catalyzed Cross-Coupling of Allyl Alcohols with Aryl- and Vinylboronic Acids in Ionic Liquids

1.2.1 Introduction

As discussed in Chapter 1, ionic liquids, especially ambient-temperature ionic liquids consisting of 1,3-dialkylimidazolium cations (Figure 1-2-1), have shown great promise as environmentally benign reaction media because of their negligible vapor pressure as well as their excellent chemical and thermal stabilities.[71] Furthermore, their compatibility with transition-metal catalysts and their limited miscibility with common solvents simplifies catalyst recycling.

Transition-metal-catalyzed allylic alkylation using π-allyl complexes represents an important carbon-carbon bond forming reaction that is widely used for constructing complex organic molecules.[72] Allylic halides,[33b, 73] carboxylates,[74] carbonates,[75] phosphates,[38] and related compounds are generally utilized as allylation reagents. On the basis of the viewpoint of atom economy,[76] the ability to use allylic alcohols in allylation reactions would be highly beneficial. However, they are rarely used because hydroxide is a poor leaving group. A few approaches have been reported, but they require either severe reaction conditions or unique ligands.[77]

Boronic acids are widely used reagents in organic synthesis because they are commercially available, stable, generally nontoxic, and compatible with a variety of functional groups. Coupling reactions of boronic acids with allyl halides[33b] and esters[74b]

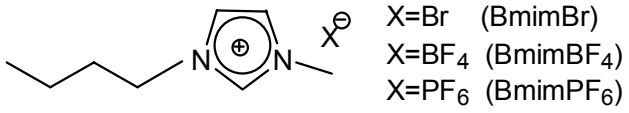


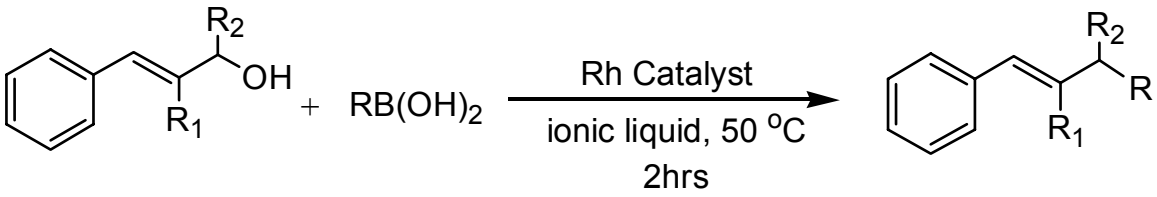
Figure 1-2-1: Common room-temperature ionic liquids.

are well-known, but the direct coupling of boronic acids with allylic alcohols has not been reported. A direct allylation of cinnamyl alcohols using boronic acids catalyzed by ligandless rhodium catalysts (Figure 1-2-2) was developed during this study.

1.2.2 Results and Discussion

1.2.2.1 Optimization of Reaction Conditions

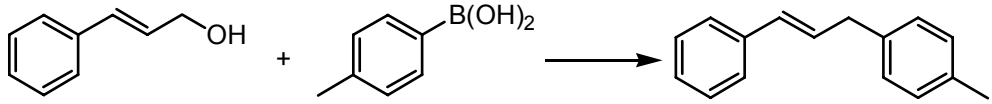
Various rhodium catalysts, solvents, and reaction conditions were examined using *p*-tolylboronic acid and cinnamyl alcohol as model substrates (Table 1-2-1). Dramatic differences in yields were observed (Table 1-2-1, entries 1-4). 1-Butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6) was found to be the most effective solvent. No reaction was observed in polar solvents such as water and DMF. Three common rhodium catalysts were evaluated (Table 1-2-1, entries 4-7), and both Rh(I) and Rh(III) were found to be effective. Although bases are commonly used in transition-metal catalyzed coupling reactions,[32] they inhibited this reaction (Table 1-2-1, entry 8). However, addition of acids increased the reaction rate (Table 1-2-1, entries 9 and 10). The addition of copper salts such as cupric acetate enhanced reaction yields by approximately 10%. This effect had been observed previously.[78] The highest yields were



R = aryl, alkenyl, heteroaryl
R_1 = H, CH_3
R_2 = H, Ph

Figure 1-2-2: Cross-coupling of boronic acids with cinnamyl alcohols.

Table 1-2-1: Effect of catalysts and solvents on the reaction of cinnamyl alcohol with p-tolylboronic acid.



Entry	Catalyst[a]	Reaction Media	Temperature (ºC)	Reaction time (hrs)	Isolated yield (%)
1	$RhCl_3 \cdot xH_2O$	CH_2Cl_2	50	5	10
2	$RhCl_3 \cdot xH_2O$	toluene	50	12	Trace
3	$RhCl_3 \cdot xH_2O$	$bmimBF_4$	50	5	Trace
4	$RhCl_3 \cdot xH_2O$	$bmimPF_6$	r.t.	12	0
5	$RhCl_3 \cdot xH_2O$	$bmimPF_6$	50	2	62
6	Rh(acac)(1,5-cyclooctadiene)Cl	$bmimPF_6$	50	2	62
7	$Rh(PPh_3)_3Cl$	$bmimPF_6$	50	2	61
8	$RhCl_3 \cdot xH_2O$ and KOAc (10 mol %)	$bmimPF_6$	50	2	0
9	$RhCl_3 \cdot xH_2O$ and CH_3COOH (10 mol %)	$bmimPF_6$	50	1.5	66
10	$RhCl_3 \cdot xH_2O$ and HF[b]	$bmimBF_4$	50	2	59
11	$RhCl_3 \cdot xH_2O$ and CuI (10 mol %)	$bmimPF_6$	50	2	67
12	$RhCl_3 \cdot xH_2O$ and $Cu(OAc)_2$ (10 mol %)	$bmimPF_6$	50	2	72

[a] 3 mol % of Rh catalyst used. [b]One equivalent of aqueous HF (48%) used.

obtained using a mixture of $RhCl_3 \cdot xH_2O$ (3 mol %) and $Cu(OAc)_2$ (10 mol %) in $BmimPF_6$ at 50 °C for 2 h.

1.2.2.2 Scope of the Reaction

To enhance the utility of the reaction, a variety of organoboronic acids (aryl, alkenyl, heteroaryl) and allylic alcohols were evaluated (Table 1-2-2). Electron-rich boronic acids generated higher yields than electron-deficient boronic acids. Steric factors also affected the yield. *Ortho*- and *meta*-substituted arylboronic acids (Table 1-2-2, entries 9 and 10) typically gave lower yields than the *para*-substituted arylboronic acids. Sterically hindered alcohols (Table 1-2-2, entries 12 and 13) also led to lower yields. Aliphatic alcohols were found to be unreactive. It is noteworthy that the catalyst system can be recycled with no significant loss in reaction yields (Table 1-2-3).

1.2.2.3 Proposed Mechanism

Although a detailed mechanistic study has not been undertaken, the reaction most likely proceeds via the pathway outlined in Figure 1-2-3. Oxidative addition of cinnamyl alcohol to rhodium would generate π-allylrhodium intermediate **D**. The formation of intermediate **E** drives the reaction by elimination of water in the presence of the HF that is present in $BmimPF_6$ due to the relatively facile decomposition of PF_6 anion in the presence of trace amounts of water.[79] Subsequently, the transmetallation of **E** by the boronic acid produces intermediate **F**. Reductive elimination of rhodium then generates the product. It is noteworthy that the reaction does not occur in $BmimBF_4$

Table 1-2-2: Coupling of organoboronic acids with allylic alcohols.[a]

Entry	Boronic acid	Alcohol	Product	Yield (%)[b]
1	*p*-Tolyl	Cinnamyl	**1-201**	72
2	Phenyl	Cinnamyl	**1-202**	65
3	*p*-Methoxyphenyl	Cinnamyl	**1-203**	76
4	*p*-Chlorophenyl	Cinnamyl	**1-204**	41
5	*p*-Methylthiophenyl	Cinnamyl	**1-205**	78
6	*p*-Acylphenyl	Cinnamyl	**1-206**	0
7	*trans*-β-styrenyl	Cinnamyl	**1-207**	50
8	2-Thiophene	Cinnamyl	**1-208**	33
9	*o*-Tolyl	Cinnamyl	**1-209**	55
10	*m*-Tolyl	Cinnamyl	**1-210**	61
11	1-naphthyl	α-Methylcinnamyl	**1-211**	52
12	*p*-Tolyl	1,3-Diphenyl-2-propen-1-ol	**1-212**	60
13	*p*-Methoxyphenyl	1,3-Diphenyl-2-propen-1-ol	**1-213**	65

[a] Reactions were carried out using $RhCl_3.xH_2O$ (3 mol %) and $Cu(OAc)_2$ (10mol %) in $bmimPF_6$ at 50ºC for 2 hrs. [b]Isolated yields.

Table 1-2-3: Reaction of *p*-tolylboronic acid with cinnamyl alcohol using recycled catalytic system.[a]

Entry	Isolated yield (%)
1st cycle	70
2nd cycle	72
3rd cycle	73
4th cycle	71
5th cycle	68

[a]Catalyst was recovered by filtration and utilized in subsequent experiment (cycle).

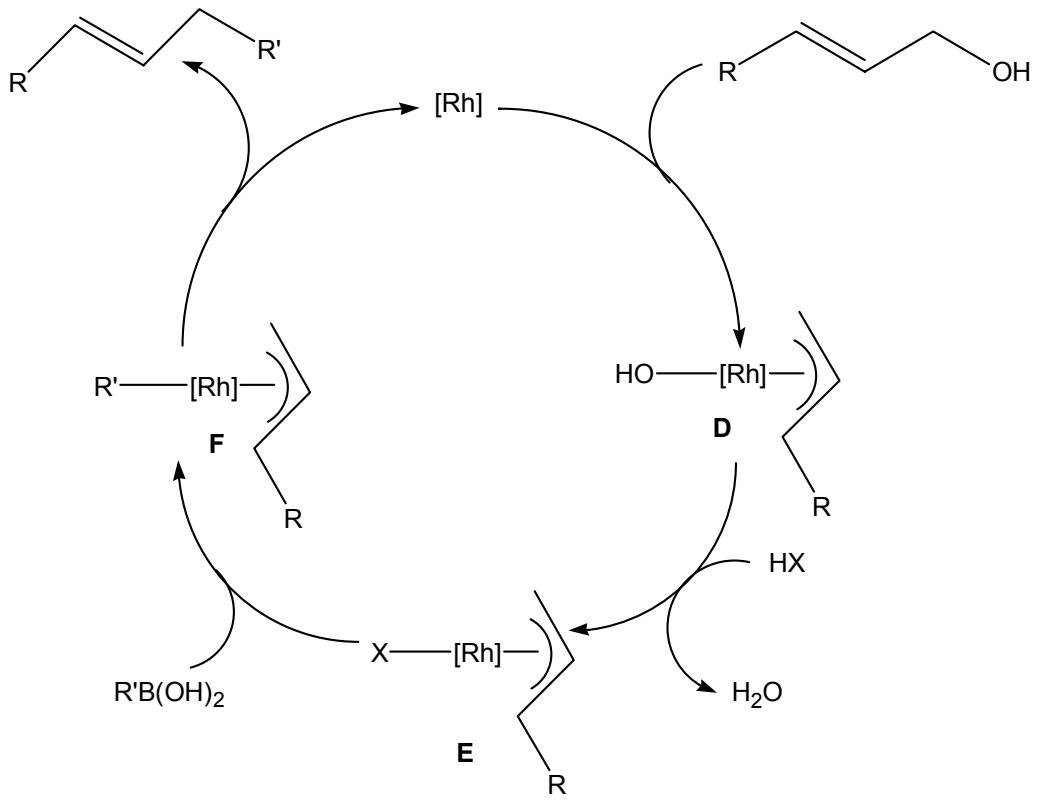


Figure 1-2-3: Proposed Mechanism.

(Table 1-2-1, entry 3) unless HF is added to the reaction media (Table 1-2-1, entry 10). At this time, it is not possible to rule out a mechanism involving the conversion of the allylic alcohol to the corresponding halide or phosphate. However, control experiments in which cinnamyl alcohol was heated in $BmimPF_6$ at 50 ^oC for 2 h led to recovery of only the alcohol. In addition, an experiment carried out using toluene (which would obviate the formation of a halo or phosphate intermediate) in place of $BmimPF_6$ produced a 10% yield of the coupled product.

1.2.3 Conclusion

In summary, the coupling reactions of a wide variety of boronic acids with cinnamyl alcohols have been studied. The protocol is applicable to aryl, vinyl, and heteroarylboronic acids and aromatic allyl alcohols. The catalyst system and the ionic liquid can be recycled several times without significant loss in product yield.

1.2.4 Experimental Section

1.2.4.1 General Considerations

All glassware was oven dried at 120 ^oC and flushed with dry nitrogen. All reactions were carried out under a nitrogen atmosphere. All chemicals were purchased from commercial sources and used as received. Products were purified by flash chromatography using silica gel (60 Å, 230–400 mesh) with hexanes as eluent. Elemental

analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a 250 MHz instrument with chemical shifts reported relative to TMS.

1.2.4.2 Representative Procedure for the Synthesis of (*E*)-1-Phenyl-3-*p*-tolylpropene (1-201)

Cinnamyl alcohol (1 mmol) and *p*-tolylboronic acid (1.2 mmol) were dissolved in $BmimPF_6$ (1.5 ml) contained in a two-necked round-bottomed flask and $RhCl_3.xH_2O$ (3 mole %) along with $Cu(OAc)_2$ (10 mole %) were added. The reaction mixture was allowed to stir for 2 hrs at 50 ºC under a nitrogen atmosphere. The mixture was then cooled to room temperature and the product extracted into diethyl ether (4 x 3 ml). The combined extracts were dried over anhydrous $MgSO_4$, concentrated, and purified by flash chromatography using silica gel. ^{1}H NMR: δ 7.05–7.36 (m, 9H), 6.42 (d, 1H, J = 15.9 Hz), 6.30 (dt, 1H, J = 16 Hz, J = 6 Hz), 3.49 (d, 2H, J = 5.8 Hz), 2.31 (s, 3H). ^{13}C NMR: δ 137.5, 131.0, 130.6, 129.5, 129.1, 128.9, 128.5, 128.1, 127.0, 126.1, 38.9, 21.0.

1.2.4.3 Analytical Data

(*E*)-1,3-Diphenylpropene (1-202). ^{1}H NMR: δ 7.12–7.38 (m, 10H), 6.46 (d, 1H, J = 15.75 Hz), 6.36 (dt, 1H, J = 15.75 Hz, J = 6 Hz), 3.52 (d, 2H, J = 6.25 Hz). ^{13}C NMR: δ 140.7, 138.0, 131.6, 129.7, 129.2, 129.0, 127.6, 126.6, 39.6.

(*E*)-1-Phenyl-3-*p*-methoxyphenylpropene (1-203). ^{1}H NMR: δ 6.80–7.36 (m, 9H), 6.43 (d, 1H, *J* = 15.9 Hz), 6.33 (dt, 1H, *J* = 15.7 Hz, *J* = 5.8 Hz), 3.77 (s, 3H), 3.47 (d, 2H, *J* = 5.8 Hz). ^{13}C NMR: δ 137.5, 132.1, 130.7, 129.6, 128.4, 127.0, 126.1, 113.9, 55.2, 38.4.

(*E*)-1-Phenyl-3-*p*-chlorophenylpropene (1-204). ^{1}H NMR: δ 7.15–7.36 (m, 9H), 6.44 (d, 1H, *J* = 16 Hz), 6.32 (dt, 1H, *J* = 15.9 Hz, *J* = 6 Hz), 3.51 (d, 2H, *J* = 6.2 Hz). ^{13}C NMR: δ 138.6, 137.2, 131.5, 130.0, 128.5, 127.2, 126.1, 38.8.

(*E*)-1-Phenyl-3-*p*-methylthiophenylpropene (1-205). ^{1}H NMR: δ 7.13–7.35 (m, 9H), 6.43 (d, 1H, *J* = 15.9 Hz), 6.31 (dt, 1H, *J* = 15.8 Hz, *J* = 6.2 Hz), 3.48 (d, 2H, *J* = 6.2 Hz), 2.45 (s, 3H). ^{13}C NMR: δ 137.3, 137.1, 135.8, 131.1, 129.2, 129.0, 128.5, 127.9, 127.1, 126.1, 38.7, 16.2. Anal. Calcd for $C_{16}H_{16}S$: C, 79.95; H, 6.71; Found: C, 80.20; H, 6.78.

(*E*), (*E*) -1,5-Diphenyl-1,4-pentadiene (1-206). ^{1}H NMR: δ 7.10–7.39 (m, 10H), 6.47 (d, 2H, *J* = 15.9 Hz), 6.29 (dt, 2H, *J* = 15.9 Hz, *J* = 6.5 Hz), 3.12 (t, 2H, *J* = 6.5 Hz). ^{13}C NMR: δ 137.6, 131.0, 128.5, 128.2, 127.1, 126.1, 36.2.

2-(3-Phenylallyl)thiophene (1-207). ^{1}H NMR: δ 7.18–7.39 (m, 8H), 6.47 (d, 1H, *J* = 15.9 Hz), 6.29 (dt, 1H, *J* = 15.8 Hz, *J* = 6.3 Hz), 3.13 (d, 2H, *J* = 6.3 Hz). ^{13}C NMR: δ 137.6, 131.0, 128.5, 128.2, 127.1, 126.1, 36.2.

(*E*)-1-Phenyl-3-*o*-tolylpropene (1-208). ^{1}H NMR: δ 7.11–7.37 (m, 9H), 6.40 (d, 1H, *J* = 15.9 Hz), 6.33 (dt, 1H, *J* = 16 Hz, *J* = 5.9 Hz), 3.50 (d, 2H, *J* = 5.8 Hz), 2.31 (s, 3H). ^{13}C

NMR: δ 138.2, 137.5, 137.3, 136.4, 135.6, 130.9, 130.2, 129.2, 128.5, 127.0, 126.4, 126.1, 38.9, 21.2.

(*E*)-1-Phenyl-3-*m*-tolylpropene (1-209). ^{1}H NMR: δ 7.03–7.36 (m, 9H), 6.39 (d, 1H, *J* = 15.8 Hz), 6.33 (dt, 1H, *J* = 15.9 Hz, *J* = 6 Hz), 3.47 (d, 2H, *J* = 6 Hz), 2.30 (s, 3H). ^{13}C NMR: δ 138.2, 137.5, 137.0, 135.6, 130.8, 130.2, 129.5, 129.1, 128.5, 127.0, 126.2, 126.1, 38.9, 21.1.

(*E*)-2-Methyl-1-phenyl-3-(1-naphthyl)propene (1-210). ^{1}H NMR: δ 7.15–8.11 (m, 12H), 6.29 (s, 1H), 3.93 (s, 2H), 1.87 (s, 3H). ^{13}C NMR: δ 138.3, 137.7, 135.6, 133.9, 128.8, 128.6, 128.0, 127.3, 127.0, 126.0, 125.8, 125.5, 124.2, 43.8, 18.2. Anal. Calcd. for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 92.86; H, 7.18.

(*E*)-1,3-Diphenyl-3-*p*-tolylpropene (1-211). ^{1}H NMR: δ 7.12–7.37 (m, 14H), 6.66 (dd, 1H, *J* = 15.8 Hz, *J* = 7.5 Hz), 6.33 (d, 1H, *J* = 15.8 Hz), 4.84 (d, 1H, *J* = 7.5 Hz), 2.31 (s, 3H). ^{13}C NMR: δ 144.0, 140.5, 137.3, 135.9, 132.8, 131.2, 129.2, 128.6, 128.5, 127.2, 126.3, 53.8, 21.0. Anal. Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 92.63; H, 7.24.

(*E*)-1,3-Diphenyl-3-*p*-methoxyphenylpropene (1-212). ^{1}H NMR: δ 6.79–7.33 (m, 14H), 6.62 (dd, 1H, *J* = 16 Hz, *J* = 7.5 Hz), 6.30 (d, 1H, *J* = 16 Hz), 4.80 (d, 1H, *J* = 7.4 Hz), 3.66 (s, 3H). ^{13}C NMR: δ 158.1, 143.7, 137.2, 135.5, 132.8, 131.1, 129.5, 128.4, 127.2, 126.2, 125.7, 113.8, 55.0, 53.2.

Chapter 3

Palladium-Catalyzed Cross-Coupling of Acetates of Baylis-Hillman Adducts with Potassium Organotrifluoroborates

1.3.1 Introduction

The palladium-catalyzed cross-coupling of organoboron compounds and organic electrophiles to form carbon-carbon bonds is an important synthetic reaction.[32] The availability of the prerequisite reagents and the mild reaction conditions all contribute to the versatility of the reaction. Significantly, the reaction is unaffected by water, and a broad range of functional groups is tolerated. The cross-coupling is both regio- and stereoselective.

Palladium catalysts have been used in a wide variety of synthetically useful reactions involving stabilized carbon nucleophiles.[80] However, few studies have been reported in which boron reagents are used as nucleophiles in allylic coupling reactions.[33] Hayashi and co-workers described the reaction of phenylboronic acid with allyl acetates in water using a resin-supported palladium catalyst;[33c] later, Balme extended the reaction utilizing various Pd catalytic systems and difference solvents.[39] These results formed the foundation of a study of reactions of organoborates with Baylis-Hillman acetates.

The Baylis-Hillman reaction provides molecules possessing hydroxyl, alkene, and electron-withdrawing groups in close proximity, which makes it valuable in a number of stereoselective processes.[81] In a continuation of our study of allylation reactions

involving organoboron reagents, the cross-coupling reaction of organoboron reagents with acetates of Baylis-Hillman adducts was investigated.

1.3.2 Results and Discussion

1.3.2.1 Potassium Acetate as Base in Ionic Liquids

We first examined the reaction of *p*-tolylboronic acid with a Baylis-Hillman acetate adduct in ionic liquids; however, no reaction occurred. Potassium acetate was then added as a base but the acetate behaved as a nucleophile and the S_N2' substitution product formed instead of desired coupling product. For example, methyl 3-acetoxy-3-phenyl-2-methylenepropanoate was converted to methyl (*E*)-2-(acetoxymethyl)-3-phenylprop-2-enoate in high yields (Figure 1-3-1). Previously reported isomerizations of acetates of Baylis–Hillman adducts required catalysts such as TMSOTf,[82a] DABCO[82b] or montmorillonite K10 clay.[82c] The present method utilizes simple protocols and provides high yields in an environmentally benign system.

Prior to this study of the cross-coupling reaction of Baylis-Hillman acetate adducts with organoboron compounds, the reactions of Baylis-Hillman adducts with potassium acetate were investigated. The reaction of methyl 3-acetoxy-3-phenyl-2-methylenepropanoate with potassium acetate in various ionic liquids as well as in conventional solvents (Table 1-3-1) was examined first. Interestingly, the reaction proceeded well in ionic liquids whereas little reaction occurred in conventional solvents.

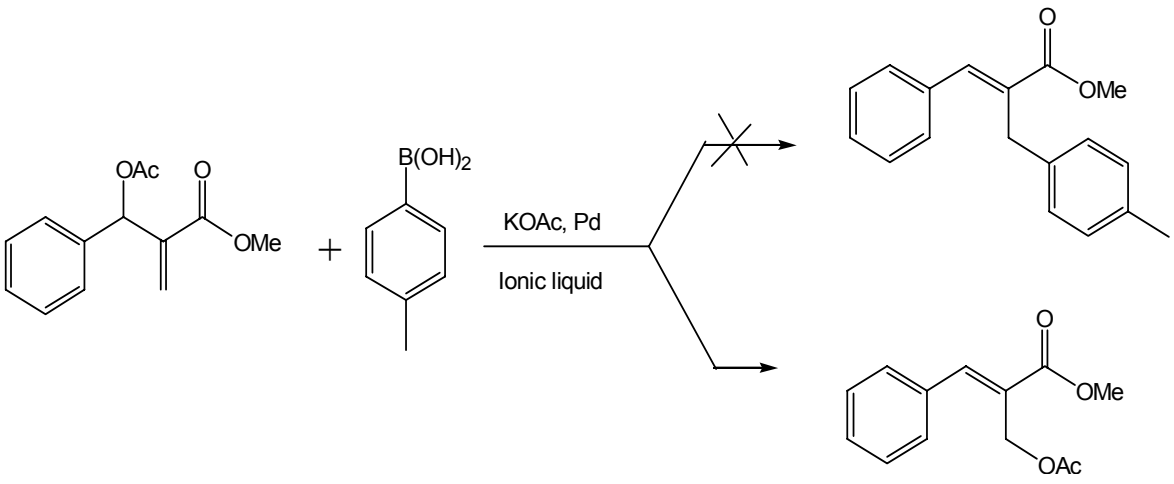
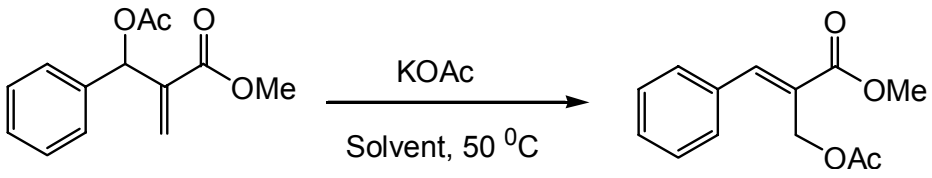


Figure 1-3-1: S_N2' reaction of Baylis-Hillman adduct with potassium acetate.

Table 1-3-1: Solvent Study.



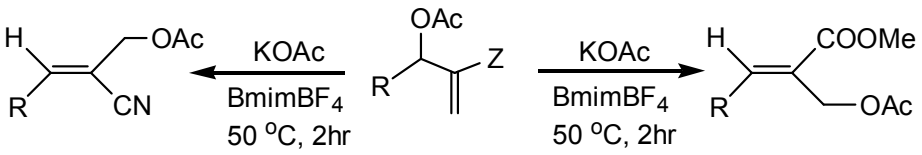
Entry	Solvent	Isolated Yield (%)
1	BmimBr	92
2	$BmimBF_4$	95
3	$BmimiPF_6$	52
4	THF	0
5	Dioxane	0
6	Acetonitrile	8
7	DMF	43
8	Recycled $BmimBF_4$	94

The best results were obtained when butylmethylimidazolium tetrafluoroborate ($BmimBF_4$) was used as the reaction media (Table 1-3-1, entry 2).

In order to establish the generality of the reaction, various Baylis–Hillman acetate adducts that had been prepared according to literature procedures were utilized.[82] Similar reactions were observed for both ester and nitrile derivatives but stereochemical directive effects were reversed.[82, 83] Although no mechanistic studies have been carried out, related stereochemical reversals have been attributed to differences in the relative stabilities of the transition states.[83e] *E*:*Z* ratios in all cases were greater than 9:1 (Table 1-3-2). The stereochemistry of the products was assigned on the basis of the ^{1}H NMR chemical shift values of the olefinic protons by comparison with the values reported in the literature.[82]

The new reaction was applied to the preparation of allylsulfones by allowing Baylis–Hillman acetate adducts to react with the sodium salt of *p*-toluenesulfinic acid. The results are summarized in Table 1-3-3. It is interesting to note that the reaction of acetates of Baylis–Hillman adducts with KOAc does not occur when R is alkyl group (Table 1-3-2, entries 5 and 8). However, this is not a limitation when the reaction is carried out using the sodium salt of *p*-toluenesulfinic acid (Table 1-3-3, entries 5 and 8). The product allylsulfones are important intermediates in organic synthesis[84] and are generally prepared by displacement of halides by sodium arenesulfinates.[85] The structures of the product allylsulfones were established by comparing the ^{1}H NMR spectra values of olefin and methylene protons with those of related compounds.[83, 85a] In the crude ^{1}H NMR spectrum of the allylsulfones synthesized from Baylis-Hillman esters, the *β*-vinylic proton, *cis* to the ester group (*Z*-isomer), appears at δ 7.09 and a minor peak for the *E*-isomer appears at δ 6.08 when R is alkyl. Similarly, the same proton appears at δ 7.90

Table 1-3-2: Reactions of acetate of Baylis-Hillman adducts with KOAc in $BmimBF_4$.[a]



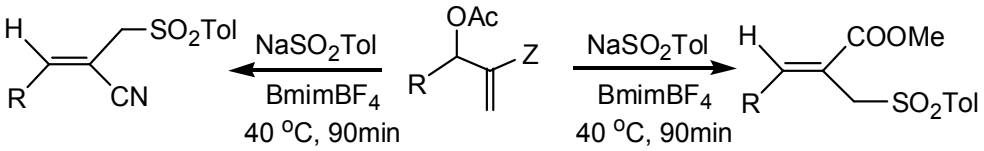
Entry	R	Z	Product	Isolated yield(%)[b]	*E*/*Z* ratio[c]
1	Phenyl	COOMe	**1-301**	95	96/4
2	4-Chlorophenyl	COOMe	**1-302**	92	94/6
3	3-Nitrophenyl	COOMe	**1-303**	92	91/9
4	4-Nitrophenyl	COOMe	**1-304**	93	100/0
5	Octyl	COOMe		0	--
6	Phenyl	CN	**1-305**	91	5/95
7	4-Chlorophenyl	CN	**1-306**	92	4/96
8	Octyl	CN		0	

[a] All reactions were carried out at 50°C for 2 h.

[b] Isolated yields.

[c] *E*/*Z* ratio determined by ^1H NMR.

Table 1-3-3: Reactions of acetate of Baylis-Hillman adducts with $NaSO_2Tol$ in $BmimBF_4$.[a]



Entry	R	Z	Product[b]	Isolated yield(%)[c]	*E*/*Z* ratio[d]
1	Phenyl	COOMe	**1-307**	97	3/96
2	4-Chlorophenyl	COOMe	**1-308**	96	5/95
3	3-Nitrophenyl	COOMe	**1-309**	96	8/92
4	4-Nitrophenyl	COOMe	**1-310**	95	10/90
5[e]	Octyl	COOMe	**1-311**	90	6/94
6	Phenyl	CN	**1-312**	94	92/8
7	4-Chlorophenyl	CN	**1-313**	95	94/6
8[e]	Octyl	CN	**1-314**	91	95/5

[a]Reactions were carried out at 40°C for 90 min.

[b]All structures were characterized by NMR spectroscopy and elemental analyses.

[c]Isolated yields.

[d]*E*/*Z* ratio determined by ^1H NMR.

[e]Reaction time was 3 h.

and δ 6.85 for *Z*- and *E*-isomers, respectively when R is aryl. Purification of the major isomer is readily achieved by column chromatography. In the crude ^{1}H NMR spectrum of allylsulfones synthesized from Baylis-Hillman nitrile adducts, the *β*-vinylic proton *trans* to the nitrile group (*E*-isomer) appears at δ 6.33 and a minor peak for *Z*-isomer appears at δ 6.60 when R is alkyl. Similarly, the same proton appears at δ 7.08 and δ 7.48 for the *E*- and *Z*-isomers, respectively, when R is aryl. The products were also compared with samples prepared using known methods.[86] For example reactions of methyl (*E*)-2-(acetoxymethyl)-3-phenylprop-2-enoate with *p*-toluenesulfinic acid sodium salt in the presence of $Pd(PPh_3)_4$ and triphenylphosphine gave (*Z*)-(2-methoxycarbonylstyryl)-tolylsulfone.

The preparation of substituted allylsulfones from Baylis–Hillman acetate adducts has not been reported. Reaction yields are very high. Product isolation can be achieved by distillation but, for convenience, the products were extracted using diethyl ether. Pure products were obtained and the ionic liquid can be reused without loss in reaction yield (Table 1-3-1, entry 10). No catalyst is required and the procedure is very straightforward.

1.3.2.2 Utilization of Potassium Organotrifluoroborates

A reaction using cesium fluoride as a base was then carried out since it has been shown to be effective in Suzuki coupling reactions.[87, 88] The desired reaction occurred, but a significant quantity of the homo-coupling product formed. Potassium organotrifluoroborate salts, which are more nucleophilic than the corresponding boronic acids, were then utilized.[48] Reactions of Baylis-Hillman acetate adducts with potassium organotrifluoroborates take place in the presence of 3 mol % $Pd(OAc)_2$ in methanol at

room temperature in good yields (Figure 1-3-2). 3-Acetoxy-2-methylenealkanoates react with a variety of potassium organotrifluoroborates to provide (*E*)-2-substituted 2-alkenoates as the major products. Regioisomers were also observed (Figure 1-3-2).[12] However, the *E*-isomer and *Z*-isomer are readily separated by column chromatography. The reaction of 3-acetoxy-2-methylenealkanenitriles provides (*Z*)-2-substituted alk-2-enenitriles (Figure 1-3-2). In this case, the formation of the regioisomer was not observed.

To determine the generality of the method, reactions of potassium *p*-tolyltrifluoroborate with a variety of Baylis-Hillman acetate adducts were investigated (Table 1-3-4).The formation of esters and nitriles was consistent with earlier studies.[81, 89] The stereochemistry of the products was established by comparing NMR values of olefinic and methylene protons with literature values.[90] In all cases, the stereoselectivity

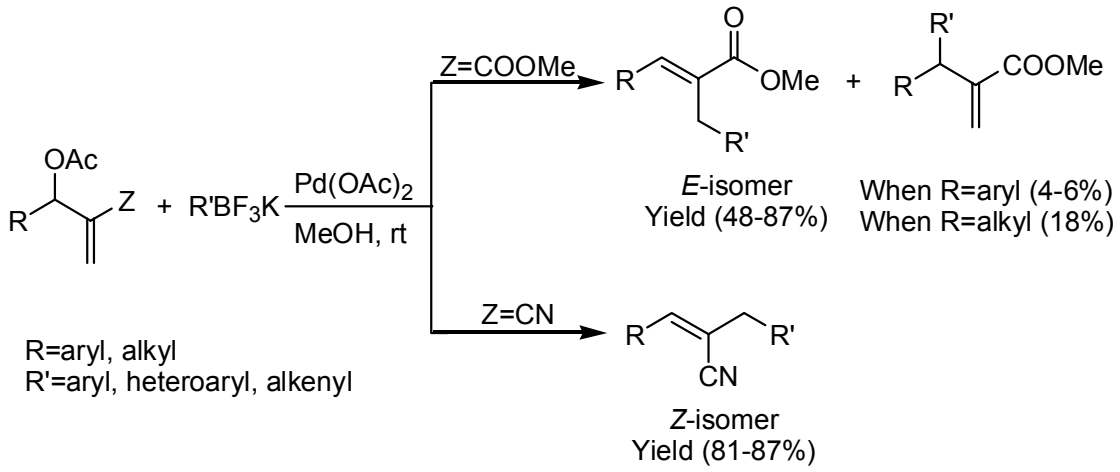
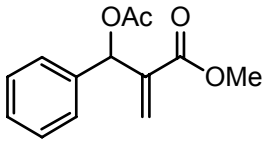
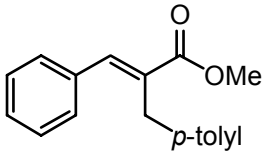
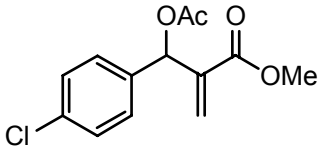
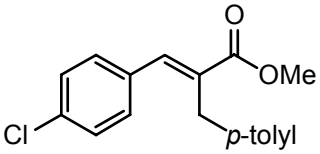
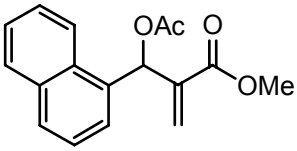
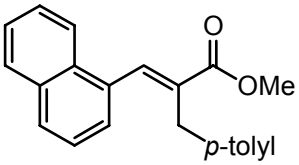
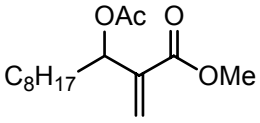
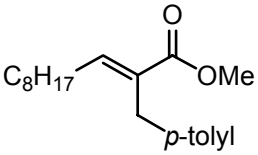
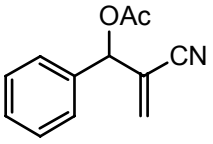
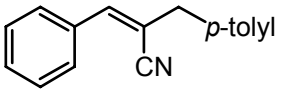
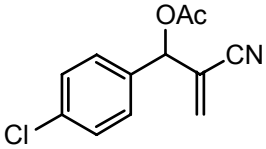
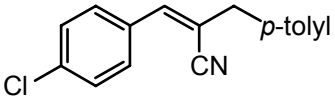
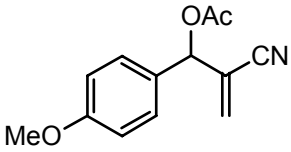
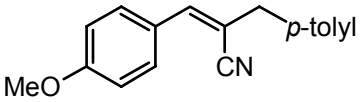


Figure 1-3-2: Reaction of Baylis-Hillman adducts with potassium organotrifloroborates.

Table 1-3-4: Reaction of potassium *p*-tolyltrifluoroborate with Baylis-Hillman adduct acetates.[a]

Entry	B-H acetate adduct	Product[b]	Yield (%)[c]
1		 **1-315**	87
2		 **1-316**	83
3		 **1-317**	84
4		 **1-318**	48
5		 **1-319**	84
6		 **1-320**	87
7		 **1-321**	81

[a]All reactions carried out in the presence of 3 mol % of $Pd(OAc)_2$ at room temperature for 3 hours.
[b]All products exhibited satisfactory spectral (^1H, ^{13}C NMR) and analytical properties.
[c]Isolated yields.

was found to be >98:2, as determined by ^{1}H NMR analysis. Several types of potassium trifluoroborates participate in this reaction (Table 1-3-5). These include aryl, heteroaryl, and even sterically hindered trifluoroborate salts. Alkenyltrifluoroborates can also be utilized (Figure 1-3-3). It is noteworthy that (*E*)- and (*Z*)-alkenyl trifluoroborates couple with Baylis-Hillman acetates stereospecifically.

1.3.3 Conclusion

In conclusion, we have developed a palladium-catalyzed coupling of potassium organotrifluoroborates with Baylis-Hillman acetate adducts. The protocol is applicable to aryl, heteroaryl, and alkenyltrifluoroborate salts and the reaction of vinylborates is stereospecific. No additional base or ligand is required and the reaction takes place at room temperature in a straightforward fashion.

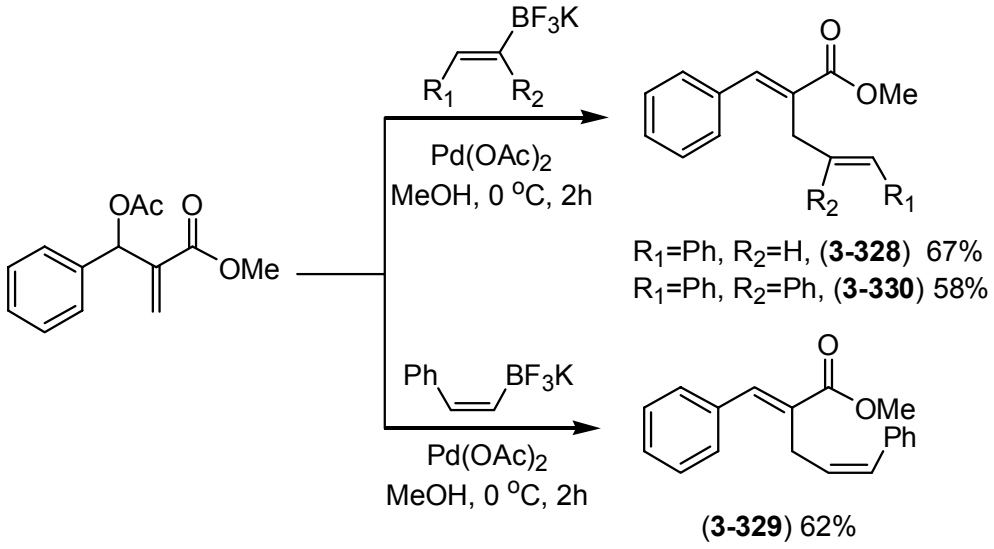
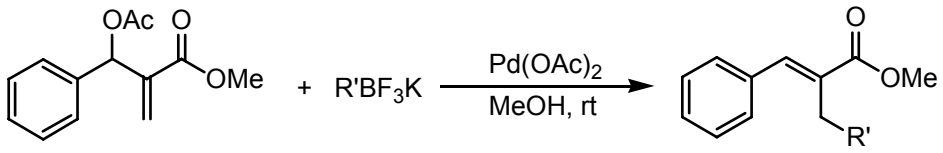


Figure 1-3-3: Reactions of Baylis-Hillman adduct with potassium (*Z*)- and (*E*)-vinyltirfluoroborates.

Table 1-3-5: Reaction of different potassium organotrifluoroborates with Baylis-Hillman adduct methyl 3-acetoxy-3-phenyl-2-methylenepropanoate.[a]



Entry	R'	Time (h)	Product	Isolated yield (%)[b]
1	Phenyl	3	**1-322**	86
2	*p*-Methoxyphenyl	8	**1-323**	76
3	3-Thiofuryl	3	**1-324**	61
4	2-Methylphenyl	5	**1-325**	76
5	2,6-Dimethylphenyl	12	**1-326**	53
6	2,6-Difluorophenyl	48	**1-327**	68

[a]All reactions carried out in the presence of 3 mol % of $Pd(OAc)_2$ at room temperature for 3 hours.

[b]All products exhibited satisfactory spectral (^1H, ^{13}C NMR) and analytical properties.

[c]Isolated yields.

1.3.4 Experimental Section

1.3.4.1 General Considerations

All glassware was dried in an oven at 120 ^{o}C and flushed with dry nitrogen. Reactions were carried out under a nitrogen atmosphere. All reagents were purchased from Aldrich Chemical Company and used as received. Products were purified by flash chromatography using silica gel (60 C, 230 400 mesh) with hexanes and ethyl acetate (Hexanes:EtOAc 20:1) as eluent. Elemental Analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker 250 MHz or Varian 300 MHz instrument with chemical shifts reported relative to TMS.

1.3.4.2 General Procedure for the Reaction of Baylis-Hillman Adduct with Potassium Acetate or Sodium *p*-Toluenesulfinate

A mixture of the acetate of the Baylis–Hillman adduct (1 mmol) and bmimBF_4 (500 mg) was placed in a 10 ml round-bottomed flask followed by addition of potassium acetate or sodium *p*-toluenesulfinate (1.5 mmol). The mixture was stirred at the appropriate temperature until the reaction was complete (TLC), the product extracted into diethyl ether (3×5 ml), and purified by column chromatography (hexane and ethyl acetate). The ionic liquid was dried under vacuum and reused.

1.3.4.3 General Procedure for Potassium Aryltrifluoroborate Synthesis

Preparation of Potassium Phenyltrifluoroborate: Phenylboronic acid (26.2 mmol, 3.20 g) and potassium hydrogen fluoride (65.8 mmol, 5.14 g) were placed in a 100-mL round-bottom flask and were vigorously stirred in a mixture of methanol (7.5 mL) and water (14 mL) for 2 h. The resulting amber solid was allowed to stand for 2 h at 4 °C and was then filtered and washed with a minimum amount of cold methanol. The solid was then taken up in hot acetone and filtered again. The filtrate was cooled to room temperature and ethyl ether was added in portions, with stirring, until no cloudiness was observed in the supernatant. The mixture was allowed to stand for 1 h at 4 °C to complete crystallization. The solid was filtered and washed with cold ethyl ether until white crystals were obtained. The crystalline solid was dried on a high-vacuum line to give 4.24 g (88%) of the desired material. The spectral data obtained were in accordance with those described in the literature.[51b]

1.3.4.4 General Procedure for the Synthesis of Vinyltrifluoroborates

Preparation of Potassium *trans*-Styryl Trifluoroborate: To a solution of *trans*-2-phenylethenylboronic acid (1.48 g, 10.0 mmol) in diethyl ether (20 mL) was added KHF_2 (2.18 g, 28 mmol), followed by water (9 mL) during 30 min. After stirring at rt for 3 h, the solution was concentrated and the crude material was dissolved in acetone, filtered, and concentrated. The resulting white solid was purified by dissolving in hot acetone and precipitating with Et_2O, resulting in a white solid (1.89 g, 9.0 mmol, 90%): mp > 260 °C. The spectral data obtained were in accordance with those described in the literature.[51c]

1.3.4.5 General Procedure for the Cross-Coupling of Baylis-Hillman Adducts with Potassium Organotrifluoroborates

The acetate of Baylis-Hillman adduct (1 mmol) and 3 mol% of $Pd(OAc)_2$ was added to a solution of potassium organotrifluoroborate salt (1 mmol) in methanol (5 mL) at 0 ^oC under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature until completion of the reaction (TLC monitoring). The mixture was then diluted with diethyl ether (10 ml) and filtered to remove solids. The solvent was removed under reduced pressure and the product purified by chromatography (silica gel) to afford analytically pure product.

1.3.4.6 Analytic Data

2-Acetoxymethyl-3-phenylacrylic acid methyl ester (1-301). ^1H NMR ($CDCl_3$): δ 7.98 (s, 1H), 7.35 – 7.38 (m, 5H), 4.95 (s, 2H), 3.83 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.4, 167.0, 145.2, 134.0, 129.4, 129.2, 128.5, 126.5, 59.1, 52.0, 20.7.

2-Acetoxymethyl-3-(4-chlorophenyl)acrylic acid methyl ester (1-302). ^1H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.38 (d, 2H, J = 8 Hz), 7.32 (d, 2H, J = 8 Hz), 4.93 (s, 2H), 3.84 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.3, 166.7, 143.6, 135.0, 132.3, 130.5, 128.7, 126.9, 58.7, 52.0, 20.6.

2-Acetoxymethyl-3-(3-nitrophenyl)acrylic acid methyl ester (1-303). ^{1}H NMR ($CDCl_3$): δ 8.14 – 8.30 (m, 1H), 8.01 (s, 1H), 7.60 – 7.72 (m, 3H), 4.90 (s, 2H), 3.89 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.3, 167.1, 148.2, 142.4, 135.9, 134.9, 129.7, 129.3, 123.9, 123.8, 58.6, 52.4, 20.8.

2-Acetoxymethyl-3-(4-nitrophenyl)acrylic acid methyl ester (1-304). ^{1}H NMR ($CDCl_3$): δ 8.28 (d, 2H, *J* = 8.8 Hz), 7.99 (s, 1H), 7.59 (d, 2H, *J* = 8.8 Hz), 4.92 (s, 2H), 3.89 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.2, 166.3, 147.8, 142.2, 140.4, 130.0, 123.7, 58.5, 52.5, 20.9.

Acetic acid 2-cyano-3-phenylallyl ester (1-305). ^{1}H NMR ($CDCl_3$): δ 7.66 – 7.80 (m, 2H), 7.42 – 7.45 (m, 3H), 7.23 (s, 1H), 4.80 (s, 2H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.1, 147.2, 132.4, 131.0, 129.0, 128.8, 117.1, 105.6, 65.1, 20.6.

Acetic acid 3-(4-chlorophenyl)-2-cyanoallyl ester (1-306). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 2H, *J* = 8.5 Hz), 7.40 (d, 2H, *J* = 8.5 Hz), 7.18 (s, 1H), 4.80 (s, 2H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.1, 145.6, 137.0, 130.9, 130.5, 130.3, 129.1, 116.8, 106.4, 64.9, 20.6.

3-Phenyl-2-(toluene-4-sulfonylmethyl)acrylic acid methyl ester (1-307). ^{1}H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.68 (d, 2H, *J* = 8 Hz), 7.32 –7.43 (m, 5H), 7.23 (d, 2H, *J* = 8 Hz), 4.47 (s, 2H), 3.59 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.6, 145.7, 144.5, 135.9, 133.3, 129.3, 128.9, 128.4, 128.2, 120.8, 54.8, 52.0, 21.3.

3-(4-Chlorophenyl)-2-(toluene-4-sulfonylmethyl)acrylic acid methyl ester (1-308). ^{1}H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.68 (d, 2H, *J* = 8.2 Hz), 7.43 (d, 2H, *J* = 8.7 Hz), 7.31 (d, 2H, *J* = 8.7 Hz), 7.26 (d, 2H, *J* = 8.2 Hz), 4.44 (s, 2H), 3.60 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.4, 144.7, 144.3, 135.9, 135.4, 131.9, 130.3, 129.4, 128.6, 128.2, 121.3, 54.7, 52.2, 21.3.

3-(3-Nitrophenyl)-2-(toluene-4-sulfonylmethyl)acrylic acid methyl ester (1-309). ^{1}H NMR ($CDCl_3$): δ 8.20 – 8.22 (m, 1H), 7.94 (s, 1H), 7.83 – 7.85 (m, 1H), 7.70 (d, 2H, *J* = 7.9 Hz), 7.50 – 7.69 (m, 2H), 7.28 (d, 2H, *J* = 7.9 Hz), 4.43 (s, 2H), 3.70 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.0, 146.1, 145.1, 142.8, 135.8, 135.2, 134.5, 129.6, 128.7, 128.3, 123.8, 123.6, 54.5, 52.6, 21.4.

3-(4-Nitrophenyl)-2-(toluene-4-sulfonylmethyl)acrylic acid methyl ester (1-310). ^{1}H NMR ($CDCl_3$): δ 8.22 (d, 2H, *J* = 8.7 Hz), 7.96 (s, 1H), 7.71 (d, 2H, *J* = 8.2 Hz), 7.66 (d, 2H, *J* = 8.7 Hz), 7.30 (d, 2H, *J* = 8.2 Hz), 4.40 (s, 2H), 3.65 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.0, 145.2, 143.2, 141.3, 136.0, 129.7, 129.2, 128.4, 124.3, 123.7, 123.2, 54.8, 52.6, 21.6.

2-(4-Methylbenzyl)undec-2-enoic acid methyl ester (1-311). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 2H, *J* = 8 Hz), 7.31 (d, 2H, *J* = 8 Hz), 7.10 (t, 1H, *J* = 1.8 Hz), 4.22 (s, 2H), 3.51 (s, 3H), 2.43 (s, 3H), 2.12 – 2.18 (m, 2H), 1.26 – 1.39 (m, 12H), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C

NMR ($CDCl_3$): δ 166.0, 151.5, 144.5, 135.8, 129.4, 128.6, 120.4, 53.9, 51.8, 31.6, 29.3, 29.2, 29.0, 28.1, 22.4, 21.4, 13.9.

3-Phenyl-2-(toluene-4-sulfonylmethyl)acrylonitrile (1-312). ^{1}H NMR ($CDCl_3$): δ 7.79 (d, 2H, *J* = 8.1 Hz), 7.67 – 7.69 (m, 2H), 7.41 – 7.44 (m, 3H), 7.37 (d, 2H, *J* = 8.1 Hz), 7.09 (s, 1H), 4.04 (s, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.7, 145.7, 134.5, 132.4, 131.4, 130.1, 129.2, 128.9, 128.7, 117.1, 98.1, 61.3, 21.6.

3-(4-Chlorophenyl)-2-(toluene-4-sulfonylmethyl)acrylonitrile (1-313). ^{1}H NMR ($CDCl_3$): δ 7.78 (d, 2H, *J* = 8.2 Hz), 7.63(d, 2H, *J* = 8.1 Hz), 7.34 – 7.40 (m, 4H), 7.06 (s, 1H), 4.04 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 150.2, 145.8, 137.5, 134.5, 130.9, 130.4, 130.1, 129.2, 128.6, 116.9, 98.7, 61.1, 21.6.

2-(Toluene-4-sulfonylmethyl)undec-2-enenitrile (1-314). ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 2H, *J* = 8.2 Hz), 7.37 (d, 2H, *J* = 8.2 Hz), 6.33 (t, 1H, *J* = 6.2 Hz), 3.91 (s, 2H), 2.44 (s, 3H), 2.30 – 2.35 (m, 2H), 1.16 – 1.25 (m, 12H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 158.0, 145.2, 134.1, 129.6, 128.3, 115.3, 102.6, 59.2, 31.7, 31.4, 28.8, 28.7, 28.6, 27.6, 22.2, 21.2, 13.7.

2-(4'-Methylbenzyl)-3-phenylacrylic acid methyl ester (1-315). ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.34 7.05 (m, 9H), 3.91 (s, 2H), 3.71 (s, 3H), 2.29 (s, 3H); ^{13}C NMR

($CDCl_3$): δ 166.5, 140.8, 136.1, 135.9, 135.4, 135.2, 129.1, 128.6, 128.4, 128.1, 127.6, 51.6, 32.6, 20.6.

2-(4'-Chlorophenyl)-2-(4'-methylbenzyl)acrylic acid methyl ester (1-316). M. P. 58 ^{o}C, ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.30 7.05 (m, 8H), 3.87 (s, 2H), 3.73 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (CDCl3): δ 168.3, 139.3, 135.7, 135.6, 134.6, 133.6, 131.3, 130.4, 129.2, 128.8, 127.5, 52.0, 32.6, 20.9. Anal. Calcd. for $C_{18}H_{17}ClO_2$: C, 71.88; H, 5.70. Found: C, 71.69; H, 5.76.

2-(4'-Methylbenzyl)-3-napthalene-1-ylacrylic acid methyl ester (1-317). M. P. 94 ^{o}C, ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 1H), 8.0 6.9 (m, 11H), 3.77 (s, 2H), 3.74 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.1, 138.7, 136.4, 135.2, 133.4, 133.3, 132.5, 131.4, 128.9, 128.7, 128.4, 127.8, 126.3, 126.0, 125.8, 125.0, 124.4, 51.8, 33.0, 20.8. Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.26; H, 6.33.

2-(4'-Methylbenzyl)-3-octylacrylic acid methyl ester (1-318). ^{1}H NMR ($CDCl_3$): δ 7.07 (s, 4H), 6.92 (t, J = 6 Hz, 1H), 3.67 (s, 3H), 3.63 (s, 2H), 2.28 (s, 3H), 2.21 (m, 1H); 1.60 1.20 (m, 12H), 0.90 (t, J = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 168.1, 144.2, 136.6, 135.2, 130.8, 128.8, 128.0, 51.6, 31.8, 29.3, 29.1, 28.8, 28.6, 22.6, 20.9, 14.0. Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.37; H, 10.09.

2-(4'-Methylbenzyl)-3-phenylacrylonitrile (1-319). ^{1}H NMR (CDCl3): δ 7.68 (m, 2H), 7.36 (m, 3H), 7.15, (s, 4H), 6.91 (s, 1H); 3.62 (s, 2H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 143.7, 136.8, 133.8, 133.3, 129.9, 129.5, 128.6, 116.6, 110.9, 41.7, 21.0.

3-(4'-Chlorophenyl)-2-(4'-methylbenzyl)acrylonitrile (1-320). M.P. 42 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 7.58 (d, *J* = 9 Hz, 2H), 7.27 (d, *J* = 9 Hz, 2H), 7.12 (s, 4H), 6.83 (s, 1H), 3.58 (s, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) 142.0, 136.8, 135.6, 132.9, 131.8, 129.6, 129.4, 128.7, 128.5, 116.2, 111.5, 41.4, 20.8. Anal. Calcd. for $C_{17}H_{14}CIN$: C, 76.26; H, 5.27; N, 5.23. Found: C, 76.32; H, 5.35; N, 5.17.

3-(4'-Methoxyphenyl)-2-(4'-methylbenzyl)acrylonitrile (1-321). ^{1}H NMR ($CDCl_3$): δ 7.66 (d, *J* = 9 Hz, 2H), 7.10 (s, 4H), 6.63 (d, *J* = 9 Hz, 2H), 6.62 (s, 1H), 3.71 (s, 3H), 3.53 (s, 2H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) 160.6, 143.1, 136.4, 133.5, 130.1, 129.2, 128.4, 126.0, 119.0, 113.8, 107.5, 54.9, 41.4, 20.8. Anal. Calcd. for $C_{18}H_{17}NO$; C, 82.10; H, 6.51; N, 5.32. Found: C, 82.20; H, 6.53; N, 5.40.

2-Benzyl-3-phenylacrylic acid methyl ester (1-322). ^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H), 7.34 7.15 (m, 10H), 3.94 (s, 2H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.4, 140.6, 139.2, 130.5, 129.0, 128.6, 128.4, 128.2, 127.9, 126.4, 125.9, 51.7, 33.0.

2-(4'-Methoxybenzyl)-3-phenylacrylic acid methyl ester (1-323). ^{1}H NMR ($CDCl_3$) 7.90 (s, 1H), 7.34 6.80 (m, 9H), 3.88 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H); ^{13}C NMR

($CDCl_3$): δ 168.6, 157.9, 140.6, 135.3, 131.2, 131.0, 129.2, 128.7, 128.6, 128.4, 113.9, 55.1, 52.0, 32.2. Anal. Calcd. for $C_{18}H_{18}O_3$; C, 76.57; H, 6.43. Found: C, 76.48; H, 6.48.

3-Phenyl-2-(3-thiophenyl)methylacrylic acid methyl ester (1-324). ^{1}H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.34 6.85 (m, 8H), 3.88 (s, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.3, 140.2, 139.5, 135.0 130.6, 129.1, 128.6, 128.4, 127.8, 125.5, 120.5, 51.9, 28.3. Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.69; H, 5.40.

2-(2'-Methylbenzyl)-3-phenylacrylic acid methyl ester (1-325). ^{1}H NMR ($CDCl_3$): δ 7.99 (s, 1H), 7.24 7.05 (m, 9H), 3.83 (s, 2H), 3.70 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4, 141.0, 137.2, 135.9, 135.1, 130.2, 129.9, 129.0, 128.5, 128.3, 126.4, 126.3, 125.9, 51.8, 30.7, 19.5. Anal. Calcd. for $C_{18}H_{18}O_2$: 81.17; H, 6.81. Found: C, 81.17; H, 6.80.

2-(2',6'-Dimethylbenzyl)-3-phenylacrylic acid methyl ester (1-326). M.P. 68 º C, ^{1}H NMR ($CDCl_3$): δ 7.63 (s, 1H), 7.36 6.90 (m, 8H), 3.91 (s, 2H), 3.54 (s, 3H), 2.16 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.2, 138.5, 137.1, 135.6, 135.5, 132.1, 129.0, 128.2, 128.0, 127.9, 127.6, 125.8, 51.4, 28.6, 20.4. Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.20; H, 7.26.

2-(2',6'-Difluorobenzyl)-3-phenylacrylic acid methyl ester (1-327). ^{1}H NMR ($CDCl_3$): δ 7.82 (s, 1H), 7.37 6.75 (m, 8H), 3.91 (s, 2H), 3.73, (s, 3H); ^{13}C NMR ($CDCl_3$): δ167.0,

163.5, 159.6, 140.5, 135.4, 129.6, 128.9, 128.3, 127.6, 115.2, 111.2, 110.8, 51.8, 21.5. Anal. Calcd. for $C_{17}H_{14}F_2O_2$: C, 70.83; H, 4.89. Found: C, 70.80; H, 4.87.

2-Benzylidene-5-phenylpent-4*E*-enoic acid methyl ester (1-328). ^{1}H NMR ($CDCl_3$): δ 7.85 (s, 1H), 7.35 7.20 (m, 10H), 6.40 (d, *J* = 16 Hz, 1H) 6.38 6.20 (m, 1H), 3.76 (s, 3H), 3.57 (d, *J* = 12 Hz, 1H), 3.45 (d, *J* = 4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 168.12, 140.3, 137.1, 135.1, 134.2, 132.5, 132.3, 128.5, 128.3, 127.9, 127.6, 127.1, 126.1, 126.0, 125.9, 51.8, 30.7. Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.96; H, 6.56.

2-Benzylidene-5-phenylpent-4*Z*-enoic acid methyl ester (1-329). ^{1}H NMR ($CDCl_3$): δ 7.72 (s, 1H), 7.31 7.10 (m, 10H), 6.55 (dd, *J* = 12, 1.5 Hz, 1H), 5.75 (m, 1H), 3.79 (s, 3H), 3.58 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 168.4, 140.0, 137.1, 134.9, 131.0, 129.7, 129.4, 128.8, 128.4, 128.2, 128.0 126.7, 52.0, 27.5. Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.85; H, 6.53.

2-Benzylidene-4,5-diphenylpent-4-enoic acid methyl ester (1-330). ^{1}H NMR ($CDCl_3$) 7.95 (s, 1H), 7.43 6.90 (m, 15H), 6.37 (s, 1H) 3.77 (s, 3H), 3.67 (s, 1H), ^{13}C NMR ($CDCl_3$): δ 168.4, 141.6, 141.4, 140.3, 136.9, 135.2, 129.6, 129.0, 128.7, 128.5, 128.3, 128.2, 127.7, 127.0, 126.2, 126.0, 52.0, 37.9. Anal. Calcd. for $C_{25}H_{22}O_2$: C, 84.72; H, 6.26. Found: C, 84.52; H. 6.24.

Chapter 4

Pd Catalyzed Cross-Coupling Reactions of Baylis-Hillman Acetate Aducts with Organosiloxanes

1.4.1 Introduction

The palladium-catalyzed cross-coupling reaction of organosilicon reagents with organic halides in the presence of fluoride ion (pioneered by Hiyama) has emerged as a viable and powerful alternative to the analogous boron and tin-based reactions.[91] Recent reports from different laboratories have demonstrated that simple organosilicon compounds bearing a single oxygen substituent can serve effectively as donors in palladium-catalyzed cross-coupling reactions.[92-94] Treatment of aryltrimethoxysilane with an equivalent amount of tetraammonium fluoride (TBAF) resulted in the *in situ* formation of hypervalent fluorosilicate anion (Figure 1-4-1).[95-100] Subsequent coupling of the organosilicate with aryl halide or triflate (or other electrophiles) in the presence of a Pd(0) catalyst afforded the cross-coupled product.

Compared to many other organometallic reagents, silicon compounds have the advantages of (1) low molecular weight, (2) high stability, (3) ease of activation, and (4) ready conversion to harmless byproducts. In view of the strong similarities between boron and silicon chemistry, the cross-coupling reactions of Baylis-Hillman acetate adducts with silicon reagents was explored using palladium catalysis. Herein, the

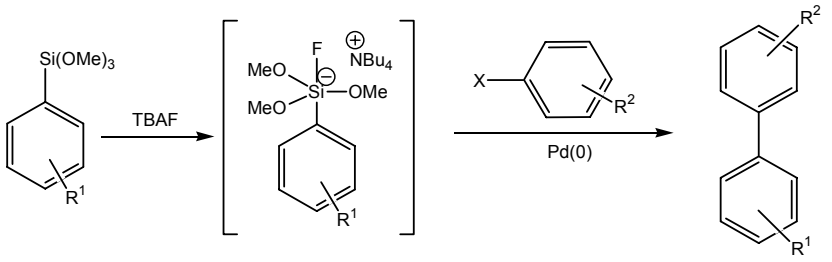


Figure 1-4-1: Coupling of siloxanes with electrophiles.

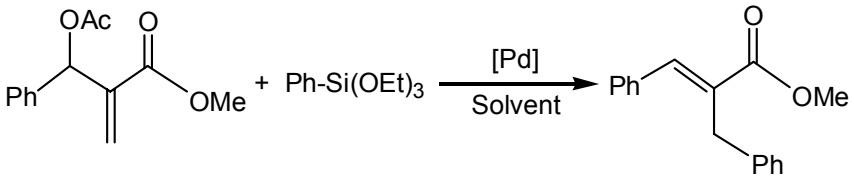
newly developed palladium-catalyzed coupling reaction of organosiloxanes with Baylis-Hillman acetate aducts are described.

1.4.2 Results and Discussion

1.4.2.1 Optimization of Reaction Conditions

The coupling reaction of methyl 3-acetoxy-3-phenyl-2-methylenepropanoate and phenyltriethoxysilane was chosen as a model to define the optimum reaction conditions (Table 1-4-1). When the reaction was performed in THF/H_2O in the presence of 3 mol % of $Pd_2(dba)_3$ and 2 equivalent of KF at 50 ^oC for five hours, only 35% yield of coupling product was obtained. When the catalyst was changed to $Pd(OAc)_2$, it proved even less effective. Only trace quantities of the desired product were formed. Encouraging results were achieved when KF was replaced by tetrabutylammonium fluoride as the silane activator. Treatment of a Baylis-Hillman adduct (0.5 mmol) with phenyltriethoxysilane (0.65 mmol) in the presence of 3 mol % of $Pd_2(dba)_3$ and two equivalents of TBAF yielded 72% of the desired cross-coupled product.

Table 1-4-1: Optimization of reaction conditions.



Entry	Catalyst[a]	Base[b]	Solvent	T (^{o}C) / T (h)	Yield (%)[d]
1	$Pd_2(dba)_3$	KF	THF/H_2O[c]	50 / 5	35
2	$Pd(OAc)_2$	KF	THF/H_2O[c]	50 / 5	trace
3	$Pd_2(dba)_3$	*n*-Bu_4NF	THF	50 / 2	72
4	$Pd_2(dba)_3$	*n*-Bu_4NF	Toluene	50 / 2	74
5	$Pd_2(dba)_3$	*n*-Bu_4NF	$BmimBF_4$	50 / 6	N. R.
6	$Pd_2(dba)_3$	*n*-Bu_4NF	PEG	rt / 3	92
7	$Pd_2(dba)_3$	*n*-Bu_4NF[e]	PEG	rt / 3	80
8	$Pd(OAc)_2$	*n*-Bu_4NF	PEG	rt / 3	85

[a]3 mol % of $Pd_2(dba)_3$ was used. 5 mol % of $Pd(OAc)_2$ was used.

[b]2 equivalent of base was used.

[c]ratio of THF / H_2O was 20 / 1.

[d]Isolated yields.

[e]1 equivalent of *n*-Bu_4NF was used.

However, 27% of the regional isomeric product of the Baylis-Hillman adduct was also formed. To increase the yield of the desired product and suppress the formation of the regioisomer, other solvents were evaluated. In toluene, 25% of the regional isomer was formed although 74% of desired product was also obtained. Due to the great interest in non-conventional solvents, the reactions were carried out in an ionic liquid, $bmimBF_4$. Unfortunately, no reaction occurred in $bmimBF_4$. However, polyethylene glycol (PEG) was found to be a suitable solvent for the reaction. When PEG-600 was used, the isomerization reaction was inhibited and an excellent yield was obtained at room temperature. The quantity of TBAF was also evaluated. One equivalent of TBAF afforded lower yields (80%) but two equivalents of TBAF led to high yields. Although $Pd(OAc)_2$ is generally less reactive than $Pd_2(dba)_3$, a good yield can also be obtained (85%) when PEG was used as solvent.

On the basis of the results summarized in Table 1-4-1, the optimal reaction conditions for coupling of phenyltrioxysilane with Baylis-Hillman acetate adducts were found to be 3 mol % of $Pd_2(dba)_3$ and two equivalents of TBAF in PEG-600 at room temperature.

1.4.2.2 Study of the Reaction Scope

With an optimal set of reaction conditions established, the scope of the reaction was then surveyed. Baylis-Hillman acetate adducts derived from aryl aldehydes, heteroaryl aldehydes, and aliphatic aldehydes with methyl acrylate, acrylonitrile, or *α, β*-unsaturated cycloketones were subjected to the coupling reaction process.

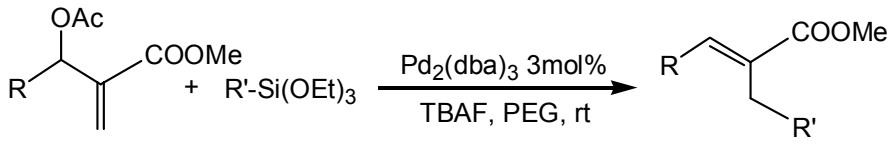
1.4.2.2.1 Coupling of Baylis-Hillman Adducts Derived from Methyl Acrylate and Methyl Acronitrile

The generality of the reaction of various Baylis-Hillman acetate adducts, prepared based on literature procedures from methyl acrylate and representative aldehydes, with phenyltriethoxysilane was first studied. The results are summarized in Table 1-4-2 (entries 1-9). Notably, the reaction is only slightly influenced by the substituents and their substitution patterns on the aromatic ring of the Baylis-Hillman adducts, although reagents containing electron-donating groups gave a slightly higher yields. Baylis-Hillman acetate adducts prepared from heteroaryl and aliphatic aldehydes also readily participated in the reaction.

The reaction is highly stereoselective. The stereochemistry of the products was established by comparing NMR shift values of olefinic and methylene protons with literature values.[82] The ratio of *E*/*Z* isomers was determined by ^{1}HNMR analysis. The ratio was normally found to be greater than 90/10 even for aliphatic Baylis-Hillman adducts.

The results of coupling Baylis-Hillman adducts with various organotriethoxysilanes are summarized in Table 1-4-2 (entries 10-13). Aryl and heteroarylsilanes all participate in this reaction and yields are good to excellent. The results demonstrated that the electronic character of the substituents on the aromatic ring has little affect on the reaction yields. Heteroarylsiloxanes afford lower yields than arylsiloxanes.

Table 1-4-2: Coupling of various Baylis-Hillman Acetate adducts with different organosiloxanes.

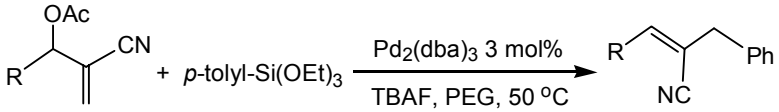


Entry	R	R'	Product	Yield (%)	E/Z
1	Phenyl	Phenyl	**1-322**	92	93/7
2	*p*-Chlorophenyl	Phenyl	**1-401**	91	99/1
3	*p*-Tolyl	Phenyl	**1-402**	89	95/5
4	Naphthyl	Phenyl	**1-403**	87	94/6
5	2-Furyl	Phenyl	**1-404**	78	99/1
6	*p*-Methoxyphenyl	Phenyl	**1-405**	94	99/1
7	2-Chlorophenyl	Phenyl	**1-406**	86	92/8
8	*n*-Octyl	Phenyl	**1-407**	85	90/10
9	*p*-Nitrophenyl	Phenyl	**1-408**	62	96/4
10	Phenyl	*p*-Tolyl	**1-315**	86	97/3
11	Phenyl	*p*-Chlorophenyl	**1-409**	92	98/2
12	Phenyl	2-Thiofuryl	**1-410**	70	93/7

The protocol was then applied to coupling reactions of various 3-acetoxy-2-methylenealkanenitriles with phenyltriethoxysilane. Unfortunately, the reaction did not occur at room temperature. However, the desired coupling product was obtained after heating the reaction mixture to 50 ^{o}C for longer periods of time (Figure 1-4-2). Although this minor modification of the original optimum conditions was required, the reactions afforded the desired products with excellent stereoselectivity. For Baylis-Hillman nitrile adducts, the *Z* isomer is the major product, which is consistent with the result we obtained in Chapter 3.

1.4.2.2.2 Coupling of Baylis-Hillman Adducts Derived from Acylic and Cyclic *α,β*-Unsaturated Ketones

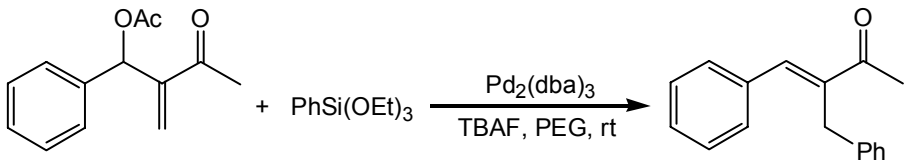
The reactions of Baylis-Hillman adducts derived from vinyl ketones with organosiloxyanes were then surveyed. The Baylis-Hillman adduct prepared from benzaldehyde and methyl vinyl ketone was first examined (Figure 1-4-3). The reaction proceeded smoothly under optimized conditions in excellent (90%) yield. No stereoisomer formation was observed in the reaction and only S_N2' coupling product formed.



R = *p*-Chlorophenyl 50% (**1-320**)

R = *p*-Methoxyphenyl 54% (**1-321**)

Figure 1-4-2: Coupling of Baylis-Hillman nitrile adducts.



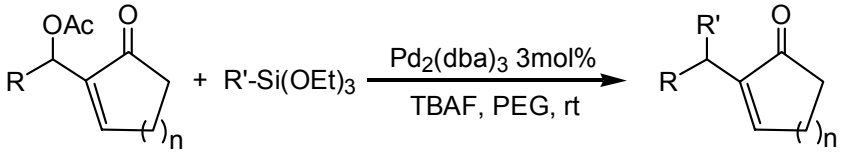
90% (**1-411**)

Figure 1-4-3: Coupling of Baylis-Hillman adduct derived from vinyl ketone.

Having demonstrated that acyclic vinyl ketone derived Baylis-Hillman adducts underwent coupling with phenyltriethoxysilane, reaction of the Baylis-Hillman adducts derived from α, β-unsaturated cyclopentenone and cyclohexenone were examined. Unexpected results were obtained.

The reaction of acetic acid (6-oxocyclohex-1-enyl)phenylmethyl ester, which was prepared from benzaldehyde and 2-cyclohexenone with phenyltriethoxysilane, was carried out under the optimized conditions. After isolation and characterization of the product, it was determined that S_N2' rearrangement did not occur. Instead, the phenyl group of the phenyltriethoxysilane replaced the acetoxy group at its original position (S_N2 coupling). This type of coupling reactions had not been reported previously. It is noteworthy that there is a chiral center produced in the product. Representative results of the cross-coupling reaction of a variety of cyclic ketone derived Baylis-Hillman adducts are summarized in Table 1-4-3. Among the *α, β*-unsaturated cyclic ketones derived Baylis-Hillman adducts examined, 2-cyclohexenone derivatives produced higher yields than 2-cyclopentenone derivatives. The substituents on the aromatic ring of organosiloxane only slightly affected the reaction yields. The cross-coupling reactions of Baylis-Hillman adducts with potassium organotrifluoroborates (discussed in Chapter 3)

Table 1-4-3: Coupling of various Baylis-Hillman adducts derived from α, β-unsaturated cyclopentenones and cyclohexenones with different triethoxysilanes.



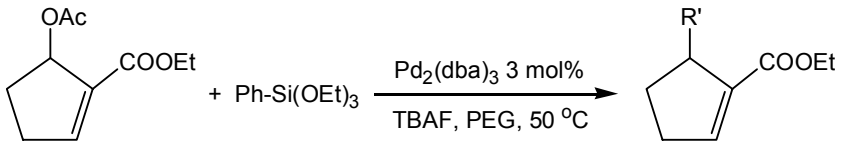
Entry	R	n	R'	Product	Yield(%)
1	Phenyl	1	Phenyl	**1-412**	51
2	Phenyl	1	*p*-Tolyl	**1-413**	53
3	Phenyl	2	Phenyl	**1-414**	70
4	Phenyl	2	*p*-Tolyl	**1-415**	66
5	Phenyl	2	*p*-Chlorophenyl	**1-416**	77
6	2-Methoxyphenyl	2	Phenyl	**1-417**	61
7	2-Methoxyphenyl	2	*p*-Tolyl	**1-418**	65

were also studied. However, attempts to couple potassium organotrifluoroborates with cyclic ketone derived Baylis-Hillman adducts failed.

1.4.2.2.3 Coupling of Functionally Substituted Allylic Cycloalkenol Acetates with Organotriethoxysilanes

Allylic cycloalkenol acetates are important synthetic precursors in organic and medicinal synthesis. For example, Casara utilized them as key precursors in the synthesis of cyclopentanecarboxylic acid matrix metalloproteinase (MMP) inhibitors.[101] Amri converted allylic cycloalkenol acetates to alkylcarbethoxycycloalkenes as the key step in a short synthesis of (±)-mitsugashiwalactone.[102, 103]

To extend the scope of the new reaction, the reaction of a 5-acetoxy-cyclopent-1-enecarboxylic acid ethyl ester was investigated (Figure 1-4-4). The yields were moderate.



R' = Phenyl 48% (**1-419**)

R' = *p*-chlorophenyl 55% (**1-420**)

Figure 1-4-4: Coupling of 5-acetoxy-cyclopent-1-enecarboxylic acid ethyl ester.

1.4.3 Conclusion

An efficient palladium-catalyzed coupling reaction of aryltrialkoxysilanes with various Baylis-Hillman acetate adducts has been developed. PEG was shown to be an effective solvent because it suppressed the formation of regional isomers of the Baylis-Hillman adducts. The coupling reaction of *α, β*-unsaturated cyclic ketone derived Baylis-Hillman adducts with siloxanes was also developed. Further application of this chemistry to an asymmetric reaction is currently under investigation.

1.4.4 Experimental Section

1.4.4.1 General Considerations

Nuclear magnetic resonance (^{1}H and ^{13}C NMR) were recorded on either a Varian 300 MHz or a Bruker 250 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (δ) relative to TMS. Coupling constants (*J* values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Thin-layer chromatography (TLC) was performed with the compounds being identified in UV (254 nm). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

All glassware was dried in an oven at 120 ^{o}C and flushed with dry nitrogen. Reactions were carried out under a nitrogen atmosphere. All reagents were purchased from Aldrich Chemical Company and used as received. Baylis-Hillman adducts were prepared according to the literature procedure.[81, 84] Products were purified by flash

chromatography using silica gel (60 C, 230 400 mesh) with hexanes and ethyl acetate (hxanes:EtOAc 20:1) as eluent.

1.4.4.2 General Procedure for the Coupling of Baylis–Hillman Acetate Adducts with Organosiloxanes

To a solution of the acetate of a Baylis-Hillman adduct (0.5 mmol, 1.0 equiv), organosiloxane (0.65 mmol, 1.3 equiv), 3 mol % of $Pd_2(dba)_3$ in 3 ml of PEG-600 was added 2.0 ml of TBAF THF solution (1.0 M, 1.0 mmol) via syringe. The system was evacuated and purged with nitrogen gas. The reaction mixture was stirred at the indicated temperature for 4-8 h. After completion of the reaction (TLC), the mixture was extracted with 4 x 5 ml of Et_2O, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator. Purification of the residue by flash chromatography yielded the desired product. The spectral data of the individual compounds are reported below.

1.4.4.3 Analytic Data

2-Benzyl-3-phenylacrylic acid methyl ester (1-322). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.12 g (92%) of **1-322** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.18 – 7.34 (m, 10H), 3.95 (s, 2H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 140.9, 139.3, 135.2, 130.5, 129.1, 128.7,

128.5, 128.4, 127.8, 126.0, 52.0, 33.1.Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39; Found: C, 80.87; H, 6.40.

2-Benzyl-3-(4-chlorophenyl)acrylic acid methyl ester (1-401). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.13 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.13 g (91%) of **1-401** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.87 (s, 1H), 7.16 – 7.30 (m, 9H), 3.92 (s, 2H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4, 139.6, 139.0, 134.5, 133.7, 131.2, 130.5, 128.8 128.6, 127.8, 126.2, 52.2, 33.1. Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27; Found: C, 71.02; H, 5.32.

2-Benzyl-3-*p*-tolylacrylic acid methyl ester (1-402). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.12 g (89%) of **1-402** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.92 (s, 1H), 7.11 – 7.30 (m, 9H), 3.97 (s, 2H), 3.74 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.8, 141.1, 139.4, 139.0, 132.4, 129.6, 129.3, 128.5, 127.9, 126.0, 52.1, 33.1, 21.3. Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81; Found: C, 81.36; H, 6.64.

2-Benzyl-3-naphthalen-1-ylacrylic acid methyl ester (1-403). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.14 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.13 g (87%) of **1-403** as a waxy solid: ^{1}H NMR ($CDCl_3$): δ ^{13}C NMR ($CDCl_3$): δ 168.2, 139.7, 139.1, 133.4, 133.3, 132.7, 131.5 128.9, 128.5, 128.3, 128.1, 126.5, 126.2, 126.0, 125.9, 125.2, 124.6, 52.1, 33.5. Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00; Found: C, 83.32; H, 6.06.

2-Benzyl-3-furan-2-ylacrylic acid methyl ester (1-404). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.11 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.09 g (78%) of **1-404** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.58 (s, 1H), 7.49 (d, 1H, J = 2.1 Hz), 7.20 – 7.25 (m, 5H), 6.60 (d, 1H, J = 3.3 Hz), 6.45 (dd, 1H, J_1 = 2.1 Hz, J_2 = 3.3 Hz), 4.14, (s, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.5, 151.3 144.4, 139.4, 128.3, 128.2, 127.2, 126.7, 125.9, 115.8, 112.0, 52.0, 33.3. Anal. Calcd. for C15H14O3: C, 74.36; H, 5.82; Found: C, 74.53; H, 5.68.

2-Benzyl-3-(4-methoxyphenyl)acrylic acid methyl ester (1-405). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.13 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash

chromatography gave 0.13 g (94%) of **1-405** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.34 (d, 2H, *J* = 9 Hz), 7.20 – 7.32 (m, 5H), 6.85 (d, 2H, *J* = 9 Hz), 3.98 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.9, 160.1, 147.4, 140.8, 139.4, 131.1, 128.5, 128.1, 127.8, 127.7, 126.0, 114.0, 55.2, 52.0, 33.1. Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.72; H, 6.35.

2-Benzyl-3-(2-chlorophenyl)acrylic acid methyl ester (1-406). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.13 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.12 g (86%) of **1-406** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.12 – 7.44 (m, 9H), 3.81(s, 2H), 3.75(s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.0, 147.4, 139.2, 137.8, 134.1, 134.0, 132.9, 129.7, 129.6, 128.5, 127.9, 126.6, 126.1, 52.1, 33.2. Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27; Found: C, 71.07; H, 5.21.

2-Benzylundec-2-enoic acid methyl ester (1-407). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.14 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.12 g (85%) of **1-407** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.15 – 7.28 (m, 5H), 6.95 (t, 1H, *J* = 7.5 Hz), 3.67 – 3.69 (m, 5H), 2.27 (q, 2H, *J* = 7.2 Hz), 1.23 – 1.47 (m, 12H), 0.88 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 168.2, 144.5, 139.8, 130.6, 128.3, 128.2, 125.9, 51.7, 32.3,

31.8, 29.4, 29.3, 29.2, 29.0, 28.7, 22.6, 14.1. Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78; Found: C, 78.93; H, 10.03.

2-Benzyl-3-(4-nitrophenyl)acrylic acid methyl ester (1-408). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.14 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.09 g (62%) of **1-408** as a white crystal: ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, J = 9 Hz), 7.93 (s, 1H), 7.50 (d, 2H, J = 9 Hz), 7.14 – 7.31 (m, 5H), 3.92 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$): δ Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71; Found: C, 68.43; H, 4.93; N, 4.62.

2-(4-Methylbenzyl)-3-phenylacrylic acid methyl ester (1-315). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.11 g (86%) of **1-315** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.08 – 7.35 (m, 9H), 3.91 (s, 2H), 3.73 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.8, 140.7, 138.2, 135.5, 135.3, 130.9, 129.2, 128.7, 128.5, 127.7, 52.0, 32.7, 21.0. Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81; Found: C, 81.34; H, 6.73.

2-(4-Chlorobenzyl)-3-phenylacrylic acid methyl ester (1-409). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.13 g (92%) of **1-409** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.93 (s, 1H), 7.32 (m, 5H), 7.23 (d, 2H, J = 8.4 Hz), 7.10 (d, 2H, J = 8.4 Hz), 3.90 (s, 2H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.3, 141.2, 137.9, 135.1, 131.9, 130.2, 129.2, 129.0, 128.8, 128.6, 52.1, 32.5. Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27; Found: C, 71.43; H, 5.40.

3-Phenyl-2-thiophen-2-ylmethyl-acrylic acid methyl ester (1-410). The ester **1-410** was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 4 hours. Purification of the residue by flash chromatography gave 0.09 g (70%) of **1-410** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.33 – 7.41 (m, 5H), 7.14 (m, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 4.01 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.9, 140.9, 130.4, 129.6, 129.2, 128.9, 128.6, 128.3, 126.8, 124.6, 123.6, 52.2, 28.1. Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; Found: C, 70.02; H, 5.33.

3-Benzyl-4-phenylbut-3-en-2-one (1-411). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.11 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for

4 hours. Purification of the residue by flash chromatography gave 0.11 g (90%) of **1-411** as a white solid: ^{1}H NMR ($CDCl_3$): δ 7.75 (s, 1H), 7.13 – 7.38 (m, 10H), 3.94 (s, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 199.7, 141.2, 139.8, 139.4, 135.3, 129.2, 128.9, 128.6, 128.5, 127.9, 126.0, 32.1, 26.3. Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.82; Found: C, 86.12; H, 6.76.

2-Benzhydrylcyclopent-2-enone (1-412). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash chromatography gave 0.06 g (51%) of **1-412** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.10 – 7.31 (m, 11H), 5.16 (s, 1H), 2.58 – 2.61 (m, 2H), 2.45 – 2.49 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 207.8, 160.4, 148.8, 141.8, 128.6, 128.4, 126.5, 47.2, 34.8, 26.5. Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49; Found: C, 86.85; H, 6.41. Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49; Found: C, 87.13; H, 6.36.

2-(Phenyl-*p*-tolylmethyl)-cyclopent-2-enone (1-413). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash chromatography gave 0.07 g (53%) of **1-413** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 6.99 – 7.29 (m, 10H), 5.13 (s, 1H), 2.59 – 2.62 (m, 2H), 2.45 – 2.48 (m, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 208.0, 160.4, 149.0,

142.1, 138.8, 136.0, 129.1, 128.5, 128.4, 128.3, 126.4, 46.8, 34.8, 26.5, 21.0. Anal. Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.92; Found: C, 86.76; H, 6.88.

2-Benzhydrylcyclohex-2-enone (1-414). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash chromatography gave 0.09 g (70%) of **1-414** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.08 – 7.29 (m, 10H), 6.41 (t, 1H, J = 3.9 Hz), 5.51 (s, 1H), 2.45 (t, 2H, J = 6.3 Hz), 2.36 (m, 2H), 2.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 197.9, 148.0, 142.4, 129.0, 128.2, 126.2, 49.3, 38.6, 26.1, 22.8. Anal. Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.92; Found: C, 86.87; H, 6.82.

2-(Phenyl-*p*-tolylmethyl)-cyclohex-2-enone (1-415). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash chromatography gave 0.09 g (66%) of **1-415** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 6.96 – 7.26 (m, 9H), 6.41 (t, 1H, J = 3.8 Hz), 5.46 (s, 1H), 2.30 – 2.47 (m, 4H), 1.98 – 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 197.9, 147.7, 142.7, 142.6, 139.4, 135.7, 128.9, 128.2, 126.1, 48.9, 38.6, 26.1, 22.8, 21.0. Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29; Found: C, 86.78; H, 7.24.

2-[(4-Chlorophenyl)phenylmethyl]cyclohex-2-enone (1-416). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.12 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash chromatography gave 0.11 g (77%) of **1-416** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.00 – 7.30 (m, 9H), 6.39 (t, 1H, *J* = 3.7 Hz), 5.46 (s, 1H), 2.33 – 2.47 (m, 4H), 1.97 – 2.02 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 197.7, 148.2, 142.1, 141.8, 141.0, 132.0, 130.2, 128.9, 128.3, 126.4, 48.7, 38.5, 26.1, 22.7. Anal. Calcd. for $C_{19}H_{17}ClO$: C, 76.89; H, 5.77; Found: C, 77.14; H, 5.86.

2-[(2-Methoxyphenyl)phenylmethyl]cyclohex-2-enone (1-417). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.14 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash chromatography gave 0.09 g (61%) of **1-417** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.08 – 7.27 (m, 6H), 6.82 – 6.85 (m, 3H), 6.34 (t, 1H, *J* = 3.9 Hz), 5.80 (s, 1H), 3.73 (s, 3H), 2.44 (t, 2H, *J* = 6.6 Hz), 2.32 – 2.37 (m, 2H), 1.95 – 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 197.8, 156.8, 146.8, 142.2, 142.0, 131.3, 129.2, 129.0, 128.1, 127.4, 126.0, 119.9, 110.6, 55.5, 42.6, 38.6, 26.1, 22.9. Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89; Found: C, 82.22; H, 6.87.

2-[(2-Methoxyphenyl)-*p*-tolylmethyl]cyclohex-2-enone (1-418). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.14 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room

temperature for 8 hours. Purification of the residue by flash chromatography gave 0.10 g (65%) of **1-418** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.14 – 7.21 (m, 1H), 7.06 (d, 2H, *J* = 8.1 Hz), 6.98 (d, 2H, *J* = 8.1 Hz), 6.79 – 6.94 (m, 3H), 6.34 (t, 1H, *J* = 4.2 Hz), 5.76 (s, 1H), 3.73 (s, 3H), 2.43 (t, 2H, *J* = 6.6 Hz), 2.29 – 2.36 (m, 2H), 1.94 – 2.03 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 197.8, 156.8, 146.6, 142.1, 139.0, 135.4, 131.4, 129.1, 128.9, 128.8, 127.3, 119.9, 110.6, 55.4, 42.2, 38.6, 26.1, 22.9, 21.0. Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24; Found: C, 82.61; H, 7.29.

5-Phenylcyclopent-1-enecarboxylic acid ethyl ester (1-419). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.10 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash chromatography gave 0.05 g (48%) of **1-419** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.24 – 7.29 (m, 3H), 7.14 – 7.19 (m, 2H), 6.98 (t, 1H, *J* = 1.8 Hz), 4.01 – 4.14 (m, 3H), 2.48 – 2.68 (m, 3H), 1.85 – 1.97 (m, 1H), 1.11 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 164.8, 145.3, 144.4, 139.6, 128.3, 127.0, 126.1, 59.9, 50.1, 34.0, 32.2, 14.0. Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46; Found: C, 77.80; H, 7.53.

5-(4-Chlorophenyl)cyclopent-1-enecarboxylic acid ethyl ester (1-420). The ester was prepared according to the general procedure for the cross-coupling reaction employing 0.10 g (0.50 mmol) of the Baylis-Hillman acetate adduct. The reaction mixture was stirred at room temperature for 8 hours. Purification of the residue by flash

chromatography gave 0.06 g (55%) of **1-420** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.23 (dd, 2H, J_1 = 2.1 Hz, J_2 = 8.4 Hz), 7.09 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz), 6.98 (t, 1H, J = 1.8 Hz), 4.01 – 4.14 (m, 3H), 2.47 – 2.68 (m, 3H), 1.84 – 1.89 (m, 1H), 1.13 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$): δ 164.5, 144.8, 143.8, 139.2, 131.7, 128.4, 128.3, 60.0, 49.5, 33.9, 32.1, 14.0. Anal. Calcd. for $C_{14}H_{15}ClO_2$: C, 67.07; H, 6.03; Found: C, 67.25; H, 6.13.

Chapter 5

Palladium-Catalyzed Cross-Coupling of Baylis-Hillma Acetate Adducts with Bis(pinacolato)diboron: An Efficient Route to Functionalized Allyl Borates

1.5.1 Introduction

Allylmetal reagents of boron, silicon, and tin have found widespread use in organic synthesis.[104] The addition of allylmetal reagents to carbonyl compounds has proven to be enormously successful for the synthesis of homoallylic alcohols and is widely used in organic synthesis. Among allylmetal reagents, allylboron compounds are very useful because of the high yield and excellent stereocontrol they provide in reactions with carbonyl compounds via a six-membered, cyclic chair transition state characterized by internal activation of the aldehyde by the boron.[105] Brown,[106] Hoffman,[107] and Roush[108] have investigated this transformation in detail.

However, availability of functionalized allylboron reagents remains limited. In addition to traditional methods,[108a, 109] the prerequisite allylboronates can be prepared via transition metal mediated processes,[110] cross-metathesis reactions of olefins and allylboronates,[111] and a three-component assembly of allenes, acyl chlorides, and bis(pinacolato)diboron.[112] Recently, Kennedy and Hall reported the preparation of 2-alkoxycarbonylallylboronates by carbocupration of alkynoate esters.[113] These results encouraged us to investigate the preparation of substituted 2-alkoxycarbonyl allylboron

reagents from Baylis-Hillman adducts. In a continuation of our study of reactions involving organoboron reagents, the cross-coupling reactions of *bis*(pinacolato)diboron with acetates of Baylis-Hillman adducts in the presence of palladium to form highly functionalized allyl boronates and the corresponding trifluoroborates were investigated.[114]

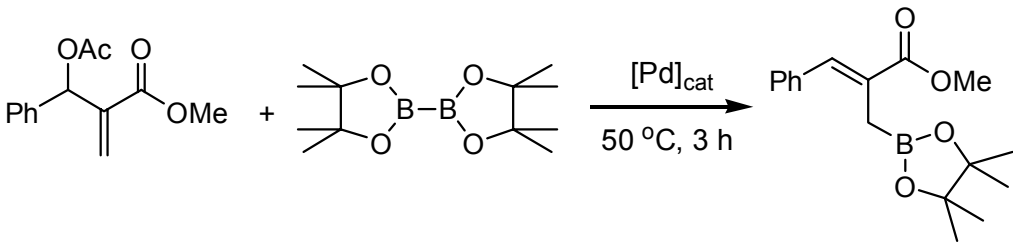
1.5.2 Results and Discussion

1.5.2.1 Syntheses of Potassium Allyltrifluoroborates

The preparation of allylboronate using the Baylis-Hillman adduct, methyl 3-acetoxy-3-phenyl-2-methylenepropanoate, and bis(pinacolato)diboron in the presence of various palladium catalysts was first investigated (Table 1-5-1). Among the catalysts used, $Pd(OAc)_2$ and $Pd_2(dba)_3$ worked well without additional ligands. The reactions were most efficient in THF and toluene. The highest yields were obtained utilizing $Pd_2(dba)_3$, but the allylboronate products readily decomposed during silica gel chromatography.[111] To solve this problem, we converted the boronate products to the corresponding trifluoroborate derivatives (Figure 1-5-1) because trifluoroborates are air- and moisture-stable while remaining chemically reactive.

The reaction procedure is straightforward. The Baylis-Hillman acetate adduct is allowed to react with bis(pinacolato)diboron in the presence of 5 mol % $Pd(OAc)_2$ or 3 mol % Pd_2 $(dba)_3$ in THF at 50 °C for 3 h. This produces the 2-alkoxycarbonyl-3-substituted allylboronate pinacol ester, which is then treated with excess aqueous KHF_2

Table 1-5-1: Optimizing reaction conditions for the preparation of allylboronate from Baylis-Hillman adduct.



Solvent	Catalyst[a]	Ligand[b]	Yield (GC-MS)
THF	$Pd(OAc)_2$	PPh_3	36
THF	$Pd(OAc)_2$	dppf	48
THF	$Pd(OAc)_2$	–	92
THF	$Pd(PPh_3)_2Cl_2$	–	0
THF	$PdCl_2(dppf)_2$	–	0
THF	$Pd_2(dba)_3$[c]	–	95
Ether	$Pd(OAc)_2$	–	82
Toluene	$Pd(OAc)_2$	–	96
Toluene	$Pd_2(dba)_3$[c]	–	96

[a]5 mol% of catalyst was used unless otherwise mentioned.

[b]10 mol% of ligand was used.

[c] 3 mol% of catalyst was used.

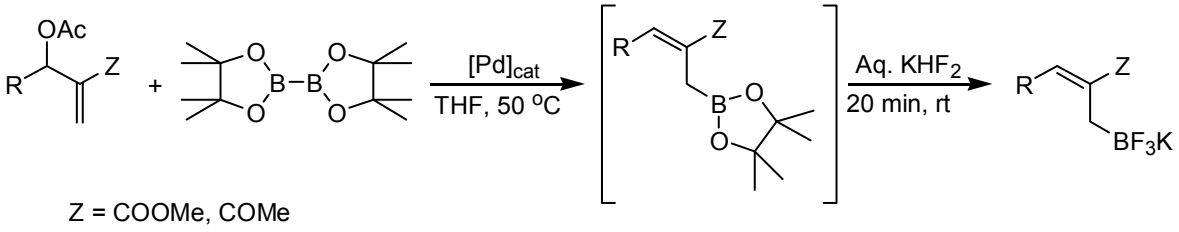


Figure 1-5-1: Conversion of allylboronate to potassium organotrifluoroborate.

and stirred at room temperature for 20 min to obtain the (*E*)-2-alkoxy-3-substituted allyltrifluoroborate potassium salt. The stereochemistry of the allylboronate was determined to be *E*, using ^{1}H and ^{13}C spectroscopy as well as protonolysis.[115] The results are consistent with earlier studies.[89] It is important to note that allyl trifluoroborate salts are air and water stable solids that can be stored at room temperature, whereas allylboronates react with water. Several types of Baylis-Hillman acetate adducts readily participate in the reaction. As shown in Table 1-5-2, Baylis-Hillman acetate adducts derived from methyl acrylate and methyl vinyl ketone were transformed into the corresponding (*E*)-allylborates.

1.5.2.2 Synthesis of Homoallylic Alcohols Utilizing Allylboranes

With the functionalized allylboranes in hand, their utility in organic syntheses was investigated.The functionalized allylboranes were first utilized in the synthesis of homoallylic alcohols.

The reaction of allyl trifluoroborate salts with *p*-nitrobenzaldehyde were examined. It was found that the reaction proceeded smoothly in the presence of

Table 1-5-2: Preparation of substituted allylboron reagents from Baylis-Hillman acetate adducts.

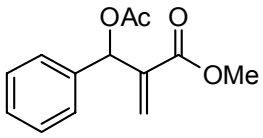
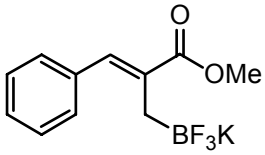
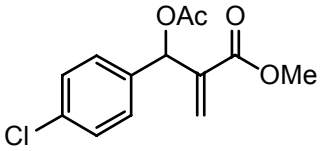
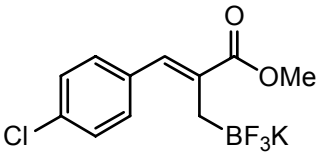
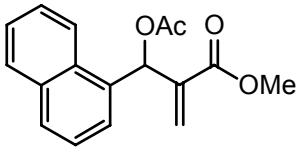
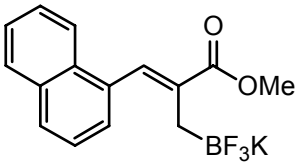
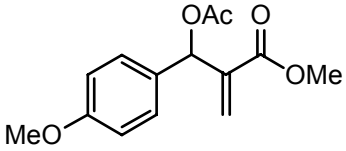
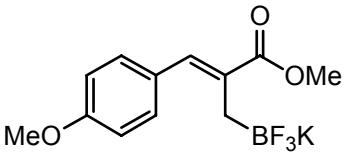
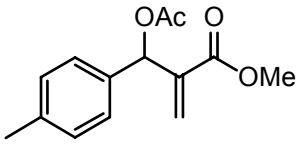
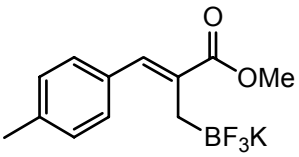
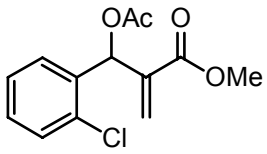
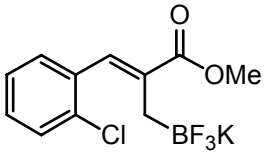
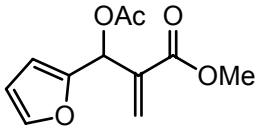
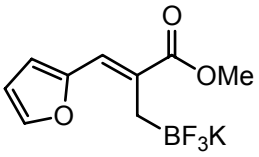
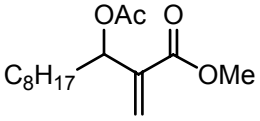
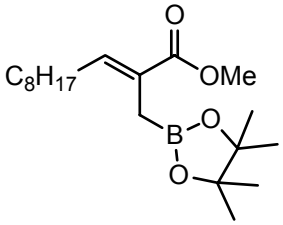
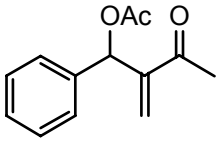
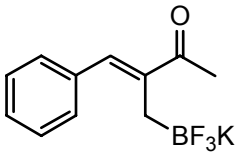
B-H acetate adduct	Product[b]	Yield (%)
	 **1-501**	70
	 **1-502**	57
	 **1-503**	65
	 **1-504**	72
	 **1-505**	68

Table 1-5-2 Continued.

B-H acetate adduct	Product[b]	Yield (%)
	 **1-506**	56[d]
	 **1-507**	67
		72[e,f]
	 **1-508**	62

[a]The cross-coupling reaction was performed at 50 °C for 3 h using 5 mol% of $Pd(OAc)_2$ in THF unless otherwise noted.

[b]Structures confirmed using spectral (^1H, ^{13}C, ^{19}F) and elemental analyses.

[c]3 mol% of $Pd_2(dba)_3$ used.

[d]*E*:*Z* ratio is 97:3.

[e]Reaction time was 6 hr.

[f]GC/MS yield.

tetrabutylammonium iodide to give the corresponding homoallylic alcohols in high yields with excellent diastereoselectivity (Figure 1-5-2, eq 1).[114c]

The allylboration reactions that did not involve isolating the boron intermediates were included (Figure1-5-2, eq 2).[116] Addition of *p*-nitrobenzaldehyde to the crude cross-coupling reaction mixture furnished the corresponding homoallylic alcohols. However, the reaction required longer reaction times (8 days). There are several reports that Lewis acids catalyze the addition reaction of allylsilanes and allyltin reagents with carbonyl compounds.[117] Recently Hall[118] reported that Lewis acids such as $Sc(OTf)_3$ also accelerate allylboration reactions of carbonyl compounds and Miyaura showed that regio- and stereo-selectivity is very high in $AlCl_3$ catalyzed allylboration reactions.[119] Thus, the effect of various Lewis acids on the new reaction was examined. In searching for suitable Lewis acids, $BF_3{\cdot}Et_2O$ was found to be an effective catalyst for the *in situ* allylboration reaction. To increase the utility of the present reaction, a solid Lewis acid (silica supported BF_3 - $BF_3{\cdot}SiO_2$) was prepared and used in the reaction.

Several examples were carried out using different types of Baylis-Hillman adducts derived from aromatic, heteroaromatic, and aliphatic aldehydes (Table 1-5-3). Baylis-Hillman adducts derived from heteroaromatic and aliphatic aldehydes gave lower yields when compared with Baylis-Hillman adducts derived from aromatic aldehydes. Steric factors affected the reaction yields. For example, Baylis-Hillman adducts derived from naphthaldehyde (Table 1-5-3 entry 4) and *ortho*-chlorobenzaldehyde (Table 1-5-3 entry 5) gave lower yields.

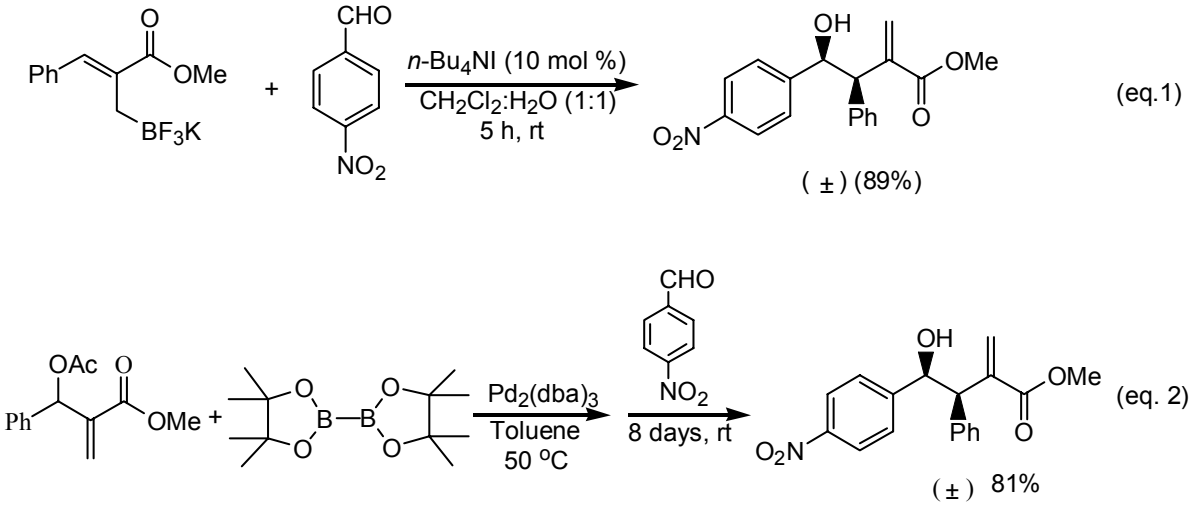
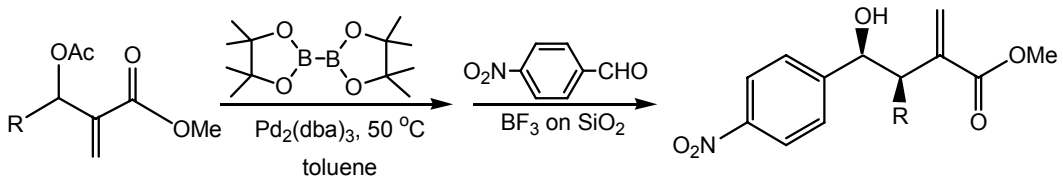


Figure 1-5-2: (eq. 1) Reaction of potassium allyltrifluoroborate with *p*-nitrobenzaldehyde; (eq. 2) *In situ* reaction of allylborane with *p*-nitrobenzaldehyde.

Table 1-5-3: Synthesis of homoallylic alcohols from various Baylis-Hillman adducts and *p*-nitrobenzaldehyde.



Entry	R	Time (h)	Product	Yield (%)
1	*p*-Tolyl	24	**1-509**	80
2	*p*-Chlorophenyl	24	**1-510**	73
3	*p*-Methoxyphenyl	24	**1-511**	84
4	1-Naphthyl	36	**1-512**	68
5	*o*-Chlorophenyl	24	**1-513**	69
6	2-Furyl	24	**1-514**	56
7	Octyl	20	**1-515**	64

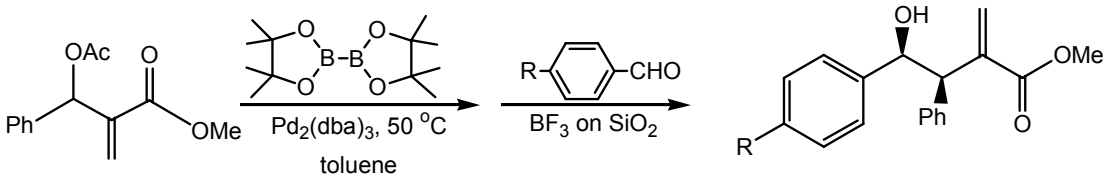
Finally, the reaction of various aldehydes with Baylis-Hillman adducts was examined (Table 1-5-4). The results demonstrated that substituents on the aromatic ring of aldehyde played an important role in the reaction. The presence of electron-withdrawing groups increased the reaction yields whereas electron-donating groups decreased the yields.

The homoallylic alcohols prepared using this protocol are all *syn* isomers. No *anti* isomers were observed. The single crystal structure of 4-hydroxy-2-methylene-4-(4-nitrophenyl)-3-*p*-tolylbutyric acid methyl ester (**1-509**) clearly reveals the stereochemistry (Figure 1-5-3).

1.5.3 Conclusion

In conclusion, Baylis-Hillman acetate adducts couple with bis(pinacolato)diboron to give 3-substituted-2-alkoxycarbonyl allylboronates which can be transformed into air and water stable allyltrifluoroborate salts by addition of aqueous KHF_2. It is noteworthy that the reaction is *E*-stereoselective and is applicable to Baylis-Hillman acetate adducts derived from aryl, heteroaryl, and aliphilic aldehydes. Alternatively, the reagents can be utilized directly in allylboration reactions with carbonyl compounds to obtain highly functionalized homoallylic alcohols. The reaction is highly stereoselective and only *syn* isomers are obtained. The stereochemistry has been verified by single crystal structure analysis.

Table 1-5-4: Synthesis of homoallylic alcohols from various aldehydes and Baylis-Hillman adducts.



Entry	R	Time (h)	Product	Yield (%)
1	*p*-Nitrophenyl	24	**1-516**	83
2	*p*-Trifluoromethylphenyl	24	**1-517**	84
3	Phenyl	48	**1-518**	67
4	*p*-Methoxyphenyl	48	**1-519**	62
5	p-Cyanophenyl	20	**1-520**	84
6	p-Chlorophenyl	24	**1-521**	78
7	Pentafluorophenyl	24	**1-522**	87

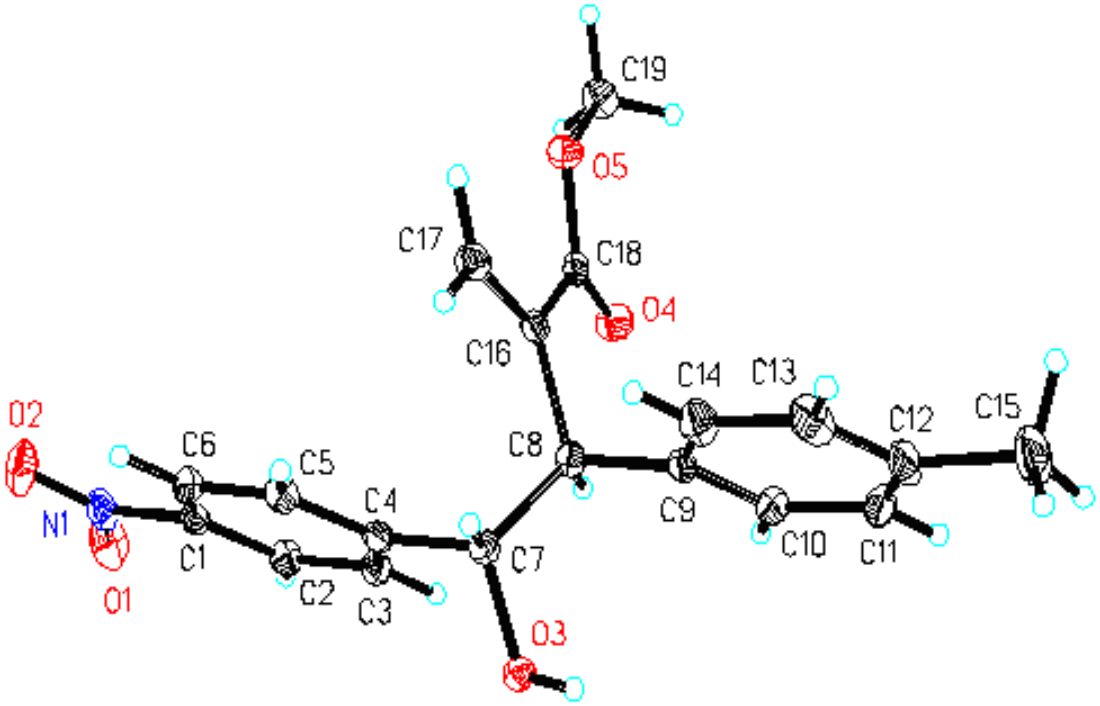


Figure 1-5-3: Single crystal structure of compound **1-509**.

1.5.4 Experimental Section

1.5.4.1 General Procedure for the Preparation of Functionalized Potassium Allyltrifluoroborate Salts

To a mixture of the Baylis-Hillman acetate adduct (1.0 mmol) and bis(pinacolato)diboron (1.1 mmol) in 4 mL of THF, was added the Pd catalyst ($Pd(OAc)_2$, 5 mol % or $Pd_2(dba)_3$, 3 mol %) and the mixture stirred at 50 ^oC. After completion of the reaction (TLC), the mixture was treated with excess aqueous KHF_2 (6.0 mmol) and allowed to stir for 20 min. at room temperature. All solvents were removed under reduced pressure using a rotary evaporator and the resultant solid was washed with acetone (4 x 10 mL), the combined acetone fractions concentrated under reduced pressure, and the residue washed with Et_2O (2 x 5 mL) to obtain the final allyltrifluoroborate salt as a solid.

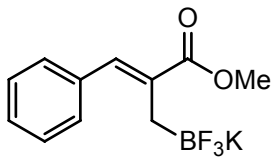
1.5.4.2 General Procedure for the Allylation Reaction Using Potassium Allyltrifluoroborate Salts

To a solution of the aldehyde (0.50 mmol) and tetrabutylammonium iodide (10 mol %, 0.05 mmol) in CH_2Cl_2 (2 mL) was added the potassium allyltrifluoroborate salt (0.50 mmol) and water (2 mL). The biphasic reaction mixture was vigorously stirred at room temperature for 5 hr, diluted with CH_2Cl_2 (5 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml), the combined extracts dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to obtain the product homoallylic alcohol.

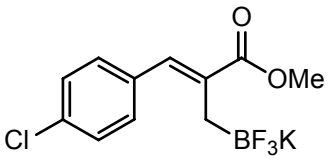
1.5.4.3 General Procedure for the *in situ* Preparation of Homoallylic Alcohols

To a mixture of the Baylis-Hillman acetate adduct (1.0 mmol) and bis(pinacolato)diboron (1.1 mmol) in toluene (4 mL) was added 3 mol % of $Pd_2(dba)_3$ and the mixture stirred at 50 ^oC under nitrogen. After completion of the reaction (TLC), the mixture was cooled to 0 ^oC and aldehyde (1.0 mmol) and $BF_3 \cdot SiO_2$ (20 mol %) were added. The reaction mixture was allowed to stir at room temperature for 2 days, quenched with aqueous $NaHCO_3$, and extracted into ether. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by column chromatography to obtain the homoallylic alcohol.

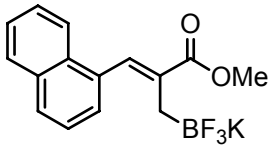
1.5.4.4 Analytical Data



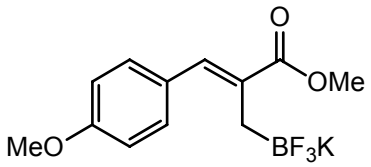
Compound (1-501). ^1H NMR (d_6 DMSO): δ 7.61 (d, J = 8 Hz, 2H), 7.32-7.22 (m, 3H), 7.05 (s, 1H), 3.63 (s, 3H), 1.55 (m, 2H); ^{13}C NMR (d_6 DMSO): δ 170.6, 138.2, 137.0, 130.2, 129.5, 127.8, 126.9, 51.2; ^{19}F (d_6 DMSO): δ –134.388. Anal. Caolcd. For $C_{11}H_{11}BF_3$: C, 46.83; H, 3.98. Found: C, 46.94; H, 3.82.



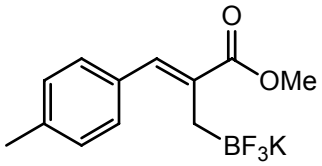
Compound (1-502). ^{1}H NMR (d_6 DMSO): δ 7.65 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H), 7.03 (s, 1H), 3.64 (s, 3H), 1.55 (brs, 2H); ^{13}C NMR (d_6 DMSO): δ 170.4, 139.0, 136.0, 131.5, 131.2, 128.9, 127.8, 51.4; ^{19}F (d_6 DMSO): δ –134.474. Anal. Calcd. For $C_{11}H_{10}BClF_3KO_2$: C, 41.70; H, 3.18. Found: C, 17.87; H, 3.08.



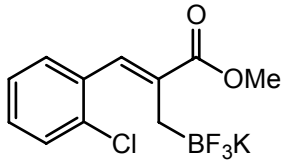
Compound (1-503). ^{1}H NMR (d_6 DMSO): δ 8.10-7.40 (m, 8H), 3.69 (s, 3H), 1.46 (m, 2H); ^{13}C NMR (d_6 DMSO): δ 170.6, 133.4, 132.9, 131.4, 128.4, 127.3, 126.8, 126.0, 125.6, 125.3, 124.0, 51.3; ^{19}F (d_6 DMSO): δ –134.581. Anal. Calcd. for $C_{15}H_{13}BF_3KO_2$: C, 54.24; H, 3.94. Found: C, 54.11; H, 3.92.



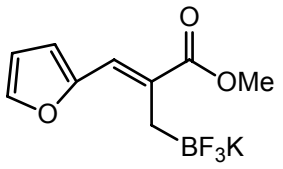
Compound (1-504). ^{1}H NMR (d_6 DMSO): δ 7.59 (d, *J* = 8 Hz, 2H), 7.04 (s, 1H), 6.88 (d, *J* = 8 Hz, 2H), 3.75 (s, 3H), 3.62 (s, 3H), 1.53 (m, 2H); ^{13}C NMR (d_6 DMSO): δ 170.7, 158.4, 136.0, 131.0, 130.4, 129.7, 113.3, 55.0, 51.2; ^{19}F (d_6 DMSO): δ –134.356. Anal. Calcd. for $C_{12}H_{13}BF_3KO_3$: C, 46.18; H, 4.20. Found: C, 45.92; H, 4.14.



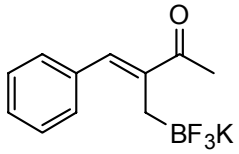
Compound (1-505). ^{1}H NMR (d_6 DMSO): δ 7.50 (d, *J* = 8 Hz, 2H), 7.11 (d, *J* = 8 Hz, 2H), 7.01 (s, 1H), 3.61 (s, 3H), 2.28 (s, 3H), 1.52 (m, 2H); ^{13}C NMR (d_6 DMSO): δ 170.7, 137.3, 136.2, 134.3, 130.3, 129.5, 128.4, 51.2, 20.9; ^{19}F (d_6 DMSO): δ –134.335. Anal. Calcd. for $C_{12}H_{13}BF_3KO_2$: C, 48.67; H, 4.42. Found: C, 48.86; H, 4.22.



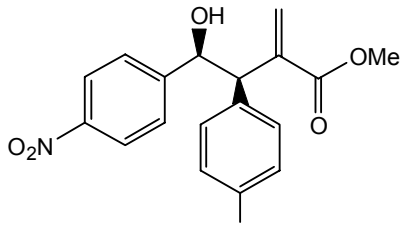
Compound (1-506). ^{1}H NMR (d_6 DMSO): δ 8.03 (dd, *J* = 8, 1.5 Hz, 1H), 7.44 – 7.25 (m, 3H), 7.08 (s, 1H), 3.65 (s, 3H), 1.46 (brs, 2H); ^{13}C NMR (d_6 DMSO): δ 170.4, 140.3, 134.7, 132.9, 131.5, 128.9, 128.8, 126.6, 126.0, 51.5; ^{19}F (d_6 DMSO): δ –134.495.Anal. Calcd. for $C_{11}H_{10}BClF_3KO_2$: C, 41.74; H, 3.18. Found: C, 41.82; H, 3.16.



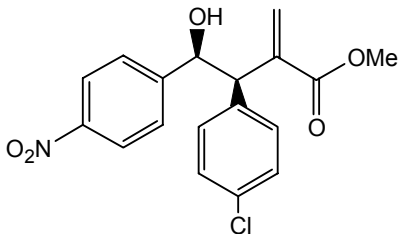
Compound (1-507). ^{1}H NMR (d_6 DMSO): δ 7.64 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.92 (s, 1H), 6.80 (d, *J* = 3.4 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.9 Hz, 1H), 3.61 (s, 3H), 1.59 (m, 2H); ^{13}C NMR (d_6 DMSO): δ 169.6, 152.6, 142.5, 135.9, 119.0, 111.9, 111.6, 51.4; ^{19}F (d_6 DMSO): δ –134.014. Anal. Calcd. for $C_9H_9BF_3KO_3$:C, 39.73; H, 3.33. Found: C, 39.87; H, 3.25.



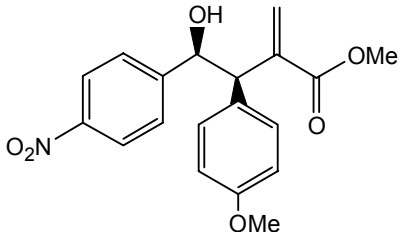
Compound (1-508). ^{1}H NMR (d_6 DMSO): δ 7.43 (d, *J* = 8 Hz, 2H), 7.14 – 6.98 (m, 3H), 6.80 (s, 1H), 2.10 (s, 3H), 1.39 (m, 2H); ^{13}C NMR (d6 DMSO): δ 202.9, 146.2, 137.4, 130.0, 129.8, 127.9, 127.1, 27.6; ^{19}F (d_6 DMSO): δ –133.960. Anal. Calcd. for $C_{11}H_{11}BF_3KO$: C, 49.65; H, 4.17. Found: C, 49.81; H, 4.09.



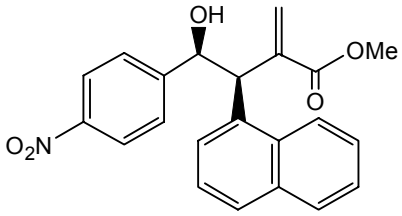
4-Hydroxy-2-methylene-4-(4-nitrophenyl)-3-*p*-tolylbutyric acid methyl ester (1-509). ^{1}H NMR ($CDCl_3$): δ 8.10 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 6.26 (s, 1H), 5.81 (s, 1H), 5.37 (m, 1H); 4.19 (d, *J* = 7 Hz, 1H), 3.59 (s, 3H), 2.53 (brs, 1H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.8, 149.7, 147.1, 140.5, 137.1, 134.2, 129.3, 128.9, 127.6, 127.3, 123.2, 74.5, 54.3, 51.9, 20.9. Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28; Found: C, 66.21, H, 5.14; N, 4.08.



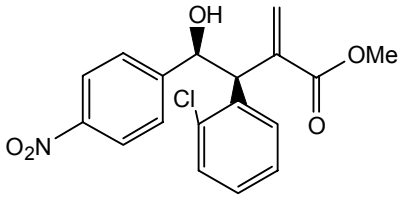
3-(4-Chlorophenyl)-4-hydroxy-2-methylene-4-(4-nitrophenyl)butyric acid methyl ester (1-510). ^{1}H NMR ($CDCl_3$): δ 8.09 (d, *J* = 8 Hz, 2H), 7.41 (d, *J* = 8 Hz, 2H), 7.24 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 6.29 (s, 1H), 5.83 (s, 1H), 5.41 (m, 1H); 4.18 (d, *J* = 7 Hz, 1H), 3.63 (s, 3H), 2.59 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.8, 149.5, 147.2, 140.2, 135.9, 133.2, 130.7, 128.5, 127.9, 127.4, 123.3, 74.2, 54.1, 52.1. Anal. Calcd. for $C_{18}H_{16}ClNO_5$: C, 59.76; H, 4.46; N, 3.87; Found: C, 59.82, H, 4.35; N, 3.85.



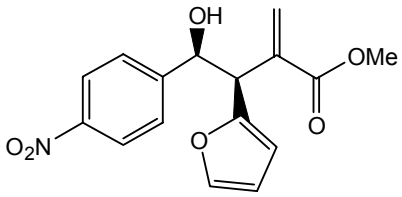
4-Hydroxy-3-(4-methoxyphenyl)-2-methylene-4-(4-nitrophenyl)butyric acid methyl ester (1-511). ^{1}H NMR ($CDCl_3$): δ 8.12 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 6.82 (d, *J* = 8 Hz, 2H), 6.27 (s, 1H), 5.83 (s, 1H), 5.39 (d, *J*=7 Hz, 1H), 4.18 (d, *J* = 7 Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 2.35 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.9, 158.8, 149.8, 147.1, 140.6, 130.2, 129.0, 127.5, 127.2, 123.1, 113.9, 74.4, 55.0, 53.9, 51.9. Anal. Calcd. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92; Found: C, 63.71; H, 5.22; N, 3.87.



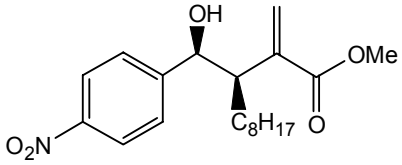
4-Hydroxy-2-methylene-3-naphthalen-1-yl-4-(4-nitrophenyl)butyric acid methyl ester (1-512). ^{1}H NMR ($CDCl_3$): δ 8.10 (d, J = 8 Hz, 2H), 7.96-7.42 (m, 8H), 6.25 (s, 1H), 5.67 (s, 1H), 5.45 (d, J = 7 1H); 5.21 (d, J = 7 Hz, 1H), 3.50 (s, 3H), 2.48 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.7, 149.0, 147.2, 140.4, 134.2, 134.1, 132.2, 128.8, 128.3, 128.1, 127.9, 126.4, 125.7, 125.0, 123.1, 123.0, 75.0, 52.0, 48.2. Anal. Calcd. for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71; Found: C, 70.15, H, 5.03; N, 3.58.



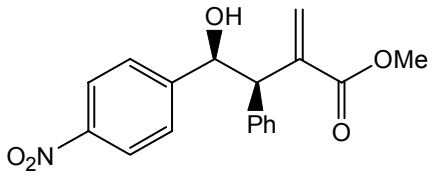
3-(2-Chlorophenyl)-4-hydroxy-2-methylene-4-(4-nitrophenyl)butyric acid methyl ester (1-513). ^{1}H NMR ($CDCl_3$): δ 8.09 (d, J = 8 Hz, 2H), 7.74 (dd, J = 8, 1.5 Hz, 1H), 7.47 (d, J = 8 Hz, 2H), 7.32-7.16 (m, 3H), 6.33 (s, 1H), 5.74 (s, 1H), 5.52 (d, J = 7 1H); 4.83 (d, J = 7 Hz, 1H), 3.63 (s, 3H), 2.62 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.6, 149.4, 147.1, 139.2, 135.3, 130.1, 129.8, 128.9, 128.4, 127.4, 126.6, 123.2, 122.9, 73.8, 52.0, 49.8. Anal. Calcd. for $C_{18}H_{16}ClNO_5$: C, 59.76; H, 4.46; N, 3.87; Found: C, 60.00, H, 4.42; N, 3.83.



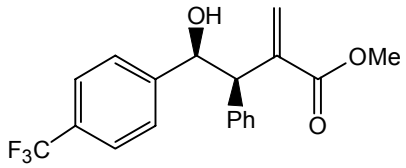
3-Furan-2-yl-4-hydroxy-2-methylene-4-(4-nitrophenyl)butyric acid methyl ester (1-514). ^{1}H NMR ($CDCl_3$): δ 8.13 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8, Hz, 2H), 7.35 (m, 1H), 6.37 (s, 1H), 6.30 (m, 1H), 6.20 (m, 1H), 5.82 (s,1H), 5.29 (d, *J* = 6 Hz, 1H); 4.43 (d, *J* = 6 Hz, 1H), 3.70 (s, 3H), 3.00 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.7, 151.2, 148.9, 147.2, 142.1, 137.7, 129.1, 127.2, 123.2, 110.4, 109.0, 74.3, 52.2, 48.3. Anal. Calcd. for $C_{16}H_{15}NO_6$: C, 66.05; H, 5.23; N, 4.28; Found: C, 60.57, H, 4.86; N, 4.18.



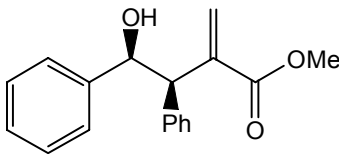
3-[Hydroxy-(4-nitrophenyl)methyl]-2-methyleneundecanoic acid methyl ester (1-515). ^{1}H NMR ($CDCl_3$): δ 8.16 (d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8 Hz, 2H), 6.28 (s, 1H), 5.48 (s, 1H), 4.96 (m, 1H); 3.78 (s, 3H), 3.36 (brs, 1H), 2.94 (m, 1H), 1.52-1.0 (m, 14H), 0.86 (t, *J* = 7 Hz, 3H); ^{13}C NMR (CDCl3): δ 168.5, 150.2, 147.0, 139.9, 127.7, 127.2, 123.2, 75.4, 52.3, 49.6, 31.7, 29.3, 29.1, 27.2, 26.6, 22.6, 14.0. Anal. Calcd. for $C_{20}H_{20}NO_5$: C, 66.09; H, 8.04; N, 3.85; Found: C, 66.27; H, 8.12; N, 3.72.



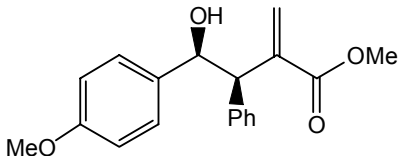
4-Hydroxy-2-methylene-4-(4-nitrophenyl)-3-phenylbutyric acid methyl ester (1-516). ^{1}H NMR ($CDCl_3$): δ 8.08 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 7.30-7.20 (m, 5H), 6.26 (s, 1H), 5.82 (s, 1H), 5.39 (m, 1H); 4.21 (d, *J* = 7 Hz, 1H), 3.58 (s, 3H), 2.69 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 168.7, 149.6, 147.0, 140.2, 137.3, 129.1, 128.4, 127.5, 123.1, 74.3, 54.5, 51.9. Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28; Found: C, 66.21, H, 5.14; N, 4.08.



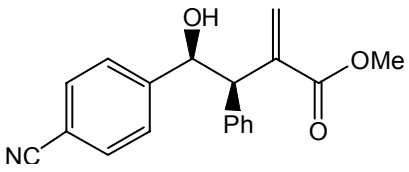
4-Hydroxy-2-methylene-3-phenyl-4-(4-trifluoromethylphenyl)butyric acid methyl ester (1-517). ^{1}H NMR ($CDCl_3$): δ 7.52 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.35-7.20 (m, 5H), 6.23 (s, 1H), 5.77 (s, 1H), 5.29 (d, *J* = 7 Hz1H); 4.24 (d, *J* = 7 Hz, 1H), 3.54 (s, 3H), 2.38 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 167.1, 146.1, 140.7, 137.9, 129.2, 128.5, 127.3, 127.2, 125.0, 75.0, 54.5, 51.9. Anal. Calcd. for $C_{19}H_{17}F_3O_3$: C, 65.14; H, 4.89; Found: C, 64.94, H, 4.83.



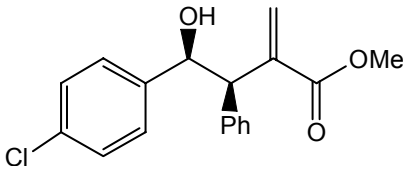
4-Hydroxy-2-methylene-3,4-diphenylbutyric acid methyl ester (1-518). ^{1}H NMR ($CDCl_3$): δ 7.35-7.24 (m, 10H), 6.24 (s, 1H), 5.81 (s, 1H), 5.26 (d, *J* = 7 Hz 1H); 4.31 (d, *J* = 7 Hz, 1H), 3.56 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.9, 147.4, 142.0, 141.0, 138.6, 129.2, 128.5, 128.2, 127.8, 127.2, 126.9, 126.8, 75.7, 54.3, 51.9. Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.31, H, 6.54.



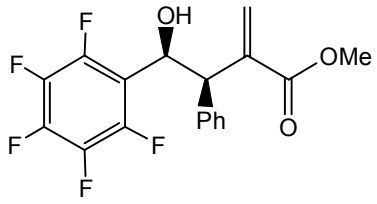
4-Hydroxy-4-(4-methoxyphenyl)-2-methylene-3-phenylbutyric acid methyl ester (1-519). ^{1}H NMR ($CDCl_3$): δ 7.35-7.25 (m, 5H), 7.21 (d, *J* = 8 Hz, 2H), 6.81 (d, *J* = 8 Hz, 2H), 6.21 (s, 1H), 5.76 (s, 1H), 5.18 (d, *J* = 7 Hz 1H); 4.28 (d, *J* = 7 Hz, 1H), 3.76 (s, 3H), 3.55 (s, 3H), 2.03 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 167.0, 159.0, 141.1, 138.9, 134.2, 129.1, 128.4, 128.1, 127.1, 126.6, 113.5, 75.3, 55.1, 54.3, 51.8. Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; Found: C, 73.01, H, 6.50.



4-(4-Cyanophenyl)-4-hydroxy-2-methylene-3-phenylbutyric acid methyl ester (1-520). ^{1}H NMR ($CDCl_3$): δ 7.54 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 7.35-7.24 (m, 5H), 6.27 (s, 1H), 5.81 (s, 1H), 5.35 (d, *J* = 7 Hz 1H); 4.21 (d, *J* = 7 Hz, 1H), 3.60 (s, 3H), 2.45 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.8, 147.6, 140.5, 137.5, 131.8, 129.2, 128.6, 127.5, 111.2, 74.7, 54.5, 52.0. Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56; Found: C, 74.12, H, 5.61; N, 4.57.



4-(4-Chlorophenyl)-4-hydroxy-2-methylene-3-phenylbutyric acid methyl ester (1-521). ^{1}H NMR ($CDCl_3$): δ 7.31-7.18 (m, 9H), 6.23 (s, 1H), 5.77 (s, 1H), 5.24 (m, 1H), 4.21 (d, *J* = 7 Hz, 1H), 3.57 (s, 3H), 2.19 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.8, 140.8, 140.5, 138.1, 133.3, 129.1, 128.5, 128.3, 127.3, 127.0, 74.9, 54.5, 51.9. Anal. Calcd. for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41; Found: C, 67.97, H, 5.40.



4-Hydroxy-2-methylene-4-pentafluorophenyl-3-phenylbutyric acid methyl ester (1-522). ^{1}H NMR ($CDCl_3$): δ 7.39-7.25 (m, 5H), 6.25 (s, 1H), 5.82 (s, 1H), 5.57 (m, 1H), 4.59 (d, J = 7 Hz, 1H), 3.59 (s, 3H), 2.38 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 166.3, 143.0, 140.1, 138.1, 135.2, 128.9, 128.6, 127.7, 126.6, 115.2, 67.9, 52.0, 51.8. Anal. Calcd. for $C_{18}H_{13}F_5O3$: C, 58.07; H, 3.52; Found: C, 58.31, H, 3.41.

Chapter 6

Palladium Catalyzed Cross-Coupling of Baylis-Hillman Adducts with Silicon and Germanium Bimetals

1.6.1 Introduction

Allylsilanes are extensively used in carbonyl addition reactions,[120] coupling reaction,[91a] and they have also been employed as key intermediates for the total synthesis of natural products.[121] Among allylsilanes, those containing a carbonyl group at the β-position (2-carbonylallylsilanes) have a functionality that can react with both electrophiles and nucleophiles.[122] Several methods for the preparing allylsilanes catalyzed by transition metals are known.[123] However, the syntheses of 2-carbonyl allylsilanes are limited.[122, 124] Relative to other allylmetals, very few studies on the synthesis of allylgermanes have been reported.[125] However, they are used in allylation reactions with carbonyl,[126] imine[127] compounds and in the [3 + 2] cycloaddition[128] reactions.

In chapter 5, the palladium catalyzed coupling reactions of *bis*(pinacolato)diboron with Baylis-Hillman acetate adducts were discussed. They led to functionalized allylborates. The feasibility of the coupling reaction of Baylis-Hillman acetate adducts with bimetals of both silicon and germanium were then examined.

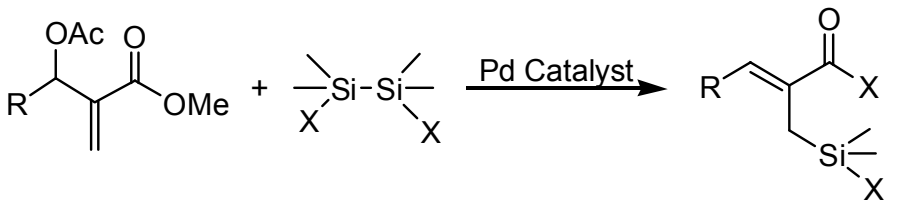
1.6.2 Result and Discussions

The reaction of Baylis-Hillman acetate adducts and disilane compound in the presence of palladium catalyst generates 2-carboxylmethyl allylsilanes. The reaction yields are very high. In an effort to optimize reaction conditions, a variety of catalysts and solvent systems were examined. Highest yields were obtained when reactions were carried out in toluene using 4 mol% of $Pd_2(dba)_3$ at 50 ^oC. Several types of Baylis-Hillman adducts readily participate in the reaction as shown in Table 1-6-1. Adducts derived from aryl, heteroaryl, and aliphatic aldehydes were readily transformed into the corresponding allylsilanes. The stereochemistry of the allylsilanes was determined to be *Z* using ^1H and ^{13}C spectroscopy by comparision of the observed chemical shifts with those reported in the literature.[124, 129] Only trace amounts of the *E* isomers were detected.

The methodology was then extended to the preparation of functionalized allylgermanes. Baylis-Hillman acetate adducts were found to react with hexamethyldigermanium in the presence of a Pd catalyst to form allylgermanes. Reactions proceeded at 50 ^oC and allylgermane products formed in high yields. A variety of Baylis-Hillman acetate adducts reacted with hexamethyldigermanium in the presence of 4 mol % of $Pd_2(dba)_3$ to give the functionalized allylgermane compounds stereoselectively (Table 1-6-2). This is the first report of synthesis of 2-carbonylallyl germanium compounds.

Baylis-Hillman adducts derived from methyl vinyl ketone readily reacted with hexamethyldisilane to give (1:1) mixtures of (*Z*)-allylsilanes and their regio isomers,

Table 1-6-1: Pd-catalyzed coupling of Baylis-Hillman adducts with disilanes.[a]



R	X	Product[b]	Yield (%)[c]	*Z*:*E*[d]
Ph	Me	**1-601**	87	100:0
p-Methylphenyl	Me	**1-602**	84	96:4
p-Methoxyphenyl	Me	**1-603**	82	100:0
p-Chlorophenyl	Me	**1-604**	80	97:3
o-Chlorophenyl	Me	**1-605**	69	92:8
1-Furyl	Me	**1-606**	86	94:6
1-Napthyl	Me	**1-607**	85	98:2
n-Octyl	Me	**1-608**	64	92:8[e]
Phenyl	Phenyl	**1-609**	73	100:0

[a]Reactions carried out at 50 ^{o}C using 4 mol of Pd catalyst for 5 h;

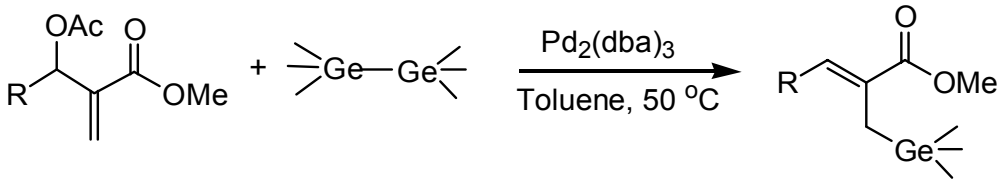
[b]All products exhibited satisfactory special (^{1}H, ^{13}C) and elemental data;

[c]Isolated yields;

[d]*E*/*Z* ratio determined by ^{1}H NMR;

[e]Reaction time is 10 h.

Table 1-6-2: Reaction of Baylis-Hillman adduct and hexamethyldigermanium in the presence of Pd catalyst.[a]



R	Product[b]	Yield (%)[c]	*Z*:*E*[d]
Ph	**1-610**	84	100:0
p-Methylphenyl	**1-611**	82	98:2
p-Methoxyphenyl	**1-612**	85	97:3
p-Chlorophenyl	**1-613**	80	98:2
o-Chlorophenyl	**1-614**	70	95:5
2-Furyl	**1-615**	81	100:0
1-Napthyl	**1-616**	76	100:0
n-Octyl	**1-617**	64	85:15[e]

[a]Reactions carried out at 50 °C using 4 mol of Pd catalyst for 5 h;

[b]All products exhibited satisfactory special (^{1}H, ^{13}C) and elemental data;

[c]Isolated yields;

[d]*E*/*Z* ratio determined by ^{1}H NMR;

[e]Reaction time is 10 h.

whereas in hexamethyldigermanium reactions yielded (*Z*)-allylgermane exclusively (Figure 1-6-1).

1.6.3 Conclusion

In conclusion, palladium catalyzed coupling reactions of Baylis-Hillman acetate adducts and bimetallic reagents (Si-Si, Ge-Ge) were developed. The reactions provide a convenient synthetic method for preparing a wide range of 2-carbonyl allylmetal reagents that are difficult to prepare by other methods. The method leads to functionalized allyl metal reagents in excellent yields. The catalytic reaction proceeds with high regio- and stereoselectivity under mild conditions. Phosphine-free palladium catalyzes the reaction and no additional base and ligand are required.

1.6.4 Experimental Section

1.6.4.1 General Considerations

All glassware was dried in an oven at 120 ^{o}C and flushed with dry nitrogen. Reactions were carried out under a nitrogen atmosphere. All reagents were purchased from Aldrich Chemical Company and used as received. Baylis-Hillman adducts were prepared according to the literature procedure. Products were purified by flash chromatography using silica gel (60 C, 230-400 mesh) with hexanes and ethyl acetate (Hexanes:EtOAc 20:1) as eluent. Elemental Analyses were performed by Atlantic

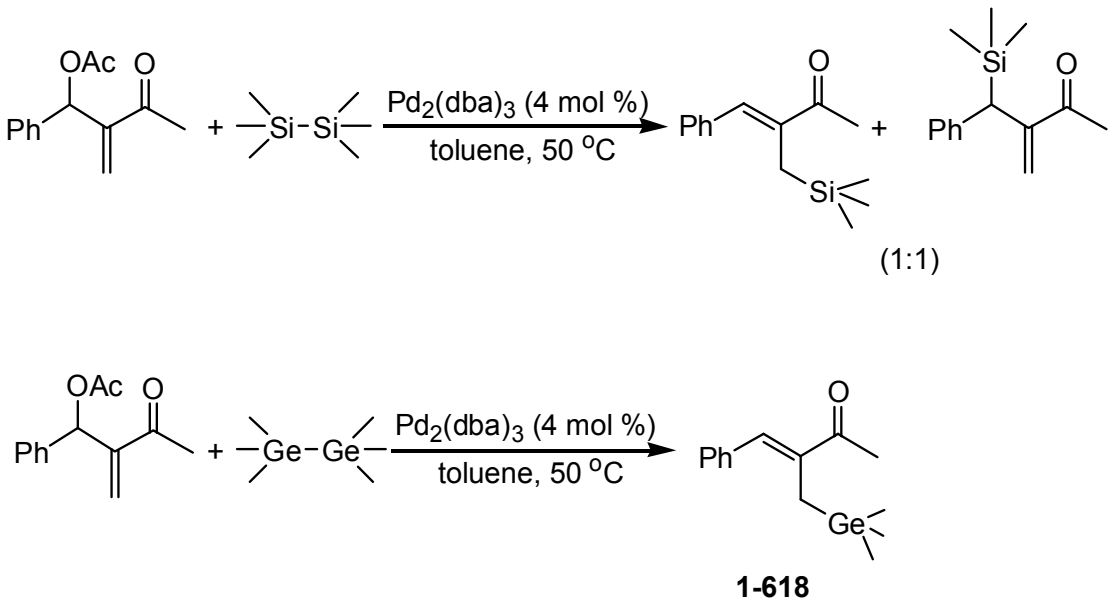


Figure 1-6-1: Reactions of Baylis-Hillman adduct derived from methyl vinyl ketone with disiliane and digermanium reagents.

Microlabs Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker 250 MHz and Variant 300 MHz instruments with chemical shifts reported relative to TMS.

1.6.4.2 General Procedure for the Synthesis of Allylsilanes

To a two-necked round-bottomed flask, the acetate of the Baylis-Hillman adduct (1.0 mmol) and disilane compound (1.1 mmol) were added. The system was evacuated and purged with nitrogen gas. Toluene (4 mL), followed by 4 mol % of $Pd_2(dba)_3$ (36 mg), were then added. The reaction mixture was stirred at 50 ^{o}C. After completion of the reaction (TLC), the mixture was concentrated under reduced pressure and the product isolated by column chromatography.

1.6.4.3 General Procedure for the Synthesis of Allylgermanes

To a two-necked round-bottomed flask, the acetate of the Baylis-Hillman adduct (1.0 mmol) and hexamethyldigermanium (1.1 mmol) were added. The system was evacuated and purged with nitrogen gas. Toluene (4 mL), followed by 4 mol % of $Pd_2(dba)_3$ (36 mg), were added. The reaction mixture was stirred at 50 ^{o}C. After completion of the reaction (TLC), the mixture was concentrated under reduced pressure and the product isolated by column chromatography.

1.6.4.4 Analytical Data

Methyl (*Z*)-3-Phenyl-2-(trimethylsilylmethyl)prop-2-enoate (1-601). ^{1}H NMR ($CDCl_3$): δ 7.56 (s, 1H), 7.39-7.25 (m, 5H), 3.80 (s, 3H), 2.20 (s, 2H), -0.07 (s, 9H); ^{13}C

NMR ($CDCl_3$): δ 169.3, 136.5, 134.9, 131.5, 129.1, 128.3, 127.7, 51.8, 17.8, -0.9. Anal. Calcd. for $C_{14}H_{20}O_2Si$: C, 67.70; H, 8.12. Found: C, 67.65; H, 8.20.

Methyl (*Z*)-3-(*p*-Tolyl)-2-(trimethylsilylmethyl)prop-2-enoate (1-602). ^1H NMR ($CDCl_3$): δ 7.50 (s, 1H), 7.28 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 3.77 (s, 3H), 2.34 (s, 3H), 2.17 (s, 2H), -0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.5, 137.8, 135.0, 133.5, 130.5, 129.2, 129.0, 51.9, 21.3, 17.9, -0.9. Anal. Calcd. for $C_{15}H_{22}O_2Si$: C, 68.65; H, 8.45. Found: C, 68.76; H, 8.56.

Methyl (*Z*)-3-(*p*-Methoxyphenyl)-2-(trimethylsilylmethyl)prop-2-enoate (1-603). ^1H NMR ($CDCl_3$): δ 7.52 (s, 1H), 7.35 (d, *J* = 8 Hz, 2H), 6.90 (d, *J* = 8 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.19 (s, 2H), -0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.4, 159.2, 134.6, 130.7, 129.1, 128.8, 113.7, 55.0, 51.7, 17.7, -0.9. Anal. Calcd. for $C_{15}H_{22}O_3Si$: C, 64.71; H, 7.96. Found: C, 64.70; H, 8.03.

Methyl (*Z*)-3-(*p*-Chlorophenyl)-2-(trimethylsilylmethyl)prop-2-enoate (1-604). ^1H NMR ($CDCl_3$): δ 7.40 (s, 1H), 7.26 (d, *J* = 8 Hz, 2H), 7.25 (d, *J* = 8 Hz, 2H), 3.72 (s, 3H), 2.08 (s, 2H), -0.09 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.1, 134.9, 133.5, 132.1, 130.4, 129.6, 128.6, 52.0, 18.0, -0.9. Anal. Calcd. for $C_{14}H_{19}ClO_2Si$: C, 59.45; H, 6.77. Found: C, 59.67; H, 6.81.

Methyl (*Z*)-3-(*o*-Chlorophenyl)-2-(trimethylsilylmethyl)prop-2-enoate (1-605). ^1H NMR ($CDCl_3$): δ 7.56 (s, 1H), 7.40-7.15 (m, 4H), 3.81 (s, 3H), 2.03 (s, 2H), -0.01 (s, 3H),

-0.07 (s, 3H), -0.08 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.8, 135.2, 133.9, 133.3, 132.3, 129.8, 129.5, 129.3, 126.4, 52.0, 17.7, -1.12. Anal. Calcd. for $C_{14}H_{19}ClO_2Si$: C, 59.45; H, 6.77. Found: C, 59.66; H, 6.73.

Methyl (*Z*)-3-(1'-Furyl)-2-(trimethylsilylmethyl)prop-2-enoate (1-606). ^{1}H NMR ($CDCl_3$): δ 7.39 (s, 1H), 7.19 (s, 1H), 6.41 (d, *J* = 3 Hz, 1H), 6.35 (m, 1H), 3.67 (s, 3H), 2.27 (s, 2H), -0.10 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 168.5, 152.3, 143.1, 127.8, 121.8, 113.9, 111.8, 51.9, 18.9, -1.3. Anal. Calcd. for $C_{12}H_{18}O_3Si$: C, 60.47; H, 7.61. Found: C, 60.18; H, 7.37.

Methyl (*Z*)-3-(1'-Mapthyl)-2-(trimethylsilylmethyl)prop-2-enoate (1-607). ^{1}H NMR ($CDCl_3$): δ 8.03 (s, 1H), 8.00-7.80 (m, 3H), 7.55-7.40 (m, 4H), 3.89 (s, 3H), 2.05 (s, 2H), -0.10 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.0, 133.9, 133.6, 133.4, 131.4, 128.4, 128.1, 126.1, 126.0, 125.1, 124.8, 52.0, 18.0, -1.04. Anal. Calcd. for $C_{18}H_{22}O_2Si$: C, 72.44; H, 7.43. Found: C, 72.60; H, 7.47

Methyl (*Z*)-2-(Trimethylsilylmethyl)undec-2-enoate (1-608). ^{1}H NMR ($CDCl_3$): δ 6.63 (t, *J* = 6 Hz, 1H), 3.73 (s, 3H), 2.09 (m, 2H), 1.82 (s, 2H), 1.50-1.20 (m, 12H), 0.9 (t, *J* = 7 Hz, 3H), -0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 168.8, 139.0, 129.6, 51.5, 31.8, 31.5, 29.7, 29.6, 29.3, 28.8, 22.6, 17.3, 14.1, -1.16. Anal. Calcd. for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.82; H, 11.44.

Methyl (*Z*)-3-Phenyl-2-(dimethylphenylsilylmethyl)prop-2-enoate (1-609). ^{1}H NMR ($CDCl_3$): δ 7.54 (s, 1H), 7.45-7.20 (m, 10H), 3.65 (s, 3H), 2.39 (s, 2H), 0.25 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 169.1, 138.5, 136.2, 135.5, 133.5, 130.9, 129.0, 128.2, 127.6, 51.7, 17.4, -2.68. Anal. Calcd. for $C_{19}H_{22}O_2Si$: C, 73.50; H, 7.14. Found: C, 73.51; H, 7.32.

Methyl (*Z*)-3-Phenyl-2-(trimethylgermanyllmethyl)prop-2-enoate (1-610). ^{1}H NMR ($CDCl_3$): δ 7.52 (s, 1H), 7.37–7.20 (m, 5H), 3.80 (s, 3H), 2.27 (s, 2H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.2, 136.4, 134.3, 132.2, 129.2, 128.3, 127.8, 51.9, 18.2, –0.9. Anal. Calcd. for $C_{14}H_{20}GeO_2$: C, 57.41; H, 6.88. Found: C, 57.56; H, 7.02.

Methyl (*Z*)-3-(*p*-Tolyl)-2-(trimethylgermanylmethyl)prop-2-enoate (1-611). ^{1}H NMR ($CDCl_3$): δ 7.50 (s, 1H), 7.28 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 3.79 (s, 3H), 2.36 (s, 3H), 2.29 (s, 2H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.4, 137.8, 134.4, 133.5, 131.2, 129.3, 129.0, 51.9, 21.3, 18.2, -1.3. Anal. Calcd. for $C_{15}H_{22}GeO_2$: C, 58.69; H, 7.22. Found: C, 58.85; H, 7.27

Methyl (*Z*)-3-(*p*-Methoxyphenyl)-2-(trimethylgermanylmethyl)prop-2-enoate (1-612). ^{1}H NMR ($CDCl_3$): δ 7.48 (s, 1H), 7.35 (d, J = 8 Hz, 2H), 6.90 (d, J = 8 Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 2.29 (s, 2H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.5, 159.2, 134.2, 130.9, 129.9, 128.9, 113.7, 55.2, 51.9, 18.1, –1.2. Anal. Calcd. for $C_{15}H_{22}GeO_3$: C, 55.79; H, 6.87. Found: C, 55.88; H, 6.90.

Methyl (*Z*)-3-(*p*-Chlorophenyl)-2-(trimethylgermanylmethyl)prop-2-enoate (1-613). ^{1}H NMR ($CDCl_3$): δ 7.45 (s, 1H), 7.34 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 3.80 (s,

3H), 2.52 (s, 2H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.0, 134.8, 133.5, 132.9, 130.4, 128.6, 52.0, 18.2, –1.3. Anal. Calcd. for $C_{14}H_{19}ClGeO_2$: C, 51.37; H, 5.85. Found: C, 51.64; H, 5.95.

Methyl (*Z*)-3-(*o*-Chlorophenyl)-2-(trimethylgermanylmethyl)prop-2-enoate (1-614). ^{1}H NMR ($CDCl_3$): δ 7.56 (s, 1H), 7.30-7.15 (m, 4H), 3.81 (s, 3H), 2.13 (s, 2H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 168.7, 135.1, 134.1, 131.6, 130.0, 129.6, 128.9, 126.3, 52.0, 18.0, –1.4. Anal. Calcd. for $C_{14}H_{19}ClGeO_2$: C, 57.37; H, 5.85. Found: C, 51.58; H, 6.01.

Methyl (*Z*)-3-(1'-Furyl)-2-(trimethylgermanylmethyl)prop-2-enoate (1-615). ^{1}H NMR ($CDCl_3$): δ 7.48 (d, *J* = 1.5 Hz, 1H), 7.26 (s, 1H), 6.49 (d, *J* = 3 Hz, 1H), 6.46 (m, 1H), 3.77 (s, 3H), 2.47 (s, 2H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.0, 152.4, 143.0, 128.7, 121.0, 113.6, 111.8, 51.9, 18.9, -1.7. Anal. Calcd. for $C_{12}H_{18}GeO_3$: C, 50.95; H, 6.41. Found: C, 51.24; H, 6.31.

Methyl (*Z*)-3-(1'-Napthyl)-2-(trimethylgermanylmethyl)prop-2-enoate (1-616). ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 8.00–7.70 (m, 3H), 7.56-7.30 (m, 4H), 3.84 (s, 3H), 2.05 (s, 2H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.0, 134.3, 133.7, 133.4, 133.0, 131.4, 128.4, 128.1, 126.1, 126.0, 125.0, 124.8, 52.0, 18.3, -1.04. Anal. Calcd. for $C_{18}H_{22}GeO_2$: C, 63.03; H, 6.47. Found: C, 63.24; H, 6.56.

Methyl (*Z*)-2-(Trimethylgermanylmethyl)undec-2-enoate (1-617). ^{1}H NMR ($CDCl_3$): δ 6.63 (t, *J*=6 Hz, 1H), 3.71 (s, 3H), 2.10 (m, 2H), 1.92 (s, 2H), 1.35-1.20 (m, 12H), 0.9 (t,

J=7 Hz, 3H), -0.13 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 168.7, 138.5, 130.5, 51.5, 34.6, 31.8, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 22.6, 17.3, 14.1, -1.5. Anal. Calcd. for $C_{16}H_{32}GeO_2$: C, 58.40; H, 9.80. Found: C, 58.69; H, 9.86.

4-Phenyl-3-Trimethylgermanylmethylbut-3-en-2-one (1-618). ^{1}H NMR ($CDCl_3$) 7.41 (s, 1H), 7.40-7.25 (m, 5H), 2.47 (s, 3H), 2.26 (s, 2H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) 200.2, 142.6, 136.4, 1355, 129.1, 128.3, 128.0, 25.6, 16.8, -1.17. Anal. Calcd. for $C_{14}H_{20}GeO$: C, 60.72; H, 7.28. Found: C, 60.50; H, 7.38.

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Part II. Application of Potassium Alkynyltrifluoroborates

Chapter 1

Introduction

2.1.1 Alkynylation Reaction

Over the past few decades, Pd-catalyzed alkynylation has emerged as one of the most general and reliable methods for the synthesis of alkynes.[1,2] Currently, the most widely used alkynylation is a hybrid of the Cu-promoted Castro-Stephens reaction[3] and the alkyne version of the Heck reaction,[4] known as the Sonogashira reaction[5-10] which was originally reported in 1975[5] (Figure 2-1-1). The latter reaction is considered generally superior to either the Castro-Stephens reaction[3] or the Heck protocol[4] and has emerged as one of the most straightforward and powerful methods for the preparation of alkynes.[11] Many applications of this method in natural product syntheses and material science have been reported.[9, 12] However, few if any synthetic methods work well in

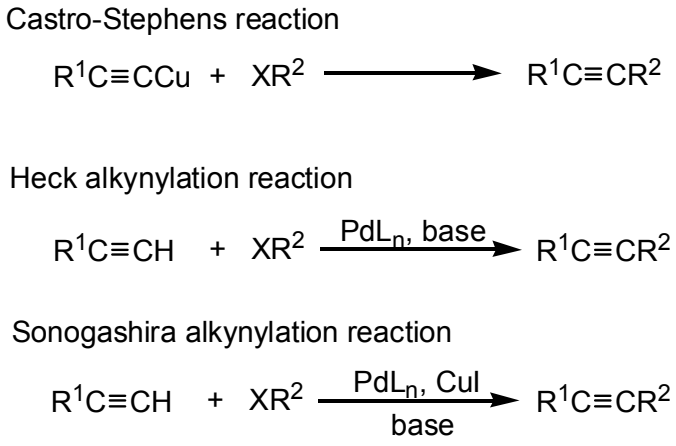


Figure 2-1-1: Commonly used alkynylation reaction.

every situation, and the Sonogashira coupling reaction, as it was initially conceived, is no exception. In the quest for improving this palladium-catalyzed cross-coupling reaction, several recent publications have described the use of new ligand systems to accommodate a wider range of coupling partners under mild conditions.[13] As an example, $P(t\text{-}Bu)_3$ and phosphonium salt derivatives have proven effective for efficient Sonogashira coupling at room temperature.[14]

2.1.2 Overview of the Alkynylation Reaction Utilizing Organometallic Reagents

Even with recent improvements, there are instances in which the Sonogashira coupling fails to deliver acceptable yields. As a result, alternative methods employing alkynylmetallic reagents have been developed.

Negishi and coworkers reported the Pd-catalyzed alkynylation reactions of alkynylzincs[15-19] and of 1-halo-1-alkynes.[20] Although the Pd-catalyzed alkynylation using alkynylsodiums has been known since 1975,[21] it is a sluggish reaction of limited scope, requiring refluxing MeOH. Similarly, alkynylmetals containing other alkali metals, e.g., Li, are generally unsatisfactory.

Pd-catalyzed alkynylation reactions using alkynylmetals containing Mg,[17,22] B,[17] Al,[17,23,24] and Sn[17] has also been reported by Negishi[15-19]. More systematic investigations of Pd-catalyzed alkynylation with alkynylstannanes were performed later by Bumagin and Beletskaya,[25] and later by Stille.[26]

Among main group metals tested in Negishi's initial investigation,[17] Hg and Si were ineffective. Although there are some Pd-catalyzed cross coupling reactions of organomercurials known in the literature,[27] their scope is very limited. In view of the relative ease of Hg(II)-to-Hg(0) reduction,[28] organomercurials may interfere with Pd catalysis involving shuttle between Pd(0) and Pd(II) complexes. The inherent toxicity associated with Hg is another serious concern. The inability of alkynylsilicon derivatives to undergo facile alkynylation[17,18] must be due to their intrinsically low reactivity. In fact, silicon has been used as part of alkyne protecting groups, such as Me_3Si, and as precursors to alkynylmetals containing other metals. In some cases where fluoride and oxy bases are used as activators, it is likely that alkynylsilicon compounds containing a hypervalent Si are generated as actual reactants.[29-39]

Over the past few years, the Pd-catalyzed cross-coupling reaction of tris(alkynyl)indiums to give disubstituted alkynes has been reported.[40, 41] All three alkynyl groups participate in the reaction. Thus, despite its limited scope, the reaction appears to be promising. Although several other main group metals, such as Cd,[42] Ge[43, 44] Pb,[45-47] and Bi,[48] have been employed in the Pd-catalyzed cross-coupling, little has appeared concerning their use in Pd-catalyzed alkynylation.

Stoichiometric amounts of Cu are used in the Castro-Stephens reaction[3] without the use of Pd catalysts, while a catalytic amount of Cu is used in the Sonogashira reaction.[5-11] Recently, the corresponding Pd-catalyzed reaction of preformed alkynylsilver reagents with alkenyl triflates has been reported.[49, 50] In view of the relatively high cost of silver compared to other less expensive metals, the practical synthetic value of the Pd-catalyzed alkynylsilver reaction is questionable. Among relatively inexpensive transition metals,

manganese and some other first transition series metals, such as Ti, Cr, Mo, Fe, Co, and Ni, as well as some lanthanide metals, might be proved to be useful. Indeed, one reaction of an alkynylmanganese with an aryl bromide, catalyzed by $Pd(dppf)Cl_2$, has recently been reported, as shown in Figure 2-1-2.[51] However, little or nothing appears to be known about the use of other transition metal reagents in the Pd-catalyzed alkynylation.

2.1.3 Alkynylboron Reagents in Alkynylation Reaction

Although numerous organometallic acetylide intermediates have been explored, organoboron compounds present several advantages.[52] For example, organoboron compounds are less toxic than organostannane reagents[53] and, unlike alkynylzinc and magnesium reagents, many organoboron compounds possess remarkable oxidative and thermal stabilities.[54]

However, boron was rarely used in alkynylation reactions in early studies.[17] Soderquist reported the Suzuki coupling reactions of the B-alkynyl-9-borabicyclononane (B-alkynyl-9-BBN) "ate" complexes (generated *in situ* by the addition of an alkynyllithium to B-methoxy-9-BBN) to a variety of aryl- and alkenyl bromides (Figure 2-1-3).[55]

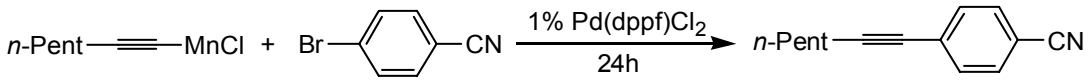


Figure 2-1-2: Alkynylation reaction utilizing alkynylmanganese.

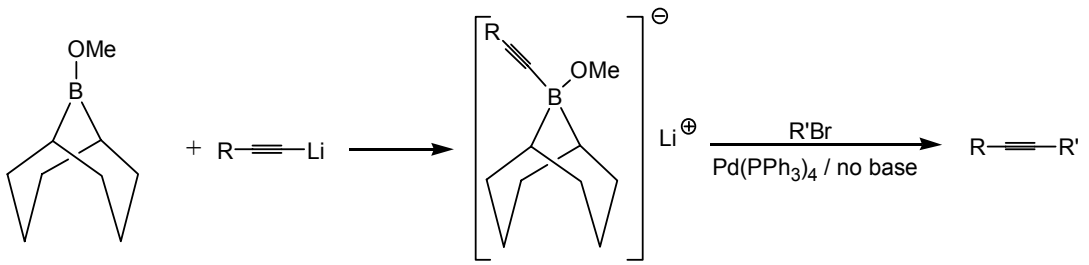


Figure 2-1-3: Reaction of B-alkynyl-9-BBN "ate" complexes.

At the same time, Fürstner reported a similar reaction.[56] The prerequisite alkynylborates are prepared from 9-methoxy-9-BBN and a polar organometallic reagent, such as 1-alkynyl sodium, potassium, and lithium reagents, and not as usual from boranes and bases. The method is highly chemoselective and turns out to be compatible with aldedydes, amides, ketones, esters and cyano functionalities, as well as with basic nitrogen atoms in the substrates. By utilizing the B-alkynyl-9-BBN complex, Fürstner and Nikolakis synthesized Combretastatin A-4, which is an exceptionally strong inhibitor of tubulin polymerization and one of the most cytotoxic agents tested so far against murine lymphocytic leukemia, human ovarian, and human colon cancer cell lines (Figure 2-1-4).[57] However, this "ate" complex approach highlights some of the disadvantages of dealing with coupling agents incorporating the 9-BBN moiety: the difficulty in isolating the intermediate boron complexes and the lack of atom economy.[12a, 52a, b, 54]

Two reports on the use of alkynyltrialkoxyborate complexes have been communicated. In the first, an effective Suzuki-Miyaura coupling reaction between alkynyl "ate" complexes generated *in situ* from acetylenic derivatives and unactivated

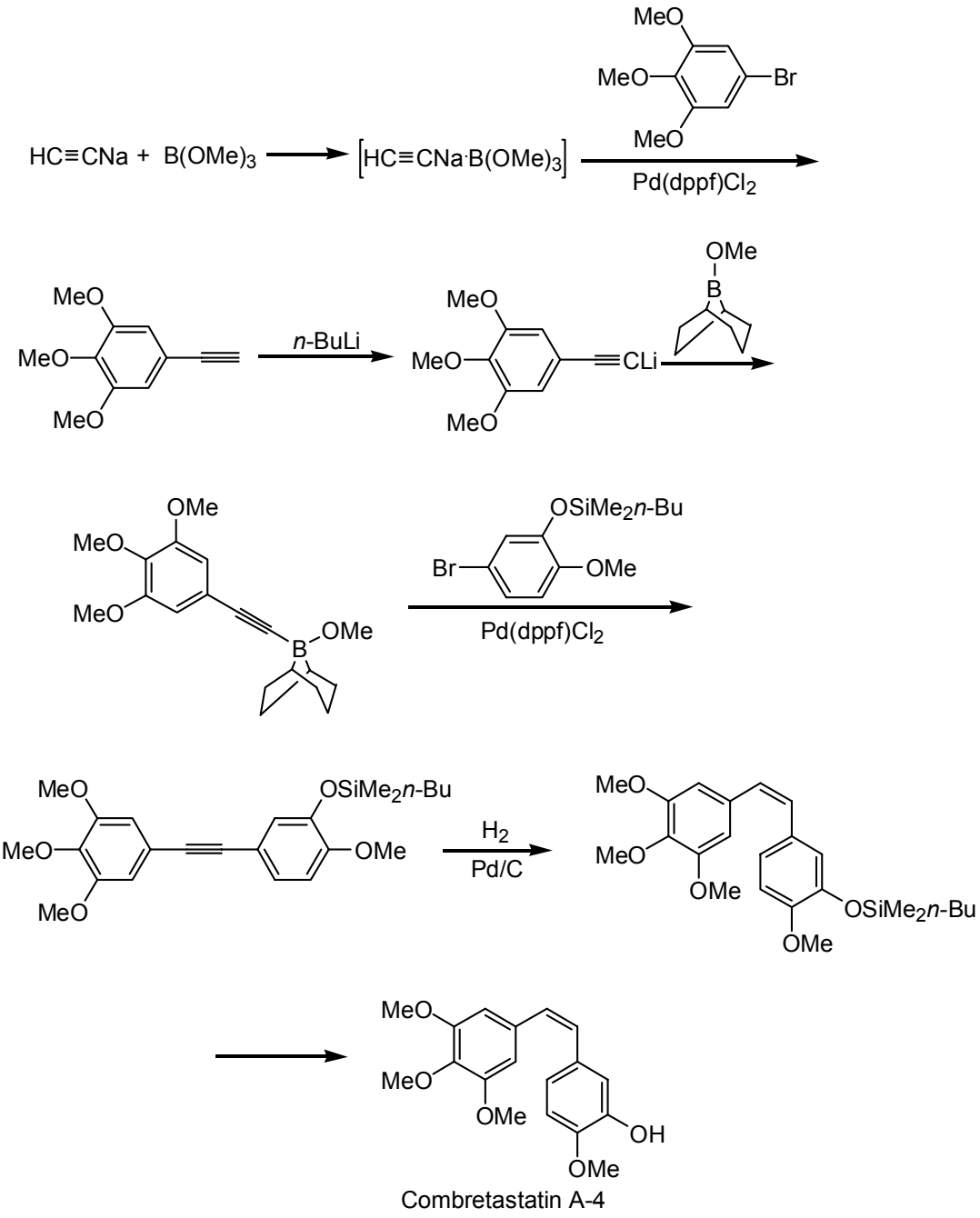


Figure 2-1-4: Synthesis of Combretastatin A-4.

aryl or alkenyl bromides was reported.[58] The influence of fluoride anions (CsF, KF, or TBAF) in the reaction was demonstrated using the ate complex obtained by treatment of octynyllithium with triisopropoxyborane. In this case, a 30% excess of the alkynylboron "ate" complex generated *in situ* was required for the cross-coupling reaction. In the second report, lithium 1-alkynyl(triisopropoxy)borates were prepared quantitatively in diethyl ether by borination of the alkynyllithium species. These were isolated and proved to be quite stable for long periods of time at low temperature. They were subsequently used in Suzuki cross-coupling reactions with aryl halide derivatives. Moderate to good yields were achieved in these reactions, but two equivalents of the lithium 1-alkynyl(triisopropoxy)borates were required for effective cross-coupling.[59]

2.1.4 Potassium Alkynyltrifluoroborates in Alkynylation Reaction

Given the overall desirability of using organoboron compounds for cross-coupling reactions, further modifications of these reagents appeared reasonable. Genêt first reported the preparation of potassium alkynyltrifluoroborates by sequential deprotonation of alk-1-ynes, boronation, and *in situ* treatment with KHF_2 .[60] But the cross-coupling reactions of potassium alkynyltrifluoroborates with electrophiles was not satisfactory until Molander demonstrated the feasibility of the cross-coupling reaction of potassium alkynyltrifluoroborates in the presence of $Pd(dppf)Cl_2$ as a catalyst.[61]

2.1.5 Scope of Part II

The application of potassium alkynyltrifluoroborates in Pd-catalyzed alkynylation reaction has been limited. Due to the importance of alkynylation reaction in organic synthesis, a study of the application of potassium alkynyltrifluoroborates to alkyne syntheses was investigated. The newly developed reactions include: (a) syntheses of 4-(1-alkynyl)-2(5H)-furanones and coumarins; (b) utilization of potassium alkynyltrifluoroborates in the synthesis of conjugated enediynes; and (c) application of potassium alkynyltrifluoroborates as a new partner in the Petasis reaction.

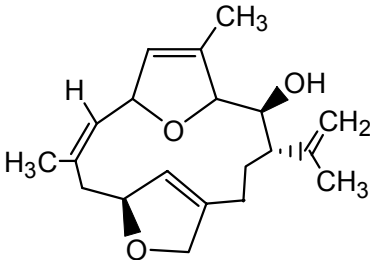
Chapter 2

Syntheses of 4-(1-Alkynyl)-2(5H)-Furanones and Coumarins via the Palladium Catalyzed Cross-Coupling Reactions of Potassium Alkynyltrifluoroborates

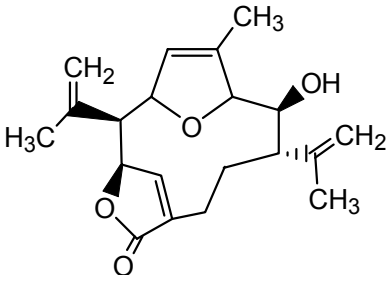
2.2.1 Introduction

Unsaturated five-membered lactones are important synthetic targets because they are core units in many natural products[62] and medicinally important materials (Figure 2-2-1).[63] Compounds containing the 2(5H)-furanone moiety have been evaluated as insecticides, fungicides, antitumor agents, allergy inhibitors, cyclooxygenase inhibitors, and phospholipase A2 inhibitors.[64]

Examples of alkynyl-substituted heterocycles that exhibit significant cytotoxicity have also been reported.[65] Recently, 4-(1-alkynyl)-2(5H)-furanones were found to exhibit potent cytotoxicity (Figure 2-2-2).[66] Syntheses of 2(5H)-furanones with varying substitution patterns have been reported.[67, 68] However, synthetic routes to 4-alkynyl-substituted 2(5H)-furanones are limited.[69] Existing methods involve transition metal catalyzed coupling methodologies such as the Sonogashira[69c] and Stille[66, 69b] reactions. These methods have limitations. The Sonogashira reaction requires a catalyst mixture and a strong base, in addition brominated substrates generate only modest yields of the desired products. The Stille reaction involves the use of organotin compounds that are often difficult to separate from the desired product.



Bipinnatin J



Kallolide A

Figure 2-2-1: Furanone contained natural products.

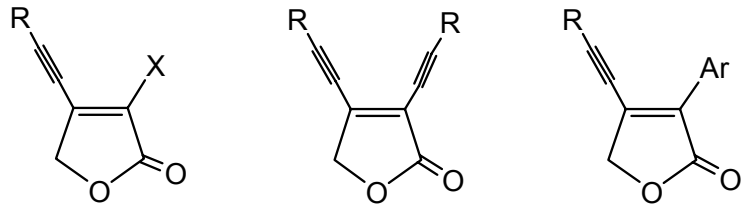


Figure 2-2-2: 4-(1-Alkynyl)-2(5H)-furanones.

Due to their ready availability and chemical stability, potassium organotrifluoroborates have attracted significant attention.[60, 61, 70] An efficient synthesis of 4-alkynyl-substituted 2(5H)-furanones using alkynyltrifluoroborates was developed during the course of this study.

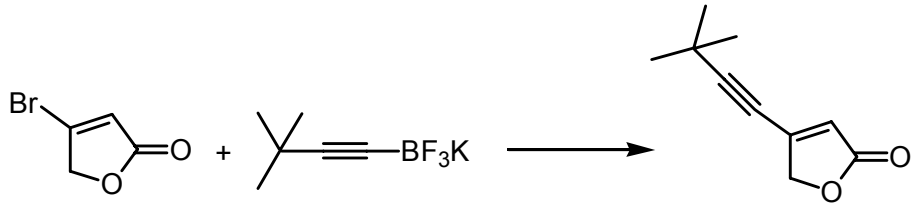
2.2.2 Results and Discussion

The reaction of *β*-tetronic acid bromide with potassium (3,3-dimethyl-1-butyn-1-yl)trifluoroborate was first examined in an effort to optimize the reaction conditions. The use of $Pd(OAc)_2$ afforded a moderate yield of the desired product (Table 2-2-1, entry 3). $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ produced only modest yields of the expected product (Table 2-2-1, entries 1 and 2). Molander successfully coupled potassium alkynyltrifluoroborates with aryl halides using $Pd(dppf)Cl_2$.[24b] It was found that lesser quantities of $Pd(dppf)Cl_2$ catalyzed the new reaction quite effectively (Table 2-2-1, entries 5 and 6).

The new base-free conditions were applied to a variety of potassium alkynyltrifluoroborates. Typical results are summarized in Table 2-2-2. Under the optimized conditions, the new reaction resulted in high isolated yields of the desired products.

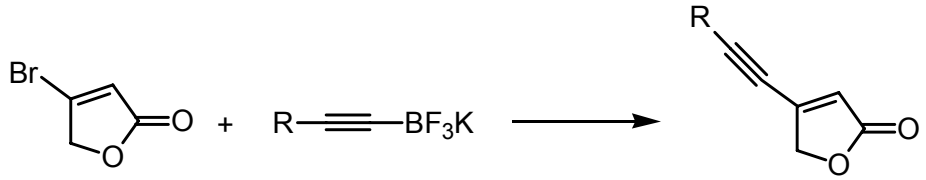
Coumarins are found in nature and act as structural subunits of more complex natural products.[71] The new method was applied to the synthesis of 4-alkynylcoumarins. Interestingly, the reaction of 4-bromocoumarin with potassium alkynyltrifluoroborates requires the presence of base. The reactions of 4-bromocoumarin with various potassium alkynyltrifluoroborates are summarized in Table 2-2-3.

Table 2-2-1: Reaction of β-tetronic acid bromide with (3,3-dimethyl-1-butyn-1-yl)trifluoroborate.



Entry	Reaction conditions	Isolated yield (%)
1	$Pd(PPh_3)_2Cl_2$ (5 mol %), PPh_3 (10 mol %), 3 Cs_2CO_3, THF/H_2O (20:1), reflux, 8 h.	15
2	$Pd(PPh_3)_2Cl_2$ (5 mol %), Cs_2CO_3, THF/H2O (20:1), reflux, 7 h.	12
3	$Pd(OAc)_2$ (5 mol %), Cs_2CO_3, THF/H_2O (20:1), reflux, 4 h.	52
4	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (9 mol %), Cs_2CO_3, THF/H_2O (20:1), 50 ^oC, 2 h.	95
5	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol %), Cs_2CO_3, THF/H_2O (20:1), 50 ^oC, 2 h.	95
6	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol %), THF, 3 h	95

Table 2-2-2: Cross-coupling of *β*-tetronic acid bromide with potassium alkynyltrifluoroborates.[a]



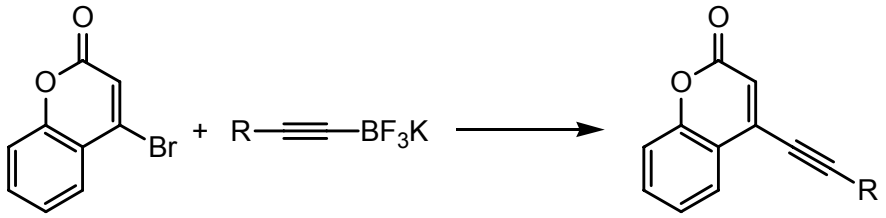
Entry	R	Time (h)	Product[b]	Yield (%)[c]
1	*t*-Butyl	3	**2-201**	95
2	*n*-Butyl	4	**2-202**	95
3	Isopropenyl	3	**2-203**	88
4	3-Chloropropyl	3	**2-204**	89
5	1-Cyclohexenyl	5	**2-205**	80
6	Phenyl	6	**2-206**	91
7	*p*-Tolyl	6	**2-207**	87
8	TMS	4	**2-208**	71

[a]Reactions were carried out using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol %) in THF at room temperature.

[b]All products were characterized by ^1H, ^{13}C NMR spectroscopy and elemental analysis.

[c]Isolated yields.

Table 2-2-3: Cross-coupling reactions of 4-bromocoumarin with various potassium alkynyltrifluoroborates.[a]



Entry	R	Time (h)	Product[b]	Yield (%)[c]
1	*t*-Butyl	1	**2-209**	97
2	*n*-Butyl	1.5	**2-210**	91
3	1-Cyclohexenyl	1.5	**2-211**	82
4	Phenyl	2	**2-212**	92
5	*p*-Tolyl	2	**2-213**	85

[a]Reactions were carried out using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol %) and Cs_2CO_3 (3 equiv.) in THF/H_2O (20:1) at 50 ^oC.

[b]All products were characterized by ^1H, ^{13}C NMR spectroscopy and elemental analysis.

[c]Isolated yields.

2.2.3 Conclusion

In conclusion, an efficient method for the synthesis of 4-(1-alkynyl)-2(5H)-furanones has been developed utilizing the Pd-catalyzed coupling reaction of β-tetronic acid bromide with potassium alkynyltrifluoroborates in the absence of base under mild conditions. 4-Alkynylcoumarins were also successfully synthesized via coupling reactions of 4-bromocoumarin with potassium alkynyltrifluoroborates in the presence of Cs_2CO_3. The reaction procedures are straightforward and the yields are excellent.

2.2.4 Experimental Section

2.2.4.1 General Considerations

All glassware was dried in an oven at 120 ^{o}C and flushed with dry nitrogen. Reactions were carried out under a nitrogen atmosphere. Potassium alkynyltirfluoroborates were prepared utilizing literature methods.[15] Products were purified by flash chromatography using silica gel (60 C, 230 400 mesh) with hexanes and ethyl acetate (hexanes:EtOAc 20:1) as eluent. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Varian 300MHz instrument with chemical shifts reported relative to TMS.

2.2.4.2 General Procedure for Synthesis of Potassium Salt (1-Hexyn-1-yl)trifluoroborate.

A solution of 1-hexyne (0.82 g, 10.0 mmol, 1 equiv) in 20 mL of dry THF was cooled to -78 °C under argon. *n*-BuLi (6.25 mL, 1.6 M in hexane, 10 mmol, 1 equiv) was added dropwise, and the solution was stirred for 1 h at this temperature. Trimethylborate (1.6 g, 15 mmol, 1.5 equiv) was then added dropwise at -78 °C. The solution was stirred at this temperature for 1 h after which it was allowed to warm to -20 °C for 1 h. A saturated aqueous solution of potassium hydrogen difluoride (4.7 g, 60 mmol, 6.0 equiv) was added to the vigorously stirred solution. The resulting mixture was allowed to stir for 1 h at -20 °C after which it was allowed to warm to room temperature for 1 h. The solvent was removed under reduced pressure, and the resulting white solid was dried under high vacuum for 2 h to remove all water. The solid was then washed with acetone and then with hot acetone. The resulting organic solution was filtered, and the solvent was removed to afford a fluffy white solid. This solid was then dissolved in hot acetone and precipitated with diethyl ether, after which the solution was cooled to -20 °C to complete precipitation of the solid. The product was collected as a white crystalline solid (1.7 g, 78%). The spectra obtained were in agreement with previously reported data.[15]

2.2.4.3 Representative Procedure for the Coupling Reaction of β-Tetronic Acid Bromide with Potassium Alkynyltrifluoroborates.

The synthesis of 4-(3,3-Dimethylbut-1-ynyl)-5H-furan-2-one (2-201): *β*-Tetronic acid bromide (33mg, 0.2 mmol) was placed in an oven-dried, round-bottomed flask under a nitrogen atmosphere. Dry THF (2.0 mL) was added and the resultant

solution stirred. Potassium 3,3-dimethylbut-1-ynyltrifluoroborate (41mg, 0.22mmol), Pd(dppf)Cl_2 (8mg, 5 mol %) were then added. The mixture was stirred at room temperature for three hours. The resultant mixture was extracted with ethyl ether (4 x 5 ml). The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the product purified by silica gel chromatography (ethyl acetate/hexane = 1:20 as effluent). The product was collected as (31mg, 95%). ^{1}H NMR: δ 6.09 (t, 1H, *J* = 1.9 Hz), 4.77 (d, 2H, *J* = 1.8 Hz), 1.30 (s, 9H); ^{13}C NMR: δ 173.7, 148.2, 121.2, 115.6, 73.2, 70.0, 30.2, 28.5. Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; Found: C, 72.80; H, 7.69.

2.2.4.4 Analytical Data

4-Hex-1-ynyl-5H-furan-2-one (2-202). ^{1}H NMR: δ 6.09 (t, 1H, *J* = 1.8 Hz), 4.77 (d, 2H, *J* = 2.1 Hz), 2.46 (t, 2H, *J* = 7.2 Hz), 1.54 – 1.61 (m, 2H), 1.38 – 1.49 (m, 2H), 0.94 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR: δ 173.8, 148.2, 121.3, 108.2, 73.2, 71.4, 29.9, 21.9, 19.5, 13.4.

4-(3-Methylbut-3-en-1-ynyl)-5H-furan-2-one (2-203). ^{1}H NMR: δ 6.19 (t, 1H, *J* = 1.9 Hz), 5.48 – 5.53 (m, 2H), 4.84 (d, 2H, *J* = 1.8 Hz), 1.97 (t, 3H, *J* = 1.2 Hz); ^{13}C NMR: δ 173.2, 147.1, 126.1, 125.3, 122.1, 105.9, 78.0, 72.9, 22.6. Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44; Found: C, 72.97; H, 5.12.

4-(5-Chloropent-1-ynyl)-5H-furan-2-one (2-204). ^{1}H NMR: δ 6.13 (t, 1H, *J* = 2.1 Hz), 4.79 (d, 2H, *J* = 2.1 Hz), 3.66 (t, 2H, *J* = 6.3 Hz), 2.68 (t, 2H, *J* = 6.9 Hz), 2.02 – 2.11 (m, 2H); ^{13}C NMR: δ 173.4, 147.6, 122.0, 105.7, 73.1, 72.1, 43.3, 30.5, 17.2.

4-Cyclohex-1-enylethynyl-5H-furan-2-one (2-205). ^{1}H NMR: δ 6.34 – 6.37 (m, 1H), 6.12 (t, 1H, *J* = 1.9 Hz), 4.81 (d, 2H, *J* = 1.8 Hz), 2.16 – 2.21 (m, 4H), 1.60 – 1.72 (m, 4H); ^{13}C NMR: δ 173.6, 147.7, 140.3, 121.0, 119.6, 107.4, 77.1, 73.0, 28.4, 26.0, 21.9, 21.1. Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; Found: C, 76.42; H, 6.51.

4-Phenylethynyl-5H-furan-2-one (2-206). ^{1}H NMR: δ 7.37 – 7.54 (m, 5H), 6.27 (t, 1H, *J* = 2.1 Hz), 4.92 (d, 2H, *J* = 2.1Hz); ^{13}C NMR: δ 173.3, 147.1, 132.0, 130.3, 128.7, 122.1, 120.8, 105.0, 79.2, 73.0.

4-*p*-Tolylethynyl-5H-furan-2-one (2-207). ^{1}H NMR: δ 7.42 (d, 2H, *J* = 8.1 Hz), 7.21 (d, 2H, *J* = 8.1 Hz), 6.24 (t, 1H, *J* = 1.8 Hz), 4.90 (d, 2H, *J* = 1.8 Hz), 2.40 (s, 3H); ^{13}C NMR: δ 173.4, 147.3, 141.0, 132.0, 129.5, 121.6, 117.7, 104.9, 79.1, 73.0, 21.7.

4-Trimethylsilanylethynyl-5H-furan-2-one (2-208). ^{1}H NMR: δ 6.21 (t, 1H, *J* = 1.8 Hz), 4.81 (d, 2H, *J* = 1.8 Hz), 0.25 (s, 9H); ^{13}C NMR: δ 173.4, 147.0, 123.1, 113.0, 93.7, 73.0, -0.7.

4-(3,3-Dimethylbut-1-ynyl)-chromen-2-one (2-209). ^{1}H NMR: δ 7.79 – 7.83 (m, 1H), 7.51 – 7.55 (m, 1H), 7.29 – 7.34 (m, 2H), 6.47 (s, 1H), 1.41 (s, 9H); ^{13}C NMR: δ 160.4, 153.5, 137.9, 132.0, 126.6, 124.3, 118.7, 117.9, 116.8, 112.7, 13.4, 30.5, 28.6. Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24; Found: C, 79.50; H, 6.30.

4-Hex-1-ynylchromen-2-one (2-210). ^{1}H NMR: δ 7.83 – 7.86 (m, 1H), 7.51 – 7.57 (m, 1H), 7.28 – 7.34 (m, 2H), 6.48 (s, 1H), 2.57 (t, 2H, J = 7.1 Hz), 1.66 – 1.73 (m, 2H), 1.50 – 1.58 (m, 2H), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR: δ 160.4, 153.5, 138.1, 132.0, 126.7, 124.3, 118.8, 118.1, 116.8, 105.1, 74.8, 30.2, 22.0, 19.5, 13.5. Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24; Found: C, 79.37; H, 6.24.

4-Cyclohex-1-enylethynylchromen-2-one (2-211). ^{1}H NMR: δ 7.82 – 7.85 (m, 1H), 7.51 – 7.57 (m, 1H), 7.28 – 7.34 (m, 2H), 6.46 –6.49 (m, 2H), 2.20 – 2.32 (m, 4H), 1.64 – 1.76 (m, 4H); ^{13}C NMR: δ 160.4, 153.4, 140.1, 137.7, 132.0, 126.6, 124.3, 119.8, 118.5, 117.5, 116.9, 104.6, 80.6, 28.7, 26.0, 22.0, 21.1.

4-Phenylethynylchromen-2-one (2-212). ^{1}H NMR: δ 7.94 – 7.97 (m, 1H), 7.54 – 7.64 (m, 3H), 7.27 – 7.45 (m, 5H), 6.62 (s, 1H); ^{13}C NMR: δ 160.2, 153.5, 137.2, 132.3, 132.2, 130.2, 128.6, 126.6, 124.4, 121.0, 118.3, 117.0, 102.1, 82.7. Anal. Calcd. for $C_{17}H_{10}O_2$: C, 82.91; H, 4.09; Found: C, 82.88; H, 4.07.

4-*p*-Tolylethynylchromen-2-one (2-213). ^{1}H NMR: δ 7.94 – 7.97 (m, 1H), 7.52 – 7.58 (m, 3H), 7.22 – 7.37 (m, 4H), 6.59 (s, 1H), 2.41 (s, 3H); ^{13}C NMR: δ 160.3, 153.5, 140.8, 137.4, 132.2, 132.1, 129.4, 126.6, 124.4, 118.4, 118.0, 117.9, 116.9, 102.7, 83.4, 21.7.

Chapter 3

Synthesis of Conjugated Enediynes via Palladium Catalyzed Cross-Coupling Reactions of Potassium Alkynyltrifluoroborates

2.3.1 Introduction

Cross-conjugated enediynes have recently received considerable attention due to their extensive applications in non-linear optics (NLO),[72] macrocyclic ligands,[73] optical switches,[74] and the synthesis of polycyclic aromatic hydrocarbons (PAHs).[75] Preparative methods for enediynes are limited although the Sonogashira reaction can be utilized[76] as well as the palladium catalyzed coupling reaction of ketene butyltelluroacetals with alkynes.[77] The Sonogashira reaction normally produces a mixture of bromoenyne, enediyne, and recovered starting dibromoalkene.[76e, 78] In some cases the yields are low.[76c, d] The butyltelluroacetal method involves the use of vinylic telluride compounds that are toxic and often difficult to prepare. Thus, the development of a simple and efficient approach to cross-conjugated enediynes is of great interest.

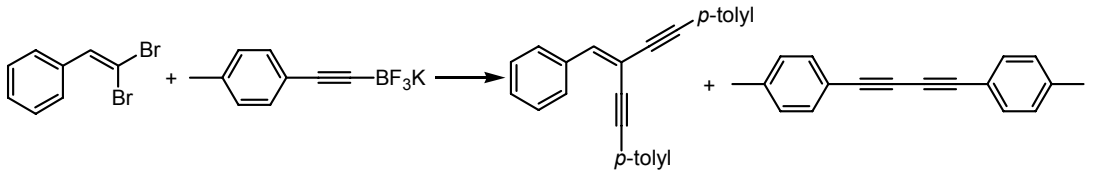
During the past twenty years, Suzuki-Miyaura cross-coupling reactions have provided preparative methods for effectively creating carbon-carbon bonds. The coupling reactions of aryl-, alkyl-, and alkenylboron compounds (including boronate esters, boranes, and boronic acids) have been investigated extensively.[52] However, as noted in Chapter 1, coupling reactions involving alkynylboron compounds have been limited to B-alkynyl-9-BBN borate complexes,[55, 56] alkynyltrialkoxyborate complexes,[58] and lithium 1-alkynyl(triisopropoxy)borates.[59] Because alkynylboronic esters are stronger

Lewis acids than aryl- and alkenylboronate esters and are easily hydrolyzed,[79] their use in organic reactions can be problematic. We developed an efficient synthesis of cross-conjugated mono-enediynes using the cross-coupling of potassium alkynyltrifluoroborates with 1,1-dibromo-1-alkenes.

2.3.2 Results and Discussion

Various palladium catalysts, solvents and reaction conditions were examined using 2,2-dibromovinylbenzene and potassium *p*-tolylethynyltrifluoroborate as model substrates (Table 2-3-1). 2,2-Dibromovinylbenzene (1 equivalent) was treated with potassium *p*-tolylethynyltrifluoroborate (2 equiv) in the presence of 5 mol % of $Pd(dppf)Cl_2/Cs_2CO_3$ (3 equiv) at 50 ^oC in methanol (Table 2-3-1, entry 1). Under these conditions, the reaction was sluggish. Fifty-two percent of the starting material, 2,2-dibromovinylbenzene, was recovered after 12 hours. The corresponding enediyne was obtained in 10% yield, and 1,3-diyne was isolated as the major product in 36% yield. The homocoupling product of 2,2-dibromovinylbenzene and monosubstituted bromoenyne was not detected although it is commonly reported as byproducts in Sonogashira reactions.[76, 77] Using DMF and toluene as solvents, the isolated yields of enediyne were 21% and 18% respectively (Table 2-3-1, entries 2 and 3). When THF was used as solvent, the yield of the disubstituted product increased to 43% and only 26% of starting material was recovered (Table 2-3-1, entry 4). The addition of a small amount of water increased the yield of enediyne to 52% as well as decreased the reaction time to 4 hours (Table 2-3-1, entry 5).[80] As the reaction proceeds, the mixture becomes black. Gas

Table 2-3-1: Optimization of reaction conditions.[a]



Entry	Conditions[b]	Yield %[c]		
		3	4	1(recovered)
1	$Pd(dppf)Cl_2$, MeOH, 12 h	10	36	52
2	$Pd(dppf)Cl_2$, DMF, 16 h	21	20	56
3	$Pd(dppf)Cl_2$, Toluene 12 h	18	12	64
4	$Pd(dppf)Cl_2$, THF, 6 h	43	19	26
5	$Pd(dppf)Cl_2$, THF/H_2O(20:1), 4 h	52	16	14
6	$Pd(dppf)Cl_2$ 10 mol%, THF/H_2O(20:1), 2h	76	8	0
7	$Pd(OAc)_2$ 10 mol%, THF/H_2O(20:1), 16h	23	26	45
8	$Pd(PPh_3)_4$ 10 mol%, THF/H_2O(20:1), 12h	21	22	54
9[d]	$Pd(dppf)Cl_2$, THF/H_2O(20:1), 16 h	30	18	50

[a]The ratio of 2,2-dibromovinylbenzene and potassium *p*-tolylethynyltrifluoroborate was 1:2.

[b]Reaction carried out at 50 ^oC in the presence of 5 mol% of catalyst and 3 equivalents of Cs_2CO_3.

[c]Isolated yield.

[d]3 equivalents of $(i\text{-}Pr)_2NEt$ were used in place of Cs_2CO_3.

chromatographic analysis of the black reaction mixture (presumably due to metallic palladium) indicated formation of the desired product. Increasing the amount of catalyst to 10 mol % generated the disubstituted product in 76% yield (Table 2-3-1, entry 6). Other palladium catalysts, such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$, were less effective (Table 2-3-1, entries 7 and 8). Cs_2CO_3 gave higher yields of enediyne than diisopropylethylamine (Table 2-3-1, entry 9). Optimum conditions for the reaction were found to be 10 mol % of $Pd(dppf)Cl_2$ and 3 equivalents of Cs_2CO_3 in THF/H_2O (20:1) at 50 ^oC for 2 hours.

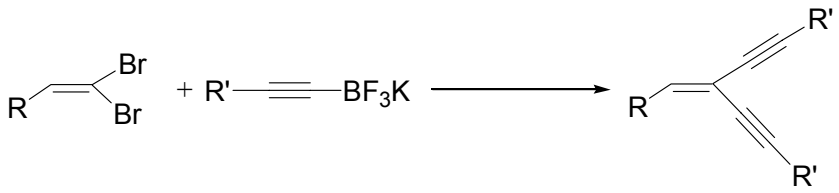
To enhance the utility of the reaction, a variety of potassium alkynyltrifluoroborates were prepared via deprotonation of 1-alkynes, followed sequentially by transmetallation with boronic esters and treatment *in situ* with KHF_2. 1,1-Dibromo-1-alkenes were prepared by literature methods.[81] Under the optimized conditions, reactions of various potassium alkynyltrifluoroborates with different 1,1-dibromo-1-alkenes were evaluated and the results are summarized in Table 2-3-2. The reaction resulted in good isolated yields. No significant differences in reactivity with respect to the electronic and steric effects of the substituents were observed. 1-(2,2-Dibromovinyl)-4-nitrobenzene also gave a good yield, 54%.

2.3.3 Experimental Section

2.3.3.1 General Considerations

All glassware was dried in an oven at 120 ^oC and flushed with dry nitrogen. Reactions were carried out under a nitrogen atmosphere. 1,1-Dibromo-1-alkenes and

Table 2-3-2: Cross-coupling of 1,1-dibromo-1-alkenes with potassium alkynyltrifluoroborates.[a]



Entry	R	R'	Product	(Yield %)[b]
1	Phenyl	*n*-Butyl	**2-301**	85
2	Phenyl	3-Chloropropyl	**2-302**	82
3	Phenyl	Isopropenyl	**2-303**	74
4	Phenyl	Phenyl	**2-304**	73
5	Phenyl	*p*-Tolyl	**2-305**	76
6	*p*-Chlorophenyl	Phenyl	**2-306**	81
7	*p*-Chlorophenyl	3-Chloropropyl	**2-307**	73
8	*p*-Tolyl	3-Chloropropyl	**2-308**	76
9	*o*-Tolyl	3-Chloropropyl	**2-309**	66
10	1-Naphthyl	3-Chloropropyl	**2-310**	82
11	*p*-Nitrophenyl	3-Chloropropyl	**2-311**	64
12	Octyl	Phenyl	**2-312**	75

[a]Reactions carried out using 10 mol% of $Pd(dppf)Cl_2$ with 3 equiv. of Cs_2CO_3 in THF/H_2O (20:1) at 50 ^oC for 2 hr.

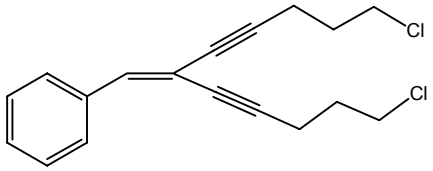
[b]Isolated yield.

potassium alkynyltirfluoroborates were prepared using literature methods.[81, 61] Products were purified by flash chromatography using silica gel (60 C, 230 400 mesh) with hexanes and ethyl acetate (hexanes:EtOAc 20:1) as eluent. Elemental Analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Varian 300MHz instrument with chemical shifts reported relative to TMS.

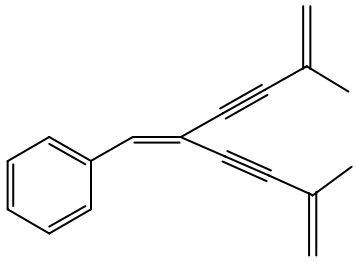
2.3.3.2 Representative Procedure

The Synthesis of 2-Hex-1-ynyloct-1-en-3-ynylbenzene (2-301): 2,2-dibromovinylbenzene (52mg, 0.20 mmol) was placed in an oven-dried, round-bottomed flask under a nitrogen atmosphere. THF (2.0 mL) and H_2O (0.1ml) were added and the resultant solution stirred. Potassium 1-hexanyltrifluoroborate (75mg, 0.4mmol), Cs_2CO_3 (196mg, 0.60mmol), and $Pd(dppf)Cl_2$ (16mg, 10 mol%) were then added. The mixture was stirred at 50ºC for 2 hours. The resultant mixture was extracted with ethyl ether (4 x 5 ml). The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the product purified by silica gel chromatography (ethyl acetate–hexane) to give **2-301** as a pure colorless oil in 85% yield (45mg). ^{1}H NMR ($CDCl_3$): δ 7.81-7.84 (m, 2H), 7.28-7.34 (m, 3H), 6.88 (s, 1H), 2.45 (t, 2H, *J* = 6.9Hz), 2.37 (t, 2H, *J* = 6.9Hz), 1.44-1.61 (m, 8H), 0.92-0.97 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 141.0, 136.0, 128.5, 128.4, 128.1, 104.0, 96.1, 88.9, 81.0, 78.6, 30.7, 30.4, 22.0, 21.9, 19.5, 19.2, 13.6, 13.6. Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15; Found: C, 90.62; H, 9.08.

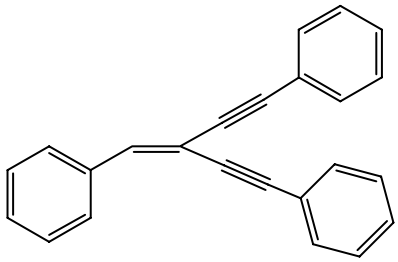
2.3.3.3 Analytical Data



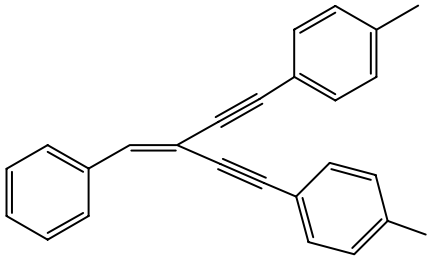
7-Chloro-2-(5-chloropent-1-ynyl)hept-1-en-3-ynylbenzene (2-302): ^{1}H NMR ($CDCl_3$): δ 7.78-7.81 (m, 2H), 7.25-7.38 (m, 3H), 6.92 (s, 1H), 3.62-3.71 (m, 4H), 2.66 (t, 2H, *J* = 6.6Hz), 2.57 (t, 2H, *J* = 6.6Hz), 1.99-2.10 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 142.1, 135.6, 128.8, 128.5, 128.3, 103.2, 93.8, 86.8, 81.6, 79.3, 43.7, 43.6, 31.3, 30.9, 17.2, 16.9. Anal. Calcd. for $C_{18}H_{18}Cl_2$: C, 70.83; H, 5.94; Found: C, 70.78; H, 5.90.



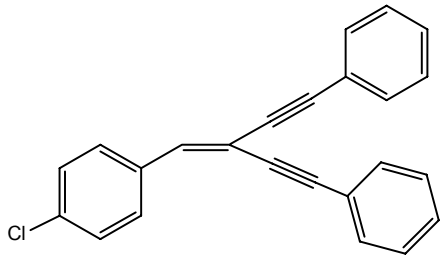
5-Methyl-2-(3-methylbut-3-en-1-ynyl)hexa-1,5-dien-3-ynylbenzene (2-303): ^{1}H NMR ($CDCl_3$): δ 7.83-7.86 (m, 2H), 7.30-7.36 (m, 3H), 7.02 (s, 1H), 5.30-5.43 (m, 4H), 2.00 (t, 3H, *J* = 1.2Hz), 1.97 (t, 3H, *J* = 1.2Hz); ^{13}C NMR ($CDCl_3$): δ 142.9, 135.7, 129.1, 128.9, 128.3, 126.6, 123.0, 122.5, 103.2, 100.1, 95.7, 89.3, 88.2, 85.9, 23.3, 22.9. Anal. Calcd. for $C_{18}H_{16}$: C, 93.06; H, 6.94; Found: C, 92.90; H, 6.87.



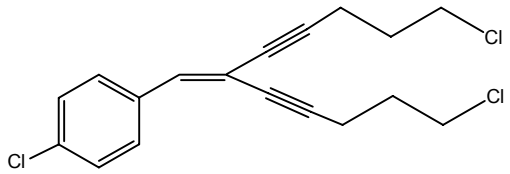
1,1'-[2-(phenylethynyl)-1-buten-3-yne-1,4-diyl]bisbenzene (2-304): ^{1}H NMR ($CDCl_3$): δ 7.93-7.96 (m, 2H), 7.53-7.57 (m, 4H), 7.33-7.42 (m, 9H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 143.2, 135.7, 131.7, 131.7, 129.2, 129.1, 128.8, 128.4, 128.3, 122.9, 122.8, 103.3, 94.6, 89.1, 88.3, 86.9. Anal. Calcd. for $C_{24}H_{16}$: C, 94.70; H, 5.30; Found: C, 94.48; H, 5.41.



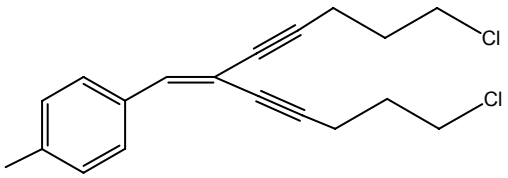
1,1'-[2-(phenylethynyl)-1-buten-3-yne-1,4-diyl]bistoluene (2-305): ^{1}H NMR ($CDCl_3$): δ 7.93-7.96 (m, 2H), 7.31-7.46 (m, 7H), 7.13-7.18 (m, 5H), 2.37 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.5, 139.0, 138.6, 135.9, 131.6, 131.5, 129.2, 129.1, 129.0, 128.4, 120.0, 119.8, 103.5, 94.8, 88.7, 88.4, 86.4, 21.6, 21.5. Anal. Calcd. for $C_{26}H_{20}$: C, 93.94; H, 6.06; Found: C, 94.11; H, 5.98.



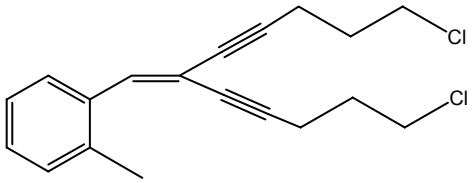
1,1'-[2-(*p*-chlorophenylethynyl)-1-buten-3-yne-1,4-diyl]bisbenzene (2-306): ^{1}H NMR ($CDCl_3$): δ 7.86-7.89 (m, 2H), 7.52-7.55 (m, 4H), 7.33-7.38 (m, 8H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 141.5, 134.7, 134.1, 131.7, 131.6, 130.2, 128.9, 128.6, 128.5, 128.4, 128.3, 122.7, 122.6, 103.9, 95.1, 88.9, 88.8, 86.6. Anal. Calcd. for $C_{24}H_{15}Cl$: C, 85.07; H, 4.46; Found: C, 84.84; H, 4.42.



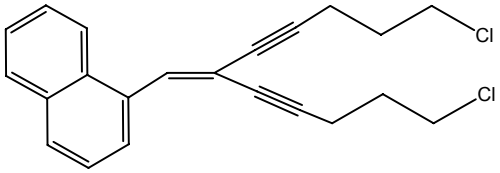
1-Chloro-4-[7-chloro-2-(5-chloropent-1-ynyl)hept-1-en-3-ynyl]benzene (2-307): ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 2H, *J* = 8.7Hz), 7.32 (d, 2H, *J* = 8.7Hz), 6.85 (s, 1H), 3.66-3.71 (m, 4H), 2.66 (t, 2H, *J* = 6.6Hz), 2.56 (t, 2H, *J* = 6.9Hz), 1.97-2.07 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 140.5, 134.3, 134.1, 129.7, 128.5, 103.8, 94.4, 87.3, 81.4, 79.1, 43.7, 43.5, 31.2, 30.8, 17.1, 16.9. Anal. Calcd. for $C_{18}H_{17}Cl_3$: C, 63.64; H, 5.04; Found: C, 63.39; H, 5.28.



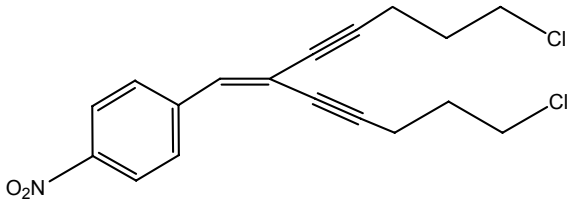
1-[7-Chloro-2-(5-chloropent-1-ynyl)hept-1-en-3-ynyl]-4-methylbenzene (2-308): ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 2H, *J* = 8.4Hz), 7.16 (d, 2H, *J* = 8.4Hz), 6.89 (s, 1H), 3.64-3.72 (m, 4H), 2.65 (t, 2H, *J* = 6.9Hz), 2.56 (t, 2H, *J* = 6.9Hz), 2.36 (s, 3H), 1.92-2.10 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 142.1, 139.0, 132.9, 129.0, 128.5, 102.1, 93.6, 86.4, 81.7, 79.4, 43.7, 43.6, 31.3, 30.9, 21.4, 17.2, 16.9. Anal. Calcd. for $C_{19}H_{20}Cl_2$: C, 71.48; H, 6.31; Found: C, 71.61; H, 6.27.



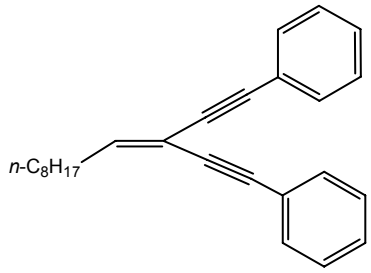
1-[7-Chloro-2-(5-chloropent-1-ynyl)hept-1-en-3-ynyl]-2-methylbenzene (2-309): ^{1}H NMR ($CDCl_3$): δ 8.02-8.04 (m, 1H), 7.17-7.21 (m, 3H), 7.10 (s, 1H), 3.57-3.72 (m, 4H), 2.46-2.60 (m, 4H), 2.33 (s, 3H), 1.97-2.07 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 140.4, 136.6, 134.4, 130.1, 128.6, 128.0, 125.4, 104.2, 92.5, 86.8, 81.4, 79.0, 43.8, 43.6, 31.3, 30.9, 19.9, 17.1, 16.9. Anal. Calcd. for $C_{19}H_{20}Cl_2$: C, 71.48; H, 6.31; Found: C, 71.26; H, 6.34.



1-[7-Chloro-2-(5-chloropent-1-ynyl)hept-1-en-3-ynyl]naphthalene (2-310): ^{1}H NMR ($CDCl_3$): δ 8.03-8.12 (m, 2H), 7.79-7.85 (m, 2H), 7.62 (s, 1H), 7.44-7.54 (m,3H), 3.71 (t, 2H, *J* = 6.4Hz), 3.46 (t, 2H, *J* = 6.4Hz), 2.80 (t, 2H, *J* = 7.5Hz), 2.50 (t, 2H, *J* = 7.5Hz), 1.85-2.09 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 139.5, 133.3, 132.1, 131.0, 128.9, 128.4, 126.3, 126.1, 125.7, 124.8, 123.5, 105.5, 92.1, 87.1, 81.1, 78.6, 43.5, 43.3, 31.1, 30.6, 17.2, 16.8. Anal. Calcd. for $C_{22}H_{20}Cl_2$: C, 74.37; H, 5.67; Found: C, 74.31; H, 5.72.



1-[7-Chloro-2-(5-chloropent-1-ynyl)hept-1-en-3-ynyl]-4-nitrobenzene (2-311): ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, *J* = 9.3Hz), 7.94 (d, 2H, *J* = 9.3Hz), 6.94 (s, 1H), 3.67-3.72 (m, 4H), 2.70 (t, 2H, *J* = 6.9Hz), 2.60 (t, 2H, *J* = 6.9Hz), 2.03-2.10 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 147.0, 141.7, 139.0, 129.0, 123.6, 107.7, 96.1, 89.4, 81.3, 78.91 43.6, 43.5, 31.1, 30.6, 17.1, 16.9. Anal. Calcd. for $C_{18}H_{17}Cl_2NO_2$: C, 61.73; H, 4.89; N, 4.00; Found: C, 61.52; H, 4.95; N, 3.97.



3-[2-(Phenylethynyl)]-3-dodecen-1-ynylbenzene (2-312): ^{1}H NMR ($CDCl_3$): δ 7.47-7.52 (m, 4H), 7.30-7.36 (m, 6H), 6.47 (t, 1H, *J* = 7.8Hz), 2.45-2.52 (m, 2H), 1.27-1.54 (m, 12H), 0.87 (t, 3H, *J* = 6.6Hz); ^{13}C NMR ($CDCl_3$): δ 149.8, 131.6, 128.4, 128.3, 128.2, 128.2, 123.0, 105.5, 92.7, 87.5, 84.9, 31.9, 31.0, 29.4, 29.3, 29.2, 28.6, 22.7, 14.1. Anal. Calcd. for $C_{26}H_{28}$: C, 91.71; H, 8.29; Found: C, 91.63; H, 8.33.

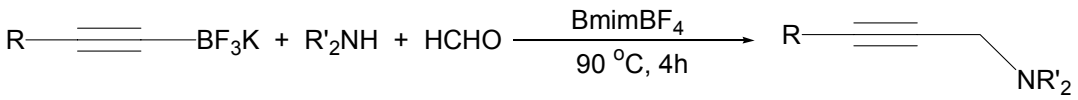
Chapter 4

The Use of Potassium Alkynyltrifluoroborates in Mannich Reactions

2.4.1 Introduction

The Petasis reaction is a modern variation of the Mannich reaction involving an amine, a carbonyl compound, and an organoborane.[82] The method has attracted considerable interest because the three-component process is applicable to a variety of boronic acids, amines, and carbonyl compounds such as α-ketoacids,[83, 84] α-hydroxyaldehydes,[85] and salicylaldehydes.[86] α-Heterocyclic aldehydes have also been shown to participate.[87] Examples of the Petasis reaction involving alkenylboronates and arylboronates are well documented but alkynylboron derivatives have not been utilized.

Potassium alkynyltrifluoroborates have been found to be suitable reagents for carrying out Mannich reactions in ionic liquid media. The reaction of potassium alkynyltrifluoroborate salts with formaldehyde and various amines in butylmethylimidazolium tetrafluoroborate ($BmimBF_4$) is described in this chapter. Propargylamines were obtained in high yields (Figure 2-4-1). The resultant products are of biological interest because they are selective inhibitors of the rat squalene epoxidase enzyme.[88]



R	Amine	Product	Yield (%)
n-Butyl	Dibenzylamine	**2-401**	92
n-Butyl	Morpholine	**2-402**	90
Phenyl	Piperidine	**2-403**	83

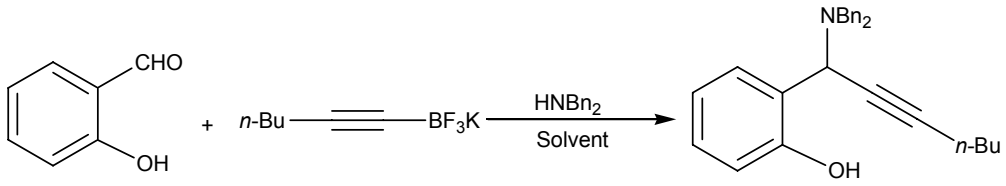
Figure 2-4-1: Potassium alkynyltrifluoroborates in Mannich reaction.

2.4.2 Results and Discussion

In an initial study, the reaction of salicylaldehyde with potassium 1-hexynyltrifluoroborate and dibenzylamine in $bmimBF_4$ produced only 10% of desired product (Table 2-4-1, entry 1). It was then found that the addition of one equivalent of benzoic acid increased the reaction yields dramatically (Table 2-4-1, entry 2). The benzoic acid presumably catalyzes the condensation of the aldehyde with the amine to generate an iminium ion, which then reacts more efficiently with the borate salt.[89] The reaction was most efficient in $bmimBF_4$ and DMF; whereas, THF, acetonitrile, 1,4-dioxane, and ionic liquids such as bmimBr, $bmimPF_6$ were less effective.

The reactions of a variety of alkynyltrifluoroborates and carbonyl compounds were then investigated (Table 2-4-2). Benzaldehyde derivatives lacking an *ortho*-hydroxy substitutent were found to be unreactive. The reaction is limited to secondary amines, but both aliphatic and aromatic alkynyltrifluoroborates participate. Under the reaction conditions utilized, no heterocycle formation was observed.[86a]

Table 2-4-1: Three component Mannich reaction in various solvents.[a.,b]



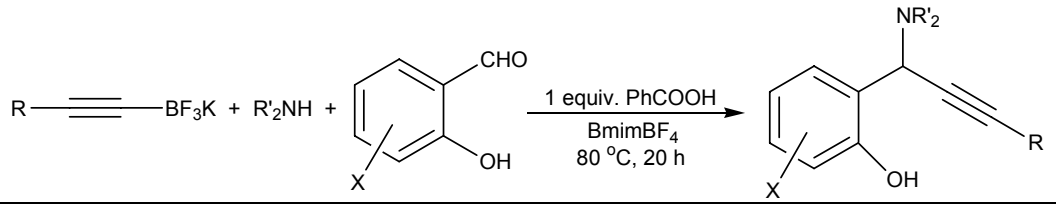
Entry	Solvent	Isolated Yield (%)
1	$BmimBF_4$	10[c]
2	$BmimBF_4$	81
3	BmimBr	17
4	$BmimPF_6$	41
5	DMF	73
6	THF	6
7	1,4-Dioxane	11
8	Acetonitrile	0

[a]All reactions were carried out at 80 ^{o}C for 20 hrs.

[b]Unless noted, 1 equivalent of benzoic acid was added to the reaction

[c]Benzoic acid was not added.

Table 2-4-2: Three component condensation of potassium alkynyltrifluoroborates, amines and salicylaldehydes.



Entry	R	Amine (2)	X	Product	Yield %[a]
1	*n*-Butyl	Dibenzylamine	H	**2-404**	81
2	*n*-Butyl	Dibenzylamine	5-NO_2	**2-405**	83
3	*n*-Butyl	Morpholine	H	**2-406**	76
4	*n*-Butyl	Morpholine	3-Me	**2-407**	63
5	*n*-Butyl	Morpholine	5-*t*-Bu	**2-408**	76
6	*n*-Butyl	Morpholine	5-Cl	**2-409**	53
7	Phenyl	Dibenzylamine	H	**2-410**	81
8	Phenyl	Morpholine	5-NO_2	**2-411**	79
9	p-Tolyl	Morpholine	5-NO_2	**2-412**	78
10	*t*-Butyl	Morpholine	H	**2-413**	72
11	1-Cyclohexenyl	Morpholine	H	**2-414**	78
12	1-Cyclohexenyl	Tetrahydroisoquinoline	H	**2-415**	58b
13	Trimethylsilyl	Morpholine	H	**2-416**	55c

[a]Isolated yields.

b DMF was used as solvent.

c The trimethylsilyl group was removed under the reaction conditions.

2.4.3 Mechanism

The mechanism of the reaction presumably involves the initial formation of an iminium ion. Coordination of the borate moiety with the phenolate oxygen[90] would then form an intermediate that would deliver the propargylamine (Figure 2-4-2).[86]

2.4.4 Conclusion

In conclusion, an efficient benzoic acid promoted, three-component coupling of potassium alkynyltrifluoroborates, amines, and salicylaldehydes in ionic liquid media has been developed. The process is simple and generates functionalized propargylamines in good yields. The products can be utilized as precursors to a variety of functionally substituted heterocycles.[91]

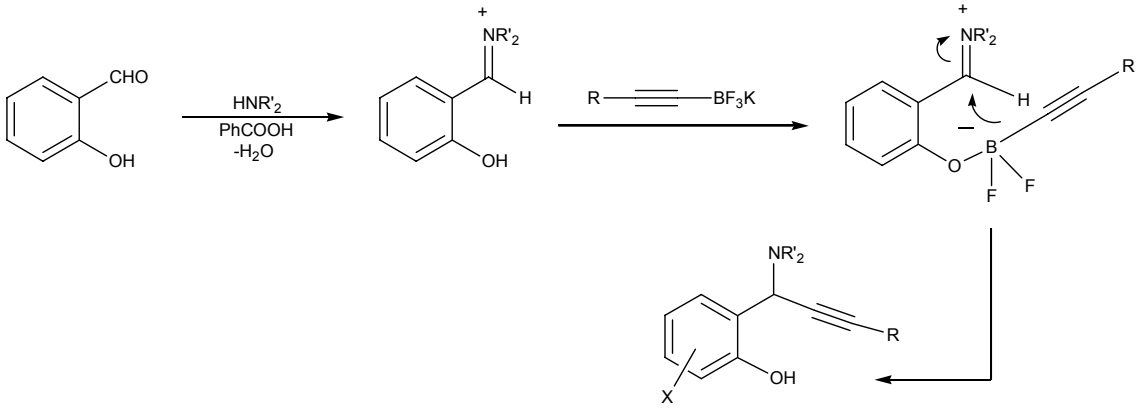


Figure 2-4-2: Proposed mechanism.

2.4.5 Experimental Section

2.4.5.1 General Considerations

All glassware was dried in an oven at 120 °C and flushed with dry nitrogen. All reactions were carried out under nitrogen atmosphere. All chemicals were purchased from Aldrich Chemical Co. and used as received. Products were purified by flash chromatography using silica gel (60 C, 230-400 mesh) with hexanes as eluent. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker 250 MHz instrument with chemical shifts reported relative to TMS.

2.4.5.2 Representative Procedure

The Synthesis of 2-(1-Dibenzylaminohept-2-ynyl)phenol (2-404): To a mixture of salicylaldehyde (122mg, 1.00 mmol) and dibenzylamine (197 mg, 1.00 mmol) in butylmethylimidazolium tetrafluoroborate ($BmimBF_4$, 800 mg), potassium 1-hexynyltrifluoroborate (188mg, 1.00 mmol) and benzoic acid (122mg, 1.00 mmol) were added. The mixture was stirred at 80 °C for 20 h, the product was extracted into diethyl ether (3 x 5 ml), the solvent removed, and the crude product purified by column chromatography (silica gel). The product was collected as colorless oil (311mg, 81%). ^{1}H NMR ($CDCl_3$): δ 7.60 (d, J = 8 Hz, 1H), 7.40 – 6.80 (m, 13H), 4.95 (brs, 1H), 3.78 (d, J = 13 Hz, 2H), 3.48 (d, J = 13 Hz, 2H), 2.50 (m, 2H), 1.80 – 1.55 (m, 4H), 1.0 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 156.5, 137.2, 129.7, 129.2, 128.9, 128.6, 127.7, 122.4, 119.2,

116.2, 90.9, 72.1, 54.7, 54.5, 31.1, 22.1, 18.5, 13.6. Anal. Calcd. for $C_{27}H_{29}NO$: C, 84.55; H, 7.62; N, 3.65. Found: C, 84.33; H, 7.67; N, 3.53.

2.4.5.3 Analytical Data

Dibenzylhept-2-ynyl amine (2-401). ^{1}HNMR ($CDCl_3$): δ 7.40-7.20 (m, 10H), 3.85 (s, 4H), 3.22 (s, 2H), 2.25 (m, 2H), 1.50 (m, 4H), 0.97 (t, *J* = 7 Hz, 3H); ^{13}CNMR ($CDCl_3$): δ 139.1, 128.9, 128.1, 126.9, 85.7, 74.4, 57.4, 41.6, 31.1, 21.9, 16.3, 13.5.

4-Hept-2-ynylmorpholine (2-402). ^{1}HNMR ($CDCl_3$): δ 3.73 (t, *J* = 4.5 Hz, 4H), 3.23 (t, *J* = 1.5 Hz, 2H), 2.56 (t, *J* = 4.5 Hz, 4H), 2.20 (m, 2H), 1.60 - 1.30 (m, 4H), 0.93 (t, *J* = 7 Hz, 3H); ^{13}CNMR ($CDCl_3$): δ 85.3, 74.2, 66.6, 52.2, 47.5, 30.7, 21.8, 18.2, 13.3.

4-(3-Phenlprop-2-ynyl)piperidine (2-403). ^{1}H NMR ($CDCl_3$): δ 7.43 (m, 2H), 7.27 (m, 3H), 3.47 (s, 2H), 2.58 (m, 4H), 1.83 (m, 4H), 1.43 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 131.5, 128.0, 127.8, 123.2, 85.0, 84.8, 53.3, 48.3, 25.8, 23.8.

2-(1-Dibenzylaminohept-2-ynyl)-4-nitrophenol (2-405). M.P. 82 °C; ^{1}H NMR ($CDCl_3$): δ 8.52 (d, *J* = 2 Hz, 1H), 8.10 (dd, *J* = 8, 2 Hz, 1H), 7.50 – 7.15 (m, 10H), 6.84 (d, *J* = 8 Hz, 1H), 4.93 (brs, 1H), 3.80 (d, *J* = 13 Hz, 2H), 3.50 (d, *J* = 13 Hz, 2H), 2.54 (m, 2H), 1.90 – 1.55 (m, 4H), 1.05 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 162.9, 140.2, 136.1, 129.6, 128.7, 127.9, 125.6, 125.3, 122.7, 116.4, 92.6, 70.5, 54.7, 54.5, 30.8, 22.0, 18.5,

13.5. Anal. Calcd. for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.66; H, 6.49; N, 6.49.

2-(1-Morpholin-4-ylhept-2-ynyl)phenol (2-406). ^{1}H NMR ($CDCl_3$): δ 7.48 (d, *J* = 8 Hz, 1H), 7.16 (m, 1H), 6.83 (m, 2H), 4.82 (brs, 1H), 3.74 (brs, 4H), 2.65 (brs, 4H), 2.35 (m, 2H), 1.70 – 1.40 (m, 4H), 0.96 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 156.9, 129.3, 128.6, 120.9, 119.0, 116.1, 90.8, 71.9, 66.8, 60.1, 48.5, 30.7, 21.9, 18.3, 13.4. Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.49; H, 8.57; N, 5.11.

2-Methyl-6-(1-morpholin-4-ylhept-2-ynyl)phenol (2-407). ^{1}H NMR ($CDCl_3$): δ 7.32 (d, *J* = 8, Hz, 1H), 7.05 (d, *J* = 8 Hz, 1H), 6.75 (dd, *J* = 8, 8 Hz, 1H), 4.80 (brs, 1H), 3.74 (brs, 4H), 2.84 (brs, 4H), 2.34 (m, 2H), 2.22 (s, 3H), 1.80 – 1.50 (m, 4H), 0.95 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 155.0, 130.4, 126.2, 124.8, 120.2, 118.4, 90.6, 72.2, 66.8, 60.2, 48.3, 30.8, 21.8, 16.3, 15.5, 13.4. Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.37; H, 8.78; N, 4.83.

4-*t*-Butyl-2-(1-morpholin-4-ylhept-2-ynyl)phenol (2-408). ^{1}H NMR ($CDCl_3$): δ 7.52 (d, *J* = 2, Hz, 1H), 7.20 (dd, *J* = 8, 2 Hz, 1H), 6.75 (d, *J* = 8, Hz, 1H), 4.82 (brs, 1H), 3.74 (brs, 4H), 2.66 (brs, 4H), 2.36 (m, 2H), 1.70 – 1.45 (m, 4H), 1.29 (s, 9H), 0.96 (t, *J* = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 154.4, 141.7, 126.0, 125.5, 120.1, 115.5, 90.8, 72.3, 66.7, 60.5, 48.5, 34.0, 31.5, 30.8, 21.9, 16.3, 13.5. Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.68; H, 9.57; N, 4.24.

4-Chloro-2-(1-morpholin-4-ylhept-2-ynyl)phenol (2-409). ^{1}H NMR ($CDCl_3$): δ 7.45 (d, *J* = 2, Hz, 1H), 7.15 (dd, *J* = 8, 2 Hz, 1H), 6.74 (d, *J* = 8, Hz, 1H), 4.80 (s, 1H), 3.75 (brs, 4H), 2.65 (brs, 4H), 2.38 (m, 2H), 1.70 – 1.40 (m, 4H), 0.98 (t, *J* = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 155.6, 129.1, 128.5, 123.8, 122.5, 117.4, 91.5, 71.3, 66.6, 59.9, 48.2, 30.7, 21.9, 16.3, 13.3. Anal. Calcd. for $C_{17}H_{22}ClNO_2$: C, 66.33; H, 7.20; N, 4.55. Found: C, 66.36; H, 7.22; N, 4.49.

2-(1-Dibenzylamino-3-phenylprop-2-ynyl)phenol (2-410). M.P. 148 °C; ^{1}H NMR ($CDCl_3$): δ 7.66 (d, *J* = 8 Hz, 1H), 7.50 – 7.10 (m, 17H), 6.88 (d, *J* = 8 Hz, 1H), 5.17 (s, 1H), 3.90 (d, *J* = 13 Hz, 2H), 3.55 (d, *J* = 13 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.4, 136.9, 131.9, 129.6, 129.4, 128.6, 128.4, 127.7, 122.4, 121.7, 119.3, 116.3, 90.4, 81.7, 55.0, 54.7. Anal. Calcd. for $C_{29}H_{25}NO$: C, 86.32; H, 6.24; N, 3.47. Found: C, 85.97; H, 6.18; N, 3.42.

2-(1-Morpholin-4-yl-3-phenylprop-2-ynyl)-4-nitrophenol (2-411). M.P. 156 °C; ^{1}H NMR ($CDCl_3$): δ 8.53 (d, *J* = 2, Hz, 1H), 8.15 (dd, *J* = 8, 2 Hz, 1H), 7.58 (m, 2H), 7.40 (m, 3H), 6.91 (d, *J* = 8, Hz, 1H), 5.13 (s, 1H), 3.83 (brs, 4H), 2.83 (brs, 4H); ^{13}C NMR ($CDCl_3$): δ 163.3, 140.4, 131.9, 129.2, 128.5, 126.0, 125.3, 121.4, 120.8, 116.8, 91.7, 79.6, 68.5, 60.5, 49.2. Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.62; H, 5.29; N, 8.26.

2-(1-Morpholin-4-yl-3-*p*-tolylprop-2-ynyl)-4-nitrophenol (2-412). M.P. 167 °C; ^{1}H NMR (DMSO): δ 8.52 (d, *J* = 2, Hz, 1H), 8.14 (dd, *J* = 8, 2 Hz, 1H), 7.47 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8, Hz, 1H), 5.10 (s, 1H), 3.82 (brs, 4H), 2.83 (brs, 4H), 2.40 (s, 3H); ^{13}C NMR (*d*-DMSO): δ 160.3, 137.9, 137.8, 129.8, 127.3, 125.9, 125.4, 116.2, 115.5, 114.6, 88.8, 78.3, 61.5, 53.4, 47.6, 19.3. Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.28; H, 5.71; N, 7.91.

2-(4,4-Dimethyl-1-morpholin-4-ylpent-2-ynyl)phenol (2-413). ^{1}H NMR ($CDCl_3$): δ 7.48 (dd, *J* = 8, 1.5 Hz, 1H), 7.26 (m, 1H), 6.85 (m, 2H), 4.86 (s, 1H), 3.78 (brs, 4H), 2.68 (brs, 4H),1.35 (s, 9H). Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.72; H, 8.48; N, 5.08.

2-(3-Cyclohex-1-enyl-1-morpholin-4-ylprop-2-ynyl)phenol (2-414). M.P. 78 °C; ^{1}H NMR ($CDCl_3$): δ 7.54 (d, *J* = 8 Hz, 1H), 7.20 (m, 1H), 6.82 (m, 2H), 6.22 (m, 1H), 4.95 (s, 1H), 3.75 (brs, 4H), 2.68 (brs, 4H), 2.12 (m, 4H), 1.72 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 156.9, 135.6, 129.5, 128.7, 120.7, 119.9, 119.1, 116.2, 92.1, 78.5, 66.7, 60.5, 48.0, 29.3, 25.5, 22.2, 21.3.

2-[3-Cyclohex-1-enyl-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)-prop-2-ynyl]henol (2-415). ^{1}H NMR ($CDCl_3$): δ 7.23 – 6.78 (m, 8H), 6.09 (m, 1H), 4.80 (s, 1H), 4.08 (d, *J* = 14 Hz, 1H), 3.95 (d, *J* = 14 Hz, 1H) 3.20 – 2.7 (m, 4H), 2.08 (m, 4H), 1.60 (m, 4H); ^{13}C NMR

($CDCl_3$): δ 157.9, 135.0, 134.6, 132.9, 129.0, 128.7, 127.7, 127.1, 126.0, 121.1, 119.2, 116.0, 89.3, 82.7, 58.2, 54.1, 44.9,29.3, 28.5, 25.5, 22.2, 21.4.

2-(1-Morpholin-4-ylprop-2-ynyl)phenol (2-416). M.P. 63 °C; ^{1}H NMR ($CDCl_3$): δ 10.60 (brs, 1H), 7.49 (d, J = 8 Hz, 1H), 7.22 (m, 1H), 6.85 (m, 2H), 4.85 (s, 1H), 3.75 (brs, 4H), 2.70 (brs, 5H); ^{13}C NMR ($CDCl_3$): δ 156.8, 129.7, 128.4, 119.8, 119.3, 116.4, 78.2, 75.9, 66.6, 59.9, 48.7. Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.10; H, 6.98; N, 6.35.

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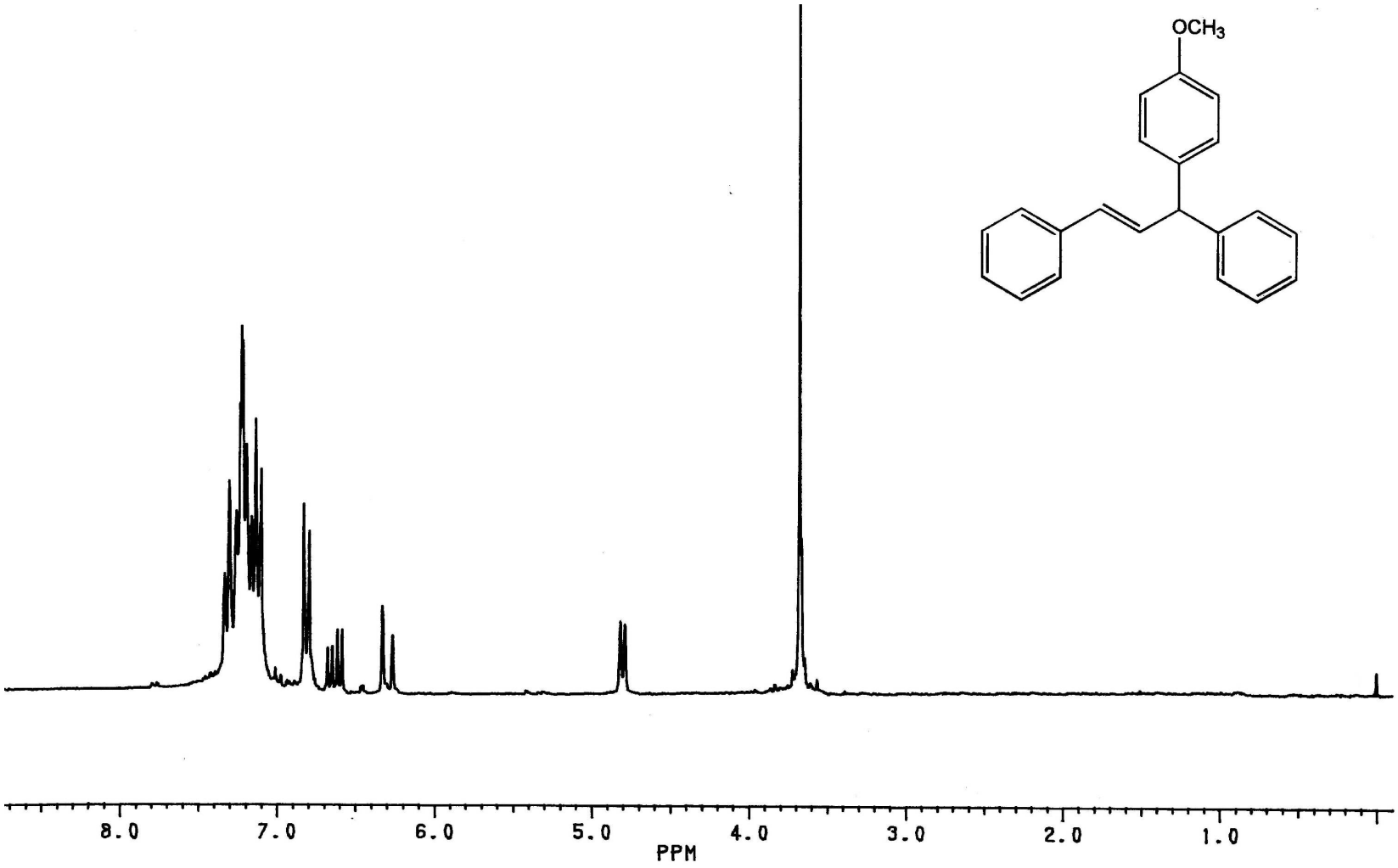
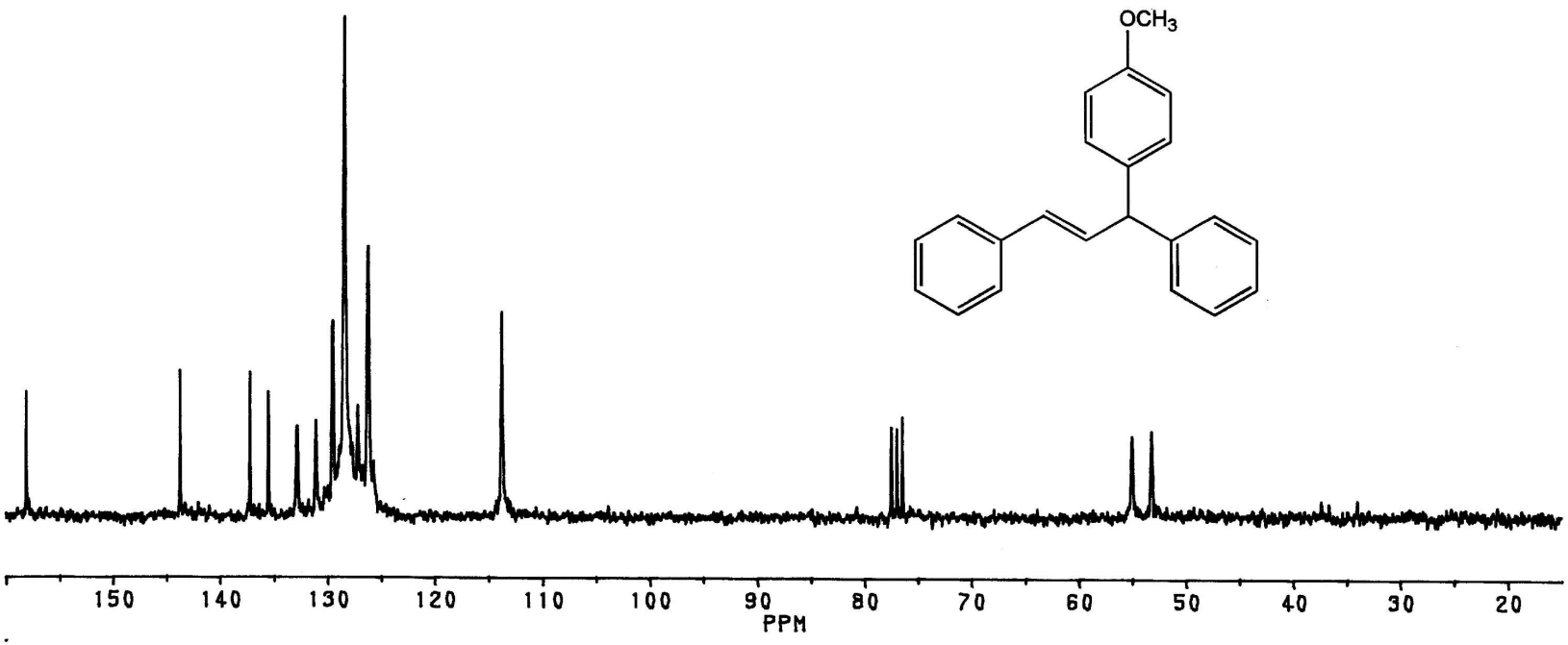
APPENDIX I

NMR Spectra of Representative Compounds



^{1}H NMR of Compound **1-213**



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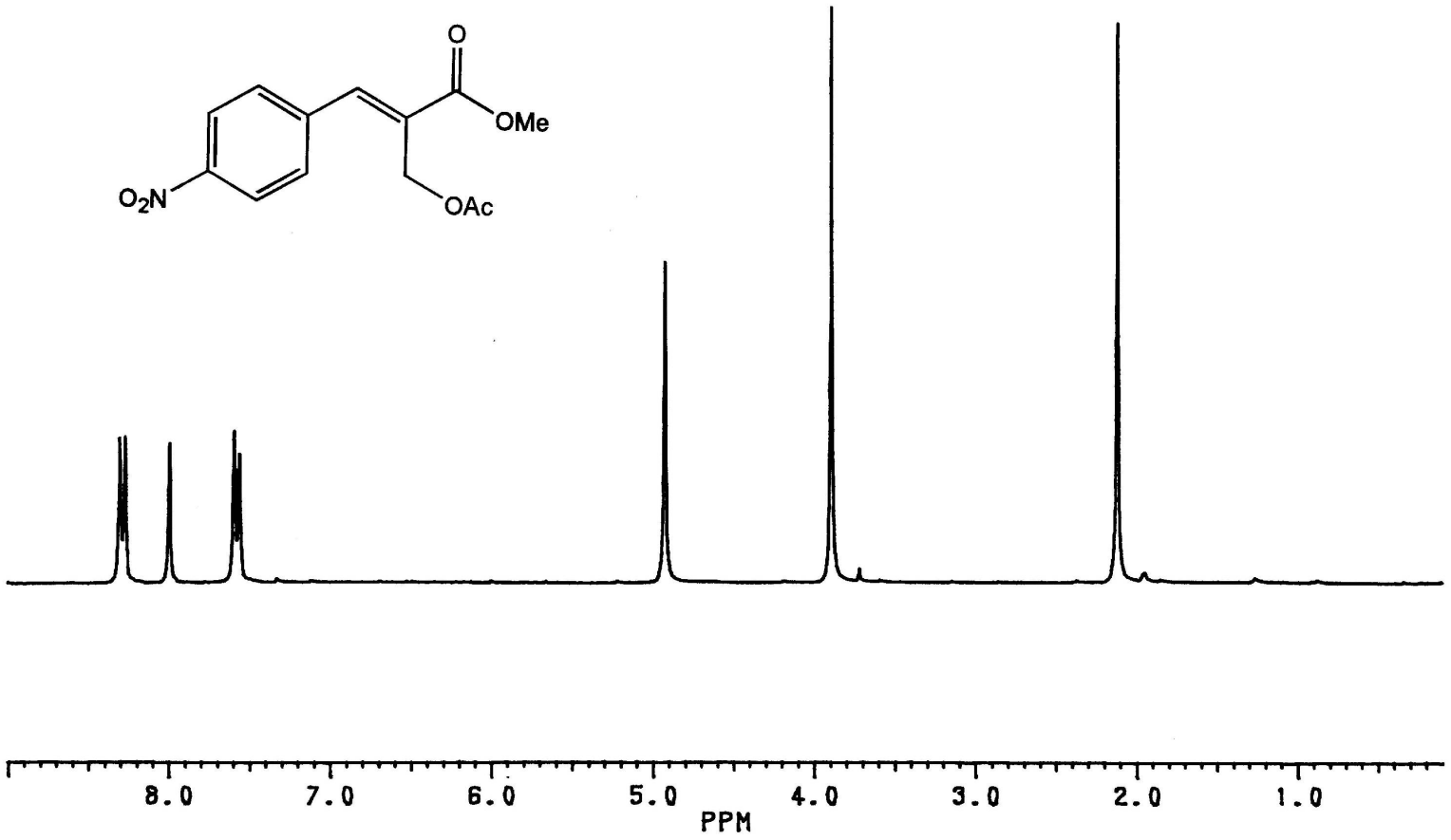

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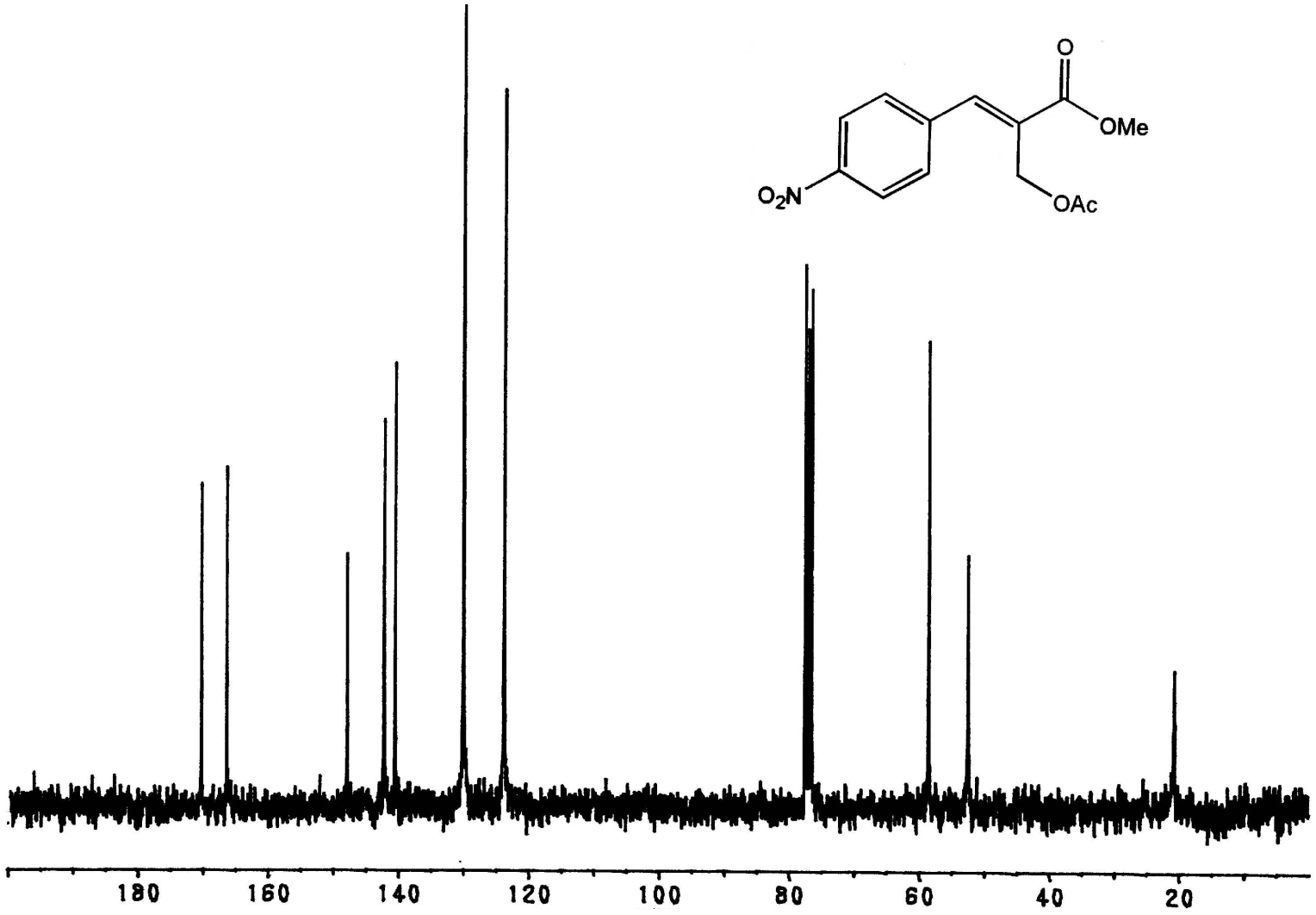

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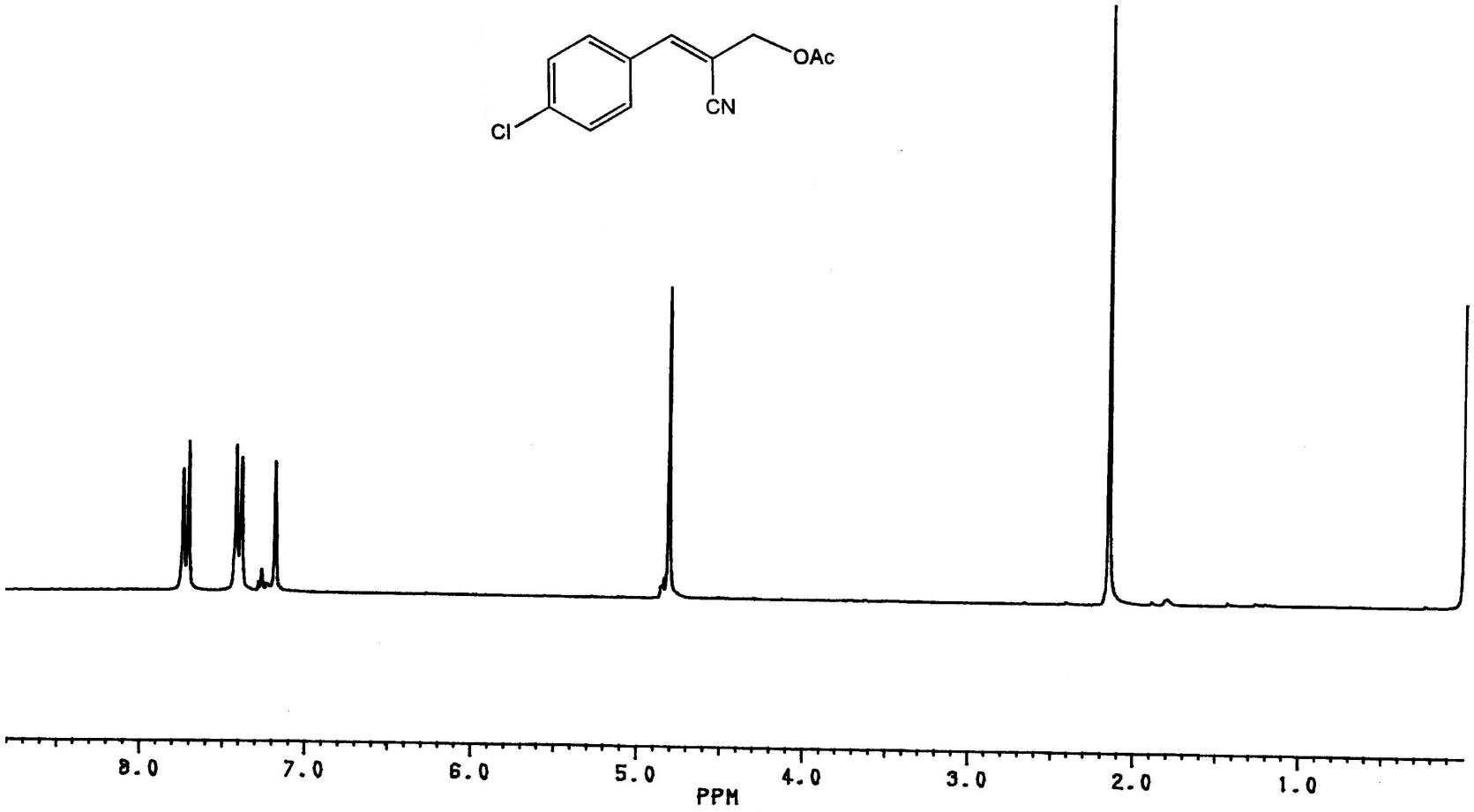

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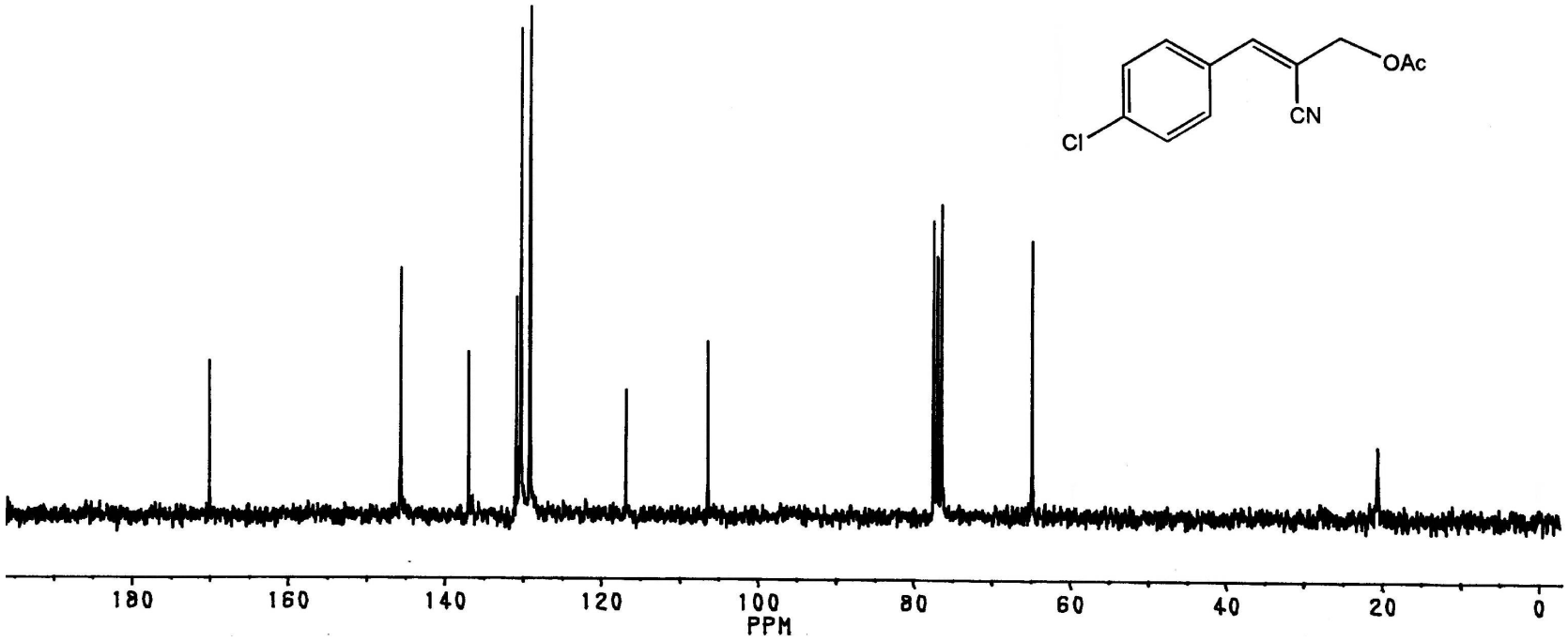

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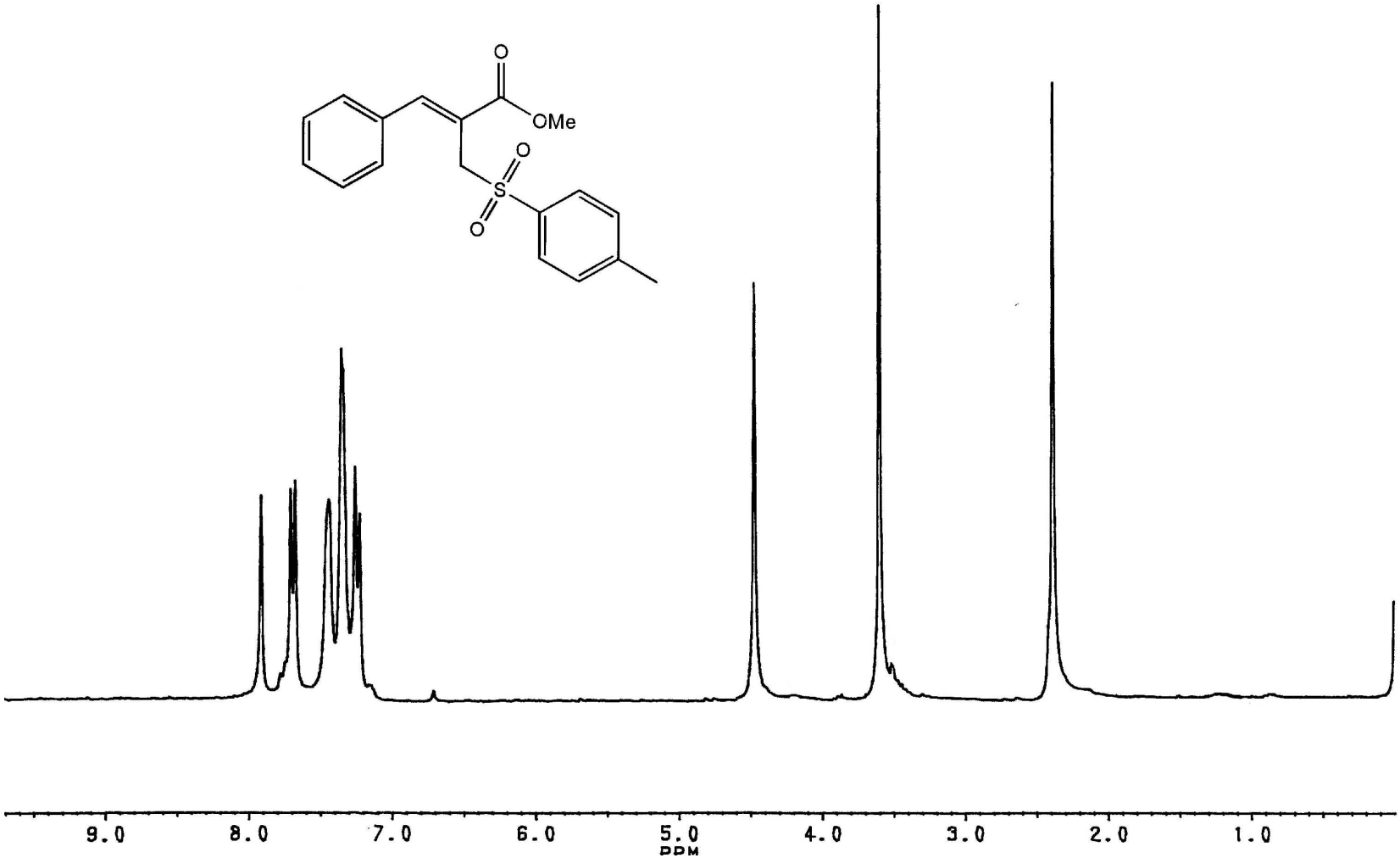

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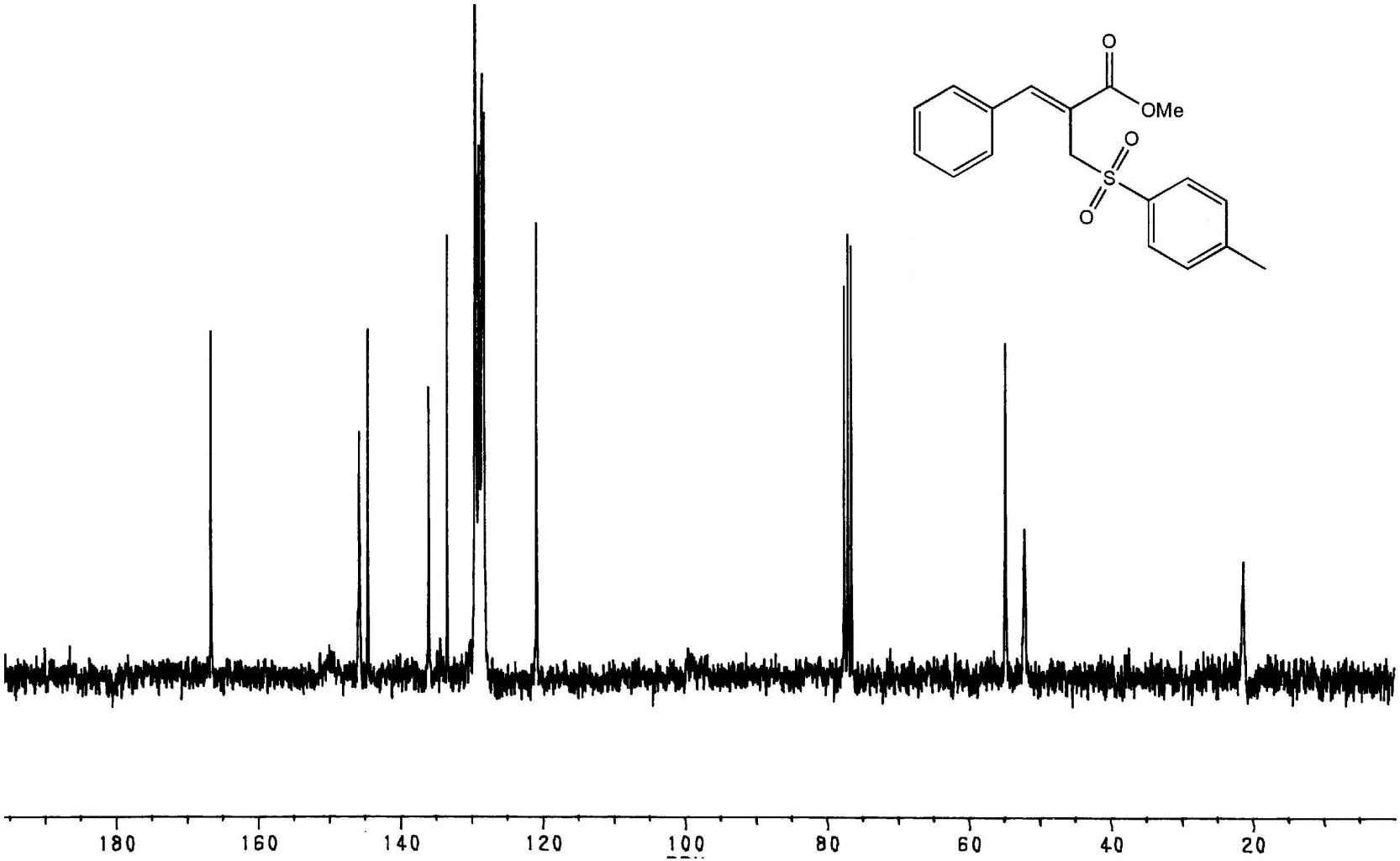
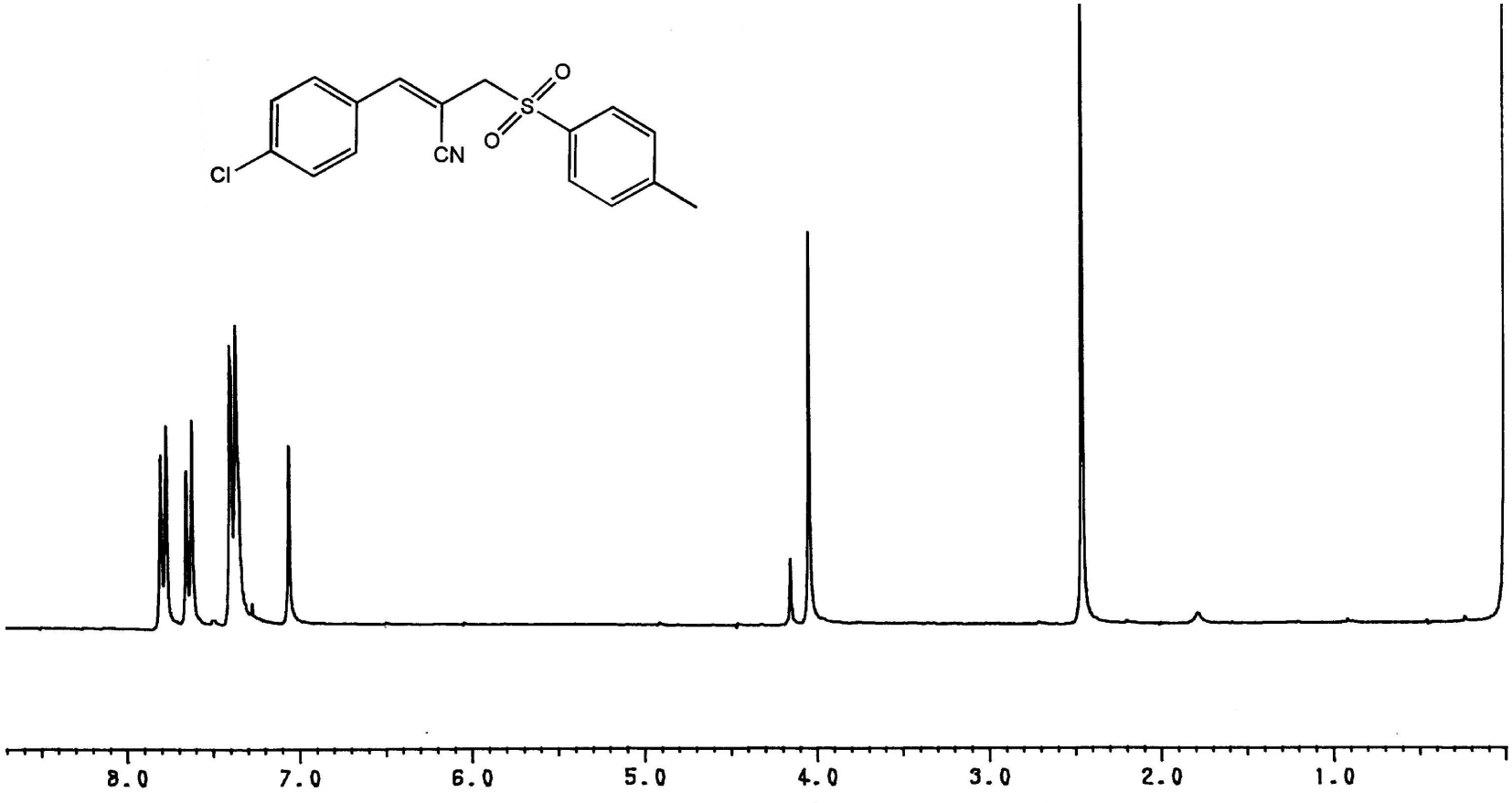
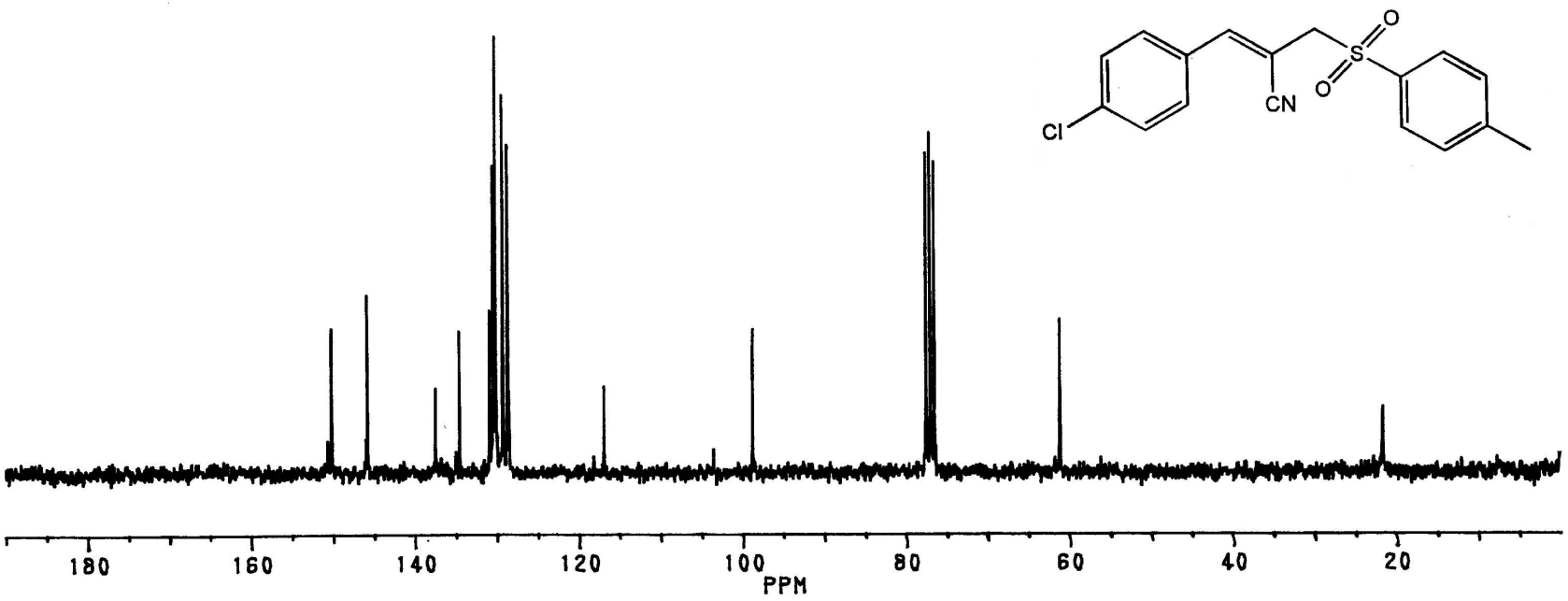


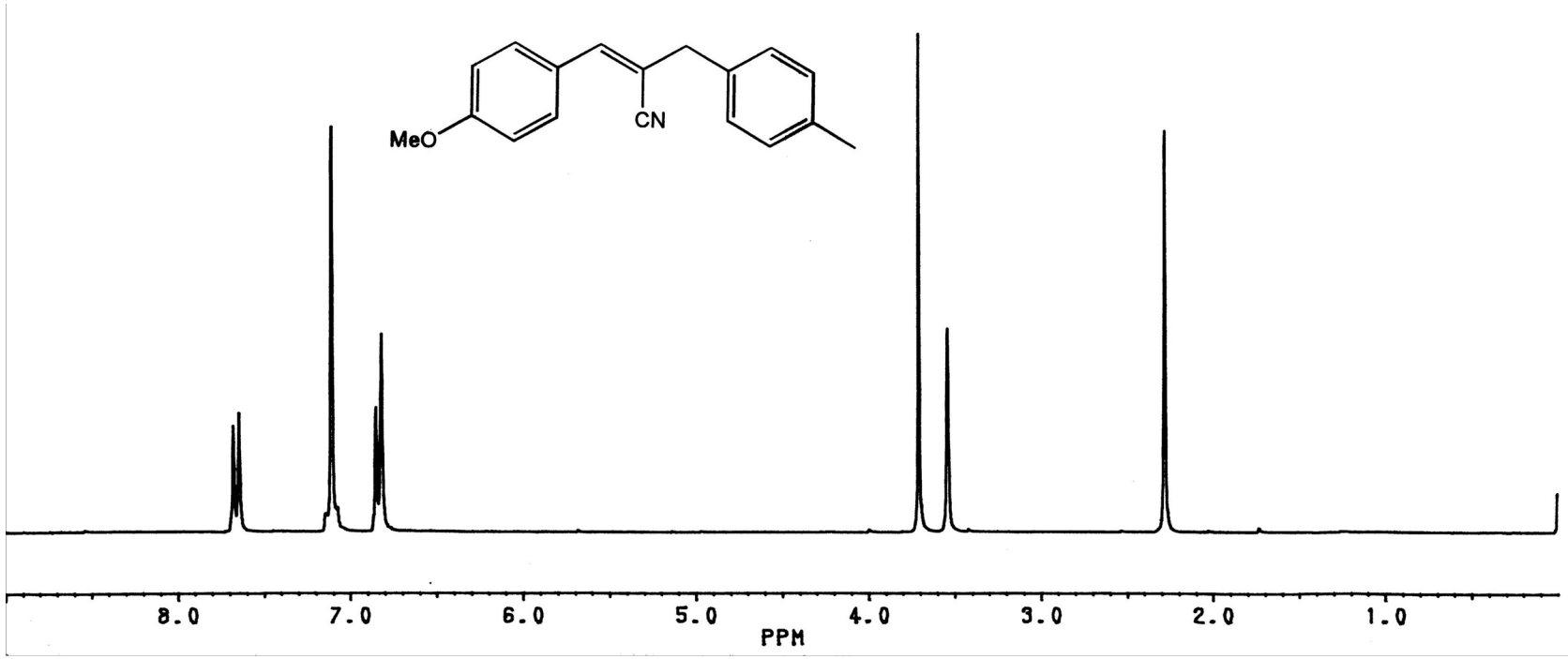
^{13}C NMR of Compound **1-307**



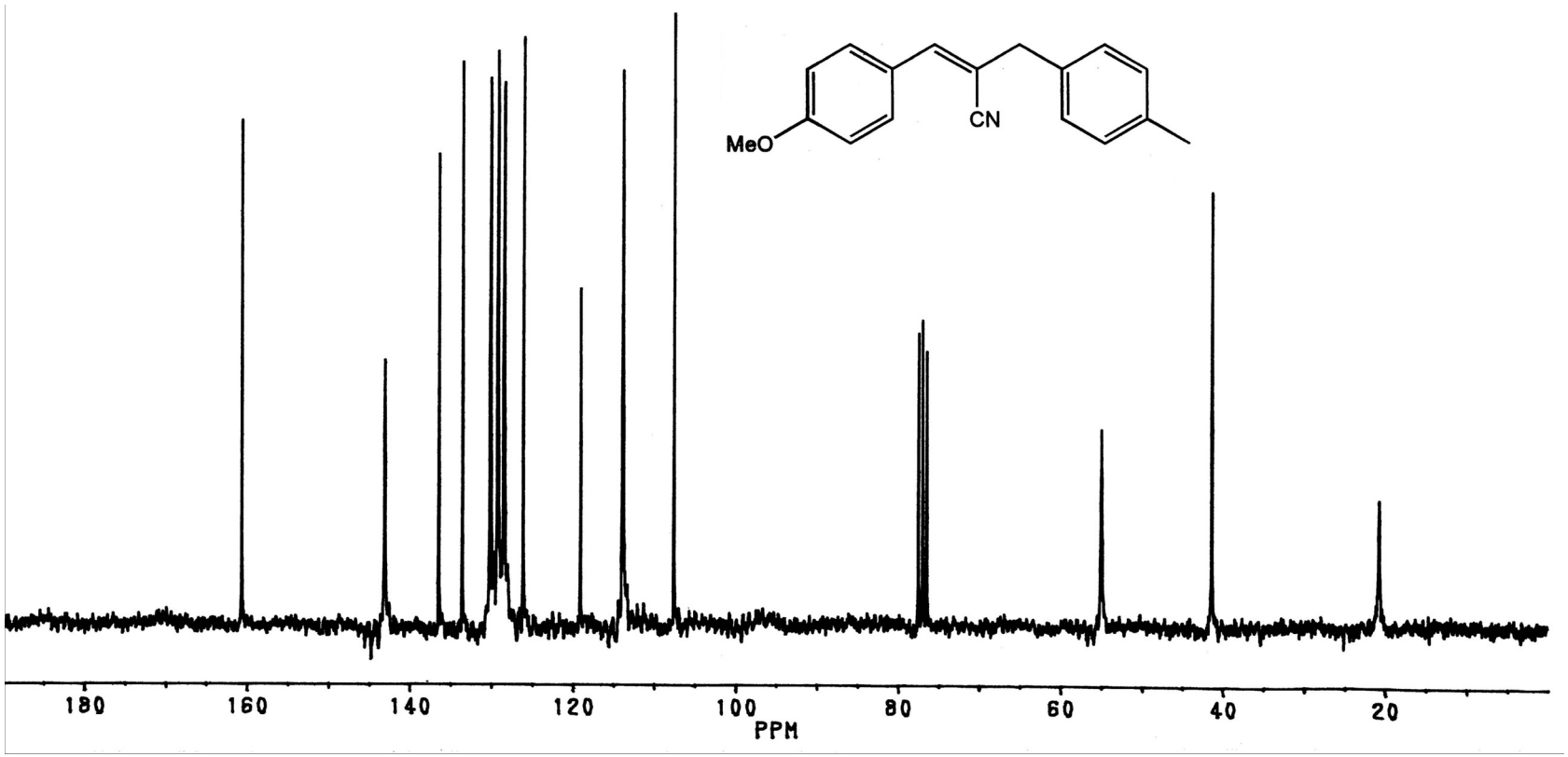
^{1}H NMR of Compound **1-313**



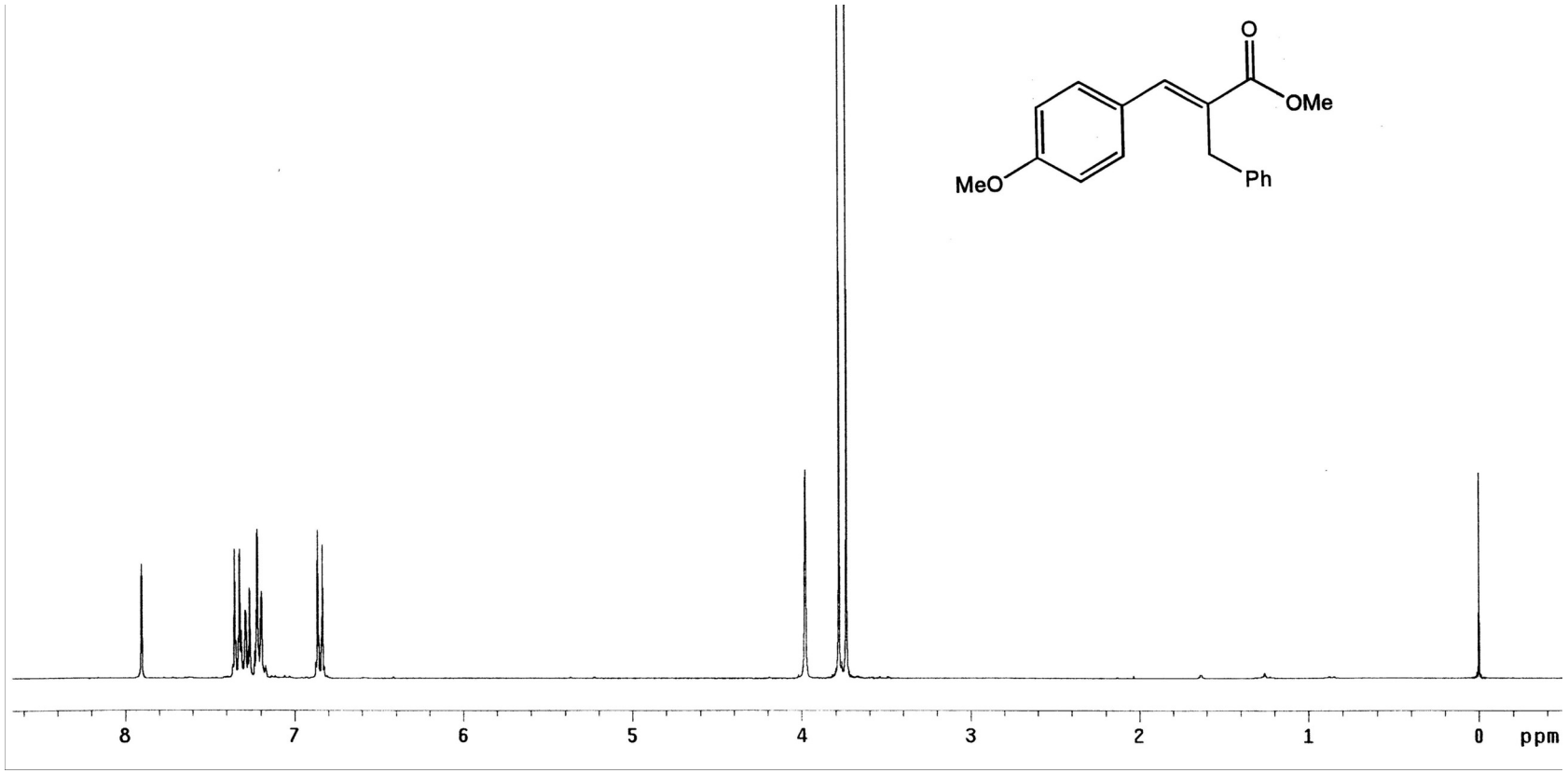
^{13}C NMR of Compound **1-313**



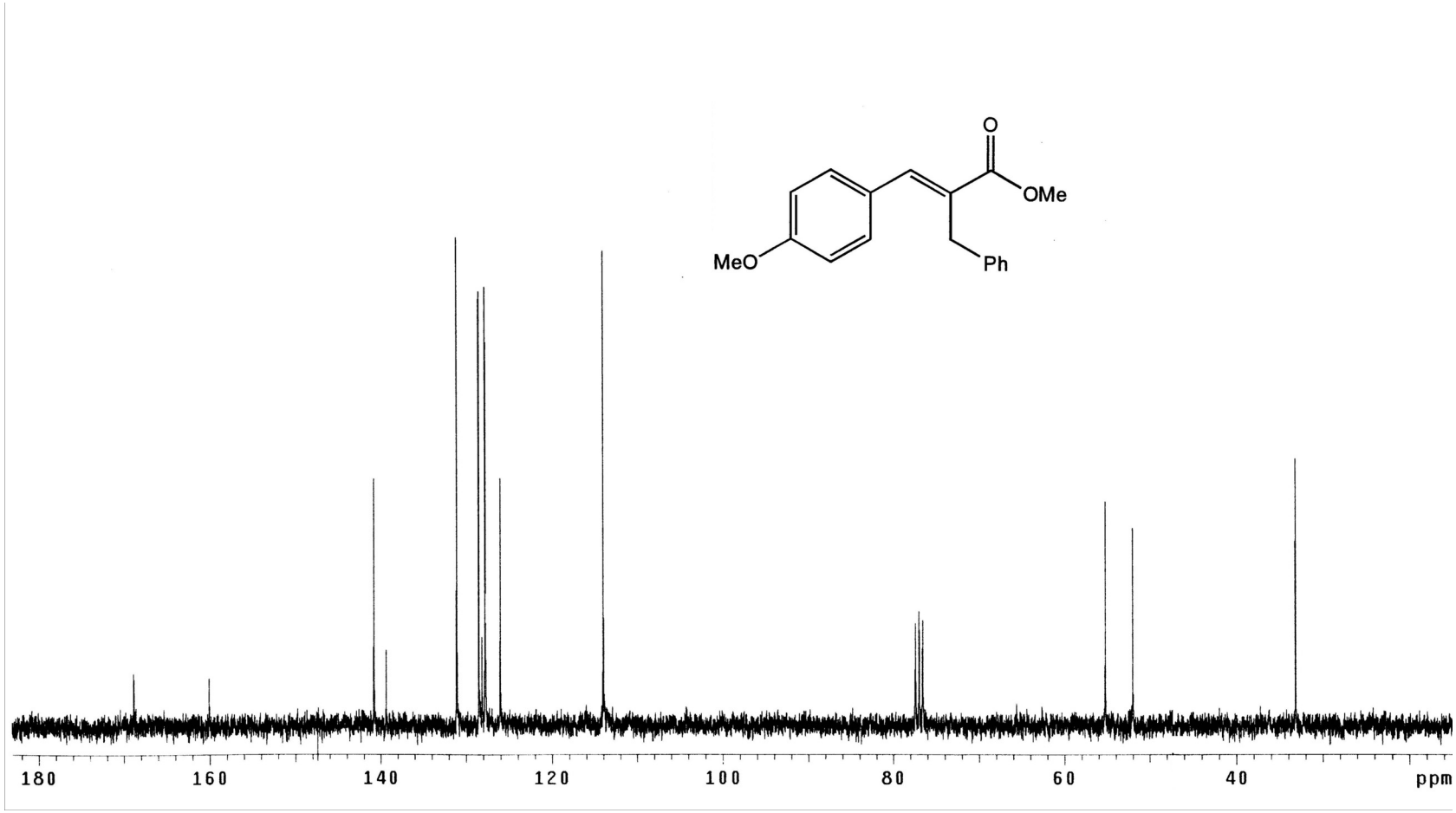
^{1}H NMR of Compound **1-321**



^{13}C NMR of Compound **1-321**

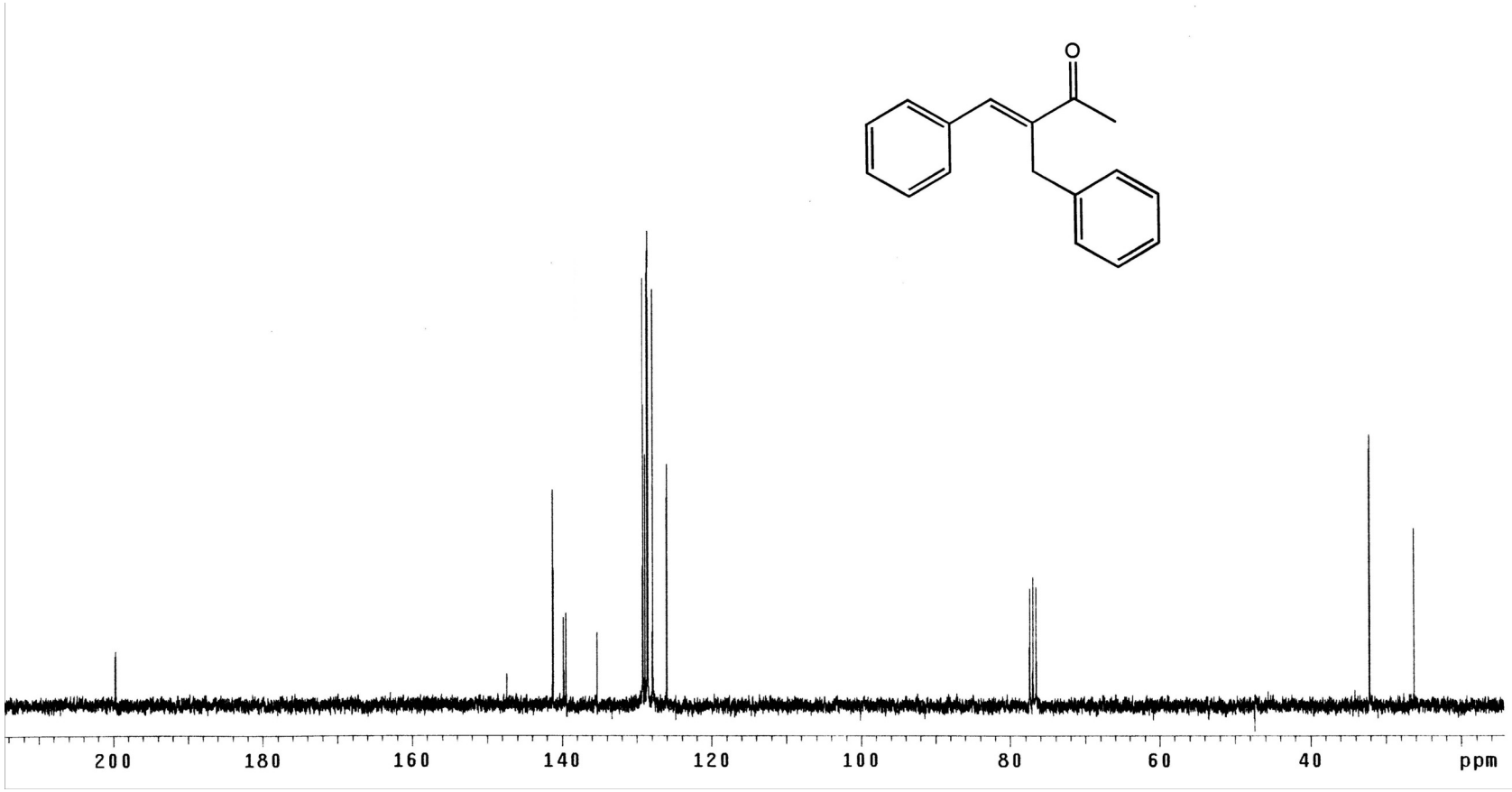


^{1}H NMR of Compound **1-405**

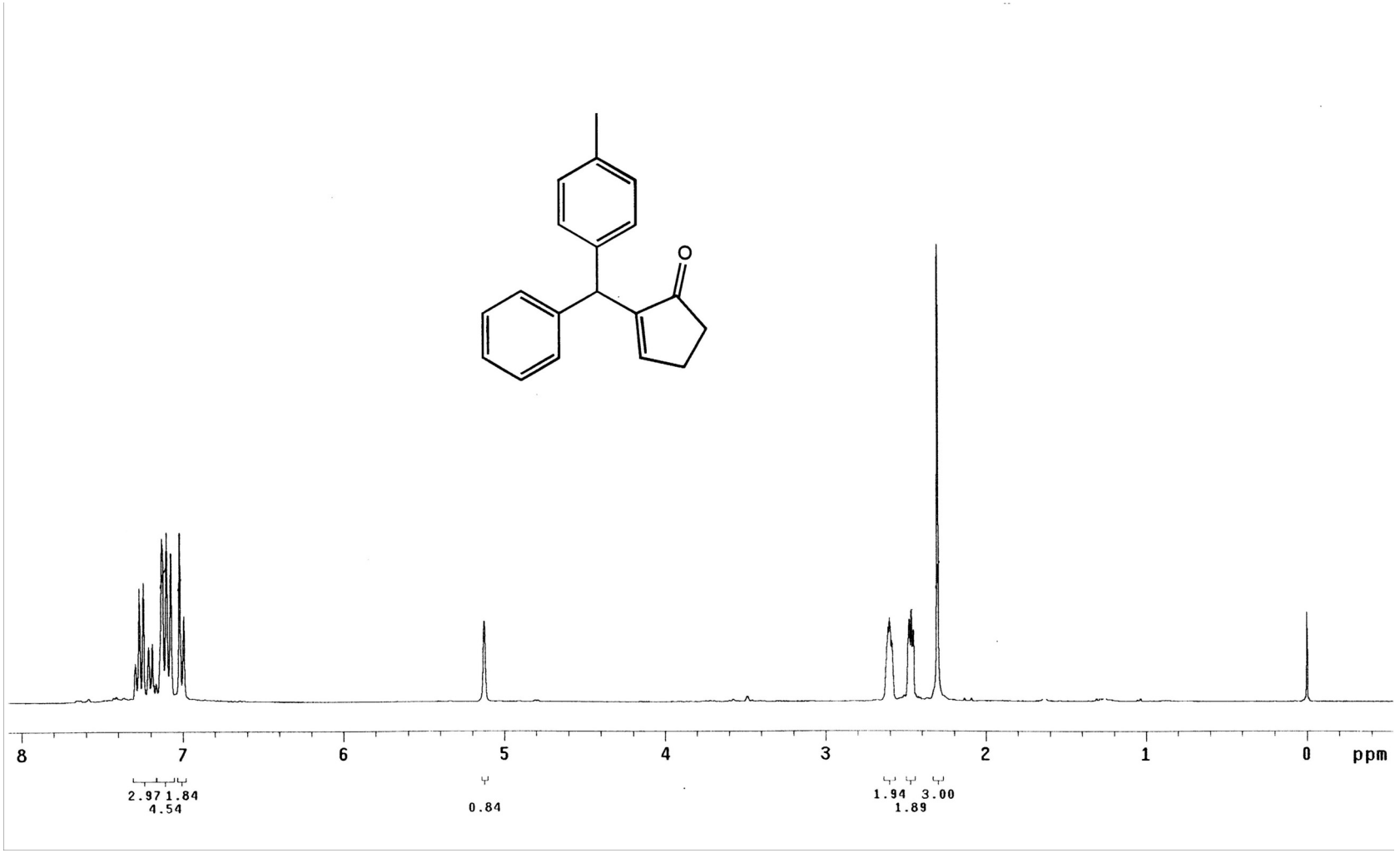


^{13}C NMR of Compound **1-405**

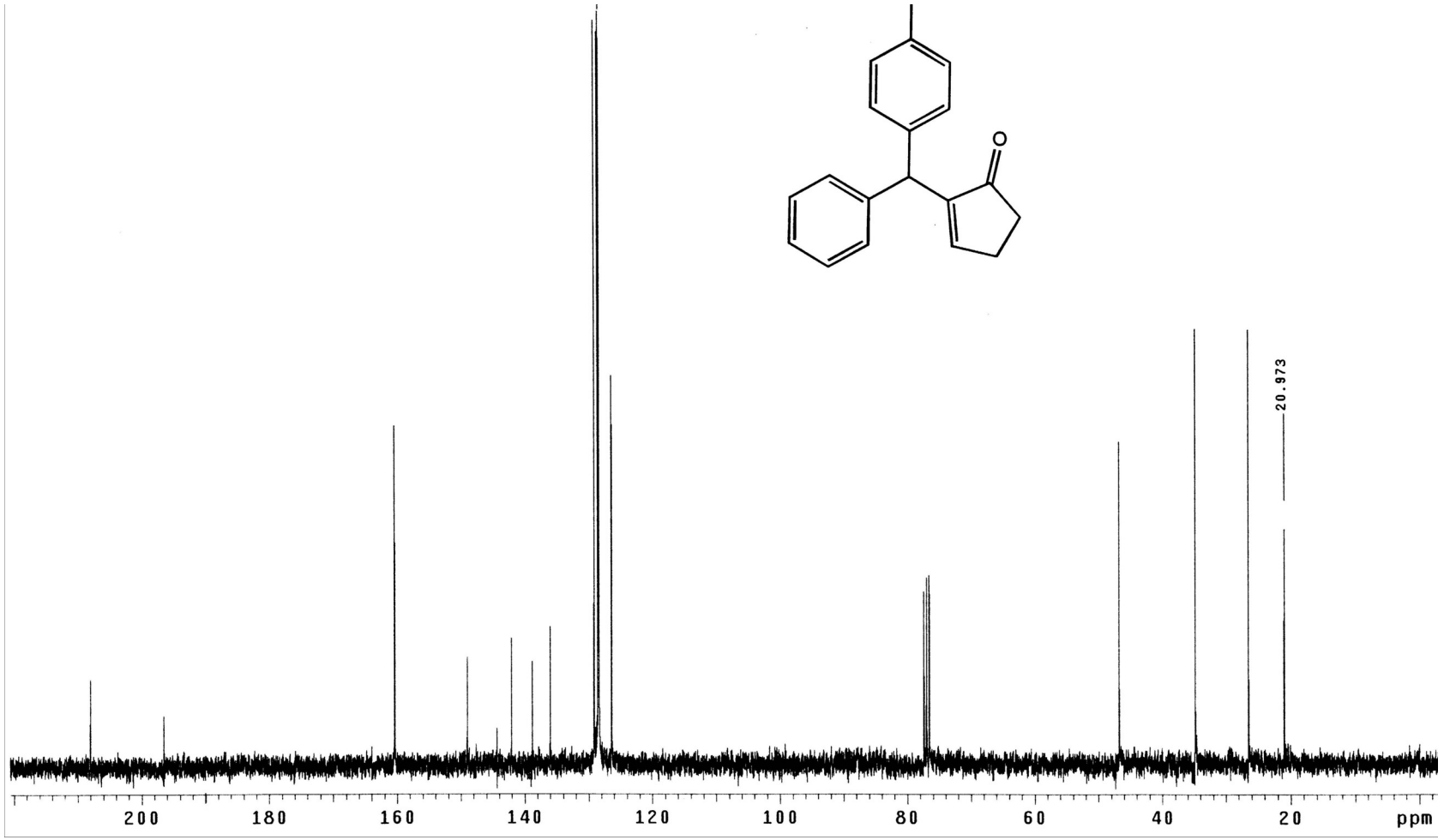
^{1}H NMR of Compound **1-411**



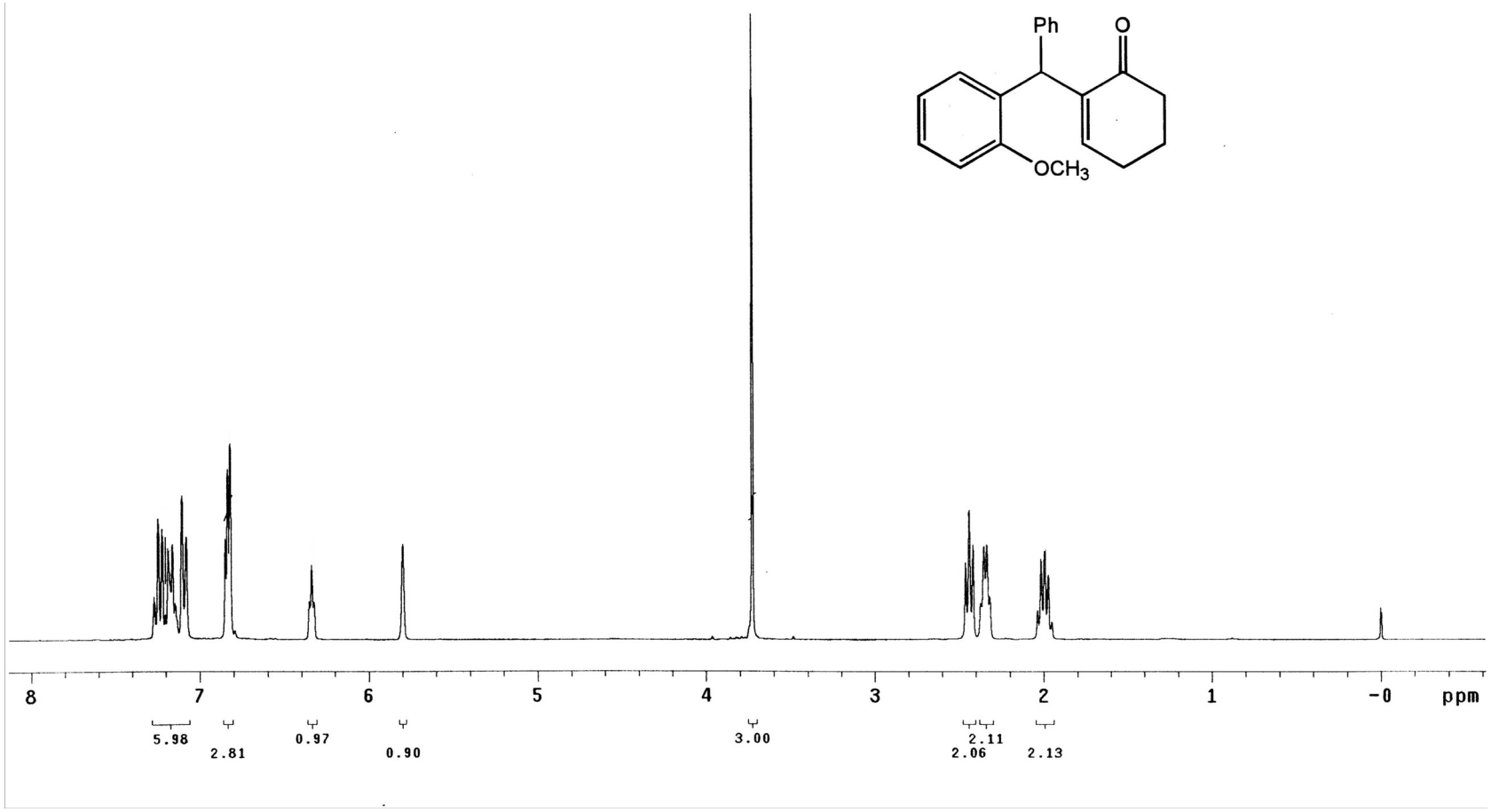
^{13}C NMR of Compound **1-411**



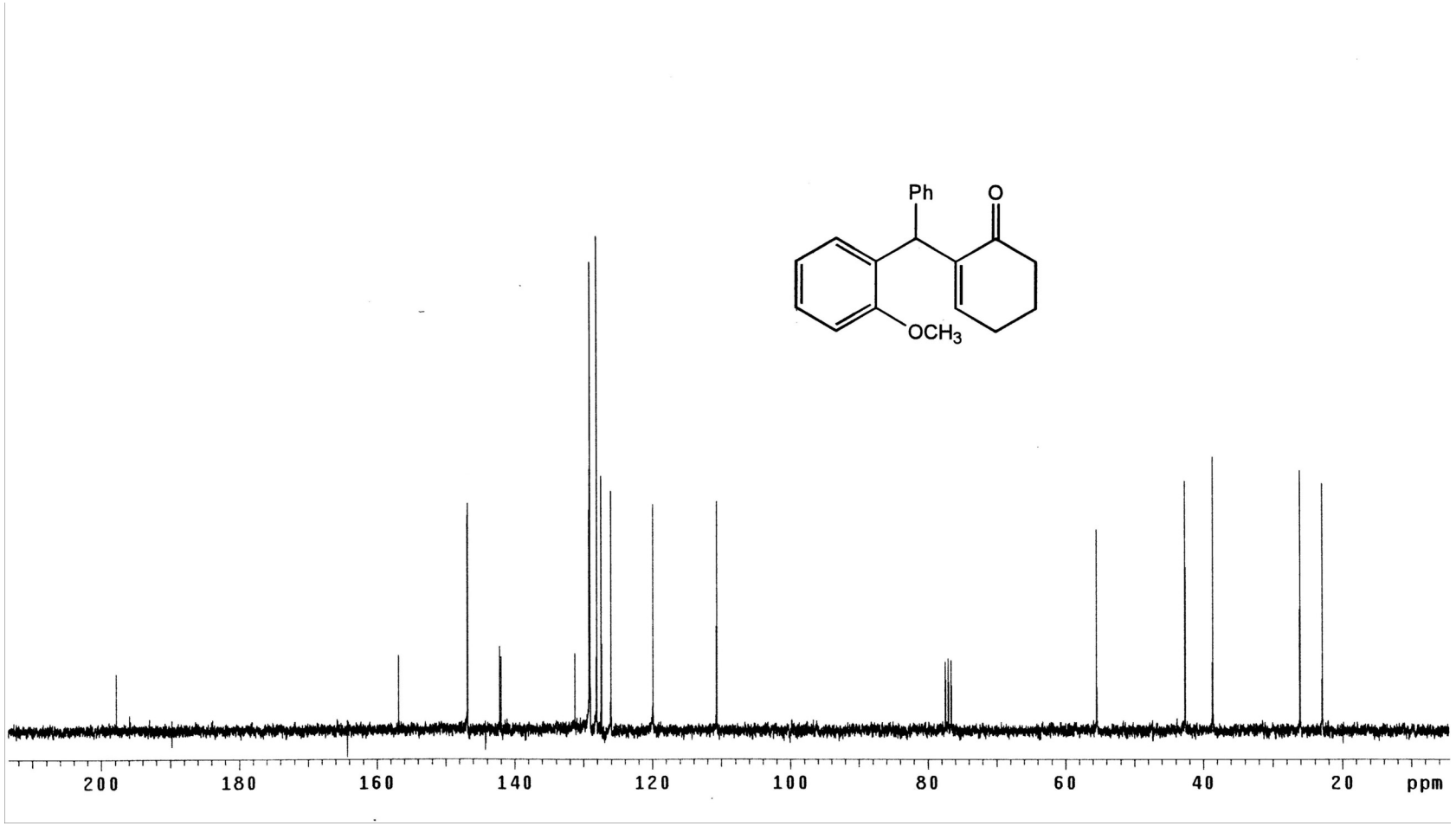
^{1}H NMR of Compound **1-413**



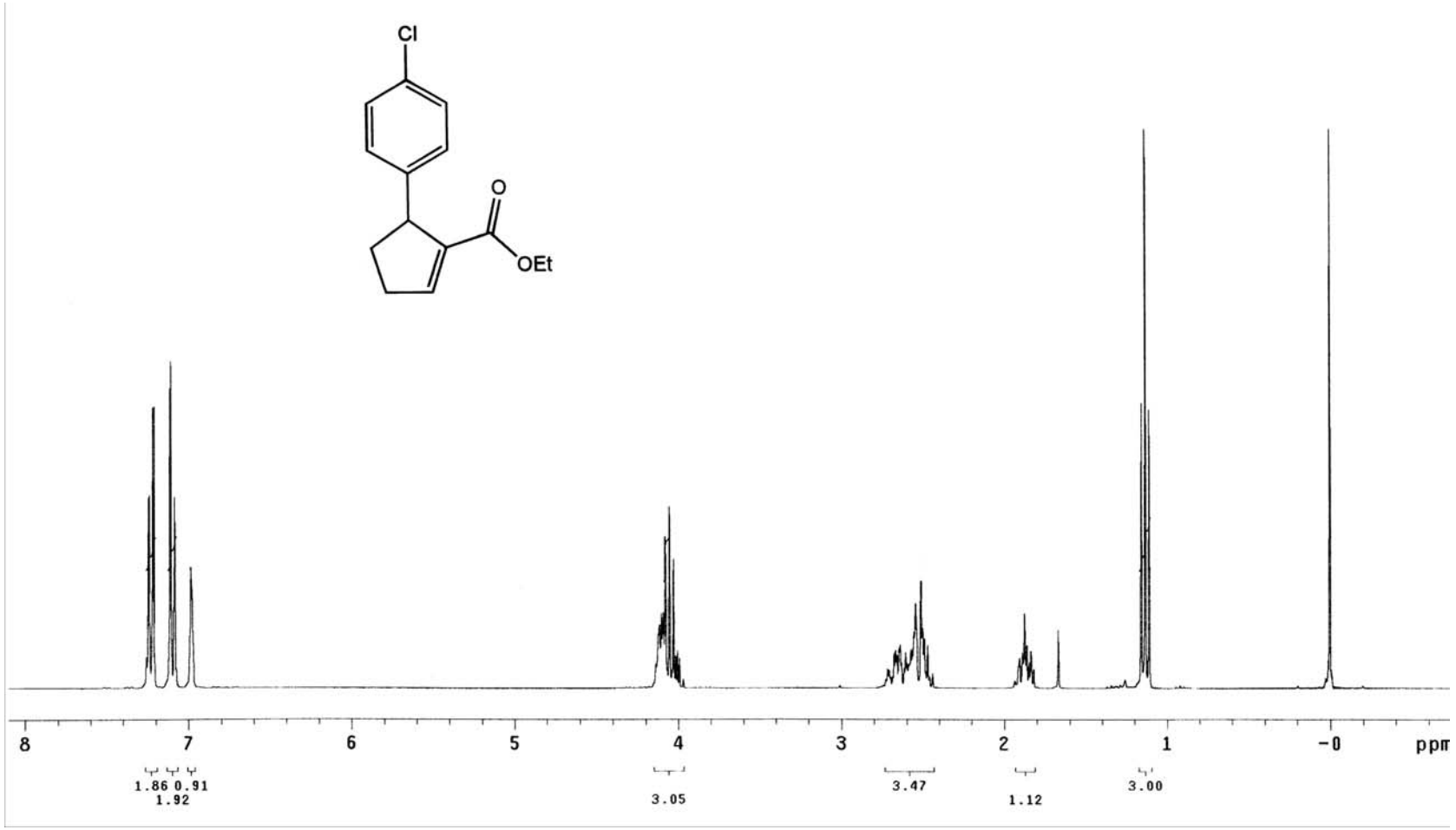
^{13}C NMR of Compound **1-413**



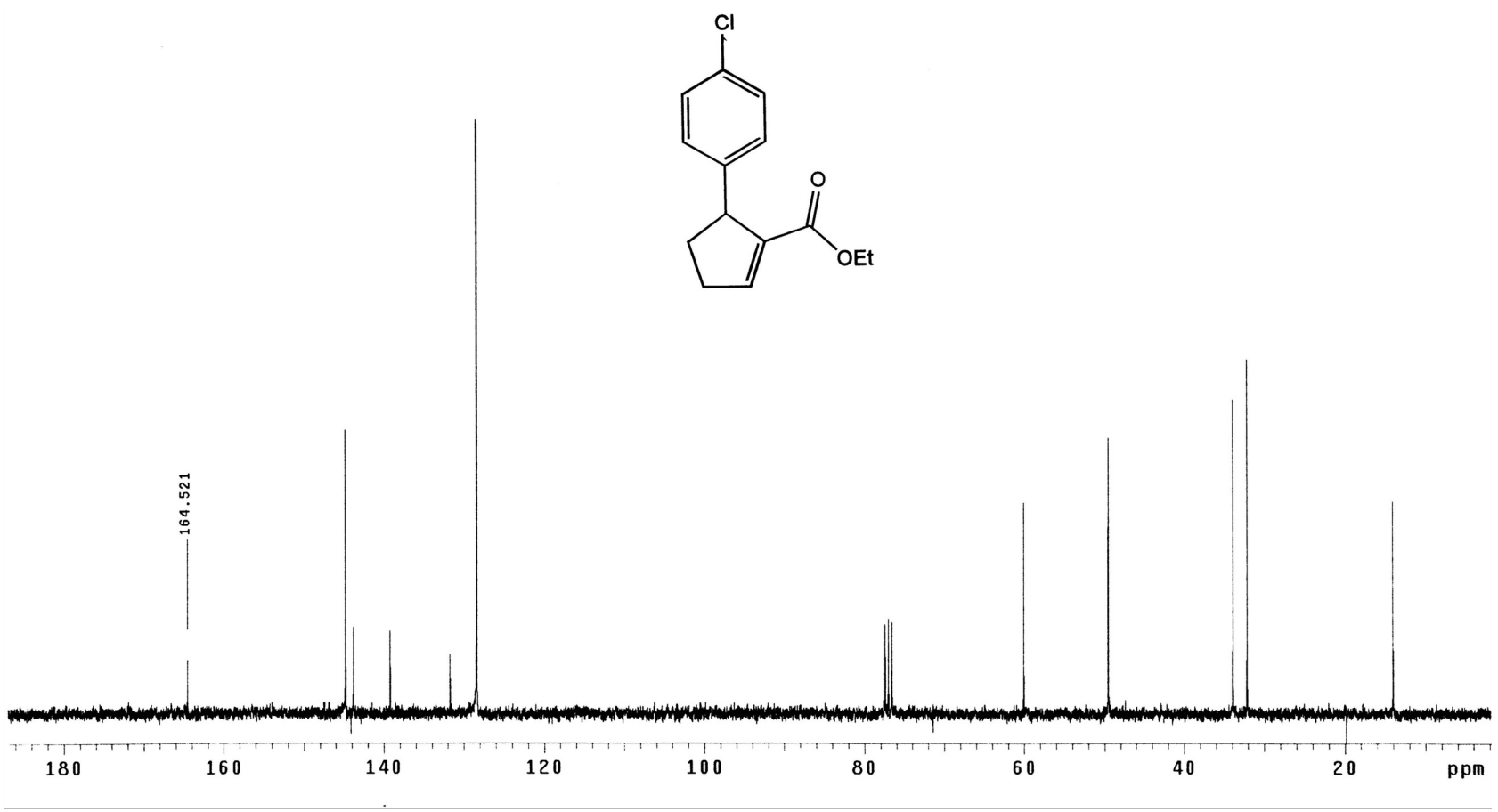
^{1}H NMR of Compound **1-417**



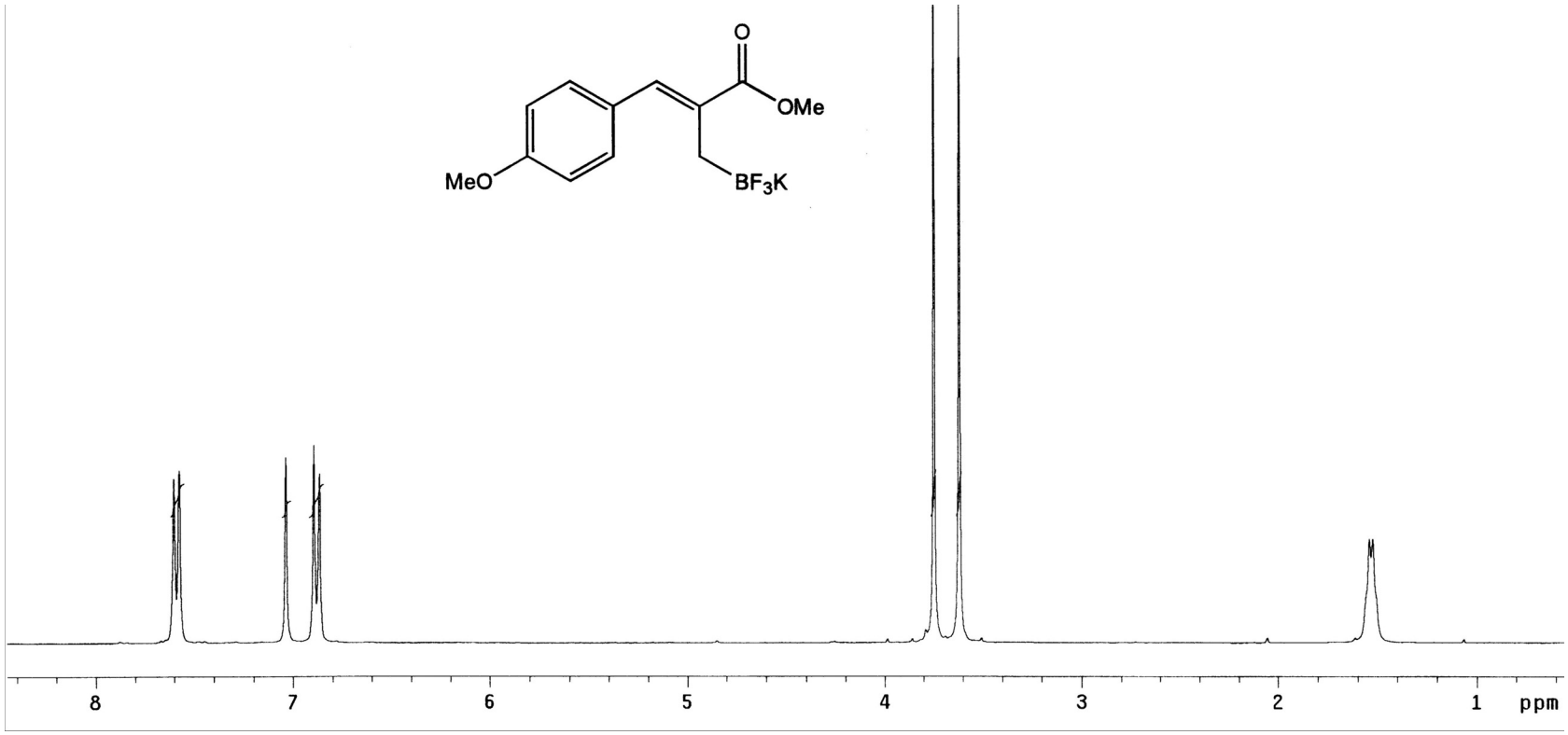
^{13}C NMR of Compound **1-417**



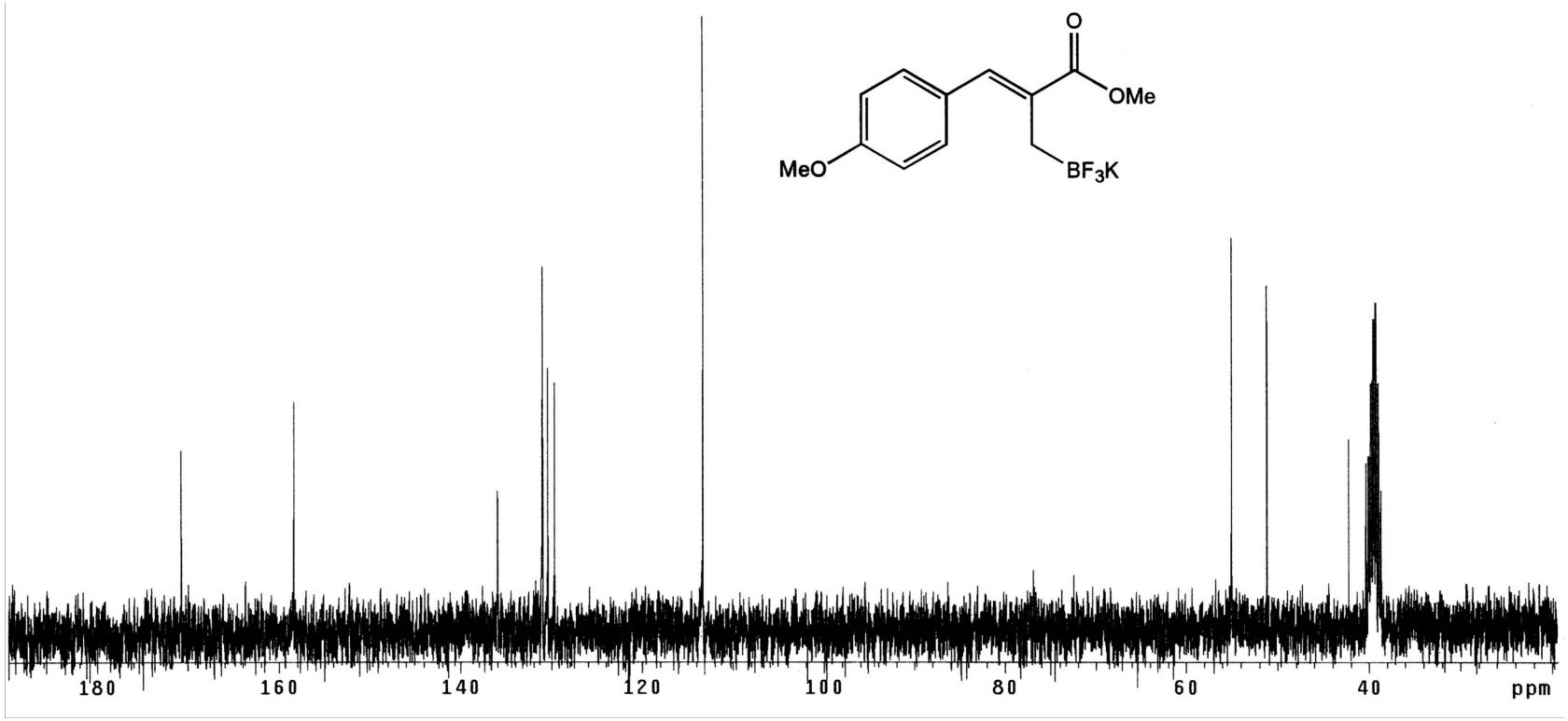
^{1}H NMR of Compound **1-420**



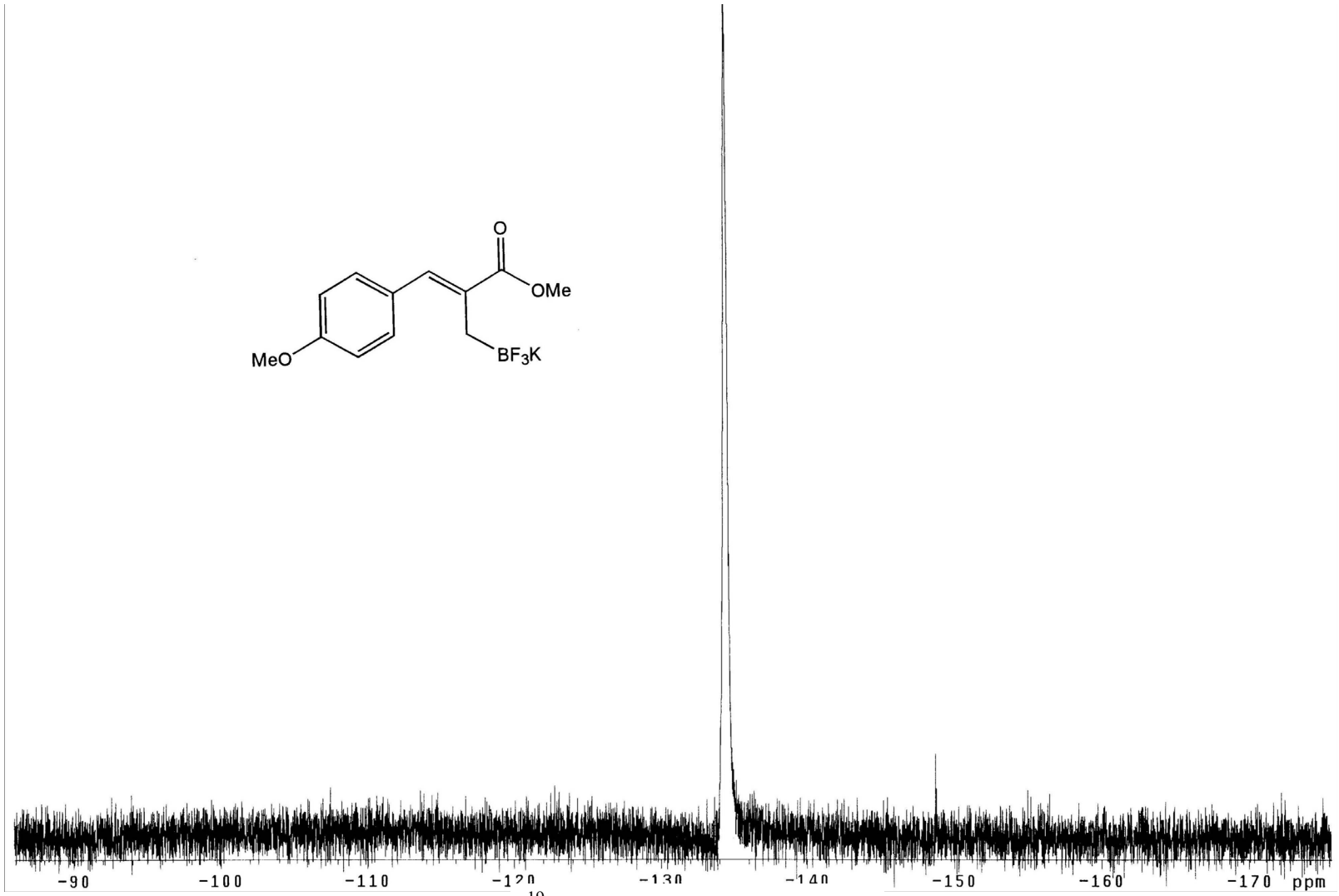
^{13}C NMR of Compound **1-420**



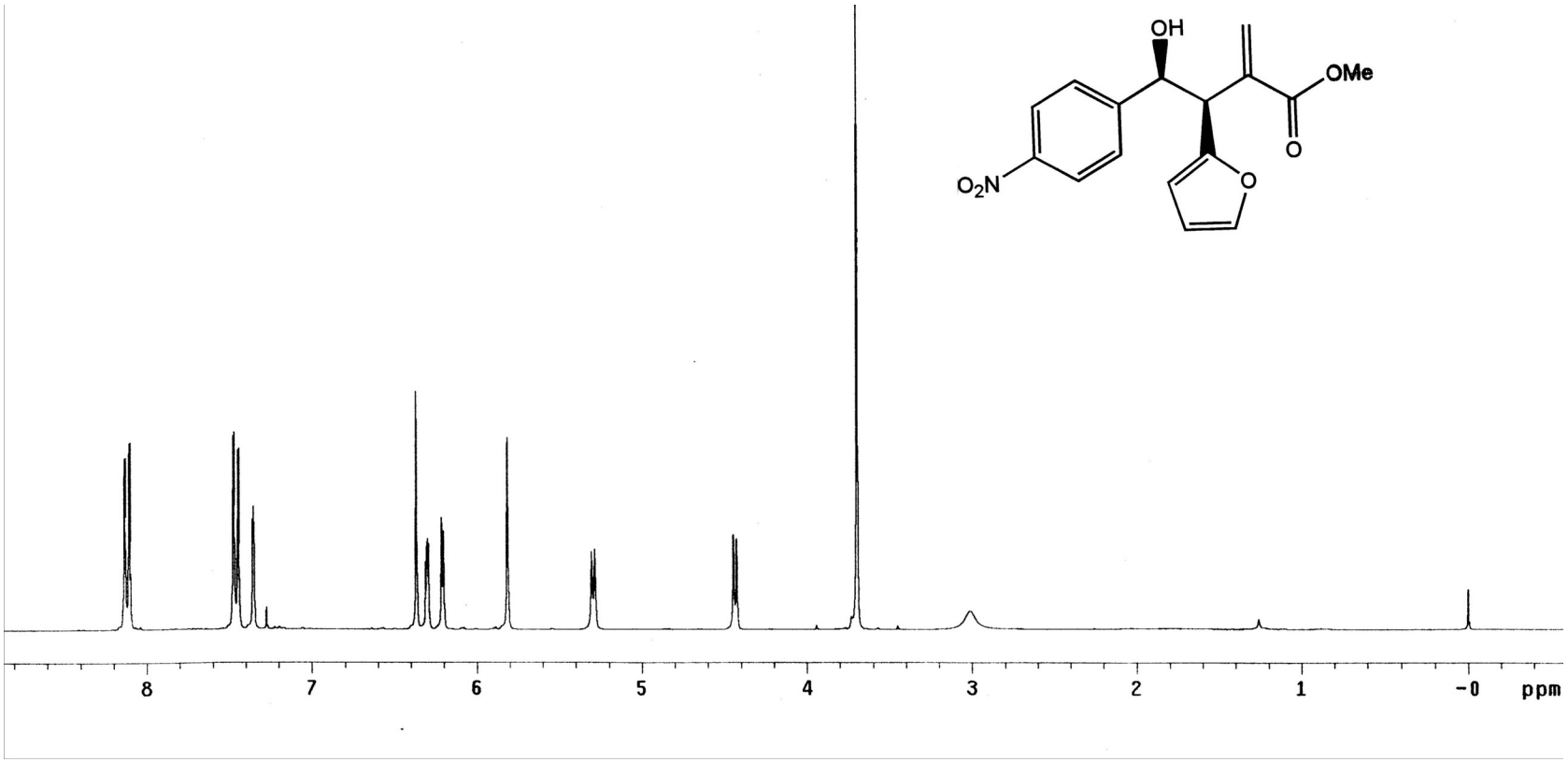
^{1}H NMR of Compound **1-504**



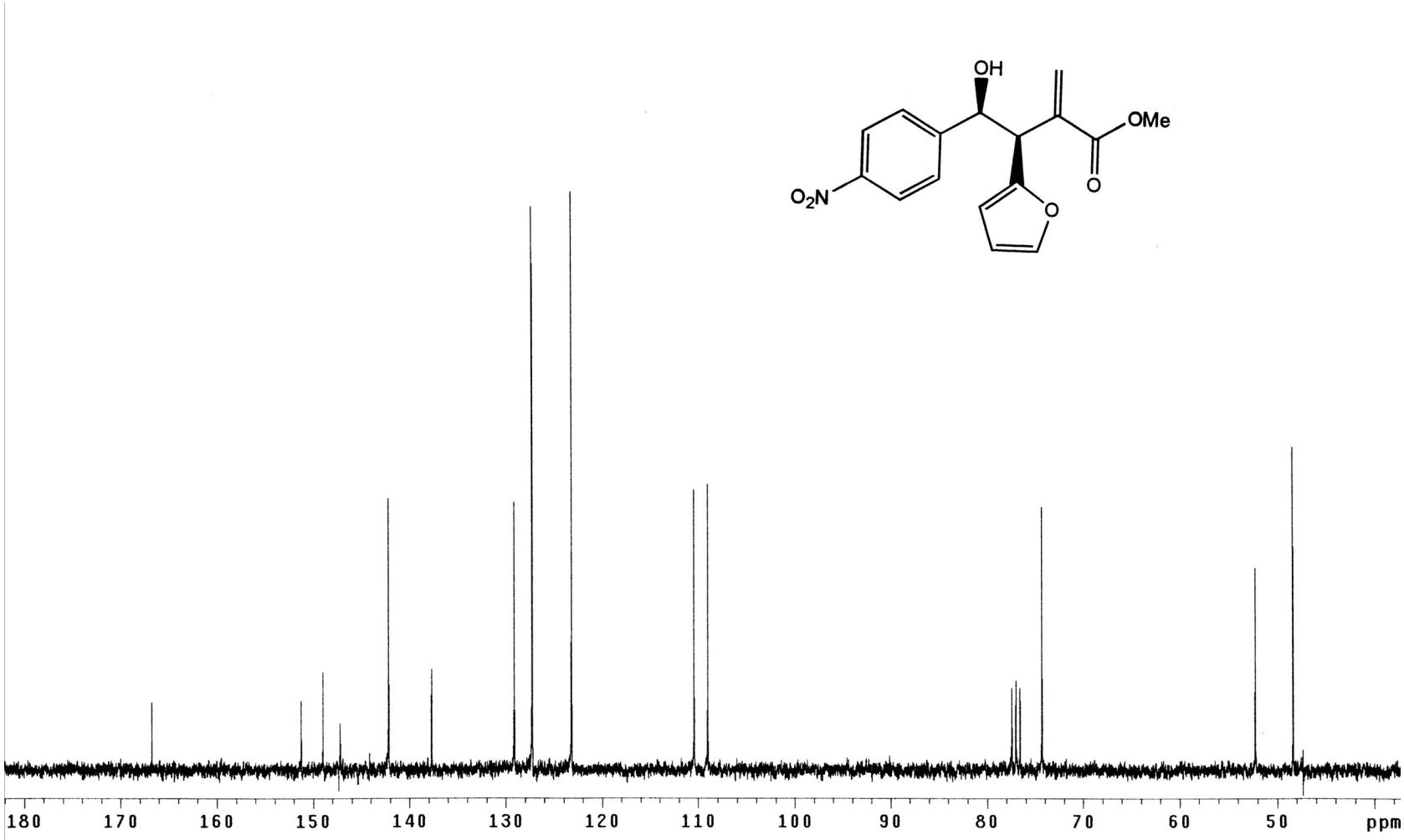
^{13}C NMR of Compound **1-504**



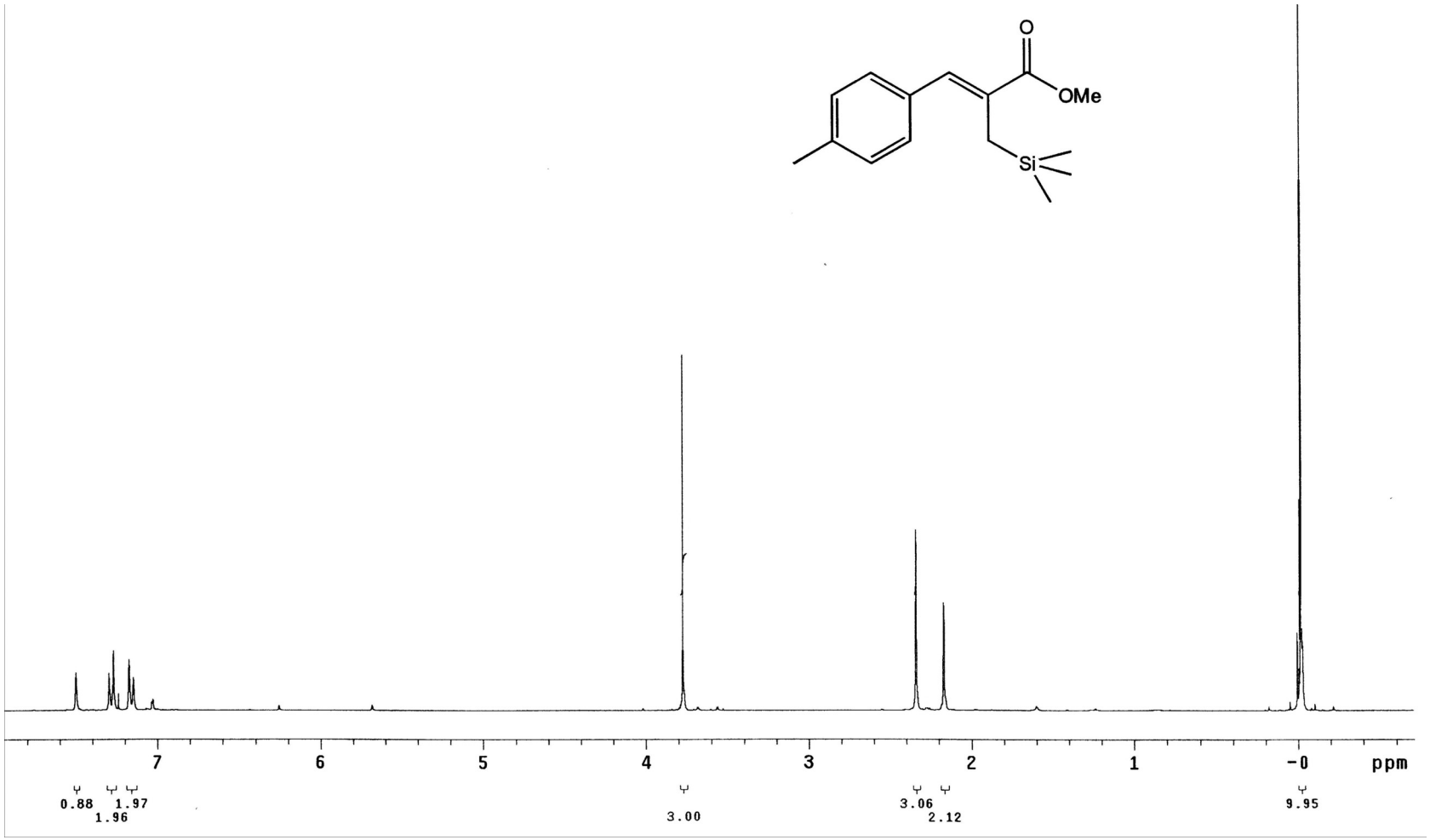
^{19}F NMR of Compound **1-504**



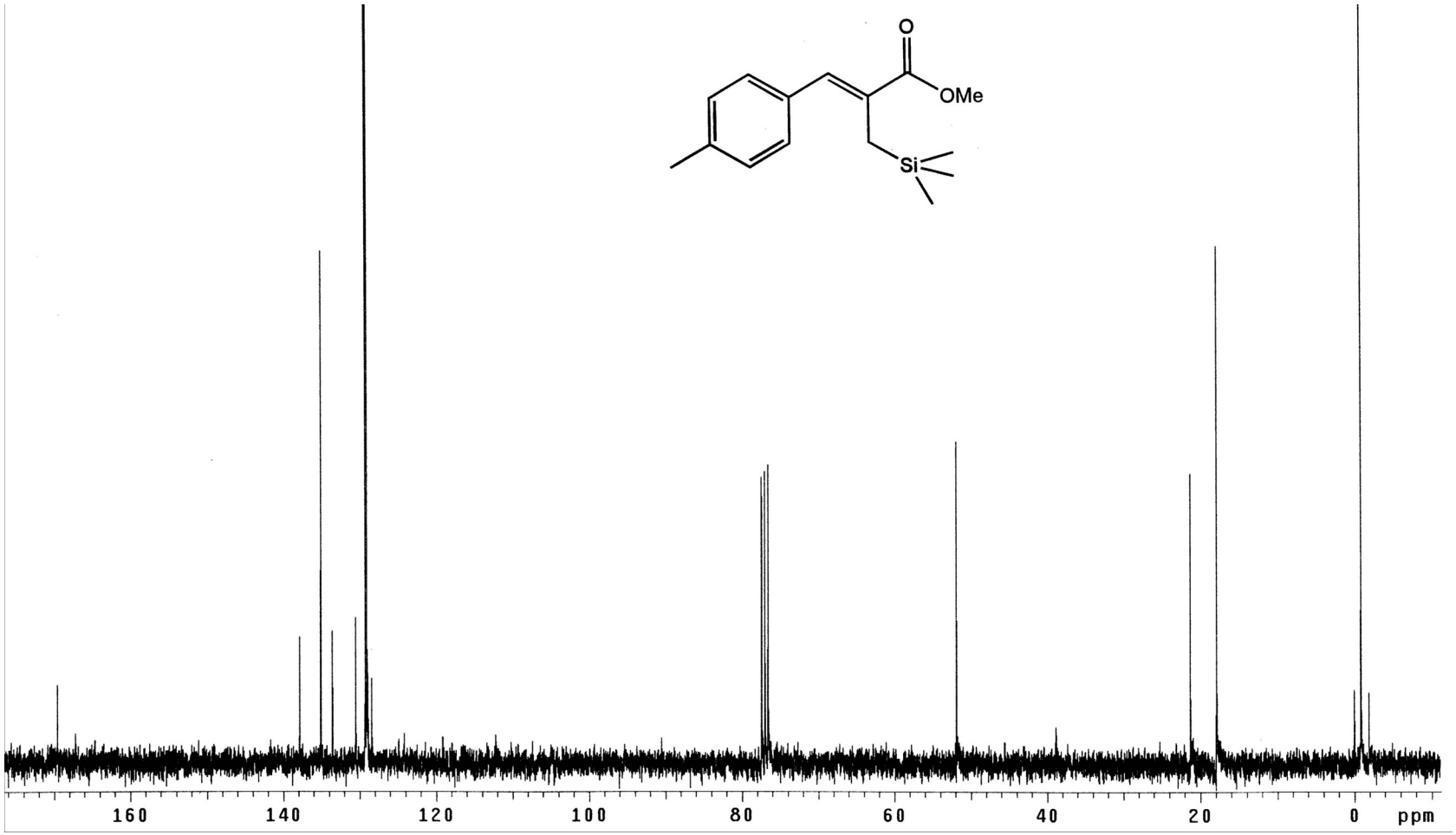
^{1}H NMR of Compound **1-514**



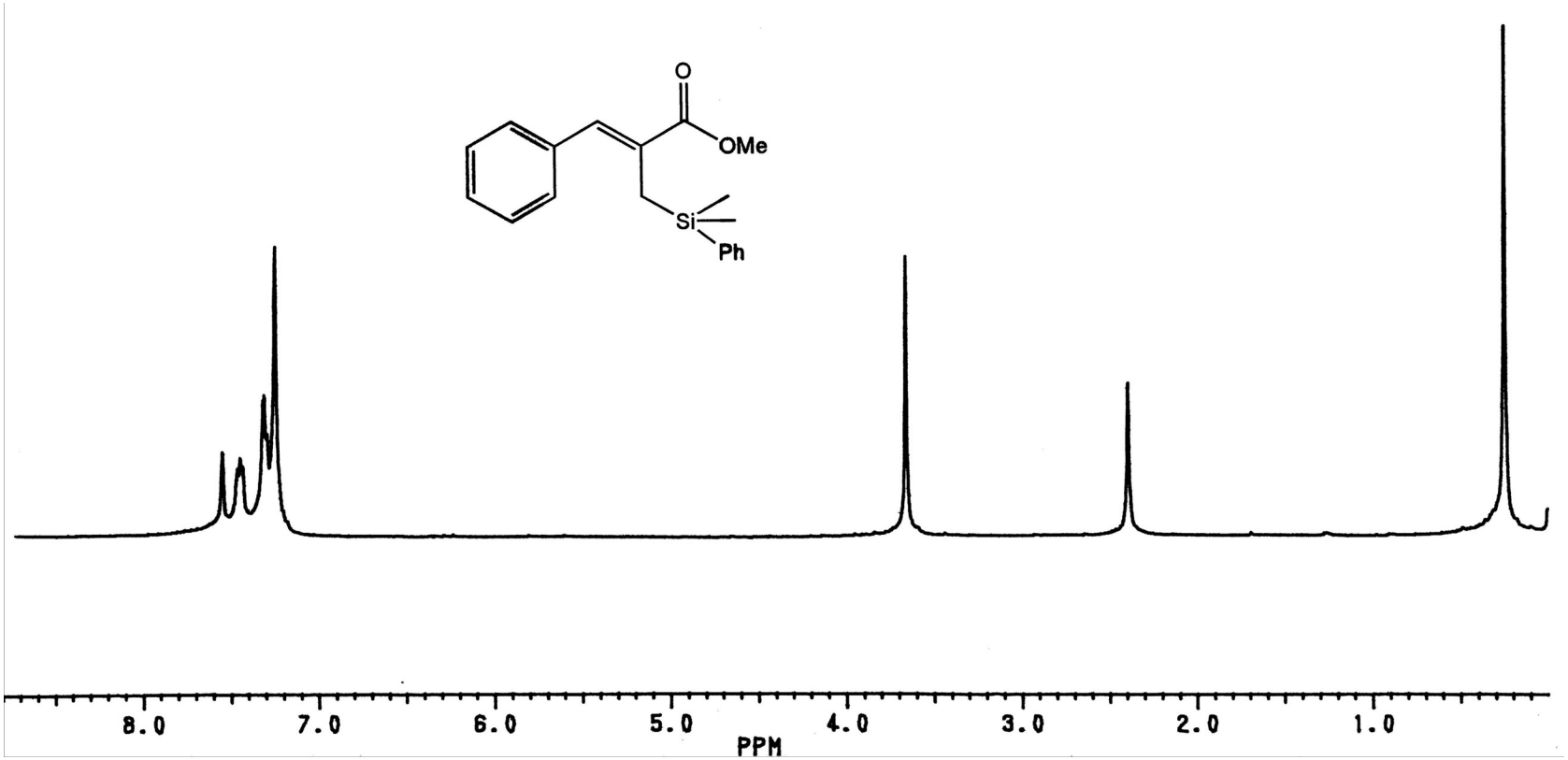
^{13}C NMR of Compound **1-514**



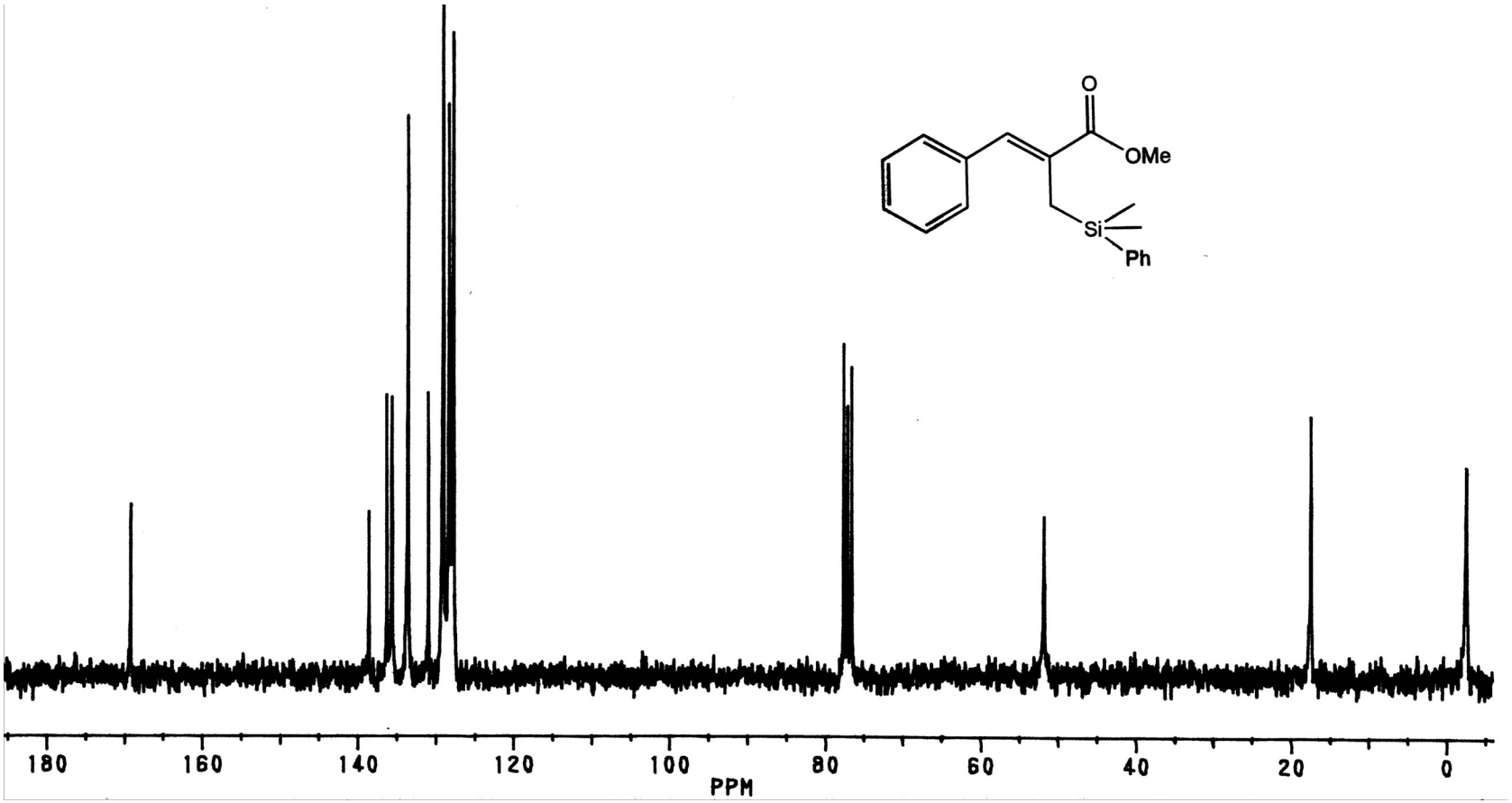
^{1}H NMR of Compound **1-602**



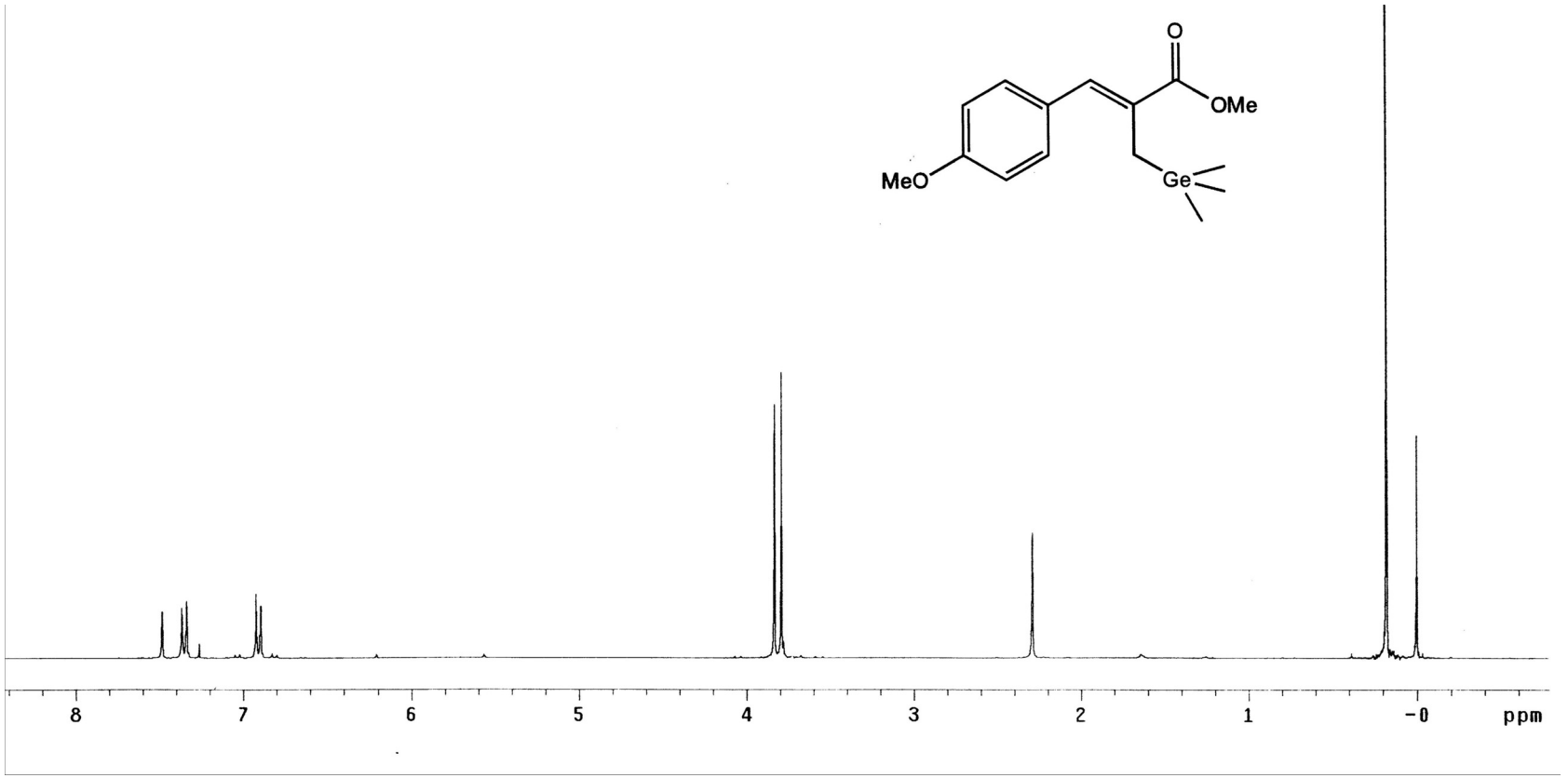
^{13}C NMR of Compound **1-602**



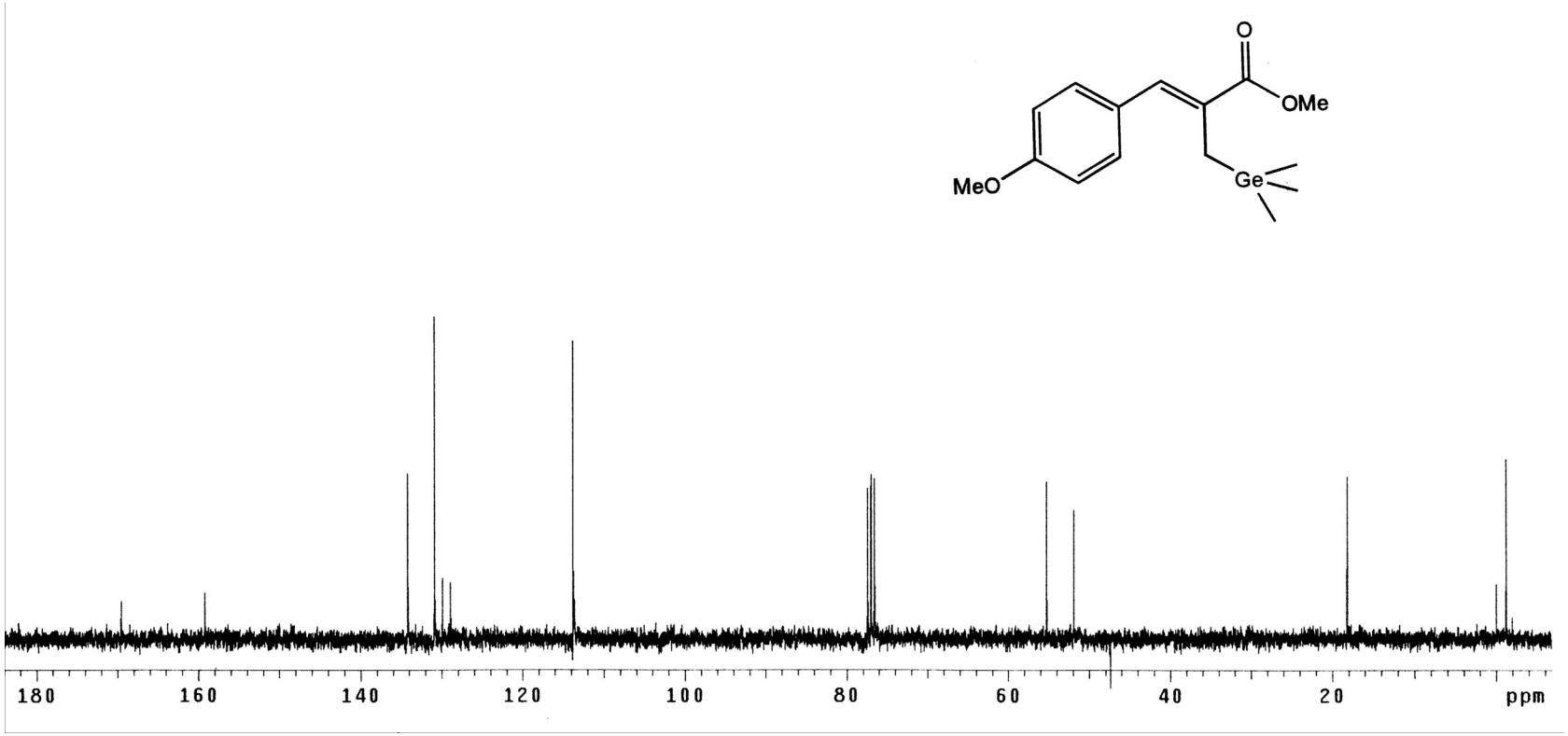
^{1}H NMR of Compound **1-609**



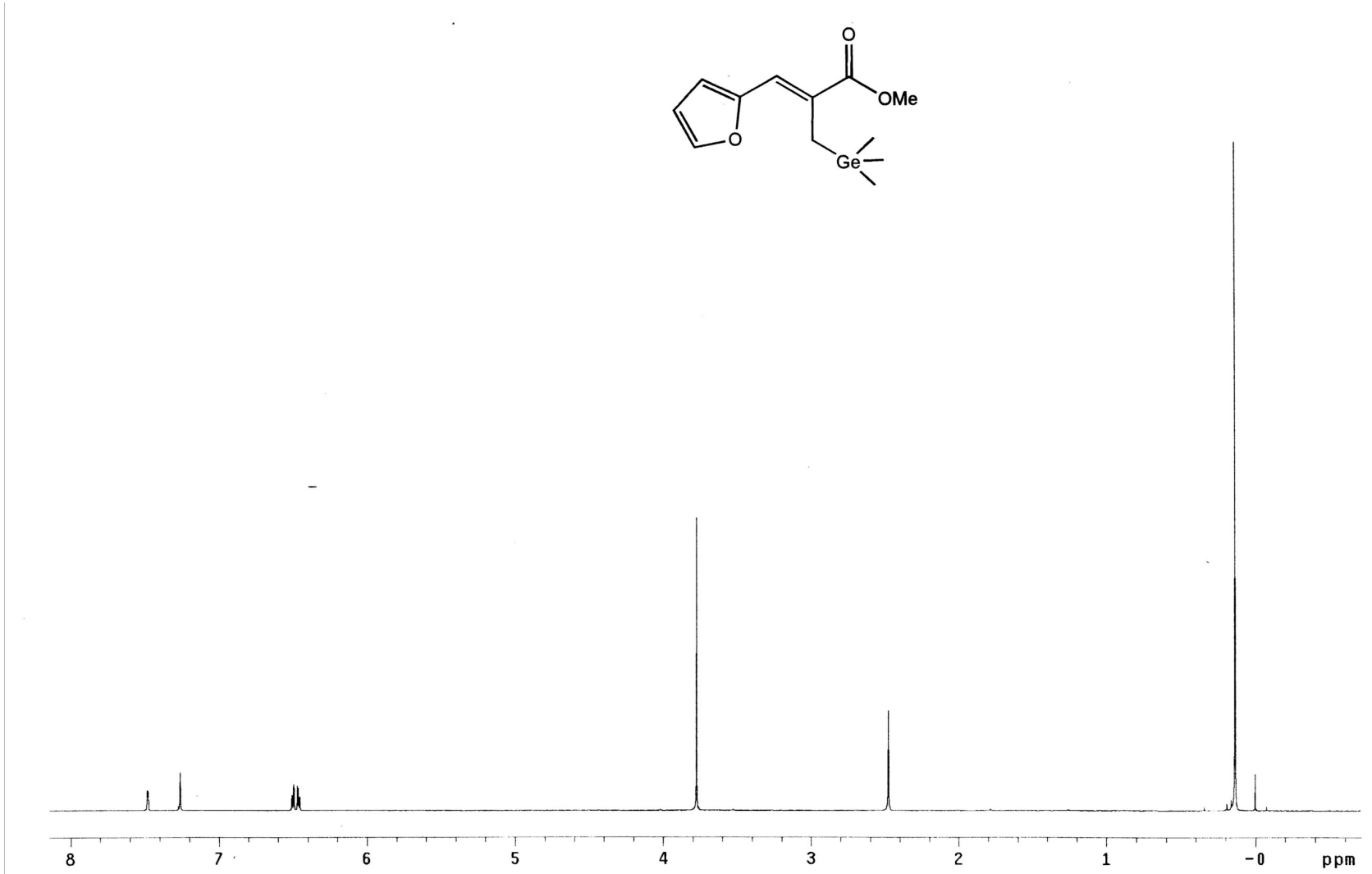
^{13}C NMR of Compound **1-609**



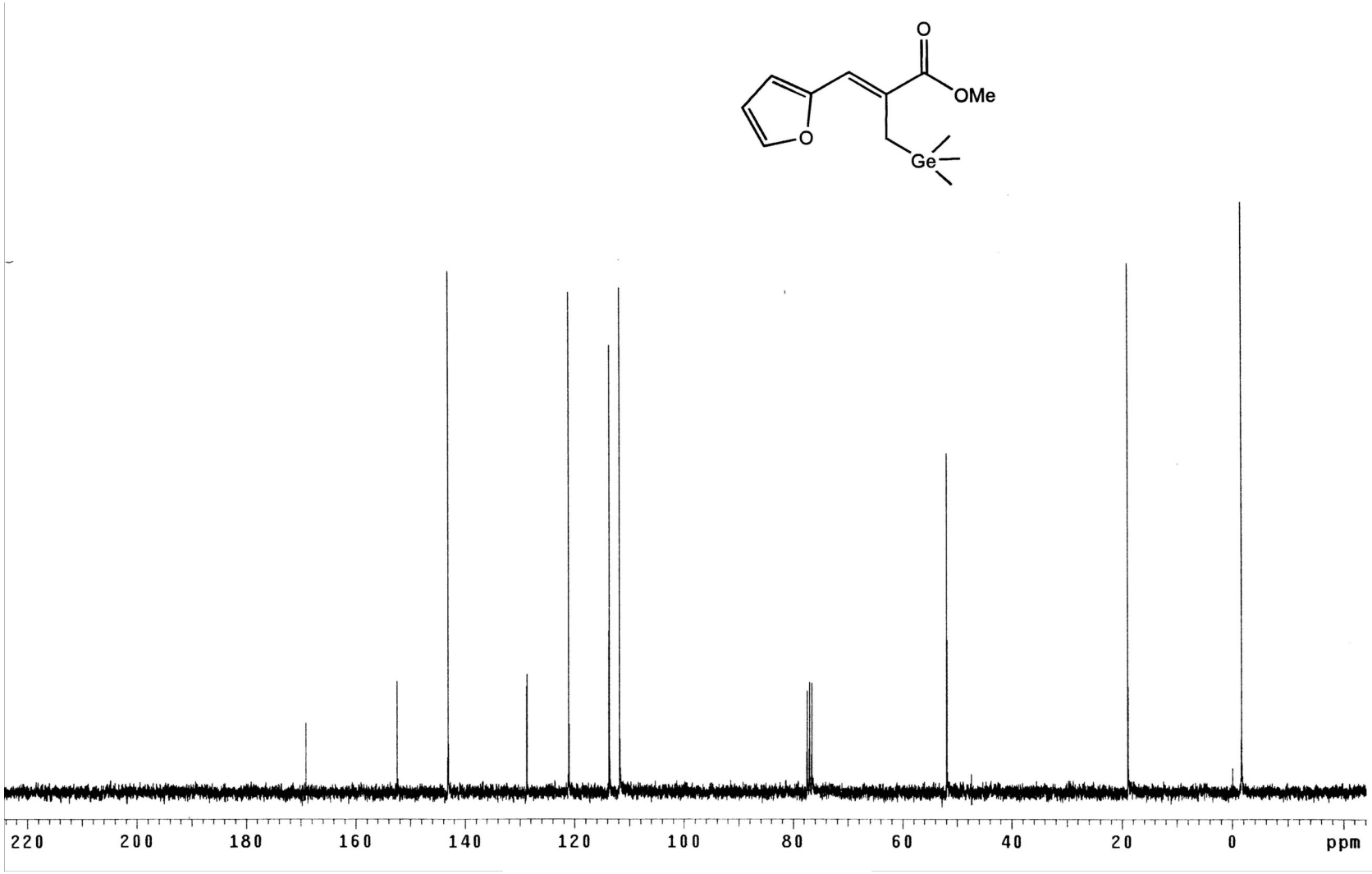
^{1}H NMR of Compound **1-612**



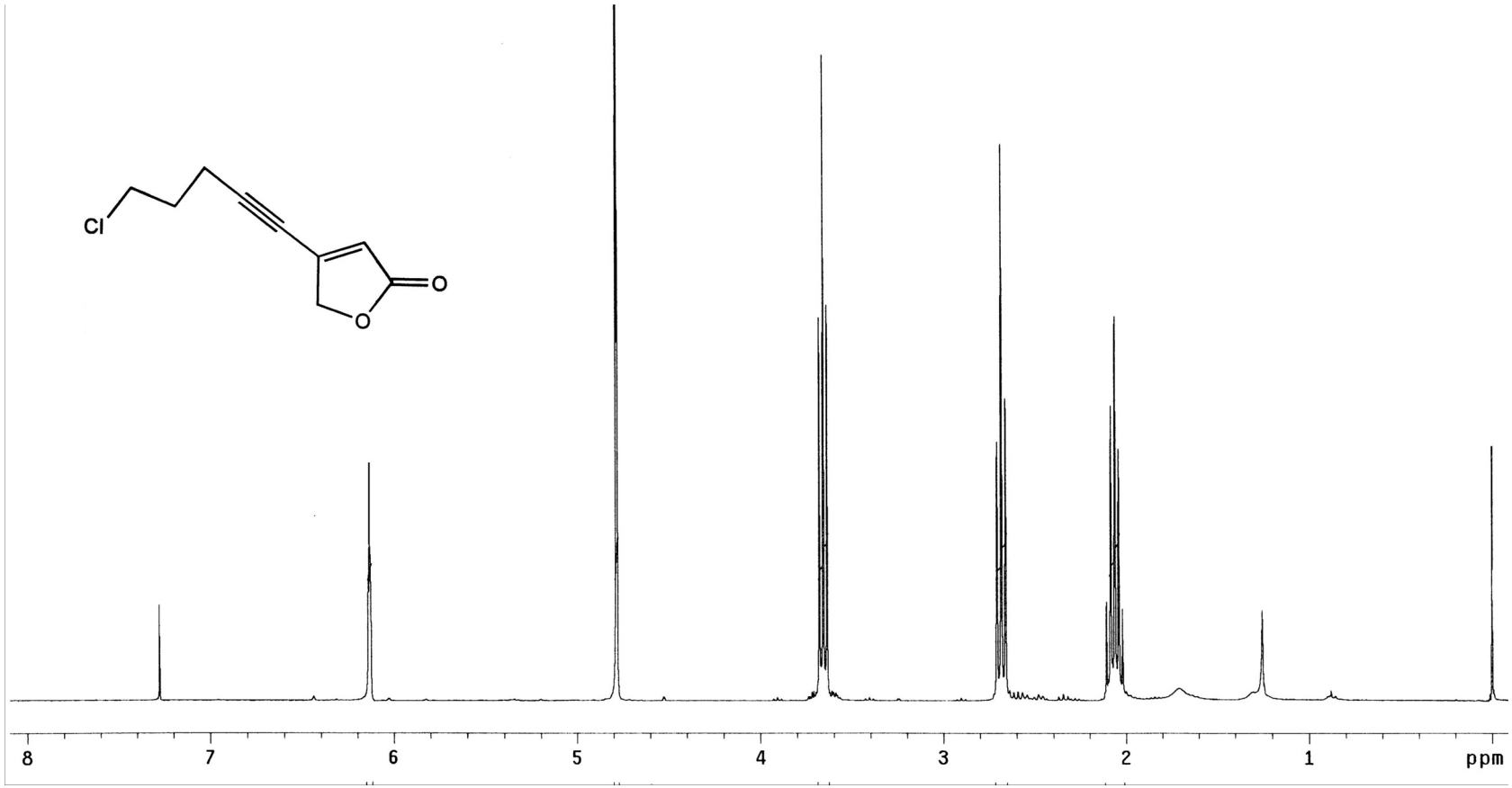
^{13}C NMR of Compound **1-612**



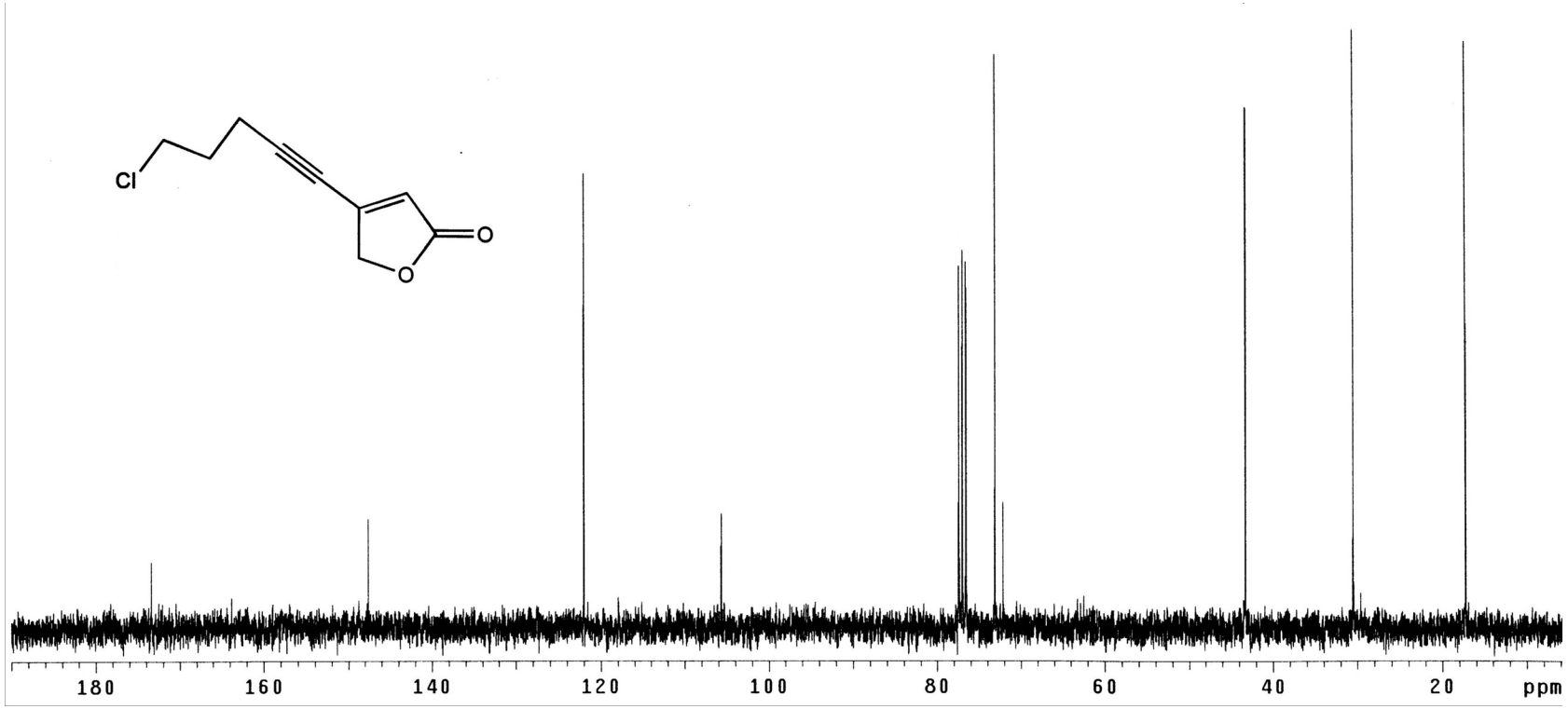
^{1}H NMR of Compound **1-615**



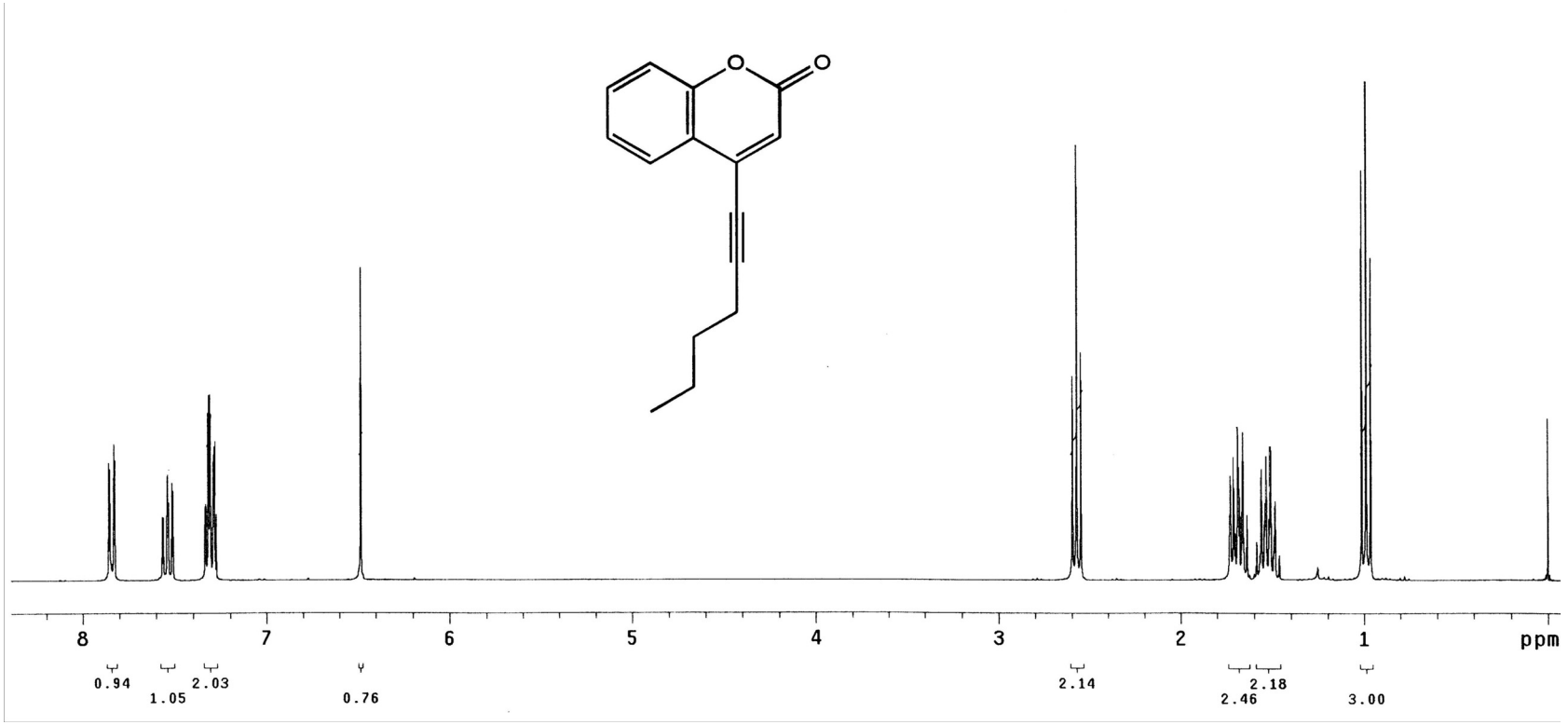
^{13}C NMR of Compound **1-615**



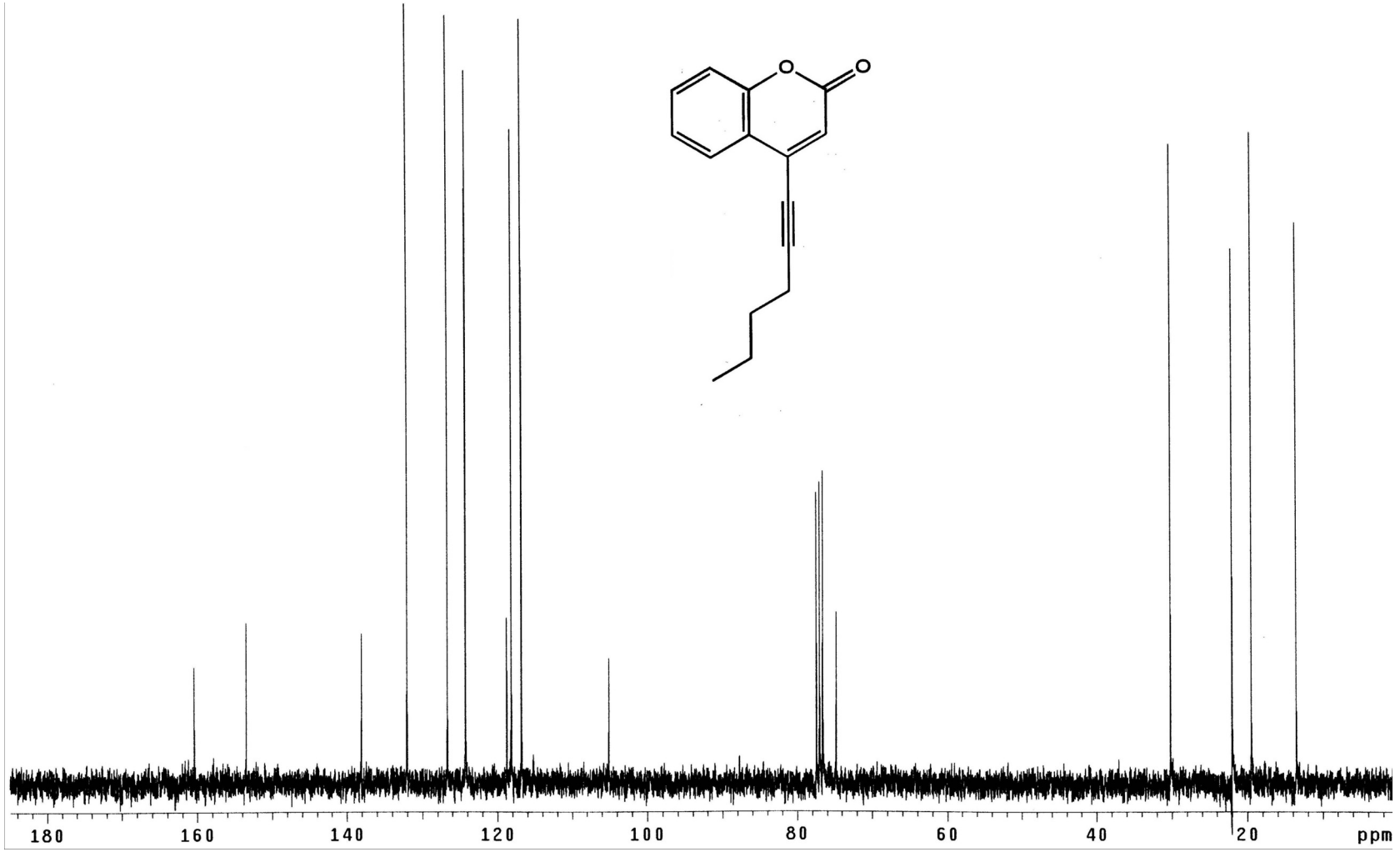
^{1}H NMR of Compound **2-204**



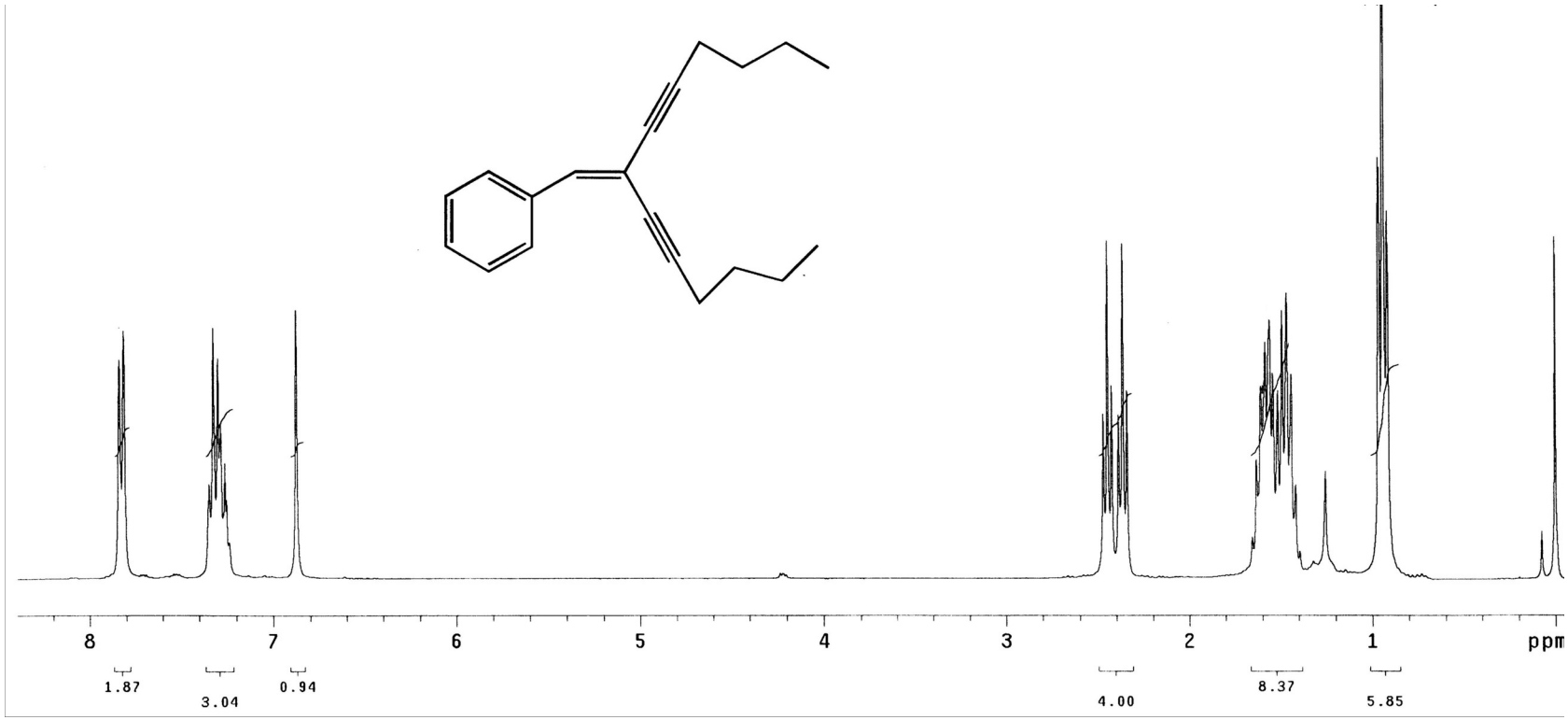
^{13}C NMR of Compound **2-204**



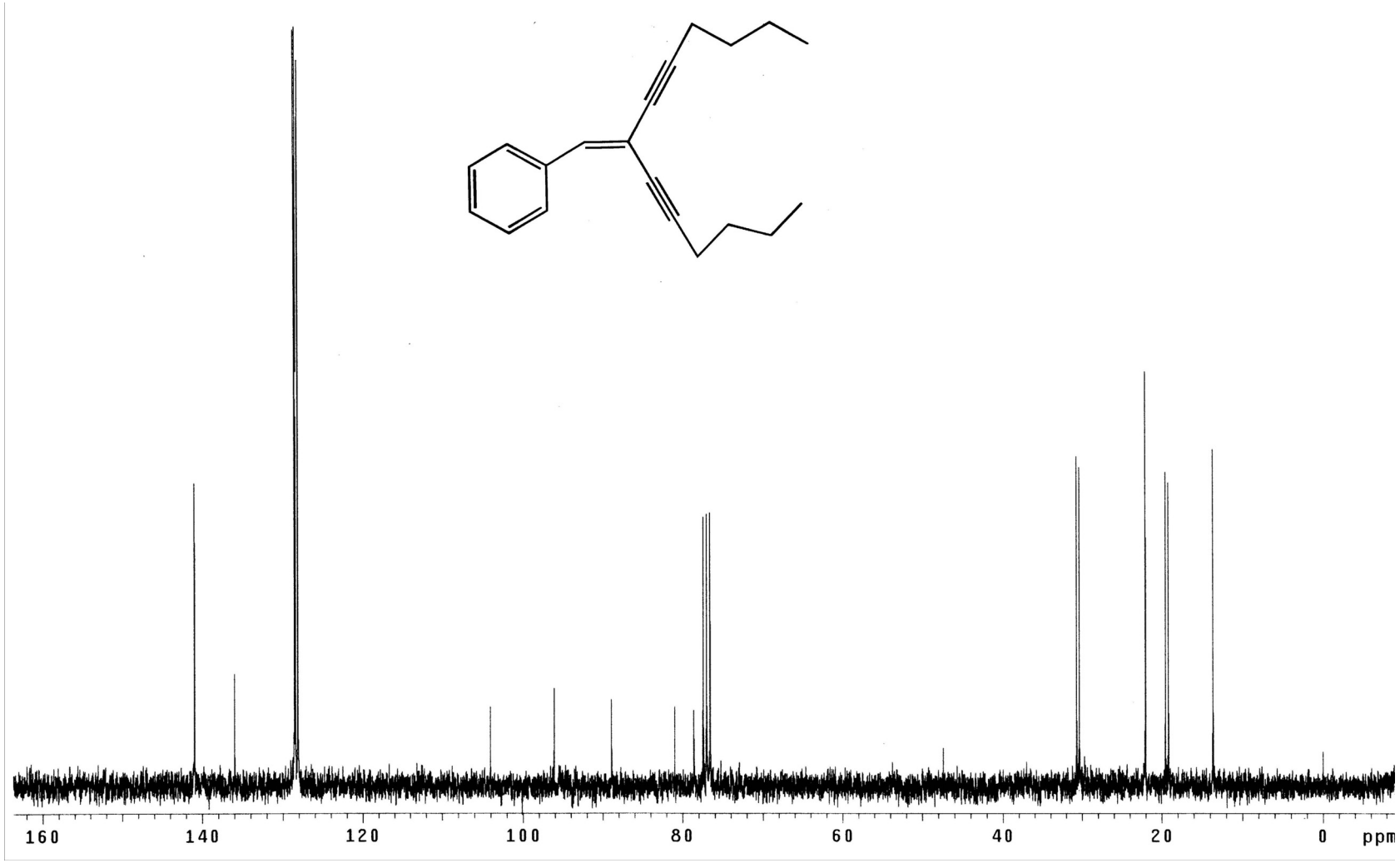
^{1}H NMR of Compound **2-210**



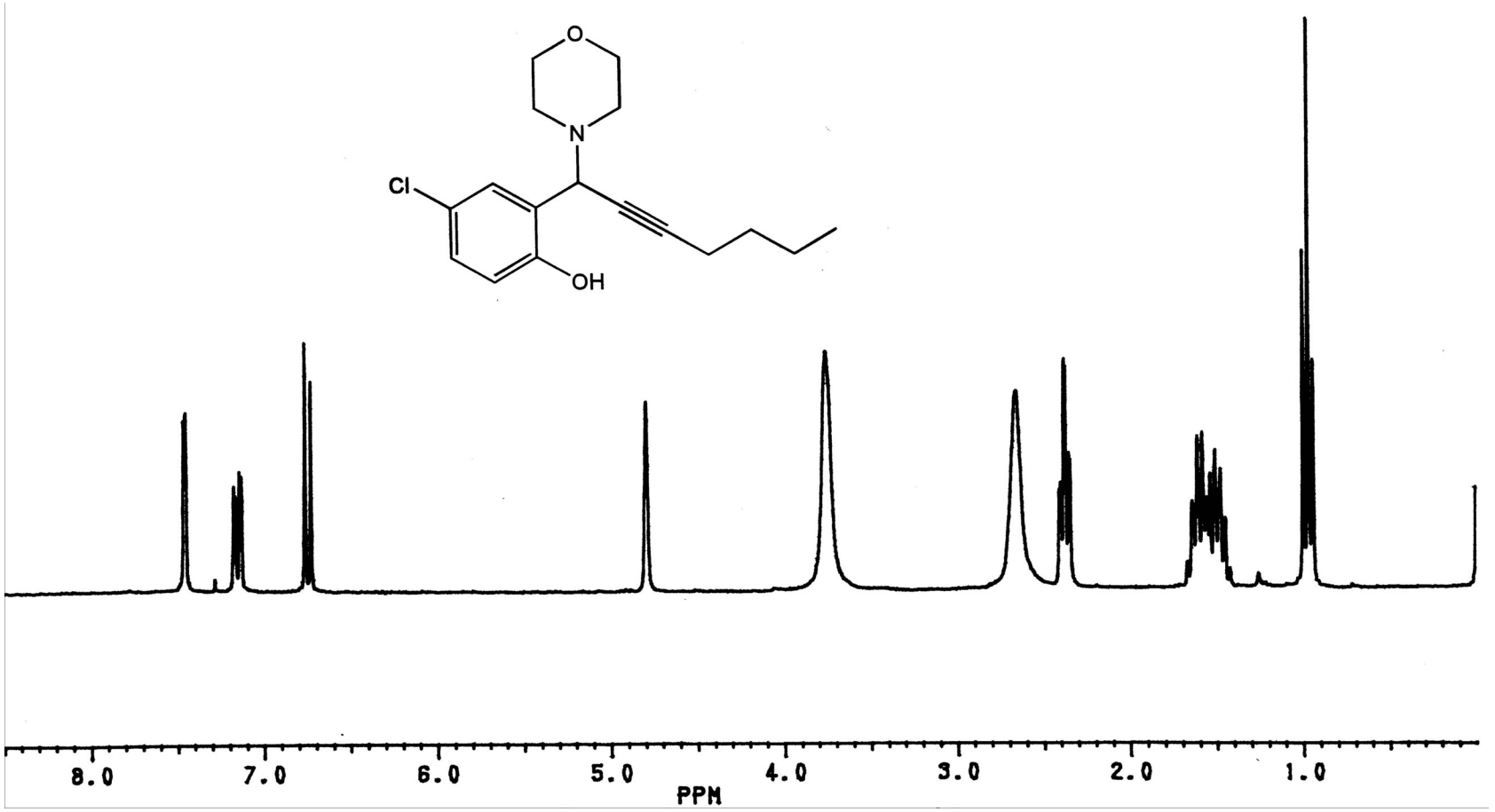
^{13}C NMR of Compound **2-210**



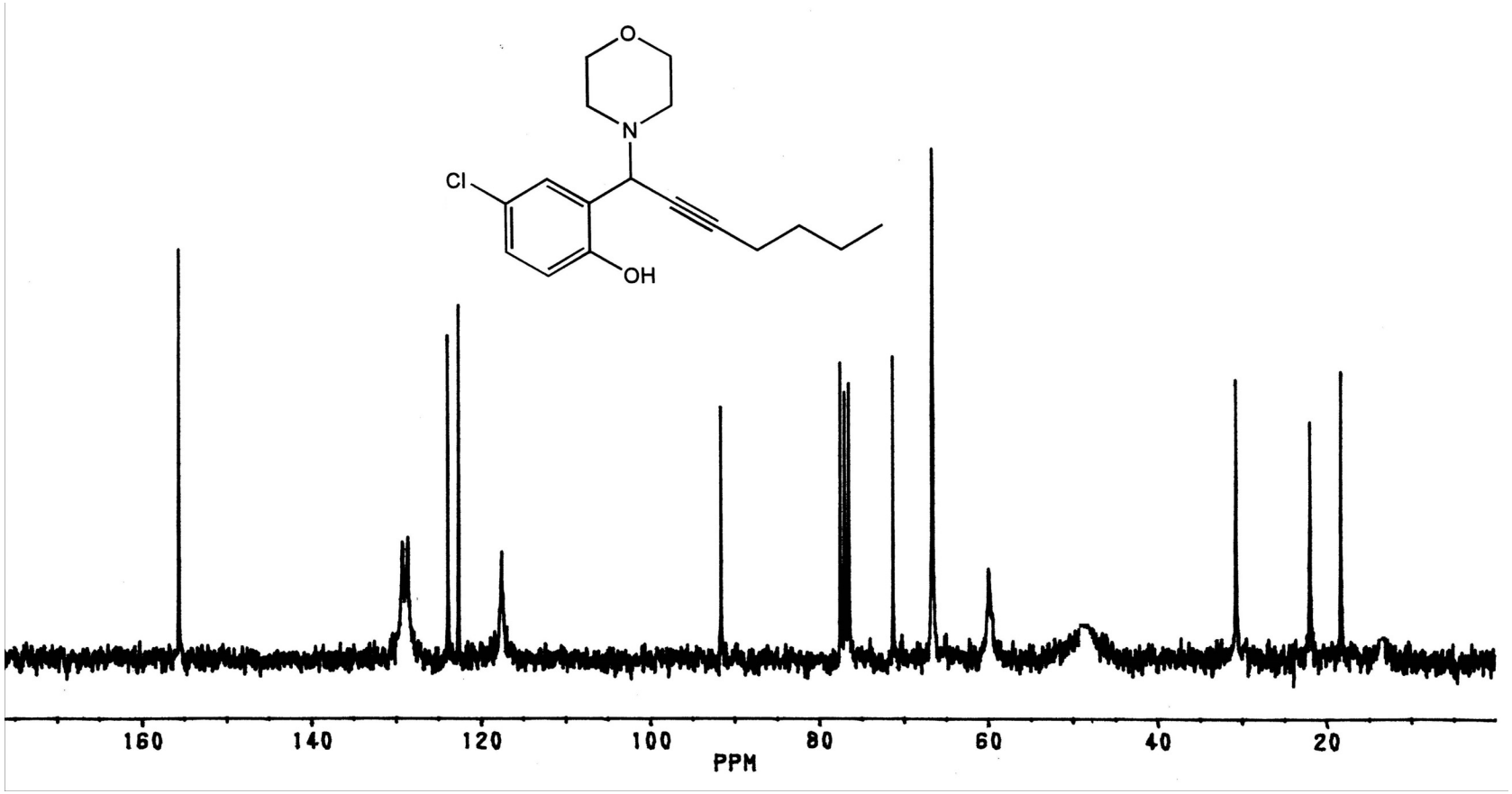
^{1}H NMR of Compound **2-301**



^{13}C NMR of Compound **2-301**



^{1}H NMR of Compound **2-409**

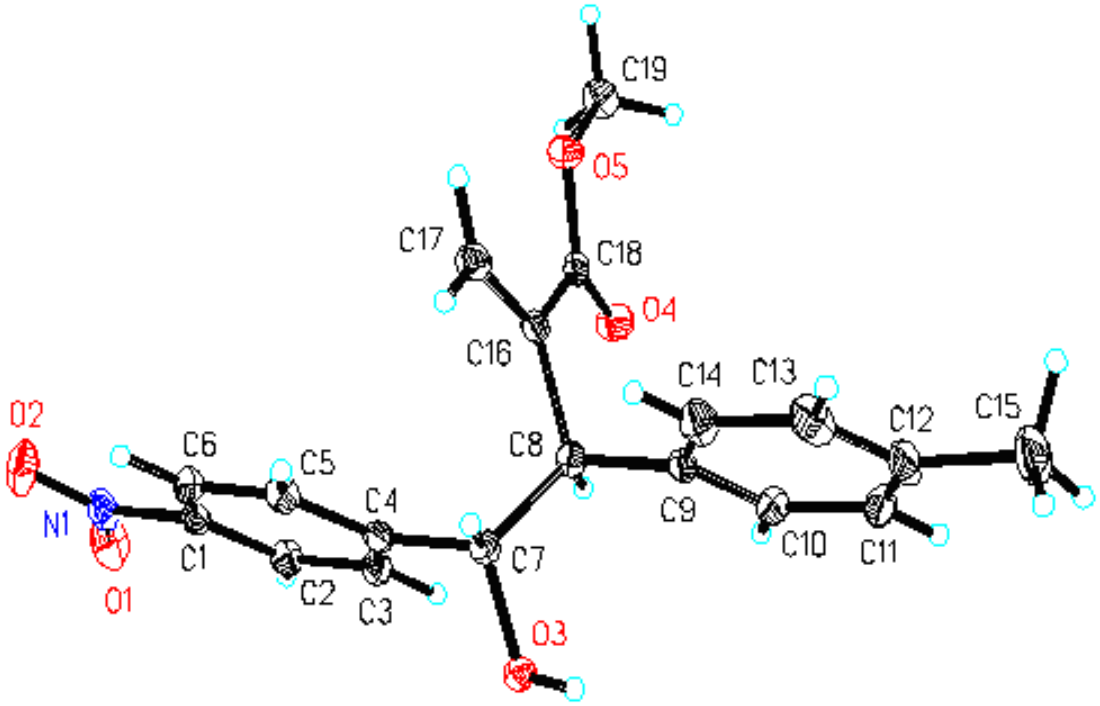


^{13}C NMR of Compound **2-409**

Appendix II

Molecular Drawing, Crystallographic Data, and Bond Distances and Angles of Compound 1-509

Molecular drawing of 1-509 showing 30% probability thermal ellipsoids.



Crystal data and structure refinement for 1-509

Empirical formula	$C_{19}H_{19}NO_5$	
Formula weight	341.35	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.026(4) Å	α = 90°
	b = 12.776(5) Å	β = 97.634(6)°
	c = 13.526(5) Å	γ = 90°
Volume	1717.1(11) $Å^3$	
Z	4	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	720	
Crystal size	0.45 x 0.42 x 0.38 mm^3	
Theta range for data collection	2.05 to 28.42°	
Index ranges	$-13 \le h \le 13$, $-17 \le k \le 17$, $-17 \le l \le 18$	
Reflections collected	18132	
Independent reflections	4181 [R(int) = 0.0336]	
Completeness to theta = 28.42°	96.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9644 and 0.9580	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4181 / 0 / 229	
Goodness-of-fit on F^2	0.683	
Final R indices [I>2sigma(I)]	R1 = 0.0500, wR2 = 0.1609	
R indices (all data)	R1 = 0.0628, wR2 = 0.1889	
Largest diff. peak and hole	0.564 and -0.216 $e.Å^{-3}$	

Bond distances of 1-509

C(1)-C(6)	1.380(2)	C(9)-C(14)	1.392(3)
C(1)-C(2)	1.385(2)	C(10)-C(11)	1.398(2)
C(1)-N(1)	1.474(2)	C(11)-C(12)	1.383(3)
C(2)-C(3)	1.396(2)	C(12)-C(13)	1.386(3)
C(3)-C(4)	1.398(2)	C(12)-C(15)	1.515(3)
C(4)-C(5)	1.386(2)	C(13)-C(14)	1.395(3)
C(4)-C(7)	1.522(2)	C(16)-C(17)	1.329(2)
C(5)-C(6)	1.387(2)	C(16)-C(18)	1.494(2)
C(7)-O(3)	1.4316(19)	C(18)-O(4)	1.213(2)
C(7)-C(8)	1.543(2)	C(18)-O(5)	1.3341(19)
C(8)-C(16)	1.523(2)	C(19)-O(5)	1.4514(19)
C(8)-C(9)	1.535(2)	N(1)-O(2)	1.217(2)
C(9)-C(10)	1.384(2)	N(1)-O(1)	1.221(2)

Bond angles of 1-509

C(6)-C(1)-C(2)	122.52(14)	C(14)-C(9)-C(8)	121.89(15)
C(6)-C(1)-N(1)	118.25(15)	C(9)-C(10)-C(11)	120.50(19)
C(2)-C(1)-N(1)	119.23(14)	C(10)-C(11)-C(12)	121.11(19)
C(1)-C(2)-C(3)	118.04(14)	C(11)-C(12)-C(13)	118.29(16)
C(2)-C(3)-C(4)	120.58(14)	C(11)-C(12)-C(15)	121.5(2)
C(5)-C(4)-C(3)	119.42(14)	C(13)-C(12)-C(15)	120.2(2)
C(5)-C(4)-C(7)	119.22(14)	C(12)-C(13)-C(14)	121.01(19)
C(3)-C(4)-C(7)	121.36(14)	C(13)-C(14)-C(9)	120.47(18)
C(6)-C(5)-C(4)	120.84(14)	C(17)-C(16)-C(18)	120.81(14)
C(1)-C(6)-C(5)	118.61(14)	C(17)-C(16)-C(8)	126.33(14)
O(3)-C(7)-C(4)	106.81(12)	C(18)-C(16)-C(8)	112.81(13)
O(3)-C(7)-C(8)	109.87(12)	O(4)-C(18)-O(5)	122.64(14)
C(4)-C(7)-C(8)	110.95(12)	O(4)-C(18)-C(16)	124.01(14)
C(16)-C(8)-C(9)	108.43(12)	O(5)-C(18)-C(16)	113.35(13)
C(16)-C(8)-C(7)	113.45(12)	O(2)-N(1)-O(1)	122.59(16)
C(9)-C(8)-C(7)	111.58(12)	O(2)-N(1)-C(1)	118.55(16)
C(10)-C(9)-C(14)	118.60(15)	O(1)-N(1)-C(1)	118.85(15)
C(10)-C(9)-C(8)	119.42(15)	C(18)-O(5)-C(19)	116.02(13)

VITA

Gang Dong was born on March 6th, 1973 in Kaifeng, P. R. China. He enrolled in the Kaifeng High School, one of the best high schools in Henan Province, in 1987. He entered Wuhan University in 1990 and was awarded the Bachelor of Science degree majored in organic chemistry in 1994. He earned his Master's degree majored in organic chemistry from Nanjing University in 1997 and was honored as the Outstanding Graduate Student. Gang Dong and Chunlan Chen got married in April 1997. He had worked in Liming Science & Technology Company as a research scientist and department manager since July1997. On August 30th, 1998, his son Ziqing Dong was born in Nanjing, China.

In August 2001, Gang Dong joined Dr. George W. Kabalka's research group in the Department of Chemistry, University of Tennessee, Knoxville and received his Ph.D degree in May, 2005. During the study in the University of Tennessee, he was awarded a variety of awards and fellowships including Gleb Mamantov Graduate Chemistry Scholar, D. A. Shirley Graduate Award in Organic Chemistry, Burchfield Burridge Warner Graduate Fellowship in Chemistry Award, and UT Scholarly Activity Research Incentive Fund Research Assistant Award. He has accepted a postdoctoral postion at the University of Texas at Austin.