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Development of Novel Synthetic Methods Utilizing Organometallic Reagents and Total Synthesis of Eupomatilone 2

Chunlan Chen
University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a thesis written by Chunlan Chen entitled "Development of Novel Synthetic Methods Utilizing Organometallic Reagents and Total Synthesis of Eupomatilone 2." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

George W. Kabalka, Major Professor

We have read this thesis and recommend its acceptance:

Richard Pagni, Bin Zhao

Accepted for the Council:
Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

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Anne Mayhew
Vice Chancellor and
Dean of Graduate Studies

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Development of Novel Synthetic Methods Utilizing Organometallic Reagents and the Total Synthesis of Eupomatilone 2

A Thesis
Presented for the
Master of Science Degree

The University of Tennessee, Knoxville

Chunlan Chen
December 2006

DEDICATION

This dissertation is dedicated to my beloved husband Gang Dong for his 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 Haozhou Chen and Aizhen Zhou for their understanding, patience, encouragement and support.

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Most importantly, I would like to thank my husband, Gang Dong, for his love, support, patience and encouragement. I would also like to thank my parents, my sister and brother for their constant support and understanding.

ABSTRACT

This dissertation summarizes the development of novel synthetic methods involving organometallic reagents and their application in the total synthesis of the natural product eupomatilone 2. These newly discovered reactions include the palladium-catalyzed cross-coupling of allyl acetates with organosiloxanes and the diastereoselective synthesis of *cis*- and *trans*-α-methylene-γ-lactones utilizing Baylis-Hillman adducts as precursors. Another important aspect of the research is the application of some of the methods in total synthesis of eupomatilone 2.

The new synthetic methodologies involving organometallic reagents developed in this dissertation are important transformations in modern organic synthesis. Mild reaction conditions, tolerance of various organic functional groups, and high selectivity are advantages of these methodologies. The ability to recycle the catalytic system in some cases is another attractive feature for PEG-involved methods. The short and efficient strategy for the synthesis of eupomatilone 2 could serve as a catalyst for research in this area.

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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
$BmimBF_4$	1-Butyl-3-methylimidazolium tetrafluoroborate
brs	Broad peaks
Bu	Butyl
n-BuLi	*n*-Butyl lithium
n-Bu_4NF	Tetrabutylammonium fluoride
t-Bu	*tert*-Butyl
^oC	Degree Celsius
^{13}C nmr	Carbon-13 nuclear magnetic resonance
$CDCl_3$	Chloroform-*d*
CH_2Cl_2	Methylene chloride
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
Et	Ethyl

Et_2O	Diethyl ether
EtOAc	Ethyl acetate
g	Gram
GC	Gas Chromatography
^1H nmr	Proton nuclear magnetic resonance
Hg	Mercury
H_2O	Water
h	Hour
Hz	Hertz
In	Indium
J	Proton-proton coupling constant
KF	Potassium fluoride
m	Multiplet
Me	Methyl
MeOH	Methanol
Me_3Si	Trimethylsilyl
mg	milligram
Mg	Magnesium
$MgSO_4$	Magnesium sulfate
min	Minutes
mL	Mililiter
mmol	Milimole
MS	Mass Spectroscopy

$NaHCO_3$	Sodium bicarbonate
NMR	Nuclear magnetic resonance spectroscopy
OAc	Acetoxy
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
PMA	Phosphomolybdic acid
PPh_3	Triphenylphosphine
R	Alkyl
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

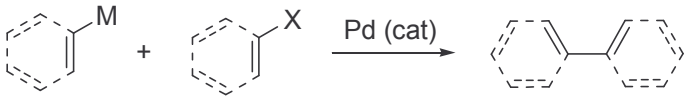
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
UV	Ultraviolet Spectroscopy

Chapter 1. Introduction

1.1 Transition-Metal Catalyzed Reactions

1.1.1 Introduction

Cross-coupling reactions, now accessible via a variety of organometallic reagents, provide important fundamental synthetic methods (Figure 1.1). In 1972, Kumada and Tamao[1] and Corriu[2] independently reported that reactions of organomagnesium reagents with alkenyl or aryl halides were catalyzed by Ni(II) complexes. Kochi[3] 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[4], the synthetic utility of which was then demonstrated by Negishi[5] using the reactions of organic derivatives of aluminum, zinc, and zirconium. Since that time, many other organometallic reagents have proven to be highly useful as nucleophiles for cross-coupling reactions. These include the use of organolithium by Murahashi,[6] organostannane by Migita[7] and Stille,[8] 1-alkenylcopper(I) by Normant,[9] and organosilicon by Hiyama.[10]



M = SnR_3 (Stille-Migita-Kosugi)
BR_2 or $B(OR)_2$ (Suzuki-Miyaura)
$SiR_{(3-n)}Fn$ (Hiyama)
$Si(OR)_3$ (Tamao-Ito)

X = I, Br, Cl, OTf

Figure 1.1: Cross couplings of organometallic reagents

1.1.2 Mechanism of the Cross-Coupling Reaction

A general catalytic cycle for the cross-coupling reaction of organometallics, which involves oxidative addition - transmetalation - reductive elimination sequences, is depicted in Figure 1.2. Although each step involves other processes including ligand exchange, intermediates 1 and 2 have been characterized by isolation or spectroscopic analysis.[11, 12] It is significant that the great majority of cross-coupling reactions catalyzed by Ni(0), Pd(0), and Fe(I) are rationalized in terms of this common catalytic cycle.

Oxidative addition[11, 13] of 1-alkenyl, 1-alkynyl, allyl, benzyl, and aryl halides to a palladium(0) complex affords a stable *trans*-α-palladium(II) complex **(1)**. The reaction proceeds with complete retention of configuration for alkenyl halides and with inversion for allylic and benzylic halides. Alkyl halides having β-hydrogen are rarely useful because the oxidative addition step is very slow and may compete with β-hydride elimination from the α-organopalladium(II) species. However, it has been recently shown that iodoalkanes undergo the cross-coupling reaction with organoboron compounds.[14]

Oxidative addition is often the rate-limiting step in the catalytic cycle. For the halogenated precursor the relative reactivity decreases in the order of I > OTf > Br >> C1. Aryl and 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those posscssing donating groups. A very wide range of palladium(0) catalysts or precursors can be used for cross-coupling reactions.

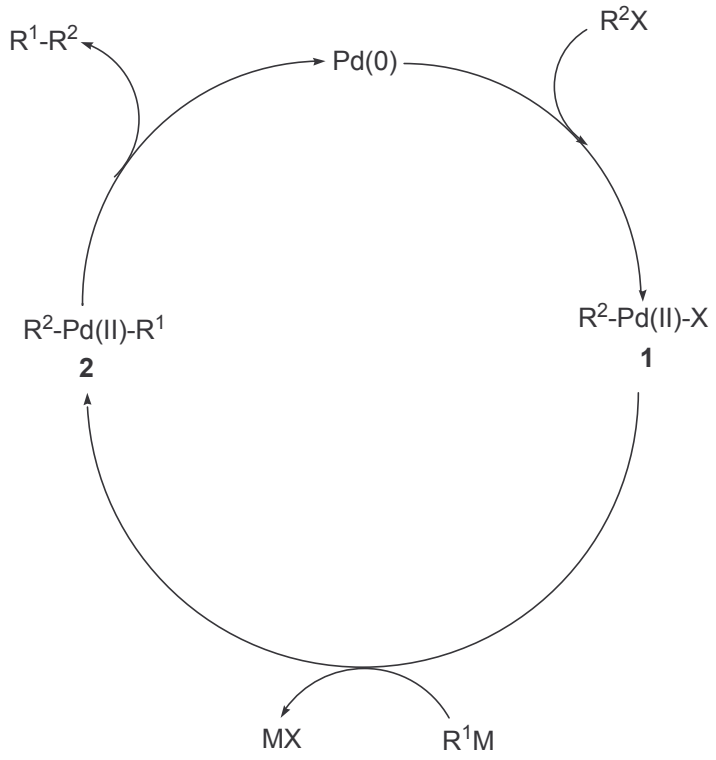


Figure 1.2: Mechanism of palladium-catalyzed coupling of organometallic reagents

$Pd(PPh_3)_4$ is most commonly used, but $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$, along with PPh_3 or other phosphine ligands, are also efficient since they are stable to air and readily reduced to active Pd(0) complexes with organometallics or phosphines used for the cross-coupling.[15] Palladium complexes that contain fewer than four phosphine ligands or bulky phosphines such as tris(2,4,6-tri-methoxypheny1)phosphine are, in general, highly reactive for the oxidative addition because of the ready formation of coordinate unsaturated palladium species.[16]

Reductive elimination of organic partners from **2** regenerates the palladium(0) complex.[17-19] The reaction takes place directly from *cis*-**2,** but *trans*-**2** reacts only after isomerizing to the corresponding *cis*-complex (Figures 1.3 and 1.4). The order of reactivity is diaryl- > (alky1)aryl- > dipropyl- > diethyl- > dimethylpalladium(II), suggesting participation by the n-orbital of aryl group during the bond formation (Figure 1.3).[19b] Although this mechanistic step has not been examined for 1-alkenyl- or l-alkynylpalladium(II) complexes, a similar effect is observed in the reductive elimination of related platinum(II) complexes.[20]

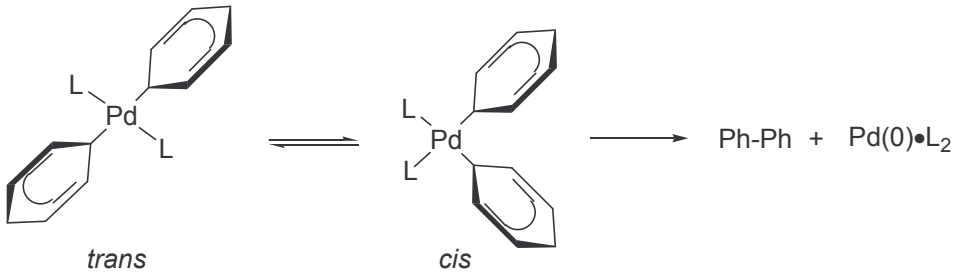


Figure 1.3: Reductive elimination: nondissociative-nonassociative mechanism

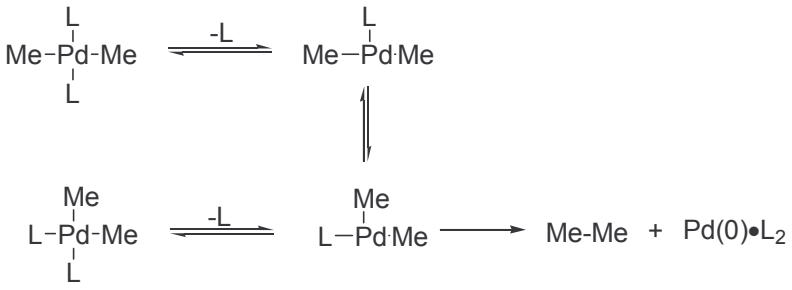


Figure 1.4: Reductive elimination: Dissociative mechanism

The thermolysis of *cis*-(dialkyl)palladium(II)·L_2, which is an intermediate in alkyl-alkyl coupling, is inhibited by excess phosphine (L)**,** Hence the rection is considered to be initiated by the rate-limiting dissociation of phosphine ligand **(**L**)** producing a three-coordinated *cis*-(dialkyl)palladium(II)·L complex (dissociative mechanism, Figure 1.4).[18] Thus, the effect of phosphine ligands is comparable to the order of ease of their dissociation: dppe << PEt_3 < PEt_2Ph < $PMePh_2$ < $PEtPh_2$ < PPh_3.

On the other hand, *cis*-alkenyl- and *cis*-arylpalladium(II) complexes, which are intermediates in most of cross-coupling reactions, directly eliminate organic partners from the four-coordinated complex (nondissociative-nonassociative mechanism, Figure 1.3).[19]

Although the mechanism of oxidative addition and reductive elimination sequences are reasonably well understood and are presumably fundamentally common processes for all cross-coupling reactions of organometallics, less is known about the transmetallation step because the mechanism is highly dependent on metal and the conditions used for coupling. The transmetalation between 1-hexenylboronic acid and

palladium(II) acetate was first reported by Heck.[21] The *in situ* preparation of *(E)*- or (*Z*)-1-alkenylpalladium(II) species and its addition to ethyl acrylate readily proceed at room temperature while retaining their original configurations (Figure 1.5).[22] Before this observation, Davidson and Triggs reported the dimerization of phenylboronic acid with Na_2PdCl_4 catalyst (Figure 1.6),[23] although it still remains uncertain as to whether the reaction proceeds through a transmetallation or some other processes.

1.1.3 Organoboron Compounds in Coupling Reactions

1.1.3.1 Introduction

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 groups on boron.[24] However, intermolecular transfer reactions analogous to the Grignard reaction with carbonyl groups are relatively rare. Fortunately, organoboron compounds, even organoboronic acids and esters, have sufficient reactivity to participate in transmetallation reactions. Transmetallations to silver(I),[25] magnesium(II),[26] zinc(II),[27] aluminum(II),[28] tin(IV),[29] copper(I),[30] and mercury(II)[31] 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).[5i]

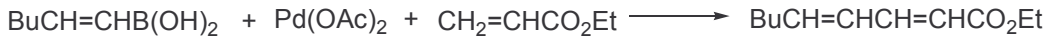


Figure 1.5: Coupling of ethyl acrylate with vinyl boronic acid

Figure 1.6: Dimerization of phenylboronic acid

The cross-coupling of organoboron compounds, involving transmetallation to palladium(II) halides, 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.[32]

Although a variety of organometallic reagents undergo cross-coupling reactions, much attention has been focused on the use of organoboronic acids 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.[33] Rather surprisingly, few studies[34] focused 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.[35] In 1984, his group applied an intramolecular coupling reaction of allyl halides with an alkenylborane as the key step to successfully synthesize humulene.[36] Allyl phenoxides,[34a] allyl acetates,[37] allyl

carbonates,[38] and allyl phosphates[39] have also been utilized in the coupling reaction with organoborane reagents. Two recent articles initiated a breakthrough in this field. The first one[34b] reported the coupling of arylboronic acids with allyl bromides under basic conditions in refluxing benzene (58 - 91% yield), while the second one[34c] 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.[40]

Unlike other organometallic reagents, organoboron compounds were thought to be less likely to participate in the catalytic cycle of cross-coupling reaction since they are inert to the organopalladium(II) halides **(1)** such as $PdC1_2$, $PdCl_2(PPh_3)_2$, or $PhPdI(PPh_3)_2$. However, there was some experimental evidence for the transmetallation to the transition metals. The reaction of organoboranes with organomercurials proceeds under neutral conditions when $Hg(OAc)_2$, $Hg(OR)_2$, or HgO is used.[41] It had also been reported that the addition of sodium hydroxide or other bases exerts a remarkable effect on the transmetallation rate of organoboron reagents with metallic halides, such as mercuric,[31, 41] silver,[25] auric,[42] and platonic halides.[43] Thus, the transmetallation of borane reagents with transition-metal complexes does proceed, but the choice of suitable bases and ligands on transition-metal complexes is essential.

1.1.3.2 Synthesis of Organoboron Reagents

1.1.3.2.1 From Organolithium or Magnesium Reagents

The classical synthesis of aryl- and l-alkenylboronic acids or their esters from Grignard reagents or lithium reagents and trialkyl borates is an efficient method for preparing relatively simple boron compounds in large quantities (Figure 1.7).[44] However, the application of these classical procedures for preparing organoboronic acids or esters can suffer from contamination by small a mounts of the opposite stereoisomer, or due to bis-alkylation leading to the borinic acid derivatives, or even the formation of trialkylboranes. A recent useful variant utilizes organolithium reagents and triisopropyl borate, followed by acidification with HCl to give alkyl-, aryl-, 1-alkynyl-, and 1-alkenylboronic esters in high yields, often over 90%.[45] Triisopropyl borate has proven to be the best of available alkyl borates in these reactions.

Very recently, arylboronic esters have been directly obtained from aryl halides via the cross-coupling reaction of (a1koxy)diboron (Figure 1.8).[46] The reaction tolerates various functional groups such as ester, nitrile, nitro, and acyl groups.

1.1.3.2.2 Hydroboration of Alkenes and Alkynes

The addition of dialkylboranes such as 9-borabicyclo-[3.3.1]nonane (9-BBN), disiamylborane, or dicyclohexylborane to 1-alkenes gives mixed alkylboron compounds.[47] The reaction is essentially quantitative, proceeds through a *cis anti*-

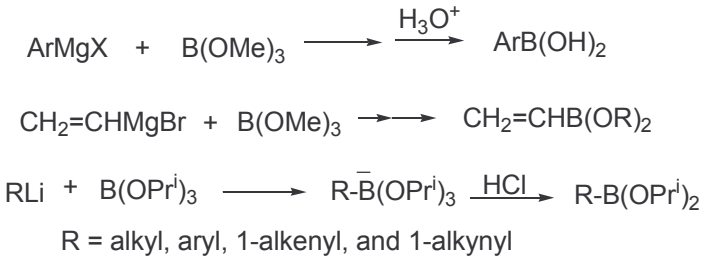


Figure 1.7: Preparation of organoboron reagents from Grignard or lithium reagents

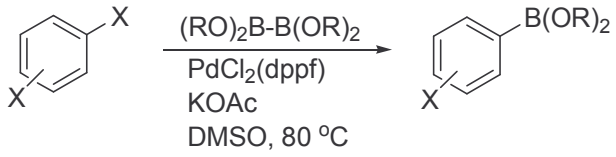


Figure 1.8: Preparation of organoboron reagents from aryl halides with diboron

Markovnikov addition from the less hindered side of double bond, and can tolerate various functional groups. The 9-alkyl-9-BBN derivatives thus obtained are particularly useful for the transfer of primary alkyl groups by the palladium-catalyzed cross-coupling reaction since the 9-alkyl group participates quite effectively in the catalytic reaction cycle (Figure 1.9).

The use of the hydroboration reaction is especially valuable for the synthesis of stereodefined or functionalized alkenylboronic acids and their esters. The general, and most convenient, method involves the hydroboration of a terminal alkyne with catecholborane to produce a 1-alkenylboronic ester.[47, 48] The hydroboration of alkynes with dihaloboranes ($HBCl_2 \cdot SMe_2$ or $HBBr_2 \cdot SMe_2$), followed by hydrolysis to vinylboronic acids or alcoholysis to boronic esters[47, 49] have been used for the same purpose. However, a recent and more convenient variant is the *in situ* preparation of $HBCl_2$ in a hydrocarbon solvent from $BC1_3$ and $HSiEt_3$.[50] The reagent exhibits extremely high reactivity to alkenes and alkynes allowing the hydroboration to proceed at -78 ^{o}C. Disiamylborane is also one of the mildest and selective hydroboration reagents for functionalized alkynes, but its use for the cross coupling can be more difficult than that of boronic acids or their esters. Hydroboration of terminal alkynes with 9-BBN leads to the formation of significant quantities of dihydroboration products. However, dihydroboration of l-alkynes, followed by deboration with benzaldehyde provides 9-[(*E*)-l-alkenyl]-9-BBN derivatives in high yields with high *trans* selectivity (Figure 1.10).[51]

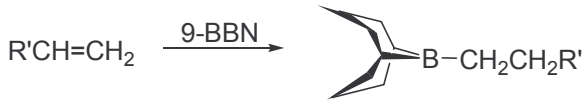


Figure 1.9: Addition of 9-BBN to 1-alkenes

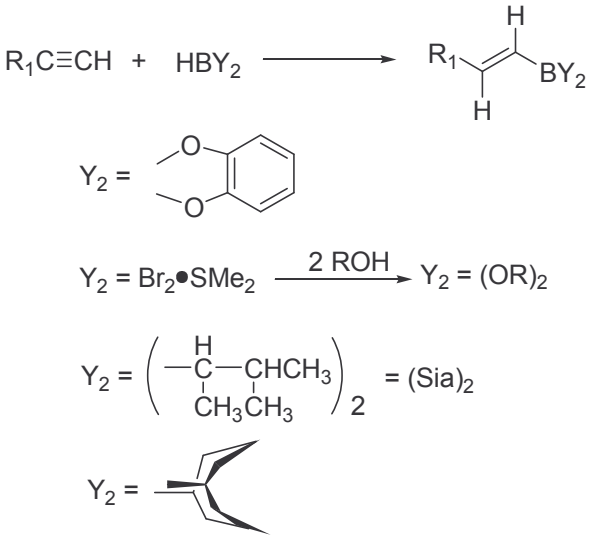


Figure 1.10: Hydroboration of terminal alkynes

1.1.3.2.3 Haloboration of Terminal Alkynes

2,2-Diorgano-l-alkenylboronates are made by bromoboration of a terminal alkyne to form a *β*-bromo-1-alkenylboronic ester;[52] this is followed by the palladium-catalyzed displacement of the *β*-halogen using organozinc reagents which proceeds with retention of configuration (Figure 1.11).[53]

Haloboranes add to terminal alkynes in a *cis anti*-Markovnikov manner; however, the bromoboration of acetylene itself provides the trans adduct which gives the corresponding (*E*)-1-alkenylborates by the reaction with organozinc halides (Figure 1.12).[54] The addition of tribromoborane to acetylene gives the *cis*-adduct which then isomerizes to the *trans*-isomer during isolation.

1.1.4 Organosilicon Compounds in Coupling Reactions

1.1.4.1 Introduction

The preeminence of palladium-catalyzed, cross-coupling reactions among methods of carbon-carbon bond formation arises from the highly successful development of the Stille-Migita-Kosugi coupling reactions of organostannanes[8e, 55] and the Suzuki-Miyaura coupling reactions of organoboranes.[33a, 33b] Both employ organometals that can be synthesized by several methods and are nonreactive in the absence of a catalyst. These characteristics are conducive to their application in the synthesis complex molecules wherein controlled bond construction and functional group compatibility are vital. However, certain drawbacks to these methods, including the toxicity and high molecular

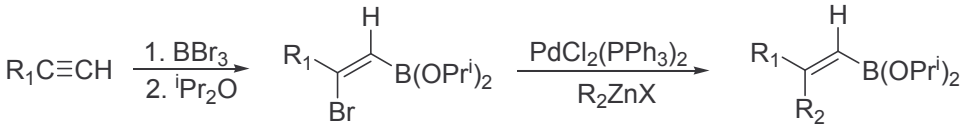


Figure 1.11: Haloboration of terminal alkynes

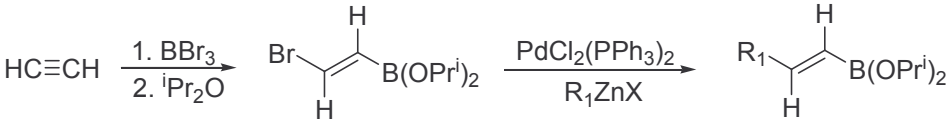


Figure 1.12: Preparation of (*E*)-1-alkenylborates

weight associated with tin and the limited stability and coupling efficiency of organoboranes.

The pioneering work of Hiyama demonstrated that organosilanes, when suitably functionalized and in the presence of a nucleophilic activator, can undergo cross-coupling reactions using palladium catalysis.[10a] This discovery stimulated investigations that revealed the utility of chloro- and fluorosilanes[56] and alkoxysilanes[57] as cross-coupling partners with a variety of electrophiles. A common limitation of the aforementioned silicon based coupling reactions is the harsh conditions (high temperatures and long reaction times) that are usually necessary. Because of the small electronegativity difference between silicon and carbon, the nucleophilic component in these reactions is relatively weak, transmetallation is the rate-limiting step in these cross-couplings. In addition, the ideal silicon moiety should be

(1) low molecular weight;

(2) easily synthesized;

(3) stable toward many reaction conditions;

(4) readily activated and converted to harmless byproducts.

1.1.4.2 Mechanism

Results from Hiyama,[10, 56] Denmark,[58] Deshong,[59] and others[60] have shown palladium-catalyzed, fluoride-promoted reactions of silicon derivatives to be viable alternatives to the Stille and Suzuki coupling methodologies. The commonly accepted mechanism, initially proposed by Hiyama and Hatanaka, involves three steps (Figure 1.13).[61]

The first step involves oxidative addition of the aryl halide to the palladium(0) complex. In the second step, transmetallation of the arylpalladium complex with the anionic arylsilicate occurs. Finally, the cross-coupled product is produced and the palladium(0) catalyst regenerated through reductive elimination of the bis(aryl)palladium(II) species. The key intermediate in the process, and the distinguishing feature of silicon-based couplings, is the pentacoordinate arylsilicate anion.[62] This species is formed by treatment of the corresponding tetracoordinate silane with an activating anion, typically fluoride.

It is notable that experimental evidence shows pentacoordinate silicates to be much more reactive than the corresponding tetracoordinate silane.[62] These results are supported by calculations, which show the positive charge on the central silicon atom is

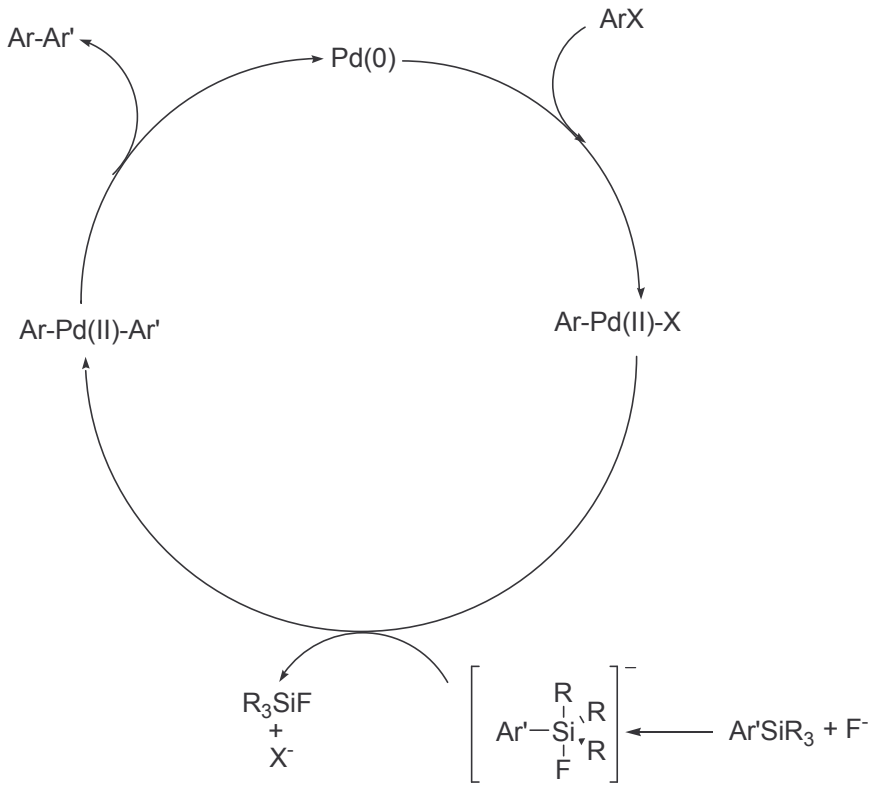


Figure 1.13: Mechamism of Pd-catalyzed couplings of organosilanes with aryl halides

maintained, or even increased, by coordination of the fifth ligand.[63, 64] This holds true, even with the addition of anionic ligands such as fluoride, hydroxide, or hydride.[62] The residual positive charge on silicon, in addition to lengthening the silicon–ligand bonds, accounts for the higher reactivity of the pentacoordinate silicon species.[62]

1.1.4.3 Synthesis of Siloxanes

Like the corresponding preparations of Stille and Suzuki reagents, the synthesis of siloxanes falls into one of two categories. The first, being of an aryl Grignard or aryllithium reagent with a silicon electrophile (Figure 1.14). The trend in reactivity observed is that the organolithium reagents are more reactive than the corresponding Grignard reagents. However, this method fails for aryl halides bearing electrophilic substituents (i.e., esters and ketones).[65] An additional limitation is over addition of the organometallic reagent to silicon, displacing more than one ethoxy group.[66] The study revealed, however, that strict control of the reaction temperature suppressed the formation of di- and tri-arylated siloxanes. A wide range of substituted siloxanes were synthesized using Grignard and organolithium reagents.

The second method involves silylation of aryl iodides by triethoxysilane ($(EtO)_3SiH$) in the presence of a palladium catalyst.[67] This method offers the advantage of tolerating a larger range of functional groups. Unfortunately, good yields are obtained only when electron-rich aryl iodides and bromides are used. Similar chemistry recently developed by Masuda et al. addresses this issue.[68] This silylation of aryl halides employs

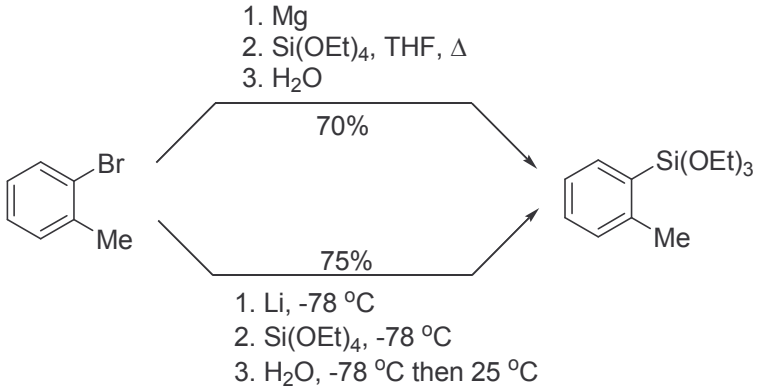


Figure 1.14: Preparation of arylsiloxanes from Mg and Li reagents

a rhodium catalyst and, allows for the preparation of an even wider range of substituted siloxanes (Figure 1.15). These conditions work for substrates bearing electron-withdrawing substituents such as the ester, as well as those that possess *ortho*-substitution, such as 2-iodoanisole.

1.2 Baylis-Hillman Reaction

1.2.1 General

Carbon-carbon bond formation is one of the most fundamental reactions in organic chemistry. The development of efficient and selective methods for the construction of carbon-carbon bonds has been and continues to be a challenging and exciting endeavor in organic synthesis.

Several carbon-carbon bond-forming reactions have been discovered and their applications in organic chemistry have also been well-documented in the literature. The most important ones include the aldol reaction,[69, 70] Reformatsky reaction,[71] Claisen rearrangement,[72] Friedel-Crafts reaction,[73, 74] Grignard reaction,[75] Diels-Alder reaction,[76, 77] Wittig reaction,[78] Heck reaction,[79] Suzuki coupling,[33] and the Grubb's ring closing metathesis.[80, 81] Very recent developments in organic chemistry have clearly established that atom economy, selective (chemo-, regio-, and stereo-) transformations and catalytic processes have become essential requirements for the development of any efficient synthetic reaction.[82-85]

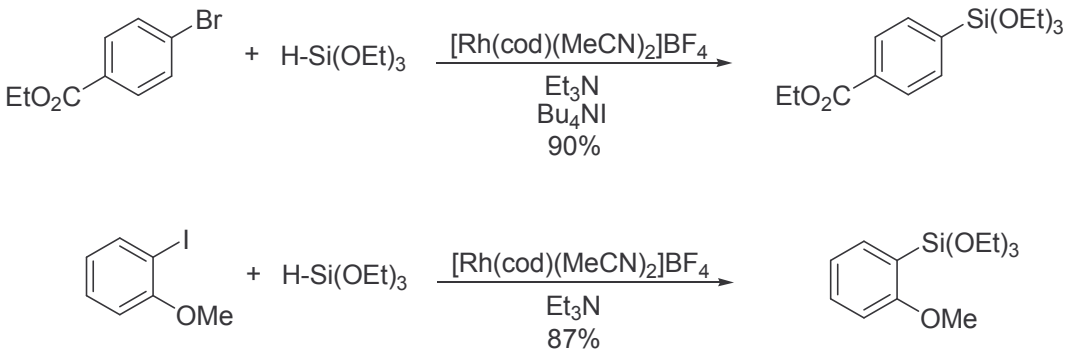


Figure 1.15: Preparation of arylsiloxanes from Rh-catalyzed silylation

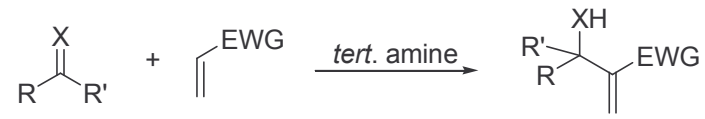
The Baylis-Hillman reaction is an efficient carbon-carbon bond forming reaction. It involves the coupling of activated alkenes with carbon electrophiles in the presence of a tertiary amine. It has all the basic properties that an efficient synthetic method should have *i.e.* it is selective (chemo, regio, diastereo and enantio),[86] economical in atom count,[85] requires mild conditions, and provides synthetically useful multifunctional molecules.

1.2.2 Definition and Origin

The Baylis-Hillman reaction, originating from a German patent,[87] may be broadly defined as *"a reaction that results in the formation of a carbon-carbon bond between the α-position of activated alkenes and carbon electrophiles containing electron-deficient sp^2 carbon atom under the influence of a suitable catalyst, particularly a tertiary amine, producing multifunctional molecules"* (Figure 1.16).

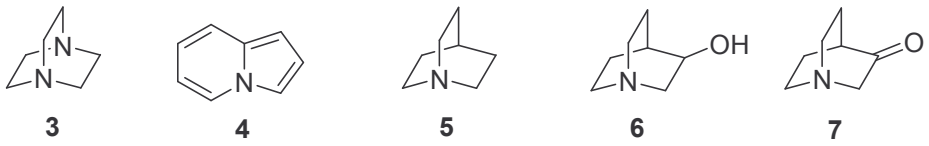
The Baylis-Hillman reaction involves three components: an activated alkene, an electrophile and a tertiary amine. Research over the last decade has resulted in considerable expansion of the reaction in terms of all the three essential components. Though Baylis and Hillman originally used DABCO (diazabicyclo[2.2.2]octane) **(3)**, pyrrocoline **(4)**, quinuclidine **(5)**, 3-HQD **(6)**, and 3-quinuclidone **(7)** as catalysts (Figure 1.17), DABCO (1) has become the catalyst of choice.[87-91]

A variety of activated alkenes such as alkyl vinyl ketones,[92-94] alkyl (aryl) acrylates,[95-97] acrylonitrile,[93, 98] vinyl sulfones,[99] acrylamides,[100] allenic esters,[101, 102] vinyl



R = aryl, alkyl, heteroaryl; R' = H, COOR, alkyl
X = O, NCOOR, NTs, NSO_2Ph
EWG = electron withdrawing group: COR, CHO,
CN, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh etc.

Figure 1.16: Baylis-Hillman reaction



3 **4** **5** **6** **7**

Figure 1.17: Common bases in Baylis-Hillman reaction

sulfonates,[103] vinyl phosphonates,[104] and acrolien[105, 106] couple with a number of carbon electrophiles to provide a wide range of multifunctional molecules (Figure l.18). However, the activated alkenes having α-substituents such as crotononitrile,[107, 108] crotonic acid esters,[107] and less reactive alkenes such as phenylvinyl sulfoxide[109] require high pressure to participate in this reaction.

Aldehydes[87-90] have been the primary source of electrophiles; thus, various aliphatic, aromatic, and hetero-aromatic aldehydes have been extensively employed in obtaining interesting Baylis-Hillman adducts. Also α-keto esters,[110-112] nonenolizable 1,2-diketones,[106] aldimine derivatives,[113-115] fluoroketones,[116] and activated alkenes[117-120] have also been employed as electrophiles in this reaction. However, simple ketones require high pressure to undergo Baylis-Hillman reaction.[105, 107] In the absence of an added electrophile, the activated alkenes such as vinyl ketones, acrylonitrile, acrylic esters *etc.* themselves can act as electrophiles in these Baylis-Hillman processes. Vinyl ketones and acrylonitrile undergo Michael type dimerization under the catalytic influence of DABCO to provide the corresponding dimmers (Figure 1.19).[121]

1.2.3 Mechanism

The mechanism of the reaction is believed to proceed through the Michael-initiated addition-elimination sequence. The most generally accepted mechanism of the reaction is illustrated in Figure 1.20 (Path I), using the reaction between methyl acrylate (as an activated olefin) and benzaldehyde (as an electrophile) under the catalytic influence of DABCO **(3)**, as a model case.[88-91, 122-124]

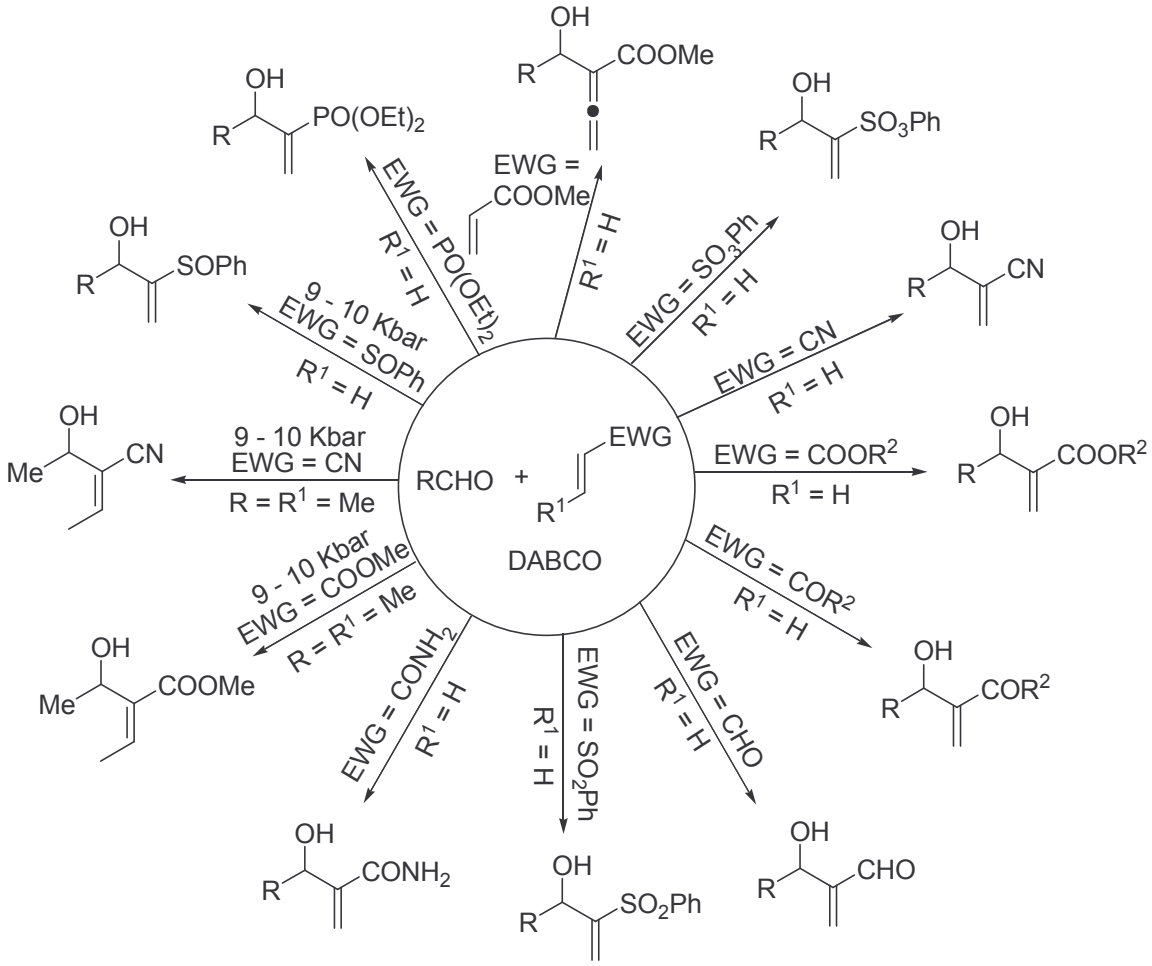


Figure 1.18: Scope of Baylis-Hillman reactions

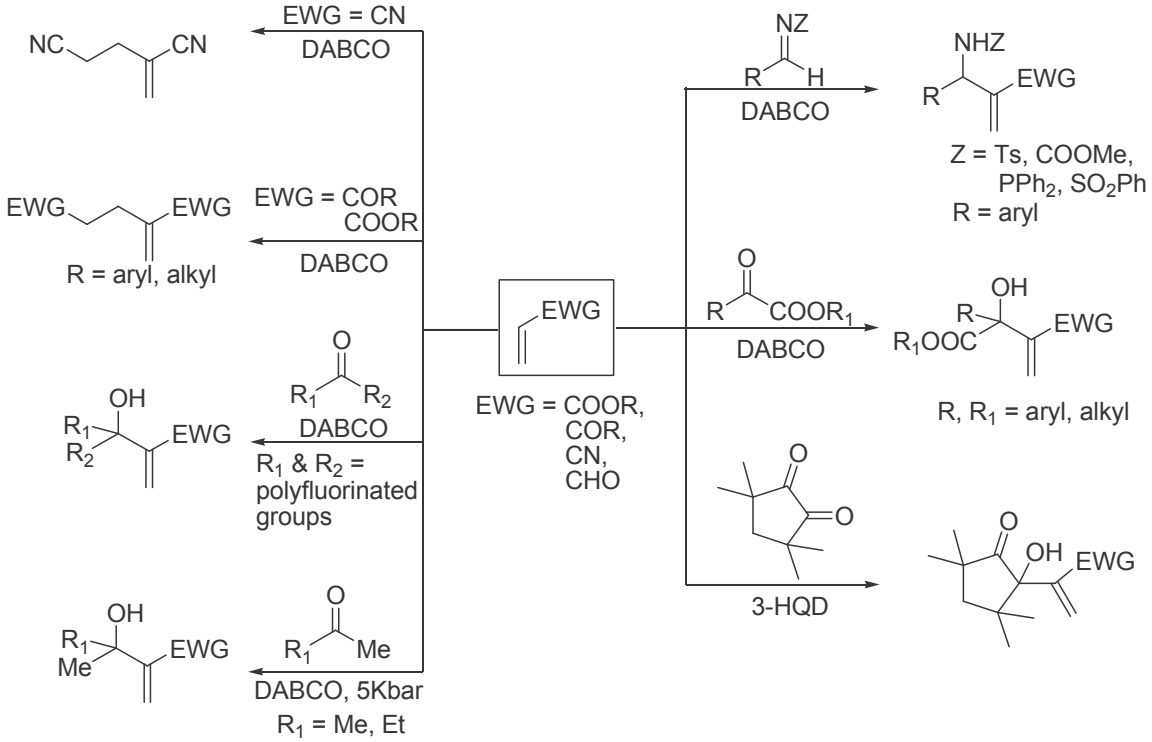


Figure 1.19: Scope of electrophiles in Baylis-Hillman reactions

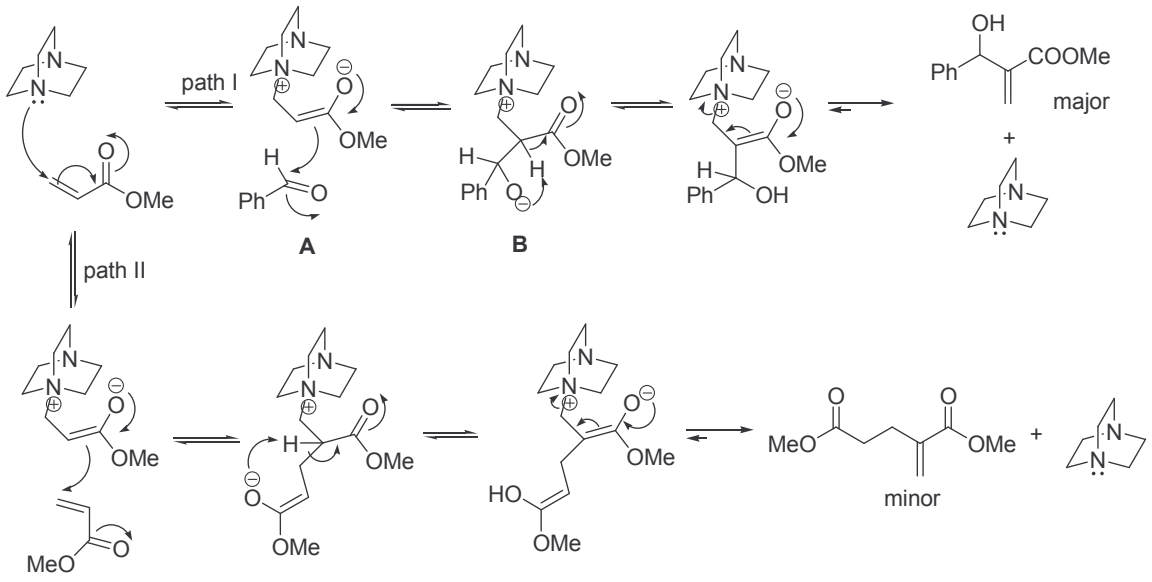


Figure 1.20: Mechanism of Baylis-Hillman reaction

The first step in this catalytic cycle involves the Michael-type nucleophilic addition of the tertiary amine to the activated alkene to produce a zwitterionic enolate **A**, which makes a nucleophilic attack onto the aldehyde in an aldol fashion to generate zwitterion **B**. Subsequent proton migration and release of the catalyst provide the desired multifunctional molecule. In the case of reactive activated alkenes (such as alkyl vinyl ketones), Michael-type dimers are formed as side products because they themselves act as electrophiles (Figure 1.20, Path II).

1.3 Indium Mediated Reactions

1.3.1 Introduction

Even though indium, named for the luminous indigo line in its spectrum, was discovered in 1863 by Reich,[125] it has only recently emerged as one of the metals of interest in organic synthesis. The low natural abundance of indium may have been a deterrent in explorations involving this metal. Indium, however, enjoys a superior position among other metals as far as its chemical behaviour is concerned and this can be attributed to the following properties:

1. Indium metal is unaffected by air or oxygen at ambient temperature, this being a major advantage over most of the other metals;
2. Indium is practically unaffected by water, unlike other metals such as Li, Na, etc;
3. The first ionization potential of indium (5.8 eV) is on par with the alkali metals, for example, lithium or sodium (~ 5 eV), and quite low when compared to zinc

(9.4 eV), tin (7.3 eV) and magnesium (7.6 eV). Indium is therefore an ideal candidate for single electron transfer (SET) reactions;

4. Indium exhibits low heterophilicity in organic reactions, which makes it a suitable reagent for mediating C–C bond-forming reactions where it can tolerate oxygen and nitrogen functionalities. In addition, indium reagents display low nucleophilicity, thus permitting chemoselective transformations at groups with similar reactivity;
5. Most importantly, the element is without any apparent toxicity, whereas lead and tin reagents are highly and moderately toxic, respectively.

In the late 1980s, Araki and co-workers introduced indium metal for the first time in the Barbier reactions.[126] Since then, indium has been used to mediate a range of reactions which are synthetically useful, amongst which, the carbon–carbon bond-forming reaction occupies a pivotal position. Indium mediated carbon–carbon bond-forming reactions can be broadly classified into the following categories:

(1) Allylation reactions

(2) Palladium-catalyzed reactions

(3) Propargylation reactions

(4) Reformatsky reactions

(5) Aldol reactions

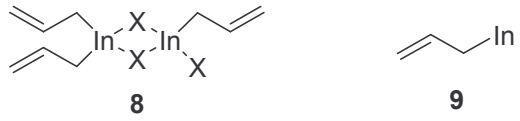
(6) Miscellaneous reactions

1.3.2 Indium Mediated Allylation Reaction

Indium-mediated allylation reactions in highly polar organic solvents such as THF or DMF proceed through an indium sesquihalide, $Allyl_3In_2X_3$ **(8)**.[127] Further treatment with KI or KBr enables the isolation of dialkylindium halides. In reactions under aqueous conditions, the existence of allylindium **(9)** as a transient, but discrete, intermediate was established by Chan and Yang (Figure 1.21).[128]

1.3.2.1 Allylation Reactions of Compounds with Carbon-Oxygen Multiple Bonds

A variety of ketones and aldehydes undergo indium-mediated allylation in DMF to afford the homoallylic alcohols in good yields. Allylic iodides and bromides are equally reactive, but the reactivity of allyl chloride is markedly diminished. Even the less reactive allylic phosphates react with carbonyl compounds in the presence of indium and indium iodide, but ester and cyano groups are not susceptible to allylation under these conditions. It is worthy to note that substrates with active hydrogen such as ethyl acetoacetate and salicylaldehyde can be allylated using indium in good yields. With *α,β*-unsaturated aldehydes, the addition takes place in a 1,2-fashion (Figure 1.22).[126] Indium can also mediate the allylation of aldehydes and ketones in water.[129] The indium-mediated allylation of aldehydes and ketones in ionic liquids has no significant advantage over similar reactions in conventional solvents.[130] Enantioselectivity can also be induced in indium-mediated reactions using external chiral ligands.[131]



8 **9**

Figure 1.21: Indium sesquihalide and transient allylindium

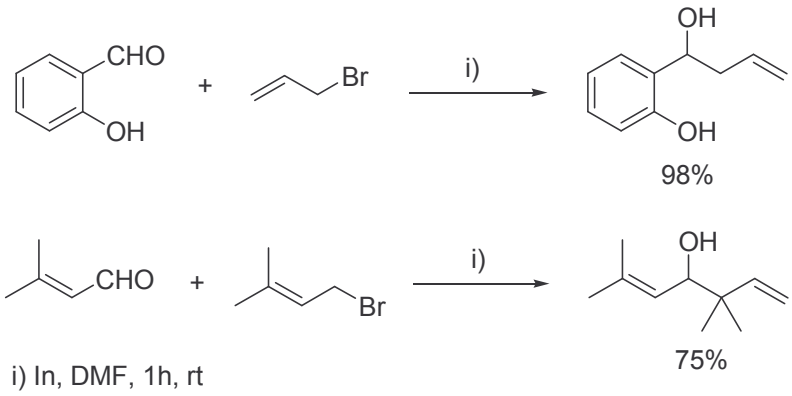


Figure 1.22: Allylation of salicylaldehyde and α, β-unsaturated aldehyde

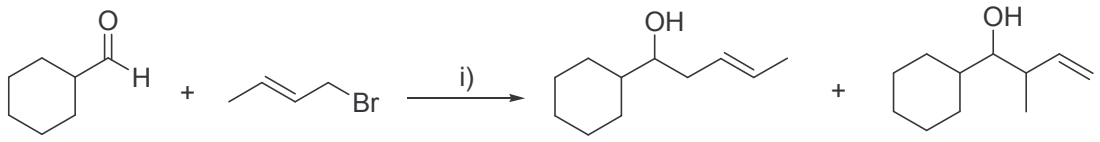
In general, allylation of an aldehyde with a γ-substituted allylic indium reagent occurs regioselectively at the γ-position to afford the γ-homoallylic alcohol in the absence of a sterically-bulky substituent at the carbonyl or allyl bromide. Loh succeeded in synthesizing the α-homoallylic alcohol via indium-mediated allylation without the use of a sterically-hindered substituent (Figure 1.23).[132] Interestingly, the solvent plays an important role in determining the regioselectivity in these reactions. While water (10 M) and water/dichloromethane (10 m/10 m) exhibit excellent α-selectivity, DMF, ethanol, THF and water (0.5 m) show exclusive γ-selectivity.

1.3.2.2 Allylation Reactions of Compounds with Carbon-Nitrogen Multiple Bonds

Aldimines can be allylated in a simple Barbier-type reaction using allyl bromide and indium powder in THF to afford the homoallylic amines.[133] A variety of other C-N multiple bonds containing compounds such as hydrazones derived from aromatic aldehydes and ketones,[134] oxime ethers derived from 2-pyridinecarboxaldehyde and glyoxylic acid,[135] pyridinium salts,[136] and activated nitriles,[137] all react with allylindium compounds (Figure 1.24).

1.3.2.3 Allylation Reactions of Compounds with Carbon-Carbon Multiple Bonds and Other Functional Groups

Hydroxyl-bearing cyclopropenes undergo clean allylindation with allylindium reagents in both organic and aqueous media, in which chelation of the hydroxyl group to indium plays a central role (Figure 1.25).[138] The allylindation of non-activated carbon–



DMF (10M) 65% (0:100)
H_2O (10M) 85% (99:1)

i) In, Solvent

Figure 1.23: Preparation of α-homoallylic alcohol via indium-mediated allylation

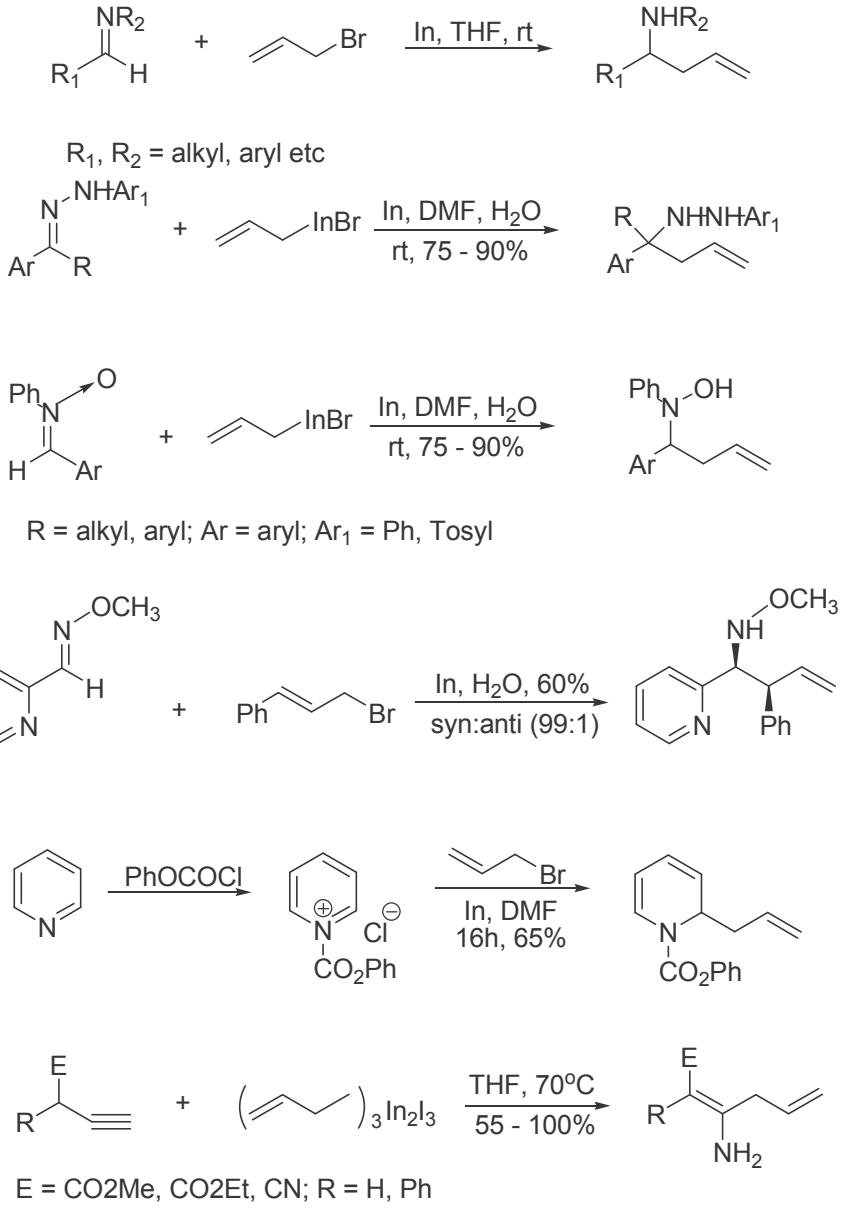


Figure 1.24: Allylation reactions with carbon-nitrogen multiple bonds

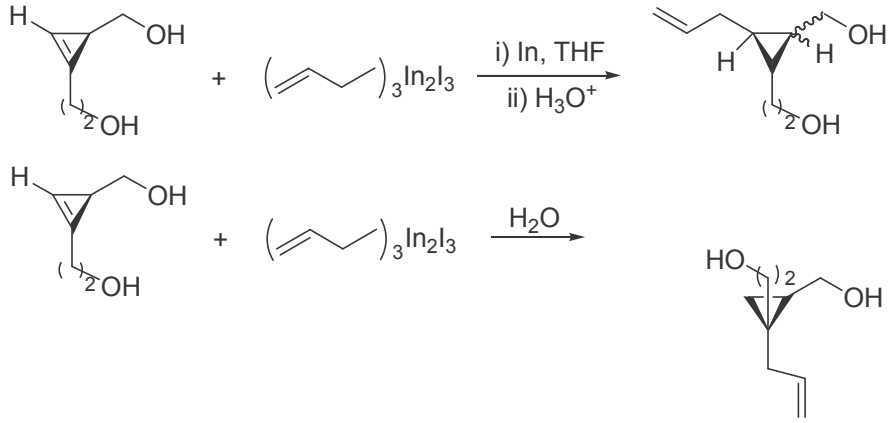


Figure 1.25: Allylindation of hydroxyl-bearing cyclopropenes with allylindium reagents

carbon double bonds of norbornenols proceeds with high regio- and stereoselectivity to afford the allylated products, together with iodinated and oxygenated products.[139] The product distribution can be controlled by changing the reaction solvent. In these reactions, the regio- and stereochemistry of the addition of the indium reagents is highly regulated via chelation with the neighbouring hydroxyl group (Figure 1.26).

The reaction of allylic indium sesquihalides to allenols has been found to proceed with high regio- and stereoselectivity.[140] The reaction of unactivated terminal alkynes with allyl bromide and indium in THF at room temperature produces the 1,4-dienes via regioselective addition.[141] Acetals and ketals undergo indium-mediated allylation and propargylation reactions with various allyl or propargylbromides in aqueous media to provide the corresponding homoallylic (and allenylic) or homopropargylic alcohols, respectively, in moderate to good yields.[142] Allylindium, prepared from allyl bromide and indium metal in THF, reacts with terminal epoxides at room temperature to afford the corresponding bishomoallyl alcohols in excellent yields and with good regioselectivity (Figure 1.27).[143]

1.4 Scope of This Thesis

This thesis focuses on two newly discovered novel synthetic methods involving organometallic catalysts and reagents. The novel synthetic methods include: (a) palladium-catalyzed cross couplings of allyl acetates and Baylis-Hillman acetate adducts with organosiloxanes; and (b) diastereoselective synthesis of *cis* and *trans* α-methylene-γ-

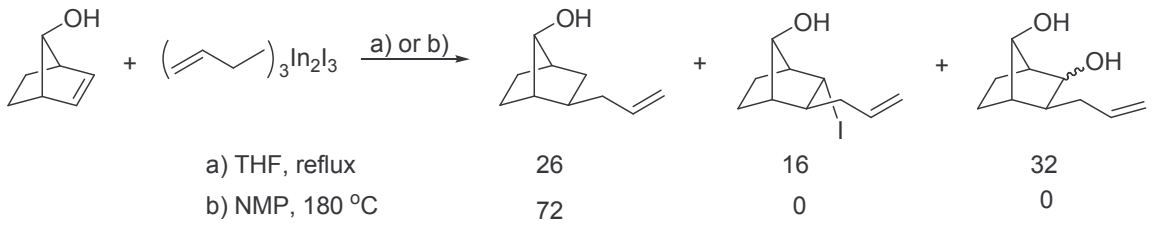


Figure 1.26: Allylindation of non-activated carbon–carbon double bonds of norbornenols

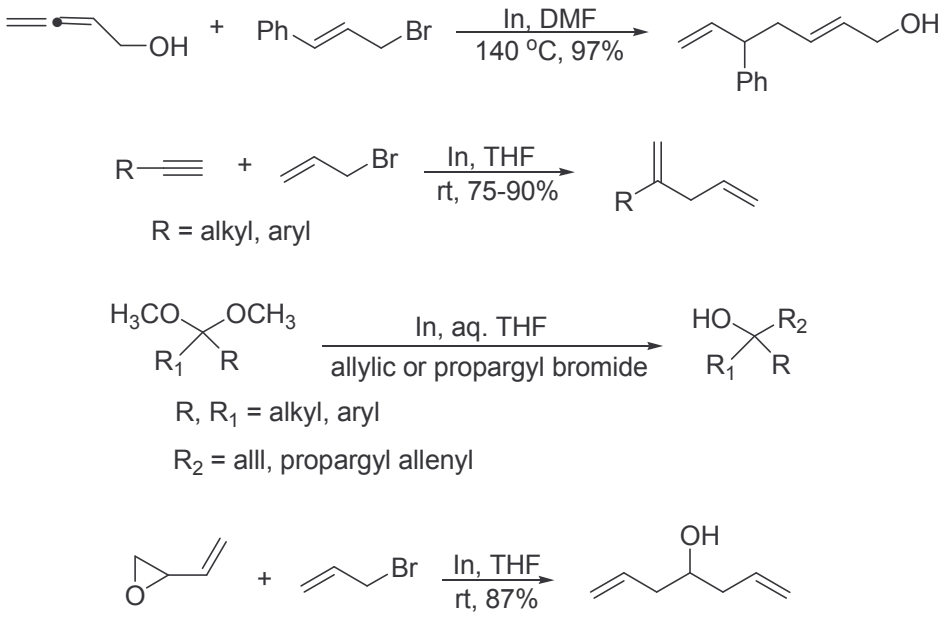


Figure1.27: Allylation with other functional groups

lactones. Another important part is the application of some of the methods in the total synthesis of eupomatilone 2. A brief description of palladium-catalyzed cross coupling reactions, organoboron and organosilane reagents in organic synthesis, Baylis-Hillman chemistry, and indium metal in organic synthesis has been presented in this chapter because they are fundamental to the new chemistry discussed in this thesis.

Chapter 2. Palladium Catalyzed Cross Couplings of Allyl Acetate and Baylis-Hillman Acetate Adducts with Organosiloxanes

2.1 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.[56] 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.[57-59] Treatment of aryltrimethoxysilane with an equivalent amount of tetrabutylammonium fluoride (TBAF) results in the *in situ* formation of hypervalent fluorosilicate anion (Figure 2.1).[59, 144, 145] Subsequent coupling of the organosilicate with aryl halide or triflate (or other electrophiles) in the presence of a Pd(0) catalyst affords the cross-coupled product.

Compared to many other organometallic reagents, organic 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, the cross-coupling reactions of allyl acetate and Baylis-Hillman acetate adducts with silicon reagents was explored using palladium catalysis.

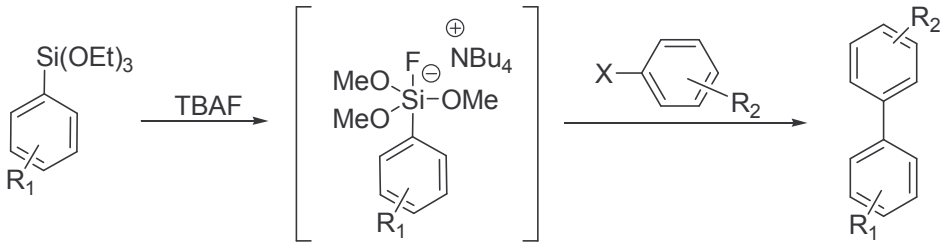


Figure 2.1: Coupling of siloxanes with electrophiles.

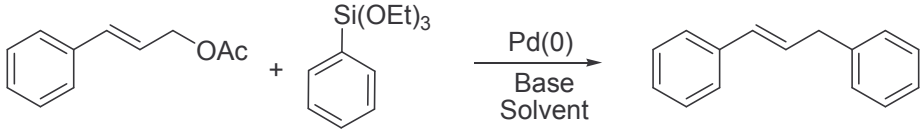
Herein, the newly developed palladium-catalyzed coupling reactions of organosiloxanes with allyl acetate and Baylis-Hillman acetate aducts are described.

2.2 Results and Discussion

2.2.1 Optimization of Reaction Conditions

The coupling reaction of cinnamyl acetate and phenyltriethoxysilane was chosen as a model to define the optimum reaction conditions (Table 2-1). When the reaction was performed in THF/H_2O (20:1) in the presence of 3 mol % of $Pd_2(dba)_3$ and 2 equivalent of KF at 50 ^oC for five hours, only 23% yield of desired 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 cinnamyl acetate (0.5 mmol) with phenyltriethoxysilane (0.65 mmol) in the presence of 3 mol % of $Pd_2(dba)_3$ and two equivalents of TBAF in THF yielded 65% of the desired cross-coupled product.

Table 2-1: 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	23
2	$Pd(OAc)_2$	KF	THF/H_2O[c]	50 / 5	trace
3	$Pd_2(dba)_3$	*n*-Bu_4NF	THF	50 / 2	65
4	$Pd_2(dba)_3$	*n*-Bu_4NF	Toluene	50 / 2	68
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	87
7	$Pd(OAc)_3$	*n*-Bu_4NF	PEG	rt / 3	87
8	$Pd(OAc)_2$[2nd]	*n*-Bu_4NF	PEG	rt / 3	83
9	$Pd(OAc)_2$[3rd]	*n*-Bu_4NF	PEG	rt / 3	80

[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.

To increase the yield of the desired product, other conditions were evaluated. In toluene, a slightly better yield (68%) of desired product was obtained. Due to the great interest in non-conventional solvents, the reactions were also carried out in an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ($bmimBF_4$) (Table 2-1, entry 5). 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, an excellent yield was obtained using $Pd_2(dba)_3$ as catalyst at room temperature. Due to the fact of PEG is not miscible with diethyl ether, we attempted to recycle the expensive catalyst. However, $Pd_2(dba)_3$ totally lost its activity after the product was extracted from the PEG system. Fortunately, $Pd(OAc)_2$ produced similar yield as $Pd_2(dba)_3$ and, more importantly, the catalytic system could be recycled at least two more times without significant loss of its activity. For example, The second and third subsequent reactions afforded the desired product in 83% and 80% respectively.

On the basis of the results summarized in Table 2-1, the optimal reaction conditions for coupling of phenyltriethoxysilane with allyl acetate were found to be 5 mol % of $Pd(OAc)_2$ and two equivalents of TBAF in PEG-600 at room temperature.

2.2.2 Coupling of Allyl Acetates with Organosiloxanes

With an optimal set of reaction conditions established, the scope of the reaction was then surveyed employing a variety of arylsiloxane derivatives and the results are summarized in Table 2-2. The yields of arylated products were generally excellent with

Table 2-2: Coupling of cinnamyl acetate with various organosiloxanes

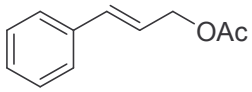
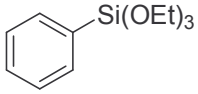
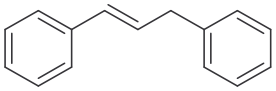
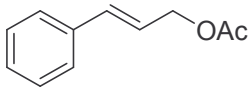
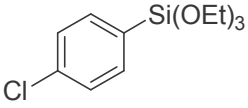
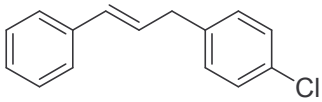
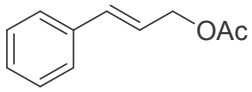
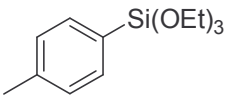
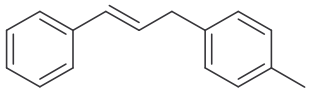
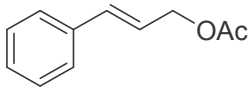
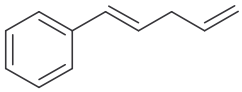
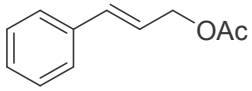
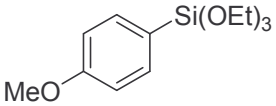
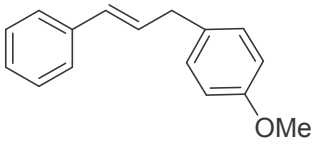
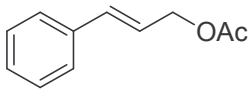
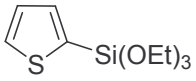
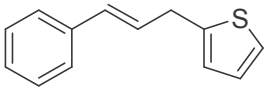
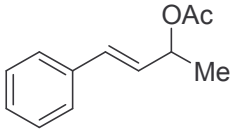
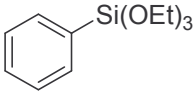
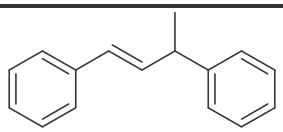
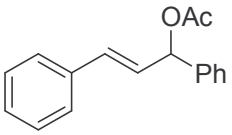
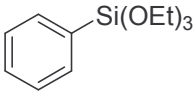
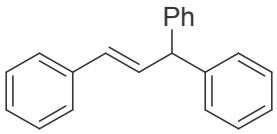
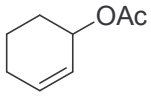
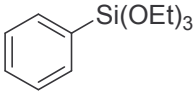
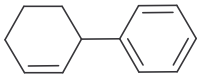
Entry	Alyl acetate	Organosiloxane	Product	Yield (%)[a]
1			 2-201	87
2			 2-202	83
3			 2-203	92
4			 2-204	30[b]
5			 2-205	91
6			 2-206	47

Table 2-2 (Continued)

Entry	Allyl acetate	Organosiloxane	Product	Yield (%)
7			 2-207	87
8			 2-208	62
9			 2-209	51

[a] Isolated yield;

[b] Reaction was kept at 50 °C.

siloxanes having methyl and methoxy substituents on the phenyl group (Table 2-2, entries 3 and 5). Heteroarylsiloxane gave 47% moderate yield (Table 2-2, entry 6). For vinylsiloxane, however, no reaction occurred at room temperature. A 30% yield was obtained when the reaction was kept at 50 ^{o}C. This coupling reaction also worked well with siloxanes having chlorine on the phenyl group. A variety of allyl acetates coupled with phenyltriethoxysilane and the results were summarized in Table 2-2 (entries 7-9).

The coupling reaction worked well with (*E*)-4-phenylbut-3-en-2-yl acetate (Table 2-2, entry 7) and (*E*)-1,3-diphenylallyl acetate (Table 2-2, entry 8). The regioselectivity of the coupling reaction was excellent. Only one isomer was obtained in both cases. Interestingly, cyclohex-2-enyl acetate also gave a moderate yield (Table 2-2, entry 9).

2.2.3 Coupling of Baylis-Hillman Acetate Adducts with Organosiloxanes

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.[88, 89] The synthesis and reaction mechanism have been discussed in Chapter 1. Because the product of Baylis-Hillman reaction is a multi-functionalized allyl alcohol, the cross-coupling reaction of organosiloxane reagents with acetates of Baylis-Hillman adducts was investigated.

The optimized conditions afforded 85% yield of the desired product when methyl 3-acetoxy-3-phenyl-2-methylenepropanoate coupled with phenyltriethoxysilane (Figure

2.2). Interestingly, 3 mol % $Pd_2(dba)_3$ gave better result with 91% yield. So $Pd_2(dba)_3$ was used in the coupling reactions instead of $Pd(OAc)_2$.

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 surveyed. The results are summarized in Table 2-3 (entries 1-9). Notably, the reaction is only slightly influenced by the substituents and their substitution patterns on the aromatic ring in 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.

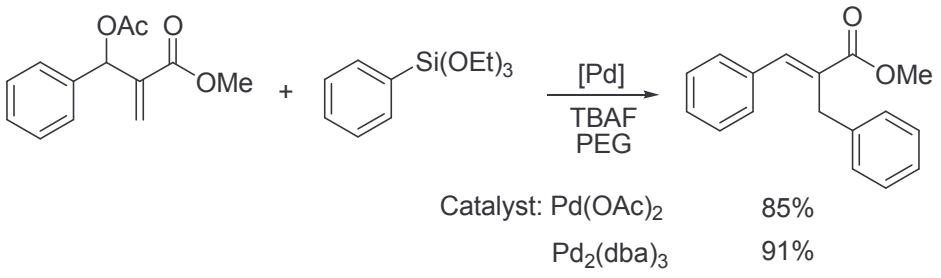
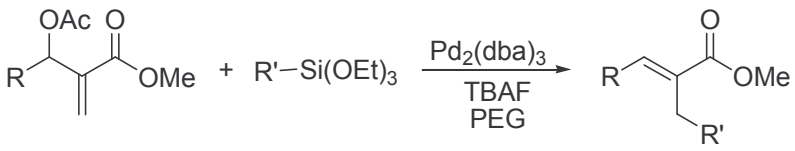


Figure 2.2: Selection of catalyst

Table 2-3: Coupling of various Baylis-Hillman Acetate adducts with different organosiloxanes



Entry	R	R'	Product	Yield (%)	E/Z
1	Phenyl	Phenyl	**2-301**	92	93/7
2	*p*-Chlorophenyl	Phenyl	**2-302**	91	99/1
3	*p*-Tolyl	Phenyl	**2-303**	89	95/5
4	Naphthyl	Phenyl	**2-304**	87	94/6
5	2-Furyl	Phenyl	**2-305**	78	99/1
6	*p*-Methoxyphenyl	Phenyl	**2-306**	94	99/1
7	2-Chlorophenyl	Phenyl	**2-307**	86	92/8
8	*n*-Octyl	Phenyl	**2-308**	85	90/10
9	*p*-Nitrophenyl	Phenyl	**2-309**	62	96/4
10	Phenyl	*p*-Tolyl	**2-310**	86	97/3
11	Phenyl	*p*-Chlorophenyl	**2-311**	92	98/2
12	Phenyl	2-Thiofuryl	**2-312**	70	93/7

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. 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 2-3 (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.

2.3 Conclusions

An efficient palladium-catalyzed coupling reaction of aryltrialkoxysilanes with various allyl acetates and Baylis-Hillman acetate adducts has been developed. PEG was shown to be an effective solvent and the $Pd(OAc)_2$ catalyst could be recycled at least two times without loss of its activity. The reaction conditions are mild and the reaction yields are good to excellent. For the couplings of Baylis-Hillman acetate adducts with organosiloxanes, the stereoselectivity is excellent with the *E* isomer formed as the major product.

2.4 Experimental Section

Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 250 MHz Bruker or 300 MHz Varian spectrometer in $CDCl_3$ unless otherwise noted. 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), br s (broad singlet). Thin-layer chromatography (TLC) was performed with the compounds being identified in one or more of the following manners: UV (254 nm), iodine, or PMA. Products were purified by flash chromatography using silica gel (60 Å, 230–400 mesh) with hexanes / ethyl acetate as eluent. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

All glassware was oven dried at 120 ^{o}C and flushed with dry nitrogen. All reactions were carried out under a nitrogen atmosphere. Organotriethoxysilanes, tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF), $Pd(OAc)_2$ and $Pd_2(dba)_3$ were purchased from Aldrich and used as received.

2.4.1 General Experimental Procedure for The Synthesis of Baylis-Hillman Acetate Adducts

The Baylis-Hillman alcohols were prepared from aldehydes and methyl acrylate in the presence of tertiary amine DABCO. At room temperature, the aldehyde (13.5 mmol, 1 equiv.) was added to a stirred mixture of methyl acrylate (20 mmol. 1.3 equiv.)

and DABCO (2.0 mmol, 0.13 equiv.) under an air atmosphere. The reaction mixture was stirred until the reaction was complete (monitored by GC). After completion of the reaction, methylene chloride (30 mL) was added. The solution was washed first with 30 mL of HCl (10%) and then with 30 mL of water. The solvent was removed under vacuum. Alpha-hydroxylated acrylic esters were isolated by flash chromatography.

The Baylis-Hillman acetate adducts were prepared by mixing the relevant Baylis-Hillman alcohol with acetic anhydride in pyridine. The products were purified by flash chromatography and identified by comparison of their spectroscopic properties with those of samples prepared according to known procedures.[88, 89]

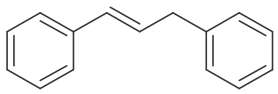
2.4.2 General Procedure For The Cross-Coupling Reactions Utilizing Allylic Acetates

To a solution of 1.0 mmol of the allylic acetate, 0.05 mmol of $Pd(OAc)_2$, and 2.0 mmol of arylsiloxane in 3 mL of PEG-600 was added 2.0 mmol of TBAF via syringe. The reaction mixture was degassed to remove oxygen and then flushed with nitrogen. The reaction mixture was stirred at room temperature for 5 hours and then extracted with diethyl ether (4 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated in vacuo. Purification of the residue by flash chromatography yielded the cross-coupled adduct. The spectral data of the individual compounds are reported below.

2.4.3 General Procedure For The Cross-Coupling Reactions Utilizing Baylis-Hillman Acetate Adducts

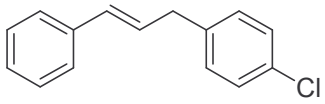
To a solution of the acetate of a Baylis-Hillman adduct (0.5 mmol), organosiloxane (0.65 mmol), 3 mol % of $Pd_2(dba)_3$ in 3 ml of PEG-600 was added 2.0 ml of TBAF in THF (1.0 m, 1.0 mmol) via syringe. The system was evacuated and then purged with nitrogen gas. The reaction mixture was stirred at the indicated temperature for 4-8 h. After completion of the reaction (monitored by TLC), the mixture was extracted with Et_2O (4 x 5 mL), and the combined organic layer was dried over anhydrous $MgSO_4$, and the mixture 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.

2.4.4 Analytical data



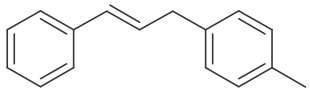
2-201

^{1}H NMR ($CDCl_3$): δ 7.36 – 7.16 (m, 10H), 6.45 (d, 1H, J = 15.9 Hz), 6.35 (dt, 1H, J_1 = 6.3 Hz, J_2 = 15.9 Hz), 3.53 (d, 2H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$): δ 147.3, 140.1, 137.4, 131.0, 129.2, 128.6, 128.5, 127.1, 126.1, 126.0, 39.3. Anal. Calcd. for $C_{15}H_{14}$: C, 92.74; H, 7.26; Found: C, 92.69; H, 7.22.



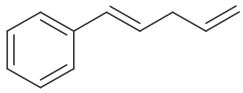
2-202

^{1}H NMR ($CDCl_3$): δ 7.36 – 7.13 (m, 9H), 6.44 (d, 1H, J = 16.2 Hz), 6.28 (dt, 1H, J_1 = 6.6 Hz, J_2 = 16.2 Hz), 3.48 (d, 2H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 138.5, 137.2, 131.9, 131.4, 130.0, 128.5, 127.2, 126.1, 38.6. Anal. Calcd. for $C_{15}H_{13}Cl$: C, 78.77; H, 5.73; Found: C, 78.71; H, 5.77.



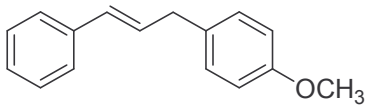
2-203

^{1}H NMR ($CDCl_3$): δ 7.35 – 7.08 (m, 9H), 6.43 (d, 1H, J = 15.6 Hz), 6.32 (dt, 1H, J_1 = 6.3 Hz, J_2 = 15.6 Hz), 3.49 (d, 2H, J = 6.3 Hz), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 137.5, 137.0, 135.6, 130.8, 129.5, 129.1, 128.5, 128.4, 127.0, 126.1, 38.9, 21.0. Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74; Found: C, 92.25; H, 7.71.



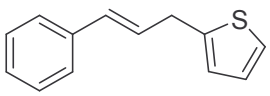
2-204

^{1}H NMR ($CDCl_3$): δ 7.20–7.40 (m, 5 H), 6.45 (d, 1H, J = 15.6 Hz), 6.24 (dt, 1H, J_1 = 15.6 Hz, J_2 = 6.4 Hz), 5.92 (m, 1H), 5.10 (m, 2 H), 2.99 (t, 2H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ 136.5, 130.8, 128.5, 127.0, 115.6, 37.0. Anal. Calcd. for $C_{11}H_{12}$: C, 91.61; H, 8.39; Found: C, 91.48; H, 8.31.



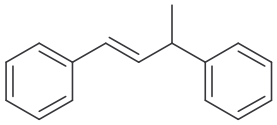
2-205

^{1}H NMR ($CDCl_3$): δ 7.35 – 7.13 (m, 7H), 6.87 – 6.83 (m, 2H), 6.42 (d, 1H, J = 15.9 Hz), 6.33 (dt, 1H, J_1 = 6.1 Hz, J_2 = 15.9 Hz), 3.77 (s, 3H), 3.47 (d, 2H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 158.0, 137.4, 132.1, 130.6, 129.6, 129.5, 128.4, 127.0, 126.0, 113.8, 55.2, 38.4. Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19; Found: C, 85.71; H, 7.13.



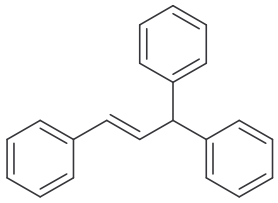
2-206

^{1}H NMR ($CDCl_3$): δ 7.38 – 7.16 (m, 6H), 6.95 (m, 1H), 6.87 (m, 1H), 6.52 (d, 1H, J = 15.6 Hz), 6.37 (dt, 1H, J_1 = 6.6 Hz, J_2 = 15.6 Hz), 3.74 (d, 2H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 131.3, 128.5, 128.3, 128.1, 127.3, 126.2, 123.8, 29.7. Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; Found: C, 77.81; H, 6.02.



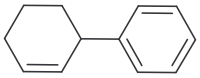
2-207

^{1}H NMR ($CDCl_3$): δ 7.38 – 7.15 (m, 10H), 6.39 (m, 2H), 3.63 (m, 1H), 1.46 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 145.6, 137.5, 135.2, 128.7, 128.5, 128.4, 127.9, 127.3, 127.0, 126.5, 126.2, 126.1, 42.5, 21.2. Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74; Found: C, 92.15; H, 7.67.



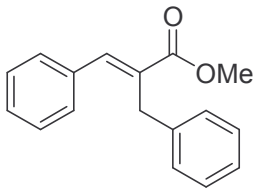
2-208

^{1}H NMR ($CDCl_3$): δ 7.37 – 7.17 (m, 15H), 6.46 (d, 1H, J = 15.9 Hz), 6.36 (dt, 1H, J_1 = 6.3 Hz, J_2 = 15.9 Hz), 3.55 (d, 1H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$): δ 140.1, 137.4, 131.0, 129.2, 128.6, 128.5, 127.1, 126.2, 126.1, 39.3. Anal. Calcd. for $C_{21}H_{18}$: C, 93.29; H, 6.71; Found: C, 93.31; H, 6.65.



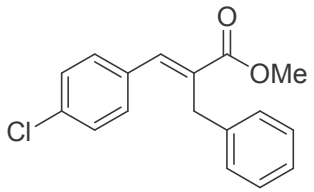
2-209

^{1}H NMR ($CDCl_3$): δ 7.33 – 7.15 (m, 5H), 5.91 – 5.85 (m, 1H), 5.74 – 5.68 (m, 1H), 3.43 – 3.38 (m, 1H), 2.12 – 1.50 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 146.6, 130.2, 128.3, 128.2, 127.7, 125.9, 41.9, 32.6, 25.0, 21.2. Anal. Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92; Found: C, 91.03; H, 8.82.



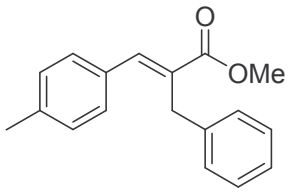
2-301

^{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.



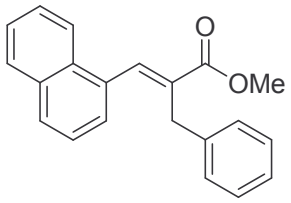
2-302

^{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.



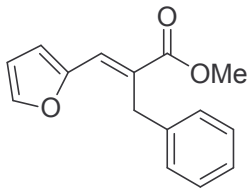
2-303

^{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.



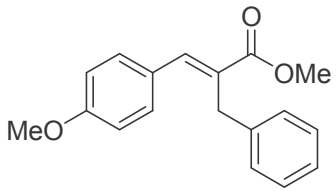
2-304

^{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);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.



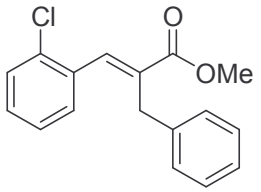
2-305

^{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 $C_{15}H_{14}O_3$: C, 74.36; H, 5.82; Found: C, 74.53; H, 5.68.



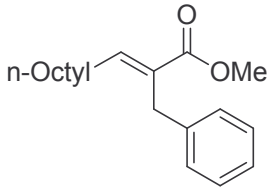
2-306

^{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.



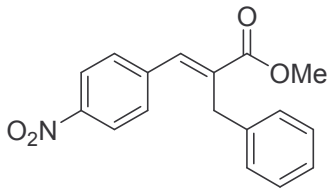
2-307

^{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.



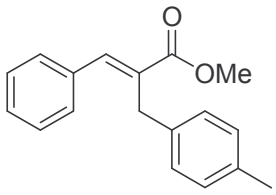
2-308

^{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.



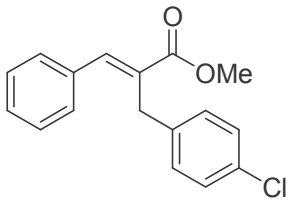
2-309

^{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.



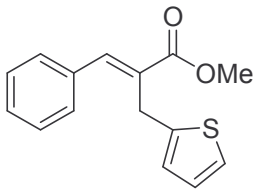
2-310

^{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.



2-311

^{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.



2-312

^{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.

Chapter 3: Synthesis of *cis* and *trans* α-Methylene-γ-lactones

3.1 Introduction

α-Methylene-*γ*-lactone derivatives have attracted attention over the years, since they are important functional components in a wide range of natural products.[146] The *α*-methylene-*γ*-lactone moiety, due to its propensity for Michael-type addition reactions, may play an important role in the biological activity of many naturally occurring products.[147] A variety of methodologies have been developed to synthesize *α*-methylene-*γ*-lactones; the most common method involves the reaction of allylic derivatives with carbonyl compounds.[148] This chemistry has been used successfully employing allyl derivatives of zinc,[148a] tin,[148b] chromium,[148c] and indium.[148d] Recently, substituted allylborates were also used for the synthesis of *α*-methylene-*γ*-lactones.[149] However, the reported procedures generally result in the generation of *cis*-*α*-methylene-*γ*-lactones. Paquette and Andino used organoindium chemistry to produce 3:2 ratio of *cis* and *trans* substituted *α*-methylene-*γ*-lactones.[148d] Liu utilized a tungsten-promoted, intramolecular alkoxycarbonylation to prepare a *trans*-*α*-methylene-*γ*-lactone.[150] However, available syntheses of *trans*-*α*-methylene-*γ*-lactones remain limited. In this chapter, we describe straightforward methods for preparing both *trans*- and *cis*-*α*-methylene-*γ*-lactones using Baylis–Hillman adducts as precursors.

The Baylis–Hillman reaction is one of the most versatile carbon–carbon bond-forming reactions in modern organic synthesis. It has drawn considerable attention in the past few decades due to its atom economy, mild reaction conditions, and functional group compatability.[88, 151] As part of our general interest in Baylis–Hillman chemistry, our lab recently developed a cross-coupling reaction of Baylis–Hillman adducts with bis(pinacolato)diboron that produces 3-substituted-2-alkoxycarbonylallylboronates;[152] these boronates readily react with aldehydes in the presence of a silica supported BF_3 catalyst[153] to form highly functionalized homoallylic alcohols in excellent yields (Figure 3.1).

3.2 Results and Discussion

The homoallylic alcohols **3-2** obtained in this reaction are useful due to the presence of multiple functionalities in close proximity. We felt that these alcohols would be excellent precursors to certain biologically important heterocycles. As part of our investigation, we attempted to brominate the *syn*-homoallylic alcohol with carbon tetrabromide and triphenylphosphine. Surprisingly, the reaction did not produce the expected brominated intermediate, but yielded the corresponding *trans*-α-methylene-γ-lactone (Figure 3.2).

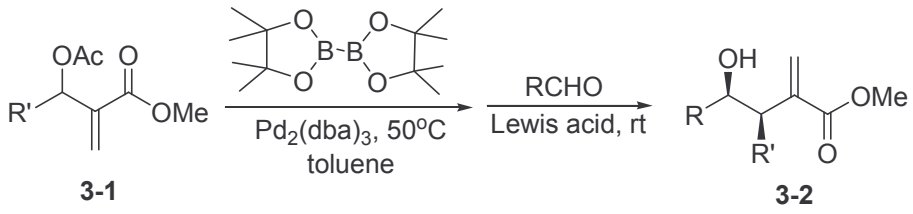


Figure 3.1: Synthesis of homoallylic alcohol

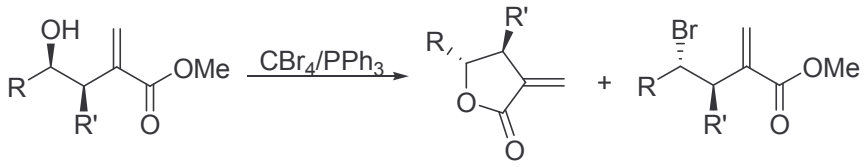
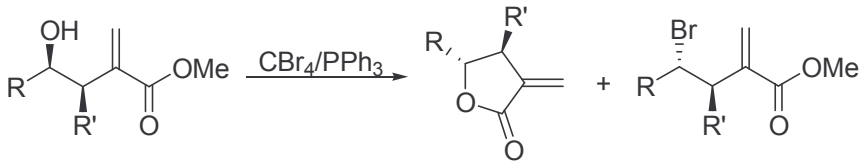


Figure 3.2: Synthesis of trans-α-methylene-γ-lactone

The *trans* stereochemistry was somewhat surprising in light of the earlier studies.[148,152] Several homoallylic alcohols were synthesized using the one pot cross-coupling /allylboration reaction (Figure 3.1), and then treated with CBr_4 and PPh_3 at room temperature. *Trans*-*α*-methylene-*γ*-lactones were produced in moderate to good yields (Table 3-1). The reaction yields were quite good when electron withdrawing groups were present on the aromatic ring. However, the presence of electron donating groups inhibited the formation of the lactone, and bromination products were isolated instead (Table 3-1, entry 10). Homoallylic alcohols derived from aliphatic Baylis–Hillman adducts also gave the corresponding *trans*-*α*-methylene-*γ*-lactones along with a small quantity of the brominated byproducts (Table 3-1, entry 2).

The reaction does not appear to be limited to the use of CBr_4 /PPh_3 as the bromination reagent. Indeed, a good yield of the lactone was obtained utilizing NBS (Table 3-1, entry 5). In contrast, lactonization of **3-2** using *p*-toluenesulfonic acid (PTSA) produced the expected *cis*-*α*-methylene-*γ*-lactones **3-5** in isolated yields ranging from 94% to 99%. (Figure 3.3 and Table 3-2).[154]

Table 3-1: Synthesis of *trans*-α-methylene-γ-lactones[a,b,c]



3-2 **3-3** **3-4**

Entry	R	R'	**3-3**	**3-4**
1	Phenyl	Phenyl	56 (**3-301**)	0
2	Phenyl	Methyl	49 (**3-302**)	17
3	*p*-Nitrophenyl	Phenyl	68 (**3-303**)	0
4	*p*-Nitrophenyl	*p*-Tolyl	71 (**3-304**)	0
5[c]	*p*-Nitrophenyl	*p*-Tolyl	66 (**3-304**)	0
6	*p*-Nitrophenyl	*p*-Methoxyphenyl	70 (**3-305**)	0
7	*p*-Nitrophenyl	1-Napthyl	52 (**3-306**)	0
8	*p*-Nitrophenyl	*p*-Chlorophenyl	63 (**3-307**)	0
9	p-trifluoromethylphenyl	Phenyl	67 (**3-308**)	0
10	*p*-Methoxyphenyl	*p*-Tolyl	0	59

[a] Unless otherwise noted reactions were carried out at rt for 15 hr in the presence of 1.5 equivalents of CBr_4 and PPh_3 in CH_2Cl_2 to obtain **3**;

[b] Isolated yields;

[c] Reaction carried out in the presence of 1.5 eq. of NBS in CH_2Cl_2 for 12 hr.

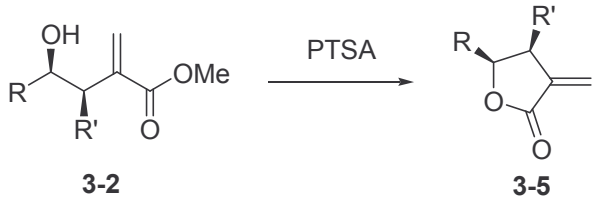


Figure 3.3: Synthesis of cis-α-methylene-γ-lactone

Table 3-2: Synthesis of *cis*-*α*-methylene-*γ*-lactones[a]

Entry	R	R'	**3-5**[b]
1	Phenyl	Phenyl	98 (**3-501**)
2	Phenyl	Methyl	96 (**3-502**)
3	*p*-Nitrophenyl	Phenyl	97 (**3-503**)
4	*p*-Nitrophenyl	*p*-Tolyl	97 (**3-504**)
5	*p*-Nitrophenyl	*p*-Methoxyphenyl	99 (**3-505**)
6	*p*-Nitrophenyl	1-Napthyl	94 (**3-506**)
7	*p*-Nitrophenyl	*p*-Chlorophenyl	95 (**3-507**)
8	*p*-trifluoromethylphenyl	Phenyl	96 (**3-508**)

[a] Reactions carried out at rt overnight in the presence of 10 mol % *p*-toluenesulfonic acid in dichloromethane;

[b] Isolated yield.

3.3 Mechanism

Although a detailed mechanistic study has not been undertaken for the formation of *trans*-*α*-methylene-*γ*-lactones, we believe that the reaction does not proceed via a brominated intermediate. We base this conclusion on a series of experiments in which the brominated product isolated from the reaction of methyl 4-hydroxy-3-methyl-2-methylene-4-phenylbutanoate (see entry 2, Table 3-1) was allowed to react with CBr_4 /PPh_3 under the same reaction conditions used for lactone formation. None of the expected *α*-methylene-*γ*-lactone formed. Additional experiments were carried out in which the same butanoate was allowed to react separately with CBr_4 and PPh_3. Again, none of the lactone formed. It is possible that triphenylphosphine reacts with the brominating agent to form dibromotriphenylphosphorane **3-6**, which would then be expected to react with the 4-hydroxy substituent in **3-2** to form a benzylic phosphonium intermediate **3-7** (**Figure 3-4**). An intramolecular cyclization of **3-7** via a Mitsunobu-like substitution (or via a benzylic cation[154]) would result in the formation of the thermodynamically more stable *trans* lactone **3-3**.

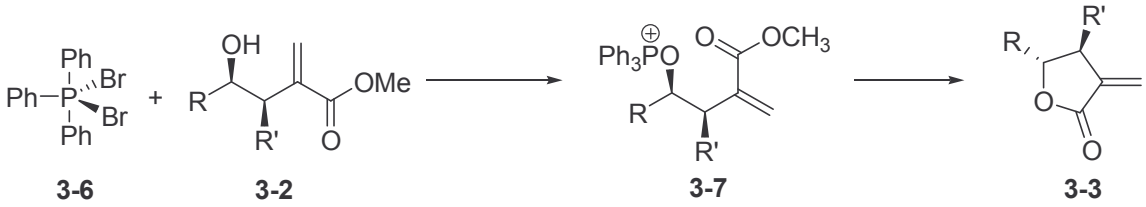


Figure 3.4: Mechanism for the synthesis of cis-α-methylene-γ-lactone

3.4 Conclusion

In conclusion, we have utilized *syn*-homoallylic alcohols, prepared via a one pot cross-coupling /allylboration reaction, to synthesize *cis*- and *trans*-α-methylene-γ-lactones. The methods are quite straightforward; by simply changing the ring closing reagent one can diastereoselectively obtain either the *cis* or *trans*, bioactive α-methylene-γ-lactones.

3.5 Experimental Section

Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 250 MHz Bruker or 300 MHz Varian spectrometer in $CDCl_3$ unless otherwise noted. 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), br s (broad singlet). Thin-layer chromatography (TLC) was performed with the compounds being identified in one or more of the following manners: UV (254 nm), iodine, or PMA. Products were purified by flash chromatography using silica gel (60 Å, 230–400 mesh) with hexanes / ethyl acetate as eluent. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

All glassware was oven dried at 120 ^{o}C and flushed with dry nitrogen. All reactions were carried out under a nitrogen atmosphere. All chemicals were purchased from Aldrich and used as received.

3.5.1 General experimental procedure for the synthesis of Baylis-Hillman acetate adducts

The synthesis of Baylis-Hillman acetate adducts was described in the experimental section of Chapter 2.

3.5.2 Synthesis of Silica Gel Supported BF_3 Catalyst

Silica gel was dried for 24 hours at 300 °C, then stirred under a N_2 atmosphere with a mixture of the BF_3 etherate diluted in 100 ml of toluene at. The catalyst slurry was stirred for 2 hours, then dried slowly on a rotary evaporator at 50 °C.

3.5.3 General experimental procedure for the synthesis of homoallylic alcohols

In a typical reaction, the corresponding Baylis–Hillman acetate adduct **3-1** (1.0 mmol) and bis(pinacolato)diboron (1.1 mmol) were dissolved in 5 mL of toluene. The palladium catalyst $Pd_2(dba)_3$ (3 mol %) was then added and the mixture stirred for 3 h under a nitrogen atmosphere at 50 ^oC [For Baylis–Hillman adducts derived from aliphatic aldehydes, the time was increased to 6 h.]. After cooling to 0 ^oC, the aldehyde (1.2 mmol) and silica supported BF_3 catalyst (100 mg) were added and the mixture stirred at room temperature for the indicated time. The mixture was then filtered to remove the solid catalyst. The filtrate was concentrated under reduced pressure and homoallylic alcohol **3-2** was isolated by silica gel chromatography using hexanes/ethyl acetate (3:1) as eluent.

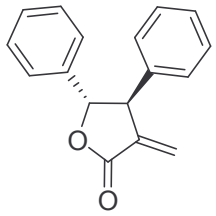
3.5.4 General experimental procedure for the synthesis of *trans*-*α*-methylene-*γ*-lactones

The homoallylic alcohol **3-2** (1.0 mmol) was dissolved in dichloromethane (5 mL) and the solution cooled to 0 ^{o}C. Carbon tetrabromide (1.5 mmol) and triphenylphosphine (1.5 mmol) were added sequentially, and the reaction mixture allowed stirring at room temperature overnight under a nitrogen atmosphere (reaction monitored by TLC). After completion of the reaction, the solvent was removed and the product was isolated and purified by flash chromatography using hexanes/ethyl acetate (4:1) as eluent. The analytical data of all *trans*-*α*-methylene-*γ*-lactones are shown below.

3.5.5 General experimental procedure for the synthesis of *cis*-*α*-methylene-*γ*-lactones

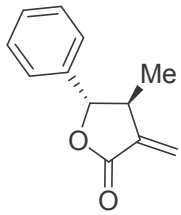
The homoallylic alcohol **3-2** (1.0 mmol) was dissolved in dichloromethane (5 mL) and the solution cooled to 0 ^{o}C. *p*-Toluenesulfonic acid (0.1 mmol) was then added, and the reaction mixture allowed to stir at room temperature overnight under a nitrogen atmosphere (reaction monitored by TLC). After completion of the reaction, the solvent was removed and the product was isolated and purified by flash chromatography using hexanes/ethyl acetate (4:1) as eluent. The analytical data of all *trans*-*α*-methylene-*γ*-lactones are shown below.

3.5.6 Analytical Data



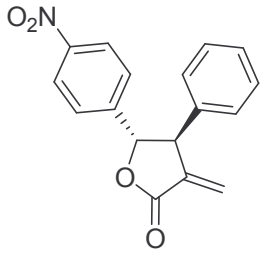
3-301

^{1}H NMR ($CDCl_3$): δ 7.39 – 7.14 (m, 10H), 6.42 (d, 1H, *J* = 3.1 Hz), 5.43 (d, 1H, *J* = 3.1 Hz), 5.37 (d, 1H, *J* = 7.7 Hz), 4.04 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 169.3, 139.8, 138.2, 138.1, 129.1, 128.6, 128.4, 127.9, 125.4, 123.9, 85.8, 55.3. Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; Found: C, 81.63; H, 5.52.



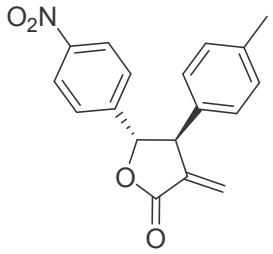
3-302

^{1}H NMR ($CDCl_3$): δ 7.41 – 7.30 (m, 5H), 6.28 (d, 1H, *J* = 3.0 Hz), 5.57 (d, 1H, *J* = 3.0 Hz), 4.88 (d, 1H, *J* = 7.7 Hz), 2.94 (m, 1H), 1.30 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 169.9, 140.3, 138.2, 128.6, 125.7, 120.8, 85.7, 43.2, 15.7. Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; Found: C, 76.43; H, 6.50.



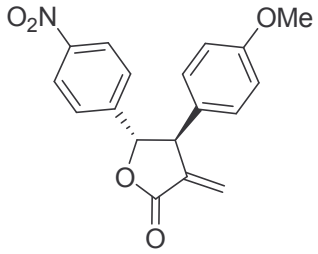
3-303

^{1}H NMR ($CDCl_3$): δ 8.21 (d, 2H, *J* = 8.7 Hz), 7.43 – 7.35 (m, 5H), 7.21 – 7.17 (m, 2H), 6.48 (d, 1H, *J* = 3.3 Hz), 5.49 – 5.47 (m, 2H), 3.98 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 168.7, 148.0, 145.2, 144.1, 138.9, 137.0, 129.5, 128.5, 128.4, 126.1, 124.9, 124.0, 84.3, 55.5. Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74; Found: C, 69.02; H, 4.42; N, 4.65.



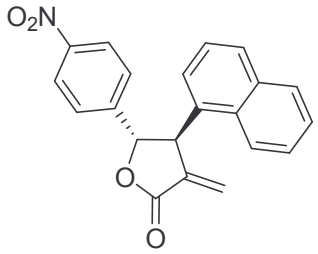
3-304

^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, *J* = 8.5 Hz), 7.38 (d, 2H, *J* = 8.5 Hz), 7.23 (d, 2H, *J* = 7.8 Hz), 7.08 (d, 2H, *J* = 7.8 Hz), 6.45 (d, 1H, *J* = 3.3 Hz), 5.48 (d, 1H, *J* = 3.3 Hz), 5.46 (d, 1H, *J* = 9.3 Hz), 3.95 (m, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.8, 147.8, 147.3, 145.2, 139.1, 138.2, 133.7, 130.0, 128.4, 126.0, 124.6, 123.9, 84.4, 55.1, 21.0. Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53; Found: C, 69.76; H, 4.87; N, 4.41.



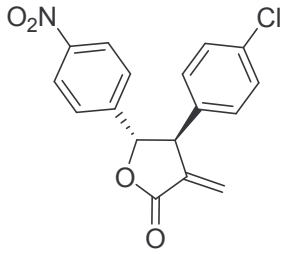
3-305

^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, *J* = 8.7 Hz), 7.37 (d, 2H, *J* = 8.7 Hz), 7.11 (d, 2H, *J* = 6.6 Hz), 6.93 (d, 2H, *J* = 6.6 Hz), 6.45 (d, 1H, *J* = 3.1 Hz), 5.47 (d, 1H, *J* = 3.1 Hz), 5.42 (d, 1H, *J* = 8.7 Hz), 3.91 (m, 1H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.8, 159.5, 147.9, 147.4, 145.2, 139.3, 129.7, 128.6, 126.0, 124.5, 123.9, 114.8, 84.5, 55.3, 54.9. Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31; Found: C, 66.42; H, 4.59; N, 4.23.



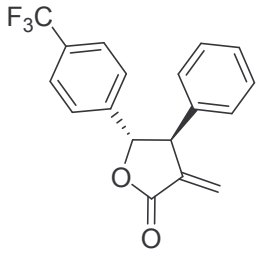
3-306

^{1}H NMR ($CDCl_3$): δ 8.16 (d, 2H, *J* = 8.4 Hz), 7.96 – 7.90 (m, 2H), 7.62 – 7.35 (m, 7H), 6.48 (d, 1H, *J* = 3.0 Hz), 5.77 (br, 1H), 5.46 (d, 1H, *J* = 3.0 Hz), 4.76 (br, 1H); ^{1}H NMR ($CDCl_3$): δ 169.9, 147.2, 143.5, 136.2, 133.4, 131.7, 131.6, 129.3, 128.4, 126.9, 126.7, 126.5, 126.3, 126.1, 126.0, 124.9, 124.5, 121.8, 80.7, 45.9. Anal. Calcd. for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06; Found: C, 72.89; H, 4.32; N, 3.97.



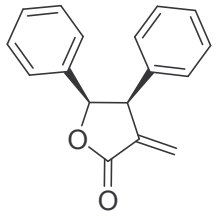
3-307

^{1}H NMR ($CDCl_3$): δ 8.21 (d, 2H, J = 8.8 Hz), 7.39 (m, 4H), 7.16 (d, 2H, J = 8.5 Hz), 6.48 (d, 1H, J = 3.3 Hz), 5.49 (d, 1H, J = 3.3 Hz), 5.44 (d, 1H, J = 8.3 Hz), 4.0 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 168.3, 148.0, 144.8, 138.6, 135.5, 134.4, 129.8, 126.1, 125.0, 124.0, 84.7, 54.7. Anal. Calcd. for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; N, 4.25; Found: C, 62.01; H, 3.59; N, 4.11.



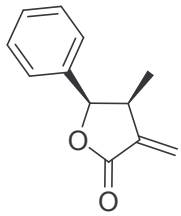
3-308

^{1}H NMR ($CDCl_3$): δ 7.61 (d, 2H, J = 8.4 Hz), 7.42 – 7.17 (m, 7H), 6.46 (d, 1H, J = 3.3 Hz), 5.47 (d, 1H, J = 3.3 Hz), 5.44 (d, 1H, J = 8.4 Hz), 3.99 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 169.0, 147.4, 142.2, 139.3, 137.4, 129.3, 128.5, 128.3, 125.8, 125.7, 125.6, 125.5, 124.5, 84.8, 55.5. Anal. Calcd. for $C_{18}H_{13}F_3O_2$: C, 67.92; H, 4.12; Found: C, 67.89; H, 4.01.



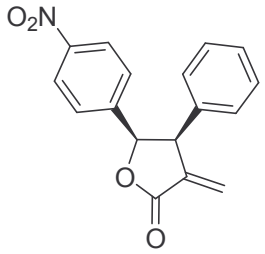
3-501

^{1}H NMR ($CDCl_3$): δ 7.12 – 6.72 (m, 10H), 6.52 (d, 1H, *J* = 3.0 Hz), 5.83 (d, 1H, *J* = 8.3 Hz), 5.57 (d, 1H, *J* = 3.0 Hz), 4.67 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 137.9, 136.2, 136.0, 129.2, 128.0, 127.8, 127.3, 125.7, 124.7, 82.5, 51.6. Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; Found: C, 81.43; H, 5.54.



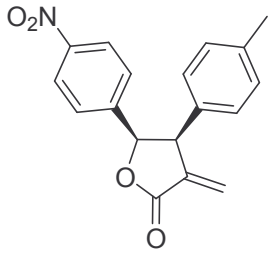
3-502

^{I}H NMR ($CDC1_3$): δ 7.39 – 7.32 (m, 3 H), 7.18-7.15 (m, 2 H), 6.35 (d, 1H, *J* = 2.9 Hz), 5.61 (d, 1H, *J* = 8.1 Hz), 5.56 (d, 1H, *J* = 2.9 Hz), 3.45 (m, 1 H), 0.81 (d, 3 H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 170.4, 140.0, 136.0, 128.3, 125.8, 121.7, 82.3, 38.9, 15.3. Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; Found: C, 76.43; H, 6.36.



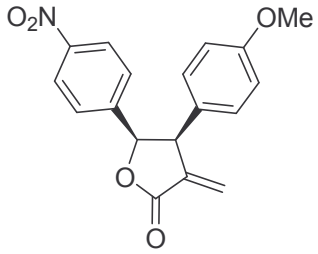
3-503

^{1}H NMR ($CDCl_3$): δ 7.96 (d, 2H, *J* = 8.8 Hz), 7.11 – 7.05 (m, 5H), 6.79 – 6.75 (m, 2H), 6.58 (d, 1H, *J* = 2.9 Hz), 5.94 (d, 1H, *J* = 8.4 Hz), 5.67 (d, 1H, *J* = 2.9 Hz), 4.79 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 169.8, 147.3, 143.5, 137.0, 136.0, 128.9, 128.6, 127.9, 126.7, 126.0, 123.0, 81.2, 51.4. Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74; Found: C, 69.23; H, 4.31; N, 4.55.



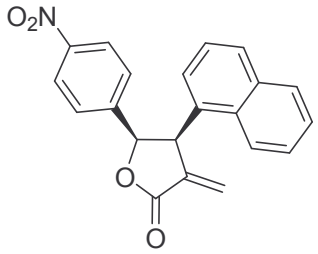
3-504

^{1}H NMR ($CDCl_3$): δ 7.98 (d, 2H, *J* = 8.7 Hz), 7.07 (d, 2H, *J* = 8.7 Hz), 6.90 (d, 2H, *J* = 8.1 Hz), 6.65 (d, 2H, *J* = 8.1 Hz), 6.55 (d, 1H, *J* = 3.0 Hz), 5.93 (d, 1H, *J* = 8.1 Hz), 5.65 (d, 1H, *J* = 3.0 Hz), 4.74 (m, 1H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.0, 147.3, 143.6, 137.6, 137.2, 132.7, 130.1, 129.7, 128.7, 126.7, 125.8, 123.0, 81.2, 50.9, 20.9. Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53; Found: C, 69.79; H, 4.77; N, 4.50.



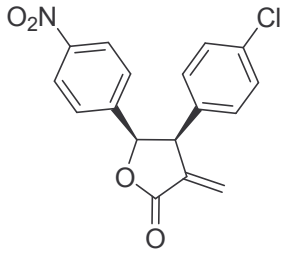
3-505

^{1}H NMR ($CDCl_3$): δ 7.99 (d, 2H, *J* = 8.7 Hz), 7.09 (d, 2H, *J* = 8.7 Hz), 6.69 (d, 2H, *J* = 9.0 Hz), 6.62 (d, 2H, *J* = 9.0 Hz), 6.54 (d, 1H, *J* = 2.7 Hz), 5.94 (d, 1H, *J* = 8.7 Hz), 5.63 (d, 1H, *J* = 2.7 Hz), 4.76 (m, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.9, 158.8, 147.1, 143.7, 137.2, 129.9, 127.6, 126.7, 125.6, 122.9, 113.7, 81.2, 55.0, 50.5. Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31; Found: C, 66.52; H, 4.61; N, 4.27.



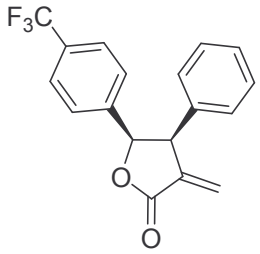
3-506

^{1}H NMR ($CDCl_3$): δ 8.07 (d, 1H, J = 8.1 Hz), 7.80 (d, 1H, J = 8.1 Hz), 7.72 – 7.50 (m, 5H), 7.14 (t, 1H, J = 7.5 Hz), 6.83 (m, 3H), 6.73 (d, 1H, J = 3.0 Hz), 6.16 (d, 1H, J = 8.4 Hz), 5.77 (d, 1H, J = 3.0 Hz), 5.68 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 170.1, 147.2, 143.5, 136.2, 133.4, 131.7, 131.6, 129.3, 128.4, 126.9, 126.7, 126.5, 126.3, 126.1, 126.0, 124.9, 122.5, 121.8, 80.7, 45.9. Anal. Calcd. for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06; Found: C, 72.94; H, 4.25; N, 3.85.



3-507

^{1}H NMR ($CDCl_3$): δ 8.02 (d, 2H, *J* = 8.8 Hz), 7.12 (d, 2H, *J* = 8.8 Hz), 7.08 (d, 2H, *J* = 6.6 Hz), 6.76 (d, 2H, *J* = 6.6 Hz), 6.56 (d, 1H, *J* = 2.8 Hz), 5.98 (d, 1H, *J* = 8.4 Hz), 5.66 (d, 1H, *J* = 2.8 Hz), 4.83 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 169.5, 147.3 143.2, 136.9, 134.6, 133.6, 130.2, 128.6, 126.7, 126.1, 123.2, 80.8, 50.5. Anal. Calcd. for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; N, 4.25; Found: C, 62.05; H, 3.65; N, 4.21.



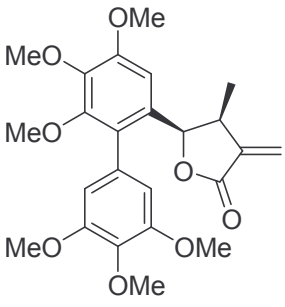
3-508

^{1}H NMR ($CDCl_3$): δ 7.35 (d, 2H, *J* = 8.8 Hz), 7.09 – 7.06 (m, 3H), 6.96 (d, 2H, *J* = 8.8 Hz), 6.76 – 6.71 (m, 2H), 6.54 (d, 1H, *J* = 2.9 Hz), 5.88 (d, 1H, *J* = 8.3 Hz), 5.62 (d, 1H, *J* = 2.9 Hz), 4.72 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 170.2, 140.3, 137.4, 136.0, 129.0, 128.4, 127.7, 126.2, 125.5, 124.8, 124.7, 81.6, 51.6. Anal. Calcd. for $C_{18}H_{13}F_3O_2$: C, 67.92; H, 4.12; Found: C, 67.85; H, 4.01.

Chapter 4: The total synthesis of Eupomatilone 2

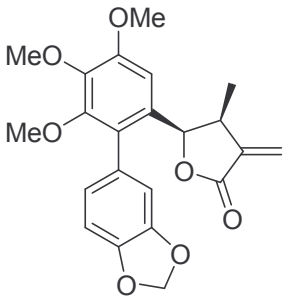
4.1 Introduction

As noted in Chapter 3, the α-methylene-γ-lactone moiety is widely found in naturally occurring compounds. Eupomatilones (1-7) are structurally novel lignans, first isolated in 1991 by Carrol and Taylor from shrubs of *eupomatia bennettii* and are charactarized by a biaryl system with a substituted γ-lactone ring system attached to one of the aryl rings (Figure 4.1).[155] Three synthetic approaches to eupomatilone-6 (**4-3**) (in which the olefin on the lactone moiety is hydrogenated) have been reported; however there are no reports relating to the syntheses of eupomatilones that contain an α-methylene-γ-lactone.[156] In Chapter 3 we reported that functionalized homoallylic alcohols could be cyclized to form α-methylene-γ-lactones. These results encouraged us to carry out the total synthesis of eupomatilones to explore the application of the new reactions. In this chapter the total synthesis of eupomatilones-2 (**4-1**) was realized using Baylis-Hillman adducts as synthetic precursor and the method described in Chapter 3.



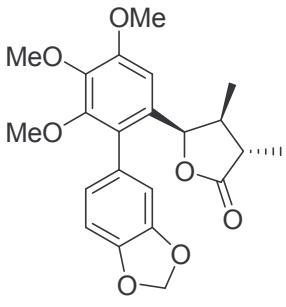
eupomatilone 2

4-1



eupomatilone 5

4-2



eupomatilone 6

4-3

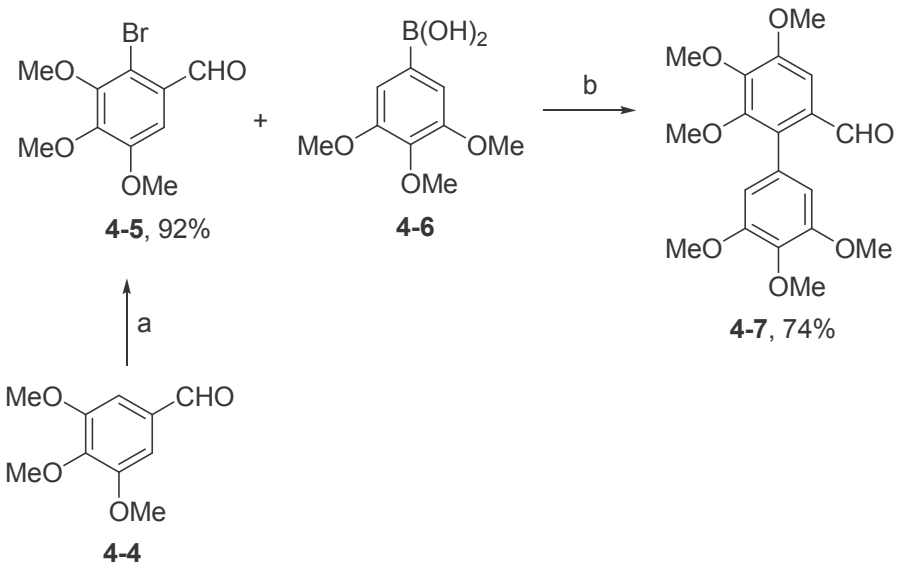
Figure 4.1: Eupomatilones 2, 5, and 6

4.2 Results and Discussion

The synthesis began with the reaction of arylboronic acids **4-6** and 2-bromo-3,4,5-trimethoxy benzaldehyde ,**4-5**, which was easily synthesized from commercially available 3,4,5-trimethoxy benzaldehyde ,**4-4**, in the presence of 4 mol % of $PdCl_2(PPh_3)_3$ catalyst.[157] The cross-coupling was achieved without using external ligand and KF was used as base in aqueous toluene solvent at 70 ^oC for 18 hr to obtain biaryl aldehydes **4-7** in good yields (Figure 4.2).

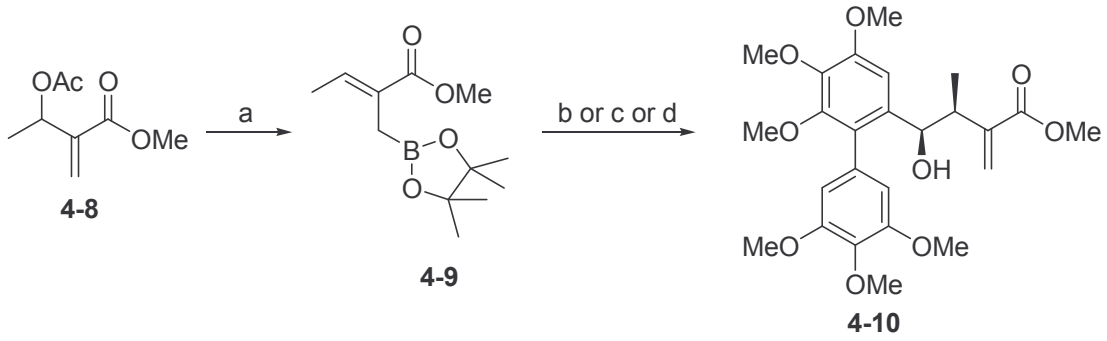
The eupomatilone's lactone ring was initially constructed by the addition of 3-methyl-2-methoxycarbonyl allylboronate **4-9** to the biaryl aldehyde **4-7**. Allylboronate **4-9** was prepared by using Baylis-Hillman acetate adduct **4-8** and bis(pinacoloto)diboron in the presence of a palladium catalyst as shown in Figure 4.3. Since the allylboronates are moisture sensitive and can be difficult to purify, allylboronate **4-9** was used directly in the preparation of **4-10**. A variety of conditions were employed but the reaction yields were poor presumably due to steric factors and the presence of the electron donating methoxy groups on the aromatic ring of the aldehyde **4-10**.

Since the boronate-based coupling reactions generated only modest yields of the desired products, we investigated the use of indium moderated reactions developed by Paquette and others.[158] Allylbromide **4-12** was synthesized from Baylis-Hillman adduct **4-11**.[159] Bromination using N-bromosuccinamide and triphenylphosphine in DCM at room temperature occurred regioselectively to afford the thermodynamically favored *Z*-isomer with allylic rearrangement.



Reagents and conditions: (a) NBS, $CHCl_3$, reflux, 2h; (b) $PdCl_2(PPh_3)_2$ (4 mom %), Toluene:H_2O (10:1), KF (2 eq.), 70^oC, 18h.

Figure 4.2: Synthesis of compound 4-7



Reagents and conditions: (a) Bis(pinacoloto)diboron (1.1 eq.), $Pd_2(dba)_3$ (3 mol %), Toluene, 50 ^oC, 5 h; (b) $Sc(OTf)_3$ (10 mol %), rt, 3 days, 12%; (c) BF_3 on SiO_2 (100 mg), rt, 3 days, 15%; (d) 90 ^oC, 3 dyas, 19%.

Figure 4.3: Synthesis of homoallylic alcohol utilizing allylboronate

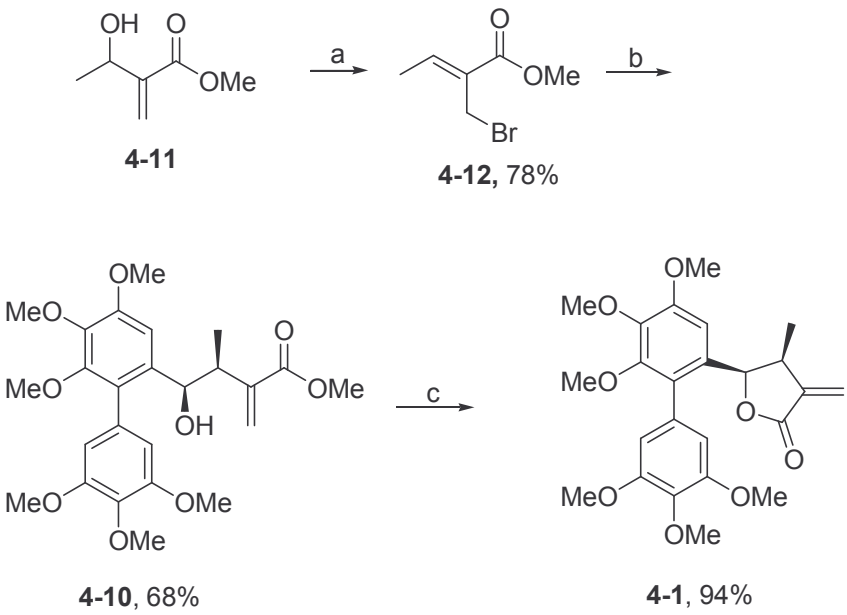
Allylation of biarylaldehyde **4-7** with **4-12** was most efficiently carried out with powdered indium metal in mixture of water and tetrahydrofuron (1:1) solvent.[158a] The homoallylic alcohol **4-10** formed as the desired *syn* isomers (95:5) (minor amounts of the *anti* isomers were observed, however, they were easily separated from the desired product). Cyclization of alcohol **4-10** was achieved under mild acidic conditions (PTSA, CH_2Cl_2) to form final product **4-1** (Figure 4.4). ^{1}H-NMR and ^{13}C-NMR spectra of **1** proved identical with that of published for eupomatilone 2.[155]

4.3 Conclusion

In conclusion, we have successfully completed the synthesis of eupomatilone 2 using Suzuki coupling and allylation reactions as the key steps. Although no reports have appeared describing the biological activity of eupomatilone 2, our short and efficient strategy could serve as a catalyst for research in this area.

4.4 Experimental Section

Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 250 MHz Bruker or 300 MHz Varian spectrometer in $CDCl_3$ unless otherwise noted. 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), br s (broad singlet). Thin-layer chromatography (TLC) was performed with the compounds being identified in one or more of the following manners: UV (254 nm), iodine, or PMA.



Reagents and conditions: (a) NBS, PPh_3, rt, 12 h; (b) In, THF:H_2O (1:1), 2h; (c) PTSA (10 mol%), DCM, rt, 12 h.

Figure 4.4: Synthesis of eupomatilone 2 (continued)

Products were purified by flash chromatography using silica gel (60 Å, 230–400 mesh) with hexanes / ethyl acetate as eluent. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

All glassware was oven dried at 120 ^{o}C and flushed with dry nitrogen. All reactions were carried out under a nitrogen atmosphere. All chemicals were purchased from Aldrich and used as received.

4.4.1 Synthesis of Biarylaldehyde 4-7

Bromoaldehyde **4-5** (2.75g, 10.0 mmol) and 3,4,5-trimethoxyphenylboronic acid **4-6** (2.54g, 12.0 mmol) were weighed and transferred to a 50 ml round-bottomed flask equipped with a magnetic stir bar and 20.0 mL of toluene. KF (1.74g, 30 mmol), $PdCl_2(PPh_3)_2$ (281mg, 0.4 mmol) and 2.0 mL of water were added to the reaction mixture. The reaction mixture was allowed to stir under N_2 for 18 h at 70 ^{o}C. The reaction mixture was transferred to a separatory funnel and diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic layer was washed with 20 mL of water and 20 mL of brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was removed by rotary evaporation under reduced pressure. The resulting residue was subjected to flash column on silica gel to give 2.68g (74%) light yellow solid biarylaldehyde **4-7**: ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 6.56 (s, 1H), 6.74 (s, 1H), 7.35 (s, 1H), 9.70 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 55.9, 56.0, 60.6, 60.8, 61.0, 104.4, 104.9, 108.2, 126.1, 129.6, 134.0, 137.3, 137.5, 147.3, 150.8, 152.5, 152.9, 153.2, 190.9.

4.4.2 Procedure For The Preparation of Allylboronates 4-9 Followed By Allylation with Biarylaldehyde 4-7

To a mixture of Baylis-Hillman acetate adduct **4-8** (172 mg, 1.00 mmol) and bis(pinacolato)diboron (279 mg, 1.10mmol) in toluene (4.0 mL) was added 3 mol % of $Pd_2(dba)_3$ and the mixture stirred at 50 ^oC under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 0 ^oC and biarylaldehyde **4-7** (362 mg, 1.00 mmol) and 100 mg $BF_3 \cdot SiO_2$ were added. The reaction mixture was allowed to stir at room temperature for 3 days, quenched with 10 mL of saturated aqueous $NaHCO_3$, and extracted with ether (3 x 10 ml). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by column chromatography to obtain the homoallylic alcohol **4-10** 15% as a colorless oil: ^1H NMR ($CDCl_3$): δ 1.04 (d, 3H, J = 7.0 Hz), 2.88 (m, 1H), 3.09(brs, 1H), 3.61 (s, 3H), 3.64 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.88 (s, 6H), 3.98 (s, 3H), 4.71 (m, 1H), 5.17 (s, 1H), 5.95 (s, 1H), 6.40 (d, 1H, J = 1.5 Hz), 6.44 (d, 1H, J = 1.5 Hz), 7.01 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.0, 41.9, 51.8, 55.6, 55.9, 60.6, 61.1, 72.7, 105.7, 106.7, 108.0, 125.6, 127.1, 131.6, 136.1, 137.2, 140..6, 143.3, 150.2, 152.6, 152.8, 160.1.

4.4.3 Synthesis of Allylbromide 4-12

To a solution of Baylis-Hillman adduct (1.30 g, 10.0 mmol) and NBS (2.67 g, 15.0 mmol) in 10 mL of dry DCM was added triphenylphospine (3.93 g, 15.0 mmol dissolved in 10 mL of DCM) dropwise over five minutes at -5 ^oC. This produced a clear yellow solution that was stirred for 16 h at 25 ^oC before being diluted with pentane (50

mL) and poured into a 50 mL of chilled mixture of H_2O and brine (1:l). The aqueous layer was separated and extracted with Et_2O (3 X 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo, and the resulting crude product was purified by silica gel chromatography (5:l hexane-ether), giving 1.51 g (78%) known allylbromide **4-12**.[160] ^{1}H NMR ($CDCl_3$) δ 7.07 (q, 1H, *J* = 6.9 Hz), 4.23 (s, 2 H), 3.79 (s, 3H), 1.91 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDC1_3$): δ 169.5, 143.3, 130.1, 52.1, 23.9, 14.5.

4.4.4 Indium Mediated Allylation

To a mixture of allylbromide **4-12** (212 mg, 1.1 mmol) and biarylaldehyde **4-7** (362 mg, 1 mmol) in THF (5.0 ml) and water (5.0 ml) was added indium (1.1 mmol, 126 mg of 100 mesh powder) and the resulting mixture was stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl then extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by silica gel column chromatography afforded 324 mg (68%) homoallylic alcohol **4-10**.

4.4.5 Synthesis of Eupomatilones 2 (4-1)

Homoallylic alcohol **4-10** (477 mg, 1.00 mmol) was stirred overnight in CH_2Cl_2 (5.0 ml) with 17.0 mg (10 mol %) of *p*-TSA. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5.0 mL) and extracted with ether (3 x 5 ml). The combined ether layers were washed with brine (5.0 ml), dried over anhydrous Na_2SO_4 and concentrated to give 417 mg (94%) the eupomatilone 2 (**4-1)**: ^{1}HNMR ($CDCl_3$): δ 0.85 (d,

3H, J = 7.5 Hz), 2.87 (m, 1H), 3.70 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 5.52 (d, 1H, J = 7.2 Hz), 5.56 (d, 1H, J = 2.0 Hz), 6.24 (d, 1H, J = 2.0 Hz), 6.36 (d, 1H, J = 1.5 Hz), 6.47 (d, 1H, J = 1.5 Hz), 6.69 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 16.6, 38.1, 55.9, 60.6, 61.1, 79.0, 104.4, 104.7, 106.3, 107.3, 121.7, 127.5, 129.7, 130.8, 137.1, 140.7, 141.7, 151.0, 152.7, 152.8, 169.8. HRMS (EI) for $C_{24}H_{28}O_8$: Exact Mass $(M+Na)^+$: 467.1682; Found $(M+Na)^+$: 467.1665.

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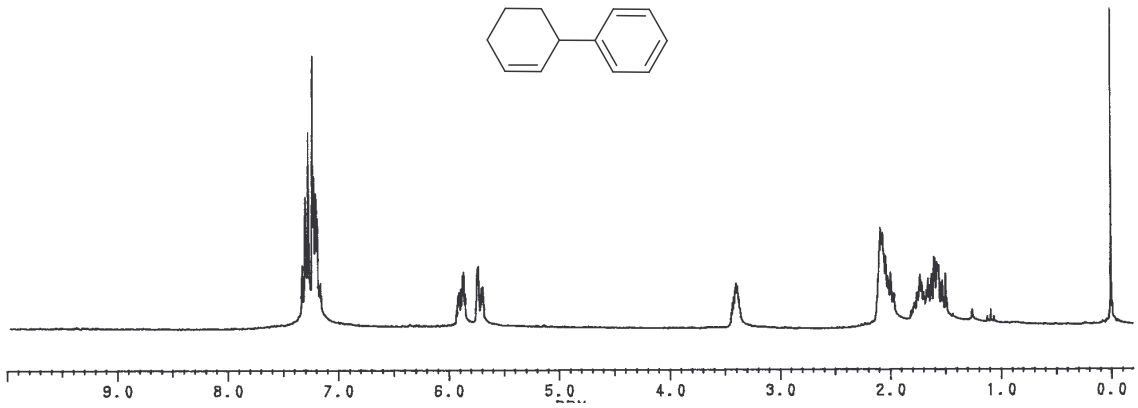
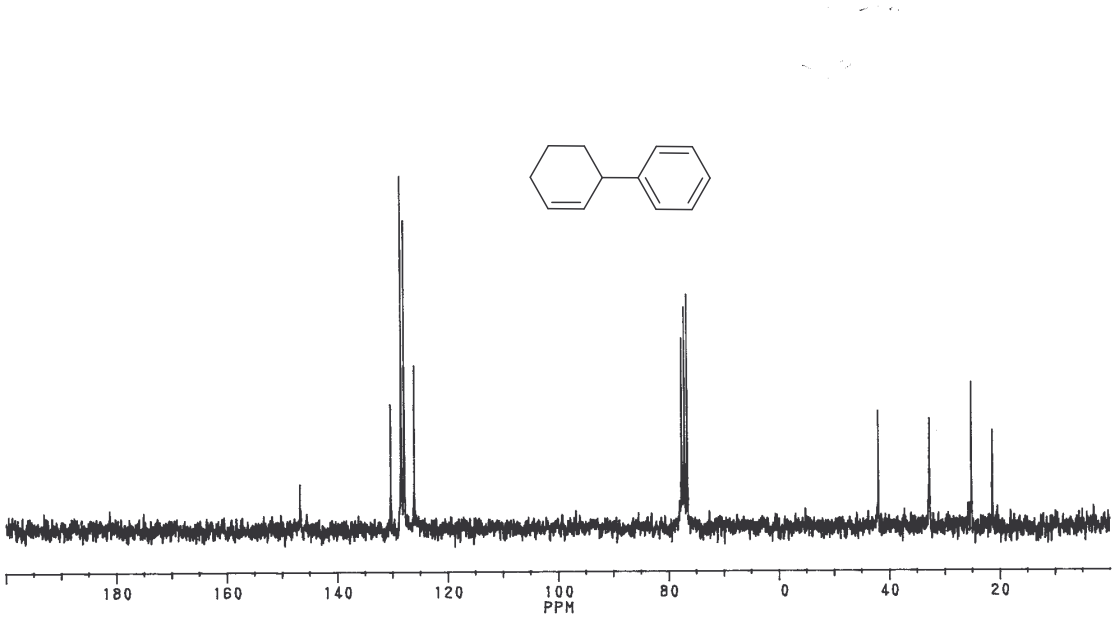
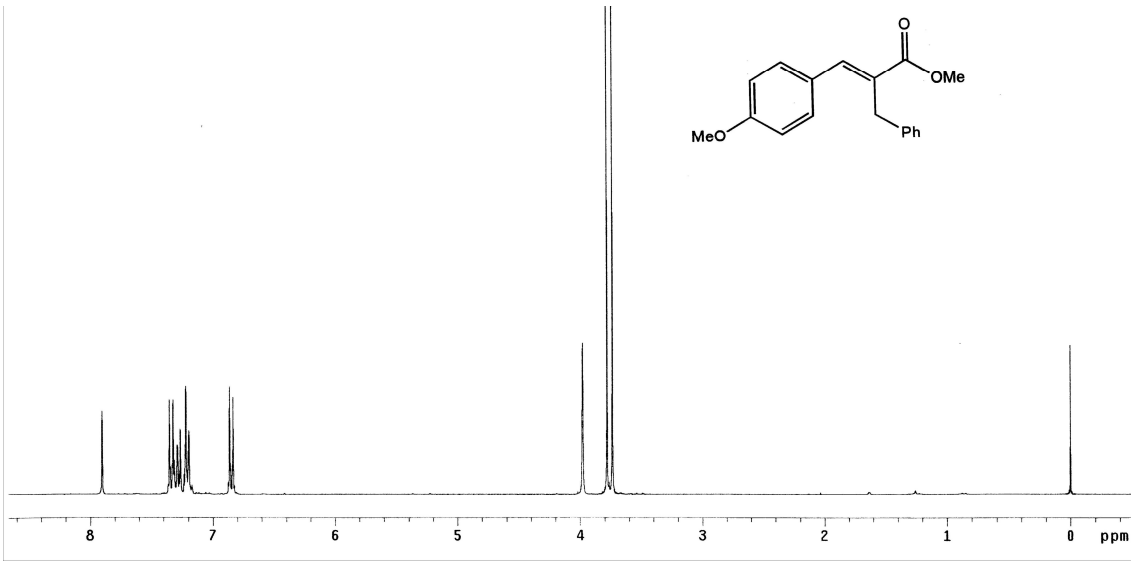
APPENDIX: NMR Spectra of Representative Compounds



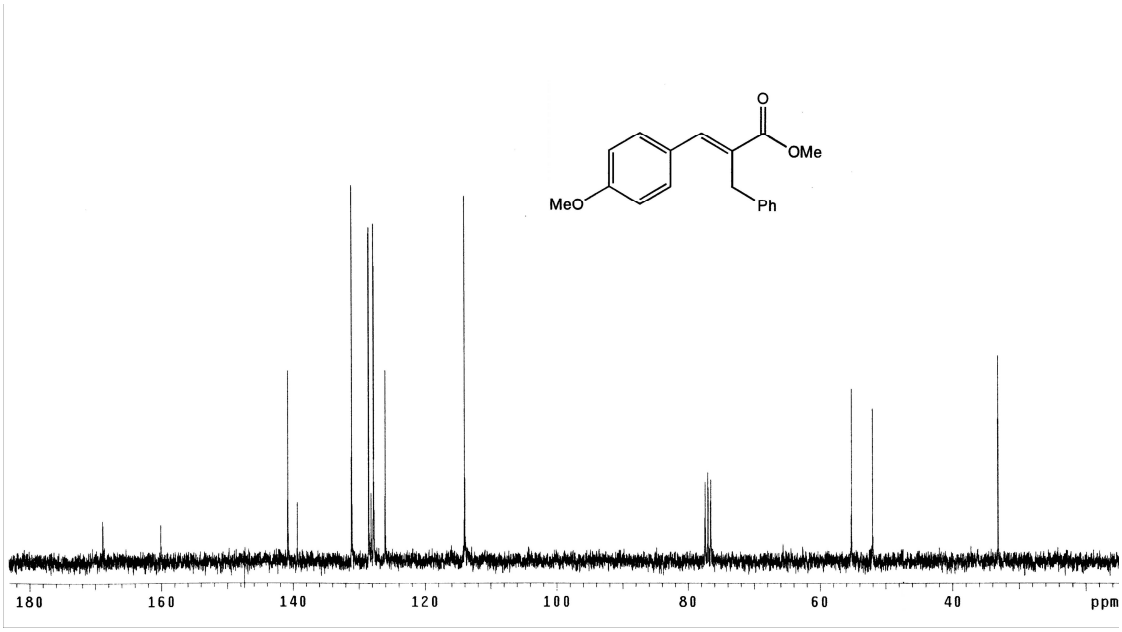
250 MHz ^{1}H NMR of compound **2-209**



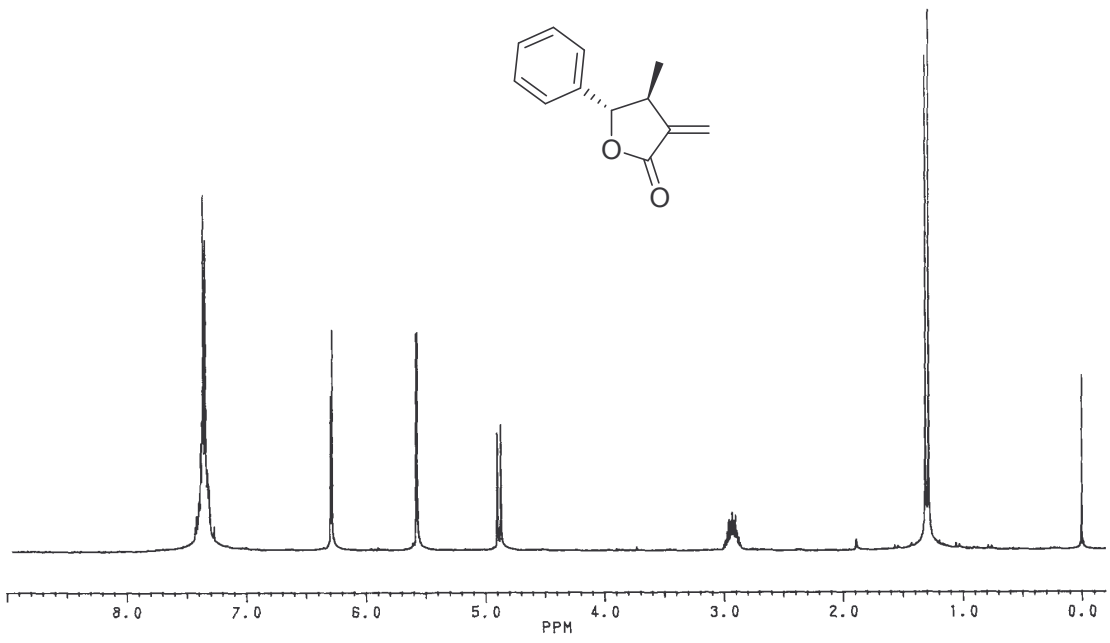
62.5 MHz 13C NMR of compound **2-209**



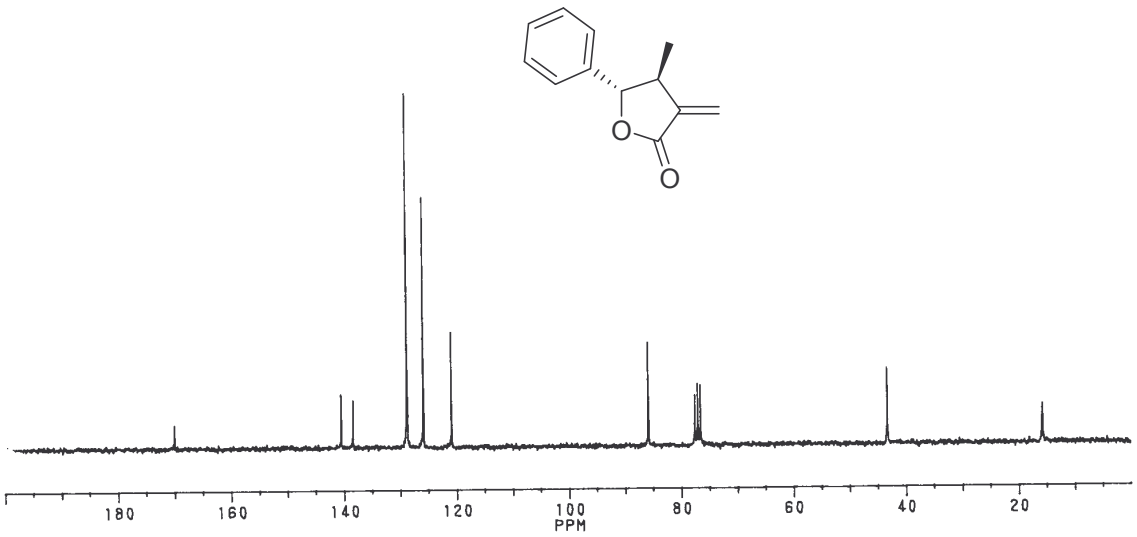
300 MHz ^{1}H NMR of compound **2-306**



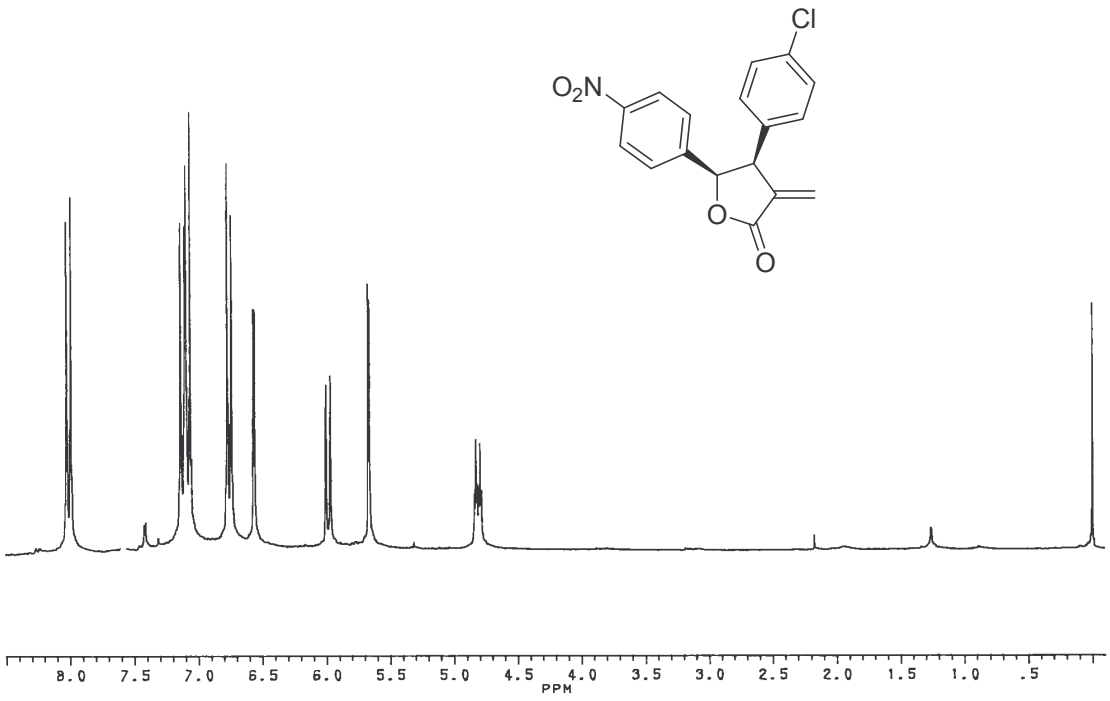
75 MHz ^{13}C NMR of compound **2-306**



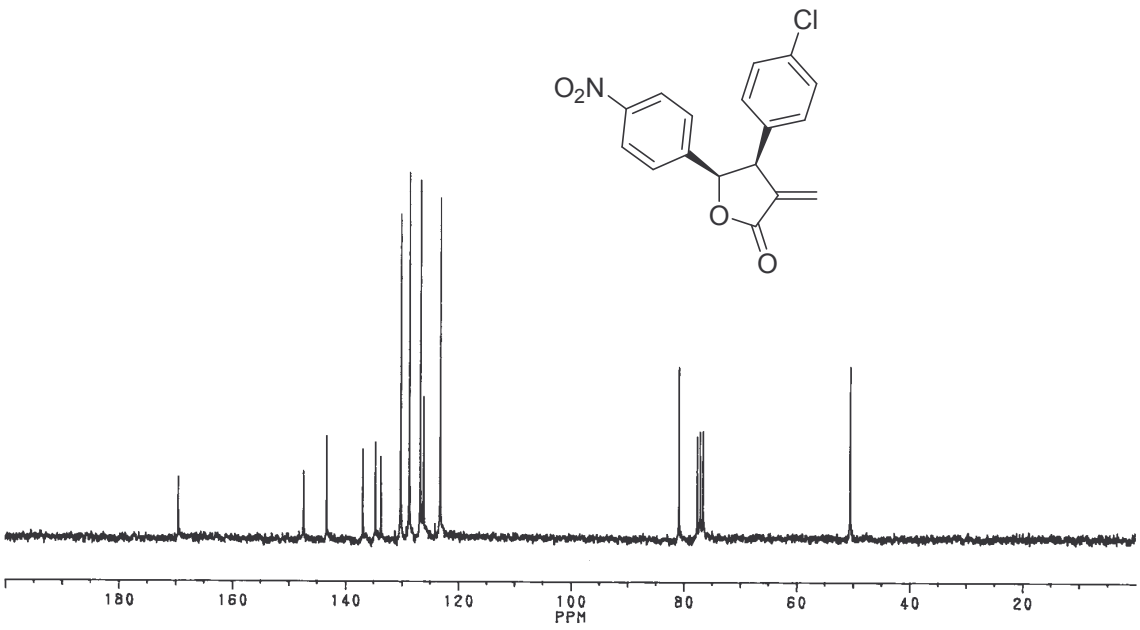
250 MHz ^{1}H NMR of compound **3-302**



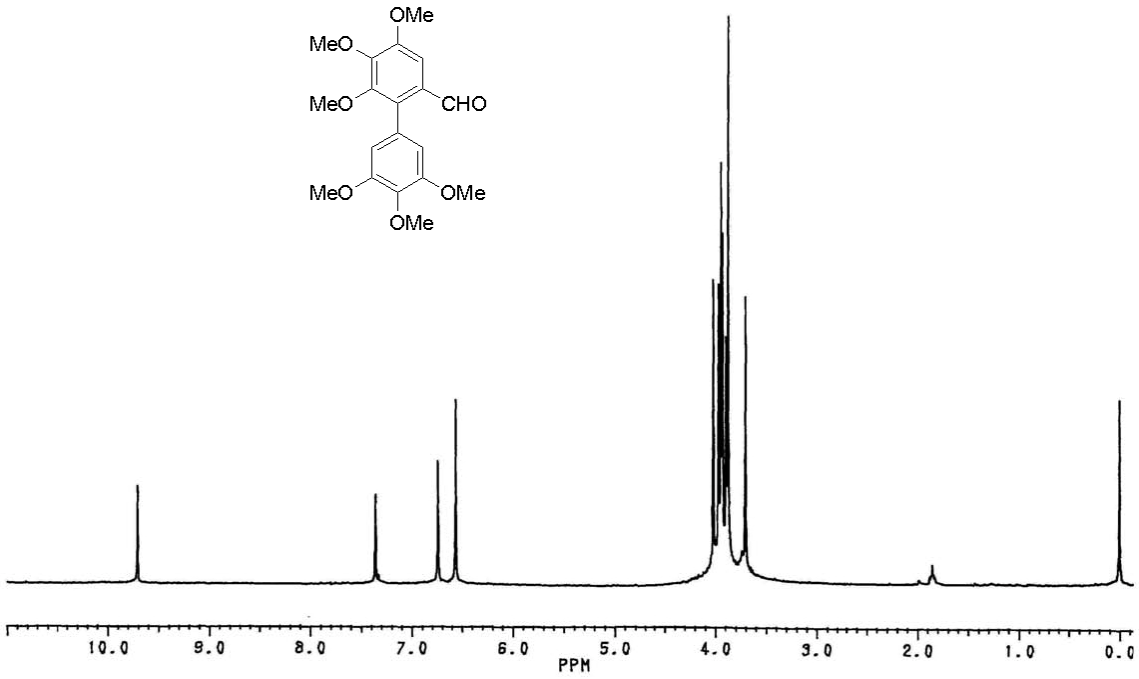
62.5 MHz ^{13}C NMR of compound **3-302**



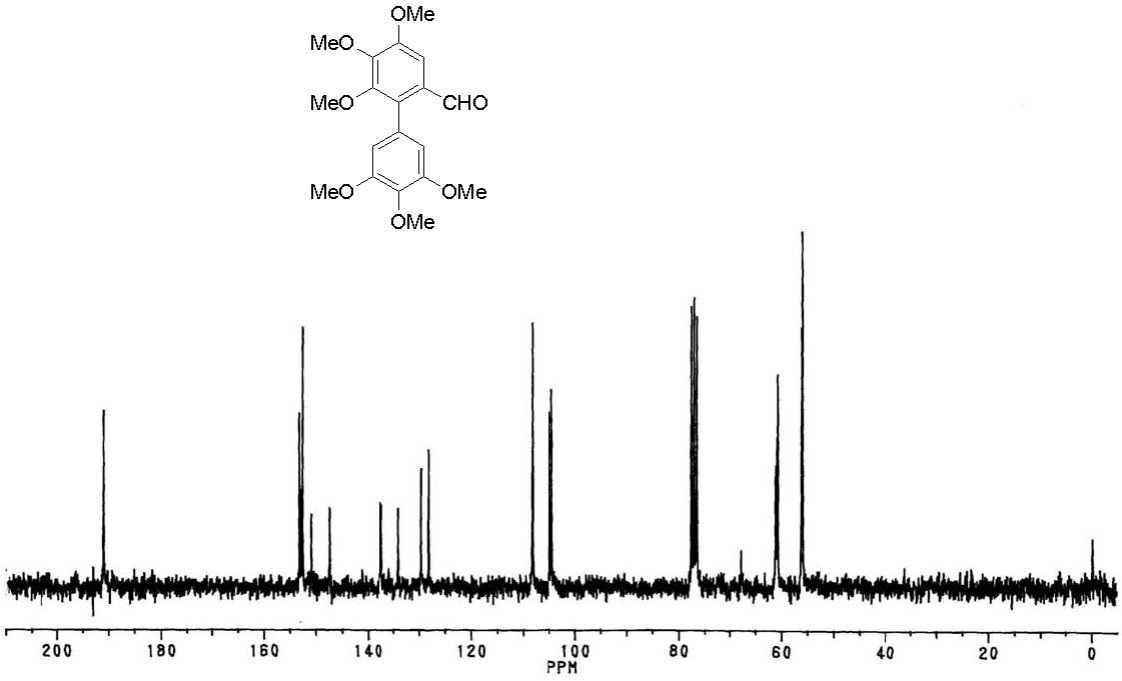
250 MHz ^{1}H NMR of compound **3-507**



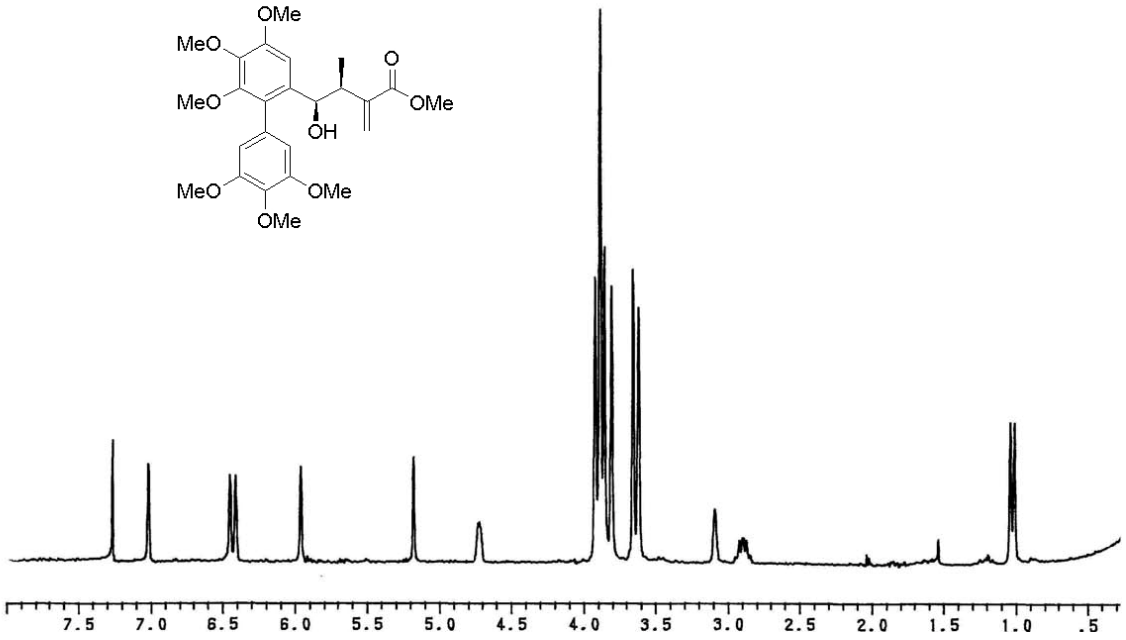
62.5 MHz ^{13}C NMR of compound **3-507**



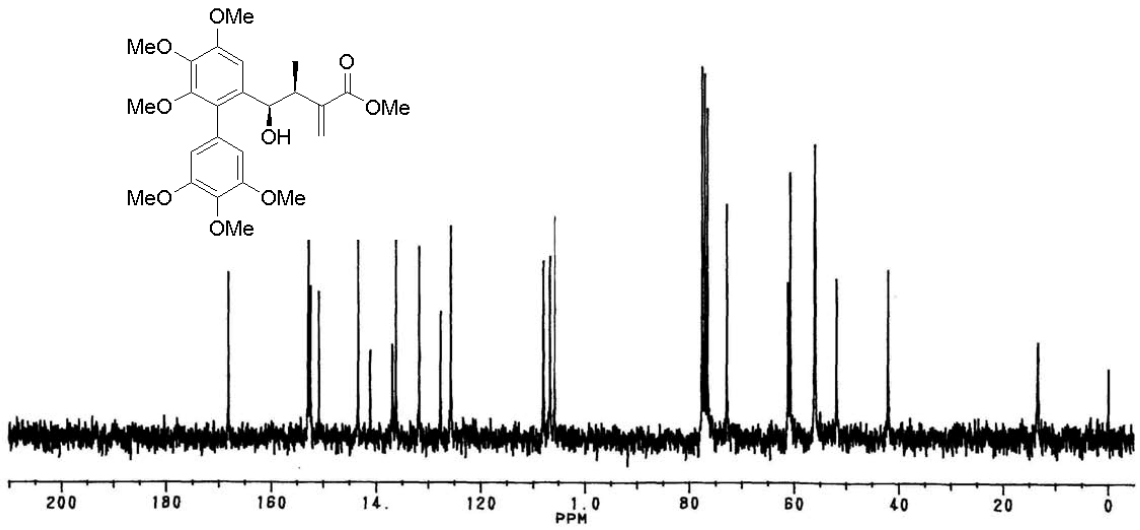
250 MHz ^{1}H NMR of compound **4-7**



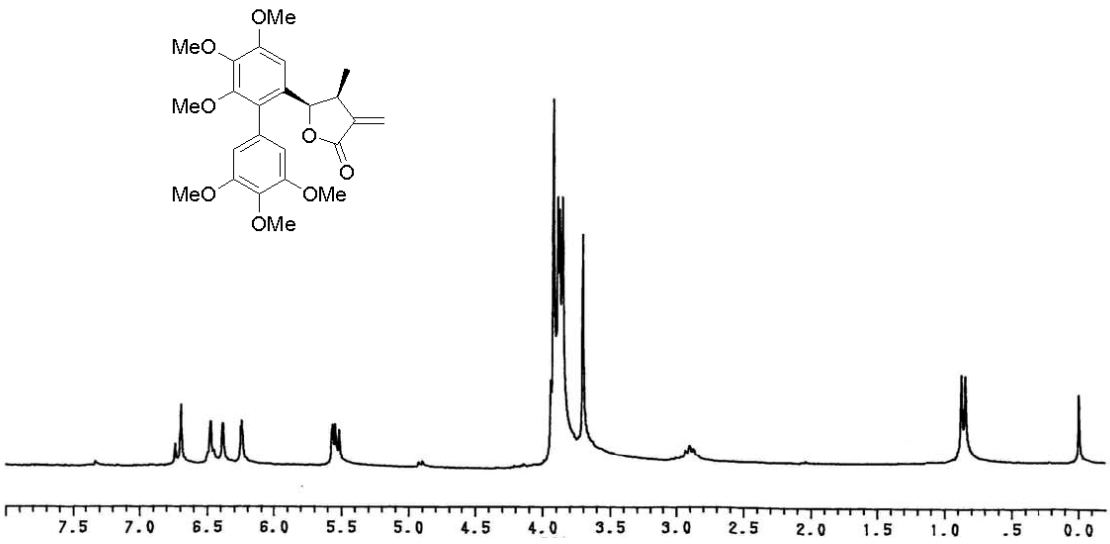
62.5 MHz ^{13}C NMR of compound **4-7**



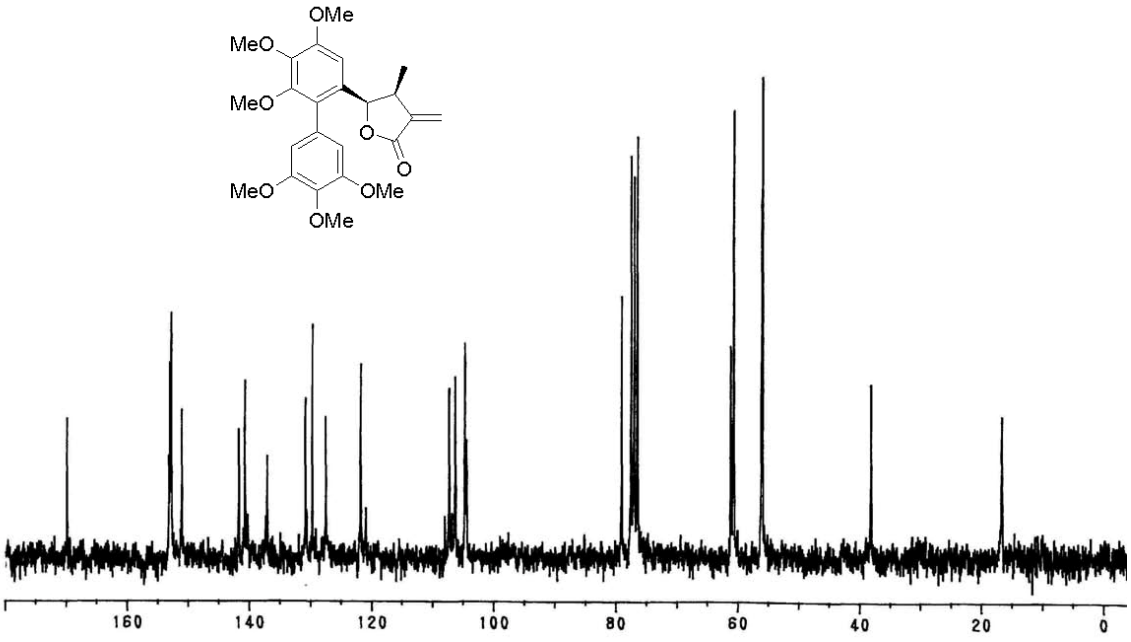
250 MHz ^{1}H NMR of compound **4-10**



62.5 MHz ^{13}C NMR of compound **4-10**



250 MHz ^{1}H NMR of Eupomatilone 2 **4-1**



62.5 MHz ^{13}C NMR of Eupomatilone 2 **4-1**

VITA

Chunlan Chen was born in April in Liyang, P. R. China. She entered Wuhan University in 1990 and was awarded the Bachelor of Science degree majored in organic chemistry in 1994. Chunlan Chen and Gang Dong got married in April 1997. She joined Sinopec Jinling Petrochemical Corp., Ltd. in 1994 and worked as a project manager and instrumental administrator of GC and GC-IR. On August 30th, 1998, her son Ziqing Dong was born in Nanjing, China.

In August 2004, Chunlan Chen joined Dr. George W. Kabalka's research group in the Department of Chemistry, University of Tennessee at Knoxville and received her Master's degree in December, 2006.