University of Alberta

Design and Evaluation of a New Lewis Acid-Assisted Lewis Acid Catalyst System and Further Applications of a Double-Allylation Reagent

By

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Abstract

Asymmetric synthesis is one of the most important areas of organic chemistry. Despite of the prevalence of asymmetric catalysts, there is still room for improved catalyst systems.

Chapter 2 describes the design and evaluation of a new Lewis acid-assisted Lewis acid (LLA) catalyst system. Many boronic esters were prepared for this purpose and combined with different Lewis acids to form LLA catalyst systems. These LLA species were examined in carbonyl allylation reactions. In a few cases, higher product conversions were observed with the new LLA catalyst systems compared to the corresponding background reactions (Lewis acid alone).

A novel class of chiral double-allylation reagent **7** was recently introduced by our group. Hall and Peng showed the stereoselective synthesis of trisubstituted furans, vinylcyclopropanes, and smaller oxabicyclic compounds using this double allylation reagent.

Chapter 3 describes further applications of double allylation reagent **7**. In this chapter, the synthesis of larger oxabicyclic compounds, a one-pot synthesis of furan rings, and the synthesis of pyrrolidines were examined. From the preliminary studies, it was observed that the synthesis of pyrrolidines may be feasible. Moreover, trisubstituted tetrahydrofurans **46**–**49** were prepared in a one-pot protocol with excellent diastereoselectivities (20:1).

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Ac	Acetyl
Ar	Aryl
BBA	Brønsted acid-assisted Brønsted acid
BINOL	1,1'-bis2,2'-naphthol
BLA	Brønsted acid-assisted Lewis acid
Bn	Benzyl
Br	Bromide
br s	Broad singlet
Bu	Butyl
CAB	Chiral (acyloxy) borane
d	Doublet
3-D	3-Dimension
dd	Doublet of doublets
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DIBAL⁻H	Diisobutylaluminium hydride
DMAP	N,N-4-dimethylaminopyridine
DNA	Deoxyribonucleic acid
dr	Diastereomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron impact

Equiv	Equivalent
ES	Electrospray
Et	Ethyl
FTIR	Fourier-transformation infrared
FW	Formula weight
h	Hour/hours
H-Bond	Hydrogen-bond
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
I	Iodide
*i*Bu	Isobutyl
Ipc	Isopinocampheyl
*i*Pr	Isopropyl
IR	Infrared
L.A.	Lewis acid
LBA	Lewis acid-assisted Brønsted acid
LLA	Lewis acid-assisted Lewis acid
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
M	Molarity
MABR	Methylaluminium bis(4-bromo-2,6-di-tert-butylphenoxide)
MBH	Morita-Baylis-Hillman

Me	Methyl
MEM	(2-methoxyethoxy)methyl
MHz	Megahertz
min	Minutes
Mol	Mole
M.S.	Molecular sieves
MS	Mass spectrometry
Ms	Methanesulfonyl
NMR	Nuclear magnetic resonance
OTf	Trifluoromethanesulfonate
p	Pentet
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
PTSA	p-Toluenesulfonic acid
q	Quartet
qd	Quartet of doublet
R_f	Retention factor
RT	Room temperature
s	Singlet
sat.	Saturated
SOMO	Singly Occupied Molecular Orbital
t	Triplet

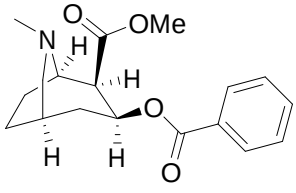
TADDOL	(−)-*Trans*-*alpha*,*alpha*'-(dimethyl-1,3-dioxolane-4,5-diyl)-*bis*-diphenylmethanol
*t*Bu	Tert-butyl
TBAF	Tetra-n-butylammonium fluoride
TBS	Tert-butyldimethylsilyl
TES	Triethylsilyl
Tf_2O	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	p-Toluenesulfonyl
UV	Ultraviolet

Stereoselective Synthesis

Chapter 1: Introduction

1.1 Asymmetric Catalysis

Asymmetric synthesis has become one of the most important fields in organic chemistry, mainly due to the increased demand for optically pure drugs in the market.[1a,b,c] Enantiomeric purity plays a crucial role when a compound is being considered as a drug candidate because only one of the optical isomers may be biologically active while the other one may be inactive or toxic in the same organism. For example, (–)-cocaine is active in humans while (+)-cocaine is inactive.[1e] Several methods are available in asymmetric synthesis to prepare enantiomerically pure molecules. Even though new asymmetric reactions are being constantly developed, there remain cases where asymmetric synthesis does not provide the most efficient method for the synthesis of particular chiral molecules. On the other hand, it certainly provides the avenue to prepare a more diverse range of enantiomerically enriched molecules.[1]



(1*R*,2*R*,3*S*,5*S*)–(–)–cocaine

Asymmetric catalysis is one of the preferred methodologies in asymmetric synthesis because the stereochemistry of a compound in a reaction can be controlled by a substoichiometric amount of a catalyst (frequently less than 1 mol %).[1d] In many cases, the catalyst can also be recycled for use in further reactions.[1]

Reactions involving asymmetric catalysis often involve the conversion of a planar sp^2 carbon centre into a tetrahedral sp^3 carbon centre. Asymmetric hydrogenation of alkenes and ketones, as well as the nucleophilic addition to these groups are examples of such asymmetric reactions (Figure 1.1).[1d]

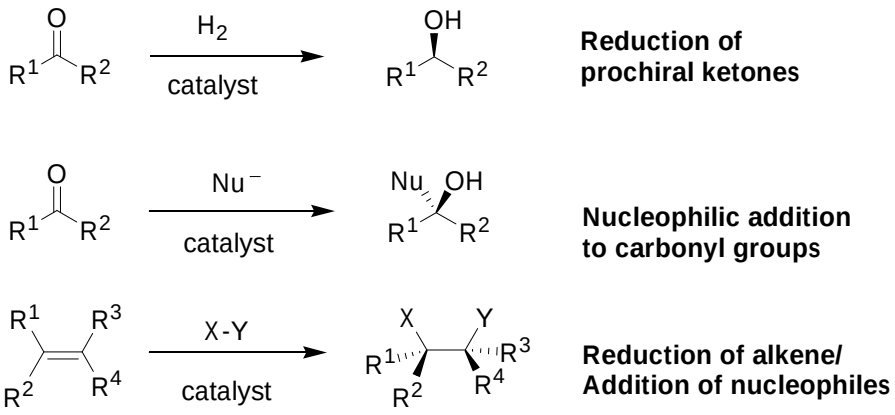


Figure 1.1 Conversion of sp^2 carbon centres to sp^3 carbon centres in asymmetric synthesis.[1d]

1.2 Modes of Activation in Asymmetric Catalysis

Chiral catalysts operate via several common modes of activation such as:[2]

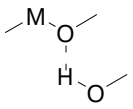
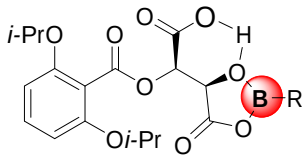
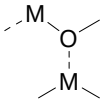
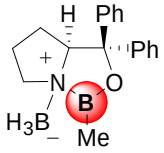
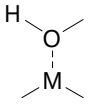
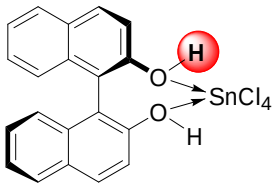
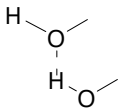
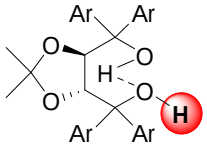
- Modulation of Highest Occupied Molecular Orbital (HOMO)
- Modulation of Lowest Unoccupied Molecular Orbital (LUMO)

- Modulation of Singly Occupied Molecular Orbital (SOMO)
- Hydrogen-bonding (H-bond)
- σ-Bond insertion
- π-Bond insertion
- Atom transfer
- Combined acid system.

1.3 Combined Acid Systems

In asymmetric catalysis, Lewis acids and Brønsted acids can be utilized to obtain high reactivity and stereochemical selectivity. The combination of a Lewis acid with a Brønsted acid *vice versa* is expect to give enhanced catalytic activity.[3a] Yamamoto classified combined acid systems into Brønsted acid-assisted Lewis acid (BLA), Lewis acid-assisted Lewis acid (LLA), Lewis acid-assisted Brønsted acid (LBA), and Brønsted acid-assisted Brønsted acid (BBA) (Table 1.1). [3a] Combined acid systems in asymmetric catalysis can provide an effective chiral environment via associative interactions and more organized structures.[3]

Table 1.1 General types of combined acid systems in catalytic asymmetric synthesis.[3a]

Catalyst system	General structure	Examples
Brønsted acid assisted Lewis acid catalyst (**BLA**)		
Lewis acid assisted Lewis acid catalyst (**LLA**)		
Lewis acid assisted Brønsted acid catalyst (**LBA**)		
Brønsted acid assisted Brønsted acid catalyst (**BBA**)		

1.3.1 Brønsted Acid-Assisted Chiral Brønsted Acid (BBA)

Hydrogen-bonding (H-bond) plays an essential role in human life and is responsible for the 3D-structures of proteins and deoxyribonucleic acid (DNA). The concerted proton transfer in the rate limiting step of heme oxygenase catalytic pathway could be an ideal example (Figure 1.2).[3c] A similar idea can be applied to asymmetric catalysis especially for Brønsted acid catalysis. In this manner, the BBA catalytic concept was developed. It does not only provide a highly organized chiral cavity but also increases the Brønsted acidity of the terminal proton in a much milder fashion. An excellent example of a chiral BBA system was reported by the Rawal

group in 2003 where (-)-*trans-alpha,alpha'*-(dimethyl-1,3-dioxolane-4,5-diyl)-*bis*-diphenylmethanol (TADDOL) was used as an enantioselective catalyst for a hetero Diels-Alder reaction to form a dihydropyran ring system (Scheme 1.1).[4]

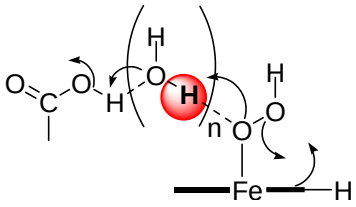
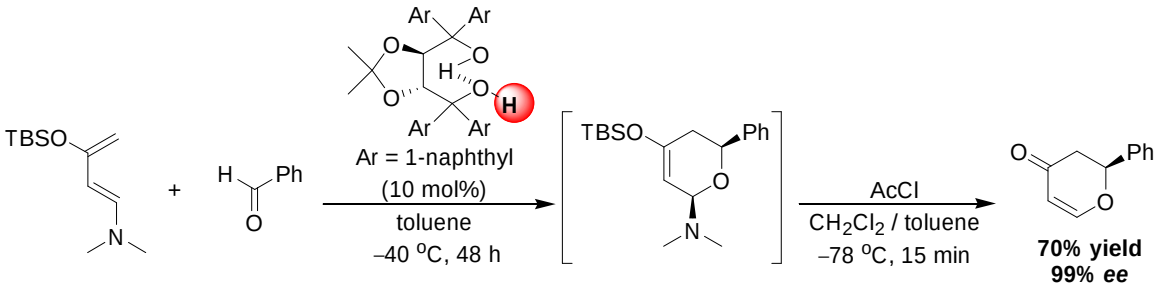
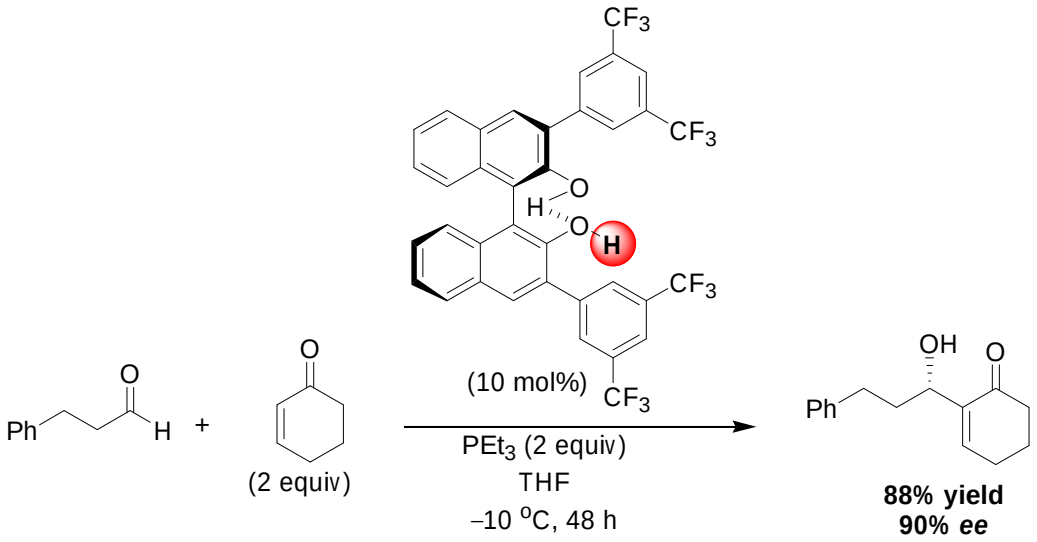


Figure 1.2 Concerted proton transfer in the rate limiting step of heme oxygenase.[3c]



Scheme 1.1 Rawal group's BBA catalyst system for the hetero-Diels-Alder reaction.[4]

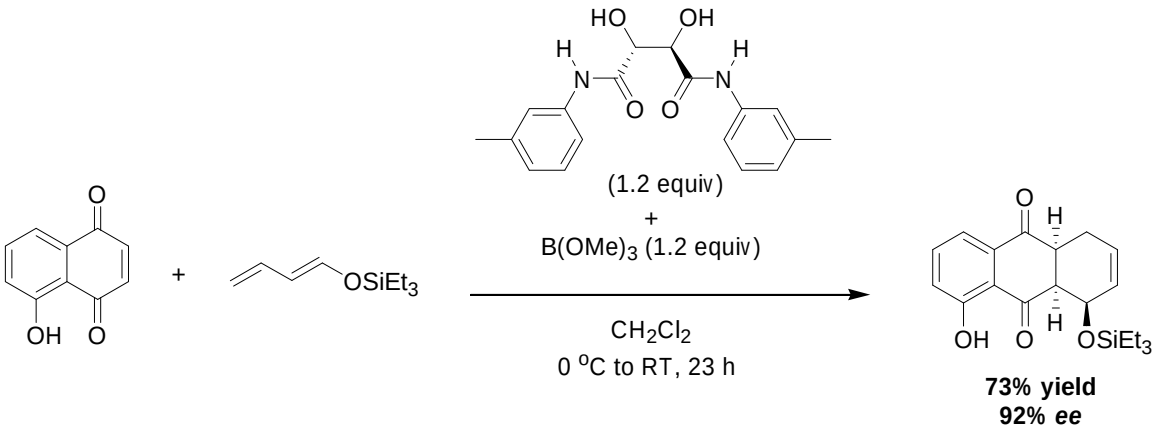
In 2003, Schaus and co-workers[5] reported a catalytic enantioselective variant of Morita-Baylis-Hillman (MBH) reaction between cyclohexenone and aldehydes, catalyzed by a chiral binol-derived BBA catalyst system (Equation 1.1). The asymmetric MBH reaction required two equivalents of triethylphosphane and 2-20 mol% of the chiral catalyst to obtain the products with moderate to good yields (39-88%) and good to excellent enantioselectivities (67-96% *ee*).[5]



Equation 1.1 Binol based BBA catalyst for the asymmetric MBH reaction.[5]

1.3.2 Brønsted Acid-Assisted Lewis Acid (BLA)

In 1986, Yamamoto and co-workers reported a chiral boron reagent derived from $B(OMe)_3$ and (*R*,*R*)-(+)-tartaric acid.[6] This reagent was an efficient promoter of an asymmetric Diels-Alder reaction between naphthoquinone derivatives and various dienes (Equation 1.2). The products were obtained in good to excellent yields (73-96%) and moderate to excellent enantioselectivities (75-92% *ee*). In this paper, Yamamoto and co-workers described the activation mechanism of the catalyst as intramolecular H-bonding between the amide-hydrogens and the naphthoquinone carbonyl group.[6] Later, they proposed another mechanism, in which the Lewis acidity of the boron was increased due to an intramolecular H-bonding between amide-hydrogens and the oxygens attached to the boron center as shown in Figure 1.3.[3]



Equation 1.2 Yamamoto's BLA catalyst system for the asymmetric Diels-Alder reaction.[6]

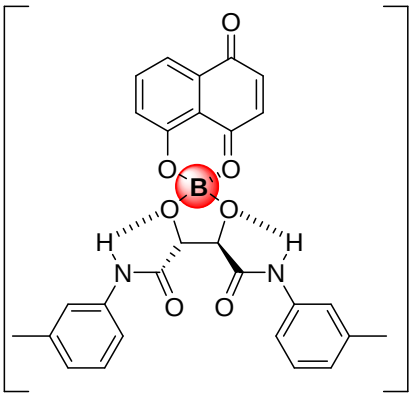
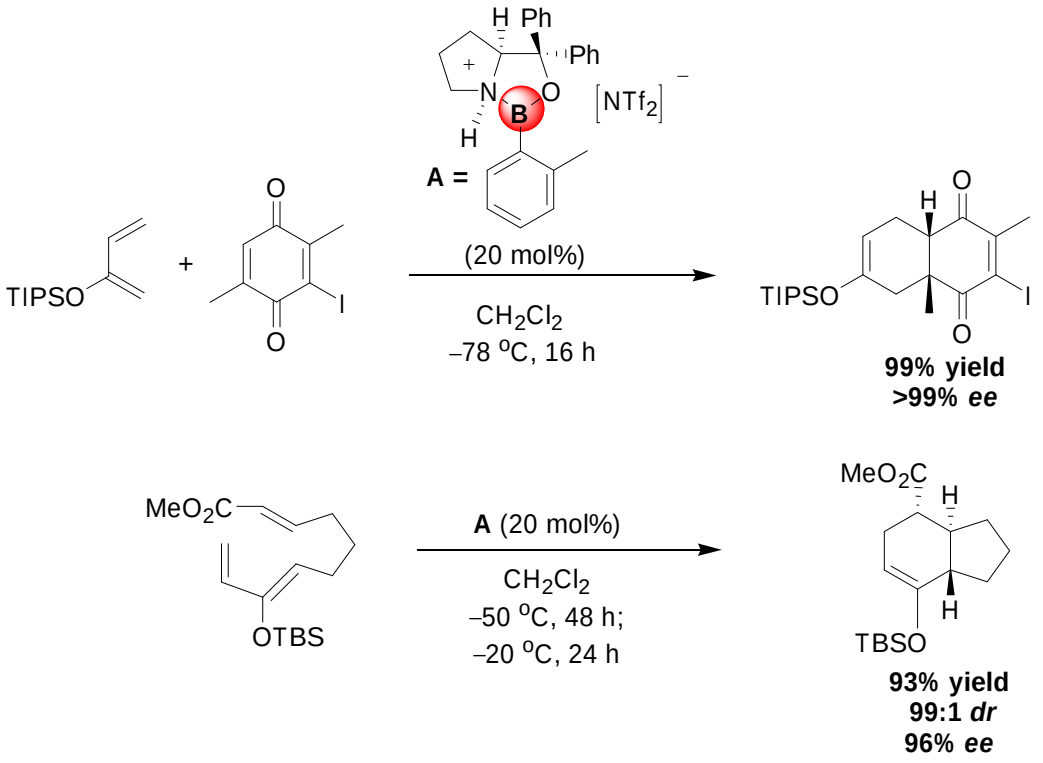


Figure 1.3 Proposed mechanism by Yamamoto and co-workers for their CAB catalyst.[3]

In 2002, Corey and co-workers revealed a new type of catalytic enantioselective Diels-Alder reaction using a chiral oxazaborolidine-derived Brønsted acid-assisted chiral Lewis acid (BLA).[7a] A proline-derived oxazaborolidine as a pre-catalyst and triflic acid as an activator were combined to form a potent chiral cationic Lewis acid.[7a,b] Subsequently, the same group reported a more active and stable chiral Lewis acid, obtained via protonation of a chiral oxazaborolidine with a stronger

Brønsted acid, triflimide ($(CF_3SO_2)_2NH$) (Scheme 1.2).[7c,d] A wide variety of enantioselective Diels-Alder reactions, which were previously beyond the reach of synthetic chemists, were made accessible with these types of catalysts (Scheme 1.2).

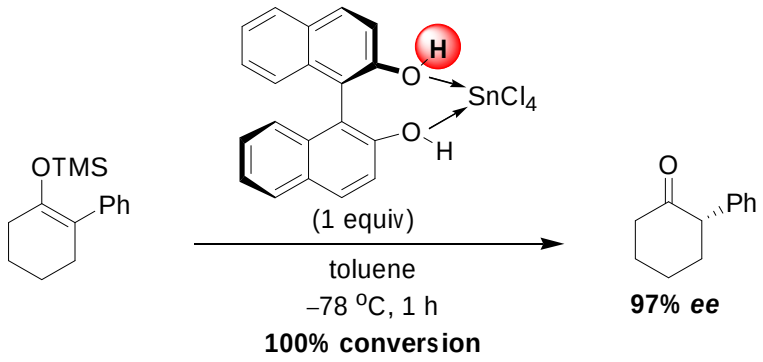


Scheme 1.2 Corey's oxazaborolidinium catalyst in Diels-Alder reactions.[7c,d]

1.3.3 Lewis Acid-Assisted Brønsted Acid (LBA)

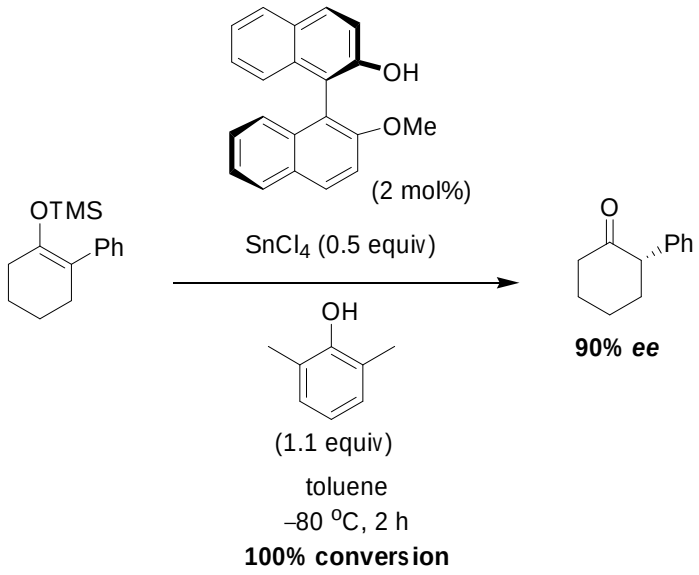
In 1994, Yamamoto and co-workers reported an LBA catalyst system derived from binol and $SnCl_4$ in toluene and this catalyst system was found to be stable in solution even at room temperature.[8a] They demonstrated that silyl enol ethers could be

stereoselectively protonated in the presence of a stoichiometric amount of (*R*)-binol·$SnCl_4$ (Equation 1.3).[8a]



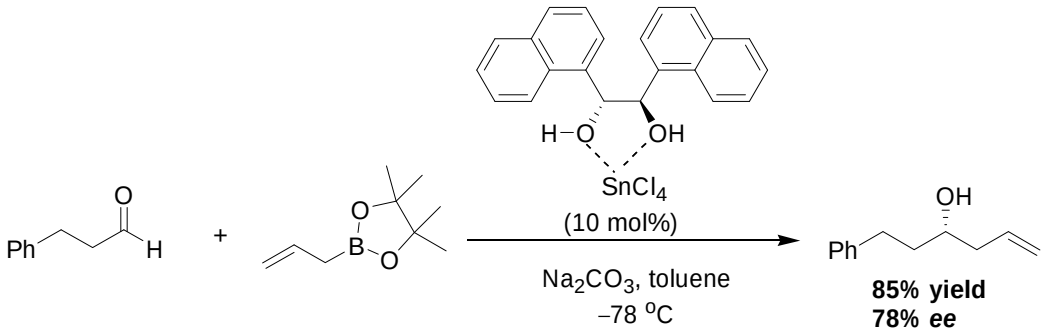
Equation 1.3 Asymmetric protonation with a LBA catalyst by Yamamoto and co-workers.[8a]

In 1996, the Yamamoto group reported an enantioselective variant of the above reaction (Equation 1.3) using a catalytic amount of chiral LBA in the presence of a stoichiometric amount of a proton source such as 2,6-dimethylphenol (Equation 1.4).[8b]



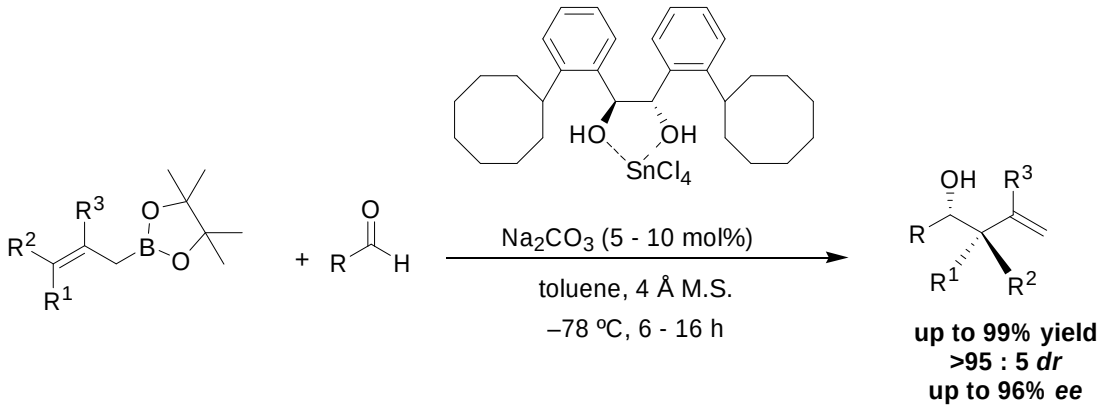
Equation 1.4 A catalytic asymmetric protonation with the LBA catalyst. [8b]

In 2006, the Hall group published the enantioselective allylboration of aldehydes in the presence of a catalytic amount of chiral LBA.[9a] In this report, a chiral LBA catalyst was obtained by combining commercially available (*R*,*R*)-(+)-1,2-di(1-naphthyl)-1,2-ethanediol and tin tetrachloride ($SnCl_4$). Allylation products were obtained in good to excellent yields, but the enantioselectivites were moderate (Equation 1.5).[9a]



Equation 1.5 Chiral LBA catalyzed asymmetric allylation reported by the Hall group.[9a]

In their later studies, the Hall group optimized the chiral LBA system to obtain excellent enantioselectivities in the allylation of aldehydes using a new chiral diol (Vivol) as the diol component (Equation 1.6).[9b]

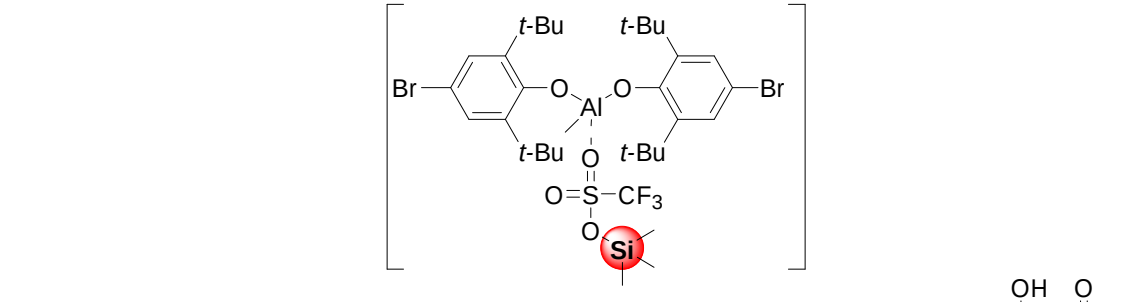


Equation 1.6 An improved LBA system for asymmetric allylation reported by the Hall group.[9b]

1.3.4 Lewis Acid-Assisted Lewis Acid (LLA)

Lewis acid-promoted carbon-carbon bond forming reactions are one of the most important processes in organic synthesis. Many classical organic reactions such as the Friedel-Crafts reaction, the ene reaction, the Diels-Alder reaction, the Mukaiyama aldol synthesis, and allylation reactions are catalyzed by common Lewis acids such as $AlCl_3$, $TiCl_4$, $BF_3{\cdot}Et_2$, or $SnCl_4$. The activity of these Lewis acids depends on the ligands attached to them. The reactivity of a Lewis acid normally increases with more electronegative ligands as substituents on the metal centre. For example, trimethylsilyl trifluoromethane sulfonate (TMSOTf) is more reactive than chlorotrimethylsilane (TMSCl) towards a variety of reactions.[3,10]

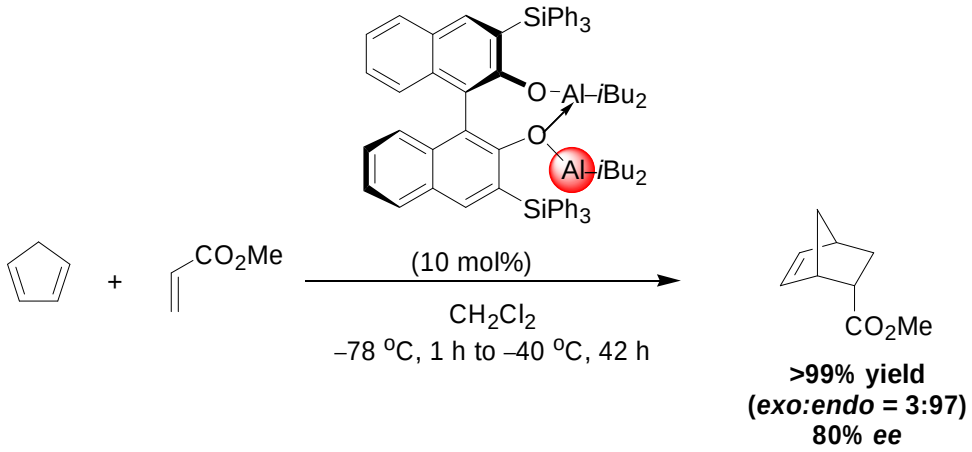
More reactive Lewis acids can also be obtained through a combination with Brønsted acids (BLA, which was discussed in the previous section 1.3.2) or with other Lewis acids (LLA). In 1998, Yamamoto and co-workers reported that the reactivity of a Lewis acid could be enhanced in the presence of another Lewis acid (Equation 1.7).[11] In their report, a Mukaiyama aldol reaction between silyl enol ethers and aldehydes was catalyzed by TMSOTf in the presence of the bulky reagent methylaluminium bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR). In their control experiments, the reactions were found to proceed to give only small amounts of product when either Lewis acids was used independently (Equation 1.7).[11]



Catalyst	Yield (%) (*syn*:*anti*)
MABR	**7** (42:58)
Me_3SiOTf	**15** (75:25)
MABR + Me_3SiOTf	**76** (89:11)

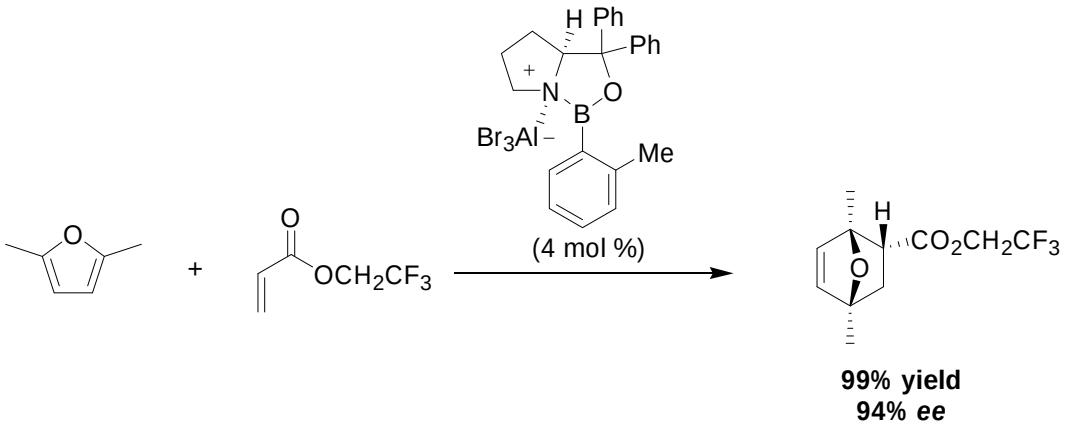
Equation 1.7 The LLA catalyst system for Mukaiyama aldol reactions by Yamamoto.[11]

In 2001, Kobayashi and co-workers reported a chiral LLA catalyst system for asymmetric Diels-Alder reactions of cyclopentadiene and methyl acrylate (Equation 1.8).[12] The chiral dialuminium catalyst was prepared by reacting (*R*)-3,3'-bis(triphenylsilyl)binaphthol with diisobutylaluminium hydride.[12]



Equation 1.8 LLA catalyzed Diels-Alder reaction reported by the Kobayashi group.[12]

In 2007, the Corey group introduced a new and unusually powerful and effective chiral oxazaborolidine-aluminum bromide complex as an LLA catalyst system for enantioselective Diels-Alder reactions (Equation 1.9).[13]



Equation 1.9 Corey's LLA oxazaborolidine catalyst in a Diels-Alder reaction.[13]

1.4 Carbonyl Allylation Chemistry

Asymmetric allylation and other carbonyl additions are important and very popular ways of making carbon–carbon bonds in a stereocontrolled fashion. The products obtained from carbonyl allylation and crotylation are acetate or propionate units respectively, which occur in many biologically active natural products. Boron (B), silicon (Si), tin (Sn), titanium (Ti), and zinc (Zn) based allylation reagents are commonly used in allylation chemistry.[14,15] Denmark classified these allyl metal reagents into three mechanistically different types. The two most common types are shown in Figure 1.4.[16]

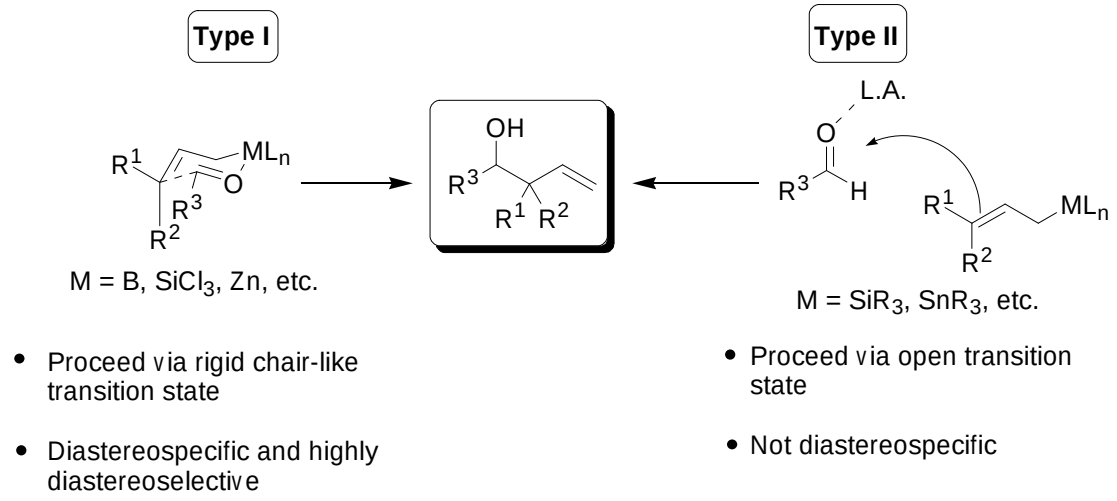
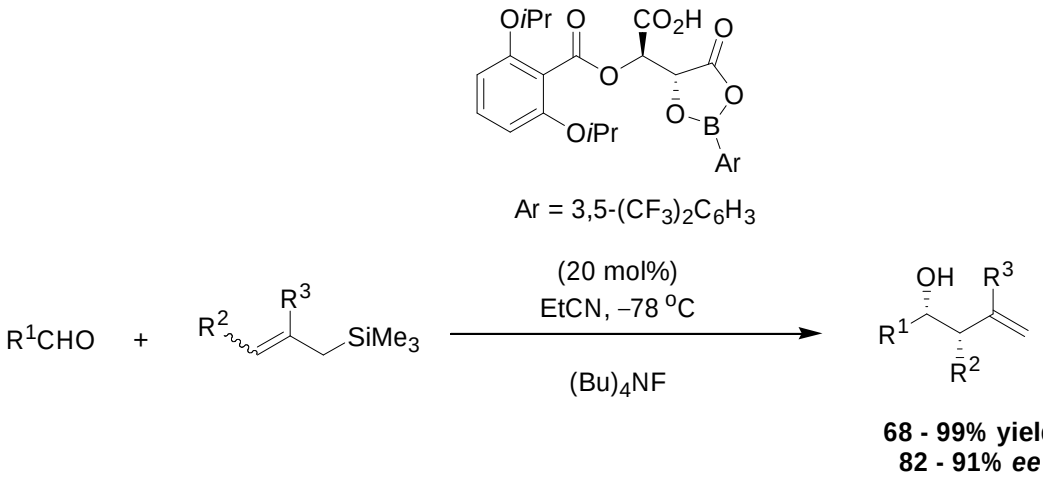


Figure 1.4 Denmark's mechanistic interpretation of allylic metal reagents.[16]

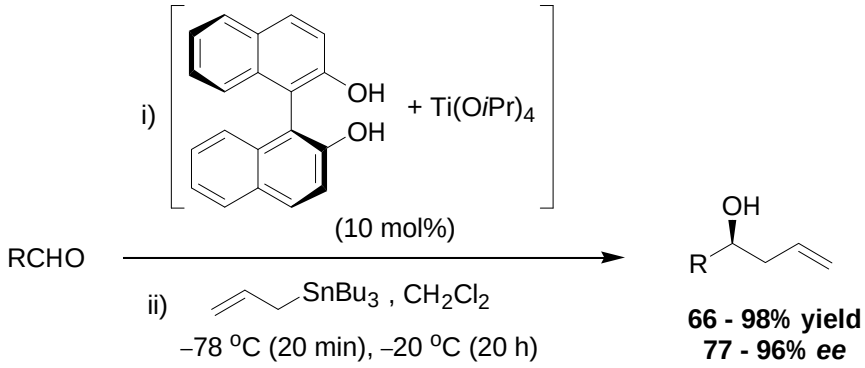
1.4.1 Chiral Lewis Acid Activation in Allylation Chemistry

One of the important allylation reactions is the external Lewis acid-catalyzed addition of allylsilane and stannane reagents to carbonyl compounds. These reactions usually occur through an open (acyclic) transition state via an S_E' mechanism (Type II). One advantage of these asymmetric allylation reactions is that they require only a substoichiometric amount of a chiral source. There are many chiral Lewis acids reported in asymmetric allylation chemistry to date.[17] Frequently, chiral catalysts developed for other reactions, such as Mukaiyama aldol and Diels-Alder reactions, can also be used in asymmetric allylation chemistry. In 1991, Yamamoto and co-workers illustrated that Sakurai-Hosomi allylation of aldehydes could be catalyzed by a chiral acyloxyborane (CAB) Lewis acid to yield homoallylic alcohols in moderate to excellent yields and good enantioselectivities (Equation 1.10).[18]



Equation 1.10 Asymmetric allylation with a CAB catalyst by Yamamoto.[18]

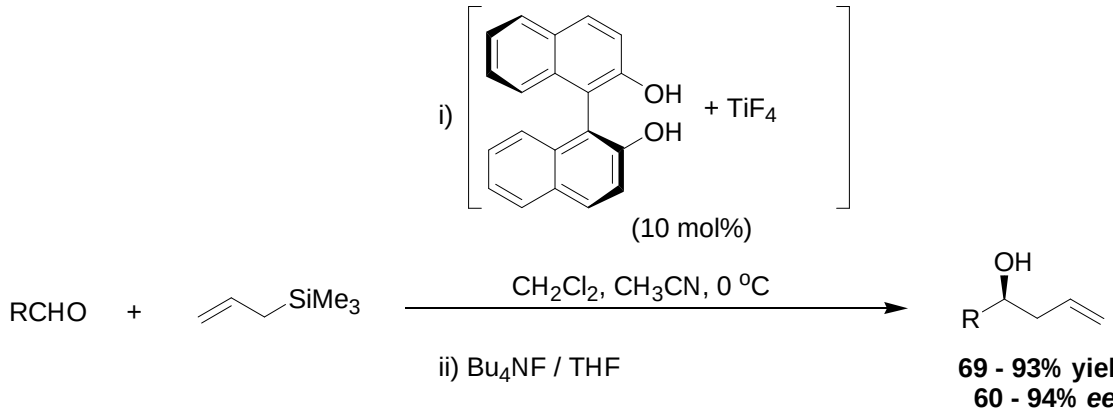
In 1993, Keck and co-workers demonstrated that asymmetric allylation could be achieved with the chiral Lewis acid catalyst system obtained by combining chiral binol with titanium tetra-*iso*propoxide (Equation 1.11). The products were obtained in moderate to excellent yields and enantioselectivities.[19]



Equation 1.11 Keck allylation of aldehydes with a chiral LA system.[19]

In 1996, Carreira and co-workers reported a new catalyst system for the asymmetric allylation between aldehydes and allyltrimethylsilane (Equation 1.12).[20] The chiral catalyst was obtained by reacting (*S*)- or (*R*)-binol with titanium tetrafluoride. It was

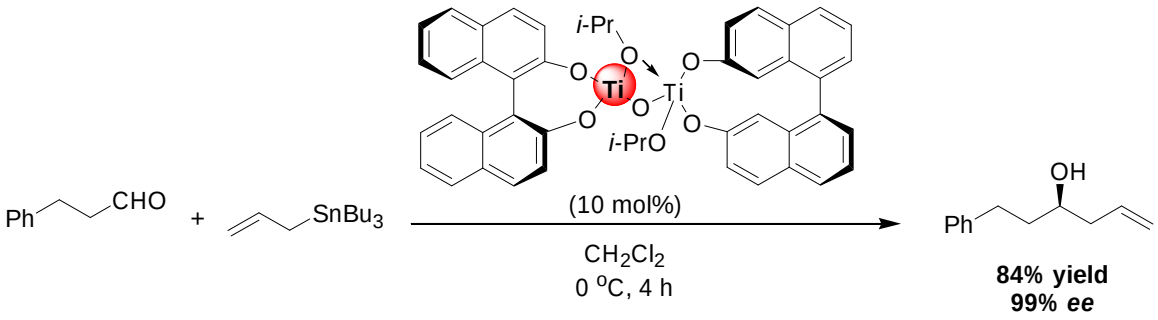
found to be more reactive than the catalyst system[19] reported by Keck and co-workers.



Equation 1.12 Allylsilation catalyzed by a new chiral LA reported by the Carreira group.[20]

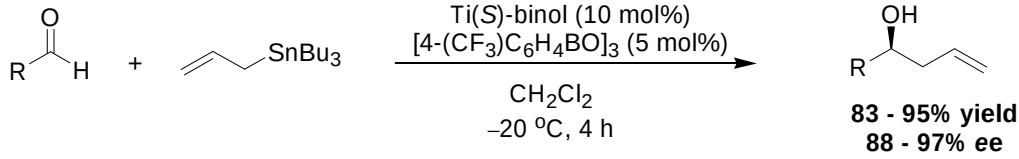
1.4.2 Lewis Acid Assisted Lewis Acid Catalyzed Allylation

In 2003, Maruoka and co-workers developed a new chiral bis-Ti^{IV} oxide as a strong carbonyl activator (Equation 1.13).[21] The chiral bis-Ti^{IV} complex was produced either by reacting bis(triisopropoxy)titanium oxide [(iPrO)$_3$Ti-O-Ti(OiPr)$_3$] with (*S*)-binol or by treating ((*S*)-binaphthoxy)isopropoxytitanium chloride with silver (I) oxide.



Eqaution 1.13 LLA assisted allylation published by Maruoka and co-workers.[21]

In 2004, Yamamoto's group revealed a new chiral Lewis acid assisted Lewis acid catalyst system for the asymmetric allylation of aldehydes with allyltin compounds.[22] Boroxine was used to activate the Ti-binol-catalyzed system in this case (Equation 1.14).



Equation 1.14 Allylation catalyzed by the LLA system reported by the Yamamoto group.[22]

1.5 Double Allylation Reagents

Multifunctional reagents that display chemodivergent reactivity are very useful in organic synthesis.[23,24] Using these reagents, highly complex molecules can be prepared in fewer steps with high stereoselectivity. Towards this end, chiral double-allylation reagents are one type of multifunctional reagents. They are very attractive

and useful in synthetic chemistry because these reagents can react with simple starting materials such as aldehydes and ketones to produce complex products. There are three structural types of double-allylation reagents depending on the position of the second metal atom (Figure 1.5).[23] The second metal provides a latent allyl metal that can be unmasked after the first allylation with different electrophiles.

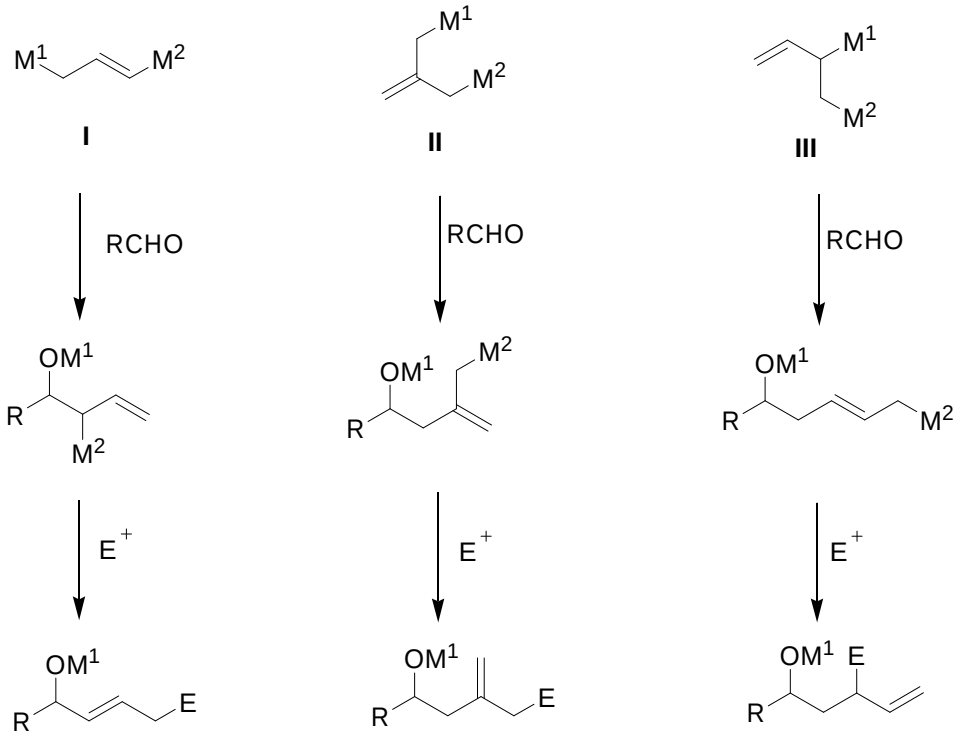
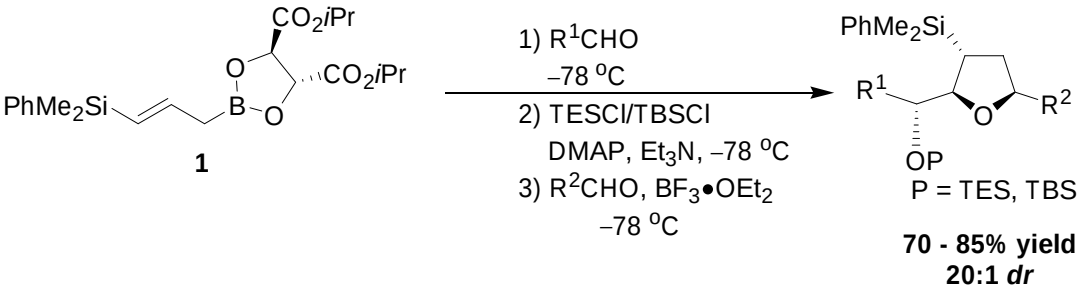


Figure 1.5 Three different types of double allylation reagents.

In 1990, Roush and co-workers introduced the first double allylation reagent **1** based on boron and silicon metals (Equation 1.15).[24a] In this double allylation reagent **1**, the silicon atom was placed at the γ position of an allylboronate reagent. They demonstrated the synthesis of 1,2-*syn*[24a] and 1,2-*anti*-diols[24b], and polysubstituted

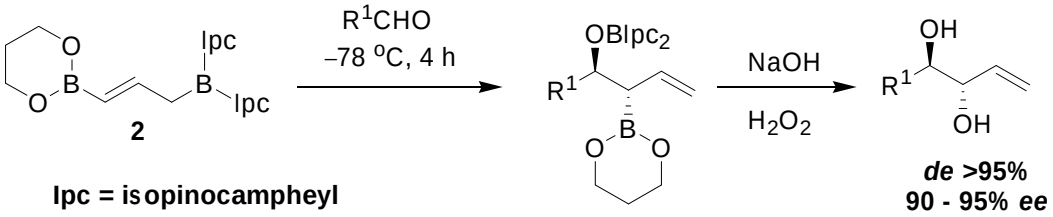
tetrahydrofurans[24c] with high diastereoselectivities (Equation 1.15) and moderate enantioselectivities.



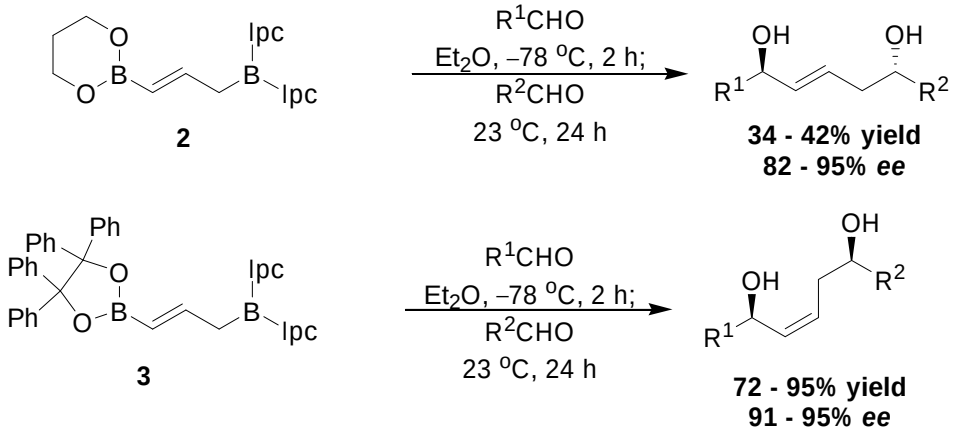
Equation 1.15 Preparation of an all *cis*-trisubstituted tetrahydrofuran with Roush group's bimetallic reagent **1**.[24c]

In 1995, Brown and co-workers reported another type of double allylation reagent, borane **2**, in which a second boron atom was placed at the γ position of an allylborane reagent. [25] In their report, they used this reagent to synthesize 1,2-*anti*-diols (Equation 1.16). After the first allylation, the second boronate was oxidatively cleaved under hydrogen peroxide conditions to produce 1,2-*anti*-diols. They obtained diastereoselectivities of >20:1 and enantioselectivities of 90 to 95% *ee* for the 1,2-diol products. In 2002, Roush and co-workers showed that reagent **2** could be used as a double allylation reagent (Scheme 1.3).[26a] In a one-pot procedure, 1,5-*anti*-diols were obtained with allylation reagent **2** and different aldehydes. They observed moderate to good yields (65-87%), excellent diastereoselectivities (20:1), and good to excellent enantioselectivities (87-95% *ee*). In order to obtain 1,5-*syn*-diols, they reported another double allylation reagent, tetraphenyl pinacol derivative **3** (Scheme 1.3).[26a] They observed excellent yields (88-95%) and good to excellent

enantioselectivities (92-95% ee) with reagent **3**. Fragments C(1)-C(25)[26b] and C(43)-C(67)[26c] of a marine natural product, amphidiol **3,** were also synthesized by Roush and co-workers using these double allylation reagents.



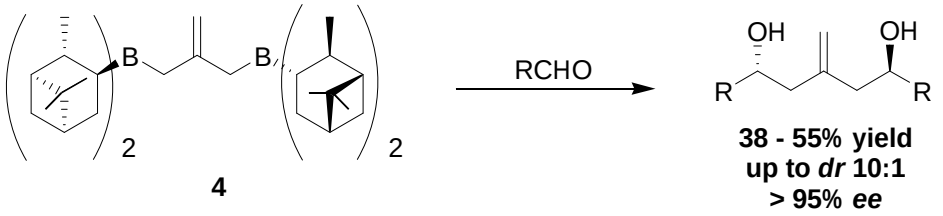
Equation 1.16 Synthesis of 1,2-*trans*-diols by Brown.[25]



Scheme 1.3 Preparation of 1,5-diols with double allylation reagents.[26a]

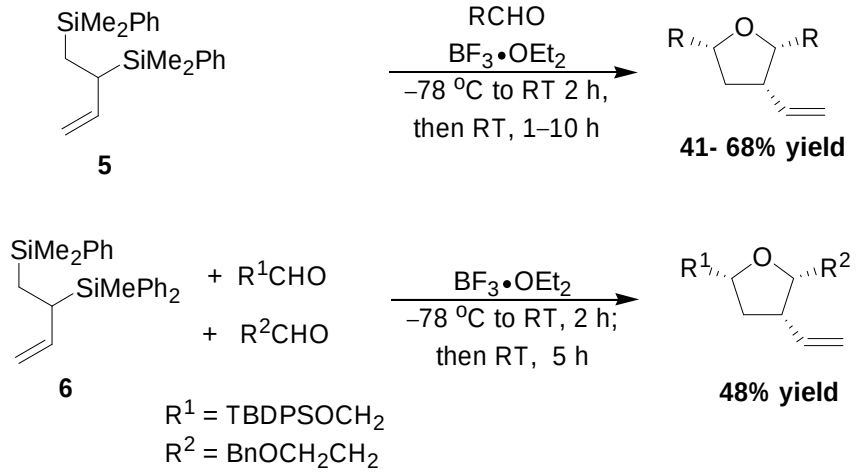
In 1999, Barrett and co-workers developed double allylation reagent **4** based on two boron atoms (Equation 1.17).[27a] In this reagent, both boron atoms are placed at the β position of a central vinyl unit. C_2–symmetric 3-methylene-pentane-1,5-*anti*-diols could be achieved with excellent enantioselectivities using this double allylation reagent **4** in a one-pot process. These diols were previously obtained via a double

addition of aldehydes to 2-methylpropene dianion and products derived from these reactions often produced low diastereoselectivity (1:1) and low enantioselectivity.[27]



Equation 1.17 Preparation of C_2–symmetric 1,5-*anti*-diols with Barrett's double allylation reagent.[27a]

In 2004, Sarkar and co-workers developed racemic type III double allylation reagents **5** and **6** based on silicon atoms (Scheme 1.4).[28] In these reagents, the second silicon atom was placed at the α position of an allylsilane moiety. They demonstrated the synthesis of polysubstituted tetrahydrofurans (THF) via these double allylation reagents, either using the same aldehyde or with two different aldehydes. The products were obtained in moderate yields and low diastereoselectivities (3.1:1) favoring the desired products.[28]



Scheme 1.4 Syntheses of polysubstituted tetrahydrofurans with Sarkar's double allylation reagents.[28]

In 2007, a novel class of chiral double-allylation reagents examplified by **7** was introduced by the Hall group.[23] In this double allylation reagent, **7**, the silicon atom is placed at the α position of an allylboronate moiety (Figure 1.6). Unlike other double allylation reagents, this reagent contains a stereogenic centre α to the allylboronate moiety, which is expected to transfer its chirality to the product. Lewis acid assisted allylboration was preferentially observed over allylsilation with reagent **7** and carbonyl substrates, thereby allowing a controlled, chemoselective reactivity.[23] Hall and Peng have shown the utility of these double-allylation reagents in the stereoselective synthesis of trisubstituted furans, vinylcyclopropanes, and smaller oxabicyclic compounds (Figure 1.6).[23]

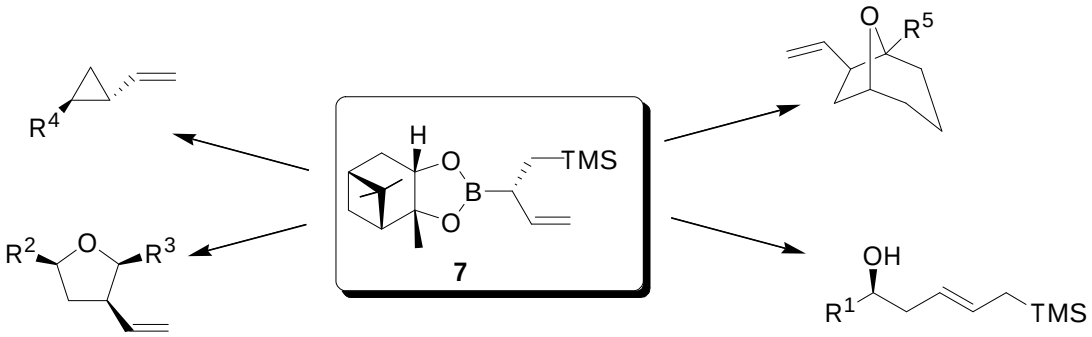


Figure 1.6 The many uses of Hall group's double allylation reagents.[23]

1.6 Thesis Objectives

1.6.1 Project I: Design and Evaluation of a New Lewis Acid Assisted Lewis Acid Catalyst System (LLA)

Despite of the prevalence of asymmetric catalysts, there is still room for improved catalyst systems. In particular, catalyst systems incorporating stable and environmentally friendly atoms (Si or B) and requiring low catalyst loading are desirable. The first part of the project is to explore a chiral catalyst system based on the boron atom, with applications in asymmetric allylation chemistry and other transformations.

In 2002, the Hall group[29] and the Miyaura group[30] discovered that Lewis acids could catalyze allylboration of aldehydes. Since the stereospecificity was preserved under these new conditions, Hall and co-workers hypothesized that the reaction proceeds through a closed six-membered transition state (Figure 1.7).[31] This transition model was later supported by a molecular orbital calculation study by Sakata and Fujimoto.[32]

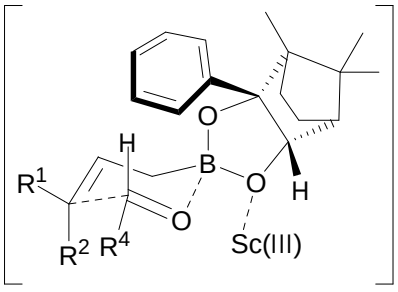
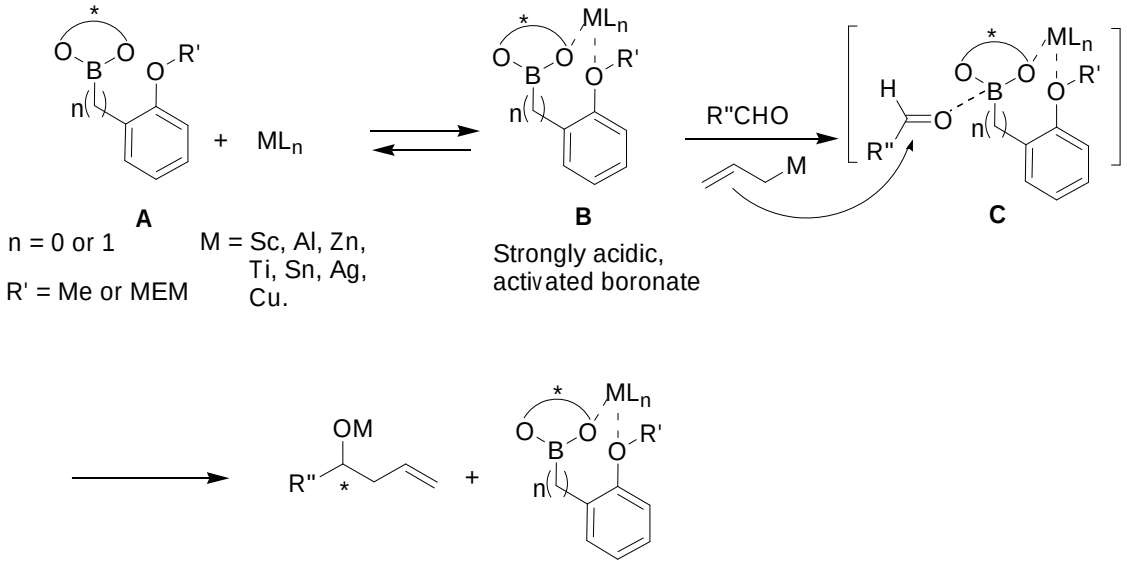


Figure 1.7 A proposed transition state for Lewis acid assisted allylboration.[31]

From this observation, it was hypothesized that the internal allyl moiety could be replaced with an external nucleophile (allylmetal, enol ether, etc…). Therefore, it was predicted that the allylation reaction could proceed as shown in Scheme 1.5, where the addition of an allyl metal reagent is catalyzed by an LLA catalyst system. In this LLA catalyst system, a metal Lewis acid will coordinate first with one of the oxygen atoms of a boronic ester pre-catalyst (Scheme 1.5, **A**) to make the boron atom more Lewis acidic (Scheme 1.5, **B**). This activated boronic ester pre-catalyst can now activate a carbonyl moiety as shown in Scheme 1.5 (**C**) to promote enantioselective reactions.



Scheme 1.5 A generic scheme for an allylation reaction catalyzed by Lewis acid assisted Lewis acid catalyst system.

In this section of the thesis, many boron based pre-catalysts similar to the one shown in Scheme 1.5 (**A**) were synthesized and their activity as pre-catalysts were tested on

allylation reactions between allyl metal reagents and benzaldehyde or hydrocinnamaldehyde in the presence of many other Lewis acids.

1.6.2 Project II: Further Applications of Double-Allylation Reagent 7

In previous studies, Hall and Peng disclosed the utility of the double-allylation reagent **7** (see Figure 1.6) in the stereoselective synthesis of trisubstituted furans, vinylcyclopropanes, and smaller oxabicyclic compounds (see previous section 1.5 of this thesis).[23] As the second part of my thesis, further applications of reagent **7** towards the synthesis of larger oxabicyclic compounds, a one-pot synthesis of furan rings, and the synthesis of pyrrolidines were examined (Figure 1.8).

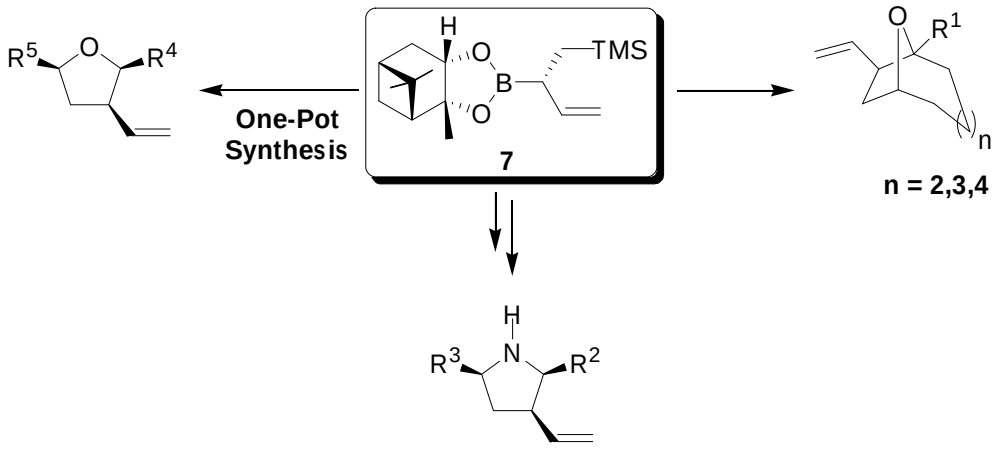
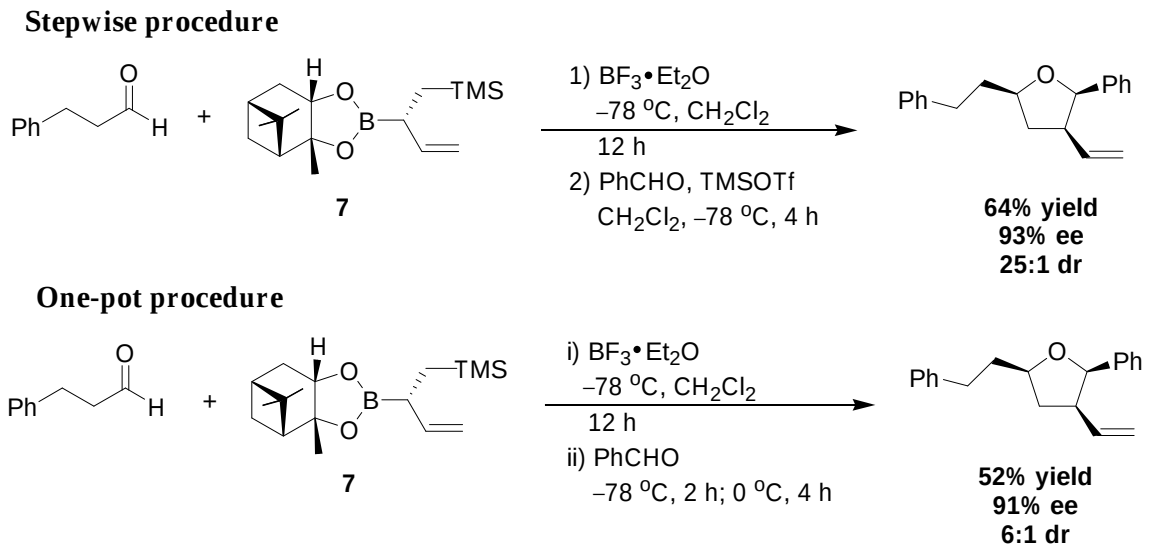


Figure 1.8 A schematic representation of target compounds using the double allylation reagent **7**.

Previously, the synthesis of trisubstituted furans in high diastereoselectivities (>25:1) was achieved via a stepwise procedure with isolation of the first allylation intermediate (Scheme 1.6, top), but when subjected to the one-pot protocol, the diastereoselectivities were moderate (Scheme 1.6, bottom, 6:1 *dr*). I investigated the

optimization of one-pot reaction conditions with the goal of improving diastereoselectivities.



Scheme 1.6 An illustration of stepwise and one-pot syntheses of a substituted furan ring.

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Chapter 2: Design and Evaluation of a New Lewis Acid–Assisted Lewis Acid Catalyst System (LLA)

2.1 Syntheses of Boronic Ester Components of LLA Catalysts

Based upon the hypothesis presented in the previous section (1.6.1), the following boronate molecules were synthesized in order to examine our theory (Figure 2.1). Based upon previous observations of Lewis acid-catalyzed allylboration reactions,[1,2] we decided to synthesize boronic ester compounds **8**-**14** (Figure 2.1). In particular, we expected alkylboronic esters **10**, **11**, and **14** to be better mimics of the allylboronate as shown in Figure 1.7 (previous section of this thesis). The chirality of the molecules was introduced through the use of known chiral auxiliaries such as (+) or (–)–pinane diol and Hoffman's camphordiol.

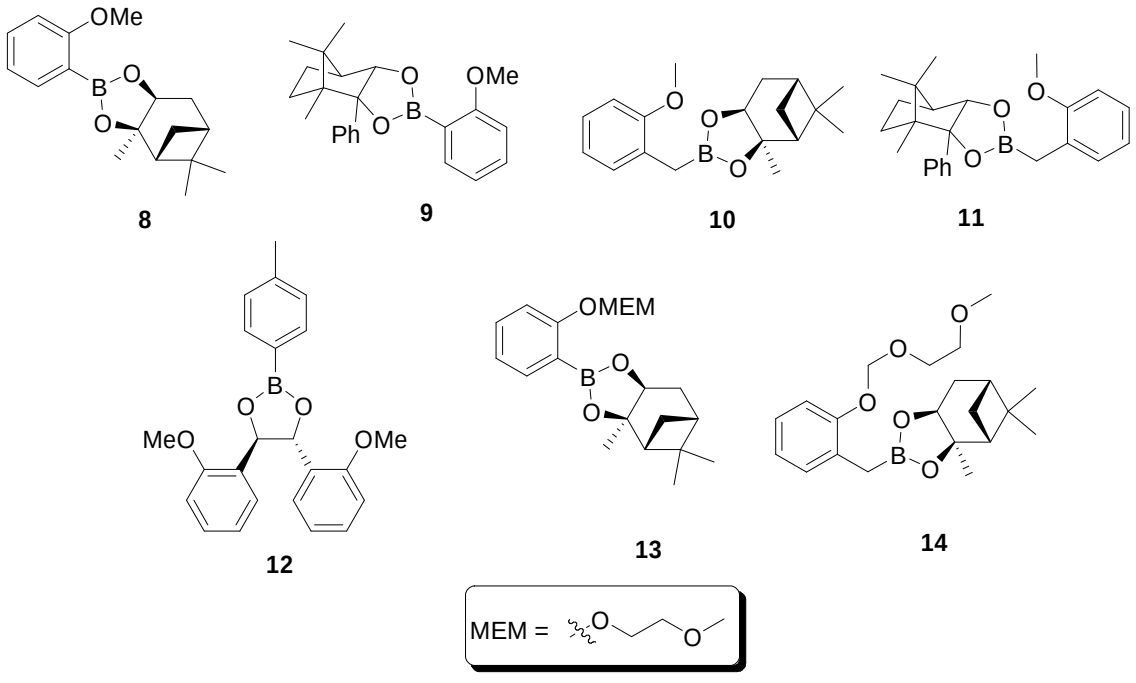


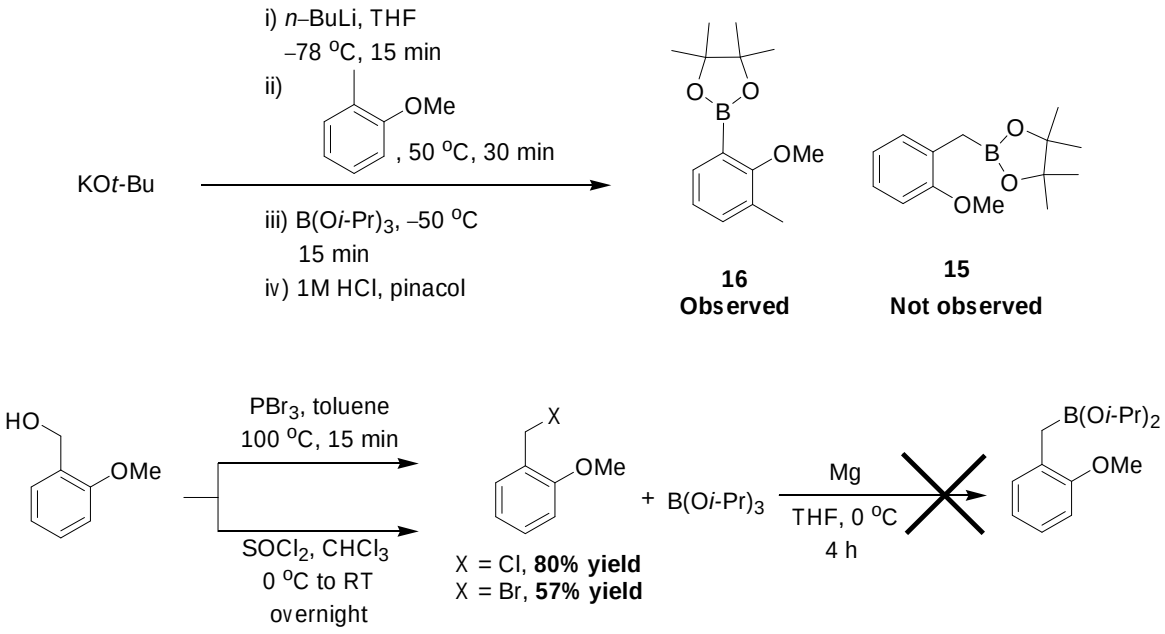
Figure 2.1 Structures of targeted boronic ester pre–catalysts to test our hypothesis.

2.1.1 Preparation of Compound 15

Racemic desired product is needed to obtain high performance liquid chromatography conditions to separate enantiomeric peaks. This will facilitate calculations to determine the enantiomeric excess of the product. In addition, development of the synthetic route of achiral pre-catalyst could be used to obtain an optimized synthetic route for the preparation of chiral versions of boronic esters without wasting expensive known chiral auxiliaries in the optimization process.

The procedure outlined in Scheme 2.1 (top) was first attempted for the synthesis of achiral boronic ester pre-catalyst **15**, but all attempts towards the synthesis of this boronic ester yielded none of the desired product. It was expected that the Schlosser base would predominantly deprotonate the hydrogen of the methyl group in 1-methoxy-2-methyl benzene (Scheme 2.1, top), but it deprotonated the aromatic hydrogen instead. Consequently, arylboronic ester **16** was obtained instead of benzylicboronic ester **15** (Scheme 2.1, top). Then, another approach for the synthesis of boronic ester **15** was carried out as outlined in Scheme 2.1 (bottom). It was expected that boronic ester **15** could be achieved via reacting a Grignard reagent with triisopropyl borate as shown in Scheme 2.1 (bottom). Therefore, the hydroxyl group of *o*-methoxybenzyl alcohol was first converted to a bromide with PBr_3 reagent.[3] Next, the following steps were carried out in sequences to produce the boronic ester **15**; preparation of the Grignard reagent, addition of triisopropyl borate to the Grignard reagent, acid hydrolysis, and treatment of the reaction mixture with pinacol. Unfortunately, no desired boronic ester **15** was obtained, only the

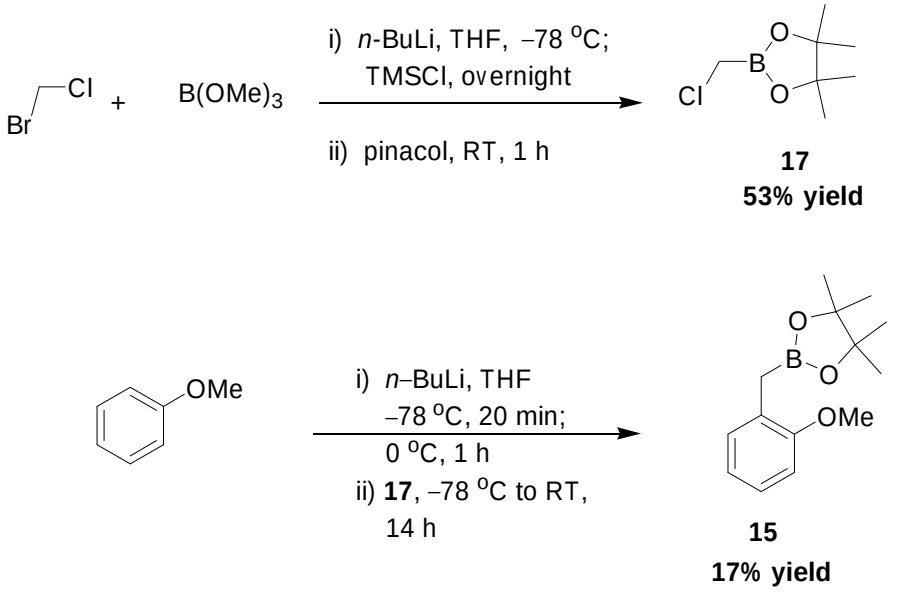
homocoupling product was obtained in all cases. The less the reactive chloro–Grignard reagent was prepared as the next step to try to minimize homocoupling. The hydroxyl group was transformed into a chloride group[4a] using $SOCl_2$ (Scheme 2.1) followed by organomagnesium formation and addition of triisopropyl borate to the resulting Grignard reagent. Unfortunately, a similar result was observed with the chloro–Grignard reagent like as in the case of the bromo–Grignard reagent. There was no desired product observed even when triisopropyl borate was present during the formation of the Grignard reagent.[4b]



Scheme 2.1 Unsuccessful attempts towards the synthesis of boronic ester **15**.

Therefore, another approach was then taken to obtain pre–catalyst **15** (Scheme 2.2). Since the Schlosser base deprotonates the *ortho*–position of methoxy benzene, this lithium *ortho*-benzene anion molecule could be reacted with a α-haloboronic ester[5]

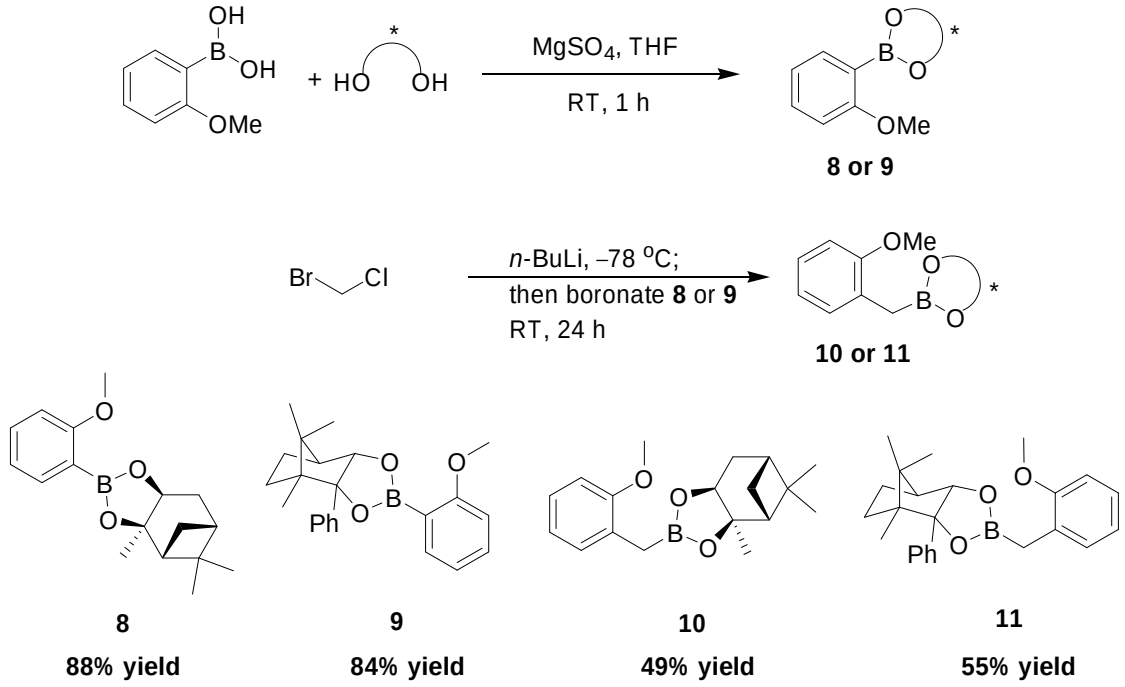
to access boronic ester **15**. To this end, α-chloroboronic ester **17** was synthesized first as outlined in Scheme 2.2 using Matteson homologation chemistry.[6] Next, this boronic ester **17** was reacted with lithium *o*-methoxy benzene anion formed *in situ* to obtain boronic ester **15**.[7] This method produced the desired boronic ester in a very low yield (17%).



Scheme 2.2 Synthetic scheme for the preparation of achiral boronic ester **15**.

Because the above procedure (Scheme 2.2) was lengthy and yielded the desired product in low yield, another approach was explored to prepare the target molecule. Since numerous boronic acids are available on the market, using them as starting materials would be advantageous. After careful consideration of all the commercially available boronic acids, *o*-methoxy phenyl boronic acid was selected as a suitable starting boronic acid for the preparation of the desired boronic esters **8**–**11** (Scheme 2.3). First, the boronic acid was coupled with the corresponding diols

to produce boronic esters **8** and **9** and subsequent Matteson homologation with the lithium anion derived from bromochloromethane led to the formation of desired boronic ester **10** and **11**.[6,8] This approach was short and provided sufficient quantities of the desired products with moderate yields (Scheme 2.3).



Scheme 2.3 A short and efficient method to synthesize chiral boronic esters **8**–**11**.

2.1.2 Syntheses of Chiral Boronic Ester Pre-Catalysts 13, 14, 19, and 20

After successful syntheses of the desired boronic esters **8**–**11**, further modification of the catalysts to enhance the coordinating ability was carried out, which may facilitate the formation of a complex between chiral boronic ester pre-catalysts with other Lewis acids. More oxygen atoms adjacent to the boron center should increase the chelating ability with incoming Lewis acids (Figure 2.2). Therefore, the

methoxyethoxymethyl (MEM) protecting group was envisioned for this route and could be introduced at the *ortho*-position of the benzene ring in the boronic esters. The synthesis of the desired catalysts was initially planned as outlined in Scheme 2.4. First, *o*-bromophenol was protected with the MEM group[9] followed by metal halogen exchange of bromide to lithium with *n*-BuLi, addition of trimethylborate to the reaction mixture, and an acidic work up produced the corresponding boronic acid.[8] The crude boronic acid was coupled with (+) or (-)-pinane diol or pinacol to provide the desired boronic esters **13** and **19**. Finally, the target pre-catalyst molecules **14** and **20** were obtained via a Matteson homologation methodology as in Scheme 2.4.

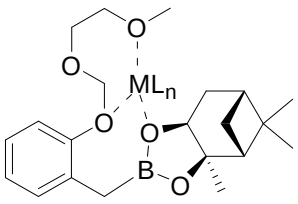
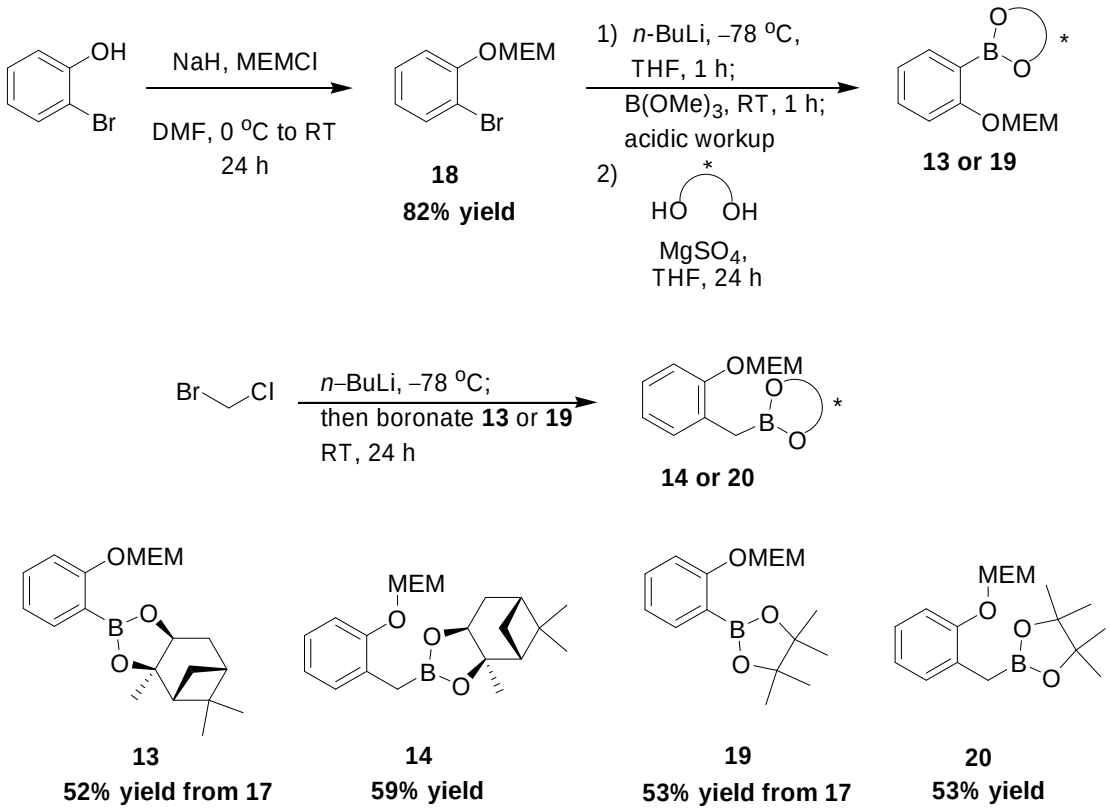


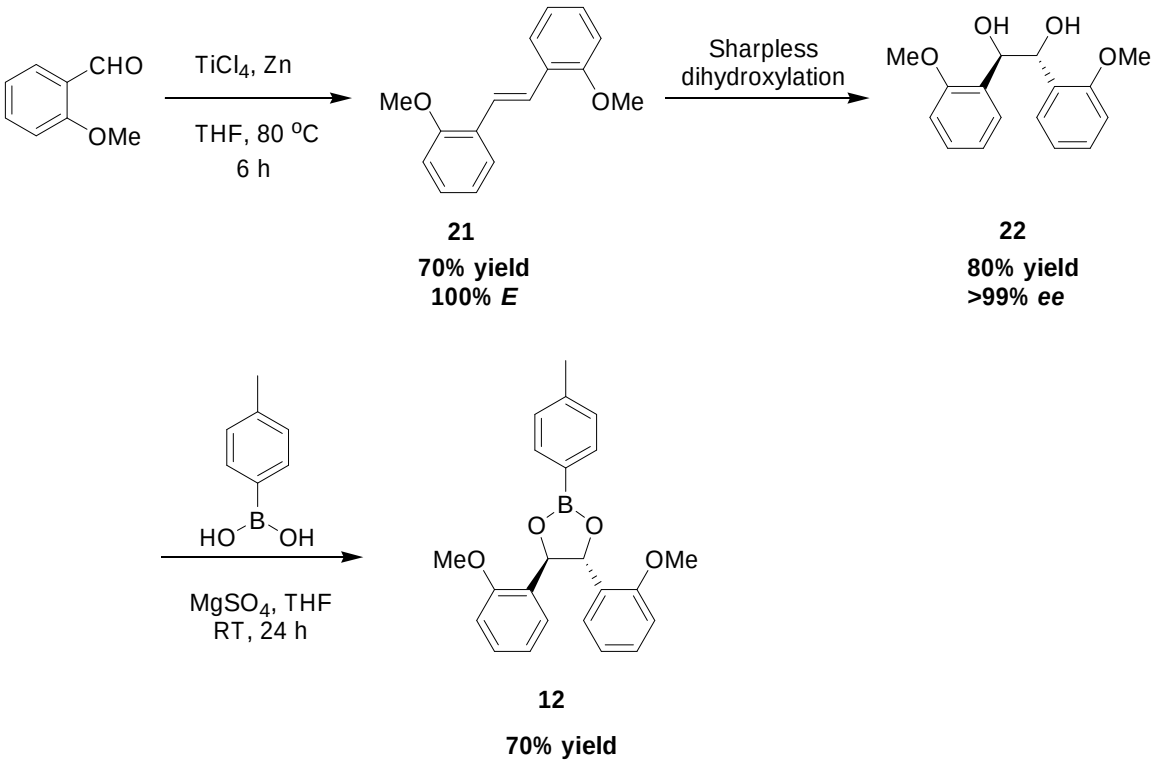
Figure 2.2 Example of putative structure of complex between MEM-protected boronic ester with another Lewis acid.



Scheme 2.4 Preparation of MEM-containing boronic esters **13**, **14**, **19**, and **20**.

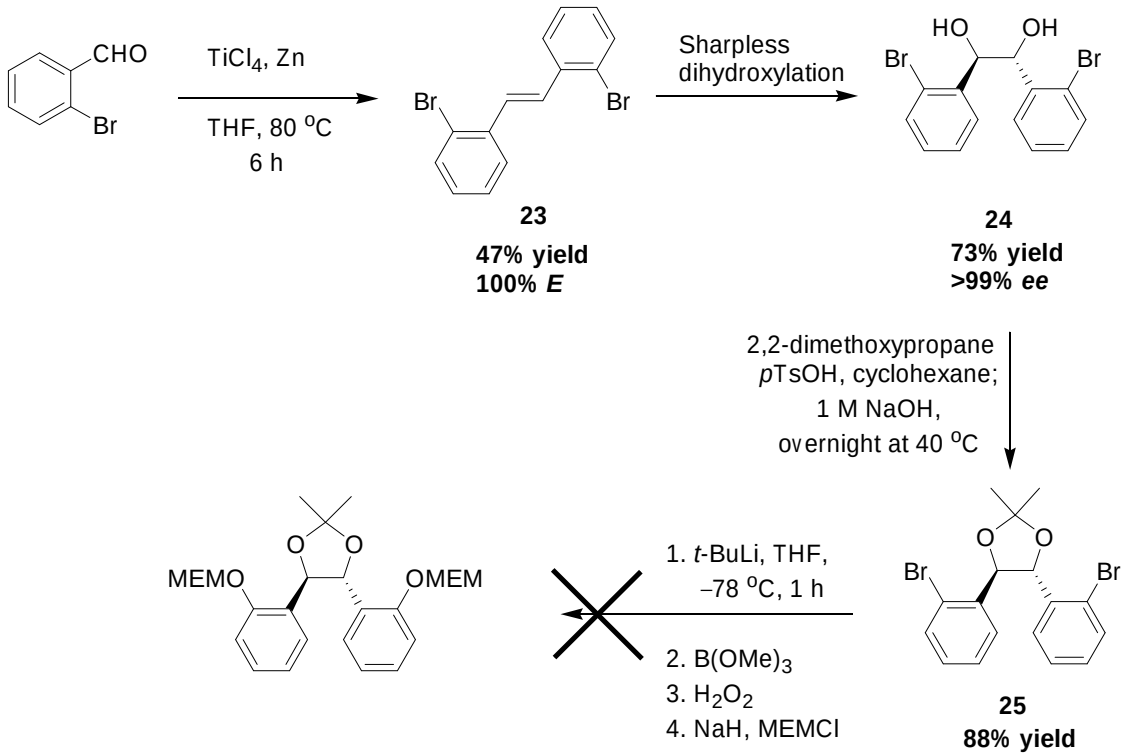
2.1.3 Preparation of Boronic Ester 12

Boronic ester pre-catalyst **12** was synthesized as shown in Scheme 2.5. First, *o*-methoxy benzaldehyde was reacted under McMurry coupling conditions[10] to produce styrene derivative product **21** with only the *trans* isomer observed as product. Compound **21** was then subjected to a Sharpless asymmetric dihydroxylation[11] to yield diol **22** with excellent enantiomeric purity (>99% ee). Finally, *p*-tolyl boronic acid was reacted with chiral diol **21** to yield the desired boronic ester **12** with good yield.



Scheme 2.5 Synthetic scheme for the preparation of boronic ester **12**.

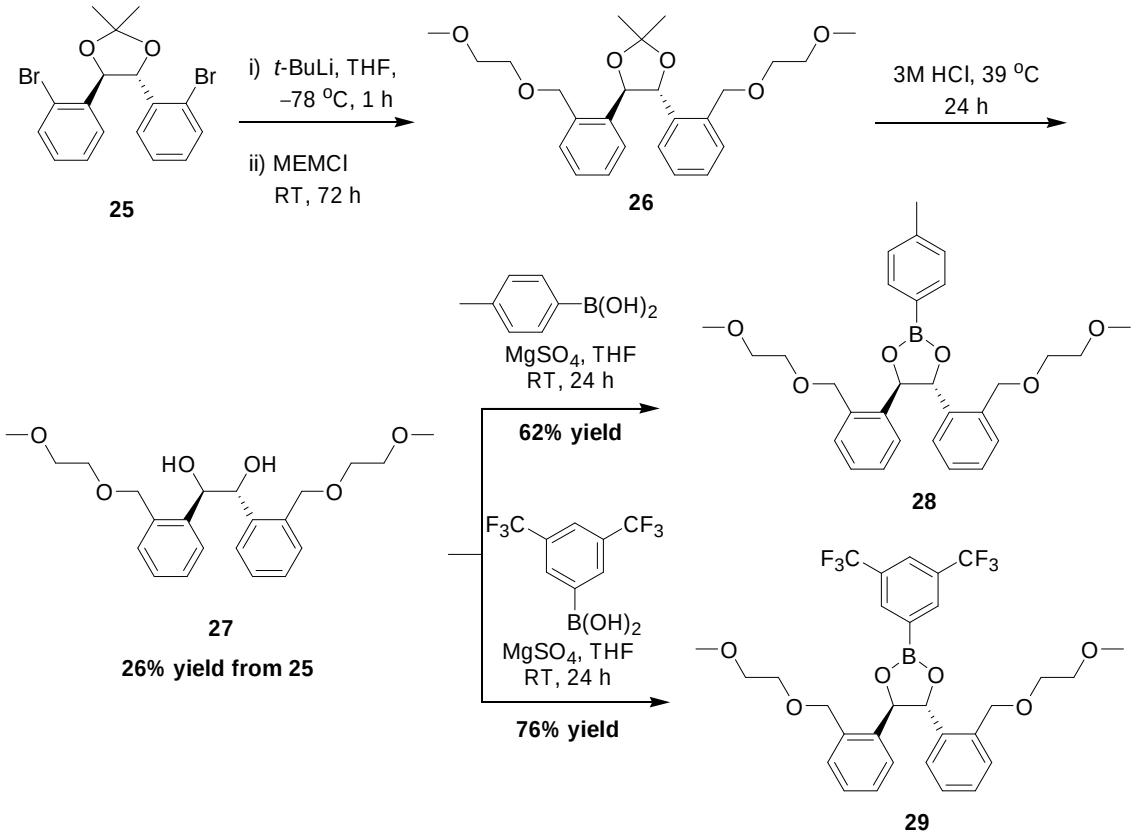
Next, it was decided to replace the methoxy group in the pre-catalyst **12** with a MEM group to enhance the coordinating ability (Figure 2.2). Since MEM-protected *o*-hydroxy benzaldehyde failed to yield *trans*-alkene product under McMurry coupling conditions, it was decided to install the MEM group at the end of the synthetic sequence. First, *o*-bromo benzaldehyde was converted to bromo-diol product **24** via McMurry coupling/Sharpless asymmetric dihydroxylation sequence as shown in Scheme 2.6. This diol **24** was then protected as acetonide **25**[12] with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid. Many approaches towards installing the MEM-protected hydroxyl group at the *ortho*-position were unsuccessful (Scheme 2.6).



Scheme 2.6 Synthetic strategy towards the synthesis of MEM-protected pre–catalyst.

2.1.4 Preparation of Boronic Esters 28 and 29

An alternative approach was taken, wherein instead of installing the protected MEM-hydroxyl group at the *ortho*-position, the MEM group would be directly attached at the *ortho*-position (Scheme 2.7). Therefore, the bromo-acetonide product **25** was treated with *t*-BuLi to undergo a metal-halogen exchange followed by addition of MEMCl to produce acetonide **26**. Finally, this crude acetonide **26** was subjected to acidic hydrolysis conditions to obtain diol **27**.[13] This diol **27** was coupled to the corresponding boronic acids to yield desired boronic esters **28** and **29**.



Scheme 2.7 Syntheses of MEM-containing boronic ester **28** and **29**.

2.2 Results and Discussion

With the targeted boronic esters in hand, I examined their catalytic activities with Lewis acids according to the LLA concept on a model carbonyl allylation using an allyltributyltin and aldehydes such as benzaldehyde or hydrocinnamaldehyde. In order to compare the catalytic activities of this LLA catalytic systems, background reactions were carried out where only the added Lewis acid was used to promote the reactions.

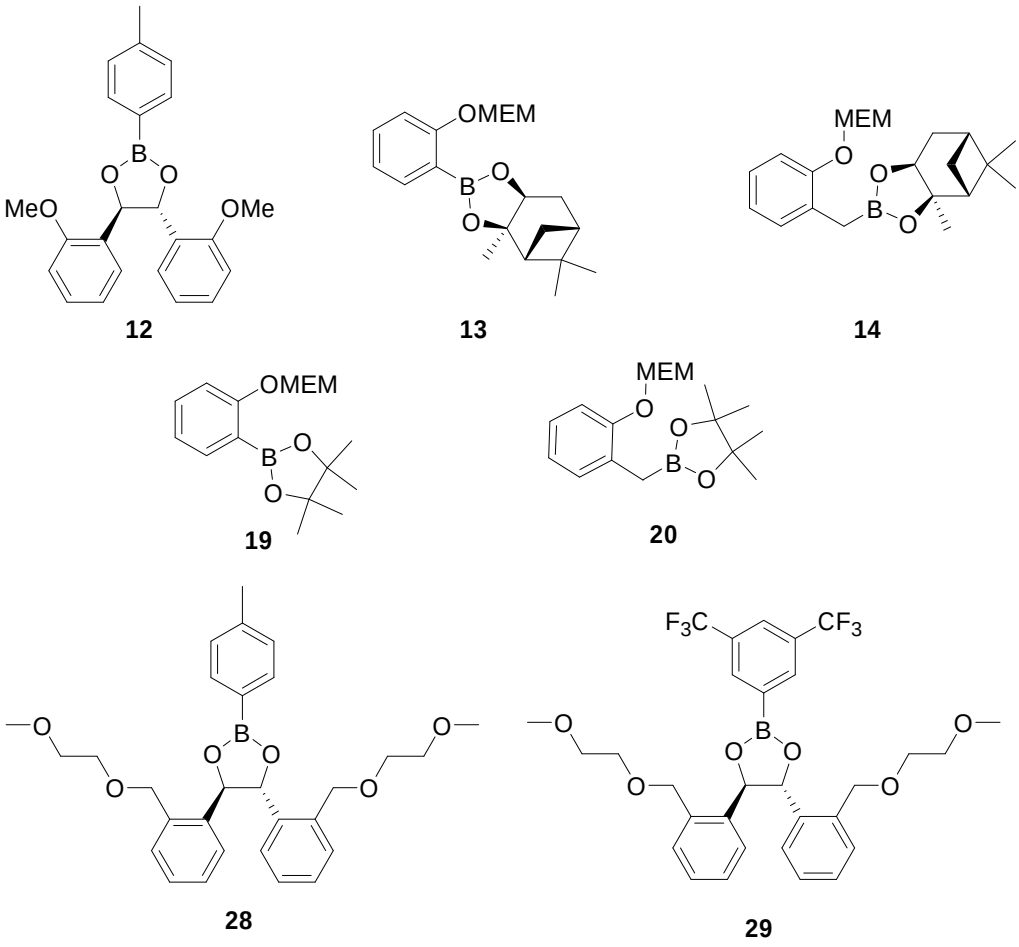


Figure 2.3 Structures of boronic esters used in carbonyl allylation chemistry.

Acetonitrile was used as the solvent because the solid Lewis acids used are completely soluble in this solvent. Catalytic activities of LLA systems formed between boronic esters **13**, **14**, and **19** and zinc triflate ($Zn(OTf)_2$) were first examined for the reaction between the allyltributyltin and benzaldehyde. Accordingly, the boronic ester pre-catalysts were stirred with $Zn(OTf)_2$ in acetonitrile for 30 minutes at room temperature and another 30 minutes at 0 ^oC. Next, benzaldehyde was added to the reaction mixture at 0 ^oC and stirred for 30

minutes before the addition of the allyltributyltin. After 1 h at 0 °C, diisobutylaluminium hydride (DIBAL–H) was added to the reaction mixture to quench unreacted benzaldehyde. After 15 minutes, water was added to the reaction mixture to hydrolyze the reaction mixture. The reaction mixture was extracted with ethyl acetate and the solvent was removed by rotary evaporation to yield the crude product. The product conversion was calculated based on the integration of the benzylic hydrogens of benzyl alcohol versus the hydrogen (Figure 2.4) of the secondary alcohol of the crude allylation product by ^{1}H NMR Spectroscopy. From this experiment, it was noticed that there was no catalytic activity was obtained with pre–catalysts **13**, **14**, and **19** (Table 2.1, entries 1-5) in the presence of $Zn(OTf)_2$ because the background reaction with $Zn(OTf)_2$ alone produced almost the same conversion. No enantioselectivity was observed for the product. The boronic ester **19** alone did not promote any conversion towards the desired products. Similar experiments as above were carried out with scandium triflate ($Sc(OTf)_3$) and boronic esters **19** and **20** to examine their catalytic activities. The LLA catalyst systems produced lower conversion than $Sc(OTf)_3$ alone (Table 2.1, entries 6-9). A possible explanation is that since acetonitrile is a coordinating solvent, it may be affecting the LLA catalyst system by sequestering one or both components. Therefore, reactions were also carried out in non-coordinating solvents such as dichloromethane (CH_2Cl_2) even though some solid Lewis acids would not be completely soluble in this solvent.

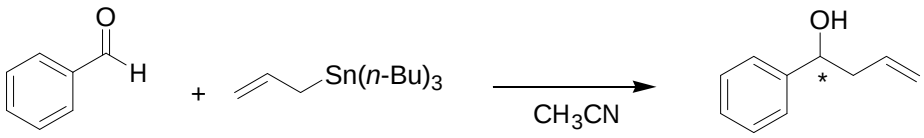


Table 2.1 Results obtained from allyltributyltin addition to benzaldehyde in acetonitrile.

Entry	B.E.	L.A.	Loading (mol%)	Time (h)	Temp (^{o}C)	Conversion (%)	Yield (%)	*ee* (%)
1	-	$Zn(OTf)_2$	21	1	0	47	-	-
2	**13**	$Zn(OTf)_2$	21	1	0	48	36	0
3	**14**	$Zn(OTf)_2$	19	1	0	46	30	0
4	**19**	-	20	1	0	0	-	-
5	**19**	$Zn(OTf)_2$	20	1	0	53	35	0
6	-	$Sc(OTf)_3$	19	1	0	50	48	-
7	**19**	-	22	1	0	0	0	-
8	**19**	$Sc(OTf)_3$	20	1	0	31	-	-
9	**20**	$Sc(OTf)_3$	20	1	0	33	-	-

Rxn = reaction, B.E. = boronic ester, L.A. = Lewis acid, Temp = temperature, ee = enantiomeric excess, 0 = ee was measured and zero, - = ee was not measured.

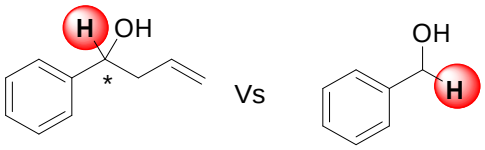


Figure 2.4 Protons (circled) used to calculate the percentage conversion of allylation reactions.

In CH_2Cl_2, the LLA catalyst system obtained by combining boronic ester **12**, **13**, **14**, **19**, or **29** with $Zn(OTf)_2$, led to higher conversions of starting material into desired product than $Zn(OTf)_2$ alone (Table 2.2, entries 1-7). The highest conversion was

obtained with boronic esters **19** (Table 2.2, entry 5) and **29** (Table 2.2, entry 7) when combined with $Zn(OTf)_2$.

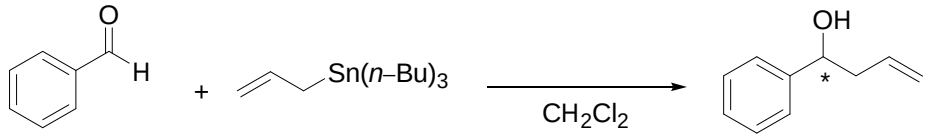


Table 2.2 Results of LLA System formed between boronic esters and $Zn(OTf)_2$.

Entry	B.E.	L.A.	Loading (mol%)	Rxn Time (h)	Temp (^oC)	Conversion (%)	*ee* (%)
1	-	$Zn(OTf)_2$	20	1	0	Trace	-
2	**12**	$Zn(OTf)_2$	20	1	0	12	0
3	**13**	$Zn(OTf)_2$	20	1	0	11	-
4	**14**	$Zn(OTf)_2$	20	1	0	15	0
5	**19**	$Zn(OTf)_2$	21	1	0	27	-
6	**29**	$Zn(OTf)_2$	17 (1:1)[a]	5	0	23	0
7	**29**	$Zn(OTf)_2$	9 (1:2)[b]	5	0	27	1.0

Rxn = reaction, B.E. = boronic ester, L.A. = Lewis acid, Temp = temperature**,** ee = enantiomeric excess**, a**: The mole ratio is 1:1 of boronic ester versus LA. **b**: The mole ratio is 2:1 of boronic ester versus LA.

Except in the case of boronic ester **12**, all other LLA catalytic systems yielded similar conversion as $Sc(OTf)_3$ alone. An increased amount of conversion was achieved with the LLA catalytic system formed between boronic ester **12** and $Sc(OTf)_3$ (Table 2.3, entry 2). Boronic esters with other Lewis acids such as $TiCl_4$, $SnCl_4$, $Al(OTf)_3$, $AlCl_2Me$, and $Cu(OTf)_2$, did not give any better conversion compared to the use of the Lewis acids alone (Table 2.3, entry 6-22).

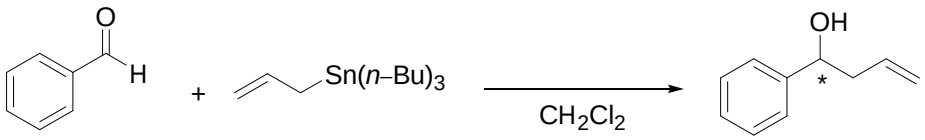


Table 2.3 Summarized results of LLA systems formed with other Lewis acids.

Entry	B.E.	L.A.	Loading (mol%)	Rxn Time (h)	Temp (^{o}C)	Conversion (%)	Yield (%)	*ee* (%)
1	-	$Sc(OTf)_3$	20	1	0	55	-	-
2	**12**	$Sc(OTf)_3$	20	1	0	83	73	0
3	**12**	$Sc(OTf)_3$	20	3	−78	22	-	0
4	**13**	$Sc(OTf)_3$	22	1	0	52	35	1.5
5	**14**	$Sc(OTf)_3$	20	1	0	58	48	1.5
6	-	$SnCl_4$	21	1	0	100	-	-
7	**14**	$SnCl_4$	19	0.5	0	100	75	0
8	-	$SnCl_4$	20	3	−78	47	-	-
9	**12**	$SnCl_4$	20	3	−78	51	-	0
10	**13**	$SnCl_4$	20	3	−78	33	15	0
11	-	$TiCl_4$	21	1	0	100	-	-
12	**12**	$TiCl_4$	20	1	0	100	49	0
13	**13**	$TiCl_4$	21	1	0	38	38	1.8
14	**14**	$TiCl_4$	19	1	0	53	35	0
15	-	$Al(OTf)_3$	20	1	0	21	-	-
16	**13**	$Al(OTf)_3$	20	1	0	17	7	1.3
17	-	$AlCl_2Me$	21	1	0	42	-	-
18	**12**	$AlCl_2Me$	20	1	0	39	20	0
19	**13**	$AlCl_2Me$	21	1	0	13	7	0.9
20	**14**	$AlCl_2Me$	19	1	0	35	25	0
21	**12**	$Cu(OTf)_2$	20	1	0	1.8	-	-
22	**13**	$Cu(OTf)_2$	17	1	0	28	10	0

Rxn = reaction, B.E. = boronic ester, L.A. = Lewis acid, Temp = temperature, ee = enantiomeric excess.

The catalytic activities of LLA systems formed between boronic esters **12**, **13**, **14**, **28**, and **29** and Lewis acids were further examined in a reaction between allyltributyltin and hydrocinnamaldehyde. There was a slight increase in conversions with boronic ester **28** and **29** in the presence of $Zn(OTf)_2$ (Table 2.4, entries 5 and 6) compared to the control reaction or with other LLA systems (Table 2.4, entries 1-6). The boronic ester **29** also produced better product conversions when combined with $Sc(OTf)_3$ (Table 2.4, entry 12) or $SnCl_4$ (Table 2.4, entry 17) compared to other boronic esters combined with $Sc(OTf)_3$ or $SnCl_4$ or those two Lewis acids alone (Table 2.4, entries 7-17). Boronic ester **12** yielded only a very small amount of product conversion when it formed an LLA system with $TiCl_4$ (Table 2.4, entry 19) compared to other LLA systems with $TiCl_4$ or $TiCl_4$ alone (Table 2.4, entries 18-20). In these LLA systems (formation of complex from boronic esters **12** and **29** with $TiCl_4$), very low enantioselectivities were observed for the products (Table 2.4, entries 19 and 20). All the LLA systems obtained with $BF_3 \cdot Et_2O$ did not produce any better results than $BF_3 \cdot Et_2O$ alone in the reaction.

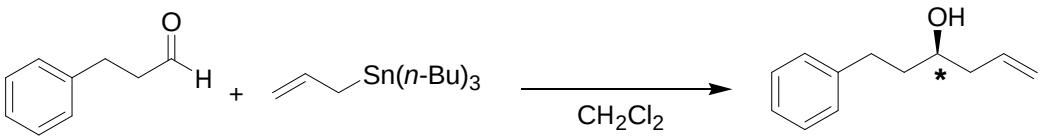


Table 2.4 Results of allyltributyltin addition to hydrocinnamaldehyde in dichloromethane.

Entry	B.E.	L.A.	Loading (mol%)	Rxn Time (h)	Temp (^{o}C)	Conversion (%)	Yield (%)	*ee* (%)
1	-	$Zn(OTf)_2$	21	2	0	20	-	-
2	**12**	$Zn(OTf)_2$	21	2	0	13	13	0
3	**13**	$Zn(OTf)_2$	22	2	0	26	25	0
4	**14**	$Zn(OTf)_2$	22	2	0	28	23	0
5	**28**	$Zn(OTf)_2$	17	2	0	30	24	0
6	**29**	$Zn(OTf)_2$	17	2	0	35	32	0
7	-	$Sc(OTf)_3$	20	2	0	85	40	-
8	**12**	$Sc(OTf)_3$	20	2	0	77	55	1.0
9	**13**	$Sc(OTf)_3$	20	2	0	82	25	2.3
10	**14**	$Sc(OTf)_3$	20	2	0	66	24	0
11	**28**	$Sc(OTf)_3$	17	2	0	92	55	0
12	**29**	$Sc(OTf)_3$	17	2	0	98	45	0
13	-	$SnCl_4$	20	2	0	92	-	-
14	-	$SnCl_4$	21	6	−78	83	-	-
15	**13**	$SnCl_4$	20	6	−78	83	35	0
16	**14**	$SnCl_4$	17	6	−78	51	39	1.3
17	**29**	$SnCl_4$	17	6	−78	100	45	0
18	-	$TiCl_4$	21	2	0	36	-	-
19	**12**	$TiCl_4$	21	2	0	57	41	6.1
20	**29**	$TiCl_4$	17	2	0	47	40	6.2
21	-	$BF_3{\cdot}Et_2O$	20	7	−78› R T	75	-	-
22	**12**	$BF_3{\cdot}Et_2O$	20	7	−78› R T	46	29	1
23	**14**	$BF_3{\cdot}Et_2O$	20	7	−78› R T	58	30	0

2.3 Conclusion

From these experiments, it was observed that in a few cases, the new LLA catalytic systems formed between a boronic ester and a Lewis acid accelerated the reactions compared to the corresponding background reactions. Even though there were better conversions of starting materials to products with some LLA systems, there was no noticeable enantioselectivity seen for the products. Despite a modest synergetic effect, these LLA systems did not provide stereochemical discrimination to promote enantioselective reactions between an allyltributyltin and aldehydes. At this point, we are not sure of the cause for the higher conversions observed in some cases. One possible postulation for this observation could be due to bi-coordination of both Lewis acids to the carbonyl moiety.

2.4 Experimental

2.4.1 General

Unless otherwise noted, all reactions were carried out under an argon atmosphere using flame-dried glassware. CH_2Cl_2, toluene and CH_3CN were distilled over CaH_2. THF and $CHCl_3$ were distilled over sodium/benzophenone. DMF and cyclohexane were used directly from Aldrich bottles. All aldehydes were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ or Magic stains. NMR spectra were recorded on 300, 400 or 500 MHz instruments. The residual

solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^{1}H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets. The estimated accuracy of coupling constants is ± 0.5 Hz. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra and optical rotations were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab.

Magic stain was prepared from:

20g $(NH_4)_2MoO_4$

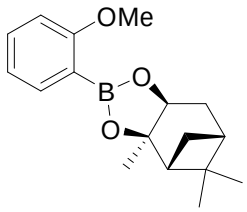
0.4 g $Ce(SO_4)_2$

500 mL of 10% H_2SO_4

2.4.2 Preparations of Boronic Esters 8 and 9

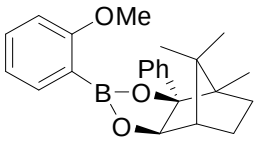
In a 25 mL long-neck round bottom flask, *o*-methoxyphenyl boronic acid (0.23 g, 1.51 mmol, 1.00 equiv), (+)-pinane diol (0.29 g, 1.70 mmol, 1.10 equiv), and anhydrous $MgSO_4$ (~1.00 g) in 10 mL of THF were stirred at RT for 1 h. Then, the reaction mixture was filtrated by gravity filtration and removal of solvent produced a light yellow oil as crude product.

4-Bora-3,5-dioxa-4-(2-methoxy phenyl)-2,9,9-trimethyl tricyclo[6.1.1.$0^{2,6}$]decane (8)



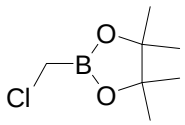
Flash chromatography (3% EtOAc in hexanes) yielded a clear oil (0.38 g, 88.0%). TLC (20% EtOAc in hexanes, $KMnO_4$): R_f 0.38; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (dd, J = 7.2, 1.8 Hz, 1H), 7.41 (td, J = 8.0, 2.2 Hz, 1H), 6.96 (td, J = 7.2, 1.1 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 4.49 (dd, J = 8.8, 1.9 Hz, 1H), 3.86 (s, 3H), 2.42 (ddt, J = 8.7, 14.4, 2.4 Hz, 1H), 2.24 (m, 1H), 2.17 (dd, J = 5.9, 5.2 Hz, 1H), 2.01 (ddd, J = 14.4, 3.1, 2.3 Hz, 1H), 1.94 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H), 1.29 (s, 1H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 136.8, 132.4, 120.2, 110.4, 85.6, 78.4, 55.7, 51.5, 39.7, 38.3, 35.8, 28.9, 27.3, 26.7, 24.2, one carbon signal is missing in the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.5; IR (CH_2Cl_2, cast film): cm ^{1} 2918, 1600, 1455, 1360, 1344, 1077, 759; HRMS (EI, *m*/*z*) calculated for $C_{17}H_{23}O_3{}^{11}B$: 286.1740, found: 286.1741 [M^+].

4-Bora-3,5-dioxa-4-(2-methoxy benzyl)-2-phenyl-1,10,10-trimethyl tricyclo[5.2.1.$0^{2,6}$]decane (9)



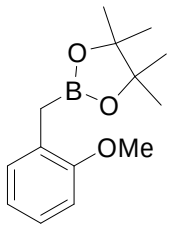
The reaction scale was 2.30 mmol of the boronic acid. Flash chromatography (3% EtOAc in hexanes) yielded a white solid (0.70 g, 84.0%). TLC (25% EtOAc in hexanes, Magic stain): R_f 0.53; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (dd, J = 7.3, 1.9 Hz, 1H), 7.53 (d, J = 7.0 Hz, 2H), 7.34 (m, 4H), 6.95 (dd, J = 7.3, 0.8 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 4.95 (s, 1H), 3.83 (s, 3H), 2.30 (d, J = 5.2 Hz, 1H), δ 1.88 (m, 1H), 1.30 (s, 3H), 1.26 (m, 2H), 1.12 (m, 1H), 1.04 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.3, 142.1, 137.4, 132.7, 127.4, 127.2, 126.9, 120.3, 110.6, 95.3, 89.5, 55.8, 52.3, 50.4, 49.0, 29.7, 24.9, 23.8, 21.2, 9.5, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.7; IR (CH_2Cl_2, cast film): cm ^{1} 3064, 2999, 2956, 1600, 1575, 1489, 1457, 1433, 1346, 1274, 1248, 1073, 758, 702; HRMS (EI, *m*/*z*) calculated for $C_{23}H_{27}O_3{}^{11}B$: 362. 2053, found: 362.2055 [M^+]; $[\alpha]^{25}_D$ −30.30 (c = 0.84, $CHCl_3$).

2.4.3 Synthesis of 2-chloromethyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (17)



Boronic ester **17**[5] was prepared following slight modifications of literature procedures. In a 250 mL round bottom flask, bromochloromethane (5.00 mL, 76.9 mmol, 1.10 equiv) and trimethylborate (8.00 mL, 71.4 mmol, 1.00 equiv) in 70.0 mL of THF were cooled to −78 °C and *n*-BuLi (1.50 M, 46.1 mL, 71.4 mmol 1.00 equiv) was added slowly. The reaction mixture was stirred for 30 minutes at −78 °C prior to addition of TMSCl (10.9 mL, 85.9 mmol, 1.20 equiv) dropwise to the reaction mixture. Next, the reaction mixture was allowed to warm to room temperature (RT) and stirred overnight. Then, pinacol (7.52 g, 63.7 mmol, 0.90 equiv) in 10.0 mL of diethyl ether was added and stirred for an another hour. The reaction mixture was quenched with H_2O (50 mL) and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporator to yield a clear oil product. The crude product was distilled using Kugelrohr distillation apparatus to obtain pure boronic ester **17** as a clear liquid (6.00 g, 53.0% yield).

2.4.4 Synthesis of 2-(2-methoxy benzyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (15)[7]

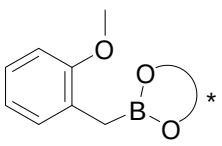


In a 100 mL round bottom flask, 1-methoxy-benzene (1.50 mL, 13.8 mmol, 1.05 equiv) in 20.0 mL of THF was cooled down to −78 °C and *n*-BuLi (8.60 mL, 13.3 mmol, 1.00 equiv) was added to the flask slowly. The reaction mixture was stirred for 15 minutes at −78 °C and warmed to 0 °C to stir for an additional hour. The reaction mixture was cooled to −78 °C and boronic ester **17** (2.34 g, 13.3 mmol, 1.00 equiv) in 2 mL of THF was added slowly. The flask was allowed to warm to RT and stirred overnight. Then, the reaction mixture was quenched with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporation.

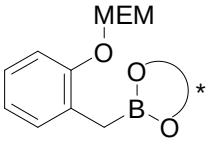
Flash chromatography (5% EtOAc in hexanes) yielded a clear oil (0.55 g, 17.0% yield). TLC (30% EtOAc in hexanes, $KMnO_4$): R_f 0.5; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.13 (m, 2H), 6.84 (m, 2H), 3.78 (s, 3H), 2.17 (s, 2H), 1.22 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2, 130.5, 128.1, 126. 3, 120.5, 109.8, 83.1, 55.1, 24.7, one carbon signal is missing in the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 33.3; IR (CH_2Cl_2 cast

film): cm ^{1} 2979, 1600, 1494, 1353, 751; HRMS (EI, *m*/*z*) calculated for $C_{14}H_{21}O_3{}^{11}B$: 248.1584, found: 248.1586 [M^+].

2.4.5 Syntheses of Boronic esters 10, 11, 14, and 20[6,8]



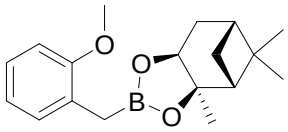
10 or 11



14 or 20

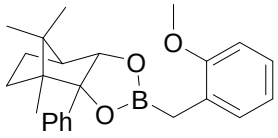
In a 25 mL long-neck round bottom flask, boronic esters (**8**, **9**, **13**, or **19**) (2.00 mmol, 1.00 equiv) and bromochloromethane (0.15 mL, 2.20 mmol, 1.10 equiv) in 4 mL of THF were cooled to −78 ^{o}C and *n*-BuLi (1.40 mL, 2.20 mmol, 1.10 equiv) was added dropwise. The reaction mixture was stirred at −78 ^{o}C for another 30 minutes before warm to RT and stirred for 24 h. Next, the reaction mixture was quenched with saturated NH_4Cl (5.00 mL) and it was extracted with diethyl ether (4 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporator.

4-Bora-3,5-dioxa-4-(2-methoxy benzyl)-2,9,9-trimethyl tricyclo[6.1.1.$0^{2,6}$]decane (10)



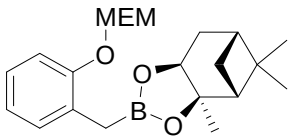
The reaction scale was 2.04 mmol of corresponding boronic ester. Flash chromatography (0 to 3% EtOAc in hexanes) yielded a clear oil (0.30 g, 49.0% yield). TLC (20% EtOAc in hexanes, $KMnO_4$): R_f 0.43; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 (dd, J = 7.0, 1.6 Hz, 1H), 7.12 (dd, J = 8.0, 1.6 Hz, 1H), 6.86 (td, J = 7.0, 0.9 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.26 (dd, J = 8.8, 2.0 Hz, 1H), 3.81 (s, 3H), 2.24 (m, 4H), 2.05 (t, J = 5.6 Hz, 1H), 1.89 (m, 1H), 1.80 (ddd, J = 14.8, 5.5, 2.2 Hz, 1H), 1.38 (s, 3H), 1.28 (s, 3H), 1.25 (d, 10.8 Hz, 1H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2, 130.4, 128.1, 126.3, 120.6, 109.9, 85.6, 77.8, 55.2, 51.3, 39.5, 38.2, 35.6, 28.7, 27.1, 26.3, 24.1, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 32.6; IR (CH_2Cl_2, cast film): cm ^{1} 2917, 1600, 1494, 1376, 1358, 1242, 1050, 750; HRMS (EI, *m*/*z*) calculated for $C_{18}H_{25}O_3{}^{11}B$: 300.1897, found: 300.1894 [M^+]. $[\alpha]^{25}_D$ 16.67 (c = 1.48, $CHCl_3$).

4-Bora-3,5-dioxa-4-(2-methoxy benzyl)-2-phenyl-1,10,10-trimethyl tricyclo[5.2.1.$0^{2,6}$]decane (11)



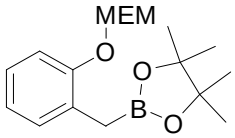
The reaction scale was 1.79 mmol of corresponding boronic ester. Flash chromatography (0 to 3% EtOAc in hexanes) provided a clear oil (0.37 g, 55.0% yield). TLC (20% EtOAc in hexanes, $KMnO_4$): R_f 0.5; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (m, 2H), 7.31 (m, 3H), 7.08 (m, 2H), 6.83 (ddd, J = 9.0, 7.0, 1.1 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.70 (s, 1H), 3.26 (s, 3H), 2.16 (br s, 2H), 2.12 (d, J = 5.2 Hz, 1H), 1.80 (m, 1H), 1.26 (s, 3H), 1.18 (m, 2H), 1.08 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.9, 142.2, 130.4, 127.8, 127.3, 127.0, 126.8, 126.1, 120.2, 109.6, 95.6, 88.8, 54.5, 52.0, 50.3, 48.9, 29.7, 24.8, 23.8, 20.9, 9.5, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 34.4; IR (CH_2Cl_2, cast film): cm ^{1} 2956, 1600, 1492, 1349, 1243, 1033, 751, 702; HRMS (EI, *m*/*z*) calculated for $C_{24}H_{29}O_3{}^{11}B$: 376.2210, found: 376.2208 [M^+]. $[\alpha]^{25}_D$ 16.67 (c = 1.48, $CHCl_3$).

4-Bora-3,5-dioxa-4-[2-(2-methoxy ethoxymethoxy)-benzyl]-2,9,9-trimethyl tricyclo[6.1.1.$0^{2,6}$]decane (14)



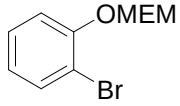
The reaction scale was 0.95 mmol of corresponding boronic ester. Flash chromatography (0 to 3% EtOAc in hexanes) provided a clear oil (0.21 g, 59.0% yield). TLC (30% EtOAc in hexanes, $KMnO_4$) R_f 0.44; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.15 (d, J = 8.1 Hz, 1H), 7.10 (m, 2H), 6.90 (m, 1H), 5.27 (s, 1H), 5.26 (s, 1H), 4.24 (dd, J = 8.7, 2.0 Hz, 1H), 3.83 (m, 2H), 3.56 (m, 2H), 3.38 (s, 3H), 2.28 (br s, 2H), 2.20 (m, 1H), 2.04 (dd, J = 6.0, 4.8 Hz, 1H), 1.88 (m, 1H), 1.80 (ddd, J = 14.4, 3.3, 2.1 Hz, 1H), 1.38 (s, 3H), 1.28 (s, 3H), 1.18 (d, J = 11.1 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.0, 130.4, 128.5, 126.3, 121.8, 114.1, 93.7, 85.7, 77.9, 71.7, 67.5, 59.1, 51.4, 39.6, 38.3, 35.6, 28.9, 27.2, 26.4, 24.1, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 32.9; IR (CH_2Cl_2, cast film): cm ^{1} 2918, 1600, 1491, 1376, 1358, 1340, 1228, 1104, 1007, 752; HRMS (EI, *m*/*z*) calculated for $C_{21}H_{31}O_5{}^{11}B$: 374.2264, found: 374.2282 [M^+]. $[\alpha]^{25}_D$ 12.54 (c = 0.70, $CHCl_3$).

2-[2-(2-Methoxy ethoxymethoxy)-benzyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (20)



The reaction scale was 1.39 mmol of corresponding boronic ester. Flash chromatography (0 to 3% EtOAc in hexanes) provided a clear oil (0.23 g, 51.0% yield). TLC (30% EtOAc in hexanes, $KMnO_4$): R_f 0.36; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 (m, 1H), 7.10 (m, 3H), 6.90 (m, 1H), 5.26 (s, 2H), 3.84 (m, 2H), 3.56 (m, 2H), 3.38 (s, 3H), 2.22 (br s, 2H), 1.23 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.1, 130.6, 128.6, 126.3, 121.8, 114.1, 93.7, 83.2, 71.7, 67.5, 59.1, 24.8, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 33.2; IR (CH_2Cl_2, cast film): cm ^{1} 2978, 2929, 1600, 1492, 1379, 1352, 1328, 1228, 1164, 1144, 1005, 847, 752; HRMS (EI, *m*/*z*) calculated for $C_{17}H_{27}O_5{}^{11}B$: 322.1952, found: 322.1951 [M^+].

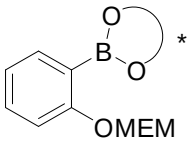
2.4.6 Synthesis of 1-Bromo-2-(2-methoxy ethoxymethoxy)-benzene (18)



o-Bromo phenol ether **18**[9a.b] was prepared following literature procedures with some modifications. In a 100 mL of round bottom flask, *o*-bromo-phenol (1.00 mL, 8.50 mmol, 1.00 equiv) in 25 mL of dimethylformamide (DMF) was cooled to 0 ^{o}C and

sodium hydride (NaH) (60% in mineral oil, 0.38 g, 9.50 mmol, 1.10 equiv) was added portion wise to the flask. The reaction mixture was stirred at 0 ^{o}C for another 45 minutes followed by dropwise addition of methoxyethoxy methyl chloride (1.06 mL, 9.30 mmol, 1.10 equiv). The reaction mixture was stirred for 10 minutes at 0 ^{o}C before being allowed to RT and stirred for additional 24 h. The reaction mixture was then poured into 20 mL of H_2O and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed on a rotary evaporator and the crude product was purified on silica with 10% EtOAc in hexanes to obtain pure product **18** as a clear oil (1.79 g, 82.0 % yield).

2.4.7 Syntheses of Boronic Esters 13 and 19[9a,c]

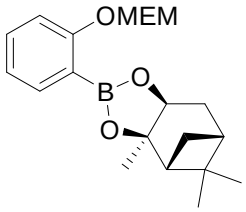


13 or 19

In a 250 mL of round bottom flask, bromo-phenol ether **18** (1.79 g, 6.90 mmol, 1.00 equiv) in 100 mL of THF was cooled to −78 ^{o}C and *n*-BuLi (6.50 mL, 10.4 mmol, 1.50 equiv) was added slowly. After 30 minutes of stirring at −78 ^{o}C, $B(OMe)_3$ (1.60 mL, 13.8 mmol, 2.00 equiv) was added at once and the reaction mixture was allowed to RT and stirred for 1 h at RT. Next, the reaction mixture was poured into 25.0 mL of H_2O and acidified with 1M HCl to about pH 2. The reaction mixture was extracted with EtOAc (4 x 30 mL) and the combined organic layers were

washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. It was filtered and the most of the solvent was removed by rotary evaporator and the crude product in diethyl ether was carried to the next step. The crude boronic acid from the previous step, corresponding diol, and enough amount of anhydrous $MgSO_4$ in diethyl ether were stirred at RT for 48 h. The reaction mixture was filtered using gravity filtration.

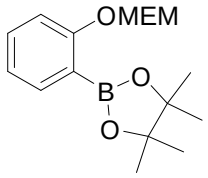
4-Bora-3,5-dioxa-4-[2-(2-methoxy ethoxymethoxy)-phenyl]-2,9,9-trimethyl tricyclo[6.1.1.$0^{2,6}$]decane (13)



The reaction scale was 5.62 mmol of pinane diol. Flash chromatography (3% EtOAc in hexanes) provided a clear oil (1.12 g, 52.0% yield). TLC (30% EtOAc in hexanes, $KMnO_4$): R_f 0.32; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (dd, J = 7.2, 1.7 Hz, 1H), 7.38 (ddd, J = 8.0, 6.9, 1.9 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.02 (td, J = 7.4, 0.9 Hz, 1H), 5.30 (s, 2H), 4.46 (dd, J = 8.4, 1.9, 1H), 3.89 (m, 2H), 3.58 (m, 2H), 3.36 (s, 3H), 2.41 (m, 1H), 2.22 (m, 1H), 2.14 (t, J = 6.0 Hz, 1H), 1.95 (m, 2H), 1.49 (s, 3H), 1.31 (s, 3H), 1.24 (d, J = 10.9 Hz, 1H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 136.6, 132.7, 121.8, 115.5, 94.2, 85.7, 78.2, 71.7, 67.7, 59.0, 51,5, 39.7, 38.3, 35.7, 28.8, 27. 2, 26.6, 24.2, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.1; IR ($CDCl_3$, cast film): cm ^{1} 2916, 1600, 1575, 1488, 1446, 1387,

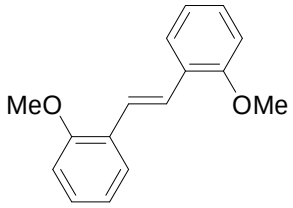
1360, 1343, 1224, 1123, 1104, 1069, 989, 760; HRMS (EI, *m*/*z*) calculated for $C_{20}H_{29}O_5{}^{11}BNa$: 383.2000, found: 383.2002 [(M^+]. $[\alpha]^{25}{}_D$ 11.32 (c = 0.80, $CHCl_3$).

2-[2-(2-Methoxy ethoxymethoxy)-phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (19)



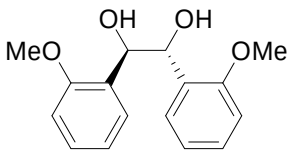
The reaction scale was 7.22 mmol of pinacol. Flash chromatography (3% EtOAc in hexanes) provided a clear oil (1.18 g, 53.0% yield). TLC (30% EtOAc in hexanes, $KMnO_4$): R_f 0.29; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (dd, J = 7.3, 1.8 Hz, 1H), 7.37 (ddd, J = 8.4, 7.4, 1.9 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.00 (td, J = 7.3, 1.0 Hz, 1H), 5.28 (s, 2H), 3.88 (m, 2H), 3.56 (m, 2H), 3.37 (s, 3H), 1.34 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 136.5, 132.3, 121.7, 115.6, 94.3, 83.4, 71.7, 67.8, 59.0, 24.9, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.98; IR ($CDCl_3$, cast film): cm ^{1} 2978, 2928, 1601, 1574, 1488, 1445, 1316, 1145, 1066, 989, 861, 762; HRMS (EI, *m*/z) calculated for $C_{16}H_{25}O_5{}^{11}B$: 308.1795, found: 308.1801 [M^+].

2.4.8 Synthesis of (*E*)-1,2-Bis-(2-methoxyphenyl)-ethene (21)



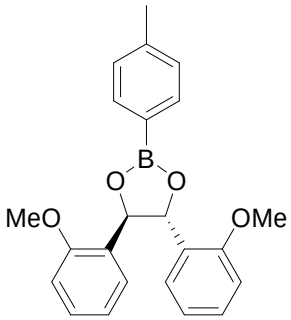
Compound **21**[10] was synthesized following literature procedures. In a 500 mL 3-neck round bottom flask, Zn (12.9 g, 197 mmol, 6.00 equiv) in 200 mL of THF was cooled to 0 ^{o}C and $TiCl_4$ (11.6 mL, 106 mmol, 3.20 equiv) was added slowly to the flask. The reaction mixture was refluxed at 80 ^{o}C for 1.5 h. Next, the reaction mixture was cooled to 0 ^{o}C and *o*-methoxy benzaldehyde (4.00 mL, 33.1 mmol 1.00 equiv) was added dropwise to the flask. The reaction mixture was stirred at 0 ^{o}C for additional 30 minutes and it was refluxed at 80 ^{o}C for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (100 mL) and filtrated through a pad of celite. The filtrate was then extracted with CH_2Cl_2 (4 x 150 mL) and combined organic layers were washed with saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporator. The yellowish solid crude was subjected to undergo two successive recrystallization steps to produce white crystals as pure alkene product **21**.

2.4.9 Synthesis of 1,2-bis-(2-methoxy phenyl)-ethane-1,2-diol (22)



Diol **22**[11] was synthesized following literature procedures. In a 250 mL round bottom flask, $K_3Fe(CN)_6$ (6.00 g, 18.2 mmol, 3.00 equiv), K_2CO_3 (2.56 g, 18.2 mmol, 3.00 equiv), $(DHQD)_2PHAL$ (50.1 mg, 0.06 mmol, 0.01 equiv) in 30 mL of H_2O and 30 mL of *t-Bu*OH were down to 0 ^oC and $K_2OsO_2(OH)_4$ (17.5 mg, 0.05 mmol, 0.01 equiv) and $MeSO_2NH_2$ (0.59 g, 6.16 mmol, 1.00 equiv) were added to the flak respectively. Next, compound **21** (1.43 g, 5.95 mmol, 0.97 equiv) was added to the reaction mixture and allowed to warm to RT, where it was stirred for 48 h. The reaction mixture was quenched by adding 9.50 g of $Na_2S_2O_3$. It was extracted with EtOAc (4 x 50 mL) and the combined organic layers were washed with 1M KOH followed by H_2O and brine respectively. Finally, the organic layer was dried over anhydrous Na_2SO_4, filtered and removal of solvent gave brown yellow sticky solid. The crude product was purified on silica with 10% EtOAc followed by recrystallization to produce white crystals of diol **22**.

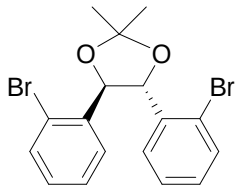
2.4.10 Synthesis of 4,5-Bis-(2-methoxy phenyl)-2-*p*-tolyl-[1,3,2]dioxalborolane (12)



In a 10 mL round bottom flask, diol **22** (0.18 g, 0.63 mmol, 1.00 equiv), anhydrous $MgSO_4$ (~0.5 g), and *p*-methylphenyl boronic acid (85.7 mg, 0.63 mmol, 1.00 equiv) in 3 mL of THF were stirred at RT for overnight. Next, the reaction mixture was filtered using gravity filtration and the solvent was removed by rotary evaporator.

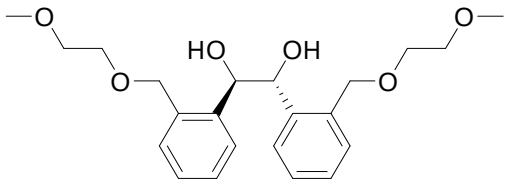
Flash chromatography (0 to 5% EtOAc in hexanes) provided white solid (0.17 g, 70.0% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 8.0 Hz, 2H), 7.42 (dd, J = 7.5, 1.7 Hz, 2H), 7.30 (ddd, J = 9.9, 7.5, 1.7 Hz, 2H), 7.25 (m, 2H), 6.98 (td, J = 7.5, 1.1 Hz, 2H), 6.89 (dd, J = 8.2, 0.9 Hz, 2H), 5.55 (s, 2H), 3.67 (s, 6H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.9, 141.3, 135.0, 130.3, 128.9, 128.5, 127.4, 120.3, 110.4, 82.6, 54.9, 21.7, one carbon signal is missing on the ^{13}C NMR spectrum due to quadrupolar broadening because of boron; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.50; IR (CH_2Cl_2, cast film): cm ^{1} 3002, 2938, 2837, 1604, 1590, 1493, 1438, 1379, 1351, 1248, 1119, 1089, 1028, 977, 754; HRMS (EI, *m*/*z*) calculated for $C_{23}H_{23}O_4{}^{11}B$: 374.1690, found: 374.1696 [M^+]. $[\alpha]^{25}_D$ −111 (c = 0.80, $CHCl_3$).

2.4.11 Synthesis of 4,5-Bis-(2-bromo phenyl)-2,2-dimethyl-[1,3]dioxolane (25)



Acetonide **25** was prepared according to a literature procedure.[12] In a 25 mL 3-neck round bottom flask, bromo-diol **24** (0.36 g, 1.00 mmol, 1.00 equiv), *p*-toluene sulfonic acid (10.0 mg, 0.05 mmol, 0.05 equiv), and dimethoxy propane (0.48 mL, 3.90 mmol, 4.00 equiv) in 8 mL of cyclohexane were heated at 50 ^{o}C for 10 minutes. Next, the reaction mixture was refluxed at 40 ^{o}C for 2 h. 1M NaOH (3.90 mL) was added to the flask and stirred for over night. Finally, the reaction mixture was extracted with diethyl ether (4 x 5 mL) and the combined organic layers were washed with H_2O and brine respectively. The organic layer was dried over anhydrous Na_2SO_4, filtered, and removal of solvent yielded white solid **25** (1.02 g, 88.0% yield), which was pure enough for the next step.

2.4.12 Preparation of 1,2-Bis-[2-(2-methoxy ethoxymethyl)-phenyl]-ethane-1,2-diol (27)[13]

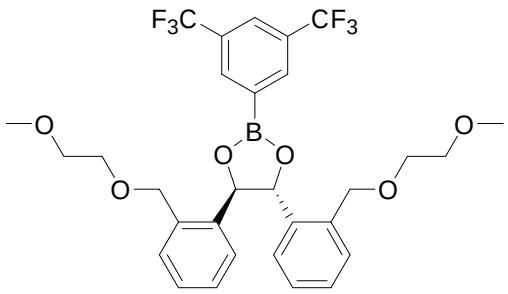


In a 250 mL round bottom flask, bromo acetonide **25** (4.45 g, 10.8 mmol, 1.00 equiv) in 46 mL of THF was cooled to −78 ^{o}C and *t*-BuLi (33.8 mL, 54.0 mmol, 5.00 equiv) was added drop wise. The reaction mixture was stirred at −78 ^{o}C for 1 h and then, it was allowed to warm to −60 ^{o}C. Next, MEMCl (2.84 mL, 24.9 mmol, 2.30 equiv) was added to the flask and stirred for 15 minutes. Then, the reaction mixture was allowed to warm to RT and stirred for 72 h. The reaction mixture was quenched with saturated NH_4Cl solution (35.0 mL) and extracted with diethyl ether (4 x 30 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by rotary evaporator. Crude product **26** was used in the next step without further purification.

In a 100 mL round bottom flask, crude acetonide **26** (4.87 g, 10.8 mmol) in 20 mL of THF was reacted with 27 mL of 3M HCl and the reaction mixture was stirred at 39 ^{o}C for 24 h. Next, 15 mL of H_2O was added and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 1M NaOH, H_2O, and brine respectively. The organic layer was then dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporator.

Flash chromatography (100% EtOAc) provided a white solid (1.10 g, 26.0% yield). TLC (100% EtOAc, $KMnO_4$): R_f 0.29; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.51 (d, J = 7.8 Hz, 2H), 7.25 (m, 2H), 7.18 (m, 4H), 5.23 (s, 2H), 4.45 (d, J = 12.2 Hz, 2H), 4.12 (d, J = 12.2 Hz, 2H), 3.48 (m, 8H), 3.33 (s, 6H), 2.05 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.4, 135.5, 129.1, 128.0, 127.5, 73.5, 71.7, 71.1, 68.6, 58.8; IR ($CDCl_3$, cast film): cm ^{1} 3411, 3064, 2918, 2881, 1768, 1724, 1602, 1488, 1451, 1386, 1086, 1043, 766; HRMS (ES, *m*/*z*) calculated for $C_{22}H_{30}O_6Na$: 413.1935, found: 413.1932 [(M^+]. $[\alpha]^{25}_D$ −16.14 (c = 0.96, $CHCl_3$).

2.4.13 Synthesis of 2-(3,5-bis-trifluoromethyl phenyl)-4,5-bis-[2-(2-methoxy ethoxy methyl)-phenyl]-[1,3,2]dioxaborolane (29)



Boronic ester **29** was prepared by following the procedure described in section 2.4.10 with a reaction time was 24 h instead of overnight.

The reaction scale was 0.61 mmol of corresponding boronic acid. Flash chromatography (10% EtOAc in hexanes) yielded a white solid (0.28 g, 76.0% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.38 (br s, 1H), 8.02 (br s, 1H), 7.56 (d, J =

7.5 Hz, 2H), 7.28 (m, 7H), 5.88 (s, 2H), 4.35 (d, J = 12.0 Hz, 2H), 4.23 (d, J = 12.0 Hz, 2H), 3.32 (m, 8H), 3.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 135.7, 135.1, 131.2, 129.8, 128.9, 128.7, 126.5, 124.8, 122.1, 83.9, 71.7, 71.0, 69.4, 65.9, 58.9; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.79; ^{19}F NMR ($CDCl_3$, 376 MHz), δ −63.3 (s, 6F); IR ($CDCl_3$, cast film): cm ^{1} 3068, 2881, 1618, 1454, 1299, 1281, 1182, 1134, 979, 907, 761, 708, 691; HRMS (EI, *m*/*z*) calculated for $C_{30}H_{31}O_6{}^{11}BF_6$: 612.2118, found: 612.2136 [(M^+]. $[\alpha]^{25}{}_D$ −10.71 (c = 0.70, $CHCl_3$).

2.5 References

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Chapter 3: Further Applications of Double-Allylation Reagent 7

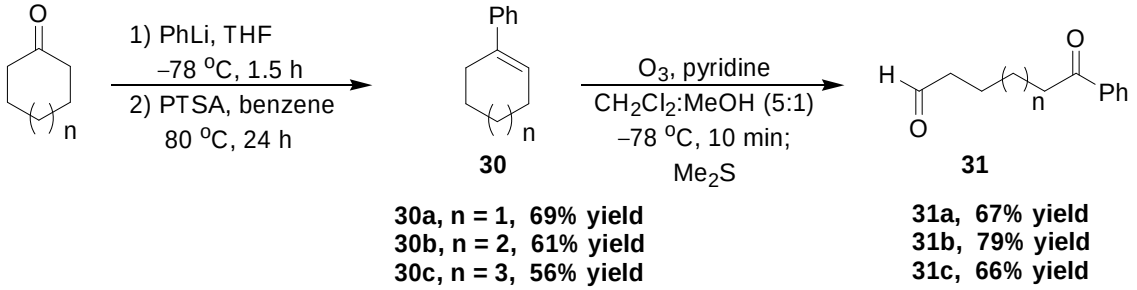
3.1 Introduction

Bimetallic reagents displaying chemodivergent reactivity are very useful in organic synthesis. Asymmetric synthesis of complex molecules can be achieved via chiral, bimetallic double-allylation reagents.[1,2] In this respect, a novel class of chiral double-allylation reagents based on boron and silicon were recently introduced by Hall and Peng.[3] The simplest example is reagent **7** (Equation 3.1). Lewis acid assisted allylboration was preferentially observed over allylsilation with reagent **7** and carbonyl substrates, thereby allowing a controlled, chemoselective reactivity. In previous studies, the Hall group has shown the utility of this double-allylation reagent **7** in the stereoselective synthesis of trisubstituted furans, vinylcyclopropanes, and smaller oxabicyclic compounds.[3] In this thesis, further applications of reagent **7** towards the synthesis of larger oxabicyclic compounds, a one-pot synthesis of polysubstituted furan, and the synthesis of pyrrolidines have been examined.

3.2 Synthesis of Larger Oxabicyclic Compounds 32a-c

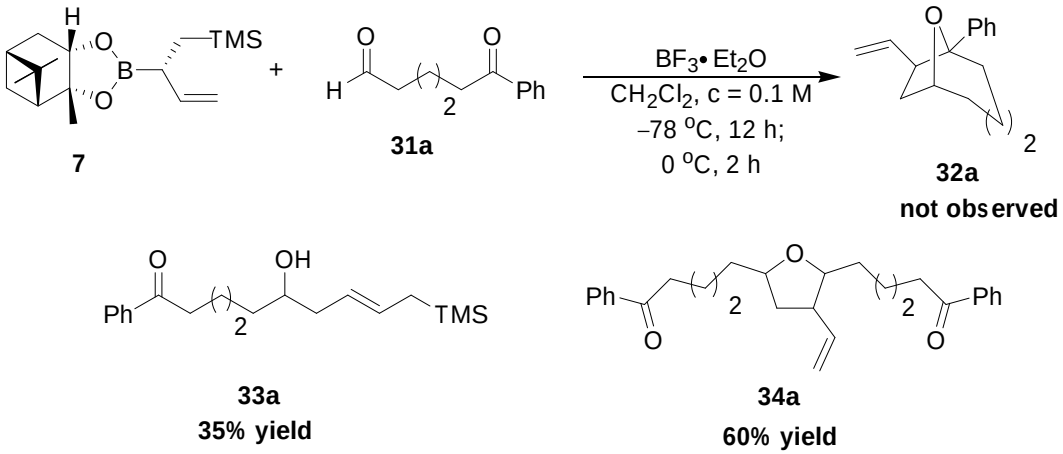
In previous studies,[3] Hall and Peng showed that 7-membered oxabicyclic compounds could be accessed using reagent **7**. For further development in this direction, syntheses of 8, 9, and 10 membered oxabicylic compounds were examined. The corresponding starting keto-aldehydes **31a-c** for this transformation

were prepared as shown in Scheme 3.1 in three steps from commercially available cyclic ketones.[4,5]



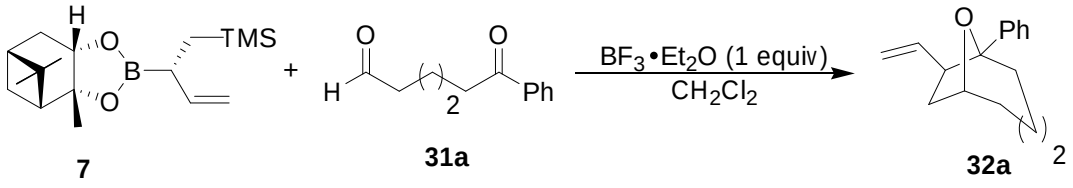
Scheme 3.1 Preparations of keto-aldehydes **31a-c** for syntheses of oxabicyclic compounds.[4,5]

After successful preparation of starting keto–aldehydes **31a-c**, the syntheses of oxabicylcic compounds **32a-c** were attempted. The synthesis of 8-membered oxabicyclic compound **32a** was first examined under conditions similar to that reported by Hall and Peng[3] (Equation 3.1). Under these conditions, monoallylation product **33a** (35% yield) and bisallylation product **34a** (60% yield) were observed (Equation 3.1). No desired oxabicyclic compound **32a** was observed.



Equation 3.1 Synthesis of oxabicyclic compound **32a** using previous reaction conditions reported by Hall and Peng.[3]

As a first step in the optimization process, the reaction concentration was changed from 0.1 M to 0.01 M to decrease the possibility of intermolecular reactions but desired product **32a** (40%) and bisallylation product **34a** (30%) were observed as almost 1 to 1 mixture (Table 3.1, entry 2). Increasing the reaction time at −78 °C did not change the product distribution (Table 3.2, entry 3). Further dilution of reaction concentration (0.004 M) yielded a 5:1 product ratio of **32a** to **33a** (Table 3.1, entry 4).



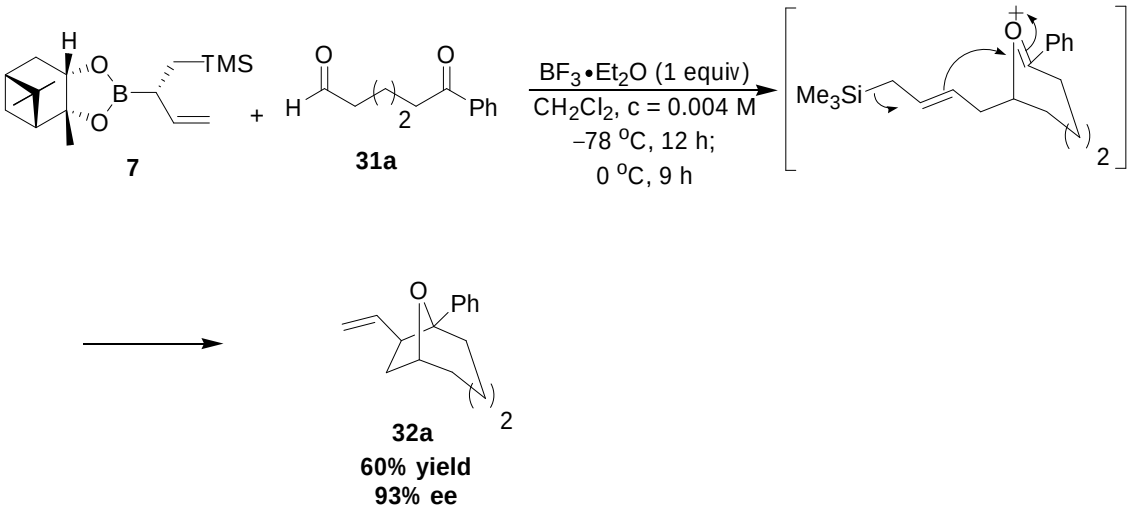
7 **31a** **32a**

Table 3.1 Summarized results of optimization process toward the synthesis of oxabicyclic compounds.

Entry	Concentration (M)	Rxn Time (h)	Temperature (°C)	32a: 33a: 34a Yield (%)
1	0.1	12 2	−78 0	0:35:60
2	0.01	13 6	−78 0	40:0:30
3	0.01	20 5	−78 0	45:0:30
4	0.003	13 9 4.5	−78 0 5	50: 0: 10

Rxn = reaction.

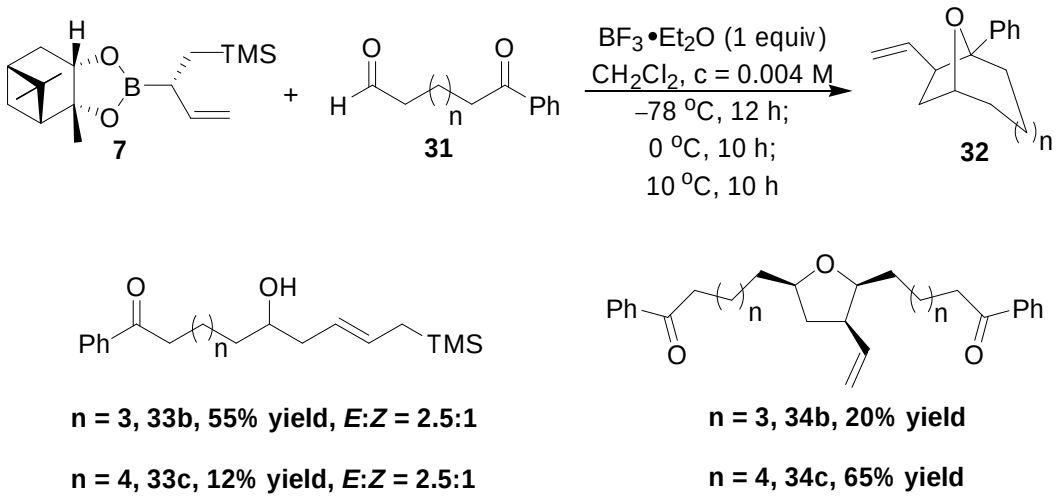
After further optimization of the reaction conditions of Table 3.1, reaction conditions for the formation of oxabicyclic compound **32a** were obtained as indicated in Scheme 3.2. Under the optimized reaction conditions, the desired product **32a** was obtained as a major product (60%) with good enantioselectivity (93% *ee*).



Scheme 3.2 Optimized reaction conditions for the synthesis of oxabicyclic compound **32a**.

Next, syntheses of 9-membered oxabicyclic **32b** and 10-membered oxabicyclic **32c** were attempted under the same optimized reaction conditions of Scheme 3.2, but only monoallylation product **33** and bisallylation product **34** were observed (Equation 3.2) for these transformations. On attempting the synthesis of **32b**, monoallylation product **33b** was isolated as a major product (55% yield) and bisallylation compound **34b** as a minor product (20% yield, Equation 3.2). The bisallylation compound **34c** (75% yield) was isolated as a major product and monoallylation compound **33c** (12% yield) as a minor product in the attempt to

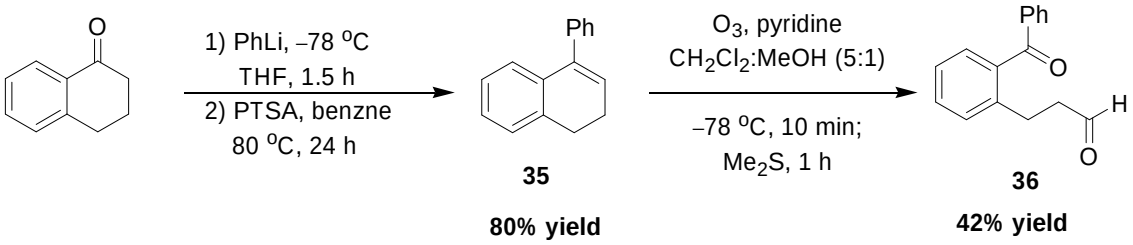
prepare 10-membered oxabicyclic **32c** (Equation 3.2). Any attempts to prepare oxabicyclic compounds **32b** and **32c** failed under any other reaction conditions.



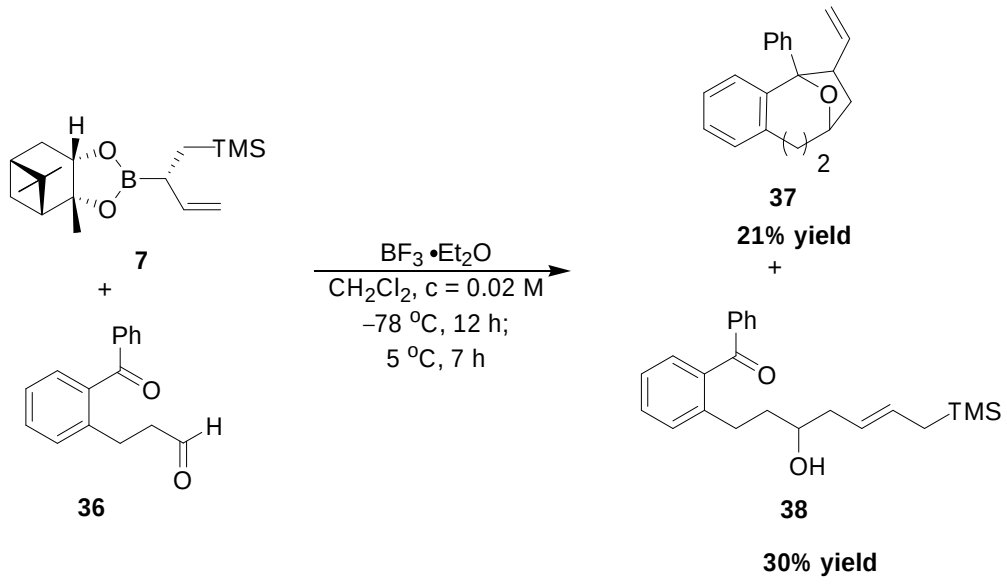
Equation 3.2 Attempted syntheses of 9 and 10 membered oxabicyclic compounds **32b** and **32c**.

It was predicted that if both carbonyl groups in a keto-aldehyde molecule could be brought closer in proximity, 9 and 10–membered oxabicyclic compounds could be achieved. To facilitate the intramolecular Prins-like cyclization process, a *cis*-double bond was introduced into the backbone of starting keto-aldehyde structures. As a starting point, 8-membered oxabicyclic compound **37** was first examined. The starting keto-aldehyde **36**[6] was synthesized as shown in Scheme 3.3 in three steps from a commercially available 3,4-dihydro-2*H*-naphthalen-1-one. When this substrate **36** was subjected to reaction conditions as shown in Equation 3.3, an approximately 1:1 mixture of desired product **37** and monoallylation product **38** was obtained (Equation 3.3). A higher concentration (0.02 M) than in previous cases

(0.004 M) was used to test its limitation because high dilution is not practically useful in synthesis. No bisallylation product was obtained with this concentration (0.02 M). This reaction did not give an excellent result (low yield of desired product) and syntheses of starting ketoaldehydes were too lengthy. This approach was not pursued further due to time constraints.



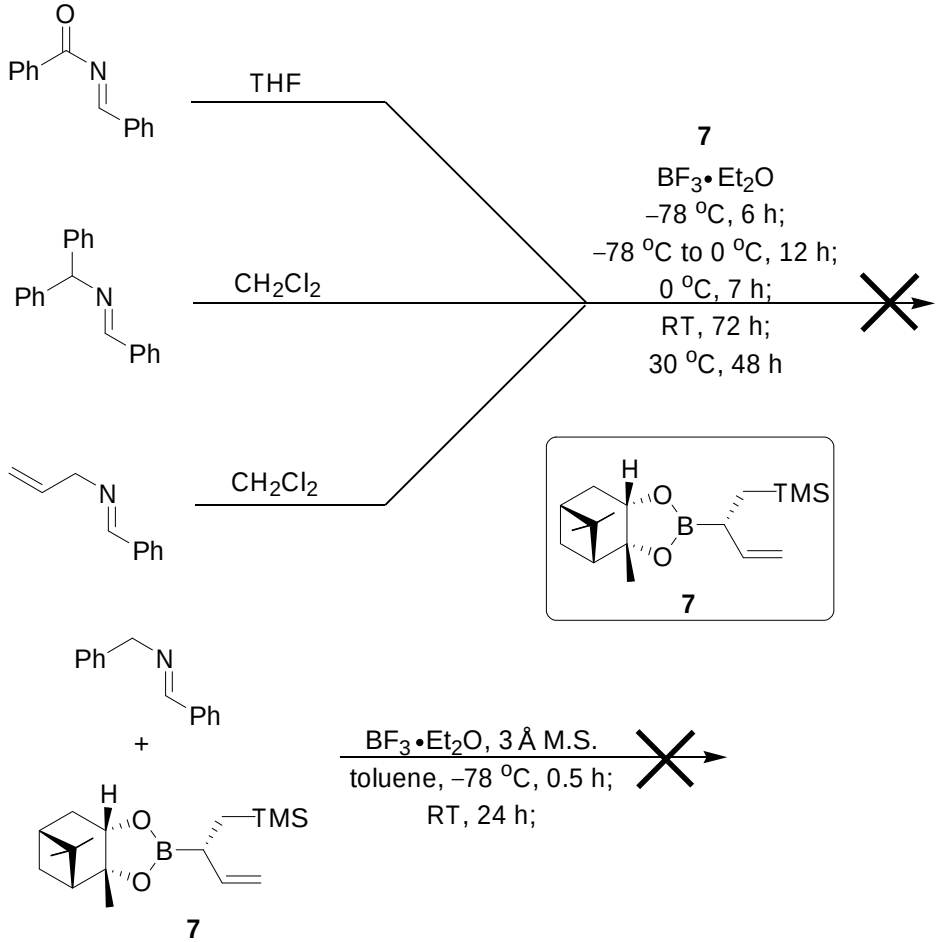
Scheme 3.3 Synthetic scheme for the preparation of keto-aldehyde **36.**[6]



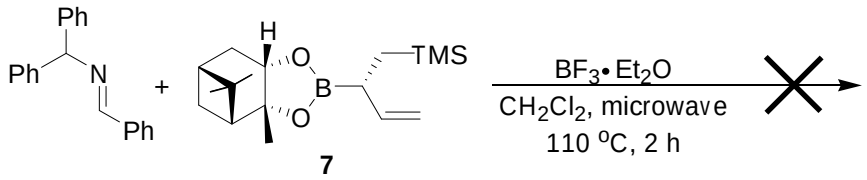
Equation 3.3 Synthesis of oxabicyclic compound **37** by reaction of **7** with ketoaldehyde **36**.

3.3 Imine Allylboration with Reagent 7

Imine allylborations between reagent **7** and different imine derivatives were examined under $BF_3{\cdot}Et_2O$ and $TiCl_4$ promoted conditions.[7] All attempts towards imine allylboration reactions with reagent **7** did not give any desired product (Scheme 3.4) and the starting reagent **7** was recovered in yields of 80–90%. Therefore, I decided to carry out the imine allylation at elevated temperature. An imine allylboration as shown in Equation 3.4 was carried out in a microwave reactor at 110 ^oC for 2 h with TLC monitoring every 30 minutes. No desired product was observed after a 2 h time period and the starting reagent **7** was recovered (85%).

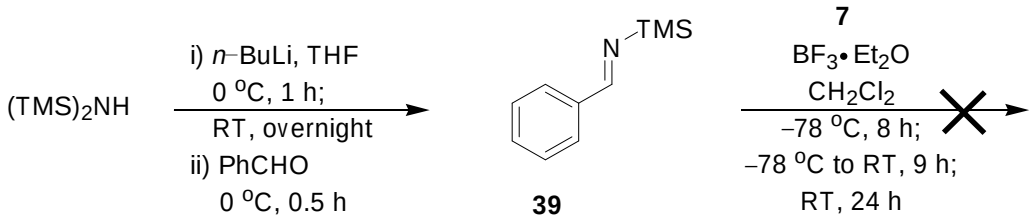


Scheme 3.4 Attempts toward imine allylboration reactions between reagent **7** and different imine derivatives.



Equation 3.4 An imine allylboration under microwave heating.

Next, a very reactive imine derivative[7d] was examined for imine allylboration with reagent **7** under various reaction conditions. The starting imine **39** was prepared as shown in Scheme 3.5 and reacted with reagent **7**, but no desired product was observed and starting reagent **7** was recovered back in 80-90% yields in all the cases.



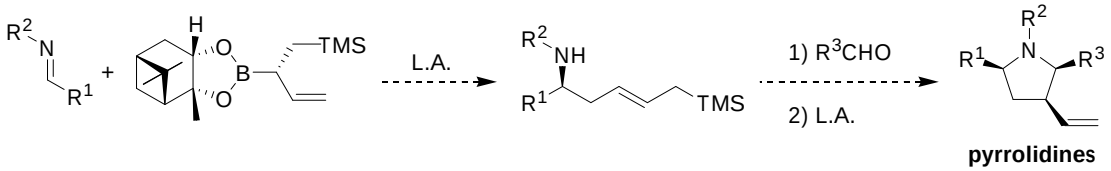
Scheme 3.5 An attempted allylboration between a reactive imine, **39,** and reagent **7**.[7d,8]

3.4 Synthesis of Pyrrolidines

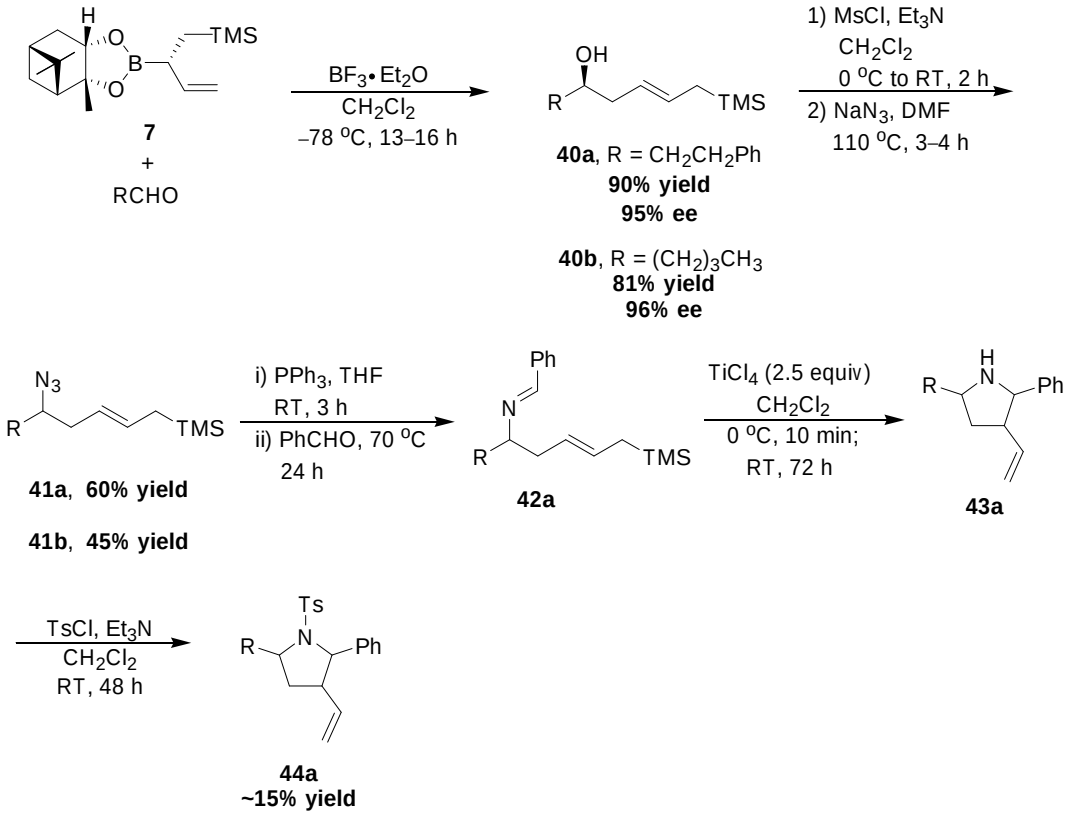
The structure of the pyrrolidine ring system is found in many biologically active molecules.[9] For example, pyrrolidine moieties are found in glycosidase inhibitors such as alexine[10] and australine,[11] antiviral agents such as preussin,[12] the angiotensin-converting enzyme inhibitor rampril,[13] antileukemia agents such as harringtonine[14] and crambescidin,[15] insecticide agents nicotine,[16] and in many

alkaloids such as hygrine.[17] Pyrrolidine structures are also commonly found in many pharmaceutical drugs such as procyclidine[18] and bepridil.[19] Therefore, synthesis of pyrrolidine derivatives draws considerable attention from synthetic chemists around the globe.

The synthesis of pyrrolidine molecules was initially planned as shown in Scheme 3.6. Since imine allylboration failed to yield the desired product, another route was considered to access polysubstituted pyrrolidines (Scheme 3.7).



Scheme 3.6 Initial synthetic plan for the preparation of polysubstituted pyrrolidines.



Scheme 3.7 Synthetic schemes for the preparation of pyrrolidine derivatives via homoallylic amines and preliminary result of **44a**.

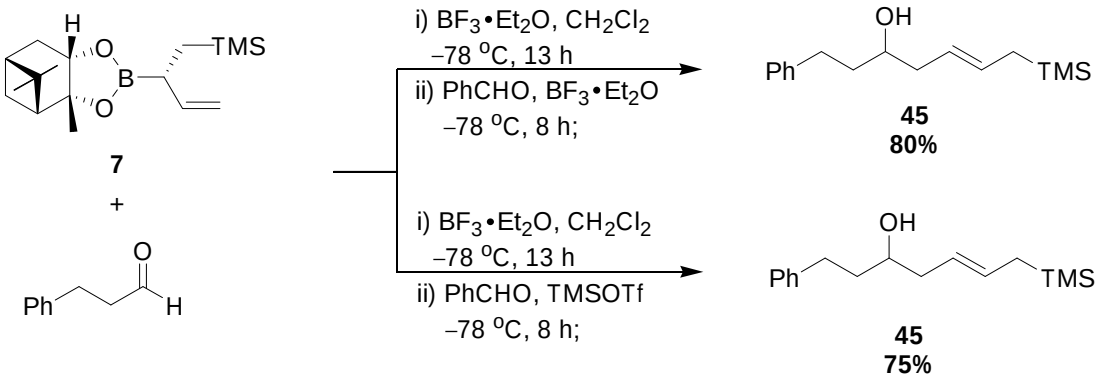
As shown in Scheme 3.7, homoallylic alcohols **40a** and **40b** were first synthesized with excellent yields and enantioselectivities using conditions described in Scheme 3.7.[3] The hydroxyl group was then converted to a mesylate, which was then replaced with an azide group to produce compounds **41a** and **41b**.[20] Next, the azide group of **41a** was transformed into the corresponding imine precursors **42a** via a Staudinger reaction followed by condensation with benzaldehyde.[21] This imine intermediate **42a** was subjected to a $TiCl_4$ catalyzed intramolecular allylsilation[22b] conditions to yield pyrrolidine derivative **43a**, which was protected as a sulfonamide to generate pyrrolidine derivative **44a** in low yield (~15% yield from azide **41a**).[23] This preliminary result towards the synthesis of pyrrolidine derivative **44a** indicates

that pyrrolidine derivatives could be attained via this methodology. Further studies are needed in this direction. The azide **41b** did not yield any desired pyrrolidine **44b** in the early studies.

3.5 One-Pot Syntheses of Polysubstituted Tetrahydrofurans.

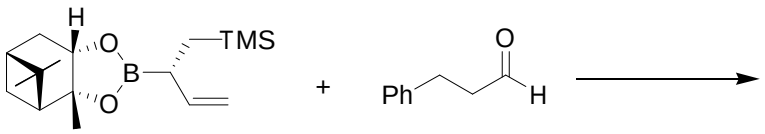
In the previous study by Hall and Peng,[3] syntheses of polysubstituted tetrahydrofurans were achieved with good diastereoselectivity (>20:1) via a stepwise protocol. When a one-pot protocol was attempted, the diastereoselectivity was moderate (5:1). In this thesis, we sought to develop an improved one-pot protocol for the preparation of trisubstituted tetrahydrofurans. To improve the diastereoselectivities, different reaction conditions were examined with respect to reaction temperature, Lewis acid, and reaction time.

The first approach to optimize the reaction was to add another equivalent of $BF_3 \cdot Et_2O$ or TMSOTf Lewis acids to the reaction mixture after the addition of a second aldehyde. Unfortunately, only allylboration product **45** was observed as a single product (Scheme 3.8).



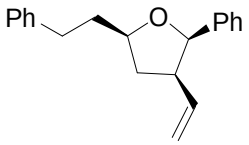
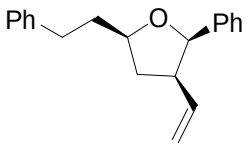
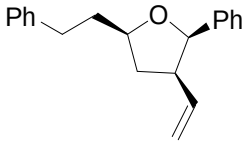
Scheme 3.8 Initial attempts towards the synthesis of polysubstituted tetrahydrofurans.

Next, different reaction temperatures and times were examined in the optimization process. From this study (Table 3.2), it was observed that better diastereoselectivity could be obtained at −40 °C (Table 3.2, entry 3). Therefore, this condition was chosen as an optimal condition for the one-pot synthesis of polysubstituted tetrahydrofurans. A few examples of one-pot preparation of polysubstituted tetrahydrofurans were examined and the results are summarized in Scheme 3.9 using the optimized conditions of Table 3.2.

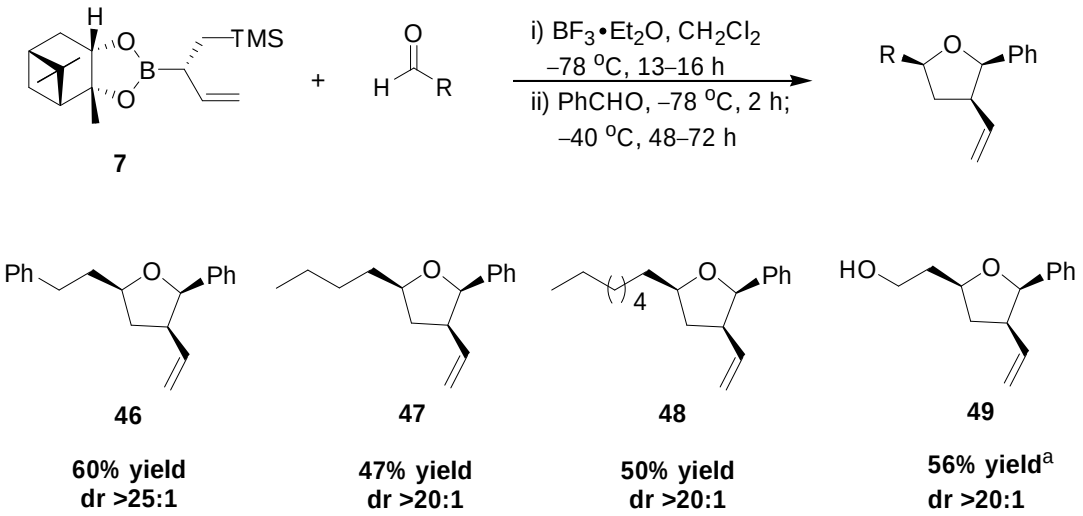


7

Table 3.2 Optimization of a one-pot synthesis of polysubstituted tetrahydrofurans.

Entry	Rxn Conditions	Product
1	i) $BF_3 \bullet Et_2O$, CH_2Cl_2 –78 °C, 13 h ii) PhCHO –78 °C, 2 h; 0 °C, 4 h	 **46** **50%** **7:1 *dr***
2	i) $BF_3 \bullet Et_2O$, CH_2Cl_2 –78 °C, 13 h ii) PhCHO –78 °C, 1 h; –20 °C, 20 h	 **46** **50%** **16:1 *dr***
3	i) $BF_3 \bullet Et_2O$, CH_2Cl_2 –78 °C, 13 h ii) PhCHO –78 °C, 1 h; –40 °C, 20 h	 **46** **40%** **>25:1 *dr***

Rxn = reaction, dr = diastereomeric ratio.



a: The OH in the aldehyde was protected as TBS and it was removed during purification process.

Scheme 3.9 An optimal one-pot preparation of trisubstituted tetrahydrofurans.

The diastereoselectivity of polysubstituted tetrahydrofurans can be explained by the pseudo-diequatorial arrangement of R^1 and R^2 in the transition state model (Figure 3.1). This model was proposed by our group[3] and other research groups[24]. The stereochemistry of all cis-substituents of polysubstituted tetrahydrofurans were experimentally observed and proved using NOE experiments by our group[3] and others[24a,25].

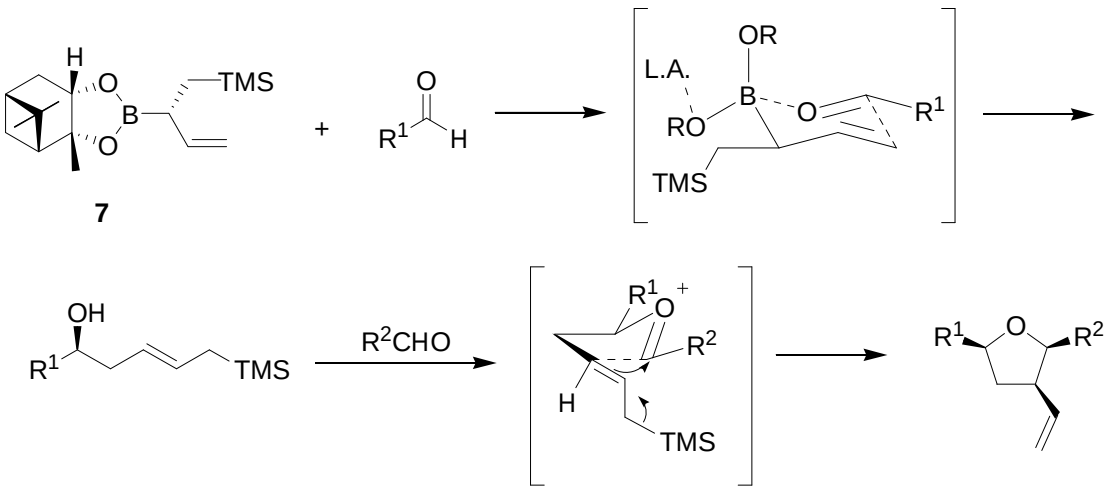


Figure 3.1 Explanation for the diastereoselectivity of polysubstituted tetrahydrofurans.[3,24]

3.6 Syntheses of Cyclopentene Derivatives

It was predicted that cyclopentenes could be obtained via an intramolecular S_N2' type reaction as shown in Figure 3.2. To examine this prediction, two different homoallylic alcohols **50** and **51** were synthesized using the usual conditions (Scheme 3.10).[26] Next, these alcohols **50** and **51** were investigated under several S_N2' reaction conditions, but only elimination products **52** and **54** and cyclopropane product **53** were obtained and no desired product was observed (Scheme 3.11).[27]

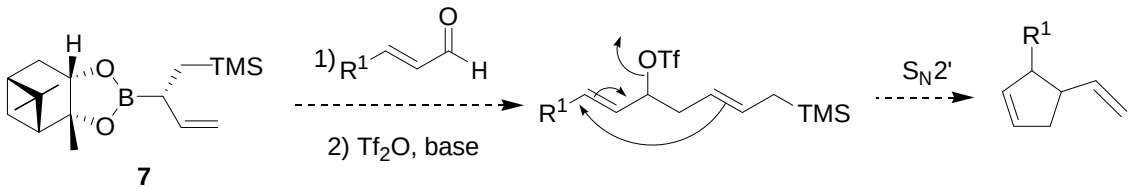
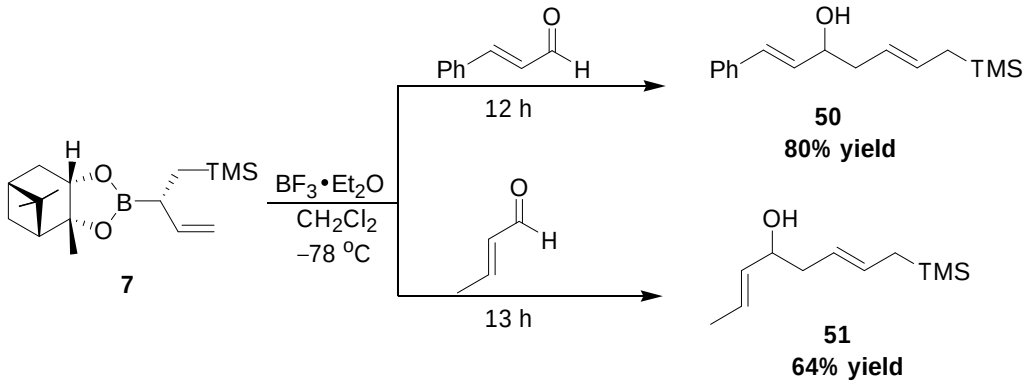
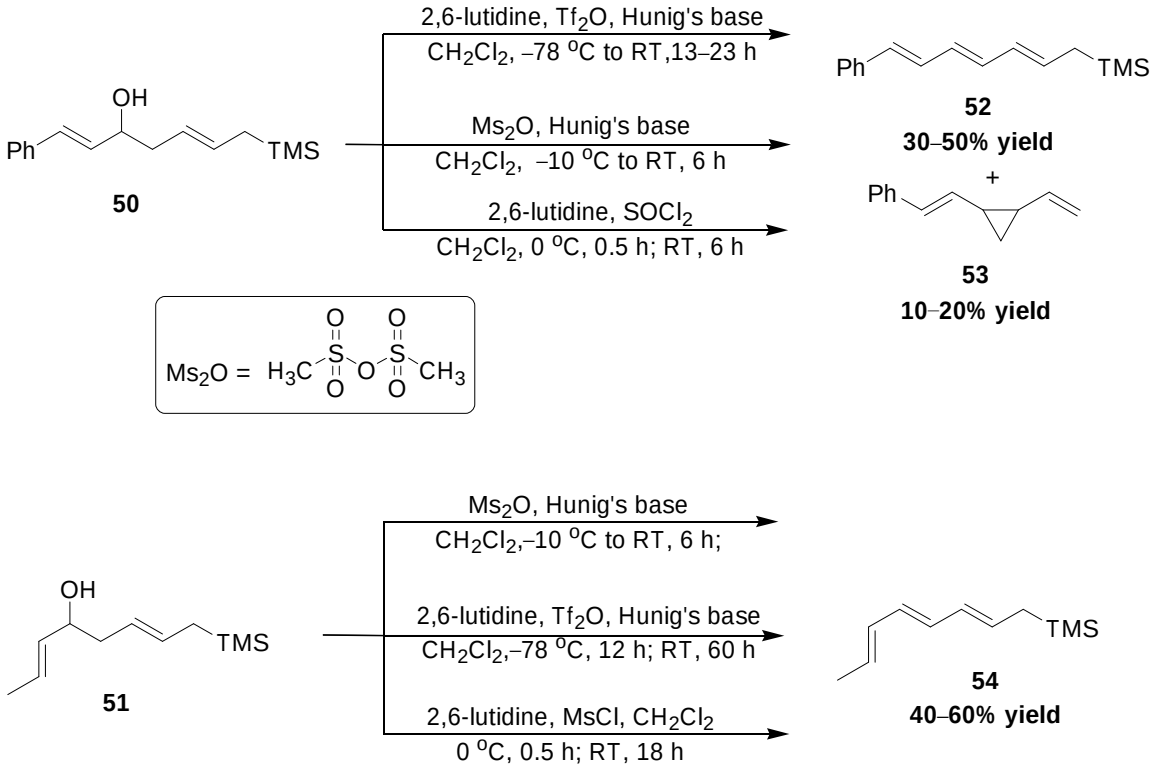


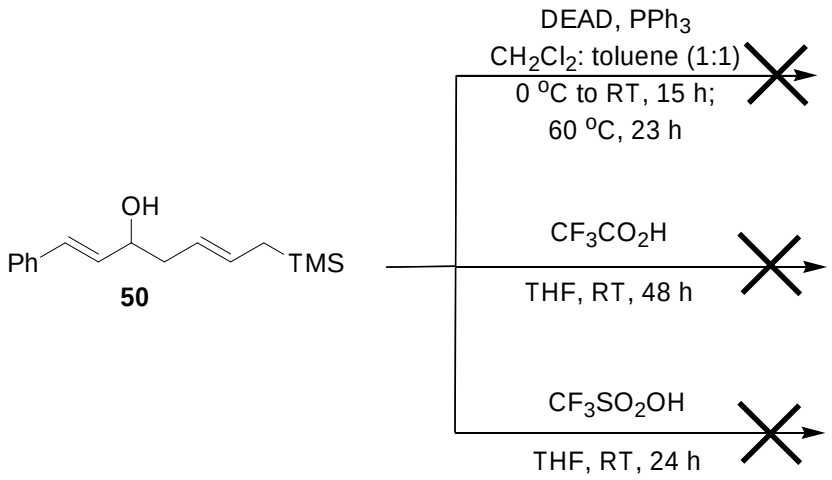
Figure 3.2 A proposed scheme for the preparation of cyclopentene derivatives.



Scheme 3.10 Syntheses of alcohols **50** and **51**.



Scheme 3.11 Investigation of cyclopentene synthesis under several S_N2' reaction conditions.[27]



Scheme 3.12 Investigation of cyclopentene synthesis under non-basic S_N2' reaction conditions.

3.7 Conclusion

Further developments of reagent **7** were examined in this chapter. The largest oxabicyclic compound synthesized was the 8-membered **32a**. The 9- and 10-membered precursors produced only bisallylation product **34** and monoallylation product **33**. All attempts towards imine allylboration between reagent **7** and various kinds of imine derivatives failed to yield desired products. In the preliminary studies toward the synthesis of pyrrolidine derivatives, it was observed that pyrrolidine derivative **44a** could be attained. Therefore, further studies are needed in this direction for the synthesis of pyrrolidines. Moreover, trisubstituted tetrahydrofurans **46**–**49** were prepared in a one-pot protocol with excellent diastereoselectivities (20:1).

3.8 Experimental

3.8.1 General

Unless otherwise noted, all reactions were carried out under an argon atmosphere using flame-dried glassware. CH_2Cl_2, methanol, and toluene were distilled over CaH_2. THF was distilled over sodium/benzophenone. All aldehydes were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ or Magic stains. NMR spectra were recorded on 300 or 400 or 500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3{\cdot}OEt_2$. ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; ddd, doublet of doublet of doublets. The estimated accuracy of coupling constants is ± 0.5 Hz. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra and optical rotations were recorded by the University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab.

Magic stain was prepared from:

20g $(NH_4)_2MoO_4$

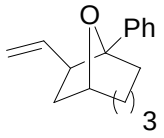
0.4 g $Ce(SO_4)_2$

500 mL of 10% H_2SO_4

3.8.2 Syntheses of Oxabicyclic Compounds

In a 250 mL round bottom flask, ketoaldehyde **31a** (126 mg, 0.66 mmol, 1.05 equiv) and reagent **7** (193 mg, 0.63 mmol, 1.00 equiv) in 150 mL of CH_2Cl_2 were mixed and cooled to −78 °C and stirred for 30 minutes. Next, $BF_3{\cdot}Et_2O$ (0.13 mL, 1.00 mmol, 1.59 equiv) was added to the flask and stirred for 12 h at −78 °C, followed by 9 h at 0 °C (different bath). The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (20 mL) and extracted with diethyl ether (4 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed by rotary evaporator.

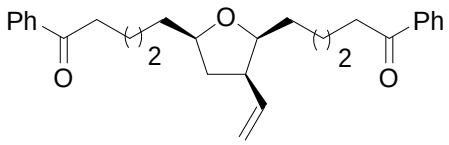
9-Oxa-1-phenyl-8-vinylbicyclo[4.2.1]nonane (32a)



Flash chromatography (0−5% EtOAc in hexanes) provided a clear oil (85.0 mg, 59.2% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.69; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (dd, J = 1.4, 8.5 Hz, 2H), 7.31 (m, 3H), 5.99 (ddd, J = 7.3, 10.2, 17.5 Hz, 1H), 5.15 (ddd, J = 1.0, 1.9, 10.3 Hz, 1H), 5.00 (ddd, 1.2, 1.9, 17.0 Hz, 1H), 4.70 (m, 1H), 3.02 (dt, J = 5.1, 8.2 Hz, 1H), 2.71 (q, J = 9.9 Hz, 1H),

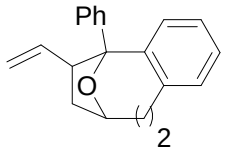
2.44 (td, J = 9.4, 12.9 Hz, 1H), 2.10 (m, 3H), 1.72 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.4, 136.7, 128.1, 126.1, 124.9, 117.7, 87.0, 76.6, 56.1, 44.5, 38.4, 34.7, 25.1, 24.9; IR ($CDCl_3$, cast film): cm ^{1} 3077, 3026, 2927, 2859, 1638, 1602, 1492, 1470, 1446, 1350, 1095, 1072, 1013, 914, 753, 700; HRMS (EI, *m*/*z*) calculated for $C_{16}H_{20}O$: 228.1514, found: 228.1515 [M^+]. HPLC: Chiralcel OD, 5% *i*PrOH/Hexanes, 0.50 mL/min., UV detection at 210 nm, major peak at 7.1 min., minor peak at 8.5 min., 93% ee.

5-[5-(5-Oxo-5-phenylpentyl)-3-vinyltetrahydrofuran-2-yl]-1-phenylpentan-1-one (34a)



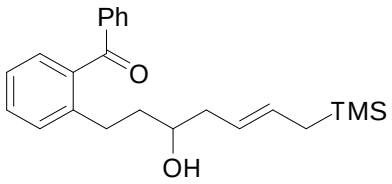
Flash chromatography (0–5% EtOAc in hexanes) yielded a white gel (28.0 mg, 10.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.39; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (m, 4H), 7.55 (m, 2H), 7.46 (m, 4H), 5.74 (ddd, J = 9.0, 9.3, 18.0 Hz, 1H), 5.00 (d, J = 5.2 Hz, 1H), 4.97 (s, 1H), 3.79 (m, 2H), 2.97 (ddd, J = 8.0, 8.4, 9.0 Hz, 4H), 2.81 (m, 1H), 2.19 (ddd, J = 6.8, 8.0, 15.8 Hz, 1H), 1.76 (m, 5H), 1.46 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.3, 138.7, 137.1, 132.8, 128.5, 128.0, 115.0, 81.3, 78.4, 46.7, 38.5, 38.3, 36.2, 31.6, 26.2, 24.5; IR ($CDCl_3$, cast film): cm ^{1} 3066, 2936, 2862, 1686, 1598, 1449, 1224, 1002, 752, 691; HRMS (ES, *m*/*z*) calculated for $C_{28}H_{34}O_3Na$: 441.2400, found: 441.2402 [$(M+Na)^+$]. $[\alpha]^{25}_D$ 16.61 (c = 0.92, $CHCl_3$).

13-Oxa-1-phenyl-12-vinyltricyclo[8.2.1.0^{2,7}]trideca-2(7),3,5-triene (37)



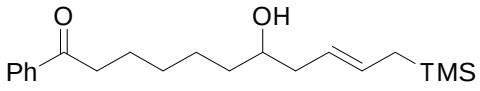
The reaction scale was 0.50 mmol in the respect of the starting ketoaldedhyde. Flash chromatography (20–50% CH_2Cl_2 in hexanes, then 5–15% EtOAc in hexanes) a clear liquid (30.0 mg, 21.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.59; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58 (dd, J = 1.8, 8.1 Hz, 2H), 7.30 (m, 4H), 7.15 (dd, J = 7.5, 1.4 Hz, 1H), 7.07 (dt, J = 1.4, 7.2 Hz, 1H), 6.98 (ddt, J = 0.6, 1.6, 7.8 Hz, 1H), 6.58 (dd, J = 1.44, 7.8 Hz, 1H), 5.54 (ddd, J = 9.0, 10.2, 15.9 Hz, 1H), 5.34 (ddd, J = 0.8, 2.0, 17.1 Hz, 1H), 5.10 (ddd, J = 0.6, 2.0, 10.2 Hz, 1H), 4.62 (ddt, J = 1.7, 5.7, 6.3 Hz, 1H), 3.71 (ddd, J = 5.7, 12.0, 14.4 Hz, 1H), 3.45 (dd, J = 8.7, 10.5 Hz, 1H), 2.66 (dt, J = 4.2, 14.1 Hz, 1H), 2.52 (m, 2H), 1.92, (dddd, J = 1.7, 4.5, 12.0, 13.5 Hz, 1H), 1.53, (ddd, J = 6.3, 10.8, 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.2, 141.2, 140.3, 138.5, 131.1, 131.0, 128.3, 127.5, 127.4, 126.8, 125.2, 116.6, 92.2, 73.9, 52.6, 41.5, 37.0, 31.6; IR ($CDCl_3$, cast film): cm ^{1} 3061, 3016, 2934, 2866, 1666, 1638, 1598, 1486, 1446, 1296, 1183, 1116, 1048, 1008, 917, 766, 750, 699; HRMS (EI, *m*/*z*) calculated for $C_{20}H_{20}O$: 276.1514, found: 276.1518 [(M^+]. [α]$^{25}_D$ 43.36 (c = 1.4, $CHCl_3$).

[2-(3-Hydroxy-7-trimethylsilanyl-hept-5-enyl)-phenyl]-phenyl methanone (38)



The reaction scale was 0.50 mmol in the respect of the starting ketoaldedhyde. Flash chromatography (20–50% CH_2Cl_2 in hexanes, then 5–15% EtOAc in hexanes) provided a clear liquid (58.4 mg, 30.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.38; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (dd, J = 1.4, 8.4 Hz, 2H), 7.58 (dt, J = 1.4, 6.6 Hz, 1H), 7.44 (m, 4H), 7.27 (m, 2H), 5.46 (m, 1H), 5.18 (m, 1H), 3.49 (bs, 1H), 2.79 (m, 2H), 2.17 (bs, 1H), 2.06 (m, 2H), 1.74 (m, 2H), 1.42 (d, J = 8.1 Hz, 2H), –0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 141.7, 138.6, 138.1, 133.5, 130.7, 130.6, 130.6, 130.6, 129.1, 128.7, 125. 4, 124.4, 70.3, 41.0, 38.8, 29.5, 23.2, -1.7; IR ($CDCl_3$, cast film): cm ^{1} 3436, 3002, 3063, 3020, 2952, 1664, 1598, 1580, 1484, 1448, 1267, 850; HRMS (ES, *m*/*z*) calculated for $C_{23}H_{30}O_2Si$: 389.1907, found: 389.1905 [$(M+Na)^+$]. $[\alpha]^{25}_D$ 14.02 (c = 0.80, $CHCl_3$).

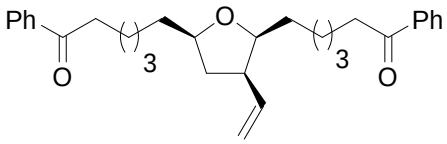
7-Hydroxy-1-phenyl-11-trimethylsilanyl-undec-9-en-1-one (33b)



The reaction scale was 0.33 mmol in the respect of the starting ketoaldedhyde. Flash chromatography (0–15% EtOAc in hexanes) provided a clear liquid (60.0 mg,

55.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.40; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, J = 8.0 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 5.57 (m, 1H), 5.28 (ddt, J = 1.4, 6.5, 14.5 Hz, 1H), 3.60 (m, 1H), 3.02 (dd, J = 7.0, 7.5 Hz, 2H), 2.28 (m, 1H), 2.22 (t, J = 6.5 Hz, 1H), 2.09 (dt, J = 8.0, 14.0 Hz, 1H), 1.80 (m, 3H), 1.65 (bs, 1H), 1.51 (m, 6H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.5, 137.1, 132.9, 130.9, 128.6, 128.1, 124.1, 71.0, 41.1, 38.6, 36.7, 29.4, 25.6, 24.3, 23.1, -1.9; IR ($CDCl_3$, cast film): cm ^{1} 3446, 3086, 3062, 3012, 2933, 2859, 1687, 1598, 1581, 1449, 1409, 1248, 1155, 1002, 969, 853, 730, 691; HRMS (EI, *m*/*z*) calculated for $C_{20}H_{32}O_2Si$: 332.2172, found: 332.2169 [M^+].

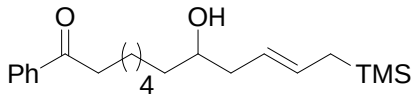
6-[5-(6-Oxo-6-phenyl hexyl)-3-vinyltetrahydrofuran-2-yl]-1-phenyl hexan-1-one (34b)



The reaction scale was 0.33 mmol in the respect of the starting ketoaldedhyde. Flash chromatography (0–15% EtOAc in hexanes) provided a clear liquid (28.0 mg, 20.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.50; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (m, 4H), 7.55 (m, 2H), 7.46 (m, 4H), 5.74 (dt, J = 9.6, 17.6 Hz, 1H), 5.00 (m, 1H), 4.97 (s, 1H), 3.78 (m, 2H), 2.96 (ddd, J = 4.8, 7.2, 10.0 Hz, 4H), 2.81 (m, 1H), 2.18 (ddd, J = 6.8, 8.0, 12.8 Hz, 1H), 1.74 (m, 4H), 1.40 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.6, 138.8, 137.2, 133.0, 128.6, 128.1,

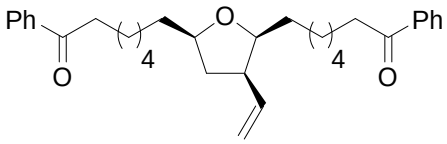
114.9, 81.5, 78.6, 46.8, 38.6, 36.4, 31.7, 29.5, 26.3, 24.4; IR ($CDCl_3$, cast film): cm ^{1} 3065, 3027, 2930, 2857, 1687, 1598, 1581, 1449, 1366, 1270, 1220, 1002, 914, 753, 691; HRMS (EI, *m*/*z*) calculated for $C_{30}H_{38}O_3$: 446.2821, found: 446.2819 [M^+].

8-Hydroxy-1-phenyl-12-trimethylsilanyl-dodec-10-en-1-one (33c)



The reaction scale was 0.34 mmol in the respect of the starting ketoaldedhyde. Flash chromatography (5–25% EtOAc in hexanes) provided a clear liquid (15.1 mg, 12.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.48; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, J = 8.0 Hz, 2H), 7.55 (m, 1H), 7.46 (t, J = 7.2 Hz, 2H), 5.52 (td, J = 1.2, 8.4 Hz, 1H), 5.25 (m, 1H), 3.55 (m, 1H), 2.97 (t, J = 7.2, 2H), 2.23 (m, 1H), 2.17 (t, J = 6.8 Hz, 1H), 2.05 (dt, J = 6.8, 14.0 Hz, 1H), 1.75 (dt, J = 7.2, 14.4 Hz, 3H), 1.60 (d, J = 4.4 Hz, 1H), 1.41 (m, 7H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.5, 137.1, 132.8, 130.7, 128.5, 128.0, 124.1, 70.9, 41.0, 38.6, 36.6, 29.5, 29.3, 25.6, 24.3, 23.0, –2.0; IR ($CDCl_3$, cast film): cm ^{1} 3440, 3061, 3013, 2932, 2857, 1687, 1598, 1581, 1449, 1408, 1248, 968, 854, 752, 691; HRMS (ES, *m*/*z*) calculated for $C_{21}H_{34}O_2SiNa$: 369.2220, found: 369.2221 [$(M+Na)^+$]. $[\alpha]^{25}_D$ 6.55 (c = 1.20, $CHCl_3$).

7-[5-(7-Oxo-7-phenyl heptyl)-3-vinyltetrahydrofuran-2-yl]-1-phenyl-heptan-1-one (34c)



The reaction scale was 0.34 mmol in the respect of the starting ketoaldedhyde. Flash chromatography (0–15% EtOAc in hexanes) provided a clear liquid (105 mg, 65.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96 (d, J = 7.8 Hz, 4H), 7.55 (td, J = 2.1, 7.5 Hz, 2H), 7.45 (t, J = 7.5 Hz, 4H), 5.74 (dt, J = 9.6, 17.7 Hz, 1H), 5.00 (ddd, J = 0.8, 2.0, 5.1 Hz, 1H), 3.76 (m, 2H), δ 2.95 (dt, J = 2.6, 7.5 Hz, 4H), 2.80 (dt, J = 7.2, 16.2 Hz, 1H), 2.17 (ddd, J = 6.9, 8.1, 12.6 Hz, 1H), 1.74 (m, 4H), 1.38 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.5, 138.8, 137.0, 132.8, 128.5, 128.0, 114.7, 81.4, 78.5, 46.7, 38.5, 38.3, 29.5, 29.2, 26.2, 24.3; HRMS (EI, *m*/*z*) calculated for $C_{32}H_{42}O_3$: 474.3134, found: 474.3128 [M^+].

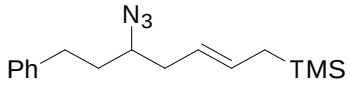
3.8.3 Syntheses of Azides 41a and 41b

In a 50 mL long neck round bottom flask, homoallylic alcohol **40a** (0.73 g, 2.80 mmol, 1.00 equiv) and Et_3N (1.15 mL, 8.25 mmol, 3.00 equiv) in 10 mL of CH_2Cl_2 were mixed and cooled to 0 ^oC. Next, MsCl (0.32 mL, 4.10 mmol, 1.50 equiv) was added to the flask and the flask was warmed to RT over 2 h. Then, the reaction mixture was quenched with 10 mL of aqueous sat. NH_4Cl and the reaction mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried

over anhydrous Na_2SO_4, filtered, and the solvent was removed under rotary evaporator. The crude product was filtered through a pad of silica (5:1, hexanes : EtOAc) and removal of solvent yielded mesylate product as a clear liquid.

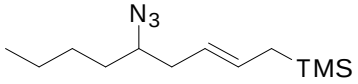
In a 3-neck round bottom flask, the mesylate product (2.6 mmol, 1.0 equiv) and NaN_3 (0.69 g, 10.5 mmol, 4.00 equiv) in 9 mL of DMF were refluxed at 110 ^oC for 3 h. The reaction mixture was cooled to RT and extracted with diethyl ether (4 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by rotary evaporator.[20]

(5-Azido-7-phenyl hept-2-enyl)-trimethyl silane (41a)



Flash chromatography (0–5% EtOAc in hexanes) provided a yellow liquid (0.49 g, 60.0% yield). TLC (25% EtOAc in hexanes, KMNO4 stain): R_f 0.71; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (m, 2H), δ 7.21 (m, 3H), δ 5.53 (m, 1H), δ 5.23 (m, 1H), δ 3.28 (m, 1H), δ 2.80 (ddd, J = 6.0, 9.6, 15.2 Hz, 1H), δ 2.68 (m, 1H), δ 2.30 (t, J = 6.8, 2H), 1.80 (m, 2H), 1.44 (d, J = 8.0, 2H), δ 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.3, 130.6, 128.5, 128.4, 126.0, 123.1, 62.2, 37.8, 35.5, 32.4, 23.0, -1.8; IR ($CHCl_3$, cast film): cm ^{1} 3062, 3026, 2952, 2917, 2096, 1604, 1497, 1454, 1248, 851, 699; HRMS (ES, *m*/*z*) calculated for $C_{16}H_{25}N_3Si$: 288.1891, found: 288.1894 $[(M+H)^+]$. $[\alpha]^{25}_D$ 22.51 (c = 1.08, $CHCl_3$).

(5-Azido-non-2-enyl)-trimethylsilane (41b)

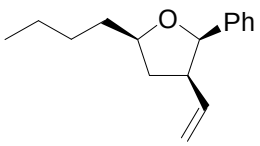


The reaction scale was 1.48 mmo in the respect of the starting homoallylic alcohol. Flash chromatography (0–5% EtOAc in hexanes) provided a yellow liquid (0.16 g, 45.0% yield). TLC (25% EtOAc in hexanes, $KMNO_4$ stain): R_f 0.79; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.52 (m, 1H), 5.24 (m, 1H), 3.24 (m, 1H), 3.24 (t, J = 6.6 Hz, 2H), 1.45 (m, 8H), 0.92 (t, J = 7.2, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 130.2, 123.5, 63.1, 37.7, 33.4, 28.2, 22.9, 22.5, 14.0, -2.0; IR ($CHCl_3$, cast film): cm ^{1} 3021, 2957, 2936, 2874, 2098, 1649, 1467, 1248, 1155, 966, 851, 748, 694; HRMS (ES, *m*/*z*) calculated for $C_{12}H_{26}N_3Si$: 240.1891, found: 240.1880 [$(M+H)^+$]. $[\alpha]^{25}_D$ 14.32 (c = 1.26, $CHCl_3$).

3.8.4 One-pot syntheses of trisubstituted tetrahydrofurans 46–49

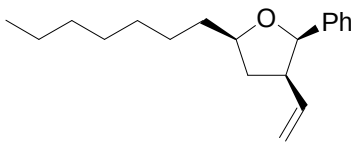
In a test tube reaction vessel, aldehyde (0.50 mmol, 1.00 equiv) and reagent **7** (0.50 mmol, 1.00 equiv) in 3 mL of CH_2Cl_2 were mixed and cooled to –78 °C. Next, $BF_3{\cdot}Et_2O$ (0.50 mmol, 1.00 equiv) was added and stirred at –78 °C for 13–16 h. Then, benzaldehyde (0.50 mmol, 1.00 equiv) was added and stirred at –78 °C for 2 h at –78 °C. Next, the reaction mixture was warmed to –40 °C (same bath) and stirred for 24–72 h at –40 °C. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (20 mL) and extracted with diethyl ether (4 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by rotary evaporator.

5-Butyl-2-phenyl-3-vinyltetrahydrofuran (47)



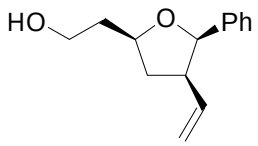
The reaction scale was 0.42 mmol in the respect of the starting pentanal aldedhyde. Flash chromatography (0–5% EtOAc in hexanes) provided a clear liquid (50.0 mg, 47.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.63; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (m, 2H), 7.23 (m, 3H), 5.18 (ddd, J = 9.0, 10.0, 17.0 Hz, 1H), 5.05 (d, J = 8.5 Hz, 1H), 4.90 (ddd, 1.0, 1.6, 17.0 Hz, 1H), 4.76 (ddd, J = 0.7, 2.0, 10.0 Hz, 1H), 4.02 (ddt, J = 6.5, 9.5, 12.0 Hz, 1H), 3.18 (m, 1H), 2.20 (ddd, J = 5.5, 7.5, 10.5 Hz, 1H), 1.85 (m, 1H), 1.70 (m, 1H), 1.55 (m, 2H), 1.40 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), 0.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.6, 138.7, 127.8, 126.9, 126.8, 114.8, 83.2, 79.6, 48.9, 38.4, 35.3, 28.7, 22.9, 14.1**;** IR ($CHCl_3$, cast film): cm ^{1} 3066, 3029, 2957, 2927, 2858, 1729, 1641, 1494, 1454, 1056, 912, 721, 698; HRMS (ES, *m*/*z*) calculated for $C_{16}H_{22}ONa$: 253.1563, found: 253.1564 [$(M+Na)^+$].

5-Heptyl-2-phenyl-3-vinyltetrahydrofuran (48)



The reaction scale was 0.45 mmol in the respect of the starting aldedhyde. Flash chromatography (0–5% EtOAc in hexanes) provided a clear liquid (66.0 mg, 50.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.69; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.20 (m, 5H), 5.18 (ddd, J = 9.0, 10.2, 17.1 Hz, 1H), 5.05 (d, J = 8.2 Hz, 1H), 4.90 (ddd, J = 0.8, 2.0, 17.0 Hz, 1H), 4.76 (dd, J = 2.1, 10.2 Hz, 1H), 4.02 (m, 1H), 3.18 (m, 1H), 2.20 (ddd, J = 5.4, 7.5, 12.3 1H), 1.85 (m, 1H), 1.68 (m, 1H), 1.40-1.25 (m, 11H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6, 138.7, 127.7, 126.9, 126.8, 114.7, 83.1, 79.6, 48.9, 38.3, 35.6, 31.8, 30.0, 29.3, 26.5, 22.7, 14.1; IR ($CDCl_3$, cast film): cm ^{1} 3067, 3030, 2956, 2928, 2857, 1730, 1641, 1494, 1454, 1359, 1110, 1095, 995, 912, 721, 698; HRMS (ES, *m*/*z*) calculated for $C_{19}H_{28}ONa$: 295.2032, found: 295.2032 [$(M+Na)^+$].

2-(5-Phenyl-4-vinyltetrahydrofuran-2-yl)-ethanol (49)



The alcohol was protected with TBS in the starting aldehyde and it was removed during the purification on silica column. The reaction scale was 0.43 mmol in the respect of the starting aldedhyde. Flash chromatography (10–80% EtOAc in

hexanes) provided a yellow liquid (58.0 mg, 56.0% yield). TLC (50% EtOAc in hexanes, $KMnO_4$ stain): R_f 0.50; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 2H), δ 7.21 (m, 3H), δ 5.18 (ddd, J = 8.7, 9.9, 17.1 Hz, 1H), δ 5.09 (d, J = 8.4 Hz, 1H), 4.92 (ddd, J = 0.9, 2.0, 17.1 Hz, 1H), 4.78 (ddd, J = 0.8, 2.0, 9.9 Hz, 1H), 4.22 (m, 1H), 3.89 (m, 2H), 3.18 (m, 1H), 2.60 (t, J = 5.4, 1H), 2.23 (ddd, J = 5.4, 7.2, 12.3 Hz, 1H), 2.02 (m, 2H), 1.65 (td, 9.3, 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.9, 138.1, 127.9, 127.1, 126.7, 115.3, 83.7, 79.3, 62.0, 48.4, 38.6, 37.5; IR ($CHCl_3$, cast film): cm ^{1} 3388, 3076, 3029, 2929, 2878, 1641, 1604, 1493, 1453, 1068, 914, 752, 722, 699; HRMS (ES, *m*/*z*) calculated for $C_{14}H_{18}O_2Na$: 241.1199, found: 241.1195 [$(M+Na)^+$].

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Chapter 4: Thesis Conclusions

In the first half of this thesis, design and evaluation of a new Lewis acid-assisted Lewis acid (LLA) catalyst system was examined. A variety of chiral boronic esters were prepared as pre-catalysts and the chirality of the molecules was introduced through use of known chiral diol auxiliaries such as (+) or (−)-pinane diol and Hoffman's camphordiol. These boronic ester pre-catalysts were complexed with other Lewis acids to form Lewis acid-assisted Lewis acid catalysts, which were examined in the allylation between allyltributyltin and benzaldehyde or hydrocinnamaldehyde.

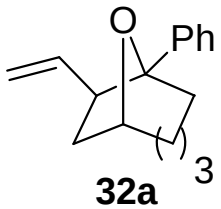
It was observed that in some cases, the LLA catalyst systems accelerated the reactions compared to the background reactions. In the case of reaction between allyltributyltin and benzaldehyde, the LLA catalyst system obtained by combining boronic ester **12**, **13**, **14**, **19**, or **28** with $Zn(OTf)_2$, led to higher conversions of starting material into desired product than $Zn(OTf)_2$ alone (Table 2.2). Except in the case of boronic ester **12**, all other LLA catalytic systems formed by combining boronic esters **13** or **14** with $Sc(OTf)_3$ yielded similar conversion as $Sc(OTf)_3$ alone. Boronic esters with other Lewis acids such as $TiCl_4$, $SnCl_4$, $Al(OTf)_3$, $AlCl_2Me$, and $Cu(OTf)_2$, did not give any better conversion compared to the use of the Lewis acids alone (Table 2.3).

In the case of reaction between allyltributyltin and hydrocinnamaldehyde, there was a slight increase in conversions with boronic esters **27** and **28** in the presence of $Zn(OTf)_2$ compared to background reactions (Table 2.4). The boronic ester **28** also produced better product conversions when combined with $Sc(OTf)_3$ or $SnCl_4$. Boronic ester **12** yielded only a very small amount of product conversion when it formed an LLA system with $TiCl_4$ (Table 2.4). In these LLA systems (formation of complex from boronic esters **12** and **28** with $TiCl_4$), very low enantioselectivities were observed for the products. All the LLA systems obtained with $BF_3 \cdot Et_2O$ did not produce any better results than $BF_3 \cdot Et_2O$ alone in the reaction. Even though there are some higher product conversions with some LLA systems, no noticeable enantioselectivities were observed and the cause of higher product conversions is still subject to speculation at this time.

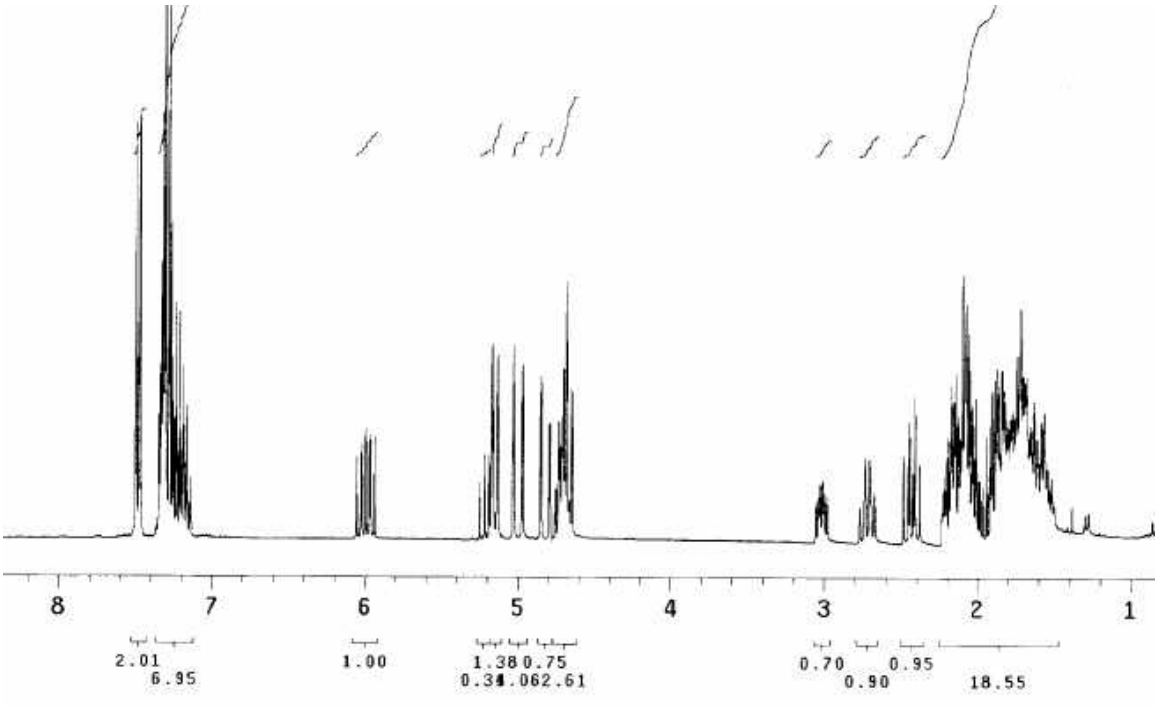
In the second part of the thesis, further applications of double allylation reagent **7** were examined. The largest oxabicyclic compound synthesized was the 8-membered **32a** with good yield (60%). The 9- and 10-membered precursors produced only bisallylation and monoallylation products. All attempts towards imine allylboration between reagent **7** and various kinds of imine derivatives failed to yield desired products. In preliminary studies toward the synthesis of pyrrolidine derivatives, it was observed that pyrrolidine derivative **44a** could be obtained in low yield (~15%), but further studies are needed in this direction. Syntheses of trisubstituted tetrahydrofurans **46**–**49** were successfully achieved in a new one-pot protocol with excellent diastereoselectivities (20:1).

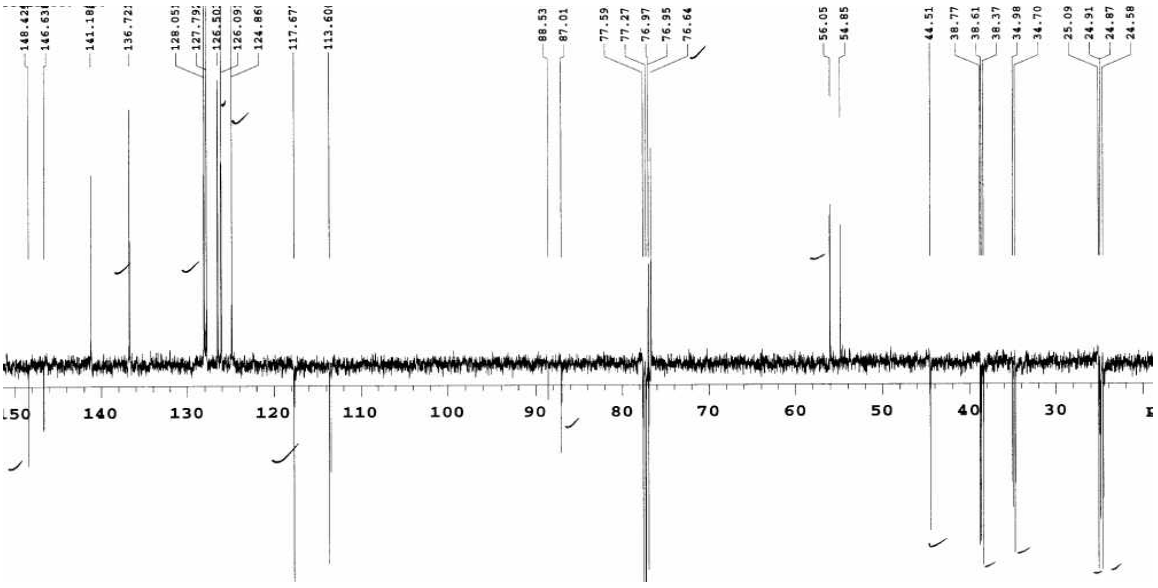
Appendix

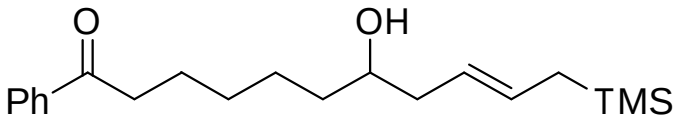
Copies of ^{1}H and ^{13}C NMR Spectra



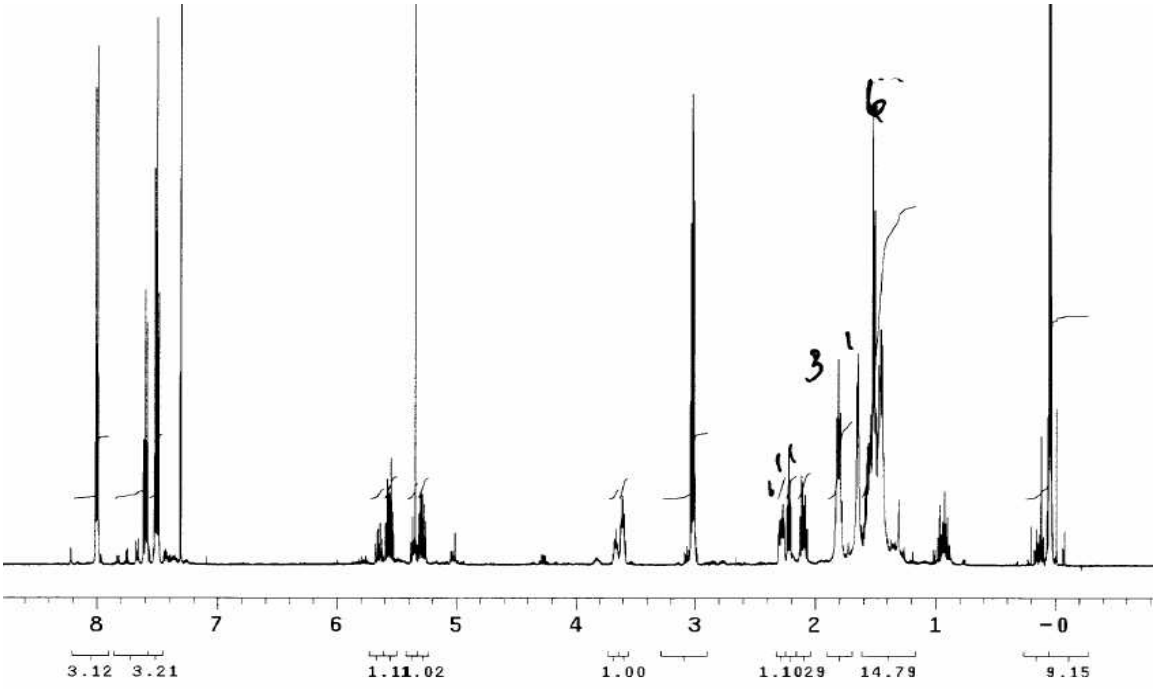
32a

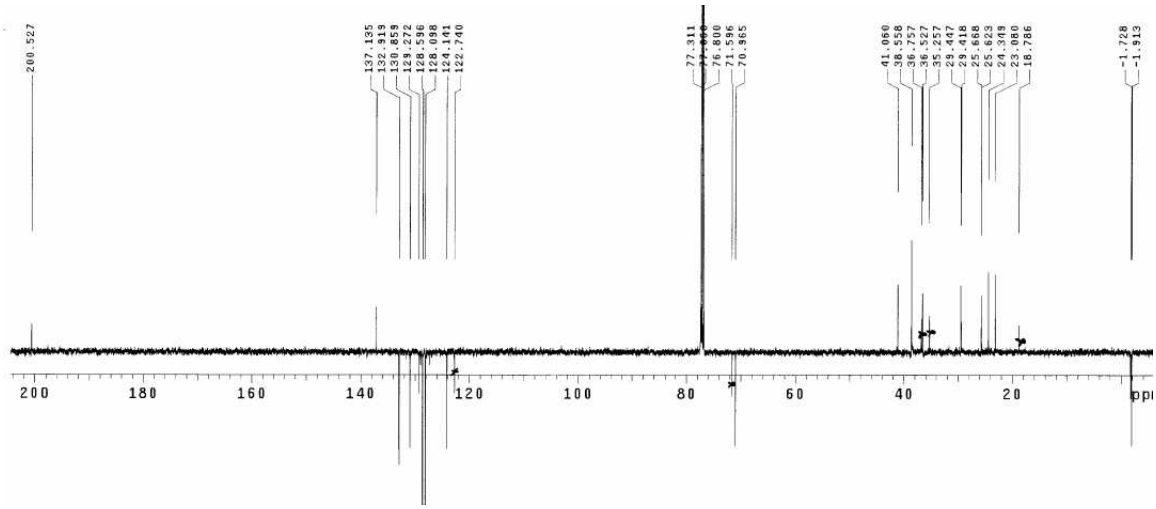





O
OH
Ph
TMS

33b


8
7
6
5
4
3
2
1
−0
3.12
3.21
1.11
1.02
1.00
1.1029
14.79
9.15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132.919
130.859
129.272
128.596
128.098
124.141
122.740
77.311
76.800
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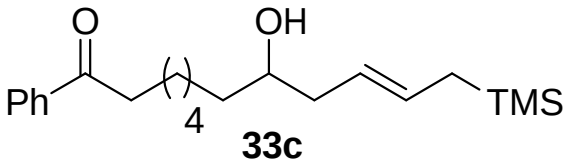
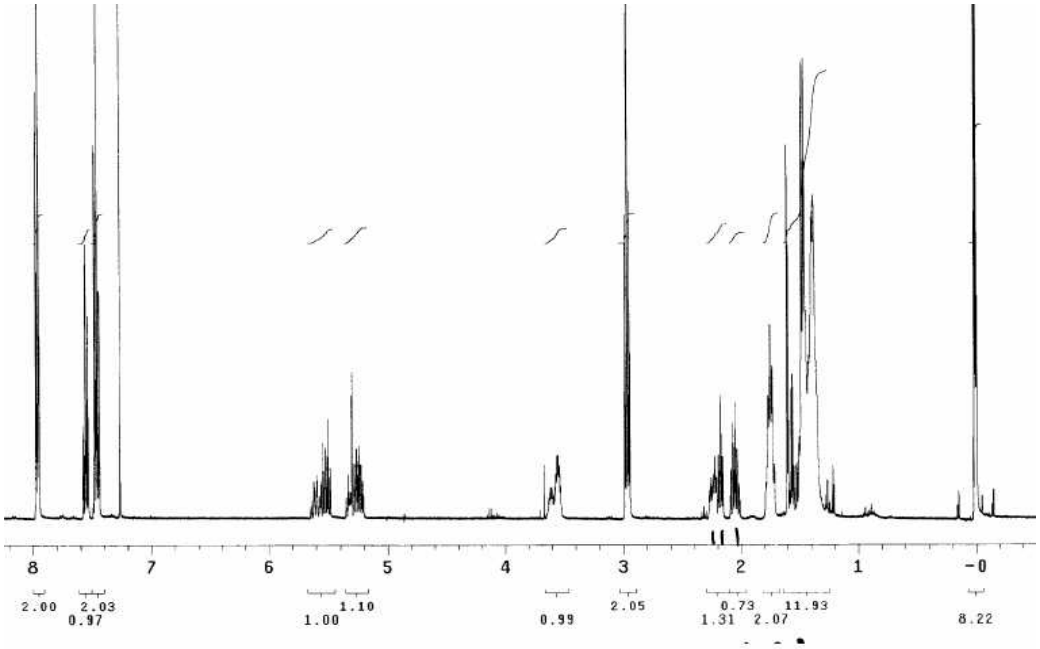
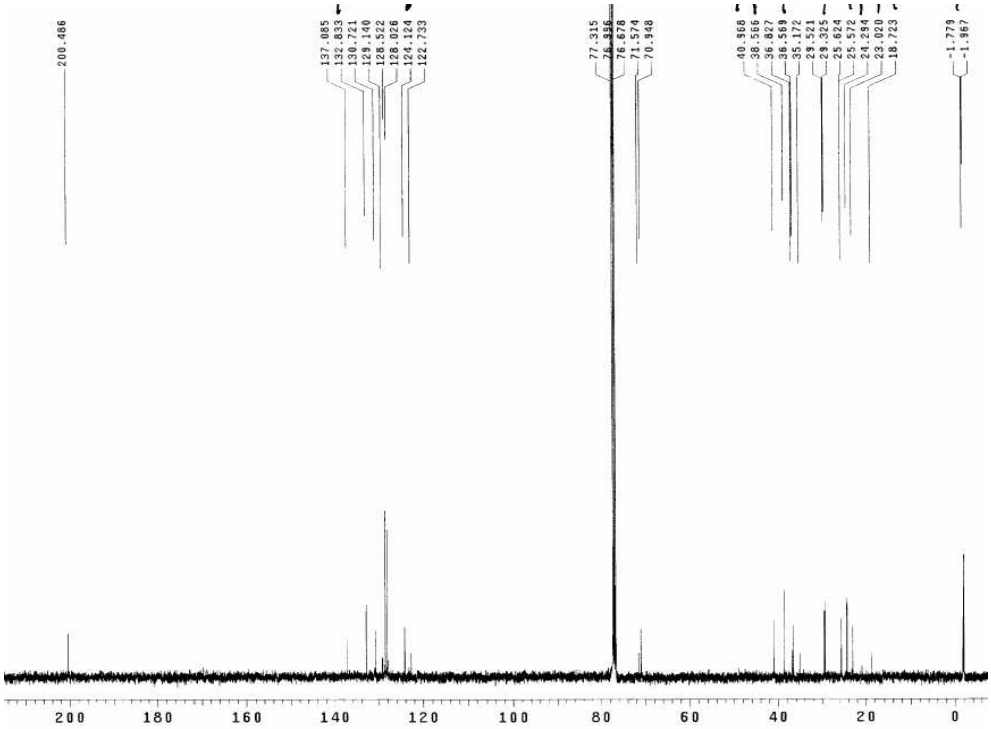
70.965
41.060
38.558
36.757
36.527
35.257
29.447
29.418
25.606
25.623
24.349
23.080
18.786
-1.728
-1.913
200
180
160
140
120
100
80
60
40
20


O
OH
Ph
4
TMS

33c


8
7
6
5
4
3
2
1
-0
2.00
2.03
0.97
1.00
1.10
0.99
2.05
0.73
11.93
1.31
2.07
8.22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129.140
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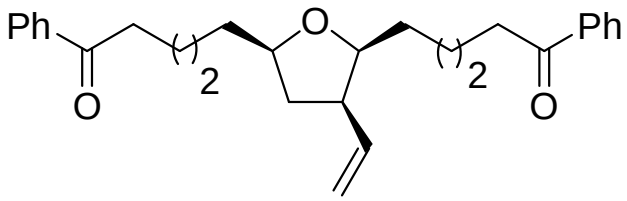
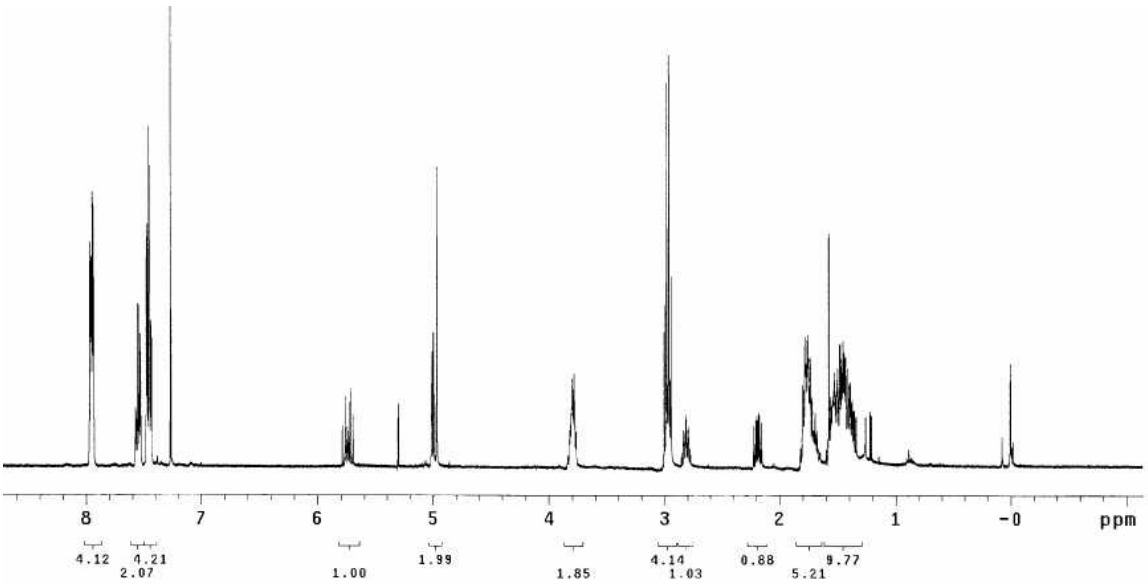
124.124
122.733
77.315
76.678
71.574
70.948
40.968
38.566
36.827
35.172
29.521
29.325
25.624
25.572
24.294
23.020
18.723
-1.779
-1.967
200
180
160
140
120
100
80
60
40
20
0


Ph
O
2
O
2
O
Ph

34a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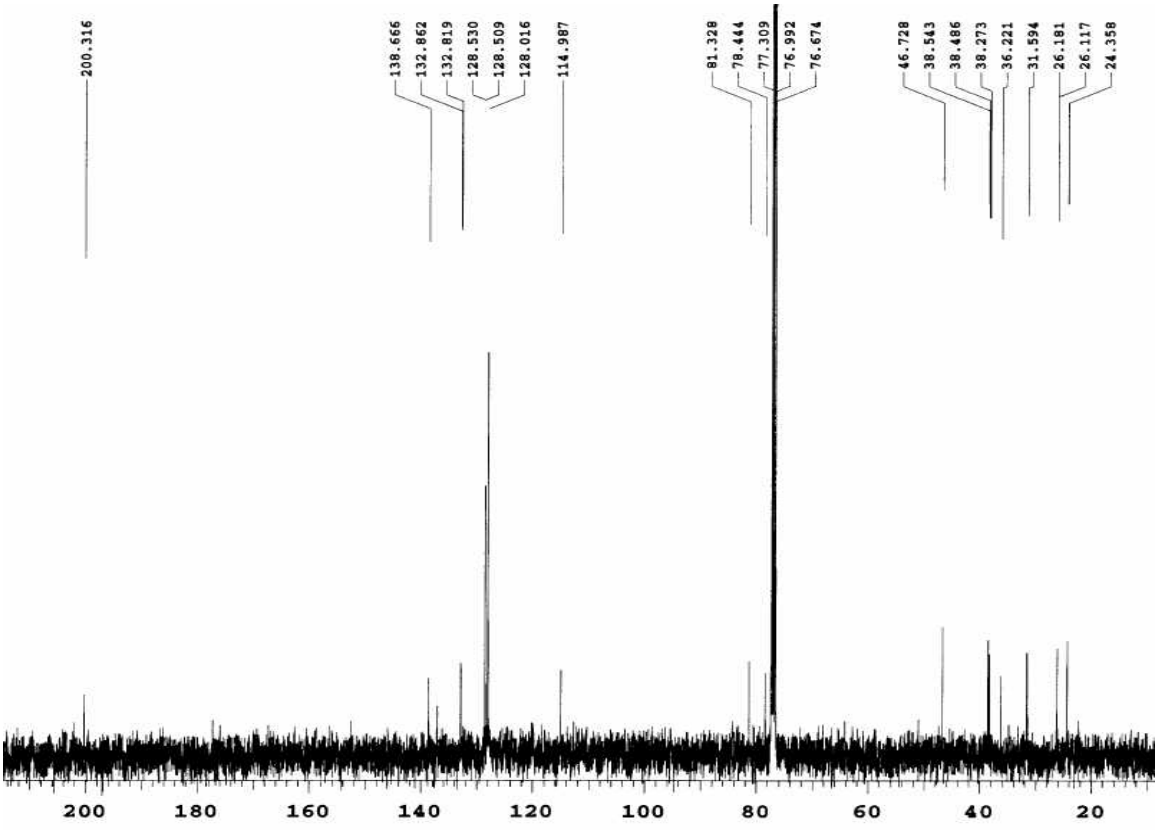
7
6
5
4
3
2
1
-0
ppm
4.12
4.21
2.07
1.00
1.99
1.85
4.14
1.03
0.88
9.77
5.21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128.016
114.987
81.328
78.444
77.309
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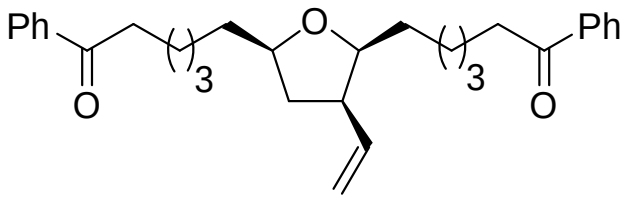
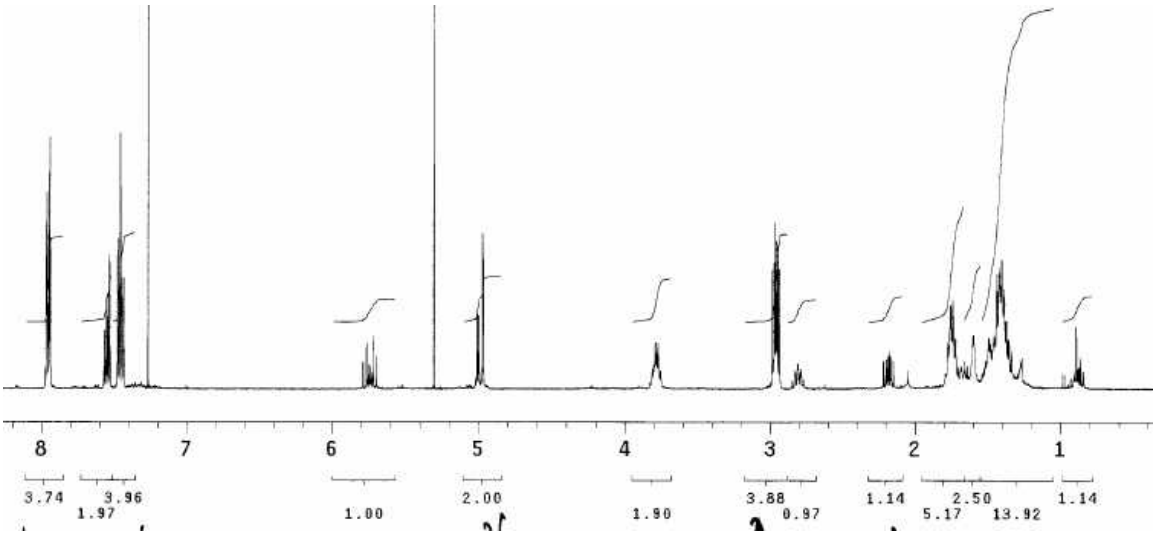
76.674
46.728
38.543
38.486
38.273
36.221
31.594
26.181
26.117
24.358
200
180
160
140
120
100
80
60
40
20


Ph
O
3
O
3
O
Ph

34b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7
6
5
4
3
2
1
3.74
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1.97
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2.00
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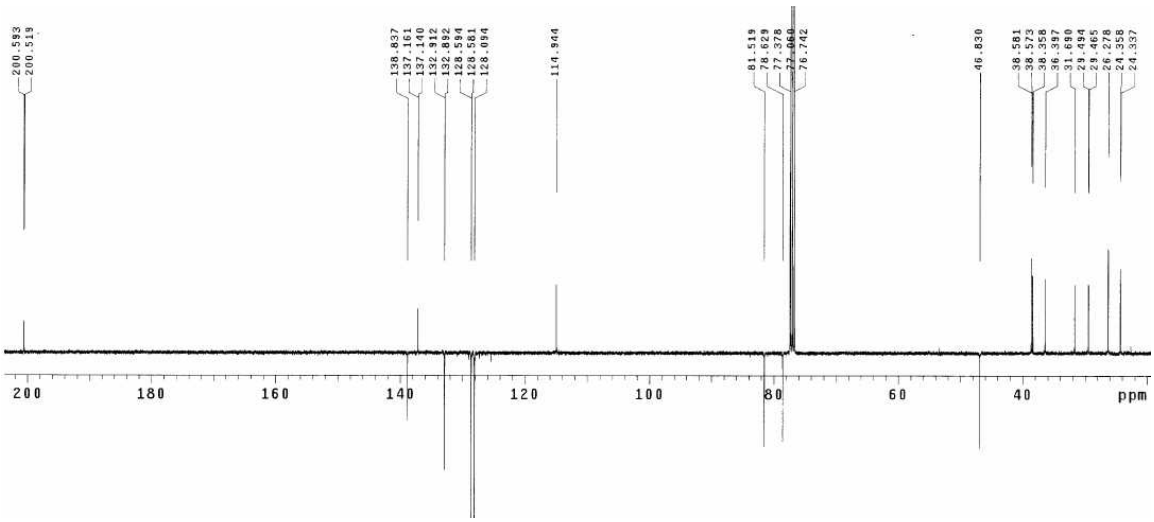
0.97
1.14
2.50
5.17
13.92
1.14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132.892
128.594
128.561
128.094
114.944
81.519
76.629
77.378
77.062
76.742
46.830
36.581
36.573
34.355
34.355
31.698
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26.278
21.358
24.337
200
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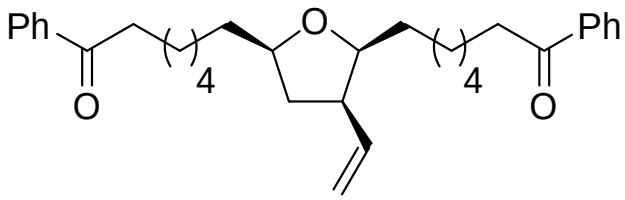
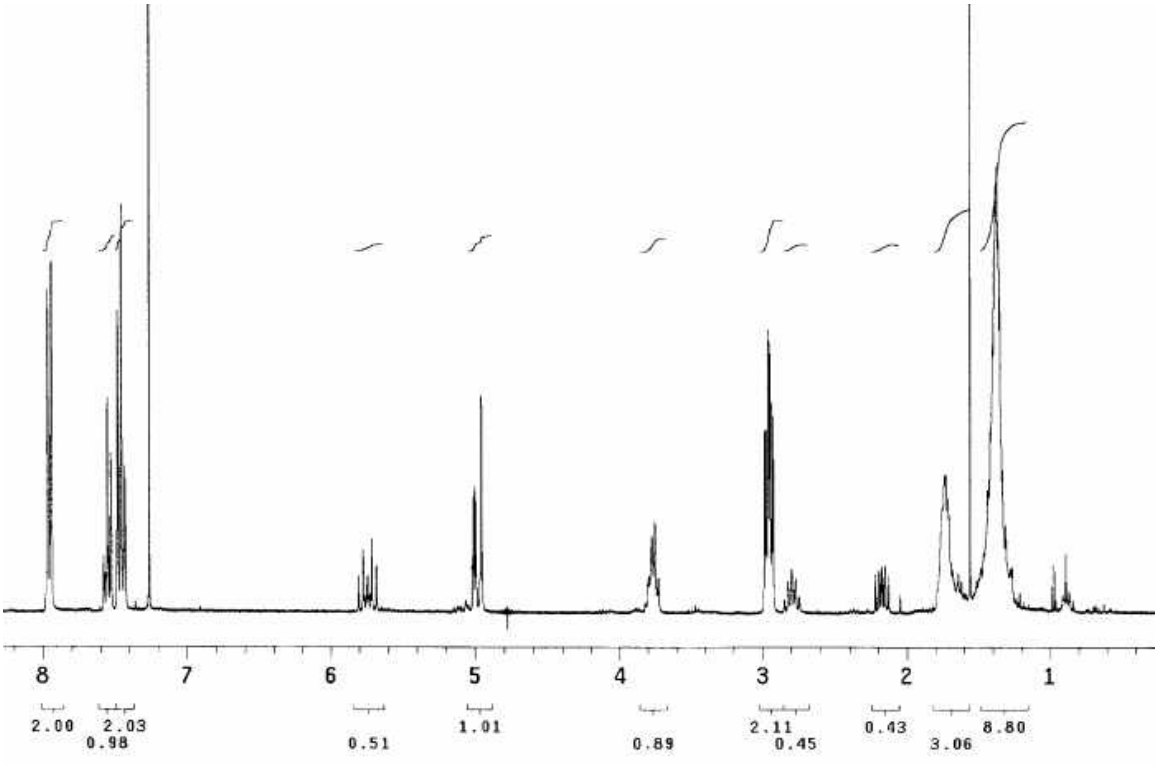
160
140
120
100
80
60
40
ppm


Ph
O
4
O
4
O
Ph

34c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7
6
5
4
3
2
1
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1.01
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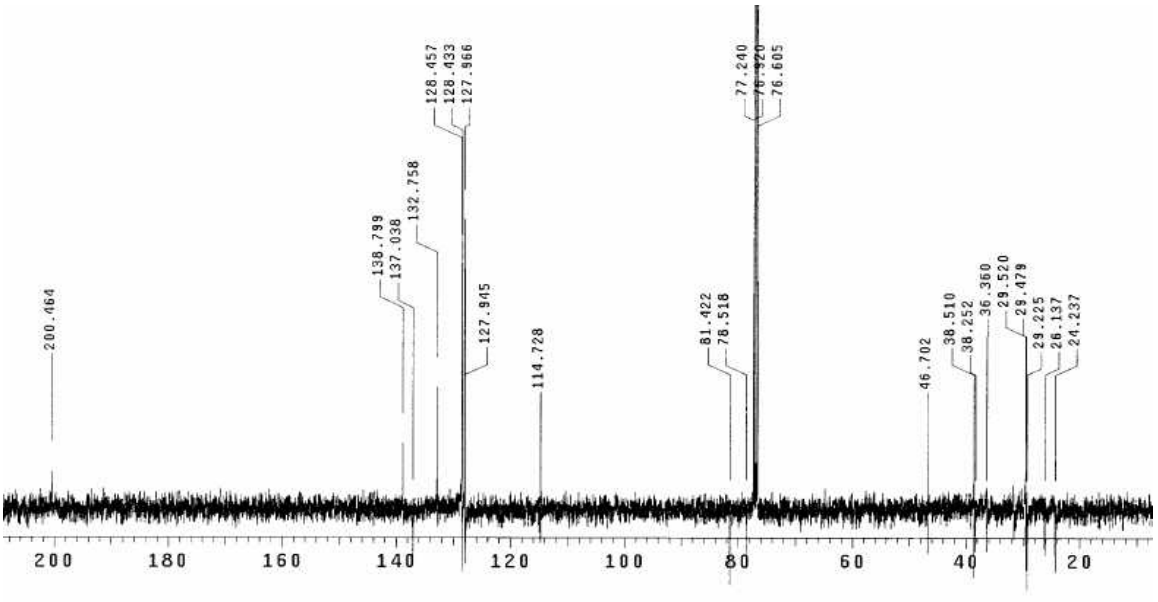
2.11
0.45
0.43
3.06
8.80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128.433
127.966
127.945
114.728
81.422
78.518
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76.605
46.702
38.510
38.252
36.360
29.520
29.479
29.225
26.137
24.237
200
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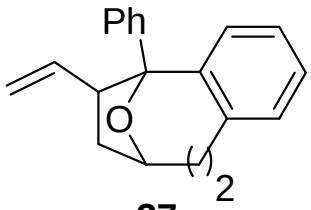
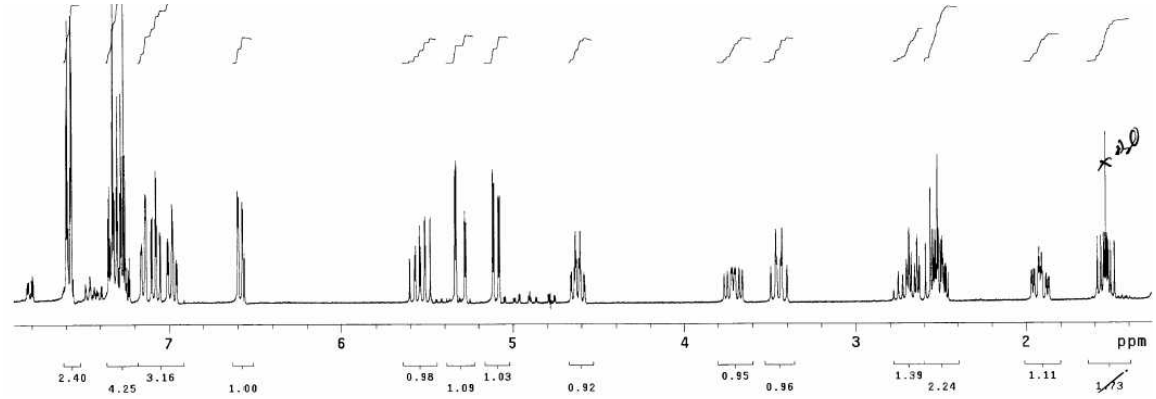
160
140
120
100
80
60
40
20


Ph
O
2

37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6
5
4
3
2
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0.95
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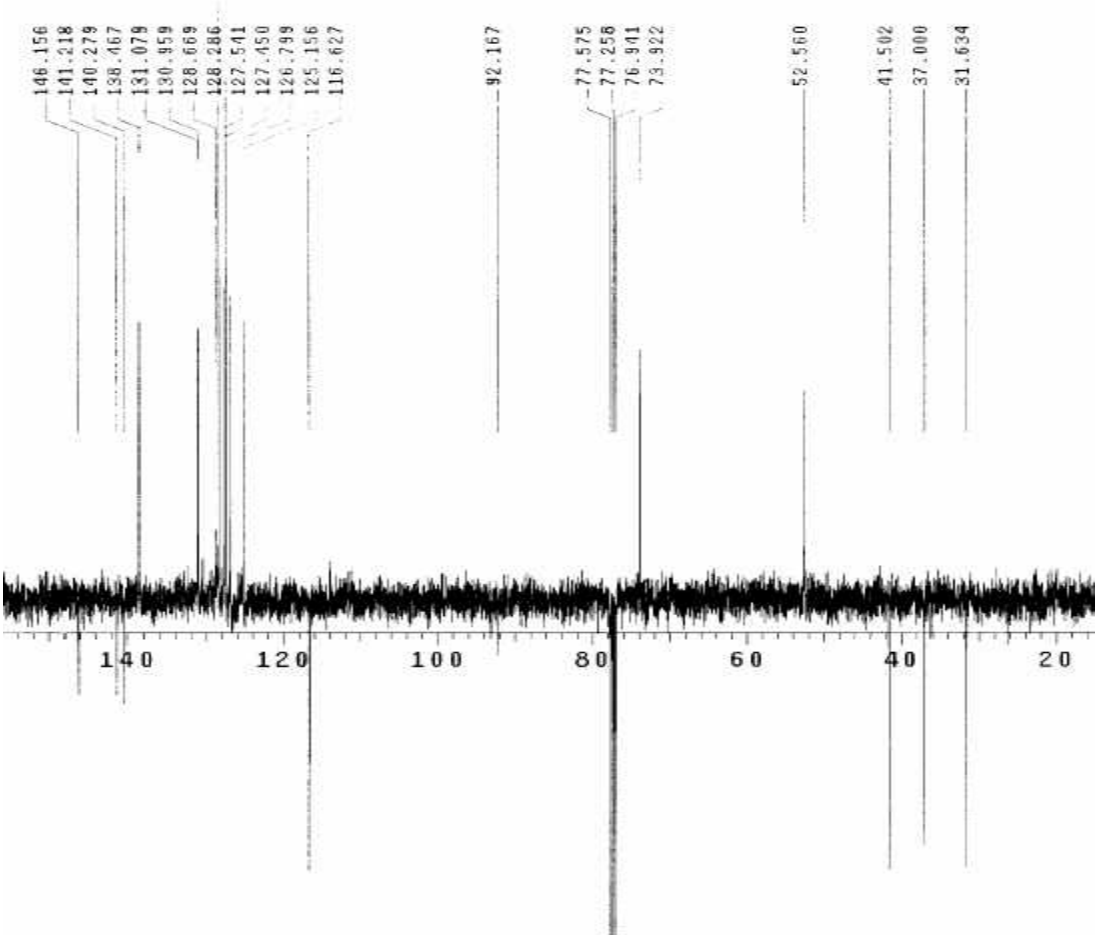
2.24
1.11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128.286
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127.450
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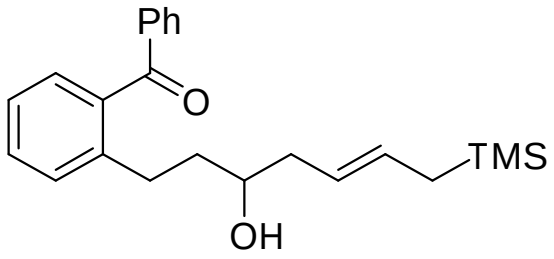
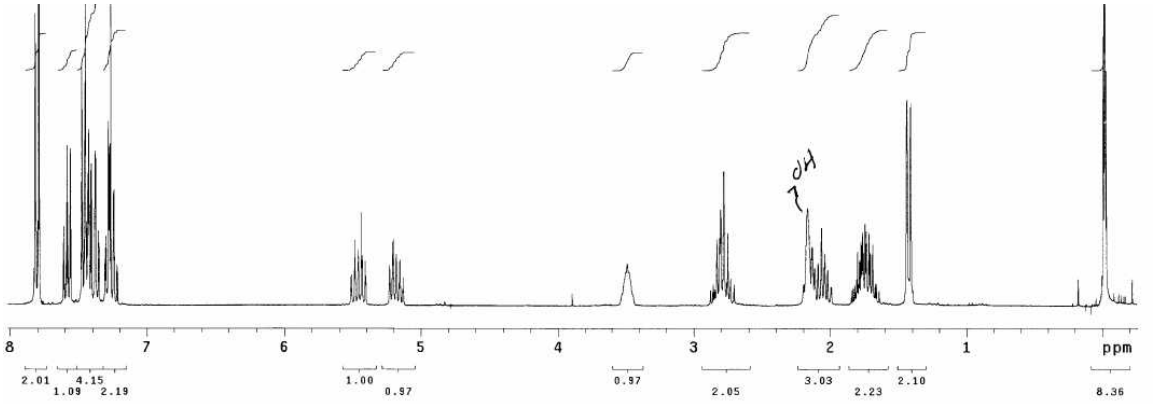
125.156
116.627
92.167
77.575
77.256
76.941
73.922
52.560
41.502
37.000
31.634
140
120
100
80
60
40
20


Ph
O
TMS
OH

38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7
6
5
4
3
2
1
ppm
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1.00
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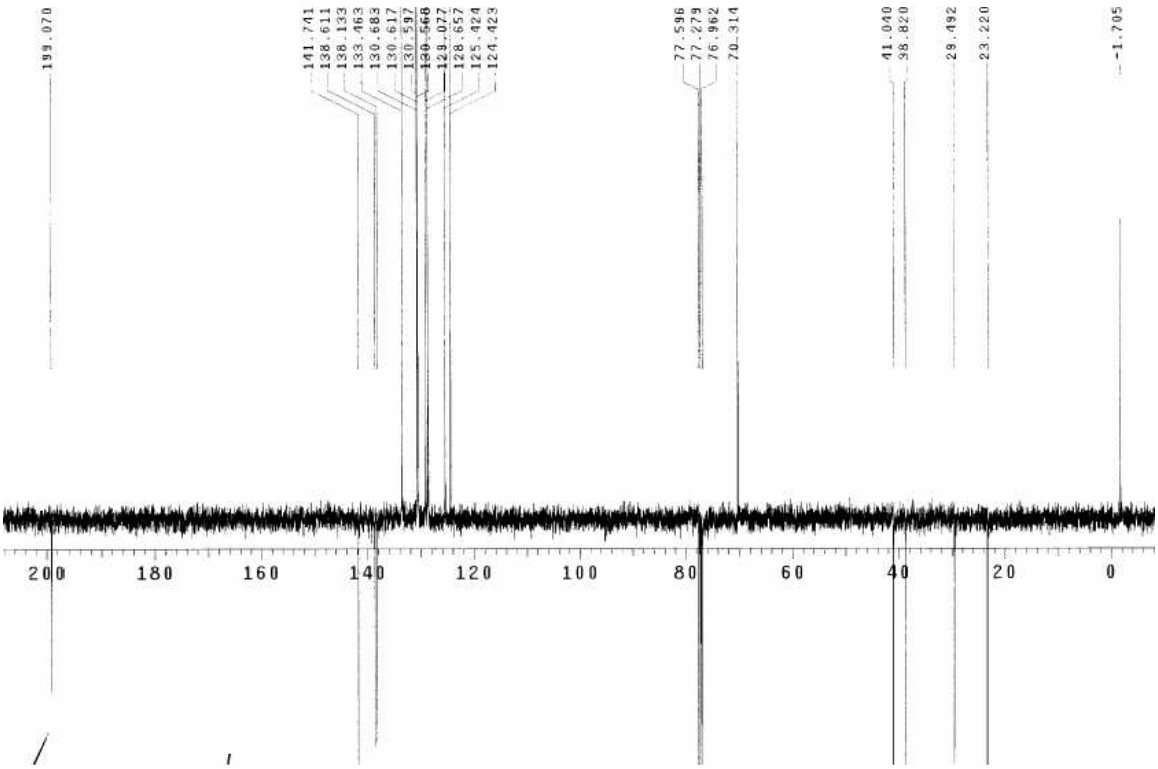
0.97
2.05
3.03
2.23
2.10
8.36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70.314
41.040
38.820
29.492
23.220
-1.705
200
180
160
140
120
100
80
60
40
20
0