Method development towards the synthesis of the alkaloid Alexine using 3-alkoxy, 3-acyloxy or 3-trialkylsilyl allyl organo indium, zinc, or boron reagents

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Declaration

I, Asma Ashour Said Alyamani, declare that this thesis, submitted in fulfillment of the requirements for the award of the Master of Philosophy, in the School of Chemistry and Molecular Bioscience, University of Wollongong, is entirely of my own work unless references or acknowledgements are provided. This document has not been submitted for qualifications at any other academic institutions.

Asma Alyamani
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List of abbreviations:

γ  gamma
NJ  nojirimycin
α  alpha
DNJ  1-Deoxynojirimycin
DMJ  1-Deoxymannojirimycin
α-HNJ  α-homonojirimycin
DMJ  α-homomannonojirimycin
DMDP  2,5-Dihydroxymethyl-3,4-dihydroxyprrolidine
β  beta
D-AB1  1,4-dideoxy-1,4-imino-D-arabinitol
D-RB1  1-Deoxy-D-ribosimine
nM  nanomolarity
μM  micromolarity
mg  milligram
g  gram
mmol  millimole
TS  Transition state
°C  celius
min  minute
h  hour
%  percentage
dr  diastereoselectivity
EtOH  ethanol
Et3N  triethylamine
d  day
rt  room temperature
DCM  dichloromethane
MeOH  methanol
PdCl2  palladium dichloride
In  indium
THF  tetrahydrofuran
Zn  zinc
H$_2$O water
aq aqueous
DMF dimethylformamide
t-BuOK potassium tert-butoxide
NBS N-bromosuccinimide
AIBN azobisisobutyronitrile
CCl$_4$ carbon tetrachloride
PTSA $p$-toluenesulfonic acid
Ni(cod)$_2$ bis(1,5-cyclooctadiene)nickel
EtOAc ethyl acetate
PS petroleum spirit
B$_2$(pin)$_2$ bis(pinacolato)diboron
equiv equivalent
TMS $\gamma$-trimethylsilyl
KOAc potassium acetate
TLC thin layer chromatography
s singlet
d doublet
dd doublet of doublet
ddd doublet of doublet of doublet
dt doublet of triplet
t triplet
ddt doublet of doublet of triplet
td triplet of doublet
[M]$^+$ molecular ion
$J$ coupling constant
CDCl$_3$ chloroform-d
Hz hertz
gCOSY gradient correlation spectroscopy
gHSQC gradient heteronuclear single quantum coherence
ESIMS electrospray ionization mass spectrometry
$m/z$ mass/charge ratio
DMSO dimethylsulfoxide
Pd(dba)$_2$  bis(dibenzylideneacetone)palladium (0)
PPh$_3$  triphenylphosphine
dppf  bis(diphenylphosphino)ferrocene
P(OPh)$_3$  triphenylphosphite
PCy$_3$  tricyclohexylphosphine
q  quaternary
K$_2$CO$_3$  potassium carbonate
PMB  para-methoxy benzyl
TfOH  trifluoromethanesulfonic acid
Sc(OTf)$_3$  trifluoromethanesulfonate
BF$_3$.Et$_2$O  boron trifluoride. etherate
B(OCH$_3$)$_3$  trimethyl borate
9-BBN  9-borabicyclo[3.3.1]nonane
NCS  N-chlorosuccinimide
NaI  sodium iodide
NIS  N-iodosuccinimide
[B(OH)$_2$]$_2$  diboronic acid
PTS  $p$-tolunene sulfonic acid
Abstract

This thesis reports on the development of synthetic methodology which could be used in further studies for synthesis of the alkaloid alexine. To achieve this the addition reactions of 3-alkoxy, 3-acyloxy or 3-trialkylsilyl allyl organo indium, zinc, or boron reagents to in situ formed or preformed imines were studied.

In Chapter 2, the efficiency of 3-acyloxyallyl indium or zinc reagents to produce the corresponding 1,2-amino alcohol products were explored using the imine formed between salicylaldehyde and benzylamine, either formed in situ or preformed. The combination of 3-methoxycarbonylallyl bromide and indium powder and the preformed imine gave the desired 1,2-\(N\)-benzylamino O-methyloxycarbonyl product 75 in only 12% yield but with good diastereoselectivity (dr = 95:5). The corresponding 3-benzoxyallyl bromide under similar conditions failed to produce any of the desired product. This study then focused on reactions of related allyl boronates which were reported in Chapter 3.

In Chapter 3, an attempt to synthesize pinacol 3-\(O\)-benzylallylboronate 67 through a cross-coupling borylation of the allyl dibenzylacetel 77 with \(\text{B}_2(\text{pin})_2\) failed. However, the \(\text{Pd}\)-catalyzed borylation of 3-benzoxyallyl bromide 66b successfully gave the pinacol 3-\(O\)-benzoylallyl boronate 68. The use of boronate 68 as an allylating agent was limited due to its limited shelf stability, therefore the use of freshly prepared samples was essential for achieving reasonable chemical yields in its subsequent reactions. The reaction of pinacol 3-\(O\)-benzoylallyl boronate 68 with imines 73, 83, 84 and 85 prepared from salicylaldehyde and primary amines afforded the corresponding 1,2-amino alcohol products 78, 86, 87 and 88 in moderate yields (31-69%) but with high diastereoselectivities (dr = 91:9 to 95:5) for the syn-isomer. A chair-like transition state, involving H-bonding between the \(ortho\)-hydroxy group on the imine to the pinacol ester oxygen, was proposed to explain the stereochemical outcomes of these reactions. The reaction of pinacol 3-\(O\)-benzoylallyl boronate 68 with imine 89 derived from \(O\)-methyl salicylaldehyde and benzylamine produced the amine alcohol product 90 with very low diastereoselectivity (dr = 58:42) showing the importance of the presence of the \(ortho\)-hydroxy group on the imine in controlling the diastereoselectivity.

In Chapter 4, an attempt to synthesize the \(\gamma\)-TMS allylboronate 70 through a \(\text{Pd}\)-catalyzed borylation reaction of the 3-iodovinylsilane 69 with \(\text{B}_2(\text{pin})_2\) could not be attempted, due to the unsuccessful synthesis of the starting vinyl silane 69 through iodination of the 3-TMS-allyl alcohol. However, the \(\text{Pd}\)-catalyzed borylation of 3-TMS-allyl alcohol with
B$_2$(pin)$_2$ successfully gave the pinacol $\gamma$-TMS allylboronate 70. The use of the boronate 70 as an allylating agent was limited due to its limited shelf stability, therefore the use of freshly prepared samples was essential for achieving reasonable chemical yields in its subsequent reactions. The reaction of pinacol pinacol $\gamma$-TMS allylboronate 70 with imines 73, 83, 84 and 89 prepared from either salicylaldehyde or O-methyl salicylaldehyde and primary amines afforded the corresponding 3,4-amino silyl products 99, 103, 104 and 105 in moderate yields (27-43%) but with high diastereoselectivities (dr = 90:10 to 94:6) for the syn-isomer. A chair like transition state, involving H-bonding between the ortho-hydroxy group on the imine to the pinacol ester oxygen, was proposed to explain the stereochemical outcomes of these reactions. The reaction of $\gamma$-TMS allylboronate 70 with the imine formed between benzaldehyde and benzylamine formed in situ produced the amine silyl product 102 with modest diastereoselectivity (dr = 83:17). The reaction of $\gamma$-TMS allylboronate 70 with the imine formed between aliphatic aldehydes (glyoxylate and paraformaldehyde) and benzylamine formed in situ produced the amine silyl product 110 and 111 in low yields (13% and 4%, respectively).
Chapter 1: Introduction

1.1. Outline of the thesis:
The aims of the MSc thesis were to develop synthetic methodology using γ-substituted allyl organoboron, zinc or indium reagents, that could be used in the future to prepare polyhydroxylated pyrrolizidine alkaloids. Accordingly, this Introduction will first describe the polyhydroxylated alkaloids and then organoboron, zinc and indium chemistry that is relevant to this project.

1.2. Definition and structural classification of polyhydroxylated alkaloids:
Polyhydroxylated alkaloids are considered as structural mimics of monosaccharides, in which the ring oxygen of the monosaccharides has been replaced by a nitrogen atom. These alkaloids are also known as iminosugars, azasugars, aminosugars or sugar-shaped alkaloids. These alkaloids are widely distributed in plants and microorganisms. However, they were not detected for a relatively long time due to the fact that these alkaloids cannot be detected by commonly used reagents for detecting alkaloids such as Dragendorff’s and iodoplatinate reagents. Polyhydroxylated alkaloids have been the interest of several research studies because of their possible medical applications. Many are potent glycosidase inhibitors with the potential use as antidiabetic, antiviral and anticancer drugs. Chemically, they are classified into five classes: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes.

1.2.1. Polyhydroxylated Piperidines:
The polyhydroxylated piperidine alkaloid nojirimycin (NJ) 1 was the first natural polyhydroxylated alkaloid to be isolated by Inouye in 1966 (Figure 1.1) from Streptomyces bacteria. NJ (5-amino-5-deoxy-D-glucopyranose) is a glucose mimic with the pyranose configuration in which the ring oxygen of the sugar is replaced by a nitrogen atom. NJ was originally known as glucosimine and was first isolated from Streptomyces roseochromogenes R-468. Following its structural characterization and its isolation from S. nojirimycin, glucosamine was given its currently used name ‘nojirimycin’. In addition to its antimicrobial activity, NJ was found to be a potent α- and β-glycosidase inhibitor. Its natural analogues, nojirimycin B 2 (5-amino-5-deoxy-D-mannopyranose), from S.
lavandulae SF 425, and galactostatin 3 (5-amino-5-deoxy-D-galactopyranose), from S. lydicus PA-5726, were found to be potent inhibitors of α-mannosidase and β-galacosidase, respectively (Figure 1.1).\textsuperscript{5,6}

\[ \text{Figure 1.1. Nojirimycin 1 and its natural analogues 2 and 3} \]

Fagomine 4 (2-hydroxymethyl-3,4-dihydroxypiperidine) is another nojirimycin analogue (1,2-dideoxynojirimycin) (Figure 1.2). It was isolated from Japanese buckwheat seeds (\textit{Fagopyrum esculentum}, Polygonaceae).\textsuperscript{7} 1-Deoxynojirimycin (DNJ) (5, Figure 1.2) is structurally identical to NJ except it lacked the hydroxy group at the anomeric (aminal) carbon. It was prepared from either L-sorbofuranose or by the catalytic hydrogenation of nojirimycin.\textsuperscript{4,8} Later compound 5 was discovered as a natural product and was named as moranoline, which was isolated from Mulberry trees. Moranoline was also obtained from many strains of \textit{Bacillus} and \textit{Streptomyces} bacteria.\textsuperscript{9} Another nojirimycin derivative was found in the legumes \textit{Lonchocarpus sericeus} and \textit{L. costaricensis} named as 1-deoxymannojirimycin DMJ 6. DMJ is an epimer of DNJ with a different configuration of its hydroxy group at C-2 (Figure 1.2).\textsuperscript{10} Other nojirimycin analogues were found having a hydroxymethyl group, instead of a hydroxy group, at the anomeric carbon such as α-homonojirimycin (α-HNJ) 7 (Figure 1.2) which was isolated from \textit{Omphalea diandra} (Euphorbiaceae).\textsuperscript{11} Another derivative was found in \textit{Aglaonema treubii} (Araceae) known as α-homomannonojirimycin (HMJ) in which the anomeric hydroxy group of nojirimycin is replaced by a hydroxymethyl group. Both α- and β-anomers, (α-HMJ) 8 and (β-HMJ) 9, respectively, are known (Figure 1.2).\textsuperscript{12}
1.2.2. Polyhydroxylated pyrrolidines:

2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) 10 was the first isolated natural pyrrolidine alkaloid and was isolated in 1976. It was first isolated from the leaves of the legume *Derris elliptica* (Figure 1.3).\(^3\) DMDP was firstly described as a β-D-fructofuranose mimic in which the ring oxygen of the sugar was replaced by a nitrogen atom. However, other studies demonstrated that DMDP probably should be considered as a β-D-arabinosimine mimic in its furanose form.\(^2,4\) The 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1) 11 is a derivative of DMDP lacking one hydroxymethyl group. D-AB1 was isolated from the legume *Angylocalyx boutiqueanus* and the fern *Arachniodes standishii*.\(^14\) 1-Deoxy-D-ribosimine (D-RB1) 12 is a C-2 epimer of D-AB1, and was isolated from *Morus alba* (Figure 1.3).\(^15\)

![Figure 1.3. DMDP 10 and its analogues 11-12](image)

The broussonetine alkaloids were isolated between 1996 and 2003 from the branch extracts of *Broussonetia kazinoki* (Moraceae), a tree distributed commonly in China and Japan where it is used in folk medicine.\(^16\) To date 30 different alkaloids have been isolated. In general, they structurally feature a polyhydroxylated 2-hydroxymethyl...
pyrrolidine ring substituted at C-5 with a 13-carbon side chain. This side chain can be either linear, as in the case of broussonetine F 16, or include a ring structure, as found in broussonetines G 17, J1 19, J2 20, W 23 and Z 24 (Figure 1.4).17,18 Most of these alkaloids have the 2R,3R,4R,5R configuration around the pyrrolidine ring periphery. Some compounds have the 3S configuration, while others have undefined stereogenic centres in the side chains (for example, broussonetic Z 24).19 Many of these alkaloids are potent glycosidase inhibitors and have potential for further development as anti-cancer, anti-viral, anti-diabetes and anti-obesity drugs.17 Most of these alkaloids have shown potent inhibitory activities against β-galactosidase. For example, broussonetines E 15, F 16 and G 17 are potent nano molar inhibitors (IC\textsubscript{50} 2-4 nM) of β-galactosidase,17,20 while broussonetine C 13 and D 14 are potent β-mannosidase inhibitors with IC\textsubscript{50} values of 0.32 and 0.34 μM, respectively.17 Other broussonetines G 17, H 18, K 21 and L 22 are relatively efficient inhibitors of β-glucosidase.20

1.2.3. Polyhydroxylated indolizidines:

The indolizidine structure consists of one five-membered nitrogen containing ring (pyrrolidine) fused with one six-membered ring. Indolizidine alkaloids (Figure 1.5) are structurally different to sugars, except in their hydroxy substituents and their configurations. Swainsonine 25 was the first indolizidine alkaloid isolated from the Australian legume \textit{Swainsona canescens}.21 Swainsonine showed potent activity as an anticancer agent and as an α-D-mannosidase inhibitor.22 Following swainsonine, another polyhydroxylated indolizidine alkaloid was isolated in 1981 from the Australian legume \textit{Castanospermum australe}.23 This alkaloid is known as castanospermine 26, which is a potent inhibitor of both α- and β-glucosidases, and has shown a relatively potent inhibitory effect against dengue virus infection.24 The discovery of both 25 and 26 was due to toxicity effects on Australian livestock following the consumption of the legumes, \textit{S. canescens} and \textit{C. australe}, respectively. These animals suffered from neurologic disorders similar to the lysosomal storage disease’s symptoms. The lysosomal storage disease or mannosidosis is a syndrome characterized by accumulation of high levels of mannose-rich oligosaccharides in cells, which is due to a deficiency of catabolising lysosomal enzymes, such as mannosidase.25
Castanospermine was considered as bicyclic derivative of DNJ, with the presence of an ethylene bridge between the hydroxymethyl group and the ring nitrogen. Furthermore, castanospermine has a similar configuration of its hydroxy substituents as DNJ. In addition to castanospermine, *C. australe* contained the 6-epimer of castanospermine, 27
(a human α-mannosidase inhibitor), and its 7-deoxy derivative 28 along with 6,7-diepi-castanospermine 29. Both 28 and 29 were found to be relatively weak inhibitors of fungal amyloglucosidase. Other deoxy derivatives of swainsonine were isolated from the leaves of *Astragalus lentiginosus*, including, lentiginosine 30 and 2-epi-lentiginosine 31. More recently, another polyhydroxylated indolizidine alkaloid was isolated from the leaves of *Stevia rebaudiana* (Asteraceae) and leaves and bulbs of *Veltheimia capensis* (Hyacintaceae) known as steviamine 32. Steviamine 32 is the first polyhydroxylated alkaloid with a methyl group attached to the piperidine moiety at position C-5.

![Chemical structures](image)

**Figure 1.5.** Polyhydroxylated indolizidine alkaloids 25-32

1.2.4. Polyhydroxylated pyrrolizidines:
Polyhydroxylated pyrrolizidines (Figure 1.6) are characterized by a carbon substituent at C-3. Alexine 33 was the first isolated polyhydroxylated pyrrolizidine from plants. It was isolated from the legume *Alexa leiopetala*. Following alexine, another alexine analogue, known as australine 34, was isolated from the seeds of *C. australe*. Australine was regarded as the 7a-epimer of alexine, as a ring-contracted form of castanospermine or a DMDP analogue with the presence of an ethylene bridge between the hydroxymethyl group and the ring nitrogen. *C. australe* was found to be a rich source of other alexine derivatives such as 1,7a-di-epi-alexine 35 and 3,7a-di-epi-alexine 36. Casuarine 37 is also a pyrrolizidine found in the bark of *Casuarina equisetifolia* (Casuarinaceae) which is regarded as the 6-hydroxy derivative of australine. Uniflorine A 38, a pyrrolizidine imminosugar, was isolated from *Eugenia uniflora* leaves (Myrtaceae). Uniflorine A 38 is regarded as the 6-epimer of casuarine, and has shown its potency as a potential
antidiabetic agent due to its inhibitory effect against the α-glucosidases, maltase and sucrase.\textsuperscript{34}

![Chemical structures of polyhydroxylated pyrrolizidine alkaloids](image)

**Figure 1.6.** Polyhydroxylated pyrrolizidine alkaloids 33-38

1.2.5. Polyhydroxylated nortropanes:
Calystegines are the most well-known nortropane alkaloids of plant origin (Figure 1.7). These alkaloids are similar to tropane alkaloids except that they lack the methyl substituent on the ring nitrogen and have a bridgehead hydroxy group at the link between the two fused rings. Calystegines were first isolated from the roots of *Calystegia sepium* (Convolvulaceae) by a research group looking for the identification of plant components affecting rhizosphere organisms. By using the paper electrophoresis technique, these alkaloids have been classified into four classes: calystegines A, B, C and N. Calystegines A, B and C have three, four and five hydroxy substituents, respectively.\textsuperscript{35} Calystegine A was separated by HPLC into four molecules: A\textsubscript{1} (18%), A\textsubscript{2} (10%), A\textsubscript{3} (60%) and A\textsubscript{4} (12%). The major molecule A\textsubscript{3} 39 was described as 1α,2β,3α-trihydroxynortropane. Calystegine B was separated by HPLC into two molecules: B\textsubscript{1} 42 as 1α,2β,3α,6α-tetrahydroxynortropane and B\textsubscript{2} 43 as 1α,2β,3α,4β-tetrahydroxynortropane.\textsuperscript{36} After these, other calystegines were found in *M. bombycis* and *M. alba* (Moraceae) such as calystegine C\textsubscript{1} 45 which was described as 1α,2β,3α,4β,6α-pentahydroxynortropane.\textsuperscript{15} Subsequently, in addition to calystegines A\textsubscript{3}, B\textsubscript{1} and B\textsubscript{2}, the roots of *Physalis alkekengi* (Solanaceae) were found to contain the calystegines A\textsubscript{5} 40 and B\textsubscript{3} 44.\textsuperscript{37} Some genera of tropane rich plants were found to be a relatively good source of calystegine alkaloids such as
Hyoscyamus niger (Solanaceae) which contains the calstegines A₅, A₆ 41, B₁, B₂, B₃ and N₁ 46 (1α-amino-2β,3α,4β-trihydroxynortropane).  

![Polyhydroxylated nortropane alkaloids examples](image)

**Figure 1.7.** Polyhydroxylated nortropane alkaloids examples include, calystegines A₃ 39, A₅ 40, A₆ 41, B₁ 42, B₂ 43, B₃ 44, C₁ 45 and N₁ 46

In summary, the polyhydroxylated alkaloids have been classified into five structural classes with the pyrrolidine alkaloids showing the largest structural diversity. The role of these compounds as glycosidase inhibitors follows in the next section.

**1.3. Polyhydroxylated alkaloids as glycosidase inhibitors:**

**1.3.1. Mechanism of glycosidase inhibition:**

Glycosidases are a class of enzymes that are biochemically important and widely found in Nature. These enzymes work through enhancing the cleavage of glycosidic bonds in carbohydrates and glycoconjugates to produce relatively low molecular weight monosaccharides and oligosaccharides. According to the concept that inhibition of such enzymes may be useful in the treatment of diabetes, viral infections and cancers, polyhydroxylated alkaloids have been studied widely. Polyhydroxylated alkaloids structurally mimic monosaccharides, in which the ring oxygen of the monosaccharides has been replaced by a nitrogen atom. Therefore, iminosugars inhibit glycosidases by mimicking the natural substrates in their pyranose or furanose configuration. Iminosugars are considered as reversible and competitive transition state mimic inhibitors. Iminosugars are protonated at physiological pH and bind to the active site of the glycosidase. This binding involves formation of an ion pair between the protonated inhibitor and the carboxylate group at the active site of the enzyme. The protonated
inhibitor mimics the natural substrate transition state, which accounts for the affinity of the glycosidases to the inhibitor.\textsuperscript{39,40} In 2002, Wrodnigg \textit{et al.} described the mechanism of inhibiting glycosidases by DMDP.\textsuperscript{41} DMDP 10 inhibits glycosidases by mimicking the charge and the conformation of the furanosyl moiety of the natural substrate (10 mimics the oxonium ion intermediate formed at the active site of the enzyme) (Figure 1.8).\textsuperscript{41} The inhibitory activity of these alkaloids depends on several factors including the number, position and configuration of their hydroxy substituents. For example, inhibition of Golgi \(\alpha\)-mannosidases I and II is extremely dependent on the configuration of the iminosugars. It was observed that the enzyme I was preferentially inhibited by iminosugars with the pyranose configuration such as DNJ 5, while enzyme II was inhibited by iminosugars in the furanose configuration such as swainsonine 25.\textsuperscript{42} In addition to the previous factors affecting the inhibitory effect of polyhydroxylated alkaloids, pH also plays a critical role in their effects, where decreasing the pH from basic to pH 7 enhances the inhibitory effect of these alkaloids toward the glycosidases, indicating that the protonated nitrogen is essential for the activity of the polyhydroxylated alkaloids.\textsuperscript{43}

![Figure 1.8.](image)

**Figure 1.8.** (a) Transition state (TS) structure for cleavage of a glycoside bond by a glycosidase (b) glycosidase inhibitor (DMDP) 10 mimicking the oxonium ion TS

1.3.2. Therapeutic applications:

1.3.2.1. Anti-diabetic agents:

Several glycosidases such as \(\alpha\)-glucosidases and \(\alpha\)-amylases are responsible for the degradation of dietary sugars to simple monosaccharides which can be absorbed through the intestinal wall into the blood stream. During the 1970s it was observed that inhibition of these enzymes contributes in regulating the monosaccharide uptake into the blood and therefore the use of these inhibitors can be very effective medically in the treatment of
the non-insulin-dependent type diabetes.\textsuperscript{44} Acarbose \textbf{47} (Figure 1.9) was the first $\alpha$-glucosidase inhibitor (IC\textsubscript{50} value of 0.5 $\mu$M) approved clinically as an antidiabetic for treating non-insulin-dependent type diabetes in 1990. Acarbose was isolated from \textit{Actinoplanas utahensis}.\textsuperscript{45} Following acarbose, in 1994, voglibose \textbf{48} (Figure 1.9) was approved as a potent oral anti-diabetic agent, especially against the intestinal $\alpha$-glucosidases. Voglibose was synthesized from valiolamine \textbf{49} which was isolated from validamycin producing \textit{Streptomyces} species. Valiolamine displayed its potent activity as an inhibitor of both pig intestinal maltase and sucrase with IC\textsubscript{50} values of 2.2 and 0.049 $\mu$M, respectively. However, voglibose has a higher inhibitory potency than the parent with IC\textsubscript{50} values of 0.015 and 0.0046 $\mu$M for maltase and sucrase, respectively.\textsuperscript{46} Later, miglitol \textbf{50} (Figure 1.9) which is an $N$-hydroxyethyl derivative of DNJ, was introduced as an effective therapeutic for diabetes.\textsuperscript{47}

\textbf{Figure 1.9.} Anti-diabetic iminosugars 47-50

\subsubsection*{1.3.2.2. Anti-viral agents:}
Several iminosugars have displayed variable activities as antivirals. Both castanospermine \textbf{26} and DNJ \textbf{5} have shown their anti-viral potency against HIV, where castanospermine \textbf{26} acts as a glucosidase I inhibitor and DNJ \textbf{5} acts as a glucosidase I and II inhibitor. HIV infection mainly depends on the interaction between the highly glycosylated glycoproteins in the viral coat and the CD4 receptors on the surface of T-lymphocyte cells. Castanospermine and DNJ exert their effect through alteration of the
glycosylation pattern of the viral glycoproteins so that these proteins will no longer be able to bind at the CD4 receptors.\textsuperscript{48,49} Alexine 33 and its derivative australine 34 have also shown their relatively limited antiviral activity (IC\textsubscript{50} = 0.1-10 mM)\textsuperscript{50} compared with castanospermine 26 (IC\textsubscript{50} = 0.02 mM).\textsuperscript{51} 7,7a-Diepalexine, another alexine derivative isolated from \textit{C. australis}, displayed its moderate antiviral activity through inhibition of the pig kidney \(\alpha\)-glucosidase I with an IC\textsubscript{50} value of 0.38 mM\textsuperscript{51}. Other iminosugars which act as \(\alpha\)-mannosidase inhibitors, such as DMJ 6 and swainsonine 25, were found to be inactive toward HIV.\textsuperscript{52,53} Later, \textit{N}-butyl-DNJ and the 6-\(O\)-butanoyl derivative of castanospermine were synthesized and were shown to have a higher inhibitory potency than their parent compounds.\textsuperscript{49,54}

\textbf{1.3.2.3. Anti-cancer agents:}

Cancer patients have relatively high levels of glycosidases which contribute to the degradation of the glycoconjugates in the extracellular matrix during metastasis. Many polyhydroxylated alkaloids have displayed their potent activity as anti-cancer agents through different mechanisms of action.\textsuperscript{55} Swainsonine 25 is the most effective glycosidase inhibitor with anti-metastatic potential. In addition to the activity of swainsonine as a glycosidase inhibitor, it acts as an immune system stimulator due to its ability to induce the body defense mechanisms towards tumor cells. Swainsonine induces the anti-proliferative effect of \(\alpha/\beta\)-interferon, the proliferative response of T-cells to foreign antigens, natural killer cells activity and increases the IL-1 secretion and activity in macrophages.\textsuperscript{56} Other iminosugars such as castanospermine and a \(N\)-methyl derivative of DNJ have shown their potency in cancer therapy by inhibiting cellular transformations by altering oncogene glycosylation, inhibiting the platelet aggregation of the tumor cells and decreasing adhesion of the metastatic cells to the vascular endothelium.\textsuperscript{57,58} In summary, the therapeutically variability of the polyhydroxylated alkaloids as antidiabetic, antiviral and anticancer agents have increased the interest in their isolation and chemical synthesis. In the next sections, this thesis is focusing on study the synthetic chemistry toward one of the pyrrolizidine alkaloids, alexine 33.

\textbf{1.4. Research Project Aims:}

Alexine 33 was isolated in 1987 and was considered as the first polyhydroxylated pyrrolizidine isolated from plants.\textsuperscript{59} Despite its weak inhibitory effect toward the
mammalian β-glucosidase and β-galactosidase,\textsuperscript{28} alexine has displayed potent inhibitory activity against fungal glucan 1,4-α-glucosidase, amyloglucosidase,\textsuperscript{59} and thioglucosidase.\textsuperscript{60} The aims of this project were to perform model studies that could be extended in the future to synthesize alexine 33. This is a synthetically challenging target as it requires the synthesis of the syn-1,2-amino alcohols C from a sugar derived imine derivative and a functional allyl organo boron A (borono-Mannich reaction), indium or zinc reagent B (Scheme 1.1). While the borono-Mannich reaction has been widely used for the synthesis of polyhydroxylated alkaloids, these reactions normally give anti-1,2-amino alcohols and thus the development of a syn-selective version would be highly useful.

Scheme 1.1. Proposed synthetic pathway to alexine

The following sections summarize the literature relevant to the synthesis of syn and anti 1,2-amino alcohols.

1.5. The Petasis Borono-Mannich reaction:
Petasis \textit{et al.} reported in 1993 the efficiency of the borono Mannich reaction. The first boronic acid Mannich reaction was conducted by heating a mixture of a secondary amine
and paraformaldehyde in dioxane or toluene at 90 °C for 10 min, and then a vinyl boronic acid was added to the reaction mixture and the mixture was stirred at 25 °C for 3 h or at 90 °C for 30 min (Scheme 1.2) to give the $E$-allylamines 51 in high yields (75-96%).

$$\begin{align*}
\text{R}_1\text{B(OH)}_2\text{OH} + \text{H}_2\text{N}\text{R}_2\text{N}_3 & \rightarrow \text{R}_1\text{N}\text{R}_2\text{N}_3 \\
1. (\text{CH}_2\text{O})_n \text{ and amine in dioxane} \text{ or toluene, } 90 \, ^{@}\text{C}, 10 \text{ min} & \\
2. \text{Boronic acid, } 90 \, ^{@}\text{C}, 30 \text{ min} \text{ or rt, } 3 \, \text{h} & \\
\text{51} & \text{75-96%}
\end{align*}$$

**Scheme 1.2. The first borono-Mannich reaction**

In 1998, Petasis *et al.* reported a one-step highly stereocontrolled synthesis of *anti*-β-amino alcohols involving three components: a chiral α-hydroxy aldehyde, a primary or secondary amine and an organoboronic acid. The *anti*-β-amino alcohol products 52 were produced in very high yields and diastereoselectivities (dr > 99%) (Scheme 1.3).

$$\begin{align*}
\text{R}_1\text{B(OH)}_2\text{OH} + \text{H}_2\text{N}\text{R}_2\text{N}_3 + \text{O} \rightarrow \text{R}_1\text{N}\text{R}_2\text{N}_3 \text{R}_4\text{O}_4 \text{OH} & \\
\text{EtOH, rt, 12-48 h} & \\
\text{52} & \text{up to 99%}
\end{align*}$$

**Scheme 1.3. One-pot reaction synthesis of *anti*-β-amino alcohols**

Using boronic acids in the Mannich reaction is quite important because of their relative unreactivity toward the aldehyde component while they efficiently trap the more reactive iminium ion intermediates. Furthermore, boronic acids have good air and water stability and their boronic acid by-product is water soluble and easily removed. Reactions of several organoboronic acids were used and examined such as phenylvinylboronic acid, $p$-methoxyphenylboronic acid and $N$-Boc-$1H$-pyrrol-2-yl-boronic acid (Table 1.1). They all worked very efficiently and their related products 53, 54 and 55 were obtained in relatively good yields (84%, 63% and 73%, respectively). In addition, these products were formed in high diastereoselectivities (dr > 99%) and enantiopurities.
Table 1.1. Selected results from Petasis’s paper\textsuperscript{62}

<table>
<thead>
<tr>
<th>Boronic acid</th>
<th>Amine</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield %</th>
<th>dr (anti: syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-OH-B-OH</td>
<td>Ph-N-Me</td>
<td>O-C_{3}H_{11}</td>
<td>Ph-N-Me-C_{3}H_{11}</td>
<td>84</td>
<td>99:1</td>
</tr>
<tr>
<td>MeO-OH-B-OH</td>
<td>Ph-N-PPh</td>
<td>O-Me</td>
<td>Ph-N-PPh-Me</td>
<td>63</td>
<td>99:1</td>
</tr>
<tr>
<td>NHBoc-OH</td>
<td>Ph-N-Me</td>
<td>O-OH</td>
<td>Ph-N-Me-OH</td>
<td>73</td>
<td>99:1</td>
</tr>
</tbody>
</table>

The mechanism of this reaction is shown in Scheme 1.4. The amine reacts with the aldehyde to form the iminium ion, the $\alpha$-hydroxy group possibly forms a boronate complex intermediate A with the boronic acid, and the nucleophile R\textsuperscript{1} is delivered intramolecularly to the C=N double bond to form the anti product.

![Scheme 1.4](image)

scheme 1.4. Proposed mechanism of the borono-Mannich reaction

The Pyne group has made a successful use of the boron Mannich reaction using vinyl organoboron reagents to prepare bioactive polyhydroxylated indolizidine, pyrrolizidine and nortropane alkaloids. A recent example is the Pyne group’s concise synthesis of (-)-steviamine \textsuperscript{57} which is shown in Scheme 1.4.\textsuperscript{64} In this synthesis, the three component borono-Mannich reaction between the partially protected sugar, the amine and $\beta$-styrenylboronic acid was employed to secure the desired 1,2-anti-configuration of the 1,2-amino alcohol moiety in the product \textsuperscript{56} (Scheme 1.5). This configuration is thought
to be occurring through the reactive intermediate B which adopts the conformation shown to minimize 1,3-allylic strain between the N-substituent of the iminium ion and the α-carbon. This intermediate arises from the initial iminium ion intermediate that is formed between the amine and the ring-opened form of the sugar which then forms a boronate complex between the free α-hydroxy group and the organoboronic acid. Compound 56 was then efficiently converted to the natural product (-)-steviamine 57 in a further three synthetic steps.

Scheme 1.5. Synthesis of (-)-Steviamine 57

As discussed previously, the borono-Mannich reactions using organoboronic acids have successfully produced anti-1,2-amino alcohols. In one study, borono-Mannich reactions were performed using various allylboronates with ammonia and aldehydes. However, using the pinacol allylboronate as the allylating agent was the most preferred due to its higher stability. Kobayashi et al. demonstrated that borono-Mannich-type reactions using allylorganoboronates give syn-1,2-amino alcohol products in very high diastereoselectivities and enantiopurities (Scheme 1.6).
1.6. Hydroxyallylation of carbonyl compounds using allyl indium or Zinc reagents:
The metal mediated allylation reactions of carbonyl compounds were used successfully
in the synthesis of a range of monoprotected allyl alcohols. Lombardo et al. demonstrated
the application of zinc and indium-promoted reactions of 3-bromopropenyl methyl
carbonate and 3-bromopropenyl esters with aldehydes (Scheme 1.7).\textsuperscript{66,67} The reaction of
3-bromopropenyl methyl carbonate with either benzaldehyde or
cyclohexanecarboxaldehyde in the presence of Zn metal in aqueous ammonium chloride
under Barbier conditions afforded the monoacylated alcohols in high yields, but with
different diastereoselectivity (Scheme 1.7a). The stereochemistry of the product is
controlled by the nature of the aldehyde substituent where aromatic and conjugated
aldehydes give the \textit{syn} adduct \text{dr (anti:syn)} = 30:70, and aliphatic and saturated aldehydes
give the \textit{anti}-adduct \text{dr (anti:syn)} = 95:5.\textsuperscript{67} Similar results were reported when the reaction
of 3-bromopropenyl methyl carbonate with different aldehydes was mediated using In
metal in a THF/H\textsubscript{2}O (1:1) solvent mixture (Scheme 1.7b). The monoacylated alcohol
product was obtained mainly in the \textit{syn}-configuration in case of the conjugated aldehyde
\text{dr (anti:syn)} = 30:70, while the unconjugated aldehyde gave the \textit{anti}-adduct \text{dr (anti:syn)} = 80:20.\textsuperscript{66}
Zn-mediated allylation of aldehydes using 3-bromopropenyl benzoate was expected to
show similar results with those of 3-bromopropenyl methyl carbonate, however the
outcome was completely different (Scheme 1.7c). A poor diastereoselectivity was
obtained with the benzaldehyde \text{dr (anti:syn)} = 45:55, while the
cyclohexanecarboxaldehyde gave the anti-adduct as the main isomer dr \((\text{anti:} \text{syn}) = 85:15\). The In-mediated allylation of aldehydes using 3-bromopropenyl benzoate were not reported.

Scheme 1.7 (a, b, c). Zn and In mediated hydroxyallylation reactions

Lombardo further demonstrated that the Zn-mediated hydroxyallylation of \(\alpha\)-amidoalkylaryl sulfone by 3-bromopropenyl methyl carbonate in DMF gave the \(\text{anti}-1,2\)-amino alcohol product 58 in a high yield (Scheme 1.8).  

Scheme 1.8. Zn mediated synthesis of 58
1.7. Indium/ Zinc Allylation of \textit{in situ} formed aldimine:

The metal mediated allylation reactions of carbonyl compounds with amines were used successfully in the synthesis of a range of 1,2-amino allyl alcohols. This project is focusing on examining the reactivity of using either indium or zinc reagent toward synthesis of the \textit{syn} 1,2-amino alcohols. Skaanderup \textit{et al.} found that allylindium, prepared \textit{in situ} from allylbromide and In metal under Barbier reaction conditions, gives \textit{syn}-1,2-amino \textit{O}-benzyl products in high yield and selectivity (Scheme 1.9a). In related studies, Behr \textit{et al.} found that In-mediated allylation of the xylosylamine gives the \textit{syn}-homo allyl aminopolyol. When the reaction was repeated with Zn as the promoter, no desired product was observed, and the starting xylose was recovered (Scheme 1.9b). Performing the same reaction using the D-xylose, also gave the \textit{syn}-1,2-amino alcohol product (Scheme 1.9c). The mechanism of this reaction is shown in Scheme 1.10. This involves a chelation-control mechanism via the chelated intermediate C that leads to the \textit{syn}-product.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme1.png}
\caption{Scheme 1.9 (a, b, c). Indium mediated synthesis of amino alcohols}
\end{figure}
Another related study conducted by Gonzalez-Gomez et al. found that the reaction of an aldehyde, chiral tert-butanesulfinamide and indium in the presence of titanium ethoxide, and then allyl bromide, produced the homoallylsulfinylamine 59 in high yield (92%) and diastereoselectivity (dr 91:9) (Scheme 1.11). Performing the same reaction using the Zn-reagent instead of the indium, also gave the product 59 in relatively low yield (20%), and the diastereoselectivity outcome of this attempt was not reported.

**Scheme 1.11. Indium mediated synthesis of homoallylsulfinylamine 59**

**1.8. Indium-mediated allylation of preformed imines:**

Allylation reactions of imines have not been studied extensively due to the poorer electrophilic properties of imines towards nucleophiles in comparison with the more reactive carbonyl compounds. However, studies have indicated that the low electrophilicity of the imines can be overcome by either increasing the electrophilicity of the imines through substitution of the imine N with an electron withdrawing group such as acyl, benzyl, phosphonyl, sulfinyl or sulfonyl, or by coordinating of the imine N with a Lewis acid. The indium was the metal of choice to mediate the allylation reaction of
imines for several reasons. Indium has a very low first ionization potential IP$_1$ = 5.8 eV, which means a very low amount of energy is needed for the single electron transfer process. Furthermore, indium has shown its friendly environmental properties in comparison with other metals, its stability to air exposure, and can be used with a wide range of solvents and functional groups.

In 2001, Yanada illustrated that the indium mediated allylation of isopropyl benzylimine occurs through the coordination of allyl indium intermediate with the OH group and N of the chiral imine 60 (Scheme 1.12). In this coordination complex, the bulky iso-propyl group auxiliary shields the Re-face of the imine, which encourages the allylic addition to occur at the Si-face of the imine affording the allyl amino product 61 in high yield 95% and high diastereoselectivity (dr > 99%).

![Scheme 1.12. Indium mediated synthesis of 61](image)

In related studies, it has been found that the In-mediated reaction of N-sulfinyl aldimine with the silylated propargyl bromide 62 under Barbier reaction conditions; gave the desired propargylated product 63 with high regioselectivity (propargyl:allene = 98:2) (Scheme 1.13).
The mechanism of this reaction is shown in Scheme 1.14. Interaction of the propargyl bromide with indium generates two intermediates: propargylindium I and allenylindium II at equilibrium. However, in this reaction: (1) due to the presence of the silicon atom and its strong stabilizing effect on α-carbanions, the allenylindium II is the most stable form; and (2) for the allenylindium species γ-addition is more preferred than α-addition. Thus, the transition state III is preferred leading to formation of the observed propargyl product 63.75
Another study conducted by Lin et al. found that adding a more bulky silyl group (TIPS) to the silylated propargyl bromide 64 gives the allenylated product 65 in good yield and regioselectivity (allene:propargyl = 96:4) (Scheme 1.15).76

![Scheme 1.15. Indium-mediated synthesis of 65](image)

1.9. Detailed synthetic plans:
In order to develop methods to prepare syn 1,2-amino alcohols, initial studies on the reactions of 66-70 will be performed on salicylaldehyde as shown in Scheme 1.16 to optimize the reaction conditions and examine the diastereoselectivities and stereochemical outcomes. Salicylaldehyde was chosen since in related reactions, the ortho hydroxy group assists in the addition reactions of nucleophiles by metal coordination.77

![Scheme 1.16. Proposed indium, zinc or boron-mediated allylation reactions](image)
1.9.1. Synthesis of allylic reagents and precursors:

In the following sections a summary of the allylation reactions of imines with 3-bomopropenyl esters 66a and 66b (Chapter 2), 3-0-benzylallyl boronate 67 (Chapter 3), 3-O-benzyolallyl boronate 68 (Chapter 3) and TMS allylboronate 70 (Chapter 4) will be covered.

In Chapter 2, the 3-bomopropenyl methyl carbonate 66a will be prepared using the method of Lombardo et al. according to Scheme 1.17(a). The 3-0-benzoyl allyl bromide 66b will be prepared using the method of Lombardo et al. according to Scheme 1.17(b).

![Scheme 1.17 (a, b). Synthesis of allyl bromides 66a and 66b](image)

In Chapter 3, the reactions of 3-benzyloxy and 3-benzyloxy allyl boronates will also be examined: 3-0-benzylallyl boronate 67 and the 3-0-benzyolallyl boronate 68 (Figure 1.10). These reagents will be reacted with aldehydes and amines under Petasis reaction conditions.

![Figure 1.10. Allyl boronates 67 and 68](image)

The 3-0-benzyolallyl boronate 67 will be prepared starting from benzyl propargyl ether using the procedure of Trost et al. giving the isomeric allene which then could be used to prepare the desired boronate 67 in another two steps using the procedures of Sato et al. and Zhang et al., sequentially (Scheme 1.18).
Scheme 1.18. Proposed synthesis of 3-O-benzylallyl boronate 67

The 3-O-benzoylallyl boronate 68 will be prepared from allylic bromide 66b using the procedure of Zhang et al.\textsuperscript{80} to prepare other allylboronates from allyl chlorides (Scheme 1.19).

Scheme 1.19. Proposed synthesis of 3-O-benzoylallyl boronate 68

In Chapter 4, an alternative reagent to 67 and 68 will be examined, γ-trimethylsilyl (TMS) allylboronate 70. The γ-TMS allylboronate 70 is proposed to be synthesized by following Zhang et al.\textsuperscript{80} procedure through the borylation of 3-iodovinylsilane 69 with B\(_2\)(pin)\(_2\) in the presence of PdCl\(_2\) and KOAc (Scheme 1.20). However, the starting 3-iodovinylsilane 69 needs to be prepared first from the TMS allyl alcohol using the procedure of Singletary et al.\textsuperscript{81}

Scheme 1.20. Proposed synthesis of γ-TMS allylboronate 70
Chapter 2: Synthesis of homo allylic amines 72 and 75 using Allyl bromide/ Indium reactions

This chapter will cover the In-mediated allylation reactions of imines with 3-bromopropenyl esters 66a and 66b. Initially by using allyl bromide, the efficiency of allylindiums to produce the desired homoallyl amines will be examined.

2.1. In-mediated allylation of salicylaldehyde using allyl bromide:

As an initial model study of the use and efficiency of functionalized allylindiums to produce amino allyl products, the reaction of salicylaldehyde 71, benzylamine, allyl bromide and indium to produce the homoallyl amino compound 72 was first examined (Scheme 2.1).

Scheme 2.1. Indium mediated synthesis of 72

Following the method of Behr, a solution of salicylaldehyde 71 in anhydrous methanol was stirred in the presence of benzylamine at 45 °C for 1 h, then at room temperature for 2 h to form the corresponding imine 73 in situ. Allyl bromide and powdered indium were then added, and the solution was stirred at room temperature for 18 h under a nitrogen atmosphere. This reaction is thought to produce the In(III) species (allyl)3In2Br3. TLC analysis of the crude mixture indicated the presence of a relatively large amount of the starting materials (71 and BnNH2) plus spots for two additional new products. The crude reaction product mixture was purified by column chromatography to afford the desired amino allyl product 72 in 27% yield. The corresponding imine 73 was also isolated in 9% yield. The former product 72 has not been previously reported.
The $^1$H-NMR spectrum of compound 72 (Figure 2.1) showed resonances for the terminal alkene protons H1 at $\delta$ 5.11-5.13 (m, 2H). The diastereotopic $N$-benzyl methylene protons resonated as doublets at $\delta$ 3.58 (d, $J = 13.1$ Hz, 1H, C4-$\text{NHCH}_2$Ph) and $\delta$ 3.85 (d, $J = 13.1$ Hz, 1H, C4-$\text{NHCH}_2$Ph). The NH proton resonated at $\delta$ 5.14 (s, 1H, C4-$\text{NHCH}_2$Ph). The protons attached to C2, C3 and C4 resonated at $\delta$ 5.66-5.75 (m, 1H, H2), $\delta$ 2.49 (ddt, $J = 7.9$, 6.6, 1.2 Hz, 2H, H3) and $\delta$ 3.80 (t, $J = 8.0$, 6.5 Hz, 1H, H4), respectively. The phenyl ring protons of the $N$-benzyl moiety resonated at $\delta$ 7.24-7.35 (m, 5H), while the other aromatic ring protons resonated at $\delta$ 6.95 (dd, $J = 7.5$, 1.7 Hz, 1H, H6'), $\delta$ 6.85 (dd, $J = 9.5$, 2.5 Hz, 1H, H3'), $\delta$ 6.80 (td, $J = 7.5$, 1.5 Hz, 1H, H5') and $\delta$ 7.16 (ddd, $J = 8.1$, 7.3, 1.7 Hz, 1H, H4').
Figure 2.2. $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of compound 72

The $^{13}$C-NMR spectrum of compound 72 (Figure 2.2) showed resonances for the alkene carbons at $\delta$ 119.3 (C1) and $\delta$ 134.6 (C2). The N-benzyl methylene carbon resonated at $\delta$ 51.6 (NH$\text{C}$H$_2$Ph), while C3 and C4 resonated at $\delta$ 40.8 and $\delta$ 62.1, respectively. Furthermore, there were several resonances in the range $\delta$ 128.5-128.8 assigned to the ArCH protons of the benzylamine aromatic ring and the resonance $\delta$ 138.5 was for the ipso aromatic carbon (Ar-C). The quaternary aromatic carbon resonances at $\delta$ 124.8 and $\delta$ 157.6 were assigned to C1' and C2', respectively. The phenyl ring carbons 3' and 6' attached to C4-PhOH resonated at 117.0 and 128.9 $\delta$, respectively. These and other assignments (see Experimental section) were made through running of gCOSY (Appendix A-1) and gHSQC (Appendix A-2) experiments. The ESIMS data showed an [M+H$^+$] ion peak at m/z 254.1557 (calculated for C$_{17}$H$_{20}$NO: 254.1545) which confirmed the correct molecular formula of compound 72.

2.2. Indium-mediated allylation of preformed imine using allyl bromide:

Based on the relatively low yield of 72 from the indium mediated allylation of salicylaldehyde and benzylamine under Barbier reaction conditions, it was proposed that
using the corresponding preformed imine 73 as a starting material could improve the yield of 72 in this reaction.

To prepare the known N-benzylimine 73, the salicylaldehyde 71 was dissolved in distilled water, and then the reaction mixture was treated with benzylamine in one portion and stirred at rt for 3 h to afford the desired imine 73 in 98% yield after extraction into dichloromethane (Scheme 2.2).  

\[
\begin{array}{c}
\text{Scheme 2.2. Synthesis of imine 73} \\
\end{array}
\]

The \(^1\)H-NMR spectrum of compound 73 (Appendix A-3) showed a singlet resonance for the N-benzyl methylene protons at \(\delta 4.81\) (s, 2H, C=NC\(_2\)Ph). The HC=NC\(_2\)Ph proton resonated as a singlet at \(\delta 8.44\). The phenyl ring protons attached to NH\(_2\)Ph resonated at \(\delta 7.25-7.31\) (m, 5H, Ar-CH). The other aromatic ring protons resonated at \(\delta 6.96\) (d, \(J = 8.5\) Hz, 1H, H3'), \(\delta 6.88\) (t, \(J = 7.5\) Hz, 1H, H5'), \(\delta 7.34\) (d, \(J = 7.5\) Hz, 1H, H6'), respectively. The hydroxy group proton resonated at \(\delta 13.37\) (s, 1H, O\(\text{H}\)), its highly downfield chemical shift indicated it was H-bonded to the imine nitrogen. The NMR spectroscopic data of compound 73 matched with those reported in the literature. The ESIMS data showed an [M+H\(^+\)] ion peak at \(m/z\) 212.2027 (calculated for C\(_{14}\)H\(_{14}\)NO\(^+\): 212.2036) which confirmed the correct molecular formula of compound 73.

As a model study, the reaction of N-benzylimine 73, allyl bromide and indium to produce the homoallyl amino compound 72 was also examined. TLC analysis was used to monitor the formation of the desired product 72. After 16 h TLC analysis of the crude mixture indicated the presence of a relatively large amount of the desired homoallyl amine compound 72. The crude reaction product was purified by column chromatography to afford the desired amino allyl product 72 in 48% yield (Scheme 2.3). The corresponding alcohol product 74 was also formed in 3% yield, presumably this was formed from salicylaldehyde formed from the hydrolysis of the starting imine by traces of water in the MeOH solvent.
To optimize the yield of this reaction, different reaction conditions were examined (Table 2.1). First, we repeated the reaction of 73 under the same conditions but with THF as solvent instead of MeOH. This modification gave the desired product 72 in only 22% yield (Table 2.1, entry 2).

In another attempt, the reaction mixture was sonicated in MeOH at 45 °C for 2 h (Table 2.1, entry 3). TLC analysis of the crude mixture indicated the presence of a relatively large amount of the starting imine 73. The crude reaction mixture was purified by column chromatography to afford the desired amino allyl product 72 in only 21% yield. The corresponding alcohol adduct 74 was also formed in 3% yield. Similar results were realized when the reaction mixture was sonicated at 45 °C in THF for 5 h, where the product 72 was only formed in 25% yield (Table 2.1, entry 4).

Following the reaction conditions of Lombardo et al., 68 1.2 equiv of zinc metal was slowly added at 0 °C to a mixture of the N-benzylimine 73 (1 equiv) and allyl bromide (1.2 equiv) in anhydrous DMF. The reaction mixture was stirred vigorously at 0 °C for 30 min, and then at rt for 2 h (Table 2.1, entry 5). TLC analysis indicated the presence of a relatively large amount of the starting imine and only a trace amount of the desired product. Using DMF as the solvent was not valuable due to the relatively poor solubility shown by the reactants. Furthermore, the reaction was set up for only a short time which was not sufficient for product formation.

In summary, In-mediated allylation of the preformed imine 73 using allyl bromide gave the desired homoallyl amine 72 in better yield (48%) compared with the results obtained from using salicylaldehyde as the starting material (27%). The efficiency of allylindiums using 3-bromopropenyl esters 66a and 66b to produce the desired 1,2 amino alcohols follows in the next sections.
Table 2.1. Conditions screening for synthesis of compound 72

<table>
<thead>
<tr>
<th>Entry</th>
<th>AllylBr</th>
<th>Metal</th>
<th>Solvent</th>
<th>T °C</th>
<th>Time</th>
<th>Product yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 equiv</td>
<td>In (2 equiv)</td>
<td>MeOH</td>
<td>rt</td>
<td>16 h</td>
<td>72 48%</td>
</tr>
<tr>
<td>2</td>
<td>3 equiv</td>
<td>In (2 equiv)</td>
<td>THF</td>
<td>rt</td>
<td>16 h</td>
<td>72 22%</td>
</tr>
<tr>
<td>3</td>
<td>3 equiv</td>
<td>In (2 equiv)</td>
<td>MeOH</td>
<td>sonicated 45</td>
<td>2 h</td>
<td>72 21%</td>
</tr>
<tr>
<td>4</td>
<td>3 equiv</td>
<td>In (2 equiv)</td>
<td>THF</td>
<td>45</td>
<td>5 h</td>
<td>72 25%</td>
</tr>
<tr>
<td>5</td>
<td>1.2 equiv</td>
<td>Zn (1.2 equiv)</td>
<td>DMF</td>
<td>0 to rt</td>
<td>30 min to 2 h</td>
<td>72 (traces in the crude mixture) + Recovery of SM 73</td>
</tr>
</tbody>
</table>

2.3. Indium-mediated allylation using methyl carbonates:

2.3.1. Synthesis of 3-bromopropenyl methyl carbonate 66a:

Based on the report by Lombardo et al., the 3-bromopropenyl methyl carbonate 66a was obtained by the radical bromination of allyl methyl carbonate with the N-bromosuccinimide (NBS). NBS is widely used as a brominating agent for the allylic positions of alkenes (Wohl-Ziegler bromination reaction), and it is a suitable source of bromine for radical substitution and electrophilic addition reactions due to its ability to release bromine (Br₂) slowly during the reaction. The presence of bromine in high concentration may lead to an alternative 1,2-addition reaction to the alkene resulting in the formation of the dibromide product in competition with radical abstraction (Scheme 2.4).

![Diagram](image)

**Scheme 2.4. Synthesis of compound 66a**
NBS reacts with the HBr formed from the H-atom abstraction step to keep the bromine in low concentration. Therefore, this will promote the rate of C-H radical abstraction which leads to formation of the allylic bromination product 66a in a higher yield and overcomes the dibromoniation reaction.

The mechanism of this reaction is shown in Scheme 2.5. First, the generation of isobutynitrile radicals from the azobisisobutyronitrile (AIBN) initiator which can abstract a hydrogen atom by breaking the weakest C-H bond at the allylic position to form the resonance stabilized radical intermediate X. The resulting allylic radical intermediate attacks the bromine at the least hindered allylic position to form the desired product with regeneration of the bromine radical (propagation step).

**Initiation**

(a) \[ \text{AIBN} \rightarrow \text{CN} + \cdot \text{N} + \cdot \text{CN} \] 

\[ \text{66-72 } ^{\circ} \text{C} \]

(b) \[ \text{Br-Br} \xrightarrow{\text{heat}} \cdot \text{Br} + \cdot \text{Br} \]

**H-atom abstraction step**

\[ \text{O} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{O} \]

\[ \xrightarrow{\text{H-atom abstraction}} \]

\[ \text{Y} = \text{Br} \quad \text{or} \quad \cdot \text{CN} \]

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \]

\[ \xrightarrow{\text{H-atom abstraction}} \]

\[ \text{X} \quad \text{+} \quad \text{HY} \]

\[ \text{NBS} + \text{HBr} \rightarrow \text{N-H} + \text{Br}_2 \]

**Propagation step**

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \]

\[ \xrightarrow{\text{Br-Br}} \]

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \]

\[ \xrightarrow{\text{Br-Br}} \]

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \]

**Scheme 2.5.** Mechanism of radical bromination of allyl methyl carbonate

Allyl methyl carbonate in dichloroethane was treated with NBS in the presence of the radical initiator benzoyl peroxide. The reaction mixture was heated for 2-3 mins and then stirred at 80-90 °C for 2 h (Table 2.2, entry 1). The reaction was then cooled to rt.
Formation of a white precipitate (succinimide) was clearly observed. After filtration of the crude reaction mixture was analyzed by TLC and $^1$H-NMR spectroscopy. Both analyses indicated the presence of the starting material with no formation of the desired product. In Lombardo's method, carbon tetrachloride was the solvent of choice for this reaction. However, the use of this solvent usage has been restricted due to its carcinogenicity and its harmful environmental effects. Therefore, in this study, dichloroethane was used as alternative solvent to CCl$_4$.

This reaction was repeated under the same reaction conditions but with using the AIBN instead of the benzoyl peroxide (Table 2.2, entry 2). $^1$H-NMR analysis of the crude reaction mixture showed presence of traces amounts of the desired product. The best results were obtained when a freshly purified NBS was used and the reaction was set for longer time (9 h) (Table 2.2, entry 5) (Scheme 2.6). Based on TLC and $^1$H- NMR analysis, we observed the formation of the desired 3-bromopropenyl methyl carbonate 66a. After purification of the crude reaction mixture by column chromatography, the desired brominated product 66a was obtained in 14% yield as a mixture of E:Z (30:70) isomers.

The diastereoselectivity of 66a (E:Z = 30:70) was determined by integration of the $^1$H-NMR doublet resonances at $\delta$ 5.74 and $\delta$ 5.25 for H2 in the major and minor diastereomers, respectively (Figure 2.3). The yield of 3-bromopropenyl methyl carbonate 66a was relatively low in comparison to the yield described in the literature, where the compound 66a was obtained in 70% yield (E:Z = 35:65) using CCl$_4$.

Scheme 2.6. Synthesis of compound 66a
Table 2.2. Reaction conditions for the synthesis of compound 66a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>Br₂ source</th>
<th>Radical initiator</th>
<th>Solvent</th>
<th>T °C</th>
<th>Time</th>
<th>Product yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allyl methyl carbonate</td>
<td>NBS</td>
<td>Benzoyl peroxide</td>
<td>CICH₂CH₂Cl</td>
<td>80-90</td>
<td>2</td>
<td>No reaction Recovered SM</td>
</tr>
<tr>
<td>2</td>
<td>Allyl methyl carbonate</td>
<td>NBS</td>
<td>AIBN</td>
<td>CICH₂CH₂Cl</td>
<td>80-90</td>
<td>2</td>
<td>Recovered SM + traces of 66a</td>
</tr>
<tr>
<td>3</td>
<td>Entry 2 crude</td>
<td>NBS</td>
<td>AIBN</td>
<td>CICH₂CH₂Cl</td>
<td>80-90</td>
<td>3</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>Allyl methyl carbonate</td>
<td>NBS</td>
<td>AIBN</td>
<td>CICH₂CH₂Cl</td>
<td>80-90</td>
<td>9</td>
<td>SM:66a (1:1)</td>
</tr>
<tr>
<td>5</td>
<td>Allyl methyl carbonate</td>
<td>Purified NBS</td>
<td>AIBN</td>
<td>CICH₂CH₂Cl</td>
<td>80-90</td>
<td>9</td>
<td>66a 14%</td>
</tr>
</tbody>
</table>

Figure 2.3. ¹H-NMR spectrum (CDCl₃, 500 MHz) of compound 66a

The E isomer of compound 66a (Figure 2.3) showed ¹H-NMR resonances for the vinyl protons H2 and H3 at δ 5.74 (dt, J = 12.2, 8.4 Hz, 1H) and δ 7.25 (d, J = 12.2 Hz, 1H), respectively. The Br-methylene protons (HC=CHCH₂Br) resonated at δ 3.99 (d, J = 8.4
Hz, 2H) and the methoxy protons at δ 3.87 (s, 3H). The Z isomer of 66a (Figure 2.6) showed 1H-NMR resonances for the vinyl protons H2 and H3 at δ 5.25 (td, J = 8.4, 6.1 Hz, 1H) and δ 7.00 (d, J = 6.2 Hz, 1H), respectively. The Br-methylene protons resonated at δ 4.08 (d, J = 8.4 Hz, 2H) while the methoxy protons resonated at δ 3.89 (s, 3H). The NMR spectroscopic data of compound 66a matched with those in literature.67 The ESIMS data showed an [M+H+] ion peak at m/z 196.1245 (calculated for C5H879BrO3+: 196.1234) which confirmed the correct molecular formula of compound 66a.

2.3.2. Model Study of efficiency of 3-bromopropenyl methyl carbonate 66a as an allylating agent:
As a model study the use of 3-bromopropenyl methyl carbonate 66a as an allylating agent in an indium mediated allylation reaction was studied using the N-benzylimine 73 (Scheme 2.7).

Scheme 2.7. Indium mediated synthesis of 75

The N-benzylimine 73 was dissolved in MeOH under a nitrogen atmosphere, and then a 1:1 mixture of allyl methyl carbonate and 3-bromopropenyl methyl carbonate 66a E:Z (30:70) obtained from entry 4, Table 2.2, (3 equiv) and powdered indium (2 equiv) were added to the reaction mixture which was stirred at rt for 16 h. TLC analysis was then used to check the formation of the desired product 75, which indicated the presence of a relatively small amount of the desired homoallyl amine compound. The crude reaction product mixture was purified by column chromatography to afford the desired amino allyl product 75 in 12% yield based on the moles of 73 used (dr = 95:5). The diastereoselectivity of this reaction was determined by integration of the 1H-NMR doublet resonances at δ 4.06 and δ 4.10 for H4 in the major and minor diastereomers, respectively (Figure 2.4). The 1H-NMR spectrum of 75 revealed the presence of several impurities,
the main one was allyl methyl carbonate which co-eluted from the column with 75 (Figure 2.4).

Figure 2.4. $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of impure compound 75

The $^1$H-NMR spectrum of compound 75 (Figure 2.4) showed resonances for the H1 and H3 protons at $\delta$ 5.35-5.25 (m, 3H) while H2 resonated at $\delta$ 5.90-5.80 (m, 1H). The methoxy protons resonated at $\delta$ 3.71 (s, 3H) while H4 resonated at $\delta$ 4.06 (d, $J = 5.5$, 1H). The N-benzyl methylene protons resonated as doublets at $\delta$ 3.60 (d, $J = 13.2$ Hz, 1H, Hb) and $\delta$ 3.91 (d, $J = 13.2$ Hz, 1H, Ha). The phenyl ring protons attached to NHCH$_2$Ph resonated at $\delta$ 7.35-7.23 (m, 5H). The other aromatic ring protons resonated at $\delta$ 6.85-6.79 (m, 2H, C7, C9), $\delta$ 7.03 (d, $J = 7.7$ Hz, 1H, H10) and $\delta$ 7.20 (t, $J =7.5$ Hz, 1H, H8), respectively.
The $^{13}$C-NMR spectrum of compound 75 (Figure 2.5) showed a resonance for the N-benzyl methylene carbon at $\delta$ 51.8 while C1, C2, C3 and C4 resonated at $\delta$ 120.3, 131.3, 80.7 and 65.4, respectively. The methoxy carbon resonated at $\delta$ 54.9 while the carbonyl carbon of the carbonate group resonated at $\delta$ 158.4. The carbon attached to the hydroxy group C6 resonated at $\delta$ 154.6. For the allyl methyl carbonate C1’ resonated at $\delta$ 121.5 while C3’ was observed at $\delta$ 82.5. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running a gHSQC (Appendix A-4) experiment. The LRMS of compound 75 did not confirm the molecular formula of compound 75.

Therefore, In-mediated allylation of the preformed imine 73 using the methylcarbonate 66a afforded the 1,2 amino alcohol 75 in 12% yield (dr = 95:5). These poor results are probably related to using an impure sample of 66a.

2.4. Indium-mediated allylation using benzoates:

2.4.1. Synthesis of 3-bromopropenyl benzoate 66b:

Based on the publication by Lombardo et al., 2003, 66 3-bromopropenyl benzoate 66b was obtained by haloacylation of acrolein with benzoyl bromide. The 3-bromopropenyl benzoate was prepared by adding the benzoyl bromide at 0 °C to a mixture of acrolein in anhydrous DCM. Then the reaction mixture was stirred at rt for 3 d. After work up the
desired 3-bromopropenyl benzoate $66b$ was obtained in 74% as the pure $E$ isomer after recrystallization from petroleum ether (Scheme 2.8).

\[
\begin{align*}
\text{O} & \quad \text{Br} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

1) 0 °C, DCM
2) rt, 3 d

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{1} & \quad \text{2} \\
\text{3} & \quad \text{4} \\
\end{align*}
\]

\[66b\]

74% $E$ isomer

Scheme 2.8. Synthesis of compound 66b

Acylation of the aldehyde oxygen atom of acrolein initially take places to produce the intermediate A which then gradually undergoes 1,3-allylic rearrangement of Br affording the desired product $66b$ (Scheme 2.9).

\[
\begin{align*}
\text{Ph} & \quad \text{Br} \\
\text{O} & \quad \text{Br} \\
\text{1,2-addition} & \\
\text{1} & \quad \text{2} \\
\text{3} & \quad \text{4} \\
\end{align*}
\]

\[66b\]

Scheme 2.9. Mechanism of synthesis of compound 66b

Figure 2.6. $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of compound 66b
An examination of the $^1$H-NMR spectrum of compound 66b (Figure 2.6) showed resonances for the vinyl protons H2 and H3 at $\delta$ 5.90 (dt, $J = 12.3, 8.4$ Hz, 1H) and $\delta$ 7.67 (dt, $J = 12.3, 1.2$ Hz, 1H), respectively. The Br-methylene protons (HC=CHCH$_2$Br) resonated at $\delta$ 4.07 (dd, $J = 8.5, 1.5$ Hz, 2H). The phenyl ring protons (Ar-CH) resonated at $\delta$ 7.41-7.58 (m, 2H, H6 and H8), $\delta$ 7.62 (td, $J = 7.4, 1.3$ Hz, 1H, H7) and $\delta$ 8.04-8.19 (m, 2H, H5 and H9). The $^{13}$C-NMR spectrum of compound 66b (Appendix A-5) showed resonances for the propenyl carbons C1, C2 and C3 at $\delta$ 28.4, 111.8 and 139.4 respectively. The aromatic carbons C5, C6, C7, C8 and C9 resonated at $\delta$ 130.1, 128.5, 133.7, 128.6 and 130.2, respectively while the carbonyl carbon resonated at $\delta$ 163.2. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix A-6) and gHSQC (Appendix A-7) experiments. The spectral data of compound 66b matched with those reported in literature. The ESIMS data showed an [M+Na$^+$] ion peak at $m/z$ 262.9684 (calculated for C$_{10}$H$_9$BrO$_2$Na$^+$: 262.9684) which confirmed the correct molecular formula of compound 66b.

2.4.2. Model Study of efficiency of 3-bromopropenyl benzoate 66b as an allylating agent:

As a model study of the use of 3-bromopropenyl benzoate as an allylating agent, the reaction of the N-benzylimine 73 with 3-bromopropenyl benzoate 66b and indium was examined (Scheme 2.10).

\[
\text{Scheme 2.10. Efficiency of 3-bromopropenyl benzoate 66b as an allylating agent}
\]

The N-benzylimine 73 was dissolved in anhydrous MeOH under a nitrogen atmosphere, and then 3-bromopropenyl benzoate 66b and powdered indium were added to the reaction mixture and then stirred at rt for 18 h. The $^1$H-NMR spectrum of the crude reaction product indicated a complex mixture of products with no signs for formation of the desired product. Because of the possibility of ester exchange between 66b and methanol,
DMF was used as the solvent. Similar results were also observed in this solvent with stirring at rt for 18 h. Based on these disappointing results, an alternative study was conducted as described in Chapter 3.

In conclusion, the efficiency of 3-acyloxyallyl indium or zinc reagents to produce the corresponding 1,2-amino alcohol products were explored using the imine formed between salicylaldehyde and benzylamine, either formed in situ or preformed. The combination of 3-methoxycarbonylallyl bromide and indium powder and the preformed imine gave the desired 1,2-N-benzylamino O-methyloxycarbonyl product 75 in only 12% yield but with good diastereoselectivity (dr = 95:5). The corresponding 3-benzoyloxyallyl bromide under similar conditions failed to produce any of the desired product. This study then focused on reactions of related allyl boronates which are reported in Chapter 3.
Chapter 3: Synthesis of 1,2-amino allyl alcohols using Pinacol 3-O-benzoyl allyl boronate

Allyl boronates have been the interest of several research studies due to their valuable roles as building blocks in the synthesis of homo allylic alcohols and amines and other synthetic compounds. The borono-Mannich reactions were performed through reactions of various allylboronates with ammonia and aldehydes (Scheme 1.6). However, using the pinacol allylboronate as the allylating agent was the most preferred due to its tolerance to a wide range of functional groups, its straightforward reaction conditions, and its ability to afford the desired products with high level of stereoselectivity.\textsuperscript{86,87}

In 1996 Miyaura \textit{et al.} reported an efficient synthetic procedure for allyl boronates through the cross-coupling reaction between C-allyl electrophiles and B-boryl nucleophiles. In this procedure, the allyl acetate was borylated by using bis(pinacolato)diboron \([\text{B}_2(\text{pin})_2]\) as the boryl nucleophile in the presence of bis(dibenzylideneacetone)palladium(0) \([\text{Pd(dba)}_2]\) as catalyst to afford the desired allyl boronate in 89\% yield (Scheme 3.1).\textsuperscript{86}

\begin{align*}
\text{Ph}\text{OAc} & \quad + \quad \begin{tikzpicture}
  \node at (0,0) {\text{Ph}};
  \node at (1.2,0) {\text{O}};
  \node at (2.4,0) {\text{B}};
  \node at (3.6,0) {\text{O}};
  \node at (4.8,0) {\text{B}};
  \node at (6,0) {\text{Ph}};
  \node at (7.2,0) {\text{O}};
  \node at (8.4,0) {\text{B}};
  \node at (9.6,0) {\text{Ph}};
\end{tikzpicture} & \quad \xrightarrow{\text{Pd(dba)}_2, \text{DMSO, 50 }\degree \text{C, 16 h}} & \begin{tikzpicture}
  \node at (0,0) {\text{Ph}};
  \node at (1.2,0) {\text{O}};
  \node at (2.4,0) {\text{B}};
  \node at (3.6,0) {\text{O}};
  \node at (4.8,0) {\text{B}};
\end{tikzpicture} & \text{Ph} & \quad + \quad \begin{tikzpicture}
  \node at (0,0) {\text{Ph}};
  \node at (1.2,0) {\text{O}};
  \node at (2.4,0) {\text{B}};
\end{tikzpicture} & \text{Ph} & \quad 89\% & \quad 10\%
\end{align*}

\textbf{Scheme 3.1.} Synthesis of an allyl boronate through the cross-coupling reaction

The cross coupling borylation take places through several steps as shown in Scheme 3.2. First, the palladium(0) catalyst \text{Pd(dba)}_2 undergoes an oxidative addition reaction to the allyl acetate to form a \(\pi\)-allylPd(II)acetate. Then transmetalation take places between the \(\pi\)-allylPd(II)acetate and \text{B}_2(\text{pin})_2 leading to formation of \(\pi\)-allyl(boryl)Pd(II) intermediate. Reductive elimination of this \(\pi\)-allyl(boryl)Pd(II) intermediate affords the
desired allyl boronate product accompanied by regeneration of the initial palladium(0) catalyst.\(^8\)

\[ \text{Pd(dba)}_2 \text{ and Pd(OAc)}_2 \text{ were the catalysts of choice for this reaction with no need for an additional ligand. Furthermore, it was observed that the addition of phosphine ligands such as, triphenylphosphine (PPh}_3\text{), bis(diphenylphosphino)ferrocene (dppf) or triphenylphosphite P(O\text{Ph})_3 \text{ during the reaction may slow the rate of product formation. DMSO was the solvent of choice in this reaction. When the reaction was carried out by using either DMF, dioxane or benzene as solvents, formation of a black precipitate was observed a short time after starting the reaction due to decomposition of palladium catalyst. As a result, the desired allyl boronate was formed in relatively low yield.}^8 \]

Despite that fact the desired allyl boronate was afforded in good yield, there are several disadvantages to this method. To obtain a good yield of the product, an excess amount of the boryl nucleophile was used as well as the use of DMSO, both can complicate the purification of the produced compound.\(^8\) On another hand, the product formation in this reaction was accompanied by generation of a 1,5-diene byproduct which negatively affects the product formation by either consuming the starting allyl acetate or forming a complex with the palladium catalyst.\(^8\) The diene byproduct is presumed to be formed via

---

**Scheme 3.2.** Proposed mechanism for the cross-coupling reaction

Pd(dba)\(_2\) and Pd(OAc)\(_2\) were the catalysts of choice for this reaction with no need for an additional ligand. Furthermore, it was observed that the addition of phosphine ligands such as, triphenylphosphine (PPh\(_3\)), bis(diphenylphosphino)ferrocene (dppf) or triphenylphosphite P(O\text{Ph})\(_3\) during the reaction may slow the rate of product formation. DMSO was the solvent of choice in this reaction. When the reaction was carried out by using either DMF, dioxane or benzene as solvents, formation of a black precipitate was observed a short time after starting the reaction due to decomposition of palladium catalyst. As a result, the desired allyl boronate was formed in relatively low yield.\(^8\) Despite that fact the desired allyl boronate was afforded in good yield, there are several disadvantages to this method. To obtain a good yield of the product, an excess amount of the boryl nucleophile was used as well as the use of DMSO, both can complicate the purification of the produced compound.\(^8\) On another hand, the product formation in this reaction was accompanied by generation of a 1,5-diene byproduct which negatively affects the product formation by either consuming the starting allyl acetate or forming a complex with the palladium catalyst.\(^8\) The diene byproduct is presumed to be formed via
an allyl-allyl coupling process (Scheme 3.3), in which the formed allyl boronate reacts with the \( \pi \)-allylPd(II)acetate to produce the bis-allyl Pd complex. The later compound undergoes allyl-allyl coupling reaction to give the unwanted diene byproduct.\(^89\)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{B} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

\( \text{bis-allyl Pd complex} \)  
1,5-diene byproduct

**Scheme 3.3.** Proposed mechanism for the allyl-allyl coupling reaction

Later, a study conducted by Zhang *et al.* indicated another method to synthesize substituted and functionalized allyl boronates. The borylation of allyl dimethyl acetal with \( \text{B}_2(\text{pin})_2 \) was conducted in presence of bis(1,5-cyclooctadiene)nickel \([\text{Ni(cod)}_2]\) as catalyst affording the desired \( \text{E}-\gamma \)-oxygenated allyl boronate in 52\% yield (Scheme 3.4). In this reaction, 1 equiv of the boryl electrophile was enough to afford the product in good yield. Furthermore, the ligand tricyclohexylphosphine (PCy\(_3\)) was preferred in this transformation rather than PPh\(_3\) because of it can be more easily removed from the desired product.\(^80\)

\[
\begin{align*}
\text{OMe} & \quad \text{OMe} \\
\text{MeO} & \quad \text{B} & \quad \text{B} \\
\text{OMe} & \quad \text{OMe}
\end{align*}
\]

\( 10\% \text{Ni(cod)}_2, 10\% \text{PCy}_3, \text{EtOAc, 60 }^\circ\text{C, 12 h} \)

52\% (\( \text{E} \) isomer)

\[
\begin{align*}
\text{Ni} & \quad \text{cod} \\
\text{Ni} & \quad \text{cod}
\end{align*}
\]

\( \text{Ni(cod)}_2 = \text{bis(1,5-cyclooctadiene)nickel} \)

**Scheme 3.4.** Ni-catalyzed allylic boronate synthesis from allylic acetal

42
This chapter will report on the allylation reactions of imines with 3-O-benzyl allyl boronate 67 and 3-O-benzyol allyl boronate 68 (Scheme 3.5). Furthermore, the results of the one pot, three component reactions of the boronates 67 and 68 with different aldehydes and amines will also be reported.

![Scheme 3.5. Proposed boron-mediated allylation reactions](image)

3.1. Synthesis of benzyl allyl boronate 67:
The 3-O-benzyl allylboronate 67 can be prepared by following the procedure of Zhang et al. through the borylation of allyl dibenzyl acetal 77 with $\text{B}_2(\text{pin})_2$ in presence of Ni(cod)$_2$ as catalyst (Scheme 3.6). However, first the starting allyl dibenzyl acetal 77 needs to be prepared from the benzyl propargyl ether using the procedure of Trost et al. giving the allene 76 which then could be used to prepare the desired boronate in another two steps using the procedures of Sato et al. and Zhang et al., sequentially.

![Scheme 3.6. Proposed synthetic pathway to benzyl allyl boronate 67](image)

3.1.1. Synthesis of 1-O-benzyl allene 76:
Following the procedure of Trost et al., 3-O-benzyl allene 76 was synthesized through a base induced isomerization of benzyl propargyl ether. A solution of the benzyl propargyl ether in THF was stirred in presence of potassium tert-butoxide ($t$-BuOK) at rt
for 3 h. The crude product mixture was purified by column chromatography to afford the
1-O-benzyl allene 76 in 98% yield (Scheme 3.7).

\[
\begin{align*}
\text{O} & \quad \text{KO}^\text{Bu} \\
\text{THF, rt, 3 h} & \quad \text{H} \\
\text{76} & \quad \text{98%}
\end{align*}
\]

Scheme 3.7. Synthesis of compound 76

The $^1$H-NMR spectrum of compound 76 (Figure 3.1) showed resonances for the terminal
allene protons H1 and H3 at $\delta$ 6.83 (t, $J = 5.9$ Hz, 1H, H1) and $\delta$ 5.48 (d, $J = 5.9$ Hz, 2H, H3), respectively. The O-benzyl methylene protons resonated at $\delta$ 4.62 (s, 2H, -OCH$_2$Ph) while the aromatic ring protons resonated at $\delta$ 7.40-7.26 (m, 5H). The $^1$H-NMR spectroscopic data of this compound matched with those for 76 reported in the literature.$^{78}$

**Figure 3.1.** $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of compound 76

3.1.2. Synthesis of allyl dibenzyl acetal 77:
Following the procedure of Sato et al.$^{79}$ the allyl dibenzyl acetal was synthesized through
regioselective addition of benzyl alcohol to the 1,2-double bond of alkoxy allene 76 in
presence of an acid catalyst (Scheme 3.8). A solution of the benzyloxyallene in CH$_2$Cl$_2$
was stirred with benzyl alcohol at -10 °C in presence of $p$-toluenesulfonic acid (PTSA)
for 2 h. The crude product mixture was purified by column chromatography to afford
the corresponding acetal 77 in 66% yield.
This addition reaction takes place through generation of stable allyl cation (also stabilized by the electron donating OBn group) by regioselective protonation at the centre carbon of the allene, which then undergoes nucleophilic attack at the \( O \)-benzyl substituted \( \alpha \)-position affording the desired dibenzyl acetal 77 (Scheme 3.9).

**Scheme 3.9.** Mechanism of the addition reaction to 76

**Figure 3.2.** \(^1\)H-NMR spectrum (CDCl\(_3\), 500 MHz) of compound 77
The $^1$H-NMR spectrum of compound 77 (Figure 3.2) showed resonances for the terminal alkene protons at C1 at $\delta$ 5.37 (d, $J = 10.6$ Hz, 1H, H1 cis) and $\delta$ 5.51 (d, $J = 17.4$ Hz, 1H, H1 trans), respectively. The two O-benzyl methylene protons showed resonates at $\delta$ 4.58 (d, $J = 11.8$ Hz, 2H, C3-OCH$_2$H$_8$Ph) and $\delta$ 4.67 (d, $J = 11.8$ Hz, 2H, C3-OCH$_2$H$_8$Ph), respectively. The protons attached to C2 and C3 resonated at $\delta$ 5.95 (ddd, $J = 17.3, 10.6, 4.7$ Hz, 1H, H2) and $\delta$ 5.14 (d, $J = 4.6$ Hz, 1H, H3), respectively. It should be noted that the assignment for H1, H2 and H3 in the literature was not very specific ($\delta$ 6.14-5.10, m, 4H, H1, H2 and H3).

The $^{13}$C-NMR spectrum of compound 77 (Appendix B-1) showed resonances for the terminal alkene carbons at $\delta$ 119.1 (C1) and $\delta$ 135.6 (C2). The two O-benzyl methylene carbons resonated at $\delta$ 67.2 while C3 resonated at $\delta$ 100.3. The NMR spectroscopic data of compound 77 matched with those reported for 77 in the literature. The ESIMS data showed an [M+Na$^+$] ion peak at $m/z$ 277.3311 (calculated for C$_{17}$H$_{18}$O$_2$Na$: 277.3301) which confirmed the correct molecular formula of compound 77.

3.1.3. Attempted synthesis of benzyl allyl boronate 67:

Based on the report of Zhang et al., the 3-O-benzyl allylboronate can be prepared through the borylation of allyl dibenzyl acetal 77 with B$_2$(pin)$_2$ in presence of Ni(cod)$_2$ as catalyst (Scheme 3.10).

![Scheme 3.10. Proposed synthesis of compound 67](image)

The allyl dimethyl acetal was added to a mixture of Ni(cod)$_2$ and PCy$_3$ in THF under a nitrogen atmosphere. Then the B$_2$(pin)$_2$ was added then the reaction mixture was stirred at 60 °C for 12 h. TLC analysis was used to check the formation of the desired product. $^1$H-NMR analysis of the crude product mixture showed the presence of the starting material with no sign of product formation. The reaction was repeated using the PPh$_3$ as ligand, however no product formation was observed. During the reaction, a change of the Ni catalyst color from yellow to black was noticed in an early stage of the reaction. This was due to the air sensitivity of this catalyst. Due to
this and the lack of access to a glove box, PdCl$_2$ was used instead because of its commercially availability and its more air stable properties (Scheme 3.11).

![Scheme 3.11. Proposed synthesis of compound 67](image)

The allyl dimethyl acetal was added to a mixture of PdCl$_2$, B$_2$(pin)$_2$ and KOAc in THF, then the reaction mixture was stirred at 60 °C for 12 h. TLC analysis was used to check the formation of the desired product. TLC and $^1$H-NMR analysis of the crude product mixture showed the presence of the starting material with no sign of product formation. The reaction was repeated using toluene as the solvent with heating at 100 °C for 12 h, however no desired product could be isolated.

In summary, the metal-mediated borylation of allyl dibenzyl acetal 77 to synthesize the desired boronate 67 was not successful. The next section will focus on synthesis of its benzoyl derivative 68 following the procedure of Zhang et al.$^{80}$ procedure.

3.2. Synthesis of benzoyl allyl boronate 68:

The previous observations have indicated the inefficiency of allylboronate synthesis through the cross-coupling borylation of allyl dimethyl acetal substrate with B$_2$(pin)$_2$ in presence of Ni(cod)$_2$ or PdCl$_2$ as catalyst. A study conducted by Zhang et al.$^{80}$ indicated that allylboronate synthesis can be efficiently proceed via the cross-coupling reaction of organoboron reagents with the organic halides in presence of Pd catalyst and base. The base has a critical role in the cross-coupling borylation reaction. Based on Miyaura et al.$^{91}$ and Zhang et al.$^{80}$ reports, KOAc was the base of choice for this reaction. KOAc accelerates the crossing coupling reaction through acceleration of the transmetalation step.

This transformation takes place through several steps as shown in Scheme 3.12. First, the palladium(0) catalyst undergoes oxidative addition to the allyl halide to form π-allylPd(II)X. Then the base KOAc displaces the Pd halide to give the acetoxoPd(II) species (π-allylPd(II)OAc). Then transmetalation takes place between the π-allylPd(II)OAc and B$_2$(pin)$_2$ leading to formation of π-allyl(boryl)Pd(II) intermediate. Reductive elimination of π-allyl(boryl)Pd(II) intermediate affords the desired allyl
boronate product accompanied by regeneration of the initial palladium(0) catalyst complex.\textsuperscript{91}

\[ \text{Scheme 3.12. Proposed mechanism for the cross-coupling reaction in the presence of KOAc as base} \]

In contrast, other research studies conducted by Murata \textit{et al.} reported that using weak bases such as KOAc may lead to formation of undesirable byproducts, while using stronger bases such as tertiary amine (Et\textsubscript{3}N) afforded the desired allylboronate in high yield and selectivity.\textsuperscript{92,93}

3-\textit{O}-Benzoyl allyl boronate 68 was synthesized by the reaction involving 3-bromopropenyl benzoate 66\textit{b}, \textit{PdCl}_2, B\textsubscript{2}(pin)\textsubscript{2} and KOAc in THF, with stirring at 60 °C for 16 h (Scheme 3.13). TLC analysis was used to check the formation of the desired product. \textit{\textsuperscript{1}H-NMR} analysis of the crude reaction product mixture showed formation of the desired product. The crude product mixture was purified by column chromatography giving the desired allyl boronate 68 in 92% yield as the pure \textit{E} isomer. This compound has not been previously reported, although its MIDA analogue (\textit{N}-methylimidodiacetic acid) is known.\textsuperscript{94}

\[ \text{Scheme 3.13. Synthesis of compound 68} \]
The $^1$H-NMR spectrum of this compound 68 (Figure 3.3) showed resonances for the vinyl protons of C2 and C3 at $\delta$ 5.65 (dt, $J = 12.0, 8.0$ Hz, 1H, H2) and $\delta$ 7.31 (d, $J = 12.0$ Hz, 1H, H3), respectively. The methylene protons attached to the boron resonated at $\delta$ 1.69 (d, $J = 8.0$ Hz, 2H). The methyl protons attached to boronate ester ring resonated at $\delta$ 1.32-1.18 (m, 12 H). The phenyl ring protons resonated at $\delta$ 7.46 (dt, $J = 9.8, 7.7$ Hz, 2H, H2' and 4'), 7.64-7.53 (m, 1H, H3') and 8.09 (t, $J = 8.3$ Hz, 2H, H1' and 5'). The $E$-configuration of 68 was based on the magnitude of $J_{2,3}$ of 12.0 Hz. In the analogous $\gamma$-methoxy-allyl boronate, the $E$-isomer has a $J_{2,3}$ value of 12.6 Hz, while for the $Z$-isomer $J_{2,3} = 6.5$ Hz.
The \(^{13}\)C-NMR spectrum of compound 68 (Figure 3.4) showed resonances for the vinyl carbons C2 and C3 at \(\delta 111.2\) and \(\delta 135.7\), respectively. The carbon signal for C1 resonated at \(\delta 38.6\) while the methyl carbons attached to the boronate ester ring resonated at \(\delta 24.6\). The two quaternary carbons C7' and C8' in the boronate ester ring resonated at \(\delta 83.3\) and \(\delta 83.7\), which probably correspond to the RB(OH)OC(Me\(_2\))C(Me\(_2\))OH species, that formed due to hydrolysis of the boron ester group. The LRMS showed some ion peaks between \(m/z\) 300 and 311. Furthermore, there were several peaks assigned to the aromatic carbons (Ar-C) at \(\delta 128.54\) (C2'), \(\delta 128.57\) (C4'), \(\delta 130.0\) (C1'), \(\delta 130.3\) (C5') and \(\delta 133.4\) (C3'). Assignment of both the \(^1\)H-NMR and \(^{13}\)C-NMR spectra was confirmed through running of gCOSY (Appendix B-4) and gHSQC (Appendix B-5) experiments. The ESIMS data showed an [M+Na\(^+\)] ion peak at \(m/z\) 311.1444 (calculated for \(C_{16}H_{21}BO_4Na^+: 311.1431\) which confirmed the correct molecular formula of compound 68.
3.3. Model reactions using preformed imines and 3-O-benzoyl allyl boronate 68:
In this section, the allylation reactions of different imines with 3-O-benzoyl allyl boronate 68 will be examined. Furthermore, the stereochemistry of the obtained 1,2 amino alcohols will be investigated.

3.3.1. Using preformed imine derived from salicylaldehyde and benzylamine:
As a model study of the use of benzoyl allyl boronate 68 as an allylating agent the reaction of the N-benzylimine 73 with 3-O-benzoyl allyl boronate 68 was examined (Scheme 3.14).

Scheme 3.14. Synthesis of racemic compound 78

The N-benzylimine 73 was dissolved in chloroform-d (CDCl₃) under a nitrogen atmosphere, and then the 3-O-benzoyl allyl boronate 68 (1 equiv) was added to the reaction mixture and then stirred at rt for 5 min (Table 3.1., entry 1). Then an aliquot of the crude reaction mixture was analyzed by ¹H-NMR spectroscopy which indicated no product formation. By repeating the reaction with stirring for 1 h under the same reaction conditions (Table 3.1., entry 2), initial formation of the product was observed by ¹H-NMR analysis of an aliquot of the reaction mixture. Repeating the reaction in CDCl₃ for a longer time (16 h) resulted in the desired amino allyl product 78 in 15% yield (Table 3.1., entry 3).
In attempt to optimize the yield of this reaction, different reaction conditions were examined (Table 3.1.). We repeated the reaction by using different molar equivalents of the 3-\textit{O}-benzoyl allyl boronate 68 (1, 1.5 and 2 equiv), and the reaction mixture was then stirred at rt for different period of time (5 min, 10 min and 15 min) which gave the desired product, in 21%, 23% and 25% yields, respectively (Table 3.1., entry 4, 5 and 6). The
best result was obtained when 2 equiv of the 3-O-benzyol allyl boronate 68 was used and the reaction was stirred at rt for 16 h. The crude reaction product was purified by column chromatography to give the desired product in 27% yield (Table 3.1., entry 7). In other attempts, the reaction was examined with DCM and DMF as solvents, however limited product formation was observed (Table 3.1., entry 8, 9 and 10).

Practically it was noticed the limited shelf stability of 3-O-benzyol allyl boronate 68 although it was stored under inert conditions. The $^1$H-NMR analysis of a stored sample of the allyl boronate showed decomposition was occurring from the additional resonances observed. For this reason, we thought that using a fresh sample of the allyl boronate may improve the reaction yields. The reaction of the preformed N-benzylimine 73 with freshly prepared 3-O-benzyol allyl boronate 68 in MeOH was re-examined (Table 3.1., entry 11). The crude reaction product was purified by column chromatography to give the amino allyl alcohol product 78 in 69% yield and in high diastereoselectivity (dr = 95:5) as determined by integration of the $^1$H-NMR doublet resonances at $\delta$ 4.05 and $\delta$ 4.15 for H4 for the major and minor diastereomers, respectively (Figure 3.5). By comparing the results in entries 7 and 11, using a freshly prepared sample of boronate 68 has markedly increased the yield of compound 78 from 27% to 69%. Therefore, the following described reactions were set up using freshly prepared samples of 68.

![Figure 3.5. $^1$H-NMR spectrum (CDCl$_3$, 300 MHz) of compound 78](image-url)
The $^1$H-NMR spectrum of compound 78 (Figure 3.5) showed resonances for the vinyl H1 protons at $\delta$ 5.20 (d, $J_{cis} = 9.0$ Hz, 1H) and (d, $J_{trans} = 17.1$ Hz, 1H). The diastereotopic N-benzyl methylene protons resonated as doublets at $\delta$ 3.93 (d, $J = 13.2$ Hz, 1H, H$a$) and $\delta$ 3.63 (d, $J = 13.2$ Hz, 1H, H$b$) while H2 and H3 resonated at $\delta$ 5.77-5.64 (m, 2H, H2 and H3). The proton attached to C4 resonated at $\delta$ 4.05 (d, $J = 7.3$ Hz, 1H, H4). The phenyl ring protons of the benzyl moiety resonated at $\delta$ 7.38-7.18 (m, 5H). The other aromatic ring protons resonated at $\delta$ 6.96 (dd, $J = 7.6$, 1.7 Hz, 1H, H10) and $\delta$ 6.83 (dt, $J = 7.5$, 1.5 Hz, 2H, H8 and H9). The hydroxy group proton resonated at $\delta$ 11.45 (s, 1H). The phenyl ring protons of the benzoate group resonated at $\delta$ 8.04 (d, $J = 7.5$ Hz, 1H, H2'), $\delta$ 7.58 (t, $J = 7.4$ Hz, 1H, H3') and $\delta$ 7.45 (t, $J = 7.6$ Hz, 1H, H4')

![Figure 3.6. $^{13}$C-NMR spectrum (CDCl₃, 75 MHz) of compound 78](image)

The $^{13}$C-NMR spectrum of compound 78 (Figure 3.6) showed resonances for the terminal alkene carbons at $\delta$ 118.9 (C1) and $\delta$ 133.2 (C2). The N-benzyl methylene carbon resonated at $\delta$ 51.2 (C4-NHCH₃Ph). The carbon signals for C3 and C4 were at $\delta$ 76.6 and $\delta$ 65.6, respectively. The carbon attached to the hydroxy group resonated at $\delta$ 158.2. The phenyl ring carbons 8, 9 and 10 resonated at $\delta$ 119.2, 117.2 and 130.7, respectively. The phenyl ring carbons 2', 3' and 4' resonated at 129.8, 133.4 and 128.6 ppm, respectively. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running
of gCOSY (Figure 3.7) and gHSQC (Figure 3.8) experiments. The ESIMS data showed an [M+H$^+$] ion peak at $m/z$ 374.1739 (calculated for C$_{24}$H$_{24}$NO$_3$+: 374.1756) which confirmed the correct molecular formula of compound 78.

**Figure 3.7.** gCOSY experiment of compound 78

**Figure 3.8.** gHSQC experiment of compound 78
3.3.2. Determination of the relative stereochemistry of 78 via derivatisation:
The relative stereochemistry of 1,2-amino alcohols can be verified through conversion to their corresponding oxazolidinone derivatives. The $^1$H-NMR coupling constants values of the vicinal protons at C4 and C5 along with NOE studies have been used to assign the relative stereochemistry of the starting amino alcohol. Futagawa et al. indicated that oxazolidinones with vicinal coupling constant $J_{4,5} = 4$ to $6$ Hz, are consistent with trans-4,5-stereochemistry which confirm the syn-stereochemistry structure of the starting amino alcohol compound. On the other hand, the vicinal coupling constants of oxazolidinones with cis-4,5-stereochemistry ranges from $J_{4,5} = 7$ to $10$ Hz, which can be used to assign the anti-stereochemistry of the starting amino alcohol compound.

To achieve this, first the benzoyl group at C3 in compound 78 needs to be deprotected then the deprotected compound 79 will be treated with triphosgene and Et$_3$N to give the desired oxazolidinone 80 (Scheme 3.15).

![Scheme 3.15. Proposed synthesis of oxazolidinone 80](image)

The benzoyl group at C3 in compound 78 was deprotected through hydrolysis of the benzoate in the presence of K$_2$CO$_3$ and MeOH (Scheme 3.16). The crude reaction mixture was analyzed by $^1$H-NMR spectroscopy which indicated the desired product had formed. After work up the crude product was purified by column chromatography to give compound 79 in 61% yield.

![Scheme 3.16. Synthesis of compound 79](image)
The $^1$H-NMR spectrum of compound 79 (Figure 3.9) showed resonances for the terminal alkene protons attached to C1 at $\delta$ 5.08 (d, $J = 10.5$ Hz, 1H, H1 \textit{cis}) and $\delta$ 5.14 (d, $J = 17.4$ Hz, 1H, H1 \textit{trans}). The diastereotopic $N$-benzyl methylene protons resonated at $\delta$ 3.85 (d, $J = 13.0$ Hz, 1H, Ha) and $\delta$ 3.59 (d, $J = 13.0$ Hz, 1H, Hb). The H2, H3 and H4 protons resonated at $\delta$ 5.70 (ddd, $J = 16.6$, 10.5, 5.6 Hz, 1H), $\delta$ 4.38 (t, $J = 8.4$ Hz, 1H) and $\delta$ 3.66 (d, $J = 8.7$ Hz, 1H), respectively. The phenyl ring protons of the $N$-benzyl group resonated at $\delta$ 6.78 (t, $J = 7.3$ Hz, p-position, 1H) while the other aromatic protons resonated at $\delta$ 6.87 (dd, $J =11.1$, 7.5 Hz, 1H, H3'), $\delta$ 7.19 (td, $J =7.7$, 1.7 Hz, 1H, H4') and $\delta$ 7.30 (dd, $J =15.9$, 6.0 Hz, 1H, H6').
The $^{13}$C-NMR spectrum of compound 79 (Figure 3.10) showed resonances for the terminal alkene carbons at $\delta$ 116.9 (C1) and $\delta$ 137.6 (C2). The N-benzyl methylene carbon resonated at $\delta$ 51.2 (C4-NHC\textsubscript{2}H\textsubscript{2}Ph). The carbon signals for C3 and C4 were at $\delta$ 73.9 and $\delta$ 68.2, respectively. The aromatic carbon attached to the hydroxy group resonated at $\delta$ 158.0. A phenyl ring carbon resonated at $\delta$ 119.0 ($p$-position) while the other aromatic carbons C3’, C4’ and C6’ resonated at $\delta$ 130.8, 129.2 and 128.6, respectively. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix B-6) and gHSQC (Appendix B-7) experiments. The ESIMS data showed an [M+H$^+$] ion peak at $m/z$ 270.1486 (calculated for C\textsubscript{17}H\textsubscript{20}NO\textsubscript{2}$^+$: 270.1494) which confirmed the correct molecular formula of compound 79.

The relative stereochemistry of 1,2-amino alcohol 78 can be verified now through conversion of compound 79 to its corresponding oxazolidinone derivative 80 using triphosgene (Scheme 3.17).\textsuperscript{97}

Scheme 3.17. Attempted synthesis of compound 80

A solution of the amino alcohol 79 in DCM under an atmosphere of nitrogen was treated with Et\textsubscript{3}N and triphosgene at 0°C. Then the reaction mixture was warmed to rt and allowed to stir for 16 h. The crude reaction mixture was then washed with H\textsubscript{2}O and extracted with DCM. The $^1$H-NMR spectrum of the crude reaction product mixture was not clear enough to verify whether the desired product was formed or not. However, after purification of the crude product by column chromatography no desired product could be isolated. Due to the failure in the synthesis of the oxazolidinone 80, the next section will
discuss determination of the relative stereochemistry of 78 via comparison of the coupling constant value \((J_{3,4})\) of compound 78 with similar compounds from the literature.

### 3.3.3. Determination of relative stereochemistry of 78 via literature comparisons:

In 2009 Venkataiah et al. reported the synthesis of \((1S,2S)-N\)-allyl-2-(benzyloxy)-1-phenylbut-3-en-1-amine 82 through stereoselective addition of phenyl Grignard reagent (phenylmagnesium bromide) to the allyl imine 81 (Scheme 3.18). The amino alcohol 82 was afforded in 78% yield with the \(\text{syn}\) configuration. The mechanism of this reaction was illustrated via a chelation-control Cram model, through coordination of the \(O\)-benzyl with the metal ion forming an \(\alpha\)-chelate intermediate (Scheme 3.19).

![Scheme 3.18. Synthesis of compound 82](image)

Scheme 3.18. Synthesis of compound 82

![alpha-chelate intermediate](image)

alpha-chelate intermediate

![syn-addition](image)

syn-addition

Scheme 3.19. Proposed mechanism of \(\alpha\)-chelate controlled \(\text{syn}\) addition

The reported \(^1\text{H}-\text{NMR}\) data of the amino alcohol 82, indicated that the protons attached to C3 and C4 resonated at \(\delta\) 3.82 (t, \(J = 7.9\) Hz, 1H) and \(\delta\) 3.69 (d, \(J = 8.1\) Hz, 1H), respectively. Based on the structural similarity between our compound 78 and the literature compound 82, we assumed that the configuration of our compound 78 can be determined by comparing the coupling constant values of H3 and H4 \((J_{3,4})\) with the reported coupling constant of compound 82 (Scheme 3.20). The \(^1\text{H}-\text{NMR}\) spectrum of compound 78 (Figure 3.5) showed resonances for H3 and H4 at \(\delta\) 5.64 (m, 1H) and \(\delta\) 4.05
(d, $J = 7.3$ Hz, 1H), respectively. Based on the quite similarity between the coupling constant values of our racemic compound 78 ($J_{3,4} = 7.3$ Hz) and literature compound 82 ($J_{3,4} = 8.1$ Hz), compound 78 was tentatively assigned with syn-relative configuration (Scheme 3.20). It should be noted that the NMR data on anti amino alcohols related to 82 are not available in the literature.

Scheme 3.20. Comparison of $J_{3,4}$ values for similar compounds 78 and 82

The syn-configuration of compound 78 can be afforded via reaction of the imine with 3-$O$-benzoyl allyl boronate 68 at the $\gamma$-position of the allyl boron reagent resulting in allyl transposition. The mechanism of this configuration is believed to be proceed through six-membered cyclic chair transition state (TS), in which the imine group substituents $R^1$ and $R^2$ are in an $E$-geometry and occupy pseudo axial positions. This way of arrangement of the substituents in the TS structure leads to formation of the product in the syn form (Scheme 3.21).
3.4. Model reactions using preformed imines derived from salicylaldehyde and other amines using freshly prepared 3-O-benzoyl allyl boronate 68:

To further examine the scope of this reaction by varying the amine component the imines 83, 84 and 85 were prepared first according to Scheme 3.22.  

\[
\begin{align*}
\text{Scheme 3.22. Imine synthesis}
\end{align*}
\]  

The NMR spectroscopic data for the imines 83 and 85 (Appendix B-8 to B-11) and (Appendix B-15 to B-18), respectively were identical to the literature values. While imine 84 is a known compound, its NMR data were not reported. The \(^1\)H-NMR spectrum of compound 84 (Figure 3.11) showed a singlet resonance for the O-methyl and N-benzylic protons at \(\delta 3.81\) (s, 3H, OCH\(_3\)) and \(\delta 4.75\) (s, 2H, C=NC\(_\text{H}_2\)Ph), respectively. The \(\text{HC}=\text{NCH}_2\text{Ph}\) proton resonated at \(\delta 8.41\) (s, 1H). The aromatic ring protons attached
to the PMB group resonated at $\delta$ 6.89 (d, $J = 8.1$ Hz, 2H, H2 and H6) and $\delta$ 6.96 (d, $J = 8.4$ Hz, 2H, H3 and H5). The other aromatic ring protons resonated at $\delta$ 7.26 (m, 4H). The hydroxy group proton resonated at $\delta$ 13.44 (s, 1H, OH), its highly downfield chemical shift indicated it was H-bonded to the imine nitrogen. The $^{13}$C-NMR spectrum of compound 84 (Appendix B-12) showed a signal for the HC=N carbon at $\delta$ 165.3. The N-benzyl carbon (-NHCH$_2$Ph) resonated at $\delta$ 62.7. The resonance at $\delta$ 161.2 was for the carbon C2' attached to the hydroxy group. The methoxy group carbon resonated at $\delta$ 55.5 while the aromatic ring carbons C2 and C6 at $\delta$ 129.2, C3 and C5 at $\delta$ 114.2, and C4 resonated at $\delta$ 159.0. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix B-13) and gHSQC (Appendix B-14) experiments. The ESIMS data showed an [M+H$^+$] ion peak at $m/z$ 242.1192 (calculated for C$_{15}$H$_{16}$NO$_2$+: 242.1181) which confirmed the correct molecular formula of compound 84.

![Figure 3.11. $^1$H-NMR spectrum (CDCl$_3$, 300 MHz) of imine 84](image)

The results of the reactions of 3-O-benzoyl allyl boronate 68 with imines 83, 84 and 85 follows in the next sections.
3.4.1. Using preformed imine derived from salicylaldehyde and allyl amine:

As a model study of the use of benzoyl allyl boronate 68 as an allylating agent the reaction of the N-allylimine 83 with benzoyl allyl boronate 68 was examined (Scheme 3.23).

![Scheme 3.23. Synthesis of racemic compound 86](image)

The N-allylimine 83 was treated with a freshly prepared benzoyl allyl boronate 68 in MeOH at rt for 16 h. Then the crude reaction mixture was analyzed by $^1$H-NMR spectroscopy which indicated formation of the desired product with presence of fair amount of the starting allylimine. The crude reaction product was purified by column chromatography to give the desired product 86 in 47% yield and in high diastereoselectivity (dr = 95:5) as determined by integration of the $^1$H-NMR doublet resonances at $\delta$ 4.11 and $\delta$ 4.19 for H4 in the major and minor diastereomers (Appendix B-19). Copies of the NMR spectra for the product 86 are reported in Appendix B-19 to B-22.

3.4.2. Using preformed imine derived from salicylaldehyde and p-methoxybenzyl amine:

The N-(p-methoxy)-benzylimine 84 was treated with a freshly prepared 3-O-benzoyl allyl boronate 68 in MeOH at rt for 16 h (Scheme 3.24). Then the crude reaction mixture was analyzed by $^1$H-NMR spectroscopy which indicated formation of the desired product with presence of fair amount of the starting imine 84. The crude reaction product was purified by column chromatography to give the desired product 87 in 40% yield and in high diastereoselectivity (dr = 95:5) as determined by integration of the $^1$H-NMR doublet resonances at $\delta$ 8.04 and $\delta$ 7.79 for H2' in the major and minor diastereomers (Appendix B-23). Copies of the NMR spectra for the product 87 are reported in Appendix B-23 to B-26.
3.4.3. Using preformed imine derived from salicylaldehyde and N-diphenylmethanamine:
The reaction of N-diphenylmethanamine 85 with benzoyl allyl boronate 68 was then examined (Scheme 3.25). The imine 85 was treated with a freshly prepared benzoyl allyl boronate 68 in MeOH at rt for 16 h. Then the crude reaction mixture was analyzed by $^1$H-NMR spectroscopy which indicated formation of the desired product with presence of fair amount of the starting imine 85. The crude reaction product was purified by column chromatography to give the desired product 88 in 31% yield and in high diastereoselectivity (dr = 91:9) as determined by integration of the $^1$H-NMR doublet resonances at δ 5.14 and δ 5.32 for H1 in the major and minor diastereomers (Appendix B-27). Copies of the NMR spectra for the product 88 are reported in Appendix B-27 to B-30.

3.4.4. Using preformed imine derived from the methyl ether of salicylaldehyde and benzylamine:
To examine the effect of the ortho-hydroxy group on the imine, the reaction of a freshly prepared 3-O-allyl boronate 68 with N-benzyl-2-methoxyphenyl imine 89 was examined under identical reaction conditions as described earlier (Scheme 3.26).
The crude reaction product was purified by column chromatography to give the desired product **90** in 26% yield as a mixture of two isomers (dr = 42:58) as determined by integration of the $^1$H-NMR doublet resonances at $\delta$ 4.40 and $\delta$ 4.34 for H4 in the major and minor diastereomers, respectively (Figure 3.12). The corresponding alcohol product **91** was also formed in 24% yield (dr = 100:0).

As previously stated in the proposed mechanism of this reaction, we recognized importance of the E-geometry in imines used in our reaction to afford the allyl amino alcohols in the syn form. In 1966, Curtin et al. presumed that at ambient temperature, $N$-aryl imines in solution found to be exist in an equilibrium between E and Z isomers. However, after recrystallization these imines present as a single stereoisomer. The ratio of E/Z imine isomers in solution may vary based on several factors such as stabilization, steric and resonance factors. To avoid the steric repulsive interactions, the C-bulkier substituent on the imine carbon prefers to be trans to the imine $N$-substituent. For that reason, aldimines prefer existence in the E-configuration. Furthermore, other studies reported that substitution on the C-phenyl group of the imine at the ortho position have an effect on the E/Z ratio. Based on our results, it was observed that allyl amino alcohol **78** formed from reaction of 3-$O$-allyl boronate **68** with the $N$-benzylimine **73** showed high diastereoselectivity, in comparison with the allyl amino alcohol **90** formed from the reaction of allyl boronate **68** with the $N$-benzyl-2-methoxyphenyl imine **89**. We presume that diastereoselectivity of our reaction mainly depends on the presence of the ortho-hydroxy substituent on the imine carbon. When the hydroxy group was replaced by a methoxy group, the stereoselectivity of the allyl amino alcohol decreased markedly from (dr = 95:5 to dr = 42:58), as noticed in products **78** and **90**, respectively.
the \textit{ortho}-hydroxy group on the imine carbon in a free form, enforce the \textit{syn}-configuration of the product through formation of H-bonding with the axial oxygen atom of the dioxaborolane (Scheme 3.27a), while introducing a methoxy group at the \textit{O}-position destabilized the \textit{syn}-transition state (TS) due to the unfavorable steric interactions and perhaps the an alternative TS involving the \textit{Z}-imine is also involved (Scheme 3.27b).

\textbf{Scheme 3.27. (a, b) Proposed mechanism of effect of the O-hydroxy substituent of the imine on diastereoselectivity}

The corresponding alcohol product 91 was first synthesized in this project as no literature match was found. The relative stereochemistry was determined via comparing the coupling constant value ($J_{3,4}$) of compound 91 with similar compounds from the literature.

Lombardo \textit{et al.}\textsuperscript{66} developed an In-mediated synthesis of the alken-1-ene-3,4-diol 92 by reaction of the bromide ester 66a with benzaldehyde (Scheme 3.28). The desired 3,4-diol 92 was afforded in a mixture with other side products including the monoacylated compound 93, which was obtained in 13\% ($\text{syn:anti} = 95:5$).
Scheme 3.28. Synthesis of compound 92

The reported $^1$H-NMR data of compound 93, indicated that the protons attached to C3 and C4 of the syn-isomer resonated at $\delta$ 4.76 (d, $J = 6.5$ Hz, 1H) and $\delta$ 5.42-5.52 (m, 1H), while H3 and H4 of the anti-isomer were at $\delta$ 4.90 (d, $J = 4.4$ Hz, 1H) and $\delta$ 5.48 (ddt, $J = 6.8, 4.4, 1.2$ Hz, 1H), respectively. Based on the structural similarity between compound 91 and the literature compound 93, it was assumed that the configuration of compound 91 can be determined by comparing the coupling constant values of H3 and H4 ($J_{3,4}$) with the reported coupling constant of compound 93 (Scheme 3.29). The $^1$H-NMR spectrum of compound 91 (Figure 3.14) showed resonances for H3 and H4 at $\delta$ 5.84 (t, $J = 5.7$ Hz, 1H) and $\delta$ 5.19 (t, $J = 5.8$ Hz, 1H), respectively. Based on the quite similarity between the coupling constant values of compound 91 ($J_{3,4} = 5.8$ Hz) and the syn-isomer of literature compound 93 ($J_{3,4} = 6.5$ Hz), compound 91 was tentatively assigned with syn-relative configuration (Scheme 3.29).
The $^1$H-NMR spectrum of compound 90 (Figure 3.12) showed resonances for the vinyl protons H1 of the major isomer at $\delta$ 5.23 (dd, $J = 14.1, 10.2 \text{ Hz}, 2\text{H})$ while for the minor isomer the H1 protons were at $\delta$ 5.11 (dd, $J = 13.8, 5.1 \text{ Hz}, 2\text{H})$. The diastereotopic N-benzyl methylene protons resonated at $\delta$ 3.61 (d, $J = 13.5 \text{ Hz}, 2\text{H}, \text{C4-NHC}_2\text{H}_2\text{Ph}, \text{major isomer})$ and $\delta$ 3.54 (d, $J = 13.5 \text{ Hz}, 2\text{H}, \text{C4-NHC}_2\text{H}_2\text{Ph}, \text{minor isomer})$. The other vinyl proton H2 resonated at $\delta$ 6.02-5.90 (m, 1H, H2) and H3 proton was at $\delta$ 5.86-5.74 (m, 1H, H3). The H4 proton resonated at $\delta$ 4.40 (d, $J = 6.0 \text{ Hz}, 1\text{H}, \text{major isomer})$ and at $\delta$ 4.34 (d, $J = 6.3 \text{ Hz}, 1\text{H}, \text{minor isomer})$. The methoxy group protons resonated at $\delta$ 3.82 (s, 3H, major) and at $\delta$ 3.75 (s, 3H, minor). The aromatic ring protons attached to the benzoate group resonated at $\delta$ 8.03 (d, $J = 7.2 \text{ Hz}, 1\text{H}, \text{H2}', \text{minor isomer}), \delta$ 7.92 (d, $J = 7.5 \text{ Hz}, 1\text{H}, \text{H2}', \text{major isomer})$ and $\delta$ 7.62-7.45 (m, 1H, H3', H4', H5' and H6'). The aromatic ring protons of the benzyl moiety resonated at $\delta$ 7.39-7.18 (m, 5H) while the other aromatic ring protons resonated at $\delta$ 6.96 (dd, $J = 7.8, 15.6 \text{ Hz}, 1\text{H}, \text{H10}), \delta$ 6.87 (d, $J = 8.1 \text{ Hz}, 1\text{H}, \text{H9})$ and $\delta$ 7.50-7.33 (m, 2H, H7 and H8).
The $^{13}$C-NMR spectrum of compound 90 (Figure 3.13) showed resonances for two diastereoisomers (doubling of peaks was observed for most resonances). The terminal alkene carbon C1 resonated at $\delta$ 117.8 (major isomer) and $\delta$ 117.7 (minor isomer) while C2 was at $\delta$ 134.0 (major) and $\delta$ 134.3 (minor). The N-benzyl methylene carbon (C4-NHCH$_2$Ph) resonated at $\delta$ 51.6 (major) and $\delta$ 51.3 (minor). The carbon signals for C3 were at $\delta$ 77.7 (major) and $\delta$ 76.8 (minor) while C4 resonated at $\delta$ 59.5 (major) and $\delta$ 59.2 (minor). The methoxy group carbon resonated at $\delta$ 55.5 (major) and $\delta$ 55.3 (minor). The aromatic ring carbons C9 and C10 resonated at $\delta$ 110.6 and $\delta$ 120.6, respectively. The aromatic C2' attached to the benzoate group resonated at $\delta$ 129.7 (major) and $\delta$ 129.8 (minor). The carbonyl carbon of the benzoate group resonated at $\delta$ 165.5 (major) and $\delta$ 165.9 (minor). There are multiple signals for the aromatic carbons resonated between $\delta$ 132.8-128.3. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix B-31) and gHSQC (Appendix B-32) experiments. The ESIMS data showed an [M+H$^+$] ion peak at m/z 388.1917 (calculated for C$_{25}$H$_{26}$NO$_3^+$: 388.1913) which confirmed the correct molecular formula of compound 90.
The $^1$H-NMR spectrum of compound 91 (Figure 3.14) showed resonances for the vinyl protons H1 and H2 at $\delta$ 5.39 - 5.24 (m, 2H, H1) and $\delta$ 5.98 (ddd, $J = 16.9, 10.6, 6.0$ Hz, 1H, H2), respectively while H3 and H4 resonated at $\delta$ 5.84 (t, $J = 5.7$ Hz, 1H, H3) and $\delta$ 5.19 (t, $J = 5.8$ Hz, 1H, H4), respectively. The methoxy group protons resonated at $\delta$ 3.87 (s, 3H). The aromatic ring protons attached to the benzoate group resonated at $\delta$ 8.02 (d, $J = 7.7$ Hz, 2H, H2' and H6'), $\delta$ 7.56 (t, $J = 7.4$ Hz, 1H, H4') and $\delta$ 7.42 (dd, $J = 7.5, 15.3$ Hz, 2H, H3' and H5') while the other aromatic ring protons resonated at $\delta$ 6.95 (t, $J = 7.5$ Hz, 1H, H10), $\delta$ 6.88 (d, $J = 8.1$ Hz, 1H, H9) and $\delta$ 7.26 (t, $J = 8.7$ Hz, 2H, H7 and H8).
The $^{13}$C-NMR spectrum of compound 91 (Figure 3.34) showed resonances for the terminal alkene carbons at $\delta$ 118.8 (C1) and $\delta$ 132.7 (C2) while C3 and C4 were at $\delta$ 70.1 and $\delta$ 72.5, respectively. The methoxy group carbon resonated at $\delta$ 55.5. The aromatic ring carbons 2’ and 4’ attached to the benzoate group resonated at $\delta$ 129.8 (C2’) and $\delta$ 133.2 (C4’). The other aromatic ring carbons C9, C10 and C6 resonated at $\delta$ 110.6, 120.7 and 156.7, respectively. The carbonyl carbon of the benzoate group resonated at $\delta$ 165.5.

There are multiple signals for the aromatic carbons between $\delta$ 129.2-128.4 correspond to C7, C8, C3’ and C5’. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix B-33) and gHSQC (Appendix B-34) experiments. The ESIMS data showed an [M+Na$^+$] ion peak at $m/z$ 321.1107 (calculated for C$_{18}$H$_{18}$O$_4$Na$^+$: 321.1103) which confirmed the correct molecular formula of compound 91.

The results of the reactions of benzoyl 3-O-allyl boronate 68 with imines 73, 83, 84, 85 and 89 are summarized in Table 3.2.
Table 3.2. Summary of the reactions of the 3-O-allyl boronate 68 with different imines

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
<th>δr (syn:anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>H</td>
<td>Ph</td>
<td>69%</td>
<td>95:5</td>
</tr>
<tr>
<td>86</td>
<td>H</td>
<td></td>
<td>47%</td>
<td>95:5</td>
</tr>
<tr>
<td>87</td>
<td>H</td>
<td>OMe</td>
<td>40%</td>
<td>95:5</td>
</tr>
<tr>
<td>88</td>
<td>H</td>
<td>Ph</td>
<td>31%</td>
<td>91:9</td>
</tr>
<tr>
<td>90</td>
<td>Me</td>
<td>Ph</td>
<td>26%</td>
<td>42:58</td>
</tr>
<tr>
<td>91</td>
<td></td>
<td>Ph</td>
<td>24%</td>
<td>100:0</td>
</tr>
</tbody>
</table>

Table 3.2 summarizes the results of reaction of the 3-O-allyl boronate 68 with the five different imines. The N-benzyl imine gave the highest yield; however, all reactions were highly diastereoselective except the reaction with imine 89, where the hydroxy substituent on the imine carbon was occupied by a methoxy group. The $J_{3,4}$ coupling constants and $^{13}$C-NMR chemical shifts for C3 and C4 for these four products 78, 86, 87 and 88 suggested that they all had the same, syn relative configurations (Table 3.3), while the reaction with imine 89 gave a diastereomeric mixture of 90 ($syn:anti = 42:58$).

Table 3.3. Comparison of $J_{3,4}$ values for 78, 86, 87, 88 and 90

<table>
<thead>
<tr>
<th>Product</th>
<th>$\delta_{H3}$</th>
<th>$\delta_{H4}$</th>
<th>$\delta_C$ C3</th>
<th>$\delta_C$ C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>5.64 (m)</td>
<td>4.05 (d, $J = 7.3$ Hz)</td>
<td>76.6</td>
<td>65.6</td>
</tr>
<tr>
<td>86</td>
<td>5.75 (m)</td>
<td>4.11 (d, $J = 7.1$ Hz)</td>
<td>76.8</td>
<td>65.6</td>
</tr>
<tr>
<td>87</td>
<td>5.63 (m)</td>
<td>4.08 (d, $J = 6.9$ Hz)</td>
<td>76.8</td>
<td>65.4</td>
</tr>
<tr>
<td>88</td>
<td>5.80 (dd, $J = 7.9, 6.0$ Hz)</td>
<td>3.91 (d, $J = 8.0$ Hz)</td>
<td>76.7</td>
<td>64.1</td>
</tr>
<tr>
<td>90</td>
<td>5.80 (m)</td>
<td>4.40 (d, $J = 6.0$ Hz, maj)</td>
<td>77.7 maj</td>
<td>59.5 maj</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.34 (d, $J = 6.3$ Hz, min)</td>
<td>76.8 min</td>
<td>59.2 min</td>
</tr>
</tbody>
</table>

3.5. Three component model reactions using freshly prepared 3-0-benzoyl allyl boronate 68:

3.5.1. Using salicylaldehyde and benzylamine:

The one pot, three component allylation reaction between salicylaldehyde, N-benzylamine and the freshly prepared 3-0-benzoyl allyl boronate 68 to produce syn-1,2 amino alcohol 78, was also examined (Scheme 3.30).

![Scheme 3.30. One pot, three components synthesis of racemic compound 78](image)

The benzylamine was added to the salicylaldehyde 71 in MeOH and then the mixture was stirred at 45 °C for 1 h, then at room temperature for 2 h to form the corresponding imine 73 in situ. Then freshly prepared benzoyl allyl boronate 68 was added to the reaction mixture and stirring was continued at rt for 16 h. The crude reaction product was purified by column chromatography to give the desired product 78 in 32% yield and in good diastereoselectivity (dr = 88:12). In terms of yield and diastereoselectivity, the synthesis of the syn-1,2 amino alcohol 78 from the preformed imine (69%, dr = 95:5) was more efficient than the one pot, three component reaction (32%, dr = 88:12). The lower yield and diastereoselectivity compared to the reaction of 68 with preformed imine 73 may be due to the effect of the 1 equiv of water generated in the one pot reaction which could disrupt the H-bonding in the (TS) shown in Scheme 3.27.
3.5.2. Using the methyl ether of salicylaldehyde and benzylamine:
The one pot, three component allylation reaction between 2-methoxybenzylaldehyde, N-benzylamine and the freshly prepared 3-O-benzoyl allyl boronate 68 to produce syn-1,2 amino alcohol 90, was also examined under the reaction conditions described above (Scheme 3.31).

Scheme 3.31. One pot, three components synthesis of racemic compound 90

The crude reaction product was purified by column chromatography to give the desired product 90 in 25% yield as a mixture of two isomers (syn:anti = 32:68). In terms of yield and diastereoselectivity, the synthesis of the syn-1,2 amino alcohol 90 from the preformed imine 89 (26%, dr = 42:58) was quite similar to the results obtained from the one pot, three component reaction (25%, dr = 32:68).

3.5.3. Using salicylaldehyde and morpholine:
The one pot, three component allylation reaction between salicylaldehyde, morpholine and the freshly prepared benzyol allyl boronate 68 to produce syn-1,2 amino alcohol product 94, was also examined under the reaction conditions described above (Scheme 3.32). The crude reaction product mixture was analyzed by 1H-NMR spectroscopy which showed the presence of the alcohol adduct 91 in trace amount. The lack of reactivity for the morpholine may be due to the slow formation of the iminium ion, which consequently led to formation of the alcohol product.
**Scheme 3.32.** Attempted one pot, three components synthesis of compound 94

Table 3.4 summarizes the results of one pot, three component reactions of aldehydes (salicylaldehyde, methoxybenzaldehyde), amines (benzylamine, morpholine) with the allyl boronate 68. In summary, the reaction of 3-O-benzoyl allyl boronate 68 with the preformed benzylimine was more efficient than the three, component reaction using salicylaldehyde and benzylamine. The case was a bit different when the methyl ether of salicylaldehyde and benzylamine were used. The 1,2 amino alcohol 90 was obtained either in-situ or from the preformed imine in a similar yield and diastereoselectivity. In addition, the three-component reaction using 3-O-benzoyl allyl boronate 68, salicylaldehyde and a secondary amine was not successful.

**Table 3.4.** One pot, three component reactions of the allyl boronate 68 with different aldehydes and amines.

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>Yield %</th>
<th>dr (syn:anti)</th>
<th>J³,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>32%</td>
<td>88:12</td>
<td>7.2 Hz</td>
</tr>
<tr>
<td>90</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>25%</td>
<td>Major 5.5 Hz</td>
<td>Minor 6.5 Hz</td>
</tr>
<tr>
<td>94</td>
<td>H</td>
<td>H</td>
<td>Traces of alcohol adduct in the crude reaction mixture</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
3.6. BF$_3$.Et$_2$O-promoted allylboration of the imines:

In 2005, Hall et al. reported that in the allylboration reaction of aldehydes the presence of a catalytic mount of a Lewis or Bronsted acid, could promote the formation of the homoallylic alcohol products with high yields and stereoselectivity.$^{108}$ As reported, the addition of allylboration 95 to the benzaldehyde in presence of catalytic amount of trifluoromethanesulfonic acid (TfOH) promoted the formation of the desired lactone markedly from less than 5% yield (with no catalyst) to a yield of 99% (Scheme 3.33).$^{108}$

$$\text{Scheme 3.33. Lewis acid-catalyzed addition of allylboronate 95 to benzaldehyde}$$

In another study demonstrated by Chen et al.,$^{109}$ allylboration of hydrocinnamaldehyde with α-methyl allylboration 96 was examined (Scheme 3.34). When the reaction was performed with no catalyst, a mixture of the two homoallyl alcohols E and Z was obtained in 71% yield ($E:Z = 1.5:1$). A better selectivity was obtained when the reaction was carried out in presence of 10% scandium(III) trifluoromethanesulphonate Sc(OTf)$_3$ as catalyst. In this case, the two homoallyl alcohols E and Z were obtained in 64% yield ($E:Z = 3:1$). In another attempt,$^{109}$ Chen et al. found that addition of 10% boron trifluoride etherate (BF$_3$.Et$_2$O) as catalyst, afforded the E-homoallylic alcohol as a main product in 79% yield and high stereoselectivity ($E:Z = 30:1$) 94% ee (Scheme 3.34).

$$\text{Scheme 3.34. BF}_3$.Et$_2$O-promoted allylboration of hydrocinnamaldehyde}$$
BF₃.Et₂O-mediated allylboration of aromatic aldehydes such as benzaldehyde with α-methyl allylboronate 96 was also studied by Chen et al. The E-homoallylic alcohol product was produced in 75% and high stereoselectivity (E:Z = 30:1) 94% ee (Scheme 3.35).^{109}

![Scheme 3.35. BF₃.Et₂O-promoted allylboration of benzaldehyde](image)

To our knowledge, no studies have been conducted on the allylboration reaction of imines in presence of a Lewis acid catalyst. Based on these observations, we examined the effect of adding BF₃.Et₂O as catalyst in the allylboration reactions of imines with the boronate 68 (Scheme 3.36).

![Scheme 3.36. BF₃.Et₂O-promoted allylboration of different imines](image)

The BF₃.Et₂O-catalyzed reaction of 3-O-enzoyl allyl boronate 68 with N-benzylimine 73 in anhydrous DCM was examined. The crude reaction mixture was analyzed by ¹H-NMR spectroscopy which indicated product formation. The crude reaction product was purified by column chromatography to give the amino alcohol 78 in 20% yield with reduced diastereoselectivity (dr = 80:20). BF₃.Et₂O-promoted allylboration of the other imines N-allylimine 83, N-(p-methoxy)-benzylimine 84 and N-diphenylmethanimine 85 (Table 3.5) were also examined. The reactions of boronate 68 with N-allylimine 83 or N-diphenylmethanimine 85, did not afford the desired amino alcohol products. The ¹H-NMR analysis of their crude reaction mixture products showed the possibility of the presence of the desired products in trace amount. However, after purification of the crude reaction mixture products by column chromatography, no desired products could be obtained. Only the reaction with N-(p-methoxy)-benzylimine 84 worked and gave the desired amino allyl alcohol 87 in a relatively low yield (21%, dr = 93:7) in comparison to
our previous results. In this case, the same major syn-diastereomer was favored based on $^1H$ NMR analysis (Table 3.5).

### Table 3.5. BF$_3$.Et$_2$O-promoted allylboration of different imines

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Yield</th>
<th>$dr$ (syn:anti)</th>
<th>$J_{3,4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>Ph</td>
<td>20%</td>
<td>80:20</td>
<td>7.2 Hz</td>
</tr>
<tr>
<td>86</td>
<td></td>
<td>Traces in the crude reaction mixture</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>87</td>
<td>OMe</td>
<td>21%</td>
<td>93:7</td>
<td>6.9 Hz</td>
</tr>
<tr>
<td>88</td>
<td>Ph, Ph</td>
<td>Traces in the crude reaction mixture</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The proposed mechanism of this reaction is shown in Scheme 3.37a. As proposed in literature, because of the electron withdrawing effect of the BF$_3$, it coordinates with one of the oxygen atoms of the dioxaborolane in the allylboronate 68 in a closed transition state structure, which then leads to decrease the electron density around the boron atom. Consequently, this enhances the electrophilicity and affinity of the boron atom toward the lone pair of the nitrogen atom in the imine, resulting further promotion of B-N bond formation.$^{110,111}$ As mentioned previously, the imine group substituents R$^1$ and R$^2$ exist in an E-geometry in the TS structure. This arrangement leads to formation of the product in the syn form. An alternative TS leading to the syn product is an open TS as shown in Scheme 3.37b.

In summary, the BF$_3$.Et$_2$O-mediated allylboration of different imines using 3-0-allylboronate 68 was not an efficient way to synthesize the 1,2 amino alcohols as expected. The reactions of boronate 68 with benzylimine 73 and PMB-imine 84 gave the desired amino allyl alcohols 78 and 87, respectively in relatively low yields in comparison to our previous results, while using the allylimine 83 or diphenylmethyl-imine 88, did not afford the desired amino alcohol products.
Scheme 3.37(a, b). Proposed mechanism of BF₃·Et₂O-promoted allylboration of imines

In conclusion, an attempt to synthesize the pinacol benzylallylboronate 67 through a cross-coupling borylation of the allyl dibenzylacetal 77 with B₂(pin)₂ was unsuccessful. However, the Pd-catalyzed borylation of 3-benzoyloxyallyl bromide 66b was successful in providing the 3-O-benzoxyallyl boronate 68. The use of this boronate as an allylating agent was limited due to its relatively short shelf life, therefore the use of freshly prepared samples was essential for achieving reasonable chemical yields in its subsequent reactions. The efficiency of 3-O-benzoxyallyl boronate 68 to produce the corresponding 1,2-amino alcohols were explored using the imine formed between salicylaldehyde and different amines, either formed in situ or preformed. The best results were obtained when preformed imines were used. The reaction of 3-O-benzoxy allyl boronate 68 with the imines 73, 83, 84 and 85 afforded the corresponding 1,2-amino alcohol products 78, 86, 87 and 88, respectively in moderate yields (31-69%) but with high diastereoselectivities (dr = 91:9 to 95:5) for the syn-isomer. A chair like transition state, involving H-bonding
between the ortho-hydroxy group on the imine to the pinacol ester oxygen, was proposed to explain the stereochemical outcomes of these reactions. The reaction of 3-O-benzoyl allyl boronate 68 with imine 89 derived from O-methyl salicylaldehyde and benzylamine produced the amine alcohol product 90 with very low diastereoselectivity (dr = 42:58) showing the importance of the presence of the ortho-hydroxy group on the imine in controlling the diastereoselectivity. Furthermore, promotion of the allylboration of different imines using BF₃.Et₂O to synthesize the 1,2 amino alcohols was unsuccessful. The next chapter will focus on synthesis of TMS allyl boronate 70, and its efficiency to produce the 1,2-amino alcohols will be explored.
Chapter 4: Synthesis of 1,2 amino allyl silyl compounds using Pinacol TMS allyl boronate reactions

As mentioned in Chapter 3, the significant contribution of functionalized and substituted allyl boronates in organic synthesis has promoted the researchers to develop new strategies to their synthesis. In this chapter, we have focused on developing and verifying a valuable synthetic pathway to produce the γ-trimethylsilyl (TMS) allylboronate pinacol ester and investigate its effectivity in homoallyl amine products synthesis. In 1981, Mattesson et al. reported the synthesis of γ-TMS allyl boronate pinacol ester 70 through borylation of 3-TMS allyl lithium with trimethyl borate B(OCH₃)₃, and then ester exchange with pinacol. The reaction takes place through generation of stable TMS allyl anion, which then undergoes borylation at the γ-position affording the silyl boronate 70 in 53% yield (Scheme 4.1).¹¹²

\[
\text{Me}_3\text{Si} \quad \text{Li}^+ \quad \begin{array}{c} \text{1) } \text{B(OCH}_3\text{)}_3 \\ \text{2) } \text{NH}_4\text{-pinacol} \end{array} \quad \text{Me}_3\text{Si} \quad \begin{array}{c} \text{C} \quad \text{O} \\ \text{O} \end{array} \quad 70 \quad 52\%
\]

**Scheme 4.1.** Synthesis of γ-TMS allylboronate pinacol ester through borylation of TMS allyl anion

Wang et al. reported the synthesis of E-TMS allylboronate 97 through monohydroboration of an allenyl silane (Scheme 4.2).¹¹³ The hydroboration reaction was performed using 9-borabicyclo[3.3.1]nonane (9-BBN),¹¹³ which has shown its remarkable borylating efficiency towards olefins.¹¹⁴ The 9-BBN prefers to attack the least sterically hindered C=C of the allene¹¹⁵ affording the desired boronate 97 in 50% yield.¹¹³

\[
\text{Me}_3\text{Si} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad \text{THF or Toluene, } \pi, 2 \text{ h} \quad \text{Me}_3\text{Si} \quad \begin{array}{c} \text{B} \\ \text{Me} \end{array} \quad 97 \quad 50\%
\]

**Scheme 4.2.** Synthesis of a silyl allylboronate through monohydroboration of an allenyl silane

Based on our observations in Chapter 3, the synthesis of 3-O-benzoyl allyl boronate 68 was efficiently performed via the cross-coupling reaction of organoboron reagent B₂(pin)₂
with the allyl halides in presence of Pd catalyst and base (Scheme 3.13). Therefore, this chapter will examine the synthesis of γ-TMS allylboronate 70 by following a similar synthetic pathway. Furthermore, it will report on the allylation reactions of imines with γ-TMS allylboronate 70 (Scheme 4.3), and the results of the one pot, three component reactions of the boronates 70 with different aldehydes and amines will also be reported.

**Scheme 4.3.** Proposed TMS allylboronate-mediated allylation reactions

### 4.1. Synthesis of γ-TMS allyl pinacol boronate 70 via borylation of silyl allyl halide:

The TMS allyl pinacol boronate 70 will be synthesized using the procedure of Zhang et al.\(^80\) through the borylation of 3-iodovinylsilane 69 with \(\text{B}_2(\text{pin})_2\) in the presence of \(\text{PdCl}_2\) and \(\text{KOAc}\) (Scheme 4.4). However, first the starting 3-iodovinylsilane 69 needs to be prepared from the TMS allyl alcohol using the procedure of Singletary et al.\(^81\)

**Scheme 4.4.** Proposed synthesis of compound 70

In 1974, Stork et al.\(^{116}\) developed a synthetic pathway to prepare an iodomethyl vinylsilane in two steps (Scheme 4.5). First the silyl allylic alcohol was treated with \(N\)-chlorosuccinimide (NCS) and \(\text{PPh}_3\) to afford the corresponding silyl allyl chloride in 60% yield. In the second step, the conversion of vinylsilane chloride to the corresponding iodide (80% yield) was achieved using sodium iodide (NaI).\(^{116}\)

**Scheme 4.5.** Stork's synthetic pathway of a halomethyl vinylsilane
Later, Singletary et al. described a convenient one step procedure for preparing iodomethyl vinylsilane from silyl allyl alcohol (Scheme 4.6). Treatment of the silyl allylic alcohol with N-iodosuccinimide (NIS) and PPh₃ directly gave the desired silyl allyl iodide in 82% yield.⁸¹

**Scheme 4.6.** Singletary's synthetic pathway of the halomethyl vinylsilane

Following Singletary et al. procedure,⁸¹ TMS allyl alcohol was treated with NIS in the presence of PPh₃ in anhydrous DCM under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h, and then at rt for 3 h (Scheme 4.7). The crude mixture was washed with petroleum ether and filtered through silica gel. Both TLC and ¹H-NMR analyses indicated the presence of the starting material with no formation of the desired product. This reaction was repeated under the same condition but with using a freshly purified NIS. ¹H-NMR analysis of the filtrate showed formation of the desired iodo vinylsilane 69 in a mixture with the allyl iodide 98 (69:98 in 26:74). The yields of compounds 69 (15%) and 98 (60%) were calculated from the ¹H-NMR spectrum using the ratio of the integrals at H3 and H3′ to give their molar ratio. Further purification of the filtrate led to decomposition of the desired product. These results limited the opportunity to proceed to the next proposed borylation reaction as described in Scheme 4.4.

**Scheme 4.7.** Proposed synthesis of compound 69

The mechanism of this reaction is shown in Scheme 4.8. The reason for the formation of allyl iodide in this reaction was not clear, but perhaps the TMS group was cleaved on silica gel due to its acidic nature.
Scheme 4.8. Proposed mechanism of compound 69 synthesis

The 1H-NMR spectrum of compound 69 (Figure 4.1) showed resonances for the vinyl protons H1 and H2 at δ 5.83 (d, J = 18.3 Hz, 1H, SiMe3-CH) and δ 6.16 (dt, J = 18.1, 7.4 Hz, 1H, CH-CH3I), respectively. The protons attached to C3 resonated at δ 3.81 (d, J = 11.1 Hz, 2H, -CH2I). A singlet resonance for the SiMe3 is shown at δ 0.06 (s, 9H). The NMR spectroscopic data of compound 69 matched with those reported in the literature. The EIMS data showed an [M+K+] ion peak for C6H13SiK+ at m/z 279. The 1H-NMR
spectrum also showed the resonances of the allyl iodide \( \text{98} \), where the vinyl protons H' resonated at \( \delta 4.88 \) (d, \( J = 9.6 \) Hz, 1H, H' \( \text{cis} \)) and \( \delta 5.09 \) (dt, \( J = 16.5, 1.1 \) Hz, 1H, H' \( \text{trans} \)), respectively. The other vinyl proton H2' resonated at \( \delta 5.97-5.89 \) (m, 1H, H2') while H3' protons were at \( \delta 3.87 \) (d, \( J = 7.5 \) Hz, 2H, H3'), respectively. The NMR spectroscopic data of allyl iodide \( \text{98} \) matched with those reported in the literature.\(^{117}\) The spectrum also showed resonances at \( \delta 7.70-7.43 \) which corresponded to Ph3P=O.

In summary, synthesis of the 3-iodovinylsilane \( \text{69} \) from TMS allyl alcohol was not successful. As a result, this led to failure to proceed to the next proposed borylation reaction as described in Scheme 4.4. The next section will focus on synthesis of TMS allyl boronate \( \text{70} \) following the Dutheuil \textit{et al.}\(^{118}\) procedure.

### 4.2. Synthesis of \( \gamma \)-TMS allyl boronate pinacol ester \( \text{70} \) through borylation of silyl allyl alcohol:

Inexpensive and readily commercially available allyl alcohols have been used efficiently as synthetic precursors in the synthesis of allylic boronic acids and their ester derivatives. In 2006, Olsson \textit{et al.} reported an efficient synthetic procedure for preparation of allylic boronic acids from allyl alcohols. In this procedure, the allyl alcohol was boronated by using diboronic acid \( \text{[B(OH)\(_2\)]\(_2\)} \) as the boryl nucleophile in presence of Pd pincer complex as a catalyst (Scheme 4.9). Due to the instability issues related to the formed allyl boronic acids, they were converted directly to their more stable trifluoroborate derivatives.\(^{119}\)

![Scheme 4.9. Pd-catalyzed direct boronation of allyl alcohols](image_url)

Pd pincer complex was the catalyst of choice in this reaction. When the reaction was carried out by using either \( \text{Pd\(_2\)(dba)\(_3\)} \) or \( \text{Pd(PPPh\(_3\))\(_4\)} \) as catalysts, no formation of the desired product was observed. Due to the poor solubility properties of the pincer complex in pure MeOH, using DMSO and MeOH as the solvent system was essential to proceed the boronation reaction in good yields and rates. Furthermore, the conversion rate of the allyl alcohol to the desired boron compound was markedly decreased when the reaction was...
performed in pure DMSO as the solvent. It was also observed that conversion rate of the allyl alcohol to the desired boronated compound was accelerated the 4-fold when p-toluene sulfonylic acid (PTS) was added to the reaction mixture.\(^{119}\)

For the borylation reaction to be proceed effectively, the hydroxy group of the allylic alcohol needs to be converted to a better leaving group. In the presence of MeOH, esterification of the hydroxy group takes place through coordination of the diboronic acids boron with the hydroxy group forming the six membered ring TS. Rearrangement of this intermediate by elimination of a water molecule facilitates formation of the desired boronic acid ester group (Scheme 4.10). The use of PTS as cocatalyst promotes the borylation reaction through catalyzing the esterification process.\(^{119}\)

![Scheme 4.10](image)

**Scheme 4.10.** Mechanism of activation of the hydroxy group allyl alcohols

In 2007, Selander and coworkers developed a Pd catalyzed one pot synthetic procedure, in which the allyl boronic acid was generated in situ and then was subsequently reacted with functionalized electrophiles to produce the corresponding homoallyl alcohols and \(\alpha\)-amino acids. In this procedure, the allyl alcohol was borylated by diboronic acid \([\text{B(OH)}_2]_2\) in the presence of a Pd pincer complex as a catalyst and PTS as cocatalyst, followed by C-C coupling with the corresponding allyl electrophiles (Scheme 4.11).\(^{120}\)

![Scheme 4.11](image)

**Scheme 4.11.** One-pot synthesis of homoallyl alcohols and \(\alpha\)-amino acids via catalytic generation of allyl boronic acids
Because of its difficult commercial accessibility, use of the diboronic acid as the boron source reagent was limited. Proceeding the Pd catalyzed boronation reaction by using commercially available B₂(pin)₂ in place of [B(OH)₂]₂ was not efficient. In this case, the borylation rate was much slower as result of repulsive steric interactions between the pincer ligand of the Pd complex and the pinacolato of B₂(pin)₂. As reported by Selander et al., inducing the in-situ hydrolysis of B₂(pin)₂ to [B(OH)₂]₂ could improve the borylation reaction rate. This can be achieved by adding 8 equivalents of water and an extra amount of PTS (20 mol%) to the reaction mixture. In terms of accelerating the reaction rate, using the Pd-SCS complex as a catalyst in place of the Pd-SeCSe complex led to performing the coupling borylation in 4 h rather than 16 h.

The cross coupling borylation takes place through several steps as shown in Scheme 4.12. First, in the presence of PTS, the hydroxy group of the allylic alcohol is activated through reacting with the in situ hydrolyzed diboronic acid to form the allyl boronic acid ester A. Then transmetallation takes place between the Pd pincer catalyst and compound A leading to formation of both the boron-Pd intermediate B and the activated hydroxy allyl intermediate C. Further reaction of the intermediate C with the boron-Pd intermediate B affords the desired allyl boronic acid.

Scheme 4.12. Proposed mechanism of the Pd-catalyzed boronation of allyl alcohols

Later, Dutheuil et al. reported an efficient synthetic procedure for the preparation of the more stable allylic boronic esters from allyl alcohols. In this procedure, the TMS allyl alcohol was borylated by B₂(pin)₂ in presence of palladacycle [di-μ-chlorobis[2-[(dimethylamino)methyl]phenyl-C,N]dipalladium(II)] as a catalyst and PTS as cocatalyst which afforded the desired γ-TMS allyl pinacol boronate 70 in 57% yield. As reported
by Dutheuil et al., conversion the allyl alcohol to the corresponding allyl boronate in good rates and yields depends on the following: (i) As the B$_2$(pin)$_2$ was the boryl nucleophile, using 5 mol% of PTS was essential to proceed the borylation reaction. When the reaction was carried out without PTS, no formation of the desired product was observed. (ii) The reaction yield was markedly increased when an excess amount of the B$_2$(pin)$_2$ was used (2 equiv). (iii) The reaction was performed in less time when the palladacycle was employed as catalyst.

The mechanism of this transformation is described in Scheme 4.13. The chloride of the palladacycle catalyst is decoordinated and then transmetalated with the boron nucleophile leading to formation of the boron-Pd intermediate. Coordination of the boron-Pd intermediate with B-activated allyl alcohol affords the desired allylboronate compound 70 accompanied by regeneration of the initial palladacycle catalyst.$^{118}$

![Scheme 4.13. Dutheuil's proposed mechanism of Pd-catalyzed borylation of TMS allyl alcohol](image)

Following the procedure of Dutheuil et al.,$^{118}$ γ-TMS allyl pinacol boronate 70 was synthesized by reaction of 3-TMS allylic alcohol in a mixture of anhydrous DMSO and anhydrous MeOH with a freshly dried PTSA, palladacycle and B$_2$(pin)$_2$, and then the mixture was stirred at 50 °C for 16 h (Scheme 4.14). $^1$H-NMR analysis of the crude
reaction mixture showed the formation of the desired product. Because of the relatively unstable nature of the desired product to silica gel purification, the crude product was characterized and used in subsequent reactions.

\[
\text{Me}_3\text{Si} + \text{OH} \xrightarrow{\text{Palladacycle, PTSA}} \text{Si} = \xrightarrow{\text{DMSO/MeOH, 50 °C, 16 h}} \text{3} \quad \text{70}
\]

**Scheme 4.14. Synthesis of compound 70**

The \(^1\text{H}-\text{NMR} \) spectrum of compound 70 (Figure 4.2) showed resonances for the vinyl protons H2 and H3 at \(\delta 6.04 \) (dt, \( J = 18.5, 7.0 \) Hz, 1H, H2) and \(\delta 5.59 \) (d, \( J = 18.0 \) Hz, 1H, H3), respectively. The methylene protons H1 attached to the boron ring resonated at \(\delta 1.78 \) (d, \( J = 7.0 \) Hz, 2H, CH=CHCH\(_2\)B). The methyl protons attached to the pinacol ester ring resonated at \(\delta 1.23-1.20 \) (m, 12H), while those attached to silyl group resonated at \(\delta 0.00 \) (s, 9H). It should be noted that the chemical shift for H1 in the literature\(^{118} \) was
different, $\delta$ 2.36 (brd, $J = 7.1$ Hz, 2H). This may be a reporting error as analogous methylene protons in the related compound (E)-PhCH=CHCH$_2$Bpin have a chemical shift of $\delta$ 1.87 ($J = 7.1$ Hz, 2H).$^{118}$

![Figure 4.3. $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of compound 70](image)

The $^{13}$C-NMR spectrum of compound 70 (Figure 4.3) showed resonances for the vinyl carbons C2 and C3 at $\delta$ 142.1 and $\delta$ 130.8, respectively. The carbon signals for the methyl carbons attached to the pinacol ester ring resonated at $\delta$ 25.1 and 24.9. The two quaternary carbons C4 and C5 in the pinacol ester ring resonated at $\delta$ 83.6. The carbon signals for the methyl protons attached to silyl group resonated at $\delta$ -0.1. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix C-1) and gHSQC (Appendix C-2) experiments. The spectroscopic data of compound 70, except for $\delta_H$ for H1, matched with those reported in the literature.$^{112,118}$ While the LRMS of C$_{12}$H$_{25}$BO$_2$Si$^+$ ($m/z$ 309) did not matched the expected molecular formula of compound 70, its spectroscopic data were clear enough to confirm its structure.
4.3. Alkylation reactions of γ-TMS allyl pinacol boronate 70 with preformed N-benzylimine 73:

In 1981, allylboration reactions of aldehydes with γ-TMS allyl pinacol boronate 70 was reported for the first time by Mattesson et al.,\textsuperscript{112} which afforded the homoallylic silyl alcohols in high yields and diastereoselectivities (Scheme 4.15).

![Scheme 4.15. Reaction of γ-TMS allylboronate 70 with aldehydes](image)

More recently, Barrio \textit{et al.} reported the use of a chiral BINOL-derived phosphoric acid as an efficient catalyst for the asymmetric allylboration of aldehydes with boronate 70 to give the corresponding homoallylic silyl alcohols in good yields and high diastereoselectivities (Scheme 4.16).\textsuperscript{121}

![Scheme 4.16. Bronsted acid allylboration of aldehydes with boronate 70](image)

Allylboration of aldehydes proceed through a six-membered ring cyclic chair transition state (TS), in which the BINOL-derived phosphoric acid catalyst forms two hydrogen bonds: one is formed between the catalyst hydroxy group (P-OH) and the pseudoaxial
oxygen of the boronate, and the second one is formed between the catalyst phosphoryl oxygen \((P=O)\) and the formyl hydrogen of the aldehyde. Therefore, the pinacol methyl groups of the boronate occupy the empty pocket of the catalyst active site, while the \(\text{SiMe}_3\) occupies the sterically hindered pocket. This way of arrangement of the substituents is believed to stabilize the TS structure and leads to the formation of silyl allyl alcohols in the \textit{anti} form (Figure 4.4).\textsuperscript{121,122}

![Figure 4.4. Proposed mechanism of the Bronsted acid catalyzed allylboration of aldehydes](image)

To the best of our knowledge, no further work on the related additions of \(\gamma\)-silyl allyl pinacol boronate 70 to the imines has been reported in the literature. Therefore, the performance of TMS boronate 70 in allylation of the imines 73, 83, 84 and 89 will be examined under the same reaction conditions applied in Chapter 3.

4.3.1. Using preformed imine derived from salicylaldehyde and benzylamine:

The reaction of \(\gamma\)-TMS allylboronate 70 and \(N\)-benzylimine 73 in MeOH at rt was examined (Scheme 4.17). The crude reaction product mixture was analyzed by \(^1\text{H-NMR}\) spectroscopy which indicated formation of the desired product. The crude reaction product was purified by column chromatography to give the desired product 99 in 43\% yield and with good stereoselectivity (\(\text{dr} = 93:7\)) as determined by integration of the \(^1\text{H-NMR}\) doublet resonances at \(\delta = 3.91\) and \(\delta = 3.62\) for Hb for the major and minor diastereomers, respectively (Figure 4.5). The \(^1\text{H-NMR}\) spectrum also showed resonances for pinacol which co-eluted with product 99 which represents 29\% of the total mass of the product mixture (total mass of the product mixture = 52.8 mg, weight of pinacol = 22.5 mg).
Scheme 4.17. Synthesis of racemic compound 99

Figure 4.5. $^1$H-NMR spectrum (CDCl$_3$, 300 MHz) of compound 99

The $^1$H-NMR spectrum of compound 99 (Figure 4.5) showed resonances for the vinyl H1 protons at $\delta$ 5.13 (dd, $J = 10.0, 1.5$ Hz, 1H cis) and (dd, $J = 16.5, 1.5$ Hz, 1H trans). The diastereotopic N-benzylic protons resonated at $\delta$ 4.12 (d, $J = 12.9$ Hz, 1H, Ha) and $\delta$ 3.91 (d, $J = 12.9$ Hz, 1H, Hb). The other vinyl proton H2 resonated at $\delta$ 5.94 (dt, $J = 16.7, 10.6$ Hz, 1H, H2) while H3 and H4 protons were at $\delta$ 2.33 (dd, $J = 11.0, 6.0$ Hz, 1H, H3) and $\delta$ 4.34 (d, $J = 6.0$ Hz, 1H, H4), respectively. The methyl protons attached to silyl group resonated at $\delta$ 0.26 (s, 9H). The methyl protons attached to pinacol resonated at $\delta$ 1.57 (m, 12H). The aromatic ring protons attached to the N-benzylic group resonated at $\delta$ 7.67-7.56 (m, 5H) while the other aromatic protons resonated at $\delta$ 7.16 (dd, $J = 8.0, 1.0$ Hz, 1H, H3).
1H, H7), δ 7.48 (td, J = 7.7, 1.7 Hz, 1H, H8), δ 7.09 (td, J = 7.4, 1.2 Hz, 1H, H9) and δ 7.27 (dd, J = 7.5, 1.5 Hz, 1H, H10).

**Figure 4.6.** $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz) of compound 99

The $^{13}$C-NMR spectrum of compound 99 (Figure 4.6) showed resonances for two diastereoisomers (doubling of peaks was observed for some resonances; the ratio of these peaks did not correspond to the ratios seen in the $^1$H-NMR spectrum). The terminal alkene carbons resonated at δ 114.7 (C1) and 135.8 (C2). The N-benzylic carbon resonated at δ 51.9, while C3 resonated at δ 44.2 (major) and δ 44.0 (minor), and C4 were at δ 63.8 (major) and δ 63.3 (minor), respectively. The carbon attached to the hydroxy group C6 resonated at δ 158.1. The aromatic ring carbons C7 and C9 resonated at δ 117.0 and 118.6, respectively. The carbon signals for the methyl protons attached to silyl group resonated at δ -1.9. The quaternary carbons Cq of the pinacol resonated at δ 25.1 and 83.6. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Figure 4.7) and gHSQC (Figure 4.8) experiments. The ESIMS data showed an [M+H$^+$] ion peak at m/z 326.1739 (calculated for C$_{20}$H$_{28}$NO$_2$Si$: 326.1756$) which confirmed the correct molecular formula of compound 99.
Figure 4.7. gCOSY experiment of compound 99

Figure 4.8. gHSQC experiment of compound 99
4.3.2. Determination of relative stereochemistry of 99 via literature comparisons:
The relative stereochemistry of the 1,2-amino allyl silyl compound 99 can be verified via comparison of the coupling constant value \(J_{3,4}\) of compound 99 with similar compounds from the literature. In 1991, Wuts et al. reported synthesis of N-benzyl-l-phenyl-2-(trimethylsilyl)-3-butenylamine 102 through allylboration of imine 100 with ethylene glycol TMS-allyl boronate 101 (Scheme 4.18). As reported in the literature, the \(^1\)H-NMR analysis of the crude product indicated formation of the desired amino silyl compound as two diastereomers (anti:syn = 50:1). However, after purification of the crude product by column chromatography only the anti isomer 102 was isolated in 94% yield.

Scheme 4.18. Allylboration of imines with ethylene glycol TMS-allyl boronate 101

The mechanism of this reaction was illustrated via a six-membered cyclic chair transition state TS, in which the imine coordinates with allyl silyl boron reagent 101 at the \(\gamma\)-position resulting in allyl transposition. Wuts et al. presumed that the stereochemistry of the product is controlled by the nature of the imine R substituent where the aryl substituent gives the anti-adduct (R = Ph, anti:syn = 50:1), and the alkyl substituent gives the syn-adduct (R = i-Pr, anti:syn = 1:10.7). The formation of 102 was reported to be proceed through a six-membered cyclic chair transition state B, in which the imine group substituents R and Bn have the less stable Z-geometry and the R group occupies a pseudo equatorial position. The amount of energy needed for \(E/Z\) isomerization was less than the energy needed to proceed the reaction via transition state A, therefore the Z-geometry of the imine was preferred. This way of arrangement of the substituents in the TS structure led to formation of the compound 102 in the anti form (Scheme 4.19).
The reported $^1$H-NMR data of the amino allyl silyl compound 102, indicated that H3 and H4 protons resonated at $\delta$ 1.98 (t, $J = 9.5$ Hz, 1H) and $\delta$ 3.68 (d, $J = 9.5$ Hz, 1H), respectively. Based on the structural similarity between compound 99 and the literature compound 102, the configuration of compound 99 can be determined by comparing the vicinal coupling constant values between H3 and H4 ($J_{3,4}$) with the reported coupling constant of compound 102. An examination of the $^1$H-NMR spectrum of compound 99 (Figure 4.5) showed resonances for H3 and H4 protons at $\delta$ 2.33 (dd, $J = 11.0$, 6.0 Hz, 1H) and $\delta$ 4.34 (d, $J = 6.0$ Hz, 1H), respectively. Based on the lack of conformity between the coupling constant values of compound 99 ($J_{3,4} = 6.0$ Hz) and the literature compound 102 ($J_{3,4} = 9.5$ Hz), compound 99 was tentatively assigned with syn-relative configuration.
The syn-configuration of compound 99 can be afforded via reaction of the imine with allyl silyl boron reagent 70 at the γ-position resulting in allyl transposition. The mechanism of this configuration is believed to be proceed through six-membered cyclic chair transition state (TS), in which the imine group substituents R and Ph are in an E-geometry and occupy pseudo axial positions. Based on earlier observations in Chapter 3, the presence of the ortho-hydroxy group on the imine carbon in a free form, enforce the syn-configuration of the product through formation of H-bonding with the axial oxygen atom of the dioxaborolane. This way of arrangement leads to formation of the product in the syn form (Scheme 4.20a). An alternative TS leading to the syn product is an open TS as shown in Scheme 4.20b.
4.4. Alkylation reactions of \( \gamma \)-TMS allyl pinacol boronate 70 with other preformed imines:

To further examine the scope of this reaction by varying the amine component, the reaction of \( \gamma \)-TMS allylboronate 70 with imines 83, 84 and 89 were examined.

4.4.1. Using preformed imine derived from salicylaldehyde and allyl amine:

As a model study of the use of \( \gamma \)-TMS allylboronate 70 as an allylating agent the reaction of the \( N \)-allylimine 83 with \( \gamma \)-TMS allylboronate 70 was examined (Scheme 4.21).

Scheme 4.21. Synthesis of racemic compound 103

The crude reaction mixture was analyzed by \(^1\)H-NMR spectroscopy which indicated formation of the desired product. The crude reaction product was purified by column chromatography to give the desired product 103 in 29% yield and with high stereoselectivity (dr = 90:10) as determined by integration of the \(^1\)H-NMR doublet resonances at \( \delta \) 3.56 and \( \delta \) 3.65 for H3' in the major and minor diastereomers (Appendix C-3). Copies of the NMR spectra for the product 103 are reported in Appendix C-4 to C-6.

4.4.2. Using preformed imine derived from salicylaldehyde and \( p \)-methoxybenzyl amine:

The reaction of \( \gamma \)-TMS allylboronate 70 with \( N \)-(\( p \)-methoxy)-benzylimine 84 in MeOH at rt was examined (Scheme 4.22). The crude reaction mixture was analyzed by \(^1\)H-NMR spectroscopy which indicated formation of the desired product. The crude reaction product was purified by column chromatography to give the desired product 104 in 27% yield and with high stereoselectivity (dr = 94:6) as determined by integration of the \(^1\)H-NMR doublet resonances at \( \delta \) 5.12 and \( \delta \) 5.29 for H1 in the major and minor diastereomers.
(Appendix C-7). Copies of the NMR spectra for the product 104 are reported in Appendix C-8 to C-10.

Scheme 4.22. Synthesis of racemic compound 104

4.4.3. Using preformed imine derived from the methyl ether of salicylaldehyde and benzylamine:

To examine the effect of the ortho-hydroxy group on the imine, the reaction of a freshly prepared γ-TMS allylboronate 70 with N-benzyl-2-methoxyphenyl imine 89 was examined under identical conditions as described earlier (Scheme 4.23). The crude reaction mixture was analyzed by 1H-NMR spectroscopy which indicated formation of the desired product with recovery of fair amount of the starting imine 89. The crude reaction product was purified by column chromatography to give the desired product 105 in 31% yield and with high stereoselectivity (dr = 93:7) as determined by integration of the 1H-NMR doublet resonances at δ 4.11 and δ 4.20 for OMe in the major and minor diastereomers (Appendix C-11). Copies of the NMR spectra for the product 105 are reported in Appendix C-12 to C-14.

Scheme 4.23. Synthesis of racemic compound 105
The results of the reactions of $\gamma$-TMS allylboronate 70 with imines 73, 83, 84 and 89 are summarized in Table 4.1.

**Table 4.1. Summary of the reactions of the $\gamma$-TMS allylboronate 70 with different imines**

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
<th>dr (syn:anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>H</td>
<td>(\text{Ph} )</td>
<td>43%</td>
<td>93:7</td>
</tr>
<tr>
<td>103</td>
<td>H</td>
<td>(\text{CH}_2=\text{CH} )</td>
<td>29%</td>
<td>90:10</td>
</tr>
<tr>
<td>104</td>
<td>H</td>
<td>(\text{Ph} )</td>
<td>27%</td>
<td>94:6</td>
</tr>
<tr>
<td>105</td>
<td>Me</td>
<td>(\text{Ph} )</td>
<td>31%</td>
<td>93:7</td>
</tr>
</tbody>
</table>

Table 4.1 summarizes the results of reaction of the $\gamma$-TMS allylboronate 70 with the four different imines. The N-benzyl imine gave the highest yield; however, all reactions were highly diastereoselective. The $J_{3,4}$ coupling constants for these four products suggested this all had the same, syn relative configurations (Table 4.2). All products were isolated contaminated with pinacol. In contrast with the results reported in Chapter 3 when reaction of 3-O-benzoyl allyl boronate 68 with the imine 93 gave a diastereomeric mixture of the 1,2-amino alcohol 90 (syn:anti = 42:58), the diastereoselectivity obtained by proceeding the same reaction with using TMS boronate 70 was quite unexpected. Blocking the hydroxy group in case of imine 89 did not changed the diastereoselectivity, and it gave the amino alcohol 105 mainly as the syn-isomer (dr = 93:7).
Table 4.2. Comparison of $J_{3,4}$ values for 99, 103, 104 and 105

<table>
<thead>
<tr>
<th>Product</th>
<th>$\delta_{H3}$</th>
<th>$\delta_{H4}$</th>
<th>$\delta_c C3$</th>
<th>$\delta_c C4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>2.33 (dd, $J = 11.0, 6.0$ Hz)</td>
<td>4.34 (d, $J = 6.0$ Hz)</td>
<td>44.2</td>
<td>63.8</td>
</tr>
<tr>
<td>103</td>
<td>2.33 (dd, $J = 11.0, 5.7$ Hz)</td>
<td>4.32 (d, $J = 5.8$ Hz)</td>
<td>44.4</td>
<td>63.6</td>
</tr>
<tr>
<td>104</td>
<td>2.32 (dd, $J = 11.0, 6.0$ Hz)</td>
<td>4.34 (d, $J = 6.0$ Hz)</td>
<td>44.2</td>
<td>63.7</td>
</tr>
<tr>
<td>105</td>
<td>2.32 (dd, $J = 11.0, 6.0$ Hz)</td>
<td>4.34 (d, $J = 6.1$ Hz)</td>
<td>44.2</td>
<td>63.7</td>
</tr>
</tbody>
</table>

4.5. Three component model reactions of $\gamma$-TMS allylboronate 70:

To further examine the efficiency of TMS pinacol boronate 70 in homoallyl amine synthesis, the allylation of different aldehydes and amines under borono-Mannich reaction conditions will be investigated in this section.

4.5.1. Using salicylaldehyde and benzylamine:

The one pot, three component allylation reaction between salicylaldehyde, the $N$-benzylamine and the freshly prepared $\gamma$-TMS allylboronate 70 to produce syn-1,2 amino silyl allyl product 99, was also examined (Scheme 4.24).

![Scheme 4.24. One pot, three component synthesis of racemic compound 99](image)

The benzylamine was added to a solution of salicylaldehyde 71 in anhydrous MeOH and then the mixture was stirred at 45 °C for 1 h, then at room temperature for 2 h to form the corresponding imine 73 in situ. Then freshly prepared silyl allyl boronate 74 was added to the reaction mixture and stirring was continued at rt for 16 h. The crude reaction product was purified by column chromatography to give the desired product 99 in 33% yield and with good diastereoselectivity ($dr = 89:11$). The $^1H$-NMR spectrum also showed
resonances for pinacol which co-eluted with product 99 which represents 28% of the total mass of the product mixture (total mass of the product mixture = 61.58 mg, weight of pinacol = 17.24 mg).

In terms of yield and diastereoselectivity, the synthesis of the syn-1,2 amino alcohol 99 from the preformed imine 73 (43%, dr = 93:7) was more efficient than the one pot, three component reaction (33%, dr = 89:11). The lower yield and diastereoselectivity compared to the reaction of 74 with preformed imine 73 may be due to the effect of the 1 equiv of water generated in the one pot reaction which could disrupt the H-bonding in the (TS) shown in Scheme 4.20.

4.5.2. Using benzaldehyde and benzylamine:
As mentioned earlier, Wuts et al. reported synthesis of amine 102 through allylboration of imine 100 with ethylene glycol TMS-allyl boronate 101 (Scheme 4.18)\(^1\), which afforded only the anti isomer of 102 in 94% yield and diastereoselectivity (syn:anti = 0:100). In this reaction, the effect of the ortho-hydroxy group on the carbonyl compounds will be examined through setting up an one pot, three component allylation reaction between benzylaldehyde, N-benzylamine and the freshly prepared \(\gamma\)-TMS allylboronate 70 (1 equiv) to produce the syn-1,2 amino silyl product 102 (Scheme 4.25). The crude reaction product was purified by column chromatography to give the desired product 102 in 24% yield and with modest diastereoselectivity (dr = 83:17) as determined by integration of the \(^1\)H-NMR doublet resonances at \(\delta 3.91\) and \(\delta 3.82\) for Hb for the major and minor diastereomers, respectively (Figure 4.9). Repeating the reaction with using 2 equiv of \(\gamma\)-TMS allylboronate 70 gave the alcohol adduct 106 in 14% (dr = 23:77) (Scheme 4.25). The \(^1\)H-NMR spectrum (Figure 4.11) also showed resonances for pinacol which co-eluted with 106 which represents 45% of the total mass of the product mixture (total mass of the product mixture = 25.8 mg, weight of pinacol = 11.69 mg). Furthermore, the \(^1\)H-NMR spectrum of 106 revealed the presence of several impurities (Figure 4.11).
Scheme 4.25. One pot, three component synthesis of racemic compound 102

Figure 4.9. $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of compound 102

The $^1$H-NMR spectrum of compound 102 (Figure 4.9) showed resonances for the vinyl H1 protons at $\delta$ 5.16 (dd, $J = 10.0$, 1.5 Hz, 1H cis) and $\delta$ 5.09 (dd, $J = 17.0$, 1.0 Hz, 1H trans). The diastereotopic N-benzyllic protons resonated at $\delta$ 4.11 (d, $J = 12.9$ Hz, 1H, Ha) and $\delta$ 3.91 (d, $J = 12.9$ Hz, 1H, Hb). The other vinyl proton H2 resonated at $\delta$ 5.94 (ddd, $J = 16.7$, 12.3, 8.6 Hz, 1H, H2) while H3 and H4 protons were at $\delta$ 2.33 (dd, $J = 11.0$, 6.0 Hz, 1H, H3) and $\delta$ 4.34 (d, $J = 6.0$ Hz, 1H, H4), respectively. The methyl protons attached
to silyl group resonated at δ 0.26 (s, 9H). The aromatic ring protons attached to the N-benzyl group resonated at δ 7.67-7.56 (m, 5H) while the other aromatic protons resonated at δ 7.52 (d, J = 7.0 Hz, 1H, H6), δ 7.16 (dd, J = 8.0, 1.0 Hz, 1H, H7), δ 7.48 (td, J = 7.7, 1.7 Hz, 1H, H8), δ 7.09 (td, J = 7.4, 1.2 Hz, 1H, H9) and δ 7.28 (dd, J = 7.5, 1.5 Hz, 1H, H10).

Figure 4.10. $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of compound 102 (major = maj, minor = min)

The $^{13}$C-NMR spectrum of compound 102 (Figure 4.10) showed resonances for two diastereoisomers (doubling of peaks was observed for some resonances). The terminal alkene carbons at δ 114.7 (C1) and 135.8 (C2). The N-benzylic carbon resonated at δ 51.9 (major) and δ 51.2 (minor). The C3 resonated at δ 44.2 (major) and 40.6 (minor), while C4 resonated at δ 63.8 (major) and 63.0 (minor), respectively. The aromatic ring carbons C7 and C9 resonated at δ 117.0 and 118.6, respectively. The carbon signals for the methyl protons attached to silyl group resonated at δ -2.0. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix C-15) and gHSQC (Appendix C-16) experiments. The ESIMS data showed an [M+H$^+$] ion peak at
m/z 310.1739 (calculated for C_{20}H_{28}NSi\(^{+}\): 310.1756) which confirmed the correct molecular formula of compound 102.

Figure 4.11. \(^1\)H-NMR spectrum (CDCl\(_3\), 500 MHz) of compound 106

The \(^1\)H-NMR spectrum of compound 106 (Figure 4.11) showed resonances for the vinyl \(H1\) protons at \(\delta\) 5.05 (dd, \(J_{\text{cis}} = 10.3\), 1.9 Hz, 1H, H1) and \(\delta\) 4.97 (dd, \(J_{\text{trans}} = 17.0\), 1.9 Hz, 1H, H1), respectively while the other vinyl proton \(H2\) was at \(\delta\) 5.81 (dt, \(J = 17.1\), 10.3 Hz, 1H, H2). The protons of H3 and H4 resonated at \(\delta\) 2.02 (t, \(J = 9.5\) Hz, 1H, H3) and \(\delta\) 4.74 (d, \(J = 8.5\) Hz, 1H, H4), respectively. The methyl protons attached to the silyl group resonated at \(\delta\) -0.25 (s, 9H). The aromatic ring protons resonated at \(\delta\) 7.36-7.25 (m, 5H). The spectral data of compound 106 matched with those reported in the literature.\(^{124}\) The LRMS of C\(_{13}\)H\(_{20}\)OSiNa\(^{+}\) showed an [M+Na\(^{+}\)] ion peak at m/z 243 which confirmed the correct molecular formula of compound 106.

4.5.3. Using salicylaldehyde and allyl amine:

The one pot, three component allylation reaction between salicylaldehyde, \(N\)-allylamine and the freshly prepared \(\gamma\)-TMS allylboronate 70 to produce \textit{syn}-1,2 amino silyl product
103, was also examined under the reaction conditions described above (Scheme 4.26). The crude reaction product was purified by column chromatography to give the desired product 103 in 16% yield and with modest diastereoselectivity (dr = 79:21). A pinacol was co-eluted with 103 which represents 36% of the total mass of the product mixture (total mass of the product mixture = 27.8 mg, weight of pinacol = 10.13 mg). In terms of yield and diastereoselectivity, the synthesis of the syn-1,2 amino silyl product 103 from imine 83 (29%, dr = 90:10) was more efficient than the one pot, three component reaction (16%, dr = 79:21).

Scheme 4.26. One pot, three component synthesis of racemic compound 103

4.5.4. Using salicylaldehyde and p-methoxybenzylamine:
The one pot, three component allylation reaction between salicylaldehyde, p-methoxybenzylamine and the freshly prepared γ-TMS allylboronate 70 to produce syn-1,2 amino silyl product 104, was also examined under the reaction conditions described earlier (Scheme 4.27). The crude reaction product was purified by column chromatography to give the desired product 104 in 25% yield and with modest diastereoselectivity (dr = 77:23). In terms of diastereoselectivity, the synthesis of the syn-1,2 amino silyl product 104 from imine 84 (27%, dr = 94:6) was more selective than the one pot, three component reaction (25%, dr = 77:23).

Scheme 4.27. One pot, three component synthesis of racemic compound 104
4.5.5. Using the methyl ether of salicylaldehyde and benzylamine:
The one pot, three component allylation reaction between 2-methoxybenzylaldehyde, N-benzylamine and the freshly prepared γ-TMS allylboronate 70 to produce syn-1,2 amino silyl product 105, was also examined (Scheme 4.28). The crude reaction mixture was analyzed by $^1$H-NMR spectroscopy which showed formation of the alcohol adduct 107 in a mixture with the starting aldehyde. The yield of compound 107 (17%) was calculated from the $^1$H-NMR spectrum using the ratio of the integrals at δ 3.88 (OMe of starting aldehyde) and δ 3.79 (OMe of 107) to give their molar ratio (Figure 4.12).

![Scheme 4.28. Proposed one pot, three component synthesis of compound 105](image)

![Figure 4.12. $^1$H-NMR spectrum (CDCl3, 300 MHz) of compound 107 plus 2-methoxybenzylaldehyde](image)
4.5.6. Using salicylaldehyde and morpholine:

The one pot, three component allylation reaction between salicylaldehyde, morpholine and the freshly prepared γ-TMS allylboronate 70 to produce syn-1,2 amino silyl allyl product 108, was also examined (Scheme 4.29). The crude reaction mixture was analyzed by $^1$H-NMR spectroscopy which showed formation of the alcohol adduct 109 instead of the desired amine in 27% yield (dr = 78:22). The lack of reactivity for the morpholine may be due to the slow formation of iminium ion, which consequently led to formation of the alcohol product. The $^1$H-NMR spectrum of 109 revealed the presence of several impurities (Figure 4.13).

Scheme 4.29. Attempted one pot, three component synthesis of compound 108

Figure 4.13. $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of compound 109
The $^1$H-NMR spectrum of compound 109 (Figure 4.13) showed resonances for the vinyl H1 protons at $\delta$ 5.06 (dd, $J_{cis} = 10.2, 1.9$ Hz, 1H, H1) and $\delta$ 4.94 (dd, $J_{trans} = 17.0, 1.0$ Hz, 1H, H1), respectively while the other vinyl proton H2 was at $\delta$ 5.78 (dt, $J = 17.0, 10.0$ Hz, 1H, H2). The protons of H3 and H4 resonated at $\delta$ 2.51 (t, $J = 9.5$ Hz, 1H, H3) and $\delta$ 5.16 (d, $J = 9.0$ Hz, 1H, H4), respectively. The methyl protons attached to the silyl group resonated at $\delta$ 0.26 (s, 9H). The aromatic ring protons resonated at $\delta$ 7.35 (td, $J = 8.0, 1.5$ Hz, 1H, H10), $\delta$ 7.20 (m, 1H, H8), $\delta$ 7.08 (ddd, $J = 18.3, 7.8, 1.5$ Hz, 1H, H7) and $\delta$ 6.99 (td, $J = 7.4, 1.2$ Hz, 1H, H9). While the LRMS of C$_{13}$H$_{20}$O$_2$Si$^+$ m/z 356 did not match the expected molecular formula of compound 109, its spectroscopic data were consistent with the proposed structure.

Table 4.3 summarizes the results of the one pot, three component reactions of aldehydes (salicylaldehyde, benzaldehyde, 2-methoxybenzaldehyde), and amines (benzylamine, allylamine, p-methoxybenzylamine, morpholine) with the allyl boronate 70.

**Table 4.3.** One pot, three component reactions of the allyl boronate 70 with different aldehydes and amines.

<table>
<thead>
<tr>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Yield</th>
<th>$dr$ (syn:anti)</th>
<th>$J_{S,A}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>Ph</td>
<td>99</td>
<td>89:11</td>
<td>6.0 Hz</td>
</tr>
<tr>
<td>OH</td>
<td>≡≡≡</td>
<td>103</td>
<td>79:21</td>
<td>5.8 Hz</td>
</tr>
<tr>
<td>OH</td>
<td>≡≡≡O</td>
<td>104</td>
<td>77:23</td>
<td>6.0 Hz</td>
</tr>
<tr>
<td>OH</td>
<td>≡ ≡ ≡</td>
<td>alc. adduct 109</td>
<td>22:78</td>
<td>9.0 Hz</td>
</tr>
<tr>
<td>OMe</td>
<td>Ph</td>
<td>alc. adduct 107</td>
<td>4:96</td>
<td>7.6 Hz</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>1 eq 70 (102 17%)</td>
<td>83:17</td>
<td>102 6.0 Hz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 eq 70 (alc. adduct 106 14%)</td>
<td>23:77</td>
<td>106 8.5 Hz</td>
</tr>
</tbody>
</table>
In summary, the reactions of TMS allyl boronate 70 with the preformed imines 83, 84 and 85 were more efficient than the three, component reactions in which the imines were formed in situ. The case was a bit different when the methyl ether of salicylaldehyde and benzylamine were used. The 1,2 amino alcohol 105 was not formed under borono-Mannich reaction conditions and the alcohol adduct 107 was formed instead. In addition, the three-component reaction using TMS allyl boronate 70, salicylaldehyde and a secondary amine was not successful. The three-component reaction using 1 equivalent of TMS allyl boronate 70, benzaldehyde and benzylamine gave the 1,2 amino alcohol 102 as the syn-isomer, while using 2 equivalents of 70 gave the corresponding alcohol adduct 106.

4.6. Three component model reactions of γ-TMS allylboronate 70 with benzyamine and aliphatic aldehydes:
To further examine the efficiency of TMS pinacol boronate 70 in homoallyl amine synthesis, the allylation of different aliphatic aldehydes with benzylamine under borono-Mannich reaction conditions was investigated and this is reported in the following section.

4.6.1. Using ethyl glyoxylate:
The one pot, three component allylation reaction between ethyl glyoxylate, N-benzylamine and the freshly prepared γ-TMS allylboronate 70 to produce syn-1,2 amino silyl product 110, was also examined under the reaction conditions described above (Scheme 4.30). The crude reaction product was purified by column chromatography to give the desired product 110 in 13% yield and with modest diastereoselectivity (dr = 73:27) as determined by integration of the 1H-NMR doublet resonances at δ 3.77 and δ 3.70 for Ha for the major and minor diastereomers, respectively (Figure 4.14).

Scheme 4.30. One pot three components synthesis of racemic compound 110
The $^1$H-NMR spectrum of compound 110 (Figure 4.14) showed resonances for the vinyl H1 protons at $\delta$ 4.87 (m, 2H, H1) while the other vinyl proton H2 resonated at $\delta$ 5.63 (m, 1H, H2, major isomer) and $\delta$ 5.75 (dt, $J = 17.0$, 10.4 Hz, 1H, H2, minor isomer). The diastereotopic N-benzylic proton Ha resonated at $\delta$ 3.77 (d, $J = 12.5$ Hz, 1H, major isomer) and $\delta$ 3.70 (d, $J = 13.0$ Hz, 1H, minor isomer) while Hb proton was at $\delta$ 3.51 (d, $J = 12.5$ Hz, 1H, major isomer) and $\delta$ 3.57 (d, $J = 13.0$ Hz, 1H, minor isomer). The H3 proton resonated at $\delta$ 1.96 (dd, $J = 11.5$, 4.5 Hz, 1H, major isomer) and $\delta$ 1.90 (dd, $J = 19.5$, 10.0 Hz, 1H, minor isomer) while H4 proton was at $\delta$ 3.39 (d, $J = 4.5$ Hz, 1H, major isomer) and $\delta$ 3.32 (d, $J = 9.0$ Hz, 1H, minor isomer), respectively. The methyl protons attached to silyl group resonated at $\delta$ 0.00 (s, 9H, major isomer) and $\delta$ 0.06 (s, 9H, minor isomer). The ethyl protons H5 and H6 attached to the ester group resonated at $\delta$ 4.15 (m, 2H, H5) and $\delta$ 1.22 (m, 3H, H6), while the NH proton resonated at $\delta$ 4.32 (s, 1H). The aromatic ring protons attached to the N-benzylic group resonated at $\delta$ 7.33-7.19 (m, 5H). Unfortunately, due to compound decomposition no further characterizations were made. The LRMS of C$_{17}$H$_{28}$NO$_{2}$Si$^+$ showed an [M+H$^+$] ion peak at $m/z$ 306 which confirmed the correct molecular formula of compound 110.
4.6.2. Using paraformaldehyde:

The one pot, three component allylation reaction between paraformaldehyde, N-benzylamine and the freshly prepared γ-TMS allylboronate 70 to produce syn-1,2 amino silyl product 111, was examined. The benzylamine and freshly prepared silyl allyl boronate 70 was added to a solution of paraformaldehyde in anhydrous EtOH. Then the reaction mixture was heated to reflux for 2 days (Scheme 4.31). The crude reaction product was purified by column chromatography to give the desired product 111 in 4% yield.

\[
\text{(CH}_2\text{O)}_\text{n} + \text{BnNH}_2 + \begin{array}{c}
\text{O} \\
\text{O} \\
\text{SiMe}_3
\end{array}_{70} \xrightarrow{\text{reflux, 90-100 °C, 2 d}} \text{EtOH}
\]

\[\begin{array}{c}
\text{Ha} \\
\text{HN} \\
\text{SiMe}_3
\end{array}_{111} \text{ 4%}
\]

Scheme 4.31. Synthesis of compound 111

![Scheme 4.31. Synthesis of compound 111](image)

**Figure 4.15.** $^1\text{H-NMR}$ spectrum (CDCl$_3$, 500 MHz) of compound 111

The $^1\text{H-NMR}$ spectrum of compound 111 (Figure 4.15) showed resonances for the vinyl H1 protons at $\delta$ 4.96 (dd, $J = 10.0$, 1.0 Hz, 1H cis) and $\delta$ 4.91 (d, $J = 17.0$ Hz, 1H trans). The diastereotopic N-benzylic protons resonated at $\delta$ 3.82 (d, $J = 13.0$ Hz, 1H, Ha) and $\delta$ 3.70 (d, $J = 13.0$ Hz, 1H, Hb). The other vinyl proton H2 resonated at $\delta$ 5.62 (dt, $J = 17.0$, 10.0 Hz, 1H, H2) while H3 was at $\delta$ 1.89 (td, $J = 10.5$, 3.7 Hz, 1H, H3). The H4 protons...
were at $\delta$ 2.76 (dd, $J = 11.5, 3.5$ Hz, 1H, Hc) and $\delta$ 2.70 (t, $J = 11.5$ Hz, 1H, Hd), respectively. The methyl protons attached to silyl group resonated at $\delta$ - 0.02 (s, 9H). The aromatic ring protons attached to the N-benzyl group resonated at $\delta$ 7.36-7.21 (m, 5H). The $^1$H-NMR spectrum showed resonances for pinacol which co-eluted with product 111 which represents 23% of the total mass of the product mixture (total mass of the product mixture = 5.4 mg, weight of pinacol = 1.225 mg).

![Figure 4.16. $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of compound 111](image)

The $^{13}$C-NMR spectrum of compound 111 (Figure 4.16) showed resonances for the terminal alkene carbons at $\delta$ 114.0 (C1) and 138.4 (C2). The N-benzylic carbon resonated at $\delta$ 53.6, while C3 and C4 resonated at $\delta$ 36.0 and 48.4, respectively. The aromatic ring carbons resonated at $\delta$ 128.5-127.1. The carbon signals for the methyl protons attached to silyl group resonated at $\delta$ - 2.9. Assignment of both the $^1$H-NMR and $^{13}$C-NMR spectra was confirmed through running of gCOSY (Appendix C-17) and gHSQC (Appendix C-18) experiments. The LRMS of C$_{14}$H$_{24}$NSi$^+$ showed an [M+H$^+$] ion peak at $m/z$ 234 which confirmed the correct molecular formula of compound 111.
Table 4.4 summarizes the results of one pot, three component reactions of different aldehydes (ethylglyoxylate and paraformaldehyde), benzylamine with the allyl boronate 70. In summary, the reactions of γ-TMS-allylboronate 70 with the imines formed between aliphatic aldehydes (glyoxylate and paraformaldehyde) and benzylamine formed in situ produced the corresponding amine silyl products in very low yields. These results indicate that the synthesis of amine silyl products using in-situ formed N-aryl imines were more efficient than those using in-situ formed N-alkyl imines.

Table 4.4. One pot three components reaction of the allyl boronate 70 with different aldehydes

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Solvent</th>
<th>T °C</th>
<th>Time</th>
<th>Product yield %</th>
<th>dr (syn:anti)</th>
<th>J3,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>O=CHCH=O</td>
<td>EtOH</td>
<td>then rt (2 h)</td>
<td>(CHO+amine) 45 (1 h) then rt (2 h) add 74 rt (16 h)</td>
<td>110 13%</td>
<td>73:27</td>
<td>4.5 Hz</td>
</tr>
<tr>
<td>O=CHCH=O</td>
<td>EtOH</td>
<td>90-100</td>
<td>2 d</td>
<td>111 4%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In conclusion, an attempt to synthesize the γ-TMS allylboronate 70 through a Pd-catalyzed borylation of 3-iodovinylsilane 69 with B2(pin)2, were unsuccessful due to problems of synthesizing the starting vinyl silane 69 through iodination of the 3-TMS-allyl alcohol. However, the Pd-catalyzed borylation of 3-TMS-allyl alcohol with B2(pin)2 was successful in providing the pinacol γ-TMS allylboronate 70. The use of boronate 70 as an allylating agent was limited due to its limited shelf stability, therefore the use of freshly prepared samples was essential for achieving reasonable chemical yields in its subsequent reactions. The efficiency of pinacol γ-TMS allylboronate 70 to produce the corresponding 1,2-amino silyl products was explored using the imines formed between salicyaldehyde or O-methyl salicylaldehyde and different amines, either in situ or preformed. The best results were obtained when preformed imines were used. The reaction of pinacol γ-TMS allylboronate 70 with imines 73, 83, 84 and 89 afforded the corresponding 1,2-amino silyl products 99, 103, 104 and 105, respectively in moderate
yields (27-43%) but with high diastereoselectivities (dr = 90:10 to 94:6) for the syn-isomer. A chair like transition state, involving H-bonding between the ortho-hydroxy group on the imine to the pinacol ester oxygen, was proposed to explain the stereochemical outcomes of these reactions. The reaction of γ-TMS-allylboronate 70 with the imine formed between benzaldehyde and benzylamine formed in situ produced the amine silyl product 102 with modest diastereoselectivity (dr = 83:17). The reaction of γ-TMS-allylboronate 70 with the imine formed between aliphatic aldehydes (glyoxylate and paraformaldehyde) and benzylamine formed in situ produced the amine silyl product 110 and 111 in low yields (13% and 4%, respectively).
Chapter 5: Conclusions and future directions

5.1. Conclusions:

We have developed synthetic methodology for preparing 1,2-amino alcohols and 1,2-amino trimethylsilanes from the addition reactions of 3-alkoxy, 3-acyloxy or 3-trialkylsilyl allyl organo indium, zinc or boron reagents to in situ formed or preformed imines. This methodology could potentially be used in future studies for synthesis of the alkaloid alexine.

In Chapter 2, we reported the efficiency of the reactions between 3-acyloxyallyl indium or zinc reagents with the imine formed between salicylaldehyde and benzylamine, either formed in situ or preformed, to produce the corresponding 1,2-amino alcohol products. The combination of 3-methoxycarbonylallyl bromide and indium powder and the preformed imine gave the desired 1,2-N-benzylamino O-methyloxy carbonyl product 75 in only 12% yield but with good diastereoselectivity (dr = 95:5). Under similar reaction conditions, the corresponding 3-benzoyloxyallyl bromide failed to produce any of the desired product. This study then focused on reactions of related allyl boronates which were reported in Chapter 3.

In Chapter 3, we reported an unsuccessful attempt to synthesize pinacol 3-O-benzylallylboronate 67 through a cross-coupling borylation of the allyl dibenzylacetal 77 with B$_2$(pin)$_2$. However, the Pd-catalyzed borylation of 3-benzoyloxyallyl bromide 66b was successful in providing the pinacol 3-O-benzoxyallyl boronate 68. The use of this boronate as an allylating agent was limited due to its relatively short shelf life, therefore the use of freshly prepared samples was essential for achieving reasonable chemical yields in its subsequent reactions. The reaction of pinacol 3-O-benzoxyallyl boronate 68 with imines 73, 83, 84 and 85 prepared from salicylaldehyde and primary amines afforded the corresponding 1,2-amino alcohol products 78, 86, 87 and 88 in moderate yields (31-69%) but with high diastereoselectivities (dr = 91:9 to 95:5) for the syn-isomer. A chair like transition state, involving H-bonding between the ortho-hydroxy group on the imine to the pinacol ester oxygen, was proposed to explain the stereochemical outcomes of these reactions. The reaction of pinacol 3-O-benzoxyallyl boronate 68 with imine 89 derived from O-methyl salicylaldehyde and benzylamine produced the amine alcohol product 90.
with very low diastereoselectivity (dr = 58:42) showing the importance of the presence of the ortho-hydroxy group on the imine in controlling the diastereoselectivity.

In Chapter 4, we reported an unsuccessful attempt to synthesize the γ-TMS allylboronate 70 through a Pd-catalyzed borylation of 3-iodovinylsilane 69 with B₂(pin)₂, due to the unsuccessful synthesis of the starting vinyl silane 69 through iodination of the 3-TMS-allyl alcohol. However, the Pd-catalyzed borylation of 3-TMS-allyl alcohol with B₂(pin)₂ successfully gave the pinacol γ-TMS allylboronate 70. The use of boronate 70 as an allylating agent was limited due to its limited shelf stability, therefore the use of freshly prepared samples was essential for achieving reasonable chemical yields in its subsequent reactions. The reaction of pinacol pinacol γ-TMS allylboronate 70 with imines 73, 83, 84 and 89 prepared from either salicylaldehyde or O-methyl salicylaldehyde and primary amines afforded the corresponding 3,4-amino silyl products 99, 103, 104 and 105 in moderate yields (27-43%) but with high diastereoselectivities (dr = 90:10 to 94:6) for the syn-isomer. A chair like transition state, involving H-bonding between the ortho-hydroxy group on the imine to the pinacol ester oxygen, was proposed to explain the stereochemical outcomes of these reactions. The reaction of γ-TMS-allylboronate 70 with the imine formed between benzaldehyde and benzylamine formed in situ produced the amine silyl product 102 with modest diastereoselectivity (dr = 83:17). The reaction of γ-TMS-allylboronate 70 with the imine formed between aliphatic aldehydes (glyoxylate and paraformaldehyde) and benzylamine formed in situ produced the amine silyl product 110 and 111 in low yields (13% and 4%, respectively).

5.2. Future directions:

The one pot condensation reaction between silyl allyl amine 99 and the more reactive aldehyde (ethyl glyoxylate) in the presence of a Lewis acid (for example InCl₃) could be examined to produce the 2,6-tetrahydropyridine 112 (Scheme 5.1).¹²⁵,¹²⁶

Scheme 5.1. Proposed synthesis of tetrahydropyridine 112
Furthermore, the dimethylphenylsilyl analogue of 70 will be prepared (Scheme 5.2) which may be more stable to silica gel chromatography and allow the synthesis of the corresponding amino alcohols via Fleming-Tamao oxidation (Scheme 5.3).127,128 The ethylene glycol ester analogues of 70 and its corresponding Me₂PhSi derivative will also be prepared which may solve the problem of having pinacol impurities in the final products.

The extension of this chemistry to the use of other imines, including relating to the sugar derivative in Scheme 1.17 will be examined with the aim of preparing azasugar alkaloids, including alexine.

**Scheme 5.2.** Proposed synthesis of Me₂PhSi allylboronate

**Scheme 5.3.** Fleming/Tamao oxidation to give 1,2-amino alcohols
Chapter 6: Experimental

6.1. General experimental:

6.1.1. Reaction conditions:
All reactions performed in oven dried glassware under an atmosphere of nitrogen, unless otherwise stated. Reactions were monitored by thin-layer chromatographic analysis. Evaporation refers to the removal of solvent under reduced pressure using a rotator evaporator and then the removal of the last traces of solvent under high vacuum. "Dried" refers to the drying of organic extracts over anhydrous MgSO₄.

6.1.2. Nuclear Magnetic Resonances (NMR) Spectroscopy:
¹H and ¹³C NMR spectra were recorded on a Varian Inova and Varian Mercury NMR spectrometers (¹H NMR at 500 and 300 MHz, and ¹³C NMR at 126 and 75 MHz) instruments. CDCl₃ (internal reference at δ 7.26 for ¹H NMR and δ 77.0 for ¹³C NMR) was used as the NMR solvent unless otherwise stated. The following abbreviations were used; s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dddd = doublet of doublet of doublet of doublet, dt = doublet of triplet, ddt = doublet of doublet of triplet, , t = triplet, td = triplet of doublet, q = quartet, m = multiplet. NMR assignments were based on gCOSY and gHSQC experiments unless otherwise stated.

6.1.3. Chromatography:
TLC analyses were performed using aluminium backed Merck silica gel TLC plates. Compounds were detected under a 254 nm ultraviolet lamp if applicable, or by staining with an acidified aqueous solution of ammonium molybdate, followed by development with a 1400 W heat gun. Flash column chromatography was performed using Merck silica gel (40-63 µm) packed by the slurry method.

6.1.4. Mass Spectrometry:
Low-resolution mass spectra were obtained on a Waters LCZ single quadruple (LRESI). High-resolution mass spectra (exact masses) were obtained on a Water QTOF (HRESI).
6.2. Experimental for Chapter 2:
2-(1-(Benzylamino)but-3-en-1-yl)phenol 72

**Method A.** Salicylaldehyde 71 (100 mg, 87 μL, 0.82 mmol) in anhydrous MeOH (0.31 ml) was stirred in the presence of benzylamine (1 equiv, 71 μL, 0.82 mmol) at 45 °C for 1 h, then at room temperature for 2 h to form the corresponding imine 73 *in situ*. Allyl bromide (3 equiv, 213 μL, 2.46 mmol) and powdered indium (2 equiv, 188.3 mg, 1.64 mmol) were then added and the solution was stirred at room temperature for 18 h under a nitrogen atmosphere. Then the reaction mixture was diluted with saturated sodium bicarbonate solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (1:9, 250 mL) to afford the title compound 72 (55 mg, 27%) as yellow crystals. The corresponding imine 73 was also isolated (15 mg, 9%). The spectroscopic data of imine 73 is discussed later in Chapter 3 experimental.

**Method B.** The N-benzylimine 73 (1 equiv, 101 mg) was dissolved in anhydrous MeOH (0.5 mL) under a nitrogen atmosphere, and then allyl bromide (3 equiv, 124 μL, 1.43 mmol) and powdered indium (2 equiv, 109.78 mg, 0.96 mmol) were added to the reaction mixture and then stirred at rt for 16 h. Then the reaction mixture was diluted with saturated NH₄Cl solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (4:96, 250 mL) to afford the title compound 72 (57 mg, 48%) as yellow crystals and 74 (2 mg, 3%) as a white solid.

**^1H-NMR (500 MHz, CDCl₃):** δ 7.24-7.35 (m, 5H, Ar-CH), 7.16 (ddd, J =8.1, 7.3, 1.7 Hz, 1H, H4'), 6.95 (dd, J = 7.5, 1.7 Hz, 1H, H6'), 6.85 (dd, J = 9.5, 2.5 Hz, 1H, H3'), 6.80 (td, J =7.5, 1.5 Hz, 1H, H5'), 5.66-5.75 (m, 1H, H2), 5.14 (s, 1H, C4-NHCH₂Ph), 5.11-5.13 (m, 2H, H1), 3.85 (d, J = 13.1 Hz, 1H, C4-NHCHHPh), 3.80 (t, J =8.0, 6.5 Hz, 1H, H4), 3.58 (d, J = 13.1 Hz, 1H, C4-NHCHHPh), 2.49 (ddt, J = 7.9, 6.6, 1.2 Hz, 2H, H3).
$^{13}$C-NMR (126 MHz, CDCl$_3$): δ 157.6 (C2'), δ 138.5 (Ar-C$_{ipso}$), 134.6 (C2), 128.9 (C6'), 128.5-128.8 (Ar-C), 124.8 (C1'), 119.3 (C1), 117.0 (C3'), 62.1 (C4), 51.6 (NHCH$_2$Ph), 40.8 (C3).

ESIMS m/z 254 (100%) [M+H$^+$].

HRMS (ESI): m/z calculated for C$_{17}$H$_{20}$NO [M+H$^+$]: 254.1545, found 254.1557.

2-(1-Hydroxybut-3-en-1-yl)phenol 74

![Chemical structure of 2-(1-Hydroxybut-3-en-1-yl)phenol 74]

$^1$H-NMR (500 MHz, CDCl$_3$): δ 7.18 (td, 1H, H8), 6.98 (dd, $J = 7.6$, 1.7 Hz, 1H, H10), 6.86 (m, 3H, Ar-CH), 5.86 (dddd, $J = 17.8, 9.8, 8.0, 6.3$ Hz, 1H, H2), 4.89 (dd, $J = 8.5, 5.0$ Hz, 1H, H4), 2.72-2.57 (m, 2H, H1).

$^{13}$C-NMR (126 MHz, CDCl$_3$): δ 155.7 (C6), δ 134.0 (C2), 129.1 (C10), 127.2-117.5 (Ar-C), 119.9 (C1), 74.8 (C4), 42.3 (C3).

ESIMS m/z 163 (100%) [M-H$^-$].

HRMS (ESI): m/z calculated for C$_{10}$H$_{11}$O$_2$ [M-H$^-$]: 163.0759, found 163.0762.

3-Bromopropenyl methyl carbonate 66a

Allyl methyl carbonate (2.73 mL, 24 mmol) in 1,2-dichloroethane (100 mL) was treated with purified NBS (3.56 g, 20 mmol) in the presence of the radical initiator AIBN (0.334 g, 2 mmol). The reaction mixture was heated for 2-3 mins and then stirred at 80-90 °C for 9 h. The reaction was then cooled to rt. After evaporation of the reaction solvent, the crude reaction mixture was washed with PS and then dried over magnesium sulfate, filtered, and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography (10% EtOAc: PS (1:9), 250 mL) to afford the title compound 66a (0.669 g, 14%) as a mixture of E:Z (30:70) isomers.
$^1$H-NMR (500 MHz, CDCl$_3$):

$E$ isomer: $\delta$ 7.25 (d, $J = 12.2$ Hz, 1H, H3), 5.74 (dt, $J = 12.2$, 8.4 Hz, 1H, H2), 3.99 (d, $J = 8.4$ Hz, 2H, HC=CHCH$_2$Br), 3.87 (s, 3H, OMe).

$Z$ isomer: $\delta$ 7.00 (d, $J = 6.2$ Hz, 1H, H3), 5.25 (td, $J = 8.4$, 6.1 Hz, 1H, H2), 4.08 (d, $J = 8.4$ Hz, 2H, HC=CHCH$_2$Br), 3.89 (s, 3H, OMe).

ESIMS m/z 196 (100%) [M+H$^+$].

HRMS (ESI): m/z calculated for C$_5$H$_8$BrO$_3$ [M+H$^+$]: 196.1234, found 196.1245.

$^{15,25}_S$-1-(Benzylamino)-1-(2-hydroxyphenyl)but-3-en-2-yl methyl carbonate 75

The N-benzylimine 73 (1 equiv, 105 mg, 0.497) was dissolved in MeOH (0.7 mL) under a nitrogen atmosphere, and then a 1:1 mixture of allyl methyl carbonate and 3-bromopropenyl methyl carbonate 66a $E$:$Z$ (30:70) (3 equiv, 0.291 g, 1.49 mmol) and powdered indium (2 equiv, 0.114 g, 0.994 mmol) were added to the reaction mixture which was stirred at rt for 16 h. Then the reaction mixture was diluted with saturated NH$_4$Cl solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (4:96, 250 mL) to afford the title compound 75 (20 mg, 12%, dr = 95:5) as yellow crystals.

$^{1}$H-NMR (500 MHz, CDCl$_3$):

$\delta$ 7.35-7.23 (m, 5H, NHCH$_2$Ph), 7.20 (t, $J =$7.5 Hz, 1H, H8), 7.03 (d, $J =$ 7.7 Hz, 1H, H10), 6.85-6.79 (m, 2H, H7 and H9), 5.90-5.80 (m, 1H, H2), 5.35-5.25 (m, 3H, H1 and H3), 4.06 (d, $J =$ 5.5, 1H, H4), 3.91 (d, $J =$ 13.2 Hz, 1H, Ha), 3.71 (s, 3H, OMe), 3.60 (d, $J =$ 13.2 Hz, 1H, Hb).

$^{13}$C-NMR (126 MHz, CDCl$_3$):

$\delta$ 158.4 (C=O), 154.6 (C6), 131.3 (C2), 120.3 (C1), 80.7 (C3), 65.4 (C4), 51.8 (N-CH$_2$), 54.9 (OMe).

The LRMS of compound 75 did not confirm the molecular formula of compound 75.
3-Bromopropenyl benzoate 66b

Benzoyl bromide (1 equiv, 2.114 mL, 20 mmol) was added at 0 °C to a mixture of acrolein (1 equiv, 1.33 mL, 20 mmol) in anhydrous DCM (20 mL). Then the ice bath was removed, and reaction mixture was stirred at rt for 3 d. Then the reaction mixture was diluted with saturated NaHCO₃ solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated in vacuo. The title compound 66b was obtained (4 g, 74%) as black crystals of the pure E isomer after recrystallization from PS.

¹H-NMR (500 MHz, CDCl₃):
δ 8.04-8.19 (m, 2H, H5 and H9), 7.67 (dt, J = 12.3, 1.2 Hz, 1H, H3), 7.62 (td, J = 7.4, 1.3 Hz, 1H, H7), 7.41-7.58 (m, 2H, H6 and H8), 5.90 (dt, J = 12.3, 8.4 Hz, 1H, H2), 4.07 (dd, J = 8.5, 1.5 Hz, 2H, HC=CHCΗ₂Br).

¹³C-NMR (126 MHz, CDCl₃):
δ 163.2 (C=O), 139.4 (C3), 133.7 (C7), 130.2 (C9), 130.1 (C5), 128.6 (C8), 128.5 (C6), 111.8 (C2), 28.4 (C1).

ESIMS m/z 262 (100%) [M+H⁺].
HRMS (ESI): m/z calculated for C₁₀H₉BrO₂Na [M+Na⁺]: 262.9684, found 262.9684.

6.3. Experimental for Chapter 3:
1-O-Benzyl allene 76

A solution of the benzyl propargyl ether (1 equiv, 1.22 g, 8.345 mmol) in THF (0.65 mL) was stirred in presence of t-BuOK (0.29 equiv, 0.27 g, 2.42 mmol) at rt for 3 h. Then the reaction solvent was evaporated, and the crude product was diluted with Et₂O (50 mL) and filtered through a celite pad. Then the residue was purified by column chromatography Et₂O:PS (1:9, 250 mL) to afford the title compound 76 (98%, 1 g) as a yellowish liquid.

¹H-NMR (500 MHz, CDCl₃):
δ 7.40-7.26 (m, 5H, Ar-CH), 6.83 (t, J = 5.9 Hz, 1H, H1), 5.48 (d, J = 5.9 Hz, 2H, H3),
4.62 (s, 2H, -OCH₃Ph).

**Allyl dibenzyl acetal 77**

A solution of the benzyloxyallene 76 (1 equiv, 1.3 g, 8.9 mmol) in DCM (4.45 mL) was stirred with benzyl alcohol (1 equiv, 1.53 g, 8.9 mmol) at -10 °C in the presence of PTSA (27 mg, 0.25 mol %) for 2 h. Then the reaction was terminated by adding Et₃N (one drop). Then the reaction mixture was diluted with saturated NaHCO₃ solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined and washed with 5% Na₂CO₃ (15 mL), dried over magnesium sulfate, filtered and evaporated in vacuo. The crude product mixture was purified by column chromatography 200 mL DCM/PS (1:1) to afford the title compound 77 (1.5 g, 66%) as yellow crystals.

**1H-NMR (500 MHz, CDCl₃):**

δ 7.35-7.28 (Ar-CH, 10H), 5.95 (ddd, J = 17.3, 10.6, 4.7 Hz, 1H, H2), δ 5.51 (d, J = 17.4 Hz, 1H, H1 *trans*), 5.37 (d, J = 10.6 Hz, 1H, H1 *cis*), 5.14 (d, J = 4.6 Hz, 1H, H3), 4.67 (d, J = 11.8 Hz, 2H, C3-OCH₃Ph), 4.58 (d, J = 11.8 Hz, 2H, C3-OCH₃Ph).

**13C-NMR (75 MHz, CDCl₃):**

δ 135.6 (C2), 119.1 (C1), 100.3 (C3), 67.2 (OCH₃Ph).

**ESIMS m/z 277 (100%) [M+Na⁺].**

**HRMS (ESI): m/z** calculated for C₁₇H₁₈O₂Na [M+Na⁺]: 277.3301, found 277.3311.

**3-O-Benzoyl allyl boronate 68**

In two neck round bottom flask under a nitrogen atmosphere 3-bromopropenyl benzoate 66b (0.5 g, 2.074 mmol) was added to a mixture of PdCl₂ (0.0089 g, 10% mol), B₂(pin)₂ (1 equiv, 0.53 g) and KOAc (1 equiv, 0.203 g) in THF (1.5 mL), with stirring at 60 °C for 16 h. Then the reaction mixture was diluted with Et₂O and filtered through a silica pad. Then the residue was purified by column chromatography Et₂O:PS (5:95, 150 mL) to afford the title compound 68 (0.548 g, 92%, *E* isomer) as a colorless oil.
$^1$H-NMR (500 MHz, CDCl$_3$):
8.09 (t, $J = 8.3$ Hz, 2H, H1' and 5'), 7.64-7.53 (m, 1H, H3'), 7.46 (dt, $J = 9.8$, 7.7 Hz, 2H, H2' and 4'), 7.31 (d, $J = 12.0$ Hz, 1H, H3), 5.65 (dt, $J = 12.0$, 8.0 Hz, 1H, H2), $\delta$ 1.69 (d, $J = 8.0$ Hz, 2H, H1), $\delta$ 1.32-1.18 (m, 12 H, Me$_4$).

$^{13}$C-NMR (126 MHz, CDCl$_3$):
$\delta$ 135.7 (C3), 133.4 (C3'), 130.3 (C5'), 130.0 (C1'), 128.57 (C4'), 128.54 (C2'), 111.2 (C2), 83.7 (C8'), 83.3 (C7'), 38.6 (C1), 24.6 (Me).

ESIMS m/z 311 (100%) [M+Na$^+$].
HRMS (ESI): m/z calculated for C$_{16}$H$_{21}$BO$_4$Na [M+Na$^+$]: 311.1431, found 311.1444.

General Method 1 for imine synthesis:
Benzylimine ((E)-2-((benzylimino)methyl)phenol) 73

Salicylaldehyde 71 (1 equiv, 0.85 g, 7.0 mmol) was dissolved in distilled water (10.5 mL), and then the reaction mixture was treated with benzylamine (1.1 equiv, 0.82 g, 7.7 mmol) in one portion and stirred at rt for 3 h. the reaction mixture was cooled to 0 °C in an ice bath forming a yellow solid. The solid was collected and dissolved in DCM and dried over magnesium sulfate, filtered and evaporated in vacuo to afford the title compound 73 (1.45 g, 98%) as yellow crystals.

$^1$H-NMR (500 MHz, CDCl$_3$):
$\delta$ 13.37 (s, 1H, OH), 8.44 (s, 1H, H$_2$C=NCH$_2$Ph), 7.34 (d, $J =$7.5 Hz, 1H, H6'), 7.25-7.31 (m, 5H, Ar-CH$_3$), 6.96 (d, $J =$8.5 Hz, 1H, H3'), 6.88 (t, $J =$7.5 Hz, 1H, H5'), 4.81 (s, 2H, C=NCNCH$_3$Ph).

ESIMS m/z 212 (100%) [M+H$^+$].
HRMS (ESI): m/z calculated for C$_{14}$H$_{14}$NO [M+H$^+$]: 212.2036, found 212.2027.
(E)-2-((Allylimino)methyl)phenol 83

The title compound was prepared by Method 1 using allylamine (1.1 equiv, 0.44 g, 7.7 mmol) instead of benzylamine to afford 83 (1.07 g, 95%) as yellow crystals.

\(^1\)H-NMR (500 MHz, CDCl\(_3\)):
\(\delta\) 13.42 (s, 1H, OH), 8.36 (s, 1H, H\(_{\text{C=N}}\)), 7.31 (ddd, \(J = 8.6, 7.4, 1.7\) Hz, 1H, H\(_4'\)), 7.26 (dd, \(J = 1.5, 7.5\) Hz, 1H, H6'), 6.97 (d, \(J = 8.2\) Hz, 1H, H5'), 6.88 (td, \(J = 7.5, 1.1\) Hz, 1H, H3'), 6.02 (ddt, \(J = 17.3, 10.5, 5.5\) Hz, 1H, H2), 5.23 (dd, \(J_{\text{cis}} = 10.5, 1.5\) Hz, 1H, H3), 5.18 (dd, \(J_{\text{trans}} = 17.0, 1.5\) Hz, 1H, H3), 4.24 (dd, \(J = 5.5, 1.0\) Hz, 2H, H1).

\(^{13}\)C-NMR (126 MHz, CDCl\(_3\)):
\(\delta\) 165.7 (H\(_{\text{C=N}}\)), 161.3 (C2'), 134.9 (C2), 132.4 (C4'), 131.4 (C6'), 118.7 (C3'), 117.2 (C5'), 116.6 (C3), 61.5 (C1).

ESIMS \(m/z\) 162 (100%) [M+H\(^+\)].
HRMS (ESI): \(m/z\) calculated for C\(_{10}\)H\(_{12}\)NO [M+H\(^+\)]: 162.0919, found 162.0916.

(E)-2-(((4-Methoxybenzyl)imino)methyl)phenol 84

The title compound was prepared by Method 1 using \(p\)-methoxybenzylamine (1.1 equiv, 1.05 g, 7.7 mmol) instead of benzylamine to afford 84 (1.59 g, 94%) as yellow crystals.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)):
\(\delta\) 13.44 (s, 1H, OH), 8.41 (s, 1H, H\(_{\text{C=N}}\)), 7.26 (m, 4H, Ar-CH), 6.96 (d, \(J = 8.4\) Hz, 2H, H3 and H5), 6.89 (d, \(J = 8.1\) Hz, 2H, H2 and H6), 4.75 (s, 2H, C=NH\(_2\)Ph), 3.81 (s, 3H, OCH\(_3\)).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)):
\(\delta\) 165.3 (H\(_{\text{C=N}}\)), 161.2 C2', 159.0 C4, 129.2 (C2, C6), 114.2 (C3, C5), 62.7 (-NHCH\(_2\)Ph), 55.5 (OMe).
ESIMS m/z 242 (100%) [M+H⁺].

HRMS (ESI): m/z calculated for C₁₅H₁₆NO₂ [M+H⁺]: 242.1181, found 242.1192.

(E)-2-((Benzhydrylimino)methyl)phenol 85

The title compound was prepared by Method 1 using N-diphenylmethanamine (1.1 equiv, 1.41 g, 7.7 mmol) instead of benzylamine to afford 85 (2.03 g, 99%) as yellow crystals.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{Ph} \\
\text{H} & \quad \text{O} \\
\end{align*}
\]

\textbf{85}

\(^1\)H-NMR (500 MHz, CDCl₃):

δ 13.48 (s, 1H, OH), 8.48 (s, 1H, H₂C=NCH₂Ph), 7.38 - 7.22 (m, 11H, Ar-CH and H₄), 7.34 (d, J = 4.4 Hz, 1H, H₃), 6.96 (d, J = 8.3 Hz, 1H, H₆), 6.88 (td, J = 7.5, 1.2 Hz, 1H, H₅), 5.63 (s, 1H, C=NCH₂Ph).

\(^{13}\)C-NMR (126 MHz, CDCl₃):

δ 165.1 (H₂C=N), 161.2 (C₂), 142.6 (C₄), 132.7 (C₃), 131.8 (C₄), 128.8-127.5 (Ar-C), 118.9 (C₅), 117.2 (C₆), 77.4 (C=NCH₂Ph).

ESIMS m/z 288 (100%) [M+H⁺].

HRMS (ESI): m/z calculated for C₂₀H₁₈NO [M+H⁺]: 288.1388, found 288.1387.

General Method 2 for allyl boronate 68 reactions with imines:

(1S,2S)-1-(Benzy lamino)-1-(2-hydroxyphenyl)but-3-en-2-yl benzoate 78

The N-benzylimine 73 (1 equiv, 0.05 g, 0.2367 mmol) was dissolved in MeOH (0.5 mL) under a nitrogen atmosphere, and then the 3-O-benzoyl allyl boronate 68 (2 equiv, 0.136 g, 0.473 mmol) was added to the reaction mixture which was stirred at rt for 16 h. The reaction mixture was diluted with saturated NaHCO₃ solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude reaction mixture was then purified by column.
chromatography EtOAc:PS (4:96, 150 mL) to afford the title compound 78 (61 mg, 69%, dr = 95:5) as a thick yellowish-brown oil.

\(^{1}\)H-NMR (300 MHz, CDCl\(_3\)):
\[ \delta 11.45 (s, 1H, OH), 8.04 (d, J = 7.5 Hz, 1H, H2'), 7.58 (t, J = 7.4 Hz, 1H, H3'), 7.45 (t, J = 7.6 Hz, 1H, H4'), 7.38-7.18 (m, 5H, Ar-CH\(_2\)) \]
\[ 6.96 (dd, J = 7.6, 1.7 Hz, 1H, H10), 6.83 (dt, J = 7.5, 1.5 Hz, 2H, H8 and H9), 5.77-5.64 (m, 2H, H2 and H3), 5.20 (d, J\textsubscript{cis} = 9.0 Hz, 1H, H1), 5.20 (d, J\textsubscript{trans} = 17.1 Hz, 1H, H4), 3.93 (d, J = 13.2 Hz, 1H, Ha), 3.63 (d, J = 13.2 Hz, 1H, Hb). \]

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)):
\[ \delta 158.2 (C6), 133.4 (C3'), 133.2 (C2), 130.7 (C10), 129.8 (C2'), 128.6 (C4'), 119.2 (C8), 118.9 (C1), 117.2 (C9), 76.6 (C3), 65.6 (C4), 51.2 (C4-NHCH\(_2\)Ph). \]

ESIMS \( m/z \) 374 (100%) [M+H\(^+\)].
HRMS (ESI): \( m/z \) calculated for C\(_{24}\)H\(_{24}\)NO\(_3\) [M+H\(^+\)]: 374.1756, found 374.1739.

2-(2-Hydroxy-1-((2-phenylpropan-2-yl)amino)but-3-en-1-yl)phenol 79

To a solution of the amino ester 78 (1 equiv, 0.051 g, 0.1366 mmol) in MeOH (0.5 mL) was added, K\(_2\)CO\(_3\) powder (2 equiv, 0.0377 g, 0.273 mmol). The mixture was stirred at rt for 1 h. Then the reaction mixture was diluted with saturated NH\(_4\)Cl solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (1:1, 50 mL) to afford the title compound 79 (22 mg, 61%) as a pale yellow oil.

\(^{1}\)H-NMR (300 MHz, CDCl\(_3\)):
\[ \delta 7.30 (dd, J = 15.9, 6.0 Hz, 1H, H6'), 7.19 (td, J = 7.7, 1.7 Hz, 1H, H4'), 6.87 (dd, J = 11.1, 7.5 Hz, 1H, H3'), 6.78 (t, J = 7.3 Hz, 1H, Ar-CHp-position), 5.70 (ddd, J = 16.6, 10.5, 5.6 Hz, 1H, H2), 5.14 (d, J = 17.4 Hz, 1H, H1 \textit{trans}), 5.08 (d, J = 10.5 Hz, 1H, H1 \textit{cis}), 4.38 (t, J = 8.4 Hz, 1H, H3), 3.85 (d, J = 13.0 Hz, 1H, Ha), 3.66 (d, J = 8.7 Hz, 1H, H4), 3.59 (d, J = 13.0 Hz, 1H, Hb). \]
$^{13}$C-NMR (75 MHz, CDCl$_3$):
$\delta$ 158.0 (C2'), 137.6 (C2), 130.8 (C3'), 129.2 (C4'), 128.6 (C6'), 119.0 (Ar-Cp-position), 116.9 (C1), 73.9 (C3), 68.2 (C4), 51.2 (C4-NHCH$_2$Ph).

ESIMS $m/z$ 270 (100%) [M+H$^+$].
HRMS (ESI): $m/z$ calculated for C$_{17}$H$_{20}$NO$_2$ [M+H$^+$]: 270.1494, found 270.1486.

(15$^\circ$,25$^\circ$)-1-(Allylamino)-1-(2-hydroxyphenyl)but-3-en-2-yl benzoate 86

The title compound was prepared by Method 2 using N-allylimine 83 (1 equiv, 0.0793 g, 0.4919 mmol) instead of N-benzylimine 73 and allyl boronate 68 (2 equiv, 0.283 g, 0.9838 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 86 (75 mg, 47%, dr = 95:5) as a thick yellowish-brown oil.

$^1$H-NMR (500 MHz, CDCl$_3$):
$\delta$ 8.09 (d, $J = 7.0$ Hz, 2H, H5' and H9'), 7.59 (ddt, $J = 7.5$, 6.0, 3.0 Hz, 1H, H7'), 7.47 (t, $J = 7.8$ Hz, 2H, H6' and H8'), 7.17 (ddd, $J = 8.8$, 7.4, 1.7 Hz, 1H, H10), 6.94 (dd, $J = 7.5$, 1.7 Hz, 1H, H8), 6.79 (m, 2H, H7 and H9), 5.91-5.83 (m, 2H, H2 and H2'), 5.75 (m, 1H, H3), 5.20 (m, 4H, H1 and H1'), 4.11 (d, $J = 7.1$ Hz, 1H, H4), 3.37 (ddt, $J = 14.4$, 4.9, 1.7 Hz, 1H, H3'), 3.17 (dd, $J = 14.5$, 7.5 Hz, 1H, H3').

$^{13}$C-NMR (75 MHz, CDCl$_3$):
$\delta$ 158.3 (C6), 134.6 (C3), 133.5 (C7'), 133.3 (C2), 130.6 (C8), 129.9 (C5'), 129.5 (C10), 128.7 (C6'), 119.1 (C7), 118.9 (C1), 117.8 (C1'), 117.2 (C9), 76.8 (C2'), 65.6 (C4), 49.3 (C3').

ESIMS $m/z$ 324 (100%) [M+H$^+$].
HRMS (ESI): $m/z$ calculated for C$_{20}$H$_{22}$NO$_3$ [M+H$^+$]: 324.1480, found 324.1587.
(15°,25°)-1-(2-Hydroxyphenyl)-1-((4-methoxybenzyl)amino)but-3-en-2-yl benzoate

The title compound was prepared by Method 2 using \( N-(p\text{-methoxy})\)-benzylimine \(84\) (1 equiv, 0.0574 g, 0.2378 mmol) instead of \( N\)-benzylimine \(73\) and allyl boronate \(68\) (2 equiv, 0.14 g, 0.4757 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave \(87\) (38.2 mg, 40%, dr = 95:5) as a thick yellowish-brown oil.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)):
\(\delta\) 11.55 (br, 1H, OH), \(\delta\) 8.04 (d, \(J = 7.2\) Hz, 1H, H2'), \(\delta\) 7.58 (t, \(J = 7.5\) Hz, 1H, H3') and \(\delta\) 7.45 (t, \(J = 7.6\) Hz, 1H, H4'), 7.23 (m, 1H, H8), 7.17 (d, \(J = 8.4\) Hz, 2H, H9' and H11'), 6.95 (dd, \(J = 7.5, 1.7\) Hz, 1H, H10), 6.88 (d, \(J = 8.4\) Hz, 2H, H8' and H12'), 6.81 (m, 2H, H7 and H9), 5.74 - 5.63 (m, 2H, H2 and H3), 5.18 (d, \(J = 6.9\) Hz, 1H cis), 5.18 (d, \(J = 16.2\) Hz, 1H trans), 4.08 (d, \(J = 6.9\) Hz, 1H), 3.87 (d, \(J = 13.1\) Hz, 1H, Ha), 3.81 (s, 3H, OCH\(_3\)), 3.57 (d, \(J = 13.1\) Hz, 1H, Hb).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)):
\(\delta\) 159.2 (C10'), 158.3 (C6), 133.4 (C3'), 133.2 (C2), 130.7 (C10), 129.9 (C2'), 128.5 (C4'), 119.2 (C9), 118.9 (C1), 117.2 (C7), 76.8 (C3), 65.4 (C4), 55.4 (OMe).

ESIMS \(m/z\) 404 (100%) [M+H\(^+\)].
HRMS (ESI): \(m/z\) calculated for C\(_{25}\)H\(_{26}\)NO\(_4\) [M+H\(^+\)]: 404.1862, found 404.1845.

(15°,25°)-1-(Benzhydrylamino)-1-(2-hydroxyphenyl)but-3-en-2-yl benzoate \(88\)

The title compound was prepared by Method 2 using \( N\)-diphenylmethanimine \(85\) (1 equiv, 0.0514 g, 0.1789 mmol) instead of \( N\)-benzylimine \(73\) and allyl boronate \(68\) (2 equiv, 0.11 g, 0.358 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave \(88\) (25 mg, 31%, dr = 91:9) as a thick yellowish-brown oil.
$^1$H-NMR (500 MHz, CDCl$_3$):
\[ \delta 11.09 (s, 1H, OH), 8.06 (d, J = 7.5 Hz, 1H, H2'), 7.60 (t, J = 7.4 Hz, 1H, H3'), 7.48 (t, J = 7.6 Hz, 1H, H4'), 7.43-7.37 (m, 2H, H5' and H6'), 7.26-7.19 (m, 10H, Ar-CH), 6.88 (t, J = 6.8 Hz, 1H, H9), 6.80 (m, 3H, H7, H8 and H10), 5.80 (dd, J = 7.9, 6.0 Hz, 1H, H3), 5.57 (ddd, J = 17.0, 10.5, 6.0 Hz, 1H, H2), 5.14 (d, J = 11.0 Hz, 1H cis, H1), 5.14 (d, J = 17.0 Hz, 1H trans, H1), 4.86 (s, 1H, NCH$_2$Ph), 3.91 (d, J = 8.0 Hz, 1H, H4).

$^{13}$C-NMR (126 MHz, CDCl$_3$):
\[ \delta 158.2 (C6), 133.5 (C2), 133.3 (C3'), 130.9 (C10), 129.9 C2', 129.2-128.4 (Ar-C), 128.6 (C4'), 119.4 (C1), 118.9 (C8), 117.3 (C9), 76.7 (C3), 64.1 (C4), 62.6 (NCH$_2$Ph).

ESIMS $m/z$ 450 (100%) [M+H$^+$].
HRMS (ESI): $m/z$ calculated for C$_{30}$H$_{28}$NO$_3$ [M+H$^+$]: 450.2069, found 450.2062.

(1R,2S)-1-(Benzylamino)-1-(2-methoxyphenyl)but-3-en-2-yl benzoate 90

The title compound was prepared by Method 2 using N-benzyl-2-methoxyphenyl imine 89 (1 equiv, 0.05 g, 0.2219 mmol) instead of N-benzylimine 73 and allyl boronate 68 (2 equiv, 0.128 g, 0.4439 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 90 (22 mg, 26%, dr = 58:42) as a thick yellowish-brown oil.

$^1$H-NMR (300 MHz, CDCl$_3$):
Major isomer: $\delta$ 7.92 (d, J = 7.5 Hz, 1H, H2'), 7.62-7.45 (m, 1H, H3', H4', H5' and H6'), 7.50-7.33 (m, 2H, H7 and H8), 7.39-7.18 (m, 5H, Ar-CH), 6.96 (dd, J = 7.8, 15.6 Hz, 1H, H10), 6.87 (d, J = 8.1 Hz, 1H, H9), 6.02-5.90 (m, 1H, H2), 5.86-5.74 (m, 1H, H3), 5.23 (dd, J = 14.1, 10.2 Hz, 2H, H1), 4.40 (d, J = 6.0 Hz, 1H), 3.82 (s, 3H, OMe), 3.61 (d, J = 13.5 Hz, 2H, C4-NHCH$_2$Ph).
Minor isomer: $\delta$ 8.03 (d, J = 7.2 Hz, 1H, H2'), 5.11 (dd, J = 13.8, 5.1 Hz, 2H, H1), 4.34 (d, J = 6.3 Hz, 1H), $\delta$ 3.75 (s, 3H, OMe), 3.54 (d, J = 13.5 Hz, 2H, C4-NHCH$_2$Ph).
**13C-NMR (75 MHz, CDCl3):**

Major: δ 165.5 (C=O), 134.0 (C2), 132.8-128.3 (Ar-C), 129.7 (C2'), 120.6 (C10), 117.8 (C1), 110.6 (C9), 77.7 (C3), 59.5 (C4), 55.5 (OMe), 51.6 (C4-NHCH2Ph).

Minor: δ 165.9 (C=O), 134.3 (C2), 129.8 (C2'), 117.7 (C1), 76.8 (C3), 59.2 (C4), 51.3 (OMe).

ESIMS m/z 388 (100%) [M+H+].


(1R,2R)-1-Hydroxy-1-(2-methoxyphenyl)but-3-en-2-yl benzoate 91

The title compound was prepared by Method 2 using N-benzyl-2-methoxyphenyl imine 89 (1 equiv, 0.05 g, 0.2219 mmol) instead of N-benzylimine 73 and allyl boronate 68 (2 equiv, 0.128 g, 0.4439 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 91 (16 mg, 24%, dr = 100:0) as a colorless oil.

**1H-NMR (300 MHz, CDCl3):**

δ 8.02 (d, J = 7.7 Hz, 2H, H2' and H6'), 7.56 (t, J = 7.4 Hz, 1H, H4'), 7.42 (dd, J = 7.5, 15.3 Hz, 2H, H3' and H5'), 7.26 (t, J = 8.7 Hz, 2H, H7 and H8), 6.95 (t, J = 7.5 Hz, 1H, H10), 6.88 (d, J = 8.1 Hz, 1H, H9), 5.98 (ddd, J = 16.9, 10.6, 6.0 Hz, 1H, H2), 5.84 (t, J = 5.7 Hz, 1H, H3), 5.39 - 5.24 (m, 2H, H1), 5.19 (t, J = 5.8 Hz, 1H, H4), 3.87 (s, 3H, OMe).

**13C-NMR (75 MHz, CDCl3):**

δ 165.5 (C=O), 156.7 (C6), 133.2 (C4'), 132.7 (C2), 129.8 (C2'), 129.2-128.4 (C7, C8, C3' and C5'), 120.7 (C10), 118.8 (C1), 110.6 (C9), 72.5 (C4), 70.1 (C3), 55.5 (OMe).

ESIMS m/z 321 (100%) [M+Na+].

General Method 3 for One pot, three component allylation reactions using allyl boronate 68:

\((1S,2S)-1-(Benzylamino)-1-(2-hydroxyphenyl)but-3-en-2-yl benzoate 78\)

To a solution of salicylaldehyde 71 (1 equiv, 0.05 g, 0.41 mmol) in anhydrous MeOH (0.5 mL) was added benzylamine (1 equiv, 0.0439 g, 0.41 mmol) and the solution was stirred at 45 °C for 1 h, then at room temperature for 2 h to form the corresponding imine 73 in situ. Then freshly prepared 3-\(O\)-benzoyl allyl boronate 68 (2 equiv, 0.236, 0.82 mmol) was added to the reaction mixture and stirring was continued at rt for 16 h. The reaction mixture was diluted with saturated NaHCO\(_3\) solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (4:96, 150 mL) to afford the title compound 78 (49 mg, 32%, dr = 88:12) as a thick yellowish-brown oil.

\((1R^*,2S^*)-1-(Benzylamino)-1-(2-methoxyphenyl)but-3-en-2-yl benzoate 90\)

The title compound was prepared by Method 3 2-methoxybenzylaldehyde (1 equiv, 0.05 g, 0.3676 mmol) instead of salicylaldehyde 71 and allyl boronate 68 (2 equiv, 0.212 g, 0.7353 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 90 (36 mg, 25%, dr = 68:32) as a thick yellowish-brown oil.

General Method 4 for BF\(_3\).Et\(_2\)O-promoted allyl boronate 68 reactions with imines:

\((1S,2S)-1-(Benzylamino)-1-(2-hydroxyphenyl)but-3-en-2-yl benzoate 78\)

To a mixture of allyl boronate 68 (2 equiv, 0.167 g, 0.58 mmol) and \(N\)-benzylimine 73 (1 equiv, 0.0613 g, 0.29 mmol) in anhydrous DCM (0.5 mL) at 0 °C, BF\(_3\).Et\(_2\)O (2 equiv, 0.082 g, 0.58 mmol) was slowly added via a syringe. The reaction mixture then was left to warm to rt and stirred for 16 h. The reaction mixture was diluted with saturated NaHCO\(_3\) solution (10 mL) and extracted with DCM (15 mL). The organic extracts were combined,
dried over magnesium sulfate, filtered, and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (1:1, 150 mL) to afford the title compound 78 (22 mg, 20%, dr = 80:20) as a thick yellowish-brown oil.

(1S*,2S*)-1-(2-Hydroxyphenyl)-1-((4-methoxybenzyl)amino)but-3-en-2-yl benzoate 87

The title compound was prepared by Method 4 using N-(p-methoxy)-benzylimine 84 (1 equiv, 0.0513 g, 0.2126 mmol) instead of N-benzylimine 73, allyl boronate 68 (2 equiv, 0.1225 g, 0.4252 mmol) and BF₃·Et₂O (2 equiv, 0.0604 g, 0.4252 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (1:1, 150 mL) gave 87 (18 mg, 21%, dr = 93:7) as a thick yellowish-brown oil.

6.4. Experimental for Chapter 4:

3-Iodovinylsilane 69

In two neck round bottom flask under a nitrogen atmosphere the TMS allyl alcohol (1 equiv, 0.2 g, 1.535 mmol) was treated with freshly purified NIS (1.1 equiv, 0.38 g, 1.69 mmol) in the presence of PPh₃ (1.1 equiv, 0.443 g, 1.69 mmol) in anhydrous DCM (3.5 mL). Then the flask was wrapped with aluminum foil and the reaction mixture was stirred at 0 °C for 1 h, and then at rt for 3 h. The crude mixture was washed with PS (150 mL) and filtered through silica gel pad to afford the title compound 69 (55 mg, 15%) as a thick yellowish-brown oil.

1H-NMR (300 MHz, CDCl₃):

δ 6.16 (dt, J = 18.1, 7.4 Hz, 1H, CH–CH₂I), 5.83 (d, J = 18.3 Hz, 1H, SiMe₃–CH), 3.81 (d, J = 11.1 Hz, 2H, -CH₂I), 0.06 (s, 9H, SiMe₃).

ESIMS m/z 279 (100%) [M+K⁺] (C₆H₁₃ISiK⁺).
γ-TMS allyl boronate pinacol ester 70

3-TMS allylic alcohol (1 equiv, 0.1 g, 0.7677 mmol) was dissolved in a mixture of anhydrous DMSO (1.54 mL) and anhydrous MeOH (1.54 mL). Then freshly dried PTSA (0.05 equiv, 0.00661 g, 0.03838 mmol), palladacycle (0.025 equiv, 0.0106 g, 0.01919 mmol) and B₂(pin)₂ (2 equiv, 0.39 g, 1.5354 mmol) were added to the reaction mixture, and then the mixture was stirred at 50 °C for 16 h. The reaction mixture was cooled to rt then diluted with distilled water (5 mL) and extracted with Et₂O (2 x 5 mL). Then the aqueous layer was re-extracted with Et₂O (2 x 10 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. Because of the relatively unstable nature of the desired product to silica gel purification, the crude product (0.3134 g, colorless thick oil) was characterized and used in subsequent reactions.

1H-NMR (500 MHz, CDCl₃):
δ 6.04 (dt, J = 18.5, 7.0 Hz, 1H, H2), 5.59 (d, J = 18.0 Hz, 1H, H3), 1.78 (d, J = 7.0 Hz, 2H, CH=CHCH₃), 1.23-1.20 (m, 12 H, Bpin-Me₄), 0.00 (s, 9 H, SiMe₃).

13C-NMR (126 MHz, CDCl₃):
δ 142.1 (C2), 130.8 (C3), 83.6 (C4 and C5), 25.1 and 24.9 (Bpin-Me₄), -0.1 (SiMe₃).

ESIMS m/z 309 (100%) [M+H⁺] C₁₂H₂₅BO₂Si⁺ did not matched the expected molecular formula of compound 70.

General Method 5 for γ-TMS allyl pinacol boronate 70 reactions with imines:
2-((1S,2S)-1-(Benzydamino)-2-(trimethylsilyl)but-3-en-1-yl)phenol 99

The N-benzylinine 73 (1 equiv, 0.052 g, 0.2461 mmol) was dissolved in MeOH (0.5 mL) under a nitrogen atmosphere, and then the γ-TMS allylboronate 70 (2 equiv, 0.1183 g, 0.4923 mmol) was added to the reaction mixture and then stirred at rt for 16 h. The reaction mixture was diluted with saturated NaHCO₃ solution (10 mL) and extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. The crude reaction mixture
was then purified by column chromatography EtOAc:PS (4:96, 150 mL) to afford the title compound 99 (34 mg, 43%, dr = 93:7) as a thick yellowish-brown oil.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)):
δ 7.67-7.56 (m, 5H, NHCH\(_2\)Ph), 7.48 (td, \(J = 7.7, 1.7\) Hz, 1H, H8), 7.27 (dd, \(J = 7.5, 1.5\) Hz, 1H, H10), 7.16 (dd, \(J = 8.0, 1.0\) Hz, 1H, H7), 7.09 (td, \(J = 7.4, 1.2\) Hz, 1H, H9), 5.94 (dt, \(J = 16.7, 10.6\) Hz, 1H, H2), 5.13 (dd, \(J = 10.0, 1.5\) Hz, 1H \(\text{cis}\)) (dd, \(J = 16.5, 1.5\) Hz, 1H \(\text{trans}\)), 4.34 (d, \(J = 6.0\) Hz, 1H, H4), 4.12 (d, \(J = 12.9\) Hz, 1H, Ha), 3.91 (d, \(J = 12.9\) Hz, 1H, Hb), 2.33 (dd, \(J = 11.0, 6.0\) Hz, 1H, H3), 1.57 (m, 12 H, Bpin-Me\(_4\)), 0.26 (s, 9 H, SiMe\(_3\)).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)):
δ 158.1 (C6), 135.8 (C2), 118.6 (C9), 117.0 (C7), 114.7 (C1), 83.6 (Cq, pin), 63.8 (C4, major), 63.3 (C4, minor), 51.9 (N-C\(_2\)H\(_2\)), 44.2 (C3, major), 44.0 (C3, minor), 25.1 (Cq, pin), -1.9 (SiMe\(_3\)).

ESIMS m/z 326 (100% [M+H\(^+\]).
HRMS (ESI): m/z calculated for C\(_{20}\)H\(_{28}\)NOSi [M+H\(^+\)]: 326.1756, found 326.1739.

2-((1S,2S)-1-(Allylamino)-2-(trimethylsilyl)but-3-en-1-yl)phenol 103

The title compound was prepared by Method 5 using \(N\)-allylimine 83 (1 equiv, 0.0614 g, 0.3809 mmol) instead of \(N\)-benzylimine 73 and allyl boronate 70 (2 equiv, 0.183 g, 0.7618 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 103 (30 mg, 29%, dr = 90:10) as a thick yellowish-brown oil.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)):
δ 7.43 (td, \(J = 7.7, 1.7\) Hz, 1H, H8), 7.22 (dd, \(J = 7.5, 1.2\) Hz, 1H, H10), 7.10-6.97 (m, 2H, H7 and H9), 6.17 (dddd, \(J = 17.3, 10.4, 7.2, 5.1\) Hz, 1H, H2'), 5.94 (dt, \(J = 16.8, 10.6\) Hz, 1H, H2), 5.44 (m, 2H, H1'), 5.15 (m, 2H, H1), 4.32 (d, \(J = 5.8\) Hz, 1H, H4), 3.56 (ddt, \(J = 14.4, 4.9, 1.7\) Hz, 1H, H3'), 3.42 (dd, \(J = 14.1, 7.2\) Hz, 1H, H3'), 2.33 (dd, \(J = 11.0, 5.7\) Hz, 1H, H3), 1.55 (m, 12 H, Bpin-Me\(_4\)), 0.28 (s, 9 H, SiMe\(_3\)).
13C-NMR (75 MHz, CDCl3):
δ 158.1 (C6), 135.9 (C2), 135.0 (C2'), 129.9 (C10), 128.7 (C8), 118.5 (C9), 117.2 (C7), 116.9 (C1'), 114.6 (C1), 113.4 (Cq, pin), 83.6 (C4), 55.4 (OCH3), 51.3 (N-CH2), 44.2 (C3), 25.2 (Cq, pin), -2.0 (SiMe3).

ESIMS m/z 276 (100%) [M+H+].
HRMS (ESI): m/z calculated for C16H26NO2Si [M+H+]: 276.1784, found 276.1783.

2-((1S,2S)-1-((4-Methoxybenzy)amino)-2-(trimethylsilyl)but-3-en-1-yl)phenol 104

The title compound was prepared by Method 5 using N-(p-methoxy)benzylimine 85 (1 equiv, 0.0515 g, 0.2134 mmol) instead of N-benzylimine 73 and allyl boronate 70 (2 equiv, 0.1025 g, 0.4269 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 104 (20 mg, 27%, dr = 94:6) as a thick yellowish-brown oil.

1H-NMR (300 MHz, CDCl3):
δ 7.61 (m, 1H, H8), 7.49 (d, J = 8.4 Hz, 2H, H3' and H5'), 7.27 (dd, J = 7.5, 1.2 Hz, 1H, H10), 7.18 (d, J = 9.0 Hz, 2H, H2' and H6'), 7.09 (m, 2H, H7 and H9), 5.93 (dt, J = 16.8, 10.5 Hz, 1H, H2), 5.12 (dd, J = 10.2, 1.8 Hz, 1H cis, H1) (dd, J = 16.8, 1.5 Hz, 1H trans, H1'), 4.34 (d, J = 6.0 Hz, 1H, H4), 4.11 (s, 3H, OCH3), 4.07 (d, J = 12.8 Hz, 1H, Ha), 3.85 (d, J = 12.8 Hz, 1H, Hb), 2.32 (dd, J = 11.0, 6.0 Hz, 1H, H3), 1.57 (m, 12 H, Bpin-Me4), 0.26 (s, 9 H, SiMe3).

13C-NMR (75 MHz, CDCl3):
δ 159.1 (C4'), 158.1 (C6), 135.9 (C2), 129.9 (C10), 118.6 (C9), 116.9 C7, 114.1 (C1), 83.6 (Cq, pin), 63.7 (C4), 55.4 (OCH3), 51.3 (N-CH2), 44.2 (C3), 25.2 (Cq, pin), -2.0 (SiMe3).

ESIMS m/z 356 (100%) [M+H+].
HRMS (ESI): m/z calculated for C21H30NO2Si [M+H+]: 356.2046, found 356.2037.
(1S,2S)-N-Benzyl-1-(2-methoxyphenyl)-2-(trimethylsilyl)but-3-en-1-amine 105

The title compound was prepared by Method 5 using N-benzyl-2-methoxyphenyl imine 89 (1 equiv, 0.0518 g, 0.2299 mmol) instead of N-benzylimine 73 and allyl boronate 70 (2 equiv, 0.1105 g, 0.4599 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 105 (24 mg, 31%, dr = 93:7) as a thick yellowish-brown oil.

1H-NMR (500 MHz, CDCl3):
δ 7.49 (m, 5H, Ar-CH), 7.27 (dd, J = 7.0, 1.5 Hz, 1H, H10), 7.16 (m, 2H, H7 and H8), 7.09 (td, J = 7.4, 1.2 Hz, 1H, H9), 5.93 (dt, J = 16.8, 10.5 Hz, 1H, H2), 5.16 (dd, J = 10.1, 1.9 Hz, 1H cis, H1), 5.08 (dd, J = 17.0, 1.5 Hz, 1H trans, H1), 4.34 (d, J = 6.1 Hz, 1H, H4), 4.11 (s, 3H, OCH3), 4.04 (d, J = 12.8 Hz, 1H, Ha), 3.85 (d, J = 12.8 Hz, 1H, Hb), 2.32 (dd, J = 11.0, 6.0 Hz, 1H, H3), 1.57 (m, 12 H, Bpin-Me4), 0.26 (s, 9 H, SiMe3).

13C-NMR (75 MHz, CDCl3):
δ 158.1 (C6), 135.9 (C2), 129.9 (C10), 118.6 (C9), 116.9 (C8), 114.6 (C1), 114.1 (C7), 83.6 (Cq, pin), 63.7 (C4), 55.4 (OCH3), 51.3 (C4-NHCH2Ph), 44.2 (C3), 25.1(Cq, pin), -2.0 (SiMe3).

ESIMS m/z 356 (100%) did not matched the expected molecular formula of compound 105 C21H30NOSi⁺.

General Method 6 for One pot, three component allylation reactions using γ-TMS allylboronate 70:

2-((1S,2S)-1-(Benzylamino)-2-(trimethylsilyl)but-3-en-1-yl)phenol 99

To a solution of salicylaldehyde 71 (1 equiv, 0.05 g, 0.41 mmol) in anhydrous MeOH (0.5 mL) was added benzylamine (1 equiv, 0.0439 g, 0.41 mmol) and the solution was stirred at 45 °C for 1 h, then at room temperature for 2 h to form the corresponding imine 73 in situ.

Then freshly prepared silyl allyl boronate 70 (2 equiv, 0.197, 0.82 mmol) was added to the reaction mixture and stirring was continued at rt for 16 h. The reaction mixture was diluted with saturated NaHCO3 solution (10 mL) and extracted with
DCM (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (4:96, 150 mL) to afford the title compound 99 (44 mg, 33%, dr = 89:11) as a thick yellowish-brown oil.

(1S,2S)-N-Benzyl-1-phenyl-2-(trimethylsilyl)but-3-en-1-amine 102

The title compound was prepared by Method 6 using benzylaldehyde (1 equiv, 0.05 g, 0.4712 mmol) instead of salicylaldehyde 71, benzylamine (1 equiv, 0.0505 g, 0.4712 mmol) and silyl allyl boronate 70 (1 equiv, 0.113 g, 0.4712 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 102 (35 mg, 24%, dr = 83:17) as a thick yellowish-brown oil.

\(^1\)H-NMR (500 MHz, CDCl\(_3\)):
\[ \delta 7.67-7.56 \text{ (m, 5H, Ar-CH)} , \]
\[ 7.52 \text{ (d, } J = 7.0 \text{ Hz, 1H, H6), } 7.48 \text{ (td, } J = 7.7, 1.7 \text{ Hz, 1H, H8), } 7.28 \text{ (dd, } J = 7.5, 1.5 \text{ Hz, 1H, H10), } 7.16 \text{ (dd, } J = 8.0, 1.0 \text{ Hz, 1H, H7), } 7.09 \text{ (td, } J = 7.4, 1.2 \text{ Hz, 1H, H9), } 5.94 \text{ (ddd, } J = 16.7, 12.3, 8.6 \text{ Hz, 1H, H2), } 5.16 \text{ (dd, } J = 10.0, 1.5 \text{ Hz, 1H cis, H1), } 5.09 \text{ (dd, } J = 17.0, 1.0 \text{ Hz, 1H trans, H1), } 4.34 \text{ (d, } J = 6.0 \text{ Hz, 1H, H4), } 4.11 \text{ (d, } J = 12.9 \text{ Hz, 1H, Ha), } 3.91 \text{ (d, } J = 12.9 \text{ Hz, 1H, Hb), } 2.33 \text{ (dd, } J = 11.0, 6.0 \text{ Hz, 1H, H3), } 0.26 \text{ (s, 9 H, SiMe}_3\text{).}

\(^{13}\)C-NMR (126 MHz, CDCl\(_3\)):
\[ \delta 135.8 \text{ (C2), } 118.6 \text{ (C9), } 117.0 \text{ (C7), } 114.7 \text{ (C1), } 63.8 \text{ (C4, major), } 63.0 \text{ (C4, minor), } 51.9 \text{ (N-CH}_2\text{, major), } 51.2 \text{ (N-CH}_2\text{, minor), } 44.2 \text{ (C3, major), } 40.6 \text{ (C3, minor), } -2.0 \text{ (SiMe}_3\text{).}

ESIMS $m/z$ 310 (100%) [M+H\(^+\)].
HRMS (ESI): $m/z$ calculated for C\(_{20}\)H\(_{28}\)NSi [M+H\(^+\)]: 310.1756, found 310.1739.
(1R,2S)-1-Phenyl-2-(trimethylsilyl)but-3-en-1-ol 106

The title compound was prepared by Method 6 using benzylaldehyde (1 equiv, 0.05 g, 0.4712 mmol) instead of salicylaldehyde 71, benzylamine (1 equiv, 0.0505 g, 0.4712 mmol) and silyl allyl boronate 70 (2 equiv, 0.226 g, 0.9423 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 106 (14 mg, 14%, dr = 77:23) as a colorless oil.

1H-NMR (500 MHz, CDCl3):
δ 7.36-7.25 (m, 5H, Ar-CH), 5.81 (dt, J = 17.1, 10.3 Hz, 1H, H2), 5.05 (dd, Jcis = 10.3, 1.9 Hz, 1H, H1), 4.97 (dd, Jtrans = 17.0, 1.9 Hz, 1H, H1), 4.74 (d, J = 8.5 Hz, 1H, H4), 2.02 (t, J = 9.5 Hz, 1H, H3), -0.25 (s, 9 H, SiMe3).

ESIMS m/z 243 (100%) [M+Na+] C13H20OSiNa+.

2-((1S,2S)-1-(Allylamino)-2-(trimethylsilyl)but-3-en-1-yl)phenol 103

The title compound was prepared by Method 6 using N-allylamine (1 equiv, 0.234 g, 0.4094 mmol) instead of benzylamine and silyl allyl boronate 70 (2 equiv, 0.197 g, 0.8188 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 103 (18 mg, 16%, dr = 79:21) as a thick yellowish-brown oil.

2-((1S,2S)-1-((4-Methoxybenzyl)amino)-2-(trimethylsilyl)but-3-en-1-yl)phenol 104

The title compound was prepared by Method 6 using p-methoxybenzylamine (1 equiv, 0.562 g, 0.4094 mmol) instead of benzylamine and silyl allyl boronate 70 (2 equiv, 0.197 g, 0.8188 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 104 (36 mg, 25%, dr = 77:23) as a thick yellowish-brown oil.
2-((1R,2S)-1-Hydroxy-2-(trimethylsilyl)but-3-en-1-yl)phenol 109

The title compound was prepared by Method 6 using morpholine (1 equiv, 0.357 g, 0.4094 mmol) instead of benzylamine and silyl allyl boronate 70 (2 equiv, 0.197 g, 0.8188 mmol). Purification by column chromatography on silica gel eluting with EtOAc:PS (4:96, 150 mL) gave 109 (33 mg, 27%, dr = 78:22) as a colorless oil.

\[^1\]H-NMR (500 MHz, CDCl\textsubscript{3}): 
\[ \delta = 7.35 \text{ (td, } J = 8.0, 1.5 \text{ Hz, } 1\text{H, H10}), 7.20 \text{ (m, } 1\text{H, H8}), 7.08 \text{ (ddd, } J = 18.3, 7.8, 1.5 \text{ Hz, } 1\text{H, H7}), 6.99 \text{ (td, } J = 7.4, 1.2 \text{ Hz, } 1\text{H, H9}), 5.78 \text{ (dt, } J = 17.0, 10.0 \text{ Hz, } 1\text{H, H2}), 5.16 \text{ (d, } J = 9.0 \text{ Hz, } 1\text{H, H4}), 5.06 \text{ (dd, } J_{cis} = 10.2, 1.9 \text{ Hz, } 1\text{H, H1}), 4.94 \text{ (dd, } J_{trans} = 17.0, 1.0 \text{ Hz, } 1\text{H, H1}), 2.51 \text{ (t, } J = 9.5 \text{ Hz, } 1\text{H, H3}), 0.26 \text{ (s, 9 H, SiMe3).}

ESIMS \( m/z \) 356 (100%) did not match the expected molecular formula of compound 112 C\textsubscript{13}H\textsubscript{20}O\textsubscript{2}Si\textsuperscript{+}.

General Methods for \( \gamma \)-TMS allyl pinacol boronate 70 reactions with aliphatic aldehydes:

**Ethyl (2S,3S)-2-(Benzylamino)-3-(trimethylsilyl)pent-4-enoate 110**

To a solution of ethyl glyoxylate (50% in toluene, 1 equiv, 0.1 g, 97.0 \( \mu \)L, 0.4898 mmol) in anhydrous EtOH (0.5 mL) was added benzylamine (1 equiv, 0.0525 g, 0.4898 mmol) and the solution was stirred at 45 \( ^\circ \)C for 1 h, then at room temperature for 2 h to form the corresponding imine \textit{in situ}. Then freshly prepared silyl allyl boronate 70 (2 equiv, 0.235, 0.9795 mmol) was added to the reaction mixture and stirring was continued at rt for 16 h. The reaction mixture was diluted with saturated NaHCO\textsubscript{3} solution (10 mL) and extracted with DCM (2 \( \times \) 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (5:95, 150 mL) to afford the title compound 110 (20 mg, 13%, dr = 73:27) as a thick yellowish-brown oil.
1H-NMR (500 MHz, CDCl3):

Syn isomer: δ 7.33-7.19 (m, 5H, Ar-C), 5.63 (m, 1H, H2), 4.87 (m, 2H, H1), 4.32 (s, 1H, NH), 4.15 (m, 2H, H5), 3.77 (d, J = 12.5 Hz, 1H, Ha), 3.51 (d, J = 12.5 Hz, 1H, Hb), 3.39 (d, J = 4.5 Hz, 1H, H4), 1.96 (dd, J = 11.5, 4.5 Hz, 1H, H3), 1.22 (m, 3H, H6), 0.00 (s, 9H, SiMe3).

Anti isomer: δ 5.75 (dt, J = 17.0, 10.4 Hz, 1H, H2), 3.70 (d, J = 13.0 Hz, 1H, Ha), 3.57 (d, J = 13.0 Hz, 1H, Hb), 3.32 (d, J = 9.0 Hz, 1H, H4), 1.90 (dd, J = 19.5, 10.0 Hz, 1H, H3), 0.06 (s, 9H, SiMe3).

ESIMS m/z 306 (100%) [M+H+] C17H28NO2Si++.

(S)-N-Benzyl-2-(trimethylsilyl)but-3-en-1-amine 111

To a solution of paraformaldehyde (1 equiv, 0.015 g, 0.5 mmol) in anhydrous EtOH (0.5 mL) was added benzylamine (2 equiv, 0.107 g, 1.0 mmol) and freshly prepared silyl allyl boronate 70 (2 equiv, 0.24 g, 1.0 mmol). Then the reaction mixture was stirred and heated to reflux in EtOH at 90-100 °C for 2 days. The reaction mixture was then washed with distilled H2O (10 mL) and extracted with Et2O (2 x 15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. The crude reaction mixture was then purified by column chromatography EtOAc:PS (7:3, 150 mL) to afford the title compound 111 (4 mg, 4%) as a thick yellowish-brown oil.

1H-NMR (500 MHz, CDCl3):

δ 7.36-7.21 (m, 5H, Ar-C), 5.62 (dt, J = 17.0, 10.0 Hz, 1H, H2), 4.96 (dd, J = 10.0, 1.0 Hz, 1H cis, H1), 4.91 (d, J = 17.0 Hz, 1H trans, H1), 3.82 (d, J = 13.0 Hz, 1H, Ha), 3.70 (d, J = 13.0 Hz, 1H, Hb), 2.76 (dd, J = 11.5, 3.5 Hz, 1H, Hc), 2.70 (t, J = 11.5 Hz, 1H, Hd), 1.89 (td, J = 10.5, 3.7 Hz, 1H, H3), - 0.02 (s, 9H, SiMe3).

13C-NMR (126 MHz, CDCl3):

δ 138.4 (C2), 128.5-127.1 (Ar-C), 114.0 (C1), 53.6 (N-CH2), 48.4 (C4), 36.0 (C3), - 2.9 (SiMe3).

ESIMS m/z 234 (100%) [M+H+] C14H24NSi++.
References:


27. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. Lentiginosine, a dihydroxyindolizidine alkaloid that inhibits amyloglucosidase. Biochemistry. 1990, 29, 1886-1891.


deoxynojirimycin (SC48334) and zidovudine in patients with HIV-1 infection and 200-500 CD4 cells/mm³. *J. AIDS.* **1994**, *7*, 139-147.


Appendices:

Appendix A-1 gCOSY experiment of compound 72

Appendix A-2 gHSQC experiment of compound 72
Appendix A-3 $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of imine 73

Appendix A-4 gHSQC experiment of impure compound 75
Appendix A-5 $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of compound 66b

Appendix A-6 gCOSY experiment of compound 66b
Appendix A-7 gHSQC experiment of compound 66b

Appendix B-1 $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz) of compound 77
Appendix B-2 gCOSY experiment of compound 77

Appendix B-3 gHSQC experiment of compound 77
Appendix B-4 gCOSY experiment of compound 68

Appendix B-5 gHSQC experiment of compound 68
Appendix B-6 gCOSY experiment of compound 79

Appendix B-7 gHSQC experiment of compound 79
Appendix B-8 $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of imine 83

Appendix B-9 $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of imine 83
Appendix B-10 gCOSY experiment of imine 83

Appendix B-11 gHSQC experiment of imine 83
Appendix B-12 $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz) of imine 84

Appendix B-13 gCOSY experiment of imine 84
Appendix B-14 gHSQC experiment of imine 84

Appendix B-15 $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of imine 85
Appendix B-16 $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of imine 85

Appendix B-17 gCOSY experiment of imine 85
Appendix B-18 gHSQC experiment of imine 85

Appendix B-19 $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of compound 86
Appendix B-20 $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz) of compound 86

Appendix B-21 gCosy experiment of compound 86
Appendix B-22 gHSQC experiment of compound 86

Appendix B-23 $^1$H-NMR spectrum (CDCl$_3$, 300 MHz) of compound 87
Appendix B-24 $^1$H-NMR spectrum (CDCl₃, 75 MHz) of compound 87

Appendix B-25 gCOSY experiment of compound 87
Appendix B-26 $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of compound 88
Appendix B-28 $^{13}$C-NMR spectrum (CDCl$_3$, 126 MHz) of compound 88

Appendix B-29 gCOSY experiment of compound 88
Appendix B-30 gHSQC experiment of compound 88

Appendix B-31 gCOSY experiment of compound 90
Appendix B-32 gHSQC experiment of compound 90

Appendix B-33 gCOSY experiment of compound 91
Appendix B-34 gHSQC experiment of compound 91

Appendix C-1 gCOSY experiment of compound 70
Appendix C-2 gHSQC experiment of compound 70

Appendix C-3 $^1$H-NMR spectrum (CDCl$_3$, 300 MHz) of compound 103
Appendix C-4 $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz) of compound 103

Appendix C-5 gCOSY experiment of compound 103
Appendix C-6 gHSQC experiment of compound 103

Appendix C-7 $^1$H-NMR spectrum (CDCl$_3$, 300 MHz) of compound 104
Appendix C-8 $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz) of compound 104

Appendix C-9 gCOSY experiment of compound 104
Appendix C-10 $^g$HSQC experiment of compound 104

Appendix C-11 $^1$H-NMR spectrum (CDCl$_3$, 500 MHz) of compound 105
Appendix C-12 $^{13}$C-NMR spectrum (CDCl₃, 75 MHz) of compound 105

Appendix C-13 gCOSY experiment of compound 105
Appendix C-14 gHSQC experiment of compound 105

Appendix C-15 gCOSY experiment of compound 102
Appendix C-16 gHSQC experiment of compound 102

Appendix C-17 gCOSY experiment of compound 111
Appendix C-18 gHSQC experiment of compound 111