Development of New Reactions Employing Boron-Enolate Wittig Rearrangements

by

Renata K. Everett

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry) in the University of Michigan 2015

Doctoral Committee:
Professor John P. Wolfe, Chair
Professor John Montgomery
Assistant Professor Pavel Nagorny
Assistant Professor Matthew B. Soellner
Dedication

To J.B.P.
# Table of Contents

Dedication ................................................................................................................................. ii

List of Tables ............................................................................................................................. v

List of Schemes .......................................................................................................................... vi

List of Abbreviations ................................................................................................................ viii

Abstract ................................................................................................................................... x

Chapter 1 .................................................................................................................................. 1

The Wittig Rearrangement ........................................................................................................... 1

1.1 Background and Significance ............................................................................................... 1

1.2 Wittig Rearrangements of Propargyl Ethers ....................................................................... 2

1.3 The Aza-Wittig Rearrangement ........................................................................................... 4

1.4 Enolate Wittig Rearrangement ............................................................................................ 6

1.5 Tandem Wittig Rearrangement/Aldol Reactions ................................................................. 8

1.6 Aldol Reactions with Ketone Electrophiles ........................................................................ 13

1.7 References .......................................................................................................................... 16

Chapter 2 .................................................................................................................................. 18

Synthesis of Substituted 3-Hydroxy-2-Furanone Derivatives via an Unusual Enolate Wittig Rearrangement/Alkylative Cyclization Sequence. .................................................. 18

2.1 Introduction ........................................................................................................................ 18

2.2 Preliminary Results ............................................................................................................. 18

2.3 Synthesis of 3-Hydroxy-2-Furanones ................................................................................ 19

2.4 Effect of Boron Reagent ..................................................................................................... 21

2.5 Mechanistic Studies ........................................................................................................... 21

2.6 Conclusion .......................................................................................................................... 24

2.7 Experimental ..................................................................................................................... 24

2.8 References .......................................................................................................................... 38

Chapter 3 .................................................................................................................................. 41

Aza-Wittig Rearrangements of N-Benzyl and N-Allyl Glycine Methyl Esters ......................... 41

3.1 Introduction ........................................................................................................................ 41

3.2 Initial Studies ....................................................................................................................... 42

3.3 Synthesis of 1,4,2-Oxazaborole Derivatives ....................................................................... 43

3.4 Aza-Wittig Optimization .................................................................................................... 45

3.5 Aza-[1,2]-Wittig Rearrangement ......................................................................................... 45

3.6 Aza-[1,2]-Wittig Scope ....................................................................................................... 46
3.7 Aza-[2,3]-Rearrangement .................................................................................. 47
3.8 Tandem Aza-[2,3]-Wittig Rearrangement/Hydroboration Oxidation ................. 50
3.9 Asymmetric Aza-Wittig Rearrangements ............................................................ 52
3.10 Conclusion ......................................................................................................... 53
3.11 Experimental ..................................................................................................... 53
3.12 References ........................................................................................................ 99

Chapter 4 .................................................................................................................. 102

Generation of Vicinal Stereocenters via Asymmetric Tandem Wittig Rearrangement/Aldol Reactions ........................................................................................................... 102

4.1 Introduction ......................................................................................................... 102
4.2 Preliminary Results ............................................................................................. 103
4.3 Synthesis of Boronate Esters ............................................................................. 103
4.4 Synthesis of α,β-Dihydroxy Esters .................................................................... 105
4.5 Chiral Auxiliary Removal ................................................................................... 106
4.6 Conclusions and Future Directions .................................................................... 108
4.7 Experimental ....................................................................................................... 108
4.8 References .......................................................................................................... 123
List of Tables

Table 1.1 Representative Wittig/aldol products\textsuperscript{a} ........................................................................................................ 9
Table 1.2 Asymmetric Tandem Wittig/Aldol and Wittig/Mannich Reactions\textsuperscript{a} .................. 11
Table 1.3 Denmark’s Catalytic, Enantioselective Aldol Addition to Ketones ............... 14
Table 1.4 Tandem Wittig/Aldol Reactions with Ketones .......................................................... 15
Table 2.1 Tandem Wittig Rearrangement/Alkylative Cyclization Reactions\textsuperscript{a} ........... 20
Table 3.1 Formation of 1,4,2-Oxazaborole Derivatives\textsuperscript{a} ........................................ 43
Table 3.2 Aza-[1,2]-Wittig Rearrangement\textsuperscript{a} ........................................................................ 46
Table 3.3 Aza-[2,3]-Wittig Rearrangement\textsuperscript{a} ........................................................................ 49
Table 3.4 Aza-[2,3]-Wittig Rearrangement/Hydroboration\textsuperscript{a} ........................................ 51
Table 3.5 Asymmetric Aza-Wittig Rearrangement .................................................................. 53
Table 4.1 Formation of Boronate Ester\textsuperscript{a} ........................................................................ 104
Table 4.2 Boron Cleavage\textsuperscript{a} .......................................................................................... 105
Table 4.3 Asymmetric Wittig Rearrangement/Aldol Reaction\textsuperscript{a} ................................. 106
Table 4.4 Chiral Auxiliary Cleavage\textsuperscript{a} .......................................................................... 107
List of Schemes

Scheme 1.1 [1,2] and [2,3] Wittig Rearrangements.................................................................1
Scheme 1.2 Propargyl Substituents as Anion Stabilizing Groups (a) or Migrating Groups (b) in Wittig Rearrangements ........................................................................3
Scheme 1.3 Proposed Transition State for Propargyl [2,3] Wittig Rearrangement ..........4
Scheme 1.4 Small-ring Assisted Aza-[2,3]-Wittig Rearrangement ..........................5
Scheme 1.5 First Acyclic Aza-[2,3]-Rearrrangement ..................................................5
Scheme 1.6 Aza-[1,2]-Wittig Rearrangement .................................................................6
Scheme 1.7 [2,3] Wittig Rearrangement of a Boron Enolate ........................................7
Scheme 1.8 [2,3] vs [3,3] Sigmatropic Rearrangements of Allylic Glycolate Esters ....7
Scheme 1.9 Asymmetric Wittig Rearrangements of Boron Enolates ........................8
Scheme 1.10 Unexpected Tandem Wittig/Aldol Reaction ...........................................8
Scheme 1.11 Proposed Mechanism for Tandem Wittig Rearrangement/aldol Reaction 9
Scheme 1.12 Key Step in the Synthesis of Alternaric Acid ........................................11
Scheme 1.13 Representative Examples Wittig/Mannich Reactions of N-Boc Electrophiles .................................................................12
Scheme 1.14 Generation of Vicinal Quaternary Stereocenters via Tandem Wittig/Aldol Reactions .................................................................13
Scheme 1.15 Enantioselective Reductive Aldol Reactions with Ketone Electrophiles ..14
Scheme 1.16 Boronate Ester Cleavage .............................................................................15
Scheme 2.1 Boron-mediated Tandem Wittig Rearrangement/aldol Reaction ............18
Scheme 2.2 Unexpected 3-hydroxy-2-furanone Formation ........................................19
Scheme 2.3 Allene Formation .........................................................................................20
Scheme 2.4 Attempted Rearrangement of Terminal Alkyne ......................................20
Scheme 2.5 Rearrangement using of 9-BBNOTf .........................................................21
Scheme 2.6 Alternative Acidic Workup Procedure ......................................................21
Scheme 2.7 Radical Cage Mechanism for Conversion of 4-24 to 4-31 .....................22
Scheme 2.8 Radical Chain Mechanism ......................................................................23
Scheme 2.9 Crossover Experiment ..............................................................................24
Scheme 3.1 Tandem Wittig Rearrangement/Aldol Reaction ........................................... 42
Scheme 3.2 Formation of 1,4,2 Oxazaborole Derivative .................................................. 43
Scheme 3.3 Suzuki Reaction of Oxazaborole with Aryl Halides .................................... 45
Scheme 3.4 Scope and Stereocontrol of Aza-[1,2]-Rearrangement .................................. 47
Scheme 3.5 Initial Results of aza-[2,3]-Wittig Rearrangement ....................................... 48
Scheme 3.6 Decomposition of α-Substituted Substrate .................................................. 52
Scheme 4.1 Tandem Wittig Rearrangement/Aldol Reaction ........................................... 103
Scheme 4.2 Preliminary Tandem Wittig/Aldol Results .................................................. 103
Scheme 4.3 Previous Method of Chiral Auxiliary Removal ............................................ 107
Scheme 4.4 Methanolysis Resulting in Retro-Aldol Reaction ......................................... 108
Scheme 4.5 Silyl Protection .............................................................................................. 108
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>9-BBNOTf</td>
<td>9-Borabicyclo[3.3.1]nonyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bu₂BOTf</td>
<td>di-n-butylboron trifluoromethanesulfonate</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>DIBAIH</td>
<td>diisobutyl aluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>dimethylaniliminopyridine</td>
</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>iPr₂NEt</td>
<td>diisopropyl ethylamine</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamine</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>nBuLi</td>
<td>n-buty lithium</td>
</tr>
<tr>
<td>NEt₃</td>
<td>triethylamine</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-methoxyphenyl</td>
</tr>
</tbody>
</table>
TBAF ............................................................... tetra n-butylammonium fluoride
'Bu ............................................................... tert-butyl
THF ............................................................... tetrahydrofuran
TLC ............................................................... thin layer chromatography
TMS ............................................................... trimethylsilyl
Ts ............................................................... tosyl
Abstract

Wittig rearrangements are useful carbon-carbon bond forming reactions that have been prominently featured in a number of total syntheses, however narrow functional group tolerance and issues with competing reaction pathways have limited the utility of these transformations. Consequently, recent innovations focus on improving functional group tolerance and selectivity. The Wolfe group has reported a tandem Wittig rearrangement/aldol reaction of O-allyl or O-benzyl glycolate esters to generate enantioenriched α-alkyl-α,β-dihydroxy esters and α-alkyl-α-hydroxy-β-amino esters under mild Lewis acid conditions with excellent stereoselectivity. The work herein describes recent advances in the application of this Wittig rearrangement methodology for the synthesis of 3-hydroxy-2-furanones, N-aryl phenylalanine and allylglycine methyl esters, and α-alkyl-α,β-dihydroxy esters.

Under strongly basic conditions, O-propargyl ethers are capable of undergoing [2,3] Wittig rearrangements to afford structurally rearranged allenic alcohols. However, O-propargyl glycolate methyl esters, when subjected to dibutylboron triflate and Hunig’s base, were observed to undergo a [2,3] Wittig rearrangement and subsequent alkylative cyclization sequence resulting in 3-hydroxy-2-furanone derivatives that have incorporated an alkyl group from the boron reagent. This unusual reaction sequence is explored in Chapter 2. Nitrogen analogs of Wittig rearrangements are investigated in Chapter 3. These aza-Wittig rearrangements of tertiary amines are less common and typically less facile than rearrangements of the corresponding ethers. Rearrangements of N-benzyl and N-allyl glycine methyl esters required higher temperatures and N-aryl protecting groups in order to undergo the desired [1,2] and [2,3] rearrangements. When N-carbonyl protecting groups were used, 1,4,2-oxazaborole derivatives were formed instead of the expected secondary amines. Additionally, N-allyl N-aryl glycine methyl esters in the presence of excess dibutylboron triflate undergo the [2,3] rearrangement as well as a hydroboration reaction to generate secondary amines bearing pendant
primary alcohols. The final chapter describes an asymmetric tandem Wittig rearrangement/aldol reaction of O-benzyl and O-allyl glycolate esters coupled with ketone electrophiles. With the use of the trans-2-phenylcyclohexyl chiral auxiliary, these reactions generate α,β-dihydroxy esters bearing vicinal quaternary stereocenters with excellent enantio- and diastereoselectivity.
Chapter 1
The Wittig Rearrangement

1.1 Background and Significance

The Wittig rearrangement is a powerful and well-known method of carbon-carbon bond formation. The [1,2] rearrangement of a metallated benzylic ether into an α-benzyl alcohol was first observed in 1924, though extensive work by Wittig led to significant improvement in understanding this transformation. Wittig rearrangements are classified using a notation system in which the atoms are numbered in both directions starting at the bond that is breaking. The type of rearrangement is titled numerically according to the numbers assigned to the atoms forming the new bond. [1,2] and [2,3] rearrangements are most common, although [1,4] and [3,4] rearrangements are also known.

Scheme 1.1 [1,2] and [2,3] Wittig Rearrangements

a. [1,2] Wittig Rearrangement

\[
\text{EWG}_1 \text{O}_1 \text{Ph} \xrightarrow{\text{base}} \text{EWG}_1 \text{O}_1 \text{Ph} \rightarrow \left[ \begin{array}{c} \text{EWG}_1 \text{O}_1 \text{Ph} \end{array} \right] \xrightarrow{\text{workup}} \text{EWG}_1 \text{OH}
\]

b. [2,3] Wittig Rearrangement

\[
\text{EWG}_2 \text{O}_2 \xrightarrow{\text{base}} \text{EWG}_2 \text{O}_2 \rightarrow \left[ \begin{array}{c} \text{EWG}_2 \text{O}_2 \end{array} \right] \xrightarrow{\text{workup}} \text{EWG}_2 \text{OH}
\]

Typically, both [1,2] and [2,3] Wittig rearrangements require strongly basic conditions. Several studies have determined that base-mediated [1,2] Wittig rearrangements proceed through a radical pathway via metallation, homolytic cleavage, and recombination (Scheme 1.1a). As such, the yield of this [1,2] shift is highly
dependent on the radical stability of the migrating group. [2,3] rearrangements, however, proceed through a thermally allowed sigmatropic rearrangement pathway via a highly ordered 5-membered cyclic transition state (Scheme 1.1b).

Despite the incredible potential of Wittig rearrangements in organic synthesis, the utility of these transformations is limited for a number of reasons. In order to initiate the reaction, a strong base, typically n-BuLi, is required. These harsh conditions severely limit the classes of compounds able to employ this method. Additionally, these reactions display insufficient chemoselectivity, as deprotonation can occur on either side of the oxygen atom, or at any other acidic site on the substrate. This issue is commonly remedied by incorporating an anion-stabilizing group on the appropriate side of the oxygen atom in order to favor the desired deprotonation. Due to the nature of radical intermediates in the [1,2] mechanistic pathway, the transformations suffer from low stereoselectivity. Furthermore, these rearrangements can proceed in low yield, due to competing processes, such as E2 elimination or radical rearrangement.

A number of modern variants of Wittig rearrangements have been developed. These new methods aim to circumvent the practical limitations of the transformation with the use of milder conditions in order to increase the functional group tolerance. Additionally, the reaction conditions have been applied to several other types of substrates in addition to the relatively common O-allyl and O-benzyl ethers. The following chapter will describe a number of Wittig rearrangement variations as well as recent advances in tandem Wittig reactions.

**1.2 Wittig Rearrangements of Propargyl Ethers**

In Wittig rearrangements, propargyl substituents are commonly utilized as anion stabilizing groups, for example in the rearrangement of allyl propargyl ether 1-1\(^3\) (Scheme 1.2a). However, propargyl groups can also function as the migrating fragment in a [2,3] Wittig rearrangement resulting in allenic alcohols. In arylmethyl propargyl\(^4\) or bis-propargyl\(^5\) ethers, selective deprotonation can be achieved under certain conditions (Scheme 1.2b), though competing [1,2] and [2,3] rearrangement pathways can be problematic.
Scheme 1.2 Propargyl Substituents as Anion Stabilizing Groups (a) or Migrating Groups (b) in Wittig Rearrangements

a. [2,3] allyl shift

\[
\begin{align*}
\text{O} & \text{Ph} \\
\text{N} & \text{S} \\
1-3 & \\
\end{align*}
\]

\[\overset{\text{BuLi}}{\text{OH}} \]

By comparison, Wittig rearrangements of O-propargyl glycolic acid derivatives are easier to control, as enolate formation is much more favorable than deprotonation at the propargylic position. Enolate Wittig rearrangements will be discussed in detail in section 1.4.

Under basic conditions, these O-propargyl ethers typically undergo [2,3] Wittig rearrangements to afford allenic alcohols. Alkyl substitution at the propargylic position is tolerated, as these substrates generate allenic alcohols in high yield and diastereoselectivity.\(^6\) Rearrangements of these nonracemic propargyl ethers occur with high stereoselectivity, due to the rigidity of the proposed five-centered transition state (Scheme 1.3).
**Scheme 1.3 Proposed Transition State for Propargyl [2,3] Wittig Rearrangement**

\[
\begin{align*}
\text{HO} & \quad \text{O,CH}_3 \\
\text{1-5} & \quad \text{\textrightarrow} \\
\text{LDA, THF} & \quad -78 \, ^\circ\text{C} \\
\text{1-6} & \quad \text{\textrightarrow} \\
\text{1-7} & \quad \text{major} \\
\text{1-8} & \quad \text{\textrightarrow} \\
\text{1-9} & \quad \text{minor}
\end{align*}
\]

**1.3 The Aza-Wittig Rearrangement**

Analogous to the Wittig Rearrangement, the aza-Wittig rearrangement is the conversion of an α-metallated tertiary amine to a structurally rearranged secondary amine. The mechanisms of these transformations are believed to parallel to those of the oxygen analog, that is, a [1,2] radical mediated pathway and a [2,3] sigmatropic rearrangement. Aza-Wittig rearrangements are less prevalent than Wittig rearrangements of metallated ethers, though the transformation provides a useful synthetic tool for the formation of homoallylic and phenethyl secondary amines.

The driving force of the Wittig rearrangement is the transfer of electron density from the metallated carbanion to the more electronegative oxygen atom. The difference in electronegativity between oxygen and nitrogen atoms makes the aza-Wittig rearrangement slightly less favorable than the corresponding Wittig rearrangement. Consequently, aza-Wittig rearrangements by comparison are typically slower and less facile. Initial reports of aza-Wittig rearrangements required extremely harsh conditions; for example, in a 1960 report by Johnstone and Stevens, an aza-Wittig rearrangement is induced by treating tertiary benzylic amines with potassium hydroxide or methyllithium at 110–300 ºC for 0.5–3 hr.\(^7\) As such, acyclic aza-Wittig rearrangements were initially scarce. Instead, many studies were focused on small-ring assisted rearrangements. Aza-Wittig rearrangements of vinyl aziridines, for example, are high yielding even at low temperature due to the relief of ring strain.\(^8,9\) An aza-[2,3]-Wittig
rearrangement of a vinyl aziridine 1-10 was a key step in the enantioselective total synthesis of (−)-indolizines 209B and 209D (Scheme 1.4).\(^\text{10}\)

**Scheme 1.4** Small-ring Assisted Aza-[2,3]-Wittig Rearrangement

![Scheme 1.4 Small-ring Assisted Aza-[2,3]-Wittig Rearrangement](image)

The first example of acyclic aza-[2,3]-Wittig rearrangements in synthetically useful yields was reported by Anderson in 1995.\(^\text{11}\) Though yields are good, diastereoselectivity is modest (Scheme 1.5). Aza-[2,3]-rearrangements are believed to proceed through a five-membered envelope-like cyclic transition state. Therefore, the diastereoselectivity is determined by the relative energy difference between the two transition state configurations. Excellent stereoselectivity can be obtained, though the results are highly substrate-dependent.

**Scheme 1.5** First Acyclic Aza-[2,3]-Rearrangement

![Scheme 1.5 First Acyclic Aza-[2,3]-Rearrangement](image)

Though aza-[2,3]-Wittig rearrangements are not uncommon, reports of aza-[1,2]-Wittig rearrangements are relatively rare. Most frequently, these transformations are observed as side products from competing [1,2] vs [2,3] reaction pathways.\(^\text{12,13}\) An aza-[1,2]-Wittig rearrangement in synthetically useful yield has only been reported on a single occasion.\(^\text{14}\) This rearrangement occurred unexpectedly in the synthesis of polysubstituted piperidines *via* radical cyclization. [1,2] Wittig rearrangement was observed in substrates bearing an *N*-benzyl group. The authors hypothesize that two
equivalents of SmI$_2$ generate the α-amino carbanion, which undergoes a [1,2] benzyl shift, resulting in the observed product (Scheme 1.6).

**Scheme 1.6 Aza-[1,2]-Wittig Rearrangement**

1.4 Enolate Wittig Rearrangement

Wittig rearrangements require the formation of an α-alkoxy anion. In order to facilitate this deprotonation/metallation, an anion-stabilizing group, such as an aryl, alkenyl, or alkynyl group, is required. One variant of this transformation involves the use of an electron-withdrawing group such an acid, ester, or amide moiety, which can stabilize the anion through the formation of a metallated enolate. Due to the relative acidity of these α-protons, enolate Wittig rearrangements can occur under significantly milder conditions, such that the typical strong bases, e.g. $^n$BuLi or LDA, are not required.

The reactivity and diastereoselectivity of enolate rearrangements differs slightly depending on the variety of metal enolate in question. Though lithium enolates are most common, several enolate rearrangements have been reported with the use of tin, titanium, boron, and zirconium reagents, often in higher yield and diastereoselectivity when compared to the corresponding lithium enolate.$^{15}$

Enolate [1,2] Wittig rearrangements are rare, and there are currently no examples of [1,2] Wittig rearrangements of boron enolates with the exception of those published by the Wolfe group. Enolate [2,3] rearrangements, however, are more prevalent, and the rearrangements of boron enolates in particular have been studied in detail.$^{16}$ It was found that Bu$_2$BOTf and 'Pr$_2$NEt promote [2,3] Wittig rearrangement in moderate yield and diastereoselectivity. In a representative example, 1-18 underwent rearrangement in 55% yield and 4:1 dr (Scheme 1.7).
Scheme 1.7 [2,3] Wittig Rearrangement of a Boron Enolate

\[
\begin{align*}
\text{MeO} &\text{O} &\text{O} &\text{MeO} \\
\text{Bu}_2\text{BOTf, Pr}_2\text{NEt} &\rightarrow & -78^\circ\text{C} &55\%, 4:1 \text{ dr} \\
\text{MeO} &\text{O} &\text{OH} &\text{1-19} \\
\end{align*}
\]

Enolate [2,3] Wittig rearrangements appear to bypass the issue of competitive [1,2] Wittig rearrangement pathways, consistently providing the [2,3] product exclusively.\(^{17}\) However, these enolate rearrangements can suffer from competitive sigmatropic rearrangements: [2,3] Wittig vs [3,3] Claisen rearrangements (Scheme 1.8).\(^{18,19}\) Through several studies, it has been determined that metal enolates of esters or amides preferentially undergo a [2,3] Wittig rearrangement, whereas metal enolates of ketones provide mixtures of [2,3] and [3,3] products.\(^{16,20,21}\)

Scheme 1.8 [2,3] vs [3,3] Sigmatropic Rearrangements of Allylic Glycolate Esters

Additionally, asymmetric variants of [2,3] Wittig rearrangements have been developed.\(^{22}\) Specifically, asymmetric Wittig rearrangements of boron enolates have been explored with the use of chiral auxiliaries\(^{23}\) or chiral boron reagents. Nakai successfully utilized the chiral bis-sulfonamide boron reagent 1-27 for an asymmetric Wittig rearrangement. In a representative example, 1-24 performed [2,3] rearrangement in 57% yield, and though diastereoselectivity was modest, the major diastereomer was generated in 90% ee (Scheme 1.9).\(^{24}\)
1.5 Tandem Wittig Rearrangement/Aldol Reactions

In the course of study towards anisomycin, Wolfe and Bertrand discovered an unusual tandem Wittig rearrangement/aldol reaction. In the presence of dibutylboron triflate and triethylamine, O-benzyl glycolate esters undergo an enolate [1,2] Wittig rearrangement, followed by a subsequent aldol reaction with the addition of an aldehyde (Scheme 1.10).

Further experimentation revealed that the transformation was both general and highly stereoselective for the syn-diol. Under the described reaction conditions, O-benzyl and O-allyl glycolate methyl esters undergo the tandem rearrangement/aldol reaction with a variety of alkyl, alkenyl, and aryl aldehyde coupling partners (Table 1.1).
Table 1.1 Representative Wittig/aldol products

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield, b dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>CHCH₂</td>
<td>67%, &gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>Ph</td>
<td>72%, &gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>C₉H₁₉</td>
<td>78%, &gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>Allyl</td>
<td>Pr</td>
<td>66%, &gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>Allyl</td>
<td>Ph</td>
<td>75%, &gt;20:1</td>
</tr>
</tbody>
</table>

aConditions: 1.0 equiv of ester, 3.2 equiv of Bu₂BOTf, 4.0 equiv of Et₃N, CH₂Cl₂, 0.2 M, rt, 15 min, then add 1.5 equiv of aldehyde, 0 °C to rt. bYields represent average isolated yields of two or more experiments. cDiastereomeric ratio obtained upon purification. In most cases, the crude product was obtained in >20:1 dr prior to purification. dThe crude product was obtained in 20:1 dr.

The reactions are high yielding and generate syn-diol products with excellent stereoselectivity. It was determined that the Wittig rearrangement occurs first in the tandem sequence. When aldehyde is excluded from the reaction conditions, an aqueous workup generates the Wittig product in 81% yield. Thus, the proposed mechanism involves an initial enolate Wittig rearrangement, followed by formation of a second boron enolate, which undergoes the subsequent aldol reaction (Scheme 1.11). The high syn-stereoselectivity of the diol product is likely due to the selective formation of the E(O)-enolate 1-34, due to chelation between the ester carbonyl and the boron alkoxide.

Scheme 1.11 Proposed Mechanism for Tandem Wittig Rearrangement/aldol Reaction
Next, asymmetric variants of this reaction were explored.\textsuperscript{26} Several chiral auxiliaries were examined, and optimal results were obtained with the use of \textit{trans}-2-phenylcyclohexanol. This chiral auxiliary is commercially available, though large quantities of the enantioenriched auxiliary can be prepared easily in two steps from cyclohexene oxide.\textsuperscript{27} Furthermore, the 2-phenylcyclohexanol can be removed from the diol product via two methods: reduction using lithium aluminum hydride or a two-step sequence of acetonide formation followed by hydrolysis. When the O-benzyl glycolate ester bearing this chiral auxiliary was subjected to the reaction conditions previously employed, the diol product was obtained in 83% yield and >20:1 dr. LiAlH\textsubscript{4} reduction of this product generated the enantioenriched triol in 59% yield and 89% ee. With these promising results, the scope of this transformation was explored.

As previously observed, both O-benzyl and O-allyl glycolate esters underwent the tandem Wittig rearrangement/aldol reaction in good yield and excellent selectivity. With the use of alkyl, alkenyl, or aryl aldehyde coupling partners, diol products were generated with a high \textit{syn}-selectivity. After reduction of the auxiliary, enatioenriched triols were afforded in 75–95% ee (Table 1.2, Entries 1–4).
Table 1.2 Asymmetric Tandem Wittig/Aldol and Wittig/Mannich Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>Y</th>
<th>Yield, b dr c</th>
<th>ee after LAH reduction d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>Ph</td>
<td>O</td>
<td>83%, 20:1</td>
<td>89%</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>Cy</td>
<td>O</td>
<td>71%, 20:1</td>
<td>91%</td>
</tr>
<tr>
<td>3</td>
<td>Allyl</td>
<td>Ph</td>
<td>O</td>
<td>83%, 20:1</td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>Allyl</td>
<td>iPr</td>
<td>O</td>
<td>68%, 20:1</td>
<td>89%</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>Ph</td>
<td>NBn</td>
<td>71%, &gt;20:1</td>
<td>96%</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>2-furyl</td>
<td>NBn</td>
<td>70%, 20:1</td>
<td>90%</td>
</tr>
<tr>
<td>7</td>
<td>Allyl</td>
<td>p-F-Ph</td>
<td>NBn</td>
<td>69%, &gt;20:1</td>
<td>94%</td>
</tr>
</tbody>
</table>

*Conditions: 1.0 equiv 1-36 or 1-37, 1.5–2 equiv aldehyde or imine, 3.2 equiv Bu₂BOTf, 4 equiv Et₃N (R₁ = Bn) or 1-Pr₂NEt (R₁ = allyl), CH₂Cl₂, 0°C → rt → 0°C. bIsolated yield (average of two or more experiments). cRatios were determined by ¹H NMR analysis. All products were obtained with >20:1 syn:anti selectivity. dEnantiomeric excess was determined by chiral HPLC or Mosher ester analysis after reduction to the corresponding triol with LiAlH₄.

This tandem Wittig/aldol methodology was utilized in the synthesis of 1-39, a key intermediate in the synthesis of the antifungal agent alternaric acid. This intermediate 1-39 had previously been generated via a seven-step sequence in Trost’s total synthesis. However, the aforementioned tandem Wittig rearrangement/aldol sequence allowed this intermediate to be prepared in just three steps. The key Wittig/aldol step afforded 1-39 in 80% yield and >20:1 dr (Scheme 1.12).

Scheme 1.12 Key Step in the Synthesis of Alternaric Acid

Additional studies were performed to examine the use of this tandem sequence in an asymmetric Wittig rearrangement/Mannich reaction in the hopes of affording
enantioenriched α-hydroxy-β-amino acids from O-benzyl and O-allyl glycolate esters. A number of protecting groups were examined for the aldimine coupling partner. Expectedly, the nature of the protecting group had a significant impact on the outcome of the reaction. Imines bearing electron-withdrawing groups such as tosyl groups failed to undergo the reaction. The best results were obtained with the use of an aldimine bearing a benzyl protecting group. A number of benzyl protected aryl aldimines were successfully coupled with 1-36 and 1-37 in good yield and at least 20:1 dr, though unbranched alkyl imines failed to undergo the Mannich reaction. After cleavage of the chiral auxiliary, the desired α-hydroxy-β-amino acids were obtained in 93–96% ee (Table 1.2, Entries 5–8).

**Scheme 1.13** Representative Examples Wittig/Mannich Reactions of N-Boc Electrophiles

![Scheme 1.13](image)

Though imines bearing other electron-poor protecting groups were unsuccessful coupling partners for these reactions, N-Boc imine electrophiles were used successfully to perform the desired Wittig/Mannich reaction. However, isoxazolidin-2-one 1-41 was formed rather than the expected amino alcohol (Scheme 1.13a). Furthermore, reactions with N-Boc-2-(phenylsulfonyl)amine electrophiles proceeded in excellent yield, though, interestingly, with high anti-stereoselectivity (Scheme 1.13b).

The mechanism of these transformations likely begins with an enolate Wittig rearrangement followed by the generation of a second boron enolate. The stereoselectivity of the Mannich reaction is dependent on the electrophile being utilized.
Mannich reactions with $N$-benzyl or $N$-Boc imines proceed through a boat-like six-membered cyclic transition state, yielding products with high syn-selectivity, whereas Mannich reactions with $N$-Boc-2-(phenylsulfonyl)amine electrophiles proceed through an open transition state, yielding products with high anti-selectivity.

1.6 Aldol Reactions with Ketone Electrophiles

Given the success of these tandem Wittig/aldol and Wittig/Mannich reactions, we hoped to further develop the scope of these transformations. We envisioned a tandem Wittig/aldol reaction between 1-36 or 1-37 and a ketone electrophile, which could potentially generate vicinal quaternary stereocenters rapidly and selectively, as depicted in Scheme 1.14.

Scheme 1.14 Generation of Vicinal Quaternary Stereocenters via Tandem Wittig/Aldol Reactions

While aldol reactions between ketone enolates and aldehyde electrophiles are ubiquitous, there are a number of inherent difficulties when attempting to employ ketone electrophiles in these reactions. Relative to aldehydes, ketones are less electrophilic, leading to low conversion to the tertiary alcohol product. Furthermore, the retro-aldol reaction of this transformation is rapid. Additionally, the lack of steric and electronic differences between the ketone substituents generally leads to low stereo-discrimination.\textsuperscript{31,32} Therefore, the scope of these reactions is extremely narrow and the practical applications are limited.

Despite these challenges, a variety of conditions have been developed for aldol reactions with ketone coupling partners. In order to circumvent the aforementioned complications, a number of adaptations have been adopted. Frequently, Mukaiyama aldol conditions are used, as pre-formed silyl enol ethers permit milder conditions and
reduce the risk of self-coupling of the ketone components.\textsuperscript{33} These pre-formed nucleophiles are effectively paired with Lewis acids or Lewis bases in aldol reactions with ketone acceptors.\textsuperscript{34-37} Denmark developed an enantioselective aldol reaction with ketones utilizing chiral Lewis base catalysts. A number of ketone electrophiles were successfully coupled, though the nucleophilic partner is limited to the highly reactive trichlorosilyl enolate of methyl acetate (Table 1.3).

Table 1.3 Denmark’s Catalytic, Enantioselective Aldol Addition to Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>Promoter</th>
<th>Yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Et</td>
<td>1-44</td>
<td>92%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1-44</td>
<td>1-45</td>
<td>90%</td>
<td>90:10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Me (CH\textsubscript{2})\textsubscript{2}Ph</td>
<td>1-44</td>
<td>94%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1-45</td>
<td></td>
<td>91%</td>
<td>66:33</td>
<td></td>
</tr>
</tbody>
</table>

However, the poor atom economy of these reactions has led to the development of reductive aldol reactions of copper enolates, which do not require pre-generation of the enolate (Scheme 1.15).\textsuperscript{38,39}

Scheme 1.15 Enantioselective Reductive Aldol Reactions with Ketone Electrophiles

Initial experiments exploring our tandem Wittig/aldol reaction were conducted with 1-46 and 1-47 and a variety of methyl ketones.\textsuperscript{40} Rather than the anticipated diols, however, boronate esters were generated instead. Acetophenone derivatives proved to
be excellent coupling partners, affording boronate esters in high yield and selectivity (Table 1.4, entry 4). However, reactions with di-aliphatic ketones proceed with low stereoselectivity due to the lack of steric differentiation between the two similarly sized substituents (Table 1.4, entries 1–3).

**Table 1.4 Tandem Wittig/Aldol Reactions with Ketones**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Yield</th>
<th>dr</th>
<th>ee after LAH reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>74%</td>
<td>4:1</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>67%</td>
<td>3:1</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>Allyl</td>
<td>Ph</td>
<td>55%</td>
<td>7:1</td>
<td>79%</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>p-F-Ph</td>
<td>56%</td>
<td>20:1</td>
<td>91%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: 1.0 equiv ester, 1.5 equiv ketone, 3.2 equiv Bu<sub>2</sub>BOTf, 4.0 equiv base, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → rt → 0 °C → rt.<br><sup>b</sup>Isolated yield (average of two or more experiments).<br><sup>c</sup>Diastereomeric ratio of isolated material (determined by <sup>1</sup>H NMR analysis). The dr value of the crude product could not be determined due to signal overlap with boron-containing by-products.<br><sup>d</sup>The enantiomeric excess was determined by Mosher ester analysis after reduction to the diol.

By resubjecting the boronate ester to hydrogen peroxide, the diol can be freed (Scheme 1.16). Enantiopurity of the products was determined via Mosher ester analysis of the triol resulting from boronate ester cleavage and LiAlH<sub>4</sub> reduction.

**Scheme 1.16 Boronate Ester Cleavage**

Though these preliminary results show promise, further experimentation is required in order to fully explore the scope and limitation of these transformations. The
examination of these tandem Wittig/aldol reaction with ketone coupling partners will be elaborated in Chapter 4.

1.7 References

Chapter 2
Synthesis of Substituted 3-Hydroxy-2-Furanone Derivatives via an Unusual Enolate Wittig Rearrangement/Alkylative Cyclization Sequence.

2.1 Introduction

In recent years our group has explored the development and applications of boron-mediated cascade Wittig rearrangement/aldol reactions of glycolate ester derivatives 2-1 for the stereoselective construction of α-alkyl-α,β-dihydroxy esters 2-2 (Scheme 2.1).1-3 These reactions proceed with excellent diastereoselectivity, and use of the readily available chiral auxiliary trans-2-phenylcyclohexanol provides access to enantiomerically enriched products with up to 94% ee after auxiliary cleavage. Although these reactions have demonstrated synthetic utility, the scope of this method is currently limited to substrates bearing O-allyl or O-benzyl migrating groups. Substrates that contain simple O-alkyl or O-aryl groups fail to undergo the initial Wittig rearrangement.

Scheme 2.1 Boron-mediated Tandem Wittig Rearrangement/aldol Reaction

2.2 Preliminary Results

In order to further expand the scope of this method, we sought to employ substrates bearing O-propargyl groups. Related substrates are known to undergo 2,3-Wittig rearrangement when treated with a strong base,4-6 and the resulting products 2-2 where R is an allenyl group could be valuable intermediates for the construction of substituted heterocycles.7,8 To this end we prepared ester substrate 2-3 and subjected this compound to our standard reaction conditions whereby the ester was treated with
Bu₂BOTf and iPr₂NEt, stirred at rt for ca 15 min, and then an aldehyde was added to the resulting mixture. We were quite surprised to discover that 2-3 failed to undergo the sequential rearrangement/aldol reaction, and instead was transformed to the substituted 3-hydroxy-2-furanone 2-4 (Scheme 2.2). Interestingly, although the aldehyde electrophile apparently did not participate in the reaction, a butyl group from the Bu₂BOTf reagent was incorporated at the product C5 position. Omission of the aldehyde from the reaction mixture led to the formation of 2-4 in 62% yield.

**Scheme 2.2 Unexpected 3-hydroxy-2-furanone Formation**

![](image)

2.3 Synthesis of 3-Hydroxy-2-Furanones

Given the potential synthetic utility and biological relevance of substituted furanone derivatives, we sought to further examine this unusual transformation. Efforts to optimize reaction conditions by modifying temperature, solvent, base, etc. did not lead to significant improvements in yield. As such, we proceeded to explore the effect of substrate structure on reactivity. As shown in Table 2.1, the best results were obtained with substrates bearing aryl groups on the alkyne moiety (entries 1–4 and 8). These substrates were converted to substituted furanones in moderate yield. In contrast, substrates that contain alkyl-substituted alkynes were transformed in low yields (entries 5–7).
Table 2.1 Tandem Wittig Rearrangement/Alkylative Cyclization Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>( R^1 )</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu</td>
<td>Ph (2-3)</td>
<td>2-4</td>
<td>62%</td>
</tr>
<tr>
<td>2</td>
<td>Bu</td>
<td>( p\text{-F-C}_6\text{H}_4 ) (2-5)</td>
<td>2-6</td>
<td>47%</td>
</tr>
<tr>
<td>3</td>
<td>Bu</td>
<td>2-naphthyl (2-7)</td>
<td>2-8</td>
<td>56%</td>
</tr>
<tr>
<td>4</td>
<td>Bu</td>
<td>( p\text{-Me-C}_6\text{H}_4 ) (2-9)</td>
<td>2-10</td>
<td>43%</td>
</tr>
<tr>
<td>5</td>
<td>Bu</td>
<td>Ph(CH(_2))(_2) (2-11)</td>
<td>2-12</td>
<td>29%</td>
</tr>
<tr>
<td>6</td>
<td>Bu</td>
<td>( \text{Pr} ) (2-13)</td>
<td>2-14</td>
<td>23%</td>
</tr>
<tr>
<td>7</td>
<td>Bu</td>
<td>Me (2-15)</td>
<td>2-16</td>
<td>20%</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>Ph (2-3)</td>
<td>2-17</td>
<td>50%</td>
</tr>
</tbody>
</table>

\(^a\)Conditions: i) 1.0 equiv ester, 3.2 equiv \( R_2\text{BOTf} \), 4.0 equiv \( \text{Pr}_2\text{NET} \), \( \text{CH}_2\text{Cl}_2 \), 0.25 M, 0 °C \( \rightarrow \) rt. ii) \( \text{H}_2\text{O}_2 \), pH 7 buffer. \(^b\) Isolated yields (average of two experiments).

Attempts to employ substrate 2-18 bearing an ethyl group at the propargylic position led to formation of allene 2-19 in 52% yield; no furanone product was observed (Scheme 2.3). The rearrangement/cyclization reactions appear to be limited to internal alkyne substrates, as subjection of terminal alkyne substrate 2-20 to the standard reaction conditions resulted in generation of substituted allylic alcohol 2-21 in low yield rather than a substituted furanone (Scheme 2.4).\(^{13}\)

Scheme 2.3 Allene Formation

Scheme 2.4 Attempted Rearrangement of Terminal Alkyne
2.4 Effect of Boron Reagent

We also briefly examined the influence of the dialkylboron reagent structure on reactivity. As anticipated, use of diethylboron triflate resulted in the formation of furanone product 2-17 in which an ethyl group had been incorporated at C5 (Table 2.1, entry 8). However, use of the hindered and less electrophilic Cy$_2$BCl reagent led to no observable reaction. Interestingly, treatment of 2-3 with 9-BBN-OTf/Pr$_2$NEt led to clean formation of allene 2-22 in 53% yield (Scheme 2.5).

**Scheme 2.5 Rearrangement using of 9-BBNOTf**

During the course of our initial optimization studies, we examined an alternative workup procedure in which the reaction of substrate 2-3 with Bu$_2$BOTf/Pr$_2$NEt was quenched with aqueous HCl rather than treated with H$_2$O$_2$ and pH 7 buffer. Interestingly, use of this acidic workup led to the formation of 2-23 (39% yield) (Scheme 2.6); the furanone product was not observed by NMR analysis of the crude reaction mixture.

**Scheme 2.6 Alternative Acidic Workup Procedure**

2.5 Mechanistic Studies

Taken together, the results illustrated in equations 3–6 provide a considerable amount of information about the likely mechanism of the rearrangement/cyclization reactions. The conversion of 2-20 to 2-21, 2-3 to 2-22, and 2-3 to 2-23 suggest the
mechanism of this unusual rearrangement/alkylation involves initial [2,3]-Wittig rearrangement of the substrate to generate an intermediate allene.\textsuperscript{14} A subsequent alkyl transfer from the boron reagent to the allene leads to carbon–carbon bond formation, and likely proceeds via a radical pathway that is presumably initiated by small amounts of oxygen.\textsuperscript{15-19,20} Finally, the fact that the modified (acidic) workup generates \textbf{2-23} rather than \textbf{2-31} suggests that \(\alpha\)-ketoester \textbf{2-23} may be an intermediate in the alkylation/cyclization reactions, and that conversion of \textbf{2-29} to \textbf{2-31} may occur during the \(\text{H}_2\text{O}_2/\text{pH} 7\) buffer workup step.

\textbf{Scheme 2.7} Radical Cage Mechanism for Conversion of \textbf{4-24} to \textbf{4-31}

On the basis of these results, two plausible mechanisms for the conversion of \textbf{2-3} to \textbf{2-4} are illustrated in Schemes 2.7–2.8; the former involves a radical cage process whereas the latter proceeds via a radical chain mechanism. In both pathways treatment of ester \textbf{2-24} with the dialkylboron triflate and Hüning’s base leads to formation of boron enolate \textbf{2-25}, which undergoes 2,3-Wittig rearrangement to afford allene \textbf{2-26}. In the cage mechanism (Scheme 2.7), the oxygen-mediated transfer of an alkyl radical from the boron group to the allene would occur within a solvent cage to generate allyl radical
2-27. An intramolecular 1,5-hydrogen atom transfer of 2-27 would then afford enolate 2-28. Upon workup, protonation of the enolate would generate 2-29, which can then undergo conjugate addition of water or hydroxide to provide alcohol 2-30.\textsuperscript{21-24} Intramolecular acylation of the alcohol then yields the product 2-31.\textsuperscript{25}

Alternatively, the radical reaction may also occur via a chain mechanism (Scheme 2.8) whereby oxygen could lead to generation of an alkyl radical from 2-26 in the initiation step. Propagation would then involve addition of the alkyl radical to a second molecule of 2-26 to yield 2-32, which could be captured by oxygen to afford 2-33 along with another alkyl radical. Base-mediated elimination of 2-34 (or the analogous boronate ester derived from homolysis of the O–O bond and rearrangement) would provide 2-35, which upon workup could be transformed to 2-26 and then 2-31.

\textbf{Scheme 2.8 Radical Chain Mechanism}

Regardless of which pathway is operational, the formation of allene product 2-19 in the reaction of ethyl-substituted substrate 2-18 may result from disfavored intramolecular alkyl transfer due to the increased steric bulk of the more highly
substituted allene intermediate. The reason behind the failed cyclization of terminal alkene substrate 2-20 is less clear. However, the radical intermediate generated from rearrangement and alkyl transfer of 2-20 (2-32, R^1 = H) is considerably less stable than analogous intermediates derived from internal alkynes.

In order to further probe the question of cage vs. chain mechanism, we carried out a crossover experiment in which the rearrangement of 2-3 was carried out in the presence of 3.2 equiv of Et_3B (Scheme 2.9). This reaction provided a ca. 1:1 mixture of 2-4 and 2-17, which indicates an intermolecular (i.e. non-cage) alkyl radical transfer to the allene is a viable mechanistic pathway and suggests that the mechanism illustrated in Scheme 2.8 may be operational (although this does not unambiguously rule out the radical cage mechanism shown in Scheme 2.7).^{26}

**Scheme 2.9 Crossover Experiment**

![Scheme 2.9 Crossover Experiment](image)

### 2.6 Conclusion

In conclusion, we have discovered an unusual Wittig rearrangement/alkylative cyclization reaction of methyl O-propargyl glycolate derivatives. The reactions produce potentially useful 3-hydroxy-furan-2-one products in moderate yield, and appear to proceed via radical alkylation of an intermediate allene. Future studies will be directed towards improving and expanding the scope of these transformations.

The work described in this chapter was published in Organic Letters.^{27}

### 2.7 Experimental

**General:** All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents were obtained from commercial sources and were used as
obtained unless otherwise noted. Dichloromethane, THF, and triethylamine were purified using a GlassContour solvent purification system. Hüning’s base was purified by distillation from CaH$_2$ prior to use. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by $^1$H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Table 2.1 and schemes 2.3–2.6 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 2.1 and schemes 2.3–2.6.

Handling of Dialkylboron reagents: Dibutylboron triflate (1.0 M solution in methylene chloride) was obtained from Aldrich Chemical Co. and used as obtained. Diethylboron triflate was prepared according to Evans’ procedure.$^{28}$ Due to the air and moisture sensitivity of these reagents, they must be stored and transferred under a rigorously maintained nitrogen atmosphere.

Synthesis and Characterization of Substrates

General Procedure 1: A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of the alkyne substrate in THF (1.0 equiv, 0.8 M). The solution was cooled to $-78$ °C and a solution of 1.6 M n-BuLi in hexanes (1.2 equiv) was added dropwise. The mixture was stirred at $-78$ °C for 40 min before the aldehyde substrate (1.4 equiv) was added. The reaction mixture was warmed to rt over 16 hours and then quenched with saturated NH$_4$Cl. The mixture was transferred to a separatory funnel and then extracted twice with Et$_2$O. The combined organic layers were dried over anhydrous sodium sulfate then concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 20–40% ethyl acetate/hexanes as the eluent, unless stated otherwise.
4-Methylpent-2-yn-1-ol.\textsuperscript{29} General procedure 1 was used for the alkylation of 3-methylbut-1-yne (1 g, 14.7 mmol) with paraformaldehyde (620 mg, 20.6 mmol) except the product was not purified by chromatography. This procedure afforded 1.2 g (83%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 4.25 (dd, \(J = 2.0, 6.0\) Hz, 2 H), 2.56–2.63 (m, 1 H), 1.45–1.49 (m, 1 H), 1.17 (d, \(J = 6.8\) Hz, 6 H).

5-Phenylpent-2-yn-1-ol.\textsuperscript{30} General procedure 1 was used for the alkylation of but-3-yn-1-ylbenzene (1 g, 7.68 mmol) with paraformaldehyde (323 mg, 10.8 mmol). This procedure afforded 1.22 g (99%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.32 (t, \(J = 7.6\) Hz, 2 H), 7.24 (d, \(J = 8.1\) Hz, 3 H), 4.25 (dd, \(J = 2.2, 4.2\) Hz, 2 H), 2.85 (t, \(J = 7.6\) Hz, 2 H), 2.53 (tt, \(J = 2.1, 7.6\) Hz, 2 H), 1.47 (t, \(J = 6.1\) Hz, 1 H).

1-Phenylpent-1-yn-3-ol.\textsuperscript{31} General procedure 1 was used for the alkylation of phenylacetylene (2.0 g, 19.6 mmol) with propionaldehyde (1.97 mL, 27.4 mmol). This procedure afforded 2.33 g (74%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.43–7.41 (m, 2 H), 7.30–7.29 (m, 3 H), 4.54 (q, \(J = 6.2\) Hz, 1 H), 1.85–1.78 (m, 3 H), 1.07 (t, \(J = 14\) Hz, 3 H).

3-(p-Tolyl)prop-2-yn-1-ol.\textsuperscript{32} General procedure 1 was used for the alkylation of 4-ethynyltoluene (1.0 g, 8.58 mmol) with paraformaldehyde (361 mg, 12.0 mmol). This procedure afforded 1.21 g (97%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) \(\delta\) 7.31 (d, \(J = 7.9\) Hz, 2 H), 7.10 (d, \(J = 7.8\) Hz, 2 H), 4.47 (d, \(J = 6.2\) Hz, 2 H), 2.33 (s, 3 H), 1.64 (m, br, \(J = 2.1, 6.0\) Hz, 1 H).
General Procedure 2:

(a) Sonogashira Coupling: A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with Pd(PPh)$_3$Cl$_2$ (1 mol%), Cul (1 mol%), and the appropriate aryl bromide (1.0 equiv). The tube was purged with nitrogen before triethylamine and (trimethylsilyl)acetylene were added via syringe. The resulting mixture was heated to 70 °C until the starting material had been consumed as judged by TLC analysis (ca. 14 h). After cooling the reaction to rt, the solution was filtered through celite, which was washed with Et$_2$O until the washes appeared colorless. The filtrate was concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel.

(b) Desilylation and Alkylation: A flame-dried flask was cooled under a stream of nitrogen and charged with dry paraformaldehyde (3.0 equiv). The flask was purged with nitrogen and a 0.5 M solution of the aryl substrate (1.0 equiv) in THF was added. To this was added a 1.0 M solution of TBAF in THF (3.0 equiv.). The reaction was stirred at 40 °C until the starting material had been completely consumed, as judged by TLC analysis (ca. 20 h). The reaction was quenched with saturated NH$_4$Cl, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 20–40% ethyl acetate/hexanes as the eluent.

3-(Naphthalen-2-yl)prop-2-yn-1-ol.$^{33}$ General procedure 2(a) was used for the alkylation of 2-bromonaphthalene (1.04 g, 5.0 mmol) with (trimethylsilyl)acetylene (0.8
mL, 7.5 mmol). This procedure afforded 908 mg (81%) of trimethyl(naphthalen-2-ylenethynyl)silane as a pale orange solid with spectroscopic properties identical to those previously reported.\textsuperscript{34} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 8.00 (s, 1 H), 7.75–7.81 (m, 3 H), 7.47–7.51 (m, 3 H), 0.29 (s, 9 H).

General procedure 2(b) was used for the alkylation of trimethyl(naphthalen-2-ylenethynyl)silane (1.0 g, 4.46 mmol) with paraformaldehyde (187 mg, 6.24 mmol). This procedure afforded 667 mg (82%) of the title compound as a white solid, mp 53–59 °C. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.97 (s, 1 H), 7.82–7.72 (m, 3 H), 7.51–7.47 (m, 3 H), 4.55 (d, \( J \) = 6.4 Hz, 2 H), 1.67 (t, \( J \) = 6.4 Hz, 1 H).

3-(4-Fluorophenyl)prop-2-yn-1-ol. General procedure 2(a) was used for the alkylation of 1-bromo-4-fluorobenzene (1.5 g, 8.57 mmol) with (trimethylsilyl)acetylene (1.83 mL, 12.9 mmol). This procedure afforded 1.24 g (75%) of [(4-fluorophenyl)ethynyl]trimethylsilane as a pale orange oil with spectroscopic properties identical to those previously reported.\textsuperscript{35} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.45 (dd, \( J \) = 3.2, 8.6 Hz, 2 H), 6.99 (t, \( J \) = 8.6 Hz, 2 H), 0.24 (s, 9 H).

General procedure 2(b) was used for the alkylation of [(4-fluorophenyl)ethynyl]trimethylsilane (181 mg, 0.94 mmol) with paraformaldehyde (85 mg, 2.82 mmol). This procedure afforded 116 mg (82%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.41 (dd, \( J \) = 5.4, 8.8 Hz, 2 H), 7.00 (t, \( J \) = 8.7 Hz, 2 H), 4.47 (d, \( J \) = 6.0 Hz, 2 H), 1.64 (t, \( J \) = 6.3 Hz, 1 H).

\[ \text{HO} \equiv \text{C} \equiv \text{R} \]

1. NaH, THF

2. MeO

\[ \text{Br} \]

\[ \text{MeO} \equiv \text{O} \equiv \text{C} \equiv \text{R} \]

**General Procedure 3:** A flame-dried flask was cooled under a stream of nitrogen and charged with 60% NaH in mineral oil (1.2 equiv), which was then suspended in THF and
cooled to 0 °C. A solution of the alcohol substrate (1.0 equiv) in THF was added dropwise, and the mixture was stirred at rt for 30 min. The reaction solution was again cooled to 0 °C and neat methyl 2-bromoacetate (1.0 equiv) was added. The resulting mixture was stirred at rt overnight (ca. 16 h). Water was then added, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 5–20% ethyl acetate/hexanes as the eluent.

Methyl-2-[(3-phenylprop-2-yn-1-yl)oxy]acetate (2-3). General procedure 3 was employed for the alkylation of 3-phenylprop-2-yn-1-ol (2 g, 15.1 mmol) with methyl 2-bromoacetate (1.44 mL, 15.1 mmol). This procedure afforded 1.94 g (63%) of the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.44 (dd, J = 1.2, 8.3 Hz, 2 H), 7.32 (t, J = 6.6 Hz, 3 H), 4.53 (s, 2 H), 4.28 (s, 2 H), 3.78 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 131.8, 128.7, 128.3, 122.3, 87.4, 83.7, 66.2, 59.1, 52.0; IR (film) 1754, 1213, 1119 cm⁻¹. MS (ESI) 227.0676 (227.0679 calcd for C₁₂H₁₂O₃, M + Na⁺).

Methyl 2-[(3-(4-fluorophenyl)prop-2-yn-1-yl)oxy]acetate (2-5). General procedure 3 was employed for the alkylation of 3-(4-fluorophenyl)prop-2-yn-1-ol (819 mg, 5.64 mmol) with methyl 2-bromoacetate (0.52 mL, 5.64 mmol). This procedure afforded 615 mg (51%) of the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.42 (dd, J = 5.4, 9.1 Hz, 2 H), 7.01 (t, J = 8.8 Hz, 2 H), 4.51 (s, 2 H), 4.26 (s, 2 H), 3.78 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 162.7 (d, J = 249.9 Hz), 133.8 (d, J = 8.6 Hz), 118.3, 115.6 (d, J = 22.9 Hz), 86.3, 83.4, 66.3, 59.1, 52.0; IR (film) 1755, 1220, 1120 cm⁻¹. MS (ESI) 245.0587 (245.0584 calcd for C₁₂H₁₁FO₃, M + Na⁺).
Methyl 2-[[3-(naphthalen-2-yl)prop-2-yn-1-yl]oxy]acetate (2-7). General procedure 3 was employed for the alkylation of 3-(naphthalen-2-yl)prop-2-yn-1-ol (195 mg, 1.07 mmol) with methyl 2-bromoacetate (0.10 mL, 1.07 mmol). This procedure afforded 175 mg (64%) of the title compound as a pale yellow solid, mp 46–50 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.98 (s, 1 H), 7.82–7.77 (m, 3 H), 7.51–7.47 (m, 3 H), 4.59 (s, 2 H), 4.32 (s, 2 H), 3.79 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.4, 132.9, 132.8, 131.9, 128.3, 128.0, 127.8, 127.7, 126.9, 126.6, 119.5, 87.7, 84.0, 66.3, 59.2, 52.0; IR (film) 1754, 1213, 1118 cm$^{-1}$. MS (EI) 254.2 (254.09 calcd for C$_{16}$H$_{14}$O$_3$, M$^+$).

Methyl 2-[[3-(p-tolyl)prop-2-yn-1-yl]oxy]acetate (2-9). General procedure 3 was employed for the alkylation of 3-(p-tolyl)prop-2-yn-1-ol (1.25 g, 8.58 mmol) with methyl 2-bromoacetate (0.81 mL, 8.58 mmol). This procedure afforded 835 mg (45%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 (d, $J = 8.3$ Hz, 2 H), 7.12 (d, $J = 8.3$ Hz, 2 H), 4.52 (s, 2 H), 4.27 (s, 2 H), 3.78 (s, 3 H), 2.35 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 138.8, 131.7, 129.1, 119.2, 87.5, 83.0, 66.2, 59.2, 51.9, 21.5; IR (film) 1755, 1213, 1120 cm$^{-1}$. MS (ESI) 241.0837 (241.0835 calcd for C$_{13}$H$_{14}$O$_3$, M + Na$^+$).

Methyl-2-[[5-phenylpent-2-yn-1-yl]oxy]acetate (2-11). General procedure 3 was employed for the alkylation of 5-phenylpent-2-yn-1-ol (250 mg, 1.56 mmol) with methyl 2-bromoacetate (0.15 mL, 1.56 mmol). This procedure afforded 264 mg (73%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29 (t, $J = 7.8$ Hz, 2 H), 7.22 (t, $J = 7.8$ Hz, 3 H), 4.26 (t, $J = 4.5$ Hz, 2 H), 4.13 (s, 2 H), 3.77 (s, 3 H), 2.83 (t, $J = 7.6$ Hz, 2 H), 2.52 (tt, $J = 1.7$, 7.6 Hz, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 140.4,
128.4, 126.3, 87.5, 75.4, 65.9, 58.8, 51.9, 34.8, 20.9 (one carbon signal is missing due to incidental equivalence); IR (film) 1754, 1212 cm\(^{-1}\). MS (ESI+) 255.0993 (255.0992 calcd for C\(_{14}\)H\(_{16}\)O\(_{3}\), M + Na\(^+\)).

**Methyl-2-[(4-methylpent-2-yn-1-yl)oxy]acetate (2-13).** General procedure 3 was employed for the alkylation of 4-methylpent-2-yn-1-ol (226 mg, 2.31 mmol) with methyl 2-bromoacetate (0.22 mL, 2.31 mmol). This procedure afforded 163 mg (42%) of the title compound as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.28 (s, 2 H), 4.20 (s, 2 H), 3.78 (s, 3 H), 2.63–2.56 (m, 1 H), 1.18 (d, \(J = 6.8\) Hz, 6 H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.6, 93.8, 73.7, 65.9, 58.9, 51.9, 22.8, 20.5; IR (film) 1736, 1239, 1114 cm\(^{-1}\). MS (ESI) 193.0833 (198.0835 calcd for C\(_9\)H\(_{14}\)O\(_3\), M + Na\(^+\)).

**Methyl-2-(but-2-yn-1-yloxy)acetate (2-15).**\(^{36}\) General procedure 3 was employed for the alkylation of 2-butyn-1-ol (1.60 mL, 21.4 mmol) with methyl 2-bromoacetate (2.03 mL, 21.4 mmol). This procedure afforded 1.42 g (47%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.27 (d, \(J = 2.4\) Hz, 2 H), 4.21 (s, 2 H), 3.78 (s, 3 H), 1.87 (t, \(J = 2.3\) Hz, 3 H).

**Methyl-2-(prop-2-yn-1-yloxy)acetate (2-20).**\(^{37}\) General procedure 3 was employed for the alkylation of propargyl alcohol (0.52 mL, 8.92 mmol) with methyl 2-bromoacetate (0.85 mL, 8.92 mmol). This procedure afforded 769 mg (67%) of the title compound as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.31 (dd, \(J = 1.0, 2.5\) Hz, 2 H), 2.21 (s, 2 H), 3.77 (s, 3 H), 2.48 (t, \(J = 2.5\) Hz, 1 H).
Methyl-2-[(1-phenylpent-1-yn-3-yl)oxy]acetate (2-18). General procedure 3 was employed for the alkylation of 1-phenylpent-1-yn-3-ol (336 mg, 2.10 mmol) with methyl 2-bromoacetate (0.20 mL, 2.10 mmol). This procedure afforded 217 mg (45%) of the title compound as a colorless oil. \[^1^H\text{NMR}(500\text{MHz},\text{CDCl}_3)\delta 7.45\text{ (dd, } J = 2.9, 4.9\text{ Hz, } 2\text{ H}), 7.33\text{ (d, } J = 7.1\text{ Hz, } 3\text{ H}), 4.45\text{ (t, } J = 6.4\text{ Hz, } 1\text{ H}), 4.34\text{ (m, } 2\text{ H}), 3.78\text{ (s, } 3\text{ H}), 1.86\text{ (m, } 2\text{ H}), 1.11\text{ (t, } J = 7.3\text{ Hz, } 3\text{ H}); \[^{13}\text{C NMR}(125\text{MHz},\text{CDCl}_3)\delta 170.8, 131.8, 128.5, 128.3, 122.4, 86.8, 86.7, 71.8, 65.5, 51.8, 28.8, 9.7; \text{IR (film) } 1756, 1211, 1119\text{ cm}^{-1}.\text{MS (EI) } 231.1\text{ (231.10 calcd for } C_{14}H_{16}O_3,\ M - H^+)\].

**Synthesis and Characterization of Furanone Products**

General Procedure 4: A flame-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dialkylboron triflate in methylene chloride (3.2 equiv). The solution was cooled to 0 °C and Hüning's base (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in methylene chloride was then added, and the resulting solution was warmed to rt over 15 min, at which point the flask was opened to air and quenched by the addition of pH 7 buffer (2 mL/mmol substrate). The heterogeneous mixture was transferred to a larger flask and diluted with MeOH (ca. 5–8 mL/mmol substrate) to afford a clear and homogeneous solution. This solution was cooled to 0 °C, 30% aqueous H₂O₂ (ca. 4 mL/mmol substrate) was added slowly, and the resulting mixture was warmed to rt and stirred for 1 h. The solution was then diluted with water and extracted twice with Et₂O. The combined organic layers were washed with water, saturated Na₂S₂O₃, and brine. The aqueous washes were extracted once more with Et₂O, and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was
purified by flash chromatography on silica gel using 10–30% ethyl acetate/hexanes as the eluent.

**5-Butyl-3-hydroxy-5-methyl-4-phenylfuran-2(5H)-one (2-4).** General procedure 4 was employed to cyclize substrate 2-3 (50 mg, 0.238 mmol) to form lactone 2-4 using dibutylboron triflate. This procedure afforded 37 mg (62%) of the title compound as a pale yellow solid, mp 107–112 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 8.6$ Hz, 2 H), 7.44 (td, $J = 1.7, 7.6$ Hz, 2 H), 7.37 (t, $J = 7.3$ Hz, 1 H), 6.19 (s, br, 1 H), 2.08 (dt, $J = 4.9, 12.7$ Hz, 1 H), 1.99 (dt, $J = 4.8, 11.3$ Hz, 1 H), 1.70 (s, 3 H), 1.06–1.31 (m, 4 H), 0.83 (t, $J = 7.1$ Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.7, 137.2, 133.0, 130.2, 128.8, 128.7, 127.9, 87.9, 38.5, 26.1, 25.3, 22.5, 13.8; IR (film) 3295, 1727 cm$^{-1}$. MS (ESI) 247.11 (246.13 calcd for C$_{15}$H$_{18}$O$_3$, M + H$^+$).

![Structure of 5-Butyl-3-hydroxy-5-methyl-4-phenylfuran-2(5H)-one (2-4).]

**5-Butyl-4-(4-fluorophenyl)-3-hydroxy-5-methylfuran-2(5H)-one (2-6).** General procedure 4 was employed to cyclize substrate 2-5 (75 mg, 0.338 mmol) to form lactone 2-6 using dibutylboron triflate. This procedure afforded 49 mg (41%) of the title compound as a pale yellow solid, mp 87–90 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.77 (dd, $J = 5.4, 9.1$ Hz, 2 H), 7.14 (t, $J = 8.6$ Hz, 2 H), 2.08 (td, $J = 4.4, 13.6$ Hz, 1 H), 1.95 (td, $J = 5.0, 13.1$ Hz, 1 H), 1.69 (s, 3 H), 1.04–1.29 (m, 4 H), 0.82 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.6, 162.5 (d, $J = 250.8$ Hz), 137.0, 132.2, 129.9 (d, $J = 7.6$ Hz), 126.3 (d, $J = 2.9$ Hz), 116.0 (d, $J = 21.0$ Hz), 87.7, 38.4, 26.0, 25.2, 22.4, 13.8; IR (film) 3292, 1727 cm$^{-1}$. MS (ESI) 265.1229 (265.1234 calcd for C$_{15}$H$_{17}$FO$_3$, M + H$^+$).
5-Butyl-3-hydroxy-5-methyl-4-(naphthalen-2-yl)furan-2(5H)-one (2-8). General procedure 4 was employed to cyclize substrate 2-7 (50 mg, 0.197 mmol) to form lactone 2-8 using dibutylboron triflate. This procedure afforded 47 mg (81%) of the title compound as a pale yellow viscous oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.17 (s, 1 H), 7.96–7.84 (m, 3 H), 7.56–7.51 (m, 3 H), 6.68 (s, br, 1 H), 2.05–2.19 (m, 2 H), 1.79 (s, 3 H), 1.31–1.11 (m, 4 H), 0.83 (t, $J$ = 14 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.5, 137.3, 133.1, 133.0, 132.8, 128.6, 128.5, 127.6, 127.5, 127.2, 126.6, 125.1, 88.0, 38.6, 26.3, 25.3, 22.5, 13.8 (one carbon signal is missing due to incidental equivalence); IR (film) 3290, 1725 cm$^{-1}$. MS (ESI) 297.1491 (297.1485 calcd for C$_{19}$H$_{20}$O$_3$, M + H$^+$$)$.

5-Butyl-3-hydroxy-5-methyl-4-(p-tolyl)furan-2(5H)-one (2-10). General procedure 4 was employed to cyclize substrate 2-9 (100 mg, 0.458 mmol) to form lactone 2-10 using dibutylboron triflate. This procedure afforded 52 mg (44%) of the title compound as a pale yellow solid, mp 114–118 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68 (d, $J$ = 8.3 Hz, 2 H), 7.25 (d, $J$ = 8.3 Hz, 2 H), 7.03 (s, br, 1 H), 2.39 (s, 3 H), 2.08 (td, $J$ = 4.4, 13.4 Hz, 1 H), 1.98 (td, $J$ = 5.5, 13.0 Hz, 1 H), 1.69 (s, 3 H), 1.07–1.29 (m, 4 H), 0.82 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.8, 139.0, 136.7, 133.3, 129.5, 127.8, 127.3, 87.8, 38.5, 26.1, 25.3, 22.5, 21.4, 13.8; IR (film) 3293, 1724 cm$^{-1}$. MS (ESI) 261.1487 (261.1485 calcd for C$_{16}$H$_{20}$O$_3$, M + H$^+$$)$. 
5-Butyl-3-hydroxy-5-methyl-4-phenethylfuran-2(5H)-one (2-12). General procedure 4 was employed to cyclize substrate 2-11 (100 mg, 0.431 mmol) to form lactone 2-12 using dibutylboron triflate. This procedure afforded 39 mg (33%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.30 (t, $J$ = 7.3 Hz, 2 H), 7.20–7.24 (m, 3 H), 5.70 (s, br, 1 H), 3.03 (t, $J$ = 7.8 Hz, 2 H), 2.49–2.55 (m, 1 H), 2.39–2.45 (m, 1 H), 1.74–1.80 (m, 1 H), 1.50–1.56 (m, 1 H), 1.31 (s, 3 H), 1.11–1.24 (m, 3 H), 0.94–1.03 (m, 1 H), 0.84 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.8, 141.1, 137.0, 135.6, 128.5, 128.3, 126.4, 87.2, 37.0, 32.1, 27.2, 25.1, 24.1, 22.5, 13.9; IR (film) 3320, 1731 cm$^{-1}$. MS (APCI) 275.1636 (275.1642 calcd for C$_{17}$H$_{22}$O$_3$, M + H$^+$).

5-Butyl-3-hydroxy-4-isopropyl-5-methylfuran-2(5H)-one (2-14). General procedure 4 was employed to cyclize substrate 2-13 (75 mg, 0.441 mmol) to form lactone 2-14 using dibutylboron triflate. This procedure afforded 27 mg (29%) of the title compound as a white solid, mp 97–99 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.41 (s, br, 1 H), 2.28–2.34 (m, 1 H), 1.82 (dt, $J$ = 4.8, 13.3 Hz, 1 H), 1.61 (dt, $J$ = 4.8, 12.9 Hz, 1 H), 1.43 (s, 3 H), 1.12–1.32 (m, 10 H), 0.87 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 143.4, 136.3, 87.3, 37.1, 25.9, 25.4, 24.1, 22.6, 20.6, 19.8, 13.9; IR (film) 3332, 1728 cm$^{-1}$. MS (ESI) 235.1305 (235.1305 calcd for C$_{12}$H$_{20}$O$_3$, M + Na$^+$).

5-Butyl-3-hydroxy-4,5-dimethylfuran-2(5H)-one (2-16). General procedure 4 was employed to cyclize substrate 2-15 (50 mg, 0.351 mmol) to form lactone 2-16 using
dibutylboron triflate. This procedure afforded 15 mg (23%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 5.74 (s, br, 1 H), 1.81–1.85 (m, 4 H), 1.60 (dd, $J$ = 4.6, 12.1 Hz, 1 H), 1.42 (s, 3 H), 1.26–1.31 (m, 2 H), 1.15–1.21 (m, 1 H), 1.03–1.09 (m, 1 H), 0.87 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.8, 136.6, 134.5, 87.1, 36.8, 25.0, 24.1, 22.5, 13.9, 8.7; IR (film) 3330, 1737 cm$^{-1}$. MS (EI) 184.1100 (184.1099 calcd for C$_{10}$H$_{16}$O$_3$, M$^+$).

5-Ethyl-3-hydroxy-5-methyl-4-phenylfuran-2(5H)-one (2-17). General procedure 4 was employed to cyclize substrate 2-3 (75 mg, 0.367 mmol) to form lactone 2-17 using diethylboron triflate. This procedure afforded 45 mg (56%) of the title compound as a pale yellow solid, mp 109–113 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J$ = 7.3 Hz, 2 H), 7.44 (t, $J$ = 7.3 Hz, 2 H), 7.37 (t, $J$ = 7.6 Hz, 1 H), 2.01–2.17 (m, 1 H), 1.98–2.06 (m, 1 H), 1.70 (s, 3 H), 0.79 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 170.8, 139.1, 132.0, 130.8, 128.6, 128.2, 127.7, 87.7, 31.7, 25.8, 7.6; IR (film) 3296,1726 cm$^{-1}$. MS (EI) 218.0935 (218.0943 calcd for C$_{13}$H$_{14}$O$_3$, M$^+$).

Methyl-2-hydroxy-3-phenylhepta-3,4-dienoate (2-19). General procedure 4 was employed to rearrange substrate 2-18 (75 mg, 0.32 mmol) to form allene 2-19 using dibutylboron triflate. This procedure afforded 39 mg (53%) of the title compound as a yellow oil. This compound was isolated as a ca. 1:1 mix of diastereomers. Data are for the mixture. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67–7.62 (m, 2 H), 7.36–7.31 (m, 2 H), 7.24–7.20 (m, 1 H), 5.80–5.75 (m, 1 H), 5.20 (s, 0.5 H), 5.16 (s, 0.5 H), 3.77 (s, 3 H), 3.03–2.99 (m, 1 H), 2.13–2.19 (m, 2 H), 1.09–1.06 (m, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 203.1, 173.7, 134.5, 128.5, 127.2, 126.4, 99.4, 71.0, 52.5, 23.5, 21.8, 13.0; IR (film) 3475, 1740 cm$^{-1}$. MS (ESI) 255.0987 (255.0992 calcd for C$_{14}$H$_{16}$O$_3$, M + Na$^+$).
(E/Z)-Methyl-2-hydroxy-4-methyloct-3-enoate (2-21). General procedure 4 was employed to transform substrate 2-20 (50 mg, 0.39 mmol) into product 2-21 using dibutylboron triflate. This procedure afforded 9 mg (12%) of the title compound as a colorless oil. This material was judged to be a ca 1:1 mixture of E:Z isomers by $^1$H NMR analysis. Data are for the mixture. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.15 (s, 0.5 H), 5.13 (s, 0.5 H), 4.88–4.84 (m, 1 H), 3.77 (s, 3 H), 2.82–2.76 (m, 1 H), 2.18–2.14 (m, 1 H), 2.05–2.01 (m, 1 H), 1.77–1.75 (m, 3 H), 1.45–1.25 (m, 4 H), 0.84–0.94 (m, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.9, 143.9, 143.4, 121.6, 121.1, 68.1, 67.7, 52.7, 39.2, 32.2, 30.2, 29.6, 23.5, 22.7, 22.3, 16.8, 14.0, 13.9; IR (film) 3472, 1742 cm$^{-1}$. MS (ESI) 209.11 (209.11 calcd for C$_{10}$H$_{18}$O$_3$, M + Na$^+$).

Methyl-2-hydroxy-3-phenylpenta-3,4-dienoate (2-22). General procedure 4 was employed to rearrange substrate 2-3 (100 mg, 0.490 mmol) to form allene 2-22 using 9-BBNOTf. This procedure afforded 53 mg (53%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J$ = 7.6 Hz, 2 H), 7.34 (t, $J$ = 7.6 Hz, 2 H), 7.25 (t, $J$ = 7.3 Hz, 1 H), 5.26 (s, 2 H), 5.18 (d, $J$ = 7.6 Hz, 1 H), 3.79 (s, 3 H), 3.10 (d, $J$ = 7.8 Hz, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 208.4, 173.5, 133.2, 128.6, 127.4, 126.6, 105.5, 80.7, 71.0, 52.8; IR (film) 3470, 1744 cm$^{-1}$. MS (ESI) 277.0681 (277.0679 calcd for C$_{12}$H$_{12}$O$_3$, M + Na$^+$).

(E/Z)-Methyl 4-methyl-2-oxo-3-phenyloct-3-enoate (2-23). A modified general procedure 4 was employed to transform substrate 2-3 (100 mg, 0.490 mmol) into product 2-23 using dibutylboron triflate. The H$_2$O$_2$/pH 7 buffer workup step was omitted,
and instead the reaction was quenched with 2 mL of 1 M HCl. The resulting mixture was stirred at rt for 5 min, then was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et₂O then the organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting crude product was purified by flash chromatography on silica gel to afford 49 mg (39%) of the title compound as a yellow oil. This material was judged to be a ca 1:1 mixture of E:Z isomers. Data are for the mixture. ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.39 (m, 6 H), 7.19–7.17 (m, 4 H), 3.57 (s, 3 H), 3.55 (s, 3 H), 2.55–2.50 (m, 2 H), 2.22 (s, 3H), 2.09–2.04 (m, 2 H), 1.80 (s, 3H), 1.60–1.54 (m, 2 H), 1.47–1.37 (m, 4 H), 1.23–1.15 (m, 2 H), 0.97 (t, J = 7.3 Hz, 3 H), 0.79 (t, J = 7.3 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 187.8, 187.4, 164.8, 164.5, 157.9, 157.2, 136.2, 136.1, 133.8, 133.5, 130.4, 130.3, 128.4, 128.3, 127.8, 52.1, 52.0, 37.2, 35.8, 30.6, 29.9, 22.9, 22.6, 22.3, 20.6, 13.9, 13.8, 13.7; IR (film) 1739, 1680 cm⁻¹. MS (ESI) 261. 1480 (261.1485 calcd for C₁₆H₂₀O₃, M + H⁺).

2.8 References

12. The modest yields appear to be due to difficulties with isolation of these products or the formation of volatile or water soluble side products.
13. Compound **2-27** was the only isolable product obtained from this reaction. The low yield may be due to the volatility of either the product or of other low molecular weight side products.


20. Reactions of **2-3** conducted with measured amounts of added air failed to provide improved results over the standard conditions. However, a rearrangement of **2-3** conducted in a nitrogen-filled glovebox afforded a ca 2:1 mixture of allene **8** and lactone **2-4**, which suggests a stoichiometric amount of oxygen is needed to facilitate the transformation of **2-3** to **2-4**.


25. Attempts to subject **2-23** to the workup conditions failed to generate significant amounts of product **2-4**. However it is possible that cleavage of the B–O bond is relatively slow, and that either **2-28** or a boron-complexed ketone analog of **2-29** is the actual electrophile that participates in the conjugate addition of water or hydroxide.

26. Treatment of **2-3** with dibutylboron triflate/Hunig's base in the presence of excess (5 equiv) TEMPO as a radical trap resulted in no reaction; substrate **2-3** failed to undergo rearrangement. This may be due to inhibition of enolate generation due to undesired reaction of the Lewis acidic dibutylboron triflate with TEMPO.


Chapter 3
Aza-Wittig Rearrangements of N-Benzyl and N-Allyl Glycine Methyl Esters

3.1 Introduction

Wittig rearrangements of α-alkoxy carbanions have been well established over the past 70 years\textsuperscript{1,2,3} and provide a useful synthetic method for carbon-carbon bond formation. Our group has recently reported a tandem Wittig rearrangements/aldol reaction sequence, which affords substituted α,β-dihydroxy esters in good yield and high diastereoselectivity using mild, boron-mediated conditions (Scheme 3.1).\textsuperscript{4} With the use of 2-phenylcyclohexanol as a chiral auxiliary, these reactions can be performed asymmetrically yielding the diol products in up to 95% ee.\textsuperscript{5} Furthermore, analogous tandem Wittig rearrangement/Mannich reactions provide access to the corresponding amino alcohols.\textsuperscript{6} We sought to expand the scope of these enolate Wittig rearrangements, given the synthetic utility of the aforementioned transformations. We hypothesized that the corresponding enolate aza-Wittig rearrangement could be achieved under similar conditions from a tertiary amine.\textsuperscript{7} The rearrangement itself would provide access to unnatural amino acid derivatives, and if coupled with a subsequent aldol reaction, this sequence could produce biologically interesting β-hydroxy-α-amino acid derivatives.
Though Wittig rearrangements of α-alkoxy carbanions are well documented, the corresponding nitrogen analogue has been less explored. Moreover, while there is no lack of aza-[2,3]-Wittig rearrangements, reports of aza-[1,2]-Wittig rearrangements are much less frequent. In fact, the migration of benzyl groups in synthetically useful yields (>60%) has only been reported on a single occasion. More frequently, these transformations have been reported as side reactions in aza-[2,3]-Wittig rearrangements. Aza-Wittig rearrangements are typically slower and less facile than the analogous oxy-rearrangements, so the development of mild, boron-mediated conditions for the proposed transformation could prove to be synthetically useful.

**3.2 Initial Studies**

We elected to begin our initial studies by focusing solely on the aza-rearrangement (rather than the tandem rearrangement/aldol sequence) in order to determine the optimal conditions for the transformation. Considering the scarcity of successful aza-[1,2]-Wittig rearrangements, we first elected to first examine the migration of benzyl groups. N-benzyl-N-boc-glycine methyl ester was prepared for this purpose, as prior studies on aza-[2,3]-Wittig rearrangements have shown that electron-withdrawing N-substituents have improved reactivity. However, as illustrated in equation 1, when 3-6 was subjected to the reaction conditions we have previously employed in [1,2]-Wittig rearrangements of 3-1, no rearrangement occurred. Instead, 1,4,2-oxazaborole derivative 3-7 was formed (Scheme 3.2).
3.3 Synthesis of 1,4,2-Oxazaborole Derivatives

The reactivity of other N-benzyl glycine methyl ester derivatives was briefly explored. Substrates bearing N-pivalolyl or N-acetyl groups gave similar results (Table 3.1), as did the use of a substrate bearing an N-allyl rather than an N-benzyl group (Table 3.1, entry 4). Furthermore, similar reactivity was observed when 9-BBNOTf was used in place of Bu$_2$BOTf (Table 3.1, Entry 5).

Table 3.1 Formation of 1,4,2-Oxazaborole Derivatives$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_2$BOTf</th>
<th>Product</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>O'Bu</td>
<td>(3-6)</td>
<td>Bu$_2$BOTf</td>
<td>3-7</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>t'Bu</td>
<td>(3-9)</td>
<td>Bu$_2$BOTf</td>
<td>3-10</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>CH$_3$</td>
<td>(3-11)</td>
<td>Bu$_2$BOTf</td>
<td>3-12</td>
</tr>
<tr>
<td>4</td>
<td>Allyl</td>
<td>O'Bu</td>
<td>(3-13)</td>
<td>Bu$_2$BOTf</td>
<td>3-14</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>t'Bu</td>
<td>(3-9)</td>
<td>9-BBNOTf</td>
<td>3-15</td>
</tr>
</tbody>
</table>

$^a$Conditions: (i) 1.0 equiv of ester, 3.2 equiv of $R_2$BOTf, 4.0 equiv of t'Pr$_2$NEt, CH$_2$Cl$_2$, 0.25 M, 15 min, 0° C to rt. (ii) H$_2$O$_2$, pH 7 buffer, MeOH, 1 h, 0° C to rt. $^b$Isolated yield, average of two or more experiments.

The structure of 3-15 was confirmed via x-ray crystallography,$^{19}$ which clearly revealed the presence of a boron-oxygen bond (Figure 3.1). Unfortunately, even with an
increase in temperature and reaction time, these compounds failed to undergo the desired rearrangement. Moreover these compounds were also unreactive towards acids, bases, and oxidants such as alkaline hydrogen peroxide.

**Figure 3.1 X-Ray Structure of Compound 3-15**

The reactivity of these compounds towards palladium-catalyzed coupling reactions was briefly explored. We envisioned a Suzuki-like coupling reaction occurring between an aryl halide and the oxazaborole at the carbon–boron bond in the presence of a palladium catalyst. However, under the described conditions, we observed a mixture of products, none of which were the results of the desired coupling reaction (Scheme 3.3). With various ligands and bases, unreacted starting material was always obtained in addition to 3-17, which results from the cleavage of the boron, and occasionally 3-18, which results from a coupling reaction between the aryl halide and one of the butyl groups from the boron species.
3.4 Aza-Wittig Optimization

Considering the fact that substrates 3-6 failed to undergo rearrangement, efforts were focused on modifying the glycine N-substituent in hopes that the desired transformation could be facilitated with alterations to the steric or electronic properties of the nitrogen atom. $N$-benzyl glycine methyl esters bearing $N$-alkyl, $N$-phosphoryl, and $N$-tosyl groups were examined, though efforts to effect rearrangements of these substrates were also unsuccessful. However, we were gratified to find that the desired [1,2] rearrangement could be achieved with the use of an $N$-benzyl substrate bearing an $N$-phenyl group. Further experimentation revealed that by extending reaction time and increasing temperature, the desired amine could be isolated in 65% yield (Table 3.2, Entry 1).\textsuperscript{20}

3.5 Aza-[1,2]-Wittig Rearrangement

Once the optimized reaction conditions had been determined, additional substrates were prepared in order to examine the scope of the transformation. The requisite substrates were prepared in three steps from substituted anilines and benzaldehyde derivatives via imine formation, reduction, and $N$-alkylation with $\alpha$-bromo methyl acetate. As shown in Table 3.2, substitution on both the $N$-aryl group and benzyl group was tolerated. Additionally, substrates bearing heteroaromatic groups underwent the [1,2] rearrangement in good yield (Table 3.2, Entries 7–9).\textsuperscript{21} However, due to a combination of slow reaction rate and product decomposition as a result of the extended reaction time, the rearrangement of 3-25, which contains an $N$-$p$-trifluoromethylphenyl group, proceeded in poor yield.
Table 3.2 Aza-[1,2]-Wittig Rearrangement\textsuperscript{a}

\[
\begin{array}{cccc}
\text{Entry} & \text{R} & \text{Ar} & \text{Product} & \text{Yield}\textsuperscript{b} \\
1 & H & \text{Ph (3-19)} & 3-20 & 64\% \\
2 & \text{p-Br} & \text{Ph (3-21)} & 3-22 & 54\% \\
3 & \text{p-OMe} & \text{Ph (3-23)} & 3-24 & 65\% \\
4 & \text{p-CF}_3 & \text{Ph (3-25)} & 3-26 & 24\% \\
5 & H & \text{p-BrPh (3-27)} & 3-28 & 67\% \\
6 & H & \text{o-BrPh (3-29)} & 3-30 & 53\% \\
7 & H & \text{2-furyl (3-31)} & 3-32 & 68\% \\
8 & H & \text{2-thiophenyl (3-33)} & 3-34 & 66\% \\
9 & H & N-Ts-2-pyrrolyl (3-35) & 3-36 & 54\% \\
\end{array}
\]

\textsuperscript{a}Conditions: (i) 1.0 equiv of ester, 3.2 equiv of Bu\textsubscript{2}BOTf, 4.0 equiv of \textsuperscript{i}Pr\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C → 40 °C (ii) H\textsubscript{2}O\textsubscript{2}, pH 7 buffer. \textsuperscript{b}Isolated yield, average of two or more experiments.

3.6 Aza-[1,2]-Wittig Scope

The scope and stereocontrol of this reaction was explored by preparing substrates 3-37 and 3-39, which bear a methyl group at the benzylic position or adjacent to the ester, respectively. The rearrangement of 3-37 to 3-38 proceeded in good yield, though the diastereoselectivity of this reaction was low (Scheme 3.3a). The diastereoselectivity was not improved with the use of 9-BBN-OTf in place of Bu\textsubscript{2}BOTf; a similar mixture of diastereomers was obtained under these conditions. Though substitution at the benzylic position was tolerated (Scheme 3.3a), substrate 3-39 proved to be unreactive toward our standard conditions (Scheme 3.3b). We hypothesize that the lack of reactivity is due to difficulty generating the requisite boron enolate from the more sterically encumbered substrate. This is consistent with our observation that no aldol product was generated when 3-19 was treated with excess Bu\textsubscript{2}BOTf/\textsuperscript{i}Pr\textsubscript{2}NEt followed by addition of an aldehyde to the reaction mixture (Scheme 3.3c), unlike the reactivity that was previously observed in reactions of 3-1 (Scheme 3.1).
Scheme 3.4 Scope and Stereocontrol of Aza-[1,2]-Rearrangement

\[ a. \text{benzylic substitution} \]
\[
\begin{array}{c}
\text{MeO} & \text{N} & \text{Ph} \\
\text{3-37} & \text{NH} & \text{Ph} \\
\text{CH}_3 & & \\
\end{array}
\]
\[
\xrightarrow{\text{Bu}_2\text{BOTf, Pr}_2\text{NEt, CH}_2\text{Cl}_2}
\]
\[
\begin{array}{c}
\text{MeO} & \text{N} & \text{Ph} \\
\text{3-38} & \text{NH} & \text{Ph} \\
\text{H}_3\text{C} & & \\
\end{array}
\]
66%, 1.6:1 d.r.

\[ b. \text{\(\alpha\)-carbonyl substitution} \]
\[
\begin{array}{c}
\text{MeO} & \text{N} & \text{Ph} \\
\text{3-39} & \text{NH} & \text{Ph} \\
\text{CH}_3 & & \\
\end{array}
\]
\[
\xrightarrow{\text{Bu}_2\text{BOTf, Pr}_2\text{NEt, CH}_2\text{Cl}_2}
\]
no reaction

\[ c. \text{tandem aldol reaction} \]
\[
\begin{array}{c}
\text{MeO} & \text{N} & \text{Ph} \\
\text{3-19} & \text{NH} & \text{Ph} \\
\text{CH}_3 & & \\
\end{array}
\]
\[
\xrightarrow{\text{1. excess Bu}_2\text{BOTf, Pr}_2\text{NEt, CH}_2\text{Cl}_2}
\]
\[
\begin{array}{c}
\text{MeO} & \text{N} & \text{Ph} \\
\text{3-20} & \text{NH} & \text{Ph} \\
\text{PhCHO} & & \\
\end{array}
\]
(no aldehyde incorporation)

3.7 Aza-[2,3]-Rearrangement

In order to explore the feasibility of the analogous aza-[2,3]-Wittig rearrangements, \(N\)-allyl-\(N\)-phenyl glycine methyl ester was prepared. However, when 3-40 was subjected to the standard conditions, a mixture of two products was observed (Scheme 3.4). Both products appear to be the consequence of a [2,3] rearrangement, though 3-42 appears to have undergone a subsequent alkene oxidation. Efforts to reproduce this result provided variable mixtures of 3-41 and 3-42, and further experimentation revealed that temperature variation led to the inconsistent distribution of products. By lowering reaction temperature to 35 °C and reducing the amount of \(\text{Bu}_2\text{BOTf}\) to 1.5 equivalents, 3-41 could be isolated as the sole product in 70% yield (Table 3.3, entry 1).
A number of N-allyl substrates were prepared in a manner analogous to the synthesis of the substrates used in Table 2 in order to explore the scope of this [2,3] rearrangement. When subjected to the optimized reaction conditions, a variety of substrates cleanly underwent [2,3] rearrangement, as shown in Table 3. Terminal and internal substitution on the alkene was tolerated as well as substitution on the N-aryl group. Substrates bearing internal alkenes underwent diastereoselective rearrangement to provide products in 5:1 and 8:1 dr in most cases. However, substrate 3-45 rearranged in much higher dr (>20:1), and selectivity was low with cyclohexene derived substrate 3-55 (2:1 dr). Aza-[2,3]-Wittig rearrangements are believed to proceed through a highly ordered cyclic transition state analogous to that of the corresponding allylic ethers. Two substrates, 3-45 and 3-47 yielded a mixture of [1,2] and [2,3] rearrangement products (Table 3.3, entries 2 and 3), indicating competing pathways, which is common in Wittig rearrangements of allylic compounds. Additionally, a substrate bearing a cyclic N-allyl group (Table 3.3, entry 8) underwent the [2,3] rearrangement in modest yield and diastereoselectivity.
Table 3.3 Aza-[2,3]-Wittig Rearrangement

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Product</th>
<th>yield(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-41</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-44</td>
<td>60%, (7:1 dr)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-46</td>
<td>73%(^{c}), (&gt;20:1 dr)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-48</td>
<td>75%(^{d})</td>
</tr>
<tr>
<td>5</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-50</td>
<td>55%</td>
</tr>
<tr>
<td>6</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-52</td>
<td>58%, (5:1 dr)</td>
</tr>
<tr>
<td>7</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-54</td>
<td>62%, (8:1 dr)</td>
</tr>
<tr>
<td>8</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>(\text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R}_1\text{R}_2\text{R}_3)</td>
<td>3-56</td>
<td>56%, (2:1 dr)</td>
</tr>
</tbody>
</table>

\(^{a}\)Conditions: (i) 1.0 equiv of ester, 1.5 equiv of Bu\(_2\)BOTf, 1.7 equiv of \(\text{Pr}_2\text{NEt}, \text{CH}_2\text{Cl}_2, 35^\circ\text{C}\), 0.25 M, 4 hr, 0\(^\circ\)C to 35\(^\circ\)C. (ii) \(\text{H}_2\text{O}_2, \text{pH} 7\) buffer, MeOH, 1 h, 0\(^\circ\)C to rt. \(^{b}\)Isolated yield, average of two or more experiments. \(^{c}\)Product was generated as a 4:1 mixture of [2,3] and [1,2] rearrangement products, respectively. \(^{d}\)Product was generated as a 2:1 mixture of [2,3] and [1,2] rearrangement products, respectively.
3.8 Tandem Aza-[2,3]-Wittig Rearrangement/Hydroboration Oxidation

The curious hydroboration reaction observed previously warranted additional investigation (Scheme 3.5). Further experimentation revealed that higher temperatures and a large excess of Bu₂BOTf favor the subsequent hydroboration reaction, though complete conversion from the alkene intermediate is difficult to achieve. Optimal results were attained when 3-40 was reacted with two sequential additions of 2.0 equivalents of Bu₂BOTf at 40 °C, which generated 3-42 in 56% yield (Table 3.4, entry 1). The remaining mass balance, however, was observed to be alkene 3-41, which failed to undergo the hydroboration after the [2,3] rearrangement. Additionally, we observed that hydroboration only occurred on terminal alkenes. In cases where competing reaction pathways resulted in two products, only the [2,3] rearrangement product, which bears a terminal alkene, was observed to undergo the subsequent oxidation (Table 3.4, entries 3 and 4).
Table 3.4 Aza-[2,3]-Wittig Rearrangement/Hydroboration⁹

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Product</th>
<th>Yield*, dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 3-40" /></td>
<td><img src="image" alt="Product 3-42" /></td>
<td>3-42</td>
<td>52%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 3-43" /></td>
<td><img src="image" alt="Product 3-57" /></td>
<td>3-57</td>
<td>54%, 10:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 3-45" /></td>
<td><img src="image" alt="Product 3-58" /></td>
<td>3-58</td>
<td>57%, &gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 3-47" /></td>
<td><img src="image" alt="Product 3-59" /></td>
<td>3-59</td>
<td>51%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Substrate 3-49" /></td>
<td><img src="image" alt="Product 3-60" /></td>
<td>3-60</td>
<td>41%, 1:1</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Substrate 3-51" /></td>
<td><img src="image" alt="Product 3-61" /></td>
<td>3-61</td>
<td>44%, 9:1</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Substrate 3-53" /></td>
<td><img src="image" alt="Product 3-62" /></td>
<td>3-62</td>
<td>48%, 13:1</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Substrate 3-55" /></td>
<td><img src="image" alt="Product 3-63" /></td>
<td>3-63</td>
<td>38%, 3:1</td>
</tr>
</tbody>
</table>

⁹Conditions: (i) 1.0 equiv of ester, 2.0 equiv of Bu₂BOTf, 4.0 equiv of iPr₂NET, CH₂Cl₂, 0.25 M, 2 hr, 0° C to 35° C. (ii) 2.0 equiv of Bu₂BOTf, 4 hr, 0° C to 40° C. (iii) H₂O₂, pH 7 buffer, MeOH, 1 h, 0° C to rt. *Isolated yield, average of two or more experiments.
The observed alkene oxidation likely occurs via hydroboration. We hypothesize that β-hydride elimination of dibutylboron triflate can occur at elevated temperatures, leading to \textit{in situ} generation of an alkyl borohydride species. This intermediate can react with an alkene in an \textit{anti} Markovnikov manner similar to that of a traditional hydroboration reagent. The organoboron species is then oxidized in the workup by hydrogen peroxide, generating the observed terminal alcohol.

To assess the limitations of this transformation, compound 3-64, which bears a methyl group adjacent to the ester moiety, was prepared. As observed previously (Scheme 3.3b), the [2,3]-rearrangement did not occur. However, in this case, the methyl ester was hydrolyzed, likely due to decomposition of the boron enolate under thermal conditions, leading to a ketene intermediate 3-65 that can be hydrolyzed during the aqueous workup to form the observed product, 3-66 (Scheme 3.5). Additionally, no aldol product was generated when 3-40 was treated with excess Bu₂BOTf/iPr₂NEt followed by addition of an aldehyde to the reaction mixture.

\textbf{Scheme 3.6} Decomposition of α-Substituted Substrate

\begin{center}
\begin{tikzpicture}
\node at (0,0) {3-64};
\node at (2,0) {3-65};
\draw[->] (0.5,0) -- (1.5,0);
\node at (1,0) {$\text{Bu}_2\text{BOTf, }\text{iPr}_2\text{NEt, }\text{CH}_2\text{Cl}_2$};
\end{tikzpicture}
\end{center}

\textbf{3.9 Asymmetric Aza-Wittig Rearrangements}

Finally, we have conducted preliminary studies on asymmetric enolate aza-Wittig rearrangements. We have previously executed asymmetric Wittig rearrangement/aldol reactions of glycolate esters successfully with the use of 2-phenylcyclohexanol as a chiral auxiliary. Thus, substrates 3-68 and 3-70 bearing this chiral auxiliary were synthesized and subjected to the standard reaction conditions. Unfortunately, although the yields of these transformations were good, the diastereoselectivity in each case was
modest (Table 3.5). Nonetheless, this experiment indicates the possibility of achieving asymmetric induction, although further optimization is clearly needed.

**Table 3.5 Asymmetric Aza-Wittig Rearrangement**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzyl</td>
<td>85%</td>
<td>1.6:1</td>
</tr>
<tr>
<td>2</td>
<td>allyl</td>
<td>64%</td>
<td>1.3:1</td>
</tr>
</tbody>
</table>

*a*Conditions: (i) 1.0 equiv of 3-68, 3.2 equiv of Bu₂BOTf, 4.0 equiv of Pr₂NET, CH₂Cl₂, 0.25 M, 2 h, 0º C to 40 ºC. (ii) H₂O₂, pH 7 buffer, MeOH, 1 h, 0º C to rt. *b*Conditions: (i) 1.0 equiv of 3-70, 1.5 equiv of Bu₂BOTf, 1.7 equiv of Pr₂NET, CH₂Cl₂, 0.25 M, 4 h, 0º C to 35 ºC. (ii) H₂O₂, pH 7 buffer, MeOH, 1 h, 0º C to rt. *c*Isolated yield.

3.10 Conclusion

In conclusion, we have developed a new aza-[1,2]-Wittig rearrangement of N-aryl-N-benzyl glycine methyl esters. These transformations constitute rare examples of benzyl group migration in aza-Wittig rearrangements and provide a concise four-step approach to the construction of substituted N-aryl phenylalanine derivatives. Additionally, we have developed an analogous aza-[2,3]-Wittig rearrangement of N-aryl-N-allyl glycine methyl esters. With slightly modified reaction conditions, we have shown that these same substrates can undergo an aza-[2,3]-rearrangement and consecutive hydroboration oxidation. These reactions do not require the use of the strong reducing agents or strong bases, and proceed under relatively mild conditions.

A portion of the work described in this chapter was published in Tetrahedron Letters.²⁷

3.11 Experimental

**General:** All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. Dichloromethane was purified using a GlassContour
solvent purification system. Hünig's base was distilled under nitrogen from CaH₂. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ¹H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Tables 3.1–3.5 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 3.1–3.5.

**Handling of Dialkylboron reagents:** Dibutylboron triflate (1.0 M solution in dichloromethane) and 9-BBN triflate (0.5 M solution in hexanes) were purchased from Aldrich Chemical Co. and used as obtained. Due to the air and moisture sensitivity of these reagents, they must be stored and transferred under a rigorously maintained nitrogen atmosphere.

**Synthesis of N-Boc- and N-Acyl-N-Benzyl Glycine Methyl Ester Substrates**

**Methyl 2-(benzylamino)acetate.** A flame dried flask was cooled under a stream of nitrogen and charged with benzylamine (2.36 mL, 21.6 mmol) in THF (10 mL, 1 M). This solution was cooled to 0 ºC before methyl bromoacetate (0.93 mL, 9.8 mmol) was added dropwise. The mixture was allowed to warm to rt over 2.5 h, at which point the starting material had been completely consumed as judged by TLC analysis. The mixture was concentrated in vacuo and the resulting residue was dissolved in Et₂O and filtered. The filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography to afford 1.12 g (63%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.¹⁸ ¹H NMR (500 MHz, CDCl₃) δ 7.30 (d, J = 4.3 Hz, 4 H), 7.29–7.24 (m, 1 H), 3.81 (s, 2 H), 3.73 (s, 3 H), 3.43 (s, 2 H), 1.93 (s, br, 1 H).
Methyl 2-[benzyl(tert-butoxycarbonyl)amino]acetate (3-6). A flame dried flask was cooled under a stream of nitrogen and charged with methyl 2-(benzylamino)acetate (400 mg, 2.23 mmol), dichloromethane (11 mL, 0.2 M), Boc₂O (536 mg, 2.46 mmol), and triethylamine (0.94, 6.70 mmol). The resulting solution was stirred at rt overnight and then concentrated in vacuo. The crude product was purified by flash chromatography to afford 618 mg (99%) of the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.21 (m, 5 H), 4.53 (d, J = 7.8, 2 H), 3.93 (s, 1 H), 3.79 (s, 1 H), 3.70 (d, J = 2.5 Hz, 3 H), 1.47 (d, J = 5.7, 9 H); ¹³C NMR (176 MHz, CDCl₃) δ 170.4, 155.8, 155.6, 137.5, 137.3, 128.6, 128.1, 127.5, 127.4, 80.7, 80.5, 52.0, 51.9, 51.5, 51.0, 47.9, 47.5, 28.3, 28.2 (three carbon signals are missing due to incidental equivalence); IR (film) 1749, 1690 cm⁻¹. MS (ESI+) 302.1366 (302.1363 calcd for C₁₅H₂₁NO₄, M + Na⁺).

Methyl 2-(N-benzylpivalamido)acetate (3-9). A flame dried flask was cooled under a stream of nitrogen and charged with methyl 2-(benzylamino)acetate (400 mg, 2.23 mmol), pyridine (5.6 mL, 0.4 M), and pivaloyl chloride (0.5 mL, 3.78 mmol). The resulting solution was stirred at rt for 1 h and then concentrated in vacuo. The resulting material was dissolved in Et₂O, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography to afford 495 mg (84%) of the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.26 (m, 3 H), 7.21 (d, J = 7.2 Hz, 2 H), 4.83 (s, 2 H), 3.91 (s, 2 H), 3.71 (s, 3 H), 1.35 (s, 9 H); ¹³C NMR (176 MHz, CDCl₃) δ 170.4, 155.8, 155.6, 137.5, 137.3, 128.6, 128.1, 127.5, 127.4, 80.7, 80.5, 52.0, 48.4, 38.9, 28.4, 27.1 (two carbon signals are missing due to incidental equivalence); IR (film) 1748, 1634 cm⁻¹. MS (ESI+) 264.1596 (264.1594 calcd for C₁₅H₂₁NO₃, M + H⁺).

Methyl 2-(N-benzylacetamido)acetate (3-11). A flame dried flask was cooled under a stream of nitrogen and charged with methyl 2-(benzylamino)acetate (370 mg, 2.06
mmol), DCM (4.1 mL, 0.5 M), acetyl chloride (0.22 mL, 3.09 mmol), and triethylamine (0.43 mL, 3.09 mmol). The resulting solution was stirred at rt for 14 h then was poured into water. The layers were separated, and the organic layer was extracted twice with DCM. The combined organic layers were washed with water then brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography to afford 236 mg (52%) of the title compound as a colorless oil. The compound was isolated as a mixture of rotamers with spectroscopic properties identical to those previously reported.  

\[ ^{1}H\text{ NMR}\ (700\text{ MHz, CDCl}_{3})\ \delta\ 7.36\ (t, J = 7.6\text{ Hz}, 1.4\text{ H}), 7.34–7.23\ (m, 1.6\text{ H}), 7.24–7.20\ (m, 0.6\text{ H}), 7.21–7.16\ (m, 1.4\text{ H}), 4.63\ (s, 0.6\text{ H}), 4.61\ (s, 1.4\text{ H}), 4.05\ (s, 1.4\text{ H}), 3.91\ (s, 0.6\text{ H}), 3.70\ (s, 3\text{ H}), 2.21\ (s, 2.15\text{ H}), 2.11\ (s, 0.85\text{ H}); ^{13}C\text{ NMR}\ (126\text{ MHz, CDCl}_{3})\ \delta\ 171.4, 171.0, 169.7, 169.5, 136.6, 136.0, 128.9, 128.6, 128.4, 127.8, 127.6, 126.6, 52.9, 52.3, 52.0, 49.4, 49.0, 46.8, 21.4, 21.2. \]

**Methyl N-allylglycinate.** A flame dried flask was cooled under a stream of nitrogen and charged with allylamine (2.16 mL, 18.8 mmol) in THF (13 mL, 1 M). This solution was cooled to 0 °C before methyl bromoacetate (1.24 mL, 13.0 mmol) was added dropwise. The mixture was allowed to warm to rt over 2.5 h, at which point the starting material had been completely consumed as judged by TLC analysis. The mixture was concentrated in vacuo and the resulting residue was dissolved in Et\(_2\)O and filtered. The filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography to afford 1.28 g (75%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.  

\[ ^{1}H\text{ NMR}\ (400\text{ MHz, CDCl}_{3})\ \delta\ 5.89–5.79\ (m, 1\text{ H}), 5.20–5.08\ (m, 2\text{ H}), 3.71\ (s, 3\text{ H}), 3.39\ (s, 2\text{ H}), 3.24\ (dd, J = 6.1, 1.2\text{ Hz}, 2\text{ H}), 1.64\ (s, br, 1\text{ H}). \]

**Methyl-N-allyl-N-(tert-butoxycarbonyl)glycinate (3-13).** A flame dried flask was cooled under a stream of nitrogen and charged with methyl allylglycinate (98.3 mg, 0.76
mmol), dichloromethane (4 mL, 0.2 M), Boc₂O (183 mg, 0.84 mmol), and triethylamine (0.32, 2.28 mmol). The resulting solution was stirred at rt overnight and then concentrated in vacuo. The crude product was purified by flash chromatography to afford 170 mg (98%) of the title compound as a colorless oil. The product was isolated as a mixture of rotamers and displayed spectroscopic properties identical to those previously reported.³¹ ¹H NMR (400 MHz, CDCl₃) δ 5.84–5.73 (m, 1 H), 5.18–5.10 (m, 2 H), 3.96–3.84 (m, 4 H), 3.73 (s, 3 H), 1.47–1.43 (m, 9 H); ¹³C NMR (176 MHz, CDCl₃) δ 170.6, 133.7, 133.6, 117.6, 116.8, 80.4, 51.9, 51.8, 50.7, 50.2, 47.9, 47.5, 28.3, 28.2 (four carbon signals are missing due to incidental equivalence).

**Synthesis of 1,2,4-Oxazaborole Derivatives**

**General Procedure 1:** An oven-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dialkylboron triflate in methylene chloride (3.2 equiv). The solution was cooled to 0 ℃ and iPr₂NEt (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in dichloromethane was then added, and the resulting solution was warmed to rt. After stirring for 15 min, the mixture was cooled to 0 ℃, opened to air, diluted with diethyl ether, and quenched by the addition of water. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted twice with Et₂O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 5–10% ethyl acetate in hexanes as the eluent.
Methyl 2-[benzyl(tert-butoxycarbonyl)amino]-2-(dibutylboryl)acetate (3-7). General procedure 1 was employed for the transformation of 3-6 (84 mg, 0.3 mmol) using 1 M dibutylboron triflate solution in dichloromethane (0.96 mL, 0.96 mmol) and iPr₂NEt (0.21 mL, 1.2 mmol). This procedure afforded 48 mg (40%) of the title compound as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.37–7.25 (m, 3 H), 7.16 (d, \(J = 6.8\) Hz, 2 H), 4.80 (d, \(J = 15.2\) Hz, 1 H), 4.09 (d, \(J = 15.2\) Hz, 1 H), 3.63 (s, 3 H), 3.33 (s, 1 H), 1.54 (s, 9 H), 1.34–1.08 (m, 6 H), 1.00–0.91 (m, 2 H), 0.85 (t, \(J = 7.1\) Hz, 3 H), 0.80 (t, \(J = 7.3\) Hz, 3 H), 0.42–0.25 (m, 2 H), 0.25–0.18 (m, 2 H); \(^1\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 175.6, 162.1, 135.3, 128.7, 127.9, 127.8, 87.9, 57.4, 50.7, 49.0, 29.7, 28.3, 28.2, 28.0, 27.7, 26.6, 26.5, 14.3, 14.2; IR (film) 1723 cm\(^{-1}\). MS (ESI+) 426.2795 (426.2786 calcd for C\textsubscript{23}H\textsubscript{38}BNO\textsubscript{4}, M + Na\textsuperscript{+}).

Methyl 2-(N-benzylpivalamido)-2-(dibutylboryl)acetate (3-10). General procedure 1 was employed for the transformation of 3-9 (103 mg, 0.39 mmol) using 1 M dibutylboron triflate solution in dichloromethane (1.22 mL, 1.25 mmol) and iPr\textsubscript{2}NEt (0.26 mL, 1.56 mmol). This procedure afforded 133 mg (90%) of the title compound as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.40–7.27 (m, 3 H), 7.15 (d, \(J = 6.7\) Hz, 2 H), 5.20 (d, \(J = 15.5\) Hz, 1 H), 4.42 (d, \(J = 15.5\) Hz, 1 H), 3.59 (s, 3 H), 3.31 (s, 1 H), 1.41 (s, 9 H), 1.35–1.07 (m, 6 H), 1.02–0.94 (m, 2 H), 0.83 (t, \(J = 7.2\) Hz, 6 H), 0.35–0.07 (m, 4 H); \(^1\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 183.0, 175.4, 133.9, 129.0, 128.3, 127.5, 51.2, 50.7, 36.2, 28.0, 27.8, 27.7, 26.6, 26.5, 14.3; IR (film) 1717 cm\(^{-1}\). MS (ESI+) 410.2834 (410.2837 calcd for C\textsubscript{23}H\textsubscript{38}BNO\textsubscript{3}, M + Na\textsuperscript{+}).

Methyl 2-(N-benzylacetamido)-2-(dibutylboryl)acetate (3-12). General procedure 1 was employed for the transformation of 3-11 (44 mg, 0.20 mmol) using 1 M dibutylboron
triflate solution in dichloromethane (0.64 mL, 0.64 mmol) and \textsuperscript{1}Pr\textsubscript{2}NEt (0.14 mL, 0.80 mmol). This procedure afforded 23 mg (33%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.42–7.30 (m, 3 H), 7.16 (d, \(J = 6.9\) Hz, 2 H), 4.78 (d, \(J = 15.7\) Hz, 1 H), 4.46 (d, \(J = 15.7\) Hz, 1 H), 3.64 (s, 3 H), 3.46 (s, 1 H), 2.28 (s, 3 H), 1.32–1.09 (m, 6 H), 1.00–0.90 (m, 2 H), 0.83 (dt, \(J = 13.3, 7.2\) Hz, 6 H), 0.38–0.30 (m, 2 H), 0.25–0.17 (m, 2 H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 175.6, 175.1, 133.7, 129.1, 128.5, 127.5, 51.3, 50.9, 27.9, 27.7, 26.8, 26.5, 16.0, 14.3; IR (film) 1719, 1582 cm\(^{-1}\). MS (ESI+) 368.2359 (368.2367 calcd for C\textsubscript{20}H\textsubscript{32}BNO\textsubscript{3}, M + Na\textsuperscript{+}).

4-Allyl-5-(tert-butoxy)-2,2-dibutyl-3-(methoxycarbonyl)-2,3-dihydro-1,4,2-oxazaborol-4-ium-2-uide (3-14). An oven-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dialkylboron triflate in methylene chloride (1.39 mL, 1.39 mmol). The solution was cooled to 0 °C and \textsuperscript{1}Pr\textsubscript{2}NEt (0.30 mL, 1.74 mmol) was added dropwise. A 1 M solution of 3-13 (100 mg, 0.44 mmol) in dichloromethane was then added, and the resulting solution was warmed to rt. After stirring for 15 min, the mixture was cooled to 0 °C, opened to air, diluted with diethyl ether, and quenched by the addition of water. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted twice with Et\textsubscript{2}O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel using 5–10% ethyl acetate in hexanes as the eluent. This procedure afforded 134.2 mg (87%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 5.76–5.65 (m, 1 H), 5.21–5.15 (m, 2 H), 4.10 (dd, \(J = 15.7, 5.0\) Hz, 1 H), 3.64–3.52 (m, 4 H), 3.47 (s, 1 H), 1.53 (s, 9 H), 1.35–1.03 (m, 8 H), 0.84 (dt, \(J = 12.4, 7.2\) Hz, 6 H), 0.43–0.35 (m, 2 H), 0.23–0.16 (m, 2H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) \(\delta\) 175.6, 162.0, 131.3, 118.3, 87.6, 76.6, 57.8, 50.7, 47.9, 28.2, 28.0, 27.6, 26.6, 26.5, 14.3, 14.2 (one carbon signal is missing due to incidental overlap); IR (film) 1730, 1594 cm\(^{-1}\). MS (ESI+) 376.2630 (376.2630 calcd for C\textsubscript{19}H\textsubscript{36}BNO\textsubscript{4}, M + Na\textsuperscript{+}).
Methyl 2-[benzyl(tert-butoxycarbonyl)amino]-2-(9-borabicyclo[3.3.1]nonan-9-yl)acetate (3-15). General procedure 1 was employed for the transformation of 3-9 (103 mg, 0.39 mmol) using 0.5 M 9-BBN triflate solution in hexanes (2.50 mL, 1.25 mmol) and iPr₂NEt (0.27 mL, 1.56 mmol) except using a modified workup protocol. The reaction was quenched with 0.5 mL pH 7 buffer solution, 1.0 mL methanol, and 0.2 mL 30% H₂O₂. This mixture was allowed to stir for 1 h before 1 mL sodium thiosulfate was added. The biphasic mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted three times with diethyl ether. The crude product was purified using flash column chromatography. This procedure afforded 135 mg (90%) of the title compound as a white solid, mp 171–173 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.39–7.38 (m, 3 H), 7.16 (d, J = 7.6 Hz, 2 H), 5.25 (d, J = 15.9 Hz, 1 H), 4.27 (d, J = 16.0 Hz, 1 H), 3.64 (s, 3 H), 3.50 (s, 1 H), 1.95–1.31 (m, 21 H), 0.52 (s, 2 H); ¹³C NMR (126 MHz, CDCl₃) δ 183.0, 175.2, 134.2, 129.1, 128.2, 126.9, 51.6, 50.8, 36.2, 32.1, 31.3, 30.9, 30.8, 27.7, 24.6, 24.3; IR (film) 1718, 1547 cm⁻¹. MS (ESI+) 384.2712 (384.2705 calcd for C₂₃H₃₄BNO₃, M + H⁺).

Synthesis and Characterization of N-Aryl-N-(Arylmethyl) Glycine Methyl Esters

General Procedure 2: A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of aryl amine (1.0 equiv), aldehyde (1.0 equiv), triethylamine (1.0 equiv) and methanol (0.5 M). This mixture was allowed to stir at rt until the starting material had been completely consumed as judged by TLC analysis. The mixture was then cooled to 0 °C and NaBH₄ (1.4 equiv) was added slowly. The mixture was allowed
to warm to rt and stirred until the intermediate imine had been completely consumed as judged by TLC analysis. The reaction mixture was then diluted with water and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted twice with hexanes. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 5–20% ethyl acetate in hexanes as the eluent.

**General Procedure 3:** A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of aryl amine (1.0 equiv), methyl bromoacetate (1.5–3.0 equiv), and iPr$_2$NEt (3.0 equiv) in acetonitrile (0.1 M). The mixture was heated to 80 °C for ca 16 h then was cooled rt, concentrated in vacuo, then partitioned between saturated NaHCO$_3$ and CH$_2$Cl$_2$. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 3–10% ethyl acetate in hexanes as the eluent.

**N-Benzylaniline.** General procedure 2 was used for the condensation and subsequent reduction of aniline (0.86 mL, 9.42 mmol) and benzaldehyde (0.96 mL, 9.42 mmol). This procedure afforded 1.55 g (90%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.$^{32}$ $^1$H NMR (700 MHz, CDCl$_3$) δ 7.37 (d, $J = 7.5$ Hz, 2 H), 7.34 (t, $J = 7.3$ Hz, 2 H), 7.27 (t, $J = 7.4$ Hz, 1 H), 7.17 (t, $J = 7.6$ Hz, 2 H), 6.72 (t, $J = 7.3$ Hz, 1 H), 6.65 (d, $J = 7.8$ Hz, 2 H), 4.33 (s, 2 H), 4.12 (s, br, 1 H).

**N-Benzyl-4-bromoaniline.** General procedure 2 was used for the condensation and subsequent reduction of 4-bromoaniline (0.57 mL, 5 mmol) and benzaldehyde (0.51 mL, 5 mmol). This procedure afforded 990 mg (76%) of the title compound as a colorless oil
with spectroscopic properties identical to those previously reported.\textsuperscript{33} \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 (d, \(J = 4.5\) Hz, 4 H), 7.30–7.22 (m, 3 H), 6.52–6.49 (m, 2 H), 4.30 (s, 2 H), 4.08 (s, br, 1 H).

\(\text{N-Benzyl-4-methoxyaniline.}\) General procedure 2 was used for the condensation and subsequent reduction of 4-anisidine (616 mg, 5 mmol) and benzaldehyde (0.51 mL, 5 mmol). This procedure afforded 857 mg (80%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.\textsuperscript{34} \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.38–7.26 (m, 5 H), 6.80–6.78 (m, 2 H), 6.63–6.59 (m, 2 H), 4.29 (s, 2 H), 3.79 (s, br, 1 H), 3.74 (s, 3 H).

\(\text{N-Benzyl-4-(trifluoromethyl)aniline.}\) General procedure 2 was used for the condensation and subsequent reduction of 4-(trifluoromethyl)aniline (0.78 mL, 6.20 mmol) and benzaldehyde (0.64 mL, 6.20 mmol). This procedure afforded 0.734 g (47%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.\textsuperscript{35} \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.40–7.26 (m, 7 H), 6.63 (d, \(J = 8.6\) Hz, 2 H), 4.38 (s, 3 H).

\(\text{N-(4-Bromobenzyl)aniline.}\) General procedure 2 was used for the condensation and subsequent reduction of aniline (0.46 mL, 5 mmol) and 4-bromobenzaldehyde (0.93 g, 5 mmol). This procedure afforded 1.14 g (87%) of the title compound as a pale yellow oil with spectroscopic properties identical to those previously reported.\textsuperscript{Error! Bookmark not defined.} \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.47–7.44 (m, 2 H), 7.26–7.23 (m, 2 H), 7.19–7.14 (m, 2 H).
H), 6.72 (t, J = 1.2, 7.4 Hz, 1 H), 6.62–6.59 (m, 2 H), 4.30 (d, J = 4.3 Hz, 2 H), 4.06 (s, br, 1 H).

\[ \text{H} \]

**N-(2-Bromobenzyl)aniline.** General procedure 2 was used for the condensation and subsequent reduction of aniline (0.46 mL, 5.0 mmol) and 2-bromobenzaldehyde (0.58 mL, 5.0 mmol). This procedure afforded 753 mg (57%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.\[^{36}\] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55 (d, \(J = 7.9\) Hz, 1 H), 7.40 (d, \(J = 7.7\) Hz, 1 H), 7.27–7.24 (m, 1 H), 7.19–7.11 (m, 3 H), 6.71 (t, \(J = 7.3\) Hz, 1 H), 6.62 (d, \(J = 7.6\) Hz, 2 H), 4.40 (s, 2 H), 4.18 (s, br, 1 H).

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

**N-(Furan-2-ylmethyl)aniline.** General procedure 2 was used for the condensation and subsequent reduction of aniline (0.95 mL, 10.4 mmol) and furfural (0.86 mL, 10.4 mmol). This procedure afforded 1.46 g (81%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.\[^{37}\] \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.36 (s, 1 H), 7.18 (dd, \(J = 6.3, 7.5\) Hz, 2 H), 6.74 (t, \(J = 7.6\) Hz, 1 H), 6.68 (d, \(J = 8.6\), 2 H), 6.31 (dd, \(J = 2.0, 3.2\) Hz, 1 H), 6.23 (dd, \(J = 0.7, 3.1\) Hz, 1 H), 4.32 (s, 2 H), 4.04 (s, br, 1 H).

\[ \text{O} \]

**N-(Thiophen-2-ylmethyl)aniline.** General procedure 2 was used for the condensation and subsequent reduction of aniline (0.46 mL, 5.0 mmol) and thiophene-2-carboxaldehyde (0.47 mL, 5.0 mmol). This procedure afforded 190 mg (20%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.\[^{38}\] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.22–7.17 (m, 3 H), 7.02–7.00 (m, 1 H), 6.97
(dd, J = 5.1 Hz, 1 H), 6.74 (tt, J = 7.4, 1.1 Hz, 1 H), 6.69–6.67 (m, 2 H), 4.51 (d, J = 1.0 Hz, 2 H), 4.05 (s, br, 1 H).

\[ \text{N-((1-Tosyl-1H-pyrrol-2-yl)methyl)aniline.} \] A slightly modified general procedure 2 was used for the condensation (16 h, 60 °C) and subsequent reduction of aniline (0.11 mL, 1.22 mmol) and 1-tosyl-1H-pyrrole-2-carbaldehyde (304 mg, 1.22 mmol). This procedure afforded 68.4 mg (17%) of the title compound as a white solid (m.p. 78–82 °C) with spectroscopic properties identical to those previously reported.\(^\text{39}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.64 (d, \(J = 8.4\) Hz, 2 H), 7.30–7.24 (m, 3 H), 7.10 (dd, \(J = 8.4, 7.6\) Hz, 2 H), 6.68 (t, \(J = 7.2\) Hz, 1 H), 6.45 (d, \(J = 7.9\) Hz, 2 H), 7.20–7.18 (m, 2 H), 4.38 (d, \(J = 5.0\) Hz, 2 H), 4.05 (s, br, 1 H), 2.40 (s, 3 H).

\[ \text{Methyl 2-[benzyl(phenyl)amino]acetate (3-19).} \] General procedure 3 was used for the alkylation of \(N\)-benzylaniline (712 mg, 3.9 mmol) with bromoacetic acid (0.74 mL, 7.8 mmol) and \(\text{^1}\)Pr\(_2\)NEt (2.0 mL, 11.7 mmol) in 39 mL of CH\(_3\)CN. This procedure afforded 539 mg (54%) of the title compound as a pale yellow solid (m.p. 52–55 °C) with spectroscopic properties identical to those previously reported.\(^\text{40}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.34–7.24 (m, 5 H), 7.22–7.19 (m, 2 H), 6.77 (t, \(J = 7.4\) Hz, 1 H), 6.70 (d, \(J = 7.8\) Hz, 2 H), 4.65 (s, 2 H), 4.10 (s, 2 H), 3.74 (s, 3 H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 171.6, 148.4, 138.2, 129.3, 128.7, 127.1, 126.8, 117.9, 112.7, 55.7, 52.3, 52.0.

\[ \text{Methyl 2-[benzyl(4-bromophenyl)amino]acetate (3-21).} \] General procedure 3 was used for the alkylation of \(N\)-benzyl-4-bromoaniline (350 mg, 1.33 mmol) with
bromoacetic acid (0.38 mL, 3.99 mmol) and \(^{3}\text{Pr}_2\text{NEt} (0.70 \text{ mL}, 3.99 \text{ mmol}) \) in 13 mL of CH\(_3\)CN. This procedure afforded 289 mg (65\%) of the title compound as a pale yellow oil. \(^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3 \ \delta 7.22 \ (t, \ J = 7.0 \text{ Hz}, \ 2 \text{ H}), 7.28–7.24 \ (m, \ 5 \text{ H}), 6.56–6.53 \ (m, \ 2 \text{ H}), 4.61 \ (s, \ 2 \text{ H}), 4.07 \ (s, \ 2 \text{ H}), 3.74 \ (s, \ 3 \text{ H}); \ ^{13}\text{C NMR} \ (176 \text{ MHz, CDCl}_3 \ \delta 171.2, 147.5, 137.7, 131.9, 128.8, 127.3, 126.7, 114.2, 109.7, 55.7, 52.4, 52.1; \text{ IR (film)} 1745 \text{ cm}^{-1}. \text{ MS (ESI+) } 334.0436 \ (334.0437 \text{ calcd for C}_{16}\text{H}_{16}\text{BrNO}_2, \text{ M + H}^+).\)

Methyl 2-[benzyl(4-methoxyphenyl)amino]acetate (3-23). General procedure 3 was used for the alkylation of N-benzy-4-methoxylaniline (540 mg, 2.53 mmol) with bromoacetic acid (0.72 mL, 7.59 mmol) and \(^{3}\text{Pr}_2\text{NEt} (1.32 \text{ mL}, 7.59 \text{ mmol}) \) in 25 mL of CH\(_3\)CN. This procedure afforded 487 mg (67\%) of the title compound as a yellow oil. \(^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3 \ \delta 7.34–7.25 \ (m, \ 5 \text{ H}), 6.80–6.78 \ (m, \ 2 \text{ H}), 6.69–6.66 \ (m, \ 2 \text{ H}), 4.59 \ (s, \ 2 \text{ H}), 4.04 \ (s, \ 2 \text{ H}), 3.74 \ (s, \ 3 \text{ H}), 3.72 \ (s, \ 3 \text{ H}); \ ^{13}\text{C NMR} \ (176 \text{ MHz, CDCl}_3 \ \delta 171.4, 152.2, 143.1, 138.7, 128.6, 127.1, 127.0, 114.8, 114.4, 56.2, 55.7, 52.8, 51.9; \text{ IR (film)} 1741 \text{ cm}^{-1}. \text{ MS (ESI+) } 286.1439 \ (286.1438 \text{ calcd for C}_{17}\text{H}_{19}\text{NO}_3, \text{ M + H}^+).\)

Methyl 2-[benzyl[4-(trifluoromethyl)phenyl]amino]acetate (3-25). General procedure 3 was used for the alkylation of N-benzy-4-(trifluoromethyl)aniline (130 mg, 0.517 mmol) with bromoacetic acid (0.1 mL, 1.03 mmol) and \(^{3}\text{Pr}_2\text{NEt} (0.27 \text{ mL}, 1.55 \text{ mmol}) \) in 5 mL of CH\(_3\)CN. This procedure afforded 37 mg (22\%) of the title compound as a yellow oil. \(^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3 \ \delta 7.43 \ (d, \ J = 8.6 \text{ Hz}, \ 2 \text{ H}), 7.34 \ (t, \ J = 7.1 \text{ Hz}, \ 2 \text{ H}), 7.29–7.24 \ (m, \ 3 \text{ H}), 6.69 \ (d, \ J = 8.6 \text{ Hz}, \ 2 \text{ H}), 4.69 \ (s, \ 2 \text{ H}), 4.14 \ (s, \ 2 \text{ H}), 3.76 \ (s, \ 3 \text{ H}); \ ^{13}\text{C NMR} \ (126 \text{ MHz, CDCl}_3 \ \delta 170.8, 150.8, 137.2, 128.9, 127.4, 126.64, 126.61,
Methyl 2-[(4-bromobenzyl)(phenyl)amino]acetate (3-27). General procedure 3 was used for the alkylation of N-(4-bromobenzyl)aniline (459 mg, 1.75 mmol) with bromoacetic acid (0.50 mL, 5.25 mmol) and iPr₂NEt (0.91 mL, 5.25 mmol) in 18 mL of CH₃CN. This procedure afforded 368 mg (63%) of the title compound as a yellow solid (m.p. 97–100 °C). ¹H NMR (500 MHz, CDCl₃) δ 7.46–7.43 (m, 2 H), 7.22–7.17 (m, 4 H), 6.80 (t, J = 7.3 Hz, 1 H), 6.65 (d, J = 8.1 Hz, 2 H), 4.59 (s, 2 H), 4.08 (s, 2 H), 3.74 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ 171.5, 148.2, 137.5, 131.8, 129.3, 128.5, 120.8, 118.0, 112.6, 55.3, 52.4, 52.0; IR (film) 1746 cm⁻¹. MS (ESI+) 334.0437 (334.0437 calcd for C₁₆H₁₆BrNO₂, M + H⁺).

Methyl 2-[(2-bromobenzyl)(phenyl)amino]acetate (3-29). General procedure 3 was used for the alkylation of N-(2-bromobenzyl)aniline (700 mg, 2.67 mmol) with bromoacetic acid (0.76 mL, 8.01 mmol) and iPr₂NEt (1.40 mL, 8.01 mmol) in 27 mL of CH₃CN. This procedure afforded 256 mg (40%) of the title compound as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.59–7.58 (m, 1 H), 7.29–7.18 (m, 4 H), 7.15–7.12 (m, 1 H), 6.77 (t, J = 7.4 Hz, 1 H), 6.59 (d, J = 8.1 Hz, 2 H), 4.65 (s, 2 H), 4.14 (s, 2 H), 3.78 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ 171.5, 147.9, 136.8, 132.9, 129.3, 128.6, 128.1, 127.6, 122.7, 117.8, 112.3, 56.7, 52.8, 52.1; IR (film) 1748 cm⁻¹. MS (ESI+) 334.0435 (334.0437 calcd for C₁₆H₁₆BrNO₂, M + H⁺).
Methyl 2-[(furan-2-ylmethyl)(phenyl)amino]acetate (3-31). General procedure 3 was used for the alkylation of \( N \)-(furan-2-ylmethyl)aniline (455 mg, 2.63 mmol) with bromoacetic acid (0.37 mL, 3.94 mmol) and \( \text{Pr}_2\text{NEt} \) (1.37 mL, 7.88 mmol) in 26 mL of CH\(_3\)CN. This procedure afforded 534 mg (83%) of the title compound as a pale yellow oil. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \( \delta \) 7.37 (s, 1 H), 7.22 (t, \( J = 7.9 \) Hz, 2 H), 6.79–6.76 (m, 3 H), 6.31 (d, \( J = 3.0 \) Hz, 1 H), 6.24 (d, \( J = 3.0 \) Hz, 1 H), 4.55 (d, 2 H), 4.07 (s, 2 H), 3.73 (s, 3 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 171.6, 151.8, 148.1, 142.2, 129.2, 118.0, 112.9, 110.3, 107.8, 52.0, 51.8, 48.5; IR (film) 1735 cm\(^{-1}\). MS (ESI+) 246.1129 (246.1125 calcd for C\(_{14}\)H\(_{15}\)NO\(_3\), M + H\(^+\)).

Methyl N-phenyl-N-(thiophen-2-ylmethyl)glycinate (3-33). General procedure 3 was used for the alkylation of \( N \)-(thiophene-2-ylmethyl)aniline (155.5 mg, 0.821 mmol) with bromoacetic acid (0.12 mL, 1.23 mmol) and \( \text{Pr}_2\text{NEt} \) (0.43 mL, 2.46 mmol) in 8.2 mL of CH\(_3\)CN. This procedure afforded 160.6 mg (75%) of the title compound as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.28–7.19 (m, 3 H), 7.00–6.93 (m, 2 H), 6.83–6.73 (m, 3 H), 4.78 (s, 2 H), 4.09 (s, 2 H), 3.74 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 171.6, 151.8, 148.1, 142.2, 129.2, 118.0, 112.9, 110.3, 107.8, 52.0, 51.8, 48.5; IR (film) 1735 cm\(^{-1}\). MS (ESI+) 262.0893 (262.0896 calcd for C\(_{14}\)H\(_{15}\)NO\(_2\)S, M + H\(^+\)).

Methyl N-phenyl-N-((1-tosyl-1H-pyrrol-2-yl)methyl)glycinate (3-35). General procedure 3 was used for the alkylation of \( N \)-(thiophene-2-ylmethyl)aniline (150 mg, 0.46 mmol) with bromoacetic acid (0.07 mL, 0.69 mmol) and \( \text{Pr}_2\text{NEt} \) (0.24 mL, 1.38 mmol) in 4.6 mL of CH\(_3\)CN. This procedure afforded 119.2 mg (65%) of the title compound as a
pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J = 8.2$ Hz, 2 H), 7.38 (dd, $J = 3.3$, 1.8 Hz, 1 H), 7.29 (d, $J = 8.1$ Hz, 2 H), 7.13–7.05 (m, 2 H), 6.72 (t, $J = 7.1$ Hz, 1 H), 6.37 (d, $J = 8.1$ Hz, 2 H), 6.21 (t, $J = 3.3$ Hz, 1 H), 6.14–6.09 (m, 1 H), 4.67 (s, 2 H), 3.81 (s, 2 H), 3.71 (s, 3 H), 2.44 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.4, 147.6, 145.0, 136.1, 130.8, 130.0, 129.1, 126.9, 123.4, 117.9, 114.2, 112.5, 111.5, 52.0, 51.6, 49.1, 21.6; IR (film) 1749, 1505, 1365 cm$^{-1}$. MS (ESI+) 421.1197 (421.1192 calcd for C$_{21}$H$_{22}$N$_2$O$_4$S, M + Na$^+$).

![Structure](image)

2-[Phenyl(1-phenylethyl)amino]acetic acid. A flame dried flask was cooled under a stream of nitrogen and charged with N-phenylglycine (200 mg, 1.32 mmol) and THF (2.7 mL), and the resulting solution was cooled to -78 °C. To this solution was added n-BuLi (1.16 mL, 2.5 M soln in hexanes). After stirring 15 min, 1-(bromoethyl)benzene (0.2 mL, 1.46 mmol) was added dropwise, and the mixture was allowed to warm to rt over 2 h. The reaction was then quenched with saturated sodium bicarbonate solution, and the resulting mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer washed was twice with ethyl acetate. The aqueous layer was then acidified with H$_2$SO$_4$ and then extracted three times with diethyl ether. The combined ether layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 167 mg (49%) of the title compound as a white solid, mp 108–114 °C. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 10.68 (s, br, 1 H), 7.37–7.30 (m, 4 H), 7.25–7.22 (m, 3 H), 6.79 (t, $J = 7.3$ Hz, 1 H), 6.75 (d, $J = 8.3$ Hz, 2 H), 5.18 (q, $J = 6.9$ Hz, 1 H), 3.95 (s, 2 H), 1.62 (d, $J = 6.9$ Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 176.9, 148.1, 141.9, 129.4, 128.7, 127.3, 127.0, 118.6, 113.9, 57.0, 48.5, 17.9; IR (film) 1720 cm$^{-1}$. MS (ESI$^+$) 254.1187 (254.1187 calcd for C$_{16}$H$_{17}$NO$_2$, M - H$^+$).
Methyl 2-[phenyl(1-phenylethyl)amino]acetate (3-37). A flame dried flask was cooled under a stream of nitrogen and charged with methanol (16 µL, 0.407 mmol) and dichloromethane (2.0 mL, 0.2 M), and the resulting solution was cooled to 0 °C. DMAP (25 mg, 0.204 mmol), EDC (78 mg, 0.407 mmol), and 2-(phenyl(1-phenylethyl)amino)acetic acid (104 mg, 0.407 mmol) were added, and the mixture was allowed to warm to rt overnight. The dichloromethane was removed in vacuo, and the resulting crude oil was diluted with water and ethyl acetate. The mixture was transferred to a separatory funnel, the layers were separated, and the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 84 mg (76%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.35–7.28 (m, 4 H), 7.27–7.17 (m, 3 H), 6.77–6.68 (m, 3 H), 5.17 (q, $J = 7.0$ Hz, 1 H), 3.95 (s, 2 H), 3.69 (s, 3 H), 1.60 (d, $J = 7.0$ Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 172.2, 148.5, 142.4, 129.3, 128.6, 127.1, 127.0, 117.7, 113.2, 56.5, 52.0, 48.5, 18.1; IR (film) 1750, 1597 cm$^{-1}$. MS (ESI+) 270.1496 (270.1496 calcd for C$_{17}$H$_{19}$NO$_2$, M + H$^+$).

Methyl 2-[phenyl(1-phenylethyl)amino]acetate (3-39): A flame-dried flask was cooled under a stream of nitrogen and then charged with $^1$Pr$_2$NH (0.11 mL, 0.76 mmol) in THF (0.5 mL). The reaction mixture was cooled to −78 °C then a 1.6 M solution of n-BuLi in hexanes (0.4 mL, 0.65 mmol) was added and the resulting solution was stirred for 5 min. To this solution was added compound 3-19 (150 mg, 0.59 mmol) in THF (0.5 mL). After stirring for 15 min, iodomethane (0.44 mL, 0.71 mmol) was added and the resulting solution was stirred for 15 min at -78 °C and then 1 h at 0 °C. The mixture was warmed to rt, diluted with NH$_4$Cl and EtOAc, and transferred to a separatory funnel. The layers were separated, and the organic layers were washed with brine, dried over
sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 78 mg (49%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31 (d, $J = 4.4$ Hz, 4 H), 7.23–7.19 (m, 1 H), 7.19–7.15 (m, 2 H), 6.74 (t, $J = 7.4$ Hz, 1 H), 6.70 (d, $J = 8.1$ Hz, 2 H), 4.70–7.53 (m, 3 H), 3.70 (s, 3 H), 1.50 (d, $J = 7.4$, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.3, 148.9, 140.1, 129.1, 128.5, 126.6, 126.3, 117.9, 113.7, 56.7, 52.1, 52.0, 16.2; IR (film) 1733 cm$^{-1}$. MS (ESI+) 270.1491 (270.1489 calcd for C$_{17}$H$_{19}$NO$_2$, M$^+$).

**Synthesis of N-Arylphenylalanine Methyl Esters via Aza-[1,2]-Wittig Rearrangement**

**General Procedure 4:** A flame-dried Schlenk tube was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dibutylboron triflate in dichloromethane (3.2 equiv). The solution was cooled to 0 °C and $^i$Pr$_2$NEt (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in methylene chloride was then added, and the resulting solution was warmed to 40 °C. After stirring for 1–7 h the starting material had been completely consumed and the mixture was cooled to 0 °C, opened to air, and quenched by the addition of pH 7 buffer solution (ca. 3 mL/mmol substrate), methanol (ca. 6–8 mL/mmol substrate), and 30% aqueous H$_2$O$_2$ (ca. 1 mL/mmol substrate). This mixture was warmed to rt and stirred for 1 h. The solution was then cooled to 0 °C and Na$_2$S$_2$O$_3$ (ca. 7 mL/mmol substrate) was added. This solution was allowed to stir for 1 min before it was diluted with water and extracted twice with Et$_2$O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 5–10% diethyl ether in hexanes as the eluent.
Methyl 3-phenyl-2-(phenylamino)propanoate (3-20): General procedure 4 was used for the rearrangement of 3-19 (51 g, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and iPr₂NEt (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. This procedure afforded 33 mg (65%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.⁴¹ ¹H NMR (700 MHz, CDCl₃) δ 7.30–7.28 (m, 2 H), 7.25–7.23 (m, 1 H), 7.18–7.16 (m, 4 H), 6.74 (t, J = 7.3 Hz, 1 H), 6.60 (d, J = Hz, 2 H), 4.37 (t, J = 6.3 Hz, 1 H), 4.16 (s, br, 1 H), 3.67 (s, 3 H), 3.16 (dd, J = 13.7, 6.0 Hz, 1 H), 3.10 (dd, J = 13.6, 6.5 Hz, 1 H); ¹³C NMR (176 MHz, CDCl₃) δ 173.6, 146.3, 136.3, 129.4, 129.2, 128.5, 127.0, 118.4, 113.6, 57.7, 52.0, 38.6.

Methyl 2-[(4-bromophenyl)amino]-3-phenylpropanoate (3-22): General procedure 4 was used for the rearrangement of 3-21 (67 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and iPr₂NEt (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. This procedure afforded 39 mg (59%) of the title compound as an orange oil. ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.23 (m, 5 H), 7.13 (d, J = 6.9 Hz, 2 H), 6.47–6.44 (m, 2 H), 4.31 (t, J = 6.3 Hz, 1 H), 4.16 (s, br, 1 H), 3.67 (s, 3 H), 3.14 (dd, J = 13.7 Hz, 1 H), 3.08 (dd, J = 13.7 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ 173.2, 145.4, 136.0, 132.1, 129.2, 128.6, 127.1, 115.1, 110.1, 57.6, 52.1, 38.5; IR (film) 3395,1736 cm⁻¹. MS (ESI+) 334.0432 (334.0437 calcd for C₁₆H₁₆BrNO₂, M + H⁺).
Methyl 2-[(4-methoxyphenyl)amino]-3-phenylpropanoate (3-24): General procedure 4 was used for the rearrangement of 3-23 (50 mg, 0.18 mmol) with dibutylboron triflate (0.56 mL, 0.56 mmol) and Pr₂NEt (0.12 mL, 0.7 mmol) in 0.18 mL of dichloromethane. This procedure afforded 35 mg (70%) of the title compound as an orange oil. ¹H NMR (500 MHz, CDCl₃) δ 7.31–7.23 (m, 3 H), 7.17 (d, J = 7.1 Hz, 2 H), 6.77–6.74 (m, 2 H), 6.59–6.56 (m, 2 H), 4.27 (t, J = 6.4 Hz, 1 H), 3.88 (s, br, 1 H), 3.73 (s, 3 H), 3.64 (s, 3 H), 3.15–3.06 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 173.9, 152.9, 140.4, 136.5, 129.2, 128.5, 126.9, 115.3, 114.9, 59.0, 55.7, 52.0, 38.9; IR (film) 3337, 1684 cm⁻¹. MS (ESI⁺) 286.1438 (286.1438 calcd for C₁₇H₁₉NO₂, M + H⁺).

Methyl 3-phenyl-2-[(4-(trifluoromethyl)phenyl)amino]propanoate (3-26): General procedure 4 was used for the rearrangement of 3-25 (97 mg, 0.3 mmol) with dibutylboron triflate (0.96 mL, 0.96 mmol) and Pr₂NEt (0.21 mL, 1.2 mmol) in 0.3 mL of dichloromethane. This procedure afforded 23 mg (24%) of the title compound as a yellow oil. ¹H NMR (700 MHz, CDCl₃) δ 7.39 (d, J = 8.4 Hz, 2 H), 7.32–7.22 (m, 3 H), 7.15–7.11 (m, 2 H), 6.59 (d, J = 8.4 Hz, 2 H), 4.48 (d, J = 8.4 Hz, 1 H), 4.42–4.39 (m, 1 H), 3.70 (s, 3 H), 3.18 (dd, J = 13.7, 5.9 Hz, 1 H), 3.11 (dd, J = 13.8, 6.2 Hz, 1 H); ¹³C NMR (176 MHz, CDCl₃) δ 172.7, 148.8, 135.8, 129.2, 128.6, 127.2, 126.74, 126.71, 112.6, 57.0, 52.3, 38.3, 29.7; IR (film) 3390, 1739 cm⁻¹. MS (ESI⁺) 324.1206 (324.1206 calcd for C₁₇H₁₆F₃NO₂, M + H⁺).
Methyl 3-(4-bromophenyl)-2-(phenylamino)propanoate (3-28): General procedure 4 was used for the rearrangement of 3-27 (75 mg, 0.22 mmol) with dibutylboron triflate (0.72 mL, 0.72 mmol) and iPr₂NEt (0.16 mL, 0.88 mmol) in 0.25 mL of dichloromethane. This procedure afforded 53 mg (70%) of the title compound as a yellow oil. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.40 (d, \(J = 8.2\) Hz, 2 H), 7.17 (t, \(J = 5.5\) Hz, 2 H), 7.02 (d, \(J = 7.8\) Hz, 2 H), 6.75 (td, \(J = 1.1, 7.4\) Hz, 1 H), 6.60 (d, \(J = 8.5\) Hz, 2 H), 4.37–4.34 (m, 1 H), 4.14 (d, \(J = 8.3\) Hz, 1 H), 3.67 (s, 3 H), 3.11 (dd, \(J = 6.0, 13.7\) Hz, 1 H), 3.04 (dd, \(J = 6.2, 13.8\) Hz, 1 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 173.2, 146.0, 135.3, 131.6, 129.4, 121.0, 118.6, 113.5, 57.4, 52.2, 37.9; IR (film) 3405, 1738 cm\(^{-1}\). MS (ESI+) 334.0440 (334.0437 calcd for C\(_{16}\)H\(_{16}\)BrNO\(_2\), M + H\(^+\)).

Methyl 3-(2-bromophenyl)-2-(phenylamino)propanoate (3-30): General procedure 4 was used for the rearrangement of compound 3-29 (67 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and iPr₂NEt (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. This procedure afforded 31 mg (47%) of the title compound as a white solid (m.p. 100–102 °C). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.55 (d, \(J = 8.0\) Hz, 1 H), 7.22–7.20 (m, 2 H), 7.13 (t, \(J = 7.6\) Hz, 2 H), 7.11–7.08 (m, 1 H), 6.72 (t, \(J = 7.3\) Hz, 1 H), 6.60 (d, \(J = 7.8\) Hz, 2 H), 4.45 (t, \(J = 6.6\) Hz, 1 H), 4.23 (s, br, 1 H), 3.63 (s, 3 H), 3.28 (dd, \(J = 7.5, 13.6\) Hz, 1 H), 3.21 (dd, \(J = 7.8, 13.8\) Hz, 1 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 173.7, 146.4, 136.3, 133.0, 131.4, 129.3, 128.7, 127.5, 124.8, 118.5, 113.6, 56.7,
52.1, 39.4; IR (film) 3385, 1736 cm\(^{-1}\). MS (ESI+) 334.0438 (334.0437 calcd for C\(_{16}H_{16}BrNO_2, M + H^+\)).

**Methyl 3-(furan-2-yl)-2-(phenylamino)propanoate (3-32):** General procedure 4 was used for the rearrangement of compound 3-31 (49 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and \(^i\)Pr\(_2\)NEt (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. This procedure afforded 36 mg (73%) of the title compound as a pale yellow solid (m.p. 66–68 °C). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.33 (d, \(J = 1.6\) Hz, 1 H), 7.17 (t, \(J = 8.0\) Hz, 2 H), 6.74 (t, \(J = 7.3\) Hz, 1 H), 6.60 (d, \(J = 6.9\) Hz, 2 H), 6.28 (dd, \(J = 3.2, 1.9\) Hz, 1 H), 6.10 (d, \(J = 3.2\) Hz, 1 H), 4.38 (dt, \(J = 8.2, 5.9\) Hz, 1 H), 4.24 (d, \(J = 8.4\) Hz, 1 H), 3.70 (s, 3 H), 3.17 (d, \(J = 6.0\) Hz, 2 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 173.3, 150.6, 146.3, 142.1, 129.3, 118.5, 113.6, 110.4, 107.8, 55.9, 52.2, 31.4; IR (film) 3393, 1737 cm\(^{-1}\). MS (ESI+) 246.1134 (246.1125 calcd for C\(_{14}H_{15}NO_3, M + H^+\)).

**Methyl 2-(phenylamino)-3-(thiophen-2-yl)propanoate (3-34):** General procedure 4 was used for the rearrangement of compound 3-33 (52.3 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and \(^i\)Pr\(_2\)NEt (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. This procedure afforded 36.8 mg (70%) of the title compound as a pale yellow oil. \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.23–7.13 (m, 3 H), 6.94 (dd, \(J = 5.2, 3.4\) Hz, 1 H), 6.84 (d, \(J = 3.4\) Hz, 1 H), 6.67 (t, \(J = 7.3\) Hz, 1 H), 6.43 (d, \(J = 7.5\) Hz, 2 H), 4.41–4.37 (m, 1 H), 4.29 (d, \(J = 8.8\) Hz, 1 H), 3.73 (s, 3 H), 3.40 (dd, \(J = 14.6, 5.3\) Hz, 1 H), 3.33 (dd, \(J = 14.8, 6.7\) Hz, 1 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.0, 146.1, 137.9,
Methyl 2-(phenylamino)-3-(1-tosyl-1H-pyrrol-2-yl)propanoate (3-36): General procedure 4 was used for the rearrangement of compound 3-35 (64.9 mg, 0.163 mmol) with dibutylboron triflate (0.52 mL, 0.521 mmol) and iPr₂NEt (0.11 mL, 0.652 mmol) in 0.15 mL of dichloromethane. This procedure afforded 36.3 mg (59%) of the title compound as a pale yellow oil. ¹H NMR (700 MHz, CDCl₃) δ 7.63 (d, J = 8.4 Hz, 2 H), 7.29 (dd, J = 3.4, 1.7 Hz, 1 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.20–7.11 (m, 2 H), 6.72 (t, J = 7.3 Hz, 1 H), 6.56 (d, J = 7.9 Hz, 2 H), 6.19 (t, J = 3.3 Hz, 1 H), 6.09 (dd, J = 3.4, 1.7 Hz, 1 H), 4.36 (q, J = 7.0 Hz, 1 H), 4.20 (s, br, 1 H), 3.63 (s, 3 H), 3.22 (dd, J = 15.1, 7.4Hz, 1 H), 3.17 (dd, J = 15.2, 6.6 Hz, 1 H), 2.38 (s, 3 H); ¹³C NMR (176 MHz, CDCl₃) δ 173.8, 146.4, 145.1, 136.2, 130.1, 129.9, 129.3, 126.6, 123.4, 118.4, 115.0, 113.5, 111.8, 56.8, 52.1, 31.0, 21.6; IR (film) 3370,1736, 1601, 1362 cm⁻¹. MS (ESI+) 399.1379 (399.1373 calcd for C₂₁H₂₂N₂O₄S, M + H⁺).

Methyl 3-phenyl-2-(phenylamino)butanoate (3-38): General procedure 4 was used for the rearrangement of 3-37 (48.4 mg, 0.18 mmol) with dibutylboron triflate (0.58 mL, 0.58 mmol) and iPr₂NEt (0.13 mL, 0.72 mmol) in 0.2 mL of dichloromethane. This procedure afforded 32 mg (66%) of the title compound as a white solid (m.p. 55–57 °C). The diastereoselectivity of the transformation could not be determined through ¹H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1.6:1 dr following
purification. Data are for the mixture. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.37–7.20 (m, 5 H), 7.12 (t, $J$ = 7.6 Hz, 2 H), 6.73–6.69 (m, 1 H), 6.58–6.54 (m, 2 H), 4.22–4.17 (m, 1.4 H), 3.90 (d, $J$ = 8.7 Hz, 0.6 H), 3.68 (s, 1.8 H), 3.49 (s, 1.2 H), 3.32–3.29 (m, 0.6 H), 3.22–3.20 (m, 0.4 H), 1.46 (d, $J$ = 7.2 Hz, 1.2 H), 1.40 (d, $J$ = 7.1 Hz, 1.8 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 173.9, 147.1, 142.0, 129.3, 128.6, 127.8, 127.2, 118.5, 113.8, 63.1, 52.0, 43.0, 18.4; IR (film) 3387, 1734 cm$^{-1}$. MS (ESI+) 270.1480 (270.1489 calcd for C$_{17}$H$_{19}$NO$_2$, M + H$^+$).

**Synthesis and Characterization of N-Allyl-N-Aryl Glycine Methyl Esters**

**General Procedure 5:** A flame-dried flask was cooled under a stream of nitrogen and then charged with a solution of aniline (1.0 equiv), aldehyde (1.0 equiv), triethylamine (1.4 equiv) and methanol (0.5 M). This mixture was allowed to stir at rt until complete as judged by TLC. When complete, the solution was cooled to 0 °C and NaBH$_4$ (1.0 equiv) was added slowly. The solution was allowed to warm to rt and stirred until complete as judged by TLC. When complete, the reaction mixture was diluted with water and extracted twice with hexanes. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5-20% ethyl acetate in hexanes as the eluent.

**General Procedure 6:** A flame-dried flask was cooled under a stream of nitrogen and then charged with a solution of aryl amine (1.0 equiv), methyl bromoacetate (2.0-3.0 equiv), and Hunig’s base (3.0 equiv) in acetonitrile (0.1 M). The mixture was stirred at reflux for 24 h. After cooling to rt, the solution was concentrated *in vacuo*, then partitioned between saturated NaHCO$_3$ and CH$_2$Cl$_2$. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 3-10% ethyl acetate in hexanes as
the eluent.

**N-Crotylaniline.** General procedure 5 was used for the condensation of crotonaldehyde (0.41 mL, 5.0 mmol) with aniline (0.46 mg, 5.0 mmol) and NEt₃ (0.7 mL, 5.0 mmol) in 10 mL of methanol. The subsequent reduction was carried out with NaBH₄ (265 mg, 7.0 mmol). This procedure afforded 406 mg (55%) of 4-methylpent-2-yn-1-ol as a colorless oil with spectroscopic properties identical to those previously reported. ¹H NMR (500 MHz, CDCl₃) δ 7.15–7.19 (m, 2 H), 6.68–6.71 (m, 1 H), 6.60–6.63 (m, 2 H), 5.68–5.74 (m, 1 H), 5.57–5.62 (m, 1 H), 3.68–3.69 (m, 3 H), 1.70 (dd, J = 1.5, 6.4 Hz, 3 H).

**N-Cinnamylaniline.** General procedure 5 was used for the condensation of cinnamaldehyde (1 g, 14.7 mmol) with aniline (620 mg, 20.6 mmol) and NEt₃ (11.0 mL, 17.6 mmol) in 18 mL of methanol. The subsequent reduction was carried out with LiAlH₄ (1.47 mL, 5 mmol). This procedure afforded 1.2 g (55%) of 4-methylpent-2-yn-1-ol as a pale yellow oil with spectroscopic properties identical to those previously reported. ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.29 (m, 4 H), 7.24–7.17 (m, 3 H), 6.74–6.61 (m, 4 H), 6.37–6.30 (m, 1 H), 3.94 (d, J = 5.6 Hz, 2 H), 3.84 (s, br, 1 H).

**N-(2-Methylallyl)aniline.** A flame dried flask was cooled under a stream of nitrogen and charged with a solution of 3-chloro-2-methylpropene (0.69 mL, 7 mmol) in acetonitrile (28 mL, 0.25 M). To this solution was added aniline (1.28 mL, 14 mmol) and NEt₃ (1.95 mL, 14 mmol). This solution was heated to reflux overnight. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel. This procedure afforded 394 mg (38%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported. ¹H NMR (400 MHz, CDCl₃) δ 7.13–7.18 (m, 2 H), 6.68 (td, J = 1.0, 7.4, 1 H), 6.59 (dd, J = 1.0, 8.5, 2 H),
4.96 (s, 1 H), 4.87 (s, 1 H), 3.67 (s, 2 H), 1.78 (s, 3 H).

**N-(3-Methylbut-2-en-1-yl)aniline.** General procedure 5 was used for the condensation of 3-methyl-2-butenal (0.48 mL, 5 mmol) with aniline (0.46 mL, 5 mmol) and NEt₃ (0.7 mL, 5 mmol) in 10 mL of methanol. The subsequent reduction was carried out with NaBH₄ (265 mg, 7 mmol). This procedure afforded 655.7 mg (81%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.⁴⁵ ¹H NMR (400 MHz, Chloroform-d) δ 7.23–7.13 (m, 2 H), 6.71 (t, J = 7.3 Hz, 1 H), 6.66–6.58 (m, 2 H), 5.34 (t, J = 6.7 Hz, 1 H), 3.69 (d, J = 6.7 Hz, 2 H), 3.57 (s, br, 1 H), 1.74 (d, J = 14.7 Hz, 6 H).

**N-(3-Methylbut-2-en-1-yl)aniline.** General procedure 5 was used for the condensation of 3-methyl-2-butenal (0.48 mL, 5 mmol) with aniline (0.46 mL, 5 mmol) and NEt₃ (0.7 mL, 5 mmol) in 10 mL of methanol. The subsequent reduction was carried out with NaBH₄ (265 mg, 7 mmol). This procedure afforded 655.7 mg (81%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.⁴⁵ ¹H NMR (400 MHz, Chloroform-d) δ 7.23–7.13 (m, 2 H), 6.71 (t, J = 7.3 Hz, 1 H), 6.66–6.58 (m, 2 H), 5.34 (t, J = 6.7 Hz, 1 H), 3.69 (d, J = 6.7 Hz, 2 H), 3.57 (s, br, 1 H), 1.74 (d, J = 14.7 Hz, 6 H).

**E)-4-Methoxy-N-(oct-2-en-1-yl)aniline.** General procedure 5 was used for the condensation of 2-octenal (0.75 mL, 5 mmol) with anisidine (616 mg, 5 mmol) and NEt₃ (0.7 mL, 5 mmol) in 10 mL of methanol. The subsequent reduction was carried out with NaBH₄ (265 mg, 7 mmol). This procedure afforded 711 mg (61%) of the title compound as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 6.79 (d, J = 8.8 Hz, 2 H), 6.60 (d, J = 8.9 Hz, 2 H), 5.72–5.66 (m, 1 H), 5.62–5.51 (m, 1 H), 3.75 (s, 3 H), 3.65 (d, J = 6.1 Hz, 2 H), 3.42 (s, br, 1 H), 2.02 (q, J = 7.4 Hz, 2 H), 1.44–1.21 (m, 6 H), 0.89 (t, J = 7.1 Hz, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ 152.1, 142.5, 133.4, 127.0, 114.8, 114.3, 55.8, 47.1, 32.3, 31.4, 28.9, 22.5, 14.0; IR (film) 3394, 1511, 1233 cm⁻¹. MS (ESI+) 234.1850 (234.1852 calcd for C₁₅H₂₃NO, M + H⁺).

**E)-4-Chloro-N-(pent-2-en-1-yl)aniline.** General procedure 5 was used for the condensation of 2-pentenal (0.49 mL, 5 mmol) with 4-chloroaniline (638 mg, 5 mmol) and NEt₃ (0.7 mL, 5 mmol) in 10 mL of methanol. The subsequent reduction was carried out with NaBH₄ (265 mg, 7 mmol). This procedure afforded 504.7 mg (52%) of the title compound...
compound as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.09 (d, $J = 8.0$ Hz, 2 H), 6.51 (d, $J = 8.2$ Hz, 2 H), 5.76–5.69 (m, 1 H), 5.58–5.45 (m, 1 H), 3.72–3.61 (m, 3 H), 2.08–2.01 (m, 2 H), 0.98 (td, $J = 7.5$, 1.0 Hz, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 146.8, 135.2, 129.0, 125.3, 114.0, 46.1, 25.3, 13.5; IR (film) 3415, 1600 cm$^{-1}$. MS (ESI+) 196.0885 (196.0888 calcd for C$_{11}$H$_{14}$ClN, M + H$^+$).

$N$-(Cyclohex-1-en-1-ylmethyl)aniline. General procedure 5 was used for the condensation of 1-cyclohexene-1-carboxaldehyde (0.52 mL, 4.54 mmol) with aniline (0.42 mL, 4.54 mmol) and NEt$_3$ (0.63 mL, 4.54 mmol) in 9 mL of methanol. The subsequent reduction was carried out with NaBH$_4$ (240 mg, 6.36 mmol). This procedure afforded 682 mg (80%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.$^{46}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.15 (dd, $J = 8.6$, 7.2 Hz, 2 H), 6.67 (t, $J = 7.3$ Hz, 1 H), 6.67–6.56 (m, 2 H), 5.66 (s, 1 H), 3.74 (s, 1 H), 3.59 (s, 2 H), 2.06–1.95 (m, 5 H), 1.69–1.51 (m, 3 H).

Methyl-2-(allyl(phenyl)amino)acetate (3-40). General procedure 6 was used for the alkylation of $N$-allylaniline (418 mg, 3.14 mmol) with methylbromoacetate (0.60 mL, 6.28 mmol) and $^3$Pr$_2$NEt (1.64 mL, 9.42 mmol) in 31 mL of CH$_3$CN. This procedure afforded 546 mg (85%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.$^{40}$ $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.21 (td, $J = 1.8$, 7.3 Hz, 2 H), 6.75 (t, $J = 7.3$ Hz, 1 H), 6.66 (d, $J = 8.1$ Hz, 2 H), 5.86–5.92 (m, 1 H), 5.18–5.25 (m, 2 H), 4.04 (s, 2 H), 4.03 (d, $J = 4.9$ Hz, 2 H), 3.74 (s, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 171.8, 148.1, 133.7, 129.2, 117.5, 116.6, 112.4, 54.2, 52.0, 51.9.
**Methyl-2-(allyl(phenyl)amino)acetate (3-43).** General procedure 6 was used for the alkylation of N-crotylaniline (353 mg, 2.40 mmol) with methylbromoacetate (0.34 mL, 3.6 mmol) and \( \text{tPr}_2\text{NEt} \) (1.25 mL, 7.2 mmol) in 24 mL of CH\(_3\)CN. This procedure afforded 389 mg (74%) of the title compound as a colorless oil. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \( \delta \) 7.21 (t, \( J = 7.3 \) Hz, 2 H), 6.73 (t, \( J = 7.2 \) Hz, 1 H), 6.70 (t, \( J = 8.0 \) Hz, 2 H), 5.68–5.60 (m, 1 H), 5.54–5.50 (m, 1 H), 4.01 (s, 2 H), 3.94 (d, \( J = 5.6 \) Hz, 2 H), 3.72 (s, 3 H), 1.70 (d, \( J = 6.3 \) Hz, 3 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 171.9, 148.3, 129.2, 128.1, 126.4, 117.3, 112.5, 53.3, 52.0, 51.6, 17.7; IR (film) 1746 cm\(^{-1}\). MS (ESI+) 220.1332 (220.1332 calcd for C\(_{13}\)H\(_{17}\)NO\(_2\), M + H\(^+\)).

![Methyl-2-(allyl(phenyl)amino)acetate (3-43)](image)

**Methyl-2-(cinnamyl(phenyl)amino)acetate (3-45).** General procedure 6 was used for the alkylation of N-cinnamylaniline (168 mg, 0.805 mmol) with methylbromoacetate (0.11 mL, 1.2 mmol) and \( \text{tPr}_2\text{NEt} \) (0.42 mL, 2.4 mmol) in 8 mL of CH\(_3\)CN. This procedure afforded 148 mg (65%) of the title compound as a pale yellow solid, m.p. 46–49 ºC. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.35–7.37 (m, 2 H), 7.25–7.32 (m, 2 H), 7.21–7.25 (m, 3 H), 6.77 (t, \( J = 7.3 \) Hz, 1 H), 6.72 (dd, \( J = 1.0, 9.0 \) Hz, 2 H), 6.56 (d, \( J = 15.9 \) Hz, 1 H), 6.28 (dt, \( J = 5.3, 15.8 \) Hz, 1 H), 4.19 (dd, \( J = 1.4, 5.3, 2 \) H), 4.09 (s, 2 H), 3.74 (s, 3 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 171.8, 148.3, 136.7, 131.6, 129.3, 128.6, 127.5, 126.4, 125.5, 117.6, 112.5, 53.8, 52.0, 51.9; IR (film) 1747 cm\(^{-1}\). MS (ESI+) 282.1492 (282.1489 calcd for C\(_{19}\)H\(_{19}\)NO\(_2\), M + Na\(^+\)).

![Methyl-2-(cinnamyl(phenyl)amino)acetate (3-45)](image)

**Methyl-2-((3-methylbut-2-en-1-yl)(phenyl)amino)acetate (3-47).** General procedure 6 was used for the alkylation of N-(3-methylbut-2-en-1-yl)aniline (666 mg, 4.13 mmol) with methylbromoacetate (0.59 mL, 6.19 mmol) and \( \text{tPr}_2\text{NEt} \) (2.16 mL, 12.38 mmol) in 41 mL of CH\(_3\)CN. This procedure afforded 869 mg (90%) of the title compound as a colorless
oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.24–7.15 (m, 2 H), 6.76–6.62 (m, 3 H), 5.31–5.20 (m, 1 H), 4.03–3.93 (m, 4 H), 3.71 (s, 3 H), 1.71 (d, $J$ = 14.5 Hz, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 172.0, 148.5, 135.6, 129.2, 120.9, 117.3, 112.6, 51.9, 51.7, 49.1, 25.8, 17.9; IR (film) 1745, 1598 cm$^{-1}$. MS (ESI+) 234.1484 (234.1489 calcd for C$_{14}$H$_{19}$NO$_2$, M + H$^+$).

**Methyl-2-((2-methylallyl)(phenyl)amino)acetate (3-49).** General procedure 6 was used for the alkylation of N-(2-methylallyl)aniline (394 mg, 2.67 mmol) with methylbromoacetate (0.38 mL, 4.05 mmol) and $i$Pr$_2$NEt (1.40 mL, 8.1 mmol) in 27 mL of CH$_3$CN. This procedure afforded 436.7 mg (75%) of 4-methylpent-2-yn-1-ol as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.19 (t, $J$ = 7.4 Hz, 2 H), 6.71 (t, $J$ = 7.3 Hz, 1 H), 6.61 (d, $J$ = 8.3 Hz, 2 H), 4.86 (s, 2 H), 4.02 (s, 2 H), 3.88 (s, 2 H), 3.72 (s, 3 H), 1.73 (s, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 171.8, 148.5, 140.9, 129.1, 117.3, 112.2, 111.1, 57.7, 51.91, 51.89, 19.9; IR (film) 1746 cm$^{-1}$. MS (ESI+) 220.1331 (220.1332 calcd for C$_{13}$H$_{17}$NO$_2$, M + H$^+$).

**((E))-Methyl 2-((4-methoxyphenyl)(oct-2-en-1-yl)amino)acetate (3-51).** General procedure 6 was used for the alkylation of (E)-4-methoxy-N-(oct-2-en-1-yl)aniline (710 mg, 3.04 mmol) with methylbromoacetate (0.43 mL, 4.56 mmol) and $i$Pr$_2$NEt (1.59 mL, 9.12 mmol) in 30 mL of CH$_3$CN. This procedure afforded 554 mg (89%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.79 (d, $J$ = 9.2 Hz, 2 H), 6.65 (d, $J$ = 9.0 Hz, 2 H), 5.70–5.55 (m, 1 H), 5.52–5.39 (m, 1 H), 3.95 (s, 2 H), 3.87 (d, $J$ = 5.9 Hz, 2 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 2.06–1.96 (m, 2 H), 1.40–1.16 (m, 6 H), 0.86 (t, $J$ = 6.9 Hz, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.1, 152.1, 143.2, 133.9, 125.5, 114.7, 114.6, 55.7, 54.0, 52.2, 51.8, 32.2, 31.3, 28.9, 22.5, 14.0; IR (film) 1745, 1512 cm$^{-1}$. MS (ESI+) 306.2069 (306.2064 calcd for C$_{18}$H$_{27}$NO$_3$, M + H$^+$).
(E)-Methyl 2-((4-chlorophenyl)(pent-2-en-1-yl)amino)acetate (3-53). General procedure 6 was used for the alkylation of (E)-4-chloro-N-(pent-2-en-1-yl)aniline (505 mg, 2.58 mmol) with methylbromoacetate (0.37 mL, 3.87 mmol) and \( \text{\textsuperscript{1}}\text{Pr}_2\text{NEt} \) (1.35 mL, 7.74 mmol) in 26 mL of CH\(_3\)CN. This procedure afforded 479 mg (69%) of the title compound as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.17–7.08 (m, 2 H), 6.61–6.50 (m, 2 H), 5.65 (dt, \( J = 15.5, 6.3 \) Hz, 1 H), 5.49–5.37 (m, 1 H), 3.98 (s, 2 H), 3.90 (d, \( J = 5.7 \) Hz, 2 H), 3.71 (s, 3 H), 2.09–2.02 (m, 2 H), 0.96 (t, \( J = 7.4 \) Hz, 3 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 171.5, 147.0, 135.4, 128.9, 123.7, 122.1, 113.6, 53.5, 52.0, 51.7, 25.2, 13.5; IR (film) 1745, 1598, 1498 cm\(^{-1}\). MS (ESI+) 268.1099 (268.1099 calcd for C\(_{14}\)H\(_{18}\)ClNO\(_2\), M + H\(^+\)).

Methyl 2-[(cyclohex-1-en-1-ylmethyl)(phenyl)amino]acetate (3-55). General procedure 6 was used for the alkylation of N-(cyclohex-1-en-1-ylmethyl)aniline (0.5 mg, 2.67 mmol) with methylbromoacetate (0.38 mL, 4.01 mmol) and \( \text{\textsuperscript{1}}\text{Pr}_2\text{NEt} \) (1.40 mL, 8.01 mmol) in 27 mL of CH\(_3\)CN. This procedure afforded 554 mg (78%) of the title compound as a colorless oil. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \( \delta \) 7.19 (t, \( J = 8.1 \) Hz, 2 H), 6.71 (t, \( J = 7.3 \) Hz, 1 H), 6.64 (d, \( J = 8.1 \) Hz, 2 H), 5.57 (s, 1 H), 4.00 (s, 2 H), 3.84 (s, 2 H), 3.72 (s, 3 H), 2.00 (s, 2 H), 1.91 (s, 2 H), 1.65–1.62 (m, 2 H), 1.62–1.53 (m, 2 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 171.9, 148.8, 133.3, 129.1, 122.9, 117.1, 112.3, 57.6, 51.9, 51.5, 26.3, 25.0, 22.6, 22.5; IR (film) 1748 cm\(^{-1}\). MS (ESI+) 260.1653 (260.1645 calcd for C\(_{16}\)H\(_{21}\)NO\(_2\), M + H\(^+\)).

Synthesis of Allylglycine Derivatives via Aza-[2,3]-Wittig Rearrangement
**General Procedure 7**: A flame-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dibutylboron triflate in methylene chloride (1.5 equiv). The solution was diluted to ca. 0.5 M with methylene chloride then cooled to 0 ºC before Hunig’s base (1.7 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in methylene chloride was then added, and the resulting solution was warmed to 35 ºC. After stirring for 2–4 h, the mixture was cooled to 0 ºC, opened to air, and quenched by the addition of pH 7 buffer solution (ca. 3 mL/mmol substrate), methanol (ca. 6-8 mL/mmol substrate), and 30% aqueous H₂O₂ (ca. 1 mL/mmol substrate). This mixture was warmed to rt and stirred for 1 h. The solution was then cooled to 0 ºC and Na₂S₂O₃ (ca. 7 mL/mmol substrate) was added. The solution was allowed to stir for 1 min before it was diluted with water and extracted twice with Et₂O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5–10% diethyl ether in hexanes as the eluent.

**Methyl-2-(phenylamino)pent-4-enoate (3-41)**. General procedure 7 was used for the reaction of 3-40 (41.1 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and iPr₂NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 28.8 mg (70%) of the title compound as a pale yellow oil. ¹H NMR (700 MHz, CDCl₃) δ 7.19–7.14 (m, 2 H), 6.74 (t, J = 7.4 Hz, 1 H), 6.63–6.59 (m, 2 H), 5.81–5.75 (m, 1 H), 5.19–5.13 (m, 2 H), 4.15 (s, 1 H), 3.72 (s, 3 H), 2.64–2.53 (m, 2 H); ¹³C NMR (176 MHz, CDCl₃) δ 173.9, 146.5, 132.7, 129.3, 119.0, 118.4, 113.4, 56.0, 52.1, 37.0; IR (film) 3400, 1737, 1603 cm⁻¹. MS (ESI⁺) 206.1171 (206.1176 calcd for C₁₂H₁₅NO₂, M + H⁺).
(2S*,3R*)-Methyl-3-methyl-2-(phenylamino)pent-4-enoate (3-44). General procedure 7 was used for the reaction of 3-43 (43.9 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and \( \text{iPr}_2\text{NEt} \) (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 25.7 mg (59%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through \(^1\)H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 7:1 dr following purification. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \( \delta \) 7.19–7.14 (m, 2 H), 6.76–6.71 (m, 1 H), 6.64–6.58 (m, 2 H), 5.79–5.73 (m, 1 H), 5.19–5.08 (m, 2 H), 4.15 (d, \( J = 9.6 \) Hz, 1 H), 4.01 (dd, \( J = 9.4, 5.8 \) Hz, 1 H), 3.69 (s, 3 H), 2.67–2.64 (m, 1 H), 1.16 (d, \( J = 7.0 \) Hz, 3 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 173.4, 146.9, 139.1, 129.3, 118.4, 116.5, 113.6, 61.1, 51.8, 41.4, 16.5; IR (film) 3396, 1735, 1602 cm\(^{-1}\). MS (ESI+) 220.1335 (220.1332 calcd for C\(_{13}\)H\(_{17}\)NO\(_3\), M + H\(^+\)).

(2S*,3S*)-Methyl-3-phenyl-2-(phenylamino)pent-4-enoate (3-45). General procedure 7 was used for the reaction of 3-45 (56.3 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and \( \text{iPr}_2\text{NEt} \) (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 41.1 mg (73%) of a 4:1 mixture of 15c and a product resulting from the aza-[1,2]-Wittig rearrangement. Small amounts of each compound were isolated for characterization. The title compound was isolated as a yellow solid, mp 71–74 ºC. The diastereoselectivity of the transformation could not be determined through \(^1\)H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.34–7.30 (m, 2 H), 7.32–7.19 (m, 3 H), 7.21–7.10 (m, 2 H), 6.73 (t, \( J = 7.3 \) Hz, 1 H), 6.60 (d, \( J = 7.8 \) Hz, 2 H), 6.19–6.11 (m, 1 H),
5.26–5.16 (m, 2 H), 4.38 (t, \( J = 7.6 \text{ Hz} \), 1 H), 3.99 (d, \( J = 8.1 \text{ Hz} \), 1 H), 3.79 (t, \( J = 8.1 \text{ Hz} \), 1 H), 3.65 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 173.2, 146.6, 139.2, 136.8, 129.2, 128.8, 127.9, 127.3, 118.6, 117.7, 113.7, 61.3, 53.2,, 51.8; IR (film) 3384, 1737, 1601 cm\(^{-1}\). MS (ESI+) 282.1491 (282.1489 calcd for C\(_{18}\)H\(_{19}\)NO\(_2\), M + H\(^{+}\)).

![Chemical structure](image)

**Side Product Methyl (E)-5-phenyl-2-(phenylamino)pent-4-enoate** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.36–7.13 (m, 7 H), 6.78–6.74 (m, 1 H), 6.64 (d, \( J = 8.0 \text{ Hz} \), 2 H), 6.51 (d, \( J = 15.7 \text{ Hz} \), 1 H), 6.17–6.14 (m, 1 H), 4.26–4.24 (m, 2 H), 3.74 (s, 3 H), 2.81–2.71 (m, 2 H).

![Chemical structure](image)

**Methyl-3,3-dimethyl-2-(phenylamino)pent-4-enoate (3-48).** General procedure 7 was used for the reaction of 3-47 (46.7 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and \(^{3}\)Pr\(_2\)NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 35.1 mg (75%) of a 2:1 mixture of 15d and a product resulting from the aza-[1,2]-Wittig rearrangement. Small amounts of each compound were isolated for characterization. The title compound was isolated as a white solid, mp 45–47 °C.

**Title Compound X:** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.14 (dd, \( J = 8.5, 7.2 \text{ Hz} \), 2 H), 6.71 (t, \( J = 7.3 \text{ Hz} \), 1 H), 6.64–6.56 (m, 2 H), 5.97–5.90 (m, 1 H), 5.20–5.06 (m, 2 H), 4.09 (d, \( J = 9.9 \text{ Hz} \), 1 H), 3.84 (d, \( J = 9.8 \text{ Hz} \), 1 H), 3.66 (s, 3 H), 1.16 (d, \( J = 13.7 \text{ Hz} \), 6 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 173.4, 147.2, 143.2, 129.3, 118.3, 114.2, 113.6, 64.6, 51.6, 40.2, 24.9, 23.7; IR (film) 3384, 1736, 1603 cm\(^{-1}\). MS (ESI+) 234.1488 (234.1489 calcd for C\(_{14}\)H\(_{19}\)NO\(_2\), M + H\(^{+}\)).
Side Product Methyl-5-methyl-2-(phenylamino)hex-4-enoate. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20–7.11 (m, 2 H), 6.71 (t, \(J = 7.3\) Hz, 1 H), 6.59 (d, \(J = 8.0\) Hz, 2 H), 5.11 (t, \(J = 7.5\) Hz, 1 H), 4.08 (t, \(J = 6.1\) Hz, 1 H), 3.70 (s, 3 H), 2.61–2.44 (m, 2 H), 1.71 (s, 3 H), 1.60 (s, 3 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 174.2, 146.7, 136.0, 129.3, 118.2, 118.1, 113.4, 56.5, 52.1, 31.4, 25.9, 17.9; IR (film) 3369, 1738, 1604 cm\(^{-1}\). MS (ESI+) 234.1486 (234.1489 calcd for C\(_{14}\)H\(_{19}\)NO\(_2\), M + H\(^+\)).

Methyl-4-methyl-2-(phenylamino)pent-4-enoate (3-50). General procedure 7 was used for the reaction of 3-49 (43.9 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and \(^3\)Pr\(_2\)NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 24 mg (55%) of the title compound as a colorless oil. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.24–7.13 (m, 2 H), 6.74 (t, \(J = 7.3\) Hz, 1 H), 6.64–6.58 (m, 2 H), 4.89 (s, 1 H), 4.83 (s, 1 H), 4.17 (q, \(J = 6.7\) Hz, 1 H), 4.06 (s, br, 1 H), 3.71 (s, 3 H), 2.58 (dd, \(J = 13.8, 6.1\) Hz, 1 H), 2.50 (dd, \(J = 13.8, 8.2\) Hz, 1 H), 1.76 (s, 3 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 174.4, 146.6, 140.7, 129.3, 118.4, 114.5, 113.3, 55.0, 52.1, 41.2, 21.8; IR (film) 3318, 1738, 1603 cm\(^{-1}\). MS (ESI+) 220.1325 (220.1332 calcd for C\(_{13}\)H\(_{17}\)NO\(_2\), M + H\(^+\)).

(2\(S^*\),3\(R^*\))-Methyl-2-((4-methoxyphenyl)amino)-3-vinloctanoate (3-52). General procedure 7 was used for the reaction of 3-51 (61.6 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and \(^3\)Pr\(_2\)NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 35.5 mg (58%) of the title compound as a
colorless oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 5:1 dr following purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.79–6.70 (m, 2 H), 6.63–6.52 (m, 2 H), 5.66–5.57 (m, 1 H), 5.21–5.05 (m, 2 H), 3.97–3.91 (m, 2 H), 3.73 (s, 3 H), 3.66 (s, 3 H), 2.42–2.38 (m, 1 H), 1.64–1.59 (m, 1 H), 1.43–1.26 (m, 7 H), 0.88 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 173.7, 152.8, 141.0, 137.8, 118.1, 115.3, 114.9, 61.4, 55.7, 51.6, 47.7, 31.7, 30.9, 26.8, 22.5, 14.0; IR (film) 3394, 1735, 1512 cm$^{-1}$. MS (ESI+) 306.2062 (306.2064 calcd for C$_{18}$H$_{27}$NO$_3$, M + H$^+$).

(2$^S$,3$^R$)-Methyl-2-((4-chlorophenyl)amino)-3-ethylpent-4-enoate (3-54). General procedure 7 was used for the reaction of 3-53 (56.3 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^3$Pr$_2$NET (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 34.7 mg (62%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 8:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.12–7.07 (m, 2 H), 6.56–6.49 (m, 2 H), 5.61–5.56 (m, 1 H), 5.20–5.12 (m, 2 H), 4.18 (d, $J$ = 10.0 Hz, 1 H), 4.00 (dd, $J$ = 10.0, 5.9 Hz, 1 H), 3.67 (s, 3 H), 2.34–2.31 (m, 1 H), 1.69–1.62 (m, 1 H), 1.40–1.31 (m, 1 H), 0.91 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 173.1, 145.4, 137.1, 129.2, 123.0, 118.8, 114.7, 59.9, 51.8, 49.4, 24.0, 11.8; IR (film) 3394, 1734, 1600 cm$^{-1}$. MS (ESI+) 268.1094 (268.1099 calcd for C$_{14}$H$_{18}$ClNO$_2$, M + H$^+$).

(2$^S$,1$'$S$^*$)-Methyl-2-(2$'$-methylenecyclohexyl)-2-(phenylamino)acetate (3-56).
General procedure 7 was used for the reaction of 3-55 (69.5 mg, 0.27 mmol) with dibutylboron triflate (0.4 mL, 0.4 mmol) and \( {\text{Pr}_2\text{NEt}} \) (0.08 mL, 0.46 mmol) in 1.0 mL of dichloromethane. This procedure afforded 39.0 mg (56%) of the title compound as a white solid, mp 65–71 ºC. The diastereoselectivity of the transformation could not be determined through \(^1\)H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 2:1 dr following purification. Data are for the mixture. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.20–1.14 (m, 2 H), 6.76–6.71 (m, 1 H), 6.66 (d, \( J = 8.0 \) Hz, 1.25 H), 6.60 (d, \( J = 8.0 \) Hz, 0.75 H), 4.86 (s, 0.38 H), 4.82 (s, 0.38 H), 4.73 (s, 0.62 H), 4.66 (s, 0.62 H), 4.32 (d, \( J = 9.4 \) Hz, 0.62 H), 4.12 (d, \( J = 9.9 \) Hz, 0.38 H), 3.74 (s, 1.14 H), 3.62 (s, 1.86 H), 2.59–2.52 (m, 1 H), 2.35–2.27 (m, 0.75 H), 2.21–2.07 (m, 2.25 H), 1.75–1.43 (m, 5 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \( \delta \) 174.4, 148.2, 147.1, 129.4, 129.3, 118.5, 118.2, 113.5, 113.0, 110.3, 109.7, 76.2, 57.7, 57.3, 52.1, 51.6, 47.2, 46.3, 33.0, 29.9, 28.5, 28.2, 28.0, 27.9, 22.6, 22.2 (two carbon signals missing due to incidental overlap); IR (film) 3385, 1737, 1603 cm\(^{-1}\). MS (ESI+) 260.1642 (260.1645 calcd for C\(_{16}\)H\(_{21}\)NO\(_2\), M + H\(^+\)).

Synthesis and Characterization of [2,3] Rearrangement/Hydroboration Products

General Procedure 8: A flame-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dibutylboron triflate in methylene chloride (1.5–2.0 equiv). The solution was cooled to 0 ºC and Hunig’s base (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in methylene chloride was then added, and the resulting solution was warmed to 35–40 ºC. After stirring for 2 h, the mixture was cooled to 0 ºC, and additional Bu\(_2\)BOTf (2.0 eq, 1 M solution in CH\(_2\)Cl\(_2\)) was added. The reaction was heated to 40 ºC and allowed to stir for 4 hours. The flask was then cooled to 0 ºC, opened to air, and quenched by the addition
of pH 7 buffer solution (ca. 3 mL/mmol substrate), methanol (ca. 6-8 mL/mmol substrate), and 30% aqueous H₂O₂ (ca. 1 mL/mmol substrate). This mixture was warmed to rt and stirred for 1 h. The solution was then cooled to 0 °C and Na₂S₂O₃ (ca. 7 mL/mmol substrate) was added. This solution was allowed to stir for 1 min before it was diluted with water and extracted twice with Et₂O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 30–40% ethyl acetate in hexanes as the eluent.

**Methyl-5-hydroxy-2-(phenylamino)pentanoate (3-42).** General procedure 8 was used for the reaction of 3-40 (41.1 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and iPr₂NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. This procedure afforded 24.1 mg (54%) of the title compound as a colorless oil. ′H NMR (400 MHz, CDCl₃) δ 7.17 (t, J = 7.4 Hz, 2 H), 6.75 (t, J = 7.2 Hz, 1 H), 6.62 (d, J = 7.7 Hz, 2 H), 4.11 (dd, J = 5.4, 7.0 Hz, 1 H), 3.72 (s, 3 H), 3.67 (t, J = 6.0 Hz, 2 H), 2.01–1.80 (m, 2 H), 1.74–1.67 (m, 2 H); ′C NMR (126 MHz, CDCl₃) δ 174.6, 146.7, 129.4, 118.6, 113.6, 62.2, 56.6, 52.2, 29.7, 28.8; IR (film) 3382, 1732 cm⁻¹. MS (ESI+) 224.1288 (224.1281 calcd for C₁₂H₁₇NO₃, M + H⁺).

**(2S*,3R*)-Methyl-5-hydroxy-3-methyl-2-(phenylamino)pentanoate (3-57).** General procedure 8 was used for the reaction of 3-43 (43.9 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and iPr₂NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. This procedure afforded 26.3 mg (55%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through ′H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 10:1
dr following purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.17 (t, $J = 7.4$ Hz, 2 H), 6.75 (t, $J = 7.4$ Hz, 1 H), 6.64 (d, $J = 7.8$ Hz, 2 H), 4.06 (d, $J = 4.5$ Hz, 1 H), 3.81–3.64 (m, 5 H), 2.31–2.20 (m, 1 H), 1.83–1.74 (m, 1 H), 1.59–1.51 (m, 1 H), 1.03 (d, $J = 7.0$ Hz, 3 H);

$^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 174.1, 147.2, 129.4, 118.6, 113.9, 60.9, 60.4, 52.1, 36.2, 33.0, 15.3; IR (film) 3388, 1731 cm$^{-1}$. MS (ESI+) 238. 1445 (238.1438 calcd for C$_{13}$H$_{17}$NO$_3$, M + H$^+$).

(2S*,3S*)-Methyl-5-hydroxy-3-phenyl-2-(phenylamino)pentanoate (3-58). General procedure 8 was used for the reaction of 3-45 (56.3 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and iPr$_2$NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. This procedure afforded 34.3 mg (57%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33–7.24 (m, 3 H), 7.19 (d, $J = 7.0$ Hz, 2 H), 7.12 (t, $J = 7.4$ Hz, 2 H), 6.71 (t, $J = 7.4$ Hz, 1 H), 6.58 (d, $J = 7.9$ Hz, 2 H), 4.32 (d, $J = 6.0$ Hz, 1 H), 3.90 (s, br, 1 H), 3.66 (s, 3 H), 3.63–3.57 (m, 1 H), 3.49–3.37 (m, 2 H), 2.10–2.05 (m, 2 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.6, 147.1, 139.0, 129.3, 128.7, 128.3, 127.5, 118.6, 113.8, 61.5, 60.5, 52.0, 45.1, 34.9; IR (film) 3388, 1731 cm$^{-1}$. MS (ESI+) 300.1600 (300.1594 calcd for C$_{18}$H$_{21}$NO$_3$, M + H$^+$).

Methyl-5-hydroxy-3,3-dimethyl-2-(phenylamino)pentanoate (3-59). General procedure 8 was used for the reaction of 3-47 (46.7 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and iPr$_2$NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. This procedure afforded 22.7 mg (45%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.22–7.10 (m, 2 H), 6.75 (t, $J = 7.3$ Hz, 1 H), 6.72 (d, $J = 7.3$ Hz, 2 H), 4.38 (s, 1 H), 3.76 (s, 3 H), 3.60 (s, 3 H), 2.69–2.61 (m, 10 H), 1.26–1.17 (m, 8 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.6, 147.1, 139.0, 129.3, 128.7, 128.3, 127.5, 118.6, 113.8, 61.5, 60.5, 52.0, 45.1, 34.9; IR (film) 3388, 1731 cm$^{-1}$. MS (ESI+) 292.1447 (292.1439 calcd for C$_{18}$H$_{21}$NO$_3$, M + H$^+$).
Methyl-5-hydroxy-4-methyl-2-(phenylamino)pentanoate (3-60). General procedure 8 was used for the reaction of 3-49 (43.9 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and iPr₂NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. This procedure afforded 24.4 mg (51%) of the title compound as a pale yellow oil. The diastereoselectivity of the transformation could not be determined through ¹H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1:1 dr following purification. Data are for the mixture. ¹H NMR (500 MHz, CDCl₃) δ 7.23–7.13 (m, 2 H), 6.76 (td, J = 7.3, 3.7 Hz, 1 H), 6.65 (dd, J = 7.5, 3.3 Hz, 2 H), 4.20–4.17 (m, 1 H), 4.14–4.11 (m, 1 H), 3.70 (d, J = 5.9 Hz, 3 H), 3.61–3.44 (m, 2 H), 1.99–1.79 (m, 2 H), 1.72–1.67 (m, 1 H), 1.02 (d, J = 6.8 Hz, 2 H), 0.97 (d, J = 6.8 Hz, 2 H); ¹³C NMR (126 MHz, CDCl₃) δ 175.1, 146.8, 129.4, 118.9, 118.8, 114.0, 113.8, 68.0, 67.5, 55.6, 55.0, 52.2, 52.1, 37.6, 37.1, 33.3, 32.6, 17.0, 16.9 (three carbon signals are missing due to incidental equivalence); IR (film) 3372, 1733, 1601 cm⁻¹. MS (ESI⁺) 238.1438 (238.1438 calcd for C₁₃H₁₉NO₃, M + H⁺).

(2S*,3R*)-Methyl-3-(2-hydroxyethyl)-2-((4-methoxyphenyl)amino)octanoate (3-61). General procedure 8 was used for the reaction of 3-51 (61.1 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and iPr₂NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. This procedure afforded 28.2 mg (44%) of the title compound as a
pale yellow oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 9:1 dr following purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.78–6.75 (m, 2 H), 6.66–6.64 (m, 2 H), 4.06 (d, $J = 4.1$ Hz, 1 H), 3.77–3.63 (m, 8 H), 2.08–2.03 (m, 1 H), 1.80–1.64 (m, 2 H), 1.45–1.23 (m, 8 H), 0.90 (t, $J = 6.8$ Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 174.4, 153.2, 140.9, 116.1, 114.8, 61.3, 60.3, 55.6, 52.0, 38.6, 33.8, 31.9, 29.6, 26.8, 22.5, 14.0; IR (film) 3397, 1732, 1512 cm$^{-1}$. MS (ESI+) 324.2172 (324.2169 calcd for C$_{18}$H$_{29}$NO$_4$, M + H$^+$).

(2$S^*$,3$R^*$)-Methyl-2-((4-chlorophenyl)amino)-3-ethyl-5-hydroxypentanoate (3-62).

General procedure 8 was used for the reaction of 3-53 (56.3 mg, 0.2 mmol) with dibutylboron triflate (0.8 mL, 0.7 mmol) and iPr$_2$NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. This procedure afforded 27.3 mg (48%) of the title compound as a yellow oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 13:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.13–7.08 (m, 2 H), 6.57–6.52 (m, 2 H), 4.31 (s, br, 1 H), 4.10 (d, $J = 4.5$ Hz, 1 H), 3.77–3.75 (m, 1 H), 3.70 (s, 3 H), 3.68–3.65 (m, 1 H), 2.00–1.97 (m, 1 H), 1.75–1.66 (m, 1 H), 1.64–1.59 (m, 1 H), 1.54–1.49 (m, 1 H), 1.47–1.38 (m, 1 H), 0.97 (t, $J = 7.4$ Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 173.9, 145.7, 129.2, 123.2, 114.8, 60.8, 59.2, 52.1, 40.0, 33.0, 23.1, 11.6; IR (film) 3402, 3336, 1728, 1600 cm$^{-1}$. MS (ESI+) 286.1203 (286.1204 calcd for C$_{14}$H$_{20}$ClNO$_3$, M + H$^+$).
(2S*,1S,2S)-Methyl-2-(2-(hydroxymethyl)cyclohexyl)-2-(phenylamino)acetate (3-63). General procedure 8 was used for the reaction of 3-55 (71.5 mg, 0.28 mmol) with dibutylboron triflate (0.95 mL, 0.95 mmol) and iPr$_2$NEt (0.19 mL, 1.1 mmol) in 1.0 mL of dichloromethane. This procedure afforded 29.4 mg (38%) of the title compound as a yellow solid, mp 90–93 ºC. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.22–7.14 (m, 2 H), 6.80 (t, $J = 7.3$ Hz, 1 H), 6.74–6.64 (m, 2 H), 4.15 (d, $J = 26.1$ Hz, 1 H), 4.07–3.95 (m, 1 H), 3.68 (s, 3 H), 3.60 (dd, $J = 11.6$, 5.6 Hz, 1 H), 2.12–1.98 (m, 2 H), 1.82 (s, 2 H), 1.78–1.71 (m, 1 H), 1.53–1.25 (m, 5 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.5, 146.5, 129.4, 119.8, 114.9, 61.6, 60.7, 52.1, 43.4, 40.6, 29.8, 26.4, 22.9, 21.3; IR (film) 3381, 1730, 1602 cm$^{-1}$. MS (ESI+) 278.1752 (278.1751 calcd for C$_{16}$H$_{23}$NO$_3$, M + H$^+$).

Methyl N-allyl-N-phenylalaninate (3-64): A flame-dried flask was cooled under a stream of nitrogen and then charged with iPr$_2$NH (0.09 mL, 0.63 mmol) in THF (0.4 mL). After cooling to -78 ºC, a 2.5 M solution of n-BuLi in hexanes (0.21 mL, 0.54 mmol) was added and the resulting solution was stirred for 5 min. To this solution was added 3-40 (100 mg, 0.49 mmol) in THF (0.4 mL). After stirring for 15 min, iodomethane (0.036 mL, 0.58 mmol) was added and the resulting solution was stirred for 15 min at -78 ºC and then 1 h at 0 ºC. The mixture was warmed to rt and diluted with NH$_4$Cl and EtOAc. The layers were separated, and the organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 65 mg (61%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27–7.17 (m, 2 H), 6.78–6.70 (m, 3 H), 5.96–5.89 (m, 1 H), 5.28–5.23 (m, 1 H), 5.18–5.14 (m, 1 H), 4.48 (q, $J = 7.2$ Hz, 1 H), 4.07–4.02 (m, 1 H), 3.96–3.90 (m, 1 H), 3.70 (d, $J = 3.8$ Hz, 3 H), 1.50 (d, $J = 7.2$ Hz, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.3, 148.7, 136.1, 129.1, 117.6, 115.6, 113.5, 56.3, 52.0, 50.5, 16.0; IR (film) 1734 cm$^{-1}$. MS (ESI+) 220.1333 (220.1332 calcd for C$_{13}$H$_{17}$NO$_2$, M + H$^+$).

\[ \text{MeO} \quad \text{O} \quad \text{N} \quad \text{Ph} \]

\[ \text{HO} \quad \text{C} \quad \text{Ph} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{CH}_3 \]
Methyl-3-phenyl-2-(phenylamino)pent-4-enoate (3-66). General procedure 3 was used for the reaction of 3-64 (44.0 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and 'Pr₂NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. This procedure afforded 8.5 mg (21%) of the title compound as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃)  δ 7.29–7.16 (m, 2 H), 6.89–6.76 (m, 2 H), 5.99–5.92 (m, 1 H), 5.27–5.00 (m, 2 H), 4.45 (q,  J = 7.2 Hz, 1 H), 4.06–3.96 (m, 2 H), 1.52 (d,  J = 7.2 Hz, 3 H); ¹³C NMR (126 MHz, CDCl₃)  δ 178.1, 148.3, 135.7, 129.3, 129.1, 118.7, 116.3, 114.6, 57.2, 51.0, 15.3; IR (film) 1711, 1599 cm⁻¹. MS (ESI+) 206.1176 (206.1176 calcd for C₁₂H₁₅NO₂, M + H⁺).

(1S,2R)-2-phenylcyclohexyl 2-[benzyl(phenyl)amino]acetate (3-68). A flame dried flask was cooled under a stream of nitrogen and charged with trans-2-phenylcyclohexanol (140 mg, 0.792 mmol) and dichloromethane (4 mL, 0.2 M), and the resulting solution was cooled to 0 °C. DMAP (48 mg, 0.396 mmol), EDC (151 mg, 0.792 mmol), and 2-(benzyl(phenyl)amino)acetic acid (191 mg, 0.792 mmol), which was prepared according to published procedure,⁴⁷ were added, and the mixture was allowed to warm to rt overnight. The dichloromethane was removed in vacuo, and the crude oil was diluted with water and ethyl acetate. The mixture was transferred to a separatory funnel, the layers were separated, and the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 214 mg (68%) of the title compound as a white solid (mp 110–112 °C). ¹H NMR (700 MHz, CDCl₃)  δ 7.31–7.16 (m, 8 H), 7.12 (d,  J = 7.4 Hz, 2 H), 7.09–7.04 (m, 2 H), 6.68 (t,  J = 7.3 Hz, 1 H), 6.33 (d,  J = 7.8 Hz, 2 H), 5.07 (td,  J = 10.8, 4.4 Hz, 1 H), 4.38 (d,  J = 17.1 Hz, 1 H), 4.28 (d,  J = 17.1 Hz, 1 H), 3.74 (d,  J = 4.3 Hz, 2 H), 2.68–2.61 (m, 1 H), 2.12–2.07 (m, 1 H), 1.93 (d,  J = 13.4 Hz, 1 H), 1.86–1.84 (m, 1 H), 1.79–1.74 (m, 1 H), 1.59–1.31 (m, 4 H); ¹³C NMR (176 MHz, CDCl₃)  δ 170.3, 148.6, 142.9, 138.5, 129.0, 128.5, 128.4, 127.6, 126.9, 126.7, 126.5, 117.3, 112.3, 76.6, 55.3, 52.0, 50.0, 33.8, 32.2, 25.7, 24.7; IR (film) 1744 cm⁻¹. MS (ESI+)
2-(allyl(phenyl)amino)acetic acid A flame dried flask was cooled under a stream of nitrogen and charged with N-phenylglycine (302 mg, 2 mmol) and THF (4.0 mL, 0.5 M), and the resulting solution was cooled to -78 °C. To this solution was added n-BuLi (1.76 mL, 2.5 M soln in hexanes). After stirring 15 min, allylbromide (0.26 mL, 2.2 mmol) was added dropwise, and the mixture was allowed to warm to rt over 2 h. The reaction was then quenched with 1 M HCl, and the resulting mixture was extracted three times with ethyl acetate. The combined ether layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 349 mg (91%) of the title compound as a brown oil. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.26–7.19 (m, 2 H), 6.78 (t, \(J = 7.3\) Hz, 1 H), 6.69 (d, \(J = 7.9\) Hz, 2 H), 5.91–5.88 (m, 1 H), 5.26–5.21 (m, 2 H), 4.05 (s, 2 H), 4.00 (d, \(J = 5.3\) Hz, 2 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 177.4, 148.0, 133.5, 129.3, 117.9, 117.0, 112.6, 54.2, 51.8; IR (film) 2920, 1722 cm\(^{-1}\). MS (ESI+) 192. 1017 (192.1019 calcd for C\(_{11}\)H\(_{13}\)NO\(_2\), M + H\(^+\)).

(1'S,2'R)-1-(Allyl(phenyl)amino)-3-(2'-phenylcyclohexyl)propan-2-one (3-70). A flame dried flask was cooled under a stream of nitrogen and charged with trans-2-phenylcyclohexanol (322 mg, 1.83 mmol) and dichloromethane (9.1 mL, 0.2 M), and the resulting solution was cooled to 0 °C. DMAP (112 mg, 0.92 mmol), EDC (349 mg, 1.83 mmol), and 2-(allyl(phenyl)amino)acetic acid (349 mg, 1.83 mmol) were added, and the mixture was allowed to warm to rt overnight. The dichloromethane was removed in vacuo, and the crude oil was diluted with water and ethyl acetate. The mixture was transferred to a separatory funnel, the layers were separated, and the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 309.7 mg (49%) of the title compound as a white solid (mp 101–104 °C). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.33–7.16
(m, 5 H), 7.12–7.05 (m, 2 H), 6.72 (t, J = 7.1 Hz, 1 H), 6.36 (d, J = 8.0 Hz, 2 H), 5.81–5.76 (m, 1 H), 5.14–5.09 (m, 3 H), 3.82–3.68 (m, 4 H), 2.72–2.68 (m, 1 H), 2.17–2.15 (m, 1 H), 1.99–1.96 (m, 1 H), 1.91–1.88 (m, 1 H), 1.82–1.80 (m, 1 H), 1.63–1.37 (m, 4 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 170.4, 148.3, 143.0, 133.9, 129.1, 128.4, 127.7, 126.6, 117.1, 116.2, 112.3, 76.6, 54.0, 51.7, 50.0, 33.9, 32.4, 25.8, 24.8; IR (film) 1745, 1600 cm\(^{-1}\). MS (ESI+) 350.2125 (350.21 calc for C\(_{23}\)H\(_{27}\)NO\(_2\), M + H\(^{+}\)).

(1S,2R)-2-phenylcyclohexyl 3-phenyl-2-(phenylamino)propanoate (3-69). General procedure 8 was used for the rearrangement of 3-68 (79.9 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and iPr\(_2\)NEt (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. This procedure afforded 68.1 mg (85%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through \(^1\)H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1.6:1 dr following purification. Data are for the mixture. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta 7.35–7.09\) (m, 8 H), 7.08 (t, J = 7.9 Hz, 1.2 H), 7.04 (d, J = 7.2 Hz, 0.8 H), 7.00 (t, J = 7.7 Hz, 0.8 H), 6.79–6.63 (m, 2.2 H), 6.42 (d, J = 8.0 Hz, 1.2 H), 6.23 (d, J = 8.0 Hz, 0.8 H), 5.00–4.92 (m, 1 H), 4.11–4.09 (m, 0.6 H), 3.96–3.94 (m, 0.4 H), 3.88 (d, J = 7.5 Hz, 1 H), 2.88 (dd, J = 12.4, 6.1 Hz, 0.4 H), 2.81 (dd, J = 13.9, 7.1 Hz, 0.4 H), 2.74 (td, J = 12.6, 3.7 Hz, 0.6 H), 2.68–2.60 (m, 1 H), 2.45 (dd, J = 14.0, 6.9 Hz, 0.6 H), 2.15–2.13 (m, 0.6 H), 1.97–1.91 (m, 1 H), 1.85–1.83 (m, 0.4 H), 1.80–1.74 (m, 1 H), 1.87–1.63 (m, 5 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta 172.4, 146.5, 146.3, 143.1, 136.4, 129.3, 129.2, 128.5, 128.4, 127.7, 126.9, 118.1, 113.5, 77.6, 57.5, 49.8, 38.5, 33.9, 32.4, 25.8, 24.7; IR (film) 3396, 1731 cm\(^{-1}\). MS (ESI+) 400.2284 (400.2271 calc for C\(_{27}\)H\(_{29}\)NO\(_2\), M + H\(^{+}\)).
(1S,2R)-2-Phenylcyclohexyl 2’-(phenylamino)pent-4-enoate (3-71). General procedure 8 was used for the reaction of 3-70 (49.0 mg, 0.14 mmol) with dibutylboron triflate (0.21 mL, 0.21 mmol) and 1Pr₂NEt (0.04 mL, 0.24 mmol) in 0.5 mL of dichloromethane. This procedure afforded 31.4 mg (64%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through 1H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1.3:1 dr following purification. Data are for the mixture. 1H NMR (500 MHz, CDCl₃) δ 7.33–7.16 (m, 5 H), 7.12–7.08 (m, 1.12 H), 7.04–7.01 (m, 0.87 H), 6.69 (dt, J = 12.5, 7.3 Hz, 1 H), 6.49 (d, J = 8.0 Hz, 1.12 H), 6.27 (d, J = 8.0 Hz, 0.87 H), 5.48–5.42 (m, 0.44 H), 5.15–4.97 (m, 2.43 H), 4.89–4.78 (m, 1.12 H), 3.95 (s, br, 1 H), 3.88 (t, J = 5.7 Hz, 0.56 H), 3.78 (t, J = 6.1 Hz, 0.44 H), 2.73–2.66 (m, 1 H), 2.36–2.31 (m, 1 H), 2.16–1.77 (m, 5 H), 1.59–1.28 (m, 4 H); 13C NMR (126 MHz, CDCl₃) δ 172.5, 172.4, 146.5, 146.4, 143.0, 132.7, 132.6, 129.2, 129.1, 128.5, 128.4, 127.5, 127.4, 126.6, 126.5, 118.8, 118.5, 118.2, 118.0, 113.4, 113.2, 77.1, 76.9, 55.6, 55.5, 49.9, 49.7, 36.8, 36.3, 34.1, 34.0, 32.4, 32.1, 25.8, 25.7, 24.7, 24.6 (one carbon signal missing due to incidental overlap); IR (film) 3416, 1734, 1603 cm⁻¹. MS (ESI+) 350.2113 (350.2115 calcd for C₂₃H₂₇NO₂, M + H⁺).

**Determination of stereochemistry**

The relative stereochemistry of compounds 3-44 and 3-56 were assigned via 1D and 2D NOESY experiments of the following lactones generated by acid catalyzed cyclization of 3-44 and 3-56. Significant nOe relationships are shown below. The stereochemistry of 3-45, 3-52, and 3-54 were assigned based on analogy to 3-44.

![Chemical structure](attachment:image.png)

**General Procedure 9:** A flame-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of the [2,3] rearrangement product in
methylene chloride. To this solution was added \( p \)-toluenesulfonic acid (1 equiv). The solution was heated to 40 °C until the cyclization was complete as judged by TLC. When the reaction was complete, the mixture was cooled to rt, before it was quenched with saturated sodium bicarbonate solution and extracted twice with DCM. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel using 5-20% ethyl acetate in hexanes as the eluent.

\[
\text{O} \begin{array}{c}
\text{N}^{+} \\text{Ph}
\end{array} \begin{array}{c}
\text{O}
\end{array}
\]

(3\textit{S},4\textit{R})-4-Methyl-3-(phenylamino)tetrahydro-2H-pyran-2-one. General procedure 9 was used for the reaction of 3-57 (26.3 mg, 0.11 mmol) with \( p \)-toluenesulfonic acid (21.1 mg, 0.11 mmol) in 1.1 mL of dichloromethane. This procedure afforded 10.2 mg (45%) of the title compound as a pale yellow oil. \( ^1 \)H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.22–7.11 (m, 2 H), 6.75 (t, \( J = 7.3 \) Hz, 1 H), 6.67 (d, \( J = 7.9 \) Hz, 2 H), 4.45–4.27 (m, 2 H), 4.10 (s, br, 1 H), 3.75 (d, \( J = 10.9 \) Hz, 1 H), 2.26–2.17 (m, 1 H), 2.05–1.98 (m, 1 H), 1.76–1.69 (m, 1 H), 1.25 (d, \( J = 6.7 \) Hz, 3 H); \( ^{13} \)C NMR (126 MHz, CDCl\textsubscript{3}) \( \delta \) 173.4, 147.8, 129.3, 118.8, 113.9, 66.1, 59.5, 33.8, 30.1, 20.3; IR (film) 1746 cm\textsuperscript{-1}. MS (ESI+) 206.1171 (206.1176 calcd for C\textsubscript{12}H\textsubscript{15}NO\textsubscript{2}, M + H\textsuperscript{+}).

\[
\text{O} \begin{array}{c}
\text{N}^{+} \text{Ph}
\end{array} \begin{array}{c}
\text{O}
\end{array}
\]

(4\textit{S},4\textit{aR},8\textit{aR})-4-(Phenylamino)hexahydro-1H-isochromen-3(4H)-one. General procedure 8 was used for the reaction of 3-63 (29.4 mg, 0.11 mmol) with \( p \)-toluenesulfonic acid (20.2 mg, 0.11 mmol) in 1.1 mL of dichloromethane. This procedure
afforded 10.2 mg (39%) of the title compound as a white solid, mp 110–112 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.15 (dd, $J$ = 8.6, 7.3 Hz, 2 H), 6.67 (t, $J$ = 7.3 Hz, 1 H), 6.65 (d, $J$ = 8.0 Hz, 2 H), 4.32 (dd, $J$ = 11.5, 3.2 Hz, 1 H), 4.25 (dd, $J$ = 11.2, 5.4 Hz, 1 H), 4.02 (d, $J$ = 8.9 Hz, 1 H), 3.84 (s, br, 1 H), 3.59 (s, 2 H), 2.06–1.95 (m, 2 H), 1.79–1.39 (m, 8 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 1728, 147.4, 129.3, 118.6, 113.8, 72.1, 55.3, 38.5, 34.3, 26.6, 25.0, 23.4, 21.4; IR (film) 3384, 1730, 1602 cm$^{-1}$. MS (ESI+) 246.1489 (246.1489 calcd for C$_{15}$H$_{19}$NO$_2$, M + H$^+$).

3.12 References

19. See experimental section for details.
20. When a single equivalent of dibutylboron triflate was used the rearrangement reaction proceeded to 74% conversion (26% unreacted starting material) as judged by \(^1\)H NMR analysis. This experiment suggests that the reaction proceeds through a boron enolate that contains a single equivalent of an organoboron species, rather than an intermediate that bears two dialkylboron units (one bound to oxygen and one bound to nitrogen). We have elected to classify this as a Wittig-type rearrangement as it does not appear that an ammonium ion resulting from protonation of the amino group (as in a Stevens-type rearrangement) is required. However, there likely is a Lewis acid/base chelate interaction between the O-BR\(_2\) group and the amino group, so in this case there may not be a clean division between classification as a Wittig rearrangement vs. a Stevens rearrangement.

21. We were unable to examine the reactivity of the corresponding NH or N-alkylpyrrole derivatives as these compounds were unstable and rapidly decomposed upon isolation.


Chapter 4
Generation of Vicinal Stereocenters via Asymmetric Tandem Wittig Rearrangement/Aldol Reactions

4.1 Introduction

The aldol reaction is an extremely valuable method of carbon-carbon bond formation, and it has been utilized extensively in organic synthesis, with particular focus on diastereo- and enantioselective methods. While ketone-aldehyde aldol reactions are ubiquitous, ketone-ketone reactions remain a significant challenge. Compared to aldehydes, ketones are less electrophilic and the intrinsic retro-aldol reaction is rapid. Furthermore, the lack of steric and electronic disparity between the two ketone substituents leads to low stereo-differentiation. Current methods typically involve the use of a pre-formed enol ether paired with a Lewis acid or Lewis base in order to create favorable conditions and to prevent ketone self-coupling. Despite the inherent challenges, aldol reactions using ketone coupling partners are capable of generating tertiary alcohols containing up to two new stereocenters. Recent studies have focused on catalytic, enantioselective methods.

Our group has recently developed asymmetric tandem Wittig/aldol and Wittig/Mannich reactions for the synthesis of α,β-dihydroxy esters and α-hydroxy-β-amino esters, respectively. We envisioned using this tandem reaction sequence for the asymmetric synthesis of vicinal quaternary stereocenters, which is still a difficult problem in organic synthesis. Though aldol reactions to ketones remain challenging, we hypothesized that the doubly-boronated enolate 4-3, which is generated in situ in these reactions, may be reactive enough to undergo the desired coupling reaction (Scheme 4.1).
4.2 Preliminary Results

By employing ketone coupling partners in these reactions, we hoped to generate \(\alpha,\beta\)-dihydroxy ester derivatives, however, preliminary results\textsuperscript{14} indicated an unexpected transformation. When compound 4-6 was subjected to the previously employed rearrangement conditions followed by ketone addition, boronate ester 4-7 was generated in good yield and diastereoselectivity. The boron was not cleaved by the typical oxidative workup, however resubjecting the purified boronate ester to the peroxide conditions did successfully free the desired diol 4-8 (Scheme 4.2).

### Scheme 4.2 Preliminary Tandem Wittig/Aldol Results

4.3 Synthesis of Boronate Esters

A number of methyl ketones were examined in this transformation (Table 4.1). Expectedly, conversion of starting material to product was low, due to the attenuated reactivity of ketones relative to aldehydes. Aryl methyl ketones afforded the boronate esters in moderate yield, though excellent diastereoselectivity. For example, the reaction of 4-9 and p-bromoacetophenone generated boronate ester 4-12 in 56% yield and >20:1 dr. While di-aliphatic ketones produced boronate esters in similar yield, the
diastereoselectivity of these reactions was modest, due to the steric similarity between the two ketone substituents. Reactions with branched aliphatic methyl ketones were unsuccessful. When substrate 4-9 was subjected to rearrangement conditions followed by the addition of 3-methyl-2-butanone, no ketone was incorporated into the product; rather, only the rearranged starting material was observed (Table 4.1, entry 9).

Table 4.1 Formation of Boron Ester

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn (4-9)</td>
<td>4-10</td>
<td>73%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>4-11</td>
<td>50%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>4-12</td>
<td>56%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>4-13</td>
<td>50%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>Bn (CH₂)₂Ph</td>
<td>4-14</td>
<td>45%</td>
<td>4:1</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>4-15</td>
<td>42%</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>4-16</td>
<td>54%</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>4-17</td>
<td>46%</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>-</td>
<td>NR</td>
<td>-</td>
</tr>
</tbody>
</table>

*aConditions: (i) 1.0 equiv of 4.9, 3.2 equiv of Bu₂BOTf, 4.0 equiv of NEt₃ or Pr₂NEt, CH₂Cl₂, 0 °C to rt. (ii) 1.0–1.5 equiv. of ketone, 0 °C to rt, 16 hr (iii) Rochelle salt, 0 °C to rt. *Isolated yield, average of two or more experiments.

Resubjection of the purified boronate esters to the peroxide workup conditions freed the α,β-dihydroxy ester products (Table 4.2), though we sought to find a more direct path to the desired diol. By using a large excess of peroxide in the initial workup step, the boronate ester could be cleaved completely, allowing the desired diol to be accessed directly from the substrate 4-9. Under these conditions, the α,β-dihydroxy ester could be generated in a single step, though conversion remained low.
Table 4.2 Boron Cleavage

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R₁</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>p-OMe-Ph (4-11)</td>
<td>4-19</td>
<td>34%</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>p-Br-Ph (4-12)</td>
<td>4-20</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>Ph (4-13)</td>
<td>4-21</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>(CH₂)₂Ph (4-14)</td>
<td>4-22</td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>C₆H₅ (4-15)</td>
<td>4-23</td>
<td>59%</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>CH₃ (4-16)</td>
<td>4-24</td>
<td>75%</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>C₄H₉ (4-18)</td>
<td>4-25</td>
<td>53%</td>
</tr>
</tbody>
</table>

*aConditions: (i) 1.0 equiv of boronate ester, H₂O₂ (1 mL/mmol substrate), MeOH, 0.1 M, 0° C to rt. *Isolated yield, average of two or more experiments.

4.4 Synthesis of α,β-Dihydroxy Esters

With optimized workup conditions in hand, the tandem reaction was examined again. A number of methyl ketones successfully underwent the Wittig/aldol sequence to generate the α,β-dihydroxy esters in a single step (Table 4.3). As before, aryl and alkenyl methyl ketones formed the diol in moderate yield and excellent diastereoselectivity. Additionally, the [2,3] Wittig rearrangement/aldol reaction was explored when O-allyl substrate 4-26 was subjected to the optimized reaction conditions. Diol products were generated in modest yield with both p-bromo-acetophenone as well as cyclohexanone, though a large quantity of starting material was recovered, indicating potential water contamination.
Table 4.3 Asymmetric Wittig Rearrangement/Aldol Reaction

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn (4-9)</td>
<td>Ph</td>
<td>4-27</td>
<td>45%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>p-Me-Ph</td>
<td>4-28</td>
<td>43%</td>
<td>17:1</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>p-Br-Ph</td>
<td>4-20</td>
<td>42%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>4-21</td>
<td>58%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>4-23</td>
<td>52%</td>
<td>4:1</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>Me</td>
<td>4-24</td>
<td>57%</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>−C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;−</td>
<td>4-25</td>
<td>24%</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>iPr</td>
<td>-</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>m-F-Ph</td>
<td>4-29</td>
<td>20%</td>
<td>15:1</td>
</tr>
<tr>
<td>10</td>
<td>Allyl (4-26)</td>
<td>p-Br-Ph</td>
<td>4-30</td>
<td>15%</td>
<td>10:1</td>
</tr>
<tr>
<td>11</td>
<td>Allyl</td>
<td>−C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;−</td>
<td>4-31</td>
<td>16%</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: (i) 1.0 equiv of 4-9 or 4-26, 3.2 equiv of Bu<sub>2</sub>BOTf, 4.0 equiv of NEt<sub>3</sub> or iPr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0.25 M, 15 min, 0º C to rt. (ii) 1.0–1.5 equiv. of ketone, 0 ºC to rt, 16 hr (iii) pH 7 buffer, H<sub>2</sub>O<sub>2</sub>, 1 hr, 0º C to rt. <sup>b</sup>Isolated yield, average of two or more experiments.

4.5 Chiral Auxiliary Removal

In order to assess optical purity of the products, and in order for this tandem reaction to be utilized in practical applications, a method must be developed for the removal of the chiral auxiliary. Previously, our group has employed two alternate methods of chiral auxiliary removal: a two-step process consisting of acetonide formation followed by ester hydrolysis (Scheme 4.3a) or ester reduction using LiAlH<sub>4</sub> (Scheme 4.3b).
Acetonide formation proved unsuccessful for these diol products, as only unreacted starting material was recovered from these reactions, presumably due to the additional steric hindrance around the adjacent quaternary centers. As depicted in Table 4.4, LiAlH₄ reduction showed moderate success, though this method appears to be limited to diols resulting from di-aliphatic ketones. LiAlH₄ reduction of diols generated from aryl ketones resulted in removal of the chiral auxiliary as well as complete retro-aldol reaction.

### Table 4.4 Chiral Auxiliary Cleavage

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield%^d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (4-24)</td>
<td>4-35</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td>(\gamma)-Ph (4-21)</td>
<td>4-36</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>Ph (4-27)</td>
<td>-</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

*aConditions: (i) 1.0 equiv of diol, 3.0 equiv of LiAlH₄, THF, 0.1 M, 16 hr, 0° C to rt.*

*bIsolated yield, average of two or more experiments.

A number of alternate chiral auxiliary removal methods were explored, though none were successful, and retro-aldol reaction remains a significant issue. Methanolation under both acidic and basic conditions were unsuccessful; the former resulted in unreacted starting material and the latter resulted in retro-aldol reaction (Scheme 4.4).
Scheme 4.4 Methanolysis Resulting in Retro-Aldol Reaction

\[
\begin{align*}
\text{Scheme 4.4} & \quad \text{Methanolysis Resulting in Retro-Aldol Reaction} \\
\begin{array}{c}
\text{4-37} \quad \text{Ph} \quad \text{HO} \quad \text{HO} \quad \text{Bn} \\
\text{NaOCH}_3 \quad \text{CH}_2\text{OH} \\
\rightarrow \quad \text{4-38} \quad \text{Ph} \quad \text{HO} \\
\text{4-39} \quad \text{MeO} \quad \text{CO} \quad \text{OH} \\
\text{4-40} \quad \text{H}_2 \quad \text{C} \quad \text{R}
\end{array}
\end{align*}
\]

The diol ester products were unreactive towards DIBAIH as well as Lewis acid-catalyzed Weinreb amide conditions (AlMe\textsubscript{3} and N,O-dimethylhydroxylamine). Furthermore, subjection to LiBH\textsubscript{4} resulted in the retro-aldol reaction.

Scheme 4.5 Silyl Protection

\[
\begin{align*}
\text{Scheme 4.5} & \quad \text{Silyl Protection} \\
\begin{array}{c}
\text{4-20} \quad \text{Ph} \quad \text{HO} \quad \text{HO} \quad \text{Bn} \\
\text{TMS-imidizole} \\
\rightarrow \quad \text{4-41} \quad \text{Ph} \quad \text{HO} \\
\text{TMS} \quad \text{O} \quad \text{CH}_3 \\
\text{LiAlH}_4 \quad \text{or} \quad \text{NaOMe} \quad \text{decomposition}
\end{array}
\end{align*}
\]

Though acetonide formation was unsuccessful, a protecting group appeared to be necessary in order to prevent the undesirable retro-aldol reaction. Thus, silyl protecting groups were briefly explored. A mono-protected diol 4-41 was subjected to LiAlH\textsubscript{4} or NaOMe, however, each reaction resulted in the removal of the protecting group followed by the retro-aldol reaction (Scheme 4.5).

4.6 Conclusions and Future Directions

Though removal of the chiral auxiliary remains a significant obstacle, we have developed a tandem Wittig/aldol sequence that constructs two contiguous stereocenters in a single reaction with excellent selectivity. The asymmetric generation of vicinal quaternary stereocenters is still a challenging problem in organic synthesis, and our tandem sequence affords highly substituted enantioenriched diols from simple starting materials. Efforts are currently underway to find a suitable method for chiral auxiliary removal that will not result in a retro-aldol reaction.

4.7 Experimental
General Considerations: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. Dichloromethane was purified using a GlassContour solvent purification system. Hunig’s base was distilled from CaH$_2$. Yields refer to isolated yields of compounds estimated to be $\geq 95\%$ pure as determined by $^1$H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Tables 4.1–4.4 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 4.1–4.4.

Handling of Dialkylboron reagents: Dibutylboron triflate (1.0 M solution in methylene chloride) was obtained from Aldrich Chemical Co. and used as obtained. Due to the air and moisture sensitivity of this reagent, it must be stored and transferred under a rigorously maintained nitrogen atmosphere.

Synthesis and Characterization of Diol Products

General Procedure 1: An oven-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dibutylboron triflate in methylene chloride (3.2 equiv). The solution was cooled to 0 °C and triethylamine (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.5 equiv) in methylene chloride was then added, and the resulting solution was warmed to rt over 15–20 min, at which point the solution was again cooled to 0 °C and a 1 M solution of the appropriate ketone was added. The reaction was allowed to stir 14–24 hours at room temperature. When the reaction was complete, the flask was opened to air and quenched by the addition of Rochelle Salt (ca. 6–8 mL/mmol substrate) and diluted with Et$_2$O. The resulting solution was stirred at rt for 10 min before extracting three times with Et$_2$O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in
vacuo. The crude product was purified by flash chromatography on silica gel using 5% diethyl ether in hexanes as the eluent.

**General Procedure 2:** The purified boron chelate was dissolved in methanol (0.1 M) and cooled to 0 °C before 30% aqueous H₂O₂ (ca. 1 mL/mmol substrate) was added slowly. The mixture was allowed to stir at rt until the reaction was judged complete by TLC. The solution was then cooled to 0 °C and Na₂S₂O₃ (ca. 6–8 mL/mmol substrate) was added. The mixture was stirred at rt for 10 min before extracting three times with Et₂O. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 3–10% ethyl acetate in hexanes as the eluent.

![Chemical reaction diagram](image)

**General Procedure 3:** A flame-dried flask was evacuated and backfilled with nitrogen three times then charged with a 1 M solution of dibutylboron triflate in methylene chloride (3.2 equiv). The solution was cooled to 0 °C and triethylamine (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in methylene chloride was then added, and the resulting solution was warmed to rt over 15 min, at which point the solution was again cooled to 0 °C and a 1 M solution of the appropriate ketone was added. The reaction was allowed to stir 14–24 hours at room temperature. When the reaction was complete, the flask was opened to air and quenched by the addition of methanol (ca. 19 mL/mmol substrate). The resulting solution was transferred to a larger flask and cooled to 0 °C before 30% aqueous H₂O₂ (ca. 26 mL/mmol substrate) was added slowly. This mixture was warmed to rt and stirred for 1 h. The solution was then diluted with water and extracted twice with Et₂O. The combined organic layers were washed with water, saturated Na₂S₂O₃, and brine then dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 5–20% ethyl acetate in hexanes as the eluent.
(1R,2S,2'R,3'S)-2-phenylcyclohexyl-2'-benzyl-5'-butyl-3'-phenyl-3'-methyl-4',6'-dioxa-5'-borolane-4'-carboxylate (4-10). General procedure 1 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (100 mg, 0.308 mmol) to form boronate ester 4-10 using dibutylboron triflate solution (1.0 mL) and acetophenone (54 µL, 0.462 mmol). This procedure afforded 115.0 mg (73%) of the title compound as a pale yellow oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32–7.31 (m, 4 H), 7.28–7.26 (m, 4 H), 7.21–7.18 (m, 1 H), 7.13–7.12 (m, 3 H), 7.07–7.05 (m, 3 H), 5.11–5.06 (m, 1 H), 2.83–2.78 (m, 1 H), 2.41 (d, $J =$ 14.7 Hz, 1 H), 2.22 (d, $J =$ 14.7 Hz, 1 H), 1.97–1.94 (m, 1 H), 1.87–1.82 (m, 1 H), 1.74–1.71 (m, 2 H), 1.53–1.33 (m, 9 H), 1.03–0.99 (m, 3 H), 0.94–0.91 (m, 4 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.2, 143.6, 141.5, 135.8, 130.2, 128.8, 127.8, 127.7, 127.5, 127.4, 127.3, 127.0, 126.5, 125.9, 90.6, 87.2, 78.4, 49.6, 42.9, 35.5, 31.6, 26.1, 25.9, 25.7, 25.4, 24.6, 13.9; IR (film) 1739 cm$^{-1}$. MS (ESI+) 528.3284 (528.3280 calcd for C$_{33}$H$_{39}$BO$_4$, M + NH$_4^+$).

(1R,2S,2'R,3'S)-2-phenylcyclohexyl-2'-benzyl-5'-butyl-3'-(4-methoxyphenyl)-3'-methyl-4',6'-dioxa-5'-borolane-4'-carboxylate (4-11). General procedure 1 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (50 mg, 0.154 mmol) to form boronate ester 4-11 using dibutylboron triflate solution (0.49 mL) and p-methoxyacetophenone (23.2 mg, 0.231 mmol). This procedure afforded 41.5 mg (50%) of the title compound as a colorless oil. The diastereoselectivity of the
transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36–7.24 (m, 4 H), 7.26–7.08 (m, 6 H), 6.93 (s, 2 H), 6.82–6.75 (m, 2 H), 5.06 (td, $J = 10.9, 4.2$ Hz, 1 H), 3.81 (s, 3 H), 2.82–2.75 (m, 1 H), 2.37 (d, $J = 14.7$ Hz, 1 H), 2.31–2.17 (m, 1 H), 1.99–1.89 (m, 1 H), 1.87–1.76 (m, 1 H), 1.76–1.66 (m, 2 H), 1.56–1.20 (m, 7 H), 0.95 (t, $J = 7.5$ Hz, 3 H), 0.93–0.87 (s, 6 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 170.3, 158.8, 143.6, 136.0, 133.7, 130.2, 128.8, 127.7, 127.5, 127.1, 127.0, 126.5, 113.1, 90.7, 87.0, 78.3, 55.2, 49.6, 42.9, 35.5, 31.6, 31.5, 26.1, 25.9, 25.8, 25.7, 25.5, 25.4, 24.6, 14.0, 13.9; IR (film) 1742 cm$^{-1}$. MS (ESI) 558.3391 (558.3385 calcd for C$_{34}$H$_{41}$BO$_5$, M + NH$_4^+$).

(1R,2S,2'R,3'S)-2-phenylcyclohexyl-2'-benzyl-5'-butyl-3'-(4-bromophenyl)-3'-methyl-4',6'-dioxa-5'-borolane-4'-carboxylate (4-12). General procedure 1 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (50 mg, 0.154 mmol) to form boronate ester 4-12 using dibutylboron triflate solution (0.49 mL) and p-bromoacetophenone (46.1 mg, 0.231 mmol). This procedure afforded 54.6 mg (60%) of the title compound as a pale yellow oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.38 (d, $J = 7.5$ Hz, 2 H), 7.29–7.33 (m, 4 H), 7.20 (t, $J = 7.0$ Hz, 1 H), 7.12–7.15 (m, 3 H), 7.06 (dd, $J = 2.7, 7.7$ Hz, 2 H), 6.91 (s, br., 2 H), 5.11 (dt, $J = 4.2, 10.9$ Hz, 1 H), 2.79 (dt, $J = 3.9, 11.2$ Hz, 1 H), 2.37 (d, $J = 14.4$ Hz, 1 H), 2.23 (d, $J = 15.6$ Hz, 1 H), 1.96 (d, $J = 13.6$ Hz, 1 H), 1.81–1.84 (m, 1 H), 1.71–1.74 (m, 2 H), 1.29–1.53 (m, 9 H), 1.02–1.08 (m, 1 H), 0.99 (t, $J = 9.0$ Hz, 2 H), 0.85 (t, $J = 7.3$ Hz, 3 H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 169.8, 143.5, 140.6, 135.4, 131.0, 130.9, 130.2, 128.9, 127.8, 127.4,
127.1, 126.6, 121.5, 90.3, 86.9, 49.6, 43.1, 35.7, 31.7, 26.0, 25.9, 25.7, 25.4, 24.6, 14.0, 13.9; IR (film) 1742 cm\(^{-1}\). MS (ESI+) 606.2395 \(\text{calcd for } C_{33}H_{38}BBrO_4, M + NH_4^+\).

\(1R,2S,2'R,3'S\)-2-phenylcyclohexyl-2’-benzyl-5’-butyl-3’-styryl-3’-methyl-4’,6’-dioxa-5’-borolane-4’-carboxylate (4-13). General procedure 1 was employed to transform \((-\)-(1R,2S)-2-phenylcyclohexyl-2’-benzyl(2,3-dihydro-1H-inden-1-yl)acetate (50 mg, 0.154 mmol) to form boronate ester 4-13 using dibutylboron triflate solution (0.49 mL) and benzylideneacetone (33.8 mg, 0.231 mmol). This procedure afforded 45.7 mg (55\%) of the title compound as a yellow oil. The diastereoselectivity of the transformation could not be determined through \(^1\)H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta 7.45–7.33\) (m, 4 H), 7.34–7.25 (m, 4 H), 7.28–7.14 (m, 7 H), 6.58 (d, \(J = 15.9\) Hz, 1 H), 5.85 (d, \(J = 15.9\) Hz, 1 H), 4.92 (td, \(J = 10.9, 4.3\) Hz, 1 H), 2.91 (d, \(J = 14.4\) Hz, 1 H), 2.79–2.75 (m, 2 H), 1.96–1.92 (m, 2 H), 1.76 (d, \(J = 12.3\) Hz, 2 H), 1.62–1.26 (m, 6 H), 1.00–0.94 (m, 1 H), 0.96–0.85 (m, 6 H), 0.51 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 169.5, 143.5, 136.6, 135.8, 130.2, 129.0, 128.9, 128.8, 128.6, 127.9, 127.8, 127.6, 127.1, 126.7, 126.6, 89.6, 85.4, 78.9, 49.8, 42.1, 34.6, 31.8, 29.7, 26.0, 25.7, 25.4, 24.6, 23.7, 13.9; IR (film) 1750 cm\(^{-1}\). MS (ESI) 554.3443 (554.3436 \text{calcd for } C_{35}H_{41}BO_4, M + H\(^+\)).

\(1R,2S,2'R,3'S\)-2-phenylcyclohexyl-2’-benzyl-5’-butyl-3’-phenethyl-3’-methyl-4’,6’-dioxa-5’-borolane-4’-carboxylate (4-14). General procedure 1 was employed to transform \(-\)-(1R,2S)-2-phenylcyclohexyl-2’-(benzyl oxy)acetate (50 mg, 0.154 mmol) to
form boronate ester 4-14 using dibutylboron triflate solution (0.49 mL) and benzylacetone (35 µL, 0.231 mmol). This procedure afforded 43.9 mg (53%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 4:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.34–7.13 (m, 14 H), 7.14–6.95 (m, 14 H), 4.87 (td, J = 10.9, 4.3 Hz, 1 H), 2.98 (d, J = 14.0 Hz, 1 H), 2.93–2.86 (m, 1 H), 2.70–2.59 (m, 2 H), 2.41 (td, J = 13.0, 5.4 Hz, 1 H), 1.93–1.79 (m, 4 H), 1.79 (dt, J = 12.3, 3.8 Hz, 1 H), 1.63–1.38 (m, 10 H), 1.06–0.97 (m, 1 H), 0.97–0.81 (m, 3 H), 0.36 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.5, 143.6, 142.3, 135.8, 130.3, 128.7, 128.5, 128.4, 128.0, 127.6, 126.8, 126.7, 126.0, 89.9, 84.7, 78.6, 49.7, 39.7, 37.4, 34.7, 31.8, 30.0, 29.7, 26.0, 25.7, 25.4, 24.6, 20.9, 13.9; IR (film) 1751 cm$^{-1}$. MS (ESI) 556.3604 (556.3593 calcd for C$_{35}$H$_{43}$BO$_4$, M + NH$_4^+$).

(1R,2S,2'R,3'S)-2-phenylcyclohexyl-2'-benzyl-5'-butyl-3'-propyl-3'-methyl-4',6'-dioxa-5'-borolane-4'-carboxylate (4-15). General procedure 1 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (50 mg, 0.154 mmol) to form boronate ester 4-15 using dibutylboron triflate solution (0.49 mL) and 2-pentanone (25 µL, 0.231 mmol). This procedure afforded 35 mg (48%) of the title compound as a white solid m.p. 54–60 ºC. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 3:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.30–7.11 (m, 10 H), 4.78 (dt, J = 30.0, 10.8 Hz, 1 H), 3.00 (d, J = 20.6 Hz, 1 H), 2.86 (d, J = 14.0 Hz, 1 H), 2.73–2.64 (m, 1 H), 1.99–1.83 (m, 2 H), 1.76–1.69 (m, 2 H), 1.57–1.17 (m, 13 H), 1.40–1.07 (m, 1 H), 0.98–0.80 (m, 6 H), 0.27 (s, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 169.5, 143.5, 135.9, 130.3, 128.6, 128.0, 127.5, 126.8, 126.7, 89.8, 85.0, 78.7, 49.7,
39.7, 37.4, 34.5, 31.8, 26.0, 25.7, 25.4, 24.6, 21.1, 16.9, 14.5, 13.9; IR (film) 1752 cm⁻¹. MS (ESI+) 494.3447 (494.3436 calcd for C₃₀H₄₁BO₄, M + NH₄⁺).

(1R,2S,2'R)-2-phenylcyclohexyl-2'-benzyl-5'-butyl-3',3'-dimethyl-4',6'-dioxo-5'-borolane-4'-carboxylate (4-16). General procedure 1 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (50 mg, 0.154 mmol) to form boronate ester 4-16 using dibutylboron triflate solution (0.49 mL) and acetone (17 µL, 0.231 mmol). This procedure afforded 33.8 mg (49%) of the title compound as a white solid, mp 90–93 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.17 (m, 10 H), 4.80 (td, J = 10.8, 4.2 Hz, 1 H), 2.97 (d, J = 14.2 Hz, 1 H), 2.90 (d, J = 14.2 Hz, 1 H), 2.67 (dd, J = 12.4, 10.9 Hz, 1 H), 1.95–1.82 (m, 2 H), 1.73 (d, J = 13.4 Hz, 2 H), 1.58–1.44 (m, 1 H), 1.44–1.24 (m, 6 H), 1.11 (s, 3 H), 1.15–0.99 (m, 1 H), 1.01–0.74 (m, 5 H), 0.35 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 169.7, 143.4, 136.0, 130.2, 128.6, 128.0, 127.6, 126.8, 126.7, 89.1, 83.2, 78.9, 49.7, 40.1, 34.3, 31.7, 26.0, 25.7, 25.4, 24.7, 24.5, 23.4, 13.9; IR (film) 1738 cm⁻¹. MS (ESI) 466.3132 (466.3123 calcd for C₂₈H₃₇BO₄, M + NH₄⁺).

(1R,2S,2'R)-2-phenylcyclohexyl-4'-benzyl-5'-butyl-4',6'-dioxo-5'-boraspiro[4.4]nonane-4'-carboxylate (4-17). General procedure 1 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (50 mg, 0.154 mmol) to form boronate ester 4-17 using dibutylboron triflate solution (0.49 mL) and cyclopentanone (20.5 µL, 0.231 mmol). This procedure afforded 34 mg (46%) of the title compound as a white solid, mp 84–85 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.18 (m, 10 H), 4.81 (td, J = 10.8, 4.2 Hz, 1 H), 3.01 (d, J = 14.3 Hz, 1 H), 2.94 (d, J = 14.3 Hz, 1 H), 2.66 (dd, J = 12.3, 10.8 Hz, 1 H), 1.94–1.83 (m, 2 H), 1.72 (d, J = 13.4 Hz, 2 H), 1.69–1.61 (m, 2 H), 1.63–1.43 (m, 1 H), 1.54–1.28 (m, 8 H), 1.16–1.00 (m, 4 H), 1.02–
(1R,2S,2'R,3'S)-2-Phenylcyclohexyl-2'-benzyl-3'-phenyl-2',3'-dihydroxybutanoate (4-27). General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (100 mg, 0.308 mmol) to form diol 4-27 using dibutylboron triflate solution (1.0 mL) and acetophenone (54 µL, 0.462 mmol). This procedure afforded 75 mg (48%) of the title compound as a white foam, mp 48–50 °C. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.47 (t, $J = 7.7$ Hz, 2 H), 7.34 (t, $J = 7.3$ Hz, 1 H), 7.32–7.23 (m, 4 H), 7.20–7.15 (m, 4 H), 7.13–7.11 (m, 2 H), 6.70–6.66 (m, 2 H), 4.53 (td, $J = 10.7$, 4.0 Hz, 1 H), 3.34–3.27 (m, 2 H), 3.14 (d, $J = 14.1$ Hz, 1 H), 2.84 (s, br, 1 H), 2.71 (dd, $J = 12.3$, 10.7 Hz, 1 H), 1.91 (d, $J = 13.8$ Hz, 1 H), 1.73–1.67 (m, 1 H), 1.61–1.50 (m, 6 H), 1.32–1.17 (m, 2 H), 0.80–0.71 (m, 1 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.4, 143.4, 143.1, 136.4, 130.5, 129.2, 127.9, 127.6, 127.5, 127.4, 126.9, 126.6, 125.7, 82.3, 81.3, 77.4, 49.4, 38.4, 34.0, 30.8, 25.6, 24.4, 23.1; IR (film) 3560, 3506, 1726 cm$^{-1}$. MS (ESI) 467.2188 (467.2193 calcd for C$_{29}$H$_{32}$O$_4$, M + Na$^+$).
using dibutylboron triflate solution (0.74 mL) and p-methylacetophenone (31 µL, 0.231 mmol). This procedure afforded 43.7 mg (41%) of the title compound as a white foam, mp 52–56 °C. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 17:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.49–7.46 (m, 2 H), 7.37–7.26 (m, 5 H), 7.23–7.12 (m, 3 H), 6.91 (d, $J$ = 7.9 Hz, 2 H), 6.50 (d, $J$ = 7.9 Hz, 2 H), 4.52 (td, $J$ = 10.7, 3.9 Hz, 1 H), 3.34–3.26 (m, 2 H), 3.12 (d, $J$ = 14.1 Hz, 1 H), 2.75–2.66 (m, 2 H), 2.27 (s, 3 H), 1.91 (d, $J$ = 13.8 Hz, 1 H), 1.71 (d, $J$ = 12.6 Hz, 1 H), 1.61–1.53 (m, 3 H), 1.47 (s, 3 H), 1.31–1.17 (m, 3 H), 0.75–0.72 (m, 1 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 173.5, 143.1, 140.4, 136.5, 136.4, 130.5, 129.2, 128.2, 127.9, 127.6, 127.5, 126.6, 125.5, 82.4, 81.3, 77.3, 49.4, 38.3, 33.9, 30.8, 25.6, 24.4, 23.1, 21.0; IR (film) 3561, 3506, 1725 cm$^{-1}$. MS (ESI) 476.2794 (476.2795 calcd for C$_{30}$H$_{34}$O$_4$, M + NH$_4^+$).

(1R,2S,2'R,3'S)-2-Phenylcyclohexyl-2'-benzyl-3'-(p-bromophenyl)-2',3'-dihydroxybutanoate (4-20). General procedure 2 was employed to convert boronate ester 4-12 (41.5 mg, 0.077 mmol) to the title compound. This procedure afforded 12.4 mg (34%) of the title compound.

General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzylloxy)acetate (50 mg, 0.154 mmol) to form diol 4-20 using dibutylboron triflate solution (0.49 mL) and p-bromoacetophenone (30.7 mg, 0.154 mmol). This procedure afforded 34.3 mg (42%) of the title compound as a white solid, mp 119–124 °C. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.49–7.42 (m, 2 H), 7.38–7.22 (m, 1 H), 7.23–7.14 (m, 4 H), 7.20–7.17 (m, 5 H), 6.50 (d, $J$ = 8.2 Hz, 2 H), 4.54 (td, $J$ = 10.7, 3.9 Hz, 1
H), 3.33 (s, br, 1 H), 3.26 (d, J = 14.1 Hz, 1 H), 3.12 (d, J = 14.1 Hz, 1 H), 2.81 (s, br, 1 H), 2.71 (dd, J = 12.3, 10.7 Hz, 1 H), 1.91 (d, J = 13.8 Hz, 1 H), 1.65–1.58 (m, 1 H), 1.58–1.48 (m, 3 H), 1.44 (s, 3 H), 1.27–1.24 (m, 2 H), 0.91–0.77 (m, 1 H); \textsuperscript{13}C NMR (175 MHz, CDCl\textsubscript{3}) \textsuperscript{δ} 173.3, 143.1, 142.6, 136.1, 130.4, 129.3, 127.9, 127.7, 127.6, 126.8, 121.2, 82.0, 81.6, 76.8, 49.4, 38.4, 34.0, 31.0, 25.5, 24.4, 23.2; IR (film) 3555, 3501, 1726 cm\textsuperscript{−1}. MS (ESI) 540.1742 (540.1744 calcd for C\textsubscript{29}H\textsubscript{31}BrO\textsubscript{4}, M + \textsubscript{NH\textsubscript{4}}\textsuperscript{+}).

(1R,2S,2'R,3'S)-2-Phenylcyclohexyl-2'-benzyl-3'-methyl-5'-phenyl-2',3'-dihydroxypent-4'-enoate (4-21). General procedure 2 was employed to convert boronate ester 4-13 (41.2 mg, 0.077 mmol) to the title compound. This procedure afforded 25.4 mg (70%) of the title compound.

General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (75 mg, 0.231 mmol) to form diol 4-21 using dibutylboron triflate solution (0.75 mL) and benzylideneacetone (50.8 mg, 0.347 mmol). This procedure afforded 62.9 mg (58%) of the title compound as a white foam, mp 46–50 °C. The diastereoselectivity of the transformation could not be determined through \textsuperscript{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) \textsuperscript{δ} 7.35 (t, J = 7.6 Hz, 2 H), 7.34–7.15 (m, 13 H), 6.28 (d, J = 16.0 Hz, 1 H), 5.96 (d, J= 16.0 Hz, 1 H), 4.97 (td, J = 10.8, 4.2 Hz, 1 H), 3.54 (s, br, 1 H), 3.10 (d, J = 14.1 Hz, 1 H), 3.05 (d, J = 14.1 Hz, 1 H), 2.80 (dd, J = 12.3, 10.9 Hz, 1 H), 2.34 (s, br, 1H), 1.94 (d, J = 14.0 Hz, 1 H), 1.90–1.85 (m, 1 H), 1.81–1.71 (m, 2 H), 1.52–1.36 (m, 4H), 0.88–0.80 (m, 3 H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) \textsuperscript{δ} 171.1, 142.9, 137.3, 136.2, 131.8, 130.5, 129.2, 128.5, 128.4, 127.8, 127.3, 127.3, 127.2, 126.7, 126.6, 81.5, 80.1, 75.8, 49.8, 38.3, 35.1, 31.9, 31.8, 29.7, 25.6, 24.6, 22.8, 14.1; IR (film) 3549, 1715 cm\textsuperscript{−1}. MS (ESI+) 488.2791 (488.2795 calcd for C\textsubscript{31}H\textsubscript{34}O\textsubscript{4}, M + \textsubscript{NH\textsubscript{4}}\textsuperscript{+}).
(1R,2S,2’R,3’S)-2-Phenylcyclohexyl-2’-benzyl-3’-methyl-5’-phenyl-2’,3’-dihydroxypentanoate (4-22). General procedure 2 was employed to convert boronate ester 4-14 (36.9 mg, 0.069 mmol) to the title compound. This procedure afforded 23.4 mg (72%) of the title compound.

General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2’-(benzyloxy)acetate (50 mg, 0.154 mmol) to form diol 4-22 using dibutylboron triflate solution (0.49 mL) and benzylacetone (35 µL, 0.231 mmol). This procedure afforded 35.8 mg (43%) of the title compound as a white solid, mp 99–104 °C. The diastereoselectivity of the transformation could not be determined through 1H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. 1H NMR (700 MHz, CDCl3) δ 7.34–7.13 (m, 15 H), 4.99 (td, J = 10.8, 4.2 Hz, 1 H), 3.45 (s, br, 1 H), 3.16 (d, J = 13.7 Hz, 1 H), 3.05 (d, J = 13.7 Hz, 1 H), 2.39 (dd, J = 9.7, 7.6 Hz, 2 H), 1.93–1.87 (m, 2 H), 1.81–1.74 (m, 3 H), 1.71–1.66 (m, 1 H), 1.46–1.27 (m, 5 H), 1.18–1.09 (m, 1 H), 0.83 (s, 3 H); 13C NMR (176 MHz, CDCl3) δ 174.4, 142.9, 142.6, 136.3, 130.6, 129.2, 128.3, 128.2, 127.8, 127.2, 127.1, 126.6, 125.6, 82.3, 80.0, 75.3, 49.8, 37.9, 37.6, 35.0, 32.0, 29.4, 25.6, 24.6, 19.4; IR (film) 3561, 3502, 1715 cm⁻¹. MS (ESI) 495.2904 (495.2506 calcd for C₃₁H₃₆O₄, M + Na⁺).

(1R,2S,2’R,3’S)-2-Phenylcyclohexyl-2’-benzyl-3’-methyl-2’,3’-dihydroxyhexanoate (4-23). General procedure 2 was employed to convert 4-15 (31.0 mg, 0.065 mmol) to the title compound. This procedure afforded 16.8 mg (63%) of the title compound.

General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2’-(benzyloxy)acetate (64.8 mg, 0.2 mmol) to form diol 4-22 using dibutylboron triflate
solution (0.64 mL) and 2-pentanone (21 µL, 0.2 mmol). This procedure afforded 43.0 mg (52%) of the title compound as a white solid, mp 125–128 °C. The diastereoselectivity of the transformation could not be determined through \(^1\)H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 4:1 dr following purification. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36–7.24 (m, 2 H), 7.28–7.12 (m, 8 H), 5.05–4.87 (m, 1 H), 3.37 (s, br, 1 H), 3.16 (d, \(J = 13.8\) Hz, 1 H), 3.11–2.95 (m, 1 H), 2.83–2.71 (m, 1 H), 1.98–1.87 (m, 1 H), 1.89–1.70 (m, 3 H), 1.56 (d, \(J = 6.8\) Hz, 1 H), 1.55–1.14 (m, 5 H), 1.10–0.89 (m, 2 H), 0.79–0.64 (m, 6 H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 174.7, 143.0, 136.5, 130.6, 129.1, 127.8, 127.7, 127.2, 127.1, 126.6, 82.4, 80.2, 75.4, 49.8, 38.7, 37.6, 34.9, 32.0, 25.6, 24.6, 19.2, 16.3, 14.5; IR (film) 3552, 1713, 1259 cm\(^{-1}\). MS (ESI+) 433.2347 (433.2349 calcd for C\(_{26}\)H\(_{34}\)O\(_4\), M + H\(^+\)).

(1R,2S,2’R)-2-Phenylcyclohexyl-2’-benzyl-3’-methyl-2’,3’-dihydroxybutanoate (4-23). General procedure 2 was employed to convert 4-16 (28 mg, 0.062 mmol) to the title compound. This procedure afforded 19.6 mg (82%) of the title compound. General procedure 3 was employed to transform (–)-(1R,2S)-2-phenylcyclohexyl-2’-(benzyloxy)acetate (50 mg, 0.154 mmol) to form diol 4-24 using dibutylboron triflate solution (0.49 mL) and acetone (11 µL, 0.154 mmol). This procedure afforded 35.3 mg (60%) of the title compound as a white solid, mp 116–121 °C. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.32 (t, \(J = 7.6\) Hz, 2 H), 7.19–7.26 (m, 8 H), 5.01 (dt, \(J = 4.2\), 10.5 Hz, 1 H), 3.36 (s, 1 H), 3.15 (d, \(J = 13.7\) Hz, 1 H), 2.99 (d, \(J = 13.9\) Hz, 1 H), 2.78 (dt, \(J = 3.6\), 11.3 Hz, 1 H), 1.95 (d, \(J = 13.7\) Hz, 1 H), 1.75–1.88 (m, 4 H), 1.26–1.51 (m, 4 H), 0.83 (s, 3 H), 0.60 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.6, 142.9, 136.4, 130.6, 129.2, 127.8, 127.3, 126.6, 81.8, 79.9, 73.3, 49.9, 37.8, 34.9, 32.1, 25.6, 24.7, 24.2, 23.6; IR (film) 3549, 3406, 1724 cm\(^{-1}\). MS (ESI) 405.2030 (405.2036 calcd for C\(_{24}\)H\(_{30}\)O\(_4\), M + Na\(^+\)).
(1R,2S,2’R)-2-Phenylcyclohexyl-2’-benzyl-3’-cyclohexyl-2’,3’-dihydroxypropanoate (4-25). General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2’-(benzyl)acetate (75 mg, 0.231 mmol) to form diol 4-25 using dibutylboron triflate solution (0.74 mL) and cyclohexanone (24 µL, 0.231 mmol). This procedure afforded 23.7 mg (24%) of the title compound as a white solid, mp 159–160 °C. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.33 (t, \(J = 7.6\) Hz, 2 H), 7.29–7.15 (m, 8 H), 4.94 (td, \(J = 10.9, 3.9\) Hz, 1 H), 3.37 (s, br, 1 H), 3.17 (d, \(J = 13.9\) Hz, 1 H), 2.96 (d, \(J = 13.8\) Hz, 1 H), 2.80–2.73 (m, 1 H), 1.93 (d, \(J = 14.2\) Hz, 1 H), 1.81–1.71 (m, 3 H), 1.54 (d, \(J = 9.9\) Hz, 1 H), 1.50–1.41 (m, 2 H), 1.41–1.31 (m, 4 H), 1.32–1.22 (m, 3 H), 1.11 (d, \(J = 13.2\) Hz, 1 H), 0.96 (q, \(J = 13.3\) Hz, 1 H), 0.86–0.82 (m, 1 H), 0.25–0.20 (m, 1 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.8, 142.9, 136.4, 130.5, 129.3, 127.8, 127.3, 127.2, 126.6, 84.6, 80.2, 79.9, 49.8, 39.1, 34.8, 33.5, 32.1, 25.6, 24.7, 23.6, 23.5; IR (film) 3546, 3376, 1726 cm\(^{-1}\). MS (ESI) 445.2348 (445.2349 calcd for C\(_{27}\)H\(_{34}\)O\(_4\), M + Na\(^+\)).

(1R,2S,2’R)-2-Phenylcyclohexyl-2’-benzyl-3’-cyclopentyl-2’,3’-dihydroxypropanoate (4-25). General procedure 2 was employed to boronate ester 4-18 (34.0 mg, 0.072 mmol) to the title compound. This procedure afforded 15.6 mg (53%) of the title compound as a white solid, mp X–X. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.33 (t, \(J = 7.5\) Hz, 2 H), 7.24–7.19 (m, 8 H), 4.97 (td, \(J = 10.6, 4.4\) Hz, 1 H), 3.33–3.24 (m, 2 H), 2.88 (d, \(J = 14.0\) Hz, 1 H), 2.78 (td, \(J = 11.6, 3.8\) Hz, 1 H), 2.04–1.26 (m, 12 H), 0.91–0.79 (m, 4 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.8, 142.9, 136.4, 130.5, 129.3, 127.8, 127.3, 127.2, 126.6, 84.6, 80.2, 79.9, 49.8, 39.1, 34.8, 33.5, 32.1, 25.6, 24.7, 23.6, 23.5; IR (film) 3538, 1728, 1186 cm\(^{-1}\). MS (ESI+) 421.2193 (421.2193 calcd for C\(_{26}\)H\(_{32}\)O\(_4\), M + Na\(^+\)).
(1R,2S,2'R,3'S)-2-Phenylcyclohexyl-2'-benzyl-3'-(m-fluorophenyl)-2',3'-dihydroxybutanoate (4-29). General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(benzyl oxy)acetate (75 mg, 0.230 mmol) to form diol 4-29 using dibutylboron triflate solution (0.74 mL) and m-fluoroacetophenone (28 µL, 0.154 mmol). This procedure afforded 21.5 mg (20%) of the title compound as a white foam, mp 46–51 °C. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 15:1 dr following purification. $^1$H NMR (700 MHz, CDCl$_3$) 7.44 (t, $J = 7.7$ Hz, 2 H), 7.36–7.28 (m, 1 H), 7.29–7.13 (m, 7 H), 7.14–7.01 (m, 1 H), 6.85 (t, $J = 8.39$ Hz, 1 H), 6.66–6.58 (m, 1 H), 6.44 (d, $J = 7.8$ Hz, 1 H), 4.54 (td, $J = 10.8, 4.0$ Hz, 1 H), 3.30 (s, br, 1 H), 3.25 (d, $J = 14.1$ Hz, 1 H), 3.11 (d, $J = 14.1$ Hz, 1 H), 2.79 (s, br, 1 H), 2.69 (dd, $J = 12.3, 10.7$ Hz, 1 H), 1.90 (dt, $J = 13.4, 3.0$ Hz, 1 H), 1.72–1.54 (m, 3 H), 1.57–1.48 (m, 1 H), 1.44 (d, $J = 0.9$ Hz, 3 H), 1.33–1.17 (m, 2 H), 0.83–0.72 (m, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.2, 162.1 (d, $J = 244$ Hz), 146.4 (d, $J = 6.8$ Hz), 142.8, 136.1, 130.4, 129.4, 128.9, 128.8, 127.9, 127.5 (d, $J = 6.8$ Hz), 126.7, 121.3 (d, $J = 2.7$ Hz), 113.8 (d, $J = 21.1$ Hz), 113.3 (d, $J = 22.4$ Hz), 82.1, 81.4, 49.5, 38.5, 34.0, 30.9, 25.5, 24.4, 23.2 (one signal absent due to incidental equivalence); IR (film) 3555, 3454, 1726 cm$^{-1}$. MS (ESI) 480.2545 (480.2545 calcd for C$_{29}$H$_{31}$FO$_4$, M + NH$_4^+$).

(1R,2S,2'R,3'S)-2-Phenylcyclohexyl-2'-allyl-3'-(p-bromophenyl)-2',3'-dihydroxybutanoate (4-30). General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2'-(allyloxy)acetate (75 mg, 0.231 mmol) to form diol 4-30 using dibutylboron triflate solution (0.74 mL) and p-bromoacetophenone (54.4 mg, 0.231 mmol). This procedure afforded 19.7 mg (15%) of the title compound as a white solid,
mp 129–134 °C. The diastereoselectivity of the transformation could not be determined through \(^1\)H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 10:1 dr following purification. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.40 (t, \(J = 7.6\) Hz, 2 H), 7.35–7.29 (m, 1 H), 7.31–7.22 (m, 3 H), 7.21–7.14 (m, 1 H), 6.72 (d, \(J = 8.2\) Hz, 2 H), 5.21–5.16 (m, 1 H), 5.08–5.00 (m, 1 H), 4.93–4.88 (m, 1 H), 4.77 (td, \(J = 10.9, 4.3\) Hz, 1 H), 3.20 (s, br, 1 H), 3.09 (s, br, 1 H), 2.72–2.65 (m, 2 H), 2.46–2.39 (m, 1 H), 2.01–1.89 (m, 1 H), 1.92–1.84 (m, 1 H), 1.82–1.71 (m, 2 H), 1.59–1.48 (m, 1 H), 1.37 (s, 3 H), 1.41–1.23 (m, 2 H), 1.12–1.05 (m, 1 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 173.7, 142.9, 132.6, 129.1, 127.9, 127.5, 127.3, 121.1, 119.7, 80.9, 80.2, 76.7, 49.4, 38.0, 34.2, 31.7, 25.5, 24.5, 23.1; IR (film) 3546, 3387, 1724 cm\(^{-1}\). MS (ESI) 495.1133 (495.1141 calcd for C\(_{25}\)H\(_{29}\)BrO\(_4\), M + Na\(^+\)).

(1R,2S,2′R)-2-Phenylcyclohexyl-2′-allyl-3′-cyclohexyl-2′,3′-dihydroxybutanoate (4-31). General procedure 3 was employed to transform (−)-(1R,2S)-2-phenylcyclohexyl-2′-(allyloxy)acetate (82 mg, 0.299 mmol) to form diol 4-31 using dibutylboron triflate solution (0.96 mL) and cyclohexanone (31 µL, 0.299 mmol). This procedure afforded 17.7 mg (16%) of the title compound as a white solid, mp 128–130 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.32 (t, \(J = 7.6\) Hz, 2 H), 7.30–7.13 (m, 3 H), 5.62–5.56 (m, 1 H), 5.15–5.00 (m, 3 H), 3.32 (s, br, 1 H), 2.74 (dd, \(J = 12.3\), 10.9 Hz, 1 H), 2.61 (dd, \(J = 13.9, 8.2\) Hz, 1 H), 2.39 (dd, \(J = 14.0, 6.1\) Hz, 1 H), 2.18 (d, \(J = 12.4\) Hz, 1 H), 2.00–1.90 (m, 1 H), 1.87 (d, \(J = 11.8\) Hz, 1 H), 1.83–1.74 (m, 1 H), 1.57–1.29 (m, 6 H), 1.30–0.97 (m, 3 H), 0.92–0.72 (m, 2 H), 0.35 (d, \(J = 13.2\) Hz, 1 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 175.0, 142.9, 132.6, 129.1, 127.2, 127.1, 119.0, 81.5, 79.2, 73.9, 49.8, 36.2, 34.8, 32.2, 31.3, 29.8, 25.6, 25.2, 24.6, 21.6, 21.2; IR (film) 3557, 3498, 1726 cm\(^{-1}\). MS (ESI) 395.2198 (395.2193 calcd for C\(_{23}\)H\(_{32}\)O\(_4\), M + Na\(^+\)).

4.8 References