Transition Metal-Catalyzed Carbon-Carbon/Carbon-Heteroatom Bond Formation Reactions Utilizing Strained Ring Systems

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Chemistry
University of Toronto

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TRANSITION METAL-CATALYZED CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION REACTIONS UTILIZING STRAINED RING SYSTEMS

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ABSTRACT

This thesis focuses on the development of carbon-carbon/carbon-heteroatom bond forming reactions using strained ring systems under transition metal catalysis. The first chapter describes the use of bifunctional organoboron reagents with a rhodium catalyst to synthesize carbocycles through a cascade sequence. The reaction of norbornene derivatives gives vinylcyclopropane and cyclopentene products in moderate to good yield. The mechanistic proposal and insights into the reaction mechanism are presented. Preliminary results from studies toward an enantioselective sequential addition/cyclization process are described. The methodology is subsequently applied in the synthesis of a variety of polycyclic heteroaromatics using bifunctional heteroaryl boronate esters.

The second chapter describes studies toward the formation of carbon-heteroatom bonds using cyclopropane derivatives. Under a recently developed Pd(OAc)$_2$/PhI(OAc)$_2$ catalytic system, methylenecyclopropanes are isomerized to substituted pyridines via a sequential fragmentation/cyclization process. Under same reaction conditions, allylic acetate products are obtained from the isomerization of cyclopropanes through a similar process.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>amphos</td>
<td>1-dialkylphosphino-2-(N,N,N-trimethylammonium)ethane</td>
</tr>
<tr>
<td>Anal.</td>
<td>analysis</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1’-carbonyldiimidazole</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>decomp.</td>
<td>decomposition</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppb</td>
<td>1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1’-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>FG</td>
<td>functional group</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
</tr>
<tr>
<td>IMes</td>
<td>(N,N^{\prime})-bis(mesityl)imidazol-2-ylidene</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>M</td>
<td>generic metal</td>
</tr>
<tr>
<td>MCP</td>
<td>methylenecyclopropane or methylenecyclopropyl</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>μwave</td>
<td>microwave</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>n</td>
<td>normal</td>
</tr>
<tr>
<td>NMP</td>
<td>1-methyl-2-pyrrolidinone</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>N.R.</td>
<td>no reaction</td>
</tr>
<tr>
<td>OAc</td>
<td>acetate</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak Ridge Thermal Ellipsoid Plotting</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pin</td>
<td>pinacolate</td>
</tr>
<tr>
<td>PMB</td>
<td>(\text{para})-methoxybenzyl</td>
</tr>
<tr>
<td>PTSA</td>
<td>(\text{para})-toluene sulfonic acid</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>R</td>
<td>generic alkyl group</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor</td>
</tr>
<tr>
<td>S_N2’</td>
<td>nucleophilic substitution with allylic rearrangement</td>
</tr>
<tr>
<td>t</td>
<td>tert</td>
</tr>
<tr>
<td>TBS</td>
<td>(\text{tert})-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>(N,N^{\prime},N^{\prime})-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane or trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>tolyl</td>
</tr>
<tr>
<td>TPPDS</td>
<td>bis(p-sulfonatophenyl)phenylphosphine</td>
</tr>
<tr>
<td>Ts</td>
<td>(\text{para})-toluenesulfonyl</td>
</tr>
</tbody>
</table>
1.0 FORMATION OF CARBOCYCLES VIA A RHODIUM-CATALYZED CASCADE ADDITION/CYCLIZATION SEQUENCE USING BIFUNCTIONAL ORGANOBORONATE ESTERS WITH STRAINED ALKENES

1.1 INTRODUCTION

1.1.1 Rhodium Catalysis in Aqueous Media

The development of new methods for carbon-carbon bond formation is a prime topic in organic chemistry. In the past three decades, tremendous effort has been devoted into the transition-metal catalyzed cross coupling reactions, which permits the formation of carbon-carbon or carbon-heteroatom bonds in a way that is not accessible through traditional methods. In addition to the widely-used palladium-based catalysts, increased attention has been paid to the development of new reactions using rhodium catalysts in recent years. One of the advantages for rhodium catalysis is that water is commonly used as cosolvent or even the sole solvent in some cases, which allows the possibility for tuning these reactions into reduced environmental impact processes.

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Because rhodium tends to show novel and complementary reactivity to commonly used metals such as palladium, nickel, and platinum, much interest has been focused on rhodium-catalyzed carbon-carbon bond forming reactions, particularly with organometallic reagents. Reagents used in palladium chemistry such as boronates,\textsuperscript{6} stannanes,\textsuperscript{7} zincates,\textsuperscript{8} and silane/siloxanes\textsuperscript{9} could also be applied with rhodium catalyst. However, these organometallic reagents may generate novel products or give different selectivities due to the unique characteristics of rhodium. This difference in reactivity becomes clear if we compare the generalized catalytic cycles of rhodium with other metal catalyst.

Group 10 metals undergo catalytic reactions between the oxidation states of (0) and (II) (Scheme 1.1.1).\textsuperscript{10,4b} The cycle begins with oxidative addition of an aryl halide to a metal(0) to form the organometal(II) B. The transmetallation only occurs with the metal(II) species and produces the Ar-M\textsuperscript{II}-Ar’ complex C, which undergoes subsequent reductive elimination to give the coupled product Ar-Ar’ and regenerates the metal(0) catalyst.

In contrast, when reacting with organometallic reagents, rhodium and iridium shuttle between oxidation state (I) and (III) in the catalytic cycles. As a result, transmetallation can theoretically occur at either stage since no pre-oxidation of the metal catalyst is required. In the generalized catalytic cycle (Scheme 1.1.2), metal complex B is generated from transmetallation with the metal(I) catalyst. Complex B can undergo carbometallation with an unsaturated functional group to afford intermediate C while remaining the metal(I) state. Alternatively, oxidative insertion to an aryl halide can occur to afford metal(III) species D. Metal catalyst A can be regenerated from D after reductive elimination or from the protodemetallation of intermediate C.
Catalytic demetallation of organometallic reagents is one of the common side reactions associated with rhodium catalysis in protic solvent systems.\textsuperscript{11} This unproductive pathway is due to the higher reactivity of the rhodium-carbon bond toward the protolytic cleavage process compared to the parent organometallic compounds. In order to achieve high conversion, a excess amount of organometallic reagent may be required. The protolytic cleavage process is believed to proceed through an oxidative addition/reductive elimination sequence. This type of reaction has been observed using rhodium-hydride complexes with water or D\textsubscript{2}O and can also be applied to introduce deuterium in organic molecules.\textsuperscript{12}

Several research groups have utilized organorhodium intermediates, generated from different organometallic precursors,\textsuperscript{13} to add to unsaturated functional groups such as


\textsuperscript{13} For examples using boron reagents, see: a) Sakai, M.; Hayashi, H.; Miyaura, N. \textit{Organometallics} \textbf{1997},
activated alkenes, alkynes, aldehydes, and imines. Several selected examples of these reactions will be presented in following sections.

1.1.2 Rhodium-Catalyzed Conjugate Addition

Conjugate addition of organometallic reagents to activated alkenes is an important processes in organic synthesis. Organometallics such as organolithiums, organomagnesiums, and organozincs were employed in the presence of a copper catalyst to afford the desired conjugate adduct. However, due to the high reactivities of these organometallics, noncatalyzed 1,2-addition is common side reaction. In addition, the introduced organic groups are usually restricted to primary alkyl groups with limited functional tolerance.

In 1997, Miyaura and co-workers reported a conjugate addition reaction of aryl boronic acids to α,β-unsaturated ketones and aldehydes under rhodium catalysis (Scheme 1.1.3). Excellent yields were obtained using a bidentate phosphine ligand with a large bite angles and the presence of water was required to achieve high reactivity. This pioneering work demonstrated several advantages over the copper-catalyzed conjugate

addition reactions. For instance, using a less reactive aryl boronic acid significantly reduced the noncatalyzed background reactions and demonstrated wide functional group compatibility. In addition, organoboron reagents are generally non-toxic, relatively stable against air and moisture, and widely available from various commercial suppliers.\textsuperscript{19} Furthermore, this method allows for the introduction of aryl nucleophiles, which is not possible with copper catalysis.

\begin{center}
\textbf{Scheme 1.1.3 Rhodium-catalyzed 1,4-addition with aryl boronic acids}
\end{center}

\begin{align*}
\text{RC} = R + \text{ArB(OH)}_2 & \xrightarrow{\text{Rh(acac)(CO)}_2 (3 \text{ mol\%})} \text{Rh(acac)(CO)}_2 \\
& \xrightarrow{\text{dppb (3 mol\%)} \text{ MeOH/H}_2\text{O (6:1)}} \xrightarrow{50 ^\circ\text{C}, 16 \text{ h}} \text{ArCR} \\
R = & \text{Me, Ar = Ph; 99\%} \\
R = & \text{Me, Ar = (4-MeO)C}_6\text{H}_4; 86\% \\
R = & \text{H, Ar = Ph; 59\%}
\end{align*}

Soon after the initial report, Hayashi and Miyaura reported the first asymmetric version of the conjugate addition reaction (Scheme 1.1.4).\textsuperscript{20} The bidentate ligand (S)-BINAP was used to introduce chiral information, using Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} as catalyst precursor in dioxane / water with elevated reaction temperature. A change of rhodium source from Rh(acac)(CO)\textsubscript{2} to Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} was required to increase the rate of ligand exchange which facilitated the in situ formation of the rhodium-BINAP complex.

Scheme 1.1.4 Asymmetric variation of rhodium-catalyzed 1,4-addition reactions

\[
\text{O} \quad \text{+ ArB(OH)}_2 \quad \xrightarrow{\text{Rh(acac)}(\text{C}_2\text{H}_4)_2 \quad (3 \text{ mol\%})} \quad \xrightarrow{(S)-\text{BINAP} (3 \text{ mol\%})} \quad \text{Ar} \quad \text{O} \\
\text{dioxane/H}_2\text{O (10:1)} \quad 100 \, ^\circ\text{C}, 5 \, \text{h}
\]

\[
\begin{align*}
\text{Ar} &= \text{Ph}; 93\%, 97\% \text{ ee} \\
\text{Ar} &= \text{4-CF}_3\text{C}_6\text{H}_4; 70\%, 99\% \text{ ee} \\
\text{Ar} &= \text{3-MeOC}_6\text{H}_4; 97\%, 96\% \text{ ee}
\end{align*}
\]

The scope of this reaction was found to be broad and products were obtained in good yield with excellent enantioselectivity. Aryl boronic acids with electron-rich and electron-poor substituents are both tolerated and alkenyl boronic acids can also be employed in this system. However, a large excess of aryl boronic acid was required (up to 5 equiv.), is due to the competitive deboration reaction.

In 2002, Hayashi and co-workers reported detailed studies on the mechanism of the asymmetric conjugate addition and also revealed the important role of the solvent in the reaction.\textsuperscript{21} The proposed catalytic cycle is illustrated in Scheme 1.1.5. The validity of each key intermediate was supported by the NMR studies and independent stoichiometric experiments. The highly active rhodium hydroxide catalyst was formed under aqueous conditions from the rhodium precursors via ligand exchange. Transmetallation with the aryl boronic acid gave the aryl-rhodium complex, which can undergo two different reactions. An unproductive pathway involves the direct hydrolysis of this aryl-rhodium intermediate generating the protonated Ar-H side product. Alternatively, this intermediate can coordinate with alkene of the enone, and carry out a regio- and stereoselective alkene

insertion into the aryl-rhodium bond. Protodemetallation of the resulting oxo-π-allylrhodium species will afford the conjugate addition product and regenerate the rhodium hydroxide catalyst. The mechanistic study also revealed that the presence of the acac ligand will dramatically decrease the formation of the more-reactive rhodium hydroxide catalyst, which led to the development of a new acac-free catalyst [Rh(OH)(BINAP)]₂. Due to the higher reactivity of this new catalyst, the reaction temperature could be lowered to 35 °C, which gave better enantioselectivity. The lower reaction temperature also helped to suppress the competitive hydrolysis of the aryl boronic acids. Miyaura and co-workers also observed a similar increasing efficacy in the conjugate addition reaction using a rhodium hydroxide or alkoxide catalyst, which was formed in situ using an inorganic base in aqueous media.²²

Scheme 1.1.5 Mechanistic proposal for the rhodium-catalyzed 1,4-addition reaction

$$\text{[Rh(acac)(C_2H_4)_2] + (S)-BINAP}$$

$$\text{[Rh(acac)((S)-BINAP)]}$$

$$\text{H}_2\text{O}$$

$$\text{[Rh(acac)((S)-BINAP)]}$$

$$\text{[Rh] = Rh((S)-BINAP)}$$

$$\text{[Rh] = Rh((S)-BINAP)}$$

$$\text{[Rh]-OH}$$

$$\text{[Rh] - OH}$$

$$\text{ArB(OH)_2}$$

$$\text{[Rh]-Ar}$$

$$\text{H}_2\text{O}$$

$$\text{Ar-H + [Rh]-OH}$$

The substrate scope of the rhodium-catalyzed conjugate addition has been demonstrated to be very broad. In addition to cyclic and acyclic enones, alkenes bearing various electron-withdrawing groups, such as esters, amides, phosphonates, and nitro groups all gave the corresponding products with good yield and excellent enantioselectivity. However, some modification of the reaction conditions was required in several cases to avoid competitive hydrolysis of the boron reagents. Some selected examples of rhodium-catalyzed conjugate addition reactions are shown in Scheme 1.1.6.


In addition to boronic acids, organometallic reagents such as organozincs,\textsuperscript{13e} -stannanes,\textsuperscript{13g} -siloxanes,\textsuperscript{13b} and -titaniums,\textsuperscript{13d} have also been used as nucleophiles in the rhodium-catalyzed conjugate additions. For example, organotrifluoroborates,\textsuperscript{27} which are very stable toward air and moisture while maintaining high reactivity under transition-metal catalysis, was first used by Batey\textsuperscript{28} and later by Genêt\textsuperscript{29} in the asymmetric reaction (Scheme 1.1.7).
Among these nucleophiles, reactions with organotitaniums\textsuperscript{13d}, -zincs,\textsuperscript{13e} and 9BBN derived organoborons\textsuperscript{30} were found to proceed in aprotic solvents, which allow further transformation of the resulting enolate intermediate. Hayashi reported a tandem conjugate addition-aldol reaction,\textsuperscript{31} which gave the syn-product in excellent yield, using \( B\-\text{Ar-9BBN} \) (Scheme 1.1.8). This example also demonstrated the potential of forming multiple carbon-carbon bonds via a sequential chemoselective addition with rhodium catalysis.

Scheme 1.1.8 Rhodium-catalyzed tandem conjugate addition-aldol reaction

More recently, rhodium-catalyzed asymmetric conjugate addition using sp-hybridized carbon nucleophiles has been disclosed (Scheme 1.1.9). In Hayashi’s report, terminal alkynes were used without prior activation, affording the addition product with high yield and good enantioselectivity. In order to avoid the undesired dimerization reaction of the alkynyl-rhodium intermediate, the use of bulky ligands in combination with sterically hindered alkynes is essential. However, this limits the scope of nucleophiles that may be used in the reaction.

Scheme 1.1.9 Rhodium-catalyzed 1,4-addition with alkyne nucleophile

[Chemical equation]

1.1.3 Rhodium-Catalyzed Ring-Opening Reaction of Bicyclic Alkenes

Metal-catalyzed ring-opening reactions of heterobicyclic alkenes have been recognized as an efficient method to construct highly functionalized carbocycles bearing multiple stereocenters from simple starting materials.\(^{34}\) Thus, ring-opening reactions of strained alkenes using rhodium catalysis have also attracted much attention. The first example of a ring-opening reaction of oxabicyclic compounds with rhodium catalyst was reported by Hogeveen and Middelkoop in 1973 (Scheme 1.1.10).\(^ {35}\) The rhodium precursor \([\text{Rh}(\text{CO})_2\text{Cl}]_2\) was used in the presence of MeOH to afford the ring-open product in


moderate yield with cis stereochemistry of methoxy and hydroxyl groups. Since the early 1990’s, the rhodium-catalyzed ring-opening of heterocyclic alkenes has been a major focus of research in the Lautens group.\textsuperscript{34a,34c,d} In general, rhodium-catalyzed ring-opening reactions can be classified by two categories based on the property of nucleophiles and each of them will be discussed separately.

Scheme 1.1.10 Ring-opening reaction of oxabicyclic alkene with rhodium catalyst

\[
\begin{align*}
\text{[Rh(CO)\textsubscript{2}Cl\textsubscript{2}}]_{(5 \text{ mol\%})} & \quad \text{MeOH, 50 oC, 1 h} \\
\text{CO}_{2}\text{Me} & \quad \text{CO}_{2}\text{Me} \\
\text{MeO} & \quad \text{CO}_{2}\text{Me}
\end{align*}
\]

60%

In 2000, Lautens reported the asymmetric ring-opening reaction of oxabenzonorbornadienes using a rhodium catalyst\textsuperscript{36} and chiral phosphine ligand PPF-Pr-Bu\textsubscript{2}.\textsuperscript{37} Alcohols and phenols (soft nucleophiles) gave the ring-opened products with trans stereochemistry of alkoxy and hydroxyl substituents in excellent enantioselectivity and high yield (Scheme 1.1.11).

The ring-opening reaction of oxabenzonorbornadienes with alcohol nucleophiles was believed to follow the mechanism illustrated in Scheme 1.1.12.\textsuperscript{38} The rhodium catalyst monomer was generated from dimeric rhodium complex by ligand exchange. The catalytic cycle was then initiated by the reversible coordination of active catalyst from the more accessible \textit{exo}-face. Following the enantioselective insertion of the rhodium catalyst into the C-O bond gave the σ-rhodium alkoxide complex. This oxidative insertion process was believed to be irreversible, due to the release of ring strain in the system. The resulting complexes were protonated by alcohol and then undergo a S\textsubscript{N}2' displacement from the opposite face of rhodium catalyst with alkoxide to afford the product with \textit{trans} configuration.

The studies on scope exploration reveal that various soft nucleophiles, such as amines,\textsuperscript{39} malonates,\textsuperscript{39b} carboxylates,\textsuperscript{39b, 40} and sulfides,\textsuperscript{41} could be used to generate various enantiomerically enriched 1,2-dihydronaphthalene derivatives. In addition to oxabenzonorbornadienes, \textit{N}-Boc-azabenzonorbornadiene was found to undergo the same type of ring opening reaction under the slightly modified conditions to afford a variety of chiral diamines (Scheme 1.1.13).\textsuperscript{42a,b} The products were used in the preparation of

\textsuperscript{40} Lautens, M.; Fagnou, K. \textit{Tetrahedron} \textbf{2001}, \textit{57}, 5067.
biologically active agents,\textsuperscript{42a} chiral ligands,\textsuperscript{42c} and polycyclic heterocycles.\textsuperscript{42d}

Scheme 1.1.13 Ring-opening reaction with amine nucleophiles

\[
\begin{align*}
\text{N}^\text{Boc} & + \text{HNR}_2 & \xrightarrow{[\text{Rh}(\text{cod})\text{Cl}]_2} & \text{R}_2\text{N}^\text{Boc} \\
\text{C}_2\text{-Ferriphos} \quad (5 \text{ mol\%}) & & \text{Et}_3\text{NHCl} & \text{THP, 100 °C} \\
& & &
\end{align*}
\]

77\%, 86\% ee \quad 85\%, 84\% ee \quad 90\%, 84\% ee
(without \text{Et}_3\text{NHCl})

Ring opening reactions of oxabicyclic alkenes with hard nucleophiles, such as organometallic reagents, have also been developed. In 2002, Murakami\textsuperscript{43} and Lautens\textsuperscript{44} independently reported the rhodium-catalyzed addition of aryl boronic acids to oxanorbornenes (Scheme 1.1.14). In Murakami’s report, a [Rh(cod)Cl]_2/P(OEt)_3 catalyst system in refluxing MeOH was used to generate various benzylic alcohols from oxabenzonorbornadienes. Lautens described an asymmetric version by using the same rhodium precursor in combination with a chiral ferrocenylbisphosphine ligand, \((R)-(S)\)-PPF-\text{Pt-Bu}_2, affording the ring-opened products with excellent enantiomeric excess. The stereochemistry of aryl and hydroxyl groups was determined to be \textit{cis}, which is opposite to the previously discussed ring-opening reactions with soft nucleophiles, suggesting a different mechanism is involved.

\textsuperscript{44} Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. \textit{Org. Lett.} \textbf{2002}, 4, 1311.
Both reactions were believed to follow a very similar catalytic cycle (Scheme 1.1.15). The aryl rhodium intermediate, generated from transmetallation between the rhodium catalyst and the aryl boronic acid, undergoes an enantioselective exo-face carborhodation. The resulting alkyl rhodium complexes then undergoes β-oxygen elimination to form the alkoxy rhodium intermediate, which was hydrolyzed under aqueous conditions to give the alcohol product and regenerate the active rhodium hydroxide catalyst.
Recently, Pineschi\textsuperscript{45} and Lautens\textsuperscript{46} subsequently described catalytic systems using rhodium complexes and diazabicyclo[2.2.1]heptanes to synthesize various enantiomerically enriched cyclopentenyl hydrazines (Scheme 1.1.16).\textsuperscript{46a} In addition, using the same conditions for the corresponding conjugate addition, Hayashi reported the ring-opening reaction of \( N \)-Boc-azabenzonorbornadiene with (triisopropylsilyl)acetylene, affording the benzylic amine products in high yield and high enantioselectivity (Scheme 1.1.17).\textsuperscript{47}

**Scheme 1.1.16 Ring-opening reactions using diazabicyclic alkene**

\[
\begin{align*}
\text{N-HOBoc} & + \text{ArB(OH)2} \quad \text{[Rh(cod)OH]2 (5 mol\%)} \\
& \quad \text{(R)-S-PPF-Pt-Bu2 (12 mol\%)} \\
& \quad \text{THF/H2O r.t., 16 h} \\
\text{Ar} = 2-\text{FC6H4}; 53\%, 99\% \text{ ee} \\
\text{Ar} = 2-\text{MeOC6H4}; 75\%, 99\% \text{ ee} \\
\text{Ar} = \text{Ph}; 85\%, 68\% \text{ ee}
\end{align*}
\]

**Scheme 1.1.17 Ring-opening reaction with alkyne nucleophile**

\[
\begin{align*}
\text{N-HOBoc} & + \text{TIPS} \quad \text{[Rh(μ-OAc)(C2H4)2]2 (2.5 mol\%)} \\
& \quad \text{(R)-DTBM-SEGPHOS (6 mol\%)} \\
& \quad \text{dioxane, 80 °C, 12 h} \\
\text{R1} = \text{R2} = \text{H}; 93\%, 99\% \text{ ee} \\
\text{R1} = \text{F}, \text{R2} = \text{H}; 90\%, 99\% \text{ ee} \\
\text{R1} = \text{Br}, \text{R2} = \text{Me}; 88\%, 99\% \text{ ee}
\end{align*}
\]


1.1.4 Rhodium-Catalyzed Addition Reactions to Alkenes and Alkynes

In addition to the conjugate addition and ring-opening reactions discussed in previous sections, rhodium catalysts can also promote the cross coupling between organoboronic acids and simple alkenes and alkynes. In 2000, Miura described a rhodium-catalyzed “merry-go-round” multiple alkylation of arylboronic acids with norbornene (Scheme 1.1.18).48 In this communication, the polysubstituted aromatic product was generated through a series of carborhodation/migration reactions via rhodium(III) hydride intermediates, which were confirmed by deuterium labeling studies.49

Scheme 1.1.18 Rhodium-catalyzed multiple alkylation reactions with norbornene

Our group has also looked into the addition reaction of aryl boronic acids to styrene and vinyl heteroaryl type olefin derivatives using catalyst precursor [Rh(cod)Cl]₂ in conjunction with water soluble phosphine ligand TPPDS 50 (Scheme 1.1.19).51

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49 For a short review on rhodium 1,4-migration, see: Ma, S.; Gu, Z. Angew. Chem. Int. Ed. 2005, 44, 7512.
50 For review on sulfonated aryl group containing phosphines, see: Stelzer, O.; Rossenbach, S.; Hoff, D. In Aqueous-Phase Organometallic Catalysis: Concepts and Applications, 2nd Ed.; Cornils, B.; Herrmann, W.
Heck-type products were obtained with styrene via a similar addition/β-H elimination process as described in palladium chemistry. When the vinylpyridine or vinyl heteroaromatics were employed, the corresponding reductive Heck-type products were generated, presumably through an addition/hydrolysis pathway. Because water was used as the only solvent, competitive deboronation remains the major side reaction and excess amounts of aryl boronic acids are required to achieve high chemical yields.

Scheme 1.1.19 Rhodium-catalyzed Heck-type coupling reactions

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

As an extension of the studies on conjugate addition reactions, Hayashi reported the hydroarylation of alkynes with aryl boronic acids or boroxines under rhodium catalysis (Scheme 1.1.20).\(^{52}\) The mono-arylated products were formed in high yield with excellent

---

regio- and syn-selectivity when symmetric or highly polarized alkynes were employed. Further studies on the reaction mechanism using deuterium-labeled phenylboronic acids suggested a rhodium 1,4-migration process was involved, giving high deuterium incorporation at the vinylic position.\(^{49}\)

Scheme 1.1.20 Addition to alkyne with aryl boronic acids

\[
\begin{align*}
n-Pr & \quad \xrightarrow{\text{Rh(acac)}(C_2H_4)_2 (3 \text{ mol\%})} \quad \text{dppb (3.3 mol\%)} \quad \text{dioxane/H}_2\text{O (10:1)} \quad 100 ^\circ\text{C, 3 h}} \\
& \quad n-Pr + \text{ArB(OH)_2} \\
\rightarrow & \quad \text{Ar} \quad \text{H(D)} \\
& \quad n-Pr \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = \text{Ph; 87\%} \\
\text{Ar} = 4-\text{CF}_3\text{C}_6\text{H}_4; 93\% \\
\text{Ar} = 4-\text{MeC}_6\text{H}_4; 92\% \\
\text{Ar} = \text{C}_6\text{D}_5\text{B(OH)}_2; 86\%
\end{align*}
\]

In 2002, Lautens demonstrated a similar hydroarylation reaction of alkynes using a pyridine functionality as directing group (Scheme 1.1.21).\(^{53}\) The reaction was carried out using a combination of [Rh(cod)Cl]\(_2\) and water soluble pyridinylphosphine ligand\(^{54}\) in water. In addition to high regio- and stereoselectivities, the reaction also showed high chemoselectivity, as only the alkynyl group adjacent to pyridinyl nitrogen undergoes the arylation reaction. It was speculated that this is due to the internal coordination of the nitrogen atom to the rhodium catalyst, which stabilizes the reaction intermediate.


\(^{54}\) Herd, O.; Langhans, K. P.; Stelzer, O.; Weferling, N.; Sheldrick, W. S. Angew. Chem. Int. Ed. 1993, 32, 1058.
Scheme 1.1.21 Addition of aryl boronic acids to pyridinylalkynes

1.1.5 Rhodium-Catalyzed Cascade Addition Reactions toward the Formation of Carbocycles

As an extension of the studies on the addition of organoboron reagents to alkenes and alkynes, a methodology toward the formation of carbocycles through a sequential carbon-carbon bond forming process was developed by a doctoral student, John Mancuso. In this approach, an electrophilic accepting group, which was known to react with organorhodium species, is tethered to the arylboron reagents (Scheme 1.1.22). Under rhodium catalysis, this bifunctional arylboron 1.1.1 species was expected to undergo an intermolecular addition with an alkene 1.1.2, and the resulting organorhodium intermediate 1.1.3 will then react with the tethered electrophilic groups at later stage to

---

give annulated products.

Scheme 1.1.22 Cascade addition reaction using bifunctional arylboron reagents

\[
\begin{align*}
\text{E} & \quad \text{B(OR)₂} \\
\text{1.1.1} & \quad [\text{Rh}] \\
\end{align*}
\]

\[E = \text{electrophilic functional groups}\]

To test the validity of this strategy, a phenyl boronate ester was prepared with a Michael acceptor at the ortho position. This allows for the intramolecular conjugate addition of an organorhodium intermediate. Norbornene was chosen as the coupling partner, which is unable to undergo a β-hydride elimination pathway, as demonstrated by Miura.\(^{48}\) Under the optimal conditions using [Rh(cod)Cl]₂ and t-Bu-amphos, the corresponding cyclized products were obtained in good to excellent yield (Scheme 1.1.23).\(^{56}\)

Scheme 1.1.23 Cascade addition/cyclization reaction with norbornene derivatives

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The mechanistic proposal is illustrated in Scheme 1.1.24. The catalytic cycle is triggered by transmetallation between the aryl boronate ester and rhodium(I) hydroxide, which is generated in situ. Carborhodation of the aryl rhodium intermediate on the exo-face of norbornene follows, as described in Miura’s previous report. The resulting organorhodium(I) species undergoes an intramolecular conjugate addition to the tethered electron-deficient olefin to afford the cyclized product after the protodemetallation with water. The steric interactions between the ester group and bridged methylene group in norbornene were speculated to contribute to the diastereoselectivity of the products.

Scheme 1.1.24 Mechanistic proposal for cascade addition/cyclization reaction

This method for the synthesis of carbocycles using ortho-functionalized aryl boronate esters has been extended to various norbornene derivatives and alkynes. Furthermore, it has been demonstrated that a wide variety of tethered functional groups, such as

aldehydes and ketones,\textsuperscript{58} nitriles,\textsuperscript{59} ethers,\textsuperscript{60} bromides,\textsuperscript{61} and benzylic chlorides,\textsuperscript{62} react by a similar process.

In addition to the strategies using bifunctional organoboron reagents, rhodium-catalyzed addition reactions to substrates containing multiple electrophilic accepting groups provides an alternative pathway toward the formation of carbocycles (Scheme 1.1.25). This type of reaction will require an electrophilic group with high reactivity to interact with arylrhodium species as an entry point (1.1.5), which allows the subsequent reaction with the less reactive functional groups to generate the cyclic products (1.1.6).

Scheme 1.1.25 Cascade addition to substrate containing multiple electrophilic groups

\[
\begin{array}{c}
\text{E}_1, \text{E}_2 = \text{electrophilic functional groups} \\
1.1.4 & \xrightarrow{[\text{Rh}]} & 1.1.5 & \xrightarrow{\text{ArB(OH)}_2} & 1.1.6
\end{array}
\]

Krische reported the synthesis highly substituted chiral cyclopentanol via a conjugate addition-aldol reaction process (Scheme 1.1.26).\textsuperscript{63} This reaction could be viewed as a cyclic variation of Hayashi’s previous report,\textsuperscript{31} which was initiated by an asymmetric conjugate addition to $\alpha,\beta$-unsaturated ketone moiety. The cyclic product was obtained after the aldol reaction of the resulting oxo-$\pi$-allyl rhodium intermediate with another

ketone functionality. This method has also been applied to the desymmetrization of diketones, which generated four contiguous stereocenters with high enantiomeric excess.\(^{64}\)

**Scheme 1.1.26 Cascade conjugate addition-aldol reaction**

\[
\begin{align*}
\text{O} & \quad \text{Ph(B(OH)}_2
\end{align*}
\]

\[
\begin{align*}
\text{[Rh(cod)Cl]}_2 & \quad \text{(2.5 mol\%)} \\
(R)-\text{BINAP} & \quad \text{(7.5 mol\%)} \\
\text{H}_2\text{O} & \quad \text{(5 equiv)} \\
dioxane, 95^\circ\text{C}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Ph} \\
\text{O} & \quad \text{n} = 1; 88\%, 94\% \text{ ee} \\
\text{O} & \quad \text{n} = 2; 69\%, 95\% \text{ ee}
\end{align*}
\]

In 2005, Hayashi\(^{65}\) and Murakami\(^{66}\) independently reported the synthesis of 2-norbornanones via a sequential addition reaction to 1,6-enynes with arylboronic acids (Scheme 1.1.27). The reaction was proposed to proceed via three consecutive carborphodation processes, with an alkyne, an alkene and then ester groups, eventually terminating with a hydrolysis or $\beta$-methoxy elimination. In addition to the racemic


reaction developed by Hayashi, (R)-BINAP was reported to express high asymmetric induction in Murakami’s studies.  

Scheme 1.1.27 Cascade addition reaction to alkyne and alkenes

\[
\text{MeO}_2\text{C} \quad \text{Et} \quad \text{PhB(OH)}_2 \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh(cod)OH]}_2 \quad (3.5 \text{ mol%}) \\
\text{dioxane/H}_2\text{O} (10:1) \quad 70 \degree \text{C}, 5 \text{ h} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{OMe} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{O} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{O} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{OMe} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{O} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{OMe} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{O} \\
\rightarrow \text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{OMe} \\
\rightarrow \text{Ar} \\
\text{MeO}_2\text{C} \quad \text{Et} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{[Rh]} \quad \text{O} \\
\rightarrow \text{Ar} = \text{Ph}; 60\%, 89\% \text{ ee} \\
\text{Ar} = 3\text{-MeOC}_6\text{H}_4; 65\%, 80\% \text{ ee} \\
\text{Ar} = 3\text{-ClC}_6\text{H}_4; 80\%, 94\% \text{ ee}
\]

In addition to enyne systems, various combinations of alkynes or electron-deficient alkenes with unsaturated functional groups, such as aldehydes, ketones, isocyanates, nitriles, imines, allylic ethers, and allenes, have been

---

demonstrated to participate in similar types of reactions to synthesize a wide range of carbocycle containing molecules.

1.2 RHODIUM-CATALYZED VINYL CYPHO PRPANATION/CYCLOPENTENATION UTILIZING DIENYLBORONATE ESTERS

1.2.1 Results and Discussions

1.2.1.1 Goal of Study

Following the development of the rhodium-catalyzed cascade addition/cyclization process for the synthesis of indanes\(^{56}\) and indenes,\(^{57}\) we sought to extend this strategy to other classes of bifunctional organoboronate esters, such as dienylboronate esters 1.2.1. The initial goal was to replace the aromatic system with a simple olefin group, which would presumably give the corresponding carbocycles containing substituted cyclopentene moieties (Scheme 1.2.1).

Scheme 1.2.1 Expansion of reaction scope using dienylboronate esters

1.2.1.2 Coupling of Dienylboronate Esters with Bicyclic Alkenes under Rhodium Catalysis
Dienylboronate ester 1.2.6 was prepared based on literature procedures (Scheme 1.2.2). Ethyl (Z)-β-iodoacrylate 1.2.3, which was prepared from ethyl propiolate, was reduced with Dibal, and subjected to Wittig olefination to afford the dienyl iodide 1.2.4 and 1.2.5. Conversion of iodide to boronate ester 1.2.6 was accomplished via an in-situ trapping of the vinyllithium intermediate with triisopropylborate, which was then esterified with pinacol.

Scheme 1.2.2 Synthesis of dienylboronate ester 1.2.6

We subsequently screened for optimal reaction conditions using dienylboronate ester 1.2.6 with oxabicyclic alkene 1.2.7. According to the previous report, the cyclized product 1.2.8 was obtained as a mixture of diastereomers and the structure was proposed based on analogy to the previous studies. The initial results are summarized in Table

---

1.2.1.

Table 1.2.1 Optimization of rhodium-catalyzed cyclopentenation using bifunctional dienylboronate esters

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>base</th>
<th>solvent</th>
<th>temperature (°C)</th>
<th>time (h)</th>
<th>yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-Bu-amphos</td>
<td>NaOH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>t-Bu-amphos</td>
<td>NaOH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH₃CN</td>
<td>50</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu-amphos</td>
<td>KOH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH₃CN</td>
<td>50</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu&lt;sub&gt;3&lt;/sub&gt;P&lt;sup&gt;d&lt;/sup&gt;H&lt;sup&gt;b&lt;/sup&gt;B&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;d&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Na₂CO₃</td>
<td>dioxane/H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt;</td>
<td>80</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu&lt;sub&gt;3&lt;/sub&gt;P&lt;sup&gt;d&lt;/sup&gt;H&lt;sup&gt;b&lt;/sup&gt;B&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;d&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Na₂CO₃</td>
<td>dioxane/H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt;</td>
<td>80</td>
<td>16</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu&lt;sub&gt;3&lt;/sub&gt;P&lt;sup&gt;d&lt;/sup&gt;H&lt;sup&gt;b&lt;/sup&gt;B&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;d&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>KOH&lt;sup&gt;b&lt;/sup&gt;</td>
<td>dioxane/H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt;</td>
<td>80</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>t-Bu&lt;sub&gt;3&lt;/sub&gt;P&lt;sup&gt;d&lt;/sup&gt;H&lt;sup&gt;b&lt;/sup&gt;B&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;d&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>KF</td>
<td>dioxane/H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt;</td>
<td>80</td>
<td>3</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield. <sup>b</sup> d.r. = 1.1:1 – 1.2:1 <sup>c</sup> 5M solution in H₂O. <sup>d</sup> 10:1 ratio.

Initial studies were carried out using the t-Bu-amphos ligand, which showed high reactivity in the previous report. However, the standard conditions afforded poor results (entry 1). Raising the reaction temperature was found to be beneficial, giving a higher yield and reduced reaction time (entry 2). Changing the base from NaOH to KOH led to a slight improvement (entry 3). A significant increase in yield was observed by using bulky...
phosphine ligand \( t\)-Bu\(_3\)PH\(^+\)BF\(_4\) \(^79\) under the previously-described optimal conditions (entry 4). \(^57\) Extending the reaction time to 16 h did not further increase the yield (entry 5). Among the several inorganic bases screened, potassium fluoride \(^80\) showed the highest reactivity, giving the product in 65\% yield (entries 4, 6, 7).

We then set out to explore the scope of this reaction by varying the bicyclic alkenes. To our surprise, the X-ray structure of the product 1.2.10, obtained by the reaction of oxabicyclic alkene 1.2.9, revealed an unexpected structure (Scheme 1.2.3). Instead of the expected cyclopentene structure, a highly strained vinylcyclopropane moiety was incorporated in the product with the Z-olefin geometry (Figure 1.2.1). In order verify the structure of this cyclopropanation reaction, norbornene 1.2.11 was used as the alkene partner (Table 1.2.2, entry 1). The resulting product 1.2.12 was further derivatized (Scheme 1.2.4) and subjected to X-ray crystallographic analysis (Figure 1.2.2), which unambiguously shows a vinylcyclopropane moiety. In contrast, product mixture 1.2.8 gives a much different proton NMR spectrum than either 1.2.10 or 1.2.12, suggesting a non-vinylcyclopropane structure in 1.2.8. The factors that account for the observed difference in reactivity using oxabicycle 1.2.7 remain unclear.

\(^{80}\) Using of fluorides as base has been reported to facilitate the transmetallation process in Suzuki coupling. For example, see: Wright, S. W.; Hageman, D. L.; McClure, L. D. J. Org. Chem. 1994, 59, 6095.
Scheme 1.2.3 Coupling reaction with oxabicyclic alkene 1.2.9

Scheme 1.2.3

Figure 1.2.1 ORTEP plot of 1.2.10 at 30% probability

81 CCDC 297153 contains the supplementary crystallographic data, which can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.
Scheme 1.2.4 Synthesis of derivative 1.2.14

![Chemical Structures and Reactions]

Based on the reaction conditions described above, additional studies varying the phosphine ligand, including PPh₃, Cy₃PH⁺BF₄⁻, dppe, dppf, all gave the vinylcyclopropane product, though in lower yield, and showed no influence on the

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82 CCDC 297154.
chemoselectivity. Thus, $t$-Bu$_3$PH$^+$BF$_4^-$ was chosen as optimal ligand for further studies, as it demonstrated the highest reactivity.

We then set out to explore the scope of this vinylcyclopropanation reaction with a variety of alkenes. In general, norbornene and norbornene derivatives gave the desired product in moderate to good yield. Benzonorbornene 1.2.15 showed lower reactivity toward this process, even after doubling the amount of the catalyst loading, affording the corresponding product 1.2.16 in 51% (Table 1.2.2, entry 2). Norbornene derivatives 1.2.17 and 1.2.19 demonstrated the chemoselectivity of this transformation, as the vinylcyclopropanation only occurred at the strained and more electron-rich olefins, giving the products in moderate to good yield (entries 3 and 4). Reaction of bicyclo[2.2.2]oct-2-ene 1.2.21 gave the product 1.2.22 in low yield, suggesting the reduced strain energy of this substrate led to the lower reactivity of this process (entry 5).

Table 1.2.2 Reaction with norbornene derivatives$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>product</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Norbornene Derivative" /></td>
<td><img src="image" alt="Product" /></td>
<td>84</td>
</tr>
</tbody>
</table>

$^a$ Reaction with norbornene derivatives

$^b$ Yield in %
All reactions were run under the following conditions: 1.2.6 (0.20 mmol, 1 equiv), alkene (0.20-0.22 mmol, 1.0-1.1 equiv), [Rh(cod)Cl]$_2$ (0.006 mmol, 3 mol%), $t$-Bu$_3$PH$^+$BF$_4$ (0.012 mmol, 6 mol%), KF (0.40 mmol, 2 equiv), in 3.0 mL of dioxane and 0.3 mL of H$_2$O. $^b$ Isolated by column chromatography. $^c$ Yield obtained by using [Rh(cod)Cl]$_2$ (0.012 mmol, 6 mol%) and $t$-Bu$_3$PH$^+$BF$_4$ (0.024 mmol, 12 mol%).

Aza- and oxabicyclic alkenes, which have been previously used in transition metal catalyzed ring-opening reactions, were also examined. The reaction with [3.2.1] oxabicyclic alkenes, such as 1.2.23 and 1.2.9, gave the desired product in good to excellent yield (Table 1.2.3, entries 1 and 2). These results showed that ketone and silyl ether groups are compatible under the reaction conditions, as no 1,2-addition or desilylation were observed. [2.2.1] Oxabicyclic alkene 1.2.25 gave 1.2.26 in low yield, perhaps due to an interaction of the sulfone group with the rhodium catalyst (entry 3). Oxabicyclic alkene 1.2.27 did not give the expected product, presumably due to a
competitive acylation of an organorhodium intermediate with the anhydride functional group, as previously reported by Frost and co-workers (entry 4).\textsuperscript{83} Using less than half an equivalent of bisoxabicyclic alkene \textbf{1.2.28} gave the double vinylcyclopropanation product in good yield (entry 5). The monocyclized product \textbf{1.2.30} could also be obtained in moderate yield by controlling the amount of boronate ester (entry 6). Extension of this method to nitrogen-containing alkenes such as \textbf{1.2.31} and \textbf{1.2.32} proved to be problematic and gave no desired product (entries 7 and 8). It is speculated that the nitrogen atom might strongly coordinate to the catalyst and impede the catalytic cycle. However, we found that by employing an azabicyclic alkene with the nitrogen atoms further away from the alkene moiety, such as \textbf{1.2.33}, afforded an interesting diamine product, albeit in low yield (entry 9).

Table 1.2.3 Reaction with aza- and oxabicyclic alkenes\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>product</th>
<th>yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pinB\textsuperscript{c}</td>
<td>[Rh(cod)Cl]\textsubscript{2} t-Bu\textsubscript{3}PH\textsuperscript{+}BF\textsubscript{4}\textsuperscript{-}</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>OTIPS</td>
<td>t-BuO\textsubscript{2}C</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Frost, C. G.; Wadsworth, K. J. \textit{Chem. Commun.} \textbf{2001}, 2316.

1.2.9

1.2.10

1.2.25

1.2.26

1.2.27

1.2.28

1.2.29

1.2.30

1.2.31

1.2.32
All reactions were run under the following conditions: 1.2.6 (0.20 mmol, 1 equiv), alkene (0.08-0.22 mmol, 0.40-1.10 equiv), [Rh(cod)Cl]2 (0.006 mmol, 3 mol%), t-Bu3PH+BF4− (0.012 mmol, 6 mol%), KF (0.40 mmol, 2 equiv), in 3.0 mL of dioxane and 0.3 mL of H2O. b Isolated by column chromatography. c Yield obtained using 0.40 equiv of oxabicyclic alkene (0.08 mmol). d Yield obtained using 1.05 equiv of oxabicyclic alkene (0.21 mmol).

We also screened a variety of non-bicyclic alkenes under the optimal reaction conditions.

The unstrained 1,2-dihydronaphthalene 1.2.35 was found to undergo cyclopropanation, albeit in low yield (Table 1.2.4, entry 1). Using an analogous alkene, such as indene 1.2.37, did not afford any product (entry 2). Styrene 1.2.38 only gave the Heck-type product in low yield (entry 3).51 Reacting with 1-cyclohexenone 1.2.40 only afforded the 1,4-addition product 1.2.41 in moderate yield (entry 4).13a Using other strained alkenes, such as methylenecyclopropane 1.2.42 and cyclopropene 1.2.43,84 did not give any of the desired product (entries 5 and 6).

Table 1.2.4 Reaction with nonbicyclic alkenes

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
</table>

All reactions were run under the following conditions: 1.2.6 (0.20 mmol, 1 equiv), alkene (0.21-0.24 mmol, 1.05-1.20 equiv), [Rh(cod)Cl]$_2$ (0.006 mmol, 3 mol%), $t$-Bu$_3$PHBF$_4^-$ (0.012 mmol, 6 mol%), KF (0.40 mmol, 2 equiv), in 3.0 mL of dioxane and 0.3 mL of H$_2$O. $^b$ Isolated by column chromatography.

We next screened several boronate esters containing the diene framework, but with different electron-withdrawing groups, and different groups on boron. Changing the $t$-butyl ester to tertiary amide gave 1.2.45 in low yield (Table 1.2.5, entry 1). Reaction of a boronate ester bearing a nitrile functional group afforded the desired product 1.2.47 in moderate yield as a mixture of $E/Z$ isomers (entry 2). Switching the pinacol boronate
ester to potassium trifluoroborate $1.2.48^{28,29}$ gave the corresponding product in lower yield (entry 3). Using boronate ester $1.2.49$, containing only one olefin group, did not afford any product (entry 4), indicating that the diene framework plays a crucial role in the vinylcyclopropanation process.

Table 1.2.5 Reaction with different boronate esters$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>boronate ester</th>
<th>product</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pinB=CH₂=CHNO</td>
<td>[Rh(cod)Cl]₂</td>
<td>t-Bu₃PH⁺BF₄⁻</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KF, dioxane/H₂O</td>
<td>80 °C, 3 h</td>
</tr>
<tr>
<td>1.2.44</td>
<td></td>
<td>O=CHCH₄</td>
<td>32</td>
</tr>
<tr>
<td>1.2.45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>pinB=CHCN</td>
<td>[Rh(cod)Cl]₂</td>
<td>t-Bu₂O₂C⁻</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KF, dioxane/H₂O</td>
<td>80 °C, 3 h</td>
</tr>
<tr>
<td>1.2.46</td>
<td></td>
<td>NC</td>
<td>59</td>
</tr>
<tr>
<td>1.2.47, Z : E = 3.3 : 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>pinB=CH₂=CO₂t-Bu</td>
<td>[Rh(cod)Cl]₂</td>
<td>t-Bu₂O₂C⁻</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KF, dioxane/H₂O</td>
<td>80 °C, 3 h</td>
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<td>1.2.48</td>
<td></td>
<td>CO₂t-Bu</td>
<td>35</td>
</tr>
<tr>
<td>1.2.12</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>pinB=CH₂=CO₂t-Bu</td>
<td>[Rh(cod)Cl]₂</td>
<td>t-Bu₂O₂C⁻</td>
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<tr>
<td></td>
<td></td>
<td>KF, dioxane/H₂O</td>
<td>80 °C, 3 h</td>
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<tr>
<td>1.2.49</td>
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<td>CO₂t-Bu</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

$^a$ All reactions were run under the following conditions: organoboron reagent (0.20 mmol, 1 equiv), norbornene (0.22 mmol, 1.1 equiv), [Rh(cod)Cl]₂ (0.006 mmol, 3 mol%),

41
In order to probe the influence of olefin geometry on this vinylcyclopropanation reaction, various $E,Z$ isomeric boronate esters were tested. To our surprise, all olefin isomers gave the same product as was obtained using 1.2.6, albeit in lower yield (Table 1.2.6, entries 1-3).

We then examined substituent effects on the dienyl fragment. When methyl-substituted...
boronate ester 1.2.53 was used, the reductive Heck-type product 1.2.54 was obtained in low yield (Table 1.2.7, entry 1). Reacting boronate ester 1.2.55 bearing a methyl substituent β to the ester group gave the vinylcyclopropane product, though in low yield (entry 2). In contrast, methyl-substituted boronate esters 1.2.57 and 1.2.59 afforded the cyclopentene products in moderate yield (entries 3 and 4), which were speculated to follow the mechanism in the previous report.56,57 In addition, the structure of the cyclopentene 1.2.58 was further confirmed by X-ray crystallography (Figure 1.2.3) of a derivative 1.2.62 (Scheme 1.2.5).

Table 1.2.7 Reaction with substituted boronate esters

<table>
<thead>
<tr>
<th>entry</th>
<th>boronate ester</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pinB&lt;sub&gt;R1&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;t-Bu</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;R2&lt;/sub&gt;/Bu&lt;sub&gt;R3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;t-Bu</td>
<td>5-10</td>
</tr>
<tr>
<td>2</td>
<td>pinB&lt;sub&gt;R1&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;t-Bu</td>
<td>t-BuO&lt;sub&gt;R2&lt;/sub&gt;C&lt;sub&gt;H&lt;/sub&gt;</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>pinB&lt;sub&gt;R1&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;t-Bu</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;R2&lt;/sub&gt;/Bu&lt;sub&gt;R3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;t-Bu</td>
<td>66&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
All reactions were run under the following conditions: boronate ester (0.20 mmol, 1 equiv), norbornene (0.22 mmol, 1.1 equiv), [Rh(cod)Cl]_2 (0.006 mmol, 3 mol%), \( t\text{-Bu}_3\text{PH}^+\text{BF}_4^- \) (0.012 mmol, 6 mol%), KF (0.40 mmol, 2 equiv), in 3.0 mL of dioxane and 0.3 mL of H_2O. \(^b\) Isolated by column chromatography. \(^c\) Yield obtained by using boronate ester 1.2.57 (1.00 mmol, 1 equiv), norbornene (1.10 mmol, 1.1 equiv), [Rh(cod)Cl]_2 (0.03 mmol, 3 mol%), \( t\text{-Bu}_3\text{PH}^+\text{BF}_4^- \) (0.06 mmol, 6 mol%), KF (2.00 mmol, 2 equiv), in 10 mL of dioxane and 1 mL of H_2O.

Scheme 1.2.5 Synthesis of derivative 1.2.62
We wanted to test the generality of this cyclopentenation reaction by varying the substituents on the boronate esters and the acceptor alkene. Reacting with boronate esters bearing phenyl or isopropyl groups afforded the corresponding cyclopentene products in moderate to good yield (Table 1.2.8, entries 1-3). We also attempted to switch the alkyl or aryl substituents to other functional groups. However, conversion of dienyl iodides to boronate esters was problematic when groups such as CF₃, BnOCH₂-, and TMS were incorporated at the R₁ position. Benzonorbornene and norbornene derivative gave the products in moderate yield with methyl substituted boronate esters (entries 4-7). More interestingly, using norbornadiene as coupling partner only gave the monocyclized product, though in unsatisfactory yield (entries 8 and 9).
Table 1.2.8 Reaction with substituted boronate esters with different alkenes$^a$

\[
\text{R}_2\text{R}_1\text{C}O_2\text{t-Bu} \xrightarrow{[\text{Rh(cod)Cl}]_2, \text{t-Bu}_3\text{PH}^+\text{BF}_4^-; \text{KF, dioxane/H}_2\text{O}} \text{80 }^\circ\text{C, 3 h}} \rightarrow \text{R}_1\text{R}_2\text{R}_1\text{H}^+\text{CO}_2\text{t-Bu}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>$\text{R}_1$</th>
<th>$\text{R}_2$</th>
<th>product</th>
<th>yield (%)$^b$</th>
</tr>
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<td>1.2.11</td>
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<td>1.2.63</td>
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</tr>
<tr>
<td>2</td>
<td>1.2.11</td>
<td>H</td>
<td>$i$-Pr</td>
<td><img src="#" alt="product" /></td>
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<td></td>
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<td>1.2.64</td>
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</tr>
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<td>3</td>
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<td>Ph</td>
<td>H</td>
<td><img src="#" alt="product" /></td>
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<td>1.2.15</td>
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<td>1.2.66</td>
<td></td>
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</tbody>
</table>
All reactions were run under the following conditions: boronate ester (0.20 mmol, 1 equiv), alkene (0.22-0.24 mmol, 1.1-1.2 equiv), [Rh(cod)Cl]₂ (0.006 mmol, 3 mol%), t-Bu₃PH⁺BF₄⁻ (0.012 mmol, 6 mol%), KF (0.40 mmol, 2 equiv), in 3.0 mL of dioxane and 0.3 mL of H₂O. Isolated by column chromatography.

1.2.1.3 Mechanistic Proposal for Rhodium-Catalyzed Vinylcyclopropanation Reactions
This unexpected rhodium-catalyzed vinylcyclopropanation reaction is believed to follow the mechanism proposed in Scheme 1.2.6. The active catalyst $L_n\text{Rh(I)}\text{OH}$ I, formed \textit{in situ}, transmetalates with the boronate ester to give the dienylrhodium(I) intermediate II and B(pin)OH. This kind of Z-vinylrhodium species has been proposed as reactive intermediate and usually does not undergo olefin isomerization prior to the addition reactions.\textsuperscript{52,53,57-62,65-75} Subsequent carborhodation at the \textit{exo} face of norbornene 1.2.11 affords the organorhodium(I) complex III,\textsuperscript{48} which preferentially undergoes intramolecular 1,6-addition,\textsuperscript{85} presumably due to the close proximity of the $\delta$ carbon to the rhodium catalyst. Protodemetalation of the resulting oxo-$\pi$-allylrhodium(I) IV gives the vinylcyclopropane product 1.2.12 and regenerates the catalyst $L_n\text{Rh(I)}\text{OH}$ I.

Scheme 1.2.6 Proposed reaction mechanism with dienylboronate ester 1.2.6

In addition to literature precedent, the presence of rhodium(I) hydroxide in the catalytic cycle is supported by control experiment. A comparable result was obtained by using \([\text{Rh(cod)OH}]_2\) as precatalyst while no conversion was observed by excluding water from the reaction conditions. Furthermore, \([\text{Rh(cod)Cl}]_2\) dimer is known to undergo hydrolysis at room temperature in a aqueous basic solution to afford the rhodium(I) hydroxide complexes. Due to its weak basicity, using fluoride as a base in the reaction has proven to contribute to functional group compatibilities and the presence of fluorides is believed to promote the formation of \(\text{R(BF}_n\text{OH}_{3-n})\) ate species, which facilitates the transmetallation process.

When using methyl-substituted dienylboronate esters 1.2.57 and 1.2.59 (Table 1.2.7. entries 3 and 4), cyclopentene products were generated rather than vinylcyclopropanes. These results suggested that the rate of intramolecular 1,4- versus 1,6-addition of organorhodium(I) III was strongly influenced by the presence of substituents at \(\gamma\) or \(\delta\) positions. No products were observed by using boronate ester 1.2.49 (Table 1.2.5, entry 4), which contains only one olefin group, presumably due to the inability of this substrate to form the double coordinated intermediate III. This outcome suggests that this modification of the diene framework is not favorable in the vinylcyclopropanation reaction.

The presence of the oxo-\(\pi\)-allylrhodium(I) complex IV is supported by deuterium quenching studies, which show >95% deuterium incorporation at the \(\alpha\) carbon (Scheme 1.2.6). The observed Z-olefin in the product is believed to be formed as a consequence of

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internal coordination of the carbonyl group in oxo-π-allylrhodium(I) IV. This hypothesis was supported by the formation of \( E/Z \) isomeric mixture when a nitrile-containing boronate ester (Table 1.2.5, entry 2). We speculated that the linear geometry of the nitrile group has a weaker coordination than proposed for intermediate IV, leading to a mixture of olefins.

Scheme 1.2.7 Deuterium labeling study in D\(_2\)O

When the reaction was conducted with various \( E/Z \) isomeric boronate esters, the same product 1.2.12 was generated (Table 1.2.2, entry 1, and Table 1.2.6, entries 1-3). However, boronate ester 1.2.6, which has \( E,Z \) configuration, gave the highest yield, presumably due to a more favorable conformation in intermediate III compared to the other isomers (Figure 1.2.4). In addition, the Z-olefin geometry in the product was retained from different isomeric boronate esters, which suggests that the reaction mechanism must involve an olefin isomerization step, possibly due to the presence of an equilibrium between (oxo-π-allyl)rhodium(I) IV and (oxo-π-pentadienyl)rhodium(I) V\(^{85a}\).

Figure 1.2.4 Proposed conformation of intermediate III with boronate esters 1.2.6 and 1.2.50-1.2.52
1.2.2 Conclusions and Future Work

In summary, we have developed a vinylcyclopropane-forming reaction via a rhodium-catalyzed cascade addition/cyclization sequence. This process works best when strained bicyclic alkenes were used. We also discovered that by using alkyl or aryl substituted boronate esters, the reaction will undergo a different pathway to afford cyclopentene products. A wide variety of polycyclic molecules containing vinylcyclopropane or cyclopentene moieties can be synthesized via this convergent rhodium-catalyzed, substrate-controlled process.

To make this methodology more synthetically valuable and practical, further investigation should focus on utilization of unstrained alkenes. In addition, application of this method in post-modifications, such as using transition metal catalyst in combination with chiral ligand to carry out the rearrangement of vinylcycloproapnes to cyclopentenes or cyclohexanones would be also desirable.88

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1.2.3 Experimental

Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. $^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra were recorded using Mercury 300 MHz, Mercury 400 MHz or Unity 500 MHz spectrometers. $^1$H spectra were referenced to tetramethylsilane (TMS, 0 ppm) or solvent protons (CD$_2$CN, 1.94 ppm) and $^{13}$C spectra were referenced to solvent carbons (CDCl$_3$, 77.0 ppm or CD$_3$CN, 1.39 ppm). IR spectra were obtained as thin films on NaCl plates. High resolution mass spectra were obtained at 70 eV for electron impact ionization (EI) or at a spray voltage of 5500 V for electrospray ionization (ESI).

Toluene, dioxane and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone immediately prior to use. Dichloromethane and benzene were distilled under nitrogen from CaH$_2$ immediately before use. All reagents were used as received from Sigma-Aldrich or Strem unless otherwise indicated. Analytical thin layer chromatography was performed with Silicycle™ normal phase 0.25 mm aluminum or glass backed TLC plates. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel. All experiments were performed under anhydrous conditions under an atmosphere of nitrogen or argon unless otherwise noted.
Synthesis of dienylboronate ester 1.2.6:

1. (i-PrO)₃B, n-BuLi, THF/toluene, -78 °C
2. pinacol, -78 °C to r.t.

84%

Ethyl (Z)-β-iodoacrylate (1.2.3): A mixture of ethyl propiolate (1.00 g, 10.2 mmol) and sodium iodide (2.44 g, 16.3 mmol) in AcOH (3.7 mL, 65 mmol) was heated to 115 °C for 2 h. The reaction mixture was diluted with water and Et₂O, washed with saturated aqueous NaHCO₃ solution (x 2). The aqueous layer was then extracted with Et₂O (x 3) and the combined organic layers were washed with saturated Na₂S₂O₃ solution, dried with MgSO₄, filtered, and concentrated in vacuo to afford the ethyl (Z)-β-iodoacrylate 1.2.3 (2.20 g, 96%). The material was sufficiently pure as determined by NMR spectroscopy to be used for subsequent reactions. Spectral data also matched the previously reported data.77
(2E,4Z)-tert-Butyl 5-iodopenta-2,4-dienoate (1.2.4) and (2Z,4Z)-tert-butyl 5-iodopenta-2,4-dienoate (1.2.5): To a solution of ethyl (2Z)-3-iodoacrylate 1.2.3 (2.00 g, 8.85 mmol) in 20 mL of dichloromethane at -78 °C was added a 1M solution of diisobutylaluminum hydride in heptane (9.8 mL, 9.8 mmol) dropwise via syringe pump over 10 min. The reaction was stirred for another 30 min at -78 °C and conversion was monitored by TLC analysis. The reaction was quenched at -78 °C by the addition of 5 mL of methanol and 40 mL of saturated aqueous potassium sodium tartrate solution and was allowed to warm to 25 °C. After stirring vigorously at 25 °C for 1 h, the solution was diluted with H₂O and the aqueous phase was extracted with Et₂O (× 3). The combined organic layers were dried with Na₂SO₄, filtered and concentrated in vacuo to afford the aldehyde as a yellow oil. The aldehyde was dissolved in 20 mL benzene and tert-butyl(triphenylphosphoranylidene) acetate (3.67 g, 9.74 mmol) was added. The mixture was then allowed to stir at 25 °C for 16 h. The solvent was removed in vacuo and Et₂O was added. The suspension was filtered to remove the triphenylphosphine oxide and the filtrate was concentrated in vacuo to give the crude product. Chromatography on silica gel using 20% Et₂O in hexane gave the E,Z-dienyl iodide 1.2.4 (1.519 g, 61%, R_f = 0.53) as an yellow solid (the solid resulting from the evaporation of Et₂O and hexane), mp = 37 – 39 °C and the Z,Z-dienyl iodide 1.2.5 (0.256 g, 10%, R_f = 0.81) as yellow oil. E,Z-dienyl iodide 1.2.4: ¹H NMR (400 MHz, CDCl₃): δ 7.33 (ddd, J = 15.4, 10.3, 0.9 Hz,
1H), 6.87 (ddd, J = 10.4, 7.8, 0.7 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.07 (d, J = 15.4 Hz, 1H), 1.51 (s, 9H); 13C NMR (100 MHz, CDCl3): δ 165.8, 142.1, 136.6, 127.6, 91.2, 80.8, 28.1; IR (neat): 2977, 1709, 1564, 1392, 1367, 1317, 1259, 1222, 1146, 1071, 981, 870, 848, 677 cm⁻¹; HRMS (EI) calcd for C₉H₁₃IO₂ [M⁺] 279.9960, found 279.9973.

Z,Z-dienyl iodide 1.2.5: ¹H NMR (400 MHz, CDCl₃): δ 7.99 (ddd, J = 10.4, 7.7, 1.3 Hz, 1H), 6.77 (ddd, J = 7.8, 1.3, 1.3 Hz, 1H), 6.64 (ddd, J = 11.5, 10.4, 1.1 Hz, 1H), 5.82 (ddd, J = 11.4, 1.3, 1.3 Hz, 1H), 1.49 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 165.2, 141.6, 134.6, 123.7, 93.0, 80.9, 28.2; IR (neat): 2978, 2932, 1710, 1479, 1456, 1407, 1368, 1315, 1285, 1248, 1223, 1148, 989, 934, 862, 830, 748, 659, 555 cm⁻¹; HRMS (EI) Calcd for C₉H₁₃IO₂ [M⁺] 279.9960, Found 279.9962.

(2E,4Z)-tert-Butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (1.2.6): To a solution of E,Z-dienyl iodide 1.2.4 (0.708 g, 2.53 mmol) and triisopropylborate (0.64 mL, 2.8 mmol) in 16 mL of toluene and 4 mL of THF at -78 °C, was added a 1.6M solution of n-butyllithium in hexane (1.74 mL, 2.78 mmol). The reaction was stirred at -78 °C for 30 min and pinacol (0.360 g, 3.04 mmol) was added at -78 °C. The reaction was protected from light (aluminum foil), warmed to 25 °C and stirred for 16 h. The reaction mixture was then diluted with Et₂O, washed with saturated aqueous ammonium chloride solution, water and brine. The organic layer was dried with MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel using 20% Et₂O in hexane (Rf = 0.35 using 10% Et₂O in hexane) gave compound 1.2.6 (0.597 g,
84%) as a yellow oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.97 (ddd, $J$ = 15.4, 11.5, 1.0 Hz, 1H), 6.90 (apparent t, $J$ = 12.4 Hz, 1H), 5.88 (d, $J$ = 15.4 Hz, 1H), 5.76 (d, $J$ = 13.3 Hz, 1H), 1.50 (s, 9H), 1.30 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.1, 146.9, 142.6, 127.0, 83.5, 80.2, 28.1, 24.8; IR (neat): 2979, 2933, 1711, 1632, 1588, 1425, 1392, 1969, 1337, 1304, 1261, 1233, 1142, 1072, 1015, 980, 968, 879, 846, 793, 723 cm$^{-1}$; HRMS (EI) Calcd for C$_{15}$H$_{25}$BO$_4$ [M$^+$] 280.1846, Found 280.1848.

Synthesis of boronate esters 1.2.44:

(2E,4Z)-5-Iodo-1-(pyrrolidin-1-yl)penta-2,4-dien-1-one (1.2.74): To a solution of ethyl (Z)-β-iodoacrylate 1.2.3 (2.00 g, 8.85 mmol) in 20 mL of dichloromethane at -78 °C was added a 1M solution of diisobutylaluminum hydride in heptane (9.8 mL, 9.8 mmol) dropwise via syringe pump over 10 min. The reaction was stirred for another 30 min at -78 °C and conversion was monitored by TLC analysis. The reaction was quenched at -78 °C by the addition of 5 mL of methanol and 40 mL of saturated aqueous potassium sodium tartrate solution and was allowed to warm to 25 °C. After stirring vigorously at 25 °C for 1 h, the solution was diluted with H$_2$O and the aqueous phase was extracted with
The combined organic layers were dried with Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the aldehyde as a yellow oil. Separately, $N,N$-tetramethylene-$\alpha$-(diethylphosphono)acetamide$^{89}$ (4.40 g, 17.7 mmol) was added dropwise to a suspension of NaH (478 mg, 15.9 mmol) in THF (40 mL) at 0 °C. After stirring at 0 °C for 30 min, a solution of the crude aldehyde in 15 mL of THF was added dropwise and the reaction was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NaHCO$_3$ solution and the aqueous layer was extracted with Et$_2$O (x 3). The combined organic layers were dried with MgSO$_4$, filtered, and concentrated in vacuo. Chromatography on silica gel using 80% EtOAc in hexane (R$_f$ = 0.38) gave the vinyl iodide 1.2.74 (1.64 g, 67%) as a yellow solid (the solid resulting from the evaporation of EtOAc and hexane), m.p. = 114-117 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 (ddd, $J$ = 14.9, 10.5, 1.1 Hz, 1H), 6.91 (ddd, $J$ = 10.4, 7.8, 0.8 Hz, 1H), 6.73 (dd, $J$ = 7.8, 0.8 Hz, 1H), 6.45 (dd, $J$ = 14.9, 0.4 Hz, 1H), 3.54 (apparent q, $J$ = 6.9 Hz, 4H), 2.02-1.86 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 164.2, 140.2, 137.0, 126.6, 89.9, 46.5, 46.0, 26.1, 24.2; IR (neat): 3058, 2969, 2869, 1653, 1605, 1568, 1442, 1336, 1300, 1231, 1166, 1041, 989, 876, 811, 751, 735, 711, 669, 653 cm$^{-1}$; HRMS (El) calcd for C$_9$H$_{12}$INO [M$^+$] 276.9964, found 276.9963.

![Image of 1.2.44](image)

(2E,4Z)-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(pyrrolidin-1-yl)penta-2,4

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-dien-1-one (1.2.44): To a solution of vinyl iodide 1.2.74 (0.500 g, 2.20 mmol) and triisopropylborate (0.54 mL, 2.4 mmol) in 20 mL of toluene and 5 mL of THF at -95 °C, was added a 1.6M solution of n-butyllithium in hexane (1.52 mL, 2.42 mmol). The reaction was stirred at -95 °C for 30 min and pinacol (310 mg, 2.64 mmol) was added at -95 °C. The reaction was protected from light (aluminum foil), warmed to 25 °C and stirred for 16 h. The reaction mixture was then diluted with Et₂O, washed with saturated aqueous ammonium chloride solution, water and brine. The organic layer was dried with MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel using 80% EtOAc in hexane (Rf = 0.43) gave compound 1.2.44 (0.266 g, 44%) as a brown oily solid (the solid resulting from the evaporation of EtOAc and hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.01 (ddd, J = 14.9, 11.5, 0.9 Hz, 1H), 6.94 (t, J = 12.4 Hz, 1H), 6.27 (d, J = 14.9 Hz, 1H), 5.73 (d, J = 13.4 Hz, 1H), 3.55 (apparent q, J = 7.0 Hz, 4H), 2.00–1.84 (m, 4H), 1.30 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 164.8, 147.4, 140.7, 126.0, 83.5, 46.5, 45.9, 26.1, 24.8, 24.3; IR (neat): 2975, 2872, 1648, 1611, 1586, 1442, 1406, 1371, 1335, 1300, 1281, 1260, 1143, 1010, 967, 879, 846, 786, 718 cm⁻¹; HRMS (El) calcld for C₁₅H₂₄BNO₃ [M⁺] 277.1849, found 277.1852.

Synthesis of boronate ester 1.2.46:

\[ \text{CO}_2\text{Et} \xrightarrow{\text{1. DIBAL, CH}_2\text{Cl}_2, -78 \degree \text{C}} \xrightarrow{\text{2. (EtO)}_2\text{(O)P}} \xrightarrow{\text{NaH, THF, 0 \degree \text{C to r.t. 1 h, 24%}}} \text{CN} \]

\[ \text{CN} \xrightarrow{\text{1. (i-PrO)}_3\text{B, n-BuLi, THF/toluene, -78 \degree \text{C}}} \xrightarrow{\text{2. pinacol, -78 \degree \text{C to r.t. 42%}}} \text{BO} \]

1.2.46

1.2.75

1.2.75
(2E,4Z)-5-Iodopenta-2,4-dienitrile (1.2.75): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.74. Using the reaction conditions described above with (Z)-β-iodoacrylate 1.2.3 (2.00 g, 8.85 mmol) and diethyl cyanomethylphosphonate (3.10 g, 17.7 mmol) as the starting material, followed by chromatography on silica gel using 20% Et₂O in hexane (Rᵢ = 0.54) gave the vinyl iodide 1.2.75 (0.436 g, 24%) as an orange oil. ¹H NMR (400 MHz, CDCl₃): δ 7.19 (dd, J = 16.0, 10.1 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.90 (dd, J = 10.3, 7.9 Hz, 1H), 5.63 (d, J = 15.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 149.3, 135.8, 117.5, 103.0, 94.0; IR (neat): 3066, 2217, 1615, 1558, 1317, 1255, 968, 833, 708, 652 cm⁻¹; HRMS (EI) calcd for C₅H₄IN [M⁺] 204.9388, found 204.9386.

(2E,4Z)-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienitrile (1.2.46): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.6. Using the reaction conditions described above with vinyl iodide 1.2.75 (0.540 g, 2.63 mmol) as the starting material, followed by chromatography on silica gel using 30% Et₂O in hexane (Rᵢ = 0.48) gave compound 1.2.46 (0.229 g, 42%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 74-77 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.86 (ddd, J = 16.1, 11.2, 1.0 Hz, 1H), 6.83 (t, J = 12.2 Hz, 1H), 5.85 (d, J = 13.2 Hz, 1H), 5.45 (d, J = 16.1 Hz, 1H), 1.30 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 149.6, 145.6, 118.0, 102.2, 83.9, 24.8; IR (neat): 2981, 2218, 1580, 1424, 1261, 1142, 967, 845 cm⁻¹; HRMS (EI) calcd for C₁₁H₁₆BNO₂ [M⁺]
Synthesis of potassium organotrifluoroborate 1.2.48.\(^9\)

(1.2.48): To a solution of \(E,Z\)-dienyl iodide 1.2.4. (0.20 g, 0.71 mmol) and triisopropylborate (0.18 mL, 0.78 mmol) in 6 mL of toluene and 1.5 mL of THF at -78 °C, was added a 1.6M solution of \(n\)-butyllithium in hexane (0.49 mL, 0.78 mmol). The reaction was stirred at -78 °C for 30 min, and then hydrolyzed by addition of aqueous 2N HCl. The resulting solution was stirred at 25 °C for 20 min and the aqueous layer was extracted with Et\(_2\)O (× 3). The combined organic layers were dried with MgSO\(_4\), filtered, and concentrated in \textit{vacuo} to afford the intermediate as yellow oil. A 4 M KHF\(_2\) solution was added and the mixture was stirred at 25 °C for 20 min, then stored at 4 °C for 16 h. The yellow precipitate was collected by vacuum filtration and dried in \textit{vacuo} to afford the title compound as yellow solid (0.136 g, 74%), m.p. = 121-124 °C. \(^1\)H NMR (400 MHz, CD\(_3\)CN): \(\delta\) 7.83 (dd, \(J = 15.6, 11.6\) Hz, 1H), 6.36 (bs, 1H), 5.99 (dq, \(J = 13.4, 5.4\) Hz, 1H), 5.57 (d, \(J = 15.4\) Hz, 1H), 1.45 (s, 9H); \(^13\)C NMR (100 MHz, CD\(_3\)CN): \(\delta\) 168.1, 147.1, 134.1, 121.1, 80.1, 28.5; IR (neat): 2974, 1703, 1626, 1455, 1393, 1367, 1310, 1273, 1158, 978, 870, 740 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_9\)H\(_{13}\)BF\(_3\)O\(_2\) [M-K\(^+\)] 221.0966, found 221.0955.

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(Z)-tert-Butyl 3-iodoacrylate (1.2.76): The title compound was prepared according to the previously reported procedure for the synthesis of 1.2.3. Using reaction conditions described in literature with tert-butyl propiolate (1.00 g, 7.93 mmol) as the starting material, gave the title compound 1.2.76 (0.807 g, 40%) as yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.29 (d, $J = 8.8$ Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 1.53 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.8, 131.4, 92.5, 81.8, 28.1; IR (neat): 3063, 2979, 2933, 1725, 1598, 1479, 1394, 1369, 1286, 1257, 1218, 1148, 946, 850, 812, 772, 753, 639 cm$^{-1}$; HRMS (EI) calcd for C$_7$H$_{11}$IO$_2$ [M$^+$] 253.9804, found 253.9808.

Synthesis of boronate ester 1.2.49:

(Z)-tert-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (1.2.49): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.6. Using the reaction conditions described above with tert-butyl (Z)-β-iodoacrylate 1.2.76 (0.807 g, 3.18 mmol) as the starting material, followed by chromatography on silica gel using 20% Et$_2$O in hexane (R$_f$ = 0.48), gave the title compound 1.2.49 (0.418 g, 52%) as yellow solid (the solid resulting from the evaporation of Et$_2$O and hexane), m.p. = 61-63 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.27 (d, $J = 12.8$
Hz, 1H), 6.15 (d, \( J = 13.2 \) Hz, 1H), 1.47 (s, 9H), 1.35 (s, 12H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 166.5, 135.3, 83.8, 80.7, 28.1, 24.8; IR (neat): 2979, 2934, 1715, 1627, 1482, 1456, 1404, 1371, 1315, 1268, 1228, 1140, 968, 952, 878, 864, 846, 818, 794, 754, 672, 578, 540 cm\(^{-1}\); HRMS (EI) calcd for C\(_9\)H\(_{14}\)BO\(_4\) [M-(C\(_4\)H\(_9\))\(^+\)] 197.0985, found 197.0984

Preparation of boronate ester 1.2.50:

\[ \textbf{1.2.50} \]

\((2Z,4Z)-\text{tert-Butyl \ 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (1.2.50):} The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.6. Using the reaction conditions described above with vinyl iodide 1.2.5 (0.739 g, 2.64 mmol) as the starting material, followed by chromatography on silica gel using 10% Et\(_2\)O in hexane (R\(_f\) = 0.45), gave the title compound 1.2.50 (0.479 g, 65%) as a colorless oily solid. \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 8.03 (t, \( J = 12.5 \) Hz, 1H), 7.33 (t, \( J = 11.3 \) Hz, 1H), 5.42 (dt, \( J = 13.5, 1.2 \) Hz, 1H), 5.72 (dt, \( J = 11.4, 1.2 \) Hz, 1H), 1.49 (s, 9H), 1.29 (s, 12H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 165.6, 144.5, 141.6, 122.6, 83.4, 80.4, 28.2, 24.8; IR (neat): 2979, 2934, 1713, 1577, 1458, 1390, 1375, 1329, 1301, 1281, 1262, 1223, 1141, 1112, 1047, 1016, 968, 933, 918, 877, 864, 846, 806, 748, 715, 681, 630, 579 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{11}\)H\(_{17}\)BO\(_4\) [M-(C\(_4\)H\(_9\))\(^+\)] 224.1220, Found 224.1223.

Synthesis of boronate ester 1.2.51:
(2E,4E)-tert-Butyl 5-iodopenta-2,4-dienoate (1.2.77): To a solution of ethyl (Z)-β-iodoacrylate 1.2.3 (2.00 g, 8.85 mmol) in 20 mL of dichloromethane at -78 °C was added a 1M solution of diisobutylaluminum hydride in heptane (9.8 mL, 9.8 mmol) dropwise via syringe pump over 10 min. The reaction was stirred for another 30 min at -78 °C and conversion was monitored by TLC analysis. The reaction mixture was warmed to 0 °C and stirred for 15 min before recooling to -78 °C and quenching by the addition of 5 mL of methanol and 40 mL of saturated aqueous potassium sodium tartrate solution. After warming to 25 °C, the mixture was stirred vigorously at 25 °C for 1 h. The solution was diluted with H2O and the aqueous phase was extracted with Et2O (× 3). The combined organic layers were dried with Na2SO4, filtered, and concentrated in vacuo to afford the aldehyde as a yellow oil. Separately, tert-butyl P,P-dimethyl-phosphonoacetate (3.5 mL, 18 mmol) was added dropwise to a suspension of NaH (478 mg, 15.9 mmol) in THF (40 mL) at 0 °C. After stirring at 0 °C for 30 min, a solution of the crude aldehyde in 15 mL of THF was added dropwise and the reaction was warm to 25 °C and stirred for 2 h. The reaction was quenched with saturated aqueous NaHCO3 solution and the aqueous layer was extracted with Et2O (× 3). The combined organic layers were dried with MgSO4, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% EtOAc in hexane (Rf = 0.68) gave the vinyl iodide 1.2.77 (1.28 g, 52%) as a yellow oily
solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.15 (dd, $J = 14.3$, 11.2 Hz, 1H), 7.04 (dd, $J = 15.1$, 11.1 Hz, 1H), 6.87 (d, $J = 14.1$ Hz, 1H), 5.83 (d, $J = 14.9$ Hz, 1H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.8, 143.1, 141.9, 123.7, 88.5, 80.8, 28.1; IR (neat): 2920, 1708, 1626, 1457, 1368, 1318, 1277, 1218, 1147, 1116, 988 cm$^{-1}$; HRMS (EI) calcd for C$_9$H$_{13}$IO$_2$ [M$^+$] 279.9960, found 279.9965.

(2E,4E)-$^{2}$-$^{2}$-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (1.2.51): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.44. Using the reaction conditions described above with vinyl iodide 1.2.77 (0.20 g, 0.71 mmol) as the starting material, gave the title compound as a yellow oily solid (0.195 g, 98%). The material was sufficiently pure as determined by NMR spectroscopy to be used for subsequent reactions. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.17 (dd, $J = 15.1$, 11.1 Hz, 1H), 7.03 (dd, $J = 17.2$, 11.1 Hz, 1H), 5.91 (d, $J = 16.5$ Hz, 1H), 5.91 (d, $J = 15.2$ Hz, 1H), 1.49 (s, 9H), 1.29 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.0, 146.4, 144.1, 126.3, 83.6, 80.6, 28.1, 24.8; IR (neat): 2978, 2929, 1713, 1631, 1600, 1366, 1330, 1264, 1143, 1121, 1012, 969, 849 cm$^{-1}$; HRMS (EI) calcd for C$_{15}$H$_{25}$BO$_4$ [M$^+$] 280.1846, found 280.1850.

Synthesis of boronate ester 1.2.52:
The title compound was prepared according to the previously reported procedure. Using reaction conditions described in literature with tert-butyl 2-bromoacetate (3.00 g, 15.4 mmol) as the starting material, gave the title compound 1.2.78 (4.22 g, 76%) as yellow oil. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 4.49-4.41 (m, 4H), 3.08 (d, \(J = 20.9\) Hz, 2H), 1.48 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 163.6 (d, \(J = 3.8\) Hz), 122.4 (qd, \(J = 277.6, 8.4\) Hz), 83.4, 62.5 (qd, \(J = 38.2, 5.6\) Hz), 35.3 (d, \(J = 141.6\) Hz), 27.8; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \(\delta\) -75.8 (t, \(J = 7.6\) Hz); \(^{31}\)P NMR (121 MHz, CDCl\(_3\)): \(\delta\) 25.2; IR (neat): 2983, 1728, 1458, 1419, 1373, 1298, 1172, 1073, 964, 898, 845, 710, 654, 555 cm\(^{-1}\); HRMS (EI) calcd for C\(_6\)H\(_6\)F\(_6\)O\(_4\)P \([M^+\] 286.9908, found 286.9918.

(2Z,4E)-tert-butyl 5-iodopenta-2,4-dienoate (1.2.79): To a solution of ethyl (Z)-β-iodoacrylate 1.2.3 (2.00 g, 8.85 mmol) in 20 mL of dichloromethane at -78 °C was added a 1M solution of diisobutylaluminum hydride in heptane (9.8 mL, 9.8 mmol) dropwise via syringe pump over 10 min. The reaction was stirred for another 30 min at -78 °C and conversion was monitored by TLC analysis. The reaction mixture was warmed to 0 °C and stirred for 15 min before quenched at -78 °C by the addition of 5 mL of methanol and 40 mL of saturated aqueous potassium sodium tartrate solution and was allowed to warm to 25 °C. After stirring vigorously at 25 °C for 1 h, the solution was diluted with H₂O and the aqueous phase was extracted with Et₂O (× 3). The combined organic layers were dried with Na₂SO₄, filtered and concentrated in vacuo to afford the aldehyde as a yellow oil. Separately, to a solution of phosphonate 1.2.78 (4.80 g, 13.4 mmol) in 40 mL of THF was added 18-C-6 (2.67 g, 10.1 mmol). The solution was cooled to 0 °C before KH (0.43 g, 10.7 mmol, freshly washed with dry hexane) was added and the mixture was cooled to -78 °C. The crude aldehyde in 20 mL of THF, cooled to -78 °C, was added via cannula and stirred at this temperature for 30 min. The reaction was quenched with saturated aqueous NH₄Cl solution and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers was dried with Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 3% EtOAc in hexane (R_f = 0.55) gave the vinyl iodide 1.2.79 (0.797 g, 32%) as a yellow oily solid. ¹H NMR (400 MHz, CDCl₃): δ 8.38 (ddd, J = 14.5, 11.4, 1.1 Hz, 1H), 6.84 (dt, J = 14.7, 0.7 Hz, 1H), 6.36 (apparent td, J = 11.4, 0.7 Hz, 1H), 5.57 (ddd, J = 11.4, 1.1, 0.7 Hz, 1H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 165.2, 141.6, 141.4, 119.6, 90.2, 80.6, 28.1; IR (neat): 3064, 3033, 2977, 2932, 1708, 1615, 1554, 1480, 1454, 1408, 1392, 1367, 1311. 1274, 1247, 1219, 1150, 1064, 990, 954, 935, 918, 836, 832, 788, 749, 691, 554 cm⁻¹; HRMS (EI) calcd for
C₅H₄IO [M-(OC₄H₉)+] 206.9307, found 206.9299.

1.2.52

(2Z,4E)-tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (1.2.52): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.44. Using the reaction conditions described above with vinyl iodide 1.2.79 (0.20 g, 0.71 mmol) as the starting material, gave the title compound 1.2.52 (0.193 g, 97%) as a yellow oily solid. The material was sufficiently pure as determined by NMR spectroscopy to be used for subsequent reactions. ¹H NMR (400 MHz, CDCl₃): δ 8.15 (dd, J = 17.8, 11.2 Hz, 1H), 6.52 (t, J = 11.3 Hz, 1H), 5.83 (d, J = 17.8 Hz, 1H), 5.68 (d, J = 11.4 Hz, 1H), 1.51 (s, 9H), 1.27 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 165.2, 144.25, 144.18, 122.5, 83.5, 80.5, 28.1, 24.7; IR (neat): 2978, 1715, 1590, 1370, 1341, 1220, 1142, 1016, 970, 849 cm⁻¹; HRMS (EI) calcd for C₁₄H₂₂BO₄ [M-(CH₃)+] 265.1611, found 265.1621.

Preparation of boronate ester 1.2.53:
(2E,4Z)-**tert-Butyl 5-ido-2-methylpenta-2,4-dienoate** (1.2.81): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.74. Using the reaction conditions described above with (Z)-β-iodoacrylate 1.2.3 (2.00 g, 8.85 mmol) and phosphonate 1.2.80\(^92\) (4.00 g, 17.7 mmol) as the starting materials, followed by chromatography on silica gel using 2% Et\(_2\)O in hexane (R\(_f\) = 0.41) gave the vinyl iodide 1.2.81 (1.45 g, 56%) as a orange oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.23 (ddq, J = 10.6, 1.5, 1.5 Hz, 1H), 7.01 (dd, J = 11.0, 7.7 Hz, 1H), 6.73 (dt, J = 7.3, 0.9 Hz, 1H), 1.93 (d, J = 1.5 Hz, 3H), 1.53 (s, 9H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ 166.9, 136.0, 134.0, 133.4, 90.6, 80.6, 28.0, 13.9; IR (neat): 3067, 2977, 2930, 1703, 1624, 1558, 1475, 1456, 1392, 1367, 1296, 1255, 1169, 1126, 1070, 983, 850, 760, 701, 608 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{10}\)H\(_{15}\)IO\(_2\) [M\(^{+}\)] 294.0117, found 294.0117.

(2E,4Z)-**tert-Butyl 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate** (1.2.53): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.6. Using the reaction conditions described above with

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vinyl iodide 1.2.81 (1.45 g, 4.93 mmol) as the starting material, followed by chromatography on silica gel using 10% Et\(_2\)O in hexane (R\(_f\) = 0.49), gave the title compound 1.2.53 (1.16 g, 80%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 7.92 (dt, \(J = 11.7, 1.3 \text{ Hz}, 1\)H), 7.18 (t, \(J = 12.7 \text{ Hz}, 1\)H), 5.73 (d, \(J = 13.2 \text{ Hz}, 1\)H), 1.93 (d, \(J = 1.5 \text{ Hz}, 3\)H), 1.52 (s, 9H), 1.31 (s, 12H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta \) 167.7, 144.4, 136.1, 132.3, 83.4, 80.1, 28.1, 24.9, 12.2; IR (neat): 2978, 2931, 1702, 1627, 1578, 1429, 1391, 1369, 1352, 1323, 1259, 1218, 1173, 1144, 968, 846, 750 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{16}\)H\(_{27}\)BO\(_4\) [M\(^+\)] 294.2002, found 294.2006.

Synthesis of boronate ester 1.2.55:

\(\text{(E)}\)-\text{tert-Butyl 3-formylbut-2-enoate (1.2.82)}: The title compound was prepared according to the previously reported procedure.\(^{93}\) Using reaction conditions described in literature with 1,1-dimethoxypropan-2-one (3.00 g, 25.4 mmol) and \text{tert-}butyl P,P-dimethylphosphonoacetate (5.8 mL, 29 mmol) as the starting materials, followed by chromatography on silica gel using 10% Et\(_2\)O in hexane (R\(_f\) = 0.68), gave the title compound 1.2.82 (2.86 g, 66%) as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 9.52 (s,

1H), 6.43 (q, J = 1.6 Hz, 1H), 2.12 (d, J = 1.6 Hz, 3H), 1.54 (s, 9H); 13C NMR (100 MHz, CDCl3): δ 194.9, 164.8, 149.1, 137.8, 82.1, 28.1, 10.6; IR (neat): 2980, 1715, 1703, 1395, 1370, 1356, 1300, 1283, 1180, 1152, 1028, 827 cm⁻¹; HRMS (EI) Calcd for C₅H₅O₃ [M-C₄H₉⁺] 113.0239, found 113.0239.

(2E,4Z)-tert-Butyl 5-iodo-3-methylpenta-2,4-dienoate (1.2.83): To a solution of iodomethyltriphenylphosphonium iodide 94 (4.05g, 7.64 mmol) in 30 mL of THF at 25 °C was added dropwise a 1M solution of sodium hexamethyldisilazaine (7.6 mL, 7.6 mmol) in THF. The mixture was stirred at 25 °C for another 15 min and cooled to -78 °C. A solution of aldehyde 1.2.82 in 10 mL of THF was added dropwise and the resulting reaction mixture was stirred at -78 °C for 15 min, then warmed to 25 °C and stirred for another 30 min. The reaction was quenched by addition of hexane, the precipitate was removed by filtered through a pad of Celite, H₂O was added and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers was dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 3% Et₂O in hexane with 1% Et₃N (Rf = 0.36) gave the vinyl iodide 1.2.83 (0.597 g, 35% as a yellow oil). ¹H NMR (400 MHz, CDCl₃): δ 6.81 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.92-5.91 (m, 1H), 2.33 (d, J = 1.6 Hz, 3H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 165.9, 150.4, 141.3, 122.6, 81.0, 80.3, 28.2, 17.7; IR (neat): 2978, 2932, 1709, 1638, 1613, 1456, 1435, 1391, 1366, 1352, 1319, 1298, 1246, 1234, 1142, 868 cm⁻¹; HRMS (EI) Calcd for

C\textsubscript{10}H\textsubscript{15}IO\textsubscript{2} [M\textsuperscript{+}] 294.0117, found 294.0112.

(2\textit{E},4\textit{Z})-\textit{tert}-Butyl 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (1.2.55): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.6. Using the reaction conditions described above with vinyl iodide 1.2.83 (0.339 g, 1.15 mmol) as the starting material, followed by chromatography on silica gel using 15\% Et\textsubscript{2}O in hexane (R\textsubscript{f} = 0.46), gave the title compound 1.2.55 (0.230 g, 68\% as a yellow oil). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 6.66 (d, \(J\) = 14.5 Hz, 1H), 5.79-5.77 (m, 1H), 5.58 (d, \(J\) = 14.6 Hz, 1H), 2.29 (d, \(J\) = 1.4 Hz, 3H), 1.48 (s, 9H), 1.29 (s, 12H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 166.3, 152.7, 149.0, 121.7, 83.8, 79.8, 28.2, 24.8, 16.5; IR (neat): 2978, 2932, 1709, 1601, 1368, 1341, 1314, 1248, 1138 cm\textsuperscript{-1}; HRMS (EI) Calcd for C\textsubscript{16}H\textsubscript{27}BO\textsubscript{4} [M\textsuperscript{+}] 294.2002, found 294.2013.

Preparation of boronate ester 1.2.57:
(2E,4Z)-tert-Butyl 5-iodo-4-methylpenta-2,4-dienoate (1.2.85): MnO₂ (7.58 g, 87.2 mmol) was added to a solution of (Z)-3-iodo-2-methyl-prop-2-en-1-ol 1.2.84⁹⁵ (0.864 g, 4.36 mmol) in 15 mL of dichloromethane at 25 °C and stirred for 16 h. Then the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to afford the crude aldehyde as a yellow oil. Separately, tert-butyl P,P-dimethylphosphonoacetate (1.8 mL, 8.7 mmol) was added dropwise to a suspension of NaH (240 mg, 7.85 mmol) in THF (30 mL) at 0 °C. After stirring at 0 °C for 30 min, a solution of the crude aldehyde in 15 mL of THF was added dropwise and the reaction was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NaHCO₃ solution and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% EtOAc in hexane (Rₖ = 0.65) gave the vinyl iodide 1.2.85 (0.986 g, 77%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (dd, J = 15.8, 0.7 Hz, 1H), 6.58 (q, J = 0.7 Hz, 1H), 5.98 (dd, J = 15.8, 0.8 Hz, 1H), 1.99 (d, J = 1.5 Hz, 3H), 1.52 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 165.9, 143.9, 140.9, 124.5, 87.4, 80.8, 28.1, 21.0; IR (neat): 3060, 2978, 2930, 1710, 1624, 1566, 1440, 1392, 1367, 1309, 1277, 1147, 1029, 978, 868, 842, 770, 740, 721, 672 cm⁻¹; HRMS (EI) Calcd for C₁₀H₁₅IO₂ [M⁺] 294.0117, found 294.0123.

(2E,4Z)-tert-Butyl 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-
2,4-dienoate (1.2.57): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.6. Using the reaction conditions described above with vinyl iodide 1.2.85 (0.986 g, 3.35 mmol) as the starting material, followed by chromatography on silica gel using 10% EtOAc in hexane ($R_f = 0.50$), gave the title compound 1.2.57 (0.821 g, 83%) as a white solid (the solid resulting from the evaporation of EtOAc and hexane), m.p. = 63-65 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.15 (d, $J = 16.1$ Hz, 1H), 5.90 (d, $J = 16.1$ Hz, 1H), 5.64 (br. s, 1H), 1.99 (d, $J = 1.2$ Hz, 3H), 1.52 (s, 9H), 1.30 (s, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.4, 152.7, 143.8, 122.9, 83.4, 80.1, 28.2, 24.8, 22.2; IR (neat): 2978, 2932, 1711, 1626, 1593, 1450, 1380, 1368, 1335, 1282, 1213, 1141, 1108, 1030, 995, 970, 905, 879, 850, 769, 731, 643, 578, 514 cm$^{-1}$; HRMS (ESI) Calcd for C$_{16}$H$_{27}$BNaO$_4$ [M+Na$^+$] 317.1894, found 317.1894.

Synthesis of boronate ester 1.2.59:

(2E,4Z)-tert-Butyl 5-iodohexa-2,4-dienoate (1.2.87): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.85. Using the reaction conditions described above with (Z)-3-iodo-2-butenol 1.2.86 (1.00 g, 5.10 mmol) as the starting material, followed by chromatography on silica gel using 5% Et$_2$O in hexane

(R_f = 0.53) gave the vinyl iodide 1.2.87 (0.850 g, 57%) as a yellow oil. ^1H NMR (400 MHz, CDCl3): δ 7.24 (ddd, J = 15.4, 10.3, 0.4 Hz, 1H), 6.21 (ddd, J = 10.3, 1.5, 0.9 Hz, 1H), 5.93 (dt, J = 15.4, 0.7 Hz, 1H), 2.66 (t, J = 0.8 Hz, 3H), 1.50 (s, 9H); ^13C NMR (100 MHz, CDCl3): δ 166.1, 145.0, 132.7, 125.2, 111.0, 80.5, 34.8, 28.1; IR (neat): 2977, 1705, 1630, 1560, 1540, 1477, 1457, 1391, 1367, 1323, 1255, 1225, 1168, 1136, 1074, 1031, 978, 880, 851, 765, 744, 715 cm⁻¹; HRMS (EI) Calcd for C_{10}H_{15}IO_{2} [M⁺] 294.0117, Found 294.0111.

(2E,4E)-tert-Butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-2,4-dienoate (1.2.59): The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.6. Using the reaction conditions described above with vinyl iodide 1.2.87 (0.808 g, 2.75 mmol) as the starting material, followed by chromatography on silica gel using 10% Et₂O in hexane (R_f = 0.45) gave compound 1.2.59 (0.553 g, 68%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 38-42 °C. ^1H NMR (400 MHz, CDCl3): δ 7.95 (dd, J = 15.2, 11.6 Hz, 1H), 6.64 (d, J = 11.4 Hz, 1H), 5.75 (d, J = 15.4 Hz, 1H), 1.92 (d, J = 0.88 Hz, 3H), 1.50 (s, 9H), 1.31 (s, 12H); ^13C NMR (100 MHz, CDCl3): δ 166.6, 142.9, 142.0, 124.1, 83.6, 79.8, 28.2, 24.8, 23.0; IR (neat): 2978, 1703, 1627, 1592, 1393, 1368, 1271, 1141, 1093, 945, 863, 683 cm⁻¹; HRMS (EI) Calcd for C_{16}H_{27}BO_{4} [M⁺] 294.2002, Found 294.2002.
(2E,4Z)-tert-Butyl 5-iodo-5-phenylpenta-2,4-dienoate (1.2.88): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.85. Using the reaction conditions described above with (Z)-3-iodo-3-phenylprop-2-en-1-ol\textsuperscript{97} (1.00 g, 3.85 mmol) as the starting material, followed by chromatography on silica gel using 5% EtOAc in hexane (R\textsubscript{f} = 0.54) gave compound 1.2.88 (1.10 g, 80%) as a yellow oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.56-7.46 (m, 3H), 7.36-7.29 (m, 3H), 6.66 (dd, J = 10.4, 0.8 Hz, 1H), 6.11 (dd, J = 15.2, 1.0 Hz, 1H), 1.52 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 165.9, 145.4, 142.3, 133.7, 129.4, 128.8, 128.4, 127.3, 113.9, 80.7, 28.1; IR (neat): 2976, 1705, 1618, 1443, 1393, 1368, 1323, 1285, 1256, 1213, 1161, 1134, 980, 885, 760, 692, 631 cm\textsuperscript{-1}; HRMS (El) Calcd for C\textsubscript{15}H\textsubscript{17}IO\textsubscript{2} [M\textsuperscript{+}] 356.0273, found 356.0288.

Synthesis of boronate ester 1.2.89:\textsuperscript{98}

\[
\text{Ph} \quad \begin{array}{c}
\text{O} \\
(2E,4E) - \text{tert-Butyl} \
\begin{array}{c}
\text{5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-phenylpenta-2,4-dienoate} \quad \text{1.2.89}\end{array}
\end{array}
\]

(2E,4E)-tert-Butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-phenylpenta-2,4-dienoate (1.2.89): To a solution of Pd(OAc)\textsubscript{2} (5.1 mg, 0.02 mmol), 2-(dicyclohexylphosphino)biphenyl (31.4 mg, 0.090 mmol) and Et\textsubscript{3}N (0.22 mL, 1.6 mmol) at 25 °C was added vinyl iodide 1.2.88 (0.400 g, 1.12 mmol). The reaction mixture was heated to 80 °C and pinacolborane (0.43 mL, 3.0 mmol) was added dropwise. After heating at 80 °C for 3 h, the reaction was cooled to 25 °C and quenched by addition of H\textsubscript{2}O. The reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} and filtered through a pad of


Celite to remove the precipitate. The aqueous layer was extracted with CH₂Cl₂ (× 3), the combined organic layers was dried with Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% Et₂O in hexane (Rf = 0.41) gave the boronate ester 1.2.89 (0.231 g, 58%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 76-79 °C. ^1H NMR (400 MHz, CDCl₃): δ 7.90 (dd, J = 15.2, 11.7 Hz, 1H), 7.45-7.40 (m, 2H), 7.35-7.19 (m, 3H), 6.98 (d, J = 11.7 Hz, 1H), 5.94 (dd, J = 15.0, 0.8 Hz, 1H), 1.51 (s, 9H), 1.38 (s, 12H); ^13C NMR (100 MHz, CDCl₃): δ 166.1, 142.3, 141.5, 140.2, 128.3, 127.6, 127.3, 126.3, 84.2, 80.1, 28.2, 24.8; IR (neat): 2978, 2932, 1703, 1579, 1493, 1453, 1391, 1369, 1283, 1213, 1137, 1032, 968, 923, 855, 764, 721, 696 cm⁻¹; HRMS (EI) Calcd for C₂₁H₂₉BO₄ [M⁺] 356.2159, found 356.2164.

(2E,4Z)-tert-Butyl 5-iodo-6-methylhepta-2,4-dienoate (1.2.90): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.85. Using the reaction conditions described above with (Z)-3-iodo-4-methyl-pent-2-en-1-ol⁹⁹ (1.00 g, 4.42 mmol) as the starting material, followed by chromatography on silica gel using 5% Et₂O in hexane (Rf = 0.48) gave compound 1.2.90 (1.12 g, 79%) as a yellow oil. ^1H NMR (400 MHz, CDCl₃): δ 7.38 (dd, J = 15.3, 10.3 Hz, 1H), 6.35 (d, J = 10.2 Hz, 1H), 5.95 (d, J = 14.6 Hz, 1H), 2.44-2.33 (m, 1H), 1.50 (s, 9H), 1.09 (d, J = 6.6 Hz, 6H); ^13C NMR (100 MHz, CDCl₃): δ 166.1, 145.2, 130.8, 129.3, 125.7, 80.5, 42.4, 28.1, 23.2; IR (neat): 2969, 2929, 1709, 1628, 1453, 1391, 1367, 1344, 1306, 1278, 1254, 1167, 1138,

Synthesis of boronate ester 1.2.91:

\[
\begin{align*}
\text{(2E,4E)-} & \text{tert-Butyl 6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4-dienoate (1.2.91):} \\
& \text{The title compound was prepared according to the procedure for the synthesis of boronate ester 1.2.89. Using the reaction conditions described above with vinyl iodide 1.2.90 (0.500 g, 1.55 mmol) as the starting material, followed by chromatography on silica gel using 5% Et}_2\text{O in hexane gave compound 1.2.91 (0.185 g, 36%) as a yellow oil.} \\
& \text{\textsuperscript{1}H NMR (400 MHz, } \text{CDCl}_3\text{: } \delta 7.82 \text{ (dd, } J = 15.2, 11.5 \text{ Hz, 1H),} \\
& 6.56 \text{ (d, } J = 11.5 \text{ Hz, 1H),} 5.77 \text{ (d, } J = 15.2 \text{ Hz, 1H),} 2.63-2.51 \text{ (m, 1H),} 1.49 \text{ (s, 9H),} 1.33 \text{ (s, 12H),} 1.07 \text{ (d, } J = 6.8 \text{ Hz, 6H)}; \\
& \text{\textsuperscript{13}C NMR (100 MHz, } \text{CDCl}_3\text{: } \delta 166.5, 143.1, 136.8, 124.2, 83.6, 79.8, 34.9, 28.2, 24.8, 22.1; \text{ IR (neat): 2977, 1706, 1628, 1586, 1467, 1404, 1391, 1368, 1306, 1280, 1204, 1141, 1112, 979, 876, 854, 723, 706 cm}^{-1}; \text{ HRMS (EI)} \\
& \text{Calcd for C}_{14}\text{H}_{23}\text{BO}_4 [M-C}_4\text{H}_8^+ \text{] 266.1689, found 266.1696.}
\end{align*}
\]

\[
\text{(2E,4E)-} \text{tert-Butyl 5-iodo-4-phenylpenta-2,4-dienoate (1.2.92):} \text{ The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.85. Using}
\]
the reaction conditions described above with (Z)-3-iodo-2-phenyl- prop-2-en-1-ol\textsuperscript{98} (1.00 g, 3.85 mmol) as the starting material, followed by chromatography on silica gel using 5% Et\textsubscript{2}O in hexane (R\textsubscript{f} = 0.45) gave compound \textbf{1.2.88} (0.584 g, 43%) as a yellow solid (the solid resulting from the evaporation of Et\textsubscript{2}O and hexane), m.p. = 60-63 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.74 (d, J = 15.6, 1H), 7.39-7.34 (m, 3H), 7.22-7.18 (m, 2H), 6.77 (s, 1H), 5.75 (d, J = 15.6, 1H), 1.49 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 165.9, 148.0, 143.7, 128.52, 128.48, 128.3, 128.58, 128.57, 89.3, 80.8, 28.1; IR (neat): 3055, 2976, 2930, 1699, 1622, 1476, 1454, 1443, 1393, 1368, 1308, 1281, 1258, 1206, 1196, 1148, 1063, 980, 875, 853, 773, 762, 727, 700, 664 cm\textsuperscript{-1}; HRMS (El) Calcd for C\textsubscript{15}H\textsubscript{17}IO\textsubscript{2} [M\textsuperscript{+}] 356.0273, found 356.0277.

Synthesis of boronate ester \textbf{1.2.93}:

![Image of compound 1.2.93](image)

\textbf{(2\textit{E},4\textit{E})-\textit{tert}-Butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-phenylpenta-2,4-dienoate (1.2.93)}: The title compound was prepared according to the procedure for the synthesis of boronate ester \textbf{1.2.89}. Using the reaction conditions described above with vinyl iodide \textbf{1.2.92} (0.700 g, 1.97 mmol) as the starting material, followed by chromatography on silica gel using 15% Et\textsubscript{2}O in hexane (R\textsubscript{f} = 0.48) gave compound \textbf{1.2.93} (0.251 g, 34%) as a yellow solid (the solid resulting from the evaporation of Et\textsubscript{2}O and hexane), m.p. = 98-101 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 8.31 (d, J = 16.0 Hz, 1H), 7.37-7.30 (m, 3H), 7.27-7.23 (m, 2H), 5.76 (s, 1H), 5.72 (d, J = 15.8 Hz, 1H), 1.49 (s,
9H), 1.34 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.3, 157.5, 143.2, 141.4, 128.17, 128.16, 127.8, 126.3, 83.6, 80.2, 28.1, 24.9; IR (neat): 2978, 2932, 1709, 1626, 1586, 1574, 1368, 1360, 1337, 1321, 1306, 1281, 1242, 1213, 1142, 982, 968, 887, 849, 702 cm$^{-1}$; HRMS (EI) Calcd for C$_{21}$H$_{29}$BO$_4$ [M$^+$] 356.2159, found 356.2152.

Synthesis of dienyl iodide 1.2.96:

(Z)-Ethyl 4,4,4-trifluoro-3-iodobut-2-enoate (1.2.95): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.3. Using the reaction conditions described above with 1.2.94$^{100}$ (0.78 g, 4.7 mmol), sodium iodide (1.13 g, 7.52 mmol) and AcOH (1.9 mL, 30 mmol) as the starting materials, gave the vinyl iodide 1.2.95 (0.90 g, 65%) as a yellow oil.$^{101}$ Spectral data matched the previously reported data. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.16-7.14 (m, 1H), 4.31 (q, $J = 7.3$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H).

(2E,4Z)-tert-Butyl 6,6,6-trifluoro-5-iodohexa-2,4-dienoate (1.2.96): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.74. Using the reaction conditions described above with 1.2.95 (0.90 g, 3.1 mmol) and tert-butyl P,P-dimethylphosphonoacetate (0.73 mL, 3.7 mmol) as the starting materials, followed by chromatography on silica gel using 1% Et2O in pentane (Rf = 0.39) gave the vinyl iodide 1.2.96 (0.92 g, 86%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.22 (m, 1H), 7.12 (d, J = 10.6 Hz, 1H), 6.27 (d, J = 15.2 Hz, 1H), 1.52 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 164.7, 140.7, 138.3 (q, J = 6 Hz), 132.9, 122.3, 119.6, 81.6, 28.0; HRMS (EI) Calcd for C₁₀H₁₂F₃IO₂ [M⁺] 347.9834, found 347.9828.

(2E,4Z)-tert-Butyl 6-(benzyloxy)-5-iodohexa-2,4-dienoate (1.2.97): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.85. Using the reaction conditions described above with (Z)-4-(benzyloxy)-3-iodobut-2-en-1-ol¹⁰² (1.29 g, 4.24 mmol) as the starting material, followed by chromatography on silica gel using 10% EtOAc in hexane (Rf = 0.53) gave the vinyl iodide 1.2.97 (1.00 g, 59%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.43-7.28 (m, 6H), 6.68 (d, J = 10.6 Hz, 1H), 6.03 (d, J = 16.0 Hz, 1H), 4.54 (s, 2H), 4.28 (s, 2H), 1.51 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 165.8, 143.5, 137.3, 132.1, 128.5, 127.9, 127.8, 127.3, 113.4, 80.7, 77.9, 72.1, 28.1; IR (neat): 2982, 2978, 2932, 1699, 1630, 1454, 1393, 1368, 1321, 1287, 1256, 1200, 1163, 1138, 1101, 980, 739, 698

(2E,4Z)-tert-Butyl 5-iodo-5-(trimethylsilyl)penta-2,4-dienoate (1.2.98): The title compound was prepared according to the procedure for the synthesis of vinyl iodide 1.2.85. Using the reaction conditions described above with (Z)-3-iodo-3-(trimethylsilyl)prop-2-en-1-ol\textsuperscript{103} (2.51 g, 9.80 mmol) as the starting material, followed by chromatography on silica gel using 5% EtOAc in hexane gave the vinyl iodide 1.2.98 (2.00 g, 58%) as a yellow oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.41 (dd, \(J = 15.2, 10.0\) Hz, 1H), 6.79 (d, \(J = 10.0, 0.8\) Hz, 1H), 6.06 (d, \(J = 15.4, 0.8\) Hz, 1H), 1.51 (s, 9H), 0.22 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 166.0, 144.9, 141.6, 127.7, 124.3, 80.7, 28.1, -1.6; IR (neat): 2976, 1711, 1624, 1560, 1479, 1456, 1392, 1368, 1317, 1289, 1255, 1218, 1154, 1119, 1040, 981, 876, 843, 809, 755, 712, 623 cm\textsuperscript{-1}; HRMS (EI) Calcd for C\textsubscript{12}H\textsubscript{21}IO\textsubscript{2}Si [M\textsuperscript{+}] 352.0356, found 352.0347.

**General Procedure for Rhodium-Catalyzed Cascade Addition/Cyclization Reactions:**

A solution of 0.3 mL of water and 3 mL of dioxane in a 5 mL 2-neck round bottom flask was purged with argon and stirred for 10 min at 25 °C. [Rh(cod)Cl]\textsubscript{2} (3.0 mg, 0.006 mmol), tri-tert-butylphosphonium tetrafluoroborate (3.5 mg, 0.012 mmol) and potassium fluoride (23.3 mg, 0.40 mmol) were added to the solution and stirred at 25 °C for 10 min. To the bright yellow solution was added the alkene (0.09-0.24 mmol), followed by

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addition of the boronate ester (0.20 mmol) and the reaction mixture was stirred at 80 °C for 3 h. The reaction was quenched with brine, and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtrated and concentrated in vacuo. The crude material was then purified by column chromatography on silica gel.

(1.2.12): Using the general procedure above with norbornene 1.2.11 (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 10% Et₂O in hexane (Rf = 0.65) gave compound 1.2.12 (41.9 mg, 84%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 5.41 (dtd, J = 10.6, 7.1, 0.7 Hz, 1H), 4.86 (dddd, J = 10.5, 9.8, 1.6, 1.6 Hz, 1H), 3.09 (dd, J = 7.1, 1.6 Hz, 2H), 2.32 (s, 2H), 1.46 (s, 9H), 1.45-1.41 (m, 3H), 1.27-1.21 (m, 2H), 1.03-0.97 (m, 1H), 0.75 (d, J = 2.2 Hz, 2H), 0.66 (d, J = 10.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 134.5, 119.3, 80.4, 35.9, 34.7, 29.4, 28.4, 28.1, 24.6, 12.9; IR (neat): 2954, 2870, 1735, 1458, 1392, 1367, 1328, 1256, 1146, 1113, 956, 833, 702 cm⁻¹; HRMS (ESI) Calcd for C₁₆H₂₄NaO₂ [M+Na⁺] 271.1668, Found 271.1672. Deuterium labeling study using D₂O gave the deuterated 1.2.73 as yellow oil (23.8 mg, 42%).

(1.2.16): Using the general procedure above with benzonorbornene 1.2.15 (28 mg, 0.20
mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O in hexane
(R_f = 0.33) gave compound **1.2.16** (22.5 mg, 39%) as a yellow oil. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta 7.19\) (dd, \(J = 5.2, 3.3\) Hz, 2H), 7.02 (dd, \(J = 5.3, 3.1\) Hz, 2H), 5.39 (dtd, \(J = 10.7, 7.2, 0.9\) Hz, 1H), 4.95 (dddd, \(J = 10.7, 9.7, 1.8, 1.6\) Hz, 1H), 3.34 (s, 2H), 3.15 (dd, \(J = 7.2, 1.8\) Hz, 2H), 2.55 (dt, \(J = 9.7, 2.2\) Hz, 1H), 1.59-1.54 (m, 1H), 1.48 (s, 9H), 1.29-1.21 (m, 1H), 1.09 (d, \(J = 2.3\) Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta 171.2, 150.7, 133.0, 124.9, 120.8, 119.2, 80.6, 43.1, 38.7, 34.8, 29.4, 28.1, 26.7\); IR (neat): 2976, 1732, 1456, 1392, 1367, 1328, 1254, 1146, 951, 838, 753, 732 cm\(^{-1}\); HRMS (ESI) Calcd for C₂₀H₂₄NaO₂ [M+Na\(^+\)] \(319.1668\), Found 319.1675.

![Image](1.2.18)

**1.2.18**: Using the general procedure above with **1.2.17** (44 mg, 0.21 mmol) as the alkene, followed by chromatography on silica gel using 1:2 Et₂O:hexane (R_f = 0.20) gave compound **1.2.18** (53.2 mg, 74%) as a colorless oil. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta 5.44\) (dt, \(J = 10.7, 7.2\) Hz, 1H), 5.02 (dd, \(J = 10.7, 9.4\) Hz, 1H), 3.79 (s, 6H), 3.33 (s, 2H), 3.11 (dd, \(J = 7.2, 1.5\) Hz, 2H), 2.72-2.65 (m, 1H), 1.46 (s, 9H), 1.44-1.41 (m, 2H), 1.34 (d, \(J = 10.1\) Hz, 1H), 1.20 (d, \(J = 10.1\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta 170.9, 165.3, 149.2, 132.3, 120.2, 80.6, 52.0, 45.7, 37.3, 34.8, 30.4, 30.3, 28.0\); IR (neat): 2980, 1732, 1614, 1435, 1393, 1368, 1329, 1256, 1148, 1104, 1082, 1037, 966, 844, 812, 781 cm\(^{-1}\); HRMS (ESI) Calcd for C₂₀H₂₆NaO₆ [M+Na\(^+\)] \(385.1621\), Found 385.1630.
(1.2.20): Using the general procedure above with dicyclopentadiene 1.2.19 (29 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O in hexane (Rᵣ = 0.38) gave compound 1.2.20 (37.3 mg, 63%) as a colorless oil. ᵃ¹H NMR (400 MHz, CDCl₃): δ 5.71-5.68 (m, 1H), 5.55-5.51 (m, 1H), 5.41 (dtd, J = 10.7, 7.1, 0.8 Hz, 1H), 4.86 (ddddd, J = 10.8, 9.7, 6.6, 1.6 Hz, 1H), 3.09 (dd, J = 7.1, 1.6 Hz, 2H), 2.58-2.50 (m, 1H), 2.43-2.40 (m, 1H), 2.31-2.28 (m, 2H), 2.25-2.15 (m, 1H), 1.58-1.53 (m, 1H), 1.45 (s, 9H), 1.14 (d, J = 10.5 Hz, 1H), 0.92-0.86 (m, 2H), 0.62-0.57 (m, 1H); ᵃ¹C NMR (100 MHz, CDCl₃): δ 171.5, 134.9, 132.2, 130.7, 80.4, 54.7, 43.1, 39.6, 38.3, 34.7, 31.4, 31.3, 28.1, 22.2, 19.2, 12.1; IR (neat): 3041, 2942, 1733, 1392, 1367, 1327, 1255, 1146, 978, 846, 821, 740, 700 cm⁻¹; HRMS (EI) Calcd for C₁₅H₁₈O₂ [M-(C₄H₈)+] 230.1307, Found 230.1310.

(1.2.22): Using the general procedure above with bicyclo[2.2.2]oct-2-ene 1.2.21 (24 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 5% EtOAc in hexane (Rᵣ = 0.51) gave compound 1.2.22 (9.5 mg, 15%) as a yellow oil. ᵃ¹H NMR (400 MHz, CDCl₃): δ 5.46 (dt, J = 10.6, 7.1 Hz, 1H), 4.95 (dd, J = 10.1, 10.1 Hz, 1H), 3.17 (dd, J = 7.0, 1.1 Hz, 2H), 1.92 (s, 2H), 1.64-1.58 (m, 2H), 1.58-1.54 (m, 2H), 1.54-1.49 (m, 2H), 1.47 (s, 9H), 1.45-1.37 (m, 3H), 1.37-1.25 (m, 3H), 0.94 (d, J = 2.4 Hz, 2H); ᵃ¹C
NMR (100 MHz, CDCl₃): δ 171.5, 135.8, 119.3, 80.4, 34.7, 28.1, 26.0, 24.7, 24.0, 24.0, 14.9; IR (neat): 2933, 2865, 1733, 1654, 1457, 1392, 1367, 1328, 1257, 1146, 952, 847, 802 cm⁻¹; HRMS (EI) Caled for C₁₇H₂₆O₂ [M⁺] 262.1933, Found 262.1935.

(1.2.24): Using the general procedure above with 1.2.23 (68 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 10% Et₂O in hexane (R_f = 0.26) gave compound 1.2.24 (72.9 mg, 79%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), mp = 125 – 127 °C. ¹H NMR (400 MHz, CDCl₃): δ 5.46 (dt, J = 10.7, 7.2 Hz, 1H), 5.02 (dd, J = 10.5, 10.5 Hz, 1H), 4.06 (t, J = 4 Hz, 1H), 3.81 (d, J = 3.1 Hz, 2H), 3.11 (dd, J = 7.1, 1.6 Hz, 2H), 2.05-1.97 (m, 2H), 1.68 (dt, J = 10.3, 3.2 Hz, 1H), 1.57 (d, J = 3.1 Hz, 2H), 1.45 (s, 9H), 1.19-1.14 (m, 3H), 1.12 (d, J = 4.8 Hz, 18H), 1.00 (d, J = 7.5 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 133.2, 120.0, 80.4, 78.1, 73.4, 40.1, 34.5, 28.1, 25.1, 19.1, 18.6, 13.9, 13.1; IR (neat): 2943, 1733, 1463, 1367, 1257, 1148, 1092, 1037, 1015, 950, 885, 811, 677 cm⁻¹; HRMS (EI) Caled for C₂₇H₄₈O₄Si [M⁺] 464.3322, Found 464.3331.

(1.2.10): Using the general procedure above with 1.2.9 (32 mg, 0.21 mmol) as the alkene, followed by chromatography on silica gel using 1:2 Et₂O:hexane (R_f = 0.43) gave
compound 1.2.10 (62.2 mg, 97%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), mp = 127 – 130 °C. ¹H NMR (500 MHz, CDCl₃): δ 5.52 (dtd, J = 10.7, 7.3, 0.9 Hz, 1H), 4.94 (ddddd, J = 10.7, 9.0, 1.7, 1.7 Hz, 1H), 4.29 (d, J = 4.4 Hz, 2H), 3.10 (dd, J = 7.3, 1.7 Hz, 2H), 2.78-2.71 (m, 2H), 1.75 (dt, J = 10.0, 3.2, 0.9 Hz, 1H), 1.47-1.46 (m, 2H), 1.04 (d, J = 7.1 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 209.7, 170.9, 131.1, 121.7, 80.6, 79.9, 49.7, 34.5, 28.1, 24.0, 16.0, 9.2; IR (neat): 2976, 2935, 1732, 1709, 1652, 1448, 1408, 1394, 1373, 1362, 1259, 1202, 1151, 1064, 981, 966, 954, 939, 894, 861, 844, 799, 763, 736, 701 cm⁻¹; HRMS (EI) Calcd for C₁₄H₁₈O₄ [M-(C₄H₈)+] 250.1205, Found 250.1212. X-ray quality crystals were obtained by recrystallization of purified 1.2.10 from EtOAc.

![1.2.26](image_url)

(1.2.26): Using the general procedure above with 1.2.25 (53 mg, 0.21 mmol) as the alkene, followed by chromatography on silica gel using 30% EtOAc in hexane (Rf = 0.45) gave compound 1.2.26 (26.5 mg, 31%) as a white solid (the solid resulting from the evaporation of EtOAc and hexane), m.p. = 68-71 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.81-7.76 (m, 2H), 7.39-7.35 (m, 2H), 5.54 (dtd, J = 10.7, 7.2, 1.0 Hz, 1H), 5.03 (apparent tt, J = 10.4, 1.7 Hz, 1H), 4.57 (d, J = 4.7 Hz, 1H), 4.52 (d, J = 4.1 Hz, 1H), 3.59 (dd, J = 10.5, 5.5, 4.3 Hz, 1H), 3.09 (dd, J = 7.2, 1.8 Hz, 2H), 2.46 (s, 3H), 2.10 (dd, J = 12.1, 5.7 Hz, 1H), 2.00 (ddd, J = 12.1, 10.5, 4.9 Hz, 1H), 1.94 (dd, J = 6.6, 2.9 Hz, 1H), 1.70 (dt, J = 10.0, 2.9, 1.0 Hz, 1H), 1.45 (s, 9H), 1.39 (dd, J = 6.7, 2.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.2, 144.8, 137.7, 130.9, 130.1, 127.7, 121.8, 80.6, 78.1,
77.1, 68.0, 34.6, 32.5, 28.1, 24.7, 21.6, 21.1, 11.5; IR (neat): 2980, 1732, 1597, 1455, 1393, 1367, 1312, 1259, 1148, 1088, 1047, 991, 889, 851, 815, 731, 669 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{22}\)H\(_{28}\)NaO\(_5\)S [M+Na\(^+\)] 427.1549, found 427.1548.

(1.2.29): Using the general procedure above with 1.2.28 (38 mg, 0.08 mmol) as the alkene, followed by chromatography on silica gel using 40% Et\(_2\)O in hexane (R\(_f\) = 0.59) gave compound 1.2.29 (47.7 mg, 78%) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.51 (dtd, \(J = 10.6, 7.4, 0.8\) Hz, 2H), 5.04 (tt, \(J = 10.2, 1.6\) Hz, 2H), 4.38 (s, 2H), 3.76 (d, \(J = 10.6\) Hz, 2H), 3.64 (d, \(J = 10.2\) Hz, 2H), 3.13 (dd, \(J = 7.2, 1.8\) Hz, 4H), 1.77-1.73 (m, 2H), 1.47 (s, 6H), 1.45 (s, 18H), 1.32 (dd, \(J = 5.9, 2.4\) Hz, 2H), 1.28 (dd, \(J = 5.9, 2.4\) Hz, 2H), 0.91 (s, 18H), 0.08 (s, 12H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 171.4, 132.4, 121.1, 87.2, 80.5, 64.0, 60.5, 34.4, 30.9, 28.1, 27.5, 25.8, 24.3, 18.0, 16.6, 11.9, -5.4, -5.5; IR (neat): 2956, 2930, 2888, 2857, 2246, 1737, 1651, 1494, 1471, 1463, 1392, 1367, 1330, 1256, 1200, 1150, 1078, 1005, 973, 938, 912, 840, 776, 733, 681, 667, 656, 646 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_{44}\)H\(_{75}\)O\(_8\)Si\(_2\) [M+H\(^+\)] 787.4995, found 787.5015.

(1.2.30): Using the general procedure above with 1.2.28 (101 mg, 0.21 mmol) as the alkene, followed by chromatography on silica gel using 40% Et\(_2\)O in hexane gave 1.2.30
as a yellow oil (74.2 mg, 55%) and 1.2.29 (31.8 mg, 19%) as yellow oil. Compound 1.2.30: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.50 (d, \(J = 5.3\) Hz, 1H), 6.37 (d, \(J = 5.7\) Hz, 1H), 5.51 (dt, \(J = 10.6, 7.2\) Hz, 1H), 5.08 (t, \(J = 10.4\) Hz, 1H), 4.93 (s, 1H), 4.51 (s, 1H), 3.72 (d, \(J = 10.4\) Hz, 1H), 3.60 (d, \(J = 10.4\) Hz, 1H), 3.13 (d, \(J = 7.0\) Hz, 2H), 3.06 (d, \(J = 10.4\) Hz, 1H), 2.95 (d, \(J = 10.4\) Hz, 1H), 1.93 (d, \(J = 9.8\) Hz, 1H), 1.66 (s, 3H), 1.54 (s, 3H), 1.46 (s, 9H), 1.38 (dd, \(J = 5.9, 2.3\) Hz, 1H), 1.34 (dd, \(J = 5.9, 2.2\) Hz, 1H), 0.91 (s, 18H0, 0.05 (s, 12H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 171.3, 141.8, 137.9, 132.3, 120.9, 90.3, 87.2, 80.5, 80.4, 64.3, 64.0, 63.1, 61.9, 34.4, 28.4, 28.1, 25.80, 25.76, 25.5, 18.0, 16.6, 14.8, -5.5, -5.59, -5.64, -5.7; IR (neat): 2931, 2886, 2740, 2243, 1732, 1651, 1470, 1463, 1455, 1435, 1392, 1367, 1328, 1312, 1258, 1148, 1067, 1005, 969, 938, 916, 846, 778, 732, 712, 685, 667, 649 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_{35}\)H\(_{61}\)O\(_6\)Si\(_2\) [M+H\(^+\)] 633.4001, found 633.4016.

![1.2.34](image)

(1.2.34): Using the general procedure above with 1.2.33 (65 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 10% EtOAc in hexane (\(R_f = 0.13\)) gave compound 1.2.34 (32.1 mg, 32%) as a yellow amorphous foam. NMR data was acquired at 55 °C in order to resolve the rotamers. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.53 (dt, \(J = 10.7, 7.3\) Hz, 1H), 4.86 (dd, \(J = 10.6, 9.2\) Hz, 1H), 4.64 (bs, 2H), 3.05 (dd, \(J = 7.2, 1.6\) Hz, 2H), 1.59-1.55 (m, 1H), 1.49 (bs, 20H), 1.46 (s, 9H), 1.44-1.42 (m, 2H), 1.41-1.39 (m, 1H), 1.19 (d, \(J = 11.3\) Hz, 1H); \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 170.6, 156.9, 131.2, 122.4, 81.3, 80.7, 61.3, 34.9, 29.2, 28.3, 28.1, 22.6, 16.3; IR (neat): 2978,
(1.2.36): Using the general procedure above with 1,2-dihydronaphthalene 1.2.35 (27 mg, 0.21 mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O in hexane (Rf = 0.38) gave compound 1.2.36 (11.2 mg, 20%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.22 (m, 1H), 7.14-7.00 (m, 3H), 5.51 (dt, J = 10.7, 7.1 Hz, 1H), 5.14 (dd, J = 10.7, 9.2 Hz, 1H), 3.05 (d, J = 7.1 Hz, 2H), 2.68-2.61 (m, 1H), 2.57-2.47 (m, 1H), 2.23-2.16 (m, 1H), 1.96-1.91 (m, 2H), 1.79-1.69 (m, 1H), 1.64-1.56 (m, 1H), 1.41 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 171.3, 137.1, 134.6, 133.6, 128.6, 128.4, 126.0, 125.1, 120.1, 80.5, 34.6, 28.0, 25.9, 25.3, 23.6, 20.8, 18.8; IR (neat): 3064, 3008, 2978, 2928, 2857, 1732, 1652, 1604, 1579, 1493, 1456, 1424, 1392, 1368, 1334, 1287, 1257, 1205, 1149, 1076, 1057, 1037, 1005, 951, 889, 846, 816, 796, 755, 730, 701, 638, 573, 480 cm⁻¹; HRMS (EI) Calcd for C₁₅H₁₆O₂ [M-(C₄H₈)⁺] 228.1150, Found 228.1145.

(1.2.39): Using the general procedure above with styrene 1.2.38 (25 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O in hexane gave
compound 1.2.39 (7.8 mg, 15%) as white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 63-65 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.40 (m, 2H), 7.36-7.29 (m, 2H), 7.28-7.23 (m, 2H), 6.90-6.82 (m, 1H), 6.74-6.65 (m, 1H), 6.42 (dd, J = 15.4, 11.3 Hz, 1H), 5.85 (d, J = 15.2 Hz, 1H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 166.5, 143.3, 140.1, 136.7, 136.2, 130.4, 128.7, 128.3, 128.1, 126.7, 123.0, 80.2, 28.2; IR (neat): 2975, 2930, 1705, 1628, 1607, 1570, 1478, 1450, 1390, 1366, 1305, 1259, 1229, 1163, 1130, 1006, 976, 889, 858 cm⁻¹; HRMS (EI) calcd for C₁₇H₂₀O₂ [M⁺] 256.1363, found 256.1467.

![Structure](image)

**1.2.41**

(2E,4Z)-**tert-Butyl 5-(3-oxocyclohexyl)penta-2,4-dienoate (1.2.41):** Using the general procedure above with 1-cyclohexenone 1.2.40 (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using Et₂O:hexane = 1:2 (Rₐ = 0.25) gave compound 1.2.41 (34.6 mg, 69%) as yellow solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 68-70 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.43 (ddd, J = 15.2, 11.7, 1.0 Hz, 1H), 6.07 (dd, J = 11.5, 10.9 Hz, 1H), 5.85 (d, J = 15.2 Hz, 1H), 5.64 (apparent t, J = 10.3 Hz, 1H), 3.16-3.3.02 (m, 1H), 2.46-2.35 (m, 2H), 2.35-2.26 (m, 1H), 2.26-2.15 (m, 1H), 2.15-2.05 (m, 1H), 1.91-1.81 (m, 1H), 1.81-1.69 (m, 1H), 1.62-1.54 (m, 1H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 209.8, 166.3, 141.7, 137.4, 126.0, 124.7, 80.5, 47.2, 41.0, 37.9, 31.4, 28.1, 25.0; IR (neat): 2976, 2934, 1713, 1638, 1606, 1448, 1414, 1392, 1368, 1313, 1280, 1259, 1222, 1155, 1127, 996, 980, 943, 871, 851, 768, 713 cm⁻¹; HRMS (EI) calcd for C₁₅H₂₂O₃ [M⁺] 250.1569, found
1.2.45: Using the general procedure above with boronate ester 1.2.44 (55 mg, 0.20 mmol) and norbornene 1.2.11 (21.0 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 100% EtOAc (Rf = 0.39) gave compound 1.2.45 (16.3 mg, 32%) as yellow oil. $^{1}H$ NMR (400 MHz, CDCl$_3$): $\delta$ 5.47 (dtd, $J$ = 10.7, 7.0, 0.7 Hz, 1H), 4.87 (dddd, $J$ = 10.7, 9.8, 1.8, 1.6 Hz, 1H), 3.47 (apparent td, $J$ = 6.8, 3.1 Hz, 4H), 3.17 (dd, $J$ = 7.0, 1.8 Hz, 2H), 2.32 (s, 2H), 2.00-1.81 (m, 4H), 1.50-1.42 (m, 3H), 1.27-1.25 (m, 2H), 1.03-0.98 (m, 1H), 0.76 (d, $J$ = 2.2 Hz, 2H), 0.67 (d, $J$ = 10.5 Hz, 1H); $^{13}C$ NMR (100 MHz, CDCl$_3$): $\delta$ 170.1, 134.0, 119.9, 46.6, 45.8, 35.9, 34.6, 29.4, 28.5, 26.2, 24.7, 24.4, 13.0; IR (neat): 2952, 2870, 1644, 1434, 1342, 1284, 1192, 1113, 986, 834, 520 cm$^{-1}$; HRMS (EI) calcd for C$_{16}$H$_{23}$NO [M$^+$] 245.1780, found 245.1775.

1.2.47: Using the general procedure above with boronate ester 1.2.46 (41 mg, 0.20 mmol) and norbornene 1.2.11 (21.0 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 10% Et$_2$O in hexane (Rf = 0.33) gave compound 1.2.47 (20.9 mg, 59%) as yellow solid (the solid resulting from the evaporation of Et$_2$O and hexane), m.p. = 49-52 °C; Z-1.2.47 (major) $^{1}H$ NMR (400 MHz, CDCl$_3$): $\delta$ 5.24 (dtd,
\[ J = 10.4, 7.0, 0.8 \text{ Hz}, 1\text{H}) \]
\[ J = 10.1, 10.1, 1.6, 1.6 \text{ Hz}, 1\text{H}) \]
\[ J = 6.9, 1.6 \text{ Hz}, 2\text{H}) \]
\[ J = 4.99, 10.1, 10.1, 1.6, 1.6 \text{ Hz}, 1\text{H}) \]
\[ J = 3.18, 6.9, 1.6 \text{ Hz}, 2\text{H}) \]
\[ J = 2.35, 2.35 \text{ (s, 2H)} \]
\[ J = 2.2 \text{ Hz}, 2\text{H}) \]
\[ J = 0.82, 10.5 \text{ Hz} \]; 13C NMR (100 MHz, CDCl3): \[ \delta 137.6, 118.4, 114.3, 35.8, 29.2, 28.3, 24.8, 16.0, 12.8 \]; IR (neat): 2954, 2870, 2249, 1651, 1416, 1312, 1113, 985, 832 cm\(^{-1}\); HRMS (EI) calcd for C12H15N [M\(^{+}\)] 173.1204, found 173.1202.

\[ E-1.2.47 \] (minor) \[ ^1\text{H} \text{ NMR (400 MHz, CDCl}_3) \]: \[ \delta 5.36-5.25 \text{ (m, 2H)} \]
\[ 3.03 \text{ (dd, } J = 4.6, 0.9 \text{ Hz, 2H)} \]
\[ 2.32 \text{ (s, 2H)} \]
\[ 1.49-1.42 \text{ (m, 2H)} \]
\[ 1.40-1.35 \text{ (m, 1H)} \]
\[ 1.28-1.22 \text{ (m, 2H)} \]
\[ 0.99-0.93 \text{ (m, 1H)} \]
\[ 0.80 \text{ (d, } J = 2.2 \text{ Hz, 2H)} \]
\[ 0.66 \text{ (d, } J = 10.8 \text{ Hz, 1H)} \]; 13C NMR (100 MHz, CDCl3): \[ \delta 137.8, 117.8, 114.1, 35.8, 29.2, 28.3, 24.4, 20.3, 16.6 \]; IR (neat): 2954, 2870, 2249, 1651, 1416, 1312, 1113, 985, 832 cm\(^{-1}\); HRMS (EI) calcd for C12H15N [M\(^{+}\)] 173.1204, found 173.1202.

(2\text{E,4Z})\text{-tert-Butyl} 5-((1\text{R,2R,4S})\text{-bicyclo[2.2.1]heptan-2-yl})\text{-2-methylpenta-2,4-dienoate} (1.2.54): Using the general procedure above with boronate ester 1.2.53 (59 mg, 0.20 mmol) and norbornene 1.2.11 (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 2\% Et\(_2\)O (R\(_f\) = 0.50) gave compound 1.2.54 (2.6 mg, 5\%) as colorless oil. \[ ^1\text{H} \text{ NMR (400 MHz, CDCl}_3) \]: \[ \delta 7.45 \text{ (ddq, } J = 11.9, 1.4, 1.4 \text{ Hz, 1H)} \]
\[ 6.11 \text{ (ddd, } J = 12.0, 10.8, 1.3 \text{ Hz, 1H)} \]
\[ 5.67 \text{ (apparent t, } J = 10.4, 1.4 \text{ Hz, 1H)} \]
\[ 2.67-2.59 \text{ (m, 1H)} \]
\[ 2.26 \text{ (s, 1H)} \]
\[ 2.03 \text{ (s, 1H)} \]
\[ 1.88 \text{ (d, } J = 1.2 \text{ Hz, 3H)} \]
\[ 1.63 \text{ (ddd, } J = 12.1, 9.0, 2.7 \text{ Hz, 1H)} \]
\[ 1.55-1.48 \text{ (m, 2H)} \]
\[ 1.51 \text{ (s, 1H)} \]
\[ 1.44-1.38 \text{ (m, 1H)} \]
\[ 1.31-1.15 \text{ (m, 4H)} \]; 13C NMR (100 MHz, CDCl3): \[ \delta 168.1, 145.4, 132.6, 128.3, 121.4, 80.1, 43.2, 40.4, 39.4, 36.5, 36.0, \]
Using the general procedure above with boronate ester 1.2.55 (59 mg, 0.20 mmol) and norbornene 1.2.11 (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 2% Et₂O (Rf = 0.31) gave compound 1.2.56 (21.2 mg, 36%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 4.67 (dd, J = 9.2, 0.8 Hz, 1H), 3.02 (s, 2H), 2.30 (s, 2H), 1.73 (d, J = 1.6 Hz, 3H), 1.45 (s, 9H), 1.44-1.40 (m, 3H), 1.27-1.20 (m, 2H), 1.04-0.98 (m, 1H), 0.69 (d, J = 2.5 Hz, 2H), 0.64 (d, J = 10.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.1, 130.0, 127.2, 80.2, 39.6, 35.9, 29.5, 28.4, 28.0, 24.4, 23.9, 13.2; IR (neat): 3007, 2955, 2870, 1732, 1368, 1298, 1254, 1153 cm⁻¹; HRMS (EI) Calcd for C₁₇H₂₆O₂ [M⁺] 262.1933, found 262.1932.

(1.2.58): Using the general procedure above with boronate ester 1.2.57 (294 mg, 1.00 mmol) and norbornene 1.2.11 (94 mg, 1.1 mmol) as the alkene in 10 mL of dioxane and 1 mL of H₂O, followed by chromatography on silica gel using 5% Et₂O (Rf = 0.54) gave compound 1.2.58 (174.2 mg, 66%) as yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 5.12 (d,
$J = 1.6 \text{ Hz, 1H}$, 2.50-2.46 (m, 1H), 2.47 (dd, $J = 14.1, 4.3 \text{ Hz, 1H}$), 2.42-2.36 (m, 1H), 2.02-1.99 (m, 1H), 1.94-1.91 (m, 1H), 1.82 (dd, $J = 7.0, 3.1 \text{ Hz, 1H}$), 1.62 (dd, $J = 2.7, 1.6 \text{ Hz, 3H}$), 1.49-1.41 (m, 2H), 1.46 (s, 9H), 1.32-1.26 (m, 1H), 1.20-1.07 (m, 2H), 0.97-0.92 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.5, 142.9, 128.2, 80.1, 54.5, 52.2, 51.8, 42.9, 40.9, 40.4, 32.2, 29.0, 28.7, 28.1, 14.5; IR (neat): 2949, 2870, 1732, 1475, 1455, 1392, 1367, 1332, 1322, 1291, 1256, 1153, 1049, 954, 912, 867, 847, 830, 757 cm$^{-1}$; HRMS (EI) Calcd for C$_{17}$H$_{26}$O$_2$ [M$^+$] 262.1933, found 262.1931.

(1.2.60): Using the general procedure above with boronate ester 1.2.59 (59 mg, 0.20 mmol) and norbornene 1.2.11 (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 5% Et$_2$O (R$_f$ = 0.63) gave compound 1.2.60 (37.7 mg, 70%) as colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.17 (dd, $J = 3.3, 1.5 \text{ Hz, 1H}$), 2.54-2.46 (m, 1H), 2.38 (d, $J = 7.5 \text{ Hz, 1H}$), 2.25 (dd, $J = 14.3, 6.2 \text{ Hz, 1H}$), 2.13 (dd, $J = 14.3, 8.8 \text{ Hz, 1H}$), 2.09 (d, $J = 4.2 \text{ Hz, 1H}$), 2.02 (d, $J = 4.2 \text{ Hz, 1H}$), 1.75 (dd, $J = 7.4, 2.3 \text{ Hz, 1H}$), 1.63 (dd, $J = 3.0, 1.4 \text{ Hz, 3H}$), 1.57-1.39 (m, 2H), 1.45 (s, 9H), 1.31-1.26 (m, 1H), 1.21-1.07 (m, 2H), 0.98-0.93 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.4, 141.6, 128.7, 79.9, 58.9, 52.1, 48.9, 43.1, 42.8, 38.1, 32.2, 29.0, 28.5, 28.2, 15.2; IR (neat): 2948, 2869, 1995, 1728, 1653, 1555, 1540, 1506, 1470, 1455, 1385, 1366, 1297, 1258, 1143, 848, 824 cm$^{-1}$; HRMS (EI) Calcd for C$_{13}$H$_{17}$O$_2$ [M-(C$_4$H$_9$)$_2$]$^+$ 205.1229, found 205.1233.
Using the general procedure above with boronate ester \textbf{1.2.89} (73 mg, 0.20 mmol) and norbornene \textbf{1.2.11} (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 5\% Et\textsubscript{2}O gave compound \textbf{1.2.63} (54.8 mg, 84\%) as colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.45 (d, \(J = 7.2\) Hz, 2H), 7.33-7.27 (m, 2H), 7.24-7.18 (m, 1H), 6.02 (s, 1H), 3.07 (dd, \(J = 7.7, 2.3\) Hz, 1H), 2.79-2.71 (m, 1H), 2.37 (dd, \(J = 15.2, 6.4\) Hz, 1H), 2.25 (dd, \(J = 14.6, 8.6\) Hz, 1H), 2.19 (d, \(J = 3.3\) Hz, 1H), 2.12 (d, \(J = 3.3\) Hz, 1H), 1.92 (dd, \(J = 7.5, 3.0\) Hz, 1H), 1.56-1.49 (m, 2H), 1.46 (s, 9H), 1.40-1.29 (m, 2H), 1.24-1.20 (m, 1H), 1.00 (d, \(J = 10.0\) Hz, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 172.4, 143.9, 136.1, 130.2, 128.5, 127.3, 126.5, 80.4, 55.7, 52.1, 49.5, 43.1, 43.0, 39.5, 32.8, 29.3, 28.8, 28.4; IR (neat): 2950, 2869, 1727, 1599, 1494, 1453, 1391, 1366, 1326, 1303, 1257, 1144, 945, 849, 756, 693 cm\textsuperscript{-1}; HRMS (EI) Calcd for C\textsubscript{18}H\textsubscript{19}O\textsubscript{2} [M-C\textsubscript{4}H\textsubscript{9}\textsuperscript{+}] 267.1385, found 267.1372.

Using the general procedure above with boronate ester \textbf{1.2.91} (65 mg, 0.20 mmol) and norbornene \textbf{1.2.11} (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 3\% Et\textsubscript{2}O (R\textsubscript{f} = 0.43) gave compound \textbf{1.2.64} (35.6 mg,
65%) as yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.16 (apparent q, $J$ = 1.6 Hz, 1H), 2.59-2.48 (m, 2H), 2.29-2.16 (m, 2H), 2.14-2.07 (m, 2H), 2.01 (d, $J$ = 4.1 Hz, 1H), 1.73 (dd, $J$ = 7.3, 2.6 Hz, 1H), 1.56-1.46 (m, 2H), 1.46 (s, 9H), 1.31-1.26 (m, 1H), 1.21-1.10 (m, 2H), 1.05 (d, $J$ = 6.6 Hz, 3H), 1.00 (d, $J$ = 7.0 Hz, 3H), 0.97-0.92 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.6, 152.3, 125.9, 80.1, 56.7, 52.0, 48.8, 43.4, 43.0, 38.8, 32.4, 29.3, 28.9, 28.4, 28.2, 22.3, 21.6; IR (neat): 2958, 2870, 1731, 1643, 1454, 1392, 1366, 1332, 1298, 1258, 1144, 1040, 951, 919, 848, 796, 757 cm$^{-1}$; HRMS (EI) Calcd for C$_{19}$H$_{30}$O$_2$ [M$^+$] 290.2246, found 290.2241.

![Diagram](image)

(1.2.65): Using the general procedure above with boronate ester 1.2.93 (71 mg, 0.20 mmol) and norbornene 1.2.11 (21 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 5% Et$_2$O ($R_f$ = 0.40) gave compound 1.2.65 (37.4 mg, 58%) as yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38-7.27 (m, 4H), 7.24-7.18 (m, 1H), 5.80 (t, $J$ = 2.1 Hz, 1H), 3.18-3.11 (m, 1H), 2.75-2.69 (m, 1H), 2.58 (dd, $J$ = 14.8, 3.3 Hz, 1H), 2.16 (d, $J$ = 3.5 Hz, 1H), 2.05 (d, $J$ = 3.5 Hz, 1H), 2.00 (dd, $J$ = 14.8, 11.3 Hz, 1H), 1.98-1.94 (m, 1H), 1.56-1.47 (m, 2H), 1.46 (s, 9H), 1.40-1.35 (m, 1H), 1.29-1.14 (m, 2H), 1.03-0.98 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.4, 146.2, 135.7, 130.1, 128.4, 127.0, 126.3, 80.2, 55.1, 51.7, 49.0, 43.3, 41.3, 40.5, 32.4, 29.0, 28.8, 28.2; IR (neat): 2951, 2870, 1728, 1493, 1447, 1391, 1368, 1327, 1279, 1254, 1146, 1126, 768, 754, 696 cm$^{-1}$; HRMS (EI) Calcd for C$_{22}$H$_{28}$NaO$_2$ [M+Na$^+$] 347.1981, found 347.1991.
(1.2.66): Using the general procedure above with boronate ester 1.2.59 (59 mg, 0.20 mmol) and benzonorbornene 1.2.15 (34 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 3% Et₂O (Rᵣ = 0.33) gave compound 1.2.66 (43.6 mg, 69%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.17-7.09 (m, 2H), 7.06-7.01 (m, 2H), 5.34 (d, J = 1.3 Hz, 1H), 3.17 (s, 1H), 3.12 (s, 1H), 2.75-2.66 (m, 1H), 2.58 (d, J = 7.3 Hz, 1H), 2.30 (dd, J = 14.7, 6.2 Hz, 1H), 2.16 (dd, J = 14.7, 9.0 Hz, 1H), 1.96-1.91 (m, 1H), 1.80-1.76 (m, 1H), 1.74 (s, 3H), 1.70-1.65 (m, 1H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 172.2, 148.8, 138.6, 140.9, 130.6, 125.53, 125.48, 120.8, 120.6, 80.1, 58.2, 51.5, 49.6, 47.0, 45.5, 42.9, 42.8, 28.2, 15.2; IR (neat): 2965, 2930, 1728, 1466, 1391, 1366, 1317, 1279, 1257, 1143, 956, 848, 825, 748 cm⁻¹; HRMS (El) Calcd for C₂₁H₂₆O₂ [M⁺] 310.1933, found 310.1933.

(1.2.67): Using the general procedure above with boronate ester 1.2.57 (59 mg, 0.20 mmol) and benzonorbornene 1.2.15 (34 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O (Rᵣ = 0.48) gave compound 1.2.67 (42.6 mg, 68%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.14-7.07 (m, 2H), 7.05-7.00 (m, 2H), 5.30 (d, J = 1.6 Hz, 1H), 3.12 (s, 1H), 3.02 (s, 1H), 2.69-2.64 (m, 1H), 2.62-2.57 (m,
1H), 2.55(dd, \( J = 14.2, 4.2 \text{ Hz}, 1H \)), 2.02 (dd, \( J = 14.0, 9.9 \text{ Hz}, 1H \)), 1.99-1.96 (m, 1H), 1.78-1.74 (m, 1H), 1.69 (s, 3H), 1.68-1.64 (m, 1H), 1.49 (s, 9H); \(^{13}\text{C} \text{NMR (100 MHz, } \text{CDCl}_3\)): \( \delta \) 172.4, 149.0, 148.7, 144.9, 127.4, 125.5, 125.4, 120.8, 120.6, 80.3, 53.8, 51.0, 50.4, 49.7, 47.7, 42.7, 40.8, 28.2, 14.9; IR (neat): 2968, 2875, 1729, 1454, 1391, 1367, 1330, 1280, 1257, 1146, 1040, 1012, 964, 947, 847, 751, 729 cm\(^{-1}\); HRMS (ESI) Calcd for \( \text{C}_{21}\text{H}_{26}\text{NaO}_2 [\text{M+Na}^+] \) 333.1825, found 333.1841.

![Image](image.png)

**1.2.68**

(1.2.68): Using the general procedure above with boronate ester 1.2.59 (59 mg, 0.20 mmol) and 1.2.17 (46 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 1:2 Et\(_2\)O:hexane (R\(_f\) = 0.36) gave compound 1.2.68 (49.7 mg, 64%) as colorless oil. \(^1\text{H} \text{NMR (400 MHz, } \text{CDCl}_3\)): \( \delta \) 5.33 (q, \( J = 1.5 \text{ Hz}, 1H \)), 3.78 (s, 3H), 3.75 (s, 3H), 3.10 (s, 1H), 3.06 (s, 1H), 2.79 (d, \( J = 7.5 \text{ Hz}, 1H \)), 2.63-2.55 (m, 1H), 2.32 (dd, \( J = 15.0, 6.2 \text{ Hz}, 1H \)), 2.21 (dd, \( J = 15.2, 9.0 \text{ Hz}, 1H \)), 2.16-2.12 (m, 1H), 1.69 (t, \( J = 2.1 \text{ Hz}, 3H \)), 1.64-1.55 (m, 2H), 1.46 (s, 9H); \(^{13}\text{C} \text{NMR (100 MHz, } \text{CDCl}_3\)): \( \delta \) 171.8, 165.4, 165.1, 145.5, 145.2, 140.4, 131.1, 80.3, 56.6, 51.9, 51.8, 50.9, 50.1, 47.1, 46.0, 42.8, 41.5, 28.1, 15.1; IR (neat): 2977, 2951, 1993, 1868, 1826, 1725, 1650, 1623, 1557, 1541, 1520, 1508, 1454, 1435, 1391, 1367, 1336, 1263, 1152, 1094, 1017, 968, 848, 829, 784, 757 cm\(^{-1}\); HRMS (ESI) Calcd for \( \text{C}_{21}\text{H}_{28}\text{NaO}_6 [\text{M+Na}^+] \) 399.1778, found 399.1797.
(1.2.69): Using the general procedure above with boronate ester 1.2.57 (59 mg, 0.20 mmol) and 1.2.17 (46 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 1:2 Et₂O:hexane (R₆ = 0.53) gave compound 1.2.69 (40.0 mg, 52%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.26 (d, J = 1.6 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.06 (s, 1H), 2.95 (s, 1H), 2.91-2.86 (m, 1H), 2.56 (dd, J = 14.9, 4.3 Hz, 1H), 2.51-2.44 (m, 1H), 2.20-2.16 (m, 1H), 2.08 (dd, J = 14.8, 10.1 Hz, 1H), 1.67 (d, J = 1.0 Hz, 3H), 1.61-1.53 (m, 2H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 172.0, 165.4, 165.1, 145.54, 145.51, 145.1, 126.8, 80.5, 52.2, 51.9, 51.8, 50.9, 49.5, 49.4, 49.2, 41.5, 40.7, 28.1, 15.0; IR (neat): 2975, 2950, 2364, 1720, 1622, 1435, 1391, 1367, 1335, 1263, 1150, 1092, 1044, 1015, 968, 843, 775 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₈NaO₆ [M+Na⁺] 399.1778, found 399.1785.

(1.2.71): Using the general procedure above with boronate ester 1.2.59 (59 mg, 0.20 mmol) and norbornadiene 1.2.70 (20 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 2% Et₂O in hexane (R₆ = 0.30) gave compound 1.2.71 (24.8 mg, 46%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 6.10-6.02 (m, 2H), 5.26 (d, J = 1.6 Hz, 1H), 2.67 (s, 1H), 2.61 (s, 1H), 2.53-2.44 (m, 2H), 2.28 (dd, J = 14.5, 6.1
Hz, 1H), 2.17 (dd, \( J = 14.6, 8.6 \) Hz, 1H), 1.89-1.85 (m, 1H), 1.65 (s, 3H), 1.46 (s, 9H), 1.45-1.42 (m, 1H), 1.33-1.29 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 172.3, 141.5, 137.4, 137.2, 130.2, 80.0, 56.8, 50.2, 47.7, 45.9, 43.4, 43.1, 42.0, 28.1, 15.2; IR (neat): 2967, 2930, 1730, 1458, 1368, 1283, 1258, 1179, 1148, 945, 910, 845, 700 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{17}\)H\(_{24}\)O\(_2\) [M\(^+\)] 260.1776, found 260.1776.

![1.2.72](image)

**1.2.72**: Using the general procedure above with boronate ester 1.2.57 (59 mg, 0.20 mmol) and norbornadiene 1.2.70 (20 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 2% Et\(_2\)O in hexane (R\(_f\) = 0.30) gave compound 1.2.72 (24.0 mg, 44%) as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 6.08-6.00 (m, 2H), 5.22 (d, \( J = 1.6 \) Hz, 1H), 2.60 (s, 1H), 2.57-2.48 (m, 3H), 2.42-2.34 (m, 1H), 2.05 (dd, \( J = 14.5, 10.0 \) Hz, 1H), 1.94-1.90 (m, 1H), 1.64 (s, 3H), 1.47 (s, 9H), 1.44-1.40 (m, 1H), 1.31-1.27 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 172.5, 144.5, 137.5, 137.0, 128.0, 80.2, 52.3, 49.5, 49.3, 47.8, 45.6, 41.9, 40.9, 28.1, 15.0; IR (neat): 2967, 2934, 2916, 1728, 1452, 1391, 1368, 1325, 1283, 1260, 1148, 1040, 706 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{17}\)H\(_{24}\)O\(_2\) [M\(^+\)] 260.1776, found 260.1772.

![1.2.13](image)

**1.2.13**: LiAlH\(_4\) (0.049 g, 1.29 mmol) was added in small portions to a solution of 1.2.12
(0.11 g, 0.44 mmol) in 15 mL of THF at 0 °C. After the addition, the reaction mixture was allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was diluted with diethyl ether and quenched by slow addition of saturated potassium sodium tartrate solution with vigorous stirring. After stirring at 25 °C for 1 h, the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel using 40% Et₂O in hexane (Rf = 0.29) gave alcohol 1.2.13 (70 mg, 89%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 5.24 (dtd, J = 10.8, 7.4, 0.8 Hz, 1H), 4.87 (ddddd, J = 10.9, 9.8, 1.4, 1.4 Hz, 1H), 3.70-3.64 (m, 2H), 2.43 (dtd, J = 7.3, 6.5, 1.4 Hz, 2H), 2.32 (s, 2H), 1.58-1.52 (m, 2H), 1.47-1.41 (m, 2H), 1.26-1.21 (m, 2H), 1.04-0.98 (m, 1H), 0.74 (d, J = 2.0 Hz, 2H), 0.66 (d, J = 10.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 135.0, 122.8, 62.4, 35.9, 31.2, 29.4, 28.4, 24.7, 12.8; IR (neat): 3333, 3010, 2952, 2869, 1652, 1460, 1312, 1296, 1254, 1183, 1138, 1116, 1048, 984, 890, 874, 834, 780, 721, 608 cm⁻¹; HRMS (EI) Calcd for C₁₂H₁₈O [M⁺] 178.1358, Found 178.1353.

(1.2.14): To a solution of the alcohol 1.2.13 (47 mg, 0.27 mmol) in 5 mL of dichloromethane at 0 °C, was added pyridine (0.04 mL, 0.41 mmol), followed by the addition of p-nitrobenzoyl chloride (0.06 g, 0.32 mmol) in one portion. The reaction mixture was allowed to warm to 25 °C and stirred for 16 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtrated and concentrated in vacuo.
Chromatography on silica gel using 10% Et$_2$O in hexane (R$_f$ = 0.28) gave the ester 1.2.14 (68 mg, 76%) as a yellow solid (the solid resulting from the evaporation of Et$_2$O and hexane), m.p. = 56 – 58 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.30-8.27 (m, 2H), 8.24-8.19 (m, 2H), 5.30 (dt, $J$ = 10.7, 7.5 Hz, 1H), 4.86 (dd, $J$ = 10.7, 9.9 Hz, 1H), 4.40 (t, $J$ = 6.7 Hz, 2H), 2.64 (dt, $J$ = 7.3, 6.8, 1.4 Hz, 2H), 2.28 (s, 2H), 1.56 (dt, $J$ = 9.8, 2.2 Hz, 1H), 1.46-1.41 (m, 2H), 1.26-1.21 (m, 2H), 1.03-0.98 (m, 1H), 0.74 (d, $J$ = 2.2 Hz, 2H), 0.66 (d, $J$ = 10.6 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 164.6, 150.4, 135.7, 135.0, 130.6, 123.4, 121.6, 65.3, 35.8, 29.3, 28.4, 27.2, 24.6, 12.8; IR (neat): 2954, 2870, 1725, 1608, 1529, 1459, 1411, 1349, 1274, 1102, 1015, 873, 833, 784, 719 cm$^{-1}$; HRMS (EI) Calcd for C$_{19}$H$_{22}$NO$_4$ [M+H$^+$] 328.1549, Found 328.1540. X-ray quality crystals were obtained by recrystallization from THF and hexane.

(1.2.61): LiAlH$_4$ (31 mg, 0.81 mmol) was added in small portions to a solution of 1.2.58 (77 mg, 0.29 mmol) in 10 mL of THF at 0 °C. After the addition, the reaction mixture was allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was diluted with diethyl ether and quenched by slow addition of saturated potassium sodium tartrate solution with vigorous stirring. After stirring at 25 °C for 1 h, the aqueous layer was extracted with Et$_2$O ($\times$ 3). The combined organic layers were dried with MgSO$_4$, filtered and concentrated in vacuo. Chromatography on silica gel using 30% EtOAc in hexane (R$_f$ = 0.58) gave alcohol 1.2.61 (45 mg, 80%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.12 (d, $J$ = 1.8 Hz, 1H), 3.80-3.63 (m, 2H), 2.47 (d, $J$ = 6.4 Hz, 1H), 2.08 (d, $J$ = 9.7
(1.2.62): To a solution of the alcohol 1.2.61 (43 mg, 0.23 mmol) in 4 mL of dichloromethane at 0 °C, was added pyridine (0.03 mL, 0.35 mmol), followed by the addition of p-bromobenzoyl chloride (62 mg, 0.28 mmol) in one portion. The reaction mixture was allowed to warm to 25 °C and stirred for 16 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with EtOAc ($\times$ 3). The combined organic layers were dried with MgSO$_4$, filtrated and concentrated in vacuo. Chromatography on silica gel using 5% EtOAc in hexane ($R_f = 0.60$) gave the ester 1.2.62 (73 mg, 85%) as a white solid (the solid resulting from the evaporation of EtOAc and hexane), m.p. = 76-78 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.93-7.88 (m, 2H), 7.60-7.56 (m, 2H), 5.14 (d, $J = 1.5$ Hz, 1H), 4.43-4.30 (m, 2H), 2.49 (d, $J = 6.2$ Hz, 1H), 2.17-2.10 (m, 1H), 2.10-2.01 (m, 1H), 1.94 (d, $J = 3.5$ Hz, 1H), 1.91 (d, $J = 3.5$ Hz, 1H), 1.85 (dd, $J = 7.1$, 3.2 Hz, 1H), 1.66 (dd, $J = 2.6$, 1.5 Hz, 3H), 1.64-1.59 (m, 1H),
1.52-1.37 (m, 2H), 1.28 (ddq, $J = 9.7, 2.0, 2.0$ Hz, 1H), 1.21-1.07 (m, 2H), 0.95 (ddq, $J = 9.9, 1.5, 1.5$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.9, 142.9, 131.7, 131.1, 129.4, 128.1, 127.9, 64.1, 54.6, 52.5, 51.8, 42.9, 40.5, 32.6, 32.2, 29.0, 28.9, 14.6; IR (neat): 3028, 2947, 2868, 1721, 1591, 1484, 1471, 1451, 1398, 1270, 1172, 1115, 1103, 1069, 1012, 918, 847, 828, 756, 708, 683, 627 cm$^{-1}$; Anal. Calcd for C$_{20}$H$_{23}$BrO$_2$: C, 64.01; H, 6.18. Found: C, 63.92; H, 6.14. X-ray quality crystals were obtained by recrystallization of purified 1.2.62 from hexane.
1.3 STUDIES TOWARD ENANTIOSELECTIVE CYCLOPENTENATION REACTIONS UNDER RHODIUM-CATALYSIS

1.3.1 Results and Discussions

1.3.1.1 Goal of Study

Following the development of the rhodium-catalyzed cascade addition/cyclization process for the synthesis of cyclopentene- and vinylcyclopropane-containing molecules, we then sought to expand this methodology into an enantioselective process. While there are many examples of the asymmetric addition of alkenyl- or arylboronic acids to electrophiles, only a few instances involving bifunctional organoboron reagents have been reported. We aimed to develop an enantioselective synthesis of cyclopentene- or indene-containing molecules using rhodium catalysis (Scheme 1.3.1). These core structures are useful building blocks for the preparation of biologically active molecules.\(^{104,105}\)

---


1.3.1 Extension of reaction toward an enantioselective process

![Scheme 1.3.1](image)

\[ R_2 \text{Bpin} \quad \text{Rh catalyst} \quad \text{ligand}\]

\[ R_2 \text{H} \quad \text{CO}_2\text{R} \]

1.3.1.2 Coupling of Methyl-Substituted Dienylboronate Ester with Benzonorbornene under Rhodium Catalysis with Chiral Ligands

From previous studies, we found that under the same reaction conditions, different carbocycles were generated depending on the substitution pattern on the parent dienylboronate esters. When using unsubstituted dienylboronate esters, most of the vinylcyclopropane products were obtained as meso molecules, which precludes the ability to introduce chirality. Therefore, we decide to focus our attention on the studies using substituted dienylboronate esters, which generated non-symmetrical cyclopentene containing products.

Initial studies were carried out with boronate ester 1.2.59 with benzonorbornene 1.2.15, which contains an aromatic chromophore moiety for HPLC detection. The preliminary screenings using achiral ligands were summarized in Table 1.3.1. Among the monodentate phosphine ligands tested (entries 1-4), a bulky one such as \(\text{t-Bu}_3\text{P}\) shows the highest reactivity. A similar yield was obtained by switching to a \(\text{N}\)-heterocyclic carbene.
Surprisingly, no products were observed using bidentate ligands such as dppe and dppf, which are analogous to ligand \textit{1.3.5}.\textsuperscript{107} These results suggested that utilizing bidentate ligands is not favorable in this transformation. Therefore, we focused our attention on chiral monodentate ligands to induce chirality in this process.

Table 1.3.1 Screening of achiral ligands using boronate ester \textit{1.2.59}

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$t$-Bu$_3$PH$^+$BF$_4^-$</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>(furyl)$_3$P</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>\textit{1.3.5}</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>\textit{1.3.6}</td>
<td>70</td>
</tr>
</tbody>
</table>

\textsuperscript{106} For a recent review on N-heterocyclic carbene ligand, see: Wolfgang, A. H. \textit{Angew. Chem. Int. Ed.} \textbf{2002}, \textit{41}, 1290.

6  dppe  0
7  dppf  0

\(^a\) Isolated yield.

In contrast to the number of chiral bidentate phosphine ligands that are available, only a limited number of chiral monodentate phosphine ligands has been employed in asymmetric reactions. The results of the chiral ligand screening were summarized in Table 1.3.2 and the structure of each chiral ligand can be found in Figure 1.3.1. The MeO-MOP ligand 1.3.7,\(^{108}\) which has been used in asymmetric palladium-catalyzed hydrosilylations, did not induce any asymmetry (entry 1). Similarly, reactions using phosphoramidite ligands, such as 1.3.8 and 1.3.9,\(^{109}\) only afforded the racemic product in good yield (entries 2 and 3). A small amount of asymmetric induction was observed when BINEPINE 1.3.10\(^{110}\) was employed, albeit in low yield (entry 4). Ferrocenyl ligands 1.3.11\(^{111}\) and 1.3.12,\(^{112}\) which were developed by Hayashi, gave the corresponding product in good yield, yet, without any enantiomeric excess (entries 5 and 6). In addition, JOSIPHOS-type ligand 1.3.13,\(^{113}\) the optimal ligand in rhodium-catalyzed ring-opening reactions,\(^{44}\) did not afford any satisfactory results (entry 7).
Table 1.3.2 Screening of monodentate chiral ligands

![Chemical structure image]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3.7</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1.3.8</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1.3.9</td>
<td>67</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>1.3.10</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>1.3.11</td>
<td>77</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.3.12</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1.3.13</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by chiral HPLC.
The reaction is proposed to proceed via a similar pathway as in our previous studies (Scheme 1.3.2). Based on this mechanistic proposal, the second carborhodation to the Michael acceptor is a diastereoselective process. Therefore, the stereochemistry of the product is controlled upon the asymmetric addition of the dienylrhodium intermediate to benzonorbornene. The rhodium-catalyzed asymmetric addition to norbornene derivatives has been demonstrated in previous reports by using bidentate phosphine ligands. However, it is speculated that the formation of highly-coordinated intermediate 1.3.14 limits the potential of using multi-coordinative ligands, which exhibit higher degrees of asymmetric induction than monodentate ligands.
We then aimed to develop an asymmetric variation of the cascade addition/cyclization for the formation of indene derivatives using ortho-functionalized aryl boronate ester 1.3.15 (Scheme 1.3.3). In contrast to the reactions using dienylboronate esters (Scheme 1.3.2), the intermediate 1.3.18 generated from the initial carborhodation is achiral. As a result, the stereochemistry in the indene product 1.3.17 will be controlled in the second step, which is a Michael addition of a vinylrhodium species. Since the rhodium-catalyzed asymmetric 1,4-addition reaction has been thoroughly studied and, in addition, the stereodiscriminating step is an intramolecular process, we expected to see a higher degree of enantioselectivity by using chiral ligands in this transformation.
The screening of several commonly-used chiral phosphine ligands is summarized in Table 1.3.3. Phosphoramidite ligand 1.3.8 gave good conversion; however, without any asymmetric induction. JOSIPHOS ligand 1.3.13 afforded the product in poor yield and enantiomeric excess. When using BINAP 1.3.24, which is commonly used in rhodium-catalyzed 1,4-addition reactions, the product was obtained in 23% ee in good yield. Surprisingly, no enantioselectivity was observed when the structurally-similar ligand Tol-BINAP 1.3.25 was employed. A similar level of enantioselectivity was obtained when C2-Ferriphos 1.3.26 was used, which is the optimal ligand in the rhodium-catalyzed ring-opening reactions. Sterically hindered ligands, such as SEGPHOS 1.3.27, did not improve the enantiomeric excess of the product.
Table 1.3.3 Screening of chiral ligands with aryl boronate ester 1.3.13

\[
\begin{align*}
\text{entry} & \quad \text{ligand} & \text{yield (\%)}^a & \text{ee (\%)$^b$} \\
1 & \text{1.3.8} & 89 & 0 \\
2 & \text{1.3.13} & 20 & 3 \\
3 & \text{1.3.19} & 73 & 23 \\
4 & \text{1.3.20} & 43 & 0 \\
5 & \text{1.3.21} & 65 & 4 \\
6 & \text{1.3.22} & 29 & 5 \\
\end{align*}
\]

$^a$ Isolated yield. $^b$ Determined by chiral HPLC.

Figure 1.3.2 Structures of chiral ligands

- 1.3.19 (R)-BINAP
- 1.3.20 (R)-Tol-BINAP
- 1.3.21 (S,S)-(R,R)-C2-Ferriphos
- 1.3.22 (R)-DTBM-SEGPHOS
1.3.2 Conclusions and Future Work

The development of an enantioselective addition/cyclization process using dienylboronate esters is still underway. One of the major challenges is the ligand requirement, which is restricted to the monodentate chiral ligands that usually exhibit a weaker effect on asymmetric induction.

A more promising result was obtained from the preliminary studies of ortho-functionalized arylboronate esters toward the formation of chiral indenes. To improve the enantioselectivity, future investigations should include a full screening of various bidentate chiral ligands. In addition, chiral diene ligands 1.3.23\textsuperscript{116} and 1.3.24\textsuperscript{117}, which has been previously employed in the synthesis of chiral indenols by Hayashi\textsuperscript{48}, would be worthwhile for further examination.

Figure 1.3.3 Structure of chiral diene ligands

\begin{align*}
1.3.23 & \quad (R,R)-\text{Ph-bod}^* \\
1.3.24 & \quad (S,S)-\text{Bn-bod}^*
\end{align*}


1.3.3 Experimental

$^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra were recorded using Mercury 300 MHz, Mercury 400 MHz or Unity 500 MHz spectrometers. $^1$H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and $^{13}$C spectra were referenced to solvent carbons (CDCl$_3$, 77.0 ppm). IR spectra were obtained as thin films on NaCl plates. High resolution mass spectra were obtained at 70 eV for electron impact ionization (EI) or at a spray voltage of 5500 V for electrospray ionization (ESI). HPLC analysis was conducted with an Agilent 1100 series HPLC with photodiode array and Chiralcel or ChiralPak chiral columns with Uniguard pre-column filters.

Toluene, dioxane and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone immediately prior to use. Dichloromethane and benzene were distilled under nitrogen from CaH$_2$ immediately before use. All reagents were used as received from Sigma-Aldrich or Strem unless otherwise indicated. Analytical thin layer chromatography was performed with Silicycle™ normal phase 0.25 mm aluminum or glass backed TLC plates. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel. All experiments were performed under anhydrous conditions under an atmosphere of nitrogen or argon unless otherwise noted.
Acetylferrocene (1.3.25): To a solution of acetyl chloride (4.2 mL, 59 mmol) in CH₂Cl₂ at 0 °C was added aluminum chloride (7.90 g, 59.13 mmol) in small portions. The resulting mixture was added dropwise to a solution of ferrocene (10.0 g, 53.8 mmol) in 150 mL of CH₂Cl₂ at 0 °C over 30 min. The reaction mixture was then warmed to 25 °C and stirred for 1 h. The reaction was then quenched with ice cold water and the aqueous layer was extracted with CH₂Cl₂ (× 3). The combined organic layers were washed with saturated NaHCO₃ aqueous solution, dried over MgSO₄, filtered, and concentrated in vacuo to afford the acetylferrocene 1.3.25 (11.52 g, 94%). The material was sufficiently pure as determined by NMR spectroscopy to be used for subsequent reactions and the
spectral data match the previously reported data.\textsuperscript{118}

\begin{center}
\begin{tikzpicture}
  \node (fe) at (0,0) [circle, draw] {Fe};
  \node (oh) at (-0.5,0.5) [circle, draw] {OH};
  \node (1.3.26) at (0,0) [circle, draw] {1.3.26};
\end{tikzpicture}
\end{center}

**1S-Hydroxyethylferrocene (1.3.26):** To a solution of borane dimethyl sulfide complex (0.70 mL, 7.3 mmol) in 6.4 mL of THF was added \((R)\)-CBS catalyst solution in toluene (11.0 mL, 11.0 mmol). The mixture was cooled to 0 \(^\circ\)C, then a solution of acetylferrocene 1.3.25 (8.30 g, 36.4 mmol) in THF (32 mL) and a solution of borane dimethyl sulfide (2.8 mL, 29 mmol) in THF (26 mL) were added simultaneously over 45 min. The reaction was then stirred at the same temperature for another 30 min and quenched with the addition of 4 mL of MeOH. The saturated aqueous ammonium chloride solution was added to the reaction mixture and the aqueous layer was extracted with Et\(_2\)O \((\times 3)\). The combined organic layers were washed with brine, dried over MgSO\(_4\), filtered, and concentrated in \textit{vacuo}. Chromatography on silica gel using 30\% EtOAc in hexane \((R_f = 0.43)\) gave the \((S)-(3\text{-hydroxyethyl})\)ferrocene 1.3.26 (8.08 g, 97\%). The spectral data match the previously reported data.\textsuperscript{118}

\begin{center}
\begin{tikzpicture}
  \node (nme2) at (0,0) [circle, draw] {NMe\(_2\)};
  \node (1.3.27) at (0,0) [circle, draw] {1.3.27};
\end{tikzpicture}
\end{center}

**\((1S)\)-N\(_2\)N-Dimethyl-1-ferrocenylethylamine (1.3.27):** To a solution of 1.3.26 (1.69 g, 7.32 mmol) in 7.3 mL of pyridine at 25 \(^\circ\)C was added acetic anhydride (6.6 mL, 70 mmol) dropwise. The resulting mixture was stirred at 25 \(^\circ\)C for another 16 h and quenched with

water. The aqueous layer was extracted with EtOAc (× 3) and the combined organic layers was dried with MgSO₄, filtered, and concentrate in vacuo to afford the crude intermediate. The acetate intermediate was dissolved in 30 mL of MeOH and a solution of dimethylamine (18.5 mL, 40% in water, 147 mmol) was added slowly at 25 °C. The reaction mixture was then stirred at same temperature for 16 h before quenched with water. The aqueous layer was extracted with EtOAc (× 3) and the combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 30% EtOAc in hexane (Rₜ = 0.15) gave the (1S)-N,N-Dimethyl-1-ferrocenylethylamine 1.3.27 (1.68 g, 89%). The spectral data match the previously reported data.¹¹⁸

![1.3.27](image)

(1S)-N,N-Dimethy-1-[(R)-2-iodoferrocenyl]ethylamine (1.3.28): To a solution of 1.3.27 (3.51 g, 13.7 mmol) in 150 mL of Et₂O at 25 °C, a solution of sec-BuLi (14.0 mL, 16.4 mmol) was added dropwise over 1 h. The reaction mixture was stirred at same temperature for 2 h before cooled to -78 °C and a solution of iodine (3.82 g, 15.0 mmol) in 50 mL of THF was then added dropwise. After stirring at -78 °C for 1 h, the reaction mixture was warmed to 25 °C and quenched with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with Et₂O (× 3), dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 20% Et₂O in EtOAc (Rₜ = 0.38) gave (1S)-N,N-Dimethy-1-[(R)-2-iodoferrocenyl]ethylamine 1.3.28 (4.70 g, 67%). The spectral data match the previously reported data.¹¹⁷

![1.3.28](image)
To a solution of 1.3.28 (2.00 g, 5.22 mmol) in 11 mL of CH₃CN at 25 °C was added 1.5 mL of MeI (24 mmol) dropwise. The resulting mixture was stirred at same temperature for 2 h and the volatiles were removed in vacuo. The remaining residue was dissolved in 15 mL of MeOH and the mixture was heated to reflux for 2 h. The reaction mixture was cooled to 25 °C and quenched with water. The aqueous layer was extracted with Et₂O (× 3) and the combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% EtOAc in hexane gave 1.3.29 (1.75 g, 91%). The spectral data match the previously reported data.¹¹⁹

To a solution of 1.3.29 (0.20 g, 0.54 mmol) in 8 mL of THF at -78 °C was added a solution of n-BuLi (0.45 mL, 0.65 mmol) dropwise. After the mixture was stirred at -78 °C for 1.5 h, chlorodiphenylphosphine (0.15 mL, 0.81 mmol) was added slowly. The reaction mixture was heated to reflux for 2 h, then cooled to 25 °C and quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with Et₂O (× 3) and the

combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 5% EtOAc in hexane (R_f = 0.18) gave 1.3.11 (0.034 g, 15%). The spectral data match the previously reported data.¹¹¹

![Diagram of compound 1.3.12](image)

**Bis[(R)-2-((S)-1-methoxyethyl)ferrocenyl]phenylphosphine (1.3.12):** Ligand 1.3.12 was prepared according to the procedure for the synthesis of ligand 1.3.11. Using the reaction condition described above with dichlorophenylphosphine (0.12 mL, 0.85 mmol) as starting material, followed by chromatography on silica gel using EtOAc:hexane = 10:1 (R_f = 0.43) gave 1.3.12 (0.27 g, 27%). The spectral data match the previously reported data.¹¹²,¹¹³

![Diagram of compound 1.3.15](image)

**(E)-Methyl 3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acrylate (1.3.15):** Boronate ester 1.3.15 was prepared according to the previously reported procedure.⁵⁶ Using the reaction conditions described in literature with commercial ortho-formylphenylboronic acid (0.50 g, 3.3 mmol) as starting material, followed by chromatography on silica gel using 20% EtOAc in hexane gave the title compound 1.3.15 (0.90 g, 94%) as a yellow solid (the solid resulting from the evaporation of EtOAc and hexane). The spectral data match the previously reported data.⁵⁶
(1.2.66): A solution of 0.3 mL of water and 3 mL of dioxane in a 5 mL 2-neck round bottom flask was purged with argon and stirred for 10 min at 25 °C. [Rh(cod)Cl]_2 (3.0 mg, 0.006 mmol), (S)-Ph-BINEPINE (4.7 mg, 0.012 mmol) and potassium fluoride (23.3 mg, 0.40 mmol) were added to the solution and stirred at 25 °C for 10 min. To the bright yellow solution was added the benzonorbornene (43 mg, 0.24 mmol), followed by addition of the boronate ester 1.2.59 (59 mg, 0.20 mmol) and the reaction mixture was stirred at 80 °C for 3 h. The reaction was quenched with brine, and the aqueous layer was extracted with Et_2O (x 3). The combined organic layers were dried with MgSO_4, filtered and concentrated in vacuo. The crude material was then purified by column chromatography on silica gel using 5% Et_2O in hexane. The spectral data match the previously reported data. Assay of enantiomeric excess was performed using chiral HPLC under the following conditions: ChiralPak AD, 0.5% isopropanol in hexane, 0.3 mL/min, 15 °C, λ = 220 nm; t_\text{r} (minor) = 18.2 min., t_\text{r} (major) = 19.2 min., 22% ee.

Ethyl 1-((methoxycarbonyl)methyl)-3-methyl-1H-indene-2-carboxylate (1.3.17): A solution of 0.3 mL of water and 3 mL of dioxane in a 5 mL 2-neck round bottom flask was purged with argon and stirred for 10 min at 25 °C. [Rh(cod)Cl]_2 (3.0 mg, 0.006 mmol), (R)-BINAP (7.5 mg, 0.012 mmol) and sodium carbonate (42 mg, 0.40 mmol)
were added to the solution and stirred at 25 °C for 10 min. To the bright yellow solution was added the alkyne 1.3.16 (29 mg, 0.26 mmol), followed by addition of the boronate ester 1.3.15 (58 mg, 0.20 mmol) and the reaction mixture was stirred at 80 °C for 3 h. The reaction was quenched with brine, and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtrated and concentrated in vacuo. The crude material was then purified by column chromatography on silica gel using Et₂O:hexane = 1:3. The spectral data match the previously reported data. Assay of enantiomeric excess was performed using chiral HPLC under following the conditions: Chiralcel OD-H, 3% isopropanol in hexane, 1 mL/min, 25 °C, λ = 254 nm; tᵣ (major) = 7.4 min., tᵣ (minor) = 9.2 min., 23% ee.
1.4 SYNTHESIS OF POLYCYCLIC HETEROAROMATICS VIA A RHODIUM-CATALYZED ADDITION/CYCLIZATION SEQUENCE

1.4.1 Results and Discussions

1.4.1.1 Goal of Study

Our efforts in the rhodium-catalyzed sequential addition/cyclization reaction have focused on utilizing either bifunctional phenyl- or alkenyl- boronate esters. We shifted our attention to extend this methodology by using heteroaromatic boronate esters, such as 1.4.1 (Scheme 1.4.1). We expected that by applying this strategy, it would provide an efficient approach to generate a variety of polycyclic heteroaromatics.

Scheme 1.4.1 Reaction with heteroaromatic boronate ester

1.4.1.2 Synthesis of Polycyclic Heteroaromatic Molecules using Rhodium-Catalyzed Addition/Cyclization Sequence

In previous studies, the rhodium-catalyzed coupling reaction with thiophenyl boronate ester 1.4.3 proved to be problematic.\textsuperscript{56b} An unproductive pathway, which led to the noncyclized hydroarylation product 1.4.4, dominated in the reaction, presumably due to a highly favorable 1,4-rhodium migration\textsuperscript{49} to C4 of the thiophene moiety (eq. 1, Scheme
1.4.2). In order to avoid this undesired C-H insertion, we decided to focus our attention on benzothiophene substrate 1.4.6, which lacks the hydrogen that participates in the rhodium migration (eq. 2). Benzothiophene moieties can be found in a wide variety of pharmaceutical agents and biologically active compounds. Therefore, by extending this rhodium-catalyzed carbocycle formation reaction to heteroaromatic boronate esters, a new class of interesting polycyclic heterocycles would be available.

Scheme 1.4.2 Rhodium-catalyzed cascade addition/cyclization reaction

Benzothiophene boronate ester 1.4.9 was prepared as illustrated in Scheme 1.4.3.

---

Benzothiophene was dibrominated to afford 1.4.10, and the formyl group was introduced at 2-position via a metal-halogen exchange protocol. 3-Bromo-2-benzothiophene-carbaldehyde 1.4.11 was protected with ethylene glycol to generate dioxolane 1.4.12. Conversion to boronic acid 1.4.13 was achieved by in situ trapping with triisopropyl borate of the aryllithium species generated from metal-halogen exchange. The boronic acid was then protected with pinacol and subject to the subsequent olefination to give boronate ester 1.4.9.

Scheme 1.4.3 Synthesis of boronate ester 1.4.9

References:

The benzothiophenyl boronate ester 1.4.9 was used for the initial studies to identify optimal reaction conditions. The choice of base for this coupling reaction was found to be crucial, as potassium fluoride led to predominantly deboronation of the starting material, while sodium carbonate gave the desired product in good yield. Overall, the optimal conditions were found to use [Rh(cod)Cl]2 as the rhodium source, with a bulky phosphine ligand t-Bu3PH+BF4− and sodium carbonate as base in dioxane/water (10:1) solution with norbornene as the coupling partner. At 80 °C, product 1.4.15 was obtained in 84% isolated yield in 3 hours (Table 1.4.1, entry 1). The stereochemistry of the product was predicted based on analogy to the previous report,56 which found that the exo-carborhodation of the norbornene followed by the diastereoselective cyclization to the Michael acceptor was the dominant pathway.

We examined the scope of this reaction by screening a variety of strained alkenes. Benzonorbornene 1.2.15 gave the desired product in excellent yield (Table 1.4.1, entry 2). Reacting with norbornadiene derivative 1.2.17 showed the coupling occurred selectively at the electron-rich, unsubstituted double bond (entry 3). Reaction of norbornadiene 1.2.70 could potentially give the double addition product. However, we found that careful control of stoichiometry led to monocyclized product 1.4.18 (entry 4). Oxabicyclic alkenes such as 1.2.7 and 1.2.23, which tend to ring-open under rhodium-catalyzed conditions,34d,38 were found to be compatible and afforded the corresponding products with no ring-opening observed (entries 5 and 6). The nitrogen-containing strained alkene 1.2.33 was also tested and gave an interesting diazabicyclic product in moderate yield (entry 7). Surprisingly, the extension of nitrogen-containing alkene to 1.4.22 was not successful. Under the standard reaction conditions, no desired product was obtained,
presumably due to the low solubility of the diazabicyclic alkene 1.4.22 (entry 8)

Table 1.4.1 Screening of strained bicyclic alkenes as coupling partners$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>product</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>84</td>
</tr>
<tr>
<td>2</td>
<td><img src="1.2.15" alt="alkene" /></td>
<td><img src="1.4.16" alt="product" /></td>
<td>98</td>
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<tr>
<td>3</td>
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<td>84</td>
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<tr>
<td>4</td>
<td><img src="1.2.70" alt="alkene" /></td>
<td><img src="1.4.18" alt="product" /></td>
<td>76</td>
</tr>
</tbody>
</table>
All reactions were run under the following conditions: \( \text{1.4.9} \) (0.20 mmol, 1.0 equiv.), alkene (0.20-0.38 mmol, 1.0-1.9 equiv.), \([\text{Rh(cod)Cl}]_2\) (0.006 mmol, 3 mol%), \(\text{t-Bu}_3\text{PH}^+\text{BF}_4^-\) (0.012 mmol, 6 mol%), \(\text{Na}_2\text{CO}_3\) (0.40 mmol, 2 equiv.) in 3.0 mL of dioxane and 0.3 mL of \(\text{H}_2\text{O}\). \(^b\) Isolated by column chromatography.

We also screened several different electron-withdrawing groups on the benzothiophene boronate esters. Changing from a \(\text{t}-\text{butyl}\) to methyl ester gave \(\text{1.4.23}\) in comparable yield to \(\text{1.4.15}\) (Table 1.4.2, entry 1). We hoped that use of a methylenecyclopropane-containing boronate ester \(\text{1.4.25}\) would enable addition, followed by fragmentation of the methylenecyclopropane.\(^{125,126}\) However, \(\text{1.4.25}\) failed to react, perhaps due to the lack of

electron withdrawing group on the alkene (entry 2). Other heteroaromatic boronate esters such as benzofuran 1.4.26 and indole 1.4.28 were also examined. The corresponding polycyclic heteroaromatic products were obtained in low to moderate yield (entries 3 and 4). Increasing the amount of norbornene to 3 equivalents only led to a slightly higher yield of 1.4.27 (22%). The major side products of entries 3 and 4 were identified as the deboronated alkenyl heterocycles.

Table 1.4.2 Screening of different heteroaromatic boronate esters

<table>
<thead>
<tr>
<th>entry</th>
<th>boronate ester</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td>---</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td>22^c</td>
</tr>
</tbody>
</table>

All reactions were run under the following conditions: boronate ester (0.20 mmol, 1.0 equiv.), norbornene (0.24 mmol, 1.2 equiv.), [Rh(cod)Cl]₂ (0.006 mmol, 3 mol%), t-Bu₃PH⁺BF₄⁻ (0.012 mmol, 6 mol%), Na₂CO₃ (0.40 mmol, 2 equiv.) in 3.0 mL of dioxane and 0.3 mL of H₂O. b Isolated by column chromatography. c Yield obtained using 3 equivalent of norbornene (0.60 mmol).

In addition to the synthesis of benzothiophene containing molecules, we aimed to modify the boronate ester, by tethering the Michael acceptor through a linker such as 1.4.30, to construct carbocycles 1.4.31 with larger ring size (Scheme 1.4.4). We envisioned that by using heteroatoms as a bridging group, it would provide an efficient synthetic pathway to generate a variety of heterocycles. Nitrogen-containing heterocycles, such as tetrahydroquinoline¹²⁷ and indole¹²⁸ moieties, represent a unique class of core structure in medicinal chemistry, as could be easily found in a wide variety of biologically active or therapeutic agents.¹²⁹ Therefore, we set out to test our cascade strategy toward the formation of nitrogen-containing heterocycles by employing aniline-type aryl boronate


The aniline-type boronate esters 1.4.32 and 1.4.33 were prepared according to the synthetic route illustrated in Scheme 1.4.5. Aryl boronic acid 1.4.34 was synthesized from N-Boc-aniline using directed ortho-metallation chemistry\textsuperscript{130} and subsequently converted to boronate ester 1.4.35. Following formylation with acetic formic anhydride 1.4.37,\textsuperscript{131} the electron-deficient olefin was constructed by Wittig reaction to afford N-Boc-aniline boronate ester 1.4.32. Similarly, boronate ester 1.4.33 was prepared using same pathway from commercially available N-Tosyl-aniline boronate ester 1.4.36.


The preliminary screenings on rhodium-catalyzed cascade addition reaction using the aniline-type aryl boronate esters is summarized in Table 1.4.3. Under the optimal reaction condition from previous studies, no conversion of the starting material was observed (entry 1). The low boronate ester conversion is perhaps due to a slower transmetallation process. Switching to potassium fluoride, which is known to facilitate the transmetallation of organoboron reagents,\(^\text{80}\) did not improve reaction (entry 2). Changing the coupling partner from norbornene \textit{1.2.11} to alkyne \textit{1.3.21} shows no improvement on conversion. In addition, reducing the basicity of aniline nitrogen with a tosyl group did not show any effects on increasing reactivity of this process.

![Screening of aniline-type aryl boronate esters](image)

Table 1.4.3 Screening of aniline-type aryl boronate esters

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene or alkyne</th>
<th>R</th>
<th>base</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\textit{1.2.11}</td>
<td>Boc</td>
<td>\textit{Na}_2\textit{CO}_3</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>\textit{1.2.11}</td>
<td>Boc</td>
<td>KF</td>
<td>no conversion</td>
</tr>
<tr>
<td>3</td>
<td>\textit{1.3.21}</td>
<td>Boc</td>
<td>\textit{Na}_2\textit{CO}_3</td>
<td>no conversion</td>
</tr>
<tr>
<td>4</td>
<td>\textit{1.2.11}</td>
<td>Ts</td>
<td>\textit{Na}_2\textit{CO}_3</td>
<td>no conversion</td>
</tr>
</tbody>
</table>

In addition to the low reaction conversion described above, only a small amount of
deboronated starting material was observed, which was generated from the a competing rhodium-catalyzed protodemetallation process. These results suggest that the observed low reactivity might come from the absence of an active catalyst. We speculated that the undesirable interactions of catalyst and the coordinative protecting group, such as Boc and Ts (Figure 1.4.1), might prevent the reaction to proceed.

Figure 1.4.1 Proposed intermediate generated from boronate esters 1.4.32 and 1.4.33

To examine our hypothesis, we decided to change the substrate backbone from aniline to indole. This kind of modification of aryl boronate ester would eliminate the problematic nitrogen protecting group and reduce possibility of catalyst poisoning. Therefore, indole boronate ester 1.4.40 was synthesized as illustrated in Scheme 1.4.6. 7-Bromoindole 1.4.41,132 prepared from 1-bromo-2-nitrobenzene, was formylated with acetic formic anhydride 1.4.37.131 Following the conversion to boronate ester 1.4.42 using palladium-catalyzed borylation reaction,133 the olefin was introduced by Wittig reaction to afford the indole boronate ester 1.4.40.

The indole boronate ester 1.4.40 was then tested under various reaction conditions using norbornene 1.2.11 as the coupling partner. However, only incomplete conversion and decomposition of starting material was observed under the standard reaction conditions (Table 1.4.4, entries 1-3). A change in the coupling partner to ethyl 2-butynoate gave the desired heterocyclic product in low yield (entry 4). Switching the base from sodium carbonate to potassium fluoride gave the corresponding product in slightly higher yield (entry 5). However, in both cases, we observed the incomplete conversion of indole boronate ester, indicating the unsatisfactory yield might result from reduced catalyst activity.

Table 1.4.4 Screening indole boronate ester 1.4.40 with alkene or alkyne

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene or alkyne</th>
<th>base</th>
<th>product</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.2.11 Na$_2$CO$_3$ decomposition ---

2$^b$ 1.2.11 Na$_2$CO$_3$ decomposition ---

3 1.2.11 KF decomposition ---

4 CO$_2$Et

1.3.21 Na$_2$CO$_3$

1.4.44

5 1.3.21 KF 1.4.44 50

$^a$ Isolated by column chromatography. $^b$ Performed with extended reaction time (16 h).

1.4.2 Conclusions and Future Work

In summary, we have developed an efficient method to synthesize a series of polycyclic heteroaromatic compounds as an extension of previously-studied rhodium-catalyzed cascade addition reactions. The unproductive pathway arising from a rhodium 1,4-shift could be excluded by using the bifunctional benzothiophene boronate esters. Among the examined heteroaromatic boronate esters, benzothiophene shows the highest reactivity.

In contrast to the benzothiophene substrate, the reaction using aniline-type boronate esters proved to be difficult. However, by changing the substrate backbone from aniline to indole, the desired heteroaromatic product could be obtained in moderate yield. To make this reaction synthetically practical, further optimization on the catalyst system would be required.
1.4.3 Experimental

$^1$H, and $^{13}$C NMR spectra were recorded using Mercury 300 MHz, Mercury 400 MHz or Unity 500 MHz spectrometers. $^1$H spectra were referenced to tetramethysilane (TMS, 0 ppm) or solvent protons (DMSO-d$_6$, 2.50 ppm) and $^{13}$C spectra were referenced to solvent carbons (CDCl$_3$, 77.0 ppm or DMSO-d$_6$, 39.51 ppm). IR spectra were obtained as thin films on NaCl plates. High resolution mass spectra were obtained at 70 eV for electron impact ionization (EI) or at a spray voltage of 5500 V for electrospray ionization (ESI).

Toluene, dioxane and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone immediately prior to use. Dichloromethane and benzene were distilled under nitrogen from CaH$_2$ immediately before use. All reagents were used as received from Sigma-Aldrich or Strem unless otherwise indicated. Analytical thin layer chromatography was performed with Silicycle™ normal phase 0.25 mm aluminum or glass backed TLC plates. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel. All experiments were performed under anhydrous conditions under an atmosphere of nitrogen or argon unless otherwise noted.
2,3-Dibromobenzothiophene (1.4.10): To a solution of benzothiophene (4.85 g, 36.1 mmol) in 18 mL of CHCl₃ at 25 °C, a solution of bromine (3.7 mL, 72 mmol) in 10 mL of CHCl₃ was added dropwise. The reaction mixture was stirred at 25 °C for 16 h before being quenched with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with CHCl₃ (× 3) and the combined organic layers were washed with saturated aqueous Na₂S₂O₃, dried over Na₂SO₄, filtered and concentrated in vacuo. Chromatography on silica gel using hexane (Rₜ = 0.85) gave 1,2-dibromobenzothiophene 1.4.10 (9.62 g, 91%). Spectral data match the previously reported data.¹²²

3-Bromo-2-benzo[b]thiophenecarbaldehyde (1.4.11): To a solution of 1,2-dibromobenzothiophene 1.4.10 (3.00 g, 10.3 mmol) in Et₂O at -78 °C was added a 1.34M solution of n-butyllithium in hexane (8.7 mL, 12 mmol) dropwise. The reaction mixture was stirred at -78 °C for 1 h before N,N-dimethylformamide (0.84 mL, 11 mmol) was added dropwise. The reaction was warmed to 25 °C and stirred at this temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride solution and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% Et₂O in hexane gave 3-bromo-2-benzo[b]thiophenecarbaldehyde 1.4.11 (1.56
g, 51%). Spectral data match the previously reported data.\textsuperscript{134}

\begin{center}
\includegraphics[width=0.2\textwidth]{1.4.13}
\end{center}

**2-Formyl-3-benzothiopheneboronic acid (1.4.13):** \textit{p}-Toluenesulfonic acid monohydrate (86 mg, 0.45 mmol) was added to a mixture of 3-bromo-2-benzo[\textit{b}]thiophene-carbaldehyde 1.4.11 (2.17 g, 9.00 mmol) and ethylene glycol (2.0 mL, 36 mmol) in benzene (22 mL).\textsuperscript{135} The reaction mixture was heated to reflux and the water removed by a Dean-Stark trap for 3 h. The mixture was then cooled to room temperature, diluted with Et\textsubscript{2}O, washed with water (× 3) and saturated aqueous sodium bicarbonate solution. The organic layer was dried with MgSO\textsubscript{4}, filtered and concentrated in vacuo to afford crude 3-bromo-2-(2-dioxolanyl)thiophene 1.4.12. To a solution of crude 3-bromo-2-(2-dioxolanyl)thiophene 1.4.12 (9.00 mmol) and tri-isopropylborate (2.2 mL, 9.6 mmol) in 30 mL of toluene and 7.5 mL of THF at -78 °C, was added a 1.6M solution of \textit{n}-butyllithium in hexane (6.0 mL, 9.6 mmol). The reaction was stirred at -78 °C for 1 h, and then warmed to 25 °C for another 1 h. The reaction mixture was cooled to 0 °C and hydrolyzed with saturated aqueous ammonium chloride solution and 2N HCl aqueous solution and stirred at 0 °C for 30 min. The aqueous layer was extracted with Et\textsubscript{2}O (× 3), then the combined organic layers were extracted with 2N NaOH aqueous solution (× 3). The combined aqueous layers were cooled to 0 °C and acidified with 2N HCl aqueous solution to pH = 2. The precipitated boronic acid was collected by vacuum filtration,


washed with water (× 3), and dried in vacuo to afford 2-formyl-3-benzothiopheneboronic acid 1.4.13 (1.49 g, 81%) as a brown solid, m.p. = 130 °C (decomp.). \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 10.0 (s, 1H), 8.95-8.91 (m, 1H), 8.00-7.96 (m, 1H), 7.59-7.49 (m, 2H), 7.17 (s, 2H); \( ^{13}C \) NMR (75 MHz, DMSO-d\(_6\)): \( \delta \) 186.7, 147.2, 142.7, 141.6, 127.9, 127.8, 125.0, 123.1; IR (neat): 3296, 1645, 1591, 1501, 1433, 1405, 1372, 1334, 1311, 1285, 1254, 1204, 1160, 1109, 1160, 1041, 940, 758, 721 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_9\)H\(_6\)BO\(_3\)S [M-H\(^+\)] 205.0136, found 205.0144.

![1.4.9](image)

**tert-Butyl (2E)-3-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzothien-2-yl]-acrylate (1.4.9):** 2-Formyl-3-benzothiopheneboronic acid 1.4.13 (1.49 g, 7.22 mmol) and pinacol (939 mg, 7.94 mmol) were dissolved in benzene (24 mL). The mixture was heated to reflux and the water was removed by a Dean-Stark trap for 6 h. The reaction mixture was cooled to 25 °C, dried with MgSO\(_4\), filtered and concentrated in vacuo to afford crude intermediate 1.4.14. Separately, tert-butyl P,P-dimethylphosphonoacetate (1.7 mL, 8.3 mmol) was added dropwise to a suspension of NaH (318 mg, 7.94 mmol) in THF (25 mL) at 0 °C, After stirring at 0 °C for 30 min, a solution of the crude intermediate in 20 mL of THF was added dropwise and the reaction was warmed to 25 °C and stirred for 16 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution and the aqueous layer was extracted with Et\(_2\)O (× 3). The combined organic layers were dried with MgSO\(_4\), filtered, and concentrated in vacuo. Chromatography on silica gel using 10% Et\(_2\)O in hexane (R\(_f\) = 0.43) gave title compound
1.4.9 (2.54 g, 91%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 115-118 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.59 (d, J = 15.8 Hz, 1H), 8.38-8.34 (m, 1H), 7.79-7.74 (m, 1H), 7.38-7.31 (m, 2H), 6.31 (d, J = 15.8 Hz, 1H), 1.55 (s, 9H), 1.41 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 165.8, 150.9, 144.2, 139.9, 137.9, 126.3, 125.8, 124.7, 122.8, 121.7, 83.8, 80.4, 28.2, 24.9; IR (neat): 2977, 1707, 1621, 1500, 1458, 1430, 1371, 1280, 1233, 1142, 973, 857, 764, 735 cm⁻¹; HRMS (EI) Calcd for C₂₁H₂₇BO₄S [M⁺] 386.1723, found 386.1741.

[Chemical Structure Image]

Methyl (2E)-3-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzothien-2-yl]-acrylate (1.4.23): 2-Formyl-3-benzothiopheneboronic acid 1.4.13 (263 mg, 1.28 mmol) and pinacol (166 mg, 1.41 mmol) was dissolved in benzene (10 mL). The mixture was heated to reflux and the water was removed by a Dean-Stark trap for 6 h. The reaction mixture was cooled to 25 °C, the trap was removed and methyl (triphenylphosphoranylidene)acetate (471 mg, 1.41 mmol) was added. The mixture was stirred at 25 °C for 16 h, then filtered through a pad of silica gel and the pad was washed with Et₂O. The organic layer was dried with MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel using 30% Et₂O in hexane (Rₐ = 0.5) gave title compound 1.4.23 (200 mg, 45%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 150-153 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.68 (d, J = 15.8 Hz, 1H), 8.40-8.34 (m, 1H), 7.81-7.75 (m, 1H), 7.40-7.33 (m, 2H), 6.39 (d, J = 15.8 Hz, 1H), 3.82 (s, 3H), 1.42 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 167.2, 150.3, 144.2, 140.0,
3-Bromo-2-(cyclopropyldenemethyl)-1-benzothiophene (1.4.45): The title compound was prepared according to the previously reported procedure for the synthesis of 2-bromobenzylidene-cyclopropane.\textsuperscript{136} Using reaction condition described in literature with 3-bromo-2-benzothiophenecarbaldehyde 1.4.11 (0.50 g, 2.1 mmol) as the starting material, followed by chromatography on silica gel using 0.5% Et\textsubscript{2}O in hexane gave title compound (0.29 g, 52%) as a white solid (the solid resulting from the evaporation of Et\textsubscript{2}O and hexane), m.p. = 67-70 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.77 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.43-7.30 (m, 2H), 7.24-7.22 (m, 1H), 1.46-1.40 (m, 2H), 1.39-1.33 (m, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 138.50, 138.46, 137.1, 130.0, 125.3, 124.9, 122.8, 122.2, 112.0, 105.6, 4.7, 3.2; IR (neat): 3049, 2966, 2361, 2336, 1770, 1682, 1556, 1540, 1458, 1434, 1398, 1326, 1308, 1287, 1253, 1189, 1155, 1132, 998, 972, 919, 806 cm\textsuperscript{-1}; HRMS (EI) Calcd for C\textsubscript{12}H\textsubscript{8}S [M-Br\textsuperscript{+}] 185.0425, found 185.0418.

2-[2-(Cyclopropyldienemethyl)-1-benzothien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.4.25): To a solution of 3-bromo-2-(cyclopropyldienemethyl)-1-benzothiophene 1.4.45 (0.25 g, 0.94 mmol) and triisopropylborate (0.24 mL, 1.0 mmol) in 6 mL of toluene and 1.5 mL of THF at -78 °C, was added a 1.6M solution of n-butyllithium in hexane (0.65 mL, 1.0 mmol). The reaction was stirred at -78 °C for 30 min and pinacol (130 mg, 1.13 mmol) was added at -78 °C. The reaction was protected from light (aluminum foil), warmed to 25 °C and stirred for 16 h. The reaction mixture was then diluted with Et₂O, washed with saturated aqueous ammonium chloride solution, water and brine. The organic layer was dried with MgSO₄, filtrated and concentrated in vacuo. Chromatography on silica gel using 2% Et₂O in hexane (R_f = 0.39) gave the title compound 1.4.25 (0.16 g, 55%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 114-116 °C. ^1H NMR (400 MHz, CDCl₃): δ 8.36-8.31 (m, 1H), 7.85-7.81 (m, 1H), 7.76-7.72 (m, 1H), 7.35-7.22 (m, 2H), 1.47-1.35 (m, 4H), 1.41 (s, 12H); ^13C NMR (100 MHz, CDCl₃): δ 156.7, 144.3, 139.5, 129.1, 125.4, 124.2, 124.0, 121.3, 114.8, 83.3, 25.0, 5.0, 3.2; IR (neat): 2977, 1508, 1456, 1376, 1332, 1286, 1233, 1142, 984, 860, 762, 735 cm⁻¹; HRMS (EI) Calcd for C_{18}H_{21}BO₂S [M⁺] 312.1355, found 312.1358.
**2,3-Dibromobenzofuran (1.4.46):** To a solution of bromine (1.3 mL, 25 mmol) in 5 mL of CHCl₃ at 25 °C was added a solution of benzofuran (1.50 g, 12.7 mmol) and potassium acetate (0.25 g, 2.5 mmol) in 15 mL of CHCl₃ dropwise. The reaction was heated at 50 °C for 5 h before being quenched with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with CHCl₃ (× 3), dried with Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using hexane (R_f = 0.68) gave 1,2-dibromobenzofuran 1.4.46 (2.19 g, 63%). Spectral data match the previously reported data.¹³⁷

![1.4.47](image)

**3-Bromo-1-benzofuran-2-carbaldehyde (1.4.47):** The title compound was prepared according to the previously reported procedure¹³³ for the synthesis of 3-bromo-2-benzo[b]thiophenecarbaldehyde 1.4.11. Using reaction the conditions described in the literature with 2,3-dibromobenzofuran 1.4.46 (2.12 g, 7.68 mmol) as the starting material, followed by chromatography on silica gel using 10% Et₂O in hexane (R_f = 0.49) gave the title compound 1.4.47 (1.18 g, 68%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 66-69 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.01 (s, 1H), 7.74-7.70 (m, 1H), 7.63-7.56 (m, 2H), 7.46-7.40 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 178.2, 154.9, 147.4, 130.5, 127.3, 124.8, 122.0, 113.0, 110.3; IR (neat): 2842, 2355, 1674, 1608, 1557, 1541, 1441, 1326, 1288, 1260, 1198, 1020, 1000, 903, 871, 702, 668, 616 cm⁻¹; HRMS (EI) Calcd for C₉H₅BrO₂ [M⁺] 223.9473.

2-Formyl-3-benzofuranboronic acid (1.4.48): The title compound was prepared according to the procedure for the synthesis of 2-formyl-3-benzothiophene-boronic acid 1.4.13. Using the reaction conditions described above with 3-bromo-1-benzofuran-2-carbaldehyde 1.4.47 (1.14 g, 5.07 mmol) as the starting material gave the title compound (0.84 g, 87%) as a orange solid, m.p. = 131 °C (decomp.). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.03 (s, 1H), 8.35-8.31 (m, 1H), 7.63-7.54 (m, 2H), 7.40 (ddd, $J = 8.1, 6.8, 1.2$ Hz, 1H), 7.02 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 182.2, 156.0, 155.1, 130.3, 128.9, 125.4, 123.9, 112.0; IR (neat): 3315, 3177, 1661, 1558, 1477, 1450, 1436, 1404, 1378, 1296, 1259, 1246, 1160, 1121, 1107, 943, 861, 849, 814, 764, 740 cm$^{-1}$; HRMS (EI) Calcd for C$_9$H$_6$BO$_4$ [M-H$^+$] 189.0364, found 189.0369.

tert-Butyl (2E)-3-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzofuran-2-yl] acrylate (1.4.26): The title compound was prepared according to the procedure for the synthesis of 1.4.9. Using the reaction conditions described above with 2-formyl-3-benzofuranboronic acid 1.4.48 (0.60 g, 3.2 mmol) as the starting material, followed by chromatography on silica gel using 10% Et$_2$O in hexane (R$_f$ = 0.56) gave the title compound 1.4.26 (0.81 g, 69%) as a white solid (the solid resulting from the
evaporation of Et₂O and hexane), m.p. = 143-145 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.99 (d, J = 15.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.35-7.30 (m, 1H), 7.27-7.22 (m, 1H), 6.22 (d, J = 15.8 Hz, 1H), 1.55 (s, 9H), 1.38 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 166.1, 160.0, 155.3, 131.8, 131.3, 126.1, 123.5, 123.2, 122.4, 110.8, 83.8, 80.5, 28.2, 24.9; IR (neat): 2979, 2357, 1709, 1639, 1548, 1478, 1450, 1426, 1403, 1391, 1380, 1367, 1306, 1256, 1246, 1185, 1145, 1107, 1028, 983, 921, 881, 854, 793, 777, 752, 668 cm⁻¹; HRMS (ESI) Calcd for C₂₁H₂₇BO₅Na [M+Na⁺] 393.1843, found 393.1831.

![Image of 2,3-Dibromo-1-methyl-1H-indole](image)

2,3-Dibromo-1-methyl-1H-indole (1.4.49): To a solution of 1-methylindole (2.00 g, 15.3 mmol) in 50 mL of DCE and 2 mL of water was added tetrabutylammonium bromide (0.49 g, 1.5 mmol) and copper(II) bromide (13.6 g, 61.0 mmol) at 25 °C. The reaction was allowed to stir at same temperature for 16 h. The mixture was filtered through a pad of silica gel and the organic layer was dried with Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 15% CH₂Cl₂ in hexane (R_f = 0.50 in 15% CH₂Cl₂ in hexane) gave 2,3-dibromo-1-methyl-1H-indole 1.4.49 (1.90 g, 43%). Spectral data match the previously reported data.¹³⁸

3-Bromo-1-methyl-1H-indole-2-carbaldehyde (1.4.50): The title compound was prepared according to the previously reported procedure\(^{133}\) for the synthesis of 3-bromo-2-benzo[b] thiophenecarbaldehyde 1.4.11. Using the reaction conditions described in the literature with 2,3-dibromo-1-methyl-1H-indole 1.4.39 (1.59 g, 5.48 mmol) as the starting material, followed by chromatography on silica gel using 30% CH\(_2\)Cl\(_2\) in hexane (R\(_f\) = 0.5) gave the title compound 1.4.50\(^{139}\) (0.94 g, 73%) as a yellow solid (the solid resulting from the evaporation of CH\(_2\)Cl\(_2\) and hexane), m.p. = 86-89 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 10.13 (s, 1H), 7.69 (d, \(J = 8.2\) Hz, 1H), 7.49-7.44 (m, 1H), 7.38 (d, \(J = 8.6\) Hz, 1H), 7.27-7.22 (m, 1H), 4.08 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 182.6, 139.4, 130.0, 128.1, 126.1, 121.61, 121.55, 110.5, 106.0, 31.8; IR (neat): 2357, 2331, 1666, 1610, 1504, 1469, 1393, 1329, 1238, 1180, 1158, 1122, 1106, 948, 870, 737 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{10}\)H\(_8\)BrNO [M\(^+\)] 236.9789, found 236.9794.

(2-Formyl-1-methyl-1H-indol-3-yl)boronic acid (1.4.51): The title compound was prepared according to the procedure for the synthesis of 2-formyl-3-benzo[\(h\)] thiopheneboronic acid 1.4.13. Using the reaction conditions described above with

3-bromo-1-methyl-1\textit{H}-indole-2-carbaldehyde 1.4.50 (0.72 g, 3.0 mmol) as the starting material, gave the title compound 1.4.51 (0.61 g, 46%) as a yellow solid, m.p. = 128 °C (decomp.). $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 10.25 (s, 1H), 8.37 (bs, 2H), 8.06 (dt, $J$ = 8.1, 1.0 Hz, 1H), 7.59 (dt, $J$ = 8.5, 0.8 Hz, 1H), 7.40 (ddd, $J$ = 8.4, 7.0, 1.2 Hz, 1H), 7.06 (ddd, $J$ = 8.1, 7.0, 1.0 Hz, 1H), 4.07 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 186.0, 140.0, 139.4, 130.8, 126.2, 125.9, 120.7, 110.7, 31.5; IR (neat): 3315, 1648, 1509, 1458, 1421, 1385, 1342, 1304, 1241, 1204, 1128, 1077, 1010, 962, 931, 855, 814, 748 cm$^{-1}$; HRMS (ESI) Calcd for C$_{10}$H$_9$BNO$_3$ [M-H$^+$] 202.0680, found 202.0691.

\[\text{Bpin} \ CO_2 \text{t-Bu} \]

1.4.28

tert-Butyl \ (2\textit{E})-3-[1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1\textit{H}-indol-2-yl]acrylate (1.4.28): The title compound was prepared according to the procedure for the synthesis of 1.4.9. Using the reaction conditions described above with (2-fromyl-1-methyl-1\textit{H}-indol-3-yl) boronic acid 1.4.51 (0.23 g, 1.1 mmol) as the starting material, followed by chromatography on silica gel using 20% Et$_2$O in hexane (R$_f$ = 0.48) gave the title compound 1.4.28 (0.40 g, 92%) as a yellow solid (the solid resulting from the evaporation of Et$_2$O and hexane), m.p. = 142-145 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.21 (d, $J$ = 16.4 Hz, 1H), 8.10 (d, $J$ = 8.0 Hz, 1H), 7.33-7.24 (m, 2H), 7.16 (t, $J$ = 7.0 Hz, 1H), 6.48 (d, $J$ = 16.6 Hz, 1H), 3.87 (s, 3H), 1.57 (s, 9H), 1.39 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.3, 142.6, 139.9, 133.5, 132.5, 123.7, 123.3, 122.8, 120.8, 109.3, 83.0, 80.3, 31.9, 28.2, 25.0; IR (neat): 2972, 2923, 1703, 1622, 1495, 1468, 1408, 1388, 1368, 1316, 1285, 1256, 1235, 1205, 1165, 1137, 1103, 1010, 977, 909, 858, 780, 768, 147
General Procedure for Rhodium-Catalyzed Cascade Addition/Cyclization Reactions:

A solution of 0.3 mL of water and 3 mL of dioxane in a 5 mL 2-neck round bottom flask was purged with argon and stirred for 10 min at 25 °C. [Rh(cod)Cl]₂ (3.0 mg, 0.006 mmol), tri-tert-butylyphosphonium tetrafluoroborate (3.5 mg, 0.012 mmol) and sodium carbonate (42.4 mg, 0.40 mmol) were added to the solution and stirred at 25 °C for 10 min. To the bright yellow solution was added the alkene 2, followed by addition of the boronate ester (0.20 mmol) and the reaction mixture was stirred at 80 °C for 3 h. The reaction was quenched with brine, and the aqueous layer was extracted with Et₂O (× 3 mL). The combined organic layers were dried with MgSO₄, filtrated and concentrated in vacuo.

(1.4.15): Using the general procedure above with 1.4.9 (77 mg, 0.20 mmol) as the boronate ester and norbornene 1.2.11 (23 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O in hexane (R_f = 0.43) gave compound 1.4.15 (59.6 mg, 84%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 78-81 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.34-7.29 (m, 1H), 7.26-7.21 (m, 1H), 3.35-3.28 (m, 1H), 3.16 (d, J = 7.2 Hz, 1H), 2.60 (dd, J = 15.6, 7.4 Hz, 1H), 2.52 (dd, J = 15.6, 7.6 Hz, 1H), 2.46 (d, J = 3.9 Hz, 1H), 2.46 (d, J = 3.9 Hz, 1H), 2.42 (dd, J = 7.0, 2.2 Hz, 1H), 1.68-1.51 (m, 2H),
1.49 (s, 9H), 1.44-1.36 (m, 1H), 1.29-1.20 (m, 2H), 1.07 (dt, J = 10.1, 1.4 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.5, 146.4, 145.5, 141.7, 134.5, 124.0, 123.5, 123.3, 121.4, 80.7, 58.4, 50.0, 45.8, 43.3, 42.7, 39.6, 33.1, 28.9, 28.5, 28.1; IR (neat): 2949, 2870, 1726, 1455, 1432, 1392, 1366, 1294, 1249, 1151, 1018, 937, 849, 752, 731 cm$^{-1}$; HRMS (EI) Calcd for C$_{22}$H$_{26}$O$_2$S [M$^+$] 354.1654, found 354.1661.

![1.4.16](image)

**1.4.16**: Using the general procedure above with 1.4.9 (77 mg, 0.20 mmol) as the boronate ester and benzonorbornene 1.2.15 (54 mg, 0.38 mmol) as the alkene, followed by chromatography on silica gel using 10% Et$_2$O in hexane (R$_f = 0.58$) gave compound 1.4.16 (77.0 mg, 98%) as a white solid (the solid resulting from the evaporation of Et$_2$O and hexane), m.p. = 53-56 $^\circ$C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.80-7.75 (m, 2H), 7.41-7.35 (m, 1H), 7.31-7.22 (m, 2H), 7.22-7.18 (m, 1H), 7.15-7.06 (m, 2H), 3.56-3.49 (m, 2H), 3.37-3.32 (m, 2H), 2.64 (dd, J = 15.8, 7.2 Hz, 1H), 2.60-2.56 (m, 1H), 2.56 (dd, J = 15.8, 7.8 Hz, 1H), 1.80-1.75 (m, 1H), 1.73-1.67 (m, 1H), 1.52 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.3, 148.2, 147.8, 147.5, 145.3, 140.2, 134.3, 126.0, 125.9, 124.2, 123.57, 123.55, 121.4, 121.1, 120.9, 80.9, 57.5, 49.6, 49.0, 46.9, 44.6, 43.6, 43.2, 28.2; IR (neat): 2970, 2932, 1724, 1458, 1366, 1269, 1244, 1148, 945, 910, 845, 752, 735 cm$^{-1}$; HRMS (EI) Calcd for C$_{26}$H$_{26}$O$_2$S [M$^+$] 402.1654, found 402.1657.
(1.4.17): Using the general procedure above with 1.4.9 (77 mg, 0.20 mmol) as the boronate ester and 1.2.17 (50 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 20% EtOAc in hexane (R_f = 0.35) gave compound 1.4.17 (76.6 mg, 84%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.37 (td, J = 7.6, 1.1 Hz, 1H), 7.31-7.25 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.56 (d, J = 7.2 Hz, 1H), 3.45-3.40 (m, 2H), 3.30 (s, 1H), 2.78 (d, J = 7.0 Hz, 1H), 2.65 (d, J = 2.3 Hz, 1H), 2.63 (d, J = 2.5 Hz, 1H), 1.71-1.66 (m, 1H), 1.50 (s, 9H), 1.49-1.45 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.0, 165.1, 164.9, 147.7, 145.4, 145.1, 144.8, 139.2, 133.9, 124.3, 123.8, 123.5, 121.4, 81.1, 55.9, 52.1, 52.0, 50.8, 48.4, 47.4, 43.9, 43.2, 42.1, 28.1; IR (neat): 2978, 2951, 2951, 1732, 1717, 1622, 1456, 1435, 1393, 1368, 1337, 1269, 1227, 1190, 1152, 1094, 1015, 918, 783, 758, 733 cm⁻¹; HRMS (EI) Calcd for C₂₆H₂₈O₆S [M⁺] 468.1607, found 468.1624.

(1.4.18): Using the general procedure above with 1.4.9 (77 mg, 0.20 mmol) as the boronate ester and norbornadiene 1.2.70 (21 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O in hexane (R_f = 0.43) gave compound 1.4.18
(52.0 mg, 76%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 101-104 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.33 (td, J = 7.5, 1.1 Hz, 1H), 7.28-7.22 (m, 1H), 6.26-6.21 (m, 1H), 6.17-6.12 (m, 1H), 3.37-3.30, (m, 1H), 3.23 (d, J = 7.0 Hz, 1H), 3.01 (s, 1H), 2.84 (s, 1H), 2.62 (dd, J = 15.8, 7.6 Hz, 1H), 2.55 (dd, J = 15.8, 7.6 Hz, 1H), 2.52-2.48 (m, 1H), 1.50 (s, 9H), 1.44-1.39 (m, 1H), 1.37-1.32 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 147.4, 145.1, 140.7, 137.6, 137.0, 134.4, 124.1, 123.5, 123.4, 121.4, 80.8, 56.1, 47.6, 47.3, 44.7, 43.8, 43.3, 42.9, 28.1; IR (neat): 2972, 2932, 1726, 1603, 1466, 1454, 1433, 1393, 1368, 1325, 1260, 1246, 1234, 1150, 1040, 754, 733, 712 cm⁻¹; HRMS (EI) Calcd for C₂₂H₂₄O₂S [M⁺] 352.1497, found 352.1493.

(1.4.19): Using the general procedure above with 1.4.9 (77 mg, 0.20 mmol) as the boronate ester and oxabicycle 1.2.7 (87 mg, 0.22 mmol) as the alkene, followed by chromatography on silica gel using 30% EtOAc in hexane (Rᵣ = 0.48) gave compound 1.4.19 (114.3 mg, 88%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.33 (td, J = 7.5, 1.1 Hz, 1H), 7.28-7.25 (m, 1H), 7.23 (d, J = 8.2 Hz, 4H), 6.88 (d, J = 8.0 Hz, 4H), 4.45 (s, 2H), 4.42 (d, J = 11.3 Hz, 1H), 4.42 (s, 2H), 4.38 (d, J = 11.3 Hz, 1H), 3.812 (s, 3H), 3.807, 3.63-3.57 (m, 1H), 3.49-3.43 (m, 1H), 3.33 (td, J = 9.1, 2.3 Hz, 2H), 2.75 (dd, J = 7.2, 3.1 Hz, 1H), 2.61 (dd, J = 15.8, 7.2 Hz, 1H), 2.52 (dd, J = 15.8, 7.8 Hz, 1H), 2.35 (td, J = 9.1, 6.1 Hz, 1H), 2.23 (td, J =
9.2, 5.9 Hz, 1H), 1.44 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 171.0, 159.2, 147.1, 145.4, 139.1, 134.1, 130.4, 130.3, 129.4, 129.2, 124.2, 123.6, 123.4, 121.0, 113.82, 113.77, 85.2, 81.1, 81.0, 72.9, 68.4, 68.3, 60.4, 58.7, 55.3, 50.7, 45.5, 45.3, 45.0, 43.0, 28.0, 21.0, 14.2; IR (neat): 2976, 2934, 2859, 2837, 2361, 2332, 1722, 1613, 1514, 1464, 1568, 1302, 1248, 1173, 1152, 1088, 1036, 820, 756, 731 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{31}\)H\(_{35}\)O\(_6\)S [M-C\(_8\)H\(_9\)O\(^+\)] 535.2154, found 535.2144.

(1.4.20): Using the general procedure above with 1.4.9 (77 mg, 0.20 mmol) as the boronate ester and oxabicycle 1.2.23 (62 mg, 0.20 mmol) as the alkene, followed by chromatography on silica gel using 15% Et\(_2\)O in hexane (\(R_f = 0.35\)) gave compound 1.4.20 (71.2 mg, 62%) as a yellow solid (the solid resulting from the evaporation of Et\(_2\)O and hexane), m.p. = 60-63 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.75 (dt, \(J = 7.9, 0.9\) Hz, 1H), 7.50 (d, \(J = 7.6\) Hz, 1H), 7.34-7.29 (m, 1H), 7.26-7.21 (m, 1H), 4.29 (dd, \(J = 7.4, 2.9\) Hz, 1H), 4.13 (t, \(J = 3.8\) Hz, 1H), 4.10 (d, \(J = 3.5\) Hz, 1H), 3.97 (d, \(J = 3.1\) Hz, 1H), 3.59-3.52 (m, 1H), 3.40 (dd, \(J = 7.4, 3.3\) Hz, 1H), 2.67 (dd, \(J = 16.6, 6.4\) Hz, 1H), 2.50 (dd, \(J = 16.6, 8.6\) Hz, 1H), 2.17-2.05 (m, 2H), 1.50 (s, 9H), 1.24 (d, \(J = 7.4\) Hz, 3H), 1.22-1.13 (m, 21H), 1.06 (d, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 171.2, 145.7, 145.5, 140.6, 134.4, 124.1, 123.6, 123.3, 120.6, 86.4, 81.6, 80.7, 74.1, 55.9, 47.0, 46.4, 43.0, 40.2, 39.8, 28.2, 18.72, 18.69, 14.0, 13.9; IR (neat): 2932, 2865, 1726, 1460, 1432, 1365, 1242, 1174, 1145, 1088, 1038, 1010, 959, 883, 848, 812, 787, 755, 728 cm\(^{-1}\);
HRMS (EI) Calcd for C_{33}H_{50}O_{4}Si [M^+] 570.3199, found 570.3193.

(1.4.21): Using the general procedure above with 1.4.9 (77 mg, 0.20 mmol) as the boronate ester and diazabicyclo 1.2.33 (71 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 20% EtOAc in hexane (R_f = 0.49) gave compound 1.4.21 (69.2 mg, 61%) as a yellow solid (the solid resulting from the evaporation of Et_2O and hexane), m.p. = 76-79 °C. NMR run at 75 °C, ¹H NMR (500 MHz, DMSO-d_6): δ 7.87 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 4.56 (s, 1H), 4.52 (s, 1H), 3.62 (s, 1H), 3.36 (s, 1H), 3.09 (s, 1H), 2.94-2.89 (m, 1H), 2.71-2.58 (m, 2H), 1.51 (s, 9H), 1.46 (s, 10H), 1.43 (s, 9H); ¹³C NMR (125 MHz, DMSO-d_6): δ 169.8, 155.3, 147.0, 144.4, 137.9, 132.9, 124.2, 123.5, 123.3, 120.3, 80.1, 79.9, 62.8, 61.0, 54.8, 47.4, 42.3, 41.5, 31.6, 27.6, 27.5, 27.4; IR (neat): 2978, 2933, 1728, 1695, 1455, 1392, 1367, 1258, 1143, 1105, 919, 853, 754, 732 cm⁻¹; HRMS (EI) Calcd for C_{30}H_{40}N_{2}O_{6}S [M^+] 556.2607, found 556.2599.

(1.4.24): Using the general procedure above with 1.4.23 (69 mg, 0.20 mmol) as the boronate ester and norbornene 1.2.11 (23 mg, 0.24 mmol) as the alkene, followed by
chromatography on silica gel using 5% Et₂O in hexane (R_f = 0.30) gave compound 1.4.24 (44.9 mg, 76%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.26-7.21 (m, 1H), 3.75 (s, 3H), 3.39-3.33 (m, 1H), 3.17 (d, J = 7.2 Hz, 1H), 2.66 (dd, J = 7.6, 4.5 Hz, 2H), 2.46 (d, J = 3.7 Hz, 1H), 2.39 (dd, J = 7.1, 2.3 Hz, 1H), 2.27 (d, J = 3.7 Hz, 1H), 1.68-1.50 (m, 2H), 1.43-1.36 (m, 1H), 1.28-1.19 (m, 2H), 1.07 (d, J = 10.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 145.9, 145.5, 141.9, 134.5, 124.1, 123.5, 123.4, 121.4, 58.7, 51.7, 50.0, 45.5, 42.6, 41.7, 39.6, 33.1, 28.9, 28.5; IR (neat): 3054, 2948, 1736, 1571, 1508, 1463, 1433, 1364, 1295, 1248, 1165, 1083, 1044, 1019, 984, 935, 896, 850, 802, 753, 732, 706, 679 cm⁻¹; HRMS (EI) Calcd for C₁₉H₂₀O₂S [M⁺] 312.1184, found 312.1177.

(1.4.27): Using the general procedure above with 1.4.26 (74 mg, 0.20 mmol) as the boronate ester and norbornene 1.2.11 (23 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 5% Et₂O in hexane (R_f = 0.38) gave compound 1.4.27 (10.8 mg, 17%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.44-7.36 (m, 2H), 7.21-7.16 (m, 2H), 3.17-3.10 (m, 1H), 2.98 (d, J = 6.7 Hz, 1H), 2.70 (dd, J = 15.1, 5.3 Hz, 1H), 2.47-2.42 (m, 1H), 2.41 (dd, J = 14.9, 9.0 Hz, 1H), 2.35 (d, J = 4.3 Hz, 1H), 2.24 (d, J = 4.3 Hz, 1H), 1.69-1.57 (m, 2H), 1.45 (s, 9H), 1.38-1.21 (m, 3H), 1.12-1.07 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.2, 163.6, 160.6, 125.8, 122.9, 122.8, 122.5, 119.0, 111.9, 80.6, 58.5, 45.4, 42.4, 41.2, 40.8, 39.4, 33.0, 29.1, 28.6, 28.1; IR (neat): 2950, 2870, 1728, 1630, 1477, 1446, 1391, 1367, 1257, 1154, 1010, 943, 846, 744 cm⁻¹; HRMS
(1.4.29): Using the general procedure above with 1.4.28 (77 mg, 0.20 mmol) as the boronate ester and norbornene 1.2.11 (23 mg, 0.24 mmol) as the alkene, followed by chromatography on silica gel using 10% Et₂O in hexane (R_f = 0.41) gave compound 1.4.29 (32.3 mg, 45%) as a yellow solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 93-96 °C. ^1H NMR (400 MHz, CDCl₃): δ 7.46 (d, J = 7.6 Hz, 1H), 7.23-7.20 (m, 1H), 7.13 (td, J = 7.6, 1.1 Hz, 1H), 7.08-7.04 (m, 1H), 3.65 (s, 3H), 3.22-3.17 (m, 1H), 3.12 (d, J = 6.8 Hz, 1H), 2.73 (dd, J = 14.6, 3.6 Hz, 1H), 2.46 (d, J = 7.0 Hz, 1H), 2.40 (dd, J = 14.6, 10.1 Hz, 1H), 2.35 (d, J = 3.9 Hz, 1H), 2.19 (d, J = 4.1 Hz, 1H), 1.64-1.50 (m, 3H), 1.41 (s, 9H), 1.27-1.15 (m, 2H), 0.98 (dt, J = 10.0, 1.5 Hz, 1H); ^13C NMR (100 MHz, CDCl₃): δ 171.4, 146.7, 142.1, 123.5, 120.4, 120.3, 118.9, 118.6, 109.2, 80.6, 59.5, 47.3, 42.8, 42.0, 41.6, 40.0, 33.0, 30.6, 28.83, 28.79, 28.0; IR (neat): 2943, 2866, 1726, 1611, 1572, 1463, 1417, 1384, 1365, 1338, 1288, 1250, 1239, 1207, 1139, 1033, 1010, 973, 940, 925, 914, 878, 849, 822, 798, 763, 727 cm⁻¹; HRMS (EI) Calcd for C₂₃H₂₉NO₂ [M⁺] 351.2198, found 351.2197.

[2-(N-Boc-Amino)phenyl]boronic acid (1.4.34): To a solution of N-Boc-aniline (1.93 g,
10.0 mmol) in 40 mL of THF at -78 °C was added a solution of 1.7M \( t \)-butyllithium (14.1 mL, 24.0 mmol) dropwise. The reaction was stirred at -78 °C for 15 min before warmed to -20 °C and stirred for another 2 h. Triisopropylborate (8.7 mL, 38 mmol) was then added dropwise and the mixture was allowed to warm to 25 °C. The reaction was cooled to 0 °C before being quenched with water and acidified with aqueous HCl solution. The aqueous layer was extracted with CH₂Cl₂ (× 3) and the combined organic layers were dried with Na₂SO₄, filtered, and concentrated in vacuo. The crude mixture was purified by acid-base extraction and gave [2-(N-Boc-amino)phenyl]boronic acid 1.4.34 (0.74 g, 31%). Spectral data match the previously reported data.¹³⁰

Acetic formic anhydride (1.4.37): The title compound was prepared according to the previously reported procedure.¹³¹ Using the reaction condition described in the literature with sodium formate (20.0 g, 294 mmol) and acetyl chloride (17.8 mL, 250 mmol) as starting materials, gave the title compound 1.4.37 (11.89 g, 54%). Spectral data match the previously reported data.

\[\text{Acetic formic anhydride (1.4.37): }\]

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\[\text{1.4.37}\]

tert-Butyl formyl[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.4.38): [2-(N-Boc-amino)phenyl]boronic acid 1.4.34 (500 mg, 2.11 mmol) and pinacol (274 mg, 2.32 mmol) were dissolved in benzene (20 mL). The mixture was heated to
reflux and the water was removed by a Dean-Stark trap for 3 h. The reaction mixture was cooled to 25 °C and the solvent was removed in vacuo to afford the crude aniline boronate ester 1.4.35. To a solution of crude 1.4.35 in 25 mL of THF at 0 °C was added NaH (271 mg, 6.75 mmol) in one portion and the resulting mixture was warmed to 25 °C and stirred for 2 h. The reaction was then cooled to 0 °C before the acetic formic anhydride 1.4.37 (688 mg, 7.81 mmol) was added dropwise. The mixture was then warmed to 25 °C and stirred for 16 h. The reaction was quenched with saturated aqueous NaHCO₃ solution and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 30% Et₂O in hexane (Rₐ = 0.43) gave the title compound 1.4.38 (520 mg, 71%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.37 (s, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.51 (td, J = 7.4, 1.6 Hz, 1H), 7.38 (td, J = 7.4, 1.2 Hz, 1H), 7.09 (d, J = 7.0 Hz, 1H), 1.46 (s, 9H), 1.28 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 163.9, 152.5, 140.2, 136.5, 132.0, 128.6, 128.0, 83.7, 83.4, 28.0, 24.8; HRMS (EI) Calcd for C₁₅H₂₀BNO₄ [M-C₃H₆O⁺] 289.1485, found 289.1475.

![1.4.32](image)

**tert-Butyl (2E)-3-[(tert-butoxycarbonyl)2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino]acrylate (1.4.32):** To a solution of 1.4.38 (419 mg, 1.21 mmol) in 15 mL of benzene at 25 °C was added (tert-butoxycarbonylmethylene) triphenylphosphorane (545 mg, 1.45 mmol), and the reaction mixture was heated to 90 °C for 16 h. The mixture was then cooled to 25 °C and filtered through a pad of silica gel and the pad was washed
with Et₂O. The organic layer was dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 30% Et₂O in hexane (Rf = 0.53) gave title compound 1.4.32 (521 mg, 97%) as a yellow amorphous foam. ¹H NMR (400 MHz, CDCl₃): δ 8.34 (d, J = 13.9 Hz, 1H), 7.87 (d, J = 7.0 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.10 (bs, 1H), 4.35 (d, J = 13.9 Hz, 1H), 1.42 (bs, 18H), 1.26 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 166.9, 151.8, 144.9, 143.0, 136.6, 132.1, 128.3, 127.6, 100.4, 83.5, 81.8, 78.9, 28.0, 27.8, 25.0, 24.0; IR (neat): 2978, 2931, 1728, 1699, 1622, 1604, 1570, 1492, 1446, 1354, 1327, 1292, 1273, 1249, 1132, 1084, 1051, 983, 869, 860 cm⁻¹; HRMS (EI) Calcd for C₂₄H₃₆BNO₆ [M⁺] 445.2636, found 445.2627.

N-Formyl-4-methyl-N-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzenesulfonamide (1.4.39): The title compound was prepared according to the procedure for the synthesis of 1.4.38. Using the reaction conditions described above with commercially available aniline boronate ester 1.4.36 (0.30 g, 0.80 mmol) and acetic formic anhydride (0.26 g, 3.0 mmol) as starting materials, followed by chromatography on silica gel using 30% Et₂O in hexane (Rf = 0.41) gave title compound 1.4.39 (0.30 g, 94%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 109-112 °C. ¹H NMR (400 MHz, CDCl₃): δ 9.25 (bs, 1H), 7.91-7.86 (m, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.44-7.37 (m, 2H), 7.25 (d, J = 8.6 Hz, 2H), 6.84-6.79 (m, 1H), 2.42 (s, 3H), 1.23 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 161.6, 145.0, 136.8, 135.0, 131.7, 129.8, 129.6, 129.1, 128.3, 84.0, 24.7, 21.6; IR (neat): 2979, 1714, 1602, 1489, 1443, 1353, 1170, 1065,
998, 859, 670 cm⁻¹; HRMS (ESI) Calcd for C₂₀H₂₄BNO₅S [M+H⁺] 402.1541, found 402.1551.

1.4.33

**tert-Butyl (2E)-3-{{(4-methylphenyl)sulfonyl}[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}acrylate (1.4.33):** The title compound was prepared according to the procedure for the synthesis of 1.4.32. Using the reaction conditions described above with aniline boronate ester 1.4.39 (0.26 g, 0.65 mmol) and (tert-butoxycarbonylmethylene) triphenylphosphorane (0.29 mg, 0.78 mmol) as starting materials, followed by chromatography on silica gel using 30% Et₂O in hexane gave title compound 1.4.33 (0.28 g, 87%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 115-118 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.26 (d, J = 13.7 Hz, 1H), 7.55-7.51 (m, 2H), 7.43-7.35 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.74-6.70 (m, 1H), 4.46 (d, J = 13.7 Hz, 1H), 2.41 (s, 3H), 1.42 (s, 9H), 1.27 (s, 6H), 1.22 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 167.0, 144.4, 144.1, 137.1, 131.8, 129.5, 129.4, 128.9, 128.0, 100.7, 83.9, 79.6, 28.3, 24.9, 24.7, 24.5, 21.6; IR (neat): 2978, 2931, 1702, 1622, 1600, 1491, 1442, 1355, 1322, 1250, 1171, 1130, 1112, 1090, 1068, 930, 858, 710, 671, 659 cm⁻¹; HRMS (ESI) Calcd for C₂₆H₃₄BNO₆S [M+H⁺] 500.2272, found 500.2251.

1.4.41
**7-Bromoindole (1.4.41):** To a solution of 1-bromo-2-nitrobenzene (4.00 g, 19.80 mmol) in 120 mL of THF at -45 °C was added dropwise a 1M solution of vinylmagnesium bromide in THF (65.0 mL, 65.0 mmol) and the mixture was stirred at same temperature for 45 min. The reaction was quenched with saturated aqueous ammonium chloride solution and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% EtOAc in hexane gave the title compound 1.4.41 (1.73 g, 45%). Spectral data match the previously reported data.¹⁴⁰

![1.4.42]

**7-Bromo-1H-indole-1-carbaldehyde (1.4.42):** The title compound was prepared according to the procedure for the synthesis of 1.4.38. Using the reaction condition described above with 7-bromoindole 1.4.41 (1.50 g, 7.65 mmol) and acetic formic anhydride (1.35 g, 15.3 mmol) as starting materials, followed by chromatography on silica gel using 5% Et₂O in hexane gave title compound 1.4.42 (1.35 g, 79%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 75-77 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.52 (bs, 1H), 7.95(s, 1H), 7.60-7.51 (m, 2H), 7.14 (t, J = 7.7 Hz, 1H), 6.69 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 157.9, 134.5, 132.5, 129.8, 124.4, 123.9, 120.9, 109.9, 104.5; IR (neat): 3151, 3113, 1706, 1416, 1403, 1306, 1250, 1208, 1189, 1131, 916, 788, 770, 722 cm⁻¹; HRMS (EI) Calcd for C₉H₆BrNO [M⁺] 222.9633, found 222.9639.

7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carbaldehyde (1.4.43): Indole 1.4.42 (500 mg, 2.23 mmol), Pd(OAc)$_2$ (10.6 mg, 0.050 mmol), 2-(dicyclohexyl-phosphino)biphenyl (62.5 mg, 0.180 mmol), and Et$_3$N (0.44 mL, 3.2 mmol) was dissolved in 5 mL of dioxane at 25 °C. The solution was heated to 80 °C before pinacolborane (0.86 mL, 6.0 mmol) was added dropwise and stirred at 80 °C for 1 h. The reaction was quenched by dilution with water and CH$_2$Cl$_2$ then filtered through a pad of Celite to remove the black precipitate. The aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic layers were dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% EtOAc in hexane ($R_f = 0.50$) gave 1.4.43 (452 mg, 75%) as a white solid (the solid resulting from the evaporation of EtOAc and hexane), m.p. = 83-86 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.18 (bs, 1H), 7.82 (bs, 2H), 7.70 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.32-7.25 (m, 1H), 6.71 (dd, $J = 3.8, 0.9$ Hz, 1H), 1.41 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 161.0, 133.2, 131.1, 124.8, 123.2, 123.0, 110.2, 84.5, 24.9; IR (neat): 3110, 3053, 2978, 2941, 1694, 1589, 1548, 1456, 1407, 1303, 1246, 1212, 1194, 1129, 974, 861, 851, 812, 733, 680 cm$^{-1}$; HRMS (EI) Calcd for C$_{15}$H$_{18}$BO$_3$ [M$^+$] 271.1380, found 271.1381.

**tert-Butyl** (2E)-3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl]
acrylate (1.4.40): The title compound was prepared according to the procedure for the synthesis of 1.4.32. Using the reaction conditions described above with 1.4.43 (0.44 g, 1.6 mmol) and (tert-butoxycarbonylmethylene)triphenylphosphorane (730 mg, 1.93 mmol) as starting materials, followed by chromatography on silica gel using 10% Et₂O in hexane (R_f = 0.50) gave title compound 1.4.40 (0.56 g, 93%) as a white solid (the solid resulting from the evaporation of Et₂O and hexane), m.p. = 94-97 °C. ¹H NMR (400 MHz, CDCl₃)-major conformer: δ 9.12 (d, J = 13.7 Hz, 1H), 7.78 (dd, J = 7.2, 1.4 Hz, 1H), 7.68 (dd, J = 7.8, 1.2 Hz, 1H), 7.40 (d, J = 3.5 Hz, 1H), 7.24-7.17 (m, 1H), 6.68 (d, J = 3.5 Hz, 1H), 5.58 (d, J = 13.7 Hz, 1H), 1.53 (s, 9H), 1.44 (s, 12H); minor conformer: δ 8.20 (d, J = 14.1 Hz, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 3.5 Hz, 1H), 7.34-7.29 (m, 1H), 6.71 (d, J = 3.5 Hz, 1H), 5.90 (d, J = 14.1 Hz, 1H), 1.55 (s, 9H), 1.44 (s, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 166.8, 166.6, 140.4, 139.6, 136.4, 132.6, 129.9, 129.8, 124.5, 124.3, 123.8, 123.6, 122.3, 121.4, 121.3, 110.0, 108.4, 108.1, 103.4, 102.6, 84.5, 80.5, 79.7, 34.3, 30.0, 28.3, 24.7; IR (neat): 2976, 1708, 1630, 1535, 1459, 1426, 1364, 1320, 1292, 1243, 1147, 974, 844, 798, 722 cm⁻¹; HRMS (EI) Calcd for C₂₁H₂₈BNO₄ [M⁺] 369.2111, found 369.2116.

![Image](image-url)

Ethyl 4-(2-tert-butoxy-2-oxoethyl)-6-methyl-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxylate (1.4.44): A solution of 0.3 mL of water and 3 mL of dioxane in a 5 mL 2-neck round bottom flask was purged with argon and stirred for 10 min at 25 °C. [Rh(cod)Cl]₂ (3.0 mg, 0.006 mmol), tri-tert-butylphosphonium tetrafluoroborate (3.5 mg,
0.012 mmol) and potassium fluoride (23.2 mg, 0.40 mmol) were added to the solution and stirred at 25 °C for 10 min. To the bright yellow solution was added the ethyl 2-butynoate (27 mg, 0.24 mmol), followed by addition of the indole boronate ester 1.4.40 (74 mg, 0.20 mmol) and the reaction mixture was stirred at 80 °C for 3 h. The reaction was quenched with brine, and the aqueous layer was extracted with Et₂O (x 3). The combined organic layers were dried with MgSO₄, filtrated and concentrated in vacuo. Chromatography on silica gel using 20% Et₂O in hexane (Rᵣ = 0.39) gave 1.4.44 (33.8 mg, 50%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 7.0 Hz, 1H), 7.23 (d, J = 3.1 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.49 (d, J = 3.1 Hz, 1H), 6.02 (dd, J = 7.8, 2.0 Hz, 1H), 4.39-4.25 (m, 2H), 2.63 (dd, J = 15.7, 3.1 Hz, 1H), 2.55 (s, 3H), 2.53 (dd, J = 15.7, 7.8 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.32 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 169.8, 166.6, 141.9, 132.8, 126.3, 125.6, 123.1, 122.0, 120.2, 119.8, 117.8, 102.8, 81.0, 60.7, 53.2, 44.9, 27.8, 15.1, 14.3; IR (neat): 3060, 2979, 2932, 1720, 1630, 1571, 1492, 1458, 1366, 1276, 1222, 1153, 1099, 1062, 1037, 975, 951, 847, 795, 727 cm⁻¹; HRMS (El) Calcd for C₂₁H₂₅NO₄ [M⁺] 355.1784, found 355.1779.
2.0 Palladium-Catalyzed Isomerization of Strained Small Ring Systems under Oxidative Conditions\textsuperscript{141}

2.1 Introduction

2.1.1 Acetoxylation of C–H Bonds under Palladium Catalysis with Hypervalent Iodine

Many organic transformations typically require a pre-existing functional group in the substrates, such as a heteroatom, halide, or unsaturation, in order to introduce a new functional group (Scheme 2.1.1, pathway a). An attractive alternative to this pathway is to utilize the ubiquitous C–H bond as a functionality to perform the same types of transformations (Scheme 2.1.1, pathway b). Hence, the development of efficient methods to directly functionalize C–H bonds is highly desirable and has attracted a significant amount of attention.\textsuperscript{142}

Scheme 2.1.1 Synthetic pathway for introduction of functional groups

\begin{equation}
\text{R} \xrightarrow{\text{FG}_1} \text{FG}_1 \quad \text{pathway a} \quad \text{R} \xrightarrow{\text{FG}_2} \text{FG}_2 \quad \text{pathway b} \quad \text{R} \xrightarrow{\text{H}}
\end{equation}

Due to the unreactive and robust nature of the C–H bond,\textsuperscript{142b,143} direct functionalization is very difficult and in addition, issues such as chemo- and regioselectivity make this type of process an even more formidable challenge. Therefore, systems using transition-metal catalysis have been developed to facilitate such a process, via the conversion of C–H

\textsuperscript{141} These studies were carried out in collaboration with Dr. Mark E. Scott. Portions of this work have appeared in print, see: Tseng, N.-W.; Scott, M.; Lautens, M. Org. Synth. 2008, 85, 172.


bonds to more active carbon-metal bonds, which may undergo subsequent functionalization reactions (Scheme 2.1.2). Based on this strategy, there are numerous synthetic methodologies focusing on formation of carbon-carbon or carbon-heteroatom bonds have been reported.\textsuperscript{144,145}

Scheme 2.1.2 Functionalization of C-H bonds under transition-metal catalysis

\[
\begin{align*}
R\text{H} & \xrightarrow{[M]} R\text{[M]} \xrightarrow{\text{functionalization}} R\text{FG} \\
M &= \text{Pd, Ru, Rh, Ir}
\end{align*}
\]

Among these studies, the direct conversion of carbon-hydrogen bonds to carbon-oxygen bonds represents a powerful synthetic application in organic chemistry, because alcohol-containing molecules can be easily found either as products in commodity chemicals or as intermediates in the pharmaceutical industry. In 1996, Crabtree disclosed a process to directly transform an aromatic C-H bond to a C-OAc bond under palladium catalysis with PhI(OAc)\textsubscript{2}\textsuperscript{146} as a stoichiometric oxidant (Scheme 2.1.3).\textsuperscript{147} In this report, the acetoxylated product was obtained as a mixture of regioisomers. The reaction mechanism was believed to involve the oxidation of a PhPd(II)OAc species with PhI(OAc)\textsubscript{2} to generate a PhPd(IV)OAc intermediate, which would undergo a subsequent


\textsuperscript{146} For a recent review on using hypervalent iodines in organic synthesis, see: Deprez, N. R.; Sanford, M. S. Inorg. Chem. 2007, 46, 1924.

reductive elimination process to afford the corresponding products. While this report demonstrates the acetoxylation of aromatic C—H bonds could be achieved under mild conditions, there are several drawbacks, such as the use of an excess amount of starting material and lack of regioselectivity, which needs to be addressed to make this process synthetically useful.

Scheme 2.1.3 Palladium-catalyzed acetoxylation of halobenzenes

To address some of these issues, Sanford reported a chelate-directed process to acetoxylate sp² or sp³ C-H bonds (Scheme 2.1.4). Nitrogen-containing, coordinating functional groups such as nitrogen heterocycles, were used to bind with the palladium catalyst. Specific C—H bonds preferentially undergo acetoxylation, affording the corresponding acetate products. Furthermore, the reaction has a high tolerance toward moisture and air, which demonstrates the practical value of this process and offers an alternative method to the well-established ortho-metallation/electrophilic termination protocol.


In addition to benzylic or aromatic C—H bonds, simple alkyl C-H bonds were found to undergo a similar transformation by using O-methyl oxime or pyridine as the directing group (Scheme 2.1.5).\textsuperscript{150} Under similar reaction conditions, the acetoxylated products, generated from C-H activation followed by oxidation, were obtained in moderate to good yield. These β-oxygenated O-methyl oximes could be easily converted into carbonyls\textsuperscript{151} and amines,\textsuperscript{152} which could potentially be used in the synthesis of β-hydroxy ketones and β-amino alcohols. The reactions have been found to be extremely selective, as the acetoxylation only occurred with primary C—H bonds on the β carbon in the acyclic alkanes. Nonetheless, the oxidation of secondary C—H bonds can also be achieved by using structurally rigid cyclic alkanes.

Scheme 2.1.5 Palladium-catalyzed acetoxylation of alkyl C-H bonds

The reaction is believed to follow the generalized mechanistic proposal illustrated in Scheme 2.1.6. The palladium(II) intermediate $B^{153}$ is generated via a chelate-directed C─H activation with palladium catalyst $A$ which is supported by the high levels of regioselectivity and catalyst reactivity observed in the reaction. This palladacycle species $B$ is further oxidized with PhI(OAc)$_2$ to afford the palladium(IV) intermediate $C$, which undergoes a subsequent carbon─oxygen bond forming reaction to give the acetoxylated products. In addition to the implication of such a Pd(IV) complex in the literature, no product was obtained when using the typical oxidant in Pd(0)/Pd(II) system, also supporting the proposed Pd(II)/Pd(IV) reaction pathway. Furthermore, carbon─oxygen bond formation is believed to follow a reductive elimination process, as

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implicated from mechanistic studies of other Pd(IV) model system.\textsuperscript{155,156}

Scheme 2.1.6 Proposed mechanism for palladium-catalyzed acetoxylation of C-H bonds

The oxidative palladium-catalyzed C–H activation/functionalization strategy has been expanded to incorporate a variety of terminating steps. Organopalladium(II) species are common and versatile intermediates, having been utilized in the formation of various carbon–carbon\textsuperscript{157} or carbon–halide bonds processes\textsuperscript{158}. Furthermore, instead of using PhI(OAc)\textsubscript{2} as terminal oxidant, a combination of Oxone and acetic acid or methanol offers an economically attractive alternative to afford the corresponding oxygenated products.\textsuperscript{159} Some selected examples are illustrated in Scheme 2.1.7


\textsuperscript{159} a) Desai, L. V.; Malik, H. A.; Sanford, M. S. \textit{Org. Lett.} \textbf{2006}, \textit{8}, 1141. For reactions using peroxyster
Scheme 2.1.7 Selected examples of alternative terminating reactions

In addition to their utility in direct C–H functionalization, reactions using the combination of Pd(OAc)\textsubscript{2} and PhI(OAc)\textsubscript{2} demonstrated a novel and complementary reactivity to conventional Pd(0)/Pd(II) processes. By utilizing the unique reactivity of Pd(II)/Pd(IV) catalysis, Sanford\textsuperscript{160} and Beller and Tse\textsuperscript{161} independently reported the synthesis of bicyclo[3.1.0]hexane\textsuperscript{162} molecules via a cascade cyclization of simple enyne derivatives\textsuperscript{163} (Scheme 2.1.8). The formation of bicyclo[3.1.0]hexane products is

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proposed to follow the mechanism illustrated in Scheme 2.1.8. The cascade cyclization sequence is initiated by acetoxy palladation of the alkyne moiety to afford vinylpalladium(II) species B. Following intramolecular cyclization via an olefin insertion process, complex C is generated and subsequently oxidized with PhI(OAc)₂. The resulting Pd(IV) intermediate D then undergoes intramolecular S_N2-type attack of the electron-rich olefin to give a cyclopropane-containing intermediate, which is further hydrolyzed to the bicyclo[3.1.0]hexane, and regenerates the palladium catalyst A.

Scheme 2.1.8 Synthesis of bicyclo[3.1.0]hexanes under Pd(II)/Pd(IV) catalysis

Recently, an asymmetric variation of a cascade cyclization sequence using a Pd(II)/Pd(IV)
system has been developed. Furthermore, the reaction scope of the oxidative palladium catalysis with hypervalent iodine has been expanded to aminoxygension and dioxygenation using simple alkenes.

2.1.2 Methylene Cyclopropanes in Transition Metal-Catalyzed Addition Reactions

Methylene cyclopropanes (MCPs), which exhibit a diverse range of reactivity derived from their strained ring structure, have been extensively studied in the development of new synthetic methodologies. In particular, transition metal-catalyzed addition reactions using MCPs have attracted a significant amount of attention due to their unique and novel reactivity. In general, the addition pattern of organotransition metallics (R–MLn) can be divided into two types based on regioselectivity; the addition of R–MLn to C-1 (pathway a) give the anti-Markovnikov intermediate, or addition to C-2 (pathway b) to generate the Markovnikov intermediate (Scheme 2.1.9).

Scheme 2.1.9 Addition patterns of organotransition metallic species to MCPs

The transition metal-catalyzed hydrometallation reactions of MCPs are believed to involve the formation of an anti-Markovnikov intermediate (pathway a, Scheme 2.1.9).

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For example, hydrosilylation of disubstituted-MCPs was achieved by using triethylsilane and a platinum catalyst, giving the corresponding (cyclopropylmethyl)silane products 2.1.1 (Scheme 2.1.10). On the other hand, a dramatic change in reactivity was observed when monosubstituted substrates were used, which affords the isomeric olefin 2.1.2 as sole product under similar reaction conditions.

Scheme 2.1.10 Platinum-catalyzed hydrosilylation of mono- and disubstituted MCPs

The proposed reaction mechanism is summarized in Scheme 2.1.11. The reaction is initiated by the oxidative addition of the platinum catalyst into Si-H bond to generate a platinum hydride species, which undergoes subsequent regioselective hydrometallation to the MCP. Depending on the substitution pattern, the resulting (cyclopropylmethyl)platinum intermediate could reductively eliminate to afford product 2.1.1 (pathway a). Alternatively, this complex could undergo β-carbon elimination, presumably driven by the release of ring strain, to generate a homoallylplatinum species. Reductive elimination forms the C-Si bond to give homoallylsilane 2.1.2 as the ring-opened product (pathway b).

---

Similar types of ring-opened products, generated from a similar pathway as the formation of 2.1.2, were also observed in reactions of MCPs with various metal reagents such as Sn–H,\textsuperscript{172} Si–H,\textsuperscript{169,173} Si–Si,\textsuperscript{174} Si–CN,\textsuperscript{175} B–B,\textsuperscript{176} and Si–B\textsuperscript{177} species. Some selected examples are shown in Scheme 2.1.12.

\textsuperscript{176} Ishiyama, T.; Momota, S.; Miyaura, N. Synlett 1999, 1790.
Scheme 2.1.12 Selected examples of addition reactions of MCPs with metal reagents

In contrast to metal reagents, transition metal-catalyzed hydroamination reactions of MCPs with simple amines generally proceeded through Markovnikov intermediates (pathway b, Scheme 2.1.9). For instance, the hydroamination of MCPs under palladium catalysis afforded the corresponding allylamine 2.1.3 (Scheme 2.1.13).\(^{178}\) Nevertheless, a reverse in regioselectivity was observed when phthalimide was used in the addition reaction, giving the isomeric allylamine 2.1.4 as a sole product.

Scheme 2.1.13 Palladium-catalyzed hydroamination of MCPs

This nucleophile-controlled, palladium-catalyzed hydroamination reaction is believed to follow the proposed mechanism in Scheme 2.1.14. The catalytic cycle is initiated by the

oxidative addition of the palladium catalyst into the N–H bond, affording an aminopalladium(II) hydride species, which undergoes regioselective hydropalladation across the olefin of the MCP to yield a cyclopropylpalladium(II) intermediate (pathway a). Subsequent β-carbon elimination gives a π-allylpalladium(II) species, which undergoes reductive elimination to afford allylamine 2.1.3 and regenerate the palladium(0) catalyst. The formation of isomeric allylamine 2.1.4 with phthalimide is believed to follow a similar reaction pathway, with a reversed regioselectivity of hydropalladation to the MCP. The resulting (cyclopropylmethyl)palladium(II) species undergoes β-carbon elimination, affording a homoallylpalladium(II) intermediate. Migration of palladium(II) complex via reversible β-H elimination/hydropalladation, generates a π-allylpalladium species, which upon reductive elimination affords the isomeric allylamine 2.1.4.

Scheme 2.1.14 Proposed reaction mechanism of palladium-catalyzed hydroamination reaction of MCPs

In addition to hydroaminations, various pronucleophiles have been successfully utilized in similar addition reactions with MCPs to give a variety of ring-opened products, generated from a similar catalytic cycles as illustrated in Scheme 2.1.14. Some selected examples using oxygen and carbon based pronucleophiles are illustrated in Scheme 2.1.15.

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Scheme 2.1.15 Selected examples of addition reactions of MCPs with pronucleophiles

\[
\begin{align*}
\text{Scheme 2.1.15 Selected examples of addition reactions of MCPs with pronucleophiles} \\
\text{n-C}_7\text{H}_{15} & \quad \text{Pd(PPh}_3\text{)}_4 (5 \text{ mol\%}) \\
\text{(o-tol)}_3\text{P} (10 \text{ mol\%}) \\
R-\text{OH} & \quad \text{THF, 100} \text{ °C} \\
\text{R} & \quad \text{R} = \text{Bn; 69\%} \\
& \quad \text{R} = \text{CF}_3\text{CH}_2; 68\% \\
& \quad \text{R} = n-\text{Bu; 63\%}
\end{align*}
\]

Recently, methylenecyclopropanes have been employed as acceptors in a ruthenium-catalyzed C–H bond activation-functionalization sequence (Scheme 2.1.16).\textsuperscript{182} The reaction is believed to follow a similar addition pattern as the hydrosilylation reaction (pathway a, Scheme 2.1.11), giving the corresponding hydroarylated products with conservation of the cyclopropyl ring.

Scheme 2.1.16 Hydroarylation of MCPs via a ruthenium-catalyzed C-H activation/functionalization sequence

\[
\begin{align*}
\text{Scheme 2.1.16 Hydroarylation of MCPs via a ruthenium-catalyzed C-H activation/functionalization sequence} \\
\text{MeO} & \quad \text{Ph} \\
\text{[RuCl}_2\text{(cod)}\text{]}_n & \quad \text{ligand (10 mol\%)} \\
& \quad \text{dioxane, 120 °C} \\
\text{MeO} & \quad \text{78\%}
\end{align*}
\]

2.2 Palladium-Catalyzed Oxidative Isomerization of O-Methyl Oxime Methylenecyclopropanes and Cyclopropanes

2.2.1 Results and Discussions

2.2.1.1 Goal of Study

Due to their ease of preparation and versatile reactivity, utilizing methylenecyclopropanes in the development of synthetic methodologies has been an area of research in our group since the 1990’s. Inspired by the recent advances in palladium-catalyzed C-H activation/acetoxylation reactions, we sought to study the reactions of methylenecyclopropanes under these newly-developed conditions, which could potentially lead to the development of novel organic transformations (Scheme 2.2.1).

Scheme 2.2.1 Testing MCP derivatives under palladium catalysis with oxidants

2.2.1.2 Isomerization of O-Methyl Oxime Methylenecyclopropanes to Pyridines

To examine the proposed idea, methylenecyclopropane derivative 2.2.2 was prepared according to Scheme 2.2.2. Cyclopropane 2.2.3 was synthesized by rhodium-catalyzed cyclopropanation of 2-bromopropene with ethyl diazoacetate. Base-induced elimination of HBr from 2.2.3, gave ethyl 2-methylenecyclopropanecarboxylate 2.2.4. Following

hydrolysis with K$_2$CO$_3$, carboxylic acid 2.2.5$^{183}$ was coupled with $O,N$-dimethylhydroxyamine to afford the MCP Weinreb amide 2.2.6. To install the $O$-methyl oxime directing group, the MCP amide was reacted with methylmagnesium bromide and the resulting ketone was converted to methylenecyclopropane derivative 2.2.2, upon treatment with methoxyamine hydrochloride in pyridine.$^{150}$

Scheme 2.2.2 Synthesis of methylenecyclopropane 2.2.2

Preliminary results using MCP 2.2.2 under oxidative palladium catalysis are summarized in Table 2.2.1. Upon reacting with Pd(OAc)$_2$ and PhI(OAc)$_2$ in EtOAc for 16 hours, MCP 2.2.2 was isomerized to pyridine 2.2.7, whose identity was further confirmed by comparing the spectroscopy data of an independently prepared authentic sample.$^{186}$ The reaction gave comparable yields using either freshly distilled anhydrous or commercial

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$^{186}$ The authentic sample was prepared from acylation of commercially available 5-hydroxy-2-methylpyridine.
solvents and similar results were obtained by varying the reaction temperature (entries 1-4). Nevertheless, no product was observed in control experiment, suggesting that this process only occurs in the presence of palladium catalyst (entry 5).

Table 2.2.1 Screening of MCP 2.2.2 with Pd(OAc)$_2$ and Phl(OAc)$_2$ in EtOAc$^d$

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temperature ($^\circ$C)</th>
<th>Solvent</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>60</td>
<td>EtOAc$^c$</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>60</td>
<td>EtOAc$^d$</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>80</td>
<td>EtOAc$^c$</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>80</td>
<td>EtOAc$^d$</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>---</td>
<td>60</td>
<td>EtOAc$^d$</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ All reactions were run under the following conditions: 2.2.2 (0.28 mmol, 1.0 equiv.), Pd(OAc)$_2$ (0.014 mmol, 5 mol%), Phl(OAc)$_2$ (0.56 mmol, 2.0 equiv.), in 1.3 mL of EtOAc. $^b$ Determined by HPLC. $^c$ Anhydrous. $^d$ Taken from commercial bottle.

We then examined the effects of various polar and nonpolar organic solvents (Table 2.2.2). Reactions using polar aprotic solvents such as DMF, DMSO, NMP (entries 15-17) gave the product in low yield. Switching to protic solvents such as AcOH, MeOH, $i$-PrOH (entries 9, 12, 13) only led to a significant decrease in yield. The highest yield was obtained using nonpolar solvents (entries 3, 4, 14, 18).
Table 2.2.2 Screening of solvent effects$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield (%)$^b$</th>
<th>entry</th>
<th>solvent</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>8</td>
<td>11</td>
<td>CH$_3$NO$_3$</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>5</td>
<td>12</td>
<td>MeOH</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>16</td>
<td>13</td>
<td>$i$-PrOH</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>benzene</td>
<td>16</td>
<td>14</td>
<td>decane</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>DME</td>
<td>15</td>
<td>15</td>
<td>NMP</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>CHCl$_3$</td>
<td>2</td>
<td>16</td>
<td>DMSO</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>CH$_3$CN</td>
<td>4</td>
<td>17</td>
<td>DMF</td>
<td>5</td>
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<td>DCE</td>
<td>6</td>
<td>18</td>
<td>xylene</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>AcOH</td>
<td>4</td>
<td>19</td>
<td>toluene/H$_2$O</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>EtOAc</td>
<td>14</td>
<td>20</td>
<td>toluene/AcOH</td>
<td>13</td>
</tr>
</tbody>
</table>

$^a$ All reactions were run under the following conditions: 2.2.2 (0.28 mmol, 1.0 equiv.), Pd(OAc)$_2$ (0.014 mmol, 5 mol%), PhI(OAc)$_2$ (0.56 mmol, 2.0 equiv.), in 1.3 mL of solvent. $^b$ Determined by HPLC.

From the results obtained from the solvent screening, reaction using toluene gave cleaner crude reaction mixture. Therefore, it was chosen as the optimal solvent for further studies on the other reaction parameters. To probe the effects of the catalyst, a variety of palladium complexes were screened and the results are summarized in Table 2.2.3. Using either recrystallized palladium(II) acetate (entry 1) or IMesPd(OAc)$_2$ (entry 2), which has
been used in direct arylation of indoles by Sanford,\textsuperscript{157b} did not improve the reaction yield. Switching to a palladium catalyst with a bidentate nitrogen ligand\textsuperscript{187} only led to a decrease in yield (entry 3). Similarly, other Pd(II) catalysts such as Pd(CO\textsubscript{2}CF\textsubscript{3})\textsubscript{2}, Pd(acac)\textsubscript{2}, Pd(PPh\textsubscript{3})\textsubscript{2}(OAc)\textsubscript{2}, Pd(OH)\textsubscript{2}, and PdCl\textsubscript{2} did not increase the product yield (entries 4-8).

\begin{table}
\centering
\caption{Screening on varying palladium catalyst\textsuperscript{a}}
\begin{tabular}{lll}
\hline
entry & catalyst & yield (\%)\textsuperscript{b} \\
\hline
1 & Pd(OAc)\textsubscript{2}\textsuperscript{c} & 15 \\
2 & IMesPd(OAc)\textsubscript{2}\textsuperscript{157b} & 11 \\
3 & Pd(TMEDA)Cl\textsubscript{2} & 1 \\
4 & Pd(CO\textsubscript{2}CF\textsubscript{3})\textsubscript{2} & 7 \\
5 & Pd(acac)\textsubscript{2} & 14 \\
6 & Pd(PPh\textsubscript{3})\textsubscript{2}(OAc)\textsubscript{2} & 10 \\
7 & Pd(OH)\textsubscript{2} & 0 \\
8 & PdCl\textsubscript{2} & 7 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} All reactions were run under the following conditions: \textbf{2.2.2} (0.28 mmol, 1.0 equiv.), Pd(OAc)\textsubscript{2} (0.014 mmol, 5 mol\%), Phl(OAc)\textsubscript{2} (0.56 mmol, 2.0 equiv.), in 1.3 mL of toluene. \textsuperscript{b} Determined by HPLC. \textsuperscript{c} Recrystallized from CHCl\textsubscript{3}.

\textsuperscript{187} Bidentate nitrogen ligands have been used to stabilize higher oxidation state palladium catalyst in the preparation of Pd(IV) complexes. For example, see ref. 155 and reference therein.
To probe the influence of oxidizing agents, a selection of oxidants were examined (Table 2.2.4). Oxidants such as K$_2$S$_2$O$_8$, Oxone, and CH$_3$CO$_3$H were found to be incompatible with this process, giving no pyridine products (entries 1-3). Using copper as a co-oxidant, which has been used in Pd(II) oxidation processes, gave unsatisfactory results (entries 4-8).

Table 2.2.4 Screening of oxidants and co-oxidant additives$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>oxidant</th>
<th>co-oxidant additive$^b$</th>
<th>yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^d$</td>
<td>K$_2$S$_2$O$_8$</td>
<td>---</td>
<td>0</td>
</tr>
<tr>
<td>2$^d$</td>
<td>Oxone</td>
<td>---</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$CO$_3$H</td>
<td>---</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>PhI(OAc)$_2$</td>
<td>CuCl</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>PhI(OAc)$_2$</td>
<td>CuCl$_2$</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>PhI(OAc)$_2$</td>
<td>CuBr</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>PhI(OAc)$_2$</td>
<td>CuI</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>PhI(OAc)$_2$</td>
<td>Cu(OAc)$_2$</td>
<td>11</td>
</tr>
</tbody>
</table>

$^a$ All reactions were run under the following conditions: 2.2.2 (0.20 mmol, 1.0 equiv.), oxidant (0.40 mmol, 2 equiv), Pd(OAc)$_2$ (0.01 mmol, 5 mol%), in 1.0 mL of toluene. $^b$ With 1 equiv of additive. $^c$ Determined by HPLC. $^d$ With 2 equiv of AcOH.

$^{188}$ For recent review, see: Beccalli, E. M.; Brogini, G.; Martinelli, M.; Sottocornola, S. Chem. Rev. 2007, 107, 5318.
We also examined the effects of the heating method, and the influence of catalyst loading on the reaction. Furthermore, to ensure the reaction proceeded in an acid free environment, a selection of basic additives were tested (Table 2.2.5). Higher catalyst loading only led to dramatic decrease in yield (entry 1). Switching the heating method to the microwave afforded the pyridine products in comparable yield (entries 3 and 4) with significantly reduced reaction time. Microwave irradiation was used for further screening of additives. However, using basic additives in reaction only led to unsatisfactory yields.

Table 2.2.5 Screening of basic additives, heating method, and catalyst loadings

<table>
<thead>
<tr>
<th>entry</th>
<th>temperature (°C)</th>
<th>additive&lt;sup&gt;c&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>60</td>
<td>---</td>
<td>14</td>
</tr>
<tr>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60</td>
<td>---</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>150 (μwave)</td>
<td>---</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>170 (μwave)</td>
<td>---</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>150 (μwave)</td>
<td>NaOAc</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>150 (μwave)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>150 (μwave)</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>150 (μwave)</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>150 (μwave)</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>14</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were run under the following conditions: 2.2.2 (0.20 mmol, 1.0 equiv.), Phl(OAc)<sub>2</sub> (0.40 mmol, 2 equiv), Pd(OAc)<sub>2</sub> (0.01 mmol, 5 mol%), in 1.0 mL of toluene. <sup>b</sup>
Determined by HPLC. c With 1 equiv of additive. d With Pd(OAc)$_2$ (0.004 mmol, 2 mol%). e With Pd(OAc)$_2$ (0.10 mmol, 50 mol%).

### 2.2.1.3 Mechanistic Proposal for Palladium-Catalyzed Isomerization of O-Methyl Oxime Methylene cyclopropanes

Based on our understanding of MCP reactivity and the reactivity of palladium catalysis with hypervalent iodine reagents, the proposed reaction mechanism is illustrated in Scheme 2.2.3. In the presence of palladium catalyst I, the O-methyl oxime undergoes C–H activation to afford cyclopropylpalladium(II) species II.$^{148,150}$ Subsequent β-carbon elimination generates the vinylpalladium(II) intermediate III, which is oxidized with PhI(OAc)$_2$ and upon reductive elimination gives vinylacetate IV. The resulting vinylacetate is believed to isomerize under the reaction conditions, and the cis-isomer could undergo 6π-electrocyclization.$^{189}$ Finally, upon the elimination of MeOH, the cyclic intermediate V is converted to pyridine 2.2.7.

---

$^{189}$ For recent example, see: Andersson, H.; Almqvist, F.; Olsson, R. Org. Lett. 2007, 9, 1335.
Alternatively, the reaction could also proceed through another mechanism which does not involve a C–H activation process (Scheme 2.2.4). As proposed by Sanford and Tse, palladium catalyst I could undergo acetoxypalladation of the olefin group in the MCP to give a (cyclopropylmethyl)palladium(II) species II. Subsequent β-carbon elimination generates the alkylpalladium(II) complex III, which undergoes oxidation with PhI(OAc) and reductive elimination to afford acetate IV. Elimination of AcOH from acetate IV generates the vinylacetate V, which undergoes the further transformation to give pyridine 2.2.7. Another possible reaction pathway involves the β-H elimination of alkylpalladium(II) species III to generate intermediate V, which will be further converted...
to pyridine 2.2.7.

Scheme 2.2.4 Alternative mechanism involving acetoxy palladation

2.2.1.4 Isomerization of O-Methyl Oxime Cyclopropanes to Allylic Acetates

In addition to reactions using MCPs, we also sought to test the oxidative palladium catalysis on the similar cyclopropanes. Preliminary results obtained by doctoral student Mark Scott, demonstrated the isomerization of O-methyl oxime cyclopropanes 2.2.8 to allylic acetate (2.2.9 and 2.2.10) under similar reaction conditions (Scheme 2.2.5). However, the low molecular weights of both starting material and products make isolation and characterization a challenge. Therefore, to further explore this type of isomerization, oxime cyclopropane 2.2.11, which contains a heavy alkyl side chain, was prepared according to Scheme 2.2.6. Reaction of cyclopropynitrile with
decylmagnesium bromide gave ketone \textit{2.2.12},\textsuperscript{190} which was converted to oxime \textit{2.2.11} with methoxyamine hydrochloride in pyridine.\textsuperscript{150}

Scheme 2.2.5 Preliminary screening using \textit{O}-methyl oxime cyclopropanes

![Scheme 2.2.5](image)

Scheme 2.2.6 Synthesis of cyclopropane \textit{2.1.11}

![Scheme 2.2.6](image)

We then examined solvent effects on the isomerization reaction (Table 2.2.6). The results showed that the reaction is highly solvent dependent in terms of yield and \textit{cis}/\textit{trans} selectivity. Most protic solvents gave allylic acetates \textit{2.2.13} and \textit{2.2.14} in trace amounts (entries 7-9, 16), whereas CH\textsubscript{2}Cl\textsubscript{2} gave the highest combined yield 50 % (entry 1). Reactions using CH\textsubscript{3}CN afforded only the \textit{trans} product (entry 12), while CCl\textsubscript{4} showed a reverse \textit{cis}/\textit{trans} selectivity (entry 3). Because of the high \textit{trans} selectivity with good yield, CH\textsubscript{3}CN was chosen as optimal solvent for screening other reaction parameters.

Table 2.2.6 Screening of solvents of palladium-catalyzed isomerization using cyclopropane $^{2.2.11}$

![Cyclopropane Reaction Diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield (%) $^b$</th>
<th></th>
<th>entry</th>
<th>solvent</th>
<th>yield (%) $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$(cis : trans)$</td>
<td></td>
<td></td>
<td></td>
<td>$(cis : trans)$</td>
</tr>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>17 33</td>
<td></td>
<td>10</td>
<td>DMF</td>
<td>trace  trace</td>
</tr>
<tr>
<td>2</td>
<td>CHCl$_3$</td>
<td>trace trace</td>
<td></td>
<td>11</td>
<td>DCE</td>
<td>18 25</td>
</tr>
<tr>
<td>3</td>
<td>CCl$_4$</td>
<td>14 4</td>
<td></td>
<td>12</td>
<td>CH$_3$CN</td>
<td>trace 40</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>decomp.</td>
<td></td>
<td>13</td>
<td>benzonitrile</td>
<td>trace trace</td>
</tr>
<tr>
<td>5</td>
<td>Et$_2$O</td>
<td>N.R. N.R.</td>
<td></td>
<td>14</td>
<td>acetone</td>
<td>decomp.</td>
</tr>
<tr>
<td>6</td>
<td>EtOAc</td>
<td>decomp.</td>
<td></td>
<td>15</td>
<td>CH$_3$NO$_2$</td>
<td>trace trace</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>N.R. N.R.</td>
<td></td>
<td>16</td>
<td>AcOH</td>
<td>trace trace</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>N.R. N.R.</td>
<td></td>
<td>17</td>
<td>toluene</td>
<td>decomp.</td>
</tr>
<tr>
<td>9</td>
<td>$i$-PrOH</td>
<td>N.R. N.R.</td>
<td></td>
<td>18</td>
<td>hexane</td>
<td>9 8</td>
</tr>
</tbody>
</table>

$^a$ All reactions were run under the following conditions: $^{2.2.11}$ (0.20 mmol, 1.0 equiv.), Phl(OAc)$_2$ (0.40 mmol, 2 equiv), Pd(OAc)$_2$ (0.02 mmol, 10 mol%), in 2.5 mL of solvent.

$^b$ Isolated yield.

To probe the influence of the catalyst and catalyst loading, several palladium complexes were examined (Table 2.2.7). Pd(OAc)$_2$ was found to be the optimal catalyst, giving a higher yield than other Pd(II) catalysts (entries 1-3). Control experiments without catalyst gave no allylic acetate products ($^{2.2.13}$ and $^{2.2.14}$), indicating the isomerization is
catalyzed by palladium (entry 4). A decrease or increase in the amount of catalyst loading led to an unsatisfactory yield.

Table 2.2.7 Screening of catalyst and catalyst loading

<table>
<thead>
<tr>
<th>Entry</th>
<th>catalyst</th>
<th>catalyst loading</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>10</td>
<td>trace 26</td>
</tr>
<tr>
<td>2</td>
<td>IMesPd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>10</td>
<td>4 4</td>
</tr>
<tr>
<td>3</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>10</td>
<td>trace 17</td>
</tr>
<tr>
<td>4</td>
<td>---</td>
<td>0</td>
<td>N.R. N.R.</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5</td>
<td>trace 5</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>20</td>
<td>trace 36</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were run under the following conditions: 2.2.11 (0.20 mmol, 1.0 equiv.), PhI(OAc)<sub>2</sub> (0.40 mmol, 2 equiv), Pd catalyst (0-0.04 mmol, 0-20 mol%), in 2.5 mL of CH<sub>3</sub>CN. <sup>b</sup> Isolated yield.

A small selection of bidentate nitrogen ligands were screened in the palladium-catalyzed isomerization reactions. In addition, to explore the effects on reaction temperature and heating method, several different heating profiles were tested (Table 2.2.8). However, reactions using bidentate nitrogen ligands only afforded the acetate product in low yield (entries 1-3) Similarly, varying reaction temperature and heating method led to
unsatisfactory results.

Table 2.2.8 Screening on bidentate nitrogen ligand and heating method

<table>
<thead>
<tr>
<th>Entry</th>
<th>ligand</th>
<th>temperature (°C)</th>
<th>yield (%)(^b)</th>
<th>(cis:trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.2.15</td>
<td>80</td>
<td>11(^c)</td>
<td>18(^c)</td>
</tr>
<tr>
<td>2</td>
<td>2.2.16</td>
<td>80</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>2.2.17</td>
<td>80</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>---</td>
<td>70</td>
<td>trace</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>---</td>
<td>90</td>
<td>trace</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>---</td>
<td>160 (μwave)</td>
<td>trace</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>---</td>
<td>180 (μwave)</td>
<td>trace</td>
<td>9</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were run under the following conditions: 2.2.11 (0.20 mmol, 1.0 equiv.), Phl(OAc)\(_2\) (0.40 mmol, 2 equiv), Pd(OAc)\(_2\) (0.02 mmol, 10 mol%), in 2.5 mL of CH\(_3\)CN.

\(^b\) Isolated yield. \(^c\) NMR yield using NMP as internal standard.

Finally, we sought to investigate the effects of oxidants and co-oxidant additives (Table 2.2.9). Examination of various combinations of Phl(OAc)\(_2\), Cu(OAc)\(_2\), and oxygen led to
low yield of the products (entries 1-7).

Table 2.2.9 Screening of oxidants and co-oxidant additives

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>(cis : trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI(OAc)&lt;sub&gt;2&lt;/sub&gt; (1 equiv)</td>
<td>trace</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>PhI(OAc)&lt;sub&gt;2&lt;/sub&gt; (3 equiv)</td>
<td>trace</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt; (2 equiv)</td>
<td>trace&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>PhI(OAc)&lt;sub&gt;2&lt;/sub&gt; (1 equiv) + Cu(OAc)&lt;sub&gt;2&lt;/sub&gt; (1 equiv)</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>PhI(OAc)&lt;sub&gt;2&lt;/sub&gt; (2 equiv) + O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>trace&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt; (2 equiv) + O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>trace&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were run under the following conditions: 2.2.11 (0.20 mmol, 1.0 equiv.), oxidant (0.20-0.60 mmol, 1-3 equiv), Pd(OAc)<sub>2</sub> (0.02 mmol, 10 mol%), in 2.5 mL of CH<sub>3</sub>CN. <sup>b</sup> Isolated yield. <sup>c</sup> NMR yield using NMP as internal standard.

To understand the correlation between the catalyst and yield of the allylic acetate 2.2.13, control experiments with an additional amount of Pd(OAc)<sub>2</sub> added over time were carried out. However, a decrease in yield was observed when fresh palladium catalyst (10-30 mol%) was added to the reaction mixture every 16 h (Scheme 2.2.7). In addition, when allylic acetate 2.2.13 was re-subjected to the reaction condition, only 54% of the starting
material was recovered (Scheme 2.2.8). These results suggest that the allylic acetate 2.2.13 may not be stable under the reaction conditions, which might account for the moderate yield of the reaction process.

Scheme 2.2.7 Reactions with increasing amount of palladium catalyst over time

![Scheme 2.2.7](image)

Scheme 2.2.8 Re-subjecting allylic acetate 2.2.13 to reaction conditions

![Scheme 2.2.8](image)

To avoid the formation of chemically labile allylic acetate functional groups, we sought to incorporate either nucleophilic or electrophilic functional groups in the O-methyl oxime cyclopropane starting material. These functional groups could be used to intercept the organopalladium intermediates in the catalytic cycles, which would presumably afford the cyclic products and avoid the formation of sensitive allylic acetates. However, when cyclopropane 2.2.18 or 2.2.19 was tested under the optimal reaction conditions, only allylic acetate 2.2.20 was obtained but in low yield (Scheme 2.2.10).
Scheme 2.2.10 Reactions of cyclopropanes with electrophilic or nucleophilic functional groups

![Reaction scheme](image)

2.2.15 Mechanistic Proposal for Palladium-Catalyzed Isomerization of O-Methyl Oxime Cyclopropanes

The proposed reaction mechanism of palladium-catalyzed isomerization of O-methyl oxime cyclopropanes 2.2.11 to allylic acetate 2.2.13 and 2.2.14 is illustrated in Scheme 2.2.11. Under the reaction conditions, cyclopropane 2.2.11 undergoes C–H activation in the presence of palladium catalyst I to generate cyclopropylpalladium(II) species II. Subsequent β-carbon elimination gives allylicpalladium(II) intermediate III, which is oxidized with PhI(OAc)₂. Reductive elimination follows to afford the allylic acetates 2.2.13 and 2.2.14.
Scheme 2.2.11 Proposed mechanism of palladium catalyzed isomerization involving Pd(II)/Pd(IV) system

2.2.2 Conclusions and Future Work

The development of an efficient method for the synthesis of substituted pyridines via a palladium-catalyzed isomerization of methylenecyclopropanes proved to be challenging. To date, the screening of reaction parameters only showed marginal effects on improving the reaction yield. Future studies should focus on tuning the reactivity of methylenecyclopropane by structure modification.

In contrast, a more promising result was obtained from the study on palladium-catalyzed isomerizations of cyclopropanes. However, problems associated with product stability need to be solved to make this process synthetically useful. Screening for additives that give slower rates of allylic acetate decomposition might be a potential solution.
2.2.3 Experimental

$^1$H, and $^{13}$C, NMR spectra were recorded using Mercury 300 MHz, Mercury 400 MHz or spectrometers. $^1$H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and $^{13}$C spectra were referenced to solvent carbons (CDCl$_3$, 77.0 ppm). IR spectra were obtained as thin films on NaCl plates. High resolution mass spectra were obtained at 70 eV for electron impact ionization (EI) or at a spray voltage of 5500 V for electrospray ionization (ESI). HPLC analysis was conducted with an Agilent 1100 series HPLC with photodiode array and Waters silica columns with Uniguard pre-column filters.

Toluene, dioxane and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone immediately prior to use. Dichloromethane and benzene were distilled under nitrogen from CaH$_2$ immediately before use. All reagents were used as received from Sigma-Aldrich or Strem unless otherwise indicated. Analytical thin layer chromatography was performed with Silicycle™ normal phase 0.25 mm aluminum or glass backed TLC plates. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel. All experiments were performed under anhydrous conditions under an atmosphere of nitrogen or argon unless otherwise noted.
Ethyl 2-bromo-2-methycyclopropanecarboxylate (2.2.3): To a solution of Rh$_2$(OAc)$_4$ (47.4 mg, 0.21 mmol) in 2-bromopropene (18.5 mL, 217 mmol) at 25 °C was slowly added ethyl diazoacetate (10.5 mL, 89.0 mmol) over 48 h. The reaction mixture was distilled to remove the excess of 2-bromopropene, and then distilled under reduced pressure (65-73 °C, 19-22 mm Hg) to afford the title compound 2.2.3 (15.7 g, 85%) as colorless oil. Spectral data matched the previously reported data.$^{184}$

Ethyl 2-methyleneisocyclopropanecarboxylate (2.2.4): To a solution of NaH (5.08 g, 127 mmol) in 110 mL of Et$_2$O was added a solution of 2.2.3 (15.5 g, 74.9 mmol) in 10 mL of Et$_2$O dropwise. The reaction mixture was heated to reflux before 1 mL of EtOH was added dropwise and stirred under reflux for 16 h. The mixture was filtered through a pad of Celite to remove excess amount of NaH. The resulting solution was distilled to remove Et$_2$O and then distilled under reduced pressure to afford the title compound (5.90 g, 62%) as colorless oil. Spectral data matched the previously reported data.$^{184}$
2-Methylenecyclopropanecarboxylic acid (2.2.5): To a solution of 2.2.4 (7.89 g, 62.5 mmol) in 248 mL of MeOH and 62 mL of water, was added K₂CO₃ (31.8 g, 230 mmol) at 25 °C. After stirring at 25 °C for 48 h, the reaction mixture was acidified with 2N aqueous HCl and the aqueous layer was extracted with CH₂Cl₂ (x 3). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo to afford the title compound 2.2.5 (5.03 g, 82%) as colorless oil. Spectral data matched the previously reported data.¹⁸⁴

N-Methoxy-N-methyl-2-methylenecyclopropanecarboxamide (2.2.6): To a solution of 2.2.5 (3.13 g, 31.9 mmol) in 163 mL of CH₂Cl₂ at 0 °C was added carbonyldiimidazole (6.17 g, 38.1 mmol). The mixture was stirred at 0 °C for 1 h before the O,N-dimethylhydroxyamine hydrochloride (7.78 g, 79.8 mmol) was added. The resulting mixture was warmed to 25 °C and stirred for 16 h. The reaction solution was filtered through a pad of Celite and concentrated in vacuo. Chromatography on silica gel using Et₂O:hexane = 2:3 (R₉ = 0.21), gave the title compound 2.2.6 (4.21 g, 93%) as colorless oil. Spectral data matched the previously reported data.¹⁸³c
(2.2.2): To a solution of 2.2.6 (4.21 g, 29.8 mmol) in 169 mL of Et₂O at -78 °C was added a 3.0M solution of methylmagnesium bromide (12.5 mL, 37.5 mmol) dropwise. The reaction mixture was warmed to 25 °C and stirred for 6 h. The reaction was quenched by addition of water and 2N aqueous HCl and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo to afford the crude ketone. The crude product was dissolved in 31 mL of pyridine, and methoxyamine hydrochloride (3.45 g, 41.3 mmol) was added. The resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with CH₂Cl₂, washed with 2N aqueous HCl (× 3), dried with Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 25% Et₂O in hexane gave the title compound 2.2.2 (2.73 g, 73%) as yellow oil. E-2.2.2 (major) ¹H NMR (400 MHz, CDCl₃): δ 5.55-5.49 (m, 2H), 3.84 (s, 3H), 2.38-2.31 (m, 1H), 1.57 (s, 3H), 1.55-1.48 (m, 1H), 1.38-1.32 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 156.5, 131.4, 105.5, 61.1, 20.0, 9.7, 8.5; IR (neat): 2993, 2957, 2940, 2899, 2816, 1439, 1063, 878 cm⁻¹; HRMS (El) Calcd for C₇H₁₀NO [M-H⁺] 124.0762, found 124.0765.

6-Methylpyridin-3-yl acetate (2.2.7): To a microwave vial was added 1 mL of toluene, Pd(OAc)₂ (2.25 mg, 0.01 mmol), PhI(OAc)₂ (128.8 mg, 0.40 mmol), and 2.2.2 (25 mg,
201

0.20 mmol). The reaction flask was sealed and heated under microwave irradiation at 150 °C for 10 min. The reaction mixture was diluted with Et2O and the organic layer was extracted with 2N aqueous HCl (× 3). The combined aqueous layers were neutralized with saturated aqueous NaHCO3 solution and this aqueous layer was extracted with Et2O (× 3). The combined organic layers were dried with MgSO4, filtered, and concentrated in vacuo to afford the title compound 2.2.7 as yellow oil. The crude product was diluted with i-PrOH for HPLC analysis to determine the yield. 1H NMR (400 MHz, CDCl3): δ 8.29 (d, J = 2.7 Hz, 1H), 7.36 (dd, J = 8.6, 2.9 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 2.55 (s, 3H), 2.32 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 169.1, 155.8, 145.2, 142.3, 129.5, 123.4, 23.8, 21.0; IR (neat): 3022, 2928, 1766, 1761, 1599, 1581, 1485, 1371, 1197, 1026, 925, 898, 850, 721 cm⁻¹; HRMS (EI) Calcd for C8H9NO2 [M⁺] 151.0633, found 151.0634. The HPLC analysis was performed under following conditions: Waters silica column, 10% isopropanol in hexane, 1 mL/min, 25 °C, λ = 205 nm; tᵣ = 13.3 min.

2.2.12

1-Cyclopropylundecan-1-one (2.2.12): To a flame-dried round-bottom flask equipped with reflux condenser was added magnesium (490 mg, 20.1 mmol), Et2O (20 mL), and 1-bromodecane (4.0 mL, 19 mmol) at 25 °C. The mixture was heated with heat gun until the reaction was initiated and stirred at 25 °C for 1.5 h. To a solution of cyclopropylnitrile (1.00 g, 14.9 mmol) in Et2O at 0 °C was added the freshly prepared Grignard reagent solution dropwise.¹⁹⁰ Upon the completion of the addition, the mixture was warmed to 25 °C and stirred for 16 h. The reaction was quenched by addition of 2N aqueous HCl
solution and stirred at 25 °C for 30 min. The aqueous layer was extracted with Et₂O (× 3) and the combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 10% Et₂O in hexane (Rf = 0.56) gave the title compound 2.2.12 (2.44 g, 78%) as colorless oil. 

\[ \text{δ} 2.56-2.50 \text{ (m, 2H)}, 1.96-1.88 \text{ (m, 1H)}, 1.65-1.57 \text{ (m, 2H)}, 1.34-1.22 \text{ (m, 14H)}, 1.03-0.97 \text{ (m, 2H)}, 0.91-0.81 \text{ (m, 5H)}; \]

\[ \text{δ} 211.3, 43.5, 31.9, 29.6, 29.5, 29.3, 24.1, 22.7, 20.3, 14.1, 10.5; \]


(2.2.11): To a solution of 2.2.12 (1.00 g, 4.75 mmol) in 10 mL of pyridine was added methoxyamine hydrochloride (600 mg, 7.13 mmol) at 25 °C and the resulting mixture was stirred at 25 °C for 16 h. The reaction was quenched by dilution with Et₂O and the organic layer was washed with 2N aqueous HCl (× 3), dried with MgSO₄, filtered, and concentrated in vacuo to afford 2.2.11 (1.12 g, 99%, E:Z = 3:1) as a red oil. The material was sufficiently pure as determined by NMR spectroscopy to be used for subsequent reactions. E-2.2.11 (major) 

\[ \text{δ} 3.77 \text{ (s, 3H)}, 2.16-2.11 \text{ (m, 2H)}, 1.54-1.42 \text{ (m, 3H)}, 1.34-1.22 \text{ (m, 14H)}, 0.92-0.85 \text{ (m, 4H)}, 0.73-0.69 \text{ (m, 3H)}; \]

\[ \text{δ} 161.9, 61.0, 31.9, 29.9, 29.6, 29.5, 29.4, 29.3, 27.6, 27.4, 26.3, 22.7; \]

IR (neat): 2924, 2854, 1464, 1378, 1177, 1057, 913, 724 cm⁻¹;

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191 The E/Z isomer refers to the relationship between the cyclopropyl and methoxy moieties.
HRMS (EI) Calcd for C_{15}H_{29}NO \ [M^+] 239.2249, found 239.2248.

\[ \text{NOMe} \]
\[ \text{OAc} \]

**2.2.13** and **2.2.14**

(2.2.13) and (2.2.14): To a microwave vial was added 2.5 mL of CH\_2Cl\_2, Pd(OAc)\_2 (4.50 mg, 0.02 mmol), PhI(OAc)\_2 (128.8 mg, 0.40 mmol), and **2.2.11** (47.9 mg, 0.20 mmol). The reaction flask is sealed and heated at 80 °C for 16 h. The reaction mixture was diluted with Et\_2O, dried with MgSO\_4, filtered, and concentrated in vacuo. Chromatography on silica gel using 2% Et\_2O in CH\_2Cl\_2 (R\_f = 0.59, 0.43) gave **2.2.13** (20.5 mg, 33%) as yellow oil and **2.2.14** (10.8 mg, 17%) as yellow oil. **2.2.13** \( ^1H \) NMR (400 MHz, CDCl\_3): \( \delta 6.25 \) (d, \( J = 16.4 \) Hz, 1H), \( 6.06 \) (dt, \( J = 16.0, 5.9 \) Hz, 1H), 4.68 (dd, \( J = 5.9, 1.6 \) Hz, 2H), 3.89 (s, 3H), 2.46-2.40 (m, 2H), 2.09 (s, 3H), 1.49-1.40 (m, 2H), 1.34-1.29 (m, 14H), 0.91-0.85 (m, 3H); \( ^{13}C \) NMR (100 MHz, CDCl\_3): \( \delta 170.6, 158.5, 129.9, 127.5, 64.3, 61.8, 31.9, 29.8, 29.6, 29.5, 29.4, 29.3, 26.5, 24.7, 22.7, 20.9, 14.1; IR (neat): 2956, 2926, 2854, 1747, 1446, 1361, 1228, 1053, 1028, 970 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{17}\)H\(_{31}\)NO\(_3\) [M\(^+\)] 297.2304, found 297.2294. **2.2.14** \( ^1H \) NMR (400 MHz, CDCl\_3): \( \delta 5.85 \) (dt, \( J = 11.7, 2.0 \) Hz, 1H), 5.77 (dt, \( J = 11.7, 5.3 \) Hz, 1H), 4.93 (dd, \( J = 5.3, 2.0 \) Hz, 2H), 3.89 (s, 3H), 2.37-2.32 (m, 2H), 2.08 (s, 3H), 1.46-1.41 (m, 2H), 1.32-1.23 (m, 14H), 0.91-0.85 (m, 3H); \( ^{13}C \) NMR (100 MHz, CDCl\_3): \( \delta 170.8, 156.8, 131.3, 125.6, 63.2, 62.0, 31.9, 29.6, 29.5, 29.3, 28.9, 26.0, 22.7, 21.0, 14.1; IR (neat): 2925, 2862, 1745, 1373, 1228, 1049, 919 cm\(^{-1}\); HRMS (EI) Calcd for C\(_{17}\)H\(_{31}\)NO\(_3\) [M\(^+\)]
297.2304, found 297.2303.

\[ \text{2.2.21} \]

\[ \text{N-Methoxy-N-methylcyclopropanecarboxamide (2.2.21):} \] To a solution of cyclopropanecarboxylic acid (2.00 g, 23.2 mmol) in 90 mL of CH\(_2\)Cl\(_2\) at 0 °C was added carbonyldiimidazole (4.52 g, 27.9 mmol). The mixture was stirred at 0 °C for 1 h before the \(O,N\)-dimethylhydroxyamine hydrochloride (5.66 g, 58.1 mmol) was added. The resulting mixture was warmed to 25 °C and stirred for 16 h. The reaction solution was filtered through a pad of Celite and concentrated in \textit{vacuo}. Chromatography on silica gel using 50% Et\(_2\)O in hexane, gave the title compound 2.2.21 (2.52 g, 84%) as a colorless oil. Spectral data matched the previously reported data.\(^{192}\)

\[ \text{2.2.18} \]

\[ \text{(2.2.18):} \] To a flame dried round-bottom flask equipped with reflux condenser was added magnesium (280 mg, 11.4 mmol), THF (12 mL), and (3-bromopropoxy)-\textit{tert}-butyldimethylsilane\(^{193}\) (2.7 mL, 11 mmol) at 25 °C. The mixture was heated with heat gun until the reaction was initiated and stirred at 25 °C for 2 h. To a solution of 2.2.21 (720 mg, 5.55 mmol) in 10 mL THF at -78 °C was added the freshly prepared


Grignard reagent solution dropwise. Upon the completion of the addition, the mixture was warmed to 25 °C and stirred for 16 h. The reaction was quenched with saturated ammonium chloride solution and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were dried Na₂SO₄, filtered, and concentrated in vacuo. The crude ketone was dissolved in pyridine (5 mL), followed by the addition of methoxyamine hydrochloride (290 mg, 3.52 mmol) at 25 °C and the resulting mixture was stirred at 25 °C for 16 h. The mixture was diluted with Et₂O, washed with 2N aqueous HCl solution (× 3), dried with MgSO₄, filtered, and concentrated in vacuo. The crude oxime was dissolved in 6 mL of THF and a 1M solution of tetrabutylammonium fluoride in THF (4.7 mL, 4.7 mmol) was added dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 2 h and quenched with water. The aqueous layer was extracted with Et₂O (× 3) and the combined organic layers were dried with Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 80% Et₂O in hexane (Rf = 0.58, 0.40) gave the title compound 2.2.18 (364 mg, 41%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 3.80 (s, 3H), 3.58 (t, J = 6.1, 2H), 2.31 (t, J = 7.3 Hz, 2H), 1.81-1.72 (m, 2H), 0.88-0.81 (m, 1H), 0.75-0.68 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 161.4, 61.5, 61.2, 29.1, 23.6, 14.0, 5.3; IR (neat): 3379, 2938, 1620, 1463, 1445, 1393, 1179, 1049, 937, 911, 821, 744 cm⁻¹; HRMS (EI) Calcd for C₈H₁₅NO₂ [M⁺] 157.1103, found 157.1106.

(2.2.19): To a solution of oxalyl chloride (0.19 mL, 2.2 mmol) in 1 mL of CH₂Cl₂ at -78
C was added anhydrous DMSO (0.32 mL, 4.5 mmol) dropwise and the mixture was stirred at -78 °C for 15 min. To this solution was added dropwise a solution of 2.2.18 (280 mg, 1.79 mmol) in 3 mL of CH₂Cl₂ at -78 °C. After stirred for 1 h, Et₃N (1.0 mL, 7.2 mmol) was added dropwise at -78 °C then the reaction mixture was warmed to 25 °C and stirred for 16 h. The reaction was quenched with saturated aqueous ammonium chloride solution and 2N aqueous HCl solution, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with water (× 2), dried with Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using 30% Et₂O in hexane (Rf = 0.54) gave the title compound 2.2.19 (0.23 g, 83%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 9.76 (s, 1H), 3.78 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 1.54-1.46 (m, 1H), 0.78-0.67 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 200.9, 159.9, 61.3, 40.3, 20.2, 14.1, 5.1; IR (neat): 3085, 3002, 2939, 2894, 2811, 2718, 1720, 1700, 1620, 1389, 1051, 822 cm⁻¹; HRMS (EI) Calcd for C₈H₁₃NO₂ [M⁺] 155.0946, found 155.0946.

(2.2.20): The title compound was prepared according to the procedure for the synthesis of 2.2.13. Using the reaction conditions described above with 2.2.19 (31 mg, 0.20 mmol) as starting material, followed by chromatography on silica gel using 30% Et₂O in hexane (Rf = 0.20) gave title compound 2.2.20 (6.7 mg, 13%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.77 (t, J = 1.2 Hz, 1H), 6.28 (dt, J = 16.0, 1.6 Hz, 1H), 6.08 (dt, J = 16.4, 5.5 Hz, 1H), 4.68 (dd, J = 5.9, 1.6 Hz, 2H), 3.90 (s, 3H), 2.76-2.70 (m, 2H),
2.65-2.59 (m, 2H), 2.09 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 200.6, 170.6, 156.5, 129.0, 128.1, 64.0, 62.1, 40.2, 20.9, 17.4; IR (neat): 2921, 2730, 1731, 1581, 1453, 1385, 1365, 1228, 1046, 971, 900 cm$^{-1}$; HRMS (EI) Calcd for C$_{10}$H$_{15}$NO$_4$ [M$^+$] 213.1001, found 213.1004.
APPENDIX:

PROTON AND CARBON NMR SPECTRA FOR NEW COMPOUNDS
F₃CH₂CO₂⁻
F₃CH₂CO⁻

1.2.78

Chemical Shift (ppm)

Chemical Shift (ppm)
Chemical Shift (ppm)

Chemical Shift (ppm)
Chemical Shift (ppm)

0.66  0.89  0.84  9.00  7.79

Chemical Shift (ppm)
t-BuO₂C

Chemical Shift (ppm)

220 200 180 160 140 120 100 80 60 40 20 0

Chemical Shift (ppm)
Chemical Shift (ppm)

O
CO₂t-Bu

1.2.41
Chemical Shift (ppm)

Chemical Shift (ppm)
H₃C
\(\text{CO}_2\text{-t-Bu}\)

1.2.58
Chemical Shift (ppm)
CO$_2$-Bu

1.2.66
Chemical Shift (ppm)

1.2.71

$\text{CO}_2$-Bu
Bpin

Chemical Shift (ppm)

16.00 2.41 0.83 0.58 1.425
Chemical Shift (ppm)
B(OH)$_2$
Chemical Shift (ppm)

- 1.06
- 1.00
- 0.96
- 0.93
- 0.92
- 1.05
- 0.98
- 0.00
- 1.06

Chemical Shift (ppm)
1.4.24
N

Bpin

Ts

1.4.33

Chemical Shift (ppm)

220 200 180 160 140 120 100 80 60 40 20 0

Chemical Shift (ppm)

220 200 180 160 140 120 100 80 60 40 20 0

302
2.2.19