Syntheses and Applications of Vinylstannanes

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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____________________________________
Abstract

The development of methods for the synthesis of vinylstannanes is reported. The applications of these useful compounds are highlighted in a variety of total syntheses of natural products.

Cyclic and acyclic vinylstannanes were prepared conveniently in a simple one-pot procedure from the corresponding ketones. The scope of ketones was illustrated and the limitations were highlighted. Moderate to high yields of vinylstannanes are reported that compare favourably with other methods. Two cases of unsymmetrical ketones provided the less substituted vinylstannanes. A straight-forward purification procedure was developed for non-polar vinylstannanes that allowed for the separation from Bu$_3$SnH contamination.

*Trans*-1-stannyl-1-alkenes were prepared in high regioselectivity (95:5, *trans*:gem) from unhindered 1-alkynes by using Pd$_2$dba$_3$/Cy$_3$PHBF$_4$/i-Pr$_2$NEt on a wide range of terminal alkynes. This system exhibited higher selectivities and yields for *trans*-vinylstannanes than the original PPh$_3$-based catalysts that are widely adopted. Contrary to popular belief, it was found that ligands have a dramatic effect on the regioselectivity of palladium-catalyzed hydrostannations of 1-alkynes. Steric and electronic arguments were used to explain the observed regioselectivities. An insect sex pheromone was synthesized using the hydrostannation methodology that was developed. An inseparable 95:5 mixture of *trans* and *geminal* vinylstannanes did not pose a problem during the synthesis, as the *geminal* isomer did not participate in the Stille coupling.
A two-step synthesis of *trans*-1-stannylbutadiene, as an extension of hydrostannation of terminal alkynes, is reported. A convergent synthesis of a trienic sex pheromone was demonstrated as a convenient route to this class of compounds.

Another extension of hydrostannation chemistry, synthesis of *trans*-vinyl iodides in excellent selectivities (95:5 to 99:1 *trans:*gem) in a one-pot procedure from unhindered terminal alkynes, is reported. Purities of *trans*-vinyl iodides were improved from the hydrostannation regioselectivity of 95:5 to 99:1 by using less than 1 equivalent of iodine to quench the reaction. Two dienyl sex pheromones were synthesized to illustrate the application of this methodology. Also, inseparable 95:5 mixture of *trans* and *geminal* vinyl iodides did not pose a problem during the syntheses, as the *geminal* isomer did not participate in the Sonogashira couplings.

*Trans*-1-stannylbutadiene was able to undergo Diels-Alder reactions with various cyclic, five-membered ring, doubly activated dienophiles. Enantioselective Diels-Alder reaction was obtained in 33% ee by using a Mikami catalyst. The allylstannane from a racemic Diels-Alder reaction was able to undergo allylstannation with an aldehyde and a ketone using SnCl$_2$/MeCN or SnCl$_4$/CH$_2$Cl$_2$ systems to provide γ-addition products as the major isomers with high diastereoselectivity. A diastereoselective Diels-Alder reaction was effected by using Waldner’s chiral dienophile to provide isomeric allylstannanes in a 10:1 ratio; the major product could be purified by flash chromatography. A Diels-Alder/allylstannation sequence was achieved with Waldner’s dienophile and *trans*-1-stannylbutadiene to provide a pure functionalized cyclohexene in 60% yield in a one-pot procedure.
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To

my caring Mom and Dad
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<th>Definition</th>
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<tr>
<td>Ac</td>
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<td>Aq</td>
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</tr>
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<td>m</td>
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<td>Full Form</td>
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</tr>
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<td>phenyl</td>
</tr>
<tr>
<td>Pin</td>
<td>pinacol</td>
</tr>
<tr>
<td>PMHS</td>
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</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
</tr>
<tr>
<td>Pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
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<td>rt</td>
<td>room temperature</td>
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<td>singlet</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>sBuLi</td>
<td>sec-butyllithium</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-$n$-butylammonium fluoride</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>tBu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>tBuLi</td>
<td>tert-butyllithium</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
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<tr>
<td>TMEDA</td>
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<td>TMS</td>
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<td>Ts</td>
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</tr>
<tr>
<td>TTMPP</td>
<td>tris(2,4,6-trimethoxyphenyl)phosphine</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

1.1 General

In 1850, the first preparation of an organotin compound was reported by Frankland (Scheme 1.1), where tin metal reacted with ethyl iodide to form diethyltin diiodide 1-3.

\[
\text{Sn} + 2 \text{EtI} \rightarrow \text{Et}_2\text{SnI}_2
\]

Scheme 1.1

By the mid 1950s, tin’s role in organometallic chemistry increased rapidly as new applications for organotin compounds emerged. Kuivila et al. demonstrated the reaction between trialkyltin hydrides with alkyl halides to produce reduction products 1-6, via a radical chain reaction involving short-lived trialkyltin radicals (Scheme 1.2).

\[
\text{RX} + \text{R}_3\text{SnH} \rightarrow \text{RH} + \text{R}_3\text{SnX}
\]

Scheme 1.2
Newmann and Sommer illustrated addition of trialkyltin hydrides across double and triple bonds in a process called hydrostannation (Scheme 1.3).\textsuperscript{4,5}

\[ R_3\text{SnH} + \quad \xrightarrow{\Delta} \quad R_3\text{Sn} + \text{H} \]

\textbf{Scheme 1.3}

Like hydrostannolysis, hydrostannation proceeds \textit{via} radical chain reaction involving tin radicals.

The ability of tin to exchange with other metals, \textit{via} transmetallation processes, expanded the application of organotin chemistry dramatically.\textsuperscript{2} Seyferth and Weiner were able to demonstrate the exchange between organotin 1-11 and butyllithium 1-12 (Scheme 1.4).\textsuperscript{6}

\[ (\equiv)\text{Sn} + n\text{-BuLi} \quad \rightarrow \quad (\equiv)\text{Li} + n\text{-Bu}_3\text{Sn} \]

\textbf{Scheme 1.4}

Vinyl lithium 1-13 was treated with various electrophiles, as 1-13 was unstable for isolation.
More recently, cross-coupling reactions have garnered a great deal of attention due to their versatility in forming new carbon-carbon bonds. Kosugi et al. were able to accomplish the first cross coupling reaction involving tin (Scheme 1.5).

\[
\begin{align*}
\text{ArX} & \quad + \quad \text{Bu}_3\text{Sn} & \quad \xrightarrow{\text{cat. Pd(0)}} & \quad \text{Ar} & \quad + \quad \text{Bu}_3\text{SnX} \\
1-15 & \quad + \quad 1-16 & \quad & \quad 1-17 & \quad + \quad 1-18
\end{align*}
\]

Scheme 1.5

Cross coupling reaction between aryl halides and allylstannane proceeded by applying catalytic amounts of palladium (0). Milstein and Stille also demonstrated a cross coupling reaction between acyl chlorides and tetraalkyltin compounds (Scheme 1.6).

\[
\begin{align*}
\text{ArCl} & \quad + \quad R'_4\text{Sn} & \quad \xrightarrow{\text{BnPd(PPh_3)_2Cl, HMFA}} & \quad \text{Ar} & \quad + \quad R'_3\text{SnCl} \\
1-19 & \quad + \quad 1-20 & \quad & \quad 1-21 & \quad + \quad 1-22
\end{align*}
\]

Scheme 1.6

Cross-coupling reactions involving tin are generally known as the Stille coupling. These illustrated reactions serve as the basis for many important organic synthetic methods.
1.2 Applications of Vinylstannanes

Vinylstannanes are a particularly important class of organostannanes, that have been employed in many syntheses of natural products.\textsuperscript{9-17} They are stable to many substances such as water, air, bases and silica gel, which makes them attractive species to handle.\textsuperscript{18} Synthetically speaking, vinylstannanes are synthetic equivalents of vinyl carbanions (Figure 1.1).

![Figure 1.1 Vinylstannanes as synthetic equivalents of vinyl carbanions](image)

The tin-carbon bond of vinylstannanes can be functionalized selectively. There are many transformations that vinylstannanes can undergo. Some of the more common applications are highlighted here in Scheme 1.7.
Scheme 1.7

Vinylstannanes can be used successfully in metal-catalyzed cross-coupling reactions (Scheme 1.7, path b), known as the Stille coupling, with organic halides or triflates. Complete retention of configuration of the double bond is observed (Scheme 1.8).¹⁹
Vinylstannanes can undergo stereospecific Sn-Li exchange with alkyllithiums to generate a highly reactive vinyllithium species (Scheme 1.7, path d), which can react with carbonyls in the same fashion as Grignard reagents do (Scheme 1.9).  

Vinylstannanes can undergo transmetallation with reactive copper species (Scheme 1.7, path c) to generate highly reactive vinylcopper intermediates that could participate in substitution reactions or 1,4-addition reactions (Scheme 1.10).
Vinylstannanes readily react with dihalides such as bromine and iodine (Scheme 1.7, path a) to produce the corresponding vinylhalides with complete retention of configuration of the double bond (Scheme 1.11).\(^{22}\)
Vinylstannanes can undergo a radical chain process that generates a vinyl radical \textit{in situ} (Scheme 1.7, path e); potentially leading to processes such as intramolecular cyclizations (Scheme 1.12).²³

\begin{align*}
\text{Scheme 1.11} \\
\text{Scheme 1.12}
\end{align*}

1.3 Syntheses of Vinylstannanes

There are several methodologies that are used commonly in preparation of vinylstannanes. Hydrostannation of alkynes by radical or metal-catalyzed processes are two of the most commonly used preparations of vinylstannanes (Scheme 1.13).²⁴,²⁵
Stannylmetallation of alkynes is another methodology that has gained attention in preparation of vinylstannanes (Scheme 1.14).\textsuperscript{26,27}

Hydrometallation of a triple bond followed by stannylation of the corresponding vinyl metal formed \textit{in situ} provides the corresponding vinylstannane (Scheme 1.15).\textsuperscript{28-30}
Also, vinylstannanes can be prepared from the corresponding carbonyl compounds (Scheme 1.16).\textsuperscript{31-35}

![Scheme 1.16](image_url)

Methodologies that involve preparation of vinylstannanes from alkynes will be discussed in detail in Chapter 3, while methodologies that provide vinylstannanes from carbonyl compounds will be discussed in detail in Chapter 2.
Chapter 2

Synthesis of Vinylstannanes from Ketones via Addition-Elimination Chemistry

2.1 Introduction

2.1.1 General

Cyclic vinylstannanes, just as other vinylstannanes, have been employed in total syntheses of natural products. They serve as convenient building blocks in organic synthesis,\textsuperscript{1} including, for example, their transformation to vinyllithiums via transmetalation (Scheme 2.1).\textsuperscript{2}

\[
\text{SnBu}_3 \quad \text{BuLi} \quad \text{Li}
\]

\[2-1 \quad n = 0,1,2,3,\ldots\quad \text{quantitative conversion} \quad 2-2\]

Scheme 2.1
Paquette has demonstrated the use of these convenient building blocks to develop the skeleton of terpenoid 2-6 (Scheme 2.2).³

![Scheme 2.2](image)

Sunnemann et al. applied cyclic vinylstannane 2-8 in part of the total synthesis of steroid 2-10 (Scheme 2.3).⁴

![Scheme 2.3](image)
Yoshida et al. obtained antibiotic 2-14 by employing vinylstannane 2-12 (Scheme 2.4).\(^5\)

\[
\begin{align*}
\text{MeO}_2\text{C}- & \quad \text{N} - \text{Cl} & \quad \text{MeO}_2\text{C}- & \quad \text{N} - \text{Boc} \\
\text{2-11} & + & \text{SnBu}_3 & \quad \overset{\text{[Pd}_{3}\text{db}_{3}]\cdot\text{CHCl}_3}{\text{CsF, tBu}_{3}P/}
\end{align*}
\]

\[
\text{dioxane, } 80 \, ^\circ \text{C} \quad 75\%
\]

\[
\begin{align*}
\text{MeO}_2\text{C}- & \quad \text{N} - \text{Boc} & \quad \text{MeO}_2\text{C}- & \quad \text{N} - \text{Boc} \\
\text{2-12} & + & \text{2-13} & \quad \text{2-14}
\end{align*}
\]

Scheme 2.4

The convenience of these building blocks has made them desirable to implement in total syntheses. The majority of methodologies devoted to the preparation of cyclic vinylstannanes begin from the corresponding carbonyl compounds. Syntheses of cyclic and acyclic vinylstannanes that adopt this approach will be discussed in detail.

2.1.2 Synthesis of vinylstannanes from carbonyl compounds

Wulff et al. developed a route to vinylstannanes based on an observation made by Stille et al.\(^6\) that tetrakis(triphenylphosphine)palladium can catalyze the coupling of vinyl triflates with a variety of organostannanes (Scheme 2.5).
Expanding this methodology, Wulff et al. were able to couple hexamethylditin with vinyl triflates derived from symmetrical and unsymmetrical ketones (Scheme 2.6).

Highly selective preparations of kinetic and thermodynamic enolates from unsymmetrical ketones have been reported.7,8 The selective formation of enolates from unsymmetrical
ketones allows regioselective formation of vinylstannanes from unsymmetrical carbonyl compounds. Representative results are shown in Table 2.1.

**Table 2.1** Palladium-catalyzed coupling of enol triflates and hexamethyldistannane

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>enol triflate</th>
<th>yield (%)</th>
<th>vinylstannane</th>
<th>yield (%) (h)</th>
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<tr>
<td>1</td>
<td>2-22</td>
<td>2-23 OTf</td>
<td>84b</td>
<td>2-24 SnMe3</td>
<td>81(3)</td>
</tr>
<tr>
<td>2</td>
<td>2-17</td>
<td>2-18 OTf (97:3)</td>
<td>91b</td>
<td>2-19 SnMe3</td>
<td>84(9)</td>
</tr>
<tr>
<td>3</td>
<td>2-17</td>
<td>2-20 (97:3)</td>
<td>63c</td>
<td>2-21 (98:2)</td>
<td>80(168)</td>
</tr>
<tr>
<td>4</td>
<td>2-25</td>
<td>2-26 OTf</td>
<td>89b</td>
<td>2-27 SnMe3</td>
<td>73(0.75)</td>
</tr>
<tr>
<td>5</td>
<td>2-28</td>
<td>2-29 (94:6)</td>
<td>70b</td>
<td>2-30 (99.6:0.4)</td>
<td>74(6)</td>
</tr>
</tbody>
</table>

*a* Coupling reactions were carried out at 60 °C with 0.2 M THF solutions of the enol triflate with 0.9 equiv of hexamethyldistannane, 6.0 equiv of lithium chloride, and 0.018 equiv of Pd cat. under Ar.

*b* LDA, N-phenyltrifluoromethanesulfonimide.

*c* i-Pr₂NMgBr, N-phenyltrifluoromethanesulfonimide
This methodology proved to be useful for cyclic and acyclic, symmetrical and unsymmetrical ketones.

This chemistry was limited to the use of (Me₃Sn)₂, as (Bu₃Sn)₂ provided very low yields. This limitation was overcome by applying highly reactive stannylcuprates. The coupling of vinyl triflates with highly reactive stannylcuprates was found to provide a convenient method for the preparation of vinylstannanes (Scheme 2.7).

![Scheme 2.7]

This methodology can also be applied to unsymmetrical ketones, since vinyl triflates can be regioselectively prepared from ketones (Table 2.2).
Table 2.2 The coupling of vinyl triflates with stannylcuprates

<table>
<thead>
<tr>
<th>Entry</th>
<th>enol triflate</th>
<th>stannylcuprate</th>
<th>vinylstannane</th>
<th>reaction time (h) (temperature)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-23 OTf</td>
<td>(Bu₃Sn)₂CuLi·LiCN (1.1 equiv)</td>
<td>2-33 SnBu₃</td>
<td>2 (-20 °C)</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>2-20 OTf</td>
<td>(Bu₃Sn)₂CuLi·LiCN (1.1 equiv)</td>
<td>2-34 SnBu₃</td>
<td>2 (-20 °C)</td>
<td>91</td>
</tr>
</tbody>
</table>

Shorter reaction times were another advantage to this route; as well, isolated yields were higher compared to the previous methodology.⁹

Adam and Klug¹⁰ applied the same methodology developed by Cohen and Doubleday (Scheme 2.8)¹¹ to obtain vinyllithium compounds from enol phenyl thioethers such as 2-35. This method involves the formation of vinyl sulfides from ketones followed by reductive lithiation by means of the radical anion lithium \( p,p'\)-di-tert-butylbiphenylide (LDBB).¹¹ In the formation of vinyl sulfides from unsymmetrical ketones, the more highly substituted enol thioether 2-35 was formed as the major product (95:5, from ketone 2-17) (Scheme 2.8).¹²
Adam and Klug were able to treat vinyllithium 2-39 (Scheme 2.9), formed *in situ*, with Bu$_3$SnCl to provide the corresponding vinylstannane 2-40.$^{10}$

Methodology by Cohen and Doubleday proved to be selective for the more substituted vinyllithium when dealing with unsymmetrical ketones.$^{11}$
Adam and Klug\textsuperscript{10} applied the methodology of Chamberlin \textit{et al.} (Scheme 2.10)\textsuperscript{13} to attain the less-substituted vinyllithiums from unsymmetrical ketones.

\begin{center}
\begin{tikzpicture}


\node[draw,shape=circle,fill=white] (1) at (0,0) {2-17};
\node[draw,shape=circle,fill=white] (2) at (3,1) {2-41};
\node[draw,shape=circle,fill=white] (3) at (3,0) {2-42};
\node[draw,shape=circle,fill=white] (4) at (3,-1) {2-38};

\draw[->,thick] (1) -- (2) node[midway,above]{trisylhydrazine};
\draw[->,thick] (2) -- (3) node[midway,above]{94\% isolated yield};
\draw[->,thick] (2) -- (4) node[midway,right]{(trace of other isomer present)};
\draw[->,thick] (3) -- (4) node[midway,above]{-78 \degree C};
\draw[->,thick] (4) -- (1) node[midway,above]{warm to 0 \degree C};

\end{tikzpicture}
\end{center}

**Scheme 2.10**

Hydrazone 2-41 was formed in excellent yield, \textit{via} the Shapiro reaction, by the addition of 2,4,6-trisopropylbenzenesulfonylhydrazine (trisylhydrazine) to unsymmetrical ketone 2-17. Addition of 2 equivalents of \textit{sec}-BuLi to hydrazone 2-41 leads to the formation of dianion 2-42.\textsuperscript{13} Dianion 2-42 underwent decomposition as the reaction temperature was raised to 0 \degree C to provide vinyllithium 2-38 as the major isomer.\textsuperscript{13} Unlike the Cohen and
Doubleday procedure, the less substituted vinyllithium was formed in this case which eventually led to the formation of the less substituted vinylstannane upon treatment with Bu$_3$SnCl (Scheme 2.11).$^{10,13}$

![Scheme 2.11](image)

Duboudin et al. reported a one-pot synthesis of cyclic and acyclic vinylstannanes from carbonyl compounds (Scheme 2.12).$^{14}$

![Scheme 2.12](image)

This method involved the addition of Bu$_3$SnMgCl to a carbonyl compound, followed by conversion of the hydroxystannane intermediate to the corresponding stannyl acetate or
thiocarbonate. A subsequent thermolysis at 600-950 °C furnished the desired vinylstannane in moderate yields (Table 2.3).

Table 2.3  Thermolysis of stannyl acetates and thiocarbonates.

<table>
<thead>
<tr>
<th>entry</th>
<th>carbonyl compound</th>
<th>vinylstannane</th>
<th>yield (%)</th>
<th>temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-48</td>
<td>2-49</td>
<td>61a (A)</td>
<td>800</td>
</tr>
<tr>
<td>2</td>
<td>2-50</td>
<td>2-51</td>
<td>75 (A)</td>
<td>800</td>
</tr>
<tr>
<td>3</td>
<td>2-52</td>
<td>2-53a</td>
<td>30b</td>
<td>650</td>
</tr>
<tr>
<td>4</td>
<td>2-22</td>
<td>2-33</td>
<td>59 (A)</td>
<td>700</td>
</tr>
<tr>
<td>5</td>
<td>2-55</td>
<td>2-56</td>
<td>29 (B)</td>
<td>820</td>
</tr>
</tbody>
</table>
Aldehydes and ketones shown in Table 2.3 were able to provide the corresponding vinylstannanes. Aldehyde 2-48 afforded two stereoisomeric vinylstannanes in 42/58 (cis/trans) ratio. Ketone 2-52 afforded two regioisomeric vinylstannanes 2-53a (cis/trans : 54:46) and 2-53b in 2:3 ratio, respectively. Unsymmetrical cyclic ketone 2-17 provided exclusively the less substituted vinylstannane 2-54.

Ratier et al. improved the thermolysis methodology, as a route to vinylstannanes, using triethylammonium N-carbomethoxysulfamate (Scheme 2.13).
Salt 2-57 was obtained from carbomethoxysulfamoyl chloride and triethylamine by a modified Burgess procedure. An advantage to this route is the ability of intermediate 2-58 to eliminate at milder temperatures than reported previously.

Chong and Park have also developed a methodology that generated vinylstannanes from aldehydes (Scheme 2.14).

![Scheme 2.14](image)

This methodology was a result of a serendipitous observation that came about during an investigation into the chemistry of α-aminoorganostannanes (Scheme 2.15). Thus iodide 2-64 did not provide the desired amide 2-66 but gave a modest yield of 2-65.
Scheme 2.15

The formation of $\alpha$-iodostannanes in good yields was made possible (typically 70-80% from aldehydes) by a procedure reported by Lange and Gottardo.\textsuperscript{18} DBU proved to be an effective base, consistently providing high isolated yields of elimination products (Table 2.4).\textsuperscript{17}

Table 2.4  Formation of vinylstannanes from $\alpha$-iodostannanes.\textsuperscript{17}

<table>
<thead>
<tr>
<th>entry</th>
<th>iodide (aldehyde)</th>
<th>vinylstannane (%) yield</th>
<th>$E:Z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSO\texthypertext{-}C\text{=O}SnBu\textsubscript{3}</td>
<td>(75)</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>TBSO\texthypertext{-}C\text{=C}SnBu\textsubscript{3}</td>
<td>(100)</td>
<td></td>
</tr>
</tbody>
</table>
Elimination of HI from α-iodostannanes by DBU provided excellent stereoselectivities of corresponding vinylstannanes (Table 2.4, 9:1 to 150:1 (E:Z)); branching of α-iodostannanes lead to increased selectivity.¹⁷
Other preparative methods of vinylstannanes from carbonyl or carbonyl derivatives have been developed also, but have not been widely adopted. Vinylstannane 2-81 was prepared by conjugate addition of stannyl anion to 2-80 followed by elimination of the phosphate group (Scheme 2.16).\textsuperscript{19}

![Scheme 2.16](image)

Opening of oxazoline 2-83 by KOtBu followed by deselenative stannylation with Bu$_3$SnH and AIBN provided vinylstannane 2-85 in a moderate yield (Scheme 2.17).\textsuperscript{20}
Tetramethylene sulfoxide 2-86 undergoes a tin mediated Pummerer type conversion to generate vinylstannane 2-87 (Scheme 2.18). 21

Scheme 2.18
Vinylstannane 2-89 was obtained in good yield from aldehyde 2-88 *via* a chromium(II)-mediated process using Bu₃SnCHI₂ (Scheme 2.19).²²

![Scheme 2.19](image)

### 2.2 Proposed Work

Despite the fact that there are many routes that provide cyclic and acyclic vinylstannanes from carbonyl compounds, most involve the isolation of an intermediate or a step that may be low-yielding.

The goal of the project is to establish a convenient route to vinylstannanes from carbonyl compounds. The scope of substrates will be tested by applying this methodology to many carbonyl derivatives. Also, unsymmetrical carbonyl compounds will be screened to examine the potential stereo- and regioselectivity.
2.3 Results and Discussion

In the initial experiments, Bu$_3$SnLi$^{23}$ was made in situ by adding Bu$_3$SnH to lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0 °C. After 30 min of stirring at that temperature, cyclohexanone was added in a dropwise fashion at -78 °C. The reaction was left stirring for an additional 30 min, followed by an aqueous workup. α-Hydroxystannane 2-90 was obtained in high (93%) isolated yield (Scheme 2.20).

![Scheme 2.20](image)

It is known that α-hydroxystannanes are not particularly stable,$^{23}$ although α-hydroxystannane 2-90 was stable enough to be chromatographed through silica gel without any noticeable loss in yield. However, α-hydroxystannane 2-91 (Scheme 2.21) did experience considerable decomposition upon silica gel chromatography. Bu$_3$SnH and cyclopentanone were recovered as verified by $^1$H and $^{13}$C NMR spectra. Destannylation of hydroxystannanes could occur in the presence of acid or base. Silica is acidic and can serve as a proton donor for this process to occur (Scheme 2.21).
Scheme 2.21

The next step toward the synthesis of vinylstannane 2-33 was to dehydrate \( \alpha \)-hydroxystannane 2-90. To accomplish this, crude \( \alpha \)-hydroxystannane 2-90 was treated with methanesulfonyl chloride (MsCl) and \( \text{Et}_3\text{N} \) in THF at -78 °C and let warm to room temperature gradually (Scheme 2.22).

Scheme 2.22

The dehydration occurred cleanly to afford the desired cyclic vinylstannane 2-33 in 97% isolated yield. Since there were many routes that were developed to obtain cyclic vinylstannanes, this route needed to have an advantage.
A one-pot procedure was developed wherein $\alpha$-hydroxystannane intermediate was not quenched but rather treated directly with MsCl/Et$_3$N. The reaction did not go to completion when 1-2 equivalents of MsCl were applied; however, the reaction did proceed to completion when 4 equivalents of MsCl were applied to afford cyclic vinylstannane 2-33 in 82% isolated yield (Scheme 2.23).$^{24}$

![Scheme 2.23](image)

Complete consumption of $\alpha$-hydroxystannane intermediate 2-90 was observed by TLC. The requirement of excess MsCl is likely due to the presence of diisopropylamine in the reaction. Diisopropylamine was deprotonated to make LDA base, which is the base used to convert Bu$_3$SnH to Bu$_3$SnLi. Diisopropylamine is suspected to react directly with MsCl or with sulfene 2-94, an intermediate formed from MsCl, hence the need for excess MsCl (Scheme 2.24).
Fortunately, MsCl is relatively inexpensive and the suspected polar by-products such as 2-95 were easily removed by liquid-liquid separation between hexane and acetonitrile. The non-polar stannanes remained in the hexane layer, while the polar materials were removed by the acetonitrile layer.

Other ketones were subjected to the one-pot protocol which illustrated the wide scope of this methodology (Table 2.5).
Table 2.5  Synthesis of vinylstannanes from ketones

\[
\text{entry} \quad \text{ketone} \quad \text{stannane} \quad \text{yield (%)}^a
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>stannane</th>
<th>yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Cyclohexanone" /></td>
<td><img src="image" alt="1-Bu_3SnLi" /></td>
<td>82</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Cyclohexane" /></td>
<td><img src="image" alt="SnBu_3" /></td>
<td>2-22</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Cyclopentanone" /></td>
<td><img src="image" alt="SnBu_3" /></td>
<td>83</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Cyclopentane" /></td>
<td><img src="image" alt="SnBu_3" /></td>
<td>2-96</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Cyclohexanone" />(t-Bu)</td>
<td><img src="image" alt="SnBu_3" /></td>
<td>81</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Cyclohexane" />(t-Bu)</td>
<td><img src="image" alt="SnBu_3" /></td>
<td>2-97</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Cyclopentanone" /></td>
<td><img src="image" alt="SnBu_3" /></td>
<td>81</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Cyclopentane" /></td>
<td><img src="image" alt="SnBu_3" /></td>
<td>2-54</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Benzophenone" /></td>
<td><img src="image" alt="SnBu_3" /></td>
<td>80</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Benzene" /></td>
<td><img src="image" alt="SnBu_3" /></td>
<td>2-99</td>
</tr>
</tbody>
</table>

1. Bu\(_3\)SnLi (1 equiv.)
2. MsCl (4 equiv.)/Et\(_3\)N (8 equiv.)
THF/ -78 °C
Examining the scope of this reaction, cyclic ketones subjected to this route provided yields consistently between 80-83% regardless of the ring size (5 or 6). Ketones conjugated with an aromatic ring provided vinylstannanes in great yields. Also, the reaction was operational whether the ring is carbocyclic or heterocyclic. The scale of the reaction (1 to 15 mmol) did not have any effect on the yields.\textsuperscript{24}

The reactions proceeded very smoothly and cleanly as determined by \textsuperscript{1}H NMR spectroscopic analysis of the crude mixtures. Only tin-containing materials were observed and consisted mainly of the desired vinylstannane along with traces of Bu\textsubscript{3}SnH (< 5%, determined by \textsuperscript{13}C NMR).\textsuperscript{24}

Vinylstannanes that contained functionalities other than hydrocarbons separated easily from Bu\textsubscript{3}SnH by silica gel chromatography. Initially, vinylstannanes that did not contain any functionality presented a challenge in purification from Bu\textsubscript{3}SnH contamination. Even with the use of hexane as eluant, vinylstannanes were not separable from Bu\textsubscript{3}SnH by silica gel chromatography.

There are many methods that have been developed for the removal of organotin residue,\textsuperscript{25,26} but they are primarily intended for the removal of organotin halides which would not be of use in this case. This challenge was initially solved by using reverse phase silica. Reverse phase silica contains C-18 units that are used to cap hydroxyl...
groups in regular silica, making the silica non-polar. This allows for the separation of non-polar impurities from the desired non-polar compounds. Reverse phase silica is commercially available but expensive. Alternatively, it can be made very easily from regular silica, and columns may be used multiple times.\(^\text{27}\)

The second procedure for removing \(\text{Bu}_3\text{SnH}\), which was the adopted procedure, involved stirring of the crude reaction mixture in warm chloroform containing a catalytic amount of azobis(isobutynitrile) (AIBN) for 4 h. \(\text{Bu}_3\text{SnH}\) reacts with chloroform to form \(\text{Bu}_3\text{SnCl}\), while leaving the vinylstannane unaffected, which can be filtered by simple silica gel chromatography.

This procedure was inspired by the serendipitous observation made when recording a \(^{13}\text{C}\) NMR spectrum of \(\text{Bu}_3\text{SnH}\) in CDCl\(_3\). Peaks for \(\text{Bu}_3\text{SnCl}\) and CHDCl\(_2\) were observed. This observation can be explained by a radical reaction that occurred between \(\text{Bu}_3\text{SnH}\) and CDCl\(_3\) initiated by light. Now, \(^{13}\text{C}\) NMR spectra of \(\text{Bu}_3\text{SnH}\) are recorded in C\(_6\)D\(_6\) to avoid such side reactions.\(^\text{28}\)

Up to this point, ketones that have been discussed have only one possible outcome for an elimination product. \(\text{2-methylcyclohexanone 2-17}\) contains two possible sites for elimination, but only the less substituted vinylstannane \(\text{2-54}\) was isolated in 81% yield (Scheme 2.25).
Scheme 2.25

This can be explained by axial attack of Bu₃SnLi on 2-methylcyclohexanone. It has been previously shown that addition of Bu₃SnLi to 4-tert-butylcyclohexanone, under the same conditions that we performed our reactions, proceeds with an axial : equatorial selectivity of 93:7 (Figure 2.1).

Sawyer et al. illustrated that the major axial stannyl isomer exhibited a higher ¹³C NMR frequency for the quaternary carbon (C₁ on compound 2-117) and that ³J_{Sn-C} for C₃/C₅ was different for the two isomers. This was determined by the dihedral angle between...

Figure 2.1 Illustration of dihedral angles of 2-117 and 2-118
C₁-Sn and C₂-C₃ bonds. In the axial isomer, these two bonds are almost orthogonal to one another (shown in Figure 2.2), which would give rise to a smaller coupling constant (< 3 Hz) according to the Karplus curve.²⁹

![Newman projections of 2-119 and 2-120](image)

**Figure 2.2** Newman projections of 2-119 and 2-120

On the other hand, the equatorial isomer contains a dihedral angle of 135 degrees between C₁-Sn and C₂-C₃ bonds (shown in Figure 2.2). One would expect a larger $^{119}$Sn-$^{13}$C₃ coupling in this case, and the recorded coupling is 40 Hz.²⁹ Having this in mind, the same experiment was repeated with 2-methylcyclohexanone instead of 4-tert-butylcyclohexanone (Figure 2.3).

![Illustration of dihedral angles of 2-121 and 2-122](image)

**Figure 2.3** Illustration of dihedral angles of 2-121 and 2-122
α-Hydroxystannane intermediates were trapped with methoxymethyl chloride (MOMCl) to form the corresponding ethers (2-121 & 2-122). The formation of two diastereomers with selectivity of 95:5 was observed. Inspecting the $^{13}$C NMR spectrum, the major isomer (2-121) did not show any resolved $^{119}$Sn-$^{13}$C$_3$ coupling. The minor isomer (2-122) did have $^{3}J_{\text{Sn-C}}$ of 40 Hz. These results were consistent with what was reported by Sawyer et al.$^{29}$

Since the axial isomer is the major isomer, a ring-flip is required to place the mesyloxy group in the axial position to facilitate E$_2$ elimination as shown below (Scheme 2.26).

![Scheme 2.26](image)

In this conformation, there is only one proton available for abstraction that is anti-periplanar to the mesyloxy group. Elimination of this methylene proton produces the less substituted double bond.

It is still unclear what exactly happens to the remaining 5% hydroxystannane formed from the equatorial attack. The mesyloxy group in 2-125 is in the axial position and is aligned to eliminate readily. But in this case, there are two available protons that are anti-
periplanar with the mesyloxy group. Since the less substituted vinylstannane is observed exclusively, the least hindered proton is abstracted, suggesting the vinylstannane produced is the kinetic product (Scheme 2.27).

Scheme 2.27

Acyclic ketones were also subjected to this methodology. Aryl methyl ketones such as acetophenone 2-103 worked very well, as did alkynyl methyl ketones 2-105 and 2-107. However, propiophenone 2-126 provided a low yield of a mixture of stereoisomers (Z:E = ~ 5:1) (Scheme 2.28).

Scheme 2.28
Dialkyl ketones such as acetone gave satisfactory results. It was necessary to carefully dry and distill the acetone prior to use in order to obtain the yields shown in Table 2.5. Acetone is very hygroscopic; the removal of water is necessary.

Methyl isopropyl ketone **2-109**, just like 2-methylcyclohexanone **2-17**, produced exclusively the less substituted vinylstannane in moderate yield. **2-hexanone 2-129**, unlike methyl isopropyl ketone **2-109**, had less differentiation around the carbonyl, resulted in a mixture of isomers. The ratio was determined to be 1:1:1 between the three possible isomers, but would not be synthetically useful due to low yield and multiple isomeric products (Scheme 2.29).

$$
\begin{align*}
\text{2-129} & \xrightarrow{1. \text{Bu}_3\text{SnLi}} \text{SnBu}_3 + \text{SnBu}_3 + \text{SnBu}_3 \\
& \xrightarrow{2. \text{MsCl/Et}_3\text{N}} \text{2-130} + \text{2-131} + \text{2-132} \\
\end{align*}
$$

<table>
<thead>
<tr>
<th>2-130</th>
<th>2-131</th>
<th>2-132</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1:1:1</td>
</tr>
</tbody>
</table>

**Scheme 2.29**

It was found that acyclic dialkyl ketones required the use of a relatively fresh $n$-BuLi bottle to obtain good yields. This finding was interesting due to the fact that this sensitivity was not observed for cyclic ketones, aryl ketones or the alkynyl ketones. It
was suspected that traces of alkoxides found in older bottles promoted undesirable reactions with dialkyl ketones that are more susceptible to side reactions.

Cyclic ketone 2-tetralone 2-133 failed completely at forming the $\alpha$-hydroxystannane intermediate (Scheme 2.30).

\[
\begin{array}{c}
\text{2-133} \\
\text{Bu}_3\text{SnLi} \\
\text{2-134}
\end{array}
\]

**Scheme 2.30**

$\text{Bu}_3\text{SnLi}$ could act as a base as a result of highly acidic $\alpha$-protons activated by the aromatic ring (Scheme 2.31).

\[
\begin{array}{c}
\text{2-133} \\
\text{Bu}_3\text{SnLi} \\
\text{2-133}^\alpha \\
+ \text{Bu}_3\text{SnH}
\end{array}
\]

**Scheme 2.31**

Similarly, camphor 2-136 was resistant to the addition of $\text{Bu}_3\text{SnLi}$. This may be due to the steric nature around the carbonyl and/or competing enolization (Scheme 2.32).
Scheme 2.32

Cycloheptanone 2-138 and cyclooctanone 2-139 also failed at forming hydroxystannanes (Figure 2.4).

Figure 2.4   Cycloheptanone 2-138 and cyclooctanone 2-139

This suggested that five and six member rings possess a privileged geometry that allows for the addition of Bu3SnLi. Lactone γ-butyrolactone 2-140 and lactam 1-butylpyrrolidin-2-one 2-141 were also subjected to this methodology, since it seemed that five and six member rings are the ideal ring sizes for the addition of Bu3SnLi (Scheme 2.5).
Figure 2.5  Lactone $\gamma$-butyrolactone 2-140 and lactam 1-butylpyrrolidin-2-one 2-141

Unfortunately, the corresponding hydroxystannanes did not form. This might be due to the electronic state of the carbonyls. Ketones are much more electrophilic than their ester and amide counterparts.

Aliphatic aldehydes were also subjected to this methodology. Isovaleraldehyde 2-143 and hexanal 2-63 formed the corresponding hydroxystannanes very smoothly (Scheme 2.33).

Scheme 2.33
Unfortunately, treatment of these hydroxystannanes with MsCl/Et$_3$N did not produce vinylstannanes but rather unidentified materials, possibly $\alpha$-chlorostannanes 2-147 arising from displacement rather than elimination of the intermediate mesylates (Scheme 2.34).$^{30}$

![Scheme 2.34](image)

Other elimination conditions, such as trifluoromethanesulfonic anhydride (Tf$_2$O)/iPr$_2$NEt (Hünig’s base) were also applied in attempts to provide vinylstannane 2-148 but with no success. Unidentifiable materials were obtained that could possibly contain the dimeric ether stannane 2-149 (Scheme 2.35).

![Scheme 2.35](image)
2.4 Summary

A simple one-pot procedure for the preparation of cyclic and acyclic vinylstannanes from the corresponding ketones was developed. Appropriate ketones that can be used with this method were highlighted. Limitations of this method were highlighted by noting which carbonyl compounds are not compatible. Isolated yields compare very favourably with other methodologies. Reagents and materials used are inexpensive and readily available, while the procedure is operationally straightforward. A simple purification procedure was developed for non-polar hydrocarbon vinylstannanes. This procedure allows for the separation of non-polar vinylstannanes from non-polar Bu$_3$SnH, and is applicable on multigram scale. The route established here for the preparation of vinylstannanes should be very convenient and useful to obtain these important building blocks.
2.5 Experimental

2.5.1 General experimental

All reactions were carried out under argon using flame-dried glassware. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ at 300 MHz and 75 MHz, respectively, unless otherwise noted. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 ev) ionization unless otherwise specified. Couplings to $^{117}$Sn and $^{119}$Sn are reported as averages of the two values. THF was distilled from Na/benzophenone, and acetone was distilled from B$_2$O$_3$. Dichloromethane, triethylamine and diisopropylethylamine (Hünig’s base) were freshly distilled from calcium hydride. Solvent grade chloroform was used in the purification process of vinylstannanes from Bu$_3$SnH contamination. Tributyltin hydride was prepared by reduction of bis(tributyltin)oxide with NaBH$_4$ in ethanol and was distilled (Kugelrohr) before use.\(^{31}\) Samples were checked by $^{13}$C NMR spectroscopy (in C$_6$D$_6$ since Bu$_3$SnH reacts with CDCl$_3$) for the presence of Bu$_3$SnSnBu$_3$ and were re-distilled if necessary.\(^{28}\) Methanesulfonyl chloride was freshly distilled from P$_2$O$_5$ prior to use. Other reagents were purchased from Sigma-Aldrich and used without further purification. Alkynyl ketones \textbf{2-105} and \textbf{2-107} were prepared by reaction of the appropriate alkynyllithium with dimethylacetamide.\(^{32}\) \textit{n}-BuLi was titrated using \textit{N}-benzylbenzamide.\(^{33}\)
2.5.2 General procedure for preparation of vinylstannanes from carbonyl compounds

To a cold (0 °C), stirred solution of diisopropylamine (5 mmol, 1.0 eq) in THF (15 mL) was added $n$-BuLi (1.6 M in hexanes, 5 mmol, 1.0 eq). The solution was stirred at 0 °C for 10 min then Bu$_3$SnH (5 mmol, 1.0 eq) was added and the resulting yellow solution was stirred at 0 °C for an additional 30 min. The solution was then cooled to -78 °C and the ketone (5 mmol, 1.0 eq) was added dropwise. After 10 minutes, Et$_3$N (40 mmol, 8 eq) and MsCl (20 mmol, 4 eq) were added. The reaction mixture was then allowed to warm to rt. After 30 min at rt, hexanes (200 mL) was added and the organic layer was washed with CH$_3$CN (3 x 100 mL). Concentration of the hexanes layer by rotary evaporation provided crude vinylstannanes. Traces of Bu$_3$SnH could be removed by stirring the sample with a small amount (30 mg) of AIBN in CHCl$_3$ (15 mL per gram of crude material) at 40 °C for 4 h followed by flash chromatography on silica gel (10 g/g of crude material). Alternatively, purification could be effected using flash column chromatography on reverse-phase silica gel$^{27,34}$ using 40% CH$_2$Cl$_2$ in CH$_3$CN. In all cases, vinylstannanes were isolated as colorless liquids.
2.5.2.1 1-Tributylstannylecyclohexene (2-33)$^9$

```
SnBu_3
```

Stannane 2-33 was made in 82% isolated yield from ketone 2-22 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.78 (1H, s, $J_{\text{Sn-H}} = 68.9$ Hz), 2.70 – 2.50 (4H, m), 2.14 – 2.04 (4H, m), 1.54 - 0.82 (27H, m).

2.5.2.2 1-Tributylstannylecyclopentene (2-96)$^{35}$

```
SnBu_3
```

Stannane 2-96 was made in 83% isolated yield from ketone 2-92 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.86 (1H, t, $J = 2.1$ Hz, $J_{\text{Sn-H}} = 35.2$ Hz), 2.50 –2.28(2H, m), 2.39 – 2.34 (4H, m), 1.58 - 0.86 (27H, m).
2.5.2.3 4-Tert-butyl-1-tributylstannylcyclohexene (2-98)\textsuperscript{36}

\begin{center}
\includegraphics[width=0.2\textwidth]{snbutylstannylcyclohexene.png}
\end{center}

Stannane 2-98 was made in 81\% isolated yield from ketone 2-97 using the general procedure.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 5.78 (1H, s, J\textsubscript{Sn-H} = 66.8 Hz), 2.31 – 1.65 (7H, m), 1.55 – 0.84 (36H, m); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 140.0, 137.5, 44.1, 33.7, 32.4, 29.4, 29.3, 27.5 (J\textsubscript{Sn-C} = 60.4 Hz), 27.2, 13.8, 8.9 (J\textsubscript{Sn-C} = 326.0 Hz).

2.5.2.4 6-Methyl-1-tributylstannylcyclohexene (2-54)\textsuperscript{37}

\begin{center}
\includegraphics[width=0.2\textwidth]{snbutylstannylcyclohexene.png}
\end{center}

Stannane 2-54 was made in 81\% isolated yield from ketone 2-17 using the general procedure.
$^1$H NMR (300 MHz, CDCl$_3$) \( \delta \) 5.73 (1H, m, \( J_{Sn-H} = 70.2 \) Hz), 2.24(1H, m), 2.00 (2H, m), 1.85 – 1.60 (4H, m), 1.57 - 0.82 (30H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) \( \delta \) 146.9, 137.0, 35.2, 32.0, 30.7, 29.3, 27.5 (\( J_{Sn-C} = 60.4 \) Hz), 23.0, 20.5, 13.8, 9.8 (\( J_{Sn-C} = 339.6 \) Hz).

2.5.2.5 1-Tributylstannyl-3,4-dihydronaphthalene (2-100)

Stannane 2-100 was made in 80% isolated yield from ketone 2-99 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) \( \delta \) 7.11 (3H, m), 6.94 (1H, d, \( J = 7.2 \) Hz), 6.23 (1H, t, \( J = 4.3 \) Hz, \( J_{Sn-H} = 59.6 \) Hz), 2.71 (2H, t, \( J = 7.8 \) Hz), 2.27 (2H, m), 1.55 - 0.84 (27H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) \( \delta \) 140.5, 139.9, 138.7, 136.0, 127.8, 126.4, 126.3, 29.2, 28.2, 27.4 (\( J_{Sn-C} = 65.3 \) Hz), 24.8, 13.8, 10.1 (\( J_{Sn-C} = 326.3 \) Hz); IR (neat) 2871, 2853, 1463, 754 cm$^{-1}$; MS (EI) \( m/\ell \) 420 (M$^+$, 1%), 363(M – nBu, 100%); Anal. Calcd for C$_{22}$H$_{36}$Sn: C, 63.03; H, 8.66. Found: C, 63.00; H, 8.66.
2.5.2.6 1-Tributylstannyl-1-indene (2-102)

![Image of 1-Tributylstannyl-1-indene](image)

Stannane 2-102 was made in 81% isolated yield from ketone 2-101 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.50 (1H, d, $J = 7.2$ Hz), 7.36 (1H, d, $J = 7.4$ Hz), 7.27(1H, t, $J = 7.3$ Hz), 7.17 (1H, t, $J = 7.3$Hz), 6.68 (1H, s, $J_{\text{Sn-H}} = 31.2$ Hz), 3.46 (2H, s), 1.58 – 0.85 (27H,m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 150.0, 145.0, 144.8, 143.9, 126.2, 124.2, 123.6, 122.4, 41.5 ($J_{\text{Sn-C}} = 48.3$ Hz), 29.3,27.4 ($J_{\text{Sn-C}} = 72.4$ Hz), 13.8, 9.5 ($J_{\text{Sn-C}} = 350.2$ Hz ); IR (neat) 2871, 2859, 1604, 1456, 774 cm$^{-1}$; MS(EI) $m/z$ 406 ($M^+$, 0.7%), 349 ($M$ – nBu, 100%); Anal. Calcd for C$_{21}$H$_{34}$Sn: C, 62.25; H, 8.46. Found: C, 62.20; H, 8.26.

2.5.2.7 1-Tributylstannyl-1-phenylethylene (2-104)

![Image of 1-Tributylstannyl-1-phenylethylene](image)

Stannane 2-104 was made in 88% isolated yield from ketone 2-103 using the general procedure.
\[ ^1 \text{H NMR (300 MHz, CDCl}_3 \] \delta 7.31 - 7.16 (5H, m), 6.03 (1H, d, J = 2.4 \text{ Hz}, J_{\text{Sn-H}} = 130.6 \text{ Hz}), 5.42 (1H, d, J = 2.4 \text{ Hz}, J_{\text{Sn-H}} = 60.8 \text{ Hz}), 1.55 - 0.82 (27H, m); ^{13} \text{C NMR (75 MHz, CDCl}_3 \] \delta 154.7, 146.5, 128.3 (2C), 126.8, 126.4 (2C), 126.3, 29.1, 27.4 (J_{\text{Sn-C}} = 60.4 \text{ Hz}), 13.7, 10.3 (J_{\text{Sn-C}} = 350.6 \text{ Hz}).

2.5.2.8 2-Tributylstannyln-\text{dec-1-en-3-yne (2-106)}

\[
\text{n-C}_6\text{H}_{13}-\equiv-\text{SnBu}_3
\]

Stannane 2-106 was made in 91% isolated yield from ketone 2-105 using the general procedure.

\[ ^1 \text{H NMR (300 MHz, CDCl}_3 \] \delta 6.10 (1H, d, J = 3.3 \text{ Hz}, J_{\text{Sn-H}} = 117.8 \text{ Hz}), 5.42 (1H, d, J = 3.4 \text{ Hz}, J_{\text{Sn-H}} = 55.2 \text{ Hz}), 2.33 (2H, t, J = 6.6 \text{ Hz}), 1.55 – 0.85 (38H, m); ^{13} \text{C NMR (75 MHz, CDCl}_3 \] \delta 135.1, 133.9, 95.6, 84.3, 31.3, 28.9, 28.8, 28.5, 27.4 (J_{\text{Sn-C}} = 60.3 \text{ Hz}), 22.5, 19.7, 13.9, 13.6, 10.0 (J_{\text{Sn-C}} = 338 \text{ Hz}); IR (neat) 2856, 1464, 668 cm\(^{-1}\); MS (EI) m/z 426 (M\(^+\), 0.5%), 369 (M – nBu, 100%); Anal. Calcd for C\(_{22}\)H\(_{42}\)Sn: C, 62.13; H, 9.95. Found: C, 61.92; H, 9.89.
2.5.2.9 2-Tributylstannyl-4-trimethylsilylbut-1-en-3-yne (2-108)

\[
\text{(CH}_3\text{)}_3\text{Si} \equiv \text{SnBu}_3
\]

Stannane 2-108 was made in 72% isolated yield from ketone 2-107 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.23 (1H, d, J = 3.3 Hz, $J_{\text{Sn-H}}$ = 112.5 Hz), 5.53 (1H, d, J = 3.3 Hz, $J_{\text{Sn-H}}$ = 54.0 Hz), 1.52 – 0.84 (27H, m), 0.15 (9H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 136.3, 134.7, 108.9, 99.3, 28.9, 27.4 ($J_{\text{Sn-C}}$ = 57 Hz), 13.8, 10.3 ($J_{\text{Sn-C}}$ = 320 Hz), 0.2; IR (neat) 2854, 2109, 842 cm$^{-1}$; MS (EI) $m/z$ 414 (M$^+$, 0.4%), 357 (M – nBu, 100%); Anal. Calcd for C$_{19}$H$_{38}$SiSn: C, 55.21; H, 9.27. Found: C, 55.35; H, 9.50.

2.5.2.10 2-Tributylstannylpropene (2-51)$^{15}$

$\text{SnBu}_3$

Stannane 2-51 was made in 78% isolated yield from ketone 2-50 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.67 (1H, s, $J_{\text{Sn-H}}$ = 138.1 Hz), 5.07 (1H, s, $J_{\text{Sn-H}}$ = 66.0 Hz), 1.95 (3H, s, $J_{\text{Sn-H}}$ = 42.0 Hz), 1.56 - 0.85 (27H, m); $^{13}$C NMR (75 MHz, CDCl$_3$)
δ 150.2, 125.4 (J_{Sn-C} = 28.4 Hz), 29.0 (J_{Sn-C} = 19.9 Hz), 27.3 (J_{Sn-C} = 55.1 Hz), 13.5, 9.0 (J_{Sn-C} = 321 Hz).

2.5.2.11 2-Tributylstannyl-3-methyl-1-butene (2-110)\textsuperscript{15}

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{C} & \quad \text{H} \\
\end{align*}
\]

Stannane \textbf{2-110} was made in 61% isolated yield from ketone \textbf{2-109} using the general procedure.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 5.66 (1H, s, J\textsubscript{Sn-H} = 143.1 Hz), 5.01 (1H, s, J\textsubscript{Sn-H} = 66.0 Hz), 2.46 (1H, septet, J = 6.8 Hz), 1.52 - 0.85 (33H, m); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 162.5, 121.7 (J_{Sn-C} = 28.5Hz), 38.6 (J_{Sn-C} = 42.7 Hz), 29.0 (J_{Sn-C} = 21.0 Hz), 27.3 (J_{Sn-C} = 57.0 Hz), 23.0 (J_{Sn-C} = 14.8 Hz), 13.5, 10.0 (J_{Sn-C} = 315.8 Hz).

2.5.2.12 4-Tributylstannyl-3,6-dihydro-2H-pyran (2-112)\textsuperscript{39}

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{C} & \quad \text{H} \\
\end{align*}
\]
Stannane 2-112 was made in 75% isolated yield from ketone 2-111 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.78 (1H, m, J$_{\text{Sn-H}}$ = 64.3 Hz), 4.11 (2H, m), 3.74 (2H, t, J = 5.3 Hz), 2.24 (2H, m), 1.55 - 0.84 (27H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 137.7, 135.9 (J$_{\text{Sn-C}}$ = 18.0 Hz), 66.7 (J$_{\text{Sn-C}}$ = 49.7 Hz), 64.6 (J$_{\text{Sn-C}}$ = 27.7 Hz), 31.6 (J$_{\text{Sn-C}}$ = 27.2 Hz), 29.0 (J$_{\text{Sn-C}}$ = 19.9 Hz), 27.2 (J$_{\text{Sn-C}}$ = 54.7 Hz), 13.6, 8.7 (J$_{\text{Sn-C}}$ = 325.4 Hz).

2.5.2.13 4-Tributylstannyl-3,6-dihydro-2H-thiopyran (2-114)

\[
\begin{array}{c}
\text{SnBu}_3 \\
\text{S}
\end{array}
\]

Stannane 2-114 was made in 79% isolated yield from ketone 2-113 using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.90 (1H, m, J$_{\text{Sn-H}}$ = 66.9 Hz), 3.11(2H, m), 2.65 (2H, t, J = 5.6 Hz), 2.43 (2H, m), 1.48 - 0.82 (27H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.9 (J$_{\text{Sn-C}}$ = 395.9Hz), 132.4 (J$_{\text{Sn-C}}$ = 25.5 Hz),31.5 (J$_{\text{Sn-C}}$ = 35.2 Hz), 28.9 (J$_{\text{Sn-C}}$ = 19.7 Hz), 27.3 (J$_{\text{Sn-C}}$ = 55.5 Hz),26.4(J$_{\text{Sn-C}}$ = 58.1 Hz), 25.1 (J$_{\text{Sn-C}}$ = 33.4 Hz), 13.6, 8.8 (J$_{\text{Sn-C}}$ = 323.0 Hz).
2.5.2.14 1-Tert-butoxycarbonyl-4-tributylstanny1,2,3,6-tetrahydropyridine (2-12)\(^{39}\)

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{N} \\
& \quad \text{Boc}
\end{align*}
\]

Stannane 2-12 was made in 80% isolated yield from ketone 2-115 using the general procedure.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.69 (1H, s, \(J_{\text{Sn-H}} = 63.0\) Hz), 3.86 (2H, s), 3.40 (2H, t, \(J = 5.4\) Hz), 2.22 (2H, s), 1.42 (9H, s), 1.52 - 0.82 (27H, m); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 154.8, 138.7, 133.4, 79.1, 45.1, 39.8, 39.0, 31.5, 28.9 (\(J_{\text{Sn-C}} = 19.9\) Hz), 28.3, 27.2 (\(J_{\text{Sn-C}} = 54.4\) Hz), 13.5, 8.9 (\(J_{\text{Sn-C}} = 325.5\) Hz).

2.5.3  Addition of \(\text{Bu}_3\text{SnLi}\) to 2-methylcyclohexanone 2-17

To examine the stereochemistry of addition of \(\text{Bu}_3\text{SnLi}\) to ketone 2-17, an experiment was carried out according to the general procedure described earlier but saturated aqueous NH\(_4\)Cl was added to quench the reaction instead of MsCl/Et\(_3\)N. The resulting unstable hydroxystannanes were isolated after standard aqueous workup and immediately treated with excess MOMCl/i-Pr\(_2\)NEt. Examination of the \(^1\)H NMR spectrum of the crude reaction mixture indicated a 95:5 mixture of 2 diastereomers. These diastereomers were readily separated by flash chromatography on silica gel. The major, more polar (\(R_f = 0.38,\) hexanes-ether, 10:1) isomer was assigned as the “axial”
isomer based on data previously reported for the Bu$_3$SnLi adducts to 4-\textit{t}-butylcyclohexanone (2-97). Of particular significance is $^3$J$_{\text{Sn-C}}$ for C$_3$ which is $\sim$0 when the Bu$_3$Sn group is axial and $\sim$40 Hz when the Bu$_3$Sn group is equatorial, values consistent with a Karplus relationship.

2.5.3.1 \textit{Axial-tributyl(1-(methoxymethoxy)-2-methylcyclohexyl)stannane} (2-121)

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

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.70, 4.67 (2H, AB quartet, $J_{\text{AB}}$ = 6.9 Hz), 3.34 (3H, s), 2.18 (1H, br d, $J$ = 12.2 Hz), 1.73-0.85 (7H, m), (27H, m), 0.96 (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 93.9 (C$_1$, $J_{\text{Sn-C}}$ = 435.4 Hz), 92.2 ($J_{\text{Sn-C}}$ = 24.7 Hz), 55.4 (OCH$_3$), 41.6 (C$_2$, $J_{\text{Sn-C}}$ = 26.0 Hz), 36.8 (C$_6$, $J_{\text{Sn-C}}$ = 31.7 Hz), 32.6 (C$_3$, $J_{\text{Sn-C}}$ $\sim$ 0 Hz), 29.3 ($J_{\text{Sn-C}}$ = 19.5 Hz), 27.7 ($J_{\text{Sn-C}}$ = 59.4 Hz), 25.4 (C$_5$, $J_{\text{Sn-C}}$ $\sim$ 0 Hz), 24.9 (C$_4$, $J_{\text{Sn-C}}$ = 7.5Hz) 20.2 ($J_{\text{Sn-C}}$ = 19.5 Hz), 13.6, 11.3 ($J_{\text{Sn-C}}$ = 282.7 Hz).

The minor, less polar ($R_f$ = 0.49, hexanes-ether, 10:1) isomer was assigned as the “equatorial” isomer.
2.5.3.2 \textit{Equatorial-tributyl(1-(methoxymethoxy)-2-methylcyclohexyl)stannane}

\textbf{(2-122)}

\[
\begin{array}{c}
\text{OMOM} \\
\begin{array}{c}
\text{SnBu}_3 \\
3 \quad 2 \quad 5 \quad 6
\end{array}
\end{array}
\]

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.66, 4.57 (2H, AB quartet, $J_{AB} = 6.6$ Hz), 3.36 (3H, s), 2.26 (1H, br d, $J = 11.5$ Hz), 1.65-0.80 (7H, m), (27H, m), 0.94 (3H, d, $J = 6.6$Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 94.7 ($J_{Sn-C} = 19.2$ Hz), 85.8 ($C_1$), 55.9, 41.1 ($C_2$), 36.2 ($C_6$, $J_{Sn-C} = 21.7$ Hz), 29.6 ($C_3$, $J_{Sn-C} = 34.7$ Hz), 29.4 ($J_{Sn-C} = 19.3$ Hz), 27.7 ($J_{Sn-C} = 57.4$ Hz), 26.5 ($C_4$), 20.6 ($J_{Sn-C} = 19.5$ Hz), 20.4 ($C_5$, $J_{Sn-C} = 40.0$ Hz), 13.6, 10.5 ($J_{Sn-C} = 280.9$ Hz).
Chapter 3

The Use of Phosphine Ligands to Control the Regiochemistry of Pd-Catalyzed Hydrostannations of 1-Alkynes: Synthesis of (E)-1-Tributylstannyl-1-alkenes

3.1 Introduction

3.1.1 General

Acyclic vinylstannanes have made great impact on organic chemistry, and have been used in a wide variety of synthetic applications.\(^1\) As a result, numerous methods for preparing vinylstannanes, particularly \(E\)-vinylstannanes have been developed.\(^1\)

The most common way of forming vinylstannanes is the overall addition of \(\text{Bu}_3\text{SnH}\) to an alkyne (Scheme 3.1), which is accomplished in several ways.

\[
\begin{align*}
\text{R} & \quad \text{Bu}_3\text{SnH} \quad \text{H} \\
\text{R} & \quad \text{SnBu}_3
\end{align*}
\]

Scheme 3.1

The first method is radical induced hydrostannation, which is the oldest and most reliable method for preparing vinylstannanes.\(^2\) The second method involves metal-catalyzed hydrostannation, which has also enjoyed wide use. The third method consists of
stannylmetallation followed by protonation. These methods are discussed in greater
detail below.

The addition of Bu$_3$SnH to terminal alkynes can provide three possible isomers (Figure 3.1).

![Figure 3.1](image)

Three possible isomers produced by hydrostannation of a terminal alkyne

The ability to control the reaction to produce a sole product has been a challenge for
organic chemists. Factors influencing selectivity under free-radical hydrostannation are
better understood than the metal-catalyzed hydrostannation, which has limited the
advancement of this reaction.

3.1.2 Synthesis of E-vinylstannanes under free-radical hydrostannation

Free-radical hydrostannation typically produces a mixture of stereo- and regioisomers. The outcome is usually controlled by the stability of the intermediate radical that gives
rise to the corresponding vinylstannanes. These reactions require a catalytic amount of a radical initiator such as 2,2’-azobisisobutyronitrile (AIBN) (Scheme 3.2).

Scheme 3.2

Tributylstannyl radical adds across the triple bond in an anti fashion (Scheme 3.2). The tin radical addition on terminal alkynes forms two possible radical intermediates. The stabilization of radicals is similar to carbocations; therefore, the more substituted stannyl radical intermediate 3-5 is favoured. The stability of this intermediate translates into higher selectivity for cis-vinylstannane 3-4 as the kinetic product.\(^1\)

To obtain trans-vinylstannane 3-2, longer reaction times with excess Bu\(_3\)SnH are required.\(^4\) It has been shown that the Bu\(_3\)Sn radical catalyzes the rearrangement of the
cis-vinylstannane to the corresponding trans-vinylstannane (Scheme 3.3).\textsuperscript{5} This is believed to proceed by the addition of the Bu$_3$Sn radical to the double bond to form intermediate 3-7.

![Scheme 3.3](image)

Elimination of Bu$_3$Sn radical, from intermediate 3-7, leads to trans-vinylstannane 3-2. Compound 3-2 is the thermodynamic vinylstannane. Regio-, chemo- and stereoselectivity of radical reactions can be predicted by radical-stabilizing effects,\textsuperscript{6} steric effects,\textsuperscript{2,7} and polar effects.\textsuperscript{8}

Jung and Light demonstrated the importance of the number of equivalents used of Bu$_3$SnH with respect to the alkyne and its effect on the regio- and stereoselectivity (Scheme 3.4).\textsuperscript{9}
Scheme 3.4

Use of excess alkyne with respect to Bu$_3$SnH resulted in \textit{cis}-vinylstannane 3-10 being the major isomer.$^9$ On the other hand, when a slight excess of Bu$_3$SnH was used \textit{trans}-vinylstannane 3-11 was the major isomer. In both trials, \textit{geminal}-vinylstannane 3-9 was a minor component.$^9$

Free-radical hydrostannation of alkynylboranes has been reported by Lhermitte and Carboni (Scheme 3.5).$^{10}$

Scheme 3.5
According to the report, boryl substituents have a decisive role in the course of these reactions. Only attack at the $\beta$-position, with respect to the boron, was observed (Table 3.1).\textsuperscript{10}

**Table 3.1** Free-radical hydrostannation of alkynylboranes.\textsuperscript{10}

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>method\textsuperscript{a}</th>
<th>(Z)</th>
<th>(E)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( ^{\equiv} - B - ^{\equiv} ) ( \text{NiPr}_2 )</td>
<td>A</td>
<td>&lt;2</td>
<td>&gt;98</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>( ^{\equiv} - B - ^{\equiv} ) ( \text{NiPr}_2 )</td>
<td>B</td>
<td>95</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>( ^{\equiv} - B - ^{\equiv} ) ( \text{NCy}_2 )</td>
<td>A</td>
<td>7</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>( ^{\equiv} - B - ^{\equiv} ) ( \text{NCy}_2 )</td>
<td>B</td>
<td>&gt;98</td>
<td>&lt;2</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>( ^{\equiv} - B - ^{\equiv} ) ( \text{Ph} - \text{NiPr}_2 )</td>
<td>B</td>
<td>&gt;98</td>
<td>&lt;2</td>
<td>80</td>
</tr>
</tbody>
</table>

\textsuperscript{a} A – Toluene, 90 °C, AIBN. B – Toluene, 0 °C, hv

Additions are highly stereoselective with the less stable $Z$-isomers being produced in highly pure forms at low temperature. The exclusive formation of $Z$-isomers probably resulted from the steric hindrance of $\text{Bu}_3\text{Sn}$ that prevents the $\text{syn}$ addition of the hydrogen on the $\pi$-radical \textbf{3-18} and on the $\sigma$-radical and \textbf{3-20} (Scheme 3.6).\textsuperscript{11}
Scheme 3.6

Higher temperatures promoted isomerisation of $Z$-isomers to the more stable $E$-isomers.$^{10}$

Dodero et al. have explored the use of a bulky organic tin hydride, trineophyltin hydride, and its effect on stereochemistry of free-radical hydrostannations (Table 3.2).$^{12}$

**Table 3.2** Trineophyltin hydride radical addition to terminal alkynes.$^{12}$

$$\begin{align*}
R &= \text{NeoPhyl}_2\text{SnH} \\
\text{cat. AIBN} &\rightarrow \text{3-21} + \text{3-22}
\end{align*}$$

NeoPhyl = PhMe$_2$CCH$_2$
<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>method&lt;sup&gt;a&lt;/sup&gt;</th>
<th>cis</th>
<th>trans</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph≡</td>
<td>A, B or C</td>
<td>0</td>
<td>100</td>
<td>99-100</td>
</tr>
<tr>
<td></td>
<td>3-23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>HO≡</td>
<td>A, B or C</td>
<td>100</td>
<td>0</td>
<td>49-69</td>
</tr>
<tr>
<td></td>
<td>3-8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>A</td>
<td>34</td>
<td>66</td>
<td>87&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>B</td>
<td>91</td>
<td>9</td>
<td>65&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>C</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>3-24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>The reaction was carried out under a nitrogen atmosphere; ratio hydride/alkyne = 1:1. Method A – AIBN 0.01 equiv., 90 °C, neat. Method B – AIBN 0.01 equiv., 90 °C, toluene. Method C – UV radiation, toluene.

<sup>b</sup>Isolated yield of both isomers combined.

High regioselectivity was observed as only β-addition products (cis and trans) were obtained (Table 3.2).<sup>12</sup> Depending on the alkynyl substrate and the method used, stereoselectivity can be influenced greatly.<sup>12</sup>

A highly-selective free-radical hydrostannation that provides cis-vinylstannanes from propargyl alcohols has been reported.<sup>13</sup> A wide variety of propargyl alcohols and ethers have been screened, thus illustrating the generality of this method (Table 3.3).<sup>13</sup>
Table 3.3  Free-radical hydrostannation of propargyl alcohols.\textsuperscript{13}

\[
\begin{align*}
\text{HO} & \text{C} & \text{SnBu}_3 & \text{Bu}_3\text{Sn} \\
\begin{array}{cc}
\text{HO} & \text{C} \\
\text{R}^1 & \text{R}^2
\end{array}
\end{align*}
\]
Terminal alkynes bearing a hydroxyl group at a more remote position were used also for the present hydrostannation, but low to moderate trans stereoselectivity was observed and lower reactivity to Bu₂SnClH\textsuperscript{13}.

The mechanism of this reaction involves a radical chain process in which stannate complex 3-32 is initially formed. Anion radical 3-33 generated from 3-32 reacts with propargyl alcohol 3-25 to give vinyl radical intermediate 3-34\textsuperscript{13}. Subsequent elimination of LiCl and internal coordination by the hydroxyl oxygen converts 3-34 into a neutral vinyl radical 3-36 (Scheme 3.7).\textsuperscript{13}

\[
\begin{align*}
\text{Bu}_2\text{SnClH} + \text{LiCl} &\rightarrow [\text{Bu}_2\text{SnCl}_2\text{H}]^- \text{Li}^+ \\
3-32 \\
\text{R}^- &\rightarrow -\text{RH (R}^\text{=} = 3-36 \text{ or other radical)} \\
3-33 \\
3-25 &\rightarrow \text{Cl}_2\text{Bu}_2\text{Sn}^- \text{Li}^+ \\
3-35 \\
3-34 &\rightarrow -\text{LiCl} \\
3-36
\end{align*}
\]

\textbf{Scheme 3.7}
Kinetic and thermodynamic reasons favour the formation of intermediate 3-34 over 3-35; thus, providing high regioselectivities.\textsuperscript{13}

Free-radical hydrostannation have been implemented in many syntheses of natural products;\textsuperscript{14,15} a few representative cases are highlighted below.

Cliff and Pyne used free-radical hydrostannation toward the total synthesis of 2-acetyl-4(5)-(1,2,4-trihydroxybutyl)imidazole (THI) 3-43 (Scheme 3.8).\textsuperscript{14}
Free-radical hydrostannation afforded trans- and cis-vinylstannanes in a 9:1 ratio. The stannanes were not isolated but taken directly to the next reaction, the Stille coupling. Separation occurred after the Stille coupling, as traces of cis-coupling product was
observed due to its slower coupling rate, relative to the trans substrate.\textsuperscript{14} THI 3-43 has been found to depress blood lymphocyte counts in both mice and rats.\textsuperscript{16}

Bansal et al. utilized free-radical hydrostannation to provide trans-vinylstannane 3-38. Reactive cuprate 3-44 was obtained from trans-vinylstannane 3-38 (Scheme 3.9).\textsuperscript{15} Free-radical hydrostannation of propargyl alcohol 3-8 afforded trans-vinylstannane 3-11 in 35\% isolated yield. Vinylstannane 3-11 was treated with TBSCI to give ether 3-38, which was then converted to highly reactive copper intermediate 3-44 via transmetallation with BuLi and CuCN (Scheme 3.9).
Total synthesis of prostaglandin analogue **3-45** was achieved via coupling of cuprate **3-44** and an alkyl iodide.\(^\text{15}\)
3.1.3 Metal-catalyzed hydrostannation

Metal-catalyzed hydrostannation usually provides two possible isomers. The reaction proceeds with syn addition across an alkyne, which produces trans and geminal vinylstannanes 3-2 and 3-3 (Scheme 3.10).

Scheme 3.10

The outcome of the regiochemistry is controlled by many factors. The choice of catalyst can have a drastic effect on the outcome. Palladium is the catalyst of choice for hydrostannation of terminal alkynes if trans-vinylstannanes are desired (Table 3.4).\(^\text{17}\)

Table 3.4 Palladium-catalyzed hydrostannation.\(^\text{17}\)
<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>trans</th>
<th>geminal</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="3-46" alt="HO-alkyne" /></td>
<td>67</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td><img src="3-47" alt="N-alkyne" /></td>
<td>68</td>
<td>32</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="3-48" alt="TBSO-alkyne" /></td>
<td>72</td>
<td>28</td>
<td>94&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="3-49" alt="alkyne" /></td>
<td>65</td>
<td>35</td>
<td>98&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="3-50" alt="alkyne" /></td>
<td>100</td>
<td>0</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated as a mixture of isomers.

As illustrated in Table 3.4, <i>trans</i>-vinylstannane is the major isomer when palladium is utilized as the catalyst.

Palladium-catalyzed hydrostannation is not very well understood, and the reaction mechanism is still debated,<sup>18</sup> and there are two principal proposed pathways (Scheme 3.11 & 3.12). The first route involves hydro-palladation during the catalytic cycle. Initially, palladium (0) oxidatively inserts into the tin-hydrogen bond to become palladium (II). Palladium alkyne complex <b>3-53</b> formation is followed by the hydro-palladation on to the triple bond to form intermediate <b>3-54</b> (Scheme 3.11).
Reductive elimination of palladium from intermediate 3-54 affords vinylstannane 3-2.

The second possible catalytic cycle involves stannyl-palladation. Similar to the hydro-palladation route, complex 3-53 is formed. This complex then undergoes a stannyl-palladation to afford intermediate 3-55. Palladium reductively eliminates from intermediate 3-55 to provide the same vinylstannane (3-2) obtained through the hydro-palladation pathway (Scheme 3.12).
One example of the hydro-palladation pathway was reported by Lautens et al. who developed a procedure for the preparation of methylenecyclopentanes 3-59, via hydrostannylation cyclization (Scheme 3.13). The reaction proceeded by hydro-palladation of the triple bond of enyne 3-56 to produce intermediate 3-57. Following the initial hydro-palladation step, intermediate 3-57 undergoes a carbo-palladation to form cyclic intermediate 3-58. This intermediate then reductively eliminates to afford compound 3-59 (Scheme 3.13).
One can assume there are two competing pathways, as shown in the following scheme. Hydro-palladation leads to complex 3-58, while stannyl-palladation leads to vinylstannane complex 3-60 (Scheme 3.14).

The product that was formed at the end of this reaction was the product derived from intermediate 3-58.
One can also argue that initial stannyl-palladation of the double bond followed by cyclization can lead to the same final product 3-59 (Scheme 3.15).

![Scheme 3.15](image)

This argument is not valid since alkynes are more reactive toward palladium-catalyzed hydrostannation than alkenes.19 This was demonstrated by obtaining an undesired side product when elongating the triple bond tether (Scheme 3.16).19 Side product 3-64 was a result of a palladium-catalyzed hydrostannation of the triple bond. A longer alkyne tether, four carbons rather than three carbons, did not allow for the cyclization step to occur, but halted at intermediate 3-64 (Scheme 3.16).
Side product 3-64 provides an insight into this particular reaction and evidence for the hydro-palladation pathway.

Another metal that is widely applied for metal-catalyzed hydrostannations is molybdenum. Molybdenum is utilized as a catalyst if the *geminal*-vinylstannane is the desired isomer (Table 3.5).

**Table 3.5** Molybdenum-catalyzed hydrostannation (MoBI$_3$).\(^{20}\)

\[
\begin{align*}
\text{R} \equiv \text{H} & \quad \xrightarrow{\text{Bu}_3\text{SnH}} \quad \text{MoBI}_3 & \quad \text{H} - \text{SnBu}_3 \\
3-1 & \quad + & \quad 3-2 & \quad + & \quad 3-3
\end{align*}
\]

\(\text{Bl}_3 = (\text{CO})_3(\text{CNBu})_3\)  
*trans* isomer  
*geminal* isomer
<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>trans</th>
<th>geminal</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO</td>
<td>11</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>TBDPSO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>90</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>95</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>92</td>
<td></td>
<td>98</td>
</tr>
</tbody>
</table>

$^a$ Isolated total yield of both regioisomers.

As shown in Table 3.5, the geminal isomer is the major regioisomer formed. Bulky MoBI$_3$ catalyst favours the selectivity toward geminal isomers.$^{20}$ The proposed mechanism for this reaction proceeds initially by the dissociation of several isocyanide ligands, opening coordination sites for oxidative addition (Scheme 3.17).$^{20}$
Molybdenum oxidatively inserts into the tin hydride bond and coordinates with the alkyne. Stannyl-molybdenation of alkyne 3-1 affords intermediate 3-68. The regioselectivity involved in forming intermediate 3-68 was determined by steric factors. The more sterically demanding molybdenum fragment was added to the less hindered side of the alkyne. Reductive elimination of molybdenum from 3-68 afforded vinylstannane 3-3.²⁰

Other metals such as rhodium, nickel, cobalt, zirconium, platinum and ruthenium have been applied as well (Table 3.6).¹
Table 3.6  Metal-catalyzed hydrostannation of phenylacetylene.\textsuperscript{1}

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{Bu}_3\text{SnH} \text{ cat.}} \text{Bu}_3\text{Sn} & \text{Bu}_3\text{Sn} & + & \text{Bu}_3\text{Sn} \\
3-23 & & 3-70 & + & 3-71 & + & 3-72 \\
    & \text{geminal isomer} & \text{trans isomer} & \text{cis isomer} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>geminal</th>
<th>trans</th>
<th>cis</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(PPh\textsubscript{3})\textsubscript{3}Cl</td>
<td>88</td>
<td>12</td>
<td>0</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>Ni(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}</td>
<td>45</td>
<td>50</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Pt(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}</td>
<td>34</td>
<td>52</td>
<td>14</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>Co(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}</td>
<td>43</td>
<td>48</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Ru(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}</td>
<td>11</td>
<td>42</td>
<td>47</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>ZrCl\textsubscript{4}</td>
<td>0</td>
<td>5</td>
<td>95</td>
<td>73</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated total yield of all isomers.

Rhodium catalyst (entry 1) provided good selectivity for \textit{geminal}-vinylstannane 3-70.\textsuperscript{21} Nickel, cobalt, ruthenium and platinum provided poor selectivities overall.\textsuperscript{21} The presence of \textit{cis}-vinylstannane (entries 2-5) is attributed to a spontaneous free-radical pathway.\textsuperscript{21} Zirconium catalyst provided \textit{cis}-vinylstannane 3-72 in excellent regio- and stereoselectivity.\textsuperscript{22} The mechanism of this reaction is claimed to proceed \textit{via} anti-hydrostannation pathway (Scheme 3.18).\textsuperscript{22}
Scheme 3.18

It is assumed for this mechanism that ZrCl$_4$ coordinates to the triple bond to produce complex 3-73.$^{22}$ Bu$_3$SnH would provide a hydride that would attack an electron deficient triple bond from the opposite side to ZrCl$_4$ to produce stereoselectively pentacoordinate zirconium species 3-74.$^{22}$ Zirconium intermediate 3-74 would capture Bu$_3$Sn cation 3-75 with retention of geometry to give cis-vinylstannane and ZrCl$_4$.$^{22}$

There are many tin hydride reagents that have been applied to metal-catalyzed hydrostannations.$^1$ Me$_3$SnH has been used but its volatility and toxicity make it unfriendly for use. Ph$_3$SnH has also been used but the vinylstannyl product is not very useful, since phenyl groups are transferable. By far, Bu$_3$SnH is the most commonly used reagent for any hydrostannation due to its ease of use and preparation and its reactivity.$^1$ In terms of selectivity, none of the reagents have any advantages.
Stoichiometry of the tin hydride reagent and metal catalyst in metal-catalyzed hydrostannation does not have an effect on the selectivity but rather on the conversion of the reaction. In general, catalytic loading of catalysts between 0.5-10 mol % and tin hydride loading of 110-150 mol % are applied. Slight excess of tin hydride is needed to reduce the catalyst into the “active” form, and to counteract the reductive coupling of tin hydride that produces hydrogen and distannane.\(^1\)

Recently, Gallagher and Maleczka Jr. demonstrated the ability to regenerate \(\text{Me}_3\text{SnH}\) \textit{in situ} from \(\text{Me}_3\text{SnCl}\) with poly(methylhydrosiloxane) (PMHS) for a one-pot hydrostannation/Stille coupling sequence of terminal alkynes (Scheme 3.19).\(^23\)

![Scheme 3.19](image)

The ability to use a catalytic amount of tin is attractive and could lead to greater use of metal-catalyzed hydrostannation reactions.

The effect of solvent on the selectivity in metal-catalyzed hydrostannation of disubstituted alkynes was explored by Liron \textit{et al.} (Table 3.7).\(^24\)
Table 3.7  Examining the effect of solvent on the regioselectivity of palladium-catalyzed hydrostannation.\textsuperscript{24}

\[
\text{Ph} = \text{Sn} \quad \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \quad \text{solvent} \quad \text{Bu}_3\text{SnH} \\
\begin{array}{c}
\text{Ph} = \text{C} = \text{O} \\
\text{3-78} \\
\text{Ph} = \text{Sn} = \text{Bu}_3 \\
\text{3-79} \\
\text{Ph} = \text{Sn} = \text{Bu}_3 \\
\text{3-80}
\end{array}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>3-79\textsuperscript{b}</th>
<th>3-80\textsuperscript{b}</th>
<th>conversion\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>33</td>
<td>67</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>45</td>
<td>55</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexane</td>
<td>52</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>Et\textsubscript{2}O</td>
<td>65</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>80</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>TMU</td>
<td>77</td>
<td>23</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>AcOEt</td>
<td>67</td>
<td>33</td>
<td>100</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conversion measure by \textsuperscript{1}H NMR analysis and is based on remaining alkyne.
\textsuperscript{b} Regioselectivity determined on the crude material by \textsuperscript{1}H NMR.

A modest change in regioselectivity was observed upon increasing the solvent polarity.

There are contradicting reports regarding the substituent ligands on the metal, with various steric bulk, and their effect on regioselectivity.\textsuperscript{17,20}
In 1990, Zhang et al. stated “attempts to modify the regiochemistry by changing the catalyst and, in particular, the steric bulk of the ligands, met with no success.” The bulky complexes they screened are shown below (Figure 3.2).

![Bulky complexes](image)

**Figure 3.2** Bulky ligands used for metal-catalyzed hydrostannation

However, in 2000 a report by Kazmaier et al. suggests that steric bulk around the molybdenum catalyst improved the regioselectivity, unlike the results obtained by Zhang et al. (Table 3.8).
Table 3.8 Bulky ligands and their effect on regioselectivity of molybdenum-catalyzed hydrostannation.\textsuperscript{17,20}

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>catalyst</th>
<th>trans</th>
<th>geminal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}</td>
<td>(CH\textsubscript{3}CN\textsubscript{2}Mo(CO)\textsubscript{2}(\pi-\text{allyl})Br\textsuperscript{−}</td>
<td>3-85</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>2\textsuperscript{b}</td>
<td>(tBuNC\textsubscript{2}Mo(CO)\textsubscript{3}</td>
<td>3-86</td>
<td>11</td>
<td>89</td>
</tr>
<tr>
<td>3\textsuperscript{a}</td>
<td>(CH\textsubscript{3}CN\textsubscript{2}Mo(CO)\textsubscript{2}(\pi-\text{allyl})Br\textsuperscript{−}</td>
<td>3-87</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>4\textsuperscript{b}</td>
<td>(tBuNC\textsubscript{2}Mo(CO)\textsubscript{3}</td>
<td>3-88</td>
<td>5</td>
<td>95</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Results from Zhang et al.  
\textsuperscript{b} Results from Kazmaier et al.

Kazmaier et al. indicated that the steric bulk around the molybdenum catalyst could be contributing to the selectivities observed.\textsuperscript{20}

According to literature reports, the nature of the substrate has the most profound effect on the regioselectivity.\textsuperscript{1,17,18}

88
Scheme 3.20 illustrates the effect that the steric bulk of the substituent can have on regioselectivity. Rubin et al. illustrated how polarization of the triple bond can affect the regiochemistry of the palladium-catalyzed hydrostannation (Table 3.9).25

**Table 3.9** Palladium-catalyzed hydrostannation of monosubstituted tolanes.25
| entry | alkyne | α-product<sup>a</sup> | β-product<sup>a</sup> |
|-------|--------|----------------|----------------|  |
| 1     | ![alkyne](image) | 84 | 16 |
| 2     | ![alkyne](image) | 78 | 22 |
| 3     | ![alkyne](image) | 39 | 61 |

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of crude reaction mixtures.

The regiochemistry of hydrostannation was entirely governed by the polarization of the triple bond, where the steric effects are negligible in para-substituted tolanes<sup>25</sup>. Tolanes bearing electron-withdrawing groups (entries 1, 2) yielded α-vinylstannanes as the major product, while tolanes bearing electron donating (entry 3) yielded β-vinylstannanes as the major product.

Heteroatom-metal chelation has also been shown to direct the regiochemistry of palladium-catalyzed hydrostannation reactions (Scheme 3.21)<sup>26,27</sup>. 
Hydrostannation of \( E \)-isomer 3-100 gave \( \text{trans} \)-vinylstannane 3-102 as the major product while \( Z \)-isomer gave \( \text{geminal} \)-vinylstannane 3-105 as the major product. Thus, the selectivity of the vinylstannyl isomer obtained depended on the location of the oxygen atom. Betzer et al. suggest a stabilizing complex (3-104) between palladium and oxygen atom to explain the regioselectivity observed in favour of the \( \text{geminal} \)-vinylstannane in the case of \( Z \)-isomer 3-103.\(^{27}\)

There are many examples of metal-catalyzed hydrostannation in total synthesis of natural product.\(^{28,29}\) A few representative cases are highlighted below.

---

**Scheme 3.21**

\[ \text{OH} \quad \text{Bu}_3\text{SnH} \quad \text{Pd(PPh}_3)_2\text{Cl}_2 \quad \text{OH} \]

3-100

3-101

3-102

major isomer

3-103

3-104

stabilized Pd-complex

3-105

major isomer
Applications of metal-catalyzed hydrostannations in total synthesis include the preparation of a photochromic agonist of ionotropic glutamate receptor 3-110 (Scheme 3.22). Glutamate receptors have been applied to control the active concentration of neurotransmitters in a spatially and temporally precise manner, which has revolutionized the study of the central nervous system (CNS).

![Scheme 3.22](image-url)

The synthesis was made feasible by palladium-catalyzed hydrostannation of terminal alkyne 3-106 to provide vinylstannane 3-107. Palladium-catalyzed Stille coupling of vinylstannane 3-107 with iodoazobenzene 3-108 afforded N-Boc protected azobenzene 3-110.
pyroglutamate 3-109, which upon hydrolysis of the amide and deprotection of the nitrogen afforded the target product 3-110. 28

The nicandrenone (NIC) family are structurally complex, steroid-derived natural products, 29 whose biological activities include insect repellent and antifeedant properties. 29 Rhodium-catalyzed hydrostannation was utilized to synthesize vinylstannane 3-112 (Scheme 3.23), 29 that was required for a challenging Stille coupling reaction with the complex perfluorononylsulfonate 3-114. The coupling product 3-113 contained the required skeleton to synthesize the final structure 3-115 in a modest-yielding process. 29
Scheme 3.23
3.1.4 Stannyldemetallation

Stannylcupration of alkynes to provide vinylstannanes is the most common method of the stannyldemetallation methodologies.27 Piers and Morton demonstrated how stannylcupration of $\alpha,\beta$-unsaturated esters provides vinylstannanes in high selectivities and good yields (Scheme 3.24).30

![Scheme 3.24](image)

Since addition of tin occurs only in the $\beta$ position, stannylcupration of acetylene 3-116 followed by protonation affords two possible isomeric vinylstannanes (3-117 and 3-118, Scheme 3.24).30 Depending on conditions, $trans$ or $cis$ isomers can be obtained in high selectivities and good yields (Table 3.10).
Table 3.10  Stannylcupration of α,β-unsaturated ester 3-116 with cuprate 3-119.\textsuperscript{30}

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>3-117</th>
<th>3-118</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cuprate 3-119 (2 equiv), MeOH (1.7 equiv. added with cuprate) -100 °C, 15 min; -78 °C, 3 h</td>
<td>1</td>
<td>99</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>1. cuprate 3-119 (1.2 equiv), -78 °C, 15 min; -48 °C, 4 h 2. MeOH protonation at work-up</td>
<td>98</td>
<td>2</td>
<td>76</td>
</tr>
</tbody>
</table>

Piers and Morton explain the stereoselectivities observed by kinetic and thermodynamic arguments. At low temperatures (-100 °C), the kinetic intermediate 3-120 is reasonably stable and isomerizes very slowly to the thermodynamic intermediate 3-121 (Scheme 3.25).\textsuperscript{30}

![Scheme 3.25](image)

Scheme 3.25

At relatively higher temperatures (-78 °C), intermediate 3-120 could isomerize to intermediate 3-121, but this process can be minimized if a proton source is present;
protonation of 3-120 is faster than isomerisation to 3-121.\textsuperscript{30} If the reaction temperature is allowed to rise to -48 °C in the absence of a proton source, equilibration takes place, with equilibrium largely favouring the thermodynamic intermediate 3-121.\textsuperscript{30}

Piers et al. illustrated the effect of the stannylcuprate reagent on stereoselectivity (Table 3.11).\textsuperscript{31}

**Table 3.11** Stannylcupration with various cuprate reagents and their effect on stereoselectivity.\textsuperscript{31}

<table>
<thead>
<tr>
<th>entry</th>
<th>cuprate reagent\textsuperscript{a}</th>
<th>3-123</th>
<th>3-124</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhS(Me$_3$Sn)CuLi, 3-125</td>
<td>98</td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>[Me$_3$SnCuC≡C-C(Me)$_2$OMe]Li, 3-126</td>
<td>1</td>
<td>99</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Me$_3$SnCu•LiBr•Me$_2$S, 3-127</td>
<td>1</td>
<td>99</td>
<td>68</td>
</tr>
</tbody>
</table>

\textsuperscript{a}1.3 equiv. reagent, -48 °C, 4 h.

\(\alpha,\beta\)-Unsaturated ester 3-122 was subject to different stannylcuprate reagents under the same condition. Under thermodynamic conditions, reagent 3-125 was consistent with previous results and provided the thermodynamic vinylstannane 3-123.\textsuperscript{3,30} Under the
same conditions, reagents 3-126 and 3-127 provided the opposite stereoisomer in high selectivities, thus illustrating the effect a reagent can have on stereoselectivity.

The effect of the nature of the substrate was also examined with respect to stereoselectivity (Table 3.12).

**Table 3.12** Stannylcupration of different $\alpha,\beta$-unsaturated esters and their effect on stereoselectivity.\(^{31}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>cuprate reagent</th>
<th>R</th>
<th>cis yield (%)</th>
<th>trans yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(alkyne)</td>
<td>(stannane)</td>
<td>(stannane)</td>
<td></td>
</tr>
<tr>
<td>1(^{a})</td>
<td>(3-122)</td>
<td>Me</td>
<td>1(3-131)</td>
<td>(3-132)</td>
</tr>
<tr>
<td>2(^{b,d})</td>
<td>(3-133)</td>
<td>t-Bu</td>
<td>62(3-134)</td>
<td>8(3-135)</td>
</tr>
<tr>
<td>3(^{a})</td>
<td>(3-122)</td>
<td>Me</td>
<td>1(3-131)</td>
<td>(3-132)</td>
</tr>
<tr>
<td>4(^{c,d,e})</td>
<td>(3-133)</td>
<td>t-Bu</td>
<td>80(3-134)</td>
<td>79(3-135)</td>
</tr>
</tbody>
</table>

\(^{a}\) 1.3 equiv. cuprate reagent, -48 °C, 4 h.
\(^{b}\) 3.0 equiv. cuprate reagent, 0 °C, 60 h.
\(^{c}\) 3.0 equiv. cuprate reagent, -20 °C, 4 h.
\(^{d}\) A third component, thought to be ethyl (E)-4,4-dimethyl-2-trimethylstannyl-2-pentenoate, was also present.
\(^{e}\) HMPA (10% by volume) was added prior to addition of the acetylenic ester.
In contrast to the outcome of subjecting alkyne 3-133 to cuprate reagents 3-126 and 3-127, cis-vinylstannane 3-134 emerged as the major product. According to Piers et al., the sterically bulky tert-butyl group destabilized the kinetic intermediate sufficiently to allow isomerisation to become faster than protonation, even in the presence of a proton source.\textsuperscript{31}

Unlike palladium-catalyzed hydrostannation,\textsuperscript{26,27} the regioselectivity of stannylcupration of enynols provided the distal stannane as the exclusive isomer, regardless of the orientation of the alcohol relative to the triple bond (Scheme 3.26).\textsuperscript{27}

![Scheme 3.26](image-url)
The regioselectivity of stannylcupration of enynols depended on the reaction temperature, addition of methanol to the cuprate solution, and the structure of the starting material.

Piers and Chong demonstrated stannylcupration of non-conjugated terminal alkynes to afford the corresponding 2-(trimethylstannyl)-1-alkenes as the major isomer (< 8% for other regioisomer) (Scheme 3.27).³

The presence of methanol in the reaction was important to shift the equilibrium toward the product and obtain high yields. Regioselectivity decreased as electron withdrawing groups were in close proximity of the triple bond.³

Other stannylmetallation methodologies have been reported but have not been adopted widely (Table 3.13).³²-³⁶
Table 3.13  Stannylmetallation using different metals.

\[
\begin{align*}
\text{entry} & \quad \text{R}^2, \text{R}^3 & \quad \text{condition} & \quad \text{ratio}\textsuperscript{a} & \quad \text{yield (\%)} \\
1\textsuperscript{32} & \quad \text{Bu}, \text{H} & \quad \text{Bu}_{3}\text{SnBEt}_{3}\text{Li} & \quad \text{Bu}_{3}\text{SnBEt}_{3}\text{Li} \quad \text{(2 equiv.)} & \quad 0 & \quad 100 & \quad 78 \\
2\textsuperscript{33} & \quad \text{Bu}, \text{H} & \quad \text{Bu}_{3}\text{SnAlEt}_{2} \quad \text{(3 equiv.)} & \quad \text{Bu}_{3}\text{SnAlEt}_{2} \quad \text{(10 mol\%)} & \quad 91 & \quad 9 & \quad 100 \\
3\textsuperscript{34} & \quad \text{Me}, \text{Me}, \text{Me} \quad \text{Pd(PPh}_{3}\text{)}_{4} & \quad \text{Me}, \text{Me}, \text{Me} \quad \text{Pd(PPh}_{3}\text{)}_{4} \quad \text{(1 mol\%)} & \quad - & \quad - & \quad 23 \\
4\textsuperscript{35} & \quad \text{Me}, \text{Me} \quad \text{Me}_{3}\text{SiMe}_{3} & \quad \text{Me}_{3}\text{SiMe}_{3} \quad \text{Pd(PPh}_{3}\text{)}_{4} & \quad 90 & \quad 10 & \quad 65 \\
5\textsuperscript{36} & \quad \text{Bu}, \text{H} & \quad \text{Bu}_{3}\text{SnMgMe} \quad \text{(3 equiv.)} & \quad \text{Bu}_{3}\text{SnMgMe} \quad \text{(5 mol \%)} & \quad 30 & \quad 70 & \quad 70
\end{align*}
\]
Stannylboration of terminal alkynes using CoCl$_2$(PPh$_3$)$_2$ (entry 1) afforded exclusively 1-stannyl-1-alkene isomer, as methanol was required for reaction completion.$^{32}$ Stannylalumination of terminal alkynes in THF provided 2-stannyl-1-alkene as the major isomer (entry 2). The regiochemistry of stannylalumination was greatly influenced by the choice of solvent.$^{33}$ Stannylstannation of terminal alkynes using palladium as a catalyst produces exclusively Z distannanes (entry 3).$^{34}$ Stannysilation proceeded in a regio- and stereoselective fashion to produce 2-stannyl-1-alkene as the major isomer (entry 4).$^{35}$ Stannylmagnesation of terminal alkynes provided 1-stannyl-1-alkene as the major isomer (entry 5), while stannylzincation afforded 2-stannyl-alkene as the major isomer (entry 6).$^{36}$

Applications of stannylmetallation in total synthesis are highlighted in Chapter 4.
3.2 Proposed Work

Given what was known about the metal-catalyzed hydrostannation of alkynes, it seemed very reasonable that ligands should affect the regioselectivity. Despite what was reported in the literature,\textsuperscript{17} a working hypothesis that reaction occurs \textit{via} hydro-palladation suggests that sterically demanding ligands on palladium should promote formation of the \textit{trans} isomer. The main goal was to derive a synthetically useful palladium-catalyzed hydrostannation that provides \textit{trans}-vinylstannanes in excellent yields and selectivities. Understanding the mechanism will lead to a much more efficient screening process that can improve the selectivity and yield of the desired \textit{trans}-vinylstannane 3-2.

Eventually, one could apply the methodology developed toward total syntheses of natural products to illustrate the usefulness of this chemistry.
3.3 Results and Discussion

Selective formation of trans-vinylstannane in high yield was influenced by many factors. These factors include steric and electronic effects of phosphine ligands and hydrogen bonding. These factors helped shape the understanding of selectivities observed in palladium-catalyzed hydrostannation.

3.3.1 Steric effect of phosphine ligands

Zhang et al. have shown palladium-catalyzed hydrostannation of unhindered terminal alkynes, using PPh$_3$ as ligand around the palladium, provided trans-vinylstannanes as the major isomer in most cases in ~ 2:1 ratio with the geminal isomer (Scheme 3.28).$^{17}$

\[
\begin{align*}
\text{R} & \equiv \text{H} & \xrightarrow{\text{Bu$_3$SnH}} & \text{H} & \equiv \text{SnBu$_3$} \quad & \text{Bu$_3$Sn} & \equiv \text{H} \\
\text{3-1} & & & \text{3-2} & & \text{3-3}
\end{align*}
\]

\[R = n-\text{alky}\]

Scheme 3.28

Attempts to use bulkier phosphine ligands to improve the selectivity of trans-vinylstannanes met with no success.$^{17}$
In contrast to this, a correlation has been found between phosphine ligands used on the palladium catalyst, and the regioselectivity observed from palladium-catalyzed hydrostannation of terminal alkynes.\textsuperscript{37}

This effect was initially observed with but-3-yn-2-ol (3-46), a propargyl alcohol (Table 3.14). The use of this alkyne allowed for the separation of the regioisomeric products and nonpolar stannane side products by flash chromatography.

\textbf{Table 3.14} Hydrostannation of 3-46 with various catalysts.\textsuperscript{37}

<table>
<thead>
<tr>
<th>entry (phosphine)</th>
<th>R</th>
<th>$3\text{-}146 : 3\text{-}147$ ratio$^d$</th>
<th>Isolated yield of $trans$ isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(3-148)</td>
<td>![Phenyl Ring]</td>
<td>68 : 32</td>
<td>$57%$\textsuperscript{b}</td>
</tr>
<tr>
<td>2(3-83)</td>
<td>![Phenyl Ring]</td>
<td>80 : 20</td>
<td>$60%$\textsuperscript{b}</td>
</tr>
<tr>
<td>3(3-149)</td>
<td>![Methyl Group]</td>
<td>100 : 0</td>
<td>$72%$\textsuperscript{a}</td>
</tr>
</tbody>
</table>
Use of PPh$_3$ as the ligand (entry 1) provided the reported ratio of 2:1 as (trans:geminal).

Ligands 3-150 and 3-152 (entries 4 and 6) reversed the selectivity in favour of the geminal isomer with ratios of 40:60 and 47:53 (trans:geminal), respectively. Relatively bulky phosphine ligands 3-83 and 3-153 provided selectivities of 80:20 and 77:23 (trans:geminal), respectively; these selectivities are slightly better than the traditional PPh$_3$ ligand.
Bulky phosphine ligands 3-151 and 3-154 provided great selectivities of 95:5 and 96:4, respectively, but ligand 3-151 provided the highest isolated yield of *trans*-vinylstannane 3-146.

Perfect selectivity of 100:0 was observed when using the very bulky 3-149 as a ligand, but the isolated yield of *trans*-vinylstannane 3-146 was lower than when Cy₃P was used as ligand.

Phosphine ligands applied in Table 3.14 illustrated how bulky phosphine ligands provided high selectivities toward *trans*-vinylstannane 3-146.

Tolman cone angles are used to describe or quantify a ligand’s bulkiness;³⁸ they can illustrate the correlation of the size of the ligand and the ratio they provide in palladium-catalyzed hydrostannation of alkyne 3-46 (Table 3.15).

<table>
<thead>
<tr>
<th>entry (phosphine)</th>
<th>phosphine ligand</th>
<th>Tolman cone angle</th>
<th>3-146 : 3-147 Ratio(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(3-148)</td>
<td><img src="image" alt="Phosphine Ligand" /></td>
<td>145°</td>
<td>68 : 32</td>
</tr>
</tbody>
</table>

Table 3.15   Relating Tolman cone angle and selectivity\(^b\)
Comparing the three ligands, phosphine ligand 3-148 provided the lowest selectivity (68:32, \textit{trans}:\textit{geminal}) of the desired stannane (3-146) and it has the smallest Tolman cone angle of 145°. Phosphine ligand 3-151 has a higher Tolman cone angle of 170° and it provided a higher ratio of 95:5. Phosphine ligand 3-149, with the biggest Tolman cone angle, provided \textit{trans}-vinylstannane 3-146 as the sole regioisomer.

The selectivities observed may be rationalized by considering the steric interactions between the phosphine ligand and the substituent on the alkyne (Scheme 3.29).
After the Bu$_3$SnPdH complex coordinates with the triple bond, hydro-palladation will proceed with *syn* addition. This addition can give rise to two regioisomers (3-156 and 3-157). Addition of palladium in the *geminal* position gives rise to unfavourable steric interactions with the *geminal* substituent group (3-156). Meanwhile, addition of the palladium to the *trans* position minimizes that unfavourable interaction (3-157). As the phosphine ligand increases in size, the unfavourable *geminal* interaction (experienced in 3-156) becomes larger, allowing for higher discrimination between the *trans* and *geminal* isomers.
The alternative pathway, namely via stannylpalladation process, would not produce the results shown in Table 3.14. This proposition can be explained by the model shown in Scheme 3.30. Thus initial stannylpalladation would give rise to intermediates 3-158 and 3-159 which would lead to trans-vinylstannane 3-146 and geminal isomer 3-147, respectively. Using this model, an increase in the steric bulk of the ligands on palladium would lead to enhanced amounts of geminal isomer 3-147; this is the opposite of what was observed.

Scheme 3.30
Comparing the two models shown in Schemes 3.29 and 3.30, the hydropalladation pathway explains the selectivity observed in the reaction while the stannylpalladation pathway does not.

3.3.2 Electronic effect

Data shown in Table 3.15 suggest that steric bulkiness of the phosphine is the reason for the differences in selectivities observed. However, there appears to be a strong electronic effect as well: $n$-Bu$_3$P 3-163, which has a cone angle smaller than (2-furyl)$_3$P 3-150, was found to afford higher selectivity during the hydrostannation of alkyne 3-160 (Table 3.16).

<table>
<thead>
<tr>
<th>entry (phosphine ligand)</th>
<th>Tolman cone angle</th>
<th>3-161 : 3-162 ratio$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(3-150)</td>
<td>149°</td>
<td>57</td>
</tr>
</tbody>
</table>

Table 3.16 Relating Tolman cone angle and selectivity
Steric bulk argument of the phosphine ligand would not be a good model to explain the results observed in Table 3.16. Therefore, a different model is required, such as electronics, to explain the observed outcome. In this case, the electron “richness” of the phosphine ligand, which is influenced by the alkyl or aryl group attached to the phosphine, controls the selectivity of the palladium-catalyzed hydrostannation. Therefore, the electron donating or withdrawing nature of the alkyl or aryl groups is an important factor when discussing the electronic effect in palladium-catalyzed hydrostannations. An \( n \)-butyl group (in \( n \)-Bu\(_3\)P) is considered more electron donating inductively than a furyl group (in (2-furyl)\(_3\)P), thus affording high \( trans \)-vinylstannane ratio of 90:10. A furyl group (in (2-furyl)\(_3\)P) is more electron withdrawing than an \( n \)-butyl group (in \( n \)-Bu\(_3\)P), thus affording almost an equal ratio of \( trans \) and \( geminal \) isomers (57:42, \( trans:geminal \)). A phenyl group (in PPh\(_3\)) is considered electron withdrawing, but slightly less than a furyl group, which corresponds to more of the \( trans \) isomer being formed.

\(^{a}\) Determined by \( ^{1} \text{H} \) NMR analysis of crude reaction mixtures.
An electronic effect was also evident when subjecting para-substituted phenylacetylenes to palladium-catalyzed hydrostannation (Table 3.17).³⁹

Table 3.17  Hydrostannation of para-substituted phenylacetylene.³⁹

<table>
<thead>
<tr>
<th>entry (alkyne)</th>
<th>catalyst</th>
<th>alkyne</th>
<th>trans : geminal ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(3-167)</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>O₂N-CCCCC-</td>
<td>0 : 100</td>
</tr>
<tr>
<td>2(3-23)</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>H-CCCCC-</td>
<td>56 : 44</td>
</tr>
<tr>
<td>3(3-168)</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>MeO-CCCCC-</td>
<td>76 : 24</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by ¹H NMR analysis of crude reaction mixtures.

Table 3.17 clearly demonstrates an electronic effect on palladium-catalyzed hydrostannation by the substrate. The electron withdrawing nitro group alters the selectivity in favour of the geminal-vinylstannane exclusively (entry 1), while electron donating methoxy group promotes the formation of the trans-vinylstannane (entry 3).
To rationalize how the regioselectivity in palladium-catalyzed hydrostannation is controlled by electronic effects, one must be able to explain the results obtained in Tables 3.16 and 3.17 with respect to the electronic nature of the phosphine ligand or the substrate.

Palladium-catalyzed hydrostannation is thought to proceed through a four member transition state, just like in a pericyclic reaction, electrons move in a circle and form partial charges during the transition state leading to a hydropalladated intermediate.

Inspecting the effect of phosphine ligands, electron rich phosphine ligands would be able to stabilize the partial positive charge developed on the palladium during the transition state (3-169 and 3-171, Scheme 3.31). But, this stabilization would have taken place for both adducts.

\[
\begin{align*}
\text{Scheme 3.31}
\end{align*}
\]
Therefore, the only difference is the partial charges placed on the substrate itself. During the transition state leading to the trans adduct (3-169), the partial positive charge on the substrate is placed on a secondary carbon, whereas the transition state leading to the geminal adduct (3-171), the partial positive charge on the substrate is placed on a primary carbon which is less capable of stabilizing this partial charge (Scheme 3.31). This difference, when dealing with more electron donating phosphine ligands, could be contributing to higher selectivities for the trans isomer.

Geminal-vinylstannane 3-162 was formed in higher proportions (Table 3.16, entry 1) when using relatively electron withdrawing phosphine ligand (2-furyl)₃P; suggesting that stabilization effects during the transition state are minimal, leading to some formation of the geminal isomer (Scheme 3.32).

![Scheme 3.32](image)

During transition state 3-173 leading to the trans adduct, a partial positive charge forms on the palladium which is destabilized by the electron withdrawing group, thus leading to less formation of the trans isomer.
Inspecting the electronic effect caused by the substrate, which was observed in Table 3.17, suggests polarization of the triple bond and the stability of the transition state are important factors that can explain the selectivity provided.

In the case of an electron withdrawing group attached to the triple bond; during the transition state \textbf{3-177} leading to the \textit{geminal} adduct, a partial negative on the carbon is stabilized by the electron withdrawing group, while the partial positive charge in transition state \textbf{3-175} leading to the \textit{trans} adduct is destabilized by the electron withdrawing group. This difference in stability could favour the formation of the \textit{geminal} isomer (Scheme 3.33).

\begin{center}
\begin{tikzpicture}
    \node (a) {\[ \begin{array}{c}
    \delta^- - H \text{Pd}\delta^+ \text{SnBu}_3 \\
    \delta^+ \equiv \delta^-
    \end{array} \] \[ \text{EWG} \quad \text{H} \] \[ \textbf{3-175} \text{ less favourable} \]};
    \node (b) {\[ \begin{array}{c}
    \delta^- - H \text{Pd}\delta^+ \text{SnBu}_3 \\
    \delta^+ \equiv \delta^-
    \end{array} \] \[ \text{H} \quad \text{EWG} \] \[ \textbf{3-177} \text{ more favourable} \]};
    \node (c) {\[ \begin{array}{c}
    \text{EWG} \\
    \text{H}
    \end{array} \] \[ \text{H} \text{PdSnBu}_3 \] \[ \textbf{3-176} \]};
    \node (d) {\[ \begin{array}{c}
    \text{EWG} \\
    \text{H}
    \end{array} \] \[ \text{H} \text{PdSnBu}_3 \] \[ \textbf{3-178} \]};
    \draw[->] (a) -- (c);
    \draw[->] (b) -- (d);
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.33}
The trans isomer was formed as the major product when having a electron donating group attached to the alkyne (Table 3.17, entry 3). During the transition state 3-181 leading to the geminal adduct, a partial negative on the carbon is destabilized by the electron donating group, while the partial positive charge in transition state 3-179 leading to the trans adduct is stabilized the by electron donating group. This difference in stability could favour the formation of the trans isomer (Scheme 3.34).

![Scheme 3.34](image)

As shown, there are two reasonable explanations, sterics and electronics, for the regiochemistry observed in palladium-catalyzed hydrostannation. Further studies are required to understand these factors in depth.
3.3.3 *Hydrogen bonding effect*

Phosphine ligands bearing additional hetero-atoms did not afford consistent selectivities. These ligands are capable of hydrogen-bonding (shown in Figure 3.3) with alcohols, which may affect the regioselectivity.

![Figure 3.3 Hydrogen bonding in complex 3-183](image)

When dealing with heteroatom-containing phosphine ligands, different selectivities were obtained when applied to propargylic and non-propargylic substrates. With non-heteroatom containing phosphine ligands, these differences were not observed. These results are highlighted in Table 3.18.
Table 3.18  Hydrogen bonding effect on hydrostannation

\[
\begin{align*}
\text{3-160} & \xrightarrow{\text{Bu}_3\text{SnH}} \text{Bu}_3\text{Sn} & + & \text{SnBu}_3 \\
& \text{Pd}_{2}\text{dpbb}, \text{phosphine} & \text{ligand} \\
\hline
\text{entry} & \text{alkyne} & \text{phosphine ligand} & \text{trans} & \text{geminal} \\
(\text{phosphine}) & & & \text{ratio}^a \\
\hline
1(3-148) & \begin{array}{c}
\text{3-46} \\
\text{3-160}
\end{array} & \begin{array}{c}
\text{Ph}
\end{array} & \begin{array}{c}
68 \\
32
\end{array} \\
2(3-148) & \begin{array}{c}
\text{3-160}
\end{array} & \begin{array}{c}
\text{Ph}
\end{array} & \begin{array}{c}
67 \\
33
\end{array} \\
3(3-153) & \begin{array}{c}
\text{3-46} \\
\end{array} & \begin{array}{c}
\text{MeO}
\end{array} & \begin{array}{c}
77 \\
23
\end{array} \\
4(3-153) & \begin{array}{c}
\text{3-160}
\end{array} & \begin{array}{c}
\text{MeO}
\end{array} & \begin{array}{c}
95 \\
5
\end{array} \\
5(3-150) & \begin{array}{c}
\text{3-46}
\end{array} & \begin{array}{c}
\text{MeO}
\end{array} & \begin{array}{c}
40 \\
60
\end{array} \\
6(3-150) & \begin{array}{c}
\text{3-160}
\end{array} & \begin{array}{c}
\text{MeO}
\end{array} & \begin{array}{c}
58 \\
42
\end{array} \\
7(3-151) & \begin{array}{c}
3-46
\end{array} & \begin{array}{c}
\text{MeO}
\end{array} & \begin{array}{c}
95 \\
5
\end{array} \\
8(3-151) & \begin{array}{c}
\text{3-160}
\end{array} & \begin{array}{c}
\text{MeO}
\end{array} & \begin{array}{c}
95 \\
5
\end{array} \\
\hline
\end{align*}
\]

* Determined by \(^1\)H NMR analysis of crude reaction mixtures.
Table 3.18 illustrates the effects of heteroatom versus non-heteroatom phosphine ligands and the selectivities they provided. Non-heteroatom phosphine ligands 3-148 and 3-151 maintained the same selectivities in propargylic and non-propargylic substrates; while heteroatom-containing phosphine ligands 3-150 and 3-153 afforded different selectivities in propargylic and non-propargylic substrates. *Geminal*-vinylstannane 3-165 was formed in higher ratio than *geminal*-vinylstannane 3-162 by the heteroatom-containing phosphine ligands, suggesting hydrogen bonding by the hydroxyl group, illustrated in Figure 3.3, could be the contributing factor for the differences in selectivity between the propargylic and non-propargylic substrates.

Further studies using propargyl ethers, such as methyl ether or silyl ethers, are required to illustrate if hydrogen bonding is a contributing factor for the differences in selectivities observed.

### 3.3.4 Reduction by-product formation

The hydrostannation of unhindered terminal alkynes was also investigated as a prelude towards syntheses of natural products. Alkyne 3-160 was chosen to be sterically representative of a straight-chain unhindered alkyne but contained an alcohol group to facilitate the chromatographic separation of products (Table 3.19).
Table 3.19  Hydrostannation of alkyne 3-160 with different sources of the catalyst

\[
\begin{align*}
\text{Bu}_3\text{SnH} + \text{Bu}_3\text{SnH} &\rightarrow \text{Bu}_3\text{Sn} \quad \text{(CH}_2\text{)}_2\text{OH} \quad + \quad \text{SnBu}_3 \quad \text{(CH}_2\text{)}_2\text{OH} \quad + \quad \text{(CH}_2\text{)}_2\text{OH} \\
3-160 &\rightarrow 3-161 \quad 3-162 \quad 3-184
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>3-161 : 3-162 : 3-184 ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}</td>
<td>66 : 33 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PCy\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}</td>
<td>69 : 4 : 27</td>
</tr>
<tr>
<td>3</td>
<td>Pd\textsubscript{2}dba/\textsubscript{3}/Bu\textsubscript{3}PHBF\textsubscript{4}/iPr\textsubscript{2}NEt</td>
<td>10 : 0 : 90</td>
</tr>
</tbody>
</table>

* Determined by \textsuperscript{1}H NMR analysis of crude reaction mixtures.

Hydrostannation of either 3-46 or 3-160 gave nearly identical results (2:1 mixture of regioisomers) when using Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} as a catalyst. Hydrostannation using (Cy\textsubscript{3}P)\textsubscript{2}PdCl\textsubscript{2} proceeded with the same regioselectivity as that observed for 3-46; unfortunately, a substantial amount of reduction by-product 3-184 was observed. As well, \textit{t}-Bu\textsubscript{3}P maintained the regioselectivity but an overwhelming presence of the reduction by-product 3-184 was observed.

Initially, it was thought that the reduction by-product might be formed through a proto-destannylation process under the reaction conditions (Scheme 3.35).
To test this hypothesis, vinylstannanes $\text{3-161}$ and $\text{3-162}$ were isolated and re-subjected to the same hydrostannation conditions used in trial 3 from Table 3.19 to observe if reduction by-product $\text{3-184}$ would form. This was not the case, the initial ratio between stannanes $\text{3-161}$ and $\text{3-162}$ remained the same throughout the re-subjection period without any formation of the reduction by-product $\text{3-184}$.

This result suggested that the formation of the reduction by-product comes from a competitive reaction pathway, and is not part of a degenerative pathway, such as protodestannylation.

While preparing a sample of Bu$_3$SnH for $^{13}$C NMR analysis, it was noticed that when performing $^{13}$C NMR on Bu$_3$SnH using NMR tubes that had visible traces of black palladium, spectra of Bu$_3$SnSnBu$_3$ ($\text{3-185}$) were obtained (Scheme 3.36).
Visible bubbles could be seen forming in the NMR tube, likely hydrogen gas, while Bu$_3$SnH was converting to Bu$_3$SnSnBu$_3$. This side reaction contributed to the formation of reduction by-product 3-184 which is shown in Scheme 3.37.

\[
\begin{align*}
\equiv(CH_2)_3CH + Bu_3SnH &\xrightarrow{Pd_{db}a/\alpha-Bu_3PH/Et} Bu_3Sn \equiv(CH_2)_3CH \\
3-160 &\implies 3-161 &\implies 3-162 &\implies 3-184
\end{align*}
\]

**Scheme 3.37**

This problem was solved by washing the glassware with aqua regia (Conc. HCl: Conc. HNO$_3$, 3:1 v/v) prior to use. The acidic solution oxidizes and removes any traces of Pd(0) that are embedded in glassware. Once the reaction flask was Pd(0) free, a large decline in reduction by-product 3-184 was observed. The acidic wash was adapted as a part of a regular procedure when performing these reactions (Scheme 3.37).

A large decrease in yield of hydrostannation products was observed when using both (Cy$_3$P)$_2$PdCl$_2$ and $\alpha$-Bu$_3$P/Pd$_2$dba$_3$ on non-propargyl alcohol 3-160 in comparison to propargyl alcohol 3-46. This suggests the propargyl alcohol might be contributing a role that inhibits, or slows down the formation of the reduction by-product 3-184. This role can be described by viewing the alcohol as a Lewis base. The alcohol could possibly
stabilize intermediate 3\textsuperscript{-186} (Scheme 3.38), which disfavours the path leading to reduction by-product 3\textsuperscript{-184}.

Scheme 3.38
On the other hand, intermediate $3\text{-}190$ does not contain an alcohol that can stabilize the palladium alkyne complex. This may allow formation of a palladium dihydride, which results in a dramatic increase in the amount of reduction by-product $3\text{-}184$ formed.

To test this theory, additional heteroatom and non-heteroatom phosphine ligands were chosen to demonstrate the effect of a Lewis base on the amount of reduction by-product $3\text{-}184$ formed (Table 3.20).

![Image](image_url)

**Table 3.20** Internal Lewis base effect on formation of reduction by-product $3\text{-}184$

<table>
<thead>
<tr>
<th>entry (phosphine)</th>
<th>phosphine ligand</th>
<th>$3\text{-}161$ : $3\text{-}162$ ratio$^a$ : $3\text{-}184$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1($3\text{-}193$)</td>
<td><img src="image_url" alt="Phosphine Ligand 1" /></td>
<td>78 : 8 : 14</td>
</tr>
<tr>
<td>2($3\text{-}194$)</td>
<td><img src="image_url" alt="Phosphine Ligand 2" /></td>
<td>87 : 4 : 8</td>
</tr>
</tbody>
</table>
According to Table 3.20, small but significant differences illustrate the advantage of phosphine ligands containing additional heteroatoms. While nitrogen containing phosphine ligand 3-194 reduces the amount of reduction by-product 3-184, oxygen containing phosphine ligand 3-153 was slightly better. While phosphine 3-153 proved to be a great ligand for hydrostannation of this substrate, it did not provide good selectivities with the propargyl system (95:5 vs 77:23 respectively, \textit{trans:geminal}). Unfortunately, heteroatoms can co-ordinate with alcohols in propargylic substrates, which led to lower selectivities as shown in Table 3.20.

The goal of this research was to pursue a ligand that can be general with its substrates; non-heteroatom containing phosphine ligand such as Cy₂P showed promising results with propargyl substrates.

An additional heteroatom within the phosphine ligand proved to be beneficial in reducing the amount of reduction by-product 3-184. This led to the idea of having an external Lewis base not attached to the phosphine ligand. The use of an amine as an electron donor was examined for its potential effect on the formation of the reduction by-product. Non-propargylic alkyne 3-160 was used due to its susceptibility to the formation of the reduction by-product (Table 3.21).
Table 3.21  External Lewis base effect on formation of reduction by-product 3-184

![Chemical reaction diagram](Chemical_reaction_diagram.png)

<table>
<thead>
<tr>
<th>entry</th>
<th>excess base present (%)</th>
<th>catalyst</th>
<th>3-161 : 3-162 : 3-184 ratio</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Cy3P/</td>
<td>87 : 3 : 10</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pd2dba3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>Cy3P/</td>
<td>95 : 5 : 0</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>(i-Pr2Net)</td>
<td>Pd2dba3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>Cy3PHBF4/</td>
<td>84 : 4 : 12</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pd2dba3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Cy3PHBF4/</td>
<td>92 : 4 : 4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(i-Pr2Net)</td>
<td>Pd2dba3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>Cy3PHBF4/</td>
<td>93 : 4 : 3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(i-Pr2Net)</td>
<td>Pd2dba3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>Cy3PHBF4/</td>
<td>91 : 4 : 5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(piperidine)</td>
<td>Pd2dba3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>Cy3PHBF4/</td>
<td>92 : 4 : 4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(Et3N)</td>
<td>Pd2dba3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>(Cy3P)PdCl2</td>
<td>86 : 4 : 10</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>lab-made</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
According to Table 3.21, a slight excess of base was able to reduce the amount of reduction by-product 3-184 formed. Hünig’s base, Et₃N and piperidine all showed similar results. It was found that reduction by-product 3-184 formation was reduced by 5% to 10% in most cases. The regioselectivities remained unaffected. This, again, highlights the inhibition of the reduction by-product by hetero-atoms.

As bulky phosphine ligands were screened to provide high selectivities and yields of vinylstannane 3-161, a clear trend emerged (Table 3.22).

**Table 3.22**  Propensity of electron rich bulky ligands to form 3-184

![Chemical structures](image-url)
<table>
<thead>
<tr>
<th>entry (phosphine)</th>
<th>phosphine ligand</th>
<th>3-161</th>
<th>:</th>
<th>3-162</th>
<th>:</th>
<th>3-184</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(3-148)</td>
<td><img src="image1" alt="Phosphine Ligand" /></td>
<td>66</td>
<td>33</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2(3-154)</td>
<td><img src="image2" alt="Phosphine Ligand" /></td>
<td>60</td>
<td>9</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(3-195)</td>
<td><img src="image3" alt="Phosphine Ligand" /></td>
<td>38</td>
<td>3</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4(3-196)</td>
<td><img src="image4" alt="Phosphine Ligand" /></td>
<td>34</td>
<td>2</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5(3-149)</td>
<td><img src="image5" alt="Phosphine Ligand" /></td>
<td>46</td>
<td>1</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6(3-151)</td>
<td><img src="image6" alt="Phosphine Ligand" /></td>
<td>93</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ \text{ratio}^a \]
The outcome was consistent with what was hypothesized earlier, bulky electron rich ligands have higher selectivity toward trans product. All ligands shown in Table 3.22 did show moderate (7:1) to high (46:1) selectivities toward trans-vinylstannane 3-161. Unfortunately, moderate to high levels of reduction by-product 3-184 accompanied these products in most cases. From what was observed, reactions tend to be more susceptible to the formation of the reduction by-product when bulky electron rich ligands are used. All of the results shown in Table 3.22 are optimized with respect to the formation of the reduction by-product except for trial 1 (PPh3). PPh3 is the least electron rich ligand from Table 3.22, which resulted in the least amount of reduction by-product without any optimization. As illustrated in Table 3.22, there is a fine line in obtaining a ligand that has steric bulk, or electron richness, that will not result in the formation of the reduction by-product which was achieved by ligand 3-151 (Cy3P). This table demonstrates the
susceptibility of these reactions, when using bulky electron rich ligands, toward the formation of the reduction by-product in the non propargylic substrate 3-160.

### 3.3.5 Addition rate of Bu₃SnH

Rate of addition of Bu₃SnH to the reaction was examined to determine its effects on the regioselectivity and the formation of the reduction by-product. According to Table 3.23, rate of addition of Bu₃SnH has a significant effect on the formation of the reduction by-product 3-184 but did not affect the regioselectivity (Table 3.23).

![Chemical Structures](image)

**Table 3.23** Addition rate effect of Bu₃SnH

<table>
<thead>
<tr>
<th>entry</th>
<th>Bu₃SnH addition rate</th>
<th>catalyst</th>
<th>3-161 : 3-162 : 3-184 ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>slow</td>
<td></td>
<td>73 : 4 : 23</td>
</tr>
<tr>
<td>2</td>
<td>fast</td>
<td>Pd(PCy₃)₂Cl₂</td>
<td>69 : 4 : 27</td>
</tr>
<tr>
<td>3</td>
<td>reverse addition 3-151</td>
<td>(Aldrich)</td>
<td>35 : 2 : 63</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of crude reaction mixtures.
All three trials of hydrostannation reactions performed in Table 3.23 were performed at 1 mmol scale. Trial 1 and 2 had the same sequence of addition of reagents. Preformed catalyst 3-151, at 5 mol%, was added along with the alkyne 3-160 to a solution of toluene (20 mL). Slow addition represents the addition of diluted 1.2 equivalents of Bu₃SnH (10 mL toluene) in 15 minutes; while fast addition represents the neat addition of 1.2 equivalents of Bu₃SnH within 1 minute.

Trial 3 had a different sequence of addition; 1.2 equivalents of Bu₃SnH along with alkyne 3-160 were added to a solution of toluene (20 mL). Preformed catalyst was then added to the reaction mixture, which represents the reverse-addition.

Looking back at Scheme 3.38, one can assume that high concentrations of Bu₃SnH will increase the chance of further reaction with the Bu₃SnPdH complex. This will promote the pathway leading to the reduction by-product 3-184. It is interestingly to note that trials 1 and 2 from Table 3.23, representing slow and fast addition, respectively, had similar outcomes; only in the extreme case of reverse-addition was a considerable amount of reduction by-product 3-184 observed. Regioselectivity was consistent throughout the three trials.

3.3.6 Catalyst loading

The intention of this methodology was to be used on large scale (0.1 mol) toward total syntheses of natural products. This will still require the use of 0.005 mol of Pd₂dba₃/PCy₃HBF₄ at 5% catalytic loading (2.5% Pd₂dba₃/ 10% PCy₃HBF₄). Unfortunately, these reagents are expensive to purchase (Aldrich - Pd₂dba₃ $201/0.0025
mol, Cy₃PHBF₄ $107/0.01$ mol), thus costing approximately $308 for the catalyst only at 5% catalytic loading (Table 3.24).

![Chemical structure](image)

**Table 3.24** Effect of catalyst loading

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst loading (%)</th>
<th>3-161 : 3-162 : 3-184 ratio&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>92 : 4 : 4</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>93 : 4 : 3</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>93 : 4 : 3</td>
</tr>
<tr>
<td>4</td>
<td>0.25</td>
<td>93 : 4 : 3</td>
</tr>
<tr>
<td>5</td>
<td>0.125</td>
<td>93 : 4 : 3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of crude reaction mixtures.

<sup>b</sup> Combined isolated yields of trans and geminal vinylstannanes were consistently obtained at 87% throughout the trials.

Initially, 5% catalytic loading was used as the standard loading. Catalyst loading of 0.125% mol proved to be just as efficient in time (2 h) as catalytic loading of 5%, even at large scales (0.1 mol). The operational cost of the catalyst was decreased from $308 to $15, which illustrates affordability of this reaction at large scale. The lower limit of this reaction was not tested due to difficulty in weighing small quantities of the catalyst.
3.3.7 **Solvent effect**

The effects of solvent on regioselectivity and the formation of the reduction by-product were also examined (Table 3.25).

![Chemical structure](image)

**Table 3.25** Solvent effect on hydrostannation

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>3-161 : 3-162 : 3-184 ratio&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>93 : 4 : 3</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>92 : 5 : 3</td>
</tr>
<tr>
<td>3</td>
<td>Hexane</td>
<td>95 : 4 : 1</td>
</tr>
<tr>
<td>4</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>94 : 5 : 1</td>
</tr>
<tr>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>95 : 5 : 0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of crude reaction mixtures.

<sup>b</sup> 100% conversion was observed in all trials.

The reaction proceeded smoothly with a variety of solvents. Polar and non polar solvents did not change the regioselectivity. This was consistent with what was reported about solvents not affecting the regioselectivity in palladium-catalyzed hydrostannations very
much. Also, there was not any significant changes in the formation of reduction by-product 3-184 (0%-3%). In all trials, complete conversion of the starting alkyne (3-160) was observed. This finding highlights the compatibility of the reaction with many solvents. The flexibility in the choice of solvent allowed a follow-up reaction (Stille coupling) without the need of purification of the corresponding vinylstannanes, which is illustrated later in section 3.2.14.

3.3.8 Concentration

There were unexpected results with regard to concentration of the reaction. When performing hydrostannation on alkyne 3-160, the yields and the selectivities were consistent irrespective of the concentration (0.10 M to 0.24 M) of the substrate in the reaction. Unfortunately, when dealing with alkyne 3-46, a propargyl alcohol, the reaction produced an unexpected side product (3-199) at 0.24 M concentration relative to the substrate (Scheme 3.39).

![Scheme 3.39](image_url)
Speculatively, this side product is an outcome of a hydrostannation followed by a carbopalladation addition of intermediate 3-200 to alkyne 3-46 (Scheme 3.40).

\[
\begin{align*}
\left[ \begin{array}{c}
\text{H} \\
\text{PdSnBu}_3 \\
3-200
\end{array} \right] + \left[ \begin{array}{c}
\text{OH} \\
\text{3-46}
\end{array} \right] & \rightarrow \left[ \begin{array}{c}
\text{OH} \\
\text{Bu}_5\text{SnPd} \\
3-201
\end{array} \right] \rightarrow \left[ \begin{array}{c}
\text{OH} \\
\text{Bu}_5\text{Sn} \\
3-199
\end{array} \right]
\end{align*}
\]

Scheme 3.40

The propargyl substrate 3-46 might be more susceptible to this side reaction due to the alcohol, unlike the non-propargyl substrate where it did not produce side product 3-199 at the same concentration (0.24 M). The alcohol could be acting as an activator by inductively by lowering the energy of its LUMO. Another explanation with regard to the alcohol could be attributed to the oxygen chelation to the palladium to form complex 3-202 (Figure 3.4).

Figure 3.4  Hydrogen bonding in complex 3-202
Hydrogen bonding between the alcohol of alkyne 3-46 and palladium of the palladium-stannane 3-202 (shown in Figure 3.4) allows for the two substrates to come within close proximity to allow carbo-palladation to take place on the alkyne. The explanations provided are just speculative. There have not been any experiments to support these ideas aside from the observation made by the role of the concentration. For synthetic purposes, this side reaction was avoided by keeping the substrate concentration in the reaction at or below 0.12 M.

### 3.3.9 Source of catalyst

The source of the catalyst precursor was also examined. From the findings, the source of the catalyst did not influence the regioselectivity but had a noticeable effect on the formation of the reduction by-product (Table 3.26).

**Table 3.26** Effect of palladium source on the hydrostannation using 3-151 as a catalyst

![Reaction Scheme](image)
Pre-formed catalyst purchased from Aldrich (Pd(PCy₃)₂Cl₂) was initially used. Reaction using catalyst in entry 1 was more susceptible at forming reduction by-product 3-184 (23%). Reactions using laboratory-made Pd(PCy₃)₂Cl₂ catalyst in entry 2, 3 and 4 produced 10-12% reduction by-product under the same conditions. Note that none of the trials had extra base to compare solely the effect of the source of the catalyst has on the formation of the reduction by-product. We can speculate that pre-formed catalyst purchased from Aldrich (entry 1) might contain traces of black Palladium (Pd(0)), which can be responsible in forming reduction earlier. On the other hand, during the synthesis of the pre-formed catalyst (entry 2) in the laboratory, extra care was taken to achieve...
highest quality of catalyst, which might contain less or none of the black palladium (Scheme 3.41).

\[
PdCl_2 + HCl + 2Cy_3P \rightarrow Pd(Cy_3P)_2Cl_2
\]

**Scheme 3.41**

The active catalysts that are made *in situ* could contain less free Pd(0) and be ligated to phosphine ligands.

### 3.3.10 Scale of reaction

The ability to perform this reaction on large scale is very important. Again, it was the intention of this methodology to be used toward large scale syntheses of natural products. When hydrostannation of **3-160** was carried out on 0.012 mole scale, a small side product was observed. This was identified as *cis*-vinylstannane **3-204** (Scheme 3.42).

\[
\begin{align*}
&\text{3-160} \\
&\text{3-161} \\
&\text{3-162} \\
&\text{3-204}
\end{align*}
\]

**Scheme 3.42**
Metal-catalyzed hydrostannations can only produce two possible regioisomers. This is due to the mechanism of this reaction which proceeds by syn-addition. To produce cis-vinylstannane 3-204, another pathway must have been operating. Normally, reactions are performed at ambient temperature with no external cooling. It was noted that reactions warm up as Bu₃SnH was added. This side product was only observed when the scale of the reaction exceeded 0.012 moles, suggesting that excess heat from the reaction promotes the initiation of the radical pathway. It was disadvantageous to have another isomeric vinylstannane in the crude reaction mixture, since long chain vinylstannanes such as 3-161, 3-162 and 3-204 are inseparable by silica gel chromatography. The radical pathway was inhibited by simply performing the reaction at 0 °C. The lower temperature inhibited the formation of cis-vinylstannane 3-204 while maintaining selectivity and yield.

3.3.11 Scope of substrates and limitations

To demonstrate the generality of our methodology, this reaction was carried out with other substrates (Table 3.27).

Table 3.27 Hydrostannation of various propargyl alcohols using optimal conditions
<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>isolated yield of trans isomer except in the case of entry 2 which is the isolated yield of trans and geminal isomers combined which were inseparable.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="3-215" /></td>
<td>57% 82% 65% 55%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="3-48" /></td>
<td>50% 77% 37% 28%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="3-216" /></td>
<td>55% 83% 60% 58%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="3-217" /></td>
<td>56% 86% 51% 27%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="3-29" /></td>
<td>50% 76% 31% 19%</td>
</tr>
</tbody>
</table>
Results for the hydrostannation of propargyl alcohols 3-215, 3-216, 3-217 and 3-29 and silyl ether 3-48 with phosphines 3-148, 3-151, 3-154 and 3-149 are tabulated in Table 3.27. PPh₃ is the common ligand for palladium-catalyzed hydrostannation; it provided similar selectivities with all substrates (3:1, _trans;geminal_), but slightly lower selectivity with substrate 3-29 (1.5:1, _trans;geminal_). Silyl ether substrate 3-48 gave the same ratio of vinylstannyl isomers as the alcohol counterpart 3-215. These results illustrate the unimportance of hydrogen bonding when using non-heteroatom phosphine ligands; the results also suggest that the inductive nature of the oxygen in silyl ether 3-48 is similar to the alcohol counterpart 3-215. Relatively bulky propargyl alcohols 3-216 and 3-217 did not have much affect on the regioselectivities. Phenyl-substituted propargyl alcohol 3-29 provided lower selectivities for all phosphine ligands. All of the trialkylphosphines tested afforded similar selectivities with all the substrates. Overall, Cy₃P proved to be better in terms of selectivities and isolated yields.³⁷

Non propargylic substrates were also subjected to our methodology using Cy₃P as the phosphine ligand in comparison to the traditional PPh₃ ligand (Table 3.28).

<table>
<thead>
<tr>
<th>Table 3.28</th>
<th>Hydrostannation of various alkynes using optimal conditions</th>
</tr>
</thead>
</table>

\[
\begin{align*}
\text{R} & \quad \xrightarrow{\text{Pd}_2\text{dba} \ (0.125 \text{ mol\%})} \\
& \quad \xrightarrow{\text{Cy}_3\text{PHBF}_4 \ (0.5 \text{ mol\%})} \\
& \quad \xrightarrow{\text{Bu}_3\text{N} \ (1.0 \text{ mol\%})} \\
& \quad \xrightarrow{\text{Bu}_3\text{SnH} \ (1.2 \text{ equiv.})} \\
& \quad \xrightarrow{\text{CH}_2\text{Cl}_2 / 0 \ ^\circ \text{C} / 2 \text{h}} \\
\text{R} & \quad \text{trans} \\
& \quad \text{geminal} \\
\end{align*}
\]
<table>
<thead>
<tr>
<th>entry</th>
<th>(stannanes)</th>
<th>alkyne</th>
<th>( % )</th>
<th>( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-8</td>
<td>( \equiv \mathrm{CH} )</td>
<td>( 31^a )</td>
<td>( 61^a )</td>
</tr>
<tr>
<td>2</td>
<td>3-237</td>
<td>( \equiv \mathrm{OTBS} )</td>
<td>( 37^a )</td>
<td>( 64^a )</td>
</tr>
<tr>
<td>3</td>
<td>3-238</td>
<td>( \equiv \mathrm{OH} )</td>
<td>( 42^a )</td>
<td>( 70^a )</td>
</tr>
<tr>
<td>4</td>
<td>3-239</td>
<td>( \equiv \mathrm{OTBS} )</td>
<td>( 79^b )</td>
<td>( 83^b )</td>
</tr>
<tr>
<td>5</td>
<td>3-240</td>
<td>( \equiv \mathrm{OAc} )</td>
<td>( 62:38 )</td>
<td>( 91:9 )</td>
</tr>
<tr>
<td>4</td>
<td>3-241</td>
<td>( \equiv \mathrm{CH} )</td>
<td>( 45^a )</td>
<td>( 84^a )</td>
</tr>
<tr>
<td>5</td>
<td>3-242</td>
<td>( \equiv \mathrm{OH} )</td>
<td>( 67:33 )</td>
<td>( 94:6 )</td>
</tr>
<tr>
<td>6</td>
<td>3-160</td>
<td>( \equiv \mathrm{CH} \equiv \mathrm{CH} \equiv \mathrm{CHOH} )</td>
<td>( 68:32 )</td>
<td>( 96:4 )</td>
</tr>
<tr>
<td>7</td>
<td>3-244</td>
<td>( \equiv \mathrm{CH} \equiv \mathrm{CH} \equiv \mathrm{CH} \equiv \mathrm{OH} \equiv \mathrm{OTBS} )</td>
<td>( 75:25 )</td>
<td>( 95:5 )</td>
</tr>
</tbody>
</table>
In comparison to PPh$_3$, Cy$_3$P proved to be a better ligand in most cases, affording regioselectivities of trans:geminal = 95:5 in most cases.$^{37}$ Interestingly, there was no difference in selectivities when hydrostannating 3-215 and silyl ether 3-48 (95:5 vs. 96:4, respectively, Table 3.27), but a slight difference when hydrostannating 3-8 and silyl ether 3-237 (67:33 vs. 77:23, respectively, Table 3.28). The steric effect of the TBS group in 3-237 could be a factor in improving the selectivities slightly, but did not improve the selectivities much when hydrostannating 3-48. Hydrostannation of 3-238, 3-239 and 3-240 with Cy$_3$P provided good to excellent selectivities (83:17, 91:9, 85:15, respectively). TBS-ether 3-239 provided higher selectivities than the alcohol or the acetate derivative, which could be attributed to the bulky TBS group. TBS-ether 3-243 afforded the same selectivities as its alcohol counterpart 3-160; suggesting no effect by the TBS that far away from the alkyne. Examining the proximity of the alcohol and its effect on the
selectivity, alkynyl alcohols HCC(CH$_2$)$_n$OH with chains $n = 1, 2, 3, 4$ and 9 afforded selectivities of 67:33, 83:17, 94:6, 96:4 and 96:4, respectively. The closer the alcohol, $n < 3$, the lower the selectivities obtained for the trans isomer. Conjugated alkynyl substrates 3-23 and 3-24 afforded selectivities of 81:19 and 0:100, respectively. Substrate 3-24 afforded only the geminal isomer with either ligand, suggesting strong electronic bias which cannot be overcome by Cy$_3$P ligand. On the other hand, Cy$_3$P was able to overcome the electronic bias of 3-23 and afford trans isomer as the major product. Some vinylstannyl isomeric products were inseparable from each other. Hydrostannation products of propargyl alcohol 3-8, TBS-ether 3-237 and homopropargyl alcohol 3-238 could be separated by silica gel chromatography. Meanwhile, homopropargyl TBS-ether 3-239 and its acetate derivative 3-240 were inseparable. Hydrostannation products of substrate 3-241 were separated by careful chromatography, while substrates 3-242, 3-160 and 3-243 were inseparable by silica gel chromatography. The inability to separate certain vinylstannanes was not a problem since trans and geminal vinylstannanes have different reactivity rates which we will demonstrate during applications. Overall with notable exceptions, this methodology allows a wide range of substrates to be used.$^3$
3.3.12 Applications

As mentioned earlier, isomeric stannanes such as 3-229 and 3-230 are inseparable, but it is known that geminal-vinylstannanes are notoriously slow to undergo Stille coupling,\textsuperscript{41} which is one of the major applications of vinylstannanes.

To test this theory, isomeric stannanes 3-229 and 3-230 (96:4, respectively) were treated with benzoyl chloride (1 equivalent with respect to stannanes) with a catalytic amount of Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} in THF; only enone 3-246 was isolated in 98\% yield (based on 3-229) and vinylstannane 3-230 was recovered unchanged (Scheme 3.43).

Scheme 3.43

It was demonstrated earlier the flexibility of the hydrostannation reaction with the choice of solvents. This advantage can permit a follow-up reaction in the same pot. A one-pot synthesis was developed, which involved hydrostannation/Stille coupling to produce the desired enone 3-246 in good yield (Scheme 3.44).\textsuperscript{37,42}
Scheme 3.44

To further demonstrate the usefulness of this palladium-catalyzed hydrostannation chemistry, we have applied the hydrostannation reaction to the synthesis of (E,E)-10,12-hexadecadienal 3-248, a sex pheromone component of the spotted bollworm (*Earias vittella*) and spiny bollworm (*E. insulana*) (Scheme 3.28). Hydrostannation of 3-160 led to a 96:4 mixture of 3-161 and 3-162. Treatment of this mixture with (E)-1-iodo-1-pentene under Stille conditions [cat. (CH$_3$CN)$_2$PdCl$_2$, CuI, DMF] provided the desired dienyl alcohol 3-247 in excellent yield and stereochemical purity (Scheme 3.45).
Subsequent oxidation with pyridinium dichromate (PDC) furnished pheromone 3-248.\textsuperscript{37,47} In this sequence, the longest linear sequence is 3-steps and proceeded in 82% overall yield.

Other syntheses have been developed for pheromone 3-248.\textsuperscript{47,48} Yadav et al. attained pheromone 3-248 in 32% overall yield using a longer linear sequence (Scheme 3.46).\textsuperscript{47} This sequence began by alkylation of THP-ether of 9-bromononan-1-ol with alcohol 3-249 using lithium amide in liquid ammonia to give compound 3-250. Alcohol 3-250 was converted to chloride 3-251 which was coupled with ethylmagnesium iodide in the presence of copper iodide to afford 3-252. Compound 3-252 was reduced with sodium in liquid ammonia, and further deprotection and oxidation using pyridinium fluorochromate provided pheromone 3-248 (Scheme 3.46).\textsuperscript{47}
Scheme 3.46

One advantage of hydrostannation strategies is that protection of hydroxyl groups is not necessary.
3.3 Future Work

Computational studies can be useful in mechanistic analysis, and can help us to understand the hydrostannation reaction in greater details.\textsuperscript{49} There are two types of computational method; Molecular Mechanics (M.M.) methods calculate the internal energy of a particular 3-D distribution of atoms in a molecule. Methods based on Molecular Orbitals (M.O.), deal explicitly with interactions of electrons and nuclei. M.O. methods, unlike molecular mechanics, can calculate energy minimum geometries, transition state geometries and energies as well. Since M.O. calculations deal with electrons, the calculations become very slow and the risk of failing to complete the calculation are high. Despite that, high levels of computational analysis have been done on tin containing compounds.\textsuperscript{50}

Our intention is to calculate activation energies (\(\Delta G^\ddagger\)), using GaussView\textsuperscript{®} software, for both possible routes of the hydrostannation reaction (Scheme 3.47).
Calculating energy barriers for hydro-palladation (pathway A) and stannyl-palladation (pathway B) of a terminal alkyne, to provide *trans*-vinylstannane, may demonstrate which process is more feasible, in terms of energy; thus, furthering our knowledge into the mechanism of this reaction (Figure 3.5 & 3.6).
By using GaussView®, one should be able to determine $\Delta G^\neq_A$ and $\Delta G^\neq_B$ (route A vs. B).

To obtain $\Delta G^\neq$ for both routes, one must find the energies for all the structures in Figures 3.5 & 3.6. Structures 3-253 and 3-254 are the proposed transition states (T.S.). Even though structures for the T.S. have been postulated, they are unconfirmed.
**Figure 3.6** Energy diagram for route B
3.4 Summary

In summary, it has been shown that contrary to popular belief, ligands can profoundly affect the regioselectivity of palladium-catalyzed hydrostannations of 1-alkynes. High regioselectivities to produce synthetically useful trans-1-stannyl-1-alkenes may be achieved by using Pd$_2$dba$_3$/Cy$_3$PHBF$_4$/i-Pr$_2$NEt for a wide range of alkynes. This system gives much better regioselectivities than the traditional PPh$_3$-based catalysts currently in use. Sex pheromone 3-248 was synthesized in three steps from alkynol 3-160 in 82% overall yield without the protection of the alcohols; an advantage of hydrostannation methodology. Additional work is underway to expand the scope of these hydrostannations and to better understand the different possible mechanistic pathways.
3.5 Experimental

3.5.1 General experimental

All reactions were carried out under argon using flame-dried glassware. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ at 300 MHz and 75 MHz, respectively, unless otherwise noted. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 ev) ionization unless otherwise specified. Couplings to $^{117}$Sn and $^{119}$Sn are reported as averages of the two values. Glassware used for hydrostannations were treated with hot aqua regia (conc. HCl: conc. HNO$_3$, 3:1 v/v) then rinsed with distilled water to remove traces of palladium. All reactions were performed using flame-dried glassware under an argon atmosphere. Dichloromethane and diisopropylethylamine were freshly distilled from calcium hydride. Tetrahydrofuran, diethyl ether, and toluene were freshly distilled from sodium/benzophenone. Tributyltin hydride was prepared by reduction of bis(tributyltin)oxide with NaBH$_4$ in ethanol$^{51}$ and was distilled (kugelrohr) before use. Samples were checked by $^{13}$C NMR spectroscopy (in C$_6$D$_6$ since Bu$_3$SnH reacts with CDCl$_3$) for the presence of Bu$_3$SnSnBu$_3$ and were re-distilled if necessary.$^{52}$ Other reagents were purchased from Sigma-Aldrich and used without further purification except $t$-Bu$_3$PHBF$_4$ and $t$-Bu$_2$PCH$_2$t-BuHBF$_4$ which were gifts from FMC Lithium Co. 10-Undecyn-1-ol (3-160) was prepared by bromination/dehydrobromination of 10-undecen-1-ol.$^{53}$ Commercially-unavailable propargylic alcohols were prepared by addition of lithium trimethylsilylacetylide to the appropriate aldehyde followed by treatment with K$_2$CO$_3$/MeOH.$^{54,55}$
3.5.2 **General procedure for hydrostannation of alkynes**

Pd$_2$dba$_3$ (4.6 mg, 0.005 mmol), tricyclohexylphosphonium tetrafluoroborate (7.4 mg, 0.02 mmol) and diisopropylethylamine (5.2 mg, 0.04 mol) were added successively to toluene (10 mL) and the resulting mixture was stirred at room temperature for 10 minutes. The alkyne (1.0 mmol) was added and then Bu$_3$SnH (349 mg, 1.2 mmol) diluted in toluene (3 mL) was added dropwise *via* a dropping funnel over 5 minutes. The reaction was then allowed to stir at rt for 2 hours. The reaction mixture was concentrated and purified by silica gel chromatography (hexanes:ether) to afford the corresponding vinylstannane with the regioselectivities and yields reported in Tables 3.27 and 3.28.

Subsequent to carrying out these experiments, we have found that CH$_2$Cl$_2$ gives very similar results and, being much more volatile than toluene, is more convenient to use. We have also found that, in larger scale reactions, small (~5%) amounts of Z-1-tributylstannyl-1-alkenes are sometimes formed (presumably via a competitive radical pathway) if the reaction mixture is not cooled. Thus we now routinely run these hydrostannations in CH$_2$Cl$_2$ at 0 °C (see following procedure).
3.5.2.1 \((E)-4\text{-}(\text{Tributylstannyl})\text{but-3-en-2-ol} (3-146)\)

\[
\text{Bu}_3\text{Sn} - \text{OH}
\]

Stannane 3-146 was made in 84% isolated yield as a separable mixture of isomers (95:5, trans:gem) from alkyne 3-46 using the general procedure to provide 0.303 g as a clear oil.

\(^1\text{H NMR} \delta 6.07 (\text{SnC}H\text{A}=\text{CHB}, \text{AB of ABX}, 2\text{H}, \delta_A = 6.10, \delta_B = 6.04, J_{AB} = 19.2 \text{ Hz}, J_{BX} = 4.3 \text{ Hz}, J_{\text{Sn-HA}} = 69 \text{ Hz}, J_{\text{Sn-HB}} = 66 \text{ Hz}), 4.24 (\text{CH}_3\text{CH}, 1\text{H}), 1.47-0.79 (\text{CH}_3\text{CH}, 3\text{H} and \text{Sn-nBu}, 27\text{H}, \text{m}); \(^{13}\text{C NMR} \delta 152.0 (\text{SnC}H=\text{CH}), 126.4 (\text{SnCH}=\text{CH}), 71.2 (\text{CH}_3\text{CH}, J_{\text{Sn-C}} = 62.4 \text{ Hz}), 28.9 (\text{SnCH}_2\text{CH}_2\text{CH}_3), J_{\text{Sn-C}} = 20.4 \text{ Hz}), 27.1 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), J_{\text{Sn-C}} = 53.4 \text{ Hz}), 23.0 (\text{CH}_3\text{CH}), 13.6 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 9.3 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), J_{\text{Sn-C}} = 339.6 \text{ Hz}).

3.5.2.2 \((\text{Tributylstannyl})\text{but-3-en-2-ol} (3-147)\)

\[
\text{SnBu}_3 - \text{OH}
\]

\(^1\text{H NMR} \delta 5.91 (\text{SnC}=\text{CH}_2, 1\text{H}, \text{br s}, J_{\text{Sn-H}} = 132.6 \text{ Hz}), 5.15 (\text{SnC}=\text{CH}_2, 1\text{H}, \text{br s}, J_{\text{Sn-H}} = 62.5 \text{ Hz}), 4.39 (\text{CH}_3\text{CH}, 1\text{H}, \text{m}), 1.48-0.87 (\text{CH}_3\text{CH}, 3\text{H} and \text{Sn-nBu}, 27\text{H}, \text{m}); \(^{13}\text{C NMR} \delta 160.3 (\text{SnC}=\text{CH}_2), 122.7 (\text{SnC}=\text{CH}_2), 74.7 (\text{CH}_3\text{CH}), 29.1 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 27.3 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 24.0 (\text{CH}_3\text{CH}), 13.6 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 10.0 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3).
3.5.2.3 *(E)*-11-(Tributylstannyl)undec-10-en-1-ol (3-161)\(^{57}\)

\[
\text{Bu}_3\text{Sn} \begin{array}{c}
\quad
\end{array} \text{HO}
\]

Stannane 3-161 was made in 87% isolated yield as an inseparable mixture of isomers (96:4, *trans*:gem) from alkyne 3-160 using the general procedure to provide 0.400 g as a clear oil.

\(^1\)H NMR \(\delta\) 5.87 (SnCH\(_2\)=CH\(_A\), AB of ABX\(_2\), 2H, \(\delta_A = 5.92, \delta_B = 5.82, J_{AB} = 19.0\) Hz, 

\(J_{AX} = 6.1\) Hz, \(J_{Sn-H} = 66.2\) Hz, \(J_{Sn-H} = 79.0\) Hz), 3.60 (HOC\(_2\)H, 2H, t, \(J = 6.6\) Hz), 2.09 (CHCH\(_2\), 2H, q, \(J = 6.0\) Hz), 1.55-0.80 (CH\(_2\)(CH\(_2\))\(_7\)CH\(_2\), 14H and Sn-nBu, 27H, m);

\(^{13}\)C NMR \(\delta\) 149.9 (SnCH=CH), 127.0 (SnCH=CH, \(J_{Sn-C} = 359.8\) Hz), 63.1 (HOCH\(_2\)CH\(_2\), 37.9 (CH\(_2\)CH\(_2\)CH\(_3\), \(J_{Sn-C} = 64.1\) Hz), 32.9 (HOCH\(_2\)CH\(_2\), 29.7, 29.55, 29.50, 29.2, 29.0, 25.8, 29.2 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(J_{Sn-C} = 20.2\) Hz), 27.3 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(J_{Sn-C} = 53.7\) Hz), 13.8 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 9.5 (SnCHCH\(_2\)CH\(_2\)CH\(_3\), \(J_{Sn-C} = 332.9\) Hz).

3.5.2.4 10-(Tributylstannyl)undec-10-en-1-ol (3-162)

\[
\begin{array}{c}
\quad
\end{array} \text{SnBu}_3 \text{OH}
\]

\(^1\)H NMR \(\delta\) 5.63 (SnC=CH\(_2\), 1H, s, \(J_{Sn-H} = 144.1\)Hz, \(J = 2.7\) Hz), 5.06 (SnC=CH\(_2\), 1H, \(J_{Sn-H} = 64.8\)Hz, \(J = 2.7\) Hz), 3.62 (HOCH\(_2\), 2H, t, \(J = 6.6\) Hz), 2.20 (SnCCH\(_2\), 2H, t, \(J = 6.8\) Hz, \(J_{Sn-H} = 48.0\) Hz), 1.54-0.83 (CH\(_2\)(CH\(_2\))\(_7\)CH\(_2\), 14H and Sn-nBu, 27H, m); \(^{13}\)C NMR \(\delta\) 155.7(SnC=CH\(_2\)), 124.4 (SnC=CH\(_2\), \(J_{Sn-C} = 35.3\) Hz), 61.2 (HOCH\(_2\)CH\(_2\), 41.3
(CH₂CH₂C), 32.7 (HOCH₂CH₂), 29.6, 29.5, 29.35, 29.3, 29.2, 25.6, 29.0 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 19.6 Hz), 27.3 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 56.6 Hz), 13.6 (SnCH₂CH₂CH₂CH₃), 9.5 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 322.0 Hz). IR (neat) v_max 3339(br), 3033, 2923, 2854, 1464, 1072, 912, 665 cm⁻¹. Exact mass (EI) calcd for C₁₉H₃₉O¹²₀Sn (M – n-Bu)⁺: 403.2023, found: 403.2091.

3.5.2.5 (E)-**Tert**-butyldimethyl(11-(tributylstannyl)undec-10-enyloxy)silane (3-229)⁵⁷

![Stannane 3-229](image)

Stannane 3-229 was made in 86% isolated yield as an inseparable mixture of isomers (95:5, *trans*:gem) from alkyne 3-243 using the general procedure to provide 0.493 g as a clear oil.

¹H NMR δ 5.88 (SnCH_B=CH_A, AB of ABX₂, 2H, δ_A = 5.93, δ_B = 5.84, J_{AB} = 19.0 Hz, J_{AX} = 5.3 Hz, J_{Sn-H_A} = 66.0 Hz, J_{Sn-H_B} = 77.2 Hz), 3.58 (TBSOCH₂, 2H, t, J = 6.6 Hz), 2.08 (SnCHCHCH₂, 2H, dt, J = 7.0, 6.0 Hz), 1.56-0.81 (CH₂(CH₃)₂CH₂, tBu(CH₃)₂Si), and Sn-nBu, 50H, m), 0.03 (tBu(CH₃)₂Si, 6H, s); ᵃ¹³C NMR δ 149.7 (SnCH≡CH), 126.8 (SnCH≡CH, J_{Sn-C} = 378.5 Hz), 63.1 (TBSOCH₂CH₂), 37.8 (CH₂CH₂CH, J_{Sn-C} = 57.7 Hz), 32.8, 29.5, 29.4, 29.3, 28.8, 25.7, 29.0 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 24.1 Hz), 27.2 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 52.8 Hz), 25.9 (CH₃₃C(CH₃)₂Si), 18.3 ((CH₃)_₃C(CH₃)₂Si), 13.6 (SnCH₂CH₂CH₂CH₃), 9.3 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 333.6 Hz), -5.4 ((CH₃)_₃C(CH₃)₂Si).
3.5.2.6 *Tert*-butyldimethyl(10-(tributylstannyl)undec-10-enyloxy)silane (3-230)

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{OTBS} \\
\end{align*}
\]

\(^1\)H NMR  \(\delta\) 5.63 (SnC=CH\(_2\), 1H, br s, J\(_{\text{Sn-H}}\) = 142.6 Hz), 5.06 (SnC=CH\(_2\), 1H, br s, J\(_{\text{Sn-H}}\) = 65.6 Hz), 3.56 (TBSOC\(_2\)H\(_2\), 2H, t, J = 6.6 Hz), 2.21 (SnCC\(_2\)H\(_2\), 2H, t, J = 6.8 Hz, J\(_{\text{Sn-H}}\) = 48.0 Hz), 1.52-0.83 (CH\(_2\)(C\(_7\)H\(_2\))\(_7\)CH\(_2\), 14H, m), 0.03 (tBu(CH\(_3\))\(_2\)Si, 6H, s); \(^{13}\)C NMR \(\delta\) 155.7 (SnC=CH\(_2\)), 124.4 (SnC=CH\(_2\)), 63.2 (TBSOCH\(_2\)CH\(_2\)), 41.3 (CH\(_2\)(CH\(_2\))), 32.8 (TBSOCH\(_2\)CH\(_2\)), 29.6, 29.5, 29.4, 29.3, 29.2, 25.7 (CH\(_2\)(CH\(_2\))\(_6\)CH\(_2\)OTBS), 29.0 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J\(_{\text{Sn-C}}\) = 19.7 Hz), 27.3 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J\(_{\text{Sn-C}}\) = 56.4 Hz), 25.9 ((CH\(_3\))\(_3\)C(CH\(_3\))\(_2\)Si), 18.3 ((CH\(_3\))\(_3\)C(CH\(_3\))\(_2\)Si), 13.6 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 9.5 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J\(_{\text{Sn-C}}\) = 326.0 Hz), -5.38 ((CH\(_3\))\(_3\)C(CH\(_3\))\(_2\)Si). IR (neat) \(v_{\text{max}}\) 2956, 2928, 2856, 1463, 1255, 1101, 836, 775 cm\(^{-1}\).

Exact mass (EI) calcd for C\(_{25}\)H\(_{53}\)OSi\(^{120}\)Sn (M – n-Bu): 517.2888, found: 517.2961.

3.5.2.7 (E)-3-(Tributylstannyl)prop-2-en-1-ol (3-11)\(^{56}\)

\[
\begin{align*}
\text{Bu}_3\text{Sn} & \quad \text{OH} \\
\end{align*}
\]

Stannane 3-11 was made in 61% isolated yield as a separable mixture of isomers (67:33, \textit{trans:gem}) from alkyne 3-8 using the general procedure to provide 0.212 g as a clear oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.24 (SnCH\(_A\)=CH\(_B\), AB of ABX\(_2\), 2H, \(\delta_A = 6.24\), \(\delta_B = 6.19\), J\(_{\text{AB}}\) = 19.2 Hz, J\(_{\text{BX}}\) = 4.0 Hz, J\(_{\text{Sn-HA}}\) = 68.6 Hz, J\(_{\text{Sn-HB}}\) = 62.6 Hz), 4.19 (HOCH\(_2\)CH, t,
2H, J = 4.3 Hz), 1.74 (HOCH₂CH, s, 1H), 1.55-0.89 (Sn-nBu, 27H, m); ¹³C NMR (75 MHz, CDCl₃) δ 147.0 (SnC=CH), 128.1 (SnC=CH, Jₘₙ-C = 378.5 Hz), 66.1 (HOCH₂CH, Jₘₙ-C = 64.0 Hz), 28.9 (SnCH₂CH₂CH₂CH₃, Jₘₙ-C = 20.5 Hz), 27.1 (SnCH₂CH₂CH₂CH₃, Jₘₙ-C = 64.1 Hz), 13.5 (SnCH₂CH₂CH₂CH₃), 9.3 (SnCH₂CH₂CH₂CH₃, Jₘₙ-C = 333.6 Hz).

3.5.2.8 2-(Tributylstannyld)prop-2-en-1-ol (3-9)⁵⁶

\[ \text{SnBu}_3\text{OH} \]

¹H NMR δ 5.84 (SnC=CH₂, 1H, s, Jₘₙ-H = 129.8 Hz), 5.20(SnC=CH₂, 1H, Jₘₙ-H = 61.9 Hz), 4.39 (HOCH₂C, 2H, s, Jₘₙ-H = 27.9 Hz), 1.95 (HOCH₂C, 1H, s), 1.48-0.87 (Sn-nBu, 27H, m); ¹³C NMR δ 154.6 (SnC=CH₂, Jₘₙ-C = 346.4 Hz), 122.6 (SnC=CH₂, Jₘₙ-C = 19.2 Hz), 74.7 (HOCH₂CH, Jₘₙ-C = 46.4 Hz), 29.1 (SnCH₂CH₂CH₂CH₃, Jₘₙ-C = 20.0 Hz), 27.2 (SnCH₂CH₂CH₂CH₃, Jₘₙ-C = 64.1 Hz), 13.5 (SnCH₂CH₂CH₂CH₃), 9.3 (SnCH₂CH₂CH₂CH₃, Jₘₙ-C = 333.6 Hz).
3.5.2.9 (E)-Tert-butyldimethyl(3-(tributylstanny)allyloxy)silane (3-218)\(^{58}\)

\[
\text{Bu}_3\text{Sn} \quad \begin{array}{c}
\text{OTBS}
\end{array}
\]

Stannane 3-218 was made in 64% isolated yield as a separable mixture of isomers (77:23, \textit{trans}:gem) from alkyne 3-237 using the general procedure to provide 0.295 g as a clear oil.

\(^1\)H NMR \(\delta 6.10\) (SnCH=CH, AB of ABX\(_2\), 2H, \(\delta_A = 6.16, \delta_B = 6.04, J_{AB} = 19.0\) Hz, \(J_{BX} = 4.0\) Hz, \(J_{\text{Sn-H}_A} = 75.6\) Hz, \(J_{\text{Sn-H}_B} = 62.6\) Hz), \(4.18\) (TBSOCH\(_2\)CH, d, 2H, \(J = 2.8\) Hz, \(J_{\text{Sn-C}} = 380.4\) Hz), \(29.0\) (SnCH=CH, \(J_{\text{Sn-C}} = 20.6\) Hz), \(27.1\) (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(J_{\text{Sn-C}} = 54.3\) Hz), \(25.8\) ((CH\(_3\)_2Si-tBu, 9H, s and Sn-nBu, 27H, m), \(0.90\) ((CH\(_3\)_2Si-tBu, 6H, s); \(^{13}\)C NMR \(\delta 147.2\) (SnCH=CH), \(126.7\) (SnCH=CH, \(J_{\text{Sn-C}} = 380.4\) Hz), \(66.6\) (TBSOCH\(_2\)CH, \(J_{\text{Sn-C}} = 68.8\) Hz), \(29.0\) (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(J_{\text{Sn-C}} = 20.6\) Hz), \(27.1\) (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(J_{\text{Sn-C}} = 54.3\) Hz), \(25.8\) ((CH\(_3\)_2SiC(CH\(_3\))\(_3\)), \(18.3\) ((CH\(_3\)_2SiC(CH\(_3\))\(_3\)), \(13.5\) (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(9.3\) (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(J_{\text{Sn-C}} = 339.6\) Hz), \(-5.2\) ((CH\(_3\)_2SiC(CH\(_3\))\(_3\)).

3.5.2.10 Tert-butyldimethyl(2-(tributylstanny)allyloxy)silane (3-219)\(^{58}\)

\[
\begin{array}{c}
\text{SnBu}_3
\end{array} \quad \begin{array}{c}
\text{OTBS}
\end{array}
\]

\(^1\)H NMR \(\delta 5.85\) (SnC=CH, 1H, d, \(J = 2\) Hz, \(J_{\text{Sn-H}} = 133.3\) Hz), \(5.17\) (SnC=CH, 1H, d, \(J = 2.0\) Hz, \(J_{\text{Sn-H}} = 63.6\) Hz), \(4.29\) (TBSOCH\(_2\)C, 2H, s, \(J_{\text{Sn-H}} = 26.7\) Hz), \(1.55-0.83\) ((CH\(_3\)_2Si-tBu, 9H, s and Sn-nBu, 27H, m), \(0.06\) ((CH\(_3\)_2Si-tBu, 6H, s); \(^{13}\)C NMR \(\delta 154.7\))
(SnC=CH₂, J_{Sn-C} = 366.9 Hz), 121.8 (SnC=CH₂, J_{Sn-C} = 18.9 Hz), 69.6 (TBSOCH₂CH₃, J_{Sn-C} = 46.3 Hz), 29.0 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 19.8 Hz), 27.3 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 56.8 Hz), 25.9 ((CH₃)₂SiC(CH₃)₃, 18.4 ((CH₃)₂SiC(CH₃)₃, 13.6 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 339.6 Hz), -5.5 ((CH₃)₂SiC(CH₃)₃).

3.5.2.11 *(E)*-4-(Tributylstannyl)but-3-en-1-ol (3-220)\(^{56}\)

![Bu₃SnOH](image)

Stannane 3-220 was made in 70% isolated yield as a separable mixture of isomers (83:17, *trans:*gem) from alkyne 3-238 using the general procedure to provide 0.253 g as a clear oil.

\(^1\)H NMR \(\delta\) 6.24 (SnCH\(_A\)=CH\(_B\), AB of ABX\(_2\), 2H, \(\delta_A = 6.03, \delta_B = 5.91, J_{AB} = 19.0\) Hz, J\(_{BX}\) = 6.1 Hz, J\(_{Sn-HA}\) = 74.6 Hz, J\(_{Sn-HB}\) = 63.0 Hz), 4.19 (HOCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), t, 2H, J = 6.2 Hz), 2.40 (HOCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), q, 2H, J = 6.1 Hz), 1.56-0.83 (Sn-nBu, 27H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.7(SnCH=CH\(_2\)), 132.1(SnCH=CH\(_2\)), 61.3 (HOCH\(_2\)CH\(_2\)CH\(_3\)), 41.1 (HOCH\(_2\)CH\(_2\)CH\(_3\)), 29.0 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J\(_{Sn-C}\) = 20.6 Hz), 27.1 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J\(_{Sn-C}\) = 54.3 Hz), 13.6 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 9.3 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J\(_{Sn-C}\) = 359.2 Hz).
3.5.2.12 3-(Tributylstannyl)but-3-en-1-ol (3-221)$^{56}$

\[
\text{SnBu}_3\text{OH}
\]

$^1$H NMR $\delta$ 5.77 (SnC=CH$_2$, 1H, s, $J_{\text{Sn-H}} = 135.7$ Hz), 5.26 (SnC=CH$_2$, 1H, $J_{\text{Sn-H}} = 62.4$ Hz), 4.39 (HOCH$_2$CH$_2$C, 2H, t, $J = 6.3$ Hz), 2.49 (HOCH$_2$CH$_2$C, 2H, t, $J = 6.3$ Hz, $J_{\text{Sn-H}} = 46.9$ Hz), 1.59-0.84 (Sn-nBu, 27H, m); $^{13}$C NMR $\delta$ 151.4 (SnC=CH$_2$, $J_{\text{Sn-C}} = 357.2$ Hz), 128.2 (SnC=CH$_2$, $J_{\text{Sn-C}} = 25.7$ Hz), 61.2 (HOCH$_2$CH$_2$C, $J_{\text{Sn-C}} = 11.2$ Hz), 44.1 (HOCH$_2$CH$_2$C, $J_{\text{Sn-C}} = 37.7$ Hz), 29.0 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}} = 19.8$ Hz), 27.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}} = 57.5$ Hz), 13.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}} = 326.2$ Hz).

3.5.2.13 (E)-5-(Tributylstannyl)pent-4-en-1-ol (3-225)$^{58}$

\[
\text{Bu}_3\text{Sn}\text{OH}
\]

Stannane 3-225 was made in 84% isolated yield as a separable mixture of isomers (94:6, trans:gem) from alkyne 3-241 using the general procedure to provide 0.315 g as a clear oil.

$^1$H NMR $\delta$ 5.93 (SnCH$_A$=CH$_B$, AB of ABX$_2$, 2H, $\delta_A = 5.91$, $\delta_B = 5.95$, $J_{\text{AB}} = 18.7$ Hz, $J_{\text{BX}} = 4.5$ Hz, $J_{\text{Sn-HA}} = 72.5$ Hz, $J_{\text{Sn-HB}} = 66.9$ Hz), 3.63 (HOCH$_2$CH$_2$CH$_2$CH, t, 2H, $J = 6.5$ Hz), 2.20 (HOCH$_2$CH$_2$CH$_2$CH, dt, 2H, $J = 4.5$, 6.6 Hz), 1.66 (HOCH$_2$CH$_2$CH$_2$CH, quintet, 2H, $J = 7.2$ Hz), 1.52-0.81 (Sn-nBu, 27H, m); $^{13}$C NMR $\delta$ 148.5(SnCH=CH), 125.5
(SnCH=CH, J_{Sn-C} = 390.8 Hz), 62.4 (HOCH_2CH_2CH_2CH, 34.0 (HOCH_2CH_2CH_2CH, J_{Sn-C} = 60.4 Hz), 31.7 (HOCH_2CH_2CH_2CH), 29.0 (SnCH_2CH_2CH_2CH_3, J_{Sn-C} = 20.4 Hz), 27.1 (SnCH_2CH_2CH_2CH_3, J_{Sn-C} = 53.8 Hz), 13.6 (SnCH_2CH_2CH_2CH_3), 9.3 (SnCH_2CH_2CH_2CH_3, J_{Sn-C} = 332.1 Hz).

3.5.2.14 4-(Tributylstannyl)pent-4-en-1-ol (3-226)

\[
\text{SnBu}_3\text{OH}
\]

^1H NMR δ 5.69 (SnC=CH_2, 1H, d, J = 2 Hz, J_{Sn-H} = 140.5 Hz), 5.11(SnC=CH_2, 1H, d, J = 2 Hz, J_{Sn-H} = 62.4 Hz), 3.62 (HOCH_2CH_2CH_2C, 2H, t, J = 6.5 Hz), 2.49 (HOCH_2CH_2CH_3C, 2H, t, J = 6.5 Hz, J_{Sn-H} = 48.0 Hz), 1.63(HOCH_2CH_2CH_2C, 2H, quintet, J = 7.2 Hz) 1.50-0.85 (Sn-nBu, 27H, m); \(^{13}C\) NMR δ 154.8 (SnC=CH_2), 125.1 (SnC=CH_2, J_{Sn-C} = 27.5 Hz), 62.5 (HOCH_2CH_2CH_2C), 44.1 (HOCH_2CH_2CH_2C, J_{Sn-C} = 48.2 Hz), 32.3 (HOCH_2CH_2CH_2C, J_{Sn-C} = 12.7 Hz), 29.0 (SnCH_2CH_2CH_2CH_3, J_{Sn-C} = 19.8 Hz), 27.3 (SnCH_2CH_2CH_2CH_3, J_{Sn-C} = 57.0 Hz), 13.6 (SnCH_2CH_2CH_2CH_3), 9.5 (SnCH_2CH_2CH_2CH_3, J_{Sn-C} = 326.0 Hz).
3.5.2.15 *(E)*-6-(Tributylstannyl)hex-5-en-1-ol (3-227)\(^\text{13}\)

![Bu₅Sn=CH₋OH](image)

Stannane 3-227 was made in 85% isolated yield as an inseparable mixture of isomers (96:4, \textit{trans}:\textit{gem}) from alkyne 3-242 using the general procedure to provide 0.331 g as a clear oil.

\(^1\)H NMR \(\delta 5.93\) (SnC\(_2\)H\(_{11}\) = CH\(_3\), AB of ABX\(_2\), 2H, \(\delta_A = 5.85, \delta_B = 5.91, J_{AB} = 19.0\) Hz, \(J_{BX} = 5.0\) Hz, \(J_{Sn-H_A} = 75.8\) Hz, \(J_{Sn-H_B} = 64.5\) Hz), 3.63 (HOC\(_2\)H\(_{11}\)CH\(_2\), t, 2H, \(J = 6.2\) Hz), 2.13 (HOC\(_2\)H\(_{11}\)CH\(_2\)CH, dt, 2H, \(J = 5.0\) Hz, \(J = 6.0\) Hz), 1.56-0.81 (HOC\(_2\)H\(_{11}\)CH\(_2\)CH\(_2\)CH, 4H, m and Sn-nBu, 27H, m); \(^{13}\)C NMR \(\delta 149.0\) (SnC=CH), 127.5 (SnC=CH, \(J_{Sn-C} = 396.8\) Hz), 62.6 (HOCH\(_2\)CH\(_2\)CH\(_2\)CH, 37.4 (HOCH\(_2\)CH\(_2\)CH\(_2\)CH, \(J_{Sn-C} = 63.5\) Hz), 32.1 (HOCH\(_2\)CH\(_2\)CH\(_2\)CH, 29.0 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH, \(J_{Sn-C} = 20.4\) Hz), 27.1 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH, \(J_{Sn-C} = 53.8\) Hz), 24.9 (HOCH\(_2\)CH\(_2\)CH\(_2\)CH), 13.6 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH, 9.3 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH, 332.1 Hz).

3.5.2.16 5-(Tributylstannyl)hex-5-en-1-ol (3-228)\(^\text{13}\)

![SnBu₃=CH₋OH](image)

\(^1\)H NMR \(\delta 5.64\) (SnC=CH, 1H, s, \(J_{Sn-H} = 139.7\) Hz), 5.08(SnC=CH, 1H, s, \(J_{Sn-H} = 63.0\) Hz), 3.63 (HOCH\(_2\)CH\(_2\)CH\(_2\)CH, 2H, \(J = 6.2\) Hz), 2.23 (HOCH\(_2\)CH\(_2\)CH\(_2\)C, 2H,
t, J = 7.5Hz), 1.56-0.80 (HOCH₂CH₂CH₂CH₂C, 4H, m and Sn-nBu, 27H, m); \(^{13}\)C NMR δ 155.0 (SnC=CH₂), 124.8 (SnC=C₆H₅), 62.6 (HOCH₂CH₂CH₂CH₂C), 40.1, 32.3, 29.1 (SnCH₂CH₂CH₂CH₃), 27.3 (SnCH₂CH₂CH₂CH₃), 25.5 (HOCH₂CH₂CH₂CH₂C), 13.6 (SnCH₂CH₂CH₂CH₃), 9.4 (SnCH₂CH₂CH₂CH₃, Jₘₙ = 338.1 Hz).

3.5.2.17 (E)-1-(Tributylstannyl)oct-1-en-3-ol (3-205)

Stannane 3-205 was made in 82% isolated yield as a separable mixture of isomers (95:5, trans:gem) from alkyne 3-215 using the general procedure to provide 0.342 g as a clear oil.

\(^{1}\)H NMR δ 6.04 (SnCH₃=CH₂, AB of ABX, 2H, δₓ = 6.11, δₜ = 5.98, Jₓ = 19.1 Hz, Jₜ = 5.3 Hz, Jₘₙ = 71Hz, Jₘ_s = 63 Hz), 4.03 (CH₂OH, m, 1H), 1.54-0.84 (CH₃CH₂CH₂CH₂CH₂CH₃, 11H and Sn-nBu, 27H, m); \(^{13}\)C NMR δ 151.0 (SnCH=CH₂), 127.5 (SnCH=CH₂), 75.5 (CH₂CHOHTBS, Jₘₙ = 61.1 Hz), 36.8, 31.7, 29.0 (SnCH₂CH₂CH₂CH₃, Jₘₙ = 20.6 Hz), 27.1 (SnCH₂CH₂CH₂CH₃, Jₘₙ = 53.3 Hz), 24.9, 22.5, 13.9 (CH₃CH₂CH₂CH₂CH₂CH₂), 13.6 (SnCH₂CH₂CH₂CH₃), 9.3 (SnCH₂CH₂CH₂CH₃, Jₘₙ = 340.0 Hz).
3.5.2.18 2-(Tributylstannyl)oct-1-en-3-ol (3-206)\textsuperscript{13}

![3.5.2.18](image)

\[\text{SnBu}_3\]

\[\text{OH}\]

$^{1}$H NMR $\delta$ 5.76 (SnC=CH, 1H, s, J$_{\text{Sn-H}}$ = 132.3 Hz), 5.19 (SnC=CH, 1H, s, J$_{\text{Sn-H}}$ = 62.6 Hz), 4.17 (CH$_2$OH, 1H, m), 1.50-0.85 (CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$CH, 11H and Sn-nBu, 27H, m); $^{13}$C NMR $\delta$ 159.2(SnC=CH$_2$), 123.8 (SnC=CH$_2$), 79.3(CH$_2$CH), 37.5, 31.2, 29.0 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 27.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 25.3, 22.5, 13.9(CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$CH) 13.6 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 10.0 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{\text{Sn-c}}$ = 333.6 Hz).

3.5.2.19 (E)-Tert-butyldimethyl(1-(tributylstannyl)oct-1-en-3-yloxy)silane (3-207)\textsuperscript{17}

![3.5.2.19](image)

Stannane 3-207 was made in 77\% isolated yield as an inseparable mixture of isomers (96:4, trans:gem) from alkyne 3-48 using the general procedure to provide 0.406 g as a clear oil.

$^{1}$H NMR $\delta$ 5.94 (SnCH$_A$=CH$_B$, AB of ABX, 2H, $\delta_A = 5.99$, $\delta_B = 5.90$, J$_{AB}$ = 19.1 Hz, J$_{BX}$ = 5.5 Hz, J$_{\text{Sn-HA}} = 73.5$ Hz, J$_{\text{Sn-HB}} = 63.6$ Hz), 4.0 (CH$_2$CHOTBS, 1H, dt, J = 5.5 Hz, J = 5.7 Hz), 1.55-0.83(CH$_3$CH$_3$CH$_2$CH$_2$CH$_2$CH, 11H, tBu(CH$_3$)$_2$Si, 9H, s and Sn-nBu, 27H, m), 0.02 (tBu(CH$_3$)$_2$Si, 6H, s); $^{13}$C NMR $\delta$ 152.0 (SnCH=CH), 126.2 (SnCH=CH), 76.8 (CH$_2$CHOTBS), 38.0 (CH$_3$CH$_2$CH$_2$CH$_2$CH), 31.8 (CH$_3$CH$_2$CH$_2$CH$_2$CH), 29.1
(SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 20.7 Hz), 27.2 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 52.8 Hz), 25.9
((CH₃)₃C(CH₃)₂Si), 25.0 (CH₃CH₂CH₂CH₂CH₂CH₃), 22.6 (CH₃CH₂CH₂CH₂CH₂CH₃),
18.3 ((CH₃)₃C(CH₃)₂Si), 14.0 (CH₃CH₂CH₂CH₂CH₂CH₃), 13.7 (SnCH₂CH₂CH₂CH₃), 9.4
(SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 336.6 Hz), -4.4 ((CH₃)₃C(CH₃)₂Si).

3.5.2.20 *Tert*-butyldimethyl(2-(tributylstannyl)oct-1-en-3-yloxy)silane (3-208)¹⁷

\[ \text{SnBu₃} \]
\[ \text{OTBS} \]

¹H NMR δ 5.69 (SnC=CH₂, 1H, d, J = 1.8 Hz, J_{Sn-H} = 133.4 Hz), 5.11 (SnC=CH₂, 1H, d, J = 1.8 Hz, J_{Sn-H} = 62.4 Hz), 4.09 (CH₂CHOTBS, 1H, t, J = 5.7 Hz), 1.51-0.83(CH₃CH₂CH₂CH₂CH₂CH₃, 11H, tBu(CH₃)₂Si, 9H, s and Sn-nBu, 27H, m), 0.01
tBu(CH₃)₂Si, 6H, s); ¹³C NMR δ 159.1 (SnC=CH₂), 123.3 (SnC=CH₂, J_{Sn-C} = 22.5 Hz),
80.5 (CH₂CHOTBS, J_{Sn-C} = 35.8 Hz), 38.5(CH₂CHOTBS, J_{Sn-C} = 76.7 Hz), 31.9, 29.0
(SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 19.3 Hz), 27.3 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 57.4 Hz), 25.6
((CH₃)₃C(CH₃)₂Si), 25.1, 22.6, 18.2 ((CH₃)₃C(CH₃)₂Si), 13.9 (CH₃CH₂CH₂CH₂CH₂CH₃),
13.6 (SnCH₂CH₂CH₂CH₃), 10.1 (SnCH₂CH₂CH₂CH₃, J_{Sn-C} = 330.2 Hz), -3.1
((CH₃)₃C(CH₃)₂Si).
3.5.2.21 \(^{(E)}\)-5-Methyl-1-(tributylstannyl)hex-1-en-3-ol (3-209)\(^59\)

![Chemical Structure]  

Stannane 3-209 was made in 83% isolated yield as a separable mixture of isomers (96:4, \textit{trans}:\textit{gem}) from alkyne 3-216 using the general procedure to provide 0.335 g as a clear oil.

\(^1\)H NMR \(\delta 6.04\) (SnCH\(_A\)=CH\(_B\), AB of ABX, 2H, \(\delta_A = 6.11, \delta_B = 5.97, J_{AB} = 19.1\) Hz, \(J_{BX} = 5.6\) Hz, \(J_{Sn-H_A} = 70.2\) Hz, \(J_{Sn-H_B} = 64.2\) Hz), 4.11 ((CH\(_3\))\(_2\)CHCH\(_2\)C, q, 1H, \(J = 6.5\) Hz), 1.72 ((CH\(_3\))\(_2\)CHCH\(_2\)CH, m, 1H), 1.56-0.84 ((CH\(_3\))\(_2\)CHCH\(_2\)CH, 8H, m and Sn-nBu, 27H, m); \(^{13}\)C NMR \(\delta 149.2\) (SnCH=CH, 1H, s), 128.7 (SnCH=CH), 73.8 ((CH\(_3\))\(_2\)CHCH\(_2\)CH), 46.1 ((CH\(_3\))\(_2\)CHCH\(_2\)CH), 29.0 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH, \(J_{Sn-C} = 20.5\) Hz), 27.1 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH, \(J_{Sn-C} = 60.8\) Hz), 24.5 ((CH\(_3\))\(_2\)CHCH\(_2\)CH), 23.0, 22.3 ((CH\(_3\))\(_2\)CHCHCH), 13.6 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH), 9.3 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH, \(J_{Sn-C} = 344.3\) Hz).

3.5.2.22 5-Methyl-2-(tributylstannyl)hex-1-en-3-ol (3-210)\(^59\)

![Chemical Structure]  

\(^1\)H NMR \(\delta 5.78\) (SnC=CH\(_2\), 1H, s, \(J_{Sn-H} = 136.6\) Hz), 5.17 (SnC=CH\(_2\), 1H, s, \(J_{Sn-H} = 62.2\) Hz), 4.25 ((CH\(_3\))\(_2\)CHCH\(_2\)CH, 1H, t, \(J = 6.7\) Hz), 1.75-0.84 ((CH\(_3\))\(_2\)CHCH\(_2\)CH, 9H) (Sn-
nBu, 27H, m; $^{13}$C NMR δ 159.8 (SnC=CH$_2$), 123.7 (SnC=CH$_2$), 77.3 ((CH$_3$)$_2$CHCH$_2$CH), 47.0 ((CH$_3$)$_2$CHCH$_2$CH), 29.2 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 27.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 24.7 ((CH$_3$)$_2$CHCH$_2$CH), 23.2, 22.4 ((CH$_3$)$_2$CHCHCH), 13.7 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 10.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 340.0 Hz).

3.5.2.23 (E)-4-Methyl-1-(tributylstanny)pent-1-en-3-ol (3-211)$^{17}$

![diagram]

Stannane 3-211 was made in 86% isolated yield as a separable mixture of isomers (97:3, trans:gem) from alkyne 3-217 using the general procedure to provide 0.335 g as a clear oil.

$^1$H NMR δ 6.04 (SnCH$_A$=CH$_B$, AB of ABX, 2H, δ$_A$ = 6.11, δ$_B$ = 5.98, J$_{AB}$ = 19.2 Hz, J$_{BX}$ = 5.4 Hz, J$_{Sn-H_A}$ = 71.3 Hz, J$_{Sn-H_B}$ = 63.0 Hz), 3.81 ((CH$_3$)$_2$CHCH, t, 1H, J = 5.3 Hz), 1.71-0.84 ((CH$_3$)$_2$CHCH, 7H, m and Sn-nBu, 27H, m); $^{13}$C NMR δ 149.2 (SnCH=CH), 128.7 (SnCH=CH), 80.4 (CHOH), 33.4 ((CH$_3$)$_2$CHCH), 29.0 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 21.7 Hz), 27.1 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 18.1, 17.6 ((CH$_3$)$_2$CHCH), 13.6 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.4 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 343.5 Hz).
3.5.2.24 4-Methyl-2-(tributylstannyl)pent-1-en-3-ol (3-212)\textsuperscript{17}

\[ \text{Bu}_3\text{Sn} \quad \text{OH} \]

\(^1\text{H} \text{NMR} \delta 5.75 (\text{SnC} = \text{CH}_2, 1 \text{H}, \text{s}, J_{\text{Sn-H}} = 131.7 \text{ Hz}), 5.53 (\text{SnC} = \text{CH}_2, 1 \text{H}, J_{\text{Sn-H}} = 66.2 \text{ Hz}), 3.81 ((\text{CH}_3)_2\text{CHCH}, 1 \text{H}, \text{d}, J = 7.0 \text{ Hz}), 1.70-0.82 ((\text{CH}_3)_2\text{CHCH}, 7 \text{H} \text{ and Sn-\text{nBu}}, 27 \text{H}, \text{m}); \ ^{13}\text{C} \text{NMR} \delta 158.5 (\text{SnCH} = \text{CH}_2), 125.0 (\text{SnC} = \text{CH}_2), 85.1 (\text{CHOH}), 33.3 ((\text{CH}_3)_2\text{CHCH}), 29.2 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 27.5 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 19.9 ((\text{CH}_3)_2\text{CHCH}), 13.6 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 10.3 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3).

3.5.2.25 (E)-1-Phenyl-3-(tributylstannyl)prop-2-en-1-ol (3-213)\textsuperscript{17}

\[ \text{Bu}_3\text{Sn} \quad \text{Ph} \quad \text{OH} \]

Stannane 3-213 was made in 76\% isolated yield as a separable mixture of isomers (82:12, \textit{trans:gem}) from alkyne 3-29 using the general procedure to provide 0.322 g as a clear oil. \(^1\text{H} \text{NMR} \delta 7.35-7.25 (\text{PhH}, 5 \text{H}, \text{m}), 6.22 (\text{SnCH}_A = \text{CH}_B, \text{AB of ABX}, 2 \text{H}, \delta_A = 6.29, \delta_B = 6.16, J_{\text{AB}} = 19.1 \text{ Hz}, J_{\text{BX}} = 4.8 \text{ Hz}, J_{\text{Sn-HA}} = 67.9 \text{ Hz}, J_{\text{Sn-HB}} = 60.1 \text{ Hz}), 5.16 (\text{CH}_3\text{CH}, \text{d}, 1 \text{H}, J_{\text{XB}} = 4.6 \text{ Hz}), 1.56-0.83 (\text{Sn-\text{nBu}}, 27 \text{H}, \text{m}); \ ^{13}\text{C} \text{NMR} \delta 149.3 (\text{SnCH=CH}), 142.7 (\text{SnCH=CH}), 128.5 (\text{Ph}, 1 \text{C}), 128.4 (\text{Ph}, 2 \text{C}), 127.4 (\text{Ph}, 1 \text{C}), 126.3 (\text{Ph}, 2 \text{C}), 77.5 (\text{PhCH}), 29.0 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3, J_{\text{Sn-C}} = 20.4 \text{ Hz}), 27.1 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3, J_{\text{Sn-C}} = 54.6 \text{ Hz}), 13.6 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 9.3 (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3, J_{\text{Sn-C}} = 337.0 \text{ Hz}).
3.5.2.26 1-Phenyl-2-(tributylstanny1)prop-2-en-1-ol (3-214)\textsuperscript{17}

\[
\text{SnBu}_3 \\
\text{Ph} \\
\text{OH}
\]

\(^1\text{H} \text{ NMR} \delta \ 7.45-7.21 (\text{PhH, 5H, m}), 5.90 (\text{SnC=CH}_2, 1\text{H, s, J}_{\text{Sn-H}} = 126.3 \text{ Hz}), 5.31 (\text{CH}_3\text{CH}_2, 1\text{H, s}) 5.30 (\text{SnC=CH}_2, 1\text{H, s, J}_{\text{Sn-H}} = 65.4 \text{ Hz}), (\text{Sn-nBu, 27H, m}); \ ^{13}\text{C} \text{ NMR} \delta \ 157.9 \ (\text{SnC}=\text{CH}_2), 142.9 \ (\text{SnC}=\text{CH}_2), 80.4 \ (\text{PhCH}), 28.8 \ (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 27.2 \ (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 13.5 \ (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 9.8 \ (\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3).

3.5.2.27 Methyl (E)-2-(diphenylmethyleneamino)-5-(tributylstanny1)pent-4-enoate (3-231)\textsuperscript{60}

\[
\text{Ph} \rightarrow \text{Ph} \\
\text{N} \underset{\text{C}}{\text{O}} \\
\text{O} \\
\text{SnBu}_3
\]

Stannane 3-231 was made in 79\% isolated yield as a separable mixture of isomers (84:16, \textit{trans:gem}) from alkyne 3-244 using the general procedure to provide 0.460 g as a clear oil.

\(^1\text{H} \text{ NMR} \delta \ 7.62-7.14 (\text{HPh}_2\text{N, 10H, m}), 5.87 (\text{SnCH}_A=\text{CH}_B, \text{AB of ABX}_2, 2\text{H, } \delta_A = 5.97, \delta_B = 5.77, \text{J}_{\text{AB}} = 18.8 \text{ Hz}, \text{J}_{\text{BX}} = 6.4 \text{ Hz, J}_{\text{Sn-H}_A} = 77.0 \text{ Hz, J}_{\text{Sn-H}_B} = 64.1 \text{ Hz}), 4.19 (\text{NCHCH}_2, 1\text{H, dd, J} = 5.3 \text{ Hz}), 3.70 (\text{OCH}_3, 3\text{H, s}), 2.74 (\text{NCHCH}_2, 2\text{H, m}), 1.54-0.79 (\text{Sn-nBu, 27H, m}); \ ^{13}\text{C} \text{ NMR} \delta \ 172.4 \ (\text{C}=\text{O}), 170.4 \ (\text{C}=\text{N}), 144.3 \ (\text{SnCH}=\text{CH}), 139.6, 136.4 \ (\text{Ph}), 131.6 \ (\text{SnCH}=\text{CH, J}_{\text{Sn-C}} = 375.8 \text{ Hz}), 130.2, 128.8, 128.6, 128.4, 127.9 \ (\text{Ph}).
65.3 (NCHCH₂), 51.9 (OCH₃), 42.1 (NCHCH₂, J₁Sn-C = 62.8 Hz), 29.0 (SnCH₂CH₂CH₂CH₃, J₁Sn-C = 20.2 Hz), 27.2 (SnCH₂CH₂CH₂CH₃, J₁Sn-C = 54.8 Hz), 13.5 (SnCH₂CH₂CH₂CH₃), 9.3 (SnCH₂CH₂CH₂CH₃, J₁Sn-C = 334.5 Hz).

3.5.2.28 Methyl 2-(diphenylmethyleneamino)-4-(tributylstannyl)pent-4-enoate (3-232)

![Chemical Structure]

¹H NMR δ 7.62-7.14 (HPh₂N, 10H, m), 5.70 (SnC=CH₂, 1H, s, J₁Sn-H = 134.5 Hz), 5.18 (SnC=CH₂, 1H, J₁Sn-H = 63.6 Hz, J = 2.5 Hz), 4.19 (NCHCH₂, 1H, dd, J = 6.3, 7.3 Hz), 3.70 (OCH₃, 3H, s), 2.74 (NCHCH₂, AB of ABX, 2H, δA = 2.99, δB = 2.68, JAB = 13.5 Hz, J₁AX = 6.3 Hz, J₁BX = 7.3 Hz, J₁Sn-HA = 24.0 Hz, J₁Sn-HB = 22.8 Hz), 1.40-0.67 (Sn-nBu, 27H, m); ¹³C NMR δ 172.3 (C=O), 170.2 (C=N), 150.1 (SnC=CH₂, J₁Sn-C = 356.6 Hz), 139.6, 136.3, 130.2, 128.8, 128.6 (Ph), 128.5 (SnC=CH₂), 128.4, 128.0, 127.9 (Ph), 65.7 (NCHCH₂), 51.7 (OCH₃), 44.7 (NCHCH₂, J₁Sn-C = 38.8 Hz), 29.0 (SnCH₂CH₂CH₂CH₃, J₁Sn-C = 19.6 Hz), 27.3 (SnCH₂CH₂CH₂CH₃, J₁Sn-C = 56.0 Hz), 13.5 (SnCH₂CH₂CH₂CH₃), 9.3 (SnCH₂CH₂CH₂CH₃, J₁Sn-C = 325.3 Hz).
3.5.2.29 (E)-4-(Tributylstannyl)but-3-enyl acetate (3-223)\(^{58}\)

Stannane 3-223 was made in 80\% isolated yield as an inseparable mixture of isomers (85:15, trans:gem) from alkyne 3-240 using the general procedure to provide 0.323 g as a clear oil.

\(^1\)H NMR  \(\delta\) 5.93 (SnCH\(_A\)=CH\(_B\), AB of ABX\(_2\), 2H, \(\delta_A = 5.99, \delta_B = 5.86, J_{AB} = 19.0\) Hz, \(J_{BX} = 6.0\) Hz, \(J_{Sn-HA} = 73.6\) Hz, \(J_{Sn-HB} = 64.8\) Hz), 4.08 (AcOCH\(_2\)CH\(_2\)CH, 2H, t, \(J = 6.9\) Hz), 2.41 (AcOCH\(_2\)CH\(_2\)CH\(_2\)CH, 2H, q, \(J = 6.9\) Hz, \(J_{Sn-HA} = 73.6\) Hz), 1.99 (AcO, 3H, s), 1.53-0.82 (Sn-nBu, 27H, m); \(^{13}\)C NMR \(\delta\) 170.9 (AcO), 143.7 (SnCH=CH), 131.2 (SnCH=CH, \(J_{Sn-C} = 383.1\) Hz), 63.5 (AcOCH\(_2\)CH\(_2\)CH), 36.8 (AcOCH\(_2\)CH\(_2\)CH, \(J_{Sn-H} = 67.9\) Hz), 29.0 (SnCH\(_2\)CH\(_2\)CH\(_3\)), 27.3 (SnCH\(_2\)CH\(_2\)CH\(_3\), \(J_{Sn-C} = 53.6\) Hz), 20.8 (AcO), 13.6 (SnCH\(_2\)CH\(_2\)CH\(_3\)), 9.3 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), \(J_{Sn-C} = 345.0\) Hz).

3.5.2.30 3-(Tributylstannyl)but-3-enyl acetate (3-224)\(^{58}\)

\(^1\)H NMR  \(\delta\) 5.73 (SnC=CH\(_2\), 1H, br s, \(J_{Sn-H} = 133.2\) Hz), 5.19 (SnC=CH\(_2\), 1H, br s, \(J_{Sn-H} = 61.3\) Hz), 4.06 (AcOCH\(_2\)CH\(_2\)C, 2H, t, \(J = 7.1\) Hz), 2.52 (AcOCH\(_2\)CH\(_2\)C, 2H, t, \(J = 7.6\) Hz), 2.0 (AcO, 3H, s), 1.53-0.81 (Sn-nBu, 27H, m); \(^{13}\)C NMR \(\delta\) 170.8 (AcO), 150.2 (SnC=CH\(_2\)), 127.6 (SnC=CH\(_2\)), 63.9 (AcOCH\(_2\)CH\(_2\)C), 39.7 (AcOCH\(_2\)CH\(_2\)C), 29.0
(SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 27.3 (SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, J<sub>Sn-C</sub> = 57.3 Hz), 20.8 (AcO), 13.6 (SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 9.5 (SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, J<sub>Sn-C</sub> = 332.8 Hz).

3.5.2.31 (E)-Tert-butyldimethyl(4-(tributylstannyl)but-3-enyloxy)silane (3-38)<sup>58</sup>

![Bu₃Sn=CH₂OTBS](image)

Stannane 3-38 was made in 83% isolated yield as an inseparable mixture of isomers (91:9, trans:gem) from alkyne 3-239 using the general procedure to provide 0.395 g as a clear oil.

<sup>1</sup>H NMR δ 5.95 (SnCH<sub>A</sub>=CH<sub>B</sub>, 2H, m, J<sub>Sn-HA,SB</sub> = 73.5 Hz), 3.65 (TBSOCH<sub>2</sub>CH<sub>2</sub>CH, 2H, t, J = 6.7 Hz), 2.34 (TBSOCH<sub>2</sub>CH<sub>2</sub>CH, 2H, m, J<sub>Sn-H</sub> = 66.0 Hz), 1.53-0.82 ((CH<sub>3</sub>)<sub>2</sub>Si-tBu, 9H, s and Sn-nBu, 27H, m), 0.04 ((CH<sub>3</sub>)<sub>2</sub>Si-tBu, 6H, s); <sup>13</sup>C NMR δ 145.8 (SnCH=CH), 129.7 (SnCH=CH, J<sub>Sn-C</sub> = 384.9 Hz), 62.8 (TBSOCH<sub>2</sub>CH<sub>2</sub>CH), 41.4 (TBSOCH<sub>2</sub>CH<sub>2</sub>CH, J<sub>Sn-C</sub> = 64.1 Hz), 29.0 (SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 27.3 (SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, J<sub>Sn-C</sub> = 51.3 Hz), 25.9 ((CH<sub>3</sub>)<sub>2</sub>SiC(CH<sub>3</sub>)), 18.3 ((CH<sub>3</sub>)<sub>2</sub>SiC(CH<sub>3</sub>)), 13.6 (SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 9.3 (SnCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, J<sub>Sn-C</sub> = 320.7 Hz), -5.3 ((CH<sub>3</sub>)<sub>2</sub>SiC(CH<sub>3</sub>)).
3.5.2.32 *Tert*-butyldimethyl(3-(tributylstannyl)but-3-enyloxy)silane (3-222)$^{58}$

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{OTBS} \\
\end{align*}
\]

$^1$H NMR $\delta$ 5.71 (SnC=CH$_2$, 1H, d, $J_{\text{Sn-H}}$ = 136.9 Hz, $J$ = 2.6 Hz), 5.17 (SnC=CH$_2$, d, 1H, $J_{\text{Sn-H}}$ = 62.4 Hz, $J$ = 2.7 Hz), 3.61 (TBSOCH$_2$CH$_2$C, 2H, t, $J$ = 7.7 Hz), 2.46 (TBSOCH$_2$CH$_2$C, 2H, t, $J$ = 7.0 Hz), 1.53-0.82 ((CH$_3$)$_2$Si-tBu, 9H, s and Sn-nBu, 27H, m), 0.05 ((CH$_3$)$_2$Si-tBu, 6H, s); $^{13}$C NMR $\delta$ 150.9 (SnC=CH$_2$), 127.1 (SnC=CH$_2$, $J_{\text{Sn-C}}$ = 19.2 Hz), 63.3 (TBSOCH$_2$CH$_2$C), 44.5 (TBSOCH$_2$CH$_2$C, $J_{\text{Sn-C}}$ = 41.7 Hz), 29.0 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}}$ = 19.8 Hz), 27.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}}$ = 57.7 Hz), 25.6 ((CH$_3$)$_2$SiC(CH$_3$)$_3$), 18.0 ((CH$_3$)$_2$SiC(CH$_3$)$_3$), 13.6 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}}$ = 333.6 Hz), -5.3 ((CH$_3$)$_2$SiC(CH$_3$)$_3$).

3.5.2.33 *(E)*-Tributyl(styryl)stannane (3-233)$^{61}$

\[
\begin{align*}
\text{Bu}_3\text{Sn} & \quad \text{C} \quad \text{H} \\
\end{align*}
\]

Stannane 3-233 was made in 74% isolated yield as an inseparable mixture of isomers (81:19, *trans*:gem) from alkyne 3-23 using the general procedure to provide 0.291 g as a clear oil.
\(^1\)H NMR \(\delta\) 7.44-7.17 (PhH, 5H, m), 6.87 (SnCH\textsubscript{A}=CH\textsubscript{B}, 2H, s, J\textsubscript{Sn-HA,B} = 65.3 Hz), 1.53-0.88 (Sn-nBu, 27H, m); \(^{13}\)C NMR \(\delta\) 146.0 (SnCH=CH), 138.8 (SnCH=CH), 129.4, 128.4 (2C), 127.4, 125.9(2C) (Ph), 29.1 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 27.3 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 13.7 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 9.6 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}, J\textsubscript{Sn-C} = 338.1 Hz).

3.5.2.34 Tributyl(1-phenylvinyl)stannane (3-234)

\[\text{SnBu}_3\]

\(^1\)H NMR \(\delta\) 7.46-7.19 (PhH, 5H, m), 6.07 (SnC=CH\textsubscript{2}, 1H, d, J\textsubscript{Sn-H} = 128.1 Hz, J = 2.4 Hz), 5.46 (SnC=CH\textsubscript{2}, 1H, d, J\textsubscript{Sn-H} = 60.0 Hz, J = 2.4 Hz), 1.54-0.88 (Sn-nBu, 27H, m); \(^{13}\)C NMR \(\delta\) 154.5 (SnC=CH\textsubscript{2}), 146.6 (SnC=CH\textsubscript{2}), 128.3 (2C), 126.8, 126.4 (2C), 126.3 (Ph), 29.1 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 27.3 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 13.7 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 10.2 (SnCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}, J\textsubscript{Sn-C} = 350.6 Hz).

3.5.2.35 Methyl 2-(tributylstanny)acrylate (3-236)

\[\text{SnBu}_3\]

Stannane 3-236 was made in 23% isolated yield as a single isomer from alkyne 3-24 using the general procedure to provide 0.086 g as a clear oil.
$^1$H NMR $\delta$ 6.85 (SnC=CH$_2$, 1H, d, J$_{Sn-H}$ = 109.3 Hz, J = 2.7 Hz), 5.19 (SnC=CH$_2$, 1H, d, J$_{Sn-H}$ = 54.0 Hz, J = 2.7 Hz), 3.69 (OCH$_3$, 3H, s), 1.54-0.82 (Sn-nBu$_3$, 27H, m); $^{13}$C NMR $\delta$ 180.5 (AcO), 145.8 (SnC=CH$_2$, J$_{Sn-H}$ = 318.1 Hz), 139.6 (SnC=CH$_2$, J$_{Sn-H}$ = 12.9 Hz), 51.5 (OCH$_3$), 28.8 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-H}$ = 19.5 Hz), 27.1 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 59.3 Hz), 13.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.9 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 345.3 Hz).

3.5.2.36 (2S$^*$ or 2R$^*$,5R$^*$ or 5S$^*$) and (2R$^*$ or 2S$^*$,5S$^*$ or 5R$^*$)-(E)-3-Methylene-4-((tributylstannyl)methylene)hexane-2,5-diol (3-199)

Stannane 3-199 was isolated in ~30% yield as a mixture of two diastereomers from alkyne 3-46 while performing the reaction at 0.24 M concentration and using the general procedure.

$^1$H NMR $\delta$ 5.93 (CC$_2$SnBu$_3$, s, 2H, J$_{Sn-H}$ = 60.3 Hz), 5.13 (CCH$_2$, s, 1H), 5.10 (CCH$_2$, s, 1H), 4.88 (CCH$_3$, s, 2H), 4.35 (CHOH, m, 4H), 3.41 (CHOH, m, 2H), 3.27 (CHOH, m, 2H), 1.48-0.79 (Bu$_3$Sn, m, 54H) (CH$_3$, m, 12H); $^{13}$C NMR $\delta$ 162.5, 161.5, 154.4, 154.2 (CCH$_2$) (CCH$_3$Bu$_3$), 128.5, 127.5 (CH$_3$Bu$_3$, J$_{Sn-C}$ = 384.9 Hz), 114.9, 113.9 (CHCH$_2$), 73.0, 72.4, 69.7, 68.7 (CHOH), 29.1 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 15.1 Hz), 27.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 60.4 Hz), 27.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 15.1 Hz), 22.6, 22.6, 21.6, 21.0 (CH$_3$), 13.6 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 10.7, 10.6 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J$_{Sn-C}$ = 340.0 Hz).
3.5.3 Hydrostannation of alkyne 3-160 on a 12 mmol scale

Pd$_2$dba$_3$ (54.0 mg, 0.06 mmol), tricyclohexylphosphonium tetrafluoroborate (88.0 mg, 0.238 mmol) and diisopropylethylamine (62.0 mg, 0.476 mmol) were added successively to CH$_2$Cl$_2$ (100 mL) and the resulting mixture was stirred at rt for 10 minutes. Alkyne 3-160 (2.00 g, 11.9 mmol) was added and the reaction mixture was cooled to 0 °C. Bu$_3$SnH (4.16 g, 14.3 mmol) diluted in CH$_2$Cl$_2$ (20 mL) was added dropwise via a dropping funnel over 15 minutes. The reaction was then allowed to stir at 0 °C for 4 hours. The reaction mixture was concentrated and purified by silica gel chromatography (hexanes:ether, 5:1) to afford vinylstannanes 3-161 and 3-162 (96:4, 4.75 g, 87%) as an inseparable mixture.

3.5.4 Synthesis of enone 3-246

3.5.4.1 (E)-12-(Tert-butyldimethylsilyloxy)-1-phenyldodec-2-en-1-one (3-246)

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

Pd$_2$dba$_3$ (4.0 mg, 0.004 mmol), tricyclohexylphosphonium tetrafluoroborate (6.0 mg, 0.015 mmol) and diisopropylethylamine (3.9 mg, 0.030 mmol) were added successively to THF (10 mL) and the resulting mixture was stirred at rt for 10 minutes. Alkyne 100 (211 mg, 0.748 mmol) was added and the reaction was cooled to 0 °C. Bu$_3$SnH (0.898 mmol, 261 mg) diluted in THF (3 mL) was added dropwise via a dropping funnel over 5
minutes. The reaction was then allowed to stir at 0 °C for 2 h. Benzoyl chloride (137 mg, 0.972 mmol) and Pd(PPh₃)₂Cl₂ (7.0 mg, 0.01 mmol) were then added and the reaction mixture was allowed to stir at reflux (65 °C) for 5 h. The reaction mixture was cooled, diluted with saturated aq. KF (~ 5 mL) and stirred for 30 minutes. The mixture was partitioned between Et₂O and H₂O and the aqueous phase was back extracted with Et₂O. The combined organic layer were dried over MgSO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford ketone 5 in 84% yield.

¹H NMR δ 7.89 (PhH, 2H, d, J = 7 Hz), 7.50 (PhH, 1H, t, J = 7 Hz), 7.41 (PhH, 2H, t, J = 7 Hz), 6.93 (COCH₂=CH₂, AB of ABX₂, 2H, δₐ = 7.03, δ₃ = 6.84, Jₐ₃ = 15.4 Hz, Jₐₓ = 6.8 Hz), 3.56 (TBSOCH₂, 2H, t, J = 6.5 Hz), 2.08 (CHCHCH₂, 2H, q, J = 6.9 Hz), 1.46, 1.29 (CH₂(CH₂)₇CH₂, 14H, m), 0.86 (tBu(CH₃)₂Si, 9H, s), 0.01 (tBu(CH₃)₂Si, 6H, s); ¹³C NMR δ 190.6, 149.9 (COCH=CH), 137.9(Ph, 1C), 132.4(Ph, 1C), 128.4 (Ph, 2C), 128.3 (Ph, 2C), 125.7 (COCH=CH), 63.1 (TBSOCH₂CH₂), 32.8, 32.7, 29.4, 29.3, 29.2, 29.1, 28.1, 25.7, 25.9 ((CH₃)₃C(CH₃)₂Si), 18.2 ((CH₃)₃C(CH₃)₂Si), -5.4 ((CH₃)₃C(CH₃)₂Si); IR (neat) νₘₐₓ 3059, 2927, 2856, 1674, 1622, 1463, 1255, 1097, 835, 775, 694 cm⁻¹. Exact mass (EI) calcd for C₂₄H₄₀O₂Si: 388.2798, found: 388.2801.
3.5.5 Synthesis of pheromone 3-248

3.5.5.1 (10E,12E)-Hexadeca-10,12-dien-1-ol (3-247)

To a round bottomed flask containing degassed DMF (3 mL) was added Pd(MeCN)$_2$Cl$_2$ (3.4 mg, 0.013 mmol) followed by E-1-iodo-1-pentene$^{45}$ (129 mg, 0.654 mmol). The mixture was stirred for 10 min before the addition of stannane 3-161 (mixed with 4% 3-162, 360 mg, 0.788 mmol) and CuI (125 mg, 0.654 mmol). The reaction was allowed to stir at rt for 12 h. Saturated aqueous NH$_4$Cl containing 10% NH$_4$OH and ether were added to the flask, and the two phases were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography (hexanes:ether, 5:1) to afford dienyl alcohol 6 as a waxy solid (148 mg, 0.622 mmol, 95%). m.p. 28-30 °C; lit$^6$: m.p. 34 °C.

$^1$H NMR δ 5.96 (m, 2H), 5.52 (m, 2H), 3.59 (HOCH$_2$, t, 2H, J = 6.6 Hz), 2.0 (CH$_3$CH=CH-CH=CHCH$_2$, m, 4H), 1.54-1.25 (CH$_2$CH$_2$CH=CH-CH=CHCH$_2$(CH$_2$)$_7$, m, 16H), 0.86 (CH$_3$CH$_2$, t, 3H, J = 7.3 Hz); $^{13}$C NMR δ 132.3, 132.1, 130.5, 130.3 (CH=CH-CH=CH), 62.9 (HOCH$_2$), 34.6, 32.7, 32.5, 29.5, 29.4, 29.1, 25.7, 22.5 (CH$_2$CH$_2$CH=CH-CH=CHCH$_2$(CH$_2$)$_7$), 13.7 (CH$_3$CH$_2$).
A round bottomed flask was charged with 100 mg of activated 3Å molecular sieves. PDC (296 mg, 0.786 mmol) was added followed by CH$_2$Cl$_2$ (4 mL) and dienyl alcohol 3-247 (125 mg, 0.524 mmol). The reaction mixture was stirred at rt for 2 h then filtered through a short plug of silica and concentrated to yield a yellow oil. Purification of the crude oil by column chromatography (hexanes:ether, 10:1) yielded aldehyde 3-248 as a colorless oil (123 mg, 99%).

$^1$H NMR $\delta$ 9.73 (CHO, t, 1H, J = 1.7Hz), 5.96 (m, 2H), 5.52 (m, 2H), 3.59 (HOCH$_2$, t, 2H, J = 6.6 Hz), 2.39( CH$_2$CHO, td, 2H, J = 7.3 Hz, J = 1.6Hz), 2.0 (CH$_2$CH=CH-CH=CHCH$_3$, m, 4H), 1.65-1.25 (CH$_3$CH$_2$CH=CH-CH=CHCH$_2$(CH$_2$)$_6$, m, 14H), 0.87 (CH$_3$CH$_2$, t, 3H, J = 7.3 Hz); $^{13}$C NMR $\delta$ 202.7 (CHO), 132.2, 132.1, 130.4, 130.3 (CH=CH-CH=CH), 43.8, 34.6, 32.4, 29.3, 29.2, 29.0, 28.9, 22.5, 22.0, 13.6 (CH$_3$CH$_2$).

Spectral data were in accord with literature data.
Chapter 4

Synthesis of (E)-1-Tributylstannylbutadiene and Homologues via Hydrostannation Chemistry and their Applications

4.1 Introduction

4.1.1 General

1,3-Dienyl moieties, also called butadienes, are present in many natural products and have been used in total syntheses of natural products.\(^1\)\(^-\)\(^4\)

The powerful grape fruit odorant \(4-3\), which is of use in the perfume industry, was synthesized on kilogram scale starting from a conjugated butadiene. Thus, the reaction between 2,3-dimethyl-1,3-butadiene \(4-1\) and 2,4-dimethyl-3-pentanone \(4-2\) represents the shortest access to \(4-3\), with perfect atom economy (Scheme 4.1).\(^5\)

\[\text{Scheme 4.1} \]

\[\begin{align*}
\text{4-1} & + \text{4-2} \rightarrow \text{4-3} \\
\end{align*} \]

grapefruit odorant
Following are examples of natural products containing conjugated diene moieties (Figure 4.1).

![Figure 4.1](image)

**Figure 4.1** Natural products containing conjugated butadiene moieties

N-Heterocycle 4-4 is a cytotoxic piperidine while N-heterocycle 4-5 is a potent fish-feeding-deterrent piperidine.

1,3-Butadienes can serve as intermediates (Scheme 4.1),5 or be part of the final structure of a natural product (Figure 4.1).6
4.1.2 Synthesis of (E)-1-stannyl-1,3-dienes

A particular class of butadienes of interest are (E)-1-stannyl-1,3-dienes (4-6) which have been implemented in many total syntheses due to their synthetic usefulness (Figure 4.2).

\[
\text{Figure 4.2} \quad (E)-1\text{-Stannyl-1,3-butadiene homologue}
\]

As mentioned in chapter one, vinylstannanes are versatile intermediates that can undergo many transformations. The versatility of these stannylbutadienes will be highlighted in section 4.1.3 with examples of their application in total synthesis.

Due to the importance of stannylbutadiene building blocks, many methodologies were established to obtain these valuable intermediates.

The simplest of these building blocks is stannylbutadiene 4-12 (Scheme 4.2). The first synthesis of this butadiene was developed by Wender et al.\textsuperscript{7}
Alcohol 4-7 was protected with a bulky group to provide high regioselectivity in the following hydrostannation reaction. Silyl ether 4-8 was subjected to free-radical hydrostannation to obtain (E)-vinylstannane 4-9. Deprotection followed by oxidation of the primary alcohol afforded conjugated aldehyde 4-11. Aldehyde 4-11 was subject to a Wittig reaction to furnish stannylbutadiene 4-12 in five steps (46% overall yield).\(^7\)

A modified three-step version of this synthesis was developed by Angoh and Clive (65% overall yield).\(^8\) The methodology did not require the use of bulky protection group to attain trans-vinylstannane 4-10 in good yields. This was made possible by performing the free-radical hydrostannation under thermodynamic conditions, which consist of adding excess Bu\(_3\)SnH and longer duration times.\(^9\)
Another method involved hydrozirconation of enyne 4-13 developed by Fryzuk et al. (Scheme 4.3).\(^\text{10}\)

\[
\begin{align*}
\text{Cp}_2\text{ZrHCl} & \xrightarrow{\text{Bu}_3\text{SnCl}} \text{ZrClCp}_2 \rightarrow \text{Bu}_3\text{Sn} \\
4-13 & \rightarrow 4-14 & 4-14 & \rightarrow 4-12
\end{align*}
\]

**Scheme 4.3**

The chemoselectivity of this reaction is very high, even though hydrozirconation of alkene functionality is well established.\(^\text{11}\) Complete preference of the triple bond over the double bond was observed. Also, *trans* isomer 4-14 was formed exclusively versus *geminal* isomer 4-15 shown in the figure below (Figure 4.3).

\[
\begin{align*}
\text{ClCp}_2\text{Zr} & \rightarrow \text{ZrCp}_2\text{C} \\
4-14 & \rightarrow 4-15
\end{align*}
\]

**Figure 4.3** *Trans* and *geminal* zirconium butadienes

Zirconium butadiene 4-14 was then treated with \text{Bu}_3\text{SnCl} to afford stannylbutadiene 4-12 in two steps (75% overall yield). While effective, a drawback of this method is that enyne 4-13 is no longer commercially available.
A third method was developed by Gomez et al. (Scheme 4.4).\(^\text{12}\)

![Scheme 4.4](image)

This methodology employed 2,5-dihydrothiophene \(S,S\)-dioxide \(4-16\) as a butadiene equivalent. The two-step synthesis began by stannylating \(S,S\)-dioxide \(4-16\) with \(\text{Bu}_3\text{SnI}\) in the presence of lithium hexamethyldisilazide (LHMD5) to give \(4-17\). Sulfur dioxide was extruded from \(4-17\) in refluxing xylene to afford stannylbutadiene \(4-12\). The presence of pyridine was found to be advantageous; it is thought to reduce the extent of acid-mediated polymerization.\(^\text{12}\) This route is short but each step proceeds in only modest yield so the overall yield of diene \(4-12\) is rather low (25% overall yield).

Other research groups synthesized other substituted stannylbutadienes, as they were part of total syntheses of natural products.

Lipshutz et al. devised a route to synthesize 4-substituted-(\(E\))-1-stannyl-1,3-dienes such as \(4-22\) (Scheme 4.5).
Stannylbutadiene 4-22 was prepared by the addition of stannylcuprate 4-19 to acetylenic acetal 4-18 that afforded enal 4-11 after hydrolysis. Wittig coupling between ylide 4-21 and enal 4-11 afforded 4-22 in good yields with 90:10 E/Z selectivity.\textsuperscript{13}

Stannylcupration of 4-18 was shown to exclusively afford the trans isomer by Quintard et al.\textsuperscript{14}

Pancrazi et al. utilized cuprate rearrangement to synthesize the desired stannylbutadiene 4-26 (Scheme 4.6).\textsuperscript{15}
Highly reactive stannylcuprate \textit{4-24} was formed using a modified Lipshutz exchange method.\textsuperscript{16} Stannylcuprate \textit{4-24} was allowed to react with furan \textit{4-25} which provided stannylbutadiene \textit{4-26} in good yields.\textsuperscript{15}

Cuprate rearrangement is believed to proceed \textit{via} either a dyotropic rearrangement or an alkyl migration as shown in Scheme 4.7.\textsuperscript{17}
Scheme 4.7
4.1.3 Application of (E)-1-stannyl-1,3-dienes

Retinoic acid receptors have been used for the treatment of dermatological diseases and certain cancers (Scheme 4.8).\textsuperscript{18,19}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{diagram.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 4.8}

Stereoselective construction of conjugated tetraenoic acid was achieved through Stille coupling. Cross coupling between stannyldiene 4-32 and iodidiene 4-33 afforded a stereodefined retinoid acid 4-34.\textsuperscript{20} Many other retinoid acids were also accessed through this methodology. It should be noted that the method described in the synthesis of these retinoid acids used unprotected acids, thus saving protection and deprotection steps, a key advantage for Stille coupling methodologies.

Macrolide antibiotics have earned enormous devotion from many synthetic groups due to their wide therapeutic use in human and veterinary medicine.\textsuperscript{21} Tylosin II 4-35 is
considered one of the most important early antibiotics. Many derivatives are being synthesized to overcome antibiotic resistant bacteria (Figure 4.4).

\[ R = O\beta\text{-mycinosyl}, \]
\[ R' = \beta-4-(\alpha\text{-meycarosyl})\text{mycaminosyl} \]

**Figure 4.4**  Retrosynthetic analysis of Tylosin II 4-35 and its derivative 4-36

En route to synthesis of the Tylosin II derivative des-epoxy-rosaramycin I (4-36), western and eastern fragments were joined by cross-coupling of stannydien moiety 4-26\(^{15}\) and acyl chloride 4-37 moiety (Figure 4.4). More efforts are needed to finalize the total synthesis of this antibiotic derivative.\(^{22}\)

An overwhelming majority of currently marketed medicinal compounds possess a nitrogen-containing heterocyclic skeleton.\(^{23}\) Arndtsen et al. demonstrated one can perform a cross coupling between stannanes and an iminium salt formed *in situ* (Scheme 4.9).\(^{24}\)
As shown in Scheme 4.9, intermediate 4-41 transmetallates with stannane to form intermediate 4-42. This intermediate underwent reductive elimination that afforded amide 4-43. This process allowed for Malinakova et al. to develop a copper-catalyzed three-component coupling and Diels-Alder reaction that generated libraries of hexahydro-1H-isoindolones (Scheme 4.10).25
The isoindolones formed in these multi-component reactions served as skeletons for pharmacologically active heterocycles shown in Figure 4.5. Heterocycles 4-47 and 4-48 have been recognized as tachykinin NK1 receptor antagonists, which are useful in treating emesis, urinary incontinence, depression, and anxiety.\textsuperscript{25} Macrocyclic hydroisoindolone cytochalasin 4-49 is a naturally occurring cytotoxic fungal metabolite.\textsuperscript{25} The more recently discovered cytochalasin 4-50 exhibited inhibitory activity against HIV-1 protease (Figure 4.5).\textsuperscript{25}
The ability to produce libraries of these heterocycles allows the screening of many derivatives, which is beneficiary for the pharmaceutical industry.

Medium and large ring compounds have continued, for over a century, to attain considerable attention. Research involving these types of compounds has increased dramatically due to the expanding medicinal, theoretical, and commercial interest in naturally occurring macrocycles and non-natural systems such as the crown ethers and annulenes.
Syntheses of these macromolecules have been made easier by the methodology of Wender et al. (Scheme 4.11).\textsuperscript{7}

Upon treating stannylbutadiene 4-12 with \textit{n}-BuLi, intermediate lithiobutadiene 4-51 was formed \textit{via} transmetallation. This intermediate was used twice throughout the synthesis to lead to macrocyclic ketone 4-56.\textsuperscript{7}

\textbf{Scheme 4.11}

Lithiobutadiene 4-51, formed by transmetallation of stannylbutadiene 4-12, has also proven to be useful in total syntheses of chiloscyphones (Scheme 4.12).\textsuperscript{26}
Intramolecular Diels-Alder reaction of dienyl alcohol 4-59 afforded intermediate 4-60.

Intermediate 4-60 is a skeleton for many chiloscyphones derivatives (Figure 4.6).
Chiloscyphones shown in Figure 4.6 possess biological activities, such as anticancer, fish-killing, and antifeedant properties. Having said this, other chiloscyphone derivatives (4-65, 4-66 and 4-67) have shown activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Figure 4.7).²⁶

![Figure 4.6 Biologically active chiloscyphones](image)

![Figure 4.7 Chiloscyphones against methicillin-resistant *Staphylococcus aureus*](image)
The tricyclic derivatives might be essential for anti-MRSA activity. These findings will contribute to new approach in developing anti-MSRA drugs.

All the examples shown highlight the convenience of stannyldienes. These useful building blocks have proved to be convenient in total synthesis.

4.2 Proposed Work

It seemed reasonable to develop a general and operationally simple route for providing \((E)-1\)-stannyldienes 4-6 (Figure 4.2). This will be facilitated by applying our newly developed methodology in palladium-catalyzed hydrostannation of terminal alkynes (Chapter 3).

A convergent and concise synthesis of a natural product will be illustrated to highlight the usefulness of stannyldienes.
4.3 Results and Discussion

4.3.1 Synthesis of stannylbutadiene 4-12

The synthesis of the simplest stannylbutadiene 4-12 began with propargyl alcohol 4-68. As shown in chapter 3, palladium-catalyzed hydrostannation of terminal alkyne 4-68 using our procedure afforded trans-vinylstannane 4-69 in an excellent isolated yield of 84%.\textsuperscript{27} This alcohol is easily separated from the small amount of \textit{geminal} isomer formed (Scheme 4.13).

![Reaction Scheme 4.13](image)

\textbf{Scheme 4.13}

This reaction was performed on 0.06 mole scale without any deviation in the results. The isomeric stannanes were separated by silica gel chromatography which afforded pure vinylstannane 4-69.

Elimination of the hydroxyl group, to afford stannylbutadiene 4-12, was feasible by transforming the hydroxyl group into a good leaving group (Table 4.1). Trifluoromethanesulfonic anhydride (Tf\textsubscript{2}O)/amine base were quickly screened to accomplish this transformation.
Attempts to dehydrate vinylstannane 4-69 failed when using Tf₂O and 2,6-lutidine; a complex mixture was observed instead. Stannybutadiene 4-12 was obtained in 30\% isolated yield when Et₃N was used as base, but other non-separable stannyl materials accompanied stannybutadiene 4-12. The dehydration process proceeded cleanly when using i-Pr₂NEt (Hünig’s base) to afford stannybutadiene 4-12 in 80\% isolated yield (Scheme 4.14). It is important to note that it was necessary to add the base first. Formation of any TfOH will lead to protodestannylation of the product. The presence of excess base eliminates the possibility of any protodestannylation occurring. Pure stannyldiene 4-12 obtained only if pure vinylstannane 4-69 was used.
4.3.2 Synthesis of other homologues

This methodology was also applied to other propargyl alcohols such as 4-70 (Scheme 4.15).

Scheme 4.15

Hydrostannation of propargyl alcohol 4-70 proceeded as reported (mixture of 95:5, trans:gem, respectively, major isomer separated by silica gel chromatography).\(^{27}\) The dehydration of vinylstannane 4-71 afforded two isomeric dienes 4-72 and 4-73 (E:Z, 3:1, according to \(^1\)H NMR). The isomeric dienes were inseparable using traditional silica gel chromatography. The formation of two isomers is indicative of different transition structures taking place. Unlike vinylstannane 4-69, vinylstannane 4-71 has two possible conformations for elimination (Scheme 4.16).
Further optimization is required to achieve complete selectivity for the \( E,E \) diene isomer and generality in substrates through this methodology.

### 4.3.3 Application of stannylbutadiene 4-12

To illustrate an application of stannylbutadiene 4-12, it was used as part of a convergent synthesis of grapevine sex pheromone 4-75 (Scheme 4.17).\textsuperscript{28}
Scheme 4.17

Stannylbutadiene 4-12 was coupled with vinyl iodide 4-74 to provide sex pheromone 4-75 in 97% isolated yield. In contrast to a literature report with 8 linear steps involving hydroalumination/iodination, Sonigashira coupling and Wittig olefination, this is the most convergent synthesis of this pheromone.

Coupling partner vinyl iodide 4-74 was prepared conveniently in one pot from the corresponding alkyne (Scheme 4.18).

Scheme 4.18
The methodology of preparing trans-vinyl iodides will be discussed in detail in Chapter 5.

1-Arylbutadienes have been the subject of many chemical reactions, primarily Diels-Alder reactions.\textsuperscript{29-31} They are usually prepared by Wittig olefination of aldehydes with the ylide derived from allyltriphenylphosphonium bromide. But, due to the Wittig olefination reaction, the conjugated double bonds are formed as a mixture of $E$:Z. Stannylbutadiene 4-12 allows for easy access to arylbutadienes 4-79 (Scheme 4.19).

\[
\begin{align*}
&\text{SnBu}_3 + \text{ArBr} \quad \xrightarrow{\text{5 mol\% Pd}_2\text{dba}_3/\text{TFP}} \quad \text{THF/reflux} \quad 12 \text{ h} \\
&4-12 & & 4-78 & & 4-79
\end{align*}
\]

Scheme 4.19

Using conditions set by Farina for the Stille coupling,\textsuperscript{32} a convenient 1-step synthesis was developed to prepare 1-arylbutadienes shown in Figure 4.8 in excellent yields.

\[
\begin{align*}
&\text{4-80} & & \text{95\%} \\
&\text{4-81} & & \text{92\%}
\end{align*}
\]

Figure 4.8 1-Arylbutadienes 4-80 and 4-81
Another application was a synthesis of the red-bollworm moth sex pheromone 4-83 (Table 4.2), which contains a terminal diene moiety. Previous syntheses include; coupling of dienol phosphates with Grignard reagents under iron catalysis, palladium-catalyzed deoxygenation of enediols, elimination of homoallylic sulfide, alkylation of 3-sulfolenes, Pummerer rearrangement, tellurolate-induced 1,4-elimination of 1,4-dibromo 2-enes, elimination of 1,4-dibenzensulfonyltrimethylsilane, β-elimination of β-hydroxy selenide and Wittig olefination reaction.

Initially, copper chemistry was used to perform the required coupling for installing the diene moiety. Lipshutz et al. have shown the ability of vinylstannanes to transmetallate with cuprates to generate reactive vinylcuprates that can add to enones effectively (Scheme 4.20).

\[
\begin{align*}
\text{Me}_2\text{CuLiLiCN} & \rightarrow \text{CuMeLiLiCN} \\
\text{SnBu}_3 & \rightarrow \text{CuMeLiLiCN} \\
\text{95\% isolated yield}
\end{align*}
\]

\textbf{Scheme 4.20}

Different leaving groups and copper species were screened to facilitate the desired coupling (Table 4.2).
Table 4.2  Coupling of dienyl cuprate 4-84

<table>
<thead>
<tr>
<th>Entry</th>
<th>alkyl acetate</th>
<th>source of copper reagent (4-84)</th>
<th>leaving group (X)</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(4-88)</td>
<td>Me₂Cu(CN)Li₂</td>
<td>Br</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(4-89)</td>
<td>Me₂Cu(CN)Li₂</td>
<td>OTf</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>(4-90)</td>
<td>Me₂Cu(CN)Li₂</td>
<td>I</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>(4-90)</td>
<td>CuCN</td>
<td>I</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>(4-90)</td>
<td>CuBr·SMe₂</td>
<td>I</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Combined yield with methyl transfer product in 1:1 ratio which is inseparable from 4-83.
<sup>b</sup> 2 Equivalents of lithiobutadiene was used.

Initial trials (1,2) proved to be fruitless in attaining product 4-83. Bromoacetate 4-88 and triflate acetate 4-89 were unable to provide any coupling product using the method by
Lipshutz et al. where a highly reactive copper intermediate reacts with electrophiles. It was uncertain if “dienyl cuprate” species 4-84 was forming in situ. To confirm its formation, we decided to mimic the conditions Lipshutz et al. used, which was adding the formed cuprate to an α,β-unsaturated ketone. Chalcone, as the electrophile, was added to the supposedly formed dienyl cuprate 4-84 (Scheme 4.21).

![Scheme 4.21](image)

Conjugate addition of dienyl cuprate 4-84 did take place on the chalcone, thus confirming its formation in situ. Addition product 4-86 was tentatively identified and isolated in good yield.

After confirming the presence of dienyl cuprate 4-84, it was used in attempted couplings with iodoacetate 4-90. Alkyl iodides are soft electrophiles, which can promote couplings with soft nucleophiles such as vinylcuprate 4-84. The formation of coupling product 4-83 was observed; unfortunately, the coupling was accompanied with methyl transfer product 4-87 in a 1:1 ratio (Figure 4.9).
This observation suggests that methyl transfer is as fast as dienyl transfer when coupling with iodoacetate 4-90. This result proved to be problematic since compounds 4-83 and 4-87 are inseparable by silica gel chromatography. To eliminate the competing methyl transfer, cuprates in trials 4 and 5 were made through the traditional method by adding two equivalents of alkenyllithium to copper. The reaction did proceed as anticipated in trial 4, but the less reactive cuprate resulted in a dismal yield of 25%. Trial 5 using CuBr·SMe₂ instead of CuCN did not produce any product at all.

After seeing the capability of cuprates, it was decided to abandon copper chemistry and turn to palladium chemistry. Fu et al. demonstrated palladium-catalyzed cross-coupling between vinylstannanes and primary alkyl halides (Scheme 4.22).⁴³

![Scheme 4.22](image-url)
Competing β-hydride elimination was minimized by using electron rich phosphine ligands around the palladium. The same methodology was applied to the synthesis of pheromone 4-83 (Scheme 4.23).

Scheme 4.23

It is known that transmetallation is the slowest step in cross-coupling reactions. Electron rich phosphine ligands would stabilize oxidative addition intermediate 4-100 and minimize the β-hydride elimination process, thereby allowing for the transmetallation process to proceed (Scheme 4.24).

Scheme 4.24
The conditions were optimized to minimize the formation of $\beta$-hydride elimination by-product 4-97 (Table 4.3).

### Table 4.3  Stille coupling between 4-12 and 4-82

<table>
<thead>
<tr>
<th>entry</th>
<th>equivalents of 4-12</th>
<th>palladium mol %</th>
<th>phosphine mol %</th>
<th>Solvent/ temperature</th>
<th>4-83 : 4-97 ratio$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>2.5</td>
<td>15</td>
<td>THF/rt</td>
<td>47 : 53</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>2.5</td>
<td>15</td>
<td>THF/reflux</td>
<td>26 : 74</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>2.5</td>
<td>30</td>
<td>THF/rt</td>
<td>65 : 35</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>7.5</td>
<td>45</td>
<td>THF/rt</td>
<td>69 : 31</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>10</td>
<td>60</td>
<td>THF/rt</td>
<td>85 : 15</td>
</tr>
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<td>MTBE/rt</td>
<td>70 : 30</td>
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<tr>
<td>7</td>
<td>2.0</td>
<td>15</td>
<td>90</td>
<td>THF/rt</td>
<td>72 : 28</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR analysis of crude reaction mixture

Using the same conditions reported by Fu et al.$^{43}$ (trial 1, stannane (1.1 equivalents), phosphine (15 mol %)/palladium (2.5 mol %), 6:1 ratio, rt), a 1:1 mixture of coupling product 4-83 and $\beta$-hydride by-product 4-97 was observed. Increasing the temperature to 66 °C (trial 2) favoured the formation of the $\beta$-hydride by-product 4-97 in a 3:1 ratio. Increasing the phosphine/palladium ratio from 6:1 to 12:1 (trial 3) favoured the formation of the coupling product 4-83 in a 2:1 ratio. Increasing the loading of the stannane to two equivalents (trial 4) favoured the coupling product 4-83 in a 2:1 ratio. Solvent MTBE, used by Fu et al. in some of their reactions, did not show any advantages. After
numerous trials, pheromone 4-83 was obtained in 89% combined yield with 4-97 in a ratio of 85:15 (trial 5). Unfortunately, 4-83 and 4-97 are inseparable by silica gel chromatography. Further optimizations are needed to make this synthesis efficient.

4.4 Summary

Stannylbutadiene 4-12 was synthesized in two steps in 67% overall yield. Hydrostannation of propargyl alcohol 4-68 was followed by dehydration led to the final stannylbutadiene 4-12. Further work is required to generalize the scope of substrates that this methodology can be applied to. Convergent synthesis of grapevine sex pheromone 4-75 was demonstrated as a convenient route to this class of trienic compounds. Also, a 1-step synthesis of 1-arylbutadienes was established in excellent yields. Further improvements are needed to optimize the synthesis of bollworm moth sex pheromone 4-83.
4.5  Experimental

4.5.1  General experimental

All reactions and reagents were carried out and purified as stated in Chapter 3. All instruments were used are mentioned in Chapter 3. Other reagents were purchased from Sigma-Aldrich and used without further purification.

4.5.2  Synthesis of stannylbutadiene 4-12

4.5.2.1  \((E)-4\)-(Tributylstannyl)but-3-en-2-ol  (4-69)\(^{44}\)

\[
\text{Bu}_3\text{Sn} = \text{OH}
\]

Pd\(_2\text{dba}_3\) (0.139 g, 0.149 mmol), tricyclohexylphosphonium tetrafluoroborate (0.219 g, 0.596 mmol) and Hünig’s base (0.154 g, 1.20 mmol) were added successively to CH\(_2\)Cl\(_2\) (200 mL) and the resulting mixture was stirred at rt for 15 min. 3-Butyn-2-ol was added (2.10 g, 29.9 mmol) and the reaction was cooled to 0 °C. Bu\(_3\)SnH (10.45 g, 35.9 mmol) diluted in CH\(_2\)Cl\(_2\) (50 mL) and was added dropwise via a dropping funnel over 45 min. The reaction was then allowed to stir at 0 °C for 3 h. The reaction mixture was concentrated and purified by silica gel chromatography (7/1 : hexane/ether) to afford vinylstannane \textbf{4-69} in 84% (9.07 g) isolated yield.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.07 (SnCH$_A$=CH$_B$, AB of ABX, 2H, $\delta_A = 6.10$, $\delta_B = 6.04$, $J_{AB} = 19.2$ Hz, $J_{BX} = 4.3$ Hz, $J_{Sn-H_A} = 69$ Hz, $J_{Sn-H_B} = 66$ Hz), 4.24 (CH$_3$CH, m, 1H), 1.47-0.79 (CH$_3$CH, Sn-nBu, 30H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.0 (SnCH=CH), 126.4 (SnCH=CH), 71.2 (CH$_3$CH, $J_{Sn-C} = 62.4$ Hz), 28.9 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{Sn-C} = 20.4$ Hz), 27.1 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{Sn-C} = 53.4$ Hz), 23.0 (CH$_3$CH), 13.6 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{Sn-C} = 339.6$ Hz).

4.5.2.2 (E)-1-Tributylstanny1,3-butadiene (4-12)$^7$

![Chemical structure](image)

To a flame-dried round-bottomed flask containing CH$_2$Cl$_2$ (150 mL) was added (E)-4-(tributylstannyl)but-3-en-2-ol 4-69 (8.00 g, 22.2 mmol) followed by Hünig’s base (12.88 g, 99.6 mmol) and the mixture was cooled to −78 °C. Triflic anhydride (9.36 g, 33.16 mmol) was added dropwise and the reaction was stirred for 3 h at −78 °C then allowed to rise to room temperature (2 h). The reaction mixture was passed through a short silica plug (5 g) and concentrated then purified by silica gel (20 g) chromatography (hexane as the eluant) to afford the corresponding vinylstannane 4-12 as a colourless oil in 80 % (6.09 g) isolated yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.53 (SnCH=CH-CH=CH$_2$, dd, 1H, $J = 18.7$ Hz, $J = 9.8$ Hz, $J_{Sn-H} = 59.3$ Hz), 6.31 (SnCH=CH-CH=CH$_2$, dt, 1H, $J = 16.9$ Hz, $J = 9.9$ Hz), 6.24 (SnCH=CH-CH=CH$_2$, d, 1H, $J = 18.7$ Hz, $J_{Sn-H} = 67.4$ Hz), 5.13 (SnCH=CH-CH=CH$_2$, d, 1H, $J = 17.9$ Hz), 5.02 (SnCH=CH-CH=CH$_2$, d, 1H, $J = 9.8$ Hz) 1.56-0.86 (Sn-nBu, 27H,
m; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.5 (SnCH=CH=CH=CH$_2$), 140.2 (SnCH=CH=CH=CH$_2$, $J_{\text{Sn-C}} = 67.9$ Hz), 134.7 (SnCH=CH=CH=CH$_2$, $J_{\text{Sn-C}} = 367.8$ Hz), 115.9 (SnCH=CH=CH=CH$_2$), 29.2 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}} = 22.6$ Hz), 27.4 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}} = 52.8$ Hz), 13.8 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$, $J_{\text{Sn-C}} = 333.9$ Hz).

4.5.3 *Synthesis of other homologues*

4.5.3.1 Tributyl((1E,3E)-octadienyl)stannane (4-72) and Tributyl((1E,3Z)-octadienyl)stannane (4-73)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.81(dd, 1H, $J = 18.7$ Hz, $J = 10.5$ Hz), 6.48 (dd, 1H, $J = 18.8$ Hz, $J = 9.8$ Hz), 6.17 (d, 1H, $J = 18.7$ Hz), 6.07-5.93 (m, 3H), 5.65 (m, 1H), 5.35 (m, 1H), 2.21 (q, 1H, $J = 6.3$ Hz), 2.07 (q, 1H, $J = 6.6$ Hz), 1.53-0.85 (m, 41H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.1, 142.1, 134.0, 133.6, 133.3, 131.7, 131.1, 130.4, 32.1, 31.7, 31.3, 29.0, 27.3, 27.2, 22.2, 22.1, 13.8, 13.6, 9.3, 9.3.
4.5.4 Synthesis of pheromone 4-75

4.5.4.1 Oct-7-ynyl acetate (4-77)\(^4\)

\[
\text{OAc}
\]

To a flame-dried round-bottomed flask was added 7-octyn-1-ol (0.754 g, 5.98 mmol) followed by pyridine (4.00 mL, 49.5 mmol), Ac\(_2\)O (1.25 mL, 13.2 mmol) and a crystal of DMAP. The reaction was allowed to stir at room temperature for 15 h. The reaction mixture was diluted with water (50 mL) and extracted with hexane (100 mL). The organic layer was washed with 1M HCl (3 x 50 mL), saturated NaHCO\(_3\) (2 x 75 mL), dried with Na\(_2\)SO\(_4\) and concentrated to give a yellow residue. The resulting residue was purified by silica gel chromatography (10/1 : hexane/ether) to afford 0.966 g of oct-7-ynyl acetate 4-75 as a colourless oil in 96% isolated yield.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.96 (CH\(_2\)OCOCH\(_3\), t, 2H, J = 6.6 Hz), 2.09 (HCCCH\(_2\), t, 2H, J = 6.6 Hz), 1.94 (CH\(_2\)OCOCH\(_3\), s, 3H), 1.85 (HCCCH\(_2\), s, 1H), 1.59-1.16 (CCH\(_2\)(CH\(_2\))\(_4\)CH\(_2\)O, m, 8H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.9 (OCOCH\(_3\)), 84.2 (HCCCH\(_2\)), 68.2 (HCCCH\(_2\)), 64.2 (CH\(_2\)OCOCH\(_3\)), 28.3, 28.2, 25.3, 20.8, 18.1 (CCH\(_2\)(CH\(_2\))\(_4\)CH\(_2\)OCOCH\(_3\)).
4.5.4.2 (E)-8-Iodoct-7-en-1-yl acetate (4-74)

\[\text{\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_}\n
Pd\textsubscript{2}dba\textsubscript{3} (12.8 mg, 0.014 mmol), tricyclohexylphosphonium tetrafluoroborate (20.6 mg, 0.056 mmol) and Hünig’s base (14.9 mg, 0.115 mmol) were added successively to CH\textsubscript{2}Cl\textsubscript{2} (40 mL) and the resulting mixture was stirred at rt for 15 min. Octynyl acetate 4-69 was added (0.484 g, 2.88 mmol) and the reaction was cooled to 0 °C. Bu\textsubscript{3}SnH (1.00 g, 3.46 mmol) diluted in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) was added dropwise via a dropping funnel over 10 min. The reaction was then allowed to stir at 0 °C for 3 h. Iodine (0.694 g, 2.74 mmol) was diluted in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) and added dropwise but quickly via a dropping funnel within 2 min. The reaction mixture was passed through a 10 g silica plug (washed with ether) and concentrated. The organic residue was diluted with ether (100 mL) and washed with saturated Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (1 x 80 mL), and saturated KF solution (2 x 80 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The resulting oil was purified by silica gel chromatography (10/1 : hexane/ ether) to afford 0.650 g of trans-vinyl iodide 4-74 (trans:gem, 99:1) as a colourless oil in 76 % isolated yield.

\textsuperscript{1}H NMR (300 MHz, CD\textsubscript{3}Cl) \(\delta\) 6.46 (ICH=CHCH\textsubscript{2}, dt, 1H, \(J = 14.4\) Hz, \(J = 7.2\) Hz), 5.94 (ICH=CHCH\textsubscript{2}, d, 1H, \(J = 14.4\) Hz), 4.01 (CH\textsubscript{3}OCOCH\textsubscript{3}, t, 2H, \(J = 6.7\) Hz), 2.01 (ICH=CHCH\textsubscript{2}, q, 2H, \(J = 6.8\) Hz), 2.00 (CH\textsubscript{2}OCOCH\textsubscript{3}, s, 3H), 1.62-1.28 (CHCH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}O, m, 8H); \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{3}Cl) \(\delta\) 171.1 (O\textsubscript{OCOCH\textsubscript{3}}), 146.4 (ICH=CHCH\textsubscript{2}), 74.4 (ICH=CHCH\textsubscript{2}), 64.4 (CH\textsubscript{2}OCOCH\textsubscript{3}), 35.8 (ICH=CHCH\textsubscript{2}), 28.4, 28.1, 25.6, 21.0 (CHCH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}OCOCH\textsubscript{3}).
4.5.4.3 (7E,9E)-Dodeca-7,9,11-trienyl acetate (4-75)\textsuperscript{28}

\[
\text{OAc}
\]

A round-bottomed flask containing degassed DMF (3 mL) was charged with Pd(MeCN)\textsubscript{2}Cl\textsubscript{2} (1.3 mg, 0.005 mmol). (E)-8-iodooct-7-enyl acetate (0.073 g, 0.246 mmol) was then added followed by stirring for 10 min. Stannane 4-12 (0.127 g, 0.369 mmol) was added next, followed by CuI (0.070 g, 0.369 mmol). The reaction was allowed to stir over 48 h at room temperature. 10% NH\textsubscript{4}OH/ NH\textsubscript{4}Cl solution (25 mL) and ether (25 mL) were added to the flask, and the two phases were separated. The aqueous layer was extracted with ether (2 x 25 mL). All organic solutions were combined, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude product was purified by column chromatography (5/1 : hexane/ether) to afford 0.053 g of pheromone 4-75 as a colourless oil in 97% isolated yield.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 6.31 (CH\textsubscript{2}=CH-CH=CH-CH=CH-CH\textsubscript{2}, dt, 1H, J = 16.8 Hz, J = 9.8 Hz), 6.22-5.99 (CH\textsubscript{2}=CH-CH=CH-CH=CH-CH\textsubscript{2}, m, 3H), 5.69 (CH\textsubscript{2}=CH-CH=CH-CH=CH-CH\textsubscript{2}, dt, 1H, J = 14.7 Hz, J = 7.0 Hz), 5.14 (CH\textsubscript{2}=CH-CH=CH-CH=CH-CH\textsubscript{2}, d, 1H, J = 16.7 Hz), 5.01 (CH\textsubscript{2}=CH-CH=CH-CH=CH-CH\textsubscript{2}, d, 1H, J = 9.9 Hz), 4.02 (CH\textsubscript{3}OCOCH\textsubscript{3}, t, 2H, J = 6.7 Hz), 2.07 (CH-CH\textsubscript{2}, q, 2H, J = 6.9 Hz), 2.01 (OCOCH\textsubscript{3}, s, 3H), 1.61-1.23 (CH-CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}O, m, 8H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 171.2 (OOCOCH\textsubscript{3}), 137.1, 135.7, 133.4, 131.0, 130.2, 116.2 (CH\textsubscript{2}=CH-CH=CH-CH=CH-CH\textsubscript{2}), 64.5 (CH\textsubscript{3}OCOCH\textsubscript{3}), 32.6, 29.0, 28.7, 28.5, 25.7, 20.9 (CH-CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}OCOCH\textsubscript{3}).
4.5.5 Synthesis of aryldienes

4.5.5.1 \((E)-\text{Buta-1,3-dienylbenzene (4-80)}\)\(^{46}\)

A round-bottomed flask containing THF (4 mL) was charged with Pd\(_2\text{dba}_3\) (11.1 mg, 12.1 mmol) and TFP (11.1 mg, 0.048 mmol) and let stir for 10 min. Bromobenzene (0.076 g, 0.483 mmol) was then added followed by stirring for 10 min. Stannane 4-12 (0.200 g, 0.579 mmol) was added next and the reaction was allowed to stir at reflux for 12 h. Saturated KF solution (30 mL) and ether (50 mL) were added to the flask, and the two phases were separated. The organic layer was washed with saturated KF solution (2 x 50 mL), dried over Na\(_2\text{SO}_4\) and concentrated. The crude product was purified by column chromatography (hexane as the eluant) to afford 0.060 g of aryl butadiene 4-80 as colourless oil in 95% isolated yield.

\(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 7.44 (\text{PhH, d, 2H, J = 7.3 Hz}), 7.30 (\text{PhH, t, 2H, J = 7.7 Hz}), 7.21 (\text{PhH, t, 1H, J = 7.2 Hz}), 6.88 (\text{CH}_2=\text{CH-CH=CHPh, dd, 1H, J = 15.6 Hz, J = 10.5 Hz}), 6.60 (\text{CH}_2=\text{CH-CH=CHPh, d, 1H, J = 15.6 Hz}), 6.49 (\text{CH}_2=\text{CH-CH=CHPh, dt, 1H, J = 16.7 Hz, J = 10.2 Hz}), 5.35 (\text{CH}_3=\text{CH-CH=CHPh, d, 1H, J = 17.0 Hz}), 5.16 (\text{CH}_3=\text{CH-CH=CHPh, d, 1H, J = 9.9 Hz}); \(^1\text{C NMR (75 MHz, CDCl}_3\) \(\delta 137.6, 137.8, 133.1, 130.0, 129.1 (2C), 128.1, 126.8 (2C), 118.5.\)
4.5.5.2 \((E)-1\text{-}(\text{Buta-1,3-dienyl})\text{-}4\text{-nitrobenzene (4-81)}^3\)

\[
\begin{align*}
\text{NO}_2
\end{align*}
\]

A round-bottomed flask containing THF (4 mL) was charged with Pd\textsubscript{2}dba\textsubscript{3} (11.1 mg, 12 mmol) and TFP (11.1 mg, 0.048 mmol) and let stir for 10 min. 1-bromo-4-nitrobenzene (0.098 g, 0.483 mmol) was then added followed by stirring for 10 min. Stannane 4-12 (0.200 g, 0.579 mmol) was added next and the reaction was allowed to stir at reflux over 12 h. Saturated KF solution (30 mL) and ether (50 mL) were added to the flask, and the two phases were separated. The organic layer was washed with saturated KF solution (2 x 50 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude product was purified by column chromatography (5:1, hexane/Et\textsubscript{2}O) to afford 0.078 g of aryl butadiene 4-81 as white crystals (m.p. 75-76 °C) in 92% isolated yield.

\(^1\)H NMR (300 MHz, DMSO) \(\delta 8.15\) (Ph\textsubscript{H}, d, 2H, \(J = 7.9\) Hz), 7.50 (Ph\textsubscript{H}, d, 2H, \(J = 8.0\) Hz), 6.91 (CH\textsubscript{2}=CH-CH=CHPh, dd, 1H, \(J = 15.6\) Hz, \(J = 10.6\) Hz), 6.58 (CH\textsubscript{2}=CH-CH=CHPh, d, 1H, \(J = 15.7\) Hz), 6.51 (CH\textsubscript{2}=CH-CH=CHPh, dt, 1H, \(J = 17.1\), \(J = 10.3\) Hz), 5.46 (CH\textsubscript{2}=CH-CH=CHPh, d, 1H, \(J = 16.8\) Hz), 5.16 (CH\textsubscript{2}=CH-CH=CHPh, d, 1H, \(J = 10.0\) Hz); \(^13\)C NMR (75 MHz, DMSO) \(\delta 146.7, 143.6, 136.3, 133.9, 130.3, 126.7\) (2C), 124.0 (2C), 120.9.
4.5.6 Reaction of dienyl cuprate with chalcone

4.5.6.1 (E)-1,3-Diphenylhepta-4,6-dien-1-one (4-86)

Copper cyanide (25 mg, 0.278 mmol, flame dried under vacuo) in THF (2 mL) was treated with methyllithium (0.39 mL, 0.612 mmol) at 0 °C. The cooling bath was removed and stannane 4-12 (108 mg, 0.313 mmol) in THF (1 mL) was added at rt. After 2 min of stirring at rt, chalcone (41.3 mg, 0.199 mmol) in THF (1 mL) was added at rt. After 18 h of stirring at rt, the mixture was quenched into a 9:1 saturated ammonium chloride/ ammonium hydroxide solution. Ether extraction followed by solvent removal afforded an oily residue. This oil was chromatographed (silica gel, hexane/ether, 5:1) to provide 38.1 mg of product 4-86 in 73% isolated yield.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.93-7.19 (PhH, m, 10H), 6.25 (CH$_2$=CH-CH=CHCH, dt, 1H, J = 17.0 Hz, J = 10.1 Hz), 6.00 (CH$_2$=CH-CH=CHCH, dd, 1H, J = 16.2 Hz, J = 10.0 Hz), 5.92 (CH$_2$=CH-CH=CHCH, dd, 1H, J = 16.4 Hz, J = 6.8 Hz), 5.07 (CH$_2$=CH-CH=CHCH, d, 1H, J = 16.7 Hz), 4.97 (CH$_3$=CH-CH=CHCH, d, 1H, J = 10.1 Hz), 4.17 (PhCH, dt, 1H, J = 7.0 Hz, J = 6.9 Hz), 3.40 (PhCHCH$_2$, d, 2H, J = 7.1 Hz).
4.5.7  **Synthesis of pheromone 4-83**

4.5.7.1  **(E)-Dodeca-9,11-dienyl acetate (4-83)**

![Structure of (E)-Dodeca-9,11-dienyl acetate](image)

Adopted from Fu *et al.*[^43] Allylpalladium chloride dimer (14.5 mg, 39.6 mmol), PCy(pyrrolidinyl)$_2$ (60.3 mg, 237.8 mmol) and 3Å sieves (100 mg), were added successively to THF (10 mL) and the resulting mixture was stirred at r.t. for 15 min. Tetramethylammonium fluoride (111 mg, 1.19 mol), bromoacetate 4-89 (100 mg, 0.40 mol) and stannylbutadiene 4-12 (274 mg, 0.80 mol) were added and the reaction was stirred for 24 h at rt. The reaction mixture was passed through a 5 g silica plug containing 10% KF, washed with ether) and concentrated. The resulting residue was purified by silica gel chromatography (10/1 : hexane/ ether) to afford dienylacetate 4-83 along with inseparable β-elimination by-product 4-85 (85:15, determined by GCMS) as a colourless oil in a combined yield of 89 % (79.0 mg).

[^43]: Fu *et al.*

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.23 (CH$_2$=CH-CH=CHCH$_2$, dt, 1H, $J = 16.9$ Hz, $J = 10.2$ Hz), 5.97 (CH$_2$=CH-CH=CHCH$_2$, dd, 1H, $J = 15.0$ Hz, $J = 10.5$ Hz), 5.63 (CH$_2$=CH-CH=CHCH$_2$, dt, 1H, $J = 15.1$ Hz, $J = 6.9$ Hz), 5.01 (CH$_2$=CH-CH=CHCH$_2$, d, 1H, $J = 16.9$ Hz), 4.87 (CH$_2$=CH-CH=CHCH$_2$, d, 1H, $J = 10.3$ Hz); 3.98 (CH$_2$CH$_2$OCOCH$_3$, t, 2H, $J = 6.7$ Hz), 2.01-1.97 (CH$_2$=CH-CH=CHCH$_2$, CH$_2$CH$_2$OCOCH$_3$, m, 7H), 1.75-1.21 (CH$_2$=CH-CH=CHCH$_2$(CH$_2$)$_4$, m, 8H) $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.1 (OOCCH$_3$),
138.8, 137.3, 135.3, 131.0 (CH$_2$=CH-CH=CH), 64.6 (CH$_2$OCOCH$_3$), 32.5, 29.4, 29.2 (2C), 29.1, 28.8, 25.9, 22.7 (CH$_2$=CH-CH=CH(CH$_2$)$_7$CH$_2$OCOCH$_3$).

Spectral data were in accord with literature data.
Chapter 5

Synthesis of (E)-Vinyl Iodides from (E)-Vinylstannanes and their Applications

5.1 Introduction

5.1.1 General

Recently, vinyl iodides have become important compounds in organic synthesis. They can serve as precursors for vinyl radicals which can be utilized in intramolecular cyclizations (Scheme 5.1).\(^1\)

![Scheme 5.1](image)

They can also be utilized in cross-coupling reactions to form new carbon-carbon bonds (Scheme 5.2).\(^2\)
The versatility of these compounds has made them valuable intermediates in organic chemistry.

5.1.2 Synthesis of vinyl iodides

5.1.2.1 Hydroiodination

Generally, vinyl iodides are obtained from acetylenes or carbonyl compounds. The simplest preparation of vinyl iodides is to add “H-I” across a triple bond by treating an alkyne with hydroiodic acid. Treatment of 5-4 with HI provided two stereoisomers in a ratio of ~ 4:1 (E:Z) (Scheme 5.3).

![Scheme 5.3](image-url)
Vinyl iodide 5-5 did not form in the reaction as carbocation 5-9 is much less stable than 5-8 (Scheme 5.4).

Scheme 5.4

Vinyl iodide 5-10 resulted from a syn addition of HI across the triple bond, but in the presence of excess acid, it equilibrated to the more thermodynamically stable Z isomer 5-11 (Scheme 5.5).
Scheme 5.5

Commercial HI is expensive; therefore, Kamiya et al. demonstrated the ability to form “HI” in situ by mixing TMSCl, NaI and water (Table 5.1). Acetonitrile, as a solvent, was key to the addition of “HI” to challenging terminal alkynes, whereas previous conditions failed to do so.

Table 5.1 Addition of in situ generated HI to terminal alkynes.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne isomer</th>
<th>conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>purity (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[ \text{5-15} ] geminal</td>
<td>67</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>[ \text{5-16} ] geminal</td>
<td>82</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>
Geminal-vinyl iodides, obtained from terminal alkynes, were prepared in decent yields and great selectivities. The reactions are performed at room temperature and are complete within an hour.\(^5\)

5.1.2.2 Vinyl iodides from carbonyl compounds

Vinyl iodides can also be obtained from carbonyl compounds. Takai et al. illustrated the conversion of aldehydes to vinyl iodides efficiently (Table 5.2).\(^6\)

**Table 5.2** Conversion of aldehydes to vinyl iodides.\(^6\)
<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>aldehyde</th>
<th>time (h)</th>
<th>trans/cis&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="5-21" /></td>
<td>3</td>
<td>94/6</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="5-22" /></td>
<td>2</td>
<td>83/17</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="5-23" /></td>
<td>1</td>
<td>89/11</td>
<td>78</td>
</tr>
</tbody>
</table>

<sup>a</sup> The aldehyde (1.0 mmol) was treated with iodoform (2.0 mmol) and CrCl<sub>2</sub> (6.0 mmol) in THF.

<sup>b</sup> The isomeric ratios of the vinyl iodides were determined by GLPC or NMR.

Moderate to good selectivities of *trans*-vinyl iodides were obtained using this methodology<sup>6</sup>.

There are two possible pathways for the addition of “iodomethine” onto the aldehyde (Scheme 5.6).<sup>6</sup> First, chromium reacts with iodoform to form chromium diiodocarbenoid 5-25. Second, 5-25 could react again with chromium to form carbodianion species 5-26. Chromium species 5-25 and 5-26 are believed to be possible reactive intermediates in this reaction. This methodology provided *trans*-vinyl iodides as the major products (Scheme 5.6).
Similar methodology by Stork and Zhao applies a modified Wittig reaction by using the ylide from iodomethylphosphonium iodide 5-31 (Scheme 5.7).\textsuperscript{7,8}

Unlike the methodology using chromium, Wittig chemistry provides the \textit{cis}-vinyl iodide as the major isomer in most cases.
Other methods that obtained vinyl iodides from carbonyl compounds, such as ketones, include the formation of a triflate followed by treatment with MgI$_2$, the formation of a phosphate followed by treatment with TMSI and the formation of hydrazone followed by treatment with iodine (Scheme 5.8).

Scheme 5.8

5.1.2.3 Vinyl iodides from acetylenes

Hydrometalation of terminal alkynes, followed by an iodine quench is a common methodology used to provide mainly trans-vinyl iodides.
Hydroalumination of terminal alkynes, such as 1-hexyne, is highly regioselective. Syn addition across the triple bond provided trans-vinylalane 5-38 (Scheme 5.9). Treatment of vinylalane 5-38 with iodine furnished the corresponding trans-vinyl iodide 5-39 as a pure isomer in 74% isolated yield (Scheme 5.9).

![Scheme 5.9](image)

Chong and Heuft demonstrated the effect of a proximal heteroatom to the reaction site can have on the stereochemical outcome of the hydroalumination reaction (Scheme 5.10).^13,14

![Scheme 5.10](image)
As expected, *trans*-vinyl iodide 5-45 was the major product from homopropargyl alcohol 5-40. A small percent of *cis*-vinyl iodide was present, suggesting the participation of an anti-hydroalumination mechanism. The over reduction product 5-43 was also formed. As alcohol 5-40 was protected with a *t*-butyl group, a stark difference in selectivity was observed (Scheme 5.11).

![Scheme 5.11](image)

*Cis*-vinyl iodide 5-46 was the major product when the alcohol was protected by a *t*-butyl group. Chong and Heuft speculated that the oxygen in the aluminum alkoxide intermediate 5-48 was not as effective a coordinator as the oxygen in the *t*-butyl ether 5-44 (Figure 5.1).

![Figure 5.1](image)

**Figure 5.1** Aluminum alkoxide intermediate 5-48 and *t*-butyl ether 5-44
Coordination by the oxygen in the \( t \)-butyl ether 5-44 allowed for an anti-hydroalumination process to take place, which in return, afforded \( cis \)-vinyl iodide 5-46 as the major product.\(^{13}\)

Stewart and Whiting have devised a stereoselective synthesis of vinyl iodides from vinylboronate pinacol esters using ICl.\(^{15}\) This methodology was based on an observation made by Brown \textit{et al.} that alkenylboronic acid derivatives were readily converted to alkenyl iodides, under stereochemical controlled conditions that afforded the corresponding \textit{trans}- or \textit{cis}-vinyl iodides (Scheme 5.12).\(^{16,17}\) ICl was sufficiently electrophilic to perform the following transformations, whereas I\(_2\) seemed to give no reaction with the hindered pinacol boronate esters.

\[
\begin{array}{cccc}
\text{I} & \text{R} & \text{R} \\
5-20 & 5-19 & \text{I} \\
\end{array}
\]

\[
\begin{array}{cccc}
1. \text{ICl}, \text{CH}_2\text{Cl}_2, -78 \degree \text{C} & \rightarrow & \text{1. NaOMe, -78 \degree \text{C}} & \rightarrow \\
2. \text{NaOMe, -78 \degree \text{C}} & \text{-rt} & 1. \text{NaOMe, -78 \degree \text{C}} & \text{THF} \\
\text{method B} & & 2. \text{ICl, -78 \degree \text{C}} & \text{-rt} \\
\text{method A} & & \text{method A} & 5-14 \\
\end{array}
\]

\text{Scheme 5.12}
The stereoselectivity depended on the reaction conditions adopted to perform the transformation. Treatment of the boronate with excess base resulted in the formation of the “ate” complex 5-50 (Scheme 5.13).\(^\text{15}\)

![Scheme 5.13](image)

Upon the formation of a tetrahedral boronate complex, iodination takes place by the addition of ICl with retention in configuration.

Toward the synthesis of the \(cis\) isomer, ICl was added first in the absence of base. It was assumed that ICl added across the double bond via iodonium ion formation, followed by the addition of chloride ion to the alkyl or aryl substituted carbon (Scheme 5.14).\(^\text{15}\) The addition of ICl occurred in an anti fashion across the double bond. The subsequent treatment of base formed the ate-complex 5-53, which in return, caused the chloride ion to be expelled (Scheme 5.14).\(^\text{15}\)
This methodology was applied to vinyl and dienyl boronate systems to illustrate its effectiveness (Table 5.3).
Table 5.3  Stereoselective formation of trans- and cis-vinyl iodides from boronates.\textsuperscript{15}

<table>
<thead>
<tr>
<th>entry</th>
<th>boronate</th>
<th>Method\textsuperscript{a}</th>
<th>selectivity (E:Z)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="214x597" alt="Image" /></td>
<td>A</td>
<td>100:0</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td><img src="202x596" alt="Image" /></td>
<td>B</td>
<td>0:100</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td><img src="201x576" alt="Image" /></td>
<td>A</td>
<td>98:2</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td><img src="214x583" alt="Image" /></td>
<td>B</td>
<td>13:87</td>
<td>81</td>
</tr>
</tbody>
</table>

\textsuperscript{a} refer to Scheme 5.12 for methods

Hindered pinacol esters were readily transformed into the corresponding vinyl iodides. Modest to excellent selectivities were obtained by this methodology.\textsuperscript{15}

Stamos \textit{et al.} were effective in transforming trans- and cis-vinylsilanes to their corresponding vinyl iodides by using N-iodosuccinimide (NIS) in a mixture of acetonitrile and monochloroacetonitrile (9:1, v/v) (Table 5.4).\textsuperscript{18}

Table 5.4  Formation of vinyl iodides from vinylsilanes.\textsuperscript{18}

\[ \text{R} = \text{MeCN/CHCl}_2\text{CN} \]
<table>
<thead>
<tr>
<th>entry</th>
<th>silane</th>
<th>selectivity</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(E:Z)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td><img src="5-58" alt="image" /></td>
<td>2.8:1</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td><img src="5-59" alt="image" /></td>
<td>1.2:1</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td><img src="5-60" alt="image" /></td>
<td>1:0</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td><img src="5-61" alt="image" /></td>
<td>1:12</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td><img src="5-62" alt="image" /></td>
<td>8:1</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td><img src="5-63" alt="image" /></td>
<td>1:0</td>
<td>10</td>
</tr>
</tbody>
</table>

There was a noticeable trend with substrates with bulkier allylic carbons maintained their double bond geometry better. It is thought that solvent participation allows for the opening of the iodonium ion leading to the inverted vinyl iodide 5-20, while a bulky allylic substrate minimizes the solvent participation, leading to the cis stereoisomer (Scheme 5.15).18
Trans selectivity was observed in trial 6 (Table 5.4) for cis-vinylsilane 5-63. It is thought that carbon-oxygen bond electronically destabilizes the cyclic iodonium ion and forces the equilibrium toward the trans product.\textsuperscript{18}

Hydrozirconation of simple olefins and alkynes proceeds in a highly regioselective fashion, placing the zirconium on the least hindered carbon.\textsuperscript{19} Vinylzirconium compounds can be transformed into vinyl iodides, with complete retention of the double bond, by simple treatment of iodine.\textsuperscript{19} Zhang and Ready illustrated the ability of hydrozirconation to proceed in high regioselectivity when applied to propargyl alcohols (Scheme 5.16).\textsuperscript{20}
Scheme 5.16

Hydrozirconation, leading to *trans*-vinyl iodide 5-68, proceeded by a *syn* addition of ZrH across the triple bond followed by iodination with retention of configuration. While hydrozirconation, leading to *geminal*-vinyl iodide 5-69, proceeded by formation of alkoxide intermediate first, then coordination of the alkoxide to a “ZrH” generated a *geminal*-vinylzirconium species, followed by iodination.20

Lewis acid catalyzed hydrogermylation of alkynes was demonstrated by Schwier and Gevorgyan (Scheme 5.17).21
The stereochemical outcome of hydrogermylation depended strongly on the nature of the substrate. Simple alkynes promote trans-addition of GeH across the triple bond (Scheme 5.18).

Scheme 5.18

Bulky hydride 5-79 attacks vinyl cation 5-78 at the least hindered site to give trans-addition product 5-80. Hydrogermylation of propiolates is believed to occur via a different mechanistic pathway (Scheme 5.19).
As zwitterionic complex 5-83 forms, it abstracts a hydride from germane 5-75 to form allenolate 5-84, which is trapped by a germylium-type specie from the least hindered side, cis to H, to produce the syn-addition product 5-85 (Scheme 5.19).\textsuperscript{21}

Upon treating vinylgermanes with a source of iodide, perfect retention of the double-bond geometry was observed (Table 5.5).

**Table 5.5** Formation of vinyl iodides from vinylgermanes.\textsuperscript{21}
As illustrated in Table 5.5, iododegermylation/iodination proceeded smoothly to furnish the corresponding vinyl iodides in good to excellent yields.\textsuperscript{21}

Vinylstannanes can also be converted into their corresponding vinyl iodides by a simple quench with iodine. Perfect retention of configuration of the double bond is usually observed. Factors influencing the selectivities of hydrostannation were discussed in Chapter 3. Jung and Light have demonstrated the conversion of vinylstannanes into their corresponding vinyl iodides (Table 5.6).\textsuperscript{22}
Table 5.6  Formation of vinyl iodides from vinylstannanes.\textsuperscript{22}

\[
\begin{array}{ccc}
\text{entry} & \text{vinylstannane} & \text{vinyl iodide} \\
1 & \text{HO-} & \text{HO-} \\
 & 5-92 & 5-93 \\
 & 5-94 & 5-95 \\
2 & 5-96 & 5-97 \\
 & 4 : 1 & 4 : 1^a \\
3 & \text{H}_{11}\text{C}_5\text{OH} & \text{H}_{11}\text{C}_5\text{OH} \\
 & 5-98 & 5-99 \\
4 & \text{BnO-} & \text{BnO-} \\
 & 5-100 & 5-101 \\
\end{array}
\]

\(\text{yield (\%)}\)

\(76\)

\(63\)

\(84\)

\(99\)

\(\text{\textsuperscript{a} Ratio was determined by }^1\text{H NMR analysis}\)

Iodination of vinylstannanes was straight forward. A slight excess of iodine was used (1.3 equiv.) to convert vinylstannanes to vinyl iodides. Retention of the double bond was
observed in all cases. Good to quantitative yields of vinyl iodides were obtained by this methodology.

5.1.2.4  *Hydrometallation of iodoacetylenes*

Cowell and Stille demonstrated hydroboration/protonolysis of iodoacetylenes as a method to generate pure *cis*-vinyl iodides (Table 5.7).

<table>
<thead>
<tr>
<th>entry</th>
<th>iodoacetylene</th>
<th>vinyl iodide</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![5-104]</td>
<td>![5-96]</td>
<td>N/A(^a)</td>
</tr>
<tr>
<td>2</td>
<td>![5-105]</td>
<td>![5-106]</td>
<td>61</td>
</tr>
</tbody>
</table>

\(^a\) Not determined owing to loss of product during workup

Unsubstituted vinyl iodide 5-96 proved to be a difficult substrate to isolate without considerable loss in product. Substituted vinyl iodide 5-106 was isolated in moderate yield of 61%.\(^23\)

Reduction of iodoacetylenes can also be accomplished by dipotassium azodicarboxylate (Scheme 5.20).\(^24\)
Diimide 5-108 is formed as azodicarboxylate 5-107 is treated with acid, thus liberating two equivalents of carbon dioxide. Diimide 5-108 reduces iodoacetylenes to the corresponding cis-vinyl iodide (Table 5.8).

**Table 5.8** Synthesis of cis-vinyl iodides from iodoacetylene by diimide reduction.\(^{24,25}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>iodoacetylene</th>
<th>vinyl iodide</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="5-109" /></td>
<td><img src="image" alt="5-110" /></td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="5-111" /></td>
<td><img src="image" alt="5-112" /></td>
<td>62</td>
</tr>
</tbody>
</table>
5.1.2.5 Other methods

Other methodologies that provide vinyl iodides include a radical addition of C₄F₉I to terminal alkynes with high regio- and stereoselectivity utilizing zinc as a catalyst (Scheme 5.21).

![Scheme 5.21](image)

Reaction of vinyl bromides with an iodide ion in the presence of nickel catalyst generates the corresponding vinyl iodides with complete retention of configuration (Scheme 5.22).

![Scheme 5.22](image)
5.1.3 Applications of vinyl iodides

5.1.3.1 Radical cyclizations

As stated earlier, vinyl iodides are versatile intermediates that are capable of many types of transformations.

Compounds 5-118 and 5-121 were obtained by cascade radical cyclization from vinyl iodide 5-116 and 5-119, respectively, in a single operation (Scheme 5.23).\(^1\)

![Scheme 5.23](image_url)
Tricyclic compound 5-118 was obtained through a sequential 6-endo, 6-endo, 6-exo cyclization, whereas tricyclic compound 5-121 was obtained through a 5-exo, 5-exo, 5-exo cyclization. Vinyl iodides 5-116 and 5-119 were radical precursors that facilitated these cyclizations.

5.1.3.2 Cross-coupling reactions

A major application of vinyl iodides is their ability to undergo cross-coupling reactions.

Vinyl iodide 5-122 was able to cross-couple with vinylstannane 5-123, via Stille coupling, to provide diene 5-124 in good yield (Scheme 5.24).²⁵

![Scheme 5.24]

Vinyl iodide 5-125 was able to cross-couple with terminal alkyne 5-126, via Sonogashira coupling, to furnish enyne 5-127 in good yield (Scheme 5.25).²⁷
Vinyl iodide 5-128 was able to cross-couple with vinylboronate 5-129, via Suzuki coupling, to provide triene 5-130 smoothly (Scheme 5.26).

Vinyl iodide 5-131 was able to cross-couple with alkylzinc 5-132, via Negishi coupling, to provide compound 5-133 (Scheme 5.27).
Vinyl iodide 5-128 was able to cross-couple with vinylsilane 5-134, via Hiyama coupling, to provide diene 5-135 in a quantitative yield (Scheme 5.28).\(^\text{30}\)

Vinyl iodide 5-136 was able to cross-couple with alkenylzirconium species 5-137, via Negishi coupling, to provide diene 5-138 (Scheme 5.29).\(^\text{2}\)
Vinyl iodides are also capable of cross-coupling with heteroatom-based coupling partners. Vinyl iodide 5-128 was able to couple with aryl thiol 5-139 to provide vinylsulfide 5-140 in excellent yield (Scheme 5.30).\textsuperscript{31}

\[ \text{Ph-SH} + \text{H}_{13}\text{C}_{6}\text{C}=\text{I} \xrightarrow{5 \text{ mol\% 5-141}} \text{Ph-S}==\text{C}_{6}\text{H}_{13} \]

Scheme 5.30

Vinyl iodide 5-143 was able to couple with allylic alcohol 5-142 to provide vinyl ether 5-144 in moderate yield (Scheme 5.31).\textsuperscript{32}

\[ \text{H}_{17}\text{C}_{6}\text{C}=\text{OH} + \text{H}_{17}\text{C}_{6}\text{C}=\text{I} \xrightarrow{10 \text{ mol\% Cul}} \text{C}_{6}\text{H}_{17}==\text{O}==\text{C}_{6}\text{H}_{17} \]

Scheme 5.31
5.1.3.3 Lithium-halogen exchange

Vinyl iodides are able to undergo lithium-halogen exchange to produce the corresponding vinylolithiums. Vinyl iodide 5-146 underwent lithium-halogen exchange with t-BuLi to produce the corresponding vinylolithium; subsequent treatment with CuCN produced the corresponding cuprate reagent 5-147. This cuprate reagent underwent conjugate addition to compound 5-148 to provide compound 5-149 (Scheme 5.32).\textsuperscript{33}
5.1.3.4  Substitution reactions

Substitution reactions on vinyl iodides have been performed. Vinyl iodide 5-122 was able to undergo a substitution reaction with cuprate reagent 5-151, formed in situ, to provide compound 5-152 in excellent yield (Scheme 5.33).  

![Scheme 5.33]

5.1.4  Applications of vinyl iodides in total synthesis

There are many applications of vinyl iodides in natural product synthesis. One example is a convergent synthesis of a sex pheromone of the forest tent caterpillar, *Malacosoma disstria* (Scheme 5.34).  

![Scheme 5.34]
The coupling of vinyl iodide 5-154 and vinylstannane 5-153 afforded pheromone 5-155 in 73% isolated yield.\textsuperscript{25}

Also, convergent total syntheses of pumiliotoxins A and B, major toxic alkaloids from skin extracts of the Panamanian poison frog \textit{Dendrobates pumilio},\textsuperscript{36} was possible via palladium-catalyzed cross-coupling reaction of homoallylic organozinc compounds 5-156a and 5-156b with vinyl iodides 5-157 and 5-160, respectively (Scheme 5.35).\textsuperscript{29}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme5.35}
\end{center}
\end{scheme}

\textbf{Scheme 5.35}
5.2 Proposed Work

The goal of this project is to develop a general and operationally simple route for providing (E)-1-iodoalkenes 5-14 from terminal alkynes via palladium-catalyzed hydrostannation reaction (Scheme 5.36).

\[
\begin{align*}
R\equiv & + \text{Bu}_3\text{SnH} \\
\text{5-12} & \xrightarrow{1. \text{Pd cat.}} \text{1. } & \xrightarrow{2. \text{I}_2} \text{2. I}_2 \\
\text{I} & \text{5-14}
\end{align*}
\]

Scheme 5.36

Convergent and concise syntheses of natural products will be illustrated to highlight the usefulness of this methodology.
5.3 Results and Discussion

5.3.1 Synthesis of (E)-1-vinyl iodides from (E)-1-vinylstannanes

Synthesis of vinyl iodides from unhindered terminal alkynes in high regioselectivity was made possible by recent improvements in palladium-catalyzed hydrostannation as discussed in Chapter 3.\textsuperscript{37}

Vinyl iodides were obtained by quenching the resulting vinylstannane mixture after hydrostannation with iodine. The results are illustrated in Table 5.9.
Table 5.9 Formation of vinyl iodides from terminal alkynes via hydrostannation

\[
\begin{align*}
\text{entry} & & (\text{vinyl iodide}) & & \text{R} & & \text{ratio}^d & & \text{isolated yield (\%)} \\
1 & (5-163:5-164) & & (\text{CH}_2)_2\text{OTBS} & & 95:5 & & 88^c \\
2 & (5-163:5-164) & & (\text{CH}_2)_8\text{OH} & & 99:1 & & 71^{b,c} \\
3 & (5-165:5-166) & & (\text{CH}_2)_2\text{OAc} & & 95:5 & & 93^c \\
4 & (5-165:5-166) & & (\text{CH}_2)_4\text{OH} & & 99:1 & & 75^{b,c} \\
5 & (5-167:5-168) & & (\text{CH}_2)_2\text{OH} & & 95:5 & & 76^{b,c} \\
6 & (5-169:5-170) & & (\text{CH}_2)_2\text{CH}_2\text{OH} & & 95:5 & & 94^c \\
7 & (5-169:5-170) & & (\text{CH}_2)_2\text{CH}_2\text{OH} & & 99:1 & & 76^{b,c} \\
8 & (5-169:5-170) & & \text{CH}_2\text{OH} & & 67:33 & & 67^e \\
9 & (5-169:5-170) & & (\text{CH}_2)_2\text{OH} & & 83:17 & & 83^e \\
10 & (5-172:5-173) & & \text{CH(OH)CH}_3 & & 95:5 & & 93^e \\
11 & (5-172:5-173) & & \text{CH(OH)n-C}_5\text{H}_{11} & & 95:5 & & 89^e \\
12 & (5-175:5-176) & & \text{CH(OH)Ph} & & 82:12 & & 80^f \\
\end{align*}
\]

\(\text{a} \quad \text{Pd}_2\text{dba}_3 (0.125 \text{ mol \%}), \text{Cy}_3\text{PH BF}_4 (0.5 \text{ mol \%}), i-\text{Pr}_3\text{NEt} (1 \text{ mol \%}), \text{Bu}_3\text{SnH} (1.2 \text{ eq}), \text{CH}_2\text{Cl}_2, 0^\circ \text{C, 2h, then I}_2 (1.3 \text{ eq dissolved in CH}_2\text{Cl}_2), 0^\circ \text{C, 10 min.} \)

\(\text{b} \quad 0.95 \text{ eq of I}_2 \text{ was used.} \)

\(\text{c} \quad \text{Isolated yield of both inseparable isomers.} \)

\(\text{d} \quad \text{Ratio was determined by }^1\text{H NMR analysis of the crude mixture.} \)

\(\text{e} \quad \text{Isolated yield of }^\text{trans} \text{ isomer only.} \)

Iodination of the resulting vinylstannanes resulted in perfect retention of configuration of the double bond and good to excellent isolated yields. This methodology was compatible with esters, alcohols and TBS-ethers as the selectivities and yields were consistent. Quenching the reaction with excess iodine (1.3 equivalents) provided a ratio of vinyl iodides that was consistent with the ratios obtained from vinylstannanes after hydrostannation. Yields of vinyl iodides were similar to the yields obtained of vinylstannanes. The reactions were operationally simple, as a follow up from the
hydrostannation reaction, the vinylstannanes formed in situ were quenched directly with iodine; effectively producing trans-vinyl iodides in high regioselectivities and yields in one-pot from the corresponding terminal alkyne. Vinyl iodides obtained from alkynes in trials 1-8 were inseparable by silica gel chromatography; higher selectivity of these vinyl iodides would be advantageous. An improvement in selectivity was observed when 0.95 equivalent of iodine was used to quench the reaction. This improvement was credited to the slight difference in reactivity toward iodination between the trans- and geminal-vinylstannanes. As 0.95 equivalent of iodine was used, the vinyl iodide ratio obtained improved from 95:5 to 99:1 with a slight decrease in yield (~18% on average) in trials 2, 4, 6 and 8. Lowering the equivalents of iodine from 0.95 to 0.90 and 0.80 offered no advantages in terms of selectivity but rather poorer yields of the trans-vinyl iodide were obtained. Decreasing the temperature of the reaction from 0 °C to -15 °C and -78 °C at 0.95, 1.0 and 1.3 equivalents did not affect the selectivity but lower isolated yields of trans-vinyl iodides were obtained. Also, the method used to add the iodine did not affect the selectivity, but rather the consistency of the yields obtained of trans-vinyl iodides. Adding the iodine quickly (10 min), as a solution in CH₂Cl₂ offered the most consistent results; while addition of the iodine solution, over a longer period of time (1 h), or as a solid in one, three or four portions resulted in incomplete and inconsistent reactions. In most applications, the improvement in selectivity, from 95:5 to 99:1 (E:Z), was not necessary as illustrated below in the synthesis of two sex pheromones on large scales (Scheme 5.37 and 5.38).
5.3.2 Applications

Natural product **5-179** is a sex pheromone of the pecan moth, *Acrobasis nuxvorella*.\textsuperscript{35,38,39} This pheromone was synthesized in a linear sequence of three steps in 55\% overall yield (Scheme 5.37).

![Chemical reaction scheme](image)

**Scheme 5.37**

Hydrostannation/iodination of alkyne **5-177** provided trans-vinyl iodide **5-167** in 95\% isolated yield in a 95:5 ratio with the corresponding geminal-vinyl iodide (**5-168**). The trans- and geminal-vinyl iodides were inseparable by silica gel chromatography, but it is
known that trans-vinyl iodides are more reactive toward cross-coupling reactions than the corresponding geminal-vinyl iodides.\textsuperscript{40} The 95:5 mixture of vinyl iodides was subjected to Sonogashira conditions along with 2 equivalents of 1-hexyne. As previously reported,\textsuperscript{13} only the trans coupling product \textit{5-178} was observed in 85% yield, and the geminal-vinyl iodide was recovered. Reduction of the triple bond by hydroboration/protonolysis afforded the target product \textit{5-179} in 70% yield.

A second application was the synthesis of a sex pheromone of the sugar cane borer, \textit{Diatraea saccharalis}.\textsuperscript{41} Pheromone \textit{5-183} was synthesized in a 4 step sequence in 68% overall yield without protecting the alcohol (Scheme 5.38).

Hydrostannation/iodination of alkyne \textit{5-180} provided trans-vinyl iodide \textit{5-165} in 93% isolated yield in a 95:5 ratio with the corresponding geminal-vinyl iodide (\textit{5-166}). This mixture was subjected to Sonogashira conditions with 2 equivalents of 1-hexyne. Trans coupling product \textit{5-181} was exclusively formed in 85% isolated yield, while geminal-vinyl iodide was recovered. Reduction of the triple bond by hydroboration/protonolysis afforded diene \textit{5-182} in 94% yield. Subsequent oxidation of the alcohol by PDC provided dienal \textit{5-183} in 91% yield.
Other approaches to aldehydes typically carry a protected alcohol which is deprotected then oxidized. This hydrostannation/iodination approach provides an advantage where protection of the alcohol is not necessary.
5.4 Summary

*Trans*-vinyl iodides were obtained from the corresponding terminal alkynes via palladium-catalyzed hydrostannation in great selectivities and yields. Selectivity of inseparable vinyl iodides were improved, from 95:5 to 99:1 (*E*:Z), by employing 0.95 equivalents of iodine, but with slightly less yield. It was demonstrated, during the synthesis of sex pheromones 5-179 and 5-183 that *geminal*-vinyl iodides did not participate under the Sonogashira conditions used and were recovered after the termination of the reaction. Sex pheromones 5-179 and 5-183 were synthesized in 3 step and 4 step sequences with overall yields of 55% and 68%, respectively.
5.5 Experimental

5.5.1 General experimental

All reactions and reagents were carried out and purified as in Chapter 3. Other reagents were purchased from Sigma-Aldrich and used without further purification. 10-Undecyn-1-ol 5-180 was prepared by bromination/dehydrobromination of 10-undecen-1-ol.42 Commercially-unavailable propargylic alcohols were prepared by addition of lithium trimethylsilylacetylide to the appropriate aldehyde followed by treatment with K₂CO₃/MeOH.43,44

5.5.2 General procedure for synthesis of trans-vinyl iodides

Pd₂dba₃ (65.0 mg, 0.147 mmol), tricyclohexylphosphonium tetrafluoroborate (99.0 mg, 0.294 mmol) and Hünig’s base (76.0 mg, 0.588 mmol) were added successively to CH₂Cl₂ (300 mL) and the resulting mixture was stirred at r.t. for 15 min. The corresponding alkyne was added (58.8 mmol) and the reaction was cooled to 0 °C. Bu₃SnH (20.5 g, 70.5 mmol) diluted in CH₂Cl₂ (90 mL) was added dropwise via a dropping funnel over 1.5 h. The reaction was then allowed to stir at 0 °C for 2 h. Iodine (19.4 g, 76.4 mmol) dissolved in CH₂Cl₂ (300 mL) was added dropwise but quickly via a dropping funnel within 10 min at 0 °C. The reaction mixture was washed with saturated Na₂S₂O₃ solution (1 x 250 mL), and saturated KF solution (3 x 250 mL), passed through a silica plug and concentrated. The resulting oil was purified by silica gel chromatography.
(hexane/ ether) to afford the corresponding trans-vinyl iodide in a 95:5 ratio (1.3 eq. of I₂ was used) or 99:1 ratio (0.95 eq. of I₂ was used) \((trans/gem)\).

5.5.2.1 **(E)-Tert-butyl(11-iodoundec-10-enyloxy)dimethylsilane** (5-163)\(^{45}\)

![Structure](image)

Vinyl iodide **5-163** was isolated in 88% and 71% yield in inseparable ratios of 95:5 and 99:1 \((trans/gem)\) respectively from the corresponding alkyne using the general procedure.

\(^1\)H NMR (300 MHz, CDCl₃) \(\delta 6.49\) (ICH=CHCH₂, 1H, dt, \(J = 14.3\) Hz, \(J = 7.1\) Hz), 5.94 (ICH=CHCH₂, d, 1H, \(J = 14.3\) Hz), 3.57 (TBSOCH₂, 2H, t, \(J = 6.6\) Hz), 2.08 (ICHCHCH₃, 2H, dt, \(J = 7.2\) Hz, \(J = 5.9\) Hz), 1.56-1.25 (CH₂(CH₂)₇CH₂, 14H), 0.87 (tBu(CH₃)₂Si, 9H, s), 0.03 (tBu(CH₃)₂Si, 6H, s); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta 146.7\) (ICH=CHCH₂), 74.1 (ICH=CHCH₂), 63.2 (TBSOCH₂CH₂), 35.9, 32.8, 29.4, 29.3, 29.2, 28.8, 28.3, 25.9, 25.7 (CH₂(CH₂)₇CH₂OTBS), ((CH₃)₃C(CH₃)₂Si), 18.3 ((CH₃)₃C(CH₃)₂Si), -5.4 ((CH₃)₃C(CH₃)₂Si).

5.5.2.2 **(E)-10-Iododec-9-en-1-ol** (5-165)\(^{45}\)

![Structure](image)

Vinyl iodide **5-165** was isolated in 93% and 75% yield in inseparable ratios of 95:5 and 99:1 \((trans/gem)\) respectively from the corresponding alkyne using the general procedure.
$^1$H NMR (300 MHz, CDCl$_3$) δ 6.46 (ICH=CHCH$_2$, dt, 1H, J = 14.4 Hz, J = 7.1 Hz), 5.92 (ICH=CHCH$_2$, d, 1H, J = 14.4 Hz), 5.91 (ICH=CHCH$_2$, d, 1H, J = 14.3 Hz), 3.58 (CH$_2$OH, t, 2H, J = 6.6 Hz), 1.99 (ICH=CHCH$_2$, q, 2H, J = 6.8 Hz), 1.82 (CH$_2$OH, s, 1H), 1.53-1.14 (CHCH$_2$(CH$_2$)$_6$CH$_2$OH, m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 146.8 (ICH=CHCH$_2$), 74.4 (ICH=CHCH$_2$), 63.0 (CH$_2$OH), 36.1 (ICH=CHCH$_2$), 32.8, 29.4 (2C), 28.9, 28.4, 25.8 (CHCH$_2$(CH$_2$)$_6$CH$_2$OH).

5.5.2.3 (E)-10-Iododec-9-enyl acetate (5-167)$^{46}$

![Chemical Structure](image)

Vinyl iodide 5-167 was isolated in 95% and 76% yield in inseparable ratios of 95:5 and 99:1 (trans:gem) respectively from the corresponding alkyne using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) δ 6.44 (ICH=CHCH$_2$, dt, 1H, J = 14.3 Hz, J = 7.2 Hz), 5.91 (ICH=CHCH$_2$, d, 1H, J = 14.3 Hz), 3.98 (CH$_2$OCOCH$_3$, t, 2H, J = 6.8 Hz), 1.99 (ICH=CHCH$_2$, q, 2H, J = 7.0 Hz), 1.98 (CH$_2$OCOCH$_3$, s, 3H), 1.58-1.24 (CHCH$_2$(CH$_2$)$_6$CH$_2$O, m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.0 (OOCOCH$_3$), 146.6 (ICH=CHCH$_2$), 74.3 (ICH=CHCH$_2$), 64.5 (CH$_2$OCOCH$_3$), 35.9 (ICH=CHCH$_2$), 29.1, 29.0, 28.7, 28.5, 28.2, 25.8, 20.9 (CHCH$_2$(CH$_2$)$_6$CH$_2$OCOCH$_3$).
5.5.2.4 *(E)-1-Iodooc-1-en-3-ol (5-99)*

Vinyl iodide 5-99 was isolated in 89% yield in a separable ratio of 95:5 *(trans:gem)* from the corresponding alkyne using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) δ 6.56 (ICH=CHCHOH, 1H, dd, J = 14.5 Hz, J = 6.3 Hz), 6.32 (ICH=CHCHOH, d, 1H, J = 14.6 Hz), 4.07 ((ICH=CHCHOH, 1H, p, J = 6.0Hz ), 1.56-1.28 (CHOH(CH$_2$)$_4$CH$_3$, 9H, m), 0.87 ((CH$_2$)$_4$CH$_3$, 3H, t, J = 6.2 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 148.6 (ICH=CHCHOH), 77.1 (ICH=CHCHOH), 74.7 (ICH=CHCHOH), 36.5, 31.6, 24.7, 22.5, 13.9 (CHOH(CH$_2$)$_4$CH$_3$).

5.5.2.5 *(E)-3-Iodoprop-2-en-1-ol (5-93)*

Vinyl iodide 5-93 was isolated in 67% yield in a separable ratio of 67:33 *(trans:gem)* from the corresponding alkyne using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) δ 6.67 (ICH=CHCH$_2$, dt, 1H, J = 14.6 Hz, J = 5.4 Hz), 6.37 (ICH=CHCH$_2$, d, 1H, J = 13.9 Hz), 4.07 (CH$_2$OH, s (br), 2H), 1.55 (CH$_2$OH, s, 1H), 1.53-1.14 (CHCH$_2$(CH$_3$)$_6$CH$_2$OH, m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 144.6 (ICH=CHCH$_2$), 77.8 (ICH=CHCH$_2$), 65.1 (CH$_2$OH).
5.5.2.6 (E)-6-Iodohex-5-en-1-ol (5-169)47

Vinyl iodide 5-169 was isolated in 94% and 76% yield in inseparable ratios of 95:5 and 99:1 (trans:gem) respectively from the corresponding alkyne using the general procedure. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.47 (ICH=CHCH$_2$, dt, 1H, J = 14.3 Hz, J = 7.1 Hz), 5.97 (ICH=CHCH$_2$, d, 1H, J = 14.3 Hz), 3.59 (CH$_3$OH, t, 2H, J = 5.6 Hz), 2.05 (ICH=CHCH$_2$, q, 2H, J = 6.9 Hz), 1.70 (CH$_2$OH, s, 1H), 1.57-1.39 (CHCH$_2$(CH$_2$)$_2$CH$_2$OH, m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 146.2 (ICH=CHCH$_2$), 74.8 (ICH=CHCH$_2$), 62.4 (CH$_2$OH), 35.7 (ICH=CHCH$_2$), 31.8, 24.8 (CHCH$_2$(CH$_2$)$_2$CH$_2$OH).

5.5.2.7 (E)-4-Iodobut-3-en-2-ol (5-172)48

Vinyl iodide 5-172 was isolated in 93% yield in a separable ratio of 95:5 (trans:gem) from the corresponding alkyne using the general procedure. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.58 (ICH=CHCH, dd, 1H, J = 14.5 Hz, J = 6.0 Hz), 6.32 (ICH=CHCH, dd, 1H, J = 14.4 Hz, J = 1.1 Hz), 4.25 (CHOH, m, 1H), 1.84 (CHOH, d, 1H, J = 4.2 Hz), 1.24 (CH$_3$CHOH, d, 3H, J = 6.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 149.5 (ICH=CHCH), 76.7 (ICH=CHCH), 70.6 (CHOH), 22.6 (CH$_3$CHOH).
5.5.2.8 (E)-3-Iodo-1-phenylprop-2-en-1-ol (5-175)

Vinyl iodide 5-175 was isolated in 80% yield in a separable ratio of 82:18 (trans:gem) from the corresponding alkyne using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.39-7.30 (PhH, m, 5H), 6.70 (ICH=CHCH, dd, 1H, J = 14.4 Hz, J = 5.9 Hz), 6.45 (ICH=CHCH, dd, 1H, J = 14.5 Hz, J = 1.1 Hz), 5.13 (CHOH, m, 1H), 2.21 (CHOH, d, 1H, J = 3.4 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.1 (ICH=CHCH), 141.9, 128.7 (2C), 128.2, 126.3 (2C) (Ph), 78.1 (ICH=CHCH), 76.6 (CHOH).

5.5.2.9 (E)-4-Iodobut-3-en-1-ol (5-41)

Vinyl iodide 5-41 was isolated in 84% yield in a separable ratio of 83:17 (trans:gem) from the corresponding alkyne using the general procedure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.51 (ICH=CHCH$_2$, dt, 1H, J = 14.4 Hz, J = 7.3 Hz), 6.13 (ICH=CHCH$_2$, d, 1H, J = 14.4 Hz), 3.65 (CH$_2$OH, q, 2H, J = 6.0 Hz), 2.05 (ICH=CHCH$_2$, q, 2H, J = 6.2 Hz), 1.62 (CH$_2$OH, t, 1H, J = 5.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.6 (ICH=CHCH$_2$), 77.2 (ICH=CHCH$_2$), 60.9 (CH$_2$OH), 39.1 (ICH=CHCH$_2$).
5.5.3 Synthesis of pheromones 5-179 and 5-183

5.5.3.1 (E)-Hexadec-9-en-11-ynyl acetate (5-178)

To a degassed mixture of aqueous NaOH (100 mL, 10% solution in H₂O) and benzene (55 mL), were added successively iodides (5-167 : 5-168, 95:5 ratio) (16.54 g, 51.0 mmol), BnNEt₃Cl (0.23 g, 1.0 mmol), Pd(PPh₃)₄ (1.1 g, 1.0 mmol) and CuI (0.38 g, 2.0 mmol). Hexyne (11.7 mL, 0.100 mol) was then added and the reaction mixture was stirred vigorously (to ensure the two phase system was emulsified) for 24 h. The reaction mixture was diluted with hexane the layers were separated, and the aqueous layer was extracted with hexane (2 X 150 ml). The organic layers were combined and washed with saturated NH₄Cl (3 X 100 mL), brine (2 X 100 mL), dried over Na₂SO₄ and concentrated. The resulting oil was purified by silica gel (600 g) chromatography (25/1 : hexane/ether) to afford enyne 5-178 compound in 82% (11.7 g) isolated yield.

¹H NMR (300 MHz, CDCl₃) δ 5.96 (CCCH=CHCH₂, dt, 1H, J = 15.8 Hz, J = 7.0 Hz), 5.37 (CCCH=CHCH₂, d, 1H, J = 15.0 Hz), 3.98 (CH₂OCOCH₃, t, 2H, J = 6.7 Hz), 2.20 (CH₂CC, dt, 2H, J = 7.2 Hz, J = 1.9 Hz), 2.01-1.98 (CH₂OCOCH₃, s, 3H) (CCCH=CHCH₂, q, 2H, J = 7.3 Hz), 1.55-1.23 (CHCH₂(CH₂)₆CH₂O, m, 12H) (CH₃(CH₂)₂CH₂CC, m, 4H), 0.85 (CH₃(CH₂)₃CC, t, 3H, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 171.0 (OOCOCH₃), 143.0, 109.8 (CCCH=CHCH₂), 88.5, 79.0 (CCCH=CH), 64.5 (CH₂OCOCH₃), 32.8, 30.8,
29.2, 29.1, 28.9, 28.7, 28.5, 25.8, 21.9, 20.9, 18.9, 13.5 (CH(\text{CH}_2)_7\text{CH}_2\text{OCOCH}_3) (\text{CH}_3(\text{CH}_2)_3\text{CC}).

5.5.3.2 (9E,11Z)-Hexadeca-9,11-dienyl acetate (5-179)\textsuperscript{38}

![Chemical Structure](image)

To a solution of 2-methyl-2-butene (20.8 mL, 195 mmol) in THF (65 ml) at 0 °C was added borane dimethyl sulfide (9.70 mL, 97.0 mmol). After 1 h of stirring at 0 °C, the disiamylborane was syringed, dropwise, to a solution of enyne 5-178 (17.5 g, 65.0 mmol) in THF (65 mL) at 0 °C over a period of 30 min. The reaction mixture was allowed to stir at 0 °C for 4 h followed by the addition of AcOH (22 mL, 0.39 mol) slowly. The reaction was stirred at 55 °C for 6 h, let cool to rt and stirring was continued for 18 h. This was followed by the addition of NaOH (82 mL, 25 % in H\textsubscript{2}O w/v) and H\textsubscript{2}O\textsubscript{2} (22 mL, 30 % in H\textsubscript{2}O) and stirring for 30 min at 40 °C. After cooling the reaction, it was diluted with ether (200 mL), washed with brine (2 X 100 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The resulting oil was purified by silica gel (600 g) chromatography (30/1 : hexane/ ether) to afford the corresponding diene 5-179 in 70 % (12.20 g) isolated yield as a colourless oil.
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.13 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH, dd, 1H, \(J = 14.7\) Hz, \(J = 11.3\) Hz), 5.76 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH, dd, 1H, \(J = 10.8\) Hz), 5.46 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH, dt, 1H, \(J = 15.0\) Hz, \(J = 7.0\) Hz), 5.11 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH, dt, 1H, \(J = 10.5\) Hz, \(J = 7.7\) Hz), 3.88 (CH\(_2\)OH, t, 2H, \(J = 6.7\) Hz), 2.01-1.90 (CH\(_3\)CH=CH-CH=CHCH\(_2\), m, 4H), 1.84 (OCOCH\(_3\), s, 3H), 1.62-1.16 ((CH\(_2\))\(_2\)CH\(_2\)CH=CH=CHCH\(_2\)(CH\(_2\)), m, 16H), 0.75 (CH\(_3\)CH\(_2\), t, 3H, \(J = 6.7\)Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.3 (OCOCH\(_3\)), 133.9 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH, 129.4 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH), 128.6 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH), 125.6 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH-CH=CH), 64.1 (CH\(_2\)OH, 32.7, 31.7, 29.2 (2C), 29.0, 28.9, 28.5, 27.2, 25.7, 22.1, 20.5, 13.7 (CH\(_3\)(CH\(_2\))\(_3\)CH=CH=CH-CH=CH=CHCH\(_2\)(CH\(_2\))\(_7\)CH\(_2\)OCOCH\(_3\)).

5.5.3.3 \((E)\)-Hexadec-9-en-11-yn-1-ol (5-181)\(^{50}\)

To a mixture of iodides (5-165 : 5-166, 95:5 ratio) (130 mg, 0.46 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (32.0 mg, 0.046 mmol) and CuI (18.0 mg, 0.093 mmol) in 10 ml of Et\(_3\)N, was added a dilute solution of hexyne (76.0 mg, 0.93 mmol in 2 ml Et\(_3\)N) at rt. The reaction was allowed to stir for 16 h at rt. The reaction mixture was diluted with water (25 mL) and extracted the aqueous layer with ether (2 X 25 mL). Combined the organic layers and washed with saturated NH\(_4\)Cl (2 X 30 mL), brine (2 X 30 mL), dried over NaSO\(_4\) and
concentrated. The resulting oil was purified by silica gel (7 g) chromatography (3/1 : hexane/ether) to afford enyne 5-181 in 85 % (92 mg) isolated yield as a colourless oil.

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \delta 6.02 (\text{CCCH=CHCH}_2, \text{dt, 1H, } J = 15.8 \text{ Hz}, J = 7.2 \text{ Hz}), 5.42 (\text{CCCH=CHCH}_2, \text{d, 1H, } J = 16.0 \text{ Hz}), 3.61 (\text{CH}_2\text{OH, t, 2H, } J = 6.3 \text{ Hz}), 2.27 (\text{CH}_2\text{CCCH=CH, dt, 2H, } J = 7.2 \text{ Hz}, J = 1.9 \text{ Hz}), 2.03 (\text{CCCH=CHCH}_2, \text{q, 2H, } J = 7.3 \text{ Hz}), 1.53-1.16 (\text{CHCH}_2(\text{CH}_2)_6\text{CH}_2\text{O, m, 12H}) (\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{CC, m, 4H}), 0.89 (\text{CH}_3(\text{CH}_2)_3\text{CC, t, 3H, } J = 7.2 \text{ Hz}); ^{13}C \text{NMR (75 MHz, CDCl}_3 \delta 143.0, 109.7 (\text{CCCH=CHCH}_2), 88.5, 79.0 (\text{CCCH=CH}), 63.7 (\text{CH}_2\text{OH}), 32.8, 32.6, 30.8, 29.3, 29.2, 28.9, 28.7, 25.6, 21.8, 18.9, 13.5 (\text{CH(CH}_2)_7\text{CH}_2\text{OH}) (\text{CH}_3(\text{CH}_2)_3\text{CC}).

5.5.3.4 (9E,11Z)-Hexadeca-9,11-dien-1-ol (5-182)\!

To a solution of 2-methyl-2-butene (0.15 mL, 1.44 mmol) in THF (5 mL) at 0 °C was added borane dimethyl sulfide (0.07 mL, 0.72 mmol). After 1 h of stirring at 0 °C a solution of enyne 5-181 (85 mg, 0.36 mmol) in THF (1 mL) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 4 h followed by the addition of AcOH (0.16 ml, 2.9 mmol) slowly. The reaction was stirred at 55 °C for 6 h, let cool to rt and stirring was continued for 18 h. This was followed by the addition of NaOH (0.29 mL, 50 % in H_2O w/v) and H_2O_2 (0.16 mL, 30 % in H_2O) and stirring for 30 min at 40 °C. After cooling the reaction, it was diluted with ether (30 mL), washed with brine (2 X 30
mL), dried over NaSO₄ and concentrated. The resulting oil was purified by silica gel (180 g) chromatography (3/1 : hexane/ ether) to afford diene 5-182 in 94 % (81 mg) isolated yield as a colourless oil.

¹H NMR (300 MHz, CDCl₃) δ 6.27 (CH₃(CH₂)₃CH=CH-CH=CH, dd, 1H, J = 14.6 Hz, J = 11.4 Hz), 5.90 (CH₃(CH₂)₃CH=CH-CH=CH, dd, 1H, J = 10.8 Hz), 5.60 (CH₃(CH₂)₃CH=CH-CH=CH, dt, 1H, J = 15.0 Hz, J = 6.9 Hz), 5.25 (CH₃(CH₂)₃CH=CH-CH=CH, dt, 1H, J = 10.4 Hz, J = 7.7 Hz), 3.58 (CH₂CH₃OH, t, 2H, J = 6.6 Hz), 2.14-2.01 (CH₂CH=CH-CH=CHCH₃, m, 4H), 1.92 (CH₂OH, s, 1H), 1.52-1.22 ((CH₂)₂CH₂CH=CH-CH=CHCH₂(CH₂)₆, m, 16H), 0.87 (CH₃CH₂, t, 3H, J = 6.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 134.5 (CH₃(CH₂)₃CH=CH-CH=CH), 130.0 (CH₃(CH₂)₃CH=CH-CH=CH), 128.5 (CH₃(CH₂)₃CH=CH-CH=CH), 125.6 (CH₃(CH₂)₃CH=CH-CH=CH), 62.8 (CH₂OH), 32.8, 32.7, 31.8, 29.4, 29.3 (2C), 29.1, 27.3, 25.7, 22.2, 13.7 (CH₃(CH₂)₃CH=CH-CH=CH(CH₂)₇CH₂OH).

5.5.3.5 (9E,11Z)-Hexadeca-9,11-dienal (5-183)⁴¹

A mixture of PDC (192 mg, 0.51 mmol) and 3 Å sieves (100 mg) in CH₂Cl₂ (10 mL) were stirred at rt. A solution of alcohol 5-182 (81 mg, 0.34 mmol) in CH₂Cl₂ (1 mL) was added dropwise and let stir for 18 h at rt. The reaction mixture was diluted with ether,
passed through a Celite plug and concentrated. The resulting oil was purified by silica gel chromatography (10 g, 15/1 : hexane/ether) to afford aldehyde **5-183** in 91% (73 mg) isolated yield as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.74 (CHO, s, 1H), 6.28 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH, dd, 1H, $J = 14.3$ Hz, $J = 11.7$ Hz), 5.91 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH, dd, 1H, $J = 10.8$ Hz), 5.62 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH, dt, 1H, $J = 15.0$ Hz, $J = 6.9$ Hz), 5.27 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH, dt, 1H, $J = 10.2$ Hz, $J = 7.7$ Hz), 2.39 (CH$_3$(CH$_2$)$_2$CH=CH-CH=CHCH$_2$, t, 2H, $J = 7.3$ Hz), 2.14-1.16 ((CH$_2$)$_3$CH=CH-CH=CHCH$_2$(CH$_2$)$_6$, m, 18H), 0.88 (CH$_3$CH$_2$, t, 3H, $J = 6.5$Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.4 (CHO), 134.2 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH), 129.9 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH), 128.5 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH), 125.6 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH), 43. (CH$_2$CHO), 32.7, 31.7, 29.2 (2C), 32.7, 31.8, 29.2, 29.1, 29.0, 28.9, 27.3, 22.2, 21.9, 13.8 (CH$_3$(CH$_2$)$_3$CH=CH-CH=CH(CH$_2$)$_6$CH$_2$CHO).

Spectral data were in accord with literature data.
Chapter 6

Synthesis of Functionalized Cyclohexenes from \((E)\)-1-Tributylstannyl-Butadiene

6.1 Introduction

6.1.1 General

Functionalized cyclohexenes \((6-1)\) are important intermediates in natural product synthesis (Figure 6.1).\(^1-12\)

![Functionalized cyclohexene](image)

**Figure 6.1** Functionalized cyclohexene

Due to their significance in organic chemistry, there has been numerous methodologies developed to provide functionalized cyclohexenes.\(^13-22\) It is well established that Diels-Alder reactions are the most useful and common methods for the synthesis of six-membered functionalized carbocyclic compounds (Scheme 6.1).\(^23\)
Scheme 6.1

Diels-Alder reaction between cyclopentadiene $6\text{-}5$ and chloroacetonitrile $6\text{-}6$ generated bicyclic product $6\text{-}7$ as a mixture of stereoisomers, which was an important step leading to the synthesis of Corey’s lactone $6\text{-}8$ (Scheme 6.2).$^{24}$

Scheme 6.2

Corey’s lactone $6\text{-}8$ was an important intermediate that lead to the syntheses of several prostaglandins.$^{24-26}$
Stork et al. incorporated an intramolecular Diels-Alder reaction to establish the core rings of (+)-degitoxigenin 6-11, a steroid derivative (Scheme 6.3).\textsuperscript{27}

![Scheme 6.3](image)

Intramolecular Diels-Alder reaction provided two six-membered carbocyclic rings with three additional stereocenters all in one step.\textsuperscript{27}

These examples demonstrate how Diels-Alder reactions can contribute an important role in forming functionalized cyclohexenes.
6.1.2 *Vaultier tandem reaction*

A methodology that is of interest, and utilizes Diels-Alder reaction, is the Vaultier tandem reaction. This methodology involves a 1-boronylbutadiene which undergoes a Diels-Alder reaction with a dienophile. The intermediate, an allylboronate, formed *in situ* in a stereodefined way can then react accordingly with an aldehyde in a highly diastereoselective fashion to produce a highly functionalized cyclohexene.\(^{28}\)

The stereochemistry of the Diels-Alder adducts were established on the basis of the \(^1\)H NMR data to be the *endo* adducts (Scheme 6.4).\(^{28}\)

\[ \text{Scheme 6.4} \]

Treatment of allylboronates with aldehydes reacted smoothly in a highly diastereoselective fashion to produce the corresponding cyclohexenes (Table 6.1).\(^{28}\)
Table 6.1 Synthesis of cyclohexenes via Vaultier tandem reaction.\textsuperscript{28}

<table>
<thead>
<tr>
<th>entry</th>
<th>Y</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NPh</td>
<td>Ph</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>NPh</td>
<td>iPr</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>NPh</td>
<td>Et</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>Ph</td>
<td>80\textsuperscript{a}</td>
</tr>
<tr>
<td>5</td>
<td>O</td>
<td>iPr</td>
<td>75\textsuperscript{a}</td>
</tr>
<tr>
<td>6</td>
<td>O</td>
<td>Et</td>
<td>70\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield of corresponding lactone.

The allylation process occurred \textit{syn} to the boronate, according to \textsuperscript{1}H NMR data of the products, suggesting a six-member ring transition state (Figure 6-2).\textsuperscript{28}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure6-2.png}
\caption{Transition structure of 6-22\textsuperscript{29}}
\end{figure}
Good yields of the newly formed bicyclic adducts were isolated, except for adducts with Y = O, which cyclized spontaneously upon hydrolysis to form the corresponding lactones in good yields.$^{28}$

The stereochemical assignment was confirmed by an X-ray analysis of the methyl ester of acid 6-21 (R = Ph) (Figure 6.3).$^{28}$

![Methyl ester of lactone 6-23](image)

**Figure 6.3** Methyl ester of lactone 6-23

Gao and Hall were able to improve the Vaultier tandem reaction by expanding the scope of aldehydes, shorten the reaction times and obtain higher yields by using electron-rich dienylboronate 6-24 (Table 6.2).$^{30}$
Table 6.2  Tandem [4+2]/allylboration of diene 6-24.³⁰

<table>
<thead>
<tr>
<th>entry</th>
<th>dienophile (R)</th>
<th>aldehyde (R’)</th>
<th>yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>C₆H₅</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>4-NO₂-C₆H₄</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>4-MeO-C₆H₄</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>4-Br-C₆H₄</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>i-PrCH₂</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>4-NO₂-C₆H₄</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>4-MeO-C₆H₄</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>4-Br-C₆H₄</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\) Typical reaction scale: 1.0 mmole diene, 1.1 mmole dienophile, 1.1 mmol aldehyde, 1.0 M in toluene.

Aliphatic and aromatic aldehydes (both electron-poor and electron-rich) provided the desired product in excellent selectivities and yields.³⁰ Cycloaddition proceeded with complete endo-selectivity to furnish an allylboration intermediate, which then reacts with an aldehyde, via a cyclic chair-like transition state, to provide an allylboration product.³⁰ N-acryloyl-oxazolidinone and methyl acrylate were able to react with electron-rich diene 6-24, but provided higher selectivities for the exo-adduct.³⁰
In 1996, Renard and Lallemand demonstrated an asymmetric tandem reaction by using chiral dienylboronate 6-28 derived from a tartrate ester (Scheme 6.5).\(^{31}\)

![Scheme 6.5](image)

The cycloaddition reaction occurred readily between dienylboronate 6-28 and methyl acrylate 6-29 to produce the allylboronate intermediate. The allylboronate was obtained as a 9:1 mixture of \textit{endo} and \textit{exo} adducts, respectively.\(^{31}\) This mixture of allylboronates was treated with aldehyde 6-30 and silylated to provide cyclohexene 6-31 in 49% overall yield. \(^1\)H NMR analysis using a chiral europium shift reagent showed the major \textit{endo} adduct to be composed of a 85:15 mixture of enantiomers.\(^{31}\)

This methodology was later used part of a total synthesis of Clerodin, which exhibits antifeedant activity that can be of use in the protection of crops against insects.\(^{32}\)

In 2000, Tailor and Hall introduced the tandem aza[4+2]/allylboration using hydrazonediene 6-32 (Table 6.3).\(^{29}\)
Table 6.3  Tandem aza[4+2]/allylation with diene 6-32.  

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde (R)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>i-PrCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>50</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1:2:1 mixture of diene/dienophile/aldehyde in dry toluene (0.2 M) was heated at 80 °C for 72 h

Cycloaddition followed by allylation proceeded as anticipated with diene 6-32 to provide α-hydroxyalkyl piperidine derivatives 6-35 in moderate yields.

A diastereoselective version of this reaction was also demonstrated to exhibit high degrees of stereocontrol (Scheme 6.6).
Scheme 6.6

L-Proline-derived diene 6-36 reacted with N-phenylmaleimide and benzaldehyde to provide bicyclic 6-38 in >95% de, demonstrating high diastereoselectivity.29

Optically pure functionalized piperidines were also prepared by applying Waldner’s chiral dienophile 6-39 (Table 6.4).33

Table 6.4  Aza[4+2]/Allylboration with chiral dienophile 6-39.33
<table>
<thead>
<tr>
<th>entry (adduct)</th>
<th>aldehyde (R)</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>$n$-Bu</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>44</td>
</tr>
</tbody>
</table>

$^a$ 1:1:2 mix of diene/dienophile/aldehyde, except for propionaldehyde where 5 equiv were used

Moderate yields of bicyclic piperidines were isolated. Out of the many possible regio- and stereoisomers, only one isomer was obtained. The regiochemistry of the aza-Diels-Alder reaction was controlled by the electron-rich hydrazine and the carbonyl of the dienophile, which overrode the effect of the sulfoxide group. Endo-adducts were only observed which selected the face away from the oxygen of the sulfoxide, thus providing perfect facial selectivity. This methodology was used as part of the total syntheses of natural products (-)-methyl palustramate 6-41 and (-)-methyl dihydropalustramate 6-42 (Figure 6.4).  

![Figure 6.4](image_url)

**Figure 6.4**  (-)-Methyl palustramate 6-41 and (-)-methyl dihydropalustramate 6-42
Polysubstituted pyrans can also be accessed by using the Vaultier tandem reaction. Gao and Hall have applied Jacobsen’s conditions\textsuperscript{35} to develop the first catalytic enantio- and diastereoselective inverse electron demand hetero[4+2]/allylboration reaction to provide a practical route to $\alpha$-hydroxyalkyl pyran derivatives 6-47 (Table 6.5).\textsuperscript{36}

**Table 6.5** Enantioselective hetero[4+2]/allylboration reaction.\textsuperscript{36}

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde (R)</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>4-NO\textsubscript{2} \textsubscript{-} \textsubscript{C}\textsubscript{6}H\textsubscript{4}</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO- \textsubscript{C}\textsubscript{6}H\textsubscript{4}</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>(CH\textsubscript{3})\textsubscript{2}CHCH\textsubscript{2}</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>TBSOCH\textsubscript{2}</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>C\textsubscript{10}H\textsubscript{21}</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>(E)-CH\textsubscript{3}CH=CH(CH\textsubscript{3})</td>
<td>61</td>
</tr>
</tbody>
</table>

\textsuperscript{a}2 mmol of distilled diene, 1 M in vinyl ethyl ether with 1 mol % of 6-45, rt for 14 h, followed by addition of 2.0 equiv of aldehyde and stirred for 24 h.
Aromatic aldehydes, with different electronic characteristics, and aliphatic aldehydes afforded dihydropyran adducts in high yields and enantioselectivity (96% ee). The enantioselectivity obtained in the Diels-Alder reaction was retained after the allylboration reaction.

This methodology was used to synthesize the sex pheromone 6-48 of the female Culex mosquito,\textsuperscript{36} which is capable of transmitting the West Nile virus (Figure 6.5).\textsuperscript{37}

\begin{center}
\includegraphics[width=0.3\textwidth]{6-48.png}
\end{center}

\textbf{Figure 6.5}

Just recently, Li \textit{et al.} have demonstrated the Vaultier tandem reaction using the silyl analogue (Table 6.6).\textsuperscript{38}

\begin{center}
\textbf{Table 6.6} Vaultier tandem reaction using silyl dienes.\textsuperscript{38}
\end{center}

\begin{center}
\includegraphics[width=0.6\textwidth]{table6_6.png}
\end{center}
<table>
<thead>
<tr>
<th>entry</th>
<th>diene</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Bu-SiMe₃" /> <img src="image2" alt="Bu-SiMe₃" /> 6-52</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Bu-SiMe₃" /> <img src="image4" alt="Pr-SiMe₃" /> 6-53</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="SiMe₃" /> <img src="image6" alt="SiMe₃" /> 6-54</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="SiMe₃" /> <img src="image8" alt="SiMe₃" /> 6-55</td>
<td>75</td>
</tr>
</tbody>
</table>

7-Norbornenones were formed in good yields by treating maleic anhydride with tetrasubstituted 1-silyl-1,3-butadienes and two equivalents of freshly sublimed AlCl₃. 7-Norbornenones contained well-defined *exo,exo*-disubstituted patterns. Diels-Alder adducts were isolated when 1 equivalent of AlCl₃ was used as shown in Scheme 6.7.
Scheme 6.7

X-ray analysis of Diels-Alder adduct 6-56 confirmed that it was the endo adduct. A second equivalent of AlCl₃ was required to facilitate the intramolecular allylation reaction of the carbonyl group to afford 7-norbornenones 6-57 (Scheme 6.8).³⁸

Scheme 6.8

This methodology is a synthetically useful tandem process for the preparation of exo,exo-disubstituted 7-norbornenones.³⁸
6.1.3 Tin analogue of the Vaultier tandem reaction

To our knowledge, there has not been a Vaultier tandem reaction involving tin. Diels-Alder reaction between a 1-stannylbutadiene and a dienophile, thus providing a cyclic allylstannane intermediate, has not been reported. However, cyclic allylstannanes have been synthesized by different means. Palladium-catalyzed hydrostannation of conjugated cyclohexadiene 6-58 provided a route to racemic cyclic allylstannane 6-59 (Scheme 6.9).  

![Scheme 6.9](image)

Alternatively, deprotonation of chiral carbamate 6-59 by BuLi with a chiral diamine, followed by stannylation translates the chirality of the starting material to the newly formed allylic stannane 6-63 in high selectivity (Scheme 6.10).
Allylation using cyclic allylstannanes have been reported. Allylstannation of aldehydes by 6-63 using TiCl₄ proceeded with high erythro selectivity (dr > 98:2) (Table 6.7).  

![Scheme 6.10](image)

**Scheme 6.10**

**Table 6.7** Allylstannation of aldehydes with TiCl₄.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>aldehyde (R)</th>
<th>yield (&lt;sup&gt;%&lt;/sup&gt;)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>2-naphthyl</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>p-BrPh</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>p-MeOPh</td>
<td>81</td>
</tr>
</tbody>
</table>

294
Homoaldol products were obtained from the corresponding cyclic allylstannane in moderate to good yields. The product outcome can be explained by a Sn-Ti exchange in an anti-S$_R$' fashion, followed by a syn addition of the aldehyde via a Zimmerman-Traxler transition state 6-66 (Scheme 6.11).

Yasuda et al. demonstrated cyclic allylstannations with much challenging ketones are feasible with the use of SnCl$_2$ in acetonitrile (Table 6.8).
<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>ketone (X)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>92(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Allylic stannane 1.0 mmol, ketone 1.0 mmol, SnCl\(_2\) 1.0 mmol at rt for 3 h.

\(^b\) \(\text{dr} = 88:12\); for other entries, \(\text{dr} > 99:1\).

The reactions summarized in the Table 6.8 are highly diastereoselective except for trial 5. *Erythro* product was mostly observed, suggesting closed six-member transition states (Scheme 6.12).
\[^{119}\text{Sn} \text{ NMR analysis strongly suggested the transmetallation between cyclic allylstannane 6-67 and SnCl}_2\] to generate a new allylic tin (II) species 6-70 which undergoes syn addition to the ketone (Scheme 6.12).\textsuperscript{44}

Selectivity was reversed upon allylstannation of \(\alpha\)-keto esters with InCl\textsubscript{3}, as complete \(\textit{threo}\)-diastereoselectivity was observed (Scheme 6.13).\textsuperscript{45}
Scheme 6.13

A more reactive allylic indium species formed via an S_E' process followed by a syn addition of the ketone via cyclic transition state (Scheme 6.14).

Scheme 6.14

The threo-selectivity obtained can be explained by the formation of an additional stable five-coordinate chelate exhibited in 6-76 during the transition state (Scheme 6.15).
Scheme 6.15

The extra coordinations by the oxygens to the electrophilic indium centre allow for better stability of the transition state which in return translates to better regio- and stereocontrol.\textsuperscript{45}
6.2 Proposed Work

The purpose of this project is to examine Diels-Alder reactions of stannylobutadiene 6-78 and applications of the resulting allylstannanes, such as the Vautier tandem reaction. Diastereoselective or enantioselective Diels-Alder reactions will be pursued in order to prepare isomerically pure allylic stannylcyclohexenes (Scheme 6.16).

![Scheme 6.16](image)

In the case of diastereoselective Diels-Alder reactions, a chiral auxiliary would be attached to the dienophile, while in the case of enantioselective Diels-Alder reactions, a chiral catalyst would be used to promote the reaction and induce chirality at the same time.
The allylstannation portion of the Vaultier tandem reaction must have high degrees of stereo- and regiocontrol (Scheme 6.17).

![Scheme 6.17]

In order to achieve a tandem reaction, conditions used for the Diels-Alder reaction must be compatible for the allylstannation reaction as well.
6.3 Results and Discussion

6.3.1 Diastereoselective Diels-Alder reaction between stannydiene 6-78 and chiral dienophile 6-84

There were no reports of applying 1-stannybutadiene 6-78 in Diels-Alder reaction. To pursue diastereoselective Diels-Alder reaction, diene 6-78 was tested to see whether it can undergo cycloaddition reaction with chiral crotonate dienophile 6-84\textsuperscript{46} (Table 6.9). Evans et al. have demonstrated high diastereoselectivity in Diels-Alder reactions by using chiral 2-oxazolidone 6-84 as dienophile\textsuperscript{46}.

<table>
<thead>
<tr>
<th>Table 6.9</th>
<th>Screening conditions to promote cycloaddition between 6-78 and 6-84</th>
</tr>
</thead>
<tbody>
<tr>
<td>entry</td>
<td>additives</td>
</tr>
<tr>
<td>1</td>
<td>toluene/ reflux</td>
</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}/ rt</td>
</tr>
<tr>
<td>3</td>
<td>Et\textsubscript{2}AlCl (1.4 equiv.),</td>
</tr>
<tr>
<td></td>
<td>CH\textsubscript{2}Cl\textsubscript{2}, -78 °C to -15 °C</td>
</tr>
<tr>
<td>4</td>
<td>Me\textsubscript{2}AlCl (1.4 equiv.),</td>
</tr>
<tr>
<td></td>
<td>CH\textsubscript{2}Cl\textsubscript{2}, -78 °C to -15 °C</td>
</tr>
</tbody>
</table>

302
<table>
<thead>
<tr>
<th>Trial</th>
<th>Reagents</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Et$_2$AlCl (0.15 equiv.), CH$_2$Cl$_2$, -78 °C to -15 °C</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>BF$_3$·Et$_2$O (0.15 equiv.), CH$_2$Cl$_2$, -78 °C to 0 °C</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Mg(OTf)$_2$ (0.1 equiv.), CH$_2$Cl$_2$, rt</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Sn(OTf)$_2$ (0.1 equiv.), CH$_2$Cl$_2$, rt</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Mg(OTf)$_2$ (0.1 equiv.), toluene, reflux</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Sn(OTf)$_2$ (0.1 equiv.), toluene, reflux</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Ti(O$i$Pr)$_4$ (1.0 equiv.), CH$_2$Cl$_2$, rt</td>
<td>0</td>
</tr>
</tbody>
</table>

Unfortunately, stannyliene 6-78 failed to react with dienophile 6-84 under thermal and Lewis acid promoted conditions. Starting materials were recovered in trials 1 and 2. There was considerable decomposition of stannyliene 6-78, observed by TLC, upon treatment with Lewis acids such as Et$_2$AlCl, BF$_3$·Et$_2$O, Mg(OTf)$_2$ and Sn(OTf)$_2$. Titanium Lewis acid Ti(O$i$Pr)$_4$ used in trial 11 was compatible with stannyliene 6-78 but did not promote any reaction at all.
These set of results suggested that dienophile 6-84 is not a good candidate for stannyldiene 6-78, and stannyldiene 6-78 is quite susceptible to moderate Lewis acids.

6.3.2  Screening for suitable dienophiles to react with stannyldiene 6-78

Turning to other dienophiles, stannyldiene 6-78 was screened to better understand the requirements of dienophiles for successful Diels-Alder reactions (Table 6.10).

Table 6.10  Screening diene 6-78 with various dienophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>dienophile</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(6-99)</td>
<td>6-88</td>
<td>NR</td>
</tr>
<tr>
<td>2(6-100)</td>
<td>6-83</td>
<td>NR</td>
</tr>
</tbody>
</table>
3(6-101) \[ \text{trace} \]

4(6-102) \[ \text{NR} \]

5(6-103) \[ \text{NR} \]

6(6-104) \[ \text{NR} \]

7(6-105) \[ \text{NR} \]

8(6-106) \[ \text{NR} \]

9(6-107) \[ \text{NR} \]

10(6-108) \[ \text{NR} \]
All of the acyclic dienophiles failed to react with stannydiene 6-78 under thermal conditions. Even doubly activated acyclic dienophiles (trials 4 and 5) did not promote any cycloaddition at all. Benzoquinone 6-90 was able to react with stannydiene 6-78 to provide a trace of product (detected by TLC) that was too small for isolation. Nonetheless, this small but significant result suggests that stannydiene 6-78 requires the dienophile to be cyclic in order to achieve any reactivity. Cyclic chiral dienophile 6-98\textsuperscript{47} by Koot et al. failed at achieving any reactivity with diene 6-78, suggesting single activation by the carbonyl is not enough to provide reactivity. This hypothesis was supported by results of trials 10 and 11. Five-member ring doubly activated maleic anhydride 6-50 was consumed completely after reacting with stannydiene 6-78 over the period of 16 h. According to \textsuperscript{1}H NMR data, there were two cycloadduct products formed in a 10:1 ratio (endo: exo), major being the endo-adduct 6-110. Unfortunately,

\[ a \quad 100\% \text{ conversion based on } \textsuperscript{1}H \text{ NMR of the crude reaction mixture}, \text{ endo:exo } \approx 10:1 \]
cycloadduct 6-110 was not stable enough to be chromatographed on silica gel, as very small percentage of what perceived to be a quantitative reaction, was recollected after purification through silica gel column. Five-member ring doubly activated maleimide 6-33 successfully reacted with stannyldiene 6-78, in 24 h, to provide the endo-adduct 6-112 as the sole product in 93% isolated yield. Reaction time was improved to 1 h as the reaction was heated to 50 °C without any solvent (neat). According to these results, five-member ring doubly activated dienophiles such as 6-50 and 6-33 contain the right electronic activation and structure requirement for the Diels-Alder reaction to occur with stannyldiene 6-78.

The stereochemistry of cycloadduct 6-112 was verified, by X-ray analysis of the Me₃Sn analogue 6-114, to be the endo adduct (Scheme 6.18).

\[
\begin{align*}
\text{SnBu}_3 & \xrightarrow{1. BuLi} \text{SnMe}_3 \\
6-78 & \xrightarrow{2. \text{Me}_3\text{SnCl}} \text{6-113} + \text{6-33} \\
& \xrightarrow{\text{CH}_2\text{Cl}_2/\text{rt} \ 48 \text{ h}} \text{Me}_3\text{Sn} \hspace{1cm} (\pm) \text{6-114} \\
& \text{93% yield}
\end{align*}
\]

(±) 6-114

Scheme 6.18
Stannyldiene 6-113 was prepared by treating stannyldiene 6-78 with nBuLi followed by a quench with Me₃SnCl. The crude reaction mixture was then allowed to react with maleimide 6-33 at room temperature in CH₂Cl₂ to provide cycloadduct 6-114 in 93% yield as a single isomer (endo). Crystallization of cycloadduct 6-114 was achieved by very slow evaporation of CH₂Cl₂.

6.3.3 Enantioselective Diels-Alder reaction between stannyldiene 6-78 and maleimide 6-33

The Diels-Alder reaction of stannyldiene 6-78 and maleimide 6-33 did not occur below 0 °C (not detected by TLC after 3 h), thus opening the door to enantioselective Lewis acid catalysis. From previous trials (Table 6.9), stannyldiene 6-78 was not compatible with strong or moderate Lewis acids. Considering previous results, chiral Lewis acids were applied to maleimide 6-33 and stannyldiene 6-78 to promote enantioselective Diels-Alder reactions (Table 6.11).

Table 6.11 Enantioselective Diels-Alder reaction with 6-78

![Diels-Alder reaction diagram]
<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conditions</th>
<th>ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Catalyst 1" /></td>
<td>cat. (7 mol%)</td>
<td>-78 °C to rt</td>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Catalyst 2" /></td>
<td>wet 4Å sieves</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Catalyst 3" /></td>
<td>wet 4Å sieves</td>
<td>racemic</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Catalyst 4" /></td>
<td>0 °C to rt</td>
<td>racemic</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Catalyst 5" /></td>
<td>0 °C</td>
<td>racemic</td>
<td>45</td>
</tr>
</tbody>
</table>
Protonated-oxazaborolidine 6-115 has been shown by Corey et al. to provide high enantioselectivity of the favoured exo adduct.\textsuperscript{48} α,β-Unsaturated aldehydes were able to coordinate with oxazaborolidine 6-115 and achieve high facial selectivity.\textsuperscript{48} In the case of Diels-Alder reaction between stannyldiene 6-78 and maleimide 6-33, oxazaborolidine 6-115 promoted the formation of the exo-adduct in 2:1 ratio (exo : endo), while producing no enantioselectivity at all (Figure 6.6).
Both cycloadducts were isolable on silica gel column, and the \textit{exo} adduct was tentatively characterized as the other cycloadduct by $^1$H NMR spectroscopy. Slight decomposition of the diene was observed, suggesting the protonated oxazaborolidine was not compatible with stannyldiene $6-78$. Diels-Alder products were only observed as the temperature was allowed to warm to room temperature, as no cycloadducts were formed below $0 ^\circ C$. Mikami et al. have demonstrated the use of binaphthol-derived chiral titanium $6-120$ (BINOL-Ti) catalytically to induce high enantioselectivity.\textsuperscript{49} This catalyst was used on juglone, which is a cyclic doubly activated dienophile, similar to maleimide $6-33$. Mikami catalyst $6-120$ showed significant enantioselectivity of $30\%$ along with good isolated yield of $70\%$. No reaction was observed as the temperature was maintained at $0 ^\circ C$. Chiral titanium $6-116$, a derivative of Mikami catalyst $6-120$, obtained much lower enantioselectivity excess of $6\%$, while other derivatives, $6-117$ and $6-119$, completely failed at providing any enantioselectivity. Corey et al. also demonstrated by the use of aluminum-based catalyst $6-121$ in Diels-Alder reactions, as high enantioselectivities and yields were obtained.\textsuperscript{50} Unfortunately, no reaction was observed but stannyldiene decomposition was observed on the TLC. A similar catalyst by Itsuno \textit{et al.} ($6-123$) was
applied to \( N \)-substituted maleimide and provided high enantioselectivity and yields.\(^{51} \)

Unfortunately, only racemic product and low yield was obtained when applied to stannyldiene \( 6-78 \) and maleimide \( 6-33 \). A derivative of Corey’s and Itsuno catalyst \( 6-122 \) also obtained racemic product and low yield. Free BINOL \( 6-118 \) did not provide any selectivity and hardly any reactivity at all. Titanium-binolate catalysts were much more compatible with stannyldiene \( 6-78 \), as no decomposition was observed on TLC. On the other hand, aluminum-based or protonated-CBS catalysts were not compatible with stannyldiene \( 6-78 \), as decomposition of the diene was observed on the TLC.

### 6.3.4 Diastereoselective Diels-Alder reaction between stannyldiene 6-78 and maleimide derivatives

Based on earlier reports,\(^{52,53} \) maleimide \( 6-126 \) has the potential to covalently bond to a \( C_2 \)-symmetric boronate to produce chiral maleimide \( 6-125 \) in situ, thus effecting a diastereoselective Diels-Alder reaction (Figure 6.7).

![C2-symmetric dienophile 6-125](image)

**Figure 6.7** C\(_2\)-symmetric dienophile 6-125
Chiral boronate was prepared \textit{in situ} by the addition of the corresponding BINOL, BH$_3$·THF and acetic acid (Table 6.12).\textsuperscript{52,53}

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
entry & chiral ligand & ee (%) & yield (%) \\
\hline
1 & none & racemic & 90 \\
2 & & - & NR \\
3 & & - & NR \\
\hline
\end{tabular}
\caption{Diastereoselective Diels-Alder using maleimide 6-126}
\end{table}

As expected, achiral dienophile 6-126 reacted readily with stannyldiene 6-78 under thermal conditions to provide cycloadduct 6-127 in 90\% yield. In the asymmetric version, chiral boronate was let to react with maleimide 6-126 followed by the addition of stannyldiene 6-78. Unfortunately, the asymmetric version did not achieve any reactivity.
at all. It was unclear if chiral dienophile 6-125 has formed *in situ*. The titanium analogue 6-116 was also tested but failed to react as well; it was also unclear whether or not the chiral titanium dienophile complex formed *in situ*.

The next approach tried was to install a C$_2$-symmetric moiety as part of the dienophile to effect diastereoselective Diels-Alder reactions. The chiral dienophile selected was maleimide 6-135 which has never been made. A linear six-step synthesis was devised for the preparation of dienophile 6-135 (Scheme 6.19).
Synthesis of chiral dienophile 6-135 was accomplished in six linear steps in 69% overall yield. Friedel-Craft acylation of benzene with fumaryl chloride provided compound 6-130 in 99% yield. Treatment of 6-130 with SnCl₂ hydrate in HCl furnished compound
Reduction by (R)-Me-CBS reagent and borane established the $S,S$ chirality in excellent selectivity yield;\textsuperscript{56} analysis by $^{13}$C NMR showed a $dl: meso$ ratio of $> 98:2$, while enantioselectivity was determined by HPLC to be 98% ee. Diol 6-132 was converted to dimesylate 6-133\textsuperscript{56,57} followed by double substitution by hydrazine to produce cyclic hydrazine 6-134,\textsuperscript{57} which was treated with catalytic (5 mol %) amount of TsOH and maleic anhydride to provide $C_2$-symmetric dienophile 6-135 in 74% for the three steps and 69% for the overall synthesis.\textsuperscript{58}

X-ray analysis of dienophile 6-135 illustrates the reach by the phenyl group over the carbonyl, which might result in facial selectivity by the approaching diene, thus effecting diastereoselectivity (Figure 6.8).

**Figure 6.8** Crystal structure of chiral dienophile 6-135
Dienophile 6-135 reacted very smoothly with stannyldiene 6-78 to furnish allylic stannane 6-136 in 91% isolated yield (Scheme 6.20). Unfortunately, cycloadduct 6-136 was isolated in a 1:1 mixture of diastereomers, suggesting there is no facial or regioselectivity, or both.

Next approach was to use Waldner’s chiral dienophile 6-39, which was obtained from optically active (R)-α-methylbenzylamine (Figure 6.9). \(^{33}\)

**Figure 6.9**  Waldner’s chiral dienophile 6-39
Maleimide derivative 5-39 was utilized by Toure and Hall as mentioned in section 6.1.3 to produce a single regio- and stereoisomer.\textsuperscript{33} Waldner’s dienophile is doubly activated and cyclic. Regiochemistry is controlled by the electron withdrawing carbonyl, which overrides the effect of the sulfoxide group. The chirality of the S-O bond is next to the double bond, which could apply a high degree of selectivity. The \textit{endo} transition structure should place the diene opposite to the face of the S-O bond.\textsuperscript{33}

Attempts at Diels-Alder reactions between stannyldiene 6-78 and dienophile 6-39 in CH\textsubscript{2}Cl\textsubscript{2} and toluene produced numerous cycloadducts that could not be identified (50% to 60% conversions were observed in either conditions) (Scheme 6.21).

\begin{center}
\includegraphics[width=\textwidth]{scheme6.21.png}
\end{center}

\textbf{Scheme 6.21}

Luckily, Diels-Alder reaction between stannyldiene 6-78 and dienophile 6-39, without any solvents (neat), proceeded in a cleaner fashion to provide allylic stannane 6-137 (the structure of compound 6-137 is based on speculation from results obtained by Toure and Hall\textsuperscript{33} and has not been confirmed) and an unknown isomer in a 10:1 ratio (Scheme 6.21). Stannyldiene 6-78 and dienophile 6-39 were consumed completely in 10 minutes
at 100 °C. These two isomers were separable by silica gel chromatography. Unfortunately, cycloadduct 6-137 was not very stable on the column.

6.3.5 Diastereoselective allylstannation of aldehydes and ketones by cyclicallylstitannanes

Since a diastereoselective Diels-Alder was established with stannyldiene 6-78, the second portion of the Vaultier tandem process, the allylstannation reaction, was examined. Racemic 6-112 was used as a test compound to establish optimal conditions for the allylstannation reaction (Table 6.13).

**Table 6.13** Allylstannation of aldehyde and ketone with cyclic allylstannane 6-112

<table>
<thead>
<tr>
<th>entry</th>
<th>(product)</th>
<th>R</th>
<th>conditions</th>
<th>ratio$^b$</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$\alpha : \gamma$</td>
<td></td>
</tr>
<tr>
<td>1(6-142:6-143)</td>
<td>Me</td>
<td>BF$_3$·OEt$_2$ (1 equiv.)</td>
<td>-</td>
<td>NR$^a$</td>
<td></td>
</tr>
<tr>
<td>2(6-144:6-145)</td>
<td>H</td>
<td>BF$_3$·OEt$_2$ (1 equiv.)</td>
<td>-</td>
<td>NR$^a$</td>
<td></td>
</tr>
</tbody>
</table>

319
3(6-144:6-145)  
\[
\begin{array}{c}
\text{H} \\
\text{6-120}
\end{array}
\]

20 mol %

4(6-144:6-145)  
\[
\begin{array}{c}
\text{H} \\
\text{toluene/ reflux}
\end{array}
\]

NR

5(6-144:6-145)  
\[
\begin{array}{c}
\text{H} \\
\text{SnCl}_2 \text{ (1 equiv.)}
\end{array}
\]

MeCN/ rt  
1 : 3.6  
80

6(6-142:6-143)  
\[
\begin{array}{c}
\text{Me} \\
\text{SnCl}_2 \text{ (1 equiv.)}
\end{array}
\]

MeCN/ rt  
1 : 3  
83

7(6-144:6-145)  
\[
\begin{array}{c}
\text{H} \\
\text{SnCl}_4 \text{ (1 equiv.)}
\end{array}
\]

CH\(_2\)Cl\(_2\)/-78 °C  
0 : 1  
85

\(^a\) Compound 6-146 was isolated (Scheme 6.22).
\(^b\) Ratio was determined by \(^1\)H NMR analysis of crude reaction mixture.

BF\(_3\)·OEt\(_2\) did not provide any allylstannation product, but rather compound 6-146 which was tentatively characterized by \(^1\)H NMR (Scheme 6.22).

Scheme 6.22
Destannylated compound 6-146 was also isolated when allylstannane 6-112 was stirred with BF₃·OEt₂ in the absence of a ketone or aldehyde, suggesting the source of the proton might be from the allylstannane itself or another adventitious proton source. Speculatively, the Lewis acid coordination with Lewis basic oxygen of the imide might increase the acidity of the α-protons, thus forcing allylstannane 6-112 to behave like a base instead of a nucleophile. This was also observed by Lautens et al. by using the same condition and a similar cyclic allylstannane (6-147) (Scheme 6.23).

![Scheme 6.23](image)

Refluxing cyclic allylstannane 6-112 and aldehyde 6-139 in toluene or using Mikami catalyst (6-120), which has been used for allylstannation before, did not promote any allylstannation to occur. However, allylation was observed when conditions by Yasuda et al. were applied (SnCl₂/MeCN, trial 5).¹¹ H NMR data analysis of the crude indicated the presence of two isomers in a 3.6:1 ratio. X-ray structure analysis of the two isomers could not be obtained due to difficulties in forming crystals of appropriate quality. It was unclear at that point whether the isomers formed arose from the facial selectivity of the aldehyde or the allylstannane (open or closed transition state). The two inseparable isomers 6-144 and 6-145, by silica gel chromatography, were oxidized to the ketone thus
eliminating the stereocenter at the benzylic carbon. $^1$H NMR data analysis of the crude indicated the presence of two isomers in the same starting ratio, suggesting the two allylstannation products formed are not different at the benzylic carbon, but rather at the $\gamma$-carbon of the original allylstannane. In fact, after learning how the allylstannation reaction proceeded, the two ketones were identified as 6-149 and 6-150 (Figure 6.10).

![Image](image.png)

Figure 6.10  Ketones 6-149 and 6-150

Allylstannation of ketone 6-138, under the same condition as trial 5, produced two isomers in a 3:1 ratio (entry 6). Remarkably, it was established by the X-ray structure analysis of the allylstannation products from trial 6, that the two products are in fact regioisomers ($\alpha$- and $\gamma$-addition products) and not what was believed to be stereoisomers (Figure 6.11); thus solving the structures of the previous ketones shown in Figure 6.10.
Figure 6.11  Crystal structures of allylstannation products 6-143 and 6-142

Isomer 6-143 was the major compound, thus resulting from γ-addition of the aldehyde to the same face as the tin moiety via Zimmerman-Traxler six-member transition structure (Scheme 6.24).
Isomer 6-142 was the minor compound thus resulting from $\alpha$-addition of the aldehyde to the same face as the tin moiety via Zimmerman-Traxler six-member transition structure (Scheme 6.25).

Speculatively, the two allylic tin species (6-151 and 6-153), which are formed in situ, could be a result of allylic arrangements that proceeded in an anti-$S_{E^*}$ manner between $\text{Bu}_3\text{Sn}$ and $\text{SnCl}_2$ (Scheme 6.26).
In theory, allylic tin intermediate 6-153 could have formed by a single \textit{anti-S_E} process followed by \textit{syn} addition of the carbonyl compound to afford an \textit{anti} \(\alpha\)-addition product 6-142, while allylic tin intermediate 6-151 could have formed by a double \textit{anti-S_E} process, followed by a \textit{syn} addition of the carbonyl compound to afford a \textit{syn} \(\gamma\)-addition product 6-143 (Scheme 6.26). Explanations of regiochemistry using allylic tin rearrangements have been used in literature.\textsuperscript{44}

The outcome ratio in favour of the \(\gamma\)-addition product could be explained by the extra stabilization to the allylic tin intermediate 6-151 by the neighbouring oxygen. According to crystal structure 6-114, the distance between the tin and the adjacent oxygen atom is 3.090(3) Å. Similarly, allylic tin intermediate 6-151 could have approximately the same distance between the tin and the oxygen (Figure 6.12).
The normal covalent bond distance between tin and oxygen is 2.0 Å.\textsuperscript{61} Intramolecular Sn--O interaction distances in the range from 2.72(2) to 3.206(3) Å have been confidently reported to indicate Sn--O bonding.\textsuperscript{62-64} These reports suggest that such stabilization, by the oxygen to the tin in 6-151, is plausible.

\(\alpha\)-Addition product was avoided by changing the reaction conditions to SnCl\(_4\)/-78 °C in CH\(_2\)Cl\(_2\), thus affording only the \(\gamma\)-addition product in 85% yield (entry 7, Table 6.13).

### 6.3.6 Racemic and asymmetric Vaultier tandem reactions

The advances made in the Diels-Alder reaction with stannyldiene 6-78 and the allylstannation chemistry illustrated earlier, was applied together in the multi-component Diels-Alder/allylstannation reaction in one pot, or better known as the Vaultier tandem reaction.
The first example was the racemic Vaul-tier tandem reaction with maleimide 6-33 (Scheme 6.27).

![Scheme 6.27](image)

As planned, the Vaul-tier tandem reaction proceeded to produce a single diastereomer 6-145 in 80% isolated yield. Stannyliene 6-78 was stirred with dienophile 6-33 at 50 °C in the absence of any solvent for 1 hour, followed by the addition of 6-139 in CH₂Cl₂ and cooling the reaction to -78 °C prior to the addition of 1 equivalent of SnCl₄. A highly functionalized cyclohexene was obtained as a single diastereomer in 80% isolated yield within 2 hours.

The asymmetric version with Waldner’s dienophile was also successful at producing a highly functionalized isomerically pure cyclohexene 6-155 in 60% yield (Scheme 6.28).
Scheme 6.28

The structure for cyclohexene 6-155 was proposed based on the work by Toure and Hall and tentative characterizations and has not been confirmed. Cyclohexene 6-155 was formed in a separable 10:1 ratio with another isomer, suggesting the 10:1 ratio obtained by the Diels-Alder reaction carried through without any isomerisation.
6.4 Summary

Stannyldiene 6-78 was able to undergo a Diels-Alder reaction with maleimide 6-33 to product cyclic allylstannane 6-112 in 93% isolated yield under thermal conditions. It was observed that stannyldiene 6-78 undergoes Diels-Alder reaction readily with cyclic and doubly activated dienophiles. Mikami catalyst was able to effect an enantioselective Diels-Alder reaction between stannyldiene 6-78 and maleimide 6-33 in modest selectivity of 30% ee. Diastereoselective Diels-Alder reaction between stannybutadiene 6-78 and Waldner’s dienophile resulted in a 10:1 dr.

The first Vaultier tandem reaction with a tin analogue was established to provide highly functionalized cyclohexene 6-145 in 80% yield as a racemic diastereomer. Also, the first asymmetric Vaultier tandem reaction with a tin analogue was established to furnish an isomerically pure highly functionalized cyclohexene 6-155 in 60% yield.
6.5 Experimental

6.5.1 General experimental

All reactions and reagents were carried out and purified as stated in Chapter 3. Chiral HPLC analysis was performed using a ChiralCel OD (4.6 mm x 250 mm) column using 5% iPrOH/Hex as eluant (0.5 mL/min). Dienophiles 6-84, 6-88, 6-98, 6-126 and 6-39 were made by the corresponding published procedures. Other reagents were purchased from Sigma-Aldrich and used without further purification. X-ray single-crystal structures studies were performed on an orange platelike, colourless needle, colourless plate and colourless block for 6-135, 6-114, 6-143 and 6-142, respectively. A Bruker Smart APEX CCD diffractometer with graphite-monochromator Mo-Kα radiation was used for the data collections, performed by scans of 0.3° (for samples 6-135, 6-143 and 6-142) and 0.36° (for sample 6-114) in ω in three or four blocks of 600 or 500 frames with an exposure time of 30 s at φ = 0, 90°, 180° and 270°. The data were corrected for Lorentz and polarization effects. Absorption corrections were based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements using APEX II software. The structure solution and refinements were performed with the SHELXTL program package part of APEX II. Appendix A, B, C and D summarize the crystallographic data of 6-135, 6-114, 6-143 and 6-142.
6.5.2 Synthesis of chiral dienophile 6-135

6.5.2.1 (E)-1,4-Diphenylbut-2-ene-1,4-dione (6-130)$^{55}$

\[
\text{Ph} \ \text{O} \ \text{Ph} \\
\text{Ph} \ \text{C} \ \text{C} \ \text{H}
\]

To a suspension of finely grinded aluminum chloride (50.1 g, 0.375 mol) in 250 mL of benzene was added, dropwise within 20 minutes, fumaryl chloride (22.2 g, 0.145 mol) while stirring quickly with a mechanical stirrer. The reaction mixture was stirred at reflux for 90 minutes after the initial boiling settled. Additional stirring for 60 minutes was followed as the reaction was allowed to cool to rt. To 500 mL of ice was added the pasty reaction mixture followed by stirring to free any lumps, which then was allowed to sit for 60 minutes. The benzene layer was washed with hot 1M HCl (2 x 150 mL), hot water (2 x 150 mL), and was then filtered and concentrated until crystals were visible. Ethanol (250 mL) was added to the mixture and cooled over ice. The resulting yellow crystals were suction filtered and washed with cold ethanol to provide 33.9 g of dibenzoylethylene 6-130 in 99% yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.04 (PhH, d, 4H, J = 7.3 Hz), 7.99 (COCH=CHCO, s, 2H), 7.61 (Ph, t, 4H, J = 7.3 Hz), 7.51 (Ph, t, 4H, J = 7.7 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 189.7 (CO), 136.8, 135.0, 133.7, 128.8 (PhCOCH).
6.5.2.2 1,4-Diphenylbutane-1,4-dione (6-131)\(^{55}\)

![1,4-Diphenylbutane-1,4-dione](image)

To a hot suspension (70 °C) of 6-130 (36.0 g, 0.152 mol) in 100 mL of EtOH was added, slowly, a solution of stannous chloride (43.2 g, 0.188 mol) in concentrated HCl (50 mL) followed by an additional 100 mL of EtOH. The reaction was allowed to stir for 1 h at reflux followed by the addition of 125 mL of water and stirred for 10 minutes, then cooled over ice and suctioned filtered to provide 33.9 g of diketone 6-131 as white crystals in 99% yield.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.03 (PhH, d, 4H, J = 7.4 Hz), 7.56 (PhH, t, 2H, J = 7.2 Hz), 7.46 (PhH, t, 4H, J = 7.7 Hz), 3.45 (CO\(\text{CH}_2\), s, 4H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 198.6 (CO), 136.7, 133.1, 128.5, 128.0 (Ph), 32.5 (CO\(\text{CH}_2\)).

6.5.2.3 (1S,4S)-1,4-Diphenylbutane-1,4-diol (6-132)\(^{56}\)

![1,4-Diphenylbutane-1,4-diol](image)

To a stirred solution containing (R)-Me-CBS reduction catalyst (1.0 M in toluene, 8.0 mL, 0.008 mol) and borane-dimethyl sulfide complex (8.4 mL, 0.084 mol) in 50 mL of
THF was added a diketone 6-131 solution (10.0 g, 0.042 mol) in THF (100 mL) at 0 °C over an hour. The reaction was allowed to warm up to rt and stirred for an additional hour. The resulting mixture was poured slowly over ice cold 2 M HCl. The aqueous layer was extracted with ether (3 x 100 mL), organic extracts were combined and washed with brine, dried over Na₂SO₄ and concentrated. The resulting oil was purified by silica gel chromatography (hexane/EtOAc, 2:1) to provide 9.67 g of diol 6-132 as colourless oil in 95% yield. Analysis by 13C NMR showed a dl : meso ratio of > 98:2, while enantioselectivity was determined by HPLC to be 98% ee.

13C NMR (75 MHz, CDCl₃) δ 144.6, 128.4, 127.3, 125.8 (Ph), 74.5 (CHOH), 35.9 (CHOHCH₂).

6.5.2.4 1-((2S,5S)-2,5-Diphenylpyrrolidin-1-yl)-1H-pyrrole-2,5-dione (6-135)

To a stirred solution of MsCl (3.4 mL, 0.044 mol) in 100 mL of CH₂Cl₂ at -20 °C was added a solution of diol 6-132 (4.19 g, 0.017 mol) and Et₃N (7.3 mL, 0.052 mol) in 30 mol of CH₂Cl₂. The reaction was stirred for 90 minutes at -20 °C, then quenched by 10 mL of NH₄Cl. The organic layer was concentrated to a volume of ~ 20 mL, diluted with AcOEt (75 mL), and washed with a 1:2:1 mixture of water, brine and satd. NaHCO₃ (3 x 50 mL). The organic layer was concentrated to a volume of ~ 20 mL, cooled to 0 °C then
diluted dropwise by hexane (~150 mL) to precipitate the dimesylate intermediate 6-133 as white crystals. The white crystals were dissolved in isopropanol (30 mL) followed by the addition of hydrazine monohydrate (15 mL). The reaction was allowed to stir vigorously for 4 days at 40 °C. The reaction mixture was diluted with ether (75 mL) and washed with satd. NaHCO₃ (2 x 50 mL) and brine (50 mL). The aqueous layer was re-extracted with ether (75 mL), dried over Na₂SO₄ and concentrated to provide the cyclized hydrazine 6-134. The cyclized product was suspended in 100 mL of toluene followed by the addition of maleic anhydride (2.22 g, 0.026 mol) and TsOH (0.05 g, 0.29 mmol). The reaction was allowed to stir for 1 day at reflux while removing the reaction water via a Dean-Stark apparatus. The reaction mixture was cooled, washed with satd. NaHCO₃ (50 mL), dried over Na₂SO₄ and concentrated. Silica gel chromatography (hexane/ether, 1:1) of the organic residue provided 4.08 g of dienophile 6-135 as orange crystals in 74% yield from diol 6-132.

^1H NMR (300 MHz, CDCl₃) δ 7.37 (PhH, d, 4H, J = 7.4 Hz), 7.29-7.18 (PhH, m, 6H), 6.13 (CH=CH, s, 2H), 2.45 (CH₂CH₃, m, 2H), 2.22 (CH₂CH₃, m, 2H); δ ^13C NMR (75 MHz, CDCl₃) δ 169.6, 169.5 (CON), 140.2, 131.5, 128.2, 128.1, 127.7 (Ph, CH=CH), 65.3 (PhCH), 32.2 (CH₂CH₂). Exact mass (EI) calcd for C₂₀H₁₈N₂O₂ (M)⁺: 318.1368, found: 318.1366. See Appendix A for crystal structure.
6.5.3  **General procedure for thermal Diels-Alder reaction with stannyldiene 6-78**

To a dry round bottom flask, stannyldiene 6-78 (0.075 g, 0.217 mmol) was added to the corresponding dienophile (0.197 mmol) and mixture was stirred for 1 h at 50 °C. The resulting residue was purified by silica gel chromatography to provide the corresponding cycloadduct.

6.5.3.1  (3aR\*,4R\*,7aS\*) and (3aS\*,4S\*,7aR\*)-2-Phenyl-4-(tributylstannyl)-3a,4,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-112)

![Structure of (3aR\*,4R\*,7aS\*) and (3aS\*,4S\*,7aR\*)-2-Phenyl-4-(tributylstannyl)-3a,4,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-112)](image)

Stannane 6-112 was made in 93% yield from maleimide 6-33 using the general procedure. Purification of stannane was done by silica gel chromatography using 10 g of SiO₂ (hexane/ether, 3:1) to provide 0.104 g of product 6-112 (R₇ = 0.65, hexane/ether, 3:1) as a clear oil.

$^1$H NMR (300 MHz, CDCl₃) δ 7.47-7.23 (PhH, m, 5H), 6.03 (SnCHCH=CH, dd, 1H, J = 9.2 Hz, J = 5.1 Hz), 5.74 (SnCHCH=CH, m, 1H), 3.39 (SnCHC=HCH, t, 1H, J = 8.9 Hz), 3.04 (SnCHCHCH, q, 1H, J = 8.3 Hz), 2.56 (SnCHCHCH, dt, 1H, J = 15.7 Hz, J = 6.9 Hz), 2.41 (SnCHCHCH, dd, 1H), 2.22 (SnCHCHCH, m, 1H), 1.49-0.83 (Bu₃Sn, m, 27H); $^{13}$C NMR (75 MHz, CDCl₃) δ 180.0, 179.0 (CONCO), 132.9, 131.9, 129.1, 128.4, 126.3, 121.8 (CH=CH) (Ph), 41.9, 40.3 (SnCHCHCH), 29.2
(SnCH₂CH₂CH₂CH₃, J_{Sn-H} = 19.8 Hz), 27.4 (SnCH₂CH₂CH₂CH₃, J_{Sn-H} = 60.4 Hz), 24.6 (SnCH₂CH₂CH₂CH₂), 21.7 (SnCH₂CH₂CH₂, J_{Sn-H} = 249.1), 13.7 (SnCH₂CH₂CH₂CH₃), 11.1 (SnCH₂CH₂CH₂CH₃, J_{Sn-H} = 317.0 Hz). Exact mass (EI) calcd for C₂₆H₃₉NO₂¹¹⁶Sn (M – n-Bu): 513.1998, C₂₆H₃₉NO₂¹¹⁶Sn (M – n-Bu)⁺ found: 513.1997.

6.5.3.2 (3aR*,4R*,7aS*) and (3aS*,4S*,7aR*)-4-(Tributylstannyl)-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (6-110)

![Stannane 6-110](image)

Stannane 6-110 was made from maleic anhydride 6-50 using the general procedure. Reaction was performed at rt for 24 h in CH₂Cl₂ (2 mL); 100% conversion of maleic anhydride was observed by crude ¹H NMR (endo:exo, 10:1, R_f = 0.70, R_f = 0.80, hexane/ether, 3:1), yield was not determined due to its instability during purification by silica gel chromatography (10 g of SiO₂, hexane/ether, 3:1).

¹H NMR (300 MHz, CDCl₃) δ 5.96 (SnCHCH=CH, m, 1H), 5.66 (SnCHCH=CH, m, 1H), 3.45 (SnCHCH₂CH₃, t, 1H, J = 7.2 Hz), 3.07 (SnCHCH₂CH₃, q, 1H, J = 8.1 Hz), 2.50 (SnCHCH₂CH₂, dt, 1H), 2.33 (SnCHCH₂CH₂, m, 1H), 2.15 (SnCHCH₂CH₂, m, 1H), 1.47-0.81 (Bu₃Sn, m, 27H); ¹³C NMR (75 MHz, CDCl₃) δ 175.1, 173.5 (CONCO), 132.0, 120.0 (CH=CH) 42.5, 39.5 (SnCHCH₂CH₂), 29.1 (SnCH₂CH₂CH₂CH₃, J_{Sn-H} = 20.1 Hz), 27.4 (SnCH₂CH₂CH₂CH₃, J_{Sn-H} = 57.2 Hz), 23.7 (SnCHCH₂CH₂), 21.1
(SnCHCHCHCH2), 13.7 (SnCH2CH2CH2CH3), 10.9 (SnCH2CH2CH2CH3, J_{Sn-H} = 325.5 Hz).

6.5.3.3 \((3a^R,4R^*,7aS^*)\) and \((3aS^*,4S^*,7aR^*)-2-((2S,5S)-2,5-Diphenylpyrrolidin-1-yl)-4-(tributylstannyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-136)

![Chemical structure](image)

Stannane **6-136** was made in 91% yield from maleimide **6-135** using the general procedure. Purification of stannane was done by silica gel chromatography using 10 g of SiO2 (hexane/ether, 3:1) to provide 0.130 g of product **6-136** (Rf = 0.75 and Rf = 0.70 (2 diastereomers, hexane/ether, 3:1) as a clear oil.

\(^1\)H NMR (300 MHz, CDCl3) \(\delta\) 7.41-7.22 (PhH, m, 20H), 5.78-5.11 (CH=CH, PhCH, m, 8H), 2.69-1.57 (CH2CH2,SnCHCHCHCH2, m, 18H), 1.44-0.73 (Bu3Sn, m, 27H); \(^{13}\)C NMR (75 MHz, CDCl3) \(\delta\) 179.9, 179.0, 179.0, 178.9, 178.7, 178.3, 177.9, 177.8 (CON), 140.2, 140.1, 135.1, 135.0, 130.8, 130.6, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 127.5, 121.1, 120.3, 115.1, 114.3 (Ph, CH=CH), 65.0, 64.9, 64.5, 64.3, 64.1, 64.0 (PhCH), 39.9, 39.5, 38.3, 38.2, 38.1, 37.9, 37.3, 33.5, 33.4, 33.1, 32.5, 32.2, 29.2, 29.0, 27.5, 27.3, 25.0, 24.4, 24.0, 23.5, 23.2, 20.0, 19.8, 13.7, 13.6, 10.9, 9.12, 9.0 (SnCHCHCHCH2) (CH2CH2) (Bu3Sn). Exact mass (EI) calcd for C_{36}H_{50}N_{2}O_{2}{^{116}}Sn (M – n-Bu)^+: 658.2889, C_{36}H_{50}N_{2}O_{2}{^{116}}Sn (M – n-Bu)^+ found: 658.2900.
6.5.3.4 \((3aR^*,4R^*,7aS^*)\) and \((3aS^*,4S^*,7aR^*)\)-2-(2-Hydroxyphenyl)-4-(tributylstannyl)-3a,4,7,7a-tetrahydro-1H-isoinole-1,3(2H)-dione (6-127)

Stannane 6-127 was made in 90% yield from maleimide 6-126 using the general procedure. Purification of stannane was done by silica gel chromatography using 10 g of SiO\(_2\) (hexane/ethyl acetate, 3:1) to provide 0.104 g of product 6-127 \((R_f = 0.37\), hexane/ether, 1:4) as a clear oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.24 (PhH, d, 1H, \(J = 8.6\) Hz), 7.14 (PhH, d, 1H, \(J = 7.7\) Hz), 6.98 (PhH, t, 2H, \(J = 8.8\) Hz), 6.21 (SnCHCH=C\(\_\)H, m, 1H), 6.03 (OH, s, 1H), 5.73 (SnCHCH=C\(\_\)H, d, 1H, \(J = 9.3\) Hz), 3.44 (SnCHCHCHCH\(_2\), m, 1H), 3.02 (SnCHCHCHCH\(_2\), m, 1H), 2.33-2.06 (SnCHCHCHCH\(_2\), m, 3H), 1.54-0.83 (Bu\(_3\)Sn, m, 27H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 179.1, 177.2 (CON), 150.9, 136.3, 130, 3, 127.9, 121.2, 120.3, 119.1, 114.2 (Ph) (CH=CH), 40.8, 40.3 (SnCHCHCHCH\(_2\)), 29.6 (SnCHCHCHCH\(_2\)), 29.1 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 27.4 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 23.5 (SnCH), 13.6 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 9.4 (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)). Exact mass (EI) calcd for C\(_{26}\)H\(_{39}\)NO\(_3\)^{116}\text{Sn} (M – n-Bu)^+: 529.1947, C\(_{26}\)H\(_{39}\)NO\(_3\)^{116}\text{Sn} (M – n-Bu)^+ found: 529.1943.
6.5.3.5 \((3aR^*,4R^*,7aS^*)\) and \((3aS^*,4S^*,7aR^*)\)-2-Phenyl-4-(trimethylstannyl)-3a,4,7,7a-tetrahydro-1H-isooindole-1,3(2H)-dione (6-114)

![Chemical Structure](image)

To a flame-dried round-bottomed flask was added stannylbutadiene **6-78** (0.500 g, 1.45 mmol) and THF (20 mL). The solution was cooled to -78 °C followed by the slow addition of BuLi (1.6 M in hexane, 0.91 mL, 1.45 mmol) and let stir for 10 min. Me\(_3\)SnCl (0.328 M in THF, 4.42 mL, 1.45 mmol) was added dropwise at -78 °C and let stirred for 30 min. The reaction mixture was concentrated and diluted with 5 mL of CH\(_2\)Cl\(_2\) followed by the addition of maleimide **6-33** (0.301 g, 1.74 mmol) at rt. The reaction was let stirred for 48 h at rt. Reaction mixture was concentrated and purified on silica gel (15 g of SiO\(_2\), hexane/ether, 3:1) to afford 0.526 g of cycloadduct **6-114** in 93% yield as a white solid (R\(_f\) = 0.65, hexane/ether, 3:1). The solid was recrystallised from CH\(_2\)Cl\(_2\) by slow evaporation to provide white crystals.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.47-7.25 (PhH, m, 5H), 6.03 (SnCHCH=CH, dd, 1H, J = 9.2 Hz, J = 5.4 Hz), 5.79 (SnCHCH=CH, m, 1H), 3.44 (SnCHCHCH, t, 1H, J = 9.0 Hz), 3.06 (SnCHCHCH, q, 1H, J = 7.8 Hz), 2.58 (SnCHCHCHCH, dt, 1H, J = 16.1 Hz, J = 6.6 Hz), 2.39 (SnCHCHCHCH, m, 1H), 2.21 (SnCHCHCHCH, m, 1H), 0.14 (Me\(_3\)Sn, s, 9H, J\(_{Sn-H}\) = 52.4 Hz); \(^1\)\(^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 179.9, 178.9 (CONCO), 132.5, 131.9, 129.1, 128.4, 126.3, 121.8 (CH=CH) (Ph), 41.7, 40.1 (SnCHCHCHCH), 24.4, 22.6 (SnCHCHCHCH), -7.8 (Me\(_3\)Sn). Exact mass (EI) calcd for C\(_{17}\)H\(_{21}\)NO\(_2\)\(^{120}\)Sn (M –
Me)\(^+\): 387.0589, C\(_{17}H\(_{21}\)NO\(_2\)^{116}\)Sn (M – Me)\(^+\) found: 387.0580. See Appendix B for crystal structure.

6.5.3.6 \((R,S,3aS,4R,7aS)-2-((R)-1-Phenylethyl)-4-(tributylstannyl)-3a,4,7,7a-tetrahydrobenzo[d]isothiazol-3(2H)-one-S-oxide (6-137) (Unconfirmed structure)

Stannane 6-137 was made from Waldner’s dienophile 6-39 using the general procedure. Reaction was performed at 100 °C for 10 minutes to provide stannane 6-137 solid \((R_f = 0.71, \text{hexane/ether, 1:2})\) in a 10:1 ratio with an unidentified isomer solid \((R_f = 0.76, \text{hexane/ether, 1:4})\). 100% conversion of the dienophile was observed (according to TLC), but yield was not determined due to its instability on silica gel.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.34\text{-}7.26 (\text{PhH}, \text{m}, 5\text{H}), 6.77 (\text{SnCHCH}=\text{CH}, \text{d}, 1\text{H}, J = 10.2 \text{ Hz}), 5.47 (\text{PhCHCH}_3, \text{q}, 1\text{H}, d = 7.2 \text{ Hz}), 5.20 (\text{SnCHCH}=\text{CH}, \text{m}, 1\text{H}), 3.68 (\text{SnCHCHCH}, \text{dd}, 1\text{H}, J = 8.5 \text{ Hz}, d = 5.8 \text{ Hz}, J_{\text{Sn-H}} = 78.0 \text{ Hz}), 3.19 (\text{SnCHCHCH}, \text{dt}, 1\text{H}, J = 10.9 \text{ Hz}, J = 5.6 \text{ Hz}), 2.32 (\text{SnCHCHCHCH}, \text{m}, 1\text{H}, J_{\text{Sn-H}} = 42 \text{ Hz}), 2.24\text{-}2.08 (\text{SnCHCHCHCH}, \text{m}, 2\text{H}), 1.81 (\text{PhCHCH}_3, \text{d}, 3\text{H}, J = 7.1 \text{ Hz}) 1.50\text{-}0.85 (\text{Bu}_3\text{Sn}, \text{m}, 27\text{H})\)
6.5.4 General procedure of allylstannation of carbonyl compounds

(method A):
To a solution of carbonyl compound (0.194 mmol) and SnCl₂ (37 mg, 0.194 mmol) in MeCN (2 mL), was added allylstannane 6-112 (0.100 g, 0.194 mmol). The reaction was allowed to stir for 3 h at rt and then passed through a short silica plug containing 10% KF followed by CH₂Cl₂. It was then concentrated and purified by silica gel chromatography to provide the corresponding allylstannation product.

(method B)
Vaultier tandem reaction: To a dry round bottom flask, Stannyliene 6-78 (0.075g, 0.217 mmol) and dienophile (0.198 mmol) were added and stirred for 1 h at 50 °C. Carbonyl compound (0.198 mmol) in CH₂Cl₂ (2 mL) was added followed by the addition of SnCl₄ (0.198 mmol) at -78 °C. The reaction was stirred for 1 h and then passed through a short silica plug containing 10% KF followed by CH₂Cl₂ washes. It was then concentrated and purified by silica gel chromatography to provide the corresponding Diels-Alder/allylstannation product.
6.5.4.1 (3a$S^*$,5$R^*$,7a$R^*$) and (3a$R^*$,5$S^*$,7a$S^*$)-5-((R$^*$) and (S$^*$)-(4-
Bromophenyl)(hydroxy)methyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isooindole-
1,3(2H)-dione (6-145)

γ-Addition product 6-145 was made from allylstannane 6-112 and aldehyde 6-139 in 80%
yield as a mixture of inseparable isomers ($R_t = 0.30$, hexane/ether, 1:4) in a ratio of 3.6:1
with α-addition product 6-144 being the minor isomer using method A. γ-Addition
product 6-145 was isolated in 80% yield (0.065 g) as the only isomer using method B.
Crude reaction mixture was purified by silica gel chromatography using 10 g of silica
(hexane/ethyl acetate, 3:1) to provide 0.064 of product 6-145 as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.50-7.21 (PhH, BrPhH, m, 9H), 6.18, 6.00
(CHCH=CHCH$_2$, dt, J = 9.9 Hz, J = 4.6 Hz, 1H, m, 1H), 4.67 (CHOH, d, 1H, J = 7.9
Hz) 3.53-3.25 (CHCH$_2$CHCH, dd, J = 9.3 Hz, J = 2.3 Hz, 1H, m, 1H, m, 1H), 2.52
(CHCH$_3$CHCH, m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 179.2, 179.1 (CONCO), 141.1,
131.9, 131.7, 129.1, 128.6, 128.4, 127.8, 126.3, 122.0 (CHCH=CHCH) (Ph) (BrPh), 74.5
(CHOH), 42.3, 40.2, 38.4, 23.9 (CHCH$_2$CHCH). Exact mass (CI) calcd for
C$_{21}$H$_{19}$NO$_3$ Br (M + H)$^+$: 412.0548, C$_{21}$H$_{19}$NO$_3$ Br (M + H)$^+$ found: 412.0548.
6.5.4.2 (3a$^\ast$5$^R$$^*$,7a$^R$$^*$) and (3a$^R$$^*$,5$^S$$^*$,7a$^S$$^*$)-5-((5$^S$$^*$) and (5$^R$$^*$)-1-(4-Bromophenyl)-1-hydroxyethyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-143)

\[
\text{\begin{figure}
\includegraphics[width=0.2\textwidth]{image}
\end{figure}}
\]

\(\gamma\)-Addition product 6-143 was made from allylstannane 6-112 and ketone 6-138 in 62\% yield in a separable 3:1 ratio with the minor \(\alpha\)-addition product 6-142 using method A. Crude reaction mixture was purified by silica gel chromatography using 10 g of silica (hexane/ethyl acetate, 3:1) to provide 0.051 g of product 6-143 as a white solid (\(R_f = 0.23\), hexane/ether, 1:4). Compound 6-143 was recrystallized from CH\(_2\)Cl\(_2\)/hexane by slow evaporation to provide white crystals.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.47-7.20\) (PhH, BrPhH, m, 9H), 6.18, 6.00 (CHCH=CHCHCH\(_2\), m, 2H), 3.50-3.25 (CHCH\(_2\)CHCH, m, 3H), 2.45 (CHCH\(_3\)CHCH, m, 1H), 1.99 (CHCH\(_2\)CHCH, m, 1H) 1.80 (OH, br s, 1H), 1.59 (CH\(_3\)C, s, 3H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 178.0, 176.0\) (CONCO), 144.8, 131.3, 130.9, 129.1, 128.5, 127.0, 126.4, 126.2, 124.3, 121.1 (CHCH=CHCH) (Ph) (BrPh), 75.7 (CH\(_3\)COH), 42.2, 41.7, 38.6, 28.3, 22.2 (CHCH\(_2\)CHCH) (CH\(_3\)C). Exact mass (Cl) calcd for C\(_{22}\)H\(_{21}\)NO\(_3\)\(^79\)Br (M + H): 426.0705, C\(_{22}\)H\(_{21}\)NO\(_3\)\(^79\)Br (M + H)\(^+\) found: 426.0705. See Appendix C for crystal structure.
6.5.4.3 \((3aR^*,4S^*,7aS^*)\) and \((3aS^*,4R^*,7aR^*)\)-4-((S\(^\star\)) and \((R\(^\star\)))-1-(4-Bromophenyl)-1-hydroxyethyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-142)

\[
\begin{align*}
\text{Br} & \quad \text{OH} \\
& \Downarrow \\
\text{N}_{\text{Ph}} & \quad \text{O} \\
\end{align*}
\]

\(\alpha\)-Addition product 6-142 was made from allylstannane 6-112 and ketone 6-138 in 21% yield in a separable 1:3 ratio with the major \(\gamma\)-addition product 6-143 using method A. Crude reaction mixture was purified by silica gel chromatography using 10 g of silica (hexane/ethyl acetate, 3:1) to provide 0.017 g of product 6-142 as a white solid solid (R\(_f\) = 0.33, hexane/ether, 1:4). Compound 6-142 was recrystallized from CH\(_2\)Cl\(_2\)/hexane by slow evaporation to provide white crystals.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.51-7.16 (PhH, BrPhH, m, 9H), 6.09-5.95 (CHCH=CHCH\(_2\), m, 2H), 3.26-3.01 (CHCHCHCH\(_2\), m, 3H), 2.68-2.45 (CHCHCHCH\(_2\), m, 2H), 2.11 (OH, br s, 1H), 1.56 (CH\(_3\)C, s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 179.7, 179.2 (CON\(_3\)CO), 145.0, 131.9, 131.5, 129.6, 129.0, 128.4, 127.1, 126.4, 126.2, 121.1 (CHCH=CHCH\(_2\)) (Ph) (BrPh), 78.3 (CH\(_3\)COH), 44.7, 40.0, 38.2, 28.9, 24.2 (CHCHCHCH\(_2\)) (CH\(_3\)C). Exact mass (CI) calcd for C\(_{22}\)H\(_{21}\)NO\(_3\)\(^{79}\)Br (M + H\(^+\))\(^\star\): 426.0705, C\(_{22}\)H\(_{21}\)NO\(_3\)\(^{79}\)Br (M + H\(^+\))\(^\star\) found: 426.0705. See Appendix D for crystal structure.
6.5.4.4 \((RS,3aS,6R,7aS)-6-((S)-(4-Bromophenyl)(hydroxy)methyl)-2-((R)-1-phenylethyl)-3a,6,7,7a-tetrahydrobenzo[d]isothiazol-3(2H)-one-S-oxide (6-155)\)
(Unconfirmed structure)

\[
\begin{align*}
\text{Br} & \quad \text{Me} \\
\text{OH} & \quad \text{Ph}
\end{align*}
\]

\(\gamma\)-Addition product 6-155 was made from dienophile 6-39 and aldehyde 6-139 in 60\% yield in a separable 10:1 ratio with an unidentified isomer (R\(_f\) = 0.29, hexane/ether, 1:2) using method B. Crude reaction mixture was purified by silica gel chromatography using 10 g of silica (hexane/ethyl acetate, 2:1) to provide 0.054 g of product 6-155 as a white solid (R\(_f\) = 0.14, hexane/ether, 1:2).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.49-7.24 (PhH, BrPhH, m, 9H), 5.63, 5.57 (CHCH\(=\)CHCH\(_2\), d, d, 2H, J = 10.2 Hz, J = 10.3 Hz), 5.42 (PhCHCH\(_3\), q, 1H, J = 7.2), 4.68 (CHOH, d, 1H, J = 5.4 Hz), 3.67 (CHCH\(_2\)CHCH\(_2\), d, 1H, J = 6.3 Hz), 3.67 (CHCH\(_2\)CHCH, dd, 1H, J = 15.0 Hz, J = 8.5 Hz), 3.15 (CHCH\(_2\)CHCH, m, 1H), 2.24 (CHCH\(_2\)CHCH, m, 2H), 1.74 (PhCHCH\(_3\), d, 3H, J = 7.2 Hz); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.7 (NCO), 140.2, 140.1, 131.7, 128.6, 128.0, 127.7, 127.1, 126.6, 125.3 (CHCH=CHCH) (Ph) (BrPh), 74.7 (CHOH), 55.4, 52.3, 40.9, 35.7, 29.6, 19.8 (PhCHCH\(_3\)) (CHCH\(_2\)CHCH).
6.5.5 Oxidation of allylstannation products 6-144 and 6-145 to corresponding ketones

To the crude mixture of allylstannyl addition products 6-144 and 6-145 (1:1 ratio) (0.080 g, 0.194 mmol) and 0.100 g of 3 Å molecular sieves in 4 mL of CH₂Cl₂ was added PDC (0.109 g, 0.291 mmol) at rt. The reaction was stirred for 16 h followed by a quench with brine (20 mL). The aqueous phase was extracted with CH₂Cl₂ (2 x 30 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified and separated by silica gel chromatography (hexane/ether, 1:1) to provide 0.037 g of ketone 6-150 (Rᵣ = 0.60, hexane/ether, 1:4) and 0.037 g of ketone 6-149 (Rᵣ = 0.75, hexane/ether, 1:4) in a combined yield of 92%.

6.5.5.1 (3aS*,5R*,7aR*) and (3aR*,5S*,7aS*)-5-(4-Bromobenzoyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-150)

\[
\text{Br} \quad \text{NPh}
\]

\(^1\text{H} \text{NMR (300 MHz, CDCl}_3\) \( \delta \) 7.85-7.24 (PhH, BrPhH, m, 9H), 6.18 (CHCH=CHCHCH₂, d, 1H, J = 10.1 Hz), 6.12 (CHCH=CHCHCH₂, m, 1H), 4.02-3.48 (CHCH₂CHCH, m, 3H), 2.54 (CHCH₂CHCH, dt, 1H, J = 13.6 Hz, J = 4.8 Hz), 2.01 (CHCH₃CHCH, m, 1H); \(^{13}\text{C} \text{NMR (75 MHz, CDCl}_3\) \( \delta \) 198.1 (BrPhC=O), 177.7, 175.0 (CONCO), 133.8, 132.2, 131.5, 130.0, 129.1, 128.9, 128.6, 123.7 (CHCH=CHCH) (Ph)
(BrPh), 41.5, 39.6, 38.3, 24.2 (CHCH=CHCH). Exact mass (EI) calcd for C_{21}H_{16}NO_{3}\textsuperscript{79}Br (M): 409.0314, found: 409.0316.

6.5.5.2 $\text{(3a}^\text{R},\text{4}^\text{S},7\text{a}^\text{S})$ and $\text{(3a}^\text{S},\text{4}^\text{R},7\text{a}^\text{R})$-$4$-(4-Bromobenzoyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-149)

![Chemical structure](image)

$\text{1H NMR (300 MHz, CDCl}_3\text{)}$ $\delta$ 7.85-7.24 (PhH, BrPhH, m, 9H), 6.07-5.97 (CHCH=CHCH\_2, m, 2H), 4.70 (CHCHCH\_2, d, 1H, $J = 6.5$ Hz) 3.83 (CHCHCH\_2, d, 1H, $J = 9.2$ Hz) 3.58 (CHCHCH\_2, t, 1H, $J = 8.7$ Hz), 2.54 (CHCHCH\_2, AB of ABX, 2H, $\delta_A = 2.70$, $\delta_B = 2.38$, $J_{AB} = 16.8$ Hz, $J_{AX} = 5.3$ Hz, $J_{BX} = 8.3$ Hz); $\text{13C NMR (75 MHz, CDCl}_3\text{)}$ $\delta$ 193.8 (BrPhCO), 179.2, 178.7 (CONCO), 133.8, 132.1, 131.9, 131.7, 130.3, 129.1, 128.7, 126.4, 124.3 (CHCH=CHCH\_2) (Ph (BrPh), 45.3, 41.0, 39.1, 23.5 (CHCHCH\_2). Exact mass (EI) calcd for C_{21}H_{16}NO_{3}\textsuperscript{79}Br (M): 409.0314, found: 409.0309.

Spectral data were in accord with literature data.
Chapter 1 References


Chapter 2 References


Chapter 3 References


353


Chapter 4 References

Chapter 5 References

(36) Daly, J. W.; Myers, C. W. Science 1967, 156, 970-973.
Chapter 6 References

Appendix A

X-ray Crystallographic Data

(3a$R^*$,4$R^*$,7a$S^*$) and (3a$S^*$,4$S^*$,7a$R^*$)-2-Phenyl-4-(trimethylstannyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-114)
Table 1. Crystal data and structure refinement for 6-114

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<td>Wavelength</td>
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<td>R indices (all data)</td>
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Table 3. Hydrogen coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for 6-114

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C(1) – N(1) – C(9) 
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O(1) – C(1) – N(1) 
123.9 (3)
O(1) – C(1) – C(2) 
128.1 (3)
N(1) – C(1) – C(2) 
108.0 (3)
C(1) – C(2) – C(3) 
103.8 (3)
C(1) – C(2) – C(5) 
116.7 (3)
C(3) – C(2) – C(5) 
117.0 (3)
C(1) – C(2) – H(2A) 
106.1
C(3) – C(2) – H(2A) 
106.1
C(5) – C(2) – H(2A) 
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C(4) – C(3) – C(2) 
104.5 (3)
C(8) – C(3) – C(2) 
113.1 (3)
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C(8) – C(3) – H(3A) 
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C(4) – C(3) – H(3A) 
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123.4 (4)
O(2) – C(4) – C(3) 
128.1 (3)
N(1) – C(4) – C(3) 
108.5 (3)
C(6) – C(5) – C(2) 
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C(6) – C(5) – Sn(1) 
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C(2) – C(5) – Sn(1) 
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110.0
H(8A) – C(8) – H(8B) 
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118.9 (3)
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C(12) – C(11) – C(10) 
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C(10) – C(11) – H(11A) 
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C(13) – C(12) – C(11) 
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C(11) – C(12) – H(12A) 
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C(12) – C(13) – C(14) 
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C(14) – C(13) – H(13A) 
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C(9) – C(14) – C(13) 
119.0 (4)
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C(13) – C(14) – H(14A) 
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Sn(1)–C(15)–H(15B) 109.5
H(15A)–C(15)–H(15B) 109.5
Sn(1)–C(15)–H(15C) 109.5
H(15A)–C(15)–H(15C) 109.5
H(15B)–C(15)–H(15C) 109.5
Sn(1)–C(16)–H(16A) 109.5
Sn(1)–C(16)–H(16B) 109.5
H(16A)–C(16)–H(16B) 109.5
Sn(1)–C(16)–H(16C) 109.5
H(16A)–C(16)–H(16C) 109.5
H(16B)–C(16)–H(16C) 109.5
Sn(1)–C(17)–H(17A) 109.5
Sn(1)–C(17)–H(17B) 109.5
H(17A)–C(17)–H(17B) 109.5
Sn(1)–C(17)–H(17C) 109.5
H(17A)–C(17)–H(17C) 109.5
H(17B)–C(17)–H(17C) 109.5
Appendix B

X-ray Crystallographic Data

1-((2S,5S)-2,5-Diphenylpyrrolidin-1-yl)-1H-pyrrole-2,5-dione (6-135)
Table 1. Crystal data and structure refinement for 6-135

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<th>Value</th>
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<tr>
<td>Temperature</td>
<td>200(2) K</td>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic, (P2_12_12_1)</td>
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<tr>
<td>Unit cell dimensions</td>
<td>(a = 8.564(4) \text{&quot;Å}, b = 9.399(4) \text{&quot;Å}, c = 20.445(9) \text{&quot;Å})</td>
</tr>
<tr>
<td>Volume</td>
<td>1645.5(12)  \text{&quot;Å}^3</td>
</tr>
<tr>
<td>Z, Calculated density</td>
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<tr>
<td>Absorption coefficient</td>
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<tr>
<td>(F(000))</td>
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<tr>
<td>Crystal size</td>
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<tr>
<td>Theta range for data collection</td>
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<tr>
<td>Limiting indices</td>
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<tr>
<td>Reflections collected / unique</td>
<td>16300 / 3965 [(R\text{(int)} = 0.0426)]</td>
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<td>Completeness to theta = 28.00 (\theta)</td>
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<tr>
<td>Max. and min. transmission</td>
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</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on (F^2)</td>
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<tr>
<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on (F^2)</td>
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370
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 6-135

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Table 3. Hydrogen coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for 6-135

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Table 3. Bond lengths [Å] and angles [°] for 6-135

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<td>C(18)–C(13)–C(9)</td>
<td>123.87(17)</td>
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C(14) – C(13) – C(9)       118.81 (15)  
C(15) – C(14) – C(13)       121.94 (18)  
C(16) – C(15) – C(14)       119.6 (2)    
C(17) – C(16) – C(15)       120.40 (19)   
C(16) – C(17) – C(18)       120.09 (19)   
C(13) – C(18) – C(17)       120.65 (19)   
C(24) – C(19) – C(20)       118.70 (16)   
C(24) – C(19) – C(12)       121.90 (15)   
C(20) – C(19) – C(12)       119.22 (15)   
C(21) – C(20) – C(19)       120.68 (18)   
C(22) – C(21) – C(20)       119.97 (19)   
C(21) – C(22) – C(23)       119.65 (18)   
C(22) – C(23) – C(24)       120.55 (19)   
C(19) – C(24) – C(23)       120.36 (18)   

Appendix C

X-ray Crystallographic Data

(3aR*,4S*,7aS*) and (3aS*,4R*,7aR*)-4-((S*) and (R*)-1-(4-bromophenyl)-1-hydroxyethyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-142)
Table 1. Crystal data and structure refinement for 6-142

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<tr>
<th>Parameter</th>
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<td>Wavelength</td>
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Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters ($\AA^2 x 10^3$) for 6-142

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Table 3. Hydrogen coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for 6-142

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Table 4. Bond lengths [Å] and angles [°] for 6-142

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Appendix D

X-ray Crystallographic Data

(3a$S^*$,5$R^*$,7a$R^*$) and (3a$R^*$,5$S^*$,7a$S^*$)-5-((S$^*$) and (R$^*$)-1-(4-Bromophenyl)-1-
hydroxyethyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isooindole-1,3(2H)-dione (6-143)
**Table 1. Crystal data and structure refinement for 6-143**

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Table 4. Bond lengths [Å] and angles [°] for 6-143
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C(17A) - C(22A)  1.385(2)
C(18A) - C(19A)  1.388(3)
C(19A) - C(20A)  1.385(3)
C(20A) - C(21A)  1.374(3)
C(21A) - C(22A)  1.387(3)
C(1B) - C(2B)  1.509(2)
C(2B) - C(5B)  1.531(2)
C(2B) - C(3B)  1.533(2)
C(3B) - C(8B)  1.504(2)
C(3B) - C(4B)  1.524(2)
C(5B) - C(6B)  1.537(2)
C(6B) - C(7B)  1.501(2)
C(7B) - C(8B)  1.318(3)
C(9B) - C(10B)  1.535(3)
C(11B) - C(12B)  1.382(3)
C(11B) - C(16B)  1.387(3)
C(12B) - C(13B)  1.389(3)
C(13B) - C(14B)  1.373(3)
C(14B) - C(15B)  1.366(3)
C(15B) - C(16B)  1.389(3)
C(17B) - C(18B)  1.385(2)
C(17B) - C(22B)  1.388(2)
C(18B) - C(19B)  1.391(3)
C(19B) - C(20B)  1.374(3)
C(20B) - C(21B)  1.388(3)
C(21B) - C(22B)  1.392(3)

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C(4A) - N(1A) - C(17A)  124.65(12)
C(1A) - N(1A) - C(17A)  122.78(12)
C(1B) - N(1B) - C(1B)  112.67(13)
C(1B) - N(1B) - C(17B)  125.89(13)
C(1B) - N(1B) - C(17B)  121.34(13)
O(2A) - C(1A) - N(1A)  123.73(14)
O(2A) - C(1A) - C(2A)  127.19(14)
N(1A) - C(1A) - C(2A)  108.22(12)
C(1A) - C(2A) - C(5A)  115.14(12)
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C(7A) - C(6A) - C(5A)  110.56(13)
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O(3A) - C(9A) - C(11A)  107.44(11)
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<td>C(18B)–C(17B)–N(1B)</td>
<td>119.71 (15)</td>
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<tr>
<td>Bond</td>
<td>Angle</td>
</tr>
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<td>118.94 (15)</td>
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<td>C(17B) – C(18B) – C(19B)</td>
<td>118.99 (18)</td>
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<td>120.2 (2)</td>
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<td>C(19B) – C(20B) – C(21B)</td>
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<td>C(20B) – C(21B) – C(22B)</td>
<td>119.78 (19)</td>
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<tr>
<td>C(17B) – C(22B) – C(21B)</td>
<td>119.03 (18)</td>
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