Stereoselective Cyclization of Functionalized 1,\textit{n}-Diynes Mediated by [X-Y] Reagents \[(R_2N)_{2}B-SnR_{3}^{\prime}\]. Synthesis and Properties of Atropisomeric 1,3-Dienes

DISTRIBUTION

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By
Amanda Marie Kutney
Graduate Program in Chemistry

The Ohio State University
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Dissertation Committee:
Professor T.V. RajanBabu
Professor Jovica Badjić
Professor Jonathan Parquette
Abstract

The discovery and use of transition metal-catalyzed reactions for the construction of C-H, C-C, and C-hetero-atom bonds for synthesis are important areas of current research in organic chemistry. One aspect within this area involves the use of transition metals and main-group organometallic compounds in catalytic systems by allowing access to highly chemo-, regio-, and diastereoselectivity processes. More importantly, the development of tandem reactions to construct a highly functionalized framework from a relatively simple organic precursors followed by further synthetic applications is a major goal in methodology.

Our group has paid increasing attention to the use of transition-metal-catalyzed heterobismetallic functionalization reactions of unsaturated organic compounds as tools for the construction of cyclic compounds. Among the palladium-catalyzed reactions, the simultaneous introduction of heterobimetallic reagents (X-Y), such as a borostannane (R₂B-SnR₃), onto an unsaturated system occurs with high regio- and stereoselectivity. Bismetallative cyclization between two unsaturated systems in a tether can be seen as useful in synthetic organic chemistry, leading to cyclized substrates containing two different metal functionalities allowing for numerous further synthetic applications.
A key aspect of the cyclization of diynes is that the resulting 1,3-diene adopts a non-planar, helically chiral configuration, due to the steric demands of the X- and Y-substituents, which is fluxional in nature. These appealing systems can exhibit a low activation barrier at room temperature. However, if this atropisomerization can be frozen, the helical chirality can be exploited to influence chirality of other centers in the molecule.

We have shown the reactivity and use of a borylstannane [-N(Me)CH₂CH₂(Me)N-]B–SnMe₃ in the cyclization to be far more superior than the corresponding silylstannane reactions of 1,n-diynes such as the 1,2-dipropargylbenzenes, 2,2'-dipropargylbiphenyls, 4,5-dipropargyldioxolanes and 1,4-dipropargyl-β-lactams. Analysis by NMR spectroscopy of those substrates which underwent facile cyclization has indicated the cyclization event to be atropselective for selected substrates due to the formation and observation of only one of the atropisomeric products in the spectra. Introduction of steric strain within the backbone of the diyne precursor has effectively increased the barrier of rotation between the non-planar atropisomeric (Z,Z)-1,3-diene products, resulting in the bicyclic products being static in nature at room temperature, as seen in the VT-NMR studies.

Studies also indicate that further applications of this cyclization reaction have to depend on finding proper derivatization reaction procedures. Though hydrolytically sensitive, the diazaborolidine substrates can be converted into the corresponding more stable dioxaborolidine derivatives; or be used in the tin-halide exchange reaction in the
formation of the haloborolidine substrates. Further work in the cross-coupling transformation reactions is also imperative.
Dedication

This document is dedicated to my family.
Acknowledgments

I would first like to thank my advisor, Professor T.V. RajanBabu not only for his assistance, support and guidance throughout my Ph.D., but most importantly his patience.

I thank my current and former colleagues in the chemistry department for their help during my stay at Ohio State, and perhaps more importantly their friendship. I would like to thank Dr. Singidi for his initial work in this project, as well as for providing sufficient quantities of the borylstannane reagent. I wish to acknowledge the help of Dr. Judith Gallucci for her work on the X-ray studies and Dr. Tanya Young for her help with the NMR studies. None of this work would have been possible without the financial support from the Ohio State University and the National Science Foundation.

I am grateful for my parents and family who have encouraged me during my studies at Ohio State. You have given me the strength, guidance and belief needed to get through moments of difficulty and despair and for that I am forever indebted to you all.
Vita

December 17, 1981.........................................................Born; Wilkes-Barre, PA
2000-2004 .................................................................B.S., Chemistry

Lebanon Valley College

2004 to present .........................................................Graduate Teaching Associate/

Graduate Research Associate

Department of Chemistry

The Ohio State University

Publication

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Fields of Study

Major Field: Chemistry
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LIST OF ABBREVIATIONS

\[
\begin{align*}
\alpha & \quad \text{alpha} \\
Ac & \quad \text{acetyl} \\
br & \quad \text{broad (IR and NMR)} \\
\beta & \quad \text{beta} \\
n-Bu & \quad \text{normal-butyl} \\
t-Bu & \quad \text{tert-butyl} \\
Bn & \quad \text{benzyl} \\
°C & \quad \text{degrees Celsius} \\
calcd & \quad \text{calculated} \\
cat. & \quad \text{catalytic; catalyst (in schemes and tables)} \\
COSY & \quad \text{correlation spectroscopy} \\
CSA & \quad \text{(1R)-Camphor-10-sulfonic acid} \\
Cy & \quad \text{cyclohexyl} \\
\delta & \quad \text{chemical shift in parts per million downfield from tetramethylsilane} \\
d & \quad \text{doublet (spectra); day(s)}
\end{align*}
\]
$n$-Dec  
normal-decane

dba  
dibenzyldeneacetone

DMF  
dimethylformamide

dppe  
1,2-Bis(diphenylphosphino)ethane

equiv  
equivalent

eqn  
equation

Et  
ethyl

etpo  
4-ethyl-2,6,7-trioxa-1-phospha[bicyclo[2.2.2]octane

ΔG  
free energy

γ  
gamma

g  
gram(s)

HPLC  
high-performance liquid chromatography

HRMS  
high resolution mass spectrometry

h  
hour(s)

IR  
infrared

i-Pr  
iso-Propyl

$J$  
coupling constant in Hz (NMR)

kcal  
kilocalories

kJ  
kilojoules

LDA  
lithium diisopropylamide

m  
milli; multiplet (NMR)

μ  
micro
M  moles per liter
Me  methyl
MHz  megahertz
min  minute(s)
mol  mole(s)
MS  mass spectrometry; molecular sieves
m/z  mass to charge ratio (MS)
NBS  N-bromosuccinimide
NCS  N-chlorosuccinimide
NMR  nuclear magnetic resonance
NOESY  nuclear overhauser effect spectroscopy
-\textit{tOct}  \textit{tert-Octyl}
\textit{p}  para
Ph  phenyl
pin  pinacol
pTSA  \textit{para}-toluenesulfonic acid
ppm  parts per million
pyr  pyridine
q  quartet (NMR)
rt  room temperature
s  singlet (NMR); second(s)
t  tertiary (tert)

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<td>2,2-Dimethyl-α,α',α',α'-tetraphenyldioxolane-4,5-dimethanol</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-(n)-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>(t)-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>(N,N,N',N')-tetramethylenediamine</td>
</tr>
<tr>
<td>tmtu</td>
<td>1,1,3,3-tetramethyl-2-thiourea</td>
</tr>
<tr>
<td>tol</td>
<td>toluene</td>
</tr>
<tr>
<td>Ts</td>
<td>toluenesulfonyl</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR)</td>
</tr>
<tr>
<td>VT-NMR</td>
<td>Variable-temperature nuclear magnetic resonance</td>
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CHAPTER 1: INTRODUCTION
TRANSITION-METAL CATALYZED ADDITION-BISFUNCTIONALIZATION OF
UNSATURATED SYSTEMS

1.1 Background and Significance

The discovery and use of transition metal-catalyzed processes in the construction of C-H, C-C, and C-heteroatom bond formation and for the synthesis of cyclic compounds are important areas of current research in organic chemistry.\(^1\) The use of transition metals as catalysts and main-group compounds as reagents in catalytic systems have been one of the advanced research fields in modern organic chemistry. Many of the reactions that were discovered allow for high chemo-, regio-, and diastereoselectivity, and are not often observed in the corresponding non-catalyzed transformations. More importantly, the development of tandem reactions to construct highly functionalized framework from a relatively simple organic precursor is a major goal in methodology development and synthetic chemistry.

Of the transition metals, especially within the group 10 elements, palladium has played a vital role in the discovery of metal-catalyzed element-element addition reactions.
to unsaturated systems. Several reviews have shown advances in the field, along with the wide number of catalyst systems tested, which result in transformations with high selectivity.²

The RajanBabu group interest is focused on the addition of Group 13 (boron) and Group 14 (silicon and tin) additions across π-systems. The addition of metal complexes across an alkyne results in the preparation of reactive vinyl metal species which can serve as a direct route to the formation of tri- and tetrasubstituted olefins. Amongst these vinyl metal compounds, vinyl silanes are commonly used in substitution reactions with electrophiles,³ whereas vinylboranes⁴ and vinylstannanes⁵ serve as carbon-carbon bond forming tools when subjected to Suzuki-Miyaura and Stille coupling reactions, respectively (Scheme 1.1).

**Scheme 1.1: Reactions of Vinyl Silanes, Vinyl Boranes and Vinyl Stannanes**

\[
\begin{align*}
\text{a) } & \quad \text{Me}_3\text{Si-SnBu}_3 \xrightleftharpoons{\text{AlCl}_3} \xrightarrow{\text{AcCl}} \text{Ac-SnBu}_3 \\
\text{1.1} & \quad \text{1.2} 30-50 \% \\
\text{b) } & \quad \text{C}_6\text{H}_5\text{Br} \xrightarrow{\text{Ph}} \text{C}_6\text{H}_5\text{B-O} \\
\text{1.3} & \quad \text{1.4} 86 \% \\
\text{c) } & \quad \text{SnBu}_3 \xrightarrow{\text{[(\text{H-allyl})\text{PdCl})_2, 2.5 \text{ mol \%}]} \xrightarrow{\text{Pd(Ph}_{3})_4, 1 \text{ mol \%}, \text{NaOE}_{1}, \text{C}_6\text{H}_5, \text{reflux}} \xrightarrow{\text{Me_4NF, THF, rt}} \text{SnBu}_3 \\
\text{1.5} & \quad \text{1.6} 86 \%
\end{align*}
\]
1.1.1 Palladium-Catalyzed Hydrometallation Reactions (H-Y; Y = Si, Sn, and B)

1.1.1.1 Palladium-Catalyzed Hydrosilylation of $\pi$-systems

Within the palladium-catalyzed reactions, hydrometallations (H-Y, where Y = Si$^6$, Sn$^7$, B$^8$ etc.) have been extensively studied and serve as useful applications in the formation of functionalized synthetic intermediates.$^9$ These reactions are most useful for the simultaneous introduction of both a C-H and C-Y bond with both regioselectivity and stereoselectivity.

Takahashi, Shibano and Hagihare in 1969, reported on one of the earliest palladium-catalyzed hydrosilylation reactions of 1,3-butadiene with Me$_3$SnH in the presence of a catalytic amount of bis(triphenyl-phosphine)(maleic anhydride)palladium resulting in a 2:1 adduct in 98% yield (Scheme 1.2)$^{10}$

**Scheme 1.2:** Palladium-Catalyzed Hydrosilylation of 1,3-Butadiene

Reports on the palladium-catalyzed hydrosilylation of alkynes have remained very limited. Voronkov et. al. have reported on the polyborane-containing palladium and platinum-catalyzed reactions of terminal alkynes with HSiEt$_3$ (Scheme 1.3)$^{11}$
Scheme 1.3: Palladium-Catalyzed Hydrosilylation of Acetylenes

\[
\begin{align*}
\text{HSiEt}_3 & + \text{R} \equiv \text{H} & \xrightarrow{[\text{Ph}_3\text{P}]_2\text{PdCl}_2\text{B}_{12}\text{Cl}_{12}} & \text{n-Bu} & \equiv \text{H} \\
& & & \text{Et}_3\text{Si} & \equiv \text{H} \\
\text{R} = \text{n-Bu} & 111a & \text{R} = \text{n-Bu} & 64\% & 112a & 22\% 113a \\
\text{Ph} & 111b & \text{Ph} & 15\% & 112b & 17\% 113b
\end{align*}
\]

Cascade reactions involving a palladium-catalyzed hydrosilylation reaction paired with cyclization have also been reported (Scheme 1.4).\(^{12}\)

Scheme 1.4: Palladium-Catalyzed Tandem Hydrosilylation/Cyclization

1.1.1.2 Palladium-Catalyzed Hydrostannation of π-systems

Since the first work reported in 1987,\(^{13}\) more than a dozen papers on palladium-catalyzed hydrostannation of alkynes have been reported (Scheme 1.5). In comparison to hydrosilylation, palladium-catalyzed hydrostannation is observed typically at temperatures at or above 50°C. However, another limitation of this type of H-Y addition is the unpredictable nature of the reaction resulting in varying product mixtures.\(^{7a}\)
Scheme 1.5: Palladium-Catalyzed Hydrostannation of Acetylenes Product Mixtures

For example, the reaction of terminal alkynes with HSnMe₃, HSnBu₃, and other triorganylstannanes tends to produce isomeric mixtures of α-, cis-β, and trans-β-stannyl-substituted alkenes except for some special cases, such as those shown in Scheme 1.6.

Scheme 1.6: Palladium-Catalyzed Hydrostannation of Acetylenes
1.1.1.3 Transition Metal-Catalyzed Hydroboration of $\pi$-systems

Palladium-catalyzed hydroboration of $\pi$-$\pi$-systems was first reported on in 1989 by Suzuki and co-workers on the reaction of conjugated dienes with catecholborane in the presence of palladium-complexes (Scheme 1.7).\textsuperscript{16}

**Scheme 1.7: Palladium-Catalyzed Hydroboration of 1,3-Dienes**

Suzuki and co-workers also reported on the reaction of 1-thioalkynes with catecholborane under catalytic conditions resulting in a mixture or products of $\alpha$- and $\beta$-thioalkenylboranes. They found that among the metal-catalysts Ni-complexes were the most effective, followed by Pd-complexes, and then Rh-complexes (Scheme 1.8).\textsuperscript{17}

**Scheme 1.8: Hydroboration of 1-Thioalkynes**

<table>
<thead>
<tr>
<th>Catalyst System</th>
<th>% Yield</th>
<th>1.20A: 1.20B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh$_3$)$_4$</td>
<td>54</td>
<td>8:2</td>
</tr>
<tr>
<td>RhCl(PPh$_3$)$_3$</td>
<td>40</td>
<td>58:42</td>
</tr>
<tr>
<td>NiCl$_2$(dppe)</td>
<td>100</td>
<td>&gt; 99:1</td>
</tr>
</tbody>
</table>
1.1.2 Palladium-Catalyzed Dimetallation (X-X) reactions

1.1.2.1 Palladium-Catalyzed Disilylation of \( \pi \)-systems

One of the first examples of the transition metal-catalyzed homoelement-element additions to alkynes were disilylations reported by the groups of Kumada,\(^1\) and Sakurai\(^2\) in the early 1970’s (Scheme 1.9, eqn a and b respectively).

Scheme 1.9: Palladium-Catalyzed Disilylation of Acetylenes

More recent contributions by Ito\(^3\) and Tanaka,\(^4\) have introduced more efficient palladium-catalyzed disilylation reactions of acetylenes using Pd(OAc)\(_2\)-1,1,3,3-tetramethylbutyl isocyanate and Pd(dba)\(_2\)-etpo catalytic systems (Scheme 1.10). These systems can allow for the addition of nonactivated disilanes (e.g. Me\(_3\)Si-SiMe\(_3\)) to a variety of alkyne substrates. It was also reported that though the reaction of terminal alkynes were successful, internal alkynes were unreactive unless an intramolecular
disilylation is possible, as is the case when the disilane and acetylene were tethered together by a two- or three-atom tether.

**Scheme 1.10:** Efficient Palladium-Catalyst Systems for Disilylation of Acetylenes

1.1.2.2 Palladium-Catalyzed Distannation of $\pi$-systems

As compared with other bismetal additions to unsaturated systems distannylations of unsaturated systems occur under milder conditions with a number of reactions proceeding at room temperature. Recent work by Lautens, et. al. has shown the use of mild reaction conditions in the additions of hexaalkylsilanes to a variety of acetylenes containing functional groups such as esters, ethers, amines, carbamates, sulfonamides and alcohols (Scheme 1.11).$^{22}$ The distannane addition to internally substituted activated acetylene (e.g., dimethyl acetylene dicarboxylate) was also reported. However, reactions with other internal acetylenes were unsuccessful.
Scheme 1.11: Palladium-Catalyzed Distannation of Acetylenes

\[
\begin{align*}
\text{Bu}_3\text{Sn-SnBu}_3 + \text{MeO}_2\text{C} &= \text{Bu}_3\text{Sn} \quad \text{Bu}_3\text{Sn} \\
\text{SnBu}_3 &\quad \text{SnBu}_3 \\
1.30 &\quad 1.31 \\
\end{align*}
\]

\[
\begin{align*}
\text{Bu}_3\text{Sn-SnBu}_3 + \text{MeO}_2\text{C} &= \text{Bu}_3\text{Sn} \quad \text{Bu}_3\text{Sn} \\
\text{SnBu}_3 &\quad \text{SnBu}_3 \\
1.30 &\quad 1.22 \\
\end{align*}
\]

1.1.2.3 Transition Metal-Catalyzed Diboration of \(\pi\)-systems

Diboration reactions of acetylene complexes have shown to be inactive with the use of Pd- and Rh-complexes due to the slow rate of oxidation addition of the borane-reagents to palladium(0)-phosphine complexes.\(^{23}\) Therefore a majority of reported literature has been focused on Pt-catalyzed systems (Scheme 1.12). Miyaura and co-workers have shown the addition of tetraalkoxydiboron substrates to alkynes in excellent yields.\(^{24}\)

Scheme 1.12: Diboration of Acetylenes Using a Platinum-Catalyst

\[
\begin{align*}
\text{Bpin-Bpin} + n\text{C}_6\text{H}_{17} &= n\text{C}_6\text{H}_{17} \\
\text{H} &\quad \text{H} \\
1.34 &\quad 1.35 \\
\end{align*}
\]

\[
\begin{align*}
\text{Bpin-Bpin} + n\text{C}_2\text{H}_7 &= n\text{C}_2\text{H}_7 \\
\text{SnBu}_3 &\quad \text{SnBu}_3 \\
1.34 &\quad 1.37 \\
\end{align*}
\]
1.1.3 Palladium-Catalyzed Dimetal (X-Y) Addition to $\pi$-systems (X-Y; X,Y= Si, Sn, B)

Instead of an H-Y or an X-X system being introduced, if the components of a heterobimetallic reagent (X-Y; X or Y = [Si], [Sn], [B]) were to be simultaneously introduced into an unsaturated system then the reaction is potentially more beneficial from a synthetic standpoint. This X-Y addition/cyclization strategy adds to the development of a reaction which constructs a highly functionalized framework from a relatively simple precursor in one step.

Methodologies that simultaneously introduce two different metals onto a $\pi$-system have been explored [e.g., X-Y = Si-Sn (silylstannanes); Ge-Sn (germylstannanes); Sn-P (stannylphosphanes); Sn-S (stannylsulfides); B-S (borosulfides); Si-B (silaborations) and B-Sn (borostannanes)], typically with the use of the group 10 metals Pd, Ni, and Pt in combination with a phosphine ligand. Applications of this methodology with bifunctional reagents (X-Y = Si-Sn) can be seen using substrates such as enynes, diynes, and allenynes (Scheme 1.13).
Scheme 1.13: Palladium-Catalyzed [X-Y] Addition-Cyclization of 1,\textit{n}-Diynes

a) X-Y (X-Y = Si-Sn, silylstannylation) reactions with enynes

\[
\text{Me}_3\text{Si-SnBu}_3 + \overset{1.40}{\text{EtO}_2\text{C} \text{CO}_2\text{Et}} \xrightarrow{\text{Pd}(_{\text{dba}})_3 (5 \text{ mol } \%) \text{ PCy}_2(\text{o-biphenyl}) (12 \text{ mol } \%) \text{ toluene, 60 °C, 12 h}} \overset{1.41}{\text{Bu}_3\text{Sn}\text{-SiMe}_3\text{-H}} \text{ CO}_2\text{Et} 71 \%
\]

b) X-Y (X-Y = Si-Sn, silylstannylation) reactions with diynes

\[
\text{Me}_3\text{Si-SnBu}_3 + \overset{1.42}{\text{MeO}_2\text{C} \text{CO}_2\text{Me}} \xrightarrow{\text{Pd}(_{\text{dba}})_3 (1.25 \text{ mol } \%) \text{ P(2-MeC}_6\text{H}_5)_3 (5 \text{ mol } \%) \text{ C}_6\text{H}_6, \text{rt, 2h}} \overset{1.43}{\text{Bu}_3\text{Sn}\text{-SiMe}_3\text{-H}} \text{ CO}_2\text{Me} 79 \%
\]

c) X-Y (X-Y = Si-Sn, silylstannylation) reactions with allenynes

\[
\text{tBuMe}_2\text{Si-SnBu}_3 + \overset{1.45}{\text{EtO}_2\text{C} \text{CO}_2\text{Et}} \xrightarrow{\text{Pd}(_{\text{dba}})_3 (1 \text{ mol } \%) \text{ P(}C_6\text{F}_5\text{) (2 mol } \%) \text{ C}_6\text{H}_6, \text{rt}} \overset{1.46}{\text{tBuMe}_2\text{Si-}} \text{CO}_2\text{Et} (80 \%)
\]

1.1.3.1 Palladium-Catalyzed Silylstannylation Reactions

An extensive amount of work has been reported on the addition of silylstannanes to alkynes with the use of Pd-catalysts, with the first additions reported in 1985 by Chenard/RajanBabu and Mitchell (Scheme 1.14, eqn a and b respectively). These
reactions were shown to proceed with high regio- and stereoselectivity, with the Sn-moiety adding to the internal position of the alkyne.

**Scheme 1.14: [X-Y] Additions of Silylstannanes**

\[ \text{Scheme 1.14: [X-Y] Additions of Silylstannanes} \]

(a) \[ \text{R} \equiv \text{Sn}^{BuMe_2Si} + \text{SnBu}_3 \]

\[ \text{R} \equiv \text{Pd(PPh}_3)_4 \]

THF, 65 °C

4-8 h

1.50

\[ \text{Me}_3\text{Sn} \]

\[ \text{Me}_2\text{SnBu}_3 \]

1.51 a R = Ph (93 %)

1.51 b R = nBu (74 %)

1.51 c R = iPr (87 %)

1.51 d R = tBu (10 %)

1.51 e R = -(CH}_2}_3CN (90 %)

(b) \[ \text{Me}_2\text{C} \equiv \text{C} \equiv \text{CH}_2 \]

\[ \text{Me}_3\text{Sn-S} \text{SiMe}_3 \]

Pd(PPh}_3)_4, THF

reflux, 48 h

1.52

1.53

1.54

1:1 mixture

67% isolated yield

Initial studies of hydrometallation and bismetallation type additions to unsaturated systems were shown to prepare acyclic structures, while our attention has been given towards the formation of cyclization products that incorporate the X-Y species.

### 1.1.3.2 Tandem Palladium-Catalyzed Addition-Carbocyclization Reactions

Within this category of tandem reactions are transition-metal catalyzed carbocyclization and heterocyclization reactions, including some of the more notable cyclizations such as ene-yne/ene-allene cyclizations,\textsuperscript{28} catalytic Pauson-Khand reactions,\textsuperscript{29} and intramolecular Heck reactions.\textsuperscript{30}
1.1.3.2.1 Palladium-Catalyzed Enyne Carbocyclization

Five-membered carbo- and heterocyclic rings serve as common structural units in natural products. Transition metal catalyzed ene-type carbocyclizations of 1,6-enynes such as cycloisomerization, metatheses, and the ene reaction are amongst the synthetic methods leading to five-membered rings. (Scheme 1.15).

Scheme 1.15: Typical Transition Metal-Catalyzed Carbocyclization of 1,6-enynes

Among the transition metals, Ti, Ru, Co, Rh, Ni, Cr, Pd and Pt have all been successfully employed in the enyne cyclizations. The palladium(II)-catalyzed carbocyclization reactions of 1,6-enynes have generally been performed with Pd(OAc)$_2$ or by the combined use of Pd$_2$(dba)$_3$·CHCl$_3$ and a weak acid such as acetic acid or trifluoroacetic acid (Scheme 1.16).

Scheme 1.16: Palladium-Catalyzed Carbocyclization of 1,6-Enynes
1.1.3.2.2 Palladium-Catalyzed Pauson Khand Cyclization

Another common annulations method for the formation of cyclopentane derivatives is the Pauson-Khand reaction (PKR).\textsuperscript{36} The PKR is formally a [2+2+1] cycloaddition involving an alkyne, alkene and a carbon monoxide to form a cyclopentenone. In addition to the most commonly used process catalyzed by Co-metal,\textsuperscript{37} the reactions using other transition metals have been reported.\textsuperscript{38}

More recently, the use of PdCl\textsubscript{2} coordinated to a thiourea ligand was also found to be a suitable catalytic system for an intramolecular PKR (Scheme 1.17).\textsuperscript{39} As seen in Scheme 1.17, despite a low yield, the reaction proceeds under mild conditions with temperatures of 50 °C under balloon pressure carbon monoxide.

**Scheme 1.17: Palladium-Catalyzed Intramolecular PKR**

1.1.3.2.3 Palladium-Catalyzed Heck Reaction

The palladium-catalyzed intramolecular Heck reaction is an extremely valuable approach towards the synthesis of various carbocyclic and heterocyclic ring systems\textsuperscript{40}
The first example of the intramolecular Heck reaction was reported by Mori and Ban in 1977 (Scheme 1.18).[^41] The indole is formed through a Pd-H mediated isomerization of the product olefin.

**Scheme 1.18: Palladium-Catalyzed Intramolecular Heck Reaction**

![Scheme 1.18](image)

The above palladium-catalyzed carbocyclization reactions serve as extremely valuable tools in organic synthesis. However, in comparison to our X-Y addition/cyclization reactions, one disadvantage for these more traditional cyclizations is the ‘depletion’ of the reactive π-bond (as opposed to the formation of a vinyl silanes/stannane/borane derivative) resulting in the lack of functional handles for subsequent manipulation.

1.1.3.2.4 Palladium-Catalyzed Bismetallative [X-Y] Cyclization Reaction

1.1.3.2.4.1 Silylstannylative Addition/Cyclization of Unsaturated Systems

The RajanBabu group has given increased attention to the use of transition-metal-catalyzed bismetal functionalization-cyclization of unsaturated organic compounds as
tools for the construction of cyclic compounds (Scheme 1.19). This constitutes a synthetically important method for the preparation of products containing two different metal functionalities which allow for numerous subsequent synthetic applications.

**Scheme 1.19: Model [X-Y] Cyclization of 1,\(n\)-Diyne**

Bismetallative cyclization between two unsaturated systems in a tether can be seen as useful in synthetic organic chemistry, leading to cyclized substrates containing an active metal-carbon bond. Though these bismetallative reactions can be considered uncommon, increased attention by our group has been on the transition-metal-catalyzed cyclization of unsaturated organic compounds with silylstannanes (\(X-Y = \text{Si-Sn}\)) and borostannanes (\(X-Y = \text{B-Sn}\)).

Ito has reported that *ab initio* theoretical studies support a mechanism that proceeds with high regioselectivity in the proposed catalytic cycle, which involves: a) an exothermic oxidative addition of \(R_3\text{SiSnR}_3\) to a \(\text{Pd}(0)\) species to give a \(\text{Pd}(II)\) adduct; b) coordination of the alkyne; c) insertion of the alkyne into the \(\text{Pd-Sn}\) bond as the rate determining step; d) and lastly, reductive elimination to give the silylstannane product (Scheme 1.20).\(^{42}\)
Previous work in the RajanBabu group focused on the palladium-catalyzed silylstannylation reactions of 1,6-diyynes,\textsuperscript{43} 1,6-allenyynes,\textsuperscript{43b} and allenealdehydes (Scheme 1.21).\textsuperscript{26c} It was found that cyclization was possible with 1,6-diyynes when reacted with Bu\textsubscript{3}SnSiMe\textsubscript{3} in the presence of a Pd(0)-catalyst. This results in good yields with high regio- and stereoselectivity to afford (Z,Z)-1,3-diene. In these reactions, only Z,Z-dienes are formed, and common functional groups such as silyl and alkyl ethers, esters, amides, nitriles, chlorides and even free amines and alcohols in the starting diynes are tolerated. The structures and configurations of the (Z,Z)-diene adducts have been rigorously established by multinuclear (\textsuperscript{1}H, \textsuperscript{13}C, \textsuperscript{119}Sn) NMR methods, and in one case, by X-ray crystallographic analysis of a solid derivative.
Scheme 1.21: [X-Y] Addition-Cyclizations of 1,n-Diynes, 1,n-Allenynes and Allenealdehydes

We expected the rate of the helical isomerization process in the diyne adducts (Scheme 1.22) to depend on the size of the groups on Si and Sn, and the substitution pattern around the ring. However, these fascinating systems exhibit a low activation barrier (ΔG^≠ < 60 kJ/mol at ~ 25 °C) irrespective of the substituents on the Si- and Sn-groups.

Scheme 1.22: Fluxional Behavior of Non-planar 1,3-Dienes
Dynamic NMR spectroscopy studies have shown that in solution, these monocyclic systems undergo a fast equilibration between the two helically chiral isomers at room temperature (Scheme 1.22).\textsuperscript{44} This equilibration process can be monitored by variable temperature (VT) NMR spectroscopy (Scheme 1.23). VT experiment constitutes a lowering/raising of temperature which influences the rate of equilibration observed at that particular temperature. Lowering the temperature of the reaction will ultimately slow down or freeze the isomerization of the helical isomers. At this point, the coalescence temperature (T\textsubscript{c}) of the isomers is reached, indicated by a broadening of the peaks representing the diastereotopic protons, ultimately splitting between each other. The diastereotopic methylene protons (H\textsubscript{A} and H\textsubscript{B}) in 1.61, which appear as a broad singlet above 298 K, but as two AB quartets below 257 K, were used to accurately measure the kinetic parameters for the enantiomerization by line shape analysis.\textsuperscript{44}

The fast helical isomerization of the silylstannane products at room temperature hinders our ability to explore the utility of the helically chiral system. However, if this atropisomerization can be ‘frozen’, the helical chirality can be exploited to transfer chirality to other centers in the molecule, more specifically the carbons of the newly formed carbon-carbon bond.
Scheme 1.23: a) Experimental (left) and calculated (right) $^1$H-NMR line shapes due to the methylene groups of 1.61 at various temperatures with derived rate constants b) Helical Isomerization of 1.61

One limitation associated with the silylstannane cyclization is the lack of regioselectivity with the use of unsymmetrical diynes, which results in a mixture of products (Scheme 1.24).

Scheme 1.24: Silylstannylation Regioselectivity Issue
Another disadvantage is that though the silylstannylation reactions paired with cyclizations are useful, the addition of the silylstannane moiety is not always accompanied with cyclization. Monoaddition is seen to occur with the use an unsymmetrical diyne substrate or substrates that form rings sizes other than cyclopentane derivatives (Scheme 1.25), or in certain electronically differentiated diyne precursors.

**Scheme 1.25: Silylstannane Addition Favored over Cyclization**

When the starting diyne contained an electron-rich and an electron-deficient acetylene, the addition to the electron-deficient acetylene moiety was favored, with no accompanying cyclization product observed. No cyclization product was detected even when attempting to ‘force’ the cyclization at temperature of 60 °C for 3 days, resulting only in the diaddition product.\(^{45,46}\)

Through the use of a terminal and internal-acetylene present within a given substrate, the steric influence of the acetylene moiety can be determined. It was found that addition was observed only to the terminal acetylene resulting in the chemoselective...
addition of the SnR₃ to the internal position, and the SiR₃ to the terminal position forming a (Z)-1,2-alkene (Scheme 1.26).

**Scheme 1.26:** Silylstannylation- Terminal versus Internal Acetylene

While the Pd-catalyzed silyl-stannylation-cyclization is a very useful reaction for the synthesis of highly functionalized cyclopentanoid compounds from diynes, allenynes and allene-aldehydes, its use for the synthesis of carbocyclic and heterocyclic compounds of other ring sizes is severely limited. In several substrates carrying a coordinating propargylic or homopropargylic substituent, dimerization of the starting material was observed. Two examples of this dimerization are shown in Scheme 1.27. In these cases no cyclization products were detected under the reaction conditions.

Though these addition products can be useful in their own right, we specifically want to focus our attention on the bismetallic X-Y addition-cyclization reactions where cyclization is the major product in order to study the atropisomerization effect associated with the 1,3-diene products.
**Scheme 1.27: Dimerization of Substrates 1.75 and 1.77**

In order to promote cyclization being favored as the major product, as opposed to a mixture of mono-/diaddition products identification of the most optimal \([X-Y]\) reagent is necessary. One option is the use of a different bifunctional reagent such as a borostannane which has been shown to have better reactivity towards the more challenging substrates\(^{43,45}\) (i.e. internal acetylenes and enynes) (Scheme 1.28). Another alternative is the use of a more reactive substrate, such as allenynes.\(^{43}\) However, we are currently focused on identification of an \([X-Y]\) reagent to allow facile cyclization and subsequent formation of the helically chiral diene product.
Scheme 1.28: Allenyne Cyclization with various X-Y Reagents

1.2 Palladium-Catalyzed Borostannylations of Unsaturated Systems

1.2.1 Scope of the Reaction

In 1996, Tanaka first reported on the palladium catalyzed borylstannylation of alkynes, using 1,3-dimethyl-2-(trimethylstannyl)-2-bora-1,3-diazacyclopentane 1.80 and PdCl₂(PPh₃)₂ to form, presumably, cis-boryl(stannyl)palladium species which underwent highly regioselective and stereoselective addition to alkynes in high yields (Scheme 1.29).
Scheme 1.29: Addition of Borostannane to Acetylene

![Scheme 1.29: Addition of Borostannane to Acetylene](image)

Then in 1997, Tanaka extended the use of borostannylation reagents in the palladium-catalyzed addition-cyclization of 1,6-enynes (Scheme 1.30).\(^{47}\) The proposed catalytic cycle of the borostannylation reaction was consistent with previous cyclization reactions mediated by hydrostannation and silylstannylation of enynes observed by the research groups of Lautens and Mori.\(^{48}\)

Scheme 1.30: Borostannylation Cyclization of an Enyne

![Scheme 1.30: Borostannylation Cyclization of an Enyne](image)

Tanaka also reported on the use of catalytic amounts of palladium(II) and borylstannane 1.80 in the cyclization of 1,\(n\)-diynes (Scheme 1.31).\(^{49}\)
Scheme 1.31: [B-Sn] Addition/Cyclization of 1,\(n\)-Diyne Substrates

Results have been consistent with most other borylstannane additions reactions resulting in high yields and high selectivity. This methodology was further extended to additions of 1,2- and 1,3-dienes (Scheme 1.32). Under palladium-catalysis, addition of borylstannane 1.80 to 3-methylbuta-1,2-diene gives a 1:2 telomer 1.89 as the major product, as well as regioisomers of the simple borylstannane addition product 1.90. Addition of the borylstannane to 1,3-dienes proceeded with high regio- and stereoselectivity resulting in the formation of (Z)-1-boryl-4-stannyl-2-butenes 1.92.
As mentioned, the silylstannylation chemistry has been extensively studied, and is advantageous: but it also has serious limitations as previously indicated and seen in Scheme 1.25, 1.26, and 1.27. One of our major goals was the identification of the most optimal [X-Y] reagent that would allow facile cyclization and subsequent chemistry of the installed functionality for carbon-carbon or carbon-heteroatom bond formations. However, a severe limitation of the silylstannane chemistry has been the more favorable formation of acyclic product via simple 1,2-additions as opposed to any corresponding cyclization product.
Scheme 1.33: Extension of Borylstannylation Diyne Precursors

An examination of other bismetallative cyclizations such as borostannylation reactions reveal that this reaction with a [B-Sn] reagent have been limited to simple, symmetric diyne systems with only a limited number of more ‘complex’ examples being studied (Scheme 1.33). Application of the [X-Y] addition/cyclization reaction was attempted on several substrates intended to be precursors for natural products. These include the cyclization of 1.93 towards the synthesis of indolizidines related to the pumiliotoxin core such as 1.94. Diyne 1.95 was used in the attempted synthesis of kainod derivatives, while substrate 1.97 was used in the preparation of the core of a
dibenzocyclooctadiene natural products. However, in most instances, the adducts were only incompletely characterized due to isolation issues, such as sensitivity to moisture as well as decomposition upon silica gel column chromatography purification.

Also lacking is the broadening of the borostannylation-cyclization towards the synthesis of more complex target molecules, and a study of the functional group compatibility of the reaction. Hence, we have set our goals to investigate the scope and limitations of this system. The use of more complex 1,\textit{n}-diynes will be explored in greater detail. While the use of a 1,\textit{n}-diyne can present a regioselectivity issue, other substrates such as the allenynes and enynes motifs remain mainly unexplored. It is also useful to study the backbone structure of the starting diyne in order to possibly control or limit any atropisomerization. Therefore, we want to study the effect of the formation of a bicyclic product with the hope of freezing the isomerization process at lower temperatures. Exploration of these topics, along with studies on the derivatization of the cyclic products will lay the ground work for the synthesis of natural product targets that can be approached by the bismetallative cyclization strategy.
To facilitate these studies, a modified procedure for the synthesis of the borostannane 1.80 has been developed by our group (Scheme 1.34). Modification of the original procedure reported for the preparation of borostannane 1.80 consisted the use of a cooled, slow addition of boron trichloride 1.100 to triethylamine in hexanes to maintain the temperature below 5 °C, followed by addition of N,N'-DMEDA and refluxing for 6 h to prepare intermediate 1.101. During the isolation of intermediate 1.101 it is extremely important to not expose the product to moisture. The cooled reaction mixture is then filtered using Schlenk-glassware to ensure a moisture-free environment, followed by concentration of the boryl chloride under vacuum pressure using a warm water bath. The crude diazaboracyclopentane derivative is added to a freshly prepared solution of trimethyltin lithium and the mixture stirred for 2 h at room temperature. Isolation of 1.80 occurs using a similar, corresponding method as that of intermediate 1.101 to give 1,3-dimethyl-2-trimethylstannyl-2-bora-1,3-diazacyclopentane.
as a colorless liquid in 53 % overall yield, a major improvement from the initial reported 20 % overall yield.

**Scheme 1.35: Borostannylation of Alkynes and Enynes**

Our group has also recently reported on the scope and limitations of the borylstannane addition to alkynes and enynes, as well as selected examples of further selective functionalization of the alkene products (Scheme 1.35). A number of the possible derivatization reactions have included a tandem Stille/Suzuki reaction of a borostannyl alkene, as well as utility of the bismetalated diene for a Diels-Alder reaction (Scheme 1.36).
Scheme 1.36: Functionalization Reactions of Borostannyl Alkenes

a) Tandem Stille/Suzuki Reaction

\[ \text{Scheme 1.36: Functionalization Reactions of Borostannyl Alkenes} \]

\[ \text{(1.110) PdCl}_2(\text{CH}_3\text{CN}) (5 \text{ mol}) \text{ Ph-I, DMF, rt, 14 h} \]

\[ 86 \% \]

\[ \rightarrow \]

\[ \text{(1.111) Pd(PPh}_3)_4 (2 \text{ mol}) \text{ K}_2\text{CO}_3, \text{EtOH} \]

\[ \text{toluene, 60} \degree \text{C, 2 h} \]

\[ 90 \% \]

\[ \rightarrow \]

\[ \text{(1.112)} \]

b) Diels-Alder Reaction

\[ \text{(1.113) + (1.114) benzene} \]

\[ 60 \degree \text{C, 12 h (quant.)} \]

\[ \rightarrow \]

\[ \text{(1.115)} \]
REFERENCES: CHAPTER 1


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CHAPTER 2:
DEVELOPMENT OF THE PALLADIUM-CATALYZED BOROSTANNYLATION-
CYCLIZATION REACTIONS OF 1,n-DIYNES TOWARDS THE FORMATION OF
HELICALLY CHIRAL 1,2-DIALKYLIDENECYCLOALKANES

2.1 Introduction

Chirality serves as an important concept in all areas of organic chemistry; and plays a major role in pharmaceutical and industrial practices. A chiral molecule lacks an internal plane of symmetry and has a non-superimposable mirror image. This property can be attributed to conformational or configurational effects of the structure on the compound. Compounds which do not contain an asymmetrically substituted atom may still be considered chiral if they possess an axis of chirality; comprised of two unsymmetric planes which cannot freely rotate against each other are deemed axially chiral. Stereoisomers that display axial chirality resulting from the restricted rotation about a single bond are called atropisomers.

A majority of the synthetic applications involving axial chirality include biaryl structural components, which make up a large number of optically active natural products, and serve as the basis of a versatile class of ligands used in asymmetric
catalysis. Besides these well known biaryl examples, helical chirality is also observed in substituted allenes, 1,3-buta dienes and alkylidenecycloalkanes (Figure 2.1). Despite the ever common presence of 1,3-dienes in synthetic applications, the chirality associated with these systems has not been extensively studied.

Figure 2.1: Axially Chiral Systems

![Axially Chiral Systems](image)

R¹ ≠ R²; R³ ≠ R⁴ (for examples a and b)

Development of processes that produce axially chiral products in an atropselective manner can serve as desirable tools in natural product synthesis. Conceptually, it should be possible to devise asymmetric methods for stereoselective preparation of chiral compounds as single enantiomers. Therefore a major objective of the RajanBabu group has been the examination of the catalytic and highly regio-, chemo- and stereoselective cyclization of diynes with the use of a heterobimetallic reagents (X-Y; X-Y = boron, silicon, and tin) resulting in the formation of a novel axially chiral (Z,Z)-1,3-dienes.

Scheme 2.1: Conformations of 1,3-Butadiene

![Conformations of 1,3-Butadiene](image)
1,3-Butadienes can exist as a mixture of two minimum energy conformers, the s-cis or s-trans conformations with the nearly planar s-trans rotamer separated from the s-cis rotamer by a barrier of rotation of 6-7 kcal/mol\textsuperscript{56} (Scheme 2.1) in unsubstituted 1,3-butadienes. Despite the s-trans conformation being the more stable of the two conformers, a wide variety of reactions can occur through the s-cis configuration including the commonly utilized [4+2] cycloaddition reactions. Rotation about the C\textsubscript{2}-C\textsubscript{3} sigma-bond occurs readily, especially at elevated temperatures.

Different steric interactions exist within the diene framework including those seen in Figure 2.2, all of which introduce strain into the rotamer system. Dependent upon the substitution pattern, substituted 1,3-butadiene systems can exhibit all of these steric interactions, which affect the stability of various isomers and thus our ability to prepare carbon-carbon double bonds in a particular pattern and with defined configurations.

**Figure 2.2:** Steric Interaction of a 1,3-Diene System

![Steric Interaction of a 1,3-Diene System](image)

Additional studies on the structural analysis of chiral 1,3-butadienes through the use of dynamic experiments and molecular modeling were reported by Grosu et. al.\textsuperscript{57} It was shown that the terminal R\textsubscript{1} substituents on the 1,3-butadiene system (Figure 2.2) are not directly involved in the hindrance of the rotation about the C\textsubscript{2}-C\textsubscript{3} bond. However, if
the substituents are large enough they can contribute to an increase in the barrier of rotation through a buttressing effect.

The buttressing arises from an indirect steric effect of a substituent group on a remote position in a compound that increases the repulsive forces of the \( \pi \)-system at the coplanar transition state, ultimately raising the torsional barrier (Figure 2.3) The concept of this steric effect has been known for quite some time, but is mainly used in reference with axially chiral aromatic compounds.\(^5\)

**Figure 2.3:** Buttressing Effect and Barrier of Rotations/Atropisomers

Control of the atropselectivity of the 1,3-diene system between its two conformers can occur through raising the rotational barrier by the placement of bulky substituents about the central \( \sigma \)-bond of the diene system.\(^5\) The interaction between the substituents on the 1,3-butadiene system can result in the compound adopting a non-planar configuration of the diene motifs with a high barrier of rotation about the \( \text{C}_2\text{C}_3 \) bond giving rise to atropisomers that are in equilibration on the NMR timescale. If the interconversion between the diene conformers is relatively slow then we can exploit the chirality and atropselectivity of the diene substrate for subsequent stereoselective transformations.
Initial studies on the hindered rotation around the C2-C3 bond in a 1,3-diene substrate were first reported in 1967 by Böer, et. al.\textsuperscript{59} (Figure 2.4). This rotation was considered to be frozen due to the intramolecular interaction between an electrophilic Sn-moiety and an appropriately placed Br (Figure 2.4, 2.1). Later, Köbrich demonstrated that the barrier to rotation ($\Delta G^\ddagger$) in hexasubstituted 1,3-butadienes such as 2,3-dihalo-1,4-tetrabenzyl-1,3-butadiene vary with the size of the halogen (Figure 2.4, 2a-b).\textsuperscript{60,61} The work by Böer and co-workers on the rotation barrier of substituted butadienes has shown that the restricted rotations of the substituted dialkylidenecycloalkanes are due to the intramolecular interactions between the vinyl substituents. As seen in compounds 2.1, 2.2a, and 2.2b in Figure 2.4, the interaction between the halide and the electrophilic Sn-moiety increases the barrier to rotation.

**Figure 2.4:** Examples of Axially Chiral 1,3-Diene Systems

\[
\begin{align*}
2.1 & \quad \Delta G^\ddagger = 75 \text{ kJ/mol, } 87 ^\circ \text{C} \\
2.2a & \quad X = \text{H}, \quad \Delta G^\ddagger = 75 \text{ kJ/mol, } 75 ^\circ \text{C} \\
2.2b & \quad X = \text{Cl}, \quad \Delta G^\ddagger = 88 \text{ kJ/mol, } 140 ^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
2.3a & \quad X = \text{Cl}, \quad \Delta G^\ddagger = 70 \text{ kJ/mol, } 60 ^\circ \text{C} \\
2.3b & \quad X = \text{Br}, \quad \Delta G^\ddagger = 102 \text{ kJ/mol, } 40 ^\circ \text{C} \\
2.3c & \quad X = \text{I}, \quad \Delta G^\ddagger = 143 \text{ kJ/mol, } 131 ^\circ \text{C} \\
2.4a & \quad R = \text{CH}_3, \quad \Delta G^\ddagger = 70 \text{ kJ/mol, } 54 ^\circ \text{C} \\
2.4b & \quad R = \text{H}, \quad \Delta G^\ddagger = 68 \text{ kJ/mol, } 53 ^\circ \text{C}
\end{align*}
\]
Compounds \textbf{2.3a-c} and \textbf{2.4a-b} were analyzed by X-ray diffraction revealing a perpendicular orientation of the planes of the double bonds. At room temperature these compounds exhibit conformationally biased structures resulting in prochiral center of the methylene (CH$_2$) groups. Grosu and coworkers used variable-temperature NMR (VT-NMR) experiments to determine the rotational barriers induced by the hindered rotation of the molecules \textbf{2.3a-c}, and \textbf{2.4a-b}. The corresponding barrier to rotation values of compounds \textbf{2.3a-c} increase when increasing the values of the van der Waals radii of the halogen atoms.$^{57}$

VT-NMR was also used to determine the effect of the interacting internal substituents on the barrier to rotation of butadiene systems such as \textbf{2.4a} and \textbf{2.4b}. Butadienes containing a tetrachloro-diene core have a barrier to rotation of approximately 69 kJ mol$^{-1}$. Variation of the ethereal R-groups on \textbf{2.4a} (R = CH$_3$) and \textbf{2.4b} (R = H) were observed to show a slight buttressing effect.$^{57}$

\textbf{Figure 2.5:} Rotational Barrier of Dialkylidene cycloalkanes

Free energies of activation for enantiomerization in the 1,2-bis-alkylidene cycloalkane derivatives were also determined by dynamic NMR methods, with
results indicating a relationship between the ring substituents and the activation parameters. For example, as seen in Figure 2.5 the $\Delta G^\neq$ for the N-chlorosulfonyl imine 2.5 is above 105 kJ mol$^{-1}$ and the related compound 2.6 undergoes facile isomerization at room temperature ($\Delta G^\neq = 42$ kJ mol$^{-1}$). The presence of heteroatoms (e.g., Figure 2.5, 2.7a, 2.7b) in the ring and size of the ring also were found to affect the rates of these processes.

The ability of such axially chiral systems as alkylidene cycloalkanes to undergo atropisomerization has been recognized for almost 40 years. The studies include reports on the preparation and utility of these systems, reactivity towards Diels-Alder reactions, as well as UV and NMR spectroscopic studies. However, the accompanying chirality associated with these complexes had not been widely reported on in the initial publications.

Transition-metal catalyzed carbocyclization reactions of unsaturated species are useful methods for the preparation of a variety of carbocycles or heterocycles with high efficiency and selectivity.

Construction of a new C-C bond through the [X-Y] cyclization of diynes can lead to the formation of the cyclic 1,2-bis(alkylidene) compounds while preserving the functionality of the starting material in the formation of the remaining double bond. The major synthetic utility associated with the formation of axially chiral 1,2-alkylidene cycloalkanes from simple precursors lies with the ability of the product to act as reaction partners in further transformation reactions (e.g. Diels-Alder, Sn-halogen exchange, cross coupling reactions, etc.).
Research in our group has focused on the transition metal catalyzed additions and cyclizations of unsaturated systems with a hetero-bifunctional reagent (X-Y), where we have looked at the use of silylstannanes (X-Y = Si-Sn) and borostannanes (X-Y = B-Sn). Our focus has been on the axial chirality associated with the cyclization product, as well as possible transformation reactions of the resultant dienes. One leading example deals with the silylstannane reaction with a biphenyl derivative such as compound 2.8 (Scheme 2.2).Attempts at cyclization with a silylstannane reagent resulted in addition products with and without cyclization (Scheme 2.2, 2.9, 2.10, and 2.11). In these instances, the putative Pd-Csp2 intermediates formed in the first step of the reaction are reluctant to participate in the cyclization event, leading to early reductive elimination with the formation of the 1,2-silylstannane.

While screening other similar [X-Y]-reagents, for the cyclization of the diyne 2.8 we again found that it underwent highly regio- and stereoselective (atropselective) cyclization upon reaction with Me3Sn-B[-N(Me)CH2CH2(Me)N-] 1.80 in the presence of PdCl2(PPh3)2 to give a single product 2.12 (Scheme 2.2).
Scheme 2.2: Examples of [X-Y] Additions With and Without Cyclization

Tanaka was the first to report on the formation of axially chiral 1,2-alkylidene cycloalkane via cyclization 1,n-diynes with the borylstannane reagent 1.80.\textsuperscript{68a} The cyclization product 1.81 contains both a vinyl borane and vinyl stannane motif and the structure of the diene moiety was distorted from planarity, with a dihedral angle of 39° as shown in the ORTEP drawing (Figure 2.6).

Figure 2.6: ORTEP drawing of Borostannylation Cyclization Product 1.81
Additional work by the Tanaka group reported on the borostannane additions to an acetylene in which the vinyl stannane/vinyl borane containing product undergoes subsequent cross-coupling reactions\textsuperscript{71} in the one-pot Suzuki-Miyaura and Kosugi-Stille coupling reactions (Scheme 2.3)

**Scheme 2.3: Tandem Suzuki/Stille Cross-Coupling Reaction**

![Scheme 2.3: Tandem Suzuki/Stille Cross-Coupling Reaction](image)

While recent reports by our group\textsuperscript{70,72} have shown that the utility of the alkenyl products can extend their synthetic potential in selective transformations such as an oxidation reaction (Scheme 2.4) a tandem Suzuki/Stille reaction and a Diels-Alder reaction as previously seen in Chapter 1, Scheme 1.36.

**Scheme 2.4: Oxidation Reactions of Borostannylation Products**

![Scheme 2.4: Oxidation Reactions of Borostannylation Products](image)

Additional work in the RajanBabu group is focused on the use of the borostannane reagent 1.80 in the synthesis of natural product derivatives of the
dibenzocyclooctadienes and aryltetralin class. Other efforts are directed at kainoid amino acids (Figure 2.7).

**Figure 2.7: Possible Natural Product Targets**

The choice of the biphenyl scaffolding is based on two premises besides the obvious similarity to the backbone of the dibenzocyclooctadienes (Figure 2.7), key targets in our synthesis efforts. In addition, this system would permit examination of hitherto unexplored aspects of stereocontrol via chirality transfer (axial to axial) from the biphenyl system to a newly created helical moiety. Since the cyclized product has two
elements of axial chirality, it is conceivable that there is some atropselectivity in the formation of the non-planar diene, i.e., a preference for the formation one of the diastereomers \( (R_a^*R_a^* \text{ or } R_a^*S_a^*) \).

Based upon the established precedence for the addition-cyclization of B-Sn on simple diynes, we want to further extend the scope of the borostannylation reaction to substrates with a more hindered backbone, in the hopes that the steric effects involved will influence the rate of atropisomerization. We also want to examine further modifications of the boron- and/or tin-moietys.

Despite the emergence of recent interest in the heterobismetal functionalization (X-Y) reactions of unsaturated systems, a more detailed investigation into the borostannylation process is of particular synthetic interest because of the use of relatively simple precursors (e.g. \( 1,n \)-diynes) providing regio- and stereoselective access to axially chiral \( (Z,Z) \)-1,3-dialkylidene-cycloalkanes containing vinyl borane and vinyl stannane functionalities.

The corresponding axial chirality associated with the preparation of alkylidencycloalkanes is also of interest since this chirality rarely been exploited in previous work. This approach can serve as a useful stereoselective method towards the synthesis of a number of natural products as shown in Figure 2.7.
2.2 Progress in the Borostannylation-Cyclization 1,\textit{n}-Diynes

Optimization of the borylstannane cyclization of enynes and diynes by Tanaka and co-workers has shown the use of Pd(0) and Pd(II) species as efficient catalyst systems (Scheme 2.5).

**Scheme 2.5: Borostannylation Cyclization of 1,\textit{n}-Diyne**

Borylstannane addition to 1,3-dienes were shown to proceed cleanly when done in the presence of Pd-etpo catalyst (Scheme 2.6). However, the use of PdCl$_2$(PPh$_3$)$_2$ with the reaction of isoprene under similar reaction conditions resulted in a lower yield, along with the extensive formation of the protodestannylation product.$^{73}$
The additions to 1,3-dienes were also shown to have a solvent effect under the conditions of heating at 80 °C for 1 h, revealing that the yield of addition increased in more polar solvents [e.g. THF (81 %) > benzene (37 %) > hexane (0 %)]. It was also concluded that the use of the borylstannane reagent, Me₃Sn-B(pinacolate) results in an extensive amount of disproportionation to give B₂pin₂ and Me₆Sn₂ (Scheme 2.7).

**Scheme 2.6: Borostannylation of 1,3-Diene Systems**

**Scheme 2.7: Comparison of Different Borostannane Reagents**
Initial work in this area by our group was directed towards the use of silylstannane reagents (R₃Si-SnR’₃) in the cyclization of 1,n-diynes leading to the facile synthesis of 1,4-disubstituted (Z,Z)-1,3-dienes. However, the product dienes exhibited a relatively fast equilibrium between the two enantiomers on the NMR time scale (ΔG° < 60 kJ mol⁻¹ at ~ 25 °C). Another limitation observed with the use of a silylstannane [X-Y] reagent was the preference for simple addition to the unsaturated system over cyclization on a number of substrates. Since a major goal of the RajanBabu group in this cyclization area is the stereoselective transformation reactions involved with the vinyl metal moieties, a number of objectives must first be established: a) Identification of [X-Y] reagent(s) favoring cyclization over simple addition; b) modification of the diyne substrate or [X-Y] reagent ultimately increasing the barrier for atropisomerization resulting in a relatively slow or no helical isomerization at room temperature. This will allow for the isolation of individual isomers at or near room temperature; and c) control of the stereo- and regioselectivity associated with the cyclization event. Furthermore, the scope and limitations of the borylstannane reaction have not been fully established, which poses a number of issues for future development and use of this addition-cyclization reaction.

From the introductory work focusing on the cyclization reactions, it became apparent that the cyclization reaction could easily be followed by ¹H-NMR spectroscopy. Therefore, we decided to run the optimization reactions in NMR tubes and follow those reactions by ¹H-NMR. The different reagents and products have very distinctive peaks in the spectra (acetylene protons versus vinyl protons). Taking advantage of this aspect
allows for the yields of the cyclization reactions to be determined by NMR, especially in cases in which purification techniques were difficult. When the products could be easily purified, NMR yields and isolated yields were compared and were shown to correlate.

Concerning the borylstannane cyclization our first consideration was directed towards further development in the ability to slow down the rate of the atropisomerization of the product species at or near room temperature. From previous work, we know that the use of an \([X-Y]\) reagent large than what was used in the initial silylstannane studies at the two metal centers while influencing the rate of isomerization, may not help to increase the barrier for the isomerization process. So our focus is turned to the use of diyne precursors which generate a bicyclic product, as opposed to those which in turn produce a monocyclic product (Figure 2.8, b).

**Figure 2.8:** Atropisomerization of \([X-Y]\) Cyclization Products

![Atropisomerization Diagram](image)

Extension of the cyclization to include unsymmetrical diyne substrates would also be beneficial. Even though the use of unsymmetrical diynes can lead to regioselective
issues, it was of interest to explore such substrates to see if any preference of addition can be achieved due to a difference in electronic or steric effects. We will also explore functional group compatibility, and further functionalization of the possible cyclic products including a variety of carbo- and heterocycles (Figure 2.9). Another consideration is whether the use of substrates containing a chiral backbone can lead to preferential formation of diastereomers, possibly allowing for ease of separation of the products earlier on in the derivatization process.

**Figure 2.9:** 1, *n*-Diyne Substrates

- **Symmetrical Diyne Substrates**
  - 2.27
  - 2.28
  - 2.29

- **Unsymmetrical Diyne Substrates**
  - 2.30
  - 2.31
  - 2.32
  - 2.33
  - 2.34
2.2.1 Synthesis of Substrates

The preparation of the known diyne substrates benzyl diyne 2.27,74 the C-2 symmetric dioxolane 2.3075 phenol derivative 2.31,76 aniline derivative 2.32,76 and phenol derivative 2.33,77 were carried out according to literature procedures. The β-lactam 1,6-diyne 2.30, was synthesized from commercially available acetoxyazetidinone 2.35 using a Zn-mediated Barbier type reaction78 by treatment of 2.31 with activated zinc and propargyl bromide to give 2.36 (Scheme 2.8). Propargylation of 2.36 with propargyl bromide under basic conditions led to the formation of diyne 2.30 after 3 h. If held for longer reaction times the allene by-product was observed in approximately 10% yield. Extensive NMR analysis (1H, 13C, nOe, and COSY) of 2.30 was used to determine the configuration at the C-3 chiral center was retained during the preparation of diyne 2.30.

Scheme 2.8: Preparation of Diyne 2.30

The acetate 2.34 was prepared according to Scheme 2.9. Known intermediate 2.38 was acylated using acetyl chloride and NaH, followed by desilylation with TBAF in THF to give the desired diyne 2.34.
2.2.2 Cyclization Results

The diynes were then subjected to the cyclization conditions using borylstannane 1.80 (1.02 equiv), and PdCl$_2$(PPh$_3$)$_2$ (2 mol\%) in C$_6$D$_6$ and the reactions were followed by $^1$H-NMR until completion. The cyclized products were isolated by filtration through Celite, followed by concentration in vacuo and a ‘precipitation’ from pentane with cooling (< 0 °C). The products were characterized with the use of 1D- and 2D-NMR studies (e.g. $^1$H, $^{13}$C, nOe, and COSY). Variable Temperature $^1$H-NMR studies will be discussed in Chapter 3.

Achiral substrates which can form carbocyclic products were originally tested, with all leading to cyclization products in relatively good to high yields (77 – 96 %), as can be seen in Table 2.1. The optimized reaction conditions for the cyclization of these substrates were found to be at 23 °C with 1 mol % PdCl$_2$(PPh$_3$)$_2$ as the catalyst. These substrates were chosen due to the presence of only one pair of enantiomers possible in the cyclization product mixture. Fortunately, all of the 1,n-diynes if Table 2.1 showed clean, full conversion to the cyclization product with no formation of the mono- or di-addition products evident via NMR (e.g. $^1$H, $^{13}$C, COSY, NOESY) and HRMS.
### Table 2.1: Cyclization/Additions on Symmetric Compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Diazaborolidine</th>
</tr>
</thead>
</table>
| 1     | ![Image](2.27) | 1.80 (1.02 equiv) 
PdCl₂(PPh₃)₂ (1 mol %) 
C₆D₆, 40 °C, 3 h | ![Image](2.40) (96)% |
| 2     | ![Image](2.28) | 1.80 (1.02 equiv) 
PdCl₂(PPh₃)₂ (1 mol %) 
C₆D₆, 40 °C, 5 h | ![Image](2.41) (>75)% |
| 3     | ![Image](2.29) | 1.80 (1.02 equiv) 
PdCl₂(PPh₃)₂ (1 mol %) 
C₆D₆, 23 °C, 0.5 h | ![Image](2.42) (77)% |

a. % yield based on isolation. b. % yield based on NMR.

Use of the tetrahydronaphthalene cyclization precursor 2.27 allows for the formation of a simple cyclization product as an enantiomeric mixture. This is advantageous when the cyclized products undergo derivatization reactions, allowing for the ease in product analysis. This cyclization reaction proceeds in facile manner resulting cleanly in the tetralin product 2.40 very high yields. The structure of 2.40 was determined through NMR analysis. The presence of the 1,2-bisalkylidene is confirmed by the observation of one set of vinyl peaks corresponding to a vinyl stannane and vinyl borane in the ¹H-NMR (C₆D₆) at δ 5.72 and 5.42 respectively.
The use of 2,2'-di(3-propynyl)-1,1'-biphenyl 2.28 serves as an important choice of scaffolding for a number of reasons (Scheme 2.10); the first being the similarity to a series of natural products of interest, including highly functionalized dibenzocyclo-octadienes (Figure 2.7). This substrate also allows us to explore stereocontrol aspects such as possible chirality transfer associated with the cyclization reaction and the use of a chiral biphenyl system. It should also be noted that the palladium-catalyzed silylstannylation of the diyne 2.28 resulted in extremely low yields. Substrate 2.28 was treated with the borylstannane 1.80 and PdCl₂(PPh₃)₂ (1 mol %) in benzene-d₆ as solvent until the ¹H-NMR indicated a conversion into the cyclic product 2.41 (typically 20 h at room temperature) by the appearance of vinyl peaks at δ 5.87 and 5.56 ppm corresponding to the vinyl tin and vinyl boron moieties respectively. Fortunately, the borylstannane reagent was seen to be reactive enough to show only the cyclized product in moderate yields with no monoaddition, diaddition or dimerization type products observed in either the ¹H- or ¹³C-NMR spectra. The lack of terminal acetylene protons in the ¹H-NMR indicated addition to the diyne moieties. When paired with the observation of a set of vinyl peaks it can be determined that the cyclized product was formed. The ¹³C-NMR showed only one set of peaks denoting the presence of only one of the possible two diastereomeric pairs was formed during the cyclization event.
Scheme 2.10: [X-Y] Cyclization of 2,2'-Di(3-propynyl)-1,1'-biphenyl 2.28

The cyclization of the biphenyl species can be carried out using PdCl$_2$(PPh$_3$)$_2$ or Pd$_2$(dba)$_3$CHCl$_3$ Feringa phosphoramidite ($L$)	extsuperscript{79} as a catalyst (Scheme 2.10). The latter conditions generally gave a cleaner reaction although the product formed is nearly racemic. Variable temperature NMR spectroscopy showed that this molecule (2.41) or a boron-pinacolate derivative 2.43 prepared from 2.41 does not undergo helical isomerization up to 55 °C. This aspect will be discussed in greater detail in Chapter 3.

Scheme 2.11: [B-Sn] Cyclization of 2,2'-Dipropargylbiphenyl with a Chiral Ligand
Dioxolane 2.29 was prepared from (R,R)-tartaric acid and was chosen for its C₂-symmetry as well as its inability to cyclize under silylstannylation reaction conditions (see Chapter 1, Scheme 1.27). The ditosylate 2.45 was prepared by ditosylation of erythritol 2.44 at -20°C by a reported procedure in 55% yield (Scheme 2.12). Cyclization of 2.45 with aqueous KOH in ether followed by in situ addition of 2 equivalents of lithiated trimethylsilylacetylene followed by BF₃·Et2O to afford the diol 2.47 in 52% yield. This diol on reaction with dimethoxypropane gave the protected diol 2.48 in 92% yield. The removal of TMS groups from 2.48 with catalytic amount of KOH in methanol yielded 93% of the diyne 2.29.

The C₂-symmetry of substrate 2.29 allows for the formation of a total of only two possible products resulting from the atropisomerization of the chiral 1,3-diene product (Scheme 2.13).

**Scheme 2.12: Preparation of Diyne 2.29**

The formation of compound 2.42 was carried out using borylstannane 1.80 and PdCl₂(PPh₃)₂ (1 mol%) in benzene-d₆ as solvent until the ¹H-NMR indicated a clean
conversion into the cyclic product, 2 h at room temperature (Scheme 2.14). As determined by $^1$H- and $^{13}$C-NMR analysis, the borylstannane cyclization of substrate 2.29 was shown to result in the formation of only one of the atropisomers.

Scheme 2.13: Stereoisomers of 2.42

Only one set of vinyl peaks were observed in the $^1$H-NMR for the olefinic protons ($\delta$ 5.619 and 5.325 ppm) and one set of carbon peaks in the $^{13}$C-NMR. The selective formation of only the one isomer over another implies that the cyclization reaction is a highly atroposelective process. Though the configuration of the axially chiral diene 2.42 has yet to be determined, variable temperature $^1$H-NMR (toluene-d$_8$) of the boron-
pinacolate derivated 2.42 showed the diene system to be frozen at room temperature (see later).

**Scheme 2.14: Cyclization of Diyne 2.29**

The variety of functionalized carbo- and heterocycles resulting from the cyclization of substituted benzene derivatives can be envisioned to include the chroman, quinoline, and benzofuran derivatives resulting from cyclization of corresponding diyne derivatives (Figure 2.9). Attention therefore turned to a series of unsymmetrical diyne substrate which incorporated a variety of backbone structures, including the azetidinone motif with a fixed stereogenic center (Table 2.2).

Some obvious issues associated with these substrates relate to regioselectivity and stereoselectivity in the formation of a variety of isomeric products. Additionally, other by-products not involving cyclization (e.g. monoaddition, diaddition, dimerization, etc.) can also occur. Analytical data including NMR ($^1$H, $^{11}$B, $^{13}$C, $^{119}$Sn), IR, and HRMS were collected for all of the cyclized product(s). If monoaddition has occurred, this can easily be seen in the $^1$H NMR with the retention of a terminal alkyne proton, while the
diaddition product would be most evident in the HRMS along with NMR ($^{11}$B, $^{119}$Sn) analysis.

**Table 2.2:** Cyclization of Unsymmetrical Diynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Diazaborolidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>1.80 (1.02 equiv) PdCl$_2$(PPh$_3$)$_2$ (1 mol %) C$_6$D$_6$, 40 °C, 3 h</td>
<td><img src="image2.png" alt="Structure 2" /> 2.49 A:B 7:3 A) Y = B(N(CH$_3$)$_2$)$_2$, Z = SnMe$_3$ B) Y = SnMe$_3$, Z = B(N(CH$_3$)$_2$)$_2$</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>1.80 (1.02 equiv) PdCl$_2$(PPh$_3$)$_2$ (1 mol %) C$_6$D$_6$, 40 °C, 5 h</td>
<td><img src="image4.png" alt="Structure 4" /> 2.50 A:B* A) Y = B(N(CH$_3$)$_2$)$_2$, Z = SnMe$_3$ B) Y = SnMe$_3$, Z = B(N(CH$_3$)$_2$)$_2$</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>1.80 (1.02 equiv) PdCl$_2$(PPh$_3$)$_2$ (1 mol %) C$_6$D$_6$, rt, 0.5 h</td>
<td><img src="image6.png" alt="Structure 6" /> 2.51 A:B* A) Y = B(N(CH$_3$)$_2$)$_2$, Z = SnMe$_3$ B) Y = SnMe$_3$, Z = B(N(CH$_3$)$_2$)$_2$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>1.80 (1.02 equiv) PdCl$_2$(PPh$_3$)$_2$ (1 mol %) C$_6$D$_6$, rt, 10 h</td>
<td>Complex Mixture$^b$</td>
</tr>
<tr>
<td>5</td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>1.80 (1.02 equiv) PdCl$_2$(PPh$_3$)$_2$ (1 mol %) C$_6$D$_6$, rt, 2 h</td>
<td>Complex Mixture$^b$</td>
</tr>
</tbody>
</table>

a. Identification determined via $^1$H-NMR analysis; structure tentative. b. complex mixture in the $^1$H-NMR with no accompanying product(s) determination
As reported in Table 2.2, all of the unsymmetric diynes are shown to cyclize as evident in the appearance of vinyl protons, with the formation of cyclized regioisomers and monoaddition products in varying ratios.

**Scheme 2.15: [B-Sn] Addition-Cyclization of a β-Lactam Derivative 2.30**

As previously mentioned, isolations of the diene products were attempted by filtration through Celite, followed by concentration, and, where possible, precipitation from pentane at < 0 °C. All of these diazaborolanes are stored in a freezer in C₆D₆, with some decomposition observed after a few days. Due to the sensitivity of the diazaborolanes complexes, all of these heterocycle products were handled in a glovebox and converted to the more stable boron pinacolate derivatives in an attempt to isolate and identify the product mixture. The purification and separation of the dioxaborolane mixture will be addressed later in this chapter.

In the cyclization of β-lactam 2.30, a mixture of diastereomeric B/Sn adducts (7:3) are obtained (Scheme 2.15). The structure of the minor diastereomer has not been determined conclusively, although from NMR studies on the corresponding boron-
pinacolate it appears to be a regioisomer. Treatment of the mixture 2.49A and 2.49B gave the corresponding boron pinacolates 2.52A and 2.52B.

Figure 2.10: $^1$H-NMR Vinyl Region of Product Mixture 2.49A and 2.49B

The NMR spectrum of the cyclization product indicated a mixture of products, with one major component that contains a vinyl tin moiety, as ascertained by the vinyl-hydrogen with $^{119}$Sn couplings (Figure 2.10).

As of yet, only the major β-lactam product isomer 2.49A was isolated as highly crystalline, and its solid-structure analyzed via X-ray crystallography. As can be seen in
Figure 2.11, the solid state structure adopts a non-planar 1,3-diene configuration, helping to establish that the cyclization reaction results in the formation of a (Z,Z)-diene system.

**Figure 2.11:** X-ray structure of 2.49A with Hydrogens Omitted for Clarity

![X-ray structure of 2.49A](image)

The structures of 2.49A and 2.49B were rigorously established by NMR methods including extensive COSY and NOESY measurements of the corresponding boron pinacolate derivatives. Gratifyingly, the chemical shifts and coupling constants are highly diagnostic of a conformation indicated by the solid-state structure of 2.49A.

Variable temperature $^1$H NMR of the major product 2.49A between 27 °C and 55 °C show that these bicyclic compounds do not undergo helical isomerization under conditions where monocyclic adducts are known to be fluxional (see Chapter 3).

The use of a sensitive β-lactam diyne substrate as 2.30 not only is promising since the silylstannylation of a similar substrate resulted in a dimerization product (See Chapter 1, Scheme 1.27), but also extends the functional group compatibility of the borylstannane cyclization. The borostannylation cyclization/addition has shown to be tolerant of a wide
variety of functional groups including amides/lactams, ethers and silyl-ethers, ketals, and esters. It is also advantageous to note that 1,7-diynes and 1,9-diynes showed cyclization results as well. In comparison to the silylstannylation reactions, the use of the more reactive borylstannane towards the cyclization of 1,n-diynes has shown to be highly promising in furthering studies associated of the axially chiral 1,3-diene products as well as any derivatization reactions.

The chroman ring system is amongst an important heterocycle structural class found in many natural products and biologically active compounds. One route to preparing a chroman ring using the [B-Sn] cyclization method is through the use of a substrate such as diyne 2.31.

**Scheme 2.16: [B-Sn] Cyclization of 2.31**

The use of diyne 2.31 can result in the formation of a regioisomeric product mixture 2.50A:B (Scheme 2.16). Reaction with borylstannane 1.80 and PdCl$_2$(PPh$_3$)$_2$ at 40 °C for 5 h results in the formation of a cyclized product, as well as an unidentifiable by-product. Evidence of the cyclized product can be found in the $^1$H-NMR (C$_6$D$_6$) as a vinyl stannane and a vinyl borane signal at δ 6.38 and δ 5.45 ppm, respectively. Also the lack of the starting acetylene proton signals clearly suggests cyclization. Any attempt to isolate
and/or identify the by-product has not been successful. The reaction itself appears to be relatively cleaner via $^1$H-NMR integration analysis and results in the formation of one cyclized product in a significantly higher yield than any other possible by-product. Typical reaction procedures consist of isolation of the pinacolate derivative, however upon addition of pinacol with or without the addition of an H$^+$-source resulted in a complex mixture of products.

Tetrahydroquinoline derivatives also serve as a prominent heterocyclic ring system, attracting interest due to their role as synthetic intermediates in several natural products.$^{32}$ Therefore, the study of the cyclization of the diyne substrate 2.32 would be highly useful. Reaction of 2.32 with the borylstannane 1.80 and PdCl$_2$(PPh$_3$)$_2$ at room temperature for 30 min results in the formation of a cyclized product 2.51. This is indicated in the $^1$H-NMR (C$_6$D$_6$) by the presence of a vinyl tin proton at $\delta$ 6.26 and the corresponding vinyl borane proton at $\delta$ 5.32 ppm (Scheme 2.17).

**Scheme 2.17: [B-Sn] Cyclization of 2.32**

[Diagram showing reaction scheme]

The unknown by-product contains a set of vinyl proton peaks located at $\delta$ 5.77 and $\delta$ 5.59 ppm, however, no conclusive identification can be made at this time. Cyclization
attempts on both compounds 2.33 and 2.34 both resulted in a complex mixture of product in which no single cyclization or addition product could be identified.

2.2.3 Conversion to the Boron-Pinacolate Derivative

One important aspect not to be overlooked is the isolation and purification of the moisture-sensitive 1,2-alkylidene cycloalkane adducts. In any purification and/or transformation reactions the sensitivity of the vinyl borane and vinyl stannane groups must be taken into consideration. The susceptibility of the diaminoboranes to undergo facile hydrolysis over longer periods of time, or in the presence of a protic environment can limit the number of available purification techniques.\(^8\)

Despite this limitation however, the precipitation of these substrates with a non-polar solvent, such as pentane has proven well in removing an excess borylstannane reagent and at times have yielded solid products. One disadvantage as of yet is the lack of a general method of separation of the corresponding diazaborolidine isomers, so when necessary any analysis is done on a mixture of isomers. For this reason, use of a derivatization reaction which results in a more hydrolytically stable product is vital.

The displacement of the dialkylamine from the diazaborolidine by various alcohols to form vinyl boronates is one possible alternative to resolving the hydrolysis limitation of the diazaborolidine. This is a highly useful derivatization step due to the wide versatility associated with vinylboronic acids and esters as intermediates in organic synthesis. The boronate moiety can be converted into hydrogen,\(^8\) an aldehyde or
ketone,\textsuperscript{86} a halide,\textsuperscript{87} an amine,\textsuperscript{88} or an alkyl group.\textsuperscript{89} Notably, 1-alkenylboron compounds are excellent components in Suzuki cross-coupling reactions.\textsuperscript{97}

Conversion to the pinacolate has been investigate\textsuperscript{90} and also allows for the compound to be handled for longer periods of time under atmospheric conditions, including column chromatography, though specific substrates appear to be more or less sensitive to the acidic nature of a silica gel used for column chromatography. This sensitivity necessitates deactivation of the silica by base/solvent prior to the sample loading and elution.

**Scheme 2.18: Pathways Towards the Preparation of the Dioxaborolidine Derivative**

Previous transformations of this type were accomplished by hydrolysis via the simple addition of a slight excess of pinacol with or without heating.\textsuperscript{68c, 91} This exchange reaction, which is somewhat related to the well known acid hydrolysis of boron-nitrogen derivatives, has been used to prepare a number of alkoxyboranes. Application of this procedure to the borostannane products however have been shown to be somewhat problematic; leading at times to the formation of the desired product accompanied with
the protodestannylation product and/or an unidentifiable complex mixture was observed in the $^1$H NMR (Scheme 2.18).

**Scheme 2.19: Derivatization Reaction Conditions of 2.42**

The protodestannylation product serves as a hindrance to studies concerning the helical chirality of the non-planar diene, though in general this substrate can be more useful towards the utility of the cyclization products in selective derivatization reactions. The conversion reactions were monitored by $^1$H-NMR.

As documented in Scheme 2.19, we initially found that the H$^+$-catalyzed exchange of the 1,2-diamino-ligand on boron for a 1,2-dioxa-ligand (2.42 → 2.53) using pinacol is generally applicable to most such adducts, especially those carrying Lewis basic groups. The pinacolate formation from the diazaborolidine allows purification and isolation of the corresponding 1-(borylmethylidene)-2-(stannymethylidene)cycloalkanes.
from a variety of diynes including several instances where the corresponding silylstannylation-cyclization reactions fail (Scheme 2.18).

**Table 2.3: Dioxaborolidine Derivatization**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Diazaborolidine</th>
<th>Reaction Conditions</th>
<th>Dioxaborolidine</th>
</tr>
</thead>
</table>
| 1     | \[
\text{C}_6\text{H}_6\]

2.27 | \[
B\text{SnMe}_3
\]

2.40 | Pinacol (1.02 equiv) C\(_6\)H\(_6\), rt, 0.5 h | \[
B\text{SnMe}_3
\]

2.55 |
| 2     | \[
\text{C}_6\text{H}_6\]

2.28 | \[
B\text{SnMe}_3
\]

2.41 | Pinacol (1.02 equiv) C\(_6\)H\(_6\), rt, 6 h | \[
B\text{SnMe}_3
\]

2.43 |
| 3     | \[
\text{C}_6\text{H}_6\]

2.29 | \[
B\text{SnMe}_3
\]

2.42 | Pinacol (1.02 equiv) C\(_6\)H\(_6\), rt, 0.5 h | \[
B\text{SnMe}_3
\]

2.53 |
| 4     | \[
\text{C}_6\text{H}_6\]

2.30 | \[
B\text{SnMe}_3
\]

2.49A | Pinacol (1.02 equiv) C\(_6\)H\(_6\), rt, 1 h | \[
B\text{SnMe}_3
\]

2.52A |

Using this isolation protocol, the functional group compatibility of the [B-Sn]-mediated cyclization and its relative advantages as compared to the corresponding [SiSn]-mediated
reaction can be ascertained. Clean conversions were observed for the diazaborolidines shown in Table 2.3 in moderate to high yields. One exception was in the formation of compounds 2.49A and 2.49B as a product mixture. In this case, a significant loss of yield during the column purification step, even with deactivation of the column with a 2% triethylamine-hexanes/ethyl acetate (4:1) solvent system was seen.

Structures of the dioxaborolidines were confirmed by extensive NMR analysis including COSY and nOe measurements. As determined by $^1$H and $^{13}$C-NMR, all entries of Table 2.3, the borylstannylation cyclization proceeds exclusively to give only one of the possible atropisomers of the newly formed axially chiral 1,3-diene, including the cyclization of enantiomerically pure $\beta$-lactam 2.30. In this case a regioisomer was also formed.

Figure 2.12: $^1$H-$^1$H COSY NMR Analysis of 2.53

![COSY NMR Analysis of 2.53](image)

The conversion of biphenyl diazaborolidine 2.41 into 2.43 was complicated by destannylation (characterized by peaks at $\delta$ 5.63 (s, 1 H), 5.27 (d, $J = 2.0$ Hz, 1 H), 5.10
(d, J = 2.0 Hz, 1 H), and thus the product obtained in impure form. However, the starting diazaborolidine 2.41 was isolated as a pure compound and was fully characterized.

The structure that best fits the data for the adduct 2.53 is shown in Figure 2.12, with the assignments being confirmed by double irradiation and $^1$H-$^1$H COSY experiments.

Treatment of the mixture 2.49A and 2.49B gave the corresponding boron pinacolates 2.52A and 2.52B whose structures were rigorously established by NMR methods including extensive COSY and NOESY measurements (Figure 2.13).

**Figure 2.13: nOe Diagrams of Dioxaborolidine’s 2.49A and 2.49B**

The facile conversion of substrates 2.27, 2.28, 2.29, and 2.30 allows for the study of the fluxional behavior of the 1,2-bisalkylidenes containing a vinyl borane and vinyl stannane and this will be discussed in greater detail Chapter 3.

We then turned our attention to the extension of the cyclization reaction to include a variety of heterocycles; however using diynes 2.31-2.34 results were in general unsatisfactory with the product formation accompanied by a significant amount of destannylation and possibly deborylation (Scheme 2.20). This was concluded by the
extensive number of peaks appearing in the vinyl proton region of each $^1$H-NMR spectra of each of the dioxaborolidines. Attempts to separate any of the isomeric products by column chromatography also resulted in significant product loss (>80% from crude material) on the column, even with the base/solvent treatment of the silica gel used for separation.

The general method for the dioxaborolidine formation with clean isolation of the stable product from heterocyclic substrates still needs to be optimized. One option is analysis of a derivative via a tin-halogen exchange followed by boron-pinacolate formation to establish the structure, which will be addressed later in this chapter.

**Scheme 2.20: Dioxaborolidine Derivatization of Diynes 2.31 – 2.34**

The exchange reaction between the diaminoborane and an alcohol has consistently been tested with the use of a pinacol derivative and at times with the use of catechol. Though once the exchange reaction is optimized, one can imagine the inclusion of a variety of diol reactants, including the use of a chiral diol. These studies may be extended to the further transformation reactions of such chiral vinyl boronates.
2.3 Proposed Mechanism and Stereoselectivity

Details of the mechanism of the borostannylation cyclization remain unknown. However, on the basis of observed regio- and stereoselectivities a reasonable mechanism that accounts for these results can be formulated as shown in Scheme 2.21. Oxidative addition of the borylstannane reagent to Pd(0) species generating the cis-boryl(stannyl)palladium (II) species, which has been previously verified by X-ray crystallography. Subsequent cis- insertion of the acetylene into the Pd-B bond over the Pd-Sn, which is supported by the regioselective introduction of the boryl species into the more reactive terminal acetylene; followed by insertion of the second acetylene moiety. At this time, an alternative intermediate from the insertion of alkyne to give the palladacycle intermediate cannot be excluded until further mechanistic studies are conducted. Reductive elimination then gives the cyclized 1,3-diene product with the regenerated Pd(0) species.

Scheme 2.21: Proposed Mechanism of the Borostannylation reaction
2.4 Derivatization Reactions

The bismetal dienes, such as borylstannyl dienes which could in principle behave ultimately as dianion equivalents, serve as highly valuable intermediates upon the selective reaction of either the vinyl borane or vinyl stannane moiety. Another major objective of our group is directed towards the development of stereoselective reactions of the axially chiral 1,3-diene systems, as well as applications towards the syntheses of target compounds such as the functionalized aryltetralins and dibenzocyclooctadienes.

The chemistry of both vinyl stannanes and vinyl boranes are extensively known in a variety of synthetic applications, with select examples given in Scheme 2.22. The nucleophilicity of the carbon-tin bond can be used in reactions such as a selective Stille coupling in the presence of the vinyl-borane.92

**Scheme 2.22: Selective Stille Coupling Reaction**
Other such reactions include tin-halogen exchange, tin-lithium exchange and protodestannylation (Scheme 2.23).

Though a key aspect of these reactions has been focused on the (Z,Z)-orientation of the 1,3-diene, protodestannylation may return the 1,3-diene to a more planar configuration allowing for [4 + 2] cycloaddition-type reactions. In the coupling and halogen exchange reactions, the atropisomerization can be expected to be maintained by replacement of the boron- or tin-group with a sterically bulky group which can increase the barrier for inversion.

**Scheme 2.23: Selected Examples of Possible Derivatization Reactions**
2.4.1 Protodemetallation

2.4.1.1 Protodestannylation

A number of methods leading to the destannylation of vinylstannanes has been reported. Destannylation of compounds stable under acidic conditions is achieved with the use of trifluoroacetic acid, p-toluenesulfonic acid, aqueous hydrogen chloride, or ethanolic hydrogen chloride. Other possibilities include the use of nucleophilic conditions using reagents such as K$_2$CO$_3$ in MeOH, NaOMe in MeOH, or CsF in MeOH-NH$_3$.

During the formation of the boron pinacolate derivatives with the use of pinacol and pTSA·H$_2$O, it was also observed that the protodestannylation product was consistently one of the undesired by-products. Different protic reagents were then used to determine the extent of protodestannylation (Scheme 2.24).

**Scheme 2.24:** Attempted Protodestannylation Reactions
Treatment of 2.55, with either pTSA-H₂O or CSA leads to the formation of the desired destannylation product 2.61 with competing complete demetallation 2.62 in overall yields of 86 % and 83 % respectively. If only one equivalent of the acid is used, then the protodestannylation reaction does not go to completion. In reaction conditions where a large excess of acid is used, the protodestannylation product is observed in the ¹H-NMR, however some of the assumed protodeborylation product is also observed. This was determined by analysis of the ¹H-NMR with the presence of any additional vinyl protons, as well as analysis of the pinacol protons and methyl protons on the boron and tin moiety respectively.

2.4.1.2 Protodeborylation

Solvolysis of a carbon-boron bond is dependent upon the hybridization of the carbon atom connected to the boron atom. The ease of nucleophilic cleavage by reagents such as water, alcohol, and acids is reported as the following:

\[ B{-}C_{sp} > B{-}C_{sp2} > B{-}C_{sp3} \]

Protolytic cleavage of the C_{sp2}-B bond of the cyclization product was attempted with the reaction with dry MeOH (5.0 equiv) leading to the desired product, a mixture of the deborylated/destannylated product, along with other unidentifiable products.
Vinyl peaks corresponding to the protodeborylated product are found at δ 5.18, 4.95, and 4.401 ppm along with the methyl-tin peaks at δ 0.33 ppm.

Lowering the number of equivalents of dry methanol (1.0 equiv) or the use of isopropanol (1.0 equiv) resulted in similar results (Scheme 2.25). The use of a strong acid was not attempted due to the likelihood of competing protodestannylation. Attempted hydrolysis of the boron pinacolate derivative proved to be unsuccessful in giving a selective protodemettallation reaction. Though the protodemettallation reactions have shown some product formation, the amount of by-product associated with the reaction is still too high to be of any practical use. Therefore, further investigations into modifying the reaction conditions or alternate routes are necessary before this problem is solved.

Scheme 2.25: Attempted Protodeborylation Reactions
2.4.2 Tin-Halogen Exchange

Another important derivatization reaction involves a tin-halide exchange reaction where the resulting electrophilic product could take part in coupling reactions. Upon treatment of 2.40 with I₂ (1.02 equiv) in CH₂Cl₂, followed by conversion to the boron pinacolate by addition of pinacol (1.02 equiv) gave the desired vinyl halide product 2.65 in 70 % yield (Scheme 2.26) The corresponding transformations using NBS (1.02 equiv) also resulted in the formation of the corresponding halide complex 2.67 in 68 % yield. However, the use of NCS (1.02 equiv) resulted in the formation of an unidentifiable mixture of compounds, none of which corresponded to the expected product (Scheme 2.26).

Scheme 2.26: Attempted Sn-Halogen Exchange Reactions
Compound 2.65 was characterized by NMR (\(^1\)H, \(^{13}\)C) analysis and the geometry of the double bond was confirmed by nOe analysis. It is clear from nOe studies that the metal-exchange takes place with complete retention of stereochemistry. This new derivatization protocol offers a route to fully substituted 1-(borylmethyldene)-2-(bromomethyldene)--cycloalkanes which are, to the best of our knowledge, new kinds of bifunctional vinyl derivatives with potential applications as linchpin reagents.\(^9\) The effect of the replacement of the Sn-moiety with a halogen on the helical chirality of the compounds will be discussed in Chapter 3.

Numerous methods exist for the generation of carbanions in organic synthesis. Possible exchange reactions of this sort can be explored involving the tin-lithium exchange or halogen-lithium exchange. The tin-lithium exchange has proven to be an effective and reliable method for the preparation of a variety of organolithium reagents.\(^9\)

2.4.3 Cross Coupling Reactions

Palladium catalyzed cross-coupling reactions\(^9\) provide efficient methods for carbon-carbon bond formation and have greatly influenced the synthesis of complex molecules. Organoboranes, organostannanes, and organozinc are the most commonly employed nucleophilic reagents for cross-coupling reactions.

Future interest in these helically chiral dienes lies among others in their potential application for the synthesis of helically chiral polyenes (Scheme 2.27). These helically chiral \(\pi\)-systems are of interest due to their potential applications and uses in the area of
optoelectronics and conducting polymer systems. Development of this application requires the diene to be nonplanar with the atropisomerization is frozen at room temperature in order to produce a unidirectional continuous helix formation.

**Scheme 2.27:** Formation Helically Chiral Polyenes

2.4.3.1 Suzuki and Stille Cross-Coupling Reaction

As previously mentioned, Tanaka and co-workers have successfully reported on the tandem Stille/Suzuki reaction of a 1,2-borostannyl alkenes. A more recent report by Dr. Singidi from our group on a very similar type of reaction has also appeared.

Attempted Suzuki cross-coupling reaction of diazaborolidine 2.35 using PdCl$_2$(PPh$_3$)$_2$ (5 mol %), NaOEt (2.0 equiv) and isocrotyl bromide (1.2 equiv) in EtOH/THF resulted in a highly complex product mixture.
Scheme 2.28: Attempt at Selective Suzuki-Miyaura Cross-Coupling

![Scheme 2.28](image)

Efforts to carry out Stille coupling reaction of 2.40 with an aryl iodide involved the use of Pd(PPH₃)₄ (5 mol %) and iodobenzene (Scheme 2.29) and this also gave a complex mixture of products.

Scheme 2.29: Attempted Selective Stille Cross-Coupling

![Scheme 2.29](image)

2.5 Summary

The borostannylation cyclization of 1,n-diynes has been shown to be a fascinating reaction for the preparation of helically chiral 1,3-dienes. The studies reported conclusively demonstrate that the borylstannane [-N(Me)CH₂CH₂(Me)N-]B–SnMe₃ (1.80) is a superior reagent capable of effecting bis-functionalization-cyclization in several 1,n-diynes where the more well-known silylstannanes fail. NMR analysis of
those substrates which underwent facile cyclization has indicated the cyclization event to be atropselective for selected substrates due to the formation and observation of only one of the atropisomeric products in the NMR spectra. These include 1,2-dipropargylbenzenes, 2,2'-dipropargylbiphenyls, 4,5-dipropargyldioxolanes and 1,4-dipropargyl-β-lactams. We have shown that the use of this bicyclic motif has rendered the equilibration between the two atropisomeric products slow at room temperature. The dynamic properties associated with the 1,3-diene products, as well as the corresponding halo-derivatives will be discussed in Chapter 3. A more extensive search into the use of asymmetric diyne precursors may also add to further utility to the versatile borostannane reagent.

Despite the failures in the initial attempts towards the derivatization of the bismetallated species, the chemistry of these non-planar 1,3-diene systems remains relatively unexplored and further studies are needed to confirm the initial negative findings.
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*Synthetic Metals* 1999, 101, 94.
3.1 Stereochemistry of 1,3-Dienes

By definition, atropisomers are conformers which due to steric or electronic constraints exchange slowly enough, with a half life of less than 1000 s such that each isomer can be isolated. Atropisomerism may give rise to geometrical isomers, diastereoisomers, or enantiomers, all with the distinctive feature that they can in principle be equilibrated thermally. The use of chiral atropisomers has garnered much interest and applications as ligand for asymmetric catalysis or as chiral scaffolds in asymmetric synthesis. Literature focused on atropisomerization is generally restricted to biphenyl and binaphthyl derivatives, even though atropisomerism and axial chirality can be found in many other examples such as vinylbenzenes, 2-aryl-2-methyl-1,3-dioxolanes, and 1,3-butadienes. Therefore the development of methods which are atropselective in nature, or methods that allow for facile separation of atropisomers serve as an important topic of research within the RajanBabu group.
We have reported a facile synthesis of a new class of 1,4-disubstituted (Z,Z)-1,3-dienes via Pd(0)-catalyzed borylstannylation/cyclization of 1,\textit{n}-diynes mediated by a R₂BSnR₃ reagent. The exceptional control of regio- and stereo-selectivity, a necessary consequence of the mechanisms of the various organometallic steps involved, results in the placement of the B and Sn substituents in an “inside” orientation, thus creating a helical motif. The structures and configurations of the (Z,Z)-diene adducts have been rigorously established by multinuclear (¹H, ¹³C, ¹¹⁹Sn) NMR methods, and in one case, by X-ray crystallographic analysis of a solid derivative.

Our original goals of this study dealt (a) identification of the most optimal [X-Y] reagent to allow facile cyclization and subsequent chemistry of the installed functionality for carbon-carbon or carbon-heteroatom bond formations; (b) how to increase the activation barrier to allow the atropisomer(s) to be isolated at or near room temperature; and (c) how to control the regioselectivity of the [X-Y] addition in an unsymmetrical 1,\textit{n}-diyne.

Dynamic processes exhibiting an energy barrier between 20 and 100 kJ mol⁻¹ can often be studied by analysis of temperature-dependent NMR spectra of the interconverting species. In an achiral environment, the NMR spectra of enantiomers are indistinguishable. Conventional chromatograph techniques can be used to separate molecules with barriers to rotation greater than 20 kcal mol⁻¹. It may be possible to sterically or electronically affect the existence of atropisomers dependent upon the [X-Y] reagent, or through the use of appropriate structures for the makeup of the starting 1,\textit{n}-diyne.
The interconversion of stereoisomers exhibiting diastereotopic nuclei can be monitored by variable-temperature NMR spectroscopy (dynamic NMR), when the reaction is slow on the NMR time scale. In these examples, NMR line shape analysis would give accurate kinetic parameters for the isomerization.

**Figure 3.1: Enantiotropic and Diastereotopic Protons in VT-NMR**

Determination of the coalescence temperature allows for the identification of having either a diene that is undergoing inversion or not. In Figure 3.1 are depicted the two possible options. If the system is *not* inverting, in which the NMR should show the presence of two isomers as one set of peaks, but diastereotopic $H_a$ and $H_b$ groups. If the diene system is inverting, the NMR should show the presence of apparently one achiral compound with the methylene $H_a$ and $H_b$ groups being ‘enantiotropic’. At low temperatures the isomerization process should be frozen and the ability to observe the methylene groups as ‘diastereotopic’ methylene groups (2 AB groups) should be evident,
proving the chirality of the diene system. At higher temperatures, the peaks can coalesce showing that the helical chirality of the diene system is diminished.

**Figure 3.2:** Kinetic Parameters for Helical Isomerization and Coalescence Temperatures

![Figure 3.2: Kinetic Parameters for Helical Isomerization and Coalescence Temperatures](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta H^\circ$ (kJ mol$^{-1}$)</th>
<th>$\Delta S^\circ$ (J mol$^{-1}$ K$^{-1}$)</th>
<th>$\Delta G^\circ$ (kJ mol$^{-1}$, 300K)</th>
<th>$T_c$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>54.8</td>
<td>4.3</td>
<td>56.7</td>
<td>10</td>
</tr>
<tr>
<td>3.2</td>
<td>55.4</td>
<td>21.0</td>
<td>56.9</td>
<td>20</td>
</tr>
<tr>
<td>3.3</td>
<td>63.2</td>
<td>-11.6</td>
<td>52.5</td>
<td>20</td>
</tr>
<tr>
<td>3.4</td>
<td>48.8</td>
<td>-</td>
<td>-</td>
<td>-20</td>
</tr>
<tr>
<td>3.5</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>-60</td>
</tr>
<tr>
<td>3.6</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Recall that introductory work within our group established the 1,2-dialkyldiene-cycloalkane derivatives which include the 1,4-disubstituted-(Z,Z)-1,3-dienes with terminal silyl and stannyl substituents as being axially chiral due to their ability to undergo facile enantiomerization$^{106}$ (Figure 3.2). As observed in Figure 3.2, the initial studies strongly suggested that monocyclic compounds are most likely to be fluxional and there is little hope of increasing the $\Delta G^\#$ for the helical isomerization by simply increasing the size of the X/Y groups.$^{106}$ The kinetic parameters for the enantiomerization process determined for the series of dienes 3.1-3.6 via NMR line-shape analysis are shown in Figure 3.2. For all molecules studied, the free energies of activation are similar (52-57 kJ mol$^{-1}$ at 300 K), well within the range expected from the NMR spectra. Thus, it has not been possible to synthesize monocyclic system where the helical isomerization is frozen on the NMR time scale at or near room temperature. Note that the substitution pattern of the back-bone of the precursor diyne has a strong effect on the free energy of activation. For example, the $N$-tosyl and $N$-alkyl derivatives 3.5 and 3.6 (Figure 3.2)
have much lower coalescence temperatures compared to the corresponding geminal-bis- carbomethoxymethylene compounds 3.1 and 3.2.

**Scheme 3.1:** a) Experimental (left) and calculated (right) $^1$H-NMR line shapes due to the methylene groups of 3.3 at various temperatures with derived rate constants b) Helical Isomerization of 3.3

From our dynamic NMR studies$^{106}$ we had surmised that the backbone of a 1,2-bisalkylidene cycloalkanes significantly influence the rate of the helical isomerization process (See Chapter 2, Figure 2.8), and thus it should be possible to increase the $\Delta G^\#$ for this process by restricting the conformational mobility of this unit.

Dynamic NMR experiments of resulting monocyclic diene products have shown a fast exchange between atropisomers at room temperature. A typical example of how the
helical isomerization can be monitored by following the changes in the line shapes of the bis-allylic hydrogens in the adducts from symmetric diynes is shown in Scheme 3.1 for the compound 3.3. At the fast exchange regime, because of the pseudo-plane of symmetry, the allylic protons behave like two broad singlets at 279 K. When the exchange is slow on the NMR time scale, these appear as two AB quartets (Scheme 3.1).

3.1.1 Dynamic NMR Results

The use of borylstannane 1.80 has shown to have several advantages compared to the [SiSn] reagents including increased reactivity, better chemo- and regioselectivity in the reactions of several key substrates, and broad utility in the use of the adducts in complex molecule synthesis.107 Further, by observation of the borystannylation-cyclization products $^1$H-NMR, we find that by restricting the conformational mobility of the newly formed ring, either by having a biphenyl unit as a part of the backbone or imposing a bicyclic motif, the helical isomerization of the diene can be almost completely arrested at room temperatures. This aspect will be discussed in detail later.

Dynamic NMR experiments of resulting borostannylation monocyclic diene products such as 3.4 have shown a fast exchange between atropisomers at room temperature (Figure 3.3). Attention is given to the allylic proton signals at $\delta = 4.00$ and 3.97 in toluene-$d_8$ which are observed as a pair of singlets at room temperature, indicating a fast exchange between atropisomers taking place. In order to slow this exchange process, the temperature was decreased to -50 °C; however, only a broadening of the
peaks takes place with no observable exchange process between the pair of possible atropisomers. Lack of observance of the coalescence temperature indicates the fast and fluxional nature of the monocyclic product at room temperature and even at -50 °C.

**Figure 3.3:** Dynamic NMR of a Monocyclic Product

The introduction of strain within the backbone of the diyne, ultimately giving rise to the formation of a bicyclic product, has been able to render the dynamic process slow at room temperature for the substrates in Figure 3.4.
Figure 3.4: Dioxaborolidine Substrates Undergoing VT-NMR

As seen in the VT-NMR of compound 2.55 in Figure 3.5, at room temperature the benzylic protons appear as two distinct AB quartets centered around δ 3.806 ($v_A = 3.978$, $v_B = 3.634$, $J_{AB} = 16.8$ Hz) and 3.691 ($v_A = 3.814$, $v_B = 3.568$, $J_{AB} = 16.8$ Hz) in CDCl$_3$.

The vinyl hydrogens in this compound appear at δ 5.328 (d, $J = 1.2$ Hz, (B)-C$_{sp2}$-H) and 5.771 (t, $J = 1.2$ Hz, $J_{Sn-H} = 76$ Hz, (Sn)-C$_{sp2}$-H).

Figure 3.5: Variable Temperature $^1$H-NMR of 2.55 in Toluene-d$_8$
Upon heating the solution to 75 °C in toluene-$d_8$ slight coalescence is observed above 50 °C in the signals of the benzylic protons, however heating up to 75 °C shows overall very little change with no actual exchange between atropisomers observed. Upon consideration of the vinyl protons no change is expected due to the atropisomer and starting material having an enantiomeric relationship.

**Figure 3.6:** Variable Temperature $^1$H-NMR of 2.53 in Toluene-$d_8$

Use of this C$_2$-symmetric substrate allows for fewer reaction channels, in turn simplifying chiral induction, as well as possessing two electronically and sterically equivalent coordination centers. Use of this diyne can also be used as a model substrate in
the utilization of VT techniques in determining the stereoselectivity of the cyclization reaction.

Upon cyclization of the starting diyne that 2 diastereomeric products can be formed, whereas A = C, and B = D (For Diagram, See Chapter 2, Scheme 2.13). The observance of these two possible diastereomers can be seen in the vinyl proton region of the $^1$H-NMR. If at room temperature, both products exist and the isomerization between A and B is slow, then it can be expected that 4 different vinyl peaks would be observed. However, if at room temperature, the isomerization between A and B is very fast then it can be expected that the vinyl region would show broadening or a mixture of the corresponding vinyl-Sn and vinyl-B peaks respectively. The NMR (toluene-$d_8$) of 2.53, an enantiopure compound further indicates the atropselective nature of the cyclization in the presence of only two vinylic protons corresponding to only a single diastereomer (Figure 3.6)

Temperature dependent NMR experiments showed that upon cooling to -25 °C no change occurred. Heating up to +65 °C also showed no indication of atropisomerization demonstrating the static nature of the helical complex within the given temperature range. No coalescence or exchange is observed in either the vinyl protons δ 5.73 and 5.32, or in the methylene signals. This implies that cyclization is selective for the formation of one diastereomer over the other, and that the rotation barrier between the two diastereomers/atropisomers is very high. In order to determine which atropisomer is formed, either $M$ or $P$, isolation of the pure product by crystallization would be ideal.
The conformational restraint imposed by the backbone of β-lactam 2.52A was also shown to be freeze the isomerization as seen by the VT-NMR (toluene-$d_8$) up to temperatures of 55 °C (Figure 3.7). As can be seen, the vinyl peaks at $\delta = 5.4$ and 5.6, as well as the methylene signals at $\delta = 4.45, 3.98, 3.69$ and 2.59 show no exchange or even peak coalescence. As can be seen from the dynamic NMR’s, the use of a bicyclic diene product yields promising results towards the development of asymmetric versions of the borostannylative-cyclizations to be used in target natural products.
Variable temperature NMR studies have also been done on a select number of products resulting from the Sn-halogen exchange reaction of the cyclized product (Figure 3.8).

**Figure 3.8: Haloborolidine Derivatives**

In the $^1$H-NMR (toluene-d$_8$) of iodo-derivative 2.65, the benzylic protons appear as two singlets at $\delta = 3.50$ and 3.57 at room temperature. The fast exchange process is then slowed down by cooling to -65 °C, where as above -20 °C or so the coalescence between the signals of the two possible atropisomers is observed (Figure 3.9).
Variable temperature $^1$H-NMR of 3.7, 3.8, and 3.9 can also show the low barrier of isomerization associated with these haloboronates derivatives. No observable AB quartersat temperatures down to -70 °C (Figures 3.10) are seen.
3.1.2 HPLC Analysis

Prior to developing an enatioselective version of the borostannylative cyclization reaction, it is necessary to be able to identify an analytical method that can be used in determining the stereoselectivity of the corresponding cyclization. Chiral stationary phase HPLC analysis of the cyclization reaction products is one such method. The sensitivity of the diene products to HPLC conditions must be considered, most specifically how an increase in polarity, or increase in the amount of isopropyl alcohol as an eluent, can lead
to decomposition of the diene compound. However, thus far these attempts have been unsuccessful (Table 3.1).

**Table 3.1: HPLC Analysis of Selected Substrates**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>OJ-H column Flow = 0.5</th>
<th>Conditions Hex:i-PrOH</th>
<th>AD-H column Flow = 0.5</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1 peak 1 peak</td>
<td>100:0 99.5:0.5</td>
<td>1 peak 1 peak</td>
</tr>
<tr>
<td><img src="image2.png" alt="Substrate 2" /></td>
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<tr>
<td><img src="image3.png" alt="Substrate 3" /></td>
<td>1 peak 1 peak</td>
<td>100:0 99.5:0.5</td>
<td>-- --</td>
</tr>
</tbody>
</table>

**3.2 Developments Towards an Asymmetric Borostannylative-Cyclization of 1,\(n\)-Diynes**

Borostannylative cyclization of an achiral diyne gives rise to a pair of enantiomeric dienes which possess helical chirality. If an additional element of chirality, such as a stereogenic center or helical chirality is present in the diyne starting material, cyclization will lead to the formation of diastereomers. If cyclization takes places lacking in regioselectivity, than up to a possible of 4 isomers can be produced (two diastereomers for each regioisomer). However, it may be likely that one diastereomer for each
regioisomer can be more stable than its corresponding isomer. It is therefore deemed necessary to probe the diastereoselectivity associated with the cyclization reaction.

**Figure 3.11: Dibenzocyclooctadienes and Aryltetralin Natural Products**

This can be accomplished by looking at the cyclization of diynes which posses latent chirality, as well as a strained backbone to control the atropisomerization. If the cyclization process is found to be diastereoselective, potential applications of this effect can be found in the synthesis of substrates such as the dibenzocyclooctadienes and the aryltetralins (Figure 3.11).

The use of a biphenyl diyne can be used in a model study to probe the influence of an adjacent chiral center as well as the presence of axial chirality within the biphenyl system on the atropselectivity of the borostannylative cyclization event (Scheme 3.2).
Scheme 3.2: Influence of Latent Chirality on Atropselectivity

Initial cyclization attempts using chiral ligands have been shown to be hopeful, even though diastereoselectivity in the reaction of chiral substrates have not yet been realized. An analytical method which is capable of determining the stereoselectivity of the cyclization reaction still needs to be identified.

Scheme 3.3: Asymmetric Bismetallation Reactions
Despite currently lacking an analytical method of determining selectivity, it is still important to ensure that cyclization will occur under the given reaction conditions. Previous work with the use of stereoselective bismetallic additions to unsaturated systems have successfully used phosphoramidite and TADDOL-derived chiral ligands in corresponding borylsilylation and diboration reactions respectively (Scheme 3.3). \(^\text{108}\)

Initial work has been focused on the use of chiral Feringa ligands in the palladium-catalyzed borostannylative cyclization of 1,\(n\)-diynes. The reaction proceeds in moderate yields (Scheme 3.4). When the reaction is carried out using \(\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3\) paired with the Feringa catalyst, the cyclization event gives a cleaner reaction for each substrate tested thus far. The biphenyl product was characterized by, inter alia, the vinyl hydrogens at \(\delta\) 5.874 (s, 1 H, \(J_{\text{Sn-H}} = 72\) Hz, SnCH), 5.559 (s, 1 H, BCH).

**Scheme 3.4 Viability of the Borostannylative Cyclization with the Use of a Feringa Ligand**
3.3 Summary

As indicated by the reported studies, the reactivity of a borylstannane reagent in the cyclization of 1,\(n\)-diynes has been shown to be superior compared to the corresponding silylstannane reagents. Introduction of additional constraints within the backbone of the diyne precursor has effectively increased the barrier between the non-planar atropisomeric \((Z,Z)\)-1,3-diene products. As seen in the VT-NMR studies, the borostannylative cycylation reaction of selected 1,\(n\)-diynes also appears to be atroposelective occurring in moderate to good yields. Studies also indicate that further applications of this cyclization protocol have to depend on finding proper derivatization reaction procedures. Though hydrolytically sensitive, the diazaborolididine substrates can be converted into the corresponding more stable dioxaborolidiniine derivatives; or they can be used in the tin-halide exchange reaction in the formation of the haloborolidine substrates.

Initial cyclization attempts using chiral ligands have shown that these are viable reactions, though an analytical method which is capable of determining the stereoselectivity of the cyclization reaction still needs to be found.
REFERENCES: CHAPTER 3


CHAPTER 4:
EXPERIMENTAL PROCEDURES

4.1 General Methods

Reactions were carried out in oven- or flame-dried glassware under an inert nitrogen atmosphere using Schlenk techniques or in a Vacuum Atmosphere glovebox, unless otherwise noted. All solvents used were reagent grade. Diethyl ether, Hexanes, and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone ketyl. Methylene chloride and toluene were freshly distilled from calcium hydride under a dry atmosphere and stored over molecular sieves. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Pyridine was distilled and stored over potassium hydroxide. Anhydrous N,N-dimethylformamide was purchased from Fischer Scientific and used without purification. Commercial samples of PdCl$_2$(PPh$_3$)$_2$ and Pd$_2$dba$_3$·CHCl$_3$ were used. All Pd-reagents were stored in the drybox. Except otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography on precoated (0.25 mm) silica gel 60 F$_{254}$ plates. Flash chromatography was conducted using silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). Yields, unless otherwise stated, refer to isolated compounds. Chemical shift are reported
relative to chloroform as standard at \( \delta = 7.26 \) for \(^1\text{H}\) and \( \delta = 77.16 \) for \(^{13}\text{C}\). Coupling constants are reported in Hertz (Hz). Compounds for which exact mass is reported exhibited no significant m/z greater than the one of the parent peak.

**Synthesis of substrates.** The following starting materials/substrates were prepared according to procedures described in the literature: 2.27\(^{109}\), 2.29\(^{110}\), 2.31\(^{111}\), 2.32\(^{112}\), and 2.33\(^{112}\); Feringa ligand L\(^{113}\)

**General Procedure for borylstannylative-cyclization:**

In a glovebox, a solution of 1,3-dimethyl-2-trimethylstannyl-1,3,2-diazaborolane 1.80 (1.02 equiv) and PdCl\(_2\)(PPh\(_3\))\(_2\) (1 mol%) in C\(_6\)D\(_6\) (0.20 M) was added to a vial containing the diyne (1.00 equiv). The mixture was transferred to an NMR tube, along with additional C\(_6\)D\(_6\) (0.30 mL), capped, shaken and then sealed with parafilm. The reaction mixture sat at 23 °C and was monitored by \(^1\text{H}-\text{NMR.} \) Filtration through a plug of Celite, followed by concentration via vacuum yielded crude product.

**General Procedure for borylstannylative-cyclization with Chiral Ligand:**

In a glovebox, a solution of ligand (2.00 mol %) and Pd\(_2\)dba\(_3\)·CHCl\(_3\) (1.00 mol %) in C\(_6\)D\(_6\) (0.20 M) was added to a vial containing 1,3-dimethyl-2-trimethylstannyl-1,3,2-diazaborolane 1.80 (1.02 equiv), followed by addition of the diyne (1.00 equiv). The mixture was transferred to an NMR tube, along with additional C\(_6\)D\(_6\) (0.30 mL), capped, shaken and then sealed with parafilm. The reaction mixture sat at 23 °C and was
monitored by $^1$H-NMR. Filtration through a plug of Celite, followed by concentration via vacuum yielded the diazaborolane product.

**Typical Procedure for Pinacol Exchange Reaction:**

To a solution of the vinyl diazaborolane (1.00 equiv) in C$_6$D$_6$ (0.20 M) was added pinacol (1.02 equiv) and the reaction monitored by $^1$H-NMR. The reaction mixture is concentrated by rotavap and the crude residue purified by column chromatography (Et$_3$N buffered column) to yield the vinyl pinacol borane product.

Cyclization of 1,2-Dipropargylbenzene (2.27): Diene 2.40.

Following the typical cyclization procedure with 1,2-bis(2-propynyl)benzene (0.050 g, 0.32 mmol) at 23 °C for 3 h. Filtration through a plug of Celite, followed by concentration via vacuum yielded crude product as a yellow solid (0.13 g, 96 % yield).

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.04-7.16 (m, 2 H, Ar-H), 6.92-6.95 (m, 2 H, Ar-H), 5.72 (s, 1 H, $J_{Sn-H} = 72$ Hz CHSn), 5.42 (s, 1H, CBH), 3.06 (s, 4 H, NCH$_2$), 2.56 (s, 6 H, NCH$_3$), 0.20 (s, 9 H, Sn(CH$_3$)$_3$); $^{13}$C (NMR 125 MHz, C$_6$D$_6$): $\delta$ 155.9, 154.3, 136.7, 136.6, 128.9 (?), 128.6 (?), 126.2, 125.3, 52.0, 45.1, 44.8, 34.9, -8.6; $^{119}$Sn -52.6; IR (liquid film, cm$^{-1}$) = 3233, 3048, 2980, 2856, 2387, 2279, 1618, 1549, 1495, 1452,
Conversion of compound 2.40 to 2.55

Following the typical pinacol exchange procedure with the cyclization product (0.04 g, 0.0964 mmol) at 23 °C for 30 min to yield the product as a yellow oil (0.040 g, 94 % yield). $^1$H NMR (400 MHz, C$6$D$6$): $\delta$ 7.11-7.13 (m, 2 H, Ar-H), 7.04-7.06 (m, 2 H, Ar-H), 5.771 (t, $J = 1.2$ Hz, $J_{Sn-H} = 76$ Hz, C$sp^2$-(Sn)-H), 5.328 (d, $J = 1.2$ Hz, C$sp^2$-(B)-H), 3.806 (ABq, $v_A = 3.978$, $v_B = 3.634$, $J_{AB} = 16.8$ Hz) and 3.691 (ABq, $v_A = 3.814$, $v_B = 3.568$, $J_{AB} = 16.8$ Hz), 1.24 (s, 12 H CCH$_3$), 0.13 (s, 9 H, SnCH$_3$); $^{13}$C NMR (400 MHz, C$6$D$6$): $\delta$ 162.6, 156.3, 137.0, 136.5, 134.3, 128.9, 128.8, 128.3 (?), 127.5 (?), 126.4, 123.6, 82.8, 81.2, 71.5, 45.8, 45.4, 25.3, 24.8, 22.6, -7.8. $^{119}$Sn -55.6; HRMS (ESI) m/z calcd for C$_{21}$H$_{31}$BNaO$_2$Sn 469.1336, found (M+) 469.1323.

Variable temperature $^1$H NMR (toluene-d$_8$) showed that the AB quartets broaden above 65 °C. At 75 °C, the peak shapes are no more discernable. At higher temperature the vinyl hydrogens also showed some broadening.
Synthesis of 2,2'-dipropargyl-1,1'-biphenyl (2.28). 2,2'-bis-(3-Trimethylsilylpro-2-ynyl)-1,1'-biphenyl.\textsuperscript{114}

\begin{center}
\includegraphics[width=0.8\textwidth]{synthesis_diagram.png}
\end{center}

Bromoethane (0.30 mL, 4.0 mmol) was added to a round bottom flask containing magnesium turnings (0.097 g, 4.0 mmol) in THF (5 mL). The solution was heated to reflux for 30 min, cooled to 23 °C and trimethylsilylacetylene (0.56 mL, 4.0 mmol) in THF (5 mL) was added dropwise to the flask. The reaction mixture was heated to reflux for an additional 1 h, cooled to 23 °C, followed by the addition of Cul (0.095 g, 0.500 mmol) and 2,2'-bis(iodomethyl)-1,1'-biphenyl\textsuperscript{110} (0.434 g, 1.00 mmol). The mixture was heated to reflux for an additional 10 h. The reaction was quenched with aqueous saturated NH\textsubscript{4}Cl (5 mL), and extracted with hexanes (3 x 25 mL). The organic layer was washed with H\textsubscript{2}O (20 mL), brine (20 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to yield the crude product as a light pink oil. Purification by column chromatography (mobile phase: hexanes/ether 20:1) gave the product as an orange oil (0.30 g, 80 %). \textsuperscript{1}H (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.82 (d, \( J = 7.6 \) Hz, 2H), 7.35 (dd, \( J = 7.4, 1.5 \) Hz, 4H), 7.29-7.25 (m, 2H), 7.10 (dd, \( J = 7.4, 1.0 \) Hz, 2H), 2.94 (s, 4H), 0.17 (s, 18 H).
2,2'-Bis(prop-2-ynyl)-1,1'-biphenyl (2.28).\textsuperscript{115} A solution of 2,2'-bis[3-(trimethylsilyl)prop-2-ynyl]-1,1'-biphenyl (1.29 g, 3.45 mmol) in 95% EtOH (2 mL) was added to a solution of AgNO\textsubscript{3} (1.76 g, 10.35 mmol) in EtOH/H\textsubscript{2}O (5 mL, v/v 2.3:1) and the mixture stirred in the dark for 5 h at 23 °C. A solution of KCN (1.80 g, 27.6 mmol) in H\textsubscript{2}O (3 mL) was then added and the mixture stirred at 23 °C for an additional 1 h. The reaction mixture was concentrated on rotary evaporator and the residue was extracted with Et\textsubscript{2}O (3 x 25 mL). The organic layer was washed with brine (20 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to yield the product as a yellow oil (0.708 g, 89 %). \textsuperscript{1}H (400 MHz, CDCl\textsubscript{3}): \textdelta 7.68 (d, J = 7.6 Hz, 1 H), 7.37 (t, J = 7.6 Hz, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 7.12 (d, J = 7.6 Hz, 1 H), 3.31-3.24 (m, 2 H), 2.09 (t, J = 2.8 Hz, 1 H).

Cyclization of 2,2'-Bis-(3-propynyl)-1,1'-diphenyl (2.28): Synthesis of 2.36

To a solution of 1,3-dimethyl-2-(trimethylstanny1)-2-bora-1,3-diazocyclopentane (0.0160 g, 0.6 mmol) in benzene (0.60 mL) added PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (0.004 g, 0.0005 mmol) and the mixture was stirred at 23 °C for 15 min followed by addition of a solution of diyne 2.28 (0.0115 mg, 0.5 mmol) in benzene (0.40 mL). After stirring the reaction mixture at 23 °C for 6 h, a solution of pinacol (0.0085 g, 0.07 mmol) in benzene (0.20 mL) followed by p-toluenesulfonic acid (pTSA, 0.013 g, 0.07 mmol) were added to derivatize in situ formed
diazaborolidine 2.41 to dioxaborolidine 2.43. After 2 h, the reaction was quenched by the addition of Et$_3$N (0.10 mL) and the solvent was evaporated under reduced pressure to afford the crude product, which was purified by silica gel chromatography using 5% EtOAc/hexane as the eluent to yield the dioxaborolidine 2.43 along with 20% destannylated product in 78% combined yield. Before addition of pinacol and pTSA, the diazaborolidine 2.41 can be characterized by crude $^1$H NMR after removal of the solvent under reduced pressure.

**Cyclization of Diyne 2.28: Diene 2.43**

![Molecular structure of 2.41](image)

$^1$H (400 MHz, C$_6$D$_6$): $\delta$ 7.38-7.01 (m, 8 H), 5.874 (s, 1 H, $J_{Sn-H} = 75$ Hz, SnCH), 5.559 (s, 1 H, BCH), 3.292 (ABq, $v_A = 3.386$, $v_B = 3.199$, $J_{AB} = 12$ Hz, 2 H, benzylic CH$_2$, CH$_2$ C=C(H)B), 3.250-3.3580 (m, d, 2 H, benzylic CH$_2$ C=C(H)Sn) 3.00-3.15 (br, m, 2 H), 2.95-3.00 (m, 2 H), 2.455 (s, 6 H), 0.15 (s, 9 H). Variable temperature $^1$H NMR (toluene-d$_8$) showed that there is no change in the spectrum between -50°C and 25°C.

The reaction carried out with Pd$_2$(dba)$_3$.CHCl$_3$ (1.00 mol%) and Feringa phosphoramidite ligand L ($R_8S_4S_2$) gave a much cleaner reaction. In a glove box, a solution of the ligand (2 mol%) and Pd$_2$ (dba)$_3$.CHCl$_3$ (1.00 mol%) in C$_6$D$_6$ (0.20 M) was added the [B-Sn]-reagent (1.02 equiv) followed by the diyne (1.00 equiv). The mixture was transferred into and NMR tube and sealed. The mixture sat at 23°C while being monitored by $^1$H NMR...
NMR. Filtration though a plug of Celite followed by concentration on a pump gave the crude product.

Conversion of 2.41 to 2.43

Pinacolate formation using the standard procedure from 2.41 yielded the diene 2.43. $^1$H NMR (C$_6$D$_6$, 400 MHz): $\delta$ 7.00-7.30 (m, 8 H, aromatic H), 6.063 (s, 1 H, SnCH), 5.667 (s, 1 H, BCH), 3.10-3.70 (two sets of m AB q 4 H, benzylic H’s), 1.00-1.10 (singlets due to pinacol CH$_3$’s), 0.209 (s, SnCH$_3$). IR (neat, cm$^{-1}$): 2976.8, 2925.5, 2174.0, 1652.2, 1616.0, 1587.5, 1446.0, 1370.0, 1143.7; MS (ESI): m/z: 625.2 [M-(SnMe$_3$)+Na]$^+$. This reaction was complicated by destannylation (characterized by peaks at $\delta$ 5.63 (s, 1 H), 5.27 (d, $J$ = 2.0 Hz, 1 H), 5.10 (d, $J$ = 2.0 Hz, 1 H), and thus the product was not obtained as a clean material. However, the starting diazaborolidine-diene 2.41 was isolated as a pure compound and was fully characterized.

Cyclization of (4S, 5S)-2,2-dimethyl-4,5-di(prop-2-ynyl)-1,3-dioxolane (2.29): Synthesis of 2.42 and 2.53.
Following the typical cyclization procedure with (4S,5S)-2,2-dimethyl-4,5-di(prop-2-ynyl)-1,3-dioxolane \textbf{2.29} (0.0175 g, 0.0982 mmol), 1,3-dimethyl-2-trimethylstannyl-1,3,2-diazaborolane (0.0263 g, 0.1009 mmol), and PdCl\(_2\)(PPh\(_3\))\(_2\) (0.0007 g, 0.001 mmol) at 23 °C for 2 h. Filtration through a plug of Celite, followed by concentration via vacuum yielded crude product as a thick yellow oil (0.0333 g, 77 % yield) with some impurity present. This product can also be prepared by using Pd\(_2\)(dba)\(_3\). CHCl\(_3\)/phosphoramidite ligand as catalyst, which gave a slightly better product as judged by \(^1\)H NMR. The crude cyclization product was used in the next step without further purification. \(^1\)H NMR (C\(_6\)D\(_6\)): \(\delta\) 5.619 (d, \(J = 0.8\) Hz, \(J_{Sn-H} = 70\) Hz, 1 H, SnCH), 5.325 (d, \(J = 1.6\) Hz, 1 H, BCH), 3.50-3.65 (m, 2 H, OCH), 2.55-3.05 (m, all CH\(_2\)’s), 2.467 (s, 6 H, N-CH\(_3\)), 1.464 (s, 3 H, OCCH\(_3\)), 1.473 (s, 3 H, OCCH\(_3\)).

Conversion of \textbf{2.42} into \textbf{2.53}.

Following typical pinacol exchange reaction procedure using the crude diazaborolane at 23 °C for 30 min. Concentration via rotary evaporation at 40 °C yielded the ‘crude’ product as a yellow oil (0.0461 g, 83 % yield crude). The structure that best fits the data established is shown on the left. See the figure below for details. The following assignments were confirmed by double irradiation and \(^1\)H-\(^1\)H COSY experiments. \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.76 (d, \(J = 0.4\) Hz, \(J_{SnH} = 32\) Hz, 1 H, SnCH, H\(_8\)) 5.403 (d, \(J = 0.8\) Hz, 1 H, BCH, H\(_1\)), 3.575 (ddd, \(J = 8, 8, 3.6\) Hz 1 H, H\(_5\)), 3.535 (ddd, 3.6, 8, 8 Hz,
1H, H), 2.844 (dd, J = 8, 3.2 Hz 1H, H), 2.68 (dd, J = 8, 3.2 Hz 1H, H), 2.66 (ddd, J = 8.8 (?), 0.8, 1H, H), 2.36 (ddd J = 8, 8, 1.2 Hz, 1H, H), 1.42 (s, 3H, OCCH$_3$), 1.40 (s, 3H, OCCH$_3$), 1.06 -1.01 (singlets, B-OCCH$_3$), 0.23 (s, 9H, SnCH$_3$); HRMS (ESI) m/z calcd for C$_{20}$H$_{35}$BNaO$_4$Sn = 493.1548, found 493.1536 (M+).

There was no significant change in the NMR spectrum as a toluene-$d_8$ solution of the sample was cooled from 27 °C to -65 °C, except for the broadening most easily ascribed to change in viscosity of the solvent.

Preparation of $\beta$-lactam diyne 2.30.

A 2-neck, 25 mL round-bottom flask is charged with lactam 2.35 (0.861 g, 3.00 mmol), activated Zn (0.881 g, 13.5 mmol) and THF (5 mL) and cooled to -50 °C. Propargyl bromide (1.00 mL, 6.72 mmol, 80% in toluene) is added dropwise and the solution was kept at -50 °C for 1 h. The reaction was warmed to room temperature and allowed to stir for 6 h. The mixture was quenched with saturated aqueous NH$_4$Cl (20 mL), followed by extraction with CH$_2$Cl$_2$ (3 x 30 mL). The organic layer was dried with MgSO$_4$ and concentrated under reduced pressure to yield 2.36 as a white solid (0.661 g, 83 % yield). The crude product was consistent with known literature $^1$H-NMR values and used in the
next step without purification. $^1$H NMR CDCl$_3$ 400 MHz $\delta = 0.06$-$0.07$ (s, 3H, Si-CH$_3$), 0.09 (s, 3H, Si-CH$_3$), 0.87 (s, 9H, Si-CCH$_3$), 1.23 (d, 3H, J = 6.4 Hz, CH$_3$-CHOTBS), 2.05 (t, 1H, J = 2.6 Hz, CC-H), 2.51-2.55 (dd, 1H, J$_{AC}$ = 5.6, J$_{BC}$ = 6.8, J$_{AB}$ = 17.2 Hz, CH$_2$-CC), 2.89-2.91 (m, 1H, (O)C-CH) 3.84-2.88 (m, 1H, N-CH), 4.19-4.22 (m, 1H, CH-OTBS), 5.86 (br s, 1H, NH) ppm.

A 2-neck, 25 mL round-bottom flask is charged with NaH (0.0264 g, 1.08 mmol, 60 % in mineral oil) in THF (3.00 mL) and cooled to 0 °C (ice-bath) under N$_2$. Alkyne 2.36 (0.264 g, 0.986 mmol)$^{116}$ in THF (2.00 mL) was added dropwise and the reaction mixture stirred at 0 °C for 30 min, which was followed by addition of propargyl bromide (0.260 mL, 2.334 mmol, 80 % in toluene) ia syringe. Once the addition was complete the reaction mixture was warmed to 23 °C and stirred for 3 h. The mixture was quenched with saturated aqueous NH$_4$Cl (10 mL), and further extracted with CH$_2$Cl$_2$ (3 x 15 mL). The organic layer was dried with Na$_2$SO$_4$, and concentrated on a rotary evaporator. The crude product (92 %) was purified by column chromatography on silica (eluent: hexane/ethyl acetate 4:1) to give the diyne product 2.30 as an orange oil (0.271 g, 90 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 4.17$-$4.25$ (m, (O)CH, and part of an AB, J = 2 Hz, NCH$_2$CC, total 3 H), 3.97 (dt, J = 2, 4.4 Hz, 1 H, (N)CH), 3.87 (dd, part of an AB[?], J = 14, 1.6 Hz, 1 H, NCH$_2$CC), 2.97 (m, br, 1 H, C(=O)CH), 2.58-2.71 (dd of ABq dd, J$_{AB}$ = 14 Hz, J = 4.4, 2.4 Hz, 2 H, CCH$_2$), 2.23 (t, 1H, J = 4 Hz, 1 H, NCH$_2$CCH), 2.06 (t, 1 H, J = 4 Hz, CCH$_2$CCH), 0.87 (s, 9 H, C(CH$_3$)$_3$), 0.08 (s, 3H, SiCH$_3$), 0.07 (s, 3H, SiCH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.1, 79.2, 76.9, 72.6, 71.5, 64.9, 62.9, 51.7, 29.9, 25.9, 22.8, 22.8, 18.0, 14.3, -4.2, -4.8.; IR (CHCl$_3$) 3304, 3066, 3043, 2954, 2896,
Cyclization of β-lactam diyne (2.30): Synthesis of compound 2.49 and 2.52

Following the typical cyclization procedure with diyne 2.30 (0.0306 g, 0.1001 mmol), the reaction mixture was heated at 40 °C for 3 h (reaction monitored by 1H NMR). Filtration through a plug of Celite, followed by concentration, followed by ‘reprecipitation’ with pentane yielded the products as white crystals. The NMR spectrum of this product indicated it to be a mixture of products, with one major component that contains a vinyl tin moiety, as ascertained by the vinyl-hydrogen with 119Sn couplings. 1H NMR (inter alia) d 5.69 (s, JSnH = 34 Hz, 1 H, [Sn]CH), 5.14 (s, 1 H, (B)CH), 4.41 (d, J = 14.4 Hz, 1 H, one of NCH2), 4.00-4.20 (m, 2 H, [SiO]CH and NCH), 3.60 (dd, J = 10 Hz, 3.2 Hz, 1 H), 3.43 (d, 12.8 Hz, 1 H), 1.17 9d, J = 6 Hz, 1 H, -CH3). A second component also containing a vinyl-Sn residue with a Csp2-H at 5.343 (JSnH = ~ 50 Hz) has been tentatively identified as a regio-isomer from subsequent reactions to form the corresponding pinacolate. Since the NMR spectrum could not be interpreted fully and further purification by reprecipitation did not yield a satisfactory product, the crude product was
recrystallized from CH$_2$Cl$_2$ by slow evaporation of hexane into a concentrated solution of the lactam in CH$_2$Cl$_2$.

The crude product 2.49 was converted into the pinacolate as follows: Pinacol (0.0166 g, 0.141 mmol) in C$_6$D$_6$ (0.3 mL) was then added a solution of the product mixture. The reaction was also monitored by $^1$H NMR and TLC until completion. The mixture was concentrated and the crude product obtained as a yellow oil (47 mg, 79 % yield crude) was purified by column chromatography on silica gel using ethyl acetate/hexane solvent system with trace Et$_3$N to prevent destannylation of the product. Even with such precautions, some destannylation could not be prevented.

Major product (2.52A):

![Chemical Structure]

$^1$H-NMR (500 MHz, C$_6$D$_6$): $\delta$ 5.820 (d, $J = 0.8$ Hz, $J_{\text{SnH}} = 34$ Hz, 1 H, SnCH), 5.292 (d, $J = 1.2$ Hz, 1 H, BCH), 4.336 (d, $J_{bc} = 13$ Hz, 1 H, H$_c$), 4.099 (qd, $J_{de} = 6$ Hz, $J_{df} = 6$ Hz, 1 H, H$_d$), 3.600 (ddd $J_{gh} = 11$ Hz, $J_{gi} = 5$ Hz, $J_{fg} = 2$, 1 H, H$_g$), 3.339 (dd $J_{bc} = 13$, $J_{ab}$ (?), 2 Hz, 1 H, H$_b$), 2.645 (dd $J_{hi} = 11$ Hz, $J_{gl} = 5$ Hz, 1 H, H$_i$), 2.580 (dd, $J_{df} = 6$ Hz, $J_{fg} = 2$ Hz, 1 H, H$_f$), 2.492 (ddd, $J_{hi} = 11$, $J_{gh} = 11$, $J_{hj} = 1$ Hz, 1 H, H$_h$), 1.00-1.15 (several singlets due to pinacolate and one doublet due to SiOC – CH$_3$), 0.94 (s, C(CH$_3$), 0.09 (s, SiCH$_3$), 0.02 (s, SiCH$_3$). The results of nOe experiments with the appropriate chemical shifts and coupling constants are shown below:
$^{13}$C-NMR (500 MHz, C$_6$D$_6$) $\delta$ 165.2, 83.0; 67.4, 66.5, 54.4, 51.9, 47.5, 30.2, 25.9, 25.0, 24.8, 22.8, 18.2, 1.42, -4.14, -4.72. HRMS (ESI) m/z found (M+) 620.2379; calcd for C$_{21}$H$_{31}$BNaO$_2$Sn 620.2369. Assigned structure is consistent with X-ray crystallography of the precursor diazaborolidine 2.52A.

Minor isomer (2.52B):

$^1$H NMR (C$_6$D$_6$, 400 MHz): $\delta$ 5.67 (s, 1 H, J$_{SnH}$ = 72 Hz, SnCH), 5.47 (s, 1 H, BCH), 4.556 (d, $J$ = 13 Hz, 1 H, NCH$_2$), 4.077 (dt $J$ = 6 Hz, 6 Hz, 1 H, OCH), 3.755 (d, $J$ = 12 Hz, 1 H, NCH$_2$), 3.566 (dd $J$ = 11, 4 Hz, 1 H, NCH), 2.61 (d, $J$ = 6 Hz, (O=C)CH, 1H), 2.474 (dd, $J$ = 11, 4.4 Hz, CCH$_2$, 1 H), 2.155 (dd $J$ = 11 Hz, 11 Hz, 1 H), 1.00-1.15 (several singlets due to pinacolate and one doublet due to SiOC –CH$_3$ at 1.12 d, $J$ = 6 Hz, 3 H), 0.94 (s, C(CH$_3$)$_3$), 0.07 (s, SiCH$_3$), 0.04 (s, SiCH$_3$). The assignments were confirmed by noesy measurements. This compound has the same features as the major compound, except for the regioisomeric nature of the B/Sn residue.
However, unlike the major product its configuration has not been confirmed. HRMS (ESI) m/z found (M⁺) 620.2325; calcd for C_{21}H_{31}BNaO_{2}Sn 620.2369.

Preparation of Diyne 2.34^{117a,b}

Diyne 2.38 was prepared from commercially available 2-[2-(trimethylsilyl)ethynyl]-benzaldehyde following the literature procedure.\textsuperscript{117a, 117b} To a solution of diyne 2.38 (0.1009 g, 0.333 mmol) in THF (5.00 mL) was added dropwise to a chilled solution of NaH (0.0148 g, 0.610 mmol, 60 % in mineral oil) in THF (5.00 mL) at 0 °C. The reaction is stirred at 0 °C for 30 min and acetyl chloride (0.030 mL) is then added dropwise, and the reaction warmed to 23 °C and stirred for 6 h. The reaction is quenched with saturated aqueous NH_{4}Cl (5 mL). The aqueous layer is extracted with EtOAc (3 x 10 mL) and the organic layer dried with MgSO_{4} and concentrated via rotavap to yield the crude product as a dark red oil (0.0968 g, 88 % yield) to give known intermediate 2.39.\textsuperscript{117}
Preparation of 2.34

TBAF (0.85 mL, 0.8500 mmol, 1.0M in THF) was added dropwise to a solution of 2.34 (1.004 g, 0.3300 mmol) in THF (5 mL) at 0 °C. The reaction mixture was warmed to 23 °C and stirred for 1 h and was quenched by NH₄Cl (5 mL). The organic layer was extracted using EtOAc (3 x 10 mL), washed with brine (10 mL), dried over MgSO₄ and concentrated via rotavap. Purification via silica gel column chromatography (eluent Hex/EtOAc 9:1) yielded the product as a dark red oil along with an impurity as evident by extraneous peaks in the NMR (0.5198 g, 92 % yield). Any additional attempts in purification led to additional product impurity. ¹H NMR (CDCl₃, 400 MHz): δ 7.883 (d, 1 H, J = 1.2 Hz, Ar-H), 7.863 (d, 1 H, J = 1.2 Hz, Ar-H), 7.434 (m, 1 H, Ar-H), 7.085 (m, 1 H, Ar-H), 6.515 (d, 1H, J = 2.0 Hz, CHOAc), 2.686 (d, 1 H, J = 2.0 Hz, CCH), 2.140 (s, 3 H, C(O)CH₃), 2.120 (s, 1 H, CHCCH).

Cyclization of 1-ethyl-2-(2-propyn-1-yloxy)-benzene (2.31): Synthesis of compound 2.50

1-ethyl-2-(2-propyn-1-yloxy)-benzene 2.31 was prepared from 2-iodophenol following the literature procedure. Following the typical cyclization procedure with 1-ethyl-2-
(2-propyn-1-yloxy)-benzene \textbf{2.31} (0.0313 g, 0.200 mmol), 1,3-dimethyl-2-trimethylstannyl-1,3,2-diazaborolane \textbf{1.80} (0.0538 g, 0.206 mmol), and \(\text{PdCl}_2(\text{PPh}_3)_2\) (0.0028 g, 0.004 mmol) in \(\text{C}_6\text{D}_6\) (0.70 mL) at 23 °C for 0.5 h. The mixture was then filtered through Celite and concentrated in vacuo to yield a thick yellow oil as the crude product mixture \textbf{2.50A:B} (0.0684 g, 82 % yield).

**Major Product Isomer:** \(^1\text{H}-\text{NMR} 400\) MHz \(\text{C}_6\text{D}_6\) \(\delta = 7.471-7.453\) (m, 1H), 7.338-7.724 (m, 2H, Ar-H), 6.985-6.979 (m, 1H, Ar-H) 6.383 (s, 1H, \(J_{\text{SnH}} = 57.2\) vinyl Sn-CH), 5.45 (s, 1H, vinyl B-CH), 2.95 (s, 4H, BNCH\(_2\)), 2.40 (s, 6H, BNCH\(_3\)), 4.20 (br s, 2H, OCH\(_2\)).

**Cyclization of** \(N-(2\text{-ethynylphenyl})-N-2\text{-propyn-1-yl-acetamide} \textbf{(2.32)}\): Synthesis of compound \textbf{2.51}.

\[
\begin{array}{ccc}
\text{Me} & \text{N} & \text{Z} \\
\text{B-SnMe}_3 & \text{Me} \\
\text{N} & \text{Me} \\
\end{array}
\]

\(\text{PdCl}_2(\text{PPh}_3)_2 \text{ (2 mol %)}\)

\(\text{C}_6\text{D}_6, 40\) °C, 5 h

\(\text{76 % yield}\)

\(\textbf{2.51 A:B}\)

A) \(Y = \text{B(N(CH}_2\text{CH}_2)_2}\), \(Z = \text{SnMe}_3\)

B) \(Y = \text{SnMe}_3, Z = \text{B(N(CH}_2\text{CH}_2)_2}\)

\(N-(2\text{-ethynylphenyl})-N-2\text{-propyn-1-yl-acetamide} \textbf{2.32} \) was prepared from 2-iodophenol following the literature procedure.\(^{118}\) Following the typical cyclization procedure with \(N-(2\text{-ethynylphenyl})-N-2\text{-propyn-1-yl-acetamide} \textbf{(0.0326 g, 0.165 mmol)}\), 1,3-dimethyl-2-
trimethylstannyl-1,3,2-diazaborolane (0.0439 g, 0.168 mmol), and PdCl$_2$(PPh$_3$)$_2$ (0.0023 g, 0.0033 mmol) in C$_6$D$_6$ (0.60 mL) at 23 °C for 10 h. Filtration through a plug of Celite, followed by concentration, followed by ‘recrystallization’ with pentane yielded the products as a yellow powder (58.7 mg, 77 % yield). $^1$H NMR C$_6$D$_6$ 500 MHz (mixture of diastereomers). **Major isomer:** $\delta = 7.356$-$7.334$ (m, 1H, Ar-H), 6.957-$6.918$ (m, 3H, Ar-H), 6.334 (s, 1H, $J_{SnH} = 58.4$ Hz, SnCH), 5.318 (s, 1H, BCH), 4.329 (s, 2H, NCH$_3$), 2.988 (s, 4H, NCH$_2$), 2.439 (s, 6H, NCH$_3$), 1.836 (s, 2H, C(O)CH$_3$), 0.130 (s, 9H, SnCH$_3$). $^{13}$C NMR C$_6$D$_6$ 500 MHz (mixture of diastereomers) = 168.7, 153.1, 138.4, 127.9, 127.8, 127.5, 125.6, 125.0, 124.6, 51.8, 51.6, 35.1, 35.0, 34.3, 32.3, 30.2, 29.8, 23.1, 22.7, 14.4, 1.4, -8.4, -8.5 IR (liquid film, cm$^{-1}$) = 3234, 2926, 2856, 2344, 2279, 1663, 1618, 1452, 1376, 1330, 1265, 1162, 1104, 1015, 812. Mass spec shows destannylation product. HRMS (ESI) m/z found (M+) 318.1769; calcd for C$_{20}$H$_{30}$BN$_3$NaOSn 480.9381.

Direct Synthesis of Compound **2.65** from via Borostannylation and in situ Functionalization.

[Diagram of the reaction]

Iodine (0.0129 g, 0.051 mmol) was added to a solution of 2.35 (0.0207 g, 0.049 mmol) in THF (1.00 mL) under N$_2$. The reaction was stirred at 23 °C for 1 h while monitoring by $^1$H NMR. After 1 h, pinacol (0.006 g, 0.051 mmol) was added to the reaction mixture and
stirring was continued for another 10 h. The mixture was concentrated on a rotary evaporator and the crude residue was purified by flash column chromatography (hexane/EtOAc 20:1) to give the product 2.65 as a yellow oil (0.0136 g, 66 % yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.20-7.10 (m, 2 H, Ar-H), 7.05-7.03 (m, 2 H, Ar-H), 6.214 (d, J = 1.2 Hz, 1 H, CHI), 5.545 (d, J = 1.2 Hz, 1H, CHB), 3.811 (s, br, 2 H, CH2), 3.712 (s, br, 2 H, CH2), 1.263 (s, 12 H, OCC); $^{13}$C NMR (1205 MHz, CDCl$_3$) δ 157.7, 148.9, 135.9, 135.4, 128.7, 128.6, 128.1, 126.4, 126.3, 83.1, 73.3, 42.8, 41.8, 30.1 (?), 29.4 (?), 25.2 (?), 25.0 (?), 24.8 (?); IR (liquid film, cm$^{-1}$) 3062.9, 3045.6, 2981.9, 2684.9, 2304.9, 1431.1, 1415.7, 1286.5, 1244.0, 1157.2, 910.4, 891.1, 785.0, 678.9; HRMS (ESI) m/z calcd for C$_{18}$H$_{22}$BINaO$_2$ 431.0655 found (M$^+$) 431.0649.

The variable temperature $^1$H NMR showed that an AB quartet centered around δ 3.55 at 20 °C slowly broadens as the temperature is lowered and coalescence is seen ~ 0 °C. Further cooling results in the progressive appearance of two sets of AB quartets centered around δ 3.62 and 3.16.

Clearly the compound 2.65 shows fluxional behavior at 20 °C. The chemical shift difference between the two C$_{sp^2}$-H’s (Δδ) go from 0.31 to 0.16 ppm as the toluene solution is cooled to -60 °C from 20 °C. These peaks also show some broadening.

Direct Synthesis of Compound 2.67 from via Borostannylation and in situ Functionalization.
N-Bromosuccinimide (0.009 g, 0.059 mmol) was added to a solution of the crude diazaborolidine 2.340 (0.0207 g, 0.049 mmol) in CH₂Cl₂ (1 mL) under nitrogen. The reaction was stirred at 23 °C for 1 h, while it was monitored by \(^1\)H NMR. At this point pinacol (0.006 g, 0.051 mmol) was added to the reaction mixture and it was further stirred for 10 h. The mixture was concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel using EtOAc as the mobile phase to yield the product 2.67 (0.012 g, 70%). \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) δ 6.95 (m, br, 2 H, aromatic H), 6.68 (m, br, 2 H, aromatic H), 5.94 (s, 1 H, BrCH), 5.76 (s, 1 H, BCH), 3.45 (s, 2 H), 3.41 (s, 2 H), 1.05 (s, 12 H). HRMS (ESI) m/z observed 383.088; calcd for C\(_{18}\)H\(_{22}\)BBrNaO\(_2\) 283.089.

Cyclization/bromodestannylation of 1,5-hexadiyne: synthesis of 3.7.

To a solution of 1,3-dimethyl-2-(trimethylstannyl)-2-bora-1,3-diazocyclopentane (64 mg, 0.24 mmol) in benzene (1.5 mL) added PdCl₂(PPh₃)₂ (1.4 mg, 0.002 mmol) and the mixture was stirred at room temperature for 15 min followed by addition of a solution of 1,5-hexadiyne (18.4 mg, 0.2 mmol) in benzene (0.5 mL). After stirring the reaction mixture at room temperature for 10 h., trimethyl tin group in insitu formed diazaborolidine (X) was exchanged with bromine by addition of NBS (50 mg, 0.28 mmol) followed by CHCl₃ (0.6 mL) to the reaction mixture and stirring was continued for 6 hr. Afterwards, a solution of pinacol (34 mg, 0.29 mmol) in benzene (0.5 mL) followed by p-toluenesulfonic acid (p-TSA, 27 mg, 0.14 mmol) were added to the reaction mixture and stirred for additional 2 h. The reaction mixture was diluted with CH₂Cl₂ and
washed with saturated aq. NH₄Cl solution, water, brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure (not below 10 mm Hg) to afford the crude product, which was purified by silica gel column chromatography using 5% EtOAc/hexane as an eluent to yield the desired product 57 in 81% yield (46 mg, 0.16 mmol). Before addition of NBS, in situ formed and moisture unstable the diazaborolidine can be characterized by crude ¹H NMR after removal of the solvent under reduced pressure.

**Diazaborolidine:** ¹H NMR (400 MHz, C₆D₆) δ 5.68 (d, J = 34.6 Hz, 1 H), 5.22 (s, 1 H), 2.96 (s, 4 H), 2.59 (s, 6 H), 2.55-2.546 (m, 4 H), 0.20 (t, J = 26.4 Hz, 3 H).

**Dioxaborolidine 3.7:** ¹H NMR (500 MHz, CDCl₃) δ 5.87 (s, 1 H), 5.23 (s, 1 H), 2.59-2.56 (m, 4 H), 1.29 (s, 12 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.18, 144.98, 97.30, 83.83, 30.77, 29.09, 25.60; IR (neat, cm⁻¹): 2924.4, 2856.8, 1683.7, 1652.1, 1495.2, 1356.0, 1262.2, 1141.9, 1049.6; MS (ESI): m/z: 309.04 [M+Na]⁺.

Cyclization/bromodestannylation of N-tosylpropargylamine: synthesis of 3.9.

Dioxaborolidine 3.9 was synthesized from N-tosylpropargylamine in 72% isolated yield. **Diazaborolidine:** ¹H NMR (500 MHz, C₆D₆) δ
7.74 (d, $J = 8.5$ Hz, 2H), 6.76 (d, $J = 8.5$ Hz, 2H), 5.57 (t, $J = 31.0$ Hz, 1H), 5.12 (s, 1H), 4.03 (s, 2H), 3.99 (s, 2H), 2.88 (s, 4H), 2.28 (s, 6H), 1.86 (s, 3H), 0.01 (t, $J = 27.5$ Hz, 9H).

Dioxaborolidine (3.9): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 6.22 (s, 1H), 5.46 (s, 1H), 4.01 (d, $J = 2.0$ Hz), 3.97 (s, 2H), 2.41 (s, 3H), 1.24 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 147.33, 144.21, 137.44, 133.46, 130.08, 128.03, 104.29, 83.87, 55.29, 54.76, 25.66, 21.77; IR (neat, cm$^{-1}$): 2923.8, 2856.7, 1699.3, 1652.0, 1539.8, 1494.5, 1373.1, 1049.6, 823.2; MS (ESI): m/z: 478.05 [M+Na]$^+$.

Attempted Stille cross-coupling reaction

To a solution of 2.40 (0.0207 g, 0.0499 mmol) in THF (1.00 mL) was added Pd(PPh$_3$)$_4$ (0.0029 g, 0.00249 mmol) and iodobenzene (0.006 mL, 0.0549 mmol) and the mixture heated at 60 °C for 8 h. The solution was cooled to 23 °C, diluted with EtOAC (5 mL). The organic layer was washed with brine (3 mL), dried over Na$_2$SO$_4$ and concentrated to yield a crude yellow oil. The crude $^1$H-NMR showed an extensive number of vinyl peaks indicating a complex mixture. No further analysis was taken.
Attempted Suzuki-Miyaura Cross-coupling reaction

To a mixture of 2.40 (0.02070 g, 0.0498 mmol) in THF (1.00 mL) was added NaOEt/EtOH (0.00679 g, 0.0998 mmol), Pd(PPh₃)₄ (0.0028 g, 0.00249 mmol) and isocrotyl bromide (0.006 mL, 0.0599 mmol). The mixture was stirred at 23 °C for 10 h and diluted with Et₂O (5 mL). The organic layer was washed with H₂O (2 mL), brine (2 mL), dried over Na₂SO₄ and concentrated via rotavap to give the crude product as a yellow oil. The crude ¹H-NMR showed an extensive number of vinyl peaks indicating a complex mixture. No further analysis was taken.
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Zündorf, W. *Chem. Ber.* 1972, 105, 3794. (b) Köbrich, G.; Kolb, B.; Mannschreck,
Bödecker, H. O.; Elbe, H.L.; Kobrich, G. *Tetrahedron Lett.* 1974, 2153. (d) Bomse, D.

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APPENDIX A

$^1$H AND $^{13}$C SPECTRA OF BOROSTANNYLATION-CYCLIZATION PRECURSORS, PRODUCTS AND THEIR DERIVATIVES
COSY NMR of Diazaborolidine 2.40
$^{13}$C NMR of Diazaborolidine 2.40
$^1$H NMR of Dioxaborolidine 2.55
COSY NMR of Dioxaborolidine 2.55
NOESY NMR of Dioxaborolidine 2.55
$^1$H VT NMR of Dioxaborolidine (toluene-d$_8$)-stack plot 2.55
$^{13}$C NMR Dioxaborolidine 2.55
$^1$H NMR of Diazaborolidine- full spectra 2.41
$^1$H NMR of Diazaborolidine- zoom 2.41
$^1$H NMR of Diazaborolidine (with R$_a$S$_c$S$_c$ ligand) - full spectra 2.41
$^1$H NMR of Diazaborolidine (with R,S,S ligand) - zoom 2.41
$^{1}H-^{1}H$ NOE NMR of Diazaborolidine 2.41
$^1$H-$^1$H COSY NMR of Diazaborolidine 2.41
$^1$H VT NMR of Diazaborolidine (toluene-$d_8$)-stack full 2.41
\(^1\)H VT NMR of Diazaborolidine (toluene-d8)-stack zoom 2.41
$^{13}$C NMR of Diazaborolidine 2.41
$^1$H NMR of Dioxaborolidine 2.53
$^1$H-$^1$H COSY NMR of Dioxaborolidine 2.53
$^{1}H$ VT NMR of Dioxaborolidine room temp NMR (toluene-$d_8$) 2.53
$^1$H VT NMR of Dioxaborolidine room temp NMR (toluene-d$_8$) – stack 2.53
$^{13}$C NMR of Dioxaborolidine 2.53
$^1$H NMR of Diyne - full spectra 2.30
$^1$H NMR of Diyne - zoom 2.30
DEPT NMR of Diyne 2.30
H-H COSY NMR of Diyne 2.30
H-H NOE NMR of Diyne 2.30
$^{13}$C NMR of Diyne 2.30
$^1$H NMR of Diazaborolidine Product Mixture - full spectra 2.49A:B
\(^1\)H NMR of Diazaborolidine Product Mixture - zoom 2.49A:B
$^{13}$C NMR of Diazaborolidine Product Mixture 2.49A:B
$^1$H NMR of Dioxaborolidine Major- full spectra 2.52A
$^{1}$H NMR of Dioxaborolidine Major - zoom 2.52A
$^1$H-$^1$H NOESY NMR of Dioxaborolidine Major 2.52A
$^1$H VT NMR of Dioxaborolidine Major- full spectra 2.52A
$^1$H VT NMR of Dioxaborolidine Major- zoom 2.52A
$^{13}$C NMR of Dioxaborolidine Major 2.52A
\textsuperscript{1}H NMR of Dioxaborolidine Minor- full spectra 2.52B
$^1$H NMR of Dioxaborolidine Minor- zoom spectra 2.52B
$^1$H-$^1$H NOESY NMR of Dioxaborolidine Minor 2.52B
$^1$H NMR of Diazaborolidine Product Mixture - full spectra 2.50A:B
$^1$H NMR of Diazaborolidine Product Mixture - zoom 2.50A:B
$^{1}\text{H-}^{1}\text{H COSY NMR of Diazaborolidine Product Mixture 2.50A:B}$
$^1$H-$^1$H NOESY NMR of Diazaborolidine Product Mixture 2.50A:B
$^1$H NMR of Diazaborolidine Product Mixture - full spectra 2.51A:B
$^{13}$C NMR of Diazaborolidine Product Mixture 2.51A:B
$^1$H NMR of Dioxaborolidine (C$_6$D$_6$) 2.65
$^1$H VT NMR of Dioxaborolidine (toluene-d$_8$) – room temp 2.65
$^1\text{H}-^1\text{H}$ COSY NMR of Dioxaborolidine 2.65
$^{1}H-^{1}H$ NOESY NMR of Dioxaborolidine 2.65
$^1$H VT NMR of Dioxaborolidine (toluene-$d_8$) - zoom 2.65
$^{13}$C NMR of Dioxaborolidine 2.65
$^1$H NMR of Dioxaborolidine 2.67
$^1$H VT NMR of Dioxaborolidine (toluene-d$_8$) – room temp 3.9
$^1$H VT NMR of Dioxaborolidine (toluene-d$_8$) – room temp zoom 3.9
$^1$H VT NMR of Dioxaborolidine (toluene-d$_8$) – stack 3.9
$^1$H VT NMR of Dioxaborolidine (toluene-$d_8$) – stack full 3.7
$^1$H VT NMR of Dioxaborolidine (toluene-d$_8$) – stack zoom 3.7
APPENDIX B

X-RAY CRYSTALLOGRAPHY INFORMATION FOR β-LACTAM DIAZABOROLIDINE 2.52A

ORTEP of β -Lactam Diazaborolidine 2.52A
X-ray Crystallographic Information for β-Lactam Diazaborolidine 2.52A
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Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å$^2$ x $10^3$) for RajanBabu 1733. U(eq) is defined as one third of the trace of the orthogonalized U$^0$ tensor.

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Table 3. Bond lengths [Å] and angles [°] for RajanBabu 1733

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Table 4. Anisotropic displacement parameters (Å² x 10³) for RajanBabu 1733. The anisotropic displacement factor exponent takes the form: 

\[-2\pi² [ h²a² U^{11} + ... + 2hk a³ b³ U^{12} ]\]

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Table 5. Calculated hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\textup{Å}^2 \times 10^3$) for RajanBabu 1733.

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