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UMI
PART I. WATER-SOLUBLE ORGANOMETALLIC CATALYSTS FOR ASYMMETRIC REACTIONS IN AQUEOUS MEDIA
PART II. SILYLSTANNYLATIVE CYCLIZATION OF UNSATURATED SUBSTRATES CATALYZED BY PALLADIUM COMPLEX

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Seunghoon Shin, M.S.

The Ohio State University
2001

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Approved by
Advisor
Department of Chemistry
ABSTRACT

The major drawback of homogeneous catalysis is the difficulty of separation of the catalyst from the product. A solution to this problem was developed using water-soluble catalysts derived from a disaccharide (α,α'-trehalose) and D-mannitol. Selective functionalization of α,α'-trehalose led to several macrocyclic phosphinite/phosphine ligands, which showed high activity and selectivity in hydrogenation of dehydroamino acids in organic media. For the deprotection of these organic-soluble ligands, the choice of protecting group turned out to be a key issue. The use of acid-labile ketal protecting groups served best for this purpose, and the cyclic ketal groups from the Rh(I)-ligand complex could be easily deprotected by use of solid phase reagent, i.e., an acidic resin. The water-soluble Rh(I)-complexes thus formed are active hydrogenation catalysts for dehydroamino acids in water without any additive, albeit with the following limitations: (1) The enantioselectivities in the hydrogenation of dehydroamino acids were lower in water than in organic media. (2) The ‘water-soluble’ Rh(I) complex from disaccharide still had significant solubility in organic solvent, making the catalyst recovery difficult. Both problems could be solved by use of hydroxyphospholanes synthesized from D-mannitol. For the generation of water-soluble ligands from protected hydroxyphospholanes, tert-butyldimethylsilyl (TBS) ethers were chosen as protecting groups. Treating the TBS-protected phospholane with trifluoroacetic acid, followed by
removal of excess acid by filtration through a resin-bound tertiary amine led to a clean deprotected hydroxyphospholane ligands having the backbone of the notable DuPHOS ligand. The ligands thus formed were freely soluble in water by virtue of reduced number of phenyl rings. This was demonstrated by catalyst recovery and reuse experiments, in which the recycling was carried out six times (total of 7 cycles). The enantioselectivities in the hydrogenation of dehydroamino acids remained at 99 %ee after 4th cycle without any loss of catalytic activity. The availability of water-soluble free ligands is expected to lead to application in homogeneous catalysis with metals other than rhodium.

Silylstannanes as well as other bimetallic reagents add to triple bonds under the catalysis of palladium with very high functional group compatibility. The method can be used for the cyclization of unsaturated α,ω-bifunctional substrates. For example, cyclization of diynes was applied to a synthesis of pyrrolizidine ring structure. A lack of regioselectivity was noted as a major limitation in the cyclization of unsymmetrical diynes. Among the potential schemes for solving the regioselectivity problem, the use of allene as a substrate instead of diyne provided an attractive solution due to the higher reactivity of allene vs. acetylene. Thus, various allenynes could be efficiently cyclized in good yields to give carbo- and heterocyclic compounds with excellent regio- and stereocontrol. The use of allene in the silylstannylative cyclization reaction was further applied in the synthesis of kainoid pyrrolidines. The entry into a late intermediate of α-kainic acid was achieved by combination of silylstannane addition into an allene, followed by radical cyclization of the resulting allylstannane. Alternatively, silylstannylative cyclization of an appropriate alleneyne precursor led to both C4-epimers with α-kainic acid and allokainic acid configurations, respectively.
The silylstannylyative cyclization of cyclic diynes provided silylstannanes with sterically encumbered exo-1,3-(Z,Z)-diene system with added bicyclic ring strain. Atropisomeric properties of bicyclic silylstannane dienes were studied through low-temperature NMR spectroscopy. The coalescence temperature of the atropisomeric equilibrium depends on the silylstannane reagent as well as ring structures. In one case, the atropisomeric exchange was found to be above 70 °C, suggesting high barriers of inversions between atropisomers. Further synthetic applications will involve stereospecific transformations of these axially chiral molecules into molecules with centers of chirality and also the possible synthetic implication of the interconversion between these two types of chirality.
Dedicated to my parents
ACKNOWLEDGMENTS

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Most of all, I thank my parents for their love and sacrifice which made this work possible.
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Research Publication


FIELD OF STUDY

Major Field: Chemistry
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<tr>
<td>Acac</td>
<td>Acetylacetonate</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-Cyclooctadiene</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlated spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>Dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarization Transfer</td>
</tr>
<tr>
<td>DIBALH</td>
<td>Diisobutylaluminum hydride (<em>or</em> DIBAL)</td>
</tr>
<tr>
<td>DIPEA</td>
<td>Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalent (<em>or</em> eq.)</td>
</tr>
<tr>
<td>FAB-Ms</td>
<td>Fast atom bombardment (FAB) mass spectroscopy</td>
</tr>
<tr>
<td>Hex</td>
<td>n-Hexane</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multi Quantum Coherence</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectroscopy</td>
</tr>
<tr>
<td>(K.C.)(^x)</td>
<td>Known compound (<em>x</em>: reference at the end of each chapter)</td>
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<td>LAH</td>
<td>Lithium aluminum hydride</td>
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<td>Acetonitrile</td>
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<tr>
<td>MOP</td>
<td>2-(Diphenylphosphino)-2'-methoxy-1,1’-binaphthyl (or MeO-MOP)</td>
</tr>
<tr>
<td>N/A</td>
<td>Not applicable</td>
</tr>
<tr>
<td>nbd</td>
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<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>nOe</td>
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<td>PhCN</td>
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<tr>
<td>pin</td>
<td>Pinnacolyl</td>
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<tr>
<td>Rf</td>
<td>Retention coefficient (TLC)</td>
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<tr>
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<td>SOCl₂</td>
<td>Thionylchloride</td>
</tr>
<tr>
<td>SR</td>
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<td>TBAF</td>
<td>Tetra-n-butlammonium fluoride</td>
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<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl (or TBDMS)</td>
</tr>
<tr>
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<td>Tetrahydropyranyl</td>
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<td>TLC</td>
<td>Thin-layer chromatography</td>
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<td>tol</td>
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XX
CHAPTER 1

PART I: WATER-SOLUBLE ORGANOMETALLIC CATALYSTS FOR USE IN ASYMMETRIC HYDROGENATION IN AQUEOUS MEDIA

PART II: BISFUNCTIONALIZATION-CYCLIZATION OF α,ω-UNSATURATED COMPOUNDS

1.1.1. Water-Soluble Organometallic Catalysts in Asymmetric Synthesis

Homogeneous catalysis has many advantages over its heterogeneous counterpart because the former employs a well-defined soluble catalyst with recognizable steric and electronic properties, often influenced by the ligands. Also, higher activities and selectivities are generally exhibited under milder conditions. However, for industrial applications of homogeneous catalysis, there is one serious drawback: the separation of catalyst from the product.\(^1\) A solution to this problem is the use of biphasic conditions in which the catalyst is soluble in one phase and the organic product, in another. In this connection, water-soluble catalysts have attracted great deal of attention, because aqueous phase containing catalyst could be recovered by simple phase separation from the organic media (Figure 1.1).\(^7a\)
Figure 1.1. General Protocol for Biphasic Catalysis

The success of the Ruhrchemie/Rhône-Poulenc hydroformylation process, which uses a water-soluble sulfonated triphenylphosphine complex of Rh, stimulated application of this 'process principle' to a broad range of reactions.¹ While the use of water as an environmentally benign solvent is a debatable issue, for a homogeneously catalyzed process running in a biphasic system, the advantages offered by facile separation of catalyst and organic product phase cannot be overemphasized. In addition, selective functionalization of large water-soluble biomolecules is an area of increasing importance in connection with a number of biotechnology problems,²³ and here, water-soluble catalysts have distinct advantages over enzymes, where two major limitations have been recognized: substrate specificity and the need for large amount of solvent.

A number of different strategies have been employed to increase the solubility of phosphine ligands and their complexes in aqueous media.¹ The majority of successful applications of water-soluble phosphine ligands in aqueous homogeneous catalysis involve compounds that carry sulfonate (anionic) or quaternary ammonium (cationic) groups. Non-ionic, chiral ligands with hydrophilic groups designed to improve aqueous
solubility are beginning to receive increasing attention. Such neutral ligands may find applications for metal-catalyzed reduction of membrane lipids where catalyst transport into the bilayer membrane maybe precluded by use of highly charged ionic complexes which accumulates at the water-organic interface.

1.1.2. Asymmetric Hydrogenation Reactions

Homogeneous metal-catalyzed hydrogenation of olefins (e.g. eq. 1) represents one of the most widely used and mechanistically understood reactions in organic chemistry. It is catalyzed by a variety of metals (Pd, Rh, Ir), and uses a readily available feedstock, hydrogen gas at moderate to high pressures. The ligand that is coordinated to the metal is a key element in obtaining high enantioselectivity and activity. Most successful ligands belong to the group of bidentate phosphines, bearing chirality either on phosphorus or on the carbon backbone connecting two phosphorus atoms. Historically, the most successful ligands for the asymmetric hydrogenation were BINAP, DIPAMP, DuPHOS, and DIOP (Figure 1.2) and the excellent enantioselective hydrogenation protocols for the synthesis of a variety of products, among them, amino acids, esters, amines, and alcohols have been reported.

\[
\begin{align*}
\text{R} & \text{NHC(O)Me} \\
\text{R} & \text{CO}_2\text{R'} + \\
\text{H}_2 & \text{(0.4-0.8 mol \% Rh(I)(L))} \\
\text{THF or water} & \text{30 psi / RT} \\
\text{R} & \text{NHC(O)Me} \\
\text{R} & \text{CO}_2\text{R'}
\end{align*}
\] (1)
1.1.3. Carbohydrate-Derived Water-Soluble Ligands

Carbohydrates with their rich array of stereochemical and functional group diversity have been a popular source of starting materials in organic synthesis. Many mono- and disaccharides are abundantly available in 100 % enantiomeric purity and there is a prolific history of functional group manipulations that dates back to more than a century of carbohydrate chemistry. Therefore it is surprising that they have attracted broad attention as ligand precursors for asymmetric catalysis only recently.
In previous years, RajanBabu and coworkers have shown that carbohydrate phosphinite complexes catalyze a wide variety of reactions such as hydrocyanation (Ni), hydrogenation (Rh), hydroformylation (Rh), and allylation (Ni and Pd). While the carbohydrate backbone provided the necessary stereochemical diversity, substitution patterns around phosphorus were used to vary the steric and electronic properties of the ligand (Figure 1.3). One salient property of carbohydrates that has not been fully exploited is their water solubility due to the polyhydroxylic nature. Pioneering studies conducted by the Selke and Oehme have amply demonstrated that even phosphinite ligands derived from monosaccharides have some solubility in water (Figure 1.4). They also showed impressive enhancement of enantioslectivity in the presence of micelle-forming amphiphiles when sparingly soluble substrates are used. The high ee's of these reactions notwithstanding, anecdotal evidence seems to suggest that these complexes with monosaccharide-derived ligands (e.g. 1) have only limited aqueous solubility. Also, the use of micelle-forming additives with such amphiphilic ligands is essential in order to get high enantioselectivity and solubility. This requires further separation of the additives after the reaction. In an attempt to circumvent the limited solubility of monosaccharide-

![Figure 1.4 Water-Soluble Hydroxy Phosphinites](image-url)

5
derived ligands, others\textsuperscript{7a} and we\textsuperscript{8b} have resorted to a disaccharide like trehalose (e.g., 3 and 4), the chemistry of which will be described in Chapter 2. A cationic ligand 2 containing quaternary ammonium salt derived from D-Salicin,\textsuperscript{8b} has also been used in our group. In line with the expectations, Yan and RajanBabu recently reported that the cationic complex 2 is freely soluble in water without a micelle-forming agent, although exact distribution between organic phase and water was not measured.

1.1.4. Development of Water-Soluble Phosphinite Ligands from $\alpha,\alpha'$-Trehalose

In connection with the asymmetric hydrocyanation project, in 1992 RajanBabu and Casalnuovo first reported a number of bisphosphinite ligands from disaccharides including a few from $\alpha,\alpha'$-trehalose.\textsuperscript{11,5b} An interesting question is how the enantioselectivity of Rh-catalyzed hydrogenation reaction using the corresponding fully deprotected ligands will be affected. The incorporation of four or more hydroxyl groups (vis-à-vis monosaccharide ligands) will be expected to increase the solubility in water. This would solve one of the problems associated with the use of monosaccharide ligands in water. \textit{Can these polyhydroxylated phosphinites be used without added micelle forming reagents?} In Chapter 2, the details of the relevant chemistry for the selective functionalization of $\alpha,\alpha'$-trehalose for the synthesis of novel bisphosphinites and the application of these ligands in asymmetric hydrogenations (eq. 1) will be described. In addition, we have also studied solubility properties of the Rh-complexes of 4 (in Figure 1.4) and their stability in methanolic solution.
1.1.5. Development of Neutral, Polyhydroxy Phospholane Ligands

Our investigation of the partition coefficient for the Rh complex from ligand 4 between organic and water phases (by inductively coupled plasma spectroscopy) revealed that in spite of the increased number of hydroxyl groups, the Rh (I) complex still possessed considerable solubility in the organic medium (Figure 1.5). A comparison of the number of hydroxy groups present in the sugar backbone (6) with the number of hydrophobic aromatic phenyl rings (4) might give a good indication why this complex is still somewhat hydrophobic. In addition, a study of the stability of Rh*(4) complex indicated that after 9 days in MeOH-d$_4$ considerable deterioration occurred. Also, Ohe, Uemura and coworkers have noticed a significant deterioration of catalyst activity upon

![Figure 1.5 Distribution of Water-Soluble Catalyst between Water and Organic Solvents](image)

<table>
<thead>
<tr>
<th>solvent</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
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<td>CH$_2$Cl$_2$/water</td>
<td>1.05</td>
</tr>
<tr>
<td>EtOAc/water</td>
<td>0.63</td>
</tr>
<tr>
<td>ether/water</td>
<td>0.04</td>
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</tbody>
</table>

reuse of the aqueous phase for subsequent reaction. In our group, Dr. Yan noted that a fully deprotected 'water-soluble' salicin-derived complex [Rh*(2)(cod)]X$^-$ (Figure 1.4) had limited solubility in neat water in his attempts to take a $^{31}$P NMR spectrum. For example, compared to corresponding protected complex (in CDCl$_3$), a saturated solution of 2 (in D$_2$O) takes at least 5 times more scans of FID (free induction decay) to get a
satisfactory $^{31}$P NMR spectrum of the similar signal-to-noise ratio.\textsuperscript{8} The stability of the Rh(I) complex of 2 is also limited. A solution of 2 in D$_2$O retains the original $^{31}$P NMR signals only up to 4 days, and after 9 days, more than 50\% of the complex had undergone decomposition, with the appearance of new signals in the $^{31}$P NMR spectrum.

We believe that an attractive solution to the dual problem of hydrolytic instability and hydrophobicity can be addressed through the use of polyhydroxy phospholane bearing robust P-C bonds (vis-à-vis P-O bonds) and a reduced number of aryl substituents on the phosphorus atom.

![Chemical structures](image)

Figure 1.6. Monophospholanes and Bisphospholanes Synthesized in the Group

With these goals in mind, the C$_2$-symmetric phospholane system was chosen. These molecules have the backbone of the enormously successful DuPhos ligands discovered by Burk and coworkers (Figure 1.6).\textsuperscript{12} Last year, Dr. Yan in our group reported a synthesis of several highly functionalized mono- and bisphospholanes 7 and 8.
from readily available D-mannitol.\textsuperscript{11} The enantioselectivity imparted by these ligands depends critically on the nature and configuration of the various substituents on the phospholane ring. For example, by judicious choice of these groups, enantioselectivities approaching 100 % can be achieved in several prototypical asymmetric reactions.\textsuperscript{13b}

In this Chapter 2, the synthesis and applications of various trehalose-derived ligands (\textit{e.g.} 3 and 4 in Figure 1.4) and mono- and bisphospholane ligands (\textit{e.g.} 5 and 6 in Figure 1.6) will be described. Compared to the stereochemical divergence in the synthesis of 7 and 8, the stereochemical variation in the synthesis of 5 and 6 is quite limited. However, positioning polyhydroxy functional group near the phosphorus atom raises an interesting issue of hemi-labile ligation,\textsuperscript{41} which will be discussed under the hydrovinylation reaction in Chapter 2. Allylic reduction using formic acid with monophospholane 5 will also be described. The bisphospholane 6 (R = H) will be shown to be an excellent ligand for asymmetric hydrogenations in aqueous phase. The solubility characteristics and stability of the Rh(I) complexes have been enhanced by use of this polyhydroxy bisphospholane. For example, the reuse and recycle of the Rh(I) catalyst with 6 (R = H) was demonstrated up to 7\textsuperscript{th} cycle with no concomitant deterioration of the enantioselectivity, albeit a slight lowering of activity (Chapter 2).
Part II. Bisfunctionalization-Cyclization of α,ω-Unsaturated Compounds

1.2.1. Catalytic Synthesis of Carbocyclic and Heterocyclic Compounds

The discovery of new C-C bond forming reactions and application of these reactions for the synthesis of cyclic compounds are major goals of current research in organic chemistry. The classes of reactions that have the broadest applicability in organic synthesis are those that address the issues of stereo-, regio-, and enantiocontrol. Compatibility with a variety of functional groups adds further value to these processes. Also, reactions that introduce into the molecule, multiple of bonds, functional groups, and latent functionality from a relatively simple organic precursor are particularly important tools. Applicability of such reactions could ultimately be tested in the chemical synthesis of complex natural or ‘unnatural’ products. Many carbocyclization reactions, including cycloisomerizations and cycloadditions of organic unsaturated precursors, often mediated by various transition metal complexes, fall into this category. In more recent years, use of bisfunctionalization reagents (R₂Sn-SiR’₃, R₃Sn-BX₂, and R₃Si-SiR’₃, as well as R₂Sn-H and R₃Si-H) for the cyclization reactions has enriched the scope and utility of the end products.¹⁴

Carbocyclization of alkene, alkyne, and allene are extremely important reactions for the synthesis of a variety of carbocyclic and heterocyclic compounds. The term,
carbocyclization has been used to describe an annulation process where C-C bond formation occurs through a carbametallation which delivers C-M species across π-systems, such as C=C and C≡C. Numerous transition metal complexes are known to promote or catalyze this process, and among them palladium, which is by far the most utilized, will be introduced in more detail in the following sections.

1.2.2. Pd-Based Catalyst Systems for Carbocyclizations

Pd-catalyzed Heck reaction has been a subject of great interest\(^\text{15}\) and has become a popular annulation protocol in the field of total synthesis.\(^\text{16}\) In a typical example, as shown in eq. 2, intramolecular Heck cyclization generates a σ-alkyl-Pd\(^2\+) intermediate which is captured by nearby olefin to give a double cyclization products having a spiro or fused skeleton 10 and 11.\(^\text{17}\)

The acceptor for the σ-alkyl-Pd(II) intermediate is not limited to an alkene. Acetylene and allene also can act in the same fashion as shown in eq. 3 and eq. 4.\(^\text{18,19}\) Thus, in eq. 4, successive carbametallation into acetylene and aldehyde, delivers the indenone skeleton.
Palladium (II) also catalyzes cycloisomerization of eneynes (eq. 5) at 25-65 °C, where thermal Alder ene reaction for the equivalent conversion requires high temperatures (>250 °C). The Pd-catalyzed cycloisomerization is believed to occur via a Pd(0)-Pd(II) or Pd(II)-Pd(IV) cycle depending on the reaction conditions and choice of precatalyst. Use of a Pd(II) precursor such as Pd(OAc)$_2$ in the absence of a reducing agent favors the Pd(II)-Pd(IV) cycle, whereas Pd(0)-Pd(II) cycle is favored by the use of Pd(0) precursor such as Pd$_2$(dba)$_3$CHCl$_3$ with a carboxylic acid partner. The postulated catalytic cycles are depicted below in Scheme 1.1. The Pd(II)-Pd(IV) cycle involves formation of palladacycle followed by β-elimination, and Pd(0)-Pd(II) cycle in the presence of HOAc, forms Pd-H species which initiates the catalytic cycle.
Scheme 1.1. Postulated Mechanism for the Pd-Catalyzed Eneyne Cycloisomerization
A spectacular display of utility of 1,6-enedyne cyclization reaction is found in a so-called 'zipper-mode' cyclization (eq. 6), in which appropriately spaced polyenedyne can be cyclized up to seven spirocycles in high yield in one step.\(^2\)

Factors controlling diastereoselectivity usually reside in the substrate. In a halotropic cyclization in eq. 7, \textit{trans/cis} selectivity depends largely on the bulkiness of \textit{R'} group.\(^2\) The \textit{trans} isomer is favored when \textit{R'} = H, while \textit{cis} isomer is favored exclusively when \textit{R'} = alkyl or silyl and the stereochemistry of double bond is dependent on the amount of LiCl, present in the medium.

\[
\begin{array}{cccc}
\text{R} & \text{R'} & \text{yield} & \text{trans/cis} \\
\text{Pr} & H & 90\% & 98:2 \ (Z) \\
\text{Me} & \text{Me} & 97\% & 0:100 \ (E) \\
\text{Me} & \text{Me} & 72\% & 10:90 \ (Z) \\
\end{array}
\]

Use of PMHS (polymethylhydrosiloxane) or Et\(_3\)SiH as stoichiometric reducing agent forms a catalytic system for reductive cyclization of 1,6-enedynes (eq. 8).\(^2\) The active catalytic species of this process has been identified as \((\text{H})\text{PdL}_2(\text{OAc})\). A \(\sigma\)-bond
metathesis of (alkyl)PdL₆(OAc) with Et₃SiH generates (alkyl)PdL₆(H) species, which undergoes reductive elimination to give the alkyl-H.

In our group, Dr. Radetich reported cyclization of 1,6-diene can be accomplished by catalysis of [Pd(allyl)X]₂ or [Ni(allyl)X]₂ in the presence of AgOTf (eq. 9). The reaction conditions are compatible with a variety of functional groups such as esters, amides, sulfonamides and allyl ethers. In the mechanism proposed, initially formed [(L)M-H]* (M = Pd, Ni) undergoes hydropalladation, followed by insertion of the second olefin into M-C bond and subsequent β-hydride elimination to regenerate the catalyst.

\[
\text{Ph} \quad \text{Ph}
\]

\[
\begin{align*}
\text{[Ni(allyl)Br]}_2 (5 \text{ mol\%}) \\
(4\text{-MeO-C}_6\text{H}_4)_3\text{P}, \text{AgOTf} \\
\text{rt, 1 day}
\end{align*}
\]

\[
\text{81 \%}
\]

1.2.3. Use of Bifunctional Reagents

In recent years, the scope and the utility of the end products in metal-catalyzed cyclization reaction have been widened significantly by the use of bifunctional reagents, such as R₃Sn-SiR'₃, R₃Sn-BX₂, and R₃Si-SiR'₃, as well as the more traditional R₃Sn-H and R₃Si-H. The end product of insertion of these reagents into acetylene, namely, vinyl stannanes, vinyl silanes, and vinyl boranes are of great synthetic potential as building blocks in organic chemistry thanks to the large number of C-C bond forming reactions they undergo.

In 1985, Chenard and RajanBabu, and Mitchell independently reported the original discovery that R₃Sn-SiR'₃ reagents add to acetylenes, catalyzed by Lewis acid or
palladium complexes. Recently, in our group, Dr. Radetich discovered that the addition of R₃Sn-SiR₃ reagents to acetylenes can be used for the cyclization of diynes (eq. 10). Subsequently, Dr. Warren optimized the reaction conditions through the examination of reaction parameters including the phosphine ligand, R₃Sn-SiR₃ reagents, solvent, temperature, and reaction time. The unusual (Z,Z)-1,2-bisalkylidene cyclopentane frame imposes a strained cyclopentane geometry, which was studied in detail by dynamic NMR spectroscopy. The postulated mechanism for the insertion of R₃Sn-SiR₃ across acetylene or into diyne in a tandem fashion is shown in Scheme 1.2. The reaction is initiated by the oxidative addition of Sn-Si reagent into Pd(0) to make R₃Sn-Pd(II)-SiR₃ species (oxidative addition), followed by insertion of π-system into the Pd(II)-SiR₃ bond (silapalladation) with exclusive cis-stereochemistry. In the presence of an appropriately placed acetylene, insertion of (alkenyl)Pd(SnR₃) moiety into the coordinated acetylene occurs (carbopalladation), followed by a reductive elimination with the formation of the C-SnR₃ bond. This result in a silylstannyl carbocycle and regeneration of Pd(0). Mechanistically, the unusual (Z,Z)-1,3-diene stereochemistry is the result of cis-silapalladation and cis-carbapalladation. This proposition is in accordance with recent ab initio HF calculation in many aspects.
Figure 1.7. Isolated \((R_3Si)Pd(\text{II})(SnR'_3)\) Complex

Scheme 1.2. Proposed Mechanism of Silylstannylation-Cyclization of Diynes

Theoretical study indicated that oxidative addition of Sn-Si bond into palladium is an exothermic reaction, giving \((Si)PdL_6(Sn)\) intermediate as a resting state in the catalytic cycle. In support of such a mechanism, a related silylstannyl Pd complex was isolated recently (Figure 1.7).\(^{31}\) Theoretical calculation of the rate determining insertion step with acetylene suggested that insertion of acetylene into Pd-Sn bond (stannylpalladation; path b, Scheme 1.3) proceeds with the lowest activation energy, which is 2 kcal/mol lower than that of insertion into Pd-Si bond (silapalladation, path a). However, thermodynamic
stabilities of the resulting vinyl palladium species are significantly different, 12 being more stable than 13 by 11 kcal/mol. Since the insertion step is endothermic and potentially reversible, the formation of the thermodynamically more stable intermediate 12 may be favored.

Scheme 1.3. Theoretical Study of the Mechanism

Compared with the reaction of Sn-Si bond with acetylene in the presence of Pd(0), there are few examples where alkene is involved. Silylstannane addition to alkene is limited to the ethylene and norbornene derivatives (eq. 11). Enynes are known

\[
\text{SnR}_3 + \text{Pd(dba)}_2, \text{cat PEI}_3 \text{ or PBu}_3 \text{ toluene, } 130^\circ C \rightarrow \begin{array}{c}
\text{SnR}_3 \\
\text{SiMe}_2\text{R}'
\end{array} \text{ up to 95 %}
\]

\[
\begin{array}{c}
\text{SnR}_3 \\
\text{SiMe}_2\text{R}'
\end{array} \text{ up to 59 %}
\]
to be cyclized under these conditions, though the yield is usually low and monoaddition of Sn-Si bond to acetylene is obtained as the side product, reflecting the low reactivity of olefin towards carbbametallation to the olefin involved (eq. 12). Very recently, Mori and coworkers reported that ligandless Pd(OH)$_2$ on charcoal (Pearlman's catalyst) system was found to be very effective and the same reaction in eq. 12 proceeded to give cyclized product 15 in excellent yield (90 %) at rt in 20 h.

\[
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{Bu}_3\text{Sn-SiMe}_3 \quad \xrightarrow{\text{Ligand/Pd}} \quad \text{E} \quad \text{E} \quad \text{SnBu}_3 \quad \text{Bu}_3\text{Sn} \quad \text{SiMe}_3
\]

(entry catalyst conditions yield)
<table>
<thead>
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<th>entry</th>
<th>catalyst</th>
<th>conditions</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$ (2.5 %)</td>
<td>PPh$_3$ (5 %) 60 °C, C$_6$H$_6$, 1 day</td>
<td>14 9 %, 15 30 %</td>
</tr>
<tr>
<td>2</td>
<td>PdCl$_2$ (5 %)</td>
<td>rt, C$_6$H$_6$, 1 day</td>
<td>15 35 %</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_3$ (2.5 %)</td>
<td>P(C$_6$F$_5$)$_3$ (5 %) rt, C$_6$H$_6$, 1 day</td>
<td>15 49 %</td>
</tr>
</tbody>
</table>

Pd-catalyzed silastannanylation of allenes has been studied by Mitchell and coworkers. The product from the reaction is an allylstannane, with Si moiety always ending up on the middle carbon. The reductive elimination from alkyl-Pd-Sn species can give internal product 16 or the terminal product 17 (eq. 13). The larger alkyl substituents in allene increased the formation of internal addition product 16, while a larger substituents on Sn atom of silylstannanes increases the formation of the terminal addition product 17. Isomerization of 16 to the thermodynamically more stable 17 occurs on heating.
A reaction closely related to the above silylstannylation is the reaction of organosilylboranes with unsaturated compounds in the presence of a transition metal. The addition of Si-B bond across C-C triple bond was first realized with the aid of a Pd/alkyl isonitrile catalyst.\(^\text{37}\) Employing the pinacol derivatives of silylborane, silaboration of a variety of alkyne was examined. Many acetylenes with remote functional groups such as chloro, cyano, THPO, MEMO- and hydroxy group underwent the reaction in good yield with complete regio- and stereoselectivity (eq. 14). The reaction was successfully applied to enyne to afford the five membered cyclic products with high regio and stereoselectivity (eq. 15).\(^\text{37}\)
Also, other bimetallic X-Y type reagents, Me₅Sn-B(-N(Me)CH₂CH₂N(Me)-)₂²⁷e (RO)₂B-B(OR)₂²⁴ have been reported in a very similar context (eqs. 16-18). The Sn-B reagent shows better reactivity toward the most challenging substrate, i.e. eneynes and internal acetylenes. However, one limitation of the reagent is that the product is not stable, and only amenable methods for isolation of product is either recrystallization or distillation.²⁷e

\[
\begin{align*}
\text{EtO₂C} & \quad \text{Me₅Sn-B} \quad \text{PdCl₂(PPh₃)₂ (1 mol %)} \\
\text{EtO₂C} & \quad \text{Me₅Sn-B} \quad \text{rt, 1 h, benzene} \\
\end{align*}
\]

\[
\begin{align*}
\text{EtO₂C} & \quad \text{Me₅Sn-B} \quad \text{PdCl₂(PPh₃)₂ (1 mol %)} \\
\text{EtO₂C} & \quad \text{Me₅Sn-B} \quad \text{rt, 1 h, benzene} \\
\end{align*}
\]

Hydrostannylation is another reaction that is reported to cyclize eneyne and diynes (eq. 19, 20).²⁷e ³⁸ The proposed mechanism involves initiation via oxidative addition of Sn-H bond to Pd(II), and the resulting (H)Pd(SnR₃) is inserted into the acetylene through either stannylation or hydrometallation. Ligandless catalyst system (Pd(OH)₂ on charcoal, Pearlman's catalyst) shows better or comparable reactivity to the systems with ligands in this type of cyclizations.³⁸
Ojima and coworkers have reported the $R_3Si-H$ mediated hydrosilylation-cyclization reactions of diyne or eneyne. There are many variants for this reaction, namely silylformylation,\(^{39a}\) silylcyclocarbonylation,\(^{39b}\) and silylcarbocyclization.\(^{39c}\) One of the examples of $\text{Rh(CO)}_2(\text{acac})$ catalyzed silylcyclocarbonylation is shown in eq. 21.\(^{39c}\) Tamao and coworkers reported $\text{Ni(acac)}_2$ (1 mol %) / DIBALH (2 mol %) system for silylcarbocyclization of diyne (eq. 22).\(^{43}\) These are excellent catalysts and also applicable to internal diyne. However, for unsymmetrical diynes, the regioselectivity obtained is marginal (eq. 23).\(^{43}\)
The reactions of bisallene were studied by Kang and coworkers. The use of different bifunctional reagent gave rise to a striking reversal of diastereoselectivity, i.e. $\text{Bu}_3\text{SnSiMe}_3$ reagent showed exclusive trans selectivity, $\text{Bu}_3\text{SnSnBu}_3$ reagent showed exclusive cis selectivity (eq. 24). Although the mechanism of this behavior is largely speculative, the study of bisallenes for carbocyclization provided the possibility of generating stereocenters in a controlled fashion, which could not be realized in diyne cyclization and is seldom found in other related cyclizations.

Compared with the wealth of documented carbocyclization methodologies in the literature, the silylstannylation-cyclization method is currently at an early stage. In Chapter 3, our detailed study of substrate scope including ester, amine, amide, alcohol, electron-deficient multiple bond, and unsymmetrical diyne for silylstannylation-
cyclization methodology will be presented. The preliminary reactivity profile and functional group compatibility of the current methodology will lay the ground on which further applications will be based. At the end of Chapter 3, attempted application of diyne cyclization method toward synthesis of pumiliotoxin alkaloid skeleton is presented. The problem of inherent regioselectivity problems in diyne cyclization as well as limited applicability in the internal diyne substrate can be enhanced greatly in the cyclization of an alleneyne, which is presented in Chapter 4. Finally, the utility of silylstannylation-cyclization of diyne and alleneyne is demonstrated in a study directed toward the synthesis of α-kainic acid and related substituted pyrrolidines. Synthesis of a late intermediate with α-kainic acid skeleton and desired 2,3,4-relative stereocontrol was achieved along with synthesis of several potentially useful pyrrolidines. Some of these intermediates maybe useful for the study of atrop-diastereomeric selectivity in cyclization reactions.
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CHAPTER 2

2.1. DEVELOPMENT OF WATER-SOLUBLE CATALYSTS FROM α,α'-TREHALOSE

2.2. DEVELOPMENT OF WATER-SOLUBLE CATALYSTS FROM D-MANNITOL: TETRAHYDROXY BISPHERPHOLANE LIGANDS

2.1.1. Introduction

α,α'-Trehalose is a ubiquitous carbohydrate found in many bacteria, fungi, plants, and in the blood of most insects in nature. Along with its ready availability, a number of documented methods for the derivatization of this molecule for further functionalization are known. The C₂-symmetric structure allows easy modification as well as characterization of various derivatives. In addition, bisphosphinites and bisphosphines

Figure 2.1. C₂-Symmetric Bisphosphinite and Bisphosphine Ligands
derived from them (e.g., 18, 19, and 20) have an interesting structural feature in the large ‘natural’ bite-angle these ligands present (Figure 2.1). This could have interesting consequences in terms of reactivity and selectivity in reactions catalyzed by metal complexes containing these ligands. For example, in hydroformylations of olefins using Xantphos and related ligands (Figure 2.2), the high linear-to-branch ratio obtained was ascribed to this structural feature. Another aspect of these ligands from trehalose that attracted our attention is the potential for developing water-soluble derivatives with its polyhydroxylic nature. The interesting questions in this regard are: (1) is it possible to develop selective chemistry that would permit the synthesis of polyhydroxy phosphine and phosphinite ligands from trehalose? (2) Will the ligands make catalytically competent metal complexes that are useful for reactions in an aqueous medium? The incorporation of four or more hydroxyl groups (vis-à-vis monosaccharide ligands) will increase the solubility in water and is expected to solve the problems associated with the need for the use of micelle-forming amphiphiles when monosaccharide ligands are employed. The application of such fully deprotected tetrahydroxy disaccharide ligands for asymmetric hydrogenation will answer how the enantioselectivity and reactivity of such complexes will be affected in water as a reaction medium.
To develop water-soluble ligands, choice of the hydroxyl protecting group R, which is compatible with the appropriate phosphorus chemistry, is the most critical element (Figure 2.3). Our strategy is to use acid-labile protecting groups that are stable to P-O or P-C bond forming reactions. Thus under the appropriate conditions, the organicsoluble phosphine ligands can be easily converted into the corresponding polyhydroxy ligands by an acid. The effectiveness of this deprotection method would depend on the ease with which by-product and acid can be removed, where chromatographic separation is precluded by the high polarity and air-sensitivity of the product. Thus we reasoned that the use of solid phase reagents would be ideal for this purpose. Two other factors that need to be considered here are the relative basicity of the phosphines and the hydrolytic instability of the phosphinites. The choice of the suitable protecting group and reaction conditions for deprotection step thus become very critical.

Figure 2.3 Potential Water-Soluble Ligands Synthesized and Their Precursors (R = protecting group)

In Chapter 2.1, selective functionalization of α,α’-trehalose leading to various diarylphosphinites and phosphines will be described. Rh(I) complexes formed from these ligands exhibit high hydrogenation catalytic activities. The application of these catalysts
for hydrogenation of dehydroamino acids, as well as stability and solubility characteristics of these complexes will be described in detail.

2.1.2. Selective Functionalization of \(\alpha,\alpha'-\)Trehalose for the Synthesis of Macrocyclic Bisphosphinite Ligands

Synthesis of a series of \(C_2\)-symmetric phosphine and phosphinite ligands 23, 25, and 28 from \(\alpha,\alpha'-\)trehalose is shown in Scheme 2.1. The 4,6:4',6'-benzylidene acetal 21a (or 21b) was a key intermediate,\(^{1m}\) which was readily prepared in two steps in 73 % yield from trehalose. Selective cleavage of the benzylidene acetal using either \(\text{Na(CN)BH}_3/\text{HCl}\)^{3a} or \(\text{LiAlH}_4/\text{AlCl}_3\)^{3b} gave 4,4'- and 6,6'-unprotected trehalose derivatives 22 and 27. Treatment of these compounds with the respective diarylchlorophosphines in the presence of an equivalent of DMAP gave the corresponding bisphosphinites 23a/23b or 25a in good to excellent yields. The 6,6'-diol 27 is a useful precursor for the synthesis of bisphosphine 28.

<table>
<thead>
<tr>
<th>Phosphinite /Phosphine</th>
<th>(^{31}\text{P NMR chemical shift ((\delta))})</th>
<th>Rh(I) Complexes</th>
<th>(^{31}\text{P NMR chemical shift ((\delta))})</th>
</tr>
</thead>
<tbody>
<tr>
<td>23a</td>
<td>114.4 (s)</td>
<td>24a (cod/SbF(_6))</td>
<td>122.1 (d, (J_{\text{Rh-P}} = 181 \text{ Hz})) plus 117 (br)</td>
</tr>
<tr>
<td>23b</td>
<td>116.9 (s)</td>
<td>24b (cod/SbF(_6))</td>
<td>127.0 (d, (J_{\text{Rh-P}} = 174 \text{ Hz})) plus 119 (br)</td>
</tr>
<tr>
<td>25a</td>
<td>116.1 (s)</td>
<td>26a (nbd/BF(_4))</td>
<td>123.1 (d, (J_{\text{Rh-P}} = 184 \text{ Hz}))</td>
</tr>
<tr>
<td>28</td>
<td>-22.9 (s)</td>
<td>29 (cod/SbF(_6))</td>
<td>14.9 (d, (J_{\text{Rh-P}} = 147 \text{ Hz})) -4.3 (dd, (J = 588, 42 \text{ Hz}))</td>
</tr>
<tr>
<td>34 (Scheme 2.2)</td>
<td>-21.9 (s)</td>
<td>Rh(^{3+})(34)(cod)SbF(_6)^-</td>
<td>16.3 (d, (J_{\text{Rh-P}} = 146 \text{ Hz}))</td>
</tr>
</tbody>
</table>

Table 2.1. \(^{31}\text{P NMR Spectra of Rh(I) Complexes I}\)
Tosylation of 27 followed by substitution with diphenylphosphide anion gave 28 in 28%. Following Imamoto's borane protection protocol for purification of phosphorus compound, crude 28 was treated with BH₃·THF in THF at rt and the resulting air-stable borane complex having P-BH₃ bond was separated by silica gel column chromatography. Finally deboronation in Et₂NH at 50 °C for 12 h provided pure 28 in 45% overall yield.

Scheme 2.1. Synthesis of Bisphosphinates and Bisphosphine from α,α'-Trehalose
from the bis-tosylated 27. All bisphosphinates 23a/b, 25a and bisphosphines 28 were fully characterized by \(^1\)H, \(^{13}\)C and \(^{31}\)P spectroscopy. All of them had clean single phosphorus peak reflecting their C\(_2\)-symmetry (Table 2.1).

The bisphosphines and bisphosphinites were converted into corresponding Rh(I) complexes 24, 26, and 29 by treating them with 1.0 equivalent of [Rh(COD)\(_2\)]\(^+\)X or [Rh(nbd)\(_2\)]\(^+\) (X = SbF\(_6\) or BF\(_4\)) in CH\(_2\)Cl\(_2\). The structures of the resulting Rh (I) complexes were studied by temperature dependent NMR spectroscopy. The major \(^{31}\)P signal appeared as a doublet in 24a (X\(^-\) = SbF\(_6\)) at \(\delta\) 122.2 (d, \(J_{P,Rh} = 181\) Hz). In addition, \(^{31}\)P NMR spectrum of 24a showed broad signals between \(\delta\) 116-118 ppm. The intensity ratio of the major doublet to the broad signals was highly dependent on the temperature (< 10 % at 37 °C, and increasing as the temperature was decreased), suggesting that the latter could have come from a mixture of complexes in which the benzyloxy group was probably coordinated to Rh.\(^5\) The lack of coupling between the two phosphorus atoms (\(^2\)\(J_{P,Rh,P}\)) in the major complex is clearly an indication of the symmetry of the molecule that renders the two phosphorus atoms equal. The complex 24b (X\(^-\) = SbF\(_6\)) had the \(^{31}\)P signal at \(\delta\) 127.0 (d, \(J_{P,Rh} = 174\) Hz) with the minor broad signals at \(\delta\) 121-118 (<5 % at 25 °C). 6,6'-Bisphosphinite Rh(I) complex 26a (L = nbd, X\(^-\) = BF\(_4\)) on the other hand, had a clear doublet at \(\delta\) 123.1 (d, \(J_{P,Rh} = 184\) Hz) indicating a more C\(_2\)-symmetric structure. Corresponding 6,6'-bisphoshpine Rh(I) complex 29 (X\(^-\) = SbF\(_6\)) had major \(^{31}\)P signal at 14.9 (d, \(J_{P,Rh} = 147\) Hz) which is C\(_2\)-symmetric, along with a minor signal at -4.3 (dd, \(J_{P,Rh} = 588\) Hz, \(^2\)\(J_{P,Rh,P} = 42\) Hz) which indicated a non-symmetric structure, which remains unknown at this time. The above \(^{31}\)P NMR spectra
seems to indicate that Rh(I) complexes formed from bidentate phosphinites with phosphorus atoms at 4,4'-hydroxy group (e.g. 24a and 24b) tend to form several isomers depending on the temperature, which is likely to be the result of Rh-OBn coordination. On the other hand, Rh(I) complexes formed from phosphinite and phosphine with P atoms at 6,6'-hydroxy or 6,6'-positions of trehalose (26 and 29) have clean C2-symmetric structure without any such isomers.

2.1.3. Application of Organic-Soluble Phosphinites from α,α'-Trehalose for Asymmetric Hydrogenation

\[
\text{R} \text{NHC(O)Me} + \text{H}_2 \xrightarrow{0.4-0.8 \text{ mol % Rh(I)(L)}} \text{R} \text{NHC(O)Me} \quad (1)
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>substrate</th>
<th>% ee\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24a</td>
<td>30a</td>
<td>70 (R)</td>
</tr>
<tr>
<td>2</td>
<td>24a</td>
<td>30b</td>
<td>35 (R)</td>
</tr>
<tr>
<td>3</td>
<td>24b</td>
<td>30a</td>
<td>40 (R)</td>
</tr>
<tr>
<td>4</td>
<td>24b</td>
<td>30b</td>
<td>30 (R)</td>
</tr>
<tr>
<td>5</td>
<td>26a</td>
<td>30b</td>
<td>25 (R)</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>30a</td>
<td>N/A\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The % ee's were determined by GLC (chirasil L-Val) analysis. The absolute configuration of products was determined by the comparison of retention times of R and S products with those reported in the literature.\textsuperscript{5} \textsuperscript{b}Less than < 5 % was obtained.

Table 2.2. Hydrogenation of Dehydroarmono Acids with Organic-Soluble Trehalose-Derived Phosphinites and Phosphines in THF
The bisphosphinites were excellent ligands for Ni(0)-catalyzed asymmetric hydrocyanation\(^7\) and Rh(I)-catalyzed hydrogenation. Hydrogenations of (Z)-N-acylacrylic acid derivatives (eq. 1) were carried out using these complexes, and the results are shown in Table 2.2 (entries 1-5). As with other phosphinites,\(^7\) quantitative yields of the hydrogenation products were obtained in THF at room temperature and 30-40 psi of H\(_2\), even though the enantioselectivity of the reaction remained marginal.

2.1.4. Unsuccessful Attempts to Obtain Water-Soluble \(C_2\)-Symmetric Macrocyclic Phosphinite/Phosphine Rh(I) complexes from Trehalose

These ligands 24, 26, and 29 are insoluble in water, and under typical hydrogenation conditions using these ligands, the starting material was recovered unchanged in each case. Several attempts were made to remove the benzyl ether protecting groups from either phosphine/phosphinites 23, 25, and 28 or their Rh(I) complexes 24a, 26a, and 29. Under typical hydrogenolysis conditions (Pd/C, Pearlman's catalyst), the reaction mixture resulted in the recovery of starting material or complex mixtures, which could not be identified further (Scheme 2.2, see also experimental section).

Several attempts were made to use alternative protecting groups (Scheme 2.3), such as isopropylidene acetal, methoxymethylether (MOM), or benzoyl protecting groups. Isopropylidene derivative 32 was obtained by protection with 2-methoxy-1-propene,\(^1k\) but further selective functionalization using AlCl\(_3\)/LAH was not successful (Scheme 2.3). Methoxymethyl derivative 33 could be converted into bisphosphate 34 (for \(^{31}\)P NMR, see Table 2.1), but the deprotection of MOM-ether could not be achieved.
Scheme 2.2 Failed Attempts to Obtain Water-Soluble Phosphine/Phosphinite or their Rh(I) complexes from Trehalose.

The 6,6'-bisphosphinites Rh(I) complex derived from 33 were subjected to the acidic conditions, but the MOM-ether could not be deprotected. On the other hand, 6,6'-dibromo-4,4'-dibenzoyl compound 35 was synthesized by adaptation of literature method, using NBS in refluxing CCl₄, but the benzoyl protecting group seemed not to be compatible with basic condition in which highly nucleophilic phosphide anion is generated and the reaction of 35 with lithium phosphide resulted only in a complex mixture.
Scheme 2.3 Use of Alternative Protecting Groups

2.1.5. Use of Acid-Labile Protecting Group

Having failed to prepare the deprotected phosphinites using benzyl and methoxymethyl ethers, we turned our attention to the more hydrolytically unstable
cyclohexylidene derivatives shown in Scheme 2.4. The tris-cyclohexylidene derivative 36 was synthesized according to a procedure reported in the literature.  

![Diagram of synthesis process]

Scheme 2.4. Water-Soluble Ligands from Acid-Labile Trehalose Derivatives

This diol was easily converted into the vicinal bisphosphinites 37a/37b by treating 36 with a mixture of Ar₂PCI and DMAP, and subsequently to the corresponding Rh(I) complexes 38a/38b. As shown in the table (Table 2.3), these are excellent catalysts for hydrogenation giving isolated yields near 100% and ee's up to 92%. Note that in accordance with our previous observations the electron-rich 3,5-dimethylphenylphosphinite ligand 38b is clearly superior to the simple phenylphosphinite 38a (entries 1 vs 4 and 2 vs 5).
Table 2.4. $^{31}$P NMR Spectra of Rh(I) Complexes II
The acid-labile cyclohexylidene protecting group in 38a (or 38b) was easily removed (96% yield) by treatment of the Rh(I) complex dissolved in thoroughly degassed methanol with AG 50 WX-8 resin, which was prepared by the following procedure. The cationic exchange resin (AG 50 WX-8, 5 mequiv. per dry gram) was placed in a pressure filter funnel and was rinsed with double-distilled water, and it was immersed in distilled water overnight. Then the resin was further washed with distilled water and absolute MeOH. The resulting material was dried under vacuum (0.2 mmHg) overnight. To the solution of phosphinates 38a/b in MeOH (degassed) was added above prepared resin and the progress of the reaction was monitored by $^{31}$P NMR (Table 2.4). For example, Rh-complex 38b dissolved in degassed MeOH (and small amount of CDCl$_3$) give rise to two doublet of doublet spin systems at $\delta$ 145.0 (dd) and 134.5 (dd). When this solution was treated with the above prepared resin, a new set of doublet of doublet started to appear slowly at $\delta$ 140.2 (dd, $^1J_{\text{Rh-P}} = 179$ Hz, $^2J_{\text{P-P}} = 28$ Hz), 129.6 (dd, $^1J_{\text{Rh-P}} = 177$ Hz, $^2J_{\text{P-P}} = 28$ Hz) corresponding to 39b with gradual disappearance of the starting peaks. Upon the completion of the reaction, the reaction mixture in MeOH was filtered through a cotton plug to remove resin and the evaporation of solvent gave 39a as an yellow powder. At this point volatile side product (cyclohexanone) could be removed by evaporation under vacuum. The crude product was further purified by dissolving it in minimum amount of CH$_2$Cl$_2$ followed by re-precipitation with excess ether. Thus prepared Rh(I) complex was characterized by $^1$H, $^{13}$C, COSY, as well as FAB-MS. The FAB-MS spectrum of 39a (cod/SbF$_6^-$) showed the peaks at $m/z$ 921 (calcd 921.75 for C$_{44}$H$_{52}$O$_1$P$_2$Rh corresponding to [Rh(deprotected phosphinite)(cod)]$^+$) and at $m/z$ 813 (calcd 813.57 corresponding to [Rh(deprotected phosphinite)]$^+$). We also found that the corresponding BF$_4^-$ complex can
be deprotected in degassed methanol using 48 mol % aqueous HBF$_4$. In this case, use of same counter anion will eliminate the formation of mixed salt.

The deprotected complexes 39a and 39b are readily soluble in water and can be used for hydrogenation of α-acetamidoacrylic acids (Table 2.5). Methyl α-acetamidoacrylate was reduced quantitatively by 39a in water at 40 psi of hydrogen in 55% ee (S) using a substrate-to-catalyst ratio of 125. Under identical conditions, 39b gave 49% ee for the S isomer. However, hydrogenation in aqueous medium is less

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Substrate</th>
<th>% ee$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$O</td>
<td>39a</td>
<td>30d</td>
<td>55 (S)</td>
</tr>
<tr>
<td>2</td>
<td>H$_2$O</td>
<td>39a</td>
<td>30e</td>
<td>59(S)$^c$</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$O/THF (1/1)</td>
<td>39a</td>
<td>30c</td>
<td>65 (S)$^d$</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>39a</td>
<td>30c</td>
<td>70 (S)</td>
</tr>
<tr>
<td>5</td>
<td>H$_2$O</td>
<td>39b</td>
<td>30d</td>
<td>49 (S)</td>
</tr>
<tr>
<td>6</td>
<td>H$_2$O/EtOAc</td>
<td>39a</td>
<td>30e</td>
<td>65 (S)$^e$</td>
</tr>
</tbody>
</table>

$^a$All (COD)(SbFe) salts; S/C = 125; 40 psi H$_2$, 2 h, ~100 % yield. $^b$The % ee's were determined by GLC (chiral L-Val) analysis. $^c$Reaction in a slurry. $^d$12 % conversion in 24 h. $^e$100 % conversion in 20 h, 25 % product and the rest polymeric material.

Table 2.5. Hydrogenation of Dehydroamino Acids with Water-Soluble Trehalose-Derived Phosphinites in Water

selective in comparison to organic medium (for substrate 30d: 38a/39a, 65% vs. 55% or 39b/39b 83% vs. 49%, respectively, Table 2.3 and 2.5). One of the possible explanations for this deterioration of enantioselectivity is the intervention of protonolysis of the
putative Rh-C bond before the final reductive elimination (eq. 2). For example, when the reduction of 30d using 0.8 % of complex Rh'[39a][cod]SbF_6^- was carried out in D_2O for 12 h, 50 % α-deuterium incorporation in the product 40 was observed at 20 % conversion. The exact mechanism of this reaction and its stereochemical consequences remain unknown at this time.\textsuperscript{11}

\[
\begin{align*}
\text{NHC(O)Me} & \quad + \quad \text{H}_2 & \quad \text{0.4 mol \% 39a Rh(I) (cod/SbF}_6^-) & \quad \text{D}_2\text{O, 40 psi / RT} \\
\text{30d} & \quad \quad & \quad \text{(50 \% D)} & \quad \text{40}
\end{align*}
\]

When the substrate is more hydrophobic, and hence less soluble in water, the complex 39a is a poor catalyst for the hydrogenation. For example, (Z)-acetamidocinnamic acid (30c), which has only limited solubility in water, was reduced in a yield of only 12 % (65 %ee) in 24 h in 1:1 THF/water, as compared to 67% yield (70 %ee) in neat THF. Water clearly slowed down the reaction.

2.1.6 Problems and Prospects for Trehalose-Derived Phosphinites

One of the purported goals in developing water-soluble catalysts is the ease of recovery of the catalyst from the aqueous layer. Further, we and others\textsuperscript{8b} have shown that catalysts such as 39a can be used in biphasic media. Yet there are few reports in the literature where the actual distribution of the catalyst in biphasic medium has been measured under the reaction conditions. The traditional way of demonstrating the viability of the recovery option has been to separate the organic phase and to reuse the
aqueous phase containing the catalyst for subsequent reactions. Arguably, for highly efficient catalysts such as the Rh(I)-bisphosphinites, unless careful quantitative rate studies are done with the recovered catalyst solution, this is not a satisfactory way of demonstrating the practicality of this approach, since residual amounts of the Rh complex can still facilitate the hydrogenation. Hence, we have sought to determine the distribution of the cationic Rh complexes 39a between water and several common organic solvents by the inductively coupled plasma (ICP-MS) spectroscopy, which gives more quantitative information on the Rh-distribution under typical reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>total Rh(mg)</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$/water</td>
<td>0.32</td>
<td>1.05</td>
</tr>
<tr>
<td>2</td>
<td>EtOAc/water</td>
<td>0.17</td>
<td>0.63</td>
</tr>
<tr>
<td>3</td>
<td>ether/water</td>
<td>0.24</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*a* The Rh content was distributed in 9 mL each of solvent mixture.  
*b* Determined by ICP-MS, error limit, <4 %.

Table 2.6. Partition of Complex Rh$^+$[39a][nbd]BF$_4$ between Water and Organic Solvents in Dilute Solution.

The distribution of complex 39a between water and CH$_2$Cl$_2$, ethyl acetate, and ether are shown in Table 2.5. Surprisingly even the most water-soluble complex we have prepared has significant solubility in all these organic solvents. Ether appears to be the best solvent if the catalyst is to be recovered after the first hydrogenation, and even in this solvent up to 4% of the Rh will be lost after each subsequent cycle. Careful choice of the solvent
therefore is important if recovery of the catalyst is desired. It is our view that despite the attraction of water as a solvent, the hydrogenation of substrates other than the most soluble ones are best carried out in organic medium. Regarding the stability of the water-soluble Rh(I) complex, $^{31}\text{P}\text{NMR}$ was used to follow the decomposition of Rh(I) complex of 39a. In MeOH-$d_6$, sample of the Rh(I) complex 39a showed significant amount of $^{31}\text{P}$ signal (two sets of doublet of doublet) after 9 days at room temperature, with no other peaks appearing. However, to get the similar signal-to-noise ratio as the one taken initially, it took about at least 3 times to accumulate FID’s, indicating a significant deterioration of the complex.

Practical problems associated with degassing (repeated freeze-thaw cycles) water, especially when the reaction is to be carried out on a large scale, partial loss of enantioselectivity, and the limited solubility of the catalyst are limitations that have to be carefully considered in this context. Among these issues in the application of water-soluble catalyst, the last two could be addressed through the use of water-soluble phospholane ligands that will be described in the following section.
2.2 Development of Water Soluble Organometallic Catalysts from D-Mannitol:

Tetrahydroxy Bisphospholane Ligands

2.2.1. Introduction

The 'water-soluble' phosphinites prepared in the previous section had substantial solubility in organic solvents, as supported by ICP-MS spectroscopy, making catalyst recovery difficult. One possible origin of this hydrophobicity is the diaryl groups on the phosphorus. In addition, possible degradation of P-O bond in water may induce non-selective hydrogenation, resulting in lowering of the enantioselectivity as well as activity. As we and others\textsuperscript{8b,10} have noticed, there is significant deterioration of catalytic activity and selectivity of the phosphinite complexes upon reuse of the aqueous phase for subsequent reactions. The solution of this dual problem of hydrolytic instability and hydrophobicity can be addressed through the use of polyhydroxyphospholane bearing robust P-C bonds and reduced number of aryl substituents on phosphorus (Figure 2.4).

Figure 2.4 Mono- and Bisphospholane Ligands Derived from D-Mannitol
The latter should help to decrease the hydrophobicity of the catalyst. With this goal in mind, we chose the $C_2$-symmetric phospholane such as 42 (Figure 2.4) derived from D-mannitol which has the backbone of the enormously successful DuPhos ligands discovered by Burk and coworkers.\(^\text{13}\)

The synthesis of mono- and bis-phospholanes as well as applications of these ligands in the hydrogenation of dehydroamino acids will be described in the following sections. Another structural feature in this type of ligands is the close proximity of alkoxy group to the chelating phosphorus atom, which can potentially act as a 'hemi-labile' coordinating group. In line with this, the use of monophospholane 41 ($R = \text{TBS}$) in hydrovinylation and allylic reduction will also be described. The bisphospholane 42 ($R = \text{H}$) will be shown to be an excellent ligand for asymmetric hydrogenation in water. Also, with decreased number of aromatic substituents on phosphorus atom, the hydrophilicity was greatly enhanced, as exemplified by the catalyst recovery and reuse experiments, where activity and selectivity near 100% was repeatedly achieved.

2.2.2. The Synthesis of Ligands and Complexes

The synthesis of polyhydroxyphospholane started from D-mannitol, a readily available carbohydrate. Adoption of literature procedure\(^\text{12}\) provided tetrol 43 in 45% (4 steps) and subsequently selective TBS protection and methanesulfonylation gave 6,6'-TBDMS-protected diol 44 and the dimesylate 45 in 71%, 88% yields, respectively. The dimesylate 45 was converted into the protected bis-phospholane 46 in a very good yield as shown in Scheme 2.5. In this case, temperature control (-30 °C) in the phospholane ring formation was critical for obtaining high yield of 46. Monophospholane 47 was
synthesized similarly from dimesylate 45 using phenylphosphine instead. Tetrol 43 can be selectively protected into a known diol 48 and a similar sequence of reactions gave benzyl-ether protected monophospholane 50.

The bis- and monophospholanes (46, 47, and 50) thus obtained were fully characterized by $^1$H, $^{13}$C, $^{31}$P NMR, and COSY. All compounds gave clean spectra in all

Scheme 2.5. Synthesis of protected phospholane 46 and monophospholanes 47 and 50
NMR experiments. For example, 46 has a sharp singlet at $\delta \approx -13.4$ ppm in $^{31}$P NMR because of $C_2$-symmetry of two phosphorus atoms. The protons and carbons from two identical phospholane rings were perfectly symmetrical, so that only one phospholane ring could be seen in the $^1$H NMR and the number of aliphatic carbons in $^{13}$C NMR is half the number of what 46 has. The monophospholane 47 and 50 also have sharp singlets at $\delta \approx -4.2$ and $-2.6$ ppm in $^{31}$P NMR, respectively. In the $^1$H and $^{13}$C NMR, two silyloxymethyl (or benzyloxyxymethyl) groups of 47 and 50 were not equal, because of the lone pair on phosphorus atoms, making them diastereotopic.

Next, we attempted to deprotect both 46 and 47 to generate the corresponding hydroxyphospholanes. Since the base sensitive OH-protecting groups such as esters were incompatible with the highly nucleophilic phosphide anion used in the synthesis of the phospholanes, synthesis of the polyhydroxyphospholane turned out to be a non-trivial problem, especially when the phosphine was electron rich. Use of acid-sensitive protecting group is often the only alternative, and this procedure is fraught with problems. For example, acid hydrolysis of DIOP derivatives with aqueous mineral acids gave considerable amounts of quaternary phosphonium salts. Börner has reported that methanesulfonic acid in aqueous methanol can be used to liberate hydroxyphosphines from the corresponding THP derivatives, as long as the phosphine carried aromatic substitutents (diphenylphosphino group). In most cases reported to date, including one example of a hydroxymethyl bisphospholane system, the hydroxy protecting groups are removed after the formation of the cationic Rh chelate. This protocol, while perfectly acceptable for Rh-catalyzed reactions, imposes serious limitations if other metals are to be considered for catalysis in aqueous medium.
Therefore we thought that it would be highly desirable to have a direct route to the metal-free polyhydroxyphosphine ligands, and our initial efforts were directed toward this goal. While our early attempts to use strong acids in aqueous and alcoholic media to liberate the hydroxyl groups from 46 were facing considerable difficulties, Zhang and coworkers reported that the ligand 51 upon treatment with excess methanesulfonic acid in refluxing methanol (10 h) gave the deprotected 52 in 90% yield as an oil (Method A, in Figure 2.5). However, the $^1$H and especially the $^{31}$P NMR data (broad peaks at δ 11.9 ppm) suggested that the product of this reaction was most likely a mixed phosphonium salt 53, and not the free hydroxyphospholane as claimed. Since then, Dr. Yan in our group used the method developed in the previous sections using cationic exchange resin (AG 50 WX-50) to deprotect isopropylidene acetal 51 into 52 (Method B, Figure 2.6).

![Figure 2.5. Comparison of the Deprotection Method with That of Zhang's Group](image)

The hydroxy phospholane 52 thus prepared was obtained as a white solid and was found to have satisfactory $^1$H, $^{13}$C, $^{31}$P NMR spectra as well as elemental analysis (C, H). For example, ligand 52, prepared by our Method B, has a sharp singlet in $^{31}$P NMR, which
upon addition of 3 equivalent of methanesulfonic acid in CD$_3$OD showed a characteristic
broad absorption at $\delta$ 15 ppm, suspiciously similar to the product obtained under Method
A by Zhang.\textsuperscript{19}

Initially, the condition using cationic exchange resin was attempted for the
deprotection of 46 (eq. 3). When the solution of 46 in MeOH was treated with resin (AG
50 WX-8) at rt for 20 h, the TLC (Et$_2$O/Hex = 5/95, $R_f$ = 0.6 for 46, THF 100 $\%$, $R_f$ = 0.5
for deprotected 54) as well as $^{31}$P NMR (CD$_3$OD) indicated the complete disappearance
of starting 46 and appearance of 54. However, only trace amount of 54 was obtained even
after washing the resin with MeOH and Et$_3$N. In contrast, treatment of monophospholane
47 with the cation exchange resin for 4 h, followed by washing the resin with Et$_3$N
cleanly gave a solution containing dihydroxy monophospholane 55. We thought that high
polarity of tetrahydroxyphospholane 54 resulted in strong adsorption on to the resin and
while the less polar 55 suffers that problem much less.
We decided to use different solid phase reagent for the regeneration of 54, namely a basic resin. In the preliminary experiments, treatment of 46 with trifluoroacetic acid (CF₃CO₂H) in MeOH effected deprotection of silyl ether and after evaporation of the solvent, a gray-white solid was obtained, but the resulting material had typical broad peaks in $^{31}$P NMR (eq. 3) possibly because of the formation of a mixture of phosphonium salts. We thought the filtration of the crude mixture through the basic resin would remove the excess acidic reagents. Thus the crude solid material was re-dissolved in MeOH and was passed through a short bed of polystyrene-CH₂NEt₂ resin. Evaporation of filtrate gave the expected tetrahydroxyphospholane 54 in 84 % yield as a white solid. Furthermore, this tetrahydroxyphospholane was separable on a silica gel column chromatography (100 % THF, $R_f = 0.5$). A very sharp peak at $\delta$ -12.4 (CD₃OD) in the $^{31}$P NMR was an indication of clean free phosphine 54. The structure of bis- and monophospholane 54 and 55 obtained above were further confirmed by means of $^1$H, $^{13}$C, $^{31}$P, and COSY and HMQC NMR spectroscopy.
2.2.3. Hydrogenation Studies: Aqueous Media

The absolute configuration was determined by the comparison with literature.

Table 2.7. Hydrogenation of Dehydroamino Acid using [Rh\(^{+}\)(nbd)(54)]BF\(_4^{-}\)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligand (L)</th>
<th>Solvent</th>
<th>% ee(^a)</th>
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<tr>
<td>30d</td>
<td>54</td>
<td>MeOH</td>
<td>&gt;99 (S)</td>
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<tr>
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<td>54</td>
<td>water</td>
<td>&gt;99 (S)</td>
</tr>
<tr>
<td>30e</td>
<td>54</td>
<td>water</td>
<td>98.5 (S)</td>
</tr>
</tbody>
</table>

\(^a\) The absolute configuration was determined by the comparison with literature.

The cationic Rh complex of the fully deprotected hydroxyphospholane is an excellent catalyst for hydrogenation of dehydroamino acids (Table 2.7) in neat water. In sharp contrast to the trehalose-derived water-soluble phosphinates 39a, which gave reduced activity and enantioselectivity in neat water, Rh-complexes of 54 are superb catalyst for aqueous phase hydrogenation. For these studies and the following recycling experiments, we chose methyl acetamidoacrylate as the substrate, since this substrate is freely soluble in water, and its recovery by extractive work-up would be a good indication of how effectively the aqueous phase containing the catalyst can be recycled in repeated operations. The use of additional one equivalent of free ligand 54 in combination of [Rh\(^{+}\)(nbd)(54)]X\(^{-}\) complex is critical for prevention of precipitation of Rh.\(^{19}\)
2.2.4. Catalyst Recovery and Reuse

As often stated, yet rarely achieved goal of developing water-soluble ligands is to find conditions where the aqueous layer containing the catalyst can be recycled with no loss of activity and selectivity. While a number of examples of such recovery of catalyst containing ionic ligands, most notably phosphine ligands having ionic side-chains (-SO\textsubscript{3}\textsuperscript{-}, -NMe\textsubscript{3}\textsuperscript{-}) are known,\textsuperscript{20} ligand 54 is among the first non-ionic ligands where this has been possible with no apparent loss of selectivity. The results for methyl acetamidoacrylate 30d reduction are shown in Table 2.8. The reaction was typically carried out in neat water with 1 mol % of cationic Rh complex as catalytic precursor and 1 mol % of extra ligand 54 to suppress the precipitation of the Rh metal. The product was separated at the end after each run by extraction with ether four times. The Table 2.8 shows the results with 54, which is the best ligands (the other being the diethyl derivative of 52, developed by Dr. Yan in Figure 2.5, the recyclability of which suffers after 4\textsuperscript{th} run because of solubility of the catalyst in ether) in neat water under a recycling conditions. This

<table>
<thead>
<tr>
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<th>%ee(S)</th>
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<td>100</td>
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</tr>
<tr>
<td>4</td>
<td>4</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>100</td>
<td>&gt;96.5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>100</td>
<td>b</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>100</td>
<td>94.9</td>
</tr>
</tbody>
</table>

\textsuperscript{a} See Figure 2.6 for chromatograms. \textsuperscript{b} Not determined

Table 2.8. Catalyst Recovery and Reuse in 100 % Water with 1 Equiv. of Added Ligand: Hydrogenation of Methyl Acetamidoacrylate Using Rh\textsuperscript{+}(nbd)(54)SbF\textsubscript{6}\textsuperscript{-} in water

55
catalyst can be recycled in four sequential runs with ~100% conversion and ~99% enantioselectivity. The recycling was repeated up to seven runs with a slight loss of selectivity. The catalytic efficiency suffers in runs beyond the fourth cycle, so that the extended reaction times (6 h for run 1-4 and 12 h for run 5-7) were necessary to achieve complete conversion. A surprisingly high enantioselectivity of 95% remained even for the seventh run.

Figure 2.6. GC of hydrogenation Products (ee's in brackets) from Successive Runs Using Recycled Aqueous Solutions of [Rh*(nbd)(54)]BF₄⁻ (Table 2.7)
2.2.5. Other Reactions of Monophospholanes: Allylic Reduction and Hydrovinylation

Hayashi and coworkers reported that monophosphine ligand related to (R)-BnO-MOP ligand (56 in Figure 2.7) showed high selectivity in the reduction of allylic carbonate with $\text{HCO}_2\text{H}/\text{amine}$.\textsuperscript{21} Also, in the hydrovinylation reaction, monophosphine ligands with internal coordinating group seem to be crucial for high enantioselectivity as well as reactivity (eq. 6).\textsuperscript{22} In this respect, monophospholane 47 and 50 has an interesting structural feature, \textit{i.e.} potentially 'hemi-labile' coordinating group. In the hydrovinylation reaction, counterions play a key role in the yield of the reaction: in the absence of internal coordinating group, coordinating counter-anion such as, $\text{AgOTf}$ is essential for high

\[
\text{MeO} \quad \text{0.7 mol\%}, \quad [(\text{allyl})\text{Ni-Br]} \quad (\text{MOP})-\text{NaBAR}_{4} / \text{CH}_{2}\text{Cl}_{2}
\]

\text{ethylene (1 atm)}; -70 °C
\text{Ar = 3,5-(CF}_{3}\text{)}_{2}\text{-C}_{6}\text{H}_{3})

97 % yield
80 % ee (with MeO-(R)-MOP)

Figure 2.7. Potentially Hemi-Labile Monophosphine Ligands (56-59 were prepared by Dr. Nandi)
yields. The use of NaBAR₄ (Ar = 3,5-(CF₃)₂C₆H₃) in conjunction with MeO-MOP (see 53 for BnO-MOP in Figure 2.7) with internal coordinating group gave high %ee for the reaction whereas with AgOTf a poor reaction was observed. We wondered monophosphine ligands 47 and 50 having potentially hemilabile coordinating groups might have activity and selectivity in the hydrovinylation reaction.

These previous observations prompted us to investigate the reactivity of the monophospholanes synthesized during this study in the allylic reduction and hydrovinylation. In this section, a preliminary study of the application of monophospholane 47 and 50 in Pd-catalyzed asymmetric allylic reduction and the Ni-catalyzed hydrovinylation is described.

2.2.5.1 Allylic Reduction

In Table 2.9, reduction of geranyl methyl carbonate with Pd(0) and formate formed from HCO₂H and proton sponge (1,8-bis-(dimethylamino)naphthalene) is presented using various monophosphine ligands including monophospholanes 47 and 50. In the reaction of geranyl methyl carbonate with Pd₂(dba)₃ (1 mol% Pd), monophosphine (2 mol%), proton sponge (1.2 equiv.), and formic acid (2.2 equiv.) in THF at rt for 1~12 h, a clean S₉₂²' type product (98 % regioselectivity) was obtained with monophosphines with coordinating group (47, 50, 56, 57, and 58) (entry 2-4, 6, 7 in Table 2.9). The high regioselectivities observed are presumably a result of delivery of hydride at the less hindered allylic termini of intermediate π-allyl Pd-complex. With electron-rich non-coordinating ligand PCy₃ (entry 1, Table 2.9), the desired product was obtained only in

58
Table 2.9 Allylic Reduction Using HCO₂H/amine

34 %, the remainder being formal S_N2-type product having internal double bond (cis/trans mixture, 61 in eq. 7). Reaction using monophospholane having thioether group 59, gave a very complex mixture in the GLC analysis. Though the regioselectivity of these monophospholane ligands were excellent, the enantioselectivity obtained using the ligands were marginal. Prototypical MOP-ligand derivative 56 reported by Hayashi (entry 2, Table 2.9)²¹ outperformed any other mono-phospholanes in this asymmetric reduction condition.

2.2.5.2 Hydrovinylation

Next, we examined the hydrovinylation reaction using the monophospholane ligands 47 and 50 (eq. 8 and 9). These monophospholane ligands showed generally low enantioselectivity toward hydrovinylation of styrene and 4-bromostyrene. In one case
(entry 1, eq. 8), quite encouraging 37 % (R) enantioselectivity was obtained using TBS-protected monophospholane 47.

![Chemical structure](image)

\[
\text{entry} \quad \text{ligand} \quad \text{time} \quad \text{temperature} \quad \text{yield} \quad \% \text{ ee}^b \quad \text{of A}
\]

<table>
<thead>
<tr>
<th>entry</th>
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<th>time</th>
<th>temperature</th>
<th>yield</th>
<th>%ee (^b) of A</th>
</tr>
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<td>47</td>
<td>1.5 h</td>
<td>-40 °C</td>
<td>66:7:27</td>
<td>37 (R)</td>
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<tr>
<td>2</td>
<td>50</td>
<td>2.5 h</td>
<td>-30 °C</td>
<td>88:6:5</td>
<td>17 (R)</td>
</tr>
</tbody>
</table>

\(^a\) Determined by GC. No starting material was observed. \(^b\) %ee was determined by HPLC analysis on Chiral OJ column (0.3 mL/min Hex, 100 %). \(\text{NaBA}^4\text{Ar} (\text{Ar} = 3.5\text{-di-CF}_3\text{C}_6\text{H}_3)\)

![Chemical structure](image)

\[
\text{entry} \quad \text{ligand} \quad \text{time} \quad \text{temperature} \quad \text{yield} \quad \% \text{ ee}^b \quad \text{of A}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>time</th>
<th>temperature</th>
<th>yield</th>
<th>%ee (^b) of A</th>
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<tr>
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<td>47</td>
<td>2.5 h</td>
<td>-50 °C</td>
<td>94:2.5:1</td>
<td>21 (R)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>4 h</td>
<td>-55 °C</td>
<td>98:1:1</td>
<td>11 (R)</td>
</tr>
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</table>

\(^a\) Determined by GC. No starting material was observed. \(^b\) %ee was determined by HPLC analysis on Chiral OJ column (0.3 mL/min Hex, 100 %). \(\text{NaBA}^4\text{Ar} (\text{Ar} = 3.5\text{-di-CF}_3\text{C}_6\text{H}_3)\)

### 2.3. Conclusions

In Chapter 2.1, a synthetic methods for a synthesis of phosphinites and phosphine ligands from a readily available \(\alpha,\alpha'\)-trehalose were described. Adopting the selective functionalization methods for this molecule, various macrocyclic phosphinites and
phosphine-Rh(I) complexes were synthesized. The sugar phosphinite-Rh(I) complexes were excellent catalysts for hydrogenation of dehydroamino acids, although the enantioselectivity remained marginal. For the conversion of these phosphine/phosphinite ligands into their water-soluble forms, the choice of hydroxyl protecting groups became a critical issue when several C5-symmetric macrocyclic phosphinite and phosphines Rh(I) complexes failed in the deprotection reactions. An important consideration for the selection of protecting group was the basicity of phosphine and the nucleophilicity of phosphide anion in typical substitution reactions. We proposed an acid-labile protecting group as the most suitable for the synthesis of water-soluble ligands. Thus a very convenient method using cationic exchange resin (AG 50 WX-8) for the deprotection of cyclic acetal was developed and the water-soluble phosphinite Rh(I) complexes derived from trehalose were synthesized using the method. The utility of this method was also exemplified by the synthesis of several hydroxyphospholanes.19

The hydrogenations of prototypical substrates using water-soluble phosphinite Rh(I) complexes showed a decreasing selectivity and activity in water compared to the corresponding reactions in THF. The reduced selectivity in aqueous medium, the possible deterioration of P-O bond of catalyst and the hydrophobicity were the three major problems of trehalose-derived phosphinite Rh(I) complexes. As a solution to this problem, polyhydroxy bisphospholane with stronger P-C bond and a reduced number of hydrophobic aromatic rings on phosphorus atoms were proposed and synthesized. For the deprotection of the silyl ether groups of the hydroxyphospholanes, the method using cationic exchange resin gave some problems. The basicity of electron-rich phospholane induced adsorption of the product to the solid-phase resin. Thus another protocol was
developed, which used a resin-bound tertiary amine base to regenerate the phosphine. The TBS protecting group was efficiently deprotected with CF₃CO₂H and the excess acidic reagent was cleanly removed by filtration through poly-CH₂Net₂ resin. The free phospholane ligand thus prepared will be useful when other metals are considered for asymmetric reactions in water.

The Rh(I) complexes of hydroxyphospholane ligands synthesized were excellent hydrogenation catalysts in 100% water. Extremely high enantioselectivity and activity were observed under the recycling conditions. For example, in the reduction of methyl N-acetamidoacrylate, aqueous solution containing the [Rh(I)(54)(nbd)]⁺ complex could be recycled and reused up to 4 times with consistently high %ee (>99 %) and activity. Slight lowering of the activity was observed after 4th cycle, but significantly high enantioselectivity (95 %) remained even after 7th cycle.

Monophospholane ligands synthesized were applied for the asymmetric hydrovinylation, and allylic reduction using formate as reducing agent catalyzed by Pd complexes. Excellent regioselectivities were observed in the reduction of allylic carbonate. However, only a low enantioselectivities were observed for this reaction. In the hydrovinylation reaction, the encouraging enantioselectivity as well as regioselectivity indicated that the monophospholane ligand works in the same way as other ligands with a 'hemi-labile' coordinating group.
REFERENCE TO CHAPTER 2


(21) Hayashi, T; Iwamura, H; Naito, M; Matsumoto, Y; Uozumi, Y; Miki, M; Yanagi, K. J. Am. Chem. Soc. 1994, 116, 775.

CHAPTER 3

3.A. BIMETALLATIVE CYCLIZATION OF UNSATURATED SUBSTRATES: EXPANDING THE SCOPE OF DIYNE CYCLIZATION

3.B. FUNCTIONAL GROUP COMPATIBILITY IN THE SILASTANNYLATION REACTION

3.1 Introduction

Transition metal-catalyzed synthesis of carbocyclic and heterocyclic compounds from acyclic olefinic and acetylenic precursors is a subject of great topical interest. A wide variety of substrates including eneynes, eneallenes, dienes, and diynes have been subjected to metal-catalyzed intramolecular cyclizations.\(^1\) As outlined in Part II of Chapter 1, use of bisfunctionalization (X-Y) reagents such as \(R_3Si-SiR'_{3}\), \(R_3Si-SnR'_{3}\), \(R_3Si-BR'_{2}\), \(R_3Sn-BR'_{2}\), as well as the more traditional trialkylsilicon- and trialkyltin-hydrides for the metal-catalyzed cyclization provide a number of additional advantages (eq.1).\(^2\) For example, introduction of latent functionality (\(i.e.\) vinyl silane, -borane, and -stannane) which can act as a functional handle, will lead to further derivatization of product, through a number of C-C bond coupling reactions they can undergo.\(^3-5\) Also, various X-Y reagents that are available can be used to control the selectivity of such
reactions, along with other reaction conditions, such as phosphines and catalyst precursors.

Recently, research in our group revealed that 1,6-diynes can be cyclized with the aid of R₃Si-SnR’₃ reagents in the presence of Pd(0). Helically chiral 1,2-dialkyldiene cyclopentanes with unusual (Z,Z)-geometry at the double bonds (eq.2) are produced from a number of diyne precursors. This highly stereoselective reaction proceeds in good yield with no special care taken to avoid moisture and air, and is compatible with common functional groups such as ethers, esters, amides, and tertiary amines. However, the scope of this silylstannylative and other bimetallative cyclization has almost invariably been limited to simple symmetric diyne substrates in the discovery stage (such as in eq.2). For applications of this methodology for the synthesis of complex target molecules, the scope and limitations have to be explored in greater detail. For example, use of diynes will raise a regioselectivity issue (eq 1), while stereogenic center elsewhere in the molecule will
present problems of diastereoselectivity during the ring formation. In addition, the effect of structure of the product (for example, a bicyclic skeleton) on the atropisomerization has remained unexplored. Also, functional group compatibilities of the reagents have not been explored in detail at the time of the initial study. *Can the bimetallative cyclization be used for other substrates with eneyne, ynal, and alleneyne motifs? Will the reaction tolerate amide, free alcohol, or α,β-unsaturated carbonyl functionality?* Exploration along these lines, together with the derivatization methods of functionalized cyclic product will lay the ground for the synthesis of natural product targets that can be approached by the bimetallative cyclization strategy.

3.2 Study of Cyclization of Ynals and Eneynes

![Substrates I: Ynals and Eneynes](image)

*Figure 3.1 Substrates I: Ynals and Eneynes*
Initially, ynals 68-70 and eneynes 71-75 were considered for the cyclization study (Figure 3.1). Ynals 68, 69, 70, 71(E), and 71(Z) were prepared according to the literature. Among them, 71(E) and 71(Z) were cleanly separable. Eneyne 72 and 73 were prepared by propargylation of alcohols by treating them with KH (1.1 equiv.) in THF followed by addition of propargyl bromide. Eneyne 72 was fully characterized by $^1$H, $^{13}$C, COSY, HMQC, and IR as well as GLC analysis to confirm its structure and purity. The synthesis of 74 and 75 started with L-proline. According to a known procedure, L-proline was esterified and propargylated. The resulting ester 76 was reduced carefully with DIBAL-H in toluene at $<-65\ ^\circ\text{C}$ for 2 h to give aldehyde 77, which
was directly converted into known 74 by Wittig reaction or into 75 by Grignard reaction. The major isomer of eneyne 75 was obtained in 35 % yield (from ester 76) along with its minor isomer (7 %). The stereochemistry of the major isomer at the 2° alcohol carbon was based on the prediction by Cram-chelation model. The amino alcohol 75 was protected as a TBS-ether using TBDMS-Cl and imidazole to give 75' in 76 % yield. The eneynes 74, 75, and 75' were fully characterized by NMR spectroscopy and HRMS.

The acetylenic compounds were subjected to Pd-catalyzed silylstannylative cyclization conditions and the results for ynals 68-70 are tabulated in Table 3.1. Treatment of 68 with bimetallative reagent Bu2SnSiMe3 (1.1 equiv.) in the presence of Pd2(dba)3 (5 Pd %) and various phosphine ligands (10 %) in benzene-d6 at room temperature resulted only in recovery of starting material (Table 3.1, Entry 1). However, 69 reacted under the same conditions to give the acyclic adduct 78 (entry 2-5), which was characterized by NMR spectra and HRMS. This acyclic adduct 78 has characteristic C_\text{sp}^2=\text{CSn} peak at 6.59 ppm with $^{117}$Sn/$^{119}$Sn coupling ($^3J_{\text{Sn-H}} = 174$ Hz). The magnitude of the coupling constant $J_{\text{Sn-H}}$ served as an indication of whether the SnC_\text{sp}2-H carbon was internal (acyclic, RC(Sn)=CH(Si), $^3J_{\text{Sn-H}} = 160-180$ Hz) or terminal (cyclic, C=CH(Sn), $^2J_{\text{Sn-H}} = 40-70$ Hz) (Figure 3.3). The yield of the reaction depends on the phosphine ligand used, with the electron deficient P(C6F5)3 being the most effective for the reaction (Table 3.1, entry 5). However, the reaction of both 69 and 70 under these reaction conditions failed to give any cyclized product even after prolonged reaction time (30 h at 60 °C). It is intriguing that even a simple insertion of Si-Sn reagent into the acetylene (not cyclization) depends on the appropriate position of intramolecular functional group (the four-atom tether and the aldehyde seems to be optimum; whereas the lower homolog
does not participate in the reaction). In analogy with diyne cyclization mechanism, the putative intermediate before reductive elimination will presumably be a η²-coordinated species (A) shown in Figure 3.2. In this intermediate, the coordination of terminal unsaturated function could modulate further reactivity. It is possible that either this intermediate or the starting complex (B) is too stable to enter the catalytic cycle. The stability of such complexes would depend on the ring size of the bidentate ligand (in this case, the ynal) and this may explain the lack of reactivity in certain cases. This problem will be addressed again after following sections where reactions of other α,ω-bifunctional substrates are considered.

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</tr>
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</tbody>
</table>

The reaction condition is as follows unless otherwise noted: Pd₂(dba)₃ (1 mol %), phosphine (2 %), Bu₃Sn-SiMe₃ (1.1 equiv.), rt/24 h, benzene-d₆ (0.2 M) a Isolated yield, b Starting material remained unchanged ('H NMR). c The reaction was done for 4 d. d 5 % Pd, 10 % phosphine was used.

Table 3.1 Reactions of Ynals
Next, we turned our attention to eneynes, 71-75. Substrates 71(E), 71(Z), 72, 73, 74, and 75 having $\alpha$,\$-unsaturated ester, tertiary amine, free hydroxyl function might present interesting problems of functional group compatibility as well as possible diastereoselectivity. The results are shown in Table 3.2. When enyne 71(E) was treated with Pd$_2$(dba)$_3$ (5 % Pd), phosphine (10 %), in benzene-$d_6$, a slow conversion into acyclic monoadduct 79 (>80 %, by $^1$H NMR) was observed over 4 days at room temperature (entry 1, Table 3.2). The structure of 79 was identified by NMR spectra and HRMS and

\begin{align*}
\text{type A: } & ^3J_{Sn-H} = 140-200 \text{ Hz} \\
\text{type B: } & ^2J_{Sn-H} \text{ or } ^3J_{Sn-H} = 40-70 \text{ Hz}
\end{align*}

Figure 3.3. Sn-H Coupling Patterns and $J_{Sn-H}$ Values
the double bond geometry was deduced from $J_{Sn-H}$ value (160 Hz, type A in Figure 3.3) and coupling constant of $\alpha,\beta$-unsaturated ester ($J = 15.6$ Hz).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Phosphine</th>
<th>Product$^a$</th>
</tr>
</thead>
</table>
| 1     | 71(E)     | P(o-tol)$_3$ RT/4 d | Me$_3$SiO\(\text{SnBu}_3\)
|       |           |           | 79 (80 %) |
| 2     | 71(Z)     | P(o-tol)$_3$ RT/4 d | Me$_3$SiO\(\text{SnBu}_3\) + 71(Z) (50 %) |
| 3     | 72        | PCy$_3$ RT/13 d | \(\text{SnBu}_3\) |
|       |           |           | 81.90 % (95 %) |
| 4     | 73        | P(C$_6$F$_5$)$_3$ RT/2 d | Product could not be identified$^b$ |
| 5     | 74        | P(o-tol)$_3$ RT/19 h | \(\text{N}_{\text{SnBu}_3}\) + \(\text{N}_{\text{Bu}_{5}\text{Sn}_{3}}\) |
|       |           |           | 82.17 % |
| 6     | 75 R = H  | P(C$_6$F$_5$)$_3$ 60 oC/2 d | \(\text{N}_{\text{SnBu}_3}\) + 75.79 % |
|       |           |           | 84.21 % |
| 7     | 75' R = TBS | P(o-tol)$_3$ RT/1 d | \(\text{N}_{\text{SnBu}_3}\) |
|       |           |           | 85.41 % (69 %) |

Conditions: Pd$_2$(dba)$_3$ (2 % Pd), phosphine (4 %), Bu$_3$Sn-SiMe$_3$ (1.1 equiv.), RT, benzene-$d_6$ (0.2 M).

$^a$ Yields in parenthesis are based on recovered starting material by NMR and otherwise isolated yields. $^b$ The product could not be isolated.

Table 3.2 Reactions of Eneynes
The isomeric 71(Z), when subjected to the reaction condition, reacted much slower than 71(E) and after 4 days at rt gave a mixture of starting material and acyclic product 80 (ratio, 1/1 by $^1$H NMR, entry 2, Table 3.2). In the in-situ $^1$H NMR spectrum, the acyclic adduct 80 was characterized by the (Sn)C$_{sp2}$H peak at $\delta$ 6.81 with $J_{Sn-H}$ (180 Hz) to have the double bond geometry depicted (type A in Figure 3.3). The vinyl proton peaks appeared at $\delta$ 5.70 and 6.25 with a coupling constant between two cis-protons of 11.6 Hz. The vinyl peaks of starting material appeared at $\delta$ 5.70 and 6.41 with two cis-protons coupling constants of 11.6 Hz. Eneylene 72 underwent a slow acyclic monoadduct formation into 81 in excellent isolated yield, but no cyclization was observed (entry 3, Table 3.2). The acyclic adduct 81 was characterized by $^1$H, $^{13}$C NMR, COSY, and nOe difference spectra and the vinyl proton has a $J_{Sn-H}$ (180 Hz) of typical acyclic product. Also allylic protons $CH_2C(Sn)=CH(Si)$ have $J_{Sn-H}$ (36 Hz). When the eneylene 73 was subject to the standard reaction condition, no reaction was observed after 24 h at rt (entry 4, Table 3.2). After prolonged heating (60 °C, 12 h), only a complex unidentified mixture resulted. Eneynes 74, 75 having tertiary amine functionality, underwent silastannylation of acetylene to give corresponding acyclic adducts 82 and 84 in 17 % and 21 % isolated yield, respectively. The structure of 82 and 84 were assigned from the NMR spectra, with the type A Sn-H couplings ($J_{Sn-H} = 176, 174$ Hz, respectively) and the vinyl moiety ($RCH=CH_2$) present in the molecule. In spite of these low yields, it is notable that even amino alcohol with highly basic tertiary amine is compatible with the reaction conditions (entry 6, Table 3.2). With the protected amino alcohol derivative 75$^*$ (R = TBS), the isolated yield was higher (41 %). It is notable in the reaction of 74, that the formation of a dimerization product 83 was noted (6 %, isolated yield), which implies that
intramolecular cyclization reaction with tethered olefin is significantly slower than intermolecular addition into a second acetylene (entry 5, Table 3.2). In other words, cyclization of 74 is inherently slower than competing intermolecular side reaction even in a fairly dilute conditions (0.2 M, C₆D₆). The pseudo-C₂ symmetric structure of 83 was based on the assignment of peaks in ¹H, ¹³C, and COSY NMR spectra as well as high resolution MS. In ¹H NMR, the isolated sample of 83 showed two different vinyl moieties and in ¹³C NMR more than 6 vinyl Csp² peaks were observed. Also, 2JSn-H (70 Hz) is also consistent with Sn-H coupling of type B (Figure 3.3).

With the aim of finding the appropriate condition for the cyclization of these eneynes, several phosphine ligands were screened for the substrate shown in entry 3 in Table 3.2. For example, enyne 72 was screened with various ligands as shown in eq. 3. In ¹H NMR spectrum of this reaction with PCy₃, starting material disappeared completely to give acyclic adduct 81 in 13 h at rt, which under more forcing condition (7 h, 60 °C) resulted in a complex unidentifiable mixture with broad peaks.

\[
\begin{align*}
72 & \xrightarrow{\text{Bu₃Sn-SiMe₃}} \text{SnBu₃} \\
\text{Pd₂dba)₃ (2 %)} & \text{ligands (4 %)} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>phosphine</th>
<th>RT/ 13 h⁰</th>
<th>80 °C/ 7 h⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>81 38 %</td>
<td>Product could not be identified⁶</td>
</tr>
<tr>
<td>PCy₃</td>
<td>81 &gt;90 %</td>
<td>complex mixture</td>
</tr>
<tr>
<td>P(C₆F₅)₃</td>
<td>81 21 %</td>
<td>Product could not be identified⁶</td>
</tr>
<tr>
<td>PPh₃</td>
<td>81 4 %</td>
<td>81 (&gt;90 %)</td>
</tr>
<tr>
<td>P(OPh)₃</td>
<td>none⁵</td>
<td>none⁵</td>
</tr>
</tbody>
</table>

⁰ Yields were determined based on consumed starting material in the ¹H NMR spectrum. ⁵ Starting material remained (¹H NMR). ⁶ Product could not be isolated.
Although the desired cyclization of enynes could not be achieved, this preliminary results show the silylstannylative reaction conditions are compatible with a number of functional groups including ethers, tertiary amines, and free alcohol. Also the reaction time and yield recorded reflect preliminary observations on the reactivity profile of each class of substrates in the silylstannylative reaction conditions used. Importantly, the reactivities of enynes studied in this section indicated that enyne cyclization is inherently difficult, as evidenced by the competitive intermolecular reaction.

3.3 Reactions of Substituted Diynes

Diynes originally investigated as substrates in the discovery of bimetallative cyclization process have been symmetric ones. Unsymmetrical diynes, as explained in the introduction will present regio- and stereoselectivity issues. In this section, studies on several unsymmetrical diynes in which the two acetylenes are placed in chemically and sterically different environments are presented. The electronic and steric effects as well as functional group compatibility will be the main focus of these investigations. For example, α,ω-diene in 86 are differentiated by substitution at the propargylic position.

![Figure 3.4. Substrates II: Diynes](image-url)
while acetylenes in 87 and 88 have different electronic characters. In 89 and 90, one of acetylene is internal while the other is terminal (Figure 3.4). The preparations of these compounds are described in Scheme 3.2. The synthesis of diyne 87, 13a 88, 13b and 89 13c were carried out according to the literature procedures. The pyrrolidine 86 was synthesized from known aldehyde 77 10 via Corey-Fuchs 14 or Gilbert-Seyferth procedure. 15 Treatment of 77 with CBr4 and PPh3 in CH2Cl2 at 0 °C gave dibromovinyl compound 91, which delivers diyne 86 via elimination reaction by n-BuLi. Alternatively, treatment of 77 with Gilbert-Seyferth reagent (A, Scheme 3.2) in basic MeOH gave diyne 86 directly in 57% yield. The structure and purity of 86 was ascertained by NMR (1H, 13C, COSY, and DEPT) as well as IR and GLC analysis. In IR spectrum, diyne 86 shows two acetylenes at 3296 (w/shoulder), 2361, and 2348 cm⁻¹. The diyne 90 was synthesized using cuprate chemistry. The reaction of dipropargyl tosylamine with n-BuLi (2.0 equiv) in the presence of 1.0 equivalent of CuI at −78 °C was assumed to give corresponding

![Scheme 3.2 Preparation of Substrates II: Diynes 86 and 90](image-url)
cuprate. Treating this species with 1.0 equiv of MeI gave mono-methylated 90 exclusively.

First the diynes 86, 87, and 88 were subjected to the silylstannylation conditions (Table 3.3). Gratifyingly, diyne 86 with a tertiary amine, when treated with Bu$_3$Sn-SiMe$_3$ (1.1 equiv.), Pd$_2$(dba)$_3$ (2.5 %), and P(o-tol)$_3$ (5 %) in benzene-d$_6$ (0.2 M) at rt for 4 days, provided pyrrolizidine structure of 92 in >80 % (by $^1$H NMR). The regioisomeric and atrop-diastereomeric nature of this mixture 92 will be discussed in the following sections (Chapter 3.4), where low temperature NMR studies are described. After chromatography

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates</th>
<th>ligands/conditions*</th>
<th>product</th>
<th>yield$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>P(o-tol)$_3$, rt / 1 d$^b$</td>
<td>92a $X = $SiMe$_3$, $Y = $SnBu$_3$</td>
<td>(29 %) 1/1$^d$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P(o-tol)$_3$, rt / 7 d$^b$</td>
<td>92b $X = $SnBu$_3$, $Y = $SiMe$_3$</td>
<td>(85 %) 1/1$^d$</td>
</tr>
<tr>
<td>2</td>
<td>87</td>
<td>P(C$_8$F$_5$)$_3$, 60 °C/16 h</td>
<td>93</td>
<td>17 %</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>P(OPh)$_3$, 60 °C/3 h</td>
<td>94</td>
<td>40 % (&gt; 80 %)</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>P(OPh)$_3$, 60 °C/3 d</td>
<td>95</td>
<td>43 % (&gt; 80 %)</td>
</tr>
</tbody>
</table>

*Pd$_2$(dba)$_3$ (2.5 %), phosphine (5 %), Bu$_3$Sn-SiMe$_3$ (1.1 equiv.) in C$_6$D$_6$ (0.2 M), $^b$5 mol% of Pd precursor and 10 % of phosphine was used instead. $^c$Isolated yield (NMR yield in parenthesis), $^d$The ratio of regioisomers ($^1$H NMR).

Table 3.3 Reactions of Diynes I
(SiO₂), an inseparable mixture of two isomers of 92 in a ratio of 1:1 was isolated. The characterization of 92 was done with the help of ¹H, ¹³C, COSY and HMQC NMR spectroscopy as well as HRMS. In the ¹H NMR spectrum, about 1:1 mixture of two isomers was seen (Figure 3.8). The assignment of downfield portions of the spectrum is described in Figure 3.5. In 92a, the (Sn)Cₛᵖ₂H=CR₂ peak (H₄) appear at δ 5.71 ppm (d, J = 1.4 Hz) with characteristic ²Jₛn-H of cyclic product (type B in Figure 3.3), which is coupled to bridgehead proton at δ 3.84 (t) ppm. The (Si)CH=CR₂ proton (H₅) of 92a is coupled to NCH₂ protons (H₆, H₇). In 92b, the (Sn)Cₛᵖ₂H=CR₂ peak (H₅') appears at δ 5.78 (s br), but that proton is coupled to NCH₂ protons (H₆', H₇') and the (Si)CH=CR₂ proton (H₅') is now coupled to bridgehead proton (H₆') (Figure 3.8).

Figure 3.5 The Assignment of 92a and 92b (in-situ ¹H NMR)

Amide and ester diynes 87 and 88 underwent silylstannylation to give the corresponding acyclic mono-adducts 93 and 94 (entries 2, 3, Table 3.3). The adduct 93
was characterized by $^1$H, $^{13}$C NMR and adduct 94 was characterized by $^1$H, $^{13}$C NMR, and HMQC as well as HRMS. The $^1$H, $^{13}$C NMR spectra indicated that (Si)CH=C(Sn)R peaks of 93 and 94 appear at $\delta$ 7.18 and 7.64 ppm with $^3$J$_{Sn-H}$ (140 Hz, 143 Hz), respectively. In this case, Sn-Si reagent is first added into the electron-deficient acetylene. The difficulty of cyclization of 87 and 88 maybe related to the fact that s-cis rotamer predominates in the mixture precluding the coordination of the $\omega$-acetylene.

From the formation of di-adduct (entry 4, Table 3.3), it is clear that cyclization is disfavored over subsequent di-adduct (95) formation. Each entry of Table 3.3 was studied in detail with different ligands. When the reaction of 88 was run with several different phosphine ligands, a widely different rates were observed as shown in eq 4. The reactivities of phosphine for this type of substrate follow the order: P(oph)$_3$ > PPh$_3$ >> PCy$_3$ > PBu$_3$.

\[
\begin{array}{cc}
\text{phosphine} & \text{after 2.5 h}^a & \text{after 3 days}^a \\
\text{PCy}_3 & \text{No reaction} & \text{No reaction} \\
\text{PBu}_3 & \text{No reaction} & \text{No reaction} \\
\text{PPh}_3 & \text{No reaction} & 94 (>90\%) \\
\text{P(oph)}_3 & 94 40\% (>90\%) & 95 43\% (>80\%) \\
\end{array}
\]

\textit{a} Isolated yields (yields in parenthesis are based on $^1$H NMR).

P(oph)$_3$, after a prolonged period, (60 °C, 3 day) a conversion of primary product 94 into a secondary product 95 (di-adduct) was only observed instead of cyclization. The di-
adduct 95 was characterized by HRMS and NMR spectroscopy, where peaks due to SnBu3 and SiMe3 moieties appeared doubly. In 1H NMR of 95, the two (Si)CH=C(Sn)R peaks appear at δ 6.61 (3J_Sn-H = 160 Hz) and at δ 7.57 (3J_Sn-H = 148 Hz).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates</th>
<th>ligands/conditions</th>
<th>product</th>
<th>product\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>\includegraphics[width=0.2\textwidth]{89}</td>
<td>PCy3, rt/ 16 h PPh3, rt/ 16 h</td>
<td>Me\textsubscript{3}Si\includegraphics[width=0.3\textwidth]{89}</td>
<td>88 % (&gt;95 %) 49 % (&gt;50 %)</td>
</tr>
<tr>
<td>6</td>
<td>\includegraphics[width=0.2\textwidth]{90}</td>
<td>P(Ph\textsubscript{3})\textsubscript{3}, 60 \textdegreeC/ 3 h</td>
<td>Me\textsubscript{3}Si\includegraphics[width=0.3\textwidth]{90}</td>
<td>67%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Pd\textsubscript{2}(dba)\textsubscript{3} (2.5 %), phosphine (5 %), Bu\textsubscript{3}Sn-SiMe\textsubscript{3} (1.1 equiv.) in C\textsubscript{6}D\textsubscript{6} (0.2 M). \textsuperscript{b}Isolated yield (NMR yields in parenthesis).

Table 3.4 Reactions of Diynes II

Study of diynes 89 and 90 under silylstannylative conditions is summarized in Table 3.4. Desired cyclization failed to materialize and in both cases, the corresponding mono-adducts 96 and 97 were obtained. The structures of 96 and 97 were ascertained by NMR spectra and HRMS. In 1H NMR spectra, characteristic (Si)CH=C(Sn)R peaks appear at δ 6.67 (3J_Sn-H =158 Hz) and 6.66 (3J_Sn-H = 162 Hz) ppm, respectively for 96 and 97.

The diynes studied in this section reveal the following information about the current silylstannylative methodology. (1) Our original purpose of obtaining high
regioselectivity in the cyclization of unsymmetrical diyynes could not be achieved by simple substitution change at the propargylic position. In the case of 86 where two terminal acetylene differ by substitution at propargyl position, nearly 1:1 mixture of regioisomers were obtained. (2) Electronically different diyynes 87 and 88, on the other hand, failed to cyclize as a result of slowness of the cyclization step, as can be seen in the formation of di-adducts 95. (3) In 89 and 90, where one of the acetylene function is di-substituted failed to cyclize, because the silylstannylative reaction seems to be very sensitive to steric effects of the acetylene. Instead, monoadduct formation with the less hindered acetylene was selectively formed. (4) The rate of reaction can be optimized with proper choice of the phosphine ligands in each case. For symmetric terminal diyynes, the best ligand, $\text{P(C}_8\text{F}_3)_3$, was shown to effect cyclization with some generality. However, no such best ligand could be found for the diyynes studied in this section. (5) The last issue deals with diastereoselectivity. Pyrrolizidine 92, with a chiral center near the axis of chirality, has the potential of being formed with atrop-diastereomeric selectivity. The discussion of this structural aspect is continued in the next section.

3.4. Stereochemical Aspects of Pyrrolizidine 92.

In Figure 3.6, all possible isomers of Sn-Si adduct 92 are shown. Pairs 92a and 92b are regioisomeric and so are 92a'/92b'. Pairs 92a/92a' or 92b/92b' is diastereomeric as a result of axial chirality. When pyrrolizidine 92 is formed, about 1:1 ratio of isomers was observed in $^1$H NMR spectrum at rt (Figure 3.8, Chapter 3.3). The possibilities are (1) regioisomeric pair (92a/92b or 92a'/92b'), with atrop-diastereomers interconverting fast at rt, (2) regioisomeric pair with one atropisomer in each being the most stable entity,
or (3) one regioisomer (most likely 92a/92a', with silyl group ending up in the less hindered acetylene) with slow atrop-diastereomeric equilibrium at rt.

Figure 3.6 Possible Isomers of Pyrrolizidine 92

To determine the nature of 92, we investigated the low-temperature $^1$H NMR spectra of the derivatives. Our assumption from related compounds showing atropisomerism was that for freely inter-convertible exo-(Z,Z)-1,3-diene systems, coalescence temperature ($T_c$) above which NMR peaks due to atropisomers coalesce into

Figure 3.7 Typical Atropisomeric Coalescence Temperatures (From Dr. Warren)
Figure 3.8: H NMR spectrum of 92 (in situ, in CDCl₃)
one species is usually found between -60 °C and +10 °C. In 92, where fused ring structure exerts further restraint in the interconversion of atrop-diastereomers, the Tc is expected to be much higher than the range of -60 °C - +10 °C.

When the crude mixture of 92 was treated with NBS (1.0 equiv.) as in eq. 5, there are four broad singlets for four vinyl protons in 98: Hα, Hb, Ha', and Hb' (eq. 5). These peaks appear at δ 5.77 (s, CHBr) and 5.28 (s, CHSi) for Hα and Hb, respectively and at

Figure 3.9 Low-Temperature ¹H NMR of 98

δ 5.75 (s, CHBr) and 5.22 (s, CHSi) ppm for Hb' and Ha'. When the NMR tube containing 98 was heated in C₆D₆, no temperature dependent change was observed up to 70 °C. When that of 98 in CDCl₃ was cooled down (Figure 3.9), a significant broadening was
observed at around \(-20 \, ^\circ\text{C}\). Upon cooling below \(-40 \, ^\circ\text{C}\), the broad peaks resolved again and additional sets of peaks started to appear at \(\delta 5.67, 5.60, 5.22,\) and \(5.10 \, \text{ppm}\). The new sets of peaks were smaller in magnitude and the ratio of original sets vs. these new sets was determined to be \(\sim 3:1\). We believe that these new sets of peaks will probably correspond to the atrop-diastereomeric species of 98 (Figure 3.10). This result illustrates again the consequence of atropisomerism in this densely congested (\(Z,Z\))-1,3-diene system. At a temperature above \(T_c\), atropisomeric equilibrium occurs fast compared to NMR time scale so that the effect of axial chirality is not observed. However, below \(T_c\), atropisomeric equilibrium now freezes and diastereomers occurring from its axial chirality appeared in the NMR spectrum. In 98, such coalescence temperature was determined to be around \(-20 \, ^\circ\text{C}\). It was also determined that atrop-diastereomeric ratio \((98a/98a')\) is \(\sim 3/1\). Compared with the example in Figure 3.7, higher diastereomeric ratio is observed because chiral center is closer in 98 than the ones in Fig. 3.7 (For example, atrop-diastereomeric ratio of derivative with \(X = \text{CH} (\text{CO}_2\text{Me})\) was 1:1).

Figure 3.10 Possible Isomers of Pyrrolizidine 98
Previous arguments support the contention that 92 is a regioisomeric mixture, which can be derivatized with NBS to give 98. By cooling 98 to <-30 °C, atropoisomeric equilibrium could be frozen and all four isomers could be observed. From the similar experiments on the parent compound 92, we could determine the Tc of parent compound 92 to be around -10 °C (see Appendix for low-temperature ¹H NMR spectra). Further studies should include attempts to find atrop-diastereomeric system which has higher Tc than rt and one that can be used for stereoselective synthesis, for example, by generating centers of chirality from specific atropisomers. Another similar example will be discussed in Chapter 5, in connection with an application for the synthesis of kainoids (Section 5.5).

3.5. Derivatization of the Silylstannane Adducts

As mentioned earlier in the introduction, for silylstannane to be useful synthons for organic synthesis, development of necessary 'tools' to derivatize the vinyl silane or vinyl stannane are highly desirable. Three such efforts based on the previous work is shown in eq. 6. Vinyl silane can, in principle, undergo various reactions, including Friedel-Craft acylation (eq. 6), Nozaki-Hiyama coupling, and epoxidation-elimination to afford carbonyl compound.
Compared with vinyl silanes, the chemistry of vinyl stannanes has been more widely developed. The most well known reactions of this class of compounds are Stille coupling, Sn-halogen exchange, destannylation, and Lewis acid-catalyzed reactions.

Using the relatively high nucleophilic character of C-Sn bond, selective Stille coupling in the presence of vinyl silane compounds was carried out (eq. 7). DMF is a favored over benzene as a solvent for Stille coupling and Cul is essential for effective coupling (entry 1, eq. 7). However, the scope appears to be limited to the electron-deficient aryl bromide or aryl iodide (entry 3, eq. 7). In the reaction with electron-rich aryl bromide only reduction product 106 was obtained in 38% yield. The nOe experiments of 100 and 101 confirmed that the isolated coupling product had double bond stereochemistry drawn (Figure 3.11). Thus, completely stereospecific Stille coupling was achieved under these conditions.

\[
\begin{align*}
99 & \xrightarrow{\text{Ar-X (1 equiv.)}} \quad \text{Pd(PPh_3)_4 (5%)} \quad \text{Cul, DMF} \quad 100 \quad \text{Ar = 3-bromophenyl} \\
101 & \quad \text{Ar = 3,5-di-trifluoromethylphenyl}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar-X</th>
<th>Cul conditions</th>
<th>yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>10 %(^b) 80 °C/8 h</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>30 %(^b) 80 °C/8 h</td>
<td>100 (65 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 %(^b) 80 °C/8 h</td>
<td>100 (68 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 % 80 °C/2 h</td>
<td>100 55 % (100 %)</td>
</tr>
<tr>
<td>2</td>
<td>F_3C</td>
<td>100 % 120 °C/3 h</td>
<td>101 25 %</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>20 % 60 °C/17 h</td>
<td>106 38 %</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields (yields based in starting material in 'in-situ' or crude
\(^b\) \(^1\)H NMR), \(^b\) C_6D_6 was used as solvent.
The Stille coupling product was initially assumed to introduce further steric hindrance around (Z,Z)-1,3-diene part of the molecule 100 and 101, and as a result, higher barrier for atropisomeric inversion was expected. However, low-temperature $^1$H

**Table 3.1** Proton Chemical Shifts and NOE Contacts in 100 and 101

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift (δ)</th>
<th>NOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_a$</td>
<td>5.52 (s)</td>
<td>$H_a - H_c$ 2.8 %</td>
</tr>
<tr>
<td>$H_b$</td>
<td>6.13 (s)</td>
<td>$H_b - H_d$ 2.4 %</td>
</tr>
<tr>
<td>$H_c$</td>
<td>4.05 (d, J = 1.6 Hz)</td>
<td>TMS - $H_e$ 0.3 %</td>
</tr>
<tr>
<td>$H_d$</td>
<td>4.00 (d, J = 1.6 Hz)</td>
<td>$H_a - H_c$ 2.8 %</td>
</tr>
<tr>
<td>$H_e$</td>
<td>7.10 (s)</td>
<td>$H_b - H_d$ 3.0 %</td>
</tr>
</tbody>
</table>

NMR spectra of 101 showed that NCH$_2$ peaks of 101 split into multiplets below -40 °C: at 0 °C, the two NCH$_2$ peaks appear at δ 4.05 (d, J = 1.6 Hz) and 4.09 (d, J = 1.6 Hz), and at -60 °C, the two NCH$_2$ peaks appear as broad multiplets at δ 4.20-3.80. Such transition occurs at around -40 °C. On the other hand, no such change in the vinyl region was observed in the temperature range of 50 °C - -60 °C. The possible reason for such a low $T_c$ may be found in the rotation of bond between C(vinyl)-C(aryl) (Figure 3.12). Such a rotation, if occurs, will result in the loss of delocalization stabilization energy, but if that
energy loss is smaller than the energy needed for atropisomeric inversion (due to the removal of steric repulsion between aryl and SiMe₃ substituents), such a path could be accommodated.

On the other hand, treatment of vinylstannane 99 with NBS (1.1 equiv.) in CH₂Cl₂ at rt resulted halogen-Sn exchange to provide vinyl bromide 103 (eq. 8). Similarly, 96 and 97 was treated with I₂ (1.2 equiv) in CH₂Cl₂ at rt to afforded vinyl iodide 104 and 105 in high yields as single double bond isomers (eq. 9). The geometry of double bond was secured by nOe difference spectra in the case of 103 (Figure 3.13) and in case of 104 and 105, predicted by analogy to many examples of Sn-halogen exchange with the retention of geometry.⁶bc The compounds 103, 104, and 105 were characterized by ¹H and ¹³C NMR spectra.
Figure 3.13 Selected nOe Contacts in 103

Silylstannane 99 can be selectively destannylated with carboxylic acid as shown in eq. 10. The hydrolysis of vinyl C\(_{sp2}\)-stannane is known to be effected by carboxylic acids. Among the several carboxylic acids tried, HCO\(_2\)H (5 equiv.) gave the best results (98 %, isolated yield) with reliability (entry 3, eq. 10). The destannylated product 106 obtained was prone to polymerization gradually with exposure to light. Also in this case stereochemistry of double bond was confirmed with nOe experiments (Figure 3.14).

<table>
<thead>
<tr>
<th>entry</th>
<th>acid / equivalent</th>
<th>conditions</th>
<th>yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_3)CO(_2)H / 2 eq.</td>
<td>RT / 1 h</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td>CH(_3)CO(_2)H / 5 eq.</td>
<td>RT / 1 h</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td>CH(_3)CO(_2)H / 5 eq.</td>
<td>RT / 7 h</td>
<td>(30 %)</td>
</tr>
<tr>
<td></td>
<td>CH(_3)CO(_2)H / 5 eq.</td>
<td>RT / 4 days</td>
<td>(90 %)</td>
</tr>
<tr>
<td>2</td>
<td>CF(_3)CO(_2)H / 5 eq.</td>
<td>RT / 3 h</td>
<td>Unidentified side product</td>
</tr>
<tr>
<td>3</td>
<td>HCO(_2)H / 5 eq.</td>
<td>RT / 10 h</td>
<td>98 %</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields (Yields in parenthesis is based on starting material present, determined by \(^1\)H NMR in CD\(_2\)Cl\(_2\))
The vinyl silane 106 undergoes Diels-Alder reaction. With bulky SnBu$_3$ removed, the 1,3-diene is expected to have a near planar geometry. When 106 was mixed with maleic anhydride and was heated at 60 °C, the adduct 107 was isolated as white solid (mp 164-166 °C, eq. 11), which was characterized by $^1$H, $^{13}$C, COSY, HMGC, HMBC, IR, as well as high resolution MS. The configuration of 107 was unambiguously determined by HMGC and HMBC and the relative stereochemistry was based on the mechanism of endo transition state upon formation of the cycloadduct.
3.6. Use of B-Sn Reagents and Attempts to Derivatize Borylstannane Compounds

In 1997, Tanaka and coworkers reported the use of B-Sn reagent A for borostannylation of diynes catalyzed by Pd(0) complex (eq. 12). They showed the cyclization of internal diynes and differentiation of two acetylene termini. Borostannylation seemed to be more potent than silylstannylation for demanding substrates as internal acetylenes, but resulting product cannot be easily handled.

\[
\text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \text{ (1 mol %)} \rightarrow \text{Me}_3\text{Sn-B}^+ \rightarrow \text{C}_6\text{H}_5\text{, rt, 1 - 5 h} \rightarrow \text{eq. 12)}
\]

For example, 108 readily decompose upon exposure to atmospheric moisture and upon silica gel column chromatography. The only alternative to isolate them is recrystallization or bulb-to-bulb distillation under a very high vacuum (1-10 \(\mu\)torr). We thought development of appropriate derivatization method for borylstannane compounds would make the reagent a viable alternative to silastannylation. Our unsuccessful attempts to derivatize 108 and related compounds is described in the following sections. These include Suzuki coupling, selective protonolysis of \(\text{C}_{\text{sp}2}\)-B bond, ligand exchange on boron, and Stille coupling.

The formation of 108 was carried out using Pd(PPh\(_3\))\(_4\), Pd(PPh\(_3\))\(_2\), or Pd\(_2\)(dba\(_3\)) complex (1-2 mol %) without added ligand in benzene-\(d_6\) as solvent (0.1 M) and the \(^1\)H NMR (C\(_6\)D\(_6\)) indicated a clean conversion into the cyclic product after 2 h at rt. The
borylstannane compound 108, formed in-situ, was subjected to Suzuki coupling conditions (eq. 12). To the crude reaction mixture was added aryl iodide (1.0 equiv.) and base as shown in eq. 13. Under the typical Suzuki coupling conditions, however, the desired products could not be obtained. In one case (entry 1, eq.13),

![Reaction Scheme]

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar-I</th>
<th>Pd catalyst</th>
<th>base</th>
<th>solvent</th>
<th>conditions</th>
<th>remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>PdCl₂(PPh₃)₂</td>
<td>K₂CO₃</td>
<td>dioxane</td>
<td>70 °C, 2 h</td>
<td>110, 23%</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>(2.0 eq.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>Pd(PPh₃)₄</td>
<td>NaOEt</td>
<td>EtOH</td>
<td>80 °C, 1.5 h</td>
<td>unidentified mixture resulted</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>(2.0 eq.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>Pd(PPh₃)₄</td>
<td>NaOEt</td>
<td>EtOH</td>
<td>70 °C, 0.5 h</td>
<td>unidentified mixture resulted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.0 eq.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Me-I</td>
<td>Pd(PPh₃)₄</td>
<td>NaOEt</td>
<td>EtOH</td>
<td>rt, 20 h</td>
<td>unidentified mixture resulted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.0 eq.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Benzene was used as co-solvent with these solvents (1:1)*

where dioxane was used as co-solvent with benzene (1:1), a reduction product 110 (vide infra for structural characterizations) was obtained in a low isolated yield. In reaction conditions where EtOH was used as co-solvent, no identifiable compound was isolated (entry 2-4, eq. 13)

When the unsymmetrical diyne 90 was subjected to borostannylation conditions, corresponding borylstannane product 111 was obtained as crystallize solid (eq. 14) after
recrystallization from hexane/benzene. Several attempts were made to derivatize the cycloadduct 111 via ligand exchange reaction, with an expectation of obtaining the more stable derivatives, as shown in eq.15. When pinnacol (1.3 equiv.) was added to a solution

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

of 111 in benzene-\(d_6\), a new species appeared after 2 h at 70 °C (\(^1\)H NMR), but after 12 h unselective reactions occurred to give a complex unidentified mixture. When 111 was treated with catechol (1.1 equiv.) at rt for 1.5 h, a clean reaction into a new species occurred in 70 % conversion (\(^1\)H NMR), but the product could not be isolated or identified.
When 108 was treated with 1.0 equiv. of NBS, after 5 h at RT, several species were observed in the $^1$H NMR, but the reaction mixture resulted in a complex mixture after 24 h (eq. 16).

\[
\text{Me} + \text{NBS} \rightarrow \text{complex mixture (16)}
\]

The B-C$_{sp2}$ bond in borostannane 108 can be cleaved by the action of alcohol. For example, when the crude reaction mixture in C$_6$D$_6$ was treated with 5 equiv. of MeOH, the deboronation occurred slowly to give vinylstannane 110 in 43 % yield.

\[
\text{MeOH} \quad \text{(5 equiv.)} \quad \text{C}_6\text{D}_6 \quad \text{108} \rightarrow \text{SnMe$_3$} \quad \text{110, 43 % (17)}
\]

3.7. Application to the Synthesis of Indolizidines Related to Pumiliotoxin Core.

Having succeeded in the formation of pyrrolizidine ring structure 92 from 86 by silylstannylative cyclization (Table 3.3, Chapter 3.3), an effort was made to apply the Pd-catalyzed silylstannylative cyclization of terminal diynes for the carbocyclization to form indolizidine structures.
Initially, we envisioned that the indolizidine skeleton of allopumiliotoxin alkaloid could be assembled through the palladium catalyzed bimetalation-cyclization method. According to this scheme (Scheme 3.3), the required substrate 113 and its derivatives were synthesized (Scheme 3.4). Propargyl alcohol 114 was assembled according to a known procedure, as shown in Scheme 3.4. The alcohol 114 was converted into the bromide 115 by treatment of 114 with PPh3 and CBr4 in CH2Cl2 in 88 % yield. The purity of propargyl bromide 115 was determined by GLC analysis (95 %) and the structure was confirmed by 1H and 13C NMR spectra.

A known ketone derivative 116 from L-proline was assembled according to the literature procedure via Weinreb amide. The N-Boc protecting group was removed from the ketone 116 with CF3CO2H in CH2Cl2. A solution of the resulting ketone was added to a solution of excess lithium trimethylsilylacetylide to yield tertiary alcohol 117 in 88 % yield as off-white crystalline solid (mp 49-51 °C). This compound was characterized by 1H, 13C, COSY, HMBC, DEPT, IR, and optical rotation. IR spectrum indicates hydroxy group (3500-3000 cm⁻¹) and acetylene (3344, 2165 cm⁻¹) function. Fully assigned 1H
NMR spectra confirmed the structure of 117. A good level of diastereoselectivity was obtained (~7:1) as judged by $^1$H NMR of the crude mixture of 117. When the 117 was treated with ethereal HCl (2 equiv.) followed by evaporation, an oil resulted, which was recrystallized from pentane to give crystalline hydrochloride salt 117HCl suitable for X-ray analysis. The stereochemistry of tertiary alcohol was established by the X-ray crystallography of the HCl salt of 117 (Figure 3.15). The coupling of 117 with 115 above

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{CBr}_4, \text{PPh}_3} 62\% \\
\text{Br} & \xrightarrow{\text{n-BuLi, THF}} 84\%, 2\text{ steps} \\
X & \xrightarrow{\text{PPh}_3, \text{CBr}_4, 88\%}
\end{align*}
\]

\[
\begin{align*}
\text{NH} & \xrightarrow{1. \text{(Boc)}_2\text{O}, \text{NaOH, water}} 2. \text{ClICO}_2\text{Me, NMM}} \xrightarrow{3. \text{MeLi, 88\%}} \\
\text{Me} & \xrightarrow{1. \text{CF}_3\text{CO}_2\text{H}, \text{CH}_2\text{Cl}_2} 2. \text{TMS-acetylene, n-BuLi}} \xrightarrow{88\%, 2\text{ steps}} \\
\text{Me} & \xrightarrow{1. \text{Pr}_2\text{NEt}, 115, \text{THF}} 2. \text{TBAF, THF}} \xrightarrow{70\%, 2\text{ steps}} \xrightarrow{\text{TMS-OTf/(Me}_3\text{Si)}_2\text{NH}} \xrightarrow{85\%}
\end{align*}
\]

Scheme 3.4 Preparation of Substrate III: Diyne 113 and 118

in the presence of DIPEA in THF went especially smoothly (98%) and 113 was obtained after desilylation (71%). The structure of 113 was confirmed by IR, as well as $^1$H and $^{13}$C NMR spectra. The alcohol-protected substrate 118 was also synthesized using the reported procedure using (Me$_3$Si)$_2$NH and TMS-Cl. The diyne 118 was characterized by $^1$H, $^{13}$C, COSY, HMQC, IR, and high resolution MS.
With 113 in hand, the viability of silylstannylation-cyclization to generate indolizidine skeleton was examined (eq. 18). Use of various phosphine ligands (entry 2-7, eq. 18) resulted in a very slow reaction compared with the terminal diynes: no reaction after 6 h at 60 °C. The low reactivity of this diyne 113 is not surprising, however, considering the reactions of other internal diynes described in Chapter 3.3 (substrates 89 and 90). After a prolonged heating at 60 °C, the reaction mixture indicated a highly unselective reaction leading to a complex mixture of products. When the reaction was followed by $^1$H NMR spectroscopy, a typical reaction mixture after 48 h at 60 °C shows
several peaks in the olefinic region of spectra: 6.41 (s), 6.23 (s), 4.96 (d), and 4.63 (dd) along with the starting 113 remaining. The cleanest reaction was observed with no added phosphine. Attempts to isolate the product by chromatography failed, however.

Use of the more reactive bimetalation reagent, Sn-B reagent was attempted as shown in eq.19. When the progress of the reaction was followed by $^1$H NMR at rt, slow conversion into a complex mixture was observed over 1 day. In this case also, the isolation of the products failed.
Alternative method of carbocyclization using $\text{Cp}_2\text{Zr}^{19}$ was also tried. When the silylated alcohol substrate 118 was treated with ‘$\text{Cp}_2\text{Zr(II)}$’ reagent generated from $\text{Cp}_2\text{ZrCl}_2$ (1.0 equiv.) and n-BuLi (2.0 equiv.) in THF (1 mL) at $-78 \, ^\circ\text{C}$, followed by hydrolysis with benzoic acid, and chromatography, the reaction mixture yielded no product. The starting material was recovered in 44 % yield from the reaction mixture (eq. 20).

After finding that 113 was not an appropriate substrate for bimetallative cyclization, attention was turned to terminal diyne 119. Synthesis of 119 was similar to that of 113 except the use of propargyl bromide in the place of 115 (Schemes 3.4 and 3.5). After N-alkylation of 117 with propargyl bromide, TMS group was removed by treating the intermediate with TBAF to yield 119. This material was characterized by $^1\text{H}$, $^{13}\text{C}$, IR, COSY, HMQC, and high resolution MS. This diyne 119 was subjected to the silylstannylation conditions as shown in eq. 21.

Scheme 3.5 Preparation of Substrate IV: Diyne 119
When no ligand was used for silylstannylation, 119 underwent an unselective reaction to give at least three species. The most probable structures of these products are shown below eq. 21. These can be identified tentatively based on the chemical shift and

![Chemical structures](product_1) (product II) (product III)

$J_{Sn-H}$ coupling constants in the NMR spectra as well as correlation of peaks in the COSY spectrum. For example, one of the product present in the mixture has peaks at $\delta$ 6.03 (s, $J_{Sn-H} = 60$ Hz) and 5.37 (s), which implies a cyclic structure (product II or III, eq. 21) and the other product has peaks at $\delta$ 6.64 (s, $J_{Sn-H} = 180$ Hz) and acetylene peak at $\delta$ 1.89 (t, $J = 2.3$ Hz), which seems to be an acyclic product (product I, eq. 21). Attempts to separate these products on silica gel chromatography was made, but resulted only in isolation of mixtures. Further attempts to fully characterize these compounds failed because of the

<table>
<thead>
<tr>
<th>entry</th>
<th>phosphine</th>
<th>condition</th>
<th>remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>75 °C/18 h</td>
<td>complex mixture / no 53 remained</td>
</tr>
<tr>
<td>2</td>
<td>P(C6F5)3</td>
<td>75 °C/18 h</td>
<td>complex mixture / product seems to decompose</td>
</tr>
<tr>
<td>3</td>
<td>PPh3</td>
<td>75 °C/18 h</td>
<td>complex mixture / no 53 remained</td>
</tr>
<tr>
<td>4</td>
<td>Bu,N-NC</td>
<td>75 °C/18 h</td>
<td>complex mixture / no 53 remained</td>
</tr>
</tbody>
</table>

$^a$Ph$_3$Sn-SiMe$_2$Bu reagent was used instead of Bu$_3$Sn-SiMe$_3$. $^b$Only starting material was observed in $^1$H NMR spectra.
complexity of these mixtures in the $^1H$ NMR spectra. In the meantime, use of borylstannane reagent gave a much cleaner reaction as shown in eq. 22.

\[
\text{[Equation 22]}
\]

When diyne 119 was treated with borylstannane (1.1 equiv.) in benzene at rt, a clean conversion was observed in the $^1H$ NMR. In the $^1H$, $^{119}Sn$ NMR spectrum of the reaction mixture, several peaks seems to indicate the formation of the cycloadduct shown in eq. 22: $\delta 5.77$ (s, $J_{Sn-H} = 70$ Hz, H, (Sn)CH=C), 5.45 (d, $J = 1.2$ Hz, H, (B)CH=C), 1.52 (s, 3H, CH$_3$), and 0.20 (s, 9H, SnMe$_3$) in $^1H$ NMR, and $\delta -48.4$ ppm (s) in the $^{119}Sn$ NMR spectrum. Further attempts to isolate the product by silica gel chromatography resulted in the decomposition of the product. Attempts to purify this material by recrystallization were hampered by the incorporation of trace of catalyst or residues of B-Sn reagents. The structure of presumed product is shown in eq. 22, but unambiguous characterization has not been completed.

3.8. Conclusions

In an effort to explore the scope and functional group compatibility of silylstannylation reactions, various unsaturated compounds, including ynals, eneynes, and diynes were prepared and examined under silylstannylation conditions. The reactions of ynals and eneynes were typically slow at rt to give corresponding mono-adducts. Under
forcing condition (higher temperature and/or longer reaction times) desired cyclization product was not observed and the complex reaction mixture was obtained. The formation of intermolecular adduct in the case of one enyne (74) indicates inherent low reactivity of silylstannylation/cyclization. Diynes with unsymmetrical substitution at propargylic position gave marginal regioselectivity. Unsymmetrical diynes with internal acetylene failed to cyclize, indicating sensitivity of current method toward steric effect in the substrates.

A study of temperature-dependent nature of atropisomerism in 92 and its derivative 98 was carried out. This (Z,Z)-1,3-diene system in the bicyclic motif is expected to show higher-energy of activation to the atropisomeric interconversion. The coalescence temperature \( T_c \) of this equilibrium for a bromo-derivative 98 was determined to be about \(-20^\circ C\), while the parent compound 92 was determined to be \(-10^\circ C\). Below this temperature, two atropisomeric diastereomers from each regioisomers in 98 were seen in a ratio of 1:3. Further studies in this respect should include attempts to find a system whose atropisomeric equilibrium is reached at higher temperatures. One such example will be described in Chapter 5.5, where low temperature NMR study indicates that \( T_c \) is most probably higher than 70 °C.

Derivatization of silylstannane adduct will be important for this method to be synthetically useful. In Chapter 3.5, Stille coupling and halogen-Sn exchange of a vinylstannane, destannylation with acid, and a Diels-Alder reaction of a near-planar 1,3-diene derivative were described. Attempts at derivatization of borylstanne adduct were also made, and one example of methanolysis of B-C bond was described. Even though B-Sn reagent shows superior reactivities toward bimetallicative cyclization, especially for
internal diynne substrate, many attempts to convert one of these unstable molecules into a stable one resulted in a complex mixture.

Finally, application of this bimetallative cyclization for the construction of an indolizidine skeleton was attempted. Internal acetylene derivative 113 failed to give indolizidine product under the silylstannylation or borylstannylation conditions. Sterically less encumbered derivative 119 was also synthesized, but still unselective mixtures of product resulted. It appears that formation of six membered ring is more demanding and further optimization maybe needed before this can be successfully executed.

Further studies in this silylstannylation-cyclization should include finding more appropriate substrates having enhanced reactivity and one that will overcome the unselective pathways, especially unfavorable regioselectivity. For example, an alleneyne that will be discussed in Chapter 4 will be shown to undergo bimetallative cyclization under much milder conditions to yield desired product with high selectivity.
REFERENCE TO CHAPTER 3


(4) (a) For use of silane as a hydroxy synthon: Murakami, M.; Oike, H.; Sugawara, M.; Sugimoto, M.; Ito, Y.; Tetrahedron 1993, 49, 3933. (b) Friedel-Craft acylation of vinyl


(7) For a synthesis of 1, 2, and 4, see (a) Synthesis 1992, 1168. (b) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. Tetrahedron 1997, 53, 16449.


(11) ¹H NMR spectra of ~15 related acyclic silylstannylation adducts of acetylene and ~15 cyclic silylstannylation adducts from the reference 6b, 6c, and 2g, indicated that all Sn-H coupling constants (J_{Sn-H}) satisfy this criteria.


Chapter 4

APPLICATION OF BIMETALLATIVE CYCLIZATION STRATEGY I:
A HIGHLY STEREOSELECTIVE SILYLSTANNYLATIVE
CARBO/HETEROCYCLIZATION OF ALLENEYNES CATALYZED BY
PALLADIUM COMPLEX

4.1 Introduction

Catalytic synthesis of carbocyclic and heterocyclic compounds from acyclic olefinic and acetylenic precursors is a subject of great topical interest. A wide variety of substrates including eneynes, eneallenes, dienes, and diynes have been subjected to metal-catalyzed intramolecular cyclizations. Because of the mechanism by which transition metal catalysts operate, these reactions could provide advantages of regio- and stereocontrol of the product. As outlined in Part II of Chapter 1, use of bisfunctionalization (X-Y) reagents such as $R_3Si-SiR'$, $R_3Si-SnR'$, $R_3Si-BR'_2$, $R_3Sn-BR'_2$, as well as the more traditional trialkylsilicon- and trialkyltin- hydrides for the metal-catalyzed cyclization provide a number of additional advantages (eq.1). For example, introduction of a latent functionality (i.e. vinylsilane, vinylborane, and
vinylstannane) which can act as a functional handle, would lead to further derivatization of the product, through a number of C-C bond coupling reactions they can undergo.\textsuperscript{3-5} Also, various X-Y reagents that are available can be used to control the selectivity of such reactions. Other variables such as reaction conditions, phosphines and catalyst precursors could also affect the outcome of these reactions.

Recently, research in our group revealed that 1,6-diynes can be cyclized with the aid of R\textsubscript{3}Si-SnR\textsubscript{3} reagents in the presence of Pd(0).\textsuperscript{6} Helically chiral 1,2-dialkyldiene cyclopentanes with unusual (Z,Z)-geometry at the double bonds (eq.2) are produced from a number of diyne precursors. This highly stereoselective reaction proceeds in good yield with no special care taken to avoid moisture and air, and is compatible with common functional groups such as ethers, esters, amides, and tertiary amines. While full synthetic potential of the product dienes remain to be explored, preliminary studies reported in Chapter 3 of this thesis and from Dr. Warren show that the product dienes undergo a
number of selective transformations including proto-destannylation, Sn-halogen exchange, Stille coupling and epoxidation.\textsuperscript{6c}

In efforts to explore the synthetic potential of this reaction, one limitation of this and all other related X-Y mediated cyclizations has become apparent. This is the lack of regioselectivity in some unsymmetrical substrates as illustrated in eq. 3-5. The proline-derived diyne 86 gave essentially 1:1 mixture of regioisomeric pyrrolizidines 92a and 92b (Chapter 3.3). In other related reactions, cyclic urea derivative 167 shown in eq. 4

\[
\begin{align*}
&\text{Bu}_3\text{Sn-SiMe}_3 (1.1 \text{ equiv.)} \\
&\text{Pd}_2(\text{dba})_3 \text{CHCl}_3 (5 \%) \\
&\text{P} \left( \text{C}_8 \text{F}_3 \right) (10 \%) / \text{C}_8 \text{D}_8, 60 \text{ °C} \\
&92 \% \\
&\text{92a} \ X = \text{SnBu}_3, \ Y = \text{SiMe}_3 \\
&\text{92b} \ X = \text{SiMe}_3, \ Y = \text{SnBu}_3
\end{align*}
\]

\[
\begin{align*}
&\text{PdCl}_2(\text{PPh}_3)_2 (2 \%) \\
&\text{Me}_2\text{Sn-B} (1.1 \text{ equiv.)} \\
&\text{C}_8\text{D}_8 / 55 \text{ °C} \\
&> 90 \% \ \left( ^1\text{H NMR} \right) \\
&\text{171a} \ X = \text{B}, \ Y = \text{Sn} \\
&\text{171b} \ X = \text{Sn}, \ Y = \text{B}
\end{align*}
\]

\[
\begin{align*}
&\text{Pd}_2(\text{dba})_3 \text{CHCl}_3 (5 \%) \\
&\text{Sn-Si reagent (1.1 equiv.)} \\
&\text{C}_8\text{D}_8 \\
&\text{174/175a} \ X = \text{Si}, \ Y = \text{Sn} \\
&\text{174/175b} \ X = \text{Sn}, \ Y = \text{Si}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Sn-Si</th>
<th>conditions</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_3$Sn-SiMe$_2$Bu$^\text{t}$</td>
<td>80 °C / 2 h</td>
<td>70 % (174a/174b = 3.1/1)</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_3$Sn-SiMe$_3$</td>
<td>80 °C / 2 h</td>
<td>48 % (175a/175b = 2.2/1)</td>
</tr>
</tbody>
</table>
and eq. 5 also gave unsatisfactory selectivities with Sn-B and Si-Sn reagents (Chapter 5.3). This regioselectivity problem is a serious issue and must be resolved satisfactorily before full synthetic applications can be entertained. We envisioned several solutions to this problem:

(a) *Use of various X-Y reagents* that have different steric and electronic properties would lead to different isomeric ratio. One example is shown in eq. 5, where the ratio of two products change from 2.2:1 to 3.1:1 in going from Bu$_2$Sn-SiMe$_3$ to Ph$_3$Sn-SiMe$_3$Bu'. The details of this chemistry are described in Chapter 5.3.

(b) *Use of alleneyne rather than a diyne*: If allene react much faster than acetylene in Pd(0)-catalyzed X-Y addition, this would be a very attractive solution for the regiochemistry problem.

(c) *Use of monoacetylene adducts as cyclization substrates*: For example, regioselective silylstannylation of these acetylenes will be used to install trialkyltin residue, which will be transformed into a halide and subsequently cyclized using Heck (eq. 6)$^{6b}$ or radical chemistry (eq. 7, see Chapter 5.5).
In this chapter, we will discuss the solution (b) above, i.e. the use of an allene in the X-Y mediated cyclization. The silastannylation and distannylation/carbocyclization of bisallene catalyzed by palladium complex in a very mild condition reported by Kang and coworkers\textsuperscript{12} (eq. 8) indicated that reactivity of allene might be sufficiently higher than that of acetylene.

\begin{equation}
\text{Scheme 4.1. Possible cyclization modes with X-Y reagent}
\end{equation}
All possible cyclization modes of X-Y reagents-mediated cyclization of allenynes are shown in Scheme 4.1. Our expectation was that insertion of allene will occur first to the intermediate Pd-Si bond (path a), followed by carbametallation into acetylene to yield A selectively. In this process, a new chiral center is generated from allenenes, which could provide further synthetic value. The details of X-Y mediated cyclizations of various allenynes and the development of stereocontrol in such reactions of allene will be the subject of the following sections.

4.2. Synthesis of Substrates

The substrates used in this study are shown in Figure 4.1. The synthesis of allene was carried out mostly by a procedure developed by Crabbe. The monoacetylenes 126, 128, and 130 were treated with paraformaldehyde, CuBr, and Pr$_2$NH in refluxing THF or CH$_3$CN for 6-12 h to give the one carbon homologated allenyld derivatives, 127, 129,
and 131 respectively (Scheme 4.2). The yield was poor to marginal (23, 12, and 61 %, respectively for 127, 129, and 131). The subsequent alkylation of allenes 127, 129, and 131 was done by treating them with 1.3 equiv. of KH in THF followed by addition of 2.0 equiv. of propargyl bromide to obtain corresponding allenyenes 120, 122, and 123 in good yields. Internal acetylene derivative 121 was made by treating with 1-bromo-2-
butyne instead of propargyl bromide. The structures and purities of these allenynes (120-123) were unambiguously determined by IR, $^1$H and $^{13}$C NMR, and high resolution MS spectroscopy or GLC analysis. Characteristic feature of these allenynes is as follows: In IR spectrum, these allenynes have vibrational bands, ~1955 cm$^{-1}$ (C=C=C), ~3290 (C≡C-H, not present in 121), and ~2120 cm$^{-1}$ (C≡C). In $^{13}$C NMR, internal allene peak appears at ~210 ppm and terminal allene carbons and acetylene carbons appear at 70 ~ 85 ppm. Allenyl substrate 124 was obtained unexpectedly, when the alkylation of in-situ formed oxazolidinone with propargyl bromide was tried under basic condition (eq. 9). The exact reaction conditions that bring about the isomerization of acetylene into allene were not established, but we thought that the isomerization is presumably promoted by sodium benzyloxydride formed in the reaction mixture. The allene 125 was synthesized by $S_N2'$ reduction with LAH of corresponding propargyl THP ether derivative 133.$^9$

$$
\begin{align*}
\text{CbzHN} & \text{OH} \quad \text{NaH (2.4 eq.)} \quad \text{propargyl bromide} \\
\text{OTBS} & \quad \quad \quad \text{OTBS} \\
\end{align*}
$$

Several new trials were also made to access various allenynes. Most common problems are associated with the rearrangement of allenyl metal species into corresponding propargyl metal species (eq. 10). Also, seemingly reasonable O-alkylation with 1-bromo-2,3-butadiene failed to proceed (eq. 11).$^{13}$
4.3. Pd-catalyzed Silylstannylative Cyclization of Allenynes

The allenyne 120 (0.100 mmol), in the presence of Ph$_3$Sn-SiMe$_2$Bu' (0.110 mmol), Pd$_2$(dba)$_3$CHCl$_3$ (5 mol % Pd), and P(C$_6$F$_5$)$_3$ (10 mol %) in 1.0 mL of C$_6$D$_6$ at rt undergoes an exceptionally clean reaction. The in-situ $^1$H NMR spectrum of the reaction mixture after 17 h at room temperature indicated that the mixture consisted of 92 % of product and 8 % starting material. The product was isolated by chromatography of the reaction mixture on a silica gel column using hexane (5 % Et$_3$N) as eluent to give the cyclic product 135a in 80 % isolated yield (entry 1, Table 4.1). The lower isolated yield of the product is a measure of the instability of this relatively sensitive material. The structure and stereochemistry of 135a was unambiguously established by $^1$H and $^{13}$C NMR spectroscopy and elemental analysis as well as COSY and nOe difference spectra. Among three vinyl protons, the SnC-H signal appears at $\delta$ 6.40 ($^2J_{Sn-H}$ = 74 Hz) and the coupling constant is characteristic of stannyl-substituted vinyl R$_2$C=CH(SnR$_3$) moiety (Figure 3.3 in Chapter 3.2). The nOe difference spectra further confirmed the double bond configuration and the structure of ring as shown in Figure 4.2.
Figure 4.2 Selected nOe contacts of 135a

Several ligands were tested for this reaction. Among the ligands screened (P(C₆F₅)₃, P(3,5-di-Me-C₆H₃)₃, PPh₃, PBu₃, and PBu'), only P(C₆F₅)₃ and P(3,5-di-Me-C₆H₃)₃ gave appreciable reaction after 12 h at rt (61 % and 39 %, respectively, eq. 12), while other ligands showed no sign of reaction at all. After a prolonged period (48 h) at room temperature, all the ligands gave good conversion. The source of Pd, while not as critically important, showed a definite trend in reactivity when used in conjunction with P(C₆F₅)₃: Pd(PhCN)₂Cl₂ > Pd₂(dba)₃CHCl₃ > [Pd(allyl)Cl]₂/AgOTf >> PdCl₂ ~ Pd(PPh₃)₄ (eq.13).

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (12 h)</th>
<th>yield (48 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(C₆F₅)₃</td>
<td>61 %</td>
<td>&gt;90 %</td>
</tr>
<tr>
<td>2</td>
<td>P(3,5-di-Me-C₆H₃)₃</td>
<td>39 %</td>
<td>&gt;90 %</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃</td>
<td>&lt;10 %</td>
<td>&gt;90 %</td>
</tr>
<tr>
<td>4</td>
<td>PBu₃</td>
<td>&lt;10 %</td>
<td>&gt;90 %</td>
</tr>
<tr>
<td>5</td>
<td>PBu'</td>
<td>&lt;10 %</td>
<td>81 %</td>
</tr>
</tbody>
</table>

*No side product was observed. Yields were based on the starting material (in situ ¹H NMR).
Ph$_3$Sn-SiMe$_2$Bu$^i$ (1.1 equiv.)
Pd precursor (5 mol %)
P(C$_6$F$_5$)$_3$ (10 %)
r, C$_6$D$_6$ (0.05 M)

\[ 120 (E = CO_2Et) \rightarrow 135a \]

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd precursor</th>
<th>yield (18 h)$^a$</th>
<th>yield (4 days)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl$_2$(PhCN)$_2$</td>
<td>&gt;95 %</td>
<td>&gt;95 %</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_2$CHCl$_3$</td>
<td>&gt;90 %$^b$</td>
<td>&gt;95 %</td>
</tr>
<tr>
<td>3</td>
<td>[Pd(allyl)Cl$_2$/AgOTf</td>
<td>&gt;90 %</td>
<td>&gt;95 %</td>
</tr>
<tr>
<td>4</td>
<td>PdCl$_2$</td>
<td>&lt;10 %</td>
<td>35 %</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PP$_3$)$_4$</td>
<td>&lt;10 %</td>
<td>&lt;10 %</td>
</tr>
</tbody>
</table>

$^a$ No side product was observed. Yields were based on the starting material (in situ $^1$H NMR).

$^b$ Estimated in a separate run.

Pd$_2$(dba)$_2$CHCl$_3$ (5 mol %)
P(C$_6$F$_5$)$_3$ (10 %)
Ph$_3$Sn-SiMe$_2$Bu$^i$, rt, 17 h

\[ 120 \rightarrow 134a \]

Pd(0) (5 mol %)
P(C$_6$F$_5$)$_3$ (10 %)
Bu$_3$Sn-SiMe$_3$, r, 2 h

\[ 134b \rightarrow 135a, 135b \]

135a X = SiMe$_2$Bu$^i$, Y = SnPh$_3$
135b X = SiMe$_3$, Y = SnBu$_3$
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>X-Y</th>
<th>Conditions</th>
<th>Product</th>
<th>yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph&lt;sub&gt;3&lt;/sub&gt;Sn-SiMe&lt;sub&gt;2&lt;/sub&gt;But&lt;sup&gt;i&lt;/sup&gt;</td>
<td>120 (E = CO&lt;sub&gt;2&lt;/sub&gt;Et)</td>
<td>rt / 17 h (A)</td>
<td>80 % (&gt;95 %)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;Sn-SiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>120</td>
<td>rt / 2 h (A)</td>
<td>83 %&lt;sup&gt;c&lt;/sup&gt; (&gt;91 %)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;Sn-SiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>45 °C / 48 h (A)</td>
<td>80 °C / 8 h (B)</td>
<td>71 % (&gt;95 %)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TsN</td>
<td>122</td>
<td>rt / 24 h (A)</td>
<td>41 % (&gt;95 %)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph&lt;sub&gt;3&lt;/sub&gt;Sn-SiMe&lt;sub&gt;2&lt;/sub&gt;But&lt;sup&gt;i&lt;/sup&gt;</td>
<td>123</td>
<td>rt / 14 h (B)</td>
<td>61 % (&gt;95 %)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;Sn-SiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>123</td>
<td>rt / 12 h (B)</td>
<td>acyclic/138 = 1:3 by &lt;sup&gt;1&lt;/sup&gt;H NMR</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields are isolated (yields determined by NMR in brackets), all products were characterized by elemental analysis, or HRMS. <sup>b</sup> Condition A: 5 mol % of Pd(dba)<sub>2</sub>CHCl<sub>3</sub> with 10 % of P(Ph<sub>3</sub>F<sub>3</sub>)<sub>2</sub> was used, Condition B: 5 % Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> with 10 % of P(Ph<sub>3</sub>F<sub>3</sub>)<sub>2</sub> was used. <sup>c</sup> Isolated material contained 8 % of 135b

Table 4.1. Cyclization of Alleneyne Mediated by R<sub>3</sub>Si-SnR<sub>3</sub>
When the reaction was carried out at room temperature with a less reactive 
Bu₃Sn-SiMe₃ reagent, we were able to isolate an acyclic intermediate 134b in an 
excellent yield (83% isolated yield, rest cyclized product 135b, eq.14 and entry 2 in 
Table 4.1) and stereochemical purity. The structure of this intermediate 134b was 
unambiguously determined by nOe difference spectra (Figure 4.3). Under more vigorous 
conditions (45 °C/48 h or 80 °C/8 h) this intermediate 134b is quantitatively cyclized into 
135b (entry 3, Table 4.1). Presumably the corresponding allylstannane 134a is too 
reactive to accumulate in solution to any appreciable degree. The acyclic intermediate

![Diagram](image_url)  

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hₐ</td>
<td>1.91 (s, 2J₆-H = 64 Hz)</td>
</tr>
<tr>
<td>Hₐ</td>
<td>2.73 (d, J = 6.9 Hz)</td>
</tr>
<tr>
<td>Hₐ</td>
<td>5.18 (t, J = 6.9 Hz)</td>
</tr>
</tbody>
</table>

Figure 4.3 Selected nOe contacts of 134b

134b was characterized by ¹H, ¹³C, IR, HRMS, and nOe spectrum, and 135b was 
characterized by ¹H, ¹³C, ¹¹⁹Sn, IR, and HRMS. In IR spectrum of 134b, disappearance of 
allene peak at 1956 cm⁻¹, and a new stretching band (C=C-H) of acetylene at 3314 cm⁻¹ 
is clearly observed.

This cyclization process was tested for its generality on amide (122) and ether 
(123) (entry 4-6, Table 4.1). Reaction of Ph₃Sn-SiMe₂Bu with N-tosyl alleneyne 122 
under standard condition gives the cyclic pyrrolidine 136 in >95% yield (¹H NMR) in 24 
h at rt, whereas ether 123 gives the tetrahydrofuran 137 as a single diastereomer in 14 h
at rt in >95% yield (°H NMR). The less reactive Bu₃Sn-SiMe₃ takes 5 h at 80 °C to complete the cyclization of 123 to give the product 138 (°H NMR). When 123 was reacted with Bu₃Sn-SiMe₃ at room temperature, a mixture of acyclic allylstannane of type 134b and the cyclized product 138 were obtained after 12 h. The structure of 136 was confirmed by IR, °H and °C NMR, HMQC, COSY, and high-resolution MS as well as nOe difference spectra similar to what is shown for 135a in Figure 4.2. The structure of tetrahydrofurans 137 and 138 were also confirmed by IR, °H and °C NMR, HMQC, COSY, and high resolution MS or elemental analysis as well as nOe difference spectra. The nOe spectra of neither 137 nor 138 gave decisive evidence about the 1,2-adjacent stereochemistry. The coupling constant of 2,3-vicinal protons in 138 was 2.1 Hz, and some hints from nOe difference spectra are shown in Figure 4.4 and Figure 4.5 which

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hₐ</td>
<td>6.29 (s, J/Sn-H = 70 Hz)</td>
</tr>
<tr>
<td>Hₕ</td>
<td>5.99 (t, J = 1.8 Hz)</td>
</tr>
<tr>
<td>Hₖ</td>
<td>5.60 (t, J = 1.6 Hz)</td>
</tr>
<tr>
<td>Hₗ</td>
<td>3.70 (s br)</td>
</tr>
<tr>
<td>Hₘ</td>
<td>5.28 (s)</td>
</tr>
<tr>
<td>Hₙ</td>
<td>4.60 (dd, J = 1.6, 13.5 Hz)</td>
</tr>
<tr>
<td>Hₚ</td>
<td>4.45 (dd, J = 1.6, 13.5 Hz)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protons</th>
<th>nOe (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Protons</th>
<th>nOe (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hₐ - Hₖ/Hₗ</td>
<td>2.4</td>
<td>Hₖ - SnPh₃</td>
<td>1.8</td>
</tr>
<tr>
<td>Hₐ - SnPh₃</td>
<td>3.0</td>
<td>Hₖ - Hₗ</td>
<td>1.8</td>
</tr>
<tr>
<td>Hₖ - Hₙ/Hₙ</td>
<td>0.5</td>
<td>Hₙ - Ph</td>
<td>2.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values in the parenthesis is tentative. <sup>b</sup> The resolution of peaks due to SnPh₃ and CHPh was not clear.

Figure 4.4. nOe contacts in 137
Figure 4.5. nOe contacts in 138

favor 2,3-trans stereochemistry from the highlighted numbers in the table. Although the assignment of 2,3-relative stereochemistry was not confirmed at this time, the vicinal diastereoselectivity was excellent (only one diastereomer was observed in \textit{in situ} $^1$H NMR). In the following section, a speculation on the origin of stereoselectivity will be discussed.

On the other hand, the silylstannylation reaction of internal alleneyne 121 was much slower than terminal substrates 120, 122, and 123 (eq. 14). For example, reaction of 121 with Ph$_3$SnSiMe$_2$Bu$^\dagger$ in the typical cyclization condition, starting material remained largely unaffected even after 2 days at 80 °C, while the corresponding reaction with Bu$_3$SnSiMe$_3$ after the same reaction time gave a acyclic product 139 in a mixture with unidentified side products. The structure of acyclic adduct 139 was assigned based
on crude $^1$H NMR, where the only peak in the vinyl region at $\delta$ 5.60 (t, $J = 7.0$ Hz) was assigned to the $\text{CH} = \text{C}(\text{SiR}_3)\text{CH}_2(\text{SnR'}_3)$ by analogy with the structure of 134b.

\[
\text{Sn-Si reagent (1.1 equiv.)} \quad \text{Pd(PhCN)$_2$Cl$_2$ (5 mol %)} \quad \text{P(C$_6$F$_5$)$_3$ (10 %)} \quad \text{EtO$_2$C} \quad \text{Me} \\
\begin{array}{c}
\text{EtO$_2$C} \\
\text{EtO$_2$C} \\
\text{Sn-Si reagent (1.1 equiv.)} \\
\text{Pd(PhCN)$_2$Cl$_2$ (5 mol %)} \\
\text{P(C$_6$F$_5$)$_3$ (10 %)} \\
\text{EtO$_2$C} \\
\text{EtO$_2$C} \\
\text{Sn-Si reagent (1.1 equiv.)} \\
\text{Pd(PhCN)$_2$Cl$_2$ (5 mol %)} \\
\text{P(C$_6$F$_5$)$_3$ (10 %)} \\
\text{EtO$_2$C} \\
\text{EtO$_2$C} \\
\end{array}
\]

\[
\begin{array}{c}
\text{121} \\
\text{121} \\
\text{Sn-Si reagent (1.1 equiv.)} \\
\text{Pd(PhCN)$_2$Cl$_2$ (5 mol %)} \\
\text{P(C$_6$F$_5$)$_3$ (10 %)} \\
\text{EtO$_2$C} \\
\text{EtO$_2$C} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Sn-Si reagent</th>
<th>19 h</th>
<th>2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph$_3$SnSiMe$_2$Bu$^1$</td>
<td>no reaction</td>
<td>no reaction</td>
</tr>
<tr>
<td>Bu$_3$SnSiMe$_3$</td>
<td>50% to acyclic 139$^a$</td>
<td>only acyclic 139$^a$</td>
</tr>
</tbody>
</table>

$^a$ Conversions were based on $^1$H NMR spectra.

4.4 Use of Other Bisfunctional Reagents in the Cyclization of Allenynes

The silylstannane reagents are generally superior to other bimetallic reagents in this type of cyclizations. For comparison, reactions of 120 and 123 with Me$_3$Sn-SnMe$_3$, and Me$_3$Sn-B(-N(Me)CH$_2$CH$_2$(Me)N-) are listed in Table 5.2. Both the borostannylation and distannylation product gives the cyclization product 141-145, albeit under harsher conditions than needed for the silylstannylation. The products derived from these reagents are more unstable than the products of silylstannylation. Isolation of these compounds presented significant problems, and upon chromatography significant losses were encountered. The borylstannane compound 141 was characterized by the $^1$H NMR:

$\delta$ 5.69 (d, $J = 2.4$ Hz, H, RC(Sn)=CH$_2$), 5.60 (s, H, C=CHB), 5.15 (d, $J = 2.5$ Hz, $J_{\text{Sn-H}} = 32$ Hz, H, RC(Sn)=CH$_2$). But, the chromatographic separation of it resulted only in decomposition. Treating the reaction mixture with 2.0 equiv. of catechol with a hope of
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120 (E= CO₂Et)</td>
<td>80 °C / 1 h (A)</td>
<td><img src="image" alt="Product 141" /></td>
<td>(&gt;80 %)</td>
</tr>
<tr>
<td>2</td>
<td>120 MesSn—SnMe₃</td>
<td>RT / 22 h (A)</td>
<td><img src="image" alt="Product 142" /></td>
<td>(&gt;90 %)</td>
</tr>
<tr>
<td>3</td>
<td>120 MesSn—SnMe₃</td>
<td>45 °C / 48 h (A)</td>
<td><img src="image" alt="Product 143" /></td>
<td>46 % (&gt;90 %)</td>
</tr>
<tr>
<td>4</td>
<td>123 MesSn—SnMe₃</td>
<td>65 °C / 8 h (B)</td>
<td><img src="image" alt="Product 145" /></td>
<td>42 %d</td>
</tr>
</tbody>
</table>

Table 4.2. Cyclization of Alleneynes mediated by Sn-B or Sn-Sn Reagents

ligand exchange on boron atoms failed to give desired product after chromatography. Treating this in situ formed molecule with acid (HCO₂H or camphor sulfonic acid) presumably resulted in unselective protonolysis and failed to give any isolable product after chromatography.

As with silylstannylation reaction, at room temperature, the distannylation of 120 with MesSnSnMes leads to an acyclic intermediate 142 as the major component in the reaction mixture. The acyclic product was characterized by the characteristic C(SnMe₃)=CHCH₂ peak at δ 5.34 (t, J = 6.7 Hz) with acetylene peak RCH=CH at δ 1.67 (t,
The distannylation reaction generally gives poorer stereoselectivity and 'in-situ' \(^1\)H NMR spectra of reaction mixture shows some side products indicative of double bond isomers of 142. When reaction mixture containing 142 was further heated cyclic product 143 formed, which was isolated in 42 % yield and fully characterized by \(^1\)H, \(^3\)C, \(^{119}\)Sn NMR and COSY as well as high resolution MS. The reaction of 123 with distannane gave mixture of 144 and 145. The product was isolated as a mixture of acyclic bisadduct 144 (21 %) and cyclic adduct 145 (21 %), whose structures remained tentative.

4.5. The Reaction of Allenes: A Highly Stereoselective Formation of Allylstannanes

The reaction of allene 124 and 125 with silylstannane reagents were carried out and the result is shown in Table 5.3. The addition of silylstannane reagent to allenes occurred under exceptionally mild conditions to give corresponding allylstannane products in good to excellent isolated yields. For example, the reaction of alleneyne 124 with \(\text{Ph}_3\text{Sn-SiMe}_2\text{Bu}'\) (1.0 equiv) in the presence of \(\text{Pd(PhCN)}_2\text{Cl}_2\) (5 mol\%) and \(\text{P(CFs}_3\text{)}_3\) (10 \%) in benzene, gave the cyclic pyrrolidine 146 (60 %, >95 \% yield by \(^1\)H NMR) in 8 h at rt, whereas the reaction of THP-ether 125 with \(\text{Bu}_3\text{SnSiMe}_3\) under the same standard conditions gave the tetrahydrofuran 148 (47 \%, >95 \% by \(^1\)H NMR) in 12 h at rt. For the vinylamide products 146 and 147, the isolated yields were significantly lower than the yield based on \(^1\)H NMR spectrum, reflecting the instability of products. On the other hand, the reaction of THP-ether 125 with \(\text{Sn-Si}\) or \(\text{Sn-Sn}\) reagents under the standard reaction conditions, gave excellent isolated yields of products (entry 3,4, Table 4.3). The structures and identities of these adducts were confirmed by \(^1\)H and \(^{13}\)C, IR, COSY, HMQC, and nOe difference spectra. In IR, a very conspicuous allenyl stretching band.
disappears (~1950 cm⁻¹) and in ¹H NMR, vinyl RCH=CH(Sn or Si)CH₂(Sn) peaks appear at 5.5~6.0 ppm. In Figure 4.6, selected nOe contacts in representative compounds 146 and 148 are shown and in this way (E)-geometry of double bonds in 146, 147, and 148 was established. The ratio of E/Z isomers in each case was determined from the crude ¹H NMR. The selectivity of forming the double bond geometry as well as that of forming regioisomers is extremely high in the case of Ph₃Sn-SiMe₂Bu¹ and Bu₃Sn-SiMe₃ reagents (better than 95:5 ratio favoring (E)-geometry). With Me₃Sn-SnMe₃ reagents, (Z)-isomer begin to appear in significant amounts, but the regioselectivity to form an terminal tin adduct is still high.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>X-Y</th>
<th>Conditions</th>
<th>Product</th>
<th>yield¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃Sn-SiMe₂Bu¹</td>
<td>OTBS</td>
<td>rt / 8 h</td>
<td>146</td>
<td>60 % (&gt;95 %) E only</td>
</tr>
<tr>
<td>2</td>
<td>Bu₃Sn-SiMe₃</td>
<td></td>
<td>rt / 12 h</td>
<td>147</td>
<td>47 % (&gt;95 %) E/Z = &gt;95/&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>THPO</td>
<td>Bu₃Sn-SiMe₃</td>
<td>rt / 12 h</td>
<td>148</td>
<td>92 % (&gt;95 %) E/Z = &gt;95/&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>Me₃Sn*S-SnMe₃</td>
<td></td>
<td>rt / 12 h</td>
<td>149</td>
<td>97 % (&gt;95 %) E/Z = 2.4/1</td>
</tr>
</tbody>
</table>

¹ Yields are isolated (yields determined by NMR in brackets), all products were characterized by elemental analysis, or HRMS. ²5 % Pd(PhCN)₂Cl₂ with 10 % of P(C₆F₅)₃ was used.

Table 4.3. Reaction of Allene with Silylstannane Reagents in the Presence of Pd (0)
The reaction of allenes with these bifunctional reagents previously reported in the literature showed typically a low regio/stereoselectivity. For example, earlier publications by Mitchell and Miyaura reported that mixture of products are typically obtained in the reactions of allenes and Sn-Sn, Sn-Si, and \((RO)_2B-B(OR)_2\) reagents (eq.15-17).\(^{10}\) The results in Table 4.3 clearly show the superior regioselectivity and also double bond stereoselectivity under the milder reaction conditions reported in this thesis.

\[
\text{Figure 4.6. Selected nOe Contacts in 146 and 148}
\]

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift (δ)</th>
<th>(\text{CDCl}_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H_a)</td>
<td>2.35 (dd, (J_{\text{Sn-H}} = 90) Hz)</td>
<td></td>
</tr>
<tr>
<td>(H'_a)</td>
<td>2.46 (dd, (J_{\text{Sn-H}} = 90) Hz)</td>
<td></td>
</tr>
<tr>
<td>(H_b)</td>
<td>3.00 (t, (J = 8.0) Hz)</td>
<td></td>
</tr>
<tr>
<td>(H'_b)</td>
<td>3.82 (dd, (J = 2.9, 10.5) Hz)</td>
<td></td>
</tr>
<tr>
<td>(H_c)</td>
<td>1.80-1.90 (m)</td>
<td></td>
</tr>
<tr>
<td>(H_{c'})</td>
<td>4.01 (dd, (J = 6.3, 13.2) Hz)</td>
<td></td>
</tr>
<tr>
<td>(H_{c''})</td>
<td>4.24 (dd, (J = 5.0, 13.2) Hz)</td>
<td></td>
</tr>
<tr>
<td>(H_{c'''})</td>
<td>5.58 (t, (J = 5.7) Hz, (J_{\text{Sn-H}} = 188) Hz)</td>
<td></td>
</tr>
</tbody>
</table>

\[
\text{127}
\]
4.6 Mechanism of Silylstannylation-Cyclization of Allenynes

The isolation of product 134b is a meaningful result from mechanistic point of view. In the kinetically controlled condition (rt, 1.5 h), the reaction of 120 with Bu₃Sn-SiMe₃ in the conditions above gives 134b as only observable product. Upon warming this product at 45 °C under the reaction conditions, 134b cleanly cyclized to thermodynamic product 135b (Table 4.1, entry 2 and 3). A unified mechanism that accounts for the observed results is shown in Scheme 4.3. Coordination of the Pd(II) metal on the internal double bond of allene (150), followed by silapalladation would lead to an anti π-allyl complex 151, which upon reductive elimination with formation of the less congested allylstannane and regeneration of Pd(0) would give the primary product 134b. A more energetically demanding insertion of the acetylene into this π-allyl complex takes place at a higher temperature leading to the cyclic product 135b via 153. Our observation that
isolated 134b can be converted into 135b using Pd(0) and P(C₆F₅)₃ at elevated temperatures support such a mechanism.

Scheme 4.3 Mechanism of Silylstannylative Cyclization of Alleneyne

The observation of high regio/stereoselectivity in the insertion of allene into Sn-Si reagent can be explained well by invoking intermediacy of π-allyl Pd complex similar to 151 (Figure 4.7). The syn and anti π-allyl Pd complex in Figure 4.7 can isomerize via σ–π–σ mechanism. The subsequent β-tin reductive elimination is likely to occur from the more stable anti complex.
Very recently, both intramolecular\textsuperscript{11a} and intermolecular\textsuperscript{11b} allylstannanes insertion onto acetylene catalyzed by transition metal complexes were reported by two research groups (Echavarren and Hiyama). In the former case, the authors proposed a mechanism where activation of acetylene by transition metal complex (Ru(II), Pd(II), Pt (II), as well as Ag(I)) triggers \textit{anti}-attack of allyl stannanes or allyl silane (eq. 18). The net result is formation of (Z) double bond via the solvolysis of M-C bond.

\[
\text{PhPh} \quad \text{PtCl}_2 \left(5 \, \text{mol} \, \%\right) \quad \text{MeOH, reflux, 17 h} \quad \text{[M]}
\]

On the other hand, Shirakawa and Hiyama proposed several mechanistic possibilities from their study of intermolecular addition of allyl stannanes onto acetylene. They have demonstrated that the palladium catalyzed allylstannane insertion onto alkyne proceeds in different pathways depending on the presence of $\gamma$-substituent in the allyl stannanes. In the case of terminal allyl stannanes, addition occurs in $S_N2'$-fashion (rather
than S_{N2}) via the intermediacy of \( \pi \)-allyl Pd complex, in accordance with our contention (for example, see the conversion of 134b into 153 in Scheme 4.3).

The origin of the high diastereoselectivity observed in 137 and 138 is speculative at this point. But it can be explained on the basis of the most favorable cyclization transition state which would have the \textit{anti-} \( \pi \)-allyl Pd configuration in which the Ph group and the vinyl silane are in a pseudo-equatorial orientation as shown below (Figure 4.8).

![Figure 4.8 Possible Origin of Diastereoselectivity in the Cyclization Reaction](image)

4.7. Miscellaneous Reactions

A few derivatization studies were carried out on silylstannane 137 as shown in eqs. 19 and 20. The examples of destannylation and Sn-halogen exchange reaction are given. The conditions established in Chapter 3.5 were used to get the corresponding
products of Sn-halogen exchange (154) and protodestannylation (155). These compounds were fully characterized by $^1$H, $^{13}$C, and high resolution MS.

\[
\begin{align*}
\text{TBS} \quad \begin{array}{c}
\text{SnPh}_3 \\
\text{137}
\end{array} & \xrightarrow{\text{NBS (1.5 equiv.)}} \quad \begin{array}{c}
\text{Br} \\
\text{154}
\end{array} \\
\text{CH}_2\text{Cl}_2, \text{rt, 2 h} & \quad 74 \%
\end{align*}
\]

\[
\begin{align*}
\text{TBS} \quad \begin{array}{c}
\text{SnPh}_3 \\
\text{137}
\end{array} & \xrightarrow{\text{HCO}_2\text{H (5.0 equiv.)}} \quad \begin{array}{c}
\text{134b} \\
\text{155}
\end{array} \\
\text{CH}_2\text{Cl}_2, \text{rt, 10 h} & \quad 78 \% \text{ (in-situ from 123)}
\end{align*}
\]

4.8. Conclusions

In summary, the Pd catalyzed silylstannylative intramolecular cyclization of allene-yne is shown to provide a general and efficient method for the synthesis of carbon/heterocyclic compounds. The regioselectivity problems of bimetallative cyclization of diynes described in the introduction of this chapter could be ultimately solved by use of different reactivity of allene vs. acetylene. Especially, silylstannylative cyclization of substrates 123 gives single diastereomeric tetrahydrofuran-derivatives 137 and 138. A mechanism was proposed to explain the high regio- and stereoselectivity observed in this reaction. Isolation of acyclic intermediate 134b established the stepwise nature of the silylstannylation-cyclization of allene-yne substrates: (a) silastannylation of allene and (b) intramolecular allylstannylation of acetylene. The derivatization of the resulting
silylstannylated carbocycles and the use of this method for the synthesis of pharmacologically important natural products are currently underway.
REFERENCE TO CHAPTER 4


(13) Recently, Pd-catalyzed synthesis of allene from 2-bromo-1,3-diene precursor has been reported, for which a variety of nucleophile (N, O, and P) can be employed. See (a)
Chapter 5

APPLICATION OF BIMETALLATIVE CYCLIZATION STRATEGY II:
STUDIES TOWARD THE SYNTHESIS OF KAINOIDS AND FUNCTIONALIZED
PYRROLIDINES

5.1 Introduction

α-Kainic acid and its cogeners are neurotransmitters in the mammalian central nervous system. Since the first isolation of the parent compound\(^1\) from the marine algae *Digenea Simplex* in 1953, kainoids have attracted considerable attention because of their powerful neuroexcitatory properties. Because of their structural similarity to glutamic acid, a principal excitatory neurotransmitter, kainoids have been used to characterize receptor classes, and it has become an important reagent for investigation into neurological disorders, like Alzheimer's disease and epilepsy.\(^2\) Recently, a global shortage of kainic acid\(^3\) has handicapped the neuroscience community and an efficient synthetic source of this important compound has become an urgent goal.

5.2 Diynes as Precursors: Synthesis of Diyne Substrates

In our approach to kainoid derivatives and related pyrrolidines, dipropargylic
amines such as the one shown in Scheme 5.1 could be precursors. Our initial expectation was that the unsymmetrical diynes of the type 156 would undergo Pd-catalyzed silylstannylation-cyclization. We also expected that some control of regioselectivity in the cyclization could be achieved with derivatives such as the cyclic urethane 157.

![Scheme 5.1. Diynes as Precursor to Kainic Acid](image_url)

According to this plan, synthesis of appropriate substrates was initiated. Initial route to the diyne of type 156 (Scheme 5.2) started with DL-serine methyl ester. The

![Scheme 5.2 Synthesis of Acetylene 161 from DL-Serine](image_url)
amine function was protected as a carbamate group and the resulting product 158a was converted into the aminal 159a by treatment with 2,2'-dimethoxypropane and acid. Reduction of the methyl ester of 159 with DIBAL-H at -78 °C gave the aldehyde 160, which was either isolated (50 - 67 %) or directly used in the next step. Elongation of one carbon by Corey-Fuchs procedure provided 162a or 162b in 33 and 62 % yield respectively. The dibromovinyl compound 162b underwent elimination to give 161b. Alternatively, 160a was reacted with Gilbert-Seyferth reagent (A) in basic MeOH and 161a was obtained directly in 44 % yield. To deprotect nitrogen of Boc protected 161b selectively, it was treated with CF₃COOH but only a mixture composed of 163 and aminal-deprotected side-product resulted (eq. 1). This probably reflects the instability of N,O-aminal toward acidic condition compared with carbamate. As a solution to this problem, Cbz group could be a good alternative because catalytic hydrogenolysis of Cbz group in the presence of aminal will provide orthogonal deprotection. Thus compound
159a was hydrogenated in the presence of Rh/Al₂O₃, but still competitive deprotection of isopropylidene aminal hampered clean deprotection (eq. 2).

We thought that the cyclic carbamate as a protecting group would solve the problem of lability of isopropylidene aminal (Scheme 5.3). First, hydroxyl function in 158a was masked with t-BuMe₂Si group (164) and the ester was reduced with LiBH₄ to get the alcohol 165. Treatment of 165 with NaH (2.4 equiv.) in THF followed by propargyl bromide provided 166, where cyclic carbamate formation and propargylation occurred in a single step.⁸ Having 166 in hand, the remaining task is to adjust oxidation state and to introduce the second acetylene functionality. This was done by Swern oxidation of 166, followed by Gilbert-Seyferth reaction to provide 167.⁷

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

Scheme 5.3. Synthesis of a Diyne 167 with a Cyclic Carbamate Protecting Group

On the other hand, for comparing diynes with different propargylic substitution in bimetallative cyclization, we need to build other derivatives including acyclic versions. Such substrates would be useful in addressing the anticipated regiochemical problems in
the cyclization. Thus 165 was oxidized under Swern oxidation condition, and the aldehyde was converted into acetylene 168, and subsequent propargylation gave the diyne 169 (Scheme 5.4). Also, the cyclic carbamate 167 was hydrolyzed by base to an amino alcohol, which was protected at the nitrogen with (Boc)_2O to get the free hydroxy derivative 170 (Scheme 5.4). The substrates 167, 169, and 170 were tested for bimetallic cyclization reaction as follows.

5.3 The Reaction of Diynes with B-Sn Reagent

With 167, 169, and 170 in hand, the stage is set to test the cyclization of it to form the corresponding pyrrolidine intermediate (Scheme 5.1). First, Sn-B reagent A that was shown to be a superior than Sn-Si reagent (Chapter 3.6) was tested for the cyclization. Treatment of 167 with Sn-B reagent (eq. 3, 1.1 equiv.) and PdCl_2(PPh_3)_2 (2 mol %) in
$^{13}C_D_6$ at 55 °C for 1 h gave clean conversion (>90 %) to a mixture of two discrete isomers (isomeric ratio, 1.2/1.0) as judged by $^1H$ NMR. For example, in $^1H$ NMR (taken at 70 °C in $^{13}C_D_6$ because of conformational exchange of Cbz protecting group) spectrum, product 172 has a characteristic SnCsp$_2$-$H$ peak at 5.99 ppm (s, $^2J_{Sn-H} = 50$ Hz) and 5.71 ppm ($^2J_{Sn-H} = 52$ Hz) for major and minor isomers, respectively and BCsp$_2$-$H$ peak at 5.29 (s) and 5.44 (s) for major and minor isomers, respectively. The coupling constant ($^2J_{Sn-H} = 52$ Hz) is typical of cyclic product and the rest of the peaks (TBDMS, SnMe$_3$, NMe) showed the same isomeric ratios. Acyclic diynes 169 and 170 gives higher regioisomeric ratio than cyclic carbamate diyne 167 (eq. 3)

$$\text{A} = \text{Me}_3\text{Sn-B}$$

<table>
<thead>
<tr>
<th>substrate</th>
<th>condition</th>
<th>product</th>
<th>remarks$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>167 $^{13}R^1, R^2 =$ cyclic carbamate</td>
<td>RT / 5 h, 55 °C / 1 h</td>
<td>171, 172</td>
<td>No reaction, &gt;90 % (1.2/1.0)</td>
</tr>
<tr>
<td>169 $^{14}R^1 =$ Cbz, $R^2 =$ TBS</td>
<td>RT / 21 h</td>
<td>172, 173</td>
<td>&gt;90 % (3.3/1.0)$^b$, &gt;90 % (2.5/1.0)$^b$</td>
</tr>
<tr>
<td>170 $^{15}R^1 =$ Boc, $R^2 =$ H</td>
<td>RT / 24 h</td>
<td>172, 173</td>
<td>&gt;90 % (2.5/1.0)$^b$</td>
</tr>
</tbody>
</table>

$^a$ Yields and isomeric ratio (parenthesis) were estimated from $^1H$ NMR. The product could not be isolated. $^b$ NMR spectra were taken at 70 °C, because of conformational equilibrium. $^c$ Assignment of regioisomers was by analogy of reactivity with other substrates.

5.4. Diastereomers of the Cyclization Products

There are possibilities of several isomeric products in this reaction. Apart from the possibility of regioisomerism, there is also the possibility of observable
Figure 5.1. Variable Temperature $^1$H NMR Spectra of 171
atropisomerism, provided that the interconversion rate between two atrop-diastereomers is slow enough compared to NMR timescale for each of the regioisomers.

The isomers of 171 is characterized by the following sets of two peaks (in C₆D₆ at 60 °C): Major isomer, 5.65 (s, ²J₇a-H = 50 Hz, H, Cₛᵖ²(SnMe₃)H), 5.00 (s, H, Cₛᵖ²(B)H); Minor isomer 5.50 (s, ²J₇a-H = 49 Hz, Cₛᵖ²(SnMe₃)H), 5.23 (s, Cₛᵖ²(B)H). The nature of this mixture of isomers was further studied by variable temperature ¹H NMR spectroscopy (Figure 5.1). The mixture of two isomers can either be (1) regioisomers (e.g., mixture of 171a/171b), or (2) atropisomers resulting from a single regioisomer (171a/171a* or 171b/171b*) (Figure 5.2). Upon heating at 60 °C in C₆D₆, the ¹H NMR spectrum undergoes minor change, including coalescence of two Me₃Sn singlets from two isomers and that of ring protons, but there was no change in vinyl region of spectrum. If the two isomers are result of atropisomerism from single regioisomer (in case of (2) above), a coalescence of two sets of vinyl peaks is expected at temperatures higher than T_c (coalescence temperature), but this coalescence did not occur up to 60 °C (Figure 5.1). On the other hand, upon cooling down to -60 °C, no temperature-dependent change was observed at all between 0 °C ~ -60 °C, indicating coalescence temperature

\[
\begin{align*}
\text{171a} & \quad \xrightarrow{T_c = ?} \quad \text{171a'} \\
\text{171b} & \quad \xrightarrow{T_c = ?} \quad \text{171b'}
\end{align*}
\]
(\(T_c\)) of two sets of vinyl protons can either be below \(-60\) °C or above \(60\) °C. From the comparison with related compounds displaying atropisomerism (Figure 3.7 p 82), it is likely that the \(T_c\) is below \(-60\) °C rather than above \(60\) °C, which means that the mixture obtained 171 is most likely mixture of regioisomers (for example, 171a/171b), each of which undergoes fast equilibrium at room temperature. The long Sn-C bond and the small ring size of substituents on Sn and B atoms would facilitate the helical isomerization. Of course, the unlikely scenario that each compound is a simple atropisomer cannot be ruled out at this time.

In Chapter 3.6, several attempts to convert borylstannane cycloadduct 108 and 111, which is more readily available and related to 171, 172, and 173, into a more stable product were described. These experiments were unsuccessful. Attempts to hydrolyze B-C\(_{sp2}\) bond 108 (eq. 17, Chapter 3.6) in MeOH at elevated temperatures resulted in unselective hydrolysis and only low yield was obtained. Also, attempts to do Sn-halogen exchange using NBS, and Suzuki coupling in the presence of Sn moiety gave an unidentifiable mixtures. With this preliminary derivatization study, no further efforts to derivatize borylstannanes 171, 172, and 173 into more stable derivatives were made.

5.5 Reaction of Diyne 167 with Si-Sn Reagent: A Confirmation of Atropisomerism in 172a

Silylstannane reagents, Ph\(_3\)Sn-SiMe\(_2\)Bu\(_1\) and Bu\(_3\)Sn-SiMe\(_3\) were tested in the silylstannylnative cyclization of diyne 167. These reagents exhibited a lower reactivity compared with B-Sn reagent used in the previous section in the preliminary reactivity study (Chapter 3.6). However, treatment of 167 with Sn-Si reagents in the presence of
Pd$_2$(dba)$_3$CHCl$_3$ (5 mol %), P(C$_6$F$_5$)$_3$ (10 %) in C$_6$D$_6$ at 80 °C for 2 h gave clean conversion to a mixture of isomers, 174a/174b and 175a/175b for Ph$_3$Sn-SiMe$_2$Bu$^1$ and Bu$_3$Sn-SiMe$_3$ respectively (eq. 4). The major regioisomer, 174a was separated on silica gel chromatography and was fully characterized by NMR spectroscopy ($^1$H, $^{13}$C, COSY, HMQC, nOe, HRMS). With the help of $^1$H and COSY spectrum, it is possible to assign the structures of 174a and 174b (Figure 5.3). For example, in CDCl$_3$, C$_{sp^2}$(SnPh$_3$)$_2$H proton of 174a at $\delta$ 6.29 (d, J = 1.3 Hz, $^2$J$_{Sn-H}$ = 56 Hz) is correlated with NCH ring proton in COSY spectrum and C$_{sp^2}$(SiMe$_2$Bu$^1$)$_2$H proton of 174a at $\delta$ 5.46 (t, J = 1.6 Hz) is correlated with NCH$_2$ protons (both $\alpha$ and $\beta$). In minor isomer 174b, C$_{sp^2}$(SiMe$_2$Bu$^1$)$_2$H proton appears at $\delta$ 5.33 (d, J = 1.4 Hz) and C$_{sp^2}$(SnPh$_3$)$_2$H proton at $\delta$ 6.42 (t br, $^2$J$_{Sn-H}$ = 48 Hz). Also nOe difference spectra of 174a also confirmed the regiochemistry and double bond configuration shown. A less separable regioisomeric mixture 175a/175b were derivatized with NBS and similarly characterized as a mixture of 176a/176b to confirm the structure shown above in eq. 4 and Figure 5.3 (see experimental section).
The distribution of products was found to be different depending on the Sn-Si reagent used (eq. 4). The regioisomeric ratio was determined by the comparison of integration of vinyl peaks. Bulkier Ph₃Sn-SiMe₂Bu' gives higher selectivity (3.1/1) for what appears to be the reaction of the less substituted acetylene first (i.e. larger proportion of 174a vis-à-vis 175a) as compared to Bu₃Sn-SiMe₃ (2.2/1) and these ratio can be compared favorably with that of the Sn-B adduct 171 (1.2/1, vide supra).

The nature of atropisomerism of 174 and 176 was studied by (1) temperature-dependent behavior in the ¹H NMR spectra (Figure 5.4), and (2) molecular mechanics calculations. While the solution of 174a in CD₃OD was cooled down from 25 °C to -90 °C, the only changes observed were in the OCH₂ peaks. At room temperature, these peaks appear as doublet at δ 4.64 (d, J = 5.2 Hz, 2H, OCH₂) and between 0 °C ~ -10 °C, the doublet broadens and finally below -40 °C, it forms two separate peaks, i.e. doublet δ 4.76 (d, J = 9.5 Hz, 2H, OCH₂) and triplet at δ 4.64 (t, J = 9.4 Hz, 2H, OCH₂). These changes are interpreted as conformational changes of carbamate ring in 174a and are

Figure 5.3. Regioisomerer 174a (major isomer) and Mixture of Regiosomers 176a/176b
Figure 5.4 Temperature Dependent $^1$H NMR Spectra of 174a
Figure 5.5 Interconversion of Atrop-diastereomers of $174a$ and $A$

accompanied by the broadening of SiBu'Me$_2$ peaks ($\delta$ -0.01, -0.52 at RT; both are singlets) in $^1$H and $^{13}$C NMR at the $-30 \sim -10$ °C range. Most likely, these changes are not the result of atropisomerism, because there is no doubling of SiBu'Me$_2$, Csp$_2$(SnPh)$_3$H, Csp$_2$(SiMe$_2$Bu')H, or any other spin systems at low temperatures down to $-90$ °C (except the change of OCH$_2$ peaks). If the atropisomeric equilibrium in Figure 5.5 is frozen at the low temperatures, we should be able to observe two sets of SiBu'Me$_2$ peaks, for example, because $174a$ and $174a'$ are diastereomeric. On the other hand, when the solution of $174a$ in C$_6$D$_6$ was heated up to 70 °C, no temperature dependent changes were observed at all (Figure 5.4). For comparison, in $A$ (Figure 5.5), which as in the present case has one center of chirality, the SiBu'Me$_2$ peaks appear as pseudo AB at room temperature, but as a set of two AB's at $-60$ °C, because of the slow atropisomerization and the resulting generation of additional chirality.$^9$

On the other hand, strain energies of MM2 minimized structures of $174a/174a'$ (see experimental section for details of MM2 calculation) differ by about 1 kcal/mol favoring $174a'(R,R_A)$, indicating the formation of either isomers from $167$ is not an unreasonable reaction. At present, we cannot rule out the unlikely possibility that
atropisomeric interconversion (Figure 5.5) has unusually low free energy of activation and the mixtures are not resolved even at -90 °C.

Detailed nOe difference spectra were obtained in an attempt to decide the stereochemistry of possibly atropisomeric compound 174a/174a' (Figure 5.6). MM2 minimized structures of 174a (R, R_A) and 174a' (R, S_A) showed that in the latter case, the distances between C(Sn)H (H_a in Figure 5.6) proton and two OCH_2 (H_d and H_e in Figure 5.6) protons are similar and hence similar nOe effect is expected, and in the former case, the two distances are significantly different. Large differences of nOe effects between the two spin systems (from a comparison of nOe's of H_a-H_d and H_a-H_e) supports 174a for the

<table>
<thead>
<tr>
<th>protons</th>
<th>nOe (%)</th>
<th>protons</th>
<th>nOe (%)</th>
<th>protons</th>
<th>nOe (%)</th>
<th>protons</th>
<th>nOe (%)</th>
<th>protons</th>
<th>nOe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H_a - H_d</td>
<td>5.3 %</td>
<td>H_b - H_g</td>
<td>2.1 %</td>
<td>H_e - H_a</td>
<td>0.4 %</td>
<td>H_n - H_a</td>
<td>0.23 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H_a - H_e</td>
<td>0.3 %</td>
<td>H_d - H_e</td>
<td>10.0 %</td>
<td>H_f - H_b</td>
<td>1.1 %</td>
<td>H_n - H_b</td>
<td>0.16 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H_a - H_h</td>
<td>0.4 %</td>
<td>H_d - H_a</td>
<td>8.8%</td>
<td>H_f - H_g</td>
<td>20.8 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H_b - H_f</td>
<td>1.1 %</td>
<td>H_e - H_d</td>
<td>10.3 %</td>
<td>H_g - H_b</td>
<td>3.3 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5.6. nOe Contacts in 174a
Figure 5.7 A Rationale for the Diastereoselection of Product 174a or 174b

structure of the major atrop-diastereomer, which has also lower strain energy from MM2 calculation.

The most reasonable conclusion from the foregoing NMR study of 174a is that under the experimental condition in eq. 2, only one of the two atrop-diastereomer was obtained as a result of diastereoselection; in other words, center-chirality in carbamate ring 167 was faithfully transferred into the atropisomeric chirality of 1,3-diene in 174a. If the configuration of the product 174a is confirmed, this constitutes one of the rare
examples in which a starting material with a center of chirality is converted into a product with atrop-chirality in a cyclization reaction.\textsuperscript{10}

From the evidence cited thus far, it appears that the two products obtained are regioisomers even though we have not yet clearly determined the relative atropisomeric configuration of the respective isomers in each case. Stereochemical analysis of the reaction intermediates suggests the following structures shown for 174a and 174b (Figure 5.7). The bicyclic Pd\textsuperscript{2+} intermediate appears to have two distinct conformations (Figure 5.7). In path A, the major product arises via initiation of the reaction at the less crowded acetylene. The intervening ‘extended bicyclic’ TS (A) is less congested than the ‘closed bicyclic’ TS (A’). In the major TS (A), a hydrogen and a lone-pair occupy the two quasi-axial bridgehead positions, whereas in the minor TS (A’), these positions are occupied by a carbonyl carbon and a OCH\textsubscript{2} group. Accordingly, we predict that the major product will have Si moiety syn to the bridgehead hydrogen (as in X). Same line of reasoning applies to the formation of Y (path B, Figure 5.7), the minor regioisomer arising from initiation of the reaction at the more hindered acetylene. Of the relevant TS’s, B is the extended bicyclic and B’ the ‘closed bicyclic’. The product will have the atrop-diastereomeric structure Y with Sn moiety syn to the bridgehead hydrogen. This analysis would predict that the minor atrop-diastereomers X’ and Y’ will not be formed in the reaction.

From a synthetic viewpoint, we anticipate use of several of these intermediate 171-175 for the synthesis of highly functionalized pyrrolidine nuclei including those of kainoids. For example, the modest regioselectivity (3.1/1) and chromatographic separability in the reaction shown in eq. 4 (entry 1) set the stage for the further
derivation of the product toward the targets. We need to develop Stille coupling with chloroformate, diastereoselective hydrogenation, and derivatization of the vinyl silane. An appropriate way to utilize the atropisomeric chirality will be highly desirable in these studies.

![Scheme 5.5. Projected Approach to Kainoids](image)

5.6 Alleneyne Route to Functionalized Pyrrolidines

In Chapter 4, we described how in the bismetallation-cyclization of an alleneyne the chemoselectivity (allene vs. acetylene) eliminated the regioselectivity problems associated with cyclization of diynes. We thought this observation as well as the high 1,2-asymmetric induction observed might be used to generate three contiguous asymmetric centers in kainoids.
Scheme 5.6. Synthesis of Allene Substrates 178 and 179

Thus substrates 178 and 179 were synthesized according to Scheme 5.6. Crabbe reaction introduced an allene function from TBS-protected acetylene and desilylation gave the known allenyl alcohol 177.\textsuperscript{11} Swern oxidation followed by Wittig and Seyferth-Gilbert reaction provided 178 and 179, respectively. Both eneallene 178 and alleneyne 179 were fully characterized and had all the expected spectral characteristics as well as molecular ion by high resolution MS. For example, allene of 178 has peaks at $\delta$ 4.86 (m, 2H) and 5.07 (quintet, $J = 6.6$ Hz, H) and $\alpha,\beta$-unsaturated ester of 178 has peaks at $\delta$ 6.03 (d, $J = 15.6$ Hz, H) and 6.72 (dd, $J = 7.0, 15.6$ Hz, H) (separable mixture of E/Z = 93/7), while allene of 179 has peaks at $\delta$ 4.85 (m, 2H) and 5.11 (m, H) and acetylene of 179 has a peak at $\delta$ 2.50 (d, $J = 2.1$ Hz, H).
5.6.2 Reaction of Eneallenes

The silylstannylative cyclization of 178 was studied first. The addition of Sn-Si reagent (1.1 equiv.) to 178 in the presence of Pd$_2$(dba)$_3$·CHCl$_3$ (5 %) in C$_6$D$_6$ at RT was extremely efficient (<20 min) and clean to provide 180 in 84 % isolated yield (>95 % by $^1$H NMR, eq. 5). The allylstannane 180 was also characterized by $^1$H, $^{13}$C, HRMS, as well as nOe difference spectra, by which double bond configuration was determined; For example, Bu$_3$SnCH$_2$ peaks at $\delta$ 1.77 (d, $J = 11.7$ Hz, $^2$J$_{Sn-H} = 64$ Hz, H) and 1.83 (d, $J = 11.7$ Hz, $^2$J$_{Sn-H} = 64$ Hz, H), R(Si)C=Csp$_2$-H peak at $\delta$ 5.28 (t br, $J = 6.6$ Hz, H), and .

This insertion of Sn-Si reagent into allene was more efficient without the use of phosphine ligands (Table 5.1). Unfortunately, however, prolonged reaction at an elevated temperature (20 h at 80 °C) failed to give desired cyclic product, with the acyclic product 180 persisting. Conditions tried are summarized in Table 5.1. In Table 5.1, we projected that oxidative addition of Pd(0) to MeI, followed by insertion of allene to Pd-Me bond would generate π-allyl complex with isopropenyl unit in the ‘right’ place.$^{15}$ However, extremely fast insertion of Sn-Si reagent across allene double bonds precluded the realization of initial scheme. Irrespective of conditions tried (solvent, phosphine, Pd precursor, temperature/time), acyclic allylstannane 180 was obtained as sole product.

\[
\begin{align*}
\includegraphics[width=\textwidth]{reaction_diagram.png}
\end{align*}
\]
The allyl tin compound 180 is by itself a highly desirable intermediate, because Lewis acid catalyzed Michael addition or radical cyclization may lead to the desired heterocyclic skeleton of kainic acid.

As a first attempt, the reaction of 180 in the presence of Me3SiOTf or BF3·OEt2 was explored as in eq. 6. When 180 was treated with TMS-OTf in CD2Cl2, a slow destannylation was observed to give 181 without any cyclization. After aqueous workup, 181 was isolated in 94 % yield (characterized by IR, 1H, 13C, HRMS, COSY, and
When 180 was treated with BF$_3$OEt$_2$ in CH$_2$Cl$_2$ at -78 °C to rt over 2 h, followed by aqueous workup, 181 was isolated in 92 % yield (eq. 6). Thus, desired Michael addition failed under the conditions tried.

5.6.3. Use of Allene Adduct 180 for a Radical Cyclization

Next, our attention turned to radical cyclizations. When the mixture of AIBN (0.2 equiv.) and Bu$_3$SnH (2.0 equiv.) in benzene was added to a solution of 180 in refluxing benzene (0.01 M) through a syringe pump over 3 h, a mixture of diastereomers were obtained as an oil in a high yield (eq. 7, $dr = 7/1$, 90 % isolated yield as a mixture). The major diastereomer was separated on silica gel chromatography and was fully characterized by NMR spectroscopy including COSY, HMQC, and HMBC, high resolution MS, and nOe difference spectrum, the last one supporting the relative stereochemistry shown in Figure 5.7 (selected peaks in $^1$H NMR; $\delta$ 1.42 (m, H, SnCH), 2.50 (ddd, $J = 5.0, 8.5, 12.9$ Hz, H, CHC(Si)=CH$_2$), 2.98 (t br, $J = 4.1$ Hz, H, CHCH(Sn)CO$_2$Et), 3.64 (d, $J = 8.5$ Hz, 2H, NC$_2$H$_2$), 3.68 (dd, $J = 6.9, 8.2$ Hz, H, OCH$_2$), 4.35 (t, $J = 8.1$ Hz, H, OCH$_2$), 4.51 (ddd, $J = 6.9, 8.1, 12.3$ Hz, H, NC$_2$H).
Figure 5.8. nOe Contacts in 182 (Major Isomer)

All the peaks assigned were consistent throughout the various NMR techniques, including COSY, HMBC, and nOe. The formation of SnBu₃ adduct was can be explained by the mechanism shown in Scheme 5.9. The R₃Sn radical generated from Bu₃Sn-H and...
AIBN would reversibly add to the α,β-unsaturated carbons, then the cyclization occurs. Kinetically favored 5-exo mode will dominate to give 183 and the subsequent elimination of R₃Sn radical will give 182 with regeneration of Bu₃Sn radical.

Scheme 5.7 Radical Mechanism for the Conversion of 180 to 182

The stereochemical outcome of above radical cyclization can be rationalized in the following way based on steric arguments (Figure 5.9) In B, 1,2-strain interaction arises between radical substituents CH(SnR₃)(E) and carbamate ring OCH₂ whereas in C, bulky SiMe₃ group is placed in a concave side of the incipient bicyclic ring. Transition structure A seems to be the least sterically encumbered among the possibilities, and this would lead to the major product of 182 (eq. 7). The configuration of the α-carbonyl

Figure 5.9. Stereochemical Rationale of Radical Cyclization
carbon is uncertain, even though the purified sample appears to be a single diastereomer because no doubling of signals was observed in $^1$H and $^{13}$C NMR spectra.

5.6.4. Cyclization of Alleneyne

The alleneyne 179 would also be an appropriate substrate for the synthesis of kainic acid. When 179 was treated with Sn-Si reagent (1.1 equiv.), Pd precursor (5 %), and ligand (10 %) in C$_6$D$_6$ at 80 °C, efficient conversion into 184 or 185 was observed as shown in eq. 9. Use of Pd(PhCN)$_2$Cl$_2$ was less efficient than Pd(dba)$_3$ because of the formation of a precipitate in the former case. The 1,3-diastereoselectivity was disappointingly low (a/b in eq. 8). Use of bulkier Sn-Si reagent (Entry 3 and 4) did not improve the selectivity in the cyclization of 179. Sterically less encumbered Sn-Si reagent gave cleaner conversion and higher yield was observed.

![Diagram of cyclization reaction](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd</th>
<th>Sn-Si</th>
<th>condition</th>
<th>yield</th>
<th>a/b</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PhCN)$_2$Cl$_2$</td>
<td>Ph$_3$Sn-SiMe$_2$Bu</td>
<td>80 °C / 3 h</td>
<td>No reaction</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PhCN)$_2$Cl$_2$</td>
<td>Bu$_3$Sn-SiBu</td>
<td>80 °C / 3 h</td>
<td>59 %</td>
<td>1/1</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_3$CHCl$_3$</td>
<td>Ph$_3$Sn-SiMe$_2$Bu</td>
<td>55 °C / 1 h</td>
<td>(50 %)$^a$</td>
<td>1/1</td>
</tr>
<tr>
<td>4</td>
<td>Pd$_2$(dba)$_3$CHCl$_3$</td>
<td>Bu$_3$Sn-SiMe$_3$</td>
<td>55 °C / 1 h</td>
<td>76 %</td>
<td>1/1</td>
</tr>
</tbody>
</table>

a. Yield in parenthesis is based on 'in-situ' $^1$H NMR, otherwise isolated yield.
The mixture 185a/185b was separable on a silica gel column and the structural assignments were unambiguously made by nOe experiments as in Figure 5.10, as well as a full characterization by $^1$H, $^{13}$C, COSY, HMQC, IR, and high resolution MS: Selected $^1$H NMR signals of $^1$H NMR (CDCl₃). 185a: $\delta$ 6.19 (s, $J_{Sn-H} = 50$ Hz, H, (Sn)CH=CR₂), 5.71 (t, $J = 1.9$ Hz, H, R(Si)C=CH₂), 5.57 (t, $J = 1.8$ Hz, H, R(Si)C=CH₂), 4.39 (dd, $J = 1.9$, 3.8, 8.8 Hz, H, NCH), 3.39 (d br, $J = 6.3$ Hz, H, CHC(Si)=CH₂) 185b: $\delta$ 6.08 (t, $J = 1.9$ Hz, $J_{Sn-H} = 46$ Hz, H, (Sn)CH=CR₂), 5.71 (t, $J = 1.9$ Hz, H, R(Si)C=CH₂), 5.45 (dd, $J = 1.3$, 2.2 Hz, H, R(Si)C=CH₂), 4.24 (dd, $J = 1.8$, 7.6 Hz, NCH), 3.56 (t br, $J = 7.6$ Hz, H, CHC(Si)=CH₂). Further confirmation of structure came from nOe study that follows.

<table>
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<th>Proton</th>
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<tr>
<td>Hₐ</td>
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</tr>
<tr>
<td>H₋</td>
<td>4.44</td>
</tr>
<tr>
<td>Hₙ</td>
<td>4.67</td>
</tr>
<tr>
<td>Hₜ</td>
<td>4.26</td>
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<td>Hₖ</td>
<td>5.62</td>
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<td>6.24</td>
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<td>3.38</td>
</tr>
<tr>
<td>Hₚ₂</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*a*CDCl₃ (SR = 0)

<table>
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<tr>
<th>Protons</th>
<th>nOe (%)</th>
<th>Protons</th>
<th>nOe (%)</th>
<th>Protons</th>
<th>nOe (%)</th>
<th>Protons</th>
<th>nOe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hₐ - Hₙ</td>
<td>1.6 %</td>
<td>Hₙ - Hₕ</td>
<td>(1.0 %)</td>
<td>Hₕ - Hₐ</td>
<td>3.4 %</td>
<td>Hₐ - Hₚ₂</td>
<td>0 %</td>
</tr>
<tr>
<td>Hₙ - Hₕ</td>
<td>3.6 %</td>
<td>Hₙ - H₉</td>
<td>(0.7 %)</td>
<td>H₉ - Hₙ</td>
<td>11.0 %</td>
<td>Hₙ - Hₚ₂</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Hₙ - Hₕ</td>
<td>12.0 %</td>
<td>Hₙ - Hₚ₂</td>
<td>1.3 %</td>
<td>Hₕ - Hₚ₂</td>
<td>3.2 %</td>
<td>Hₕ - Hₙ</td>
<td>1.2 %</td>
</tr>
<tr>
<td>Hₙ - Hₕ</td>
<td>0.7 %</td>
<td>Hₕ - Hₙ</td>
<td>2.0 %</td>
<td>Hₙ - Hₕ</td>
<td>1.4 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Numbers in parenthesis may have some uncertainty because of overlap of peaks
Figure 5.10 nOe Contacts in of 185a (cis) and 185b (trans).

The more polar isomer was assigned to 185a (2,4-cis) structure: Based on the strong H_b-H_c nOe contact,α and β OCH₂ protons can be assigned as H_c and H_d, respectively. A long range nOe contact from H_c to H_d (β) would be possible because of the concave geometry and observation of this H_c-H_d contact supports 2,4-cis stereochemistry. Likewise, the less polar component was assigned to 185b (2,4-trans) structure: Strong H_c-H_b nOe contact indicates that α and β OCH₂ protons can be assigned...
as \( H_c \) and \( H_d \), respectively. The absence of \( H_c-H_c/H_d \) is a good indication that \((\text{Si})C=\text{CH}_2\) substituent is on the convex side (or pseudo-equatorial) of the bicyclic system. The observation of \( H_c-H_b \) is also a good indication.

The exact reason for the lack of stereoselectivity remains speculative at this time. Examination of models of anti-\( \pi \)-allyl \( \text{Pd}^{2+} \) complex suggests that the two intermediates that were involved could be formed with equal facility from the allene (Figure 5.11). The comparison of these model with those of intermediates leading to the cyclization of diyne 167 into 174a (Figure 5.7) shows remarkable differences. In the latter case, one of the two 'boat-like' transition states appears to be preferred. This distinction between the two transition states is less obvious in the cyclization of allene 179, especially when the TS involves a \( \pi \)-allyl \( \text{Pd}^{2+} \) species rather than a \( \sigma \text{C}_2\text{Pd} \) species which is the case in the diyne cyclization.

![Figure 5.11. Stereochemical Analysis of Formation of 185a and 185b.](image)

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In our synthetic scheme, stereochemistry of 185a and 185b correspond to kainic acid and allokainic acid, respectively. Thus, synthetic access to both epimers at C4 has been achieved, albeit in low diastereoselectivity.

5.6. Conclusions

Continuing the studies of silylstannyative cyclization of diynes and alleneynes described in chapter 3 and 4, a development of synthetic application for the synthesis of kainoid pyrrolidine skeleton of α-kainic acid and allokainic acid is described in this chapter. Silylstannyative cyclization of tethered unsaturated C-C multiple bonds led to a densely functionalized kainoid skeleton.

The cyclization of various diynes with borylstannane reagent gave a mixture of regioisomers. The ratio of these regioisomer was dependent on the substrate structure. The identity of this product as regioisomers was supported by variable-temperature NMR study. The diyne substrate 167 can also be cyclized using silylstannane reagents. One of those (174a) was separated and was analyzed in all structural aspects. First, COSY spectra confirmed that the isomers formed from such reactions are regioisomers rather than atropisomers. Accordingly, the silylstannane cycloadduct (174a) exhibited expected behavior in the variable-temperature NMR study. The coalescence of atrop-diastereomers did not occur between −90 °C and +70 °C. Comparison of coalescence temperature with related compounds showing atropisomerism, it is most likely that the product 174a is a single atrop-diastereomer at these temperatures. A stereochemical model was proposed that accounts for the preferential formation of one atrop-diastereomer. When the
structural assignments are confirmed beyond doubt, formation of 174a (or of 174b) will form a rare example of a cyclization reaction in which the center of chirality in a starting material directs the evolution of atrop-chirality in a product with nearly 100% selectivity. Continuing the allene chemistry in the silylstannylation developed in Chapter 4, more elaborate allenes were synthesized and they were subjected to cyclization studies. While the control of selectivity was marginal in the direct Pd-catalyzed cyclization, a two-step procedure which involved silylstannylation of allene, followed by radical cyclization showed very good diastereoselectivity. Further studies would involve reasonably routine functional group manipulation to complete the synthesis of various kainic acid derivatives.
REFERENCE TO CHAPTER 5


CHAPTER 6

EXPERIMENTAL PROCEDURES

General methods. All reactions were carried out under a nitrogen atmosphere by using either Schlenk techniques or Vacuum Atmosphere drybox. Solvents were distilled under nitrogen and degassed for use inside a drybox. Tetrahydrofuran (THF), n-hexane, and diethylether were distilled from sodium/benzophenone ketyl. Dichloromethane, pyridine, benzene and toluene was distilled from calcium hydride. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from anhydrous magnesium sulfate under reduced pressure. All other reagents were purified using procedures described in Purification of Laboratory Chemicals.\(^1\) 1,2-bisphosphinobenzene ($\,$100/g) were given as a generous gift from Digital Specialty Chemical. Metal complexes \([\text{Rh}^{\text{+}}(\text{COD})]\text{SbF}_6^-\), \([\text{Rh}^{\text{+}}(\text{COD})]\text{SbF}_6^-\), and \(\text{Pd}_2(\text{dba})_3\text{CHCl}_3\) were prepared from the literature methods described in Synthetic Methods of Organometallic and Inorganic Chemistry.\(^2\)

Column chromatography of air-sensitive phosphine and phosphinite compounds were performed inside a drybox on a deactivated silica gel prepared by heating it in the vacuum oven overnight, followed by addition of degassed water (15 v/v %). NMR
experiments were performed on a Bruker 250, 300, DRX-400, or DRX-500 MHz spectrometer. Samples were dissolved in C₆D₆, CDCl₃, CD₂Cl₂, or CD₃OD. Enantiomeric excesses in asymmetric hydrogenations of dehydroamino acids and asymmetric allylic reductions of geranyl methyl carbonate were determined by gas chromatography on a Hewlett Packard 5890 equipped with chiral columns (Chirasil-L-Val on WCOT fused silica 25 m x 0.25 mm or Chiraldex B-PH, γ-cyclodextrin, 10 m x 0.25 mm). Gas chromatographic analyses of achiral compounds were performed on the normal phase column (HP-untra-1 crosslinked methylsilicon, 25 m x 0.2 mm x 0.33 µm). Enantiomeric excesses in hydrovinylations of styrene and 4-bromostyrene were determined by HPLC analyses on Chirasil OJ column (25 cm x 4.6 mm, i.d.). Analytical TLC was performed on e. Merck precoated (0.25 mm) silica gel 60 F₂₅₄ plates.
6.1 EXPERIMENTAL SECTION FOR CHAPTER 2

Synthesis of 21a:

To a solution of the starting tetrahydroxy sugar (1.00 g, 1.93 mmol) in 20 mL of DMF was added NaH (370 mg, 8.0 equiv., free of mineral oil) portionwise at rt. The mixture became a thick slurry, which turned into an yellow solution after stirring further for 1 h. Benzyl bromide (2.75 mL, 12 equiv.) was added slowly and the mixture was allowed to stir overnight. The reaction mixture was quenched with MeOH (1 mL) and 100 mL of water. The mixture was extracted with ether (50 mL x 3). The organic layer was dried (MgSO₄), concentrated, and was subjected to flash chromatography (EtOAc/Hex = 3/7) to get 1.29 g (76 %) of a white solid.

(21a) ¹H NMR (250 MHz, CDCl₃): δ 3.58-3.72 (m, 6H, C2, C3, C6-H), 4.07-4.19 (m, 4H, C4, C6'-H), 4.29 (td, J = 4.0, 8.3 Hz, 2H, C5-H), 4.79 (AB, J = 10.0, 26.9 Hz, 4H, PhCH₂), 4.92 (AB, J = 9.3, 27.3 Hz, 4H, PhCH₂), 5.13 (d, J = 3.1 Hz, 2H, C1-H), 5.56 (s,
2H, PhCH), 7.20-7.55 (m, 30 H); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)): \(\delta 62.9, 69.0, 73.8, 75.2, 78.6, 78.7, 82.3, 95.0, 101.2, 126.1-137.5\) (12 carbons). (I-145, I-160)

*Synthesis of 21b:*

\[ \text{Ph} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{HO} \quad \text{HO} \quad \text{21b} \]

The starting tetrol (100 mg, 0.202 mmol) was dissolved in 3 mL of DMF. To the solution was added KH (42.1 mg, 1.05 mmol) portionwise. Immediately after addition, pale yellow gel formed, which upon further stirring for 1 h became a cloudy mixture. To the resulting mixture was added chloromethyl methyl ether (101 mg, 1.26 mmol). With evolution of heat, a white precipitate came out. The mixture was allowed to stir for 28 h. The reaction was quenched by addition of 20 mL of water, and the mixture was extracted with ether (10 mL x 3). The combined organic layer was dried (MgSO\(_4\)), evaporated, and was subjected to column chromatography (EtOAc/Hex = 1/2) to afford 75.1 mg (51 %) of a white solid (mp 105-110 °C).

(21b) \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta 3.39\) (s, 6H, OMe), 3.40 (s, 6H, OMe), 3.50-3.82 (m, 6H), 4.10-4.28 (m, 6H), 4.77 (AB, J = 8.0, 31.7 Hz, 4H), 4.87 (AB, 4H), 5.15 (d, J = 4.7 Hz, 2H, C1-H), 5.54 (s, 2H, PhCH), 7.30-7.55 (m, 10 H); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)): \(\delta 55.5, 55.9, 62.9, 69.1, 74.5, 75.8, 81.7, 95.4, 96.7, 97.4, 101.5, 126.1, 128.1, 128.9, 137.2\). (I-276, I-272)

*Synthesis of 27:*

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To a stirring solution of starting sugar 21a (996 mg, 1.13 mmol) in 5 mL of CH₂Cl₂-ether (1:1) mixture was added LAH (181 mg, 4.76 mmol) in one lot at rt. After the boiling had stopped, AlCl₃ (54.4 mg, 4.08 mmol) dissolved in 2 mL of CH₂Cl₂-ether (1:1) was added dropwise. After 2 h, the reaction mixture was quenched with 0.5 g of celite/Na₂SO₄/water (3:3:1) and was allowed to stir for 0.5 h. The mixture was extracted with EtOAc (50 mL x 4). The solvent was evaporated and the residue was purified by flash column chromatography to get 906 mg (91%) of colorless syrup.

(27) IR (mineral oil): 2922, 2853, 2725, 2358, 1459, 1376, 1154, 722 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.54 (s, 2H, 6-OH), 3.43 (dd, J = 4.0, 10.1 Hz, 2H, C2-H), 3.50 (m, 6H, C4, C5, C6-H), 3.98 (m, 4H, C3, C6-H), 4.60 (AB, J = 11.5, 19.3 Hz, 4H, PhCH₂), 4.68 (AB, J = 10.5, 114.5 Hz, 4H, PhCH₂), 4.86 (AB, J = 10.8, 54.6 Hz, 4H, PhCH₂), 5.07 (d, J = 3.7 Hz, 2H, C1-H), 7.10-7.32 (m, 30 H); ¹³C NMR (125 MHz, CDCl₃): δ 61.5, 71.4, 73.0, 75.0, 75.5, 77.4, 79.5, 81.6, 93.9, 127.48, 127.51, 127.63, 127.84, 128.04, 128.34, 128.37, 128.42, 138.06, 138.27, 138.79 (12 aromatic carbons). (I-163, I-190)

Synthesis of 23a:

172
Chlorodiphenylphosphine (157.5 mg, 0.714 mmol) and DMAP (96.0 mg, 0.340 mmol) were dissolved in 3 mL of toluene. To this solution was added diol 22 (300 mg, 0.340 mmol) dissolved in toluene (1 mL) dropwise over 40 min, keeping the temperature below 30 °C. The mixture was stirred for an additional 12 h and the precipitate was filtered through a cotton plug. This solid was rinsed with toluene (1 mL x 3). The filtrate was concentrated and was purified by flash column chromatography (ether 100 %) inside the drybox to get 380 mg (89 %) of product as a sticky solid.

\[(23a) \]^{1}H NMR (500 MHz, CDCI\textsubscript{3}): \( \delta \) 3.04-3.16 (m, 4H, C6, C6'-H), 3.59 (dd, \( J = 3.4, 9.5 \) Hz, 2H, C2-H), 4.01 (AB, 4H), 4.07 (t, \( J = 9.3 \) Hz, 2H, C3-H), 4.09-4.15 (m, 2H, C5-H), 4.17 (t, \( J = 9.3 \) Hz, 2H, C4-H), 4.52 (AB, \( J = 10.6, 266.0 \) Hz, 4H), 4.54 (AB, \( J = 11.9, 23.8 \) Hz, 4H), 5.20 (d, \( J = 3.5 \) Hz, 2H, C1-H), 6.80-7.49 (m, 50 H); \(^{13}C\) NMR (125 MHz, CDCI\textsubscript{3}): \( \delta \) 68.3, 70.84, 70.87, 72.5, 72.9, 74.2, 78.2, 78.3, 79.7, 80.5, 99.1, 127.0, 127.1, 127.2, 127.4, 127.5, 127.9, 128.03, 128.08, 128.12, 128.13, 128.17, 128.26, 128.91, 129.24, 129.80, 129.98, 130.47, 130.66, 137.94, 137.98, 138.44, 142.80 (\( J_{C,P} = 15.5 \) Hz), 143.07 (\( J_{C,P} = 19.5 \) Hz); \(^{31}P\) NMR (100 MHz, CDCI\textsubscript{3}): \( \delta \) 114.4 (s). (II-10)

**Synthesis of 23b:**

\[
\begin{align*}
\text{BnO} & \quad \text{Ar}_2\text{P} & \quad \text{BnO} \\
\text{OH} & \quad \text{DMAP} & \quad \text{OH}
\end{align*}
\]

Similar procedure as in 23a was followed except that chloro-(3,5-di-methylphenyl)phosphine was used instead of chlorodiphenylphosphine. The crude material was subjected to flash column chromatography (ether 100 %) to get 23b in 85 % yield.
(23b) $^1$H NMR (250 MHz, CD$_3$OD): $\delta$ 2.20 (s, 12H), 2.21 (s, 12H), 3.31 (s br, 4H, C6, C6'-H), 3.68 (dd, $J = 3.6, 9.2$ Hz, 2H, C2-H), 4.04 (AB, 4H), 4.10-4.30 (m, 6H, C3, C4, C5-H), 4.62 (AB, 4H), 4.64 (AB, 4H), 5.28 (d, $J = 3.6$ Hz, 2H, C1-H), 6.80-7.25 (m, 50 H); $^{31}$P NMR (100 MHz, CDCl$_3$): $\delta$ 116.9 (s). (II-128)

Synthesis of 25a:

![Chemical Structure of 27 and 25a]

Similar procedure as in 23a was followed. The crude material was subjected to flash column chromatography (ether, 100 %) to get 25a in 99 % yield as a sticky solid.

(25a) $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 3.34 (dd, $J = 3.5, 9.6$ Hz, 2H, C2-H), 3.66 (t, $J = 9.6$ Hz, 2H, C4-H), 3.86 (t br, $J = 10$ Hz, 2H, C6'-H), 3.98 (dd, $J = 3.0, 9.7$ Hz, 2H, C6-H), 4.05 (t, $J = 9.3$ Hz, 2H, C3-H), 4.17 (d br, $J = 9.8$ Hz, 2H, C5-H), 4.56-5.05 (3 AB, 12 H), 5.17 (d, $J = 3.5$ Hz, 2H, C1-H), 7.12-7.62 (50 H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 68.5 (d, $J_{C,P} = 18.3$ Hz), 71.2 (d, $J_{C,P} = 6.7$ Hz), 72.7, 75.0, 75.5, 77.5, 79.6, 81.5, 93.7, 127.3-141.9 (20 aromatic C's); $^{31}$P NMR (100 MHz, CDCl$_3$): $\delta$ 116.1 (s). (II-98)

Tosylation of 27:

![Chemical Structure of Tosylation of 27]
To a solution of the diol 27 (141 mg, 0.160 mmol) in 2 mL of pyridine was added TsCl (91.3 mg, 0.480 mmol) at 0 °C. The mixture was stirred for 1 h and kept in a refrigerator for 2 days. TLC analysis (EtOAc:Hex = 1:2) showed that ditosyl product (Rf = 0.4) was dominant over monotosyl side-product. The reaction mixture was partitioned between 20 mL of CH₂Cl₂ and 10 mL of water. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layer was washed with cold 1 N HCl (10 mL x 2), dried (MgSO₄), evaporated, and was subjected to flash chromatography (EtOAc/Hex = 1/2) to get the product as a white solid (140 mg, 74 %).

¹H NMR (250 MHz, CDCl₃): δ 2.39 (s, 6H, CH₂-Ar), 3.42-3.54 (m, 4H), 3.75-4.00 (m, 6H), 4.60 (AB, J = 13.2, 101.2 Hz, 4H, PhCH₂), 4.61 (AB, J = 15.0, 29.4 Hz, 4H, PhCH₂), 4.90 (AB, J = 13.7, 32.7 Hz, 4H, PhCH₂), 4.97 (AB, 4H, TsOCH₂), 7.03-7.75 (m, 38 H). (I-164)

**Synthesis of 28:**

![Synthesis Diagram](image)

To a solution of diphenylphosphine (226 mg, 1.22 mmol) in 1 mL of THF was added KH (49 mg, 1.22 mmol) portionwise and the resulting solution was cooled to -30 °C and left stirred for 1 h. The resulting yellow solution of Ph₂PK⁺, was added dropwise to a solution of the ditosyl compound (362 mg, 0.304 mmol) in 1 mL of THF. After the addition was over, the mixture was kept stirring at rt for 3 h. The reaction was quenched by addition of ion-exchange resin (H⁺) or solid NH₄Cl (30 mg) and was stirred for 10
min. The solvent was evaporated and the crude mixture was subjected to column chromatography (EtOAc/Hex = 1/9 ~ 2/8) to get 104 mg (28 %) of a sticky solid as pure product.

(28) $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 2.09 (ddd, $J = 2.5, 7.5, 12.5$ Hz, 2H, C6-H), 2.51 (td, $J = 2.5, 15.0$ Hz, 2H, C6'-H), 3.41 (t, $J = 9.1$ Hz, 2H, C4-H), 3.59 (dd, $J = 3.4, 9.5$ Hz, 2H, C2-H), 4.12 (t, $J = 9.1$ Hz, 2H, C3-H), 4.27 (ddd, $J = 2.6, 1.0, 19.0$ Hz, 2H, C5-H), 4.64 (AB, $J = 12.0, 28.0$ Hz, 4H, PhCH$_2$), 4.75 (AB, $J = 11.2, 83.6$ Hz, 4H, PhCH$_2$), 4.88 (AB, 33.5, 10.9 Hz, 4H, PhCH$_2$), 5.33 (d, $J = 3.3$ Hz, 2H, C1-H), 7.12-7.40 (m, 50 H);

$^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 69.8, 72.5, 75.0, 75.5, 79.6, 83.0, 91.2, 127.1-128.2 (10 C's), 132.1, 132.4, 132.8, 133.2, 138.3, 138.5, 139.0; $^{31}$P NMR (120 MHz, CDCl$_3$): $\delta$ -22.9 (s). (I-177, I-185)

**Formation of Rh(I)-Complexes From Phosphine/Phosphinite Ligands: Representative Procedure:**

To a solution of solution of [Rh$^+$($L$)$_2$X$^-$] (0.050 mmol, L = cod or nbd, X = BF$_4$ or SbF$_6$) in 2 mL of CH$_2$Cl$_2$ was added 1.0 equiv. of phosphine/phosphinite ligand (0.050 mmol) and the resulting solution was stirred at rt for 1 h. After evaporation of the solvent, the residual material was dried and used for NMR spectroscopic characterizations or as a catalyst for hydrogenation of dehydroamino acids. Rh(I)-complexes 24a/24b, 26a, and 29 were prepared from corresponding ligands 23a/23b, 25a, and 28, and were identified by the signals in their $^{31}$P NMR spectra which are described in Chapter 2.1.2.
Borane Protection-Deprotection: Purification of Phosphine

Protection (I-228, I-243), deprotection (I-231)

The crude reaction mixture of 28 (0.0839 mmol, theoretical amount) was treated with excess BH$_3$THF (1 M in THF, 2 equiv. to phosphine) and the reaction mixture was stirred overnight. The resulting borane complex was air-stable and can be manipulated in an aerobic condition. After separation of the borane complex (60 %) by column chromatography (EtOAc/hex = 1/2), it was dissolved in Et$_2$NH (2 mL) and was heated at 50 °C for 12 h. After careful column chromatography (EtOAc/hex = 1/2), 72 % of free phosphine was obtained.

$^3$P NMR (120 MHz, CDCl$_3$) of borane complex: δ 13.0 (s broad).

Attempts to Deprotect Benzyl Protecting Groups from 23a:

A solution of starting phosphinite (91.0 mg) and 10 % Pd on charcoal (32 mg) was placed in a Fisher-Porter bottle and was hydrogenated under 40 psi of H$_2$. After 1 day, starting phosphinite (83 mg, 91 %) was recovered unchanged. (II-56)
Attempts to Deprotect the Benzyl Protecting Groups from 28 or Its Phosphine Oxide:

Starting bisphosphine oxide (57.5 mg, 0.0458 mmol), phosphine, or phosphine borane complex was subjected to hydrogenolysis condition with 10 % Pd/C (25 mg) in 2 mL of EtOAc and 0.1 mL of HOAc. The reaction was followed by TLC or reverse phase HPLC. After 3 h, starting material remained. Further Pd/C catalyst was added (50 mg + 50 mg), and an unidentified complex mixture was observed after 24 h. Use of 20 % Pd(OH)₃/C was also unsuccessful. (I-194, I-220, I-236, I-246)

Attempts to Deprotect Benzyl Protecting Groups from Rh(I) complex 24a:

Starting phosphinites Rh(I) complex (54.4 mg) in MeOH (3 mL) placed in a Fisher-Porter bottle was subjected to hydrogenolysis condition under 30 psi of H₂. The inspection of reaction mixture after 7 h by ³¹P NMR indicated that two sets of doublet at δ 152.9 (d, J_Rh-P = 221 Hz) and 131.7 (d, J_Rh-P = 158 Hz). However, the reaction mixture was not soluble in MeOH at all and H NMR had aromatic protons, indicating the product mixture was not the result of debenzylation. (II-79, II-91)
Attempts to Deprotect Benzyl Protecting Groups from Rh(I) complex:

\[
\begin{array}{c}
\text{(COD) } X^- \\
(\text{P = PPh}_2, X^- = \text{SbF}_6^-)
\end{array}
\]

\[
\begin{array}{c}
\text{resin (H\textsuperscript{+})} \\
(\text{R = MOM})
\end{array}
\]

To the Rh(I) complex (30.3 mg, 0.0198 mmol) in 2 mL of MeOH-THF (1:1) mixture was added washed acidic resin (30 mg, AG 50 WX-8). After 7 h at rt, \textsuperscript{31}P NMR indicated a starting material remaining without any other peaks appearing. (II-92)

**Synthesis of 32:**

To a solution of starting 4,6;4',6'-bisbenzylidene trehalose (250 mg, 0.482 mmol) in 6 mL of dry DMF, was added 2-methoxypropene (0.23 mL, 5.0 equiv.) and camphorsulfonic acid (5 mg). The reaction mixture was stirred at RT overnight. To the reaction mixture was added 50 mL of water and the solution was extracted with ether (50 mL x 3). The combined organic layer was dried (MgSO\textsubscript{4}), evaporated, and was subjected to silica gel chromatography (EtOAc/Hex = 1/3) to get 141.2 mg (49 \%) of a white sticky solid (mp >130 °C).

(32) \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}): \delta 1.51 (s, 12 H, isopropylidene), 3.64 (dd, J = 2.9, 9.0 Hz, 2H, C2-H), 3.75-3.97 (m, 6 H, C4, C5, C6-H), 4.25 (t, J = 9.2 Hz, 2H, C3-H), 4.30-
4.35 (m, 2H, C6'-H), 5.51 (d, J = 3.0 Hz, 2H, C1-H), 5.59 (s, 2H, PhCH), 7.32-7.39 (m, 6 H), 7.47-7.58 (m, 4H). (I-158-2, I-168)

Attempts to Derivatize 32:

To a solution of starting sugar (56 mg, 0.11 mmol) in 0.7 mL of ether-CH2Cl2 mixture (1:1), LAH (6.9 mg, 0.18 mmol) was added in portions under nitrogen, followed by powdery AlCl3 (28 mg, 0.21 mmol). The resulting boiling solution was stirred for 1 h. The reaction mixture at this point showed complex mixture. Further attempts to identify the reaction mixture failed. (I-170, I-202)

Attempts of Hydrogenolysis of 32:

The starting 32 (100 mg, 0.167 mmol) was dissolved in 5 mL of EtOAc and 10 % Pd on charcoal (50 mg) was added to the mixture. The resulting mixture was subjected to hydrogenolysis using Parr apparatus under 50 psi of H2. The reaction was monitored by TLC. After 12 h, TLC indicated that the starting material remained and additionally 100 mg of Pd/C catalyst was added to the reaction mixture. After 3 h, starting material was
gone, but the crude $^1$H NMR of the resulting mixture indicated bare trehalose. (I-210, 212, I-216)

*Synthesis of 33:*

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

A mixture of the starting benzylidene acetal (100 mg, 0.144 mmol) and Pd/C (10 %, 15 mg) in EtOAc (5 mL) was subjected to hydrogenolysis with H$_2$ (35 psi) for 10 h. The crude mixture was filtered through celite pad and the solvent was evaporated to get 77.3 mg (89 %) of colorless syrup.

(33) $^1$H NMR (250 MHz, CD$_3$OD): $\delta$ 3.39 (s, 6H), 3.45 (s, 6H), 3.60 (dd, $J$ = 3.5, 9.8 Hz, 2H, C2-H), 3.70-4.03 (m, 10 H), 4.73 (AB, 4H), 4.85 (AB, 4H), 5.21 (d, $J$ = 5.3 Hz, 2H, Cl-H). (I-267, II-76)

*Selective Tosylation of 33:*

\[
\begin{align*}
\text{HO} & \quad \text{MOMO} \quad \text{O} \quad \text{O} \quad \text{MOMO} \\
\text{MOMO} & \quad \text{O} \quad \text{O} \quad \text{MOMO}
\end{align*}
\]

The starting tetrol 33 (77.0 mg, 0.127 mmol) was dissolved in pyridine (2 mL) at 0 °C. To the mixture was added slowly TsCl (72.6 mg, 0.381 mmol, 3.0 equiv) under N$_2$. The resulting mixture was stirred overnight. The solvent was evaporated azeotropically with
benzene and the residue was subjected to silica gel chromatography (EtOAc/Hex = 7/3) to get 60.0 mg (52 %) of product as colorless syrup.

$^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 2.43 (s, 6H, CH$_3$-Ar), 3.30 (s, 6H), 3.43 (s, 6H), 4.00-4.30 (m, 10H), 4.60 (dd, 4H), 4.72 (s, 4H), 4.94 (d, J = 2.9 Hz, 2H), 7.32 (d, J = 8.3 Hz, 4H), 7.76 (d, J = 8.3 Hz, 2H); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 21.5, 55.5, 55.9, 69.1, 69.2, 69.7, 73.5, 84.0, 94.0, 96.3, 98.3, 127.9, 129.7, 132.9, 144.7. (I-268)

**Synthesis of 34:**

To a solution of Ph$_2$PH (78.9 mg, 0.423 mmol) in 2 mL of THF was added KH (17.0 mg, 0.423 mmol). The resulting yellow solution was stirred for 30 min and this solution of potassium phosphide was slowly added to a cooled solution of ditosylate (64.6 mg, 0.0706 mmol) in THF (1 mL). The reaction mixture was allowed to stir for 2 h. The reaction was quenched with excess MeOH (degassed), and the solvent was evaporated to dryness. The resulting oil was subjected to silica gel chromatography inside the drybox to get 55.1 mg (84 %) of an oil.

(34) $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 2.47 (ddd, J = 1.8, 9.6, 14.6 Hz, 2H, C6-H), 3.17 (td, J = 3.3, 14.8 Hz, 2H, C6'-H), 3.55 (t, J = 8.3 Hz, 2H, C4-H), 3.93 (dd, J = 3.6, 9.7 Hz, 2H, C2-H), 4.06 (t, J = 9.5 Hz, 2H, C3-H), 4.41 (AB, J = 9.4, 21.7 Hz, 4H), 4.48-4.60 (m, 2H, C5-H), 4.69 (AB, J = 6.5, 55.4 Hz, 4H), 5.63 (d, J = 3.4 Hz, 2H, C1-H), 7.00-7.23
Synthesis of 35:

A solution of starting sugar (100 mg, 0.193 mmol) and NBS (75.5 mg, 0.424 mmol) in 7.5 mL of CCl₄ was heated at 60 °C (bath temp). CaCO₃ (193 mg, 1.93 mmol) was added and the reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the resulting solid was extracted with EtOAc (5 mL x 3). The combined organic layer was evaporated and the resulting viscous oil was subjected to chromatography (EtOAc:Hex = 3:1) to get 72.2 mg (62 %) of a white solid (mp 212-2.5 °C).

(35) ¹H (250 MHz, CD₃OD): δ 3.42 (dd, J = 6.1, 11.2 Hz, H), 3.53 (dd, J = 2.5, 11.3 Hz, H), 3.68 (dd, J = 3.6, 9.5 Hz, H), 4.13 (t, J = 9.5 Hz, H), 4.42 (m, H), 5.09 (t, J = 9.6 Hz, H), 5.26 (d, J = 3.7 Hz, H), 7.47 (t, J = 8.0 Hz, 2H), 7.60 (t, J = 6.8 Hz, H), 8.05 (d, J = 8.1 Hz, 2H). (I-127, I-144)

Attempts to Alkylate Starting Dibromide 35 with Diphenylphosphide:
To a solution of Ph$_2$PH (83.8 mg, 0.45 mmol) in 1 mL of THF was added KH (18.0 mg, 0.45 mmol) portionwise under nitrogen. The resulting orange solution was stirred at rt for 30 min and this solution of potassium phosphide was slowly added to a solution of the starting bromide (44.7 mg, 0.075 mmol) in 2.0 mL of THF at rt. The reaction progress was checked with $^{31}$P NMR by taking portions of reaction mixture after 1 h, 3 h, and 48 h. A complex mixture resulted. (1-270)

*Synthesis of 37a:*

![Diagram of synthesis](image.png)

Ph$_2$PCl (79.5 mg, 0.360 mmol), DMAP (48.2 mg, 0.395 mmol), and 1 mL of dry toluene was placed in a 20 mL vial. To this solution was added a solution of the starting diol (100 mg, 0.172 mmol) in 1 mL of toluene dropwise over 30 min, maintaining the internal temperature < 30 °C. The mixture was stirred for additional 12 h, then the precipitate was filtered through a cotton plug and the solid was rinsed with toluene (1 mL x 2). The filtrate was concentrated to dryness in vacuo to get 37a as a white solid (150 mg, 92 %). The obtained material had good purity as judged by NMR.

(37a) $^1$H NMR (500 MHz, CDCl$_3$): δ (cyclohexyl peaks were omitted), 3.50 (dd, J = 3.0, 9.1 Hz, H, C2'-H), 3.58-3.64 (m, 3H, C6’e, C6e, C4-H), 3.69 (t, J = 10.3 Hz, H, C6’a-H), 3.79 (m, 2H, C6a, C5’-H), 3.93 (t, J = 9.4 Hz, H, C4’-H), 4.00 (td, J = 3.6, 9.4 Hz, H, C2-H), 4.10 (td, J = 5.2, 10.2 Hz, H, C5-H), 4.18 (t, J = 9.3 Hz, H, C3’-H), 4.40 (pseudo q, J
$= 8.9 \text{ Hz, H, C3-H}), 5.14 (d, J = 3.4 \text{ Hz, H, C1-H}), 5.33 (d, J = 3.0 \text{ Hz, H, C1'-H}), 7.00-7.70 (m, 20 \text{ H}); ^{13}\text{C NMR (125 MHz, CDCl}_3): \delta 22.0-37.7 \text{ (cyclohexyl, 14 C's), 61.3, 61.5, 64.1, 66.5, 72.97, 73.03, 73.4, 76.3, 77.7, 80.0, 94.7, 96.1, 99.6, 112.4, 127-143 \text{ (aromatic); } ^{31}\text{P NMR (100 MHz, CDCl}_3): \delta 116.5 \text{ (s), 113.3 (s). (II-107)}$

**Synthesis of 37b:**

The same procedure as in 37a was followed except the use of chloro-di-(3,5-dimethyl phenyl)phosphine. After flash column chromatography (ether 100 %), a white solid (mp 103-105 °C) was obtained in 85 % yield.

(37b) $^1\text{H NMR (250 MHz, CDCl}_3): \delta 0.82-2.00 \text{ (m, 30 H), 2.05 (s, 3H), 2.17 (s, 3H), 2.25 (s, 3H), 2.27 (s, 3H), 3.45-3.85 \text{ (m, 8H), 3.92 (t, J = 9.4 \text{ Hz, H), 3.95-4.12 \text{ (m, H), 4.16 (t, J = 9.3 \text{ Hz, H), 4.37 (q, J = 7.5 \text{ Hz, H), 4.93 (d, J = 3.5 \text{ Hz, H), 5.22 (d, J = 3.2 \text{ Hz, H), 6.60-7.25 \text{ (m, 12 H); } ^{31}\text{P NMR (100 MHz, CDCl}_3): \delta 117.7 \text{ (s), 117.6 (s). (II-80, II-128)}}}$

**Formation of Rh-Complex 38a:**

![Diagram of 37a and 38a]
To a solution of 37a (78.5 mg, 0.0825 mmol) in 1 mL of CH₂Cl₂ was added a solution of [Rh(nbd)₂]⁺BF₄⁻ (43.1 mg, 0.0825 mmol) in 1 mL of CH₂Cl₂. The yellow orange solution was stirred at rt for 1 h. The solvent was evaporated to get an yellow solid (quantitative).

(38a) ³¹P NMR (100 MHz, CDCl₃): δ 146.0 (dd, ¹Jₐₚ = 191.4 Hz, ²Jₚₚ = 38.5 Hz), 139.5 (dd, ¹Jₐₚ = 188.5 Hz, ²Jₚₚ = 38.4 Hz). (II-110)

**Formation of Rh-Comoplex 38b:**

![Diagram of Rh-complex 38b](image)

To a solution of 37b (77.3 mg, 0.0727 mmol) in CH₂Cl₂ (1 mL) was added [Rh*(nbd)₂]SbF₆⁻ (38.0 mg, 0.0727 mmol) and the reaction mixture was stirred at rt for 1 h. After evaporation of solvent an yellow solid of 38b was obtained (quantitative).

(38b) ³¹P NMR (100 MHz, CDCl₃): δ 142.6 (dd, ¹Jₐₚ = 183.7 Hz, ²Jₚₚ = 24.3 Hz), 135.1 (dd, ¹Jₐₚ = 178.2 Hz, ²Jₚₚ = 24.3 Hz). (II-130)

**Deprotection of Rh-Complex 38a: Preparation of 39a**

![Diagram of Rh-complex 39a](image)
a. Preparation of the resin: 20 mL (wet volume) of cationic exchange resin (AG 50 WX-8, 5 meq per dry gram) was placed in a pressure filter funnel and was rinsed with double-distilled water (500 mL), and it was immersed in distilled water overnight. Then the resin was further washed with distilled water (200 mL) and absolute MeOH (100 mL). The resulting material was dried under vacuum (0.2 mmHg) overnight.

b. Deprotection of the Rh(I) complex 38a: (using AG 50 WX-8 resin)

Absolute methanol was degassed before the experiment by freeze-thaw cycles. For example, 30 mL of absolute MeOH in a Schenck tube was freezeed under nitrogen atmosphere in a lig. N\textsubscript{2} dewar flask. After MeOH completely solidified, the tube was evacuated under a high vacuum (150 \textmu mHg) for 5 min, then the headspace was refilled with nitrogen. This process was repeated three times. Inside a drybox, [Rh(cod)(L\textsuperscript{5}])SbF\textsubscript{6} complex, 38a (110 mg, 0.0797 mmol) was dissolved in 2 mL of degassed absolute methanol. To the solution was added 60 mg of above prepared dry resin. The mixture was stirred vigorously and the progress of reaction was checked by \textsuperscript{31}P NMR, showing new sets peaks. After 12 h, the reaction was complete and the resin was filtered. The solvent was evaporated to dryness, when the volatile side-product (cyclohexanone) was also removed. An orange solid (87.3 mg, 96 \%) obtained showed satisfactory \textsuperscript{31}P NMR spectrum. If desired, the product obtained can be further purified by dissolving it in minimum amount of CH\textsubscript{2}Cl\textsubscript{2} and adding excess Et\textsubscript{2}O. The yellow precipitate formed was filtered and rinsed with ether.

c. Deprotection of the Rh(I) complex 38a: (using HBF\textsubscript{4})
To a solution of 13.3 mg (0.0105 mmol) of the \([\text{Rh(cod)}(19)]^+(\text{acac})^-\) in 0.5 mL of THF was added 2.0 \(\mu\)L of \(\text{HBF}_4\) (48 % aq. soln). The mixture was left stirring overnight. To the mixture was added 2 mL of ether, when an orange precipitate came out. The precipitate was filtered and washed with ether. \(^{31}\text{P}\) NMR in \(\text{MeOH-d}_4\) indicated that a clean compound was obtained. (II-72)

\[(39a)\] \([\text{Rh(cod)}(L)]^+\text{SbF}_6^-\) complex: \(^{31}\text{P}\) NMR (100 MHz, CD\(_3\)OD): \(\delta\) 140.4 (dd, \(^1J_{\text{Rh-P}} = 181.5\) Hz, \(^2J_{\text{P-P}} = 27.4\) Hz), 132.5 (dd, \(^1J_{\text{Rh-P}} = 178.9\) Hz, \(^2J_{\text{P-P}} = 27.2\) Hz); FAB-MS, \(m/z\) 921, calcd 921.75 for \(\text{C}_{44}\text{H}_{52}\text{O}_{11}\text{P}_{2}\text{Rh}\); \(m/z\) 813, calcd 813.57 for [M-\text{C}_{8}\text{H}_{8}]^-. (II-99, II-49)

\[(39a)\] \([\text{Rh(nbd)}(L)]^+\text{BF}_4^-\) complex: \(^{31}\text{P}\) NMR (100 MHz, CD\(_3\)OD/CDCl\(_3\), 1:1): \(\delta\) 144.7 (dd, \(^1J_{\text{Rh-P}} = 188.4\) Hz, \(^2J_{\text{P-P}} = 40.8\) Hz), 135.3 (dd, \(^1J_{\text{Rh-P}} = 185.1\) Hz, \(^2J_{\text{P-P}} = 41.0\) Hz);

\[(39a)\] \([\text{Rh(nbd)}(L)]^+\text{BF}_4^-\) complex: \(^1\text{H}\) NMR (500 MHz, CD\(_3\)OD/CDCl\(_3\), 1:1): \(\delta\) 2.99 (dd, \(J = 2.5, 12.0\) Hz, \(H\)), 3.05-3.11 (m, 2\(H\)), 3.15 (t, \(J = 10.0\) Hz, \(H\), C\(4'\)-\(H\)), 3.23 (dd, \(J = 3.4, 9.7\) Hz, \(H\), C\(2'\)-\(H\)), 3.31 (t, \(H\), C\(3'\)-\(H\)), 3.27-3.34 (m, 2\(H\)), 3.42-3.48 (m, 2\(H\)), 3.81 (td, \(J = 3.8, 9.2\) Hz, \(H\), C\(2\)-\(H\)), 3.92 (s br, 2\(H\), vinyl-\(H\) of nbd), 3.97 (dd, \(J = 9.0, 18.6\) Hz, \(H\), C\(3\)-\(H\)), 4.43 (s br, \(H\), vinyl-\(H\) of nbd), 4.53 (s br, \(H\), vinyl-\(H\) of nbd), 4.60 (d, \(J = 3.9\) Hz, C\(1\)-\(H\)), 4.72 (d, \(J = 3.5\) Hz, \(H\), C\(1'\)-\(H\)), 4.90 (s br, 2\(H\), vinyl-\(H\) of nbd), 7.03-7.90 (m, 20\(H\)).

d. Deprotection of \(\text{Rh(I)}\) complex \(38b\): (AG 50 WX-8 resin)

\[39b\] (\(Ar = \text{3,5-dimethylphenyl}\))

188
(39b) $[\text{Rh(cod)(L)}]^{+}\text{SbF}_6^{-}$ complex: $^{31}$P NMR (100 MHz, CD$_3$OD): $\delta$ 140.4 (dd, $^1J_{\text{Rh-P}} = 179.7$ Hz, $^2J_{\text{P-P}} = 27.8$ Hz), 130.0 (dd, $^1J_{\text{Rh-P}} = 176.8$ Hz, $^2J_{\text{P-P}} = 28.0$ Hz). (II-83)

**Determination of Distribution Constant between Water and Organic Solvents:** (I-102)

Three organic solvents were chosen for the study, CH$_2$Cl$_2$, EtOAc, and EtO.

Under an inert atmosphere, 39a Rh(I)(cod/SbF$_6$) (0.32 mg) was dissolved in 9.0 mL of degassed distilled water and 9.0 mL of CH$_2$Cl$_2$. The mixture was shaken and left for 3 days. In the same way, 0.17 mg of 39a Rh(I)(cod/SbF$_6$) was dissolved in 9.0 mL of degassed distilled water and 9.0 mL of EtOAc, and 0.24 mg of 39a Rh(I)(cod/SbF$_6$) was dissolved in 9.0 mL of degassed distilled water and 9.0 mL of EtO. After the three samples were equilibrated for 3 days, the layers were carefully separated by Pasteur pipet. For the organic layers, the solvent was evaporated completely and the residue was dissolved in doubley distilled water (9.0 mL). For the aqueous layers, the solvent was evaporated completely to remove all traces of organic solvents and was dissolved in doubly distilled water. The Rh atom contents of the even amount aliquots from thus prepared samples were measured by ICP-MS spectroscopy (Perkin-Elmer Sciex ELAN 6000 ICP-MS)

<table>
<thead>
<tr>
<th>solvent system</th>
<th>origin of sample</th>
<th>relative Rh amount (ppb)$^a$</th>
<th>ratio (org./aq.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>water/CH$_2$Cl$_2$</td>
<td>aqueous phase</td>
<td>17</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>CH$_2$Cl$_2$</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>water/EtOAc</td>
<td>aqueous phase</td>
<td>16</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>EtOAc</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>water/CH$_2$Cl$_2$</td>
<td>aqueous phase</td>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>ether</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

$a$ Error limit < 4 %.
Hydrogenation of Methyl N-acetamidoacrylate in D$_2$O:

In a Fisher-Porter bottle, a solution of methyl N-acetamidoacrylate (35.8 mg, 0.250 mmol) and [39a]Rh*(cod)SbF$_6^-$ (2.3 mg, 0.0010 mmol) in D$_2$O (4 mL, degassed) was prepared. The bottle was evacuated and filled with hydrogen gas (40 psi) and this evacuation-refilling was repeated 4 more times. With H$_2$ pressure of 40 psi, the reaction mixture was hydrogenated at rt with efficient stirring. After 12 h, the mixture was extracted with ether (5 mL x 3) and the organic layer was dried (MgSO$_4$) and evaporated to get 26.6 mg (74 %) of product. GLC analysis (chirasil-L-Val on WCOT fused silica 25 m x 0.25 mm) indicated that 19 % conversion with 17 %ee (S). A careful analysis of $^1$H NMR spectra of the product showed the following: The ratio of integration (per hydrogen) of $\alpha$-CH(quintet, H) peak of product at 4.59 ppm to that of CO$_2$CH$_3$ (s, 3H) peak of product at 3.75 ppm was 1:2. Assuming there was very little d, this indicated that 50 % of $\alpha$-protons was deuterated, while the other 50 % of product probably existed as a mixture of compounds b and c.

Composition of Products (by $^1$H NMR):

![Diagram of products with compositions]
Synthesis of 44:

To a solution of the tetrol 43 (0.500 g, 3.33 mmol) and imidazole (0.567 g, 8.32 mmol) in 3 mL of N,N-dimethylformamide was added at 0 °C a solution of tert-butyldimethylsilyl chloride (1.104 g, 7.32 mmol) in 3 mL of DMF. The mixture was kept stirring at 0 °C for 2.5 h. The mixture was diluted with 100 mL of ether and was washed with brine (50 mL x 2) and water (50 mL). The organic layer was dried (MgSO₄) and the solvent was removed to get 0.890 g (71 %) of a white crystalline solid (mp 79-81 °C, lit.¹² 78 °C).

(44) 'H NMR (500 MHz, CDCl₃): δ 0.00 (s, 12 H), 0.83(s, 18 H), 1.54-1.41 (m, 4H, C₃/C₄-H), 2.70 (s br, 2H, OH), 3.37 (dd, J = 7.2, 9.7 Hz, 2H, C₁/C₆-H), 3.54 (dd, J = 3.8, 9.9 Hz, 2H, C₁/C₆-H), 3.59 (m, 2H, C₂/C₅-H); '³C NMR (125 MHz, CDCl₃): δ -4.99 (Me), -4.94 (Me), 18.70 (quaternary), 26.29 (t-Bu), 29.50 (C₃), 67.62 (C₁), 72.16 (C₂).

Synthesis of 45:
To a stirred solution of diol 44 (258 mg, 0.681 mmol) and triethylamine (380 μL, 2.725 mmol) in 3 mL of CH₂Cl₂ at -20 °C was added dropwise methansulfonyl chloride (158.2 μL, 2.044 mmol). After complete addition, the mixture was stirred at -20 °C for further 30 min and was diluted with 20 mL of ether. The solution was washed with water (3 mL x 2), dried (MgSO₄), and the solvent was removed. The residue was purified on silica gel column (EtOAc/Hex = 1:4) to get a colorless oil, which became a crystalline solid (322.0 mg, 88 %) upon keeping in a refrigerator overnight (mp 74-76 °C).

(45) ¹H NMR (400 MHz, CDCl₃): δ 0.00 (s, 6H, Me-Si x 2), 0.01 (s, 6H, Me-Si x 2), 0.82 (s, 18H, t-Bu x 2), 1.71 (m, 4H, C3/C4-H), 3.00 (s, 6H, CH₃ in Mesyl), 3.66 (d, J = 5.2 Hz, 4H, C1/C6-H), 4.66 (t br, J = 5.4 Hz, 2H, C2/C5-H); ¹³C NMR (100 MHz, CDCl₃) δ -5.0, 18.8, 26.3, 26.8, 39.0, 65.5, 83.6.

Synthesis of 46:

Inside a glovebox a solution of 1,2-bisphosphinobenzene (34.0 mg, 0.24 mmol) in 2 mL of THF was placed in a Schlenk flask. The flask was taken outside the glove box and was cooled at -30 °C. To the mixture was added n-BuLi (0.21 mL of 2.5 M solution in hexane, 2.2 equiv.) via syringe at -30 °C and the mixture was stirred at that temperature for 1.5 h. To the resulting orange solution was added dropwise dimesylate 45 (256.1 mg, 0.48 mmol) in 2 mL of THF at -30 °C and the mixture was slowly warmed to room
temperature over 1 h. After cooling the mixture back to –30 °C, additional 2.2 equivalent of n-BuLi was added and the reaction mixture was allowed to stir overnight slowly warming up to rt. After 16 h, the flask containing the reaction mixture was taken inside the glove box and the mixture was filtered through a celite pad and the solid was rinsed with ether. The crude product was purified by flash chromatography on silica gel inside the drybox (Hex/ether = 95/5) to get 98.3 mg (50 %) of pure bisphospholane 25 as a colorless.

\[(46) \text{ }^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta\text{ -0.13 (s, 6H), -0.10 (s, 6H), 0.04 (s, 6H), 0.06 (s, 6H), 0.77 (s, 18H), 0.90 (s, 18H), 1.64 (m, 2H, C3-H), 1.72 (m, 2H, C4-H), 2.10 (m, 2H, C4'-H), 2.25 (m, 2H, C3'-H), 2.50 (m, 2H, C5'-H, C5-H), 2.82 (m, 2H, C2'-H, C2-H), 2.86 (t, } J = 10.3 \text{ Hz, 2H, C6-H), 3.63 (m, 2H, Cl-H), 3.68 (dd, } J = 4.2, 10.3 \text{ Hz, 2H, C6'-H), 3.82 (m, 2H, C1'-H), 7.23 (m, 2H), 7.39 (m, 2H); } ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta\text{ -4.94, -4.88, -4.81, -4.79, 18.66, 18.81, 26.33, 26.39, 30.1, 30.5, 41.4 (J}_{P,C} = 7.1 \text{ Hz), 42.1, 65.7 (J}_{P,C} = 4.8 \text{ Hz), 67.2 (J}_{P,C} = 27.2 \text{ Hz), 128.6, 131.9, 141.8; } ^{31}\text{P NMR (200 MHz, CDCl}_3\text{): } \delta\text{ -13.4 ppm (s).}

**Synthesis of 51:**

Inside a glove box, a solution of 46 (64.2 mg, 0.078 mmol) in 2 mL of MeOH was placed in a Schlenck tube. To the solution was added CF$_3$CO$_2$H (44 mg, 0.38 mmol, 5.0 equiv.)
and the mixture was stirred at rt for 10 h. The completion of deprotection can be checked by TLC (THF as eluent, Rf = 0.45). After evaporation of solvent to dryness, the residue was redissolved in MeOH and was filtered through a 2 cm pad of polystyrene-CH₂NEt₂ resin to remove residual acid. The solvent was removed and the resulting white solid was purified by flash chromatography inside the glove box using THF as eluent to get 84% of 51 as a white solid.

(51) ¹H NMR (500 MHz, CD₃OD): δ 1.55 (m, 2H, C4-H), 1.64 (m, 2H, C3-H), 2.08 (m, 2H, C3'-H), 2.30 (m, 2H, C4'-H), 2.41 (m, 2H, C2-H), 2.80-2.92 (m, 4H, C5-H, Cl-H), 3.49 (dd, J = 5.4, 11.1 Hz, 2H, C1'-H), 3.55-3.72 (m, 4H, C6-H, C6'-H), 7.31 (m, 2H), 7.46 (m, 2H); ¹³C NMR (125 MHz, CD₃OD): δ 29.6 (C4), 30.5 (C3), 42.1 (C5), 42.4 (J_P,C = 6.8 Hz, C2), 64.0 (J_P,C = 3.9 Hz, C1), 65.7 (J_P,C = 22 Hz, C6), 128.8, 132.1, 141.6 (J_P,C = 4.8 Hz); ³¹P NMR (202 MHz, CD₃OD) δ -12.4 ppm (s).

Synthesis of 47:

Inside a glove box, a solution of phenylphosphine (21.3 mg, 0.194 mmol) in 2 mL of THF was placed in a Schlenck tube. To the solution was added dropwise a solution of n-BuLi (2.5 M in Hex, 2.0 equiv.) at rt. The yellow suspension was allowed to stir for 1 h. To the resulting mixture was added a solution of the dimesylate 45 (104 mg, 0.194 mmol) in 1 mL of THF over 15 min. The mixture was allowed to stir at rt overnight, then the
reaction was quenched by addition of NH₄Cl. The white precipitate was filtered off and the filtrate was concentrated and was subjected to silica gel column chromatography (Et₂O/Hex = 1/10) to get 41.8 mg (48%) of a colorless oil.

(47) 

\[ ^1H \text{ NMR (400 MHz, } C_6D_6) : \delta -0.08 \text{ (s, 3H), -0.06 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.94 (s, 9H), 0.96 (s, 9H), 1.50 (m, 2H, C-3-H, C-4-H), 2.05 (m, H, C4-H), 2.23 (m, H, C3-H), 2.42 (m, H, C5-H), 2.76 (m, H, C2-H), 3.21 (ddd, J = 9.7, 9.7, 12.6 Hz, H, C6-H), 3.51 (ddd, J = 6.1, 8.7, 12.6 Hz, H, C6-H), 3.74 (ddd, J = 9.1, 12.3, 12.3 Hz, H, C1-H), 3.82 (ddd, J = 6.9, 12.3, 14.3 Hz, C1-H), 7.04-7.12 (m, 3H), 7.48-7.55 (m, 2H); \]

\[ ^{13}C \text{ NMR (100 MHz, } C_6D_6) : \delta -5.33, -5.24, -5.16, -5.11, 18.47, 18.60, 26.19, 26.19, 27.26 (C3), 31.8 (d, J_p,C = 3.7 Hz, C4), 44.2 (d, J_p,C = 11.1 Hz, C2), 44.7 (d, J_p,C = 14.0 Hz, C5), 64.1 (d, J_p,C = 3.1 Hz, C6), 67.1 (d, J_p,C = 40.1 Hz, C1), 128.13, 128.20, 128.82, 134.75 (d, J_p,C = 19.8 Hz); \]

\[ ^{31}P \text{ NMR (162 MHz, } C_6D_6) : \delta -4.2 \text{ (s). (III-129, III-141, III-157).} \]

**Synthesis of 55:**

Inside a glove box, cationic exchange resin (AG 50-WX8, 20 mg, prepared according to the procedure described for the synthesis of 39a) was added to a solution of 47 (30.2 mg, 0.0667 mmol) in MeOH-d₄ (1 mL). The resulting mixture was stirred at rt for 4 h. After filtration of resin, the resulting filtrate contained no \(^{31}\)P signal, indicating that all products had adsorbed in the resin. The resin was suspended in 2 mL of Et₃N and was stirred for 6
h. The resin was filtered off and the filtrate was evaporated to get 40.1 mg of crude mixture. This crude material contained a lot of impurities from resin.

(55) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.48-1.70 (m, 2H, C3, C4-H), 2.08-2.19 (m, H, C4-H), 2.30-2.40 (m, 2H, C3,C5-H), 2.86-2.95 (m, H, C2-H), 3.29 (ddd, H, C6-H), 3.44 (ddd, H, C6-H), 3.79 (ddd, H, C1-H), 3.86 (ddd, H, C1-H), 7.31-7.40 (m, 3H), 7.50-7.60 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 30.7 (C4), 31.5 (d, $^2$J$_{PC}$ = 3.3 Hz, C3), 44.3 (d, $^1$J$_{PC}$ = 8.2 Hz, C5), 44.5 (d, $^1$J$_{PC}$ = 11.7 Hz, C2), 63.7 (C6), 66.3 (d, $^2$J$_{PC}$ = 33 Hz, C1), 128.7 (d, $^1$J$_{PC}$ = 7.3 Hz), 129.7, 134.5, 134.6; $^{31}$P NMR (200 MHz, CDCl$_3$): $\delta$ -5.0 ppm. (III-193, III-146)

Synthesis of 48:

A mixture of tetrol 43 (500 mg, 3.33 mmol), Bu$_2$Sn(=O) (2.07 mg, 8.32 mmol) in toluene (60 mL) was refluxed for 9 h. After cooling to rt, benzyl bromide (2.00 mL, 18.4 mmol) was added and the mixture was refluxed for another 4 h. The mixture was cooled to rt, and poured into water (120 mL), and filtered through a Celite pad. The solvent was evaporated and the residue was subjected to flash chromatography (EtOAc/Hex = 1/1) to get 0.900 g (82 %) of a pale yellow oil.

(48) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.49-1.70 (m, 4H, C3, C4-H), 2.98 (s, 2H, OH), 3.36 (dd, J = 7.6, 9.4 Hz, 2H, C1, C6-H), 3.48 (dd, J = 3.6, 9.4 Hz, 2H, C1, C6-H), 3.83 (s br,
2H, C2, C5-H), 4.55 (s, 4H, PhCH2), 7.25-7.40 (m, 10 H); 13C NMR (125 MHz, CDCl3): δ 30.0, 70.8, 73.8, 74.9, 128.2, 128.9, 138.4. (III-108, III-149)

**Synthesis of Dimesylate from 49:**

\[
\begin{array}{c}
\text{BnO} \quad \text{OH} \quad \text{O} \quad \text{Bn} \\
\text{48} \quad \text{BnO} \quad \text{O} \quad \text{Ms} \quad \text{O} \quad \text{Bn} \\
\text{49}
\end{array}
\]

To a solution of starting diol (278 mg, 0.841 mmol) and Et3N (0.469 mL, 3.36 mmol) in 6 mL of CH2Cl2 at -20 °C was added dropwise methansulfonyl chloride (0.195 mL, 2.52 mmol). The reaction mixture was stirred at -20 °C for 30 min. The reaction mixture was quenched with 10 mL of water and was extracted with Et2O (10 mL x 3). The organic layer was dried (MgSO4), evaporated, and was subjected to flash chromatography (EtOAc/Hex = 1/1) to get 292 mg (71 %) of a colorless oil.

(49) 1H NMR (500 MHz, CDCl3): δ 1.75-1.89 (m, 4H, C3,C4-H), 3.04 (s, 6H, Ms), 3.55-3.70 (m, 4H, C1,C6-H), 4.55 (AB, 4H, PhCH2), 4.95 (s br, 2H, CHOMs); 13C NMR (125 MHz, CDCl3): δ 27.0, 39.0, 72.1, 73.7, 81.6, 128.3, 128.4, 129.0, 137.8. (III-165)

**Synthesis of 50:**

\[
\begin{array}{c}
\text{BnO} \quad \text{O} \quad \text{Ms} \quad \text{O} \quad \text{Bn} \\
\text{49} \quad \text{O} \quad \text{P} \quad \text{O} \quad \text{Bn} \\
\text{50}
\end{array}
\]

To a solution of PhPH2 (45.0 mg, 0.409 mmol) in 1 mL of THF was added KH (19.8 mg, 0.451 mmol) portionwise. When the evolution of gas stopped (5 min), this solution was
dropwisedly added to the solution of starting dimesylate (161 mg, 0.409 mmol) in 1.0 mL of THF. The mixture was stirred for 15 min, then additional KH (19.8 mg, 0.451 mmol) was added to the mixture. The mixture was stirred at rt for 6 h. A small amount of HCO$_2$H was added until the yellow color disappeared. Evaporation of solvent gave an oil, which was subjected to chromatography (Et$_2$O/Hex = 1/1) to get 46.7 mg (28 %) of an oil.

(50) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.60 (m, 2H), 2.18 (m, 2H), 2.50 (m, 2H), 3.00 (m, H), 3.15 (dd, H), 3.22 (m, H), 3.66 (dd, J = 9.4, 18.3 Hz, H), 3.80 (m, H), 4.33 (dd, J = 3.6, 15.4 Hz, 2H, PhCH$_2$), 4.60 (dd, J = 12.1, 15.0 Hz, 2H, PhCH$_2$), 7.10-7.48 (m, 13 H), 7.48-7.65 (m, 2H); $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ -2.6 ppm. (III-113)

Procedure for Formation of Rh Complexes:

To a solution of tetrahydroxybisphospholane 54 (12.4 mg, 33.5 µmol) in 1 mL of MeOH-$d_4$ was added [Rh(nbd)$_2$]SbF$_6$ (15.9 mg, 30.4 µmol) and the resulting bright orange solution was stirred for 30 min at room temperature. The solvent was evaporated from the reaction mixture and the resulting yellow solid was dried in vacuo.

[Rh (46Hnbd)]BF$_4$:

$^{31}$P NMR (200 MHz, CD$_3$OD): $\delta$ 63.0 ppm (d, $J_{\text{Rh-P}} = 154.4$ Hz)

[Rh (54Hnbd)]SbF$_6$:

$^{31}$P NMR (200 MHz, CD$_3$OD): $\delta$ 66.0 ppm (d, $J_{\text{Rh-P}} = 155.4$ Hz)
**Hydrogenation reactions (Typical procedure):**

In a drybox, a Fisher-Porter tube was charged with the dehydroamino acid substrate (0.20 mmol), appropriate solvent (2 mL) and pre-formed [Rh(nbd)(L)]X- (1 mol %). After being sealed, the tube was removed from the drybox and placed behind proper shielding. After five vacuum-refilling cycles with hydrogen, the tube was brought to the appropriate pressure (40 psi) of H2 and the mixture was vigorously stirred for 6 h. After removing the catalyst on a plug of silica gel, the ee’s of the product were determined by chiral GC (chirasil-L-Val on WCOT fused silica 25 m x 0.25 mm). Base-line separation of the enantiomers is observed and the ee’s are reproducible ± 0.5 %.

**Recycling and Reuse of Catalyst in Aqueous Media:**

Hydrogenation in aqueous media was also carried out as described in the previous paragraph. Water used for these experiments was degassed by repeated freeze-thaw cycles. This was done by cooling the Schlenck tube containing distilled water in a Dewar flask of liquid nitrogen, followed by evacuation under vacuum (0.1 mmHg). The flask was refilled with nitrogen. Then the water in the flask was allowed to thaw at rt and this process repeated two more times. In the recycling experiments, the Fisher-Porter bottle was taken inside the drybox, and the product was extracted into ether (5 mL x 4). To the aqueous layer was added 0.200 mmol of substrate and the same procedure was repeated for hydrogenation. After fourth cycle, additional degassed water (0.5 mL) was added to
compensate for the amount lost during extraction and evaporation. The gas chromatograms are shown in Figure 2.6.

Allylic Reduction of geranyl methyl carbonate (Eq. 7, p 59):

\[
\begin{align*}
\text{CO}_2\text{Me} \quad \longrightarrow \\
\text{HCO}_2\text{H}
\end{align*}
\]

To a solution of Pd\(_2\)(dba)\(_3\) (2.3 mg, 0.010 mmol Pd), chiral ligand (0.020 mmol), proton sponge (257 mg, 1.2 mmol, 1,8-bis(dimethylamino)naphthalene), HCO\(_2\)H (83 \(\mu\)L, 2.2 mmol) in 2 mL of THF was added geranyl methyl carbonate\(^{23}\) (212.3 mg, 1.00 mmol). The resulting mixture was stirred at rt for 1-24 h. After the reaction, the mixture was analyzed on a chiral GLC (B-PH column, \(\gamma\)-cyclodextrin, 10 m x 0.25 mm; 45 °C/30 min - 1 °C/min - 150 °C; (S)-isomer: \(t_r = 40.5\) min; (R)-isomer: \(t_r = 41.0\) min, internal isomer: \(t_r = 51.1\) min) and normal phase GC (HP crosslinked methylsilicon, 25 m x 0.2 mm x 0.33 \(\mu\)m; 75 °C/10 min - 10 °C/min - 250 °C; product: \(t_r = 5.1\) min, internal isomers: \(t_r = 6.4\) min, proton sponge: \(t_r = 23.3\) min). The results are tabulated in Table 2.9, Section 2.2.5.1.

Results (index to Notebooks)


Hydrovinylation of Styrene (Eq. 8, p 60):
To a solution of [Ni(allyl)Br]₂ (2.6 mg, 0.0072 mmol Ni) in CH₂Cl₂ (0.5 mL) was added a solution of the monophosphine ligand (0.0144 mmol) in CH₂Cl₂ (1.5 mL) at rt in a drybox. The resulting brown solution was added to a solution of Na⁺B[(3,5-di-CF₃-C₆H₃)]₄ (15.3 mg) in 2 mL of CH₂Cl₂. After stirring at rt for 1.5 h, the mixture was filtered through celite and the precipitate was rinsed with CH₂Cl₂ (1 mL). The filtrate was collected in a Schenk flask and the flask was sealed and taken out of the drybox. The solution of catalyst was cooled to –30 – –50 °C. Under ethylene (1 atm), styrene (0.100 mL, 1.00 mmol) was added dropwise to the catalyst solution. After stirring for 2.5 h at the temperature, the reaction mixture was quenched with 15 mL of saturated NH₄Cl aqueous solution and was extracted with CH₂Cl₂ (10 mL x3). The combined organic extracts were dried (MgSO₄), and passed through a small bed of silica gel. The resulting solution was analyzed by chiral HPLC (OJ, 100 % Hex, 0.3 mL/min). (R)-product: \( t_r = 18.9 \) min, (S)-product: \( t_r = 21.2 \) min (baseline separation). The results are in eq. 8, Section 2.2.5.2.

Results (Index to notebook)


Hydrovinylation of 4-Bromostyrene (Eq. 9, p 60):
The same procedure as above was followed. The resulting solution after workup was analyzed by chiral HPLC (OJ, 100 % Hex, 0.3 mL/min). *(R)-product:* $t_r = 19.6$ min, *(S)-product:* $t_r = 23.3$ min (baseline separation). (III-251, III-253) The results are tabulated in eq. 9, Section 2.2.5.2.
To a solution of geraniol (1.73 mL, 10.0 mmol) in THF (15 mL) was added KH (441 mg, 11.0 mmol) portionwise at rt. The reaction mixture was stirred for 2 h and propargyl bromide (1.02 mL, 12.0 mmol) was added after cooling the mixture to 0 °C. The resulting mixture was allowed to stir overnight. The reaction was quenched with addition of saturated aqueous solution of NH₄Cl (50 mL) and mixture was extracted with ether (50 mL x 3). The organic layer was dried (MgSO₄) and evaporated and the residue was subjected to flash chromatography to get 1.36 g (71 %) of a colorless oil.

(72) IR (neat): 3300, 2967, 2918, 2854, 2115, 1668, 1377, 1356, 1264, 1248 cm⁻¹;

¹H NMR (500 MHz, CDCl₃): δ 1.60 (s, 3H), 1.68 (s, 3H), 1.69 (s, 3H), 2.02-2.08 (m, 2H), 2.09-2.15 (m, 2H), 2.41 (t, J = 2.4 Hz, H), 4.09 (d, J = 6.9 Hz, 2H), 4.12 (d, J = 2.4 Hz, 2H), 5.09 (t br, J = 6.9 Hz, H), 5.33 (t br, J = 6.9 Hz, H); ¹³C (125 MHz, CDCl₃): δ 16.9, 18.1, 26.1, 26.8, 40.0, 57.1, 66.4, 74.5, 80.5, 120.3, 124.3, 132.1, 142.0; GC (70 °C/5 min – 20 °C/min – 250 °C); tᵣ = 11.3 min (98%).
To a solution of the starting ester 76\(^{10}\) (807 mg, 4.82 mmol) in 10 mL of toluene was added slowly a solution of DIBAL in toluene (5.63 mL of 1.5 M soln., 8.44 mmol) over 1 h, keeping the internal temperature below -65 °C. After the addition was complete, the mixture was further stirred for 1 h. The reaction was quenched with 3 mL of MeOH slowly at <-65 °C. The resulting suspension was poured into an ice-water (50 mL) with stirring over 15 min. The mixture was basified to pH 13 using 2 N NaOH solution. The aqueous layer was extracted with EtOAc (50 mL x 3) and the organic layer was dried (MgSO\(_4\)) and evaporated to get crude 77 as an oil. To a suspension of triphenylmethylphosphonium bromide (3.45 g, 9.65 mmol) in THF (25 mL) at -78 °C was added n-BuLi (5.72 mL of 1.6 M soln in Hex, 9.17 mmol) and the mixture was stirred for 2 h. To the mixture at -78 °C was added the solution of aldehyde 77 in 20 mL of THF. The reaction mixture was stirred for 1.5 h at - 78 °C, then warmed to rt for 30 min. The reaction mixture was filtered through a pad of celite-silica gel mixture. The solvent was removed and the residue was subjected to chromatography (EtOAc/Hex = 1/2) to get 188 mg (22 % from 76) of 74 as a colorless oil.

(74) IR (neat): 2950, 2361, 1644, 1434, 1155, 1095 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.52-1.90 (m, 3H, ring CH\(_2\)), 1.91-2.02 (m, H, ring CH\(_2\)), 2.18 (t, \(J = 2.4\) Hz, H, C=CH), 2.57 (q, \(J = 8.9 \) Hz, H, NCH\(_2\)CH\(_2\)), 2.94 (q, \(J = 8.0 \) Hz, H, NCH), 3.06 (td, \(J = 2.5, 8.4\) Hz, H, NCH\(_2\)CH\(_2\)), 3.30 (dd, \(J = 2.3, 17.0\) Hz, H, NCH\(_2\)C=CH), 3.52 (dd, \(J = 2.4, 17.0\) Hz, H, NCH\(_2\)C=CH).
Hz, NCH₂C=CH), 5.12 (dd, J = 1.7, 10.0 Hz, H, CH=CH₂), 5.20 (dd, J = 1.7, 17.0 Hz, H, CH=CH₂), 5.64 (ddd, J = 8.6, 10.0, 17.2 Hz, H, CH=CH₂); ¹³C (125 MHz, CDCl₃): δ 22.5 (ring CH₂), 31.9 (ring CH₂), 40.5 (NCH₂CH₂), 52.3 (NCH₂C=CH), 66.0 (NCH), 72.9 (C=CH), 79.0 (C=CH), 117.8 (CH=CH₂), 140.0 (CH=CH₂); HRMS calcd for [M+H]⁺ 136.1121, found 136.1119. (IV-165, K.C.¹⁰)

To a solution of starting ester 76¹⁰ (418 mg, 2.50 mmol) in 5 mL of toluene was added slowly a solution of DIBAL in toluene (2.00 mL of 1.5 M soln., 3.00 mmol) over 1 h, keeping the internal temperature below -65 °C. After the addition was complete, the mixture was further stirred for 1 h. The reaction was quenched with 1 mL of MeOH, which was added slowly at <-65 °C. The resulting suspension was poured into an ice-water (20 mL) with stirring over 15 min. The mixture was basified to pH 13 using 2 N NaOH solution. The aqueous layer was extracted with EtOAc (20 mL x 3) and the organic layer was dried (MgSO₄) and evaporated, and the residue was dissolved in THF (10 mL) at -78 °C. To this solution was added vinyl magnesium bromide (5.50 mL of 1.0 M soln in THF) and the reaction mixture was stirred at -78 ~ 0 °C for 3 h. The reaction was quenched with sat. NH₄Cl solution (10 mL) then basified to pH 8-9 using 2 N NaOH solution. The layers were separated and the aqueous layer was extracted with Et₂O (10 mL x 4). The combined organic layer was dried (MgSO₄), evaporated, and the residue was subjected to column chromatography (EtOAc/Hex = 1/1) to get 29.8 mg (7 %) of the
minor isomer and 144 mg (35 %) of the major isomer along with 159 mg (45 %) of a mixture of two.

(75-major isomer) IR (neat): 3418, 3280, 2960, 2890, 2340, 2096, 1706, 1641, 1434, 1330, 1200, 1120, 996, 922 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.65-1.88 (m, 2H, 3H, ring CH₂), 1.88-1.97 (m, H, ring CH₂), 2.21 (s br, H, C≡CH), 2.81 (m, H, NCH₂CH₂), 2.97 (m, H, NCH), 3.08 (m, H, NCH₂CH₂), 3.50-3.68 (m, 2H, NCH₂C≡C), 3.91 (s br, C=OH), 5.16 (td, J = 1.6, 10.5 Hz, H, CH=CH₂), 5.35 (td, J = 1.6, 17.2 Hz, H, CH=CH₂), 5.88 (ddd, J = 5.2, 10.5, 17.2 Hz, H, CH=CH₂); ¹³C NMR (125MHz, CDCl₃): δ 24.8 (ring CH₂), 29.7 (ring CH₂), 44.0 (NCH₂C≡C), 53.8 (NCH₂CH₂), 65.5 (NCH), 72.7 (C≡CH), 75.0 (CHOH), 80.2 (C≡CH), 115.6 (CH=CH₂), 140.2 (CH=CH₂); HRMS calcd for [M+H]+ 166.1226, found 166.1229. (IV-168)

\[
\text{N} \quad \text{N} \\
\text{H} \quad \text{H} \\
\text{75} \quad \text{75} \\
\text{OH} \quad \text{OTBS}
\]

To a solution of 75 (50.0 mg, 0.304 mmol) and imidazole (31 mg, 0.46 mmol) in 1 mL of CH₂Cl₂ was added TBDMS-Cl (55 mg, 0.36 mmol) at rt. The reaction mixture was stirred at rt for 7 h. The reaction mixture was diluted with Et₂O (10 mL) and brine (10 mL) was added to the mixture. The aqueous layer was extracted with Et₂O (10 mL x 3). The organic layer was dried (MgSO₄), evaporated and the residue was subjected to flash chromatography (EtOAc/Hex = 1/16) to get 66.6 mg (78 %) of a colorless oil.
(75') $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.05 (s, 3H, Me), 0.08 (s, 3H, Me), 0.90 (s, 9H, Me), 1.50-1.78 (m, 4H, ring CH$_2$), 2.17 (s br. H, C=CH), 2.60 (m, H), 2.78 (m, H), 2.98 (m, H), 3.56 (m, 2H), 4.16 (m, H), 5.13 (m, H, $J = 10.5$ Hz, H), 5.24 (d, $J = 17.2$ Hz, H), 5.90 (ddd, $J = 5.3$, 10.5 Hz, 16.4 Hz) (IV-180)

Synthesis of Bimetallative Reagents:

Bu$_3$Sn-SiMe$_3$

Anhydrous THF (10 mL) and $i$Pr$_2$NH (0.8 mL, 5.70 mmol) was stirred under nitrogen at 0 °C while n-BuLi (5.0 mmol, 1.6 M in hexane) was added dropwise. The resulting solution was stirred for additional 5 min and Bu$_3$SnH was added (1.45 g, 5.0 mmol) via syringe. After ca. 15 min at 0 °C, the reaction was complete and TMS-Cl (0.597 g, 5.5 mmol) was added to the mixture. The resulting mixture was warmed to rt and further stirred overnight. After evaporation of the solvent, the crude product was redissolved in hexane and filtered through silica gel and the solid was rinsed with extra 20 mL of hexane. $^1$H NMR indicated the clean desired product (95% yield). (IV 68) (K.C.)

Triethylamine (27.9 mL, 200 mmol) was dissolved in 65 mL of dry hexane and the solution was cooled in an ice-bath. Boron trichloride (100 mL of 1.0 M solution in hex, 100 mmol) was added slowly with vigorous stirring, when a white precipitate came out.
The mixture was warmed to RT and solution of N,N-dimethyl ethylenediamine (10.4 mL, 100 mmol) in 45 mL hexane was added slowly. The resulting mixture was refluxed 3 h and was filtered. The solid was washed with dry hexane and the solvent was stripped off the combined filtrate. The residue was distilled under reduced pressure (42 °C, 11 mmHg, \textit{lit.}\textsuperscript{12a} 72 °C, 45 mmHg) to get ~8.0 g of yellowish liquid (The product obtained makes fumes when exposed to atmosphere.) and this portion was redistilled to get 2.57 g (20 %) of pure material. (K.C.)\textsuperscript{12a}

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 2.63 (s, 6H), 3.20 (s, 4H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 33.4 (CH\textsubscript{3}), 50.6 (CH\textsubscript{2}); \(^{11}\)B NMR (128 MHz, CDCl\textsubscript{3}): \(\delta\) 27.0.

\[
\begin{array}{c}
\text{Me}_3\text{Sn-B} \\
\text{Me}
\end{array}
\]

Prepared according to the literature from the boron chloride from the previous experiment in 73 % yield.

\(^1\)H NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta\) 0.25 (s, 9H), 2.61 (s, 6H), 2.96 (s, 4H); \(^{13}\)C NMR (100 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta\) \(-11.6\), 35.2 (CH\textsubscript{3}), 52.6 (CH\textsubscript{2}); \(^{11}\)B NMR (128 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta\) 39.4 (\(J_{\text{Sn-B}} = 446\) Hz); \(^{119}\)Sn NMR (186 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta\) \(-110.7\) (\(J_{\text{Sn-B}} = 2088\) Hz). (K.C.)\textsuperscript{12b} (V161)

\textit{Attempted Reaction of 68 with Bu\textsubscript{3}Sn-SiMe\textsubscript{3}:}

To a solution of Pd\textsubscript{2}(dba)\textsubscript{3} (4.6 mg, 0.010 mmol Pd) and tris-(o-tolyl)phosphine (6.1 mg, 0.020 mmol) was dissolved in 2 mL of C\textsubscript{6}D\textsubscript{6}. To the mixture was added Bu\textsubscript{3}Sn-SiMe\textsubscript{3} (400 mg, 1.10 mmol) followed by the alkynyl aldehyde 68\textsuperscript{7} (98.1 mg, 1.00 mmol). The
reaction was monitored by $^1$H NMR. After 30 h at rt, no reaction was observed in the $^1$H NMR spectrum, and starting material remained unchanged. (IV-91)

**Reaction of 69 with Bu$_3$Sn-SiMe$_3$:**

![Chemical structure](image)

In a 20 mL vial, Pd$_2$(dba)$_3$ (4.6 mg, 0.010 mmol Pd) and tris-(o-tolyl)phosphine (6.1 mg, 0.020 mmol) was dissolved in 2 mL of C$_6$D$_6$. To the mixture was added Bu$_3$Sn-SiMe$_3$ (400 mg, 1.10 mmol) followed by alkynyl aldehyde 69 (112 mg, 1.00 mmol). The reaction was monitored by $^1$H NMR. After 30 h, the reaction was complete, and the solvent was removed and the crude product was subjected to column chromatography (EtOAc/Hexane = 1/12) to get 0.310 g (65 %) of 78 as a pale yellow oil.

(78) IR (neat): 2957, 2853, 2726, 1731, 1637, 1561, 1464, 1376, 1247, 1102, 844 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.11 (s, 9H), 0.82-0.91 (m, 15 H), 1.27-1.40 (m, 6H), 1.40-1.55 (m, 6H), 2.67 (td, $J = 6.2$, 1.9 Hz, 2H), 3.73 (t, $J = 6.2$ Hz, 2H), 4.06 (m, 2H), 6.59 (s, $^3$J$_{Sn-H} = 174$ Hz), 9.80 (t, $J = 1.9$ Hz, H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ -2.1, 8.9, 11.5, (Me), 25.3, 27.0, 41.8, 61.6 (CCH), 81.2 (CCH), 142.2, 159.0, 199.0; HRMS calcd for [M+Na]$^+$ 499.2025, found 499.2045; The regiochemistry was confirmed by NOE difference spectra. (IV-90)

**Attempted Reaction of 70 with Bu$_3$Sn-SiMe$_3$:**

To a solution of Pd$_2$(dba)$_3$ (1.8 mg, 0.0040 mmol Pd) and tris-(o-tolyl)phosphine (1.2 mg, 0.0040 mmol) in 1 mL of C$_6$D$_6$ was added Bu$_3$Sn-SiMe$_3$ (80 mg, 0.22 mmol) followed by
alkynyl aldehyde 70\(^8\) (19.2 mg, 0.200 mmol). The reaction was monitored by \(^1\)H NMR. After 4 days at rt, no reaction was observed in the \(^1\)H NMR spectrum and starting material remained unchanged. (IV-101)

**Reaction of 71(E) with Bu\(_3\)Sn-SiMe\(_3\):**

![Reaction diagram](image)

To a solution of Pd\(_2\)(dba)\(_3\) (1.8 mg, 0.0020 mmol Pd) and \(\text{tris(o-tolyl)}\)phosphine (1.2 mg, 0.0040 mmol) in 1 mL of C\(_6\)D\(_6\) was added Bu\(_3\)Sn-SiMe\(_3\) (80 mg, 0.22 mmol) followed by enyne 71(E)\(^7\) (30.8 mg, 0.200 mmol). The reaction was monitored by \(^1\)H NMR. After 4 days at rt, \(^1\)H NMR indicated a good conversion into 79 and no starting material was left. (79) IR (neat): 2954, 2852, 1729, 1666, 1463, 1376, 1340, 1304, 1248, 1169, 1124, 1072, 1036, 965, 839 cm\(^{-1}\); \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 0.29 (s, 9H), Bu\(_3\)Sn peaks are omitted, 3.49 (s, 3H, CO\(_2\)Me), 3.80 (dd, \(J = 2.0, 4.0\) Hz, 2H, OCH\(_2\)CH=CHCO\(_2\)Me ), 4.09 (d, \(J = 1.6\) Hz, 2H), 6.33 (td, \(J = 2.2, 15.6\) Hz, H, C=CHCO\(_2\)Me), 6.77 (d, \(J = 1.4\) Hz, \(^3\)J\(_{\text{Sn-H}} = 160\) Hz, H, C(Sn)=C(Si)H), 7.06 (td, \(J = 4.2, 15.9\) Hz, H, RCH=CHCO\(_2\)Me); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 0.5 (TMS), 11.5 (SnBu\(_3\)), 14.0 (SnBu\(_3\)), 27.9 (SnBu\(_3\)), 29.6 (SnBu\(_3\)), 51.9, 68.8, 83.5, 121.2, 145.1, 145.4, 161.4, 167.2 (ester); HRMS calcd for [M+Na]\(^+\) 541.2131, found 541.2149. (IV-100)

**Reaction of 71(Z) with Bu\(_3\)Sn-SiMe\(_3\):**

210
To a solution of Pd\textsubscript{2}(dba)\textsubscript{3} (1.8 mg, 0.0020 mmol Pd) and tris-(o-tolyl)phosphine (2.4 mg, 0.0040 mmol) in 1 mL of C\textsubscript{6}D\textsubscript{6} was added Bu\textsubscript{3}Sn-SiMe\textsubscript{3} (80 mg, 0.22 mmol) followed by enyne 71(Z)\textsuperscript{7} (30.8 mg, 0.200 mmol). The reaction was monitored by \textsuperscript{1}H NMR. After 4 days at rt, \textsuperscript{1}H NMR indicated a mixture of 80 and starting material 71(Z) (ratio 1/1).

(80) \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): \delta SiMe\textsubscript{3}, SnBu\textsubscript{3} peaks are omitted, 3.41 (s, 3H, CO\textsubscript{2}Me), 3.90 (d, J = 2.2 Hz, 2H), 4.19 (d, J = 1.4 Hz, 2H), 5.70 (td, J = 2.6, 11.6 Hz, H, C=CHCO\textsubscript{2}Me), 6.25 (td, J = 4.8, 11.6 Hz, H, RCH=CHCO\textsubscript{2}Me), 6.81 (s, \textsuperscript{3}J\textsubscript{Sn-H} = 160 Hz, H, C(Sn)=C(Si)H). (IV-102)

\textit{Reaction of 72 with Bu\textsubscript{3}Sn-SiMe\textsubscript{3} (eq. 3)}

\[ 72 \rightarrow \]

To a solution of Pd\textsubscript{2}(dba)\textsubscript{3} (0.9 mg, 0.0010 mmol Pd) and PCy\textsubscript{3} (0.0020 mmol, see below) in 1 mL of C\textsubscript{6}D\textsubscript{6} was added Bu\textsubscript{3}Sn-SiMe\textsubscript{3} (40 mg, 0.11 mmol) followed by the enyne 72 (19.2 mg, 0.100 mmol). The reaction was monitored by \textsuperscript{1}H NMR. Among the various ligands used (PCy\textsubscript{3}, P(C\textsubscript{6}F\textsubscript{3})\textsubscript{3}, PPh\textsubscript{3}, P(OPh)\textsubscript{3}, and without ligand), the use of PCy\textsubscript{3} gave the best conversion. The solvent was evaporated from the reaction mixture and the residue was subjected to column chromatography (Hex, 100 %) to get a colorless oil (48.7 mg, 90 %).
(81) IR (neat): 2956, 2871, 1726, 1591, 1465, 1377, 1247, 1156, 1080, 844 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.12 (s, 9H), 0.82-1.00 (m, 15H), 1.32-1.40 (m, 6H), 1.40-1.56 (m, 6H), 1.61 (s, 3H), 1.65 (s, 3H), 1.68 (s, 3H), 2.00-2.06 (m, 4H), 3.95 (d, J = 6.7 Hz, 2H), 4.04 (s, J_Sn-H = 36 Hz, 2H), 5.11 (t br, J = 6.7 Hz, H), 5.35 (t br, J = 6.2 Hz, H), 6.61 (s, J_Sn-H = 180 Hz, H); ¹³C NMR (125 MHz, CDCl₃): δ 0.5, 11.5, 14.1, 16.9, 18.1, 26.1, 26.9, 27.9, 29.6, 40.0, 66.9, 82.4, 121.6, 124.5, 132.0, 139.6, 144.0, 162.6; HRMS calcd for [M+Na]⁺ 579.3015, found 579.3017. (IV301-2)

**Attempted Reaction of 73 with Bu₃Sn-SiMe₃:**

To a solution of Pd₂(dbq)₃ (0.9 mg, 0.0010 mmol Pd) and P(C₆F₅)₃ (0.0020 mmol) in 1 mL of C₆D₆ was added Bu₃Sn-SiMe₃ (40 mg, 0.11 mmol) followed by enyne 73⁹ (17.2 mg, 0.100 mmol). The reaction was monitored by ¹H NMR. Various ligands were used (PCy₃, P(C₆F₅)₃, PPh₃, and P(OPh)₃) under the same conditions otherwise. None of these ligands gave a clean conversion after 24 h at rt and additionally 12 h at 60 °C. The purification of the complex reaction mixture (by ¹H NMR) was attempted; No identifiable product was isolated. (V-8, V-44)

**Reaction of 74 with Bu₃Sn-SiMe₃:**

212
To a solution of Pd$_2$(dba)$_3$ (3.4 mg, 0.0075 mmol Pd) and tris-(o-tolyl)phosphine (4.6 mg, 0.015 mmol) in 1 mL of C$_6$D$_6$ was added Bu$_3$Sn-SiMe$_3$ (120 mg, 0.33 mmol) followed by enyne 74 (40.6 mg, 0.300 mmol). The reaction was monitored by $^1$H NMR. After 20 h at 60 °C, the $^1$H NMR spectrum indicated that the starting material had disappeared. Careful chromatography on a silica gel column (Hex 100 % ~ EtOAc/Hex, 1/4) gave 25.0 mg (17 %) of acyclic adduct 82 and 12.0 mg (6.2 %) of bis-adduct 83.

(82) IR (neat): 3077, 2954, 2787, 1643, 1462, 1422, 1376, 1344, 1290, 1152, 1104, 1072, 993, 919, 837 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.10 (s, 9H), SnBu$_3$ peaks are omitted, 1.40-1.50 (m, H, ring CH$_2$), 1.60-1.72 (m, H, ring CH$_2$), 1.82-1.92 (m, 2H, NCH$_2$CH$_2$ & ring CH$_2$), 2.53 (d, $J = 12.3$ Hz, H, NCH$_2$CSn), 2.61 (dd, $J = 8.2$, 10.0 Hz, H, NCH), 2.86 (td, $J = 2.3$, 10.0 Hz, H, NCH$_2$CH$_2$), 3.76 (d, $J = 12.1$ Hz, H, NCH$_2$CSn), 5.06 (d, $J = 8.0$ Hz, H, CH=CH$_2$), 5.09 (d, $J = 15.2$ Hz, CH=CH$_2$), 5.72 (ddd, $J = 8.7$, 10.0, 15.2 Hz, H, CH=CH$_2$), 6.49 (s, $^3$J$_{Sn-H} = 176$ Hz, H, SiCH=C); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 0.6 (SiMe$_3$), 11.2 (SnBu$_3$), 14.1 (SnBu$_3$), 22.4 (ring CH$_2$), 28.0 (SnBu$_3$), 29.7 (SnBu$_3$), 31.9 (ring CH$_2$), 53.8 (NCH$_2$CH$_2$), 69.2 (NCH), 71.5 (NCH$_2$CSn), 116.6 (CH=CH$_2$), 141.4 (CH=CH$_2$), 142.2 (CHSi), 165.8 (CSn); HRMS calcd for [M+H]$^+$ 500.2729, found 500.2729; selected nOe contact supports the double bond geometry shown. (IV-179)
(83) IR (neat): 3077, 2955, 2785, 1643, 1584, 1462, 1246, 1147, 1112, 993, 918, 891, 837 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.07 (s, 9H), SnBu\(_3\) peaks are omitted, 1.60-1.95 (m, 8H, ring CH\(_2\)), 1.95-2.05 (m, 2H, NCH\(_2\)CH\(_2\)), 2.41 (d, \(J = 16.2\) Hz, H, NCH\(_2\)CSn or NCH\(_2\)CSi), 2.50 (d, \(J = 15.8\) Hz, H, NCH\(_2\)CSn or NCH\(_2\)CSi), 2.68-2.78 (m, 2H, NCH\(_2\)), 3.15-3.25 (m, 2H, NCH\(_2\)CH\(_2\)), 3.47 (d, \(J = 16.0\) Hz, H, NCH\(_2\)CSn or NCH\(_2\)CSi), 3.57 (d, \(J = 15.9\) Hz, H, NCH\(_2\)CSn or NCH\(_2\)CSi), 5.04 (d, \(J = 10.0\) Hz, 2H, CH=CH\(_2\)), 5.12 (d, \(J = 17.1\) Hz, 2H, CH=CH\(_2\)), 5.57 (s, H, C=CHSi), 5.68 (t, \(J = 9.6, 18.0\) Hz, 2H, CH=CH\(_2\)), 5.93 (s, \(J_{Sn-H} = 70\) Hz, C=CHSn), \(^{13}\)C NMR (125 MHz, CDCl\(_3\)):
\(\delta\) 0.00 (TMS), 9.8 (SnBu\(_3\)), 13.3 (SnBu\(_3\)), 22.00, 22.03, 27.0 (SnBu\(_3\)), 28.9 (SnBu\(_3\)), 30.97, 30.99, 53.25, 53.30, 62.0, 68.1, 68.4, 115.6, 115.7, 122.2, 122.8, 140.81, 140.84;
HRMS calcd for [M+Na]\(^+\) 657.3597, found 657.3597. (IV-179)

**Reaction of 8 with Bu\(_3\)Sn-SiMe\(_3\):**

\[\xrightarrow{\text{Pd}(\text{dba})_3, \text{P}(\text{C}_6\text{F}_5)_3} \]

To a solution of Pd\(_2\)(dba)\(_3\) (2.9 mg, 0.0062 mmol Pd) and P(C\(_6\)F\(_5\))\(_3\) (6.6 mg, 0.012 mmol) in 1 mL of C\(_6\)D\(_6\) was added Bu\(_3\)Sn-SiMe\(_3\) (100 mg, 0.275 mmol) followed by enyne 75 (41.0 mg, 0.250 mmol). The reaction was monitored by \(^1\)H NMR. After 2 days at 60 °C, the \(^1\)H NMR spectrum indicated that the conversion into 84 did not go further. The solvent from the mixture was evaporated and the residue was subjected to flash chromatography to get 27.9 mg (21 %) of 84 and 30.0 mg (79 %) of starting 75.
(84) IR (neat): 3426, 2957, 2872, 1713, 1638, 1463, 1376, 1247, 1123, 1072, 993, 919, 837, 734 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.11 (s, 9H, TMS), SnBu\(_3\) peaks are omitted, 1.61 (m, H, ring CH\(_2\)), 1.72 (m, 2H, ring CH\(_2\)), 1.86 (m, H, ring CH\(_2\)), 2.37 (td, \(J = 7.1, 10.7\) Hz, H, NCH\(_2\)CH\(_2\)), 2.71 (m, H, NCH), 2.89 (ddd, \(J = 5.8, 6.8, 10.8\) Hz, H, NCH\(_2\)CH\(_2\)), 3.13 (ddd, \(J = 1.0, 14.0\) Hz, \(J_{Sn-H} = 40\) Hz, H, NCH\(_2\)CSn), 3.48 (s br, H, OH), 3.56 (dd, \(J = 1.8, 14.2\) Hz, \(J_{Sn-H} = 22\) Hz, H, NCH\(_2\)CSn), 3.74 (s, \(J_{Sn-H} = 6.1\) Hz, H, CHOH), 5.12 (td, \(J = 1.3, 10.6\) Hz, H, CH=CH\(_2\)), 5.29 (td, \(J = 1.4, 17.3\) Hz, H, CH=CH\(_2\)), 5.82 (ddd, \(J = 5.8, 10.5, 16.8\) Hz, H, CH=CH\(_2\)), 6.62 (s, \(J_{Sn-H} = 167\) Hz, H, CHSi); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 0.6 (SiMe\(_3\)), 11.5 (SnBu\(_3\)), 14.1 (SnBu\(_3\)), 24.1 (ring CH\(_2\)), 27.6 (ring CH\(_2\)), 27.9 (SnBu\(_3\)), 29.7 (SnBu\(_3\)), 53.5 (NCH\(_2\)CH\(_2\)), 69.8 (NCH), 72.2 (NCH\(_2\)CSn), 74.5 (CHOH), 115.9 (CH=CH\(_2\)), 139.7 (CH=CH\(_2\)), 144.4 (CSi), 163.1 (CSn); HRMS calcd for [M+Na]\(^+\) 552.2654, found 552.2643; Selected nOe confirmed the double bond geometry shown. (IV-173)

\textit{Reaction of 8' with Bu\(_3\)Sn-SiMe\(_3\):}

\[
\begin{align*}
\text{To a solution of Pd}_2(\text{dba})_3 \text{ (1.9 mg, 0.0040 mmol Pd) and tris-(o-tolyl)phosphine (2.5 mg,} \\
0.0080 \text{ mmol) in 1 mL of C}_6\text{D}_6 \text{ was added Bu}_3\text{Sn-SiMe}_3 \text{ (67 mg, 0.18 mmol) followed by} \\
eneyne 75' \text{ (46.6 mg, 0.167 mmol). The reaction was monitored by } \text{H NMR. After 24 h} \\
at 60 \text{ °C, the } \text{H NMR spectrum indicated that the starting material had mostly}
\end{align*}
\]

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disappeared, and the formation of adduct 85 was observed. After evaporation of solvent, the residue was subjected to flash chromatography (Hex, 100%) to get 43.8 mg (41%) of 85 as a colorless oil.

(85) IR (neat): 2956, 2928, 2856, 1642, 1463, 1376, 1360, 1342, 1249, 1128, 1077, 1030, 1005, 916, 837, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.04 (s, 3H, TBS), 0.11 (s, 9H+3H, TBS, TMS), 0.89 (s, 9H, TBS), SnBu₃ peaks are omitted, 1.52-1.70 (m, 4H), 2.06 (m, H, NCH₂CH₂), 2.61 (m, H, NH), 2.83 (t, J = 6.9 Hz, H, NCH₂CH₂), 3.03 (d, J = 12.6 Hz, H, NCH₂Sn), 3.71 (d, J = 12.6 Hz, H, NCH₂CSn), 4.28 (s, H, CHOH), 5.12 (d, J = 10.6 Hz, H, CH=CH₂), 5.29 (d, J = 17.5 Hz, H, CH=CH₂), 6.06 (ddd, J = 2.3, 10.6, 17.3 Hz, H, CH=CH₂), 6.59 (s, ²³JSn-H = 164 Hz, H, CHSi); ¹³C NMR (125 MHz, CDCl₃): δ -4.38 (TBS), -4.33 (TBS), 0.7 (TMS), 11.6 (SnBu₃), 14.1 (SnBu₃), 18.7 (CMe₃), 24.5 (ring CH₂), 25.6 (ring CH₂), 26.3 (C(CH₃)₃), 28.0 (SnBu₃), 29.8 (SnBu₃), 55.3 (NCH₂CH₂), 69.3 (NCH), 73.6 (NCH₂CSn), 73.7 (CHOH), 114.4 (CH=CH₂), 138.6 (CH=CH₂), 144.7 (CSn), 164.5 (CSi); HRMS calc'd for [M+Na]+ 666.3519, found 666.3531; nOe difference spectra confirmed the double bond geometry shown above.

(Synthesis of an L-Proline Derived Diyne Substrate:

N-propargyl-2-(2,2-dibromovinyl)-pyrrolidine, 91

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A solution of 76^10 (0.836 g, 5.0 mmol) in 10 mL of dry toluene was cooled to −78 °C. A solution of DIBAL (1.6 M in toluene, 3.75 mL, 6.0 mmol) which was pre-cooled at −78 °C was transferred to the above solution via cannula over 20 min period, keeping the internal temperature below −65 °C. The resulting solution was stirred for 2.5 h at −78 °C. The reaction was quenched by addition of saturated solution of sodium bisulfite (NaHSO₃, 6 mL). The mixture was swirled for 15 min and the layers were separated. The toluene layer was extracted twice with 5 mL portions of bisulfite solution, and the combined aqueous layers were basified to pH 11-13 and were extracted with ether (10 mL x 7) (Note: Initially formed emulsion disappears upon basifying) The combined organic layers were dried (MgSO₄) and evaporated and the residue was used in the next step.

Carbon tetrabromide (3.316 g, 10 mmol) and triphenylphosphine (5.246 g, 20 mmol) was dissolved in CH₂Cl₂ (20 mL) at 0 °C and was stirred for 5 min. The crude solution of aldehyde 77 in 5 mL of CH₂Cl₂ from previous procedure was added to the mixture in an ice bath. Initially the yellow suspension became dark brown upon addition of the aldehyde. After stirring for 30 min, the reaction was quenched by adding 20 mL of water. The layer was separated and the aqueous layer was basified to pH 13 and was extracted with ether (20 mL x 6). The combined organic layer was dried (MgSO₄), evaporated, and purified by flash column chromatography (EtOAc/Hex, 1/4) to get 0.300 g (22 % over 2 steps) of 91 as a yellow oil.

(91) IR (neat) 3300, 2203, 1737 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.35 (d, J = 8.4 Hz, H), 3.51 (dd, J = 17.0, 2.3 Hz, H, NCH₂CCH), 3.40-3.30 (m, 2H, NCH₂CCH and NCH),
3.07 (td, $J = 9.0$, 2.7 Hz, H, NCH$_2$CH$_2$), 2.60 (q, $J = 8.8$ Hz, H, NCH$_2$CH$_2$), 2.23 (t, $J = 2.3$ Hz, H, RCCH), 2.12-2.05 (m, H, CH$_2$), 1.92-1.75 (m, 2H, CH$_2$), 1.60-1.58 (m, H, CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 140.5, 73.3, 64.7, 52.3, 41.2, 30.5, 23.0 (A vinyl and internal alkyne carbons are missing). (IV167)

*Synthesis of diyne 86:*

\[ \begin{align*}
  &\text{Br} &\text{Br} \\
  &\text{91} &\rightarrow &\text{86}
\end{align*} \]

To a stirred solution of the dibromo compound 91 (0.221 g, 0.754 mmol) in 5 mL of THF at -78 °C was added dropwise n-BuLi (1.6 M in Hexane, 1.56 mL). The solution was stirred for 30 min at -78 °C before it was warmed to rt and was further stirred for 30 min at rt. The reaction was quenched with 5 mL of 0.5 N HCl. The layers were separated and the organic layer was extracted with 0.5 N HCl (5 mL). The combined aqueous layer was basified to pH 12, and was extracted with ether (20 mL x 3). The combined organic layer was dried (MgSO$_4$) and the solvent was removed. The crude oil was purified on a silica gel column (Et$_2$O/pentane = 1/2) to get 71 % of pure product as pale yellow liquid. GLC analysis indicated a single peak.

(86) IR (neat): 3296 (& its shoulder), 2957, 2916, 2877, 2814, 2361, 2120 cm$^{-1}$ (IV152);

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.70-1.83 (m, H, ring CH$_2$), 1.85-2.00 (m, 2H, ring CH$_2$), 2.07-2.15 (m, H, ring CH$_2$), 2.19 (t, $J = 2.4$ Hz, CH$_2$C≡CH), 2.27 (d, $J = 2.0$ Hz, H,
CHC≡CH), 2.64-2.72 (m, H, NCH₂CH₂), 2.78-2.87 (m, H, NCH₂CH₂), 3.45 (td, J = 2.0, 7.1 Hz, H, NCH), 3.56 (d, J = 2.3 Hz, NCH₂C≡C), 3.57 (d, J = 2.3 Hz, NCH₂C≡C); $^{13}$C NMR (63 MHz, CDCl₃): δ 22.6, 32.3, 40.6, 51.1, 52.6, 72.5, 73.1, 79.1, 83.3; HRMS calcd for [M+H]$^+$ 134.0964, found 134.0957. (IV-152, IV-178, IV-192)

**Synthesis of Diyne 86 via Gilbert-Seyferth Reaction:**¹⁵

\[
\text{H} \quad \text{CHO} \quad \text{H} \quad \text{CH} \quad \text{N}
\]

The crude reaction mixture containing aldehyde 77 (vide supra, 5.98 mmol, theoretical yield) was evaporated and the residue was dissolved in MeOH (5 mL). To the solution at 0 °C was added Gilbert-Seyferth reagent (A in Scheme 3.2, p 76, 1.73 g, 8.97 mmol) and K₂CO₃ (1.65 g, 12.0 mmol). The reaction mixture was stirred at rt for 10 h and the reaction was quenched by addition of saturated solution of NH₄Cl (5 mL). The resulting solution was basified to pH 13 using 2 N NaOH solution and the aqueous layer was extracted with ether (5 mL x 4). The combined organic layer was dried (MgSO₄), evaporated, and the residue was subjected to column chromatography (Et₂O/acetone = 1/2) to get 0.459 g (57 % from ester 76) of 86 as a pale yellow oil. GLC analysis of the product indicated a single peak. (IV-227)

**Synthesis of Diyne 90:**
To a solution of dipropargyl tosylamine (284 mg, 1.15 mmol) in 5 mL of THF at -78 °C was added n-BuLi (0.92 mL of 2.5 M soin in Hex, 2.30 mmol) and the reaction mixture was stirred for 30 min. To the mixture was added CuI (219 mg, 1.15 mmol), followed by MeI (0.071 mL, 1.15 mmol). The mixture was stirred at -78 °C for 1 h, then was allowed to warm to rt over 3 h while stirring. The reaction was quenched by addition of 30 mL of water. The aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL x 3). When the emulsion formed, additional brine (20 mL) was added. The combined organic layer was dried (MgSO$_4$), evaporated, and the residue was subjected to flash chromatography (EtOAc/Hex = 1/5) to get 164 mg (55 %) of pale yellow liquid. $^1$H NMR indicates a sample reasonably free of starting material or di-substituted product.

(90) $^1$H NMR (500 MHz, CDCl$_3$): δ 1.64 (t, $J = 2.3$ Hz, 3H), 2.13 (t, $J = 2.5$ Hz, H), 2.42 (s, 3H), 4.09 (q, $J = 2.2$ Hz, 2H), 4.13 (d, $J = 2.3$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.3$ Hz, 2H); $^{13}$C (125 MHz, CDCl$_3$): δ 3.8 (C=C-Me), 21.9, 36.5, 37.1, 71.7, 74.1, 77.0, 82.4, 128.4, 129.8, 135.9, 144.1. (IV-260, IV-268)

Reaction of Diyne 86 with Bu$_3$Sn-SiMe$_3$:

$$\text{86} \rightarrow \text{92a} + \text{92b}$$
To a solution of Pd$_2$(dba)$_3$ (6.2 mg, 0.013 mmol Pd) and tris-(o-tolyl)phosphine (8.2 mg, 0.027 mmol) in 1 mL of C$_6$D$_6$ was added Bu$_3$Sn-SiMe$_3$ (107 mg, 0.296 mmol) followed by diyne 86 (35.8 mg, 0.269 mmol). The reaction was monitored by $^1$H NMR. The conversion was estimated by the comparison of proton signals with o-tolyl peak from phosphine ligand. After 4 days at rt, 85 % conversion into product 92 was achieved. The crude reaction mixture was subjected to column chromatography (Et$_3$N/Hex = 5/95) to get 44.4 mg (47 %) of desired product as a mixture of 92a and 92b as yellow oil. The products were characterized as a mixture.

(92a/92b) IR (neat): 2956, 2174, 1601, 1495, 1376, 1247, 1155, 1071, 837 cm$^{-1}$: HRMS calcd for [M+H] 498.2573, found 498.2545.

(92a) $^1$H NMR (500 MHz, CDCl$_3$ at rt): $\delta$ 0.09 (s, 9H, SiMe$_3$), SnBu$_3$ peaks omitted, 1.55 (m, H, ring CH$_2$), 1.71 (m, 2H, ring CH$_2$), 2.00 (m, H, ring CH$_2$), 2.44 (m, H, NCH$_2$CH$_2$), 3.00 (t, $J = 11.2$ Hz, H, NCH$_2$C$_{sp2}$), 3.06 (m, H, NCH$_2$CH$_2$), 3.59 (d, $J = 11.7$ Hz, H, NCH$_2$C$_{sp2}$), 3.84 (t, $J = 6.5$ Hz, H, NCH), 5.34 (s, (Si)CH=CR$_2$), 5.71 (d, $J = 1.4$ Hz, $^2$J$_{Sn-H} = 49$ Hz, (Sn)CH=CR$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 1.00 (SiMe$_3$), 11.2 (SnBu$_3$), 14.1 (SnBu$_3$), 26.3 (ring CH$_2$), 27.7 (SnBu$_3$), 29.4 (SnBu$_3$), 32.3 (ring CH$_2$), 56.3 (NCH$_2$CH$_2$), 63.6 (NCH$_2$C$_{sp2}$), 69.7 (NCH), 124.5 (CHSi), 125.6 (CHSn).

(92b) $^1$H NMR (500 MHz, CDCl$_3$ at rt): $\delta$ 0.09 (s, 9H, SiMe$_3$), SnBu$_3$ peaks omitted, 1.55 (m, H, ring CH$_2$), 1.71 (m, 2H, ring CH$_2$), 2.00 (m, H, ring CH$_2$), 2.44 (m, H, NCH$_2$CH$_2$), 3.00 (t, $J = 11.2$ Hz, 2H, NCH$_2$C$_{sp2}$), 3.06 (m, H, NCH$_2$CH$_2$), 3.64 (d, $J = 11.7$ Hz, H, NCH$_2$C$_{sp2}$), 3.79 (t, $J = 6.9$ Hz, H, NCH), 5.24 (d, $J < 1$ Hz, (Si)CH=CR$_2$), 5.75 (s, $^2$J$_{Sn-H} = 52$ Hz, (Sn)CH=CR$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 0.96 (SiMe$_3$), 11.2 (SnBu$_3$),
14.1 (SnBu₃), 26.3 (ring CH₂), 27.7 (SnBu₃), 29.4 (SnBu₃), 32.3 (ring CH₂), 56.3 (NCH₂CH₂), 63.8 (NCH₂CH₂), 69.7 (NCH), 123.5 (CHSi), 126.4 (CHSn). (IV-154, IV-184, IV-194, IV-290, VI-202)

**Reaction of 87 with Bu₃Sn-SiMe₃ Reagent:**

\[
\begin{align*}
87 & \quad \rightarrow \quad 93
\end{align*}
\]

To a solution of Pd₂(dba)₃ (4.6 mg, 0.010 mmol Pd) and P(C₆F₅)₃ (10.6 mg, 0.020 mmol) in 1 mL of C₆D₆ was added Bu₃Sn-SiMe₃ (200 mg, 0.55 mmol) followed by the diyne 87¹³ (53.6 mg, 0.500 mmol). The reaction was monitored by ¹H NMR. The black precipitate came out during the reaction. After 24 h at rt, the solvent was removed from the reaction mixture and the residue was subjected to chromatography (EtOAc/Hex = 1/8) to get 40.2 mg (17 %) of yellow needles.

(93) ¹H NMR (400 MHz, CDCl₃): δ 0.20 (s, 9H), SnBu₃ peaks are omitted for clarity, 2.23 (t, J = 2.5 Hz, H), 4.05 (dd, J = 2.5, 6.6 Hz, 2H), 5.60 (t br, H), 7.18 (s H); ¹³C NMR (100 MHz, CDCl₃) δ 71.3 (alkyne), 79.7 (alkyne), 173.6 (amide). (IV-265-3, IV-257)

**Reaction of 88 with Bu₃Sn-SiMe₃ Reagent:**

\[
\begin{align*}
88 & \quad 2.5 \text{ h} \quad \rightarrow \quad 94 & \quad 3 \text{ days} \quad \rightarrow \quad 95
\end{align*}
\]
To a solution of Pd$_2$(dba)$_3$ (2.3 mg, 0.0050 mmol Pd) and P(OPh)$_3$ (3.1 mg, 0.010 mmol) in 1 mL of C$_6$D$_6$ was added Bu$_3$Sn-SiMe$_3$ (100 mg, 0.275 mmol) followed by diyne 88$^{13b}$ (15.4 mg, 0.142 mmol). The reaction was monitored by $^1$H NMR. After 2.5 h at 60 °C, the $^1$H NMR spectrum indicated a clean conversion into monoadduct 94. The solvent was removed from the reaction mixture and the residue was subjected to chromatography (EtOAc/Hex = 1/18) to get 26.7 mg (40 %) of a colorless oil.

(94) IR (neat): 3314, 2956, 1694, 1463, 1376, 1249, 1165, 1073, 1027, 961, 838, 759 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.17 (s, 9H), SnBu$_3$ peaks are omitted for clarity, 2.45 (t,$ J = 2.5$ Hz, H), 4.70 (d, $J = 2.4$ Hz, 2H), 7.64 (s, $J_{Sn-H} = 142$ Hz, H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 0.18, 12.4, 14.0, 27.7, 29.4, 52.7, 75.2, 78.3, 155.0, 160.3, 171.6; HRMS calcd for [M+Na]$^+$ 495.1712, found 495.1747. (IV-243, IV-252, IV-274-3)

In a separate run, the reaction mixture containing 94 was heated at 60 °C for 3 days. The initially formed 94 was converted into di-adduct 95 by $^1$H NMR. The solvent was removed from the reaction mixture and the residue was subjected to chromatography (EtOAc/Hex = 1/18) to get 51.3 mg (43 %) of a colorless oil.

(95) IR (neat): 2956, 1694, 1463, 1421, 1376, 1248, 1199, 1074, 1008, 838, 758 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.12 (s, 9H), 0.17 (s, 9H), SnBu$_3$ peaks are omitted for clarity, 4.69 (m, 2H), 6.61 (s, $J_{Sn-H} = 160$ Hz, H), 7.57 (s, $J_{Sn-H} = 148$ Hz, H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 0.18, 0.45, 11.5, 12.4, 14.0, 27.7, 27.8, 29.4, 29.5, 75.5, 144.4, 156.5, 157.9, 158.0, 172.0. HRMS calcd for [M+Na]$^+$ 857.3314, found 857.3298(IV-274-4)
Reaction of 89 with Bu₃Sn-SiMes Reagent:

\[
89 \quad \leftrightarrow \quad 96
\]

To a solution of Pd₂dba)₃ (0.9 mg, 0.002 mmol Pd) and phosphine ligand (0.004 mmol) in 1 mL of C₆D₆ was added Bu₃Sn-SiMes (40.0 mg, 0.110 mmol) followed by the diyne 89 (31.9 mg, 0.100 mmol). The reactions using various ligands (PCys, PBu₃, PPh₃, and P(OPh)₃) were monitored by ¹H NMR. In a reaction using PCys, the reaction was complete in 16 h at rt (¹H NMR). The solvent was removed from the reaction mixture and the residue was subjected to flash chromatography (EtOAc/Hex = 1/16) to get 60.0 mg (88 %) of 96 as off-white crystal (mp 60-62 °C)

(96) ¹H NMR (500 MHz, CDCl₃): δ -0.05 (s, 9H), 0.10 (s, 9H), SnBu₃ peaks are omitted, 2.42 (s, 3H), 3.97 (s, 2H), 3.99 (m, 2H), 6.67 (s, Jₘ-H = 158 Hz, H), 7.27 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ -0.24, 0.27, 10.5, 14.0, 21.2, 28.0, 29.7, 37.0, 60.9, 90.9, 98.5, 128.6, 129.5, 136.8, 142.9, 149.1, 157.8; HRMS calcd for [M+Na]⁺ 706.2563, found 706.2573; nOe difference spectrum confirmed the double bond geometry shown above. (IV-233, IV-263)

Reaction of 90 with Bu₃Sn-SiMes Reagent:

\[
90 \quad \leftrightarrow \quad 97
\]

To a solution of Pd₂dba)₃ (1.8 mg, 0.004 mmol Pd) and phosphine ligand (0.008 mmol) in 1 mL of C₆D₆ was added Bu₃Sn-SiMes (80 mg, 0.22 mmol) followed by diyne 90 (52.3
mg, 0.200 mmol). The reactions using various ligands (PCy₃, PBu₉, PPh₃, and P(OPh)₃) were monitored by \(^1\)H NMR. In a reaction using P(OPh)₃, the reaction was complete in 17 h at 60 °C (\(^1\)H NMR). The solvent was removed from the reaction mixture and the residue was subjected to flash chromatography (EtOAc/Hex = 1/12) to get 83.6 mg (67 \%) of 97 as a colorless oil.

(97) \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 0.13 (s, 9H), SnBu₃ peaks are omitted, 2.45 (s, 3H), 3.96 (d, \(J = 2.1\) Hz, 2H), 3.99 (s br, 2H), 6.66 (s, \(J_{Sn-H} = 162\) Hz, H), 7.32 (d, \(J = 8.1\) Hz, 2H), 7.76 (d, \(J = 8.1\) Hz, 2H); \(^1\)C NMR (100 MHz, CDCl₃): \(\delta\) -0.1, 2.9, 10.9, 13.5, 21.3, 27.2, 29.0, 36.1, 58.6, 71.2, 81.4, 127.9, 128.9, 136.0, 142.9, 146.0, 156.0. (IV-270-4, IV-279)

**Derivatization of 92 with NBS:**

\[
\begin{align*}
\text{92a} + \text{92b} & \rightarrow \text{98a} + \text{98b}
\end{align*}
\]

To a solution of Pd₂(dba)₃ (3.4 mg, 0.0075 mmol Pd) and P(C₆F₅)₃ (8.0 mg, 0.015 mmol) in 1 mL of C₆D₆ was added Bu₃Sn-SiMe₃ (120 mg, 0.330 mmol) and anisole (0.100 mmol) as an internal standard, followed by diyne 86 (40.0 mg, 0.300 mmol). The reaction was monitored by \(^1\)H NMR. After heating at 60 °C for 10 h, 35 % conversion was observed. To the reaction mixture cooled to rt, was added N-bromosuccinimide (53.4 mg, 0.300 mmol) and the mixture was heated at 70 °C for 1 h. The solvent was removed from the mixture and the residue was subjected to flash chromatography (Hex/ether = 95/5) to
get 22.6 mg (26 %, from 86) of product, though the sample of product contained some impurity.

(98a) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 5.77 (s, H, CHBr), 5.29 (s, H, CHSi), 4.04 (t, \(J = 6.4 \text{ Hz, H}\), 3.84 (d, \(J = 12.4 \text{ Hz, NCH}_2\text{C}_{sp^2}\)), 3.12 (m, H, NCH\(_2\text{CH}_2\)), 2.29 (m, H, NCH\(_2\text{CH}_2\)), upfield protons were hidden under impurity peaks of SnBu\(_3\) residue.

(98b) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 5.75 (s, H, CHBr), 5.22 (s, CHSi), 3.99 (t, \(J = 6.5 \text{ Hz, H}\), 3.83 (dd, \(J = 12.4 \text{ Hz, NCH}_2\text{C}_{sp^2}\)), 3.12 (m, H, NCH\(_2\text{CH}_2\)), 2.29 (m, H, NCH\(_2\text{CH}_2\)), upfield protons were hidden under impurity peaks of SnBu\(_3\) residue.

**Stille Coupling of Vinylstannane I:**

A solution of 3-bromo-iodobenzene (28.3 mg, 0.100 mmol), starting vinylstannane 99 (61.0 mg, 0.100 mmol), Pd(PPh\(_3\))\(_4\) (5.8 mg, 0.0050 mmol), and CuI (11 mg, 0.060 mmol) in DMF (2 mL) was heated at 80 °C for 1 h. TLC indicated that the reaction is complete. The solvent was removed from the reaction mixture and the residue was subjected to flash chromatography (EtOAc/Hex = 1/9) to get 26.0 mg (55 %) of 100 as a white solid.

(100) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) -0.35 (s, 9H), 2.35 (s, 3H), 4.00 (d, \(J = 1.6 \text{ Hz, 2H}\), 4.05 (d, \(J = 1.6 \text{ Hz, 2H}\)), 5.52 (s, H, C=Cs(Si)H), 6.13 (s, H, C=C(Ar)H), 7.05-7.18 (m, 2H), 7.28-7.32 (m, 3H), 7.37 (s, H), 7.72 (d, \(J = 8.2 \text{ Hz, 2H}\)); \(^{13}\)C NMR (100 MHz,
Stille Coupling of Vinylstannane II:

A solution of 99 (61.0 mg, 0.100 mmol), 3,5-di-(trifluoromethyl)-bromobenzene (58.6 mg, 0.200 mmol), Pd(PPh₃)₄ (11 mg, 0.010 mmol), and CuI (19 mg, 0.10 mmol) in DMF (2 mL) was heated at 120 °C for 3 h. To the reaction mixture was added 10 mL of water and the mixture was extracted with ether (10 mL x 3). The combined organic layer was dried (MgSO₄), evaporated, and was subjected to flash chromatography (EtOAc/Hex = 1/9) to get 13.5 mg (25 %) of a colorless oil.

(101) ¹H NMR (400 MHz, CDCl₃): δ -0.43 (s, 9H), 2.34 (s, 3H), 4.05 (d, J = 1.6 Hz, 2H), 4.09 (d, J = 1.6 Hz, 2H), 5.57 (s, H), 6.25 (s, H), 7.30 (d, J = 8.0 Hz, 2H), 7.62 (s, 2H), 7.69 (s, H), 7.74 (d, J = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ -1.5, 21.8, 54.9, 56.9, 124.0, 128.1, 129.3, 130.2, 131.4, 132.2, 132.5, 134.4, 138.9, 139.0, 144.3, 145.7, 12 of 12 aromatic carbons. nOe experiments support the stereochemistry shown. Temperature dependence: below -40 °C, ring NCH₂ peaks split into two multiplets and no other change in the spectra was noticed. (VI-122-1)
**Attempted Stille Coupling of Vinylstannane III:**

![Chemical Structure](image)

A solution of 99 (61.0 mg, 0.100 mmol), 6-methoxy-2-bromonaphthalene (26.1 mg, 0.110 mmol), Pd(PPh₃)₄ (5.8 mg, 0.0050 mmol), and Cul (3.8 mg, 0.020 mmol) in DMF (2 mL) was heated at 60 °C for 17 h. TLC indicated the formation of reduction product 106 instead. After workup similar to the procedure for 101, the reduction product 106 (vide infra) was isolated in 38 % yield. For NMR spectra of 106 see, *Destannylation of 99*.

**Sn-Halogen Exchange Reaction of 99:**

![Chemical Structure](image)

To a solution of vinylstannane 99 (29.7 mg, 0.0486 mmol) in CH₂Cl₂ (2 mL) at rt was added N-bromosuccinimide (10 mg, 0.056 mmol), and the mixture was stirred at rt for 10 h. The solvent was removed from the reaction mixture and the residue was subjected to flash chromatography (EtOAc/Hex = 1/6) to get 13.4 mg (70 %) of a colorless oil. (103) ¹H NMR (500 MHz, CDCl₃): δ 0.10 (s, 9H), 2.43 (s, 3H), 3.96 (s br, 4H), 5.64 (s, H), 6.12 (s, H), 7.32 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H); ¹³C NMR (125 MHz,
Sn-Halogen Exchange Reaction of 96:

To a solution of 96 (34.2 mg, 0.0500 mmol) in CH$_2$Cl$_2$ (2 mL) at rt was added I$_2$ (15 mg, 0.060 mmol) and the mixture was stirred at rt for 20 min. The solvent was evaporated and the residue was subjected to flash chromatography (EtOAc/Hex = 1/16) to get 25.5 mg (98 %) of 104 as a white crystalline solid (mp 101-102 °C).

(104) $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.00 (s, 9H), 0.20 (s, 9H), 2.42 (s, 3H), 4.08 (s, 4H), 6.75 (s, H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.72 (d, $J = 8.0$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ -1.4, -0.5, 21.4, 37.0, 61.1, 91.3, 97.2, 113.2, 127.6, 129.4, 136.0, 140.2, 143.5.

Sn-Halogen Exchange Reaction of 97:

To a solution of 97 (29.4 mg, 0.0471 mmol) in CH$_2$Cl$_2$ (2 mL) at rt was added I$_2$ (24 mg, 0.094 mmol) and the mixture was stirred at rt for 20 min. The solvent was evaporated and
the residue was subjected to flash chromatography (EtOAc/Hex = 1/9) to get 19.4 mg (90 %) of 105.

(105) $^1$H NMR (500 MHz, CDCl$_3$) δ 0.19 (s, 9H), 1.56 (t, $J = 2.3$ Hz, 3H), 2.42 (s, 3H), 4.01 (q, $J = 2.3$ Hz, 2H), 4.08 (d, $J = 1.1$ Hz, 2H), 6.72 (s, H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.72 (d, $J = 8.3$ Hz, 2H), $^{13}$C NMR (125 MHz, CDCl$_3$) δ -0.8, 3.7, 21.9, 37.4, 61.7, 71.9, 82.3, 114.3, 128.2, 129.7, 136.8, 139.6, 143.9. (IV-284-1)

Destannylation of 99:

To a solution of 99 (61.0 mg, 0.100 mmol) in CH$_2$Cl$_2$ (1 mL) at rt was added HCO$_2$H (23 mg, 0.50 mmol) and the mixture was stirred overnight. The solvent was removed from the mixture and the residue was subjected to flash chromatography (EtOAc/Hex = 1/6) to get 31.4 mg (98 %) of 106 as a colorless oil.

(106) IR (neat): 2954, 2856, 1924, 1738, 1598, 1494, 1464, 1404, 1349, 1249, 1164 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 0.11 (s, 9H, TMS), 2.41 (s, 3H, CH$_3$Ar), 3.92 (d, $J = 2.0$ Hz, 2H, NCH$_2$), 3.97 (t, $J = 2.0$ Hz, 2H, NCH$_2$), 5.06 (t, $J = 1.7$ Hz, H), 5.32 (t, $J = 2.2$ Hz, H), 5.50 (s, H), 7.31 (d, $J = 8.3$ Hz, 2H), 7.69 (d, $J = 8.3$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -0.4, 21.9, 54.5, 56.9, 111.1, 125.0, 128.4, 130.1, 133.2, 142.0, 144.2, 149.1; Anal. Calcd for C$_{16}$H$_{23}$NO$_2$Ssi: C, 59.77 %; H, 7.21 %; N, 4.36 %; found C, 59.98 %; H, 7.46 %; N, 4.23 %. (V-114)
Formation of Diels-Alder Adduct 107:

A solution of 106 (32.0 mg, 0.100 mmol) and maleic anhydride (19.6 mg, 0.200 mmol) in benzene (1 mL) was heated at 60 °C for 12 h. After evaporation of solvent, the residue was purified on silica gel column (EtOAc/Hex = ¼) to get 22.6 mg of 107 as a white solid (164-166 °C).

(107) IR (mineral oil) 2920, 2853, 1848, 1771, 1461, 1377, 1158 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.04 (s, 9H, TMS), 0.79-0.92 (m, H, CH₂Si), 2.12 (s, H, CHC=O), 2.22-2.32 (m, H, CHC=O), 2.43 (s, 3H, CH₃Ar), 3.29 (dd, J = 1.4, 9.8 Hz, H, CH₂CHC=O), 3.42 (td, J = 2.2, 9.5 Hz, H, CH₂CHC=O), 3.87-3.99 (m, 2H, NCH₂), 4.05-4.21 (m 2H, NCH₂), 7.31 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ -1.6 (TMS), 21.9 (CHC=O), 22.5 (CHC=O), 39.7 (CH₂CHC=O), 40.9 (CH₂Si), 57.3 (NCH₂), 57.8 (NCH₂), 125.5, 127.7, 130.4, 132.5, 134.2, 144.3, 173.8 (C=O), 174.6 (C=O); HRMS Calcd for [M+Na⁺]: 442.1120, found: 442.1140. (V-119)

Attempted Suzuki Coupling of Vinylborane 108, ¹:
To a solution of vinylborane 108 (0.100 mmol) in benzene-\textit{d}_6 (1 mL) formed \textit{in-situ} from corresponding diyne with Pd(PPh_3)_2Cl_2 (1.4 mg, 0.0020 mmol) as catalyst, was added K_2CO_3 (28 mg, 0.20 mmol), 3-bromo-1-iodobenzene (31.1 mg, 0.110 mmol) and dioxane (1 mL). The resulting mixture was heated at 70 °C for 2 h. The solvent was removed and the residue was subjected to recrystallization (from Et_2O/Hex) or column chromatography (EtOAc/Hex = 1/10 ~ 1/1). All the attempts to isolate the product failed. After column chromatography, only reduction product 110 (9.5 mg, 23 %) was isolated.

\[(110) \] 1H NMR (500 MHz, CDCl_3): δ 0.16 (s, \textit{J}_{Sn-H} = 54 Hz, 9H), 2.42 (s, 3H), 3.96 (m, 2H), 3.98 (m, 2H), 4.92 (s, H), 5.18 (s, H), 5.84 (s, \textit{J}_{Sn-H} = 50 Hz, H), 7.31 (d, \textit{J} = 8.2 Hz, 2H), 7.70 (d, \textit{J} = 8.2 Hz, 2H); 13C NMR (100 MHz, CDCl_3): δ -8.3, 21.9, 54.3, 55.4, 107.5, 124.8, 128.4, 130.1, 133.2, 143.2, 144.1, 149.2; 119Sn NMR (186 MHz, CDCl_3): δ -48.1 ppm; nOe experiments supported the stereochemistry shown. (V-203, V-204)

\textit{Attempted Suzuki Coupling of Vinylborane 108, II:}

\[
\begin{align*}
\text{TaN} & \quad \text{SnMe}_3 \\
\text{Me} & \quad \text{SnMe}_3 \\
\text{TaN} & \quad \text{SnMe}_3 \\
\end{align*}
\]

To a solution of vinylborane 108 (0.100 mmol) in benzene-\textit{d}_6 (1 mL) formed \textit{in-situ} from corresponding diyne with Pd(PPh_3)_4 (2.3 mg, 0.0020 mmol) as catalyst, was added
NaOEt (0.10 mL of 2 N soln in EtOH, 0.20 mmol), 3-bromo-1-iodobenzene (28.3 mg, 0.100 mmol), and additional Pd(PPh₃)₄ (2.3 mg, 0.0020 mmol). The resulting mixture was heated at 80–90 °C for 1.5 h. The solvent was evaporated and the residue was subjected to silica gel column chromatography (EtOAc/Hex = 1/10). No identifiable products were isolated. (V-217)

**Attempted Suzuki Coupling of Vinylborane 108, III:**

To a solution of vinylborane 108 (0.100 mmol) in benzene-d₆ (1 mL) formed in-situ from corresponding diyne with Pd₂(dba)₃ (1.0 mg, 0.0010 mmol) as catalyst, was added NaOEt (0.20 mL of 2 N soln in EtOH, 0.40 mmol), iodobenzene (20.4 mg, 0.100 mmol), and additional Pd(PPh₃)₄ (2.3 mg, 0.0020 mmol). The resulting mixture was heated at 70 °C for 0.5 h. The solvent was evaporated and the residue was subjected to silica gel column chromatography (EtOAc/Hex = 1/6). No identifiable products were isolated. (V-221)

**Attempted Suzuki Coupling of Vinylborane 108, IV:**

To a solution of vinylborane 108 (0.100 mmol) in benzene-d₆ (1 mL) formed in-situ from corresponding diyne with Pd₂(dba)₃·CHCl₃ (1.0 mg, 0.0010 mmol) as catalyst, was added...
NaOEt (0.20 mL of 2 N soln in EtOH, 0.40 mmol), iodobenzene (20.4 mg, 0.100 mmol), and additional Pd(PPh$_3$)$_4$ (2.3 mg, 0.0020 mmol). The resulting mixture was stirred at rt for 20 h. The solvent was evaporated and the residue was subjected to silica gel column chromatography (EtOAc/Hex = 1/6). No identifiable products were isolated. (V-253)

**Borostannylation of 90:**

A solution of 90 (35.3 mg, 0.135 mmol), B-Sn reagent (35.3 mg, 0.135 mmol), and Pd$_2$(dba)$_3$CHCl$_3$ (1.0 mg, 1 mol %) was stirred at rt for 2 h. A clean conversion was observed in $^1$H NMR spectrum. The reaction mixture was concentrated to 0.1 mL and hexane (3 mL) was added. Upon keeping the mixture in a fridge (-30 °C), white crystal came out, which was filtered and dried, 38.0 mg (73 %)

(111) $^1$H NMR (250 MHz, C$_6$D$_6$): δ 0.00 (s, $J_{Sn-H} = 50$ Hz, 9H), 1.59 (s, $J_{Sn-H} = 48$ Hz, 3H), 1.85 (s, 3H), 2.26 (s, 6H, NMe x 2), 2.89 (s, 4H, NCH$_2$CH$_2$N), 3.94 (d, J = 1.6 Hz, 2H, NCH$_2$), 4.09 (s br, 2H, NCH$_2$), 5.08 (s, H, R$_2$C=CBH), 6.77 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 7.9 Hz, 2H); $^{13}$C NMR (63 MHz, C$_6$D$_6$): δ -8.0, 21.2, 22.6, 34.8, 51.6, 51.9, 56.2, 129.8, 135.5, 137.6, 143.1, 145.2, 150.4; $^{11}$B NMR (80 MHz, C$_6$D$_6$): δ 28.1 ppm; $^{119}$Sn (186 MHz, C$_6$D$_6$): δ -33.5 ppm. (V-256)

**Attempts of Ligand Exchange on Boron of 111, I:**

234
To a solution of the vinylborane 111 (26 mg, 0.050 mmol) in 1 mL of C₆D₆ was added pinacol (7.7 mg, 0.065 mmol) and the reaction was followed by ¹H NMR. After 12 h at 70 °C, the solvent was evaporated and the residue was subjected to silica gel chromatography. No identifiable product was obtained. (V-296)

Attempts of Alcoholysis on Boron of 111, II:

To a solution of vinylborane 111 (19 mg, 0.037 mmol) in 1 mL of C₆D₆ was added catechol (4.5 mg, 0.041 mmol) and the reaction was followed by ¹H NMR. After 1.5 h at rt, about 70 % conversion into a new species was observed (¹H NMR). The solvent was evaporated and the residue was subjected to silica gel chromatography, but no identifiable product was obtained. (VI-21)

Attempt of Tin-Halogen Exchange of 108:
To a solution of vinylstannane 108 (0.100 mmol) in benzene-$d_6$ (1 mL) formed in-situ from corresponding diyne with Pd$_2$(dba)$_3$·CHCl$_3$ (1.0 mg, 0.0010 mmol) as the catalyst, was added N-bromosuccinimide (17.8 mg, 0.100 mmol). The progress of the reaction was followed by $^1$H NMR. The reaction mixture slowly turned into a complex mixture. (V-234)

**Alcoholysis of B-C$_{sp2}$ bond of 108:**

![Chemical structure](image)

To a solution of vinylstannane 108 (0.100 mmol) in benzene-$d_6$ (1 mL) formed in-situ from corresponding diyne with Pd$_2$(dba)$_3$·CHCl$_3$ (1.0 mg, 0.0010 mmol) as catalyst, was added MeOH (~0.500 mmol). The mixture was stirred at 80 °C for 6 h, when the $^1$H NMR indicated the complete hydrolysis. The solvent was removed from the reaction mixture and the residue was subjected to flash chromatography (EtOAc/Hex = 1/10) to get 110 (17.7 mg, 43 %) as a colorless oil.

(110) $^1$H NMR (500 MHz, CDCl$_3$): δ 0.16 (s, $J_{Sn-H} = 54$ Hz, 9H), 2.42 (s, 3H), 3.96 (m, 2H), 3.98 (m, 2H), 4.92 (s, H), 5.18 (s, H), 5.84 (s, $J_{Sn-H} = 50$ Hz, H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -8.3, 21.9, 54.3, 55.4, 107.5, 124.8, 128.4, 130.1, 133.2, 143.2, 144.1, 149.2; $^{119}$Sn NMR (186 MHz, CDCl$_3$): δ -48.1 (s), nOe experiments support the stereochemistry drawn. (V-263)
Synthesis of Diyne Substrate 113:

To a solution of alcohol 114 (0.982 g, 10.0 mmol) and PPh₃ (5.25 g, 20.0 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added CBr₄ under N₂. The resulting solution was stirred for 10 min at 0 °C. The reaction flask was connected to a short path distillation set and the solvent was distilled off (bath temp, 60 °C). The resulting sticky liquid was further distilled under vacuum (10 mm Hg, bath temp 70-120 °C) to produce 1.42 g (88 %) of product as a colorless oil. A GLC analysis (regular column, 70 °C-5 min-20 °C/min-250 °C) indicated a single peak: tᵣ = 4.66 min (95 %).

(115) ¹H NMR (400 MHz, CDCl₃): δ 1.16 (d, J = 6.9 Hz, 6H, CH₃), 2.61 (t of septet, J = 2.1, 6.9, H, CH), 3.93 (d, J = 2.1 Hz, 2H, CH₂Br); ¹³C NMR (100 MHz, CDCl₃): δ 15.5, 20.6, 22.4, 74.4, 93.3. (V-37)

To a stirred solution of the starting Weinreb amide 117 (1.11 g, 4.55 mmol) in THF (50 mL) at 0 °C, was added dropwise MeLi (3.25 mL, 1.4 M in ether). The reaction mixture was further stirred for 1 h at 0 °C. The reaction mixture was poured into 0.5 N HCl solution and the layers were separated. The aqueous layer was extracted with 3x50 mL of CH₂Cl₂/ether (1:1) mixture. The combined organic layer was dried (MgSO₄) and
evaporated, and the residue was subjected to silica gel chromatography (EtOAc/Hex = 2/3) to get 0.656 g (68%) of desired compound 116 as a off-white solid.\(^{17}\)

**116** \(^1^H\) NMR (500 MHz, CDCl\(_3\) at rt): \(\delta\) 1.38 (s, 9H, major), 1.43 (s, 9H, minor), 1.77-1.88 (m, 3H, major & minor), 2.07-2.20 (m, H, major & minor), 2.10 (s, 3H, OCH\(_3\), major), 2.14 (s, 3H, OCH\(_3\), minor), 3.37-3.57 (m, 2H, major & minor), 4.17 (dd, \(J = 8.9, 5.6\) Hz, H, CH, major), 4.30 (dd, \(J = 9.2, 4.6\) Hz, H, CH, minor); \(^{13}^C\) NMR (125 MHz, CDCl\(_3\) at rt): major: \(\delta\) 24.2, 25.9, 28.7, 30.2, 47.1, 66.2, 80.6, 154.3, 208.8; minor: \(\delta\) 24.8, 26.8, 28.8, 29.1, 47.2, 65.6, 80.3, 155.1, 208.6. (V-31, K.C.\(^{17}\))

\[ \text{N-Boc-2-acetylpyrrolidine 116} \]

To a solution of N-Boc-2-acetylpyrrolidine 116 (0.581 g, 2.72 mmol, azeotropically dried) in 2 mL of CH\(_2\)Cl\(_2\) was added 2 mL of CF\(_3\)CO\(_2\)H, followed by anisole (0.22 mL). Vigorous evolution of gas! After 15 min, this solution was concentrated and the resulting oil was dried azeotropically with CH\(_2\)Cl\(_2\) (3 mL x 2), and with benzene (2 mL x 2). In another flask, a solution of lithium (2-TMS)-acetylide (LiC≡CSiMe\(_3\), 5 equiv) was prepared by addition of n-BuLi (5.45 mL of 2.5 M in hexane, 13.6 mmol) to a solution of TMS-acetylene (1.92 mL, 13.6 mmol) in THF. A solution of crude amine salt in THF (10 mL) was added to the latter flask at such a rate that temperature does not exceed –70°C. The reaction mixture was maintained at –78°C for 15 min and then the mixture was poured into a mixture of brine and ether (100 mL, 1:1). The organic layer was extracted.
with ether and CH₂Cl₂ (1:1, 50 mL x 4). The combined organic layer was dried over K₂CO₃ (enough amount of solvent was used to collect adsorbed compound) and evaporated to get 0.842 g of a crude brown oil, which was purified on silica gel column using Et₂O/CH₂Cl₂/Et₃N (90/5/5) as eluent to get 0.506 g (88%) of 117 as a yellow oil. A GLC analysis (regular column, 70 °C–5 min–20 °C/min–250 °C) indicated a single peak: tᵣ = 10.95 min (92 %). The product can be recrystallized from pentane to get off-white needle (mp 49-51 °C).

(117) [α]D₂⁵ = -2.46 ° (CHCl₃, C 0.22); IR (neat): 3344, 3500-3000 (br, OH), 2165; ¹H NMR (500 MHz, CDCl₃): δ 0.14 (s, 9H, TMS), 1.38 (s, 3H, Me), 1.60-1.80 (m, 4H), 3.05-2.91 (m, 2H, NCH₂), 3.25 (t, J = 7.7 Hz, H, NCH); ¹³C NMR (125 MHz, CDCl₃): δ 0.4 (TMS), 25.0 (CH₂), 25.6 (Me), 26.1 (CH₂), 46.9 (NCH₂), 67.1 (NCH), 68.4 (quaternary), 86.4 (for 2 alkyne carbons), 110.9. (V-32)

The crystal for X-ray crystallography was obtained in the following way. The treatment with HCl (2 equiv) followed by azeotropic drying with benzene gave an oily syrup, which was recrystallized from pentane/ether to get HCl adduct of above compound. The structure obtained from X-ray crystallography was in agreement with the stereochemistry drawn.

**Coupling of 117 with 115:**

![Chemical structure](image)
To a solution of starting aminoalcohol 117 (106 mg, 0.500 mmol) and \( \text{Pr}_2\text{NEt} \) (97 mg, 0.75 mmol) in THF (3 mL) was added 2-methyl-pent-2-ynyl-1-bromide (105 mg, 0.650 mmol) at rt. The mixture was stirred under \( \text{N}_2 \) at RT for 28 h. TLC indicated a complete conversion (Et\( \text{O} \)/Hex/Et\( \text{N} \) = 200/100/15, \( R_f = 0.75 \)). The reaction mixture was diluted with ether (30 mL) and was extracted with \( \text{CH}_2\text{Cl}_2 \) (50 mL x 3). The combined organic extracts were washed with brine (20 mL), dried (MgSO\( \text{4} \)), and concentrated. The silica gel column chromatography (EtOAc:Hex:EtoN = 2:100:3) of the residue yielded 431 mg (98%) of product.

(117) IR (neat): 3429 (OH), 2240, 2165 cm\(^{-1}\); \( ^1\text{H} \) NMR (500 MHz, CDCl\( \text{3} \)): \( \delta \) 0.16 (s, 9H, TMS), 1.17 (d, \( J = 6.8 \text{ Hz} \), 6H, \( \text{^3Pr} \)), 1.40 (s, 3H, Me), 1.62-1.71 (m, 2H, \( \text{CH}_2 \)), 1.72-1.81 (m, 2H, \( \text{CH}_2 \)), 2.57 (t of septet, \( J = 2.0, 6.8 \text{ Hz} \), H), 2.85 (dd, \( J = 7.7, 15.2 \text{ Hz} \), H, NCH), 3.08-3.00 (m, 2H, NCH\( \text{2} \)CH\( \text{2} \)), 3.62 (dd, \( J = 2.0, 17.1 \text{ Hz} \), H, NCH\( \text{2} \)CCR), 4.01 (dd, \( J = 2.0, 17.1 \text{ Hz} \), H, NCH\( \text{2} \)CCR); \( ^{13}\text{C} \) NMR (125 MHz, CDCl\( \text{3} \)): \( \delta \) -0.3 (TMS), 20.4, 23.2, 24.2, 25.9, 27.1, 43.8, 54.1, 67.5, 68.4, 74.8 (for 4 alkyne carbons), 87.0, 90.1, 110.8. (V-39)

To a solution of starting TMS-acetylene compound above (431 mg, 4.18 mmol) in 10 mL of THF at 0 °C was added a solution of TBAF (1.0 M in THF, 2.22 mL, 2.22 mmol) dropwise. The mixture was stirred for 30 min and then poured into ice-water mixture (10 mL) and was extracted with ether (10 mL x 3). The combined organic layer was dried
(MgSO₄) and evaporated in vacuo. The silica gel column chromatography (EtOAc/Hex/Et₃N = 2/100/3) of the residue yielded 216.7 mg (67%) of 113 as a pale yellow liquid.

(113) IR (neat): 3425 (OH), 3302, 2239, 2107 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.16 (d, J = 6.8 Hz, 6H, ¹Pr), 1.42 (s, 3H, Me), 1.64-1.72 (m, 2H, CH₂), 1.73-1.81 (m, 2H, CH₂), 2.41 (s, H, CCH), 2.56 (t of septet, J = 2.0, 6.8 Hz, H), 2.87 (ddd, J = 7.8, 7.8, 9.5 Hz, H, NCH₂CH₂), 3.03 (ddd, J = 4.9, 5.9, 11.1 Hz, H, NCH₂CH₂), 3.05 (dd, J = 7.2 Hz, H, NCH), 3.61 (dd, J = 2.0, 17.1 Hz, H, NCH₂CCR), 3.64 (s br, H, OH), 3.95 (dd, J = 2.0, 17.1 Hz, H, NCH₂CCR); ¹³C NMR (125 MHz, CDCl₃): δ 20.4 (CH of ¹Pr), 23.2 (two peaks, ¹Pr), 24.4 (NCH₂CH₂), 25.9 (Me), 27.2 (NCHCH₂), 43.9 (NCH₂CCR), 54.0 (NCH₂CH₂), 67.5 (quaternary), 68.3 (NCH), 71.1 (for 4 alkyne carbons), 74.7, 88.8, 90.2; An HRMS was obtained on the TMS ether of 113. (V-42)

Starting alcohol 113 (112 mg, 0.511 mmol) was dissolved in pyridine (2 mL, freshly distilled from KOH) under stirring at rt. HMDS (hexamethyldisilazene: 0.115 mL, 0.562 mmol) and TMS-Cl (freshly distilled, 0.142 mL, 1.12 mmol) was added dropwise to the solution above. After 2 h at rt, 3 mL of ice-water was added. The aqueous layer was extracted with pentane (3 mL x 3) and the combined organic layer was dried (MgSO₄), evaporated, and was subjected to chromatography (Hex/Et₃N = 95/5) to get 127 mg (85%) of a colorless oil.
(118) IR (neat, NaCl) 3309, 2968, 2872, 2240, 2107, 1730, 1462, 1371, 1318, 1249, 1155, 1116, 1071 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.12 (s, 9H), 1.16 (d, J = 6.8 Hz, 6H), 1.43 (s, 3H), 1.65-1.90 (m, 4H), 2.42 (s, H), 2.56 (t of septet, J = 2.0, 6.8 Hz, H), 2.79 (ddd, J = 6.8, 9.3, 15.8 Hz, H), 2.94-3.00 (m, 2H), 3.52 (dd, J = 1.9, 17.1 Hz, H), 3.68 (dd, J = 1.9, 17.1 Hz, H); ¹³C NMR (125 MHz, CDCl₃): δ 2.3, 21.0, 23.9, 24.7, 26.9, 29.5, 44.6, 54.7, 69.7, 73.4, 73.7, 75.6, 88.4, 90.6; HRMS calcd for [M+Na]: 314.1910, found: 314.1910. (VI-60)

**Attempted Silylstannylation of 113:**

![Chemical structure](image)

A solution of 113 (21.9 mg, 0.100 mmol), Bu₃Sn-SiMe₃ (40.0 mg, 0.110 mmol), Pd₂(dba)₃ (0.9 mg, 2 mol %), and phosphine ligands (0.0040 mmol, see eq. 18) in C₈D₆ (1 mL) was heated at 60 °C. The progress of the reaction was monitored by ¹H NMR. Typical reaction gave a complex mixture of products after 2 d at 60 °C, whose structure could not be identified. The product of reaction mixture, where no ligand was used, was subjected to chromatography on silica gel (EtOAc/Hex = 1/50, 3% Et₃N). Only unidentified products resulted. (V-45, V-47, V-48)

**Attempted Borylstannylation of 113:**

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A solution of 113 (21.9 mg, 0.100 mmol), B-Sn reagent (25.6 mg, 0.110 mmol), and Pd(PPh₃)₂Cl₂ (3.5 mg, 5 mol %) in C₆D₆ (1 mL) was kept at rt. The progress of reaction was followed by ¹H NMR. After 19 h at rt, no reaction was observed. After 4 days, the complex reaction mixture resulted (¹H NMR). Further efforts to isolate the product failed (V-166).

**Attempted Zr-Promoted Cyclization of 118:**

To a solution of Cp₂ZrCl₂ (29.8 mg, 0.102 mmol) in 1 mL of THF at -78 °C was added n-BuLi (0.13 mL of 1.6 M soln in Hex, 0.204 mmol). After the solution was stirred for 15 min at -78 °C, a solution of starting diyne 118 (29.2 mg, 0.100 mmol) in 1 mL of THF was added dropwise to the above solution. The resulting mixture was slowly warmed to rt and was further stirred for 12 h at rt. To the reaction mixture was added PhCO₂H (0.400 mmol) to hydrolyze the zirconocene intermediate. The mixture was further stirred at rt for 2 h. The solvent was removed and the residue was subjected to chromatography (EtOAc/Hex = 1/2, 5 % Et₃N). Only starting material was recovered (12.8 mg, 44 %).

**Preparation of Substrate Diyne 119:**
To a solution of 117 (1.12 g, 5.30 mmol) in THF (15 mL) was added propargyl bromide (1.64 g, 6.87 mmol) and DIPEA (1.38 mL, 7.93 mmol). The reaction mixture was allowed to stir at rt overnight (~10 h). The reaction mixture was distributed between brine (50 mL) and Et₂O (50 mL). The aqueous layer was extracted with Et₂O (50 mL x 3). The combined organic layer was dried (MgSO₄), evaporated, and was subjected to silica gel column chromatography (Hex/Et₃N = 99/1) to get 0.684 g (52 %) of a pale yellow oil.

\[
\text{TMS}
\]

IR (neat): 3430 (OH), 3305, 2165 cm⁻¹; H NMR (500 MHz, CDCl₃): δ 0.16 (s, 9H), 1.40 (s, 3H), 1.66-1.75 (m, 2H), 1.78-1.83 (m, 2H), 2.18 (t, J = 2.3 Hz, H), 2.86 (dd, J = 7.4, 15.7 Hz, H), 3.07 (m, 2H), 3.49 (s br, H), 3.67 (dd, J = 2.3, 17.4 Hz, H), 4.11 (dd, J = 2.3, 17.4 Hz, H); C NMR (125 MHz, CDCl₃): δ 0.2, 24.5, 26.5, 27.5, 43.9, 54.8, 68.1, 68.8, 72.6, 80.5, 87.9. (VI-115-4)

To a solution of above alcohol (200 mg, 0.802 mmol) in THF (2 mL) at 0 °C was added a solution of TBAF (1.04 mL of 1.0 M in THF soln, 1.04 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was poured into ice-water (5 mL) and the aqueous layer was extracted with ether (5 mL x 3). The combined organic layer was dried (MgSO₄), evaporated, and was subjected to silica gel chromatography (EtOAc/Hex = 1/25, 3 % Et₃N) to get 130 mg (92 %) of 119 as a pale yellow oil.
(119) IR (neat): 3418 (OH), 3295, 2360, 2106 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)):
\[\delta\] 1.42 (s, 3H, Me), 1.55-1.76 (m, 2H, NCH\(_2\)CH\(_2\)), 1.77-1.85 (m, 2H, NCHCH\(_2\)), 2.18 (t, 
\(J = 2.3\) Hz, H, CH\(_2\)C≡CH), 2.43 (s, H, C(OH)C≡CH), 2.87 (ddd, \(J = 1.1, 8.3, 8.3\) Hz, H, 
NCH\(_2\)CH\(_2\)), 3.05 (m, H, NCH\(_2\)CH\(_2\)), 3.07 (t, \(J = 7.3\) Hz, H, NCH), 3.52 (s br, H, OH),
3.64 (dd, \(J = 2.3, 17.5\) Hz, H, NCH\(_2\)C≡CH), 4.05 (dd, \(J = 2.3, 17.5\) Hz, H, NCH\(_2\)C≡CH);
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \[\delta\] 24.7 (NCH\(_2\)CH\(_2\)), 26.5 (CH\(_3\)), 27.6 (NCHCH\(_2\)).
44.0 (NCH\(_2\)C≡CH), 54.8 (NCH\(_2\)CH\(_2\)), 68.1 (C(OH)C≡CH), 68.7 (NCH), 71.9 (C(OH)C≡CH),
72.7 (NCH\(_2\)C≡CH), 80.5 (C(OH)C≡CH), 89.2 (NCH\(_2\)C≡CH); HRMS calcd for 
C\(_{11}\)H\(_{13}\)NONa [M+Na]: 200.1051, found: 200.1071. (VI-117)

**Attempted Silylstannylation of Diyne 119:**

To a solution of Pd\(_2\)(dba)\(_3\)CHCl\(_3\) (2.6 mg, 0.0050 mmol), Bu\(_3\)Sn-SiMe\(_3\) (40 mg, 0.11 mmol),
and phosphine ligand (0.010 mmol, see eq. 21) in C\(_6\)D\(_6\) (1 mL) was added diyne 119 (17.7 mg, 0.100 mmol).
The progress of the reaction was followed by \(^1\)H NMR spectroscopy. Typical reaction mixture contains
mixtures of several species. Attempts to isolate the product by column chromatography (Hex/EtOAc = 32/1)
on silica gel resulted in mixture of products, which were not identified further. (V-92, V-118, V-120, V-121)
Attempted Borostannylation of Diyne 119:

\[
\begin{align*}
\text{Pd(PPh}_3\text{)}_2\text{Cl}_2 & \quad \text{Me}_3\text{Sn-B} \\
119 & \quad \rightarrow \quad \text{MeOH} \\
\text{Me} & \quad \text{SnMe}_3
\end{align*}
\]

To a solution of Pd(PPh₃)₂Cl₂ (3.5 mg, 0.0050 mmol) and borylstannane reagent (25.6 mg, 0.110 mmol) in 1 mL of C₆D₆ was added diyne 119 (17.7 mg, 0.100 mmol) and the progress of the reaction was followed by $^1$H NMR spectroscopy. After 1 h at rt, a clean conversion into the product was observed. Attempts to isolate this material by chromatography resulted in a decomposition of product. Attempts to isolate the material by recrystallization from hexane also failed to produce a clean product. The following peaks were obtained from the reaction mixture, although it is incomplete. The structure in eq. 22 should be considered tentative (See the $^1$H NMR spectra in the appendix).

$^1$H NMR (500 MHz, C₆D₆): $\delta$ 5.77 (s, $J_{\text{Sn-H}} = 70$ Hz, H), 5.45 (d, $J = 1.2$ Hz, H), 3.31 (d, $J = 10.7$ Hz, H), 3.22 (s, H), 1.52 (s, 3H, Me), 0.20 (s, 9H, SnMe₃); $^{119}$Sn (186 MHz, C₆D₆): $\delta$ -48.4 ppm (s). (V-165, V-167)
6.3 EXPERIMENTAL SECTION FOR CHAPTER 4

Ph$_3$Sn-SiMe$_2$Bu$^1$

To a solution of $^2$Pr$_2$NH (0.91 mL, 6.50 mmol) in anhydrous THF (10 mL) at 0 °C was added n-BuLi (2.40 mL of 2.5 M in Hex, 6.00 mmol) dropwise. The resulting solution was stirred for additional 5-10 min and Ph$_3$SnH (1.28 mL, 5.00 mmol) was added. After 20-30 min at 0 °C, the reaction was quenched with TDBMS-Cl (0.490 g, 6.50 mmol). The white suspension was further stirred for 1 h at rt. The solvent was evaporated and the residue was redissolved in EtOAc (5 mL), filtered through 3 cm of silica pad, rinsed with EtOAc, and the solvent was evaporated to dryness. The colorless oil obtained has satisfactory $^1$H $^13$C NMR spectra, which can be purified by column (eluent: Hex 100%) to get an off-white solid (mp 71-72 °C).

$^1$H NMR (500 MHz, CDCl$_3$): δ 0.45 (s, $J_{Sn-H} = 74$ Hz, 6H), 1.01 (s, 9H), 7.30-7.40 (m, 9H), 7.50-7.60 (m, 6H); $^13$C NMR (125 MHz, CDCl$_3$): δ -2.0, 19.5, 27.9, 128.6, 128.8 (s, $J_{Sn-H} = 74$ Hz), 138.0 (s, $J_{Sn-H} = 74$ Hz), 141.1 (s, $J_{Sn-H} = 372$ Hz); Anal. Calcd for C$_{24}$H$_{30}$SiSn: C, 61.95; H, 6.50, found: C, 61.82; H, 6.32. (IV-278)

*Synthesis of Alleneynes 120-123 and Allenes 124 and 125:*
To a solution of diethylpropargyl malonate (0.704 g, 3.14 mmol) in CH$_3$CN (5 mL) was added paraformaldehyde (151 mg, 5.02 mmol), CuBr (225 mg, 1.57 mmol), and iPr$_2$NH (0.53 mL, 3.8 mmol) and the mixture was heated to reflux for 6 h. The solvent was evaporated and the residue was directly loaded on a silica gel column and was eluted with EtOAc:Hex (1/10) to get a colorless oil (98 mg, 23 %). Trace amount of bisallene side product (resulting from diethyl dipropargylmalonate) can be cleanly separated (Alternatively, Gore, J. et al have provided the synthesis of this compound via the Pd catalyzed addition of malonate to 2,3-butadienyl phosphonate with complete suppression of multi-alkylation problem.$^{7b}$).

(127) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.27 (t, $J = 7.2$ Hz, 6H), 2.58 (m, 2H), 3.46 (t, $J = 7.5$ Hz, H), 4.20 (dq, $J = 1.2$, 7.2 Hz, 4H), 4.70 (m, 2H), 5.14 (quintet, $J = 6.7$ Hz, H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 13.9, 27.2, 51.4, 61.3, 76.0, 86.6, 168.7, 208.5; GC (70 $^\circ$C-5 min-20 $^\circ$C/min-250 $^\circ$C): $t_r = 10.94$ min (97 %). (V-276, V284)

To a solution of diethyl-2,3-butadienyl malonate (180 mg, 0.849 mmol) in THF (2 mL) was added KH (44.3 mg, 1.10 mmol) portionwise. The mixture was stirred for 30 min at rt and propargyl bromide (0.144 mL, 1.70 mmol) was added and the resulting mixture was stirred overnight. The reaction was quenched with saturated NH$_4$Cl solution (3 mL)
and normal extractive workup, followed by silica gel flash chromatography (EtOAc/Hex = 1/10) gave 190 mg (89 %) of a colorless oil.

(120) IR (thin film) 3291, 2123, 1956, 1732 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.25 (t, \(J = 7.1\) Hz, 6H, CH\(_3\)CH\(_2\)O), 2.00 (t, \(J = 2.7\) Hz, H, CH\(_2\)CCH), 2.77 (td, \(J = 2.4, 8.0\) Hz, 2H, CH\(_2\)CCH), 2.85 (d, \(J = 2.7\) Hz, 2H, CH\(_2\)CH=C=C), 4.20 (q, \(J = 7.1\) Hz, 4H, CH\(_3\)CH\(_2\)O), 4.67 (td, \(J = 2.4, 6.7\) Hz, 2H, RCH=C=CH\(_2\)), 4.95 (tt, \(J = 6.7, 8.0\) Hz, H, RCH=C=CH\(_2\)); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 14.4, 23.0, 32.0, 57.4, 62.1, 71.8, 75.1, 79.2, 84.2, 170.0, 210.6; GC (70 °C-5 min-20 °C/min-250 °C): \(t_r = 12.09\) min (98 %). (V-281)

To a solution of diethyl-2,3-butadienyl malonate (188 mg, 0.887 mmol) in THF (3 mL) was added KH (39.2 mg, 0.976 mmol) portionwise. The mixture was stirred for 1 h at rt and 1-bromo-2-butyne (0.144 mL, 1.698 mmol) was added and the resulting mixture was stirred overnight. The reaction was quenched with saturated NH\(_4\)Cl solution (5 mL) and normal extractive workup, followed by silica gel flash chromatography (EtOAc/Hex = 1/10) gave 186 mg (79 %) of a colorless oil.

(121) IR (neat): 3250, 2983, 2935, 2245, 1956, 1732, 1628, 1445, 1367, 1284, 1205, 1077, 1019, 857 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.25 (t, \(J = 7.0\) Hz, 6H, CO\(_2\)CH\(_2\)CH\(_3\)), 1.74 (t, \(J = 2.5\) Hz, 3H, C=C-CH\(_3\)), 2.75 (dt, \(J = 2.4, 7.9\) Hz, 2H, CH\(_2\)CH=C=C=C), 2.78 (q, \(J = 2.5\) Hz, 2H, CH\(_2\)C=C-CH\(_3\)), 4.19 (q, \(J = 7.0\) Hz, 4H,
CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}, 4.63-4.67 (m, 2H, CH=C=CH\textsubscript{2}), 4.97 (m, H, CH=C=CH\textsubscript{2}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \delta 3.8, 14.4, 23.3, 32.0, 57.7, 61.8, 73.7, 74.9, 79.2, 84.5, 170.3, 210.5; HRMS calcld for [M+H]\textsuperscript{+} 287.1254, found 287.1277. (V-288)

A solution of propargyl tosylamide (2.09 g, 10.0 mmol), paraformaldehyde (360 mg, 12.0 mmol), CuBr (0.717 mg, 5.00 mmol), and \textsuperscript{2}Pr\textsubscript{2}NH (1.68 mL, 12.0 mmol) in CH\textsubscript{3}CN (30 mL) was refluxed gently for 9 h. The crude mixture was evaporated and directly loaded on a silica gel column and was eluted with EtOAc:Hex (1/3) to get a colorless oil (0.277 g, 12%).

(129) IR (mineral oil) 3280, 1957, 1598 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}): \delta 2.42 (s, 3H), 3.53-3.64 (m, 2H), 4.67 (s br, H), 4.70-4.78 (m, 2H), 4.97-5.10 (m, H), 7.29 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H); \textsuperscript{13}C NMR (63 MHz, CDCl\textsubscript{3}): \delta 21.9, 41.9, 78.4, 87.6, 127.6, 130.1, 137.5, 143.9, 208.4. (V-301, VI-3)

To a solution of 2,3-butadienyl-(p-toluenesulfonyl)amide (98 mg, 0.44 mmol) in THF (1 mL) was added portionwise KH (21 mg, 1.2 equiv.) and the mixture was stirred at rt for 1 h. To the reaction mixture was added propargyl bromide (0.056 mL, 0.66 mmol) and the mixture was stirred overnight. The reaction was quenched with saturated NH\textsubscript{4}Cl solution
(3 mL) and normal extractive workup, followed by silica gel flash chromatography (EtOAc/Hex = 1/6) gave 92 mg (80 %) of a colorless oil.

(122) IR (thin film) 3288, 2120, 1955, 1598 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.03 (t, J = 2.5 Hz, H, CH₂CCH), 2.42 (s, 3H, Ar-CH₃), 3.88 (td, J = 2.5, 7.1 Hz, 2H, CH₂CH=C=C), 4.15 (d, J = 2.5 Hz, 2H, CH₂CCH), 4.78 (td, J = 2.5, 6.6 Hz, 2H, RCH=C=C), 5.04 (quintet, J = 6.9 Hz, H, RCH=C=C), 7.29 (d, J = 8.0 Hz, 2H), 7.7 (d, J = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 35.7, 45.5, 73.4, 76.3, 85.3, 127.5, 129.4, 136.0, 143.4, 209.7; HRMS calcd for [M] 261.0824, found 261.0824.

(V-303)

To a solution of 1-phenyl-2-propyn-1-ol (1.59 g, 12.0 mmol) in THF (50 mL) was added paraformaldehyde (722 mg, 24.1 mmol), CuBr (863 mg, 6.02 mmol), and ²Pr₂NH (2.53 mL, 18.0 mmol), and the mixture was heated to reflux for 10 h. The crude mixture was evaporated and directly loaded on a silica gel column and was eluted with EtOAc:Hex (1/4, 3 % EtOH) to get a colorless oil (1.08 g, 61 %).⁹ (VI-88)
To a solution of 131 (512 mg, 3.51 mmol) in DME (13 mL) at rt was added portionwise NaH (183 mg, 4.56 mmol, 60 % in oil) and the mixture was stirred for 1 h. To the resulting mixture was added propargyl bromide (0.89 mL, 10.5 mmol) and the mixture was further stirred at rt overnight. The reaction was quenched by addition of saturated solution of NH₄Cl (10 mL) and normal extractive workup, followed by silica gel flash chromatography (EtOAc/Hex = 1/10) gave 567 mg (88 %) of a colorless oil.

(123) IR (thin film) 3298, 3063, 3030, 2955, 2117, 1954 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.44 (t, J = 2.4 Hz, H, CH₂CCH), 4.17 (dd, J = 2.4, 15.7 Hz, H, CH₂CCH), 4.25 (dd, J = 2.4, 15.7 Hz, H, CH₂CCH), 4.84 (ddd, J = 1.5, 6.6, 11.2 Hz, H, CHCH=C=CH₂), 5.14 (td, J = 1.4, 7.8 Hz, CHCH=C=CH₂), 5.33 (td, J = 6.6, 7.8 Hz, H, OCH); ¹³C NMR (100 MHz, CDCl₃) δ 55.3, 74.3, 76.6, 78.5, 79.5, 91.9, 126.7, 127.9, 128.3, 140.3, 208.8; HRMS calcd for [M] 184.0888, found 184.0855. (VI-89)

The allene 124 was obtained as a side product as a result of base promoted isomerization of corresponding propargyl derivatives: To a stirred suspension of NaH (864 mg, 36.0 mmol) in THF (100 mL) was added the starting alcohol, 2-carbobenzyloxyamino-1-O-tert-butyldimethylsiloxypropan-3-ol (5.09 g, 15.0 mmol) in THF (10 mL) dropwise. The reaction mixture was stirred at rt for 15 h and propargyl bromide (3.83 mL, 45.0 mmol) in THF (30 mL) was added to the mixture. The reaction was quenched followed by
normal extractive workup. The resulting residue was purified by flash chromatography (EtOAc/Hex/acetone = 1/2/1) to get A (30 %) and B (124) (46 %) as a pale yellow oil.

(124) IR (thin film): 3036, 2954, 2929, 2884, 2710, 1963, 1766 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.05 (s, 6H), 0.88 (s, 9H), 3.66 (dd, J = 2.6, 10.6 Hz, H, CH₂OSi), 3.81 (dd, J = 5.0, 10.6 Hz, H, CH₂OSi), 3.92 (m, H, CHCH₂OSi), 4.38 (d, J = 3.0 Hz, H, CH₂CH), 4.39 (s, H, CH₂CH), 5.39 (dd, J = 6.5, 10.0 Hz, H, NCH=C=CH₂), 5.44 (dd, J = 6.5, 10.0 Hz, NCH=C=CH₂), 6.85 (t, J = 6.5 Hz, NCH=C=CH₂); ¹³C NMR (125 MHz, CDCl₃) δ -6.5, -5.0, 18.5, 26.1, 56.1, 61.0, 65.7, 88.1, 96.5, 155.8, 201.5; HRMS calcd for [M+H] 270.1525, found 270.1526. (V-177)

To a solution of THP ether 133° (2.54 g, 10.0 mmol) in ether (20 mL) was added LAH (455 mg, 12.0 mmol) and the resulting suspension was refluxed for 4 h. The reaction mixture was quenched with ~2 g of celite/Na₂SO₄/water (3/3/1) mixture and was further stirred for 1 h. The insoluble material was filtered and the evaporation of solvent, followed by flash chromatography (EtOAc/Hex = 1/6) of the resulting residue gave 577 mg (37 %) of an oil.

(125) ¹H NMR (500 MHz, CDCl₃): δ 1.48-1.62 (m, 4H), 1.70-1.78 (m, H), 1.80-1.88 (m, H), 3.48-3.53 (m, H), 3.82-3.89 (m, H), 4.00-4.07 (m, H), 4.19-4.25 (m, H), 4.68 (t, J =
3.6 Hz, H), 4.73-4.80 (m, 2H), 5.20-5.30 (m, H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 19.8, 25.8, 31.0, 62.6, 65.2, 76.1, 88.2, 98.1, 209.7. (VI-105)

To a solution of Pd$_2$(dba)$_3$CHCl$_3$ (1.3 mg, 0.0025 mmol Pd), P(C$_6$F$_5$)$_3$ (2.7 mg, 0.0050 mmol), and Ph$_3$Sn-SiMe$_2$Bu' (26 mg, 0.055 mmol) in 1 mL of C$_6$D$_6$ at rt was added alleneyne 120 (12.5 mg, 0.050 mmol) and the reaction mixture was kept in an NMR tube. Progress of the reaction was followed by $^1$H NMR. After 2 days at rt, the contents of the NMR tube was evaporated and the residual oil was purified by flash chromatography (Hex/Et$_3$N = 95/5) to get 29.3 mg (80%) of product as a colorless oil.

(135a) $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ -0.24 (s, 3H), -0.16 (s, 3H), 0.77 (s, 9H), 0.90 (t, $J$ = 7.1 Hz, 3H, CH$_3$CH$_2$O), 0.93 (t, $J$ = 7.1 Hz, 3H, CH$_3$CH$_2$O), 2.30 (dd, $J$ = 5.5, 13.0 Hz, H, CH$_2$CH), 3.16 (dd, $J$ = 9.1, 13.0 Hz, H, CH$_2$CH), 3.22 (d, $J$ = 15.5 Hz, H, CH$_2$C=C), 3.70-3.75 (m, 2H, CH$_2$CH, CH$_2$C=C), 3.90-4.05 (m, 4H, CH$_3$CH$_2$O), 5.36 (t, $J$ = 1.6 Hz, H, SiC=CH$_2$), 5.95 (t, $J$ = 1.8 Hz, SiC=CH$_2$), 6.40 (s, $J_{Sn-H}$ = 74 Hz), 7.25-7.35 (m, 9H), 7.68-7.85 (m, 6H); $^{13}$C NMR (100 MHz, C$_6$D$_6$) $\delta$ -6.1, -4.4, 13.4, 13.6, 26.9, 41.1, 46.4, 50.1, 59.0, 60.9, 61.0, 119.6, 126.8, 128.3 ($J_{Sn-H}$ = 50 Hz), 128.6, 137.0 ($J_{Sn-H}$ = 38 Hz), 138.9, 151.1, 163.6, 170.5, 171.1; Anal. Calcd for C$_{38}$H$_{48}$O$_4$SiSn: C, 63.78; H, 6.76, found: C, 64.16, H, 6.74; Selected nOe contacts depicted above confirmed the stereochemistry. (VI-5, V-282)
**Screening for Optimal Ligand: (eq. 12)**

To a solution of Pd$_2$(dba)$_3$CHCl$_3$ (1.3 mg, 0.0025 mmol Pd), phosphine ligand (0.0050 mmol, see eq. 12, p 117), and Ph$_3$Sn-SiMe$_2$Bu' (26 mg, 0.055 mmol) in 1 mL of C$_6$D$_6$ at rt was added alleneyne 120 (12.5 mg, 0.050 mmol) and the reaction mixture was kept in an NMR tube. Progress of the reaction was followed by $^1$H NMR. The reaction gave a clean conversion into the cyclic product and no discernable side-product was observed except starting material. The yield was based on the amount of product and starting material left. (VI-5)

**Screening for Pd precursor: (eq. 13)**

To a solution of Pd precursor (0.0025 mmol Pd, see eq. 13, p 118), P(C$_6$F$_3$)$_3$ (2.7 mg, 0.0050 mmol), and Ph$_3$Sn-SiMe$_2$Bu' (26 mg, 0.055 mmol) in 1 mL of C$_6$D$_6$ at rt was added alleneyne 120 (12.5 mg, 0.050 mmol) and the reaction mixture was kept in an NMR tube. Progress of the reaction was followed by $^1$H NMR. The reaction gave clean conversion into the cyclic product and no discernable side-product was observed except starting material. The yield was based on the amount of product and starting material left (VI-20).

![Diagram](image)

To a solution of Pd$_2$(dba)$_3$CHCl$_3$ (2.6 mg, 0.0050 mmol Pd), P(C$_6$F$_3$)$_3$ (5.3 mg, 0.0100 mmol), and Bu$_3$Sn-SiMe$_3$ (40.0 mg, 0.110 mmol) in 1 mL of C$_6$D$_6$ at rt was added
alleneyne 120 (25.0 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by \(^1\)H NMR. After 2 h at rt, \(^1\)H NMR spectrum indicated a clean conversion into an acyclic intermediate 134b. The contents of the NMR tube was evaporated and the residual oil was purified by flash chromatography (Hex/Et\(_3\)N = 95/5) to get 51.0 mg (83 %) of product as a colorless oil.

134b IR (thin film): 3314, 2956, 2827, 2853, 2359, 2340, 1738 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 0.02 (s, 9H), 0.85-0.92 (m, 15H, SnBu\(_3\)), 1.25 (t, \(J = 7.1\) Hz, 6H, CH\(_3\)CH\(_2\)O), 1.29-1.55 (m, 12H, SnBu\(_3\)), 1.91 (s, \(J_{\text{Sn-H}} = 64\) Hz, 2H, CH\(_2\)SnBu\(_3\)), 1.96 (t, \(J = 2.6\) Hz, H, CH\(_2\)CCH), 2.73 (d, \(J = 6.9\) Hz, 2H, CH\(_2\)CH=CSi), 2.78 (d, \(J = 2.6\) Hz, 2H, CH\(_2\)CCH), 4.19 (dq, \(J = 1.3, 7.1\) Hz, 4H), 5.13 (t br, \(J = 6.9\) Hz, H, CH\(_2\)CH=CSi); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 1.2, 10.5, 13.4, 14.1, 14.5, 23.2, 27.8, 29.5, 31.7, 57.3, 61.9, 71.5, 80.1, 125.9, 146.3, 170.4; HRMS calcd for [M+Na] 637.2711, found 637.2719; nOe experiments confirmed the stereochemistry depicted above. (VI-77)

\[ \text{EtO}_2\text{C} \quad \text{SnBu}_3 \quad \text{SiMe}_3 \rightarrow \quad \text{EtO}_2\text{C} \quad \text{SiMe}_3 \quad \text{SnBu}_3 \]

To a solution of Pd\(_2\)(dba\(_3\))CHCl\(_3\) (2.6 mg, 0.0050 mmol Pd), P(C\(_6\)F\(_5\))\(_3\) (5.3 mg, 0.0100 mmol), and Bu\(_3\)Sn-SiMe\(_3\) (40.0 mg, 0.110 mmol) in 1 mL of C\(_6\)D\(_6\) at rt was added alleneyne 120 (25.0 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by \(^1\)H NMR. After 1.5 h at rt, \(^1\)H NMR spectrum indicated a clean conversion into an acyclic intermediate 134b. This reaction
mixture was heated at 80 °C for 8 h. The $^1$H NMR at this point indicates a clean conversion into a cyclic product 135b with no acyclic product remaining. The contents of the NMR tube was evaporated and the residual oil was purified by flash chromatography (Hex/Et$_3$N = 95/5) to get 58.8 mg (92 %) of product as a colorless oil.

(135b) IR (film): 2956, 2926, 2872, 2854, 1732, 1615, 1463, 1376, 1368, 1249 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.14 (s, 9H), signals due to SnBu$_3$ group are omitted, 1.99 (dd, $J = 5.9, 7.1$ Hz, H, ring CH$_2$CH), 2.80 (dd, $J = 8.0, 12.4$ Hz, H, ring CH$_2$CH), 2.83 (d, $J = 15.6$ Hz, H, ring CH$_2$), 3.23 (d, $J = 15.8$ Hz, H, ring CH$_2$), 3.29 (t br, $J = 7.1$ Hz, H, CH$_2$CH), 4.12-4.22 (m, 4H, OCH$_2$CH$_3$), 5.35 (s br, H, CH$_2$=CSi), 5.67 (t br, $J = 1.9$ Hz, H, CH$_2$=CSi), 5.96 (s, $^3$J$_{Sn-H} = 64$ Hz, H, CH$_2$Sn); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 0.00, 10.3, 14.1, 14.4, 14.5, 27.8, 29.5, 41.3, 46.2, 50.0, 59.7, 61.8, 61.9, 123.8, 125.1, 153.9, 159.1, 171.9, 172.0; $^{119}$Sn NMR (186 MHz, CDCl$_3$) $\delta$ -61.4; HRMS (FAB) calcd for C$_{29}$H$_{54}$O$_4$SiSnNa [(M+Na)$^+$] 637.2717, found 637.2716. (VI-19, VI-91)

To a solution of Pd$_2$(dba)$_3$CHCl$_3$ (2.6 mg, 0.0050 mmol Pd), P(C$_6$F$_5$)$_3$ (5.3 mg, 0.0100 mmol), and Ph$_3$Sn-SiMe$_2$Bu$'$ (51 mg, 0.110 mmol) in 1 mL of C$_6$D$_6$ at rt was added alleneyne 122 (26.1 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by $^1$H NMR. After 24 h at rt, a clean conversion into cyclic product 136 was observed. The contents of the NMR tube was
evaporated and the residual oil was purified by flash chromatography (EtOAc/Hex = 1/10, 3% Et$_3$N) to get 30.0 mg (41%) of product as a colorless oil.

(136) IR (thin film) 3064, 2955, 2856, 1622, 1598, 1480, 1470, 1348, 1265, 1165 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ -0.34 (s, 3H), -0.19 (s, 3H), 0.80 (s, 9H), 2.48 (s, 3H), 3.14 (dd, $J = 6.6, 9.1$ Hz, H), 3.35 (d br, $J = 6.2$ Hz, H), 3.38 (d, $J = 9.2$ Hz, H), 4.16 (d br, $J = 14.1$ Hz, H), 5.27 (t, $J = 1.6$ Hz, H), 5.81 (t, $J = 1.8$ Hz, H), 6.28 (s, $^2J_{\text{Sn-H}} = 80$ Hz, H), 7.30-7.70 (m, 15H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ -6.2, -4.2, 16.5, 21.4, 50.4, 53.8, 54.7; HRMS calcd for [M+Na] 750.1860, found 750.1856; A selected nOe contacts confirmed the double bond configuration and ring structure depicted. (VI-7)

To a solution of Pd(PhCN)$_2$Cl$_2$ (1.9 mg, 0.0050 mmol Pd), P(C$_6$F$_5$)$_3$ (5.3 mg, 0.0100 mmol), and Ph$_3$Sn-SiMe$_2$Bu$^+$ (51 mg, 0.110 mmol) in 1 mL of C$_6$D$_6$ at rt was added allene 123 (18.4 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by $^1$H NMR. After 2.5 h at rt, $^1$H NMR of the mixture showed a mixture of starting 123 and product 137 (ratio ~ 1:1). After 12 h at rt, a clean conversion into cyclic product 137 was observed with less than <5% of starting material remaining. Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash chromatography (Hex/Et$_3$N = 95/5) followed by careful second chromatography to get 39.7 mg (61%) of product as a colorless oil.
To a solution of Pd(PhCN)$_2$Cl$_2$ (1.9 mg, 0.0050 mmol Pd), P(C$_6$F$_5$)$_3$ (5.3 mg, 0.0100 mmol), and Bu$_3$Sn-SiMe$_3$ (40.0 mg, 0.110 mmol) in 1 mL of C$_6$D$_6$ at rt was added alleneyne 123 (18.4 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by $^1$H NMR. After 14 h at rt, $^1$H NMR of the mixture showed a mixture of starting 123 and product 138 (ratio ~ 3:10) and no further progress until 22 h at rt. Then the reaction mixture was heated at 80 °C for 5 h, and $^1$H NMR of the mixture showed a clean conversion into cyclic product. Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash...
chromatography (Hex/Et$_3$N = 95/5) followed by a careful second chromatography to get 39.5 mg (72%) of product as a colorless oil.

(138) IR (thin film): 2956, 2924, 1622, 1518, 1484, 1417, 1376, 1292, 1248, 1092, 1050, 982, 933 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 0.20 (s, 9H), 0.75-0.92 (m, SnBu$_3$), 1.20-1.50 (m, SnBu$_3$), 3.48 (s br, H, CH(TMS)C=CH$_2$), 4.47 (dd, $J = 1.6$, 12.6 Hz, H, CH$_2$C=C), 4.56 (td, $J = 1.6$, 12.6 Hz, H, CH$_2$C=C), 4.98 (d, $J = 2.1$ Hz, H, OCH), 5.57 (dd, $J = 0.9$, 2.3 Hz, SiC=CH$_2$), 5.75 (t, $J = 1.8$ Hz, H, SiC=CH$_2$), 5.96 (d, $J = 1.5$ Hz, $^2$J$_{Sn-H}$ = 56 Hz, H, CHSn); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 0.4, 10.4, 14.1, 27.8, 29.5, 59.8, 74.3, 86.8, 120.8, 126.4, 127.6, 127.8, 128.8, 142.8, 152.6, 159.3; HRMS (FAB) calcd for C$_{28}$H$_{48}$OSnSi [(M+Na)$^+$] 571.2394, found 571.2395; A selected nOe supports double bond geometry shown. For a detailed nOe, refer to Figure 4.5 in Chapter 4.3. (VI-117-2)

\[
\text{EtO}_2C\text{EtO}_2C \xrightarrow{X} \begin{array}{l}
\text{EtO}_2C \\
\text{EtO}_2C
\end{array}
\]

\[
\begin{array}{l}
\text{EtO}_2C \\
\text{EtO}_2C
\end{array}
\]

\[
\begin{array}{l}
\text{EtO}_2C \\
\text{EtO}_2C
\end{array}
\]

Reaction of 121 with Ph$_3$Sn-SiMe$_2$Bu' and Bu$_3$Sn-SiMe$_3$ under the standard conditions:

To a solution of Pd(PhCN)$_2$Cl$_2$ (1.9 mg, 0.0050 mmol Pd), P(C$_6$F$_5$)$_3$ (5.3 mg, 0.0100 mmol), and Ph$_3$Sn-SiMe$_2$Bu' (51 mg, 0.110 mmol) in 1 mL of C$_6$D$_6$ at rt was added alleneyne 121 (26.4 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by $^1$H NMR. After 2 days at 80 °C, starting 121 remained intact and even after 3 days at 80 °C, starting material remained
largely intact with less than 15% conversion into an unidentified mixture. The attempts to isolate the product failed. When Bu₃Sn-SiMe₃ was used instead, after 2 days at 80 °C, the reaction mixture shows acyclic adduct 139 in a mixture with other side products and no starting material remained. However, attempts to isolate adduct 139 failed. An in-situ ¹H NMR (C₆D₆) indicated a peak at δ 5.60 (t, J = 7.0 Hz) assigned to CH=C(SiR₃)CH₂(SnR’₃) by analogy with the structure of 134b. (V-292, VI-116)

\[
\begin{align*}
\text{EtO}_2C & \quad \text{Me} \\
\text{EtO}_2C & \quad \text{Me} \\
120 & \quad \text{SnMe}_3 \\
\end{align*}
\]

To a solution of Pd₂(dba)₃.CHCl₃ (2.6 mg, 0.0050 mmol Pd), P(C₆F₅)₃ (5.3 mg, 0.010 mmol), and Me₃Sn-B(-N(Me)CH₂CH₂(MeN-)- (26.0 mg, 0.100 mmol) in 1 mL of C₆D₆ at rt was added alleneyne 120 (25.0 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube. Progress of the reaction was followed by ¹H NMR. After 17 h at rt, the ¹H NMR spectrum showed reasonable conversion into the product 141 along with some side-product with less than 10% of starting 120 remaining. However, every attempts to isolate this product failed. The following data was extracted from the in situ ¹H NMR spectra taken in C₆D₆.

(141) ¹H NMR (500 MHz, C₆D₆): δ 5.69 (d, J = 2.4 Hz, J_{Sn-H} = not determined, H, RC(Sn)=CH₂), 5.60 (s, H, C=CH₂), 5.15 (d, J = 2.5 Hz, J_{Sn-H} = 64 Hz, H, RC(Sn)=CH₂).

(V-255, V-270, V-271, V-283, V-285)
To a solution of Pd$_2$(dba)$_3$CHCl$_3$ (1.3 mg, 0.0025 mmol Pd), P(C$_6$F$_5$)$_3$ (2.7 mg, 0.0050 mmol), and Me$_3$Sn-SnMe$_3$ (18.0 mg, 0.055 mmol) in 1 mL of C$_6$D$_6$ at rt was added allene 120 (12.5 mg, 0.050 mmol) and the reaction mixture was kept in an NMR tube. Progress of the reaction was followed by $^1$H NMR. After 22 h at rt, the reaction mixture showed a clean conversion into the acyclic product 142, which after 2 days at 45 °C, was converted into 143 (>90 %) with <10 % of starting 142 remaining. Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash chromatography (Hex/Et$_3$N = 97/3) to get 13.2 mg (46 %) of product as a colorless oil.

(142) $^1$H NMR (500 MHz, CDCl$_3$): δ 0.08 (s, 9H), 0.11 (s, 9H), 0.87 (s, J = 7.0 Hz, 3H), 1.67 (t, J = 2.7 Hz, H, CH$_2$C=CH), 2.23 (s, J$_{Sn-H}$ = 72 Hz, (Me$_3$Sn)CH$_2$C(SnMe$_3$)=CH, 2H), 3.08 (d, J = 2.7 Hz, 2H, CH$_2$C=CH), 3.18 (d, J = 6.7 Hz, 2H, C(SnMe$_3$)=CHCH$_2$), 3.91 (m, 4H), 5.34 (t, J = 6.7 Hz, H, C(SnMe$_3$)=CHCH$_2$).

(143) $^1$H NMR (500 MHz, CDCl$_3$): δ 0.06 (s, 9H), 0.17 (s, 9H), 1.24 (t, J = 7.0 Hz, 6H, OCH$_2$CH$_3$), 2.00 (dd, J = 7.8, 13.2 Hz, H, ring CH$_2$CH), 2.72 (ddd, J = 1.6, 8.6, 13.2 Hz, H, ring CH$_2$CH), 2.90 (dd, J = 1.5, 17.5 Hz, H, ring CH$_2$), 3.15 (td, J = 2.4, 16.0 Hz, H, ring CH$_2$), 3.45 (t br, J = 7.9 Hz, H, CH$_2$CH), 4.10-4.23 (m, 4H, OCH$_2$CH$_3$), 5.20 (dd, J = 2.2, 0.9 Hz, $^3$J$_{Sn-H}$ = 68 Hz, H, SnC=CH$_2$), 5.70 (dd, J = 2.2, 1.3 Hz, $^3$J$_{Sn-H}$ = 150 Hz, SnC=CH$_2$), 5.91 (s, $^2$J$_{Sn-H}$ = 66 Hz, CHSn); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -7.8, -7.7,
To a solution of Pd(PhCN)$_2$Cl$_2$ (1.9 mg, 0.0050 mmol Pd), P(C$_6$F$_5$)$_3$ (5.3 mg, 0.010 mmol), and Me$_3$Sn-SnMe$_3$ (36.3 mg, 0.110 mmol) in 1 mL of C$_6$D$_6$ at rt was added allene 123 (18.4 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by $^1$H NMR. After 14 h at rt, $^1$H NMR of the reaction mixture indicated a mixture of acyclic bis-adduct 144 and cyclic product 145. Under more forcing conditions, the reaction did not progress further (80 °C, 5 h). Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash chromatography (Hex/Et$_3$N = 97/3) to get 28.7 mg (42 %) of mixture of product as a colorless oil. Investigation of $^1$H NMR spectrum of this sample indicated it to be a mixture of 144 and 145 (molar ratio of 1:1). The following $^1$H NMR spectrum for 144 and 145 was extracted from that of sample of the above mixture. Owing to the presence of multiple SnMe$_3$ moiety, the $J_{Sn-H}$ coupling was not very clear. Because of incomplete characterization, the structure of the products must be considered tentative.

(144) $^1$H NMR (500 MHz, CDCl$_3$): δ 0.10 (s, 9H), 0.11 (s, 9H), 0.16 (s, 9H), 0.18 (s, 9H), 2.11 (dd, $J = 0.9, 11.2$ Hz, H, (Sn)CH$_2$C(Sn)=CHCH(Ph)O), 2.32 (dd, $J = 1.0, 11.2$ Hz, H, (Sn)CH$_2$C(Sn)=CHCH(Ph)O).
Hz, H, (Sn)CH_{2}C(Sn)=CHCH(Ph)O), 4.50 (t, \( J = 2.0 \) Hz, H, OCH_{2}C(Sn)=CH(Sn)), 4.53 (d, \( J = 1.6 \) Hz, H, OCH_{2}C(Sn)=CH(Sn)), 5.02 (d, \( J = 7.8 \) Hz, H, (Sn)CH_{2}C(Sn)=CHCH(Ph)O), 5.52 (d, \( J = 7.8 \) Hz, H, (Sn)CH_{2}C(Sn)=CHCH(Ph)O), 6.86 (s, \( J_{Sn-H} = 60 \) Hz, H, OCH_{2}C(Sn)=CH(Sn)).

(145) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 0.02 \) (s, 9H), 0.21 (s, 9H), 3.53 (d, \( J = 5.7 \) Hz, H, CHC(Sn)=CH\(_2\)), 3.97 (dd, \( J = 1.5, 11.5 \) Hz, H, CH_{2}C=C(Sn)H), 4.14 (dd, \( J = 1.5, 11.5 \) Hz, CH_{2}C=C(Sn)H), 4.79 (d, \( J = 5.7 \) Hz, PhCHO), 5.35 (d, \( J = 2.3 \) Hz, H, CHC(Sn)=CH\(_2\)), 5.69 (dd, \( J = 0.8, 2.3 \) Hz, H, CHC(Sn)=CH\(_2\)), 5.87 (dd, \( J = 1.9 \) Hz, H, C=C(Sn)H)

(VI-117-3)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OTBS} & \quad \text{OTBDMS} \\
124 & \quad 146
\end{align*}
\]

To a solution of Pd(PhCN)\(_2\)Cl\(_2\) (1.9 mg, 0.0050 mmol Pd), P(C\(_6\)F\(_3\))\(_3\) (5.3 mg, 0.010 mmol), and Ph\(_3\)Sn-SiMe\(_2\)Bu\(^{1}\) (51 mg, 0.110 mmol) in 1 mL of C\(_6\)D\(_6\) at rt was added allene 124 (26.9 mg, 0.100 mmol) and the reaction mixture was kept in an NMR tube at rt. After 8 h at rt, the \(^1\)H NMR spectrum indicated a clean conversion into the desired product 146. Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash chromatography (Hex/Et\(_3\)N = 95/5) to get 43.6 mg (60 \%) of product as an off-white solid (mp 144-146 °C).

(146) IR (thin film) 3049, 2953, 2927, 2895, 2856, 2252, 1748, 1605 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta -0.15 \) (s, 3H), -0.10 (s, 3H), -0.01 (s, 3H), -0.00 (s, 3H), 0.84 (s, 9H), 0.86 (s, 9H), 2.35 (dd, \( J_{Sn-H} = 90 \) Hz, \( J = 1.8, 12.2 \) Hz, H, CH\(_2\)SnBu\(_3\)), 2.46 (d, \( J_{Sn-H} = 264 \) Hz, H, OCH\(_2\)C(Sn)=CH(Sn)).
90 Hz, J = 12.2 Hz, H, CH₂SnBu₃), 3.00 (t, J = 8.0 Hz, H, CH₂OTBS), 3.44 (dd, J = 2.2, 10.3 Hz, H, OCH₂CH), 3.52 (dd, J = 5.1, 10.5 Hz, H, OCH₂CH), 3.82 (dd, J = 2.9, 10.5 Hz, H, CH₂OTBS), 3.85 (m, H, OCH₂CH), 6.02 (d, J₃₅=Sn-H = 38 Hz, J = 1.8 Hz, H, NCH=CSi), 7.32-7.42 (m, 9H), 7.45-7.62 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ -6.2, -5.5, -5.1, 16.2, 17.8, 18.4, 26.0, 27.2, 57.0, 61.5, 65.3, 126.6, 126.8, 129.0 (J₃₅-C = 48 Hz), 129.5, 137.5 (J₃₅-C = 34 Hz), 139.0, 157.4; Anal Calcd for C₃₇H₃₃N₀₃Si₂Sn: C, 60.49; H, 7.27; N, 1.91; found: C, 60.57; H, 7.19; N, 1.88; A selected nOe contact confirmed the stereochemistry depicted above.(VI-78)

![Chemical Structure](image)

To a solution of Pd(PhCN)₂Cl₂ (3.8 mg, 0.010 mmol Pd), P(C₆F₅)₃ (11 mg, 0.020 mmol), and Bu₃SnSiMe₃ (79.9 mg, 0.220 mmol) in 1 mL of C₆D₆ at rt was added allene 124 (53.9 mg, 0.200 mmol) and the reaction mixture was kept in an NMR tube at rt. After 12 h at rt, the ¹H NMR spectrum indicated a clean conversion into the desired product 147 and less than 1 % of isomeric product, which could not be identified. Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash chromatography (Hex/Et₃N = 95/5) to get 59.1 mg (47 %) of product as an oil.

(147) IR (thin film) 2955, 2927, 1754, 1607, 1464, 1402, 1378, 1342, 1249, 1170, 1128, 1076, 1056, 1006, 909, 838, 802, 778, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.03 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.10 (s, 9H, SiCH₃), 0.87 (s, 9H, t-Bu), 1.70 (d, J = 12.0
Hz, H, CH₂Sn), 1.76 (d, J = 12.0 Hz, H, CH₂Sn), 3.52 (dd, J = 2.2, 10.4 Hz, H, CH₂OTBS), 3.64 (dd, J = 4.7, 10.4Hz, H, CH₂OTBS), 4.13-4.18 (m, H, OCH₂CH), 4.28-4.37 (m, 2H, OCH₂CH), 5.86 (s, J_{Sn-H} = 20 Hz, H, CH=C); \(^{13}\)C NMR (125 MHz, CDCl₃): δ -5.12, -5.09, -1.1, 10.8 (J_{Sn-C} = 312 Hz), 14.1, 18.5, 26.1, 27.8 (J_{Sn-C} = 58 Hz), 29.6 (J_{Sn-C} = 20 Hz), 57.3, 61.5, 65.4, 122.6, 132.9, 157.3; HRMS calcd for [M+Na] 656.2953, found 656.2964. A selected nOe contact confirms the double bond geometry depicted.(VI-104-2)

To a solution of Pd(PhCN)₂Cl₂ (3.8 mg, 0.010 mmol Pd), P(C₆F₅)₃ (11 mg, 0.020 mmol), and Bu₃SnSiMe₃ (79.9 mg, 0.220 mmol) in 1 mL of C₆D₆ at rt was added allene 125 (30.8 mg, 0.200 mmol) and the reaction mixture was kept in an NMR tube at rt. After 12 h at rt, the \(^1\)H NMR spectrum indicated a clean conversion into the desired product 148 and less than 5 % of unidentified isomeric product. Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash chromatography (Hex/Et₃N = 95/5) to get 95.5 mg (92 %) of product as a colorless oil.

(148) IR (thin film): 2956, 2874, 2853, 1641, 1518, 1484, 1464, 1377, 1342, 1292, 1247 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃): δ 0.06, 1.80-1.90 (m, 2H, CH₂Sn), 3.43-3.53 (m, H), 3.88 (ddd, J = 3.1, 7.9, 11.3 Hz, H), 4.01 (dd, J = 6.3, 13.2 Hz, H), 4.24 (dd, J = 5.0,
13.2 Hz, H), 4.62 (t, J = 3.8 Hz, H), 5.58 (t, J = 5.7 Hz, H, $^4J_{SN-H} = 188$ Hz, H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -1.8, 9.9, 12.9, 13.5, 19.5, 25.4, 27.3, 29.0, 30.5, 62.1, 64.7, 98.1, 129.6, 143.3: HRMS calcd for [M+Na] 541.2500, found 541.2492. Selected nOe contacts confirm the double bond geometry depicted. (VI-108-1)

![Diagram](image)

To a solution of Pd(PhCN)$_2$Cl$_2$ (3.8 mg, 0.010 mmol Pd), P(C$_6$F$_5$)$_3$ (10.6 mg, 0.020 mmol), and Me$_3$Sn-SnMe$_3$ (72.6 mg, 0.220 mmol) in 1 mL of C$_6$D$_6$ at rt was added alleneyne 125 (30.8 mg, 0.200 mmol) and the reaction mixture was kept in an NMR tube at rt. Progress of the reaction was followed by $^1$H NMR. After 12 h at rt, the starting material completely converted into a mixture of E/Z mixture of product (ratio of E/Z = 2.4/1.0). Solvent was evaporated from the contents of the NMR tube and the residual oil was purified by flash chromatography (Hex/Et$_3$N = 95/5) to get 94.1 mg (97 %) of inseparable mixture of (E) and (Z) product as a colorless oil.

(149-E/Z) $^1$H NMR (400 MHz, CDCl$_3$) δ 0.08 (s, 9H, Z-isomer), 0.10 (s, 9H, E-isomer), 0.11 (s, 9H, E-isomer), 0.18 (s, 9H, Z-isomer), 1.46-1.90 (m, 6H, from THP groups of both E and Z isomers), 1.95-2.20 (m, 2H, from CH$_2$SnMe$_3$ of both E and Z isomers), 3.50 (m, E/Z), 3.87 (m, E/Z), 4.01 (m, E-isomer), 4.20 (m, E/Z), 4.62 (m, E/Z), 5.46 (t br, E-isomer), 5.97 (t br, Z-isomer); $^{13}$C NMR (100 MHz, CDCl$_3$): mixture of E/Z isomers δ - 9.74, -9.68, -9.2, -8.3, 19.42, 19.45, 24.3, 25.4, 30.6, 30.7, 62.05, 62.15, 63.7, 68.9, 97.4, 98.0, 130.2, 130.5, 130.7, 146.6, 148.9. (VI-108-3)
To a solution of Sn-Si adduct (25.8 mg, 0.03972 mmol) 137 in CH₂Cl₂ (1 mL) was added N-bromosuccinimide (10.6 mg, 0.05958 mmol, 1.5 equiv.) at rt. The reaction mixture was stirred for 1 h and was concentrated, then was subject to column chromatography (EtOAc/Hex = 1/9) to get 11.2 mg of an oil (74 %).

(154) ¹H NMR (500 MHz, CDCl₃): δ 0.10 (s, 3H), 0.14 (s, 3H), 0.94 (s, 9H), 3.90 (s br, H), 4.48 (dd, J = 2.0, 3.6 Hz, 2H), 4.90 (d, J = 2.7 Hz, H), 5.60 (d, J = 1.7 Hz, H), 5.78 (t, J = 1.4 Hz, H), 6.20 (q, J = 1.9 Hz, H), 7.27-7.50 (M, 5H); ¹³C NMR (125 MHz, CDCl₃): δ -4.1, -4.4, 17.7, 27.4, 57.4, 71.6, 87.5, 98.5, aromatic carbons are omitted. HRMS calcd for [M+Na] 401.0912, found: 401.0903. (VI-92)

A crude reaction mixture of a solution of Sn-Si adduct 137 (64.9 mg, 0.10 mmol, theory) in CH₂Cl₂ (1 mL) was treated with HCO₂H (23.0 mg, 0.50 mmol) overnight. The solvent was evaporated and the residue was purified by flash column chromatography (EtOAc/Hex = 1/2) to get 23.3 mg (78 %) of an oil.

(155) ¹H NMR (400 MHz, CDCl₃): δ -0.42 (s, 3H), -0.01 (s, 3H), 0.78 (s, 9H), 3.32 (d br, J = 8.9 Hz, H), 4.57 (ddd, J = 2.1, 4.3, 13.2 Hz, H), 4.65 (d, J = 8.9 Hz, H), 4.76 (ddd, J = 2.1, 4.3, 13.2 Hz, H), 4.81 (d, J = 2.1 Hz, H), 5.71 (d, J = 8.9 Hz, H), 6.20 (q, J = 1.9 Hz, H), 7.27-7.50 (M, 5H); ¹³C NMR (125 MHz, CDCl₃): δ -4.1, -4.4, 17.7, 27.4, 57.4, 71.6, 87.5, 98.5, aromatic carbons are omitted. HRMS calcd for [M+Na] 401.0912, found: 401.0903. (VI-92)
= 2.2, 3.3, 13.2 Hz, H), 4.87 (dd, J = 2.4, 4.9 Hz, H), 5.00 (dd, J = 2.1, 4.8 Hz, H), 5.75
(d, J = 2.2 Hz, H), 5.97 (d, J = 2.1 Hz, H); ¹³C NMR (100 MHz, CDCl₃): δ -6.8, -5.8,
17.0, 26.5, 57.9, 71.7, 88.4, 105.3, 125.7, 127.7, 128.1, 128.4, 130.9, 136.9, 137.1;
HRMS calcd for [M+Na] 323.1807, found 323.1812. (VI-102)
To a solution of DL-serine methyl ester HCl salt (4.66 g, 30 mmol) in 125 mL of water was added NaHCO$_3$ (6.30 g, 75 mmol) and Cbz-Cl (5.16 mL, 36 mmol) at rt. The reaction mixture was stirred for 1 h at rt and it was extracted with CHCl$_3$ (100 mL x 3). The organic layer was dried (MgSO$_4$) and the residue was subjected to flash chromatography (EtOAc:Hex = 1/1) to get 7.60 g (quantitative yield) of a viscous oil. (K.C.)

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.38 (s br, H, OH), 3.77 (s, 3H, CO$_2$Me), 3.90 (dd br, H, CH$_2$OH), 3.98 (dd, $J = 2.4, 11.2$ Hz, H, CH$_2$OH), 4.44 (m, H, CH), 5.12 (s, 2H, PhCH$_2$), 5.77 (s, H, NH), 7.27-7.42 (m, 5H).

To a round-bottomed flask equipped with a reflux condenser was placed a solution of DL-$N$-Cbz-serine methyl ester 158a (1.03 g, 4.08 mmol), 2,2-dimethoxypropane (1.00 mL, 8.16 mmol), and TsOH$\cdot$H$_2$O (11.6 mg, 0.0612 mmol) in 20 mL of dry benzene. The
solution was heated under reduced pressure at 60 °C for 30 min and the solvent was evaporated over 2 h, at which time TLC (EtOAc/Hex = 1/6, Rf = 0.25) indicated that the reaction was complete. The reaction mixture was allowed to cool to rt and was partitioned between saturated NaHCO₃ (30 mL) and Et₂O (20 mL). The aqueous layer was extracted with ether (30 mL x 3) and the combined organic layer was washed with brine (30 mL), dried (MgSO₄), and concentrated to get the crude product. Silica gel chromatography (EtOAc:Hex = 1/5) gave 1.130 g (95 %) of a colorless oil. (K.C.)¹⁴

(159a) IR (neat, NaCl): 2990, 2954, 2887, 1747-1694 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂ at 75 °C): δ 1.44 (s, 3H, CH₃), 1.72 (s, 3H, CH₃), 3.25 (s, 3H, CO₂Me), 3.68 (dd, J = 7.1, 9.0 Hz, H, OCH₂CH), 3.77 (dd, J = 3.0, 9.0 Hz, H, OCH₂CH), 4.27 (m, H, CH), 4.93 (d, J =12.4 Hz, H, PhCH₂), 5.05 (d, J =12.4 Hz, H, PhCH₂), 6.95-7.00 (m, H), 7.00-7.08 (m, 2H), 7.12-7.18 (m, 2H); ¹³C NMR (125 MHz, CD₂Cl₂ at 27 °C): The ratio of major/minor conformational isomers is 3/1. At higher temperature (75 °C), broad peaks were still observed due to conformational equilibrium. The following ¹³C signals correspond to the major isomer at 27 °C. δ 24.3, 25.4, 30.1, 51.8, 59.2, 66.6, 95.7, 128.1, 128.6, 128.7, 137.2, 151.9, 171.2.

(159b) ¹H NMR (500 MHz, CDCl₃ at 60 °C): δ 1.46 (s, 9H), 1.54 (s, 3H), 1.66 (s, 3H), 3.75 (s, 3H), 4.02 (dd, J =3.2, 9.0 Hz, H), 4.14 (dd, J =7.1, 9.0 Hz, H), 4.40 (m, H). (K.C.)¹⁴b

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A dry flask (dried at 140 °C oven) was charged with 5-carboxmethoxy-N-Cbz oxazolidine 159a (1.548 g, 5.278 mmol) in 10 mL of dry toluene and the solution was cooled to −78 °C. A solution of DIBAL-H (6.16 mL of 1.5 M solution in toluene, 9.236 mmol) was added via cannula, while the rate of addition was maintained to keep the internal temperature below −65 °C. It took about 1 h to complete addition. The reaction mixture was stored for 2 h at −78 °C under N₂, when TLC (EtOAc/Hex = 1/4, Rf = 0.30) indicated the reaction was complete. The reaction was quenched by slowly adding 2 mL of MeOH, keeping the temperature below −65 °C. The resulting white emulsion was slowly poured into 50 mL of ice-cold 1 N HCl with swirling over 15 min. The aqueous layer was extracted with EtOAc (50 mL x 3), and the combined organic layer was washed with brine (50 mL), dried (MgSO₄), and concentrated. The residue was subjected to silica gel chromatography to get 0.693 g (50 %) of crude product. Alternatively, the crude reaction mixture was used without workup in the following step. (K.C.)

(160a)¹H NMR (250 MHz, CDCl₃ at 55 °C): δ 1.61 (s, 3H), 1.65 (s, 3H), 4.05-4.20 (m, 2H, OCH₂CH), 4.32 (m, H, CH), 5.17 (s, 2H, PhCH₂), 7.27-7.40 (m, 5H), 9.59 (s, H).

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A crude mixture of N-Cbz oxazolidine aldehyde 160a above (1.93 mmol, theoretical amount based on the ester used) was quenched with MeOH and the solvent was evaporated. The residue was re-dissolved in MeOH (4 mL) and Gilbert-Seyferth reagent (See Scheme 5.2 in Chapter 5.2, 694 mg, 3.85 mmol) and K$_2$CO$_3$ (532 mg, 3.85 mmol) was added at rt. The reaction mixture was stirred at rt for 17 h. The solvent was removed under vacuo and the residue was subjected to silica gel chromatography (EtOAc/Hex = 1/6, R$_f$ = 0.2) to get product as a colorless oil (222 mg, 44 % over 2 steps).

(161a) IR (neat, NaCl): 3287, 3065, 3034, 2985, 2939, 2801, 2117, 1713, 1694 cm$^{-1}$; $^1$H NMR (500 MHz, C$_6$D$_8$ at 70 °C): $\delta$ 1.40 (s, 3H, Me), 1.65 (s, 3H, Me), 1.88 (m, H, CCH), 3.51 (m, H, OCH$_2$CH), 3.68 (dd, $J$ =2.2, 8.5 Hz, H, OCH$_2$CH), 4.29 (s br, H, OCH$_2$CH), 5.01 (d, $J$ =12.5 Hz, H, PhCH$_2$), 5.07 (d, $J$ =12.5 Hz, H, PhCH$_2$), 6.95-7.15 (m, 3H), 7.21 (d, $J$ =7.4 Hz, 2H); $^{13}$C NMR (125 MHz, C$_6$D$_8$): $\delta$ 24.2, 26.3, 48.3, 66.9, 69.0, 71.0, 83.1, 95.1, 128.2, 128.4, 128.7, 137.3, 151.9; HRMS calcd for [M+Na] 282.1101, found 282.1097.

\[ \begin{array}{c}
\text{CHO} \\
\text{O} \\
\text{NBoc} \\
160b \\
\end{array} \rightarrow \begin{array}{c}
\text{CHO} \\
\text{O} \\
\text{NBoc} \\
161b \\
\end{array} \]

Similar procedure as in synthesis of 161a was followed for 161b

(161b) $^1$H NMR (500 MHz, CDCl$_3$ at 60 °C): $\delta$ 1.44 (s, 9H), 1.47 (s, 3H), 1.71 (s, 3H), 1.90 (d, $J$ =2.1 Hz, H), 3.57 (dd, $J$ =6.1, 8.4 Hz, H), 3.74 (dd, $J$ =2.4, 8.5 Hz, H), 4.30 (m, H).
To a solution of N-Boc oxazolidine aldehyde 161b (229 mg, 1.00 mmol) in CH₂Cl₂ (15 mL) was added at 0 °C CBr₄ (663 mg, 2.00 mmol) and PPh₃ (1.049 g, 4.00 mmol). The reaction mixture was stirred for 30 min and the crude mixture was filtered through cotton plug and was rinsed with EtOAc. The solvent was removed and the residue was subjected to silica gel chromatography (EtOAc/Hex = 1/6) to get the dibromovinyl compound (239 mg, 62%).

(162b) 'H NMR (500 MHz, CDCl₃ at 60 °C): δ 1.40 (s, 9H), 1.45 (s, 3H), 1.54 (s, 3H), 3.35 (dd, J = 3.1, 9.1 Hz, H, OCH₂CH), 3.63 (dd, J = 6.4, 9.0 Hz, H, OCH₂CH), 4.49 (m, H, CH), 6.38 (d, J = 8.2 Hz, H); ¹³C NMR (125 MHz, CDCl₃ at 27 °C): δ 24.0, 26.5, 28.6, 59.8, 67.1, 80.0, 128.6, 139.2, 152.0.

To a solution of the starting alcohol 158a (7.09 g, 28.0 mmol) and imidazole (2.86 g, 42.0 mmol) in DMF (30 mL) was added a solution of t-butyldimethylsilyl chloride (5.06 g, 33.6 mmol) in 30 mL of DMF at rt. The resulting solution was stirred at rt for 2 h, and the reaction mixture was poured into 500 mL of water and the aqueous layer was extracted with 300 mL of ether three times. The combined organic layer was dried (MgSO₄),
evaporated, and was subjected to column chromatography (EtOAc:Hex = 1/6) to get a colorless oil (9.710 g, 94%).

(164) IR (film, NaCl): 3444, 3348, 1724 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.01 (s, 3H, Me), 0.02 (s, 3H, Me), 0.85 (s, 9H, t-Bu), 3.74 (s, 3H, CO₂CH₃), 3.84 (dd, J = 3.8, 12.6 Hz, H, CH₂OTBS), 4.07 (dd, J = 3.3, 12.6 Hz, H, CH₂OTBS), 4.43 (td, J = 3.5, 10.9 Hz, H, CH₂OTBS), 5.13 (dd, J = 15.4, 19.1 Hz, 2H, CH₂Ph), 5.59 (d, J = 10.5 Hz, H, NH), 7.50-7.28 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ -5.8 (Me), -5.7 (Me), 18.0 (t-Bu, quaternary), 25.5 (t-Bu), 52.2, 55.8, 63.5, 66.9, 127.99, 128.03, 128.4, 136.1, 155.8, (carbamate), 170.8 (methyl ester).

**Attempted Propargylation of a O-TBS-Serine Derivative:**

To a solution of N-Cbz-O-TBS-ether serine methyl ester (36.7 mg, 0.100 mmol) in THF-DMF (1:1, 1 mL) was added NaH (26.4 mg, 0.110 mmol). After the reaction mixture was stirred for 1 h at RT, and propargyl bromide (15.5 mg, 0.130 mmol) was added. The reaction mixture was stirred overnight. To the reaction mixture was added brine (2 mL) and the aqueous layer was extracted with ether (2 mL x 3) to get a brown oil (22.0 mg, 81%) identified as the unsaturated ester shown.

¹H NMR (250 MHz, CDCl₃): δ 2.21 (t, J = 2.4 Hz, H), 3.57 (s, 3H), 4.26 (d, J = 2.4 Hz, 2H), 5.08 (s, 2H), 5.76 (s, H), 6.10 (s, H), 7.20-7.35 (m, 5H); ¹³C NMR (63 MHz,
To a solution of the starting methyl ester 164 (367 mg, 1.00 mmol) in 2 mL of ether was added solution of LiBH₄ (0.50 mmol) in 1 mL of ether at rt. The mixture was stirred at rt for 30 min, when the TLC indicated that the reaction was complete. The reaction was quenched with a powdered mixture of Celite/Na₂SO₄/water (3:3:1) until the evolution of gas stopped. After filtering the insoluble material, the filtrate was evaporated and the residue was purified on silica gel column using EtOAc/Hexane (1:4) as eluent to get 320 mg (94 %) of a colorless oil. (K.C.)

(165) IR (film): 3439 (O-H), 1704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.05 (s, 3H, Me), 0.06 (s, 3H, Me), 0.89 (s, 9H, t-Bu), 2.21 (s br, H, OH), 3.68-3.89 (m, 5H, CH₂OH, CH₂OTBS, CH), 5.11 (s br, 2H, PhCH₂), 5.37 (s br, H, N-H), 7.28-7.38 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ -5.17 (Me), -5.15 (Me), 18.6 (t-Bu, quaternary), 26.2 (t-Bu), 53.5, 64.2, 64.4, 67.3, 128.54, 128.59, 129.0, 136.8, 156.9 (carbamate).

To a suspension of NaH (57.6 mg, 2.40 mmol, free of oil) in THF (8 mL) at 0 °C was added, over 10 min, a solution of starting alcohol 165 (339 mg, 1.00 mmol) in THF (1
mL). The reaction mixture was stirred at rt for 15 h, after which time propargyl bromide (freshly distilled) was added and the mixture was stirred at rt for another 15 h. The reaction was quenched with 10 mL of saturated NH₄Cl solution and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was dried, evaporated, and was subjected to column chromatography (EtOAc/hex = 1/3) to get 229 mg of a colorless oil (99%).

IR (film): 3310, 3252, 2929, 2858, 2121, 1748 (carbamate) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.044 (s, 3H, Me), 0.046 (s, 3H, Me), 0.86 (s, 9H, t-Bu), 2.26 (t, J = 2.5 Hz, H, alkyne), 3.68 (dd, J = 4.2, 10.9 Hz, H, CH₂OTBS), 3.75 (dd, J = 4.2, 10.9 Hz, H, CH₂OTBS), 3.81 (dd, J = 2.4, 17.7 Hz, NCH₂), 4.01 (m, H, CH), 4.10 (dd, J = 5.8, 8.5 Hz, H, CH₂OCO), 4.34 (t, J = 8.7 Hz, H, CH₂OCO), 4.36 (dd, J = 2.5, 17.7 Hz, NCH₂);

¹³C NMR (125 MHz, CDCl₃): δ -5.16 (Me), -5.15 (Me), 18.5 (t-Bu, quaternary), 26.1 (t-Bu), 32.9, 56.0, 62.5, 65.2, 73.5, 77.7, 158.2 (carbamate); HRMS calcd for C₁₁H₂₃NO₃SiNa [M+Na], 292.1339, found, 292.1324.

To a solution of TBS ether above (411 mg, 1.78 mmol) in 3 mL of THF at 0 °C was added TBAF (1.87 mL of 1.0 M solution in THF, 1.05 equiv.) and the mixture was stirred at that temperature for 1 h. To the reaction mixture was added brine (5 mL), and the aqueous layer was extracted with CH₂Cl₂ (5 mL x 10) and subsequently with EtOAc (5
The remaining aqueous layer was checked by the TLC whether there remained any more product. The combined organic layer was dried (MgSO₄), evaporated, and was subjected to chromatography (EtOAc/Hex/acetone = 1:2:1) to yield 238.0 mg (86%) of a colorless oil. (K.C.)¹¹

(166) IR (film): 3418 (s, O-H), 3288, 2927, 2120, 1731 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 2.32 (t, J = 2.5 Hz, H, alkyne), 3.21 (s br, J = OH), 3.64 (td, J = 2.3, 12.2 Hz, H), 3.87 (td, J = 3.6, 12.1 Hz, H), 3.92-4.03 (m, 2H), 4.21 (dd, J = 2.4, 17.9 Hz, H), 4.26 (dd, J = 6.5, 8.6 Hz, H), 4.40 (t, J = 8.6 Hz, H); ¹³C NMR (125 MHz, CDCl₃): δ 32.8, 56.5, 60.7, 65.2, 73.6, 77.8, 158.8 (carbamate).

To a solution of DMSG (0.580 mL, 8.16 mmol) in 10 mL of CH₂Cl₂ at −60 °C was added dropwise (COCl)₂ (0.372 mL, 3.92 mmol). After 5 min, a solution of alcohol 166 (494 mg, 3.18 mmol) in 5 mL of CH₂Cl₂ was added. After stirring at −60 °C for 15 min, Et₃N (2.27 mL, 16.3 mmol) was added to the mixture. The reaction mixture was kept stirring for 5 min at this temperature and was allowed to warm to −15 °C slowly. The solvent was removed under reduced pressure and the residue was redissolved in MeOH (10 mL). At 0 °C, Gilbert-Seyferth reagent (1.23 g, 6.36 mmol) and K₂CO₃ (1.32 g, 6.36 mmol) was added to the solution. The reaction mixture was stirred for 10 h. The crude mixture after evaporation of solvent was subjected to silica gel chromatography.
(EtOAc/Hex = 1/2) to get 252 mg (53 % over 2 steps) of a pale yellow solid (mp 43–44 °C).

(167) IR (mineral oil): 3500, 3290, 2274, 2122, 1770 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 2.30 (t, J = 2.5 Hz, H, CH₂CCH), 2.54 (d, J = 2.1 Hz, H, CHCCH), 3.85 (dd, J = 2.1, 17.7 Hz, H, NCH₂), 4.26 (dd, J = 6.5, 8.5 Hz, H, OCH₂CH), 4.42 (dd, J = 2.5, 17.7 Hz, CH₂CCH), 4.51 (t, J = 8.5 Hz, H, OCH₂CH), 4.68 (td, J = 2.1, 6.5 Hz, H, CH); ¹³C NMR (125 MHz, CDCl₃): δ 32.6, 46.8, 67.5, 73.8, 76.1, 76.9, 78.2, 156.8; HRMS calcd for [M+Na] 172.0374, found 172.0378.

Swern oxidation followed by Gilbert-Seyferth homologation to acetylene via a procedure described above gave title compound in 31 % (over 2 steps).

(168) IR (neat, NaCl): 3311, 3034, 2929, 2856, 1713 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 2.25 (d, J = 2.3 Hz, H), 3.75 (d br, J = 4.4 Hz, 2H, OCH₂), 4.54 (s br, H, CH), 5.16 (s br, 2H, PhCH₂), 5.21 (s br, H, NH), 7.29-7.40 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ -4.97, -4.94, 18.8, 26.2, 45.7, 65.7, 67.5, 71.9, 82.0, 128.6, 128.9, 136.7, 155.9; HRMS calcd for [M+Na] 356.1652, found 356.1641.
To a solution of N-Cbz acetylene compound 168 (61.9 mg, 0.186 mmol) in THF (1 mL) was added NaH (4.5 mg, 0.20 mmol). The mixture was stirred for 1 h, then propargyl bromide (44.1 mg, 0.371 mmol) was added and the mixture was stirred at RT for 10 h. The reaction was quenched with saturated solution of NH₄Cl (5 mL) and the mixture was extracted with EtOAc (5 mL × 3). The residue after evaporation was subjected to silica gel chromatography (EtOAc/Hex = 1/9) to get 53.6 mg (78%) of the diyne compound 14 as a colorless oil.

(169) $^1$H NMR (400 MHz, C₆D₆, at 70 °C) $\delta$ 0.06 (s, 6H), 0.96 (s, 9H), 1.92 (t, $J = 2.3$ Hz, H), 2.01 (d, $J = 2.3$ Hz, H), 3.87 (m, 2H), 4.10-4.22 (m, H), 4.22-4.35 (m, H), 5.13 (s, 2H), 5.24 (m, H), 7.07-7.20 (m, 3H), 7.23-7.32 (m, 2H); $^{13}$C NMR (100 MHz, C₆D₆, at 70 °C) $\delta$ -5.85, -5.84, 17.9, 25.5, 34.0, 51.0, 64.4, 67.3, 70.7, 73.8, 79.3, 80.6, 127.2, 128.0, 136.6, 154.7.

The diyne 167 (72.6 mg, 0.487 mmol) was dissolved in dioxane (2 mL) and aqueous NaOH (1 mL of 3.0 N) was added. The reaction mixture was heated to 70 °C and was kept stirring for 16 h. After the reaction mixture was cooled to 0 °C, a solution of (Boc)₂O (255 mg, 1.17 mmol) in dioxane (1 mL) was added and the mixture was stirred for 2 h, slowly warming to RT. After the reaction mixture was cooled to 0 °C again, a solution of TBDMS-Cl (176 mg, 1.17 mmol) in dioxane (1 mL) was added and the
mixture was stirred for 2 h at rt. To the reaction mixture was added 10 mL of water and the resulting solution was extracted with EtOAc (10 mL x 3). The combined organic layer was dried (MgSO₄), evaporated, and was subjected to silica gel chromatography to get 9.6 mg (6%) of TBS protected product and 31 mg (29%) of 170.

(170) ¹H NMR (400 MHz, CDCl₃): δ 1.47 (s, 9H), 1.74 (s, H, OH), 2.22 (t, J = 2.5 Hz, H), 2.33 (d, J = 2.2 Hz, H), 3.53 (dd, J = 2.5, 16.7 Hz, H), 3.62 (dd, J = 2.5, 16.7 Hz, H), 3.91 (ddd, J = 2.2, 4.5, 6.7 Hz, H), 4.16 (dd, J = 6.8, 10.7 Hz, H), 4.23 (dd, J = 4.5, 10.7 Hz, H); ¹³C NMR (100 MHz, CDCl₃): δ 27.6, 35.7, 47.7, 68.0, 71.8, 73.4, 80.3, 80.9, 82.5, 152.9.

Cyclization of Substrate 167, 169, and 170 with Me₃Sn-B[-N(Me)CH₂CH₂N(Me)-]

Reagent: eq. 3 (p 142) in Chapter 5.

To a solution of PdCl₂(PPh₃)₂ (1.7 mg, 0.0025 mmol), Me₃Sn-B[-N(Me)CH₂CH₂N(Me)-] (32.1 mg, 0.138 mmol) in C₆D₆ (1 mL) at rt was added substrate (0.125 mmol). The reaction mixture was transferred to an NMR tube and the reaction was monitored by ¹H NMR spectra. The product is highly unstable to moisture and the isolation could not be done. ¹H NMR spectra of 171, 172, and 173 are as follows.

\[
\begin{align*}
167 & \quad \rightarrow \\
& \quad \text{regioisomer}
\end{align*}
\]

171 (crude mixture)

Major/minor = 1.2/1.0
(171) $^1$H NMR (500 MHz, C$_6$D$_6$): Major isomer $\delta$ 5.65 (s, $^2$J$_{Sn-H}$ = 50 Hz, H), 5.00 (s, H); Minor isomer $\delta$ 5.50 (s, $^2$J$_{Sn-H}$ = 49 Hz, H), 5.23 (s, H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): Major isomer $\delta$ -8.6, 34.8, 51.9, 54.2, 62.9, 66.1, two vinyl peaks were hidden, 152.1, 154.4, 161.8; Minor isomer $\delta$ -8.5, 34.8, 51.9, 54.5, 63.6, 66.8, two vinyl peaks were hidden, 151.9, 154.4, 161.7; $^{11}$B NMR (160 MHz, C$_6$D$_6$): $\delta$ 28.8 (s br); $^{119}$Sn NMR (186 MHz, C$_6$D$_6$): Major isomer, $\delta$ -49.3; Minor isomer, $\delta$ -44.4; starting Sn-B reagent, $\delta$ -110.7 (V-168)

![Diagram](169) → ![Diagram](172) crude mixture

Major/minor = 3.3/1.0, NMR spectra were less legible because of conformational equilibrium. For discussion of structure of 172, see Chapter 5.3.

(172) $^1$H NMR (500 MHz, C$_6$D$_6$ at 70°C): Major isomer $\delta$ 5.99 (s, $^2$J$_{Sn-H}$ = 50 Hz, H), 5.29 (s, H); Minor isomer $\delta$ 5.71 (s, $^2$J$_{Sn-H}$ = 52 Hz, H), 5.44 (s, H). (V-193)

![Diagram](170) → ![Diagram](173) crude mixture

Major/minor = 2.5/1.0, NMR spectra were less legible because of conformational equilibrium.
(173) $^1$H NMR (500 MHz, C$_6$D$_6$ at rt): **Major isomer** $\delta$ 5.89 (s, $^2J_{\text{Sn-H}} = 52$ Hz, H), 5.34 (s, H); **Minor isomer** $\delta$ 5.75 (s, $^2J_{\text{Sn-H}} = 52$ Hz, H), 5.40 (s, H). (V-171)

*The Representative Procedure for Cyclization of Diyne 167* (eq. 4 in Chapter 5.5)

A solution of Pd precursor (0.010 mmol), P(C$_6$F$_3$)$_3$ (0.020 mmol), Sn-Si reagent (0.22 mmol), and diyne 167 (0.20 mmol) in C$_6$D$_6$ (1 mL) was subjected to the reaction conditions described in the text. After the reaction, the reaction mixture was concentrated in vacuo and was subjected to silica gel column chromatography (Et$_3$N/Hex = 5/95) to get the corresponding product.

The major isomer 174a was isolated and was characterized as follows.

(174a) IR (neat, NaCl): 3066, 2958, 2600, 2497, 2252, 1953, 1878, 1770, 1732, 1621, 1470, 1429, 1392 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ -0.52 (s, 3H), -0.03 (s, 3H), 0.73 (s, 9H), 3.72 (dd, $J = 1.3$, 13.6 Hz, H, NCH$_2$), 4.09 (dd, $J = 2.2$, 13.6 Hz, H, NCH$_2$), 4.37 (ddd, $J = 1.6$, 3.1, 7.6 Hz, H, NCH), 4.54 (dd, $J = 3.1$, 9.5 Hz, H, OCH$_2$), 4.62 (dd, $J = 7.6$, 9.5 Hz, H, OCH$_2$), 5.46 (t, $J = 1.6$ Hz, H, C=C(Si)H), 6.29 (d, $J = 1.3$ Hz, $J_{\text{Sn-H}} = 56$ Hz, H, C=C(Sn)H), 7.32-7.60 (m, 15H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ -5.2, -3.0, 18.1, 26.8, 53.9, 63.0, 66.3, 122.7, 130.2; HRMS calcd for [M+Na] 638.1508, found 638.1538. (VI-188)
The solution of crude mixture of reaction of 167 with Bu$_3$Sn-SiMe$_3$ was concentrated in vacuo and was redissolved in CH$_2$Cl$_2$. N-bromosuccinimide (1.2 equiv.) was added to the mixture at RT and was stirred for 1 h. After evaporation of solvent, the residue was subjected to column chromatography to get the corresponding bromovinyl compound. From $^1$H NMR integration, the ratio of regioisomers was 1.7/1.0.

(176a/176b) $^1$H NMR (500 MHz, C$_6$D$_6$ at 70 °C): Major Regioisomer, δ 0.09 (s, 9H, TMS), 3.36 (dd, $J = 1.7$, 14.1 Hz, H, NCH$_2$), 3.42 (dd, $J = 3.3$, 9.2 Hz, H, OCH$_2$), 3.48 (ddd, $J = 1.7$, 3.3, 7.6 Hz, H, NCH), 3.62 (dd, $J = 7.6$, 9.2 Hz, H, OCH$_2$), 4.10 (dd, $J = 2.0$, 14.4 Hz, H, NCH$_2$), 5.46 (d, $J = 1.7$ Hz, H, C=C(TMS)H), 5.47 (d, $J = 1.5$ Hz, H, C=C(Br)H), Minor Regioisomer, δ 0.07 (s, 9H), 3.22 (dd, $J = 1.3$, 13.6 Hz, H, NCH$_2$), 3.52 (ddd, $J = 1.9$, 3.4, 7.8 Hz, H, NCH), 3.63 (dd, $J = 3.4$, 9.0 Hz, H, OCH$_2$), 3.73 (dd, $J = 7.9$, 9.0 Hz, H, OCH$_2$), 3.95 (dd, $J = 1.7$, 13.5 Hz, H, NCH$_2$), 5.26 (d, $J = 1.4$ Hz, H, C=C(TMS)H), 5.55 (s, H, C=C(Br)H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): Major Regioisomer, δ -0.7, 54.4, 62.6, 65.2, 102.5, 103.5, 141.3, 147.9, 161.1, Minor Regioisomer, δ -0.81, 52.7, 62.9, 66.7, 128.7, 132.2, 141.3, 148.3, 161.6; HRMS calcd for [M+Na] 324.0026, found:324.0058. (VI-186-2)
Variable Temperature NMR Study:

For rt ~ 70 °C, C₆D₆ was used as solvent and for rt ~ -90 °C, CD₃OD was used as solvent.

Low temperature NMR studies of 171 and 174a are discussed in Figure 5.1 in Chapter 5.4 and Figure 5.4 in Chapter 5.5, respectively.

MM2-Calculation:

The most significant factors determining the strain energy turned out to be the following parameters. Using the Chem 3D (Windows or Macintosh), geometry optimization was repeated until the minimum energy is reached changing these parameters. The calculation started with two un-optimized structures 174a(R,Rₐ), 174a'(R,Sₐ)

(a) rotation of Cₛᵖ²-Sn bond
(b) rotation of Cₛᵖ²-Si bond
(c) geometry optimization of each geometry from the combination of (a) and (b)
Result of MM2 calculation of 174a (R, Rₐ):

Result of MM2 calculation of 174a' (R, Sₐ):
To a solution of DMSO (0.261 mL, 3.681 mmol) in \( \text{CH}_2\text{Cl}_2 \) (2 mL) was added (COCl)_2 (0.160 mL, 1.687 mmol) dropwise at \(-60\) °C. After 5 min, starting acetylenyl alcohol 166 (238 mg, 1.53 mmol) in \( \text{CH}_2\text{Cl}_2 \) (2 mL) was added over 8 min. After stirring 15 min at that temperature, the reaction mixture was warmed to \(-15\) °C over 20 min and \( \text{Et}_3\text{N} \) (3.20 mmol) was added to the mixture. After stirring for 20 min at \(-15\) °C, carbethoxymethylene phosphorane (0.748 mg, 2.148 mmol) in \( \text{CH}_2\text{Cl}_2 \) (2 mL) was added and the mixture was brought to rt and kept stirred for 1.5 h. The reaction mixture was poured into brine (10 mL). The aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \) (10 mL x 3), dried (MgSO_4), and the residue was chromatographed (EtOAc/Hex = ½) to get 304 mg (89 %) of an oil.

IR (neat, NaCl) 3264, 2121, 1766 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 1.32-1.28 (m, 3H, \( \text{OCH}_2\text{CH}_3 \)), 2.30 (t, \( J = 2.4 \) Hz, H, \( \text{CCH} \)), 3.67 (d, \( J = 17.7 \) Hz, H, \( \text{NCH}_2 \)), 4.00-4.06 (m, H, \( \text{CH} \)), 4.17-4.25 (m, 2H, \( \text{OCH}_2\text{CH}_3 \)), 4.36 (d, \( J = 17.7 \) Hz, H, \( \text{NCH}_2 \)), 4.48-4.59 (m, 2H, \( \text{OCH}_2\text{CH} \)), 6.12 (d, \( J = 15.6 \) Hz, H, \( \text{C=CH} \)), 6.72 (dd, \( J = 15.6, 8.3 \) Hz, H, \( \text{C=CH} \)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 14.6, 32.9, 56.4, 61.5, 66.9, 74.2, 76.8, 127.5, 141.8, 157.6, 165.3; HRMS calcd for [M+Na] 246.0742, found, 246.0738.
To a solution of acetylenyl TBS ether (0.974 g, 3.61 mmol) in THF (10 mL) was added paraformaldehyde (217 mg, 7.23 mmol), \(^3\)Pr\(_2\)NH (0.760 mL, 5.42 mmol), and CuBr (259 mg, 1.81 mmol). The mixture was heated to reflux for 10 h. The reaction mixture was filtered through a Celite pad (3 cm) and rinsed with EtOAc until TLC indicated that all of the product was eluted. The resulting filtrate was concentrated and was subjected to column chromatography (EtOAc/Hex = 1/4) to get 666 mg (65 %) of allenyl TBS ether.

IR (neat, NaCl) 2929, 2857, 1957, 1747, 1471, 1416 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 0.06 (s, 6H), 0.88 (s, 9H), 3.65 (m, H, NCH\(_2\)), 3.68 (dd, \(J = 4.7, 6.3\) Hz, 2H, CH\(_2\)OTBS), 3.90 (m, H, NCH), 4.13 (dd, \(J = 5.4, 8.5\) Hz, CH\(_2\)O), 4.16 (m, H, NCH\(_2\)), 4.32 (t, \(J = 8.6\) Hz, H, CH\(_2\)O), 4.83 (m, 2H, allene), 5.13 (m, H, allene); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) -5.1, 18.5, 26.1, 41.7, 56.2, 62.4, 65.3, 77.3, 86.4, 158.6, 209.5; HRMS calcd for [M+Na] \(\text{306.1496, found 306.1485.}\)

The TBS ether (666 mg, 2.35 mmol) was dissolved in THF (5 mL) at 0 °C and a solution of TBAF (1.0 M in THF, 2.58 mL, 2.58 mmol) was added dropwise. The reaction was complete in 1 h as judged by TLC (EtOAc/Hex = 3/1, \(R_f = 0.25\)). Silica gel
chromatography of the residue after evaporation gave 345 mg (87 %) of allenyl alcohol 177.

(177) IR (neat, NaCl): 3411, 2985, 2931, 1731, 1579, 1479, 1445, 1361 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 2.64 (s br, H, OH), 3.60-3.68 (m, H, CH₂OH), 3.72-3.78 (m, H, NCH₂), 3.80 (dd, J = 11.9 Hz, H, CH₂OH), 3.90-3.96 (m, H, CH), 4.05-4.09 (m, H, NCH₂), 4.26 (dd, J = 6.0, 8.6 Hz, H, OCH₂CH), 4.35 (t, J = 8.8 Hz, H, OCH₂CH), 4.85 (t br, J = 3.2 Hz, H, C=CH₂), 5.15 (quintet, J = 6.7 Hz, H, CH=C); ¹³C NMR (125 MHz, CDCl₃): δ 41.6, 56.6, 61.0, 64.9, 77.6, 86.3, 158.9, 209.4; HRMS calcd for [M+Na] 192.0631, found 192.0613.

\[
\begin{align*}
\text{HO} & \quad \text{CO₂Et} \\
177 & \quad \rightarrow \\
178
\end{align*}
\]

To a solution of DMSO (0.18 mL, 2.5 mmol) in 2 mL of CH₂Cl₂ was added (COCl₂) (0.11 mL, 1.2 mmol) dropwise at -60 °C. After 5 min, a solution of alcohol 177 (178 mg, 1.05 mmol) in 2 mL of CH₂Cl₂ was added dropwise over 8 min. After stirring 15 min at -60 °C, Et₃N (0.59 mL, 4.2 mmol) was added and the mixture was warmed slowly to -15 °C over 20 min and the crude mixture was used in the next step.

To a reaction mixture at -15 °C above was added a solution of carbethoxymethylene-triphenylphospholane (733 mg, 2.10 mmol) in 2 mL of CH₂Cl₂ and the temperature was allowed to reach rt over 1.5 h. The reaction mixture was poured into brine (20 mL) and the aqueous layer was extracted with ether (20 mL x 4). The combined organic layer was
dried (MgSO\(_4\)), evaporated, and the residue was subjected to flash chromatography (EtOAc/Hex = 1/2) to get 202 mg (81\%) of 178 as an oil. \(^1\)H and \(^{13}\)C NMR indicated that the isolated material was a single double bond isomer.

(178) IR (neat, NaCl) 3063, 2983, 2909, 2260, 1956, 1764, 1731, 1714, 1660, 1651 cm\(^{-1}\);

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.29 (t, \(J = 7.1\) Hz, 3H, OCH\(_2\)CH\(_3\)), 3.53 (dd, \(J = 7.5, 15.3\) Hz, H, NCH\(_2\)), 3.96-4.05 (m, H, CH), 4.10 (dd br, \(J = 3.4, 15.3\) Hz, H, NCH\(_2\)), 4.21 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\)CH\(_3\)), 4.45 (d, \(J = 4.6\) Hz, 2H, OCH\(_2\)CH), 4.77-4.86 (m, 2H, allene), 5.07 (quintet, \(J = 6.6\) Hz, H, allene), 6.03 (d, \(J = 15.6\) Hz, H, C=CH), 6.72 (dd, \(J = 7.0, 15.6\) Hz, H, C=CH); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 14.6, 41.6, 56.7, 61.4, 66.7, 77.6, 85.6, 126.8, 142.6, 157.8, 165.4, 209.8; HRMS calcd for \([\text{M+Na}]\) 260.0899, found 260.0905. (VI-125)

\[
\begin{align*}
\text{177} & \xrightarrow{\text{DMSO (0.35 mL, 4.9 mmol)}} \xrightarrow{\text{COCl\(_2\) (0.21 mL, 2.2 mmol)}} \xrightarrow{\text{Et\(_3\)N (0.57 mL, 4.1 mmol)}} \text{179}
\end{align*}
\]

To a solution of DMSO (0.35 mL, 4.9 mmol) in 4 mL of CH\(_2\)Cl\(_2\) was added (COCl\(_2\)) (0.21 mL, 2.2 mmol) dropwise at -60 °C. After 5 min, a solution of alcohol 177 (345 mg, 2.04 mmol) in 4 mL of CH\(_2\)Cl\(_2\) was added dropwise over 8 min. After stirring 15 min at -60 °C, Et\(_3\)N (0.57 mL, 4.1 mmol) was added and the mixture was warmed slowly to -15 °C over 20 min and the solvent was evaporated to dryness.

The crude mixture above was dissolved in MeOH (5 mL) at 0 °C and to this solution was added Gilbert-Seyferth reagent (735 mg, 4.08 mmol, see Scheme 5.2, in Chapter 5.2) and
K$_2$CO$_3$ (564 mg, 4.08 mmol). The resulting mixture was stirred at rt for 20 h. The reaction mixture was poured into brine (40 mL) and the aqueous layer was extracted with ether (40 mL x 4). The combined organic layer was dried (MgSO$_4$), evaporated, and the residue was subjected to flash chromatography (EtOAc/Hex = 1/2) to get 187 mg (56 %) of 179 as an oil.

(179) IR (neat, NaCl): 3288, 3065, 2984, 2920, 1957, 1748, 1479, 1416, 1372, 1217, 1183, 1084, 1024 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.50 (d, $J = 2.1$ Hz, H, CCH), 3.71 (dddd, $J = 2.0$, 3.5, 7.6, 15.2 Hz, H, NCH$_2$), 4.18-4.24 (m, H, NCH$_2$), 4.22-4.28 (m, H, OCH$_2$), 4.46 (td, $J = 1.2$, 8.5 Hz, H, OCH$_2$), 4.59 (ddd, $J = 2.0$, 6.2, 8.5 Hz, H, NCH), 4.81-4.88 (m, 2H, C=C=CH$_2$), 5.08-5.14 (m, H, CH=C=C); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 41.3, 46.9, 67.4, 75.7, 77.6, 78.8, 85.6, 157.2, 209.7; HRMS calcd for [M+Na] 186.0525, found 186.0538. (VI-192)

The Representative Procedure for Cyclization of Eneallene 178 or Alleneyne 179: eq. 6 and eq. 9

A solution of Pd precursor (0.010 mmol), P(C$_6$F$_5$)$_3$ (0.020 mmol), Sn-Si reagent (0.22 mmol), and diyne or alleneyne (0.20 mmol) in C$_6$D$_6$ (1 mL) was subjected to the reaction conditions described in eq. 6 and eq. 9. After the reaction, the reaction mixture was concentrated in vacuo and was subjected to silica gel column chromatography (Et$_3$N/Hex = 5/95) to get the corresponding product.
After column chromatography, 84% of 180 as an oil was obtained. The isolated material was a single double-bond isomer ($^1$H, $^{13}$C NMR).

(180) IR (neat, NaCl) 2956, 2924, 1766, 1728, 1660, 1416, 1373, 1351, 1300 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 0.04 (s, 9H), SnBu$_3$ peaks were omitted, 1.12-1.30 (t, 3H, CO$_2$Et), 1.77 (d, $J = 11.7$ Hz, H, $J_{Sn-H} = 64$ Hz, H, CH$_2$Sn), 1.83 (d, $J = 11.7$ Hz, $J_{Sn-H} = 64$ Hz, H, CH$_2$Sn), 3.64 (dd, $J = 7.3$, 15.6 Hz, H, NCH$_2$), 3.94 (dd, $J = 5.4$, 15.6 Hz, H, NCH$_2$), 4.00 (dd, $J = 7.6$, 8.7 Hz, H, OCH$_2$), 4.15-4.27 (m, 2H, CO$_2$Et), 4.33 (dd, $J = 8.6$, 12.5 Hz, H, NCH), 4.45 (t, $J = 8.7$ Hz, H, OCH$_2$), 5.28 (t, $J = 6.6$ Hz, H, CH=CHCSi), 5.98 (d br, $J = 15.6$ Hz, H, C=CHCO$_2$Et), 6.76 (dd, $J = 8.5$, 15.6 Hz, H, CH=CHCO$_2$Et); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -1.2, 10.5, 13.6, 14.1, 14.6, 27.8, 29.5, 41.3, 57.1, 61.4, 66.7, 125.6, 126.2, 143.4, 147.7, 158.1, 165.3; HRMS calcd for [M+Na] 624.2502, found 624.2477. nOe experiments confirmed the double bond configuration above. (VI-130)

To a solution of allyltin compound (27.8 mg, 0.0463 mmol) in CH$_2$Cl$_2$ (2 mL) at -78 °C was added TMS-Otf (10.3 mg, 0.0463 mmol) dropwise. The reaction mixture was stirred
for 1 h at -78 °C, then warmed to RT, and was further stirred for 1 h. Water (3 mL) was added to the mixture and the residue was extracted with CH₂Cl₂ (2 mL x 3). The organic phase was dried (MgSO₄), evaporated, and was subjected to column chromatography to get 13.5 mg (94 %) of vinyl silane compound.

(181) IR (neat, NaCl) 2956, 2252, 1754, 1726, 1660, 1444, 1415, 1369, 1302, 1264, 1221, 1178, 1126, 1080, 1058 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.09 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H, CO₂Et), 2.28 (ddd, J = 6.3, 9.6, 15.2 Hz, H, NCH₂CH₂), 2.38 (ddd, J = 5.5, 9.8, 14.2 Hz, H, NCH₂CH₂), 3.05 (ddd, J = 5.6, 9.6, 14.2 Hz, H, NCH₂), 3.47 (ddd, J = 6.2, 9.9, 14.1 Hz, H, NCH₂), 4.01 (dd, J = 7.7, 5.3 Hz, H, OCH₂), 4.23 (q, J = 7.1 Hz, 2H, CO₂Et), 4.41 (t, J = 8.5 Hz, H, NCH), 4.44 (q, J = 8.6 Hz, H, OCH₂), 5.42 (d, J = 2.4 Hz, H, C=CH₂), 5.60 (q, J = 1.2 Hz, H, C=CH₂), 6.05 (d, J = 15.6 Hz, H, CH=CHCO₂Et), 6.75 (dd, J = 8.3, 15.6 Hz, H, CH=CHCO₂Et); ¹³C NMR (125 MHz, CDCl₃): δ -1.20, 14.6, 33.5, 42.7, 57.4, 61.5, 66.6, 126.5, 126.9, 143.2, 148.7, 157.9, 165.3; HRMS calcd for [M+Na] 344.1451, found 344.1456.

To a refluxing solution of allyltin compound 180 (56.3 mg, 0.0938 mmol) in C₆H₆ (9 mL) was added via syringe pump a mixture of AIBN (3.1 mg) and Bu₃SnH (54.6 mg, 0.1875 mmol) over 3 h. The reaction mixture was concentrated in vacuo and the residue was subjected to silica gel chromatography (Et₃N/Hex = 5/95) to get 80.0 mg (90 %) of 182.
as a mixture of products. Careful separation gives a sample of a single diastereomer (42.1 mg, 47%) as a colorless oil. Inspection of $^1$H and $^{13}$C NMR indicated that this is a single diastereomer. For the discussions for the assignment of 2,3,4-relative stereochemistry, see Figure 5.6 in Chapter 5.5.3. Stereocenter at α-carbonyl position is unknown at this time.

(182) IR (neat, NaCl) 2957, 2927, 2872, 1760, 1728, 1455, 1416, 1386, 1339, 1249, 1181, 1110, 1076 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 0.10 (s, 9H), SnBu$_3$ peaks were omitted, 1.21 (t, $J = 7.2$ Hz, 3H, CO$_2$Et), 1.42 (m, H, SnCH), 2.50 (ddd, $J = 5.0$, 8.5, 12.9 Hz, H, CHC(Si)=CH$_2$), 2.98 (t br, $J = 4.1$ Hz, H, CHCH(Sn)CO$_2$Et), 3.64 (d, $J = 8.5$ Hz, 2H, NCH$_2$), 3.68 (ddd, $J = 6.9$, 8.2 Hz, H, OCH$_2$), 3.96 (dq, $J = 7.2$, 10.9 Hz, H, CO$_2$Et), 4.07 (dq, $J = 7.2$, 10.9 Hz, H, CO$_2$Et), 4.35 (t, $J = 8.1$ Hz, H, OCH$_2$), 4.51 (ddd, $J = 6.9$, 8.1, 12.3 Hz, H, NCH$_2$), 5.40 (d, $J = 1.1$ Hz, H, C(Si)=CH$_2$), 5.49 (t, $J = 1.2$ Hz, H, C(Si)=CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ -0.8, 9.4, 14.0, 14.6, 27.9, 29.5, 31.5, 41.1, 43.8, 46.5, 54.1, 60.5, 68.9, 124.9, 151.0, 157.3, 173.5; HRMS calcd for [M+Na]$_{624.2502}$, found: 624.2485. NOe experiments support the relative stereochemistry above.

To a solution of Pd$_2$(dba)$_3$CHCl$_3$ (2.6 mg, 0.0050 mmol Pd), P(C$_6$F$_5$)$_3$ (5.3 mg, 0.010 mmol) in C$_6$D$_6$ (1 mL) was added Bu$_3$Sn-SiMe$_3$ (40.0 mg, 0.110 mmol) and the starting alleneyne 179 (16.3 mg, 0.100 mmol). The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 4 h at 80 °C, the $^1$H NMR spectrum indicated a mixture of the
acyclic adduct and cyclic product 185 (1:3) and after 12 h at 80 °C, the conversion was complete. The ratio of 185a and 185b was 1:1 as identified by \(^1\)H NMR spectrum of the crude mixture. The solvent was removed and the resulting residue was subjected to column chromatography (Et\(_3\)N/Hex = 5/95). The careful separation of diastereomers gave 185a (23.3 mg, 44.3 %) and 185b (15.4 mg, 29 %) both as colorless oils.

(185a) IR (neat, NaCl) 2955, 2923, 1760, 1619, 1461, 1387, 1296, 1250, 1201, 1150, 1073, 1023 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 0.20 (s, 9H), SnBu\(_3\) peaks were omitted, 3.34 (dd, \(J = 6.8, 11.6\) Hz, H, NCH\(_2\)), 3.39 (d br, \(J = 6.3\) Hz, ring CHC(Si)=CH\(_2\)), 3.81 (d, \(J = 11.6\) Hz, H, NCH\(_2\)), 4.26 (dd, \(J = 3.8, 8.6\) Hz, H, OCH\(_2\)), 4.39 (ddd, \(J = 1.9, 3.8, 8.8\) Hz, H, NCH), 4.62 (t, \(J = 8.8\) Hz, H, OCH\(_2\)), 5.57 (t, \(J = 1.8\) Hz, H, C(Si)=CH\(_2\) cis to Si), 5.71 (t, \(J = 1.9\) Hz, H, C(Si)=CH\(_2\) trans to Si), 6.19 (s, \(J_{Sn-H} = 50\) Hz, H, C=CH(Sn)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) -0.1, 10.4, 14.1, 27.7, 29.5, 52.7, 52.8, 63.7, 69.6, 126.6, 127.6, 152.7, 161.1, 162.5; HRMS calcd for [M+Na] 550.2134, found 550.2160.

(185b) IR (neat, NaCl) 2956, 1766, 1621, 1464, 1392, 1301, 1249, 1199, 1150, 1085, 1029 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 0.15 (s, 9H), SnBu\(_3\) peaks were omitted, 2.93 (dd, \(J = 6.2, 11.7\) Hz, H, NCH\(_2\), anti), 3.56 (t br, \(J = 7.6\) Hz, ring CHC(Si)=CH\(_2\)), 4.15 (dd, \(J = 9.1, 11.7\) Hz, H, NCH\(_2\), syn), 4.24 (dd br, \(J = 1.8, 7.6\) Hz, H, NCH), 4.35 (dd, \(J = 2.6, 8.7\) Hz, H, OCH\(_2\), anti), 4.56 (dd, \(J = dd, J = 7.8, 8.6\) Hz, H, OCH\(_2\), syn), 5.45 (dd, \(J = 1.3, 2.2\) Hz, H, C(Si)=CH\(_2\) cis to Si), 5.71 (t, \(J = 1.9\) Hz, H, C(Si)=CH\(_2\) trans to Si), 6.08 (t, \(J = 1.9\) Hz, \(J_{Sn-H} = 46\) Hz, H, C=CH(Sn)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) -0.2, 10.5, 14.1, 27.7, 29.5, 51.3, 53.3, 63.3, 68.0, 123.7, 125.4, 153.1, 157.3, 161.9; HRMS calcd for [M+Na] 550.2134, found 550.2130.
NOTE TO USERS

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APPENDIX

NMR Spectra of Selected Compounds
OTBSO
Rh
(nbd)
OTBS
TBSO
OTBS
BF₄⁻

[Rh(46)(nbd)]BF₄⁻
\( \text{HO' OH} \)

\( \text{Rh(54Xnbd)} \)

\( \text{SbF}_8 \)

67.0 66.6 66.6 66.4 66.2 66.0 65.6 65.4

\( \text{SbF}_6^- \)
339

[Chemical structure diagram with peaks labeled 0.9770, 2.1538, 2.0801, 1.0135, 1.0050, and 9.4879]
149 E/Z
2.4/1 mixture
167 \rightarrow 171 \text{(crude mixture)} + \text{regiosomer}
OTBS

172 crude mixture

regioisomer

O
N
B

Cl

Bn

Methyl
173 crude mixture
SnBu$_3$ SiMe$_3$ + SiMe$_3$ SnBu$_3$

2.2 : 1

175a

175b

SNAR

JUI

565