Syntheses and Applications of Vinylstannanes

by

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

I understand that my thesis may be made electronically available to the public.

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Abstract

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

Cyclic and acyclic vinylstannanes were prepared conveniently in a simple one-pot procedure from the corresponding ketones. The scope of ketones was illustrated and the limitations were highlighted. Moderate to high yields of vinylstannanes are reported that compare favourably with other methods. Two cases of unsymmetrical ketones provided the less substituted vinylstannanes. A straight-forward purification procedure was developed for non-polar vinylstannanes that allowed for the separation from Bu_3SnH contamination.

Trans-1-stannyl-1-alkenes were prepared in high regioselectivity (95:5, *trans*:*gem*) from unhindered 1-alkynes by using $Pd_2dba_3/Cy_3PHBF_4/i\text{-}Pr_2NEt$ on a wide range of terminal alkynes. This system exhibited higher selectivities and yields for *trans*-vinylstannanes than the original PPh_3-based catalysts that are widely adopted. Contrary to popular belief, it was found that ligands have a dramatic effect on the regioselectivity of palladium-catalyzed hydrostannations of 1-alkynes. Steric and electronic arguments were used to explain the observed regioselectivities. An insect sex pheromone was synthesized using the hydrostannation methodology that was developed. An inseparable 95:5 mixture of *trans* and *geminal* vinylstannanes did not pose a problem during the synthesis, as the *geminal* isomer did not participate in the Stille coupling.

A two-step synthesis of *trans*-1-stannylbutadiene, as an extension of hydrostannation of terminal alkynes, is reported. A convergent synthesis of a trienic sex pheromone was demonstrated as a convenient route to this class of compounds.

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

Trans-1-stannylbutadiene was able to undergo Diels-Alder reactions with various cyclic, five-membered ring, doubly activated dienophiles. Enantioselective Diels-Alder reaction was obtained in 33% ee by using a Mikami catalyst. The allylstannane from a racemic Diels-Alder reaction was able to undergo allylstannation with an aldehyde and a ketone using $SnCl_2$/MeCN or $SnCl_4/CH_2Cl_2$ systems to provide γ-addition products as the major isomers with high diastereoselectivity. A diastereoselective Diels-Alder reaction was effected by using Waldner's chiral dienophile to provide isomeric allylstannanes in a 10:1 ratio; the major product could be purified by flash chromatography. A Diels-Alder/allylstannation sequence was achieved with Waldner's dienophile and *trans*-1-stannylbutadiene to provide a pure functionalized cyclohexene in 60% yield in a one-pot procedure.

Acknowledgements

I would like to thank my supervisor Dr. Mike Chong for giving me the chance and the opportunity to work in his lab, and for giving me constant guidance and attention throughout my time at the Chong lab. I would also like to thank my supervisor for his incredible patience with my imperfections and generous assistance that allowed me to reach this point.

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I would like to acknowledge the University of Waterloo for providing funding throughout my doctoral studies.

To

my caring Mom and Dad

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List of Abbreviations and Tradenames

Ac	acetyl
Aq	aqueous
Ar	aryl
BINAL-H	2,2’-dihydroxy-1,1’-binaphthyl modified lithium aluminum hydride
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
BuLi	*n*-butyllithium
Bz	benzoyl
cat	catalyst
CBz	carbobenzyloxy
CI	chemical ionization
cm	centimetres
d	doublet
dba	dibenzylidene acetone
dd	doublet of doublets
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane

DMF	dimethylformamide
dppe	1,2-bis(diphenylphosphino)ethane
dppb	1,4-bis(diphenylphosphino)butane
dt	doublet of triplets
E^+	electrophile
EI	electron impact
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
h	hours
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
*i*Pr	isopropyl
IR	infrared
J	spin coupling constant
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m	multiplet
M	metal or molar or molecular ion

*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeLi	methyllithium
min	minutes
mL	milliliters
mmol	millimole
MOM	methoxymethyl
Ms	methanesulfonyl
MS	mass spectrometry
m/*z*	mass to charge ratio
nbd	*N*orbornadiene
NMR	nuclear magnetic resonance
Nu	nucleophile
o-tol	*ortho*-tolyl
PG	protecting group
Ph	phenyl
Pin	pinacol
PMHS	Polymethylhydrosiloxane
PPTS	pyridinium *para*-toluenesulfonate
Pyr	pyridine
q	quartet
rt	room temperature
s	singlet

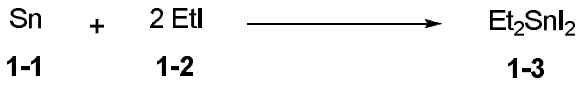
*s*BuLi	*sec*-butyllithium
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid
*t*Bu	*tertiary* butyl
*t*BuLi	*tert*-butyllithium
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Tf	trifluoromethanesulfonyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine

Chapter 1

Introduction

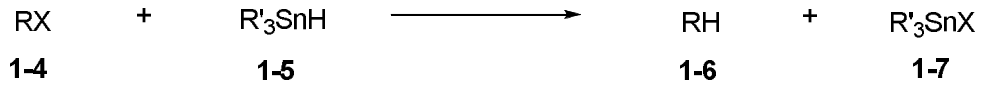
1.1 General

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



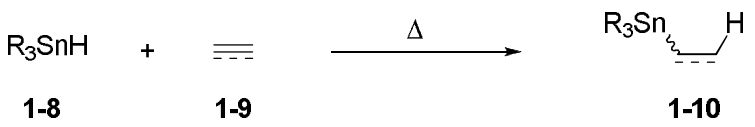
Scheme 1.1

By the mid 1950s, tin's role in organometallic chemistry increased rapidly as new applications for organotin compounds emerged.[2] Kuivila *et al*. demonstrated the reaction between trialkyltin hydrides with alkyl halides to produce reduction products **1-6**, *via* a radical chain reaction involving short-lived trialkyltin radicals (Scheme 1.2).[3]



Scheme 1.2

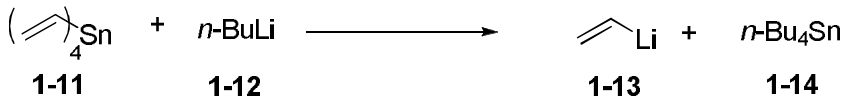
Newmann and Sommer illustrated addition of trialkyltin hydrides across double and triple bonds in a process called hydrostannation (Scheme 1.3).[4,5]



Scheme 1.3

Like hydrostannolysis, hydrostannation proceeds *via* radical chain reaction involving tin radicals.

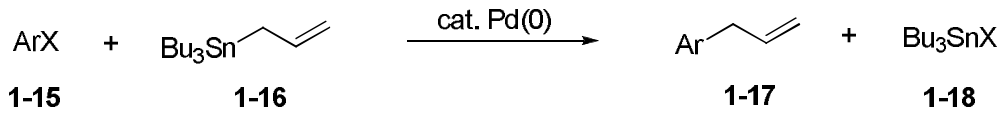
The ability of tin to exchange with other metals, *via* transmetallation processes, expanded the application of organotin chemistry dramatically.[2] Seyferth and Weiner were able to demonstrate the exchange between organotin **1-11** and butyllithium **1-12** (Scheme 1.4).[6]



Scheme 1.4

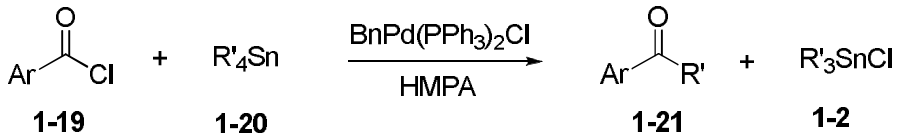
Vinyllithium **1-13** was treated with various electrophiles, as **1-13** was unstable for isolation.

More recently, cross-coupling reactions have garnered a great deal of attention due to their versatility in forming new carbon-carbon bonds. Kosugi *et al.* were able to accomplish the first cross coupling reaction involving tin (Scheme 1.5).[7]



Scheme 1.5

Cross coupling reaction between aryl halides and allylstannane proceeded by applying catalytic amounts of palladium (0). Milstein and Stille also demonstrated a cross coupling reaction between acyl chlorides and tetraalkyltin compounds (Scheme 1.6).[8]

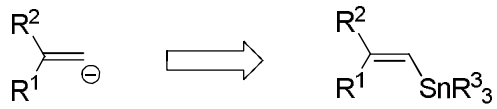


Scheme 1.6

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

1.2 Applications of Vinylstannanes

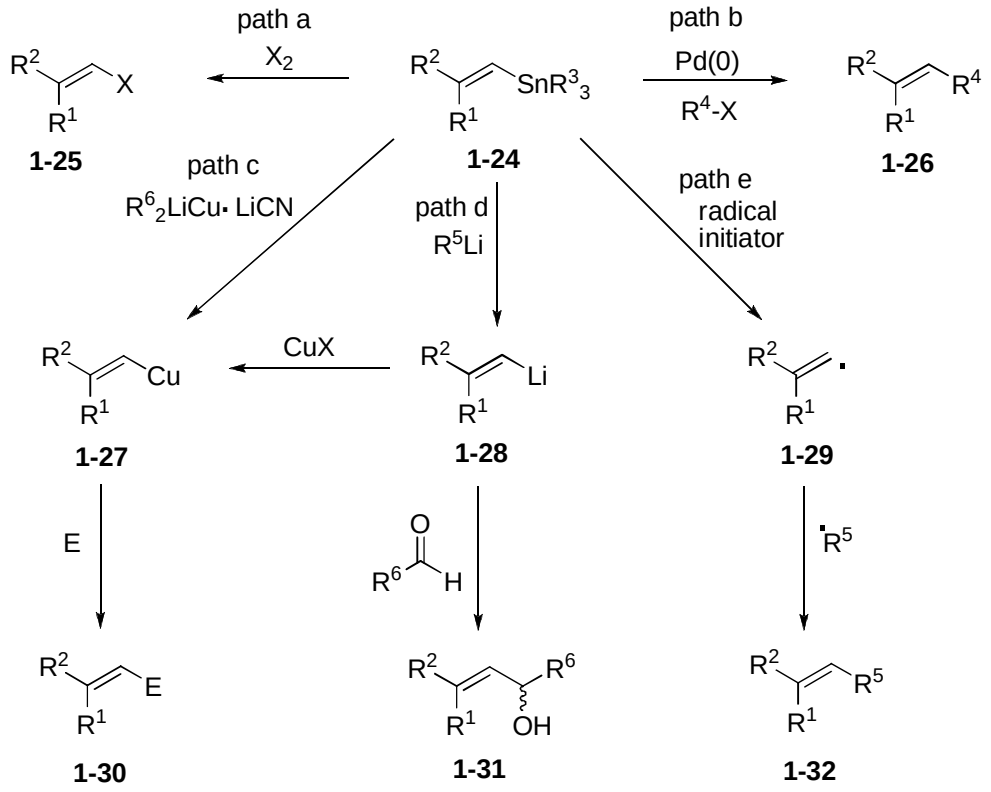
Vinylstannanes are a particularly important class of organostannanes, that have been employed in many syntheses of natural products.[9-17] They are stable to many substances such as water, air, bases and silica gel, which makes them attractive species to handle.[18] Synthetically speaking, vinylstannanes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



1-23 **1-2**

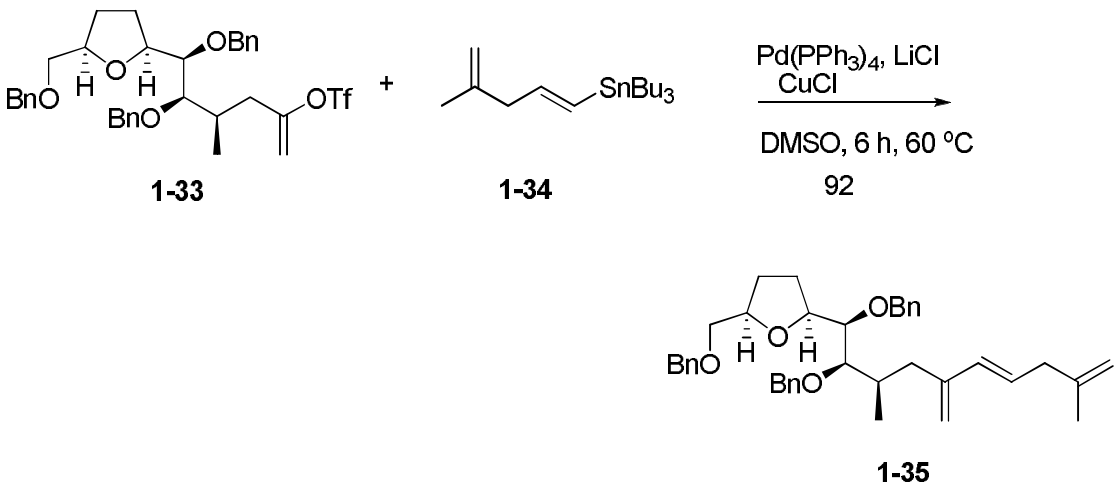
Figure 1.1 Vinylstannanes as synthetic equivalents of vinyl carbanions

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



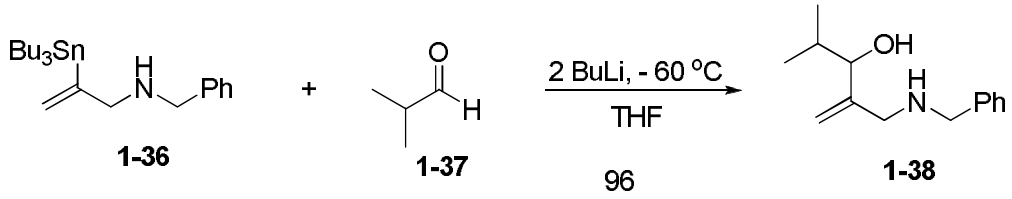
Scheme 1.7

Vinylstannanes can be used successfully in metal-catalyzed cross-coupling reactions (Scheme 1.7, path b), known as the Stille coupling, with organic halides or triflates. Complete retention of configuration of the double bond is observed (Scheme 1.8).[19]



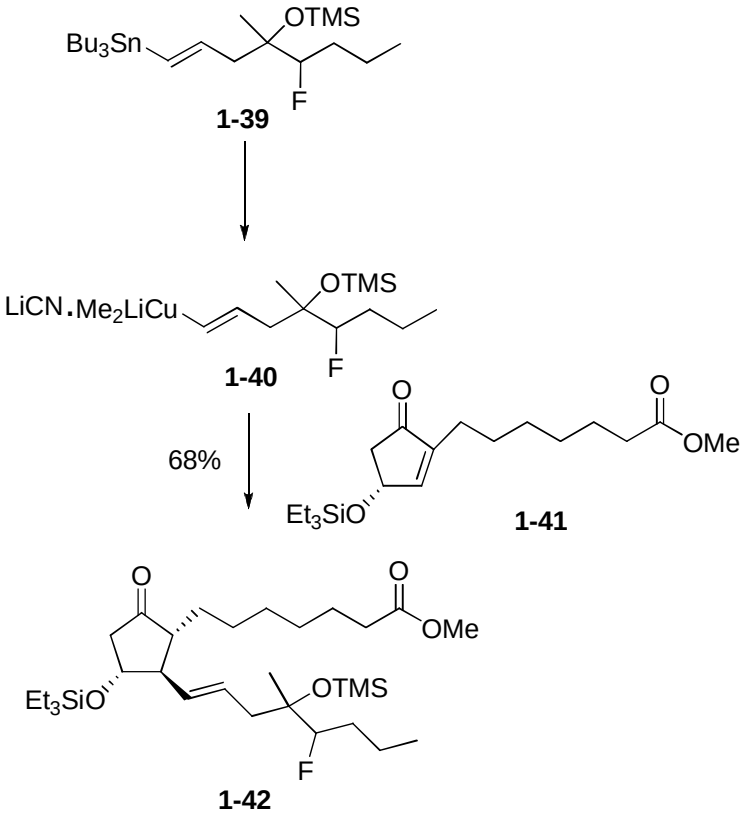
Scheme 1.8

Vinylstannanes can undergo stereospecific Sn-Li exchange with alkyllithiums to generate a highly reactive vinyllithium species (Scheme 1.7, path d), which can react with carbonyls in the same fashion as Grignard reagents do (Scheme 1.9).[20]



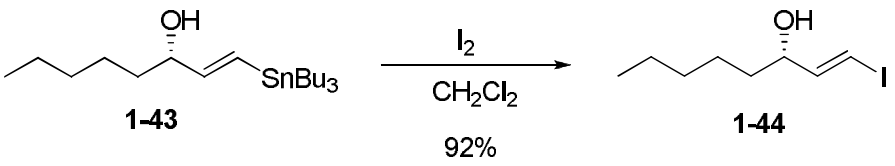
Scheme 1.9

Vinylstannanes can undergo transmetallation with reactive copper species (Scheme 1.7, path c) to generate highly reactive vinylcopper intermediates that could participate in substitution reactions or 1,4-addition reactions (Scheme 1.10).[21]



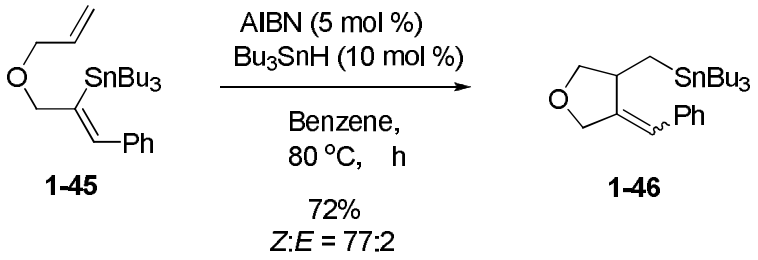
Scheme 1.10

Vinylstannanes readily react with dihalides such as bromine and iodine (Scheme 1.7, path a) to produce the corresponding vinylhalides with complete retention of configuration of the double bond (Scheme 1.11).[22]



Scheme 1.11

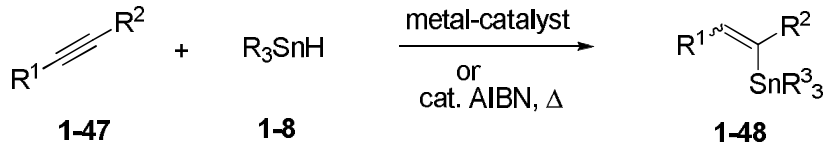
Vinylstannanes can undergo a radical chain process that generates a vinyl radical *in situ* (Scheme 1.7, path e); potentially leading to processes such as intramolecular cyclizations (Scheme 1.12).[23]



Scheme 1.12

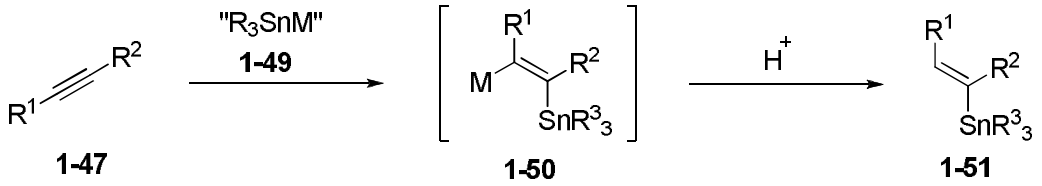
1.3 Syntheses of Vinylstannanes

There are several methodologies that are used commonly in preparation of vinylstannanes. Hydrostannation of alkynes by radical or metal-catalyzed processes are two of the most commonly used preparations of vinylstannanes (Scheme 1.13).[24,25]



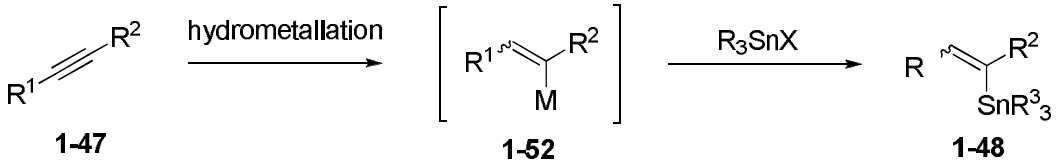
Scheme 1.13

Stannylmetallation of alkynes is another methodology that has gained attention in preparation of vinylstannanes (Scheme 1.14).[26,27]



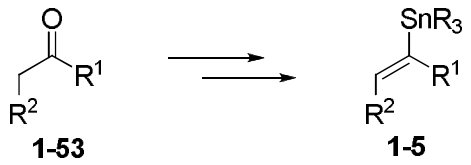
Scheme 1.14

Hydrometallation of a triple bond followed by stannylation of the corresponding vinyl metal formed *in situ* provides the corresponding vinylstannane (Scheme 1.15).[28-30]



Scheme 1.15

Also, vinylstannanes can be prepared from the corresponding carbonyl compounds (Scheme 1.16).[31-35]



1-53 **1-5**

Scheme 1.16

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

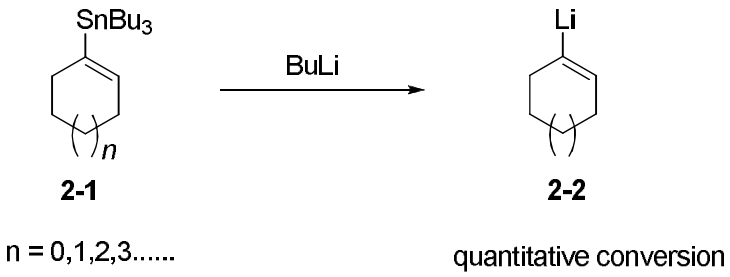
Chapter 2

Synthesis of Vinylstannanes from Ketones *via* Addition-Elimination Chemistry

2.1 Introduction

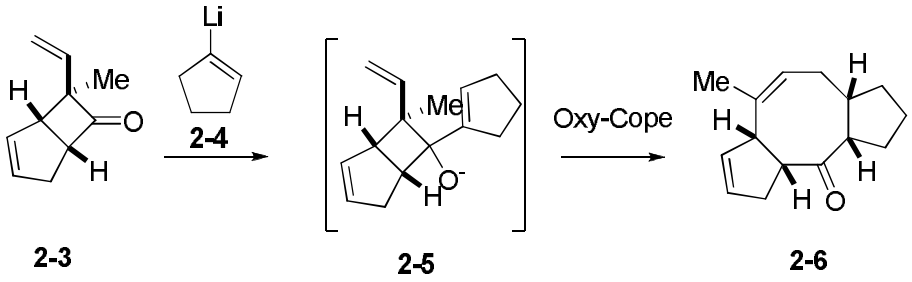
2.1.1 General

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



Scheme 2.1

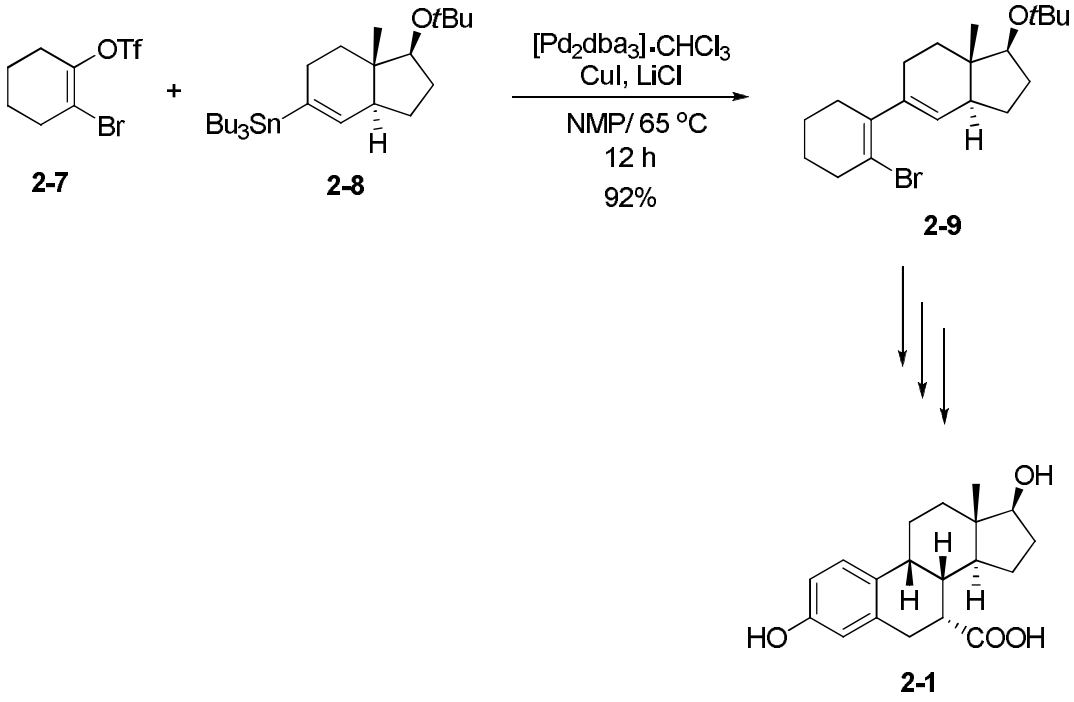
Paquette has demonstrated the use of these convenient building blocks to develop the skeleton of terpenoid **2-6** (Scheme 2.2).[3]



2-3 **2-5** **2-6**

Scheme 2.2

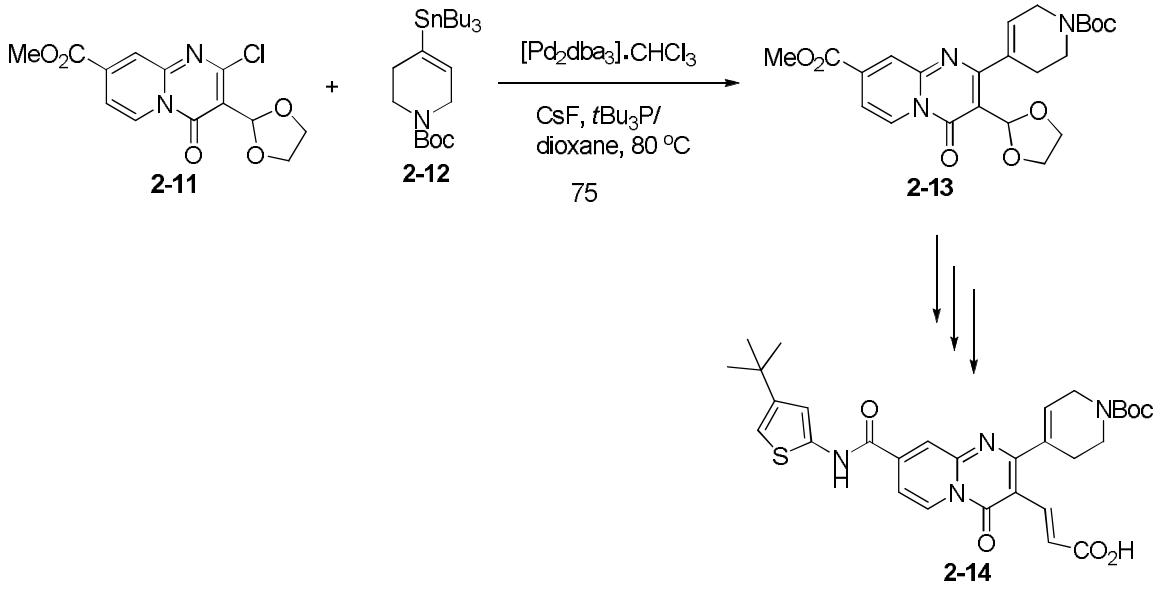
Sunnemann *et al.* applied cyclic vinylstannane **2-8** in part of the total synthesis of steroid **2-10** (Scheme 2.3).[4]



2-7 **2-8** **2-9** **2-1**

Scheme 2.3

Yoshida *et al.* obtained antibiotic **2-14** by employing vinylstannane **2-12** (Scheme 2.4).[5]

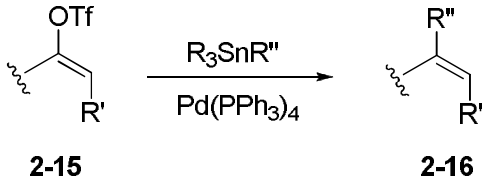


Scheme 2.4

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

2.1.2 Synthesis of vinylstannanes from carbonyl compounds

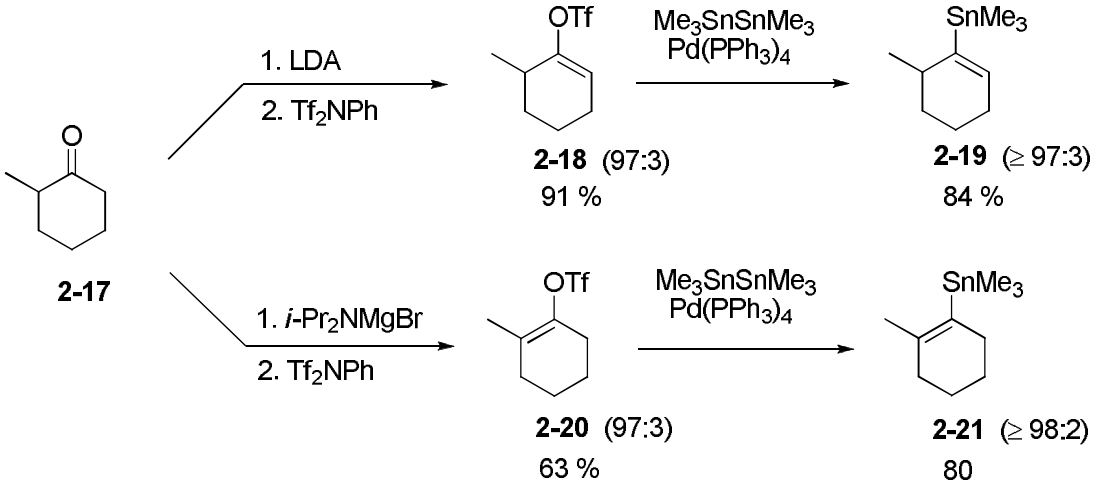
Wulff *et al.* developed a route to vinylstannanes based on an observation made by Stille *et al.*[6] that tetrakis(triphenylphosphine)palladium can catalyze the coupling of vinyl triflates with a variety of organostannanes (Scheme 2.5).



2-15 **2-16**

Scheme 2.5

Expanding this methodology, Wulff *et al.* were able to couple hexamethylditin with vinyl triflates derived from symmetrical and unsymmetrical ketones (Scheme 2.6).



2-17

2-18 (97:3)
91 %

2-19 (≥ 97:3)
84 %

2-20 (97:3)
63 %

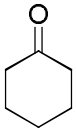
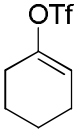
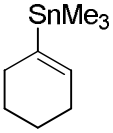
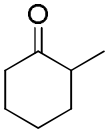
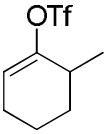
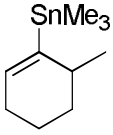
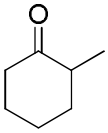
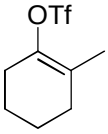
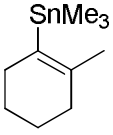
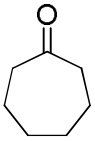
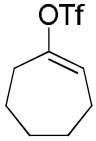
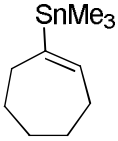
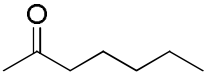
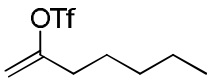
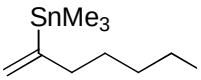
2-21 (≥ 98:2)
80

Scheme 2.6

Highly selective preparations of kinetic and thermodynamic enolates from unsymmetrical ketones have been reported.[7,8] The selective formation of enolates from unsymmetrical

ketones allows regioselective formation of vinylstannanes from unsymmetrical carbonyl compounds. Representative results are shown in Table 2.1.

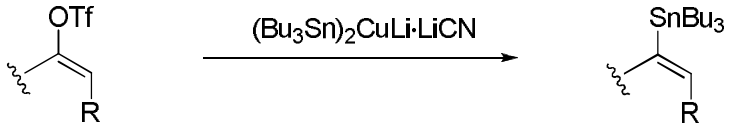
Table 2.1 Palladium-catalyzed coupling of enol triflates and hexamethyldistannane[7]

entry	ketone	enol triflate	yield (%)	vinylstannane	yield[a] (%) (h)
1	 **2-22**	 **2-23**	84[b]	 **2-24**	81(3)
2	 **2-17**	 **2-18 (97:3)**	91[b]	 **2-19 (≥ 97:3)**	84(9)
3	 **2-17**	 **2-20 (97:3)**	63[c]	 **2-21 (≥ 98:2)**	80(168)
4	 **2-25**	 **2-26**	89[b]	 **2-27**	73(0.75)
5	 **2-28**	 **2-29 (94:6)**	70[b]	 **2-30 (99.6:0.4)**	74(6)

[a] Coupling reactions were carried out at 60 °C with 0.2 M THF solutions of the enol triflate with 0.9 equiv of hexamethyldistannane, 6.0 equiv of lithium chloride, and 0.018 equiv of Pd cat. under Ar.
[b] LDA, *N*-phenyltrifluoromethanesulfonimide.
[c] *i*-Pr_2NMgBr, *N*-phenyltrifluoromethanesulfonimide

This methodology proved to be useful for cyclic and acyclic, symmetrical and unsymmetrical ketones.

This chemistry was limited to the use of $(Me_3Sn)_2$, as $(Bu_3Sn)_2$ provided very low yields. This limitation was overcome by applying highly reactive stannylcuprates. The coupling of vinyl triflates with highly reactive stannylcuprates was found to provide a convenient method for the preparation of vinylstannanes (Scheme 2.7).[9]

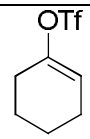
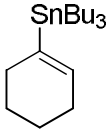
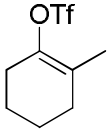
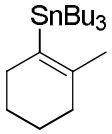


2-31 **2-3**

Scheme 2.7

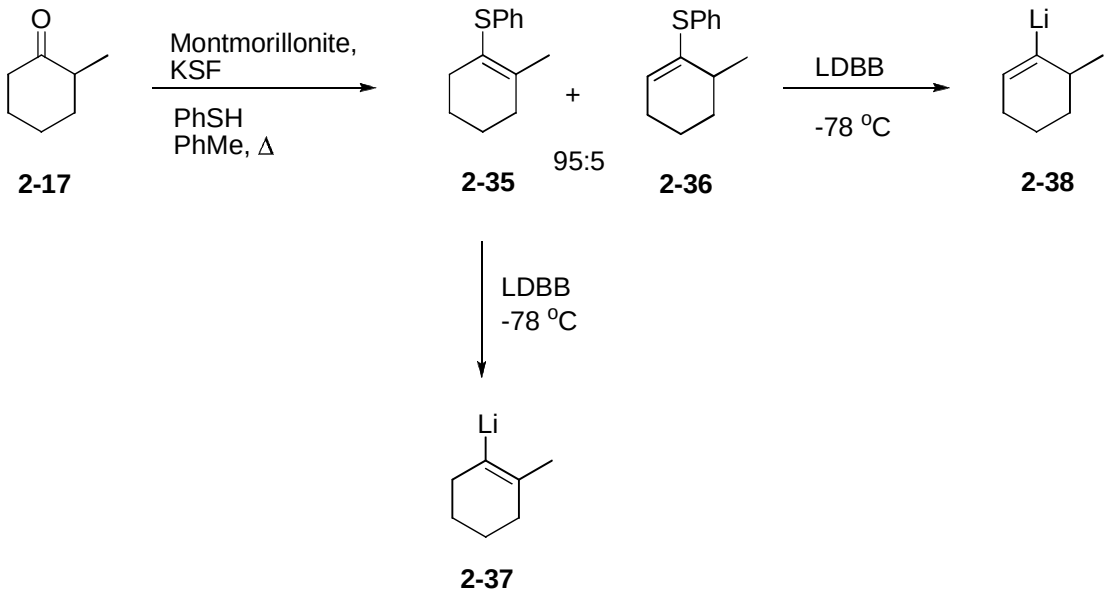
This methodology can also be applied to unsymmetrical ketones, since vinyl triflates can be regioselectivily prepared from ketones (Table 2.2).

Table 2.2 The coupling of vinyl triflates with stannylcuprates[9]

Entry	enol triflate	stannylcuprate	vinylstannane	reaction time (h) (temperature)	yield (%)
1	 **2-23**	$(Bu_3Sn)_2CuLi \cdot LiCN$ (1.1 equiv)	 **2-33**	2 (-20 °C)	97
2	 **2-20**	$(Bu_3Sn)_2CuLi \cdot LiCN$ (1.1 equiv)	 **2-34**	2 (-20 °C)	91

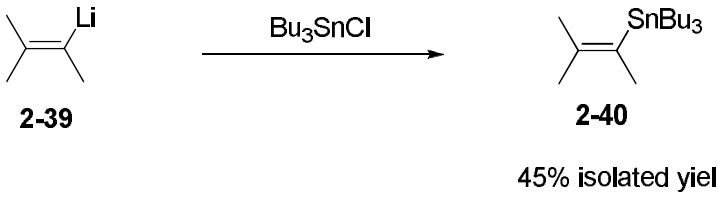
Shorter reaction times were another advantage to this route; as well, isolated yields were higher compared to the previous methodology.[9]

Adam and Klug[10] applied the same methodology developed by Cohen and Doubleday (Scheme 2.8)[11] to obtain vinyllithium compounds from enol phenyl thioethers such as **2-35**. This method involves the formation of vinyl sulfides from ketones followed by reductive lithiation by means of the radical anion lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB).[11] In the formation of vinyl sulfides from unsymmetrical ketones, the more highly substituted enol thioether **2-35** was formed as the major product (95:5, from ketone **2-17**) (Scheme 2.8).[12]



Scheme 2.8

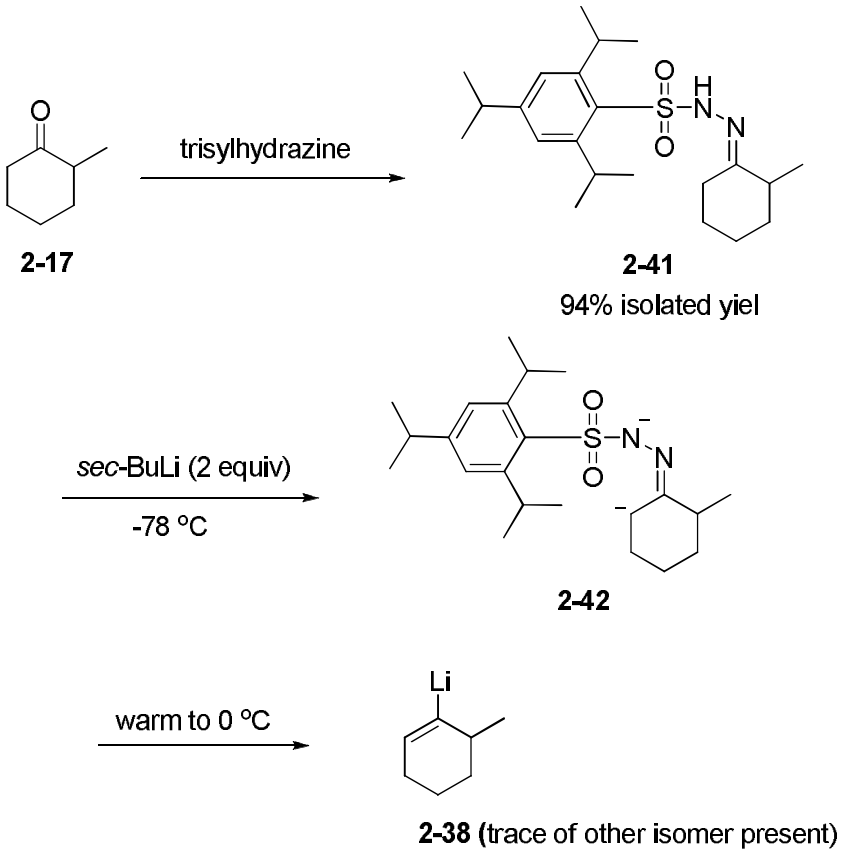
Adam and Klug were able to treat vinyllithium **2-39** (Scheme 2.9), formed *in situ*, with Bu_3SnCl to provide the corresponding vinylstannane **2-40**.[10]



Scheme 2.9

Methodology by Cohen and Doubleday proved to be selective for the more substituted vinyllithium when dealing with unsymmetrical ketones.[11]

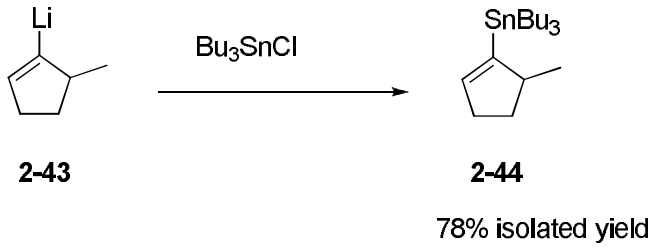
Adam and Klug[10] applied the methodology of Chamberlin *et al.* (Scheme 2.10)[13] to attain the less-substituted vinyllithiums from unsymmetrical ketones.



Scheme 2.10

Hydrazone **2-41** was formed in excellent yield, *via* the Shapiro reaction, by the addition of 2,4,6-triisopropylbenzenesulfonylhydrazine (trisylhydrazine) to unsymmetrical ketone **2-17**. Addition of 2 equivalents of *sec*-BuLi to hydrazone **2-41** leads to the formation of dianion **2-42**.[13] Dianion **2-42** underwent decomposition as the reaction temperature was raised to 0 ^{o}C to provid vinyllithium **2-38** as the major isomer.[13] Unlike the Cohen and

Doubleday procedure, the less substituted vinyllithium was formed in this case which eventually led to the formation of the less substituted vinylstannane upon treatment with Bu_3SnCl (Scheme 2.11).[10,13]

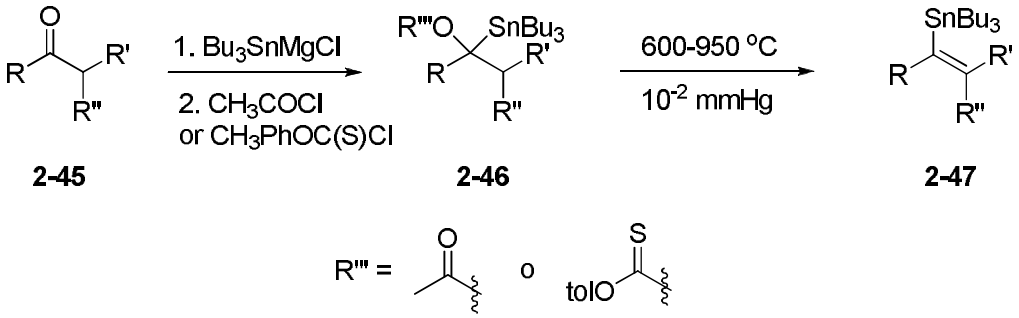


2-43 **2-44**

78% isolated yield

Scheme 2.11

Duboudin *et al.* reported a one-pot synthesis of cyclic and acyclic vinylstannanes from carbonyl compounds (Scheme 2.12).[14]



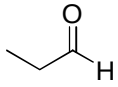
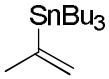
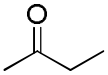
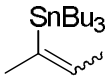
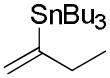
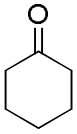
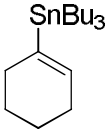
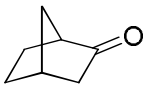
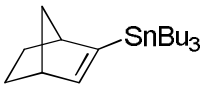
2-45 **2-46** **2-47**

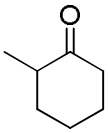
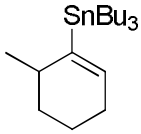
Scheme 2.12

This method involved the addition of $Bu_3SnMgCl$ to a carbonyl compound, followed by conversion of the hydroxystannane intermediate to the corresponding stannyl acetate or

thiocarbonate.[14] A subsequent thermolysis at 600-950 °C furnished the desired vinylstannane in moderate yields (Table 2.3).[14]

Table 2.3 Thermolysis of stannyl acetates and thiocarbonates.[14]

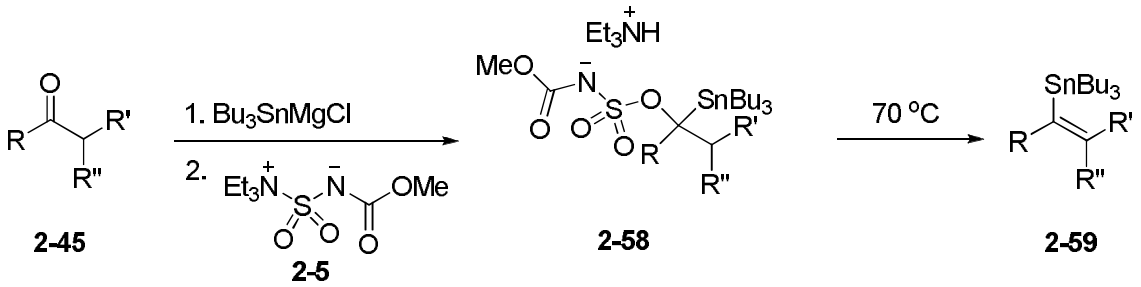
entry	carbonyl compound	vinylstannane	yield (%) (method)	temperature (°C)
1	 **2-48**	 **2-49**	61[a] (A)	800
2	 **2-50**	 **2-51**	75 (A)	800
3	 **2-52**	 **2-53a**	30[b]	650
		 **2-53b**	46 (B)	
4	 **2-22**	 **2-33**	59 (A)	700
5	 **2-55**	 **2-5**	29 (B)	820

6	 **2-17**	 **2-54**	40 (A)	750

[a] *cis*/*trans* : 42/58
[b] *cis*/*trans* : 54:46
Method A: 1. $Bu_3SnMgCl$; 2. H_2O; 3. $CH_3PhOC(S)Cl$.
Method B: 1. $Bu_3SnMgCl$; 2. CH_3COCl.

Aldehydes and ketones shown in Table 2.3 were able to provide the corresponding vinylstannanes. Aldehyde **2-48** afforded two stereoisomeric vinylstannanes in 42/58 (*cis*/*trans*) ratio. Ketone **2-52** afforded two regioisomeric vinylstannanes **2-53a** (*cis*/*trans* : 54:46) and **2-53b** in 2:3 ratio, respectively.[14] Unsymmetrical cyclic ketone **2-17** provided exclusively the less substituted vinylstannane **2-54**.[14]

Ratier *et al.* improved the thermolysis methodology, as a route to vinylstannanes, using triethylammonium *N*-carbomethoxysulfamate (Scheme 2.13).[15]

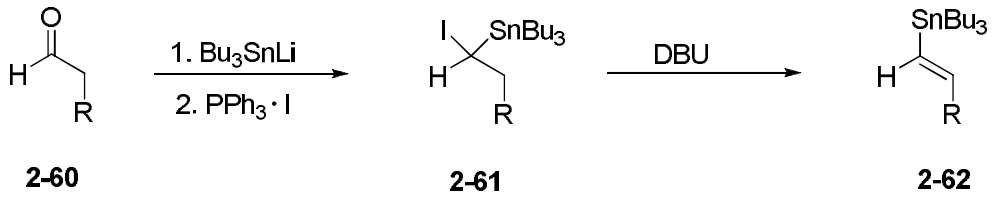


2-45 **2-5** **2-58** **2-59**

Scheme 2.13

Salt **2-57** was obtained from carbomethoxysulfamoyl chloride and triethylamine by a modified Burgess procedure.[16] An advantage to this route is the ability of intermediate **2-58** to eliminate at milder temperatures than reported previously.[15]

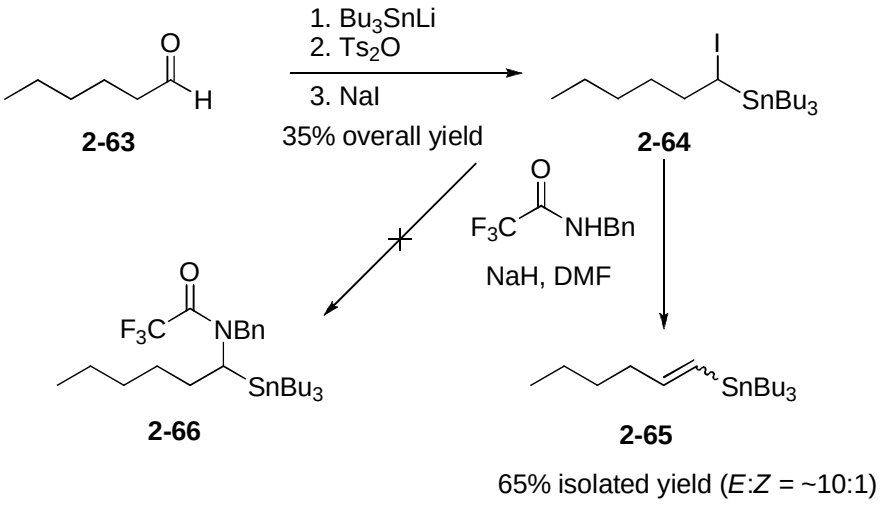
Chong and Park have also developed a methodology that generated vinylstannanes from aldehydes (Scheme 2.14).[17]



2-60 **2-61** **2-62**

Scheme 2.14

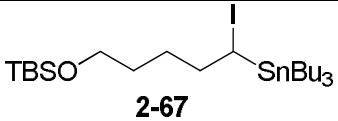
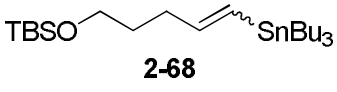
This methodology was a result of a serendipitous observation that came about during an investigation into the chemistry of α-aminoorganostannanes (Scheme 2.15). Thus iodide **2-64** did not provide the desired amide **2-66** but gave a modest yield of **2-65**.[17]

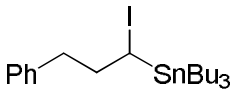
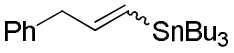
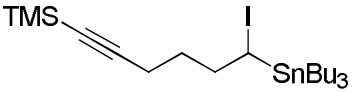
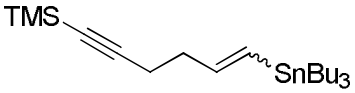
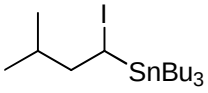
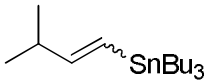
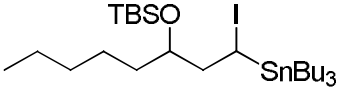
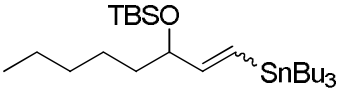
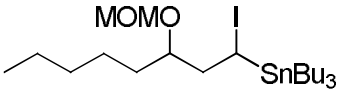
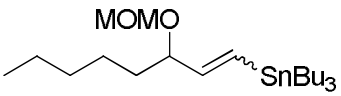


Scheme 2.15

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

Table 2.4 Formation of vinylstannanes from α-iodostannanes.[17]

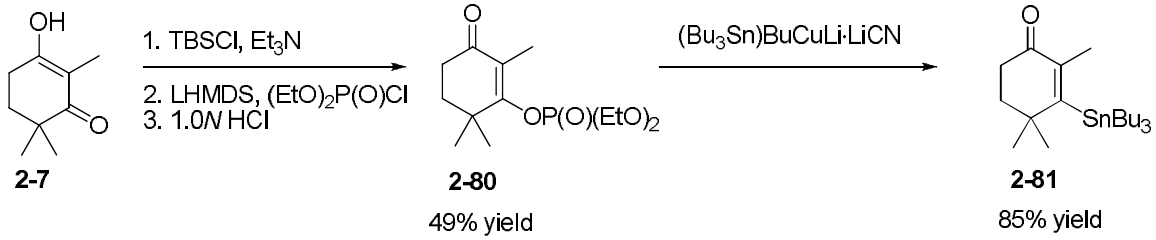
entry (aldehyde)	iodide (% yield)[a]	vinylstannane (% yield)[a]	E:Z[b]
1	 **2-67** (75)	 **2-68** (100)	9:1

2	 **2-69** (72)	 **2-70** (95)	16:1
3	 **2-71** (50)	 **2-72** (94)	10:1
4	 **2-73** (85)	 **2-74** (95)	53:1
5	 **2-75** (80)	 **2-76** (96)	150:1
6	 **2-77** (56)	 **2-78** (100)	32:1

[a] Isolated yields.
[b] Determined by GC.

Elimination of HI from α-iodostannanes by DBU provided excellent stereoselectivities of corresponding vinylstannanes (Table 2.4, 9:1 to 150:1 (*E*:*Z*)); branching of α-iodostannanes lead to increased selectivity.[17]

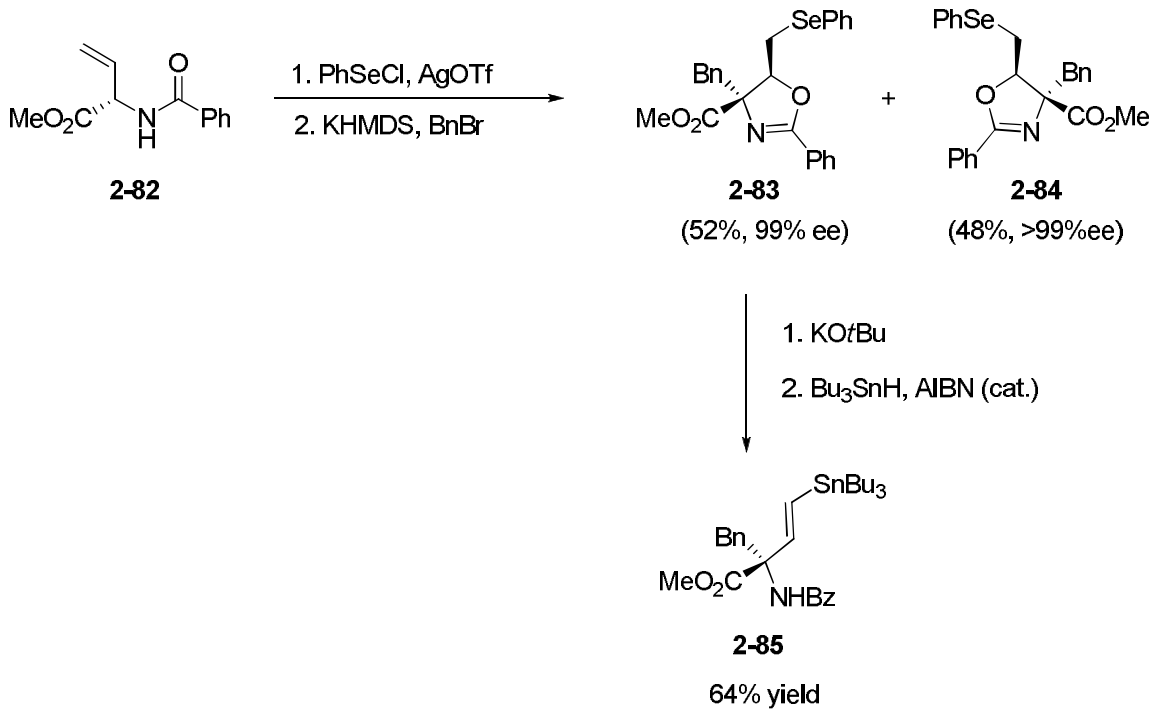
Other preparative methods of vinylstannanes from carbonyl or carbonyl derivatives have been developed also, but have not been widely adopted. Vinylstannane **2-81** was prepared by conjugate addition of stannyl anion to **2-80** followed by elimination of the phosphate group (Scheme 2.16).[19]



2-7 **2-80** 49% yield **2-81** 85% yield

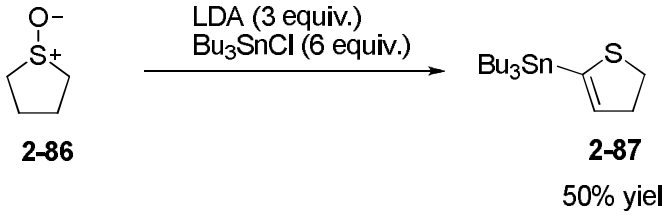
Scheme 2.16

Opening of oxazoline **2-83** by KO*t*Bu followed by deselenative stannylation with Bu_3SnH and AIBN provided vinylstannane **2-85** in a moderate yield (Scheme 2.17).[20]



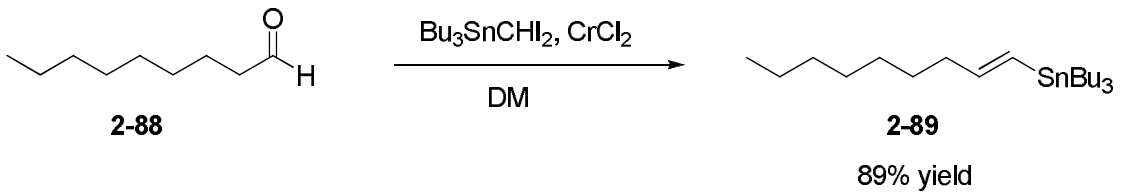
Scheme 2.17

Tetramethylene sulfoxide **2-86** undergoes a tin mediated Pummerer type conversion to generate vinylstannane **2-87** (Scheme 2.18).[21]



Scheme 2.18

Vinylstannane **2-89** was obtained in good yield from aldehyde **2-88** *via* a chromium(II)-mediated process using Bu_3SnCHI_2 (Scheme 2.19).[22]



2-88 **2-89**

89% yield

Scheme 2.19

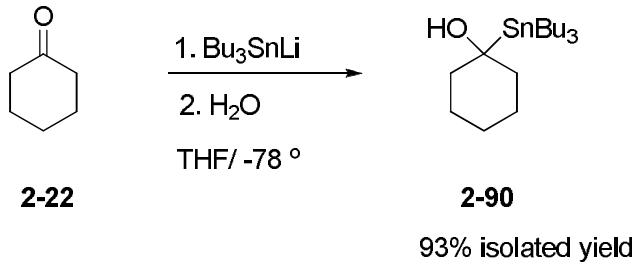
2.2 Proposed Work

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

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

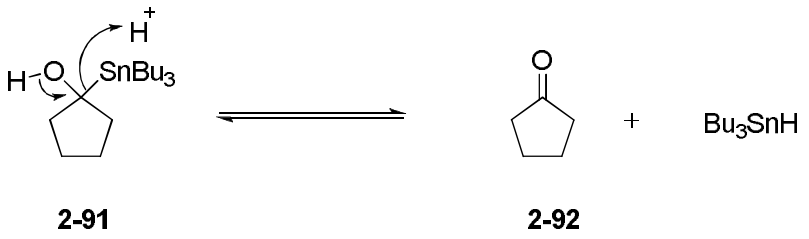
2.3 Results and Discussion

In the initial experiments, Bu_3SnLi[23] was made *in situ* by adding Bu_3SnH to lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0 ^oC. After 30 min of stirring at that temperature, cyclohexanone was added in a dropwise fashion at -78 ^oC. The reaction was left stirring for an additional 30 min, followed by an aqueous workup. *α*-Hydroxystannane **2-90** was obtained in high (93%) isolated yield (Scheme 2.20).



Scheme 2.20

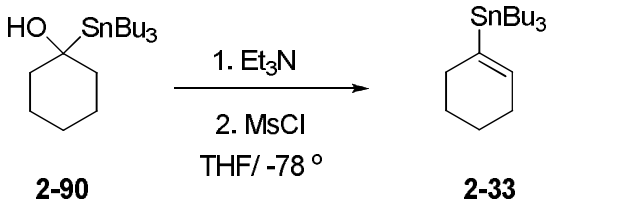
It is known that *α*-hydroxystannanes are not particularly stable,[23] although *α*-hydroxystannane **2-90** was stable enough to be chromatographed through silica gel without any noticeable loss in yield. However, *α*-hydroxystannane **2-91** (Scheme 2.21) did experience considerable decomposition upon silica gel chromatography. Bu_3SnH and cyclopentanone were recovered as verified by ^1H and ^{13}C NMR spectra. Destannylation of hydroxystannanes could occur in the presence of acid or base. Silica is acidic and can serve as a proton donor for this process to occur (Scheme 2.21).



2-91 **2-92**

Scheme 2.21

The next step toward the synthesis of vinylstannane **2-33** was to dehydrate α-hydroxystannane **2-90**. To accomplish this, crude α-hydroxystannane **2-90** was treated with methanesulfonyl chloride (MsCl) and Et_3N in THF at -78 ^oC and let warm to room temperature gradually (Scheme 2.22).



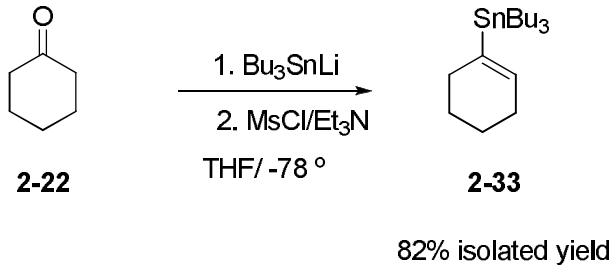
2-90 **2-33**

97% isolated yield

Scheme 2.22

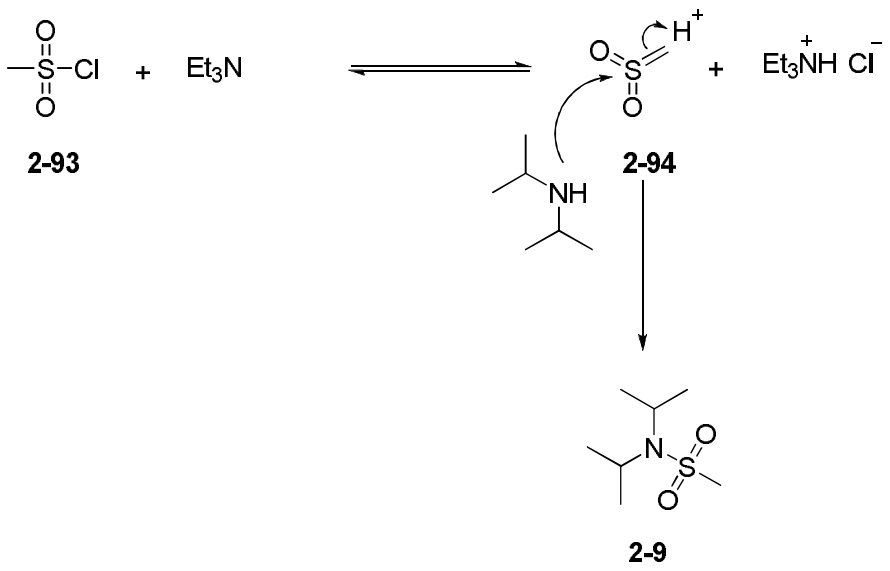
The dehydration occurred cleanly to afford the desired cyclic vinylstannane **2-33** in 97% isolated yield. Since there were many routes that were developed to obtain cyclic vinylstannanes, this route needed to have an advantage.

A one-pot procedure was developed wherein α- hydroxystannane intermediate was not quenched but rather treated directly with MsCl/Et_3N. The reaction did not go to completion when 1-2 equivalents of MsCl were applied; however, the reaction did proceed to completion when 4 equivalents of MsCl were applied to afford cyclic vinylstannane **2-33** in 82% isolated yield (Scheme 2.23).[24]



Scheme 2.23

Complete consumption of α-hydroxystannane intermediate **2-90** was observed by TLC. The requirement of excess MsCl is likely due to the presence of diisopropylamine in the reaction. Diisopropylamine was deprotonated to make LDA base, which is the base used to convert Bu_3SnH to Bu_3SnLi. Diisopropylamine is suspected to react directly with MsCl or with sulfene **2-94**, an intermediate formed from MsCl, hence the need for excess MsCl (Scheme 2.24).

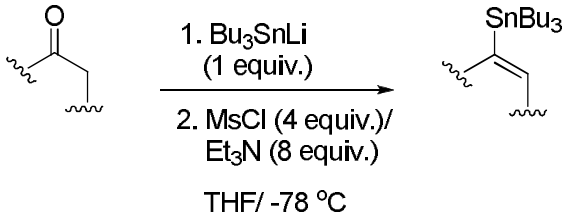


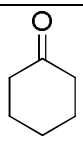
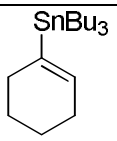
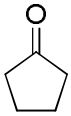
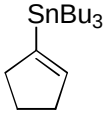
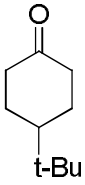
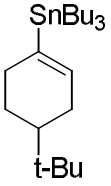
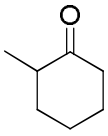
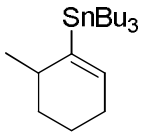
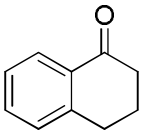
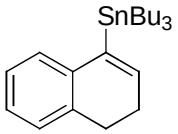
Scheme 2.24

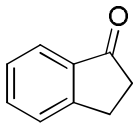
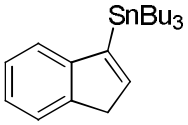
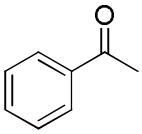
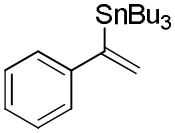
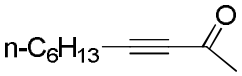
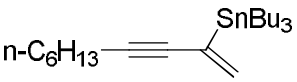
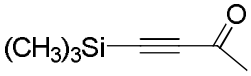
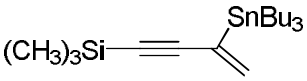
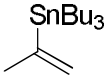
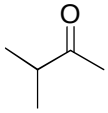
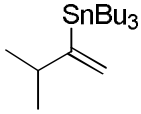
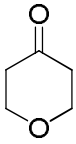
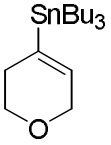
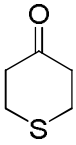
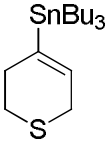
Fortunately, MsCl is relatively inexpensive and the suspected polar by-products such as **2-95** were easily removed by liquid-liquid separation between hexane and acetonitrile. The non-polar stannanes remained in the hexane layer, while the polar materials were removed by the acetonitrile layer.

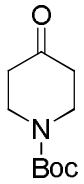
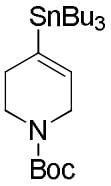
Other ketones where subjected to the one-pot protocol which illustrated the wide scope of this methodology (Table 2.5).[24]

Table 2.5 Synthesis of vinylstannanes from ketones



entry	ketone	stannane	yield (%)[a]
1	 **2-22**	 **2-33**	82
2	 **2-92**	 **2-96**	83
3	 **2-97**	 **2-98**	81
4	 **2-17**	 **2-54**	81
5	 **2-9**	 **2-100**	80

6	 **2-101**	 **2-102**	81
7	 **2-103**	 **2-104**	88
8	 **2-105**	 **2-106**	91
9	 **2-107**	 **2-108**	72
10	 **2-50**	 **2-51**	78
11	 **2-109**	 **2-110**	61
12	 **2-111**	 **2-112**	75
13	 **2-113**	 **2-11**	79

14	 **2-115**	 **2-12**	80

[a] Isolated yields of purified products

Examining the scope of this reaction, cyclic ketones subjected to this route provided yields consistently between 80-83% regardless of the ring size (5 or 6). Ketones conjugated with an aromatic ring provided vinylstannanes in great yields. Also, the reaction was operational whether the ring is carbocyclic or heterocyclic. The scale of the reaction (1 to 15 mmol) did not have any effect on the yields.[24]

The reactions proceeded very smoothly and cleanly as determined by ^{1}H NMR spectroscopic analysis of the crude mixtures. Only tin-containing materials were observed and consisted mainly of the desired vinylstannane along with traces of Bu_3SnH (< 5%, determined by ^{13}C NMR).[24]

Vinylstannanes that contained functionalities other than hydrocarbons separated easily from Bu_3SnH by silica gel chromatography. Initially, vinylstannanes that did not contain any functionality presented a challenge in purification from Bu_3SnH contamination. Even with the use of hexane as eluant, vinylstannanes were not separable from Bu_3SnH by silica gel chromatography.

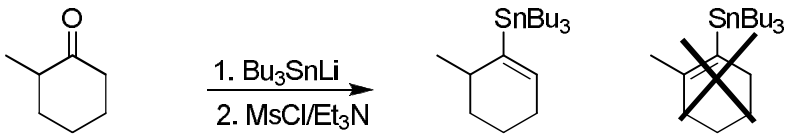
There are many methods that have been developed for the removal of organotin residue,[25,26] but they are primarily intended for the removal of organotin halides which would not be of use in this case. This challenge was initially solved by using reverse phase silica. Reverse phase silica contains C-18 units that are used to cap hydroxyl

groups in regular silica, making the silica non-polar. This allows for the separation of non-polar impurities from the desired non-polar compounds. Reverse phase silica is commercially available but expensive. Alternatively, it can be made very easily from regular silica, and columns may be used multiple times.[27]

The second procedure for removing Bu_3SnH, which was the adopted procedure, involved stirring of the crude reaction mixture in warm chloroform containing a catalytic amount of azobis(isobutyronitrile) (AIBN) for 4 h. Bu_3SnH reacts with chloroform to form Bu_3SnCl, while leaving the vinylstannane unaffected, which can be filtered by simple silica gel chromatography.

This procedure was inspired by the serendipitous observation made when recording a ^{13}C NMR spectrum of Bu_3SnH in $CDCl_3$. Peaks for Bu_3SnCl and $CHDCl_2$ were observed. This observation can be explained by a radical reaction that occurred between Bu_3SnH and $CDCl_3$ initiated by light. Now, ^{13}C NMR spectra of Bu_3SnH are recorded in C_6D_6 to avoid such side reactions.[28]

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



2-17 **2-54** **2-34**

81% isolated yield

Scheme 2.25

This can be explained by axial attack of Bu_3SnLi on 2-methylcyclohexanone. It has been previously shown that addition of Bu_3SnLi to 4-*tert*-butylcyclohexanone, under the same conditions that we performed our reactions, proceeds with an axial : equatorial selectivity of 93:7 (Figure 2.1).[29]

2-117 **2-118**

major isomer minor isome

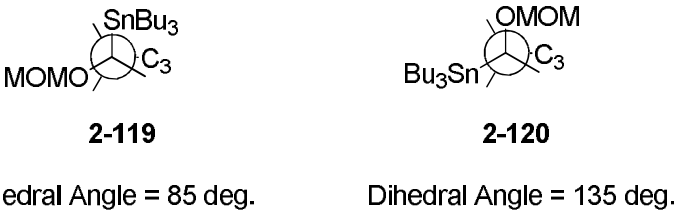
$^3J_{Sn-C}$ = < 3 Hz
C_1 = 87.8 ppm

$^3J_{Sn-C}$ = 40 Hz
C_1 = 80.9 ppm

Figure 2.1 Illustration of dihedral angles of **2-117** and **2-118**

Sawyer *et al.* illustrated that the major axial stannyl isomer exhibited a higher ^{13}C NMR frequency for the quaternary carbon (C_1 on compound **2-117**) and that $^3J_{Sn-C}$ for C_3/C_5 was different for the two isomers. This was determined by the dihedral angle between

C_1-Sn and C_2-C_3 bonds. In the axial isomer, these two bonds are almost orthogonal to one another (shown in Figure 2.2), which would give rise to a smaller coupling constant (< 3 Hz) according to the Karplus curve.[29]



2-119 Dihedral Angle = 85 deg.

2-120 Dihedral Angle = 135 deg.

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

On the other hand, the equatorial isomer contains a dihedral angle of 135 degrees between C_1-Sn and C_2-C_3 bonds (shown in Figure 2.2). One would expect a larger ^{119}Sn-$^{13}C_3$ coupling in this case, and the recorded coupling is 40 Hz.[29] Having this in mind, the same experiment was repeated with 2-methylcyclohexanone instead of 4-*tert*-butylcyclohexanone (Figure 2.3).

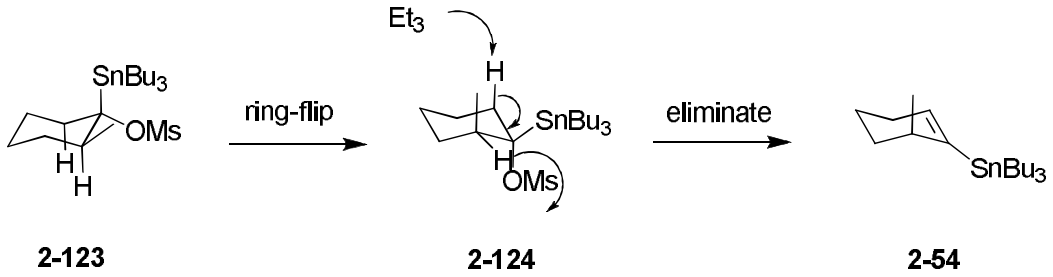
2-121
major isomer
$^3J_{Sn\text{-}C}$ = ~ 0 Hz
C_1 =93.9 ppm

2-122
minor isome
$^3J_{Sn\text{-}C}$ = 40 Hz
C_1 = 85.8 ppm

Figure 2.3 Illustration of dihedral angles of **2-121** and **2-122**

α-Hydroxystannane intermediates were trapped with methoxymethyl chloride (MOMCl) to form the corresponding ethers (**2-121** & **2-122**). The formation of two diastereomers with selectivity of 95:5 was observed. Inspecting the ^{13}C NMR spectrum, the major isomer (**2-121**) did not show any resolved ^{119}Sn-$^{13}C_3$ coupling. The minor isomer (**2-122**) did have $^{3}J_{Sn\text{-}C}$ of 40 Hz. These results were consistent with what was reported by Sawyer *et al*.[29]

Since the axial isomer is the major isomer, a ring-flip is required to place the mesyloxy group in the axial position to facilitate E_2 elimination as shown below (Scheme 2.26).

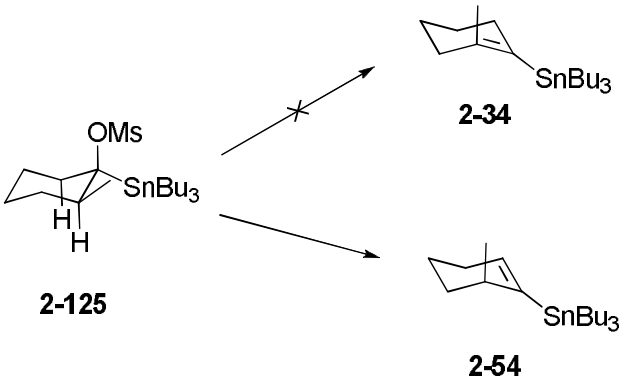


Scheme 2.26

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

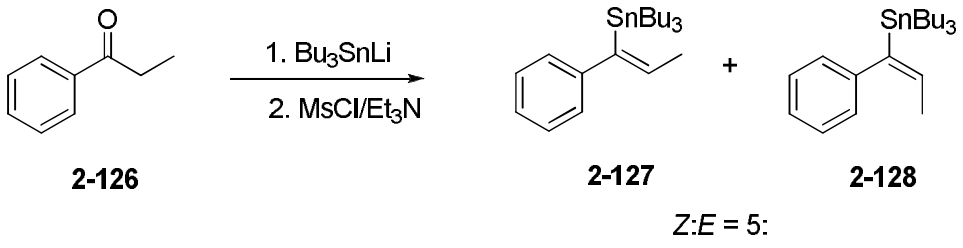
It is still unclear what exactly happens to the remaining 5% hydroxystannane formed from the equatorial attack. The mesyloxy group in **2-125** is in the axial position and is aligned to eliminate readily. But in this case, there are two available protons that are anti-

periplanar with the mesyloxy group. Since the less substituted vinylstannane is observed exclusively, the least hindered proton is abstracted, suggesting the vinylstannane produced is the kinetic product (Scheme 2.27).



Scheme 2.27

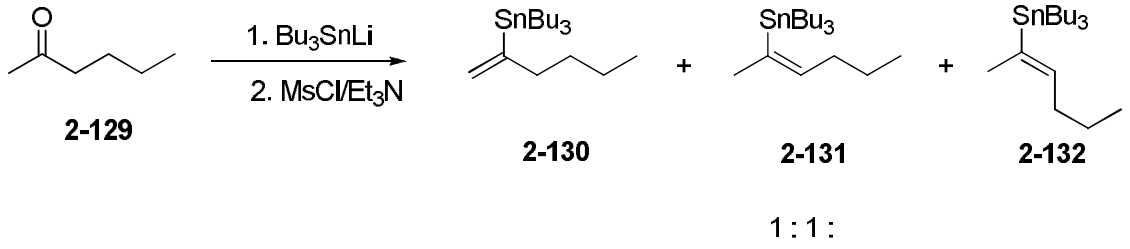
Acyclic ketones were also subjected to this methodology. Aryl methyl ketones such as acetophenone **2-103** worked very well, as did alkynyl methyl ketones **2-105** and **2-107**. However, propiophenone **2-126** provided a low yield of a mixture of stereoisomers (*Z*:*E* = ~ 5:1) (Scheme 2.28).



Scheme 2.28

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

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

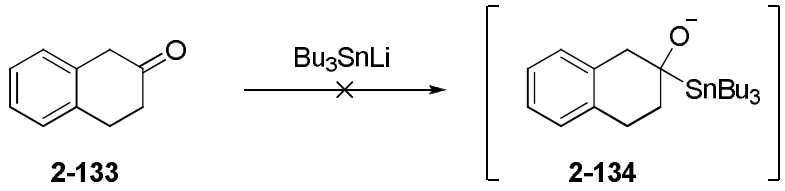


Scheme 2.29

It was found that acyclic dialkyl ketones required the use of a relatively fresh *n*-BuLi bottle to obtain good yields. This finding was interesting due to the fact that this sensitivity was not observed for cyclic ketones, aryl ketones or the alkynyl ketones. It

was suspected that traces of alkoxides found in older bottles promoted undesirable reactions with dialkyl ketones that are more susceptible to side reactions.

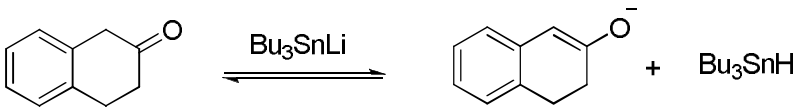
Cyclic ketone 2-tetralone **2-133** failed completely at forming the α-hydroxystannane intermediate (Scheme 2.30).



2-133 **2-134**

Scheme 2.30

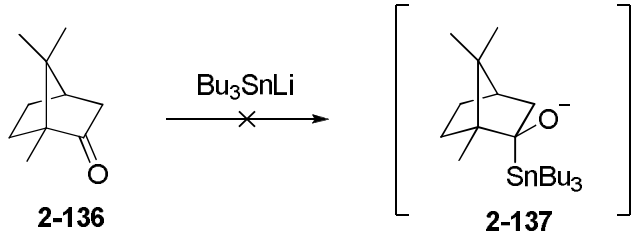
Bu_3SnLi could act as a base as a result of highly acidic α-protons activated by the aromatic ring (Scheme 2.31).



2-133 **2-13**

Scheme 2.31

Similarly, camphor **2-136** was resistant to the addition of Bu_3SnLi. This may be due to the steric nature around the carbonyl and/or competing enolization (Scheme 2.32).



2-136 **2-137**

Scheme 2.32

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

2-138 **2-13**

Figure 2.4 Cycloheptanone **2-138** and cyclooctanone **2-139**

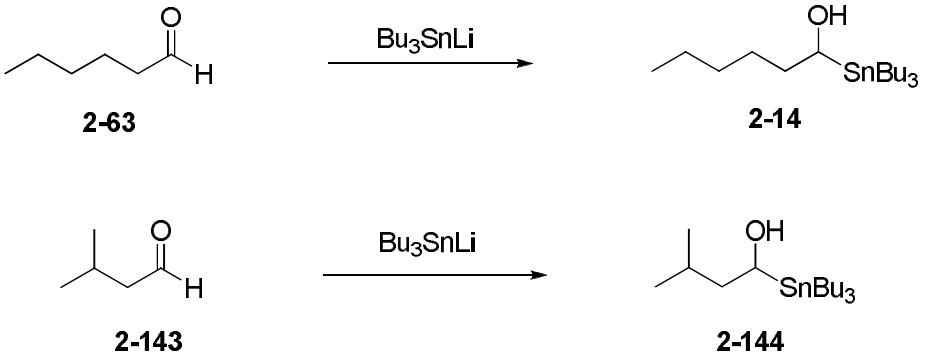
This suggested that five and six member rings possess a privileged geometry that allows for the addition of Bu_3SnLi. Lactone γ-butyrolactone **2-140** and lactam 1-butylpyrrolidin-2-one **2-141** were also subjected to this methodology, since it seemed that five and six member rings are the ideal ring sizes for the addition of Bu_3SnLi (Scheme 2.5).

2-140 **2-141**

Figure 2.5 Lactone γ-butyrolactone **2-140** and lactam 1-butylpyrrolidin-2-one **2-141**

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

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

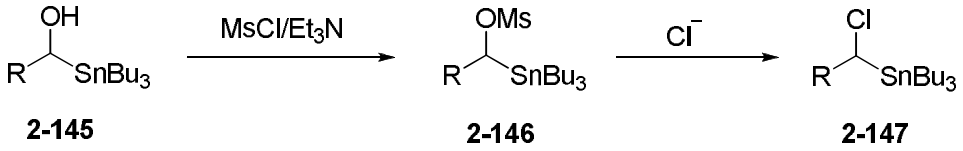


2-63 **2-14**

2-143 **2-144**

Scheme 2.33

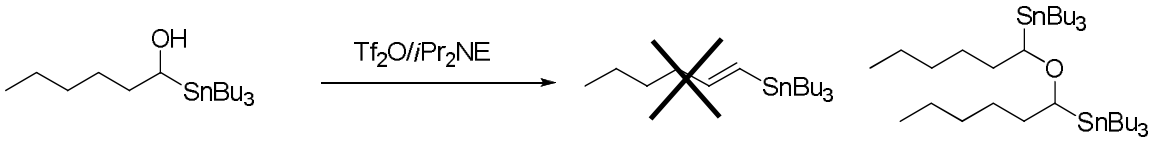
Unfortunately, treatment of these hydroxystannanes with $MsCl/Et_3N$ did not produce vinylstannanes but rather unidentified materials, possibly α-chlorostannanes **2-147** arising from displacement rather than elimination of the intermediate mesylates (Scheme 2.34).[30]



2-145 **2-146** **2-147**

Scheme 2.34

Other elimination conditions, such as trifluoromethanesulfonic anhydride (Tf_2O)/*i*Pr_2NEt (Hünig's base) were also applied in attempts to provide vinylstannane **2-148** but with no success. Unidentifiable materials were obtained that could possibly contain the dimeric ether stannane **2-149** (Scheme 2.35).



2-142 **2-148** **2-149**

Scheme 2.35

2.4 Summary

A simple one-pot procedure for the preparation of cyclic and acyclic vinylstannanes from the corresponding ketones was developed. Appropriate ketones that can be used with this method were highlighted. Limitations of this method were highlighted by noting which carbonyl compounds are not compatible. Isolated yields compare very favourably with other methodologies. Reagents and materials used are inexpensive and readily available, while the procedure is operationally straightforward. A simple purification procedure was developed for non-polar hydrocarbon vinylstannanes. This procedure allows for the separation of non-polar vinylstannanes from non-polar Bu_3SnH, and is applicable on multigram scale. The route established here for the preparation of vinylstannanes should be very convenient and useful to obtain these important building blocks.

2.5 Experimental

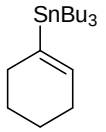
2.5.1 General experimental

All reactions were carried out under argon using flame-dried glassware. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz, respectively, unless otherwise noted. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 ev) ionization unless otherwise specified. Couplings to ^{117}Sn and ^{119}Sn are reported as averages of the two values. THF was distilled from Na/benzophenone, and acetone was distilled from B_2O_3. Dichloromethane, triethylamine and diisopropylethylamine (Hünig's base) were freshly distilled from calcium hydride. Solvent grade chloroform was used in the purification process of vinylstannanes from Bu_3SnH contamination. Tributyltin hydride was prepared by reduction of bis(tributyltin)oxide with $NaBH_4$ in ethanol and was distilled (Kugelrohr) before use.[31] Samples were checked by ^{13}C NMR spectroscopy (in C_6D_6 since Bu_3SnH reacts with $CDCl_3$) for the presence of $Bu_3SnSnBu_3$ and were re-distilled if necessary.[28] Methanesulfonyl chloride was freshly distilled from P_2O_5 prior to use. Other reagents were purchased from Sigma-Aldrich and used without further purification. Alkynyl ketones **2-105** and **2-107** were prepared by reaction of the appropriate alkynyllithium with dimethylacetamide.[32] *n*-BuLi was titrated using *N*-benzylbenzamide.[33]

2.5.2 General procedure for preparation of vinylstannanes from carbonyl compounds

To a cold (0 ºC), stirred solution of diisopropylamine (5 mmol, 1.0 eq) in THF (15 mL) was added *n*-BuLi (1.6 M in hexanes, 5 mmol, 1.0 eq). The solution was stirred at 0 ºC for 10 min then Bu_3SnH (5 mmol, 1.0 eq) was added and the resulting yellow solution was stirred at 0 ºC for an additional 30 min. The solution was then cooled to -78 ºC and the ketone (5 mmol, 1.0 eq) was added dropwise. After 10 minutes, Et_3N (40 mmol, 8 eq) and MsCl (20 mmol, 4 eq) were added. The reaction mixture was then allowed to warm to rt. After 30 min at rt, hexanes (200 mL) was added and the organic layer was washed with CH_3CN (3 x 100 mL). Concentration of the hexanes layer by rotary evaporation provided crude vinylstannanes. Traces of Bu_3SnH could be removed by stirring the sample with a small amount (30 mg) of AIBN in $CHCl_3$ (15 mL per gram of crude material) at 40 ºC for 4 h followed by flash chromatography on silica gel (10 g/g of crude material). Alternatively, purification could be effected using flash column chromatography on reverse-phase silica gel[27,34] using 40% CH_2Cl_2 in CH_3CN. In all cases, vinylstannanes were isolated as colorless liquids.

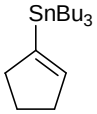
2.5.2.1 **1-Tributylstannylcyclohexene (2-33)**[9]



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, s, J_{Sn-H} = 68.9 Hz), 2.70 – 2.50 (4H, m), 2.14 – 2.04 (4H, m), 1.54 - 0.82 (27H, m).

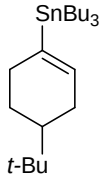
2.5.2.2 **1-Tributylstannylcyclopentene (2-96)**[35]



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (1H, t, J = 2.1 Hz, J_{Sn-H} = 35.2 Hz), 2.50 –2.28(2H, m), 2.39 – 2.34 (4H, m), 1.58 - 0.86 (27H, m).

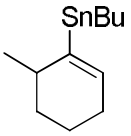
2.5.2.3 **4-*Tert*-butyl-1-tributylstannylcyclohexene (2-98)**[36]



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, s, J_{Sn-H} = 66.8 Hz), 2.31 –1.65 (7H, m), 1.55 - 0.84 (36H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 137.5, 44.1, 33.7, 32.4, 29.4, 29.3, 27.5 (J_{Sn-C} = 60.4 Hz), 27.2, 13.8, 8.9 (J_{Sn-C} = 326.0 Hz).

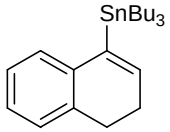
2.5.2.4 **6-Methyl-1-tributylstannylcyclohexene (2-54)**[37]



Stannane **2-54** was made in 81% isolated yield from ketone **2-17** using the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (1H, m, J_{Sn-H} = 70.2 Hz), 2.24(1H, m), 2.00 (2H, m), 1.85 – 1.60 (4H, m), 1.57 - 0.82 (30H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 137.0, 35.2, 32.0, 30.7, 29.3, 27.5 (J_{Sn-C} = 60.4 Hz), 23.0, 20.5, 13.8, 9.8 (J_{Sn-C} = 339.6 Hz).

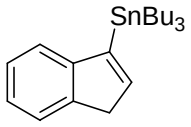
2.5.2.5 **1-Tributylstannyl-3,4-dihydronaphthalene (2-100)**



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (3H, m), 6.94 (1H, d, J = 7.2 Hz),6.23 (1H, t, J = 4.3 Hz, J_{Sn-H} = 59.6 Hz), 2.71 (2H, t, J = 7.8 Hz), 2.27 (2H, m), 1.55 - 0.84 (27H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 139.9, 138.7, 136.0, 127.8, 126.4, 126.3, 29.2, 28.2, 27.4 (J_{Sn-C} = 65.3 Hz), 24.8,13.8, 10.1 (J_{Sn-C} = 326.3 Hz); IR (neat) 2871, 2853, 1463, 754 cm^{-1}; MS (EI) *m/z* 420 (M^+, 1%), 363(M – nBu, 100%); Anal. Calcd for $C_{22}H_{36}Sn$: C, 63.03; H, 8.66. Found: C, 63.00; H, 8.66.

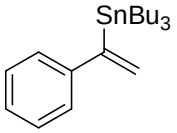
2.5.2.6 **1-Tributylstannyl-1-indene (2-102)**



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 7.2 Hz), 7.36 (1H, d, J = 7.4 Hz), 7.27(1H, t, J = 7.3 Hz), 7.17 (1H, t, J = 7.3Hz), 6.68 (1H, s, J_{Sn-H} = 31.2 Hz), 3.46 (2H, s), 1.58 – 0.85 (27H,m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 145.0, 144.8, 143.9, 126.2, 124.2, 123.6, 122.4, 41.5 (J_{Sn-C} = 48.3 Hz), 29.3,27.4 (J_{Sn-C} = 72.4 Hz), 13.8, 9.5 (J_{Sn-C} = 350.2 Hz); IR (neat) 2871, 2859, 1604, 1456, 774 cm^{-1}; MS(EI) *m/z* 406 (M^+, 0.7%), 349 (M – nBu, 100%); Anal. Calcd for $C_{21}H_{34}Sn$: C, 62.25; H, 8.46. Found: C, 62.20; H, 8.26.

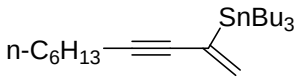
2.5.2.7 **1-Tributylstannyl-1-phenylethylene (2-104)**[38]



Stannane **2-104** was made in 88% isolated yield from ketone **2-103** using the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31- 7.16 (5H, m), 6.03 (1H, d, J = 2.4 Hz, J_{Sn-H} = 130.6 Hz), 5.42(1H, d, J = 2.4 Hz, J_{Sn-H} = 60.8 Hz), 1.55 - 0.82 (27H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7,146.5, 128.3 (2C), 126.8, 126.4 (2C), 126.3, 29.1, 27.4 (J_{Sn-C} = 60.4 Hz), 13.7, 10.3 (J_{Sn-C} = 350.6 Hz).

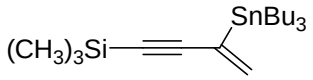
2.5.2.8 **2-Tributylstannyl-dec-1-en-3-yne (2-106)**



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (1H, d, J = 3.3 Hz, J_{Sn-H} = 117.8 Hz), 5.42(1H, d, J = 3.4 Hz, J_{Sn-H} = 55.2 Hz), 2.33 (2H, t, J = 6.6 Hz), 1.55 – 0.85 (38H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 133.9, 95.6, 84.3, 31.3, 28.9, 28.8, 28.5, 27.4 (J_{Sn-C} = 60.3 Hz), 22.5, 19.7, 13.9, 13.6, 10.0 (J_{Sn-C} = 338 Hz); IR (neat) 2856, 1464, 668 cm^{-1}; MS (EI) *m/z* 426 (M^+, 0.5%), 369 (M – nBu, 100%); Anal. Calcd for $C_{22}H_{42}Sn$: C, 62.13; H, 9.95. Found: C, 61.92; H, 9.89.

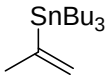
2.5.2.9 **2-Tributylstannyl-4-trimethylsilylbut-1-en-3-yne (2-108)**



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (1H, d, J = 3.3 Hz, J_{Sn-H} =112.5 Hz), 5.53 (1H, d, J = 3.3 Hz, J_{Sn-H} = 54.0 Hz), 1.52 – 0.84 (27H, m), 0.15 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 134.7, 108.9, 99.3, 28.9, 27.4 (J_{Sn-C} = 57 Hz), 13.8, 10.3 (J_{Sn-C} = 320 Hz), 0.2; IR (neat) 2854, 2109, 842 cm^{-1}; MS (EI) *m/z* 414 (M^+, 0.4%), 357 (M – nBu, 100%); Anal. Calcd for $C_{19}H_{38}SiSn$: C, 55.21; H, 9.27. Found: C, 55.35; H, 9.50.

2.5.2.10 **2-Tributylstannylpropene (2-51)**[15]

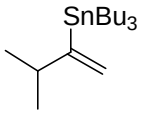


Stannane **2-51** was made in 78% isolated yield from ketone **2-50** using the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (1H, s, J_{Sn-H} = 138.1 Hz), 5.07 (1H, s, J_{Sn-H} = 66.0Hz), 1.95 (3H, s, J_{Sn-H} = 42.0 Hz), 1.56 - 0.85 (27H, m); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 150.2, 125.4 (J_{Sn-C} = 28.4 Hz), 29.0 (J_{Sn-C} = 19.9 Hz), 27.3 (J_{Sn-C} = 55.1 Hz), 13.5, 9.0 (J_{Sn-C} = 321 Hz).

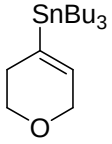
2.5.2.11 **2-Tributylstannyl-3-methyl-1-butene (2-110)**[15]



Stannane **2-110** was made in 61% isolated yield from ketone **2-109** using the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (1H, s, J_{Sn-H} = 143.1 Hz), 5.01(1H, s, J_{Sn-H} = 66.0 Hz), 2.46 (1H, septet, J = 6.8 Hz), 1.52 - 0.85 (33H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 121.7 (J_{Sn-C} = 28.5Hz), 38.6 (J_{Sn-C} = 42.7 Hz), 29.0 (J_{Sn-C} = 21.0 Hz), 27.3 (J_{Sn-C} = 57.0 Hz), 23.0 (J_{Sn-C} = 14.8 Hz), 13.5, 10.0 (J_{Sn-C} = 315.8 Hz).

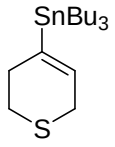
2.5.2.12 **4-Tributylstannyl-3,6-dihydro-2*H*-pyran (2-112)**[39]



Stannane **2-112** was made in 75% isolated yield from ketone **2-111** using the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, m, J_{Sn-H} = 64.3 Hz), 4.11 (2H, m), 3.74 (2H, t, J = 5.3 Hz), 2.24 (2H, m), 1.55 - 0.84 (27H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 135.9 (J_{Sn-C} = 18.0 Hz), 66.7 (J_{Sn-C} = 49.7 Hz), 64.6 (J_{Sn-C} = 27.7 Hz), 31.6 (J_{Sn-C} = 27.2 Hz), 29.0 (J_{Sn-C} = 19.9 Hz), 27.2 (J_{Sn-C} = 54.7 Hz), 13.6, 8.7 (J_{Sn-C} = 325.4 Hz).

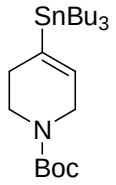
2.5.2.13 **4-Tributylstannyl-3,6-dihydro-2*H*-thiopyran (2-114)**[39]



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (1H, m, J_{Sn-H} = 66.9 Hz), 3.11(2H, m), 2.65 (2H, t, J = 5.6 Hz), 2.43 (2H, m), 1.48 - 0.82 (27H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9 (J_{Sn-C} = 395.9Hz), 132.4 (J_{Sn-C} = 25.5 Hz),31.5 (J_{Sn-C} = 35.2 Hz), 28.9 (J_{Sn-C} = 19.7 Hz), 27.3 (J_{Sn-C} = 55.5 Hz),26.4(J_{Sn-C} = 58.1 Hz), 25.1 (J_{Sn-C} = 33.4 Hz), 13.6, 8.8 (J_{Sn-C} = 323.0 Hz).

2.5.2.14 **1-*Tert*-butoxycarbonyl-4-tributylstannyl-1,2,3,6-tetrahydropyridine (2-12)**[39]



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (1H, s, J_{Sn-H} = 63.0 Hz), 3.86 (2H, s), 3.40 (2H, t, J = 5.4 Hz), 2.22 (2H, s), 1.42 (9H, s), 1.52 - 0.82 (27H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 138.7, 133.4, 79.1, 45.1, 39.8, 39.0, 31.5, 28.9 (J_{Sn-C} = 19.9 Hz), 28.3, 27.2 (J_{Sn-C} =54.4 Hz), 13.5, 8.9 (J_{Sn-C} = 325.5 Hz).

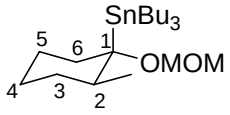
2.5.3 Addition of Bu_3SnLi to 2-methylcyclohexanone **2-17**

To examine the stereochemistry of addition of Bu_3SnLi to ketone **2-17**, an experiment was carried out according to the general procedure described earlier but saturated aqueous NH_4Cl was added to quench the reaction instead of $MsCl/Et_3N$. The resulting unstable hydroxystannanes were isolated after standard aqueous workup and immediately treated with excess MOMCl/*i*-Pr_2NEt. Examination of the ^{1}H NMR spectrum of the crude reaction mixture indicated a 95:5 mixture of 2 diastereomers.

These diastereomers were readily separated by flash chromatography on silica gel. The major, more polar (R_f = 0.38, hexanes-ether, 10:1) isomer was assigned as the “axial”

isomer based on data previously reported for the Bu_3SnLi adducts to 4-*t*-butylcyclohexanone (**2-97**).[29] Of particular significance is $^3J_{Sn-C}$ for C_3 which is ~0 when the Bu_3Sn group is axial and ~40 Hz when the Bu_3Sn group is equatorial, values consistent with a Karplus relationship.

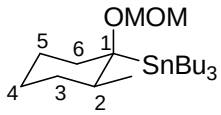
2.5.3.1 ***Axial*-tributyl(1-(methoxymethoxy)-2-methylcyclohexyl)stannane (2-121)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70, 4.67 (2H, AB quartet, J_{AB} = 6.9 Hz), 3.34 (3H, s), 2.18 (1H, br d, J = 12.2 Hz), 1.73-0.85 (7H, m), (27H, m), 0.96 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 93.9 (C_1, J_{Sn-C} = 435.4 Hz), 92.2 (J_{Sn-C} = 24.7 Hz), 55.4 (OCH_3), 41.6 (C_2, J_{Sn-C} = 26.0 Hz), 36.8 (C_6, J_{Sn-C} = 31.7 Hz), 32.6 (C_3, J_{Sn-C} ~ 0 Hz), 29.3 (J_{Sn-C} = 19.5 Hz), 27.7 (J_{Sn-C} = 59.4 Hz), 25.4 (C_5, J_{Sn-C} ~ 0 Hz), 24.9 (C_4, J_{Sn-C} = 7.5Hz) 20.2 (J_{Sn-C} = 19.5 Hz), 13.6, 11.3 (J_{Sn-C} = 282.7 Hz).

The minor, less polar (R_f = 0.49, hexanes-ether, 10:1) isomer was assigned as the "equatorial" isomer.

2.5.3.2 ***Equatorial*-tributyl(1-(methoxymethoxy)-2-methylcyclohexyl)stannane (2-122)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66, 4.57 (2H, AB quartet, J_{AB} = 6.6 Hz), 3.36 (3H, s), 2.26 (1H, br d, J = 11.5 Hz), 1.65-0.80 (7H, m), (27H, m), 0.94 (3H, d, J = 6.6Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.7 (J_{Sn-C} = 19.2 Hz), 85.8 (C_1), 55.9, 41.1 (C_2), 36.2 (C_6, J_{Sn-C} = 21.7 Hz), 29.6 (C_3, J_{Sn-C} = 34.7 Hz), 29.4 (J_{Sn-C} = 19.3 Hz), 27.7 (J_{Sn-C} = 57.4 Hz), 26.5 (C_4), 20.6 (J_{Sn-C} = 19.5 Hz), 20.4 (C_5, J_{Sn-C} = 40.0 Hz), 13.6, 10.5 (J_{Sn-C} = 280.9 Hz).

Chapter 3

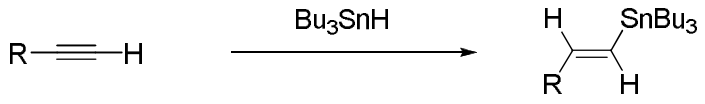
The Use of Phosphine Ligands to Control the Regiochemistry of Pd-Catalyzed Hydrostannations of 1-Alkynes: Synthesis of (*E*)-1-Tributylstannyl-1-alkenes

3.1 Introduction

3.1.1 General

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

The most common way of forming vinylstannanes is the overall addition of Bu_3SnH to an alkyne (Scheme 3.1), which is accomplished in several ways.



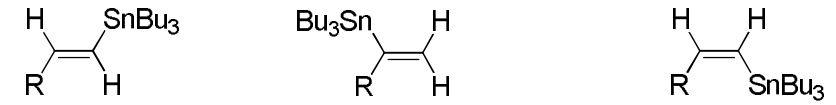
3-1 **3-**

Scheme 3.1

The first method is radical induced hydrostannation, which is the oldest and most reliable method for preparing vinylstannanes.[2] The second method involves metal-catalyzed hydrostannation, which has also enjoyed wide use. The third method consists of

stannylmetallation followed by protonation.[3] These methods are discussed in greater detail below.

The addition of Bu_3SnH to terminal alkynes can provide three possible isomers (Figure 3.1).



***trans* isome** ***geminal* isome** ***cis* isome**

3-2 **3-3** **3-4**

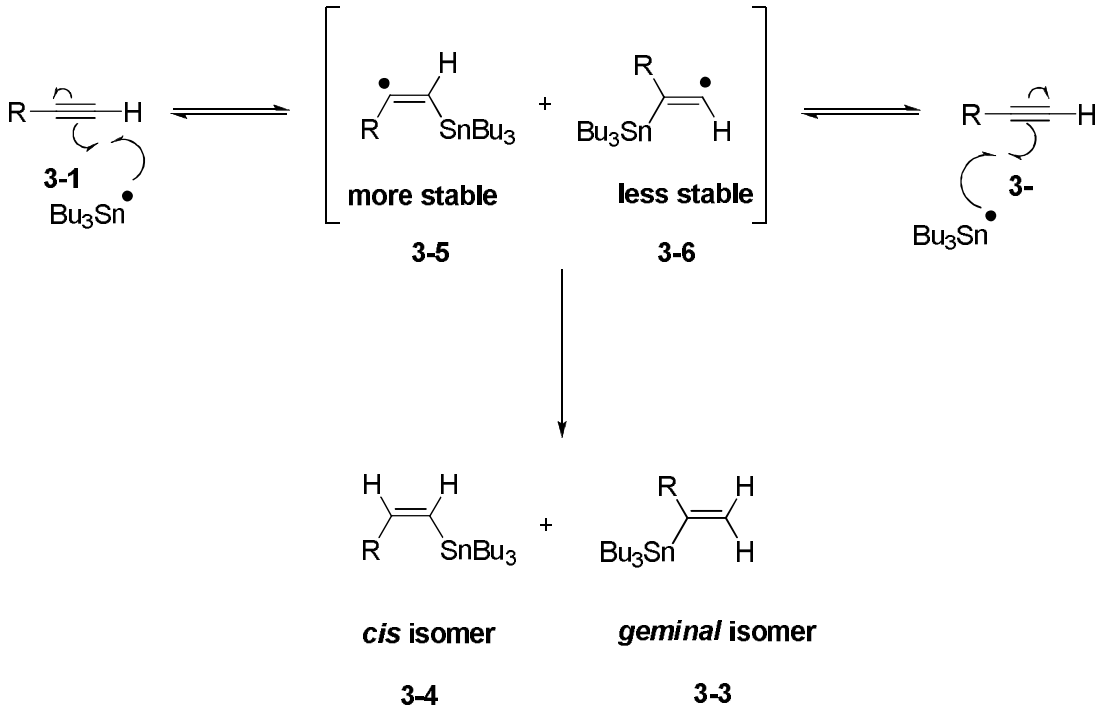
Figure 3.1 Three possible isomers produced by hydrostannation of a terminal alkyne

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

3.1.2 Synthesis of E-vinylstannanes under free-radical hydrostannation

Free-radical hydrostannation typically produces a mixture of stereo- and regioisomers.[2] The outcome is usually controlled by the stability of the intermediate radical that gives

rise to the corresponding vinylstannanes. These reactions require a catalytic amount of a radical initiator such as 2,2'-azobisisobutyronitrile (AIBN) (Scheme 3.2).

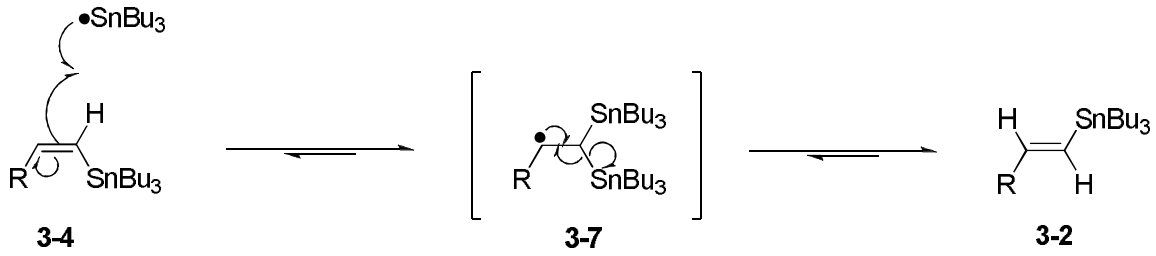


Scheme 3.2

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

To obtain *trans*-vinylstannane **3-2**, longer reaction times with excess Bu_3SnH are required.[4] It has been shown that the Bu_3Sn radical catalyzes the rearrangement of the

cis-vinylstannane to the corresponding *trans*-vinylstannane (Scheme 3.3).[5] This is believed to proceed by the addition of the Bu_3Sn radical to the double bond to form intermediate **3-7**.

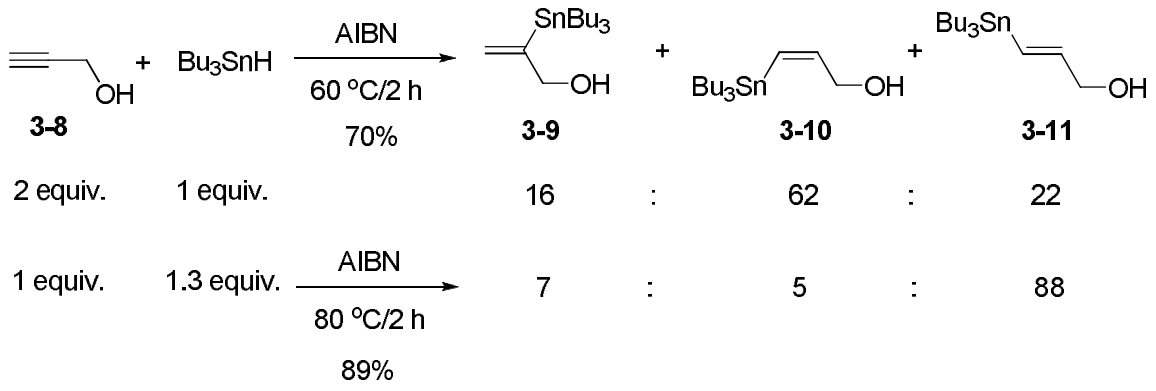


3-4 **3-7** **3-2**

Scheme 3.3

Elimination of Bu_3Sn radical, from intermediate **3-7**, leads to *trans*-vinylstannane **3-2**. Compound **3-2** is the thermodynamic vinylstannane. Regio-, chemo- and stereoselectivity of radical reactions can be predicted by radical-stabilizing effects,[6] steric effects,[2,7] and polar effects.[8]

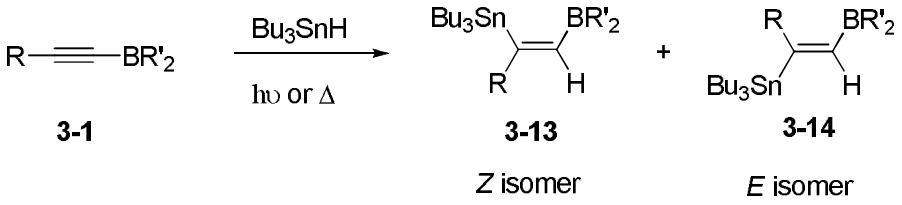
Jung and Light demonstrated the importance of the number of equivalents used of Bu_3SnH with respect to the alkyne and its effect on the regio- and stereoselectivity (Scheme 3.4).[9]



Scheme 3.4

Use of excess alkyne with respect to Bu_3SnH resulted in *cis*-vinylstannane **3-10** being the major isomer.[9] On the other hand, when a slight excess of Bu_3SnH was used *trans*-vinylstannane **3-11** was the major isomer. In both trials, *geminal*-vinylstannane **3-9** was a minor component.[9]

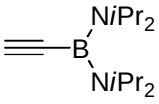
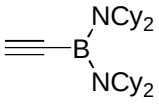
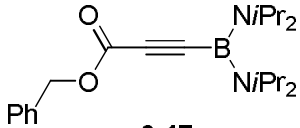
Free-radical hydrostannation of alkynylboranes has been reported by Lhermitte and Carboni (Scheme 3.5).[10]



Scheme 3.5

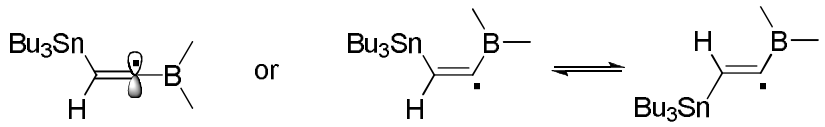
According to the report, boryl substituents have a decisive role in the course of these reactions. Only attack at the *β*-position, with respect to the boron, was observed (Table 3.1).[10]

Table 3.1 Free-radical hydrostannation of alkynylboranes.[10]

entry	alkyne	method[a]	(*Z*)	(*E*)	yield (%)
1	 **3-15**	A	<2	>98	95
2		B	95	5	95
3	 **3-16**	A	7	93	95
4		B	>98	<2	90
5	 **3-17**	B	>98	<2	80

[a] A – Toluene, 90 °C, AIBN. B – Toluene, 0 °C, hυ

Additions are highly stereoselective with the less stable *Z*-isomers being produced in highly pure forms at low temperature. The exclusive formation of *Z*-isomers probably resulted from the steric hindrance of Bu_3Sn that prevents the *syn* addition of the hydrogen on the π-radical **3-18** and on the σ-radical and **3-20** (Scheme 3.6) .[11]



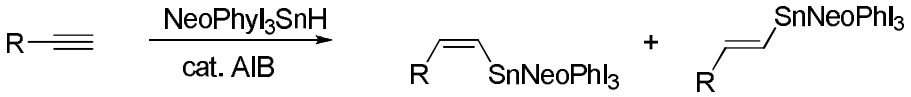
3-18 **3-19** **3-20**

Scheme 3.6

Higher temperatures promoted isomerisation of *Z*-isomers to the more stable *E*-isomers.[10]

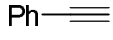
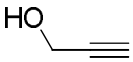
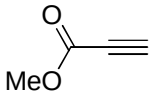
Dodero *et al.* have explored the use of a bulky organic tin hydride, trineophyltin hydride, and its effect on stereochemistry of free-radical hydrostannations (Table 3.2).[12]

Table 3.2 Trineophyltin hydride radical addition to terminal alkynes.[12]



3-1 **3-21** **3-22**

NeoPhyl = $PhMe_2CCH_2$

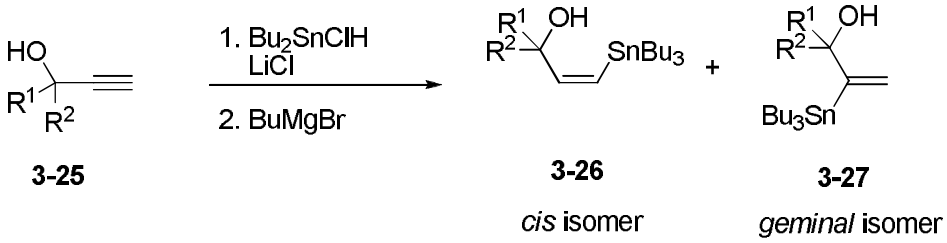
entry	alkyne	method[a]	*cis*	*trans*	yield (%)
1	 **3-23**	A, B or C	0	100	99-100
2	 **3-8**	A, B or C	100	0	49-69
3	 **3-24**	A	34	66	87[b]
4		B	91	9	65[b]
5		C	0	100	100

[a] The reaction was carried out under a nitrogen atmosphere; ratio hydride/alkyne = 1:1. Method A – AIBN 0.01 equiv., 90 °C, neat. Method B – AIBN 0.01 equiv., 90 °C, toluene. Method C – UV radiation, toluene.
[b] Isolated yield of both isomers combined.

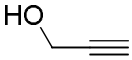
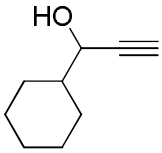
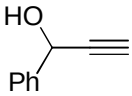
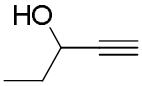
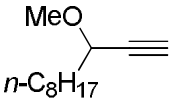
High regioselectivity was observed as only *β*-addition products (*cis* and *trans*) were obtained (Table 3.2).[12] Depending on the alkynyl substrate and the method used, stereoselectivity can be influenced greatly.[12]

A highly-selective free-radical hydrostannation that provides *cis*-vinylstannanes from propargyl alcohols has been reported.[13] A wide variety of propargyl alcohols and ethers have been screened, thus illustrating the generality of this method (Table 3.3).[13]

Table 3.3 Free-radical hydrostannation of propargyl alcohols.[13]

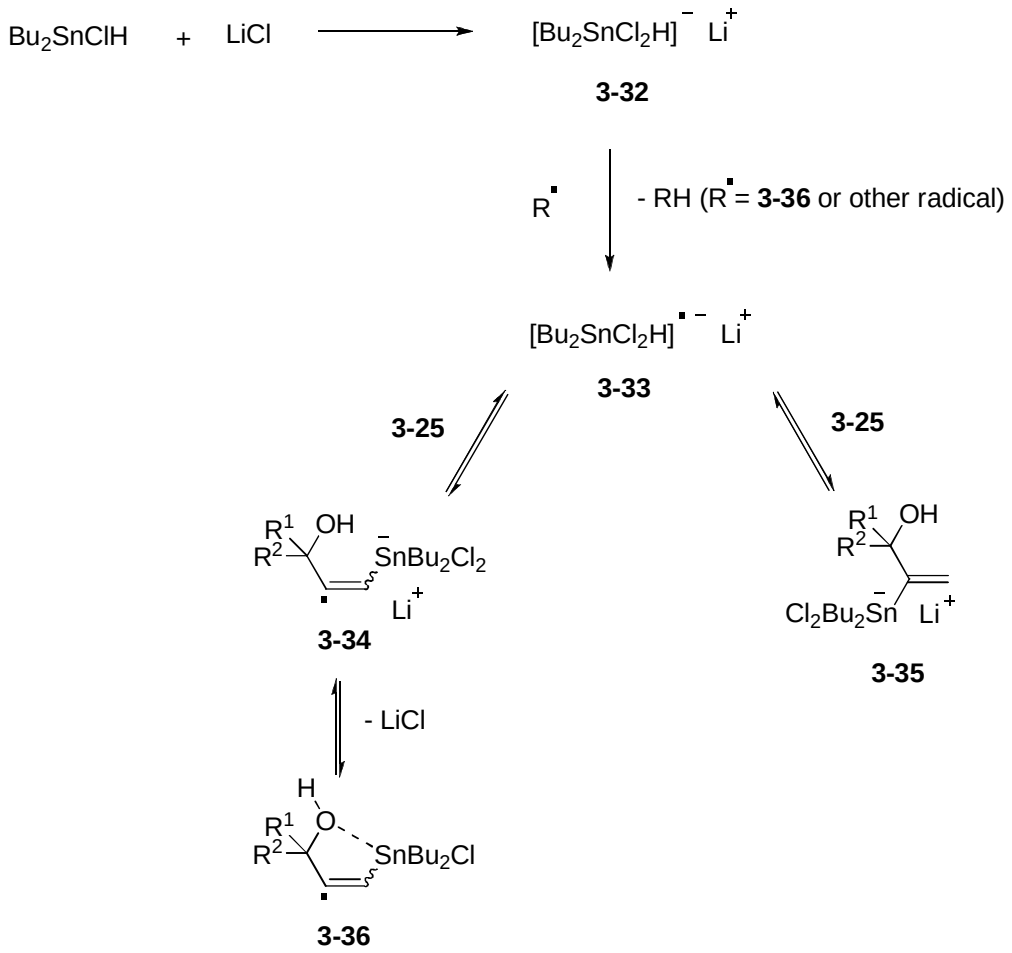


3-25 **3-26** *cis* isomer **3-27** *geminal* isomer

entry	alkyne	*cis*	*geminal*	yield (%)
1	 **3-8**	>99	<1	91
2	 **3-28**	>99	<1	98
3	 **3-29**	>99	<1	79
4	 **3-30**	>99	<1	89
5	 **3-31**	100	0	90

Terminal alkynes bearing a hydroxyl group at a more remote position were used also for the present hydrostannation, but low to moderate *trans* stereoselectivity was observed and lower reactivity to Bu_2SnClH.[13]

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

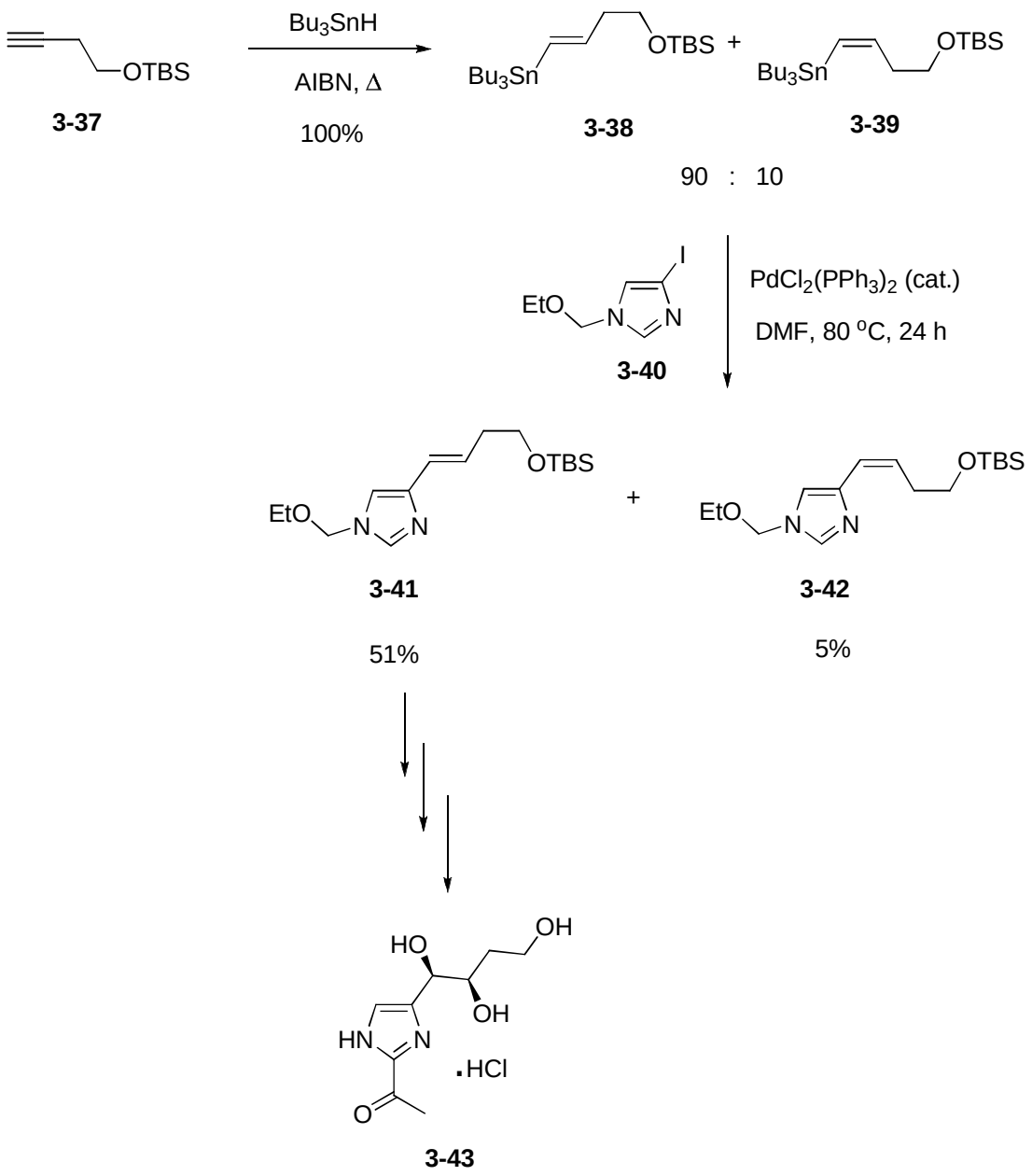


Scheme 3.7

Kinetic and thermodynamic reasons favour the formation of intermediate **3-34** over **3-35**; thus, providing high regioselectivities.[13]

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

Cliff and Pyne used free-radical hydrostannation toward the total synthesis of 2-acetyl-4(5)-(1,2,4-trihydroxybutyl)imidazole (THI) **3-43** (Scheme 3.8).[14]

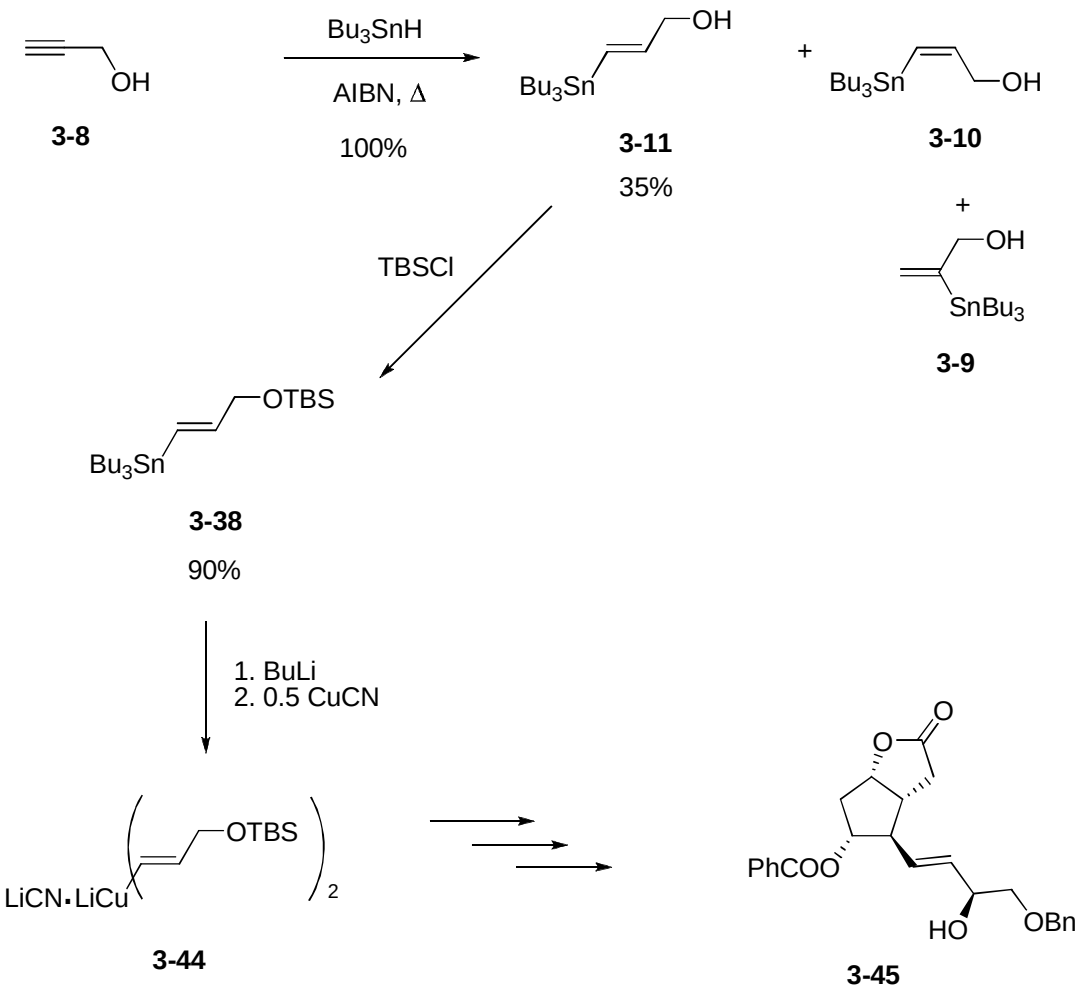


Scheme 3.8

Free-radical hydrostannation afforded *trans*- and *cis*-vinylstannanes in a 9:1 ratio. The stannanes were not isolated but taken directly to the next reaction, the Stille coupling. Separation occurred after the Stille coupling, as traces of *cis*-coupling product was

observed due to its slower coupling rate, relative to the *trans* substrate.[14] THI **3-43** has been found to depress blood lymphocyte counts in both mice and rats.[16]

Bansal *et al.* utilized free-radical hydrostannation to provide *trans*-vinylstannane **3-38**. Reactive cuprate **3-44** was obtained from *trans*-vinylstannane **3-38** (Scheme 3.9).[15] Free-radical hydrostannation of propargyl alcohol **3-8** afforded *trans*-vinylstannane **3-11** in 35% isolated yield. Vinylstannane **3-11** was treated with TBSCl to give ether **3-38**, which was then converted to highly reactive copper intermediate **3-44** *via* transmetallation with BuLi and CuCN (Scheme 3.9).

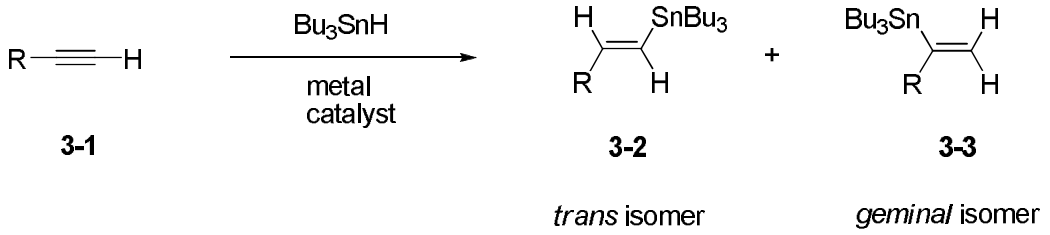


Scheme 3.9

Total synthesis of prostaglandin analogue **3-45** was achieved *via* coupling of cuprate **3-44** and an alkyl iodide.[15]

3.1.3 Metal-catalyzed hydrostannation

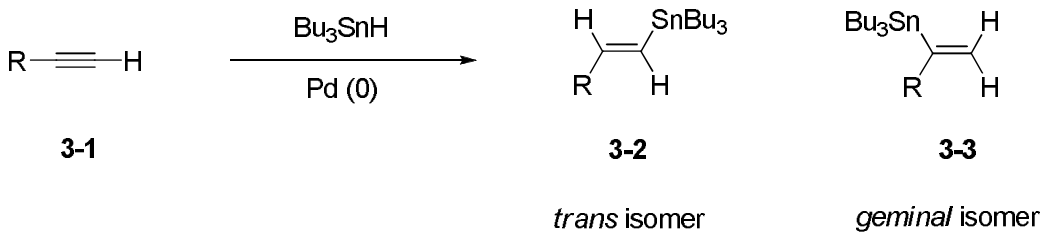
Metal-catalyzed hydrostannation usually provides two possible isomers. The reaction proceeds with *syn* addition across an alkyne, which produces *trans* and *geminal* vinylstannanes **3-2** and **3-3** (Scheme 3.10).

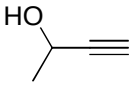
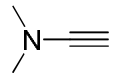
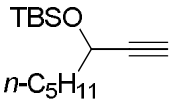
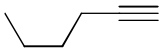
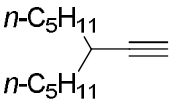


Scheme 3.10

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

Table 3.4 Palladium-catalyzed hydrostannation.[17]

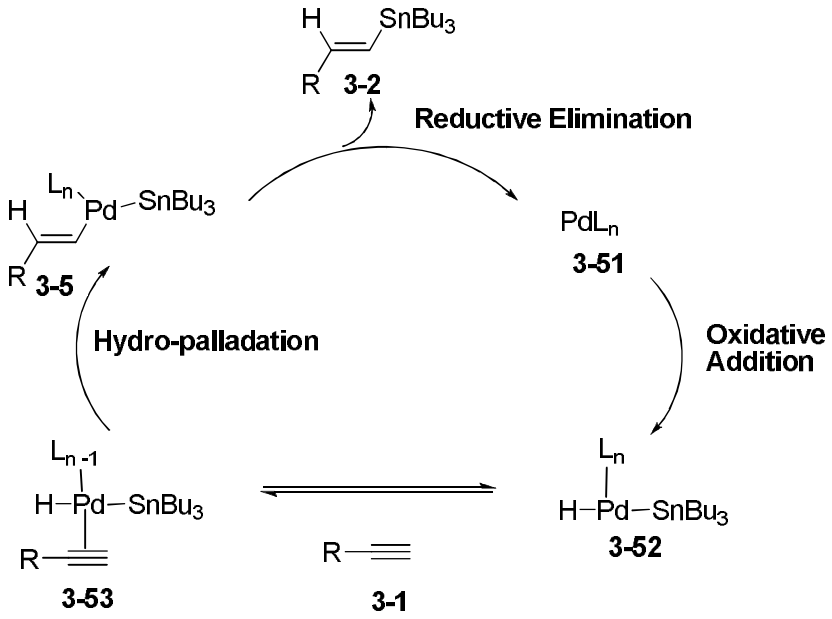


entry	alkyne	*trans*	*geminal*	yield (%)
1	 **3-46**	67	33	60
2	 **3-47**	68	32	60[a]
3	 **3-48**	72	28	94[a]
4	 **3-49**	65	35	98[a]
5	 **3-50**	100	0	90

[a] Isolated as a mixture of isomers.

As illustrated in Table 3.4, *trans*-vinylstannane is the major isomer when palladium is utilized as the catalyst.

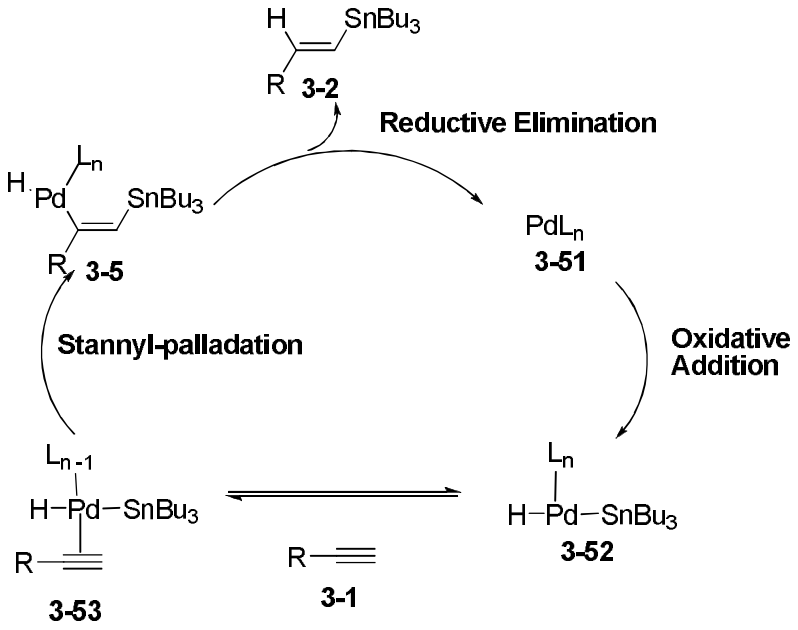
Palladium-catalyzed hydrostannation is not very well understood, and the reaction mechanism is still debated,[18] and there are two principal proposed pathways (Scheme 3.11 & 3.12). The first route involves hydro-palladation during the catalytic cycle. Initially, palladium (0) oxidatively inserts into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



Scheme 3.11

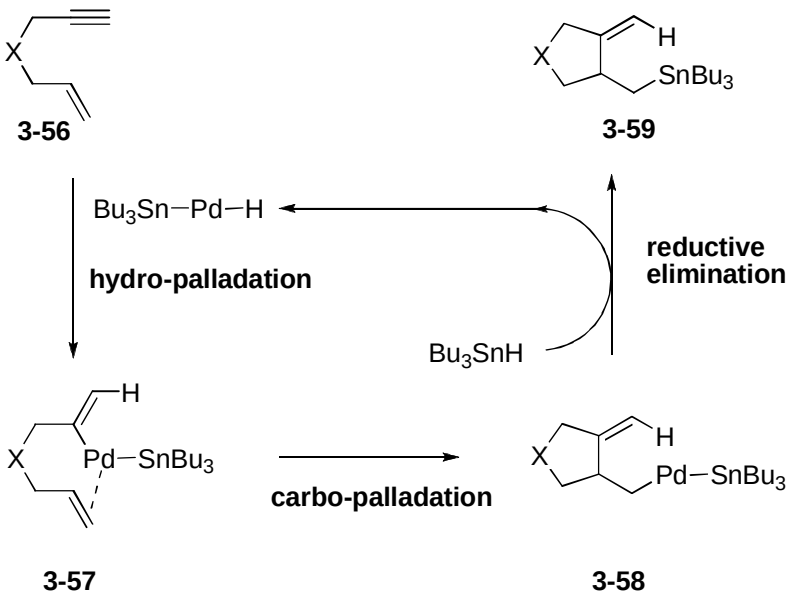
Reductive elimination of palladium from intermediate **3-54** affords vinylstannane **3-2**.

The second possible catalytic cycle involves stannyl-palladation. Similar to the hydro-palladation route, complex **3-53** is formed. This complex then undergoes a stannyl-palladation to afford intermediate **3-55**. Palladium reductively eliminates from intermediate **3-55** to provide the same vinylstannane (**3-2**) obtained through the hydro-palladation pathway (Scheme 3.12).



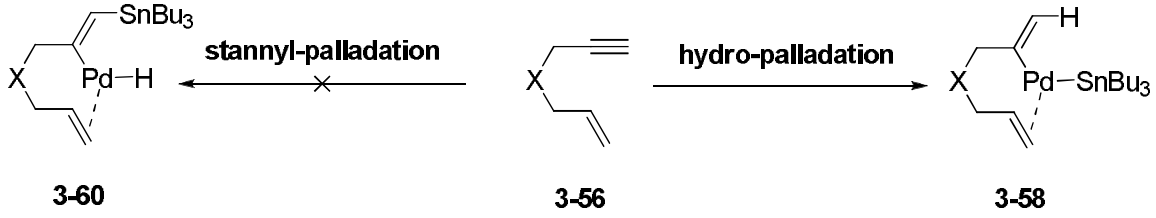
Scheme 3.12

One example of the hydro-palladation pathway was reported by Lautens *et al.* who developed a procedure for the preparation of methylenecyclopentanes **3-59**, *via* hydrostannylation cyclization (Scheme 3.13).[19] The reaction proceeded by hydro-palladation of the triple bond of enyne **3-56** to produce intermediate **3-57**. Following the initial hydro-palladation step, intermediate **3-57** undergoes a carbo-palladation to form cyclic intermediate **3-58**. This intermediate then reductively eliminates to afford compound **3-59** (Scheme 3.13).[19]



Scheme 3.13

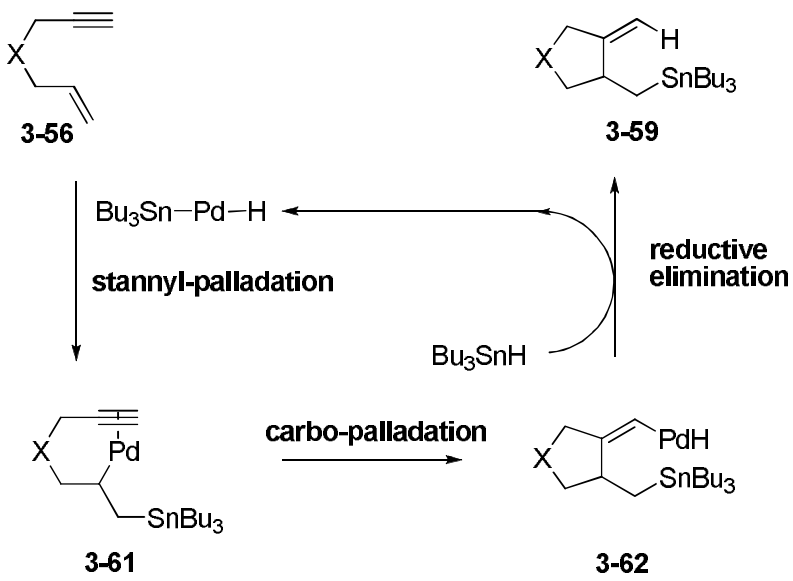
One can assume there are two competing pathways, as shown in the following scheme. Hydro-palladation leads to complex **3-58**, while stannyl-palladation leads to vinylstannane complex **3-60** (Scheme 3.14).



Scheme 3.14

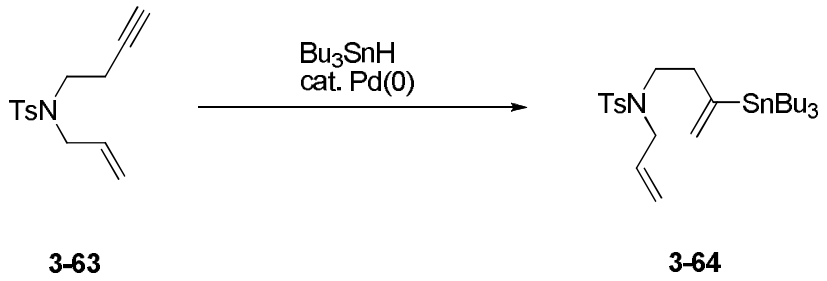
The product that was formed at the end of this reaction was the product derived from intermediate **3-58**.

One can also argue that initial stannyl-palladation of the double bond followed by cyclization can lead to the same final product **3-59** (Scheme 3.15).



Scheme 3.15

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



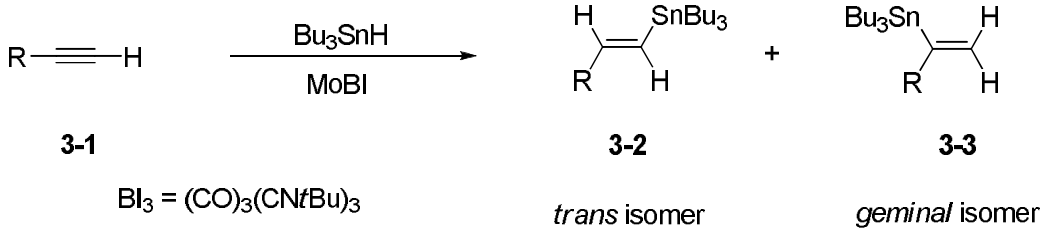
3-63 **3-64**

Scheme 3.16

Side product **3-64** provides an insight into this particular reaction and evidence for the hydro-palladation pathway.

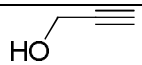
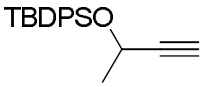
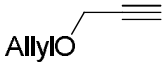
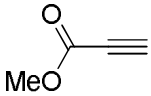
Another metal that is widely applied for metal-catalyzed hydrostannations is molybdenum. Molybdenum is utilized as a catalyst if the *geminal*-vinylstannane is the desired isomer (Table 3.5).[20]

Table 3.5 Molybdenum-catalyzed hydrostannation ($MoBI_3$).[20]



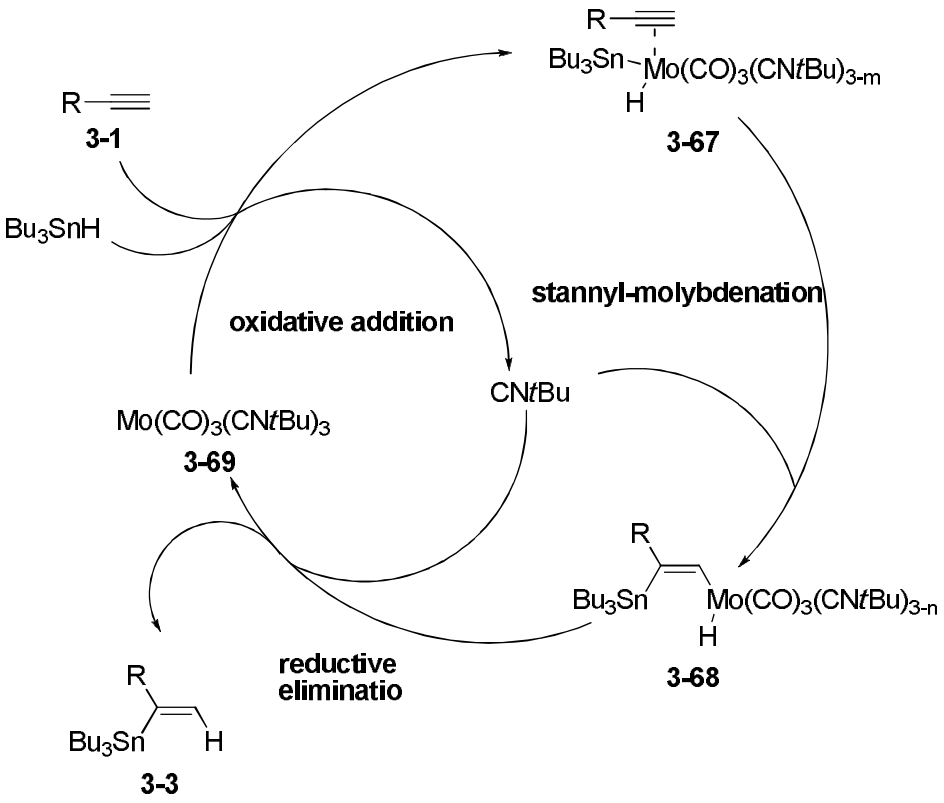
3-1 **3-2** **3-3**

$BI_3 = (CO)_3(CNtBu)_3$ *trans* isomer *geminal* isomer

entry	alkyne	*trans*	*geminal*	yield (%)[a]
1	 **3-8**	11	89	94
2	 **3-65**	10	90	88
3	 **3-66**	5	95	43
4	 **3-24**	8	92	98

[a] Isolated total yield of both regioisomers.

As shown in Table 3.5, the geminal isomer is the major regioisomer formed. Bulky $MoBI_3$ catalyst favours the selectivity toward *geminal* isomers.[20] The proposed mechanism for this reaction proceeds initially by the dissociation of several isocyanide ligands, opening coordination sites for oxidative addition (Scheme 3.17).[20]

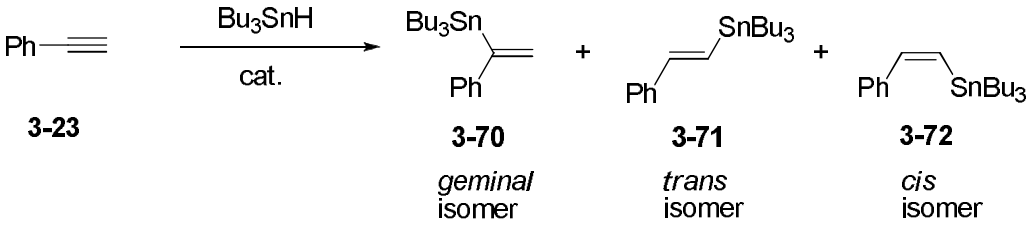


Scheme 3.17

Molybdenum oxidatively inserts into the tin hydride bond and coordinates with the alkyne. Stannyl-molybdenation of alkyne **3-1** affords intermediate **3-68**. The regioselectivity involved in forming intermediate **3-68** was determined by steric factors. The more sterically demanding molybdenum fragment was added to the less hindered side of the alkyne. Reductive elimination of molybdenum from **3-68** afforded vinylstannane **3-3**.[20]

Other metals such as rhodium, nickel, cobalt, zirconium, platinum and ruthenium have been applied as well (Table 3.6).[1]

Table 3.6 Metal-catalyzed hydrostannation of phenylacetylene.[1]

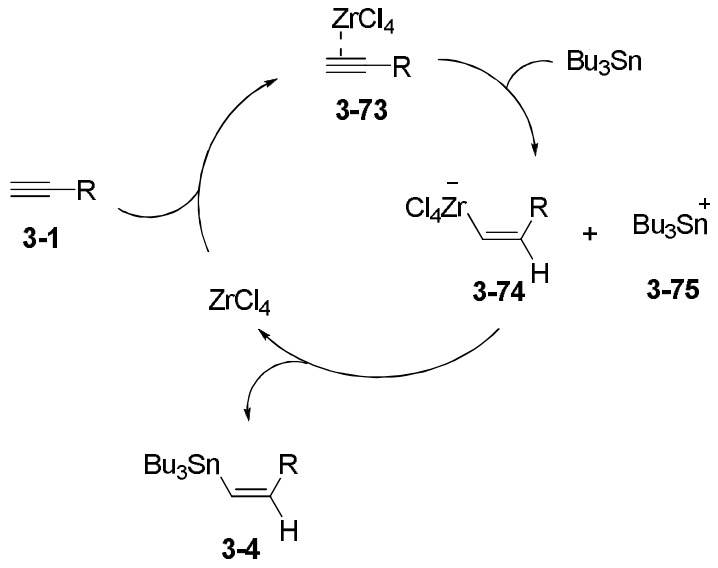


3-23 **3-70** *geminal* isomer **3-71** *trans* isomer **3-72** *cis* isomer

entry	catalyst	*geminal*	*trans*	*cis*	yield (%)[a]
1	$Rh(PPh_3)_3Cl$	88	12	0	86
2	$Ni(PPh_3)_2Cl_2$	45	50	5	80
3	$Pt(PPh_3)_2Cl_2$	34	52	14	73
4	$Co(PPh_3)_2Cl_2$	43	48	9	40
5	$Ru(PPh_3)_2Cl_2$	11	42	47	78
6	$ZrCl_4$	0	5	95	73

[a] Isolated total yield of all isomers.

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



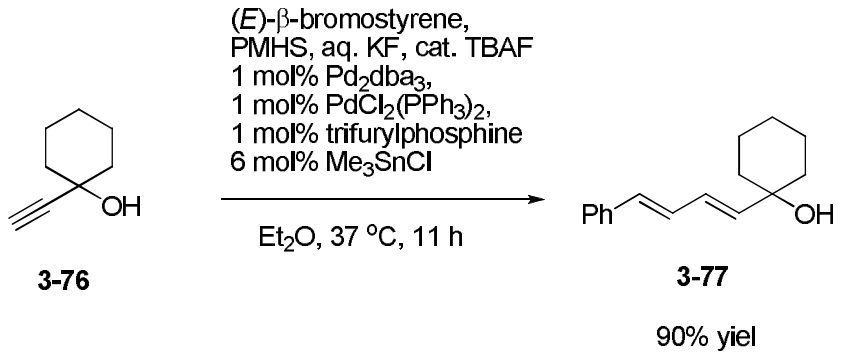
Scheme 3.18

It is assumed for this mechanism that $ZrCl_4$ coordinates to the triple bond to produce complex **3-73**.[22] Bu_3SnH would provide a hydride that would attack an electron deficient triple bond from the opposite side to $ZrCl_4$ to produce stereoselectively pentacoordinate zirconium species **3-74**.[22] Zirconium intermediate **3-74** would capture Bu_3Sn cation **3-75** with retention of geometry to give *cis*-vinylstannane and $ZrCl_4$.[22]

There are many tin hydride reagents that have been applied to metal-catalyzed hydrostannations.[1] Me_3SnH has been used but its volatility and toxicity make it unfriendly for use. Ph_3SnH has also been used but the vinylstannyl product is not very useful, since phenyl groups are transferable. By far, Bu_3SnH is the most commonly used reagent for any hydrostannation due to its ease of use and preparation and its reactivity.[1] In terms of selectivity, none of the reagents have any advantages.

Stoichiometry of the tin hydride reagent and metal catalyst in metal-catalyzed hydrostannation does not have an effect on the selectivity but rather on the conversion of the reaction. In general, catalytic loading of catalysts between 0.5-10 mol % and tin hydride loading of 110-150 mol % are applied. Slight excess of tin hydride is needed to reduce the catalyst into the "active" form, and to counteract the reductive coupling of tin hydride that produces hydrogen and distannane.[1]

Recently, Gallagher and Maleczka Jr. demonstrated the ability to regenerate Me_3SnH *in situ* from Me_3SnCl with poly(methylhydrosiloxane) (PMHS) for a one-pot hydrostannation/Stille coupling sequence of terminal alkynes (Scheme 3.19).[23]

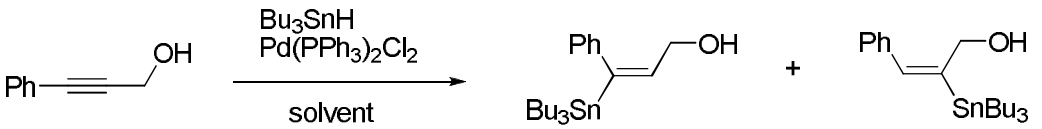


Scheme 3.19

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

The effect of solvent on the selectivity in metal-catalyzed hydrostannation of disubstituted alkynes was explored by Liron *et al.*(Table 3.7).[24]

Table 3.7 Examining the effect of solvent on the regioselectivity of palladium-catalyzed hydrostannation.[24]



3-78 **3-79** **3-80**

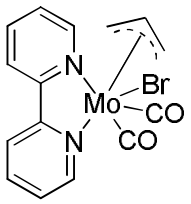
entry	solvent	**3-79**[b]	**3-80**[b]	conversion[a]
1	CH_2Cl_2	33	67	40
2	toluene	45	55	100
3	cyclohexane	52	48	67
4	Et_2O	65	35	100
5	THF	80	20	100
6	TMU	77	23	61
7	AcOEt	67	33	100

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

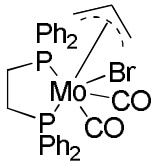
A modest change in regioselectivity was observed upon increasing the solvent polarity.

There are contradicting reports regarding the substituent ligands on the metal, with various steric bulk, and their effect on regioselectivity.[17,20]

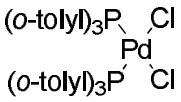
In 1990, Zhang *et al.* stated "*attempts to modify the regiochemistry by changing the catalyst and, in particular, the steric bulk of the ligands, met with no success.*"[17] The bulky complexes they screened are shown below (Figure 3.2).



3-81



3-82

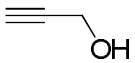
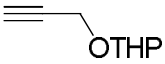


3-8

Figure 3.2 Bulky ligands used for metal-catalyzed hydrostannation

However, in 2000 a report by Kazmaier *et al.* suggests that steric bulk around the molybdenum catalyst improved the regioselectivity, unlike the results obtained by Zhang *et al*. (Table 3.8).[20]

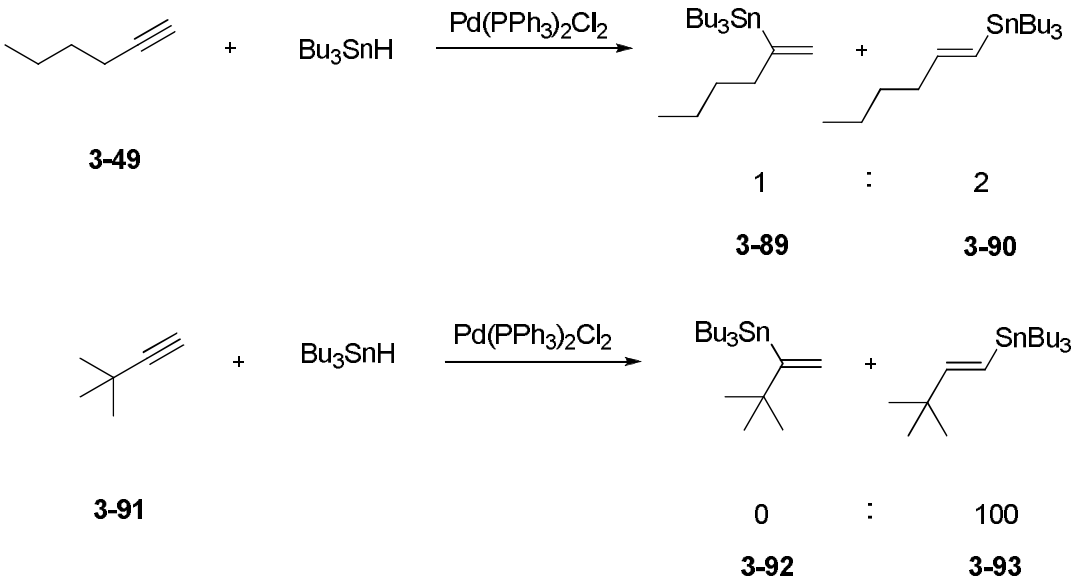
Table 3.8 Bulky ligands and their effect on regioselectivity of molybdenum-catalyzed hydrostannation.[17,20]

entry	alkyne	catalyst	*trans*	*geminal*
1[a]	 **3-8**	$(CH_3CN)_2Mo(CO)_2(\pi\text{-Allyl})Br$ **3-85**	33	67
2[b]		$(t\text{BuNC})_3Mo(CO)_3$ **3-86**	11	89
3[a]	 **3-84**	$(CH_3CN)_2Mo(CO)_2(\pi\text{-Allyl})Br$ **3-87**	36	64
4[b]		$(t\text{BuNC})_3Mo(CO)_3$ **3-88**	5	95

[a] Results from Zhang *et al.*
[b] Results from Kazmaier *et al.*

Kazmaier *et al.* indicated that the steric bulk around the molybdenum catalyst could be contributing to the selectivities observed.[20]

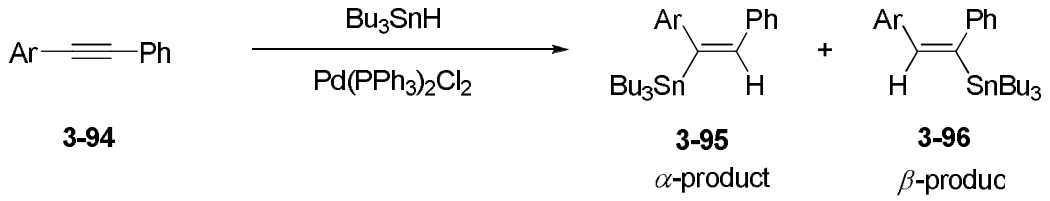
According to literature reports, the nature of the substrate has the most profound effect on the regioselectivity.[1,17,18]

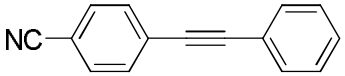
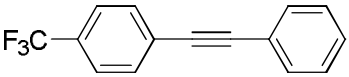
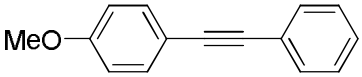


Scheme 3.20

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

Table 3.9 Palladium-catalyzed hydrostannation of monosubstituted tolanes.[25]

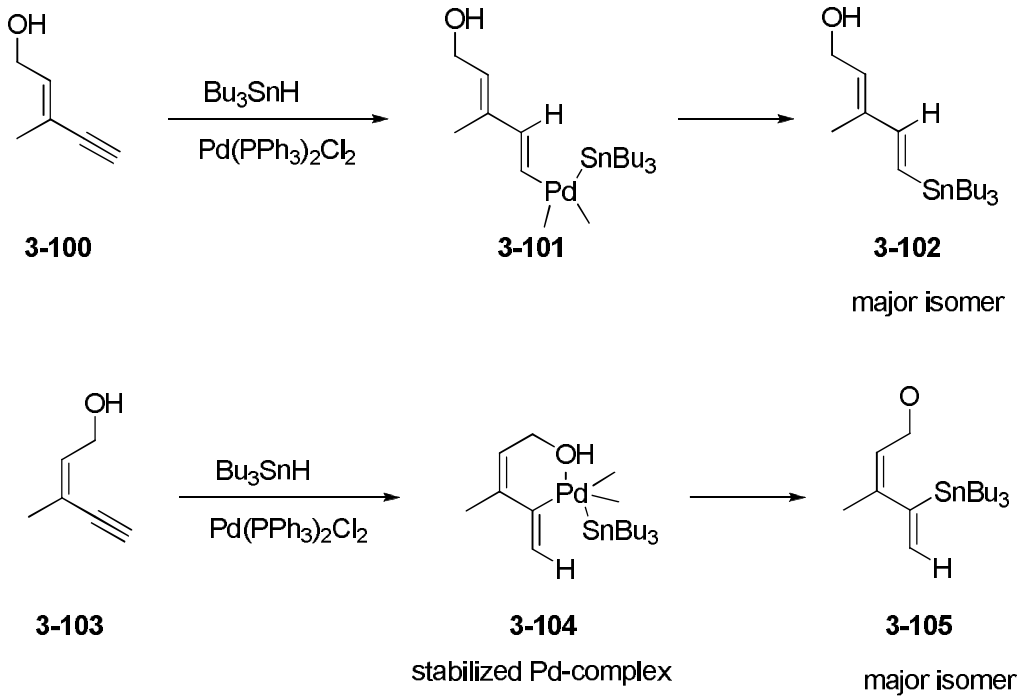


entry	alkyne	α-product[a]	β-product[a]
1	 **3-97**	84	16
2	 **3-98**	78	22
3	 **3-99**	39	61

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures.

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

Heteroatom-metal chelation has also been shown to direct the regiochemistry of palladium-catalyzed hydrostannation reactions (Scheme 3.21).[26,27]

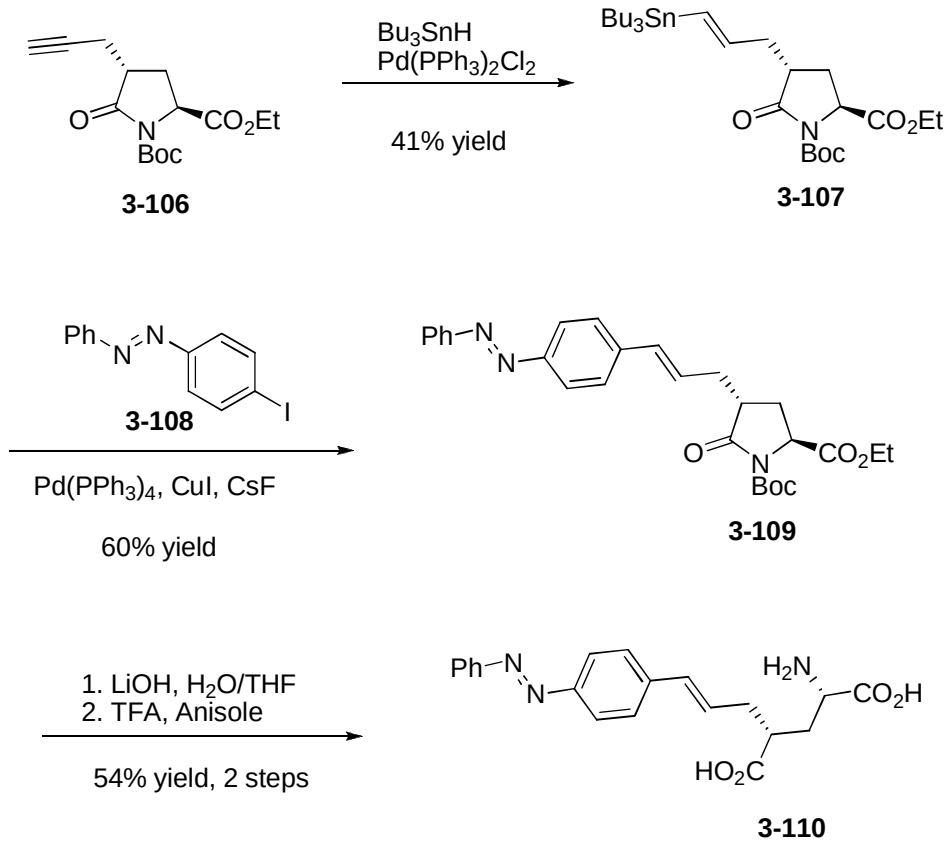


Scheme 3.21

Hydrostannation of *E*-isomer **3-100** gave *trans*-vinylstannane **3-102** as the major product while *Z*-isomer gave *geminal*-vinylstannane **3-105** as the major product. Thus, the selectivity of the vinylstannyl isomer obtained depended on the location of the oxygen atom. Betzer *et al.* suggest a stabilizing complex (**3-104**) between palladium and oxygen atom to explain the regioselectivity observed in favour of the *geminal*-vinylstannane in the case of *Z*-isomer **3-103**.[27]

There are many examples of metal-catalyzed hydrostannation in total synthesis of natural product.[28,29] A few representative cases are highlighted below.

Applications of metal-catalyzed hydrostannations in total synthesis include the preparation of a photochromic agonist of ionotropic glutamate receptor **3-110** (Scheme 3.22).[28] Glutamate receptors have been applied to control the active concentration of neurotransmitters in a spatially and temporally precise manner, which has revolutionized the study of the central nervous system (CNS).[28]

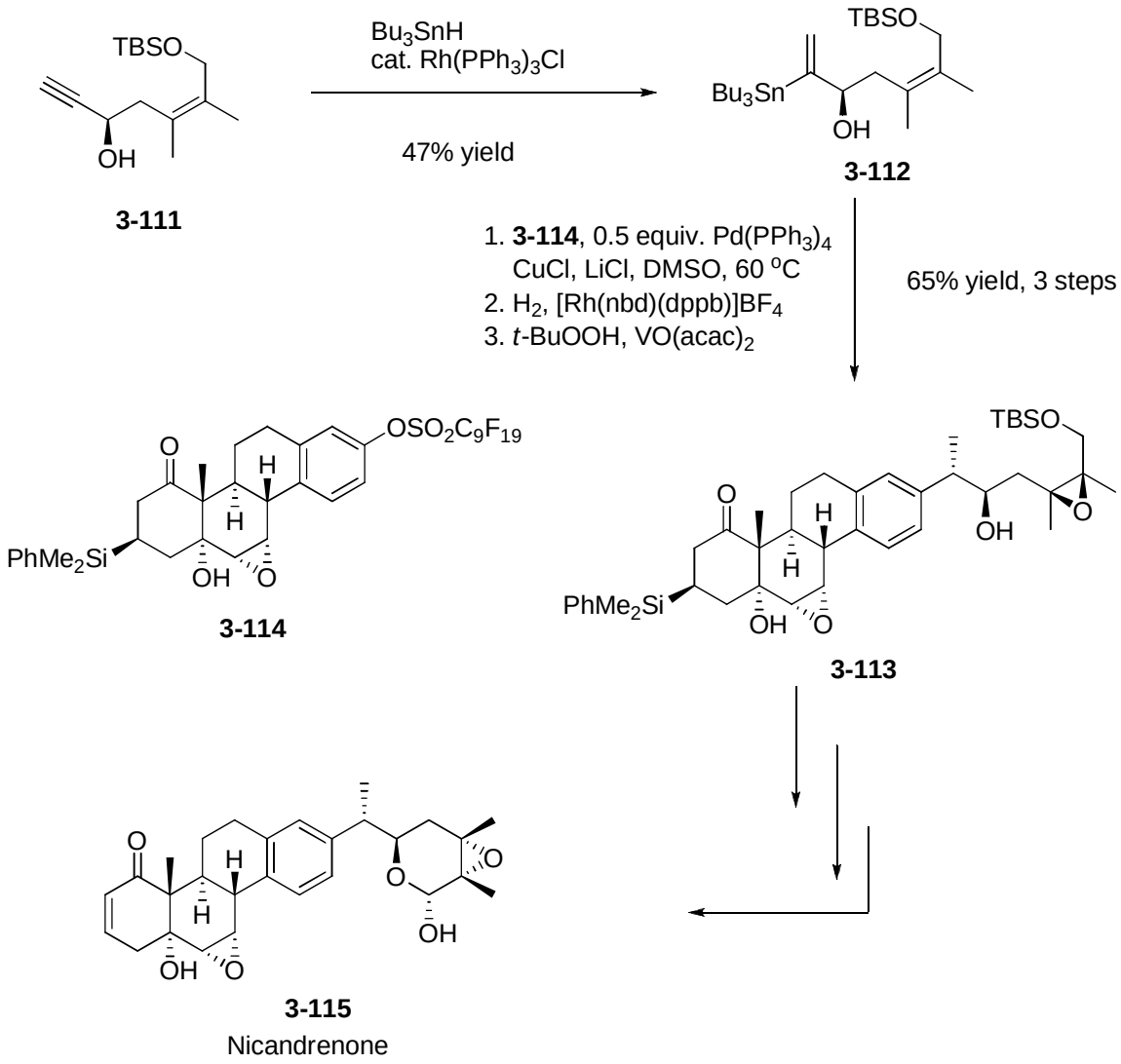


Scheme 3.22

The synthesis was made feasible by palladium-catalyzed hydrostannation of terminal alkyne **3-106** to provide vinylstannane **3-107**. Palladium-catalyzed Stille coupling of vinylstannane **3-107** with iodoazobenzene **3-108** afforded *N*-Boc protected azobenzene

pyroglutamate **3-109**, which upon hydrolysis of the amide and deprotection of the nitrogen afforded the target product **3-110**.[28]

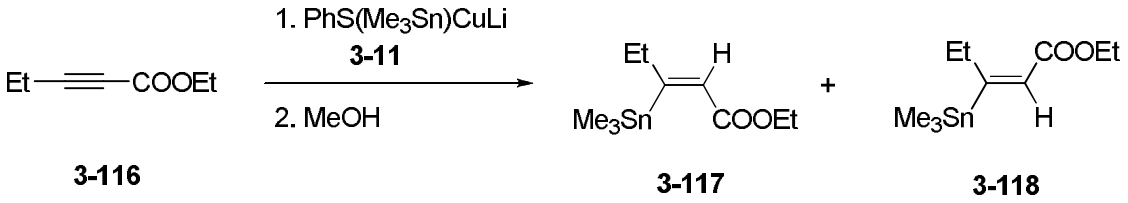
The nicandrenone (NIC) family are structurally complex, steroid-derived natural products,[29] whose biological activities include insect repellent and antifeedant properties.[29] Rhodium-catalyzed hydrostannation was utilized to synthesize vinylstannane **3-112** (Scheme 3.23),[29] that was required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


TBSO
OH
3-111
Bu3SnH
cat. Rh(PPh3)3Cl
47% yield
TBSO
Bu3Sn
OH
3-112
1. 3-114, 0.5 equiv. Pd(PPh3)4
CuCl, LiCl, DMSO, 60 °C
2. H2, [Rh(nbd)(dppb)]BF4
3. t-BuOOH, VO(acac)2
65% yield, 3 steps
OSO2C9F19
O
H
H
PhMe2Si
OH
O
3-114
TBSO
O
H
H
OH
O
PhMe2Si
OH
O
3-113
O
H
H
O
O
OH
OH
O
3-115
Nicandrenone

Scheme 3.23

3.1.4 Stannylmetallation

Stannylcupration of alkynes to provide vinylstannanes is the most common method of the stannylmetallation methodologies.[27] Piers and Morton demonstrated how stannylcupration of α,β-unsaturated esters provides vinylstannanes in high selectivities and good yields (Scheme 3.24).[30]



3-116 **3-117** **3-118**

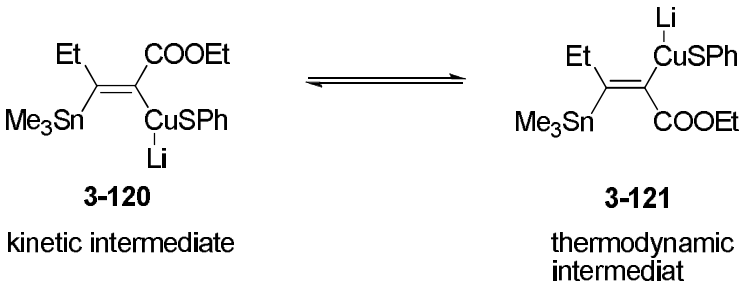
Scheme 3.24

Since addition of tin occurs only in the β position, stannylcupration of acetylene **3-116** followed by protonation affords two possible isomeric vinylstannanes (**3-117** and **3-118**, Scheme 3.24).[30] Depending on conditions, *trans* or *cis* isomers can be obtained in high selectivities and good yields (Table 3.10).

Table 3.10 Stannylcupration of α,β-unsaturated ester **3-116** with cuprate **3-119**.[30]

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

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



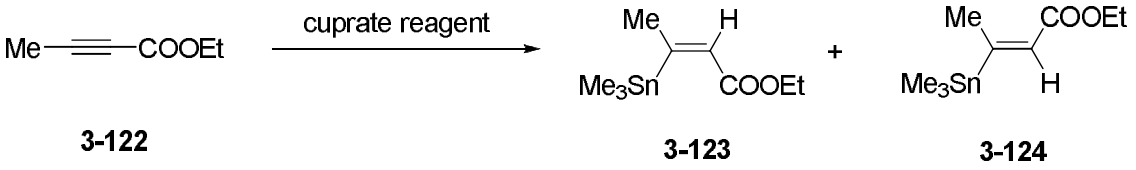
Scheme 3.25

At relatively higher temperatures (-78 °C), intermediate **3-120** could isomerize to intermediate **3-121**, but this process can be minimized if a proton source is present;

protonation of **3-120** is faster than isomerisation to **3-121**.[30] If the reaction temperature is allowed to rise to -48 °C in the absence of a proton source, equilibration takes place, with equilibrium largely favouring the thermodynamic intermediate **3-121**.[30]

Piers *et al.* illustrated the effect of the stannylcuprate reagent on stereoselectivity (Table 3.11).[31]

Table 3.11 Stannylcupration with various cuprate reagents and their effect on stereoselectivity.[31]



3-122 **3-123** **3-124**

entry	cuprate reagent[a]	**3-123**	**3-124**	yield (%)
1	$PhS(Me_3Sn)CuLi$ **3-125**	98	2	85
2	$[Me_3SnCu{\equiv}C\text{-}C(Me_2)OMe]Li$ **3-126**	1	99	82
3	$Me_3SnCu \cdot LiBr \cdot Me_2S$ **3-127**	1	99	68

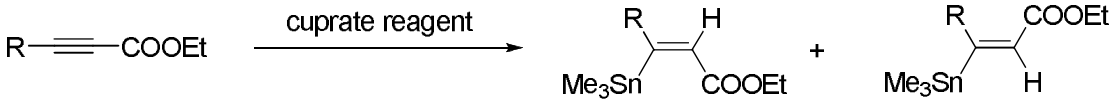
[a] 1.3 equiv. reagent, -48 °C, 4 h.

α,β-Unsaturated ester **3-122** was subject to different stannylcuprate reagents under the same condition. Under thermodynamic conditions, reagent **3-125** was consistent with previous results and provided the thermodynamic vinylstannane **3-123**.[3,30] Under the

same conditions, reagents **3-126** and **3-127** provided the opposite stereoisomer in high selectivities, thus illustrating the effect a reagent can have on stereoselectivity.

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

Table 3.12 Stannylcupration of different *α,β*-unsaturated esters and their effect on stereoselectivity.[31]



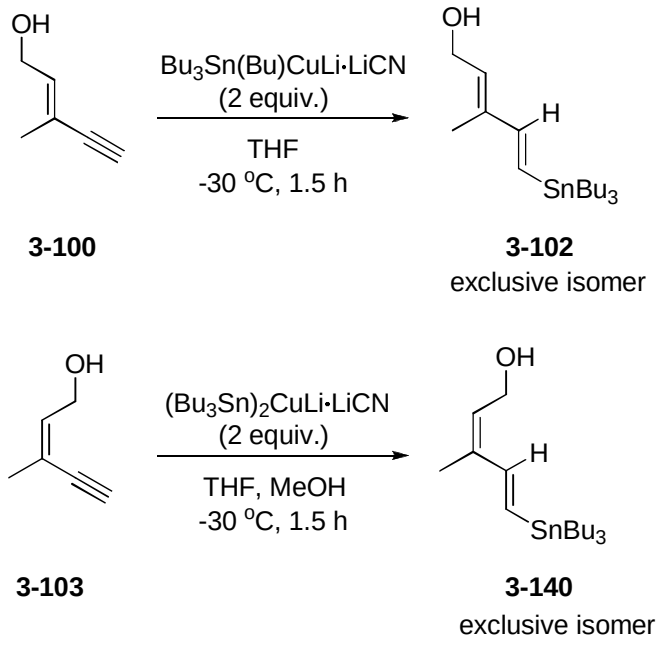
3-128 **3-129** **3-130**

entry (alkyne)	cuprate reagent	R	*cis* (stannane)	*trans* (stannane)	yield (%)
1[a](**3-122**)	$[Me_3SnCuC{\equiv}C\text{-}C(Me_2)OMe]Li$ **3-126**	Me	1(**3-131**)	99 (**3-132**)	82
2[b,d] (**3-133**)		*t*-Bu	62(**3-134**)	8(**3-135**)	76
3[a](**3-122**)	$Me_3SnCu \cdot LiBr \cdot Me_2S$ **3-127**	Me	1(**3-131**)	99 (**3-132**)	68
4[c,d,e](**3-133**)		*t*-Bu	80(**3-134**)	12 (**3-135**)	79

[a] 1.3 equiv. cuprate reagent, -48 °C, 4 h.
[b] 3.0 equiv. cuprate reagent, 0 °C, 60 h.
[c] 3.0 equiv. cuprate reagent, -20 °C, 4 h.
[d] A third component, thought to be ethyl (*E*)-4,4-dimethyl-2-trimethylstannyl-2-pentenoate, was also present.
[e] HMPA (10% by volume) was added prior to addition of the acetylenic ester.

In contrast to the outcome of subjecting alkyne **3-133** to cuprate reagents **3-126** and **3-127**, *cis*-vinylstannane **3-134** emerged as the major product. According to Piers *et al.*, the sterically bulky *tert*-butyl group destabilized the kinetic intermediate sufficiently to allow isomerisation to become faster than protonation, even in the presence of a proton source.[31]

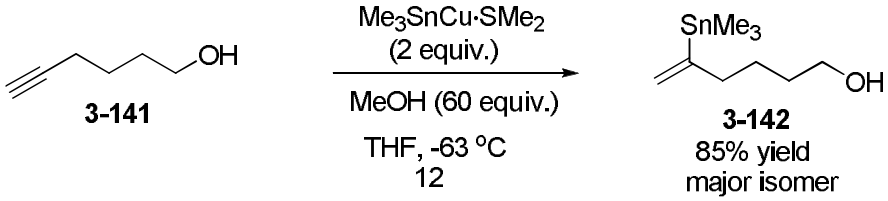
Unlike palladium-catalyzed hydrostannation,[26,27] the regioselectivity of stannylcupration of enynols provided the distal stannane as the exclusive isomer, regardless of the orientation of the alcohol relative to the triple bond (Scheme 3.26).[27]



Scheme 3.26

The regioselectivity of stannylcupration of enynols depended on the reaction temperature, addition of methanol to the cuprate solution, and the structure of the starting material.

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

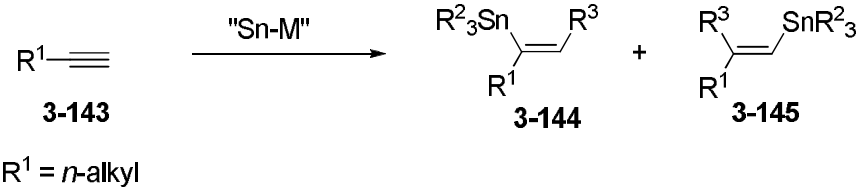


Scheme 3.27

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

Other stannylmetallation methodologies have been reported but have not been adopted widely(Table 3.13).[32-36]

Table 3.13 Stannylmetallation using different metals.



entry	R^2 , R^3	condition	ratio[a] 3-144 : 3-145		yield (%)
1[32]	Bu , H	Bu_3SnBEt_3Li (2 equiv.) $CoCl_2(PPh_3)_2$ (10 mol%)	0	100	78
2[33]	Bu , H	$Bu_3SnAlEt_2$ (3 equiv.) CuCN (16 mol%)	91	9	100
3[34]	Me , Me_3Sn	$(Me_3Sn)_2$ $Pd(PPh_3)_4$ (1 mol%)	-	-	23
4[35]	Me , Me_3Si	$Me_3SnSiMe_3$ $Pd(PPh_3)_4$	90	10	65
5[36]	Bu , H	$Bu_3SnMgMe$ (3 equiv.) CuCN (5 mol %)	30	70	70

6[36]	Bu , H	Bu_3Sn_2Zn (3 equiv.) $Pd(PPh_3)_4$ (5 mol %)	95	5	70

[a] Ratio was determined by ^1H NMR analysis

Stannylboration of terminal alkynes using $CoCl_2(PPh_3)_2$ (entry 1) afforded exclusively 1-stannyl-1-alkene isomer, as methanol was required for reaction completion.[32] Stannylalumination of terminal alkynes in THF provided 2-stannyl-1-alkene as the major isomer (entry 2). The regiochemistry of stannylalumination was greatly influenced by the choice of solvent.[33] Stannylstannation of terminal alkynes using palladium as a catalyst produces exclusively *Z* distannanes (entry 3).[34] Stannylsilation proceeded in a regio- and stereoselective fashion to produce 2-stannyl-1-alkene as the major isomer (entry 4).[35] Stannylmagnesation of terminal alkynes provided 1-stannyl-1-alkene as the major isomer (entry 5), while stannylzincation afforded 2-stannyl-alkene as the major isomer (entry 6).[36]

Applications of stannylmetallation in total synthesis are highlighted in Chapter 4.

3.2 Proposed Work

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

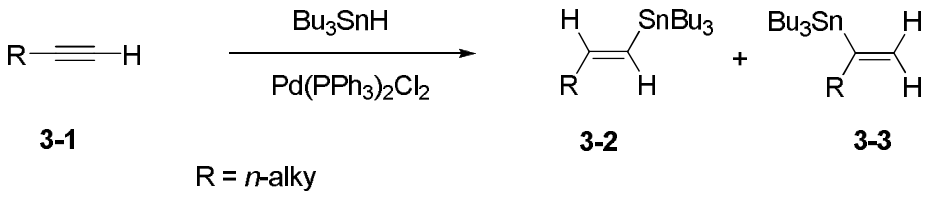
Eventually, one could apply the methodology developed toward total syntheses of natural products to illustrate the usefulness of this chemistry.

3.3 Results and Discussion

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

3.3.1 Steric effect of phosphine ligands

Zhang *et al.* have shown palladium-catalyzed hydrostannation of unhindered terminal alkynes, using PPh_3 as ligand around the palladium, provided *trans*-vinylstannanes as the major isomer in most cases in ~ 2:1 ratio with the *geminal* isomer (Scheme 3.28).[17]



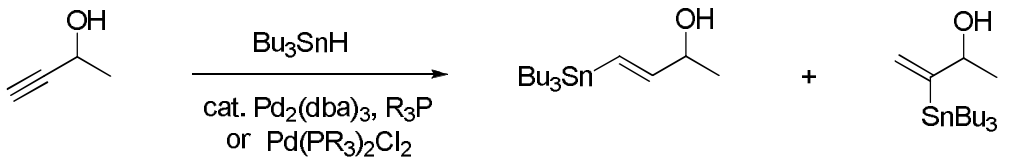
Scheme 3.28

Attempts to use bulkier phosphine ligands to improve the selectivity of *trans*-vinylstannanes met with no success.[17]

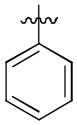
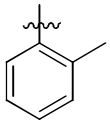
In contrast to this, a correlation has been found between phosphine ligands used on the palladium catalyst, and the regioselectivity observed from palladium-catalyzed hydrostannation of terminal alkynes.[37]

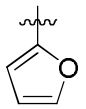
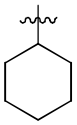
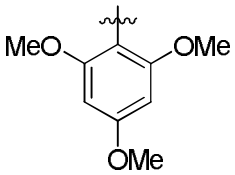
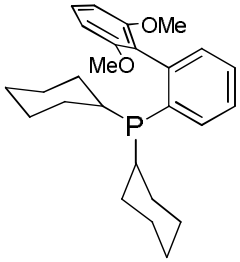
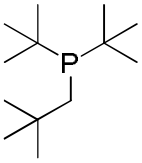
This effect was initially observed with but-3-yn-2-ol (**3-46**), a propargyl alcohol (Table 3.14). The use of this alkyne allowed for the separation of the regioisomeric products and nonpolar stannane side products by flash chromatography.

Table 3.14 Hydrostannation of **3-46** with various catalysts.[37]



3-46 **3-146** *trans* **3-147** *geminal*

entry (phosphine)	R	**3-146** : **3-147** ratio[d]		Isolated yield of *trans* isomer
1(**3-148**)		68	32	57%[b]
2(**3-83**)		80	20	60%[b]
3(**3-149**)		100	0	72%[a]

4(**3-150**)		40	60	22%[c]
5(**3-151**)		95	5	84%[b]
6(**3-152**)		47	53	45%[c]
7(**3-153**)		77	23	63%[c]
8(**3-154**)		96	4	70%[a]

[a] (1.2 eq. Bu_3SnH, 1 mol % Pd, 2 mol % phosphine, 2 mol % base, toluene)
[b] (1.2 eq. Bu_3SnH, 1 mol % Pd (pre-formed catalyst), toluene)
[c] (1.2 eq. Bu_3SnH, 1 mol % Pd, 2 mol % phosphine, toluene)
[d] Determined by ^1H NMR analysis of crude reaction mixtures.

Use of PPh_3 as the ligand (entry 1) provided the reported ratio of 2:1 as (*trans*:*geminal*). Ligands **3-150** and **3-152** (entries 4 and 6) reversed the selectivity in favour of the *geminal* isomer with ratios of 40:60 and 47:53 (*trans*:*geminal*), respectively. Relatively bulky phosphine ligands **3-83** and **3-153** provided selectivities of 80:20 and 77:23 (*trans*:*geminal*), respectively; these selectivities are slightly better than the traditional PPh_3 ligand.

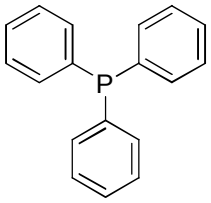
Bulky phosphine ligands **3-151** and **3-154** provided great selectivities of 95:5 and 96:4, respectively, but ligand **3-151** provided the highest isolated yield of *trans*-vinylstannane **3-146**.

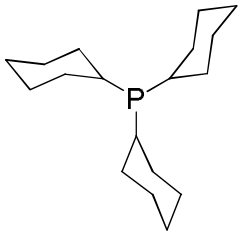
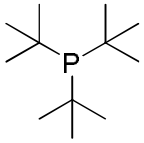
Perfect selectivity of 100:0 was observed when using the very bulky **3-149** as a ligand, but the isolated yield of *trans*-vinylstannane **3-146** was lower than when Cy_3P was used as ligand.

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

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

Table 3.15 Relating Tolman cone angle and selectivity[b]

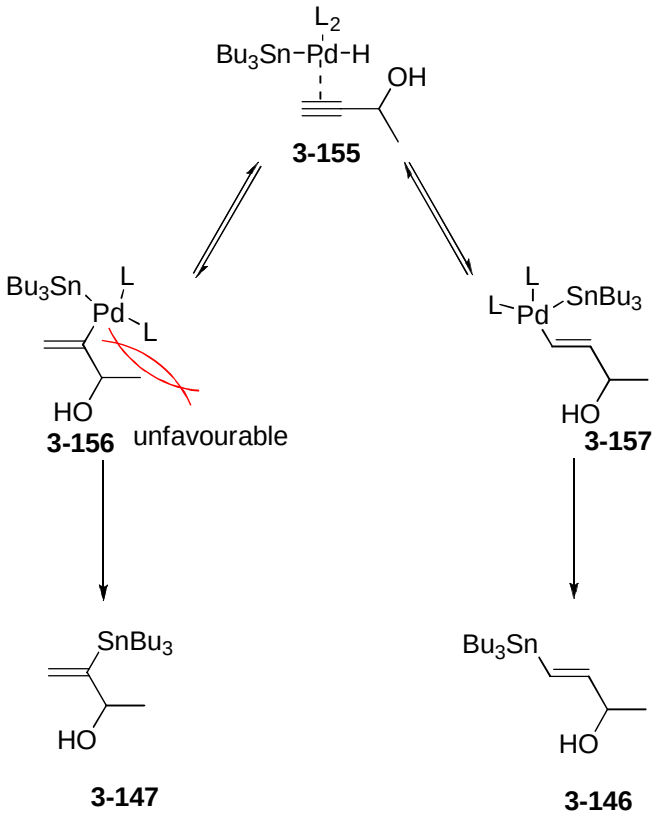
entry (phosphine)	phosphine ligand	Tolman cone angle	**3-146** : **3-147** Ratio[a]	
1(**3-148**)		145°	68	32

2(**3-151**)		170°	95	5
3(**3-149**)		182°	100	0

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures.
[b] Based on results from Table 3.14.

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

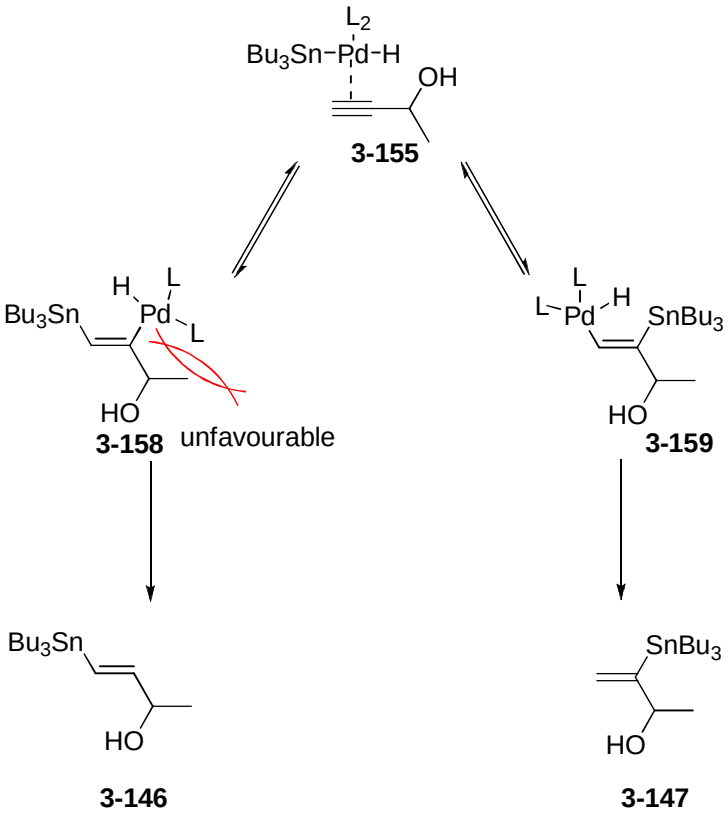
The selectivities observed may be rationalized by considering the steric interactions between the phosphine ligand and the substituent on the alkyne (Scheme 3.29).



Scheme 3.29

After the Bu_3SnPdH complex coordinates with the triple bond, hydro-palladation will proceed with *syn* addition. This addition can give rise to two regioisomers (**3-156** and **3-157**). Addition of palladium in the *geminal* position gives rise to unfavourable steric interactions with the *geminal* substituent group (**3-156**). Meanwhile, addition of the palladium to the *trans* position minimizes that unfavourable interaction (**3-157**). As the phosphine ligand increases in size, the unfavourable *geminal* interaction (experienced in **3-156**) becomes larger, allowing for higher discrimination between the *trans* and *geminal* isomers.

The alternative pathway, namely *via* stannylpalladation process, would not produce the results shown in Table 3.14. This proposition can be explained by the model shown in Scheme 3.30. Thus initial stannylpalladation would give rise to intermediates **3-158** and **3-159** which would lead to *trans*-vinylstannane **3-146** and *geminal* isomer **3-147**, respectively. Using this model, an increase in the steric bulk of the ligands on palladium would lead to enhanced amounts of geminal isomer **3-147**; this is the opposite of what was observed.



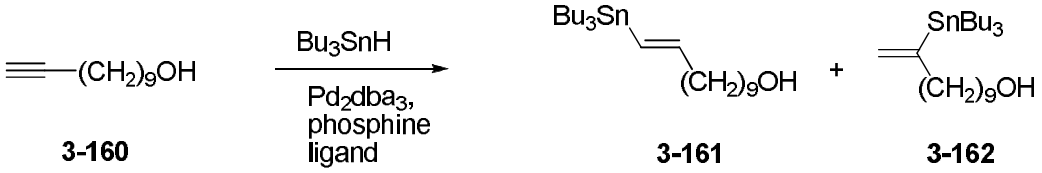
Scheme 3.30

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

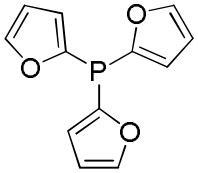
3.3.2 Electronic effect

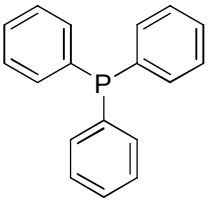
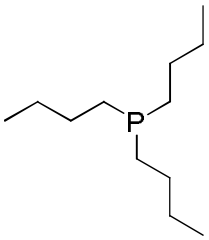
Data shown in Table 3.15 suggest that steric bulkiness of the phosphine is the reason for the differences in selectivities observed. However, there appears to be a strong electronic effect as well: *n*-Bu_3P **3-163**, which has a cone angle smaller than (2-furyl)$_3$P **3-150**, was found to afford higher selectivity during the hydrostannation of alkyne **3-160** (Table 3.16).

Table 3.16 Relating Tolman cone angle and selectivity



3-160 **3-161** **3-162**

entry (phosphine)	phosphine ligand	Tolman cone angle	**3-161** : **3-162** ratio[a]
1(**3-150**)		149°	57 : 42

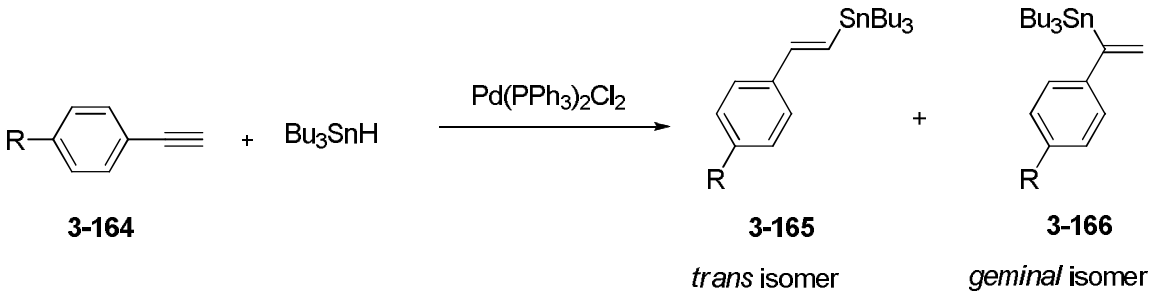
2(**3-148**)		145°	67	33
2(**3-163**)		132°	90	10

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures.

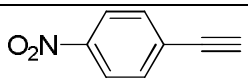
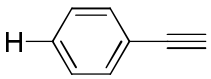
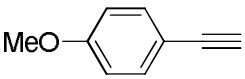
Steric bulk argument of the phosphine ligand would not be a good model to explain the results observed in Table 3.16. Therefore, a different model is required, such as electronics, to explain the observed outcome. In this case, the electron "richness" of the phosphine ligand, which is influenced by the alkyl or aryl group attached to the phosphine, controls the selectivity of the palladium-catalyzed hydrostannation. Therefore, the electron donating or withdrawing nature of the alkyl or aryl groups is an important factor when discussing the electronic effect in palladium-catalyzed hydrostannations. An *n*-butyl group (in *n*-Bu_3P) is considered more electron donating inductively than a furyl group (in (2-furyl)$_3$P), thus affording high *trans*-vinylstannane ratio of 90:10. A furyl group (in (2-furyl)$_3$P) is more electron withdrawing than an *n*-butyl group (in *n*-Bu_3P), thus affording almost an equal ratio of *trans* and *geminal* isomers (57:42, *trans*:*geminal*). A phenyl group (in PPh_3) is considered electron withdrawing, but slightly less than a furyl group, which corresponds to more of the *trans* isomer being formed.

An electronic effect was also evident when subjecting para-substituted phenylacetylenes to palladium-catalyzed hydrostannation (Table 3.17).[39]

Table 3.17 Hydrostannation of *para*-substituted phenylacetylene.[39]



3-164 **3-165** *trans* isomer **3-166** *geminal* isomer

entry (alkyne)	catalyst	alkyne	*trans* : *geminal* ratio[a]	
1(**3-167**)	$Pd(PPh_3)_2Cl_2$		0	100
2(**3-23**)	$Pd(PPh_3)_2Cl_2$		56	44
3(**3-168**)	$Pd(PPh_3)_2Cl_2$		76	24

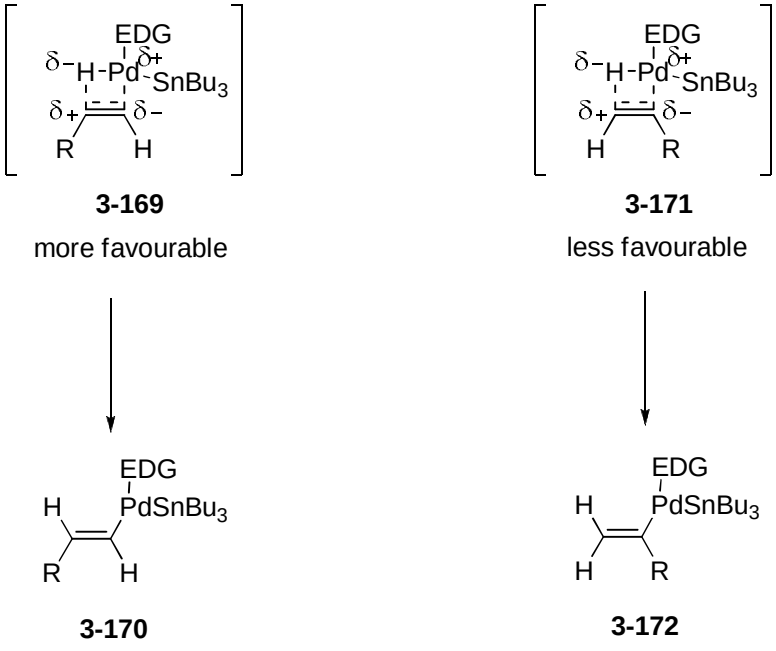
[a] Determined by ^1H NMR analysis of crude reaction mixtures.

Table 3.17 clearly demonstrates an electronic effect on palladium-catalyzed hydrostannation by the substrate. The electron withdrawing nitro group alters the selectivity in favour of the *geminal*-vinylstannane exclusively (entry 1), while electron donating methoxy group promotes the formation of the *trans*-vinylstannane (entry 3).

To rationalize how the regioselectivity in palladium-catalyzed hydrostannation is controlled by electronic effects, one must be able to explain the results obtained in Tables 3.16 and 3.17 with respect to the electronic nature of the phosphine ligand or the substrate.

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

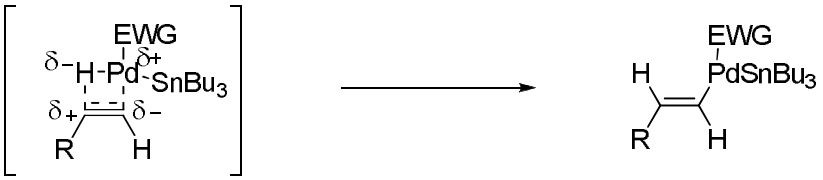
Inspecting the effect of phosphine ligands, electron rich phosphine ligands would be able to stabilize the partial positive charge developed on the palladium during the transition state (**3-169** and **3-171**, Scheme 3.31). But, this stabilization would have taken place for both adducts.



Scheme 3.31

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

Geminal-vinylstannane **3-162** was formed in higher proportions (Table 3.16, entry 1) when using relatively electron withdrawing phosphine ligand $(2\text{-furyl})_3P$; suggesting that stabilization effects during the transition state are minimal, leading to some formation of the *geminal* isomer (Scheme 3.32).

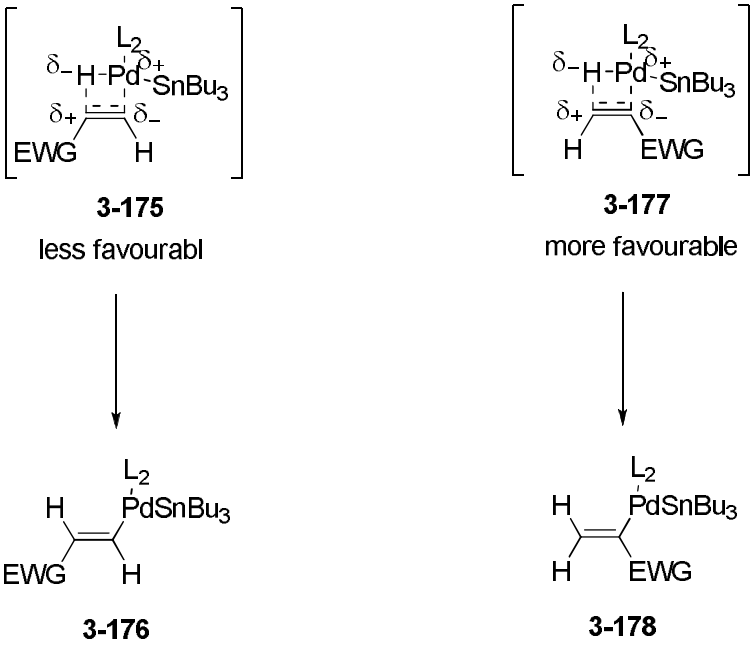


Scheme 3.32

During transition state **3-173** leading to the *trans* adduct, a partial positive charge forms on the palladium which is destabilized by the electron withdrawing group, thus leading to less formation of the *trans* isomer.

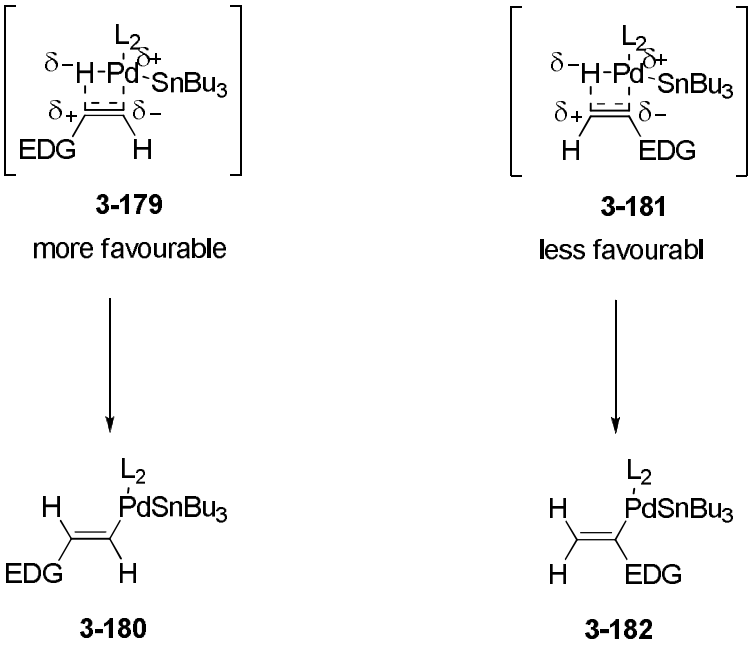
Inspecting the electronic effect caused by the substrate, which was observed in Table 3.17, suggests polarization of the triple bond and the stability of the transition state are important factors that can explain the selectivity provided.

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



Scheme 3.33

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

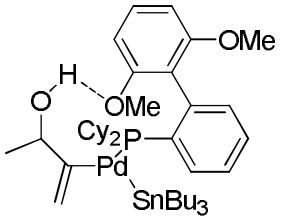


Scheme 3.34

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

3.3.3 Hydrogen bonding effect

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

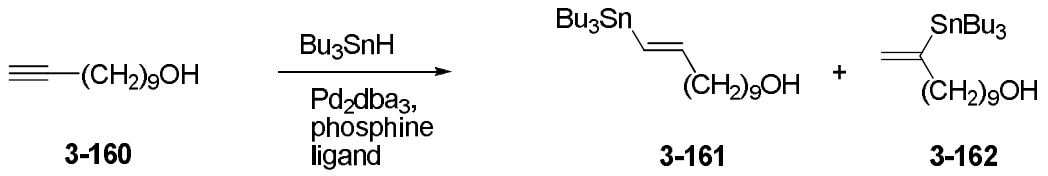


3-18

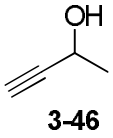
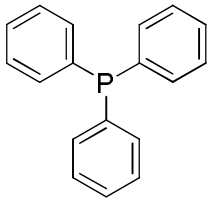
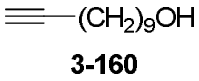
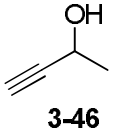
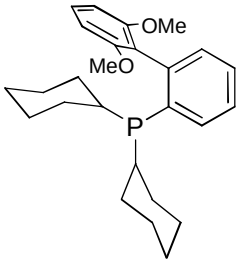
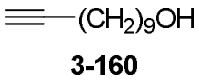
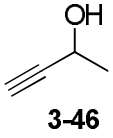
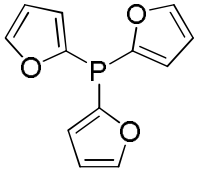
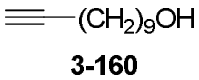
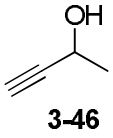
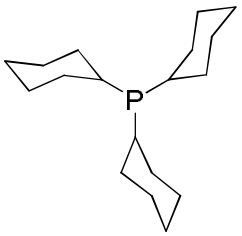
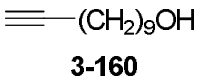
Figure 3.3 Hydrogen bonding in complex **3-183**

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

Table 3.18 Hydrogen bonding effect on hydrostannation



3-160 **3-161** **3-162**

entry (phosphine)	alkyne	phosphine ligand	*trans*	: *geminal* ratio[a]
1(**3-148**)	 **3-46**		68	32
2(**3-148**)	 **3-160**		67	33
3(**3-153**)	 **3-46**		77	23
4(**3-153**)	 **3-160**		95	5
5(**3-150**)	 **3-46**		40	60
6(**3-150**)	 **3-160**		58	42
7(**3-151**)	 **3-46**		95	5
8(**3-151**)	 **3-160**		95	5

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures.

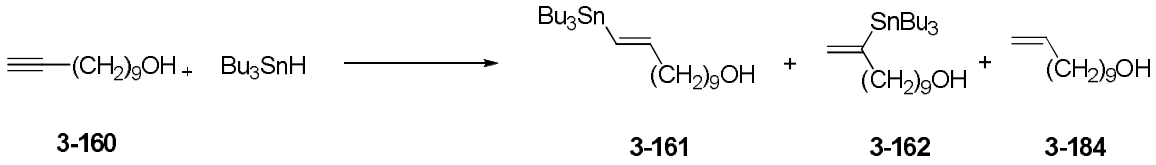
Table 3.18 illustrates the effects of heteroatom *versus* non-heteroatom phosphine ligands and the selectivities they provided. Non-heteroatom phosphine ligands **3-148** and **3-151** maintained the same selectivities in propargylic and non-propargylic substrates; while heteroatom-containing phosphine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

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

3.3.4 Reduction by-product formation

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

Table 3.19 Hydrostannation of alkyne **3-160** with different sources of the catalyst



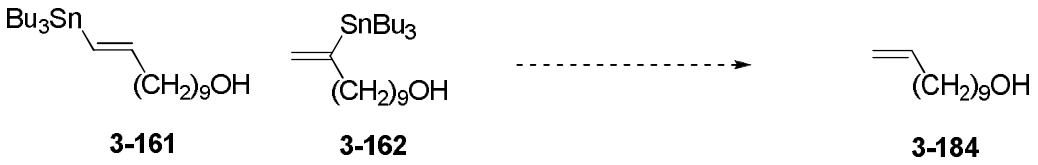
3-160 **3-161** **3-162** **3-184**

entry	catalyst	**3-161** : **3-162** : **3-184** ratio[a]
1	$Pd(PPh_3)_2Cl_2$	66 : 33 : 1
2	$Pd(PCy_3)_2Cl_2$	69 : 4 : 27
3	Pd_2dba_3/*t*Bu_3PHBF_4/ *i*Pr_2NEt	10 : 0 : 90

[a] Determined by ^1H NMR analysis of crude reaction mixtures.

Hydrostannation of either **3-46** or **3-160** gave nearly identical results (2:1 mixture of regioisomers) when using $Pd(PPh_3)_2Cl_2$ as a catalyst. Hydrostannation using $(Cy_3P)_2PdCl_2$ proceeded with the same regioselectivity as that observed for **3-46**; unfortunately, a substantial amount of reduction by-product **3-184** was observed. As well, *t*-Bu_3P maintained the regioselectivity but an overwhelming presence of the reduction by-product **3-184** was observed.

Initially, it was thought that the reduction by-product might be formed through a proto-destannylation process under the reaction conditions (Scheme 3.35).



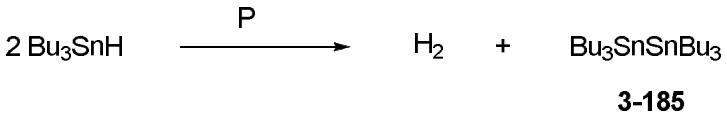
3-161 **3-162** **3-184**

Scheme 3.35

To test this hypothesis, vinylstannanes **3-161** and **3-162** were isolated and re-subjected to the same hydrostannation conditions used in trial 3 from Table 3.19 to observe if reduction by-product **3-184** would form. This was not the case, the initial ratio between stannanes **3-161** and **3-162** remained the same throughout the re-subjection period without any formation of the reduction by-product **3-184**.

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

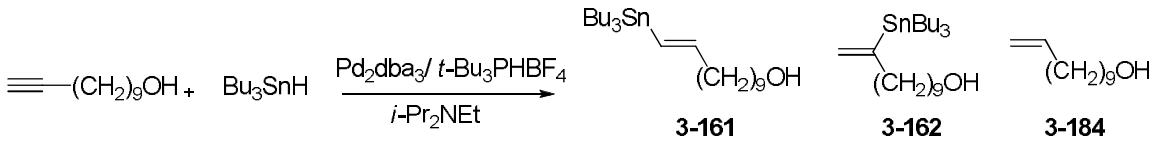
While preparing a sample of Bu_3SnH for ^{13}C NMR analysis, it was noticed that when performing ^{13}C NMR on Bu_3SnH using NMR tubes that had visible traces of black palladium, spectra of $Bu_3SnSnBu_3$ (**3-185**) were obtained (Scheme 3.36).



3-185

Scheme 3.36[17]

Visible bubbles could be seen forming in the NMR tube, likely hydrogen gas, while Bu_3SnH was converting to $Bu_3SnSnBu_3$. This side reaction contributed to the formation of reduction by-product **3-184** which is shown in Scheme 3.37.



3-160 **3-161** **3-162** **3-184**

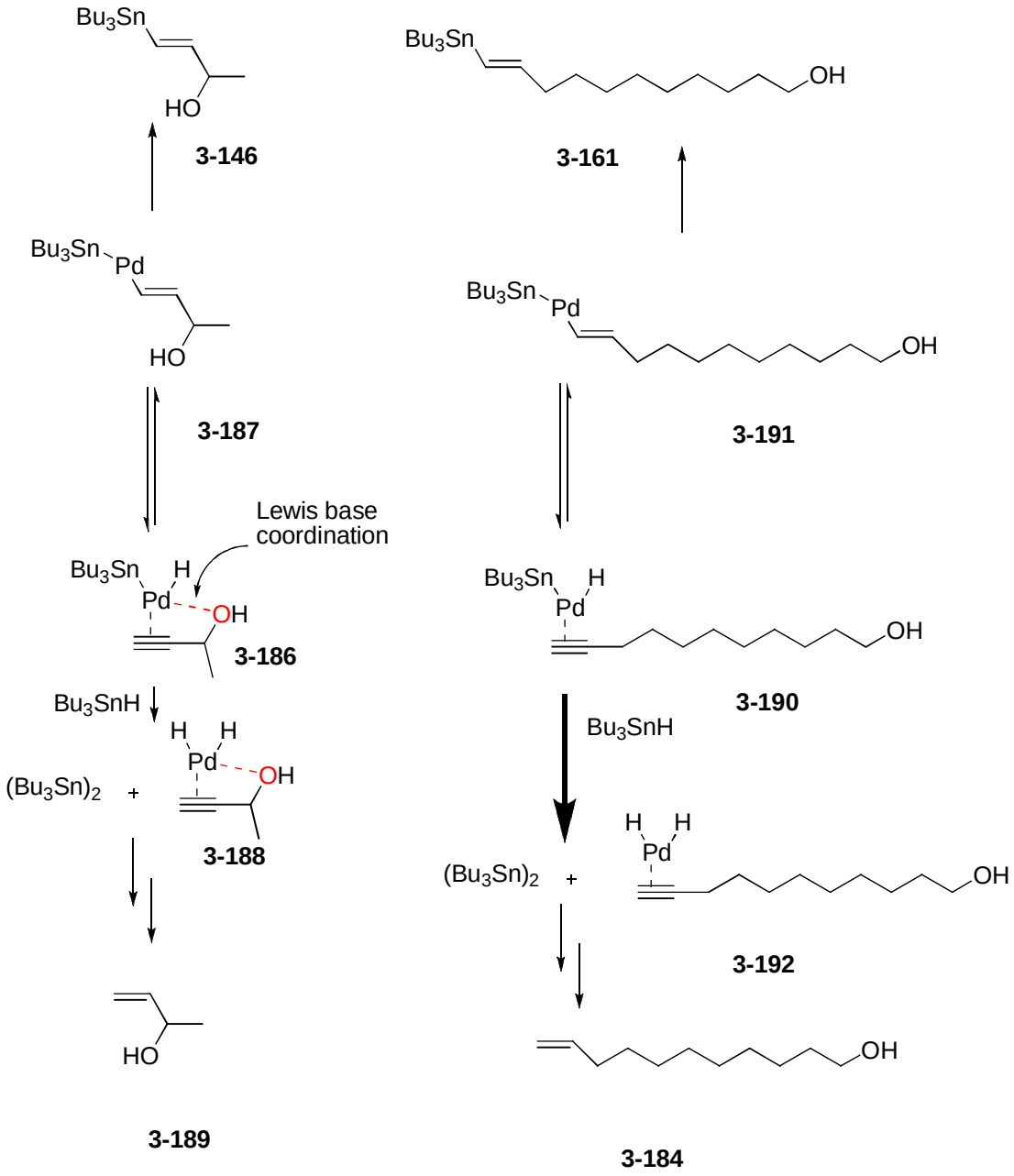
contain Pd(0) trace	10	0	90
doe not contain Pd(0) trace	46	1	53

Scheme 3.37

This problem was solved by washing the glassware with aqua regia (Conc. HCl: Conc. HNO_3, 3:1 v/v) prior to use. The acidic solution oxidizes and removes any traces of Pd(0) that are embedded in glassware. Once the reaction flask was Pd(0) free, a large decline in reduction by-product **3-184** was observed. The acidic wash was adapted as a part of a regular procedure when performing these reactions (Scheme 3.37).

A large decrease in yield of hydrostannation products was observed when using both $(Cy_3P)_2PdCl_2$ and t-Bu_3P/Pd_2dba_3 on non-propargyl alcohol **3-160** in comparison to propargyl alcohol **3-46**. This suggests the propargyl alcohol might be contributing a role that inhibits, or slows down the formation of the reduction by-product **3-184**. This role can be described by viewing the alcohol as a Lewis base. The alcohol could possibly

stabilize intermediate **3-186** (Scheme 3.38), which disfavours the path leading to reduction by-product **3-184**.

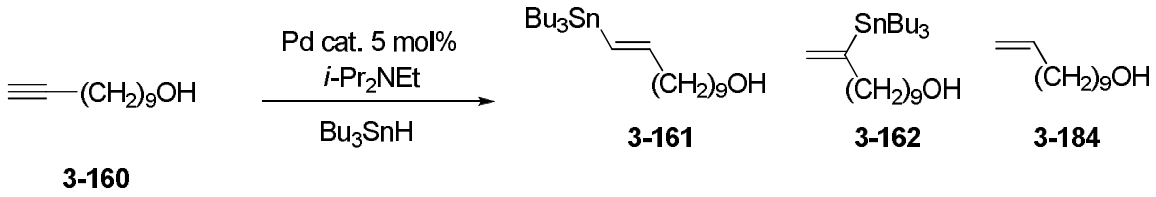


Scheme 3.38

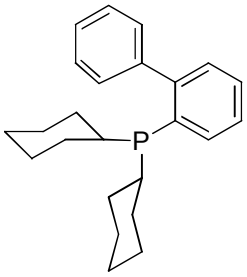
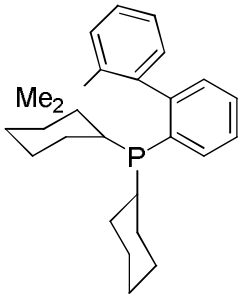
On the other hand, intermediate **3-190** does not contain an alcohol that can stabilize the palladium alkyne complex. This may allow formation of a palladium dihydride, which results in a dramatic increase in the amount of reduction by-product **3-184** formed.

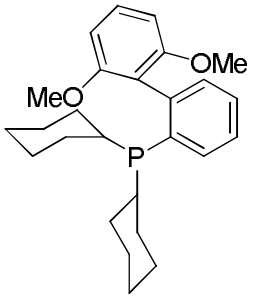
To test this theory, additional heteroatom and non-heteroatom phosphine ligands were chosen to demonstrate the effect of a Lewis base on the amount of reduction by-product **3-184** formed (Table 3.20).

Table 3.20 Internal Lewis base effect on formation of reduction by-product **3-184**



3-160 **3-161** **3-162** **3-184**

entry (phosphine)	phosphine ligand	**3-161** :	**3-162** : ratio[a]	**3-184**
1(**3-193**)		78	8	14
2(**3-194**)		87	4	8

3(**3-153**)		92	5	3

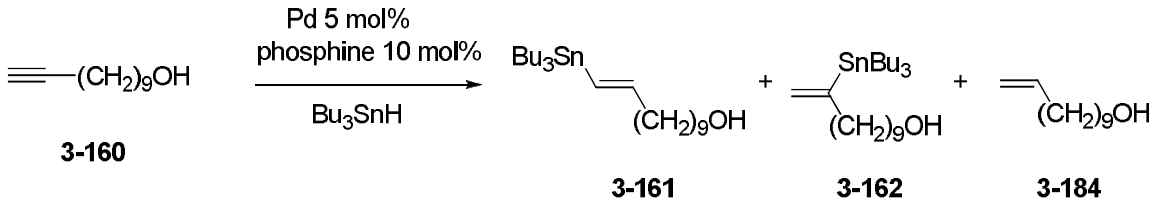
[a] Determined by ^{1}H NMR analysis of crude reaction mixtures.

According to Table 3.20, small but significant differences illustrate the advantage of phosphine ligands containing additional heteroatoms. While nitrogen containing phosphine ligand **3-194** reduces the amount of reduction by-product **3-184**, oxygen containing phosphine ligand **3-153** was slightly better. While phosphine **3-153** proved to be a great ligand for hydrostannation of this substrate, it did not provide good selectivities with the propargyl system (95:5 *vs* 77:23 respectively, *trans*:*geminal*). Unfortunately, heteroatoms can co-ordinate with alcohols in propargylic substrates, which led to lower selectivities as shown in Table 3.20.

The goal of this research was to pursue a ligand that can be general with its substrates; non-heteroatom containing phosphine ligand such as Cy_3P showed promising results with propargyl substrates.

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

Table 3.21 External Lewis base effect on formation of reduction by-product **3-184**



3-160 **3-161** **3-162** **3-184**

entry	excess base present (%)[b]	catalyst	**3-161** : **3-162** : **3-184** ratio[a]	conversion (%)
1	0	Cy_3P/ Pd_2dba_3	87 : 3 : 10	75
2	30 (i-Pr_2Net)	Cy_3P/ Pd_2dba_3	95 : 5 : 0	61
3	0	Cy_3PHBF_4/ Pd_2dba_3	84 : 4 : 12	100
4	2 (i-Pr_2Net)	Cy_3PHBF_4/ Pd_2dba_3	92 : 4 : 4	100
5	20 (i-Pr_2Net)	Cy_3PHBF_4/ Pd_2dba_3	93 : 4 : 3	100
6	20 (piperidine)	Cy_3PHBF_4/ Pd_2dba_3	91 : 4 : 5	100
7	20 (Et_3N)	Cy_3PHBF_4/ Pd_2dba_3	92 : 4 : 4	100
8	0	$(Cy_3P)PdCl_2$ lab-made	86 : 4 : 10	91

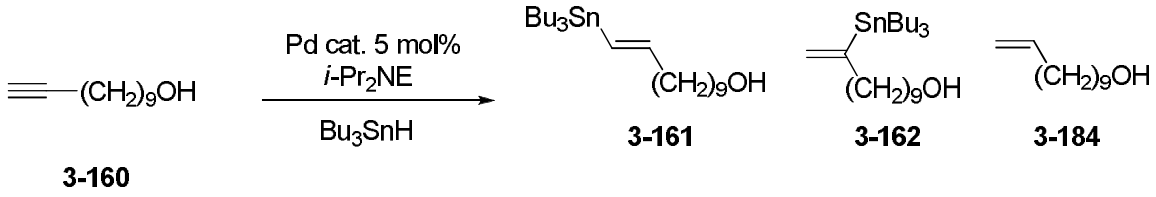
9	2 (i-Pr_2Net)	(Cy_3P)$PdCl_2$ lab-made	91	4	5	91

[a] Determined by ^1H NMR analysis of crude reaction mixtures.
[b] With respect to substrate

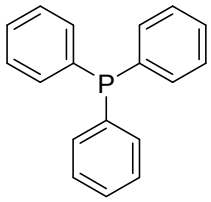
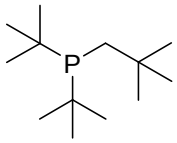
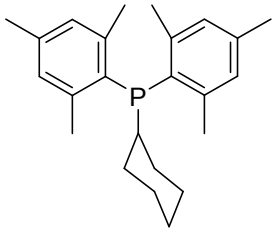
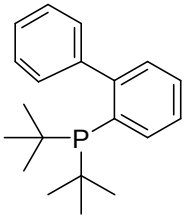
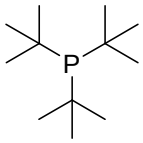
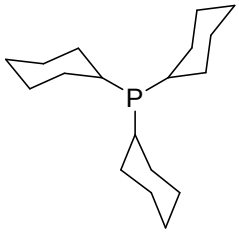
According to Table 3.21, a slight excess of base was able to reduce the amount of reduction by-product **3-184** formed. Hünig's base, Et_3N and piperidine all showed similar results. It was found that reduction by-product **3-184** formation was reduced by 5% to 10% in most cases. The regioselectivities remained unaffected. This, again, highlights the inhibition of the reduction by-product by hetero-atoms.

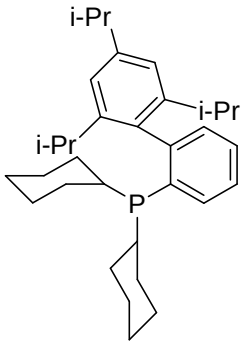
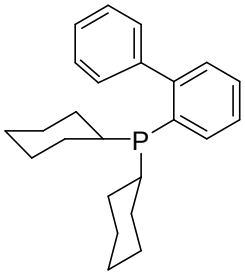
As bulky phosphine ligands were screened to provide high selectivities and yields of vinylstannane **3-161**, a clear trend emerged (Table 3.22).

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



3-160 **3-161** **3-162** **3-184**

entry (phosphine)	phosphine ligand	**3-161** :	**3-162** : ratio[a]	**3-184**
1(**3-148**)		66	33	1
2(**3-154**)		60	9	31
3(**3-195**)		38	3	59
4(**3-196**)		34	2	63
5(**3-149**)		46	1	53
6(**3-151**)		93	4	3

7(**3-197**)		83	4	13
8(**3-198**)		78	8	14

[a] Determined by ^{1}H NMR analysis of crude reaction mixtures.

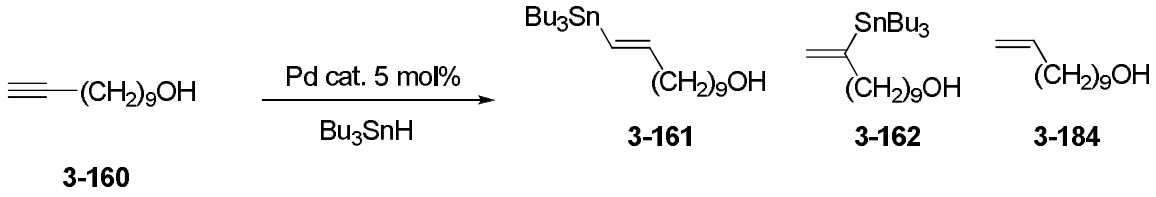
The outcome was consistent with what was hypothesized earlier, bulky electron rich ligands have higher selectivity toward *trans* product. All ligands shown in Table 3.22 did show moderate (7:1) to high (46:1) selectivities toward *trans*-vinylstannane **3-161**. Unfortunately, moderate to high levels of reduction by-product **3-184** accompanied these products in most cases. From what was observed, reactions tend to be more susceptible to the formation of the reduction by-product when bulky electron rich ligands are used. All of the results shown in Table 3.22 are optimized with respect to the formation of the reduction by-product except for trial 1 (PPh_3). PPh_3 is the least electron rich ligand from Table 3.22, which resulted in the least amount of reduction by-product without any optimization. As illustrated in Table 3.22, there is a fine line in obtaining a ligand that has steric bulk, or electron richness, that will not result in the formation of the reduction by-product which was achieved by ligand **3-151** (Cy_3P). This table demonstrates the

susceptibility of these reactions, when using bulky electron rich ligands, toward the formation of the reduction by-product in the non propargylic substrate **3-160**.

3.3.5 Addition rate of Bu_3SnH

Rate of addition of Bu_3SnH to the reaction was examined to determine its effects on the regioselectivity and the formation of the reduction by-product. According to Table 3.23, rate of addition of Bu_3SnH has a significant effect on the formation of the reduction by-product **3-184** but did not affect the regioselectivity (Table 3.23).

Table 3.23 Addition rate effect of Bu_3SnH



3-160 **3-161** **3-162** **3-184**

entry	Bu_3SnH addition rate	catalyst	**3-161** :	**3-162** :	**3-184** ratio[a]
1	slow		73	4	23
2	fast	$Pd(PCy_3)_2Cl_2$	69	4	27
3	reverse addition	**3-151** (Aldrich)	35	2	63

[a] Determined by ^1H NMR analysis of crude reaction mixtures.

All three trials of hydrostannation reactions performed in Table 3.23 were performed at 1 mmol scale. Trial 1 and 2 had the same sequence of addition of reagents. Preformed catalyst **3-151**, at 5 mol%, was added along with the alkyne **3-160** to a solution of toluene (20 mL). Slow addition represents the addition of diluted 1.2 equivalents of Bu_3SnH (10 mL toluene) in 15 minutes; while fast addition represents the neat addition of 1.2 equivalents of Bu_3SnH within 1 minute.

Trial 3 had a different sequence of addition; 1.2 equivalents of Bu_3SnH along with alkyne **3-160** were added to a solution of toluene (20 mL). Preformed catalyst was then added to the reaction mixture, which represents the reverse-addition.

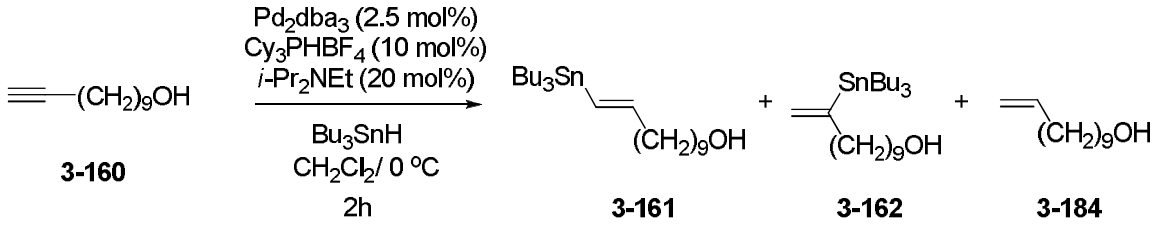
Looking back at Scheme 3.38, one can assume that high concentrations of Bu_3SnH will increase the chance of further reaction with the Bu_3SnPdH complex. This will promote the pathway leading to the reduction by-product **3-184**. It is interestingly to note that trials 1 and 2 from Table 3.23, representing slow and fast addition, respectively, had similar outcomes; only in the extreme case of reverse-addition was a considerable amount of reduction by-product **3-184** observed. Regioselectivity was consistent throughout the three trials.

3.3.6 Catalyst loading

The intention of this methodology was to be used on large scale (0.1 mol) toward total syntheses of natural products. This will still require the use of 0.005 mol of Pd_2dba_3/PCy_3HBF_4 at 5% catalytic loading (2.5% Pd_2dba_3/ 10% PCy_3HBF_4). Unfortunately, these reagents are expensive to purchase (Aldrich - Pd_2dba_3 $201/0.0025

mol, Cy_3PHBF_4 $107/0.01 mol), thus costing approximately $308 for the catalyst only at 5% catalytic loading (Table 3.24).

Table 3.24 Effect of catalyst loading



entry	catalyst loading (%)	**3-161** : **3-162** : **3-184** ratio[a,b]
1	5	92 : 4 : 4
2	1	93 : 4 : 3
3	0.5	93 : 4 : 3
4	0.25	93 : 4 : 3
5	0.125	93 : 4 : 3

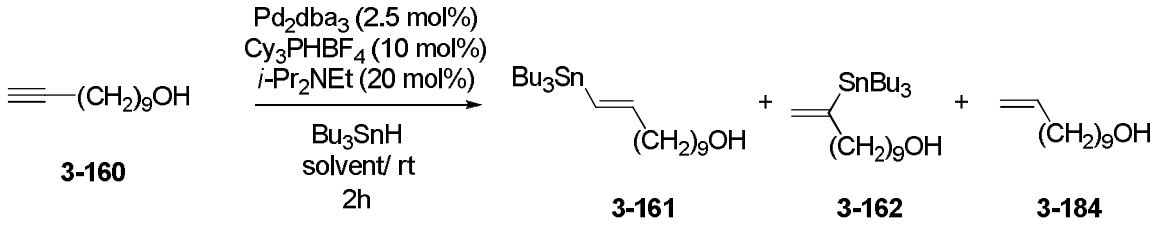
[a] Determined by ^1H NMR analysis of crude reaction mixtures.
[b] Combined isolated yields of *trans* and *geminal* vinylstannanes were consistently obtained at 87% throughout the trials.

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

3.3.7 Solvent effect

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

Table 3.25 Solvent effect on hydrostannation



entry	solvent	**3-161** : **3-162** : **3-184** ratio[a,b]		
1	toluene	93	4	3
2	THF	92	5	3
3	Hexane	95	4	1
4	Et_2O	94	5	1
5	CH_2Cl_2	95	5	0

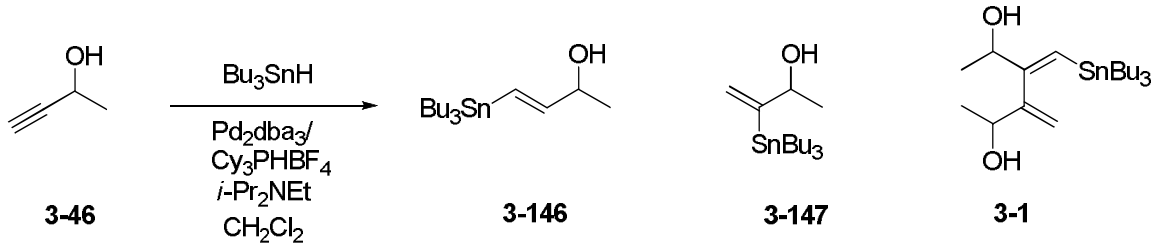
[a] Determined by ^1H NMR analysis of crude reaction mixtures.
[b] 100% conversion was observed in all trials.

The reaction proceeded smoothly with a variety of solvents. Polar and non polar solvents did not change the regioselectivity. This was consistent with what was reported about solvents not affecting the regioselectivity in palladium-catalyzed hydrostannations very

much.[40] Also, there was not any significant changes in the formation of reduction by-product **3-184** (0%-3%). In all trials, complete conversion of the starting alkyne (**3-160**) was observed. This finding highlights the compatibility of the reaction with many solvents. The flexibility in the choice of solvent allowed a follow-up reaction (Stille coupling) without the need of purification of the corresponding vinylstannanes, which is illustrated later in section *3.2.14*.

3.3.8 Concentration

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

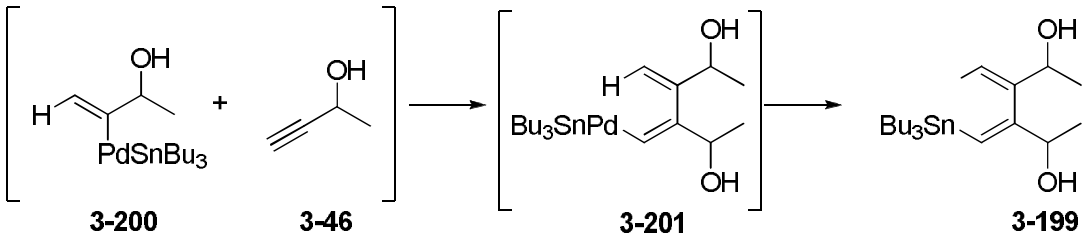


3-46 **3-146** **3-147** **3-1**

66.5% 3.5% 30%

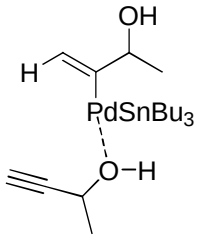
Scheme 3.39

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



Scheme 3.40

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



3-202

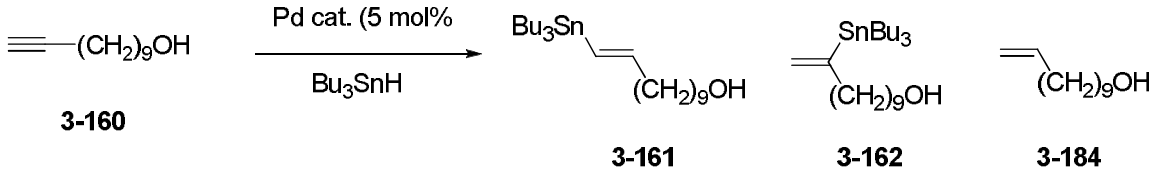
Figure 3.4 Hydrogen bonding in complex **3-202**

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

3.3.9 Source of catalyst

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

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



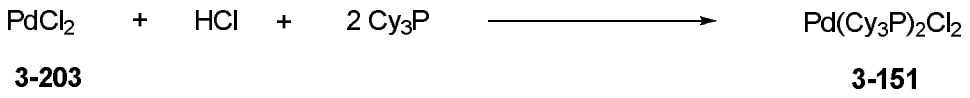
3-160 **3-161** **3-162** **3-184**

entry	source of catalyst	**3-161**	**:**	**3-162** ratio[a]	**:**	**3-184**
1	$Pd(PCy_3)_2Cl_2$ Aldrich	73		4		23
2	$Pd(PCy_3)_2Cl_2$ lab-made	86		4		10
3	PCy_3/ Pd_2dba_3	87		3		10
4	Cy_3PHBF_4/ Pd_2dba_3[b]	84		4		12

[a] Determined by ^1H NMR analysis of crude reaction mixtures.
[b] Without excess base (*i*-Pr_2NEt).

Pre-formed catalyst purchased from Aldrich ($Pd(PCy_3)_2Cl_2$) was initially used. Reaction using catalyst in entry 1 was more susceptible at forming reduction by-product **3-184** (23%). Reactions using laboratory-made $Pd(PCy_3)_2Cl_2$ catalyst in entry 2, 3 and 4 produced 10-12% reduction by-product under the same conditions. Note that none of the trials had extra base to compare solely the effect of the source of the catalyst has on the formation of the reduction by-product. We can speculate that pre-formed catalyst purchased from Aldrich (entry 1) might contain traces of black Palladium (Pd(0)), which can be responsible in forming reduction earlier. On the other hand, during the synthesis of the pre-formed catalyst (entry 2) in the laboratory, extra care was taken to achieve

highest quality of catalyst, which might contain less or none of the black palladium (Scheme 3.41).

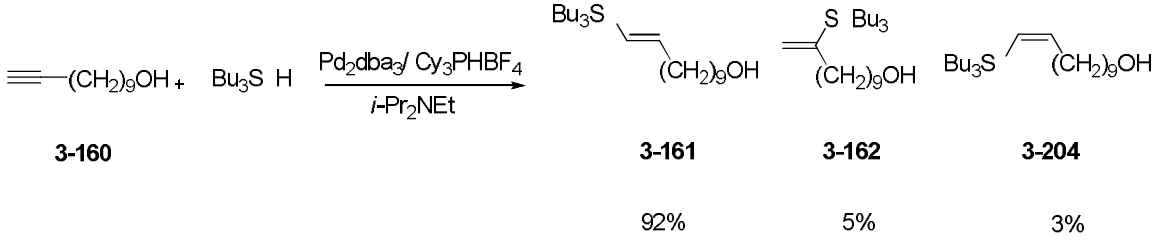


Scheme 3.41

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

3.3.10 Scale of reaction

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



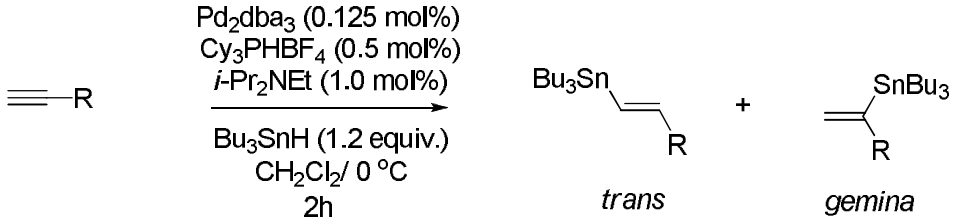
Scheme 3.42

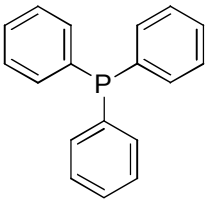
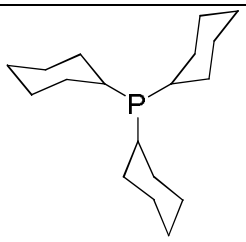
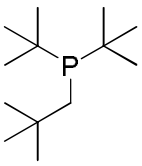
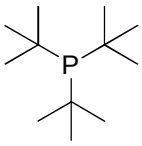
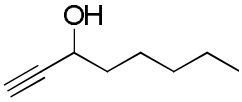
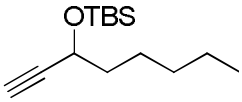
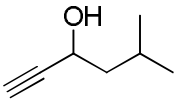
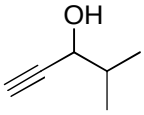
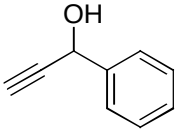
Metal-catalyzed hydrostannations can only produce two possible regioisomers. This is due to the mechanism of this reaction which proceeds by *syn*-addition. To produce *cis*-vinylstannane **3-204**, another pathway must have been operating. Normally, reactions are performed at ambient temperature with no external cooling. It was noted that reactions warm up as Bu_3SnH was added. This side product was only observed when the scale of the reaction exceeded 0.012 moles, suggesting that excess heat from the reaction promotes the initiation of the radical pathway. It was disadvantageous to have another isomeric vinylstannane in the crude reaction mixture, since long chain vinylstannanes such as **3-161**, **3-162** and **3-204** are inseparable by silica gel chromatography. The radical pathway was inhibited by simply performing the reaction at 0 ^{o}C. The lower temperature inhibited the formation of *cis*-vinylstannane **3-204** while maintaining selectivity and yield.

3.3.11 Scope of substrates and limitations

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

Table 3.27 Hydrostannation of various propargyl alcohols using optimal conditions



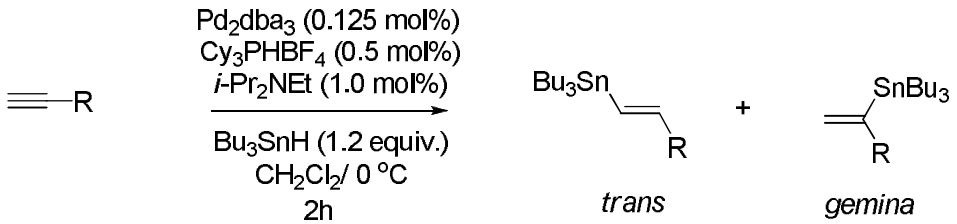
entry (stannanes)	alkyne	 **3-148**	 **3-151**	 **3-154**	 **3-149**
1 (**3-205**:**3-206**)	 **3-215**	57% 77:23	82% 95:5	65% 93:7	55% 95:5
2 (**3-207**:**3-208**)	 **3-48**	50% 77:23	77% 96:4	37% 95:5	28% 94:6
3 (**3-209**:**3-210**)	 **3-216**	55% 76:24	83% 96:4	60% 94:6	58% 95:5
4 (**3-211**:**3-212**)	 **3-217**	56% 76:24	86% 97:3	51% 93:3	27% 93:7
5 (**3-213**:**3-214**)	 **3-29**	50% 61:39	76% 82:18	31% 81:19	19% 83:17

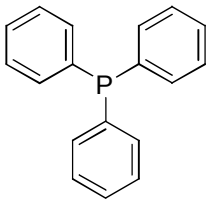
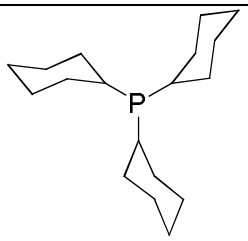
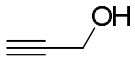
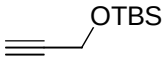
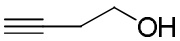
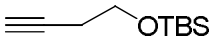
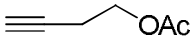
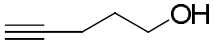
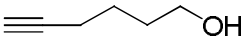
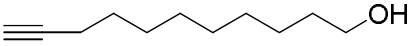
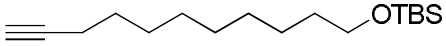
Isolated yield of *trans* isomer except in the case of entry 2 which is the isolated yield of *trans* and *geminal* isomers combined which were inseparable.

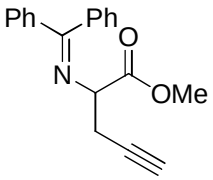
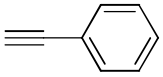
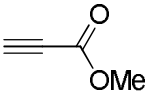
Results for the hydrostannation of propargyl alcohols **3-215**, **3-216**, **3-217** and **3-29** and silyl ether **3-48** with phosphines **3-148**, **3-151**, **3-154** and **3-149** are tabulated in Table 3.27. PPh_3 is the common ligand for palladium-catalyzed hydrostannation; it provided similar selectivities with all substrates (3:1, *trans*:*geminal*), but slightly lower selectivity with substrate **3-29** (1.5:1, *trans*:*geminal*). Silyl ether substrate **3-48** gave the same ratio of vinylstannyl isomers as the alcohol counterpart **3-215**. These results illustrate the unimportance of hydrogen bonding when using non-heteroatom phosphine ligands; the results also suggest that the inductive nature of the oxygen in silyl ether **3-48** is similar to the alcohol counterpart **3-215**. Relatively bulky propargyl alcohols **3-216** and **3-217** did not have much affect on the regioselectivities. Phenyl-substituted propargyl alcohol **3-29** provided lower selectivities for all phosphine ligands. All of the trialkylphosphines tested afforded similar selectivities with all the substrates. Overall, Cy_3P proved to be better in terms of selectivities and isolated yields.[37]

Non propargylic substrates were also subjected to our methodology using Cy_3P as the phosphine ligand in comparison to the traditional PPh_3 ligand (Table 3.28).

Table 3.28 Hydrostannation of various alkynes using optimal conditions



entry (stannanes)	alkyne	 **3-148**	 **3-151**
1 (**3-11**:**3-9**)	 **3-8**	31%[a] 40:60	61%[a] 67:33
2 (**3-218**:**3-219**)	 **3-237**	37%[a] 29:71	64%[a] 77:23
3 (**3-220**:**3-221**)	 **3-238**	42%[a] 56:44	70%[a] 83:17
4 (**3-38**:**3-222**)	 **3-239**	79%[b] 62:38	83%[b] 91:9
5 (**3-223**:**3-224**)	 **3-240**	82%[b] 48:52	80%[b] 85:15
4 (**3-225**:**3-226**)	 **3-241**	45%[a] 67:33	84%[a] 94:6
5 (**3-227**:**3-228**)	 **3-242**	52%[b] 68:32	85%[b] 96:4
6 (**3-161**:**3-162**)	 **3-160**	50%[b] 67:33	87%[b] 96:4
7 (**3-229**:**3-230**)	 **3-24**	53%[b] 75:25	86%[b] 95:5

8		43%[a]	79%[a]
(**3-231**:**3-232**)	**3-244**	50:50	84:16
9		73%[b]	74%[b]
(**3-233**:**3-234**)	**3-23**	56:44	81:19
10		76%[a]	23%[a]
(**3-235**:**3-236**)	**3-24**	0:100	0:100

[a] Isolated yield of *trans* and isomer.
[b] Isolated yield of *trans* and *geminal* isomers combined which were inseparable.

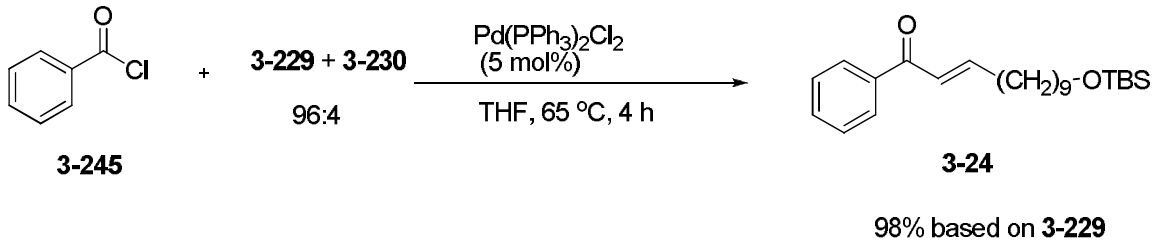
In comparison to PPh_3, Cy_3P proved to be a better ligand in most cases, affording regioselectivities of *trans*:*geminal* = 95:5 in most cases.[37] Interestingly, there was no difference in selectivities when hydrostannating **3-215** and silyl ether **3-48** (95:5 *vs.* 96:4, respectively, Table 3.27), but a slight difference when hydrostannating **3-8** and silyl ether **3-237** (67:33 *vs.* 77:23, respectively, Table 3.28). The steric effect of the TBS group in **3-237** could be a factor in improving the selectivities slightly, but did not improve the selectivities much when hydrostannating **3-48**. Hydrostannation of **3-238**, **3-239** and **3-240** with Cy_3P provided good to excellent selectivities (83:17, 91:9, 85:15, respectively). TBS-ether **3-239** provided higher selectivities than the alcohol or the acetate derivative, which could be attributed to the bulky TBS group. TBS-ether **3-243** afforded the same selectivities as its alcohol counterpart **3-160**; suggesting no effect by the TBS that far away from the alkyne. Examining the proximity of the alcohol and its effect on the

selectivity, alkynyl alcohols $HCC(CH_2)_nOH$ with chains n = 1, 2, 3, 4 and 9 afforded selectivities of 67:33, 83:17, 94:6, 96:4 and 96:4, respectively. The closer the alcohol, n < 3, the lower the selectivities obtained for the *trans* isomer. Conjugated alkynyl substrates **3-23** and **3-24** afforded selectivities of 81:19 and 0:100, respectively. Substrate **3-24** afforded only the *geminal* isomer with either ligand, suggesting strong electronic bias which cannot be overcome by Cy_3P ligand. On the other hand, Cy_3P was able to overcome the electronic bias of **3-23** and afford *trans* isomer as the major product. Some vinylstannyl isomeric products were inseparable from each other. Hydrostannation products of propargyl alcohol **3-8**, TBS-ether **3-237** and homopropargyl alcohol **3-238** could be separated by silica gel chromatography. Meanwhile, homopropargyl TBS-ether **3-239** and its acetate derivative **3-240** were inseparable. Hydrostannation products of substrate **3-241** were separated by careful chromatography, while substrates **3-242**, **3-160** and **3-243** were inseparable by silica gel chromatography. The inability to separate certain vinylstannanes was not a problem since *trans* and *geminal* vinylstannanes have different reactivity rates which we will demonstrate during applications. Overall with notable exceptions, this methodology allows a wide range of substrates to be used.[37]

3.3.12 Applications

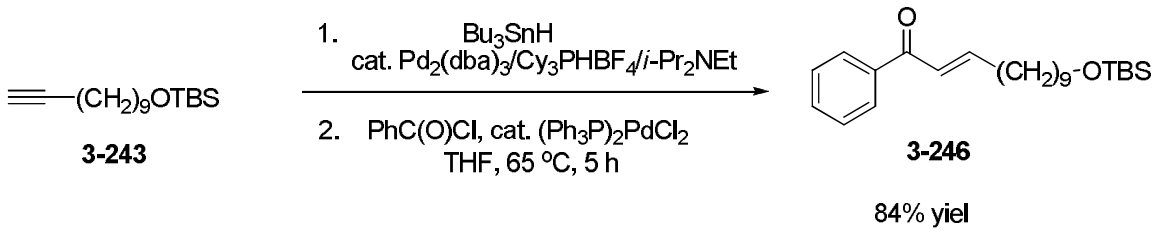
As mentioned earlier, isomeric stannanes such as **3-229** and **3-230** are inseparable, but it is known that *geminal*-vinylstannanes are notoriously slow to undergo Stille coupling,[41] which is one of the major applications of vinylstannanes.

To test this theory, isomeric stannanes **3-229** and **3-230** (96:4, respectively) were treated with benzoyl chloride (1 equivalent with respect to stannanes) with a catalytic amount of $Pd(PPh_3)_2Cl_2$ in THF; only enone **3-246** was isolated in 98% yield (based on **3-229**) and vinylstannane **3-230** was recovered unchanged (Scheme 3.43).



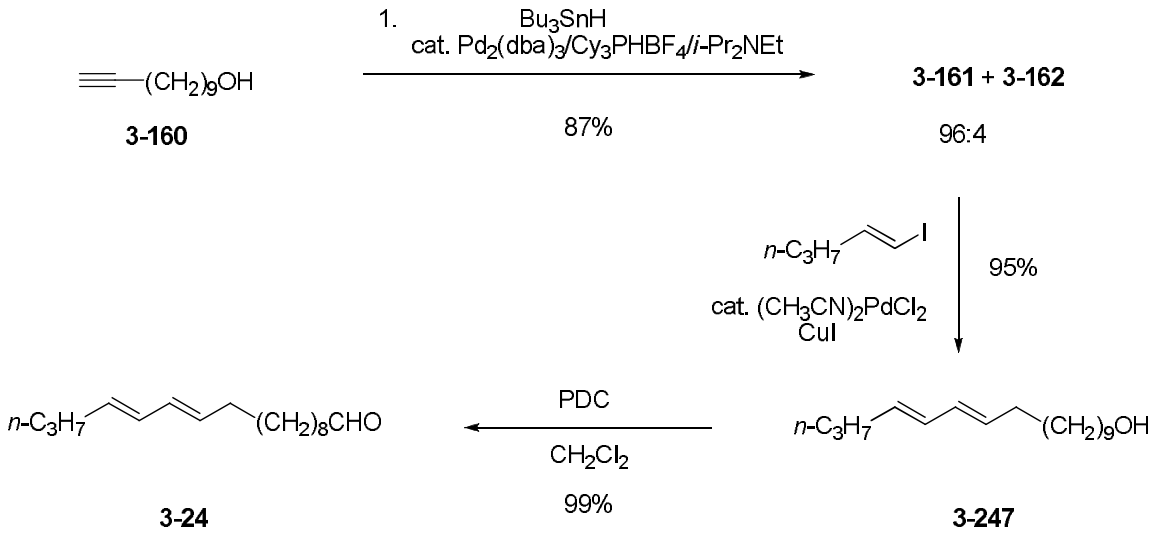
Scheme 3.43

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



Scheme 3.44

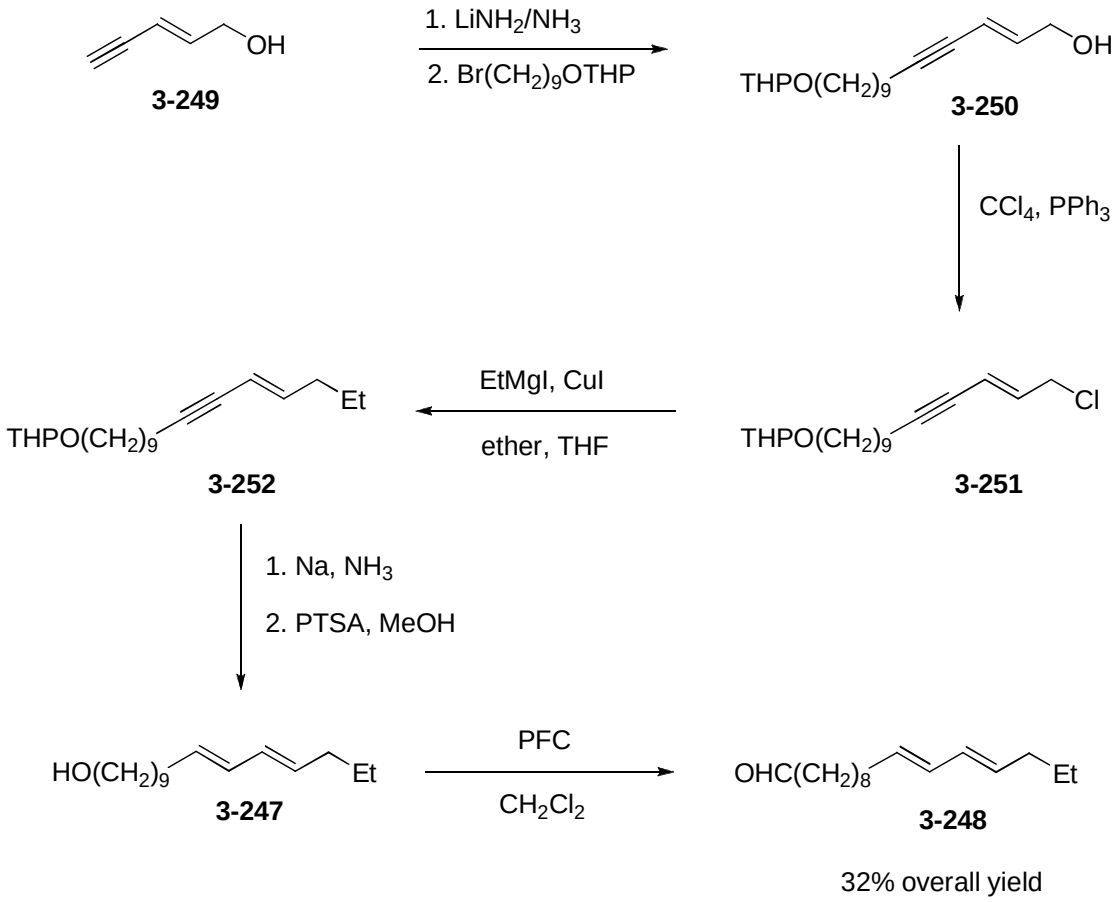
To further demonstrate the usefulness of this palladium-catalyzed hydrostannation chemistry, we have applied the hydrostannation reaction to the synthesis of (*E*,*E*)-10,12-hexadecadienal **3-248**, a sex pheromone component of the spotted bollworm (*Earias vittella*) and spiny bollworm (*E. insulana*) (Scheme 3.28).[43,44] Hydrostannation of **3-160** led to a 96:4 mixture of **3-161** and **3-162**. Treatment of this mixture with (*E*)-1-iodo-1-pentene[45] under Stille conditions [cat. $(CH_3CN)_2PdCl_2$, CuI, DMF][46] provided the desired dienyl alcohol **3-247** in excellent yield and stereochemical purity (Scheme 3.45).



Scheme 3.45

Subsequent oxidation with pyridinium dichromate (PDC) furnished pheromone **3-248**.[37,47] In this sequence, the longest linear sequence is 3-steps and proceeded in 82% overall yield.

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



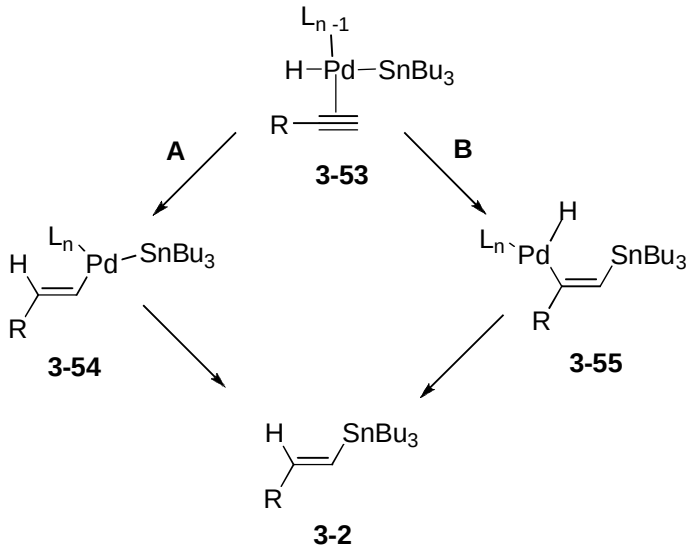
Scheme 3.46

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

3.3 Future Work

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

Our intention is to calculate activation energies ($\Delta G^{\neq}$), using GaussView® software, for both possible routes of the hydrostannation reaction (Scheme 3.47).



Scheme 3.47

Calculating energy barriers for hydro-palladation (pathway **A**) and stannyl-palladation (pathway **B**) of a terminal alkyne, to provide *trans*-vinylstannane, may demonstrate which process is more feasible, in terms of energy; thus, furthering our knowledge into the mechanism of this reaction (Figure 3.5 & 3.6).

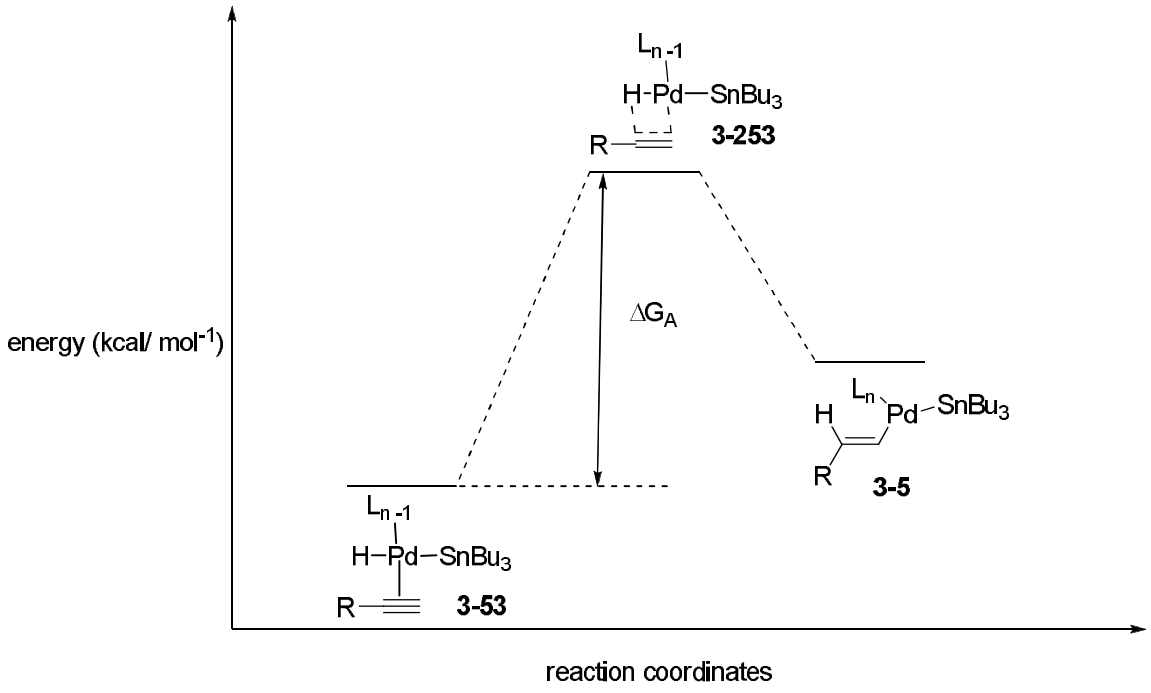


Figure 3.5 Energy diagram for route A

By using GaussView®, one should be able to determine $\Delta G^{\neq}_{A}$ and $\Delta G^{\neq}_{B}$ (route **A** *vs.* **B**). To obtain $\Delta G^{\neq}$ for both routes, one must find the energies for all the structures in Figures 3.5 & 3.6. Structures **3-253** and **3-254** are the proposed transition states (T.S.). Even though structures for the T.S. have been postulated, they are unconfirmed.

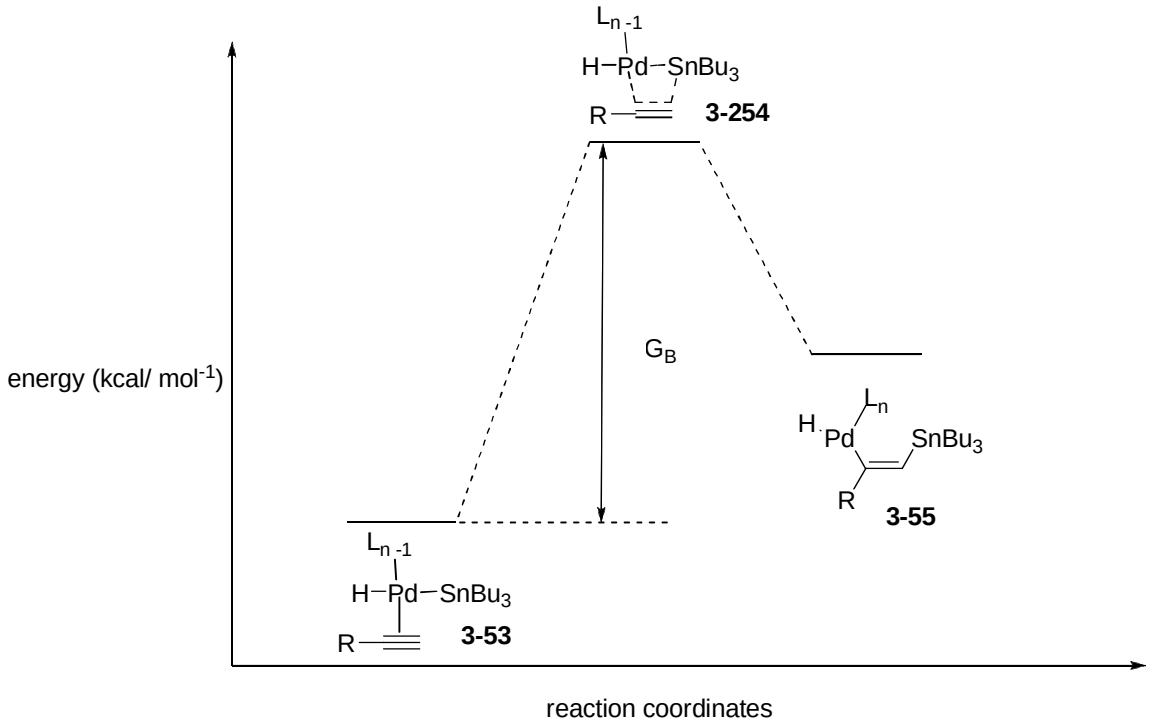


Figure 3.6 Energy diagram for route B

3.4 Summary

In summary, it has been shown that contrary to popular belief, ligands can profoundly affect the regioselectivity of palladium-catalyzed hydrostannations of 1-alkynes. High regioselectivities to produce synthetically useful *trans*-1-stannyl-1-alkenes may be achieved by using $Pd_2dba_3/Cy_3PHBF_4/i\text{-}Pr_2NEt$ for a wide range of alkynes. This system gives much better regioselectivities than the traditional PPh_3-based catalysts currently in use. Sex pheromone **3-248** was synthesized in three steps from alkynol **3-160** in 82% overall yield without the protection of the alcohols; an advantage of hydrostannation methodology. Additional work is underway to expand the scope of these hydrostannations and to better understand the different possible mechanistic pathways.

3.5 Experimental

3.5.1 General experimental

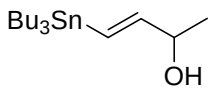
All reactions were carried out under argon using flame-dried glassware. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz, respectively, unless otherwise noted. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 ev) ionization unless otherwise specified. Couplings to ^{117}Sn and ^{119}Sn are reported as averages of the two values. Glassware used for hydrostannations were treated with hot aqua regia (conc. HCl: conc. HNO_3, 3:1 v/v) then rinsed with distilled water to remove traces of palladium. All reactions were performed using flame-dried glassware under an argon atmosphere. Dichloromethane and diisopropylethylamine were freshly distilled from calcium hydride. Tetrahydrofuran, diethyl ether, and toluene were freshly distilled from sodium/benzophenone. Tributyltin hydride was prepared by reduction of bis(tributyltin)oxide with $NaBH_4$ in ethanol[51] and was distilled (kugelrohr) before use. Samples were checked by ^{13}C NMR spectroscopy (in C_6D_6 since Bu_3SnH reacts with $CDCl_3$) for the presence of $Bu_3SnSnBu_3$ and were re-distilled if necessary.[52] Other reagents were purchased from Sigma-Aldrich and used without further purification except *t*-Bu_3PHBF_4 and *t*-Bu_2PCH_2*t*-$BuHBF_4$ which were gifts from FMC Lithium Co. 10-Undecyn-1-ol (**3-160**) was prepared by bromination/dehydrobromination of 10-undecen-1-ol,[53] commercially-unavailable propargylic alcohols were prepared by addition of lithium trimethylsilylacetylide to the appropriate aldehyde followed by treatment with K_2CO_3/MeOH.[54,55]

3.5.2 General procedure for hydrostannation of alkynes

Pd_2dba_3 (4.6 mg, 0.005 mmol), tricyclohexylphosphonium tetrafluoroborate (7.4 mg, 0.02 mmol) and diisopropylethylamine (5.2 mg, 0.04 mol) were added successively to toluene (10 mL) and the resulting mixture was stirred at room temperature for 10 minutes. The alkyne (1.0 mmol) was added and then Bu_3SnH (349 mg, 1.2 mmol) diluted in toluene (3 mL) was added dropwise *via* a dropping funnel over 5 minutes. The reaction was then allowed to stir at rt for 2 hours. The reaction mixture was concentrated and purified by silica gel chromatography (hexanes:ether) to afford the corresponding vinylstannane with the regioselectivities and yields reported in Tables 3.27 and 3.28

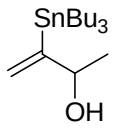
Subsequent to carrying out these experiments, we have found that CH_2Cl_2 gives very similar results and, being much more volatile than toluene, is more convenient to use. We have also found that, in larger scale reactions, small (~5%) amounts of *Z*-1-tributylstannyl-1-alkenes are sometimes formed (presumably via a competitive radical pathway) if the reaction mixture is not cooled. Thus we now routinely run these hydrostannations in CH_2Cl_2 at 0 °C (see following procedure).

3.5.2.1 **(*E*)-4-(Tributylstannyl)but-3-en-2-ol (3-146)**[56]



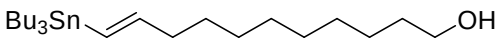
Stannane **3-146** was made in 84% isolated yield as a separable mixture of isomers (95:5, *trans*:*gem*) from alkyne **3-46** using the general procedure to provide 0.303 g as a clear oil. ^{1}H NMR δ 6.07 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX, 2H, δ_A = 6.10, δ_B = 6.04, J_{AB} = 19.2 Hz, J_{BX} = 4.3 Hz, $J_{Sn\text{-}H_A}$ = 69 Hz, $J_{Sn\text{-}H_B}$ = 66 Hz), 4.24 ($CH_3C\underline{H}$, m, 1H), 1.47-0.79 ($C\underline{H}_3CH$, 3H and Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 152.0 (SnCH=$\underline{C}$H), 126.4 (Sn$\underline{C}$H=CH), 71.2 ($CH_3\underline{C}H$, $J_{Sn\text{-}C}$ = 62.4 Hz), 28.9 ($SnCH_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 20.4 Hz), 27.1 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 53.4 Hz), 23.0 ($\underline{C}H_3CH$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.3 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 339.6 Hz).

3.5.2.2 **3-(Tributylstannyl)but-3-en-2-ol (3-147)**[56]



^{1}H NMR δ 5.91 (SnC=C$\underline{H}_2$, 1H, br s, $J_{Sn\text{-}H}$ = 132.6 Hz), 5.15 (SnC=C$\underline{H}_2$, 1H, br s, $J_{Sn\text{-}H}$ = 62.5 Hz), 4.39 ($CH_3C\underline{H}$, 1H, m), 1.48-0.87 ($C\underline{H}_3CH$, 3H and Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 160.3 (Sn$\underline{C}$=CH_2), 122.7 (SnC=$\underline{C}H_2$), 74.7 ($CH_3\underline{C}H$), 29.1 ($SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$), 24.0 ($\underline{C}H_3CH$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.0 ($Sn\underline{C}H_2CH_2CH_2CH_3$).

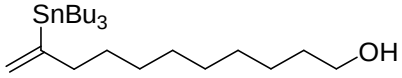
3.5.2.3 **(*E*)-11-(Tributylstannyl)undec-10-en-1-ol (3-161)**[57]



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

^{1}H NMR δ 5.87 (SnC$\underline{H}_B$=C$\underline{H}_A$, AB of ABX_2, 2H, δ_A = 5.92, δ_B = 5.82, J_{AB} = 19.0 Hz, J_{AX} = 6.1 Hz, $J_{Sn\text{-}H_A}$ = 66.2 Hz, $J_{Sn\text{-}H_B}$ = 79.0 Hz), 3.60 (HOC$\underline{H}_2$, 2H, t, J = 6.6 Hz), 2.09 (CHCHC$\underline{H}_2$, 2H, q, J = 6.0 Hz), 1.55-0.80 (CH_2($C\underline{H}_2$)$_7$$CH_2$, 14H and Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 149.9 (SnCH=$\underline{C}$H), 127.0 (Sn$\underline{C}$H=CH, $J_{Sn\text{-}C}$ = 359.8 Hz), 63.1 (HO$\underline{C}H_2CH_2$), 37.9 ($CH_2\underline{C}H_2CH$, $J_{Sn\text{-}C}$ = 64.1 Hz), 32.9 ($HOCH_2\underline{C}H_2$), 29.7, 29.55, 29.50, 29.2, 29.0, 25.8, 29.2 ($SnCH_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 20.2 Hz), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 53.7 Hz), 13.8 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.5 (Sn$\underline{C}HCH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 332.9 Hz).

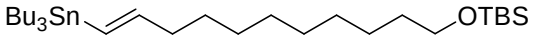
3.5.2.4 **10-(Tributylstannyl)undec-10-en-1-ol (3-162)**



^{1}H NMR δ 5.63 (SnC=C$\underline{H}_2$, 1H, s, $J_{Sn\text{-}H}$ = 144.1Hz, J = 2.7 Hz), 5.06 (SnC=C$\underline{H}_2$, 1H, $J_{Sn\text{-}H}$ = 64.8Hz, J = 2.7 Hz), 3.62 (HOC$\underline{H}_2$, 2H, t, J = 6.6 Hz), 2.20 (SnCC$\underline{H}_2$, 2H, t, J = 6.8 Hz, $J_{Sn\text{-}H}$ = 48.0 Hz), 1.54-0.83 (CH_2($C\underline{H}_2$)$_7$$CH_2$, 14H and Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 155.7(Sn$\underline{C}$=CH_2), 124.4 (SnC=$\underline{C}H_2$, $J_{Sn\text{-}C}$ = 35.3 Hz), 61.2 (HO$\underline{C}H_2CH_2$), 41.3

($CH_2\underline{C}H_2C$), 32.7 ($HOCH_2\underline{C}H_2$), 29.6, 29.5, 29.35, 29.3, 29.2, 25.6, 29.0 ($SnCH_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 19.6 Hz), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 56.6 Hz), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.5 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 322.0 Hz). IR (neat) ν_{max} 3339(br), 3033, 2923, 2854, 1464, 1072, 912, 665 cm^{-1}. Exact mass (EI) calcd for $C_{19}H_{39}O^{120}Sn$ $(M - n\text{-}Bu)^+$: 403.2023, found: 403.2091.

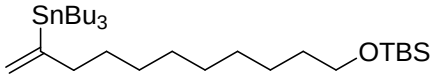
3.5.2.5 **(*E*)-*Tert*-butyldimethyl(11-(tributylstannyl)undec-10-enyloxy)silane (3-229)**[57]



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

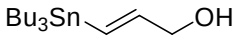
^{1}H NMR δ 5.88 ($SnC\underline{H}_B{=}C\underline{H}_A$, AB of ABX_2, 2H, δ_A = 5.93, δ_B = 5.84, J_{AB} = 19.0 Hz, J_{AX} = 5.3 Hz, $J_{Sn\text{-}H_A}$ = 66.0 Hz, $J_{Sn\text{-}H_B}$ = 77.2 Hz), 3.58 ($TBSOC\underline{H}_2$, 2H, t, J = 6.6 Hz), 2.08 ($SnCHCHC\underline{H}_2$, 2H, dt, J = 7.0, 6.0 Hz), 1.56-0.81 ($CH_2(C\underline{H}_2)_7CH_2$, $\underline{t}Bu(CH_3)_2Si$), and Sn-$\underline{n}Bu$, 50H, m), 0.03 ($t$Bu($C\underline{H}_3)_2Si$, 6H, s); ^{13}C NMR δ 149.7 ($SnCH{=}\underline{C}H$), 126.8 ($Sn\underline{C}H{=}CH$, $J_{Sn\text{-}C}$ = 378.5 Hz), 63.1 ($TBSO\underline{C}H_2CH_2$), 37.8 ($CH_2\underline{C}H_2CH$, $J_{Sn\text{-}C}$ = 57.7 Hz), 32.8, 29.5, 29.4, 29.3, 28.8, 25.7, 29.0 ($SnCH_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 24.1 Hz), 27.2 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 52.8 Hz), 25.9 ($(\underline{C}H_3)_3C(CH_3)_2Si$), 18.3 ($((CH_3)_3\underline{C}(CH_3)_2Si$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.3 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 333.6 Hz), -5.4 ($((CH_3)_3C(\underline{C}H_3)_2Si$).

3.5.2.6 ***Tert*-butyldimethyl(10-(tributylstannyl)undec-10-enyloxy)silane (3-230)**



^{1}H NMR δ 5.63 (SnC=C$\underline{H}_2$, 1H, br s, $J_{Sn\text{-}H}$ = 142.6 Hz), 5.06 (SnC=C$\underline{H}_2$, 1H, br s, $J_{Sn\text{-}H}$ = 65.6 Hz), 3.56 (TBSOC$\underline{H}_2$, 2H, t, J = 6.6Hz), 2.21 (SnCC$\underline{H}_2$, 2H, t, J = 6.8 Hz, $J_{Sn\text{-}H}$ = 48.0 Hz), 1.52-0.83 ($CH_2(C\underline{H}_2)_7CH_2$, 14H, m, $\underline{t}Bu(CH_3)_2Si$, 9H, s and Sn-$\underline{n}Bu$, 27H, m), 0.03 ($t$Bu($C\underline{H}_3)_2$Si, 6H, s); ^{13}C NMR δ 155.7(Sn$\underline{C}$=CH_2), 124.4 (SnC=$\underline{C}H_2$), 63.2 (TBSO$\underline{C}H_2CH_2$), 41.3 ($CH_2\underline{C}H_2C$), 32.8 (TBSOCH$_2\underline{C}H_2$), 29.6, 29.5, 29.4, 29.3, 29.2, 25.7 ($CH_2(\underline{C}H_2)_6CH_2CH_2$OTBS), 29.0 (SnCH$_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 19.7 Hz), 27.3 (SnCH$_2$CH$_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 56.4 Hz), 25.9 (($\underline{C}H_3)_3C(CH_3)_2$Si), 18.3 ($(CH_3)_3\underline{C}(CH_3)_2$Si), 13.6 (SnCH$_2CH_2CH_2\underline{C}H_3$), 9.5 (Sn$\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 326.0 Hz), -5.38 ($(CH_3)_3C(\underline{C}H_3)_2$Si). IR (neat) ν_{max} 2956, 2928, 2856, 1463, 1255, 1101, 836, 775 cm^{-1}. Exact mass (EI) calcd for $C_{25}H_{53}OSi^{120}Sn$ (M – *n*-Bu)$^+$: 517.2888, found: 517.2961.

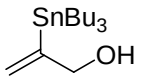
3.5.2.7 **(*E*)-3-(Tributylstannyl)prop-2-en-1-ol (3-11)**[56]



Stannane **3-11** was made in 61% isolated yield as a separable mixture of isomers (67:33, *trans*:*gem*) from alkyne **3-8** using the general procedure to provide 0.212 g as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX_2, 2H, δ_A = 6.24, δ_B = 6.19, J_{AB} = 19.2 Hz, J_{BX} = 4.0 Hz, $J_{Sn\text{-}H_A}$ = 68.6 Hz, $J_{Sn\text{-}H_B}$ = 62.6 Hz), 4.19 (HOC$\underline{H}_2$CH, t,

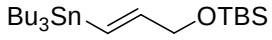
2H, J = 4.3 Hz), 1.74 (HOCH$_2$CH, s, 1H), 1.55-0.89 (Sn-nBu, 27H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0 (SnCH=CH), 128.1 (SnCH=CH, J_{Sn-C} = 378.5 Hz), 66.1 (HOCH$_2$CH, J_{Sn-C} = 64.0 Hz), 28.9 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 20.5 Hz), 27.1 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 64.1 Hz), 13.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 333.6 Hz).

3.5.2.8 **2-(Tributylstannyl)prop-2-en-1-ol (3-9)**[56]



^{1}H NMR δ 5.84 (SnC=CH$_2$, 1H, s, J_{Sn-H} = 129.8 Hz), 5.20(SnC=CH$_2$, 1H, J_{Sn-H} = 61.9 Hz), 4.39 (HOCH$_2$C, 2H, s, J_{Sn-H} = 27.9 Hz), 1.95 (HOCH$_2$C, 1H, s), 1.48-0.87 (Sn-nBu, 27H, m); ^{13}C NMR δ 154.6 (SnC=CH$_2$, J_{Sn-C} = 346.4 Hz), 122.6 (SnC=CH$_2$, J_{Sn-C} = 19.2 Hz), 74.7 (HOCH$_2$CH, J_{Sn-C} = 46.4 Hz), 29.1 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 20.0 Hz), 27.2 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 64.1 Hz), 13.5 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.3 (SnCH$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 333.6 Hz).

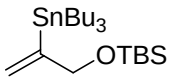
3.5.2.9 **(*E*)-*Tert*-butyldimethyl(3-(tributylstannyl)allyloxy)silane (3-218)**[58]



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

^{1}H NMR δ 6.10 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX_2, 2H, δ_A = 6.16, δ_B = 6.04, J_{AB} = 19.0 Hz, J_{BX} = 4.0 Hz, $J_{Sn\text{-}H_A}$ = 75.6 Hz, $J_{Sn\text{-}H_B}$ = 62.6 Hz), 4.18 (TBSOC$\underline{H}_2$CH, d, 2H, J = 2.8 Hz, $J_{Sn\text{-}H}$ = 72.6 Hz), 1.56-0.82 ((CH$_3$)$_2$Si-$\underline{t}$Bu, 9H, s and Sn-$\underline{n}$Bu, 27H, m), 0.09 ((C$\underline{H}_3$)$_2$Si-*t*Bu, 6H, s); ^{13}C NMR δ 147.2 (SnCH=$\underline{C}$H), 126.7 (Sn$\underline{C}$H=CH, $J_{Sn\text{-}C}$ = 380.4 Hz), 66.6 (TBSO$\underline{C}$H$_2$CH, $J_{Sn\text{-}C}$ = 68.8 Hz), 29.0 (SnCH$_2\underline{C}$H$_2$CH$_2$CH$_3$, $J_{Sn\text{-}C}$ = 20.6 Hz), 27.1 (SnCH$_2$CH$_2\underline{C}$H$_2$CH$_3$, $J_{Sn\text{-}C}$ = 54.3 Hz), 25.8 ((CH$_3$)$_2$SiC($\underline{C}$H$_3$)$_3$), 18.3 ((CH$_3$)$_2$Si$\underline{C}$(CH$_3$)$_3$), 13.5 (SnCH$_2$CH$_2$CH$_2\underline{C}$H$_3$), 9.3 (Sn$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$, $J_{Sn\text{-}C}$ = 339.6 Hz), -5.2 (($\underline{C}$H$_3$)$_2$SiC(CH$_3$)$_3$).

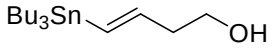
3.5.2.10 ***Tert*-butyldimethyl(2-(tributylstannyl)allyloxy)silane (3-219)**[58]



^{1}H NMR δ 5.85 (SnC=C$\underline{H}_2$, 1H, d, J = 2 Hz, $J_{Sn\text{-}H}$ = 133.3 Hz), 5.17 (SnC=C$\underline{H}_2$, 1H, d, J = 2.0 Hz, $J_{Sn\text{-}H}$ = 63.6 Hz), 4.29 (TBSOC$\underline{H}_2$C, 2H, s, $J_{Sn\text{-}H}$ = 26.7 Hz), 1.55-0.83 ((CH$_3$)$_2$Si-$\underline{t}$Bu, 9H, s and Sn-$\underline{n}$Bu, 27H, m), 0.06 ((C$\underline{H}_3$)$_2$Si-*t*Bu, 6H, s); ^{13}C NMR δ 154.7

(Sn<u>C</u>=CH_2, J_{Sn-C} = 366.9 Hz), 121.8 (SnC=<u>C</u>H_2, J_{Sn-C} = 18.9 Hz), 69.6 (TBSO<u>C</u>H_2CH, J_{Sn-C} = 46.3 Hz), 29.0 (SnCH_2<u>C</u>$H_2CH_2CH_3$, J_{Sn-C} = 19.8 Hz), 27.3 (SnCH_2CH_2<u>C</u>H_2CH_3, J_{Sn-C} = 56.8 Hz), 25.9 ((CH_3)$_2$SiC(<u>C</u>H_3)$_3$), 18.4 ((CH_3)$_2$Si<u>C</u>(CH_3)$_3$), 13.6 (Sn$CH_2CH_2CH_2$<u>C</u>H_3), 9.4 (Sn<u>C</u>$H_2CH_2CH_2CH_3$, J_{Sn-C} = 339.6 Hz), -5.5 ((<u>C</u>H_3)$_2$SiC(CH_3)$_3$).

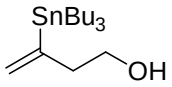
3.5.2.11 **(*E*)-4-(Tributylstannyl)but-3-en-1-ol (3-220)**[56]



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

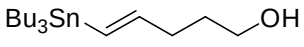
^{1}H NMR δ 6.24 (SnC<u>H</u>$_A$=C<u>H</u>$_B$, AB of ABX_2, 2H, δ_A = 6.03, δ_B = 5.91, J_{AB} = 19.0 Hz, J_{BX} = 6.1 Hz, J_{Sn-H_A} = 74.6 Hz, J_{Sn-H_B} = 63.0 Hz), 4.19 (HOC<u>H</u>$_2$$CH_2$CH, t, 2H, J = 6.2 Hz), 2.40 (HOCH_2C<u>H</u>$_2$CH, q, 2H, J = 6.1 Hz),1.56-0.83 (Sn-<u>nBu</u>, 27H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7(SnCH=<u>C</u>H), 132.1(Sn<u>C</u>H=CH), 61.3 (HO<u>C</u>H_2CH_2CH), 41.1 (HOCH_2<u>C</u>H_2CH), 29.0 (SnCH_2<u>C</u>$H_2CH_2CH_3$, J_{Sn-C} = 20.6 Hz), 27.1 (SnCH_2CH_2<u>C</u>H_2CH_3, J_{Sn-C} = 54.3 Hz), 13.6 (Sn$CH_2CH_2CH_2$<u>C</u>H_3), 9.3 (Sn<u>C</u>$H_2CH_2CH_2CH_3$, J_{Sn-C} = 359.2 Hz).

3.5.2.12 **3-(Tributylstannyl)but-3-en-1-ol (3-221)**[56]



^{1}H NMR δ 5.77 (SnC=C$\underline{H}_2$, 1H, s, J_{Sn-H} = 135.7 Hz), 5.26 (SnC=C$\underline{H}_2$, 1H, J_{Sn-H} = 62.4 Hz), 4.39 (HOC$\underline{H}_2$CH$_2$C, 2H, t, J = 6.3 Hz), 2.49 (HOCH$_2$C$\underline{H}_2$C, 2H, t, J = 6.3Hz, J_{Sn-H} = 46.9 Hz), 1.59-0.84 (Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 151.4 (Sn$\underline{C}$=CH$_2$, J_{Sn-C} = 357.2 Hz), 128.2 (SnC=$\underline{C}$H$_2$, J_{Sn-C} = 25.7 Hz), 61.2 (HO$\underline{C}$H$_2$CH$_2$C, J_{Sn-C} = 11.2 Hz), 44.1 (HOCH$_2$$\underline{C}H_2$C, J_{Sn-C} = 37.7 Hz), 29.0 (SnCH$_2$$\underline{C}H_2CH_2CH_3$, J_{Sn-C} = 19.8 Hz), 27.3 (SnCH$_2$CH$_2$$\underline{C}H_2CH_3$, J_{Sn-C} = 57.5 Hz), 13.5 (SnCH$_2$CH$_2$CH$_2$$\underline{C}H_3$), 9.5 (Sn$\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 326.2 Hz).

3.5.2.13 **(*E*)-5-(Tributylstannyl)pent-4-en-1-ol (3-225)**[58]

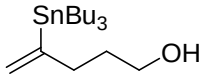


Stannane **3-225** was made in 84% isolated yield as a separable mixture of isomers (94:6, *trans*:*gem*) from alkyne **3-241** using the general procedure to provide 0.315 g as a clear oil.

^{1}H NMR δ 5.93 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX$_2$, 2H, δ_A = 5.91, δ_B = 5.95, J_{AB} = 18.7 Hz, J_{BX} = 4.5 Hz, J_{Sn-H_A} = 72.5 Hz, J_{Sn-H_B} = 66.9 Hz), 3.63 (HOC$\underline{H}_2$CH$_2$CH$_2$CH, t, 2H, J = 6.5 Hz), 2.20 (HOCH$_2$CH$_2$C$\underline{H}_2$CH, dt, 2H, J = 4.5, 6.6 Hz), 1.66 (HOCH$_2$C$\underline{H}_2$CH$_2$CH, quintet, 2H, J = 7.2 Hz), 1.52-0.81 (Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 148.5(SnCH=$\underline{C}$H), 125.5

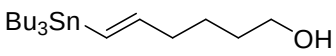
(Sn<u>C</u>H=CH, J_{Sn-C} = 390.8 Hz), 62.4 (HO<u>C</u>$H_2CH_2CH_2CH$), 34.0 ($HOCH_2CH_2$<u>C</u>H_2CH, J_{Sn-C} = 60.4 Hz), 31.7 ($HOCH_2$<u>C</u>H_2CH_2CH), 29.0 ($SnCH_2$<u>C</u>$H_2CH_2CH_3$, J_{Sn-C} = 20.4 Hz), 27.1 ($SnCH_2CH_2$<u>C</u>H_2CH_3, J_{Sn-C} = 53.8 Hz), 13.6 ($SnCH_2CH_2CH_2$<u>C</u>H_3), 9.3 (Sn<u>C</u>$H_2CH_2CH_2CH_3$, J_{Sn-C} = 332.1 Hz).

3.5.2.14 **4-(Tributylstannyl)pent-4-en-1-ol (3-226)**[58]



^{1}H NMR δ 5.69 (SnC=C<u>H</u>$_2$, 1H, d, J = 2 Hz, J_{Sn-H} = 140.5 Hz), 5.11(SnC=C<u>H</u>$_2$, 1H, d, J = 2 Hz, J_{Sn-H} = 62.4 Hz), 3.62 (HOC<u>H</u>$_2CH_2CH_2C$, 2H, t, J = 6.5 Hz), 2.49 ($HOCH_2CH_2$C<u>H</u>$_2$C, 2H, t, J = 6.5 Hz, J_{Sn-H} = 48.0 Hz), 1.63($HOCH_2$C<u>H</u>$_2CH_2$C, 2H, quintet, J = 7.2 Hz) 1.50-0.85 (Sn-<u>n</u>Bu, 27H, m); ^{13}C NMR δ 154.8 (Sn<u>C</u>=CH_2), 125.1 (SnC=<u>C</u>H_2, J_{Sn-C} = 27.5 Hz), 62.5 (HO<u>C</u>$H_2CH_2CH_2$C), 44.1 ($HOCH_2CH_2$<u>C</u>H_2C, J_{Sn-C} = 48.2 Hz), 32.3 ($HOCH_2$<u>C</u>H_2CH_2C, J_{Sn-C} = 12.7 Hz), 29.0 ($SnCH_2$<u>C</u>$H_2CH_2CH_3$, J_{Sn-C} = 19.8 Hz), 27.3 ($SnCH_2CH_2$<u>C</u>H_2CH_3, J_{Sn-C} = 57.0 Hz), 13.6 ($SnCH_2CH_2CH_2$<u>C</u>H_3), 9.5 (Sn<u>C</u>$H_2CH_2CH_2CH_3$, J_{Sn-C} = 326.0 Hz).

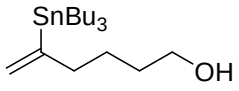
3.5.2.15 **(*E*)-6-(Tributylstannyl)hex-5-en-1-ol (3-227)**[13]



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

^{1}H NMR δ 5.93 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX_2, 2H, δ_A = 5.85, δ_B = 5.91, J_{AB} = 19.0 Hz, J_{BX} = 5.0 Hz, $J_{Sn\text{-}H_A}$ = 75.8 Hz, $J_{Sn\text{-}H_B}$ = 64.5 Hz), 3.63 (HOC$\underline{H}_2$CH$_2$CH$_2$CH$_2$CH, t, 2H, J = 6.2 Hz), 2.13 (HOCH$_2$CH$_2$CH$_2$C$\underline{H}_2$CH, dt, 2H, J = 5.0 Hz, J = 6.0 Hz), 1.56-0.81 (HOCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$CH, 4H, m and Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 149.0 (SnCH=$\underline{C}$H), 127.5 (Sn$\underline{C}$H=CH, $J_{Sn\text{-}C}$ = 396.8 Hz), 62.6 (HO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$CH), 37.4 (HOCH$_2$CH$_2$CH$_2$$\underline{C}H_2$CH, $J_{Sn\text{-}C}$ = 63.5 Hz), 32.1 (HOCH$_2$$\underline{C}H_2CH_2CH_2$CH), 29.0 (SnCH$_2$$\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 20.4 Hz), 27.1 (SnCH$_2$CH$_2$$\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 53.8 Hz), 24.9 (HOCH$_2$CH$_2$$\underline{C}H_2CH_2$CH), 13.6 (SnCH$_2CH_2CH_2$$\underline{C}H_3$), 9.3 (Sn$\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 332.1 Hz).

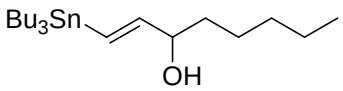
3.5.2.16 **5-(Tributylstannyl)hex-5-en-1-ol (3-228)**[13]



^{1}H NMR δ 5.64 (SnC=C$\underline{H}_2$, 1H, s, $J_{Sn\text{-}H}$ = 139.7 Hz), 5.08(SnC=C$\underline{H}_2$, 1H, s, $J_{Sn\text{-}H}$ = 63.0 Hz), 3.63 (HOC$\underline{H}_2$CH$_2$CH$_2$CH$_2$CH, t, 2H, J = 6.2 Hz), 2.23 (HOCH$_2$CH$_2$CH$_2$C$\underline{H}_2$C, 2H,

t, J = 7.5Hz), 1.56-0.80 ($HOCH_2C\underline{H}_2C\underline{H}_2CH_2C$, 4H, m and Sn-nBu, 27H, m); ^{13}C NMR δ 155.0 ($Sn\underline{C}=CH_2$), 124.8 ($SnC=\underline{C}H_2$), 62.6 ($HO\underline{C}H_2CH_2CH_2CH_2C$), 40.1, 32.3, 29.1 ($SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$), 25.5 ($HOCH_2CH_2\underline{C}H_2CH_2C$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.4 ($Sn\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 338.1 Hz).

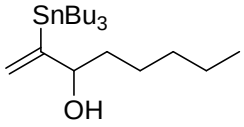
3.5.2.17 **(*E*)-1-(Tributylstannyl)oct-1-en-3-ol (3-205)**[13]



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

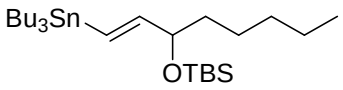
^{1}H NMR δ 6.04 ($SnC\underline{H}_A=C\underline{H}_B$, AB of ABX, 2H, δ_A = 6.11, δ_B = 5.98, J_{AB} = 19.1 Hz, J_{BX} = 5.3 Hz, J_{Sn-H_A} = 71Hz, J_{Sn-H_B} = 63 Hz), 4.03 ($C\underline{H}OH$, m, 1H), 1.54-0.84 ($C\underline{H}_3C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$, 11H and Sn-nBu, 27H, m); ^{13}C NMR δ 151.0 ($SnCH=\underline{C}H$), 127.5 ($Sn\underline{C}H=CH$), 75.5 ($CH_2\underline{C}HOTBS$, J_{Sn-C} = 61.1 Hz), 36.8, 31.7, 29.0 ($SnCH_2\underline{C}H_2CH_2CH_3$, J_{Sn-C} = 20.6 Hz), 27.1 ($SnCH_2CH_2\underline{C}H_2CH_3$, J_{Sn-C} = 53.3 Hz), 24.9, 22.5, 13.9 ($\underline{C}H_3CH_2CH_2CH_2CH_2CH$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.3 ($Sn\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 340.0 Hz).

3.5.2.18 **2-(Tributylstannyl)oct-1-en-3-ol (3-206)**[13]



^{1}H NMR δ 5.76 (SnC=C$\underline{H}_2$, 1H, s, $J_{Sn\text{-}H}$ = 132.3 Hz), 5.19 (SnC=C$\underline{H}_2$, 1H, s, $J_{Sn\text{-}H}$ = 62.6 Hz), 4.17 (C$\underline{H}$OH, 1H, m), 1.50-0.85 (C$\underline{H}_3$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH, 11H and Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 159.2(Sn$\underline{C}$=CH$_2$), 123.8 (SnC=$\underline{C}$H$_2$), 79.3(CH$_2$$\underline{C}$H), 37.5, 31.2, 29.0 (SnCH$_2$$\underline{C}H_2CH_2CH_3$), 27.3 (SnCH$_2CH_2$$\underline{C}H_2CH_3$), 25.3, 22.5, 13.9($\underline{C}H_3CH_2CH_2CH_2CH_2$CH) 13.6 (SnCH$_2CH_2CH_2$$\underline{C}H_3$), 10.0 (Sn$\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 333.6 Hz).

3.5.2.19 **(*E*)-*Tert*-butyldimethyl(1-(tributylstannyl)oct-1-en-3-yloxy)silane (3-207)**[17]

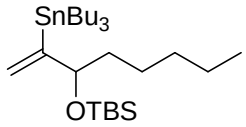


Stannane **3-207** was made in 77% isolated yield as an inseparable mixture of isomers (96:4, *trans*:*gem*) from alkyne **3-48** using the general procedure to provide 0.406 g as a clear oil.

^{1}H NMR δ 5.94 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX, 2H, δ_A = 5.99, δ_B = 5.90, J_{AB} = 19.1 Hz, J_{BX} = 5.5 Hz, $J_{Sn\text{-}H_A}$ = 73.5 Hz, $J_{Sn\text{-}H_B}$ = 63.6 Hz), 4.0 (CH$_2$C$\underline{H}$OTBS, 1H, dt, J = 5.5 Hz, J = 5.7 Hz), 1.55-0.83(C$\underline{H}_3$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH, 11H, $\underline{t}$Bu(CH$_3$)$_2$Si, 9H, s and Sn-$\underline{n}$Bu, 27H, m), 0.02 (*t*Bu(C$\underline{H}_3$)$_2$Si, 6H, s); ^{13}C NMR δ 152.0 (SnCH=$\underline{C}$H), 126.2 (Sn$\underline{C}$H=CH), 76.8 (CH$_2$$\underline{C}$HOTBS), 38.0 (CH$_3CH_2CH_2CH_2$$\underline{C}H_2$CH), 31.8 (CH$_3CH_2CH_2$$\underline{C}H_2CH_2$CH), 29.1

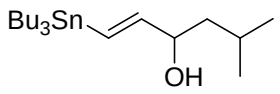
($SnCH_2\underline{C}H_2CH_2CH_3$, J_{Sn-C} = 20.7 Hz), 27.2 ($SnCH_2CH_2\underline{C}H_2CH_3$, J_{Sn-C} = 52.8 Hz), 25.9 (($\underline{C}H_3)_3C(CH_3)_2Si$), 25.0 ($CH_3CH_2\underline{C}H_2CH_2CH_2CH$), 22.6 ($CH_3\underline{C}H_2CH_2CH_2CH_2CH$), 18.3 (($CH_3)_3\underline{C}(CH_3)_2Si$), 14.0 ($\underline{C}H_3CH_2CH_2CH_2CH_2CH$), 13.7 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.4 ($Sn\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 336.6 Hz), -4.4 (($CH_3)_3C(\underline{C}H_3)_2Si$).

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



^{1}H NMR δ 5.69 ($SnC=C\underline{H}_2$, 1H, d, J = 1.8 Hz, J_{Sn-H} = 133.4 Hz), 5.11 ($SnC=C\underline{H}_2$, 1H, d, J = 1.8 Hz, J_{Sn-H} = 62.4 Hz), 4.09 ($CH_2C\underline{H}OTBS$, 1H, t, J = 5.7 Hz), 1.51-0.83($C\underline{H}_3C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$, 11H, $\underline{t}Bu(CH_3)_2Si$, 9H, s and Sn-$\underline{n}Bu$, 27H, m), 0.01 ($t$Bu($C\underline{H}_3)_2Si$, 6H, s); ^{13}C NMR δ 159.1 ($Sn\underline{C}=CH_2$), 123.3 ($SnC=\underline{C}H_2$, J_{Sn-C} = 22.5 Hz), 80.5 ($CH_2\underline{C}HOTBS$, J_{Sn-C} = 35.8 Hz), 38.5($\underline{C}H_2CHOTBS$, J_{Sn-C} = 76.7 Hz), 31.9, 29.0 ($SnCH_2\underline{C}H_2CH_2CH_3$, J_{Sn-C} = 19.3 Hz), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$, J_{Sn-C} = 57.4 Hz), 25.6 (($\underline{C}H_3)_3C(CH_3)_2Si$), 25.1, 22.6, 18.2 (($CH_3)_3\underline{C}(CH_3)_2Si$), 13.9 ($\underline{C}H_3CH_2CH_2CH_2CH_2CH$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.1 ($Sn\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 330.2 Hz), -3.1 (($CH_3)_3C(\underline{C}H_3)_2Si$).

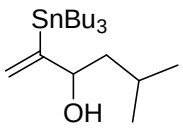
3.5.2.21 **(*E*)-5-Methyl-1-(tributylstannyl)hex-1-en-3-ol (3-209)**[59]



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

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

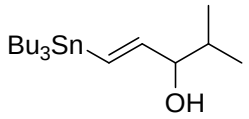
3.5.2.22 **5-Methyl-2-(tributylstannyl)hex-1-en-3-ol (3-210)**[59]



^{1}H NMR δ 5.78 (SnC=C$\underline{H}_2$, 1H, s, $J_{Sn\text{-}H}$ = 136.6 Hz), 5.17 (SnC=C$\underline{H}_2$, 1H, s, $J_{Sn\text{-}H}$ = 62.2 Hz), 4.25 ((CH$_3$)$_2$CHCH$_2$C$\underline{H}$, 1H, t, J = 6.7 Hz), 1.75-0.84 ((C$\underline{H}_3$)$_2$C$\underline{H}$C$\underline{H}_2$CH, 9H) (Sn-

nBu, 27H, m); ^{13}C NMR δ 159.8 (SnC=CH_2), 123.7 (SnC=CH_2), 77.3 ($(CH_3)_2CHCH_2CH$), 47.0 ($(CH_3)_2CHCH_2CH$), 29.2 ($SnCH_2CH_2CH_2CH_3$), 27.5 ($SnCH_2CH_2CH_2CH_3$), 24.7 ($(CH_3)_2CHCH_2CH$), 23.2, 22.4 ($(CH_3)_2CHCHCH$), 13.7 ($SnCH_2CH_2CH_2CH_3$), 10.3 ($SnCH_2CH_2CH_2CH_3$, J_{Sn-C} = 340.0 Hz).

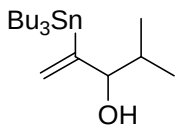
3.5.2.23 **(*E*)-4-Methyl-1-(tributylstannyl)pent-1-en-3-ol (3-211)**[17]



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

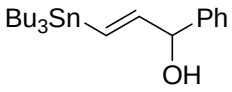
^{1}H NMR δ 6.04 (SnCH_A=CH_B, AB of ABX, 2H, δ_A = 6.11, δ_B = 5.98, J_{AB} = 19.2 Hz, J_{BX} = 5.4 Hz, J_{Sn-H_A} = 71.3 Hz, J_{Sn-H_B} = 63.0 Hz), 3.81 ($(CH_3)_2CHCH$, t, 1H, J = 5.3 Hz), 1.71-0.84 ($(CH_3)_2CHCH$, 7H, m and Sn-nBu, 27H, m); ^{13}C NMR δ 149.2 (SnCH=CH), 128.7 (SnCH=CH), 80.4 (CHOH), 33.4 ($(CH_3)_2CHCH$), 29.0 ($SnCH_2CH_2CH_2CH_3$, J_{Sn-C} = 21.7 Hz), 27.1 ($SnCH_2CH_2CH_2CH_3$), 18.1, 17.6 ($(CH_3)_2CHCH$), 13.6 ($SnCH_2CH_2CH_2CH_3$), 9.4 ($SnCH_2CH_2CH_2CH_3$, J_{Sn-C} = 343.5 Hz).

3.5.2.24 **4-Methyl-2-(tributylstannyl)pent-1-en-3-ol (3-212)**[17]



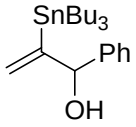
^{1}H NMR δ 5.75(SnC=C$\underline{H}_2$, 1H, s, J_{Sn-H} = 131.7 Hz), 5.53 (SnC=C$\underline{H}_2$, 1H, J_{Sn-H} = 66.2 Hz), 3.81 ((CH$_3$)$_2$CHC$\underline{H}$, 1H, d, J = 7.0 Hz), 1.70-0.82 ((C$\underline{H}_3$)$_2$C$\underline{H}$CH, 7H and Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 158.5 (Sn$\underline{C}$=CH$_2$),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

3.5.2.25 **(*E*)-1-Phenyl-3-(tributylstannyl)prop-2-en-1-ol (3-213)**[17]



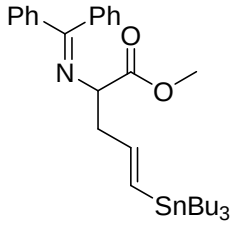
Stannane **3-213** was made in 76% isolated yield as a separable mixture of isomers (82:12, *trans*:*gem*) from alkyne **3-29** using the general procedure to provide 0.322 g as a clear oil. ^{1}H NMR δ 7.35-7.25 (Ph$\underline{H}$, 5H, m), 6.22 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX, 2H, δ_A = 6.29, δ_B = 6.16, J_{AB} = 19.1 Hz, J_{BX} = 4.8 Hz, J_{Sn-H_A} = 67.9 Hz, J_{Sn-H_B} = 60.1 Hz), 5.16 (CH$_3$C$\underline{H}$, d, 1H, J_{XB} = 4.6 Hz), 1.56-0.83 (Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 149.3 (SnCH=$\underline{C}$H), 142.7 (Sn$\underline{C}$H=CH), 128.5 ($\underline{Ph}$, 1C), 128.4 ($\underline{Ph}$, 2C), 127.4 ($\underline{Ph}$, 1C), 126.3 ($\underline{Ph}$, 2C), 77.5 (Ph$\underline{C}$H), 29.0 (SnCH$_2\underline{C}$H$_2$CH$_2$CH$_3$, J_{Sn-C} = 20.4 Hz), 27.1 (SnCH$_2$CH$_2\underline{C}$H$_2$CH$_3$, J_{Sn-C} = 54.6 Hz), 13.6 (SnCH$_2$CH$_2$CH$_2\underline{C}$H$_3$), 9.3 (Sn$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 337.0 Hz).

3.5.2.26 **1-Phenyl-2-(tributylstannyl)prop-2-en-1-ol (3-214)**[17]



^{1}H NMR δ 7.45-7.21 (Ph<u>H</u>, 5H, m), 5.90 (SnC=C<u>H</u>$_2$, 1H, s, $J_{Sn\text{-}H}$ = 126.3 Hz), 5.31 (CH_3C<u>H</u>, 1H, s) 5.30 (SnC=C<u>H</u>$_2$, 1H, s, $J_{Sn\text{-}H}$ = 65.4 Hz), (Sn-<u>nBu</u>, 27H, m); ^{13}C NMR δ 157.9 (Sn<u>C</u>=CH_2), 142.9 (SnC=<u>C</u>H_2), 80.4 (Ph<u>C</u>H), 28.8 ($SnCH_2$<u>C</u>$H_2CH_2CH_3$), 27.2 ($SnCH_2CH_2$<u>C</u>H_2CH_3), 13.5 ($SnCH_2CH_2CH_2$<u>C</u>H_3), 9.8 (Sn<u>C</u>$H_2CH_2CH_2CH_3$).

3.5.2.27 **Methyl (*E*)-2-(diphenylmethyleneamino)-5-(tributylstannyl)pent-4-enoate (3-231)**[60]

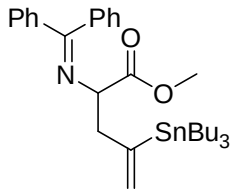


Stannane **3-231** was made in 79% isolated yield as a separable mixture of isomers (84:16, *trans*:*gem*) from alkyne **3-244** using the general procedure to provide 0.460 g as a clear oil.

^{1}H NMR δ 7.62-7.14 (<u>H</u>Ph_2N, 10H, m), 5.87 (SnC<u>H</u>$_A$=C<u>H</u>$_B$, AB of ABX_2, 2H, δ_A = 5.97, δ_B = 5.77, J_{AB} = 18.8 Hz, J_{BX} = 6.4 Hz, $J_{Sn\text{-}H_A}$ = 77.0 Hz, $J_{Sn\text{-}H_B}$ = 64.1 Hz), 4.19 (NC<u>H</u>CH_2, 1H, dd, J = 5.3 Hz), 3.70 (OC<u>H</u>$_3$, 3H, s), 2.74 (NCHC<u>H</u>$_2$, 2H, m), 1.54-0.79 (Sn-<u>nBu</u>, 27H, m); ^{13}C NMR δ 172.4 (<u>C</u>=O), 170.4 (<u>C</u>=N), 144.3 (SnCH=<u>C</u>H), 139.6, 136.4 (<u>Ph</u>), 131.6 (Sn<u>C</u>H=CH, $J_{Sn\text{-}C}$ = 375.8 Hz), 130.2, 128.8, 128.6, 128.4, 127.9 (<u>Ph</u>),

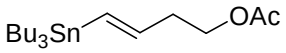
65.3 (N<u>C</u>HCH$_2$), 51.9 (O<u>C</u>H$_3$), 42.1 (NCH<u>C</u>H$_2$, J_{Sn-C} = 62.8 Hz), 29.0 (SnCH$_2$<u>C</u>H$_2$CH$_2$CH$_3$, J_{Sn-C} = 20.2 Hz), 27.2 (SnCH$_2$CH$_2$<u>C</u>H$_2$CH$_3$, J_{Sn-C} = 54.8 Hz), 13.5 (SnCH$_2$CH$_2$CH$_2$<u>C</u>H$_3$), 9.3 (Sn<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 334.5 Hz).

3.5.2.28 **Methyl 2-(diphenylmethyleneamino)-4-(tributylstannyl)pent-4-enoate (3-232)**[60]



^{1}H NMR δ 7.62-7.14 (<u>H</u>Ph$_2$N, 10H, m), 5.70 (SnC=C<u>H</u>$_2$, 1H, s, J_{Sn-H} = 134.5 Hz), 5.18 (SnC=C<u>H</u>$_2$, 1H, J_{Sn-H} = 63.6 Hz, J = 2.5 Hz), 4.19 (NC<u>H</u>CH$_2$, 1H, dd, J = 6.3, 7.3 Hz), 3.70 (OC<u>H</u>$_3$, 3H, s), 2.74 (NCHC<u>H</u>$_2$, AB of ABX, 2H, δ_A = 2.99, δ_B = 2.68, J_{AB} = 13.5 Hz, J_{AX} = 6.3 Hz, J_{BX} = 7.3 Hz, J_{Sn-H_A} = 24.0 Hz, J_{Sn-H_B} = 22.8 Hz), 1.40-0.67 (Sn-<u>nBu</u>, 27H, m); ^{13}C NMR δ 172.3 (<u>C</u>=O), 170.2 (<u>C</u>=N), 150.1 (Sn<u>C</u>=CH$_2$, J_{Sn-C} = 356.6 Hz), 139.6, 136.3, 130.2, 128.8, 128.6 (<u>Ph</u>), 128.5 (SnC=<u>C</u>H$_2$), 128.4, 128.0, 127.9 (<u>Ph</u>), 65.7 (N<u>C</u>HCH$_2$), 51.7 (O<u>C</u>H$_3$), 44.7 (NCH<u>C</u>H$_2$, J_{Sn-C} = 38.8 Hz), 29.0 (SnCH$_2$<u>C</u>H$_2$CH$_2$CH$_3$, J_{Sn-C} = 19.6 Hz), 27.3 (SnCH$_2$CH$_2$<u>C</u>H$_2$CH$_3$, J_{Sn-C} = 56.0 Hz), 13.5 (SnCH$_2$CH$_2$CH$_2$<u>C</u>H$_3$), 9.3 (Sn<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-C} = 325.3 Hz).

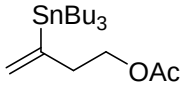
3.5.2.29 **(*E*)-4-(Tributylstannyl)but-3-enyl acetate (3-223)**[58]



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

^{1}H NMR δ 5.93 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX_2, 2H, δ_A = 5.99, δ_B = 5.86, J_{AB} = 19.0 Hz, J_{BX} = 6.0 Hz, $J_{Sn\text{-}HA}$ = 73.6 Hz, $J_{Sn\text{-}HB}$ = 64.8 Hz), 4.08 (AcOC$\underline{H}_2$CH$_2$CH, 2H, t, J = 6.9 Hz), 2.41 (AcOCH$_2$C$\underline{H}_2$CH , 2H, q, J = 6.3 Hz, $J_{Sn\text{-}H}$ = 57.6 Hz), 1.99 (Ac$\underline{O}$, 3H, s), 1.53-0.82 (Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 170.9 (Ac$\underline{O}$), 143.7 (SnCH=$\underline{C}$H), 131.2 (Sn$\underline{C}$H=CH, $J_{Sn\text{-}C}$ = 383.1 Hz), 63.5 (AcO$\underline{C}$H$_2$CH$_2$CH), 36.8 (AcOCH$_2\underline{C}$H$_2$CH, $J_{Sn\text{-}H}$ = 67.9 Hz), 29.0 (SnCH$_2\underline{C}$H$_2$CH$_2$CH$_3$), 27.3 (SnCH$_2$CH$_2\underline{C}$H$_2$CH$_3$, $J_{Sn\text{-}C}$ = 53.6 Hz), 20.8 (Ac$\underline{O}$), 13.6 (SnCH$_2$CH$_2$CH$_2\underline{C}$H$_3$), 9.3 (Sn$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$, $J_{Sn\text{-}C}$ = 345.0 Hz).

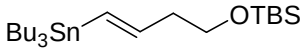
3.5.2.30 **3-(Tributylstannyl)but-3-enyl acetate (3-224)**[58]



^{1}H NMR δ 5.73 (SnC=C$\underline{H}_2$, 1H, br s, $J_{Sn\text{-}H}$ = 133.2 Hz), 5.19 (SnC=C$\underline{H}_2$, 1H, br s, $J_{Sn\text{-}H}$ = 61.3 Hz), 4.06 (AcOC$\underline{H}_2$CH$_2$C, 2H, t, J = 7.1 Hz), 2.52 (AcOCH$_2$C$\underline{H}_2$C, 2H, t, J = 7.6 Hz), 2.0 (Ac$\underline{O}$, 3H, s), 1.53-0.81 (Sn-$\underline{n}$Bu, 27H, m); ^{13}C NMR δ 170.8 (Ac$\underline{O}$), 150.2 (Sn$\underline{C}$=CH$_2$), 127.6 (SnC=$\underline{C}$H$_2$), 63.9 (AcO$\underline{C}$H$_2$CH$_2$C), 39.7 (AcOCH$_2\underline{C}$H$_2$C), 29.0

($SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 57.3 Hz), 20.8 (<u>Ac</u>O), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.5 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 332.8 Hz).

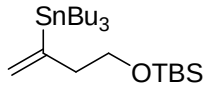
3.5.2.31 **(*E*)-*Tert*-butyldimethyl(4-(tributylstannyl)but-3-enyloxy)silane (3-38)**[58]



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

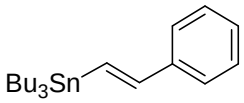
^{1}H NMR δ 5.95 ($SnC\underline{H}_A{=}C\underline{H}_B$, 2H, m, $J_{Sn\text{-}HA,B}$ = 73.5 Hz), 3.65 ($TBSOC\underline{H}_2CH_2CH$, 2H, t, J = 6.7 Hz), 2.34 ($TBSOCH_2C\underline{H}_2CH$, 2H, m, $J_{Sn\text{-}H}$ = 66.0 Hz), 1.53-0.82 ($(CH_3)_2$Si-<u>*t*Bu</u>, 9H, s and Sn-<u>nBu</u>, 27H, m), 0.04 ($(C\underline{H}_3)_2$Si-*t*Bu, 6H, s); ^{13}C NMR δ 145.8 (SnCH=<u>C</u>H), 129.7 ($Sn\underline{C}H{=}CH$, $J_{Sn\text{-}C}$ = 384.9 Hz), 62.8 ($TBSO\underline{C}H_2CH_2CH$), 41.4 ($TBSOCH_2\underline{C}H_2CH$, $J_{Sn\text{-}C}$ = 64.1 Hz), 29.0 ($SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 51.3 Hz), 25.9 ($(CH_3)_2SiC(\underline{C}H_3)_3$), 18.3 ($(CH_3)_2Si\underline{C}(CH_3)_3$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.3 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 320.7 Hz), -5.3 ($(\underline{C}H_3)_2SiC(CH_3)_3$).

3.5.2.32 ***Tert*-butyldimethyl(3-(tributylstannyl)but-3-enyloxy)silane (3-222)**[58]



^{1}H NMR δ 5.71 (SnC=C$\underline{H}_2$, 1H, d, J_{Sn-H} = 136.9 Hz, J = 2.6 Hz), 5.17 (SnC=C$\underline{H}_2$, d, 1H, J_{Sn-H} = 62.4 Hz, J = 2.7 Hz), 3.61 (TBSOC$\underline{H}_2$CH$_2$C, 2H, t, J = 7.7 Hz), 2.46 (TBSOCH$_2$C$\underline{H}_2$C, 2H, t, J = 7.0 Hz), 1.53-0.82 ((CH$_3$)$_2$Si-*t*$\underline{Bu}$, 9H, s and Sn-$\underline{nBu}$, 27H, m), 0.05 ((C$\underline{H}_3$)$_2$Si-*t*Bu, 6H, s); ^{13}C NMR δ 150.9 (Sn$\underline{C}$=CH$_2$), 127.1 (SnC=$\underline{C}$H$_2$, J_{Sn-C} = 19.2 Hz), 63.3 (TBSO$\underline{C}$H$_2$CH$_2$C), 44.5 (TBSOCH$_2$$\underline{C}H_2$C, J_{Sn-C} = 41.7 Hz), 29.0 (SnCH$_2$$\underline{C}H_2CH_2CH_3$, J_{Sn-C} = 19.8 Hz), 27.3 (SnCH$_2$CH$_2$$\underline{C}H_2CH_3$, J_{Sn-C} = 57.7 Hz), 25.6 ((CH$_3$)$_2$SiC($\underline{C}$H$_3$)$_3$), 18.0 ((CH$_3$)$_2$Si$\underline{C}$(CH$_3$)$_3$), 13.6 (SnCH$_2$CH$_2$CH$_2$$\underline{C}H_3$), 9.5 (Sn$\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 333.6 Hz), -5.3 (($\underline{C}$H$_3$)$_2$SiC(CH$_3$)$_3$).

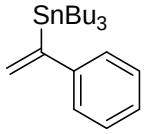
3.5.2.33 **(*E*)-Tributyl(styryl)stannane (3-233)**[61]



Stannane **3-233** was made in 74% isolated yield as an inseparable mixture of isomers (81:19, *trans*:*gem*) from alkyne **3-23** using the general procedure to provide 0.291 g as a clear oil.

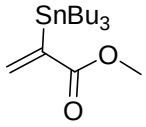
^{1}H NMR δ 7.44-7.17 (Ph<u>H</u>, 5H, m), 6.87 (SnC<u>H</u>$_A$=C<u>H</u>$_B$, 2H, s, $J_{Sn\text{-}HA,B}$ = 65.3 Hz), 1.53-0.88 (Sn-<u>nBu</u>, 27H, m); ^{13}C NMR δ 146.0 (SnCH=<u>C</u>H), 138.8 (Sn<u>C</u>H=CH), 129.4, 128.4 (2C), 127.4, 125.9(2C) (<u>Ph</u>), 29.1 ($SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$), 13.7 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.6 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 338.1 Hz).

3.5.2.34 **Tributyl(1-phenylvinyl)stannane (3-234)**[62]



^{1}H NMR δ 7.46-7.19 (Ph<u>H</u>, 5H, m), 6.07 (SnC=C<u>H</u>$_2$, 1H, d, $J_{Sn\text{-}H}$ = 128.1 Hz, J = 2.4 Hz), 5.46 (SnC=C<u>H</u>$_2$, 1H, d, $J_{Sn\text{-}H}$ = 60.0 Hz, J = 2.4 Hz),1.54-0.88 (Sn-<u>nBu</u>, 27H, m); ^{13}C NMR δ 154.5 (Sn<u>C</u>=CH_2), 146.6 (SnC=<u>C</u>H_2), 128.3 (2C), 126.8, 126.4 (2C), 126.3 (<u>Ph</u>), 29.1 ($SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$), 13.7 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.2 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 350.6 Hz).

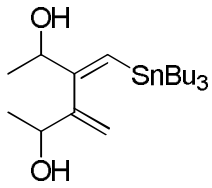
3.5.2.35 **Methyl 2-(tributylstannyl)acrylate (3-236)**[17]



Stannane **3-236** was made in 23% isolated yield as a single isomer from alkyne **3-24** using the general procedure to provide 0.086 g as a clear oil.

^{1}H NMR δ 6.85 (SnC=C$\underline{H}_2$, 1H, d, J_{Sn-H} = 109.3 Hz, J = 2.7 Hz), 5.19 (SnC=C$\underline{H}_2$, 1H, d, J_{Sn-H} = 54.0 Hz, J = 2.7 Hz), 3.69 (OC$\underline{H}_3$, 3H, s), 1.54-0.82 (Sn-nBu, 27H, m); ^{13}C NMR δ 180.5 (AcO), 145.8 (Sn$\underline{C}$=CH_2, J_{Sn-H} = 318.1 Hz), 139.6 (SnC=$\underline{C}H_2$, J_{Sn-H} = 12.9 Hz), 51.5 (O$\underline{C}H_3$), 28.8 ($SnCH_2\underline{C}H_2CH_2CH_3$, J_{Sn-H} = 19.5 Hz), 27.1 ($SnCH_2CH_2\underline{C}H_2CH_3$, J_{Sn-C} = 59.3 Hz), 13.5 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.9 (Sn$\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 345.3 Hz).

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



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

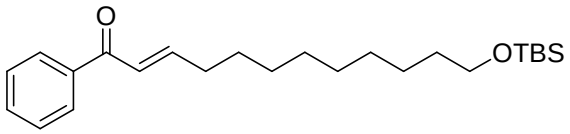
^{1}H NMR δ 5.93 (CC$\underline{H}$SnBu$_3$, s, 2H, J_{Sn-H} = 60.3 Hz), 5.13 (CC$\underline{H}_2$, s, 1H), 5.10 (CC$\underline{H}_2$, s, 1H), 4.88 (CC$\underline{H}_2$, s, 2H), 4.35 (C$\underline{H}$OH, m, 4H), 3.41 (CHO$\underline{H}$, m, 2H), 3.27 (CHO$\underline{H}$, m, 2H), 1.48-0.79 (Bu$_3$Sn, m, 54H) (C$\underline{H}_3$, m, 12H); ^{13}C NMR δ 162.5, 161.5, 154.4, 154.2 ($\underline{C}CH_2$) ($\underline{C}$CHSnBu$_3$), 128.5, 127.5 ($\underline{C}$HSnBu$_3$, J_{Sn-C} = 384.9 Hz), 114.9, 113.9 (CH$\underline{C}H_2$), 73.0, 72.4, 69.7, 68.7 ($\underline{C}$HOH), 29.1 ($SnCH_2\underline{C}H_2CH_2CH_3$, J_{Sn-C} = 15.1 Hz), 27.3 ($SnCH_2CH_2\underline{C}H_2CH_3$, J_{Sn-C} = 60.4 Hz), 22.6, 22.6, 21.6, 21.0 ($\underline{C}H_3$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.7, 10.6 (Sn$\underline{C}H_2CH_2CH_2CH_3$, J_{Sn-C} = 340.0 Hz).

3.5.3 Hydrostannation of alkyne 3-160 on a 12 mmol scale

Pd_2dba_3 (54.0 mg, 0.06 mmol), tricyclohexylphosphonium tetrafluoroborate (88.0 mg, 0.238 mmol) and diisopropylethylamine (62.0 mg, 0.476 mmol) were added successively to CH_2Cl_2 (100 mL) and the resulting mixture was stirred at rt for 10 minutes. Alkyne **3-160** (2.00 g, 11.9 mmol) was added and the reaction mixture was cooled to 0 °C. Bu_3SnH (4.16 g, 14.3 mmol) diluted in CH_2Cl_2 (20 mL) was added dropwise *via* a dropping funnel over 15 minutes. The reaction was then allowed to stir at 0 °C for 4 hours. The reaction mixture was concentrated and purified by silica gel chromatography (hexanes:ether, 5:1) to afford vinylstannanes **3-161** and **3-162** (96:4, 4.75 g, 87%) as an inseparable mixture.

3.5.4 Synthesis of enone 3-246

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



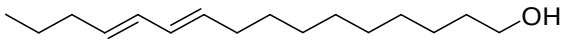
Pd_2dba_3 (4.0 mg, 0.004 mmol,), tricyclohexylphosphonium tetrafluoroborate (6.0 mg, 0.015 mmol) and diisopropylethylamine (3.9 mg, 0.030 mmol) were added successively to THF (10 mL) and the resulting mixture was stirred at rt for 10 minutes. Alkyne **100** (211 mg, 0.748 mmol) was added and the reaction was cooled to 0 °C. Bu_3SnH (0.898 mmol, 261 mg) diluted in THF (3 mL) was added dropwise *via* a dropping funnel over 5

minutes. The reaction was then allowed to stir at 0 °C for 2 h. Benzoyl chloride (137 mg, 0.972 mmol) and $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol) were then added and the reaction mixture was allowed to stir at reflux (65 °C) for 5 h. The reaction mixture was cooled, diluted with saturated aq. KF (~ 5 mL) and stirred for 30 minutes. The mixture was partitioned between Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organic layer were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford ketone 5 in 84% yield.

^{1}H NMR δ 7.89 (Ph<u>H</u>, 2H, d, J = 7 Hz), 7.50 (Ph<u>H</u>, 1H, t, J = 7 Hz), 7.41 (Ph<u>H</u>, 2H, t, J = 7 Hz), 6.93 (COC<u>H</u>$_B$=C<u>H</u>$_A$, AB of ABX_2, 2H, δ_A = 7.03, δ_B = 6.84, J_{AB} = 15.4 Hz, J_{AX} = 6.8 Hz), 3.56 (TBSOC<u>H</u>$_2$, 2H, t, J = 6.5 Hz), 2.08 (CHCHC<u>H</u>$_2$, 2H, q, J = 6.9 Hz), 1.46, 1.29 (CH_2(C<u>H</u>$_2$)$_7$$CH_2$, 14H, m), 0.86 (*t*<u>Bu</u>(CH_3)$_2$Si, 9H, s), 0.01 (*t*Bu(C<u>H</u>$_3$)$_2$Si, 6H, s); ^{13}C NMR δ 190.6, 149.9 (COCH=<u>C</u>H), 137.9(<u>Ph</u>, 1C), 132.4(<u>Ph</u>, 1C), 128.4 (<u>Ph</u>, 2C), 128.3 (<u>Ph</u>, 2C), 125.7 (CO<u>C</u>H=CH), 63.1 (TBSO<u>C</u>H_2CH_2), 32.8, 32.7, 29.4, 29.3, 29.2, 29.1, 28.1, 25.7, 25.9 ((<u>C</u>H_3)$_3$C(CH_3)$_2$Si), 18.2 ((CH_3)$_3$<u>C</u>(CH_3)$_2$Si), -5.4 ((CH_3)$_3$C(<u>C</u>H_3)$_2$Si); IR (neat) ν_{max} 3059, 2927, 2856, 1674, 1622, 1463, 1255, 1097, 835, 775, 694 cm^{-1}. Exact mass (EI) calcd for $C_{24}H_{40}O_2Si$: 388.2798, found: 388.2801.

3.5.5 Synthesis of pheromone 3-248

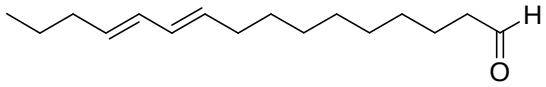
3.5.5.1 **(10*E*,12*E*)-Hexadeca-10,12-dien-1-ol (3-247)**[47]



To a round bottomed flask containing degassed DMF (3 mL) was added $Pd(MeCN)_2Cl_2$ (3.4 mg, 0.013 mmol) followed by *E*-1-iodo-1-pentene[45] (129 mg, 0.654 mmol). The mixture was stirred for 10 min before the addition of stannane **3-161** (mixed with 4% **3-162**, 360 mg, 0.788 mmol) and CuI (125 mg, 0.654 mmol). The reaction was allowed to stir at rt for 12 h. Saturated aqueous NH_4Cl containing 10% NH_4OH and ether were added to the flask, and the two phases were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexanes:ether, 5:1) to afford dienyl alcohol **6** as a waxy solid (148 mg, 0.622 mmol, 95%). m.p. 28-30 °C; lit[63] m.p. 34 °C.

^{1}H NMR δ 5.96 (m, 2H), 5.52 (m, 2H), 3.59 ($HOC\underline{H}_2$, t, 2H, J = 6.6 Hz), 2.0 ($C\underline{H}_2CH=CH-CH=CHC\underline{H}_2$, m, 4H), 1.54-1.25 ($C\underline{H}_2CH_2CH=CH-CH=CHCH_2(C\underline{H}_2)_7$, m, 16H), 0.86 ($C\underline{H}_3CH_2$, t, 3H, J = 7.3 Hz); ^{13}C NMR δ 132.3, 132.1, 130.5, 130.3 ($\underline{C}H=\underline{C}H-\underline{C}H=\underline{C}H$), 62.9 ($HO\underline{C}H_2$), 34.6, 32.7, 32.5, 29.5, 29.4, 29.1, 25.7, 22.5 ($\underline{C}H_2\underline{C}H_2CH=CH-CH=CH\underline{C}H_2(\underline{C}H_2)_7$), 13.7 ($\underline{C}H_3CH_2$).

3.5.5.2 **(10*E*,12*E*)-Hexadeca-10,12-dienal (3-248)**[48]



A round bottomed flask was charged with 100 mg of activated 3Å molecular sieves. PDC (296 mg, 0.786 mmol) was added followed by CH_2Cl_2 (4 mL) and dienyl alcohol **3-247** (125 mg, 0.524 mmol). The reaction mixture was stirred at rt for 2 h then filtered through a short plug of silica and concentrated to yield a yellow oil. Purification of the crude oil by column chromatography (hexanes:ether, 10:1) yielded aldehyde **3-248** as a colorless oil (123 mg, 99%).

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

Spectral data were in accord with literature data.

Chapter 4

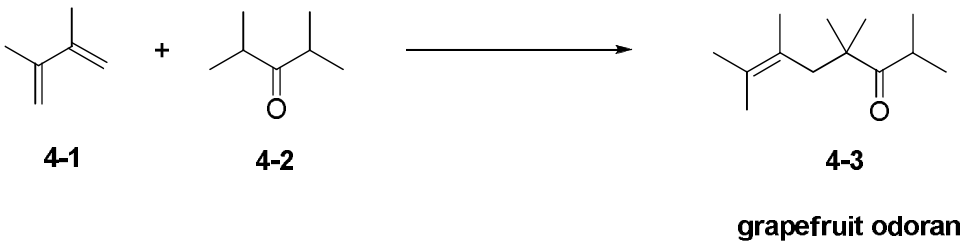
Synthesis of (*E*)-1-Tributylstannylbutadiene and Homologues *via* Hydrostannation Chemistry and their Applications

4.1 Introduction

4.1.1 General

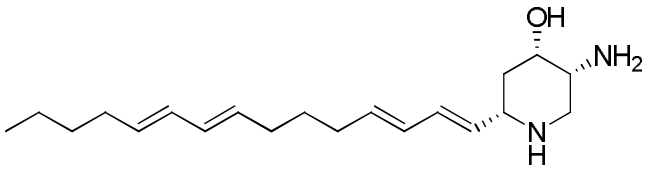
1,3-Dienyl moieties, also called butadienes, are present in many natural products and have been used in total syntheses of natural products.[1-4]

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



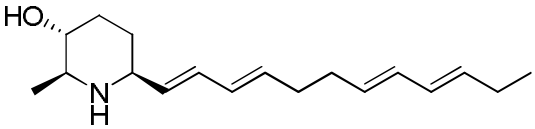
Scheme 4.1

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



4-4

pseudodistomin C



4-

corydendramine B

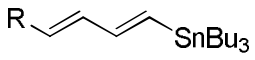
Figure 4.1 Natural products containing conjugated butadiene moieties

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

1,3-Butadienes can serve as intermediates (Scheme 4.1),[5] or be part of the final structure of a natural product (Figure 4.1).[6]

4.1.2 Synthesis of (E)-1-stannyl-1,3-dienes

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



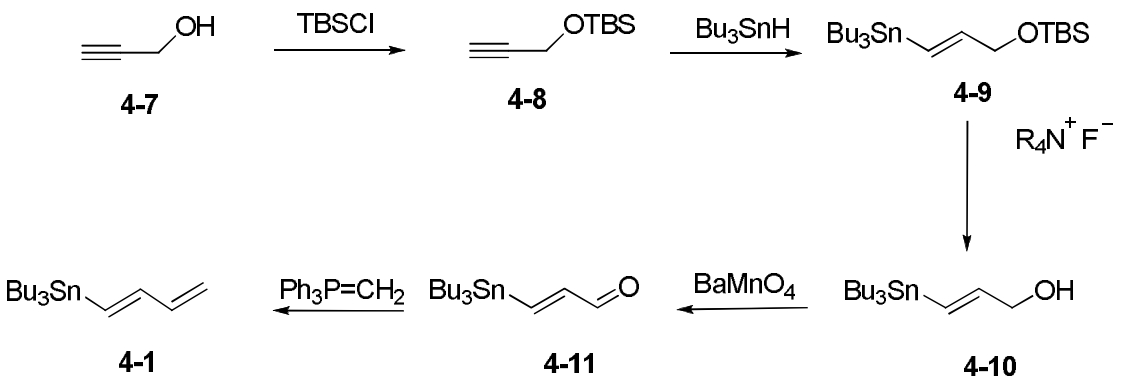
4-

Figure 4.2 (*E*)-1-Stannyl-1,3-butadiene homologue

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

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

The simplest of these building blocks is stannylbutadiene **4-12** (Scheme 4.2). The first synthesis of this butadiene was developed by Wender *et al.*[7]

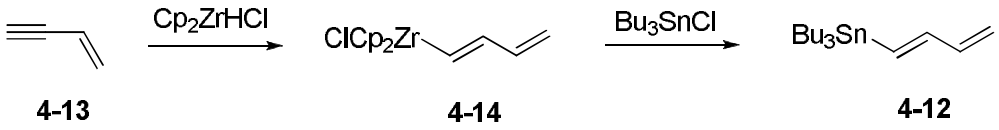


Scheme 4.2

Alcohol **4-7** was protected with a bulky group to provide high regioselectivity in the following hydrostannation reaction. Silyl ether **4-8** was subjected to free-radical hydrostannation to obtain (*E*)-vinylstannane **4-9**. Deprotection followed by oxidation of the primary alcohol afforded conjugated aldehyde **4-11**. Aldehyde **4-11** was subject to a Wittig reaction to furnish stannylbutadiene **4-12** in five steps (46% overall yield).[7]

A modified three-step version of this synthesis was developed by Angoh and Clive (65% overall yield).[8] The methodology did not require the use of bulky protection group to attain *trans*-vinylstannane **4-10** in good yields. This was made possible by performing the free-radical hydrostannation under thermodynamic conditions, which consist of adding excess Bu_3SnH and longer duration times.[9]

Another method involved hydrozirconation of enyne **4-13** developed by Fryzuk *et al.* (Scheme 4.3).[10]



4-13 **4-14** **4-12**

Scheme 4.3

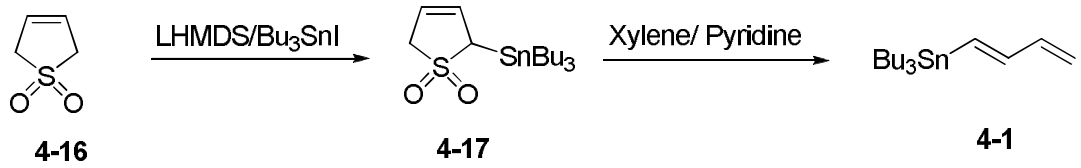
The chemoselectivity of this reaction is very high, even though hydrozirconation of alkene functionality is well established.[11] Complete preference of the triple bond over the double bond was observed. Also, *trans* isomer **4-14** was formed exclusively *versus* *geminal* isomer **4-15** shown in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

4-14 **4-15**

Figure 4.3 *Trans* and *geminal* zirconium butadienes

Zirconium butadiene **4-14** was then treated with Bu_3SnCl to afford stannylbutadiene **4-12** in two steps (75% overall yield). While effective, a drawback of this method is that enyne **4-13** is no longer commercially available.

A third method was developed by Gomez *et al*. (Scheme 4.4).[12]



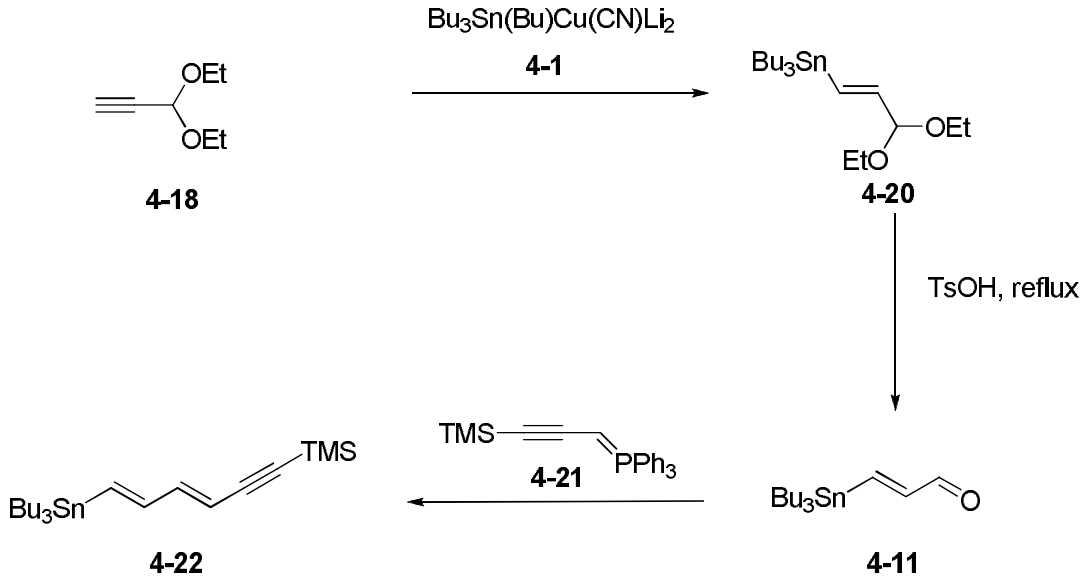
4-16 **4-17** **4-1**

Scheme 4.4

This methodology employed 2,5-dihydrothiophene *S,S*-dioxide **4-16** as a butadiene equivalent. The two-step synthesis began by stannylating *S,S*-dioxide **4-16** with Bu_3SnI in the presence of lithium hexamethyldisilazide (LHMDS) to give **4-17**. Sulfur dioxide was extruded from **4-17** in refluxing xylene to afford stannylbutadiene **4-12**. The presence of pyridine was found to be advantageous; it is thought to reduce the extent of acid-mediated polymerization.[12] This route is short but each step proceeds in only modest yield so the overall yield of diene **4-12** is rather low (25% overall yield).

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

Lipshutz *et al*. devised a route to synthesize 4-substituted-(*E*)-1-stannyl-1,3-dienes such as **4-22** (Scheme 4.5).

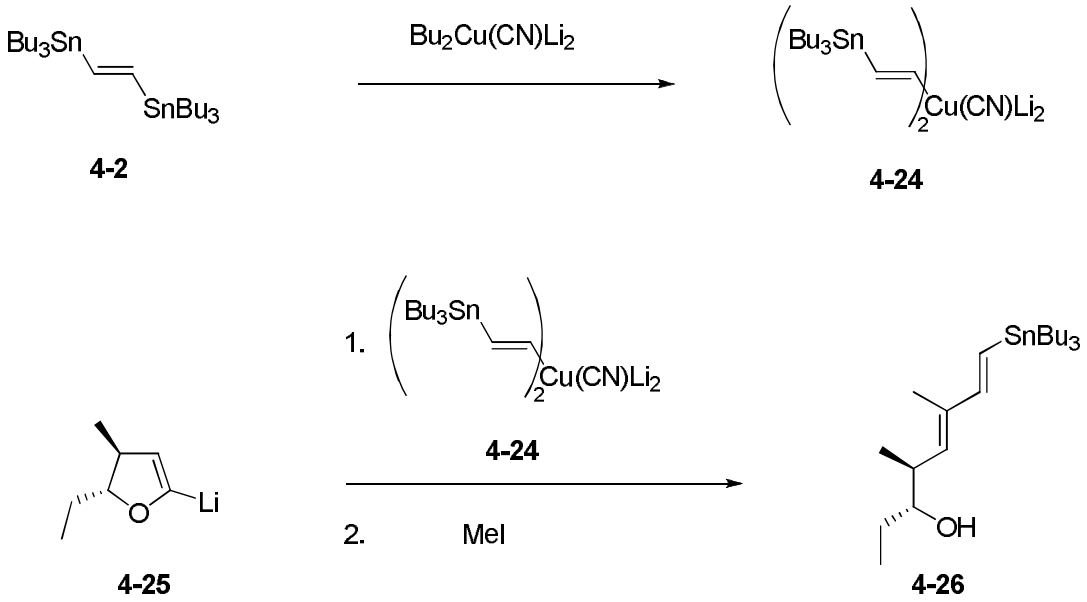


Scheme 4.5

Stannylbutadiene **4-22** was prepared by the addition of stannylcuprate **4-19** to acetylenic acetal **4-18** that afforded enal **4-11** after hydrolysis. Wittig coupling between ylide **4-21** and enal **4-11** afforded **4-22** in good yields with 90:10 *E*/*Z* selectivity.[13]

Stannylcupration of **4-18** was shown to exclusively afford the *trans* isomer by Quintard *et al.*[14]

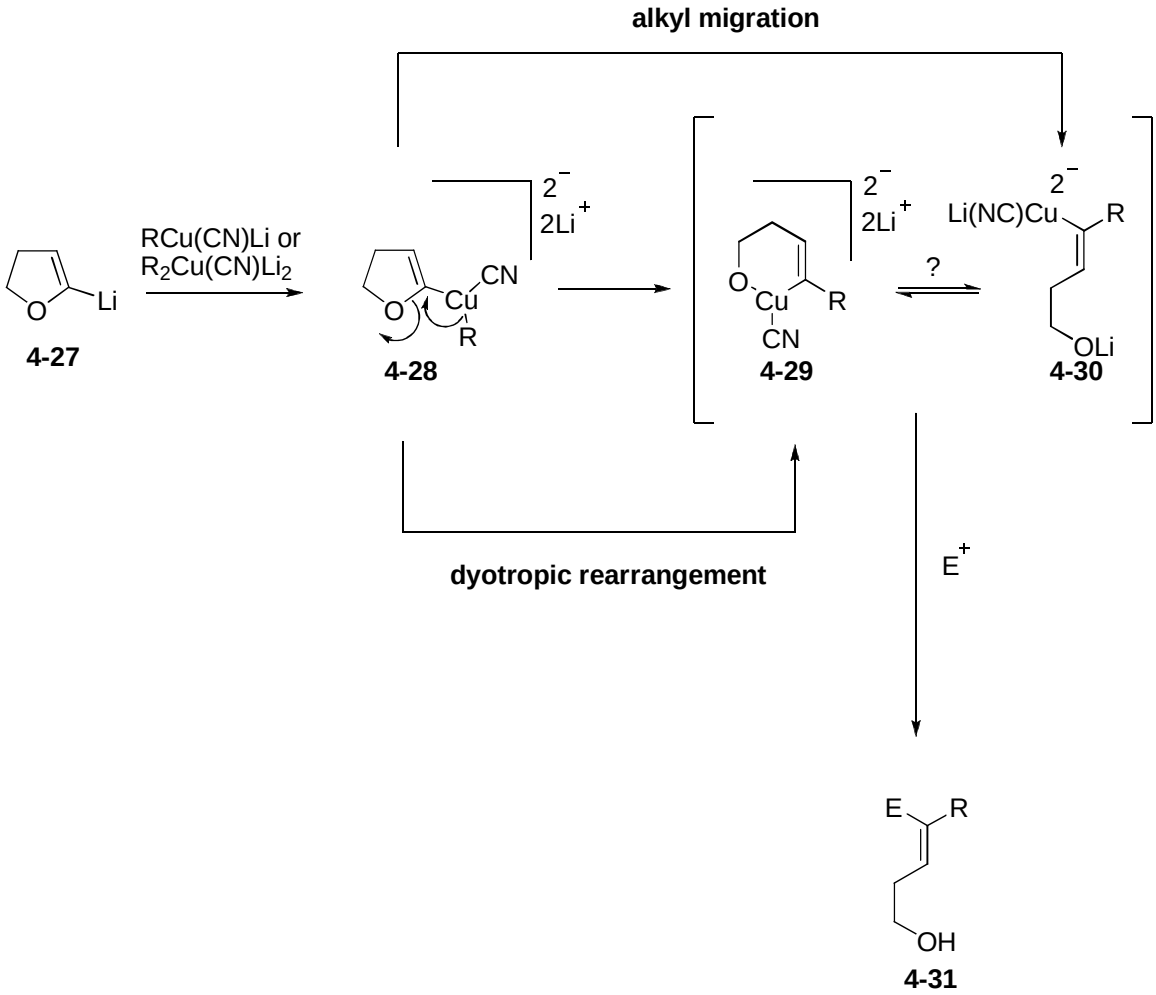
Pancrazi *et al.* utilized cuprate rearrangement to synthesize the desired stannylbutadiene **4-26** (Scheme 4.6).[15]



Scheme 4.6

Highly reactive stannylcuprate **4-24** was formed using a modified Lipshutz exchange method.[16] Stannylcuprate **4-24** was allowed to react with furan **4-25** which provided stannylbutadiene **4-26** in good yields.[15]

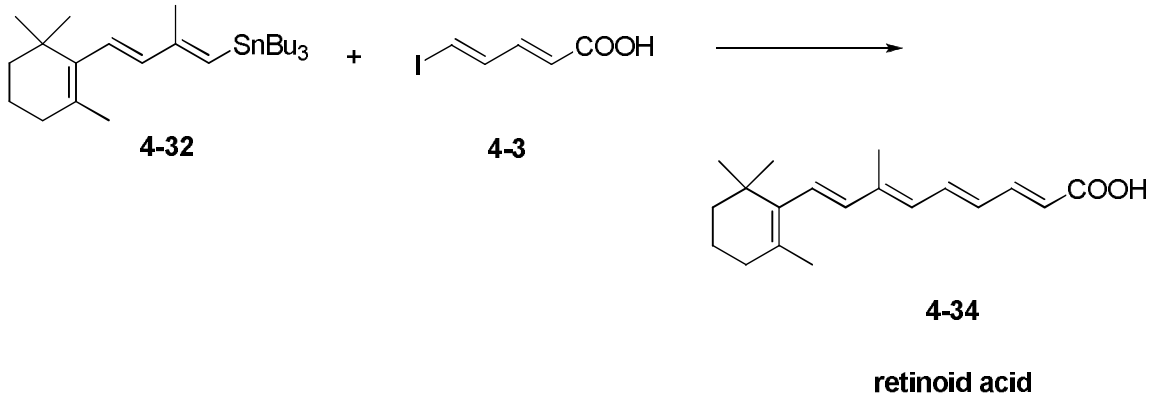
Cuprate rearrangement is believed to proceed *via* either a dyotropic rearrangement or an alkyl migration as shown in Scheme 4.7.[17]


alkyl migration
RCu(CN)Li or
R2Cu(CN)Li2
Li
O
4-27
2−
2Li+
CN
Cu
R
4-28
2−
2Li+
O
Cu
R
CN
4-29
?
2−
Li(NC)Cu
R
OLi
4-30
dyotropic rearrangement
E+
E
R
OH
4-31

Scheme 4.7

4.1.3 Application of (E)-1-stannyl-1,3-dienes

Retinoic acid receptors have been used for the treatment of dermatological diseases and certain cancers (Scheme 4.8).[18,19]



4-32 **4-3** **4-34**

retinoid acid

Scheme 4.8

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

Macrolide antibiotics have earned enormous devotion from many synthetic groups due to their wide therapeutic use in human and veterinary medicine.[21] Tylosin II **4-35** is

considered one of the most important early antibiotics. Many derivatives are being synthesized to overcome antibiotic resistant bacteria (Figure 4.4).

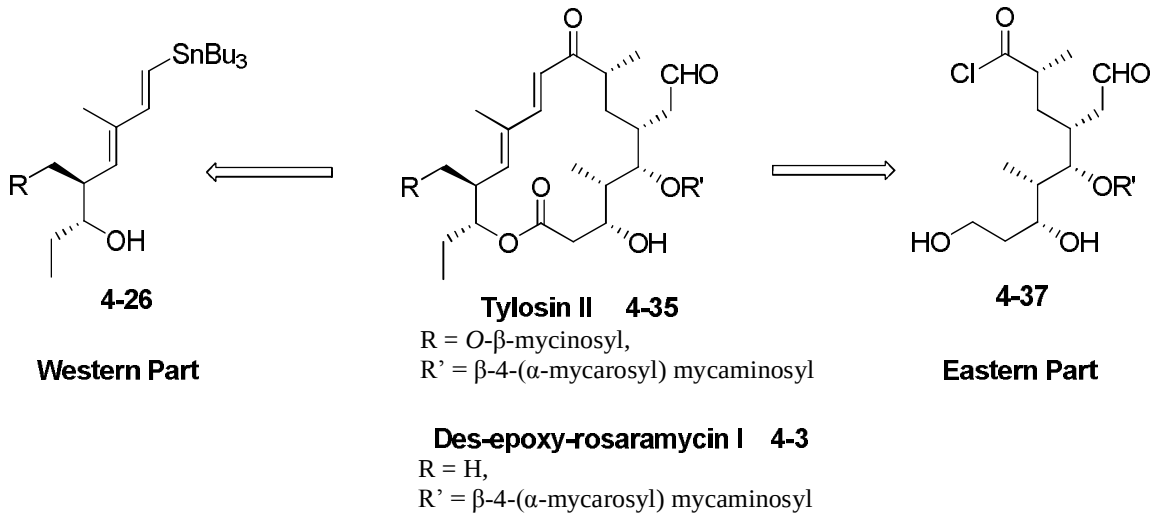
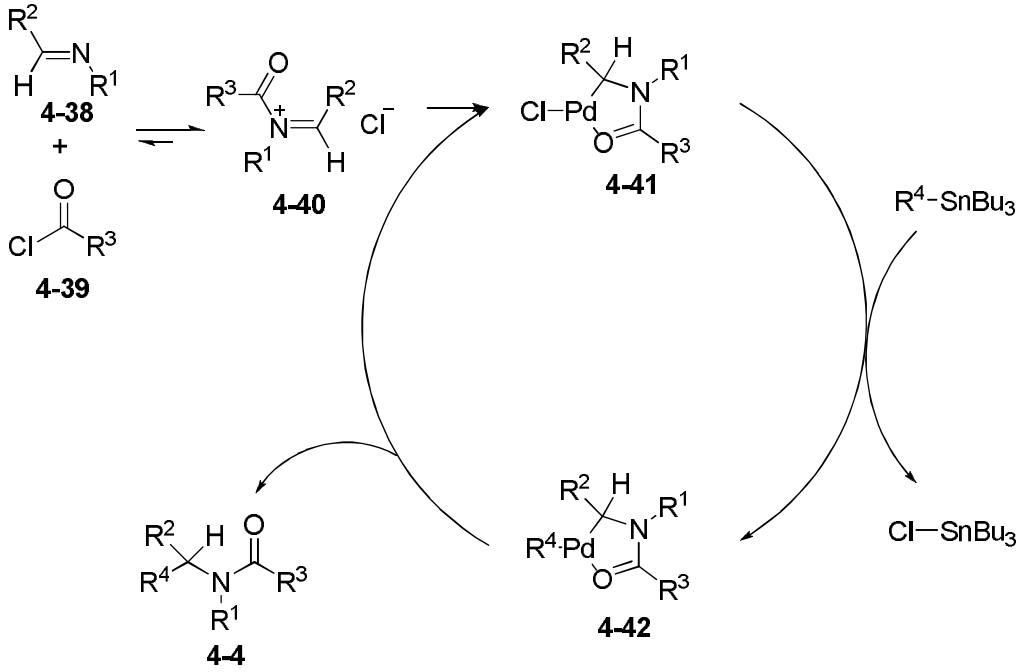


Figure 4.4 Retrosynthetic analysis of Tylosin II **4-35** and its derivative **4-36**

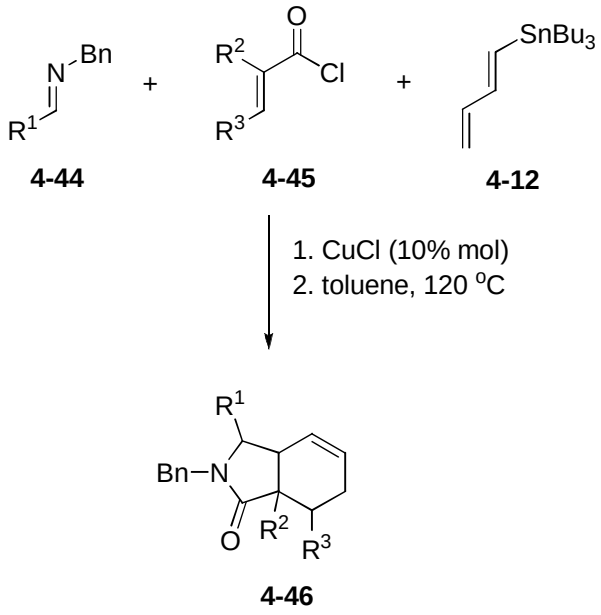
En route to synthesis of the Tylosin II derivative des-epoxy-rosaramycin I (**4-36**), western and eastern fragments were joined by cross-coupling of stannyldiene moiety **4-26**[15] and acyl chloride **4-37** moiety (Figure 4.4). More efforts are needed to finalize the total synthesis of this antibiotic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

An overwhelming majority of currently marketed medicinal compounds possess a nitrogen-containing heterocyclic skeleton.[23] Arndtsen *et al.* demonstrated one can perform a cross coupling between stannanes and an iminium salt formed *in situ* (Scheme 4.9).[24]



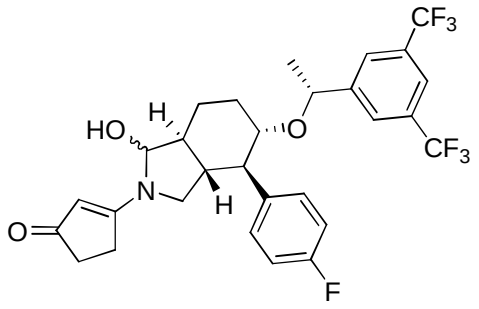
Scheme 4.9

As shown in Scheme 4.9, intermediate **4-41** transmetallates with stannane to form intermediate **4-42**. This intermediate underwent reductive elimination that afforded amide **4-43**. This process allowed for Malinakova *et al.* to develop a copper-catalyzed three-component coupling and Diels-Alder reaction that generated libraries of hexahydro-1*H*-isoindolones (Scheme 4.10).[25]

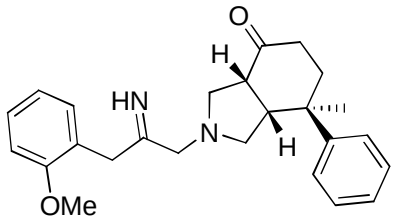


Scheme 4.10

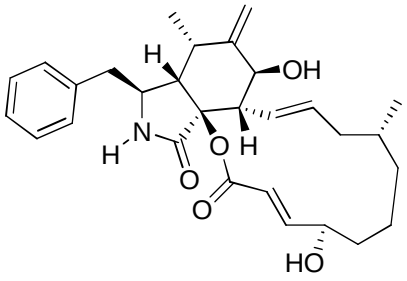
The isoindolones formed in these multi-component reactions served as skeletons for pharmacologically active heterocycles shown in Figure 4.5. Heterocycles **4-47** and **4-48** have been recognized as tachykinin NK1 receptor antagonists, which are useful in treating emesis, urinary incontinence, depression, and anxiety.[25] Macrocyclic hydroisoindolone cytochalasin **4-49** is a naturally occurring cytotoxic fungal metabolite.[25] The more recently discovered cytochalasin **4-50** exhibited inhibitory activity against HIV-1 protease (Figure 4.5).[25]



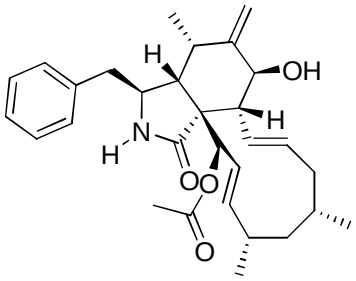
4-47



4-48



4-49



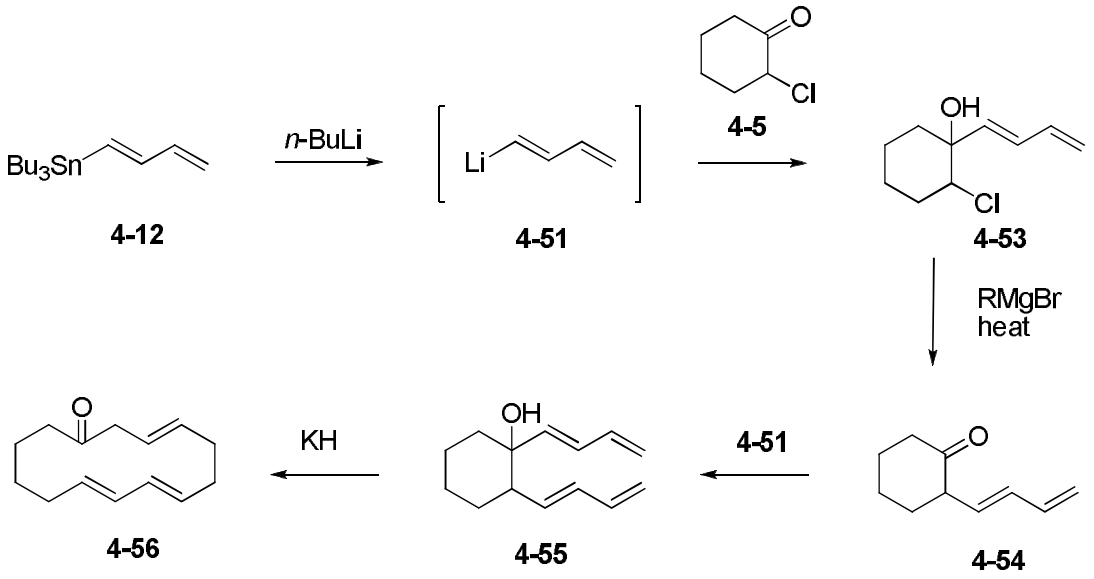
4-50

Figure 4.5 Pharmacologically active heterocycles that are formed from isoindolones

The ability to produce libraries of these heterocycles allows the screening of many derivatives, which is beneficiary for the pharmaceutical industry.

Medium and large ring compounds have continued, for over a century, to attain considerable attention.[7] Research involving these types of compounds has increased dramatically due to the expanding medicinal, theoretical, and commercial interest in naturally occurring macrocycles and non-natural systems such as the crown ethers and annulenes.[7]

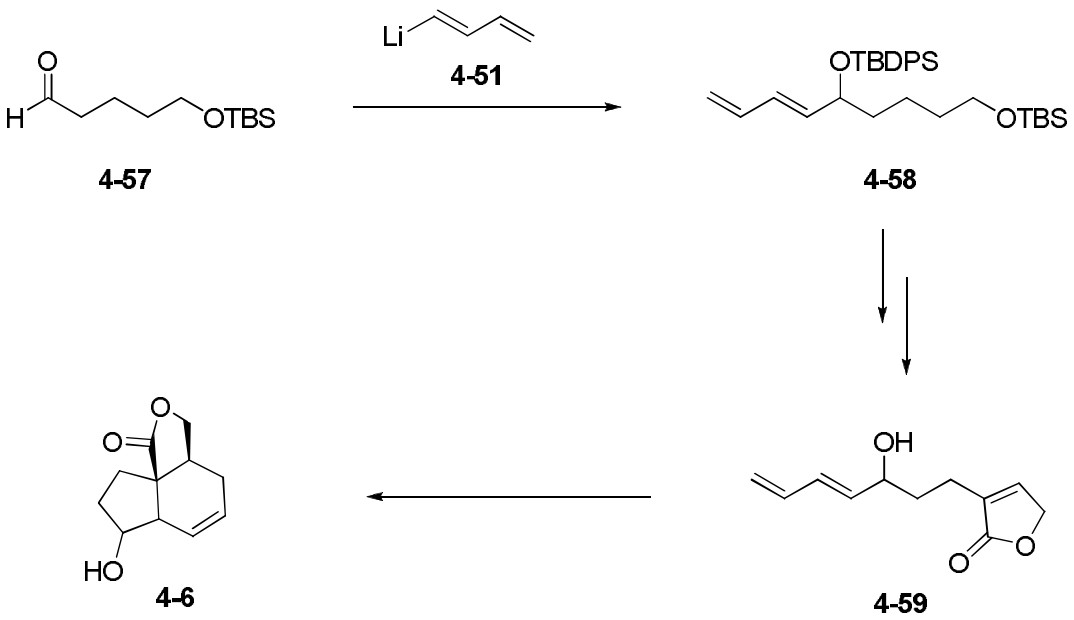
Syntheses of these macromolecules have been made easier by the methodology of Wender *et al.* (Scheme 4.11).[7]



Scheme 4.11

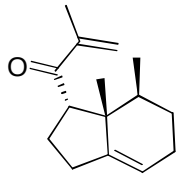
Upon treating stannylbutadiene **4-12** with *n*-BuLi, intermediate lithiobutadiene **4-51** was formed *via* transmetallation. This intermediate was used twice throughout the synthesis to lead to macrocyclic ketone **4-56**.[7]

Lithiobutadiene **4-51**, formed by transmetallation of stannylbutadiene **4-12**, has also proven to be useful in total syntheses of chiloscyphones (Scheme 4.12).[26]

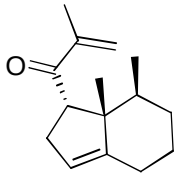


Scheme 4.12

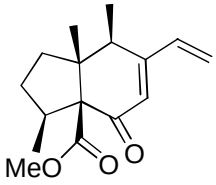
Intramolecular Diels-Alder reaction of dienyl alcohol **4-59** afforded intermediate **4-60**. Intermediate **4-60** is a skeleton for many chiloscyphones derivatives (Figure 4.6).



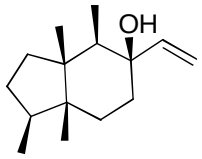
4-61



4-62



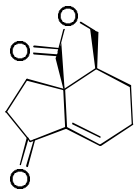
4-63



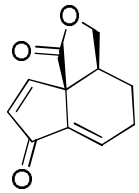
4-64

Figure 4.6 Biologically active chiloscyphones

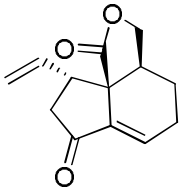
Chiloscyphones shown in Figure 4.6 possess biological activities, such as anticancer, fish-killing, and antifeedant properties. Having said this, other chiloscyphone derivatives (**4-65**, **4-66** and **4-67**) have shown activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Figure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



4-65



4-66



4-6

Figure 4.7 Chiloscyphones against methicillin-resistant *Staphylococcus aureus*

The tricyclic derivatives might be essential for anti-MRSA activity. These finding will contribute to new approach in developing anti-MSRA drugs.

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

4.2 Proposed Work

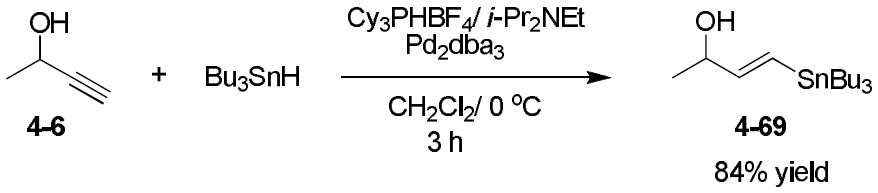
It seemed reasonable to develop a general and operationally simple route for providing (*E*)-1-stannyldienes **4-6** (Figure 4.2). This will be facilitated by applying our newly developed methodology in palladium-catalyzed hydrostannation of terminal alkynes (Chapter 3).

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

4.3 Results and Discussion

4.3.1 Synthesis of stannylbutadiene 4-12

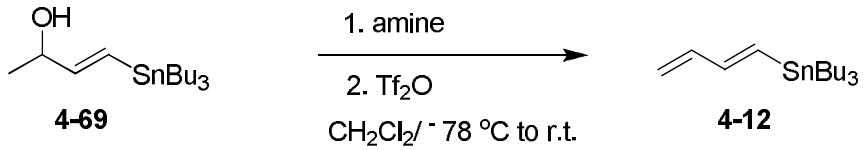
The synthesis of the simplest stannylbutadiene **4-12** began with propargyl alcohol **4-68**. As shown in chapter 3, palladium-catalyzed hydrostannation of terminal alkyne **4-68** using our procedure afforded *trans*-vinylstannane **4-69** in an excellent isolated yield of 84%.[27] This alcohol is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



Scheme 4.13

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

Elimination of the hydroxyl group, to afford stannylbutadiene **4-12**, was feasible by transforming the hydroxyl group into a good leaving group (Table 4.1). Trifluoromethanesulfonic anhydride (Tf_2O)/amine base were quickly screened to accomplish this transformation.



Scheme 4.14

Table 4.1 Amines screened for optimal dehydration conditions

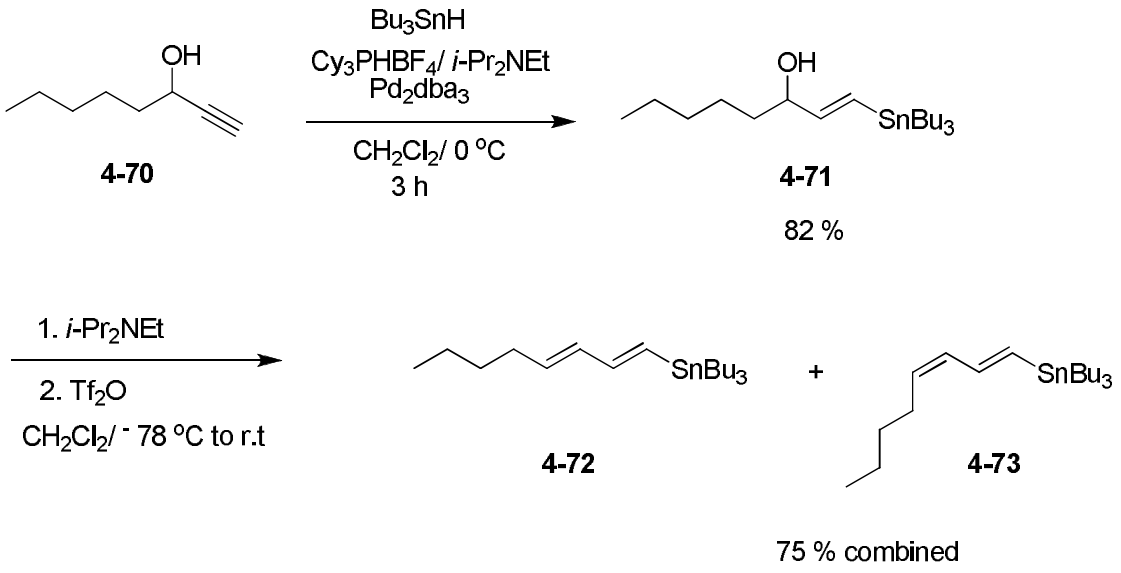
Entry	base	isolated yield of **4-12** (%)
1	2,6-lutidine	complex mixture
2	Et_3N	30[a]
3	*i*-Pr_2NEt	80

[a] Combined yield with other inseparable stannyl materials.

Attempts to dehydrate vinylstannane **4-69** failed when using Tf_2O and 2,6-lutidine; a complex mixture was observed instead. Stannylbutadiene **4-12** was obtained in 30% isolated yield when Et_3N was used as base, but other non-separable stannyl materials accompanied stannylbutadiene **4-12**. The dehydration process proceeded cleanly when using *i*-Pr_2NEt (Hünig's base) to afford stannylbutadiene **4-12** in 80% isolated yield (Scheme 4.14). It is important to note that it was necessary to add the base first. Formation of any TfOH will lead to protodestannylation of the product. The presence of excess base eliminates the possibility of any protodestannylation occurring. Pure stannyldiene **4-12** obtained only if pure vinylstannane **4-69** was used.

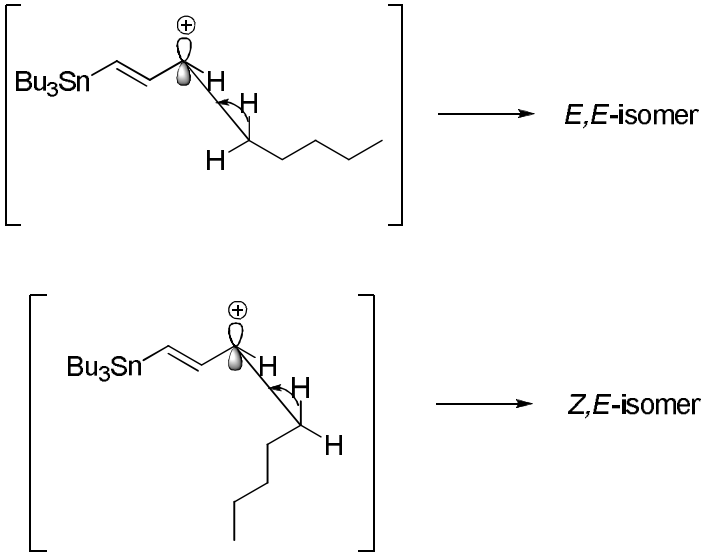
4.3.2 Synthesis of other homologues

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



Scheme 4.15

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

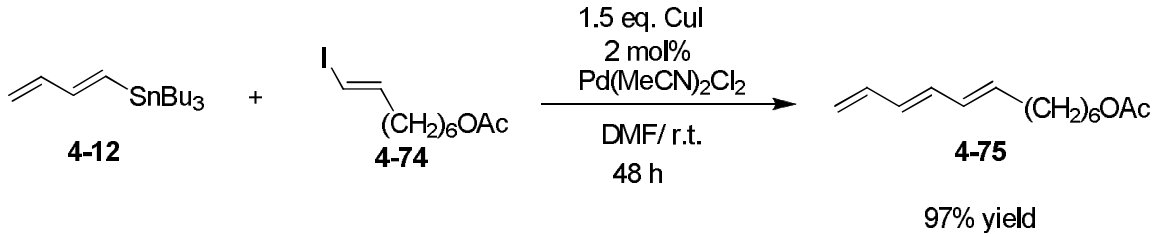


Scheme 4.16

Further optimization is required to achieve complete selectivity for the *E*,*E* diene isomer and generality in substrates through this methodology.

4.3.3 Application of stannylbutadiene 4-12

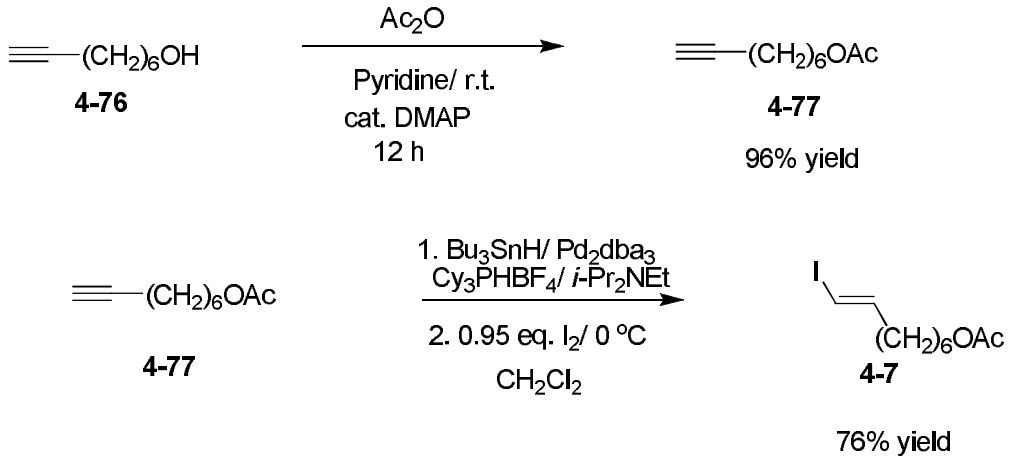
To illustrate an application of stannylbutadiene **4-12**, it was used as part of a convergent synthesis of grapevine sex pheromone **4-75** (Scheme 4.17).[28]



Scheme 4.17

Stannylbutadiene **4-12** was coupled with vinyl iodide **4-74** to provide sex pheromone **4-75** in 97% isolated yield. In contrast to a literature report with 8 linear steps involving hydroalumination/iodination, Sonigashira coupling and Wittig olefination,[28] this is the most convergent synthesis of this pheromone.

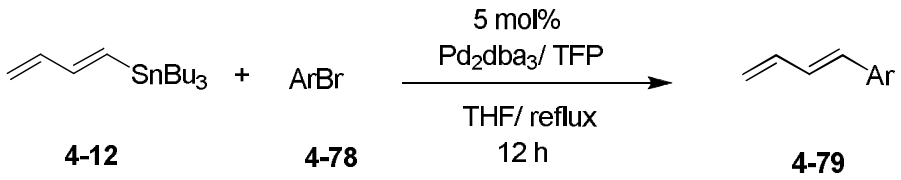
Coupling partner vinyl iodide **4-74** was prepared conveniently in one pot from the corresponding alkyne (Scheme 4.18).



Scheme 4.18

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

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



Scheme 4.19

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

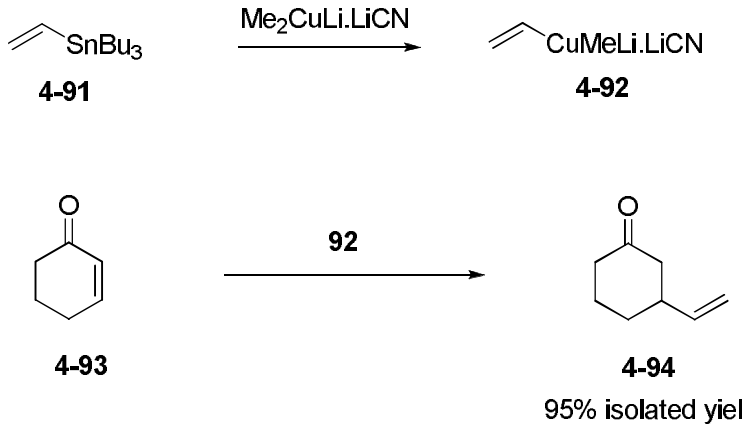
4-80 **4-8**

95% 92%

Figure 4.8 1-Arylbutadienes **4-80** and **4-81**

Another application was a synthesis of the red-bollworm moth sex pheromone **4-83** (Table 4.2), which contains a terminal diene moiety.[33] Previous syntheses include; coupling of dienol phosphates with Grignard reagents under iron catalysis,[34] palladium-catalyzed deoxygenation of enediols,[35] elimination of homoallylic sulfide,[36] alkylation of 3-sulfolenes,[37] Pummerer rearrangement,[38] tellurolate-induced 1,4-elimination of 1,4-dibromo 2-enes,[39] elimination of 1,4-dibenzenesulfonyltrimethylsilane,[40] β-elimination of β-hydroxy selenide[41] and Wittig olefination reaction.[42]

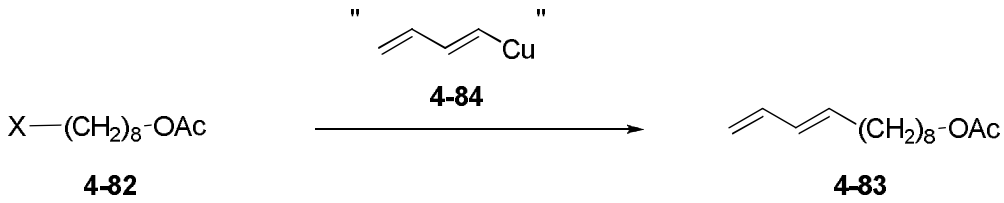
Initially, copper chemistry was used to perform the required coupling for installing the diene moiety. Lipshutz *et al.* have shown the ability of vinylstannanes to transmetallate with cuprates to generate reactive vinylcuprates that can add to enones effectively (Scheme 4.20).[16]

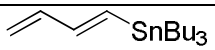
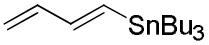
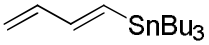
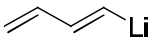
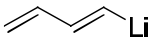


Scheme 4.20

Different leaving groups and copper species were screened to facilitate the desired coupling (Table 4.2).

Table 4.2 Coupling of dienyl cuprate **4-84**

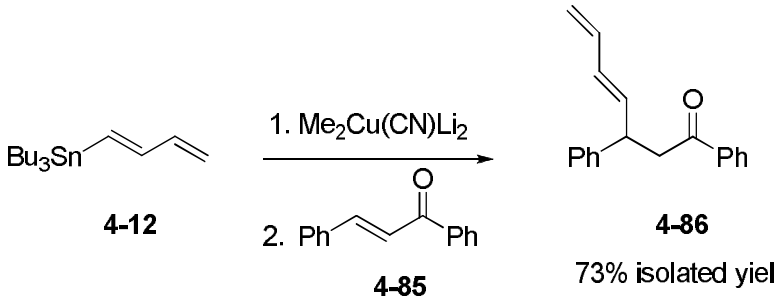


Entry (alkyl acetate)	source of copper reagent (**4-84**)	leaving group (X)	isolated yield (%)
1 (**4-88**)	 $Me_2Cu(CN)Li_2$	Br	0
2 (**4-89**)	 $Me_2Cu(CN)Li_2$	OTf	0
3 (**4-90**)	 $Me_2Cu(CN)Li_2$	I	60[a]
4 (**4-90**)	 CuCN	I	25[b]
5 (**4-90**)	 $CuBr.SMe_2$	I	0[b]

[a] Combined yield with methyl transfer product in 1:1 ratio which is inseparable from **4-83**.
[b] 2 Equivalents of lithiobutadiene was used.

Initial trials (1,2) proved to be fruitless in attaining product **4-83**. Bromoacetate **4-88** and triflate acetate **4-89** were unable to provide any coupling product using the method by

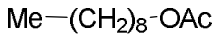
Lipshutz *et al.* where a highly reactive copper intermediate reacts with electrophiles. It was uncertain if "dienyl cuprate" species **4-84** was forming *in situ*. To confirm its formation, we decided to mimic the conditions Lipshutz *et al.* used, which was adding the formed cuprate to an α,β-unsaturated ketone. Chalcone, as the electrophile, was added to the supposedly formed dienyl cuprate **4-84** (Scheme 4.21).



Scheme 4.21

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

After confirming the presence of dienyl cuprate **4-84**, it was used in attempted couplings with iodoacetate **4-90**. Alkyl iodides are soft electrophiles, which can promote couplings with soft nucleophiles such as vinylcuprate **4-84**. The formation of coupling product **4-83** was observed; unfortunately, the coupling was accompanied with methyl transfer product **4-87** in a 1:1 ratio (Figure 4.9).

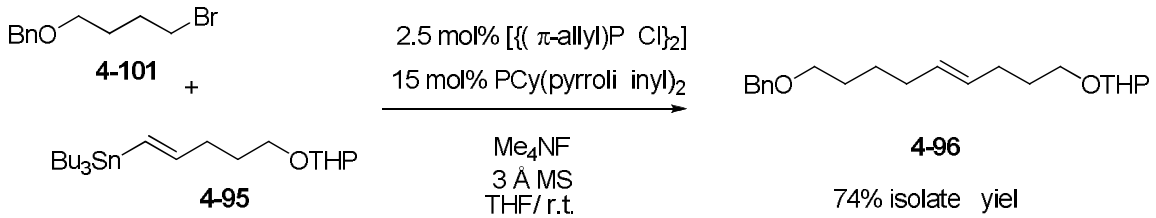


4-87

Figure 4.9 Methyl transfer product **4-87**

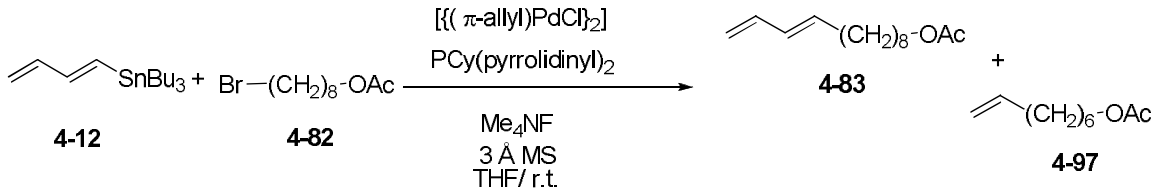
This observation suggests that methyl transfer is as fast as dienyl transfer when coupling with iodoacetate **4-90**. This result proved to be problematic since compounds **4-83** and **4-87** are inseparable by silica gel chromatography. To eliminate the competing methyl transfer, cuprates in trials 4 and 5 were made through the traditional method by adding two equivalents of alkenyllithium to copper. The reaction did proceed as anticipated in trial 4, but the less reactive cuprate resulted in a dismal yield of 25%. Trial 5 using $CuBr \cdot SMe_2$ instead of CuCN did not produce any product at all.

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



Scheme 4.22

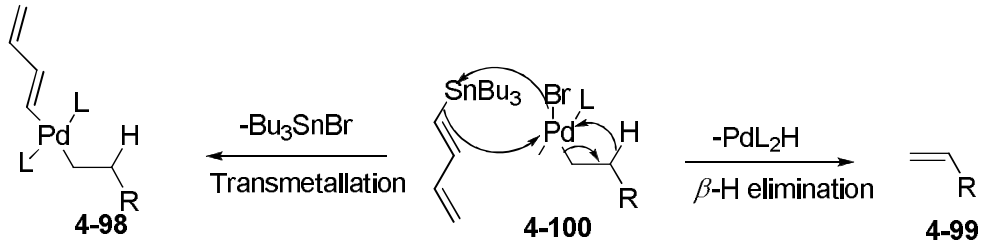
Competing β-hydride elimination was minimized by using electron rich phosphine ligands around the palladium. The same methodology was applied to the synthesis of pheromone **4-83** (Scheme 4.23).



4-12 **4-82** **4-83** **4-97**

Scheme 4.23

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



4-98 **4-100** **4-99**

Scheme 4.24

The conditions were optimized to minimize the formation of β-hydride elimination by-product **4-97** (Table 4.3).

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

entry	equivalents of **4-12**	palladium mol %	phosphine mol %	Solvent/ temperature	**4-83** : **4-97** ratio[a]	
1	1.1	2.5	15	THF/rt	47	53
2	1.1	2.5	15	THF/reflux	26	74
3	1.1	2.5	30	THF/rt	65	35
4	2.0	7.5	45	THF/rt	69	31
5	2.0	10	60	THF/rt	85	15
6	2.0	10	60	MTBE/rt	70	30
7	2.0	15	90	THF/rt	72	28

[a] Determined by ^{1}H NMR analysis of crude reaction mixture

Using the same conditions reported by Fu *et al.*[43] (trial 1, stannane (1.1 equivalents), phosphine (15 mol %)/palladium (2.5 mol %), 6:1 ratio, rt), a 1:1 mixture of coupling product **4-83** and β-hydride by-product **4-97** was observed. Increasing the temperature to 66 ^{o}C (trial 2) favoured the formation of the β-hydride by-product **4-97** in a 3:1 ratio. Increasing the phosphine/palladium ratio from 6:1 to 12:1 (trial 3) favoured the formation of the coupling product **4-83** in a 2:1 ratio. Increasing the loading of the stannane to two equivalents (trial 4) favoured the coupling product **4-83** in a 2:1 ratio. Solvent MTBE, used by Fu *et al.* in some of their reactions, did not show any advantages. After

numerous trials, pheromone **4-83** was obtained in 89% combined yield with **4-97** in a ratio of 85:15 (trial 5). Unfortunately, **4-83** and **4-97** are inseparable by silica gel chromatography. Further optimizations are needed to make this synthesis efficient.

4.4 Summary

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

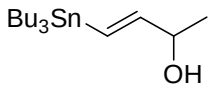
4.5 Experimental

4.5.1 General experimental

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

4.5.2 Synthesis of stannylbutadiene 4-12

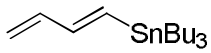
4.5.2.1 **(*E*)-4-(Tributylstannyl)but-3-en-2-ol (4-69)**[44]



Pd_2dba_3 (0.139 g, 0.149 mmol), tricyclohexylphosphonium tetrafluoroborate (0.219 g, 0.596 mmol) and Hünig's base (0.154 g, 1.20 mmol) were added successively to CH_2Cl_2 (200 mL) and the resulting mixture was stirred at rt for 15 min. 3-Butyn-2-ol was added (2.10 g, 29.9 mmol) and the reaction was cooled to 0 ^oC. Bu_3SnH (10.45 g, 35.9 mmol) diluted in CH_2Cl_2 (50 mL) and was added dropwise *via* a dropping funnel over 45 min. The reaction was then allowed to stir at 0 ^oC for 3 h. The reaction mixture was concentrated and purified by silica gel chromatography (7/1 : hexane/ether) to afford vinylstannane **4-69** in 84% (9.07 g) isolated yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (SnC$\underline{H}_A$=C$\underline{H}_B$, AB of ABX, 2H, δ_A = 6.10, δ_B = 6.04, J_{AB} = 19.2 Hz, J_{BX} = 4.3 Hz, $J_{Sn\text{-}H_A}$ = 69 Hz, $J_{Sn\text{-}H_B}$ = 66 Hz), 4.24 ($CH_3C\underline{H}$, m, 1H), 1.47-0.79 ($C\underline{H}_3CH$, Sn-nBu, 30H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0 (SnCH=$\underline{C}$H), 126.4 (Sn$\underline{C}$H=CH), 71.2 ($CH_3\underline{C}H$, $J_{Sn\text{-}C}$ = 62.4 Hz), 28.9 ($SnCH_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 20.4 Hz), 27.1 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}C}$ = 53.4 Hz), 23.0 ($\underline{C}H_3CH$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.3 (Sn$\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}C}$ = 339.6 Hz).

4.5.2.2 **(*E*)-1-Tributylstannyl-1,3-butadiene (4-12)**[7]



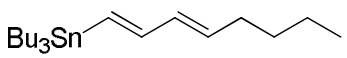
To a flame-dried round-bottomed flask containing CH_2Cl_2 (150 mL) was added (*E*)-4-(tributylstannyl)but-3-en-2-ol **4-69** (8.00 g, 22.2 mmol) followed by Hünig's base (12.88 g, 99.6 mmol) and the mixture was cooled to $^-$78 ^{o}C. Triflic anhydride (9.36 g, 33.16 mmol) was added dropwise and the reaction was stirred for 3 h at $^-$78 ^{o}C then allowed to rise to room temperature (2 h). The reaction mixture was passed through a short silica plug (5 g) and concentrated then purified by silica gel (20 g) chromatography (hexane as the eluant) to afford the corresponding vinylstannane **4-12** as a colourless oil in 80 % (6.09 g) isolated yield.

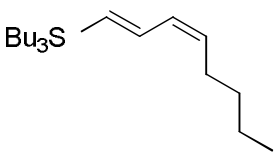
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (SnCH=C$\underline{H}$-CH=CH_2, dd, 1H, J = 18.7 Hz, J = 9.8 Hz, $J_{Sn\text{-}H}$ = 59.3 Hz), 6.31 (SnCH=CH-C$\underline{H}$=CH_2, dt, 1H, J = 16.9 Hz, J = 9.9 Hz), 6.24 (SnC$\underline{H}$=CH-CH=CH_2, d, 1H, J = 18.7 Hz, $J_{Sn\text{-}H}$ = 67.4 Hz), 5.13 (SnCH=CH-CH=C$\underline{H}_2$, d, 1H, J = 17.9 Hz), 5.02 (SnCH=CH-CH=C$\underline{H}_2$, d, 1H, J = 9.8 Hz) 1.56-0.86 (Sn-nBu, 27H,

m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5 (SnCH=<u>C</u>H-CH=CH_2), 140.2 (SnCH=CH-<u>C</u>H=CH_2, J_{Sn-C} = 67.9 Hz), 134.7 (Sn<u>C</u>H=CH-CH=CH_2, J_{Sn-C} = 367.8 Hz), 115.9 (SnCH=CH-CH=<u>C</u>H_2), 29.2 ($SnCH_2\underline{C}H_2CH_2CH_3$, J_{Sn-C} = 22.6 Hz), 27.4 ($SnCH_2CH_2\underline{C}H_2CH_3$, J_{Sn-C} = 52.8 Hz), 13.8 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.5 (Sn<u>C</u>$H_2CH_2CH_2CH_3$, J_{Sn-C} = 333.9 Hz).

4.5.3 Synthesis of other homologues

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

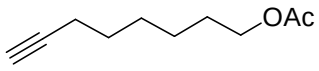




^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81(dd, 1H, J = 18.7 Hz, J = 10.5 Hz), 6.48 (dd, 1H, J = 18.8 Hz, J = 9.8 Hz), 6.17 (d, 1H, J = 18.7 Hz), 6.07-5.93 (m, 3H), 5.65 (m, 1H), 5.35 (m, 1H), 2.21 (q, 1H, J = 6.3 Hz), 2.07 (q, 1H, J = 6.6 Hz), 1.53-0.85 (m, 41H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 142.1, 134.0, 133.6, 133.3, 131.7, 131.1, 130.4, 32.1, 31.7, 31.3, 29.0, 27.3, 27.2, 22.2, 22.1, 13.8, 13.6, 9.3, 9.3.

4.5.4 Synthesis of pheromone 4-75

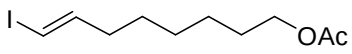
4.5.4.1 **Oct-7-ynyl acetate (4-77)**[4]



To a flame-dried round-bottomed flask was added 7-octyn-1-ol (0.754 g, 5.98 mmol) followed by pyridine (4.00 mL, 49.5 mmol), Ac_2O (1.25 mL, 13.2 mmol) and a crystal of DMAP. The reaction was allowed to stir at room temperature for 15 h. The reaction mixture was diluted with water (50 mL) and extracted with hexane (100 mL). The organic layer was washed with 1M HCl (3 x 50 mL), saturated $NaHCO_3$ (2 x 75 mL), dried with Na_2SO_4 and concentrated to give a yellow residue. The resulting residue was purified by silica gel chromatography (10/1 : hexane/ether) to afford 0.966 g of oct-7-ynyl acetate **4-75** as a colourless oil in 96% isolated yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 ($C\underline{H}_2OCOCH_3$, t, 2H, J = 6.6 Hz), 2.09 ($HCCC\underline{H}_2$, t, 2H, J = 6.6 Hz), 1.94 ($CH_2OCOC\underline{H}_3$, s, 3H), 1.85 ($\underline{H}CCCH_2$, s, 1H), 1.59-1.16 ($CCH_2(C\underline{H}_2)_4CH_2O$, m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 ($O\underline{C}OCH_3$), 84.2 ($HC\underline{C}CH_2$), 68.2 ($H\underline{C}CCH_2$), 64.2 ($\underline{C}H_2OCOCH_3$), 28.3, 28.2, 25.3, 20.8, 18.1 ($C\underline{C}H_2(\underline{C}H_2)_4CH_2OCO\underline{C}H_3$).

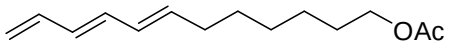
4.5.4.2 **(*E*)-8-Iodooct-7-en-1-yl acetate (4-74)**[45]



Pd_2dba_3 (12.8 mg, 0.014 mmol), tricyclohexylphosphonium tetrafluoroborate (20.6 mg, 0.056 mmol) and Hünig's base (14.9 mg, 0.115 mmol) were added successively to CH_2Cl_2 (40 mL) and the resulting mixture was stirred at rt for 15 min. Octynyl acetate **4-69** was added (0.484 g, 2.88 mmol) and the reaction was cooled to 0 ^oC. Bu_3SnH (1.00 g, 3.46 mmol) diluted in CH_2Cl_2 (10 mL) was added dropwise *via* a dropping funnel over 10 min. The reaction was then allowed to stir at 0 ^oC for 3 h. Iodine (0.694 g, 2.74 mmol) was diluted in CH_2Cl_2 (15 mL) and added dropwise but quickly *via* a dropping funnel within 2 min. The reaction mixture was passed through a 10 g silica plug (washed with ether) and concentrated. The organic residue was diluted with ether (100 mL) and washed with saturated $Na_2S_2O_3$ solution (1 x 80 mL), and saturated KF solution (2 x 80 mL), dried over Na_2SO_4 and concentrated. The resulting oil was purified by silica gel chromatography (10/1 : hexane/ ether) to afford 0.650 g of *trans*-vinyl iodide **4-74** (*trans*:*gem*, 99:1) as a colourless oil in 76 % isolated yield.

^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (ICH=C$\underline{H}$CH_2, dt, 1H, J = 14.4 Hz, J = 7.2 Hz), 5.94 (IC$\underline{H}$=CHCH_2, d, 1H, J = 14.4 Hz), 4.01 (C$\underline{H}_2$OCOCH_3, t, 2H, J = 6.7 Hz), 2.01 (ICH=CHC$\underline{H}_2$, q, 2H, J = 6.8 Hz), 2.00 (CH_2OCOC$\underline{H}_3$, s, 3H), 1.62-1.28 (CHCH_2(C$\underline{H}_2$)$_4$CH_2O, m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (O$\underline{C}$OCH_3), 146.4 (ICH=$\underline{C}$HCH_2), 74.4 (I$\underline{C}$H=CHCH_2), 64.4 ($\underline{C}H_2$OCOCH_3), 35.8 (ICH=CH$\underline{C}H_2$), 28.4, 28.1, 25.6, 21.0 (CHCH_2($\underline{C}H_2$)$_4$CH_2OCO$\underline{C}H_3$).

4.5.4.3 **(7*E*,9*E*)-Dodeca-7,9,11-trienyl acetate (4-75)**[28]

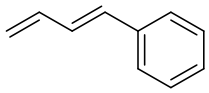


A round-bottomed flask containing degassed DMF (3 mL) was charged with $Pd(MeCN)_2Cl_2$ (1.3 mg, 0.005 mmol). (*E*)-8-iodooct-7-enyl acetate (0.073 g, 0.246 mmol) was then added followed by stirring for 10 min. Stannane **4-12** (0.127 g, 0.369 mmol) was added next, followed by CuI (0.070 g, 0.369 mmol). The reaction was allowed to stir over 48 h at room temperature. 10% NH_4OH/ NH_4Cl solution (25 mL) and ether (25 mL) were added to the flask, and the two phases were separated. The aqueous layer was extracted with ether (2 x 25 mL). All organic solutions were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (5/1 : hexane/ether) to afford 0.053 g of pheromone **4-75** as a colourless oil in 97% isolated yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (CH_2=C<u>H</u>-CH=CH-CH=CH-CH_2
, dt, 1H, J = 16.8 Hz, J = 9.8 Hz), 6.22-5.99 (CH_2=CH-C<u>H</u>=C<u>H</u>-C<u>H</u>=CH-CH_2, m, 3H), 5.69 (CH_2=CH-CH=CH-CH=C<u>H</u>-CH_2, dt, 1H, J = 14.7 Hz, J = 7.0 Hz), 5.14 (C<u>H</u>$_2$=CH-CH=CH-CH=CH-CH_2, d, 1H, J = 16.7 Hz), 5.01 (C<u>H</u>$_2$=CH-CH=CH-CH=CH-CH_2, d, 1H, J = 9.9 Hz), 4.02 (C<u>H</u>$_2$OCOCH_3, t, 2H, J = 6.7 Hz), 2.07 (CH-C<u>H</u>$_2$, q, 2H, J = 6.9 Hz), 2.01 (OCOC<u>H</u>$_3$, s, 3H), 1.61-1.23 (CH-CH_2(C<u>H</u>$_2$)$_4$$CH_2$O, m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (O<u>C</u>OCH_3), 137.1, 135.7, 133.4, 131.0, 130.2, 116.2 (<u>C</u>H$_2$=<u>C</u>H-<u>C</u>H=<u>C</u>H-<u>C</u>H=<u>C</u>H-CH_2), 64.5 (<u>C</u>H_2OCOCH_3), 32.6, 29.0, 28.7, 28.5, 25.7, 20.9 (CH-<u>C</u>H_2(<u>C</u>H_2)$_4$$CH_2$OCO<u>C</u>$H_3$).

4.5.5 Synthesis of aryldienes

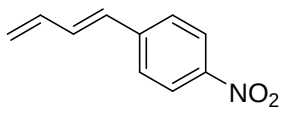
4.5.5.1 **(*E*)-Buta-1,3-dienylbenzene (4-80)**[46]



A round-bottomed flask containing THF (4 mL) was charged with Pd_2dba_3 (11.1 mg, 12.1 mmol) and TFP (11.1 mg, 0.048 mmol) and let stir for 10 min. Bromobenzene (0.076 g, 0.483 mmol) was then added followed by stirring for 10 min. Stannane **4-12** (0.200 g, 0.579 mmol) was added next and the reaction was allowed to stir at reflux for 12 h. Saturated KF solution (30 mL) and ether (50 mL) were added to the flask, and the two phases were separated. The organic layer was washed with saturated KF solution (2 x 50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane as the eluant) to afford 0.060 g of aryl butadiene **4-80** as colourless oil in 95% isolated yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (Ph<u>H</u>, d, 2H, J = 7.3 Hz), 7.30 (Ph<u>H</u>, t, 2H, J = 7.7 Hz), 7.21 (Ph<u>H</u>, t, 1H, J = 7.2 Hz), 6.88 (CH_2=CH-C<u>H</u>=CHPh, dd, 1H, J = 15.6 Hz, J = 10.5 Hz), 6.60 (CH_2=CH-CH=C<u>H</u>Ph, d, 1H, J = 15.6 Hz), 6.49 (CH_2=C<u>H</u>-CH=CHPh, dt, 1H, J = 16.7 Hz, J = 10.2 Hz), 5.35 (C<u>H</u>$_2$=CH-CH=CHPh, d, 1H, J = 17.0 Hz), 5.16 (C<u>H</u>$_2$=CH-CH=CHPh, d, 1H, J = 9.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 137.8, 133.1, 130.0, 129.1 (2C), 128.1, 126.8 (2C), 118.5.

4.5.5.2 **(*E*)-1-(Buta-1,3-dienyl)-4-nitrobenzene (4-81)**[31]

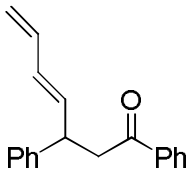


A round-bottomed flask containing THF (4 mL) was charged with Pd_2dba_3 (11.1 mg, 12 mmol) and TFP (11.1 mg, 0.048 mmol) and let stir for 10 min. 1-bromo-4-nitrobenzene (0.098 g, 0.483 mmol) was then added followed by stirring for 10 min. Stannane **4-12** (0.200 g, 0.579 mmol) was added next and the reaction was allowed to stir at reflux over 12 h. Saturated KF solution (30 mL) and ether (50 mL) were added to the flask, and the two phases were separated. The organic layer was washed with saturated KF solution (2 x 50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (5:1, hexane/Et_2O) to afford 0.078 g of aryl butadiene **4-81** as white crystals (m.p. 75-76 ^oC) in 92% isolated yield.

^1H NMR (300 MHz, DMSO) δ 8.15 (Ph<u>H</u>, d, 2H, J = 7.9 Hz), 7.50 (Ph<u>H</u>, d, 2H, J = 8.0 Hz), 6.91 (CH_2=CH-C<u>H</u>=CHPh, dd, 1H, J = 15.6 Hz, J = 10.6 Hz), 6.58 (CH_2=CH-CH=C<u>H</u>Ph, d, 1H, J = 15.7 Hz), 6.51 (CH_2=C<u>H</u>-CH=CHPh, dt, 1H, J = 17.1, J = 10.3 Hz), 5.46 (C<u>H</u>$_2$=CH-CH=CHPh, d, 1H, J = 16.8 Hz), 5.16 (C<u>H</u>$_2$=CH-CH=CHPh, d, 1H, J = 10.0 Hz); ^{13}C NMR (75 MHz, DMSO) δ 146.7, 143.6, 136.3, 133.9, 130.3, 126.7 (2C), 124.0 (2C), 120.9.

4.5.6 Reaction of dienyl cuprate with chalcone

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

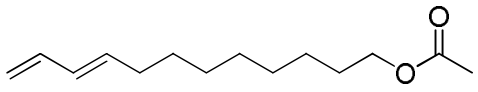


Copper cyanide (25 mg, 0.278 mmol, flame dried under vacuo) in THF (2 mL) was treated with methyllithium (0.39 mL, 0.612 mmol) at 0 ^{o}C. The cooling bath was removed and stannane **4-12** (108 mg, 0.313 mmol) in THF (1 mL) was added at rt. After 2 min of stirring at rt, chalcone (41.3 mg, 0.199 mmol)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

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.19 (Ph<u>H</u>, m, 10H), 6.25 (CH_2=C<u>H</u>-CH=CHCH, dt, 1H, J = 17.0 Hz, J = 10.1 Hz), 6.00 (CH_2=CH-C<u>H</u>=CHCH, dd, 1H, J = 16.2 Hz, J = 10.0 Hz), 5.92 (CH_2=CH-CH=C<u>H</u>CH, dd, 1H, J = 16.4 Hz, J = 6.8 Hz), 5.07 (C<u>H$_2$</u>=CH-CH=CHCH, d, 1H, J = 16.7 Hz), 4.97 (C<u>H$_2$</u>=CH-CH=CHCH, d, 1H, J = 10.1 Hz), 4.17 (PhC<u>H</u>, dt, 1H, J = 7.0 Hz, J = 6.9 Hz), 3.40 (PhCHC<u>H$_2$</u>, d, 2H, J = 7.1 Hz).

4.5.7 Synthesis of pheromone 4-83

4.5.7.1 **(*E*)-Dodeca-9,11-dienyl acetate (4-83)**[34]



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (CH_2=C<u>H</u>-CH=$CHCH_2$, dt, 1H, J = 16.9 Hz, J = 10.2 Hz), 5.97 (CH_2=CH-C<u>H</u>=$CHCH_2$, dd, 1H, J = 15.0 Hz, J = 10.5 Hz), 5.63 (CH_2=CH-CH=C<u>H</u>CH_2, dt, 1H, J = 15.1 Hz, J = 6.9 Hz), 5.01 (C<u>H$_2$</u>=CH-CH=$CHCH_2$, d, 1H, J = 16.9 Hz), 4.87 (C<u>H$_2$</u>=CH-CH=$CHCH_2$, d, 1H, J = 10.3 Hz); 3.98 (CH_2C<u>H$_2$</u>OCOCH_3, t, 2H, J = 6.7 Hz), 2.01-1.97 (CH_2=CH-CH=CHC<u>H$_2$</u>, C<u>H$_2$</u>CH_2OCOC<u>H$_3$</u>, m, 7H), 1.75-1.21 (CH_2=CH-CH=$CHCH_2$(C<u>H$_2$</u>)$_4$, m, 8H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (O<u>C</u>OCH_3),

138.8, 137.3, 135.3, 131.0 ($\underline{C}H_2=\underline{C}H-\underline{C}H=\underline{C}H$), 64.6 ($\underline{C}H_2OCOCH_3$), 32.5, 29.4, 29.2 (2C), 29.1, 28.8, 25.9, 22.7 ($CH_2=CH-CH=CH(\underline{C}H_2)_7CH_2OCO\underline{C}H_3$).

Spectral data were in accord with literature data.

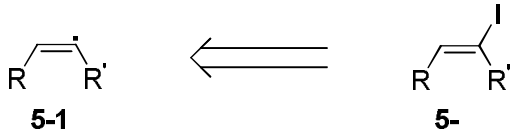
Chapter 5

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

5.1 Introduction

5.1.1 General

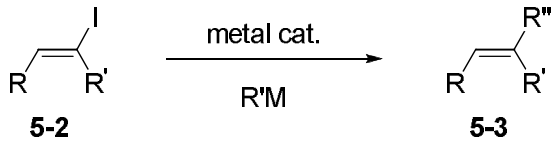
Recently, vinyl iodides have become important compounds in organic synthesis. They can serve as precursors for vinyl radicals which can be utilized in intramolecular cyclizations (Scheme 5.1).[1]



5-1 5-

Scheme 5.1

They can also be utilized in cross-coupling reactions to form new carbon-carbon bonds (Scheme 5.2).[2]



5-2 **5-3**

Scheme 5.2

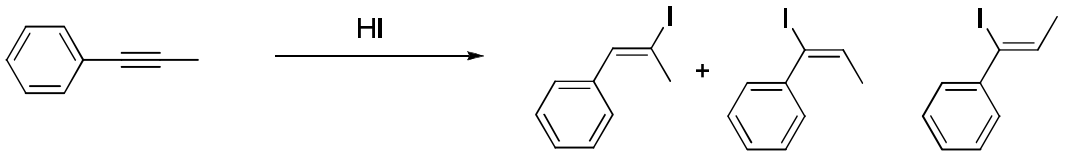
The versatility of these compounds has made them valuable intermediates in organic chemistry.

5.1.2 Synthesis of vinyl iodides

5.1.2.1 Hydroiodination

Generally, vinyl iodides are obtained from acetylenes or carbonyl compounds. The simplest preparation of vinyl iodides is to add "H-I" across a triple bond by treating an alkyne with hydroiodic acid.[3]

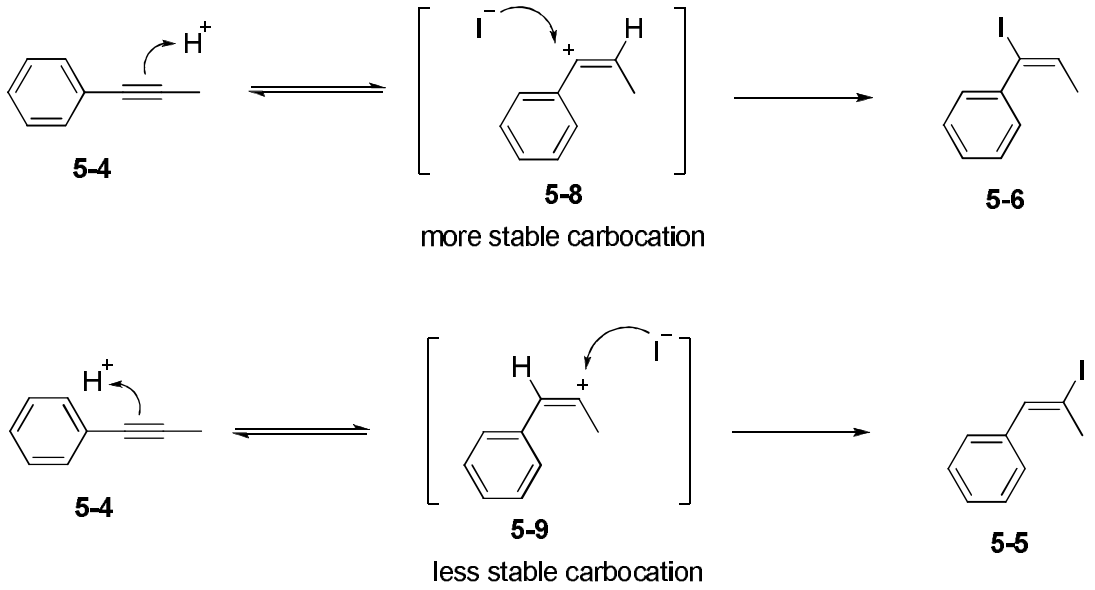
Treatment of **5-4** with HI provided two stereoisomers in a ratio of ~ 4:1 (*E*:*Z*) (Scheme 5.3).[4]



5-4 **5-5** 0% **5-6** 74% **5-7** 19%

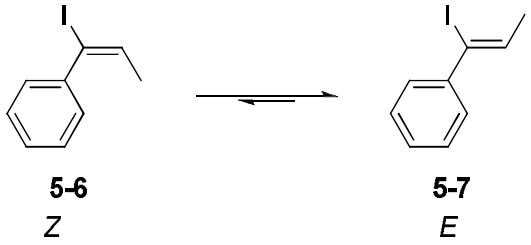
Scheme 5.3

Vinyl iodide **5-5** did not form in the reaction as carbocation **5-9** is much less stable than **5-8** (Scheme 5.4).



Scheme 5.4

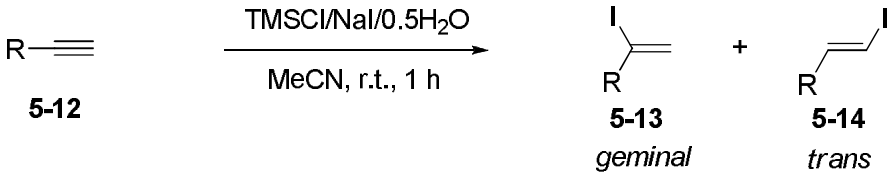
Vinyl iodide **5-10** resulted from a *syn* addition of HI across the triple bond, but in the presence of excess acid, it equilibrated to the more thermodynamically stable *Z* isomer **5-11** (Scheme 5.5).[4]

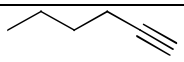
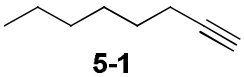


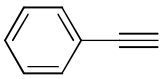
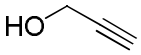
Scheme 5.5

Commercial HI is expensive; therefore, Kamiya *et al.* demonstrated the ability to form "HI" *in situ* by mixing TMSCl, NaI and water (Table 5.1).[5] Acetonitrile, as a solvent, was key to the addition of "HI" to challenging terminal alkynes, whereas previous conditions failed to do so.[5]

Table 5.1 Addition of *in situ* generated HI to terminal alkynes.[5]



entry	alkyne	isomer	conversion (%)[a]	purity (%)[a]
1	 **5-15**	*geminal*	67	95
2	 **5-1**	*geminal*	82	>98

3	 **5-17**	*geminal*	77	81
4	 **5-18**	*geminal*	62	98

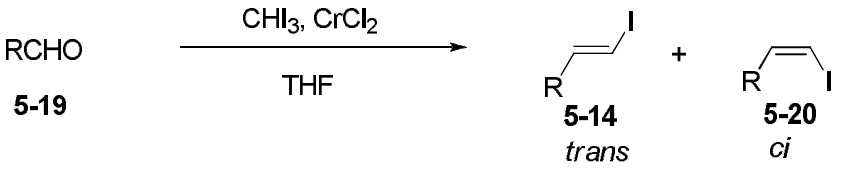
[a] Based on VPC analysis.

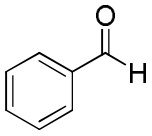
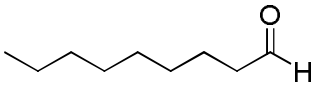
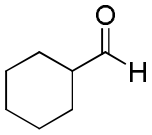
Geminal-vinyl iodides, obtained from terminal alkynes, were prepared in decent yields and great selectivities. The reactions are performed at room temperature and are complete within an hour.[5]

5.1.2.2 Vinyl iodides from carbonyl compounds

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

Table 5.2 Conversion of aldehydes to vinyl iodides.[6]

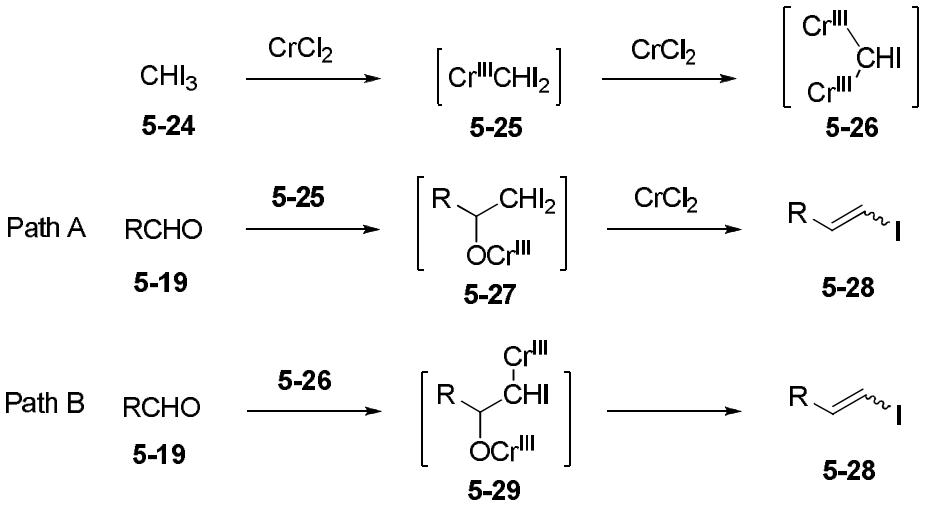


Entry[a]	aldehyde	time (h)	*trans*/*cis*[b]	yield (%)
1	 **5-21**	3	94/6	87
2	 **5-22**	2	83/17	82
3	 **5-23**	1	89/11	78

[a] The aldehyde (1.0 mmol) was treated with iodoform (2.0 mmol) and $CrCl_2$ (6.0 mmol) in THF.
[b] The isomeric ratios of the vinyl iodides were determined by GLPC or NMR.

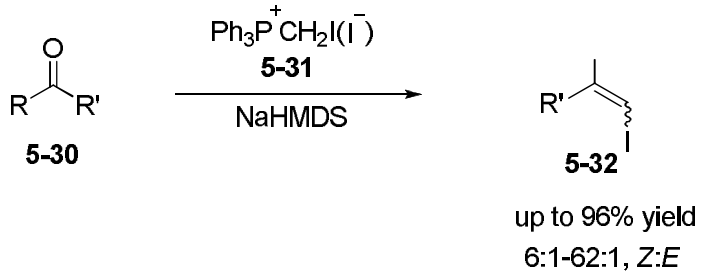
Moderate to good selectivities of *trans*-vinyl iodides were obtained using this methodology[6].

There are two possible pathways for the addition of "iodomethine" onto the aldehyde (Scheme 5.6).[6] First, chromium reacts with iodoform to form chromium diiodocarbenoid **5-25**. Second, **5-25** could react again with chromium to form carbodianion species **5-26**. Chromium species **5-25** and **5-26** are believed to be possible reactive intermediates in this reaction. This methodology provided *trans*-vinyl iodides as the major products (Scheme 5.6).



Scheme 5.6

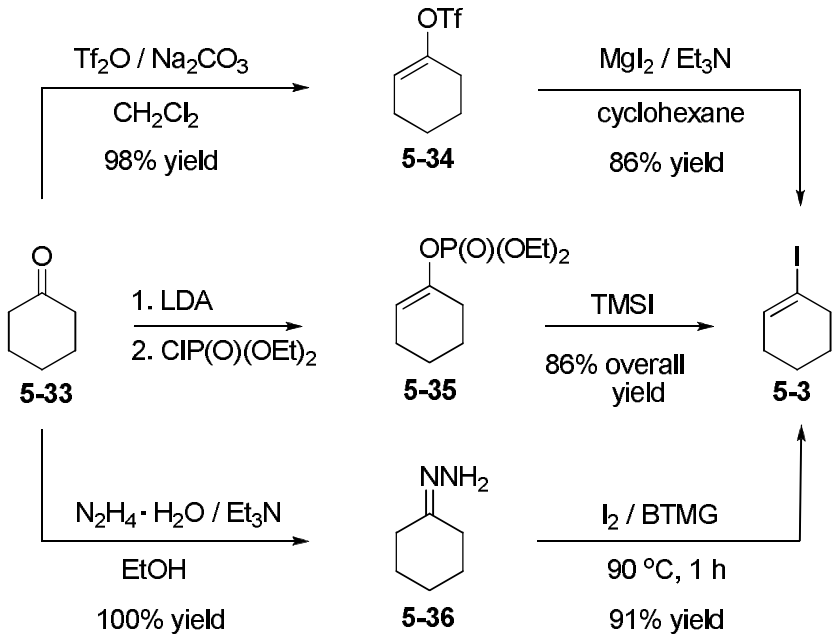
Similar methodology by Stork and Zhao applies a modified Wittig reaction by using the ylide from iodomethylphosphonium iodide **5-31** (Scheme 5.7).[7,8]



Scheme 5.7

Unlike the methodology using chromium, Wittig chemistry provides the *cis*-vinyl iodide as the major isomer in most cases.

Other methods that obtained vinyl iodides from carbonyl compounds, such as ketones, include the formation of a triflate followed by treatment with MgI_2,[9] the formation of a phosphate followed by treatment with TMSI[10] and the formation of hydrazone followed by treatment with iodine (Scheme 5.8).[11]

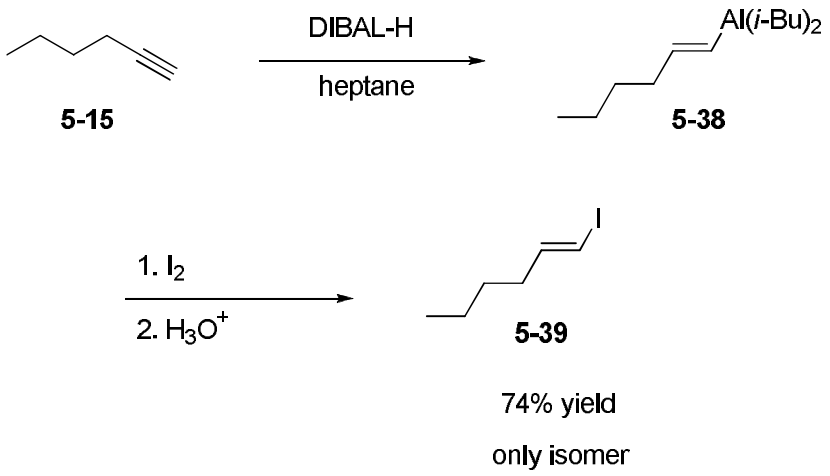


Scheme 5.8

5.1.2.3 Vinyl iodides from acetylenes

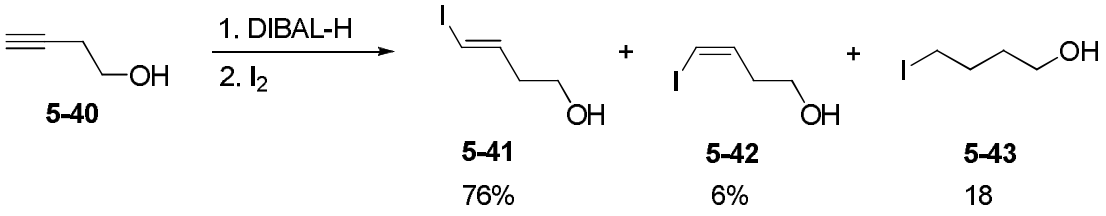
Hydrometalation of terminal alkynes, followed by an iodine quench is a common methodology used to provide mainly *trans*-vinyl iodides.

Hydroalumination of terminal alkynes, such as 1-hexyne, is highly regioselective. *Syn* addition across the triple bond provided *trans*-vinylalane **5-38** (Scheme 5.9).[12] Treatment of vinylalane **5-38** with iodine furnished the corresponding *trans*-vinyl iodide **5-39** as a pure isomer in 74% isolated yield (Scheme 5.9).[12]



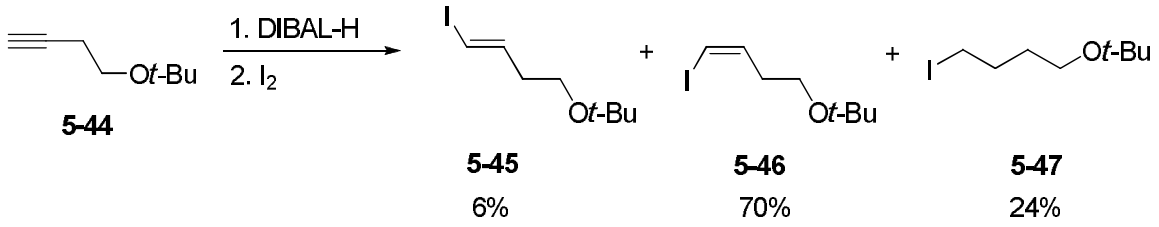
Scheme 5.9

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



Scheme 5.10

As expected, *trans*-vinyl iodide **5-45** was the major product from homopropargyl alcohol **5-40**. A small percent of *cis*-vinyl iodide was present, suggesting the participation of an anti-hydroalumination mechanism. The over reduction product **5-43** was also formed. As alcohol **5-40** was protected with a *t*-butyl group, a stark difference in selectivity was observed (Scheme 5.11).[13]



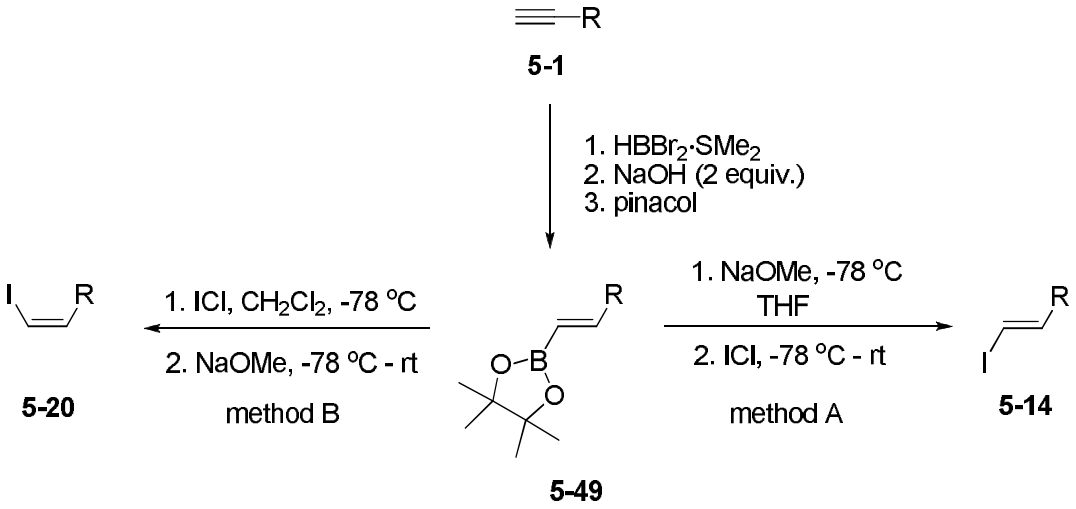
Scheme 5.11

Cis-vinyl iodide **5-46** was the major product when the alcohol was protected by a *t*-butyl group. Chong and Heuft speculated that the oxygen in the aluminum alkoxide intermediate **5-48** was not as effective a coordinator as the oxygen in the *t*-butyl ether **5-44** (Figure 5.1).[13]

Figure 5.1 Aluminum alkoxide intermediate **5-48** and *t*-butyl ether **5-44**

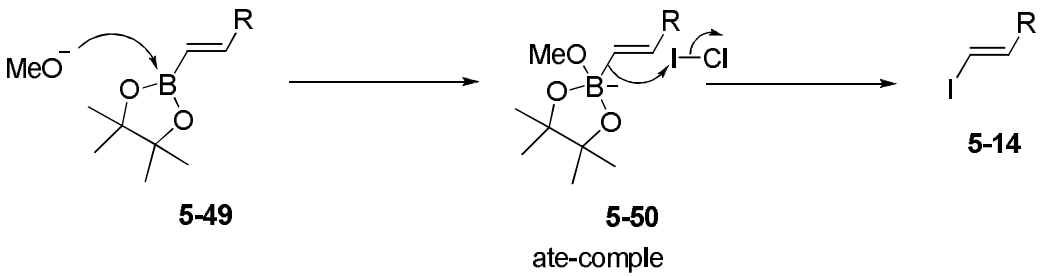
Coordination by the oxygen in the *t*-butyl ether **5-44** allowed for an anti-hydroalumination process to take place, which in return, afforded *cis*-vinyl iodide **5-46** as the major product.[13]

Stewart and Whiting have devised a stereoselective synthesis of vinyl iodides from vinylboronate pinacol esters using ICl.[15] This methodology was based on an observation made by Brown *et al.* that alkenylboronic acid derivatives were readily converted to alkenyl iodides, under stereochemical controlled conditions that afforded the corresponding *trans*- or *cis*-vinyl iodides (Scheme 5.12).[16,17] ICl was sufficiently electrophilic to perform the following transformations, whereas I_2 seemed to give no reaction with the hindered pinacol boronate esters.



Scheme 5.12

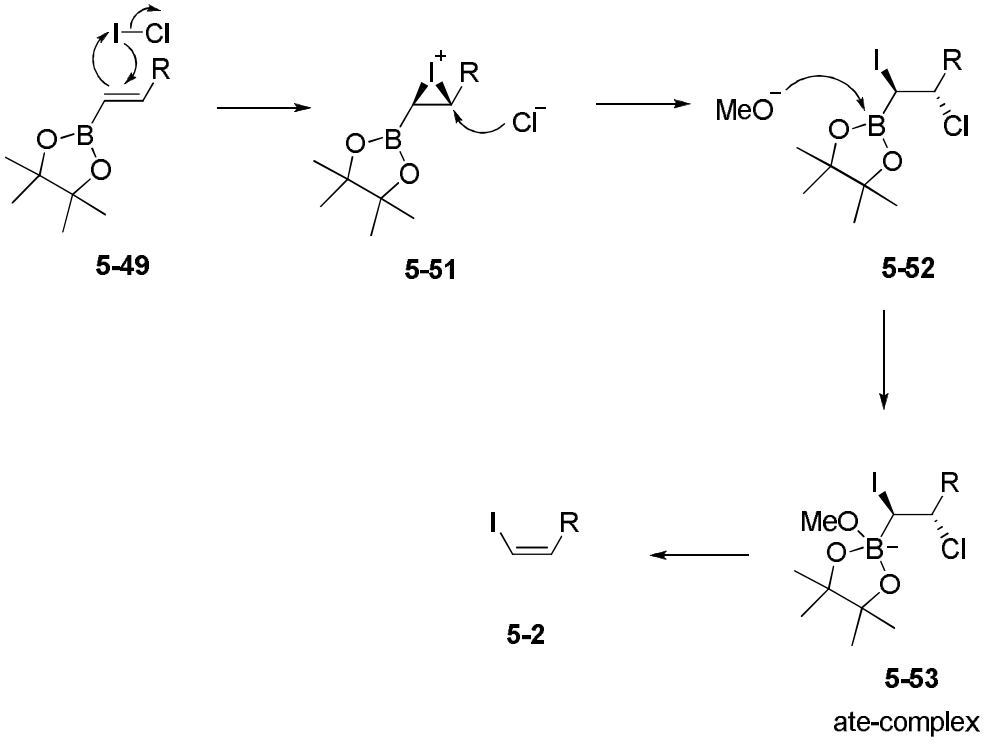
The stereoselectivity depended on the reaction conditions adopted to perform the transformation. Treatment of the boronate with excess base resulted in the formation of the "ate" complex **5-50** (Scheme 5.13).[15]



Scheme 5.13

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

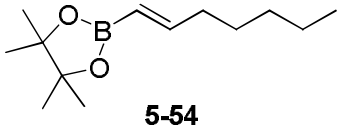
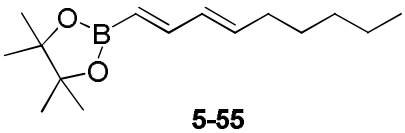
Toward the synthesis of the *cis* isomer, ICl was added first in the absence of base. It was assumed that ICl added across the double bond *via* iodonium ion formation, followed by the addition of chloride ion to the alkyl or aryl substituted carbon (Scheme 5.14).[15] The addition of ICl occurred in an anti fashion across the double bond. The subsequent treatment of base formed the ate-complex **5-53**, which in return, caused the chloride ion to be expelled (Scheme 5.14).[15]



Scheme 5.14

This methodology was applied to vinyl and dienyl boronate systems to illustrate its effectiveness (Table 5.3).

Table 5.3 Stereoselective formation of *trans*- and *cis*-vinyl iodides from boronates.[15]

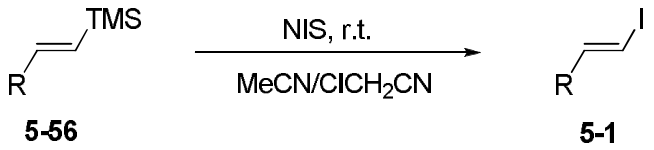
entry	boronate	Method[a]	selectivity (*E*:*Z*)	yield
1	 **5-54**	A	100:0	43
2		B	0:100	38
3	 **5-55**	A	98:2	88
4		B	13:87	81

[a] refer to Scheme 5.12 for methods

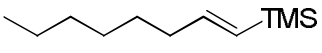
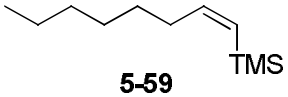
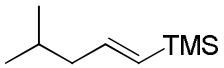
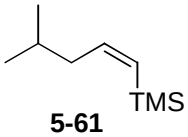
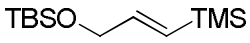
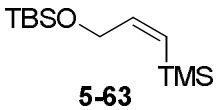
Hindered pinacol esters were readily transformed into the corresponding vinyl iodides. Modest to excellent selectivities were obtained by this methodology.[15]

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

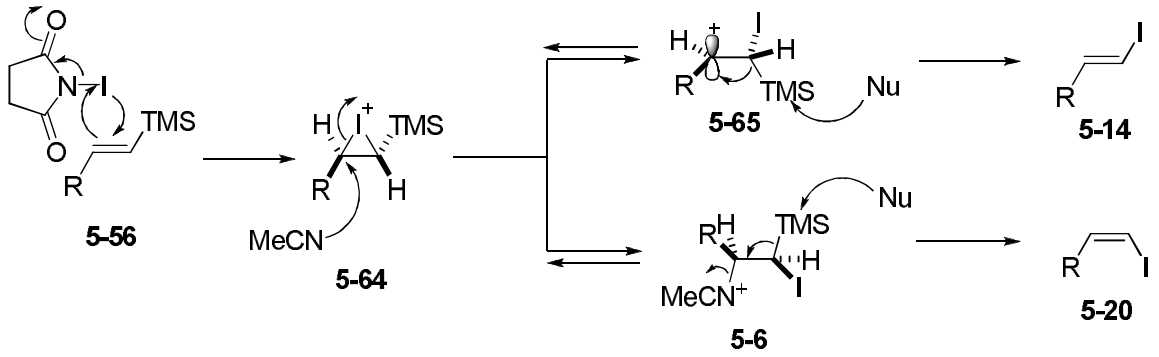
Table 5.4 Formation of vinyl iodides from vinylsilanes.[18]



5-56 **5-1**

entry	silane	selectivity (*E*:*Z*)	yield (%)
1	 **5-58**	2.8:1	75
2	 **5-59**	1.2:1	68
3	 **5-60**	1:0	72
4	 **5-61**	1:12	68
5	 **5-62**	8:1	78
6	 **5-63**	1:0	10

There was a noticeable trend with substrates with bulkier allylic carbons maintained their double bond geometry better. It is thought that solvent participation allows for the opening of the iodonium ion leading to the inverted vinyl iodide **5-20**, while a bulky allylic substrate minimizes the solvent participation, leading to the *cis* stereoisomer (Scheme 5.15).[18]

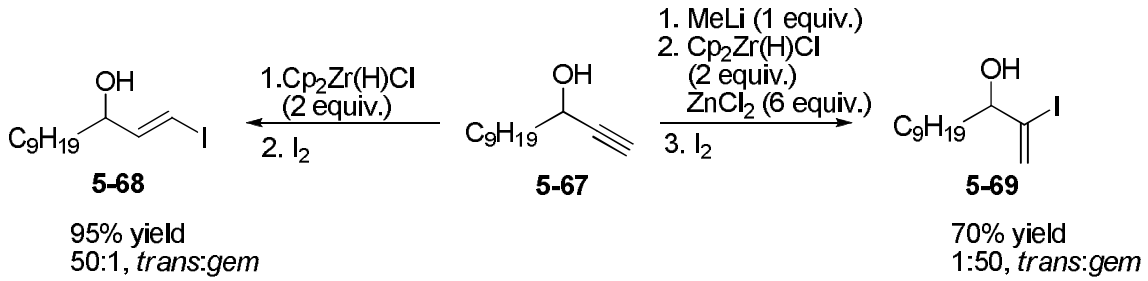


Scheme 5.15

Trans selectivity was observed in trial 6 (Table 5.4) for *cis*-vinylsilane **5-63**. It is thought that carbon-oxygen bond electronically destabilizes the cyclic iodonium ion and forces the equilibrium toward the *trans* product.[18]

Hydrozirconation of simple olefins and alkynes proceeds in a highly regioselective fashion, placing the zirconium on the least hindered carbon.[19] Vinylzirconium compounds can be transformed into vinyl iodides, with complete retention of the double bond, by simple treatment of iodine.[19]

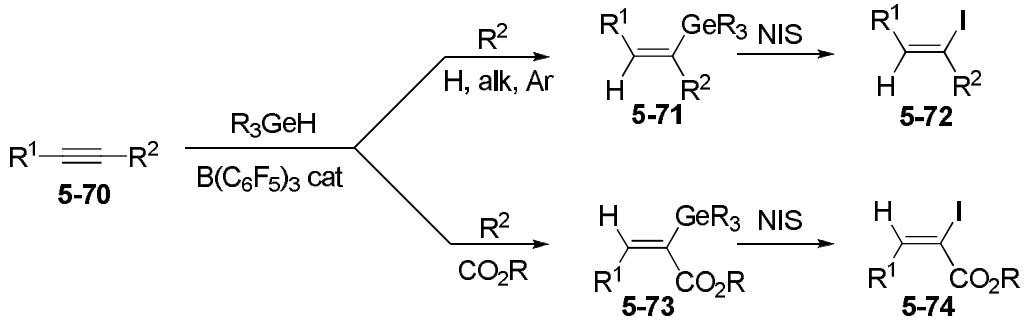
Zhang and Ready illustrated the ability of hydrozirconation to proceed in high regioselectivity when applied to propargyl alcohols (Scheme 5.16).[20]



Scheme 5.16

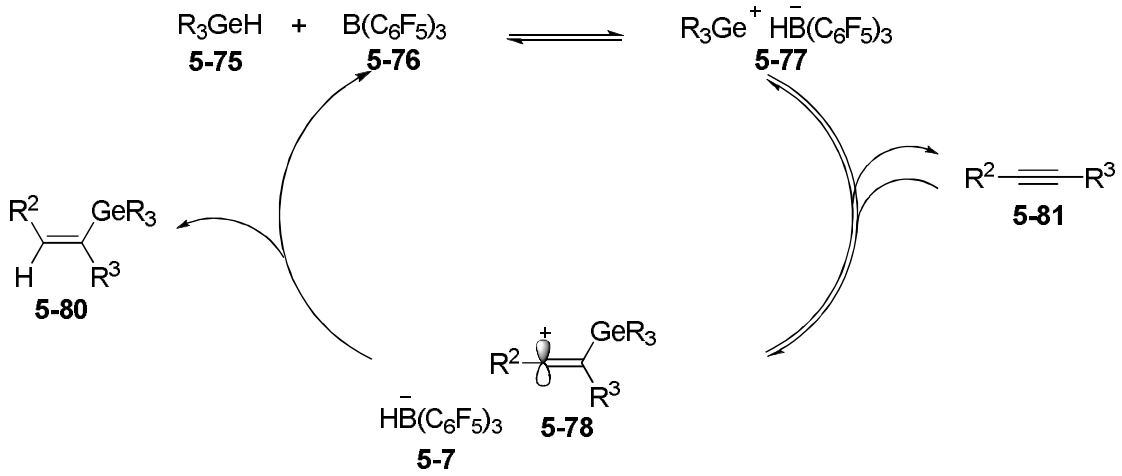
Hydrozirconation, leading to *trans*-vinyl iodide **5-68**, proceeded by a *syn* addition of ZrH across the triple bond followed by iodination with retention of configuration. While hydrozirconation, leading to *geminal*-vinyl iodide **5-69**, proceeded by formation of alkoxide intermediate first, then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

Lewis acid catalyzed hydrogermylation of alkynes was demonstrated by Schwier and Gevorgyan (Scheme 5.17).[21]



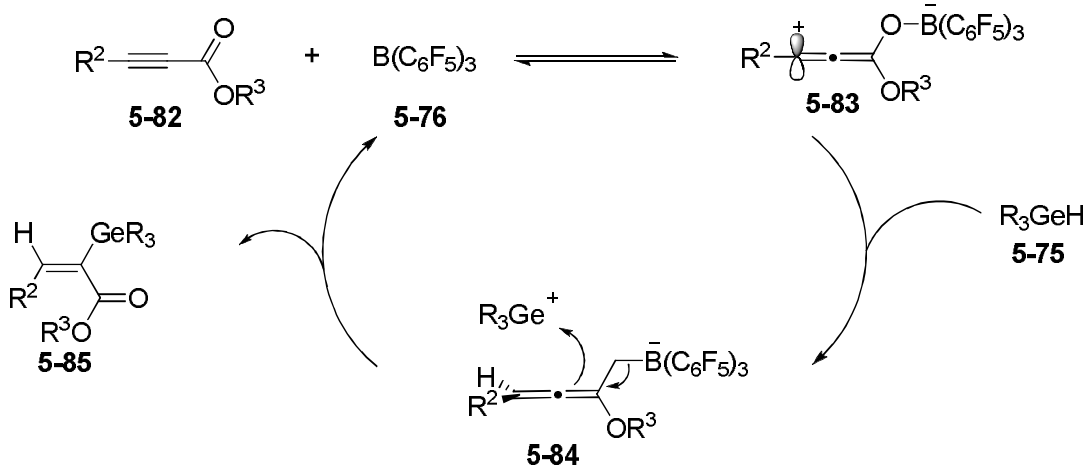
Scheme 5.17

The stereochemical outcome of hydrogermylation depended strongly on the nature of the substrate.[21] Simple alkynes promote *trans*-addition of GeH across the triple bond (Scheme 5.18).[21]



Scheme 5.18

Bulky hydride **5-79** attacks vinyl cation **5-78** at the least hindered site to give *trans*-addition product **5-80**.[21] Hydrogermylation of propiolates is believed to occur *via* a different mechanistic pathway (Scheme 5.19).

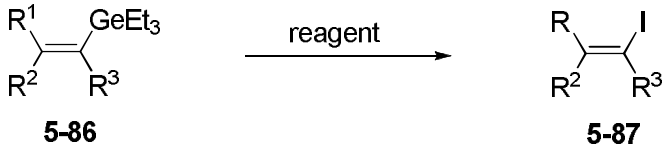


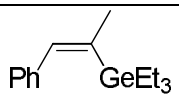
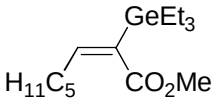
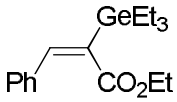
Scheme 5.19

As zwitterionic complex **5-83** forms, it abstracts a hydride from germane **5-75** to form allenolate **5-84**, which is trapped by a germylium-type specie from the least hindered side, *cis* to H, to produce the *syn*-addition product **5-85** (Scheme 5.19).[21]

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

Table 5.5 Formation of vinyl iodides from vinylgermanes.[21]



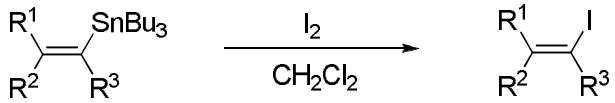
entry	vinylgermane	reagent	yield of vinyl iodide (%)
1	 **5-88**	NIS	99
2	 **5-89**	NIS/$AlCl_3$	88
3	 **5-90**	NIS/$AlCl_3$	85

As illustrated in Table 5.5, iododegermylation/iodination proceeded smoothly to furnish the corresponding vinyl iodides in good to excellent yields.[21]

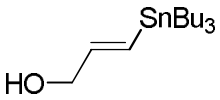
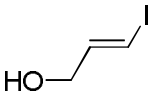
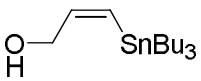
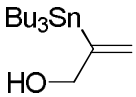
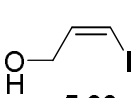
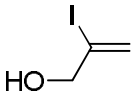
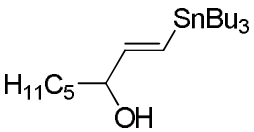
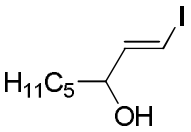
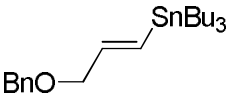
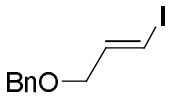
Vinylstannanes can also be converted into their corresponding vinyl iodides by a simple quench with iodine. Perfect retention of configuration of the double bond is usually observed. Factors influencing the selectivities of hydrostannation were discussed in Chapter 3.

Jung and Light have demonstrated the conversion of vinylstannanes into their corresponding vinyl iodides (Table 5.6).[22]

Table 5.6 Formation of vinyl iodides from vinylstannanes.[22]



5-91 **5-87**

entry	vinylstannane	vinyl iodide	yield (%)
1	 **5-92**	 **5-93**	76
2	 **5-94**  **5-95** 4 : 1	 **5-96**  **5-97** 4 : 1[a]	63
3	 **5-98**	 **5-99**	84
4	 **5-100**	 **5-101**	99

[a] Ratio was determined by ^{1}H NMR analysis

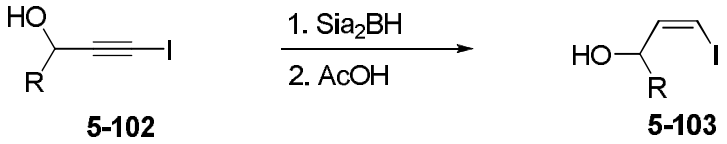
Iodination of vinylstannanes was straight forward. A slight excess of iodine was used (1.3 equiv.) to convert vinylstannanes to vinyl iodides. Retention of the double bond was

observed in all cases. Good to quantitative yields of vinyl iodides were obtained by this methodology.

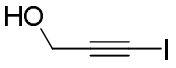
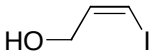
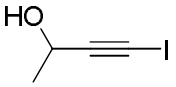
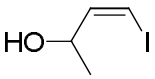
5.1.2.4 Hydrometallation of iodoacetylenes

Cowell and Stille demonstrated hydroboration/protonolysis of iodoacetylenes as a method to generate pure *cis*-vinyl iodides (Table 5.7).[23]

Table 5.7 Formation of *cis*-vinyl iodides from iodoacetylenes.[23]



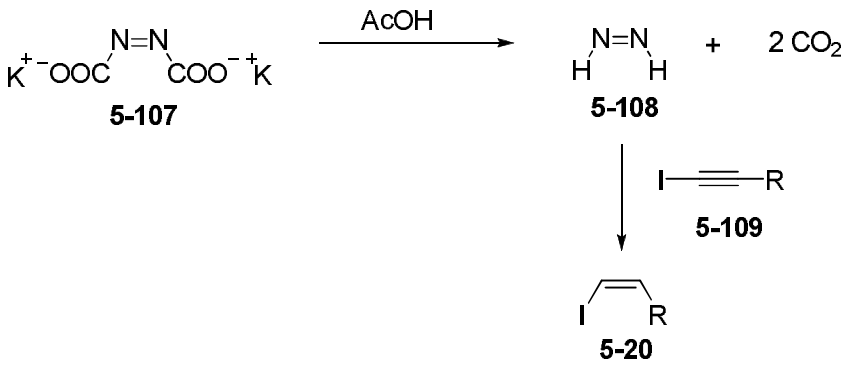
5-102 **5-103**

entry	iodoacetylene	vinyl iodide	yield (%)
1	 **5-104**	 **5-96**	N/A[a]
2	 **5-105**	 **5-106**	61

[a] Not determined owing to loss of product during workup

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

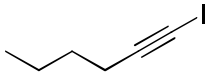
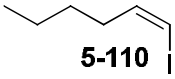
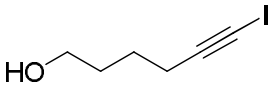
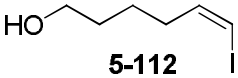
Reduction of iodoacetylenes can also be accomplished by dipotassium azodicarboxylate (Scheme 5.20).[24]



Scheme 5.20

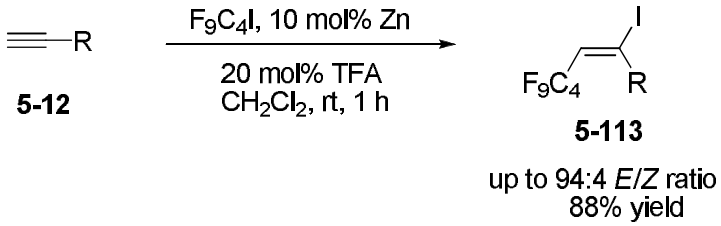
Diimide **5-108** is formed as azodicarboxylate **5-107** is treated with acid, thus liberating two equivalents of carbon dioxide. Diimide **5-108** reduces iodoacetylenes to the corresponding *cis*-vinyl iodide (Table 5.8).

Table 5.8 Synthesis of *cis*-vinyl iodides from iodoacetylene by diimide reduction.[24,25]

entry	iodoacetylene	vinyl iodide	yield (%)
1	 **5-109**	 **5-110**	56
2	 **5-111**	 **5-112**	62

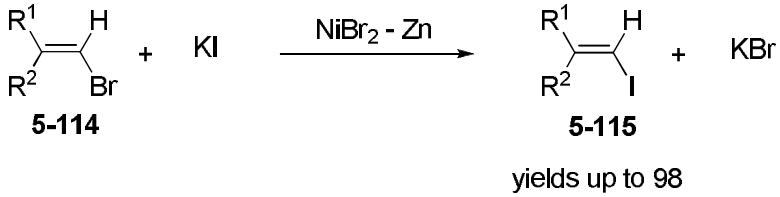
5.1.2.5 Other methods

Other methodologies that provide vinyl iodides include a radical addition of C_4F_9I to terminal alkynes with high regio- and stereoselectivity utilizing zinc as a catalyst (Scheme 5.21).[2]



Scheme 5.21

Reaction of vinyl bromides with an iodide ion in the presence of nickel catalyst generates the corresponding vinyl iodides with complete retention of configuration (Scheme 5.22).[26]



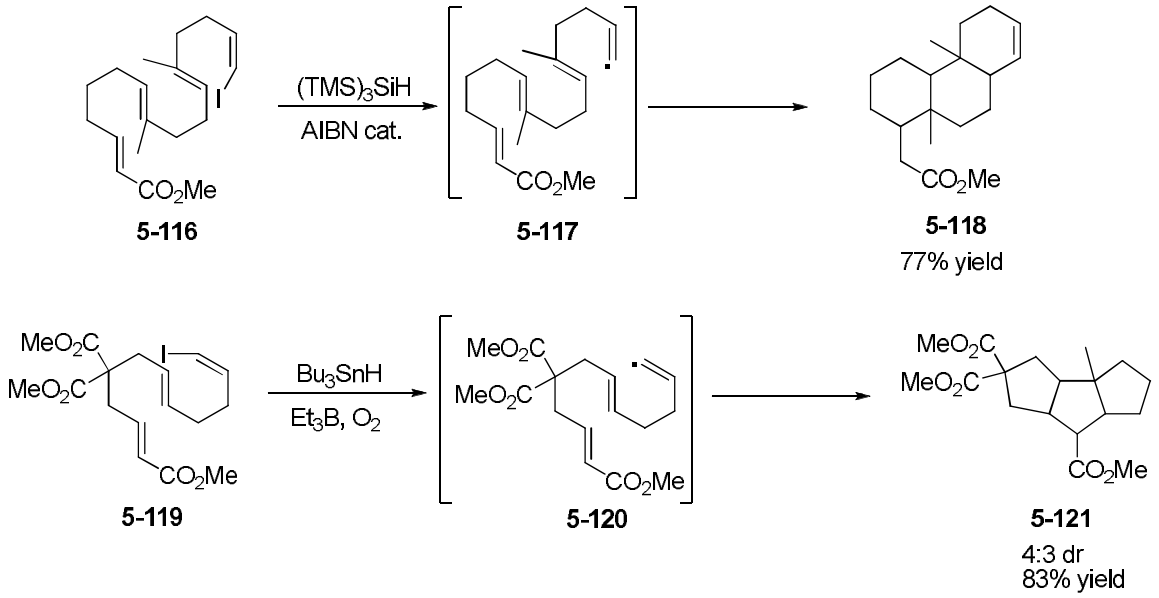
Scheme 5.22

5.1.3 Applications of vinyl iodides

5.1.3.1 Radical cyclizations

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

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



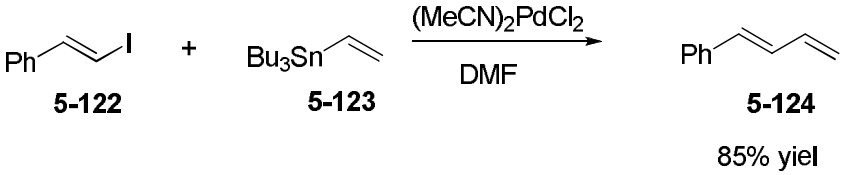
Scheme 5.23

Tricyclic compound **5-118** was obtained through a sequential 6-*endo*, 6-*endo*, 6-*exo* cyclization, whereas tricyclic compound **5-121** was obtained through a 5-*exo*, 5-*exo*, 5-*exo* cyclization. Vinyl iodides **5-116** and **5-119** were radical precursors that facilitated these cyclizations.

5.1.3.2 Cross-coupling reactions

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

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

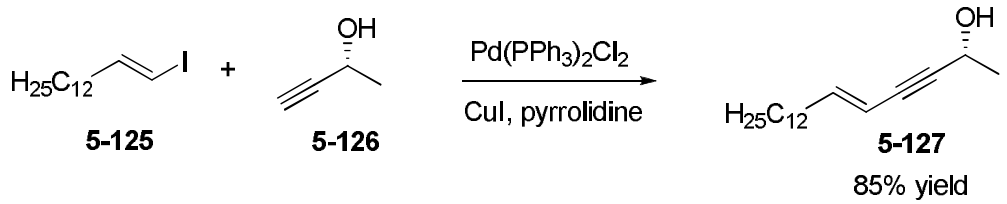


5-122 **5-123** **5-124**

85% yiel

Scheme 5.24

Vinyl iodide **5-125** was able to cross-couple with terminal alkyne **5-126**, *via* Sonogashira coupling, to furnish enyne **5-127** in good yield (Scheme 5.25).[27]

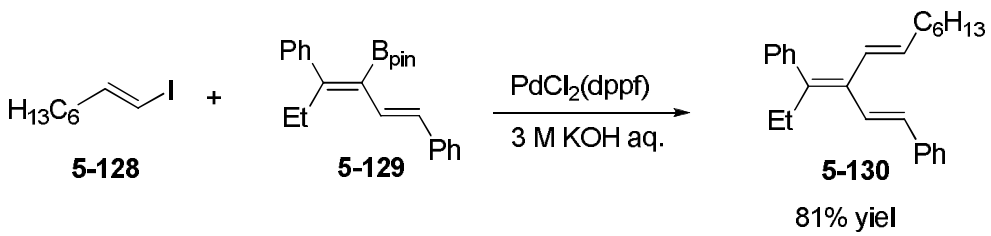


5-125 **5-126** **5-127**

85% yield

Scheme 5.25

Vinyl iodide **5-128** was able to cross-couple with vinylboronate **5-129**, *via* Suzuki coupling, to provide triene **5-130** smoothly (Scheme 5.26).[28]

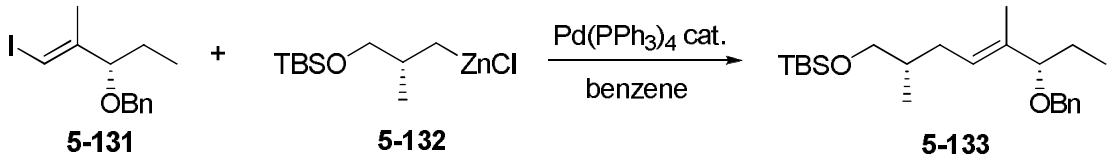


5-128 **5-129** **5-130**

81% yiel

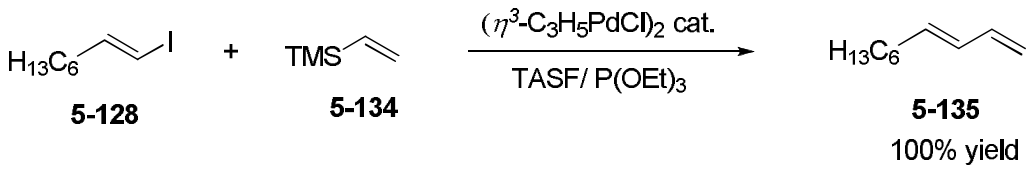
Scheme 5.26

Vinyl iodide **5-131** was able to cross-couple with alkylzinc **5-132**, *via* Negishi coupling, to provide compound **5-133** (Scheme 5.27).[29]



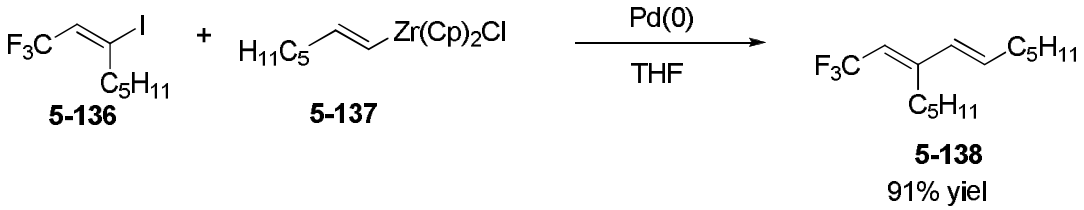
Scheme 5.27

Vinyl iodide **5-128** was able to cross-couple with vinylsilane **5-134**, *via* Hiyama coupling, to provide diene **5-135** in a quantitative yield (Scheme 5.28).[30]



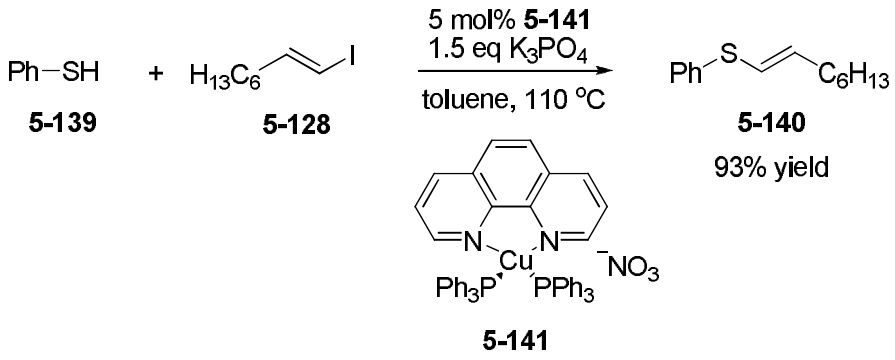
Scheme 5.28

Vinyl iodide **5-136** was able to cross-couple with alkenylzirconium species **5-137**, *via* Negishi coupling, to provide diene **5-138** (Scheme 5.29).[2]



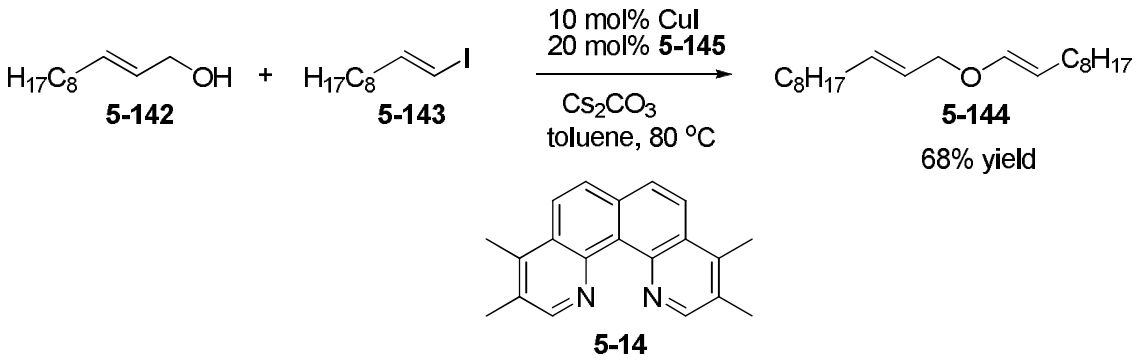
Scheme 5.29

Vinyl iodides are also capable of cross-coupling with heteroatom-based coupling partners. Vinyl iodide **5-128** was able to couple with aryl thiol **5-139** to provide vinylsulfide **5-140** in excellent yield (Scheme 5.30).[31]



Scheme 5.30

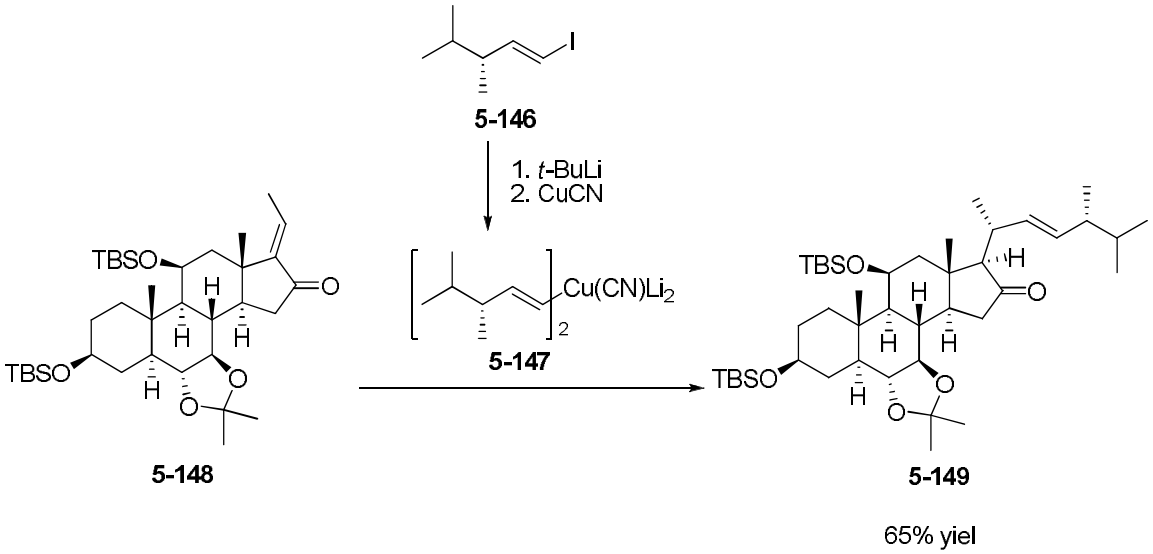
Vinyl iodide **5-143** was able to couple with allylic alcohol **5-142** to provide vinylether **5-144** in moderate yield (Scheme 5.31).[32]



Scheme 5.31

5.1.3.3 Lithium-halogen exchange

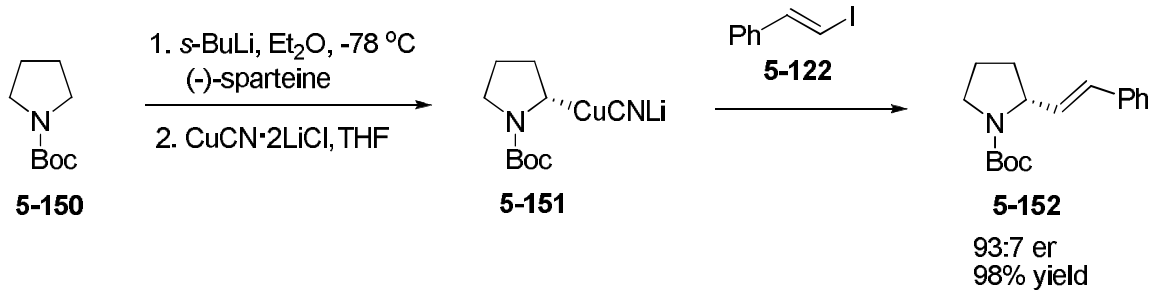
Vinyl iodides are able to undergo lithium-halogen exchange to produce the corresponding vinyllithiums. Vinyl iodide **5-146** underwent lithium-halogen exchange with *t*-BuLi to produce the corresponding vinyllithium; subsequent treatment with CuCN produced the corresponding cuprate reagent **5-147**. This cuprate reagent underwent conjugate addition to compound **5-148** to provide compound **5-149** (Scheme 5.32).[33]



Scheme 5.32

5.1.3.4 Substitution reactions

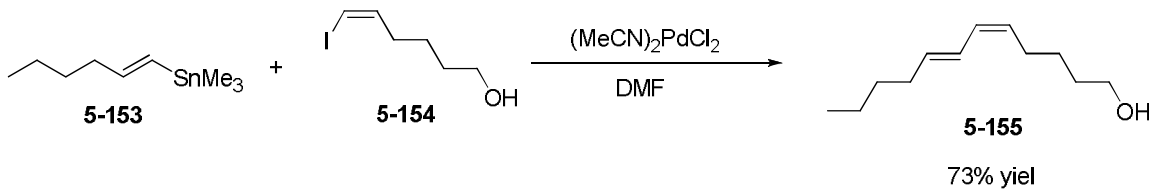
Substitution reactions on vinyl iodides have been performed. Vinyl iodide **5-122** was able to undergo a substitution reaction with cuprate reagent **5-151**, formed *in situ*, to provide compound **5-152** in excellent yield (Scheme 5.33).[34]



Scheme 5.33

5.1.4 Applications of vinyl iodides in total synthesis

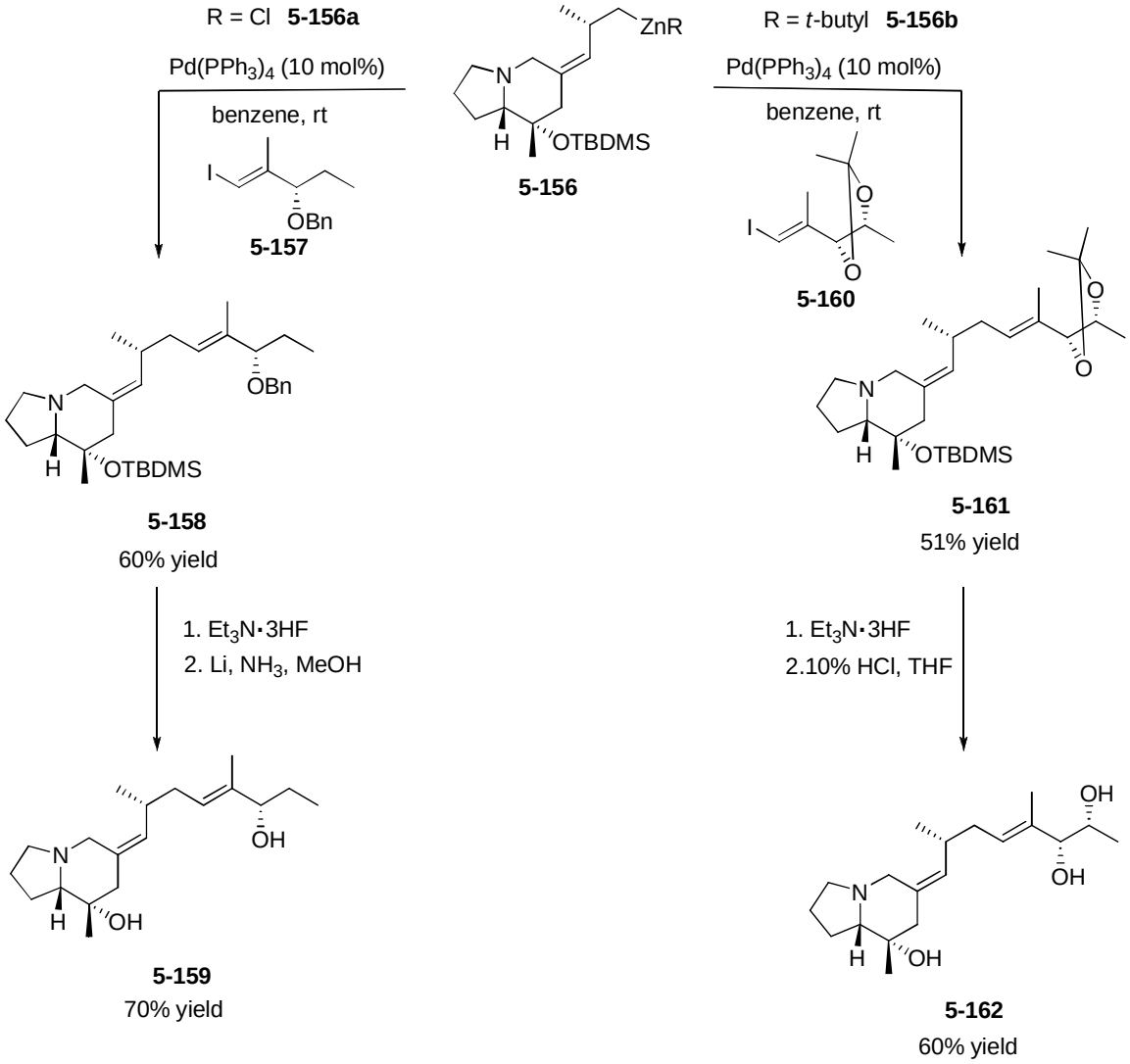
There are many applications of vinyl iodides in natural product synthesis. One example is a convergent synthesis of a sex pheromone of the forest tent caterpillar, *Malacosoma disstria* (Scheme 5.34).[35]



Scheme 5.34

The coupling of vinyl iodide **5-154** and vinylstannane **5-153** afforded pheromone **5-155** in 73% isolated yield.[25]

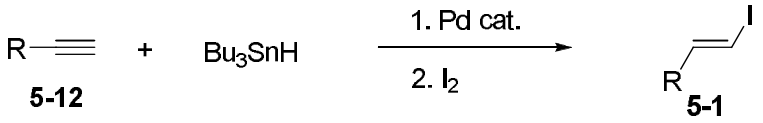
Also, convergent total syntheses of pumiliotoxins A and B, major toxic alkaloids from skin extracts of the Panamanian poison frog *Dendrobates pumilio*,[36] was possible *via* palladium-catalyzed cross-coupling reaction of homoallylic organozinc compounds **5-156a** and **5-156b** with vinyl iodides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



Scheme 5.35

5.2 Proposed Work

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



Scheme 5.36

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

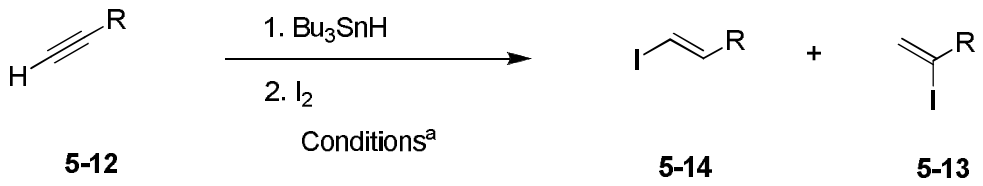
5.3 Results and Discussion

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

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

Vinyl iodides were obtained by quenching the resulting vinylstannane mixture after hydrostannation with iodine. The results are illustrated in Table 5.9.

Table 5.9 Formation of vinyl iodides from terminal alkynes *via* hydrostannation



5-12 **5-14** **5-13**

entry (vinyl iodide)	R	ratio[d] *trans* : *gem*	isolated yield (%)
1 (**5-163**:**5-164**)	$(CH_2)_9OTBS$	95:5	88[c]
2 (**5-163**:**5-164**)		99:1	71[b,c]
3 (**5-165**:**5-166**)	$(CH_2)_8OH$	95:5	93[c]
4 (**5-165**:**5-166**)		99:1	75[b,c]
5 (**5-167**:**5-168**)	$(CH_2)_8OAc$	95:5	95[c]
6 (**5-167**:**5-168**)		99:1	76[b,c]
7 (**5-169**:**5-170**)	$(CH_2)_4OH$	95:5	94[c]
8 (**5-169**:**5-170**)		99:1	76[b,c]
9 (**5-93**:**5-97**)	CH_2OH	67:33	67[e]
10 (**5-41**:**5-171**)	$(CH_2)_2OH$	83:17	83[e]
11 (**5-172**:**5-173**)	$CH(OH)CH_3$	95:5	93[e]
12 (**5-99**:**5-174**)	$CH(OH)n\text{-}C_5H_{11}$	95:5	89[e]
13 (**5-175**:**5-176**)	CH(OH)Ph	82:12	80[e]

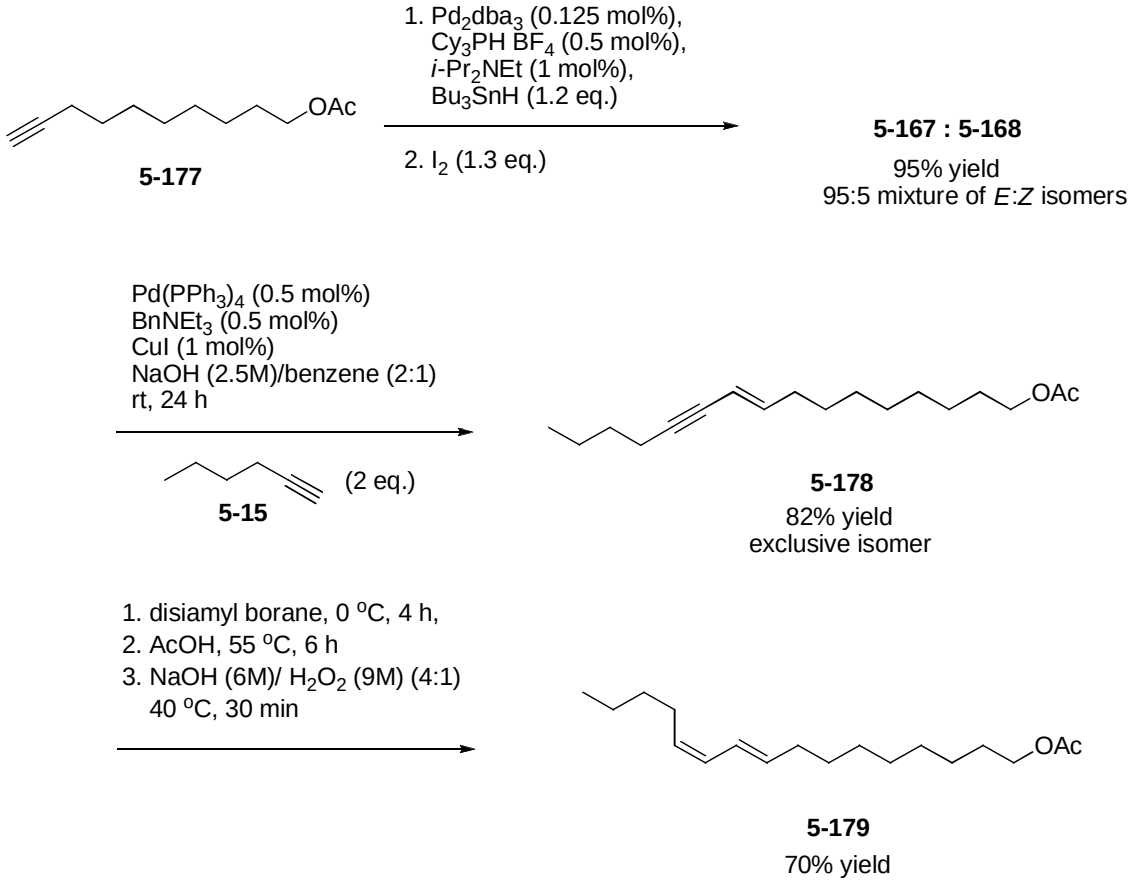
[a] Pd_2dba_3 (0.125 mol %), $Cy_3PH\ BF_4$ (0.5 mol %), *i*-Pr_2NEt (1 mol %), Bu_3SnH (1.2 eq), CH_2Cl_2, 0 °C, 2h, then I_2 (1.3 eq dissolved in CH_2Cl_2), 0 °C, 10 min.
[b] 0.95 eq of I_2 was used.
[c] Isolated yield of both inseparable isomers.
[d] Ratio was determined by ^1H NMR analysis of the crude mixture.
[e] Isolated yield of *trans* isomer only.

Iodination of the resulting vinylstannanes resulted in perfect retention of configuration of the double bond and good to excellent isolated yields. This methodology was compatible with esters, alcohols and TBS-ethers as the selectivities and yields were consistent. Quenching the reaction with excess iodine (1.3 equivalents) provided a ratio of vinyl iodides that was consistent with the ratios obtained from vinylstannanes after hydrostannation. Yields of vinyl iodides were similar to the yields obtained of vinylstannanes. The reactions were operationally simple, as a follow up from the

hydrostannation reaction, the vinylstannanes formed *in situ* were quenched directly with iodine; effectively producing *trans*-vinyl iodides in high regioselectivities and yields in one-pot from the corresponding terminal alkyne. Vinyl iodides obtained from alkynes in trials 1-8 were inseparable by silica gel chromatography; higher selectivity of these vinyl iodides would be advantageous. An improvement in selectivity was observed when 0.95 equivalent of iodine was used to quench the reaction. This improvement was credited to the slight difference in reactivity toward iodination between the *trans*- and *geminal*-vinylstannanes. As 0.95 equivalent of iodine was used, the vinyl iodide ratio obtained improved from 95:5 to 99:1 with a slight decrease in yield (~ 18% on average) in trials 2, 4, 6 and 8. Lowering the equivalents of iodine from 0.95 to 0.90 and 0.80 offered no advantages in terms of selectivity but rather poorer yields of the *trans*-vinyl iodide were obtained. Decreasing the temperature of the reaction from 0 ^{o}C to -15 ^{o}C and -78 ^{o}C at 0.95, 1.0 and 1.3 equivalents did not affect the selectivity but lower isolated yields of *trans*-vinyl iodides were obtained. Also, the method used to add the iodine did not affect the selectivity, but rather the consistency of the yields obtained of *trans*-vinyl iodides. Adding the iodine quickly (10 min), as a solution in CH_2Cl_2 offered the most consistent results; while addition of the iodine solution, over a longer period of time (1 h), or as a solid in one, three or four portions resulted in incomplete and inconsistent reactions. In most applications, the improvement in selectivity, from 95:5 to 99:1 (*E*:*Z*), was not necessary as illustrated below in the synthesis of two sex pheromones on large scales (Scheme 5.37 and 5.38).

5.3.2 Applications

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



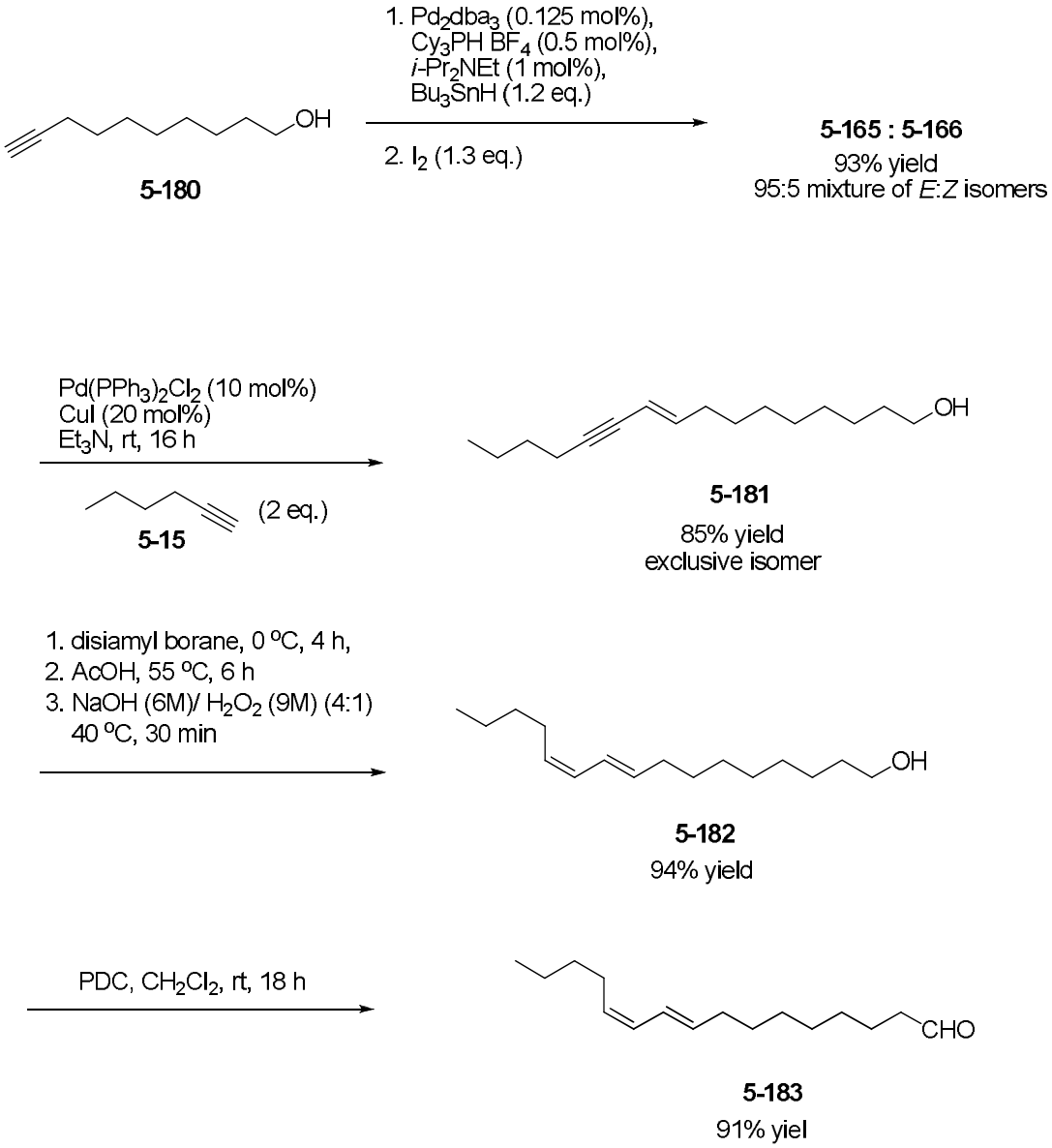
Scheme 5.37

Hydrostannation/iodination of alkyne **5-177** provided *trans*-vinyl iodide **5-167** in 95% isolated yield in a 95:5 ratio with the corresponding *geminal*-vinyl iodide (**5-168**). The *trans*- and *geminal*-vinyl iodides were inseparable by silica gel chromatography, but it is

known that *trans*-vinyl iodides are more reactive toward cross-coupling reactions than the corresponding *geminal*-vinyl iodides.[40] The 95:5 mixture of vinyl iodides was subjected to Sonogashira conditions along with 2 equivalents of 1-hexyne. As previously reported,[13] only the *trans* coupling product **5-178** was observed in 85% yield, and the *geminal*-vinyl iodide was recovered. Reduction of the triple bond by hydroboration/protonolysis afforded the target product **5-179** in 70% yield.

A second application was the synthesis of a sex pheromone of the sugar cane borer, *Diatraea saccharalis*.[41] Pheromone **5-183** was synthesize in a 4 step sequence in 68% overall yield without protecting the alcohol (Scheme 5.38).

Hydrostannation/iodination of alkyne **5-180** provided *trans*-vinyl iodide **5-165** in 93% isolated yield in a 95:5 ratio with the corresponding *geminal*-vinyl iodide (**5-166**). This mixture was subjected to Sonogashira conditions with 2 equivalents of 1-hexyne. *Trans* coupling product **5-181** was exclusively formed in 85% isolated yield, while *geminal*-vinyl iodide was recovered. Reduction of the triple bond by hydroboration/protonolysis afforded diene **5-182** in 94% yield. Subsequent oxidation of the alcohol by PDC provided dienal **5-183** in 91% yield.



Scheme 5.38

Other approaches to aldehydes typically carry a protected alcohol which is deprotected then oxidized.[41] This hydrostannation/iodination approach provides an advantage where protection of the alcohol is not necessary.

5.4 Summary

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

Sex pheromones **5-179** and **5-183** were synthesized in 3 step and 4 step sequences with overall yields of 55% and 68%, respectively.

5.5 Experimental

5.5.1 General experimental

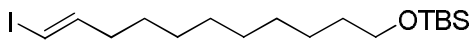
All reactions and reagents were carried out and purified as in Chapter 3. Other reagents were purchased from Sigma-Aldrich and used without further purification. 10-Undecyn-1-ol **5-180** was prepared by bromination/dehydrobromination of 10-undecen-1-ol,[42] commercially-unavailable propargylic alcohols were prepared by addition of lithium trimethylsilylacetylide to the appropriate aldehyde followed by treatment with K_2CO_3/MeOH.[43,44]

5.5.2 General procedure for synthesis of trans-vinyl iodides

Pd_2dba_3 (65.0 mg, 0.147 mmol), tricyclohexylphosphonium tetrafluoroborate (99.0 mg, 0.294 mmol) and Hünig's base (76.0 mg, 0.588 mmol) were added successively to CH_2Cl_2 (300 mL) and the resulting mixture was stirred at r.t. for 15 min. The corresponding alkyne was added (58.8 mmol) and the reaction was cooled to 0 ^oC. Bu_3SnH (20.5 g, 70.5 mmol) diluted in CH_2Cl_2 (90 mL) was added dropwise *via* a dropping funnel over 1.5 h. The reaction was then allowed to stir at 0 ^oC for 2 h. Iodine (19.4 g, 76.4 mmol) dissolved in CH_2Cl_2 (300 mL) was added dropwise but quickly *via* a dropping funnel within 10 min at 0 ^oC. The reaction mixture was washed with saturated $Na_2S_2O_3$ solution (1 x 250 mL), and saturated KF solution (3 x 250 mL), passed through a silica plug and concentrated. The resulting oil was purified by silica gel chromatography

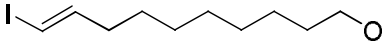
(hexane/ ether) to afford the corresponding trans-vinyl iodide in a 95:5 ratio (1.3 eq. of I_2 was used) or 99:1 ratio (0.95 eq. of I_2 was used) (*trans*/*gem*).

5.5.2.1 **(*E*)-*Tert*-butyl(11-iodoundec-10-enyloxy)dimethylsilane (5-163)**[45]



Vinyl iodide **5-163** was isolated in 88% and 71% yield in inseparable ratios of 95:5 and 99:1 (*trans*:*gem*) respectively from the corresponding alkyne using the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (ICH=C<u>H</u>CH_2, 1H, dt, J = 14.3 Hz, J = 7.1 Hz), 5.94 (IC<u>H</u>=CHCH_2, d, 1H, J = 14.3 Hz), 3.57 (TBSOC<u>H</u>$_2$, 2H, t, J = 6.6Hz), 2.08 (ICHCHC<u>H</u>$_2$, 2H, dt, J = 7.2 Hz, J = 5.9 Hz), 1.56-1.25 (CH_2(C<u>H</u>$_2$)$_7$$CH_2$, 14H), 0.87 (<u>*t*Bu</u>(CH_3)$_2$Si, 9H, s) , 0.03 (*t*Bu(C<u>H</u>$_3$)$_2$Si, 6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7 (ICH=<u>C</u>HCH2), 74.1 (I<u>C</u>H=CHCH2), 63.2 (TBSO<u>C</u>$H_2$$CH_2$), 35.9, 32.8, 29.4, 29.3, 29.2, 28.8, 28.3, 25.9, 25.7 (<u>C</u>H_2(<u>C</u>H_2)$_7$$CH_2$OTBS) ((<u>C</u>$H_3$)$_3$C($CH_3$)$_2$Si), 18.3 (($CH_3$)$_3$<u>C</u>($CH_3$)$_2$Si), -5.4 (($CH_3$)$_3$C(<u>C</u>$H_3$)$_2$Si).

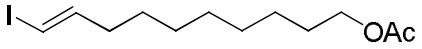
5.5.2.2 **(*E*)-10-Iododec-9-en-1-ol (5-165)**[45]



Vinyl iodide **5-165** was isolated in 93% and 75% yield in inseparable ratios of 95:5 and 99:1 (*trans*:*gem*) respectively from the corresponding alkyne using the general procedure.

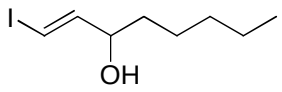
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (ICH=C<u>H</u>CH_2, dt, 1H, J = 14.4 Hz, J = 7.1 Hz), 5.92 (IC<u>H</u>=$CHCH_2$, d, 1H, J = 14.4 Hz), 3.58 (C<u>H_2</u>OH, t, 2H, J = 6.6 Hz), 1.99 (ICH=CHC<u>H_2</u>, q, 2H, J = 6.8 Hz), 1.82 (CH_2O<u>H</u>, s, 1H), 1.53-1.14 ($CHCH_2$(C<u>H_2</u>)$_6$$CH_2$OH, m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8 (ICH=<u>C</u>HCH_2), 74.4 (I<u>C</u>H=$CHCH_2$), 63.0 (<u>C</u>H_2OH), 36.1 (ICH=CH<u>C</u>H_2), 32.8, 29.4 (2C), 28.9, 28.4, 25.8 ($CHCH_2$(<u>C</u>H_2)$_6$$CH_2$OH).

5.5.2.3 **(*E*)-10-Iododec-9-enyl acetate (5-167)**[46]



Vinyl iodide **5-167** was isolated in 95% and 76% yield in inseparable ratios of 95:5 and 99:1 (*trans*:*gem*) respectively from the corresponding alkyne using the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (ICH=C<u>H</u>CH_2, dt, 1H, J = 14.3 Hz, J = 7.2 Hz), 5.91 (IC<u>H</u>=$CHCH_2$, d, 1H, J = 14.3 Hz), 3.98 (C<u>H_2</u>$OCOCH_3$, t, 2H, J = 6.8 Hz), 1.99 (ICH=CHC<u>H_2</u>, q, 2H, J = 7.0 Hz), 1.98 (CH_2OCOCH_3, s, 3H), 1.58-1.24 ($CHCH_2$(C<u>H_2</u>)$_6$$CH_2$O, m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (O<u>C</u>OCH_3), 146.6 (ICH=<u>C</u>HCH_2), 74.3 (I<u>C</u>H=$CHCH_2$), 64.5 (<u>C</u>H_2OCOCH_3), 35.9 (ICH=CH<u>C</u>H_2), 29.1, 29.0, 28.7, 28.5, 28.2, 25.8, 20.9 ($CHCH_2$(<u>C</u>H_2)$_6$$CH_2OCO$<u>C</u>$H_3$).

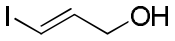
5.5.2.4 **(*E*)-1-Iodooct-1-en-3-ol (5-99)**[22]



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

^{1}H NMR (300 MHz, CDCl3) δ 6.56 (ICH=C<u>H</u>CHOH, 1H, dd, J = 14.5 Hz, J = 6.3 Hz), 6.32 (IC<u>H</u>=CHCHOH, d, 1H, J = 14.6 Hz), 4.07 ((ICH=CHC<u>H</u>OH, 1H, p, J = 6.0Hz), 1.56-1.28 (CHO<u>H</u>(C<u>H</u>$_2$)$_4$CH$_3$, 9H, m), 0.87 ((CH$_2$)$_4$C<u>H</u>$_3$, 3H, t, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6 (ICH=<u>C</u>HCHOH), 77.1 (I<u>C</u>H=CHCHOH), 74.7 (ICH=CH<u>C</u>HOH), 36.5, 31.6, 24.7, 22.5, 13.9 (CHOH(<u>C</u>H$_2$)$_4$<u>C</u>H$_3$).

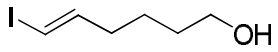
5.5.2.5 **(*E*)-3-Iodoprop-2-en-1-ol (5-93)**[22]



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

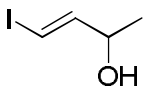
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (ICH=C<u>H</u>CH$_2$, dt, 1H, J = 14.6 Hz, J = 5.4 Hz), 6.37 (IC<u>H</u>=CHCH$_2$, d, 1H, J = 13.9 Hz), 4.07 (C<u>H</u>$_2$OH, s (br), 2H), 1.55 (CH$_2$O<u>H</u>, s, 1H), 1.53-1.14 (CHCH$_2$(C<u>H</u>$_2$)$_6$CH$_2$OH, m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6 (ICH=<u>C</u>HCH$_2$), 77.8 (I<u>C</u>H=CHCH$_2$), 65.1 (<u>C</u>H$_2$OH).

5.5.2.6 **(*E*)-6-Iodohex-5-en-1-ol (5-169)**[47]



Vinyl iodide **5-169** was isolated in 94% and 76% yield in inseparable ratios of 95:5 and 99:1 (*trans*:*gem*) respectively from the corresponding alkyne using the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (ICH=C<u>H</u>CH_2, dt, 1H, J = 14.3 Hz, J = 7.1 Hz), 5.97 (IC<u>H</u>=CHCH_2, d, 1H, J = 14.3 Hz), 3.59 (C<u>H</u>$_2$OH, t, 2H, J = 5.6 Hz), 2.05 (ICH=CHC<u>H</u>$_2$, q, 2H, J = 6.9 Hz), 1.70 (CH_2O<u>H</u>, s, 1H), 1.57-1.39 (CHCH_2(C<u>H</u>$_2$)$_2$$CH_2$OH, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2 (ICH=<u>C</u>HCH_2), 74.8 (I<u>C</u>H=CHCH_2), 62.4 (<u>C</u>H_2OH), 35.7 (ICH=CH<u>C</u>H_2), 31.8, 24.8 (CHCH_2(<u>C</u>H_2)$_2$$CH_2$OH).

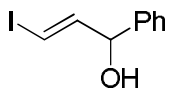
5.5.2.7 **(*E*)-4-Iodobut-3-en-2-ol (5-172)**[48]



Vinyl iodide **5-172** was isolated in 93% yield in a separable ratio of 95:5 (*trans*:*gem*) from the corresponding alkyne using the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (ICH=C<u>H</u>CH, dd, 1H, J = 14.5 Hz, J = 6.0 Hz), 6.32 (IC<u>H</u>=CHCH, dd, 1H, J = 14.4 Hz, J = 1.1 Hz), 4.25 (C<u>H</u>OH, m, 1H), 1.84 (CHO<u>H</u>, d, 1H, J = 4.2 Hz), 1.24 (C<u>H</u>$_3$CHOH, d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5 (ICH=<u>C</u>HCH), 76.7 (I<u>C</u>H=CHCH), 70.6 (<u>C</u>HOH), 22.6 (<u>C</u>H_3CHOH).

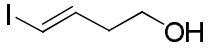
5.5.2.8 **(*E*)-3-Iodo-1-phenylprop-2-en-1-ol (5-175)**[49]



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

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.30 (Ph<u>H</u>, m, 5H), 6.70 (ICH=C<u>H</u>CH, dd, 1H, J = 14.4 Hz, J = 5.9 Hz), 6.45 (IC<u>H</u>=CHCH, dd, 1H, J = 14.5 Hz, J = 1.1 Hz), 5.13 (C<u>H</u>OH, m, 1H), 2.21 (CHO<u>H</u>, d, 1H, J = 3.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1 (ICH=<u>C</u>HCH), 141.9, 128.7 (2C), 128.2, 126.3 (2C) (<u>Ph</u>), 78.1 (I<u>C</u>H=CHCH), 76.6 (<u>C</u>HOH).

5.5.2.9 **(*E*)-4-Iodobut-3-en-1-ol (5-41)**[13]

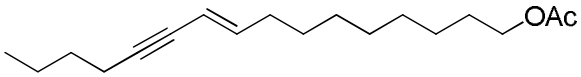


Vinyl iodide **5-41** was isolated in 84% yield in a separable ratio of 83:17 (*trans*:*gem*) from the corresponding alkyne using the general procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (ICH=C<u>H</u>CH_2, dt, 1H, J = 14.4 Hz, J = 7.3 Hz), 6.13 (IC<u>H</u>=CHCH_2, d, 1H, J = 14.4 Hz), 3.65 (C<u>H</u>$_2$OH, q, 2H, J = 6.0 Hz), 2.05 (ICH=CHC<u>H</u>$_2$, q, 2H, J = 6.2 Hz), 1.62 (CH_2O<u>H</u>, t, 1H, J = 5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6 (ICH=<u>C</u>HCH_2), 77.2 (I<u>C</u>H=CHCH_2), 60.9 (<u>C</u>H$_2$OH), 39.1 (ICH=CH<u>C</u>H$_2$).

5.5.3 Synthesis of pheromones 5-179 and 5-183

5.5.3.1 **(E)-Hexadec-9-en-11-ynyl acetate (5-178)**[50]

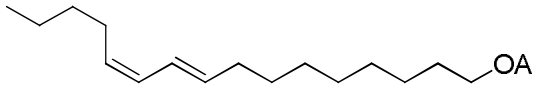


To a degassed mixture of aqueous NaOH (100 mL, 10 % solution in H_2O) and benzene (55 mL), were added successively iodides (**5-167** : **5-168**, 95:5 ratio) (16.54 g, 51.0 mmol), $BnNEt_3Cl$ (0.23 g, 1.0 mmol), $Pd(PPh_3)_4$ (1.1 g, 1.0 mmol) and CuI (0.38 g, 2.0 mmol). Hexyne (11.7 mL, 0.100 mol) was then added and the reaction mixture was stirred vigorously (to ensure the two phase system was emulsified) for 24 h. The reaction mixture was diluted with hexane the layers were separated, and the aqueous layer was extracted with hexane (2 X 150 ml). The organic layers were combined and washed with saturated NH_4Cl (3 X 100 mL), brine (2 X 100 mL), dried over Na_2SO_4 and concentrated. The resulting oil was purified by silica gel (600 g) chromatography (25/1 : hexane/ ether) to afford enyne **5-178** compound in 82% (11.7 g) isolated yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 ($CCCH=C\underline{H}CH_2$, dt, 1H, J = 15.8 Hz, J = 7.0 Hz), 5.37 ($CCC\underline{H}=CHCH_2$, d, 1H, J = 15.0 Hz), 3.98 ($C\underline{H}_2OCOCH_3$, t, 2H, J = 6.7 Hz), 2.20 ($C\underline{H}_2CC$, dt, 2H, J = 7.2 Hz, J = 1.9 Hz), 2.01-1.98 ($CH_2OCOC\underline{H}_3$, s, 3H) ($CCH=CHC\underline{H}_2$, q, 2H, J = 7.3 Hz), 1.55-1.23 ($CHCH_2(C\underline{H}_2)_6CH_2O$, m, 12H) ($CH_3(C\underline{H}_2)_2CH_2CC$, m, 4H), 0.85 ($C\underline{H}_3(CH_2)_3CC$, t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 ($O\underline{C}OCH_3$), 143.0, 109.8 ($CC\underline{C}H=\underline{C}HCH_2$), 88.5, 79.0 ($\underline{CC}CH=CH$), 64.5 ($\underline{C}H_2OCOCH_3$), 32.8, 30.8,

29.2, 29.1, 28.9, 28.7, 28.5, 25.8, 21.9, 20.9, 18.9, 13.5 ($CH(\underline{C}H_2)_7CH_2OCO\underline{C}H_3$) ($\underline{C}H_3(\underline{C}H_2)_3CC$).

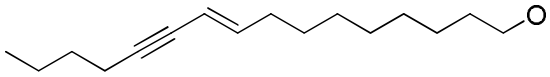
5.5.3.2 **(9*E*,11*Z*)-Hexadeca-9,11-dienyl acetate (5-179)**[38]



To a solution of 2-methyl-2-butene (20.8 mL, 195 mmol) in THF (65 ml) at 0 ^oC was added borane dimethyl sulfide (9.70 mL, 97.0 mmol). After 1 h of stirring at 0 ^oC, the disiamylborane was syringed, dropwise, to a solution of enyne **5-178** (17.5 g, 65.0 mmol) in THF (65 mL) at 0 ^oC over a period of 30 min. The reaction mixture was allowed to stir at 0 ^oC for 4 h followed by the addition of AcOH (22 mL, 0.39 mol) slowly. The reaction was stirred at 55 ^oC for 6 h, let cool to rt and stirring was continued for 18 h. This was followed by the addition of NaOH (82 mL, 25 % in H_2O w/v) and H_2O_2 (22 mL, 30 % in H_2O) and stirring for 30 min at 40 ^oC. After cooling the reaction, it was diluted with ether (200 mL), washed with brine (2 X 100 mL), dried over Na_2SO_4 and concentrated. The resulting oil was purified by silica gel (600 g) chromatography (30/1 : hexane/ ether) to afford the corresponding diene **5-179** in 70 % (12.20 g) isolated yield as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13($CH_3(CH_2)_3CH$=CH-C<u>H</u>=CH, dd, 1H, J = 14.7 Hz, J = 11.3 Hz), 5.76 ($CH_3(CH_2)_3CH$=C<u>H</u>-CH=CH, dd, 1H, J = 10.8 Hz), 5.46 ($CH_3(CH_2)_3CH$=CH-CH=C<u>H</u>, dt, 1H, J = 15.0 Hz, J = 7.0 Hz), 5.11 ($CH_3(CH_2)_3C$<u>H</u>=CH-CH=CH, dt, 1H, J = 10.5 Hz, J = 7.7 Hz), 3.88 (CH_2C<u>H</u>$_2$OCOCH_3, t, 2H, J = 6.7 Hz), 2.01-1.90 (C<u>H</u>$_2$CH=CH-CH=CHC<u>H</u>$_2$, m, 4H), 1.84 (OCOC<u>H</u>$_3$, s, 3H), 1.62-1.16 ((C<u>H</u>$_2$)$_2$$CH_2$CH=CH-CH=CH$CH_2$(C<u>H</u>$_2$)$_6$, m, 16H), 0.75 (C<u>H</u>$_3$$CH_2$, t, 3H, J = 6.7Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (O<u>C</u>OCH_3), 133.9 ($CH_3(CH_2)_3CH$=CH-CH=<u>C</u>H), 129.4 ($CH_3(CH_2)_3$<u>C</u>H=CH-CH=CH), 128.6 ($CH_3(CH_2)_3CH$=<u>C</u>H-CH=CH), 125.6 ($CH_3(CH_2)_3CH$=CH-<u>C</u>H=CH), 64.1 (<u>C</u>H_2OCOCH_3), 32.7, 31.7, 29.2 (2C), 29.0, 28.9, 28.5, 27.2, 25.7, 22.1, 20.5, 13.7 (<u>C</u>H_3(<u>C</u>H_2)$_3$$CH_D$=$CH_B$-$CH_A$=$CH_C$(<u>C</u>$H_2$)$_7$$CH_2$OCO<u>C</u>$H_3$).

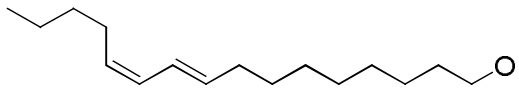
5.5.3.3 **(*E*)-Hexadec-9-en-11-yn-1-ol (5-181)**[50]



To a mixture of iodides (**5-165** : **5-166**, 95:5 ratio) (130 mg, 0.46 mmol), $Pd(PPh_3)_2Cl_2$ (32.0 mg, 0.046 mmol) and CuI (18.0 mg, 0.093 mmol) in 10 ml of Et_3N, was added a dilute solution of hexyne (76.0 mg, 0.93 mmol in 2 ml Et_3N) at rt. The reaction was allowed to stir for 16 h at rt. The reaction mixture was diluted with water (25 mL) and extracted the aqueous layer with ether (2 X 25 mL). Combined the organic layers and washed with saturated NH_4Cl (2 X 30 mL), brine (2 X 30 mL), dried over $NaSO_4$ and

concentrated. The resulting oil was purified by silica gel (7 g) chromatography (3/1 : hexane/ ether) to afford enyne **5-181** in 85 % (92 mg) isolated yield as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (CCCH=C<u>H</u>CH_2, dt, 1H, J = 15.8 Hz, J = 7.2 Hz), 5.42 (CCC<u>H</u>=$CHCH_2$, d, 1H, J = 16.0 Hz), 3.61 (C<u>H</u>$_2$OH, t, 2H, J = 6.3 Hz), 2.27 (C<u>H</u>$_2$CCCH=CH, dt, 2H, J = 7.2 Hz, J = 1.9 Hz), 2.03 (CCCH=CHC<u>H</u>$_2$, q, 2H, J = 7.3 Hz), 1.53-1.16 ($CHCH_2$(C<u>H</u>$_2$)$_6$$CH_2$O, m, 12H) ($CH_3$(C<u>H</u>$_2$)$_2$$CH_2$CC, m, 4H), 0.89 (C<u>H</u>$_3$(CH_2)$_3$CC, t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 109.7 (CC<u>C</u>H=<u>C</u>HCH_2), 88.5, 79.0 (<u>CC</u>CH=CH), 63.7 (<u>C</u>H$_2$OH), 32.8, 32.6, 30.8, 29.3, 29.2, 28.9, 28.7, 25.6, 21.8, 18.9, 13.5 (CH(<u>C</u>H$_2$)$_7$$CH_2$OH) (<u>C</u>H$_3$(<u>C</u>H$_2$)$_3$CC).

5.5.3.4 **(9*E*,11*Z*)-Hexadeca-9,11-dien-1-ol (5-182)**[41]

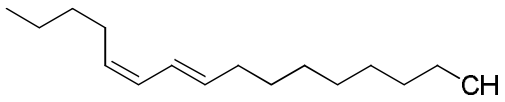


To a solution of 2-methyl-2-butene (0.15 mL, 1.44 mmol) in THF (5 mL) at 0 ^{o}C was added borane dimethyl sulfide (0.07 mL, 0.72 mmol). After 1 h of stirring at 0 ^{o}C a solution of enyne **5-181** (85 mg, 0.36 mmol) in THF (1 mL) was added dropwise. The reaction mixture was allowed to stir at 0 ^{o}C for 4 h followed by the addition of AcOH (0.16 ml, 2.9 mmol) slowly. The reaction was stirred at 55 ^{o}C for 6 h, let cool to rt and stirring was continued for 18 h. This was followed by the addition of NaOH (0.29 mL, 50 % in H_2O w/v) and H_2O_2 (0.16 mL, 30 % in H_2O) and stirring for 30 min at 40 ^{o}C. After cooling the reaction, it was diluted with ether (30 mL), washed with brine (2 X 30

mL), dried over $NaSO_4$ and concentrated. The resulting oil was purified by silica gel (180 g) chromatography (3/1 : hexane/ ether) to afford diene **5-182** in 94 % (81 mg) isolated yield as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 ($CH_3(CH_2)_3CH$=CH-C<u>H</u>=CH, dd, 1H, J = 14.6 Hz, J = 11.4 Hz), 5.90 ($CH_3(CH_2)_3CH$=C<u>H</u>-CH=CH, dd, 1H, J = 10.8 Hz), 5.60 ($CH_3(CH_2)_3CH$=CH-CH=C<u>H</u>, dt, 1H, J = 15.0 Hz, J = 6.9 Hz), 5.25 ($CH_3(CH_2)_3C$<u>H</u>=CH-CH=CH, dt, 1H, J = 10.4 Hz, J = 7.7 Hz), 3.58 (CH_2C<u>H</u>$_2$OH, t, 2H, J = 6.6 Hz), 2.14-2.01 (C<u>H</u>$_2$CH=CH-CH=CHC<u>H</u>$_2$, m, 4H), 1.92 (CH_2O<u>H</u>, s, 1H), 1.52-1.22 ((C<u>H</u>$_2$)$_2$CH$_2$CH=CH-CH=CHCH$_2$(C<u>H</u>$_2$)$_6$, m, 16H), 0.87 (C<u>H</u>$_3$CH$_2$, t, 3H, J = 6.7Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5 ($CH_3(CH_2)_3CH$=CH-CH=<u>C</u>H), 130.0 ($CH_3(CH_2)_3$<u>C</u>H=CH-CH=CH), 128.5 ($CH_3(CH_2)_3CH$=<u>C</u>H-CH=CH), 125.6 ($CH_3(CH_2)_3CH$=CH-<u>C</u>H=CH), 62.8 (<u>C</u>H$_2$OH), 32.8, 32.7, 31.8, 29.4, 29.3 (2C), 29.1, 27.3, 25.7, 22.2, 13.7 (<u>C</u>H$_3$(<u>C</u>H$_2$)$_3$CH=CH-CH=CH(<u>C</u>H$_2$)$_7$CH$_2$OH).

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



A mixture of PDC (192 mg, 0.51 mmol) and 3 ´ sieves (100 mg) in CH_2Cl_2 (10 mL) were stirred at rt. A solution of alcohol **5-182** (81 mg, 0.34 mmol) in CH_2Cl_2 (1 mL) was added dropwise and let stir for 18 h at rt. The reaction mixture was diluted with ether,

passed through a Celite plug and concentrated. The resulting oil was purified by silica gel chromatography (10 g, 15/1 : hexane/ ether) to afford aldehyde **5-183** in 91 % (73 mg) isolated yield as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (C<u>H</u>O, s, 1H), 6.28 ($CH_3(CH_2)_3CH$=CH-C<u>H</u>=CH, dd, 1H, J = 14.3 Hz, J = 11.7 Hz), 5.91 ($CH_3(CH_2)_3CH$=C<u>H</u>-CH=CH, dd, 1H, J = 10.8 Hz), 5.62 ($CH_3(CH_2)_3CH$=CH-CH=C<u>H</u>, dt, 1H, J = 15.0 Hz, J = 6.9 Hz), 5.27 ($CH_3(CH_2)_3C$<u>H</u>=CH-CH=CH, dt, 1H, J = 10.2 Hz, J = 7.7 Hz), 2.39 ($CH_3(CH_2)_2CH_2CH$=CH-CH=CHC<u>H_2</u>, t, 2H, J = 7.3 Hz), 2.14-1.29 (C<u>H_2</u>CHO, 1.62-1.16 (($C\underline{H_2})_3CH$=CH-CH=$CHCH_2(C\underline{H_2})_6$, m, 18H), 0.88 (C<u>$H_3$</u>$CH_2$, t, 3H, J = 6.5Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4 (<u>C</u>HO), 134.2 ($CH_3(CH_2)_3CH$=CH-CH=<u>C</u>H), 129.9 ($CH_3(CH_2)_3$<u>C</u>H=CH-CH=CH), 128.5 ($CH_3(CH_2)_3CH$=<u>C</u>H-CH=CH), 125.6 ($CH_3(CH_2)_3CH$=CH-<u>C</u>H=CH), 43. (<u>C</u>H_2CHO), 32.7, 31.7, 29.2 (2C), 32.7, 31.8, 29.2, 29.1, 29.0, 28.9, 27.3, 22.2, 21.9, 13.8 (<u>C</u>H_3(<u>C</u>$H_2)_3CH$=CH-CH=CH(<u>C</u>$H_2)_6CH_2$CHO).

Spectral data were in accord with literature data.

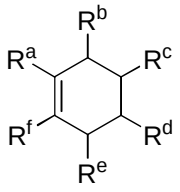
Chapter 6

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

6.1 Introduction

6.1.1 General

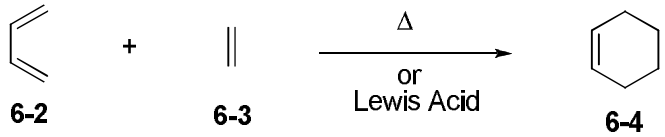
Functionalized cyclohexenes (**6-1**) are important intermediates in natural product synthesis (Figure 6.1).[1-12]



6-1

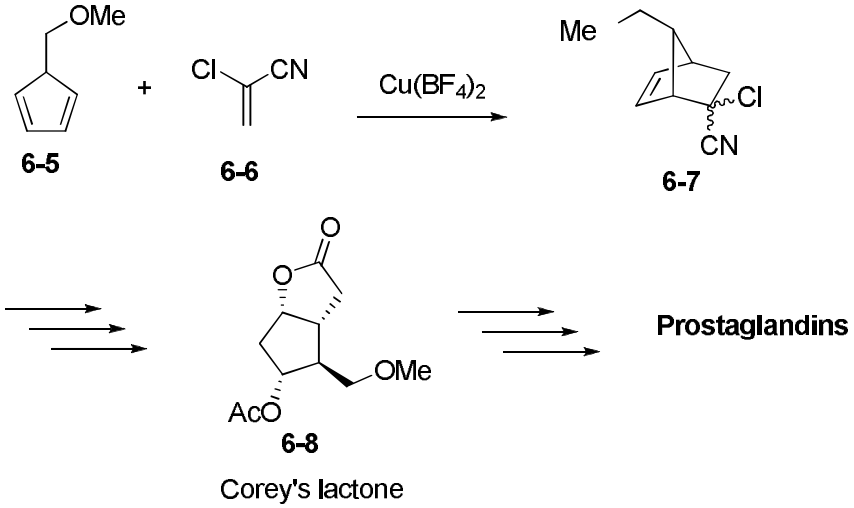
Figure 6.1 Functionalized cyclohexene

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



Scheme 6.1

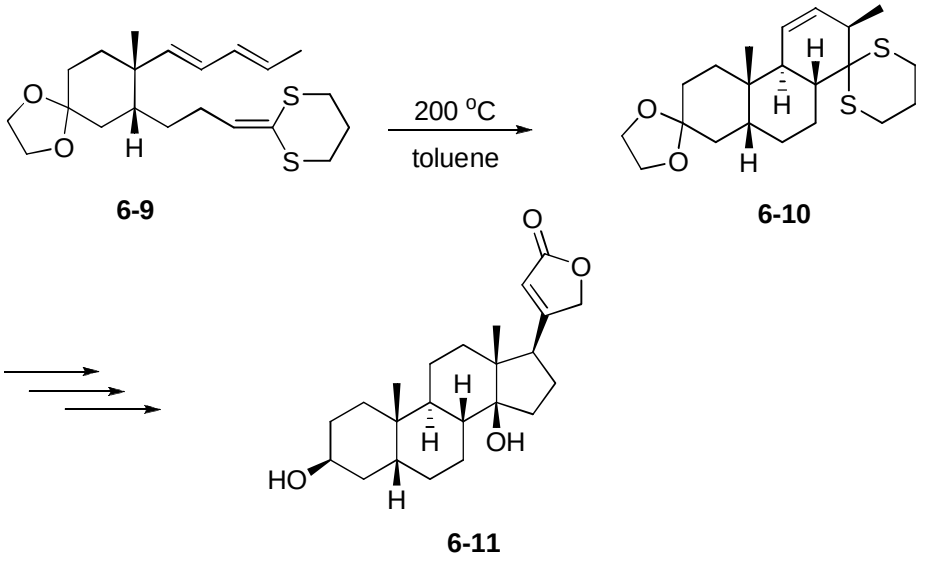
Diels-Alder reaction between cyclopentadiene **6-5** and chloroacetonitrile **6-6** generated bicyclic product **6-7** as a mixture of stereoisomers, which was an important step leading to the synthesis of Corey's lactone **6-8** (Scheme 6.2).[24]



Scheme 6.2

Corey's lactone **6-8** was an important intermediate that lead to the syntheses of several prostaglandins.[24-26]

Stork *et al.* incorporated an intramolecular Diels-Alder reaction to establish the core rings of (+)-degitoxigenin **6-11**, a steroid derivative (Scheme 6.3).[27]



Scheme 6.3

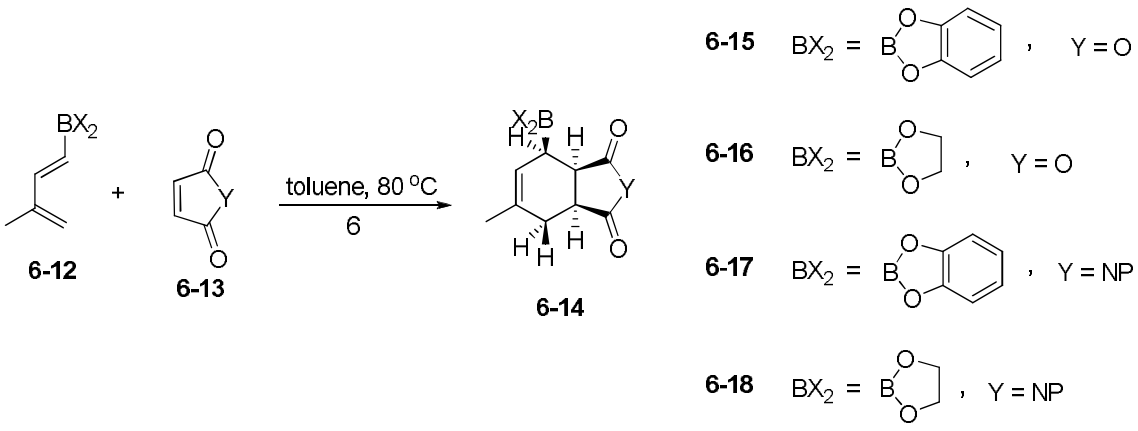
Intramolecular Diels-Alder reaction provided two six-membered carbocyclic rings with three additional stereocenters all in one step.[27]

These examples demonstrate how Diels-Alder reactions can contribute an important role in forming functionalized cyclohexenes.

6.1.2 Vaultier tandem reaction

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

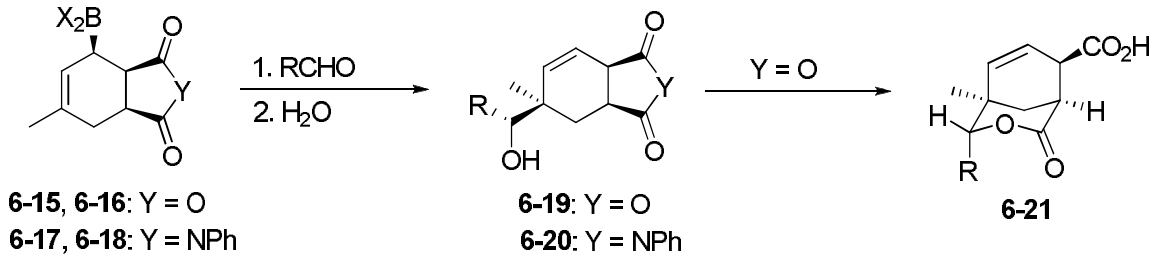
The stereochemistry of the Diels-Alder adducts were established on the basis of the ^{1}H NMR data to be the *endo* adducts (Scheme 6.4).[28]



Scheme 6.4

Treatment of allylboronates with aldehydes reacted smoothly in a highly diastereoselective fashion to produce the corresponding cyclohexenes (Table 6.1).[28]

Table 6.1 Synthesis of cyclohexenes *via* Vaultier tandem reaction.[28]



6-15, **6-16**: Y = O
6-17, **6-18**: Y = NPh

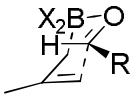
6-19: Y = O
6-20: Y = NPh

6-21

entry	Y	R	yield (%)
1	NPh	Ph	69
2	NPh	*i*Pr	67
3	NPh	Et	66
4	O	Ph	80[a]
5	O	*i*Pr	75[a]
6	O	Et	70[a]

[a] Isolated yield of corresponding lactone.

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

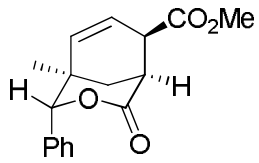


6-2
Zimmerman-Traxler transition structure

Figure 6.2 Transition structure of **6-22**[29]

Good yields of the newly formed bicyclic adducts were isolated, except for adducts with Y = O, which cyclized spontaneously upon hydrolysis to form the corresponding lactones in good yields.[28]

The stereochemical assignment was confirmed by an X-ray analysis of the methyl ester of acid **6-21** (R = Ph) (Figure 6.3).[28]

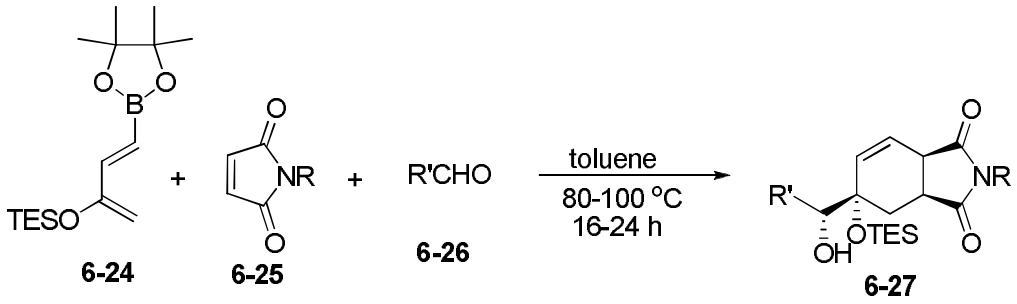


6-2

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

Gao and Hall were able to improve the Vaultier tandem reaction by expanding the scope of aldehydes, shorten the reaction times and obtain higher yields by using electron-rich dienylboronate **6-24** (Table 6.2).[30]

Table 6.2 Tandem [4+2]/allylboration of diene **6-24**.[30]

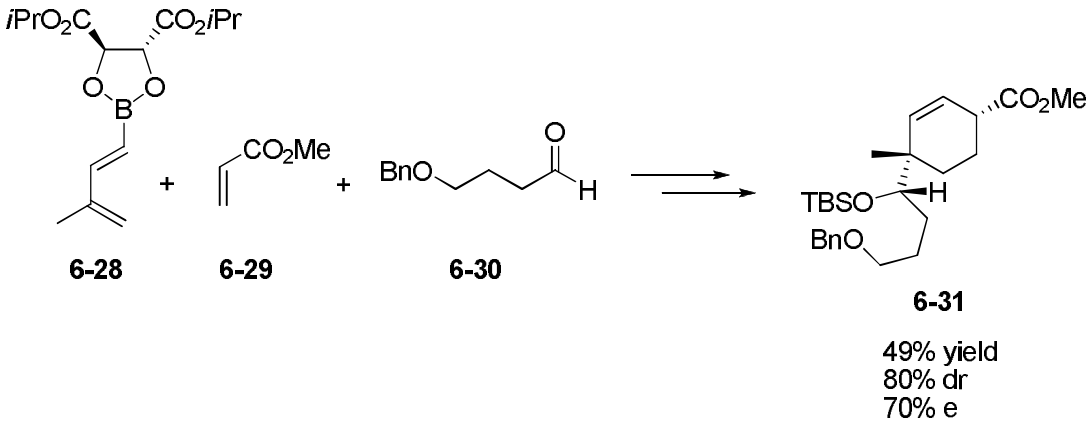


entry	dienophile (R)	aldehyde (R')	yield (%)[a]
1	Ph	C_6H_5	76
2	Ph	4-NO_2-C_6H_4	92
3	Ph	4-MeO-C_6H_4	82
4	Ph	4-Br-C_6H_4	93
5	Ph	*i*-PrCH_2	88
6	Me	4-NO_2-C_6H_4	89
7	Me	4-MeO-C_6H_4	67
8	Me	4-Br-C_6H_4	78

[a] Typical reaction scale: 1.0 mmole diene, 1.1 mmole dienophile, 1.1 mmol aldehyde, 1.0 M in toluene.

Aliphatic and aromatic aldehydes (both electron-poor and electron-rich) provided the desired product in excellent selectivities and yields.[30] Cycloaddition proceeded with complete *endo*-selectivity to furnish an allylboronate intermediate, which then reacts with an aldehyde, *via* a cyclic chair-like transition state, to provide an allylboration product.[30] *N*-acryloyl-oxazolidinone and methyl acrylate were able to react with electron-rich diene **6-24**, but provided higher selectivities for the *exo*-adduct.[30]

In 1996, Renard and Lallemand demonstrated an asymmetric tandem reaction by using chiral dienylboronate **6-28** derived from a tartrate ester (Scheme 6.5).[31]



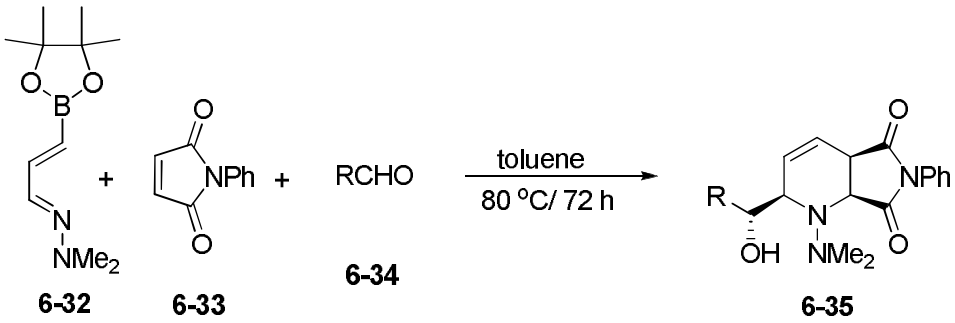
Scheme 6.5

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

This methodology was later used part of a total synthesis of Clerodin, which exhibits antifeedant activity that can be of use in the protection of crops against insects.[32]

In 2000, Tailor and Hall introduced the tandem aza[4+2]/allylboration using hydrazonediene **6-32** (Table 6.3).[29]

Table 6.3 Tandem aza[4+2]/allylboration with diene **6-32**.[29]



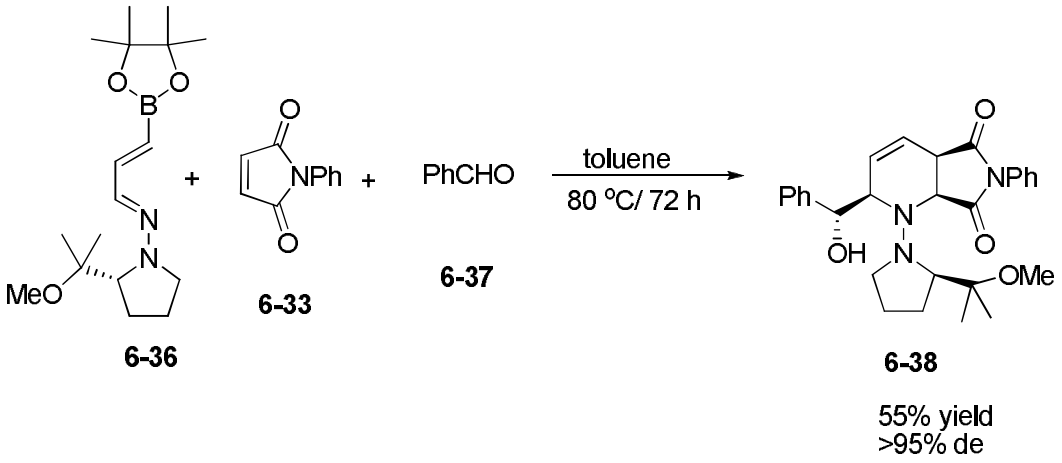
6-32 **6-33** **6-34** **6-35**

entry	aldehyde (R)	yield (%)[a]
1	Ph	47
2	4-NO_2-C_6H_4	48
3	4-MeO-C_6H_4	52
4	*i*-$PrCH_2$	50

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

Cycloaddition followed by allylation proceeded as anticipated with diene **6-32** to provide *α*-hydroxyalkyl piperidine derivatives **6-35** in moderate yields.[29]

A diastereoselective version of this reaction was also demonstrated to exhibit high degrees of stereocontrol (Scheme 6.6).[29]



6-36 **6-33** **6-37** **6-38**

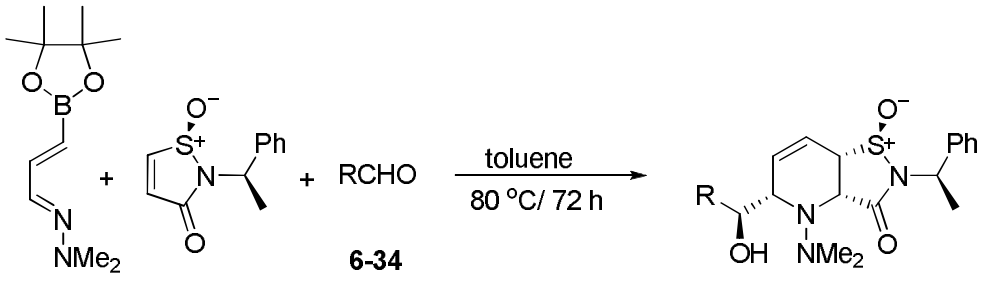
55% yield
>95% de

Scheme 6.6

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

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

Table 6.4 Aza[4+2]/Allylboration with chiral dienophile **6-39**.[33]

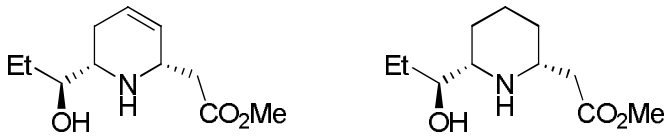


6-32 **6-39** **6-34** **6-40**

entry (adduct)	aldehyde (R)	yield (%)[a]
1	Ph	50
2	*n*-Bu	52
3	Et	44

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

Moderate yields of bicyclic piperidines were isolated. Out of the many possible regio- and stereoisomers, only one isomer was obtained.[33] The regiochemistry of the aza-Diels-Alder reaction was controlled by the electron-rich hydrazine and the carbonyl of the dienophile, which overrode the effect of the sulfoxide group.[33] *Endo*-adducts were only observed which selected the face away from the oxygen of the sulfoxide, thus providing perfect facial selectivity.[33] This methodology was used as part of the total syntheses of natural products (-)-methyl palustramate **6-41** and (-)-methyl dihydropalustramate **6-42** (Figure 6.4).[33,34]

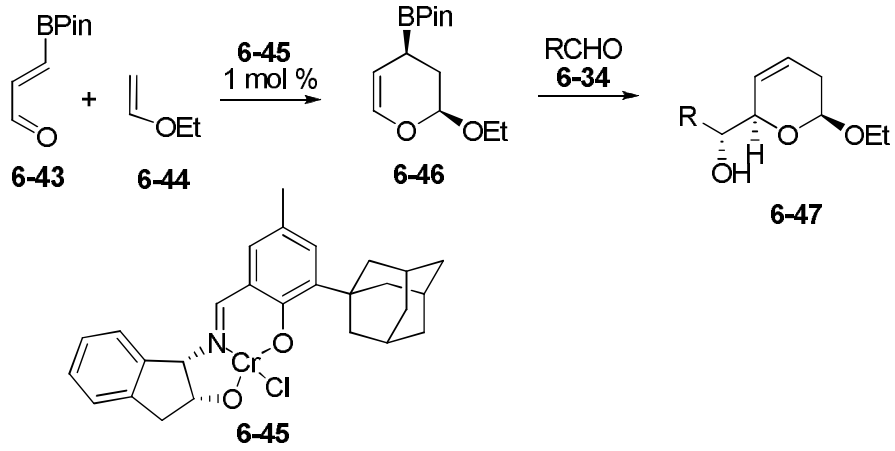


6-41 **6-4**

Figure 6.4 (-)-Methyl palustramate **6-41** and (-)-methyl dihydropalustramate **6-42**

Polysubstituted pyrans can also be accessed by using the Vaultier tandem reaction. Gao and Hall have applied Jacobsen's conditions[35] to develop the first catalytic enantio- and diastereoselective inverse electron demand hetero[4+2]/allylboration reaction to provide a practical route to *α*-hydroxyalkyl pyran derivatives **6-47** (Table 6.5).[36]

Table 6.5 Enantioselective hetero[4+2]/allylboration reaction.[36]



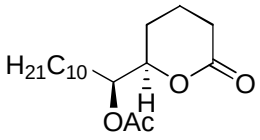
entry	aldehyde (R)	yield (%)[a]
1	C_6H_5	82
2	4-NO_2- C_6H_4	92
3	4-MeO- C_6H_4	81
4	$(CH_3)_2CHCH_2$	81
5	$TBSOCH_2$	82
6	$C_{10}H_{21}$	89
7	(*E*)-$CH_3CH{=}C(CH_3)$	61

[a] 2 mmol of distilled diene, 1 M in vinyl ethyl ether with 1 mol % of **6-45**, rt for 14 h, followed by addition of 2.0 equiv of aldehyde and stirred for 24 h.

Aromatic aldehydes, with different electronic characteristics, and aliphatic aldehydes afforded dihydropyran adducts in high yields and enantioselectivity (96% ee).

The enantioselectivity obtained in the Diels-Alder reaction was retained after the allylboration reaction.

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

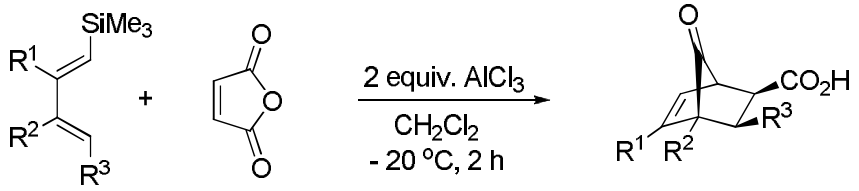


6-48

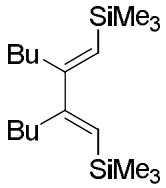
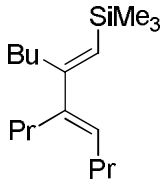
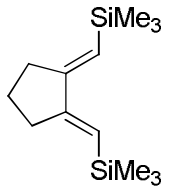
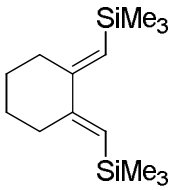
Figure 6.5

Just recently, Li *et al.* have demonstrated the Vaultier tandem reaction using the silyl analogue (Table 6.6).[38]

Table 6.6 Vaultier tandem reaction using silyl dienes.[38]

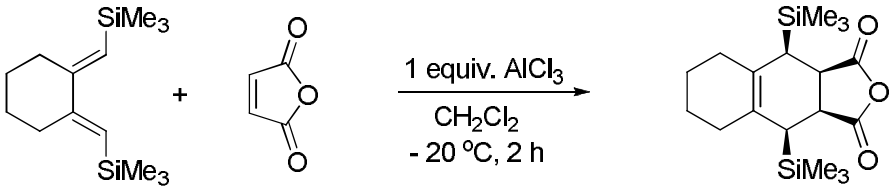


6-49 **6-50** **6-5**

entry	diene	yield (%)
1	 **6-52**	68
2	 **6-53**	76
3	 **6-54**	82
4	 **6-55**	75

7-Norbornenones were formed in good yields by treating maleic anhydride with tetrasubstituted 1-silyl-1,3-butadienes and two equivalents of freshly sublimed $AlCl_3$. 7-Norbornenones contained well-defined *exo,exo*-disubstituted patterns.

Diels-Alder adducts were isolated when 1 equivalent of $AlCl_3$ was used as shown in Scheme 6.7.

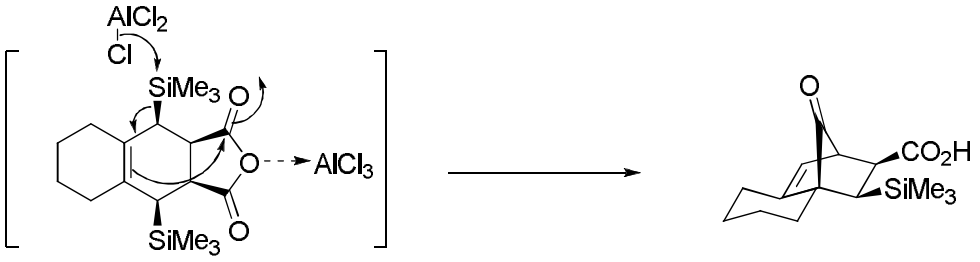


6-55 **6-50** **6-56**

72%

Scheme 6.7

X-ray analysis of Diels-Alder adduct **6-56** confirmed that it was the *endo* adduct. A second equivalent of $AlCl_3$ was required to facilitate the intramolecular allylation reaction of the carbonyl group to afford 7-norbornenones **6-57** (Scheme 6.8).[38]



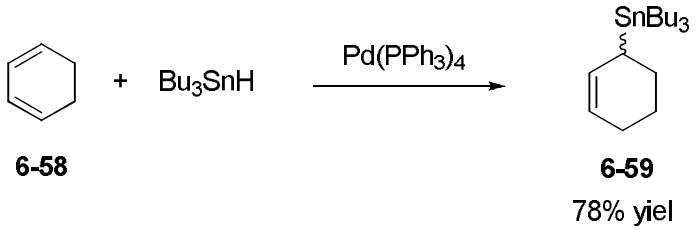
6-56 **6-5**

Scheme 6.8

This methodology is a synthetically useful tandem process for the preparation of *exo,exo*-disubstituted 7-norbornenones.[38]

6.1.3 Tin analogue of the Vaultier tandem reaction

To our knowledge, there has not been a Vaultier tandem reaction involving tin. Diels-Alder reaction between a 1-stannylbutadiene and a dienophile, thus providing a cyclic allylstannane intermediate, has not been reported. However, cyclic allylstannanes have been synthesized by different means. Palladium-catalyzed hydrostannation of conjugated cyclohexadiene **6-58** provided a route to racemic cyclic allylstannane **6-59** (Scheme 6.9).[39]

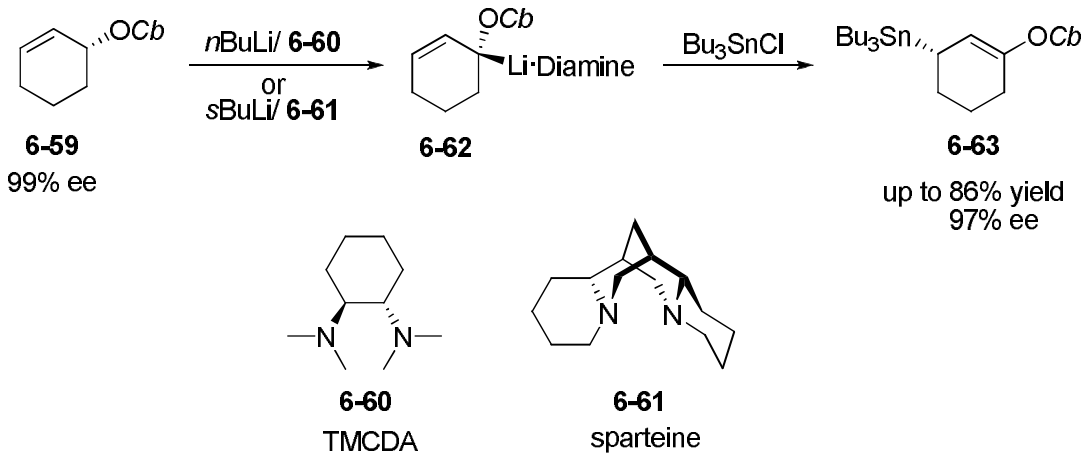


6-58 **6-59**

78% yiel

Scheme 6.9

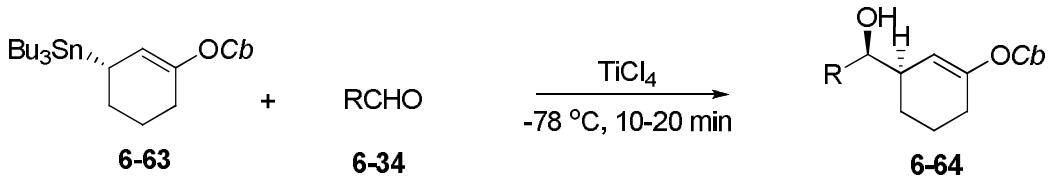
Alternatively, deprotonation of chiral carbamate **6-59** by BuLi with a chiral diamine, followed by stannylation translates the chirality of the starting material to the newly formed allylic stannane **6-63** in high selectivity (Scheme 6.10).[40]



Scheme 6.10

Allylation using cyclic allylstannanes have been reported.[41-43] Allylstannation of aldehydes by **6-63** using $TiCl_4$ proceeded with high *erythro* selectivity (dr > 98:2) (Table 6.7).[40]

Table 6.7 Allylstannation of aldehydes with $TiCl_4$.[40]

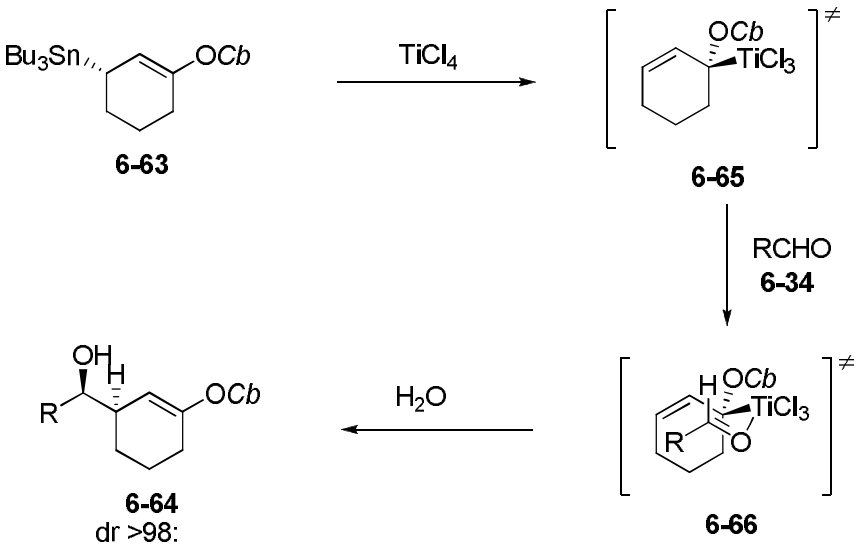


entry[a]	aldehyde (R)	yield (%)[b]
1	Ph	82
2	2-naphthyl	72
3	*p*-BrPh	80
4	*p*-MeOPh	81

5	2-furyl	50
6	Me	74
7	$CH(CH_3)_2$	70

[a] 1.3 equiv. $TiCl_4$, 1.3 equiv. RCHO.
[b] dr > 98:2 for all reactions as determined from the crude product by GC.

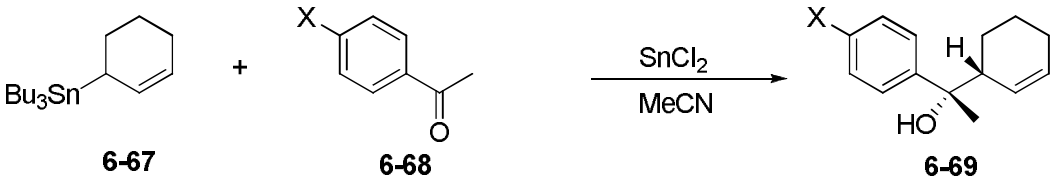
Homoaldol products were obtained from the corresponding cyclic allylstannane in moderate to good yields.[40] The product outcome can be explained by a Sn-Ti exchange in an *anti*-S_E' fashion, followed by a *syn* addition of the aldehyde *via* a Zimmerman-Traxler transition state **6-66** (Scheme 6.11).[40]



Scheme 6.11

Yasuda *et al.* demonstrated cyclic allylstannations with much challenging ketones are feasible with the use of $SnCl_2$ in acetonitrile (Table 6.8).[44]

Table 6.8 Cyclic allylstannation of ketones with $SnCl_2$.[44]

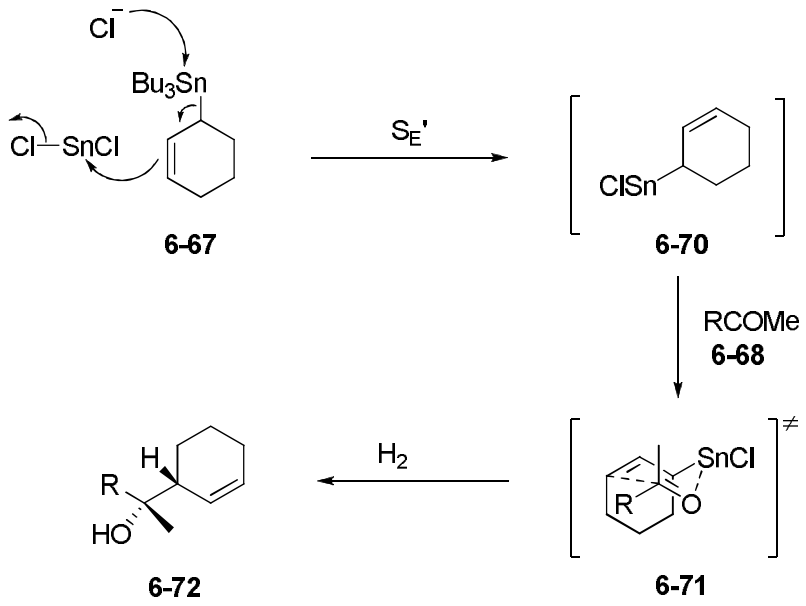


6-67 **6-68** **6-69**

entry[a]	ketone (X)	yield (%)
1	H	79
2	Cl	87
3	Br	96
4	Me	87
5	OMe	92[b]

[a] Allylic stannane 1.0 mmol, ketone 1.0 mmol, $SnCl_2$ 1.0 mmol at rt for 3 h.
[b] dr = 88:12; for other entries, dr > 99:1.

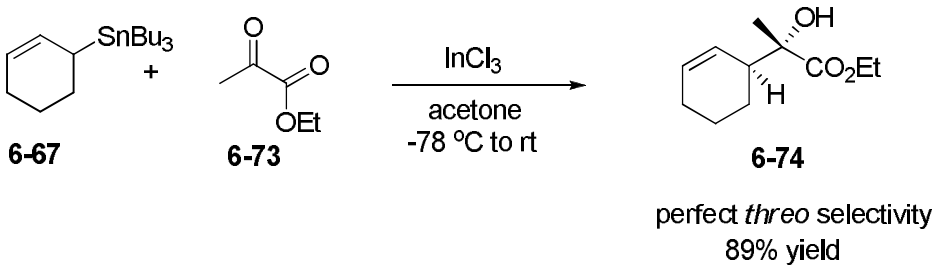
The reactions summarized in the Table 6.8 are highly diastereoselective except for trial 5. *Erythro* product was mostly observed, suggesting closed six-member transition states (Scheme 6.12).



Scheme 6.12

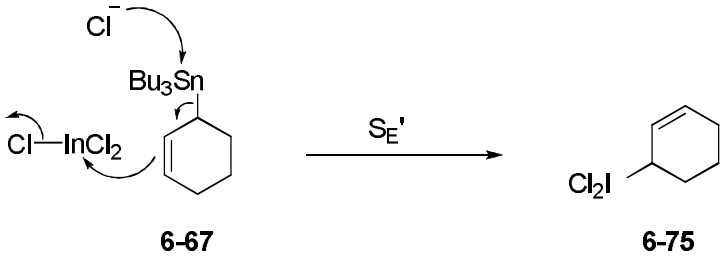
^{119}Sn NMR analysis strongly suggested the transmetallation between cyclic allylstannane **6-67** and $SnCl_2$ to generate a new allylic tin (II) species **6-70** which undergoes *syn* addition to the ketone (Scheme 6.12).[44]

Selectivity was reversed upon allylstannation of α-keto esters with $InCl_3$, as complete *threo*-diastereoselectivity was observed (Scheme 6.13).[45]



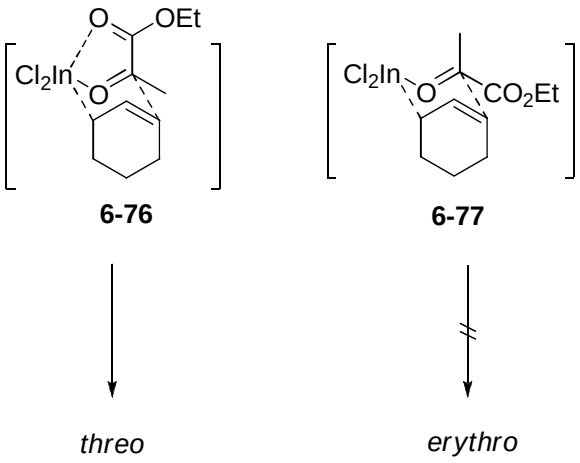
Scheme 6.13

A more reactive allylic indium species formed *via* an S_E' process followed by a *syn* addition of the ketone *via* cyclic transition state (Scheme 6.14).[45]



Scheme 6.14

The *threo*-selectivity obtained can be explained by the formation of an additional stable five-coordinate chelate exhibited in **6-76** during the transition state (Scheme 6.15).[45]

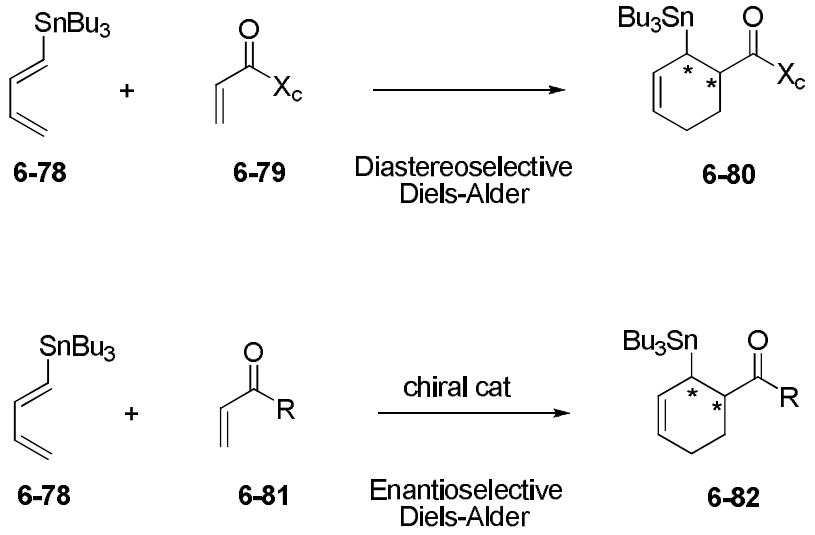


Scheme 6.15

The extra coordinations by the oxygens to the electrophilic indium centre allow for better stability of the transition state which in return translates to better regio- and stereocontrol.[45]

6.2 Proposed Work

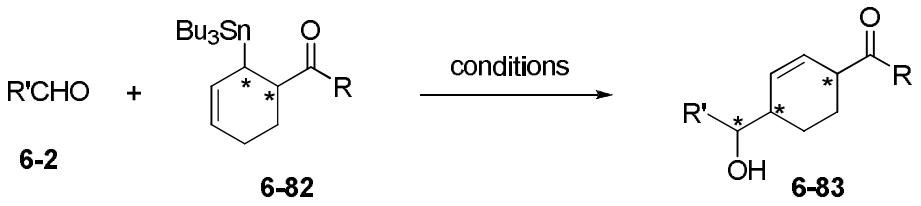
The purpose of this project is to examine Diels-Alder reactions of stannylbutadiene **6-78** and applications of the resulting allylstannanes, such as the Vaultier tandem reaction. Diastereoselective or enantioselective Diels-Alder reactions will be pursued in order to prepare isomerically pure allylic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



Scheme 6.16

In the case of diastereoselective Diels-Alder reactions, a chiral auxiliary would be attached to the dienophile, while in the case of enantioselective Diels-Alder reactions, a chiral catalyst would be used to promote the reaction and induce chirality at the same time.

The allylstannation portion of the Vaultier tandem reaction must have high degrees of stereo- and regiocontrol (Scheme 6.17).



6-2 6-82 6-83

Scheme 6.17

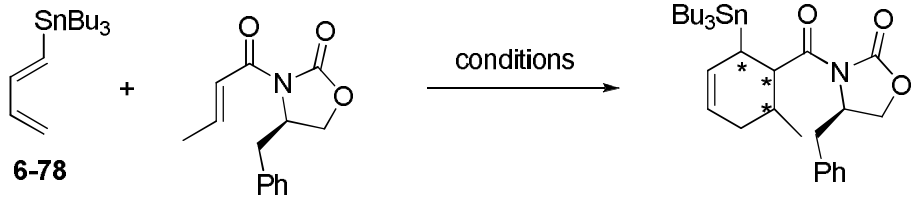
In order to achieve a tandem reaction, conditions used for the Diels-Alder reaction must be compatible for the allylstannation reaction as well.

6.3 Results and Discussion

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

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

Table 6.9 Screening conditions to promote cycloaddition between **6-78** and **6-84**



6-78 **6-84** **6-85**

entry	additives	yield (%)
1	toluene/ reflux	0
2	CH_2Cl_2/ rt	0
3	Et_2AlCl (1.4 equiv.), CH_2Cl_2, -78 ^oC to -15 ^oC	0
4	Me_2AlCl (1.4 equiv.), CH_2Cl_2, -78 ^oC to -15 ^oC	0

5	Et_2AlCl (0.15 equiv.), CH_2Cl_2, -78 ^oC to -15 ^oC	0
6	$BF_3.Et_2O$ (0.15 equiv.), CH_2Cl_2, -78 ^oC to 0 ^oC	0
7	$Mg(OTf)_2$ (0.1 equiv.), CH_2Cl_2, rt	0
8	$Sn(OTf)_2$ (0.1 equiv.), CH_2Cl_2, rt	0
9	$Mg(OTf)_2$ (0.1 equiv.), toluene, reflux	0
10	$Sn(OTf)_2$ (0.1 equiv.), toluene, reflux	0
11	$Ti(OiPr)_4$ (1.0 equiv.), CH_2Cl_2, rt	0

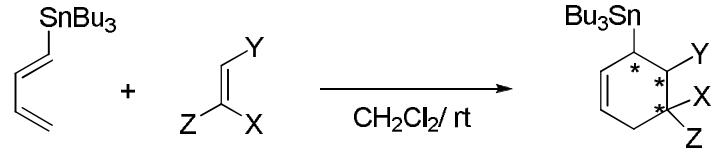
Unfortunately, stannyldiene **6-78** failed to react with dienophile **6-84** under thermal and Lewis acid promoted conditions. Starting materials were recovered in trials 1 and 2. There was considerable decomposition of stannyldiene **6-78**, observed by TLC, upon treatment with Lewis acids such as Et_2AlCl, $BF_3 \cdot Et_2O$, $Mg(OTf)_2$ and $Sn(OTf)_2$. Titanium Lewis acid $Ti(OiPr)_4$ used in trial 11 was compatible with stannyldiene **6-78** but did not promote any reaction at all.

These set of results suggested that dienophile **6-84** is not a good candidate for stannyldiene **6-78**, and stannyldiene **6-78** is quite susceptible to moderate Lewis acids.

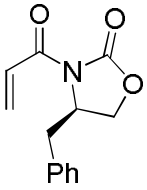
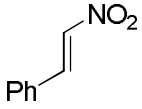
6.3.2 Screening for suitable dienophiles to react with stannyldiene 6-78

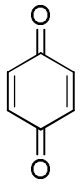
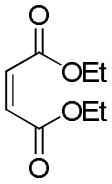
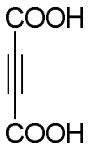
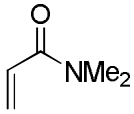
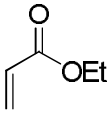
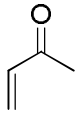
Turning to other dienophiles, stannyldiene **6-78** was screened to better understand the requirements of dienophiles for successful Diels-Alder reactions (Table 6.10).

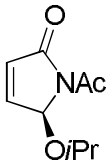
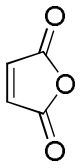
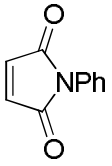
Table 6.10 Screening diene **6-78** with various dienophiles



6-78 **6-86** **6-87**

entry (product)	dienophile	yield (%)
1(**6-99**)	 **6-88**	NR
2(**6-100**)	 **6-8**	NR

3(**6-101**)	 **6-90**	trace
4(**6-102**)	 **6-91**	NR
5(**6-103**)	 **6-92**	NR
6(**6-104**)	 **6-93**	NR
7(**6-105**)	 **6-94**	NR
8(**6-106**)	 **6-95**	NR
9(**6-107**)	 **6-96**	NR
10(**6-108**)	 **6-9**	NR

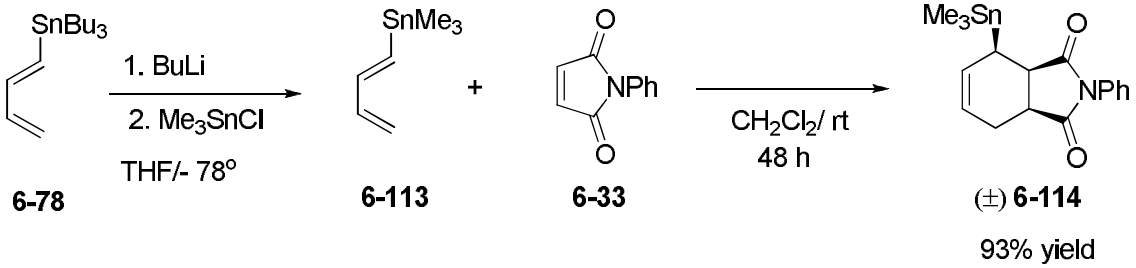
11(**6-109**)	 **6-98**	NR
12(**6-110**,**6-111**)	 **6-50**	100[a]
13(**6-112**)	 **6-33**	93

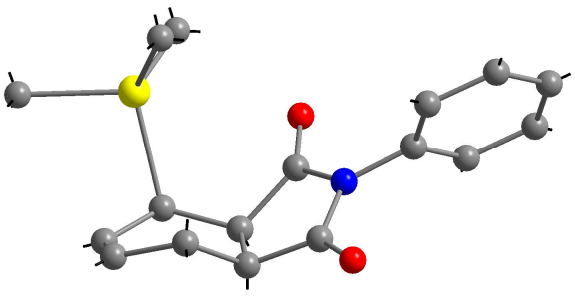
[a] 100% conversion based on ^{1}H NMR of the crude reaction mixture, *endo*:*exo* ~ 10:1

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

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

The stereochemistry of cycloadduct **6-112** was verified, by X-ray analysis of the Me_3Sn analogue **6-114**, to be the *endo* adduct (Scheme 6.18).





(±) 6-114

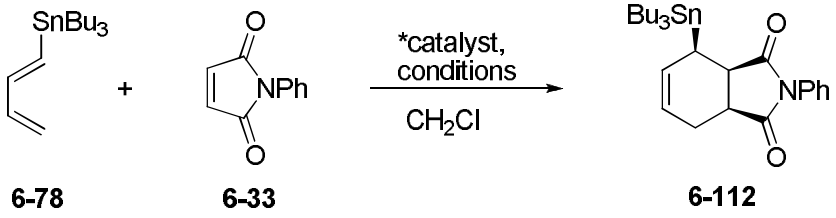
Scheme 6.18

Stannyldiene **6-113** was prepared by treating stannyldiene **6-78** with *n*BuLi followed by a quench with Me_3SnCl. The crude reaction mixture was then allowed to react with maleimide **6-33** at room temperature in CH_2Cl_2 to provide cycloadduct **6-114** in 93% yield as a single isomer (*endo*). Crystallization of cycloadduct **6-114** was achieved by very slow evaporation of CH_2Cl_2.

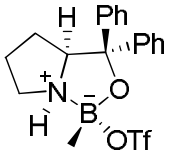
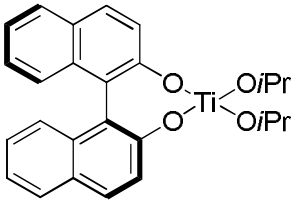
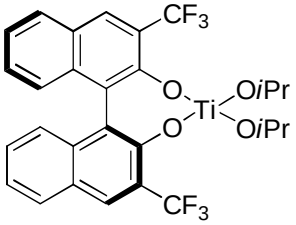
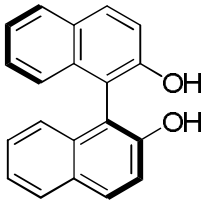
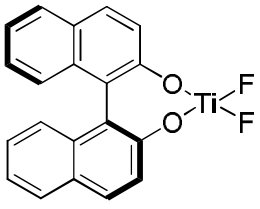
6.3.3 Enantioselective Diels-Alder reaction between stannyldiene 6-78 and maleimide 6-33

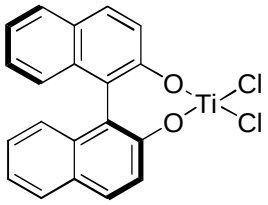
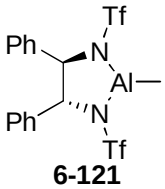
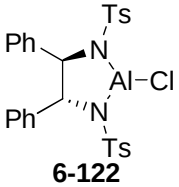
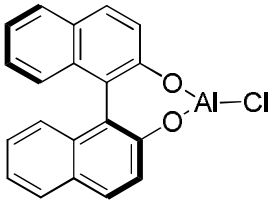
The Diels-Alder reaction of stannyldiene **6-78** and maleimide **6-33** did not occur below 0 ^oC (not detected by TLC after 3 h), thus opening the door to enantioselective Lewis acid catalysis. From previous trials (Table 6.9), stannyldiene **6-78** was not compatible with strong or moderate Lewis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

Table 6.11 Enantioselective Diels-Alder reaction with **6-78**



6-78 **6-33** **6-112**

entry	catalyst	conditions	ee (%)[b]	yield (%)
1	 **6-115**	cat. (7 mol %) -78 °C to rt	racemic	20[a]
2	 **6-116**	cat. (10 mol%) wet 4Å sieves 5 °C to rt	6	35
3	 **6-117**	cat. (10 mol%) wet 4Å sieves 10 °C to rt	racemic	25
4	 **6-118**	cat. (20 mol%) 0 °C to rt	racemic	3
5	 **6-11**	cat. (20 mol%) 0 °C	racemic	45

6	 **6-120**	cat. (20 mol%) 5 °C to rt	30	70
7	 **6-121**	cat. (20 mol%) -78 °C	-	NR
8	 **6-122**	cat. (20 mol%) 0 °C	racemic	10
9	 **6-123**	cat. (20 mol%) 0 °C	racemic	15

[a] *exo*-adduct was formed in 2:1 ratio with the *endo*-adduct.
[b] Determined by HPLC on Chiral OD

Protonated-oxazaborolidine **6-115** has been shown by Corey *et al.* to provide high enantioselectivity of the favoured *exo* adduct.[48] *α,β*-Unsaturated aldehydes were able to coordinate with oxazaborolidine **6-115** and achieve high facial selectivity.[48] In the case of Diels-Alder reaction between stannyldiene **6-78** and maleimide **6-33**, oxazaborolidine **6-115** promoted the formation of the *exo*-adduct in 2:1 ratio (*exo* : *endo*), while producing no enantioselectivity at all (Figure 6.6).

6-124
exo adduct

6-112
endo adduc

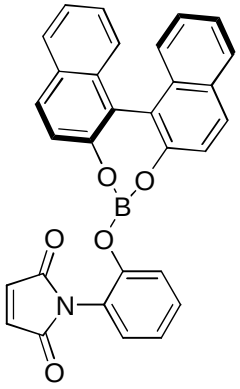
Figure 6.6 *Exo* and *endo* adducts **6-124** and **6-112**

Both cycloadducts were isolable on silica gel column, and the *exo* adduct was tentatively characterized as the other cycloadduct by ^{1}H NMR spectroscopy. Slight decomposition of the diene was observed, suggesting the protonated oxazaborolidine was not compatible with stannyldiene **6-78**. Diels-Alder products were only observed as the temperature was allowed to warm to room temperature, as no cycloadducts were formed below 0 ^{o}C. Mikami *et al.* have demonstrated the use of binaphthol-derived chiral titanium **6-120** (BINOL-Ti) catalytically to induce high enantioselectivity.[49] This catalyst was used on juglone, which is a cyclic doubly activated dienophile, similar to maleimide **6-33**. Mikami catalyst **6-120** showed significant enantioselectivity of 30% along with good isolated yield of 70%. No reaction was observed as the temperature was maintained at 0 ^{o}C. Chiral titanium **6-116**, a derivative of Mikami catalyst **6-120**, obtained much lower enantioselectivity excess of 6%, while other derivatives, **6-117** and **6-119**, completely failed at providing any enantioselectivity. Corey *et al.* also demonstrated by the use of aluminum-based catalyst **6-121** in Diels-Alder reactions, as high enantioselectivities and yields were obtained.[50] Unfortunately, no reaction was observed but stannyldiene decomposition was observed on the TLC. A similar catalyst by Itsuno *et al.* (**6-123**) was

applied to *N*-substituted maleimide and provided high enantioselectivity and yields.[51] Unfortunately, only racemic product and low yield was obtained when applied to stannyldiene **6-78** and maleimide **6-33**. A derivative of Corey's and Itsuno catalyst **6-122** also obtained racemic product and low yield. Free BINOL **6-118** did not provide any selectivity and hardly any reactivity at all. Titanium-binolate catalysts were much more compatible with stannyldiene **6-78**, as no decomposition was observed on TLC. On the other hand, aluminum-based or protonated-CBS catalysts were not compatible with stannyldiene **6-78**, as decomposition of the diene was observed on the TLC.

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

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

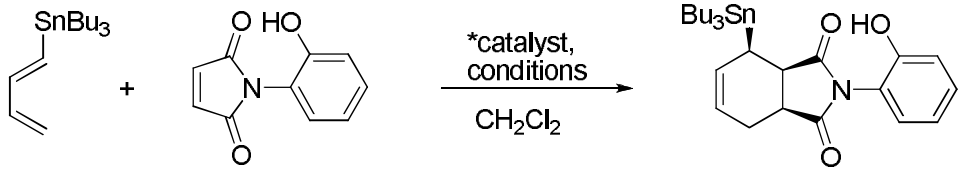


6-125

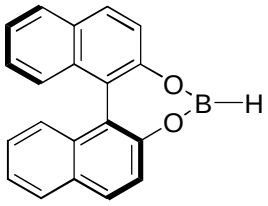
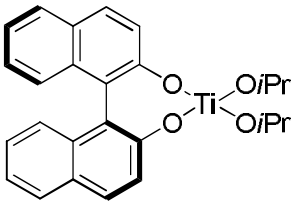
Figure 6.7 C_2-symmetric dienophile **6-125**

Chiral boronate was prepared *in situ* by the addition of the corresponding BINOL, BH_3·THF and acetic acid (Table 6.12).[52,53]

Table 6.12 Diastereoselective Diels-Alder using maleimide **6-126**



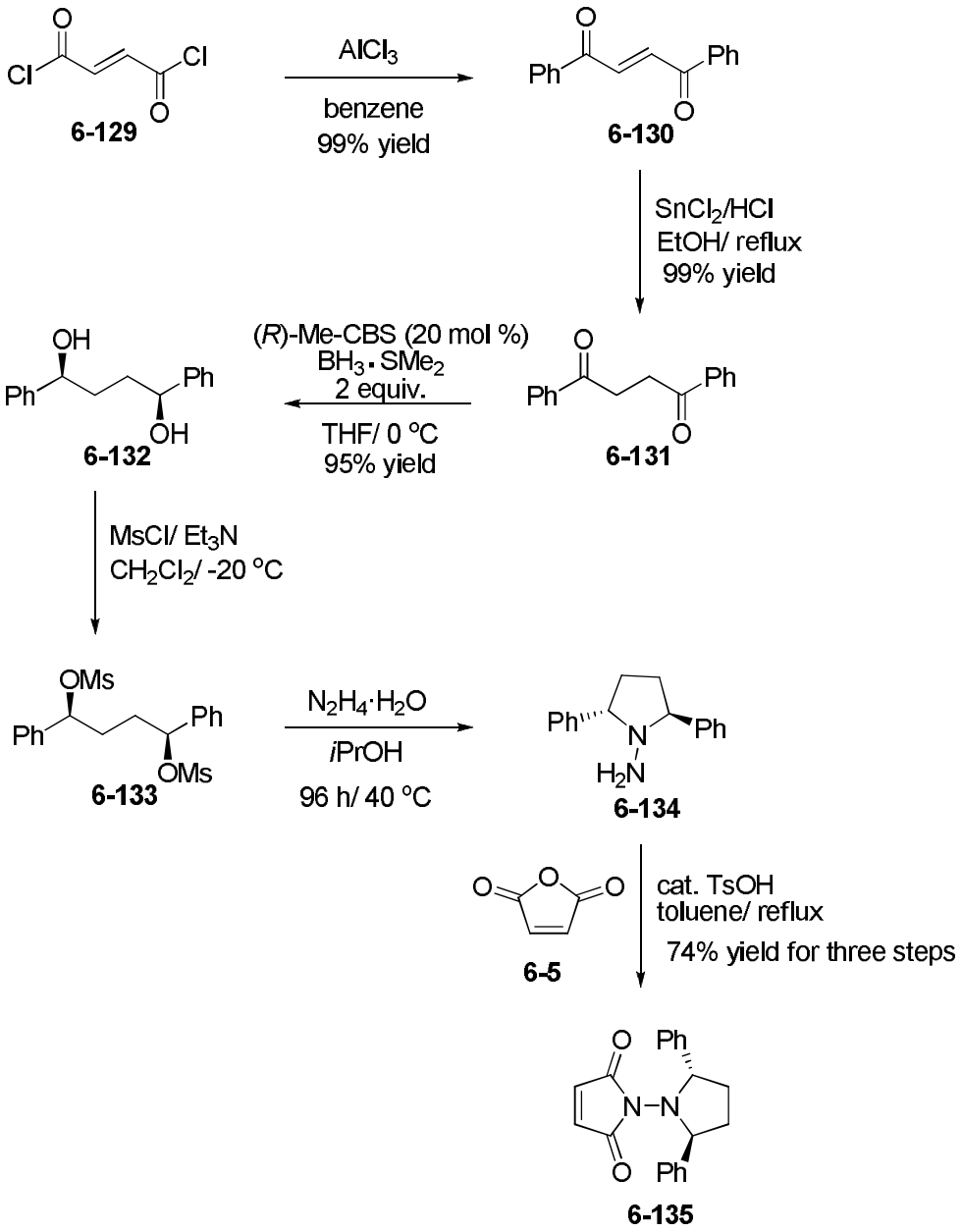
6-78 **6-126** **6-127**

entry	chiral ligand	ee (%)	yield (%)
1	none	racemic	90
2	 **6-128**	-	NR
3	 **6-116**	-	NR

As expected, achiral dienophile **6-126** reacted readily with stannyldiene **6-78** under thermal conditions to provide cycloadduct **6-127** in 90% yield. In the asymmetric version, chiral boronate was let to react with maleimide **6-126** followed by the addition of stannyldiene **6-78**. Unfortunately, the asymmetric version did not achieve any reactivity

at all. It was unclear if chiral dienophile **6-125** has formed *in situ*. The titanium analogue **6-116** was also tested but failed to react as well; it was also unclear whether or not the chiral titanium dienophile complex formed *in situ*.

The next approach tried was to install a C_2-symmetric moiety as part of the dienophile to effect diastereoselective Diels-Alder reactions. The chiral dienophile selected was maleimide **6-135** which has never been made. A linear six-step synthesis was devised for the preparation of dienophile **6-135** (Scheme 6.19).



Scheme 6.19

Synthesis of chiral dienophile **6-135** was accomplished in six linear steps in 69% overall yield. Friedel-Craft acylation of benzene with fumaryl chloride provided compound **6-130** in 99% yield.[54] Treatment of **6-130** with $SnCl_2$ hydrate in HCl furnished compound

6-131 in 99% yield.[55] Reduction by (*R*)-Me-CBS reagent and borane established the *S*,*S* chirality in excellent selectivity yield;[56] analysis by ^{13}C NMR showed a *dl* : *meso* ratio of > 98:2, while enantioselectivity was determined by HPLC to be 98% ee. Diol **6-132** was converted to dimesylate **6-133**[56,57] followed by double substitution by hydrazine to produce cyclic hydrazine **6-134**,[57] which was treated with catalytic (5 mol %) amount of TsOH and maleic anhydride to provide C_2-symmetric dienophile **6-135** in 74% for the three steps and 69% for the overall synthesis.[58]

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

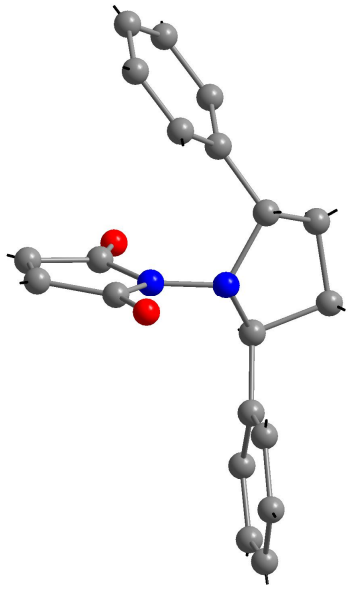
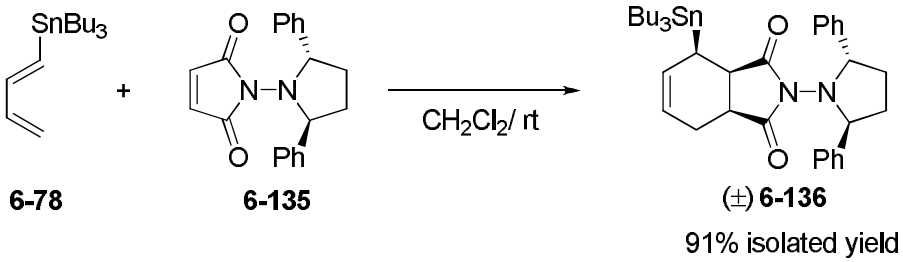


Figure 6.8 Crystal structure of chiral dienophile **6-135**



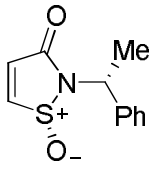
6-78 **6-135** (±) **6-136**

91% isolated yield

Scheme 6.20

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

Next approach was to use Waldner's chiral dienophile **6-39**, which was obtained from optically active (*R*)-*α*-methylbenzylamine (Figure 6.9).[33]

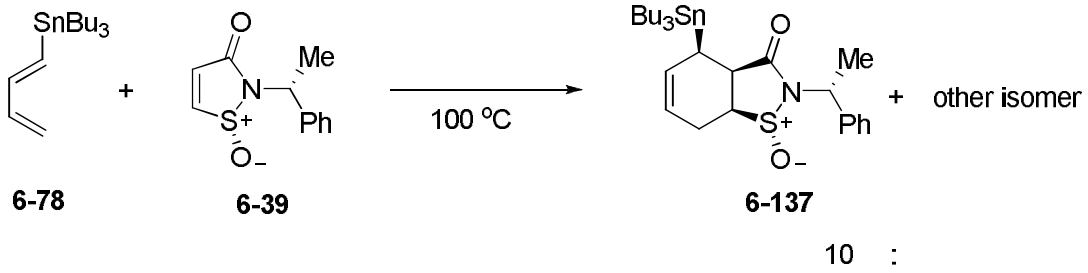


6-39

Figure 6.9 Waldner's chiral dienophile **6-39**

Maleimide derivative **5-39** was utilized by Toure and Hall as mentioned in section *6.1.3* to produce a single regio- and stereoisomer.[33] Waldner's dienophile is doubly activated and cyclic. Regiochemistry is controlled by the electron withdrawing carbonyl, which overrides the effect of the sulfoxide group. The chirality of the S-O bond is next to the double bond, which could apply a high degree of selectivity. The *endo* transition structure should place the diene opposite to the face of the S-O bond.[33]

Attempts at Diels-Alder reactions between stannyldiene **6-78** and dienophile **6-39** in CH_2Cl_2 and toluene produced numerous cycloadducts that could not be identified (50% to 60% conversions were observed in either conditions) (Scheme 6.21).



Scheme 6.21

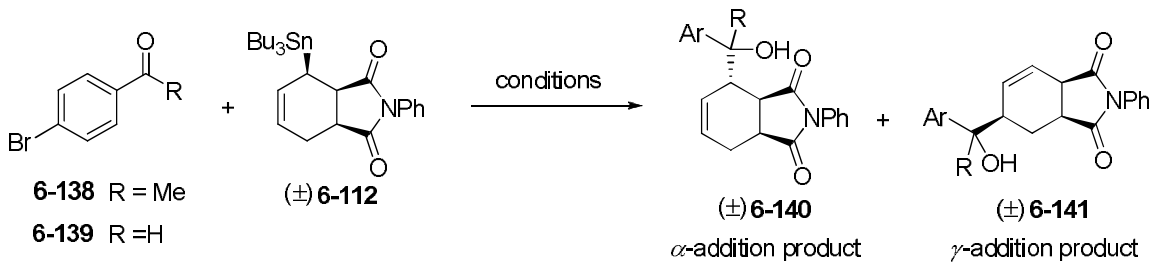
Luckily, Diels-Alder reaction between stannyldiene **6-78** and dienophile **6-39**, without any solvents (neat), proceeded in a cleaner fashion to provide allylic stannane **6-137** (the structure of compound **6-137** is based on speculation from results obtained by Toure and Hall[33] and has not been confirmed) and an unknown isomer in a 10:1 ratio (Scheme 6.21). Stannyldiene **6-78** and dienophile **6-39** were consumed completely in 10 minutes

at 100 °C. These two isomers were separable by silica gel chromatography. Unfortunately, cycloadduct **6-137** was not very stable on the column.

6.3.5 Diastereoselective allylstannation of aldehydes and ketones by cyclicallylstannanes

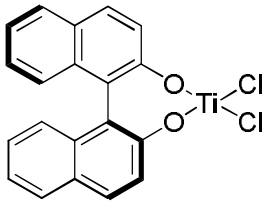
Since a diastereoselective Diels-Alder was established with stannyldiene **6-78**, the second portion of the Vaultier tandem process, the allylstannation reaction, was examined. Racemic **6-112** was used as a test compound to establish optimal conditions for the allylstannation reaction (Table 6.13).

Table 6.13 Allylstannation of aldehyde and ketone with cyclic allylstannane **6-112**



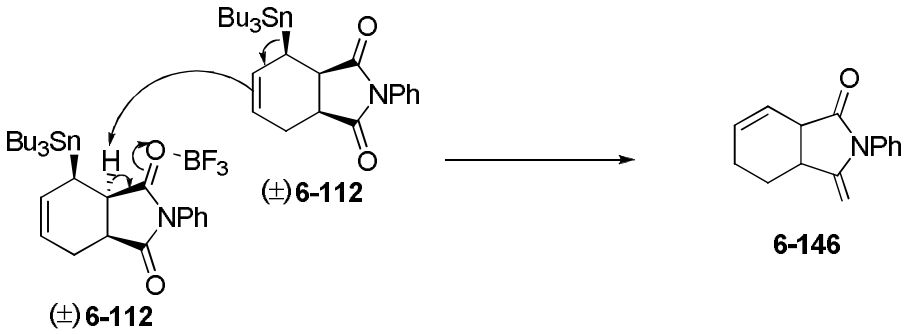
6-138 R = Me
6-139 R = H
(±) **6-112**
(±) **6-140**
α-addition product
(±) **6-141**
γ-addition product

entry (product)	R	conditions	ratio[b] α : γ	yield (%)
1(**6-142:6-143**)	Me	$BF_3 \cdot OEt_2$ (1 equiv.) CH_2Cl_2/ 0 °C	-	NR[a]
2(**6-144:6-145**)	H	$BF_3 \cdot OEt_2$ (1 equiv.) CH_2Cl_2/ 0 °C	-	NR[a]

3(**6-144:6-145**)	H	 **6-120** 20 mol %	-	NR
4(**6-144:6-145**)	H	toluene/ reflux	-	NR
5(**6-144:6-145**)	H	$SnCl_2$ (1 equiv.) MeCN/ rt	1 : 3.6	80
6(**6-142:6-143**)	Me	$SnCl_2$ (1 equiv.) MeCN/ rt	1 : 3	83
7(**6-144:6-145**)	H	$SnCl_4$ (1 equiv.) CH_2Cl_2/ -78 ^oC	0 : 1	85

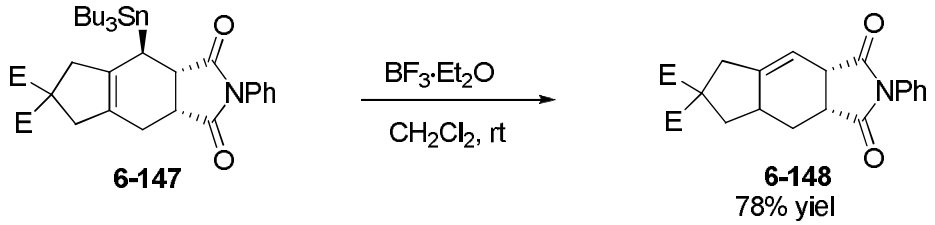
[a] Compound **6-146** was isolated (Scheme 6.22).
[b] Ratio was determined by ^1H NMR analysis of crude reaction mixture.

$BF_3 \cdot OEt_2$ did not provide any allylstannation product, but rather compound **6-146** which was tentatively characterized by ^1H NMR (Scheme 6.22).



Scheme 6.22

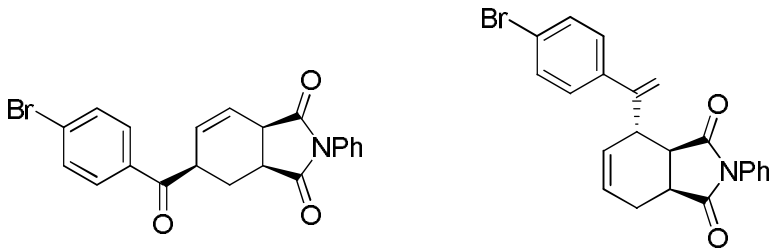
Destannylated compound **6-146** was also isolated when allylstannane **6-112** was stirred with $BF_3 \cdot OEt_2$ in the absence of a ketone or aldehyde, suggesting the source of the proton might be from the allylstannane itself or another adventitious proton source. Speculatively, the Lewis acid coordination with Lewis basic oxygen of the imide might increase the acidity of the α-protons, thus forcing allylstannane **6-112** to behave like a base instead of a nucleophile. This was also observed by Lautens *et al.* by using the same condition and a similar cyclic allylstannane (**6-147**) (Scheme 6.23).[59]



Scheme 6.23

Refluxing cyclic allylstannane **6-112** and aldehyde **6-139** in toluene or using Mikami catalyst (**6-120**), which has been used for allylstannation before,[60] did not promote any allylstannation to occur. However, allylation was observed when conditions by Yasuda *et al.* were applied ($SnCl_2$/MeCN, trial 5).[44] ^{1}H NMR data analysis of the crude indicated the presence of two isomers in a 3.6:1 ratio. X-ray structure analysis of the two isomers could not be obtained due to difficulties in forming crystals of appropriate quality. It was unclear at that point whether the isomers formed arose from the facial selectivity of the aldehyde or the allylstannane (open or closed transition state). The two inseparable isomers **6-144** and **6-145**, by silica gel chromatography, were oxidized to the ketone thus

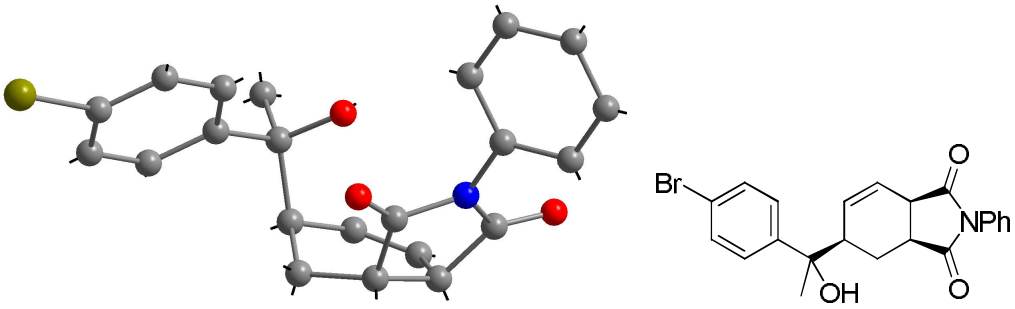
eliminating the stereocenter at the benzylic carbon. ^{1}H NMR data analysis of the crude indicated the presence of two isomers in the same starting ratio, suggesting the two allylstannation products formed are not different at the benzylic carbon, but rather at the γ-carbon of the original allylstannane. In fact, after learning how the allylstannation reaction proceeded, the two ketones were identified as **6-149** and **6-150** (Figure 6.10)



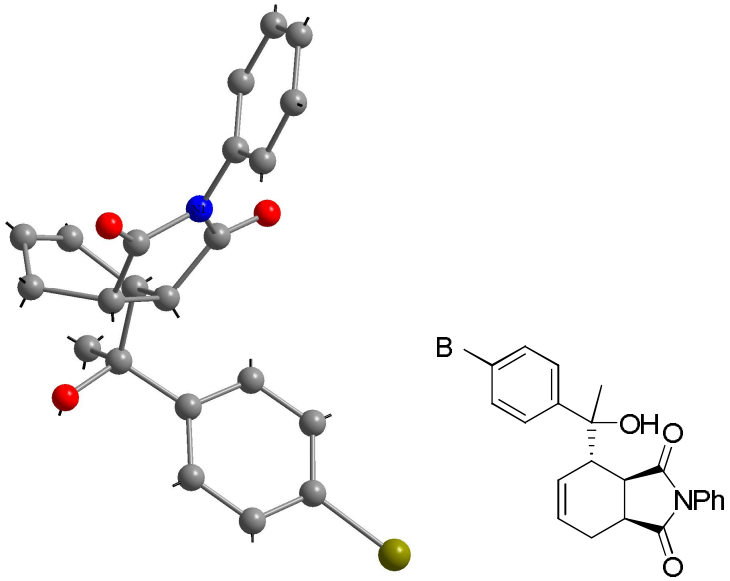
(±) **6-149** (±) **6-150**

Figure 6.10 Ketones **6-149** and **6-150**

Allylstannation of ketone **6-138**, under the same condition as trial 5, produced two isomers in a 3:1 ratio (entry 6). Remarkably, it was established by the X-ray structure analysis of the allylstannation products from trial 6, that the two products are in fact regioisomers (α- and γ-addition products) and not what was believed to be stereoisomers (Figure 6.11); thus solving the structures of the previous ketones shown in Figure 6.10.



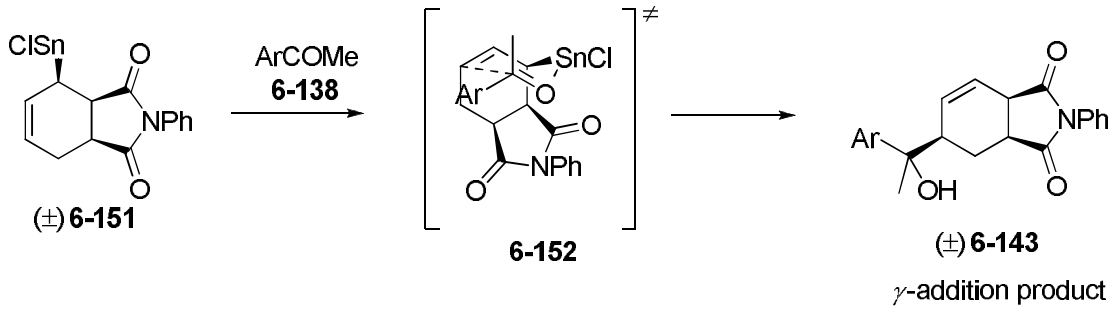
(±) 6-143 *γ*-addition product



(±) 6-142 *α*-addition product

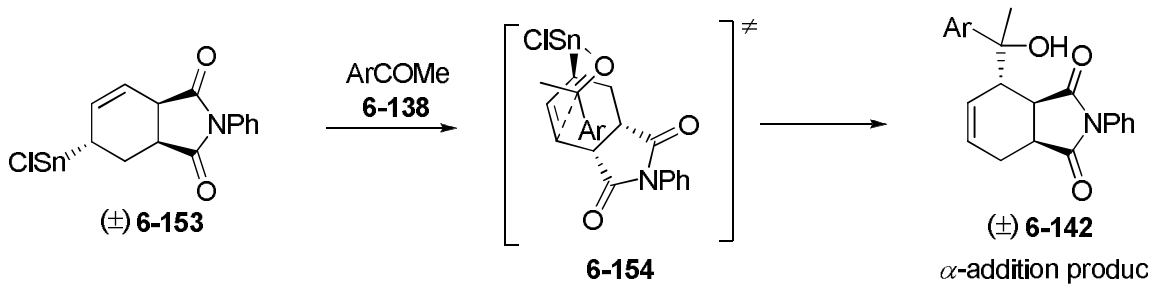
Figure 6.11 Crystal structures of allylstannation products **6-143** and **6-142**

Isomer **6-143** was the major compound, thus resulting from *γ*-addition of the aldehyde to the same face as the tin moiety *via* Zimmerman-Traxler six-member transition structure (Scheme 6.24).



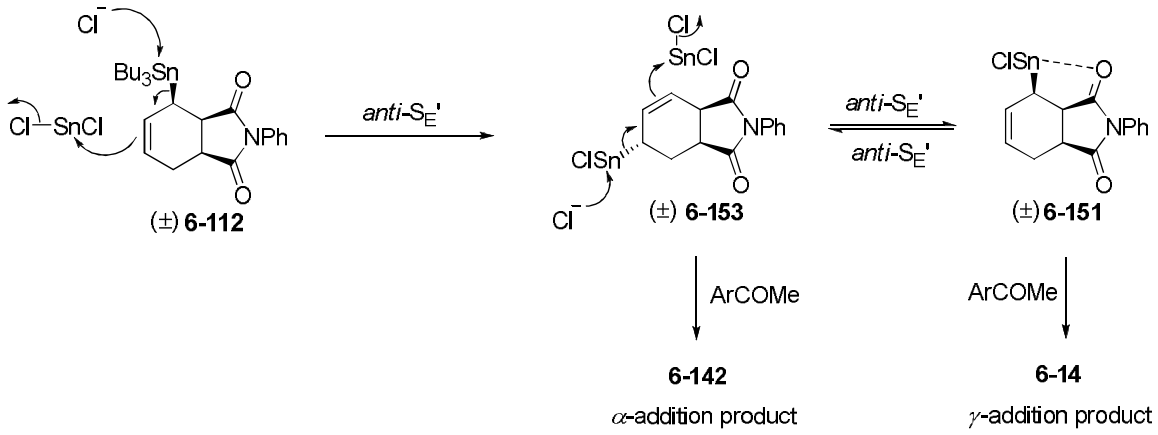
Scheme 6.24

Isomer **6-142** was the minor compound thus resulting from α-addition of the aldehyde to the same face as the tin moiety *via* Zimmerman-Traxler six-member transition structure (Scheme 6.25).



Scheme 6.25

Speculatively, the two allylic tin species (**6-151** and **6-153**), which are formed *in situ*, could be a result of allylic arrangements that proceeded in an *anti*-S_E' manner between Bu_3Sn and $SnCl_2$ (Scheme 6.26).



Scheme 6.26

In theory, allylic tin intermediate **6-153** could have formed by a single *anti*-S_E' process followed by *syn* addition of the carbonyl compound to afford an *anti* α-addition product **6-142**, while allylic tin intermediate **6-151** could have formed by a double *anti*-S_E' process, followed by a *syn* addition of the carbonyl compound to afford a *syn* γ-addition product **6-143** (Scheme 6.26). Explanations of regiochemistry using allylic tin rearrangements have been used in literature.[44]

The outcome ratio in favour of the γ-addition product could be explained by the extra stabilization to the allylic tin intermediate **6-151** by the neighbouring oxygen. According to crystal structure **6-114**, the distance between the tin and the adjacent oxygen atom is 3.090(3) Å. Similarly, allylic tin intermediate **6-151** could have approximately the same distance between the tin and the oxygen (Figure 6.12).

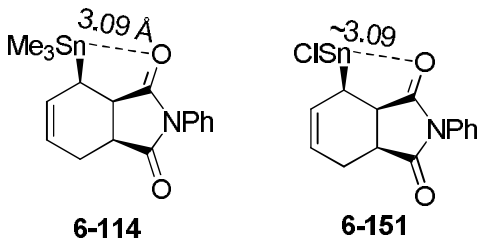


Figure 6.12 Speculation of Sn-O chelation

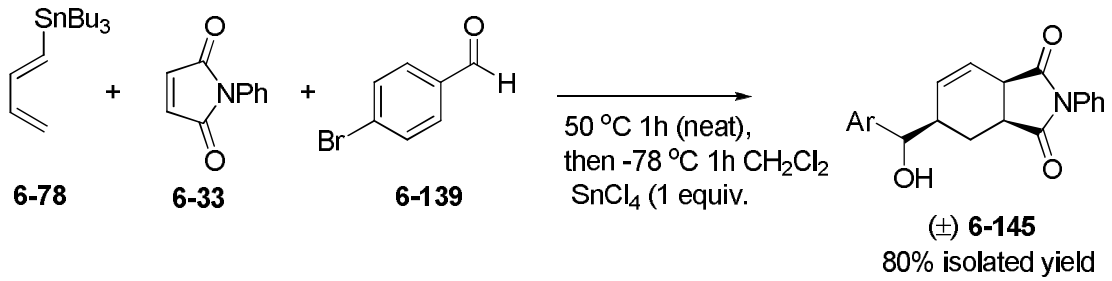
The normal covalent bond distance between tin and oxygen is 2.0 Å.[61] Intramolecular Sn--O interaction distances in the range from 2.72(2) to 3.206(3) Å have been confidently reported to indicate Sn--O bonding.[62-64] These reports suggest that such stabilization, by the oxygen to the tin in **6-151**, is plausible.

α-Addition product was avoided by changing the reaction conditions to $SnCl_4$/-78 ^oC in CH_2Cl_2, thus affording only the γ-addition product in 85% yield (entry 7, Table 6.13).

6.3.6 Racemic and asymmetric Vaultier tandem reactions

The advances made in the Diels-Alder reaction with stannyldiene **6-78** and the allylstannation chemistry illustrated earlier, was applied together in the multi-component Diels-Alder/allylstannation reaction in one pot, or better known as the Vaultier tandem reaction.

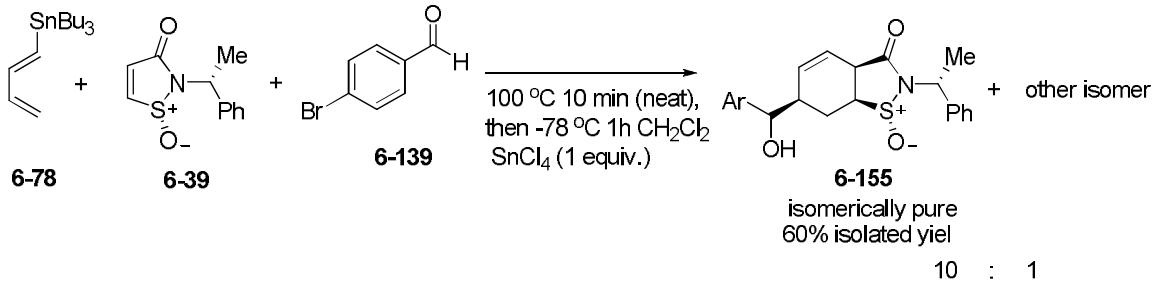
The first example was the racemic Vaultier tandem reaction with maleimide **6-33** (Scheme 6.27).



Scheme 6.27

As planned, the Vaultier tandem reaction proceeded to produce a single diastereomer **6-145** in 80% isolated yield. Stannyldiene **6-78** was stirred with dienophile **6-33** at 50 ^{o}C in the absence of any solvent for 1 hour, followed by the addition of **6-139** in CH_2Cl_2 and cooling the reaction to -78 ^{o}C prior to the addition of 1 equivalent of $SnCl_4$. A highly functionalized cyclohexene was obtained as a single diastereomer in 80% isolated yield within 2 hours.

The asymmetric version with Waldner's dienophile was also successful at producing a highly functionalized isomerically pure cyclohexene **6-155** in 60% yield (Scheme 6.28).



Scheme 6.28

The structure for cyclohexene **6-155** was proposed based on the work by Toure and Hall and tentative characterizations and has not been confirmed.[33] Cyclohexene **6-155** was formed in a separable 10:1 ratio with another isomer, suggesting the 10:1 ratio obtained by the Diels-Alder reaction carried through without any isomerisation.

6.4 Summary

Stannyldiene **6-78** was able to undergo a Diels-Alder reaction with maleimide **6-33** to product cyclic allylstannane **6-112** in 93% isolated yield under thermal conditions. It was observed that stannyldiene **6-78** undergoes Diels-Alder reaction readily with cyclic and doubly activated dienophiles. Mikami catalyst was able to effect an enantioselective Diels-Alder reaction between stannyldiene **6-78** and maleimide **6-33** in modest selectivity of 30% ee. Diastereoselective Diels-Alder reaction between stannylbutadiene **6-78** and Waldner's dienophile resulted in a 10:1 dr.

The first Vaultier tandem reaction with a tin analogue was established to provide highly functionalized cyclohexene **6-145** in 80% yield as a racemic diastereomer. Also, the first asymmetric Vaultier tandem reaction with a tin analogue was established to furnish an isomerically pure highly functionalized cyclohexene **6-155** in 60% yield.

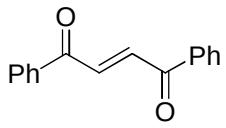
6.5 Experimental

6.5.1 General experimental

All reactions and reagents were carried out and purified as stated in Chapter 3. Chiral HPLC analysis was performed using a ChiralCel OD (4.6 mm x 250 mm) column using 5% *i*PrOH/Hex as eluant (0.5 mL/min). Dienophiles **6-84**,[46] **6-88**,[46] **6-98**,[47] **6-126**[65] and **6-39**[33] were made by the corresponding published procedures. Other reagents were purchased from Sigma-Aldrich and used without further purification. X-ray single-crystal structures studies were performed on an orange platelike, colourless needle, colourless plate and colourless block for **6-135**, **6-114**, **6-143** and **6-142**, respectively. A Bruker Smart APEX CCD diffractometer with graphite-monochromator Mo-Kα_1 radiation was used for the data collections, performed by scans of 0.3^o (for samples **6-135**, **6-143** and **6-142**) and 0.36^o (for sample **6-114**) in ω in three or four blocks of 600 or 500 frames with an exposure time of 30 s at ϕ = 0, 90^o, 180^o and 270^o. The data were corrected for Lorentz and polarization effects. Absorption corrections were based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements using APEX II software. The structure solution and refinements were performed with the SHELXTL program package part of APEX II. Appendix A, B, C and D summarize the crystallographic data of **6-135**, **6-114**, **6-143** and **6-142**.

6.5.2 Synthesis of chiral dienophile 6-135

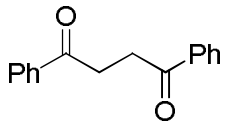
6.5.2.1 **(*E*)-1,4-Diphenylbut-2-ene-1,4-dione (6-130)**[55]



To a suspension of finely grinded aluminum chloride (50.1 g, 0.375 mol) in 250 mL of benzene was added, dropwise within 20 minutes, fumaryl chloride (22.2 g, 0.145 mol) while stirring quickly with a mechanical stirrer. The reaction mixture was stirred at reflux for 90 minutes after the initial boiling settled. Additional stirring for 60 minutes was followed as the reaction was allowed to cool to rt. To 500 mL of ice was added the pasty reaction mixture followed by stirring to free any lumps, which then was allowed to sit for 60 minutes. The benzene layer was washed with hot 1M HCl (2 x 150 mL), hot water (2 x 150 mL), and was then filtered and concentrated until crystals were visible. Ethanol (250 mL) was added to the mixture and cooled over ice. The resulting yellow crystals were suction filtered and washed with cold ethanol to provide 33.9 g of dibenzoylethylene **6-130** in 99% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (PhH, d, 4H, J = 7.3 Hz), 7.99 (COCH=CHCO, s, 2H), 7.61 (Ph, t, 4H, J = 7.3 Hz), 7.51 (Ph, t, 4H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7 (CO), 136.8, 135.0, 133.7, 128.8 (PhCOCH).

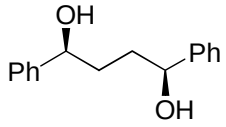
6.5.2.2 **1,4-Diphenylbutane-1,4-dione (6-131)**[55]



To a hot suspension (70 ^{o}C) of **6-130** (36.0 g, 0.152 mol) in 100 mL of EtOH was added, slowly, a solution of stannous chloride (43.2 g, 0.188 mol) in concentrated HCl (50 mL) followed by an additional 100 mL of EtOH. The reaction was allowed to stir for 1 h at reflux followed by the addition of 125 mL of water and stirred for 10 minutes, then cooled over ice and suctioned filtered to provide 33.9 g of diketone **6-131** as white crystals in 99% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (PhH, d, 4H, J = 7.4 Hz), 7.56 (PhH, t, 2H, J = 7.2 Hz), 7.46 (PhH, t, 4H, J = 7.7 Hz), 3.45 ($COCH_2$, s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6 (CO), 136.7, 133.1, 128.5, 128.0 (Ph), 32.5 ($COCH_2$).

6.5.2.3 **(1*S*,4*S*)-1,4-Diphenylbutane-1,4-diol (6-132)**[56]

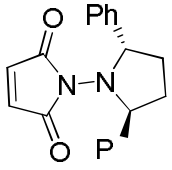


To a stirred solution containing (*R*)-Me-CBS reduction catalyst (1.0 M in toluene, 8.0 mL, 0.008 mol) and borane-dimethyl sulfide complex (8.4 mL, 0.084 mol) in 50 mL of

THF was added a diketone **6-131** solution (10.0 g, 0.042 mol) in THF (100 mL) at 0 ^{o}C over an hour. The reaction was allowed to warm up to rt and stirred for an additional hour. The resulting mixture was poured slowly over ice cold 2 M HCl. The aqueous layer was extracted with ether (3 x 100 mL), organic extracts were combined and washed with brine, dried over Na_2SO_4 and concentrated. The resulting oil was purified by silica gel chromatography (hexane/EtOAc, 2:1) to provide 9.67 g of diol **6-132** as colourless oil in 95% yield. Analysis by ^{13}C NMR showed a *dl* : *meso* ratio of > 98:2, while enantioselectivity was determined by HPLC to be 98% ee.

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 128.4, 127.3, 125.8 (Ph), 74.5 (CHOH), 35.9 ($CHOHCH_2$).

6.5.2.4 **1-((2*S*,5*S*)-2,5-Diphenylpyrrolidin-1-yl)-1H-pyrrole-2,5-dione (6-135)**



To a stirred solution of MsCl (3.4 mL, 0.044 mol) in 100 mL of CH_2Cl_2 at -20 ^{o}C was added a solution of diol **6-132** (4.19 g, 0.017 mol) and Et_3N (7.3 mL, 0.052 mol) in 30 mol of CH_2Cl_2. The reaction was stirred for 90 minutes at -20 ^{o}C, then quenched by 10 mL of NH_4Cl. The organic layer was concentrated to a volume of ~ 20 mL, diluted with AcOEt (75 mL), and washed with a 1:2:1 mixture of water, brine and satd. $NaHCO_3$ (3 x 50 mL). The organic layer was concentrated to a volume of ~ 20 mL, cooled to 0 ^{o}C then

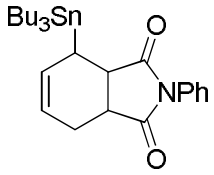
diluted dropwise by hexane (~150 mL) to precipitate the dimesylate intermediate **6-133** as white crystals. The white crystals were dissolved in isopropanol (30 mL) followed by the addition of hydrazine monohydrate (15 mL). The reaction was allowed to stir vigorously for 4 days at 40 ^{o}C. The reaction mixture was diluted with ether (75 mL) and washed with satd. $NaHCO_3$ (2 x 50 mL) and brine (50 mL). The aqueous layer was re-extracted with ether (75 mL), dried over Na_2SO_4 and concentrated to provide the cyclized hydrazine **6-134**. The cyclized product was suspended in 100 mL of toluene followed by the addition of maleic anhydride (2.22 g, 0.026 mol) and TsOH (0.05 g, 0.29 mmol). The reaction was allowed to stir for 1 day at reflux while removing the reaction water *via* a Dean-Stark apparatus. The reaction mixture was cooled, washed with satd. $NaHCO_3$ (50 mL), dried over Na_2SO_4 and concentrated. Silica gel chromatography (hexane/ether, 1:1) of the organic residue provided 4.08 g of dienophile **6-135** as orange crystals in 74% yield from diol **6-132**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (Ph<u>H</u>, d, 4H, J = 7.4 Hz), 7.29-7.18 (Ph<u>H</u>, m, 6H), 6.13 (C<u>H</u>=C<u>H</u>, s, 2H), 2.45 (C<u>H</u>$_2$C<u>H</u>$_2$, m, 2H), 2.22 (C<u>H</u>$_2$C<u>H</u>$_2$, m, 2H); δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 169.5 (<u>C</u>ON), 140.2, 131.5, 128.2, 128.1, 127.7 (<u>Ph</u>, <u>C</u>H=<u>C</u>H), 65.3 (Ph<u>C</u>H), 32.2 (<u>C</u>H$_2$<u>C</u>H$_2$). Exact mass (EI) calcd for $C_{20}H_{18}N_2O_2$ $(M)^+$: 318.1368, found: 318.1366. See Appendix A for crystal structure.

6.5.3 General procedure for thermal Diels-Alder reaction with stannyldiene 6-78

To a dry round bottom flask, stannyldiene **6-78** (0.075 g, 0.217 mmol) was added to the corresponding dienophile (0.197 mmol) and mixture was stirred for 1 h at 50 ^{o}C. The resulting residue was purified by silica gel chromatography to provide the corresponding cycloadduct.

6.5.3.1 **(3a*R**,4*R**,7a*S**) and (3a*S**,4*S**,7a*R**)-2-Phenyl-4-(tributylstannyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-112)**

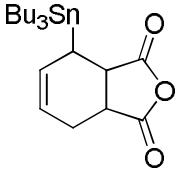


Stannane **6-112** was made in 93% yield from maleimide **6-33** using the general procedure. Purification of stannane was done by silica gel chromatography using 10 g of SiO_2 (hexane/ether, 3:1) to provide 0.104 g of product **6-112** (R_f = 0.65, hexane/ether, 3:1) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.23 (Ph<u>H</u>, m, 5H), 6.03 (SnCHC<u>H</u>=CH, dd, 1H, J = 9.2 Hz, J = 5.1 Hz), 5.74 (SnCHCH=C<u>H</u>, m, 1H), 3.39 (SnCHC<u>H</u>CH, t, 1H, J = 8.9 Hz), 3.04 (SnCHCHC<u>H</u>, q, 1H, J = 8.3 Hz), 2.56 (SnCHCHCHC<u>H</u>$_2$, dt, 1H, J = 15.7 Hz, J = 6.9 Hz), 2.41 (SnC<u>H</u>CHCHCH_2, dd, 1H), 2.22 (SnCHCHCHC<u>H</u>$_2$, m, 1H), 1.49-0.83 (<u>Bu</u>$_3$Sn, m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 179.0 (<u>C</u>ON<u>C</u>O), 132.9, 131.9, 129.1, 128.4, 126.3, 121.8 (<u>C</u>H=<u>C</u>H) (<u>Ph</u>), 41.9, 40.3 (SnCH<u>C</u>H<u>C</u>HCH_2), 29.2

($SnCH_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}H}$ = 19.8 Hz), 27.4 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}H}$ = 60.4 Hz), 24.6 ($SnCHCHCH\underline{C}H_2$), 21.7 ($Sn\underline{C}HCHCHCH_2$, $J_{Sn\text{-}H}$ = 249.1), 13.7 ($SnCH_2CH_2CH_2\underline{C}H_3$), 11.1 ($Sn\underline{C}H_2CH_2CH_2CH_3$, $J_{Sn\text{-}H}$ = 317.0 Hz). Exact mass (EI) calcd for $C_{26}H_{39}NO_2{}^{116}Sn$ $(M - n\text{-Bu})^+$: 513.1998, $C_{26}H_{39}NO_2{}^{116}Sn$ $(M - n\text{-Bu})^+$ found: 513.1997.

6.5.3.2 **(3a*R**,4*R**,7a*S**) and (3a*S**,4*S**,7a*R**)-4-(Tributylstannyl)-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (6-110)**

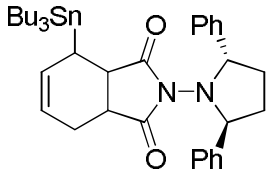


Stannane **6-110** was made from maleic anhydride **6-50** using the general procedure. Reaction was performed at rt for 24 h in CH_2Cl_2 (2 mL); 100% conversion of maleic anhydride was observed by crude ^{1}H NMR (*endo*:*exo*, 10:1, R_f = 0.70, R_f = 0.80 , hexane/ether, 3:1), yield was not determined due to its instability during purification by silica gel chromatography (10 g of SiO_2, hexane/ether, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 ($SnCHC\underline{H}$=CH, m, 1H), 5.66 ($SnCHCH$=$C\underline{H}$, m, 1H), 3.45 ($SnCHC\underline{H}CH$, t, 1H, J = 7.2 Hz), 3.07 ($SnCHCHC\underline{H}$, q, 1H, J = 8.1 Hz), 2.50 ($SnCHCHCHC\underline{H}_2$, dt, 1H), 2.33 ($SnC\underline{H}CHCHCH_2$, m, 1H), 2.15 ($SnCHCHCHC\underline{H}_2$, m, 1H), 1.47-0.81 ($\underline{Bu}_3Sn$, m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 173.5 ($\underline{C}ON\underline{C}O$), 132.0, 120.0 ($\underline{C}H$=$\underline{C}H$) 42.5, 39.5 ($SnCH\underline{C}H\underline{C}HCH_2$), 29.1 ($SnCH_2\underline{C}H_2CH_2CH_3$, $J_{Sn\text{-}H}$ = 20.1 Hz), 27.4 ($SnCH_2CH_2\underline{C}H_2CH_3$, $J_{Sn\text{-}H}$ = 57.2 Hz), 23.7 ($SnCHCHCH\underline{C}H_2$), 21.1

(Sn<u>C</u>HCHCHCH$_2$), 13.7 (SnCH$_2$CH$_2$CH$_2$<u>C</u>H$_3$), 10.9 (Sn<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$, J_{Sn-H} = 325.5 Hz).

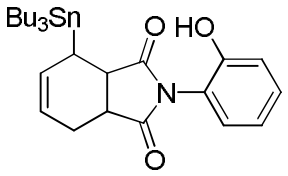
6.5.3.3 (3a*R**,4*R**,7a*S**) and (3a*S**,4*S**,7a*R**)-2-((2*S*,5*S*)-2,5-Diphenylpyrrolidin-1-yl)-4-(tributylstannyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-136)



Stannane **6-136** was made in 91% yield from maleimide **6-135** using the general procedure. Purification of stannane was done by silica gel chromatography using 10 g of SiO_2 (hexane/ether, 3:1) to provide 0.130 g of product **6-136** (R_f = 0.75 and R_f = 0.70 (2 diastereomers, hexane/ether, 3:1) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.22 (Ph<u>H</u>, m, 20H), 5.78-5.11 (C<u>H</u>=C<u>H</u>, PhC<u>H</u>, m, 8H), 2.69-1.57 (C<u>H</u>$_2$C<u>H</u>$_2$,SnC<u>H</u>C<u>H</u>C<u>H</u>C<u>H</u>$_2$, m, 18H), 1.44-0.73 (<u>Bu</u>$_3$Sn, m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 179.0,179.0, 178.9, 178.7, 178.3, 177.9, 177.8 (<u>C</u>ON), 140.2, 140.1, 135.1, 135.0, 130.8, 130.6, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 127.5, 121.1, 120.3, 115.1, 114.3 (<u>Ph</u>, <u>C</u>H=<u>C</u>H), 65.0, 64.9, 64.5, 64.3, 64.1, 64.0 (Ph<u>C</u>H), 39.9, 39.5, 38.3, 38.2, 38.1, 37.9, 37.3, 33.5, 33.4, 33.1, 32.5, 32.2, 29.2, 29.0, 27.5, 27.3, 25.0, 24.4, 24.0, 23.5, 23.2, 20.0, 19.8, 13.7, 13.6, 10.9, 9.12, 9.0 (Sn<u>C</u>H<u>C</u>H<u>C</u>H<u>C</u>H$_2$) (<u>C</u>H$_2$<u>C</u>H$_2$) (<u>Bu</u>$_3$Sn). Exact mass (EI) calcd for $C_{36}H_{50}N_2O_2{}^{116}Sn$ (M – *n*-Bu)$^+$: 658.2889, $C_{36}H_{50}N_2O_2{}^{116}Sn$ (M – *n*-Bu)$^+$ found: 658.2900.

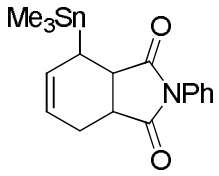
6.5.3.4 **(3a*R**,4*R**,7a*S**) and (3a*S**,4*S**,7a*R**)-2-(2-Hydroxyphenyl)-4-(tributylstannyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-127)**



Stannane **6-127** was made in 90% yield from maleimide **6-126** using the general procedure. Purification of stannane was done by silica gel chromatography using 10 g of SiO_2 (hexane/ethyl acetate, 3:1) to provide 0.104 g of product **6-127** (R_f = 0.37, hexane/ether, 1:4) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (PhH, d, 1H, J = 8.6 Hz), 7.14 (PhH, d, 1H, J = 7.7 Hz), 6.98 (PhH, t, 2H, J = 8.8 Hz), 6.21 (SnCHCH=CH, m, 1H), 6.03 (OH, s, 1H), 5.73 (SnCHCH=CH, d, 1H, J = 9.3 Hz), 3.44 (SnCHCHCHCH$_2$, m, 1H), 3.02 (SnCHCHCHCH$_2$, m, 1H), 2.33-2.06 (SnCHCHCHCH$_2$, m, 3H), 1.54-0.83 (Bu_3Sn, m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 177.2 (CON), 150.9, 136.3, 130, 3, 127.9, 121.2, 120.3, 119.1, 114.2 (Ph) (CH=CH), 40.8, 40.3 (SnCHCHCHCH$_2$), 29.6 (SnCHCHCHCH$_2$), 29.1 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 27.4 (SnCH$_2$CH$_2$CH$_2$CH$_3$, 23.5 (SnCH), 13.6 (SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.4 (SnCH$_2$CH$_2$CH$_2$CH$_3$). Exact mass (EI) calcd for $C_{26}H_{39}NO_3{}^{116}Sn$ (M – *n*-Bu)$^+$: 529.1947, $C_{26}H_{39}NO_3{}^{116}Sn$ (M – *n*-Bu)$^+$ found: 529.1943.

6.5.3.5 **(3a*R**,4*R**,7a*S**) and (3a*S**,4*S**,7a*R**)-2-Phenyl-4-(trimethylstannyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-114)**

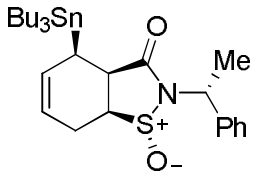


To a flame-dried round-bottomed flask was added stannylbutadiene **6-78** (0.500 g, 1.45 mmol) and THF (20 mL). The solution was cooled to -78 ^{o}C followed by the slow addition of BuLi (1.6 M in hexane, 0.91 mL, 1.45 mmol) and let stir for 10 min. Me_3SnCl (0.328 M in THF, 4.42 mL, 1.45 mmol) was added dropwise at -78 ^{o}C and let stirred for 30 min. The reaction mixture was concentrated and diluted with 5 mL of CH_2Cl_2 followed by the addition of maleimide **6-33** (0.301 g, 1.74 mmol) at rt. The reaction was let stirred for 48 h at rt. Reaction mixture was concentrated and purified on silica gel (15 g of SiO_2, hexane/ether, 3:1) to afford 0.526 g of cycloadduct **6-114** in 93% yield as a white solid (R_f = 0.65, hexane/ether, 3:1). The solid was recrystallised from CH_2Cl_2 by slow evaporation to provide white crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.25 (Ph<u>H</u>, m, 5H), 6.03 (SnCHC<u>H</u>=CH, dd, 1H, J = 9.2 Hz, J = 5.4 Hz), 5.79 (SnCHCH=C<u>H</u>, m, 1H), 3.44 (SnCHC<u>H</u>CH, t, 1H, J = 9.0 Hz), 3.06 (SnCHCHC<u>H</u>, q, 1H, J = 7.8 Hz), 2.58 (SnCHCHCHC<u>H</u>$_2$, dt, 1H, J = 16.1 Hz, J = 6.6 Hz), 2.39 (SnC<u>H</u>CHCHCH_2, m, 1H), 2.21 (SnCHCHCHC<u>H</u>$_2$, m, 1H), 0.14 (<u>Me</u>$_3$Sn, s, 9H, J_{Sn-H} = 52.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 178.9 (<u>C</u>ON<u>C</u>O), 132.5, 131.9, 129.1, 128.4, 126.3, 121.8 (<u>C</u>H=<u>C</u>H) (<u>Ph</u>), 41.7, 40.1 (SnCH<u>C</u>H<u>C</u>HCH$_2$), 24.4, 22.6 (Sn<u>C</u>HCHCH<u>C</u>H$_2$), -7.8 (<u>Me</u>$_3$Sn). Exact mass (EI) calcd for $C_{17}H_{21}NO_2{}^{120}Sn$ (M –

Me)$^+$: 387.0589, $C_{17}H_{21}NO_2{}^{116}Sn$ $(M - Me)^+$ found: 387.0580. See Appendix B for crystal structure.

6.5.3.6 **(R_S,3a*S*,4*R*,7a*S*)-2-((*R*)-1-Phenylethyl)-4-(tributylstannyl)-3a,4,7,7a-tetrahydrobenzo[d]isothiazol-3(2H)-one-S-oxide (6-137) (Unconfirmed structure)**



Stannane **6-137** was made from Waldner's dienophile **6-39** using the general procedure. Reaction was performed at 100 ^oC for 10 minutes to provide stannane **6-137** solid (R_f = 0.71, hexane/ether, 1:2) in a 10:1 ratio with an unidentified isomer solid (R_f = 0.76, hexane/ether, 1:4). 100% conversion of the dienophile was observed (according to TLC), but yield was not determined due to its instability on silica gel.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (Ph<u>H</u>, m, 5H), 6.77 (SnCHC<u>H</u>=CH, d, 1H, J = 10.2 Hz), 5.47 (PhC<u>H</u>CH_3, q, 1H, d = 7.2 Hz), 5.20 (SnCHCH=C<u>H</u>, m, 1H), 3.68 (SnCHC<u>H</u>CH, dd, 1H, J = 8.5 Hz, d = 5.8 Hz, J_{Sn-H} = 78.0 Hz), 3.19 (SnCHCHC<u>H</u>, dt, 1H, J = 10.9 Hz, J = 5.6 Hz), 2.32 (SnC<u>H</u>CHCHCH_2, m, 1H, J_{Sn-H} = 42 Hz), 2.24-2.08 (SnCHCHCHC<u>H_2</u>, m, 2H), 1.81 (PhCHC<u>H_3</u>, d, 3H, J = 7.1 Hz) 1.50-0.85 (<u>Bu_3</u>Sn, m, 27H)

6.5.4 General procedure of allylstannation of carbonyl compounds

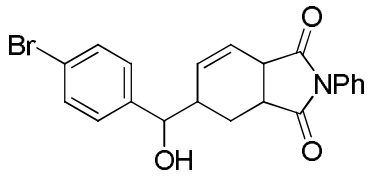
(method A):

To a solution of carbonyl compound (0.194 mmol) and $SnCl_2$ (37 mg, 0.194 mmol) in MeCN (2 mL), was added allylstannane **6-112** (0.100 g, 0.194 mmol). The reaction was allowed to stir for 3 h at rt and then passed through a short silica plug containing 10% KF followed by CH_2Cl_2. It was then concentrated and purified by silica gel chromatography to provide the corresponding allylstannation product.

(method B)

Vaultier tandem reaction: To a dry round bottom flask, Stannyldiene **6-78** (0.075g, 0.217 mmol) and dienophile (0.198 mmol) were added and stirred for 1 h at 50 ^{o}C. Carbonyl compound (0.198 mmol) in CH_2Cl_2 (2 mL) was added followed by the addition of $SnCl_4$ (0.198 mmol) at -78 ^{o}C. The reaction was stirred for 1 h and then passed through a short silica plug containing 10% KF followed by CH_2Cl_2 washes. It was then concentrated and purified by silica gel chromatography to provide the corresponding Diels-Alder/allylstannation product.

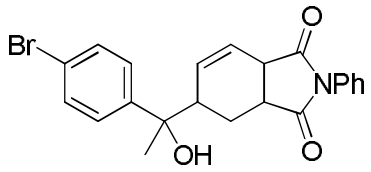
6.5.4.1 **(3a*S**,5*R**,7a*R**) and (3a*R**,5*S**,7a*S**)-5-((*R**) and (*S**)-(4-Bromophenyl)(hydroxy)methyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-145)**



γ-Addition product **6-145** was made from allylstannane **6-112** and aldehyde **6-139** in 80% yield as a mixture of inseparable isomers (R_f = 0.30, hexane/ether, 1:4) in a ratio of 3.6:1 with α-addition product **6-144** being the minor isomer using method A. γ-Addition product **6-145** was isolated in 80% yield (0.065 g) as the only isomer using method B. Crude reaction mixture was purified by silica gel chromatography using 10 g of silica (hexane/ethyl acetate, 3:1) to provide 0.064 of product **6-145** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 750-7.21 (Ph<u>H</u>, BrPh<u>H</u>, m, 9H), 6.18, 6.00 (CHC<u>H</u>=C<u>H</u>CHCH$_2$, dt, J = 9.9 Hz, J = 4.6 Hz, 1H, m, 1H), 4.67 (C<u>H</u>OH, d, 1H, J = 7.9 Hz) 3.53-3.25 (C<u>H</u>CH$_2$C<u>H</u>C<u>H</u>, dd, J = 9.3 Hz, J = 2.3 Hz, 1H, m, 1H, m, 1H), 2.52 (CHC<u>H$_2$</u>CHCH, m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 179.1 (<u>C</u>ON<u>C</u>O), 141.1, 131.9, 131.7, 129.1, 128.6, 128.4, 127.8, 126.3, 122.0 (CH<u>C</u>H=<u>C</u>HCH) (<u>Ph</u>) (Br<u>Ph</u>), 74.5 (<u>C</u>HOH), 42.3, 40.2, 38.4, 23.9 (<u>C</u>H<u>C</u>H$_2$<u>C</u>H<u>C</u>H). Exact mass (CI) calcd for $C_{21}H_{19}NO_3{}^{79}Br$ $(M + H)^+$: 412.0548, $C_{21}H_{19}NO_3{}^{79}Br$ $(M + H)^+$ found: 412.0548.

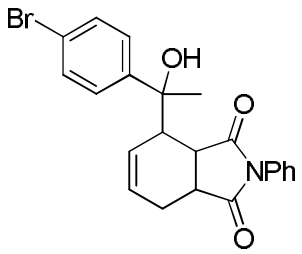
6.5.4.2 **(3a*S**,5*R**,7a*R**) and (3a*R**,5*S**,7a*S**)-5-((*S**) and (*R**)-1-(4-Bromophenyl)-1-hydroxyethyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-143)**



γ-Addition product **6-143** was made from allylstannane **6-112** and ketone **6-138** in 62% yield in a separable 3:1 ratio with the minor α-addition product **6-142** using method A. Crude reaction mixture was purified by silica gel chromatography using 10 g of silica (hexane/ethyl acetate, 3:1) to provide 0.051 g of product **6-143** as a white solid (R_f = 0.23, hexane/ether, 1:4). Compound **6-143** was recrystallized from CH_2Cl_2/hexane by slow evaporation to provide white crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.20 (PhH, BrPhH, m, 9H), 6.18, 6.00 (CHCH=CHCHCH$_2$, m, 2H), 3.50-3.25 (CHCH$_2$CHCH, m, 3H), 2.45 (CHCH$_2$CHCH, m, 1H), 1.99 (CHCH$_2$CHCH, m, 1H) 1.80 (OH, br s, 1H), 1.59 (CH$_3$C, s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 176.0 (CONCO), 144.8, 131.3, 130.9, 129.1, 128.5, 127.0, 126.4, 126.2, 124.3, 121.1 (CHCH=CHCH) (Ph) (BrPh), 75.7 (CH_3COH), 42.2, 41.7, 38.6, 28.3, 22.2 (CHCH$_2$CHCH) (CH$_3$C). Exact mass (CI) calcd for $C_{22}H_{21}NO_3{}^{79}Br$ $(M + H)^+$: 426.0705, $C_{22}H_{21}NO_3{}^{79}Br$ $(M + H)^+$ found: 426.0705. See Appendix C for crystal structure.

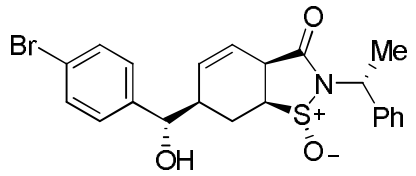
6.5.4.3 **(3aR*,4S*,7aS*) and (3aS*,4R*,7aR*)-4-((S*) and (R*)-1-(4-Bromophenyl)-1-hydroxyethyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-142)**



α-Addition product **6-142** was made from allylstannane **6-112** and ketone **6-138** in 21% yield in a separable 1:3 ratio with the major γ-addition product **6-143** using method A. Crude reaction mixture was purified by silica gel chromatography using 10 g of silica (hexane/ethyl acetate, 3:1) to provide 0.017 g of product **6-142** as a white solid solid (R_f = 0.33, hexane/ether, 1:4). Compound **6-142** was recrystallized from CH_2Cl_2/hexane by slow evaporation to provide white crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.16 (PhH, BrPhH, m, 9H), 6.09-5.95 ($CHCH{=}CHCH_2$, m, 2H), 3.26-3.01 ($CHCHCHCH_2$, m, 3H), 2.68-2.45 ($CHCHCHCH_2$, m, 2H), 2.11 (OH, br s, 1H), 1.56 (CH_3C, s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 179.2 (CONCO), 145.0, 131.9, 131.5, 129.6, 129.0, 128.4, 127.1, 126.4, 126.2, 121.1 ($CHCH{=}CHCH_2$) (Ph) (BrPh), 78.3 (CH_3COH), 44.7, 40.0, 38.2, 28.9, 24.2 ($CHCHCHCH_2$) (CH_3C). Exact mass (CI) calcd for $C_{22}H_{21}NO_3{}^{79}Br$ $(M + H)^+$: 426.0705, $C_{22}H_{21}NO_3{}^{79}Br$ $(M + H)^+$ found: 426.0705. See Appendix D for crystal structure.

6.5.4.4 **(R_S,3a*S*,6*R*,7a*S*)-6-((*S*)-(4-Bromophenyl)(hydroxy)methyl)-2-((*R*)-1-phenylethyl)-3a,6,7,7a-tetrahydrobenzo[d]isothiazol-3(2H)-one-S-oxide (6-155) (Unconfirmed structure)**



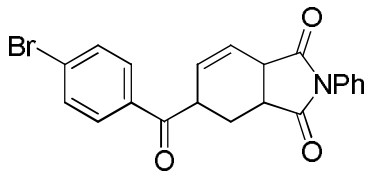
γ-Addition product **6-155** was made from dienophile **6-39** and aldehyde **6-139** in 60% yield in a separable 10:1 ratio with an unidentified isomer (R_f = 0.29, hexane/ether, 1:2) using method B. Crude reaction mixture was purified by silica gel chromatography using 10 g of silica (hexane/ethyl acetate, 2:1) to provide 0.054 g of product **6-155** as a white solid (R_f = 0.14, hexane/ether, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.24 (Ph<u>H</u>, BrPh<u>H</u>, m, 9H), 5.63, 5.57 (CHC<u>H</u>=C<u>H</u>CHCH$_2$, d, d, 2H, J = 10.2 Hz, J = 10.3 Hz), 5.42 (PhC<u>H</u>CH$_3$, q, 1H, J = 7.2), 4.68 (C<u>H</u>OH, d, 1H, J = 5.4 Hz), 3.67 (CHCH$_2$CHC<u>H</u>, d, 1H, J = 6.3 Hz), 3.67 (CHCH$_2$C<u>H</u>CH, dd, 1H, J = 15.0 Hz, J = 8.5 Hz), 3.15 (C<u>H</u>CH$_2$CHCH, m, 1H), 2.24 (CHC<u>H$_2$</u>CHCH, m, 2H), 1.74 (PhCHC<u>H$_3$</u>, d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7 (N<u>C</u>O), 140.2, 140.1, 131.7, 128.6, 128.0, 127.7, 127.1, 126.6, 125.3 (CH<u>C</u>H=<u>C</u>HCH) (<u>Ph</u>) (Br<u>Ph</u>), 74.7 (<u>C</u>HOH), 55.4, 52.3, 40.9, 35.7, 29.6, 19.8 (Ph<u>C</u>H<u>C</u>H$_3$) (<u>C</u>H<u>C</u>H$_2$<u>C</u>H<u>C</u>H).

6.5.5 Oxidation of allylstannation products 6-144 and 6-145 to corresponding ketones

To the crude mixture of allylstannyl addition products **6-144** and **6-145** (1:1 ratio) (0.080 g, 0.194 mmol) and 0.100 g of 3 Å molecular sieves in 4 mL of CH_2Cl_2 was added PDC (0.109 g, 0.291 mmol) at rt. The reaction was stirred for 16 h followed by a quench with brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified and separated by silica gel chromatography (hexane/ether , 1:1) to provide 0.037 g of ketone **6-150** (R_f = 0.60, hexane/ether, 1:4) and 0.037 g of ketone **6-149** (R_f = 0.75, hexane/ether, 1:4) in a combined yield of 92%.

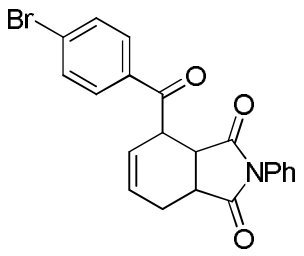
6.5.5.1 **(3a*S**,5*R**,7a*R**) and (3a*R**,5*S**,7a*S**)-5-(4-Bromobenzoyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-150)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.24 (PhH, BrPhH, m, 9H), 6.18 (CHCH=CHCHCH$_2$, d, 1H, J = 10.1 Hz), 6.12 (CHCH=CHCHCH$_2$, m, 1H), 4.02-3.48 (CHCH$_2$CHCH, m, 3H), 2.54 (CHCH$_2$CHCH, dt, 1H, J = 13.6 Hz, J = 4.8 Hz), 2.01 (CHCH$_2$CHCH, m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1 (BrPhCO), 177.7, 175.0 (CONCO), 133.8, 132.2, 131.5, 130.0, 129.1, 128.9, 128.6, 123.7 (CHCH=CHCH) (Ph)

(BrPh), 41.5, 39.6, 38.3, 24.2 (CHCH$_2$CHCH). Exact mass (EI) calcd for $C_{21}H_{16}NO_3{}^{79}Br$ $(M)^+$: 409.0314, found: 409.0316.

6.5.5.2 **(3a*R**,4*S**,7a*S**) and (3a*S**,4*R**,7a*R**)-4-(4-Bromobenzoyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-149)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.24 (PhH, BrPhH, m, 9H), 6.07-5.97 (CHCH=CHCH$_2$, m, 2H), 4.70 (CHCHCHCH$_2$, d, 1H, J = 6.5 Hz) 3.83 (CHCHCHCH$_2$, d, 1H, J = 9.2 Hz) 3.58 (CHCHCHCH$_2$, t, 1H, J = 8.7 Hz), 2.54 (CHCHCHCH$_2$, AB of ABX, 2H, δ_A = 2.70, δ_B = 2.38, J_{AB} = 16.8 Hz, J_{AX} = 5.3 Hz, J_{BX} = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8 (BrPhCO),179.2, 178.7 (CONCO), 133.8, 132.1, 131.9, 131.7, 130.3, 129.1, 128.7, 126.4, 124.3 (CHCH=CHCH$_2$) (Ph) (BrPh), 45.3, 41.0, 39.1, 23.5 (CHCHCHCH$_2$). Exact mass (EI) calcd for $C_{21}H_{16}NO_3{}^{79}Br$ $(M)^+$: 409.0314, found: 409.0309.

Spectral data were in accord with literature data.

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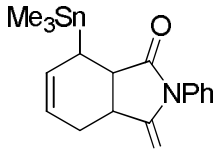
Appendix A

X-ray Crystallographic Data

(3a*R,4*R**,7a*S**) and (3a*S**,4*S**,7a*R**)-2-Phenyl-4-(trimethylstannyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-114)**



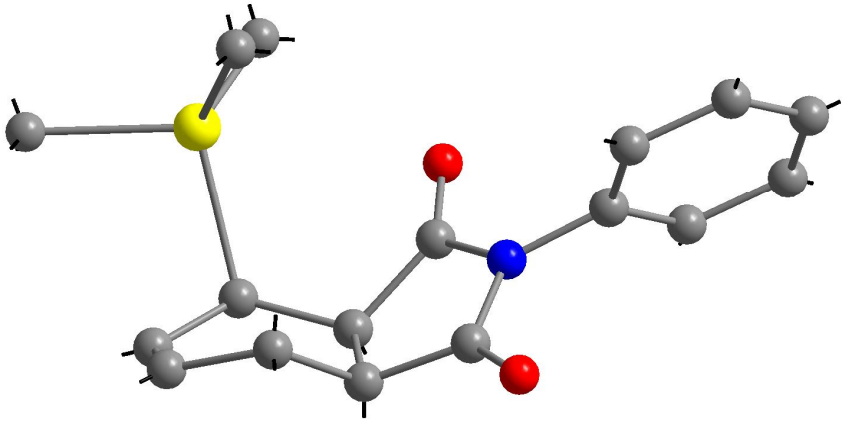


Table 1. Crystal data and structure refinement for 6-114

Empirical formula	$C_{17}H_{21}NO_2Sn$
Formula weight	390.04 g/mol
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, ***F***dd2
Unit cell dimensions	a = 30.698(9) Å, b = 33.067(10) Å, c = 6.706(2) Å
Volume	6807(4) $Å^3$
Z, Calculated density	16, 1.522 mg/m^3
Absorption coefficient	1.505 mm^{-1}
F(000)	3136
Crystal size	0.50 x 0.06 x 0.02 mm
Theta range for data collection	2.80 to 30.00º
Limiting indices	-42<=h<=42, -45<=k<=46, -9<=l<=9
Reflections collected / unique	17350 / 4861 [R(int) = 0.0278]
Completeness to theta = 30.00	99.5 %
Max. and min. transmission	0.9705 and 0.5199
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4861 / 1 / 191
Goodness-of-fit on F^2	1.109
Final R indices [I>2σ(I)]	R1 = 0.0285, wR2 = 0.0706
R indices (all data)	R1 = 0.0334, wR2 = 0.0753
Absolute structure parameter	0.03(3)
Largest diff. peak and hole	0.654 and -0.953 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 6-114

	x	y	z	U(eq)
Sn(1)	2456(1)	-1643(1)	2771(1)	35(1)
N(1)	2212(1)	-524(1)	6446(5)	32(1)
O(1)	1891(1)	-910(1)	3989(4)	43(1)
O(2)	2714(1)	-220(1)	8501(5)	50(1)
C(1)	2208(1)	-737(1)	4641(5)	31(1)
C(2)	2656(1)	-704(1)	3714(6)	34(1)
C(3)	2948(1)	-565(1)	5459(7)	39(1)
C(4)	2633(1)	-408(1)	6996(6)	37(1)
C(5)	2816(1)	-1071(1)	2480(6)	36(1)
C(6)	3281(1)	-1177(1)	2927(9)	52(1)
C(7)	3466(1)	-1113(1)	4652(9)	62(2)
C(8)	3226(1)	-910(1)	6336(8)	52(1)
C(9)	1825(1)	-407(1)	7498(5)	31(1)
C(10)	1751(1)	-550(1)	9404(6)	37(1)
C(11)	1382(1)	-421(1)	10447(7)	47(1)
C(12)	1098(1)	-152(1)	9553(6)	45(1)
C(13)	1175(1)	-11(1)	7666(8)	47(1)
C(14)	1542(1)	-138(1)	6612(5)	39(1)
C(15)	1842(1)	-1687(1)	1249(7)	50(1)
C(16)	2890(2)	-2066(2)	1371(11)	77(2)
C(17)	2388(2)	-1800(2)	5846(7)	70(2)

Table 3. Hydrogen coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 6-114

	x	y	z	U(eq)
H(2A)	2642	-471	2767	41
H(3A)	3142	-341	5003	46
H(5A)	2802	-991	1043	43
H(6A)	3450	-1297	1899	62
H(7A)	3759	-1196	4849	74
H(8A)	3436	-799	7315	63
H(8B)	3037	-1108	7027	63
H(10A)	1948	-735	10000	45
H(11A)	1327	-517	11759	57
H(12A)	846	-64	10255	54
H(13A)	978	175	7072	56
H(14A)	1597	-40	5303	47
H(15A)	1712	-1952	1505	75
H(15B)	1887	-1652	-188	75
H(15C)	1645	-1475	1736	75
H(16A)	2762	-2337	1420	115
H(16B)	3170	-2066	2075	115
H(16C)	2936	-1987	-22	115
H(17A)	2227	-2055	5959	105
H(17B)	2228	-1586	6543	105
H(17C)	2677	-1831	6446	105

Table 4. Bond lengths [Å] and angles [°] for 6-114

Sn(1)-C(17)	2.137(5)
Sn(1)-C(16)	2.148(5)
Sn(1)-C(15)	2.150(4)
Sn(1)-C(5)	2.198(3)
N(1)-C(4)	1.398(4)
N(1)-C(1)	1.401(4)
N(1)-C(9)	1.435(4)
O(1)-C(1)	1.210(4)
O(2)-C(4)	1.210(4)
C(1)-C(2)	1.515(4)
C(2)-C(3)	1.542(5)
C(2)-C(5)	1.549(5)
C(2)-H(2A)	1.0000
C(3)-C(4)	1.505(5)
C(3)-C(8)	1.541(6)
C(3)-H(3A)	1.0000
C(5)-C(6)	1.500(5)
C(5)-H(5A)	1.0000
C(6)-C(7)	1.307(7)
C(6)-H(6A)	0.9500
C(7)-C(8)	1.507(7)
C(7)-H(7A)	0.9500
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(14)	1.379(5)
C(9)-C(10)	1.383(5)
C(10)-C(11)	1.397(5)
C(10)-H(10A)	0.9500
C(11)-C(12)	1.383(6)
C(11)-H(11A)	0.9500
C(12)-C(13)	1.370(7)
C(12)-H(12A)	0.9500
C(13)-C(14)	1.395(5)
C(13)-H(13A)	0.9500
C(14)-H(14A)	0.9500
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(17)-Sn(1)-C(16)	108.9(3)
C(17)-Sn(1)-C(15)	110.8(2)
C(16)-Sn(1)-C(15)	107.0(2)
C(17)-Sn(1)-C(5)	110.14(19)
C(16)-Sn(1)-C(5)	102.11(17)
C(15)-Sn(1)-C(5)	117.15(15)
C(4)-N(1)-C(1)	112.1(3)

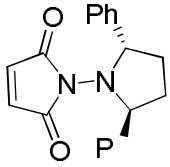
C(4)-N(1)-C(9)	124.2(3)
C(1)-N(1)-C(9)	123.5(3)
O(1)-C(1)-N(1)	123.9(3)
O(1)-C(1)-C(2)	128.1(3)
N(1)-C(1)-C(2)	108.0(3)
C(1)-C(2)-C(3)	103.8(3)
C(1)-C(2)-C(5)	116.7(3)
C(3)-C(2)-C(5)	117.0(3)
C(1)-C(2)-H(2A)	106.1
C(3)-C(2)-H(2A)	106.1
C(5)-C(2)-H(2A)	106.1
C(4)-C(3)-C(8)	110.5(4)
C(4)-C(3)-C(2)	104.5(3)
C(8)-C(3)-C(2)	113.1(3)
C(4)-C(3)-H(3A)	109.5
C(8)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3A)	109.5
O(2)-C(4)-N(1)	123.4(4)
O(2)-C(4)-C(3)	128.1(3)
N(1)-C(4)-C(3)	108.5(3)
C(6)-C(5)-C(2)	112.2(3)
C(6)-C(5)-Sn(1)	105.0(2)
C(2)-C(5)-Sn(1)	117.9(2)
C(6)-C(5)-H(5A)	107.1
C(2)-C(5)-H(5A)	107.1
Sn(1)-C(5)-H(5A)	107.1
C(7)-C(6)-C(5)	123.6(4)
C(7)-C(6)-H(6A)	118.2
C(5)-C(6)-H(6A)	118.2
C(6)-C(7)-C(8)	121.5(4)
C(6)-C(7)-H(7A)	119.3
C(8)-C(7)-H(7A)	119.3
C(7)-C(8)-C(3)	108.4(4)
C(7)-C(8)-H(8A)	110.0
C(3)-C(8)-H(8A)	110.0
C(7)-C(8)-H(8B)	110.0
C(3)-C(8)-H(8B)	110.0
H(8A)-C(8)-H(8B)	108.4
C(14)-C(9)-C(10)	121.1(3)
C(14)-C(9)-N(1)	118.9(3)
C(10)-C(9)-N(1)	120.0(3)
C(9)-C(10)-C(11)	119.5(4)
C(9)-C(10)-H(10A)	120.3
C(11)-C(10)-H(10A)	120.3
C(12)-C(11)-C(10)	119.4(4)
C(12)-C(11)-H(11A)	120.3
C(10)-C(11)-H(11A)	120.3
C(13)-C(12)-C(11)	120.7(4)
C(13)-C(12)-H(12A)	119.7
C(11)-C(12)-H(12A)	119.7
C(12)-C(13)-C(14)	120.4(3)
C(12)-C(13)-H(13A)	119.8
C(14)-C(13)-H(13A)	119.8
C(9)-C(14)-C(13)	119.0(4)
C(9)-C(14)-H(14A)	120.5
C(13)-C(14)-H(14A)	120.5
Sn(1)-C(15)-H(15A)	109.5

Sn(1)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
Sn(1)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
Sn(1)-C(16)-H(16A)	109.5
Sn(1)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
Sn(1)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
Sn(1)-C(17)-H(17A)	109.5
Sn(1)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
Sn(1)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5

Appendix B

X-ray Crystallographic Data

1-((2*S*,5*S*)-2,5-Diphenylpyrrolidin-1-yl)-1H-pyrrole-2,5-dione (6-135)



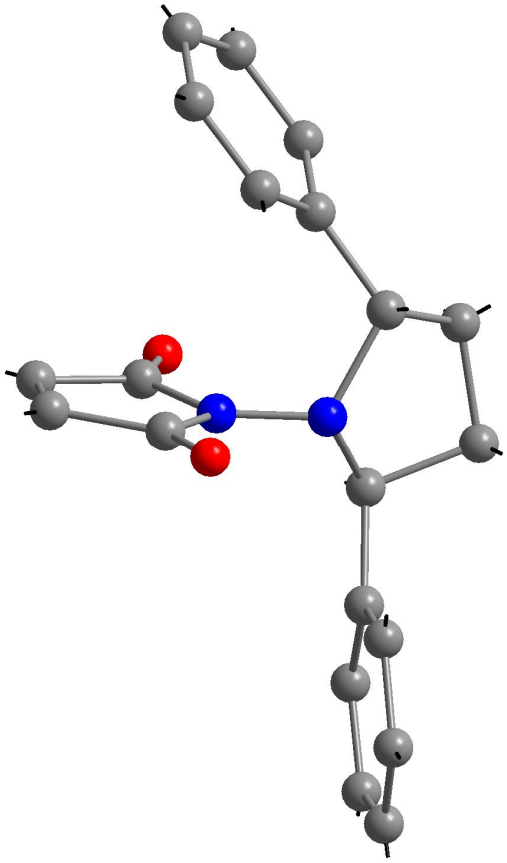


Table 1. Crystal data and structure refinement for 6-135

Empirical formula	$C_{20}H_{18}N_2O_2$
Formula weight	318.36
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 8.564(4) Å, b = 9.399(4) Å, c = 20.445(9) Å
Volume	1645.5(12) $Å^3$
Z, Calculated density	4, 1.285 g/cm^3
Absorption coefficient	0.084 mm^{-1}
F(000)	672
Crystal size	0.48 x 0.18 x 0.06 mm
Theta range for data collection	2.94 to 28.00 º
Limiting indices	-11<=h<=11, -12<=k<=12, -27<=l<=25
Reflections collected / unique	16300 / 3965 [R(int) = 0.0426]
Completeness to theta = 28.00	99.7 %
Max. and min. transmission	0.9950 and 0.9608
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3965 / 0 / 218
Goodness-of-fit on F^2	1.229
Final R indices [I>2σ(I)]	R1 = 0.0425, wR2 = 0.0851
R indices (all data)	R1 = 0.0530, wR2 = 0.0899
Absolute structure parameter	1.6(13)
Extinction coefficient	0.0267(16)
Largest diff. peak and hole	0.182 and -0.206 e-. $Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 6-135

	x	y	z	U(eq)
N(1)	6576(2)	9387(1)	1100(1)	31(1)
C(2)	7575(2)	10444(2)	1342(1)	38(1)
C(3)	9023(2)	10329(2)	950(1)	45(1)
C(4)	8882(2)	9280(2)	529(1)	44(1)
C(5)	7321(2)	8606(2)	608(1)	35(1)
O(6)	7272(2)	11243(1)	1787(1)	52(1)
O(7)	6766(2)	7607(1)	322(1)	46(1)
N(8)	5144(2)	9094(1)	1386(1)	32(1)
C(9)	5056(2)	7805(2)	1831(1)	37(1)
C(10)	3597(2)	7035(2)	1585(1)	46(1)
C(11)	2602(2)	8232(2)	1303(1)	43(1)
C(12)	3814(2)	9106(2)	926(1)	32(1)
C(13)	6540(2)	6957(2)	1887(1)	35(1)
C(14)	7820(2)	7566(2)	2203(1)	44(1)
C(15)	9215(2)	6855(2)	2270(1)	51(1)
C(16)	9360(3)	5502(2)	2028(1)	60(1)
C(17)	8132(3)	4861(2)	1722(1)	65(1)
C(18)	6712(2)	5584(2)	1653(1)	52(1)
C(19)	3270(2)	10594(2)	757(1)	34(1)
C(20)	2573(2)	10840(2)	152(1)	43(1)
C(21)	1893(2)	12146(2)	12(1)	53(1)
C(22)	1932(2)	13224(2)	468(1)	57(1)
C(23)	2674(3)	13005(2)	1059(1)	56(1)
C(24)	3340(2)	11698(2)	1204(1)	44(1)

Table 3. Hydrogen coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 6-135

	x	y	z	U(eq)
H(3A)	9896	10909	994	54
H(4A)	9640	9002	229	53
H(9A)	4814	8159	2270	45
H(10A)	3859	6341	1252	56
H(10B)	3060	6559	1941	56
H(11A)	2117	8790	1647	51
H(11B)	1799	7865	1014	51
H(12A)	4104	8601	525	39
H(14A)	7728	8479	2374	52
H(15A)	10055	7290	2478	61
H(16A)	10301	5019	2072	72
H(17A)	8238	3941	1560	78
H(18A)	5876	5138	1447	62
H(20A)	2563	10122	-161	51
H(21A)	1411	12293	-390	64
H(22A)	1461	14094	379	69
H(23A)	2728	13741	1362	67
H(24A)	3837	11562	1604	53

Table 3. Bond lengths [Å] and angles [°] for 6-135

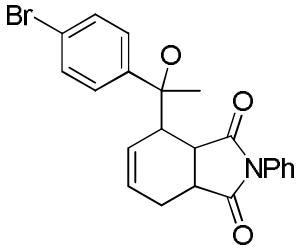
N(1)-N(8)	1.3856(18)
N(1)-C(5)	1.399(2)
N(1)-C(2)	1.401(2)
C(2)-O(6)	1.208(2)
C(2)-C(3)	1.481(3)
C(3)-C(4)	1.313(3)
C(4)-C(5)	1.488(3)
C(5)-O(7)	1.204(2)
N(8)-C(12)	1.477(2)
N(8)-C(9)	1.517(2)
C(9)-C(13)	1.504(3)
C(9)-C(10)	1.528(3)
C(10)-C(11)	1.524(3)
C(11)-C(12)	1.532(2)
C(12)-C(19)	1.514(2)
C(13)-C(18)	1.384(3)
C(13)-C(14)	1.396(3)
C(14)-C(15)	1.375(3)
C(15)-C(16)	1.369(3)
C(16)-C(17)	1.364(3)
C(17)-C(18)	1.401(3)
C(19)-C(24)	1.384(2)
C(19)-C(20)	1.392(2)
C(20)-C(21)	1.388(3)
C(21)-C(22)	1.378(3)
C(22)-C(23)	1.379(3)
C(23)-C(24)	1.387(3)
N(8)-N(1)-C(5)	127.01(13)
N(8)-N(1)-C(2)	122.18(14)
C(5)-N(1)-C(2)	110.34(14)
O(6)-C(2)-N(1)	125.12(17)
O(6)-C(2)-C(3)	129.34(18)
N(1)-C(2)-C(3)	105.53(15)
C(4)-C(3)-C(2)	109.45(17)
C(3)-C(4)-C(5)	109.32(16)
O(7)-C(5)-N(1)	125.36(16)
O(7)-C(5)-C(4)	129.33(16)
N(1)-C(5)-C(4)	105.32(15)
N(1)-N(8)-C(12)	114.42(12)
N(1)-N(8)-C(9)	117.11(13)
C(12)-N(8)-C(9)	110.44(12)
C(13)-C(9)-N(8)	115.25(14)
C(13)-C(9)-C(10)	117.71(14)
N(8)-C(9)-C(10)	102.85(14)
C(11)-C(10)-C(9)	103.39(14)
C(10)-C(11)-C(12)	102.00(15)
N(8)-C(12)-C(19)	112.96(13)
N(8)-C(12)-C(11)	101.43(13)
C(19)-C(12)-C(11)	113.69(14)
C(18)-C(13)-C(14)	117.31(17)
C(18)-C(13)-C(9)	123.87(17)

C(14)-C(13)-C(9)	118.81(15)
C(15)-C(14)-C(13)	121.94(18)
C(16)-C(15)-C(14)	119.6(2)
C(17)-C(16)-C(15)	120.40(19)
C(16)-C(17)-C(18)	120.09(19)
C(13)-C(18)-C(17)	120.65(19)
C(24)-C(19)-C(20)	118.70(16)
C(24)-C(19)-C(12)	121.90(15)
C(20)-C(19)-C(12)	119.22(15)
C(21)-C(20)-C(19)	120.68(18)
C(22)-C(21)-C(20)	119.97(19)
C(21)-C(22)-C(23)	119.65(18)
C(22)-C(23)-C(24)	120.55(19)
C(19)-C(24)-C(23)	120.36(18)

Appendix C

X-ray Crystallographic Data

(3aR*,4S*,7aS*) and (3aS*,4R*,7aR*)-4-((S*) and (R*)-1-(4-bromophenyl)-1-hydroxyethyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-142)



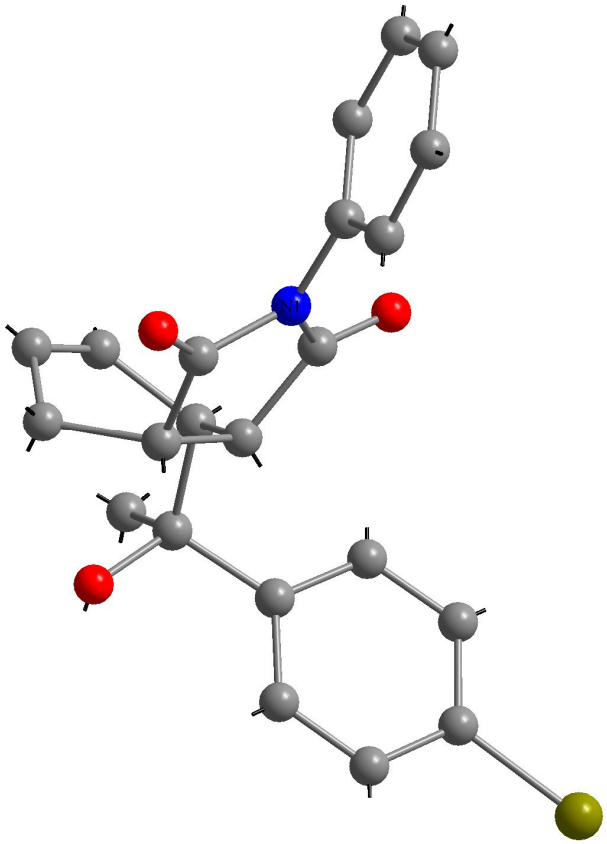


Table 1. Crystal data and structure refinement for 6-142

Empirical formula	$C_{22}H_{20}BrNO_3$
Formula weight	426.30 g/mol
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, *P*na2_1
Unit cell dimensions	a = 25.790(3) Å, b = 6.0690(7) Å, c = 11.9716(14)Å
Volume	1873.8(4) $Å^3$
Z, Calculated density	4, 1.511 mg/m^3
Absorption coefficient	2.216 mm^{-1}
F(000)	872
Crystal size	0.5 x 0.16 x 0.02 mm
Theta range for data collection	3.40 to 30.00 deg.
Limiting indices	-36<=h<=31, -8<=k<=8, -16<=l<=16
Reflections collected / unique	20756 / 5430 [R(int) = 0.0340]
Completeness to theta = 30.00	99.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5430 / 1 / 244
Goodness-of-fit on F^2	1.029
Final R indices [I>2σ(I)]	R1 = 0.0313, wR2 = 0.0659
R indices (all data)	R1 = 0.0427, wR2 = 0.0701
Absolute structure parameter	0.010(6)
Largest diff. peak and hole	0.390 and -0.318 e. $Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 6-142

	x	y	z	U(eq)
Br(1)	-542(1)	-8255(1)	-6854(1)	46(1)
O(1)	-4316(1)	-4931(3)	-6170(1)	41(1)
O(2)	-3248(1)	-10686(2)	-6970(1)	36(1)
O(3)	-2637(1)	-6755(2)	-3435(1)	33(1)
N(1)	-3843(1)	-7879(2)	-6817(2)	26(1)
C(1)	-3399(1)	-9028(3)	-6503(2)	26(1)
C(2)	-3143(1)	-7853(3)	-5539(2)	24(1)
C(3)	-3511(1)	-5955(3)	-5241(2)	27(1)
C(4)	-3942(1)	-6096(3)	-6092(2)	29(1)
C(5)	-3015(1)	-9509(3)	-4603(2)	23(1)
C(6)	-3482(1)	-9881(3)	-3876(2)	31(1)
C(7)	-3819(1)	-8303(3)	-3647(2)	34(1)
C(8)	-3750(1)	-5997(4)	-4068(2)	34(1)
C(9)	-2526(1)	-8845(3)	-3934(2)	26(1)
C(10)	-2414(1)	-10523(4)	-3013(2)	39(1)
C(11)	-2056(1)	-8667(3)	-4704(2)	25(1)
C(12)	-1896(1)	-10449(3)	-5362(2)	32(1)
C(13)	-1456(1)	-10319(4)	-6019(2)	35(1)
C(14)	-1168(1)	-8406(4)	-6029(2)	32(1)
C(15)	-1320(1)	-6608(4)	-5405(2)	37(1)
C(16)	-1760(1)	-6759(3)	-4754(2)	34(1)
C(17)	-4187(1)	-8467(3)	-7706(2)	27(1)
C(18)	-4420(1)	-10524(4)	-7714(2)	34(1)
C(19)	-4767(1)	-11019(4)	-8558(2)	42(1)
C(20)	-4890(1)	-9471(4)	-9365(2)	44(1)
C(21)	-4656(1)	-7436(4)	-9350(2)	40(1)
C(22)	-4298(1)	-6920(4)	-8527(2)	34(1)

Table 3. Hydrogen coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 6-142

	x	y	z	U(eq)
H(1A)	-2392	-6392	-3012	50
H(2A)	-2810	-7203	-5812	29
H(3A)	-3323	-4527	-5344	32
H(5A)	-2935	-10946	-4973	27
H(6A)	-3537	-11306	-3570	38
H(7A)	-4113	-8641	-3202	41
H(8A)	-3523	-5174	-3548	41
H(8B)	-4091	-5249	-4086	41
H(10A)	-2100	-10085	-2606	58
H(10B)	-2361	-11980	-3347	58
H(10C)	-2708	-10582	-2495	58
H(12A)	-2093	-11771	-5356	38
H(13A)	-1353	-11542	-6462	42
H(15A)	-1124	-5283	-5424	44
H(16A)	-1864	-5517	-4326	41
H(18A)	-4342	-11575	-7151	41
H(19A)	-4922	-12436	-8584	50
H(20A)	-5136	-9816	-9929	53
H(21A)	-4740	-6379	-9906	48
H(22A)	-4130	-5526	-8525	41

Table 4. Bond lengths [Å] and angles [°] for 6-142

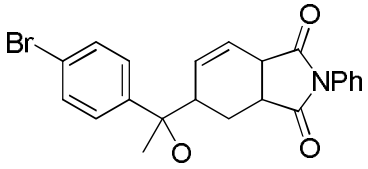
Br(1)-C(14)	1.894(2)
O(1)-C(4)	1.200(2)
O(2)-C(1)	1.215(2)
O(3)-C(9)	1.431(2)
N(1)-C(1)	1.392(2)
N(1)-C(4)	1.410(2)
N(1)-C(17)	1.431(3)
C(1)-C(2)	1.509(3)
C(2)-C(3)	1.535(3)
C(2)-C(5)	1.541(2)
C(3)-C(4)	1.510(3)
C(3)-C(8)	1.533(3)
C(5)-C(6)	1.504(3)
C(5)-C(9)	1.546(3)
C(6)-C(7)	1.322(3)
C(7)-C(8)	1.498(3)
C(9)-C(11)	1.527(3)
C(9)-C(10)	1.529(3)
C(11)-C(16)	1.388(3)
C(11)-C(12)	1.400(3)
C(12)-C(13)	1.383(3)
C(13)-C(14)	1.378(3)
C(14)-C(15)	1.379(3)
C(15)-C(16)	1.381(3)
C(17)-C(18)	1.385(3)
C(17)-C(22)	1.389(3)
C(18)-C(19)	1.382(3)
C(19)-C(20)	1.384(4)
C(20)-C(21)	1.374(4)
C(21)-C(22)	1.387(3)
C(1)-N(1)-C(4)	111.54(17)
C(1)-N(1)-C(17)	125.85(16)
C(4)-N(1)-C(17)	122.47(15)
O(2)-C(1)-N(1)	123.64(18)
O(2)-C(1)-C(2)	127.12(17)
N(1)-C(1)-C(2)	109.23(16)
C(1)-C(2)-C(3)	105.20(15)
C(1)-C(2)-C(5)	110.03(15)
C(3)-C(2)-C(5)	116.95(15)
C(4)-C(3)-C(8)	108.76(17)
C(4)-C(3)-C(2)	104.79(16)
C(8)-C(3)-C(2)	116.66(16)
O(1)-C(4)-N(1)	123.36(18)
O(1)-C(4)-C(3)	127.61(19)
N(1)-C(4)-C(3)	109.03(16)
C(6)-C(5)-C(2)	110.26(16)
C(6)-C(5)-C(9)	113.12(15)
C(2)-C(5)-C(9)	112.44(14)
C(7)-C(6)-C(5)	122.55(18)
C(6)-C(7)-C(8)	121.94(19)
C(7)-C(8)-C(3)	111.81(17)

O(3)-C(9)-C(11)	110.39(15)
O(3)-C(9)-C(10)	109.16(16)
C(11)-C(9)-C(10)	109.39(16)
O(3)-C(9)-C(5)	106.49(15)
C(11)-C(9)-C(5)	110.63(15)
C(10)-C(9)-C(5)	110.75(16)
C(16)-C(11)-C(12)	117.25(19)
C(16)-C(11)-C(9)	121.41(17)
C(12)-C(11)-C(9)	121.30(17)
C(13)-C(12)-C(11)	121.21(19)
C(14)-C(13)-C(12)	119.66(19)
C(13)-C(14)-C(15)	120.58(19)
C(13)-C(14)-Br(1)	120.28(16)
C(15)-C(14)-Br(1)	119.10(16)
C(14)-C(15)-C(16)	119.2(2)
C(15)-C(16)-C(11)	122.1(2)
C(18)-C(17)-C(22)	121.02(19)
C(18)-C(17)-N(1)	119.90(17)
C(22)-C(17)-N(1)	119.03(18)
C(19)-C(18)-C(17)	118.8(2)
C(18)-C(19)-C(20)	120.7(2)
C(21)-C(20)-C(19)	120.0(2)
C(20)-C(21)-C(22)	120.3(2)
C(21)-C(22)-C(17)	119.2(2)

Appendix D

X-ray Crystallographic Data

(3a*S,5*R**,7a*R**) and (3a*R**,5*S**,7a*S**)-5-((*S**) and (*R**)-1-(4-Bromophenyl)-1-hydroxyethyl)-2-phenyl-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6-143)**



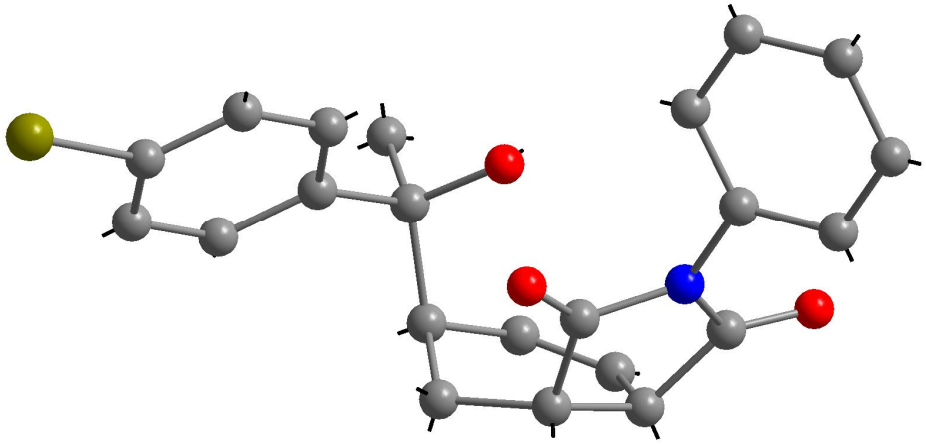


Table 1. Crystal data and structure refinement for 6-143

Empirical formula	$C_{22}H_{20}BrNO_3$
Formula weight	426.30 g/mol
Temperature	200(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, *P*-1
Unit cell dimensions	a = 8.4499(9) Å, b = 13.9121(15) Å,
	c = 16.6265(18) Å
	α = 102.888(2) º, β = 94.561(2) º, γ = 94.899(2) º
Volume	1888.5(4) $Å^3$
Z, Calculated density	4, 1.499 Mg/m^3
Absorption coefficient	2.199 mm^{-1}
F(000)	872
Crystal size	0.42 x 0.40 x 0.22 mm
Theta range for data collection	2.85 to 30.62
Limiting indices	-12<=h<=12, -19<=k<=19, -23<=l<=23
Reflections collected / unique	30084 / 11551 [R(int) = 0.0169]
Completeness to theta = 30.62	99.1 %
Absorption correction	Empirical
Max. and min. transmission	0.6433 and 0.4586
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11551 / 0 / 487
Goodness-of-fit on F^2	1.045
Final R indices [I>2σ(I)]	R1 = 0.0368, wR2 = 0.0898
R indices (all data)	R1 = 0.0506, wR2 = 0.0959
Largest diff. peak and hole	1.090 and -1.101 e. $Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 6-143

	x	y	z	U(eq)
Br(1A)	6340(1)	5044(1)	1536(1)	48(1)
Br(1B)	910(1)	14240(1)	2977(1)	65(1)
O(1A)	-674(2)	10869(1)	1052(1)	43(1)
O(2A)	2927(1)	9126(1)	2132(1)	33(1)
O(3A)	1687(1)	8276(1)	280(1)	28(1)
O(1B)	-6292(2)	20143(1)	4211(1)	40(1)
O(2B)	-3096(1)	18039(1)	2784(1)	38(1)
O(3B)	-3172(2)	18035(1)	4693(1)	38(1)
N(1A)	1395(2)	10180(1)	1611(1)	26(1)
N(1B)	-4407(2)	19266(1)	3531(1)	28(1)
C(1A)	1634(2)	9329(1)	1907(1)	26(1)
C(2A)	17(2)	8792(1)	1944(1)	26(1)
C(3A)	-1180(2)	9330(1)	1512(1)	29(1)
C(4A)	-191(2)	10221(1)	1356(1)	29(1)
C(5A)	-116(2)	7664(1)	1632(1)	28(1)
C(6A)	-472(2)	7271(1)	689(1)	28(1)
C(7A)	-1718(2)	7823(1)	348(1)	33(1)
C(8A)	-2024(2)	8726(1)	707(1)	33(1)
C(9A)	1031(2)	7274(1)	203(1)	25(1)
C(10A)	586(2)	6770(1)	-716(1)	33(1)
C(11A)	2322(2)	6738(1)	554(1)	26(1)
C(12A)	3901(2)	7155(1)	716(1)	31(1)
C(13A)	5086(2)	6650(1)	1009(1)	34(1)
C(14A)	4700(2)	5718(1)	1135(1)	31(1)
C(15A)	3143(2)	5283(1)	984(1)	44(1)
C(16A)	1970(2)	5800(1)	697(1)	42(1)
C(17A)	2681(2)	10894(1)	1549(1)	28(1)
C(18A)	2632(2)	11882(1)	1930(1)	37(1)
C(19A)	3880(2)	12572(1)	1872(1)	46(1)
C(20A)	5154(2)	12263(2)	1443(2)	50(1)
C(21A)	5203(2)	11278(2)	1079(1)	46(1)
C(22A)	3958(2)	10581(1)	1125(1)	35(1)
C(1B)	-4247(2)	18286(1)	3129(1)	28(1)
C(2B)	-5771(2)	17649(1)	3155(1)	27(1)
C(3B)	-6790(2)	18343(1)	3693(1)	28(1)
C(4B)	-5859(2)	19366(1)	3856(1)	29(1)
C(5B)	-5532(2)	16670(1)	3399(1)	30(1)
C(6B)	-5376(2)	16711(1)	4334(1)	34(1)
C(7B)	-6569(2)	17335(1)	4757(1)	37(1)
C(8B)	-7157(2)	18067(1)	4488(1)	34(1)
C(9B)	-3661(2)	17059(1)	4783(1)	36(1)
C(10B)	-3629(3)	17069(2)	5709(1)	52(1)
C(11B)	-2485(2)	16386(1)	4370(1)	37(1)
C(12B)	-1373(2)	16708(1)	3896(1)	43(1)
C(13B)	-363(2)	16075(2)	3483(1)	46(1)

C(14B)	-460(2)	15109(1)	3555(1)	44(1)
C(15B)	-1522(4)	14768(2)	4031(2)	68(1)
C(16B)	-2534(3)	15408(2)	4436(2)	63(1)
C(17B)	-3201(2)	20056(1)	3540(1)	30(1)
C(18B)	-3566(2)	20824(1)	3176(1)	38(1)
C(19B)	-2363(3)	21566(2)	3160(1)	49(1)
C(20B)	-836(3)	21529(2)	3495(1)	53(1)
C(21B)	-471(2)	20755(2)	3856(1)	48(1)
C(22B)	-1665(2)	20013(1)	3884(1)	37(1)

Table 3. Hydrogen coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 6-143

	x	y	z	U(eq)
H(3AA)	1335	8478	-133	42
H(3BA)	-3466	18455	5083	57
H(2AA)	-184	8927	2542	32
H(3AB)	-1989	9565	1897	34
H(5AA)	-971	7368	1904	33
H(5AB)	898	7430	1812	33
H(6AA)	-939	6565	593	33
H(7AA)	-2327	7501	-161	39
H(8AA)	-2833	9012	437	40
H(10A)	1542	6778	-1013	49
H(10B)	-209	7128	-955	49
H(10C)	142	6083	-767	49
H(12A)	4174	7796	625	37
H(13A)	6159	6948	1121	41
H(15A)	2879	4641	1075	53
H(16A)	896	5504	596	50
H(18A)	1756	12085	2226	44
H(19A)	3860	13253	2127	56
H(20A)	6003	12737	1399	60
H(21A)	6093	11074	794	55
H(22A)	3982	9901	869	42
H(2BA)	-6328	17475	2580	33
H(3BB)	-7822	18354	3359	34
H(5BA)	-4557	16423	3171	37
H(5BB)	-6445	16178	3132	37
H(6BA)	-5657	16020	4396	40
H(7BA)	-6924	17193	5250	44
H(8BA)	-7857	18445	4818	41
H(10D)	-4382	17514	5962	78
H(10E)	-2550	17301	5982	78
H(10F)	-3933	16396	5774	78
H(12B)	-1298	17379	3851	52
H(13B)	386	16308	3154	55

H(15B)	-1569	14101	4085	81
H(16B)	-3276	15170	4765	75
H(18B)	-4621	20844	2940	46
H(19B)	-2598	22100	2916	59
H(20B)	-22	22038	3481	63
H(21B)	590	20733	4082	58
H(22B)	-1432	19485	4136	45

Table 4. Bond lengths [Å] and angles [°] for 6-143

Br(1A)-C(14A)	1.8964(16)
Br(1B)-C(14B)	1.9030(19)
O(1A)-C(4A)	1.2128(19)
O(2A)-C(1A)	1.2033(18)
O(3A)-C(9A)	1.4290(17)
O(1B)-C(4B)	1.2120(19)
O(2B)-C(1B)	1.2045(19)
O(3B)-C(9B)	1.429(2)
N(1A)-C(4A)	1.382(2)
N(1A)-C(1A)	1.4031(18)
N(1A)-C(17A)	1.4337(19)
N(1B)-C(4B)	1.3842(19)
N(1B)-C(1B)	1.401(2)
N(1B)-C(17B)	1.431(2)
C(1A)-C(2A)	1.514(2)
C(2A)-C(5A)	1.530(2)
C(2A)-C(3A)	1.535(2)
C(3A)-C(8A)	1.500(2)
C(3A)-C(4A)	1.517(2)
C(5A)-C(6A)	1.537(2)
C(6A)-C(7A)	1.503(2)
C(6A)-C(9A)	1.559(2)
C(7A)-C(8A)	1.322(2)
C(9A)-C(11A)	1.522(2)
C(9A)-C(10A)	1.534(2)
C(11A)-C(12A)	1.389(2)
C(11A)-C(16A)	1.390(2)
C(12A)-C(13A)	1.388(2)
C(13A)-C(14A)	1.376(2)
C(14A)-C(15A)	1.380(2)
C(15A)-C(16A)	1.388(2)

C(17A)-C(18A)	1.385(2)
C(17A)-C(22A)	1.385(2)
C(18A)-C(19A)	1.388(3)
C(19A)-C(20A)	1.385(3)
C(20A)-C(21A)	1.374(3)
C(21A)-C(22A)	1.387(3)
C(1B)-C(2B)	1.509(2)
C(2B)-C(5B)	1.531(2)
C(2B)-C(3B)	1.533(2)
C(3B)-C(8B)	1.504(2)
C(3B)-C(4B)	1.524(2)
C(5B)-C(6B)	1.537(2)
C(6B)-C(7B)	1.501(2)
C(6B)-C(9B)	1.562(2)
C(7B)-C(8B)	1.318(3)
C(9B)-C(11B)	1.521(3)
C(9B)-C(10B)	1.535(3)
C(11B)-C(12B)	1.382(3)
C(11B)-C(16B)	1.387(3)
C(12B)-C(13B)	1.389(3)
C(13B)-C(14B)	1.373(3)
C(14B)-C(15B)	1.366(3)
C(15B)-C(16B)	1.389(3)
C(17B)-C(18B)	1.385(2)
C(17B)-C(22B)	1.388(2)
C(18B)-C(19B)	1.391(3)
C(19B)-C(20B)	1.374(3)
C(20B)-C(21B)	1.388(3)
C(21B)-C(22B)	1.392(3)

C(4A)-N(1A)-C(1A)	112.51(12)
C(4A)-N(1A)-C(17A)	124.65(12)
C(1A)-N(1A)-C(17A)	122.78(12)
C(4B)-N(1B)-C(1B)	112.67(13)
C(4B)-N(1B)-C(17B)	125.89(13)
C(1B)-N(1B)-C(17B)	121.34(13)
O(2A)-C(1A)-N(1A)	123.73(14)
O(2A)-C(1A)-C(2A)	127.91(14)
N(1A)-C(1A)-C(2A)	108.22(12)
C(1A)-C(2A)-C(5A)	115.14(12)
C(1A)-C(2A)-C(3A)	104.87(12)
C(5A)-C(2A)-C(3A)	116.01(13)
C(8A)-C(3A)-C(4A)	109.53(13)
C(8A)-C(3A)-C(2A)	114.87(13)
C(4A)-C(3A)-C(2A)	104.73(12)
O(1A)-C(4A)-N(1A)	124.19(15)
O(1A)-C(4A)-C(3A)	126.85(15)
N(1A)-C(4A)-C(3A)	108.95(12)
C(2A)-C(5A)-C(6A)	115.77(12)
C(7A)-C(6A)-C(5A)	110.56(13)
C(7A)-C(6A)-C(9A)	110.69(12)
C(5A)-C(6A)-C(9A)	114.28(12)
C(8A)-C(7A)-C(6A)	124.43(15)
C(7A)-C(8A)-C(3A)	124.37(14)
O(3A)-C(9A)-C(11A)	107.44(11)
O(3A)-C(9A)-C(10A)	109.64(12)
C(11A)-C(9A)-C(10A)	108.72(12)

O(3A)-C(9A)-C(6A)	109.11(12)
C(11A)-C(9A)-C(6A)	111.39(12)
C(10A)-C(9A)-C(6A)	110.47(12)
C(12A)-C(11A)-C(16A)	117.64(14)
C(12A)-C(11A)-C(9A)	121.18(13)
C(16A)-C(11A)-C(9A)	121.14(13)
C(13A)-C(12A)-C(11A)	121.14(14)
C(14A)-C(13A)-C(12A)	119.71(15)
C(13A)-C(14A)-C(15A)	120.73(15)
C(13A)-C(14A)-Br(1A)	118.92(12)
C(15A)-C(14A)-Br(1A)	120.34(12)
C(14A)-C(15A)-C(16A)	118.87(15)
C(15A)-C(16A)-C(11A)	121.90(16)
C(18A)-C(17A)-C(22A)	121.26(15)
C(18A)-C(17A)-N(1A)	119.16(14)
C(22A)-C(17A)-N(1A)	119.57(14)
C(17A)-C(18A)-C(19A)	119.17(17)
C(20A)-C(19A)-C(18A)	119.71(18)
C(21A)-C(20A)-C(19A)	120.68(17)
C(20A)-C(21A)-C(22A)	120.24(18)
C(17A)-C(22A)-C(21A)	118.93(17)
O(2B)-C(1B)-N(1B)	123.59(14)
O(2B)-C(1B)-C(2B)	127.61(15)
N(1B)-C(1B)-C(2B)	108.66(12)
C(1B)-C(2B)-C(5B)	114.64(13)
C(1B)-C(2B)-C(3B)	104.92(12)
C(5B)-C(2B)-C(3B)	116.42(13)
C(8B)-C(3B)-C(4B)	111.53(13)
C(8B)-C(3B)-C(2B)	115.19(13)
C(4B)-C(3B)-C(2B)	104.83(12)
O(1B)-C(4B)-N(1B)	124.92(15)
O(1B)-C(4B)-C(3B)	126.59(14)
N(1B)-C(4B)-C(3B)	108.49(13)
C(2B)-C(5B)-C(6B)	115.98(13)
C(7B)-C(6B)-C(5B)	110.64(14)
C(7B)-C(6B)-C(9B)	110.59(14)
C(5B)-C(6B)-C(9B)	114.63(14)
C(8B)-C(7B)-C(6B)	124.25(15)
C(7B)-C(8B)-C(3B)	124.19(15)
O(3B)-C(9B)-C(11B)	106.83(14)
O(3B)-C(9B)-C(10B)	109.21(15)
C(11B)-C(9B)-C(10B)	110.97(15)
O(3B)-C(9B)-C(6B)	109.45(13)
C(11B)-C(9B)-C(6B)	109.69(14)
C(10B)-C(9B)-C(6B)	110.61(16)
C(12B)-C(11B)-C(16B)	117.49(18)
C(12B)-C(11B)-C(9B)	121.82(16)
C(16B)-C(11B)-C(9B)	120.65(18)
C(11B)-C(12B)-C(13B)	121.60(17)
C(14B)-C(13B)-C(12B)	119.16(19)
C(15B)-C(14B)-C(13B)	120.94(19)
C(15B)-C(14B)-Br(1B)	120.11(15)
C(13B)-C(14B)-Br(1B)	118.95(16)
C(14B)-C(15B)-C(16B)	119.24(19)
C(11B)-C(16B)-C(15B)	121.6(2)
C(18B)-C(17B)-C(22B)	121.29(16)
C(18B)-C(17B)-N(1B)	119.71(15)

C(22B)-C(17B)-N(1B)	118.94(15)
C(17B)-C(18B)-C(19B)	118.99(18)
C(20B)-C(19B)-C(18B)	120.2(2)
C(19B)-C(20B)-C(21B)	120.67(18)
C(20B)-C(21B)-C(22B)	119.78(19)
C(17B)-C(22B)-C(21B)	119.03(18)