Stille Coupling Reactions Involving α-Alkoxybenzylstannanes

by

Thi Minh Ngoc Nguyen

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AUTHOR'S DECLARATION

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

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Abstract

The Stille reaction has established itself as one of the two most general and most selective palladium-catalyzed cross-coupling reactions, along with the Suzuki cross-coupling of organoboron compounds.

The Stille coupling of α-alkoxystannanes is a relatively unexplored area. A previous study showed that an α-alkoxyalkylstannane could be coupled with benzoyl chloride with retention of configuration. However, our group has recently shown that Stille couplings of sulfonamidobenzylstannanes proceeds with inversion of configuration. In order to determine whether the Stille coupling reaction of α-alkoxybenzylstannanes proceeds with inversion or retention, the stereochemistry in the Stille reaction of α-alkoxybenzylstannanes was studied. Optimized conditions for Stille coupling of α-alkoxybenzyl-tributylstannanes with benzoyl chloride were developed: highest yields were observed using Pd_2dba_3 and PPh_3 in toluene. Enantiomerically enriched α-hydroxystannanes were obtained *via* chromatographic resolution of diastereomeric carbamate derivatives.

An X-ray crystal structure was obtained for the 3,5-dinitrobenzoate derivative of (*S*)-1-hydroxyphenylmethyl-trimethylstannane. Stille coupling (cat. Pd_2dba_3, PPh_3, toluene) of the corresponding acetate with benzoyl chloride provided the acetate of (*R*)-benzoin thus establishing retention of configuration under these reaction conditions.

Acknowledgements

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Finally, I want to thank everyone in my family who has given me so much. Thank you for always being there, I could not have completed this degree without your love and support.

To

my Grandmother (Ba noi - RIP),

Mom, Dad, co Nga, chu Ky`,

and all of my family in Vietnam and in Canada

Table of Contents

List of Abbreviations and Tradenames

Ac	acetyl
acac	acetylacetonate
aq	aqueous
Ar	aryl
BINAL-H	2,2'-(1,1'-binaphthoxy)aluminum hydride
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
n-BuLi	*n*-butyllithium
Bus	*tert*-butylsulfonyl
ca.	circa
cat.	catalytic
cm	centimeter
d	doublet
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DMAP	4-*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E^+	electrophile
ee	enantiomeric excess

EDG	electron donating group
eq.	equivalent
er	enantiomeric ratio
Et	ethyl
ether	diethyl ether
EWG	electron-withdrawing group
FCC	flash column chromatography
FDA	Food and Drug Administration
Fmoc	9-fluorenylmethoxycarbonyl
$(Fu)_3P$	tri(2-furyl)phosphine
h	hour
HMPA	hexamethylphosphoric amide
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	high performance liquid chromatography
Hz	Hertz
i-Pr	isopropyl
J	spin coupling constant
L	ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m	meta
m	multiplet
M	molar/metal
Me	methyl
min	minute
mL	milliliter
mmol	millimole
MOM	methoxymethyl
MOMen	methyloxymenthyl
MPLC	medium pressure liquid chromatography
MS	mass spectrometry

MTPA	α-methoxy-α-trifluoromethylphenylacetyl
m/z	mass to charge ratio
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
Np	naphthyl
Nu	nucleophile
o	ortho
(*o*-tol)$_3$P	tri(*o*-tolyl)phosphine
p-	para-
PA-Ph	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane
Ph	phenyl
PMHS	polymethylhydrosiloxane
PNP	*p*-nitrophenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
pyr	pyridine
q	quartet
rac	racemic
R_f	retention factor
rt	room temperature
s	singlet
s-Bu	*sec*-butyl
S_N2	substitution nucleophilic bimolecular
t	triplet
t-Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine

XS	excess
UV	ultraviolet spectroscopy

List of Figures

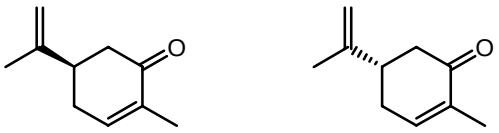
List of Tables

Chapter 1

Introduction

1.1 General

In the synthesis of complex natural products, one is frequently confronted with the task of creating intermediates that possess multiple stereogenic centers and preparing enantiomerically pure compounds. Chirality often determines the actions and behaviour of enantiopure molecules. Lemons and oranges both contain limonene, the different enantiomers giving rise to subtle differences in the aromas of these fruits.[1] Comparably, *R*-carvone smells like spearmint while *S*-carvone has the odour of caraway (Figure 1).[2]



1-1
(*R*)-carvone
spearmint odor

1-2
(*S*)-carvone
caraway

Figure 1: (*R*) and (*S*)-carvone.

The derivatives and analogues of numerous natural products have made their way into our everyday lives, from medicines to food additives.[1] Enantiomers of particular compounds could be useful or could be hazardous. For example, one enantiomer of thalidomide turned out to be potently teratogenic while the other enantiomer is an effective sedative (Figure 2). There are numerous examples of widely differing biological properties associated with enantiomers, and it is therefore necessary to construct potentially pharmaceutical compounds in their enantiopure form.

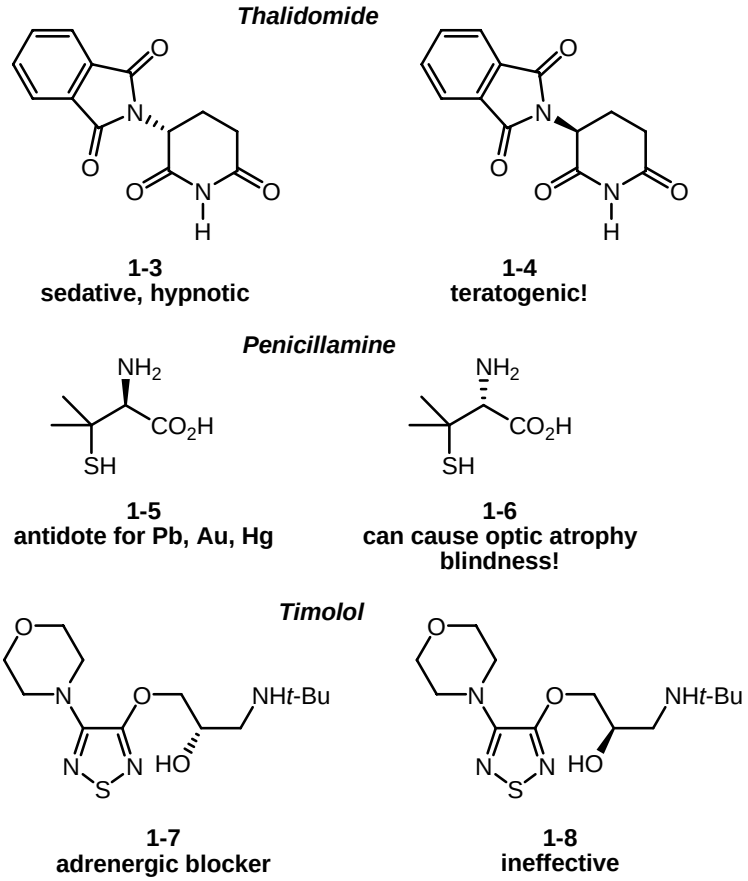


Figure 2: Examples of enantiopure compounds.

Amine functionalities and their derivatives are abundant among naturally occurring and pharmaceutically active compounds. α-Amino acids (*e.g.*, asparagine **1-9**) and β-amino alcohols are examples of amine derivatives that are commonly found in nature.[3] For example, paclitaxel **1-10** (Figure 3), which has been approved by the Food and Drug Administration (FDA) for the treatment of ovarian and breast cancers, contains a β-amidoalcohol side chain.[4]

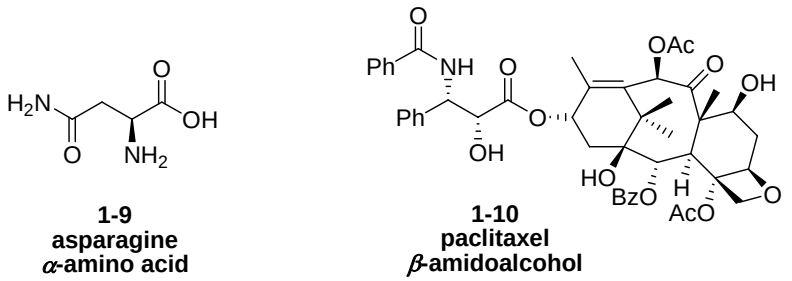


Figure 3: Examples of naturally occurring α-amino acids and β-amino alcohols

Biologically active compounds of these types often have specific stereochemistry associated with them, and their syntheses often require stereoselective transformations. Because organometallic reagents have been increasingly successful in the formation of carbon-carbon bonds, it would be very useful to apply organometallic chemistry to the synthesis of these compounds. Among the great palladium catalyzed coupling reactions which feature Mg, Zn, B and Si compounds, the Stille reaction (organotin) has proven to be one of the most powerful methods for carbon-carbon bond formation. Examples of palladium-catalyzed couplings of organotin compounds with carbon electrophiles were first reported in 1977.[5] Stille couplings have been used extensively in a large number of syntheses because they have high functional group compatibility and they proceed under mild reaction conditions. One of many examples is the total synthesis of (-) gambierol **1-11**, a complex molecule containing numerous chiral centers and functional groups, to form carbon-carbon bond at C-33 (Figure 4).[6] The Stille coupling reaction was applied to the last step in the construction of the gambierol molecule without having to protect any of the hydroxyl groups.[7]

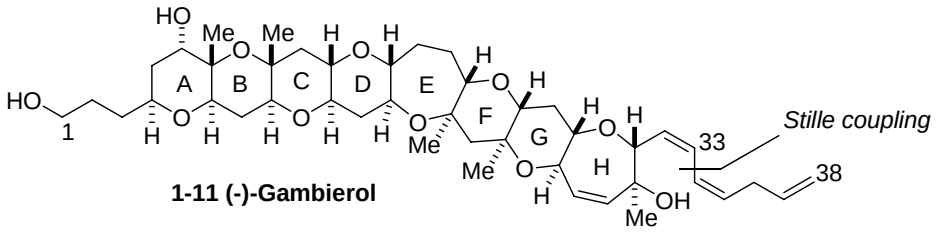


Figure 4: The structure of (-) Gambierol

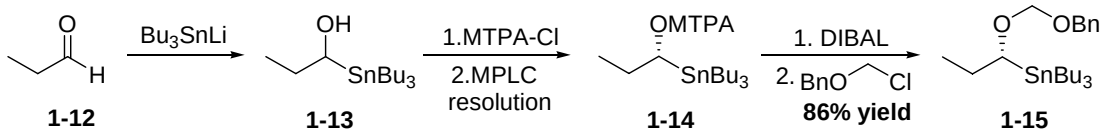
α-Aminostannanes and α-hydroxystannanes are of great interest to the Chong group since they can be applied to the synthesis of alcohol and amine derivatives. In the following sections, the chemistry of α-aminostannanes and α-hydroxystannanes will be reviewed, followed by what is known about Stille coupling reactions, and the results of research in this area will be presented.

1.2 α-Hydroxystannanes and α-Aminostannanes

Despite the numerous possible applications of α-hydroxystannanes and α-aminostannanes in organic synthesis, there are very few methods for their asymmetric synthesis. The following section will discuss the synthesis of these α-heteroatom substituted stannanes.

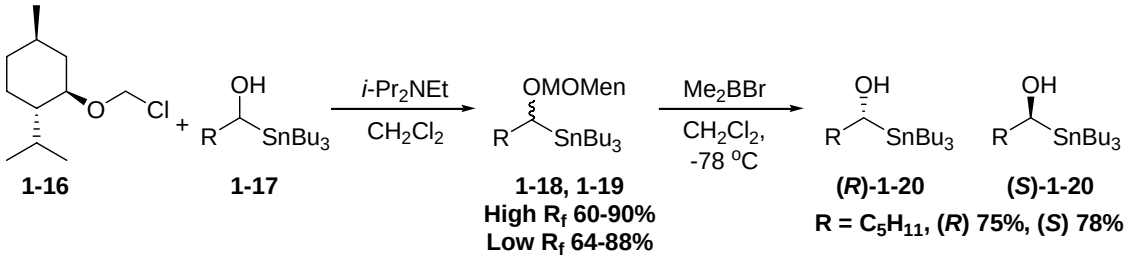
1.2.1 Synthesis of α-Hydroxystannanes

Some of the current literature methods for the asymmetric synthesis of stereodefined α-hydroxystannanes include resolution of chiral esters or acetals. One method (Scheme 1) involves the chromatographic separation of diastereomeric α-methoxy-α-trifluoromethylphenylacetates (MTPA or Mosher esters).[8]



Scheme 1

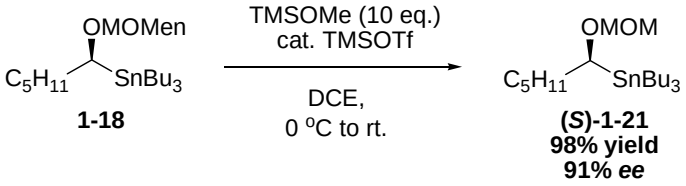
Aldehyde **1-12** was treated with Bu_3SnLi to afford the racemic hydroxystannane **1-13** which was converted into MTPA esters before resolution by medium pressure liquid chromatography (MPLC) to obtain a single diastereomer of ester **1-14** which was then taken to alkoxystannane **1-15**. Some of the limitations of this methodology which make it an impractical method for resolving α-hydroxystannanes include the high price of Mosher's acid and the required use of MPLC.



Scheme 2

Another resolution method involving the separation of menthyloxymethyl acetals has been reported (Scheme 2).[9] Derivatization of racemic hydroxystannane **1-17** with chloromethyl menthyl ether **1-16** provided diastereomeric acetals **1-18** and **1-19**, which were separated by flash column chromatography (FCC). This method provides an easy separation as the resolution could be done on larger scales but a single pass on a column could achieve only 80-85% *de*. Separation using MPLC, though, could provide material with up to 90-95% *de*. Hydroxystannanes **1-20** were then obtained by treatment of acetals **1-18** and **1-19** with Me_2BBr at -78 ^oC.

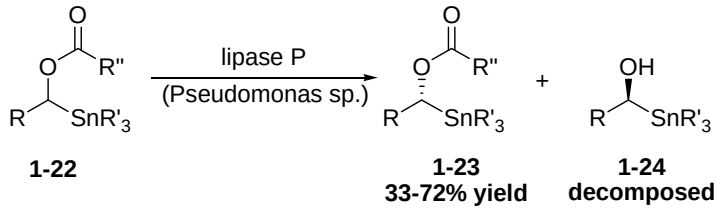
The authors also reported a direct acetal exchange reaction for one of their substrates (R = C_5H_{11}), which provided the MOM-protected α-hydroxystannane in 98% yield (Scheme 3).



Scheme 3

These methods have both been used to provide enantioenriched α-hydroxystannanes (and derivatives), but neither is practical due to expensive or commercially unavailable derivatizing agents, as well as poor to marginal separations of the diastereomers.

Another method for the synthesis of optically active α-hydroxystannanes involves enzymatic enantioselective hydrolysis of α-acyloxystannanes, which was reported by Itoh and Ohta in 1990 (Scheme 4).[10]

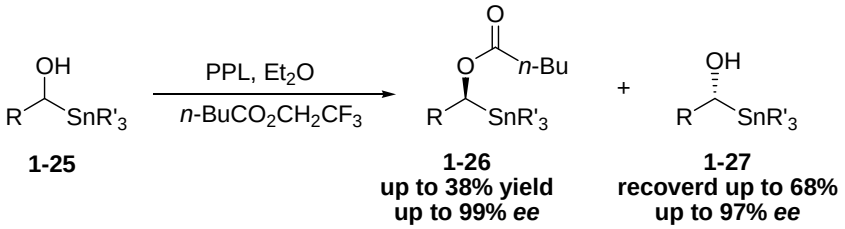


Scheme 4

In this enzymatic resolution, racemic stannanes **1-22** were hydrolyzed in the presence of a lipase to provide optically active α-acyloxystanne **1-23** (α-hydroxystannane **1-24** was not recovered, but instead decomposed under the non-anhydrous reaction conditions). Problems associated with this methodology are that the reaction does not run to completion (67% conversion was the maximum reported), and that the products were prone to racemization during the purification process. The enantiomeric excess of the

product was also satisfactory only for one case (86% *ee* for R = *n*-Bu, R' = Me, R" = CH_2SMe).

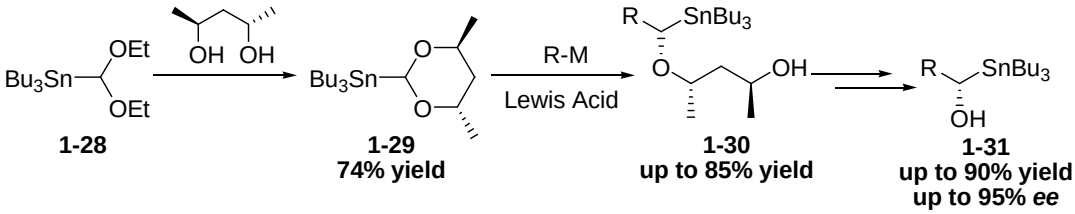
Our group has reported a related enzymatic resolution.[11] Porcine pancreatic lipase (PPL) is used in this resolution to selectively esterify one enantiomer of racemic α-hydroxystannanes using 2,2,2-trifluoroethyl valerate (Scheme 5).



Scheme 5

The resolution runs effectively when R and R' = either Me or Et. The (*S*)-valerate ester **1-26** was obtained in 99% *ee* and the unreacted (*R*)-α-hydroxystannane **1-27** could be recovered with variable enantiomeric purity (50-97% *ee*). While the selectivity achieved by this transformation is good for the reported cases, the substrate limitation is again severe. Given their toxicity, the use of trimethyl- and triethylstannyl compounds is especially undesirable.

Ring opening of chiral stannyl acetals has also been used to synthesize optically active α-hydroxystannanes as reported by Nakai et al. in 1994 (Scheme 6).[12]

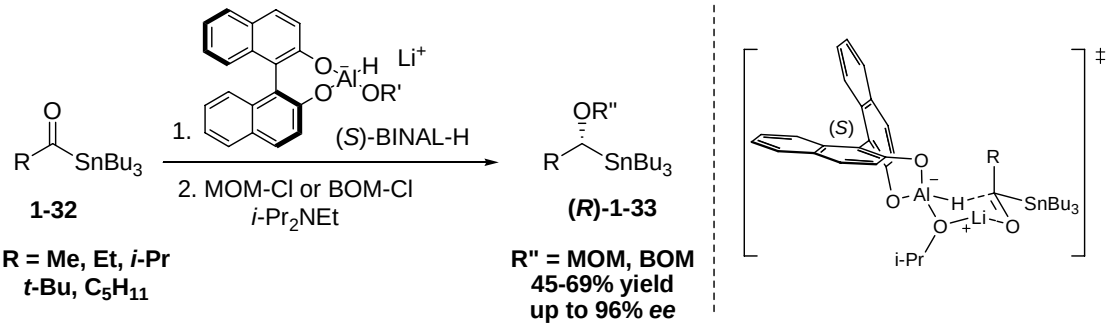


Scheme 6

While some combinations of organometallic reagent and Lewis acid gave good yields (up to 85%) and some gave good diastereoselectivities (>95% by NMR and HPLC

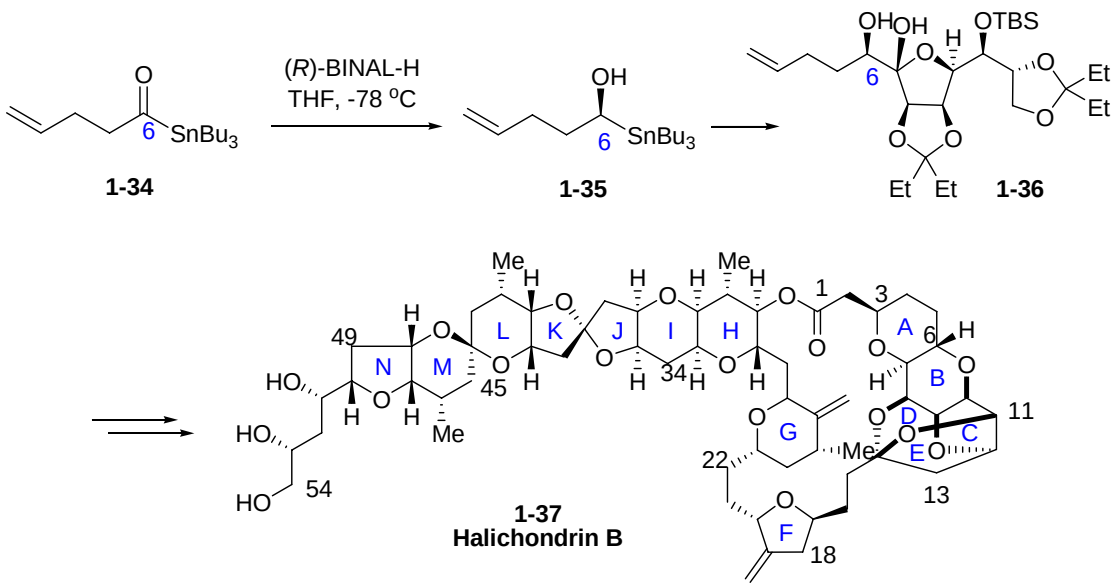
of MTPA esters), only R-M = EtMgBr gave both good yield (85%) and diastereoselectivity (>95%). The deprotection sequence could be carried out under relatively mild conditions and in high yield (90%). However, this severe substrate limitation detracts from the synthetic appeal of the methodology.

α-Hydroxystannanes can also be synthesized by the BINAL-H reduction of acyl stannanes,[13] or asymmetric deprotonation.[14] As a large number of asymmetric reducing agents had been developed, asymmetric reduction of acylstannanes was a rather obvious approach to homochiral α-alkoxystannanes in the late 1980s. The synthesis of α-alkoxystannanes using BINAL-H reduction of acyl stannanes is described in Scheme 7, where reductions using (*S*)-BINAL-H gave the (*R*)-carbinols as the major products.[13]



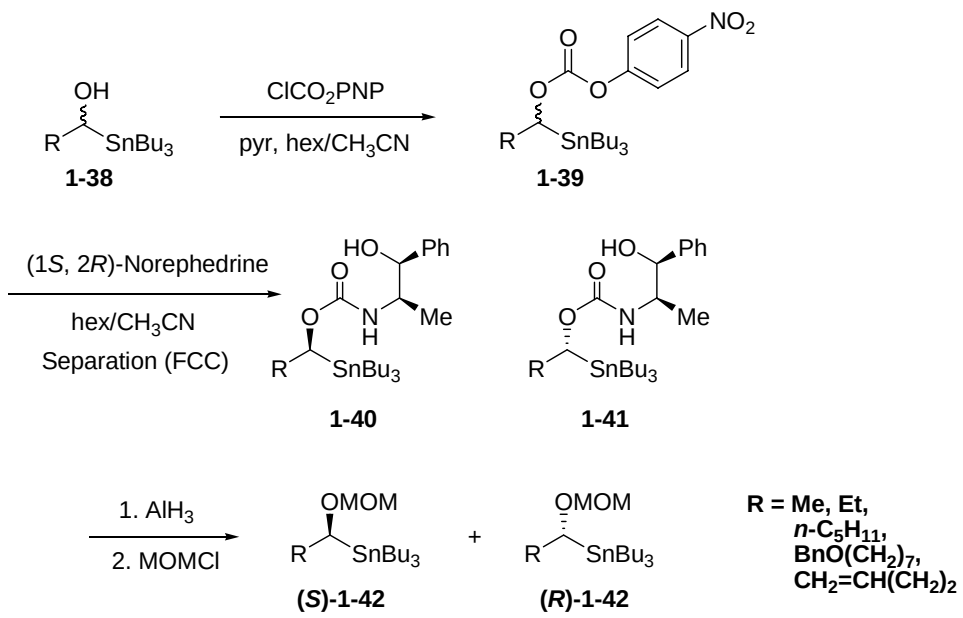
Scheme 7

An α-hydroxystannane has recently been used for the synthesis of the C_1-C_{15} subunit **1-36** of halichondrin B **1-37** (Scheme 8).[15] The authors synthesized α-hydroxystannane **1-35** asymmetrically using the BINAL-H reduction method and the product was obtained in 45% yield with 86% *ee*.



Scheme 8

Even though the BINAL-H reduction was used in the synthesis of halichondrin B, the fact that acyl stannanes are oxygen sensitive makes this reduction an unattractive method. Thus, there remained a need for a practical route to enantiopure α-hydroxystannanes. Therefore, the attention of our group turned to the resolution of racemic α-hydroxystannanes. It was discovered that racemic α–hydroxystannanes **1-38** could be converted easily to carbamates *via* *p*-nitrophenyl carbonate intermediates **1-39** (Scheme 9).[16] Carbamates derived from norephedrine are readily separable by flash chromatography and the individual diastereomers can be reduced with AlH_3 to enantiomerically enriched α-hydroxystannanes. The use of a two phase solvent system of hexanes-acetonitrile (1:1 v/v) was needed to obtain high yields of both the intermediate carbonates and the carbamate products.



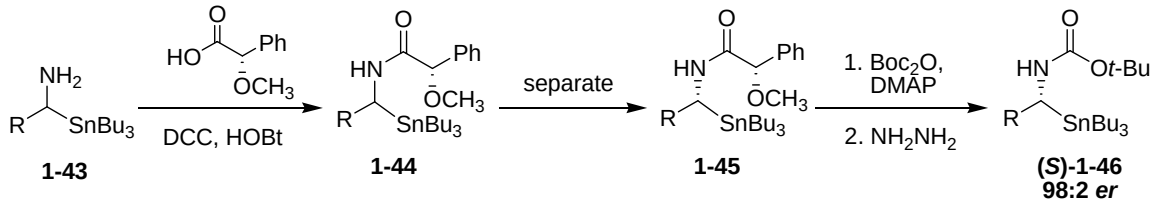
Scheme 9

The procedures are operationally simple and can be easily carried out on multigram scales. This protocol for obtaining enantiomerically enriched α-hydroxystannanes compares favourably with existing methods.

1.2.2 Synthesis of α-Aminostannanes

α-Aminostannanes have emerged as useful reagents for organic synthesis, particularly as precursors of α-aminoorganolithium reagents.[17] These organolithiums add to aldehydes to provide β-amino alcohols. However, access to enantiomerically pure α-aminostannanes is still limited. The current available methods either rely on the enantioselective deprotonation/stannylation in select (cyclic,[18] allylic[19] and benzylic[20]) cases, or *via* enantiomerically enriched α-hydroxystannanes.[11,13,21] Routes from α-hydroxystannanes, though, typically involve multiple steps, which detracts from their synthetic appeal.

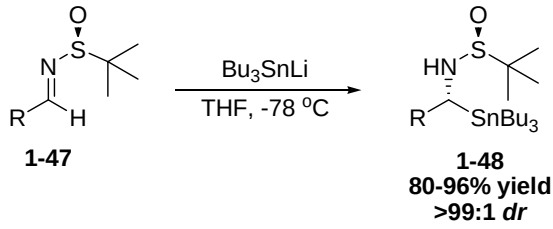
Recently we successfully resolved racemic α-aminostannanes *via* diastereomeric amides (Scheme 10).[22]



Scheme 10

The deprotection step in this sequence could not be carried out directly, but could be achieved by the addition of Boc_2O to derivatize **1-45** followed by reaction with NH_2NH_2 to obtain **1-46**. This method is practical for the synthesis of α-aminostannanes because the carbamates could be obtained up to 96% *ee* even on large scale.

More recently, another method for the asymmetric synthesis of acyclic α-aminostannanes has been developed in our group (Scheme 11).[23]



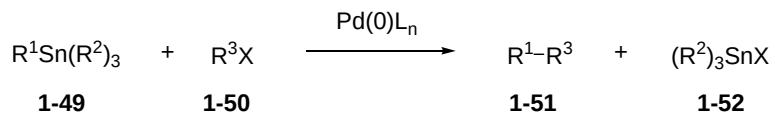
Scheme 11

The addition of Bu_3SnLi to *t*-butanesulfinimines **1-47** gave products **1-48** with very high diastereoselectivities (>98% *de* by chiral HPLC). The sulfinamides thus formed are readily transformed to enantiomerically enriched Boc-protected α-aminoorganostannanes. This approach is highly selective and efficient and may become the method of choice for the preparation of such compounds. This reaction is convenient due to the fact that both enantiomers of the chiral auxiliary (*t*-butanesulfinamide) are

readily available and the sulfinimines and stannyl sulfinamides are both stable compounds.

1.3 Stille Coupling Reactions

Palladium-catalyzed coupling reactions have been used extensively in synthetic chemistry and feature many types of reactions such as Suzuki,[24] Hiyama,[25] Negishi,[26] Kumada,[27] and also Stille couplings.[4] The first reported examples of the Stille coupling reaction were in 1977 by Kosugi, Shimizu and Migita.[4] More detailed studies on the reaction were done later by Stille and thus the reaction is known by his name.[28] The Stille coupling is schematically represented below (Scheme 12).



Scheme 12

In stannane reagents **1-49**, R^1 is typically an unsaturated moiety (*e.g.*, vinyl, aryl, heteroaryl, alkynyl, and allyl) or less often, an alkyl group. The R^2 is most commonly a butyl or a methyl group which acts as nontransferable group. Electrophiles **1-50** participating in the coupling often include halides (*e.g.*, iodides and less commonly bromides and chlorides) and sulfonates (*e.g.*, triflates), but other leaving groups have been used in many cases.

The three-step catalytic cycle below depicts the simplified general mechanism of the Stille reaction (Figure 5). This catalytic cycle was proposed as a working model and some details have been oversimplified. The cycle starts with palladium(0), which undergoes oxidative addition, where the palladium atom is inserted between the carbon and halide atoms of the organic electrophiles R-X. This is followed by a transmetalation

step, in which one group of the organostannane is transferred to the palladium. Reductive elimination then occurs to form the coupling product and regenerate Pd(0).

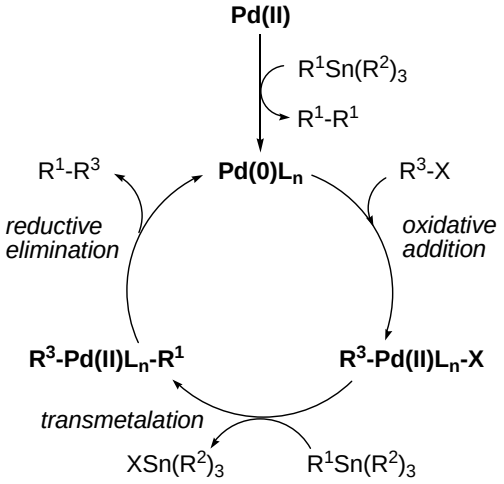
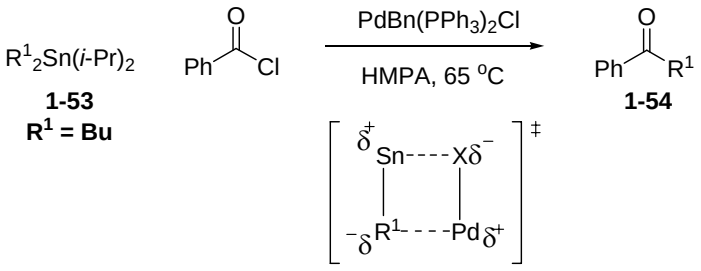


Figure 5: Catalytic cycle of the Stille reaction

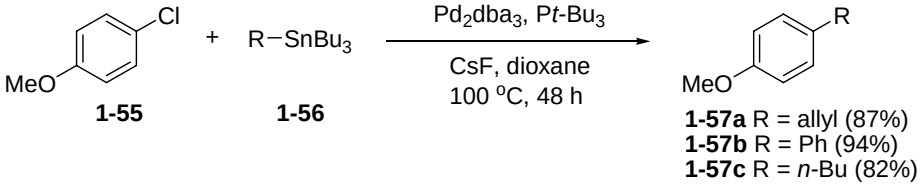
Palladium-catalyzed cross-couplings between organostannanes and organic electrophiles have been known for many years, and have shown great versatility in organic synthesis. Even in modern organic synthesis, where considerable effort is devoted to studying and developing new reagents and protocols for palladium-catalyzed cross-coupling reactions, the Stille coupling continues to be widely employed. One advantage that the Stille coupling offers is that organotin compounds are air-stable (owing to the low polarity of the carbon-tin bond) and easily prepared.

One of the early reactions reported by Stille was the coupling of unsymmetrical tetraalkyltins **1-53** with acid chlorides (Scheme 13).[29] The rate of transmetalation reaction of unsymmetrical organotrimethyltin or organotributyltin (R^1SnR_3) followed the order of R^1 PhC≡C > PrC≡C > PhCH=CH, CH_2=CH > Ph > $PhCH_2$ > CH_3OCH_2 > CH_3 > Bu, Et > *i*-Pr.[30] This trend makes sense since these groups have to be able to stabilize the developing negative charge in the transition state.



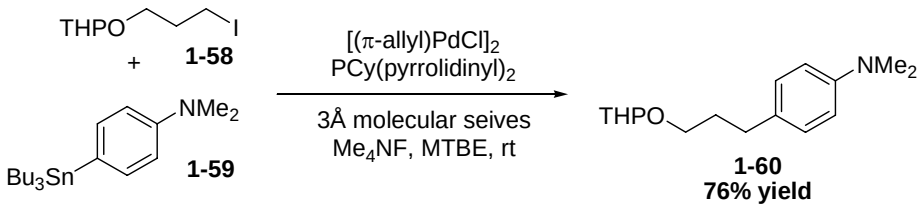
Scheme 13

Nowadays, the Stille coupling has a broader scope owing to recent progress in the area of palladium catalysis. For example, the reaction can be extended to include aryl chlorides (Scheme 14).[31] In this reaction, the catalyst system relies upon the presence of both *t*-Bu_3P, which is believed to enhance the reactivity of the palladium catalyst, and CsF, which is thought to enhance the reactivity of the organotin compounds. The coupled products **1-57** were obtained in very high yields.



Scheme 14

Fu and coworkers have since demonstrated that alkyl halides can be employed in the reaction as well (Scheme 15).[32] These electrophiles were previously ineffective in the Stille coupling, especially those possessing β-hydrogens, as β-elimination is a problematic side reaction. This reaction was the first example of a Stille cross-coupling of a simple alkyl iodide that bears β-hydrogen atoms.



Scheme 15

In terms of additives, the use of copper salts to facilitate the Stille coupling is a significant recent development in this area. The co-catalytic effect of Cu(I) in the Stille coupling was first reported by Liebeskind and Fengl.[33] Later studies have shown that in ethereal solvents such as THF or dioxane, and in conjunction with highly coordinating ligands like PPh_3, Cu(I) acts as ligand scavenger to facilitate formation of the co-ordinatively unsaturated Pd(II) intermediate which is needed to effect transmetalation (Path I, Figure 6). In highly polar solvents such as NMP formation of organo-copper species is likely (Path II, Figure 6).[34]

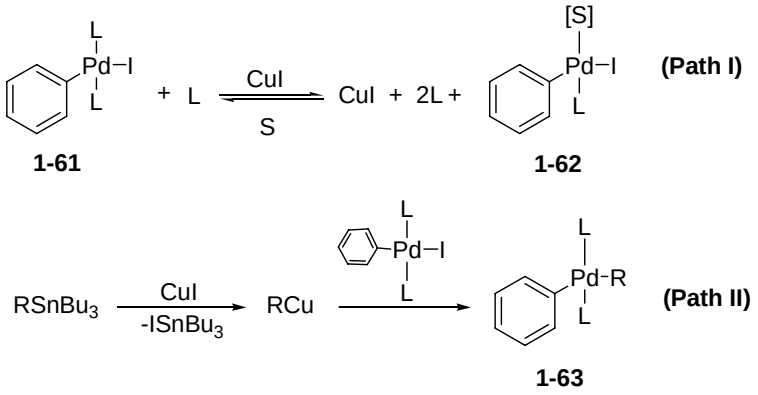
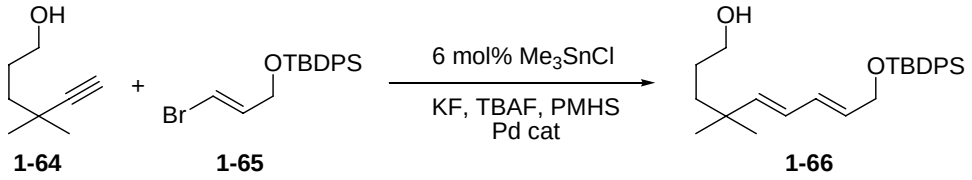


Figure 6: Copper effect on Stille coupling

Recent advances in Stille coupling methodology have made the reaction a more attractive means for preparing synthetic targets. One of the major practical drawbacks to the Stille coupling is the production of triorganotin halides as by-products. These compounds are both notoriously toxic and difficult to remove from reaction mixtures, making the Stille coupling unattractive for pharmaceutical preparations.

Another development for the Stille coupling reaction is to reduce the amount of tin by making the reaction catalytic in tin (Scheme 16).[35] In this reaction, tin hydride is generated *in situ* from tin fluoride. Hydrostannylation of alkyne **1-64** results in a *trans*-vinyl stannane that undergoes a Stille coupling with bromide **1-65**. The tin bromide by-

product is then converted in situ to the tin fluoride, which is subsequently reduced *in situ* to regenerate the tin hydride (Figure 7).



1-64 **1-65** **1-66**

Scheme 16

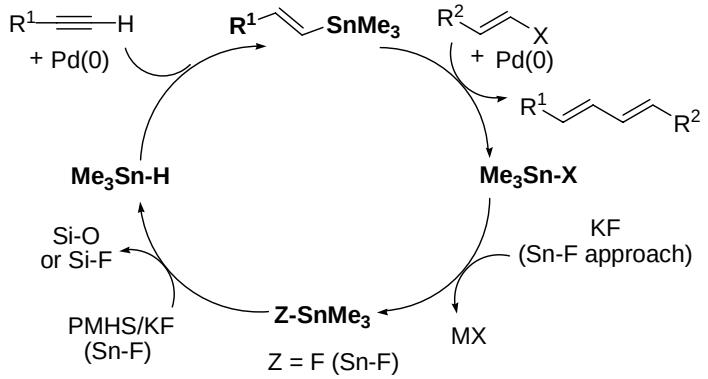


Figure 7: Proposed catalytic cycle for Hydrostannylation/Stille coupling.

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Chapter 2

Stille Coupling of α-Aminoorganostannanes

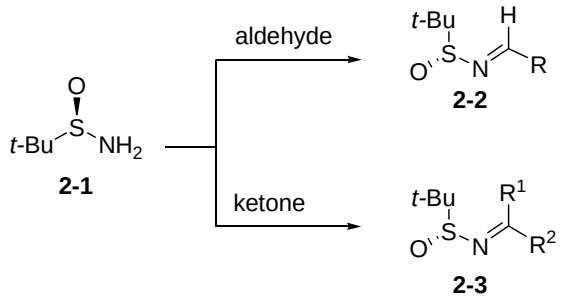
2.1 Introduction

2.1.1 General

Although α-aminoorganostannanes are potentially very useful in organic synthesis, particularly as precursors of α-aminoorganolithiums,[1] there are only few literature methods that describe their asymmetric synthesis. Until recently, the methods available were based on functional group interconversion of α-hydroxystannanes (eg. Mitsunobu),[2] which have been prepared by the BINAL-H reduction of acyl stannanes,[2b] or by norephedrine carbamate resolution[3] as described in chapter 1. Since these methods involve lengthy procedures, sensitive intermediates and low selectivity on larger scale, our laboratory investigated the preparation of α-aminostannanes through nucleophilic additions to chiral sulfinimines.

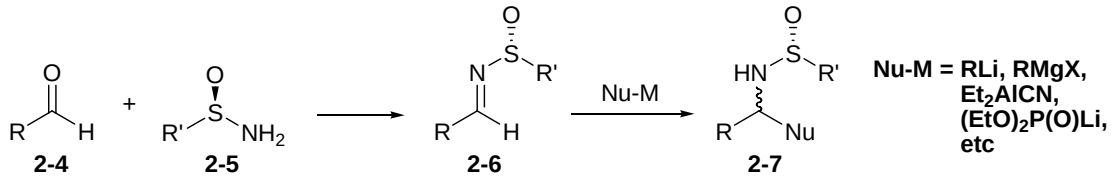
2.1.2 Chiral sulfinamides in asymmetric synthesis

Recently, chiral sulfinamides have gained popularity as auxiliaries for asymmetric synthesis.[4] The most commonly used are *p*-toluenesulfinamide and *t*-butanesulfinamide but Ellman has noted that *t*-butanesulfinamide **(S_S)-2-1** is more nucleophilic than *p*-toluenesulfinamide for direct condensation with aldehydes and ketones, as a result of the electron donating characteristics of the *t*-butyl versus the *p*-tolyl group (Scheme 17).[5]



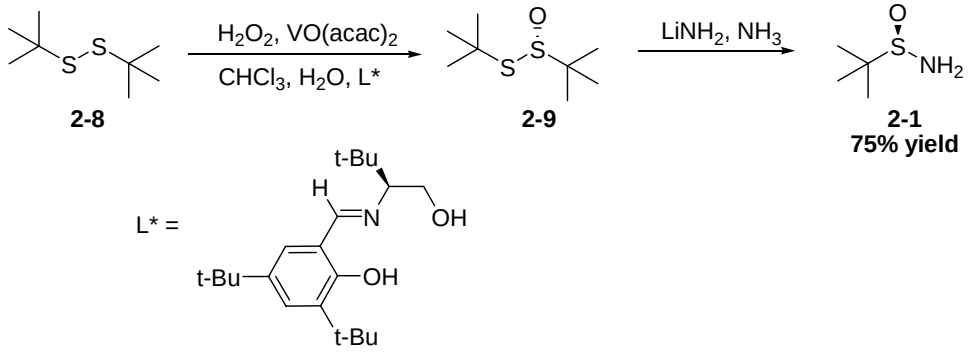
Scheme 17

A wide variety of nucleophiles has been used in stereoselective nucleophilic additions to chiral sulfinimines. Some of the successful nucleophiles for the synthesis of chiral amines are shown below in Scheme 18.[4]



Scheme 18

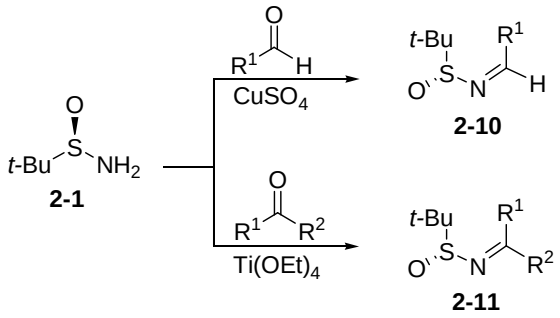
Since *t*-butanesulfinamide is the reagent of choice, Ellman showed that *t*-butanesulfinamide **2-11** can be synthesized in enantiomerically pure form *via* an asymmetric oxidation of *t*-butyl disulfide **2-8** through an intermediate **2-9** (Scheme 19).[6]



Scheme 19

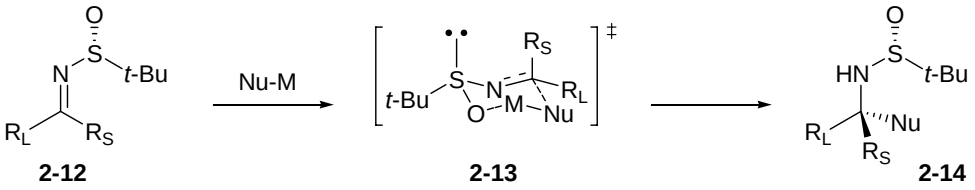
Ellman also stated that high yielding and general methods for the preparation of *t*-butanesulfinyl aldimines **2-10** and ketimines **2-11** are critical to the successful application

of *t*-butanesulfinamide to the asymmetric synthesis of amines (Scheme 20).[4] The most straightforward method for the preparation of aldimines **2-10** is the condensation of aldehydes and *t*-butanesulfinamide with $CuSO_4$ as a Lewis acid catalyst and water scavenger. For the preparation of ketimines **2-11**, $Ti(OEt)_4$ is the preferred Lewis acid and water scavenger.



Scheme 20

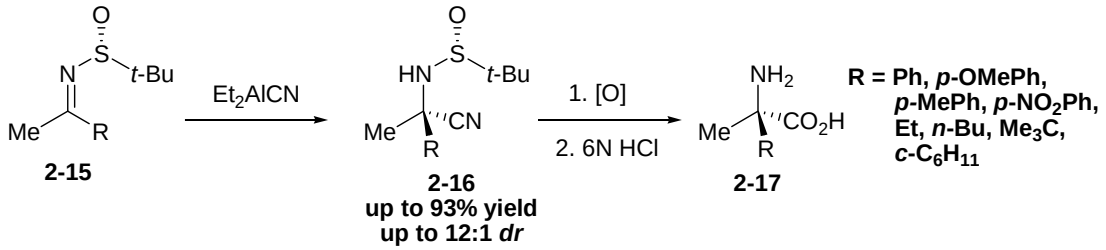
Ellman proposed a 6-membered chair transition state (**2-13**) to explain the sense of induction in this system, in which the metal is coordinated to the sulfinyl oxygen and the smaller substituent (R_S) is oriented axially (Scheme 21).



Scheme 21

The auxiliary **(S_S)-2-1** has been used in this manner by Davis and coworkers for the asymmetric synthesis of α,α-disubstituted α-amino acids *via* an asymmetric Strecker reaction (Scheme 22).[7] Et_2AlCN was added to ketimines **2-15** and sulfinamines **2-16** were obtained with good diastereoselectivity, which then gave the corresponding amino acid **2-17** following acid hydrolysis. There are relatively few methods available for the

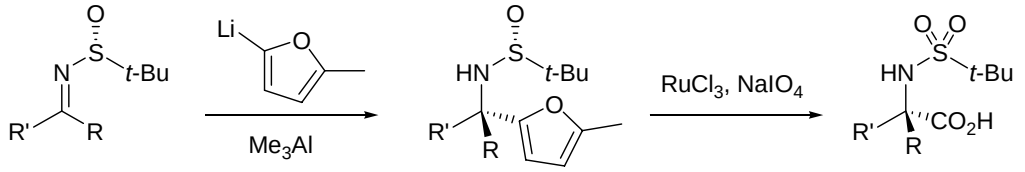
stereoselective synthesis of α,α-disubstituted α-amino acids and this has proven to be an efficient access to these compounds.



2-15 **2-16** **up to 93% yield** **up to 12:1 *dr*** **2-17**

Scheme 22

Ellman has also reported an alternative, efficient method for the asymmetric synthesis for α,α-disubstituted α-amino acids using *t*-butanesulfinimines (Scheme 23).[8] The addition of 5-methyl-2-furyllithium to *N*-sulfinyl ketimines **2-18** followed by oxidative cleavage provides *N*-*t*-butanesulfonyl (Bus) protected α,α-disubstituted amino acids **2-20**.

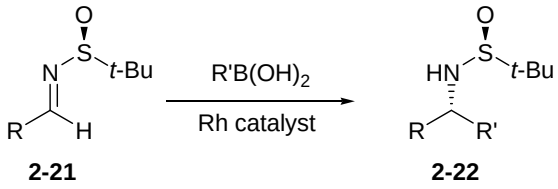


2-18 **2-19** **up to 97% yield** **up to 98% *de*** **2-20**

Scheme 23

The *t*-butylsulfonyl (Bus) in compound **2-20** is a versatile protecting group since it is stable to basic conditions and can be readily cleaved under acidic conditions.[9] Also, Ellman demonstrated that the α-sulfonamido acid adducts can be directly coupled under standard peptide coupling procedures with no negative effects from the Bus group.[4]

Chiral *t*-butanesulfinimines have also been used in combination with transition metal catalysis. Ellman has recently reported the rhodium(I) catalyzed addition of arylboronic acids to *t*-butanesulfinimines (Scheme 24).[10]



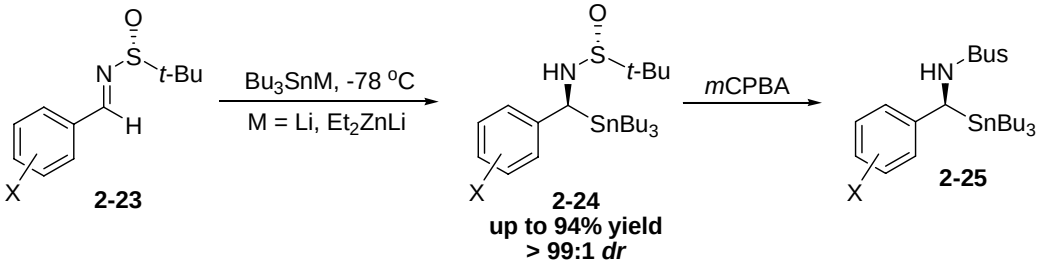
2-21 **2-22**

Scheme 24

Other uses for this chiral auxiliary include addition of titanium and zinc enolates to the sulfinimines,[11] solid phase synthesis of peptides,[12] and multistep syntheses on solid support.[13]

The excellent results obtained from Ellman and others, combined with the wide range of nucleophiles that has been successfully employed, led to the application of *t*-butanesulfinimines for the asymmetric synthesis of α-aminostannanes by our group.

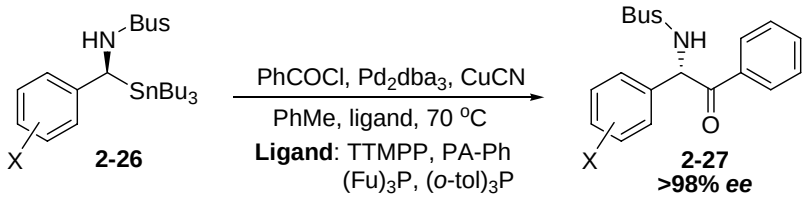
Kells and Chong applied chiral auxiliary **(S_S)-2-1** to the synthesis of α-aminostannanes **2-24** *via* aldimines **2-23** and obtained excellent yields and distereoselectivities (Scheme 25).[14] Sulfinamide **2-24** was then oxidized to sulfonamide **2-25** in order to proceed with the Stille couplings.



2-23 **2-24** **up to 94% yield** **> 99:1 *dr*** **2-25**

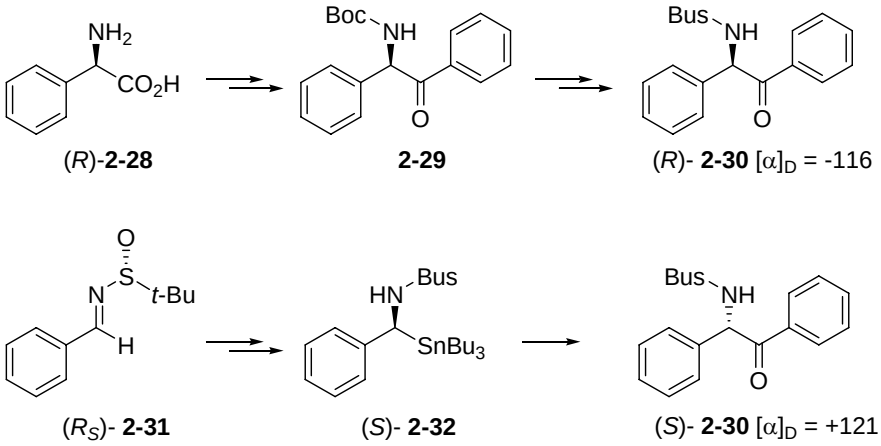
Scheme 25

The Stille coupling of stereochemically defined α-sulfonamidoorganostannanes was observed to proceed with inversion of stereochemistry (Scheme 26).[15]



Scheme 26

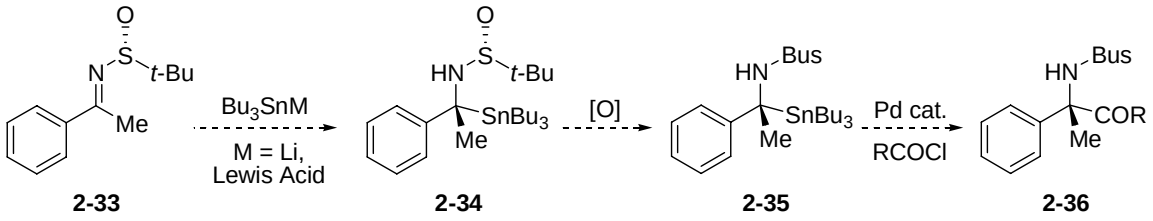
The determination of stereochemistry of coupling product **2-29** is shown in Scheme 27. A sample of (*R*)-**2-30** was prepared from (*R*)-phenylglycine **2-28**. The Stille coupling of stannane (*S*)-**2-32** with benzoyl chloride provided coupled product (*S*)-**2-31**. Comparison of two products (*R*)-**2-30** and (*S*)-**2-30** showed that they were enantiomers. Thus, inversion occurred in the Stille coupling of stannane **2-32**.



Scheme 27

Given that Ellman's addition of organolithiums to *t*-butansulfinyl ketimines such as **2-18** represents one of the first direct methods for the asymmetric synthesis of tertiary carbinamines and the highly selective addition of organotin reagents to aldimines **2-23** developed in our laboratory, a logical extension of this work would involve the addition of organotin reagents to sulfinyl ketimines **2-33** (Scheme 28). If successful, this would

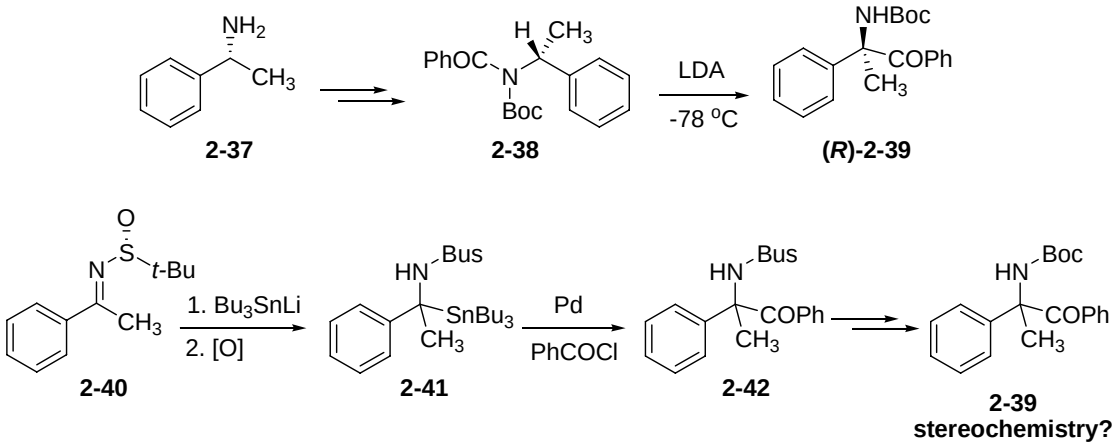
extend the versatility of this approach for the synthesis of tertiary amines since a wide variety of Stille coupling partners could be used.



2-33 **2-34** **2-35** **2-36**

Scheme 28

In addition, access to α,α-disubstituted α-aminostannanes such as **2-41** would allow further study of the mechanism of the Stille reaction and could indicate whether the additional substitution effects the stereochemical outcome of the coupling. The absolute stereochemistry of the α-aminostannanes starting material **2-41** and the Stille coupling product **2-42** could be established using a known transformation which has been studied by Hara, Ito and Hamada (Scheme 29).[16]



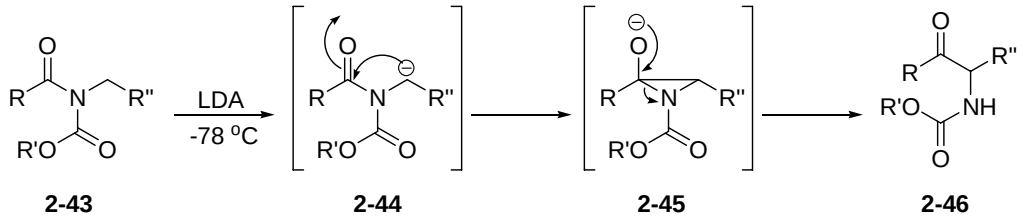
2-37 **2-38** **(*R*)-2-39**

2-40 **2-41** **2-42**

Scheme 29

For the conversion of acyclic imide **2-38** to product (*R*)-**2-39**, Hara *et al*. showed that nucleophilic attack of the benzyllithium onto the carbonyl carbon leads to a 3-membered ring intermediate, and that this intermediate then collapses to form the stable

α-amino amide, **2-46** (Scheme 30).[16]

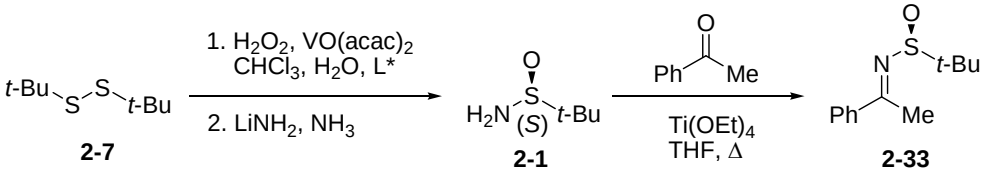


2-43 **2-44** **2-45** **2-46**

Scheme 30

2.2 Results and Discussion

To begin the study, the (S_S)-*t*-Butanesulfinamide **2-1** chiral auxiliary was prepared according to Ellman's procedure[6] and isolated in 72% yield as white crystals. The condensation of auxiliary **2-1** and acetophenone using $Ti(OEt)_4$ yielded *t*-butanesulfinylketimine **2-33** in 73% yield as one isomer, an *E* imine (Scheme 31). Only the *E* isomer was obtained due to the steric properties of the *t*-butanesulfinyl group.[6]

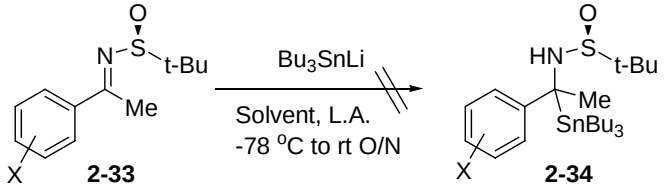


2-7 **2-1** **2-33**

Scheme 31

The first attempt at synthesizing α-aminostannanes using the sulfinimine methodology involved addition of ketimine **2-33** to a solution of Bu_3SnLi. However, none of the desired addition product **2-34** was isolated under a variety of conditions (Table 1).

Table 1: Results for addition of Bu_3SnLi to ketimine **2-33**

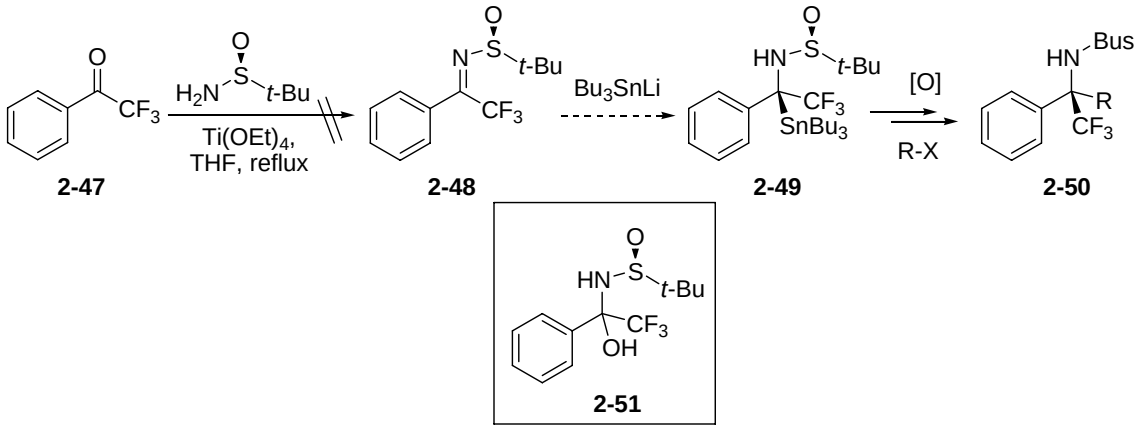


Entry	X	Solvent	Lewis Acid
1	H	THF	-
2	H	THF	Me_3Al
3	H	THF	Et_2Zn
4	H	THF	$Ti(OEt)_4$
5	H	THF	$TiCl_4$
6	H	THF	Me_2AlCl
7	H	PhMe	-
8	H	PhMe	Me_3Al
9	H	CH_2Cl_2	-
10	*p*-Cl	THF	Me_3Al
11	*p*-Cl	THF	-
12	*p*-Cl	CH_2Cl_2	Me_3Al
13	*p*-Cl	CH_2Cl_2	-

The addition of Bu_3SnLi to a solution of the ketimine **2-33** at -78 ^oC with warming to room temperature overnight was also attempted with various solvents and Lewis acids but, unfortunately, was also unproductive. It was hoped that an electron-withdrawing *p*-Cl substituent would help to activate the sulfinimine toward nucleophilic attack (entries 10-13); but none of the desired products were generated under these conditions. For all entries, either starting material or decomposition were obtained.

Similary, it was thought that a trifluoroketimine **2-48** would be activated toward nucleophilic attack by Bu_3SnLi and could lead to α-trifluoromethyl-substituted amines **2-50** (Scheme 32). Unfortunately, the product could not be detected as the condensation of the chiral auxiliary **2-1** with α,α,α-trifluoroacetophenone **2-47** did not generate the

desired sulfinimine **2-48**. Alcohol **2-51**, however, was isolated in 20% yield, the structure of which was determined by ^{19}F NMR and HMQC experiments.



Scheme 32

The fact that addition of Bu_3SnLi to sulfinyl aldimines proceeds in high yield and selectivity (Kells and Chong) indicates that the sulfinyl ketimines are unreactive to nucleophilic attack due to steric hindrance. Given our difficulties in obtaining α,α-disubstituted amino stannanes, this project was discontinued.

2.3 Summary

Although the stereoselective synthesis of α,α-disubstituted α-aminostannanes was thought to represent versatile entry into the synthesis of amines, the addition of Bu_3SnLi to sulfinyl ketimines could not be achieved.

It is thought that nucleophilic addition of Bu_3SnLi to the sulfinyl ketimine is sterically disfavoured.

2.4 Experimental

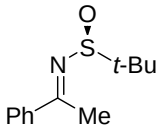
2.4.1 General experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Diethyl ether and THF were freshly distilled from Na/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively.

2.4.2 General procedure for synthesis of enantiomerically pure *t*-butanesulfinimines

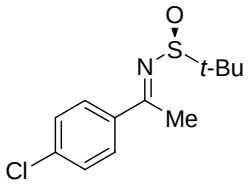
t-Butanesulfinimines were prepared by the condensation of (*R*)- or (*S*)-*t*-butanesulfinamide with ketones as described by Ellman.[6] Spectral data are as follows:

(*Ss*)-*N*-(phenylethylidene)-*t*-butanesulfinamide (2-34)



^{1}H NMR (300 MHz, $CDCl_3$) δ7.87 (2H, d, J = 9Hz), 7.46-7.39 (3H, m), 2.74 (3H, s, Me), 1.29 (9H, s, *t*-Bu).

(*Ss*)-*N*-(4-chloro-phenylethylidene)-*t*-butanesulfinamide (2-34)



^{1}H NMR (300 MHz, $CDCl_3$) δ7.70 (2H, d, J = 9Hz), 7.25 (2H, d, J = 2Hz), 2.62 (3H, s, Me), 1.20 (9H, s, *t*-Bu).

2.4.3 General procedure for the addition of Bu_3SnLi to *t*-butanesulfinimines

A solution of diisopropylamine (0.78 mmol, 0.11 mL) was added to *n*-butyllithium (0.78 mmol, 0.52 mL of 1.6 M solution in hexanes) in dry THF (6 mL) at 0 ^oC, the solution was stirred for 15 mins before tributyltin hydride (0.78 mmol, 0.21 mL) was added. The mixture was stirred at 0 ^oC for another 15 min before cooling to -78 ^oC. The ketimine **(**0.60 mmol) was dissolved in dry THF (1 mL) and added dropwise to the stirring solution followed by the Lewis acids (for example, Me_3Al, 0.66 mmol, 0.33 mL of 2.0 M in hexanes). The reaction was stirred for 1 h at -78 ^oC and gradually warmed up to room temperature overnight. No desired product was formed. Only starting material was recovered. After 15 h, the reaction was quenched with cold MeOH followed by saturated ammonium chloride and concentrated under vacuum to provide only starting material and Bu_3SnH in all cases.

2.5 References

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Chapter 3

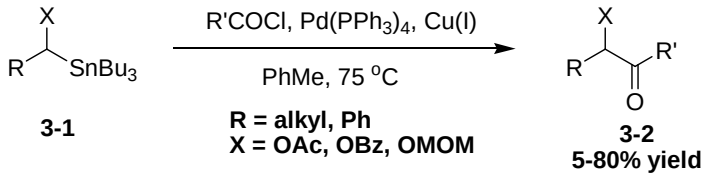
α-Alkoxystannanes in Stille Coupling Reactions

3.1 Introduction

3.1.1 α-Alkoxystannanes in Stille couplings

Recently, α-alkoxy and α-aminostannanes have been used as reagents in organic synthesis and numerous synthetic applications utilizing their transmetalation chemistry were found.[1] Tin-lithium transmetalation of these stannanes has been studied quite extensively while little synthetic effort has been dedicated to the study of the Stille couplings of α-heteroatom substituted organostannanes.

The first work with α-heteroatom-substituted stannanes was reported by Falck and co-workers in 1994.[2] The cross-coupling between various alkoxystannanes and acid chlorides was achieved with moderate success (Scheme 33). Although a lot of effort was dedicated to optimizing reaction conditions, the ligand for the palladium catalyst was not varied and PPh_3 was the ligand used in all experiments.

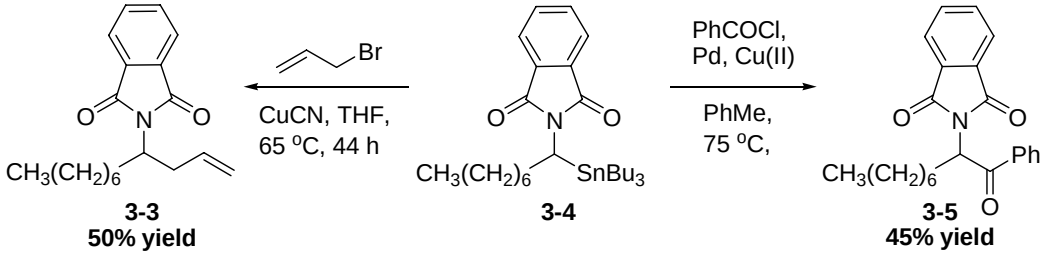


3-1 **3-2** **5-80% yield**

Scheme 33

The palladium-catalyzed cross-coupling of racemic α-aminostannane **3-4** with benzoyl chloride was also investigated by Falck (Scheme 34). The yield of coupling product **3-5** was 45%. Falck *et al.* later reported the coupling of the same racemic α-

aminostannane with allyl bromide using a catalytic amount of copper salt in the absence of Pd catalyst to yield the coupling product **3-3**.[3]



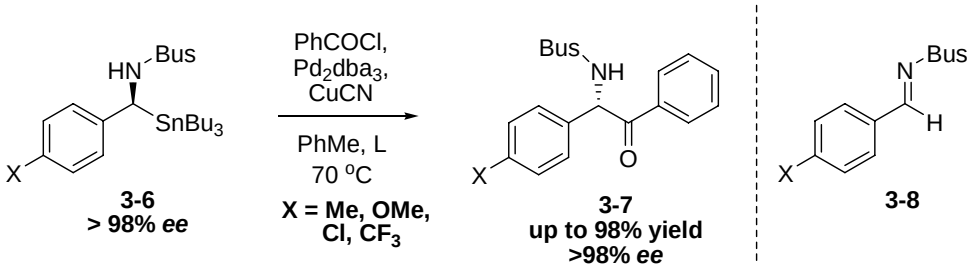
3-3
50% yield

3-4

3-5
45% yield

Scheme 34

Recently, Stille couplings of stereochemically defined α-sulfonamidoorgano-stannanes were reported by Kells and Chong (Scheme 35).[4] Sulfonamides **3-6** were coupled with benzoyl chloride to obtain coupling products **3-7** with up to 98% yield and excellent selectivity (>98% *ee*). Interestingly, trialkylphosphines gave low yields of the desired couplings product **3-7** and the β-hydride elimination product **3-8** was isolated in high yields. It was found that the most effective ligand is the highly basic tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP). All of the α-sulfonamidostannanes studied, including those with electron donating groups or electron withdrawing groups on the aromatic ring, coupled well with TTMPP.



3-6
> 98% *ee*

X = Me, OMe, Cl, CF_3

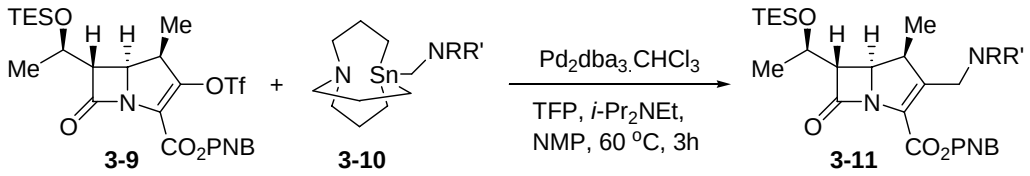
3-7
up to 98% yield
>98% *ee*

3-8

Scheme 35

Another example of a Stille coupling with α-heteroatom-substituted stannanes involves the use of a stannatrane in the palladium-catalyzed reaction for the total synthesis of a β-lactam antibiotic. The synthesis of carbapenem **3-9** for use against

methicillin-resistant *Staphylococcus aureus* (MRSA) was achieved through a stannatrane-mediated Stille coupling (Scheme 36).[5]



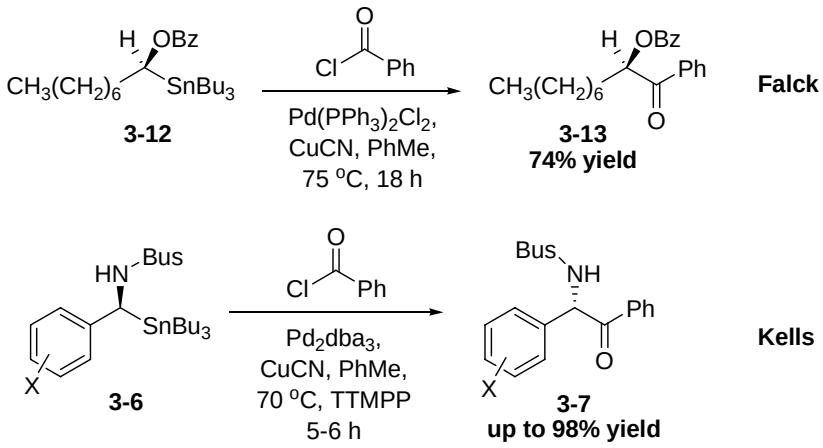
Scheme 36

The key step in the synthesis of **3-11** involves the cross-coupling of an enol triflate with an organostannane containing an amino-substituted sp^3 carbon. The authors reported that the palladium coupling of β-lactam **3-9** with Bu_3SnCH_2-OH was successful;[6] however, attempts at attaching any CH_2NRR□ to the carbapenem using either a typical Suzuki or Stille approach failed.[7]

Given that Falck had optimized conditions for Stille couplings with α-alkoxyalkylstannanes and that couplings with α-aminobenzylstannanes had been developed in our laboratory, it seemed logical to extend the scope of the Stille coupling to include α-alkoxybenzylstannanes substrates that have not been exploited extensively in synthetic applications.

3.2 Results and Discussion

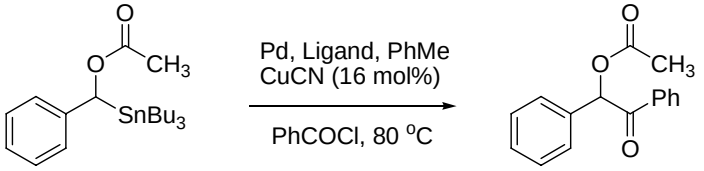
It is known that α-heteroatom substituted stannanes are good substrates for Stille couplings since Falck and Kells have shown that the couplings of α-alkoxy and α-aminostannanes proceed in high yields (Scheme 37).[2,4]



Scheme 37

Falck's couplings with α-alkylalkoxystannanes were carried out in a sealed tube under argon, while the couplings in our group with α-aminobenzylstannanes were run under argon atmosphere at atmospheric pressure. Falck also noted the use of degassed toluene and results from our laboratory also suggest that degassing improves results. Optimization of the Stille coupling between α-alkoxybenzyl stannane **3-14** and benzoyl chloride began with the conditions employed by Falck and Kells (see entries 9 and 4 respectively) involved the use of CuCN in toluene at 80 °C with variation of ligand (Table 2).

Table 2: Survey of ligands and palladium sources.



3-14 **3-15**

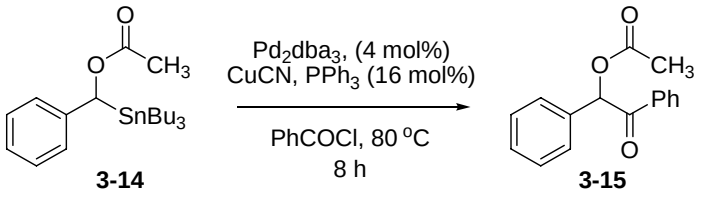
Entry	Pd Source (4 mol%)	Ligand (16 mol%)	Time (h)	Isolated Yield
1	Pd_2dba_3	$AsPh_3$	8	60%
2	Pd_2dba_3	TFP	8	70%
3	Pd_2dba_3	PPh_3	8	65%
4	Pd_2dba_3	TTMPP	24	30%
5	Pd_2dba_3	[a]$ArPCy_2$	24	46%
6	Pd_2dba_3	$(o\text{-tolyl})_3P$	24	40%
7	Pd_2dba_3	dppp	48	[b]
8	Pd_2dba_3	$(t\text{-Bu})_3P$	48	[b]
9	$Pd(PPh_3)_2Cl_2$	---	15	56%
10	$Pd(CH_3CN)_2Cl_2$	---	20	35%
11[c]	$Pd(OAc)_2$	PPh_3	20	30%
12[c]	$Pd(OAc)_2$	$AsPh_3$	20	35%

[a] Ar = 2-(2',6'-dimethoxybiphenyl)
[b] no reaction, only starting material recovered.
[c] 8 mol% of ligand was used.

In the last few years the use of bulky phosphine ligands has increased the scope of cross-coupling reactions, particularly for the coupling of less reactive organic substrates, such as aryl chlorides,[8] and alkyl electrophiles.[9] Aryl chlorides usually react more sluggishly in cross coupling reactions than the corresponding bromides, iodides, and triflates, as a result of their reluctance to undergo oxidative addition with Pd^o.[10] However, based on our results shown in Table 2, bulky ligands such as $(o\text{-tolyl})_3P$ and $(t\text{-Bu})_3P$ decreased the yield of the reaction with Pd_2dba_3 in toluene. No product was observed with a chelating diphosphine ligand such as dppp. As often observed with Stille reactions, the best results obtained in our system were found with PPh_3, $AsPh_3$, and P(2-furyl)$_3$ (TFP), possibly due to the low donor characteristic of these ligands.[11]

Since PPh_3, $AsPh_3$ and TFP gave similar results in the coupling reaction, PPh_3 was chosen due to its availability and low cost. The effect of solvent on the Stille couplings with α-alkoxybenzyl stannanes was then examined (Table 3). Similar to the results reported by Falck, toluene was found to be the best solvent among those surveyed. While THF showed a small amount of conversion from starting material to product, ether and more polar solvents such as CH_2Cl_2, CH_3CN and DMF gave no coupling product. Thus, toluene remained the solvent of choice for couplings of α-alkoxybenzylstannanes with benzoyl chloride.

Table 3: Survey of solvents for Stille coupling reactions.



3-14 **3-15**

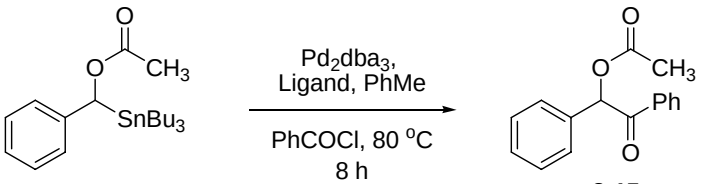
Entry	Solvent	Isolated Yield
1	PhMe	65%
2	THF	10%
3	DMF	[a]
4	Ether	[a]
5	CH_2Cl_2	[a]
6	CH_3CN	[a]

[a] no reaction, only starting material recovered.

The Stille reaction is known to be co-catalyzed by copper (I), a phenomenon known as the "copper effect", which was first studied by the research groups of Farina and Liebeskind.[31] Cu(I) was found to accelerate the couplings catalyzed by $[PdL_4]$. They concluded that the role of CuI in systems with "strong" ligands, such as PPh_3, was to scavenge free ligand. It was also found that CuI is less effective for "soft ligands" such as Ph_3As.[12] In our system, the use of CuI as the copper source proved to be less effective

than CuCN with each of the ligands used in toluene (Table 4). These results, in combination with the relatively more tedious preparation of CuI, led to the continued use of CuCN for co-catalysis.

Table 4: Variation of copper source in Stille coupling reactions.

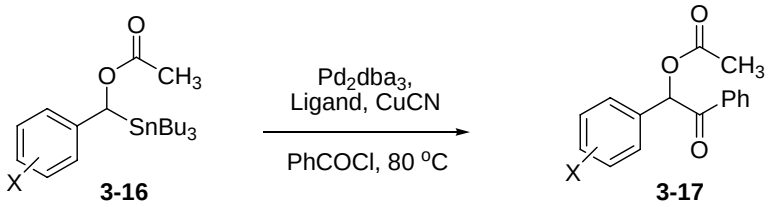


3-14 **3-15**

Entry	Ligand, co-catalyst (16 mol% each)	Isolated Yield
1	PPh_3, CuCN	65%
2	PPh_3, CuI	50%
3	$AsPh_3$, CuCN	60%
4	$AsPh_3$, CuI	50%
5	TFP, CuCN	70%
6	TFP, CuI	56%

Kells showed that the Stille coupling of α-sulfonamidostannanes, including those with electron donating groups or electron withdrawing groups on the aryl ring, with a highly basic ligand and Pd_2dba_3 in toluene, also couple well under these reaction conditions. However, with the α-alkoxybenzylstannane system, the Stille coupling reaction seems to be more effective with electron donating groups (Table 5, entries 9-11) on the aryl ring than with of electron withdrawing groups (Table 5, entries 1-8).

Table 5: Stille coupling with substituted α-alkoxybenzyl stannanes.

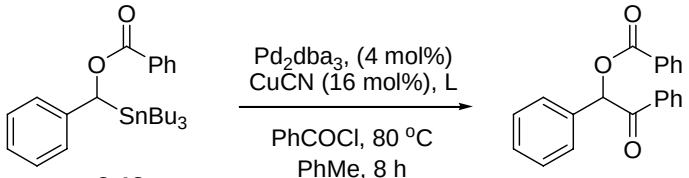


3-16 **3-17**

Entry	X	Ligand (16 mol%)	Solvent	Time (h)	Isolated Yield
1	*p*-CF_3	TFP	PhMe	10	24%
2	*p*-CF_3	$AsPh_3$	PhMe	10	25%
3	*p*-CF_3	PPh_3	PhMe	10	24%
4	*p*-Cl	PPh_3	PhMe	10	44%
5	*p*-Cl	$AsPh_3$	PhMe	10	41%
6	*p*-Cl	TFP	PhMe	10	38%
7	*p*-Cl	PPh_3	THF	24	8%
8	*p*-Cl	$AsPh_3$	THF	24	11%
9	3,4,5-OMe	PPh_3	PhMe	10	10%
10	3,4,5-OMe	TFP	PhMe	10	11%
11	3,4,5-OMe	$AsPh_3$	PhMe	10	9%

Using the optimal conditions obtained thus far (Pd_2dba_3, CuCN, PhMe, and PPh_3, $AsPh_3$ or TFP), the efficiency of the Stille coupling was investigated with the O-benzoyl-α-alkoxybenzylstannane **3-18** (Table 6).

Table 6: Stille coupling with α-alkoxybenzylstannanes **3-19**.



3-18 **3-19**

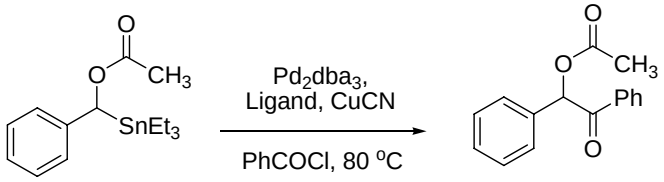
Entry	Ligand (16 mol%)	Isolated Yield
1	TFP	45%
2	$AsPh_3$	38%
3	PPh_3	44%
4	TTMPP	14%
5	(*o*-tolyl)$_3$P	[a]
6	dppp	[a]

[a] Only starting material was isolated.

The Stille coupling reactions for benzoate substrate **3-18** were found to be slightly lower yielding than the acetate **3-14** and further investigations were therefore conducted with the acetoxy-derived substrates.

In addition to the Stille couplings with the aforementioned tributylstannanes, the effects of solvent and ligand were examined in Stille couplings with triethylstannanes **3-21** (Table 7). It was found that with triethyltin system, the ligands PPh_3, $AsPh_3$ and TFP worked equally well (entries 1-3), but the coupling reaction required slightly more time than with the tributyltin counterparts.

Table 7: Stille coupling reactions with triethylstannnanes.



3-20 **3-21**

Entry	Ligand (16 mol%)	Solvent	Time (h)	Isolated Yield
1	PPh_3	PhMe	15	61%
2	$AsPh_3$	PhMe	12	60%
3	TFP	PhMe	10	65%
4	PPh_3	THF	15	36%
5	$AsPh_3$	THF	15	30%

3.3 Summary

The Stille coupling of α-alkoxybenzylstannanes has been studied under a variety of reaction conditions. A yield of up to 70% was obtained using Pd_2dba_3 (4 mol%) with CuCN (16 mol%) and TFP (16 mol%) in toluene at 80 ^oC for the coupling of α-alkoxybenzylstannanes with benzoyl chloride. These conditions are similar to those employed by Kells and Chong for Stille couplings of α-sulfonamidostannanes with respect to palladium source and copper source. The optimal ligands are low σ-donor ligands, such as Ph_3P, $AsPh_3$ and TFP, which had previously been exploited in the couplings of α-alkylalkoxystannanes developed by Falck. Mechanistic implications of these results will be discussed in more detail in chapter 4.

3.4 Experimental

General experimental.

All reactions were performed using flame-dried glassware under an argon atmosphere. Toluene and THF were freshly distilled from Na/benzophenone. Dicholoromethane was distilled from calcium hydride. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively.

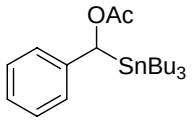
*3.4.1 General procedure for the preparation of α–alkoxybenzyl-tributylstannane substrates **3-14** and **3-18**.*

The *i*-Pr_2NH (11.8 mmol, 1.65 mL) and *n*-BuLi (11.8 mmol, 9.5 mL of 1.5 M solution in hexanes) were added to THF (20 mL) at 0 ^{o}C and stirred for 15 min. Then Bu_3SnH (11.8 mmol, 3.1 mL) was added to the LDA solution and was stirred at 0 ^{o}C for another 15 min before cooled to -78 ^{o}C. The reaction mixture was stirred for 5 min at -78 ^{o}C before the addition of benzaldehyde (9.84 mmol, 1.0 mL). The reaction mixture was stirred at -78 ^{o}C for 45 min. The mixture was quenched with saturated ammonium chloride (30 mL) at -78 ^{o}C and allowed to warm to rt before the reaction was washed with ether (3 x 30 mL), brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain the α-hydroxystannane as a yellow oil.

The crude α-hydroxystannane was quickly taken to the next step: For acetates, crude α-hydroxystannane (10.3 mmol, 4.08 g) in CH_2Cl_2 (25 mL) was cooled to 0 ^{o}C before the addition of DMAP (10 mol%), pyridine (20.6 mmol, 1.67 mL), and Ac_2O (12.4 mmol, 1.17 mL). The reaction was stirred 0 ^{o}C for 1 h and quenched with saturated

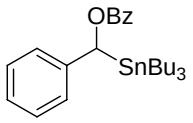
ammonium chloride (20 mL). The organic layer was diluted with ether, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting yellow oil was purified by flash column chromatography (30 g silica/1 g crude, 10:1 hexane:ether) to afford the product. A similar procedure was used to prepare the benzoate substrates, in which benzoyl chloride was used instead of acetic anhydride. Spectra data are as follows:

(Tributylstannyl)(phenyl)methyl acetate 3-14[2]



89% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.27 (2H, m, ArH), 7.07 (3H, m, ArH), 5.69 (1H, $J_{Sn\text{-}H}$ = 23.2 Hz, s, C<u>H</u>Sn), 2.12 (3H, s, C<u>H</u>$_3$), 1.65-1.37 (6H, m, SnCH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.35-1.19 (6H, m, SnCH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 1.11-0.72 (15H, SnC<u>H</u>$_2$CH$_2$CH$_2$C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.3 (<u>C</u>OCH$_3$), 141.6 (Ar), 128.0 (Ar), 125.1 (Ar), 123.3 (Ar), 71.4 (Ar<u>C</u>OSn), 29.1 (SnCH$_2$<u>C</u>H$_2$CH$_2$CH$_3$), 27.5 (SnCH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 20.8 (CO<u>C</u>H$_3$), 13.7 (SnCH$_2$CH$_2$CH$_2$<u>C</u>H$_3$), 10.1 (Sn<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$).

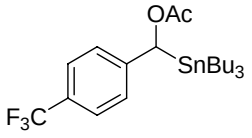
(Tributylstannyl)(phenyl)methyl benzoate 3-18



83% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.97 (2H, m, ArH), 7.40 (3H, m, ArH), 7.19 (5H, m, ArH), 5.69 (1H, $J_{Sn\text{-}H}$ = 23.0 Hz, s, C<u>H</u>Sn), 1.65-1.37 (6H, m,

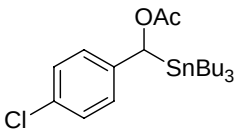
$SnCH_2\underline{C}H_2CH_2CH_3$), 1.35-1.19 (6H, m, $SnCH_2CH_2\underline{C}H_2CH_3$), 1.11-0.72 (15H, $Sn\underline{C}H_2CH_2CH_2\underline{C}H_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ166.7 ($\underline{C}OCH_3$), 141.0 (Ar), 133.1 (Ar), 130.2 (Ar), 129.9 (Ar), 129.0 (Ar), 128.7 (Ar), 127.7 (Ar), 127.2 (Ar), 57.1 ($\underline{C}OAr$), 29.1 (J = 20.4 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.5 ($J^{117}Sn/^{119}Sn$ = 54.8/57.0 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 13.7 ($J$ = 71.9 Hz, $SnCH_2CH_2CH_2\underline{C}H_3$), 10.1 ($J^{117}Sn/^{119}Sn$ = 309.0/321.0 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$).

(Tributylstannyl)(4-(trifluoromethyl)phenyl)methyl acetate 3-16a



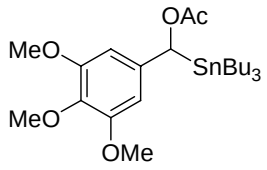
70% yield; ^1H NMR (300 MHz, $CDCl_3$) δ7.50 (2H, d, J = 8.2 Hz, ArH), 7.17 (2H, d, J = 8.2 Hz, ArH), 5. 94 (1H, J_{Sn-H} = 21.3 Hz, s, $C\underline{H}OAc$), 2.13 (3H, s, $C\underline{H}_3$), 1.65-1.37 (6H, m, $SnCH_2\underline{C}H_2CH_2CH_3$), 1.35-1.19 (6H, m, $SnCH_2CH_2\underline{C}H_2CH_3$), 1.11-0.72 (15H, $Sn\underline{C}H_2CH_2CH_2\underline{C}H_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.1 ($\underline{C}OCH_3$), 147.4 (Ar), 126.8 (q, $^2J_{C-F}$ = 30.9 Hz, $\underline{C}CF_3$), 126.2 (q, $^1J_{C-F}$ = 271.5 Hz, $\underline{C}F_3$), 125.0 (Ar), 124.6(Ar), 123.2 (Ar), 72.7 ($\underline{C}OAc$), 28.9 (J = 21.0 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.5 ($J^{117}Sn/^{119}Sn$ = 54.0/56.9 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 20.8 ($CO\underline{C}H_3$), 13.7 ($J$ = 71.0 Hz, $SnCH_2CH_2CH_2\underline{C}H_3$), 10.1 ($J^{117}Sn/^{119}Sn$ = 308.2/320.8 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$).

(Tributylstannyl)(4-chlorophenyl)methyl acetate 3-16b



80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.22 (2H, d, J = 8.4 Hz, ArH), 7.08, (2H, J = 8.4 Hz, d, ArH), 5.85 (1H, $J_{Sn\text{-}H}$ = 21.0 Hz, s, C<u>H</u>Sn), 2.11 (3H, s, C<u>H</u>$_3$), 1.65-1.37 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.35-1.19 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 1.11-0.72 (15H, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.3 (<u>C</u>OCH$_3$), 140.9 (Ar), 130.1 (Ar), 128.0 (Ar), 124.4 (Ar), 72.3 (<u>C</u>OAc), 29.1 (J = 20.3 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.5 ($J^{117}Sn/^{119}Sn$ = 54.5/57.0 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 20.8 (CO<u>C</u>H$_3$), 13.7 ($J$ = 71.7 Hz, $SnCH_2CH_2CH_2\underline{C}H_3$), 10.1 ($J^{117}Sn/^{119}Sn$ = 306.4/320.4 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$).

(Tributylstannyl)(3,4,5-trimethoxyphenyl)methyl acetate 3-16c

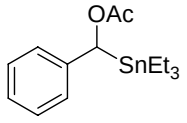


79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ6.28 (2H, s, ArH), 5.77 (1H, $J_{Sn\text{-}H}$ = 19.5 Hz, s, C<u>H</u>Sn), 3.77 (6H, s, OC<u>H</u>$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 2.10 (3H, s, COC<u>H</u>$_3$), 1.38-1.32 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.24-1.14 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.84-0.77 (15H, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.5 (<u>C</u>OCH$_3$), 153.4 (Ar), 137.9 (Ar), 135.3 (Ar), 100 (Ar), 73.3 (<u>C</u>OAc), 55.8 (O<u>C</u>H$_3$), 28.7 (J = 20.3 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.2 ($J^{117}Sn/^{119}Sn$ = 53.5/55.5 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 20.8 (CO<u>C</u>H$_3$), 13.7 ($J$ = 70.4 Hz, $SnCH_2CH_2CH_2\underline{C}H_3$), 10.1 ($J^{117}Sn/^{119}Sn$ = 307.2/319.4 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$).

3.4.2 General procedure for the preparation of α–alkoxybenzyl-triethylstannane substrates ***3-20.***

To a solution of THF (20 mL) at 0 ^{o}C, Li wire (20.7 mmol, 0.14 g) was added then followed by a solution of Et_3SnCl (4.14 mmol, 0.7 mL). The reaction mixture was stirred at 0 ^{o}C for 3 h. Then the solution of Et_3SnLi was syringed into another flask, where benzaldehyde (4.97 mmol, 0.51 mL) was added at -78 ^{o}C. The mixture was stirred at -78 ^{o}C for 1 h. The mixture was quenched with saturated ammonium chloride solution (20 mL) at -78 ^{o}C, then allowed to warm to rt. The reaction was washed with ether (3 x 20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the α-hydroxystannane as a yellow oil. The acetylation of this crude α-hydroxystannane was followed the procedure reported earlier as for the case of tributylstannanes.

(Triethylstannyl)(phenyl)methyl acetate 3-20

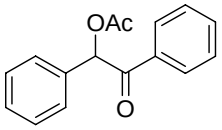


82% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.27 (2H, m, ArH), 7.07 (3H, m, ArH), 5.69 (1H, J_{Sn-H} = 22.6 Hz, s, C<u>H</u>OAc), 2.12 (3H, s, COC<u>H</u>$_3$), 1.01 (6H, m, SnC<u>H</u>$_2$CH$_3$), 0.93 (9H, m, SnCH$_2$C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.4 (<u>C</u>OCH$_3$), 141.7 (Ar), 127.8 (Ar), 125.2 (Ar), 123.4 (Ar), 71.4 (<u>C</u>OAc), 20.8 (CO<u>C</u>H$_3$), 12.3 (J = 24.1 Hz, SnCH$_2$<u>C</u>H$_3$), -5.30 (J^{117}Sn/^{119}Sn = 316.0/328.8 Hz, Sn<u>C</u>H$_2$CH$_3$).

3.4.3 General procedure for the coupling of α–alkoxybenzylstannane with benzoyl chloride.

The palladium catalyst, Pd_2dba_3 (4 mol%), CuCN (16 mol%) and ligand (e.g. PPh_3, $AsPh_3$, TFP) (16 mol%) were added to degassed PhMe. The reaction mixture was stirred for 15 min at room temperature before the addition the stannane substrates (1 eq.) followed by benzoyl chloride (1.2 eq.). The reaction was heated to 80 ^oC and stirred under argon for 8 to 15 hours. The reaction was monitored by TLC until all of the starting material was consumed, and/or until black precipitate was observed (indicating decomposition of Pd source). The reaction was allowed to cool, diluted with ether (10 mL), and quenched with a solution of 10% ammonium hydroxide in saturated ammonium chloride (5 mL). The aqueous layer was wash again with ether. The combine organic layers were washed with saturated KF solution (10 mL), and brine (10 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and all solvents were removed under reduced pressure to afford a clear to yellow oil which was purified by flash column chromatography (30 g silica/1 g crude, 5:1 hexanes:ether) to afford the coupling product. Spectra data are as follows:

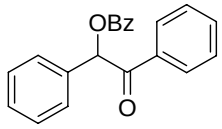
2-Oxo-1,2-diphenylethyl acetate 3-15[2]



70% yield; ^1H NMR (300 MHz, $CDCl_3$) δ7.93 (2H, d, J = 8.4 Hz, ArH), 7.50 (3H, m, ArH), 7.38 (5H, m, ArH), 6.84 (1H, s, C<u>H</u>OAc), 2.19 (3H, s, C<u>H</u>$_3$); ^{13}C NMR (75 MHz,

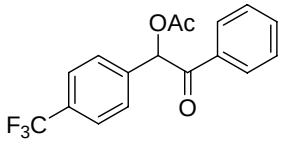
$CDCl_3$) δ194.2 (COAc), 170.1 ($\underline{C}OCH_3$), 136.5 (Ar), 133.2 (Ar), 128.9 (Ar), 128.2 (Ar), 77.4 (CHOAc), 20.8 ($CO\underline{C}H_3$).

2-Oxo-1,2-diphenylethyl benzoate 3-19



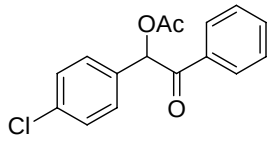
45% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.97 (2H, m, ArH), 7.86 (2H, m, ArH), 7.40 (6H, m, ArH), 6.85 (1H, s, CHOBz), 7.19 (5H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ194.3 (O=CAr), 166.1 ($O_2\underline{C}Ph$), 136.8 (Ar), 133.5 (Ar), 129.1 (Ar), 128.0 (Ar), 127.3 (Ar), 78.0 (CHAr).

1-(4-(Trifluoromethyl)phenyl)-2-oxo-2-phenylethyl acetate 3-17a



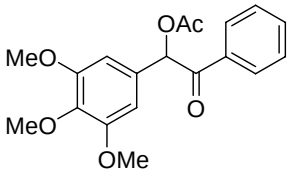
25% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.90 (2H, d, J = 7.7 Hz, ArH), 7.55 (5H, m, ArH), 7.42 (2H, m, ArH), 6.88 (1H, s, CHOAc), 2.20 (3H, s, $COC\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ193.5 (C=OAr), 170.1 ($\underline{C}OCH_3$), 140.0 (Ar), 133.8 (Ar), 133.1 (Ar), 130.5 (Ar); 127.9 (Ar), 126.1 (q, $^2J_{C\text{-}F}$ = 32.1 Hz, $\underline{C}CF_3$), 124 (Ar), 77.4 (CHOAc), 20.7 ($CO\underline{C}H_3$). (The CF_3 carbon was not observed due to limited amount of sample, it is expected to be a quartet, $^1J_{C\text{-}F} \approx 300$ Hz, $C\underline{C}F_3$).

1-(4-Chlorophenyl)-2-oxo-2-phenylethyl acetate 3-17b



44% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.88 (2H, d, *J* = 7.2 Hz, ArH), 7.50 (2H, d, *J* = 7.2 Hz, ArH), 7.33 (5H, m, ArH), 6.84 (1H, s, C<u>H</u>OAc), 2.12 (3H, s, COC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ194.0 (<u>C</u>=OAr), 170.0 (<u>C</u>OCH$_3$), 135.9 (Ar), 134.1 (Ar), 133.5 (Ar), 130.8 (Ar), 129.2 (Ar), 128.4 (Ar), 77.4 (<u>C</u>HOAc), 20.7 (CO<u>C</u>H$_3$).

1-(3,4,5-Trimethoxyphenyl)-2-oxo-2-phenylethyl acetate 3-17c



11% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* = 8.7 Hz, ArH), 7.51 (1H, m, ArH), 7.40 (2H, m, ArH), 6.75 (1H, s, C<u>H</u>OAc), 6.63 (2H, s, Ar)), 3.81 (9H, d, *J* = 7 Hz, OC<u>H</u>$_3$), 2.20 (3H, s, COC<u>H</u>$_3$).; ^{13}C NMR (75 MHz, $CDCl_3$) δ193.2 (<u>C</u>=OAr), 170.0 (<u>C</u>OCH$_3$), 153.3 (Ar), 137.8 (Ar), 134.1 (Ar), 133.0 (Ar), 127.9 (Ar), 106.2 (Ar), 77.6 (<u>C</u>HOAc), 60.7 (O<u>C</u>H$_3$), 56.1 (O<u>C</u>H$_3$), 20.7 (CO<u>C</u>H$_3$).

3.5 References

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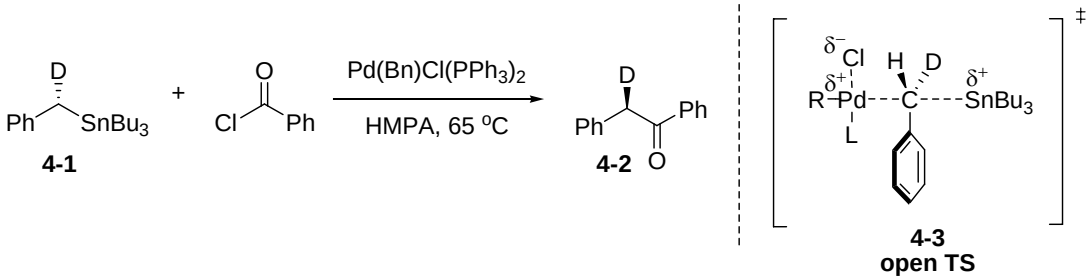
Chapter 4

Determination of Absolute Stereochemistry

4.1 Introduction

4.1.1 Previous Studies on the Stereochemistry of Stille Couplings

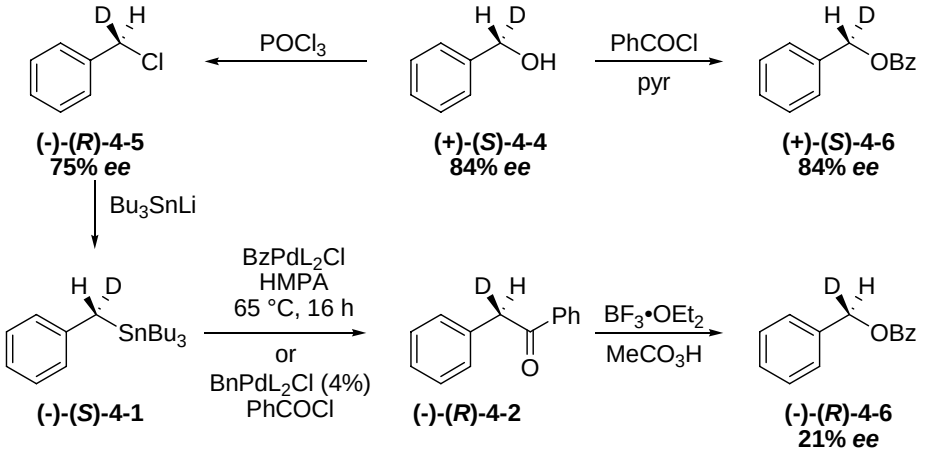
Several Stille coupling reactions of benzylic or α-heteroatom-substituted stannanes have been reported but few studies have focused on the stereochemistry associated with the reaction. Only three reports in the literature provide stereochemical information on the transmetalated carbon center. The stereochemistry of Stille coupling of benzyltrialkyl stannanes with aryl chlorides in the highly polar solvent HMPA was first reported by Stille and Labadie in 1983 (Scheme 38).[1] They observed inversion of configuration at the benzylic carbon, leading them to postulate the open transition state shown below.



Scheme 38

Since the reductive elimination is known to occur predominantly with retention of configuration, the only step of unknown stereochemical consequence is the transmetalation. By conducting the Stille coupling reaction with stereochemically defined stannane **4-1** and observation of the absolute stereochemistry of the coupling

product **4-2**, Labadie and Stille were able to establish the stereochemistry of the transmetalation process (Scheme 39).[1]

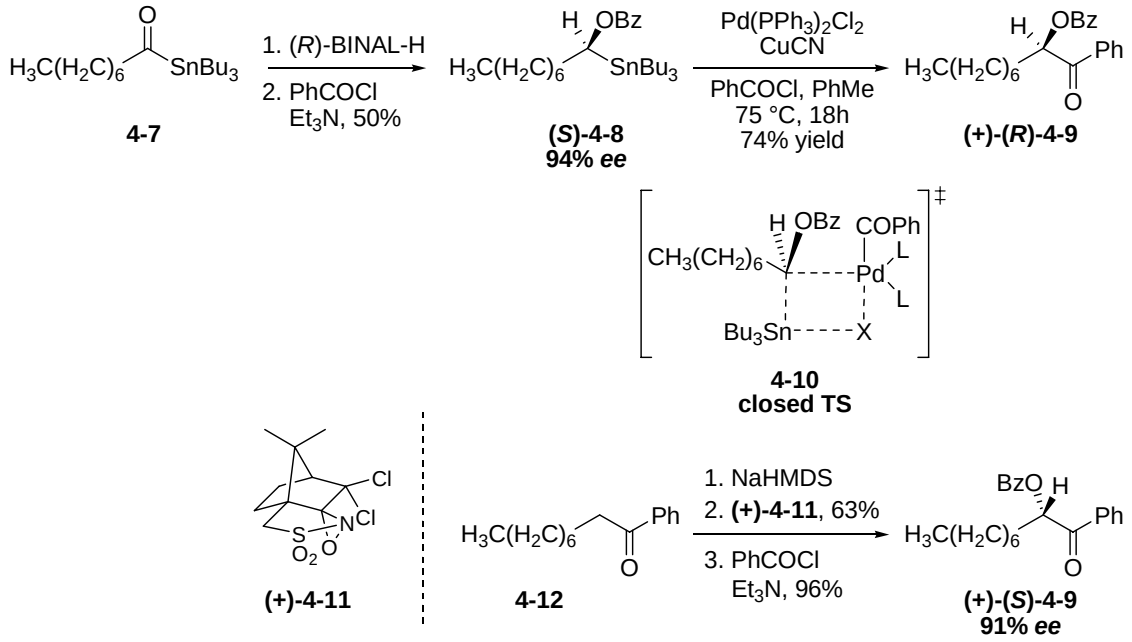


Scheme 39

Treatment of (+)-(*S*)-benzyl-α-*d* alcohol **4-4** (prepared previously by Midland *et al.*)[2] with $POCl_3$ in pyridine[3] provided the deuterated benzyl chloride (-)-(*R*)-**4-5** with inversion of configuration. Although the stereospecificity of the displacement of the chloride from **4-5** with Bu_3SnLi could not be determined and substitution could possibly occur through a single electron-transfer pathway, it is thought that the reaction proceeds with predominate inversion.[4]

In order to determine the absolute stereochemistry of the coupling product **4-2**, it was treated with BF_3 etherate and peracid to give the corresponding benzoate (-)-**4-6** with retention of configuration.[5] This material was then compared with (+)-(*S*)-**4-6** prepared by benzoylation of (*S*)-**4-4** with benzoyl chloride. Thus, it was concluded that the transmetalation occurs with inversion of configuration and led Stille to propose an open transition state **4-3**. The authors calculated that the transmetalation must have occurred with ≥65% stereospecificity given the loss in optical activity through the process.

Falck *et al*. later reported retention of configuration in the palladium/copper co-catalyzed cross-coupling of α-alkoxyalkyl stannanes **4-8** with benzoyl chloride (Scheme 40).[6]

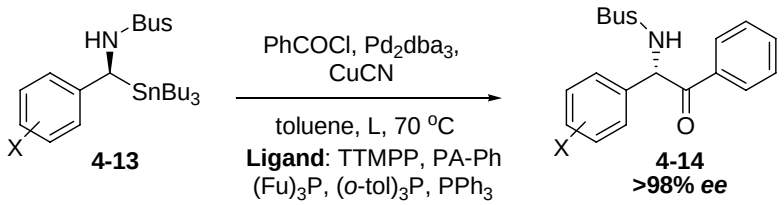


Scheme 40

Coupling of α-alkoxy-α-alkylstannanes such as **4-8** with benzoyl chloride furnished 1-(benzoyloxy)octyl phenyl ketone **4-9** in 74% yield and Falck concluded that the reaction proceeds with *ca.* 98% retention of configuration. To assess the stereochemical consequences of Pd/Cu-mediated carbon-carbon bond formation at stereogenic sites, (*S*)-[α-(benzoyloxy)octyl]tributylstannane **4-8** (94% *ee*) was prepared by sequential BINAL-H asymmetric reduction[7] of acylstannane **4-7** and benzoylation. Coupling as above furnished α-(benzoyloxy)octyl phenyl ketone **4-9**. Ketone **4-9** was also synthesized asymmetrically through oxygenation of **4-12** with the chiral oxaziridine **4-11**.[8] Chiral HPLC analysis using an independently synthesized standard revealed the coupling proceeded with retention of configuration, which is consistent with a 4-

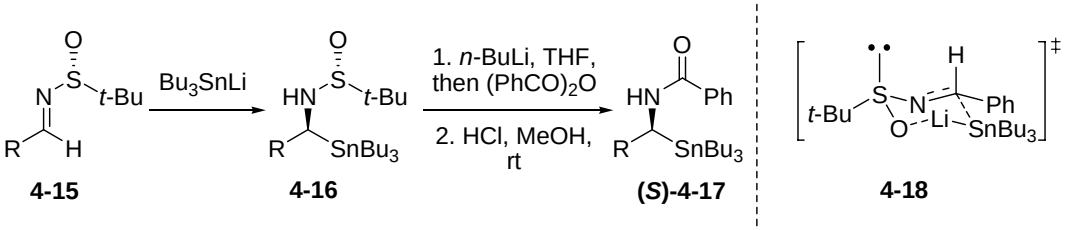
membered cyclic (closed) transition state **4-10** as shown above. Interestingly, the observation that the coupling ran well in toluene but did not occur in HMPA or dichloroethane, is in stark contrast with couplings between benzyltributylstannanes and benzoyl chloride, where inversion of configuration was demonstrated by Stille.[1]

Stille couplings involving stereochemically defined α-sulfonamido-organostannanes were reported by Kells and Chong in 2004 (Scheme 41).[9] Surprisingly, it was discovered that the reaction proceeded with inversion of stereochemistry. This stereochemical outcome is in contrast with Falck's results but followed what was originally demonstrated by Stille and Labadie.



Scheme 41

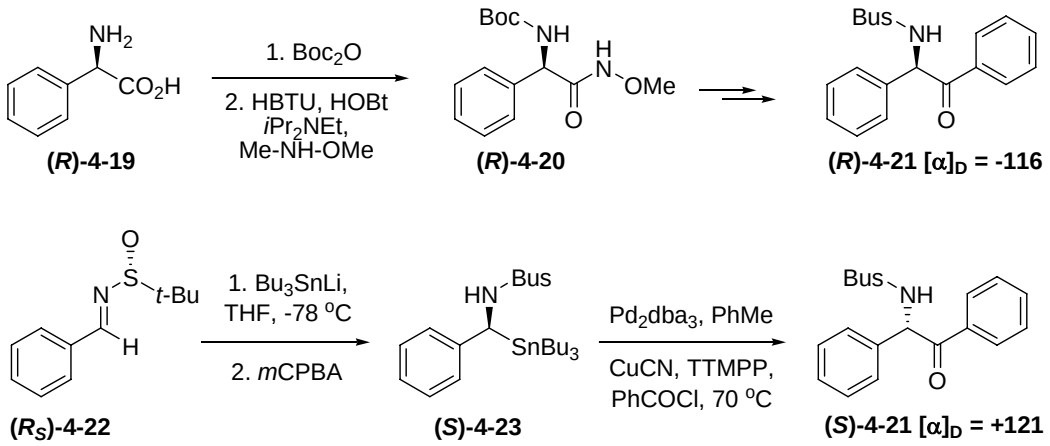
Kells' strategy for the establishment of the absolute stereochemistry of Bu_3SnLi addition to alkyl *t*-butanesulfinimines can be rationalized by the six-membered chair model TS **4-18** proposed by Ellman (Scheme 42).[10]



Scheme 42

The absolute stereochemistry of the Stille coupling product **4-21**, and thus, the stereochemistry of the transmetalation in the Stille reaction, was determined by an independent synthesis of **4-21** (Scheme 43). (*R*)-**4-21** was synthesized from

commercially available (*R*)-phenylglycine **4-19** through a six-step sequence involving the intermediate Weinreb amide **4-20**. Chiral HPLC analysis of ketones **4-21** revealed that the Stille coupling reaction had proceeded with inversion of configuration.

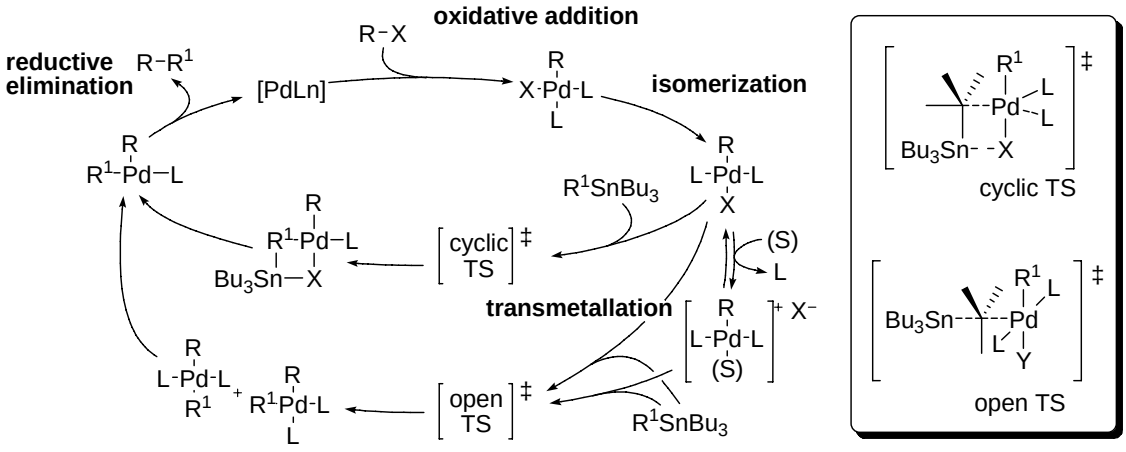


Scheme 43

4.1.2 Stille Reaction Mechanisms

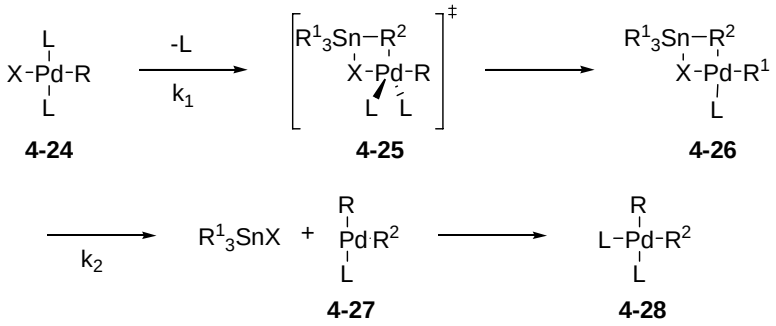
All Pd-catalyzed cross-coupling processes have in common a sequence that starts with Pd^{o}, involves oxidative addition, transmetalation, and reductive elimination steps (as well as isomerization steps when needed). The Stille coupling has been the subject of a recent review which focused considerably on the details of the transmetalation step.[11]

Based on the three results reported by Stille, Falck and Kells, mentioned in the previous section, Espinet and Casado proposed a dual catalytic cycle with two different transition states, as shown in Scheme 44 below.[12]



Scheme 44

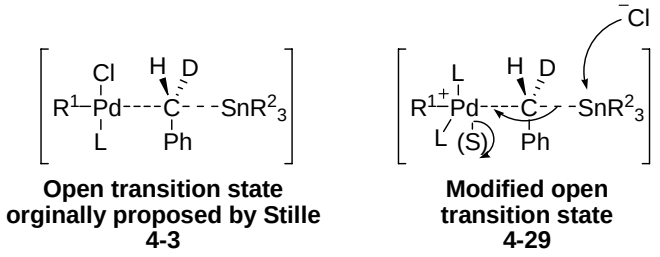
The transmetalation that underwent the cyclic (open) TS depicts an associative process assisted by the formation of a Pd-X-Sn second bridge. This mechanism leads to the exchange of L (and not X) for R^1, forces retention (and not inversion) of the configuration at C^{α}, and leads to a *cis* (rather than a *trans*) $[PdRR^1L_2]$ complex, from which coupling is immediate. For the transmetalation that leads to retention of configuration, the halo ligand on the metal centre acts as a bridging ligand to facilitate an intramolecular transmetalation (Scheme 45). [12b]



Scheme 45

This mechanism is consistent with Falck's result, which is obtained using a non-polar solvent (PhMe) and ligands that are poor σ-donors (Ph_3P). Also the conditions used by Falck strongly favour the reaction *via* a cyclic transition state because the

transmetalation would take place on *trans* [Pd(acyl)Cl(PPh_3)$_2$].[12a] However, in the case of polar solvents (*e.g.* HMPA, THF) and ligands that are rich σ-donors (*e.g.* TTMPP), the cationic metal centre is thought to facilitate the transmetalation of the stannane, which would favour the open transition state. Thus, the transition state originally proposed by Stille can be modified to TS **4-29** rather than the neutral form TS **4-3** (Figure 8). [12a]



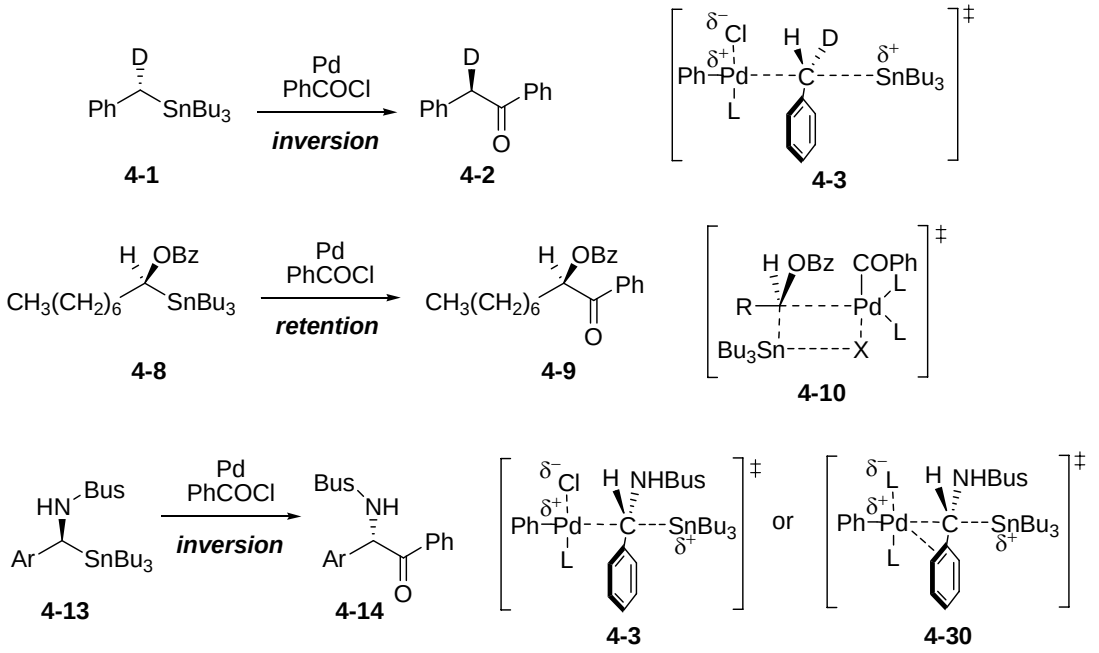
Open transition state orginally proposed by Stille 4-3

Modified open transition state 4-29

Figure 8: Orginal and modified open transition states proposed for the Stille coupling.

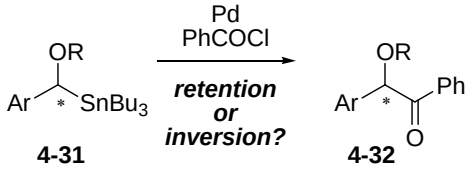
4.2 Determination of the Stereochemical Outcome of Stille Couplings with α-Alkoxybenzylstannanes

Since Stille and Kells had each demonstrated that the Stille coupling had proceeded with inversion with benzylic stannanes and Falck had shown that α-alkoxyalkylstannanes underwent Stille couplings with retention of configuration, it seemed logical for Kells to suggest that the aryl substituent could provide a rate enhancement for the open transmetalation if it were capable of coordinating to the palladium (as in **4-30**) (Scheme 46).[13]



Scheme 46

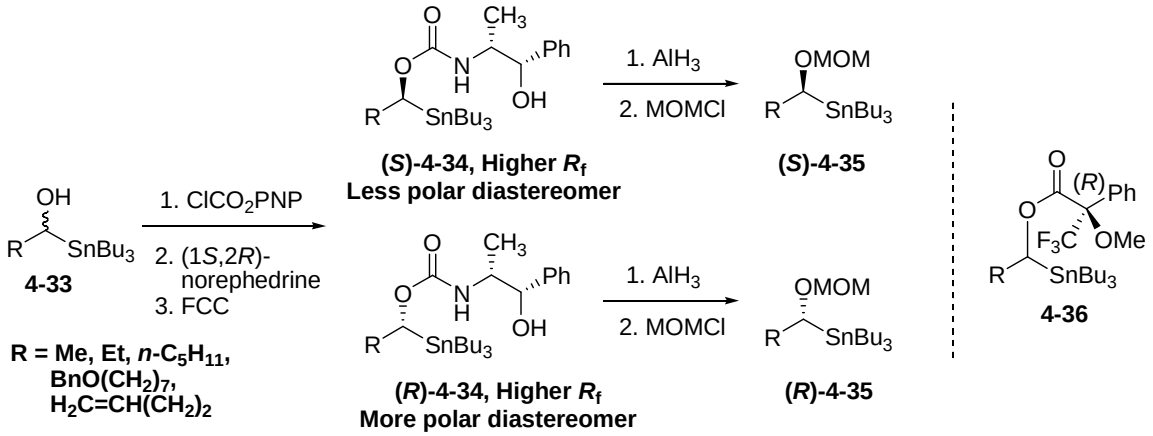
In order to gain further insights into possible mechanisms of transmetalation, a study was undertaken which involves the synthesis of stereochemically defined α-alkoxybenzylstannanes so that the stereochemical outcome of the Stille coupling with these substrates could be established (Scheme 47).



Scheme 47

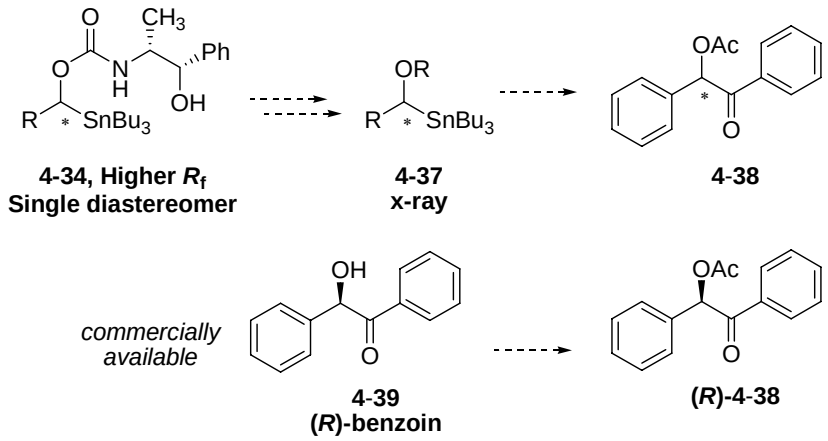
The most obvious approach for obtaining enantiomerically enriched α-alkoxybenzylstannanes involved resolution *via* norephedrine carbamates **4-34**. This was based on previous studies in our laboratory that had shown that this was an efficient method for the preparation of enantiomerically pure α-alkoxyalkylstannanes (Scheme

48).[14] It was shown that the (*S*)-diastereomer of **4-34** was less polar and the absolute stereochemistry was established by analysis of the (*R*)-Mosher esters **4-36**.



Scheme 48

Given the great importance of defining the stereochemistry associated with the Stille coupling of α-alkoxybenzylstannanes **4-37** correctly and unambiguously, it was thought that the most appropriate way to confirm the absolute stereochemistry of **4-37** was through a single-crystal x-ray diffraction study (Scheme 49). Although tributylstannanes are notorious for their non-crystalline greasy nature, several x-ray crystal structures of tributylstannyl derivatives have been solved.

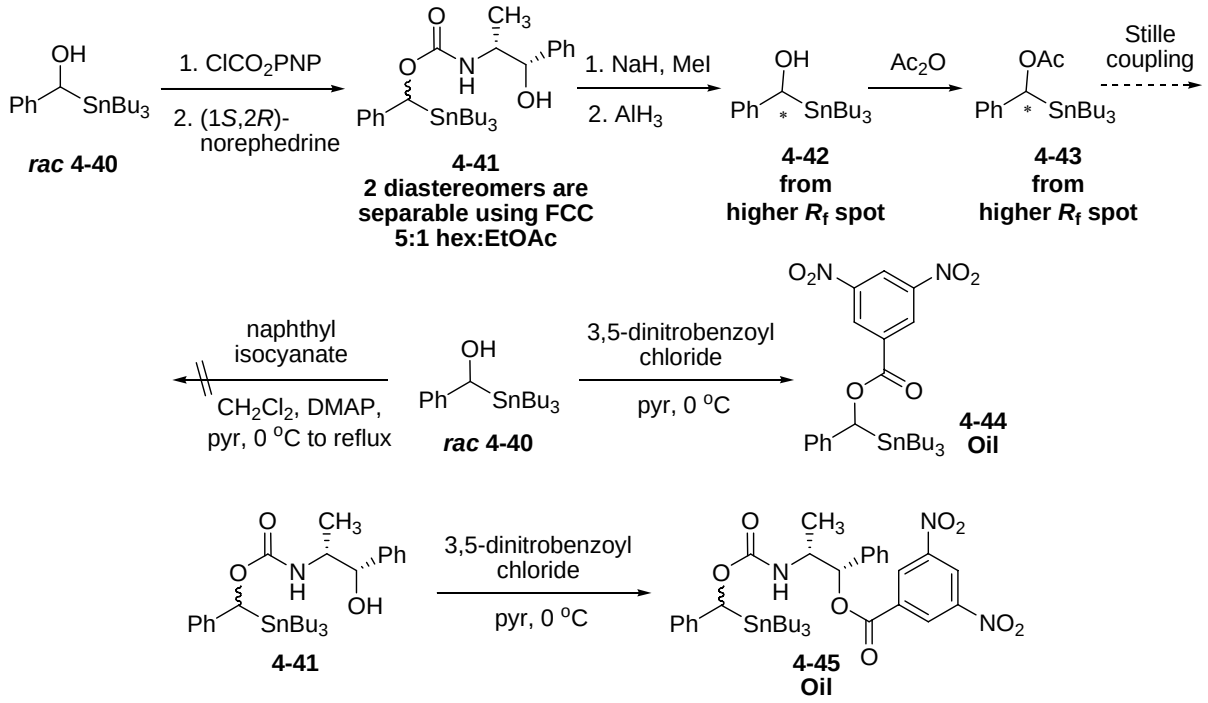


Scheme 49

Determination of the absolute stereochemistry of the Stille coupling product **4-38** could be accomplished by derivatization of commercially available (-)-(*R*)-benzoin and comparison of the products by chiral HPLC and/or optical rotation.

4.2.1 Preparation of Stereochemically Defined α-Alkoxybenzylstannanes

The α-hydroxystannane **4-40** resulting from the addition of Bu_3SnLi to benzaldehyde was immediately treated with *p*-nitrophenyl chloroformate in a two-phase hexanes-acetonitrile solvent system[14] followed by (1*S*,2*R*)-norephedrine to give a diastereomeric mixture of carbamates **4-41** (Scheme 50).

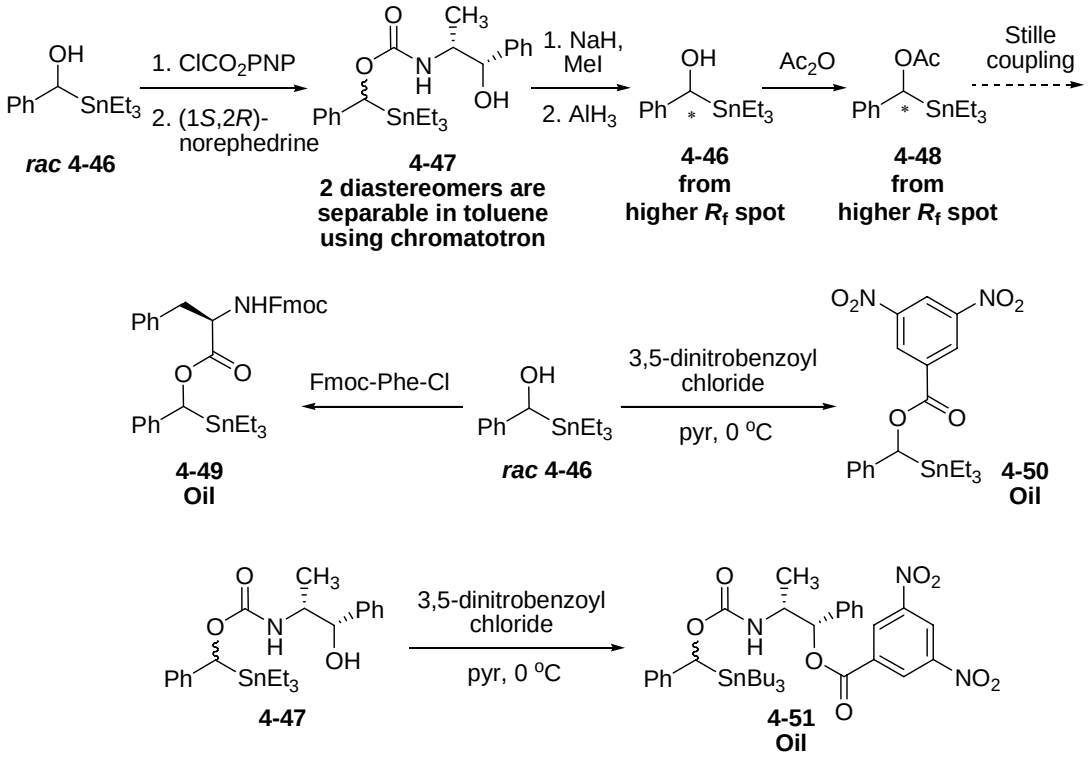


Scheme 50

Separation of the norephedrine carbamates **4-41** with flash column chromatography proceeded smoothly with 5:1 hexanes:ethyl acetate and provided each diastereomer with additional mixed fractions. The carbamate moiety of the less polar diastereomer (higher R_f) was methylated and reduced by AlH_3. The α-hydroxybenzylstannane product was quickly acetylated to furnish the α-acetoxybenzylstannane **4-43** in 98:2 *er* (chiral HPLC) as a yellow oil.

In the pursuit of crystalline α-alkoxystannanes, racemic α-alkoxybenzylstannane **4-40** was treated with naphthyl isocyanates and 3,5-dinitrobenzoyl chloride, since large aromatic substituents generally improve crystallinity. Unfortunately, the purified dinitrobenzoyl esters **4-44** and **4-45** (which was obtained from **4-41**) were obtained as oils and no reaction between the hydroxystannane **4-40** and either of 1-naphthyl isocyanate or 2-naphthyl isocyanate was observed under several different conditions. Since it was thought that the long alkyl chains of the tributyltin derivatives was the

largest obstacle in obtaining crystalline material, the analogous triethylstannanes were prepared (Scheme 51).



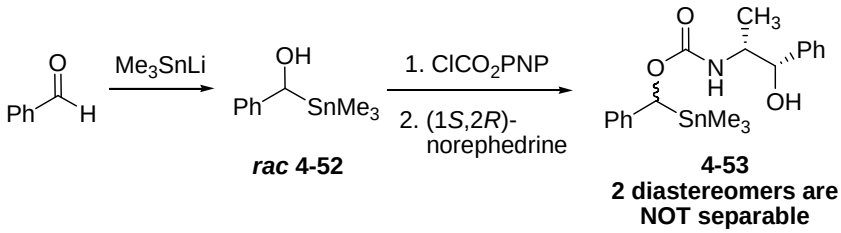
Scheme 51

Similar to the α-hydroxytributylstannanes, the triethylstannanes were resolved *via* the norephedrine carbamate **4-47**. However, chromatographic separation of the diastereomers **4-47** turned out to be much less straight forward, and little separation was obtained with the hexanes/ethyl acetate solvent system in FCC. Moderate separation of the carbamate was obtained, however, with toluene as the eluent using a rotary chromatographic "Chromatotron" apparatus.

The α-hydroxytriethylstannane **4-46** was obtained from the less polar carbamate diastereomer through methylation and alane reduction and immediately acetylated to give the acetate **4-48** in yields comparable to those of the tributylstannanes.

Unfortunately, the acetoxytriethylstannanes **4-46** and the racemic 3,5-dinitrobenzoated derivatives **4-50, 4-51** were obtained as oils. The racemic hydroxystannane was then acylated with the acid chloride of Fmoc-L-phenylanine to give a diastereomeric mixture of esters **4-49**, but even with multiple aromatic rings the Fmoc-phenylalanine derivative was isolated as an oil.

Although the use of trimethylstannanes is generally avoided in synthetic applications because of toxicity, it seemed necessary to investigate such derivatives in this context and the resolution of the α-hydroxytrimethylstannanes was attempted *via* the norephedrine carbamates as shown below (Scheme 52).

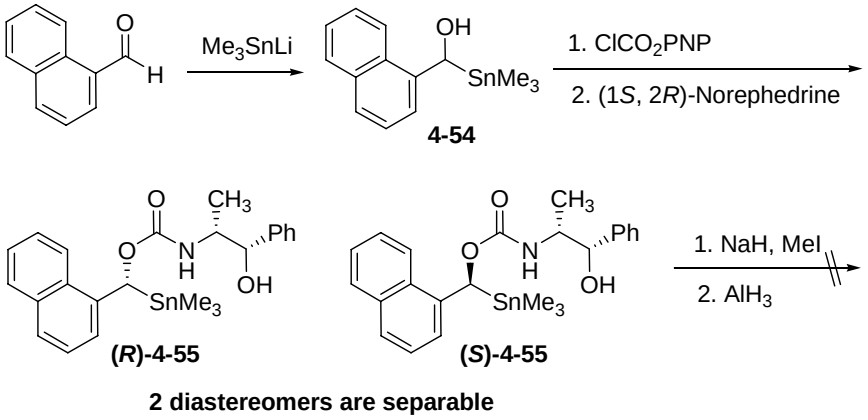


Scheme 52

The two diastereomers of norephedrine carbamates **4-53**, however, could not be separated and no resolution was observed by TLC. Clearly, the length of the alkyl groups of the stannane influence the relative polarity of the norephedrine carbamate diastereomers since moderate separation was obtained with triethylstannanes and good separation with the tributylstannanes.

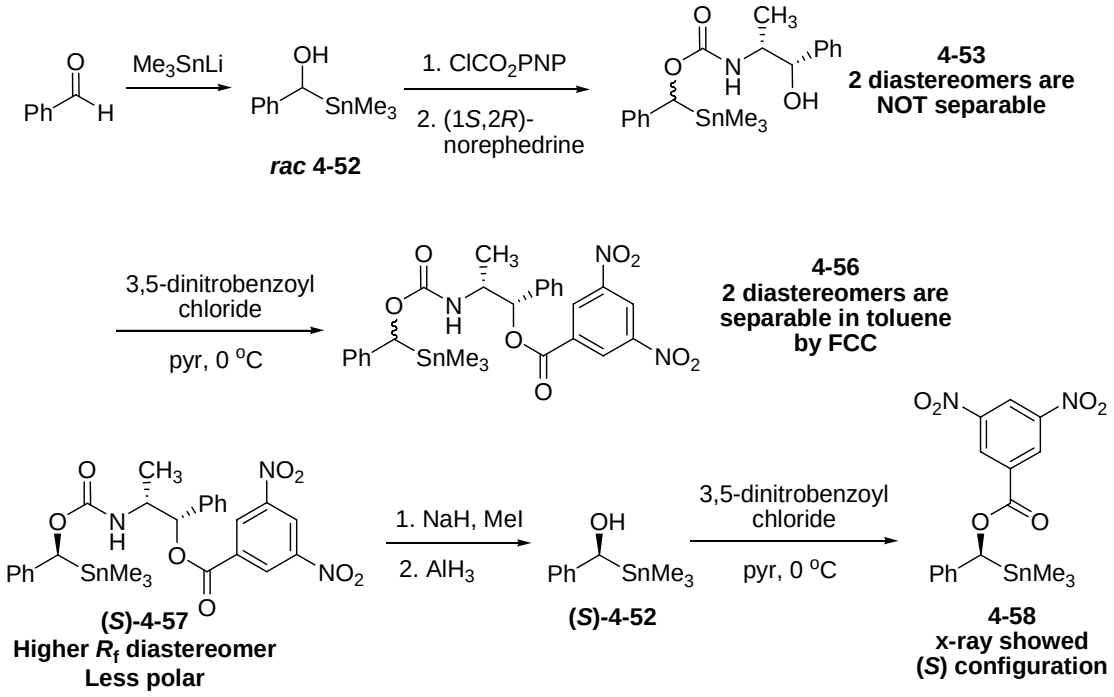
A relatively efficient separation could be achieved with norephedrine carbamates of 1-naphthyl-substituted hydroxystannanes **4-55** and each diastereomer was obtained in 30% yield. Since these compounds were also found to be oils, the cleavage of the carbamate was attempted. To our disappointment, the removal of the chiral auxiliary

could not be effected under the conditions that had been successful previously for phenyl substituted systems (Scheme 53).



Scheme 53

At this point we decided to revisit the norephedrine carbamates **4-53** and considered derivatization of the free hydroxyl group. While esterification of **4-53** with 3,5-dinitrobenzoyl chloride could not be effected with DMAP in dichloromethane, the reaction proceeded smoothly in pyridine and furnished **4-56** in 93% yield (Scheme 54).



Scheme 54

To our satisfaction, the mixture of diastereomers was obtained in semisolid form and careful separation by FCC (toluene as eluent, slow flow rate, >100 g silica/g crude product) provided a small amount of the purified less polar diastereomer in low yield. Recrystallization of the purified diastereomer **4-57** from hexanes gave material that is best described as a waxy solid.

Removal of the chiral auxiliary of **4-57** proved difficult as methylation required excess NaH and MeI and the alane reduction to follow was low-yielding. Nevertheless, the hydroxystannane **4-52** was efficiently taken to the dinitrobenzoyl ester **4-58** in 90% yield.

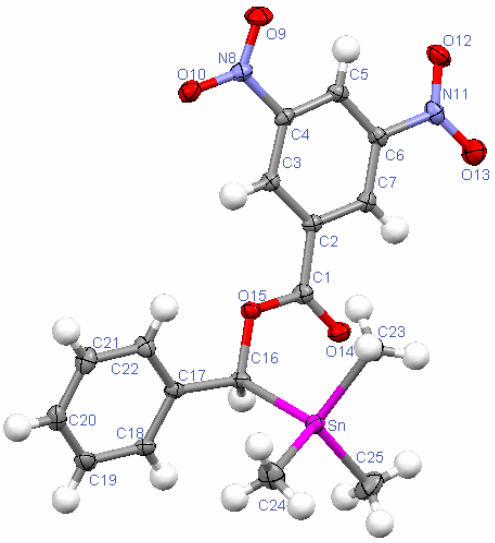
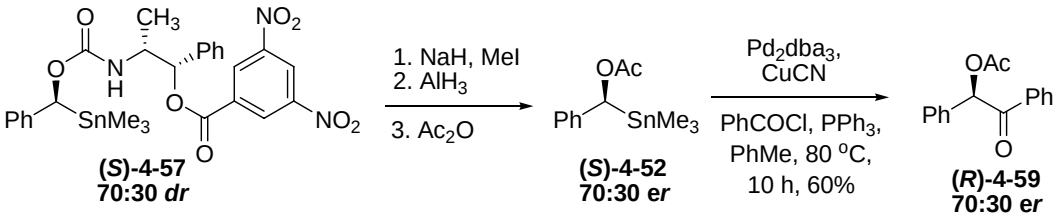


Figure 9: X-ray crystal structure of (*S*)-**4-58**.

To our delight, recrystallization of **4-58** (which was obtained from the less polar diastereomer of carbamate **4-57**) from hexanes yielded light yellow needles that were suitable for an x-ray diffraction study. The absolute configuration of the stannane was found to be (*S*)-**4-58** (Figure 9).

4.2.2 Stille Coupling of Stereochemically Defined α-Alkoxybenzylstannanes

With very little diastereomerically pure carbamate **4-57** in hand, the Stille reaction was pursued with material of 70:30 *dr* by NMR (*S*:*R*). The methylation of carbamate **4-57**, followed by alane reduction and acetylation afforded alkoxystannane **4-52** with 70:30 *er* (chiral HPLC) (Scheme 55).



Scheme 55

Conditions optimized for the Stille coupling of tributylstannanes (Chapter 3) were employed in the coupling reaction of trimethylstannane **4-52** and 60% yield of coupling product **4-59** was obtained. The coupled product **4-59** was subjected to HPLC analysis (ChiralCel ODH) and showed two peaks in a ratio of 70:30 with retention times of 14 and 25 minutes, respectively (Figure 10).

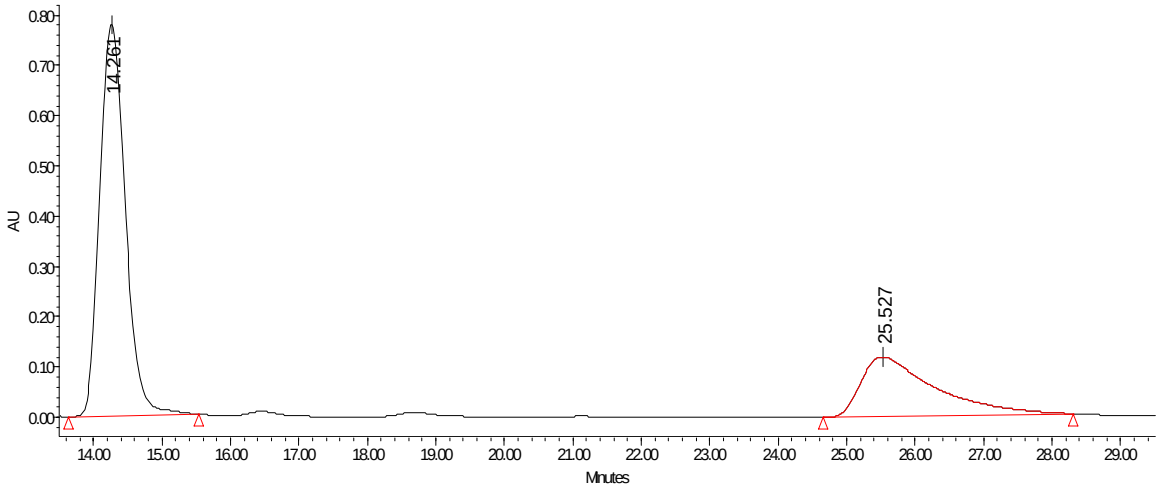
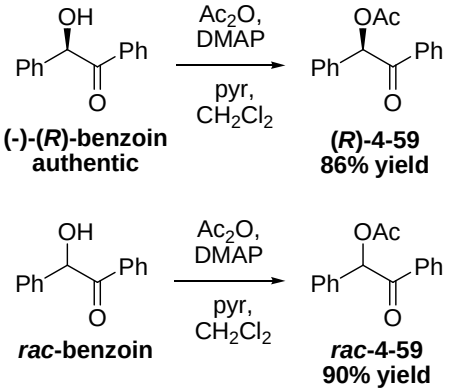


Figure 10: HPLC trace of Stille coupling product **4-59**.

In order to assess the stereochemistry of the Stille coupling reaction, the coupled product **4-59** was compared to (*R*)-**4-59**, which was obtained by acetylation of commercially available (-)-(*R*)-benzoin (Scheme 56). Racemic **4-59** was prepared in the same way.



Scheme 56

Chiral HPLC of the racemic acetate *rac*-**4-59** showed two peaks of equal integration at 14 and 24 minutes, respectively, while the major peak of enantiomerically enriched (*R*)-**4-59** appeared at a retention time of 14 minutes (Figure 11 and Figure 12).

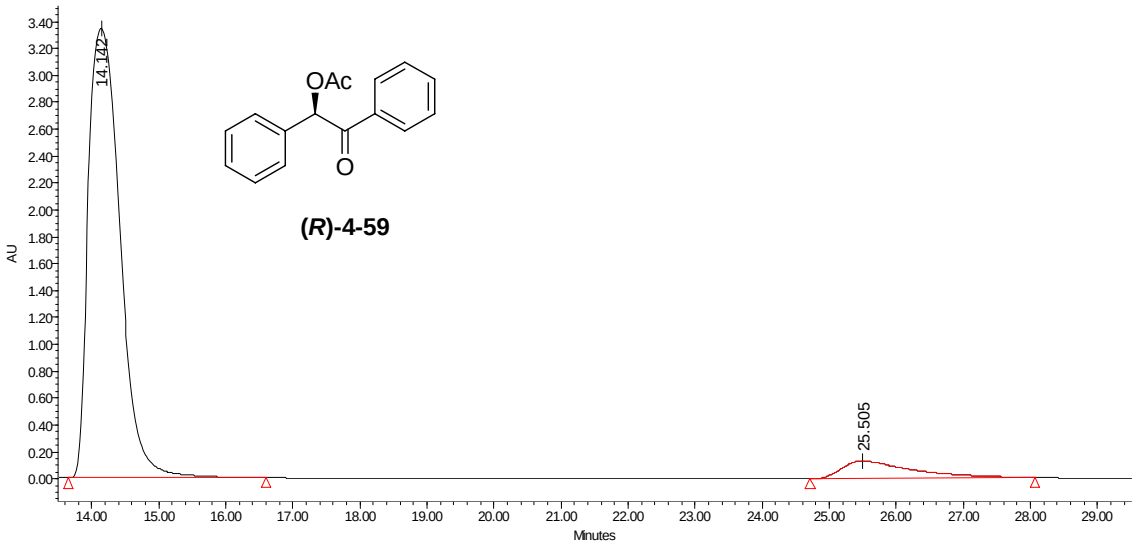


Figure 11: HPLC trace of authentic (*R*)-**4-59**.

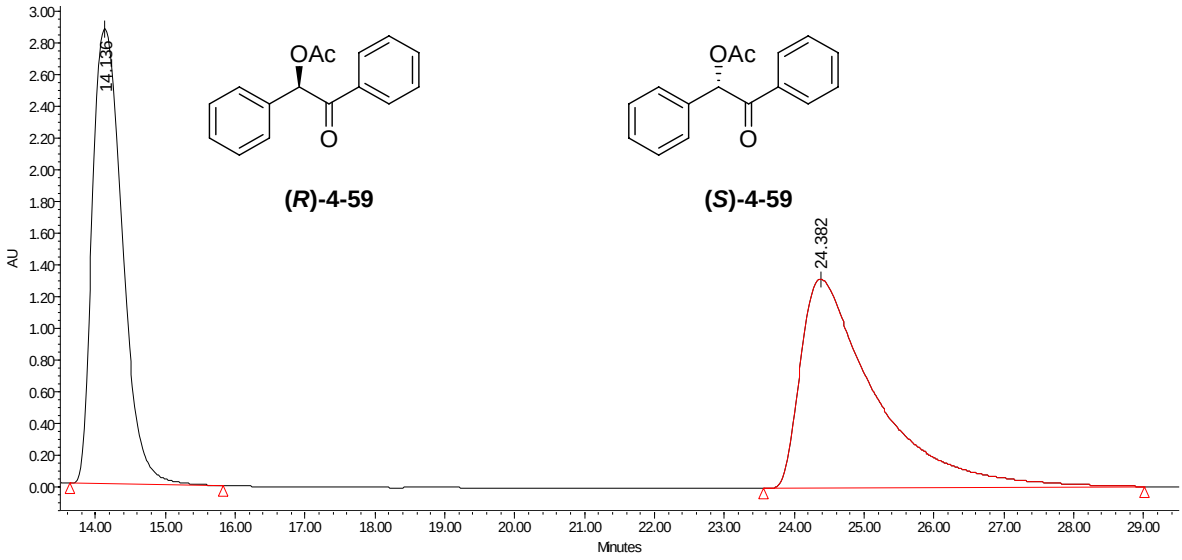


Figure 12: HPLC traces of *rac*-**4-59**.

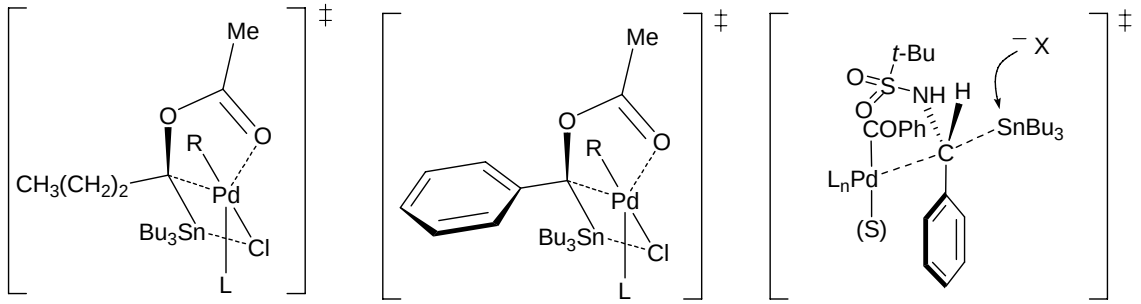
The HPLC traces of the Stille coupling product and the acetates **4-59** derived from authentic (-)-(*R*)-benzoin and racemic benzoin allowed the absolute configuration of the Stille coupling product to be assigned as (*R*)-**4-59**. Based on this HPLC data and the x-ray structure of (*S*)-**4-59**, it can be concluded unambiguously that the Stille coupling of α-alkoxybenzylstannane **4-52** proceeds with retention of configuration.

4.2.3 Discussion

The discovery that the Stille coupling with α-alkoxybenzylstannanes **4-52** follows retention of configuration was somewhat surprising based on the previous studies in our laboratory which found that the closely related α-aminobenzylstannanes proceed through the Stille coupling with inversion of configuration. Retention of configuration in the present system is consistent, however, with that observed by Falck with the α-alkoxyalkylstannanes. It is possible that the most important factor that determines the

stereochemical outcome is not the α-substituent (alkyl vs. aryl) but the heteroatom functionality (carbonyl vs. sulfonyl) since both the present system and Falck's system possess α-acetoxy groups and Kells' derivatives display the α-amidosulfonyl group.

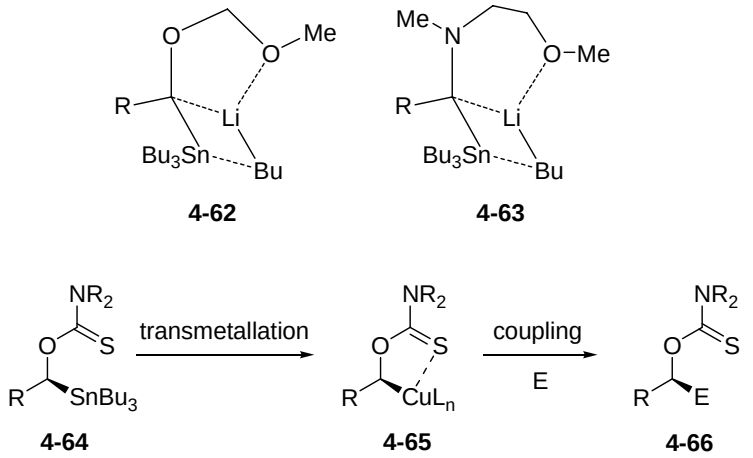
This difference could be most significant if the carbonyl were involved in coordination with the palladium in the transmetalation transition state (such as with **4-60a** and **4-60b**) since one would expect the amidosulfonyl in TS-**4-61** to have weaker coordination (Scheme 57).



Closed TS 4-60a Retention | **Closed TS 4-60b Retention** | **Open TS 4-61 Inversion**

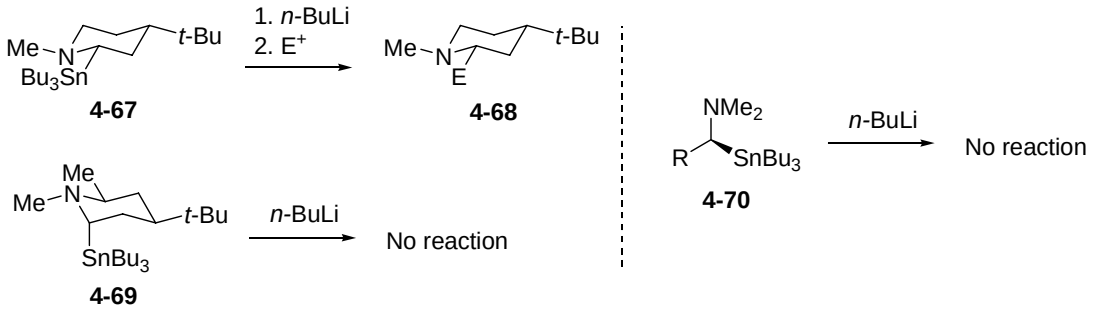
Scheme 57

The concept that coordination could be involved in the transmetalation transition state is based on previous work in our group related to tin-lithium exchange with α-alkoxy **4-62** and α-aminostannanes **4-63**[15] and similar to the proposal by Falck for copper catalyzed cross couplings (Scheme 58).[16] Falck has developed copper-catalyzed cross couplings with α-alkoxyalkylstannanes and shown that proximal thio substituents can have a profound influence on the reaction. He proposed the formation of a coordinatively stabilized organocopper intermediate (arising from tin-copper transmetalation) and found that cross couplings with aryl and alkenyl iodides proceed with retention of configuration.



Scheme 58

Several reports from our laboratory and Gawley *et al*. have demonstrated that equatorial Sn syndinal to N lone pair is required for the configurational stability of the organolithium intermediates (**4-62**, **4-63**), and in some cases, for tin lithium exchange to occur at all (Scheme 59).[15,17]



Scheme 59

In addition to the mechanistic precedent presented above for retention of configuration in transmetalations, the optimized conditions found for Stille couplings with α-alkoxybenzylstannanes are consistent with this mechanism. Firstly, the retention observed in the coupling implies that the transmetalation proceeds through the closed (cyclic) transition state, which is known to be favoured by non-polar solvents. The survey of solvents in the Stille coupling demonstrated that polar solvents resulted in little or no conversion while toluene proved optimal (Chapter 3, Table 3). The fact that highly

electron rich (basic) phosphines (TTMPP, *t*-Bu_3P, *o*-tol_3P, dppp) were poor ligands for the coupling reaction is also consistent with the proposal that coordination by the acetate carbonyl is necessary in the transition state. However, the reason for the poor efficiency of the coupling with electron-donating or electron-withdrawing aryl substituents (Chapter 3, Table 5) remains unclear.

4.3 Summary

The resolution of α-alkoxybenzylstannanes was achieved *via* the norephedrine carbamates and removal of the chiral auxiliary was accomplished by methylation and alane reduction. An enantioenriched α-hydroxybenzyl-trimethylstannane was prepared in this way and an x-ray crystal structure of the corresponding 3,5-dinitrobenzoyl ester established its absolute stereochemistry.

Following an HPLC analysis of the Stille coupling product of the stereochemically defined α-alkoxybenzylstannane with benzoyl chloride, it was concluded that the Stille coupling proceeds with retention of configuration.

4.4 Experimental

General experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Diethyl ether, tetrahydrofuran (THF) and toluene were freshly distilled from Na/benzophenone. Acetonitrile, hexanes and methylene chloride were distilled from calcium hydride. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively.

4.4.1. General procedure for the preparation of diastereomeric carbamates.

n-BuLi (3.72 mmol) were added to a solution of diisopropylamine (3.72 mmol) in THF (20 mL) at 0 ^{o}C. The reaction was stirred at 0 ^{o}C under argon for 15 min, then Bu_3SnH (3.72 mmol) was added. The reaction then stirred for another 15 min at 0 ^{o}C, and cooled to -78 ^{o}C. Then aldehyde (3.72 mmol) was added neat and the reaction was stirred for 45 min at -78 ^{o}C. The reaction was quenched at -78 ^{o}C with a saturated aqueous solution of NH_4Cl (15 mL) and allowed to warm to rt. The mixture was diluted with 100 mL of diethyl ether, the ether layer was washed with brine (30 mL), dried with sodium sulfate, and concentrated under reduced pressure (rt water bath) to yield a yellow oil. Trace amounts of solvent were removed *in vacuo*.

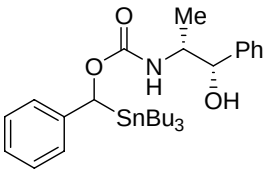
The crude hydroxystannane was dissolved in 20 mL of 1:1 hexane/acetonitrile and cooled to 0 ^{o}C. *p*-Nitrophenyl chloroformate (5.58 mmol) was added to the solution, followed by pyridine (11.16 mmol). The acetonitrile layer became cloudy upon addition of pyridine. The 0 ^{o}C ice bath was removed, and the solution was stirred for 45 min under argon. The reaction was quenched by the addition of 15 mL of water, and diluted

with 20 mL of acetonitrile and 100 mL of hexanes. The hexanes layer was washed with acetonitrile (2 x 20 mL), water (20 mL), and brine (20 mL), dried with sodium sulfate, and concentrated under reduced pressure to yield carbonate intermediate as yellow oil which was carried to the next reaction without further purification.

The crude carbonate (3.72 mmol) was dissolved in 20 mL of 1:1 hexanes/acetonitrile at 0 ^{o}C. Then (+)-(1*S*,2*R*)-norephedrine (4.84 mmol) and diisopropylethylamine (11.16 mmol) were added to the cold solution. The reaction was stirred overnight under argon, warming up to room temperature. The reaction was quenched by the addition of 15 mL of water, and diluted with 100 mL of hexanes. The hexanes layer was washed with acetonitrile (20 mL), water (20 mL), and brine (2 x 20 mL), dried with sodium sulfate, and concentrated under reduced pressure to yield a carbamate product which was obtained as a thick yellow oil. Polar impurities were removed by filtration through silica gel, using 20% ethyl acetate in hexanes. The diastereomeric carbamates were separated using flash chromatography (100 g silica/g crude material).

(Tributylstannyl)(phenyl)methyl (1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-ylcarbamate

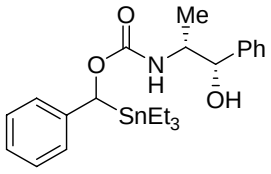
4-41-less polar diastereomer



60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.30–7.24 (7H, m, ArH), 7.09-7.07 (3H, m, ArH), 5.82 (1H, $J_{Sn\text{-}H}$ = 21.8 Hz, s, C<u>H</u>Sn), 4.96-4.93 (1H, *J* = 9.0 Hz, br d, C<u>H</u>PhOH),

4.84 (1H, br s, NHC<u>H</u>CH_3), 4.05 (1H, m, N<u>H</u>), 2.99 (1H, br s, O<u>H</u>), 1.43-1.38 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.28-1.18 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 1.01-0.99 (3H, d, J = 6.8 Hz, NHCHC<u>H</u>$_3$), 0.85-0.80 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ144.6 (<u>C</u>=O), 141.3 (Ar), 128.4 (Ar), 128.2 (Ar), 126.2 (Ar), 126.4 (Ar), 123.9 (Ar), 83.5 (NH<u>C</u>HCH$_3$), 74.3 (<u>C</u>HSn), 52.5 (Ph<u>C</u>HOH), 28.4 (J = 20.2 Hz, $SnCH_2C\underline{H}_2CH_2CH_3$), 26.9 ($J$ = 56.1 Hz, $SnCH_2CH_2C\underline{H}_2CH_3$), 14.7 (NHCH<u>C</u>H$_3$), 14.2 ($J$ = 72.3 Hz, $SnCH_2CH_2CH_2C\underline{H}_3$), 9.89 ($J^{117}$Sn/^{119}Sn = 309.0/321.5 Hz, Sn<u>C</u>$H_2CH_2CH_2CH_3$). LRMS (EI) *m/z* (relative intensity): 518 (100), 516 (77), 107 (21), 91(19).

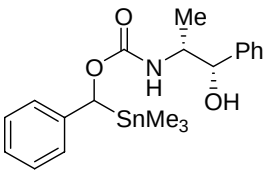
(Triethylstannyl)(phenyl)methyl (1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-ylcarbamate 4-46-less polar diastereomer



57% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.34–7.26 (7H, m, ArH), 7.10-7.07 (3H, m, ArH), 5.79 (1H, J_{Sn-H} = 22.1 Hz, s, C<u>H</u>Sn), 4.98-4.95 (1H, J = 9.0 Hz, br, d, PhC<u>H</u>OH, 4.85 (1H, s br, HNC<u>H</u>CH_3) 4.04 (1H, m, N<u>H</u>), 3.13 (1H, br s, O<u>H</u>), 1.14-1.09 (9H, m, $SnCH_2C\underline{H}_3)_3$), 0.98-0.93 (3H, d, J = 15.0 Hz, NHCHC<u>H</u>$_3$), 0.87-0.82 (6H, m, $Sn(C\underline{H}_2CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ157.7 (<u>C</u>=O), 144.3 (Ar), 140.7 (Ar), 128.4 (Ar), 128.2 (Ar), 127.5 (Ar), 126.3 (Ar), 124.9 (Ar), 123.4 (Ar), 81.5 (NH<u>C</u>HCH$_3$), 74.5 (<u>C</u>HSn), 53.1 (Ph<u>C</u>HOH), 14.9 (NHCH<u>C</u>H$_3$), 10.8 (J = 24.0 Hz, $SnCH_2\underline{C}H_3$), 1.43 (J^{117}Sn/^{119}Sn = 316.2/330.5 Hz, Sn<u>C</u>H_2CH_3). LRMS (EI) *m/z* (relative intensity): 462 (69),

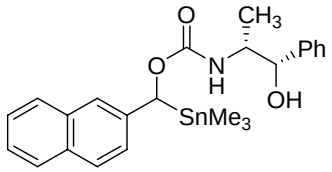
460 (54), 299 (100), 297 (77), 132 (48), 107 (43).

(Trimethylstannyl)(phenyl)methyl(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-ylcarbamate 4-51



60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.34–7.28 (7H, m, ArH), 7.08-7.07 (3H, m, ArH), 5.61 (1H, $J_{Sn\text{-}H}$ = 23.0 Hz, s, C<u>H</u>Sn), 4.93 (1H, *J* = 8.9 Hz, br d, PhC<u>H</u>OH), 4.87 (1H, s, br, HNC<u>H</u>CH_3), 4.05 (1H, br m, N<u>H</u>), 2.88 (1H, br s, O<u>H</u>), 1.02-1.00 (3H, d, *J* = 6.1 Hz, NHCHC<u>H</u>$_3$), 0.03 (9H, $J_{Sn\text{-}H}$ = 52.9 Hz, s, Sn(C<u>H</u>$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ143.6 (<u>C</u>=O), 141.3 (Ar), 128.5 (Ar), 128.3 (Ar), 127.0 (Ar), 125.4 (Ar), 123.5 (Ar), 83.2 (NH<u>C</u>HCH$_3$), 74.5 (<u>C</u>HSn), 52.1 (Ph<u>C</u>HOH), 14.9 (NHCH<u>C</u>H$_3$), -9.17 ($J_{Sn\text{-}C}$ = 330.8 Hz, Sn(<u>C</u>H$_3$)$_3$). LRMS (EI) *m/z* (relative intensity): 434 (100), 432 (76), 267 (24), 165 (49), 163 (30), 105 (70).

(Trimethylstannyl)(naphthalen-2-yl)methyl (1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-ylcarbamate 4-53-less polar diastereomer



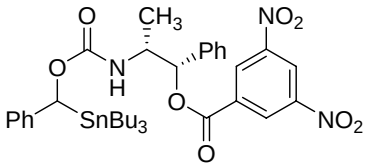
68% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.84–7.82 (2H, m, ArH), 7.64-7.62 (1H, *J* = 6.0 Hz, d, ArH), 7.48–7.31 (9H, m, ArH), 6.38 (1H, $J_{Sn\text{-}H}$ = 23.6 Hz, s, C<u>H</u>Sn), 5.10 (1H, br

d, J = 9.0 Hz, PhC<u>H</u>OH), 4.87 (1H, s br, HNC<u>H</u>CH_3), 4.11-4.07 (1H, br m, N<u>H</u>), 2.88 (1H, br s, O<u>H</u>), 1.04-1.02 (3H, d, J = 6 Hz, NHCHC<u>H</u>$_3$), 0.05 (9H, J_{Sn-H} = 53.0 Hz, s, Sn(C<u>H</u>$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ157.0 (<u>C</u>=O), 141.6 (Ar), 138.2 (Ar), 133.6 (Ar), 129.0 (Ar), 128.6 (Ar), 128.2 (Ar), 127.6 (Ar), 126.2 (Ar), 125.7 (Ar), 125.6 (Ar), 122.8 (Ar), 120.4 (Ar), 83.2 (NH<u>C</u>HCH$_3$), 72.5 (<u>C</u>HSn), 52.1 (Ph<u>C</u>HOH), 14.6 (NHCH<u>C</u>H$_3$), -8.68 (J_{Sn-C} = 330.0 Hz, Sn(<u>C</u>H$_3$)$_3$). LRMS (EI) *m/z* (relative intensity): 484 (51), 482 (37), 165 (37), 155 (100), 129 (39), 107 (24).

4.4.2 Preparation of 3,5-dinitrobenzoates of ***4-41, 4-46, 4-51****.*

The carbamate (1.0 mmol) was dissolved in pyridine (12 mmol) and treated with 3,5-dinitrobenzoyl chloride (1.2 mmol). The reaction mixture was stirred at room temperature for 5 h to afford a deep red solution. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and the product was extracted with ether (3 x 20 mL). The combined ether layers were then washed with brine and dried over sodium sulfate, filtered, and concentrated to obtain the crude product as a yellow solid. The two diastereomers were separate using flash column chromatography with toluene as eluent (1:100 loading of product: silica).

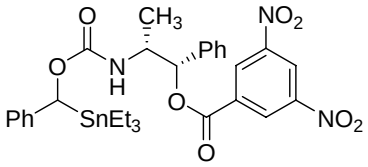
(Tributylstannyl)(phenyl)methyl (1*S*,2*R*)-1-(3,5-dinitrobenzoyloxy)-1-phenylpropan-2-ylcarbamate 4-45-less polar diastereomer



87% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.13 (1H, s, HArNO_2), 9.05 (2H, s, HArNO_2),

7.39-7.37 (6H, m, ArH), 7.04-7.01 (4H, m, ArH), 5.98 (1H, br, s, NH), 5.88 (1H, J_{Sn-H} = 22.8 Hz, s, CHSn), 4.63-4.54 (2H, br m, OCHPhCCH$_3$, HNCHMe), 1.21-1.19 (3H, J = 6.0 Hz, d, NCHCH$_3$), 1.39-1.31 (6H, m, SnCH$_2$CH$_2$CH$_2$CH$_3$), 1.28-1.19 (6H, m, SnCH$_2$CH$_2$CH$_2$CH$_3$), 0.85-0.86-0.75 (15H, m, SnCH$_2$CH$_2$CH$_2$CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ163.5 (OCHPhCCH$_3$), 157.2 (CONH), 149.2 (ArNO$_2$), 143.7 (Ar), 135.0 (Ar), 134.3 (Ar), 130.1 (Ar), 129.5 (Ar), 128.6 (Ar), 127.6 (Ar), 125.5 (Ar), 123.4 (Ar), 122.5 (Ar), 80.6 (CH$_3$CCOPh), 74.6 (CHSn), 29.8 (NHCHCH$_3$), 28.8 (J = 20.6 Hz, SnCH$_2$CH$_2$CH$_2$CH$_3$), 27.3 (J = 57.0 Hz, SnCH$_2$CH$_2$CH$_2$CH$_3$), 16.9 (NHCHCH$_3$), 13.6 (J = 72.0 Hz, SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.82 (J^{117}Sn/^{119}Sn = 308.9/323.0 Hz, SnCH$_2$CH$_2$CH$_2$CH$_3$). LRMS (EI) *m/z* (relative intensity): 712 (75), 710 (58), 301 (65), 291 (36), 195 (100), 179 (39), 91 (33).

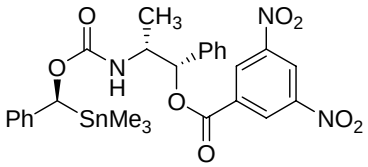
(Triethylstannyl)(phenyl)methyl (1S,2R)-1-(3,5-dinitrobenzoyloxy)-1-phenylpropan-2-ylcarbamate 4-51-less polar diastereomer



84% yield; ^{1}H NMR (300 MHz, CDCl$_3$) δ9.14 (1H, s, HArNO$_2$), 9.07 (2H, s, HArNO$_2$), 7.39-7.37 (6H, m, ArH), 7.06-6.99 (4H, m, ArH), 5.99 (1H, br s, NH), 5.87 (1H, J_{Sn-H} = 23.0 Hz, s, CHSn), 4.62 (2H, br m, OCHPhCCH$_3$, HNCHMe), 1.18-1.16 (3H, J = 6.7 Hz, d, NCHCH$_3$), 1.24-1.17 (6H, m, Sn(CH$_2$CH$_3$)$_3$), 0.81-0.77 (9H, m, Sn(CH$_2$CH$_3$)$_3$; ^{13}C NMR (75 MHz, CDCl$_3$) δ163.0 (OCHPhCCH$_3$), 157.2 (CONH), 149.2 (ArNO$_2$), 143.2 (Ar), 135.0 (Ar), 134.3 (Ar), 130.1 (Ar), 129.5 (Ar), 128.6 (Ar), 127.6 (Ar), 125.5 (Ar), 123.4 (Ar), 122.5 (Ar), 80.7 (CH$_3$CCOPh), 74.5 (CHSn), 29.8

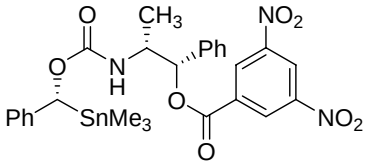
(NH<u>C</u>HCH$_3$), 16.9 (NHCH<u>C</u>H$_3$), 10.7 (J = 24.3 Hz, SnCH$_2$<u>C</u>H$_3$), 1.41 (J^{117}Sn/^{119}Sn = 315.5/329.5 Hz, Sn<u>C</u>H$_2$CH$_3$). LRMS (EI) *m/z* (relative intensity): 389 (38), 301 (69), 195 (100), 105 (20).

(*S*)-(trimethylstannyl)(phenyl)methyl 1-(3,5-dinitrobenzoyloxy)-1-phenylpropan-2-ylcarbamate 4-56- less polar diastereomer



88% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.22–9.12 (2H, m, HArNO$_2$), 9.08 (1H, s, HArNO$_2$), 7.41-7.37 (6H, m, ArH), 7.04-7.02 (4H, m, ArH), 6.03 (1H, s, N<u>H</u>), 5.71 (1H, J_{Sn-H} = 23.2 Hz, s, C<u>H</u>Sn), 4.74-4.71 (A of ABX$_3$, J_{AB} = 9.2 Hz, 1H, br d, OC<u>H</u>PhCCH$_3$), 4.54 (B of ABX$_3$, 1H, br m, HNC<u>H</u>Me), 1.21-1.19 (X$_3$ of ABX$_3$, J_{BX} = 6.9 Hz, 3H, d, NCHC<u>H</u>$_3$), 0.006 (9H, J_{Sn-H} = 53.1 Hz, s, Sn(C<u>H</u>$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ162.6 (O<u>C</u>HPhCCH$_3$), 157.1 (<u>C</u>ONH), 149.2 (ArNO$_2$), 143.2 (Ar), 135.0 (Ar), 134.3 (Ar), 130.1 (Ar), 129.5 (Ar), 128.6 (Ar), 127.6 (Ar), 125.5 (Ar), 123.4 (Ar), 122.5 (Ar), 80.5 (CH$_3$C<u>C</u>OPh), 74.1 (<u>C</u>HSn), 29.8 (NH<u>C</u>HCH$_3$), 16.9 (NHCH<u>C</u>H$_3$), -9.97 (J_{Sn-C} = 331.3 Hz, Sn(<u>C</u>H$_3$)$_3$). LRMS (EI) *m/z* (relative intensity): 628 (22), 626 (17), 301 (58), 239 (51), 195 (100), 165 (41), 105 (44).

(*R*)-(trimethylstannyl)(phenyl)methyl 1-(3,5-dinitrobenzoyloxy)-1-phenylpropan-2-ylcarbamate 4-56–more polar diastereomer



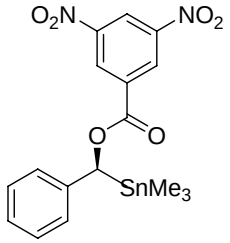
81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.22–9.12 (2H, m, $HArNO_2$), 9.08 (1H, s, $HArNO_2$), 7.41-7.37 (6H, m, ArH), 7.04-7.02 (4H, m, ArH), 6.10 (1H, s, N<u>H</u>), 5.71 (1H, J_{Sn-H} = 23.2 Hz, s, C<u>H</u>Sn), 4.74-4.71 (A of ABX_3, J_{AB} = 9.2 Hz, 1H, br d, OC<u>H</u>PhCCH_3), 4.54 (B of ABX_3, 1H, br m, HNC<u>H</u>Me), 1.21-1.19 (X_3 of ABX_3, J_{BX} = 6.9 Hz, 3H, d, NCHC<u>H</u>$_3$), 0.01 (9H, J_{Sn-H} = 53.1 Hz, s, Sn(C<u>H</u>$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ162.6 (O<u>C</u>HPhCCH_3), 157.1 (<u>C</u>ONH), 149.2 ($ArNO_2$), 143.2 (Ar), 135.0 (Ar), 134.3 (Ar), 130.1 (Ar), 129.5 (Ar), 128.6 (Ar), 127.6 (Ar), 125.5 (Ar), 123.4 (Ar), 122.5 (Ar), 80.5 (CH_3C<u>C</u>OPh), 74.1 (<u>C</u>HSn), 29.8 (NH<u>C</u>HCH_3), 16.9 (NHCH<u>C</u>H_3), -9.97 (J_{Sn-C} = 331.0 Hz, Sn(<u>C</u>H_3)$_3$). LRMS (EI) *m/z* (relative intensity): 628 (22), 626 (17), 301 (58), 239 (51), 195 (100), 165 (41), 105 (44).

4.4.3 Cleavage of carbamates.

Dry THF (2 mL) was added to the carbamate (1.4 mmol), followed by NaH (4.2 mmol) and MeI (14 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl at 0 ^{o}C, washed with ether, dried over sodium sulfate and concentrated. The crude methylated product was taken straight to the next reduction with AlH_3. AlH_3 (0.4 M in THF/Et_2O, 7.2 mmol) was then added to the methylated crude in THF (14 mL) at room temperature and the

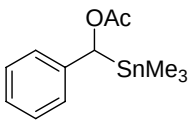
mixture was stirred overnight. The solution was cooled to 0 °C and quenched by the addition of solid $Na_2SO_4 \cdot 10H_2O$. The mixture was stirred for 20 min at rt, and then solids were filtered off and concentrated under reduced pressure (rt water bath) to yield the crude hydroxystannane, which was protected as its acetate using standard conditions (acetic anhydride with pyridine, CH_2Cl_2, 0 °C to rt.).

(S)-(Trimethylstannyl)(phenyl)methyl 3,5-dinitrobenzoate 4-58-obtained from the less polar carbamate diastereomer



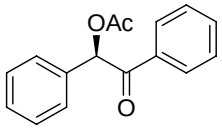
89% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.22 (1H, s, $HArNO_2$), 9.17 (2H, s, $HArNO_2$), 7.37-7.35 (3H, m, ArH), 7.19-7.17 (2H, J = 6.4 Hz, br d, ArH), 6.07 (1H, $J_{Sn\text{-}H}$ = 23.0 Hz, s, C<u>H</u>Sn), 0.09 (9H, $J_{Sn\text{-}H}$ = 53.3 Hz, s, Sn(C<u>H</u>$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ166.7 (<u>C</u>=O), 149.4 (Ar), 140.9 (Ar), 132.0 (Ar), 130.9 (Ar), 129.0 (Ar), 127.7 (Ar), 127.2 (Ar), 123.0 (Ar), 70.1 (<u>C</u>HSn), -11.7 ($J_{Sn\text{-}C}$ = 330.4 Hz, Sn(<u>C</u>H$_3$)$_3$).

(Trimethylstannyl)(phenyl)methyl acetate 4-52 (70:30-*S*:*R*)



80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.27 (2H, m, ArH), 7.07 (3H, m, ArH), 5.69 (1H, J_{Sn-H} = 23.5 Hz, s, C<u>H</u>Sn), 2.12 (3H, s, C<u>H</u>$_3$), 0.02 (9H, s, J_{Sn-H} = 52.9 Hz, Sn(C<u>H</u>$_3$)$_3$; ^{13}C NMR (75 MHz, $CDCl_3$) δ171 (<u>C</u>OCH$_3$), 141.3 (Ar), 128.6 (Ar), 125.4 (Ar), 123 (Ar), 71.4 (Ar<u>C</u>OSn), 20.8 (CO<u>C</u>H$_3$), -9.4 (J_{Sn-C} = 330.6 Hz, Sn(<u>C</u>H$_3$)$_3$).

2-Oxo-1,2-diphenylethyl acetate (*R*)-4-59



60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.93 (2H, d, *J* = 8.4 Hz, ArH), 7.50 (3H, m, ArH), 7.38 (5H, m, ArH), 6.84 (1H, s, C<u>H</u>OAc), 2.19 (3H, s, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ194.2 (<u>C</u>OAc), 170.1 (<u>C</u>OCH$_3$), 136.5 (Ar), 133.2 (Ar), 128.9 (Ar), 128.2 (Ar), 77.4 (<u>C</u>HOAc), 20.8 (CO<u>C</u>H$_3$). The enantiomeric excess of the product **4-59** was determined by HPLC (ChiralCel ODH) (5% *i*-PrOH/hexanes, flow rate = 1.0 mL/min), t_R = 14 min (*R*), t_R = 25 min (*S*).

4. 5. References

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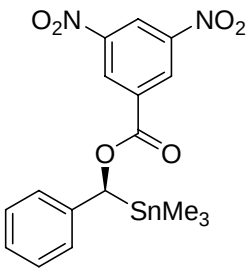
Appendix

X-Ray Crystallographic Data for
(Trimethylstannyl)(phenyl)methyl 3,5-dinitrobenzoate (compound **4-58**)



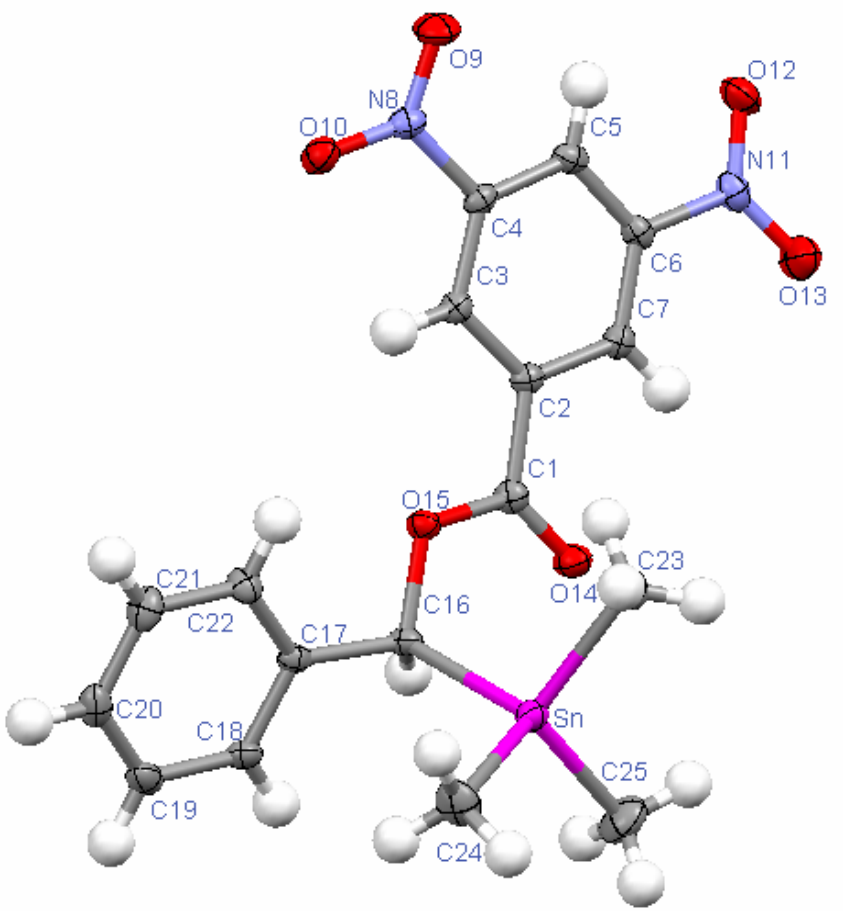


Table A. **Crystal data and structure refinement for $C_{17}H_{18}N_2O_6Sn$**.

Empirical formula	C17 H18 N2 O6 Sn
Formula weight	465.02
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 8.0349(13) Å, b = 10.5620(17) Å, c = 21.629(4) Å
Volume, Z	1835.6(5) $Å^3$, 4
Density (calculated)	1.683
Absorption coefficient	1.428 mm^{-1}
F(000)	928
Crystal size	0.41 x 0.30 x 0.12 mm^3
2θ range for data collection	3.16 to 30.00º
Limiting indices	-11< h<11, -14< k<14, -30< l<30
Reflections collected	26356
Independent reflections	5308 (R_{int} = 0.0330)
Completeness to 2θ = 30.00	99.4 %
Absorption correction	Empirical
Max. and min. transmission	0.8474 and 0.5935
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5308 / 0 / 235
Goodness-of-fit on F^2	1.079
Final R indices [I>2σ(I)]	R1 = 0.0230, wR2 = 0.0540
R indices (all data)	R1 = 0.0238, wR2 = 0.0544
Extinction coefficient	0.010(16)
Largest diff. peak and hole	0.753 and -0.918 e- $Å^{-3}$

Table B. **Atomic coordinates and equivalent isotropic for $C_{17}H_{18}N_2O_6Sn$**.

	x/a	y/b	z/c	U_{eq}
Sn	0.4077(1)	0.2240(1)	0.3987(1)	0.019(1)
C(1)	0.0733(3)	0.0371(2)	0.3669(1)	0.018(1)
C(2)	0.0135(3)	-0.0965(2)	0.3697(1)	0.016(1)
C(3)	0.0627(3)	-0.1883(2)	0.3276(1)	0.016(1)
C(4)	0.0054(3)	-0.3104(2)	0.3357(1)	0.017(1)
C(5)	-0.1027(3)	-0.3454(2)	0.3825(1)	0.019(1)
C(6)	-0.1517(3)	-0.2504(2)	0.4224(1)	0.018(1)
C(7)	-0.0954(3)	-0.1269(2)	0.4176(1)	0.017(1)
N(8)	0.0583(2)	-0.4093(2)	0.2919(1)	0.021(1)
O(9)	0.0256(3)	-0.5205(2)	0.3048(1)	0.032(1)
O(10)	0.1344(2)	-0.3772(2)	0.2457(1)	0.025(1)
N(11)	-0.2690(2)	-0.2826(2)	0.4724(1)	0.023(1)
O(12)	-0.3368(3)	-0.3857(2)	0.4708(1)	0.029(1)
O(13)	-0.2918(3)	-0.2030(2)	0.5129(1)	0.036(1)
O(14)	0.0326(2)	0.1184(2)	0.4034(1)	0.024(1)
O(15)	0.1826(2)	0.0555(2)	0.3209(1)	0.018(1)
C(16)	0.2486(3)	0.1851(2)	0.3167(1)	0.017(1)
C(17)	0.3416(3)	0.1969(2)	0.2568(1)	0.016(1)
C(18)	0.3594(3)	0.3166(2)	0.2313(1)	0.020(1)
C(19)	0.4532(3)	0.3344(3)	0.1778(1)	0.024(1)
C(20)	0.5287(3)	0.2325(3)	0.1493(1)	0.024(1)
C(21)	0.5088(3)	0.1121(3)	0.1739(1)	0.025(1)
C(22)	0.4158(3)	0.0943(2)	0.2274(1)	0.020(1)
C(23)	0.4274(4)	0.517(3)	0.4507(1)	0.030(1)
C(24)	0.6492(3)	0.2814(3)	0.3676(1)	0.033(1)
C(25)	0.2930(4)	0.3693(3)	0.4517(2)	0.039(1)

***Table C*. Bond Lengths and Bond Angles for $C_{17}H_{18}N_2O_6Sn$.**

	Length [Å]		Angle [°]
Sn-C(25)	2.126(3)	C(25)-Sn-C(24)	110.95(14)
Sn-C(24)	2.141(3)	C(25)-Sn-C(23)	111.26(13)
Sn-C(23)	2.144(3)	C(24)-Sn-C(23)	109.77(12)
Sn-C(16)	2.224(2)	C(25)-Sn-C(16)	108.25(11)
C(1)-O(14)	1.210(3)	C(24)-Sn-C(16)	108.85(10)
C(1)-O(15)	1.342(3)	C(23)-Sn-C(16)	107.66(9)
C(1)-C(2)	1.493(3)	O(14)-C(1)-O(15)	123.9(2)
C(2)-C(3)	1.387(3)	O(14)-C(1)-C(2)	123.9(2)
C(2)-C(7)	1.393(3)	O(15)-C(1)-C(2)	112.17(19)
C(3)-C(4)	1.382(3)	C(3)-C(2)-C(7)	120.4(2)
C(4)-C(5)	1.384(3)	C(3)-C(2)-C(1)	122.8(2)
C(4)-N(8)	1.472(3)	C(7)-C(2)-C(1)	116.7(2)
C(5)-C(6)	1.382(3)	C(4)-C(3)-C(2)	118.3(2)
C(6)-C(7)	1.384(3)	C(3)-C(4)-C(5)	123.5(2)
C(6)-N(11)	1.475(3)	C(3)-C(4)-N(8)	119.0(2)
N(8)-O(10)	1.221(3)	C(5)-C(4)-N(8)	117.5(2)
N(8)-O(9)	1.235(3)	C(6)-C(5)-C(4)	116.2(2)
N(11)-O(12)	1.218(3)	C(5)-C(6)-C(7)	123.0(2)
N(11)-O(13)	1.228(3)	C(5)-C(6)-N(11)	118.2(2)
O(15)-C(16)	1.470(3)	C(7)-C(6)-N(11)	118.8(2)
C(16)-C(17)	1.502(3)	C(6)-C(7)-C(2)	118.5(2)
C(17)-C(18)	1.386(3)	O(10)-N(8)-O(9)	123.7(2)
C(17)-C(22)	1.391(3)	O(10)-N(8)-C(4)	118.3(2)
C(18)-C(19)	1.394(4)	O(9)-N(8)-C(4)	118.0(2)
C(19)-C(20)	1.380(4)	O(12)-N(11)-O(13)	124.5(2)
C(20)-C(21)	1.388(4)	O(12)-N(11)-C(6)	118.1(2)
C(21)-C(22)	1.389(3)	O(13)-N(11)-C(6)	117.4(2)
		C(1)-O(15)-C(16)	114.56(17)
		O(15)-C(16)-C(17)	108.02(17)
		O(15)-C(16)-Sn	109.31(14)
		C(17)-C(16)-Sn	112.77(14)
		C(18)-C(17)-C(22)	119.0(2)
		C(18)-C(17)-C(16)	118.1(2)
		C(22)-C(17)-C(16)	122.9(2)
		C(17)-C(18)-C(19)	120.6(2)
		C(20)-C(19)-C(18)	120.1(2)
		C(19)-C(20)-C(21)	119.6(2)
		C(20)-C(21)-C(22)	120.3(2)
		C(21)-C(22)-C(17)	120.4(2)

***Table D*. Hydrogen coordinates and isotropic displacement parameters for $C_{17}H_{18}N_2O_6Sn$.**

H(3A)	0.1326	-0.1680	0.2948	0.019
H(5A)	-0.1404	-0.4282	0.3867	0.023
H(7A)	-0.1295	-0.0655	0.4457	0.021
H(16A)	0.1553	0.2449	0.3166	0.021
H(18A)	0.3082	0.3856	0.2500	0.024
H(19A)	0.4650	0.4152	0.1612	0.029
H(20A)	0.5924	0.2445	0.1139	0.029
H(21A)	0.5580	0.0430	0.1545	0.030
H(22A)	0.4030	0.0133	0.2436	0.024
H(23A)	0.3927	0.0666	0.4925	0.045
H(23B)	0.5408	0.0231	0.4504	0.045
H(23C)	0.3575	-0.0118	0.4323	0.045
H(24A)	0.7058	0.3250	0.4004	0.050
H(24B)	0.6378	0.3369	0.3327	0.050
H(24C)	0.7123	0.2081	0.3558	0.050
H(25A)	0.2337	0.3322	0.4857	0.058
H(25B)	0.2166	0.4155	0.4260	0.058
H(25C)	0.3767	0.4258	0.4672	0.058