Stille Coupling of α-Alkoxybenzylstannanes: Optimization Study and Stereochemical Outcome

by

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

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

Abstract

In order to make the stereospecific palladium-catalyzed cross-coupling of α-alkoxybenzyl-stannanes a useful synthetic methodology, optimization was undertaken to improve the coupling yields between these stannanes and benzoyl chloride as a model electrophilic substrate.

Efforts were put into synthesizing and screening of a number of protecting groups for α-hydroxystannane, followed by optimization of reaction parameters for the Stille coupling reaction of different racemic α-alkoxybenzylstannanes. These protecting groups were chosen based on the principle of "complexation-induced proximity effect" to guide the metal catalyst.

Upon obtaining an optimized reaction condition, the stereochemical outcome for the cross-coupling of enantiomerically enriched α-(trimethylacetoxy)benzylstannane with benzoyl chloride will be unambiguously presented. Influences by both the palladium ligand and the electronic property of the substituted-benzoyl chloride will be discussed.

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To my fianc é Lu and my parents…

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List of Abbreviations

Ac	acetyl
Ar	aryl
BINAL-H	lithium (1,1'-binaphthalene-2,2'-diolato)(ethanolato)hydridoaluminate
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bz	benzoyl
CIPE	complexation-induced proximity effect
COD	1,5-cyclooctadiene
Cy	cyclohexyl
DavePhos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylidene acetone
DCC	*N*,*N*'-dicyclohexyl carbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
d.e. (or de)	diastereomeric excess
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-*bis*(diphenylphosphino)ethane
E	electrophile
e.e. (or ee)	enantiomeric excess
EI	electron impact

e.s. (or es)	enantiospecificity
FCC	flash column chromatography
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	*N*-hydroxybenzotriazole
HPLC	high performance liquid chromatography
J	coupling constant
L	ligand
LDA	lithium diisopropylamide
LUMO	lowest occupied molecular orbital
M	molecular ion
m-CPBA	*meta*-chloroperbenzoic acid
Men	menthyl
MOM	methoxymethyl
M.p.	melting point
MPLC	medium pressure liquid chromatography
MTPA	*α*-methoxy-*α*-trifluoromethylphenylacetyl
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
Nuc	nucleophile
OTf	trifluoromethylsulfonate
PG	protecting group
Pin	pinacol
PNP	*para*-nitrophenyl
Q-Phos	1,2,3,4,5-Pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene

RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl
S_E2	bimolecular electrophilic substitution
S_N2	bimolecular nucleophilic substitution
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetyl
TFP	tri-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
t_R	retention time
TTMPP	tris-(2,4,6-trimethoxyphenyl)phosphine
Un	unsaturated group
X	halide
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1. Introduction

1.1 Palladium-Catalyzed Cross-Coupling in Organic Synthesis

The idea of using palladium to catalyze cross-coupling of organic compounds as a means of making carbon-carbon bonds was first discovered and systematically studied by Professor Richard Heck.[1] Even though the related coupling reactions of numerous organometallic compounds had already been reported, Heck's pioneering work on the coupling reaction of alkenes with aryl halides showcased the potential of using palladium to catalyze a great variety of coupling reactions.[2] Later on, other pioneers of the subject developed coupling reactions utilizing coupling partners that include organomagnesium[3] (Makoto Kumada), terminal alkynes[4] (Kenkichi Sonogashira), organozinc[5] (Ei-ichi Negishi), organotin[6] (John K. Stille), organoboron[7] (Akira Suzuki), and organosilane[8] (Tamejiro Hiyama) reagents. The synthetic utility of palladium-catalyzed cross-coupling reactions was demonstrated throughout the history of synthetic chemistry and received recognition as the Nobel Foundation awarded three of its pioneers (Figure 1.1) the Nobel Prize in Chemistry some 20 to 40 years later on October 2010.[1] Since their discoveries, a large volume of research effort has been spent trying to optimize the coupling efficiency, broaden substrate scopes, reduce the harshness of the reaction conditions, and gain better understandings of the operational mechanisms behind these reactions. Even though reactions involving other nucleophilic coupling partners also possess very rich chemistry, the work described in this thesis focuses primarily on the synthesis and coupling of organotin reagents. Hence this introduction will cover mainly the palladium-catalyzed Stille Coupling and the preparation of organostannane substrates.

Figure 1.1: Nobel Prize in Chemistry 2010 awardees "*for palladium-catalyzed cross coupling in organic synthesis*" [9]


Richard F. Heck

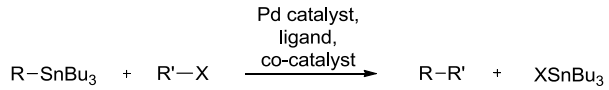

Ei-ichi Negishi


Akira Suzuki

1.2 Stille Coupling of Organotin Compounds

The Stille Coupling can be viewed as a carbon-carbon bond formation reaction when an organotin reagent is coupled with an organic electrophile (typically a halide or a triflate) catalyzed by palladium (Scheme 1.1). Prior to Stille's report on the coupling of acid chlorides with organotins, several papers were published by Kosugi and Migita's group concerning rhodium-catalyzed coupling of acid chlorides with allyl and benzyltins[10], palladium-catalyzed coupling of acid chlorides with alkyl, phenyl and vinyltin reagents[11], followed by palladium-catalyzed coupling between aryl halides with allyltin[12], where it was stated that palladium proved to be superior to rhodium. As a result of extensive mechanistic studies and on-going reaction optimization throughout 20 years, substrate scope for this coupling reaction has been expanded to encompass a broad range of functionalities to which both the tin group and the halide group can be bonded to.

Scheme 1.1: Scope of the Stille Coupling



Scope:

R : alkynyl, alkenyl, aryl, allylic, benzylic, alkyl

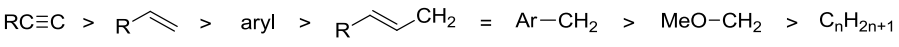
X : I, Br, OTf, Cl (under activating conditions)

R': alkenyl, aryl, acyl, allylic, benzylic

1.2.1 Substrate Scope

Some of the common electrophiles for the coupling reaction include: acid chlorides, benzyl bromides and chlorides, allyl halides and acetates, aryl or heteroaryl halides and triflates, alkenyl halides and triflates, and, to a lesser extent, alkyl or alkynyl halides.[13] While most of the electrophiles mentioned above can be coupled with high efficiency, the coupling of alkyl halides/triflates still require the use of strongly σ-donating phosphine ligands. For example, coupling of primary alkyl bromides and iodides require the use of P(*t*-Bu)$_2$Me and PCy(pyrrolidinyl)$_2$ as the ligand when vinyl- and arylstannanes are used, respectively.[14,15] Further advancement on the coupling of unactivated secondary bromides with arylstannanes requires the *in situ* generation of the corresponding aryltrichlorotin by treatment with $SnCl_4$, followed by the nickel-catalyzed coupling with the electrophile.[16] This nickel-catalyzed reaction presumably proceeds via an "organostannoate" complex formed between alkyltrichlorotin and potassium *t*-butoxide.[17, 18] To date, no coupling reaction between an alkyl chloride and any organotin reagent has been reported.

The scope of the nucleophilic tin partner for Stille Coupling has been expanded to include alkyltins, allyl- and benzyltins, aryl- and heteroaryltins, alkenyltins, alkynyltins, acyltins, hexaalkylditins, and tin hydrides.[13] One way of gauging the relative reactivity between different alkyl groups attached to the tin atom is by comparing the order for the relative rate of group transfer when trimethyl- or tributyltin are used as the anchoring group:

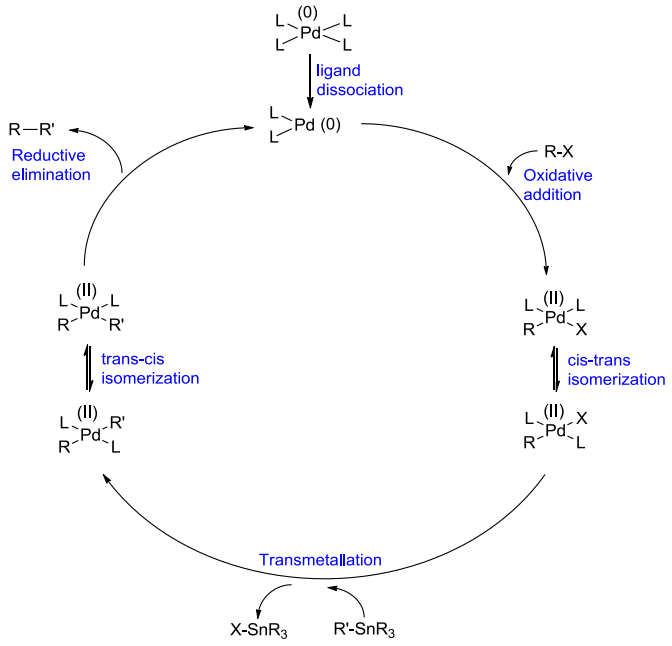


While aryl-, heteroaryl-, and alkenyltin compounds are routinely used as coupling partners with a variety of electrophiles in the synthesis of complex molecules[19], examples of using alkyltin reagents containing an sp^3-hybridized carbon-tin bond as the nucleophile are still scarce. This is partly due to the reluctance of alkyltins to undergo transmetallation, a step that brings the organic groups of both coupling partners onto the palladium center.

1.2.2 Catalytic Cycle

The Stille Coupling reaction follows a catalytic cycle with respect to palladium[20] (Figure 1.2). The underlining mechanism of the reaction is comprised of the following steps: oxidative addition of palladium(0) across a C-X bond to form an organopalladium species, subsequent transmetallation between the organopalladium(II) species and organotin generate a diorganopalladium(II) complex, which is followed by reductive elimination of the diorganopalladium(II) complex to form the coupled product and restore the active palladium(0) catalyst for the next catalytic cycle.

Figure 1.2: General catalytic cycle for Stille Coupling reactions



While palladium(0) typically undergo facile oxidative addition across iodine- and bromine-carbons bonds to generate the *cis*-[PdL_2RX] complex, chlorine-carbon bonds tend to be more difficult to insert. One can rationalize the observed differences in the reactivities of these halides by looking at their bond dissociation energies: 96 kcal/mol (Ph-Cl bond), 81 kcal/mol (Ph-Br bond), and 65 kcal/mol (Ph-I bond).[21] Triflates are widely referred to as pseudohalides. They also undergo facile oxidative addition with palladium(0) in the presence of a stoichiometric amount of LiCl to stabilize the cationic palladium(II)

species formed after oxidative addition.[22] The relative reactivity of a C-OTf bond for palladium insertion is on par with a C-Br bond, despite having a higher bond dissociation energy than a C-Cl bond, 101.5 and 90.6 kcal/mol, respectively.[23] A computational study has attributed the unique reactivity of the C-O bond of an aryl triflate to its lowering of LUMO energy to a greater extent upon sufficient C-O bond distortion prior to cleavage by the nucleophilic palladium.

Reductive elimination of the diorganopalladium(II) species takes place after transmetallation in order to liberate the coupled product and regenerate an active palladium(0) catalyst. This step is also facile provided that the diorganopalladium(II) complex has a *cis* geometry with respect to the two organic groups. Espinet and Casado have shown that through a dissociative transmetallation pathway, the corresponding T-shaped *cis*-[PdRR'L] complex is produced and undergoes the subsequent reductive elimination without the need to isomerize.[24]

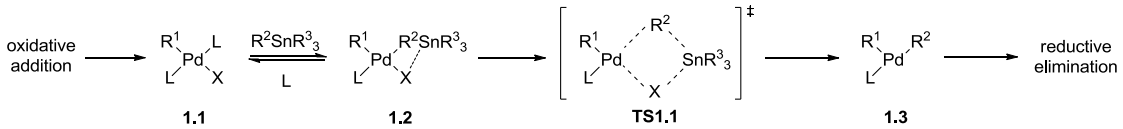
1.2.3 Transmetallation

Transmetallation is, in most cases, the rate-determining step of the overall coupling reaction.[25] Exceptions include the couplings of unactivated aryl chlorides, where oxidative addition becomes the rate-determining step.[21] This is evident as kinetic studies of Stille coupling reactions typically reveal first order rate dependences with respect to both the organostannane and the palladium catalyst, while zeroth order with respect to the electrophile.[24] Studies by Espinet and coworkers have led them to propose that, depending on the reaction conditions (solvent, ligand and the electrophile), two distinct mechanisms may operate: a closed-S_E2 or an open-S_E2 mechanism.[24,26,27]

When the coupling reaction involves the use of a vinyl or an aryl halide in a solvent of low to moderate coordinating ability and an L:Pd ratio of greater than 2:1, a closed-S_E2 mechanism is the most favoured one during transmetallation.[24] This implies that immediately following oxidative addition and *cis*-*trans* isomerization to generate *trans*-[PdR^1XL_2] complex **1.1**, a dissociative L-for-R^2 ligand

substitution takes place to produce complex **1.2.** Complex **1.2** then transmetallates with organotin via a cyclic transition state **TS1.1** to give a T-shaped three-coordinate *cis*-[PdR^1R^2L] species **1.3** that undergoes facile reductive elimination without subsequent isomerization to give the coupled product (Scheme 1.2). Since this mechanism requires dissociation of one ligand on palladium complex **1.1** prior to coordination of the stannane, having excessive ligand or the use of strongly σ-donating ligands can slow down the rate of reaction.

Scheme 1.2: Cyclic-S_E2 transmetallation mechanism



When there is a lack of bridging ligand during transmetallation and through the use of a highly polar solvent, the closed-S_E2 transmetallation mechanism is replaced by another mechanism – an open-S_E2 transmetallation.[26] The open-S_E2 transition state usually takes place when a pseudohalide (usually a triflate) is used in place of a halide, since triflates are poorly coordinating anionic ligands that lack bridging ability. However, even if a halide is present in the coordination sphere of palladium after oxidative addition, under certain conditions, the halide can still be displaced from the coordination sphere to promote an open transition state. Going through an open-S_E2 transition state during transmetallation implies an X-for-R^2 or L-for-R^2 substitution at the *trans*-[PdR^1XL_2] or *trans*-[PdR^1L_3] complex, which can lead to competitive *cis* and *trans* arrangements of the transmetallation product. The use of polar, coordinating solvents lacking bridging ability should also favour this mechanism. Espinet *et al*. proposed the involvement of an equilibrium between **1.4** and **1.5** prior to the transmetallation (Scheme 1.3).[27] The direction of this equilibrium is strongly dependent on the solvent, the ligand used and the reaction temperature. It is stated that there are two competing open-S_E2 mechanisms operating during transmetallation to give two diorganopalladium(II) complexes – S_E2 (open-*trans*) and S_E2 (open-*cis*), see Figure 3. It was concluded that the geometry of the transmetallation product, although mechanistically

very relevant, is less significant from a synthetic point of view, as the rate of isomerization between **1.6** and **1.7** contribute very little to the overall rate of reaction.

Scheme 1.3: Open-S_E2 transmetallation mechanism

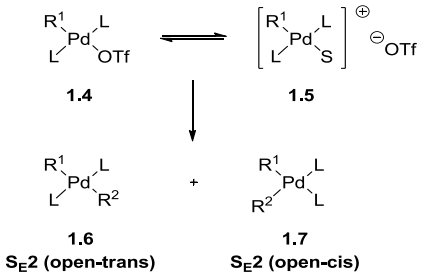
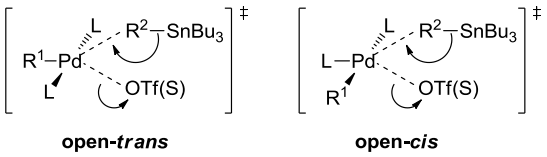


Figure 1.3: Open-S_E2 transmetallation transition states



1.2.4 Ligands

Since its inception in the 1970's to prepare ketones from acid chlorides and organotin compounds[6], Stille coupling reactions have been carried out with triphenylphosphine (PPh_3) as the standard ligand for palladium. The discovery of the use of tri-(2-furyl)phosphine (TFP) as a highly effective ligand for the coupling to make 3-(triflyloxy)cephems in 1990 by Farina and coworkers[28] marked a big advancement in the Stille methodology. The highly dissociative nature of TFP and $AsPh_3$[29] have accelerated the rate at which the coupling reactions proceed, so that they can be run under milder reaction conditions.

Ligand effects can be described in terms of their steric and electronic properties by Tolman cone angle (θ), and infrared carbonyl stretching frequency (ν), respectively.[30] Ligands having higher θ values correspond to having a greater steric bulk, and are more spatially demanding than those with comparatively lower θ values. The parameter ν is used to quantify the σ-donicity of a ligand, or how

much electron density is transmitted from the phosphine to the metal center. The infrared carbonyl stretching frequency for one particular ligand may differ from case to case depending on both the metal used and its oxidation state. In their review article on tris-(2-furyl)phosphine (TFP) as ligand for transition metal-catalyzed organic synthesis, Keay and Andersen tabulated the electronic properties of some of the common phosphine ligands.[31] As the subject of this thesis revolves heavily on the survey of phosphine ligands, the stereoelectronic properties (i.e., θ and ν) of a selected number of phosphines are displayed in Table 1.1.

Table 1.1: Steric and electronic properties of selected phosphines[31]

ligand	cone angle (θ)	ν (cm^{-1})	pka[a]
PMe_3	118°	2064.1	8.65
PEt_3	132°	2061.7	8.69
$P(2\text{-furyl})_3$	133°		
PBu_3	136°	2060.3	8.43
$AsPh_3$	142° [c]		
PPh_3	145°	2068.9	2.73
$P(4\text{-Tol})_3$	145°	2066.7	3.84
PCy_3	170°	2056.4	9.70
$P(t\text{-Bu})_3$	182°	2056.1	11.40
$P(C_6F_5)_3$	184°	2090.9	
$P(2,4,6\text{-MeO-}C_6H_2)_3$[b]	184°	2048.0	11.20
$P(2\text{-Tol})_3$	118°	2066.6	

[a] Referring to the corresponding protonated phosphonium[33]
[b] See reference 32
[c] See reference 24

It has been known that the use of PPh_3 in large amounts (L:Pd ratios of greater than 2) slows the coupling reaction. This has prompted the use of coordinatively unsaturated catalyst, "$Pd(PPh_3)_2$", which

is generated *in situ* and results in higher turnover rates. Unfortunately, the catalyst usually suffers from thermal decomposition prior to reaction completion, giving unsatisfactory results.[34] It was shown in Farina's studies[25] that ligands with high σ-donicity (those with low ν or high pK_a values) typically display both lower initial coupling rates and lower yields than those with low σ-donicity. This is because a ligand needs to dissociate from the palladium center prior to the transmetallation step, but ligands with high σ-donicity are more tightly bound to palladium. The authors concluded that no clear correlation could be drawn from the steric property of the ligand on the coupling rate, since ligands with similar cone angles, but different electronic properties, can confer drastic differences on the reaction rate. Furthermore, ligands that result in slower rates were shown to have greater inhibition factors, i.e., the ratio of rates obtained when L:Pd = 2:1 vs. those with L:Pd = 4:1, than those with smaller inhibition factors. This provides more evidence for the importance of ligand dissociation for transmetallation of vinylstannanes to take place.

1.3 Stille Coupling in Natural Products Synthesis

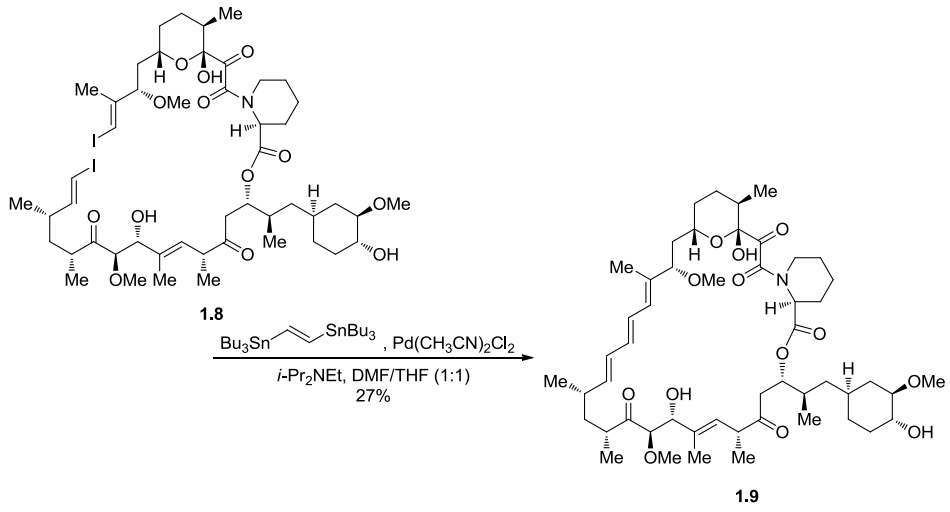
There are two distinct advantages of employing organotin compounds as intermediates in organic synthesis. First of all, the triorganotin moiety is quite tolerant to a broad range of functional groups present in organic molecules, which makes it possible to carry out reactions in the presence of functionalities such as nitro, nitrile, olefin, ether, ester, and other carbonyl derivatives.[6] Secondly, organotin compounds, unless under special circumstances, are relatively insensitive to moisture and oxygen, which makes their isolation, storage, and manipulation possible without employing stringent maneuvers. Due to these two criteria, on top of their well-known capability of undergoing carbon-carbon bond formation between two unsaturated carbon atoms, they still enjoy much popularity in the synthesis of complex natural products.[19]

One reason that Stille coupling is so reliable as a synthetic method is because of their ability to connect two alkenyl fragments without changing either of the double-bond geometries, a manifestation of

the well-established trait that all steps of the catalytic cycle proceed with retention of the double-bond geometry from both partners.[35] Because of this well-known trait, in addition to the ease of preparing vinylstannanes, chemists often apply Stille coupling as a means of stitching together cyclic moieties of natural products from their acyclic precursors.[19] Three examples of brilliantly executed synthesis of natural products are presented here to showcase the power of Stille coupling, two of which involve macrolide formations.

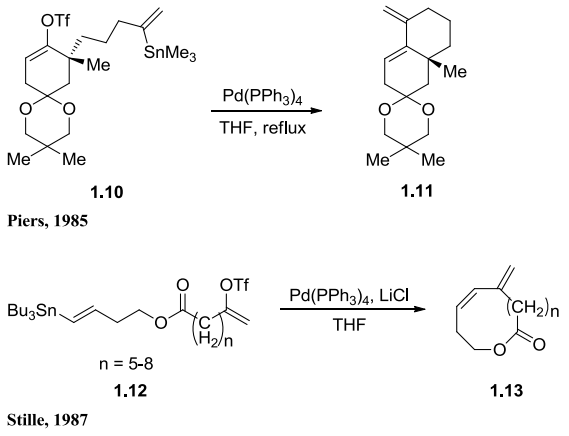
The first total synthesis of the naturally occurring enantiomeric form of rapamycin was accomplished by the Nicolaou group by incorporating a pioneering "stitching-cyclization" process using Stille coupling to effectively create a triene moiety while cyclizing the acyclic precursor.[36] Rapamycin was of great interest because it possesses potent antibiotic, cytotoxic, and immunosuppressive activities in one single, yet complex, molecule. Its structural features: a 31-membered ring, plethora of asymmetric and geometric centers, and sensitive functionality, presented the synthetic community in the early 1990's a formidable challenge. The authors' strategy was to use *trans*-vinylenedistannane to stitch together the two vinyliodides at the two termini of the acyclic precursor through Stille coupling. By employing a mild condition, $Pd(CH_3CN)_2Cl_2$ and Hunig's base in DMF/THF, they avoided substrate instability problems, deprotection steps, and late stage oxidation state adjustments in one step (Scheme 1.4).

Scheme 1.4: Stille coupling of the acyclic rapamycin precursor



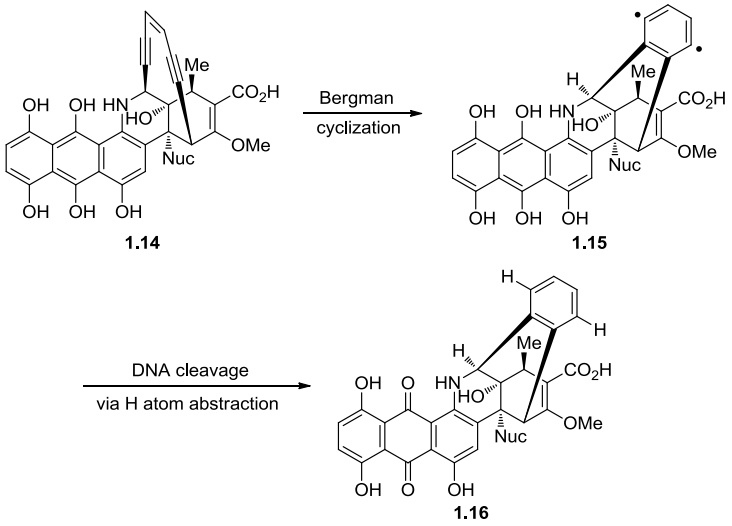
The application of Stille coupling to the construction of a macrolide moiety as part of a complex natural product was inspired and guided by Piers[37] and Stille's[38] independent reports concerning the making of cyclic structures by intramolecular coupling processes. While Piers studied the intramolecular cross-coupling of stannyl enol triflates as a novel annulation method to make fused-bicycles of five- and six-membered rings, Stille used the same method to gain access to macrolidic lactones of varying sizes (Scheme 1.5).

Scheme 1.5: Early works on cyclizations based on Stille coupling



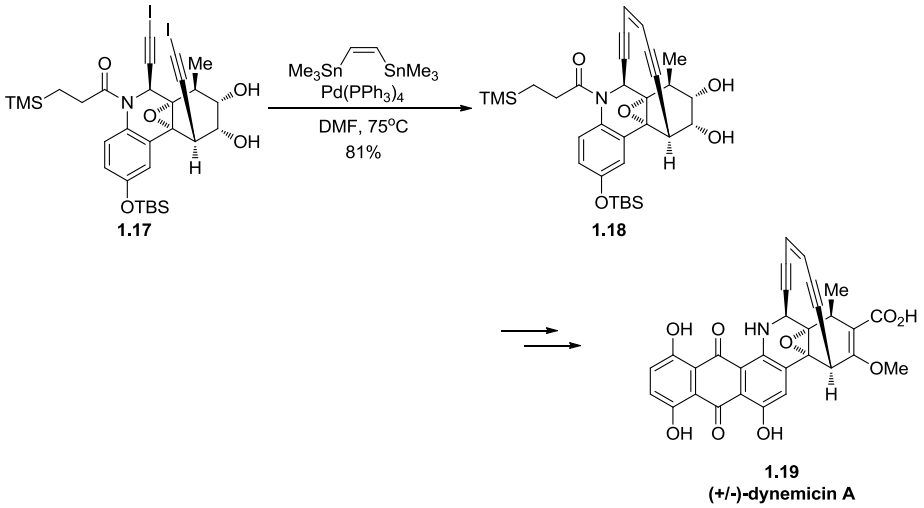
The second illustrative example of Stille coupling in natural product synthesis was another "stitching-cyclization" reaction using *cis*-vinylenedistannane with a di-alkynyliodide for making the key intermediate of (±)-dynemicin A by Danishefsky's group.[39] Dynemicin A was, at the time, the newest member of the enediyne familiy of antibiotics. It was isolated as a metabolite of *Micromonospora chersina* and displayed high levels of *in vitro* antitumor activity. In addition, upon intake of dynemicin, mice inoculated with leukemia cell lines were longer-lived. However, despite its promise as a medicinal agent, there was an inherent difficulty in its accessibility and lability. The established mode of action of dynemicin and its derivatives originates from the 1,4-aromatic diradical generated from Bergman cyclization of the enediyne moiety found in the precursor. The resulting high energy diradical can then subject DNA to cleavage through hydrogen atom abstraction.

Scheme 1.6: Biological mode of action of dynemicin A



Cyclization to form the enediyne moiety proved to be a challenge for Danishefsky's group. One of the two approaches involved stitching of the two-carbon ethylene unit with the *syn* configured diyne utilizing palladium-catalyzed cross-coupling strategy, presumably because of precedent literature examples of cyclization of unsaturated units using such methodologies. The authors first attempted cyclizing the diyne group by a Sonogashira reaction, since alkynes have been known to cross-couple with vinyl halides. Unfortunately, after numerous attempts under the standard Pd(0)/Cu(I) condition, no cyclized product was observed whatsoever. Attention was then turned to installing the ethylene unit through Stille coupling using *cis*-1,2-distannyl ethylene and bis-iodoalkyne in dilute solution to finally get the cyclized product in a good 81% yield. It is worth noting that the presence of the epoxide group was vital to the success of the tandem Stille coupling cyclization reaction, as it forced the molecule to adapt a necessary conformation that "might serve to shorten the approach of the two ethynyl units while providing some relief from the projected strain in the cyclization product".[39]

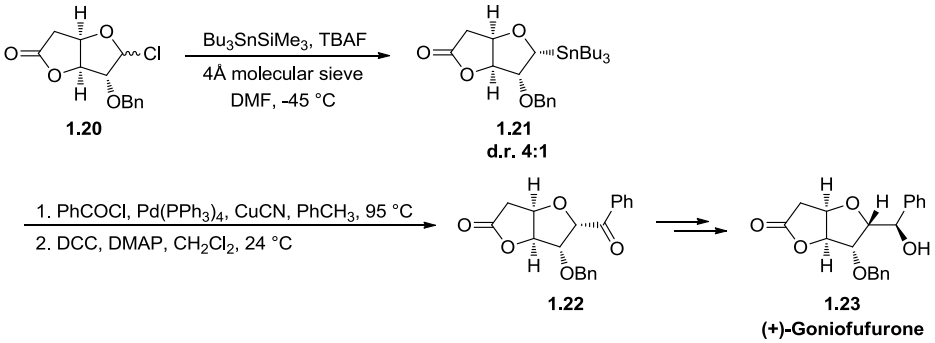
Scheme 1.7: Stille coupling cyclization of a key intermediate *en route* to dynemicin A



The third example of natural product synthesis using Stille coupling is the synthesis of (+)-goniofufurone reported by Falck and coworkers.[40] Goniofufurone was isolated from the stem bark of *Goniothalamus gigontens*, and attracted attention due to its cytotoxicity towards several human tumor cell lines. Its structural features include a highly functionalized tetrahydrofuran ring and a γ-lactone ring, the two being fused together. At the time of the reported synthesis, synthetic chemists relied mostly on intramolecular Michael additions to unsaturated ester/lactone for creating fully substituted tetrahydrofuran rings, but Falck and coworkers demonstrated the synthetic utility of their newly-developed stereospecific Stille coupling by generating a stereocenter on the tetrahydrofuran ring leading to (+)-goniofufurone. This was the very first time that a Stille coupling proceeding with almost complete retention of configuration at an sp^3 center was used reliably in a natural product synthesis. The respective chiral α-alkoxystannane was synthesized from its corresponding chloride in a diastereoselective chloride substitution, giving a 4:1 diastereomeric ratio of the stannane (Scheme 1.8). Subsequent TLC separation gave the desired diastereomer without much complication. Stille coupling followed by DCC/DMAP treatment (necessary to re-lactonize a small amount of *seco*-acid) afforded the ketone intermediate. Finally, diastereoselective reduction using lithium tri-*tert*-butoxyaluminum hydride and debenzylation furnished the target molecule in a concise fashion. Even though this last synthesis is a rather concise one,

it highlights two important aspects central to the topics of this dissertation: preparation of chiral α-alkoxystannanes and the Stille coupling of these compounds.

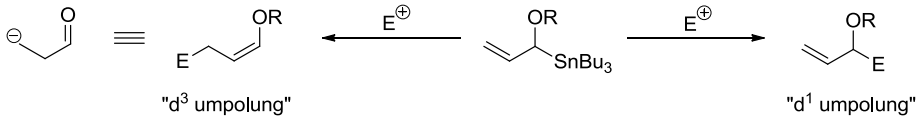
Scheme 1.8: Stille Coupling in the synthesis of (+)-goniofufurone



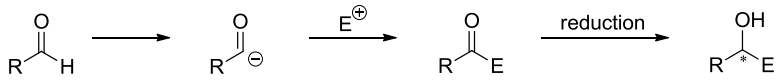
1.4 α-Alkoxyorganostannanes in Organic Synthesis

Because of the way that the carbon-tin bond is positioned adjacent to an oxygen, α-alkoxyorganostannanes display unique "umpolung" reactivity compared to ordinary aldehydes, where the carbonyl group can only behave as an electrophile. The term was appropriately used when Quintard and coworkers described the selectivities associated with using α-alkoxyallyltributyltins as synthetic reagents.[41] While allyltin compounds have been known for addition to carbonyl derivatives and cross-coupling with organic halides, putting an oxygen group introduces complexity in terms of the possible reaction outcomes. For example, allyltin derivatives have been known to react with or without allylic rearrangement to give rise to two possible regio-isomeric products. When the α-alkoxy group is considered, depending on whether an allylic rearrangement occurs or not, these stannanes can act as d^3 or d^1 "umpolung" reagents (Scheme 1.9).

Scheme 1.9: Umpolung reactivity of α-alkoxyallyltin reagents

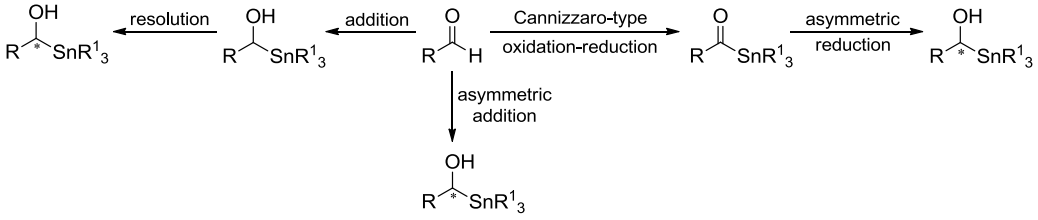


The "d^1 umpolung" reactivity of α-alkoxystannanes is of interest to us and other groups because it is the only displayed reactivity when working with non-allylic groups. One way of visualizing it is that it can be thought of as a nucleophilic aldehyde followed by subsequent reduction to the corresponding secondary alcohol:



The ability to achieve a reversal of an electrophilic aldehyde reacting with a nucleophile equates to expanding the substrate scope to include electrophilic coupling partners for the aldehyde. In addition, it is possible to achieve asymmetric variants of these umpolung reactions by introducing the α-chiral center at one point or another during the synthetic operation.

Scheme 1.10: Incorporation of chiral center into α-hydroxystannanes

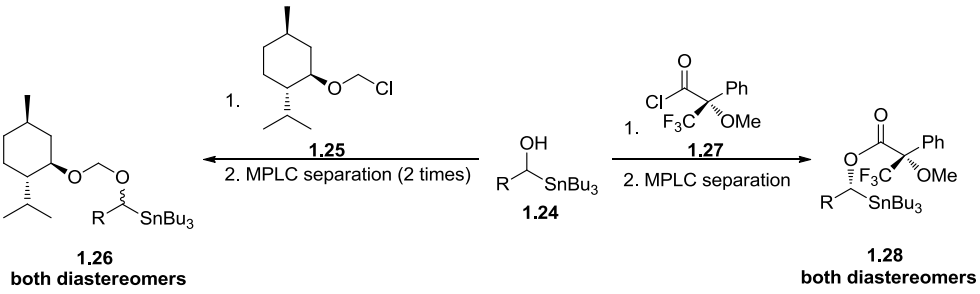


1.4.1 Asymmetric Synthesis of α-Alkoxyorganostannanes

Earlier methods for making chiral α-alkoxystannanes have relied mostly on the resolution of racemic stannanes via their diastereomeric ether or ester derivatives. The earliest example involved derivatization of the hydroxystannane with (-)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(-)-MTPA-Cl] to give a diastereomeric mixture of the MTPA ester, or better known as Mosher's ester.[42] Separation of the diastereomers can then be carried out using MPLC. Deprotection followed by protection with BOM-Cl gives the optically active substrate as essentially one enantiomer. Later on, another resolution was carried out by forming the corresponding menthyloxymethyl (MenOM) ether from chloromethylmenthyl ether. Although a modest diastereomeric excess of 80-85% could be obtained after

a single flash column run using this method, purities greater than 90-95% d.e. required two passes over MPLC.[43]

Scheme 1.11: Resolution of α-alkoxystannanes

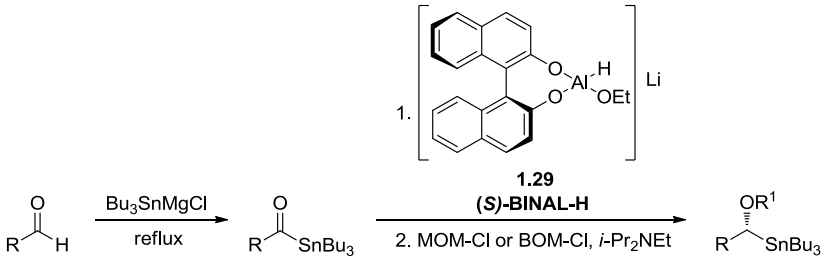


Another resolution was developed based on ring opening of chiral stannyl acetals using organometallic reagents by Nakai and coworkers.[44] While good diastereoselectivity was obtained with alkyl Grignard reagents as the nucleophile (up to >95% d.e.), changing the nucleophile to a phenyl Grignard reagent demolished the selectivity by a huge amount (20% d.e.). Enzymatic resolutions were also developed by Itoh[45] and Chong[46], that utilized lipase P (*Pseudomonas sp.*) for the selective hydrolysis of α-acyloxystannanes and porcine pancreatic lipase for selective acylation of α-hydroxystannanes, respectively. Even though the latter method showed significantly improved yields and enantioselectivities over selected substrates, it and Itoh's method both are rather limited in terms of their substrate scopes and reaction efficiencies, greatly detracting from being the ideal preparation methods.

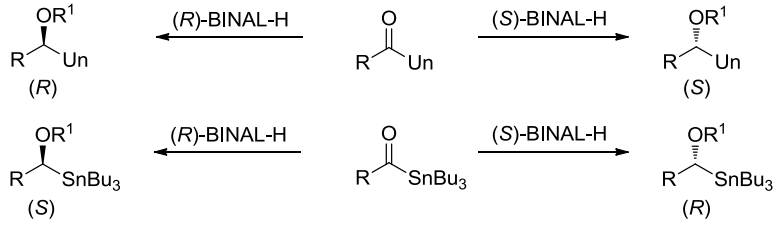
Of the possible methods for preparing chiral α-alkoxystannanes, the Chong group has developed two that rely on the asymmetric reduction of acylstannanes and the resolution of racemic carbamylstannanes. The former method[47] is another application of the chiral 2,2'-dihydroxy-1,1'-binaphthyl lithium aluminum hydride (BINAL-H) that was developed by Noyori for asymmetric reduction of ketones. The acyl-stannanes to be reduced could be prepared via a Cannizzaro-type reaction by reacting an aldehyde with tributylstannyl Grignard reagent.[48] Reduction of the resulting acylstannane could then be carried out at -78˚C to give good enantiomeric excess (Scheme 1.12). It was also

established that the sense of asymmetric induction was in line with Noyori's empirical rule provided one treats the tributyltin group like the unsaturated group (Scheme 1.13).

Scheme 1.12: Asymmetric reduction of acylstannanes using (*S*)-BINAL-H

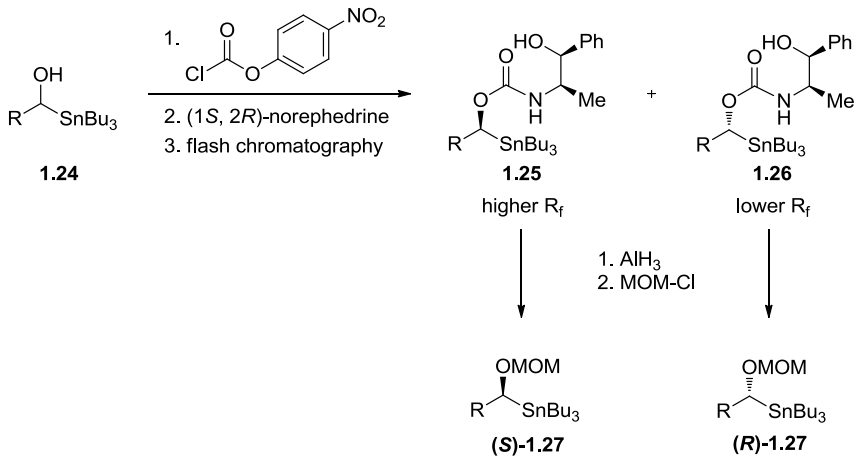


Scheme 1.13: Asymmetric induction of acylstannane reduction



Despite the promising selectivity, reduction of acylstannanes using BINAL-H on large-scales was reported to suffer from rapid decomposition of acylstannanes to the tin carboxylates in the presence of oxygen.[49] In 2002, the Chong group reported another method for the preparation of enantiomerically enriched α-alkoxystannanes by resolution of diastereomeric carbamate derivatives of racemic hydroxystannanes.[50] Using enantiomerically pure norephedrine as the derivatizing agent, various α-hydroxystannanes containing aliphatic alkyl chain were separated in good yields and selectivities. The resulting enantiomerically enriched carbamylstannanes can be deprotected with AlH_3 followed by re-protection with MOM-Cl to give the starting material for subsequent reaction (Scheme 1.14). The distinct advantages that this methodology offered compared to the older ones are that it is both operationally simple, and can easily be carried out on multigram scales.

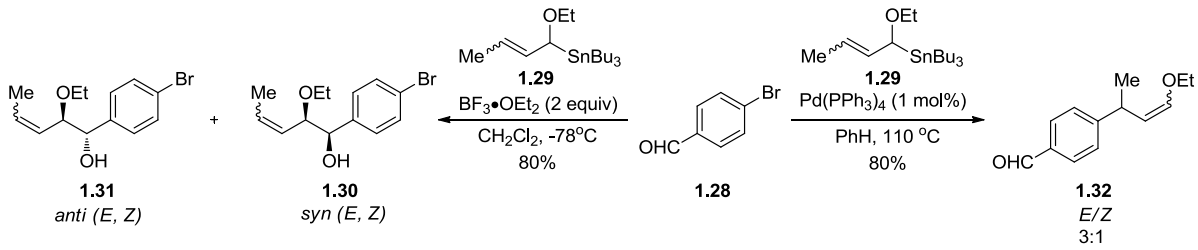
Scheme 1.14: Resolution of racemic α-carbamylstannanes



1.4.2 Reactions Involving Enantiomerically Enriched α-Alkoxyorganostannanes

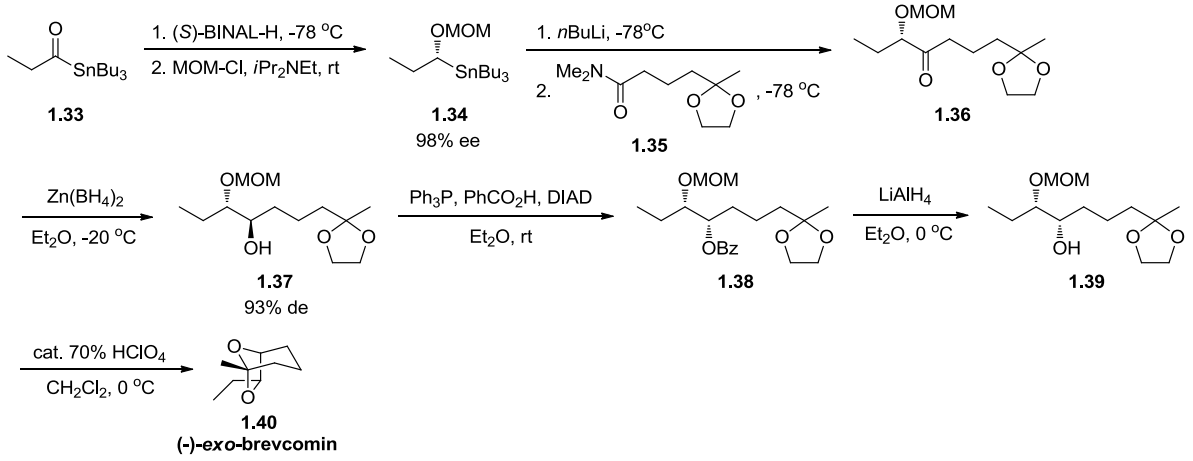
The versatility of α-alkoxystannanes lies in the ability of the trialkyltin group to undergo transmetallation with various metals to generate other organometallic species that are capable of reacting with electrophiles. In addition, excellent chemoselectivity may be displayed depending on the transmetallating agent selected. This can be best demonstrated by Quintard and coworkers' studies on α-alkoxyallyltins[41], where they reported chemoselective reactions with aldehyde or with bromine by using either stoichiometric amount of Lewis acid or palladium catalyst, respectively (Scheme 1.15). This illustrates d^3 and d^1 umpolung reactivity in action, even though stannane **1.29** is racemic.

Scheme 1.15: Chemoselective reactions of α-ethoxyallylstannane



The development of asymmetric reduction of acylstannanes using chiral BINAL-H reagent by the Chong group helped facilitate studies of stereospecific lithiations followed by carbonyl substitution reactions and Michael addition reactions. First of all, through tin-lithium exchange to generate the corresponding α-alkoxyorganolithium reagent, which is stabilized by the MOM ether, Chong and Mar showed that it is possible to generate 1,2-diols stereoselectively from an amide.[51] The amide substitution reaction by the *in situ* generated α-alkoxyorganolithium proceeded with clean stereospecificity to give the resulting α-alkoxyketone. Subsequent chelation-controlled diastereoselective reduction using $Zn(BH_4)_2$ proceeded with a good 93% d.e. of the *anti*-diol. Deprotection followed by cyclization afforded (−)-*exo*-brevicomin in seven short steps from acylstannane **1.33** (Scheme 1.16).

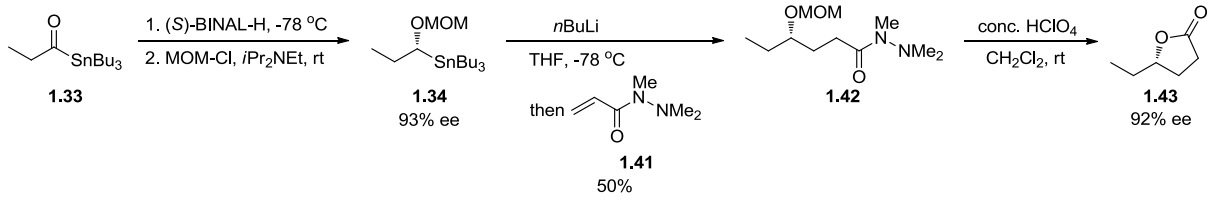
Scheme 1.16: Synthesis of (-)-*exo*-brevcomin using acylstannane



A second type of reaction involved generation of the configurationally stable α-alkoxyorganolithium species and its stereospecific electrophilic trapping uses a Michael acceptor – an acrylic acid trimethylhydrazide, as the electrophile.[52] It is note-worthy to point out that no copper is needed for this conjugate addition. Even though the highly hindered acrylic acid tetramethylpiperidide could be used as the Michael acceptor, subsequent cyclization of the γ-hydroxyamide to make the corresponding γ-lactone proved not to be possible. Fortunately, using the trimethylhydrazide analogue successfully afforded substituted γ-lactones in great yields under acidic condition (Scheme 1.17). The

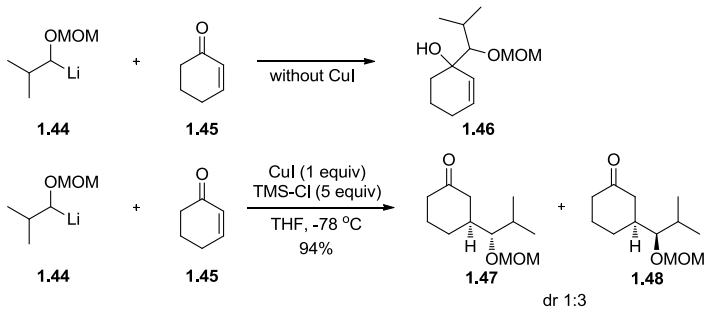
stereospecific nature of the reaction meant that the γ-carbon of the lactone possesses defined stereochemistry.

Scheme 1.17: Stereoselective synthesis of γ-lacone from acylstannane



Besides organolithium species, α-alkoxyorganostannanes can also be used as precursors to generate organocuprate reagents that can undergo 1,4-conjugate addition. Linderman and Godfrey showed that, in the absence of a copper source, namely CuI, addition of a simple α-alkoxyorganolithium to cyclohexenone occurs exclusively in a 1,2- sense, and the adduct is quite unstable.[53] Addition of CuI successfully promoted 1,4-addition to the same acceptor, presumably via formation of higher-order cuprate complex. Reaction optimization resulted in a significantly improved yield with the addition of 5 equivalents of TMS-Cl (Scheme 1.18). The improved procedure was developed by Corey and Boaz, and the explanation behind the greater yield was proposed to be due to the irreversibility and a reduction in competing enolate reactions in the presence of TMS-Cl as opposed to not having it.[54]

Scheme 1.18: Chemoselective addition of α-alkoxyorganolithium



1.5 Purpose and Scope of the Thesis

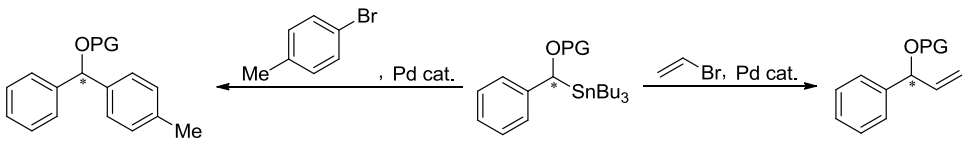
As mentioned in this chapter, palladium-catalyzed cross-coupling reactions represent one of the most powerful tools in the arsenal of organic chemists. In particular, Stille coupling of organostannanes with electrophiles can take place in a sufficiently mild manner that it is a popular choice for incorporating into natural product syntheses. What makes it such a reliable technique, particularly in constructing macrolidic structures, is its ability to faithfully retain the double bond geometry of both coupling partners. Moreover, enantioenriched α-alkoxyorganostannanes have emerged as a chiral umpolung reagents of aldehydes. Their capability to undergo transmetallation with other metals followed by stereospecific trapping provides them with potential to be used in asymmetric synthesis. The focus of this thesis will be to merge these two subjects together and examine the degree of stereospecificity for Stille coupling of α-alkoxyorganostannanes, particularly α-alkoxybenzylstannanes. Discussion will also be made regarding the optimization of the reaction.

Chapter 2. Stille Coupling of Racemic α-Alkoxybenzylstannanes

2.1 Introduction

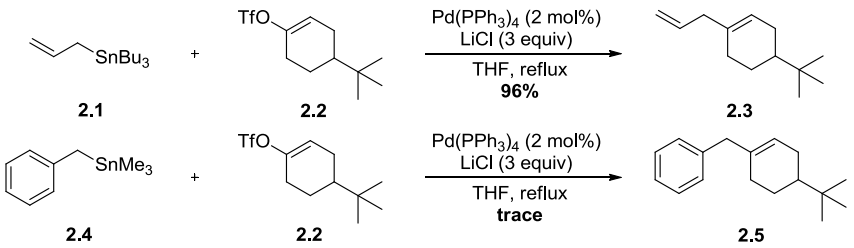
As mentioned previously, α-alkoxyorganostannanes can serve as important aldehyde umpolung reagents for building complex organic molecules because they imply the use of electrophilic partners. α-Alkoxyorganolithium reagents generated from these stannanes have been shown to add to a variety of electrophiles, including carbonyl derivatives[1,2], α, β-unsaturated carbonyls[3], alkyl halides[1,4], and CO_2.[5] Other reactions include intramolecular cyclization with allylic halides[6] and carbamate-substituted alkynes[7]. Even though these electrophiles on their own cover a broad spectrum of possible transformations for α-alkoxyorganostannanes to undergo, the use of organolithiums limits the choice of reagents to those that can withstand their high reactivity, even when the temperature is kept low. In addition, electrophiles such as alkenyl and aryl halides will not undergo substitution reactions with organolithiums. It is therefore highly desirable, from a synthetic point of view, to find ways to incorporate these sp^2 organic halides as electrophilic partners to expand the substrate scope of reactions with α-alkoxyorganostannanes. The ability to achieve this would overcome some of the challenges currently faced by the synthetic community. For example, coupling of enantiomerically enriched α-alkoxybenzylstannane with vinyl or aryl halide would give products that may otherwise be hard to obtain from conventional asymmetric reduction of ketones or 1,2-addition to aldehydes (Scheme 2.1).

Scheme 2.1: Stille coupling of α-alkoxybenzylstannane with aryl- and vinylbromides



However, cross-coupling of sp^3 organostannanes may not be as simple as the sp^2 analogues. There are several factors to consider when designing a successful coupling reaction. For instance, Stille reported the palladium-catalyzed coupling of vinyl triflates with organostannanes back in 1986[8], where attempts were made to try to couple allylstannane and benzylstannane with 4-*tert*-butylcyclohexenyl triflate. While one would not expect significant difference in terms of reactivity between an allylic group and a benzyl group in a S_N2-sense or the difference between pK_a values of an allylic proton or a benzylic proton. But a large difference was observed between the coupling of an allylstannane and a benzylstannane with vinyl triflate **2.2** (Scheme 2.2), even when benzyltrimethyltin was used to decrease the steric crowding during transmetallation.

Scheme 2.2: Difference between the reactivity of allyltributyltin and benzyltributyltin in Stille coupling



The observed difference between the yields of **2.3** and **2.5** can either be steric or electronic in nature, or both. In a sterics argument, a benzene group is larger than an ethylene group, and the transmetallation step of palladium-catalyzed reactions are known to be sensitive to sterics around the palladium center. Therefore one would think that transmetallation may not be as favourable for the benzyl group compared to the allyl group, even when the less bulky trimethyltin group is used. However, it makes more sense to consider, from an electronics perspective, that an allyltin molecule will more readily form a π-complex with palladium, leading to a greater rate of transmetallation, than does a benzyltin. Regardless of the predominant influence on the reaction yield, the observed difference is a fact, which leads to the notion of having to consider the "anatomical traits" of an α-alkoxyorganostannane if one is to have much success with its cross-coupling.

2.2 Anatomy of α-Alkoxyorganostannanes

When considering the anatomy of an α-alkoxyorganostannane, there are three structural aspects to examine: the nature of the transferable group attached to tin, the protecting group for the oxygen, and the α-alkoxy group as a whole.

2.2.1 The α-Alkyl Substituent

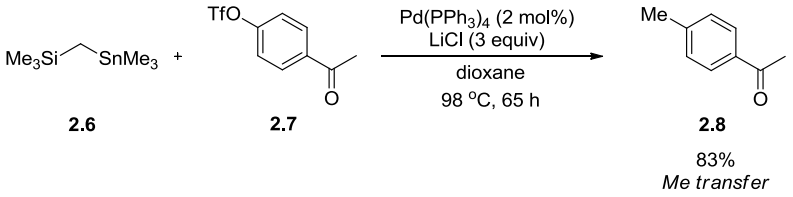
While Stille has established the well-known order of group transfer from trimethyl- or tri-*n*-butyltin compounds[9] (see Chapter 1), the focus of this work is on benzylic system, having intermediate reactivity between sp^2 organostannanes and saturated sp^3 organostannanes. One note-worthy pitfall with the trend is that although benzyltin and allyltin are widely viewed as possessing similar reactivities, due to the ability of allyltin to form π-complex more readily with the palladium center prior to transmetallation, allyltins should be considered more reactive than the corresponding benzyltins (Scheme 2.2). The π-complexation phenomenon is part of complexation-induced proximity effect (CIPE)[10], the focus of the next section.

2.2.2 The α-Alkoxy Group

The pre-formation of a π-complex between the allyltin and palladium center is what makes the allyltin much more reactive than a benzyltin. To form a π-complex requires the π-bonding electrons of the alkene to fill the empty d^*-antibonding orbital of the palladium center, and through π-backbonding between the empty π^*-antibonding orbitals and the filled d orbitals of the same substrates. The reason that such interactions are important is because together they bring the catalyst bearing one of the organic groups to close proximity with the organostannane, rendering the reaction intramolecular in nature compared to reactions that do not go through pre-complexation. For this reason, the phenomenon can be considered a type of CIPE. Another type of CIPE involves the use of heteroatoms that can provide a lone

pair of electrons from their sp^3-hybridized orbitals to interact with the empty d orbitals of the metal (in this case palladium) to achieve the same proximity effect. In one clear example for the latter case, Yoshida and coworkers demonstrated that the use of a 2-pyridyl-dimethylsilyl group as a directing group turned the otherwise extremely hard to transfer trimethylsilylmethyl group in Stille coupling into a readily transferable group.[11] It was established that no directing group influence, a trimethylsilylmethyl group is one of the hardest groups to transfer from tin in cross-coupling. In fact, when **2.6** was cross coupled with aryl triflate **2.7**, only a methyl group gets selectively transferred (Scheme 2.3).

Scheme 2.3: Competitive methyl transfer from trimethylsilylmethyl group

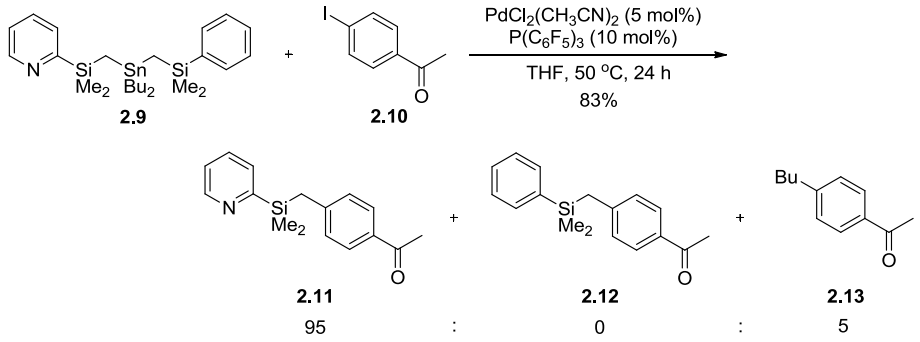


2.6 **2.7** **2.8**

83%
Me transfer

Furthermore, the use of $(Me_3SiCH_2)_4Sn$ resulted in the recovery of starting material even under harsher condition. This demonstrated that the trimethylsilylmethyl group can even act as "dummy" ligands for ordinary alkyl groups in Stille coupling. An intramolecular competition study of **2.9** with aryl iodide **2.10** showed that the 2-pyridylsilyl group far out-competed a phenylsilyl group, highlighting the importance of the nitrogen atom. Interestingly, transfer of the butyl group was also observed in little amounts (Scheme 2.4).

Scheme 2.4: Competition study between 2-pyridyldimethylsilyl group and phenyldimethylsilyl group



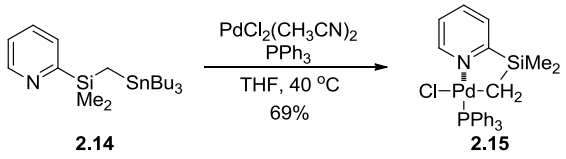
2.9 **2.10**

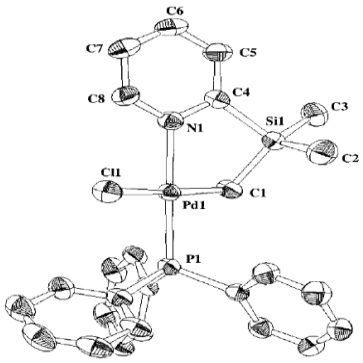
2.11 : **2.12** : **2.13**

95 : 0 : 5

In addition, through the reaction of **2.14** with a stoichiometric amount of $PdCl_2(CH_3CN)_2$, the palladium(II) complex **2.15** was prepared in 69% yield, which gave an X-ray crystal structure to support the coordination of nitrogen to palladium.

Scheme 2.5: X-ray crystal structure of 2-pyridyldimethylsilyl palladium(II) complex[11]



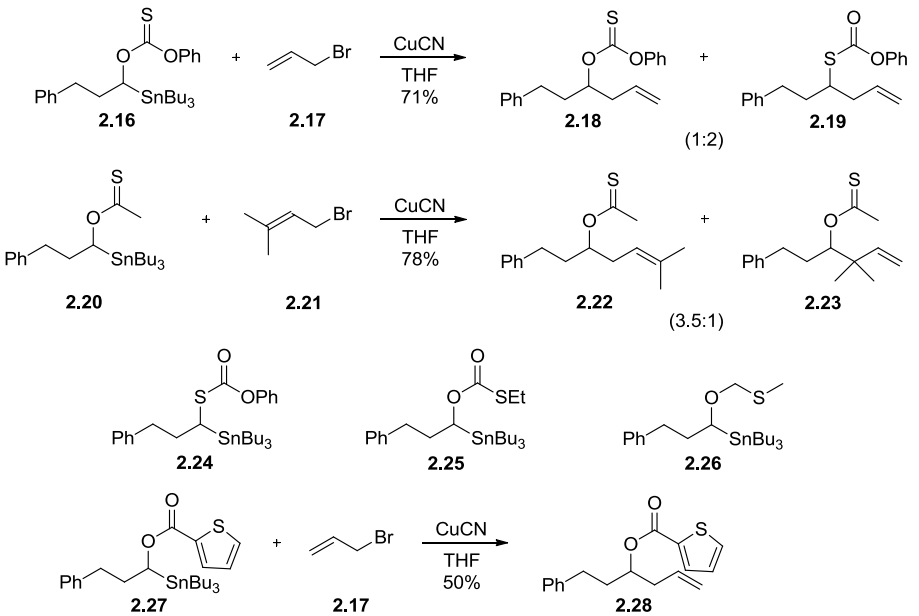


The purpose of the nitrogen-based CIPE presented here is similar to the observed reaction enhancement of allyltin cross-coupling (Scheme 2.2) in that the heteroatom lone pair and the π-electrons both act to bring the palladium center to close proximity with the stannane. In fact, the CIPE phenomenon is also seen in coupling of alkenyltins, where the palladium(II) complex is first brought close in proximity to the tin group in order to break the carbon-tin bond for subsequent transformation. It is partially because of the CIPE that arylstannane compounds are not as good of substrates as alkenylstannanes, and alkylstannanes without the ability to coordinate to palladium are among some of the hardest substrates to couple. CIPE is central to organometallic chemistry.

Having mentioned the influence of CIPE in organometallic chemistry, it is also important to recognize that for complexation between the coordinating heteroatom and the metal, a proper match of softness/hardness and the geometry for complexation are also needed to bring about maximum

effectiveness. One example is given by Falck's study on the copper-catalyzed cross-coupling of sulfur-substituted α-alkoxystannanes with allyl bromide.[12] While thiono-substituted stannanes **2.16** and **2.20** coupled with allyl bromide with satisfactory results, stannanes **2.24**, **2.25**, and **2.26** did not give any product at all. This highlights the importance of the coordination geometry between the sulfur atom and the copper. In **2.24**, the sulfur atom may not be far enough to allow a proper coordination to take place. There is also a marked difference between the softness/hardness between the sulfur atom of a thiono group and that of a sulfide group, as seen in contrasting **2.16** and **2.20** with **2.25** and **2.26**, even though both have their sulfur atoms an equal number of atoms away from where the copper will be positioned upon tin-copper transmetallation. It is interesting to note that for the coupling reaction of **2.16**, an unexpected Newman-Kwart rearrangement was observed. The fact that **2.27** also coupled with modest efficiency with allyl bromide hints at the complexity of the kind of balance that has to be obtained between the softness/hardness matching of the heteroatom with the metal atom and the coordinating geometry of the two.

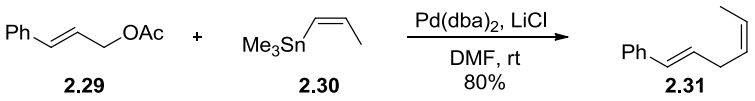
Scheme 2.6: Influence of sulfur-containing protecting group



2.2.3 Leaving Group Ability of the α-Alkoxy Group

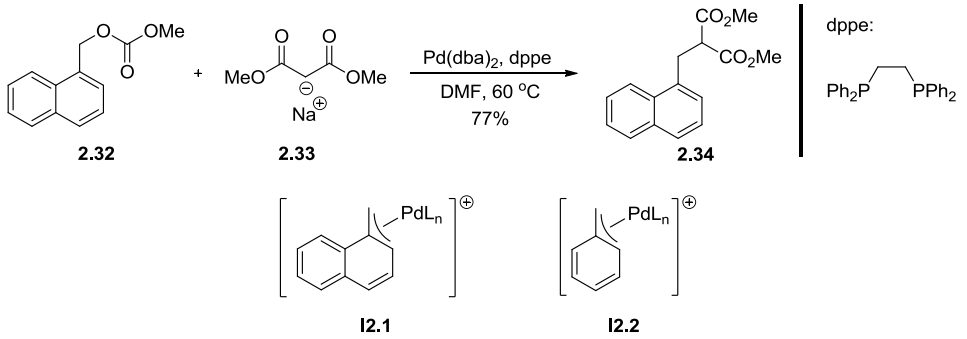
When dealing with allylic-substituted esters, one may run into problematic side-reactions associated with palladium-catalyzed cleavage of the allylic C-O bond that gives a thermodynamically stabilized η^3-allylpalladium(II) complex. This complex is electrophilic in nature and can undergo reaction in the presence of any nucleophilic species present. For example, the allylpalladium complex derived from **2.29** can readily undergo transmetallation with *cis*-alkenylstannane **2.30** to give coupled product **2.31** in high yield under conditions as mild as room temperature (Scheme 2.7).[13]

Scheme 2.7: Cross-coupling of allylic acetate and vinyltin



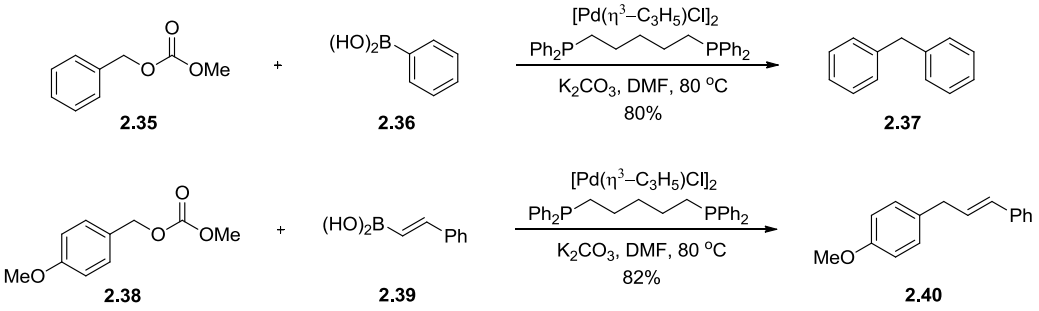
Although not as well-established and documented, benzylic esters (carbonates), having similar reactivity to their allylic counterparts, may also undergo palladium-catalyzed C-O bond fission. In one of the earliest documentations of benzylic carbonate reactions, Legros and Fiaud established the possibility to achieve benzylic C-O bond cleavage of 1-naphthylmethyl carbonate **2.32**, and subsequent trapping with sodium dimethylmalonate **2.33** (Scheme 2.8).[14] In addition, the authors found that while reactions with 1-naphthyl and 2-naphthyl carbamates both gave good yields of the products, the same reaction did not work out for a simple benzyl group. An explanation for this observation was given on the basis of the formation of η^3-allylpalladium complexes such as **I2.1** and **I2.2** as intermediates. If this is true, then it is clear that formation of **I2.1** will be less energetically demanding than complex **I2.2**, enough to set a difference between having a reaction and not having one.

Scheme 2.8: Cross-coupling of a benzylic carbonate with dimethyl malonate and benzylic π-allylpalladium complex formation



Recent advances have allowed functionalization of simple benzyl carbonates by cross-coupling with a variety of nucleophiles. For example, Kuwano[15] reported a Suzuki-Miyaura cross-coupling of benzylic carbonates with arylboronic acids under relatively mild condition using DPPpent-palladium complex (Scheme 2.9). The methodology allows for the synthesis of various pharmacologically ubiquitous diarylmethanes. Conveniently, alkenylboronic acids can also be used as the nucleophile to give aryl vinylmethane **2.40** in high yield.

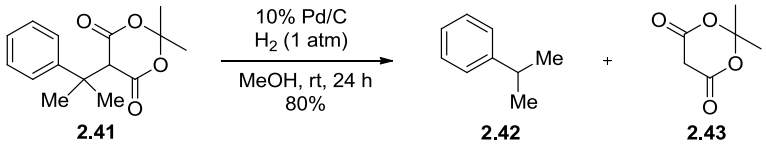
Scheme 2.9: Suzuki coupling of benzylcarbonates with phenyl- and vinylboronic acid



Moreover, Fillion and coworkers have shown that benzylic C-O is not the only bond palladium can cleave.[16] Using a carbon-based leaving group with pK_a similar to that of acetic acid, benzylic C-C bond cleavage can also be achieved. Thus, by replacing an ester with Meldrum's acid at the benzylic position, along with the presence of two other alkyl substituents, the high acidity of Meldrum's acid (pK_a

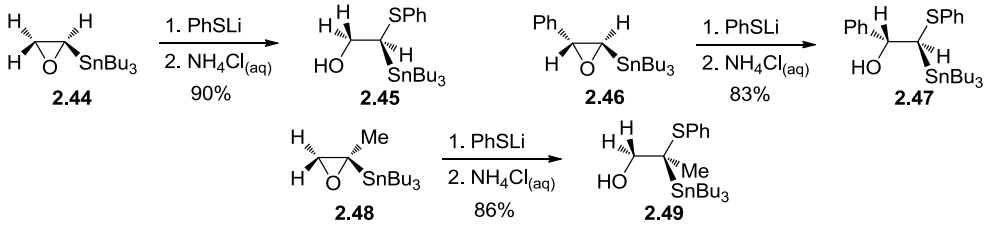
~ 4.97) allowed for palladium-catalyzed hydrogenolysis at the benzylic position, resulting in the formation of a tertiary benzylic product **2.42** (Scheme 2.10).

Scheme 2.10: Benzylic C-C bond cleavage through palladium catalysis



Thus, based on the ability of palladium to nucleophilically cleave benzylic esters and carbonates, this is worth taking into consideration when trying to optimize the Stille coupling reaction of α-alkoxybenzylstannanes. Furthermore, the chance of α-alkoxybenzylstannanes to undergo C-O cleavage may be greater than their simple benzylic counterparts, possibly due to tin-induced C-O bond weakening. Evidence of this can be seen from González-Nogal's work on the ring-opening of α-epoxystannanes by lithium phenylsulfide.[17] In their work, it was seen that lithium phenylsulfide exclusively attacks the α-position of the epoxystannane, regardless of the substutition pattern on the epoxide (Scheme 2.11). The epoxide ring-opening by lithium phenylsulfide should be a kinetic process, leading to attack on the less-hindered carbon. However, despite the presence of the sterically demanding tributyltin group, attack only occurs on the α-carbon, which would only suggest that C-O bond at the α-position should be weaker and more easily broken (a kinetic process).

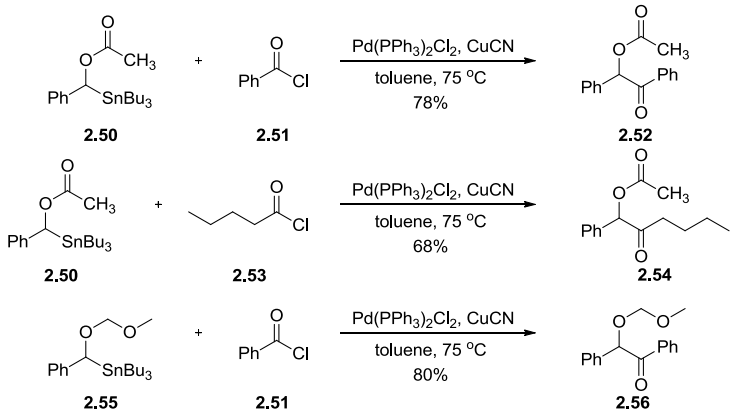
Scheme 2.11: Regioselectivity in the ring-opening of α-epoxystannanes



2.3 Stille Coupling of α-alkoxyorganostannanes with Acid Chlorides

Falck and coworkers developed reaction conditions in 1994 that achieved the coupling of various kinds of α-alkoxyorganostannanes with acid chloride electrophiles.[18] They attempted stannanes that contain saturated aliphatic, alkenyl, and phenyl on the α-carbon, as well as different α-alkoxy substituents, namely acetate, benzoate, 4-nitrobenzoate esters, as well as MOM and methyl ethers. As they cross-coupled α-alkoxybenzylstannanes with phenyl and saturated acid chlorides, it can be seen that phenyl acid chloride gives a higher yield than the saturated one (Scheme 2.12), presumably because the former is more electrophilic. As it is fairly well-known that acid chlorides are amongst the best electrophiles to undergo oxidative addition by palladium, this trait highlights the importance of electronic property of the palladium center during transmetallation, in favor of a more electron-poor palladium center that facilitates transmetallation.

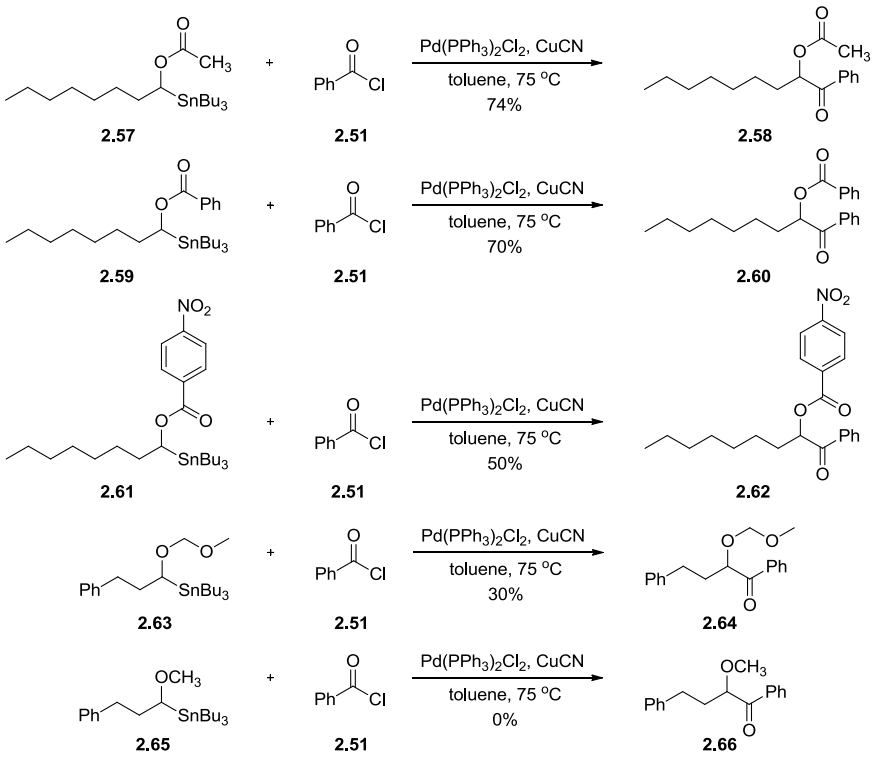
Scheme 2.12: Stille coupling of α-alkoxybenzylstannanes with acid chlorides



Furthermore, they also demonstrated the importance of the Lewis basicity of coordinating groups in the efficiency of the coupling reaction. By putting on different directing groups, yields can drastically differ, despite all of them having a saturated aliphatic group at the α-carbon, and the same electrophile was used (Scheme 2.13). Thus, by decreasing the Lewis basicity of the carbonyl group at the α-alkoxy substituent, the yield can drop from 70% to 50%. This is in direct correlation with the pK_a values of their

corresponding acids (AcOH ~4.76; BzOH ~4.2; 4-NO_2-BzOH ~ 3.44). In addition, by changing the MOM ether group that contains a coordinating oxygen atom to methyl ether, the yield dropped from a modest 30% to zero. This observation also highlights that the coordinating oxygen from an ether group is not as Lewis basic than that of a carbonyl group.

Scheme 2.13: Influence of the α-alkoxy substituent on the coupling of α-alkoxyalkylstannanes with benzoyl chloride



2.4 Proposal

As mentioned previously, Stille coupling of enantiomerically enriched α-alkoxybenzylstannanes may be a powerful way to access various chiral diarylcarbinols and aryl vinylcarbinols. However, coupling with aryl and vinyl halides may prove to be difficult, as evident from a lack of reactions performed by Falck and coworkers. In fact, the article focused exclusively on the use of acid chlorides as the electrophile, which are known to be among the most reactive. For this reason, we would like to optimize cross-coupling of α-alkoxybenzylstannanes with electrophiles to improve their synthetic

usefulness. We will start by improving the yield of coupling with benzoyl chloride as the model electrophile. Upon achieving a higher yield, attention will be shifted to optimizing coupling of saturated acid chlorides, as well as aryl halides, possibly aryl bromides and aryl iodides.

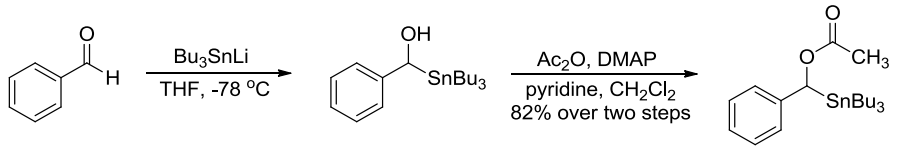
Optimization efforts will include screening of reaction conditions such as solvent, temperature, catalysts and ligand. However, based on Falck's observations that the coupling yields are very sensitive to the coordinating ability of the protecting group, and the fact that the α-alkoxy substituent as a whole may behave as a leaving group and thereby reduce the reaction yield, the main focus of the optimization effort will be spent on surveying different protecting groups on the α-alkoxybenzylstannane.

2.5 Results and Discussion

2.5.1 Preparation of (±)-α-(Acetoxy)benzylstannane and its Stille Coupling

Racemic α-(acetoxy)benzylstannane **2.50** can be prepared by *in situ* generation of tributyltinlithium from deprotonation of tributyltin hydride with lithium diisopropylamide (LDA) at 0 ˚C within a few minutes. It is then reacted with benzaldehyde at -78 ˚C to give α-hydroxybenzylstannane **2.68**, which can be acetylated using acetic anhydride. Note that the free hydroxystannane is known to be unstable under acidic conditions and can decompose somewhat on silica gel; therefore subsequent reactions must be carried out without purification (Scheme 2.14).

Scheme 2.14: Synthesis of (±)-α-(acetoxy)benzylstannane

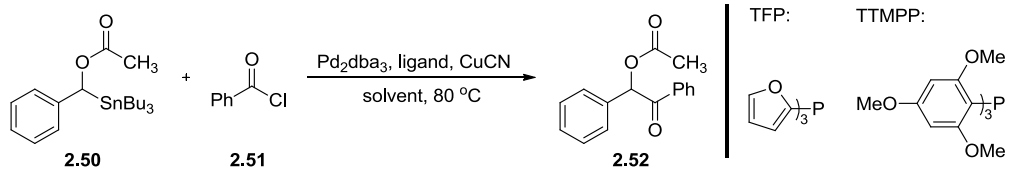


2.67 **2.68** **2.50**

Stille coupling of α-acetoxybenzylstannane with benzoyl chloride was attempted previously by the Chong group in 2007[19], with 70% being the highest yield achieved using TFP as the ligand. It was observed that, in general, ligands with lower σ-donicity gave greater yields, while ligands with higher donicity gave significantly diminished yields. In addition, (*t*-Bu)$_3$P and 1,3-bis(diphenylphosphino)-propane, a chelating ligand, failed to give any coupled product. The coupling yield was somewhat in agreement with what Falck reported using the same substrate (78% yield using PPh_3 as the ligand); hence the result was reproducible. When this chemistry was revisited, a full survey of the reaction solvent and ligand was carried out. The results are summarized in Table 2.1. Screening of the solvent showed that toluene is indeed the best solvent for this system. In contrast to the previous observation, the optimal ligand became the more electron-rich TTMPP (entry 4). Ligands of lower donicity, such as TFP and $AsPh_3$ gave the next highest yield (entries 2 and 3), in agreement with the popular belief that these ligands

tend to accelerate Stille coupling of sp^2 organostannanes. However, the yields achieved with **2.50** still needed improvement. As we decided to optimize the reaction condition, we chose ^{1}H NMR spectroscopy as a mean of quantifying the product yields using dimethyl terephthalate as the internal standard. Quantifications were made by comparing the integrals of the benzylic proton of the products to the methyl protons of dimethyl terephthalate (~δ 3.9).

Table 2.1: Reaction condition screening for Stille coupling of (±)-α-(acetoxy)benzylstannane

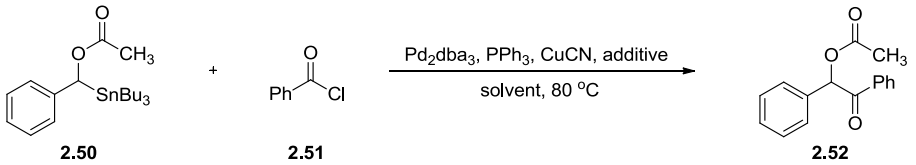


Entry	Ligand	% Yield[a]
1	PPh_3	53
2	TFP	60
3	$AsPh_3$	66
4	TTMPP	72

[a] Isolated yields after flash chromatography

Additives such as fluoride salts are known to facilitate Stille coupling in some instances by formation of more nucleophilic pentavalent stannate[20]; therefore we sought to try and improve the reaction yield by adding fluoride salts. We observed that, in general, addition of KF and CsF did not show an improved reaction (Table 2.2, entries 2, 4, 5, and 8). While using toluene as the solvent, the presence of KF did not show any beneficial effect, possibly due to the low solubility of KF. Though the use of KF in THF doubled the yield, it was not enough to compensate for the original low yield provided by the solvent. Running the reaction in NMP failed to give any product, even with the addition of KF (entries 7 and 8). Addition of 3 equivalents of LiCl that has been shown to facilitate Stille coupling of aryl triflates in THF abolished the yield altogether (entry 6).

Table 2.2: Effect of additives on the Stille coupling of (±)-α-(acetoxy)benzylstannane



2.50 2.51 2.52

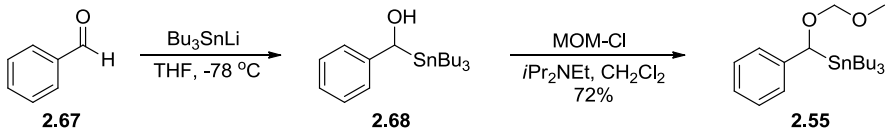
Entry	Additive (equiv)	Solvent	% Yield[a]
1	-	toluene	56
2	KF (1)	toluene	58
3	-	THF	21
4	KF (1)	THF	38
5	CsF (1)	THF	trace
6	LiCl (3)	THF	NR
7	-	NMP	NR
8	KF (1)	NMP	NR

[a] Yields were determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard

2.5.2 Preparation of (±)-α-(Methoxymethyloxy)benzylstannane and its Stille Coupling

Given the rich literature precedence on the use of methoxymethyl (MOM) ether as protecting group for α-alkoxyorganolithium species, we wanted to try protecting our α-hydroxystannane as a MOM ether to see what difference an oxygen atom from an ether group would have compared to the oxygen from an ester carbonyl group. This protecting group had already been reported by Falck and coworkers, and gave them a good yield when they coupled α-(methoxymethyloxy)benzylstannane to benzoyl chloride (Scheme 2.12). We thought that perhaps this compound could be used to incorporate other electrophiles such as saturated acid chlorides and aryl halides for Stille coupling. The compound itself was obtained without much problem by reacting the crude hydroxystannane with MOM-Cl in the presence of *i*Pr$_2$NEt in a 72% yield (Scheme 2.15).

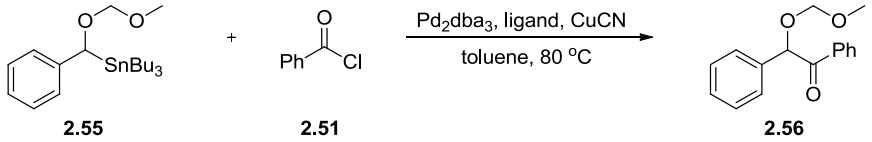
Scheme 2.15: Synthesis of (±)-α-(methoxymethyloxy)benzylstannane



2.67 2.68 2.55

Coupling of this compound with benzoyl chloride under same reaction condition as Falck's report did not provide a high yield of product as he claimed. Since these reactions gave a complex mixture of products, TLC analysis (hexanes/Et_2O 10:1) showed numerous spots in close proximity to each other. Attempts to isolate the pure product were met with no success as another compound always co-eluted with the desired product. The product yields were therefore based on comparisons of the ^1H NMR integral of the benzylic proton (~6.00 ppm[21]) to dimethyl terephthalate. Based on Table 2.3, yields never exceeded half of what was expected. This trend was in line with what Falck observed when he compared the protecting groups on α-alkoxyalkylstannanes (see Scheme 2.13); and it was suspected that an oxygen atom from an ether did not provide the right Lewis basicity for palladium to coordinate to. Furthermore, besides the complex mixture of products observed in ^1H NMR spectra, significant amounts of valerophenone were always detected as a triplet showing up at δ 2.92 in the ^1H NMR spectrum of crude reaction mixtures. We speculated the formation of valerophenone was due to competitive *n*-butyl transfer from the Bu_3Sn group. Because of the low yields observed with this protecting group, we stopped pursuing this system.

Table 2.3: Screening of reaction conditions for Stille coupling of (±)-α-(methoxymethyloxy)-benzylstannane



2.55 **2.51** **2.56**

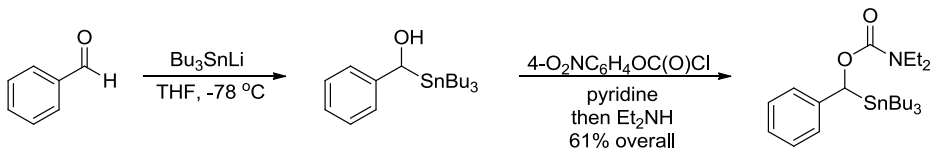
Entry	Ligand	% Yield[a]
1	PPh_3	27
2	$AsPh_3$	29
3	TFP	38

[a] Yields were determined by ^1H NMR spectroscopy using dimethyl terephthalate as the internal standard

2.5.3 Preparation of (±)-α-(N,N-diethylcarbamoyloxy)benzylstannane and its Stille Coupling

After taking into account Hoppe's study on stereospecific lithiation-electrophilic trapping of enantioenriched 1-phenylethyl *N*,*N*-diisopropyl-carbamate[22], as well as our group's previous study on the effect of protecting groups on tin-lithium exchange[23], we reasoned that the higher Lewis basicity of a carbamate carbonyl group may be able to facilitate the coupling reaction. Such an assumption was based on the ability to stabilize the palladium(II) center during transmetallation and help facilitate the overall reaction. Thus, synthesis of racemic α-(*N*,*N*-diethylcarbamoyloxy)benzylstannane was carried out. The Chong group has previously established an effective methodology of making carbamate-substituted stannanes by first making the 4-nitrophenylcarbonate intermediate from α-hydroxybenzylstannane, subsequent displacement with a secondary amine[23] afforded the product in 61% overall yield (Scheme 2.16).

Scheme 2.16: Synthesis of (±)-α-(*N*,*N*-diethylcarbamoyloxy)benzylstannane

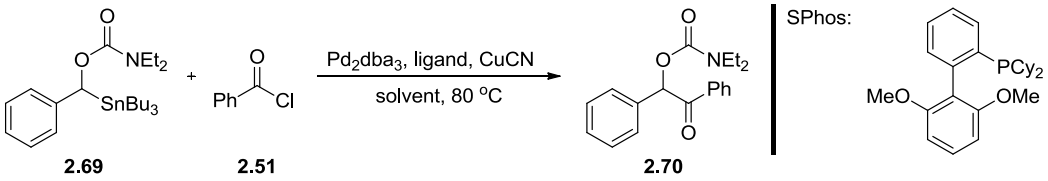


2.67 **2.68** **2.69**

With the racemic starting material **2.69** at hand, a screening of the solvent and ligand was performed again, in hope of getting better yields out of the new system. As we screened the ligands, we found that, in contrast to the acetate system, TTMPP actually gave a lower yield than ligands of lower donicity, TFP and PPh_3, for this system (compare entry 3 with 4 and 6 in Table 2.4). $AsPh_3$ had, in turn, become the worst ligand of the four that were tried. Even more surprising to us was that screening of the solvent revealed that the reaction could be run in THF just as effectively as in toluene, but in a shorter reaction time (3 hours instead of the usual 8-12 hours). Even though the reaction yield may still be low, the observation pointed out that these reactions are more complex than they seem, most likely during the

transmetallation step. It is worth noting that the product was isolated along with accompanying unidentified benzylstannane side products, exhibiting signals at δ5.54 (J_{Sn-H} = ~45 Hz) and 5.29 (J_{Sn-H} = ~42 Hz), in varying amounts, which were not observed in the acetate system. Furthermore, the amounts of the side products were somewhat dependent on the yield of the product, with a lower yield associated with more of the side product. One plausible explanation is that these peaks are compounds that result from the cleavage of the carbamate group. Addition of fluoride salts once again did not give any beneficial effect on the coupling yield.

Table 2.4: Screening of reaction condition for Stille coupling of (±)-α-(*N*,*N*-diethylcarbamoyloxy)-benzylstannane



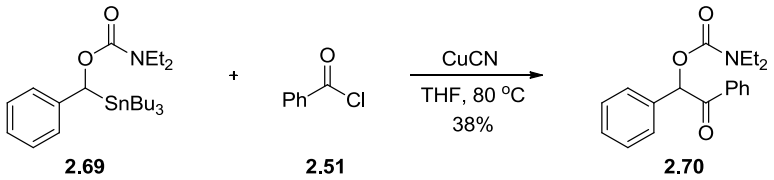
2.69 **2.51** **2.70**

Entry	Ligand	Solvent	% Yield[a]
1	P(*n*-Bu)$_3$	PhMe	NR
2	AsPh$_3$	PhMe	30
3	TTMPP	PhMe	42
4	PPh$_3$	PhMe	53
5	SPhos	PhMe	53
6	TFP	PhMe	65 (61)[c]
7	TFP	THF	64
8[b]	TFP	THF	67
9	TFP	NMP	NR

[a] Yields were determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard
[b] 1 equivalent of KF was used as additive
[c] Isolated yield after flash chromatography reported in parentheses

As Falck had reported the study on the copper-catalyzed cross coupling of α-alkoxyorganostannanes with electrophiles[12], and considering that THF is the best solvent for the coupling of this system, we sought out the possibility, for the very first time, of whether we could remove palladium and have the reaction catalyzed by only copper. It turned out that such reaction is indeed possible, albeit in a lower yield, as determined by ^{1}H NMR spectroscopy with dimethyl terephthalate as internal standard (Scheme 2.17).

Scheme 2.17: Copper-catalyzed coupling of (±)-α-(*N*,*N*-diethylcarbamoyloxy)benzylstannane with benzoyl chloride

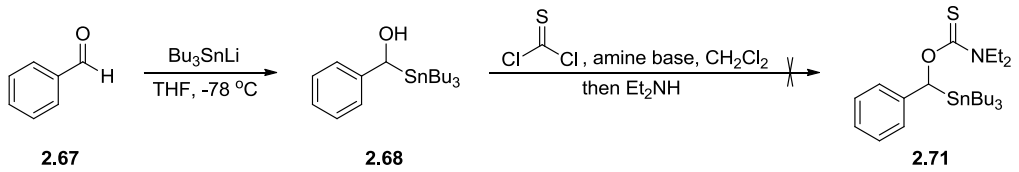


2.69 **2.51** **2.70**

2.5.4 Preparation of (±)-α-(N,N-dimethylthiocarbamoyloxy)benzylstannane and its Stille Coupling

The copper-catalyzed reaction in Scheme 2.17 could only mean that an organocopper intermediate is formed, and must be responsible for addition to benzoyl chloride. When in the presence of palladium, there might be a two-step transmetallation (from tin to copper, followed by copper to palladium) operating. Recall that Falck strategically placed a sulfur coordinating group to help stabilize the organocopper intermediate for addition to allyl bromide, giving mostly good yields of the allylation products. Thus, it seemed logical to us that employing the same strategy might facilitate cross-coupling with benzoyl chloride. As there are numerous ways to install a thiono group to an alcohol, we attempted several of them. The first method we tried was by reacting crude hydroxystannane with phenyl isothiocyanate in the presence of *i*Pr_2NEt, but the reaction did not proceed to any significant extent. We suspected that the failure to give any reaction was due to low nucleophilicity of the hydroxystannane. We then turned our attention to the use of thiophosgene, a very potent thioacylating agent. In theory, reacting hydroxystannane with thiophosgene should give a chlorothionoformate intermediate, which can then react with secondary amines to give the desired thionocarbamate. However, as potent as it is, the use of thiophosgene failed to form any chlorothionoformate, as judged by ^{1}H NMR analysis of the reaction mixture prior to addition of secondary amine that showed a complex mixture of unidentified compounds. Consequently, addition of the secondary amine gave no sign of the desired product.

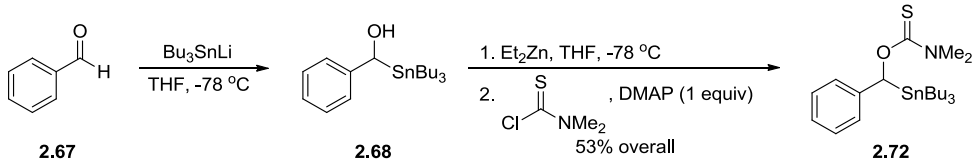
Scheme 2.18: Synthesis of (±)-α-(*N*,*N*-diethylthiocarbamoyloxy)benzylstannane through thiophosgene



2.67 **2.68** **2.71**

Finally, we used *N*,*N*-dimethylthiocarbamoyl chloride, which is commercially available, and tried reacting it with hydroxystannane. In the first few attempts, we employed an amine base along with catalytic amounts of DMAP, but no reaction took place, and on prolonged reaction time, the starting material eventually decomposed. We then switched the base to *n*-BuLi, along with a catalytic amount of DMAP, but the ^{1}H NMR spectrum of the crude reaction mixture after stirring overnight showed that the reaction was far from clean, although the starting material was all consumed. Next, we strategically chose Et_2Zn as the base, from a known chemistry[24] on generation of the zinc alkoxide of α-alkoxy-benzylstannanes. Fortunately, with the addition of a catalytic amount of DMAP, the reaction went to completion in 4 days, giving the thionocarbamate in 18% yield for the first time. Further optimization of the reaction showed that through the use of stoichiometric amount of DMAP, the reaction can be completed in 12 hours, giving the product in 53% yield (Scheme 2.19).

Scheme 2.19: Synthesis of (±)-α-(*N*,*N*-dimethylthiocarbamoyloxy)benzylstannane through thiocarbamoyl chloride

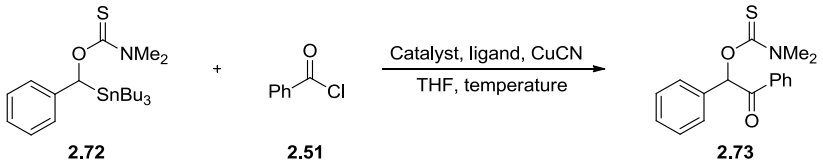


2.67 **2.68** **2.72**

Coupling of α-(*N*,*N*-dimethylthiocarbamoyloxy)benzylstannane **2.72** with benzoyl chloride gave rather low yields regardless of the solvent used. In THF, however, the reaction was complete within 15 minutes at 80 ˚C under Pd/Cu cocatalysis, as indicated by TLC and ^{1}H NMR. When CuCN alone was used to cross-couple thiocarbamoylstannane with benzoyl chloride, disappointing yields were also

observed in THF. This suggested that under Cu catalysis (in the absence of Pd), the organocopper species does not add well to acid chlorides, which is in contrast to Gilman reagents and higher-order cuprates.

Table 2.5: Screening of reaction condition for Stille coupling of (±)-α-(*N*,*N*-dimethylthiocarbamoyloxy)-benzylstannane with benzoyl chloride



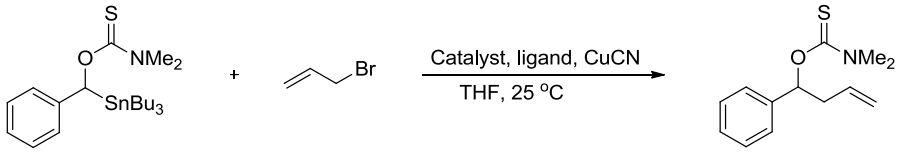
2.72 **2.51** **2.73**

Entry	Pd_2dba_3 (mol %)	L (mol %)	Temp (˚C)	% Yield[a]
1	5	PPh_3 (20)	80	35 (29)[c]
2[b]	5	PPh_3 (20)	80	27
3	5	PPh_3 (20)	25	Trace
4	-	-	80	32
5	-	-	25	20

[a] Yields determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard
[b] Toluene was used as the solvent
[c] Isolated yield after flash chromatography in parantheses

Coupling of allyl bromide, on the other hand, gave an excellent yield and a fast reaction. The reaction was finished within 15 minutes at 80 ˚C. On top of that, regardless of in the presence or absence of palladium catalyst, the reaction ran equally well (Table 2.6). However, the copper catalyst must be present or the reaction will not run.

Table 2.6: Screening of reaction condition for copper-catalyzed coupling of (±)-α-(*N*,*N*-diethyl-thiocarbamoyloxy)benzylstannane with allyl bromide



2.72 **2.17** **2.74**

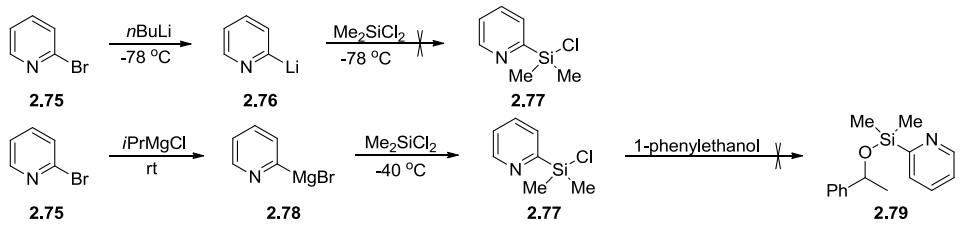
Entry	Pd_2dba_3 (mol %)	CuCN (mol %)	L (mol %)	% Yield[a]
1	5	20	PPh_3 (20)	87
2	5	-	PPh_3 (20)	NR
3	-	20	PPh_3 (20)	93

[a] Isolated yields after flash chromatography

2.5.5 Attempted Synthesis of (±)-α-(2-pyridyldimethylsilyloxy)benzylstannane

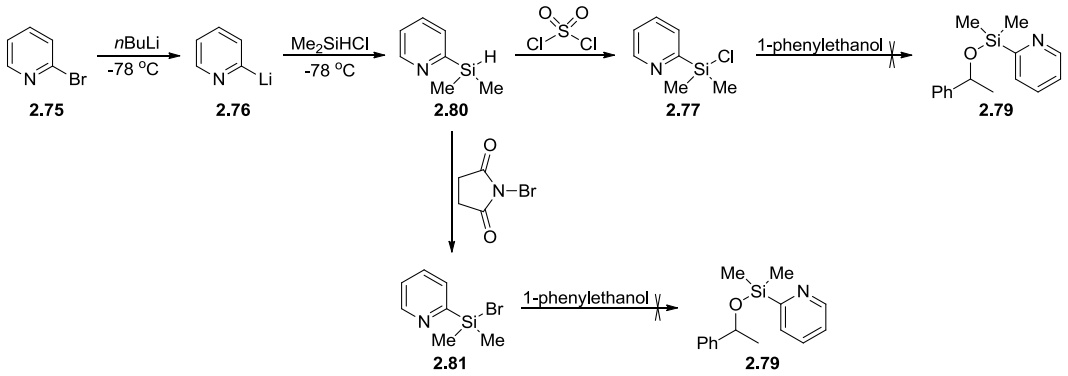
Nitrogen-based coordinating groups have found widespread use in organometallic chemistry. For example, much of Yoshida's recent works focus on the use of pyridyl coordinating group to help direct a metal atom to the vicinity of the reaction site[11] and help stabilize the metal atom. The idea of using a silyl protecting group for an alcohol has the advantage of ease of removal upon treatment with a fluoride source. As Yoshida utilized 2-pyridyldimethylsilyl group as a directing group for his palladium chemistry and enjoyed much success with it, it therefore makes sense to try the same silyl group, except on an oxygen atom instead of a carbon atom. We first attempted to make 2-pyridyldimethylsilyl chloride as an entry to the silyl ether. The immediate choice of doing so was to generate the 2-pyridylorganometallic reagent from 2-bromopyridine. Thus, 2-bromopyridine was treated with *n*-BuLi to undergo a tin-lithium exchange. However, the resulting 2-pyridyllithium is unstable unless kept at least under -78 ˚C. This made the addition of 2-pyridyllithium to Me_2SiCl_2 both operationally and chemically relatively difficult. In fact, of the numerous attempts made, either decomposition of the 2-pyridyllithium occurred before addition to a stirring solution of Me_2SiCl_2, or no desired chlorosilane was observed upon proper mixing of the two. Next, efforts were put into making 2-pyridylmagnesium halide by reacting 2-bromopyridine with *i*PrMgCl, followed by treatment with Me_2SiCl_2. Strangely enough, even though ^1H NMR showed a relatively clean peak that possibly indicated the proton at the ortho-position of the desired chlorosilane (δ9.34), subsequent treatment of the suspected chlorosilane with 1-phenylethanol as a model substrate failed to give any silyl ether product.

Scheme 2.20: Attempted generation of 2-pyridyldimethylsilyl chloride



Failure at preparing 2-pyridyldimethylchlorosilane led to another alternative; the preparation of 2-pyridyldimethylhydrosilane **2.80** that can be halogenated to produce the corresponding chlorosilane and bromosilane. The hydrosilane can be prepared relatively easily by first generating 2-pyridyllithium at low temperature, followed by subsequent trapping with Me_2SiHCl. Literature precedence indicated that it is possible to convert hydrosilanes to the corresponding chlorosilane by treatment with sulfuryl chloride[25], while bromosilanes can be made by treating hydrosilane with *N*-bromosuccinimide[26]. However, even though it was suspected that bromo- and chlorosilanes were made, which was based on the presence of the ortho-proton (δ9.27 and 8.87, respectively) in ^{1}H NMR spectrum, neither reacted with 1-phenylethanol to give the desired product (Scheme 2.21). After numerous fruitless attempts at synthesizing 2-pyridyldimethylsilyl ether, the idea was forfeited.

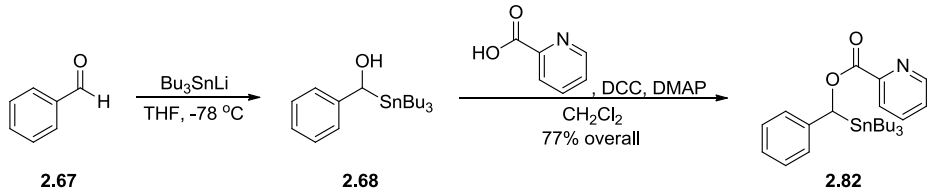
Scheme 2.21: Attempted Generation of 2-pyridyldimethylsilyl chloride from 2-pyridyldimethyl-hydrosilane



2.5.6 Preparation of (±)-α-(Picolinoyloxy)benzylstannane and its Stille Coupling

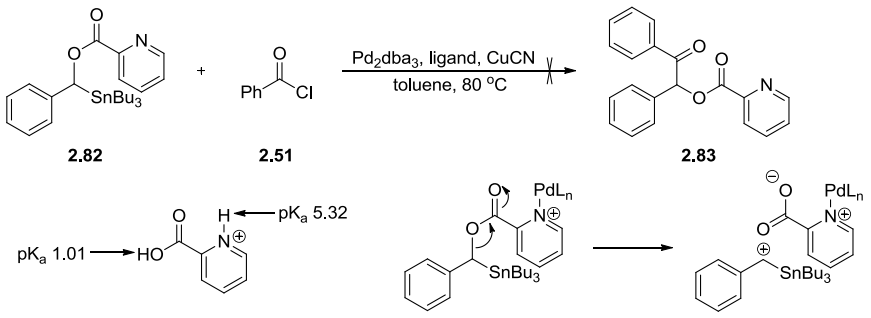
We then turned our attention to the structurally similar picolinate ester. This compound was chosen because it contains a nitrogen atom at the same number of atoms away from the tin atom. In addition, the ester can be made by a simple *N*,*N*'-dicyclohexylcarbodiimide (DCC)-mediated coupling reaction. Thus, by reacting α-hydroxystannane **2.68** with picolinic acid in the presence of a stoichiometric amount of DCC and DMAP, the picolinate ester was obtained in 47% yield (Scheme 2.22).

Scheme 2.22: Synthesis of (±)-α-(picolinoxy)benzylstannane



Upon attempt to cross-couple the picolinate ester with benzoyl chloride under Pd/Cu co-catalysis, no coupled product was obtained regardless of the ligand and solvent used. This proved to be a surprise to us at first, since even if the reaction did not improve, the yield should not have dropped to zero. However, upon careful examination of the ^{1}H NMR spectra of crude reaction mixtures, we speculated that not only was the starting material not detected, the picolinate group appeared to be cleaved. The evidence was the absence of the benzylic proton peak at δ6.15 (J_{Sn-H} = 19.6 Hz); in addition, virtually no peak was observed in the region of δ7-3. It then made sense if one considers that there are two pK_a values associated with picolinic acid.[27] The nitrogen atom on the pyridine ring has a pK_a of 5.32. When the pyridine is protonated, the adjacent carboxylic acid will have its pK_a lowered to 1.01, causing it to become a lot more acidic. It would make sense then that if the pyridine is coordinated to electron-poor palladium center, the carboxylate group would turn into a good leaving group, and may be cleaved from the stannane (Scheme 2.23).

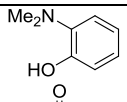
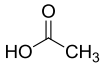
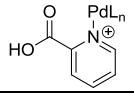
Scheme 2.23: Proposed side reaction pathway for Stille coupling of (±)-α-(picolinoxy)benzylstannane



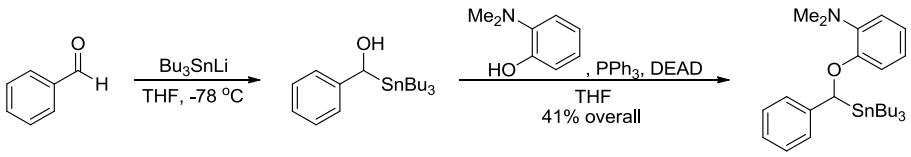
2.5.7 Preparation of (±)-α-(*N*,*N*-Dimethylaminophenoxy)benzylstannane and its Stille Coupling

Because of the observed dependence of the yields of coupling reactions on the pK_a values of the respective conjugate acid of the α-alkoxy group (Table 2.7), we then proposed the 2-*N*,*N*-dimethyl-aminophenyl ether as a protecting group for hydroxystannane **2.68**. Not only does can the amino nitrogen atom act as a coordinating atom, the pK_a of phenols are roughly 11, making them poorer leaving groups. Furthermore, the aminophenol group can be installed onto the hydroxystannane by a known Mitsunobu reaction. Thus, reaction of 2-*N*,*N*-dimethylaminophenol with PPh_3 and diethyl azodicarboxylate (DEAD) with α-hydroxystannane **2.68** afforded α-(2-*N*,*N*-dimethylaminophenoxy)-benzylstannane **2.84** in 41% overall yield (Scheme 2.24).

Table 2.7: Dependence of cross-coupling reaction yield on the α-alkoxy group conjugate acid pK_a

Conjugate acid of α-alkoxy substituent	pK_a	Highest coupling % yield
	~11	??
	4.76	72
	1.01	0

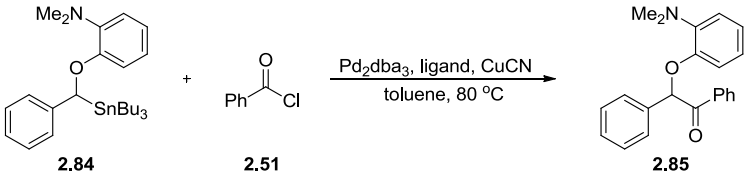
Scheme 2.24: Synthesis of (±)-α-(*N*,*N*-dimethylaminophenoxy)benzylstannane



Once again, Stille coupling of aminophenyl ether with benzoyl chloride did not give an improved coupling yield. Thus, the highest yield that was achieved was 64% through the use of TFP as the ligand in toluene (Table 2.8) as determined by ^1H NMR spectroscopy using dimethyl terephthalate as the internal

standard; comparisons were made with the benzylic proton of the product at δ6.50. Even though isolation of the pure product by flash chromatography was attempted, fractions containing the desired product was always contaminated with another impurity. The use of a fluoride salt as additive showed no beneficial effect. The reason was unclear to us.

Table 2.8: Screening of reaction conditions for Stille coupling of (±)-α-(*N*,*N*-dimethylaminophenoxy)-benzylstannane



2.84 **2.51** **2.85**

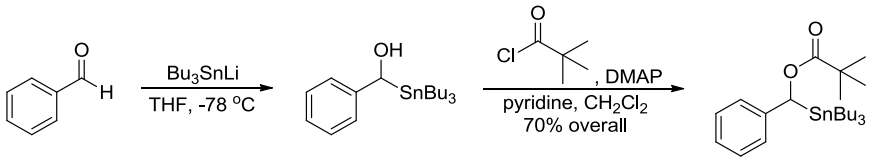
Entry	Ligand	% Yield[a]
1	$AsPh_3$	0
2	TTMPP	34
3	PPh_3	54
4	TFP	64
5[b]	TFP	57

[a] Yields were determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard
[b] CsF was used as an additive

2.5.8 Preparation of (±)-α-(Trimethylacetoxy)benzylstannane and its Associated Stille Coupling

Given that none of our proposals about using different coordinating heteroatom on the protecting groups for hydroxystannane worked to our expectation, we decided to give up that line of thinking and re-visit the group that worked reasonably well for us to start with – acetate. We reasoned that of the side reactions that could diminish the yield of coupling between α-(acetoxy)benzylstannane with benzoyl chloride, two might be associated with acetate as a leaving group and possibly nucleophilic attack on the ester carbonyl. To get around these potential problems, we proposed increasing the steric bulk of the acetate to a pivalate. By doing this, its ability to act as leaving group decreases, having a higher pK_a value than acetate (5.0 and 4.8, respectively).[28] And pivalate esters can be put on simply by treatment with pivaloyl chloride (Scheme 2.25).

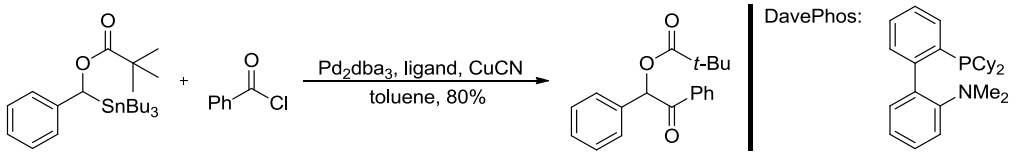
Scheme 2.25: Synthesis of (±)-α-(trimethylacetoxy)benzylstannane



2.67 **2.68** **2.86**

Stille coupling of α-(trimethylacetoxy)benzylstannane with benzoyl chloride under Pd/Cu co-catalysis showed, for the first time, an elevated yield of 92%. A detailed ligand survey using this system showed that for the yield to be high, the ligand has to achieve a balance of sterics and electronics (Table 2.9). As can be seen from the table, ligands that are too bulky (entries 2, 5 and 7) generally gave low yields, as do ligands that are more electron-rich (entry 1). The fact that both TFP and PPh_3, ligands that are both less bulky and less electron-rich, gave the highest yields is in accordance with Stille coupling of aryl- and vinylstannanes.

Table 2.9: Screening of ligands for Stille coupling of (±)-α-(trimethylacetoxy)benzylstannane



2.86 **2.51** **2.87**

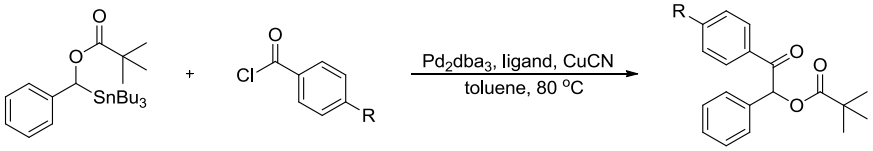
Entry	Ligand	% Yield
1	P(*n*-Bu)$_3$	30[a]
2	P(C_6F_5)$_3$	47[a]
3	P(*p*-CN-C_6H_4)$_3$	47[a]
4	$AsPh_3$	50[a]
5	P(*o*-Tol)$_3$	67[b]
6	P(*p*-CF_3-C_6H_4)$_3$	70[b]
7	TTMPP	71[b]
8	DavePhos	77[b]
9	PPh_3	91[b]
10	TFP	92[b]

[a] Yields were determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard
[b] Isolated yields after flash chromatography

Having obtained an optimal system for cross-coupling with benzoyl chloride, we also examined cross-coupling with aromatic acid chlorides having different substituents on the ring (Table 2.10). While

methoxy-, chloro-, and trifluoromethyl-substituted benzoyl chlorides gave respectable to good yields, it is worth mentioning that strong electron-withdrawing groups (cyano and nitro) gave essentially no product. Unfortunately, no correlation could be drawn based on the electronic properties of the acid chlorides and the product yield. In most cases, yields were in the modest range (Table 2.10).

Table 2.10: Screening of substituted benzoyl chlorides for Stille coupling of (±)-α-(trimethylacetoxy)-benzylstannane



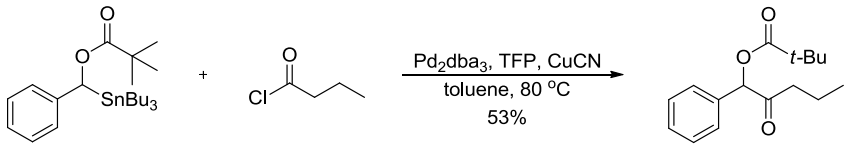
2.86 **2.88** **2.89**

Entry	R	Ligand	% Yield[a]
1	OMe	TFP	62
2	OMe	P(*p*-CF_3-C_6H_4)$_3$	87
3	Cl	TFP	74
4	Cl	P(*p*-CF_3-C_6H_4)$_3$	50
5	CF_3	TFP	51

[a] Isolated yields after flash chromatography

We further pursued coupling with aliphatic saturated acid chloride as well as a number of aryl halides using the pivalate ester. Disappointingly, using butyryl chloride as the electrophile, the reaction only gave the product in 53% yield based on ^{1}H NMR analysis using dimethyl terephthalate as an internal standard.

Scheme 2.26: Stille coupling of (±)-α-(trimethylacetoxy)benzylstannane with butyryl chloride

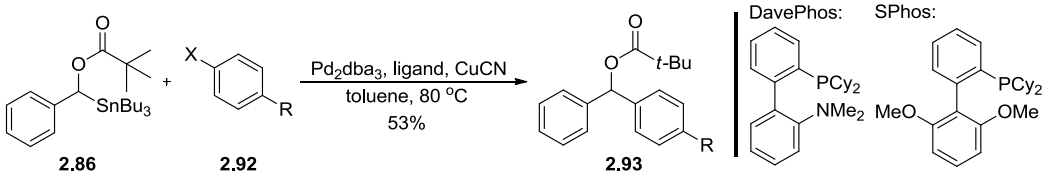


2.86 **2.90** **2.91**

In an attempt to cross-couple aryl halides, we made an interesting observation. At first, when TFP was used to cross couple an electron-poor aryl bromide and iodide, no reaction was observed, leading only to mostly starting material (Table 2.11, entries 1 and 2). When DavePhos, a bulky and

electron-rich ligand developed by Buchwald's group, was used to couple 4-chloroacetophenone, the product was formed, albeit in only 23% (entry 3). Encouraged by this, we sought to couple aryl bromides and iodides with this ligand, proposing that these two should be more reactive an aryl chloride, therefore giving us higher yield. However, when 4-bromobenzotrifluoride and iodobenzene were coupled, no product was detected, but the starting material was consumed. Finally, with the use of SPhos as the ligand for coupling of 4-chloroacetophenone, a lower yield of 13% was observed. We speculate that these observation can be explained when one takes into account that chloride is more electronegative than bromide and iodide. Because of this, the palladium(II) complex formed by oxidative addition of aryl chloride more electron-deficient than the corresponding bromide and iodide complexes, making the chloride complex more reactive. The chemoselectivity observed here was also reported by Buchwald and Fors when they tried to couple aryl chlorides with sodium nitrite to make aromatic nitro compounds.[29]

Table 2.11: Electrophile substrate scope and ligand screening for Stille coupling of (±)-α-(trimethyl-acetoxy)benzylstannane



2.86 2.92 2.93

Entry	X	R	Ligand	% Yield[a]
1	Br	CF_3	TFP	NR
2	I	NO_2	TFP	NR
3	Cl	$C(O)CH_3$	DavePhos	23
4	Br	CF_3	DavePhos	NR
5	I	H	DavePhos	0
6	Cl	$C(O)CH_3$	SPhos	13

[a] Yields determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard

2.6 Conclusion

Through the combination of a systematic examination of a number of protecting groups and screening reaction conditions, we have successfully optimized the Stille coupling reaction of α-alkoxybenzylstannane with benzoyl chloride to yields of up to 92%. As demonstrated throughout this chapter, the choice of protecting group is essential to the success of this reaction. Despite the fact that most of our proposed choices of protecting group failed to give anticipated results, the use of pivalate ester behaved as a "proof-of-principle" model system that we could use to explore the substrate scope in terms of the electrophile. In addition, cross-coupling using this model system and benzoyl chloride revealed that the success of the reaction relies on a balance between the steric and electronic properties of the ligand. Moreover, the solvent compatibility of THF to the cross-coupling of α-(*N*,*N*-diethyl-carbamoyloxy)benzylstannane suggests that more than one mechanism may be operating when different protecting groups are used. With the acetate system, lack of reactivity in THF and NMP may be because the organocopper intermediate formed is quite unreactive or does not form. All of these observations point in the direction of a complex mechanistic profile.

Unfortunately, the hope of cross-coupling with other less reactive electrophiles in synthetically useful yields was not met even with the pivalate system. The lack of coupling efficiency with aliphatic saturated acid chloride may be due to a relatively less electron-deficient palladium center during transmetallation, making it less reactive. Coupling of aryl halides also showed that the electronic property of the palladium center during transmetallation is vital to the success of the rate-determining step.

2.7 Experimental

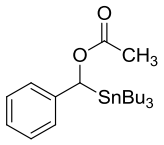
2.7.1 General Experimental

All reactions were performed using oven- or flame-dried glassware under an argon atmosphere. Diethyl ether, THF and toluene were freshly distilled from Na/benzophenone. CH_2Cl_2, NMP, acetonitrile, hexanes and amine bases were distilled from CaH_2. KF, CsF and LiCl were dried at 100 ˚C under high vacuum. Benzaldehyde was filtered through a pad of activated basic aluminum oxide (~150 mesh, 58 Å). Bu_3SnH was prepared by reduction of bis(tributyltin)oxide with $NaBH_4$ in ethanol[30] and was distilled (kugelrohr) before use. All chemicals were purchased from Sigma-Aldrich® and used as it is unless otherwise specified. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Couplings of carbon to tin are reported as two values (to ^{117}Sn and ^{119}Sn) when discernible, and as one number when two individual couplings are not discernible. All of the mass spectral data are for ^{120}Sn unless noted otherwise.

2.7.2 General Procedure for Preparation of α-Alkoxybenzylstannanes

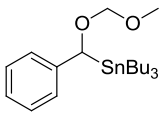
Following the method of Still[2], *i*-Pr_2NH (1.66 mL, 11.8 mmol) and *n*-BuLi (8.8 mL of 1.35 M solution in hexanes, 11.8 mmol) were added to THF at 0 ˚C sequentially and stirred for 15 min. Then, Bu_3SnH (3.2 mL, 11.8 mmol) was added to the lithium diisopropylamide solution at 0˚C and stirred for another 15 min before being cooled to -78 ˚C. The reaction mixture was stirred for 15 min at -78 ˚C before the dropwise addition of benzaldehyde (1.0 mL, 9.9 mmol). The reaction was finished as judged by TLC (hexanes/Et_2O 40:1) after 15 min and quenched with sat. NH_4Cl (50 mL) and warmed up to room temperature before rotovapping the solvent away. The crude aqueous layer was extracted with Et_2O (1 × 50 mL then 2 × 25 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to obtain the crude α-(hydroxy)benzylstannane as a yellow oil. Without delay, it was then subjected to installation of a protecting group.

2.7.2.1 (±)-α-(Acetoxy)benzylstannane[16] (2.50)



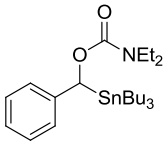
Following from the general procedure, the crude α-(hydroxy)benzylstannane was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 ˚C. DMAP (0.14 g, 1.18 mmol) and pyridine (4 mL) were added and the mixture was stirred for 15 min. Acetic anhydride (2.8 mL, 29.54 mmol) was added in dropwise at 0 ˚C and stirred for 15 min before removing the ice bath. The reaction was allowed to warm up to room temperature and stirred for 12 h. Once the reaction is complete as judged by TLC (hexanes/Et_2O 40:1) it was quenched with sat. NH_4Cl (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product. The yellow oil was purified by flash column chromatography (25 g silica / 1 g crude, hexane/Et_2O 80:1) to afford the title compound (3.57 g, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.23 (2H, m, ArH), 7.10-7.04 (3H, m, ArH), 5.89 (1H, J_{Sn-H} = 21.1 Hz, s, PhC<u>H</u>OSn), 2.11 (3H, s, CH_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, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.5 (<u>C</u>OCH_3), 142.7 (J_{Sn-C} = 12.0 Hz, Ar), 128.3 (J_{Sn-C} = 8.2 Hz, Ar), 125.0 (J_{Sn-C} = 10.2 Hz, Ar), 123.6 (J_{Sn-C} = 15.8 Hz, Ar), 73.4 (J_{Sn-C} = 291.3/304.9 Hz, Ar<u>C</u>HOSn), 28.7 (J_{Sn-C} = 20.3 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.2 ($J_{Sn-C}$ = 56.6 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 20.8 ($CO\underline{C}H_3$), 13.5 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.0 ($J_{Sn-C}$ = 307.5/321.7 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$).

2.7.2.2 (±)-α-(Methoxymethyloxy)benzylstannane[16] (2.55)



Following from the general procedure, the crude α-(hydroxy)benzylstannane was dissolved in CH_2Cl_2 (50 mL) and cooled down to 0 ˚C. *i*-Pr_2NEt (3.5 mL, 19.8 mmol) was added and stirred the mixture for 15 min. MOM-Cl (1.5 mL, 19.8 mmol) was added dropwise at 0 ˚C and stirred for 15 min before removing the ice bath. The reaction was allowed to warm up to room temperature and stirred for 12 h. Once the reaction was complete as judged by TLC (hexane/Et_2O 40:1) it was quenched with sat. NH_4Cl (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product. The yellow oil was purified by flash column chromatography (40 g silica / 1 g crude, hexane/Et_2O 40:1) to afford the title compound (3.15 g, 72%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.07 (5H, m, ArH), 5.12 (1H, s, $J_{Sn\text{-}H}$ = 31.9 Hz, PhC<u>H</u>OSn), 4.58 (2H, dd, *J* = 11.8, 6.7 Hz, OCH_2), 3.38 (3H, s, OCH_3), 1.47-1.37 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.35-1.20 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.99-0.80 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (Ar), 128.6 (Ar), 127.8 (Ar), 127.4 (Ar), 99.5 ($O\underline{C}H_2$), 67.6 (Ar<u>C</u>HOSn), 55.6 ($O\underline{C}H_3$), 29.3 ($SnCH_2\underline{C}H_2CH_2CH_3$), 27.2 ($SnCH_2CH_2\underline{C}H_2CH_3$), 13.9 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.2 ($Sn\underline{C}H_2CH_2CH_2CH_3$).

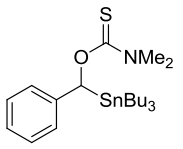
2.7.2.3 (±)-α-(*N*,*N*-diethylcarbamoyloxy)benzylstannane (2.69)



Following from the general procedure, the crude α-(hydroxy)benzylstannane was dissolved in pyridine (5.0 mL), cooled to 0 ˚C and the reaction was stirred for 15 min. *p*-Nitrophenyl chloroformate (2.19 g, 10.89 mmol) was added in small portions. After the addition the reaction was allowed to stir for 15 min before removing the ice bath and stirring for a further 2 h. After the α-(hydroxy)benzylstannane was depleted as judged by ^{1}H NMR spectroscopy, the reaction was cooled to 0 ˚C. Et_2NH was added dropwise and stirred for 15 min. The ice bath was removed and the reaction was stirred for 12 h. After the reaction was complete as judged by ^{1}H NMR spectroscopy the reaction was first diluted with Et_2O (50

mL), then washed with 2*M* HCl (2 × 25 mL), H_2O (25 mL), 3*M* NaOH (3 × 25 mL), H_2O (1 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product. The yellow oil was purified by flash column chromatography (40 g silica / 1 g crude, hexane/CH_2Cl_2 3:1 then 2:1) to afford the title compound (2.99 g, 61%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.22 (2H, m, ArH), 7.10-7.01 (3H, m, ArH), 5.82 (1H, s, J_{Sn-H} = 22.5 Hz, PhC<u>H</u>OSn), 3.34 (4H, broad, NCH_2), 1.51-1.38 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.27-1.20 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 1.17 (6H, broad, $NCH_2C\underline{H}_3$), 0.86-0.80 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (J_{Sn-C} = 17.0 Hz, O<u>C</u>(O)N), 143.9 (J_{Sn-C} = 11.1 Hz, Ar), 128.2 (Ar), 123.3 (Ar), 73.4 (J_{Sn-C} = 310.7/325.2 Hz, Ph<u>C</u>HOSn), 41.5 (N<u>C</u>H_2), 28.8 (J_{Sn-C} = 20.1 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($J_{Sn-C}$ = 55.5/57.5 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 14.1 ($NCH_2\underline{C}H_3$), 13.5 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.0 ($J_{Sn-C}$ = 306.4/320.6 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1684, 1177, 768, 756, 697 cm^{-1}; MS (EI) *m/z* 440 (M-C_4H_9, 100), 91 (32); Anal. Calcd for $C_{24}H_{43}NO_2Sn$: C, 58.08; H, 8.73. Found: C, 57.89; H, 8.57.

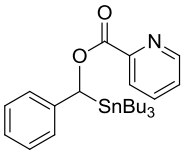
2.7.2.4 (±)-α-(*N*,*N*-Dimethylthiocarbamoyloxy)benzylstannane (2.72)



Following from the general procedure, the crude α-(hydroxy)benzylstannane was dissolved in THF (50 mL) and cooled to -78 ˚C. Et_2Zn (11.88 mL of 1.0 M solution in diethyl ether, 11.88 mmol) was added dropwise and the mixture was stirred for 15 min. *N*,*N*-dimethylthiocarbamoyl chloride (2.45 g, 19.8 mmol) and DMAP (1.21 g, 9.9 mmol) were added sequentially and the reaction mixture was stirred for a further 15 min. The dry ice/acetone bath was removed and the reaction was slowly warm up to room temperature while stirring for 15 h. Once the reaction was complete as judged by ^{1}H NMR spectroscopy, the solvent was removed by rotoevaporation. The residue was dissolved in 200 mL acetonitrile and extracted with hexanes (5 × 100 mL). The combined hexanes layers were concentrated *in vacuo* to afford the crude product as a yellow oil/solid. The crude product was purified by flash column

chromatography (30 g silica/ 1 g crude, hexane/EtOAc 30:1) to afford the title compound (2.54 g, 53%) as a colorless oil that decomposes slightly even upon sitting in -40 ˚C freezer under argon atmosphere for 2-3 days. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.19 (2H, m, ArH), 7.10-7.04 (3H, m, ArH), 6.64 (1H, s, J_{Sn-H} = 19.5 Hz, PhC<u>H</u>OSn), 3.34 (3H, s, NCH_3), 3.20 (3H, s, NCH_3), 1.45-1.35 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.28-1.19 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.86-0.81 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8 (J_{Sn-C} = 17.3 Hz, O<u>C</u>(S)N), 143.0 (J_{Sn-C} = 9.6 Hz, Ar), 128.3 (Ar), 124.8 (Ar), 123.5 (J_{Sn-C} = 15.6 Hz, Ar), 80.9 (J_{Sn-C} = 300.5/314.4 Hz, Ph<u>C</u>HOSn), 42.7 (N<u>C</u>H$_3$), 37.6 (N<u>C</u>H$_3$), 28.8 (J_{Sn-C} = 20.2 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($J_{Sn-C}$ = 55.4/57.5 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 13.5 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.5 ($J_{Sn-C}$ = 305.3/319.5 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1520, 1390, 1293, 1196, 1158 cm^{-1}; MS (EI) *m/z* 428 (M-C_4H_9, 100), 338 (92), 72 (37); Anal. Calcd for $C_{22}H_{39}NOSSn$: C, 54.56; H, 8.12. Found: C, 54.37; H, 7.93.

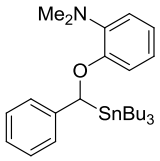
2.7.2.5 (±)-α-(Picolinoyloxy)benzylstannane (2.82)



Following from the general procedure, the crude α-(hydroxy)benzylstannane was dissolved in CH_2Cl_2 (60 mL) and cooled to 0 ˚C. Picolinic acid (1.22 g, 9.9 mmol) and DMAP (0.97 g, 7.9 mmol) were added sequentially and the reaction was stirred additional 15 min. DCC was added in small portions and stirred for 15 min before removing the ice bath. The reaction was allowed to stir for 12 h. Then the reaction mixture was filtered through a Buchner funnel and rinsed with CH_2Cl_2 (50 mL). The golden yellow filtrate was acidified with 0.5*M* HCl (120 mL), the phases were separated, and the organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude product as yellow oil containg residual solids. The crude product was purified by flash column chromatography (30 g silica/ 1 g crude, hexane/Et_2O) to afford the title compound (3.83 g, 77%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (1H, d, *J* = 4.0 Hz, Ar'H), 8.13 (1H, d, *J* = 7.84 Hz, Ar'H), 7.85-7.82 (1H, td, *J* = 7.8, 1.2 Hz, Ar'H),

7.47-7.43 (1H, m, Ar'H), 7.32-7.21 (4H, m, ArH), 7.10 (1H, t, $J_{H\text{-}H}$ = 7.09 Hz, ArH), 6.15 (1H, s, $J_{Sn\text{-}H}$ = 19.6 Hz, PhC<u>H</u>OSn), 1.39-1.35 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.22-1.17 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.88-0.76 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 ($J_{Sn\text{-}C}$ = 10.6 Hz, O<u>C</u>(O)Ar'), 149.97 (Ar'), 148.1 (Ar'), 142.3 ($J_{Sn\text{-}C}$ = 11.6 Hz, Ar), 136.7 (Ar'), 128.4 ($J_{Sn\text{-}C}$ = 7.7 Hz, Ar), 126.5 (Ar'), 125.1 ($J_{Sn\text{-}C}$ = 9.7 Hz, Ar), 124.6 (Ar'), 123.8 ($J_{Sn\text{-}C}$ = 15.3 Hz, Ar), 74.97 ($J_{Sn\text{-}C}$ = 274.8/287.8 Hz, Ph<u>C</u>HOSn), 28.6 ($J_{Sn\text{-}C}$ = 20.3 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.2 ($J_{Sn\text{-}C}$ = 55.5/57.5 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 13.4 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.2 ($J^{117}Sn/^{119}Sn$ = 308.2/322.5 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1703, 1309, 1245, 1140, 698 cm^{-1}; MS (EI) *m/z* 503 (M^+, 61), 446 (M-C_4H_9, 48), 340 (77), 269 (100); Anal. Calcd for $C_{25}H_{37}NO_2Sn$: C, 59.78; H, 7.42. Found: C, 59.58; H, 7.36.

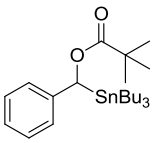
2.7.2.6 (±)-α-(*N*,*N*-Dimethylaminophenoxy)benzylstannane (2.84)



Following from the general procedure, the crude α-(hydroxy)benzylstannane was dissolved in THF (30 mL) and cooled to 0 ˚C. 2-(*N*,*N*-dimethylamino)phenol (2.04 g, 14.85 mmol) and PPh_3 (3.90 g, 14.85 mmol) were added sequentially and the reaction was stirred for a further 15 min. DEAD (2.3 mL, 14.85 mmol) was added dropwise and stirred for an additional 15 min before removing the ice bath. The reaction was allowed to stir for 12 h. After the reaction was complete as judged by ^{1}H NMR spectroscopy, the solvent was removed by rotoevaporation. The crude mixture was dissolved in acetonitrile (50 mL), and extracted with hexane (5 × 100 mL). The combined hexane layer was concentrated *in vacuo* to afford the crude product as a yellow oil and residual white solids. The crude product was purified by flash column chromatography (25 g silica/ 1 g crude, hexane/Et_2O 60:1) to afford the title compound (2.09 g, 41%) as a colorless oil that decomposes upon exposure to the air for 2-3 days. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.20 (2H, d, *J* = 7.6 Hz, ArH), 7.15-7.12 (2H, d, *J* = 8.2 Hz, ArH), 7.04-7.02 (1H, dd, *J* = 7.2, 7.2 Hz, ArH), 6.67-6.72 (4H, m, Ar'H), 5.58 (1H, s, $J_{Sn\text{-}H}$ = 28.1 Hz, PhC<u>H</u>OSn), 2.84 (6H, s, NCH_3),

1.42-1.36 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.26-1.18 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.89-0.80 (15H, m, $Sn\underline{C}H_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3 (J_{Sn-C} = 35.1 Hz, Ar'), 144.4 (J_{Sn-C} = 12.5 Hz, Ar'), 142.9 (Ar), 128.5 (J_{Sn-C} = 9.5 Hz, Ar), 124.5 (J_{Sn-C} = 11.6 Hz, Ar), 122.9 (J_{Sn-C} = 15.8 Hz, Ar), 121.4 (Ar'), 120.4 (Ar'), 117.8 (Ar'), 113.5 (Ar'), 76.6 (J_{Sn-C} = 318.9/333.4 Hz, Ph$\underline{C}$HOSn), 43.2 (N$\underline{C}H_3$) 28.8 (J_{Sn-C} = 20.2 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.4 ($J_{Sn-C}$ = 57.5 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.5 ($J_{Sn-C}$ = 300.2/314.1 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1497, 1450, 1217, 743, 698 cm^{-1}; MS (EI) *m/z* 460 (M-C_4H_9, 5), 226 (100); Anal. Calcd for $C_{27}H_{43}NOSn$: C, 62.80; H, 8.39. Found: C, 62.60; H, 8.28.

2.7.2.7 (±)-α-(Trimethylacetoxy)benzylstannane (2.86)



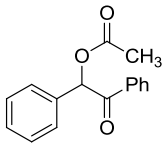
Following from the general procedure, the crude α-(hydroxy)benzylstannane was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 ˚C. DMAP (0.14 g, 1.18 mmol) and pyridine (4 mL) were added and the mixture was stirred for 15 min. Trimethylacetyl chloride (3.6 mL, 29.54 mmol) was added dropwise at 0 ˚C and stirred for 15 min before removing the ice bath. The reaction was allowed to warm up to room temperature and stirred for 12 h. Once the reaction was complete as judged by TLC (hexane/Et_2O 40:1) it was quenched with sat. NH_4Cl (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product. The yellow oil was purified by flash column chromatography (25 g silica / 1 g crude, hexane/Et_2O 40:1) to afford the title compound (3.34 g, 70%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.27 (2H, m, ArH), 7.07 (3H, m, ArH), 5.90 (1H, s, J_{Sn-H} = 21.8 Hz, PhC$\underline{H}$OSn), 1.45-1.35 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.30-1.21 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 1.30 (9H, s, CH_3), 0.88-0.80 (15H, m, $Sn\underline{C}H_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ178.0 (J_{Sn-C} = 15.1 Hz, $\underline{C}OC(CH_3)_3$), 143.2 (J_{Sn-C} = 12.0 Hz, Ar), 128.3 (J_{Sn-C} = 8.6 Hz, Ar), 124.8 (J_{Sn-C} = 10.5 Hz, Ar),

123.3 (J_{Sn-C} = 15.6 Hz, Ar), 72.7 (J_{Sn-C} = 294.6/308.3 Hz, $\underline{C}$OAr), 38.9 (CO$\underline{C}$(CH$_3$)$_3$), 28.7 (J_{Sn-C} = 20.1 Hz, SnCH$_2\underline{C}$H$_2$CH$_2$CH$_3$), 27.34 (CH$_3$), 27.28 (J_{Sn-C} = 26.4 Hz, SnCH$_2$CH$_2\underline{C}$H$_2$CH$_3$), 13.5 (SnCH$_2$CH$_2$CH$_2\underline{C}$H$_3$), 9.7 (J_{Sn-C} = 306.9/321.2, Sn$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$); IR (neat) 1732, 1711, 1169, 787, 756, 697 cm^{-1}; MS (EI) *m/z* 425 (M-C$_4$H$_9$, 100), 235 (28), 91 (66); HRMS Calcd for C$_{20}$H$_{33}$O$_2$^{112}Sn (M-C$_4$H$_9$): 417.1529, found: 417.1531.

2.7.3 General Procedure for Stille Coupling of α-Alkoxybenzylstannanes with Benzoyl Chloride

Pd_2dba_3 (0.020 g, 0.02 mmol), PPh_3 (22 mg, 0.08 mmol) and CuCN (7 mg, 0.08 mmol) were loaded into a Schlenk tube evacuated and filled with argon and dissolved with toluene (3 mL). α-(trimethylacetoxy)benzylstannane (0.200 g, 0.42 mmol) was dissolved in toluene (1 mL) and let drain into the Schlenk tube. Benzoyl chloride (60 μL, 0.50 mmol) was dissolved in toluene (1 mL) and let drain into the Schlenk tube. The Schlenk tube was sealed and the reaction was allowed to run at 80 ˚C until completion of reaction as monitored by TLC (hexane/Et_2O 5:1). The reaction was then stopped and the solvent was concentrated *in vacuo* to afford the crude product. The crude product was purified by flash column chromatography on 10% K_2CO_3/silica (*w*/*w*)[31] (30 g silica / 1 g crude, hexane/Et_2O 10:1) to afford the pure product.

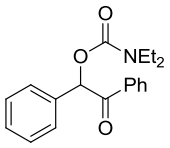
2.7.3.1 (±)-2-Oxo-1,2-Diphenylethyl Acetate (2.52)[21]



Following the general procedure described in **2.7.3**, the title compound was isolated as a colorless oil (0.083 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.93 (2H, d, *J* = 7.8 Hz, ArH), 7.48-7.31 (8H, m, ArH), 6.90 (1H, s, PhC$\underline{H}$O), 2.16 (3H, s, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ193.7 (Ph$\underline{C}$OCHO), 170.4

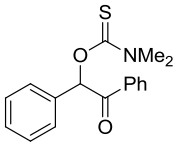
(C̲OCH$_3$), 134.5 (Ar), 133.6 (Ar), 133.4 (Ar), 129.3 (Ar), 129.1 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 77.6 (PhC̲HOCO), 20.6 (CH$_3$).

2.7.3.2 (±)-2-Oxo-1,2-Diphenylethyl-*N*,*N*-Diethylcarbamate (2.69)



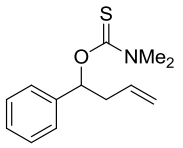
Following the general procedure described in **2.7.3**, the title compound was isolated as a white solid (0.077 g, 61%). M.p. 114-115 ˚C; ^{1}H NMR (300 MHz, CDCl$_3$) δ7.94 (2H, d, *J* = 7.4 Hz, ArH), 7.50-7.26 (8H, m, ArH), 6.83 (1H, s, PhC̲HO), 3.35 (4H, broad, NC̲H$_2$CH$_3$), 1.20-1.11 (6H, broad, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ195.2 (PhC̲(O)CHO), 155.0 (C̲(O)NEt$_2$), 135.0 (Ar), 134.3 (Ar), 133.1 (Ar), 128.8 (Ar), 128.7 (Ar), 128.4 (Ar), 128.3 (Ar), 77.5 (PhC̲HOC(O)), 41.5 (N(C̲H$_2$CH$_3$)$_2$), 13.6 (N(CH$_2$C̲H$_3$)$_2$). IR (KBr) 1680, 1173, 771, 753, 698 cm^{-1}.

2.7.3.3 (±)-*O*-2-Oxo-1,2-Diphenylethyl-*N*,*N*-Dimethylthiocarbamate (2.73)



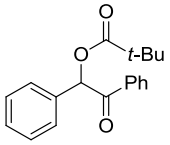
Following the general procedure described in **2.7.3**, the title compound was isolated as a white solid (0.036 g, 29%). M.p. 102-105 ˚C; ^{1}H NMR (300 MHz, CDCl$_3$) δ8.00 (2H, d, *J* = 7.6 Hz, ArH), 7.57 (1H, s, PhC̲HO), 7.51-7.25 (8H, m, ArH), 3.30 (3H, s, NC̲H$_3$), 3.19 (3H, s, NC̲H$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ194.4 (PhC̲(O)CHO), 187.0 (C̲(S)NMe$_2$), 135.1 (Ar), 133.8 (Ar), 133.3 (Ar), 129.2 (Ar), 129.0 (Ar), 128.8 (Ar), 128.6 (Ar), 82.6 (PhC̲HOC(O)), 42.9 (NCH$_3$), 38.2 (NCH$_3$). IR (KBr) 1520, 1390, 1155, 766, 754, 696 cm^{-1}.

2.7.3.4 (±)-*O*-(1-Phenylbut-3-en-1-yl)-*N*,*N*-Dimethylthiocarbamate (2.74)



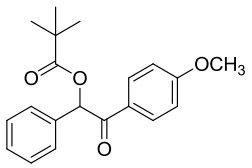
Following the general procedure described in **2.7.3**, the title compound was isolated as a colorless oil (0.090 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.33-7.23 (5H, m, ArH), 6.49 (1H, t, *J* = 6.3 Hz, PhC<u>H</u>O), 5.76-5.67 (1H, m, $CH_2C\underline{H}CH_2$), 5.10-5.02 (2H, m, $CH_2CHC\underline{H}_2$), 3.30 (3H, s, $NC\underline{H}_3$), 3.15 (3H, s, NCH_3), 2.82-2.60 (2H, m, $PhCOC\underline{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ187.2 ($O\underline{C}(S)NMe_2$), 140.0 (Ar), 132.2 ($CH_2\underline{C}HCH_2$), 128.3 (Ar), 127.7 (Ar), 126.7 (Ar), 117.4 ($CH_2CH\underline{C}H_2$), 81.5 (Ph<u>C</u>HOC(O)), 42.6 (NCH_3), 40.9 ($CHO\underline{C}H_2$), 37.7 (NCH_3). IR (KBr) 1520, 1390, 1143, 778, 754, 684 cm^{-1}.

2.7.3.5 (±)-2-Oxo-1,2-Diphenylethyl Pivalate (2.87)



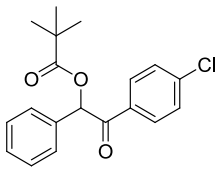
Following the general procedure described in **2.7.3**, the title compound was isolated as a white solid (0.113 g, 91%). M.p. 130-134 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.91 (2H, d, *J* = 7.2 Hz, ArH), 7.52-7.31 (8H, m, ArH), 6.77 (1H, s, PhC<u>H</u>O), 1.26 (9H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ194.2 (Ph<u>C</u>OCHO), 177.9 ($\underline{C}O(CH_3)_3$), 134.8 (Ar), 133.7 (Ar), 133.2 (Ar), 128.92 (Ar), 128.86 (Ar), 128.7 (Ar), 128.5 (Ar), 128.2 (Ar), 77.2 (Ph<u>C</u>HOCO), 38.6 ($\underline{C}(CH_3)_3$), 27.0 (CH_3). IR (KBr) 1732, 1684, 1155, 766, 754, 696 cm^{-1}; MS (EI) 296 (M^+, 8), 191 (100), 105 (90), 85 (39), 57 (53); Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.22; H, 6.81.

2.7.3.6 (±)-2-(4-Methoxyphenyl)-2-oxo-1-phenylethyl Pivalate (2.89a)



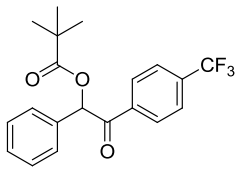
Following the general procedure describe, the title compound was isolated as a white solid (0.119 g, 87%). M.p. 107-110 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.93 (2H, d, *J* = 7.1 Hz, ArH), 7.47-7.29 (5H, m, ArH), 6.86 (2H, d, *J* = 8.8 Hz, ArH), 6.76 (1H, s, PhC<u>H</u>OCO), 3.83 (3H, s, OCH_3) 1.27 (9H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ192.5 (Ar<u>C</u>OCHO), 177.9 (<u>C</u>O$(CH_3)_3$), 163.6 (<u>C</u>OCH_3), 134.3 (Ar), 131.0 (Ar), 128.8 (Ar), 128.1 (Ar), 127.6 (Ar), 113.7 (Ar), 76.9 (Ph<u>C</u>HOCO), 55.3 (OCH_3) 38.6 (C$(CH_3)_3$), 27.0 (CH_3). IR (KBr) 1729, 1679, 1152, 861, 839, 820, 754, 771, 740 cm^{-1}; MS (EI) 326 (M^+, 1), 197 (4), 135 (100), 107 (4), 57 (5); Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.54; H, 6.83.

2.7.3.7 (±)-2-(4-Chlorophenyl)-2-oxo-1-phenylethyl Pivalate (2.89b)



Following the general procedure describe, the title compound was isolated as a white solid (0.103 g, 74%). M.p. 131-132 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.86 (2H, d, *J* = 8.0 Hz, ArH), 7.42-7.33 (7H, m, ArH), 6.72 (1H, s, PhC<u>H</u>OCO), 1.27 (9H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ193.0 (Ar<u>C</u>OCHO), 177.9 (<u>C</u>O$(CH_3)_3$), 139.7 (Ar), 133.4 (Ar), 133.0 (Ar), 130.0 (Ar), 129.1 (Ar), 128.97 (Ar), 128.8 (Ar), 128.1 (Ar), 77.2 (Ph<u>C</u>HOCO), 38.6 (C$(CH_3)_3$), 26.97 (CH_3). IR (KBr) 1731, 1694, 1154, 1096, 772, 757, 733, 701 cm^{-1}; MS (EI) 330 (M^+, 2), 191 (100), 139 (39), 107 (32), 85 (47), 57 (57); Anal. Calcd for $C_{19}H_{19}ClO_3$: C, 68.98; H, 5.79. Found: C, 69.08; H, 6.04.

2.7.3.8 (±)-2-(4-Trifluoromethylphenyl)-2-oxo-1-phenylethyl Pivalate (2.89c)



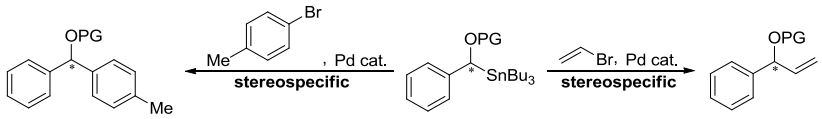
Following the general procedure describe, the title compound was isolated as white solid (0.078 g, 51%). M.p. 93-96°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.01 (2H, d, *J* = 8.1 Hz, ArH), 7.65 (2H, d, *J* = 8.2 Hz, ArH), 7.43-7.35 (5H, m, ArH), 6.72 (1H, s, PhC<u>H</u>OCO), 1.26 (9H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ193.5 (Ar<u>C</u>OCHO), 178.0 (<u>C</u>O$(CH_3)_3$), 137.6 (Ar), 134.4 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz, <u>C</u>CF_3), 133.0 (Ar), 129.3 (Ar), 129.1 (Ar), 128.9 (Ar), 128.2 (Ar), 125.6 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz, <u>C</u>CCF_3), 123.3 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz, CF_3), 77.4 (Ph<u>C</u>HOCO), 38.6 (C$(CH_3)_3$), 26.9 (CH_3). IR (neat) 1729, 1704, 1140, 775, 735, 700, 650 cm^{-1}; MS (EI) 364 (M^+, 0.4), 191 (100), 173 (21), 107 (42), 85 (50), 57 (69); Anal. Calcd for $C_{20}H_{19}F_3O_3$: C, 65.93; H, 5.26. Found: C, 65.70; H, 5.31.

Chapter 3. Stereochemical Outcome of Stille Coupling of α-Alkoxybenzylstannanes

3.1 Introduction

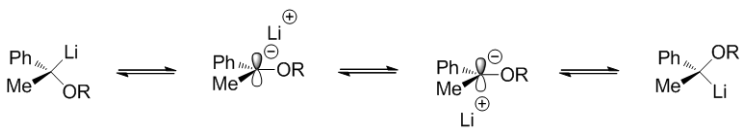
Besides the capability of incorporating vinyl- and aryl-halides as electrophiles for coupling with α-alkoxybenzystannanes through palladium catalysis, there is another advantage of the use of palladium catalyst as opposed to generation of organolithium reagents (Scheme 3.1).

Scheme 3.1: Stereospecific palladium-catalyzed reactions of α-alkoxybenzylstannanes

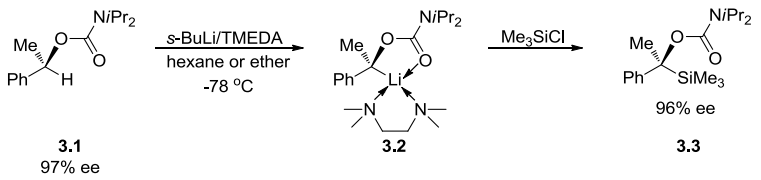


It has long been established that benzyllithiums bearing an α-chiral center are more prone to racemization than the corresponding alkyl derivatives.[1] This is because the aromatic ring effectively stabilizes the carbanion through resonance, and leads to increased planarization of the carbanionic center (Scheme 3.2).[2] In addition, it also favours the formation of solvent-separated ion pairs between the lithium cation and the carbanion. Both of these factors contribute to an increased tendency for the lithium cation to migrate from one enantiotopic face to the other, thereby promoting racemization. Hence, the use of α-alkoxybenzyllithiums to deliver the α-chiral center requires more specific reaction conditions: temperature of ≤–78 ˚C, the use of a bulky *N*,*N*-diisopropylcarbamate protecting group, and the incorporation of a chelating agent, *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA), to hamper the lithium cation from migrating between the two enantiotopic faces of the α-carbon (Scheme 3.3).

Scheme 3.2: Migration of lithium cation between enantiotopic faces of α-alkoxybenzyllithiums



Scheme 3.3: Configurationally stable α-(carbamoyloxy)benzylstannane



In comparison, palladium-catalyzed Stille coupling reaction of α-alkoxybenzylstannanes becomes more desirable. However, an issue associated with the delivery of α-chiral centers is that, unlike tin-lithium transmetallation, which can proceed with essentially complete retention of configuration with proper control, the stereochemical outcome of tin-palladium transmetallation is not as well-established. On top of that, literature examples have shown both retention and inversion of configuration at the α-chiral center depending on the identity of the α-substituent, and this phenomenon applies to coupling reactions of other organometallic reagents as well. Therefore, this chapter will be devoted to discussion on some of the literature examples related to the stereochemical outcomes of palladium-catalyzed cross-coupling reactions and to show the efforts spent on understanding the stereospecificities (e.s.) associated with Stille coupling of α-alkoxybenzylstannanes.

3.2 Stereospecificity of Palladium-Catalyzed Cross-Coupling Reactions

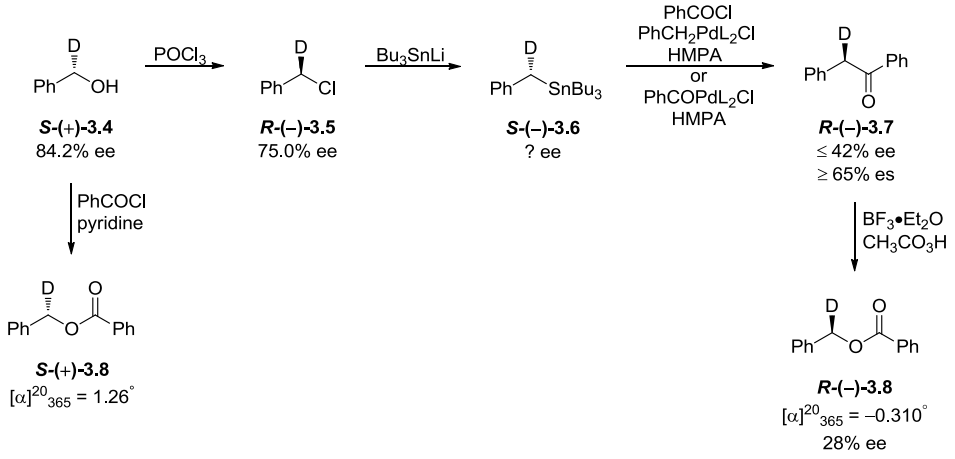
One of the reasons that palladium-catalyzed cross-couplings are such a reliable methodology in organic synthesis is because when alkenyl substrates are involved as coupling partners, each step of the catalytic cycle proceeds with well-established retention of double bond geometries, and hence the overall configurations are faithfully retained. This complete retention of stereochemistry is only applicable to sp^2 coupling partners, though. Over the decades since the discovery of the now widely-used coupling reactions, chemists have tried to establish the stereochemistry of these reactions through numerous studies. Though, as more and more examples have been reported, we seem to be less and less capable of concluding what is really happening in terms of the mechanistics; both inversion and retention of configuration at the α-chiral center have been reported in different situations, and so far there has been

little to no general pattern as to which outcome will be favoured over the other for a given reaction. This is but a consequence of the complexity of the nature of palladium-catalyzed coupling reactions.

3.2.1 Stille Coupling of Chiral Benzylstannane

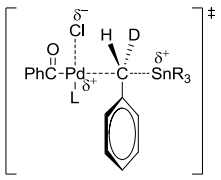
The stereochemical outcome of Stille coupling was studied and reported as early as 1983 by Stille and Labadie.[3] The coupling between (*S*)-(−)-α-(deuterio)benzylstannane **3.6** and benzoyl chloride was studied and its stereochemical outcome was defined based on **3.8**. Stannane **3.6** was prepared by chlorination of (*S*)-(+)-benzyl-*α-d* alcohol **3.4** using $POCl_3$, subsequent stannylation by tributylstannyl-lithium gave **3.6** to undergo the coupling reaction. Upon cross-coupling, the stereochemistry of the product was correlated by first performing a Baeyer-Villiger oxidative to produce the ester **(*R*)-(-)-3.8**, which can then be compared to the ester **(*S*)-(-)-3.8** derived from **3.4** by optical rotation (Scheme 3.4).

Scheme 3.4: Stille coupling of (*S*)-(−)-α-(deuterio)benzylstannane and its stereochemical outcome



Through optical rotation and circular dichroism spectroscopy, they unambiguously established that the coupling reaction, and hence the transmetallation step, proceeded with inversion of configuration. Since benzoylation of (***S*)-(+)-3.4** should not have caused any racemization, by comparing the optical purity ($[\alpha]^{20}_{365}$) of ***R*-(–)-3.8** with ***S*-(+)-3.8**, the enantiomeric excess (e.e.) of ***R*-(–)-3.8** was established to

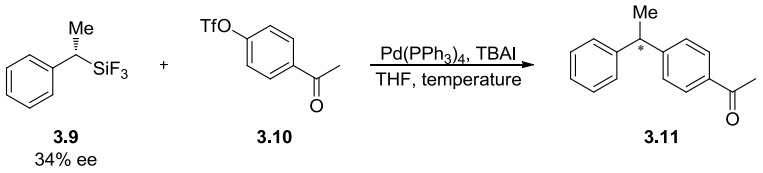
be ~28%. However, as the authors established that there could be 42% racemization going from **3.7** to **3.8** based on deuterium loss in acidic medium, the true e.e. of ***R*-(–)-3.7** could have been 43%, meaning that the Stille coupling of ***S*-(+)-3.6** could have occurred with ≥65% stereospecificity (a term that was later effectively adapted by Denmark[4] for describing the conservation of optical purity over the course of stereospecific reactions). Moreover, based on the inversion of configuration observed, Stille concluded that the transmetallation must have proceeded through an open-S_E2 mechanism, which is highly favored in highly polar solvents such as HMPA.



3.2.2 Hiyama Coupling of Chiral Secondary Benzylsilanes

Despite the fact that there is some uncertainty as to the true stereospecificity of the coupling reaction performed by Stille due to the inability to directly quantify the e.e. of stannane **3.6** or of the coupled product, ***R*-(–)-3.7**, it may be concluded with great degree of confidence that configurational inversion took place (although it is not known to what degree). In a recent study by Hiyama and Hatanaka on the cross-coupling of secondary benzylsilanes with aryl triflates, the dependence of absolute configuration and stereospecificity of the reaction on temperature and solvent was unambiguously established. They showed that when coupling **3.9** (34% ee) and **3.10** using $Pd(PPh_3)_4$ and tetra-*n*-butylammonium iodide (TBAI) in THF (Scheme 3.5), both the optical purity and the absolute configuration of the product varied depending on the temperature. At 50 ˚C, the reaction occurred with nearly complete retention of configuration (32-34% e.e.), but raising the temperature higher resulted in a linear decrease of the optical purity with respect to the temperature. At 75 ˚C, the reaction switched to another transmetallation mechanism and started displaying inversion of configuration. Finally, at a terminal temperature of 100 ˚C, the product showed opposite configuration with about 20% e.e.

Scheme 3.5: Hiyama couping of chiral secondary benzylic silane



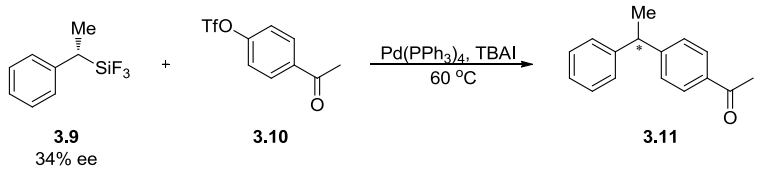
3.9
34% ee

3.10

3.11

Dependence on the solvent used was established through coupling of the same reagents in different solvent compositions (THF, HMPA/THF, DMF/THF and DMSO/THF) at 60 ˚C (Table 3.1). Thus, while THF gave coupled product with ~22% e.e., the use of DMF/THF (1:10) and DMSO/THF (1:10) resulted in a decrease of e.e. to 16% for both, but still with retention of configuration. Finally, the use of HMPA/THF (1:10) gave the opposite enantiomer in 8% e.e.

Table 3.1: Influence of solvent compositions on the stereochemical outcome of Suzuki coupling of chiral secondary benzylic silane



3.9
34% ee

3.10

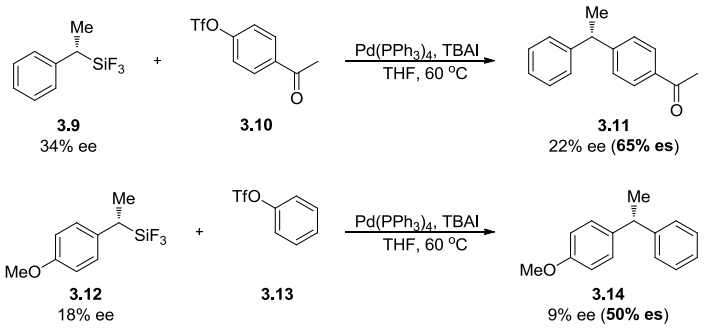
3.11

Solvent	Absolute configuration	% e.e.
THF	*S* (retention)	22
DMF/THF (1:10)	*S* (retention)	16
DMSO/THF (1:10)	*S* (retention)	16
HMPA/THF (1:10)	*R* (inversion)	8

More interestingly, it was found that altering the electronic property of the alkylsilane also caused a significant drop in the stereospecificity. Thus, the coupling of a more electron-rich alkylsilane **3.12** (18% e.e.) with phenyl iodide gave 9% e.e., which equates to 50% e.s., compared to the coupling of **3.9** that proceeded with 65% e.s (Scheme 3.6). This phenomenon was mostly due to favoring of the open-S_E2 transmetallation mechanism to a greater extent by an electron-donating group on the phenyl ring. Moreover, this indicates that the open-S_E2 mechanism for this particular reaction proceeds with C-Pd

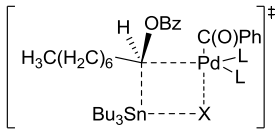
bond forming earlier than C-Si bond breaking. Such an example showcased, for the first time, substrate-controlled variation of stereospecificity.

Scheme 3.6: Influence of secondary benzylic silane substituents on the stereospecificity



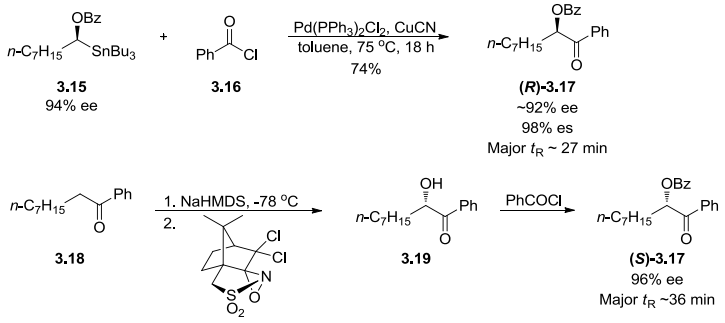
3.2.3 Stille Coupling of α-Heteroatom-Substituted-Organostannanes

The first example of stereospecific Stille coupling of α-alkoxyorganostannane was reported in 1994 by Falck and coworkers.[6] This was also the first reported case where α-alkoxyorganostannanes were subjected to Stille coupling with acid chlorides. Toward the assessment of the stereochemical outcome of the Pd/Cu-catalyzed C-C bond formation, they prepared **3.15** via BINAL-H asymmetric reduction of the corresponding acylstannane, and benzoylated the α-hydroxystannane to afford **3.15** in 94% e.e. Through the use of catalytic amounts of both $Pd(PPh_3)_4$ and CuCN in toluene, the α-alkoxyketone **(R)-3.17** was obtained in 74% yield (Scheme 3.7). Chiral HPLC analysis using a standard synthesized from a method developed by Davis *et al.*[7] showed about 98% retention of configuration (stereospecificity), which equates to about 92% e.e.. The high stereospecificity of this methodology implies a powerful entry to various chiral α-hydroxyketones. The fact that they observed nearly complete retention of configuration on the first Stille coupling of α-alkoxyorganstannanes was unexpected, because the only prior example concerning the stereochemistry of Stille coupling with enantiomerically enriched organostannane reported by Stille gave an inversion of configuration. For the retention of configuration observed, Espinet and Casado later proposed a cyclic-S_E2 transmetallation mechanism to explain it.



This was, for the first time, that people recognized the impact α-heteroatom substituents have on the stereochemistry of the Pd-catalyzed cross-coupling. The proposed transition state model for this chemistry, however, may be inappropriate since it is most likely that an organocopper intermediate undergoes transmetallation with Pd.

Scheme 3.7: Stereochemical outcome for the Stille coupling of α-alkoxyalkylstannane **3.15** and assignment of absolute configuration

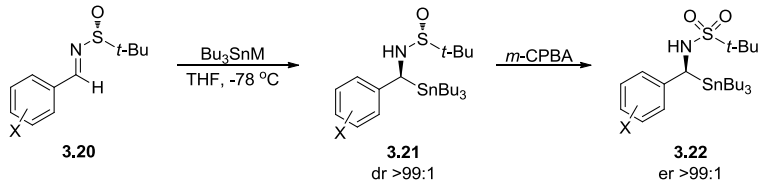


There are a few limitations imposed on the reaction conditions of these α-alkoxyorganostannanes with acid chlorides catalyzed by Pd/Cu co-catalyst, in that in order for the reaction to run well, the condition has to be quite stringent. For example, CuCN is a necessity for the reaction to run and other copper(I) salts either gave lower or no yield. In addition, toluene was the optimal solvent for these reactions, while THF gave a significantly reduced yield. The use of chlorinated solvents such as dichloroethane, as well as solvents of higher polarity (DMF, NMP, DMSO, acetone, and HMPA) stopped the reaction altogether. Particularly with the limit imposed on the choice of solvent, an investigation for trying to establish the dependence of coupling stereospecificity on the solvent polarity then became impossible. Furthermore, the use of a Cu co-catalyst implies that there is another transmetallation reaction with its own independent stereochemical consequences. Even though they also gave an example of coupling of an α-(phthalimidoyl)octylstannane, an α-aminoorganostannane, with benzoyl chloride that proceeded in 45% yield, no attempt was made to investigate its stereochemistry. However, Chong and

Kells disclosed the Stille coupling of stereochemically defined α-sulfonamidobenzylstannanes some time later.

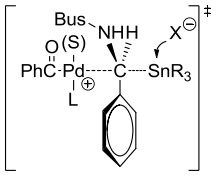
The methodology developed by Chong and Kells is very attractive considering that the enantiomerically enriched starting material, α-(*tert*-butylsulfonamido)benzylstannanes **3.22**, can be prepared as essentially one enantiomer. Subsequent cross-coupling with benzoyl chloride gave α-aminoketones also as essentially one enantiomer, making this three-step procedure very highly "enantioselective". Enantiomerically pure α-sulfonamidobenzylstannanes were made by a highly diastereoselective addition of a tributyltin group to sulfinimines **3.20** derived from the corresponding aldehydes and (*R*)-*tert*-butylsulfinamide.[9] Oxidation of sulfinimines with *m*-CPBA afforded the α-sulfonamidobenzylstannanes **3.22** (Scheme 3.8). The reason that the addition is so selective is because it goes through a six-membered chair transition state. But note that selectivities with typical alkyllithium and Grignard reagents are usually lower than the use of Bu_3SnLi. While the use of Bu_3SnLi as addition agent is very effective for substrates having electron-donating substituents on the aromatic ring, $Bu_3SnZnEtLi$ became the reagent of choice for substrates containing electron-withdrawing substituents. The difference in reactivity between the two kinds of aromatic aldehydes was thought to be due to switch in the reaction mechanism between an ionic process and a single electron-transfer process.

Scheme 3.8: Asymmetric synthesis of α-(*tert*-butylsulfonmido)benzylstannanes



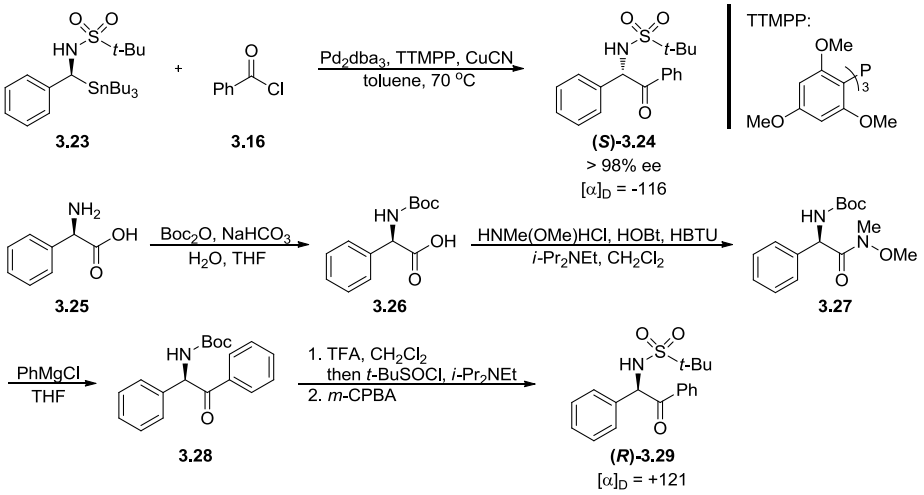
Stille coupling of these α-(*tert*-butylsulfonamidobenzylstannanes with benzoyl chloride was also Pd/Cu co-catalyzed and needed to be run in toluene (Scheme 3.9), as in Falck's procedure. However, despite the use of a non-polar solvent that is expected to give rise to retention of configuration at the α-carbon, coupling of **3.23** proceeded with essentially complete inversion of configuration (>99% e.s.). The

absolute configuration was correlated to a standard synthesized from enantiomerically pure (*R*)-phenylglycine **3.25** by optical rotation. Inversion of configuration called for the open-S_E2 transmetallation model to explain it.



Moreover, unlike Hiyama's findings (Scheme 3.6)[5], coupling of stannanes containing different substituents on the aromatic ring had no effect on lowering of product e.e.. As a result of this, coupling of these stannanes present themselves as a very special case compared to other Pd-catalyzed cross-coupling reactions presented in this chapter.

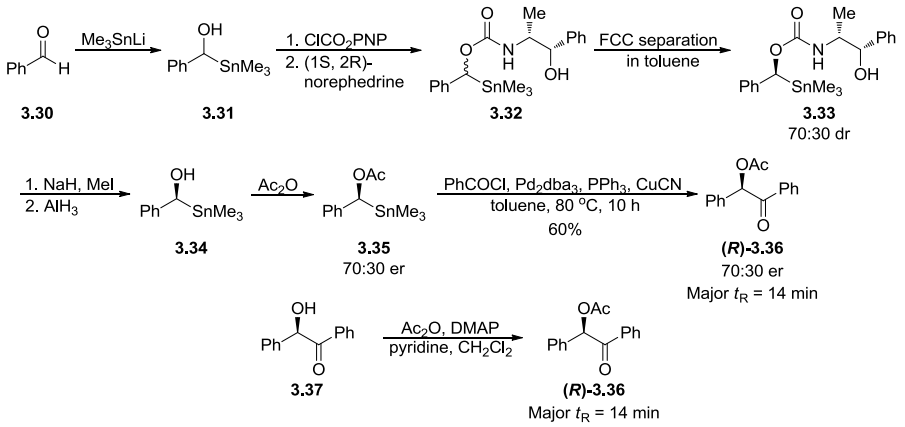
Scheme 3.9: Stereochemical outcome for Stille coupling of α-(*tert*-butylsulfonamido)benzylstannane and establishment of absolute configuration



As with Falck's procedure, use of toluene as the solvent is necessary to achieve optimal yield, this limitation prevented one from investigating the relationship between the stereochemical outcome of the reaction and the solvent. In addition, no effort was put to establish the e.e.'s that one would get by using different electrophiles.

Previously in the Chong group[11], an attempt was made to prepare enantiomerically enriched α-(acetoxy)benzylstannanes and cross-couple them with benzoyl chloride in hope of establishing the stereochemistry of the process and comparing it to the inversion of configuration reported on the coupling of α-(sulfonamido)benzylstannanes. It was hypothesized that even though Falck reported >98% retention of configuration for coupling of α-[(alkoxy)octyl]stannane **3.15** (Scheme 3.7), an α-benzyl group may offer sufficiently different reactivity and display a difference in outcome than the >98% retention. Furthermore, the unexpected inversion observed in coupling of the α-aminobenzylstannane prompted further investigation. Thus, through separation of diastereomeric α-carbamoylstannanes **3.32** derived from (1S, 2R)-norephedrine[12], enantioenriched α-alkoxystannane **3.35** was obtained in 70:30 e.r.. Acetylation followed by Pd/Cu co-catalyzed Stille coupling with benzoyl chloride gave the α-acetoxyketone **(*R*)-3.36** in 60% yield (Scheme 3.10). The absolute configuration for **(*R*)-3.36** was correlated by chiral HPLC with a standard prepared by acetylation of enantiomerically pure (−)-(*R*)-benzoin **3.37** and showed that the coupling occurred with retention of stereochemistry.

Scheme 3.10: Chiral separation of α-alkoxybenzylstannane, its Stille coupling, and assignment of absolute configuration



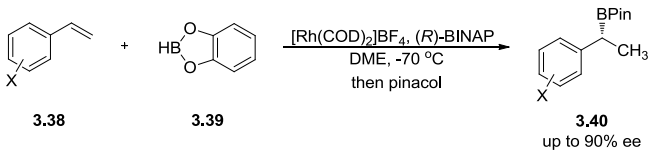
The fact that complete retention of configuration was established agreed with Falck's finding, and a close-S_E2 transition state must have been at work during transmetallation. By now a generalization can be made regarding the Stille coupling of α-heteroatom-substituted stannanes. α-Alkoxystannanes undergo

coupling with retention of configuration and α-aminobenzylstannanes with inversion of configuration. However, the very significant question of why there is such a difference remains.

3.2.4 Suzuki Coupling of Chiral Benzylboronic Esters

In 2009, the second stereospecific Pd-catalyzed Suzuki-Miyaura coupling of chiral secondary organoboronic esters, besides the coupling of potassium cyclopropyl trifluoroborates[13], was reported by Crudden and coworkers.[14] They relied on an asymmetric hydroboration method pioneered by Hayashi and Ito to gain access of the chiral secondary benzylboronates in high regio- and enantioselectivities.[15] Thus, by using Rh-(*R*)-BINAP in the presence of catecholborane (HBcat) **3.39** at -70 ˚C, styrene derivatives **3.38** underwent hydroboration in great preference for the branched isomer. Subsequent pinacol quenching afforded the corresponding (*R*)-pinacol-1-(aryl)ethyl boronates **3.40** in up to 90% e.e. (Scheme 3.11).

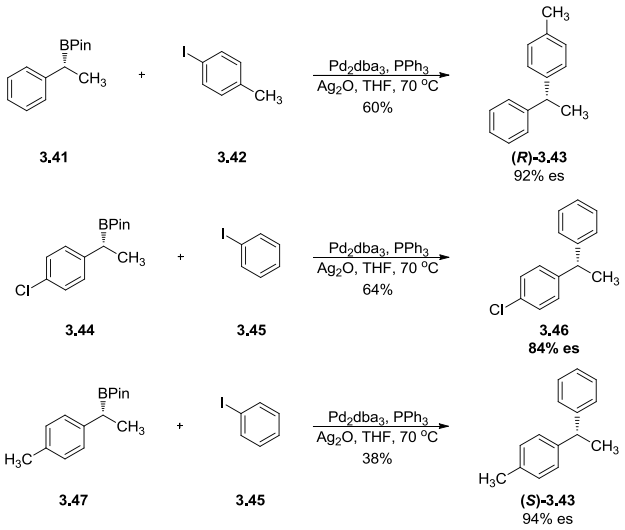
Scheme 3.11: Rhodium-catalyzed enantioselective hydroboration of styrene derivatives



3.38 **3.39** **3.40** up to 90% ee

Through coupling of **3.40** with aryl iodides in the presence of Pd_2dba_3, PPh_3, and Ag_2O, it was found that the reactions proceeded with retention of configuration, in line with Hiyama's observation for secondary alkyl benzylsilanes. Moreover, even though slight variations in the stereospecificities of coupling with different aryl iodides were observed, they are mostly in the range of 91-93% e.s. Intriguingly, by using boronate ester **3.44** with an electron-withdrawing group on the aromatic ring, erosion in stereospecificity was observed (84% e.s.), while **3.47**, bearing an electron-donating methyl group, did not exhibit the erosion problem (Scheme 3.12).

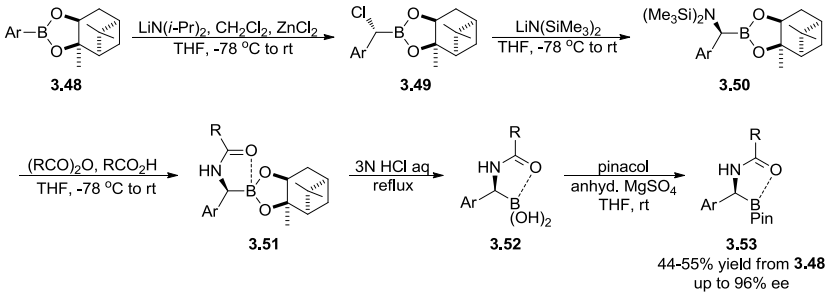
Scheme 3.12: Suzuki coupling of chiral substituted secondary benzylic boronates with aryl iorides



As specified in the report, the low yields were primarily due to difficulties in separating byproducts arising from homocoupling (~5% in each case) as well as Heck coupling products (2-3%). The erosion in e.s. for 4-chlorophenyl boronate **3.44** was most likely due to a small amount of switch to another mechanism, similar to Hiyama's case (Scheme 3.6).[5]

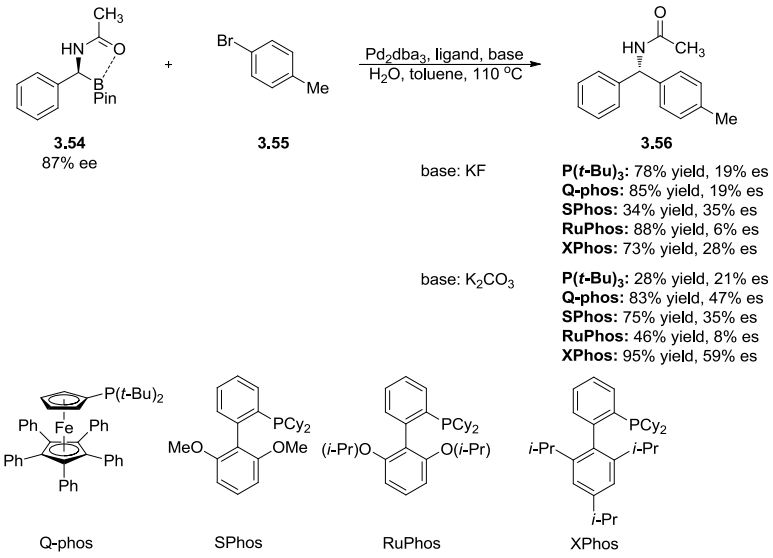
In 2010, another investigation into the stereospecific Suzuki coupling of chiral α-aminobenzyl-boronates was documented.[16] Through a series of reactions, Suginome and coworkers prepared enantiomerically enriched α-aminobenzylboronates and coupled them with aryl bromides to look into the stereochemical outcome of these reaction. The enantioenriched boronates were made first by an asymmetric Matteson homologation of the arylboronates derived from (–)-pinanediol (Scheme 3.13). The amino group was put on using with lithium hexamethyldisilazide (LiHMDS) to form **3.50**. Desilylation and acylation gave the amidoboronates **3.51**, which was then transesterified over two steps to the pinacol boronates **3.53** in respectable yields from **3.48**. More importantly, this route can lead to products with up to 96% e.e.

Scheme 3.13: Asymmetric synthesis of α-amidobenzylboronates

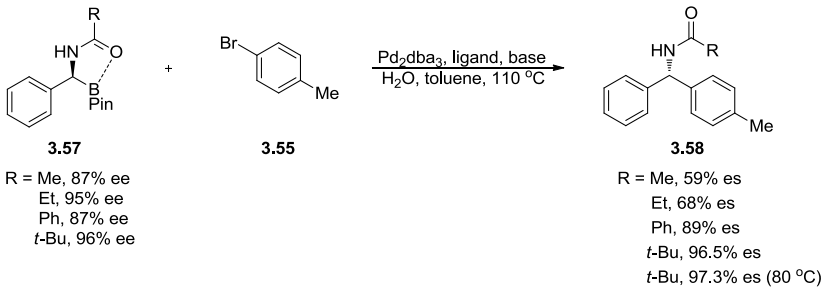


Having prepared the enantioenriched starting materials, a study of reaction optimization using two different bases (KF and K_2CO_3) in combination with several ligands was carried out (Scheme 3.14), and inversion of stereochemistry was observed. The results showed that both the yield and the stereospecificity of the reaction were highly dependent on both ligand and base. In general, K_2CO_3 gave overall faster reactions than KF (not shown) and the stereospecificities were also a bit higher. It was found that the optimal combination was with the use of XPhos in the presence of K_2CO_3, which gave 95% yield and 59% e.s.. Subsequent survey of the amido-substituents showed an interesting linear dependence of the stereospecificity on the size of the substituent (Scheme 3.15). As the steric bulk was raised, the e.s. also increased, though at the expense of a slight decrease of product yield. Hence it was decided that the combination of having a *tert*-butylamido group and the use of both XPhos and K_2CO_3 was the optimal condition.

Scheme 3.14: Screening of reaction conditions for the Suzuki coupling of chiral α-amidobenzylboronates

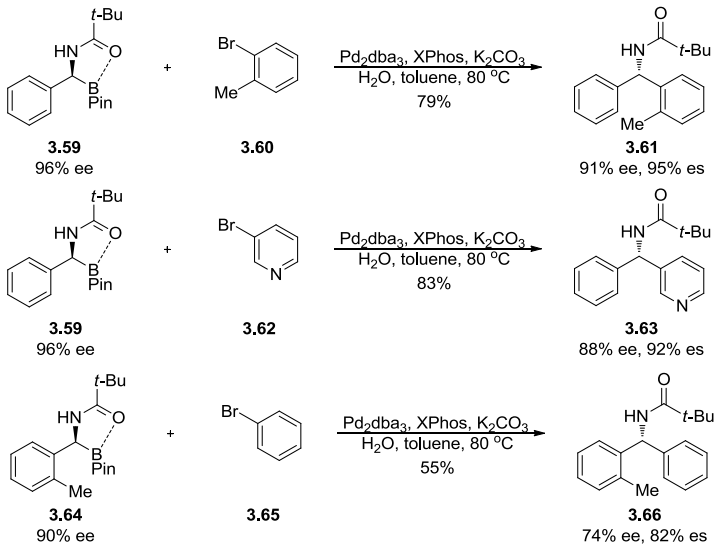


Scheme 3.15: Influence of amido substituents on the stereospecificity of Suzuki coupling



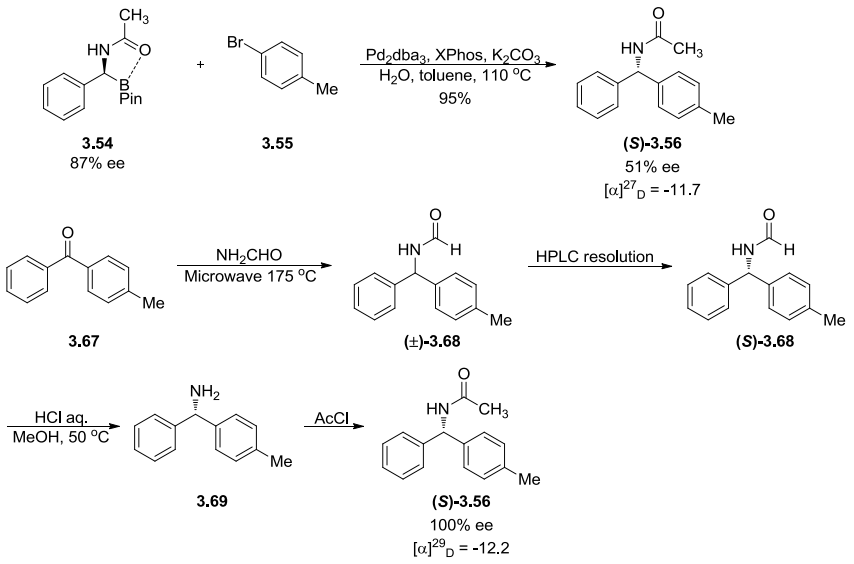
Coupling of enantioenriched boronates with electron-rich and electron-deficient aryl bromides showed that in most cases, the substituents on aryl bromide exerted no significant influence on the stereospecificity of the reaction (95-98% e.s.). In addition, sterically demanding aryl bromide **3.60** also coupled with 95% e.s. (Scheme 3.16). The only exception was with 3-bromopyridine **3.62**, where a slight erosion in e.s., 92%, was detected. This could be due to interference of the selectivity brought about by the pyridyl nitrogen coordinating to palladium, perhaps giving rise to a competitive closed-S_E2 transmetallation pathway by a small amount. Interestingly, when greater steric bulk was introduced to the boronate **3.64**, a greater drop in the coupling e.s. resulted.

Scheme 3.16: Suzuki coupling of chiral α-amidobenzylboronates with aryl bromides



The absolute configuration of the coupled product **(*S*)-3.56** was established by comparing its optical rotation to an authentic sample prepared by HPLC resolution (Scheme 3.17).

Scheme 3.17: Assignment of absolute configuration for Suzuki-coupling product of chiral α-amidobenzylboronates



3.3 Proposal

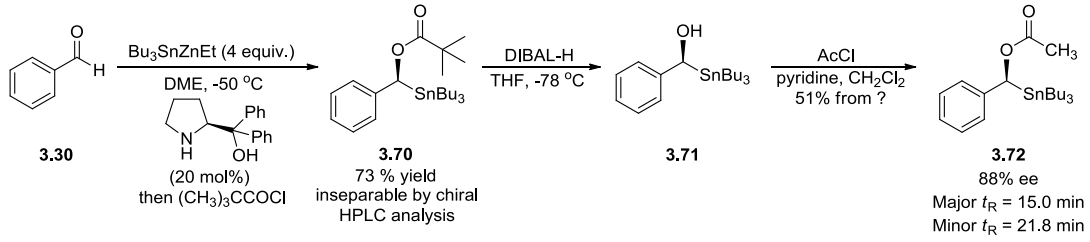
While there is a multitude of examples that have already been reported concerning the stereochemical outcome of Pd-catalyzed coupling reactions, the topic continues to hold many questions that still need to be answered. One of the most important questions is whether we can derive a working hypothesis that grants us the ability to predict whether a coupling reaction would proceed through retention or inversion. But so far our knowledge only allows us to propose transmetallation models (cyclic- vs. open-S_E2 pathways) in an after-the-fact manner to explain the outcomes. Because of this, better understanding of this topic is needed.

Due to an on-going interest in the chemistry of α-alkoxystannanes and the stereochemistry associated with them, we have been investigating the Stille coupling of stereochemically defined α-alkoxybenzylstannanes for some years now. Despite the relatively well-studied Suzuki coupling of chiral boronates, a systematic study on the Stille coupling of chiral stannanes is still lacking. In 2008, a synthetic method on the asymmetric synthesis of enantiomerically enriched α-alkoxybenzylstannanes surfaced, which granted us a reliable entry to these molecules. With this in hand, we intend to establish the relationship between the stereochemical outcome of Pd/Cu co-catalyzed cross-coupling of enantioenriched (*S*)-α-(trimethylacetoxy)benzylstannane with benzoyl chloride using different ligands. Furthermore, coupling of different substituted-benzoyl chlorides will also be examined.

3.4 Results and Discussion

In 2008, Falck and He developed a method for asymmetric addition of $Bu_3SnZnEt$ to aldehydes that relied on the use of a chiral amino alcohol ligand derived from (*S*)-proline.[17] Since the pivalate ester protecting group displayed optimal coupling efficiency, its enantiomerically enriched form was a good starting point to start the investigation. Using Falck's method for the preparation of α-hydroxystannanes, we obtained (*S*)-α-(trimethylacetoxy)-benzylstannane **3.70** in 73% yield. (Scheme 3.18). It is note-worthy to point out that a lower e.e. (88%) compared to Falck's report on the synthesis of α-(acetoxy)benzylstannane (95-96% e.e.) was obtained. A communication with the author suggested that the slight loss in enantioselectivity is an intrinsic problem upon scaling up the reaction.

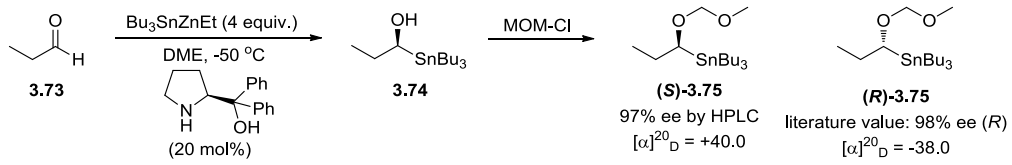
Scheme 3.18: Enantioselective synthesis of chiral α-(trimethylacetoxy)benzylstannane and determination of enantiomeric purity



Having obtained the pivalate-protected stannane **3.70**, attempts were made to characterize its e.e. using chiral HPLC analysis (CHIRACEL OD-H); however, the two enantiomers were inseparable and gave only one peak. This was believed to be because the steric bulk of the *tert*-butyl group effectively lowers the difference in binding energies between the two enantiomers with the chiral stationary phase of the column. We rationalized that decreasing the size of the *tert*-butyl group to a simple methyl group would help separation, which was indeed the case. Chiral HPLC equipped with CHIRACEL OD-H column successfully separated the two peaks to give an enantiomeric ratio (e.r.) of 94:6. Since the deprotection/acetylation sequence is not expected to lead to any racemization, we concluded that the pivalate ester was made in 88% e.e. The absolute configuration for 1,2-adducts formed by Falck's methodology (90-97% e.e. for various aldehydes as the substrate) was assigned based on the asymmetric

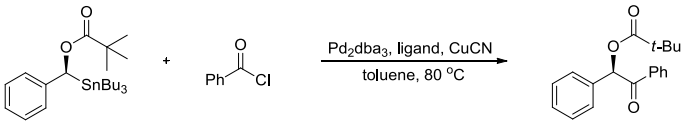
addition of $Bu_3SnZnEt$ to propionaldehyde **3.73** and protection with MOM-Cl to give **3.75**. Comparison of its optical rotation with literature value confirmed that it had (*S*)-configuration (Scheme 3.19). All other adducts were assigned based on **(*S*)-3.75**.

Scheme 3.19: Assignment of absolute configuration for enantioenriched α-alkoxyalkylstannane



Once the absolute configuration and the e.e. of **3.70** was established, Stille coupling with benzoyl chloride was undertaken. First, the effect of different ligands on the stereochemical outcome was examined (Table 3.2). In all cases retention was observed. It was found that the stereospecificities varied slightly with different ligand used, ranging from 88-95% e.s.. Furthermore, no clear relationship between the ligand and the e.s. was observed. Ligand that is poor σ-donors and not very bulky, TFP, gave a good yield, but the e.s. was below 90% (entry 4). The bulky ligand, P(*o*-Tol)$_3$, gave the higest e.s. of 95% (entry 1). A ligand that is both bulky and electron-rich, DavePhos, gave an intermediate e.s. of 90% (entry 3); but a very electron-poor but bulky ligand, $P(C_6F_5)_3$, gave the lowest e.s. of 88% (entry 5). A somewhat loose trend that can be established based on the observation made here is that for the reaction e.s. to be above 90%, ligands that are weak σ-donors should be avoided; no unambiguous trend can be extrapolated for the steric property of the ligands.

Table 3.2: Influence of ligand on the stereospecificity of Stille coupling of α-(trimethylacetoxy)benzyl-stannane **3.70**



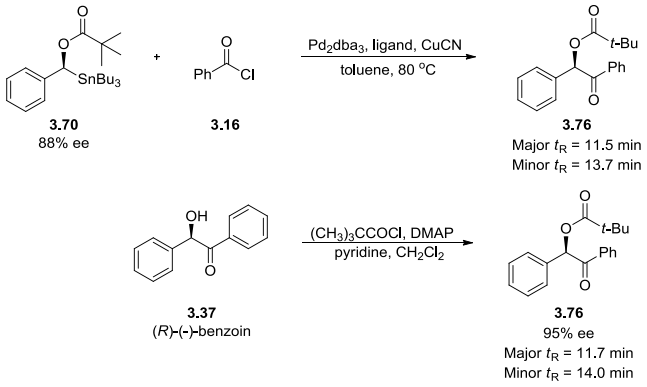
3.70 88% ee | **3.16** | **3.76**

Entry	Ligand	% Yield[a]	% e.e.[b]	% e.s.[c]
1	P(*o*-Tol)$_3$	67	83	95
2	PPh$_3$	91	82 (81)[d]	94 (92)[d]
3	DavePhos	77	79 (79)[d]	90 (90)
4	TFP	92	78	89
5	P(C$_6$F$_5$)$_3$	47	77	88

[a] Isolated yield by flash column chromatography
[b] Determined by HPLC with CHIRACEL OD-H column
[c] e.s. = (% e.e. of product/% e.e. of starting material) × 100%
[d] Indicated in the parentheses are results of a second reaction

The absolute configuration of the product was determined by comparing its HPLC retention times (t_R) to those of a standard derived from trimethylacetylation of (*R*)-(−)-benzoin **3.37** (Scheme 3.20).

Scheme 3.20: Assignment of absolute configuration of Stille coupling product of α-(trimethylacetoxy)-benzylstannane with benzoyl chloride



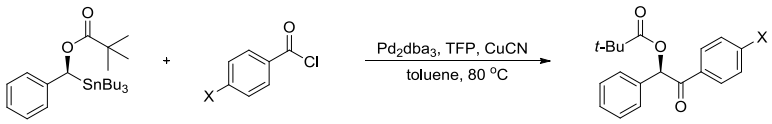
3.70 88% ee | **3.16** | **3.76** Major t_R = 11.5 min, Minor t_R = 13.7 min

3.37 (*R*)-(-)-benzoin | **3.76** 95% ee, Major t_R = 11.7 min, Minor t_R = 14.0 min

Based on this, it was concluded that all reactions, regardless of the e.s., proceeded with retention of configuration. These results were in line with Falck's observation for α-alkoxyalkylstannane **3.15**.[6] In contrast to Chong's report on the coupling of stereochemically defined α-sulfonamidobenzylstannanes, where no erosion in the stereospecificity was observed, our work showed that ligands can indeed induce, however small the amounts are, erosion in e.s. This is in line with Suginome's work on α-amidobenzyl-boronates.[16]

Based on the relationship between the coupling reaction stereospecificity and the electrophile in Pd-catalyzed cross-couplings by others, neither the steric nor the electronic properties of the electrophile had a dramatic effect on the outcome. The only exception being the use of 3-bromopyridine **3.62** as an electrophile; where Pd-to-N coordination may be influencing the reaction mechanism (Scheme 3.16).[16] If this is the case, one may rationalize this based on the argument that the electronic properties that get relayed to the Pd center during the rate-determining transmetallation step isn't significant enough to favor a different pathway in general. To examine if this observation made by others is applicable to coupling of α-alkoxybenzylstannanes, we cross-coupled **3.70** with various substituted-benzoyl chlorides having different electronic properties. The results are summarized in Table 3.3. Based on the results, while having a methoxy- and a chloro-substituents (substituent constants σ_p of -0.12 and 0.24, respectively)[18] did not give significant loss in the e.s. (entries 1 and 3); in the presence of a trifluoromethyl-substituent (σ_p of 0.53) lowered the e.s. significantly to 89% (entry 4). Surprisingly, even without any functional group (hydrogen having a σ_p value of 0) also gave a lower e.s. (entry 2). Attempts were made to cross-couple 4-cyano- and 4-nitro-benzoyl chloride, but the yields were too low such that no product could be obtained for HPLC analysis. Based on these results, no clear correlation could be drawn.

Table 3.3: Influence of electrophile on the stereospecificity of Stille coupling of α-(trimethylacetoxy)-benzylstannane **3.70**



3.70
88% ee

3.16

3.77

Entry	X	% Yield[a]	% e.e.[b]	% e.s.[c]
1	OMe	74	86	97
2	H	92	78	89
3	Cl	62	87	99
4	CF_3	53	76	89

[a] Isolated yield by flash column chromatography
[b] Determined by HPLC with CHIRACEL OD-H column
[c] e.s. = (% e.e. of product/% e.e. of starting material) × 100%

3.5 Conclusion

Palladium-catalyzed cross-coupling involving organometallic compounds containing an α-chiral center is slowly gaining importance for the synthetic community for their ability to undergo stereospecific reactions, regardless of retention or inversion of configurations. More and more researchers are undertaking studies in hopes of gaining better understanding of the process mechanisms and to be able to construct a model for predicting the stereochemical outcome of any coupling reaction involving chiral organometallic reagents. As more and more methods for the asymmetric synthesis of these chiral organometallics surface, more data will be compiled to our knowledge reserve.

The concept of stereospecificity was introduced in this chapter for describing the conservation of e.e. throughout a stereospecific reaction; which is useful considering that all starting materials have an e.e. value associated with them, but every starting material has a different e.e.. Examples presented in this chapter have shown that the stereospecificity of Pd-catalyzed coupling reactions can be influenced by essentially any factor of a reaction condition, from solvent to temperature, from ligand to the electrophile, and the organometallic reagent itself. It was seen that solvent identity and the properties of the organometallic reagent show the most prominent influence.

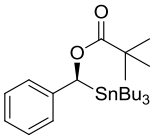
Having examined the stereochemical consequences of Stille coupling of α-alkoxybenzylstannanes, several conclusions can be made. First of all, the ligand brings about a small, but significant, impact on the stereospecificity of the reaction, ranging from some of the higher ones in 94-95% e.s. to the lower ones in 88-89% e.s.. While no correlation could be extrapolated from the influence of the steric properties of the ligands, ligands that are poor σ-donors appear to give lower e.s. values. Secondly, use of electrophiles having different electronic properties also exerts an influence on the e.s. of the reaction, although the effect is quite small, meaning a change of transmetallation mechanism to small extents. While no unambiguous trend could be derived, the extent of erosion in reaction e.s. is within similar ranges reported by others.

3.6 Experimental

3.6.1 General Experimental

All reactions were performed using oven- or flame-dried glassware under an argon atmosphere. DME, and toluene were freshly distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. Benzaldehyde was filtered through a pad of activated basic aluminum oxide (~150 mesh, 58 Å). (*S*)-diphenyl(pyrrolidin-2-yl)methanol was prepared from (*S*)-proline using Corey's method.[19] Bu_3SnH was prepared by reduction of bis(tributyltin)oxide with $NaBH_4$ in ethanol[20] and was distilled (kugelrohr) before use. All chemicals were purchased from Sigma-Aldrich® and used as received unless otherwise specified. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Couplings of carbon to tin are reported as two values (to ^{117}Sn and ^{119}Sn) when discernible, and as one number when two individual couplings are not discernible. Chiral HPLC analyses were performed using a CHIRACEL OD or OD-H column. All columns have the dimensions of 250 × 4.6 mm. Optical rotations were measured using a Rudolph Autopol III Automatic Polarimeter at room temperature.

3.6.2 Preparation of (*S*)-α-(Trimethylacetoxy)Benzylstannane (3.70)

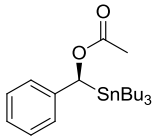


Following Falck's procedure[17], Et_2Zn (59 mL of 1.0 M solution in diethyl ether, 59 mmol) was dissolved in DME (300 mL) and cooled to -78˚C. Bu_3SnH (16 mL, 59 mmol) was added dropwise via an addition funnel. Once the addition was complete, the reaction was allowed to stir for an addition 5 min before transferring to a 4 ˚C bath and was allowed to stir overnight. The reaction mixture was cooled to -78 ˚C again on the next day, and more DME (400 mL) was added. (*S*)-diphenyl(pyrrolidin-2-yl)methanol (0.75 g, 3.0 mmol) was dissolved in DME (30 mL) and added into the reaction mixture dropwise via an

addition funnel. The reaction was stirred for 15 min after completion of addition. Benzaldehyde (1.5 mL, 14.8 mmol) was dissolved in DME (15 mL) and added into the reaction mixture dropwise via an addition funnel. The reaction was stirred for a further 5 min before the temperature was brought up to -40 ˚C and maintained there. The reaction was stirred for 6 h. After the reaction was complete as judged by TLC (hexanes/Et_2O 40:1), it was allowed to warm up to 0 ˚C and quenched with sat. NH_4Cl solution (250 mL). The solvent was rotoevaporated. The residue was extracted with Et_2O (3 × 250 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product as a yellow oil.

The crude α-(hydroxy)benzylstannane was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 ˚C. DMAP (0.14 g, 1.18 mmol) and pyridine (4 mL) were added and the mixture was stirred for 15 min. Trimethylacetyl chloride (3.6 mL, 29.54 mmol) was added dropwise at 0 ˚C and stirred for 15 min before removing the ice bath. The reaction was allowed to warm up to room temperature and stirred for 12 h. Once the reaction was complete as judged by TLC (hexane/Et_2O 40:1) it was quenched with sat. NH_4Cl (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product. The yellow oil was purified by flash column chromatography (30 g silica / 1 g crude, hexane/Et_2O 40:1) to afford the title compound (5.2 g, 73%) as colorless oil. The spectral data for this compound was identical to the data for the racemic mixture of this compound. $[\alpha]^{20}_D$ = -19.6 (c = 1.0, $CHCl_3$, 88% e.e.); attempt was made to separate the two enantiomers by chiral HPLC analysis [OD-H, 0.5% *i*-PrOH/hexanes, 1.0 mL/min, t_R = 6.8 min (*R* and *S*)]; the enantiomeric excess of the product was assigned based on HPLC analysis of **3.72**. Absolute configuration was assigned based on Falck's report.[17]

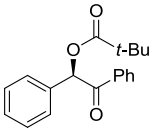
3.6.3 Preparation of (*S*)-α-(Acetoxy)benzylstannane[17] (3.72)



(*S*)-α-(Trimethylacetoxy)benzylstannane **3.73** (10 mg, 0.02 mmol) was dissolved in CH_2Cl_2 and cooled to -78 ˚C. DIBAL-H (0.05 mL of 1.0 M solution in hexanes, 0.05 mmol) was added to the reaction mixture, and allowed the reaction mixture to stir for 15 min. After the reaction has completed as judged by TLC (hexanes/Et_2O 40:1), MeOH (3-4 drops) was added at -78˚C to quench the reaction. Saturated sodium potassium tartrate (4-5 drops) was added into the reaction mixture at -78 ˚C. The reaction mixture was then allowed to warm to room temperature. More sat. sodium potassium tartrate (1 mL) was added into the crude mixture. The organic layer was separated from the aqueous layer, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude α-hydroxybenzylstannane as a pale yellow oil that was acetylated immediately without purification.

The crude hydroxystannane was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 ˚C. DMAP (1 mg, 0.01 mmol) was added, followed by pyridine (5 μL). Acetic anhydride (5 μL, 0.06 mmol) was added dropwise via a microsyringe. The reaction mixture was stirred for a further 15 min before removing the ice bath. The reaction was stirred overnight. After the reaction has completed as judged by ^1H NMR spectroscopy, it was concentrated *in vacuo* to afford the crude product that was purified by unpressurized column chromatography (40 g silica/ 1 g of crude, hexanes/Et_2O 80:1) to afford the title compound (4.5 mg, 51%) as a colorless oil. The spectral database for this compound was identical to the data for the racemic mixture of this compound. $[\alpha]^{20}_D$ = +3.5 (c = 1.0, $CHCl_3$, 88% e.e.); the enantiomeric excess was measure by chiral HPLC analysis [OD-H, 100% hexanes, 0.5 mL/min, t_{R1} = 15.0 min (*R*), t_{R2} = 21.6 min (*S*)].

3.6.4 Preparation of (*R*)-2-Oxo-1,2-Diphenylethyl Pivalate (3.76)



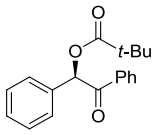
(*R*)-(-)-Benzoin (7 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 ˚C. DMAP (a crystal) was added to the reaction mixture, followed by pyridine (16 μL, 0.2 mmol). The reaction mixture was allowed to stir for a further 15 min. Trimethylacetyl chloride (25 μL, 0.2 mmol) was added dropwise using a microsyringe. The ice bath was removed and the reaction mixture was allowed to stir overnight. The reaction was quenched with sat. NH_4Cl (5 mL) and diluted with CH_2Cl_2 (20 mL). The organic layer was separated from the aqueous layer and washed with sat. NH_4Cl (5 mL). It was then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product was that purified by flash column chromatography (40 g silica/ 1 g of crude, hexanes/Et_2O 10:1) to afford the title compound (6 mg, 73%) as a white solid. The spectral data for this compound were identical to the data for the racemic mixture of this compound. M.p. 113-116˚C; $[\alpha]^{20}_D$ = -109.3 (c = 1.0, $CHCl_3$, 97% ee); enantiomeric excess was measure by chiral HPLC [OD, 5% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 7.6 min (*R*, major), t_{R2} = 10.7 min (*S*, minor)]

3.6.5 General Procedure for Stille Coupling of α-Alkoxybenzylstannanes with Benzoyl Chloride

Pd_2dba_3 (0.020 g, 0.02 mmol), PPh_3 (22 mg, 0.08 mmol) and CuCN (7 mg, 0.08 mmol) were loaded into a Schlenk tube evacuated and filled with argon and dissolved with toluene (3 mL). α-(trimethylacetoxy)benzylstannane (0.200 g, 0.42 mmol) was dissolved in toluene (1 mL) and let drain into the Schlenk tube. Benzoyl chloride (60 μL, 0.50 mmol) was dissolved in toluene (1 mL) and let drain into the Schlenk tube. The Schlenk tube was sealed and the reaction was allowed to run at 80 ˚C until completion of reaction as monitored by TLC (hexane/Et_2O 5:1). The reaction was then stopped and the

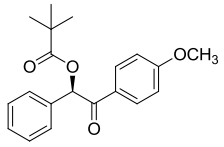
solvent was concentrated *in varuo* to afford the crude product. The crude product was purified by flash column chromatography on 10% K_2CO_3/silica (*w*/*w*)[24] (30 g silica / 1 g crude, hexane/Et_2O 10:1) to afford the pure product.

3.6.5.1 (R)-2-Oxo-1,2-Diphenylethyl Pivalate (3.76)



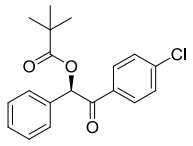
Following the general procedure described in **3.6.5**, the title compound was isolated as a white solid (0.113 g, 91%). The spectral database for this compound was identical to the data for the racemic mixture of this compound. M.p. 114-116 ˚C; $[\alpha]^{20}_D$ = -117.5 (c = 1.0, $CHCl_3$, 79% ee); enantiomeric excess was measure by chiral HPLC [OD, 5% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 7.9 min (*R*), t_{R2} = 10.8 min(*S*)]; absolute configuration was assigned based on (*R*)-3.72 prepared from (*R*)-benzoin.

3.6.5.2 (R)-Phenyl-2-oxo-2-(4-methoxyphenyl)ethyl pivalate (3.77a)



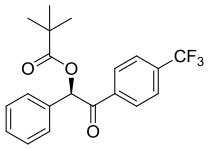
Following the general procedure described in **3.6.5**, the title compound was isolated as a white solid (0.101 g, 74%). The spectral database for this compound was identical to the data for the racemic mixture of this compound. M.p. 101-103 ˚C; $[\alpha]_D$ = -18.4 (c = 1.0, $CHCl_3$, 85% ee); enantiomeric excess was measured by chiral HPLC analysis [OD, 1% *i*-PrOH/hexanes, 0.5 mL/min, t_{R1} = 59.8 min (R), t_{R2} = 7.4 (S)]; absolute configuration was assigned based on retention of configuration for the cross-coupling.

3.6.5.3 (R)-Phenyl-2-oxo-2-(4-chlorophenyl)ethyl pivalate (3.77b)



Following the general procedure described in **3.6.5**, the title compound was isolated as a white solid (0.086 g, 62%). The spectral database for this compound was identical to the data for the racemic mixture of this compound. M.p. 90-93 ˚C; $[\alpha]_D$ = -75.4 (c = 1.0, $CHCl_3$, 87% ee); enantiomeric excess was measured by chiral HPLC analysis [OD, 1% *i*-PrOH/hexanes, 0.5 mL/min, t_{R1} = 32.6 min (*R*), t_{R2} = 38.2 min (*S*)]; absolute configuration was assigned based on retention of configuration for the cross-coupling.

3.6.5.4 (R)-1-Phenyl-2-oxo-2-(4-trifluorophenyl)ethyl pivalate (3.77c)



Following the general procedure described in **3.6.5**, the title compound was isolated as a white soild (0.081 g, 53%). The spectral database for this compound was identical to the data for the racemic mixture of this compound. M.p. 66-70 ˚C (Et_2O); $[\alpha]_D$ = -80.2 (c = 1.0, $CHCl_3$, 78% ee); enantiomeric excess was measured by chiral HPLC analysis [OD, 1% *i*-PrOH/hexanes, 0.5 mL/min, t_{R1} = 24.6 min (*R*), t_{R2} = 27.7 min (*S*)]; absolute configuration was assigned based on retention of configuration for the cross-coupling.

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