# Stille Coupling of α-Acyloxybenzylstannanes with Acid Chlorides

by

Junhui Xu

A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirements for the degree of

Master of Science

in

Chemistry

Waterloo, Ontario, Canada, 2016

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## Abstract

Two widely-accepted models (open- and cyclic- transmetalation) are applied to explain the stereochemical outcome of the Stille coupling with organotin compounds containing an $sp^3$ chiral center. However, it is still not possible to predict the stereochemical outcome of this type of Stille coupling before the reaction is conducted. To have a better understanding of the detailed mechanism involved, the Stille couplings of different α-acyloxybenzylstannanes with different acid chlorides were studied in this project.

The effects of several factors of both the yield and the stereochemical outcome of the Stille reaction containing an α-acyloxybenzylstannane have been studied. These factors were the protecting group on the organotin nucleophile, ligand, solvent and the substituent on the electrophile. It was found that both a bulky protecting group and ligand with mild σ-donicity could give good yield, while adding any substituent on the electrophile always lowered the yield of reaction.

Retention of configuration was observed in the Stille coupling reaction containing an enantiomerically enriched α-alcyloxybenzylstannane. Potential racemization was found after the reaction. Adding a base or doubling the amount of CuCN successfully achieved retention of configuration with > 90% enantiospecificity (e.s.) regardless of the nature of the protecting group, substituent on the electrophile and phosphine ligand. However, result showed that the potential racemization was not simply caused by the acid in the reaction mixture, which means that a further study is needed. Finally, to explain the stereochemical outcome, a mechanism involving a Cu-Sn exchange followed by a nucleophilic attack of the halogen atom to the electrophilic copper was proposed.

## Acknowledgments

First of all, I would like to say thank you to my supervisor Dr. Michael Chong for his tremendous help and patience during these two years. Even though I have poor language skill and a relatively weak organic chemistry background, Mike is still willing to listen to me and explain things again and again to me. I appreciate his smiles and jokes that made me enjoy the time in the lab, I am also grateful for his guidance and suggestions that took me out of the troubles. Even though he is extremely busy, he has done so much and so much for me. I will certainly remember all he has done for me, and undoubtedly I consider him as the mentor of my whole life.

Of course, I would like to thank Rosie Chong who has taught me so much in the lab. Staying in the lab with her makes me feel comfortable, not only because she knows everything in the lab, but also because she makes the lab full of fun.

I would like to thank my committee members Dr. Gary Dmitrienko and Dr. Graham Murphy for reading this thesis. I have borrowed some chemicals from Dr. Dmitrienko's lab, so I would like to thank Dr. Dmitrienko for his help. Since Chong group and Murphy group have group meeting together, Dr. Murphy has taught me so much during the group meeting; in addition, he also taught me how to utilize spectroscopy to analyze organic compound in his courses.

I thank Kai Sands for his help not only in the lab, but also in my coursework. He has spent so long in reading and correcting my English writing. He is the person that always supports me even though he is equally busy. I thank all members in Chong group, Matt, Wei, Pim, Kurtis, and all members in Dr. Murphy's group for their help in the lab and in the group meeting.

I thank Julie for her help when I was doing the teaching assistant for her and I thank Laura for her help on IR experiments and polarimetry. I would like to thank Jan Venne because she has helped me a lot when I was doing NMR experiments. I also like to thank Dr. Richard Smith for his help on the mass spectrometry. I thank Ms. Kim Rawson for her help before I became a grad student and Ms. Catherine van Esch for her assistance since I became a grad student.

My friends in China have also done so much for me during these two years. I would like to thank Zhihong Li, Zirao Huang and Hanbin Lu for their support and company.

My parents, who have given me all they have since I was born, deserve my sincere thanks. However, I don't know how to use words to express my thanks to them, so I decide to use my actions to help them, protect them, and love them in the future of my life. Last but not least, I would like to say thank you to my girl Jingyi, who accompanies me day and night. You are the one that makes me never feel lonely even though I am living alone in Canada.

To Jingyi, myself, and my parents

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## List of Schemes

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## List of Abbreviations

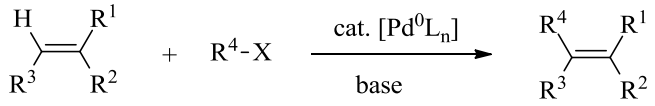
| | |
|---|---|
| Ad | adamantyl |
| Ar | aryl |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | benzyl |
| Bz | benzoyl |
| Cat | catechol |
| cat. | catalytic |
| cataCXium A | di(1-adamantyl)-n-butylphosphine |
| COD | 1,4-cyclooctadiene |
| CPME | cyclopentyl methyl ether |
| Cy | cyclohexyl |
| CyJohnPhos | (2-biphenyl)dicyclohexylphosphine |
| DavePhos | 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl |
| dba | dibenzylideneacetone |
| DCE | dichloroethane |
| dr | diastereomeric ratio |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DMAP | 4-dimethylaminopyridine |
| DMF | dimethylformamide |
| DME | dimethoxyethane |
| DMSO | dimethyl sulfoxide |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| e.e. | enantiomeric excess |
| er | enantiomeric ratio |
| e.s. | enantiospecificity |
| hex | hexane |
| HMPA | hexamethylphosphoramide |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| Ipc | isopinocampheyl |
| *J* | coupling constant |

| | |
|---|---|
| L | |
| *m*-CPBA | L |
| MOM | Ligand |
| MP | meta-chloroperbenzoic acid |
| MSDS | methoxymethyl |
| NMP | melting point |
| NMR | Material Safety Data Sheet |
| OTf | *N*-methylpyrrolidinone |
| Ph | nuclear magnetic resonance |
| PPTS | trifluoromethylsulfonate (triflate) |
| rt | phenyl |
| $S_E2$ | pyridinium *p*-toluenesulfonate |
| SPhos | room temperature |
| TBAF | bimolecular electrophilic substitution |
| *t*-Bu | 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl |
| TES | tetrabutylammonium fluoride |
| TFAA | *tert*-butyl |
| TFP | triethylsilyl |
| THF | trifluoroacetic anhydride |
| TLC | tri-(2-furyl)phosphine |
| TTMPP | tetrahydrofuran |
| Tol | thin layer chromatography |
| $t_R$ | tris(2,4,6-trimethoxyphenyl)phosphine |
| Xphos | toluene |
| | retention time |
| | 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl |

# Chapter 1: Introduction

## 1.1 Palladium-Catalyzed Cross-Coupling Reaction

After Kolbe achieved the first carbon-carbon bond formation in 1845 when he synthesiszed acetic acid,[1] carbon-carbon bond formation has become more and more important in shaping and constructing complex molecules. Amoung the noteworthy carbon-carbon bond forming methodologies are the palladium-catalyzed cross-coupling reactions, which were first reported by Mizoroki in 1971.[2] From 1973, Heck's remarkable work on developing the cross-coupling between alkenyl (or aryl) halides (or triflates) and alkenes (Scheme 1.1)[1] showed the possibility of coupling two carbon-containing moieties by using palladium catalysts.[3,4,5] Since then, various kinds of coupling partners have been reported by different pioneering researchers; these coupling partners include alkynes[6] (Sonogashira), organozincs[7] (Negishi), organotins[8] (Stille), organoborons[9] (Suzuki), organomagnesiums[10] (Kumada), allylic compounds[11] (Tsuji-Trost), as well as organosilanes[12] (Hiyama).[13] Due to the vast work by these pioneers, palladium-catalyzed cross-coupling reactions have become powerful methodologies in organic chemistry. As a result, three of the researchers above, Heck, Negishi, and Suzuki were awarded the 2010 Nobel Prize in Chemistry for their distinguishing work in this field.[13,14]




$R^4$ = aryl, benzyl, vinyl
X = Cl, Br, I, OTf

**Scheme 1.1:** Overview of the Heck coupling

## 1.2 Stille Cross-Coupling

Although Stille coupling is named after Professor J. K. Stille, the first example of transition metal-catalyzed coupling between an organotin nucleophile and a carbon halide electrophile was reported by Kosugi, Migita, and coworkers in 1977 when they reported several reactions that contained organotin reagents as the coupling partner.[15] These reactions include Rh- and Pd-catalyzed cross coupling of acid chlorides and allyltins,[16,17] as well as Pd-catalyzed cross coupling of aryl halides and allyltins.[16] One year later, Stille and coworkers successfully coupled different organotin compounds and acid chlorides using $BnPdCl(PPh_3)_2$ as the catalyst.[8] After this development, the reaction can give a higher yield under milder conditions than those[18] reported by Kosugi.[15]

As a result, Stille coupling is considered as one of the most significant palladium-catalyzed cross coupling reactions.[15] After over 40 years of study, the substrate scope has been enlarged and it has been found that the organotin reagents can tolerate a considerable amount of functionalities.[5,13,15,19] These nucleophilic organotin reagents include alkynyltins, alkenyltins, aryltins, allyltins, benzyltins, acyltins, alkyltins, aminostannanes, as well as alkoxystannanes.[13,15] Among these nucleophiles, alkynyltin compounds are considered as the most reactive species because the alkynyl group can be transferred from the tin atom to an acid chloride most easily while using tributyltin (or trimethyltin) as an anchoring group.[13,15] Using this method, the order of reactivity of organotin compounds can be represented as below:

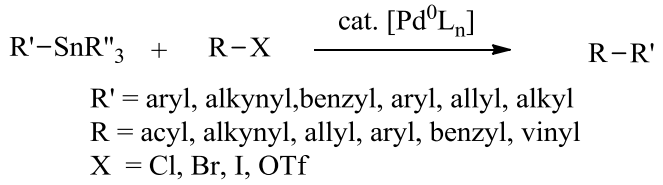
$$RC{\equiv}C \;>\; RCH{=}CH \;>\; \text{aryl} \;>\; \text{allyl, benzyl} \;>\; \text{alkyl}$$

With respect to electrophiles, organo halides and triflates are the two most widely used species which include acid chlorides, aryl halides and triflates, alkenyl halides and triflates, benzyl

halides, allyl bromides, heterocyclic halides and triflates, alkynyl halides, as well as alkyl halides.[13,15]

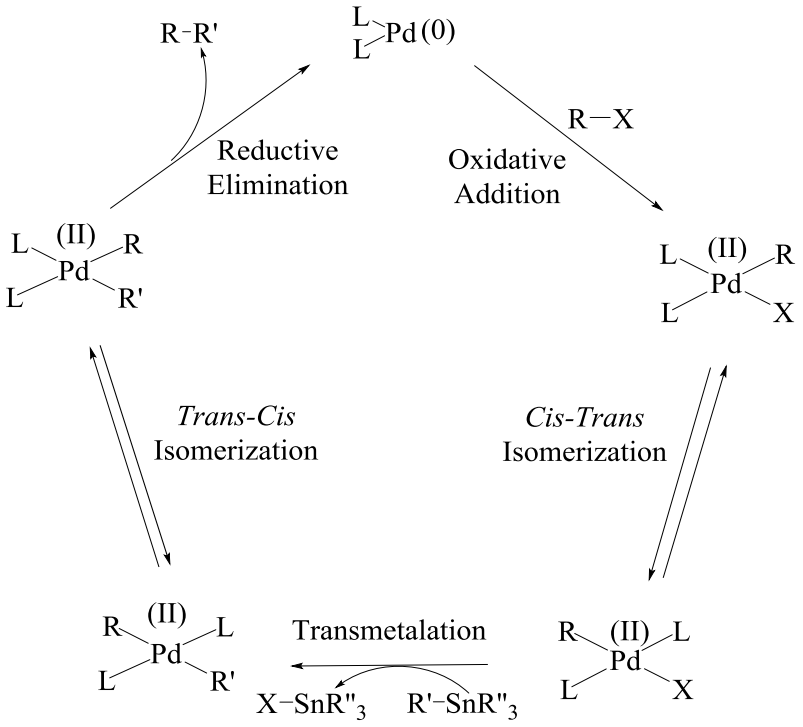
### 1.2.1 Proposed Mechanisms and Catalytic Cycle

Stille coupling uses an organotin compound as the nucleophile and it can be considered as a variation of Heck coupling (Scheme 1.2).[1] The first discussion of the detailed mechanism of Stille coupling was given by Professor Stille in 1979. In this discussion, he proposed a mechanism with two catalytic cycles in it;[15,20,21] however, due to its complexity, this mechanism is not widely accepted. The currently accepted mechanism contains four steps. These four steps are oxidative addition, transmetalation, *trans-cis* isomerization (*cis-trans* as well) and reductive elimination (Scheme 1.3).[22]




**Scheme 1.2:** Overview of the Stille coupling

The first step of this catalytic cycle is the oxidative addition. In this step, a [Pd(0)$L_2$] complex inserts into the carbon-halogen bond of the electrophile to give a square-planar complex *cis*-[Pd(II)$L_2$RX]. Alternatively, where Pd(II) is used as the palladium source directly, the Pd(II) catalyst is quickly reduced by the organotin nucleophile; this generates a [Pd(0)$L_2$] complex for the subsequent oxidative addition step.[19] However, Farina stated that the rate or yield of the Stille coupling is not likely affected by different oxidation states of the palladium species, but it is affected by ratio of the palladium catalyst and the phosphine ligand.[19,23]



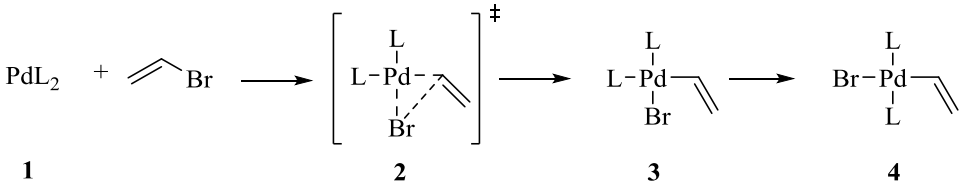

**Scheme 1.3:** Catalytic cycle for Stille coupling

The rate of the oxidative addition is influenced by the bond dissociation energy of the carbon-halogen bond. For instance, the insertion of the palladium into the carbon-chlorine bond is expected to be more difficult than into the carbon-bromine bond, because the bond dissociation energy of a C-Cl bond (79 kcal/mol) is higher than that of a C-Br bond (65 kcal/mol).[13,24] Although the transmetalation step is widely regarded as the rate determining step of the Stille coupling reaction, it has been shown that, in some cases, the oxidative addition step can also act as the rate determining step due to a high bond dissociation energy of the carbon-halide bond. One example is the coupling of aryl bromides with tetramethylstannane. In this reaction, adding electron-withdrawing substituents on the aromatic ring significantly increased the rate of the reaction. Since a similar effect was observed in the oxidative addition of aryl

halides to tris(triphenylphosphine) nickel(0), Stille and coworkers considered this as evidence that the oxidative addition behaved as the rate-determining step in this reaction.[21]

In terms of stereochemistry, the oxidative addition with a vinyl halide generally gives retention of configuration.[25] However, it was found that the oxidative addition with a benzylic halide can proceed with partial or total racemization.[19,26] Moreover, the stereochemical outcome of the oxidative addition with an allylic halide showed a strong dependence on the solvent and ligand used in the reaction. When a highly polar solvent (such as MeCN) was used in the reaction system, inversion of configuration was observed.[19,27]

With respect to the reaction mechanism, the oxidative addition step is believed to go through a three membered cyclic transition state. As shown in Scheme 1.4, vinyl bromide is added to the [$PdL_2$] complex **1** to form a three-center transition state **2**, which can subsequently give a [$PdL_2RX$] complex **3**. It can be seen that the bromide and the alkene are *cis* to each other in complex **3**; however, a fast isomerization would subsequently convert this *cis*-[$PdL_2RX$] complex to the *trans*-isomer **4** as this *trans*-isomer is lower in energy (this isomerization can be initiated with or without the assistance of the solvent-ligand exchange process).[22]

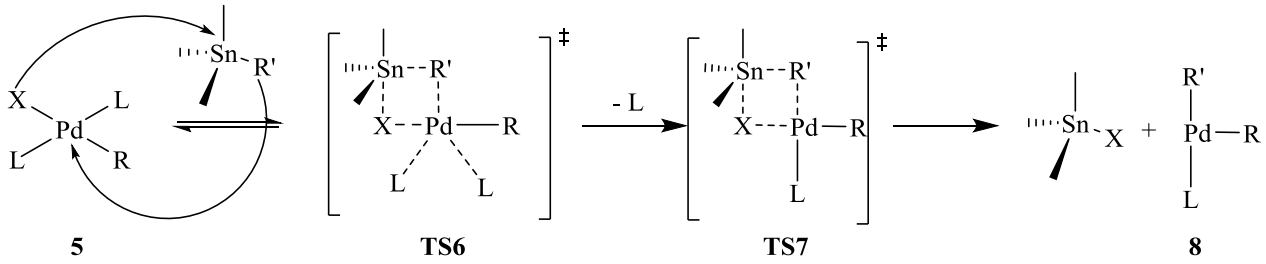



**Scheme 1.4:** The oxidative addition of vinyl bromide to $PdL_2$ complex

### 1.2.2 Transmetalation

The overall outcome of the transmetalation step is a combination of the breaking of the carbon-tin bond and the formation of the carbon-palladium bond. During this process, the organotin moiety is scavenged by the halides to give a tin halide compound. Casado and coworkers have concluded two different pathways in the transmetalation step which are the open-transmetalation and the cyclic-transmetalation.[28] Through which pathway a reaction would go strongly depends on the properties of the solvent and ligand, and the halogen atoms in the electrophiles.[28]

The cyclic-transmetalation (Scheme 1.5) would be favored while a non-polar solvent is present or when the electrophile contains good bridging leaving groups (halides).[13,28] As mentioned previously, a *trans*-[$PdL_2RX$] complex **5** would be generated after the oxidative addition step, after which its halogen atom would subsequently attack the organotin compound. As a result, the palladium center of the complex will become more electrophilic, while the α-carbon of the organotin compound becomes more nucleophilic.[29] The α-carbon of the organotin compound consequently attacks the electrophilic center of the palladium complex to give a four-membered cyclic transition state **TS6** followed by the formation of **TS7**. A three-coordinated *cis*-[PdLRR'] complex **8** is afforded after the dissociation of the tin halide compound and the palladium complex; and this T-shaped complex **8** is responsible for the following reductive elimination step.[22]

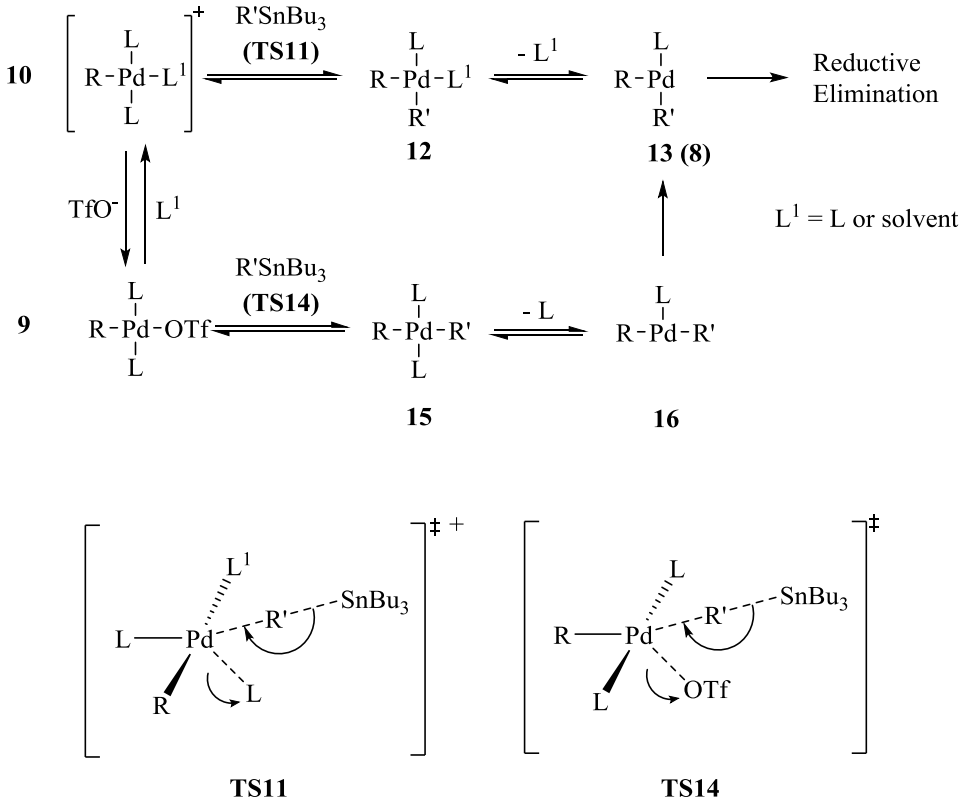



**Scheme 1.5:** Cyclic-transmetalation mechanism

The open-transmetalation (Scheme 1.6) would be favored when a polar solvent is present, or when the electrophile contains weak bridging leaving groups (usually triflates). In addition, to trigger an open-transmetalation, the palladium species should not bear any good bridging ligand.[13,28] As the triflate is an extremely good leaving group, the *trans*-[$PdL_2ROTf$] complex **9** would undergo a quick $TfO^-$ to ligand (or solvent) exchange to generate a cationic $[PdL_2L_1R]^+$ complex **10** ($L^1$ = L or solvent). This cationic complex **10** is subsequently attacked by the α carbon on the organotin reagent to afford a five-coordinate transition state **TS11**. This is followed by an $S_E2$ type cleavage which generates a *cis*-[$PdLL_1RR'$] complex **12**. Ligand dissociation finally gives a T-shaped complex **13** which is the same as the complex **8** from the cyclic-transmetalation.[28]

Surprisingly, Casado observed another *trans*-[$PdL_2RR'$] intermediate **15** instead of **12** during the reaction. Thus, they proposed another process where the α-carbon of the organotin reagent attacks complex **9** directly.[28] By going through another five-coordinate transition state **TS14**, the *trans*- intermediate **15** is formed. Subsequently, a T-shaped complex **16** in which two groups are *trans* to each other is generated following ligand dissociation.[28]

Complex **16** undergoes an isomerization to form *cis*-complex **13** which is the only isomer that can undergo a reductive elimination.[22] However, as Casado and coworkers noticed that the initial rate of the reaction was faster than that if only **15** was present. This meant that not only **15** but also **12** were present in the original reaction system. Thus they suggested that **12** and **15** are two competitive intermediates in this open-transmetalation and proposed a mechanism with two alternative pathways (Scheme 1.6). However, because the rate of the isomerization from **16** to **13** is very fast, it was stated that the geometry of the intermediate (**12** or **15**) would not significantly affect the outcome of this step.[13,28]

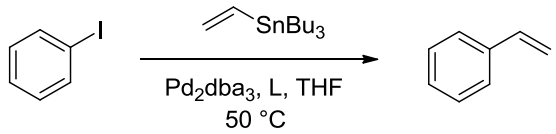



**Scheme 1.6:** Open-transmetalation mechanism and transition states

### 1.2.3 Ligands

Ligand effects can be evaluated by two factors. Steric effects can be examined by testing Tolman cone angles ($\theta$) and electronic effects can be examined by measuring the carbonyl stretching frequency ($\nu$) of the $Ni(CO)_3L$ complex.[13,30] A ligand with a larger $\theta$ value has a bigger steric bulk; and a ligand which gives rise to a smaller ν value has a higher σ-donicity.[31] However, it was shown that the Tolman cone angle of a ligand may be changed after the ligand coordinates to a metal. In addition, the carbonyl stretching frequency may vary depending on the metal center to which the ligand is bound.[23,30] For this reason, the value of the effects of the ligand strongly rely on the reaction conditions applied and the transition metal used.

The effects of the ligand in Stille coupling reactions were examined by Farina and coworkers through the coupling of iodobenzene and vinyltributyltin in tetrahydrofuran (THF) (Scheme 1.7).[19,23] This study showed that a ligand which had high σ-donicity such as $MePPh_2$ and $(4\text{-}MeOC_6H_4)_3P$ gave lower yields and slower reaction rates while ligand that had low σ-donicity such as $AsPh_3$ and tri-2-furylphosphine (TFP) gave higher yields and faster reaction rates. A possible explanation of this result could be that the ligand dissociation step during the transmetalation is retarded if the ligand-metal bond is too strong. As ligands with lower σ-donicity can make a weaker bond with the palladium metal, reaction rate with those ligands would be enhanced.[13]




**Scheme 1.7:** Study on the ligand effects

### 1.2.4 Additives

LiCl is a common additive if organotriflates are involved as the electrophile, as it is believed that LiCl can convert the unreactive [$PdL_2R'OTf$] complex to [$PdL_2R'Cl$] which is more catalytically active.[31] In addition, highly coordinating solvents such as N-methylpyrrolidinone (NMP) can also activate the unreactive [$PdL_2R'OTf$] complex by replacing the OTf moiety with a solvent molecule to afford a more reactive species [$PdL_2R'S]^+$.[19] In this case, the addition of LiCl is no longer necessary; moreover, Casado and coworkers reported that the Stille coupling with an oganotriflate in THF was actually retarded by the addition of LiCl.[28]

Other common additives for the Stille coupling are Cu(I) salts which are considered to play a dual role in the Stille coupling. The effect of the Cu(I) salt in the reaction was first discovered by Liebeskind and Fengl.[32] In their later studies, Cu(I) salts were shown to behave as a ligand scavenger as well as a co-catalyst in the reaction.[33] When the reaction is conducted with ligands such as $PPh_3$, Cu(I) cation can accelerate the reaction by scavenging the ligands tightly bound to the palladium.[19] When the reaction is conducted with a softer ligand such as $AsPh_3$ and in a highly polar solvent such as NMP, Cu(I) can behave as a co-catalyst since the organotin compound can be converted into an organocopper compound by transmetalation with the copper salt. (Scheme 1.8).[19,33]

$$R\text{-}SnBu_3 + CuI \underset{}{\overset{NMP}{\rightleftharpoons}} R\text{-}Cu + ISnBu_3$$

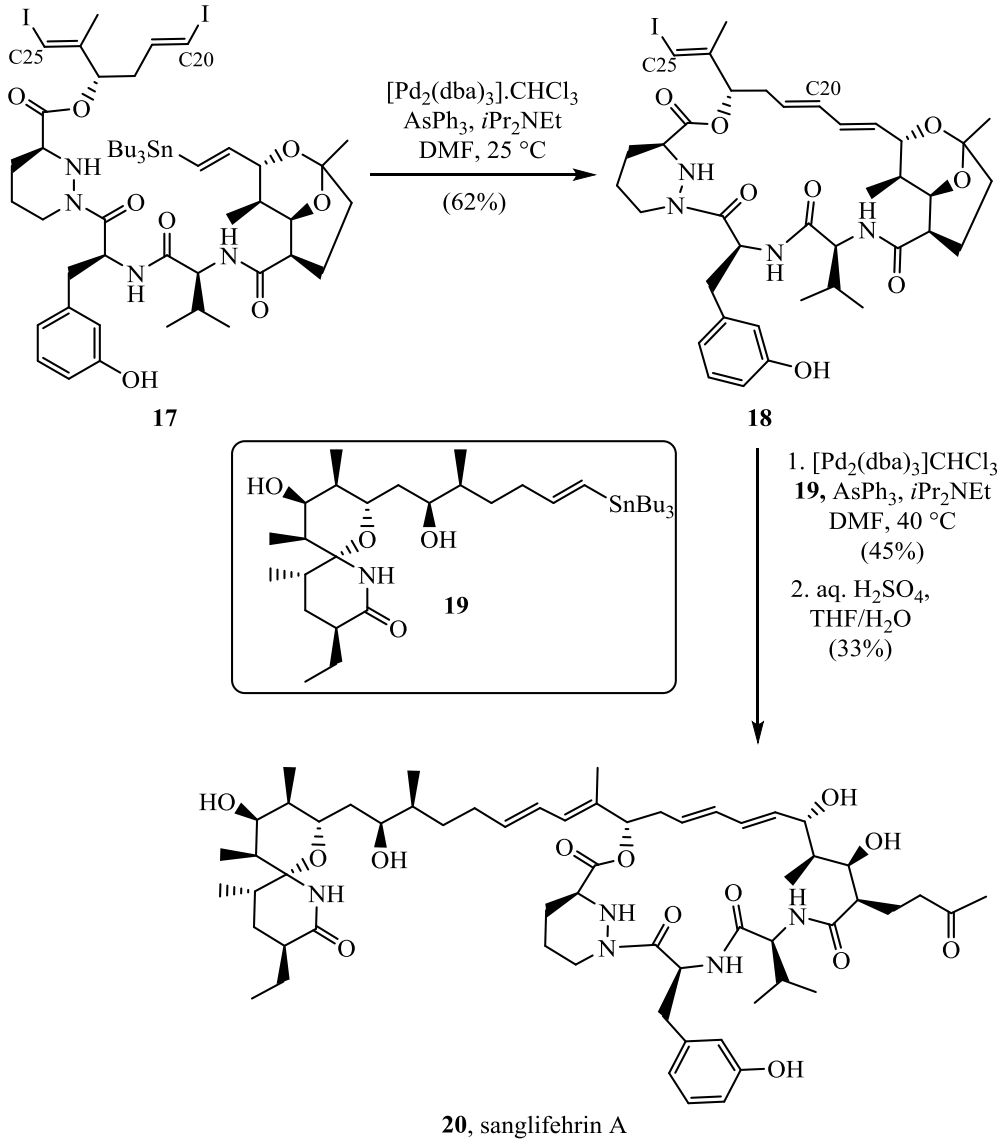
**Scheme 1.8:** Formation of organocopper compound using CuI as co-catalyst

## 1.3 Stille Coupling in Total Synthesis of Natural Products

As mentioned previously, Stille cross-coupling reactions are powerful tools in organic synthesis because they can afford impressive yields under mild conditions. Especially, intramolecular Stille couplings are considered one of the most significant methodologies in building large cyclic molecules.[1] The first example of the intramolecular Stille coupling in the total synthesis of a natural molecule was reported by Piers and coworkers in 1985 when they successfully applied numerous Stille couplings to build up different 5- and 6-membered rings.[34] Two years later, Stille and coworkers successfully utilized this strategy to construct macrocyclic compounds.[35] One of the advantages of using intramolecular Stille coupling is that it can couple two vinyl- (or aryl-) moieties not only stereoselectively but also chemoselectively to construct a large cyclic molecule.

The first example shown here is the total synthesis of sanglifehrin A which was reported by Nicolaou and coworkers.[1,36,37] In this total synthesis, after they obtained the coupling precursor **17**, they treated **17** with $Pd_2(dba)_3$ in the presence of $AsPh_3$ and *i*-$Pr_2NEt$ to conduct an intramolecular Stille coupling reaction. It can be seen that, even though there are two vinyl iodide moieties in **17** (labeled as C20 and C25 in **17**), only the less hindered vinyl iodide (C20) was coupled in the intramolecular Stille reaction; as a result, only the 22-membered-ring macrocyclic compound **18** was obtained. After the intramolecular Stille coupling, an intermolecular Stille coupling between **18** and the vinyl tin compound **19** afforded the targeted compound sanglifehrin A **20**. With respect to stereochemistry, it can be seen that all olefins involved retain their configuration after the reactions; thus, only one stereoisomer was obtained.[36,37] Due to the high chemo- and stereoselectivity of Stille reactions, another study by

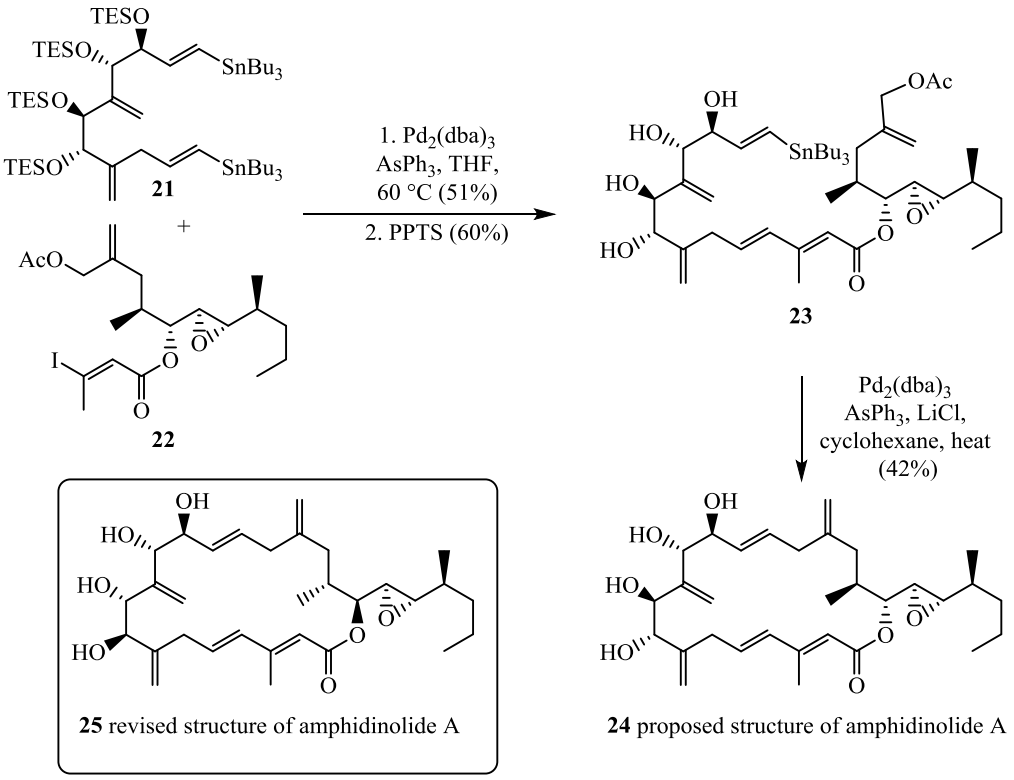
Paquette also applied an intermolecular Stille coupling between **18** and **19** as the last synthetic step to afford sanglifehrin A **20** (Scheme 1.9).[1,38]




**Scheme 1.9**: Total synthesis of sanglifehrin A

Similarly, another example of applying chemo- and stereochemically selective Stille coupling reactions was given by Pattenden and Lam in the total synthesis of the proposed structure of amphidinolide A.[1,39] In this study, the coupling precursor **21** was a bis-stannane

which contained two vinyl tin moieties, while another coupling fragment **22** also contained two coupling units (vinyl iodide and allylic acetate). However, by using $Pd_2(dba)_3$ and $AsPh_3$, the intermolecular Stille coupling reaction only occurred between the less hindered vinyl tin moiety and the more reactive coupling unit (vinyl iodide) to give the cyclization precursor.[1] After the deprotection of the triethylsilyl protecting group, compound **23** was treated with $Pd_2(dba)_3$ and $AsPh_3$ in the presence of LiCl to conduct an intramolecular Stille reaction which closed the 20-membered ring to afforded the targeted molecule **24**. Again, the three olefins involved in the reactions finally showed retention of configuration; thus, only one stereoisomer was obtained. However, two years later, Trost and coworkers corrected this proposed structure **24** to another stereoisomer **25** as the true structure of amphidinolide A (Scheme 1.10).[1,40]




**Scheme 1.10:**Total synthesis of the proposed structure of amphidinolide A

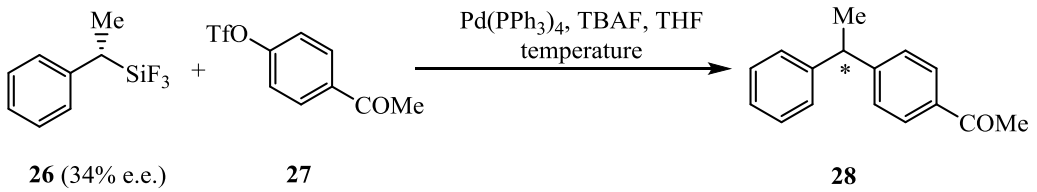
## 1.4 Cross-Coupling Reactions of Nucleophiles with $Sp^3$ Chiral Center

As shown in the previous examples of Stille coupling reactions in natural product synthesis, the coupling reaction between vinyl tin compounds and vinyl halides always gives retention of configuration on the nucleophiles. As a matter of fact, it is believed that most palladium catalyzed cross-coupling reactions with $sp^2$ nucleophile would afford complete retention of configuration. However, it seems that this observation does not hold true to a reaction where an $sp^3$ nucleophile is involved.[13] The first example of palladium catalyzed cross-coupling reaction involving a stereochemically enriched $sp^3$ nucleophile was reported by Stille and Labadie in 1983 (Scheme 1.21).[41] Since then, a lot of effort has been put into the study of the stereochemical outcome of this type of cross-coupling reaction; however, as more examples have been shown, it is more difficult to predict if a reaction will give retention or inversion of configuration on the α-carbon of the nucelophile.[13] The following examples of different cross-coupling reactions show the complexity that the reaction involving $sp^3$ nucleophiles can have.

### 1.4.1 Hiyama Couplings of Chiral Benzylsilanes

The first study of the Hiyama coupling with enantiomerically enriched $sp^3$ nucleophiles was conducted by Hiyama and Hatanaka in 1990.[42] In this study, chiral benzylsilane **26** was coupled with different aryl triflates at different temperatures and in different solvents; as a matter of fact, both of the absolute configuration of the product and the stereospecificity of the reactions showed strong dependence on the temperature and solvent used in the reaction.[13,42] While they treated alkylsilane **26** (34% e.e.) with 4-acetylphenyl triflate **27** in the presence of $Pd(PPh_3)_4$ and tetra-*n*-butylammonium fluoride at 50 ℃, 94-100% of retention of configuration was reported (32-34% e.e.). However, as the temperature increased to 60 ℃, the stereospecificity of the

reaction dropped to ~65% e.s. (~22% e.e.). Once the temperature reached 75 ℃, inversion of configuration started to dominate. As the temperature was increased above 75 ℃, the stereospecificity of the reaction rose again with inversion of configuration (Table 1.1).[13,42]




**26** (34% e.e.) **27** **28**

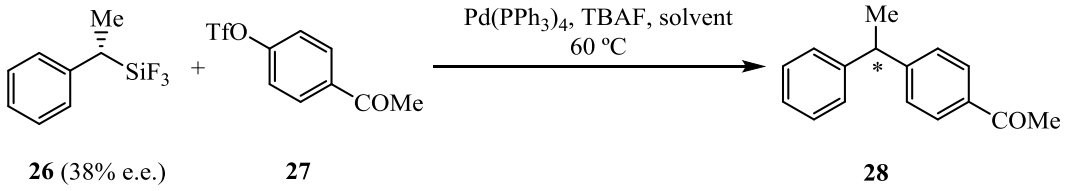
| Temperature ( ℃) | Absolute Configuration | % e.e. (% e.s.[a]) |
|---|---|---|
| 50 | retention | 32-34 (94-100) |
| 60 | retention | 22 (64) |
| 80 | inversion | 9 (26) |
| 100 | inversion | 22 (64) |

[a]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

**Table 1.1**: Hiyama coupling of chiral benzylsilane and 4-acetylphenyl triflate[42]

When THF was used as solvent in the reaction, ~65% e.s. was obtained; however, once cosolvent was added in the reaction system, the stereochemical outcome was changed. Table 1.2 shows that, the addition of 9% dimethyl sulfoxide (DMSO) and 9% dimethylformamide (DMF) in THF diminished the stereospecificity of the reaction to 42% e.s.; moreover, the addition of hexamethylphosphoramide (HMPA) in THF further enhanced the formation of the opposite enantiomer and resulted in 21% of inversion of configuration. It is noteworthy that, not only the temperature and solvent used in the reaction system, but also substituent on the nucleophile can change the stereochemical outcome of the reaction. It can be seen that the electron-donating

group (methoxy group) on the aromatic ring of the benzylsilane nucleophile sharply decreased the stereospecificity to 50% e.s. (Scheme 1.11).[13,42]

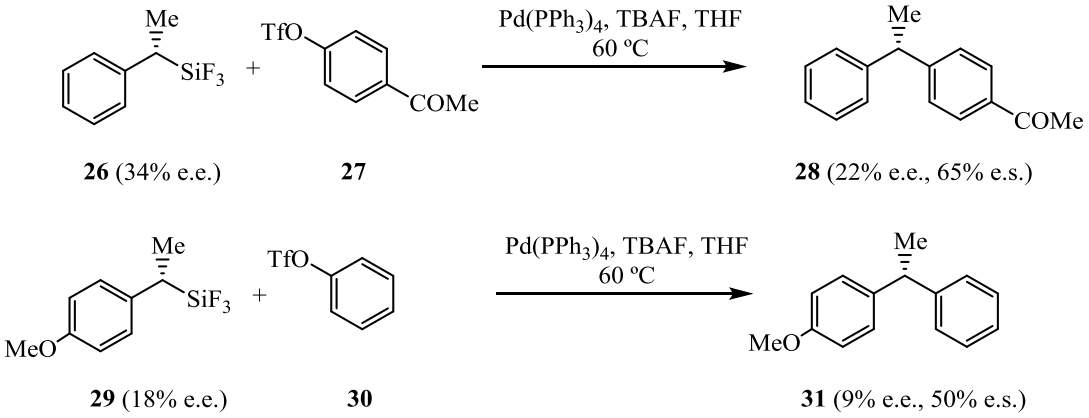



**26** (38% e.e.) **27** **28**

| Solvent | Absolute Configuration | % e.e. (%e.s.) |
|---|---|---|
| THF | retention | 22 (65)[a] |
| DMSO/THF (1:10) | retention | 16 (42) |
| DMF/THF (1:10) | retention | 16 (42) |
| HMPA/THF (1:10) | inversion | 8 (21) |

[a]This was done by using **26** with 34% e.e.

**Table 1.2**: Hiyama coupling chiral benzylsilane and 4-acetylphenyl triflate in different solvents[42]



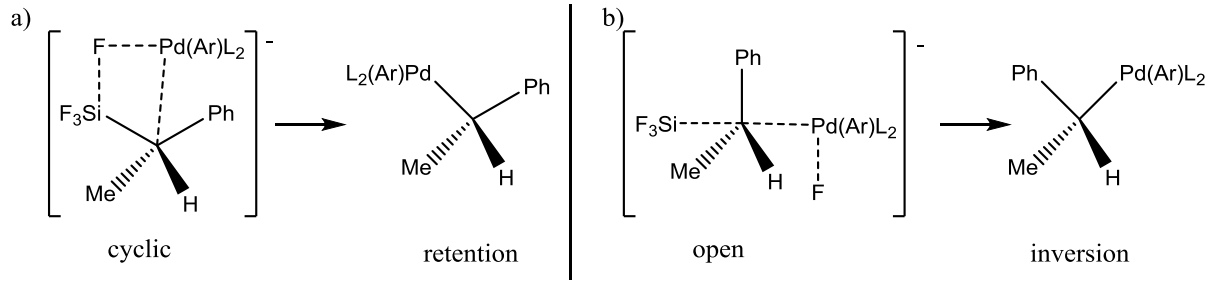

**26** (34% e.e.) **27** **28** (22% e.e., 65% e.s.)

**29** (18% e.e.) **30** **31** (9% e.e., 50% e.s.)

**Scheme 1.11:** Hiyama coupling of different nucleophiles and electrophiles

To explain these unpredictable results, they proposed two different transition states which are the cyclic- and the open-transition states as shown previously in Scheme 1.6. In the cyclic-transition state, a four-membered ring is constructed by using fluoride ion as a bridge, it can be

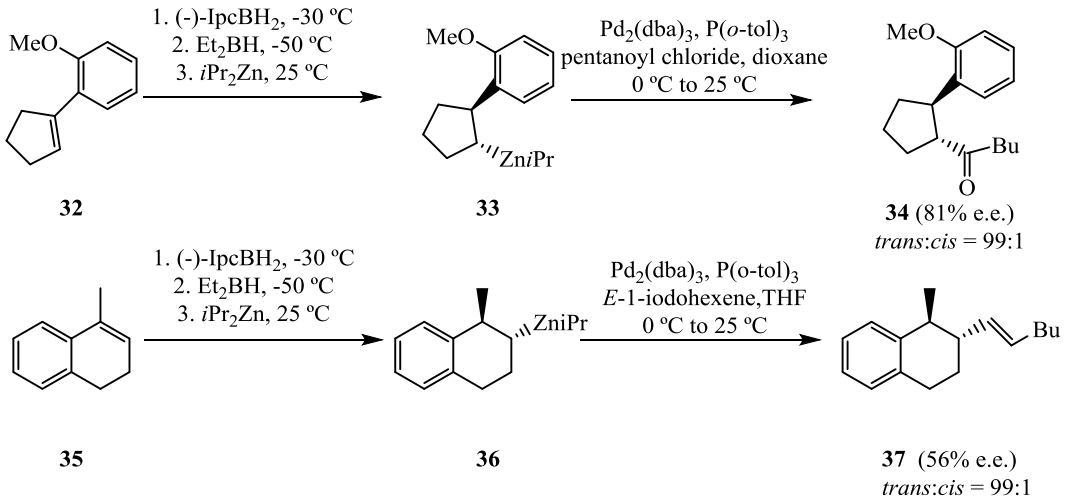
seen that, the palladium(II) complex would be placed on the same site of the tetrafluorosilyl group; thus retention of configuration would be obtained. In the open-transition state, the palladium(II) complex would be placed on the opposite site of the trifluoride silyl moiety; thus inversion of configuration would be obtained (Scheme 1.12).[42]




**Scheme 1.12:** a) Cyclic transition state; b) open transition state of the Hiyama coupling of **26**

### 1.4.2 Negishi Couplings of Diastereomerically Pure Dialkylzinc Compounds

Coupling reactions of configurationally defined alkylzinc compounds have been studied by Boudier and Knochel at 2000.[43] In this study, they first prepared different diastereomerically pure secondary organoborane compounds by asymmetric hydroboration of different olefins. This was followed by a boron-zinc exchange with *i*$Pr_2Zn$ to give diastereomerically pure dialkylzinc compounds which were subsequently coupled with different carbon halide electrophiles. As results, the *trans*:*cis* ratio for all coupled products were greater than 90:10; and some of the reactions could give 99:1 (Scheme 1.13). Even though the *trans:cis* ratio of the dialkyl zinc intermediate was not determined, the high *trans:cis* ratio for the coupled product indicates that the cross-coupling step was highly stereospecific.[43]




**Scheme 1.13:** Synthesis and Negishi coupling of the diastereomerically pure dialkylzinc compound **36**

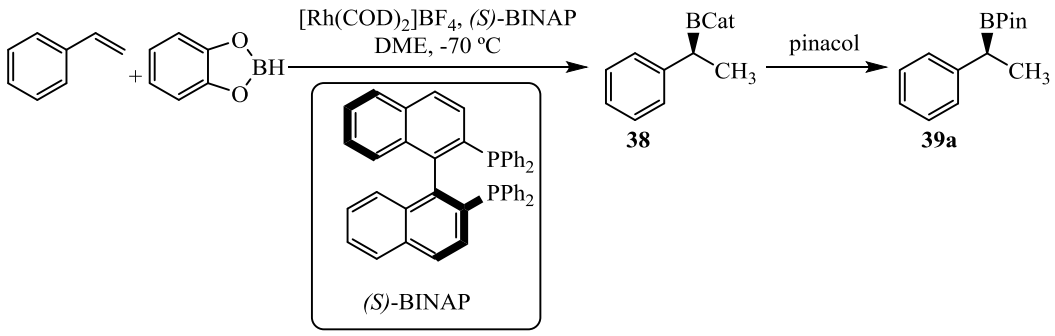
### 1.4.3 Suzuki Couplings of Different Stereochemically Active Nucleophiles

#### 1.4.3.1 Suzuki Couplings of α-Benzylboronates

Suzuki coupling is another widely used cross-coupling reaction due to the fact that most organoboron compounds have low toxicity. However, no example of Suzuki coupling with optically active secondary boronic acids (or ester) were given before Gevorgyan and coworkers reported the stereospecific Suzuki couplings of configurationally defined cyclopropylboronic acids and aryl iodides. Retention of configuration was obtained in this coupling reaction; however, the stereospecificity of the reaction was not reported.[44]

In 2008, Crudden and coworkers reported the Suzuki coupling reactions of enantiomerically enriched α-benzylboronates with aryl iodides where they found that the substrates underwent coupling with retention of configuration.[45] The enantiomerically enriched α-benzylboronate compounds were prepared through a procedure they developed in 1999.[46] In this procedure,

styrene was treated with catecholborane (HBCat), (*S*)-BINAP, and $[Rh(COD)_2]BF_4$ to generate an enantiomerically enriched intermediate **38**, which was subsequently quenched by pinacol to give the desired α-benzylboronate ester **39a** (Scheme 1.14).[45]

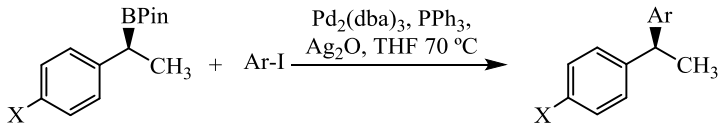



**Scheme 1.14:** Synthesis of enantiomerically enriched α-benzylboronate ester **39a**

After an optimization study, they obtained the best reaction conditions where $PPh_3$ was used as phosphine ligand and $Ag_2O$ was used as base. Applying the optimized conditions, Suzuki cross-coupling reactions with **39** and different aryl iodides were conducted. However, even after the reaction conditions had been optimized, overall isolated yields were low. It was mentioned that these low yields were caused by the difficulty of purifying the coupled product from the presence of homocoupled products.[13,45]

From Table 1.3, it can be seen that retention of configuration was obtained by all of the reactions while the stereospecificities were mostly greater than 90% e.s. As mentioned previously, in the study reported by Hiyama, when the cross-coupling reaction proceeds with retention of configuration, adding an electron-donating group on the aromatic ring of the nucleophile decreased the stereospecificity of the coupling reaction (Scheme 1.11).[42] However, entry 7 in Table 1.3 indicates that adding an electron-withdrawing substituent (chloro atom) on

electrophile can diminish the stereospecificity of a Suzuki coupling reaction as well. This opposite phenomenon implies the difficulty of predicting the stereochemical outcome of a palladium-catalyzed coupling reaction.[45]




**39a** X=H
**39b** X=Cl
**39c** X=Me

**40**

| entry | **39** | Ar-I | **40** | Yield (%)[a] | % e.s.[b] |
|---|---|---|---|---|---|
| 1 | **39a** | *p*-$CH_3COC_6H_4$ | **40a** | 65 (63) | 92 |
| 2 | **39a** | *p*-$ClC_6H_4$ | **40b** | 81 (62) | 91 |
| 3 | **39a** | *p*-$CH_3C_6H_4$ | **40c** | 86 (60) | 92 |
| 4 | **39a** | 3,5-di$MeC_6H_4$ | **40d** | 86 (64) | 93 |
| 5 | **39a** | *p*-$MeOC_6H_4$ | **40e** | 48 | 93 |
| 6 | **39a** | *o*-$CH_3C_6H_4$ | **40f** | 48 | 93 |
| 7 | **39b** | PhI | *ent*-**40b** | 84 (64) | 84 |
| 8 | **39c** | PhI | *ent*-**40c** | 54 (38) | 94 |

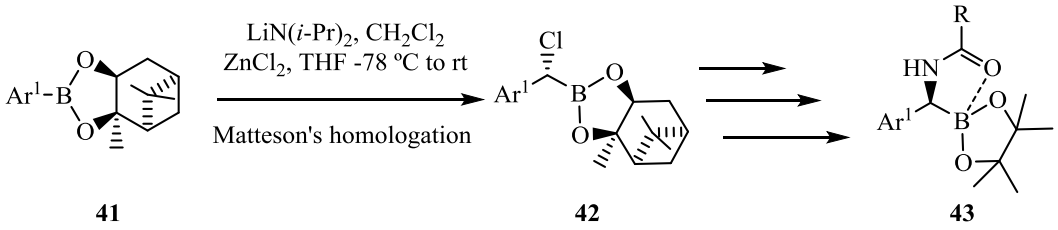
[a]Determined by $^1$H-NMR with internal standard, isolated yields are shown in parentheses
[b]All reaction proceeded with retention of configuration

**Table 1.3:** Suzuki coupling of enantiomerically enriched α-benzylboronate esters and aryl iodides[45]

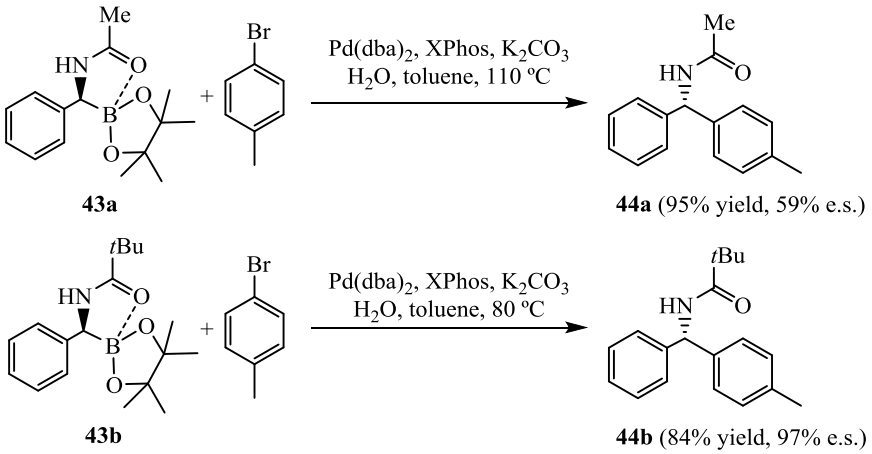
### 1.4.3.2 Suzuki Couplings of α-(Acylamino)benzylboronates

The stereospecific Suzuki coupling reactions of enantiomerically enriched α-(acylamino)-benzylboronates were studied by Suginome and coworkers.[47,48] The chiral α-(acylamino)-benzylboronate compounds **43** were synthesized via Matteson's homologation with (-)-pinanediol derivative **41** (Scheme 1.15).[49,50,51] After that, they conducted ligand and base surveys to search for the best reaction conditions. It was found that using Xphos as a ligand and $K_2CO_3$

as a base can afford the best yield and stereospecificity in the Suzuki coupling with 4-bromotoluene. Intriguingly, unlike the one reported by Crudden (Table 1.3),[45] this Suzuki reaction of α-(acylamino)benzylboronates gave inversion of configuration. Effects of the acyl group on the nitrogen atom and the temperature of reaction were also tested; as a result, running the reaction under 80 ℃ with the sterically bulky pivaloyl group afforded the highest stereospecificity (97% e.s. in Scheme 1.16).[47]



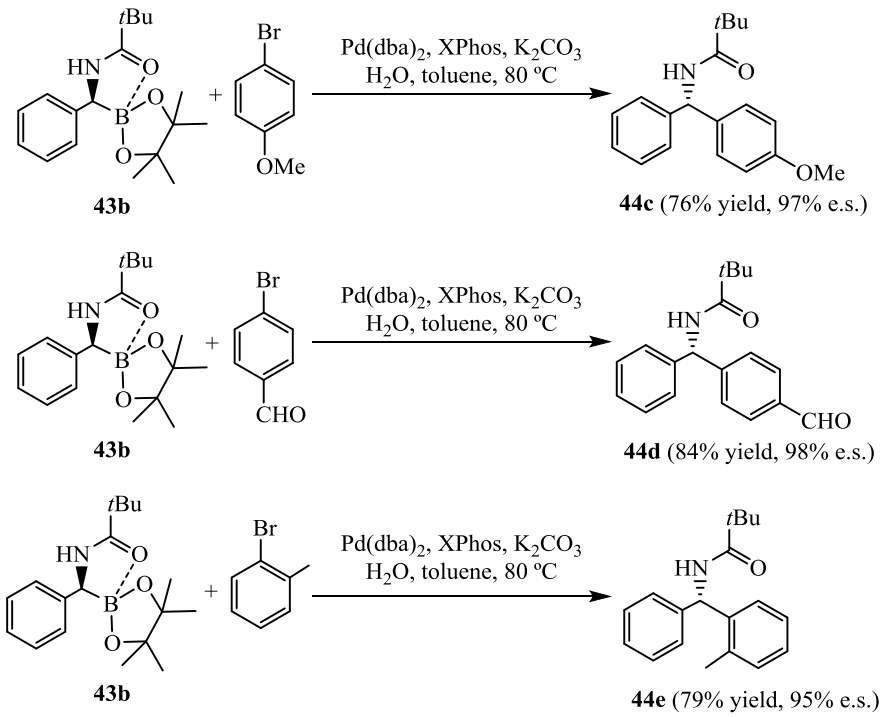

**Scheme 1.15:** Synthesis of chiral α-(acylamino)benzylboronate compounds **43**



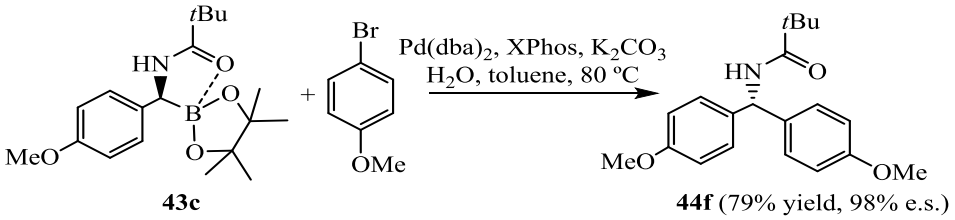

**Scheme 1.16:** Effect of the acyl group and temperature on the Suzuki coupling of **43**

Applying this optimized reaction conduction, Suzuki coupling reactions between **43b** and different electrophiles were conducted. It seems that the electronic property of the electrophiles had no influence in the reaction, as putting either a strong electron donating substituent (OMe

group) or a strong electron withdrawing substituent (CHO group) on the 4-position of the aromatic ring did not significantly change the outcome of the reaction (yield or stereospecificity). Steric property did not have an effect on the reaction either, as the stereospecificity and the yield of reaction did not change after putting a methyl substituent on the 2-position of the aromatic ring (Scheme 1.17). Moreover, adding an electron donating substituent on the aromatic ring of the nucleophile also did not change the stereochemical outcome (Scheme 1.18).[47]

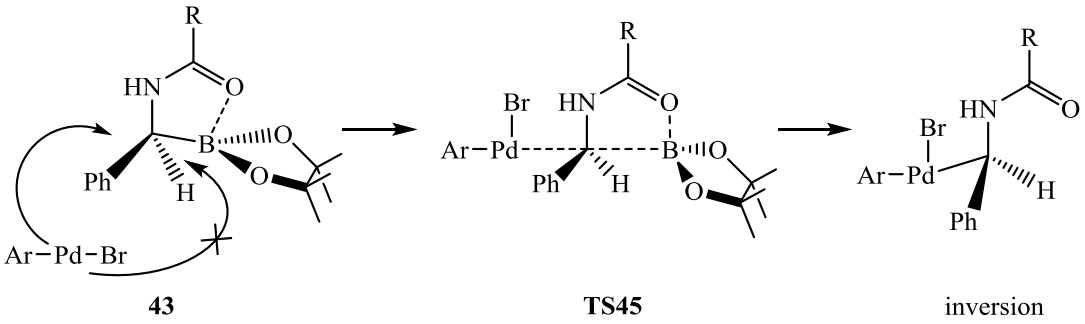



**Scheme 1.17:** Effect of the electrophile on the Suzuki coupling of **43b**




**Scheme 1.18:** Effect of the substituent on the nucleophile to the the Suzuki coupling of **43b**

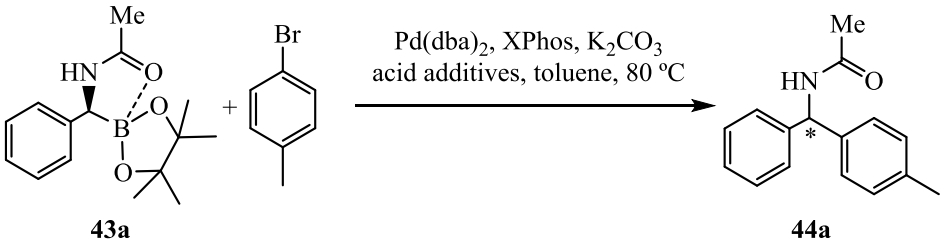
The inversion of configuration of the chiral center may be caused by the intramolecular coordination of the carbonyl oxygen atom to the boron which was already confirmed by X-ray crystallographic analysis.[47] The palladium complex can only attack the backside of benzylic carbon because the other side has been blocked by the oxygen-boron coordination. This backside attack gives an open transition state **TS45** which is similar to the transition state proposed by Casado and Hiyama (shown previously in Scheme 1.6 and Scheme 1.12). Because the palladium complex is placed on the opposite site of the boron, inversion of configuration would be given after the reductive elimination (Scheme 1.19).[47]




**Scheme 1.19:** Coordination of the oxygen to the boron helps to give open transition state

As it is proposed that the inversion of configuration is given by an intramolecular coordination of the carbonyl oxygen atom to the boron atom, Suginome predicted that addition of acidic additives to the reaction system should switch the absolute configuration to give retention of configuration.[48] However, after the addition of different protic acids into the coupling reaction between **43a** and 4-bromotoluene, it was found that most of the protic acids did not switch the absolute configuration but improved the stereospecificity of the inversion of configuration. As can be seen in Table 1.4, adding 3.0 equivalents of PhOH can increase the stereospecificity from 29% to 99% e.s. (entry 11 of Table 1.4). However, it is encouraging that

the addition of 2.0 equivalents of *i*-PrOH or *t*-BuOH can give retention of configuration albeit with very low stereospecificities (entries 8 and 9 of Table 1.4).[48]



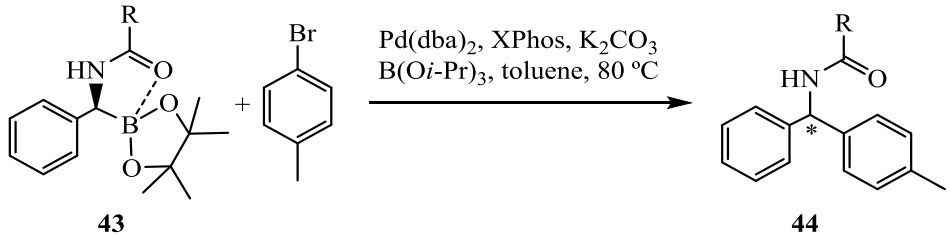

**43a** **44a**

| entry | acid additives | equiv | yield (%) | absolute configuration | % e.s. |
|---|---|---|---|---|---|
| 1 | - | - | 87 | inversion | 29 |
| 2 | $H_2O$ | 2.0 | 85 | inversion | 53 |
| 3 | PhCOOH | 2.0 | 85 | inversion | 56 |
| 4 | AcOH | 2.0 | 87 | inversion | 61 |
| 5 | PhOH | 2.0 | 85 | inversion | 96 |
| 6 | MeOH | 2.0 | 91 | inversion | 12 |
| 7 | EtOH | 2.0 | 87 | retention | 4 |
| 8 | *i*-PrOH | 2.0 | 90 | retention | 15 |
| 9 | *t*-BuOH | 2.0 | 89 | retention | 32 |
| 10 | PhOH | 1.0 | 89 | inversion | 69 |
| 11 | PhOH | 3.0 | 51 | inversion | 99 |

**Table 1.4**: Suzuki coupling of **43a** with different protic additives[48]

Since protic acids did not give the desired retention of configuration, they tried to add metal alkoxides which can act as Lewis acids in the reaction system. They found that the addition of 2.0 equivalents of triisopropyl borate can switch the absolute configuration to give inversion of configuration with up to ~60% e.s (entry 1, Table 1.5). Intriguingly, results showed that the stereochemical outcome of reaction strongly depends on the size of the acyl group. As can be seen in Table 1.5, when the boronate nucleophile contained an acetyl group on the nitrogen atom,

63% retention of configuration was obtained; however, when a bulkier acyl group was used, inversion of configuration was more favorable.[48]

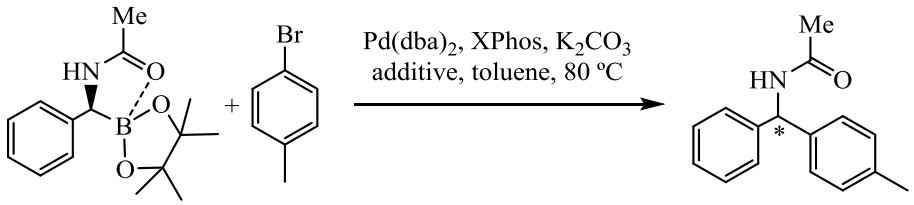



**43** **44**

| entry | R group | absolute configuration | % e.s. |
|---|---|---|---|
| 1 | Me | retention | 63 |
| 2 | Et | retention | 36 |
| 3 | Ph | retention | 11 |
| 4 | *t*-Bu | inversion | 83 |

**Table 1.5:** Effect of the acyl groups on the Suzuki coupling of **43**[48]

A further study of Lewis acid additives was conducted when they screened different metal alkoxides. Most metal alkoxides added to the reaction resulted in retention of configuration. Among these metal alkoxides, 0.5 equivalents of Zr(O*i*-Pr)$_4$·*i*-PrOH in the reaction resulted in high yield and 78% e.s. (entry 9 of Table 1.6). However, when they added the same amount of Zr(O*i*-Pr)$_4$, the reaction gave no stereospecificity and produced low yield; this indicated that a proton source is required when Zr(O*i*-Pr)$_4$ was used (entry 9 of Table 1.6). In addition, it was found that decreasing the reaction temperature improved the stereospecificity of the reaction albeit with lower yield (entry 14 of Table 1.6).[48]



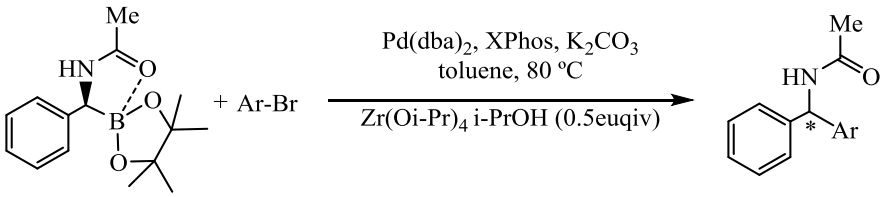

**43a** **44a**

| entry | additive | equiv | yield (%) | absolute configuration | % e.s. |
|---|---|---|---|---|---|
| 1 | $B(OMe)_3$ | 2.0 | 60 | retention | 24 |
| 2 | $B(OEt)_3$ | 2.0 | 85 | retention | 57 |
| 3 | $B(O\textit{i}\text{-}Pr)_3$ | 2.0 | 74 | retention | 62 |
| 4 | $B(O\textit{t}\text{-}Bu)_3$ | 2.0 | 80 | retention | 28 |
| 5 | $Al(O\textit{i}\text{-}Pr)_3$ | 2.0 | 68 | retention | 61 |
| 6 | $Ga(O\textit{i}\text{-}Pr)_3$ | 2.0 | 74 | retention | 75 |
| 7 | $In(O\textit{i}\text{-}Pr)_3$ | 2.0 | 55 | retention | 74 |
| 8 | $Ti(O\textit{i}\text{-}Pr)_4$ | 2.0 | 74 | retention | 36 |
| 9 | $Zr(O\textit{i}\text{-}Pr)_4$ | 2.0 | 14 | retention | 3 |
| 10 | $Zr(O\textit{i}\text{-}Pr)_4{\cdot}\textit{i}\text{-}PrOH$ | 2.0 | 10 | retention | 76 |
| 11 | $Zr(O\textit{i}\text{-}Pr)_4{\cdot}\textit{i}\text{-}PrOH$ | 1.0 | 50 | retention | 78 |
| 12 | $Zr(O\textit{i}\text{-}Pr)_4{\cdot}\textit{i}\text{-}PrOH$ | 0.5 | 86 | retention | 78 |
| 13 | $Zr(O\textit{i}\text{-}Pr)_4{\cdot}\textit{i}\text{-}PrOH$ | 0.1 | 85 | retention | 53 |
| 14[a] | $Zr(O\textit{i}\text{-}Pr)_4{\cdot}\textit{i}\text{-}PrOH$ | 0.5 | 63 | retention | 83 |

[a]Reaction was conducted under 60 ℃

**Table 1.6:** Screen of acid additives in the Suzuki coupling of **43a**[48]

With the addition of 0.5 equivalents of $Zr(O\textit{i}\text{-}Pr)_4{\cdot}\textit{i}\text{-}PrOH$, several coupling reactions were conducted with different aryl bromides to search for the effect of the property of electrophiles in the reaction. With respect to electronic effects, while an electron donating group (4-OMe) did not significantly change the outcome of reaction, an electron withdrawing moiety (4-$CF_3$) improved the performance of reaction with both higher yield and higher stereospecificity. With respect to steric effects, a bulky electrophile can increase the stereospecificity of reaction.[48]

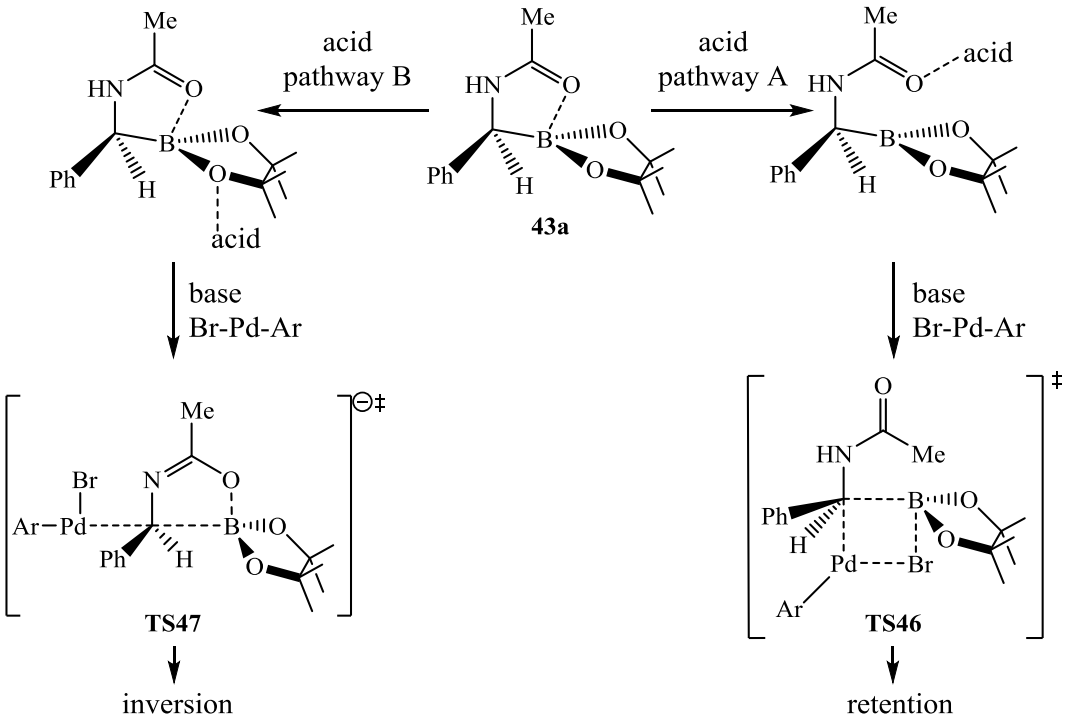



**43a** **44**

| entry | Ar | yield (%) | absolute configuration | % e.s. |
|---|---|---|---|---|
| 1 | 4-$MeC_6H_4$ | 86 | retention | 78 |
| 2 | 4-$MeOC_6H_4$ | 67 | retention | 78 |
| 3 | 4-$CF_3C_6H_4$ | 96 | retention | 83 |
| 4 | 2-$MeC_6H_4$ | 73 | retention | 86 |

**Table 1.7:** Suzuki coupling of **43a** with different electrophiles using 0.5 eq. of $Zr(O\textit{i}\text{-}Pr)_4{\cdot}\textit{i}\text{-}PrOH$[48]

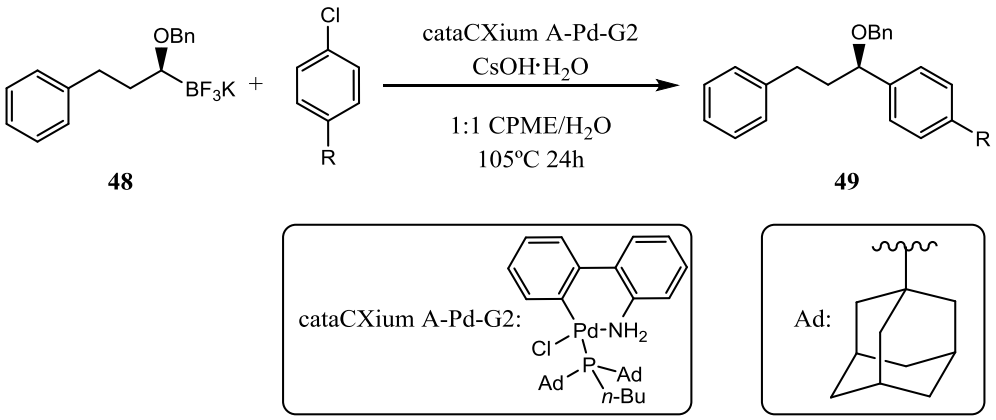
To explain the effects of the acidic additives in this coupling reaction, they proposed a mechanism where the boronate substrate can undergo two different pathways with different acidic additives. After the acidic additive is added into the reaction system, it can either coordinate to the carbonyl oxygen atom of the acyl group (pathway A, Scheme 1.20) or coordinate to the oxygen atom of the pinacol ligand (pathway B, Scheme 1.20). When the acidic additive is a metal alkoxide, pathway A would be favored. In pathway A, due to the competitive coordination of the acid to the carbonyl oxygen, the intramolecular coordination of the boron to the carbonyl oxygen would be disrupted. As a result, the boron atom remains unsaturated and it is ready for coordination to a bridging atom. This promotes the formation of the cyclic transition state **TS46** which can give retention of configuration. If the acidic additive is a protic acid, pathway B would be more likely to take place. In pathway B, the coordination of the acid to the pinacol oxygen would result in a higher electrophilicity on the boron atom, which strengthens the coordination of the boron to the carbonyl oxygen. A backside attack of the palladium complex gives transition state **TS47** which is similar to **TS45** they proposed previously.[48]




**Scheme 1.20:** Proposed mechanism of the Suzuki coupling of **43a** with different acid additives

### 1.4.3.3 Suzuki Couplings of α-(Benzyloxy)alkyltrifluoroborate

More recently, another example of Suzuki Coupling reaction involving an enantiomerically enriched nucleophile with an $sp^3$ chiral center was reported by Molander and Wisniewski where they used an α-(benzyloxy)alkyltrifluoroborate as the nucleophile in Suzuki coupling reactions.[52] After an optimization study on the reaction conditions, they found that using cataCXium A as ligand and Buchwald's second generation catalyst[53] as palladium source afforded the best results. Using these optimized conditions, Suzuki couplings of α-(benzyloxy)phenylpropyltrifluoroborate **48** and different aryl chlorides were conducted. As results, all of the reactions gave retention of configuration with impressively high stereospecificities. The electronic property of the aryl chlorides did not affect the stereochemical outcome of this reaction (Table 1.8).[52]




| entry | R | absolute configuration | yield (%) | % e.s. |
|---|---|---|---|---|
| 1 | $CF_3$ | retention | 81 | 99 |
| 2 | $CO_2Me$ | retention | 62 | 99 |
| 3 | F | retention | 75 | 99 |
| 4 | NHBoC | retention | 70 | 99 |
| 5 | OMe | retention | 87 | 99 |

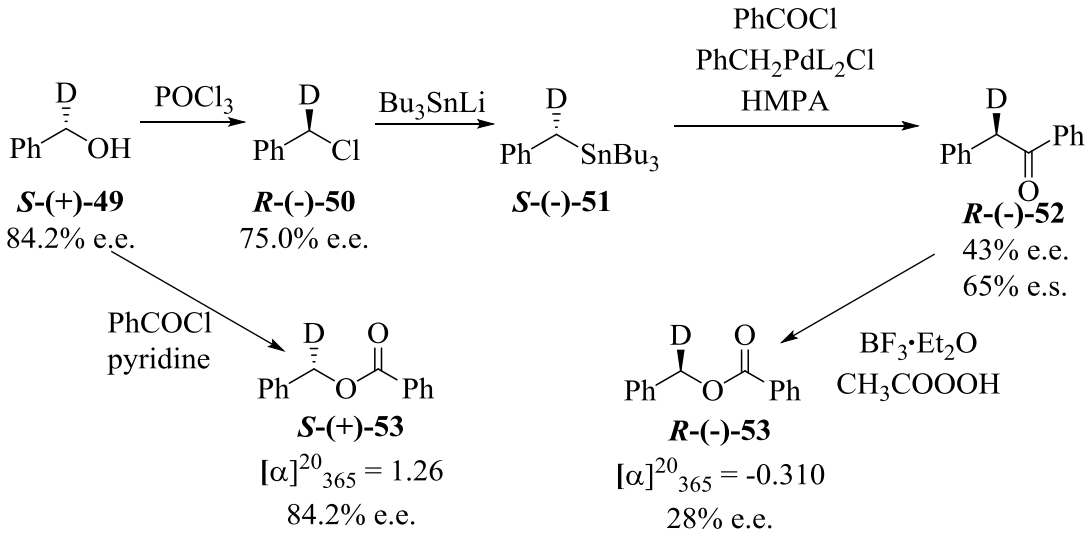
**Table 1.8:** Effect of the substituent on the electrophile to the Suzuki coupling of **48**[52]

### 1.4.4 Stille Couplings of Different Stereochemically Active Nucleophiles

#### 1.4.4.1 Stille Coupling of α-(Deuterio)benzylstannane

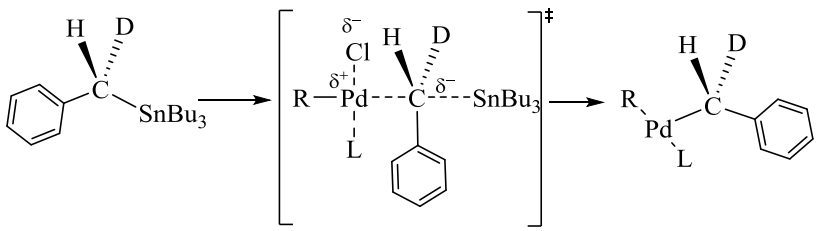
The first study about the stereochemical outcome of a Stille coupling reaction was reported by Labadie and Stille in 1983.[41] The enantiomerically enriched organotin nucleophile (*S*)-(-)-α-(deuterio)benzylstannane **S(-)-51** which was synthesized by chlorinating (*S*)-(+)-benzyl-α-D-alcohol **S-(+)-49** (84.2% ee), followed by an $S_N2$ type reaction using tributyltinlithium as the tin source. In this study, the absolute configuration and the optical purity of the cross-coupling product **R-(-)-52** were not detected directly. This cross-coupling product **(*R*)-(-)-52** was subsequently oxidized by Baeyer-Villiger oxidation to produce **(*R*)-(-)-53.** To obtain the

stereochemical outcome of this reaction, they first acylated **(*S*)-(+)-49** using benzoyl chloride and pyridine to obtain ester **(*S*)-(+)-53**. Because the chiral center of **(*S*)-(+)-49** was unchanged during the acylation, the % e.e of **(*S*)-(+)-53** was expected to be the same as that of **(*S*)-(+)-49**.[41]




**Scheme 1.21:** Stereochemical outcome of the coupling of **(*S*)-(-)-51** and benzoyl chloride

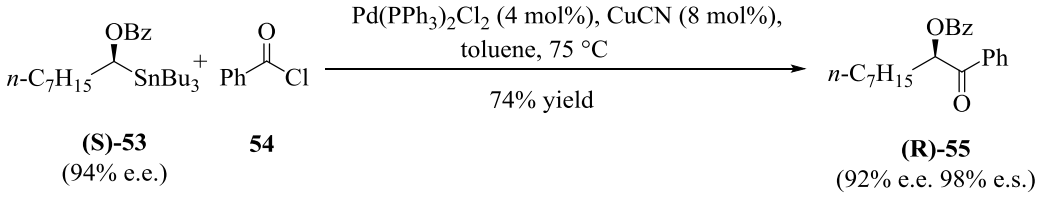
After they compared the specific rotation $[\alpha]^{20}_{365}$ of **(*R*)-(-)-53** with **(*S*)-(+)-53**, the %e.e of **(*R*)-(-)-53** was 28. However, they also stated that 42% racemization has occurred as the deuterium was lost by enolization of **(*R*)-(-)-52**; thus, the actual enantiomeric excess of **(*R*)-(-)-52** was reported as 43%. To rationalize this stereochemical outcome, they proposed the open-transmetalation for this reaction.[41] It was shown previously that this open transmetalation step gives inversion of configuration on the chiral nucleophile.[41]



**Scheme 1.22:** Open-transmetalation gives inversion of configuration

### 1.4.4.2 Stille Coupling of Chiral α-(Benzoyloxy)octylstannane

The first example of coupling reaction involving enantiomerically enriched α-(benzoyloxy)-stannanes was reported by Falck and coworkers in 1994.[54] In this study, they coupled (*S*)-[α-(benzoyloxy)octyl]tributylstannane **(*S*)-53** and benzoyl chloride in the present of CuCN and toluene. After the reaction, they obtained a complete retention of configuration (98% e.s. in Scheme 1.23). This retention of configuration can be explained by using the cyclic-transmetalation model.[13,28]

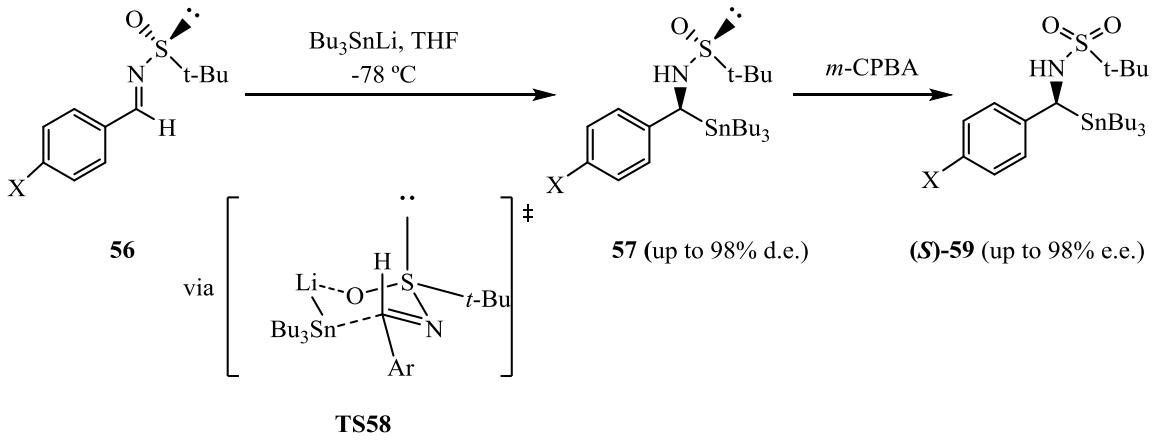


**Scheme 1.23:** Stille coupling of **(*S*)-53** and benzoyl chloride

### 1.4.4.3 Stille Coupling of Chiral α-Sulfonamidobenzylstannanes

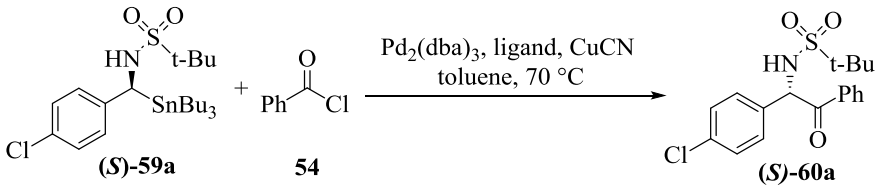
More recently, the Chong group reported the Stille cross-coupling of Chiral α-sulfonamidobenzylstannanes which gave inversion of configuration.[13,55] The stereochemically enriched α-sulfonamidobenzylstannane was synthesized by the procedure they developed in

2003.[56] In this procedure, tributyltin lithium was added in to aldimines **56** to generate diastereomerically enriched stannylsulfinamides **57** with impressively high diastereomeric ratio (higher than 98% d.e.). To rationalize the stereochemistry, they proposed a chair-like transition state **TS58** as shown in Scheme 1.24. After **57** was obtained, they oxidized the sulfinimine moiety with *m*-CPBA to generate the targeted α-(tert-butyl-sulfonamido)benzylstannanes **59** (Scheme 1.24).




**Scheme 1.24:** Synthesis of enantiomerically enriched α-(tert-butyl-sulfonamido)benzylstannanes **59**

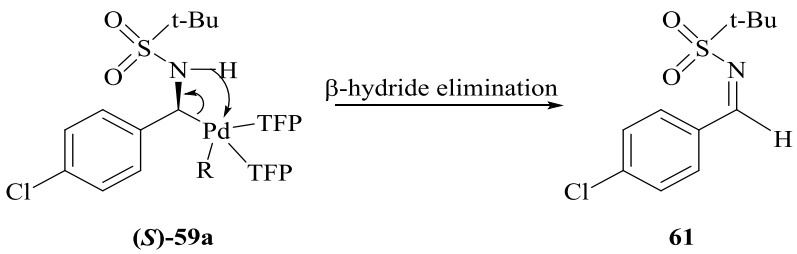
The Stille coupling reactions between **59a** and benzoyl chloride were conducted applying the condition developed by Falck in which CuCN and toluene were involved. As it was mentioned previously, a cyclic-transition state is favored when a nonpolar solvent is used.[13,28] As a matter of fact, retention of configuration was obtained by using this condition when Falck an coworkers coupled α-(benzoyloxy)octylstannane with benzoyl chloride (Scheme 1.23).[54] However, although these reactions were conducted with a nonpolar solvent (toluene), complete inversion of configuration obtained in all reactions (>98% e.s., Table 1.9) indicated that this reaction may proceed via the open-transmetalation step.[13,55]




| entry | ligand | absolute configuration | yield (%) | % e.s. |
|---|---|---|---|---|
| 1 | $Ph_3P$ | inversion | 63 | >98 |
| 2 | TFP | inversion | 23 | >98 |
| 3 | $Ph_3As$ | inversion | 37 | >98 |
| 4 | TTMPP | inversion | 86 | >98 |

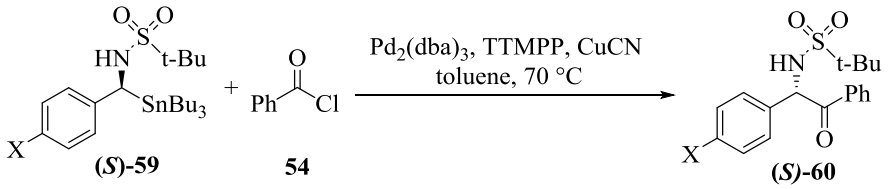
**Table 1.9:** Screen of ligand on the coupling of **(*S*)-59a**[55]

Table 1.9 also shows the effects of ligands in the reaction. As it was mentioned previously, a "hard ligand" (ligand that has a high σ-donating ability) can decrease the rate and yield of a reaction by forming a stronger palladium-ligand bond. Thus, "soft ligand" such as $AsPh_3$ and tri(2-furyl)phosphine (TFP) are considered as desirable ligands in palladium catalyzed cross-coupling reactions.[55] However, this study showed that a hard ligand such as tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) gave the best yield in the reaction while other "soft ligands" afforded low yields. Side product **61** which was likely formed through a β-hydride elimination process was found in the reactions which gave low yields. Thus, Chong and Kells hypothesized that soft ligands can accelerate the transmetalation step but can not inhibit the β-hydride elimination process which decreased the yield of the reaction (Scheme 1.25).[55]




**Scheme 1.25:** β-Hydride elimination in the Stille coupling of **(*S*)-59a**

Substituents on the aromatic ring of the nucleophile did not show any effect on the stereospecificity of the reaction. However, it seems that adding a strong electron withdrawing substituent on the electrophile reduced the yield (entry 5, Table 1.10). On the contrary, a weak electron donating substituent on the electrophile increased the yield to 98% (entry 2, Table 1.10).[55]



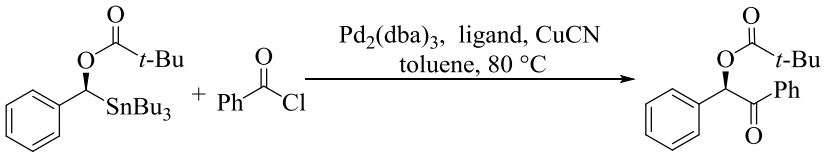

| entry | X | absolute configuration | yield (%) | % e.s. |
|---|---|---|---|---|
| 1 | H | inversion | 90 | >98 |
| 2 | Me | inversion | 98 | >98 |
| 3 | OMe | inversion | 85 | >98 |
| 4 | Cl | inversion | 86 | >98 |
| 5 | $CF_3$ | inversion | 78 | >98 |

**Table 1.10:** Effect of the substituent on the nucleophile on the coupling of **(*S*)-59**[55]

### 1.4.4.3 Stille Coupling of Chiral α-Acyloxybenzylstannane

The Stille coupling of the enantiomerically defined α-acyloxybenzylstannane was studied by the Chong group in 2011.[13] The coupling reaction between the enantiomerically enriched α-(trimethylacetoxy)benzylstannane **62** and benzoyl chloride gave retention of configuration with high stereospecificities. Unlike the coupling reactions of α-sulfonamidobenzylstannanes, the stereospecificity of the reactions of **62** showed a dependence on the nature of ligands. As can be seen in Table 1.11, stereospecificity of the reaction was increased from 88% to 95% by using different ligands. It seems that the σ-donicity of a ligand has a great effect on the

stereospecificity as hard ligands [such as tri(*o*-tolyl)phosphine] can give a higher stereospecificity than soft ligands (such as TFP).[13]

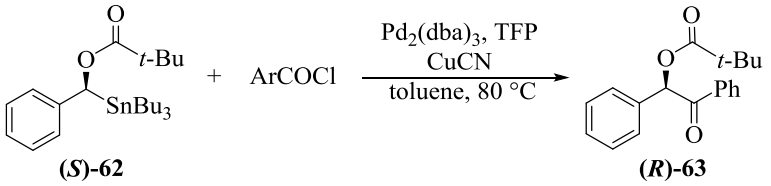



**(*S*)-62** 88% ee **54** **(*R*)-63**

| entry | ligand | yield (%) | % e.e. | % e.s. |
|---|---|---|---|---|
| 1 | P(*o*-Tol)$_3$ | 67 | 83 | 95 |
| 2 | PPh$_3$ | 91 | 82 | 94 |
| 3 | DavePhos | 77 | 79 | 90 |
| 4 | TFP | 92 | 78 | 89 |
| 5 | P(C$_6$F$_5$)$_3$ | 47 | 77 | 88 |

**Table 1.11:** Stille coupling of **(*S*)-62** with different ligands[13]

The effects of the electrophiles on the stereospecificity of reactions were also examined in this study where **(*S*)-62** was coupled with different acid chlorides.[57] However, there was no obvious correlation between the electronic properties of the electrophiles and the outcome of reaction, as both electron donating (entry 2, Table 1.12) and electron withdrawing (entry 8, Table 1.12) groups on the aromatic ring can give impressively high stereospecificities. Sterically bulky acid chlorides seemed to be correlated with low stereospecificities in the reaction (entries 4 and 5, Table 1.12). With respect to effects on the yield of reaction, it seemed that adding a substituent on the electrophiles always resulted in a lower yield in a reaction.[57]



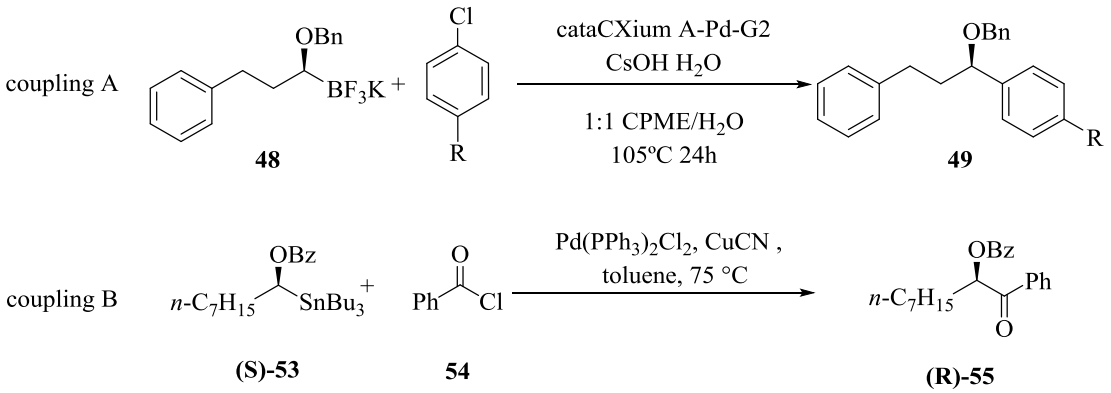

**(*S*)-62** **(*R*)-63**

| entry | Ar | yield (%) | % e.s. |
|---|---|---|---|
| 1 | Ph | 92 | 89 |
| 2 | 4-$MeOC_6H_4$ | 74 | 97 |
| 3 | 4-$MeC_6H_4$ | 84 | 69 |
| 4 | 3-$MeC_6H_4$ | 72 | 63 |
| 5 | 2-$MeC_6H_4$ | 45 | 28 |
| 6 | 4-*t*-$BuC_6H_4$ | 85 | 82 |
| 7 | 4-$CF_3C_6H_4$ | 53 | 89 |
| 8 | 4-$ClC_6H_4$ | 62 | 99 |
| 9 | 3-$ClC_6H_4$ | 77 | 32 |

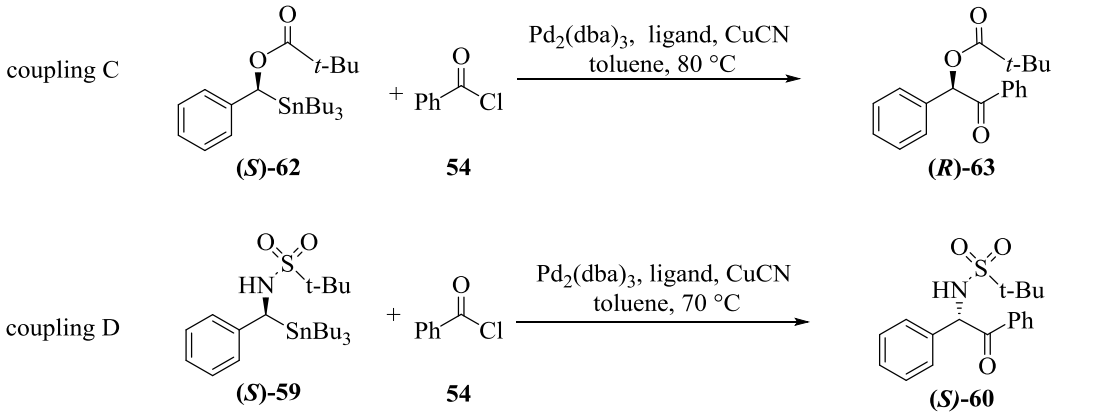
**Table 1.12:** Stille coupling of **(*S*)-62** with different substituted electrophiles[57]

### 1.4.5 Conclusions on the Cross-Coupling Reactions with $Sp^3$ Chiral Center

Several examples have been shown in this section; the data show that the stereochemical outcome of a reaction strongly is depended on the nature of nucleophiles. As can be seen in Scheme 1.26, while a coupling reaction involves alkyl nucleophiles,[52] retention of configuration is favored. However, α-benzyl moieties[41,42,45,55,57] seemed to be less well-defined because both inversion and retention of configurations have been shown in reactions involving α-benzyl nucleophiles (Scheme 1.27). A nitrogen atom on the α-position of the nucleophile (both α-acylamino-[47,48] and α-sulfonamido-[55]) gave inversion of configuration (coupling D in Scheme 1.27), while an oxygen atom on the same position (α-benzyloxy-,[52] α-benzoyloxy-,[54] and α-trimethylacetoxy-[57]) gave retention of configuration (couplings A, B in Scheme 1.26 and coupling C in Scheme 1.27).




**Scheme 1.26:** Coupling involving an alkyl nucleophile

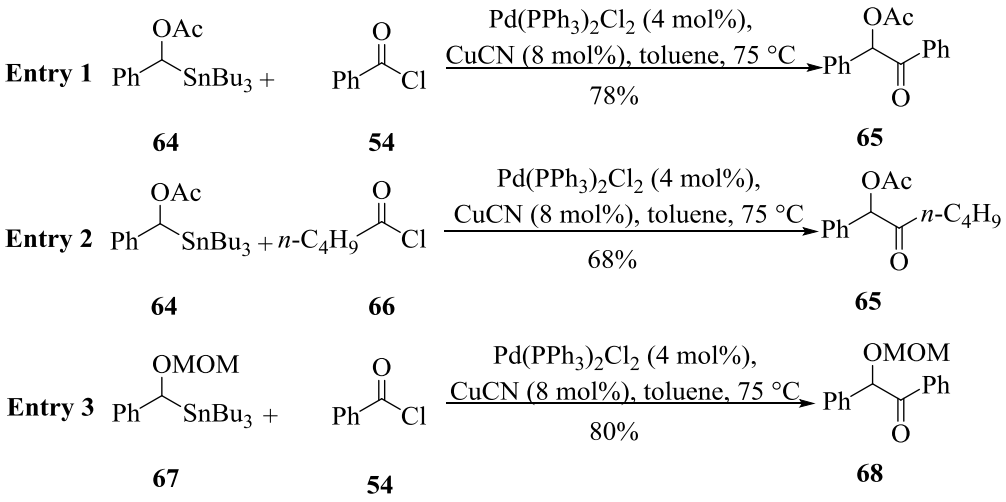



**Scheme 1.27:** Coupling involving an α-benzyl nucleophiles

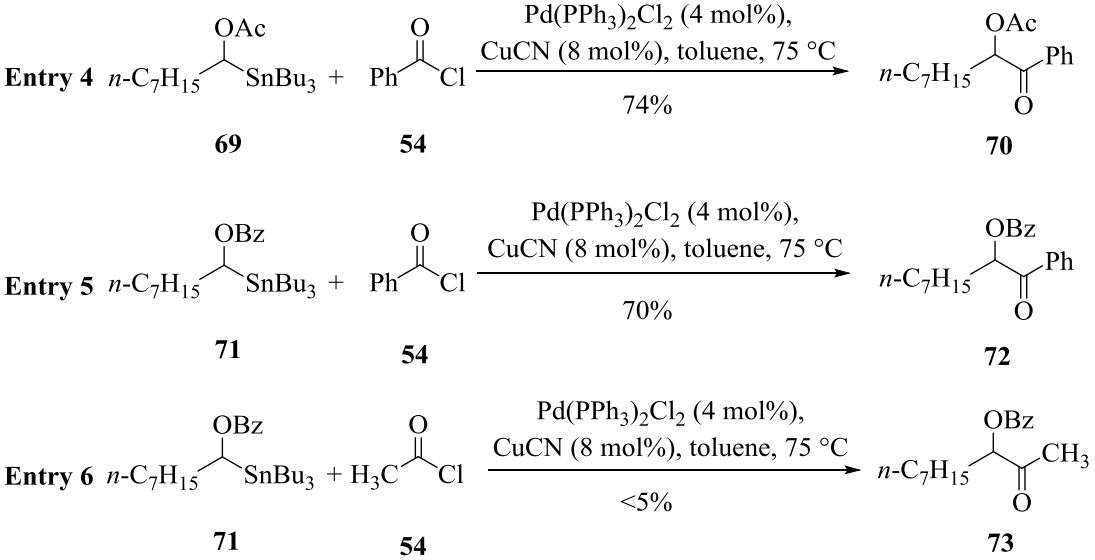
In addition to the nature of nucleophiles, the reaction conditions and the property of electrophiles also played important roles in determining the outcome of the coupling reactions. It has been shown that higher temperature can afford higher yields albeit with lower stereospecificities (entry 14 Table 1.6);[48] in addition, solvents[42] and additives[48] can change the stereochemical outcome of the reaction as well. Properties of the electrophiles may have great effects to the chemical outcome; however, no trend can be obtained.[57]

## 1.5 Stille Coupling of α-Alkoxystannanes

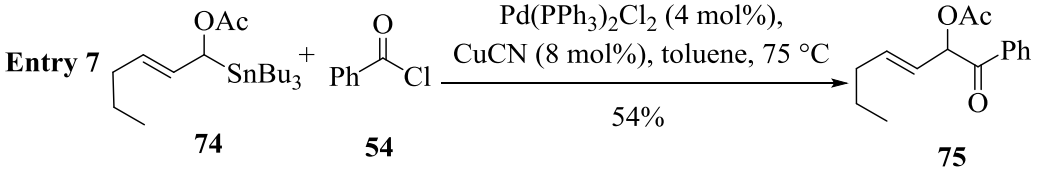
To have a better understanding of the Stille coupling involving an $sp^3$ chiral center, this thesis research focussed mainly on the α-alkoxystannanes which had been shown to always give retention of configuration.[54,57] The Stille coupling reactions between α-heteroatom-substituted stannanes with different acid chlorides were first reported by Falck and coworkers in 1994.[13,54] In this study, the coupling between α-alkoxybenzylstannanes and acid chlorides gave better yields which may be due to the fact that benzyl groups have a higher migratory aptitude than aliphatic groups (Scheme 1.28 and Scheme 1.29). Although allylic stannanes are considered as more reactive organotin nucleophiles, the yield given by **74** (entry 7 of Scheme 1.30) was lower than the yield given by **71** (entry 5 of Scheme 1.29); however, the reason of this unexpected result was not discussed in this study.[54]




**Scheme 1.28:** Coupling of **64** and **67** with acid chlorides

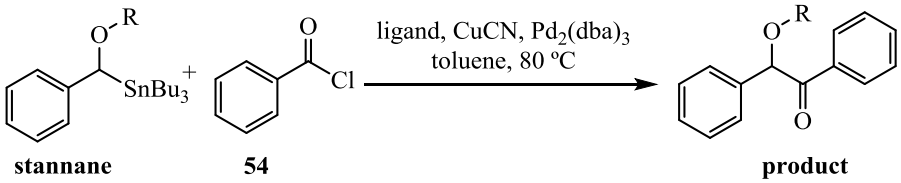



**Scheme 1.29:** Coupling of **69** and **71** with acid chlorides




**Scheme 1.30:** Coupling of **74** with benzoyl chloride

In the study carried out by Su and Chong, protecting groups on the α-oxygen atom showed decisive effects on the performance of a coupling reaction.[13] As can be seen in Table 1.14, a bulkier protecting group (entries 1 and 11 in Table 1.13) gave a better yield than a smaller protecting group (entries 8 and 10 in Table 1.13). In addition, effects of ligands were also shown in this table. It was claimed that ligands with less σ-donicity and smaller steric bulk can afford higher yield in this Stille reaction. However, an exception was found when TTMPP gave the highest yield in the coupling of **67** with benzoyl chloride; this result was similar to the one obtained with α-sulfonamidobenzylstannanes[55] (Table 1.9).




**stannane** **54** **product**

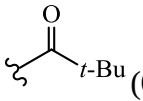
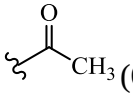
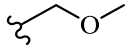
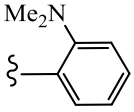
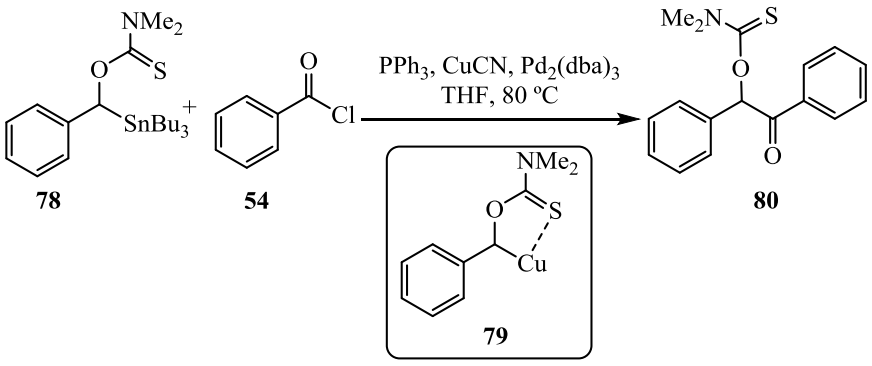
| entry | R group (**stannane**) | ligand | **product** | yield (%) |
|---|---|---|---|---|
| 1 |  (**62**) | TFP | **63** | 92 |
| 2 | | $PPh_3$ | | 91 |
| 3 | | TTMPP | | 71 |
| 4 | | P(*o*-Tol)$_3$ | | 67 |
| 5 | | $P(C_6F_5)_3$ | | 47 |
| 6 | | P(*n*-Bu)$_3$ | | 30 |
| 7 |  (**64**) | TTMPP | **65** | 72 |
| 8 | | TFP | | 60 |
| 9 | | $PPh_3$ | | 53 |
| 10 |  (**67**) | TFP | **68** | 38 |
| 11 |  (**76**) | TFP | **77** | 64 |

**Table 1.13:** Effects of the protection group and ligand on the coupling with α-alkoxybenzylstannanes[13]

Intriguingly, the coupling between the α-(thiocarbamoyloxy)benzylstannane **78** and benzoyl chloride could proceed in the absence of palladium metal (Table 1.14). This Cu-catalyzed cross-coupling reaction may be initialized by a Cu-Sn transmetalation process which generates an organocopper species.[58] That organocopper species is stabilized by a coordination of the sulfur atom to the copper (**79**).



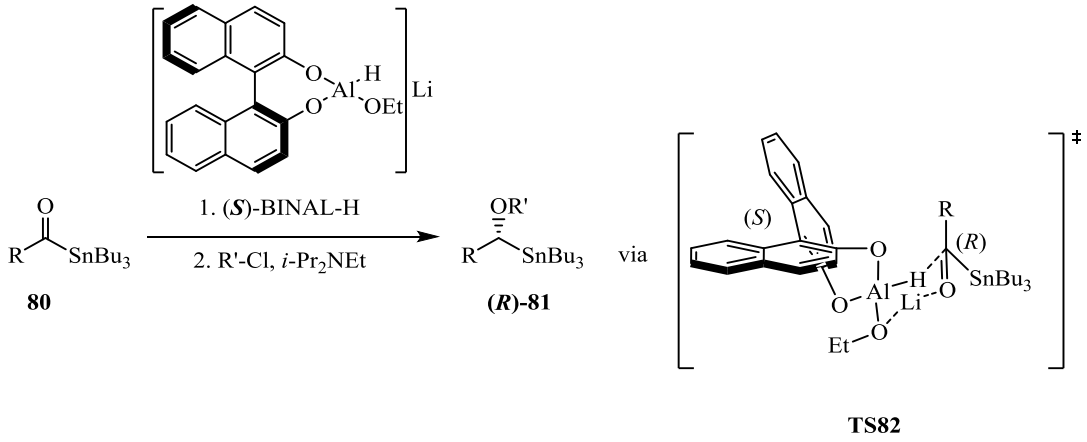

| entry | $Pd_2(dba)_3$ (mol%) | $PPh_3$ (mol%) | yield (%) |
|---|---|---|---|
| 1 | 5 | 20 | 35 |
| 2[a] | 5 | 20 | 27 |
| 3 | - | - | 32 |

[a]Using toluene as solvent

**Table 1.14:** Coupling of **78** without palladium catalyst[13]

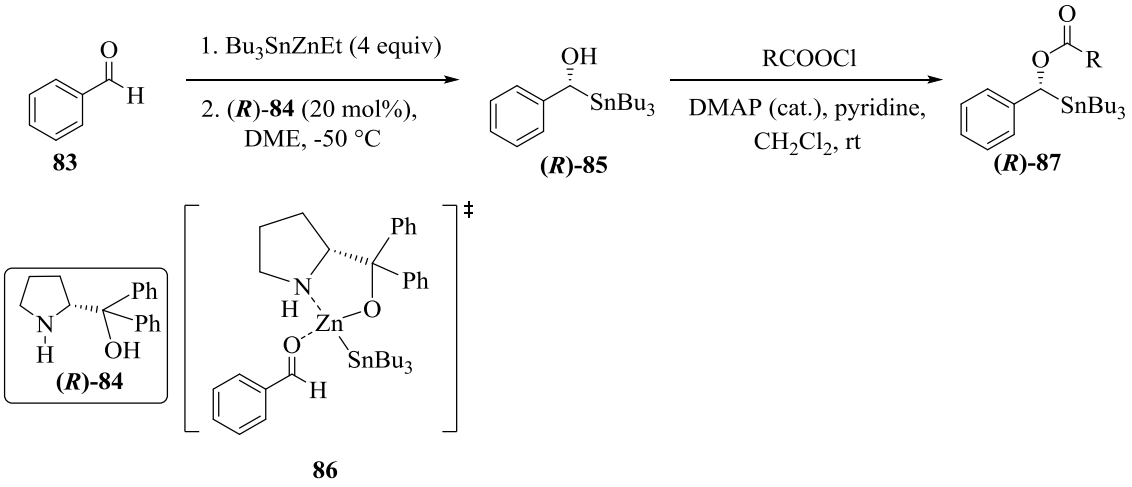
## 1.6 Asymmetric Synthesis of α-Alkoxystannanes

Early examples of synthesis of stereochemically enriched α-alkoxystannanes mostly involved the resolution of diastereomeric derivatives of racemic stannanes[59,60] or the resolution via enantioselective hydrolysis with enzymes.[61,62] However, these methods do have limitations of small substrate scope and low yields.[13] In 1988, Chan and Chong developed an asymmetric synthesis method of α-alkoxystannanes via an asymmetric reduction of acylstannanes.[63] The chiral reducing agent used in this reaction was BINAL-H which was developed by Noyori.[13,64] The BINAL-H and the acylstannane **80** would react to give a chair-like 6-membered cyclic transition state **TS82**. After the asymmetric reduction and protection of the α-hydroxy group, enantiomerically enriched stannane **81** can be obtained (Scheme 1.31).




**Scheme 1.31:** Asymmetric reduction of **80**

More recently, Falck and coworkers reported an asymmetric synthesis of α-acyloxybenzylstannanes by using chiral diphenyl(pyrrolidin-2-yl)methanol (**84**) as the catalyst.[65] Benzaldehyde (**83**) was treated with 4 equivalents of ethylzinc-tributyltin complex and 20 mol% of **84** to give complex **86**; this was followed by the formation of enantiomerically enriched α-hydroxybenzylstannane **(*R*)-85**. As **(*R*)-85** is not stable, it needs to be protected immediately by different protecting groups to give different α-acyloxybenzylstannanes (Scheme 1.32).




**Scheme 1.32:** Synthesis of enantiomerically enriched α-acyloxybenzylstannane

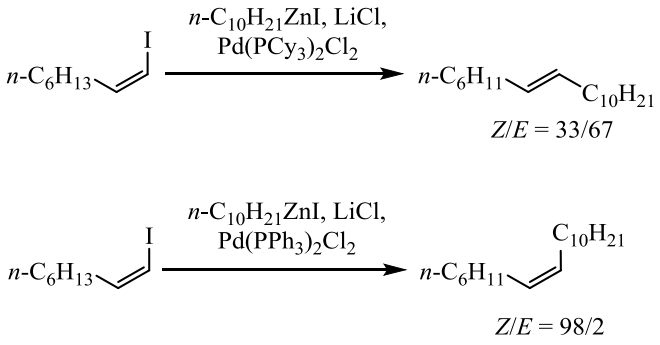
## 1.7. Research Proposal

Palladium-catalyzed cross-coupling reaction with an $sp^3$ chiral center were studied by several groups and the stereochemical outcome of the reaction was explained with either open- or cyclic-transmetalation. According to the studies given by the Falck group[54] and the Chong group,[13] Stille coupling reactions with enantiomerically enriched α-alkoxystannanes always gave retention of configuration. However, explanation about this stereochemical outcome was not given. As it was shown in Suginome's studies,[48] changing the acyl group on the nitrogen atom on the α-(acylamino)benzylboronate did affect the stereochemical outcome significantly. It is necessary to conduct other Stille couplings of different α-alkoxystannanes to see if different acyl group on the β-oxygen can give different stereochemical outcome.

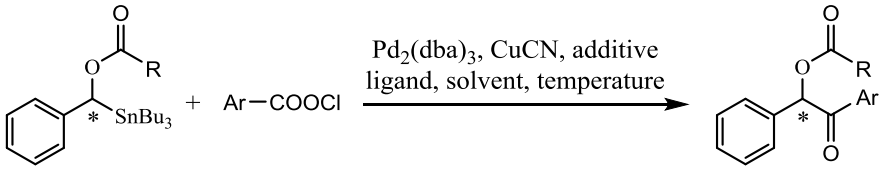
In addition, effects of the ligand and the electrophile on the stereochemical outcome are also of interest. The effects of ligands on the stereochemical outcome of a palladium catalyzed cross-coupling reaction were reported by Lipshutz group when they conducted several Negishi couplings between vinyl iodides and alkyl zinc compounds.[66] They found that using tricyclohexylphosphine as ligand, this coupling reaction gave predominantly inversion of configuration (Scheme 1.33) while $PPh_3$ gave essentially complete retention of configuration. Moreover, in Su's study, the stereospecificity of reaction strongly depended on the properties of the ligand and the electrophile.[13,57] However, because no obvious trend was found previously, a more extensive study was needed.

To have a well-performing reaction, this project first focused on optimization studies which aimed to increase the yield of the coupling reactions with different racemic α-acyloxybenzyl-stannanes **87**. After optimized reaction conditions are obtained, this project will mainly focus on

discovering the effects of different factors on the Stille coupling of enantiomerically enriched α-acyloxybenzylstannanes **87**. These factors include the protecting group on β-oxygen, ligand, additive, electrophile, solvent, and reaction temperature (Scheme 1.34).




**Scheme 1.33:** Effect of ligand on the Negishi coupling of vinyl iodide



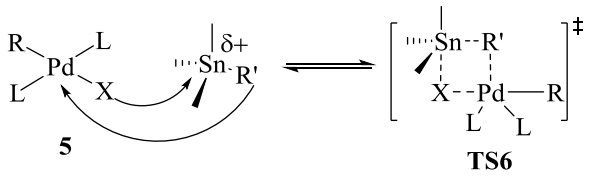

**87** **88**

**Scheme 1.34:** General scheme of the Stille coupling of enantiomerically enriched **87**

## Chapter 2: Results and Discussion

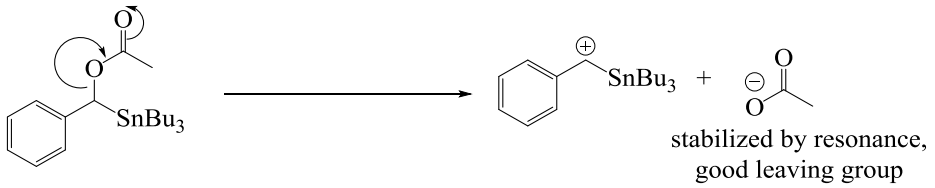
### 2.1. Preparations and Stille Couplings of (±)α-Acyloxybenzylstannanes

The cyclic-transmetalation involves the attack of the bridging atom (X) to the electrophilic tin atom. If the R' group is highly electron withdrawing, this nucleophilic attack may be facilitated; thus, the cyclic-transmetalation would be enhanced and retention of configuration would be favored (Scheme 2.1).

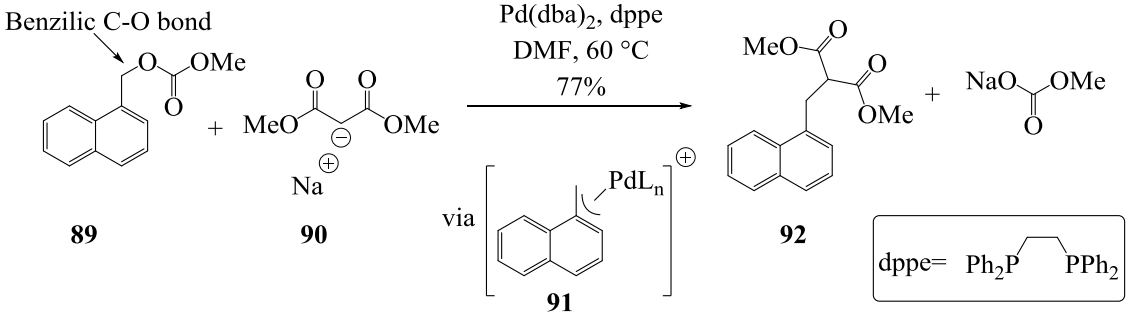



**Scheme 2.1:**Cyclic-transmetalation mechanism

However, the electron withdrawing moiety on R' group may also enhance the palladium-catalyzed benzylic C-O bond cleavage by making the carboxylate group a better leaving group (Scheme 2.2).[13] The first example of this palladium-catalyzed benzylic C-O bond cleavage was reported by Legros and Fiaud.[13,67] In this study, the 1-naphthylmethyl carbonate **89** was treated with the dimethyl malonate **90** in the presence of palladium(0) and phosphine ligand. The result showed that the benzylic C-O bond was cleaved by the attack of palladium(0) to make a $\eta^3$-benzylpalladium complex intermediate **91**, which was subsequently attacked by the dimethyl malonate anion to give the coupled product **92** (Scheme 2.3). Thus, a balance needs to be obtained between putting an electron withdrawing group to produce higher enantiospecificity and putting an electron donating group to retard the benzylic C-O bond cleavage. In addition, if the protecting group is an acyl group, this acyl group needs to be bulky enough to protect the carbonyl group from nucleophilic attack.




**Scheme 2.2:** O-acylation makes the β-oxygen a good leaving group[13]

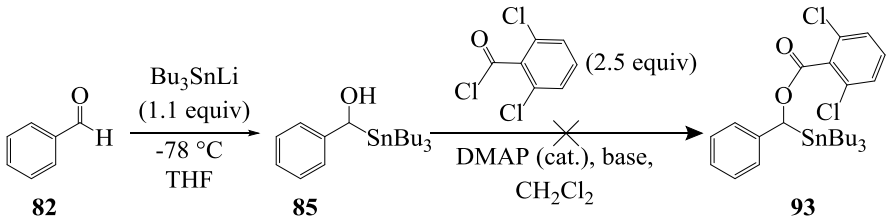



**Scheme 2.3:** Coupling between **89** and **90**

### 2.1.1 Synthesis of (±)-α-(2,6-Dichlorobenzoyloxy)benzylstannane

The first α-acyloxybenzylstannane synthesized in this project was the α-(2,6-dichlorobenzoyloxy)benzylstannane. The chlorine atoms on the phenyl group not only protect the carbonyl group sterically, but also slightly increase the electron withdrawing ability of the protecting group. The synthesis of this racemic compound was conducted by the procedure developed in the Chong group which includes a nucleophilic addition of tributyltinlithium to benzaldehyde followed by an acylation of the α-hydroxybenzylstannane **85** with the appropriate acid chloride (Scheme 2.4).[13] However, no product was obtained at room temperature when pyridine was used as a base (Table 2.1). Because compound **85** was detected by $^{1}$H NMR spectroscopy after the first step, the failure of this synthesis must be caused by the acylation step. One reason was that the 2,6-dichlorobenzoyloxy protecting group may be too bulky to add on **85**. Intriguingly, replacing pyridine with *N*,*N*-diisopropylethylamine (DIPEA) could produce a trace

amount of product. When pyridine was used as the base, no **85** was left after 12 hours of reaction time; however, when DIPEA was used as the base, a small amount of α-hydroxybenzylstannane was detected by $^1$H NMR after 12 hours. This indicates that DIPEA may stabilize the α-hydroxybenzylstannane by some unknown effects or pyridine may cause decomposition of the α-hydroxybenzylstannane.




**82** **85** **93**

| entry | base | temperature (℃) | yield (%)[a] |
|---|---|---|---|
| 1 | Pyridine | rt | 0 |
| 2 | DIPEA[b] | 0 | trace |
| 3 | DIPEA[b] | rt | trace |

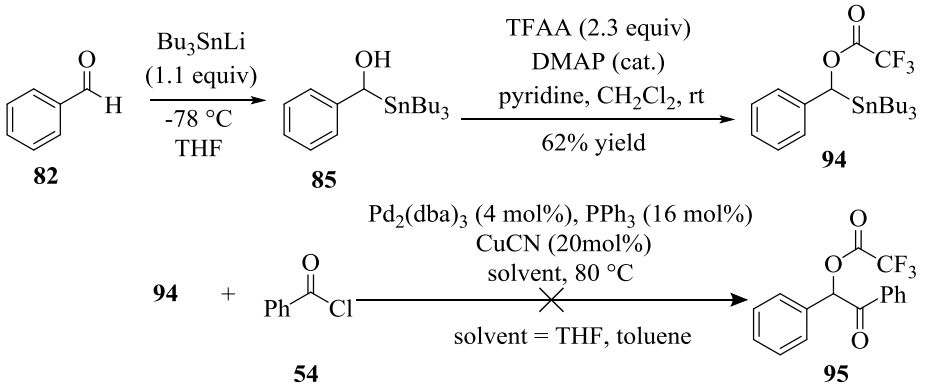
[a]By $^1$H NMR spectroscopy
[b]α-Hydroxybenzylstannane was found by TLC analysis after 12 hours of reaction time

**Table 2.1:**Preparation of (±)-α-(2,6-dichlorobenzoyloxy)benzylstannane **93**

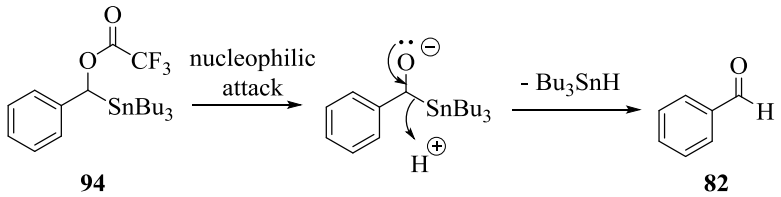
### 2.1.2 Synthesis and Stille Coupling of (±)-α-(Trifluoroacetoxy)benzylstannane

As the 2,6-dichlorobenzoyl moiety might be too bulky to add on the β-oxygen, the trifluoroacetate group was tried in this research because it had a higher electron withdrawing ability and a smaller steric bulk. The preparation of racemic α-(trifluoroacetoxy)benzylstannane **94** proceeded in 62% isolated yield in the presence of pyridine. Unfortunately, no product was obtained either in toluene or THF in the coupling reaction; however, benzaldehyde was found after the reaction (Scheme 2.4). Thus, it seemed that the $CF_3$ moiety was not bulky enough to protect the carbonyl group from the attack of nucleophile; additionally, it made the carbonyl

group more electrophilic. After **94** was deacylated, α-hydroxybenzylstannane **85** was regenerated and subsequently decomposed to benzaldehyde (Scheme 2.5).[68]



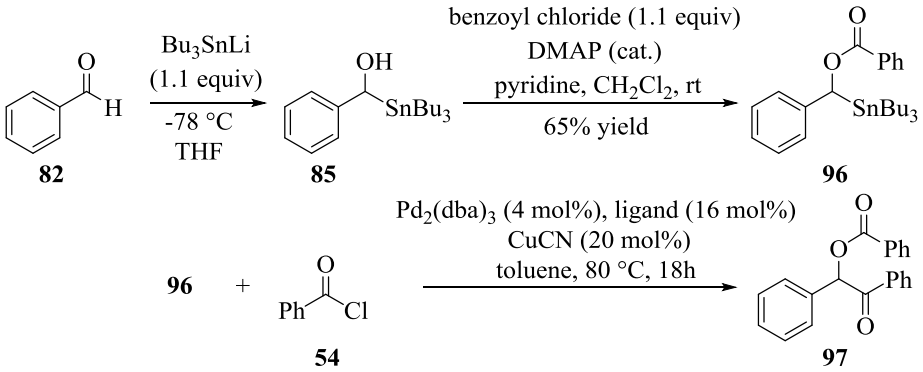

**Scheme 2.4:** Preparation and Stille coupling of (±)-α-(trifluoroacetoxy)benzylstannane **94**




**Scheme 2.5:** Decomposition of (±)-α-(trifluoroacetoxy)benzylstannane to give benzaldehyde

### 2.1.3 Synthesis and the Stille Coupling of (±)-α-Benzoyloxybenzylstannane

The third protecting group in this study was the benzoyl group which was bulky and electron withdrawing. The preparation of racemic α-benzoyloxybenzylstannane **96** gave 65% isolated yield in the presence of pyridine. The Stille coupling of **96** with benzoyl chloride gave moderate yields (Table 2.2). However, co-elution of the coupled product **97** and dibenzylideneacetone (dba) was found in the column chromatography. Thus ~10% of product may be lost during the purification.




| entry | ligand | cone angle ($\theta$)[a] | $\nu$ ($cm^{-1}$)[b] | yield (%) |
|---|---|---|---|---|
| 1 | $PPh_3$ | 145 ° | 2068.9 | 73[d] (63)[c] |
| 2 | TFP | 133 ° | | 71[d] (59)[c] |
| 3 | $P(C_6H_{11})_2Ph$ | | | 66[d] |
| 4 | P(*p*-Tol)$_3$ | 145 ° | 2066.7 | 60[d] |
| 5 | Dave Phos | | | 59[d] |
| 6 | S Phos | | | 54[d] |
| 7 | TTMPP | 184 ° | 2048.0 | 53[d] |
| 8 | CyJohn Phos | | | 53[d] |
| 9 | DPPB | | | 47[d] |
| 10 | $P(C_6F_5)_3$ | 184 ° | 2090.9 | 43[d] |
| 11 | DPPP | | | 36[d] |
| 12 | P(*o*-Tol)$_3$ | 194 ° | 2066.6 | 34[d] |
| 13 | P(Cy)$_3$ | 170 ° | 2056.4 | 17[d] |

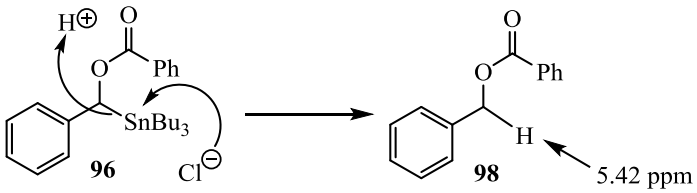
[a]See reference 30
[b]See reference 69
[c]Isolated yields
[d]Yields are determined by $^1$H NMR spectroscopy where dimethyl terephthalate was used as internal standard

**Table 2.2:** Preparation and coupling reactions of **96**

A ligand survey was done and it showed that triphenylphosphine ($PPh_3$) which has mild σ-donicity and relatively small steric bulk afforded the highest yield (73%) in this reaction (entry 1 of Table 2.2). Lower yields were afforded when a ligand contained either a larger steric bulk [by comparing P(*p*-Tol)$_3$ (60%) from entry 4 and P(*o*-Tol)$_3$ (34%) from entry 12] or a weaker σ-donicity [by comparing tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) (53%) from entry 7 and $P(C_6F_5)_3$ (43%) from entry 10]. It can be seen that a ligand with strong σ-donicity such as P(Cy)$_3$ would also decrease the yield (17% yield from entry 13); this has been discussed previously in

this thesis as a stronger donor makes the ligand dissociation more difficult. In addition, these ligand effect were consistent with the previous results obtained from the coupling reactions of the α-(trimethylacetoxy)benzylstannane **62**[13] (Table 1.11).

It is noteworthy that a small amount (~10 %) of benzyl benzoate (**98)** was observed by $^{1}H$ NMR spectroscopy after the reaction. This side product may be formed through the mechanism which is shown in Scheme 2.6. A small amount of HCl may be present in the reaction mixture. However, because all of the samples had been degassed before they were heated up, no HCl should be left before the reaction was started. Thus, this small amount of HCl may be generated during the reaction period by the reaction between acid chloride and adventitious moisture.

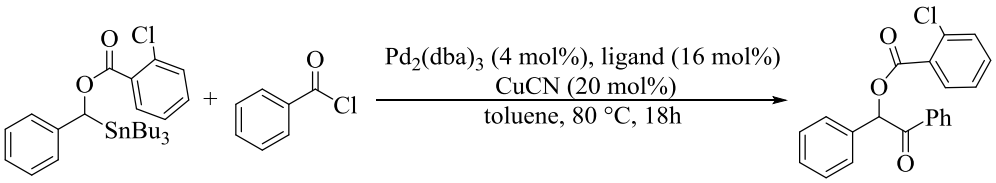



**Scheme 2.6:** Formation of the side product **98** in the presence of HCl

### 2.1.4 Synthesis and Stille Coupling of (±)-α-2-Chlorobenzoyloxybenzylstannane

The fourth protecting group in this study was the 2-chlorobenzoyl group which was slightly more electron withdrawing than the benzoyl group. The preparation of **99** gave 62% isolated yield using the same procedure (Scheme 2.4). Ligand effects in this reaction were tested and shown in Table 2.3. It can be seen that TFP and $PPh_3$ which have mild σ-donicity and relatively small steric bulk gave high yields (73% and 59% respectively) in this reaction (entries 1 and 3). However, P(*o*-Tol)$_3$ which has a large steric bulk gave the second highest yield (61%) in this study. This showed that a large ligand can also give high yield in some cases. Ligands had low σ-

donicity such as $P(C_6F_5)_3$ gave low yield (39%) in this ligand screen (entry 10, Table 2.3) while ligand had high σ-donicity such as TTMPP (57%) and dicyclohexyl-phenylphosphine $P(C_6H_{11})_2Ph$ (46%) gave moderate yields (entries 4 and 8). Unfortunately, co-elution of the coupled product **100** and dibenzylideneacetone (dba) was found in the column chromatography as well.




**99** **54** **100**

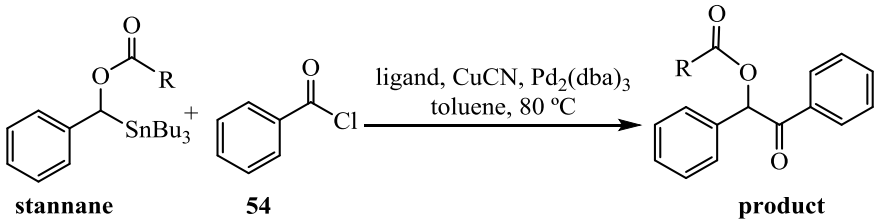
| Entry | Ligand | Cone angle (θ)[a] | ν ($cm^{-1}$)[b] | yield (%)[d] |
|---|---|---|---|---|
| 1 | TFP | 133 ° | | 73 (61[c]) |
| 2 | P(*o*-Tol)$_3$ | 194 ° | 2066.6 | 61 |
| 3 | $PPh_3$ | 145 ° | 2068.9 | 59 (49[c]) |
| 4 | TTMPP | 184 ° | 2048.0 | 57 |
| 5 | P(*p*-Tol)$_3$ | 145 ° | 2066.7 | 51 |
| 6 | DPPB | | | 50 |
| 7 | Dave Phos | | | 57 |
| 8 | $P(C_6H_{11})_2Ph$ | | | 46 |
| 9 | CyJohn Phos | | | 42 |
| 10 | $P(C_6F_5)_3$ | 184 ° | 2090.9 | 39 |
| 11 | S Phos | | | 38 |

[a]See reference 30
[b]See reference 69
[c]Isolated yields
[d]Yields are determined by $^1H$ NMR spectroscopy where dimethyl terephthalate was used as internal standard

**Table 2.3:** Preparation and coupling reactions of **99**

The effects of the protecting group on the yield of the coupling reaction is shown in Table 2.4. It can be seen that an acyloxystannane with a bulky protecting like trimethyl acetyl group gave the highest yields in the coupling reactions (entries 1, 2, Table 2.4). However, a significant amount of product was lost during the purification of **97** and **100**. They did not give higher isolated yields than **65** even though both benzoyl group and 2-chlorobenzoyl group are bulkier

than acetate group. In addition, by comparing the results of benzoyl group (entries 3, 4, Table 2.4) and 2-chlorobenzoyl group (entries 5, 6, Table 2.4), it can be seen that the electron withdrawing substituent on the aromatic ring of the protecting group did not significantly change the yield of the coupling reaction.




**stannane** **54** **product**

| Entry | R group (**stannane**) | A-value[a] | ligand | **product** | yield (%) |
|---|---|---|---|---|---|
| 1 | *t*-Bu (**62**) | >4.5 | TFP | **63** | 92[b] |
| 2 | | | $PPh_3$ | | 91[b] |
| 3 | $C_6H_5$ (**96**) | 3.0 | TFP | **97** | 59[c] (71[d]) |
| 4 | | | $PPh_3$ | | 63[c] (73[d]) |
| 5 | 2-Cl-$C_6H_4$ (**99**) | - | TFP | **100** | 61[c] (73[d]) |
| 6 | | | $PPh_3$ | | 49[c] (59[d]) |
| 7 | $CH_3$ (**64**) | 1.7 | TFP | **65** | 60[b] |
| 8 | | | $PPh_3$ | | 53[b] |

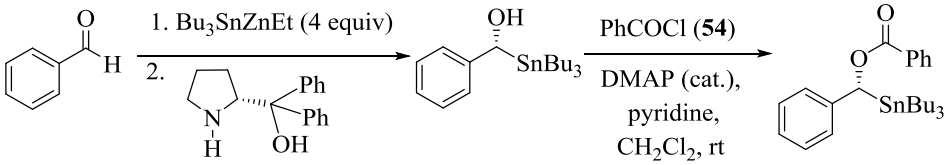
[a]See reference 70
[b]See reference 13
[c]Isolated yields
[d]Yields are determined by $^1$H NMR spectroscopy where dimethyl terephthalate was used as internal standard

**Table 2.4:** Stille coupling with different protecting groups and ligands

## 2.2 Stille Coupling of (*R*)-α-Benzoyloxybenzylstannane

### 2.2.1 Synthesis of (*R*)-α-Benzoyloxybenzylstannane

Using the strategy developed by Falck,[65] the asymmetric synthesis of (*R*)-α-benzoyloxybenzylstannane was conducted (Table 2.5). The best enantiomeric excess obtained was 93%. However, yields of this reaction were low, which may be caused by unexpected moisture in the reaction.




| trial | yield (%)[a] | % e.e.[b] |
|---|---|---|
| 1 | 75 | 75 |
| 2 | 56 | 93 |
| 3 | 60 | 81 |
| 4 | 30 | 91 |

[a]Isolated yields
[b]Determined by high performance liquid chromatography, average for two injections

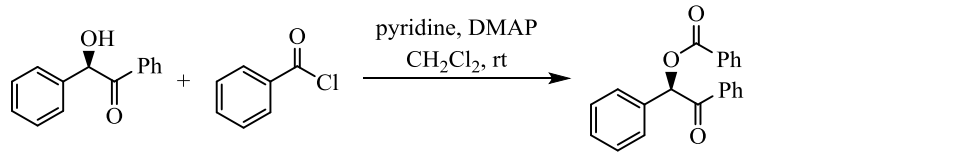
**Table 2.5:** Preparation of (*R*)-α-benzoyloxybenzylstannane **(*R*)-96**

### 2.2.2 Stille Coupling of (*R*)-α-benzoyloxybenzylstannane

Stille couplings between (*R*)-α-benzoyloxybenzylstannane **(*R*)-96** with benzoyl chloride were conducted with different ligands to search for the effects of ligand on the stereospecificity of the reaction. By comparing the HPLC retention times of **(*R*)-97** (which is the benzoylated derivative of (*R*)-(-)-benzoin **101**, Scheme 2.7) with those values obtained from the Stille coupling reaction, the absolute configuration of the coupled product **97** can be determined.

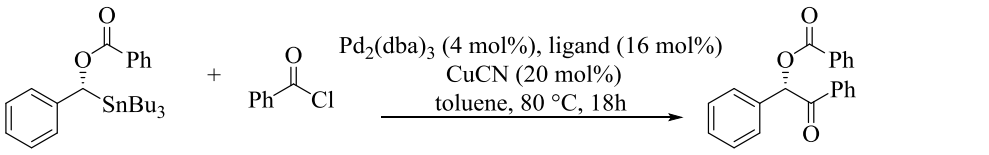
As a result, most ligands gave nearly complete of retention of configuration (>90% e.s.). Ligands with mild or low σ-donicity such as TFP and $P(C_6F_5)_3$ seemed to give higher stereospecificity in this reaction (entries 1-5 in Table 2.6) when ligands with higher σ-donicity such as DavePhos, SPhos and $P(C_6H_{11})_2Ph$ gave lower or zero stereospecificity (entries 6, 7, 8 in Table 2.6). Ligands containing larger steric bulk such as P(*o*-Tol)$_3$ and CyJohnPhos (entries 2 and 3 in Table 2.6) seemed to give higher stereospecificities compared to ligands with a smaller steric bulk such as $PPh_3$ and $P(C_6H_{11})_2Ph$ (entries 5 and 8). About 1% of deviation in % e.e. was

found for multiple injections in the HPLC; thus, the values of % e.e. (and % e.s.) in this thesis are the average values for two injections.




**101** 98% e.e. **54** **(*R*)-97** 98% e.e. major peak $t_R$ = 5.98 minor peak $t_R$ = 6.80

**Scheme 2.7:** Synthesis of **(*R*)-97** via acylation of (*R*)-(-)-benzoin **101**




**(*R*)-96** **54** **(*S*)-97** major peak $t_R$ = 6.80 minor peak $t_R$ = 5.98

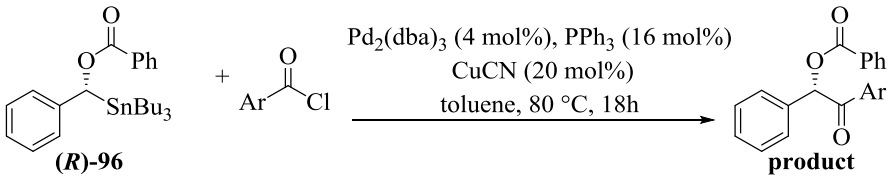
| entry | ligand | % e.e. of **(*R*)-96**[a] | % e.e. of **(*S*)-97**[a] | % e.s[b] |
|---|---|---|---|---|
| 1 | P(*o*-Tol)$_3$ | 93 | 92 | 99 |
| 2 | TFP | 93 | 90 | 97 |
| 3 | CyJohnPhos | 93 | 90 | 97 |
| 4 | $P(C_6F_5)_3$ | 93 | 87 | 94 |
| 5 | $PPh_3$ | 93 | 86 | 92 |
| 6 | DavePhos | 81 | 74 | 91 |
| 7 | SPhos | 81 | 72 | 89 |
| 8 | $P(C_6H_{11})_2Ph$ | 93 | 0 | 0 |

[a]Determined by high performance liquid chromatography, average for two injections
[b]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

**Table 2.6:** Effects of ligand in the Stille coupling of **(*R*)-96**

Stille couplings between **(*R*)-96** and different acid chlorides were conducted and the effects of electrophile on the outcomes of the reaction were studied. However, it was found that the coupling reactions gave poor stereospecificities in the presence of $PPh_3$ (%e.s. values were mostly around 60-80 in Table 2.7), while the reactions with tri-(2-furanyl)phosphine (TFP) gave better stereospecificities (% e.s. values were mostly around 80-90 in Table 2.8). It seemed that adding any substituent on the electrophile would lower both the yield and the enantiospecificity

of a coupling reaction, as the reaction with benzoyl chloride always gave the highest stereospecificity. The acid chloride with an *ortho*-substituted aromatic ring such as *o*-toluoyl chloride and 2-chlorobenzoyl chloride gave low yields in this reaction (entries 4, 6 in Table 2.7 and entry 4 in Table 2.8). The reason may be that the carbonyl group was sterically hindered and the oxidative addition step was retarded.

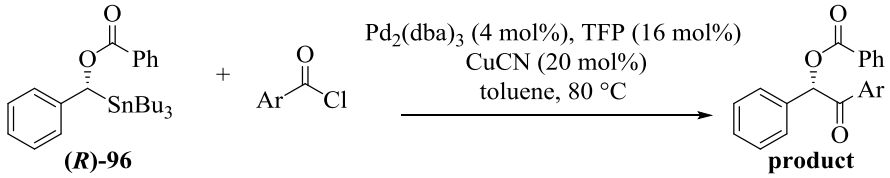



| entry | Ar | **product (% yield)**[a] | % e.e. of **(*R*)-96**[b] | % e.e. of **product**[b] | % e.s[c] |
|---|---|---|---|---|---|
| 1 | 3-$OMeC_6H_4$ | **102** (28) | 81 | 2 | 0 |
| 2 | 4-$OMeC_6H_4$ | **103** (28) | 81 | 20 | 25 |
| 3 | 3-$MeC_6H_4$ | **104** (52) | 81 | 54 | 67 |
| 4 | 2-$MeC_6H_4$ | **105** (21) | 81 | 69 | 85 |
| 5 | 4-$CF_3C_6H_4$ | **106** (34) | 81 | 53 | 66 |
| 6 | 2-$ClC_6H_4$ | **107** (0) | 81 | - | - |
| 7 | 4-$ClC_6H_4$ | **108** (32) | 81 | 58 | 69 |
| 8 | 4-$NO_2C_6H_4$ | **109** (0) | 81 | - | - |
| 9 | Ph | **97** (58) | 93 | 86 | 92 |

[a]Isolated yields
[b]Determined by high performance liquid chromatography, average for two injections
[c]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

**Table 2.7:** Stille coupling of **(*R*)-96** using $PPh_3$ with different electrophile

In the coupling reaction with $PPh_3$ (Table 2.7), both electron donating substituent (4-OMe) and electron withdrawing substituent (3-OMe) gave low stereospecificities. However, in the reaction with TFP (Table 2.8), electron withdrawing substituents (3-OMe and 4-Cl) gave lower stereospecificity than the electron donating substituent (4-OMe). In addition, it was found that the *ortho*-substituent (2-Me) gave higher % e.s. than the *meta*-substituent (3-Me) (entries 3, 4, Table 2.7; entries 3, 4, Table 2.8). Thus, no general correlation could be obtained between the properties of electrophile and the stereospecificity of the reaction.

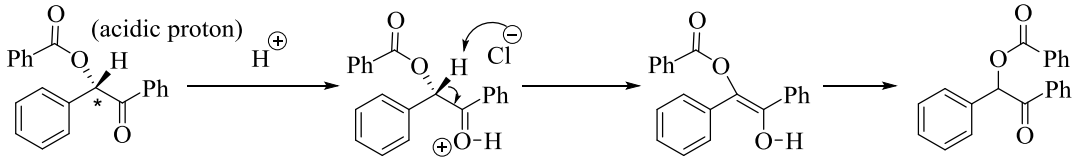



| entry | Ar | **product (% yield)**[a] | % e.e. of **(*R*)-96**[b] | % e.e. of **product**[b] | % e.s[c] |
|---|---|---|---|---|---|
| 1 | 3-$OMeC_6H_4$ | **102** (31) | 81 | 0 | 0 |
| 2 | 4-$OMeC_6H_4$ | **103** (22) | 75 | 74 | 99 |
| 3 | 3-$MeC_6H_4$ | **104** (43) | 81 | 74 | 91 |
| 4 | 2-$MeC_6H_4$ | **105** (16) | 81 | 69 | 85 |
| 5 | 4-$ClC_6H_4$ | **108** (43) | 81 | 73 | 90 |
| 6 | Ph | **97** (55) | 93 | 90 | 97 |

[a]Isolated yields
[b]Determined by high performance liquid chromatography, average for two injections
[c]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

Table 2.8: **Stille coupling of** (*R*)-96 **using TFP with different electrophile**

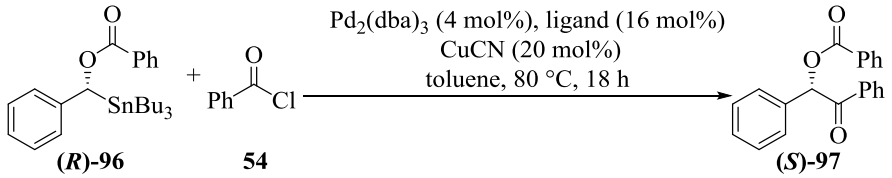
Benzyl benzoate **98** was also found as a side product in the coupling reactions between **(*R*)-96** and different acid chlorides, which indicated that small amount of HCl may be involved in the reaction mixture. The hydrogen atom on the chiral center should be relatively acidic due to those electron withdrawing moieties around it (there are benzyl group, benzoyloxy group, and carbonyl group). Thus, racemization may occur under acidic condition through the tautomerization shown in Scheme 2.7. As a result, the stereospecificity may drop significantly.




**Scheme 2.7:** Potential acid-catalyzed racemization during the coupling reaction

To stop this potential racemization, a small amount of base was added into the reaction mixture. Fortunately, after adding 10 mol% of $NaHCO_3$, the stereospecificity of the reaction increased. The yield of the coupling reaction was changed by the addition of a base in some

cases (increased: entries 1, 3, 5, 12, 15; decreased: entry 7) and result showed that using too much base would decrease the yield significantly (entry 13 in Table 2.9).




(*R*)-96 54 (*S*)-97

| entry | ligand | base | yield | % e.s[c] |
|---|---|---|---|---|
| 1 | TFP | 10 mol% $NaHCO_3$ | 65[a] | 99 |
| 2 | | - | 55[a] | 97 |
| 3 | $P(C_6F_5)_3$ | 10 mol% $NaHCO_3$ | 37[a] | 99 |
| 4 | | - | 28[a] | 93 |
| 5 | Dave Phos | 10 mol% $NaHCO_3$ | 56[a] | 99 |
| 6 | | - | 48[a] | 91 |
| 7 | CyJohn Phos | 10 mol% $NaHCO_3$ | 35[a] | 97 |
| 8 | | - | 48[a] | 97 |
| 9 | S Phos | 10 mol% $NaHCO_3$ | 42[a] | 97 |
| 10 | | - | 46[a] | 89 |
| 11 | $PPh_3$ | 5 mol% $NaHCO_3$ | 61[a] | 92 |
| 12 | | 10 mol% $NaHCO_3$ | 68[a] | 94 |
| 13 | | 15 mol% $NaHCO_3$ | trace[b] | - |
| 14 | | - | 58[a] | 92 |
| 15 | $P(C_6H_{11})_2Ph$ | 10 mol% $NaHCO_3$ | 40[a] | 78 |
| 16 | | - | 36[a] | 0 |

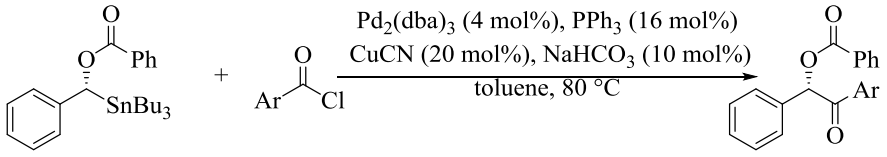
[a]Isolated yields with a small amount of dba contamination
[b]Product was observed by $^1H$ NMR spectroscopy
[c]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

**Table 2.9:** Results of the Stille coupling of **(*R*)-96** in the presence of $NaHCO_3$

After the addition of 10 mol% of $NaHCO_3$, all ligands except for the $P(C_6H_{11})_2Ph$ afforded > 94% e.s. in the coupling reaction. The reason why the $P(C_6H_{11})_2Ph$ gave low stereospecificity is still unknown. Based on the results obtained from other ligands, the properties of the ligand did not have decisive effect on the stereospecificity of the coupling reaction as both hard ligands [such as $PPh_3$ and P(*o*-Tol)$_3$] and soft ligands [such as TFP and $P(C_6F_5)_3$] gave high stereospecificities in the reaction. However, the yield of the reaction was changed by different ligands significantly as the ligands with low σ-donicity such as $P(C_6F_5)_3$ or ligands with large

steric bulk such as P(*o*-Tol)$_3$ gave low yields. These observations are similar to the ones reported by Chong in the coupling reactions of α-sulfonamidobenzylstannane **59a**[55] (Table 1.9).

Stille couplings between **(*R*)-96** and different acid chlorides were conducted again with the addition of 10% $NaHCO_3$. After the $NaHCO_3$ was added, the stereospecificity of the reactions increased dramatically. However, some entries afforded significantly lower yields after the addition of $NaHCO_3$ (entries 1, 4 and 6 in Table 2.10). Adding an electron withdrawing substituent on the *para*-position such as 4-$CF_3$ and 4-Cl gave ~100% stereospecificity (entries 5 and 6 in Table 2.10), while adding an electron donating substituent on the *para*-position such as 4-OMe did not significantly affect the stereochemical outcome of the reaction. However, when the methoxy group was placed on the *meta*-position, where it plays as an electron withdrawing substituent inductively, the stereospecificity of the reaction dropped. This means that an electron withdrawing substituent on the aromatic ring would not always give high stereospecificity. Thus, still no obvious correlation can be found between the stereospecificityof the reactions and the electronic property of the electrophiles.



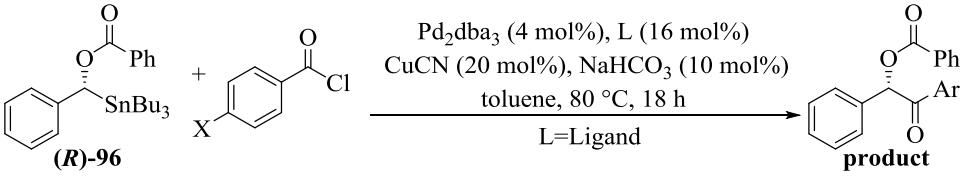

**(*R*)-96** **product**

| entry | Ar | % yield[a] | % yield without base[a] | % e.s.[b] | % e.s. without base[b] |
|---|---|---|---|---|---|
| 1 | 3-OMe$C_6H_4$ | 23 | 28 | 91 | 0 |
| 2 | 4-OMe$C_6H_4$ | 26 | 28 | 94 | 25 |
| 3 | 3-Me$C_6H_4$ | 58 | 52 | 85 | 67 |
| 4 | 2-Me$C_6H_4$ | 0 | 21 | - | 85 |
| 5 | 4-$CF_3C_6H_4$ | 27 | 34 | 99 | 66 |
| 6 | 4-Cl$C_6H_4$ | 18 | 32 | 98 | 69 |
| 7 | Ph | 68 | 58 | 94 | 92 |

[a]Isolated yields
[b]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

**Table 2.10:** Results of the Stille coupling of **(*R*)-96** with acid chlorides in the presence of $NaHCO_3$

To have a more extensive study about the effects of the ligand and electrophile on the outcomes of the coupling reactions, Stille coupling reactions of **(*R*)-96** using different ligands and acid chlorides were conducted. When the electrophile contained an electron withdrawing substituent, dicyclohexylphenylphosphine $P(C_6H_{11})_2Ph$, which is a more electron-rich ligands produced higher yields (entries A-1 and B-1 in Table 2.11). When the electrophile contained an electron donating substituent (such as 4-Me and 4-OMe), ligands that had mild σ-donicity and small steric bulk (such as $PPh_3$ and TFP) gave higher yields (entries D-2 and E-3 in Table 2.11). Ligands had low σ-donicity [such as $P(C_6F_5)_3$] did not perform well either with electron withdrawing or with electron donating substituent (4-$CF_3$ from entry A-4 and 4-OMe from entry E-4 in Table 2.11). Table 2.11 also showed that regardless of the properties of substituent, adding any substituent on the electrophile would result in lower yields as the coupling reactions with benzoyl chloride gave the highest yields (entries C in Table 2.11).




| | | % yield[a] (% e.s.[b]) | | | | |
|---|---|---|---|---|---|---|
| | | entries A | entries B | entries C | entries D | entries E |
| | | X = $CF_3$ | X = Cl | X = H | X = Me | X = OMe |
| entries | L = $P(C_6H_{11})_2Ph$[c] | 34 (81) | 38 (84) | 40 (78) | 5 (73) | 28 (79) |
| entries | L = $PPh_3$ | 27 (99) | 18 (98) | 68 (94) | 28 (94) | 26 (94) |
| entries | L = TFP | 26 (99) | 22 (95) | 65 (99) | 27 (86) | 38 (99) |
| entries | L = $P(C_6F_5)_3$ | 0 (-) | 13 (99) | 37 (99) | 26 (99) | 6 (79) |

[a]Isolated yields
[b]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%
[c]Ligand was contaminated by its phosphine oxide

**Table 2.11:** Effects of ligand and electrophile in the Stille coupling of **(*R*)-96**

With respect to the stereochemical outcome of the reaction, $PPh_3$ and TFP gave high stereospecificities with most of the acid chlorides in Table 2.11. However, TFP did not give high stereospecificity in the coupling of *p*-toluoyl chloride (Entry D-3); the reason is unknown. Dicyclohexyl-phenylphosphine ($P(C_6H_{11})_2Ph$) gave ~80% stereospecificities for different acid chlorides (entries 4 in Table 2.11); however, it was found that this reagent was contaminated by its phosphine oxide. This means that, the low stereospecificities obtained in Table 2.11 may be caused by the phosphine oxide in the reaction mixture. However, how the phosphine oxide can lower the stereospecificity of the reaction is still not known. Tris(pentafluorophenyl)phosphine [$P(C_6F_5)_3$] which is a ligand with low low σ-donicity, gave complete retention of configuration with benzoyl chloride, 4-chlorobenzoyl chloride and *p*-toluoyl chloride (entries B-4, C-4 and D-4 in Table 2.11); however, the stereospecificity dropped when 4-methoxybenzoyl chloride was used (entry E-4 in Table 2.11). With respect to the electrophile, all acid chlorides gave similar results once the ligand had been selected (one exception is the coupling of *p*-toluoyl chloride in the presence of TFP, entry D-3; this reaction gave relatively low stereospecificity compared to other coupling reactions in the presence of TFP). Thus, it seemed that the properties of electrophile did not significantly change the stereospecificity; in addition, no general correlation can be found between the properties of the reactants and the stereospecificity of the reactions.

### 2.2.3 Optimization on the Reaction Conditions of the Stille Coupling of (*R*)-96 and Acid Chlorides

As can be seen in Tables 2.10 and Table 2.11, the yields of most coupling reactions were low; in addition, dibenzylideneacetone (dba) and unknown contaminants (these unknown contaminants were usually observed when the reaction involved 3-OMe- OR 4-OMe-benzoyl

chloride) were observed even after several attempts of column chromatography. Thus, a more extensive optimization study was needed. The first factor to optimize in this study was the reaction duration. A time-controlled experiment was conducted to check if the coupled product could decompose after the reaction was finished. This coupling reaction was operated under 80 ℃ with the addition of $PPh_3$ and 10 mol% $NaHCO_3$. The result showed that the reaction was done within 10 hours and no decomposition was found once the reaction was completed (Figure 2.1). In addition, no racemization was observed either, which indicated that reaction duration was not a factor that can change the overall outcome of the coupling reaction.

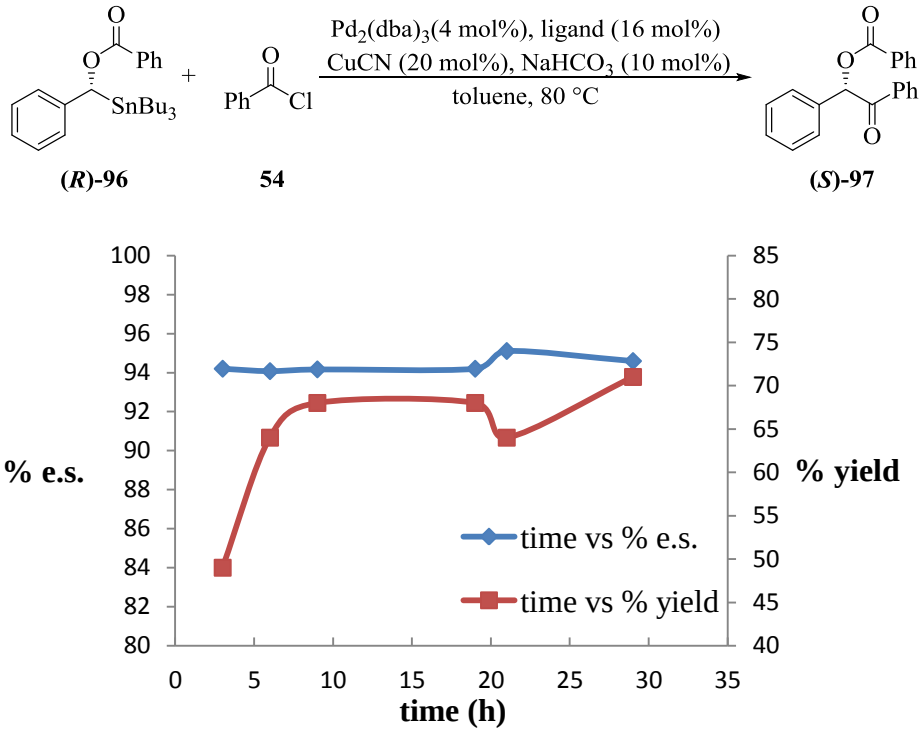
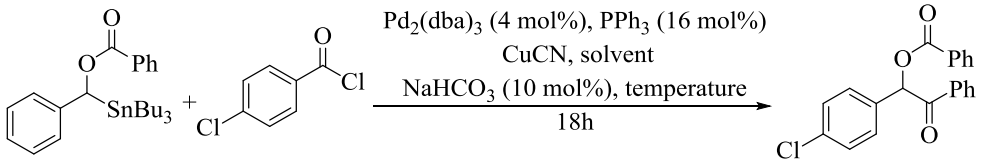



**Figure 2.1** Time-controlled experiment of the Stille coupling of **(*R*)-96** in the presence of $NaHCO_3$

Optimization on the reaction conditions of the Stille coupling between (***R***)**-96** and 4-chlorobenzoyl chloride was conducted by screening different solvents and different amounts of CuCN. As a result, doubling the amount of CuCN (to 40 mol%) can significantly increase the

yield of the reaction. However, it was stated by Falck that the actual concentration of CuCN in the reaction system would be much lower than what was expected due to the low solubility of the Cu salt in the solvent.[58] Thus, the value of amount of CuCN stated here may not be the actual value in the reaction. In addition, trifluorotoluene ($CF_3$-Ph), which can dissolve CuCN better, afforded the best yield in the solvent screen.




**96** **108**

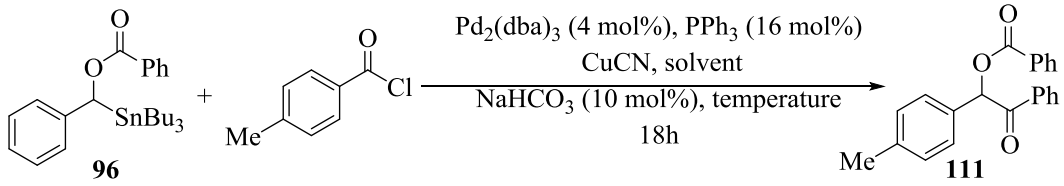
| entry | CuCN (mol %) | $NaHCO_3$ (mol %) | solvent | temp (℃) | yield[a] |
|---|---|---|---|---|---|
| 1 | 20 | 10 | tol | 80 | 18[b] |
| 2 | 40 | 10 | tol | 80 | 40 |
| 3 | 10 | 10 | tol | 80 | 9 |
| 4 | 20 | 5 | tol | 80 | 19 |
| 5 | 60 | 10 | tol | 80 | 35 |
| 6 | 40 | 10 | tol | 60 | 23[c] |
| 7 | 40 | 10 | $CF_3$-Ph | 80 | 75 (56[d]) |
| 8 | 40 | 10 | $CF_3$-Ph | 95 | 73 |
| 9 | 40 | 10 | DCE | 80 | 45 |

[a]Yields are determined by $^1$H NMR spectroscopy where dimethyl terephthalate was used as internal standard
[b]Isolated yield, experiment was done with **(*R*)-96** as seen in Table 2.10
[c]23% of **96** was recovered after 24 hours
[d]Isolated yield

**Table 2.12:** Optimization on the Stille coupling of **96** and 4-chlorobenzoyl chloride

Another optimization study was conducted with *p*-toluoyl chloride. This reaction resulted in low yield under 80 ℃ in $CF_3$-Ph (15% yield, entry 7 in Table 2.13); however, it afforded a considerable amount of product at 95 ℃ (70%, entry 8 in Table 2.13). The amount of CuCN did not affect the yield of this reaction significantly as doubling the amount of CuCN did not increase the yield (entries 1, 2 in Table 2.13). Moreover, it should be noticed that due to the issue

of co-elution of the products and dibenzylideneacetone (dba), the isolated yields were much lower than their NMR yields in Tables 2.12 and Table 2.13.




| entry | CuCN (mol %) | $NaHCO_3$ (mol %) | solvent | temp (℃) | yield[a] |
|---|---|---|---|---|---|
| 1 | 20 | 10 | tol | 80 | 28[b] |
| 2 | 40 | 10 | tol | 80 | 32 |
| 4 | 20 | 5 | tol | 80 | 34 |
| 6 | 40 | 10 | tol | 60 | 27[c] |
| 7 | 40 | 10 | $CF_3$-Ph | 80 | 15 |
| 8 | 40 | 10 | $CF_3$-Ph | 95 | 70 (48[d]) |
| 9 | 40 | 10 | DCE | 80 | 32 |

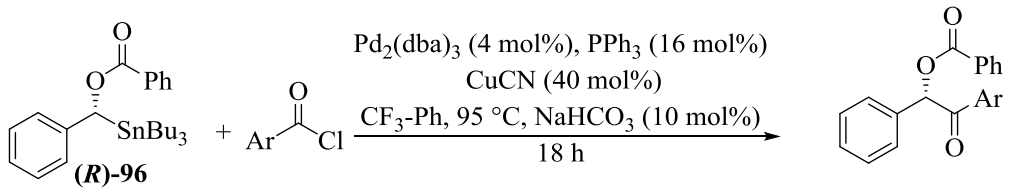
[a]Yields are determined by $^1$H NMR spectroscopy where dimethyl terephthalate was used as internal standard
[b]Isolated yields, experiment was done with **(*R*)-96** as seen in Table 2.10
[c]19% of **96** was recovered after 24 hours
[d]Isolated yield

**Table 2.13:** Optimization on the Stille coupling of **96** and *p*-toluoyl chloride

Applying this optimized reaction condition, Stille couplings of **(*R*)-96** and different acid chlorides were conducted again. The isolated yields were generally increased to the range of 30~50% and some were increased to 60~70% (entries 4, 9 in Table 2.14). Unfortunately, contaminants were still observed after the purification. Results showed that adding any substituent on the electrophile dropped down the yield of reaction, as the coupling of benzoyl chloride gave highest yield in this table (entry 9, Table 2.14). Unfortunately, the correlation between the properties of substituent and the yield of reaction was not found.

Stereospecificity of those reactions were higher than 90% e.s. in most cases; however, they were slightly lower than the ones obtained from the reactions in toluene under 80 ℃. The loss of stereospecificity may be caused by the increase of reaction temperature from 80 to 95 ℃. An

exception was found when *m*-toluoyl chloride was used as the electrophile: this Stille coupling reaction obtained a higher stereospecificity albeit with lower yield (entry 4 in Table 2.14); however, the reason is unknown. In addition, the reaction using 4-(trifluoromethyl)benzoyl chloride as the electrophile gave relatively low stereospecificity (86%) in trifluorotoluene (entry 6 in Table 2.14); however, the low stereospecificity can be increased by switching the ligand from $PPh_3$ to TFP (95% e.s., entry 7 in Table 2.14).



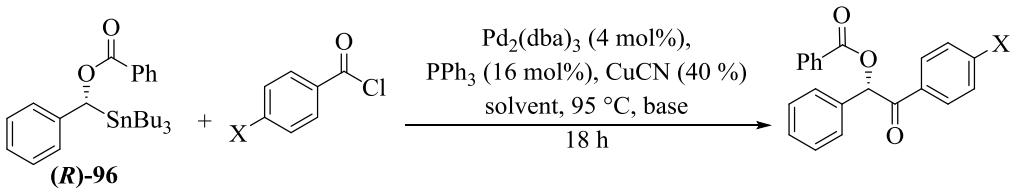

| entry | Ar | % yield[b] | % yield (unoptimized)[c] | % e.s.[d] | % e.s.(unoptimized)[e] |
|---|---|---|---|---|---|
| 1 | 3-$OMeC_6H_4$ | 34 | 23 | 92 | 91 |
| 2 | 4-$OMeC_6H_4$ | 32 | 26 | 93 | 94 |
| 3 | 2-$MeC_6H_4$ | trace | 0 | - | - |
| 4 | 3-$MeC_6H_4$ | 52 | 58 | 99 | 85 |
| 5 | 4-$MeC_6H_4$ | 49 | 28 | 90 | 94 |
| 6 | 4-$CF_3C_6H_4$ | 41 | 27 | 86 | 99 |
| 7[a] | 4-$CF_3C_6H_4$ | 35 | - | 95 | - |
| 8 | 4-$ClC_6H_4$ | 56 | 18 | 93 | 98 |
| 9 | Ph | 70 | 68 | 93 | 94 |

[a]Using TFP as ligand
[b]Isolated yields
[c]Isolated yields, reactions conducted in toluene with 20% of CuCN
[d]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%
[e]Reactions was operated in toluene with 20% of CuCN

**Table 2.14:** Results of the Stille coupling of **(*R*)-96** and acid chlorides under optimized condition

Different bases were added into the Stille coupling between **(*R*)-96** and different acid chlorides to probe the effects of different bases in these reactions. It was found that using 10 mol% of 2,4,6-trimethylpyridine as the base and trifluorotoluene as the solvent afforded the highest stereospecificities (entries 5, 10, 14 in Table 2.15). However, the yields afforded by 10

mol% 2,4,6-trimethylpyridine were not as high as the ones afforded by $NaHCO_3$ (entries 3, 8, 13 in Table 2.15). The reaction conducted with 2-phenylpyridine gave both lower yield and lower stereospecificity than 2,4,6-trimethylpyridine. Reaction with 10 mol% pyridine gave high yield and stereospecificity; however, the reaction was slowed down by an unknown reason (entry 1 in Table 2.15). Surprisingly, it seemed that after adding twice the amount of CuCN, the addition of a base was no longer necessary to obtain high stereospecificities (entries 6, 11, 15 in Table 2.15). These results indicated that CuCN can also act as a base to neutralize the HCl generated during the reaction.

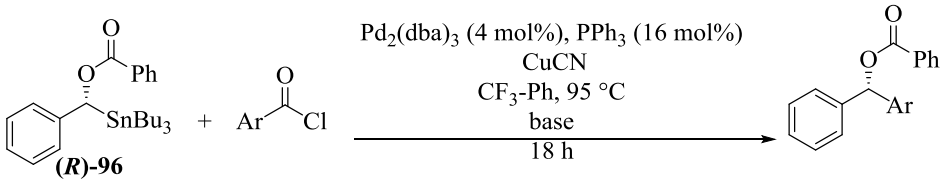



| entry | X | base | solvent | yield[a] | e.s[b] |
|---|---|---|---|---|---|
| 1[c] | H | 10 mol% pyridine | tol | 66 | 95 |
| 2[c] | | 10 mol% $NaHCO_3$ | tol | 68 | 94 |
| 3 | | 10 mol% $NaHCO_3$ | $CF_3$-Ph | 70 | 93 |
| 4 | | 10 mol% 2-phenylpyridine | $CF_3$-Ph | 52 | 93 |
| 5 | | 10 mol% 2,4,6-trimethylpyridine | $CF_3$-Ph | 58 | 98 |
| 6 | | - | $CF_3$-Ph | 35 | 96 |
| 7[c] | Cl | 10 mol% $NaHCO_3$ | tol | 18 | 98 |
| 8 | | 10 mol% $NaHCO_3$ | $CF_3$-Ph | 56 | 93 |
| 9 | | 10 mol% 2,4,6-trimethylpyridine | tol | 34 | 92 |
| 10 | | 10 mol% 2,4,6-trimethylpyridine | $CF_3$-Ph | 45 | 97 |
| 11 | | - | $CF_3$-Ph | 52 | 98 |
| 12[c] | Me | 10 mol% $NaHCO_3$ | tol | 28 | 94 |
| 13 | | 10 mol% $NaHCO_3$ | $CF_3$-Ph | 49 | 90 |
| 14 | | 10 mol% 2,4,6-trimethylpyridine | $CF_3$-Ph | 42 | 95 |
| 15 | | - | $CF_3$-Ph | 45 | 97 |

[a]Isolated yields
[b]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%
[c]Reaction was operated under 80 ℃

**Table 2.15:** Screen of different bases in the Stille coupling of **(*R*)-96** and acid chlorides

To confirm that the addition of $NaHCO_3$ was no longer necessary when the amount of CuCN had been doubled, more examples of coupling reactions were conducted in the presence of 40 mol% CuCN and without $NaHCO_3$. As a result, coupling reactions can still afford high stereospecificities without the addition of $NaHCO_3$. Regardless the electronic properties of the electrophile, these Stille coupling reactions gave 94~96% e.s. after 40 mol% of CuCN was added. An exception was found as the coupling with 3-methoxybenzoyl chloride which gave 46% e.s. using 40 mol% CuCN (entry 9 in Table 2.16); however, after the amount of CuCN was increased to 60 mol%, the reaction gave 93% e.s. (entry 10 in Table 2.16). These results showed that adding CuCN can inhibit the potential racemization. However, by comparing entries 1 and 2, it seemed that the yield of reaction may be decreased if $NaHCO_3$ was absent. This may be caused by the loss of CuCN by reaction with the HCl in the reaction mixture.



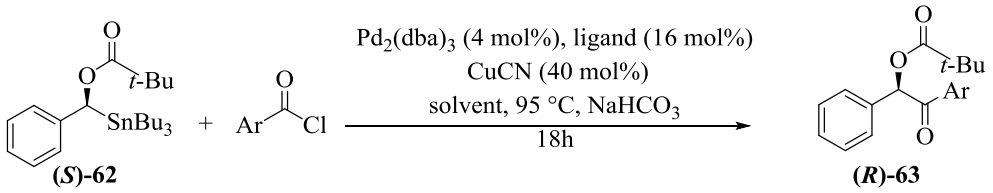

| entry | Ar | base | CuCN (mole %) | yield[a] | e.s[b] |
|---|---|---|---|---|---|
| 1 | Ph | 10% $NaHCO_3$ | 40 | 70 | 93 |
| 2 | | - | 40 | 35 | 96 |
| 3 | 4-$ClC_6H_4$ | 10% $NaHCO_3$ | 40 | 56 | 93 |
| 4 | | - | 40 | 52 | 98 |
| 5 | 4-$MeC_6H_4$ | 10% $NaHCO_3$ | 40 | 49 | 90 |
| 6 | | - | 40 | 45 | 97 |
| 7 | 3-$OMeC_6H_4$ | 10% $NaHCO_3$ | 40 | 23 | 91 |
| 8 | | - | 20 | 31 | 0 |
| 9 | | - | 40 | 29 | 46 |
| 10 | | - | 60 | 34 | 93 |
| 11 | 4-$OMeC_6H_4$ | 10% $NaHCO_3$ | 40 | 32 | 93 |
| 12 | | - | 40 | 28 | 95 |

[a]Isolated yields
[b]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

**Table 2.16:** Stille coupling of **(*R*)-96** and acid chlorides in the presence of 40% or 60% of CuCN

## 2.3 Stille Cross-Coupling of α-(Trimethylacetoxy)benzylstannane using Optimized Conditions

Those optimized conditions were applied to the cross-coupling reaction of **(*S*)-62** to see if the stereochemical outcome could be improved. Results showed that toluene was a better solvent than trifluorotoluene in this coupling reaction, as the reaction in toluene with TFP afforded 80% (with benzoyl chloride) and 77% (with *m*-toluoyl chloride) isolated yields when the ones in trifluorotoluene only afforded 66% and 72% respectively (Table 2.17). In addition, after 40% of CuCN was added, a base was not necessary to achieve highly stereospecific reactions. TFP was found to give higher stereospecificity (99% e.s., entry 3) than $PPh_3$ (89% e.s., entry 4) in this reaction. However, in Su's study, it was found that $PPh_3$ gave higher stereospecificity than TFP.[57] The reason for these results is not known. It can be seen that different ligands can change the stereospecificity significantly when α-(trimethylacetoxy)benzylstannane **(*S*)-62** was used as the nucleophile (by comparing entries 3, 4, Table 2.17).



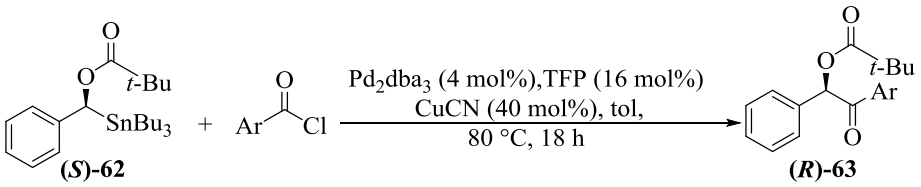

| entry | Ar | ligand | solvent | $NaHCO_3$ (mol %) | % yield[a] | % e.s.[b] |
|---|---|---|---|---|---|---|
| 1 | Ph | TFP | $CF_3$-Ph | 10 | 20 | 91 |
| 2 | | TFP | $CF_3$-Ph | 0 | 66 | 87 |
| 3 | | TFP | tol | 0 | 81 | 99 |
| 4 | | PPh3 | tol | 0 | 86 | 89 |
| 5 | 3-$MeC_6H_4$ | TFP | $CF_3$-Ph | 10 | 72 | 87 |
| 6 | | TFP | tol | 0 | 77 | 91 |

[a]Isolated yields

[b]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%

**Table 2.17:** Screen of reaction conditions in the Stille coupling of **(*S*)-62**

Stille couplings between **(*S*)-62** and different acid chlorides were conducted using 40% CuCN in toluene at 80 ℃. By comparing the results with those previously obtained by Su,[57] the stereospecificity of the reaction was sharply increased by the addition of 40 mol% CuCN in some cases. The stereospecificity given by *o*-toluoyl chloride was increased from 28% e.s. to 91% (entry 2, Table 2.18), while the stereospecificities given by *m*-toluoyl chloride and *p*-toluoyl chloride were increased from ~65% e.s. to 90% e.s. (entries 3, 4, Table 2.18). However, the stereospecificity given by 4-chlorobenzoyl chloride was decreased from 99% e.s. to 90% (entry 5, Table 2.18).




| entry | Ar | % yield[a] | % yield by Su[b] | % e.s.[c] | % e.s. by Su[d] |
|---|---|---|---|---|---|
| 1 | Ph | 78 | 92 | 99 | 89 |
| 2 | 2-$MeC_6H_4$ | 38 | 45 | 91 | 28 |
| 3 | 3-$MeC_6H_4$ | 74 | 72 | 93 | 63 |
| 4 | 4-$MeC_6H_4$ | 60 | 63 | 91 | 69 |
| 5 | 4-$ClC_6H_4$ | 71 | 62 | 90 | 99 |
| 6 | 4-$CF_3C_6H_4$ | 57 | 53 | 92 | 89 |

[a]Isolated yields
[b]Isolated yields, see Table 1.12
[c]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%
[d]% e.s. = (% enantiomeric excess. of the product/% enantiomeric excess of the starting material) × 100%[57]

**Table 2.18:** Stille coupling of **(*S*)-62** with acid chlorides under optimized condition

From Table 2.18, it seemed that adding any substituent on the electrophile decreased the stereospecificity of the reaction, as the coupling of benzoyl chloride gave the highest %e.s (99% e.s., entry 1). However, the properties of the substituent actually did not significantly affect the stereospecificity, since the stereospecificities given by different substituted acid chlorides were similar to each other (all around 90~94). This observation is consistent to the results reported by

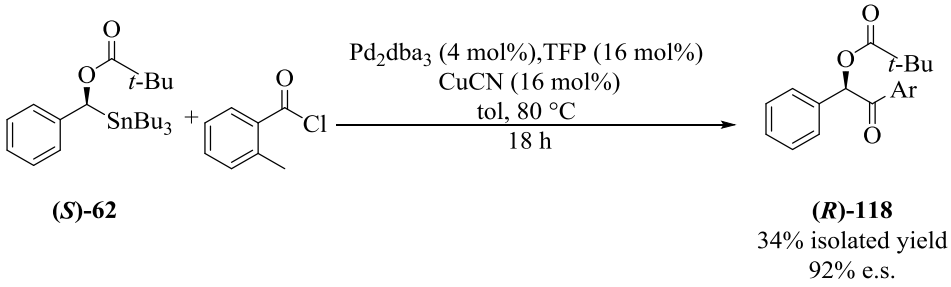
Molander in the Suzuki couplings of α-(benzyoloxy)alkyltrifluoroboronate **48** with different aryl chlorides (Table 1.8).[52] It was mentioned by Su that the stereospecificity of the reaction was changed by different substituents on the acid chloride, but no obvious correlation was observed.[57] However, it seemed that those significant differences in stereospecificity observed by Su may be simply caused by that potential racemization of the products. Once the racemization was minimized, all coupling reactions gave >90% e.s.

In addition, adding any substituent on the acid chloride decreased the yield of the reaction. It can be seen that yield of reaction was affected by the properties of the substituent on the acid chloride. However, no correlation between the properties of substituent and the yield of reaction can be obtained as both weak electron withdrawing group (4-Cl) and weak electron donating group (4-Me) can give relatively high yields on this reaction. This was consistent with the results obtained in the coupling between **(*R*)-96** and different acid chlorides (Table 2.14).

By comparing Table 2.18 and Table 2.14, it can be seen that the coupling reactions of both α-(trimethylacetoxy)benzylstannane and α-benzoyloxybenzylstannane gave retention of configuration with high stereospecificity. Since the α-(trimethylacetoxy)benzylstannane had already been able to give retention of configuration with >90% e.s., adding more electron withdrawing character on the α-carbon of the stannane could not significantly improve the stereospecificity. However, it seems that the stereospecificity of the coupling reaction with α-benzoyloxybenzylstannane was not affected by the ligand significantly (Table 2.9), while the one with α-(trimethylacetoxy)benzylstannane was changed by different ligands (Table 2.17).

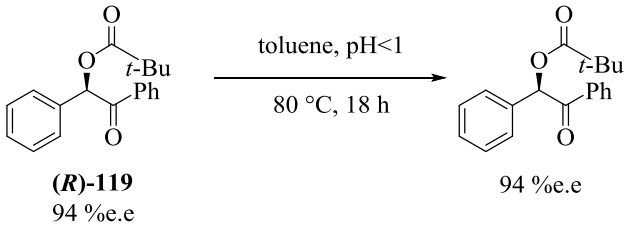
Surprisingly, when reaction of **(*S*)-62** and 2-toluoyl chloride was conducted with 16 mol% CuCN at 80 ℃ (Scheme 2.8), the stereospecificity obtained was still impressively high. This

reaction was operated under the same condition as the one reported by Su previously; however, the stereospecificity was different from the previous result (only 28% e.s was observed by Su).[57] The reason of this unexpectedly different result is not understood. This may indicate that there were other factors that can affect the stereospecificity of this reaction, or the reproducibility of the coupling reaction using 16 mol% of CuCN was not high.




**Scheme 2.8:** Reaction of **(*S*)-62** *o*-toluoyl chloride in the presence of 16% CuCN

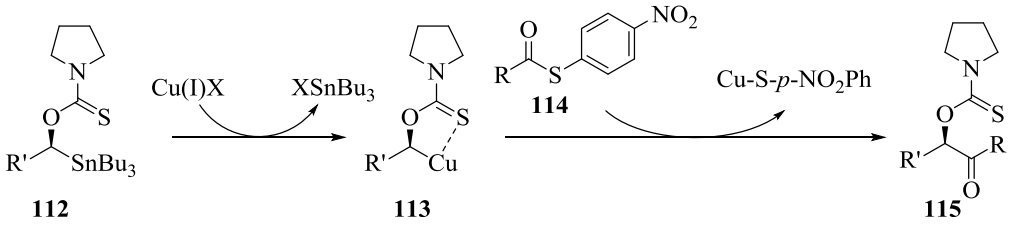
To have a further study about the potential racemization, the coupled product **(*R*)-119** was dissolved in toluene. The solution was acidified by concentrated HCl solution and heated at 80 ℃ for 18 h; however, no racemization was found after this reaction (Scheme 2.8). Thus, the proposed mechanism which is shown on Scheme 2.7 may be wrong. However, because adding a small amount of base or increasing the amount of CuCN did increase the stereospecificity of the reaction, it is still highly possible that the decrease of stereospecificity observed previously was caused by the acid in the reaction mixture. The detailed mechanism is under investigation.




**Scheme 2.8:** Study on the racemization

## 2.4 Study on the Reaction Mechanism

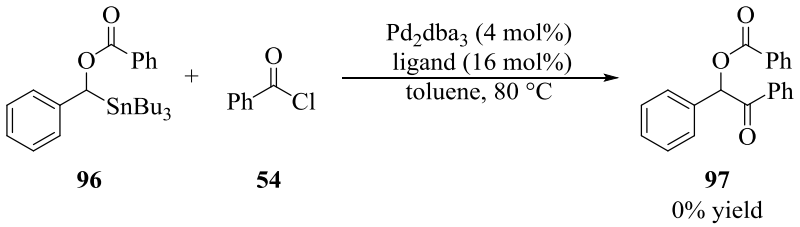
The Stille coupling of α-benzoyloxybenzylstannane and benzoyl chloride had been proved to give complete retention of configuration. Previously, Falck proposed an organocopper intermediate in the copper catalyzed coupling reaction between an α-alkoxystannane **112** and thiol esters **114**.[71] In their proposed mechanism, organocopper intermediate **113** was formed through a tin-copper exchange. Since the transmetalation of tin to other metals (such as lithium) proceeds with retention of configuration,[72,73] Falck proposed that this tin-copper exchange process would also proceed with retention of configuration. This organocopper intermediate would be added into the electrophile to give coupled the product **115** with an overall retention of configuration. Another example of copper catalyzed cross coupling reaction was given by Su (Table 1.14);[13] similarly, a δ-sulfur atom was involved. Undoubtedly, these organocopper intermediates were stabilized by the coordination from the sulfur atom to the copper atom (Scheme 2.9). This means that when the alkoxystannane does not contain a sulfur atom, this model may not apply.




**Scheme 2.9:** Proposed mechanism of the coupling between α-alkoxystannane **112** and thiol esters **114**

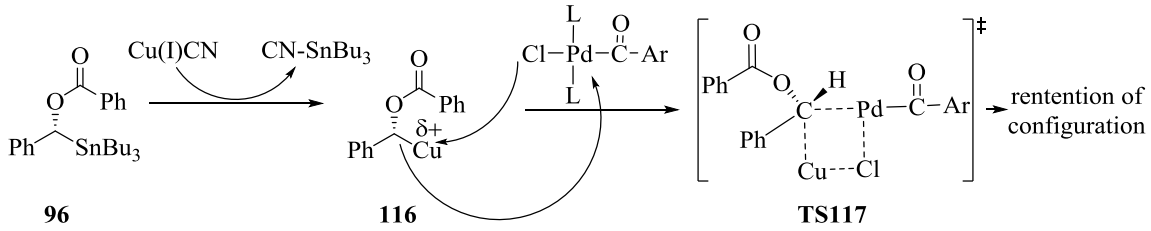
However, the coupling reaction between **96** and benzoyl chloride afforded no product in the absence of CuCN, this could be seen as evidence that CuCN acted as a co-catalyst in the reaction (Scheme 2.10). In the proposed mechanism which is shown in Scheme 2.11, an organocopper intermediate **116** is produced after transmetalation between the organotin compound and the Cu(I)

ion. Since the coordination between oxygen and copper is not as strong as between sulfur and copper, the copper atom on **116** would be open for accepting a bridging atom. In addition, the electron withdrawing β-oxygen can increase the electrophilicity of the copper atom. This allows the attack of the chlorine atom to the copper and results in the formation of the cyclic transition state **TS117**; consequently, retention of configuration would be observed. However, because there is no direct evidence for the existence of **116**, experiments that can prove that **116** exists are needed in the future work.




**96** **54** **97**
0% yield

**Scheme 2.10:** Stille coupling of **96** and benzoyl chloride in the absence of CuCN




**96** **116** **TS117**

**Scheme 2.11:** Proposed mechanism of the Stille coupling of **96** and acid chloride

## 2.5. Conclusion

Preparations of four different α-acyloxybenzylstannanes were attempted in this study. As results, the preparation of the (±)-α-(2,6-dichlorobenzoyloxy)benzylstannane did not give any product; this may be caused by the bulky substituents on the aromatic ring which can hinder the nucleophilic attack to the carbonyl group. The preparation of the (±)-α-(trifluoroacetoxy)-

benzylstannane afforded 62% yield; however, its Stille coupling did not afford any coupled product. The reason may be that the trifluoromethyl moiety was not able to protect the carbonyl group from nucleophilic attack.

The preparations of (±)-α-benzoyloxybenzylstannane and (±)-α-2-chlorobenzoyloxy-benzylstannane were achieved and their Stille couplings gave moderate yields. Results showed that ligands with mild σ-donicity and relatively small steric bulk produced higher yields in the coupling reactions. By comparing the coupling reactions with different α-acyloxybenzylstannanes, it can be concluded that a bulkier protecting on the β-oxygen of stannane can help to give a better yield.

The asymmetric synthesis of (*R*)-α-benzoyloxybenzylstannane was accomplished by several trials. Ligand screening was done in the coupling between (*R*)-α-benzoyloxybenzylstannane and benzoyl chloride. It was found that retention of configuration was obtained after the coupling reaction. Ligands with lower σ-donicity and lager steric bulk gave higher stereospecificity in this ligand screen. In the coupling reactions between (*R*)-α-benzoyloxybenzylstannane and different acid chlorides, stereospecificities were low and random. These results may be caused the racemization of the coupled product; however, it was found that this potential racemization was not simply caused by the acid in the reaction mixture.

Adding 10 mol% of $NaHCO_3$ to the reaction can inhibit the racemization. A subsequent study about the synthetic effects of the ligand and electrophile was conducted; however, no obvious correlation was found between the stereospecificity, properties of the ligand and properties of the electrophile. In addition, it was found that phosphine oxide may decrease the stereospecificity of the reaction.

Optimization of the reaction conditions was attempted by screening the solvent, reaction temperature, and the amount of CuCN used. As a result, reaction using $CF_3$-Ph and 40 mol% of CuCN at 95 ℃ gave the best yields. However, in some cases, the stereospecificity slightly dropped down after this optimization, which may be caused by the increase of the temperature. In a subsequent study, the addition of 10% of base proved unnecessary if the amount of CuCN had been increased.

The Stille coupling of α-(trimethylacetoxy)benzylstannane was conducted using the optimized reaction condition. As a result, the toluene was found as the best solvent in the coupling reaction involving α-(trimethylacetoxy)benzylstannane. After 40 mol% of CuCN was added into the coupling reaction, the coupling reaction gave >90 % e.s. with different acid chlorides. It was also found that regardless of the nature of substituent, the yield and the stereochemical outcome of the coupling reaction decreased once the aromatic ring of the electrophile was substituted. The properties of substituent did not change the stereospecificity of the coupling reaction when the yield of the reaction was significantly affected by different substituents. However, the correlation between the properties of the substituent and the yield of reaction was not found. In addition, the stereospecificity of the reaction was significantly affected by the ligand, as the ligand with lower σ-donicity gave higher stereospecificity.

Surprisingly, when only 16 mol% of CuCN was used, coupling reactions still gave high stereospecificity. These results were completely different from what were obtained in previous studies; however, the reason is unknown. This means that there may be other factors that can affect the stereospecificity of this reaction, or this coupling reaction using 16 mol% of CuCN may have low reproducibility.

Adding more electron withdrawing character on the α-carbon of the stannane did not improve the stereochemical outcome because the coupling reaction of α-(trimethylacetoxy)-benzylstannane already gave retention of configuration with high stereospecificity. However, the stereospecificity of the coupling reaction with α-benzoyloxybenzylstannane was not affected by the ligand significantly, while the one with α-(trimethylacetoxy)benzylstannane was changed by different ligands.

A mechanism including a copper-tin transmetalation step and an organocopper intermediate was proposed in this thesis. Since the coordination from the oxygen atom to the copper atom is relative weak, a cyclic transmetalation is allowed and retention of configuration is given. However, no direct evidence for the existence of the organocopper intermediate was found in this study.

# Chapter 3: Experimental

## 3.1 General Experimental

All reactions were operated in the fume hood and conducted under argon atmosphere. Glassware was dried by oven or heat gun before use. THF and DME were distilled from Na and benzophenone while dichloromethane, hexane, trifluorotoluene, pyridine and DIPEA were freshly distilled from $CaH_2$. Toluene and dichloroethane were obtained from a JC Meyer solvent drying system. Acid chlorides were distilled under reduced pressure. $NaHCO_3$, dimethyl terephthalate and the chiral catalyst (*R*)-diphenyl(pyrrolidin-2-yl)methanol were dried under high vacuum at 50 ℃. Benzaldehyde was purified before use by passing through a column filled with activated basic aluminum oxide. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 $F_{254}$ plates (0.25 mm) and visualized under short wave UV light or phosphomolybdic acid staining. All chemicals were purchased from Sigma-Aldrich® unless otherwise specified. IR spectra were recorded with neat samples on a PerkinElmer FTIR spectrometer. $^{1}H$ NMR and $^{13}C$ NMR were recorded on Bruker AVANCE 300 spectrometers (300 MHz for $^{1}H$ and 75 MHz for $^{13}C$, respectively) in *d*-chloroform ($CDCl_3$) unless otherwise specified. All NMR spectra are referenced to $CHCl_3$ ($\delta$ 7.24) in $^{1}H$ NMR and $CDCl_3$ ($\delta$ 77.0) in $^{13}C$ NMR. Mass spectra were recorded on a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer using electrospray ionisation (ESI) or direct analysis in real time mass spectrometry (DART). Optical rotations were recorded in cells with 10 cm path length on a Jasco P-2000 digital polarimeter. Enantiomeric purities were determined by HPLC analysis (4.6 x 250 mm ChiralCel OD-H or ChiralPak AD-H, hexanes/*i*-PrOH, 254 nm detection). Melting points were recorded on a SRS MPA160 DigiMelt apparatus.

## 3.2 Synthesis of Tributyltin Hydride[74]

$NaBH_4$ (1.35 g, 36 mmol ) was added to ethanol (200 mL) at room temperature. After all of the powder had been dissolved, bis(tributyltin)oxide (29.6 g, 50 mmol) was added into the reaction mixture. The reaction was allowed to stir for 30 min. The solvent was removed by rotary evaporation and crude product was extracted by hexane (3 × 10 mL). The organic layer was washed by deionized water (2 × 10 mL) and dried by $Na_2SO_4$. After the organic layer was concentrated by rotary evaporation, the crude product was distilled (by Kugelrohr) to afford tributyltin hydride (15.1 g, 51%) as a colorless liquid. $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 30.1 ($J_{Sn-C}$ = 20.2 Hz), $SnCH_2CH_2\underline{C}H_2CH_3$, 27.3 ($J_{Sn-C}$ = 59.0 Hz), $SnCH_2\underline{C}H_2CH_2CH_3$, 13.7 ($SnCH_2CH_2CH_2\underline{C}H_3$), 8.13 ($J_{Sn-C}$ = 326 /310 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$)

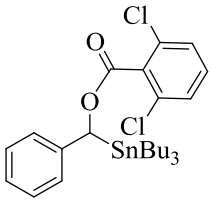
## 3.3 General Procedure for the Synthesis of α-Acyloxybenzylstannanes[13]

THF (10 mL) was cooled to -78 ℃ in a round bottom flask. *i*-$Pr_2NH$ (0.52 mL, 3.7 mmol) and *n*-BuLi (1.5 M solution in hexane, 2.4 mL, 3.6 mmol) were added into the flask and the reaction mixture was stirred for 30 min before tributyltin hydride (1 mL, 3.7 mmol) was added. The reaction was then warmed up to 0 ℃ and stirred for another 15 min. After that, the mixture was cooled to -78 ℃ again and stirred for 10 min. Benzaldehyde (0.33 mL, 3.15 mmol) was added into the cold mixture dropwise; then the reaction mixture was stirred for 30 min. Sat. $NH_4Cl$ (3 mL) was added into the mixture under -78 ℃ to quench the reaction. The reaction mixture was warmed up to room temperature and was extracted by $Et_2O$ (2 × 10 mL). The organic layer was washed by brine (10 mL), dried by $Na_2SO_4$, and concentrated by rotary evaporation to afford the crude α-hydroxybenzylstannane as a yellow liquid. After that, α-

hydroxybenzylstannane was immediately protected by different protecting groups to give different α-acyloxybenzylstannanes.

DMAP (0.25 g, 2 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and cooled to 0 ℃. Pyridine (0.5 mL, 6.2 mmol) was added into the reaction mixture; then α-hydroxybenzylstannane and acid chloride (6.3 mmol) were added into the reaction mixture. The mixture was warmed to room temperature and stirred for 15 h. The reaction was monitored using TLC (hex/diethylether = 5:1) and once there was no α-hydroxybenzylstannane observed, the reaction mixture was quenched by 10 mL of sat. $NH_4Cl$ solution. The organic layer was washed by HCl (1 M, 10 mL), sat. $NaHCO_3$ (2 × 10 mL) and brine (10 mL); then it was dried by $Na_2SO_4$ and concentrated by rotary evaporation to afford the crude product.

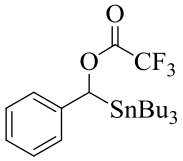
### 3.3.1 Synthesis of (±)-α-(2,6-Dichlorobenzoyloxy)benzylstannane (93)




Following the general procedure for the synthesis of α-acyloxybenzylstannanes, a small amount of **93** was observed in the $^1$H NMR spectrum. Compound **93** was isolated using column chromatography (silica/product = 30:1, hex/diethylether/$CH_2Cl_2$ = 40:10:1).[13] A trace amount of purified product was obtained as a yellow liquid (yield was not determined). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.21-7.34 (7H, m, ArH), 7.12 (1H, t, $J$ = 7.0 Hz, ArH), 5.90 (1H, s, $J_{Sn-H}$ = 19.9 Hz, PhC<u>H</u>OSn), 1.48-1.37 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.31-1.21 (6H, sextet, $J$ = 7.2 Hz, $SnCH_2CH_2C\underline{H}_2CH_3$), 1.00-0.91 (6H, m, $SnC\underline{H}_2CH_2CH_2CH_3$), 0.85 (9H, t, $J$ = 7.3 Hz,

$SnCH_2CH_2CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 165.0 (PhCO$\underline{C}$(=O)Ar), 142.0 (Ar), 134.0 (Ar), 132.0 (Ar), 130.8 (Ar), 128.4 (Ar), 127.9 (Ar), 125.4 (Ar), 124.2 (Ar), 75.0 (Ph$\underline{C}$SnOC(=O)Ar), 28.8 ($J_{Sn-C}$ = 19.6 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 27.4 ($J_{Sn-C}$ = 57.4 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 13.7 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.0 ($J_{Sn-C}$ = 324/309 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1738, 1135, 1118, 1021, 779 $cm^{-1}$; HRMS Calculated for $C_{26}H_{40}Cl_2NO_2Sn$ ($M + NH_4^+$): 584.1448, Found: 584.1449.

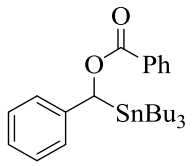
### 3.3.2 Synthesis of (±)-α-(Trifluoroacetoxy)benzylstannane (94)




Following the general procedure for the synthesis of α-acyloxybenzylstannanes, 9.5 mmol of benzaldehyde and 21.3 mmol trifluoroacetic anhydride (TFAA) was used. Compound **94** was isolated using column chromatography (silica/product = 20:1, hex/diethylether/$CH_2Cl_2$ = 40:10:1)[13] to give the purified product as a yellow liquid (2.92 g, 62%). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.31 (2H, t, $J$ = 7.6 Hz, ArH), 7.16 (1H, d, $J$ = 7.7 Hz, ArH), 7.12 (2H, d, $J$ = 7.6 Hz, ArH), 6.18 (1H, s, $J_{Sn-H}$ = 15.4 Hz, PhC$\underline{H}$OSn), 1.47-1.34 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.24 (6H, sextet, $J$ = 7.0 Hz, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.92-0.83 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 157.1 (q, $J_{F-C}$ = 42.2 Hz, PhCO$\underline{C}$(=O)$CF_3$), 142.6 ($J_{Sn-C}$ = 10.8 Hz, Ar), 128.6 ($J_{Sn-C}$ = 7.6 Hz, Ar), 125.8 ($J_{Sn-C}$ = 7.6 Hz, Ar), 123.4 ($J_{Sn-C}$ = 14.1 Hz, Ar), 114.7 (q, $J_{F-C}$ = 285.7 Hz, $CF_3$), 28.5 ($J_{Sn-C}$ = 20.6 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 27.2 ($J_{Sn-C}$ = 59.5 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 13.4 ($SnCH_2CH_2CH_2\underline{C}H_3$), 9.9 ($J_{Sn-C}$ =326/311 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1767, 1218,

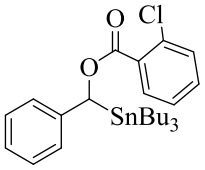
1162, 779, 696 $cm^{-1}$; HRMS Calculated for $C_{21}H_{37}F_3NO_2Sn$ (M + $NH_4^+$): 515.1793, Found: 515.1795.

### 3.3.3 Synthesis of (±)-α-benzoyloxybenzylstannane (96)




Following the general procedure for the synthesis of α-acyloxybenzylstannanes, compound **96** was isolated using column chromatography (silica/product = 20:1, hex/diethylether/$CH_2Cl_2$ = 40:10:1)[13] to give compound **96** as a colorless liquid (1.03 g, 65%). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 7.0 Hz, ArH), 7.55 (1H, t, *J* = 7.4 Hz, ArH), 7.44 (2H, t, *J* = 7.83 Hz, ArH), 7.29 (2H, t, *J* = 7.7 Hz, ArH), 7.20 (2H, t, *J* = 7.2 Hz, ArH), 7.20 (2H, d, *J* = 7.2 Hz, ArH), 7.10 (1H, t, *J* = 7.5 Hz, ArH), 6.17 (1H, s, $J_{Sn-H}$ = 20.3 Hz, PhC<u>H</u>OSn), 1.43-1.33 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.21 (6H, sextet, *J* = 7.4 Hz, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.83-0.77 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.3 (PhCSnO<u>C</u>(=O)Ph), 142.9 (Ar), 132.9 (Ar), 130.5 (Ar), 129.6 (Ar), 128.6 (Ar), 128.4 (Ar), 125.1 (Ar), 73.9 (Ph<u>C</u>SnOC(=O)Ph), 28.9 ($J_{Sn-C}$ = 20.7 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 27.3 ($J_{Sn-C}$ = 56.3 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.1 ($J_{Sn-C}$ = 319/308 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1703, 1268, 1162, 756, 710, 696 $cm^{-1}$; HRMS Calculated for $C_{26}H_{39}O_2Sn$ (M + $H^+$): 503.1967, Found: 503.1961.

### 3.3.4 Synthesis of (±)-α-2-Chlorobenzoyloxybenzylstannane (99)



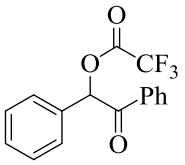

Following the general procedure for the synthesis of α-acyloxybenzylstannanes, compound **99** was isolated using column chromatography (silica/product = 25:1, hex/diethylether/$CH_2Cl_2$ = 40:10:1)[13] to give compound **99** as a colorless liquid (1.05 g, 62%). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, dd, *J* = 7.6/1.4 Hz, ArH), 7.48-7.19 (7H, ArH), 7.10 (1H, t, *J* = 7.2 Hz, ArH), 6.21 (1H, s, $J_{Sn-H}$ = 19.8 Hz, PhC<u>H</u>OSn), 1.46-1.35 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.22 (6H, sextet, *J* = 6.8 Hz, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.93-0.79 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 165.5 (PhCSnO<u>C</u>(=O)Ar), 142.5 (Ar), 133.7 (Ar), 132.5 (Ar), 131.7 (Ar), 131.2 (Ar), 130.4 (Ar), 128.5 (Ar), 126.6 (Ar), 125.2 (Ar), 123.8 (Ar), 74.9 (Ph<u>C</u>SnOC(=O)Ar), 28.9 ($J_{Sn-C}$ = 20.2 Hz, $SnCH_2CH_2\underline{C}H_2CH_3$), 27.4 ($J_{Sn-C}$ = 57.9 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 13.6 ($SnCH_2CH_2CH_2\underline{C}H_3$), 10.2 ($J_{Sn-C}$ = 320/310 Hz, $Sn\underline{C}H_2CH_2CH_2CH_3$); IR (neat) 1716, 1288, 1247, 1047, 745, 695 cm$^{-1}$; HRMS Calculated for $C_{26}H_{41}ClNO_2Sn$ ($M + NH_4^+$): 550.1838, Found: 550.1839.

## 3.4 General Procedure A: Stille Coupling of (±)-α-Acyloxybenzylstannane[13]

$Pd_2(dba)_3$ (0.0072 g, 0.008 mmol), phosphine ligand (0.032 mmol), (±)-α-alkoxybenzyl-stannane (0.20 mmol) and benzoyl chloride (40 μL, 0.048 g, 0.34 mmol) were added into the Schlenk tube. CuCN (0.0040 g, 0.044 mmol) was dissolved in 6 mL of toluene and transferred into the tube. The reaction mixture was degassed at -78 ℃ under high vacuum. After the

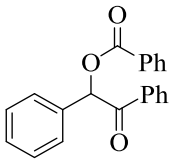
degassing, the Schlenk tube was filled with argon and sealed. Then it was heated in a sand bath at 80 ℃ and stirred for 18 h. Then the reaction mixture was allowed to cool down to room temperature. The reaction mixture was extracted by 2 × 10 mL of $Et_2O$ and washed by 10 mL of 2.8% $NH_3 \cdot H_2O$ in sat. $NH_4Cl$ solution and 10 mL of brine. The organic layer was dried by $Na_2SO_4$ and concentrated by rotary evaporator to afford the crude product.

### 3.4.1 (±)-2-Oxo-1,2-Diphenylethyl 2,2,2-Trifluoroacetate (95)



Following the general procedure A, no coupled product was found in the $^1H$ NMR spectrum; However, signals for benzaldehyde were found in the spectrum.

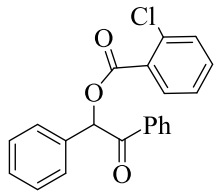
### 3.4.2 (±)-2-Oxo-1, 2-Diphenylethyl Benzoate (97)



Compound **97** was isolated using by column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give purified product with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (3 × 0.3 mL) to give compound **97** (with < 5 mol% of dba) as a white crystal (0.040g, 63%). mp = 119-125 ℃ (lit.[75] mp: 125-126 ℃); $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 7.6 Hz, ArH), 8.01 (2H, d, *J* = 7.8 Hz, ArH), 7.66-7.35 (11H, m, ArH), 7.10 (1H, s, PhC<u>H</u>O); $^{13}C$ NMR (75

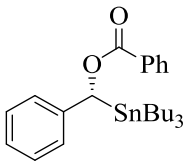
MHz, $CDCl_3$) δ 193.7 (PhC(=O)CHO), 166.0 (PhC(=O)OC), 134.6 (Ar), 133.7 (Ar), 133.5 (Ar), 133.3 (Ar), 130.0 (Ar), 129.3 (Ar), 129.3 (Ar), 129.1 (Ar), 128.8 (Ar), 128.7 (Ar), 128.7 (Ar), 128.4 (Ar), 77.9 (PhCHOC(=O)); IR (neat) 1716, 1678, 1276, 1261 $cm^{-1}$; HRMS Calculated for $C_{21}H_{17}O_3$ ($M + H^+$): 317.1172, Found: 317.1172.

### 3.4.3 (±)-2-Oxo-1, 2-Diphenylethyl Benzoate (100)




Compound **100** was isolated using by column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give purified product with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (3 × 0.3 mL) to give compound **100** as a white crystal (0.047 g, 64%). mp = 98-100 ℃; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* = 7.3 Hz, ArH), 7.98 (2H, d, *J* = 7.5 Hz, ArH), 7.57-7.27 (11H, m, ArH), 7.11 (1H, s, PhCHO); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 193.4 (PhC(=O)CHO), 164.8 (ArC(=O)OC), 134.5 (Ar), 134.2 (Ar), 133.5 (Ar), 133.3 (Ar), 132.9 (Ar), 132.0 (Ar) 131.0 (Ar), 129.3 (Ar), 129.1 (Ar), 129.0 (Ar), 128.8 (Ar), 128.7 (Ar), 128.6 (Ar), 126.5 (Ar), 78.3 (PhCHOC(=O)); IR (neat) 1722, 1685, 1242, 1052, 747, 693 $cm^{-1}$; HRMS Calculated for $C_{22}H_{16}ClO_3$ ($M + H^+$): 351.0783, Found: 351.0782.

### 3.5 Synthesis of (*R*)-α-Benzoyloxybenzylstannane (*R*)-(96)[13]

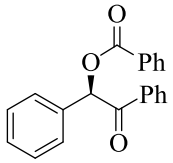



Following Falck's procedure,[65] freshly distilled DME (100 mL) was added into a round bottom flask and cooled to -40 ℃. $Et_2Zn$ (20 mL of 1.0 M solution in hexane, 20 mmol) was syringed into the flask. The reaction mixture was stirred for 10 min before tributyltin hydride (5.4 mL, 20 mmol) was syringed into the flask dropwise. Then the mixture was warmed up to 0 ℃ and stirred for 18 h. After that, the reaction mixture was cooled to -40 ℃ and stirred for 10 min. Chiral catalyst (*R*)-diphenyl(pyrrolidin-2-yl)methanol (0.25 g, 1.0 mmol) was dissolved in freshly distilled DME (100 mL) and transferred into an addition funnel, then the mixture was added into the flask dropwise. The reaction mixture was allowed to stir for 10 min. Benzaldehyde (0.51 mL, 5 mmol) was dissolved in 10 mL DME and transferred into an addition funnel, then the mixture was added into the flask dropwise. Then the reaction mixture was allowed to stir for 18 h at -40 ℃. The reaction was quenched by 100 mL of sat. $NH_4Cl$ solution and warmed up to room temperature. The organic solvent was evaporated by rotary evaporator. The mixture was extracted by 4 × 10 mL of $Et_2O$. The organic layer was then washed by 10 mL of brine, dried by $Na_2SO_4$ and then concentrated by rotary evaporator to give crude (*R*)-α-hydroxybenzylstannane as yellow liquid.

DMAP (0.25 g, 2 mmol) was dissolved in $CH_2Cl_2$ (25 mL) and cooled to 0 ℃. Pyridine (0.5 mL, 6.2 mmol) was added into the reaction mixture followed by α-hydroxybenzylstannane and benzoyl chloride (0.6 mL, 5.1 mmol). The mixture was warmed to room temperature and stirred

for 15 h. The reaction was monitored by TLC (hex/diethylether = 5:1) and once there was no α-hydroxybenzylstannane observed, it was quenched by addition of 10 mL of sat. $NH_4Cl$ solution. The organic solvent was washed with aqueous HCl (1 M, 10 mL), sat $NaHCO_3$ (2 × 10 mL) and brine (10 mL) and dried by $Na_2SO_4$. Then the crude mixture was afforded after the rotary evaporation. Compound (***R***)-**96** was isolated using column chromatography (silica/product = 25:1, hex/diethylether/$CH_2Cl_2$ = 40:10:1) to give compound (***R***)-(**96**) as a colorless liquid (1.92g, 75%). The spectral data were the same as the ones for its racemate. $[\alpha]^{25}_D$ = +7.3 (*c* 1.0, $CHCl_3$, 81% e.e.); HPLC [OD-H, 0.3% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 7.8 min (*S*), $t_{R2}$ = 8.7 min (*R*), %e.e = 81]. Absolute configuration of compound (***R***)-(**96**) was assigned according to the analogs reported by Falck[65] and Su[13].

### 3.6 Synthesis of (*R*)-2-Oxo-1,2-Diphenylethyl Benzoate (*R*)-(97)[13]



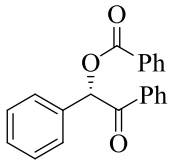

DMAP (3 crystals) was dissolved in $CH_2Cl_2$ (5 mL) and cooled to 0 ºC. Pyridine (32 μL, 0.4 mmol) was added into the reaction mixture; then (*R*)-(-)-Benzoin (12 mg, 0.05 mmol) and benzoyl chloride (45 μL, 0.38 mmol) were added into the reaction mixture. The mixture was stirred at rt for 15 h. Then the reaction was quenched by 5 mL of sat. $NH_4Cl$ solution. The organic solvent was washed by brine (5 mL) and dried by $Na_2SO_4$. Then the crude mixture was afforded after the rotary evaporation. Compound (***R***)-(**97**) was isolated using column chromatography (silica/product = 25:1, hex/diethylether = 10:1)[13] to give purified product as

white crystal (14 mg, 75%). HPLC [OD-H, 5% *i*-PrOH/hexanes, 0.5 mL/min, $t_{R1}$ = 14.6 min (*R*), $t_{R2}$ = 17.1 min (*S*), %e.e = 97].

### 3.7 General Procedure B: Stille Coupling of (*R*)-α-Benzoyloxybenzylstannane

$Pd_2(dba)_3$ (0.0036 g, 0.004 mmol), $PPh_3$ (0.0043 g, 0.016 mmol), $NaHCO_3$ (0.0008 g, 0.01 mmol), (*R*)-α-benzoyloxybenzylstannane (0.05 g, 0.10 mmol) and acid chloride (0.14 mmol) were added into the Schlenk tube. CuCN (0.0020 g, 0.022 mmol) was dissolved in 6 mL of toluene and transferred into the tube. The reaction mixture was degassed at -78 ℃ under high vacuum. After the degassing, the Schlenk tube was filled with argon and sealed. Then it was heated in a sand bath at 80 ℃ and stirred for 18 h. The reaction mixture was allowed to cool down to room temperature and was extracted by 2 × 10 mL of $Et_2O$. Then it washed by 10 mL of 2.8% $NH_3{\cdot}H_2O$ in sat. $NH_4Cl$ solution and 10 mL of brine. The organic layer was dried by $Na_2SO_4$ and concentrated by rotary evaporator to afford the crude product.

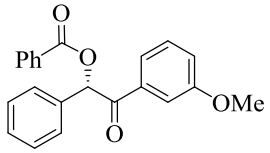
#### 3.7.1 (*S*)-2-Oxo-1, 2-Diphenylethyl Benzoate (*S*)-(97)




Following the general procedure B, 0.2 mmol of (*R*)-α-benzoyloxybenzylstannane was added as the limiting reagent. Compound (***S***)-(**97**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give purified product with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (3 × 0.3 mL) to give compound (***S***)-(**97**) (with < 5 mol% of dba) as a white crystal (0.023g, 68%). The

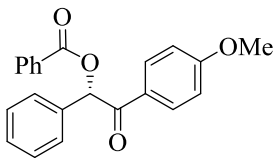
spectral data were the same as the ones for its racemate. HPLC [OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 5.9 min (*R*), $t_{R2}$ = 6.8 min (*S*), %e.e = 88]. Absolute configuration of compoung (***S***)-(**97**) was assigned according to **(*R*)-97**.

### 3.7.2 (*S*)-2-(3-Methoxyphenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(102)



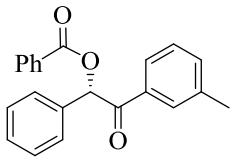

Compound (***S***)-(**102**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 30:1, hex/diethylether = 5:2)[13] to give purified product (with trace amount of unknown contaminants) as a white crystal (0.008 g, 23%). mp = 152-158 ℃; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 7.9 Hz, ArH), 7.60-7.28 (11H, m, ArH), 7.05 (1H, m, ArH), 7.05 (1H, s, PhC<u>H</u>O); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 193.4 (Ph<u>C</u>(=O)CHO), 165.9 (Ph<u>C</u>(=O)OC), 159.7 (<u>C</u>OMe), 135.9 (Ar), 133.7 (Ar), 133.3 (Ar), 129.9 (Ar), 129.5 (Ar), 129.3 (Ar), 129.2 (Ar), 129.0 (Ar), 128.6 (Ar), 128.3 (Ar), 121.3 (Ar), 120.1 (Ar), 113.0 (Ar), 78.0 (Ph<u>C</u>HOC(=O)), 55.5 ($OCH_3$); IR (neat) 1722, 1683, 1266, 1237, 758, 699 cm$^{-1}$; HRMS Calculated for $C_{22}H_{19}O_4$ ($M + H^+$): 347.1278, Found: 347.1278. HPLC [AD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 16.1 min (*S*), $t_{R2}$ = 20.3 min (*R*), %e.e = 66].

### 3.7.3 (*S*)-2-(4-Methoxyphenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(103)



Compound (***S***)-(**103**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 30:1, hex/diethylether = 10:3)[13] to give purified product with dibenzylideneacetone (dba) and unknown contaminants. The product was washed by cold hexane (3 × 0.3 mL) to give compound (***S***)-(**103**) (with < 3 mol% of unknown contaminants) as a white crystal (0.009 g, 26%). mp = 122-124 ℃; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 8.8 Hz, ArH), 7.99 (2H, d, *J* = 8.6 Hz, ArH), 7.60-7.35 (8H, m, ArH), 7.05 (1H, s, PhC<u>H</u>O), 6.88 (2H, d, *J* = 8.8 Hz, C<u>H</u>COMe); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 192.0 (Ph<u>C</u>(=O)CHO), 166.0 (Ph<u>C</u>(=O)OC), 153.8 (<u>C</u>OMe), 134.3 (Ar), 133.3 (Ar), 131.3 (Ar), 130.0 (Ar), 129.5 (Ar), 129.2 (Ar), 129.1 (Ar), 128.6 (Ar), 128.4 (Ar), 127.6 (Ar), 113.9 (Ar), 113.0 (Ar), 77.7 (Ph<u>C</u>HOC(=O)), 55.5 ($OCH_3$); IR (neat) 1715, 1682, 1593, 1248, 1230, 715, 698 $cm^{-1}$; HRMS Calculated for $C_{22}H_{19}O_4$ ($M + H^+$): 347.1278, Found: 347.1278. HPLC [OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 9.5 min (*R*), $t_{R2}$ = 14.4 min (*S*), %e.e = 68].

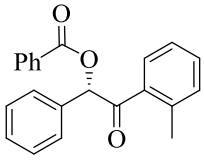
### 3.7.4 (*S*)-2-Oxo-1-Phenyl-2-(*m*-Tolyl)ethyl Benzoate (*S*)-(104)




Compound (***S***)-(**104**) was isolated using column chromatography on 15% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give purified product with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (3 × 0.3 mL) to give compound (***S***)-(**104**) (with < 5 mol% of dba) as a white crystal (0.018 g, 58%). mp = 133-138 ℃; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 7.4 Hz, ArH), 7.80-7.75 (2H, m, ArH), 7.60-7.50 (3H, m, ArH), 7.47-7.25 (7H, m, ArH), 7.07 (1H, s, PhC<u>H</u>O), 2.35 (3H, s, $CH_3$);

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 193.8 (PhC(=O)CHO), 165.9 (PhC(=O)OC), 138.4 (Ar), 133.8 (Ar), 133.2 (Ar), 129.9 (Ar), 129.4 (Ar), 129.2 (Ar), 129.2 (Ar), 129.0 (Ar), 128.9 (Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 126.0 (Ar), 77.8 (PhCHOC(=O)), 21.2 ($CH_3$); IR (neat) 1718, 1682, 1276, 1260, 1238, 757, 710, 695 cm$^{-1}$; HRMS Calculated for $C_{22}H_{19}O_3$ (M + H$^+$): 331.1329, Found: 331.1328. HPLC [OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 5.8 min (*R*), $t_{R2}$ = 6.5 min (*S*), %e.e = 61].

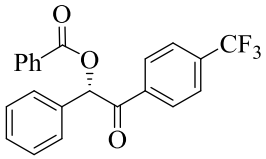
### 3.7.5 (*S*)-2-Oxo-1-Phenyl-2-(*o*-Tolyl)ethyl Benzoate (*S*)-(105)




Following the general procedure B, no product was observed in the $^1$H NMR spectrum. However, benzaldehyde and benzyl benzoate **98** were found in the spectrum. Following the general procedure A, compound (***S***)-(**105**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give purified product with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (2 × 0.1 mL) to give compound (***S***)-(**105**) (with < 5 mol% of dba) as a white crystal (0.014 g, 21%). mp = 105-107 ℃; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.15 (2H, d, *J* = 7.5 Hz, ArH), 7.83 (1H, d, *J* = 7.6 Hz, ArH), 7.58 (1H, t, *J* = 7.6 Hz, ArH), 7.50-7.10 (10H, m, ArH), 6.89 (1H, s, PhCHO), 2.21 (3H, s, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 197.5 (PhC(=O)CHO), 166.1 (PhC(=O)OC), 138.5 (Ar), 136.1 (Ar), 133.4 (Ar), 132.9 (Ar), 131.6 (Ar), 131.4 (Ar), 130.0 (Ar), 129.4 (Ar), 129.1 (Ar), 129.0 (Ar), 128.5 (Ar), 128.3 (Ar), 128.2 (Ar), 125.5 (Ar), 79.8 (PhCHOC(=O)), 20.1 ($CH_3$); IR (neat) 1707, 1690, 1176, 1097, 757, 701, 684 cm$^{-1}$; HRMS Calculated for $C_{22}H_{19}O_3$

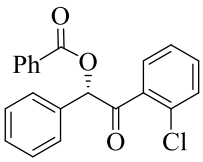
(M + $H^+$): 331.1329, Found: 331.1328. HPLC [AD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 8.1 min (*S*), $t_{R2}$ = 11.5 min (*R*), %e.e = 69].

### 3.7.6 (*S*)-2-Oxo-1-Phenyl-2-(4-(Trifluoromethyl)phenyl)ethyl Benzoate (*S*)-(106)



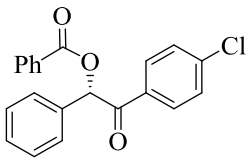

Compound (***S***)-(**106**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 10:1)[13] to give compound (***S***)-(**106**) as a white ctystal (0.011 g, 27%). mP = 67-69 ℃; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 7.6 Hz, ArH), 8.07 (2H, d, *J* = 8.6 Hz, ArH), 7.67 (2H, t, *J* = 7.4 Hz, ArH), 7.47-7.36 (5H, m, ArH), 6.02 (1H, s, PhC<u>H</u>O); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 193.0 (Ph<u>C</u>(=O)CHO), 166.1 (Ph<u>C</u>(=O)OC), 137.5 (Ar), 134.9 (Ar), 133.5 (Ar), 133.0 (Ar), 132.5 (Ar), 130.0 (Ar), 129.6 (Ar), 129.4 (Ar), 129.2 (Ar), 128.7 (Ar), 128.5 (Ar), 125.5 (q, $J_{C\text{-}F}$ = 3.34 Hz, <u>C</u>$CF_3$), 78.1 (Ph<u>C</u>HOC(=O)); IR (neat) 1713, 1695, 1319, 1280, 1167, 713, 699 $cm^{-1}$; HRMS Calculated for $C_{22}H_{19}F_3O_3$ (M + $H^+$): 385.1046, Found: 385.1046. HPLC [OD-H, 2% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 8.7 min (*R*), $t_{R2}$ = 14.1 min (*S*), %e.e = 90].

### 3.7.7 (*S*)-2-(2-Chlorophenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(107)



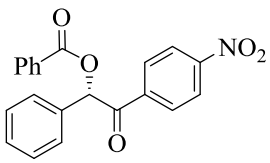
Following the general procedure B, no product was observed in the $^1$H NMR spectrum. However, signals for benzyl benzoate **98** were found in the spectrum.

### 3.7.8 (*S*)-2-(4-Chlorophenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(108)



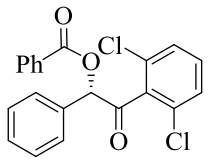

Compound (***S***)-(**108**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 10:1)[13] to give compound (***S***)-(**108**) with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (3 × 0.3 mL) to afford the title compound (with < 5 mol% of dba) as a white crystal (0.0072 g, 18%). mp = 89-92 ℃; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 7.7 Hz, ArH), 7.93 (2H, d, *J* = 8.2 Hz, ArH), 7.54 (3H, m, ArH), 7.46-7.35 (7H, m, ArH), 7.0 (1H, s, PhC<u>H</u>O); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 192.6 (Ph<u>C</u>(=O)CHO), 166.0 (Ph<u>C</u>(=O)OC), 138.9 (Ar), 133.4 (Ar), 133.0 (Ar), 130.2 (Ar), 129.9 (Ar), 129.4 (Ar), 129.2 (Ar), 129.0 (Ar), 128.5 (Ar), 128.4 (Ar), 77.8 (Ph<u>C</u>HOC(=O)); IR (neat) 1706, 1689, 1282, 1245, 1100, 1096, 757, 708, 698 $cm^{-1}$; HRMS Calculated for $C_{21}H_{16}ClO_3$ ($M + H^+$): 351.0783, Found: 351.0782. HPLC [OD-H, 3% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 9.1 min (*R*), $t_{R2}$ = 13.6 min (*S*), %e.e = 71].

### 3.7.9 (*S*)-2-(4-Nitrophenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(109)



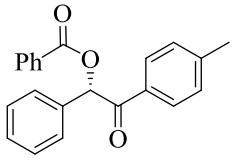
Following the general procedure B, no product was observed in the $^{1}$H NMR spectrum. However, signals for benzyl benzoate **98** were found in the spectrum.

### 3.7.10 (*S*)-2-(2,6-Dichlorophenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(110)




Following the general procedure B, no product was observed in the $^{1}$H NMR spectrum. However, signals for benzyl benzoate **98** were found in the spectrum.

### 3.7.11 (*S*)-2-Oxo-1-Phenyl-2-(*p*-Tolyl)ethyl Benzoate (*S*)-(111)



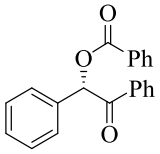

Compound (***S***)-(**111**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give compound (***S***)-(**111**) with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (3 × 0.3 mL) to afford the title compound (with < 5 mol% of dba) as a white crystal (0.0091 g, 28%). mp = 116-123 ℃; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 7.6 Hz, ArH), 7.90 (2H, d, *J* = 8.2 Hz, ArH), 7.59-7.52 (3H, ArH), 7.45-7.33 (5H, m, ArH), 7.20 (2H, *J* = 8.1 Hz, ArH), 7.07 (1H, s, PhC<u>H</u>O), 2.35 (3H, s, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 193.2 (Ph<u>C</u>(=O)CHO), 166.0 (Ph<u>C</u>(=O)OC), 144.5 (Ar), 134.0 (Ar), 133.3 (Ar), 132.1 (Ar), 130.0 (Ar), 129.5 (Ar), 129.4 (Ar), 129.2 (Ar), 129.1 (Ar), 129.0 (Ar), 128.7 (Ar), 128.4 (Ar), 77.8 (Ph<u>C</u>HOC(=O)), 21.7 ($CH_3$); IR

(neat) 1716, 1687, 1450, 1230, 1281, 1099, 1068, 715, 686 $cm^{-1}$; HRMS Calculated for $C_{22}H_{19}O_3$ ($M + H^+$): 331.1329, Found: 331.1328. HPLC [OD-H, 2% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 10.4 min (*R*), $t_{R2}$ = 15.3 min (*S*), %e.e = 68].

### 3.8 General Procedure C: Stille Coupling of (*R*)-*α*-Benzoyloxybenzylstannane under Optimized Conditions[13]

$Pd_2(dba)_3$ (0.0074 g, 0.008 mmol), ligand (0.032 mmol), and base (0.02 mol) were added into a Schlenk tube. (*R*)-α-Benzoyloxybenzylstannane (0.1 g, 0.2 mmol) and acid chloride (0.28 mmol) were added into the Schlenk tube. CuCN (0.0080 g, 0.088 mmol) was dissolved into trifluorotoluene (3 × 2 mL) and transferred into the tube. The reaction mixture was degassed at -78 ℃ under high vacuum. After the degassing, the Schlenk tube was filled with argon and sealed. Then it was heated in a sand bath at 95 ℃ and stirred for 18 h. The reaction mixture was allowed to cool down to room temperature and was extracted by 2 × 10 mL of $Et_2O$. Then it washed by 10 mL of 2.8% $NH_3 \cdot H_2O$ in Sat. $NH_4Cl$ solution and 10 mL of brine. The organic layer was dried by $Na_2SO_4$ and concentrated by rotary evaporator to afford the crude product.

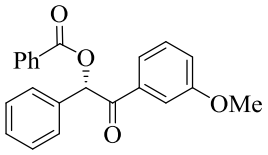
#### 3.8.1 (*S*)-2-Oxo-1, 2-Diphenylethyl Benzoate (*S*)-(97)




Following the general procedure C where $PPh_3$ was used as the ligand and 2-phenylpyridine was used as the base, compound (***S***)-(**97**) was isolated using column chromatography with 15

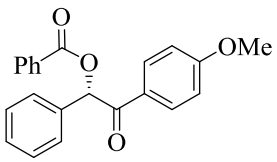
wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give compound (***S***)-(**97**) with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (3 × 0.3 mL) to afford the title compound (with < 5 mol% of dba) as a white crystal (0.036 g, 52%). The spectral data were the same as the ones for its racemate. $[\alpha]^{25}_{D}$ = +156.8 (*c* 0.2, $CHCl_3$, 76% e.e.); HPLC [OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 6.0 min (*R*), $t_{R2}$ = 7.0 min (*S*), %e.e = 76].

### 3.8.2 (*S*)-2-(3-Methoxyphenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(102)



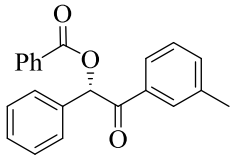

Following the general procedure C where $PPh_3$ was used as the ligand, 0.133 mmol CuCN was used and no base was added, compound (***S***)-(**102**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:2)[13] to give compound (***S***)-(**102**) (with a small amount of unknown contaminants) as a white crystal (0.021g, 32%). The spectral data were the same as the ones obtained above. $[\alpha]^{25}_{D}$ = +113.6 (*c* 0.7, $CHCl_3$, 83% e.e.); HPLC [AD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 15.6 min (*S*), $t_{R2}$ = 19.7 min (*R*), %e.e = 83].

### 3.8.3 (*S*)-2-(4-Methoxyphenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(103)



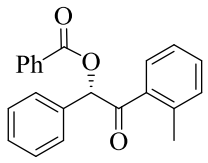
Following the general procedure C where $PPh_3$ was used as the ligand and no base was added, compound (***S***)-(**103**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 30:1, hex/diethylether = 10:3)[13] to give compound (***S***)-(**103**) with dibenzylideneacetone (dba) and unknown compounds as contaminants. The product was washed by cold hexane (2 × 0.1 mL) to afford the title compound (with trace amount of dba and unknown contaminants) as a white crystal (0.020 g, 28%). The spectral data were the same as the ones obtained above. $[\alpha]^{25}_{D}$ = +108.9 (*c* 0.7, $CHCl_3$, 79% e.e.); HPLC [OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 9.0 min (*R*), $t_{R2}$ = 13.7 min (*S*), %e.e = 79].

### 3.8.4 (*S*)-2-Oxo-1-Phenyl-2-(*m*-Tolyl)ethyl Benzoate (*S*)-(104)



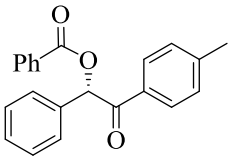

Following the general procedure C where $PPh_3$ was used as the ligand and $NaHCO_3$ was used as the base, compound (***S***)-(**104**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give compound (***S***)-(**104**) with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (2 × 0.1 mL) to afford the title compound (with < 5 mol% of dba) as a white crystal (0.033 g, 52%). The spectral data were the same as the ones obtained above. $[\alpha]^{25}_{D}$ = +129.6 (*c* 0.9, $CHCl_3$, 82% e.e.); HPLC [OD-H, 5% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 7.0 min (*R*), $t_{R2}$ = 8.0 min (*S*), %e.e = 82].

### 3.8.5 (*S*)-2-Oxo-1-Phenyl-2-(*o*-Tolyl)ethyl Benzoate (*S*)-(105)



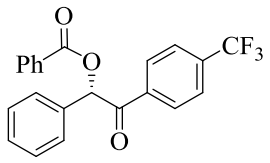
Following the general procedure C, a small amount of product was observed in the $^1$H NMR spectrum. However, signals for benzaldehyde and benzyl benzoate **98** were found in the spectrum. The amount of the product was too small to purify. The spectral data were the same as the ones obtained above.

### 3.8.6 (*S*)-2-Oxo-1-Phenyl-2-(*p*-Tolyl)ethyl Benzoate (*S*)-(111)



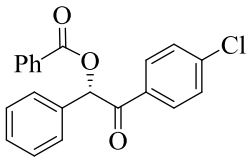
Following the general procedure C where $PPh_3$ was used as the ligand, 2,4,6-trimethylpyridine was used as the base and 0.15 mmol of (*R*)-α-benzoyloxybenzylstannane was used as the limiting reagent, compound (***S***)-(**111**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 5:1)[13] to give compound (***S***)-(**111**) with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (2 × 0.1 mL) to afford the title compound (with < 5 mol% of dba) as a white crystal (0.045 g, 42%). The spectral data were the same as the ones obtained above. $[\alpha]^{25}_{D}$ = +112.9 (*c* 0.9, $CHCl_3$, 77% e.e.); HPLC [OD-H, 5% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 7.2 min (*R*), $t_{R2}$ = 9.8 min (*S*), %e.e = 77].

### 3.8.7 (*S*)-2-Oxo-1-Phenyl-2-(4-(Trifluoromethyl)phenyl)ethyl Benzoate (*S*)-(106)




Following the general procedure C where TFP was used as the ligand, $NaHCO_3$ was used as the base and 0.1 mmol of (*R*)-α-benzoyloxybenzylstannane was used as the limiting reagent, compound (***S***)-(**106**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 10:1)[13] to give compound (***S***)-(**106**) as a white crystal (0.015 g, 35%). The spectral data were the same as the ones obtained above. $[\alpha]^{25}_{D}$ = +66.0 (*c* 0.8, $CHCl_3$, 68% e.e.); HPLC [OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 5.4 min (*R*), $t_{R2}$ = 7.3 min (*S*), %e.e = 68].

### 3.8.8 (*S*)-2-(4-Chlorophenyl)-2-Oxo-1-Phenylethyl Benzoate (*S*)-(108)



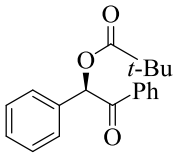

Following the general procedure C where $PPh_3$ was used as the ligand and no base was added, compound (***S***)-(**108**) was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 10:1)[13] to give compound (***S***)-(**108**) with dibenzylideneacetone (dba) as a contaminant. The product was washed by cold hexane (2 × 0.1 mL) to afford the title compound (with < 5 mol% of dba) as a white crystal (0.036 g, 52%). The spectral data were the same as the ones obtained above. $[\alpha]^{25}_{D}$ = +85.2 (*c* 1.1, $CHCl_3$, 81% e.e.);

HPLC [OD-H, 3% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 8.3 min (*R*), $t_{R2}$ = 12.1 min (*S*), %e.e = 81].

## 3.9 General Procedure D: Stille Coupling of (*S*)-α-(Trimethylacetoxy)-Benzylstannane[13]

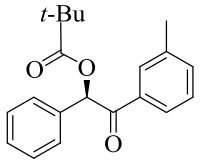
(*S*)-α-(Trimethylacetoxy)benzylstannane (94% e.e.[57]) was prepared by Su, and purified using column chromatography (silica/product = 30:1, hex/diethylether = 40:1) before use. $Pd_2(dba)_3$ (0.0092 g, 0.01 mmol ), ligand (0.038 mmol) were added in a Schlenk tube. (*S*)-α-(Trimethylacetoxy)benzylstannane (0.10 g, 0.21 mmol) and acid chloride (0.35 mmol) were added in the Schlenk tube. CuCN (0.0080 g, 0.088 mmol) was dissolved into toluene (3 × 2 mL) and transferred into the tube. The reaction mixture was degassed at -78 ℃ under high vacuum. After the degassing, the Schlenk tube was filled with argon and sealed. Then it was heated in a sand bath at 95 ℃ and stirred for 18 h. The reaction mixture was allowed to cool down to room temperature and was extracted by 2 × 10 mL of $Et_2O$. Then it washed by 10 mL of 2.8% $NH_3 \cdot H_2O$ in Sat. $NH_4Cl$ solution and 10 mL of brine. The organic layer was dried by $Na_2SO_4$ and concentrated by rotary evaporator. The product was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 10:1) to give the purified product.

### 3.9.1 (*R*)-2-Oxo-1,2-Diphenylethyl Pivalate (*R*)-(119)



TFP was used as the ligand, compound (***R***)-(**119**) was obtained as a white crystal (0.051 g, 81%). The spectral data were the same as the ones reported by Su.[57] $[\alpha]^{25}_{D}$ = -109.3 (*c* 0.8, $CHCl_3$, 94% e.e.); HPLC [OD-H, 5% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 4.7 min (*R*), $t_{R2}$ = 5.4 min (*S*), %e.e = 94].

### 3.9.2 (*R*)-2-Oxo-1-Phenyl-2-(*m*-Tolyl)ethyl Pivalate (*R*)-(120)



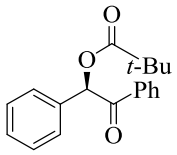

Compound (***R***)-(**120**) was obtained as a white crystal (0.052 g, 77%). The spectral data were the same as the ones reported by Su.[57] $[\alpha]^{25}_{D}$ = -101.3 (*c* 0.7, $CHCl_3$, 85% e.e.); HPLC [OD-H, 0.8% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 8.7 min (*R*), $t_{R2}$ = 12.8 min (*S*), %e.e = 85].

## 3.10 General Procedure E: Stille Coupling of (*S*)-α-(Trimethylacetoxy)-Benzylstannane under Optimized Conditions[13]

(*S*)-α-(Trimethylacetoxy)benzylstannane (94% e.e.) was prepared by Su and purified using column chromatography (silica/product = 30:1, hex/diethylether = 40:1) before use. $Pd_2(dba)_3$ (0.0092 g, 0.01 mmol ), TFP (0.0091 g, 0.038 mmol) were added into a Schlenk tube. (*S*)-α-(Trimethylacetoxy)benzylstannane (0.10 g, 0.21 mmol) and acid chloride (0.27 mmol) were added into the Schlenk tube. CuCN (0.0074 g, 0.084 mmol) was dissolved into toluene (3 × 2 mL) and transferred into the tube. The reaction mixture was degassed at -78 ℃ under high vacuum. After the degassing, the Schlenk tube was filled with argon and sealed. Then it was heated in a sand bath at 80 ℃ and stirred for 18 h. The reaction mixture was allowed to cool

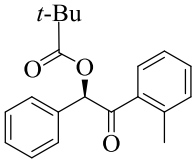
down to room temperature and was extracted by 2 × 10 mL of $Et_2O$. Then it was washed by 10 mL of 2.8% $NH_3 \cdot H_2O$ in sat. $NH_4Cl$ solution and 10 mL of brine. The organic layer was dried by $Na_2SO_4$ and concentrated by rotary evaporator. The product was isolated using column chromatography with 15 wt% KF/silica (silica/product = 25:1, hex/diethylether = 10:1) to give the purified product.[13]

### 3.10.1 (*R*)-2-Oxo-1,2-Diphenylethyl Pivalate (*R*)-(119)



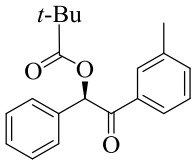

Compound (***R***)-(**119**) was obtained as a white crystal (0.050 g, 78%). The spectral data were the same as the ones reported by Su.[57] HPLC [OD-H, 5% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 4.5 min (*R*), $t_{R2}$ = 5.1 min (*S*), %e.e = 93].

### 3.10.2 (*R*)-2-Oxo-1-Phenyl-2-(*o*-Tolyl)ethyl Pivalate (*R*)-(118)



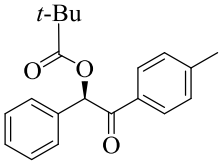

Compound (***R***)-(**118**) was obtained as a white crystal (0.026 g, 38%). The spectral data were the same as the ones reported by Su.[57] $[\alpha]^{25}_D$ = -90.6 (*c* 0.7, $CHCl_3$, 86% e.e.); HPLC [OD-H, 1% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 8.0 min (*R*), $t_{R2}$ = 14.0 min (*S*), %e.e = 86].

### 3.10.3 (*R*)-2-Oxo-1-Phenyl-2-(*m*-Tolyl)ethyl Pivalate (*R*)-(120)



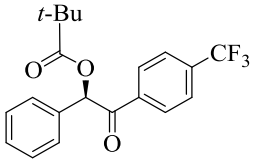

Compound (***R***)-(**120**) was obtained as a white crystal (0.051 g, 74%). The spectral data were the same as the ones reported by Su.[57] HPLC [OD-H, 5% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 4.7 min (*R*), $t_{R2}$ = 5.1 min (*S*), %e.e = 93].

### 3.10.4 (*R*)-2-Oxo-1-Phenyl-2-(*p*-Tolyl)ethyl Pivalate (*R*)-(121)



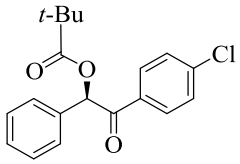

Compound (***R***)-(**121**) was obtained as a white crystal (0.040 g, 60%). The spectral data were the same as the ones reported by Su.[57] $[\alpha]^{25}_{D}$ = -100.0 (*c* 1.0, $CHCl_3$, 86% e.e.); HPLC [OD-H, 0.8% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 9.3 min (*R*), $t_{R2}$ = 14.0 min (*S*), %e.e = 86].

### 3.10.5 (*R*)-2-Oxo-1-Phenyl-2-(4-(Trifluoromethyl)phenyl)ethyl Pivalate (*R*)-(124)




Compound (***R***)-(**124**) was obtained as a white crystal (0.044 g, 57%). The spectral data were the same as the ones reported by Su.[57] $[\alpha]^{25}_{D}$ = -63.0 (*c* 0.7, $CHCl_3$, 86% e.e.); HPLC [OD-H, 0.3% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 16.6 min (*R*), $t_{R2}$ = 19.3 min (*S*), %e.e = 86].

### 3.10.6 (*R*)-2-(4-Chlorophenyl)-2-Oxo-1-Phenylethyl Pivalate (*R*)-(125)




Compound (***R***)-(**125**) was obtained as a white crystal (0.048 g, 71%). The spectral data were the same as the ones reported by Su.[57] $[\alpha]^{25}_{D}$ = -69.1 (*c* 1.0, $CHCl_3$, 84% e.e.); HPLC [OD-H, 1% *i*-PrOH/hexanes, 1.0 mL/min, $t_{R1}$ = 7.3 min (*R*), $t_{R2}$ = 8.5 min (*S*), %e.e = 84].

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