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The Modified Stereospecific Stille Reaction: Palladium-Catalyzed Cross-Coupling Reactions Involving Secondary and Tertiary Alkyl Carbastannatranes

Chao-yuan Wang
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The Modified Stereospecific Stille Reaction:  
Palladium-Catalyzed Cross-Coupling Reactions  
Involving Secondary and Tertiary Alkyl  
Carbastannatranes

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A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfilment of the requirements for the degree of Doctor of Philosophy

The City University of New York 2017
This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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THE CITY UNIVERSITY OF NEW YORK
ABSTRACT

The Modified Stereospecific Stille Reaction: Palladium-Catalyzed Cross-Coupling Reactions Involving Secondary and Tertiary Alkyl Carbastannatranes

Advisor: Prof. Mark R. Biscoe

by Chao-yuan Wang

Organic chemistry is present in all domains of everyday life, from polymer production to medicine. In order to synthesize complex compounds, it is often necessary to make new carbon-carbon bonds. Transition metal catalysts, particularly those derived from second and third row metals such as Pt, Pd, Rh, and Ir metals, display remarkable efficiency for the formation of carbon-carbon and carbon-heteroatom bonds. In the first chapter, introduction of transition metal-catalyzed cross-coupling reactions is given. While the formation of C(sp²)–C(sp³) bonds has been studied extensively, C(sp³)–C(sp³) bond formation still presents a challenge due to competitive β-hydride elimination and slow transmetallation of bulky secondary and tertiary alkyl organometallic nucleophiles. Palladium-catalyzed cross-coupling reactions (especially Stille and Suzuki cross coupling reactions) can tolerate a broad scope of reactants, and even proceed with high stereospecificity. The development of a general system that enables a broad scope of
reactants to be employed in reactions with high stereospecificity would be transformative in the field of organic synthesis and drug development. Herein, in the second chapter, we present the development of a general Pd-catalyzed process for the stereospecific cross-coupling of secondary alkyl organotin reagents with aryl chlorides, bromides, iodides and triflates. The reaction proceeds with minimal isomerization of the secondary alkyl organometallic tin nucleophile, and tolerates a wide range of functional groups with absolute configuration. In the third chapter, this work has been extended to the use of acyl electrophiles, which undergo Pd-catalyzed cross-coupling reactions with secondary alkylcarbastannatranes with exceptional stereofidelity and with net retention of absolute configuration. Because the stereochemistry of the resulting products is entirely reagent-controlled, this process may be viewed as a general, alternative approach to the preparation of products typically accessed via asymmetric enolate methodologies. Additionally, we report a new method for the preparation of optically active alkylcarbastannatranes, which should facilitate their future use in stereospecific reactions.
Dedicated to
My Family.
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1] Introduction

1.1] Background

Biological systems, in most cases, recognize a pair of enantiomers as different substances, and the two enantiomers will elicit different responses. Thus, enantioselective synthesis is a key process in modern chemistry and is particularly important in the field of pharmaceuticals, as the different enantiomers or diastereomers of a molecule often have different biological activity. Hence, one enantiomer may act as an effective therapeutic drug whereas the other enantiomer could be inactive or toxic. The potential for the individual compounds of a racemate to exhibit disparate biological effects was first observed with Thalidomide in the 1950’s.\footnote{1} It was initially prescribed as an anti-emetic to alleviate morning sickness in pregnant women. Shortly after the drug was sold in West Germany, about 7,000 infants were born with phocomelia (malformation of the limbs). Only 40% of these children survived. Throughout the world, more than 10,000 cases were reported of infants with phocomelia due to thalidomide; only 50% of them survived. Other effects included deformed eyes and hearts, deformed alimentary and urinary tracts, blindness and deafness. Worldwide, S-Thalidomide was shown to be responsible for over 20000 cases of serious birth defects in children born to women who took the racemic mixture during pregnancy. The negative effects of Thalidomide led to the development of more structured drug regulations and control over drug use and development.

Thus, it is important that synthetic chemists provide highly efficient and reliable methods for the synthesis of desired compounds in an enantiomerically pure state, so that
the biological properties of each enantiomer can be investigated. Today, pharmaceutical industries must rigorously demonstrate the safety of racemates to obtain the FDA’s approval. Several methods are used to obtain enantiomerically pure materials, which include classical optical resolution via diastereomers, chromatographic separation of enantiomers, enzymic resolution, chemical kinetic resolution, and asymmetric synthesis.

The importance and practicality of asymmetric synthesis as a tool to obtain enantiomerically pure or enriched compounds has been fully acknowledged to date by chemists in synthetic organic chemistry and medicinal chemistry. This prominence starts from the extensive development of asymmetric methods over the past few decades. Asymmetric synthesis, also called chiral synthesis or enantioselective synthesis, is a form of chemical synthesis. It is defined by IUPAC as a chemical reaction in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts. In other words, it is the synthesis of a compound by a method that favors the formation of a specific enantiomer or diastereomer.

Among the types of asymmetric reactions, the most desirable and the most challenging is catalytic asymmetric synthesis because one chiral catalyst molecule can create millions of chiral product molecules, just like what enzymes are capable of doing in biological systems. Plus, catalytic asymmetric synthesis often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. For example, a number of catalytic asymmetric reactions, including the “Takasago Process” (asymmetric isomerization), the “Sumitomo Process” (asymmetric cyclopropanation), and the “Arco Process” (asymmetric Sharpless
epoxidation) have been commercialized from the 1980s. In 2001, the Nobel Prize in Chemistry was awarded to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless in recognition of their contributions to the development of catalytic asymmetric synthesis. Their discoveries have had a significant impact on academic research, drug discovery, and material chemistry, where asymmetric catalysis is commonly employed in the creation of stereogenic centers during carbon-carbon bond construction.

1.2] The development of metal-catalyzed coupling reactions

Transition-metal-catalyzed cross-coupling reactions of aryl halides with organoboronic acids, organostannanes, organosiloxanes, organozinc compounds, and Grignard reagents have found widespread popularity during recent years. However, the development of metal-catalyzed coupling reactions begins with some of the oldest organic chemistry - stoichiometric metal-promoted homo-couplings. Historically, the first example is the copper-promoted homocoupling of metallic acetylides reported by Glaser in 1869. About a decade later, Baeyer reported the use of the Glaser coupling for the synthesis of indigo, which served as a forerunner of the modern combined transition-metal-catalyzed Sonogashira-heteroannulation strategies for indoles and related heterocycles. Following the development of $C(sp)$-$C(sp)$ homocoupling reactions, the copper-mediated method was extended to $C(sp^3)$-$C(sp^3)$ bond formation. In 1901, Ullmann reported the dimerization of 2-bromo- and 2-chloronitrobenzene promoted by the use of superstoichiometric copper sources. Although the Ullmann dimerization was similar to the Glaser-type process that preceded it, the dimerization occurs between
carbons bearing halogens rather than between simple unfunctionalized carbon systems. This theme of using carbon atoms bearing halogens for coupling chemistry was concurrently being developed in the areas of organomagnesium (Grignard) and organosodium (Wurtz-Fittig) chemistry. Despite these remarkable achievements, the early metal-promoted reactions were not only limited to the use of stoichiometric or super-stoichiometric metal reagents but also limited to homo-coupling transformations while often resulting in the formation of various undesired side products. Hence, later efforts focused on reducing metal loading and making the transformations more selective.

During the first half of the 20th century, the first systematic investigation of transition-metal-catalyzed C(sp²)-C(sp²) coupling is found in a 1941 publication by Kharasch, and in subsequent studies during the 1940s, his work was extended to the cross coupling of vinyl bromides with aryl organomagnesium species using cobalt chloride. These studies represent the earliest reports of a cross-coupling product — the use of metals to connect two different coupling partners. Although the early Kharasch-type couplings were extremely limited in substrate scope and functional group compatibility, they demonstrated that transition metals could be used in catalytic quantities to form carbon-carbon bonds. Unfortunately, the ratio of the homo-coupling to cross-coupling product observed was highly substrate specific, producing uncontrollably variable yields. Thus, during the second half of the 20th century, organic chemists sought new conditions that would increase the selectivity in favor of the cross-coupling product. In the 1960s, for the very first time, a robust solution to the selectivity problem had been found. With these first examples of truly selective C-C bond formation between C(sp) and C(sp) carbon
centers (Cadiot–Chodkiewicz)\(^9\) or \(C(sp)\) and \(C(sp^2)\) carbon centers (Castro–Stephens),\(^{10}\) the framework of the cross-coupling concept began to emerge.

### 1.3] Cross-coupling reactions

Organic chemistry is present in all domains of everyday life, from polymer production to medicine. In order to synthesize complex compounds, it is often necessary to make new C-C bonds, which can be difficult due to the stability of carbon compounds. Transition-metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as a powerful synthetic tool, and its development has reached a level of sophistication that allows for a wide range of coupling partners to be combined efficiently. In the past decades, this paradigm for C-C bond construction has allowed chemists to assemble complex molecular frameworks of diversified interests. These interests encompass applications of natural product synthesis, medicinal chemistry, and industrial process development, as well as chemical biology, material chemistry, and nanotechnology. The emergence of cross coupling as a popular method in synthesis arises from both the diversity of organometallic reagents utilized in these reactions and the broad range of functional groups which can be incorporated into these reagents.

“Cross-coupling reaction” is a general term for a variety of reactions where nucleophilic and electrophilic partners are joined with the aid of a metal catalyst. Transition-metal-catalyzed carbon-carbon cross-coupling reactions typically involve the reaction of a main group organometallic nucleophile with an organic electrophile in the presence of a transition metal catalyst. Conventional transition metal-catalyzed cross-coupling reactions generally proceed via the three fundamental steps in the reaction mechanism shown in Figure 1. The cycle begins with the electrophilic coupling partner, a
halide RX (or a pseudo-halide), undergoing oxidative addition to a low valent transition metal complex \((L_nM)\), forming the oxidative addition (OX) intermediate \((L_nMRX)\). The nucleophilic coupling partner varies and may be an alkene or an organometallic compound \(R^1M'\) (\(M'\) belonging to the series B, Sn, Zn, Mg, Si, Cu). Subsequently, the oxidative addition complex undergoes transmetallation (TM) with the main group organometallic species or migratory mechanism if an alkene is used in place of the organometallic nucleophile forming the second intermediate \((L_nMRR^1)\) and a metal species \((M'X)\). The final step is reductive elimination (RE) of the second intermediate in which a carbon-carbon bond is formed between the two coupling partners while regenerating the metal catalyst. The mechanistic details of these fundamental steps may vary depending upon the cross-coupling method employed.\(^{11}\)

![Figure1. General cross-coupling catalyzed cycle](image-url)
The chemistry of cross-coupling reactions has evolved over three successive waves (Figure 2): 1) the wave dedicated to identification and investigation of metal catalysts; 2) the wave dedicated to identification of the nucleophilic substrates (organometallic partners) able to react in these cross-coupling reactions; and 3) the wave dedicated to the development of new catalytically active species and alternative electrophilic partners. Wave one was dominated by copper, and was described earlier. Subsequently, the complexity of the coupling reactions has increased since the 1960s, concomitant with the development of nickel and palladium catalysts. This enabled the development of new synthetic methodologies based on different main group organometallic nucleophiles (wave two). The ensuing development of new powerful ligands for use in palladium catalysis has facilitated the broad application of high yielding cross-coupling reactions (wave three). The ligands used in combination with palladium in transition metal-catalyzed cross-coupling reactions are in general:
monodentate phosphines, bidentate phosphines, and N-heterocyclic carbenes. In particular, phosphine-ligated systems have been shown to have a wide range of synthetic applications and are remarkably stable.\textsuperscript{4,11} The most frequently used monodentate phosphine is triphenylphosphine (PPh\textsubscript{3}). Palladium complexes with bidentate phosphine ligands tend to be more stable than those with monodentate ligands. A supplementary advantage of the bidentate ligands relates to the acceleration of the reductive elimination step, as they enforce the cis geometry necessary for reductive elimination to occur. The impressive progress in this area has been paved by the development of electron-rich, bulky phosphines\textsuperscript{4} and N-heterocyclic carbene ligands, which comprise many highly active nickel and palladium catalysts.\textsuperscript{12} Names associated with common cross-coupling reactions relate to the main group metal nucleophile employed (Figure 3): Heck (no main group organometallic nucleophile),\textsuperscript{13} Negishi (Zn),\textsuperscript{15} Sonogashira (Cu),\textsuperscript{16} Stille (Sn),\textsuperscript{17} Hiyama (Si),\textsuperscript{18} and Kumada (Mg),\textsuperscript{19} Suzuki-Miyaura (B).\textsuperscript{14,20}

\[
\begin{array}{ccc}
R^1-X + R^2M^2Y & \xrightarrow{M^1L_m} & R-R^2 \\
R1, R2 = \text{alkenyl, alkynyl, alkyl, aryl} \\
M1 = \text{Pd, Pt, Ni, Co, Fe, Cu} \\
X = \text{Halides, OTf, OTs} \\
Y = \text{Halides, alkyl, alkynyl} \\
\end{array}
\]

\[
\begin{array}{ccc}
R^2ZnY & \text{Negishi} \\
R^2B_Y & \text{Suzuki-Miyaura} \\
R^2MgY & \text{Kumada} \\
R^2SnY & \text{Stille} \\
R^2SiY & \text{Hiyama} \\
R^2CuY & \text{Sonogashira} \\
\end{array}
\]

**Figure 3.** General types of palladium-catalyzed cross-coupling reactions

A major focus of the research in our laboratory is the development of new methods for carbon-carbon bond formation via metal-catalyzed cross-coupling reactions using alkyl nucleophiles.\textsuperscript{21} Recently, we reported general Ni-catalyzed processes for the cross coupling of secondary alkylzinc and tertiary alkylmagnesium nucleophiles with aryl
electrophiles. These methods largely circumvent the \(\beta\)-hydride elimination/reinsertion sequences that have limited previous Pd-catalyzed systems (Figure 4). To expand the versatility of the cross-coupling reactions that use secondary alkyl nucleophiles, we also want to extend the processes to the use of isolable, configurationally stable, optically active organometallic nucleophiles. The development of such transformations is impeded by the inverse relationship that exists between the nucleophilicity and configurational stability of carbon-metal bonds in main-group organometallic nucleophiles (Figure 5). Although increased covalency tends to coincide with enhanced configurational stability of the carbon-metal bond, it also tends to coincide with reduced nucleophilicity. This trend, in addition to the inherent bulk of a secondary nucleophile, results in the prohibitively slow transmetallation of a secondary nucleophile as the covalency of the C-M bond increases. Additionally, rapid reductive elimination is still required to circumvent the competing \(\beta\)-hydride elimination pathway.

The use of secondary alkyltin and secondary alkylboron nucleophiles containing a secondary \(C(sp^3)\)-alkyl carbon center has typically required remote activation via the presence of a \(C(sp^3)\) \(\alpha\)-carbon, \(\alpha\)-heteroatom, and/or a strongly coordinating \(\beta\)-carbonyl group on the nucleophile in order to accelerate transmetallation and also retard the formation of isomerized products via competitive \(\beta\)-hydride elimination pathways (Figure 6). Therefore, development of a more powerful organotin reagent capable of easy preparation with the trend for the specific and selective transfer of the desired inactivated secondary alkyl group during the organic synthesis remains challenging.
**Figure 4.** Catalytic cycle and competing processes for Pd-catalyzed cross-coupling reactions of secondary nucleophiles and aryl electrophiles.

**Figure 5.** Inverse relationship between configurational stability and nucleophilicity for main group organometallic nucleophiles.
Figure 6. Stereospesific cross-coupling reactions using isolable optically active organometallic nucleophiles.

1.4] Pd-catalyzed Stille cross-coupling reactions

The Stille reaction is one of the most useful transformations in organic synthesis. The emergence of organotin compounds as coupling mediators has led to a remarkable growth in the field of cross-coupling reactions over the past 40 years. Alongside the Suzuki reaction, the Stille reaction has established itself as one of the most general and most selective palladium-catalyzed cross-coupling reactions. Since organostannanes do not react with most common functional groups, and are stable to oxidative and reductive reaction conditions, the use of protecting groups is generally unnecessary in conjunction with the Stille reaction. More importantly, the Stille coupling is particularly popular as organostannanes are air- and moisture-stable organometallic reagents, and can be
conveniently purified and stored. In addition to this attractive feature, the reaction also has the advantage that it runs under neutral conditions, making it potentially more tolerant of functional groups than the Suzuki reaction. This particular kind of cross coupling reaction was first observed by M. Kosugi in the late 1970s and was further developed by J. K. Stille. The first examples of the coupling of organostannanes with organic electrophiles were disclosed during the period 1976-1977 by the research groups of Eaborn and Kosugi, but it was the extensive synthetic and mechanistic work carried out by Stille and co-workers from 1978 that made this reaction a standard method in organic synthesis.

Generally, Stille cross-coupling reactions involve the coupling of an organotin (IV) reagent and an organic halide or pseudohalide in the presence of a palladium catalyst to give the carbon-carbon coupled product. Palladium complexes such as Pd(PPh₃)₄, PdCl₂(PPh₃)₂, Pd₂(dba)₃, Pd(CH₃CN)₂Cl₂, Pd(Pfur₃)₂Cl₂ (dba = dibenzylideneacetone, fur = 2-furyl) and palladium nanoparticles have been employed as Pd sources. Modern chemists are actively engaged in designing new organotin compounds (organostannanes) for their wide applications as reagents in synthetic reactions.

1.5] Transmetallation of organostannanes

The currently accepted mechanism of the Stille cross-coupling reaction contains four steps. These four steps are oxidative addition, transmetallation, trans-cis isomerization (cis-trans as well) and reductive elimination. The overall outcome of the transmetallation step is a concurrent cleavage of the carbon-tin bond and formation of the
carbon-palladium bond. During this process, the organotin moiety is scavenged by the halides to give a tin halide compound. As described above, the substrate scope has been enlarged and it has been found that the organotin reagents can tolerate a considerable range of functionalities. These nucleophilic organotin reagents include alkynyltins, alkenyltins, aryltins, allyltins, benzyltins, acyltins, alkyltins, aminostannanes, as well as alkoxytannanes. Rate of transfer from tin is proportional to the amount of S-character in the C-Sn bond. Thus, alkynyltin and alkenyl/aryl tin are considered to be the most reactive organostannanes toward transmetallation. These groups can selectively transferred from the tin atom to a palladium complex in the presence of alkyl-tin bonds due to the low propensity of alkyl groups to undergo transmetallation from tin. Therefore tributyltin (or trimethyltin) units are commonly employed to enable the selective transfer of alkynyl or aryl groups. The preference was given to tributyltin derivatives in most of the cases since these are comparatively less toxic (Figure 7). There are relatively few examples of the successful transfer of primary alkyl groups in Stille cross-coupling reactions described in the literature (Figure 8).

**Figure 7.** Transmetallation rate of different substituents of Stille coupling

\[
\begin{align*}
R-SnBu_3 + Ar-X & \xrightarrow{\text{Pd/L (cat.) additives}} R-Ar \\
\text{Rate of } R \text{ transfer from tin:} & \\
\text{Alkynyl} \ > \ \text{Alkenyl} \ > \ \text{Aryl} \ > \ \text{Benzyl} \ > \ \text{Allyl} \ > \ \text{Alkyl} \ (1^o \ > \ 2^o \ > \ 3^o)
\end{align*}
\]
Although transfer of alkyl substituents from tetraalkylstannanes is preceded, it is only practical for primary alkyl (methyl or n-butyl) groups. Slow transmetallation and facile $\beta$-hydride elimination (when employing stannanes with alkyl groups bearing $\beta$-hydrogen) constitute major obstacles to the application of secondary alkyltin reagents in
Pd-catalyzed cross-coupling reactions.\textsuperscript{40}

![Chemical reaction diagram]

**Figure 9.** First use of alkylcarbastannatranes in Stille couplings.

In Stille cross-coupling reactions, it is not only difficult to transfer alkyl groups other than primary alkyl species, but during cross-coupling reactions only one out of four alkyl substituents migrates in the transmetallation step, while the other three substituents are wasted (Figure 8). The Vedejs group used methylcarbastannatrane in place of the traditional tetramethyltin reagent in a Pd-catalyzed Stille cross-coupling reaction to achieve selective, accelerated transfer of the methyl group (Figure 9).\textsuperscript{42}

Alkylcarbastannatranes were initially introduced by Jurkschat in 1985. According to X-ray crystal structures obtained by Jurkschat, carbastannatranes have a longer apical Sn-C bond compared to normal tetraalkylstannanes (i.e., enhanced nucleophilicity).\textsuperscript{41}

From our point of view, one of the best strategies to resolve common problems associated with unactivated alkyl group transfer is to increase length and to enhance polarity of the Sn-C bond of interest. Hence, carbastannatranes turned into interesting coupling mediators. In principle, use of carbastannatranes also enables the selective transfer of the single apical alkyl group, eliminating the need to sacrifice three
(potentially precious) alkyl units. Consequently, the use of carbastannatranes in Stille cross-coupling reactions may offer a number of advantages over the use of more traditional organotin reagents including milder reaction conditions, selective and stereospecific alkyl transfer, and lower toxicity (carbastannatranes).43

1.6] References


34. (a) Kosugi, M.; Fugami, K., *Overview of the Stille Protocol with Sn. In Handbook*


2] Stereospecific Pd-catalyzed Stille cross-coupling reactions of secondary alkylcarbastannatranes and aryl electrophiles

2.1] Choice of nucleophile: Importance of carbastannatranes as coupling mediators

In organotin chemistry, it has been observed that the intramolecular donation of nitrogen to tin increases the reactivity of the trans-situated Sn-R bond,¹ making some cyclic organotin reagents useful in synthetic routes.² Amongst potential organotin cyclic systems, stannatranes possess cage like structures with transannular donor-acceptor interaction.³,⁴ In stannatranes, the tin atom is coordinated to the heteroatoms of a tripod-like tetradentate ligand, which generates heterocyclic N-C-C-Y-Sn (Y: heteroatoms; Figure 1) chelate rings containing the apical Sn-N bond and tin in a bridge-head position. Depending upon the equatorial atoms (Y), stannatranes are categorized into stannatranes (Y = oxygen), azastannatranes (Y = nitrogen) and thiastannatranes (Y = sulphur), and none of them have been reported as coupling mediators. Only carbastannatranes (Y = carbon) have been used in cross-coupling reactions.

Compared to tetraalkylstannanes, alkylcarbastannatranes possess a longer apical Sn-C bond as a consequence of the intramolecular Sn-N bond according to X-ray crystal structures obtained by Jurkschat in 1985.¹ This transannular Sn-N interaction should thus result in the selective labilization of the trans-disposed alkyl substituent.⁵,⁶ The coordina-
tion of the nitrogen atom in benzyl amines (1, Figure 2) as well as carbastannatrane derivatives (2a, Figure 2) has been demonstrated to be particularly effective in facilitating the selective transfer of the alkyl group in Stille cross-coupling reactions. Thus, we proposed that the carbastannatrane backbone could be broadly employed to selectively activate apical primary, secondary, and tertiary alkyl substituent towards transmetallation, providing the more efficient reagent by which to transfer alkyl group compared to traditional tetraalkylstannane reagents.

2.2] Optimization

Different phosphine ligands were screened with sec-butyl carbastannatrane (2b) as the nucleophile and with 4-bromoanisole as the electrophile. The initial conditions were set on the 0.02 mmol scale using 5 mol % Pd(dba)$_2$ in acetonitrile (Figure 3). Reactions were conducted under an argon atmosphere and were stirred at 60 °C. Reactions were monitored by gas chromatography, and the yield of desired product was calibrated using dodecane as the internal standard. Reactions were also screened in the presence of CuCl (2 equiv) and KF (2 equiv). Low conversions and a preponderance of rearrangement product resulted from the use of most ligands (Figure 3). Only one ligand, JackiePhos (3), a bulky electron-deficient biarylphosphine, emerged as a promising ligand for this transformation. This commercially available ligand was developed by the Buchwald
group to facilitate the rate-limiting transmetallation of secondary amides in Pd-catalyzed amidation reactions of aryl halides.\textsuperscript{9-12}

In our opinion, the efficacy of Jackiephos as a supporting ligand in the cross-coupling reactions of secondary alkylcarbostannatranes likely results from the propensity of Jackiephos to facilitate transmetallation of the secondary alkyl group while still promoting rapid reductive elimination. This interpretation is supported by the use of Jackiephos analogue \textbf{L4}, which lacks trifluoromethyl group on the phenyl rings. In presence of 10 mol \% \textbf{L4}, the yield and the retention/ isomerization ratio decreased significantly (Figure 3). This is consistent with slower transmetallation and slower reductive elimination.

![Figure 3](image)

**Figure 3.** Ligand effects on the Pd-catalyzed cross-coupling reaction of \textbf{2b} and 4-bromoanisole.
As mentioned in chapter one, the Stille reaction has established itself as one of the most general and most selective palladium-catalyzed cross-coupling reactions, along with the Suzuki cross-coupling of organoboron compounds. The Stille coupling is particularly popular as organostannanes are readily prepared, purified and stored. As hydroxo ligands play a major role in the transmetallation step of the Suzuki coupling reaction and in other catalytic transformations of organoboranes, it has been found that fluoride additives enhance the reactivity of organostannanes. Among our initial scope of different additives, KF (2 equiv) was required to maximize the retention/isomerization ratio (Figure 4).

![Figure 4](image)

**Figure 4.** Solvent and additive effects.

<table>
<thead>
<tr>
<th>Additives</th>
<th>GC Yield (%)</th>
<th>sBu / n-Bu</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>15</td>
<td>4.4</td>
</tr>
<tr>
<td>2 equiv. KF</td>
<td>16</td>
<td>4.9</td>
</tr>
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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 Feng. In their later studies, Cu(I) salts were shown to behave as a ligand scavenger as well as a co-catalyst in the reaction. When the reaction is conducted with ligands such as PPh₃, Cu(I) can accelerate the reaction by...
scavenging the ligands tightly bound to the palladium.\textsuperscript{15} We found that, within our initial scope of different additives, 2 equiv of Cu(I) were required to maximize the retention/isomerization ratio and the yield (Figure 4).

2.3] \textit{Substrate scope}

To evaluate the substrate scope accommodated in this reaction, we used 2b in cross-coupling reactions with a series of aryl and heteroaryl electrophiles (Figure 5). In general, cross-coupling products were obtained with ratios of retention to isomerization greater than 50:1. A nominal dependence on the electronic properties of the aryl bromide electrophile was observed. Electron-rich, electron-neutral and electron-deficient aryl bromides all reacted to give high yields of desired product. Aryl bromides bearing electrophilic functional groups such as aldehydes, ketones, esters, amides and nitriles underwent successful cross-coupling reactions. The presence of an ortho-substituent was also well-tolerated. Importantly, heteroaromatic electrophiles could be broadly used without significant isomerization of the secondary alkyl nucleophile. Electron-deficient aryl chloride electrophiles also underwent efficient cross-coupling reactions under these conditions. When a product sample was analyzed by inductively coupled plasma mass spectrometry (ICP-MS), only 30 $\mu$g/g trace tin was found. This indicates that the stannatranes byproducts are easily removed by column chromatography.
Figure 5. sec-butylnocarbostannatrane nucleophile cross couple with a series of aryl and heteroaryl electrophiles. Reaction conditions: aryl halide (1 mmol), carbostannatrane (1.1–1.5 mmol), CuCl (2 mmol), KF (2 mmol), Pd(dba)2 (0.05 mmol), Jackiephos (0.06–0.10 mmol), CH3CN (3 ml). Average isolated yield (a%) of two runs. Ratio (ret:iso) of retention product (s-Bu) to isomerization product (n-Bu) determined by gas chromatography.

To demonstrate the general application of secondary alkylcarbostannatrane nucleophiles in Pd-catalyzed reactions, we used a variety of modified alkylcarbostannatranes. These substrates were readily generated from 4 using a modified version of the procedure developed by Vedejs (Figure 6). The judicious choice of solvent allowed secondary alkylithium, alkylmagnesium halide and alkylzinc halide nucleophiles to be used as
precursors to the secondary alkylcarbostannatrane reagents. Almost all of the alkylcarbostannatranes were air- and moisture-stable and were prepared in excellent yield. We successfully employed secondary alkyl groups bearing ethers, amines, esters and amides (Figure 7). Secondary benzylic nucleophiles and bis-α-substituted nucleophiles underwent efficient cross-coupling reactions. During these studies, we also demonstrated that the use of aryl triflates and aryl iodides could be tolerated in these reactions. Therefore, this cross-coupling reaction appears to be highly general with respect to the nucleophile and electrophile employed.

**Figure 6.** A modified version of the procedure developed by Vedejs.\(^\text{10}\)
Figure 7. Secondary alkyl groups bearing ethers, amines, esters and amides. Reaction conditions: aryl halide (0.5 mmol), carbastannatrane (0.55–1.0 mmol), CuCl (1 mmol), KF (1 mmol), Pd(dba)$_2$ (0.025 mmol), Jackiephos (0.03–0.05 mmol), CH$_3$CN (3 ml). Average isolated yield ($\alpha\%$) of two runs. Ratio ($\text{ret:iso}$) of retention product (s-Bu) to isomerization product (n-Bu) determined by gas chromatography.

2.4] Use of optically active tin nucleophiles

We evaluated the ability of non-racemic alkylcarbostannatrane derivatives to undergo a stereospecific cross-coupling reaction without erosion of the original enantiomeric excess (e.e.). Using the asymmetric lithiation procedure described by Beak and colleagues, we prepared and isolated optically active 2-stannylpyrrolidine derivative 6 with 93% e.e. (Figure. 8a). The enantiomers of racemic ($\text{rac-6}$) have also been success-
fully separated using preparatory chiral high-performance liquid chromatography (HPLC). Under ambient conditions, 6 appears to exhibit configurational stability indefinitely. When enantiopure 6 was used in a cross-coupling reaction with 4-bromobenzonitrile, only nominal erosion of enantiomeric excess was observed in cross-coupling product 7 (Figure 8b). To determine the absolute stereochemistry of the product, we obtained an X-ray crystal structure of a derivative of 7 containing a heavy atom 8 (Figure 8c). Because it has been well-established that Beak’s (−)-sparteine-mediated asymmetric lithiation of pyrrolidine selectively abstracts the pro-S hydrogen of prochiral C-1, the X-ray structure confirms that transmetallation occurs with complete retention of stereochemistry.

It has been shown that the presence of α-heteroatoms and carbonyl coordinating groups can activate alkyltin and alkylboron reagents towards stereospecific cross-coupling reactions. Therefore, it is conceivable that the successful transfer of stereochemical information in 5 arises as a result of similar activation. To demonstrate that our stereospecific cross-coupling method can be used in a general manner for unactivated secondary alkyl nucleophiles, we prepared an optically active secondary alkylstannatranes (9) without the α-heteroatom or the carbonyl coordinating group. Because heterocyclic electrophiles are generally challenging to employ in cross-coupling reactions, we specifically chose 2-bromopyridine and 6-bromo-2-methylquinoline, as well as inactivated 4-bromoanisole as the electrophilic components in these reactions. When enantioenriched 9 was used in the cross-coupling reactions, minimal erosion of enantiomeric excess was observed (Figure 9). Moreover, enantioenriched products 10 and 11 indicated there is no obvious enantiomeric excess erosion caused by the para-substituent of unacti-
vated aryl bromides. This suggests that our process is indeed general and does not require the use of an activated secondary alkyl nucleophile or activated aryl bromide.

Figure 8. Stereospecific cross-coupling reaction without erosion of the original enantiomeric excess (e.e.)
2.5) Conclusion

In conclusion, the unique features of alkylcarbostannatranes which include easy group transfer, specificity, selectivity, and high reactivity, make them highly effective reagents for alkyl group transfer in organic synthesis. Stille cross-coupling reactions are the emerging application for carbastannatranes, which enable the coupling of the apical alkyl substituent with an aryl electrophile. We have developed the first general stereospecific method to use secondary alkylcarbostannane nucleophiles in cross-coupling reactions. Using a carbostannatranne backbone, secondary alkyl groups underwent transmetallation to palladium with excellent stereofidelity, independent of the electronic properties of the alkyl nucleophile. Only nominal isomerization of the secondary alkyl nucleophile was observed using this method. Aryl chloride, bromides, iodides and triflates could be efficiently used as the electrophilic component of these cross-coupling reactions.
reactions. Furthermore, retention of configuration was observed when an optically active secondary alkylcarbostannatranne was used. The benchtop stability of optically active alkyl carbostannatranne reagents, coupled with the ease by which stereochemical information may be transferred via Pd-catalyzed cross-coupling reactions, should enable our process to be broadly applied in organic syntheses, particularly in the preparation of libraries of optically active drug candidates. To date, there are few reports on carbostannatranes in comparison to other organometallic reagents, which may be due to a lack of sufficient and systematic data on this topic. The continued exploration of the potential of carbostannatranes as coupling organometallic reagents will be facilitated by the development of new methods for the generation of unactivated alkyl carbostannatranes.

2.6] Experimental information

General Reagent Information

BDH brand ethyl ether and EMD brand Omnisolv THF (unstabilized) were purchased from VWR. These solvents were transferred to separate 20 L solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina. s-BuLi (1.4 M in cyclohexane), isopropylmagnesium chloride (2.0 M in ether), and 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane were purchased from Sigma-Aldrich. Pd(dba)₂ and JackiePhos were purchased from Strem. Acetonitrile (Sigma-Aldrich) was purged with argon prior to use. Grignard reagents were prepared from their corresponding alkyl chlorides or bromides using a literature procedure.²⁰ Molarities of Grignard
reagents were determined using iodine titration. Reagents and solvents were used as received unless otherwise noted. Flash chromatography was performed using SiliCycle silica gel (ultra pure grade).

**General Analytical Information**

All compounds were characterized by $^1$H NMR and $^{13}$C NMR spectroscopy. Copies of the $^1$H and $^{13}$C spectra for all new compounds can be found at the end of the Supporting Information. All previously unreported compounds were additionally characterized by high resolution MS. Nuclear Magnetic Resonance spectra were recorded on a Varian 300 or 500 MHz instrument. All $^1$H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm). All $^{13}$C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), and were obtained with $^1$H decoupling. High resolution MS analyses were performed on an Agilent 6520 Q-TOF instrument. All GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase, or using a 30 m x 0.32 mm chiral column (Rt®-βDEXsm from RESTEK). All GC yields were calibrated using dodecane as an internal standard.

**Procedural Information**

*General procedure for the preparation of secondary alkyl azastannatranes*

All reactions were performed in oven-dried glassware under an atmosphere of Ar. sec-Butyllithium or sec-alkyl Grignard reagents (1.5–3.0 equiv) were added to the suspension of 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1 equiv) in anhydrous solvent at -78
A mixture was stirred at -78 °C for 3 h, allowed to warm to room temperature, and stirred overnight. The reaction mixture was poured into a separatory funnel containing a mixture of water and ether. The organic layer was separated, washed with brine, dried over Na₂SO₄, and filtered. Solvent was removed under reduced pressure and dried in vacuo to provide the crude product. The crude secondary alkyl tin reagents were used without further purification. Homocoupling from Grignard formation constituted the major residual byproduct in the crude product.

**General procedure for cross-coupling reactions**

Pd(dba)₂ (5 mol %), JackiePhos (6-10 mol %), CuCl (2 equiv) and KF (2 equiv) were weighed out on the benchtop in an oven-dried Schlenk tube with stir bar. With stirring begun, the Schlenk tube was evacuated (50 mTorr) and backfilled three times with argon using a needle attached to a vacuum manifold. The tin reagent (1.1-2.0 equiv) and aryl halide/triflate (1 equiv) was then added to the Schlenk tube via microsyringe, followed by degassed CH₃CN (3 mL for 0.5-1.0 mmol scale). If the aryl halide/triflate was a solid, it was weighed out on the benchtop alongside the other solids. The Schlenk tube was sealed and heated to 60 °C for 18 h. The reaction mixture was cooled to rt, diluted with ether, washed sequentially with saturated aqueous KF and brine, and dried over Na₂SO₄. The reaction solution was filtered and concentrated to provide the crude product. The crude product was purified by column chromatography.

**Synthesis of 8 for absolute configuration determination via x-ray crystallography**
Single Crystal Structure Determination

Experimental Description

A colorless slab-like crystal with the size of $0.05 \times 0.20 \times 0.54 \text{ mm}^3$ was selected for geometry and intensity data collection with a Bruker SMART APEXII CCD area detector on a D8 goniometer at 100 K. The temperature during the data collection was controlled with an Oxford Cryosystems Series 700+ instrument. Preliminary lattice parameters and orientation matrices were obtained from three sets of frames. Data were collected using graphite-monochromated and 0.5 mm-MonoCap-collimated Mo-K$_\alpha$ radiation ($\lambda = 0.71073 \text{ Å}$) with the $\omega$ scan method.$^{22}$ Data were processed with the INTEGRATE program of the APEX2 software$^{22}$ for reduction and cell refinement. Multi-scan absorption corrections were applied by using the SCALE program for the area detector. The structure was solved by the direct method and refined on $F^2$ (SHELXTL)$^{23}$ Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms on carbons were placed in idealized positions (C-H = 0.95-1.00 Å) and included as riding
with $U_{\text{iso}}(H) = 1.2$ $U_{\text{eq}}(\text{non-H}),$ and the hydrogen atoms on the oxygen atoms were refined with a restrained O-H distance of 0.83 Å.

**Crystal Structure of 8**

[Diagram of the molecular structure]

**Compound Characterization**

![Compound Structure](image)

5-(sec-Butyl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (2.94 g, 10.0 mmol) in ether (40 mL), and s-BuLi (1.4 M in cyclohexane, 16 mL, 22.4 mmol). A yellow oil (3.18 g, 99%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 2.35 (t, $J = 6$ Hz, 6H), 1.64 (quint, $J = 6$ Hz, 6H), 1.41-1.51 (m, 3H), 1.05 (d, $J = 7.5$ Hz, 3H), 0.86 (t, $J = 7$ Hz, 3H), 0.63 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 55.0, 29.4, 26.7, 23.7, 18.5, 14.8, 5.7 ppm.
5-(*(iso-Propyl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1.47 g, 5.0 mmol) in ether (20 mL), and isopropylmagnesium chloride (2.0 M in ether, 7.5 mL, 15 mmol). A yellow oil (1.41 g, 95%) was isolated. $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$: 2.38 (t, $J = 6$ Hz, 6H), 1.67 (quint, $J = 6$ Hz, 6H), 1.09 (d, $J = 7.5$ Hz, 6H), 0.70-0.76 (m, 1H), 0.65 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 54.9, 23.6, 21.6, 17.7, 4.6 ppm. HRMS (FAB$^+$): Calcd ($^{116}$Sn) (M-H)$^+$ 298.0926; Found ($^{116}$Sn) 298.0929.

5-(1-Methylpiperidin-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1.06 g, 3.6 mmol) in THF (36 mL), and (1-methylpiperidin-4-yl)magnesium chloride (0.78 M in THF, 7 mL, 5.5 mmol). A pale yellow solid (1.25 g, 97%) was isolated. $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$: 2.76 (br. s, 2H), 2.34 (t, $J = 6$ Hz, 6H), 2.19 (s, 3H), 1.55-1.79 (m, 13H), 0.63 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 59.0, 54.8, 47.3, 30.8, 26.2, 23.5, 4.7 ppm. HRMS (FAB$^+$): Calcd ($^{116}$Sn) (M-H)$^+$ 353.1348; Found ($^{116}$Sn) 353.1356.
5-(Tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.88 g, 3.0 mmol) in THF (30 mL), and (tetrahydro-2H-pyran-4-yl)magnesium chloride (0.62 M in THF, 7 mL, 4.3 mmol). A pale yellow solid (983 mg, 95%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 3.87 (m, 2H), 3.33 (dt, $J = 11$, 2 Hz, 2H), 2.36 (t, $J = 6$ Hz, 6H), 1.64 (quint, $J = 6$ Hz, 6H), 1.50-1.55 (m, 4H), 0.89-0.95 (m, 1H), 0.64 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 71.0, 54.8, 31.3, 26.0, 23.4, 4.6 ppm. HRMS (FAB$^+$): Calcd ($^{116}$Sn) (M-H)$^+$ 340.1031; Found ($^{116}$Sn) 340.1025.

5-(1-Phenylethyl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (140 mg, 0.48 mmol) in THF (5 mL), and (1-phenylethyl)magnesium chloride (0.21 M in THF, 3 mL, 0.63 mmol). A yellow liquid (146 mg, 92%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.15 (t, $J = 7.5$ Hz, 2H), 6.90 (m, 3H), 2.30 (t, $J = 6$ Hz, 6H), 2.21 (quart, $J = 7.5$, 1H), 1.61 (quint, $J = 6$ Hz, 6H), 1.44 (d, $J = 7.5$ Hz, 3H), 0.61 (dt, $J = 6.5$, 3 Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 151.5, 128.0, 124.9, 121.7, 54.7, 32.7, 23.5, 16.7, 5.3 ppm. HRMS (FAB$^+$): Calcd ($^{116}$Sn) (M-H)$^+$ 360.1082; Found ($^{116}$Sn) 360.1072.
5-(4-Phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1.65 g, 5.6 mmol) in THF (50 mL), and (4-phenylbutan-2-yl)magnesium chloride (0.28 M in THF, 23 mL, 6.4 mmol). A yellow liquid (1.74 g, 79%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.25-7.28 (m, 2H), 7.16-7.19 (m, 3H), 2.50-2.65 (m, 2H), 2.36 (t, $J = 6$ Hz, 6H), 1.76-1.81 (m, 1H), 1.65 (quint, $J = 6$ Hz, 6H), 1.23-1.39 (m, 1H), 1.13 (d, $J = 7.5$ Hz, 3H), 0.79 (quart, $J = 7.5$ Hz, 1H), 0.67 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 143.9, 128.6, 128.3, 125.5, 54.9, 39.0, 36.5, 24.2, 23.6, 18.6, 5.6 ppm. HRMS (FAB$^+$): Calcd ($^{116}$Sn) (M-H)$^+$ 388.1396; Found ($^{116}$Sn) 388.1409.

5-(Octan-3-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.74 g, 2.5 mmol) in THF (25 mL), and octan-3-ylmagnesium chloride (0.35 M in THF, 11 mL, 3.8 mmol). A colorless liquid (190 mg, 51%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 2.36 (t, $J = 6$ Hz, 6H), 1.64 (quint, $J = 6$ Hz, 6H), 1.43-1.47 (m, 1H), 1.20-1.30 (m, 10H), 0.88 (t, $J = 7$ Hz, 3H), 0.84 (t, $J = 7.5$ Hz, 3H), 0.64 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 55.1, 34.0, 33.3, 32.6, 29.9, 26.3, 23.8, 23.0, 14.7, 14.4, 6.9 ppm. HRMS (FAB$^+$): Calcd ($^{116}$Sn) (M-H)$^+$ 368.1708; Found ($^{116}$Sn) 368.1698.
**Ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate.** The general procedure was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.88 g, 3.0 mmol) in DMF (8 mL), and (4-ethoxy-4-oxobutan-2-yl)zinc iodide (0.61 M in DMF, 10 mL, 6.1 mmol). An orange oil (509 mg, 45%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ: 4.09 (quart, J = 7 Hz, 2H), 2.39-2.43 (m, 1H), 2.35 (t, J = 6 Hz, 6H), 2.23-2.27 (m, 1H), 1.64 (quint, J = 6 Hz, 6H), 1.24 (t, J = 7 Hz, 3H), 1.02-1.13 (m, 4H), 0.65 (t, J = 6.5 Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 175.5, 60.0, 54.9, 40.7, 23.5, 19.8, 18.4, 14.6, 5.2 ppm. HRMS (FAB$^+$): Calcd ($^{116}$Sn) (M-H)$^+$ 370.1138; Found ($^{116}$Sn) 370.1136.

![Structure of ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate](structure.png)

**tert-Butyl 2-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)pyrrolidine-1-carboxylate.**

TMEDA (0.8 mL, 5.5 mmol) in ether (1 mL) was precooled to -78 ºC for 15 min. s-BuLi (1.4 M in cyclohexane, 4 mL, 5.6 mmol) was added dropwise to this solution. The resulting solution was allowed to stir for 15 min. A solution of N-Boc-pyrrolidine (855 mg, 5.0 mmol) in ether (10 mL) was then added dropwise. This reaction mixture was stirred at -78 ºC for 3h. The resulting solution (1-tert-butoxycarbonyl)pyrrolidin-2-yl)lithium (0.22 M in ether, 17 mL, 3.74 mmol)$^6$ was employed in the general procedure with 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.74 g, 2.5 mmol) in ether (25 mL). A yellow oil (854 mg, 80%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ: 3.11-3.34 (m, 2H), 2.32-2.38 (m, 6H), 2.01-2.21 (m, 1H), 1.63-1.70 (m, 10H), 1.47 (s, 4H), 1.43 (s, 5H), 0.70-0.73 (m, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 154.0, 77.9, 55.2, 51.4,
46.7, 30.3, 28.9, 27.2, 23.7, 7.0 ppm. HRMS (FAB⁺): Calcd (¹¹⁶Sn) (M-H)⁺ 425.1559; Found (¹¹⁶Sn) 425.1560.

(S)-tert-Butyl 2-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)pyrrolidine-1-carboxylate. (-)-Sparteine (258 mg, 1.1 mmol) in ether (1 mL) was precooled to -78 °C for 15 min. s-BuLi (1.4 M in cyclohexane, 0.8 mL, 1.12 mmol) was added dropwise to the solution. The resulting solution was allowed to stir for 15 min. A solution of N-Boc-pyrrolidine (171 mg, 1.0 mmol) in ether (2 mL) was then added dropwise. This mixture was stirred at -78 °C for 3 h. The resulting (1-tert-butoxycarbonyl)pyrrolidin-2-yl)lithium solution (0.23 M in ether, 4 mL, 0.9 mmol)⁶ was employed in the general procedure with 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.18 g, 0.6 mmol) in ether (6 mL), and (1-tert-butoxycarbonyl)pyrrolidin-2-yl)lithium. A yellow oil (160 mg, 62%, 93% ee) was isolated. ¹H NMR (500 MHz, CDCl₃) δ: 3.11-3.34 (m, 2H), 2.32-2.38 (m, 6H), 2.01-2.21 (m, 1H), 1.63-1.70 (m, 10H), 1.47 (s, 4H), 1.43 (s, 5H), 0.70-0.73 (m, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 154.0, 77.9, 55.2, 51.4, 46.7, 30.3, 28.9, 27.2, 23.7, 7.0 ppm.

Ethyl 4-(sec-butyl)benzoate⁷ (Table 1, row 1, column 1). The general procedure was employed using ethyl 4-bromobenzoate (229 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (348 mg, 1.1 mmol), and JackiePhos (48 mg, 0.06 mmol).
A colorless liquid (174 mg, 77%) was isolated by column chromatography (98:2 Hex/EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.97 (d, $J = 2$ Hz, 2H), 7.24 (d, $J = 2$ Hz, 2H), 4.36 (m, 2H), 2.65 (m, 1H), 1.61 (m, 2H), 1.38 (t, $J = 7$ Hz, 3H), 1.24 (d, $J = 6.5$ Hz, 3H), 0.81 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 166.8, 153.2, 129.8, 128.3, 127.2, 60.8, 41.9, 31.0, 21.7, 14.5, 12.3 ppm.

![Image](image)

**1-(sec-Butyl)-4-methoxybenzene**ref (Table 1, row 1, column 2). The general procedure was employed using 1-bromo-4-methoxybenzene (187 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). A colorless liquid (124.7 mg, 77%) was isolated by column chromatography (97:3 Hex/EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.11 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 9$ Hz, 2H), 3.80 (s, 3H), 2.56 (m, 1H), 1.58 (m, 2H), 1.23(d, $J = 7$ Hz, 3H), 0.83 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 157.9, 140.0, 128.0, 113.8, 55.4, 41.0, 31.5, 22.2, 12.4 ppm.

![Image](image)

**4-(sec-Butyl)-N,N-dimethylaniline**ref (Table 1, row 1, column 3). The general procedure was employed using 4-bromo-N,N-dimethylaniline (200 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). An oily, brown solid (110 mg, 62%) was isolated by column chromatography.
(99:1 Hex/EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.08 (d, $J = 8.5$ Hz, 2H), 6.73 (d, $J = 8.5$ Hz, 2H), 2.93 (s, 6H), 2.52 (m, 1H), 1.57 (m, 2H), 1.22 (d, $J = 7$ Hz, 3H), 0.84 (t, $J = 8.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 149.2, 136.2, 127.8, 113.1, 41.1, 40.8, 31.6, 22.2, 12.5 ppm.

3-(sec-Butyl)benzaldehyde (Table 1, row 2, column 1). The general procedure was employed using 3-bromobenzaldehyde (185 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (348 mg, 1.1 mmol), and JackiePhos (48 mg, 0.06 mmol). A oily, yellow liquid (120.1 mg, 74%) was isolated by column chromatography (98.5:1.5 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 10.00 (s, 1H), 7.70 (m, 2H), 7.46 (m, 2H), 7.04 (s, 1H), 2.69 (m, 1H), 1.63 (m, 2H), 1.27(d, $J = 7$ Hz, 3H), 0.83 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 192.8, 149.0, 136.8, 133.7, 129.1, 128.2, 128.0, 41.7, 31.2, 21.9, 12.3 ppm. HRMS (EI$^+$): Calcd (M$^+$) 162.1045; Found 162.1047.

1-(sec-Butyl)-3,5-dimethylbenzene$^{\text{ref}}$ (Table 1, row 2, column 2). The general procedure was employed using 1-bromo-3,5-dimethylbenzene (185 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). A colorless liquid (128 mg, 77%) was isolated by column chromatography
(97.5:2.5 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 6.82 (m, 3H), 2.52 (m, 1H), 2.31 (s, 6H), 1.59 (m, 2H), 1.22 (d, $J = 6.5$ Hz, 3H), 0.84 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 160.5, 148, 137.8, 127.7, 125.1, 41.8, 31.4, 22.1, 21.6, 12.6 ppm.

1-(sec-Butyl)-2,4-dimethylbenzene$^{ref}$ (Table 1, row 2, column 3). The general procedure was employed using 1-bromo-2,4-dimethylbenzene (185 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). A colorless liquid (125 mg, 74%) was isolated by column chromatography (97.5:2.5 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.08 (d, $J = 8$ Hz, 1H), 6.98 (m, 2H), 2.84 (m, 1H), 2.29 (s, 6H), 1.58 (m, 2H), 1.18 (d, $J = 6.5$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 143.1, 135.5, 134.9, 131.2, 127.0, 125.4, 36.1, 30.8, 21.5, 21.1, 19.7, 12.5 ppm.

1-(sec-Butyl)-3-(trifluoromethoxy)benzene (Table 1, row 3, column 1). The general procedure was employed using bromo-3-(trifluoromethoxy)benzene (241 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (348 mg, 1.1 mmol), JackiePhos (48 mg, 0.06 mmol). A colorless liquid (152.4, 73%) was isolated by column chromatography (98.5:1.5 Hex/Ether). $^1$H NMR (500 MHz CDCl$_3$) $\delta$: 7.30 (t, $J = 8$ Hz, 1H), 7.18 (d, $J = 7.5$ Hz, 1H), 7.04 (s, 1H), 7.02 (s, 1H), 2.62 (m,1H), 1.59 (m, 2H), 1.24 (d, $J = 6.5$ Hz, 1H), 1.18 (d, $J = 6.5$ Hz, 1H), 2.84 (m, 1H), 2.29 (s, 6H), 1.58 (m, 2H), 1.18 (d, $J = 6.5$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 143.1, 135.5, 134.9, 131.2, 127.0, 125.4, 36.1, 30.8, 21.5, 21.1, 19.7, 12.5 ppm.
Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 150.3, 129.7, 125.7, 119.8, 118.3, 41.7, 31.2, 21.8, 12.3 ppm. HRMS (EI$^+$): Calcd (M$^+$) 218.0918; Found 218.0919.

1-(sec-Butyl)-4-nitrobenzene$^{ref}$ (Table 1, row 3, column 2). The general procedure was employed using 1-chloro-4-nitrobenzene (158 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). An oily, yellow liquid (168 mg, 93%) was isolated by column chromatography (99:1 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.15 (d, J = 9 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 2.73 (M, 1H), 1.63 (m, 2H), 1.27 (d, J = 7 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 155.7, 146.5, 128.1, 123.8, 42.0, 31.1, 21.7, 12.3 ppm.

4-(sec-Butyl)benzonitrile$^{ref}$ (Table 1, row 3, column 3). The general procedure was employed using 4-chlorobenzonitrile (138 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). An oily, yellow solid (125.8 mg, 79%) was isolated by column chromatography (99:1 Hex/EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.59 (d, J = 8 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 2.67 (M, 1H), 1.61 (m, 2H), 1.25 (d, J = 7 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H) ppm.
13C NMR (125 MHz, CDCl₃) δ: 153.5, 132.4, 128.1, 119.4, 109.8, 42.1, 31.0, 21.6, 12.2 ppm.

1-(5-(sec-Butyl)benzofuran-2-yl)ethanone (Table 1, row 4, column 1). The general procedure was employed using 1-(5-bromobenzofuran-2-yl)ethanone (239 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (348 mg, 1.1 mmol), and JackiePhos (48 mg, 0.06 mmol). A pale yellow solid (175 mg, 82%) was isolated by column chromatography (97:3 Hex/EtOAc). ¹H NMR (500 MHz, CDCl₃) δ: 7.48 (m, 3H), 7.31 (m, 1H), 2.71 (m, 1H), 2.6 (s, 3H), 1.63 (m, 2H), 1.28 (d, J = 7 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 188.9, 165.3, 154.7, 143.8, 128.2, 127.3, 121.1, 113.3, 112.3, 41.8, 31.7, 26.6, 22.5, 12.4 ppm. HRMS (EI⁺): Calcd (M⁺) 216.1150; Found 216.1141.

6-(sec-Butyl)-2H-benzo[b][1,4]oxazin-3(4H)-oneref (Table 1, row 4, column 2). The general procedure was employed using 6-bromo-2H-benzo[b][1,4]oxin-3(4H)-one (228 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). A pale yellow solid (133 mg, 67%) was isolated by column chromatography (80:20 Hex/EtOAc). ¹H NMR (500 MHz, CDCl₃) δ: 9.43 (br s, 1H) 6.89 (d, J = 8 Hz, 1H), 6.79 (dd, J = 8, 2 Hz, 1H), 6.65 (s, 1H), 4.61(s, 2H), 2.53 (m,
1H), 1.55 (m, 2H), 1.20 (d, J = 7 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 167.3, 142.8, 141.8, 126.0, 122.7, 116.5, 115.0, 67.3, 41.2, 31.3, 22.1, 12.4 ppm.

3-(sec-Butyl)benzo[b]thiophene\(^\text{ref}\) (Table 1, row 4, column 3). The general procedure was employed using 3-bromobenzo[b]thiophene (213 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). A colorless liquid (85.5 mg, 45%) was isolated by column chromatography (99:1 Hex/EtOAc). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.87 (d, \(J = 7.5\) Hz, 1H), 7.80 (d, \(J = 8\) Hz, 1H), 7.37 (m, 2H), 7.09 (s, 1H), 3.12 (m, 1H), 1.86 (m, 1H), 1.68 (m, 1H), 1.37 (d, \(J = 7\) Hz, 3H), 0.95 (t, \(J = 7.5\) Hz, 3H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 142.7, 140.9, 139.0, 124.2, 123.8, 123.1, 122.1, 119.7, 34.8, 30.0, 20.5, 12.2 ppm.

1-(4-(sec-Butyl)phenyl)-1\(H\)-pyrrole\(^\text{ref}\) (Table 1, row 5, column 1). The general procedure was employed using 1-(4-bromophenyl)-1\(H\)-pyrrole (222 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (348 mg, 1.1 mmol), and JackiePhos (48 mg, 0.06 mmol). A brown liquid (131 mg, 77%) was isolated by column chromatography (99:1 Hex/EtOAc). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.32 (d, \(J = 8.5\) Hz, 2H), 7.24 (d, \(J = 8.5\) Hz, 2H), 7.08 (t, \(J = 2\) Hz, 2H), 6.35 (t, \(J = 2\) Hz, 2H), 2.64 (m, 1H), 1.62 (m, 2H),
1.27 (d, $J = 7$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 145.4, 138.9, 128.2, 120.8, 119.6, 110.2, 41.3, 31.4, 22.1, 12.4 ppm.

6-(sec-Butyl)-2-methylquinoline (Table 1, row 5, column 2). The general procedure was employed using 6-bromo-2-methylquinoline (222 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (348 mg, 1.1 mmol), and JackiePhos (48 mg, 0.06 mmol). A yellow liquid (172 mg, 86%) was isolated by column chromatography (95:5 Hex/EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.97 (m, 2H), 7.53 (m, 2H), 7.24 (d, $J = 8.5$ Hz, 1H), 2.77 (m, 1H), 2.72 (s, 3H), 1.68 (m, 2H), 1.32 (d, $J = 6$ Hz, 3H), 0.84 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 158.2, 147.1, 145.2, 136.0, 129.6, 128.7, 126.7, 124.9, 122.0, 41.8, 31.3, 25.5, 22.0, 12.4 ppm. HRMS (EI$^+$): Calcd (M$^+$) 199.1361; Found 199.1359.

2-(sec-Butyl)-6-methoxypyridine (Table 1, row 5, column 3). The general procedure was employed using 2-bromo-6-methoxypyridine (188 mg, 1 mmol), 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (475 mg, 1.5 mmol), and JackiePhos (80 mg, 0.1 mmol). A colorless liquid (92.5 mg, 56%) was isolated by column chromatography (99:1 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.46 (t, $J = 7.5$ Hz, 1H), 6.67 (d, $J = 7.5$ Hz, 1H), 6.52 (d, $J = 8$ Hz, 2H), 3.91 (s, 3H), 2.66 (M, 1H), 1.76 (m, 1H), 1.57 (m, 1H), 1.25 (d, $J = 6.5$ Hz, 3H), 0.83 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 164.6,
3-Isopropylbenzo[b]thiophene<sup>ref</sup> (Table 2, row 1, column 1). The general procedure was employed using 3-bromobenzo[b]thiophene (107 mg, 0.5 mmol), 5-(iso-Propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (166 mg, 0.55 mmol), and JackiePhos (24 mg, 0.03 mmol). A colorless liquid (125 mg, 71%) was isolated by column chromatography (99.5:0.5 Hex/EtOAc). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.86 (dd, J = 8, 0.5 Hz, 1H), 7.80 (dd, J = 8, 0.5 Hz, 1H), 7.36 (m, 2H), 7.10 (s, 1H), 3.32 (septet, J = 7 Hz, 1H), 1.39 (d, J = 7 Hz, 6H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 143.9, 141.0, 138.8, 124.3, 123.9, 123.1, 122.1, 119.1, 28.1, 23.0 ppm.

1-(5-(Tetrahydro-2H-pyran-4-yl)benzofuran-2-yl)ethanone (Table 2, row 1, column 2). The general procedure was employed using 1-(5-bromobenzofuran-2-yl)ethanone (120 mg, 0.5 mmol), 5-(tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (189 mg, 0.55 mmol), and JackiePhos (24 mg, 0.03 mmol). A brown solid (103 mg, 85%) was isolated by column chromatography (70:30 Hex/Ether). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.53 (m, 2H), 7.47 (s, 1H), 7.36 (dd, J = 8.5, 1.5 Hz, 1H), 4.12 (dd, J = 11, 4
Hz, 2H), 3.55 (td, J = 11.5, 2.5 Hz, 2H), 2.86 (m, 1H), 2.61 (s, 3H), 1.85 (m, 4H) ppm. 

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 188.5, 154.6, 153.0, 141.9, 127.8, 127.3, 120.6, 113.1, 112.4, 68.4, 41.5, 34.4, 26.5 ppm. HRMS (FAB$^+$): Calcd (M+H)$^+$ 245.1178; Found 245.1187.

**Ethyl 3-(4-(1H-pyrrol-1-yl)phenyl)butanoate** (Table 2, row 1, column 3). The general procedure was employed using 1-(4-bromophenyl)-1H-pyrrole (111 mg, 0.5 mmol), and ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (206 mg, 0.55 mmol), and JackiePhos (24 mg, 0.03 mmol). A reddish brown oil 104 mg, 81%) was isolated by column chromatography (92:8 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.27-7.33 (m, 4H), 7.06 (t, J = 2 Hz, 2H), 6.33 (t, J = 2 Hz, 2H), 4.09 (m, 2H), 3.31 (m, 1H), 2.59 (m, 2H), 1.32 (d, J = 7 Hz, 3H), 1.19 (t, J = 7 Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 172.4, 143.4, 139.4, 128.1, 120.9, 119.5, 110.4, 60.5, 43.2, 36.2, 22.1, 14.4 ppm. HRMS (FAB$^+$): Calcd (M$^+$) 257.1416; Found 257.1424.

**2-Methyl-6-(octan-3-yl)quinoline** (Table 2, row 2, column 1). The general procedure was employed using 6-bromo-2-methylquinoline (111 mg, 0.5 mmol), 5-(octan-3-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (279 mg, 0.75 mmol), and JackiePhos (40 mg, 0.05
mmol). An oily, yellow solid (128 mg, 100%) was isolated by column chromatography (80:20 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.96 (t, $J = 9$ Hz, 2H), 7.50 (dd, $J = 8.5$, 2 Hz, 1H), 7.47 (s, 1H), 7.23 (d, $J = 8$ Hz, 1H), 2.72 (s, 3H), 2.56 (m, 1H), 1.57-1.83 (m, 4H), 1.15-1.27 (m, 6H), 0.80 (t, $J = 6.5$ Hz, 3H), 0.76 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 158.2, 147.1, 143.7, 136.0, 129.7, 128.6, 126.6, 126.0, 122.0, 148.0, 36.7, 32.2, 29.8, 27.5, 25.5, 22.7, 14.3, 12.4 ppm. HRMS (FAB$^+$): Calcd (M+H)$^+$ 256.2065; Found 256.2063.

![Image of 1-Nitro-4-(1-phenylethyl)benzene](image)

**1-Nitro-4-(1-phenylethyl)benzene**$^{\text{ref}}$ (Table 2, row 2, column 2). The general procedure was employed 1-bromo-4-nitrobenzene (101 mg, 0.5 mmol), 5-(1-phenylethyl)-1-aza-5-stannabicyclo[3.3.3]undecane (273 mg, 0.75 mmol), and JackiePhos (40 mg, 0.05 mmol). A brownish liquid (104.5 mg, 92%) was isolated by column chromatography (99:1 Hex/Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.18 (m, 2H), 7.41-7.22 (m, 7H), 4.29 (quartet, $J = 7.5$ Hz, 1H), 1.72 (d, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 154.2, 146.6, 144.7, 128.9, 128.6, 127.7, 126.9, 123.9, 44.9, 21.7 ppm. HRMS (EI$^+$): Calcd (M$^+$) 227.0946; Found 227.0947.

![Image of 1-Nitro-4-(1-phenylethyl)benzene](image)
**Ethyl 4-(1-methylpiperidin-4-yl)benzoate** (Table 2, row 2, column 3). The general procedure was employed using ethyl 4-bromobenzoate (115 mg, 0.5 mmol), 5-(1-methylpiperidin-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (268 mg, 0.75 mmol), and JackiePhos (40 mg, 0.05 mmol). A brown solid (94 mg, 76%) was isolated by column chromatography (91:9 CH₂Cl₂/MeOH). ¹H NMR (500 MHz, CDCl₃) δ: 7.95 (d, J = 8 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 4.33 (m, 2H), 3.27 (d, J = 6 Hz, 2H), 2.65 (m, 1H), 2.56 (s, 3H), 2.48 (t, J = 11 Hz, 2H), 2.15 (m, 2H), 1.91 (d, J = 13 Hz, 2H), 1.35 (t, J = 7 Hz, 3H), 1.22 (s, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 166.5, 149.7, 130.1, 129.2, 127.0, 61.0, 55.6, 45.1, 41.1, 31.6, 14.5 ppm. HRMS (FAB⁺): Calcd (M+H)⁺ 248.1651; Found 248.1655.

![Chemical Structure](image)

**6-Isopropylquinoline** ref (Table 2, row 3, column 1). The general procedure was employed using quinolin-6-yl trifluoromethanesulfonate (139 mg, 0.5 mmol), 5-(isopropyl)-1-aza-5-stannabicyclo[3.3.3]undecane (166 mg, 0.55 mmol), and JackiePhos (24 mg, 0.03 mmol). A yellow liquid (74.2 mg, 88%) was isolated by column chromatography (90:10 Hex/Ether). ¹H NMR (500 MHz, CDCl₃) δ: 7.68 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8 Hz, 2H), 6.66 (s, 1H), 5.16 (br s, 2H), 2.92 (septet, J = 8.5 Hz, 1H), 1.26 (d, J = 8.5 Hz, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 149.8, 147.4, 147.3, 135.9, 129.6, 129.5, 128.5, 124.0, 121.2, 34.3, 24.0 ppm.
5-Isopropyl-1H-indole\textsuperscript{ref} (Table 2, row 3, column 2). The general procedure was employed using 3-iodo-1H-indole (122 mg, 0.5 mmol), 5-(iso-propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (166 mg, 0.55 mmol), and JackiePhos (24 mg, 0.03 mmol). A reddish brown solid (48 mg, 60%) was isolated by column chromatography (92:8 Hex/Ether). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 8.05 (br s, 1H), 7.49 (s, 1H), 7.33 (d, \(J = 8\) Hz, 1H), 7.18 (t, \(J = 3\) Hz, 1H), 7.10 (dd, \(J = 8.5, 1.5\) Hz, 1H), 6.51 (m, 1H), 3.02 (septet, \(J = 7\) Hz, 1H), 1.31 (d, \(J = 7\) Hz, 6H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 140.7, 134.5, 128.2, 124.5, 121.5, 117.8, 111.0, 102.6, 34.4, 24.9 ppm.

1,3-Dimethyl-5-(4-phenylbutan-2-yl)benzene\textsuperscript{ref} (Table 2, row 3, column 3). The general procedure was employed using 1-bromo-3,5-dimethylbenzene (93 mg, 0.5 mmol), 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (294 mg, 0.75 mmol), and JackiePhos (40 mg, 0.05 mmol). A colorless liquid (104 mg, 87%) was isolated by column chromatography (99.7:0.3 Hex/Ether). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.30 (t, \(J = 7\) Hz, 2H), 7.19 (t, \(J = 6.5\) Hz, 3H), 6.88 (s, 1H), 6.86 (s, 2H), 2.69 (m, 1H), 2.60 (m, 2H), 2.35 (s, 6H), 1.95 (m, 2H), 1.30 (d, \(J = 7\) Hz, 3H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 147.6, 142.9, 138.0, 128.6, 128.4, 127.8, 125.8, 125.1, 40.2, 39.6, 34.3, 22.7, 21.6 ppm.
**4-(4-Isopropylphenyl)thiazol-2-amine**\(^\text{ref}\) (Table 2, row 4, column 1). The general procedure was employed using 4-(4-bromophenyl)thiazol-2-amine (128 mg, 0.5 mmol), 5-(iso-propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (302 mg, 1 mmol), and JackiePhos (40 mg, 0.05 mmol). A brown oil (30.5 mg, 28%) was isolated by column chromatography (75:25 Hex/EtOAc). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.68 (d, \(J = 8.5\) Hz, 2H), 7.23 (d, \(J = 8\) Hz, 2H), 6.66 (s, 1H), 5.16 (br s, 2H), 2.92 (septet, \(J = 8.5\) Hz, 1H), 1.26 (d, \(J = 8.5\) Hz, 6H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 167.5, 151.6, 148.8, 132.5, 126.9, 126.2, 102.3, 34.1, 24.1 ppm.

![Chemical structure of 4-(4-Isopropylphenyl)thiazol-2-amine](image)

**tert-Butyl 2-(4-cyanophenyl)pyrrolidine-1-carboxylate**\(^{25}\) (Table 2, row 4, column 2). The general procedure was employed using 4-bromobenzonitrile (91 mg, 0.5 mmol) tert-butyl 2-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)pyrrolidine-1-carboxylate (429 mg, 1 mmol), and JackiePhos (40 mg, 0.05 mmol). A white solid (85 mg, 63%) was isolated by column chromatography (70:30 Hex/Ether). \(^1\)H NMR (500 MHz, CDCl\(_3\)) (two rotamers in a ratio of 3:2 were observed – major rotomer given) \(\delta\): 7.60 (d, \(J = 8\) Hz, 2H), 7.28 (d, \(J = 8.5\) Hz, 2H), 4.80 (m, 1H), 3.63 (m, 1H), 2.37 (m, 1H), 1.78-1.89 (m, 3H), 1.18-1.22 (m, 9H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) (two rotamers were observed – minor rotomer in parentheses) \(\delta\): 154.3 (154.3), 151.0 (149.0), 132.3 (132.4), 126.4 (126.4), 119.1 ppm.

![Chemical structure of tert-Butyl 2-(4-cyanophenyl)pyrrolidine-1-carboxylate](image)
Optically active stannatrane (6) prepared using Beak’s enantioselective deprotonation method

CT12022 (CCNY), racemate. OZH, acetonitrile, 1 ml./min., 25 deg. C. (5.0 mg./ml. solution, 20 uL injection).

CT12022B (CCNY), optically active sample: E.e.: 93.2 %. (5.0 mg./ml. solution, 20 uL injection).
Separation of enantiomers of 6 via preparatory chiral HPLC

![Chemical Structure](image)

99+% ee (S)

---

### Area Percent Report

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Use Multiplier & Dilution Factor with ISTDs

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![Chemical Structure](image)

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Use Multiplier & Dilution Factor with ISTDs

**Signal 1: DAD1 E, Sig=210,16 Ref=360,100**

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Chiral GC of cross-coupling reaction using 99% ee pyrrolidine stannatrane (6) (after Boc deprotection)
Separation of enantiomers of 5-(4-Phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane via preparatory chiral HPLC
HPLC of product from reactions of Figure 8

Chromatographic Conditions for the Separation of the Enantiomers of MRB-2-Pyridine on CHIRACEL OJ-3

- **Column**: CHIRACEL OJ-3 (150 x 4.6 mm i.d., 3 micron) Part # 17524
- **Mobile Phase**: Hexane/ isopropanol 95:5
- **Flow Rate**: 1.0 mL/min
- **Detection**: UV, 254 nm; ref 360 nm
- **Temperature**: 25°C
- **Sample**: ca. 2.0 mg /mL in mobile phase
- **Inject. Volume**: 5.0 microL

Chromatographic Conditions for the Separation of the Enantiomers of MRB-Quinoline on CHIRACEL OJ-3

- **Column**: CHIRACEL OJ-3 (150 x 4.6 mm i.d., 3 micron) Part # 17524
- **Mobile Phase**: Hexane/ isopropanol 95:5
- **Flow Rate**: 1.0 mL/min
- **Detection**: UV, 254 nm; ref 360 nm
- **Temperature**: 25°C
- **Sample**: ca. 2.0 mg /mL in mobile phase
- **Inject. Volume**: 5.0 microL
91.3% ee
91.3% ee
91.9% ee
91.9% ee
2.7] References


3] Stereospecific Pd-Catalyzed Acylation of Alkylcarba-
stannatrane Reagents: A General Alternative to Asymmetric
Enolate Reactions

3.1] Introduction

Synthetic approaches to the formation of ketones, especially those with other
functional groups and stereogenic centers, are of great interest due to their presence in a
wide variety of valuable chemicals and drugs. The use of carboxylic acid derivatives as
the starting material is a versatile and widely accepted approach to ketone synthesis. For
the preparation of α-stereogenic ketones, catalyst-controlled and auxiliary-controlled
asymmetric enolate reactions have been broadly employed. These approaches have been
extensively applied to the construction of complex organic molecules (Figure 1a).¹

Figure 1. Retrosynthetic approaches to the asymmetric construction of α-substituted carbonyl com-
ponents.

Ketones that have at least one α-hydrogen can undergo keto-enol tautomerization
to form an enol tautomer. This equilibrium allows ketones to be prepared via enolates.
When keto-enol tautomerism occurs, the keto or enol is deprotonated to form an anion, which is called the enolate. However, the development of a general approach to employ enolates and enolate equivalents in asymmetric reactions has been hindered by multiple complicating factors. First, a catalyst or auxiliary must broadly control facial attack on the enolate independent of the enolate carbon skeleton or the functional groups present. Second, reaction conditions must not be conducive to racemization of the newly formed stereogenic center, which is particularly challenging in arylation reactions. Third, when ketones possess two enolizable carbon atoms, the chemoselectivity of the enolization process must be efficiently controlled. In principle, a stereospecific coupling reaction between a stable, optically active organometallic nucleophile and an acyl electrophile (Figure 1b) would circumvent these constraints. Because such cross-coupling reactions would feature completely reagent-controlled enantiospecificity, the transfer of stereochemical information should be both general and predictable. However, one transformation that remains underdeveloped is the transition-metal-catalyzed cross-coupling reaction between carboxylic acid derivatives and $C(sp^3)$ organometallic reagents to prepare ketones. The reaction of acid halides and organometallic compounds (i.e., Zn, Cd, Mg) has been historically used for ketone synthesis. Although organozinc compounds were generally employed prior to the 1930s, organocadmium reagents were subsequently demonstrated to be more satisfactory. To date, transition metal catalysis has been applied widely in the synthesis of a variety of ketones constituting aryl-aryl, alkyl-aryl, and alkyl-alkyl groups. However, the scarcity of $sec$-alkyl organometallic reagent couplings with acyl derivatives is indicative of the inherent difficulties of transition metal catalyzed reactions involving $C(sp^3)$-hybridized coupling partners. Therefore,
the reaction of carboxylic acid halides and organometallic compounds has been restricted to diaryl ketone synthesis. Recently, several transition-metal-catalyzed cross-coupling reactions of acid chlorides and alkyl organometallic reagents to form ketones have been reported.\textsuperscript{4-15} In 1998, Fukuyama and co-workers reported the Pd-catalyzed coupling of thioesters and primary alkyl organozinc or hydride reagents, generating ketone or aldehyde products, respectively (Figure 2c).\textsuperscript{4} The advantages of the reactions are high chemoselectivity, mild reaction conditions and the use of less-toxic reagents. In addition, the protocol is compatible with functional groups such as ketones, acetates, sulfides, aromatic bromides, chlorides and aldehydes.

A number of functional groups are tolerated due to the relative stability of both coupling components. Seki and colleagues\textsuperscript{5} have since developed both heterogeneous and phosphine-free Pd-catalyzed Fukuyama couplings, as well as a Ni-catalyzed Fukuyama coupling. Despite these advances, the use of secondary C\textsuperscript{(sp\textsuperscript{3})} organometallic reagents still remains challenging. While α,α-disubstituted ketones can be prepared by direct attack of a variety of strongly nucleophilic organometallic species onto acyl electrophiles, such protocols are frequently accompanied by over-addition products due to the electrophilicity of the newly formed ketone.\textsuperscript{6} Specialized acyl derivatives, such as Weinreb amides, can minimize over-addition; however, these electrophiles require the use of organolithium or Grignard reagents, which suffer from poor functional group tolerance.\textsuperscript{7} Recent strategies to eliminate the need for alkyl organometallic reagents in ketone synthesis include reverse-polarity cross-couplings\textsuperscript{8} and reductive cross-couplings.\textsuperscript{9} Although substantial progress has been made on the transition-metal-catalyzed cross-coupling reactions between acyl electrophiles and primary alkyl organometallic reagents, there are
few reports describing the coupling of secondary alkyl organometallics. In an early study, Harada and Oku\textsuperscript{10} disclosed the coupling of secondary organozinc reagents with acid chlorides and obtained moderate yields of ketone product (Figure 2a), although the functional group tolerance of the reaction was not further explored. Zhang and Wang reported a high-yielding reaction between iPrZnI and the mixed anhydride generated from sodium benzoate (Figure 2e); however the additional substrate scope was not disclosed.\textsuperscript{11} Subsequently, Mori and Seki reported a Pd-catalyzed coupling of iPr\textsubscript{2}Zn that proceeds (Figure 2f).\textsuperscript{12} Rovis and Zhang have also reported a single case of a high-yielding coupling between an acid fluoride and iPr\textsubscript{2}Zn (Figure 2g).\textsuperscript{13} Also, Liebeskinde-Srogl coupling of thioesters and organoboron nucleophiles proceeds only with primary organoboron reagents despite efforts to extend the reaction to secondary reagents (Figure 2d).\textsuperscript{14} Finally, Reisman reported a general method for the cross-coupling of secondary organozinc reagents and thioesters as well as a mild, chemoselective Ni-catalyzed asymmetric reductive acyl cross-coupling reaction which provides access to a variety of \(\alpha\)-aryl-\(\alpha\)-alkyl ketones in good yields and moderate enantioselectivity (Figure 2h). This reaction is highly convergent and functional group tolerant, which enables the rapid construction of complex ketones from bench stable, easy-to-handle starting materials.\textsuperscript{15} Based upon Reisman’s result, Maulide reported the first enantioconvergent palladium-catalyzed Fukuyama cross-coupling of racemic benzylic organozinc reagents with thioesters (Figure 2i). The reaction furnishes enantioenriched acyclic \(\alpha\)-disubstituted ketone products under mild reaction conditions without racemization of the potentially labile tertiary stereocenters to provide high enantioselectivities.\textsuperscript{16}
Prior works by others:

**a. Harada and Oku, 1991**  
\[ R^1\text{Cl} \xrightarrow{\text{Pd(PPh}_3\text{)}_2 (5 \text{ mol%})} \text{R}^1\text{R}^2 \]  
\[ \text{R}^2\text{ZnI} \]  
57–75% yield  
\( R_1 = \text{alkyl, aryl} \)  
\( R_2 = \text{sec-alkyl} \)

**b. J. R. Falck, 1994**  
(The first example of coupling reaction involving enantiomerically enriched α-(benzoyloxy)-stannanes)

\[ \text{PhCl} + n\text{-C}_7\text{H}_{15}\text{SnBu}_3 \xrightarrow{\text{Pd(PPh}_3\text{)Cl}_2 (4 \text{ mol%}) \text{ CuCN (8 mol%) \text{ Toluene, 75°C}}} \text{n-C}_7\text{H}_{15}\text{OBz} \]  
94% e.e.  
74% yield, 92% e.e., 98% e.s.

**c. Tohru Fukuyama, 1998**

\[ \text{R}_1\text{SOEt} + \text{R}^2\text{ZnI} \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2} \text{R}_1\text{R}^2 \]  

**d. Liebeskind and Srogl, 2000**

\[ \text{R}_1\text{SR}^1 \xrightarrow{\text{Pd}_2(\text{dba})_3 (1 \text{ mol%}) \text{ TFP (3 mol%)} \text{ CuTc (2 equiv) \text{ THF, 50°C, 18h}}} \text{R}_2\text{R}^2 \]  
\( R_2 = \text{aryl} \)  
52–93% yield

**e. Zhang and Wang, 2003**

\[ \text{PhCONa} \xrightarrow{i\text{-PrZnI (1.2 equiv.) \text{ EtCOCl (3 equiv.) \text{ THF, 70°C, 14h}}} \text{PhCH}_3\text{CH}_3 \]  
83% yield

**f. Mori and Seki, 2004**

\[ \text{R}_2\text{SEt} \xrightarrow{i\text{-PrZn (1.0 equiv.) \text{ Zn (2.0 equiv.) \text{ Br}_2 (1.0 equiv.) \text{ Pd/C (5 mol%) \text{ THF, Toluene, DMF}}} \text{R}_3\text{CH}_3 \]  
56% yield

**g. Rovis and Zhang, 2004**

\[ \text{PhOF} \xrightarrow{\text{Ni(COD)}_2 (10 \text{ mol%}) \text{ i-Pr}_2\text{Zn (0.55 equiv.) \text{ pyphos (12mol%) \text{ 4-fluorostyrene (20 mol%) \text{ THF, 23°C, 10 min}}}} \text{PhCH}_3\text{CH}_3 \]  
91% yield
Figure 2. Acyl cross-coupling reactions with secondary organometallic reagents.4-15
Although the first stereospecific Pd-catalyzed reaction of acid chlorides with enantiomerically enriched α-(benzoyloxy)-stannanes was reported over twenty years ago by Falck group (Figure 2b),[17] the Pd-catalyzed cross-coupling reaction between acyl electrophiles and organotin reagents is still relatively unexplored. We therefore decided to investigate the efficiency of palladium-catalyzed reactions of acyl electrophiles and alkylcarbostannatranes. Based upon our successful use of enantioenriched alkyl carbastannatranes in stereospecific arylation reactions, we felt that enantioenriched alkylcarbostannatranes might be similarly applied to stereospecific acylation reactions.

3.2] Reaction Optimization

In our initial exploratory studies, we used the Pd-catalyzed coupling of benzoyl chloride and i-propylcarbostannatran (1) as a model system, and the best conditions of arylation reactions were implemented directly in the acylation reactions. We found that the yield of desired cross-coupling product (2) was only 21% GC yield in the presence of the KF due to the background formation of benzoyl fluoride. Hence, removal of KF solved the byproduct issue easily and the desired product (2) could be generated in 78% GC yield using 5 mol % Pd(dba)$_2$ with 10 mol % Jackiephos alongside two equivalents of CuCl in acetonitrile at 60 °C (Entry 1, Figure 3a).
Figure 3a. Initial optimization of the Pd-Catalyzed Cross-Coupling Reaction of Benzoyl Chloride and i-propylcarbastannatrane (1). Yields and selectivities determined by GC analysis.

No byproducts of isomerization of the secondary alkyl component from β-hydride elimination/reinsertion were observed in these reactions. When i-Pr₄Sn was used in place of carbastannatrane 1, no product 2 was formed. This highlights the unique ability of the carbastannatrane backbone to selectively labilize bulky, inactivated alkyl groups that are typically inert towards transmetallation. With the objective of expanding the synthetic utility of acyl Pd-catalyzed cross-coupling reactions, different phosphine ligands were screened using carbastannatrane 1. Reactions were performed on 0.02 mmol scale using...
different palladium complexes (5 mol %) in 1 mL acetonitrile or other solvents (Figure 3a). The reactions were done under argon atmosphere and were stirred at 60 °C. Ligand (10 mol %) screenings were monitored by gas chromatography and the yield of the desired product (2) was calibrated using tetradecane as the internal standard. After screening different combinations of Pd sources and phosphine ligands, we found that Pd(PPh$_3$)$_4$ (5 mol %) in the absence of additional ligand provided yields similar to the reaction containing a Pd source charged with Jackiephos (Entry 1 and 3, Figure 3a). Though Pd(dba)$_2$ with JackiePhos produced the highest yields, the slight difference in yield did not justify use of the more expensive JackiePhos ligand. Pd(PPh$_3$)$_4$ (2 mol %) with 2 equivalents of CuCl in the absence of additional ligand was found to be the optimal conditions under which reactions should be conducted (Entry 1, Figure 3b). The use of CuCl as a co-transmetallating reagent is essential to the success of this reaction (Entry 2, Figure 3a).$^{18}$ Therefore, these reactions were also screened in the presence of different Cu (I) salts (Figure 3b).
Figure 3b. Screening two equivalents of different Cu (I) salts (Yields and selectivities determined by GC analysis).

Using the optimized conditions, the scope of the reactions was examined using different electrophiles and nucleophiles on a larger scale (0.3 mmol) (Figure 4). We found that acyl chlorides bearing heteroaryl groups could be efficiently employed as electrophiles. Inclusion of an ortho-methyl substituent on benzyol chloride had little impact on the reaction. Acyl chlorides bearing alkyl groups underwent coupling (9 and 10, Figure 4) without evidence of alkyl isomerization via decarbonylation/β-hydride
elimination/reinsertion/re-carbonylation sequences. Chloro-substituted arenes were also well tolerated under these reaction conditions, which should enable cross-coupling products such as 4 and 5 to be further modified using existing cross-coupling technologies. In regards to the nucleophilic component, use of unactivated primary and unactivated secondary alkylcarbostannatranes was tolerated under the standard reaction conditions. No isomerization of the secondary alkyl nucleophiles was observed in these reactions. In addition to revealing the optimal reaction conditions, the results from the screens indicate the potential of using Pd(dba)$_2$ and JackiePhos for particularly unactivated substrates. Because of the special features of JackiePhos to facilitate the transmetallation and reductive elimination, it is reasonable to expect the better results from Pd(dba)$_2$/JackiePhos than Pd(PPh$_3$)$_4$. For example, the synthesis of compounds 15a and 15b using $t$-butylcarbostannatrane required the use of JackiePhos of the ligand. These examples constitute the first instances of $t$-butyl transfer from an alkylstannane in a cross-coupling reaction. With Pd(PPh$_3$)$_4$ (5 mol %), we observed significant isomerization of $t$-butyl to $i$-butyl. The use of bulky biarylphosphine ligand JackiePhos completely suppressed isomerization and increased the yields.
**Figure 4.** Pd-Catalyzed Cross-Coupling Reactions of Alkylcarbastannatranes and Acyl Chlorides

3.3] **Cross couplings of enantioenriched alkylcarbastannatranes**

Enantioenriched acyclic α,α'-disubstituted carbonyl compounds are versatile synthetic intermediates for the synthesis of natural products and pharmaceutical chemicals. Due to their ubiquity and utility, the development of new synthetic methods to prepare such compounds has been the subject of intense research. Recently, the Reisman group has generated acyclic α,α-disubstituted ketones in good yields and with high enantioselectivity via a Ni-catalyzed asymmetric reductive cross-coupling reaction of acid chlorides and racemic secondary benzyl chlorides using a Ni^{II}/(R,R)-diphenyl-BOX catalyst in the presence of Mn^0 as a stoichiometric reductant (Figure 5). However, no example
of the Pd-catalyzed cross-coupling reactions of unactivated enantioenriched tin nucleo-
philes with acyl electrophiles has been previously reported.

![Figure 5](image)

**Figure 5.** Catalytic Asymmetric Reductive Acyl Cross-Coupling reactions by the Reisman group.

We explored the use of enantioenriched alkylcarbostannatrane in Pd-catalyzed cross-coupling reactions with acyl chlorides. Using these nucleophiles, secondary alkyl groups underwent transmetallation to palladium with excellent retention of configuration when an optically active secondary alkyl carbastannatrane was employed. While we initially disclosed the use of optically active alkylcarbostannatrane reagents (16) in stereospecific arylation reactions, enantioenrichment of optically active alkylcarbas-
tannatrane reagents was achieved only via asymmetric lithiation/stannylation or via preparative HPLC separation of racemates. To address this limitation, we have developed a method to prepare enantioenriched alkylcarbostannatranes via the \( S_N^2 \) reaction of lithium...
carbastannatane\textsuperscript{21} and enantioenriched secondary alkyl mesylates (Figure 6). This reaction should significantly expand the accessibility of inactivated, enantioenriched alkyl-carbastannatranes for potential use in stereospecific reactions. Herein we implemented the unactivated, enantioenriched alkyl carbastannatranes coupled with acyl electrophiles. The substrates scope is shown in Figure 6.

**Figure 6.** Stereospecific Pd-catalyzed couplings of enantioenriched alklycarbastannatranes and acyl chlorides.

When unactivated, enantioenriched, secondary alkylcarbastannatranes 16\textsuperscript{a} and 16\textsuperscript{b} were employed in cross-coupling reactions with acyl chlorides, the corresponding products were obtained with near perfect enantiospecificity (% es)\textsuperscript{22} for most substrates (Figure 6). This constitutes the first demonstration of a stereospecific, metal-catalyzed acylation reaction using a stable, unactivated, enantioenriched nucleophile. Consistent
with our arylation reactions in second chapter\textsuperscript{23}, this process proceeds with net retention of absolute configuration. In seminal studies conducted by Falck and others, stereospecific couplings of enantioenriched alkyltin nucleophiles and acid chlorides were limited to use of specific classes of activated alkyltin nucleophiles.\textsuperscript{24} To evaluate stereoelectronic influences of the nucleophile on stereospecificity in the present system, we also studied the use of electronically activated enantioenriched carbastannatranes (16c and 16d) in these cross-coupling reactions. 16c and 16d both underwent cross-coupling reactions with exceptionally high stereofidelity. Therefore, electronic perturbations of the C(\(sp^2\)) \(\alpha\)-carbon or strongly coordinating \(\beta\)-carbonyl nucleophiles do not appear to influence stereospecificity in this process. Retrosynthetically, products 17-24 constitute formal asymmetric alkylation reactions of enolates, whereas 25 and 26 constitute formal asymmetric arylation reactions of enolates. It is noteworthy that the mild conditions employed in this process are not conducive to racemization of the enantioenriched product, even with an \(\alpha\)-aryl substituent present. The combined results of Figures 4 and 6 suggest that the nucleophilic scope of this reaction is quite broad. Primary, secondary, and tertiary alkylcarbastannatranes may be successfully employed in acylation reactions. Activated and inactivated secondary alkylcarbastannatranes all undergo highly efficient stereospecific cross-coupling reactions using identical conditions. Oxygen-containing nucleophiles could also be readily employed. Unfortunately, carbastannatranes bearing nitrogen-containing groups (e.g., piperidine and pyrrolidine derivatives) were largely unsuccessful in these reactions. This appears to be the major limitation of the present system.

As previously mentioned, thioesters are more stable and more easily handled than their corresponding acid chlorides. Inspired by Falck and Liebeskind’s research on
copper(I) mediated thioester-organostannane cross-coupling reactions, \(^2\)\(^5\) we investigated the use of thioesters as acyl electrophiles in stereospecific cross-coupling reactions. \(^2\)\(^6\) Using the standard conditions with 2 mol \% \(\text{Pd(PPh}_3\text{)}_4\) alongside 2 equivalents of \(\text{CuCl}\), or with stoichiometric \(\text{CuTc}\) (Copper(I) thiophene-2-carboxylate) in the absence of palladium, we successfully performed the cross-coupling reactions of para-substituted S-phenyl benzothioates with alkylcarbastannatranes. Reactions using \(\text{CuTc}\) resulted in acceptable yields of cross-coupling products (Figure 7a). Using both conditions, we conducted cross-coupling reactions of (S)-16b and thioester 27. Each reaction resulted in relatively high yield and respectable stereofidelity (Figure 8). Therefore, enantioenriched products from cross-coupling reactions involving a thioester and stoichiometric \(\text{CuTc}\) (without palladium) could still be generated in reasonable yields (Figure 7b). Since non-racemic thioesters can be readily prepared from enantioenriched a-chiral carboxylic acids, we felt that such thioesters might be effective substrates for diastereospecific reactions, forming optically active a,a’-disubstituted ketones with complete reagent control of stereochemistry. Using the thioester of (S)-Naproxen (28), we successfully generated syn-29 and anti-29 from stereospecific reactions with (R)-16a and (S)-16a, respectively. The products of these reactions completely retained the stereochemistry of their original coupling partners (Figure 8).
Figure 7a. Cross-coupling reactions of alkyl carbastannatranes and thioesters. \(^a\) Yields determined by GC analysis. \(^b\) Average isolation yields in two runs.

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<td>5</td>
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<tr>
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Figure 7b. Screening of alkyl carbastannatranes and thioesters. \(^a\) Yields determined by GC analysis.
3.4] Conclusion

In summary, we have found that carbastannatranes facilitate the transmetallation of unactivated primary, secondary, and tertiary alkyl units in Pd-catalyzed cross-coupling reactions with acyl electrophiles. Using an array of isolable, optically active, secondary alkylcarbastannatranes, we have developed a stereospecific process to access enantioenriched α-substituted ketones from acyl electrophiles. This process represents the first stereospecific cross-coupling reactions of unactivated alkyltin nucleophiles and acyl electrophiles. More importantly, because the stereochemistry of the resulting products is

Figure 8. Stereospecific cross-coupling reactions of enantioenriched carbastannatranes and thioesters.
entirely reagent controlled, this process constitutes an alternative, predictable synthetic route to asymmetric enolates. These reactions occur with outstanding stereofidelity and with retention of the absolute configuration. We have additionally shown that the carba-stannatranne backbone facilitates the transfer of $t$-butyl groups in Pd-catalyzed cross-coupling reactions. This represents the first example of the selective transfer of an inactivated tertiary alkyl group from tin (15a and 15b) and suggests that the stereospecific formation of quaternary centers may be possible from enantioenriched tertiary alkylcar-bastannatranes.

3.5] Experimental data

General Reagent Information

BDH brand ethyl ether was purchased from VWR. EMD brand Omnisolv THF (unstabilized) was also purchased from VWR. These solvents were transferred to separate 20 L solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina. $s$-BuLi (1.4 M in cyclohexane) and isopropylmagnesium chloride (2.0 M in ether) were purchased from SigmaAldrich. 5-Chloro-1-aza-5-stannabicyclo[3.3.3]undecane was purchased from SigmaAldrich or prepared via the method of Vedejs.27 Pd(PPh$_3$)$_4$ was purchased from Strem. Anhydrous acetonitrile (Sigma-Aldrich) was purged with argon prior to use. Grignard reagents were prepared from their corresponding alkyl chlorides or bromides using a literature procedure.28 Thioesters were prepared from their corresponding carboxylic acids or acyl chlorides using a litera-
ture procedure. Molarities of Grignard reagents were determined using iodine titration. Reagents and solvents were used as received unless otherwise noted. Flash chromatography was performed using Silicycle silica gel (ultra pure grade). Reverse-phase chromatography was performed using C18 silica gel from Silicycle (17% carbon, 40-63 mm) or from Acros (23% carbon, 40-63 mm).

**General Analytical Information**

All compounds were characterized by $^1$H NMR and $^{13}$C NMR spectroscopy. Copies of the $^1$H and $^{13}$C spectra for all new compounds can be found at the end of the Supporting Information. All previously unreported compounds were additionally characterized by high resolution MS. Nuclear Magnetic Resonance spectra were recorded on a Bruker 300 or Varian 500 MHz instrument. All $^1$H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm). All $^{13}$C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), and were obtained with $^1$H decoupling. High resolution MS analyses were performed on an Agilent 6520 Q-TOF instrument. All GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase, or using a 30 m x 0.32 mm chiral column (Rt®-βDEXsm from Restek). All GC yields were calibrated using dodecane or tetradecane as an internal standard. Chiral HPLC analyses were performed on a Shimadzu Prominence HPLC system with binary mobile phase pumps and UV-vis detector (LC-20AB, SPD-20A) using an OJ-RH (4.6 mm x 150 mm; particle size: 5 µm) chiral column (Daicel Chemical Ind., Ltd), an IA-3 (4.6 mm x 150 mm; particle size: 3 µm) chiral column (Daicel Chemical Ind., Ltd), or an IA (4.6 mm x 150 mm;
particle size: 5 μm) chiral column (Daicel Chemical Ind., Ltd). VCD analysis was performed by BioTools, Inc (Jupiter, Fl). Preparative HPLC separations were performed by Chiral Technologies, Inc. Thin layer chromatography was performed using EMD millipore normal phase silica-coated glass plates (F254, #105715), or using EMD millipore reverse phase silica-coated glass plates (F254-S, #105560).

**Procedural Information**

*General procedure A for the preparation of racemic secondary alkylcarbostannatranes.*

All reactions were performed in oven-dried glassware under an atmosphere of Ar. sec-Alkyllithium, sec-alkylmagnesium or sec-alkylzinc reagents (1.5–3.0 equiv) were added to the suspension of 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane\(^{26}\) (1 equiv) in anhydrous solvent at -78 °C. The resulting mixture was stirred at -78 °C for 3 h, allowed to warm to room temperature, and stirred overnight. The reaction mixture was poured into a separatory funnel containing a mixture of water and ether. The organic layer was separated, washed with brine, dried over Na\(_2\)SO\(_4\), and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude secondary alkyl tin reagents were used without purification, or following purification via Kugelrohr distillation or C18 chromatography. Homocoupling from Grignard formation constituted the major residual byproduct in the crude product.

*General procedure B for cross-coupling reactions.*

Pd(PPh\(_3\))\(_4\) (2 mol %) and CuCl (2 equiv) were weighed out on the benchtop in an oven-dried test tube with stir bar. With stirring begun, the septum screw top tube was evacuat-
ed (80 mTorr) and backfilled three times with argon using a needle attached to a vacuum manifold. The tin reagent (1.1 equiv) and acyl chloride (1 equiv) were then added to the test tube via microsyringe, followed by degassed CH$_3$CN (1 mL for 0.3 mmol scale). If the acyl chloride was a solid, it was weighed out on the benchtop alongside the other solids. The tube was sealed using electrical tape, and heated to 60 °C for 12 h. The reaction mixture was cooled to rt, diluted with ether, and washed with brine. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated to provide the crude product. The crude product was purified by column chromatography.

**General procedure C for cross-coupling reactions with heterocyclic acyl chlorides.**
Pd(PPh$_3$)$_4$ (2 mol %) and CuCl (2 equiv) were weighed out on the benchtop in an oven-dried Schlenk tube with stir bar. With stirring begun, the Schlenk tube was evacuated (80 mTorr) and backfilled three times with argon using a needle attached to a vacuum manifold. The tin reagent (1.1 equiv) and acyl chloride (1 equiv) was then added to the Schlenk tube via microsyringe, followed by degassed CH$_3$CN (1 mL for 0.3 mmol scale). If the acyl chloride was a solid, it was weighed out on the benchtop alongside the other solids. The Schlenk tube was sealed with a Teflon stopper, and heated to 60 °C for 12 h. The reaction mixture was cooled to rt, diluted with ether, and washed with brine. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated to provide the crude product. The crude product was purified by column chromatography.

**General procedure D for cross-coupling reactions with t-butyl carbastannatrane.**
Pd(dba)$_2$ (5 mol %), Jackiephos (10 mol %), CuCl (2 equiv), and t-butyl carbastannatrane (1.1 equiv) were weighed out on the benchtop into an oven-dried Schlenk tube with stir
bar. With stirring begun, the Schlenk tube was evacuated (80 mTorr) and backfilled three times with argon using a needle attached to a vacuum manifold. The acyl chloride (1 equiv) was then added to the Schlenk tube via microsyringe, followed by degassed CH$_3$CN (1 mL for 0.3 mmol scale). If the acyl chloride was a solid, it was weighed out on the benchtop alongside the other solids. The Schlenk tube was sealed with a Teflon stopper, and heated to 60 °C for 12 h. The reaction mixture was cooled to rt, diluted with ether, and washed with brine. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated to provide the crude product. The crude product was purified by column chromatography.

**General procedure E for cross-coupling reactions with thioesters.**

Pd(PPh$_3$)$_4$ (2-5 mol %), CuCl (2 equiv), and thioester (1 equiv) were weighed out on the benchtop into an oven-dried Schlenk tube with stir bar. With stirring begun, the Schlenk tube was evacuated (80 mTorr) and backfilled three times with argon using a needle attached to a vacuum manifold. The tin reagent (1.1 equiv) was then added to the Schlenk tube via microsyringe, followed by degassed CH$_3$CN (1 mL for 0.2 or 0.3 mmol scale). The Schlenk tube was sealed with a Teflon stopper, and heated to 60 °C for 12 h. The reaction mixture was cooled to rt, diluted with ethyl acetate, and washed with brine. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated to provide the crude product. The crude product was purified by column chromatography.

**General procedure F for the preparation of optically active secondary alkylcarbas-tannatranes**.

To an oven dried round bottom flask with stirbar, 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (588 mg, 2 mmol) and naphthalene (128 mg, 1 mmol) were
added. The flask was evacuated (<100 mtorr) and backfilled with argon three times. With the flask under a flow of argon, the septum was removed and lithium granules (free of oil) were added (250 mg, 35 mmol). This was followed by two additional evacuation/backfill cycles. Anhydrous THF (40 mL) was added to the flask via syringe, and the mixture was stirred at room temperature. The solution turned dark green/black within 30 min. Upon color change, the solution was stirred at room temperature for an additional hour. In a separate 100 mL flask under argon, with stirbar and rubber septum, the optically active alkyl mesylate (1.2–1.5 equiv) was dissolved in anhydrous THF (20 mL). The mesylate solution was heated to 60 °C. The stannatrane lithium mixture was removed from the excess lithium via cannula or needle/syringe, and transferred dropwise to the mesylate solution over 5 mins. The reaction stirred at 60 °C for an additional hour. The reaction mixture was extracted with ethyl ether (60 mL), followed by brine (100 mL), and dried over Na₂SO₄. The reaction solution was filtered and concentrated to provide the crude product. The crude product was purified (40–50% isolated yield) by C18 silica (80/20 acetonitrile/water to 100% acetonitrile), fractions analyzed using HPLC (220/254 nm) or reverse-phase TLC.
Additional optimization experiments

![Chemical structure](image)

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N-Heterocyclic carbastannatranes that failed in cross-coupling reactions

![Chemical structures](image)

Compound Characterization

5-(sec-Butyl)-1-aza-5-stannabicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (2.94 g, 10.0 mmol) in ether (40 mL) and s-BuLi (1.4 M in cyclohexane, 15 mL, 21 mmol). A yellow oil (3.18 g, 99%) was isolated. ¹H NMR (500 MHz, CDCl₃) δ: 2.35 (t, J = 6 Hz, 6H), 1.64 (app. quint, J = 6 Hz, 6H), 1.41-1.51 (m, 3H), 1.05 (d, J = 7.5 Hz, 3H), 0.86 (t, J = 7 Hz, 3H),
0.63 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 55.0, 29.4, 26.7, 23.7, 18.5, 14.8, 5.7 ppm.

(R)- and (S)-5-(sec-Butyl)-1-aza-5-stannabicyclo[3.3.3]undecane. The general procedure F was employed using (S)-(sec-butyl) mesylate or (R)-(sec-butyl) mesylate (430 µL, 3 mmol). A pale yellow oil (40–50%) was isolated. Enantiomeric excess of product ranged from 91–99% ee (determined by derivatization with 4-bromoanisole or 4-bromobenzotrifluoride – see page 21 of SI).

![5-(iso-Propyl)-1-aza-5-stannabicyclo[3.3.3]undecane](image)

5-(iso-Propyl)-1-aza-5-stannabicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1.47 g, 5.0 mmol) in ether (20 mL) and isopropylmagnesium chloride (2.0 M in ether, 7.5 mL, 15 mmol). A yellow oil (1.41 g, 95%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ: 2.38 (t, $J = 6$ Hz, 6H), 1.67 (app. quint, $J = 6$ Hz, 6H), 1.09 (d, $J = 7.5$ Hz, 6H), 0.70-0.76 (m, 1H), 0.65 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 54.9, 23.6, 21.6, 17.7, 4.6 ppm.

![5-(Tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane](image)

5-(Tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.88 g, 3.0 mmol) in THF (30 mL) and (tetrahydro-2H-pyran-4-yl)magnesium chloride (0.62 M
in THF, 7 mL, 4.3 mmol). A pale yellow solid (983 mg, 95%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 3.87 (m, 2H), 3.33 (dt, $J = 11$, 2 Hz, 2H), 2.36 (t, $J = 6$ Hz, 6H), 1.64 (app. quint, $J = 6$ Hz, 6H), 1.50-1.55 (m, 4H), 0.89-0.95 (m, 1H), 0.64 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 71.0, 54.8, 31.3, 26.0, 23.4, 4.6 ppm.

5-(4-Phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. $^{32}$ General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1.65 g, 5.6 mmol) in THF (50 mL) and (4-phenylbutan-2-yl)magnesium chloride (0.28 M in THF, 23 mL, 6.4 mmol). A pale yellow oil (1.74 g, 79%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.25-7.28 (m, 2H), 7.16-7.19 (m, 3H), 2.50-2.65 (m, 2H), 2.36 (t, $J = 6$ Hz, 6H), 1.76-1.81 (m, 1H), 1.65 (app. quint, $J = 6$ Hz, 6H), 1.23-1.39 (m, 1H), 1.13 (d, $J = 7.5$ Hz, 3H), 0.79 (quart, $J = 7.5$ Hz, 1H), 0.67 (t, $J = 6.5$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 143.9, 128.6, 128.3, 125.5, 54.9, 39.0, 36.5, 24.2, 23.6, 18.6, 5.6 ppm.

(S)-5-(4-Phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (16b). General procedure F was employed using (R)-(4-phenylbutan-2-yl)mesylate (500 $\mu$L, 2.4 mmol). A pale yellow oil (320 mg, 40%) was isolated. Enantiomeric excess of product ranged from 91–99% ee between different runs. Enantiomers could also be separated on a preparative scale using a Chiralpak OJ-H column with a 95:5 methanol:water eluent.
Ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (16c). General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.88 g, 3.0 mmol) in DMF (8 mL) and (4-ethoxy-4-oxobutan-2-yl)zinc iodide (0.61 M in DMF, 10 mL, 6.1 mmol). An orange oil (509 mg, 45%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ: 4.09 (quart, $J$ = 7 Hz, 2H), 2.39-2.43 (m, 1H), 2.35 (t, $J$ = 6 Hz, 6H), 2.23-2.27 (m, 1H), 1.64 (app. quint, $J$ = 6 Hz, 6H), 1.24 (t, $J$ = 7 Hz, 3H), 1.02-1.13 (m, 4H), 0.65 (t, $J$ = 6.5 Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 175.5, 60.0, 54.9, 40.7, 23.5, 19.8, 18.4, 14.6, 5.2 ppm. Enantiomers were separated on a preparative scale using a Chiralpak OJ-H column with a 100:0.1 hexane:IPA eluent.

5-(3-Phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (294 mg, 1 mmol) in THF (5 mL) and 3-phenylpropylmagnesium chloride (0.31 M in THF, 10 mL, 3.1 mmol). A yellow oil (189 mg, 50%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.27-7.14 (m, 5H), 2.53 (t, $J$ = 7.5 Hz, 2H), 2.36 (t, $J$ = 6.2 Hz, 6H), 1.69 (quint, $J$ = 6 Hz, 2H), 1.62 (app. quint, $J$ = 6 Hz, 6H), 0.64 (t, $J$ = 6 Hz, 6H), 0.48 (t, $J$ = 6.0 Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 143.6, 128.7, 128.3, 125.5, 54.9, 41.5, 29.9, 23.6, 16.4, 6.8 ppm. HRMS (ES$^+$): Calcd ($^{116}$Sn) (M-Na)$^+$ 394.1246; Found ($^{116}$Sn) 394.1251.
5-(1-Phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane (16d). General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (206 mg, 0.7 mmol) in THF (5 mL), and 1-phenylethyl magnesium chloride (0.21 M in THF, 10 mL, 2.1 mmol). A pale yellow oil (100 mg, 38%) was isolated and stored under argon. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.17-6.87 (m, 5H), 2.32 (t, $J$ = 6 Hz, 6H), 2.03-1.70 (m, 3H), 1.61 (app. quint, $J$ = 6 Hz, 6H), 0.92 (t, $J$ = 7.5 Hz, 3H), 0.61 (t, $J$ = 6 Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 149.8, 128.0, 125.8, 121.8, 54.8, 43.0, 25.0, 23.6, 15.5, 5.9 ppm. HRMS (ES$^+$): Calcd $^{116}$Sn (M-Na)$^+$ 402.1220; Found $^{116}$Sn 402.1226. Enantiomers were separated on a preparative scale using a Chiralcel OJ-H column with a 95:5 methanol:water eluent.

5-(tert-Butyl)-1-aza-5-stannabicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (588 mg, 2.0 mmol) in THF (20 mL) and t-butyl lithium (1.4 M in ether, 4.3 mL, 6 mmol). A pale yellow solid (0.35 g, 56%) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ: 2.35 (t, $J$ = 6 Hz, 6H), 1.65 (app. quint, $J$ = 6 Hz, 6H), 0.92 (s, 9H), 0.63 (t, $J$ = 6 Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 54.8, 30.3, 23.7, 4.2 ppm.
1-(Furan-2-yl)-4-phenylbutan-1-one (3). General procedure C was employed using 2-furoyl chloride (39 mg, 0.3 mmol) and 5-(3-phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane (125 mg, 0.33 mmol). A yellow liquid (86 mg, 89%) was isolated by column chromatography (90:10 pentane/MTBE). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.57-7.56 (dd, $J = 1.8$, 3 Hz, 1H), 7.29-7.13 (m, 6H), 6.52-6.51 (dd, $J = 1.8$, 3 Hz, 1H), 2.84 (t, $J = 7.5$ Hz, 2H), 2.71 (t, $J = 7.5$ Hz, 2H), 2.06 (q, $J = 7.5$ Hz, 2H) ppm.

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.6, 153.0, 146.4, 141.8, 128.7, 128.6, 126.2, 117.1, 112.3, 37.9, 35.4, 25.9 ppm. HRMS (ES$^+$): Calcd (M-Na)$^+$ 237.0891; Found 237.0894.

Phenyl(tetrahydro-2H-pyran-4-yl)methanone (13). General procedure B was employed using benzoyl chloride (42 mg, 0.3 mmol) and 5-(tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (113 mg, 0.33 mmol). A white solid (52 mg, 91%) was isolated by column chromatography (94:6 hexanes/ether). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.96-7.93 (m, 2H), 4.09-4.03 (m, 2H), 3.61-3.45 (m, 3H), 1.96-1.76 (m, 4H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 201.80, 135.80, 133.10, 128.80, 128.30, 67.30, 42.60, 29.10 ppm.
1-(Benzo[b]thiophen-2-yl)-2-methylpropan-1-one (7). General procedure C was employed using benzo[b]thiophene-2-carbonyl chloride (55 mg, 0.3 mmol) and 5-(iso-propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (100 mg, 0.33 mmol). A yellow liquid (42 mg, 68%) was isolated by column chromatography (95:5 hexanes/ether). $^1$H NMR (300 MHz, CDCl$_3$): 7.97 (s, 1H), 7.91-7.86 (m, 2H), 7.49-7.38 (m, 2H), 3.60 – 3.46 (septet, $J$ = 7 Hz, 1H), 1.31-1.29 (d, $J$ = 6 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.2, 143.3, 142.7, 139.43, 128.8, 127.5, 126.1, 125.2, 123.2, 37.3, 19.7 ppm. HRMS (ES$^+$): Calcd (M-Na)$^+$ 227.0507; Found 227.0527.

![Structure of 1-(Benzo[b]thiophen-2-yl)-2-methylpropan-1-one (7)](image)

1-(Benzofuran-2-yl)-2-methylpropan-1-one (8). General procedure C was employed using benzofuran-2-carbonyl chloride (54 mg, 0.3 mmol) and 5-(iso-propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (100 mg, 0.33 mmol). A yellow liquid (38 mg, 68%) was isolated by column chromatography (95:5 hexanes/ether). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.71 (d, $J$ = 9 Hz, 1H), 7.59 (dd, $J$ = 1, 9 Hz, 1H), 7.52 (d, $J$ = 1 Hz, 1H), 7.47 (dt, $J$ = 3, 5 Hz, 1H), 7.33 – 7.28 (m, 1H), 3.48 (heptet, $J$ = 6.5 Hz, 1H), 1.28 (d, $J$ = 6 Hz, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 195.5, 155.6, 152.1, 128.1, 127.1, 123.8, 123.2, 112.8, 112.5, 36.7, 18.8 ppm.

![Structure of 1-(Benzofuran-2-yl)-2-methylpropan-1-one (8)](image)
2-Methyl-1-(o-toly)butan-1-one (12). General procedure C was employed using o-toluoyl chloride (46 mg, 0.3 mmol) and 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (104 mg, 0.33 mmol). A yellow liquid (47 mg, 89%) was isolated by column chromatography (99:1 hexanes/ether). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.54-7.22 (m, 4H), 3.25-3.14 (hex, $J$ = 6.6 Hz, 1H), 2.44 (s, 3H), 1.89-1.75 (m, 1H), 1.53-1.39 (m, 1H), 1.18 (d, $J$ = 6 Hz, 3H), 0.95 (t, $J$ = 7.5 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 209.3, 139.3, 137.8, 130.9, 127.8, 125.7, 45.8, 26.4, 21.0, 16.4, 12.0 ppm. HRMS (ES$^-$): Calcd (M-Na)$^-$ 199.1099; Found 199.1113.

(S)-2-Methyl-1-(o-toly)butan-1-one (18). General procedure C was employed using o-toluoyl chloride (31 mg, 0.2 mmol) and 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (68 mg, 0.22 mmol, 99% ee). A yellow liquid (27.5 mg, 78%, 99% ee) was isolated by column chromatography. [$\alpha$]$_{20}$D (c 1.00, CHCl$_3$) = +12.4º. % ee was determined using an OJ-RH (150x4.6) HPLC column with a 55%:45% methanol:water eluent.
3-Methyl-1-phenylheptan-4-one (9). General procedure B was employed using butyryl chloride (32 mg, 0.3 mmol) and 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (129 mg, 0.33 mmol). A colorless oil (48 mg, 79%) was isolated by column chromatography (94:6 hexanes/ether). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.31-7.15 (m, 5H), 2.60-2.37 (m, 5H), 2.00 (m, 1H), 1.69-1.53 (m, 3H), 1.13-1.10 (d, \(J = 9\) Hz, 3H), 0.91 (t, \(J = 7.5\) Hz, 3H) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 214.7, 142.0, 128.61, 128.58, 126.1, 45.9, 43.3, 34.7, 33.7, 17.3, 16.7, 14.0 ppm. HRMS (ES\(^+\)): Calcd (M-Na)\(^+\) 227.1412; Found 227.1416.

![3-Methyl-1-phenylheptan-4-one](image)

2,4-Dimethyl-6-phenylhexan-3-one (10). General procedure B was employed using isobutyryl chloride (32 mg, 0.3 mmol) and 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (129 mg, 0.33 mmol). A yellow oil (55 mg, 89%) was isolated by column chromatography (94:6 hexanes/ether). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.31-7.15 (m, 5H), 2.76-2.67 (m, 2H), 2.59-2.53 (m, 2H), 2.06-1.94 (m, 1H), 1.68-1.55 (m, 1H), 1.12-1.05 (m, 9H) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 218.3, 142.1, 128.61, 128.55, 126.1, 44.1, 39.8, 34.8, 33.8, 18.62, 18.59, 17.10 ppm. HRMS (ES\(^+\)): Calcd (M-H)\(^+\) 205.1592; Found 205.1594.

![2,4-Dimethyl-6-phenylhexan-3-one](image)
**(S)**-2,4-Dimethyl-6-phenylhexan-3-one (20). General procedure B was employed using isobutyryl chloride (21.3 mg, 0.2 mmol) and **(S)**-5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (86 mg, 0.22 mmol, 98% ee). A yellow oil (35 mg, 85%, 91% ee) was isolated by column chromatography (94:6 hexanes/ether). \([a]^{20}\text{D}(\text{c} 1.00, \text{CHCl}_3) = +15.7^\circ\). % ee was determined using an IA (250x4.6) HPLC column with a 65%:35% [19:1 v/v methanol/acetonitrile]:water eluent.

![Chemical structure of (S)-2,4-Dimethyl-6-phenylhexan-3-one](image)

1-(3-Chlorophenyl)-2-methylpropan-1-one (5). General procedure B was employed using 3-chlorobenzoyl chloride (53 mg, 0.3 mmol) and 5-(iso-propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (100 mg, 0.33 mmol). A yellow liquid (47 mg, 86%) was isolated by column chromatography (95:5 hexanes/ether). \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\) 7.92 (t, \(J = 1.8\) Hz, 1H), 7.83-7.80 (m, 1H), 7.53-7.52 (m, 1H), 7.41 (t, \(J = 8.0\) Hz, 1H), 3.49 (sept, \(J = 6.8\) Hz, 1H), 1.21 (d, \(J = 6.8\) Hz, 6H) ppm. \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): 203.3, 138.0, 135.0, 132.8, 130.0, 128.5, 126.4, 35.7, 19.1 ppm.

![Chemical structure of 1-(3-Chlorophenyl)-2-methylpropan-1-one](image)

1-(4-Chlorophenyl)-2-methylpropan-1-one (4). General procedure B was employed using 4-chlorobenzoyl chloride (53 mg, 0.3 mmol) and 5-(iso-propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (100 mg, 0.33 mmol). A yellow liquid (44 mg, 81%) was isolated by column chromatography (94:6 hexanes/ether). \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\)
7.89 (d, $J = 9$ Hz, 2H), 7.43 (d, $J = 9$ Hz, 2H), 3.50 (septet, $J = 7$ Hz, 1H), 1.21 (d, $J = 9$ Hz, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 203.2, 139.2, 134.5, 129.7, 128.9, 35.4, 19.1 ppm.

1-(Benzo[d][1,3]dioxol-5-yl)-2-methylpropan-1-one (6). General procedure B was employed using piperonyloyl chloride (55 mg, 0.3 mmol) and 5-(iso-propyl)-1-aza-5-stannabicyclo[3.3.3]undecane (100 mg, 0.33 mmol). A yellow liquid (55.3 mg, 96%) was isolated by column chromatography (90:10 pentane/MTBE). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.49 (dd, $J = 8.1$, 1.7 Hz, 1H), 7.37 (d, $J = 1.7$ Hz, 1H), 6.78 (d, $J = 8.3$ Hz, 1H), 5.97 (s, 2H), 3.39 (sept, $J = 6.8$ Hz, 1H), 1.12 (d, $J = 6.9$ Hz, 6H); ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 202.6, 151.5, 148.2, 131.0, 124.3, 108.3, 107.9, 101.8, 35.1, 19.4 ppm.

Benzo[b]thiophen-2-yl(tetrahydro-2H-pyran-4-yl)methanone (14). General procedure C was employed using benzo[b]thiophene-2-carbonyl chloride (55 mg, 0.3 mmol) and 5-(tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (113 mg, 0.33 mmol). A pale yellow solid (51 mg, 69%) was isolated by column chromatography (97:3 hexanes/ether). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.99 (s, 1H), 7.91-7.87 (m, 2H), 7.51-7.39 (m, 2H), 4.13-4.07 (m, 2H), 3.63-3.44 (m, 3H), 2.06-1.84 (m, 4H) ppm. $^{13}$C NMR (75
196.2, 142.6, 142.5, 139.1, 128.80, 127.5, 125.9, 125.1, 123.0, 67.2, 44.2, 29.3 ppm. HRMS (ES$^+$): Calcd (M-Na)$^+$ 269.0612; Found 269.0615.

General procedure D was employed using 4-methoxybenzoyl chloride (51 mg, 0.3 mmol) and 5-(tert-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (104 mg, 0.33 mmol). A colorless liquid (24 mg, 42%) was isolated by column chromatography (90:10 hexanes/ether). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.85 (d, $J = 9.0$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 2H), 3.85 (s, 3H), 1.37 (s, 9H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 206.3, 162.0, 131.0, 130.1, 113.2, 55.4, 43.9, 28.4 ppm.

General procedure B was employed using 2-naphthoyl chloride (57 mg, 0.3 mmol) and 5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (104 mg, 0.33 mmol). An orange liquid (48 mg, 75%) was isolated by column chromatography (93:7 hexanes/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.47 (s, 1H), 8.06-7.87 (m, 4H), 7.57 (quintet, $J = 3$, 7.5 Hz, 2H), 3.58 (sextet, $J = 7.2$ Hz, 1H), 1.97-1.83 (m, 1H), 1.63–1.50 (m, 1H), 1.26 (d, $J = 6$ Hz, 3H), 0.96 (t, $J = 6$ Hz,
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 204.7, 135.7, 134.4, 132.8, 129.8, 129.7, 128.7, 128.5, 128.0, 126.9, 124.5, 42.4, 27.1, 17.2, 12.1 ppm.

**2,2-Dimethyl-1-(naphthalen-2-yl)propan-1-one (15a).** General procedure D was employed using 2-naphthoyl chloride (57 mg, 0.3 mmol) and 5-(tert-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (104 mg, 0.33 mmol). A pale yellow solid (44 mg, 69%) was isolated by column chromatography (95:5 hexanes/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.24 (s, 1H), 7.93-7.77 (m, 4H), 7.59-7.51 (m, 2H), 1.43 (s, 9H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 209.2, 136.0, 134.5, 132.6, 129.3, 128.7, 128.0, 127.9, 126.8, 125.1, 124.22, 44.6, 28.4 ppm.

$^{1}$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.71 (d, $J = 7.5$ Hz, 1H), 7.60-7.44 (m, 3H), 7.31 (dt, $J = 3$, 7.5 Hz, 1H), 3.32 (sextet, $J = 6.6$ Hz, 1H), 1.94-1.82 (m, 1H), 1.63-1.49 (m, 1H), 1.25 (d, $J = 6$ Hz, 3H), 0.96 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C
NMR (75 MHz, CDCl$_3$): 195.50, 155.63, 152.11, 128.07, 127.10, 123.83, 123.20, 112.80, 112.45, 36.70, 18.79 ppm. HRMS (ES$^+$): Calcd (M-H)$^+$ 203.1072; Found 203.1072.

1,4-Diphenyl-2-methyl-1-butanone (19). General procedure B (acyl chloride) was employed using benzoyl chloride (17 mg, 0.1 mmol) and (S)-5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (43 mg, 0.11 mmol, 99% ee). A colorless oil (18.5 mg, 78%, 99% ee) was isolated by column chromatography (95:5 hexanes/ether). $[^{[a]}]^{20}$D (c 1.00, CHCl$_3$) = +27.8º. % ee was determined using an IA (250x4.6) HPLC column with a 80%:20% [19:1 v/v methanol/acetonitrile]:sodium phosphate buffer (25mM, pH 7.8) eluent. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.88-7.85 (m, 2H), 7.58-7.52 (m, 1H), 7.46-7.41 (m, 2H), 7.31-7.16 (m, 5H), 3.47 (sextet, $J$ = 6.6 Hz, 1H), 2.65 (t, $J$ = 7.5 Hz, 2H), 2.24-2.12 (m, 1H), 1.81-1.70 (m, 1H), 1.24 (d, $J$ = 6.8 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 204.3, 142.0, 136.8, 133.1, 128.8, 128.7, 128.6, 128.5, 126.1, 39.9, 35.4, 33.7, 17.5 ppm.

General procedure E (thioester) was employed using Pd(PPh$_3$)$_4$ (2 mol %), CuCl (2 equiv), S-phenyl benzothioate (42.8 mg, 0.2 mmol) and (S)-5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (86 mg, 0.22 mmol, 91% ee). A colorless oil (38.5 mg, 81%, 90% ee) was isolated by column chromatography (95:5 hexanes/ether). % ee was determined using an IA (250x4.6) HPLC column with a 75%:25% methanol:sodium phosphate buffer (25mM, pH 7.8) eluent.
**1-(Isoxazol-5-yl)-2-methyl-4-phenylbutan-1-one (21).** General procedure C was employed using isoxazole-5-carbonyl chloride (26.3 mg, 0.2 mmol) and 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (86 mg, 0.22 mmol, 95% ee). A colorless oil (34.4 mg, 75%, 99% ee) was isolated by column chromatography (75:25 hexanes/ether). [α]$_{20}^{D}$ (c 1.00, CHCl$_3$) = +18.0°. % ee was determined using an OJ-RH (150x4.6) HPLC column with a 70%:30% [19:1 v/v methanol/acetonitrile]:water eluent. 

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.34 (d, $J$ = 3.0 Hz, 1H), 7.27-7.14 (m, 1H), 6.85 (d, $J$ = 3Hz, 5H), 3.38 (sextet, $J$ = 7.2 Hz, 1H), 2.65 (t, $J$ = 6 Hz, 2H), 2.25-2.12 (m, 1H), 1.88-1.73 (m, 1H), 1.28 (d, $J$ = 6 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 193.0, 166.0, 150.9, 141.5, 128.7, 128.6, 126.3, 107.4, 42.9, 34.4, 33.6, 16.5 ppm. HRMS (ES$^+$): Calcd (M-H)$_+^{2+}$ 230.1181; Found 230.1155.

**Ethyl 3-methyl-4-(naphthalen-2-yl)-4-oxobutanoate (24).** General procedure B was employed using 2-naphthoyl chloride (57 mg, 0.3 mmol) and ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (123 mg, 0.33 mmol). A colorless oil (49 mg, 71%) was isolated by column chromatography (90:10 hexanes/ether). For the enantioenriched carbastannatrane variant, general procedure B was employed using 2-naphthoyl chloride (0.05 mmol) and ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-
yl)butanoate (0.055 mmol, 97% ee). The product yield (75%, 96% ee) was determined by calibrated gas chromatography. % ee was determined using an OJ-RH (150x4.6) HPLC column with a 70%:30% [19:1 v/v methanol/acetonitrile]:sodium phosphate buffer (25mM, pH 7.8) eluent. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.53 (br s, 1H), 8.06-7.87 (m, 4H), 7.58 (dquintet, $J = 1.8$, 7.5 Hz, 2H), 4.16-4.07 (m, 3H), 3.06-2.97 (dd, $J = 9$, 18 Hz, 1H), 2.55-2.47 (dd, $J = 6$, 18 Hz, 1H), 1.29 (d, $J = 6.0$ Hz, 3H), 1.21 (t, $J = 6.0$ Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 203.0, 172.6, 135.8, 133.5, 132.8, 130.2, 129.8, 128.8, 128.7, 128.0, 127.0, 124.5, 60.8, 37.9, 37.5, 18.3, 14.4 ppm. HRMS (ES$^+$): Calcd (M-H)$^+$ 271.1334; Found 271.1335.

**Ethyl 4-(furan-2-yl)-3-methyl-4-oxobutanoate (22).** General procedure C was employed using 2-furoyl chloride (39 mg, 0.3 mmol) and ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (123 mg, 0.33 mmol). A colorless oil (50 mg, 79%) was isolated by column chromatography (80:20 hexanes/EtOAc). For the enantioenriched carbastannatrane variant, general procedure C was employed using 2-furoyl chloride (0.05 mmol) and ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (0.055 mmol, 97% ee). The product yield (78%, 96% ee) was determined by calibrated gas chromatography. % ee was determined using an IA (250x4.6) HPLC column with a 50%:50% [19:1 v/v methanol/acetonitrile]:sodium phosphate buffer (25mM, pH 7.8) eluent. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.60 (br s, 1H), 7.24 (d, $J = 3$ Hz, 1H), 6.55-6.53 (dd, $J = 3$, 3 Hz, 1H), 4.09(q, $J = 6.0$ Hz, 2H), 3.72 (sextet, $J = 6.6$ Hz, 2H).
1H), 2.95-2.87 (dd, J = 9, 15 Hz, 1H), 2.46-2.38 (dd, J = 6, 18 Hz, 1H), 1.25-1.17 (m, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 203.0, 172.6, 135.8, 133.5, 132.8, 130.2, 129.8, 128.8, 128.7, 128.0, 127.0, 124.5, 60.8, 37.9, 37.5, 18.3, 14.4 ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): 191.8, 172.3, 152.2, 146.7, 117.8, 112.5, 60.8, 38.1, 37.3, 17.8, 14.3 ppm. HRMS (ES$^+$): Calcd (M-H)$^+$ 211.0970; Found 211.0960.

**Ethyl 4-(4-chlorophenyl)-3-methyl-4-oxobutanoate (23).** General procedure C was employed using 4-chlorobenzoyl chloride (53 mg, 0.3 mmol) and ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (123 mg, 0.33 mmol). A colorless oil (71 mg, 93%) was isolated by column chromatography (90:10 hexanes/ether). For the enanti-enriched carbastannatrane variant, general procedure C was employed using 4-chlorobenzoyl chloride (0.05 mmol) and ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (0.055 mmol, 99% ee). The product yield (93%, 99% ee) was determined by calibrated gas chromatography. % ee was determined using an IA (250x4.6) HPLC column with a 70%:30% methanol:sodium phosphate buffer (25mM, pH 7.8) eluent. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.94 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 3.89 (sextet, J = 7.2 Hz, 1H), 3.00-2.91 (dd, J = 9, 18 Hz, 1H), 2.49-2.41 (dd, J = 6, 18 Hz, 1H), 1.23-1.18 (m, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 201.9, 172.4, 139.7, 134.5, 130.1, 129.2, 60.8, 37.7, 37.4, 18.0, 14.3 ppm.
1-(Benzofuran-2-yl)-2-phenylbutan-1-one (25). General procedure C was employed using benzofuran-2-carbonyl chloride (54 mg, 0.3 mmol) and 5-(1-phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane (125 mg, 0.33 mmol). A yellow oil (63 mg, 80%) was isolated by column chromatography (95:5 hexanes/ether). For the enantioenriched carbas-tannatrane variant, general procedure C was employed using benzofuran-2-carbonyl chloride (0.05 mmol) and 5-(1-phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.055 mmol, 99% ee). The product yield (78%, 97% ee) was determined by calibrated gas chromatography. % ee was determined using an OJ-RH (150x4.6) HPLC column with a 80%:20% [19:1 v/v methanol/acetonitrile]:sodium phosphate buffer (25mM, pH 7.8) eluent. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.66-7.22 (m, 10H), 4.40 (t, $J$ = 7.5 Hz, 1H), 2.30-2.21 (m, 1H), 1.93-1.86 (m, 1H), 0.94 (t, $J$ = 7.5 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 191.3, 155.8, 152.7, 139.2, 129.02, 128.6, 128.4, 127.4, 127.3, 124.0, 123.5, 113.7, 112.7, 56.3, 26.5, 12.5 ppm. HRMS (ES$^+$): Calcd (M-Na)$^+$ 287.1048; Found 287.1067.

1-(Benzo[b]thiophen-2-yl)-2-phenylbutan-1-one (26). General procedure C was employed using benzo[b]thiophene-2-carbonyl chloride (55 mg, 0.3 mmol) and 5-(1-
phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane (125 mg, 0.33 mmol). A pale yellow solid (51 mg, 69%) was isolated by column chromatography (97:3 hexanes/ether). For the enantioenriched carbastannatranne variant, general procedure C was employed using benzo[b]thiophene-2-carbonyl chloride (0.05 mmol) and 5-(1-phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.055 mmol, 99% ee). The product yield (71%, 99% ee) was determined by calibrated gas chromatography. % ee was determined using an OJ-RH (150x4.6) HPLC column with a 80:20% [19:1 v/v methanol/acetonitrile]: sodium phosphate buffer (25mM, pH 7.8) eluent. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.66-7.22 (m, 10H), 4.40 (t, $J = 7.5$ Hz, 1H), 2.30-2.21 (m, 1H), 1.93-1.86 (m, 1H), 0.94 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 191.3, 155.8, 152.7, 139.2, 129.0, 128.6, 128.4, 127.4, 127.3, 124.0, 123.5, 113.7, 112.7, 56.3, 26.5, 12.5 ppm. HRMS (ES$^+$): Calcd (M-H)$^+$ 281.1000; Found 281.0984.

(2S,4R)-2-(6-methoxynaphthalen-2-yl)-4-methylhexan-3-one (syn-29). General procedure E was employed using Pd(dba)$_2$ (5 mol %), Jackiephos (7 mol %), CuCl (2 equiv), S-phenyl (S)-2-(6-methoxynaphthalen-2-yl)propanethioate (64.5 mg, 0.2 mmol, $>$99% ee) and (R)-5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (80.4 mg, 0.26 mmol, 99% ee). A white solid (32.5 mg, 60%, 49:1 dr) was isolated by column chromatography (97:3 hexanes/ether). [$\alpha$]$^{20}$D (c 1.00, CHCl$_3$) = $+183.9^\circ$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.71-7.62 (m, 3H), 7.32-7.29 (dd, $J = 3, 9$ Hz ,1H), 7.17-7.11 (m, 2H), 4.03 (q, $J = 6$ Hz, 1H), 3.91 (s, 3H), 2.58 (app. sextet, $J = 8.4$ Hz, 1H), 1.61-1.44 (m, 4H), 1.22
(app. heptet, $J = 6$ Hz, 1H), 1.07 (d, $J = 6$ Hz, 1H), 0.89-0.79 (m, 1H), 0.55 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 214.49, 157.84, 135.64, 133.84, 129.38, 129.26, 127.51, 126.97, 126.85, 119.25, 106.81, 55.51, 51.56, 46.57, 25.63, 18.27, 17.48, 11.80 ppm. HRMS (ES$^+$): Calcd (M-Na)$^+$ 293.1517; Found 293.1515.

(2S,4S)-2-(6-methoxynaphthalen-2-yl)-4-methylhexan-3-one ($anti$-29). General procedure E was employed using Pd(dba)$_2$ (5 mol %), Jackiephos (7 mol %), CuCl (2 equiv), S-phenyl (S)-2-(6-methoxynaphthalen-2-yl)propanethioate (64.5 mg, 0.2 mmol, >99% ee) and (S)-5-(sec-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane (80.4 mg, 0.26 mmol, 91% ee). A pale yellow solid (35 mg, 65%, 22:1 dr) was isolated by column chromatography (97:3 hexanes/ether. [a]$^{20}$D (c 1.00, CHCl$_3$) = +160.9º. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.71-7.61 (m, 3H), 7.31-7.28 (dd, $J = 3$, 9 Hz ,1H), 7.17-7.11 (m, 2H), 3.98 (q, $J = 5.25$ Hz, 1H), 3.92 (s, 3H), 2.61 (sextet, $J = 6.6$ Hz, 1H), 1.65 (heptet, $J = 7$ Hz, 1H), 1.47-1.32 (m, 4H), 1.07 (d, $J = 6$ Hz, 1H), 0.89-0.84 (m, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): 215.03, 157.87, 135.91, 133.83, 129.38, 129.29, 127.59, 126.92, 126.82, 119.30, 106.81, 55.54, 52.65, 46.29, 27.13, 18.11, 16.30, 11.89 ppm. HRMS (ES$^+$): Calcd (M-Na)$^+$ 293.1517; Found 293.1515.
HPLC & NMR Data

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<td>Flow</td>
<td>1 mL/min</td>
</tr>
<tr>
<td>Detector</td>
<td>205 nm</td>
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<td>Temp</td>
<td>25°C</td>
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**CONDITIONS**

<table>
<thead>
<tr>
<th>Column</th>
<th>OJ-RH 150x4.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile Phase</td>
<td>70% : 30% [19:1 v/v Methanol/Acetonitrile] : Water</td>
</tr>
<tr>
<td>Flow</td>
<td>1.0 mL/min</td>
</tr>
<tr>
<td>Detector</td>
<td>220 nm</td>
</tr>
<tr>
<td>Temp</td>
<td>25°C</td>
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### CONDITIONS

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<tr>
<th>Parameter</th>
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<tbody>
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<td>Column</td>
<td>OJ-RH 150x4.6</td>
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<tr>
<td>Mobile Phase</td>
<td>70% : 30% [19:1 v/v Methanol/Acetonitrile] : Sodium phosphate buffer (25mM, pH 7.8)</td>
</tr>
<tr>
<td>Flow</td>
<td>0.8 mL/min</td>
</tr>
<tr>
<td>Detector</td>
<td>205 nm</td>
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<tr>
<td>Temp</td>
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<td>CONDITIONS</td>
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<td>Column</td>
<td>OJ-RH 150x4.6</td>
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<tr>
<td>Mobile Phase</td>
<td>80% : 20% [19:1 v/v Methanol/Acetonitrile] : Sodium phosphate buffer (25mM, pH 7.8)</td>
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<tr>
<td>Flow</td>
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<td>Detector</td>
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**CONDITIONS**

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<tr>
<td>Mobile Phase</td>
<td>80% : 20% [19:1 v/v Methanol/Acetonitrile] : Sodium phosphate buffer (25mM, pH 7.8)</td>
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<td>Detector</td>
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<td>------------------</td>
</tr>
<tr>
<td>Column</td>
<td>IA 250x4.6</td>
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<tr>
<td>Mobile Phase</td>
<td>70% : 30% Methanol : Sodium phosphate buffer (25mM, pH 7.8)</td>
</tr>
<tr>
<td>Flow</td>
<td>1.0 mL/min</td>
</tr>
<tr>
<td>Detector</td>
<td>210 nm</td>
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<tr>
<td>Temp</td>
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CONDITIONS

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<tr>
<th>Column</th>
<th>IA 250x4.6</th>
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</thead>
<tbody>
<tr>
<td>Mobile Phase</td>
<td>65% : 35% [19:1 v/v Methanol/Acetonitrile] : Water</td>
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<td>Flow</td>
<td>1.0 mL/min</td>
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<tr>
<td>Detector</td>
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<tr>
<td>Temp</td>
<td>25°C</td>
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CONDITIONS

<table>
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<tr>
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<tbody>
<tr>
<td>Column</td>
<td>IA 250x4.6</td>
</tr>
<tr>
<td>Mobile Phase</td>
<td>50% : 50%  [19:1 v/v Methanol/Acetonitrile] : Water</td>
</tr>
<tr>
<td>Flow</td>
<td>0.6 mL/min</td>
</tr>
<tr>
<td>Detector</td>
<td>210 nm</td>
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<tr>
<td>Temp</td>
<td>25°C</td>
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CONDITIONS

<table>
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</thead>
<tbody>
<tr>
<td>Column</td>
<td>OJ-RH 150x4.6</td>
</tr>
<tr>
<td>Mobile Phase</td>
<td>55% : 45% Methanol : Water</td>
</tr>
<tr>
<td>Flow</td>
<td>1.2 mL/min</td>
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<tr>
<td>Detector</td>
<td>220 nm</td>
</tr>
<tr>
<td>Temp</td>
<td>25°C</td>
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**CONDITIONS**

<table>
<thead>
<tr>
<th>Column</th>
<th>IA 250x4.6</th>
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<tbody>
<tr>
<td>Mobile Phase</td>
<td>60% : 40% Methanol : Water</td>
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<tr>
<td>Flow</td>
<td>1.2 mL/min</td>
</tr>
<tr>
<td>Detector</td>
<td>215 nm</td>
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<tr>
<td>Temp</td>
<td>25°C</td>
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</tbody>
</table>
22:1 dr (>98% es)
<table>
<thead>
<tr>
<th>Column</th>
<th>IA 250x4.6</th>
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<tbody>
<tr>
<td>m-Phase</td>
<td>45% : 55% Acetonitrile : Sodium phosphate buffer (25mM, pH 7.8)</td>
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<tr>
<td>Flow</td>
<td>1.2 mL/min</td>
</tr>
<tr>
<td>Detector</td>
<td>210 nm</td>
</tr>
<tr>
<td>Temp</td>
<td>25°C</td>
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</tbody>
</table>
Impurity peaks arise from Grignard homocoupling.
impurity peaks arise from Grignard homocoupling
Impurity peaks arise from Grignard homocoupling.
Impurity peaks arise from Grignard homocoupling.
**VCD analysis of absolute stereochemistry of product from acylation of (R)-19**

\[
\text{PhCl} + \text{N:Sn} \rightarrow \text{Ph} \quad \text{(R)-19 (99% ee)} \quad \text{Pd}(\text{PPh}_3)_4 (2 \text{ mol %}) \quad \text{CuCl (2 equiv)} \quad \text{CH}_3\text{CN, 60 °C} \rightarrow \text{PhCH}_3 \quad \text{99% ee}
\]

### GENERAL INFORMATION

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<tr>
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<tbody>
<tr>
<td>Sales Order Number</td>
<td>2015.147B</td>
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<tr>
<td>Sample code (Our ref.)</td>
<td>PhenAcyl</td>
</tr>
<tr>
<td>Sample description (Your ref.)</td>
<td>PhenAcul</td>
</tr>
<tr>
<td>VCD-spectrometer</td>
<td>ChiralIR w/ DualPEM</td>
</tr>
<tr>
<td>Report prepared by</td>
<td>Bo Wang</td>
</tr>
<tr>
<td>Report validated and signed by</td>
<td>Rina K Dukor</td>
</tr>
<tr>
<td>Date</td>
<td>Nov. 12, 2015</td>
</tr>
</tbody>
</table>

### RESULTS

**Absolute Configuration of PhenAcyl is (R).** Confidence Level: 90%

### MEASUREMENT PARAMETERS

| Concentration | 5.7 mg/0.15mL |
| Solvent | CDCl3 |
| Resolution | 4 cm⁻¹ |
| PEM setting | 1400 cm⁻¹ |
| Number of scans/Measurement time | 6 hours |
| Sample cell | BaF₂ |
| Path length | 100 µm |

### CALCULATION DETAILS

| Gaussian version | Gaussian 09 |
| Total low-energy conformer used for Boltzmann sum | 13 |
| Methodology and basis set for DFT calculations | B3LYP/6-31G(d) |
| Enantiomer used for calculation | (R) |
| Total calculated conformers | 13 |
| Number of low-energy conformations shown in report | 1 |

### Table 1. Numerical comparison describing the similarity in the range of 1300-1800 cm⁻¹ between the calculated IR and VCD spectra for the (R) enantiomer at the B3LYP/6-31G(d) level and the observed IR and VCD spectra for PhenAcyl.

<table>
<thead>
<tr>
<th>Cal. (1300-1800 cm⁻¹)</th>
<th>Numerical comparison</th>
<th>Observed PhenAcyl</th>
</tr>
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<tbody>
<tr>
<td>scaling factor</td>
<td>0.96</td>
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<tr>
<td>IR similarity (%)</td>
<td>65.9</td>
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<tr>
<td>( ^a \sum ) (%)</td>
<td>51.1406</td>
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</tr>
<tr>
<td>( ^b \Delta ) (%)</td>
<td>43.915</td>
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</tr>
<tr>
<td>Confidence Level (%)</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \sum \): single VCD similarity, gives the similarity between the calculated and observed VCD spectra.

\( ^b \Delta \): enantiomeric similarity index, gives the difference between the values of \( \sum \) for both enantiomers of a given diastereoisomer.
IR (lower frame) and VCD (upper frame) spectra of PhenAcyl in CDCl₃ (6.4mg/0.15mL); 0.1mm path-length cell with BaF₂ windows; 11 h collection for samples and solvent; instrument optimized at 1400 cm⁻¹. Solvent-subtracted IR and VCD spectra are shown. Uppermost trace is the VCD noise spectra.
IR (lower frame) and VCD (upper frame) spectra observed for PhenAcyl (right axes) compared with calculated Boltzmann-averaged spectra of the calculated conformations for the (R)- configuration, (left axes).
3.6] Reference


22. Enantiospecificity (es) = (ee<sub>product</sub>/ee<sub>starting material</sub>) x 100%.


