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Stereospecific Electrophilic Fluorination of Alkylcarbostannatrane Reagents

Xinghua Ma

马兴华

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

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By

Xinghua Ma

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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ABSTRACT

Stereospecific Electrophilic Fluorination of Alkylcarbastannatrane Reagents

by

Xinghua Ma

Advisor: Prof. Mark R. Biscoe

The introduction of fluorine atoms into organic molecules significantly changes their physical, chemical, and biological properties. Fluorinated organic compounds are used as pharmaceuticals, agrochemicals, materials, and tracers for positron emission tomography (PET). For example, the site-specific fluorination of drugs can block sites of phase I metabolism by cytochrome P450 enzymes as well as improve target-binding affinities. In view of the unique features of fluorine-containing compounds, there has been increasing interest in the development of novel methods for the synthesis of fluorinated molecules, especially the site-specific monofluorination of complex molecules. Herein, we present the enantiospecific conversion of chiral secondary alkylcarbastannatranes into alkylfluorides. Carbastannatranes were used as nucleophiles, with Selectfluor I as the electrophilic fluorinating agent, to afford alkylfluorides in short reaction times. The addition of styrene as a radical trap was found to enhance enantiospecificity. A broad range of alkylcarbastannatranes were converted into alkylfluorides

under mild condition by this method. Other halogenations, such as chlorination, bromination and iodination, were also applied to alkylcarbostannatranes with high enantiospecificity.

Dedicated to

My Family

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1 Introduction

1.1. Importance of Molecules with Fluorine

Originally discovered by André-Marie Ampère in 1810, fluorine is the 13th richest element in the Earth's crust, and the 24th richest element in the universe. In 1886, French chemist Henri Moissan succeeded in producing elemental fluorine by electrolyzing a mixture of potassium fluoride and hydrogen fluoride. CaF_2 is the major fluorine source for the fluorine industry.

Fluorine has interested the chemistry and pharmaceutical community since its discovery on account of its special properties such as small size, high electronegativity, and low polarisability.^[1] The length of the C-F bond is almost the same as the length as the C-H bond (1.39 and 1.09 Å, respectively) ^[1]. Therefore, introduction of one or more fluorine atoms into an organic compound can result in changes of conformation and reactivity compared to those of the non-fluorinated counterpart, without significant modification of steric properties. Perfluorinated (fully fluorinated) organic compounds show particularly special properties. One example of a fluorinated compounds that is used in everyday life is the polymer Teflon®, which is the coating used in non-stick pans.

A major area of application for organofluorine chemistry is in pharmaceutical and medicinal chemistry. The introduction of fluorine into bioactive molecules often results in significant changes in their chemical, physical, and biological properties. Fluorine uniquely affects the properties of organic molecules, increasing molecular lipophilicity and bioavailability. No drugs containing a fluorine atom had been developed prior to the synthesis of 5-fluorouracil

1 in 1957. After that, the situation changed dramatically. Nowadays, there are many successful examples of the introduction of fluorine into organic molecules, such as the anti-depressant fluoxetine (prozac) 2, the anti-cholesterol atorvastatin (lipitor) 3, the anti-bacterial ciprofloxacin (ciprobay) 4, HMG-CoA reductase inhibitor fluvastatin (atorvastatin) 5, the antibiotic fluoroquinolone (levofloxacin) 6, and the antitumor fluoronucleoside (tegafur) 7. Approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine.^[2] Therefore, fluorinating agents are useful tools to introduce fluorine for the synthesis of pharmaceutical and agricultural compounds.

Scheme 1-1. Fluorinated Bioactive Compounds Pharmaceuticals

¹⁸F radiolabeled tracer molecules are commonly applied in Positron Emission Tomography (PET), which is a nuclear medicine imaging technique used to diagnose many diseases, including cancers, neurological disorders, heart disease, gastrointestinal and endocrine diseases, and other abnormalities within the body. The general procedure for PET imaging is the

following: a) isotopically labeled tracers are synthesized prior to performing imaging studies; b) depending on the type of nuclear medicine exam, the radiotracer is either injected into the body, swallowed as pills or inhaled as a gas, eventually accumulating in the organ or area of the body being examined; and c) radioactive gamma emission from the radiotracer is detected by a special camera or imaging device indicating the site of radiotracer accumulation. In PET imaging, several radioactive isotopes with different half-lives can be employed. ^{11}C (~20 min), ^{13}N (~10 min), ^{15}O (~2 min), ^{18}F (~110 min), ^{68}Ga (~67 min), ^{89}Zr (78.4 hours) and ^{82}Rb (~1.27 min) are all PET active nuclides.^[3] The most commonly employed radiotracer for PET is ^{18}F -fluorodeoxyglucose (^{18}F -FDG) (**Scheme 1-2**), which is a radiolabeled analogue of glucose that can be used to determine the sites of abnormal glucose metabolism. This is particularly important for early detection of tumors.^[4] Several electrophilic fluorinating agents for radiofluorination have been reported (**Scheme 1-3**). Trifluoromethyl- ^{18}F -hypofluorite ($\text{CF}_3\text{-O}^{18}\text{F}$),^[5] acetyl- ^{18}F -hypofluorite ($\text{CH}_3\text{-CO}_2^{18}\text{F}$),^[6] perchloryl- ^{18}F -fluoride ($^{18}\text{F}\text{-FCIO}_3$),^[7] xenon difluoride (Xe^{18}F_2),^[8] 1- ^{18}F -fluoro-2-pyridone, N- ^{18}F -fluoropyridinium triflate, ^{18}F -fluoro-N-alkyl sulfonamide,^[9] and ^{18}F -Selectfluor bis(triflate)^[10] have all been employed in electrophilic [^{18}F]fluorination.

Scheme 1-2. ^{18}F -fluorodeoxyglucose

Scheme 1-3. Electrophilic Fluorinating Agents for Radiofluorination

1.2. Current Methodology to Introduce Fluorine into Organic Molecules

Because of the importance of fluorinated organic molecules in medicinal chemistry, many methods for installing fluorine into organic compounds have been developed. The following section mainly reviews the most useful methods for introducing fluorine into organic molecules.

1.2.1. Traditional Methodology

Though nucleophilic fluorinating agents such as KF (**Scheme 1-4**),^[11] CsF, and Bu₄NF are readily available, their reactivity is very low, and these reagents are highly hygroscopic. Therefore, nucleophilic fluorinating reagents are not commonly employed in the absence of catalysis. The most common fluorinating reactions can be classified into two categories: deoxyfluorination reactions and electrophilic fluorination reactions.

Deoxyfluorination Reagents

Deoxyfluorination reagents are used synthetically to convert a hydroxyl group into a fluorine atom (**Scheme 1-5**),^[12] often stereospecifically (**Scheme 1-6**).^[13] Diethylaminosulfur

trifluoride (DAST) is the most commonly employed deoxyfluorination reagents. Several other deoxyfluorination reagents are commercially available, such as bis(2-methoxyethyl) aminosulfur trifluoride **8** (Deoxo-Fluor[®]) (**Scheme 1-7**),^[14] 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride **9** (Fluolead[™]) (**Scheme 1-8**),^[15] Olah's reagent, and PhenoFluor[™] **10**. Deoxo-Fluor[®] exhibits similar reactivity to DAST. However, it is more thermally stable, and shows increased reactivity in some substrates, such as aldehydes, ketones and carboxylic acids. Fluolead[™] shows high thermal stability (decomposes at 232 °C) and can be handled in open air due to its low sensitivity to water. Another important deoxyfluorination reagent is PhenoFluor[™], which is a crystalline and nonexplosive solid. It was originally developed for deoxyfluorination of phenols to provide a wide variety of aryl fluorides (**Scheme 1-9**).^[16] In 2013, PhenoFluor was applied to deoxyfluorination of aliphatic alcohols under appropriate modification of the reaction conditions, that are compatible with a variety of functional groups (**Scheme 1-10**).^[17] Later, the substrate scope of deoxyfluorination was expanded to heteroaromatics (**Scheme 1-11**).^[18] One drawback of PhenoFluor is its high price (\$0.80/mg) and its larger scale synthesis has been challenging. In 2015, a new deoxyfluorination reagent, 2-pyridinesulfonyl fluoride **11** (PyFluor) was reported by Doyle,^[19] which fluorinates a broad range of alcohols (**Scheme 1-12**).

Scheme 1-4. Nucleophilic Aromatic Substitution with KF

Scheme 1-5. Cyclooctanol and Crotyl Alcohol Reacts with DAST

Scheme 1-6. DAST Reacts with Enantioenriched Alcohols

Scheme 1-7. Deoxo-Fluor Reacts with Alcohols

Scheme 1-8. Fluorination of (2S,4R)-N-Fmoc-hydroxyprolinonitrile with Fluolead™

Scheme 1-9. Deoxyfluorination of Phenols by PhenoFluor

Scheme 1-10. Deoxyfluorination of Aliphatic Alcohols by PhenoFluor

Scheme 1-11. Deoxyfluorination of Heteroaromatics by Phenofluor

Scheme 1-12. Deoxyfluorination with PyFluor

Electrophilic Fluorination

Most electrophilic fluorinating reagents are derived from fluorine gas. The traditional reagents, such as F_2 , XeF_2 , $CsSO_4F$, and CF_3OF , are highly oxidizing fluorinating reagents,^[20] which are not suitable for practical for general use due to the high reactivity of the reagents. The stable and easy-to-handle crystal, N-fluoro-pyridinium salt, was reported by the Umemoto group (**Scheme 1-13, 14**).^[21] The reactivity could may be tuned by introducing groups with different electronic properties into the pyridine ring. The counteranion also influences the reactivity, selectivity, and stability of the reagent.^[22] Another class of electrophilic fluorinating reagents is sulfonyl derivatives $RSO_2N(F)R'$, which show different reactivities depending on the alkyl

group R and R'.^[23] N-Fluorobenzenesulfonimide (NFSI) is a member^[24] of this class that became popular in the early 1990s. It allows the fluorination of enolates, silyl enol ethers, aromatic compounds, and organolithium compounds. Most recently, Selectfluor was developed as a reliable, mild, and stable electrophilic fluorinating reagent. Selectfluor has been applied to a wide scope of substrates, bearing functional groups, such as carbonyls, thioethers, and indoles. Selectfluor derivatives^[25] have also been reported, and their use in fluorination explored (Scheme 1-15). ¹⁸F-Selectfluor was synthesized and evaluated by Gouverneur for applications to radiofluorination.^[10]

Scheme 1-13. The Summary of N-fluoro-pyridinium Salts

Scheme 1-14. Fluorination by N-fluoro-pyridinium salt

a R = Me, X = TfO ⁻	g R = CH ₂ Cl, X = TfO ⁻
b R = Me, X = BF ₄ ⁻	h R = CH ₂ Cl, X = PF ₆ ⁻
c R = Me, X = PF ₆ ⁻	i R = Et, X = TfO ⁻
d R = Me, X = TfO ⁻ , X' = BF ₄ ⁻	j R = CF ₃ CH ₂ , X = TfO ⁻
e R = Me, X = TfO ⁻ , X' = PF ₆ ⁻	k R = C ₈ H ₁₇ , X = TfO ⁻
f R = Me, X = TfO ⁻ , X' = FSO ₃ ⁻	

Scheme 1-15. Selectfluor and Selectfluor derivatives

1.2.2. Fluorination of Organometallic Compounds

Organoboron Nucleophiles

Arylboron and alkylboron reagents are widely used in organic synthesis since they are nontoxic, readily synthetically accessible, and stable to many common functional groups.^[26] Several metal-mediated methods to fluorinate organoboron compounds have been reported using Pd (**Scheme 1-16**),^[27] Ag (**Scheme 1-17**),^[28] Cu (**Scheme 1-18**).^[29] A fluorination reaction of aryl boronic acids mediated by palladium forms carbon-fluorine bond at the final synthetic step, which shows the functional group tolerance, broad substrate scope, and the regiospecificity of the reaction. Fluorination of aryl trifluoroborates via copper was reported separately by Sanford and Hartwig.^[29a, b] The substrates can bear aryl aldehydes, ketones, amides and esters with good yields. In 2014, an efficient and general method for fluorination of alkylboronates using AgNO₃ in acidic aqueous solution was reported by the Li group (**Scheme 1-19**).^[30] The method can be used for alkylboronic acids, primary, secondary and tertiary alkylboronates. A radical mechanism was proposed for this process.

Scheme 1-16. Electrophilic fluorination with aryl palladium complexes

Scheme 1-17. Electrophilic Fluorination of Arylboronic Acids

Scheme 1-18. $\text{Cu}(\text{OTf})_2$ -Mediated Fluorination of Aryltrifluoroborates with KF

Scheme 1-19. Fluorination of Secondary and Tertiary Alkylboronates via AgNO_3

In 2015, Aggarwal reported the fluorination of boronate complexes in the absence of metal catalysis (**Scheme 1-20**).^[31] The same strategy had also applied to different electrophilic reagents to form C-C, C-N, C-Br, C-Cl, C-O and C-I bonds.^[32] Enantioenriched secondary alkyl boronate esters undergo enantiospecific substitution in this process. The nucleophiles were derived from boronic esters and PhLi , which formed an activated ate complex in situ. This intermediate was then treated with Selectfluor II to afford desired alkylfluorides. Styrene was required as the radical trap to improve the enantiospecificity. The proposed pathway for the reaction of boronate complex with Selectfluor II is shown in **Scheme 1-21**, including a possible side reaction involving a radical mechanism.

Scheme 1-20. Fluorination of Boronate Complexes without any Metal Catalyst

Scheme 1-21. Proposed Pathways for the Reaction of Boronate Complex with Selectfluor

Organostannanes Nucleophiles

In recent years, many research groups put focus on the fluorination of organostannanes, especially on arylstannanes. A silver-mediated process for the general fluorination of functionalized arylstannanes has been reported by Ritter.^[33] This reaction was shown to tolerate aldehydes, unprotected hydroxyls, and heteroaryl groups. Later, they also reported silver-catalyzed late-stage fluorination (**Scheme 1-22**),^[34] which was the first fluorination report exhibiting broad functional group tolerance and substrate scope, including carbohydrates, peptides, polyketides, alkaloids and derivatives from taxol and rifamycin. Sanford has reported a mild copper-mediated fluorination of aryl stannanes (**Scheme 1-23**),^[29a] which does not require

any noble metal additives. The arylstannanes can bear electron-donating and electron-withdrawing substituents.

Scheme 1-22. Silver-catalyzed Late-stage Fluorination

Scheme 1-23. Cu-Mediated Fluorination of Aryl Stannanes

Organosilicon Nucleophiles

Compared to fluorination of organoboron and organotin compounds, there are few papers involving the fluorination of aryl silanes. Aryl silanes have their own advantages, such as low toxicity, low price, and stability to a variety of reaction conditions. Reaction of aryltrimethylsilanes with xenon difluoride in C₆F₆/Pyrex[®] at room temperature has provided aryl fluorides in good yield,^[35] however, aryltrimethylsilanes cannot carry electron-withdrawing groups. In 2011, a regiospecific silver-mediated fluorination of aryl silanes was reported (**Scheme 1-24**) by Ritter.^[36] However, to get optimal results, the silver salt (Ag₂O) is used in superstoichiometric amounts.

Scheme 1-24. A Regiospecific Silver-mediated Fluorination of Aryl Silanes

Grignard and Lithium Reagents as Nucleophiles

In 1900, Grignard reagents and reactions were reported by French chemist François Auguste Victor Grignard, who was awarded the 1912 Nobel Prize in Chemistry for this work. Following their discovery, Grignard reagents have been widely used in organic synthesis. Aryl Grignard reagents have been used to form C-F bonds through reaction with electrophilic

fluorinating reagents without any metal catalyst.^[37] The fluorination of primary alkyl Grignard reagents was reported with decent yields (**Scheme 1-25**).^[38] However, for secondary alkyl Grignard reagents, few examples of fluorination exist, the yields are generally very low.^[39] Finally, lithium reagents could be applied into fluorinating process, especially for the aryl lithium reagents (**Scheme 1-26**).^[40] Up to now, the fluorination of organozinc reagents with acceptable yield has not been reported. Therefore, no general conditions exist to broadly achieve the fluorination of Grignard reagents, zinc reagents and lithium reagents.

Scheme 1-25. Fluorination of Grignard Reagents

Scheme 1-26. Fluorination of Aryl Lithium Reagents

2. Stereospecific Fluorination of Alkylcarbostannatranes

2.1. Background

Organotin compounds have been used widely since the first organotin compound was discovered in 1849. They have been applied in industry and in research labs as catalysts, stabilizers, antifungal agents, agricultural fungicides, wood preservatives, and anti-biofouling agents. Some organotin complexes have also been studied in anticancer therapy.^[41]

A major application for organotin compounds is in Stille cross-coupling reactions (**Scheme 2-1**). Aryl trialkyl tin compounds are most commonly employed in Stille reactions because nucleophilic transfer of aryl units occurs more rapidly than transfer of alkyl units. Some groups have tried to transfer alkyl groups from tetraalkyl organotin compounds to metal catalysts, however, the yields tend to be low and the reactions only work for primary alkyl groups.^[42] Therefore, tetraalkyltin compounds are rarely used in Stille reactions.

Scheme 2-1. The General Pd-catalyzed Stille Cross-coupling Reactions

In 2013, the stereoretentive Pd-catalysed Stille cross-coupling reactions of secondary alkyl carbostannatranes under mild conditions was reported by our group (**Scheme 2-2**).^[43] This was

the first general method to use secondary alkyltin reagents in cross-coupling reactions. The heightened reactivity of alkyl carbastannatrane reagents results from the intramolecular interaction between nitrogen and tin. Jurkschat and Tzschach showed that the nitrogen atom in the atrane backbone selectively lengthens the Sn–C bond of the apical alkyl substituent by 0.1 Å compared to the Sn–C bond of a tetraalkylstannane.^[44] The transannular N–Sn bond enhances the electron density of Sn atom and makes the cleavage of trans-disposed substituent easier. At the same time, the atrane backbone structure stabilizes the Sn valence shell octet through N electron donation. Therefore, the N–Sn transannular bond makes carbastannatrane efficient reagents for the selective transfer of alkyl groups in Stille cross-coupling reactions. The Palladium-catalyzed acylation of alkylcarbastannatrane was also reported by our group (**Scheme 2-3**).^[45] Based upon previous research and theory analysis, alkylcarbastannatrane remain promising candidates for applications other than Pd-catalyzed cross-coupling reactions.

Scheme 2-2. Stereospecific Pd-catalyzed Cross-coupling Reactions of Unactivated,

Enantioenriched Secondary Alkylcarbostannatranes and Aryl Bromides

Scheme 2-3. Stereospecific Palladium-Catalyzed Acylation of Enantioenriched Alkylcarbostannatranes

Metal-catalyzed fluorination was mainly achieved for aryl stannanes, as was discussed in the previous section. While no example of the fluorination of alkylstannanes has been reported, there is precedent for the use of alkylstannanes in other halogenation reactions. In 1983, Jensen had reported a mechanistic study of $\text{S}_{\text{E}}2$ reactions on secondary alkyl organotin compounds **12**, which includes chlorination, bromination, and iodination (**Scheme 2-4**).^[46] This work involved investigation into the kinetics, stereochemistry, solvent effects, mixed halogen electrophiles effects, and organotin structure effects. The stereochemistry of $\text{S}_{\text{E}}2$ reactions was affected by the nature of the electrophile and by the steric effects of the alkyltin nucleophile. However, the report suggests the possibility of halogenation of organotin compounds with acceptable yield and high enantioenriched compounds. Up to now, there has been no report of the fluorination of alkyl organotin compounds with or without metal catalyst.

Scheme 2-4. Halogenation of Organotin **12** (% net inversion or retention shown).

2.2. Fluorination of Alkylcarbastannatranes

Though no example of the electrophilic fluorination of alkylstannanes has been reported, the electrophilic fluorination reactions of boronate complexes, as demonstrated by the Aggarwal group, suggests the possibility of fluorination of nucleophilic alkyl tin compounds. The primary alkyl substrate, 5-decyl-1-aza-5-stannabicyclo[3.3.3]undecane **13**, was chosen for initial investigations of the fluorination reaction. Since Ritter has developed conditions for the Ag-mediated and Ag-catalyzed fluorination of arylstannanes, Ritter's conditions were initially employed with alkyl carbastannatranes **13**. Fortunately, the desired product was detected, and the GC yield was 28%. However, it was also found the yield increased to 64% under the same conditions in the absence of AgOTf (**Scheme 2-5**). Therefore, Ag catalysis is not necessary for the fluorination of **13** using Selectfluor I **14**. One possible reason for the low yield with AgOTf is that alkylcarbastannatranes are so reactive that they decompose in the presence of AgOTf. To investigate this proposal, 5-butyl-1-aza-5-stannabicyclo[3.3.3]undecane **15** was subjected to the fluorination conditions without Selectfluor I but with the silver salt. It was found that

5-butyl-1-aza-5-stannabicyclo[3.3.3]undecane **15** decomposed very fast (less than 10 min.), even when the reaction was conducted at 0 °C.

Scheme 2-5. Fluorination of Primary Alkylcarbostannatranes with and without Silver

A screen of temperature effects showed that fluorination was most efficient at room temperature. At low temperatures, low yields were obtained though all of carbostannatrane was consumed.

Entry	Temperature	GC yield ^b (%)
1	120 °C	36
2	90 °C	48
3	Room temperature	64
4	0 °C	55

^a Reaction condition: carbastannatranes **13** (0.01 mmol), Selectfluor I (1.5 equiv), Na₂CO₃, (1 equiv), solvent 0.1 mL, Ar; ^bdodecane as the internal standard for GC yield calculation; ^cfor 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane.

Table 2-1. Fluorination of Alkylcarbastannatranes at Different Temperatures

Because transfer of a secondary alkyl group is more difficult than transfer of a primary alkyl group, and because fluorination of secondary alkyl groups opens the possibility of stereospecific fluorination, we chose to employ secondary alkylcarbastannatranes **17** for further optimization reactions. The solvents were screened on 0.01 mmol scale reactions. Based on the results of fluorination of 5-decyl-1-aza-5-stannabicyclo[3.3.3]undecane **13**, we found that polar solvents were necessary to dissolve Selectfluor I. The screen table is shown in **Table 2-2**. From these results, it was apparent that use of CH₃CN as the solvent provided the best yield of fluorinated product.

Entry	1	2	3	4	5
Solvent	CH ₃ CN	NMP	DMF	DMA	DMSO
GC ^b yield (%)	70	26	55	49	0

^a Reaction condition: carbastannatranes **17** (0.01 mmol), Selectfluor I (1.5 equiv), solvent 0.1 mL, rt, Ar; ^b dodecane as the internal standard for GC yield calculation.

Table 2-2. Fluorination of Alkylcarbastannantranes Using Different Solvents

Since the Sanford group has reported the electrophilic fluorination of aryl stannanes using copper catalysis, the use of different copper catalysts was examined in this reaction (**Table 2-3**). Unfortunately, it was found that the reaction yields decreased with the addition of copper salts. It is possible that alkylcarbastannantranes decompose under these conditions. Indeed, transmetalation of alkyl carbastannantranes to Cu (I) salts has been previously used by our group in cross-coupling reactions.^[43, 45]

^aReaction condition: carbastannantranes **17** (0.01 mmol), Selectfluor I (1.5 equiv), copper salt (2 equiv), solvent 0.1 mL, rt, Ar; ^b dodecane as the internal standard for GC yield calculation.

Table 2-3. Fluorination of Alkylcarbastannantranes using Different Copper Additives

Because only highly polar solvents are capable of dissolving Selectfluor, lithium tetrakis(pentafluorophenyl)borate was applied to the reactions as a phase transfer catalyst (PTC).

The addition of phase transfer catalysis did not improve yields significantly (**Table 2-4**). Other additives such as Na_2CO_3 , K_3PO_4 , LiCl , $\text{Mg}(\text{OH})_2$, Cs_2CO_3 , NaOH , NaCl , ZnCl_2 , and AlCl_3 were also added into the fluorination reactions. It was found that they did not improve the yield, and in some cases resulted in lower yields of fluorinated product.

Entry	1	2	3	4	5	6
Solvent	CH_3CN	NMP	DMF	DMSO	THF	Toluene
GC ^b Yield(%)	62	32	45	0	0	0

^aReaction condition: carbastannatranes **17** (0.01 mmol), Selectfluor I (1.5 equiv), $\text{B}(\text{C}_6\text{F}_5)_4\text{Li}$ (0.5 equiv), solvent 0.1 mL, Ar, rt; ^b dodecane as the internal standard for GC yield calculation.

Table 2-4. Fluorination of Alkylcarbastannatranes with Phase Transfer Catalyst

Even though the fluorination of 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane **17** provided a decent yield, it was still necessary to perform a control of tetraalkyltin compounds using the conditions developed for alkyl carbastannatranes. The commercially available compound, tetracyclohexyl tin **19**, was used for these reactions. Using a variety of polar and non-polar solvents with and without a PTC additive, no fluorination product was observed from **19**. Entry 6 employed Ritter's conditions

for aryl stannanes, however, still did not result in formation of the desired product.

Entry	Solvent (mL)	Additive/Catalyst	Yield ^b (%)
1	CH ₃ CN (0.2)		0
2	c-Hex (0.15)/CH ₃ CN (0.15)	LiB(C ₆ F ₅) ₄ (0.2 equiv)	0
3	cyclohexane (0.3)		0
4	ether (0.3)		0
5	ether (0.15)/CH ₃ CN (0.15)		0
6	acetone (0.3)	AgOTf (2 equiv)	0

^aReaction condition: tetracyclohexyl tin **19** (0.01 mmol), Selectfluor I (1.5 equiv), solvent 0.1 mL, Ar, rt; ^b fluorobenzene as the internal standard ¹⁹F NMR yield calculation.

Table 2-5. Fluorination of Tetracyclohexyl Tin

Next, we investigated the use of different electrophilic fluorinating reagents in reactions with alkylcarbostannanes. With the development of electrophilic fluorination, several fluorination reagents with different reactivity, oxidation ability, and solubility, have become commercially available. Fluorodi(benzenesulfonyl)amine (NFSI) **21**, 1-fluoropyridinium triflate **22**, 1,1'-difluoro-2,2'-bipyridinium bis(tetrafluoroborate) **23** and N-fluoropyridinium pyridine heptafluorodiborate **24** were developed as possible alternatives to Selectfluor. The best yield

with fluorodi(benzenesulfonyl)amine (NFSI) **21** was 48% in toluene (**Table 2-6**). However, no desired product formed using other fluorinating reagents such as 1-fluoropyridinium triflate **22**, 1,1'-difluoro-2,2'-bipyridinium bis(tetrafluoroborate) **23** and N-fluoropyridinium pyridine heptafluorodiborate **24**. There was a difference between use of 1-fluoropyridinium triflate **22** and the use of 1,1'-difluoro-2,2'-bipyridinium bis(tetrafluoroborate) **23** and N-fluoropyridinium pyridine heptafluorodiborate, **24**. While the alkylcarbostannatrane starting material remained in 1-fluoropyridinium triflate reactions, there was no alkyl carbostannatrane left in 1,1'-difluoro-2,2'-bipyridinium bis(tetrafluoroborate) **23** and N-fluoropyridinium pyridine heptafluorodiborate **24** after reactions using certain solvents. Basing on those results, it was possible that BF_4^- or B_2F_7^- may affect the fluorination of alkylcarbostannatrane. Therefore, compound **25** was prepared (**Scheme 2-6**), which were verified by ^{19}F NMR. When compound **25** was applied in fluorination reactions, the yield was not improved.

Entry	Solvent (0.1mL)	GC Yield (%)		
		NFSI	22	23
1	CH_3CN	31	0 ^d	0
2	DMF	24	0 ^d	0

3	THF	39	0 ^d	0
4	toluene	48	0 ^c	0 ^c
5	CH ₃ OH	21	0 ^c	0
6	ClCH ₂ CH ₂ Cl	19	0 ^c	0 ^c

21

22

23

^aReaction condition: carbastannatranes **17** (0.01 mmol), fluorinating reagent (1.5 equiv), solvent 0.1 mL, Ar, rt; ^bdodecane as the internal standard for GC yield calculation; ^ca lot of carbastannane left; ^dsome carbastannane left.

Table 2-6. Fluorination of Alkylcarbastannatranes with different Fluorinating Reagents

Scheme 2-6. Synthesis of Selectfluor Derivative **25**

One of the most important applications for mono-fluorinated organic compound is in PET imaging using. The half-life time of ¹⁸F isotope is around 108 min. Therefore, if the reaction could be performed in minutes with decent yield, it would be more practical and alkylcarbastannatranes would be potential candidates for PET technique. When conversion of substrate **17** was monitored as a function of time, it was found that the fluorination can be done in 5 min with 60% GC yield. It was also found fluorination rate of secondary alkylcarbastannatranes would be faster than its of primary carbastannatranes. The fluorination of

primary alkylcarbstantranes requires one hour at room temperature.

Up to now, one problem for most fluorination reactions was that it would have rearrangement product or reduction/elimination product. Those byproducts would have similar physical and chemical characteristics as desired product, such as close boiling point, and polarity. Hence, the purification of desired product would be difficult. Fortunately, fluorination of alkylcarbstantranes did not form reduction/elimination or rearrangement byproducts.

Entry	Variations from above	Yield ^b (%)
1	none	62
2	0 °C instead of rt; 2 h instead of 5 min	50
3	Selectfluor II instead of Selectfluor I	50
4	NFSI 21 instead of Selectfluor I	31
5	22 Instead of Selectfluor I	0
6	DMSO instead of CH ₃ CN, 2 h instead of 5 min	0
7	DMF instead of CH ₃ CN; 2 h instead of 5 min	45
8	methanol instead of CH ₃ CN; 2 h instead of 5 min	39
9	Cy ₄ Sn instead of 17 ; 2 h instead of 5 min	0

^a Reaction condition: carbastannatranes **17** (0.01 mmol), fluorination reagent (1.5 equiv), solvent 0.1 mL, Ar, rt; ^b dodecane as the internal standard for GC yield calculation.

Table 2-7. Fluorination of Alkylcarbastanntranes

Based upon the series of screens, the optimized condition was found and representative factors was summarized in **Table 2-7**. Using the optimized condition, the substrate scope of this fluorination reaction was explored (**Scheme 2-7**). Most of racemic alkylcarbastanntranes were prepared from carbastanntranes chloride with corresponding Grignard reagents or zinc reagents. The primary alcohol carbastanntranes could be prepared by reduction of ester carbastanntranes or removal of OTBS group. The reactions were run on 0.25 mmol scale twice. The yield was calculated by ¹⁹F NMR, in which fluorobenzene was used as the internal standard. Meanwhile, it was also confirmed by GC calculation yield. Most of fluorination products were confirmed by GCMS or HRMS, for those products were volatile. The yield range was from 50% to 70%. The fluorinations were run under mild conditions, so that sensitive functional groups were well tolerated, such as alcohols, ester, boronate esters and silyl ether. For alcohol substrate **37**, it was hard to find one method to prepare it directly. Boronate ester would be potentially useful for further organic synthesis, for reactive Bpin group has a wide application, such as conversion to alcohol and Suzuki reaction nucleophile. Fluorination of an oxygen- containing heterocycle also proceeded smoothly. Because the C–Sn bond alkyl carbastanntranes tolerates even the harshest

reduction conditions, remote functional groups can be readily modified without disturbing the carbastannatrane fragment. Thus, our fluorination process should enable late-stage access to potentially important fluorinated molecules that would be particularly difficult, if not impossible, to prepare using existing methods of direct fluorine incorporation.

Scheme 2-7. Electrophilic Fluorination of Alkylcarbastannatrane

Once primary and secondary alkylcarbastannatrane were successfully fluorinated with decent yield. The tertiary alkylcarbastannatrane were tried to be synthesized and employed into fluorination. There were three possible compounds for intended testing. However, it was found that the synthesis of compound **43** and **44** failed at last step, reaction between

corresponding zinc (or lithium) reagent with carbastanntranes chloride. The reason was unknown. Up to now, we only can successfully synthesize 5-(tert-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane **45**. For the potential product would have very low boiling point, so the fluorination was run at 0 °C. On ^{19}F NMR, it showed the possible peak from 2-fluoro-2-methylpropane **46**.

Scheme 2-8. Potential Tertiary Alkyl Carbastanntranes and Fluorination of 5-(tert-butyl)-1-aza-5-stannabicyclo[3.3.3]undecane

Except fluorination, other electrophilic halogenations were employed onto alkyl carbastanntranes. In the chlorination reactions, two chlorinating reagents, trichloroisocyanuric acid (TCCA) **47** and N-chlorosuccinimide (NCS) **48**, were used for screen (**Table 2-8**). It was found that TCCA would be a better one and could be used into different solvents with decent yield, such as acetontirle, DMF, THF, and toluene. Narrowing down the range of solvent range, bromination and iodination were tested. In all, to keep the same condition as fluorination, acetonitrile was chosen for larger scale reactions. Using primary and secondary alkyl

carbastannatrane nucleophiles, the corresponding chlorinated, brominated (**Table 2-9**), and iodinated products (**Table 2-10**) were cleanly produced in good yield through reactions with trichloroisocyanuric acid **47**, N-bromosuccinimide (NBS) **49**, and iodine, respectively.

Entry	Solvent	Cl^+	GC yield ^b (%)
1	CH ₃ CN	TCCA	68
2	DMF	TCCA	68
3	DMSO	TCCA	7
4	THF	TCCA	67
5	toluene	TCCA	67
6	CH ₃ CN	NCS	55
7	DMF	NCS	11
8	THF	NCS	9
9	MTHF	NCS	13

^aReaction condition: carbastannatrane **17** (0.01 mmol), chlorinating reagents (1.5 equiv.), solvent (0.1 mL), rt, under Ar; ^b dodecane as the internal standard for GC yield calculation.

Table 2-8 Optimization of Chlorination of 5-(4-phenylbutan-2-yl)-1-aza-5- stannabicyclo [3.3.3] undecane

Entry	1	2	3
Solvent	CH ₃ CN	THF	MTHF
GC yield ^b (%)	70	71	63

^aReaction condition: carbastannane **17** (0.01 mmol), NBS (1.5 equiv.), solvent (0.1 mL), rt, under Ar; ^bdodecane as the internal standard for GC yield calculation.

Table 2-9 Optimization of Bromination of 5-(4-Phenylbutan-2-yl)-1-aza -5-stannabicyclo [3.3.3]undecane

Entry	1	2	3	4
Solvent	CH ₃ CN	DMF	THF	toluene
GC yield ^b (%)	64	53	54	53

^aReaction condition: carbastannane **17** (0.01 mmol), I₂ (1.5 equiv.), solvent (0.1 mL), rt, under Ar; ^bdodecane as the internal standard for GC yield calculation.

Table 2-10 Optimization of Iodination of 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo

[3.3.3]undecane

Using primary and secondary alkylcarbostannatrane nucleophiles, the corresponding chlorinated, brominated, and iodinated products were cleanly produced in good yield (**Scheme 2-9**) through reactions with trichloroisocyanuric acid (TCCA), N-bromosuccinimide (NBS), and iodine, respectively. Thus, alkylcarbostannatranes can be broadly utilized in electrophilic halogenation reactions with one set of reaction conditions

Scheme 2-9. Electrophilic Halogenation of alkylcarbostannatranes

Other alkylcarbostannatranes with heteroatom (**Scheme 2-10**), such as 5-(3-(thiophen-2-yl)propyl)-1-aza-5-stannabicyclo[3.3.3]undecane **60**, 9-(3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)propyl)-9H-carbazole **61**, and 5-(1-methylpiperidin-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane **62** were designed to synthesize for followd fluorination. Unfortunately, it is difficult to synthesize these

carbastannanes and the fluorination of carbastannanes **60** and **62** results in only trace of desired product.

Scheme 2-10. Alkylcarbastannanes with Heteroatom

To understand the mechanism of fluorination of alkylcarbastannanes, the enantioenriched alkylcarbastannanes were synthesized by two routines (**Scheme 2-11**). One routine was to prepare enantioenriched alkylcarbastannanes from enantioenriched mesylate by S_N2 reaction with (1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)lithium **63**. Another routine was that racemic alkylcarbastannanes prepared from Grignard or zinc reagents were separated by chiral HPLC.

Scheme 2-11. Synthesis of Enantioenriched Alkyl Carbastannanes. a) mesyl chloride, TEA, CH_2Cl_2 ; b) (1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)lithium, THF; c) carbastannane chloride; d) chiral HPLC.

Enantioenriched compound **64** was initially employed to react with Selectfluor I at room

temperature. The e.s. value was 81% on 0.01 mmol scale reaction. To improve enantiospecificity of fluorination, some conditions were screened on 0.01 mmol scale reactions. Selectfluor II provided the similar es value as Selectfluor I at -5 °C in the reaction. However, the fluorination yield from Selectfluor II was very low at -5 °C. Once some other polar solvents, such as DMF and MeOH, were used for the fluorination and provided high enantiospecific desired product. The yield went down for those solvents when reactions were run at -5 °C. Some alcohols, such as ethanol, isopropanol, and tert-butanol, were employ into fluorinations at room temperature. Unfortunately, there was no desired product. The entry 3 would be the optimized condition for fluorination of enantioenriched alkyl carbastannanes. Enantioenriched ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate also were used for screening as the substrate. It provided the similar results as of compound **64**.

Entry	Solvent (0.1 mL)	Temperature	Selectfluor	es (%)
1	CH ₃ CN	rt	I	81
2	CH ₃ CN	rt	II	65
3	CH ₃ CN	-5 °C	I	90
4	CH ₃ CN	-5 °C	II	91

5	DMF	rt	I	88
6	DMF	-5 °C	I	NA ^b
7	CH ₃ OH	rt	I	88
8	CH ₃ OH	-5 °C	I	NA ^b

^a Reaction conditions: carbasstantrane **64** (0.01 mmol), electrophile (1.5 equiv), solvent 0.1 mL, Ar.; ^b The yield was too low.

Table 2-11. Fluorination of Enantioenriched Alkylcarstantrane with Different Solvents and Temperature.

The optimized condition from 0.01 mmol scale reactions could not be applied into the larger scale fluorination, even it was just 0.025 mmol. The enantiospecificity of fluorination was 62% at -5 °C for 0.025 mmol scale reaction. As we all know, Selectfluor I reaction would undergo radical mechanism, which resulted in partially racemization. One general method was addition of radical trap, which was also reported in Aggrawal's fluorination paper. It was found that styrene would be the best radical trap at -5 °C. (**Table 2-12**)

Entry	Radical trapper	Temperature	es (%)
1	TEMPO	rt	NA ^{b,d}
2	BHT	rt	51 ^b

5	Styrene	-5 °C	83 ^c
6	Styrene	rt	58 ^c
7	Sulfide	rt	NA ^{b,d}
8	9,10-dihydroanthracene	rt	81

^a Reaction condition: carbastannane **64** (1 equiv.), electrophile (1.5 equiv), solvent (0.1 mL for 0.01 mmol reaction; 0.2 mL for 0.025 mmol reaction); ^b 0.01 mmol scale reaction; ^c 0.025 mmol scale reaction; ^d no desired product.

Table 2-12. Fluorination of Enantioenriched Alkylcarstannane with Different Radical Trap

During the fluorination procedure, it may form cation $[N(CH_2CH_2CH_2)_3Sn]^+$ **66**, which was reported by Fillion.^[47] The cation may react with enantioenriched alkylcarbastannanes to form corresponding enantiomer, which would result in racemization. To reduce the possible formation of enantiomer, some additives were added into fluorination, such as PPh₃, pyridine, triethylamine, pyrrolidine, tetrabutylammonium fluoride, and 4-(dimethylamino)pyridine. It was found that pyridine would improve the fluorination enantiospecificity.

Up to now, a series of factors have been investigated, such as solvents, reaction temperature, radical trapper, and additives. It was found that the optimized condition for fluorination required styrene and pyridine at -5 °C and this condition could be used for 0.1 mmol scale reactions. Using the optimized conditions, the scope of substrates was explored. When an enantioenriched benzylcarbastannane was employed in this fluorination reaction, low stereospecificity was observed (**Scheme 2-12**). The increased propensity of benzylic nucleophiles to react via radical pathways when in the presence of strongly oxidizing reagents such as Selectfluor I.

Scheme 2-12. Fluorination of (S)-5-(1-phenylpropyl)-1-aza-5-stannabicyclo[3.3.3]undecane

Without styrene and pyridine, highly stereospecific halogenations (chlorination, bromination and iodination) were achieved under standard conditions. For iodination, iodine was not a suitable electrophile for stereospecific reaction. To improve the enantiospecificity, two more different electrophiles, N-chlorosuccinimides (NIS) **69** and ICl , were used for screen. Based upon the results, NIS was chosen as the electrophile and THF as the solvent for iodination (**Table 2-13**). Those conditions could be used for 0.1 mmol scale reactions

Entry	Electrophile	Solvent	es ^b (%)	GC yield ^c (%)
1	I_2	CH_3CN	70 ^d	64
2	NIS	CH_3CN	97 ^e	11
3	ICl	CH_3CN	83 ^e	49
4	NIS	THF	93 ^d	55

^aReaction condition: carbastannane **64** (1 equiv), electrophile (1.5 equiv), solvent (0.1 mL for 0.01 mmol reaction; 0.2 mL for 0.025 mmol reaction); ^b at -5 °C; ^c at rt, dodecane as the internal standard; ^d 0.025 mmol; ^e 0.01 mmol.

Table 2-13. Optimization of Iodination of 5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo [3.3.3]undecane

The enantioenriched secondary alkyl carbastannanes were employed into halogenation with the best condition, as discussed above. The enantiospecificity of fluorination range is from 83% to 90%, however, other stereospecific halogenation of enantioenriched alkylcarbastannanes can be achieved with only nominal loss of enantiopurity. This enables the direct preparation of optically active alkyl halides from enantioenriched alkylcarbastannanes.

Scheme 2-13. Stereospecific electrophilic halogenations of enantioenriched alkylcarbastannanes

2.3. Investigation of Mechanism

The high stereospecific halogenations of enantioenriched alkylcarbastannanes were achieved. It was necessary to probe the proposed mechanism. Aggarwal and Jensen have

previously demonstrated the use of polar solvents such as acetonitrile and methanol support a stereoinvertive S_E2 mechanism in which charge separation is expected to occur in the transition state. Meanwhile, the intramolecular $Sn \leftarrow N$ would stabilize cation $[N(CH_2CH_2CH_2)_3Sn]^+$, that would be helpful for the S_E2 inversion mechanism. The (S)-5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane **81** was prepared from (R)-4-phenylbutan-2-ol **82** and (S)-(3-fluorobutyl)benzene **83** was prepared from (R)-4-phenylbutan-2-ol **82** with DAST. By comparing the two fluoride enantiomers on chiral HPLC results, it was confirmed that fluorination of alkylcarbastannanes was stereoinvertive S_E2 mechanism.

Scheme 2-14. Investigation of mechanism. a) mesyl chloride, TEA, CH_2Cl_2 ; b) (1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)lithium, THF; c) Selectfluor I, styrene, pyridine, CH_3CN ; d) DAST, CH_2Cl_2 .

For the fluorination of alkylcarbastannanes, there are three possible mechanism (Scheme 2-15), radical mechanism, S_E2 retention mechanism, and S_E2 inversion mechanism. Comprehensive current results analysis and literature, S_E2 inversion mechanism would be

primary.

Scheme 2-15. The Possible Mechanisms for Fluorination of Alkylcarbastanntranes

2.4. Fluorination of Arylcarbastanntranes.

Since many research groups reported fluorination of arylstannanes recently, arylcarbastanntranes would be the choice for the fluorination. It may be able to provide the very fast reaction, which will be suitable for the PET technique. The arylcarbastanntranes were prepared by Grignard reagents (or lithium reagents) with carbastanntrane chloride **86** at -78 °C (**Scheme 2-16**). The Ritter's conditions for the silver-mediated fluorination of arylstannanes were applied to the fluorination of aryl carbastanntranes (**Scheme 2-17**), fortunately, there was a product peak on ¹⁹F NMR. However, one major problem came out, there was a limitation of the aryl carbastanntranes. It was found that only 5-phenyl-1-aza-5-stannabicyclo[3.3.3]undecane (**88**) was able to be isolated. Once there were some electron-donating groups on phenyl **89**, desired

compounds were not isolable, for it may react with moisture or oxygen very quickly. Meanwhile, it was hard to prepare the phenyl lithium or Grignard reagents if they were attached with electron-withdrawing groups. The same procedure without silver catalyst was also applied onto arylcarbastannatranes with Selectfluor I. No possible product was found on ^{19}F NMR. Hence, there was no advantage over traditional tri-*n*-butyl aryl stannanes.

Scheme 2-16. Synthesis of Racemic Arylcarbastannatranes

Scheme 2-17. Fluorination of Arylcarbastannatranes via AgOTf

3. Conclusion

In summary, the fluorination of primary and secondary alkylcarbostannanes was studied. The reactions occur without the need of any catalysts or in situ activation of the nucleophile at room temperature due to carbostannane backbone activation. Meanwhile, chlorination, bromination, and iodination were also employed onto primary and secondary alkylcarbostannanes under the same conditions.

For enantioenriched alkylcarbostannanes, the fluorination reactions would proceed through a S_E2 invertive mechanism with styrene as the radical trap at 0 °C. That provides the routine to prepare optically active alkyl fluorides from enantioenriched alkylcarbostannanes. This type of stereospecific electrophilic halogenation also included chlorination, bromination and iodination.

This reaction constitutes an exceedingly rare example of the direct, stereospecific functionalization of configurationally stable, isolable, main group organometallic nucleophiles.

4. References

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5. Experimental data

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5.1. General Reagent/Analytical 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. 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane and Selectfluor I were purchased from Sigma-Aldrich. 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^[1]. Molarities of Grignard reagents and zinc reagents were determined using iodine titration^[2]. Optically active alkylcarbostannatranes were prepared via preparatory chiral HPLC of the racemate or using a previously reported literature procedure.^[3] Reagents and solvents were used as received unless otherwise noted. Flash chromatography was performed using Silicycle silica gel (ultra-pure grade).

All NMR spectra were obtained on a Varian 500 (500 MHz for ^1H and 125 MHz for ^{13}C), a Varian 300 (282 MHz for ^{19}F) or a Bruker 300 (300 MHz for ^1H , 75 MHz for ^{13}C and 282 MHz for ^{19}F). All previously unreported compounds were additionally characterized by high resolution MS. All ^1H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) unless otherwise noted. The following abbreviations are used to express the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad, app = apparent. All ^{13}C NMR spectra are reported in ppm relative to deuteriochloroform (77.23 ppm), and were obtained with ^1H 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 low boiling point fluoride compounds were confirmed by GCMS on Shimadzu GC-MS QP2010S or high resolution MS. All GC yields were calibrated using dodecane or tetradecane as an internal standard. Chiral HPLC analyses were performed using a Shimadzu Prominence HPLC system with binary mobile phase pumps and UV-vis detector (LC-20AB, SPD-20A) using an OJ-RH (dimensions: 4.6 mm x 150 mm; particle size: 5 µm) chiral column (DAICEL CHEMICAL IND., LTD.), or an IA (dimensions: 4.6 mm x 150 mm; particle size: 5 µm) chiral column (DAICEL CHEMICAL IND., LTD.)

5.2. General Procedural Information

Preparation of alkylcarbastannatranes:

General procedure A (preparation of achiral and racemic alkylcarbastannatranes):

Grignard reagents were prepared from the corresponding alkyl chlorides. All reactions were performed in oven-dried glassware under an atmosphere of Ar. The alkylmagnesium reagent (or alkylzinc reagent for ethyl butanoate nucleophile) (2.0-3.0 equiv) was added to a suspension of 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane¹ (1 equiv) in THF 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 Na₂SO₄, and filtered. Solvent was removed under reduced pressure, and the remaining compound was dried *in vacuo* to provide the crude product. The crude alkyltin 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 (preparation of enantioenriched alkylcarbastannatranes):

To an oven-dried round bottom flask containing a stirbar, 5-chloro-1-aza-5-stanna-bicyclo[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) (250 mg, 35 mmol) were added. 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.

Halogenation of racemic alkylcarbastannatranes:

General procedure C:

To an oven-dried screw-top test tube equipped with a stirbar, alkylcarbastannatrane (0.25 mmol) and halogenation reagent (1.5 equiv of Selectfluor I, trichloroisocyanuric acid,

N-bromosuccinimide, or iodine) were added. The test tube was sealed with a screw-top septum and electrical tape. The reaction tube was evacuated (ca. 100 mtorr) and backfilled with argon 3 times using a needle attached to a vacuum manifold. Acetonitrile (1 mL) was added via syringe, and the reaction mixture was allowed to stir (5 min–1 h) at rt. Once the reaction was complete, water (0.5 mL) was added to the reaction mixture. For fluorination reactions, the resulting solution was additionally diluted by ethyl acetate (0.2 mL). Fluorobenzene (0.2 mmol) was added as an internal ^{19}F NMR standard, and the solution was analyzed by unlocked ^{19}F NMR spectroscopy and GCMS. For volatile alkyl fluorides, calibrated yields were obtained by ^{19}F NMR and GC to ensure accuracy of measurement. For other halogenation reactions, the reaction mixture was diluted with ether and washed with brine. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to provide the crude product. The crude reaction products were purified by flash column chromatography (diethyl ether/pentane).

Fluorination of enantioenriched alkylcarbostannatranes:

General procedure D:

To an oven-dried screw-top test tube equipped with a stirbar, the enantioenriched alkylcarbostannatrane (0.1 mmol) was added. The test tube was sealed with a screw-top septum and electrical tape. The reaction tube was evacuated (ca. 100 mtorr) and backfilled with argon 3 times, anhydrous pyridine (0.5 equiv.) was added, and the reaction mixture was then cooled to -5°C in a NaCl/ice bath. A solution of Selectfluor I (1.5 equiv) in acetonitrile (1.1 mL) and

styrene (1 equiv) was added via syringe. After the reaction stirred for 2 h at -5 °C, water (0.2 mL) was added. Fluorobenzene (0.05 mmol) was added as an internal standard, and the solution was analyzed by unlocked ^{19}F NMR spectroscopy. The ee value was determined by HPLC or chiral GC analysis.

Halogenation (Cl, Br and I) of enantioenriched alkylcarbastannatranes:

General procedure E:

To an oven-dried screw-top test tube equipped with a stirbar, the enantioenriched alkylcarbastannatrane (0.1 mmol) was added. The test tube was sealed with a screw-top septum and electrical tape. The reaction tube was evacuated (ca. 100 mtorr) and backfilled with argon 3 times, then cooled to -5 °C in a NaCl/ice bath. A solution containing the halogenation reagent [trichloroisocyanuric acid (0.15 mmol) in CH_3CN (1 mL), *N*-bromosuccinimide (0.15 mmol) in CH_3CN (1 mL), or *N*-iodosuccinimide (0.15 mmol) in 1 mL THF] was added dropwise via syringe. After the reaction stirred for 3 h at -5 °C, water (0.2 mL) was added. The organic layer was used for GC and HPLC analysis. The GC yield was determined using tetradecane as an internal calibration standard. The ee value was determined by HPLC or chiral GC analysis.

5.3. Compound Characterization Data

1-(4-Phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3]undecane.^[1] General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1.35 mmol) and (4-phenylbutan-2-yl)magnesium chloride (4 mmol). A yellow liquid (0.413 g, 78%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 7.25-7.28 (m, 2H), 7.16-7.19 (m, 3H), 2.50-2.65 (m, 2H), 2.36 (t, *J* = 6.0 Hz, 6H), 1.68-1.81 (m, 2H), 1.65 (quint, *J* = 6.0 Hz, 6H), 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. ¹³C NMR (125 MHz, CDCl₃): δ 143.9, 128.6, 128.3, 125.5, 55.0, 39.0, 36.5, 24.2, 23.6, 18.6, 5.6 ppm.

1-(Dodecan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (1.5 mmol) and dodecan-2-ylmagnesium chloride (4.4 mmol). A yellow liquid (0.482 g, 75%) was isolated. ¹H NMR (500 MHz, CDCl₃): 2.34 (t, *J* = 5.75 Hz, 6H), 1.63 (app. quint, *J* = 6.6 Hz, 6H), 1.45-1.13 (m, 18H), 1.04 (d, *J* = 1.51, 3H), 0.88 (t, *J* = 6.6 Hz, 3H), 0.72 (m, 1H), 0.62 (t, *J* = 6.7 Hz, 6H) ppm; ¹³C NMR (125

MHz, CDCl₃): δ 54.9, 36.6, 32.2, 30.2, 30.1, 29.98, 29.90, 29.6, 24.2, 23.65, 23.55, 22.94, 18.9, 14.4, 5.6 ppm. HRMS (ES⁺): Calcd (M-Na)⁺ 444.2341; Found 444.2332.

Ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate.^[1] General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (3 mmol) and (4-ethoxy-4-oxobutan-2-yl)zinc iodide (6.1 mmol). A yellow oil (509 mg, 45%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 4.09 (quart, *J* = 7.0 Hz, 2H), 2.40 (m, 1H), 2.35 (t, *J* = 6.0 Hz, 6H), 2.25 (m, 1H), 1.64 (app. quint, *J* = 6 Hz, 6H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.02-1.13 (m, 4H), 0.65 (t, *J* = 6.5 Hz, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 175.5, 60.0, 54.9, 40.7, 23.5, 19.8, 18.4, 14.6, 5.2 ppm.

The ester derivative could also be prepared using a zincated stannatrane nucleophile via the following process: Under argon, stannatrane lithium (1 equiv) (prepared via general procedure B) was added to a 2 M solution of Et₂Zn in ether (1 equiv) at 0 °C. This mixture was allowed to stir at 0 °C for 30 min. It was then added to a solution of ethyl 3-((methylsulfonyl)oxy)butanoate in hexanes, and allowed to stir overnight at rt. The reaction mixture was washed with water, and extracted with ether three times. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by reverse phase flash chromatography (100% CH₃CN). A yellow liquid was isolated (32% yield).

5-(Tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane.^[1] General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.42 mmol) and (tetrahydro-2H-pyran-4-yl)magnesium chloride (1.26 mmol). A pale yellow solid (121 mg, 84%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 3.87 (m, 2H), 3.33 (dt, *J* = 11.0, 2.0 Hz, 2H), 2.36 (t, *J* = 6 Hz, 6H), 1.64 (app. quint, *J* = 6.0 Hz, 6H), 1.50-1.65 (m, 4H), 0.90 (tt, *J* = 12.5, 4.0 Hz, 1H), 0.64 (t, *J* = 6.5 Hz, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 71.0, 54.8, 31.3, 26.0, 23.4, 4.6 ppm.

5-(1-Phenylethyl)-1-aza-5-stannabicyclo[3.3.3]undecane.^[1] General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.3 mmol) and (1-phenylethyl)magnesium chloride (1.5 mmol). A yellow oil (90 mg, 82%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 7.15 (t, *J* = 7.5 Hz, 2H), 6.90-7.00 (m, 3H), 2.30 (t, *J* = 6.0 Hz, 6H), 2.21 (quart, *J* = 7.5 Hz, 1H), 1.61 (app. quint, *J* = 6.0 Hz, 6H), 1.44 (d, *J* = 7.5 Hz, 3H), 0.61 (dt, *J* = 6.5, 3 Hz, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 151.5, 128.0, 124.9, 121.7, 54.7, 32.7, 23.5, 16.7, 5.3 ppm.

1-(3-Phenylpropyl)-5-aza-1-stanna-bicyclo[3.3.3]undecane.^[3] General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.88 mmol) and (3-phenylpropyl)magnesium chloride (2.5 mmol). A yellow liquid (274 mg, 82%) was isolated. ¹H NMR (500 MHz, CDCl₃) 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 (app. 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. ¹³C NMR (125 MHz, CDCl₃) δ : 143.6, 128.7, 128.3, 125.5, 54.9, 41.5, 29.9, 23.6, 16.4, 6.8 ppm.

1-Decyl-5-aza-1-stanna-bicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (2 mmol) decylmagnesium chloride (5 mmol). A pale yellow solid (538 mg, 67%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 2.36 (t, J = 5.5 Hz, 6H), 1.63 (app. quint, J = 6.2 Hz, 6H), 1.26 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H), 0.62 (t, J = 6.6 Hz, 6H); 0.40 (t, J = 8 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 55.0, 34.9, 32.2, 29.96, 29.95, 29.7, 29.6, 27.4, 23.6, 22.9, 16.4, 14.4, 6.8 ppm. HRMS (ES⁺): Calcd (M-Na)⁺ 416.2028;

Found 416.2021.

1-(4-tert-Butylbenzyl)-5-aza-1-stanna-bicyclo[3.3.3]undecane. General procedure A was employed using 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (0.5 mmol) and (4-tert-butylbenzyl)magnesium chloride (1.42 mmol). A pale yellow solid (172 mg, 85%) was isolated. ^1H NMR (500 MHz, CDCl_3): δ 7.11 (d, $J = 8.3$ Hz, 2H), 6.81 (d, $J = 8.1$ Hz, 2H), 2.33 (t, $J = 5.7$ Hz, 6H), 1.90 (s, 2H), 1.62 (app. quint, $J = 6.6$ Hz, 6H), 1.27 (s, 9H), 0.64 (t, $J = 6.7$ Hz, 6H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 144.0, 143.3, 128.2, 126.0, 125.4, 124.9, 54.8, 34.3, 31.8, 26.3, 23.5, 6.7 ppm. HRMS (ES^+): Calcd ($\text{M}-\text{Na}$) $^+$ 422.1559; Found 422.1557.

5-(Pent-4-en-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane. General procedure B was employed using (1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)lithium (9 mmol, 1.5 equiv.) and pent-4-en-2-yl methanesulfonate (6 mmol, 1 equiv.). The reaction stirred at 25 °C for 3 hours. The reaction mixture was extracted with ethyl ether (60 mL), followed by brine (100 mL), and dried over Na_2SO_4 . The reaction solution was filtered and concentrated to provide the crude

product. The crude product was purified by C18 silica (100% acetonitrile). A colorless liquid (305 mg, 15%) was isolated. ^1H NMR (300 MHz, CDCl_3): 5.83-5.69 (m, 1H), 4.96-4.86 (m, 2H), 2.35 (t, $J = 5.8$ Hz, 6H), 2.27-2.05 (m, 2H), 1.68- 1.60 (m, 6H), 1.04 (d, $J = 7.5$ Hz, 3H), 0.82-0.69 (m, 1H), 0.64 (t, $J = 6.5$ Hz, 6H) ppm; ^{13}C NMR (75 MHz, CDCl_3): 140.8, 113.7, 77.43, 54.9, 40.7, 23.6, 18.3, 5.66 ppm. LCMS Calcd (M-H) $^+$ 330.1240; Found 330.1239.

5-(4,5-bis(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)-1-aza-5-stannabicyclo[

3.3.3]undecane. To an oven-dried test tube with screw-top septum, 5-(pent-4-en-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.4 mmol, 1 equiv.), K_2CO_3 (1.6 mmol, 4 equiv.) and $(\text{Bpin})_2$ (1.2 mmol, 3 equiv.) was added. The reaction tube was evacuated and backfilled with argon three times. With the tube under a positive pressure of argon, *t*-BuOH (anhydrous, 1 mL) and H_2O (degassed, 25 μL) were added. The reaction mixture was stirred at 60 $^\circ\text{C}$ for 12 h, washed with water and extracted with ether 3 times. The combined organic layers were dried over Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by reverse phase flash column chromatography (100% CH_3CN). A colorless liquid (165 mg, 71%) was isolated. The dr for the product is 1:1.2. ^1H NMR (300 MHz, CDCl_3): 2.33 (t, $J = 5.4$ Hz, 6 H), 1.66-1.61 (m, 7H), 1.51-1.34 (m, 1H), 1.22 (d, $J = 1.3$ Hz, 24H), 1.06 -0.98 (m, 3H), 0.83-0.72 (m, 4H), 0.65-0.61 (m, 6H) ppm; ^{13}C NMR (75 MHz, toluene- d_8): δ 82.6, 82.5, 54.93

(minor), 54.92 (major), 40.8, 40.3, 25.13, 25.11, 25.09, 25.05, 25.03, 24.98, 24.96, 24.94, 24.08, 23.94 (minor), 23.92 (major), 23.7, 22.5, 19.0, 18.7, 5.45 (minor), 5.39 (major) ppm. HRMS (ESI): Calcd (M-Na)⁺ 606.2932; Found 606.2934.

3-(5-Aza-1-stanna-bicyclo[3.3.3]undecan-1-yl)butan-1-ol. To an oven-dried vial with a stirbar, ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl)butanoate (0.5 mmol) and LiAlH₄ (4 mmol) were added. The vial was sealed with a screw-top septum and electrical tape. The reaction vessel was evacuated (ca. 100 mtorr) and backfilled with argon 3 times. Then, dry ether (2 mL) was added via syringe. The reaction was stirred overnight at room temperature. The reaction was quenched with an aqueous solution of NaH₂PO₄ solution and extracted with hexane 3 times. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure. A colorless liquid (141 mg, 85%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 3.61 (q, *J* = 5.6 Hz, 2H), 2.36 (t, *J* = 5.5 Hz, 6H), 1.75 (m, 1H), 1.65 (quint, *J* = 5.9 Hz, 6H), 1.16 (m, 1H), 1.07 (d, *J* = 7.5 Hz, 3H), 0.76 (m, 1H), 0.65 (t, *J* = 6.6 Hz, 6H) ppm. ¹³C NMR(125 MHz, CDCl₃): δ 63.3, 54.9, 39.2, 23.6, 19.1, 18.2, 5.4 ppm. HRMS (ES⁺): Calcd (M-H)⁺ 326.1219; Found 326.1219.

(S)-3-(5-Aza-1-stanna-bicyclo[3.3.3]undecan-1-yl)butan-1-ol The preceding procedure was employed using (S)-3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl) butanoate (0.15 equiv) and LiAlH_4 (1.2 mmol). A colorless liquid (44 mg, 88%) was isolated.

Preparation of racemic and enantioenriched alkylcarbostannatranes S1, S2, and S3.

(R)-4-((tert-Butyldimethylsilyl)oxy)butan-2-ol.^[4]

To a round bottom flask, 4-(dimethylamino)pyridine (DMAP, 0.5 mmol, 10 mol %), *tert*-butyldimethylsilyl chloride (TBDMSCl, 6 mmol, 1.2 equiv), triethylamine (TEA, 10 mmol, 2 equiv), (R)-butane-1,3-diol (5 mmol, or butane-1,3-diol for racemic reaction), and dichloromethane (DCM, 30 mL) were added. The reaction was stirred overnight at room temperature. The reaction was quenched by water and extracted with DCM three times. The

combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by purified by flash column chromatography using ethyl acetate/dichloromethane (1:9). A colorless liquid (868 mg, 85%) was isolated. ¹H NMR (300 MHz, CDCl₃): δ 4.02 (m, 1H), 3.85 (m, 2H), 3.36 (br s, 1H), 1.65 (m, 2H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 68.5, 63.0, 40.2, 26.1, 23.6, 18.3, -5.31, -5.36 ppm.

(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)butan-2-yl methanesulfonate.^[5]

To a round bottom flask, (*R*)-4-((*tert*-butyldimethylsilyl)oxy)butan-2-ol (3 mmol, 4-((*tert*-butyldimethylsilyl)oxy)butan-2-ol for racemic reaction), TEA (6 mmol, 2 equiv), and anhydrous diethyl ether (20 mL) were added. The reaction flask was cooled to 0 °C and mesyl chloride (4.5 mmol, 1.5 equiv) was added. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched by water and extracted with ether three times. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by purified by flash column chromatography (ethyl acetate/hexane = 1:9). A colorless liquid (771 mg, 91%) was isolated. ¹H NMR (300 MHz, CDCl₃): δ 4.95 (m, 1H), 3.71 (m, 2H), 3.0 (s, 3H), 1.84 (m, 2H), 1.47 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 77.7, 58.7, 39.7, 38.4, 26.1, 21.9, 18.4, -5.18, -5.19 ppm.

(S)-5-(4-((*tert*-Butyldimethylsilyl)oxy)butan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane

(S1).

General procedure B was followed.^[3] The mixture was purified by reverse phase flash column chromatography (DCM/CH₃CN = 1:9). A light yellow oil was isolated (Yield: 40%). The ee value (97% ee) was determined after deprotection to 3-(5-aza-1-stanna-bicyclo[3.3.3]undecan-1-yl)butan-1-ol. ¹H NMR (300 MHz, CDCl₃): δ 3.56 (m, 2H), 2.35 (t, *J* = 5.7 Hz, 6H), 1.65 (m, 8H), 1.06 (d, *J* = 7.2 Hz, 2H), 0.89 (s, 10H), 0.64 (t, *J* = 6.7 Hz, 6H), 0.049 (s, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 64.1, 54.9, 39.5, 26.3, 26.3, 26.2, 23.6, 19.6, 18.7, 18.6, 5.4, -4.8, -4.8 ppm. HRMS (ES⁺): Calcd (M-Na)⁺ 470.1880; Found 470.1868.

(S)-3-(5-Aza-1-stanna-bicyclo[3.3.3]undecan-1-yl)butan-1-ol (S2).

(S)-5-(4-((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-1-aza-5-stannabicyclo[3.3.3] undecane (0.01 mmol) and THF (0.2 mL) were combined in a 3 mL vial. The vial was cooled to 0 °C, and TBAF

(1.2 equiv, 1M in THF) was added dropwise. The reaction was allowed to stir at 0 °C for 30 min, and then at room temperature for 3 h. The reaction was quenched with water and extracted with ether three times. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure. The ee value (97% ee) was determined by HPLC analysis. The NMR spectra of the isolated compound matched that of the racemic sample.

(S)-3-(1-Aza-5-stannabicyclo[3.3.3]undecan-5-yl)butyl benzoate (S3).

(S)-5-(4-(((tert-butyldimethylsilyl)oxy)butan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.2 mmol) (or (5-(4-(((tert-butyldimethylsilyl)oxy)butan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane for the racemic reaction) and THF (0.5 mL) were combined in a 3 mL vial. Tetra-*n*-butylammonium fluoride (TBAF 0.24 mmol, 1.2 equiv, 1M in THF) was added dropwise to the vial at rt. The reaction was stirred for 30 min at 0 °C, and then for 3 h at room temperature. Triethylamine (0.8 mmol, 4 equiv) and benzoyl chloride (0.8 mmol, 4 equiv) were then added to the reaction, which was allowed to stir overnight at rt. The reaction was washed by NaHCO₃ (aq.) and extracted with ether three times. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by purified by reverse phase flash column chromatography (100% CH₃CN). A colorless liquid (77 mg, 88%) was isolated. The ee value (97% ee) was determined following hydrolysis to

3-(5-aza-1-stanna-bicyclo[3.3.3]undecan-1-yl)butan-1-ol. ^1H NMR (300 MHz, CDCl_3): δ 8.05 (m, 2H), 7.54 (m, 1H), 7.43 (m, 2H), 4.30 (t, $J = 6.7\text{ Hz}$, 2H), 2.36 (t, $J = 5.9\text{ Hz}$, 6H), 2.0-1.81 (m, 2H), 1.65 (m, 6H), 1.13 (d, $J = 7.5\text{ Hz}$, 3H), 0.89-0.80 (m, 1H), 0.68 (t, $J = 6.7\text{ Hz}$, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 167.0, 132.8, 131.0, 129.8, 128.5, 65.8, 54.9, 35.0, 23.6, 19.8, 18.4, 5.3 ppm. HRMS (ES^+): Calcd ($\text{M}-\text{Na}$) $^+$ 452.1301; Found 452.1315.

(3-Fluorobutyl)benzene (31) General procedure C was performed using 1-(4-phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 64% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -173.0 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm . The identity of the product was further confirmed by GCMS analysis. EIMS: m/z (%) = 152.10 (31.02), 132.05 (1.26), 117.05 (13.84), 105.05 (9.18), 91.05 (100), 92.05 (60.77), 77.05 (7.86), 65.05 (13.11), 51.05 (5.37), 39.05 (5.6).

(*R*)-(3-Fluorobutyl)benzene (73) General procedure D was performed using enantioenriched 1-(4-phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.1 mmol) and Selectfluor I (0.15 mmol). Water was added to quench the reaction. The organic layer was run on HPLC to determine ee value. The fluorinated product was formed in 56% yield as determined by ^{19}F

NMR spectroscopic analysis of the crude reaction mixture.

(1-Fluoroethyl)benzene (32) General procedure C was performed using 5-(1-Phenylethyl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 55% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -166.9 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm. The identity of the product was further confirmed by GCMS analysis. m/z (%) = 124.1 (36.53), 109.05 (100), 103.05 (8.69), 83.5 (8.94), 77.05 (8.44), 63.05 (2.77), 51.05 (9.8), 39.05 (3.55).

2-Fluorododecane (34) General procedure C was performed using 1-(dodecan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 60% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -171.6 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm. The identity of the product was further confirmed by GCMS analysis. m/z (%) = 180.1

(0.02), 168.15 (2.36), 140.1 (5.13), 125.1 (8.24), 111.1 (20.55), 98.1 (17.43), 97.1 (49.9), 84.1 (38), 83.1 (63.93), 82.1 (18.45) 71.1 (24.14), 70.1 (66.43), 69.1 (79.52), 57.1 (73.51), 56.1 (64.51), 55.1 (88.1), 43.1 (100), 42.1 (24.14), 41.1 (72.35).

Ethyl 3-fluorobutanoate (35) General procedure C was performed using ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl) butanoate (0.25 mmol) Selectfluor I (0.375 mmol). The fluorinated product was formed in 64% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -172.0 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm. The identity of the product was further confirmed by GCMS analysis. m/z (%) = 134.05 (0.19), 114.05 (5.07), 107.05 (19.46), 99.05 (7.99), 89.05 (100), 87.05 (11.65), 86.05 (9.53), 73.05 (7.52), 69.05 (12.68), 61.05 (42.88), 60 (15.83), 55.1 (5.68), 47.05 (17.48), 45.1 (26.38), 43.5 (20.87), 42.1 (42.33), 41.1 (22.66), 39.05 (6.4), 35.1 (0.01).

(R)-Ethyl-3-fluorobutanoate (75) General procedure D was performed using enantioenriched ethyl 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl) butanoate (0.1 mmol) and Selectfluor I (0.15 mmol). Water was added to quench the reaction. The organic layer was run on chiral GC to determine ee value. The fluorinated product was formed in 49% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

3-Fluorobutan-1-ol (37) General procedure C was performed using 3-(5-aza-1-stanna-bicyclo[3.3.3]undecan-1-yl)butan-1-ol (0.25 mmol) Selectfluor I (0.375 mmol). After the reaction was complete, triethylamine (2 mmol, 8 equiv) and benzoyl chloride (1 mmol, 4 equiv) were added to the reaction. The reaction mixture was stirred overnight. The 3-fluorobutyl benzoate was formed in 50% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. The reaction was washed by water and extracted with ether 3 times. The combined organic layers were dried over Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by purified by flash column chromatography. 3-Fluorobutyl benzoate is isolated as a colorless liquid. See characterization data for # below.

(*R*)-3-Fluorobutan-1-ol (74) General procedure D was performed using enantioenriched 3-(5-aza-1-stanna-bicyclo[3.3.3]undecan-1-yl) butan-1-ol (0.1 mmol) and Selectfluor I (0.15 mmol). After the reaction was complete, triethylamine (0.8 mmol, 8 equiv) and benzoyl chloride (0.4 mmol, 4 equiv) were added to the reaction. It was stirred overnight. The reaction was washed by water and extracted with ether 3 times. The combined organic layers were dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by purified by flash column chromatography. 3-Fluorobutylbenzoate was isolated as the colorless liquid and run on HPLC to determine ee value. The fluorinated product was formed in 59% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

2,2'-(4-fluoropentane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (33) General procedure C was employed using 5-(4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)-1-aza-5-stanna-bicyclo[3.3.3]undecane (0.1 mmol) and Selectfluor I (0.15 mmol) in acetonitrile (0.5 mL). The reaction was washed by water and extracted with ether 3 times. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by purified by flash column chromatography (ether/hexane = 15:85). A colorless liquid (20 mg, 58%) was isolated. ¹H NMR (300 MHz, CDCl₃): δ 4.86-4.75 (m, 0.45H) and 4.69-4.59 (m, 0.55H) *indicates a diastereomeric ratio of 1:1.2*, 1.95-1.40 (m, 2H), 1.31 (m, 3H), 1.22 (s, 24H), 1.01-0.75 (m, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 91.7 (d, *J* = 21.4 Hz, major), 89.6 (d, *J* = 21.8 Hz, minor), 83.2, 77.4, 41.24, 41.13, 40.97, 40.86, 25.11, 25.10, 25.05, 25.03, 25.02, 25, 24.97, 24.93, 21.65 (minor), 21.35 (major) ppm. . ¹⁹F NMR (282 MHz, CDCl₃): δ -170.63(minor), -172.18 (major) ppm (1F). HRMS (ESI): Calcd (M-Na)⁺ 365.2447; Found 365.2449.

(3-Fluoropropyl)benzene (38) General procedure C was performed using 1- (3-

phenylpropyl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 52% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -219.5 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm. The identity of the product was further confirmed by GCMS analysis. m/z (%) = 138.1 (31.04), 105.05 (3.52), 92.1 (19.94), 91.05 (100), 77 (4.38), 65 (11.29), 51 (4.79), 39.05 (4.97).

1-Fluorodecane (40) General procedure C was performed using 1-decyl-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 66% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -217.8 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm. The identity of the product was further confirmed by GCMS analysis. m/z (%) = 160.10 (0.18), 111.10 (10.15), 97.10 (18.91), 85.10 (15.39), 75 (5.51), 69.05 (35.52), 57.10 (68.19), 55.05 (51.08), 61.05 (10.30), 43.1 (100), 41.1 (56.9), 39.05 (9.93).

1-(*tert*-Butyl)-4-(fluoromethyl)benzene (41) General procedure C was performed using 1-(4-*tert*-butylbenzyl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 56% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -204.2 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm. The identity of the product was further confirmed by GCMS analysis. m/z (%) = 166.1 (21.51), 152.1 (11.14), 151.1 (100), 135.05 (4.28), 123.05 (38.56), 116.05 (2.52), 103.05 (4.8), 91.05 (21.99), 77(4.39), 63 (2.19), 57 (2.55), 51.05 (2.90), 41.05 (14.34), 39 (5.66).

4-Fluorotetrahydro-2H-pyran (36) General procedure C was performed using 5-(tetrahydro-2H-pyran-4-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 53% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. ^{19}F NMR (ethyl acetate/ acetonitrile, 282 MHz): δ -176.5 (m). ^{19}F NMR spectra are referenced based on the internal standard fluorobenzene, which is set at -113.6 ppm. The identity of the product was further confirmed by HRMS analysis. HRMS (ES^+): Calcd (M) $^+$ 104.0637; Found 104.0640.

3-Fluorobutyl benzoate^[6] **(39)** General procedure C was performed using 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl) butyl benzoate (0.25 mmol) and Selectfluor I (0.375 mmol). A colorless liquid (34 mg, 70%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 8.04 (d, *J* = 9.5 Hz, 2H), 7.58-7.55 (m, 1H), 7.46-7.43 (m, 2H), 4.90 (dm, *J* = 47.9 Hz, 1H), δ 4.51 – 4.41 (m, 2H), 2.15 – 1.97 (m, 2H), 1.42 (dd, *J* = 23.9, 6.2 Hz, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 166.6, 133.2, 130.4, 129.7, 128.6, 88.0 (d, *J* = 146.9 Hz), 61.2, 36.3 (d, *J* = 12.3 Hz), 21.3 (d, *J* = 12.8 Hz) ppm. ¹⁹F NMR (282 MHz, CDCl₃): δ -175.51 (1F) ppm.

(*R*)-3-Fluorobutyl benzoate (76) General procedure D was performed using enantioenriched 3-(1-aza-5-stannabicyclo[3.3.3]undecan-5-yl) butyl benzoate (0.1 mmol) Selectfluor I (0.15 mmol). After the reaction was done, water was added to quench the reaction. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by purified by flash column chromatography. 3-fluorobutyl benzoate is isolated as the colorless liquid and run on HPLC to determine ee value.

***tert*-Butyl(3-fluorobutoxy)dimethylsilane (42)** General procedure C was performed using

5-(4-((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-1-aza-5-stannabicyclo [3.3.3]undecane (0.25 mmol) and Selectfluor I (0.375 mmol). The fluorinated product was formed in 62% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. The reaction was washed by water and extracted with ether 3 times. The combined organic layers were dried over Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by flash column chromatography. *tert*-Butyl(3-fluorobutoxy)dimethylsilane is isolated as the colorless liquid. ^1H NMR (300 MHz, CDCl_3): δ 4.97-4.70 (m, 1H), 3.72 (m, 2H), 1.93-1.62 (m, 2H), 1.34 (dd, J = 24.1, 6.2 Hz, 3H), 0.93(s, 9H), 0.059 (s, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 88.2 (d, J = 162.3 Hz) 58.2 (d, J = 5.5 Hz), 40.3 (d, J = 20.4 Hz), 26.1, 21.4 (d, J = 22.3 Hz), 18.5, -5.19, -5.20 ppm. ^{19}F NMR (282 MHz, CDCl_3): δ -175.66 ppm (1F). HRMS (ES^+): Calcd ($\text{M}-\text{Na}$) $^+$ 229.1400; Found 229.1405.

(*R*)-*tert*-Butyl(3-fluorobutoxy)dimethylsilane (77) General procedure D was performed using enantioenriched 5-(4-((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.1 mmol) and Selectfluor I (0.15 mmol). After the reaction was done, TBAF (0.12 mmol, 1.2 equiv) was added to the reaction vial at 0 °C. It was stirred for 30 min at 0 °C, then 3h at room temperature. Triethylamine (0.8 mmol, 8 equiv) and benzoyl chloride (0.4 mmol, 4 equiv) were added to the reaction. It was stirred overnight. The reaction was washed by water and extracted with ether 3 times. The combined organic layers were dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by purified by flash column chromatography. 3-fluorobutyl benzoate was isolated as the colorless liquid and

run on HPLC to determine ee value. The fluorinated product was formed in 59% yield as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

1-(3-Chloropropyl)benzene^[7] (57) General procedure C was employed using 1-(3-phenylpropyl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and trichloroisocyanuric acid (0.375 mmol). A colorless liquid (25 mg, 65%) was isolated. ^1H NMR (500 MHz, CDCl_3): δ 7.31-7.28 (m, 2H), 7.22-7.19 (m, 3H), 3.54-3.52 (t, J = 6.5 Hz, 2H), 2.80-2.77 (t, J = 7.4 Hz, 2H), 2.11-2.07 (quint, J = 7.4, 6.7 Hz, 2H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 140.9, 128.7, 128.6, 126.3, 44.5, 34.2, 33.0 ppm.

1-(3-bromopropyl)benzene^[7] (58) General procedure C was employed using 1-(3-phenylpropyl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and *N*-bromosuccinimide (0.375mmol). A colorless liquid (41 mg, 82%) was isolated. ^1H NMR (500 MHz, CDCl_3): δ 7.31-7.28 (m, 2H), 7.22- 7.19 (m, 3H), 3.38 (t, J = 6.6 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H), 2.20- 2.15 (m, 2H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 140.7, 128.75, 128.7, 126.4, 34.4, 34.2, 33.3 ppm.

1-(3-iodopropyl)benzene^[7] (59) General procedure C was employed using 1-(3-phenylpropyl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and iodine (0.375 mmol). A colorless liquid (42 mg, 68%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 7.31- 7.28 (m, 2H), 7.22- 7.19(m, 3H), 3.17 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.16- 2.22 (m, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 140.6, 128.77, 128.71, 126.4, 36.4, 35.1, 6.5 ppm.

1-(3-Chlorobutyl)benzene (54)^[8] General procedure C was employed using compound 1-(4-phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3] undecane (0.25 mmol) and trichloroisocyanuric acid (0.375 mmol). A colorless liquid (26 mg, 62%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 7.31-7.28 (m, 2H), 7.21-7.20 (m, 3H), 4.03-3.96 (m, 1H), 2.88-2.83 (m, 1H), 2.77-2.71 (m, 1H), 2.06-1.95 (m, 2H), 1.54(d, *J* = 6.6 Hz, 3H) ppm. ¹³C NMR(125 MHz, CDCl₃): δ 141.3, 128.7, 128.6, 126.2, 58.1, 42.1, 33.0, 25.6 ppm.

(R)-(3-Chlorobutyl)benzene (78) General procedure E was performed using enantioenriched 1-(4-phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3] undecane (0.1 mmol) and

trichloroisocyanuric acid (0.15 mmol). After the reaction was done, water was added to quench the reaction. The ee value (93% ee) was determined by HPLC analysis of the organic layer. The yield (81%) was determined by calibrated gas chromatography.

1-(3-Bromobutyl)benzene (55)^[9] General procedure C was employed using compound enantioenriched 1-(4-phenylbutan-2-yl) -5-aza-1-stanna-bicyclo[3.3.3] undecane (0.25 mmol) and *N*-bromosuccinimide (0.375 mmol). A colorless liquid (32 mg, 60%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 7.32-7.28 (m, 2 H), 7.22-7.18 (m, 3 H), 4.11-4.05 (dq, *J* = 9.0, 6.5, 4.5 Hz, 1 H), 2.87 (ddd, *J* = 14.0, 9.0, 5.5 Hz, 1 H), 2.74 (ddd, *J* = 14.0, 9.0, 7.0 Hz), 2.17-2.02 (m, 2 H), 1.73 (d, *J* = 6.7 Hz, 3 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 141.1, 128.7, 128.6, 126.2, 51.0, 42.9, 34.2, 26.7 ppm.

(*R*)-(3-Bromobutyl)benzene (79) General procedure E was performed using enantioenriched 1-(4-phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3] undecane (0.1 mmol) and *N*-bromosuccinimide (0.15 mmol). After the reaction was done, water was added to quench the reaction. The ee value (97% ee) was determined by HPLC analysis of the organic layer. The yield (71%) was determined by calibrated gas chromatography.

1-(3-Iodobutyl)benzene (56)^[9] General procedure C was employed using compound 1-(4-phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.25 mmol) and iodine (0.375 mmol). A colorless liquid (41 mg, 63%) was isolated. ¹H NMR (500 MHz, CDCl₃): δ 7.31-7.28 (m, 2 H), 7.22-7.21 (m, 3 H), 4.15-4.08 (dq, *J* = 9.0, 7.0, 4.5 Hz, 1 H), 2.88-2.82 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1 H), 2.73-2.67 (ddd, *J* = 14.0, 9.0, 7.0 Hz, 1 H), 2.18-2.12 (dtd, *J* = 14.5, 9.0, 5.0 Hz, 1 H), 1.95 (d, *J* = 6.9 Hz, 3 H), 1.92-1.85 (dddd, *J* = 14.5, 9.0, 7.0, 5.0 Hz, 1 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 140.7, 128.7, 128.6, 126.2, 44.6, 36.0, 29.8, 29.2 ppm.

(*R*)-(3-Iodobutyl)benzene (80) General procedure E was performed using enantioenriched 1-(4-phenylbutan-2-yl)-5-aza-1-stanna-bicyclo[3.3.3]undecane (0.1 mmol) and *N*-iodosuccinimide (0.15 mmol). After the reaction was done, water was added to quench the reaction. The ee value (92% ee) was determined by HPLC analysis of the organic layer. The yield (52%) was determined by calibrated gas chromatography.

Use of enantioenriched benzylcarbostannatrane in fluorination reaction:

5.4. Investigation of the Stereochemical Course of the Fluorination Reaction.

(S)-1-(3-Fluorobutyl)benzene (S4)^[10] At -78 °C, to the vial with (R)-4-phenylbutan-2-ol (1 mmol) in DCM (5 mL) was added diethylaminosulfur trifluoride (DAST, 1.2 mmol, 1.2 equiv.) under Ar. The reaction was warmed to room temperature slowly and stirred overnight. The reaction was quenched by water and extracted with ether 3 times. The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by purified by flash column chromatography. A colorless liquid (80.6 mg, 53%) was isolated. ¹H NMR (300 MHz, CDCl₃): 7.33-7.26 (m, 2H), 7.23-7.17 (m, 3H), 4.66 (dm, *J* = 49.1 Hz, 1H), 2.86-2.64 (m, 2H), 2.08-1.71 (m, 2H), 1.35 (dd, *J* = 24.0 Hz, 6.18 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 141.7, 128.6, 126.1, 90.3 (d, *J* = 162.8 Hz), 38.9 (d, *J* = 22.5 Hz), 31.6 (d, *J* = 4.8 Hz), 21.2 (d, *J* = 22.5 Hz) ppm; ¹⁹F NMR (282 MHz, CDCl₃) δ -174.2 (1F).

(R)-1-(3-Fluorobutyl)benzene (S5). General procedure D was employed using (S)-5-(4-phenylbutan-2-yl)-1-aza-5-stannabicyclo[3.3.3]undecane (0.025 mmol, prepared from

(R)-4-phenylbutan-2-yl methanesulfonate^[3]). After the reaction was complete, water was added to quench the reaction. The ee value (84% ee) was determined by HPLC analysis of the organic layer. The yield (54%) was determined by calibrated gas chromatography.

Conditions:

Column	IA 250x4.6
Mobile phase	[19:1 v/v Methanol/Acetonitrile]:H ₂ O = 61%: 39%
Flow rate	0.8 mL/min
Detector	254 nm
Temperature	25 °C

5.5. References

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5.6. GC Data Supporting Absence of Protodestannylation

5.7. Chiral HPLC and GC Data

Conditions and results:

Column	IA-3 m 150x4.6
Mobile Phase	Hexane : IPA = 100 : 0.1
Flow	0.6 mL/min
Detector	220 nm
Temp	25°C
Result	>99% ee

Conditions and results:

Column	Chiralcel OJ-H 250x4.6
Mobile Phase	Methanol : Water = 95% : 5%
Flow	1.0 mL/min
Detector	215 nm
Temp	25°C
Result	99% ee

Compound S2

Conditions and results

Column	IA 250x4.6
Mobile phase	Hexane : IPA = 90% : 10%
Flow rate	0.3 mL/min
Detector	210 nm
Temperature	25 °C
Result	97% ee

Conditions and results:

Column	IA 250x4.6
Mobile phase	[19:1 v/v Methanol/Acetonitrile] : H ₂ O = 61% : 39%
Flow rate	0.8 mL/min
Detector	254 nm
Temperature	25 °C
Result	82 % ee, 85% es

Conditions and results:

Column	IA 250x4.6
Mobile phase	[19:1 v/v Methanol/Acetonitrile]:Sodium phosphate buffer (25mM, pH 7.8) = 60%: 40%
Flow rate	0.8 mL/min
Detector	254 nm
Temperature	25 °C
Result	89% ee, 90% es

Column	IA 250x4.6
Mobile phase	[19:1 v/v Methanol/Acetonitrile]:Sodium phosphate buffer (25mM, pH 7.8) = 60% : 40%
Flow rate	0.8 mL/min
Detector	254 nm
Temperature	25 °C
Result	86% ee, 89% es

Conditions and results:

Column	IA 250x4.6
Mobile phase	[19:1 v/v Methanol/Acetonitrile]:Sodium phosphate buffer (25mM, pH 7.8) = 60% : 40%
Flow rate	0.8 mL/min
Detector	254 nm
Temperature	25 °C
Result	80% ee, 83% es

Peak#	Ret.Time	Height	Area	Area%
1	13.148	26417	235066	50.03
2	13.659	24757	234789	49.97
Total			469855	100.00

Peak#	Ret.Time	Height	Area	Area%
1	13.165	20646	187179	93.30
2	13.709	1466	13438	6.70
Total			200617	100.00

Conditions and results:

Column	IA 250x4.6
Mobile phase	[19:1 v/v Methanol/Acetonitrile]:H ₂ O = 60% : 40%
Flow rate	0.9 mL/min
Detector	210 nm
Temperature	25 °C
Result	93% ee (95% es)

Peak#	Ret.Time	Height	Area	Area%
1	249.441	674	44509	50.81
2	251.415	651	43090	49.19
Total			87599	100.00

Peak#	Ret.Time	Height	Area	Area%
1	249.268	2497	188266	98.51
2	251.516	66	2856	1.49
Total			191122	100.00

Conditions and results:

Column	IA 250x4.6
Mobile phase	[19:1 v/v Methanol/Acetonitrile]:H ₂ O = 70% : 30%
Flow rate	0.8 mL/min
Detector	254 nm
Temperature	25 °C
Result	92% ee, 94% es

5.8. ^1H and ^{13}C NMR spectra

77.6531
 77.2298
 76.8067
 -54.9770
 32.1830
 29.9543
 29.6820
 29.6048
 27.3982
 22.9351
 16.3858
 14.3620
 -6.8287