THE DEVELOPMENT OF NEW ORGANOTIN REAGENTS FOR ORGANIC SYNTHESIS

by

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S.B. Chemistry, Massachusetts Institute of Technology

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June 1995

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ABSTRACT

Organotin compounds have proved to be useful reagents for a wide range of reactions, but relatively few of these reactions have been made either catalytic or asymmetric. In this thesis, a new catalytic method for the formation of acylated cyanohydrins and the development of a new class of chiral stannacyclohexane catalysts are described.

A convenient and efficient conversion of aldehydes to acylated cyanohydrins is catalyzed by tri-*n*-butyltin cyanide and pyruvonitrile. The reaction is carried out neat with a variety of aldehydes at 25-50 °C and affords excellent yields in 4-30 h. A catalytic cycle is proposed based on previous literature findings.

The synthesis of a novel class of chiral organotin catalysts based on the (*3S,5S*)-dimethylstannacyclohexane [(*3S,5S*)-DMSC] structure is described. The 1,1-diphenyl-, 1-chloro-1-phenyl-, 1,1-dichloro- and 1-hydrido-1-phenyl-(*3S,5S*)-DMSC are fully characterized. Some of their potential uses include the enantioselective reduction of aldehydes and ketones, the synthesis of acylated cyanohydrins, and the allylation of aldehydes with allyltributyltin.

Thesis Supervisor:	Professor Gregory C. Fu
Title:	Assistant Professor of Chemistry

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I would like to express my heartfelt gratitude to Profs. Gregory C. Fu and Frederick D. Greene for helping make this thesis a reality. Prof. Fu has been an excellent teacher, friend and mentor. He took the risk of accepting me into his lab to pursue research leading to a Masters thesis within a very short time constraint. His constant presence has been a great help, whether it is to help me perform my first flash chromatography, encourage me when experiments do not work or push me when I slacken off. Prof. Greene has been a tremendous supporter of my pursuit for the master degree. He was instrumental in helping me devise a workable course schedule and negotiate the bureaucratic constraints. He has been a great friend to the undergraduates in this department and though I will sorely miss him, I wish him the very best after his retirement.

The members of Fu group have helped in too many ways for me to list here. Their collective humor has made the tedium of lab work seem trivial.

I would also like to thank the Public Service Commission of Singapore for providing me the financial support that makes it possible for me to come to MIT in the first place.

To Mei, you ARE the Sprite of my life

PREFACE

Parts of this thesis have been adapted from the following articles co-written by the author:

> Scholl, M; Lim, C.-K.; Fu, G. C. "Convenient and Efficient Conversion of Aldehydes to Acylated Cyanohydrins Using Tributyltin Cyanide as a Catalyst", *J. Org. Chem.* , submitted for publication.

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ABBREVIATIONS

ee	enantiomeric excess
DAIB	3-*exo*-(dimethylamino)isoborneol
TBTH	tri-*n*-butyltin hydride
TBTC	tri-*n*-butyltin cyanide
AIBN	azobisisobutyronitrile
PMHS	polymethylhydrosiloxane
eq	equation
TMSCN	trimethylsilyl cyanide
DMSC	dimethylstannacyclohexane
LAH	lithium aluminium hydride
m-CPBA	3-chloroperbenzoic acid
LDA	lithium diisopropylamide
UV	ultraviolet
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid

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Chapter 1:

Introduction

1.1 Catalysis and Asymmetry

The past fifty years or so have seen organic chemistry mature at an astonishing pace. Many fundamental carbon-carbon bond-forming reactions, as well as important functional group transformations, have been well-investigated and understood. This, however, does not mean that the mission of organic chemists has been accomplished. In recent years, organic chemistry has steadily extended its reach to many exciting new directions, ranging from self-replication to molecular electronics.[1] Within the more traditional confines of organic synthesis, pressures from a more environmentally-conscious public, have challenged organic chemists to further refine reactions to reduce waste and to increase yields.

One of the best ways for industry to reduce the escalating cost of waste disposal is by reducing the amount of unwanted side products in industrial-scale reactions. Catalysis clearly stands out as an ideal solution. The use of stoichiometric amounts of reagents often results in the production of stoichiometric amounts of side products. On the other hand, catalysts with high turnovers are in effect a chemical means of recycling the reactants efficiently. Together with the ability to employ less harsh reaction conditions with catalysis (which itself will reduce waste products from unwanted side reactions) and reduce separation costs, the only reason why it is not used more often is that it is more difficult to develop.

Most natural products contain stereogenic centers. To synthesize them in multi-steps and with good yields involves using efficient asymmetric reactions. In most cases, only one enantiomer is biologically active, and the other can either be benign or have unwanted side effects. Two main driving forces have enticed drug companies to aggressively formulate enantiopure versions of the drugs. Firstly, since they are more potent, they can be administered in smaller doses. Secondly, the firms can seek new patents on enantiopure versions of their off-patent racemic counterparts.[2,3]

If existing reactions can be made both catalytic and asymmetric, this would clearly represent a major improvement in many ways. Besides the environmental, economical and biological benefits discussed above, valuable insight is also gained with regard to the mechanism and stereochemical aspects of the reactions. It is therefore not surprising that asymmetric catalysis is emerging as one of the most promising directions in which organic chemistry is headed.

1.2 Evolution of Catalytic Asymmetric Reactions

The evolution of catalytic asymmetric reactions follows a logical progression, as described by Noyori.[4] This is illustrated in Figure 1. Before the advent of asymmetric reactions, chiral compounds were derived by extraction from naturally-occurring sources. Often, these sources provide only minuscule amounts, making it necessary to find a synthetic route to the compounds.

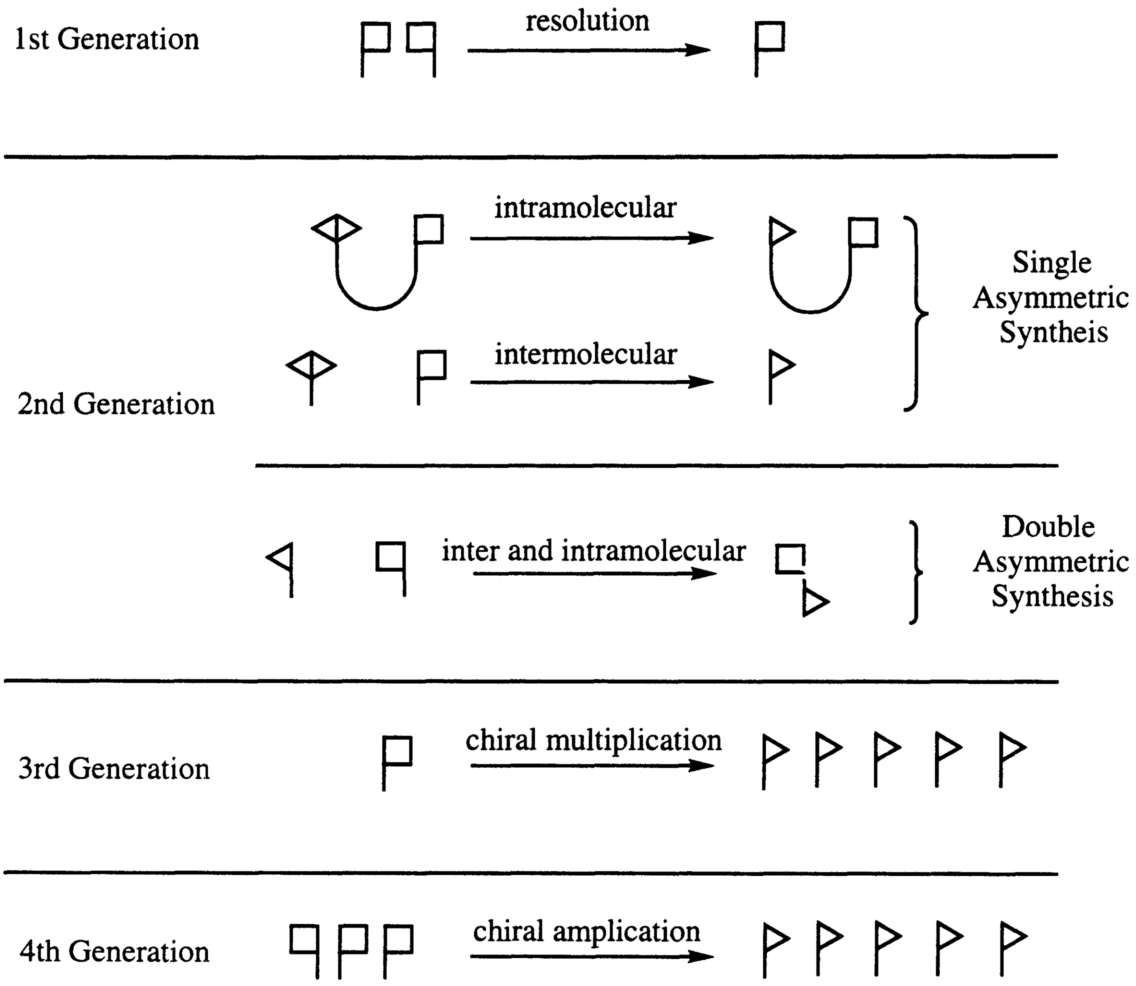


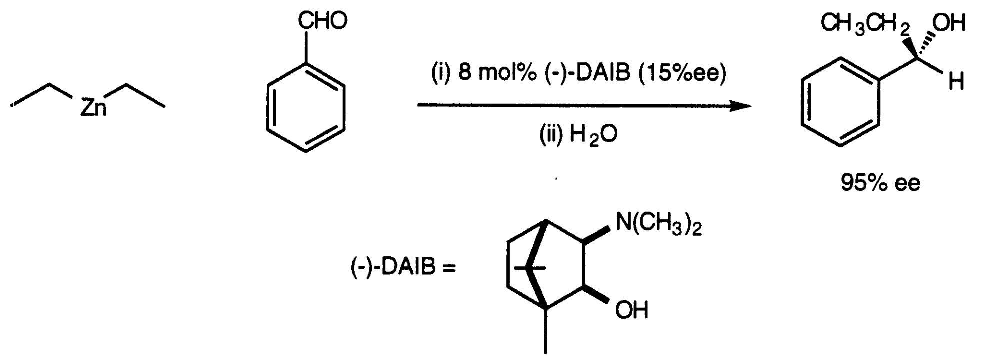
Figure 1: Evolution of catalytic asymmetric reactions.

In the first generation, chirality is derived from classical resolutions of racemates. Some resolution methods include crystal picking, conglomerate recrystallization and diastereomeric separation via resolving agents.[5]

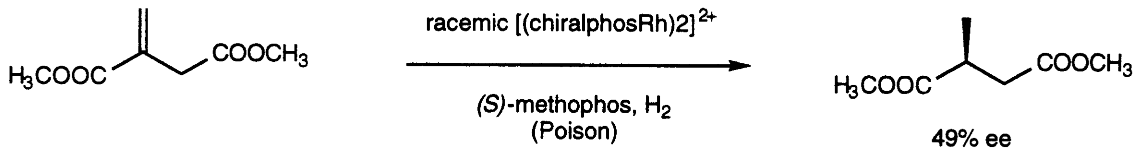
The ability to incorporate chirality transfer in chemical transformations gives rise to the second generation of stoichiometric asymmetric reactions. When one of the reactants is chiral (either derived naturally or by first generation methods), the chirality can be transferred intra- or intermolecularly to give single asymmetric reactions. When two chiral reactants are present, both intra and intermolecular chirality transfer occurs to give double asymmetric reactions.[6]

When it was found that certain metal complexes with chiral organic ligands can catalyze reactions as well as multiply chirality, the third generation of catalytic asymmetric reactions was born. Asymmetric catalysis has been applied to reactions such as hydrogenation, epoxidation, cyclopropanation and hydrosilylation.[7,8]

Fourth generation reactions were reported only recently.[9] In these reactions, a non-linear relationship is observed between the ee of the catalyst and the ee of the product. For example, Noyori and co-workers reported[10] that in the addition of diethylzinc to benzaldehyde with a catalytic amount of (-)-3-*exo*-(dimethylamino)isoborneol (DAIB), catalyst of 15% ee leads to (*S*)-1-phenyl-1-propanol with 95% ee. (eq 1) More recently, Faller added a chiral poison to a racemic ruthenium bisphosphine catalyst to achieve excellent ee in hydrogenation (eq 2).[11]



(1)



(2)

racemic $[(\text{chiralphosRh})_2]^{2+}$: (*S*)-methophos = 1 : 0.7

1.3 Organotin Compounds in Synthesis

Despite the slow beginning of organotin chemistry, the past four decades have seen a renaissance in the field.[12-14] Organotin compounds show some similarity to the versatile organosilicon compounds, and it has been predicted that in the near future, the former will surpass the latter in terms of usefulness[15]. Most organotin compounds are readily manipulated, and only a few types need to be protected from the atmosphere. This, plus their high reactivity, makes them very useful reagents in organic synthesis.[16] This section briefly reviews the chemistry of organotin hydrides as reducing agents and the role of organotin halides as Lewis acids.

1.4 Organotin Hydrides

Organotin hydrides are undoubtedly the most widely-used organotin compounds.[17] Of these, tri-*n*-butyltin hydride (TBTH) is the most popular. It can be prepared easily without special equipment and, when pure, can be stored for weeks or months. Its toxicity does not exceed that of most laboratory chemicals.[18] TBTH is primarily utilized in free-radical dehalogenation by the mechanism shown in Scheme 1.

Scheme 1

$$\mathrm{In^{\bullet}} + \mathrm{Bu_3SnH} \longrightarrow \mathrm{Bu_3Sn^{\bullet}} + \mathrm{InH}$$

$$\mathrm{Bu_3Sn^{\bullet}} + \mathrm{RX} \longrightarrow \mathrm{Bu_3SnX} + \mathrm{R^{\bullet}}$$

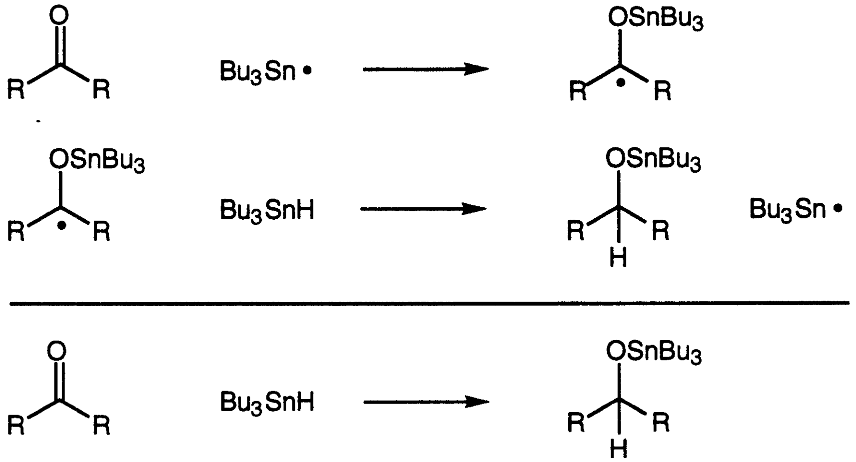
$$\mathrm{R^{\bullet}} + \mathrm{Bu_3SnH} \longrightarrow \mathrm{RH} + \mathrm{Bu_3Sn^{\bullet}}$$

The radical chain reaction is initiated either with azobisisobutyronitrile (AIBN) or UV light. The trialkyltin radical abstracts the halide, leaving the alkyl radical. This could, in the simplest case, undergo hydrogen abstraction from another TBTH molecule, or rearrangement, fragmentation, or intra- or intermolecular C-C coupling.

The use of organotin hydrides is an attractive dehalogenation method for a few reasons. It is carried out under mild conditions and is highly selective. The reactivity of the halides decreases according to the sequence RI > RBr > RCl >> RF. It is also selective with respect to the nature of the organic group, with tertiary chlorides being reduced faster than secondary ones, which in turn are reduced faster than primary ones.

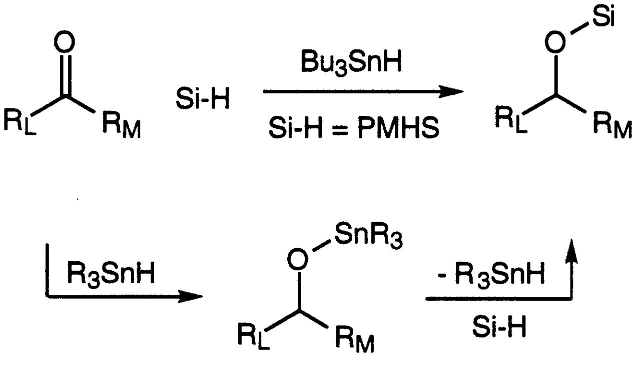
TBTH is also used in the reduction of carbonyl compounds to the corresponding alcohols.[12] Extensive studies have shown that a free-radical mechanism is involved when the reaction is carried out in a nonpolar solvent under chemical or UV initiation (Scheme 2).

Scheme 2



The above mechanism requires a stoichiometric quantity of trialkyltin hydride. A catalytic version is possible if there is a way to regenerate the tin-hydrogen bond from the tin oxygen bond. Polymethylhydrosiloxane (PMHS; $Me_3SiO(MeHSiO)_nSiMe_3$)[19] appears to be ideal for effecting the latter transformation, since it readily reduces tin alkoxides at room temperature but does not react with aldehydes or ketones.[19-23] The overall process is shown in Scheme 3.

Scheme 3



Lipowitz[24] has reported the catalytic reduction of carbonyl compounds with tin hydrides and PMHS under polar conditions. Recently, our group has observed the same reaction under radical conditions[25], although the mechanism has not yet been confirmed. For the purpose of developing an enantioselective variant of the catalytic reduction, a radical mechanism is necessary (see Chapter 3).

Recently, it has also been found that the tin alkoxides could potentially react with other silicon compounds to regenerate the Sn-X bond.[26] This opens the possibility of a whole new range of Sn-X catalyzed reactions with carbonyl compounds.

1.5 The Development of New Catalytic Asymmetric Reactions of Organotin Compounds

The brief review of the chemistry of organotin compounds touches only the tip of the iceberg. The excellent texts and reviews cited above contain a much more comprehensive survey, a testimony of the usefulness of organotin compounds in synthesis. However, few catalytic versions of these reactions and even fewer catalytic asymmetric ones exist. The chemistry of organotin compounds is therefore still languishing in the second generation.

While the search for third and fourth generations of reactions is motivated by the immense advantages mentioned above, the toxicity of organotin compounds in general makes it imperative that they should be used in only catalytic amounts.

This project is part of the Fu group's overall research mission to develop novel chiral organotin reagents for asymmetric catalysis. The objectives of this project are two-fold. First, we would like to either develop catalytic versions of reactions that currently require stoichiometric amounts of organotin reagents or discover totally new reactions that are catalytic in tin. This will involve finding ways to achieve turnover by regenerating the tin reagents. Subsequently, we would like to design chiral versions of the catalysts and apply them to enantioselective variants of the catalytic reactions.

In this thesis, the development of the catalytic cyanoacylation of carbonyl compounds, and the synthesis of a new class of chiral stannacyclohexane catalysts are documented.

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Chapter 2:

Development of Tributyltin Cyanide Catalyzed Formation of Acylated Cyanohydrins

2.1 Acylated Cyanohydrins

An insecticide must not only be effective in killing agricultural pests, but also possess low toxicity to human beings. Among the agrochemicals used as commercial insecticides, pyrethroids are among of the most popular, because not only do they satisfy the above requirement, but they are also less soluble than other carbamate, organophosphate insecticides and are thus less likely to contaminate ground water sources.[1]

Some of the naturally occurring pyrethroids are shown in Figure 2. These have limited applications in agriculture because of their low air and light stability. A major breakthrough was made when it was discovered[2] that the addition of a cyano group α to the ester functionality greatly enhances their air and light stability and in many cases, increases the insecticidal activities. These modified pyrethroids have since become a very important class of insecticides. Some of these are listed in Figure 3.

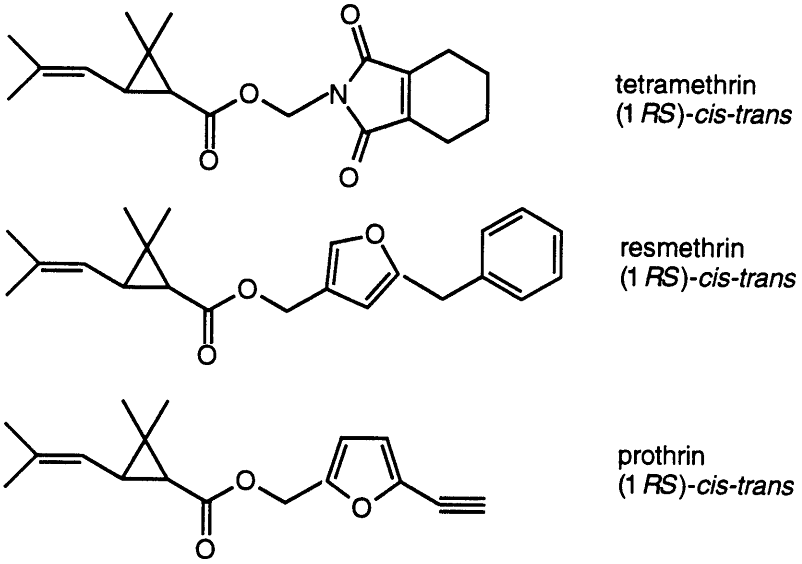


Figure 2: Some naturally occurring pyrethroids

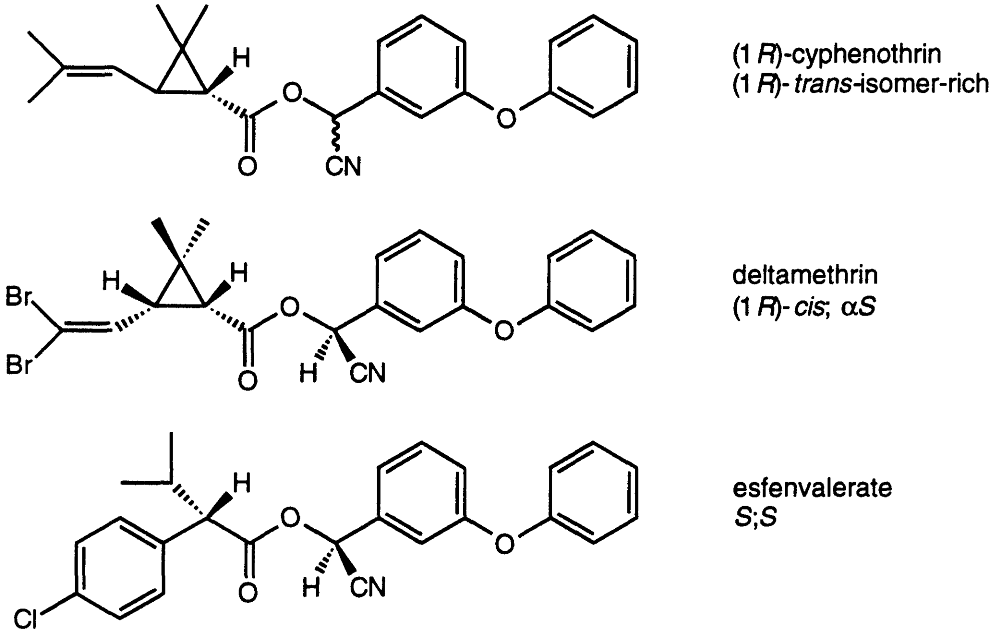


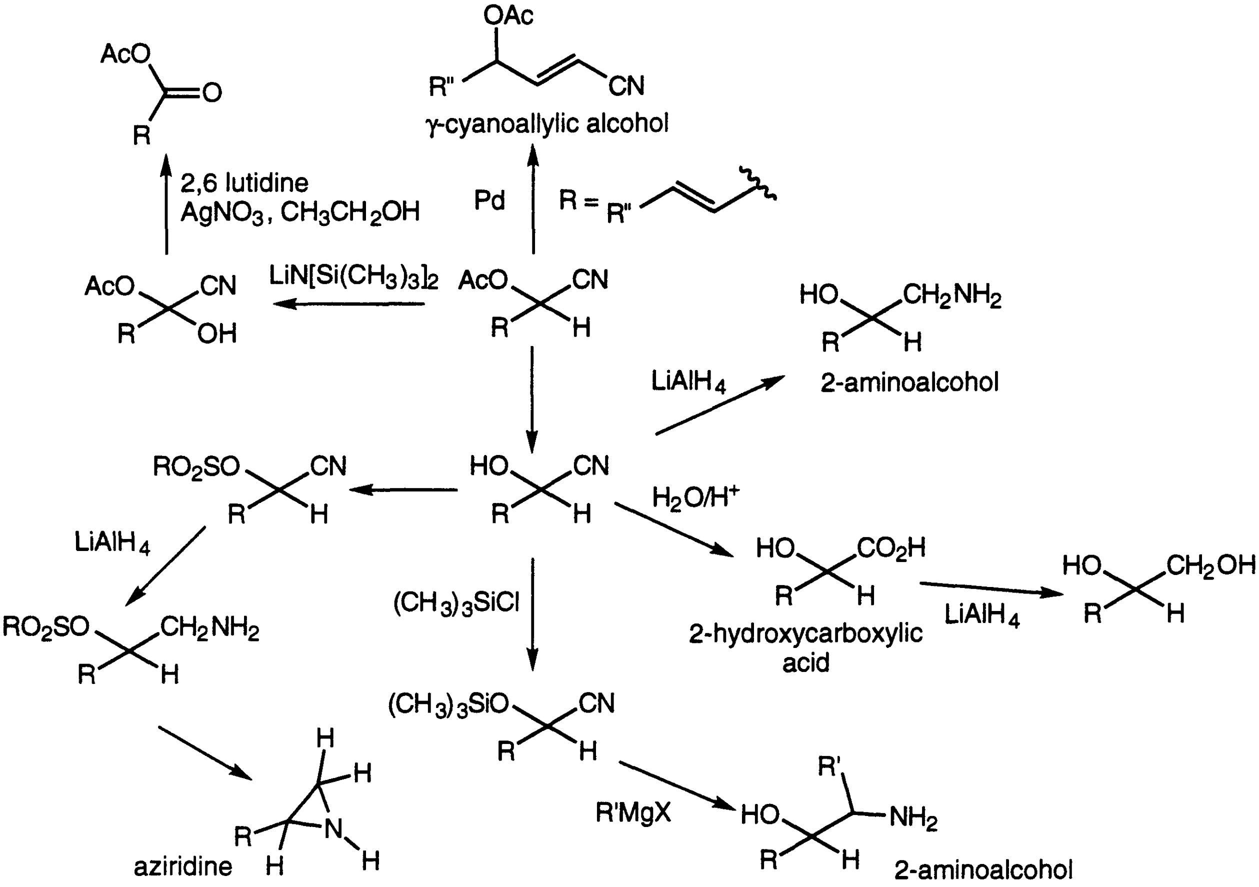
Figure 3: Some derived pyrethroids containing acylated cyanohydrins

In addition to their major use as agrochemicals, acylated cyanohydrins are also important synthetic precursors.[3] Cyanohydrins possess a stereogenic center and recent progress in obtaining them in high optical purity has made them more suitable than ever as starting materials in natural product synthesis.

Enzymatic resolution is the most common method of obtaining enantiopure cyanohydrins and their acylated counterparts.[3-8] Various whole cells or specific lipases have been used to give excellent ee's. Direct asymmetric synthesis has also been achieved with a titanium catalyst.[9]

Acylated cyanohydrins possess two very versatile functional groups that are easily manipulated in a number of ways. The nitrile group can be reduced to a primary amine and alkylated to give a secondary amine. The acetate group can be hydrolyzed to the alcohol, which can itself undergo a large array of functional group transformations. Scheme 4 below shows some of these transformations.

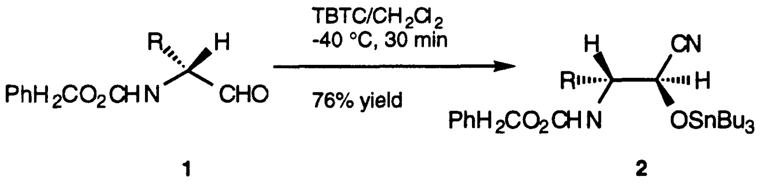
Scheme 4



In this chapter, a novel catalytic method of synthesizing acylated cyanohydrins from aldehydes and tri-*n*-butyltin cyanide (TBTC) is discussed.[6,10-13]

2.2 Design of the Catalytic Cycle

Herranz et al.[14] found that TBTC adds to aldehydes to form α-cyanotin alkoxides, as shown in eq 3.



(3)

Ratio of **2**:**3** = 4:1

The low temperature and short time of this reaction indicate that it is a very facile step. The workers have previously used trimethylsilyl cyanide (TMSCN), which took 20 days at 20 °C to achieve 80% yield. They also investigated the effect of Lewis acid catalysts on the diastereoselectivity of the reaction. The use of tin tetrachloride did not affect the selectivity, but with boron trifluoride etherate, there was a total loss of diastereoselectivity.

In order to make this process catalytic in TBTC, we need to devise a method to regenerate the tin-cyanide bond. Gorsi and Mehrotra^{15} reported that trialkyltin isopropoxides ($Bu_3Sn(O\text{-}i\text{-}Pr)$) react with acetyl cyanide to give TBTC (eq 4). This is precisely the step we need to complete the catalytic cycle.

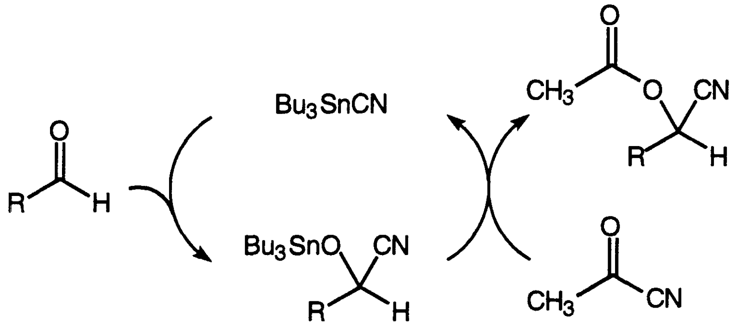
$$R_3SnOPr^i \quad + \quad CH_3COX \longrightarrow R_3SnX \quad +CH_3COOPr^i \qquad \textbf{(4)}$$

$$\text{where } R = Et,\ Pr^n \text{ or } Bu^n \text{ and } X = CN \text{ or } NCS$$

Several experiments were carried out in NMR tubes in deuterated chloroform. First, a stoichiometric amount of TBTC and cyclohexanecarboxyaldehyde were mixed and monitored by ^{1}H NMR. As expected, the α-cyanotin alkoxide formation was fast (< 15 min). Addition of one equivalent of pyruvonitrile (CH_3COCN) affords the acylated cyanohydrin within 6 h. Next, a catalytic amount (15%) of TBTC was used rather than a stoichiometric quantity. This time, the reaction was much slower ($\approx$ 20 h), but the amount of acylated cyanohydrin formed was clearly greater than the amount of TBTC added, indicating that we were achieving turnover. A control experiment was also carried out: Mixing a stoichiometric amount of aldehyde and pyruvonitrile resulted in no reaction after 20h at room temperature. We can thus conclude that the background reaction between pyruvonitrile and the aldehyde does not occur under the reaction conditions.

Based on the literature precedent and our initial investigation, we proposed the following catalytic cycle for the TBTC-catalyzed addition of pyruvonitrile to aldehydes. (Scheme 5)

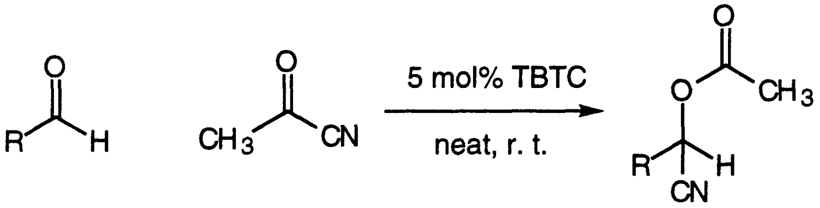
Scheme 5



2.3 Results and Discussions

Since the reaction is slow when carried out in a solvent, we explored the possibility of running the reaction neat. Although TBTC is a solid at room temperature, it readily dissolves in a mixture of aldehyde and pyruvonitrile. The catalytic cyanoacylation of cyclohexanecarboxyaldehyde was accomplished in 4 h. The amount of catalyst used was varied, and it was found that 5% catalyst loading gave a reaction time of a few hours. A lower catalyst loading is possible, but the reaction will be slowed accordingly. The final optimized reaction conditions are shown in Scheme 6.

Scheme 6



In order to investigate the scope of the reaction, a range of aldehydes were used as substrates. These aldehydes have a sufficiently high molecular mass so that the products are not volatile enough to impede their purification. The choice also reflects a diversity of electronic and steric characteristics for the aldehyde.

It is also possible to regenerate the TBTC catalyst with methyl cyanoformate (CH_3OCOCN) to form cyanocarbonates. The analogous catalytic cycle is shown in Scheme 7. The same substrates were used in this reaction. The two sets of results are shown (the latter for comparison) in Table 4.

Scheme 7

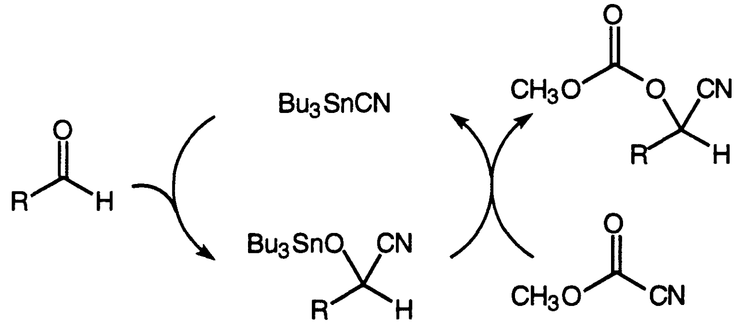
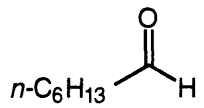
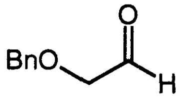
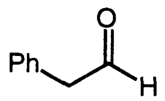
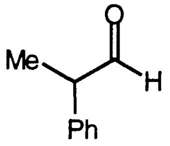
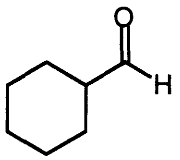
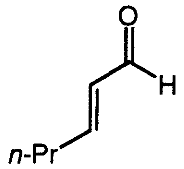
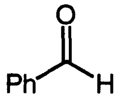
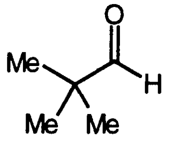


Table 1: Bu3SnCN-catalyzed cyanoacylation of aldehydes by YCOCN

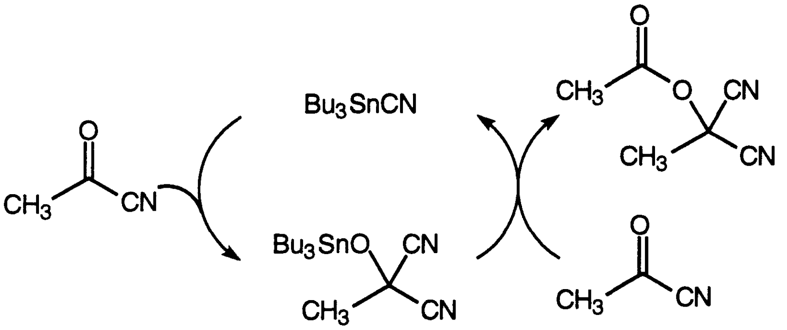
Entry	Substrate	Time (h)	Yield (%) Top: Y = OMe Bottom: Y = Me
1		1 4	92 98
2		1 4	91 94
3		36 5	94 90
4		2 4	95[a] 98[a]
5		1 5	97 96
6		6 days 30	82 78
7		36 10	92 89
8		14 5	94 83

[a] ~1.5 : 1 mixture of diastereomers.

All the substrates give excellent, nearly quantitative yields. With the exception of the electronically deactivated entries (6 & 7) and sterically hindered entry (8), the reactions were done within 1-2 h and 4-5 h for methyl cyanoformate and pyruvonitrile, respectively. The progress of the reactions is easily monitored by TLC. Purification can be done directly with flash chromatography. The corresponding control experiments (i.e., without TBTC) were performed alongside each catalytic reaction. No reaction occurs between any of the aldehydes and either acyl cyanide in the absence of TBTC. The reactions do not appear to be oxygen-sensitive -- when run in air, comparable yields of products are obtained.

In the pyruvonitrile reaction, 1.5 equivalents of pyruvonitrile are needed. Further experiments indicate that pyruvonitrile reacts with itself in a TBTC catalyzed reaction (Scheme 8). For longer reaction times (entries 6-9), up to 5 equivalents of pyruvonitrile are required. In these cases, the self-addition is faster than the cyanoacylation of the aldehyde. Since the ester resulting from the self-addition is less reactive than the pyruvonitrile itself, polymerization is not observed.

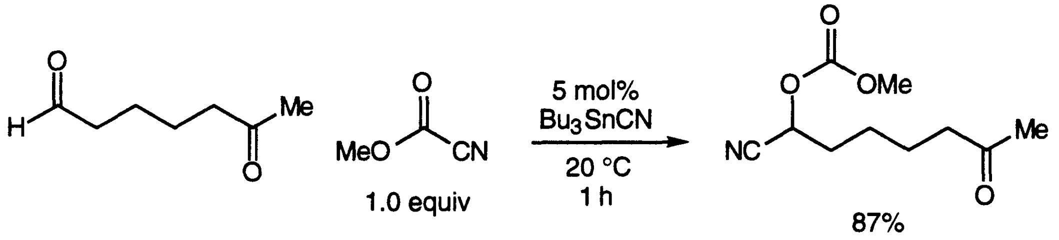
Scheme 8



trans-2-Hexenal, benzaldehyde and pivaldehyde (entries 6-8) did not undergo any perceptible reaction with pyruvonitrile at room temperature even after a day. It was thus necessary to warm these reactions to 45 °C.

A mixture of diastereomers is produced for the 2-phenylpropionaldehyde (entry 4) reactions. It is interesting to note that in both the pyruvonitrile and methyl cyanoformate reactions, the ratio of the diastereomers are similar. If the major diastereomers in both reactions have the same relative configurations, this suggests that the stereochemistry determining step is the initial addition of TBTC to form the α-cyanotin alkoxide, since the structure of the acyl cyanide does not appear to affect the diastereofacial selectivity. This is an encouraging observation, since it may be possible to effect enantioselective catalysis when a chiral trialkyltin cyanide is used in place of TBTC.

Another important aspect of this reaction is the selectivity between ketones and aldehydes. Ketones do not undergo addition under the standard catalytic conditions and the selective cyanoacylation of a ketoaldehyde can therefore be achieved (eq 5).



(5)

In conclusion, the TBTC-catalyzed cyanoacylation of aldehydes is a convenient, efficient and selective method for synthesizing acylated cyanohydrins, a highly versatile class of compounds for organic synthesis. Having developed this reaction, the next logical step is to employ a chiral trialkyltin cyanide catalyst to effect a catalytic asymmetric version of this reaction.

Experimental Section

General. All substrates were obtained from Aldrich, with the exception of *trans*-2-hexenal and benzaldehyde, which were purchased from Alfa and Fisher, respectively; each substrate was purified by distillation immediately prior to use. Tributyltin cyanide (*toxic!*) was obtained from Aldrich and recrystallized from hexanes. Pyruvonitrile was purchased from Aldrich and purified by distillation.

Analytical thin layer chromatography was accomplished using EM Reagents 0.25 mm silica gel 60 plates. Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh).

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian XL-300 NMR spectrometer at ambient temperature. ^{1}H data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane (δ scale), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constant (Hz), and assignment. ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). All ^{13}C spectra were determined with complete proton decoupling.

Infrared spectra were obtained on a Perkin-Elmer Series 1600 FT-IR spectrophotometer. Microanalyses were performed by E + R Microanalytical Laboratory, Inc. High resolution mass spectra were recorded on a Finnegan MAT System 8200 spectrometer.

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

Representative Procedure (Entries 1-5, 8). Reaction of Heptanal with Pyruvonitrile Catalyzed by Tributyltin Cyanide. *n*-Heptanal (114 mg, 1.0 mmol) was added to a colorless solution of tributyltin cyanide (15.8 mg, 0.05 mmol) in pyruvonitrile (103.6 mg, 1.5 mmol). The resulting homogeneous reaction mixture was stirred at room temperature for four hours, at which time TLC showed the reaction to be complete. The product was purified directly by flash chromatography (10% EtOAc/hexanes), which afforded 179 mg (98%) of the acylated cyanohydrin, a colorless oil. *Notes:* (1) The reaction does not appear to be oxygen-sensitive--when it is run in air, a comparable yield of product is observed.

Reaction of *trans*-2-Hexenal (Entry 6) with Pyruvonitrile Catalyzed by Tributyltin Cyanide. *trans*-2-Hexenal (98.2 mg, 1.0 mmol) was added to a colorless solution of tributyltin cyanide (31.6 mg, 0.10 mmol) in pyruvonitrile (310.8 mg, 4.5 mmol). The resulting homogeneous reaction mixture was stirred in a 50 °C oil bath for ten hours, at which time TLC showed the reaction to be complete. The product was purified directly by flash chromatography (10% EtOAc/hexanes), which afforded 143 mg (79%) of the acylated cyanohydrin, a colorless oil. (Physical data are reported below.)

Reaction of benzaldehyde (Entry 7) with Pyruvonitrile Catalyzed by Tributyltin Cyanide. Benzaldehyde (106.1 mg, 1.0 mmol) was added to a colorless solution of tributyltin cyanide (31.6 mg, 0.10 mmol) in pyruvonitrile (345.3 mg, 4.5 mmol). The resulting homogeneous reaction mixture was stirred in a 45 °C oil bath for thirty hours, at which time TLC showed the reaction to be complete. The product was purified directly by flash chromatography (10% EtOAc/hexanes), which afforded 156 mg (89%) of the acylated cyanohydrin, a colorless oil. (Physical data are reported below.)

Heptaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (t, 1H, J = 6.8, C*H*O), 2.12 (s, 3H, COC*H*$_3$), 1.88 (app. q, 2H, J = 7.5, C*H*$_2$CHO), 1.55-1.20 (m, 8H, (C*H*$_2$)$_4$CH$_3$), 0.87 (t, 3H, J = 6.7, C*H*$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 116.9, 61.1, 32.2, 31.4, 28.4, 24.4, 22.4, 20.4, 13.9; IR (neat) 2931, 2860, 1755, 1467, 1373, 1219, 1121, 1037, 914, 726 cm^{-1}; Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35. Found: C, 65.36; H, 9.27.

(Benzyloxy)acetaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H, aromatic H), 5.48 (t, 1H, J = 5.8, C*H*O), 4.62 (d, 2H, J = 2.9, C*H*$_2$Ph), 3.77 (d, 2H, J = 5.3, C*H*$_2$CHO), 2.14 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 136.6, 128.5, 128.1, 127.7, 115.2, 73.6, 68.0, 60.3, 20.2; IR (neat) 2871, 1754, 1454, 1372, 1218, 1124, 1046, 743, 700 cm^{-1}; HRMS: Calcd for $C_{12}H_{13}NO_3$: 219.0895. Found: 219.0898.

Phenylacetaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H, aromatic H), 5.46 (t, 1H, J = 7.1, C*H*O), 3.17 (d, 2H, J = 7.1, PhC*H*$_2$), 2.10 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 133.2, 129.5, 128.8, 127.8, 116.4, 61.8, 38.5, 20.2; IR (neat) 3032, 1755, 1497, 1456, 1373, 1224, 1084, 1036, 753, 701 cm^{-1}; HRMS: Calcd for $C_{11}H_{11}NO_2$: 189.0789. Found: 189.0788.

2-Phenylpropionaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) **major isomer** δ 7.40-7.20 (m, 5H, aromatic H), 5.41 (d, 1H, J = 5.9, C*H*O), 3.28 (m, 1H, PhC*H*), 2.11 (s, 3H, COCH_3), 1.45 (d, 3H, J = 7.5, CH_3CH); **minor isomer** δ 7.40-7.20 (m, 5H, aromatic H), 5.43 (d, 1H, J = 7.0, C*H*O), 3.28 (m, 1H, PhC*H*), 2.04 (s, 3H, COCH_3), 1.51 (d, 3H, J = 6.4, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.8, 138.8, 138.7, 128.7, 127.9, 127.8, 127.6, 115.9, 115.8, 66.0, 65.5, 41.8, 41.8, 20.2, 20.2, 16.2, 15.7; IR (neat) 2977, 1754, 1496, 1454, 1373, 1219, 1039, 763, 702 cm^{-1}; HRMS: Calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0948.

Cyclohexanecarboxaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (d, 1H, J = 6.0, C*H*O), 2.12 (s, 3H, COCH_3), 1.95-1.05 (m, 11H, ring H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 116.1, 65.5, 39.9, 28.0, 27.8, 25.7, 25.3, 25.2, 20.3; IR (neat) 2933, 2857, 1755, 1452, 1372, 1221, 1030 cm^{-1}; HRMS: Calcd for $C_{10}H_{15}NO_2$: 181.1102. Found: 181.1101.

***trans*-2-Hexenal, pyruvonitrile adduct:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (dt, 1H, J = 15.0, 7.1, C*H*CH_2), 5.78 (d, 1H, J = 6.9, C*H*O), 5.52 (dd , 1H, J = 15.4, 6.6, C*H*CHO), 2.12 (s, 3H, COCH_3), 2.09 (app. q, 2H, J = 7.7, CH_3CH_2CH_2), 1.43 (app. sex, 2H, J = 7.4, CH_3CH_2), 0.90 (t, 3H, J = 7.3, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 140.3, 120.1, 115.7, 61.4, 33.9, 21.4, 20.3, 13.4; IR (neat) 2962, 2934, 1754, 1372, 1218, 1023, 969 cm^{-1}; HRMS: Calcd for $C_9H_{13}NO_2$: 167.0946. Found: 167.0948.

Benzaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.40 (m, 5H, aromatic H), 6.40 (s, 1H, C*H*O), 2.15 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 131.7, 130.3, 129.1, 127.8, 116.0, 62.7, 20.3; IR (neat) 3038, 2944, 1756, 1496, 1457, 1372, 1211, 1024, 1002, 962, 899, 759, 697 cm^{-1}; HRMS: Calcd for $C_{10}H_9NO_2$: 175.0633. Found: 175.0633

Trimethylacetaldehyde, pyruvonitrile adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (s, 1H, C*H*O), 2.15 (s, 3H, COCH_3), 1.07 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 116.0, 69.3, 34.5, 25.1, 20.2; IR (neat) 2971, 1755, 1481, 1468, 1373, 1232, 1219, 1055, 1026, 903 cm^{-1}; Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 62.13; H, 8.58.

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Chapter 3:

Development of New Chiral Organotin Catalysts

3.1 The Need for Chiral R_3SnX Catalysts

We have so far seen many examples of tin reagents of the type R_3SnX (X=H, CN, halide, etc.) being used in a variety of organic reactions.[1] The importance of these reactions in terms of their selectivity and sometimes milder conditions has been discussed earlier. As catalytic versions of these reactions are developed, it becomes worthwhile to explore the asymmetric versions. While chiral tin reagents are expected to be more expensive and more difficult to synthesize than achiral reagents, if they are used catalytically, the magnification of chirality would certainly be worthwhile. However, there are virtually no reports of discrete chiral organotin catalysts.

3.2 Design of New Chiral Organotin Catalysts

One of the problems of chiral tetravalent organotin compounds is the susceptibility of the tin center to racemization.[2] Sn-C and Sn-H bonds are weaker than C-C and C-H bonds. For example, in the case of chiral trialkytin hydrides, the presence of a trace amount of radicals can lead to abstraction of the hydrogen from tin and cause the hydride to racemize via the rapidly inverting trialklytin radical. As a consequence, rather than having tin as the stereogenic center, it is preferable to put the chirality elsewhere in the molecule.

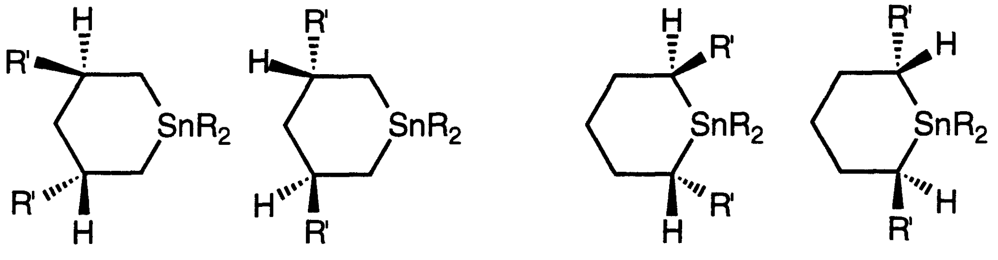
The logical way to do this is to design a cyclic structure around tin that takes up two of its four valencies. A cyclic structure minimizes the conformational flexibility of the molecule. Stannacycloalkanes (or stannacycles) **(1)**, are known.[3,4] Diphenylstannacyclohexane **(2)** was the first stannacycle reported.[5] More recently, stannacyclopentanes **(3)**, stannacyclohexanes **(4)** and stannacycloheptanes **(5)** have been made and their stability studied in detail.[6-9] Stannacyclopentanes **(3)** display unusually high reactivity of the endocyclic Sn-C bond which indicates a strained, unstable ring system.[9] Stannacyclohexane systems are the most studied, and they appear to be very stable under a variety of reaction conditions.[6-9]

1 **2** **3** **4** **5**

Figure 4: Some stannacycloalkanes

The next step is to introduce chirality into the stannacyclohexane. Some of the most successful catalysts are C_2-symmetric.[10] C_2 symmetry brings with it some features that are desirable for a chiral catalyst. For example, the presence of symmetry limits the number of possible catalyst-substrate arrangements as well as the number of competing diastereomeric transition states. This greatly simplifies the problem of predicting the three-dimensional structure of the substrate-catalyst complex and greatly facilitates the analysis of the individual interactions between catalyst and substrate which determine the selectivity of the process.[11] C_2 symmetry also renders the other two ligand sites of tin to be equivalent.

There are two possible ways to introduce substituents into the six-membered ring to make it C_2-symmetric, either at the 2,6 or 3,5 positions. The 2,6- **(6a-b)** and 3,5- **(7a-b)** substituted stannacycles could very well function as effective chiral catalysts since alkyl or aryl substituents can possibly affect the steric environment of the transition state.



6a **6b** **7a** **7b**

Figure 5: C_2-symmetric stannacyclohexanes

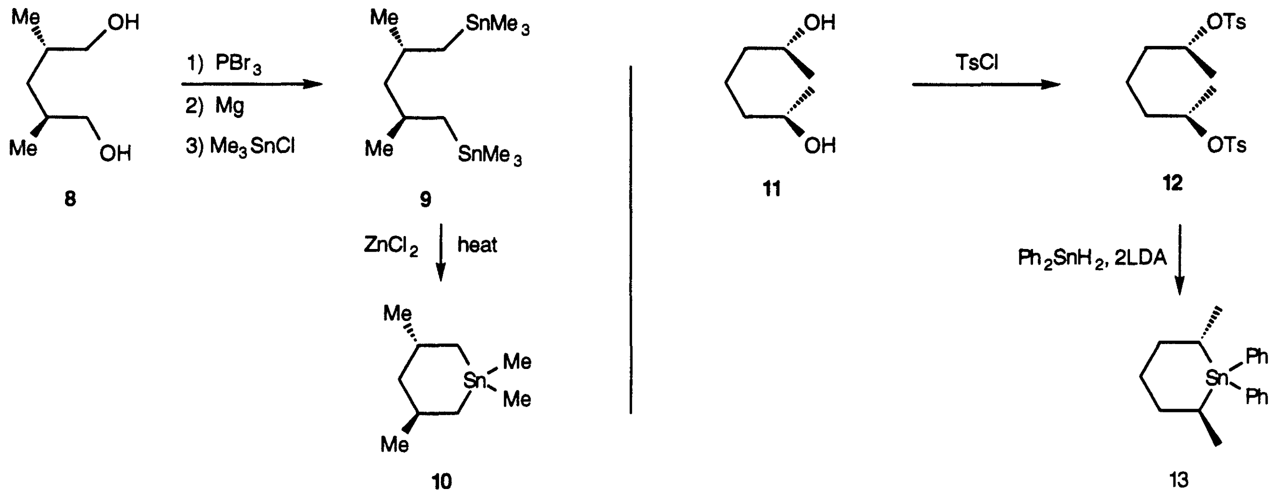
It is important to note that the 2,6- **(6a-b)** and 3,5- **(7a-b)** substituted stannacycles are not strictly C_2-symmetric in their ground-state configuration. The most stable conformation of the six-membered ring is the chair and even if the exocyclic ligands on tin are identical, one would be axial and the other equatorial. However, like many other catalysts that are not strictly C_2-symmetric, the underlying feature is not perfect symmetry, but rather the lack of stereochemistry of the atoms lying on the pseudo C_2 axis.

For the purpose of this thesis, we will only put methyl substituents ($R' = CH_3$) on the ring, but it is logical for future investigations to use various alkyl or aryl substituents to "tune" the catalyst.

3.3 Synthetic Strategy

The initial synthetic strategy for making the two dimethylstannacyclohexanes (DMSC) is shown in Scheme 9.

Scheme 9



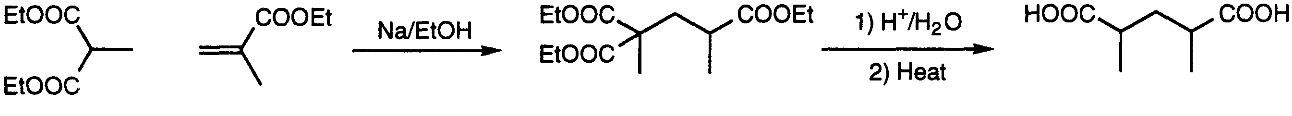
It is logical to start off with diols because many methods have been developed to obtain them in high enantiomeric purity. For the 3,5-DMSC synthesis, the diol **(8)** is converted to the dibromide and then the bis(stannane) **(9)** via the bis-Grignard intermediate. Disproportionation of the bis(stannane) in the presence of a catalytic amount of $ZnCl_2$ is known to afford the 1,1-dimethyl-3,5-DMSC **(10)**.[6] For the 2,6-DMSC, diol **(11)** is converted to the bis(tosylate) **(12)** Diphenyltin dihydride is deprotonated twice to form **(13)** by two nucleophilic substitutions.

3.4 Results and Discussions

3,5-Dimethylstannacyclohexane

An excellent precursor to the racemic 2,4-dimethylpentane-1,5-diol **(8)** is 2,4-dimethylpentane-1,5-dioic (or 2,4-dimethylglutaric) acid **(17)** Although the latter is available commercially, it is rather expensive. A simple preparation for **(17)** by Noller and Pannell[12] can easily be scaled up to produce hundreds of grams of the diacid (Scheme 10). Ethyl methylmalonate **(14)** is added via base-catalyzed Michael addition to the ethyl methacrylate **(15)** to give the triester **(16)**. which hydrolyzes and decarboxylates to give the dimethylglutaric acid.

Scheme 10



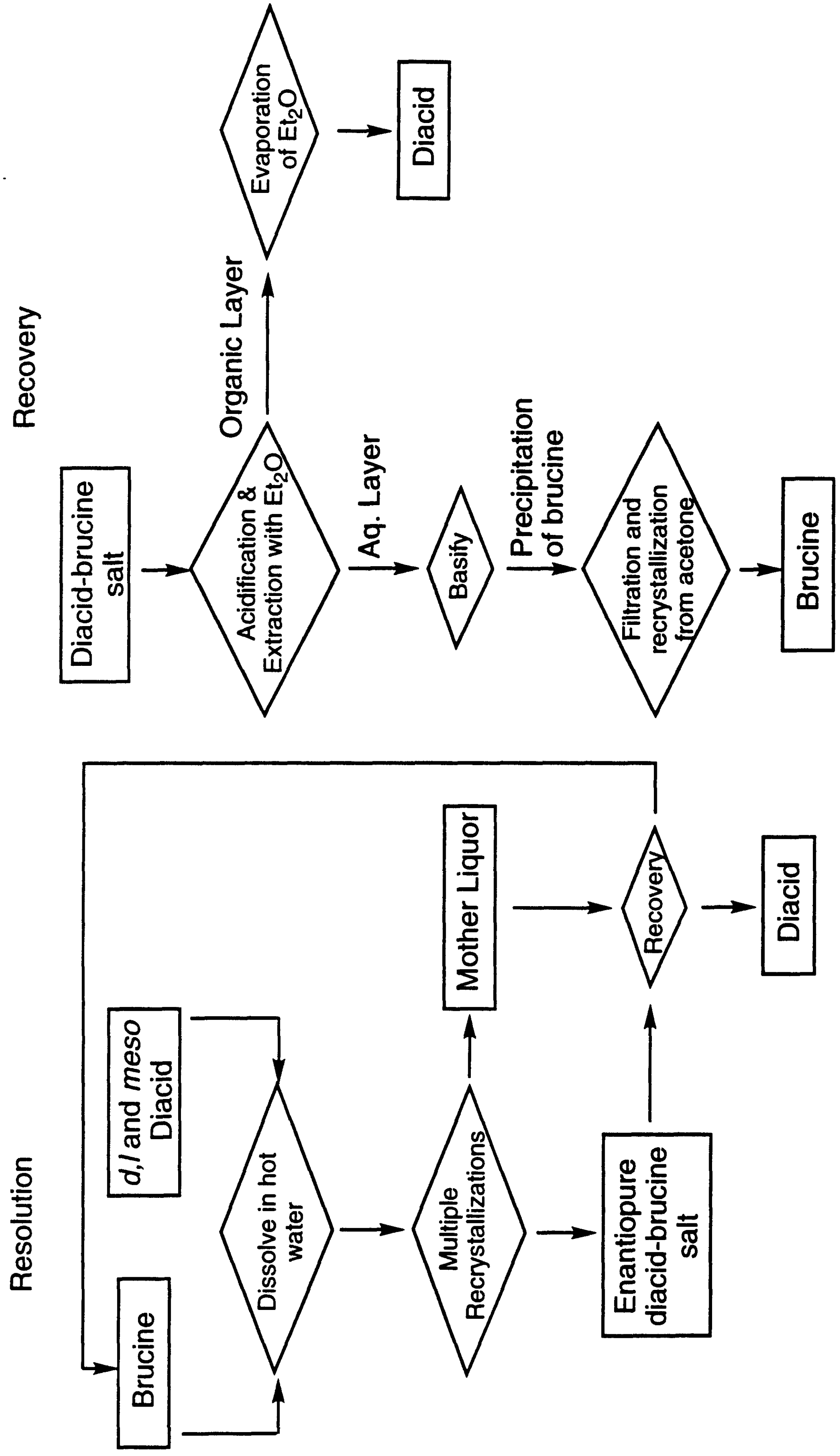
14 **15** **16** **17**

The 2,4-dimethylglutaric acid obtained from the above synthesis is a statistical mixture of *d, l* and *meso* isomers in the ratio 1:1:2. The *meso* isomer is unsuitable for our purpose, and we need to obtain the *d* or *l* (or both) separately in high enantiomeric purity. Fortunately, the enantiopure diacid has been used as a popular starting material and a variety of methods have been developed to resolve it.[13-15] These include elution with a chiral HPLC column,[16] resolution with chiral resolving agents such as (+)- or (-)-2-methylbenzylamine and with strychnine and brucine,[17,18] and via enzymatic resolution.[19-23] The need for special equipment ruled out the HPLC method.

Since (+)- and (-)-2-methylbenzylamine are both more expensive than strychnine or brucine and the literature reports did not indicate that they work better, that method was eliminated from consideration. Preliminary small-scale resolutions with both strychnine and brucine show that brucine is better because the lower solubility of the brucine-diacid salt enables its recovery in higher yield. Scheme 11 shows the algorithm for the recovery of all 3 stereoisomers of the acid with this method.

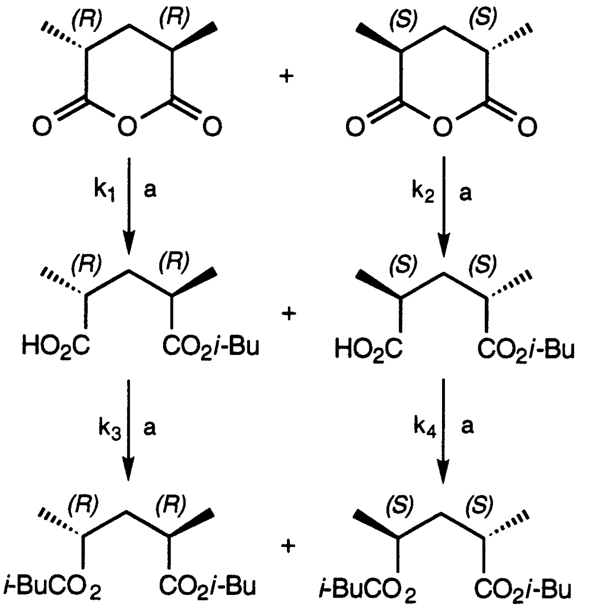
An equimolar amount of diacid and brucine is dissolved in hot boiling distilled water and then cooled. The first batch of salt crystals is subjected to two further recrystallizations from water to obtain the enantiomerically pure (+)-diacid-brucine salt. The acid and brucine can be fully recovered by first acidifying the salt and extracting the acid with diethyl ether, and then basifying the aqueous solution to precipitate out the brucine. The brucine can thus be re-used for further resolutions, making this a very economical and environmentally-friendly procedure. Up to 13.5% (out of a theoretical maximum of 25%) of the diacid can be recovered with high enantiomeric purity. It is possible to recover the other (-)-diacid by further resolution of the recovered diacid.

Scheme 11


Resolution
Brucine
d,l and *meso* Diacid
Dissolve in hot water
Multiple Recrystallizations
Mother Liquor
Enantiopure diacid-brucine salt
Recovery
Diacid
Recovery
Diacid-brucine salt
Acidification & Extraction with Et_2O
Organic Layer
Evaporation of Et_2O
Diacid
Aq. Layer
Basify
Precipitation of brucine
Filtration and recrystallization from acetone
Brucine

Although resolution with brucine is an excellent method, enzymatic resolution is probably the best way to go in the long run. Classical resolution is tedious and requires repeated crystallizations, whereas enzymes make it possible to obtain both enantiomers from a one-pot reaction. Most of the enzymes used to resolve 2,4-dimethylglutaric acids are esterases, which selectively catalyze the esterification of diols. Due to the higher selectivity, better yields of the enantiomerically pure diacid are possible. The most promising enzyme route has been recently reported.[9] A *d, l* mixture of the anhydride of **(17)** was separated by stepwise esterification with Novozym 435, and each enantiomer is obtained in 40-48% yield (out of a theoretical maximum of 50%) and 90% ee (Scheme 12).

Scheme 12



$k_1 = k_2$; $k_3 < k_4$

a = Novozym 435, *i*-BuOH, cyclohexane, 4Å sieves

The diacid is easily reduced to the diol with lithium aluminium hydride (LAH) in nearly quantitative yield. Since subsequent steps in the synthesis do not affect the two stereogenic centers in the molecule, the enantiomeric purity of the diacid and diol would give the overall ee of the final catalyst. Several different methods were used to determine this. There was no *meso* isomer in either the diacid or the diol according to ^{1}H NMR analysis.

Attempts to separate a mixture of stereoisomers of the diacid and diol via

GC with a chiral column were unsuccessful. NMR studies with the lanthanide shift reagent Eu(hfc)$_3$ did not resolve the enantiomers of the diol. Derivatizing the diol with Mosher acid (α-methoxy-α-trifluoromethylphenylacetic acid, MTPA)[24] did not give baseline resolution of any of the resonances in the ^{1}H NMR spectrum.

As a result, we were forced to resort to optical rotation measurements. The optical rotations of the diacid[25] and diol[15] have been reported previously. The optical rotations of our resolved diacid and diol, as well as the literature values, are shown in Table 2.

Table 2: Comparision of $[\alpha]_D$ values for the diacid and diols

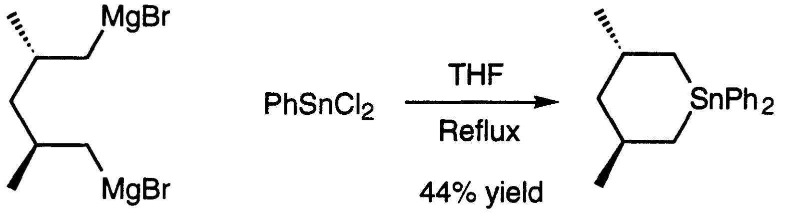
$[\alpha]_D$	**Literature Value**	**Found**
(2*S*, 4*S*)-dimethylglutaric acid in EtOAc	+39.8 (*c* 1.14)[25]	+41.5 (*c* 1.16)
(2*S*, 4*S*)-dimethylglutaric acid in H_2O	+40.3 (*c* 1.20)[25]	+40.0 (*c* 1.13)
(2*S*, 4*S*)-dimethylpentane-1,5-diol in EtOH	-34.3 (*c* 2.36)[15]	-35.4 (*c* 2.38)
(2*S*, 4*S*)-dimethylpentane-1,5-diol in EtOAc	N/A	-33.1(*c* 1.22)

Fredga[25] has extensively studied the variation of melting points with different ratios of *d*- and *l*- diacid mixtures, and the calibrated melting point of our resolved acid corresponds to >99% enantiomeric purity. Despite the various limitations of optical measurements (e.g., non-linearity), we have used two independent physical measures to indicate that the ee of the diacid and diol is at least 95%.

The diol is converted to the dibromide with PBr$_3$, and then the bis-Grignard is formed. In the latter step, the possibility of intramolecular cyclization of the mono-Grignard was not observed. The bis(stannane) was made by reacting the bis-Grignard with trimethyltin chloride (*caution ! extremely toxic!*).

There was a lot of difficulty in getting the intramolecular disproportionation to work. Bulten and Budding[6] reported that a major problem with this reaction is the formation of polymeric species, an unwanted reaction that is catalyzed by ZnCl$_2$ which reduces the yield of the stannacycle to only 47%. They further showed that the cyclization reaction involves an equilibrium. They solved the problem by distilling the reaction at 270-300°C and removing the more volatile stannacycle. However, despite numerous attempts to replicate the conditions of the reactions, we could not obtain greater than 20% yield (compared to their reported 94%). A major problem we encountered is that at 270-300°C, decomposition of the reaction mixture into a tarry black residue was observed.

Bulten and Budding were interested in the disproportionation method of cyclization because cyclization directly with the bis-Grignard and a dialkyltin dihalide gave only about 25% yield. However, we were able to obtain the stannacycle from the bis-Grignard and diphenyltin dichloride in 44% yield (eq 7). Moreover, the Sn-C bond with the phenyl ligand is weaker than with the methyl ligand, making it easier to further functionalize the stannacycle under milder conditions. Besides, this cyclization route avoids the extremely toxic trimethyltin chloride.

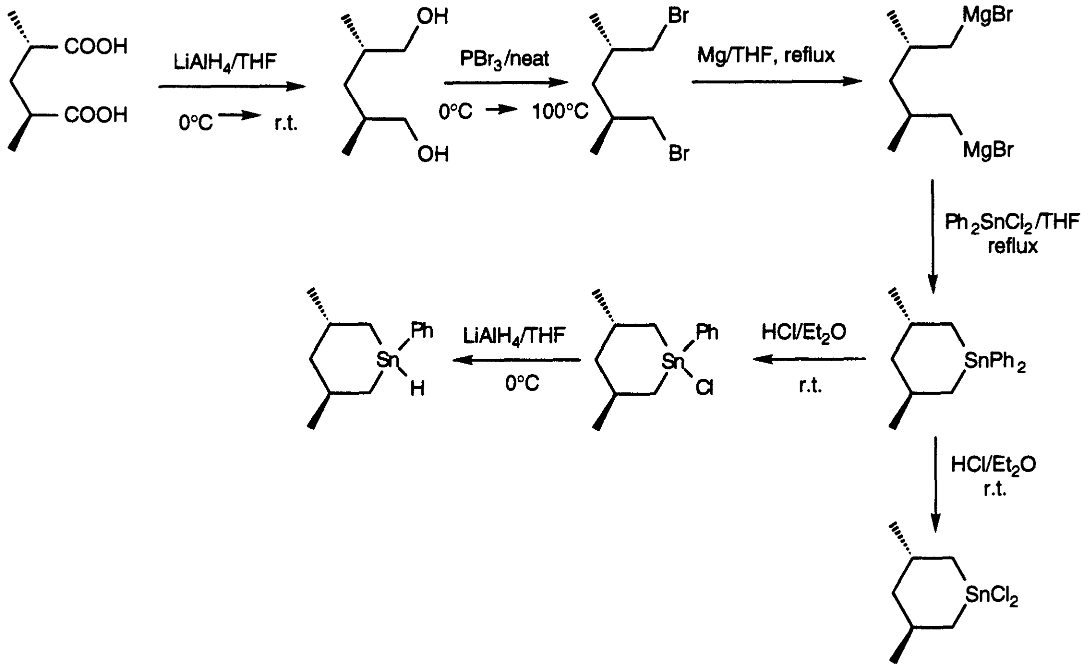


(7)

We believe that the low yield of this route is due to competing intermolecular polymerization reactions. However, the order of addition and dilution of the bis-Grignard did not give any significant yield improvement. It is important that during the formation of the bis-Grignard, the reaction is initiated (as seen from its exothermicity). Heating the Mg metal under a vacuum until it breaks into small pieces helps to activate it. It was also found that some impurities from the bromination step which co-distil with the dibromide inhibit the initiation of the bis-Grignard. The impurities are removable by elution on a silica column via flash chromatography, but the dibromide appears to be somewhat unstable to silica.

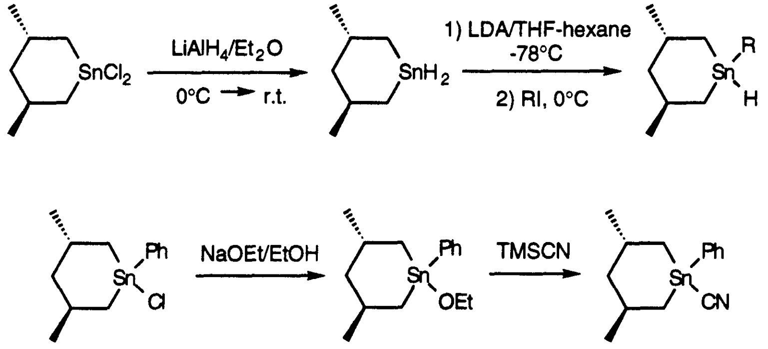
Having formed the 1,1-diphenyl-3,5-DMSC, the functional group manipulations to form the various catalysts are straightforward. The two phenyl ligands are sequentially cleaved by HCl in diethyl ether to give the monochloride in 4 hours and the dichloride in 4 days. Reduction of the monochloride by LAH gives the hydride in good yield. The final synthesis is summarized in Scheme 20.

Scheme 13



Other possible functional group transformations of the stannacycle to give other catalysts are shown in Scheme 14.

Scheme 14

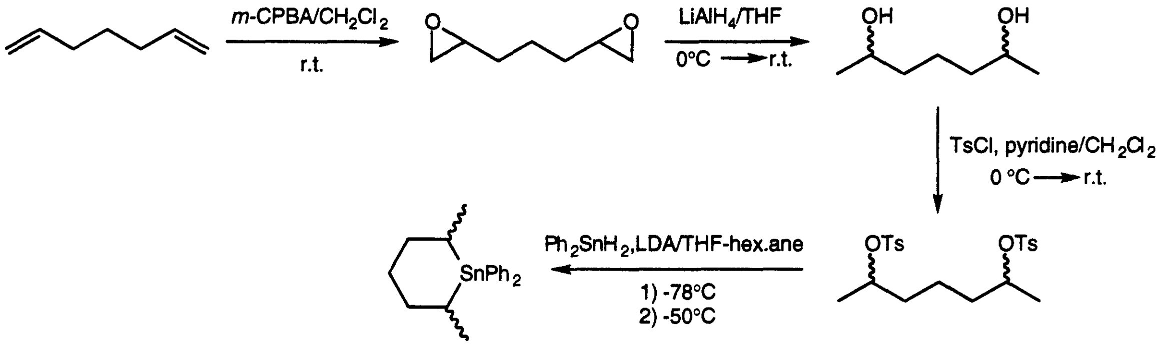


3.4.2 2,6-Dimethylstannacyclohexane

In this synthesis, the stereogenic centers reside on the carbons that are directly attached to the tin, making this a more challenging task. Cyclization via anionic terminals of the carbon backbone onto a dialkyltin dihalide is not a viable route because of racemization at the stereogenic carbons. The reverse strategy will have to be employed, by attaching the carbon ligands to an anionic tin molecule with complete inversion at the stereogenic carbons.

Preliminary work has been done on this synthesis. In order for the cyclization to occur with complete inversion, we need to put good S_N2 leaving groups to the stereogenic carbons. An obvious choice is the *p*-toluenesulfonate (tosylate) group. This was synthesized according to Scheme 15.

Scheme 15



Epoxidation of the commercially available 1,6-heptadiene with *m*-chloroperbenzoic acid (*m*-CPBA) gives the bis(epoxide), which opens up to the 2,6-diol upon treatment with LAH. Reaction with *p*-toluenesulfonyl chloride gives the bis(tosylate). A recent report by Connil et al. [26] indicates that it is possible to alkylate tin anions or stannates successively (formed from deprotonation of the hydride via lithium diisopropylamide [LDA]) with alkyl halides. Since tosylates are better leaving groups, they should work even better. Diphenyltin dichloride can be reduced to the dihydride with LAH. Treatment with 2 equivalents of LDA and bis(tosylate) resulted in no stannacycle formation. Instead, the reaction appeared to produce a polymeric product.

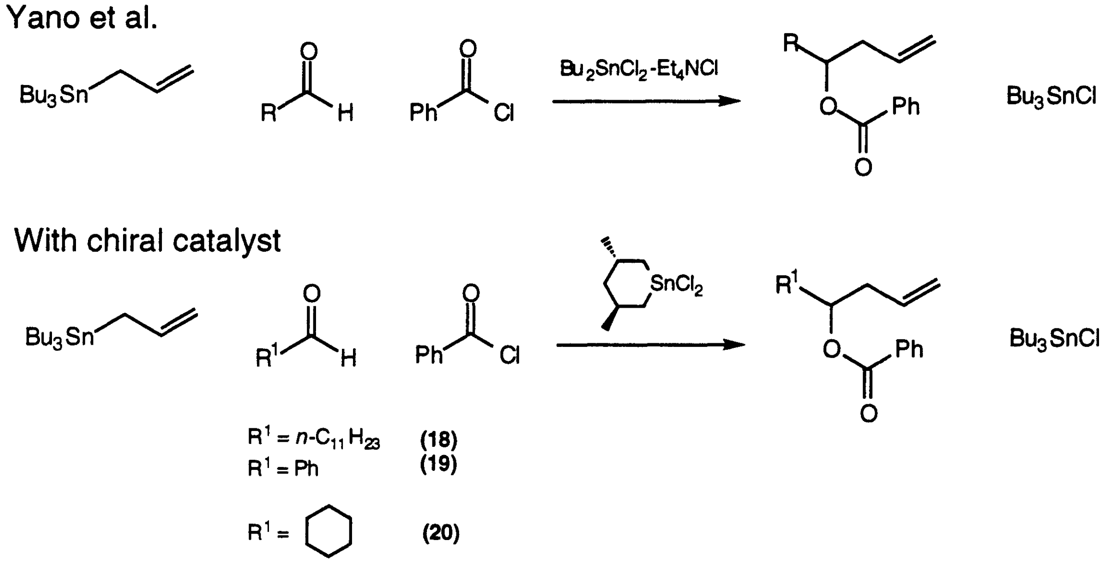
Filippo and Silbermann[27] reported that although tin anions react with tosylates with complete inversion, these reactions gave very low yields (4%). Though chlorides do not normally undergo substitution with complete inversion with tin anions, they can be made to do so under specified reaction temperatures and concentrations. The remaining diol was converted to the dichloride using thionyl chloride. However, when the cyclization reaction was attempted under the same conditions as for the bis(tosylate), no stannacycle was formed.

This leaves room for more work to be done to synthesize the 2,6-DMSC. It appears that the strategy we have used so far may not be experimentally feasible. Other approaches that are worth exploring includes asymmetric alkylation of the known stannacycle diene[28] or preforming the racemic stannacycle and resolving it by dimerization.

Application of the chiral catalyst to catalytic allylation of aldehydes

Yano et al.[29] recently reported the catalytic allylation of aldehydes with allyltributyltin (Scheme 16). The catalyst used was a dibutyltin dichloride-tetraethylammonium chloride complex. We could potentially use the 1,1-dichloro-3S,5S-DMSC as the catalyst and investigate the possibility of asymmetric induction.

Scheme 16

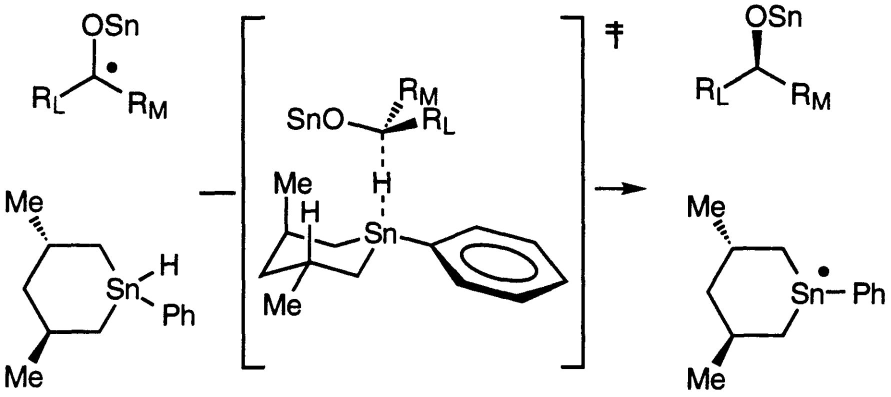


Control experiments showed that the tetraethylammonium chloride additive is not necessary for the reaction and does not affect its rate. Also, instead of running the reaction at the reported 40-60 °C, we conducted it at room temperature, with the expected increase in reaction time. We have screened three aldehyde substrates, namely dodecyl aldehyde **(18)**, benzaldehyde **(19)** and cyclohexanecarboxaldehyde **(20)**.

The reaction does not proceed completely to the ester; a small amount of the alcohol remains regardless of the reaction time. However, the overall yield of the combined ester and alcohol is comparable to what was reported by Yano. The alcohol and ester are combined and reduced to the alcohol. A small amount of the resulting alcohol was reacted with (*S*)-Mosher acid chloride. Separate analysis of the Mosher ester of the racemic alcohol that is synthesized independently showed there is baseline resolution in at least one resonance in the ^{1}H NMR. The analysis showed that the alcohols derived from the allylation had very low ee's (<5%). Thus, there is no significant asymmetric induction with the chiral 1,1-dichloro-(3*S*,5*S*)-DMSC catalyst.

A perhaps more promising reaction that may show asymmetric induction is the reduction of aldehydes and ketones. The free-radical catalytic mechanism has already been explained in the Introduction. Using 1-hydrido-1-phenyl-(3*S*,5*S*)-DMSC as the catalyst, we propose the transition state illustrated in Scheme 17 for the hydrogen abstraction steps.

Scheme 17



The stannacyclohexane will adopt a chair conformation with the tin-bound hydrogen occupying the more hindered axial position. The preferred geometry for hydrogen abstraction is linear and steric factors favor a staggered conformation about this Sn-H-C axis. The stannacycle thus presents three highly differentiated groups (a methyl, a hydrogen and a "void") to the substituents of the radical. This highly-ordered transition state makes it possible to make a clear prediction of the stereochemistry of the reduction product. Further work has to be done to screen a variety of aldehydes and see if the above model is valid.

Last, but definitely not least, the catalytic cyanoacylation reaction could be carried out with the chiral 1-cyano-1-phenyl-(3*S*,5*S*)-DMSC. These are examples of only a few of the possible reactions where the chiral (3*S*,5*S*)-DMSC based catalysts could be used.

Experimental Section

General Methods. All reagents were obtained from Aldrich. Diphenyltin dichloride was purified by recrystallization from petroleum ether and hexane. 2,4-dimethylglutaric acid was prepared as described by Noller[12]. (Ethyl methacrylate was used instead of methyl methacrylate). Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried and deoxygenated by refluxing over sodium/benzophenone followed by distillation under nitrogen. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

Analytical thin layer chromatography was accomplished using EM Reagents 0.25 mm silica gel 60 plates. Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh).

^{1}H, ^{13}C and ^{119}Sn nuclear magnetic resonance spectra were recorded on a Varian XL-300 NMR spectrometer at ambient temperature. ^{1}H data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane (δ scale), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constant (Hz), and assignment. ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). ^{119}Sn chemical shifts are reported in ppm downfield from tetramethyltin (δ scale). All ^{13}C and ^{119}Sn spectra were determined with complete proton decoupling.

Infrared spectra were obtained on a Perkin-Elmer Series 1600 FT-IR spectrophotometer. Microanalyses were performed by E + R Microanalytical Laboratory, Inc. High resolution mass spectra were recorded on a Finnegan MAT System 8200 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.

Resolution of (2*S*,4*S*)-dimethylglutaric acid. Brucine (109.3 g, 0.28 mol) and 2,4-dimethylglutaric acid (44.4 g, 0.28 mol) were weighed in a 1L Erlenmeyer flask. 400 ml of boiling distilled water were used to dissolve the mixture with constant stirring and heating on a hot plate. A very dark brown solution was formed. This was vacuum-filtered while it was still hot. The filtrate was left to cool to room temperature. Amorphous, white clumps of salt crystals formed during the process. This first batch of crystals was recovered by vacuum filtration. The mother liquor was concentrated by boiling off the water to 300 ml. This was cooled to room temperature and then to 0 °C. After seeding with some first-batch crystals, a second batch of amorphous crystals was obtained and filtered off. A small amount of crystals was acidified separately and extracted with diethyl ether. The solvent was removed from the organic layer and ^{1}H NMR analysis of the acid showed the *d,l:meso* composition to be 3.8:1 and 2.1:1 respectively. The two batches were similarly recrystallized two more times in 250 ml and 200 ml of boiling distilled water, respectively. The final crop of crystals recovered was 20.9 g (13.5% of initial dissolved mass).

Brucine and the diacid were recovered from the salt crystals (and mother liquor from the recrystallization) as follows: 100 ml of water were added to the salt and then acidified by adding conc. HCl dropwise until the pH was 0-1. This was extracted three times with Et_2O, the organic fractions were combined, and the solvent rotary-evaporated to provide the diacid. Solid NaOH was added with stirring to the aqueous layer until the brucine abruptly precipitated out. This was filtered and recrystallized from acetone.

$[\alpha]_D$ +41.5 (*c* 1.16, EtOAc); +40.0 (*c* 1.13, H_2O); m.p. 79.0 °C.

Reduction of (2*S*,4*S*)-dimethylglutaric acid to (2*S*,4*S*)-dimethylpentane-1,5-diol. (2*S*,4*S*)-Dimethylglutaric acid (5.10 g, 31.8 mmol) was dissolved in 160 ml THF and cooled in an ice-water batch to 0 °C. An 80 ml solution of lithium aluminium hydride (3.02 g, 79.6 mmol) in THF was added dropwise via an addition funnel over 2 h. On completion of addition, the reaction mixture was left in the ice-water bath and allowed to warm to room temperature overnight. The following day, the reaction flask was immersed in a fresh ice-water bath, and the reaction was quenched with 3 ml of distilled water, 3 ml of 15% NaOH solution, and 9 ml of distilled water. This was diluted with 100 ml of Et_2O and vacuum-filtered through Celite. The solvent was removed by rotary-evaporation to give a viscous, colorless liquid. This was purified by flash chromatography (EtOAc) to give a clear, colorless and viscous liquid. The isolated yield was 4.0g (95%).

$[\alpha]_D$ -35.4 (*c* 2.38, abs. alc.); -33.1 (*c* 1.22, EtOAc).

Preparation of 1,5-dibromo-(2*S*,4*S*)-dimethylpentane (2*S*,4*S*)-dimethylpentane-1,5-

diol (4.0 g, 30.3 mmol) was put in a round-bottom flask and cooled in an ice-water bath to 0 °C. PBr_3 (18.1 g, 66.7 mmol) was added dropwise using an addition funnel over 1 h. On completion of addition, the reaction was allowed to warm to room temperature over 1 h. This was refluxed overnight in a 100 °C oil bath. The following day, the reaction was quenched with 30 g of ice and saturated NaCl solution, and then diluted with Et_2O. This was extracted with 3 x 100 ml of Et_2O, dried with $MgSO_4$, and the solvent was removed by rotary-evaporation. Purification was done by distilling under full vacuum at 50 °C with a Kugelrhor apparatus to give a clear, colorless liquid. The isolated yield was 7.9g (77%).

^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (ddd, 4H, J = 5.0, CH_2Br), 1.86 (app. sex, 2H, J = 6.4, $CH(CH_3)$), 1.34 (t, 2H, J = 7.1, $CH_2(CH(CH_3))_2$), 0.99 (d, 6H, J = 6.1, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.4, 40.3, 32.7, 18.5; IR (neat) 2963, 2928, 2872, 1457, 1433, 1380, 1230, 653 cm^{-1}; HRMS: Calcd for $C_7H_{14}Br_2$: 257.9442. Found: 257.9446. $[\alpha]_D$ -18.4 (*c* 1.69, CH_2Cl_2).

Preparation of the bis-Grignard of 1,5-dibromo-(2*S*,4*S*)-dimethylpentane. Mg metal strips (3.0 g, 123.4 mmol) were heated under full vacuum over 2 days to activate it. 1,5-dibromo-(2*S*,4*S*)-dimethylpentane (4.02 g, 15.5 mmol) was dissolved in 30 ml THF and added dropwise slowly onto the Mg metal. After a short while, an exothermic reaction occured. On completion of addition, the reaction solution was refluxed overnight to give a grayish solution. This was used without further purification to form the stannacycle.

Preparation of 1,1-diphenyl-(3*S*,5*S*)-dimethylstannacyclohexane. Diphenyltin dichloride (5.85 g, 17.0 mmol) was dissolved in 27 ml THF. The bis-Grignard solution (from previous procedure) was transferred using a cannula into an additional funnel and added dropwise to the solution. A slightly exothermic reaction occured. On completion of addition, the reaction was refluxed overnight. The following day, the reaction was quenched with saturated NH_4Cl and NaCl solutions and diluted with Et_2O. This was extracted with a combination of hexane/Et_2O, adding excess saturated NaCl solutions to remove the emulsion. The organic layers were combined, dried with $MgSO_4$. and the solvent was removed by rotary-evaporation. The crude product was purified by flash chromatography (eluted with a gradient of 2%, 4% and 6% EtOAc/hexane). The isolated yield was 5.7g (44%).

^{1}H NMR (300 MHz, CDCl3) δ 7.70-7.30 (m, 10H, aromatic H), 2.36 (app. sex, 2H, C*H*(CH$_3$)), 1.51 (dd, 2H, J = 8.7, 4.6, C*H*HSn), 1.49 (t, 2H, C*H*$_2$(CH(CH$_3$))$_2$), 1.16 (dd, 2H, J = 12.9, 8.3, CH*H*Sn), 1.08 (d, 6H, J = 3.4, C*H*$_3$); ^{13}C NMR (75 MHz, CDCl3) δ 140.4, 136.6, 128.5, 128.3, 45.0, 27.8, 25.9, 17.4; ^{119}Sn NMR (112 MHz, CDCl$_3$) δ -97.0; IR (neat) 3062, 2947, 2898, 2861, 1452, 1428, 1074, 726, 698 cm^{-1}; HRMS: Calcd for $C_{19}H_{24}Sn$: 372.0900. Found: 372.0895. $[\alpha]_D$ -17.1 (*c* 1.87, hexane).

Preparation of 1-chloro-1-phenyl-(3*S*,5*S*)-dimethylstannacyclohexane. 1,1-diphenyl-(3*S*,5*S*)-dimethylstannacyclohexane (0.52 g, 1.40 mmol) was dissolved in 7.5 ml of Et$_2$O. 1.40 ml of 1.0 M solution of HCl in Et$_2$O (0.05 g, 1.40 mmol) were added, and the reaction was stirred at room temperature for 4 h. The solvent was then removed by rotary-evaporation, and the crude product was distilled under full vacuum at 120 °C with a Kugelrohr apparatus to give a clear, colorless liquid. The isolated yield was 0.38 g (84%).

^{1}H NMR (300 MHz, CDCl3) δ 7.70-7.35 (m, 5H, aromatic H), 2.44 (dm, 2H, J = 4.6, C*H*(CH$_3$)), 1.65 (dd, 2H, J = 13.2, 4.3, C*H*HSn), 1.50 (m, 2H, C*H*$_2$(CH(CH$_3$))$_2$), 1.35 (dd, 2H, J = 13.2, 8.4, CH*H*Sn), 1.16 (d, 3H, J = 6.96, C*H*$_3$CHCH$_2$CHCH$_3$), 1.06 (d, 3H, J = 6.84, CH$_3$CHCH$_2$CHC*H*$_3$); ^{13}C NMR (75 MHz, CDCl3) δ 139.8, 135.3, 129.9, 128.8, 43.8, 28.3, 27.5, 25.7, 25.1, 24.8; ^{119}Sn NMR (112 MHz, CDCl$_3$) δ 72.4; IR (neat) 2949, 2905, 2864, 1453, 1430, 1319, 729, 696 cm^{-1}; HRMS: Calcd for $C_{13}H_{19}SnCl$: 330.0197. Found: 330.0188. $[\alpha]_D$ -12.6 (*c* 1.42, CH$_2$Cl$_2$).

Preparation of 1,1-dichloro-(3*S*,5*S*)-dimethylstannacyclohexane. 1,1-Diphenyl-(3*S*,5*S*)-dimethylstannacyclohexane (0.15 g, 0.40 mmol) was dissolved in 3.0 ml of Et$_2$O. 0.80 ml of 1.0 M solution of HCl in Et$_2$O (0.03 g, 0.80 mmol) were added, and the reaction was stirred at room temperature for 4 days. The solvent was then removed by rotary-evaporation, and the crude product was distilled under full vacuum at 120°C with a Kugelrohr apparatus to give a clear, colorless liquid. The isolated yield is 0.092 g (80%)

^{1}H NMR (300 MHz, CDCl3) δ 2.54 (app. sex, 2H, C*H*(CH$_3$)), 1.94 (dd, 2H, J = 12.8, 5.3, C*H*HSn), 1.62 (dd, 2H, J = 13.2, 7.7, C*H*HSn), 1.48 (t, 2H, J = 5.4, C*H*$_2$(CH(CH$_3$))$_2$), 1.08 (d, 6H, J = 6.9, C*H*$_3$); ^{13}C NMR (75 MHz, CDCl3) δ 42.5, 33.4, 28.9, 24.9; ^{119}Sn NMR (112 MHz, CDCl$_3$) δ 128.9; IR (neat) 2953, 2921, 2868, 1455, 1382, 1318, 1177, 746, 643, 613 cm^{-1}; HRMS: Calcd for $C_7H_{14}SnCl$: 287.9495. Found: 287.9494. $[\alpha]_D$ -15.5 (*c* 1.61,

CH_2Cl_2).

Preparation of 1-hydrido-1-phenyl-(3*S*,5*S*)-dimethylstannacyclohexane 1,1-dichloro-(3*S*,5*S*)-dimethylstannacyclohexane (0.10 g, 0.30 mmol) was dissolved in 2.0 ml of Et_2O and the solution was cooled in an ice-water bath at 0 °C. 0.30 ml of 1.0 M solution of $LiAlH_4$ in Et_2O (0.012 g, 0.30 mmol) was added. The reaction was slowly warmed to room temperature over 4 h. This was then quenched with 0.01 ml of H_2O, 0.01 ml 15% NaOH solution and 0.03 ml of H_2O. After dilution with Et_2O, this was filtered over Celite, and the solvent was removed by rotary-evaporation. The crude was distilled under full vacuum at 100 °C with a Kugelrohr apparatus to give a clear, colorless liquid. The pure hydride is stored under a N_2 atmosphere. The isolated yield was 0.080 g (89%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.10 (m, 5H, aromatic H), 5.48 (t, 1H, J = 2,9, Sn*H*), 2.30-1.80 (m, 2H, $CH(CH_3)$), 0.75-1.40 (m, 6H, CH_2), 0.97 (d, 3H, J = 8.8, $CH_3CHCH_2CHCH_3$), 0.92 (d, 3H, J = 6.9, $CH_3CHCH_2CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.2, 128.7, 128.6, 44.9, 28.3, 27.9, 26.2, 25.2, 15.7; ^{119}Sn NMR (112 MHz, $CDCl_3$) δ -160.5; IR (neat) 2947, 2900, 2861, 1828, 1452, 1428, 1319, 741, 727, 698 cm^{-1}; HRMS: Calcd for $C_{13}H_{20}Sn$: 296.0587. Found: 296.0594. $[\alpha]_D$ -8.47 (*c* 1.42, hexane).

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