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THE DEVELOPMENT OF ORGANOTIN REAGENTS FOR ORGANIC SYNTHESIS

by

David Scott Hays

B. S. Chemistry, University of Illinois

Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

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ABSTRACT

A method for the intramolecular pinacol coupling of dialdehydes and ketoaldehydes is described. The method was found to be useful for synthesizing 1,2-cyclopentanediols with very high degrees of diastereoselectivity in favor of the cis stereochemistry. 1,2-Cyclohexanediols were generated with lower degrees of stereoselection. This free radical chain process involves as the key steps: 1) an intramolecular addition of a tin ketyl radical to a pendant carbonyl group, followed by 2) a rapid intramolecular homolytic displacement by an oxygen radical at the tin center to liberate an alkyl radical.

The development of a Bu_3SnH-catalyzed carbon-carbon bond forming reaction (the reductive cyclization of enals and enones) is described, followed by a catalytic variant of the Barton-McCombie deoxygenation reaction. Both of these methods rely on the reduction of an intermediate Sn-O species to a Sn-H species by a silicon hydride reagent in the turnover step.

A new fundamental reaction of organotin compounds is described: the generation of Sn-H bonds by treatment of tin amides with silicon hyrdides. The scope of organotin hydride catalysis was broadened to include reactions which generate Sn-N bonds, and in this context, a new Bu_3SnH-catalyzed reduction of azides to amines was developed.

Thesis Supervisor: Gregory C. Fu

Title: Assistant Professor of Chemistry

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A number of individuals have had a significant impact on my professional career. I will always be indebted to my friends and mentors at the Eastman Kodak Company who took unselfish interests in my success. First, Ms. Jeanne Kaeding, who taught me the difference between labwork and bookwork. I will always be deeply indebted to Dr. (Professor) Mike Detty for his chemistry lessons, friendship, and advice, and I hope we have the chance to work together again. The experience I gained while working with Dr. Doug Bugner will always stand out as some of the most valuable: in particular, his early confidence that I could handle much more responsibility than I'm sure I had earned.

At the University of Illinois, I was fortunate to have the opportunity to work with a model scientist and academician: Professor Scott Denmark. I couldn't have been given a better undergraduate project, nor could I have asked for a better balance of guidance and freedom. My collaboration with Dr. David Forbes led to some of the most productive 12-hour days (and 12-ounce curls) I've ever known.

I will always be grateful to my thesis advisor, Professor Greg Fu, for allowing me to help start up his lab and his projects, and I expect to hear lots of great chemistry from him over the course of what will certainly be a long academic career.

My blood brothers and sisters (fellow Fu group pioneers Chris Garrett, Diego Hoic, Mike Amendola, and Matthias Scholl) deserve a recognition which couldn't be accommodated between the covers of this Thesis. I hope that my future coworkers are as talented, honest, dedicated, responsible, trustworthy, and open to discussion as they have been, as well as the remaining Fu group members: Shuang Qiao, Adam Littke, Dr. Ken Stockman, Dr. Jordi Tormo, Dr. Rosa Lopez, Jack Liang, Dr. Hallie Latham, Beata Tao, and Michael Lo.

My parents have always served as an endless source of inspiration, and I only hope I can do the same for my own children. They, as well as Jack and Phoebe Harden, helped to make the last 5 years a success.

And finally my wife Jennifer, the most natural and capable mother on the planet, who earned this degree as much as I did. It would not have been possible without her unconditional optimism and support. She, along with our children Samuel and Brooke, taught me everything that is important.

DEDICATION

To my beautiful wife Jennifer,
and to our spectacular children Samuel, Brooke,
and those not yet conceived.

PREFACE

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

Hays, D. S.; Fu, G. C. "Metal Hydride Mediated Intramolecular Pinacol Coupling of Dialdehydes and Ketoaldehydes," *J. Am. Chem. Soc.* **1995**, *117*, 7283-7284.

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Tormo, J.; Hays, D. S.; Fu, G. C. "Diastereoselective Synthesis of β-Amino Alcohols via Bu_3SnH-Mediated Reductive Cyclization of Carbonyl-Oxime Ethers," *J. Org. Chem.* **1998**, *63*, 201-202.

Hays, D. S.; Fu, G. C. "The Development of Bu_3SnH-Catalyzed Processes: Efficient Reduction of Azides to Amines," *J. Org. Chem.*, **1998**, *63*, 2796-2797.

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ABBREVIATIONS

ACHN	1,1'-Azobis(cyclohexnanecarbonitrile)
AIBN	2,2'-Azobisisobutyronitrile
d	doublet
DBATO	bis(dibutylacetoxytin) oxide
eq	equation
equiv	equivalent(s)
GC	gas chromatography
h	hour(s)
HRMS	high resolution mass spectroscopy
IR	infrared
min	minute(s)
NMR	nuclear magnetic resonance
PMHS	polymethylhydrosiloxane
PMHS dimer	1,3-bis(trimethylsiloxy)-1,3-dimethyldisiloxane
ppm	parts per million
q	quartet
quint	quintet
r.t.	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin-layer chromatography

Introduction

Over the last 30-40 years, organotin reagents have become indispensible tools for synthetic organic chemists.[1] Their utility can largely be attributed to the unmatched ability with which organotin species participate in radical chain reactions, thus carving out a niche distinct from polar chemistry. As a consequence, modes of reactivity which cannot be accessed in the polar realm are readily available in a mild, neutral, often chemo- and stereoselective manner[2] by using organotin reagents.

As a testimony to the synthetic utility of organotin reagents, chemists continue to widely use them despite two significant drawbacks: toxicity[3-5] and difficulty in removal of organotin residues from crude reaction mixtures.[6] Both of these issues could be addressed by a protocol which requires less than stoichiometric quantities of the organotin reagent.[7-10] Thus, the development of organotin *catalysis* is the central focus of this thesis.

The development of a new catalytic cycle can be envisioned as occurring in three stages. In the first stage, a mechanism for catalysis must be proposed. Subsequently, in the second stage, stoichiometric reactions must be identified in order to test the catalytic proposal. The source of these reactions can be the literature or the laboratory, and our first endeavor was an attempt to draw upon the latter.

Thus, in Chapter 1, the development of a new stoichiometric reaction, the intramolecular pinacol coupling of dialdehydes and ketoaldehydes mediated by Bu_3SnH, is described. In order to proceed with the development of a new catalytic cycle, the mechanism of the stoichiometric pinacol coupling had to be understood. It was during this phase that we discovered an unexpected mechanistic twist which rendered the pinacol coupling reaction not susceptible to our catalytic strategy. However, much was learned about the fundamental reactivity of this chemical

system.

In the third stage of development, the catalytic proposal is tested by attempting to modify the stoichiometric reactions selected in stage 2 in order to render them catalytic. This undertaking is described in Chapter 2 beginning with the reductive cyclization of enals and enones. As is typical for this line of work, the initial catalytic proposal proved fruitless. However, our discovery of a minor side product in a 30-year-old reaction[11] allowed us to identify the source of the rather complex problem, and some minor procedural modifications led to the solution (Section 2.2). Building on what was learned from the catalytic reductive cyclization of enals and enones, we were able to apply our catalytic strategy to a variety of other chemical transformations, thus demonstrating the generality of our method.

In the process of extending the scope of organotin catalysis to include reactions which generate species containing Sn-N bonds (Section 3.3), we discovered a new fundamental reaction of organotin compounds: the formation of tin hydrides by reacting tin amides with silicon hydrides (Section 3.2).

The goal of this work was to address the major drawbacks of organotin reagents (toxicity and removal) by bringing to fruition a new strategy for organotin catalysis. In having successfully done so, the foundation for *asymmetric* catalysis with chiral organotin reagents has also been established. Despite the valiant efforts of Chee-Kiang Lim, Jack Liang, and Dr. Jordi Tormo in these laboratories, no effective chiral tin catalyst has yet become available, but the author is optimistic that future efforts from this group will meet with success.

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Chapter 1. Bu_3SnH-Mediated Intramolecular Pinacol Coupling of Dialdehydes and Ketoaldehydes

Background

The inter- and intramolecular reductive coupling of carbonyls is an extremely powerful method for the construction of carbon-carbons bonds.[1] The most synthetically useful variant of this transformation utilizes low valent titanium(0) as the the reducing agent which is typically generated in situ by the reduction of $TiCl_3(DME)_2$ with Zn-Cu.[2] Under mild conditions, the diol product can be isolated, but more vigorous conditions allow for further reduction to the corresponding olefin. A variety of ring sizes (from 3 through 20) can be accessed by this methodology. An additional reagent, SmI_2, has recently received much attention in the context of pinacol coupling reactions as well.[1]

The reductive cyclization of enals and enones, first reported by Beckwith[3-5] and later systematically explored by Enholm (Figure 1.1),[6,7] served as a foundation for a propsed Bu_3SnH-mediated intramolecular pinacol coupling reaction (Figure 1.2). The pinacol coupling was predicted to proceed in a mechanistically similar fashion to the Beckwith/Enholm system, but rather than forming a *carbon*-centered radical intermediate, the tin ketyl is proposed to form an *oxygen*-centered radical (Figure 1.2, **C**) by intramolecular addition to a carbonyl. Prior to our work, no literature precedent for this step existed. The anticipated pre-hydrolysis product was thus the cyclic 1,2-diol (Figure 1.2, **D**) in monostannylated form.

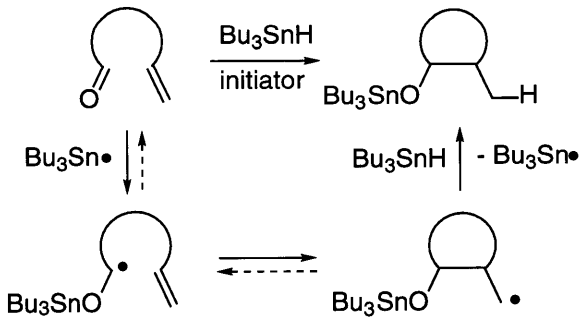


Figure 1.1. The Bu_3SnH-mediated reductive cyclization of enals and enones: a foundation for a proposed Bu_3SnH-mediated pincacol cyclization.

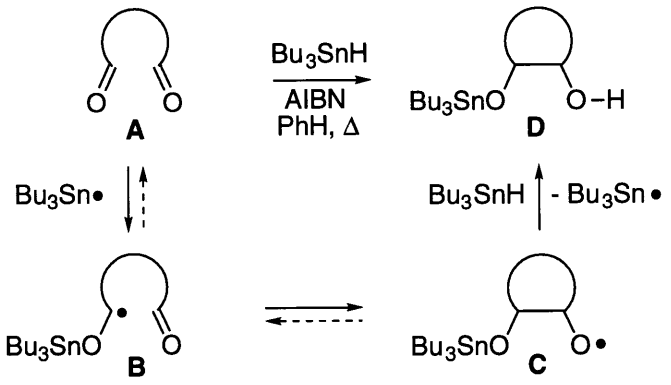
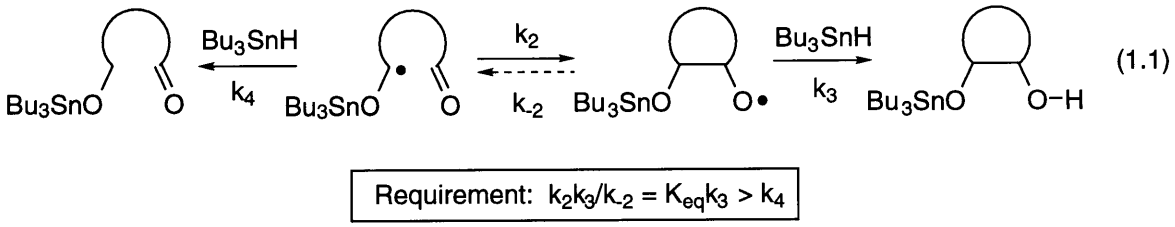


Figure 1.2. A proposed Bu_3SnH-mediated intramolecular pincacol coupling.

A necessary requirement for the success of this strategy is that the ketyl radical must cyclize and trap (eq 1.1, steps 2,3) faster than it abstracts a hydrogen atom from Bu_3SnH (eq 1.1, step 4). Otherwise, undesired acyclic reduction products will predominate. By applying the steady-state assumption to the alkoxy radical intermediate, the kinetic requirement is that $k_2k_3/\{k_{-2} + k_3[Bu_3SnH]\} > k_4$. Under conditions of infinite dilution, this expression reduces to $k_2k_3/k_{-2} > k_4$.



Beckwith has determined that the equilibrium constants for the cyclizations of 4-formylbutyl radicals and 5-formylpentyl radicals are 2×10^{-3} and 1×10^{-1} respectively at 80 °C.[8] Adding a 1-stannyloxy substituent should stabilize the open form by ca. 5 kcal/mol,[9] thus reducing the equilibrium constants for the proposed ketyl/carbonyl cyclizations to 1.5×10^{-6} and 8.2×10^{-5} respectively (Figure 1.3).

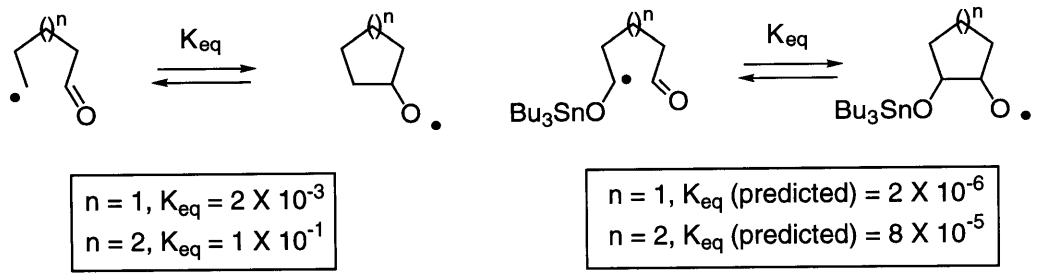


Figure 1.3. Known equilibrium constants for the reversible cyclization of 4-formylbutyl/5-formylpentyl radicals and predicted equilibrium constants for the analogous ketyl radicals.

The bimolecular rate constant for the abstraction of a hydrogen atom from Bu_3SnH by *tert*-butoxy radical has been determined to be 4×10^8 at 80 °C and provides an approximation for k_3 (eq 1.1).[10] Thus, the kinetic requirement at infinite dilution for the successful formation of 6-membered ring pinacols is that $k_4 < 3 \times 10^4$, but 5-membered ring pinacols require that $k_4 < 6 \times 10^2$. Unfortunately, no values for k_4 have been published, so the only recourse was to test the proposed pinacol coupling reaction in the laboratory.

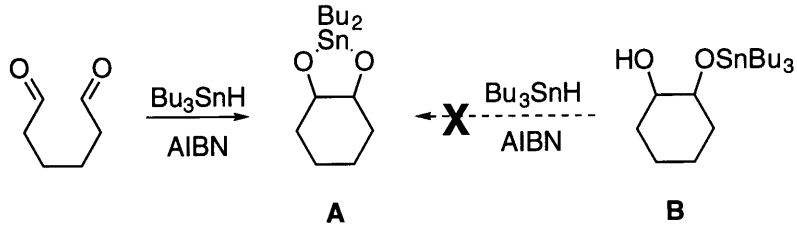
Results and Discussion

When a series of 1,5- and 1,6-dicarbonyl substrates were treated with Bu_3SnH in refluxing benzene (AIBN), followed by hydrolytic workup, the cyclic pinacol products were formed in moderate to good yields (Table 1.1). Of particular note is that the 1,5-dicarbonyl substrates were all converted to the corresponding cis-diols with very high diastereoselectivities (Table 1.1, entries 1, 2, and 5), a surprising result in light of the published data on tin ketyl radical formations of 5- and 6-membered rings.[3,5-7,11-15]

The yield from the pinacol coupling of glutaraldehyde (46%, Table 1.1, entry 1) is significantly lower than from adipaldehyde (84%, Table 1.1, entry 3), and this is attributable to a larger percentage of the acyclic reduction products (eq 1.1, step 4) in the

fomer than in the latter. This observation is consistent with the findings of Beckwith that alkyl radical cyclizations onto carbonyls are less favored kinetically and thermodynamically for 5-membered rings than for 6-membered rings.[8] In order to minimize this side reaction, more dilute conditions were required for glutaraldehyde (0.025 M), than for adipaldehyde (0.10 M).

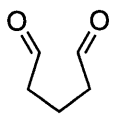
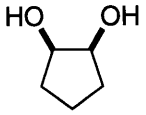
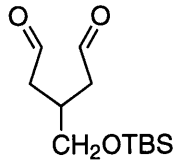
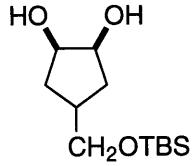
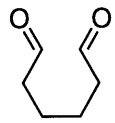
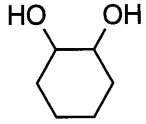
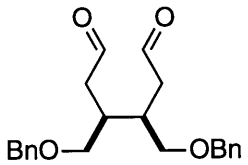
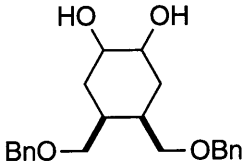
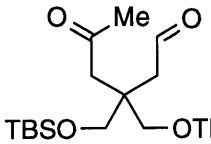
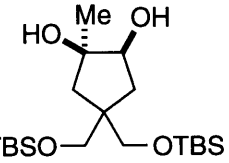
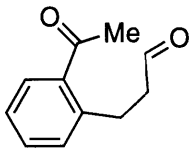
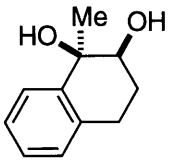
Subsequently, upon examination of the crude reaction mixture prior to hydrolysis, it was discovered that adipaldehyde was converted *not* to the predicted tin alkoxide (eq 1.2, **B**). Rather, the 1,3,2-dioxastannolane was isolated in a 60% yield (eq 1.2, **A**). An independently prepared sample of the predicted product (**A**) was found to be stable to the reaction conditions, so it cannot lie on the reaction pathway. Thus, our mechanistic proposal was in need of revision.



(1.2)

The first two steps of the revised mechanism (Figure 1.4) are identical to those from the original mechanism (Figure 1.2), but instead of the alkoxy radical (**C**) abstracting a hydrogen atom from Bu_3SnH, we now believe that it undergoes a homolytic displacement (S_H2) reaction at the tin center.[16,17] The liberated primary butyl radical is responsible for propagating the radical chain. Thus, the final, irreversible step in the reaction is believed to be driven by the strength of the Sn-O bond (90 kcal/mol) versus the relatively weak Sn-C bond (61 kcal/mol).

Table 1.1 Metal Hydride-Mediated Intramolecular Pinacol Coupling.

Entry	Substrate	Product	Stereoselectivity[a,b] (cis : trans)	Yield[a] (%)
1			98 : 1	46[c]
2			>99 : 1[d]	64
3			1 : 2.4	84
4			1 : 1.6[d]	88
5			>20 : 1[e]	62
6			20 : 1	53[f]

[a] Average of two runs.
[b] Based on analysis by capillary gas chromatography, except as noted.
[c] Isolated by crystallization as the 1,3,2-dioxastannolane.
[d] ~ 1 : 1 mixture of the two diastereomeric cis diols.
[e] Based on analysis by ^{1}H NMR.
[f] Isolated as the acetonide.

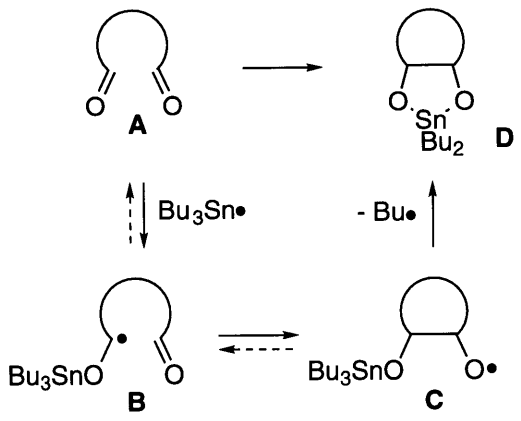
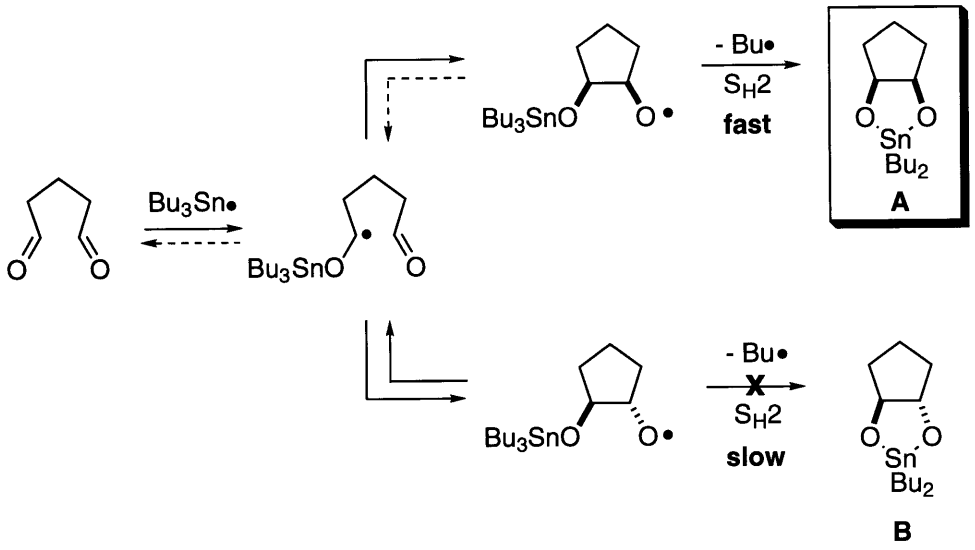


Figure 1.4 Revised mechanism for the Bu_3SnH-mediated intramolecular pinacol coupling.

In contrast to the original mechanism, the revised mechanism accounts for the observation that the 1,5-dicarbonyl substrates afford pinacol products with high diastereoselectivities in favor of the cis geometry. If the ketyl radical initially cyclizes in the trans fashion (Scheme 1.1, bottom pathway), the ensuing intramolecular homolytic displacement reaction is expected to proceed slowly because the product would be a strained *trans*-5,5-fused ring system (Scheme 1.1, **B**). Consequently, the oxygen radical is believed to revert to the ketyl via β-scission.

Alternatively, if the ketyl radical cyclizes in the cis fashion (Scheme 1.1, top pathway), the ensuing intramolecular homolytic displacement reaction is expected to proceed rapidly, because the product (Scheme 1.1, **A**) is not subject to the ring strain experienced by the trans isomer.

Scheme 1.1



In order to probe the reversibility of the carbon-carbon bond forming step, we synthesized both diastereomers of 1,2-cyclohexane diol mononitrate[18] in stannylated form (Figure 1.5, **1.1** and **1.2**). Both isomers, when subjected to the pinacol coupling conditions, converged on a mixture of the *cis* and *trans* 1,3,2-dioxastannolanes. This provides evidence that the carbon-carbon bond-forming step is reversible.

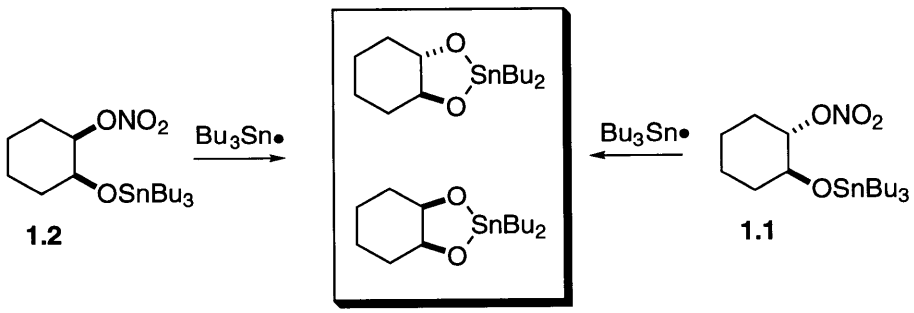


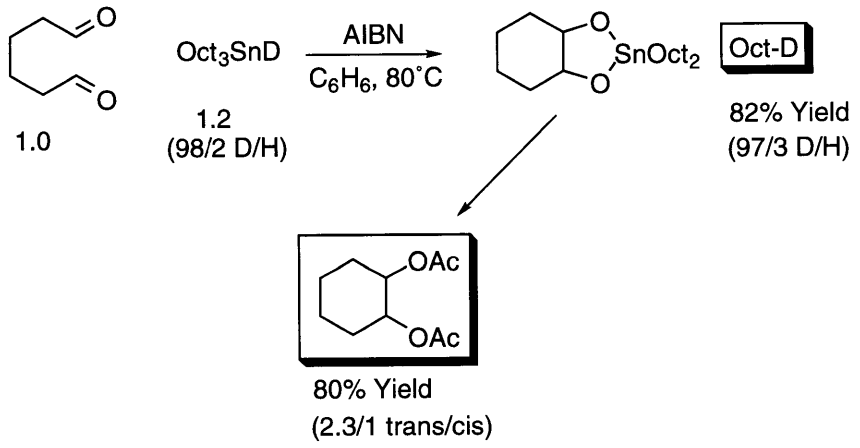
Figure 1.5. Evidence for reversibility of carbon-carbon bond formation.

Taken alone, the isolation of 1,3,2-dioxastannolanes does not preclude the possibility that *both* the original mechanism and the revised mechanism are operative in a

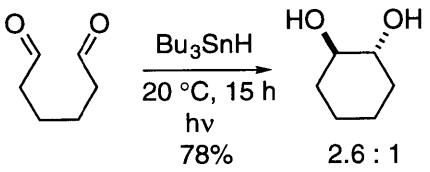
competitive fashion. However, the 5-membered rings provide stereochemical evidence (very little *trans* product observed) that no significant contribution to product formation is being made by the original mechanism for these substrates.

In contrast, the 1,6-dicarbonyls have no such stereochemical test since their diastereoselectivities are more modest. In order to probe for the presence of the original mechanism in the 6-membered rings, we replaced Bu_3SnH with Oct_3SnD and subjected adipaldehyde to the pincacol coupling conditions (Scheme 1.2). If there is a significant contribution from the original mechanism, then the yield of pinacol product should exceed the yield of octane. In fact, the yield of the pinacol product (assayed as the bis-acetate, 80%) is within experimental error of the yield of octane (82%), so no significant contribution from the original mechanism is present. Furthermore, since complete deuterium incorporation into the octane is observed, we can conclude that in the chain propagating step, the primary alkyl fragment reacts *only* with the tin hydride (deuteride) reagent.

Scheme 1.2



Other main group metal hydrides (e.g., Ph_3SnH, $(TMS)_3SiH$, and Bu_3GeH) also effect the intramolecular pinacol coupling of dicarbonyl compounds, although they are somewhat less efficient than Bu_3SnH. Initiation by ultraviolet irradiation at 20 °C (eq 1.3) affords results comparable to thermal initiation with AIBN (Table 1.1, entry 4).



(1.3)

The preparation of both medium (1,2-cycloheptanediol) and large (1,2-cyclododecanediol) rings proved unsuccessful according to our methodology. Only acyclic reduction products were observed.

Selective pinacol cyclization of a dialdehyde in the presence of a ketoaldehyde or a diketone can be accomplished when Bu_3SnH is used as the reducing agent (Figure 1.6). We believe that the high selectivity of the Bu_3SnH-mediated reaction is a consequence of the *reversibility* of tributyltin radical addition to the carbonyl group (**A** $\rightleftharpoons$ **B**, Figure 1.4). The product distribution is therefore guided not simply by the relative ease of formation of the tin ketyl (**A** $\rightarrow$ **B**), but by the relative facility with which the ketyl radical adds to the pendant carbonyl (**B** $\rightarrow$ **C**). The slower the latter reaction (e.g., due to steric effects), the more likely that **B** will fragment to starting material (**B** $\rightarrow$ **A**) rather than proceed toward product (**B** $\rightarrow$ **C**).

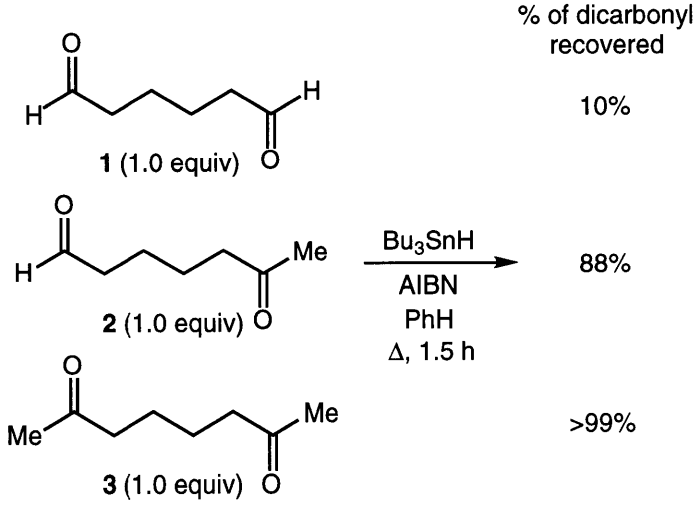
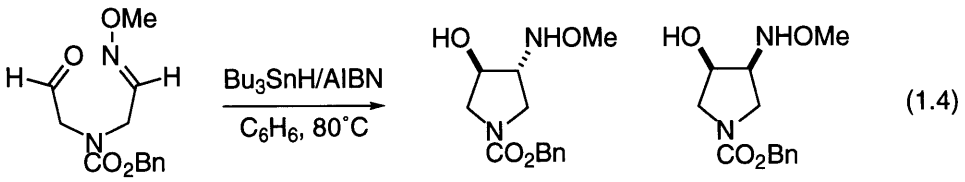


Figure 1.6. Selective intramolecular pinacol coupling of dialdehydes by Bu_3SnH.

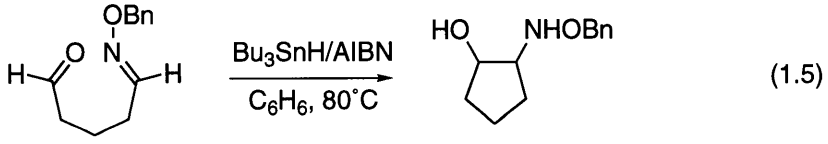
While our study was in progress, Naito published a method for the preparation of β-aminoalcohols from carbonyl-oxime ether systems (eq 1.4). Only modest diastereoselectivity was observed in the formation of a five-membered ring.



(1.4)

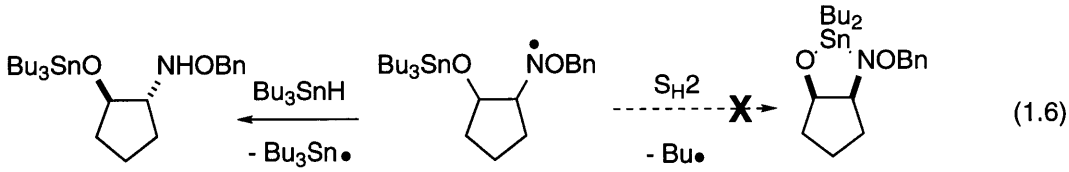
2.3 : 1

In contrast, we found that the all-carbon analog cyclized to afford only one diastereomer of unknown relative stereochemistry (eq 1.5). In light of the results from our intramolecular pinacol coupling reaction, we postulated that if the product is the *cis* isomer, then this reaction might be proceeding through an analogous intramolecular homolytic displacement pathway (eq 1.6, right side). If, however, the *trans* isomer is formed, then an intramolecular homolytic displacement pathway is unlikely (eq 1.6, left side).



(1.5)

One diastereomer formed in large excess



(1.6)

A postdoc in our lab (Dr. Jordi Tormo) subsequently demonstrated that the trans isomer is the preferred product,[19] so simple hydrogen atom abstraction, and not

intramolecular S_H2, is responsible for product formation.

In summary, we have discovered a Bu_3SnH-mediated intramolecular pinacol coupling reaction. The key steps are the addition of a tin ketyl radical to a carbonyl group followed by the formation of a second Sn-O bond at the expense of a Sn-C bond by an intramolecular S_H2 process. As a consequence, high diastereoselectivities are observed in the 5-membered rings. Mechanistic studies have demonstrated that no appreciable contribution from the originally proposed mechanism (Figure 1.1) is present, and that the carbon-carbon bond-forming step is reversible. The analogous carbonyl/oxime ether cyclization does not involve and intramolecular S_H2 reaction.

Experimental

General

AIBN was obtained from Eastman and used without purification. Tributyltin hydride was purchased from Aldrich and distilled prior to use. Glutaric dialdehyde (50 wt. % solution in water) was purchased from Aldrich and purified as described below. Hexanedial was prepared according to a literature method.[20]

Solvents were distilled from the indicated drying agents: benzene (sodium/benzophenone); toluene (molten sodium); dichloromethane (calcium hydride).

Analytical thin layer chromatography was performed using EM Reagents 0.25 mm silica gel 60 plates, and visualization was accomplished with anisaldehyde/H_2SO_4/EtOH/HOAc or with ethanolic phosphomolybdic acid. Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh).

^1H, ^{13}C, ^2H 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, and coupling constant (Hz). ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). All ^{13}C spectra were determined with complete proton decoupling. ^{119}Sn chemical shifts are reported in ppm downfield from tetramethyltin (neat, external reference, δ scale) and were determined with pulse intervals of 0.3 s. Broad band ^{1}H NMR decoupling was only applied during acquisition.

Gas chromatography was performed on a Hewlett Packard 5890 Series II instrument utilizing DB-1 or DB-1701 capillary columns (J & W Scientific).

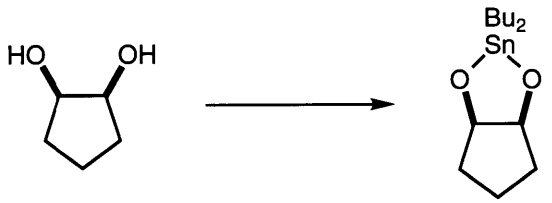
Infrared spectra were obtained on a Perkin-Elmer Series 1600 FT-IR spectrophotometer. Microanalyses were performed by E + R Microanalytical Laboratory, Inc. High resolution mass spectra were recorded on a Finnegan MAT System 8200 spectrometer.

Photochemical initiation was accomplished with a Canrad-Hanovia 450 watt medium pressure mercury vapor lamp through three walls of Pyrex.

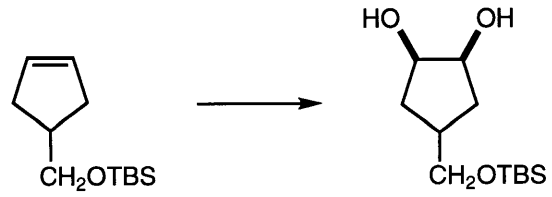
Ozonolysis reactions were performed utilizing a Welsbach model T-816 ozone generator.

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated.

Preparation of Authentic Products

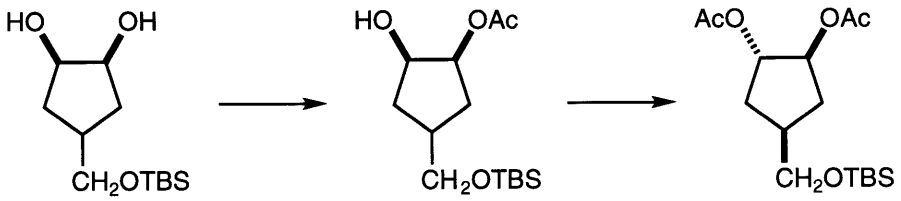


***cis*-2,2-Dibutyltetrahydro-4H-cyclopenta[d]-1,3,2-dioxastannole.** To a solution of *cis*-cyclopentane-1,2-diol (Aldrich; 102 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added $Bu_2Sn(OMe)_2$ (295 mg, 1.00 mmol). After stirring for 1 h at room temperature, the solvent was removed to afford the dioxastannolane as a white powder. The ^1H NMR was identical to that reported in the literature.[21] ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (br s, 2H), 1.90-1.12 (m, 18H), 0.90 (t, 3H, J = 7.4), 0.89 (t, 3H, J = 7.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.0, 33.7, 27.5, 27.3, 27.0, 26.9, 22.5 (br), 20.8, 13.6, 13.5. ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ -104 (br).

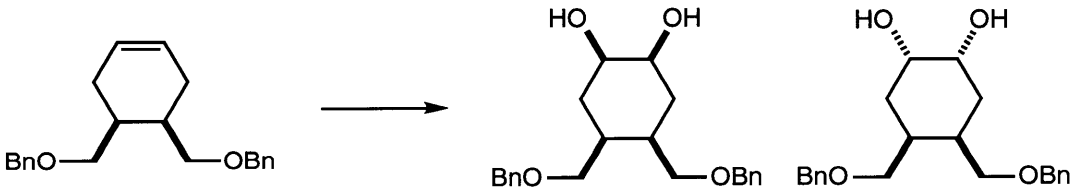


4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1,2-cyclopentanediol. Cis dihydroxylation of the olefin[22] was accomplished by the Upjohn method.[23] The two diastereomeric cis diols were separated by column chromatography. Less polar diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (m, 2H), 3.56 (d, 2H, J = 2.7), 3.12 (d, 2H, J = 9.3), 2.28 (m, 1H), 2.06 (m, 2H), 1.52 (dt, 2H, J_1 = 14.1, J_2 = 5.1), 0.93 (s, 9H), 0.10

(s, 6H). More polar diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (br s, 2H), 3.43 (d, 2H, J = 5.3), 2.96 (br s, 2H), 2.42 (m, 1H), 1.77 (m, 2H), 1.64 (m, 2H), 0.87 (s, 9H), 0.01 (s, 6H).

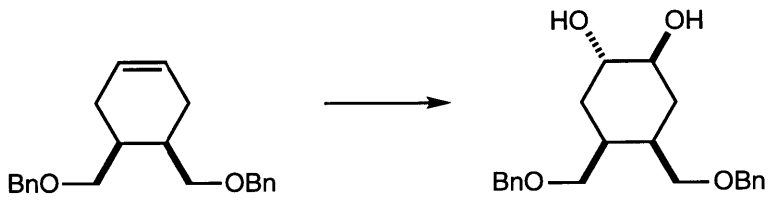


4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1,2-cyclopentanediol bis acetate. The mixture of cis diols was mono-acetylated and purified by column chromatography. After subjection to standard Mitsunobu inversion conditions[24] and column chromatography, the trans diacetate was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11-5.03 (m, 2H), 3.52 (d, 2H, J = 5.7), 2.37-2.22 (m, 2H), 2.03 (s, 6H), 1.92-1.81 (m 1H), 1.77-1.68 (m, 1H), 1.47-1.37 (m, 1H), 0.88 (s, 9H), 0.03 (s, 6H).

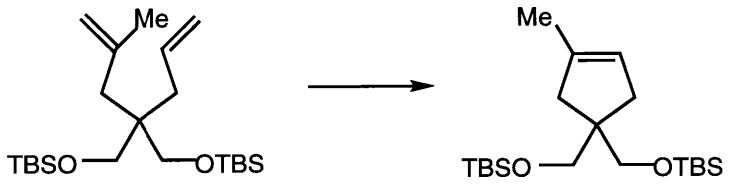


(1-alpha., 2 alpha., 4 alpha., 5 alpha)-4,5-bis[(phenylmethoxy)methyl]-1,2-cyclohexanediol and **(1-alpha., 2 alpha., 4 beta., 5 beta)-4,5-bis[(phenylmethoxy)methyl]-1,2-cyclohexanediol.** Cis dihydroxylation of the olefin[25] was accomplished by the Upjohn method.[23] The product was purified by column chromatography to afford a mixture of diastereomeric cis diols. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.38-7.24 (m, 10H), 4.48-4.40 (m, 4H), 3.87-3.31 (m, 6H), 2.37-1.62 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 137.4, 128.4, 128.3, 128.0, 127.9, 127.6, 127.5, 73.4, 73.0, 71.8, 70.7, 69.5, 68.5, 33.4, 30.7.

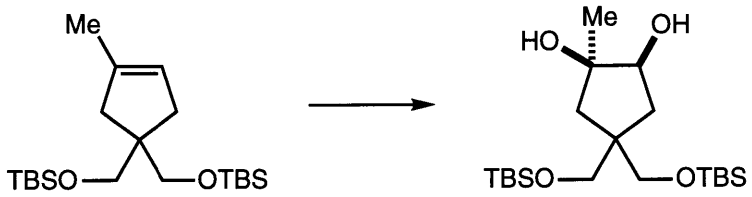


(1-alpha., 2 beta., 4 alpha., 5 alpha)-4,5-bis[(phenylmethoxy)methyl]-1,2-cyclohexanediol. Net trans dihydroxylation of the olefin[25] was accomplished by acid-induced ring-opening of the derived epoxide.[26] After aqueous workup and column chromatography, the trans diol was isolated as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (m, 10H), 4.47 (d, 1H, J = 12.0), 4.45 (s, 2H), 4.41 (d, 1H, J = 12.0), 3.62-3.54 (m, 1H), 3.48-3.31 (m, 5H), 2.8-2.2 (br s, 2H), 2.31-2.23 (m, 1H), 2.15 (dt, 1H, J_1 = 12.0, J_2 = 3.7), 2.04 (m, 1H), 1.93 (dt, 1H, J_1 = 12.0, J_2 = 4.0), 1.45-1.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.2, 128.3, 127.6, 127.5, 75.0, 73.1, 73.0, 72.2, 71.9, 69.1, 37.8, 35.1, 34.3, 31.9.

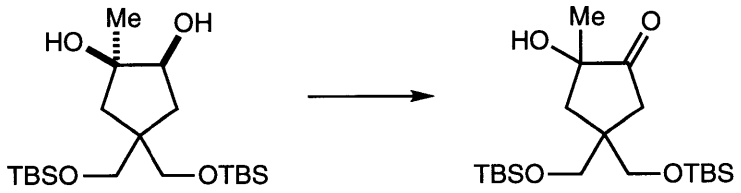


4,4-bis-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methylcyclopentene. The diolefin (prepared by TBS protection of the known diol)[27] (399 mg, 1.00 mmol) was subjected to standard olefin metathesis conditions using $(PCy_3)_2Cl_2RuCHCHCPh_2$ (ca.

11 mg) to obtain 353 mg (95%) of the cyclopentene as a clear, colorless oil following flash chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (m, 1H), 3.46 (s, 4H), 2.03 (m, 2H), 1.98 (m, 2H), 1.66 (m, 3H), 0.88 (s, 18H), 0.021 (s, 12H).

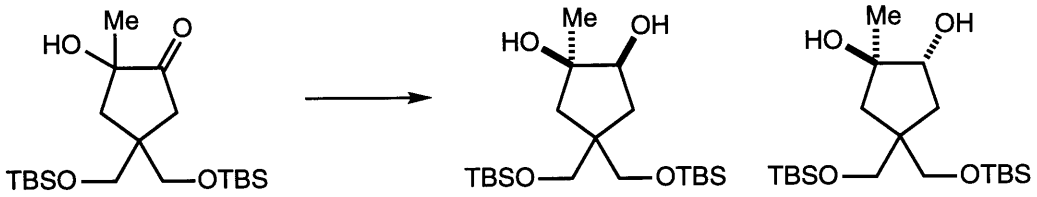


cis-4,4-bis-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1-methyl-1,2-cyclopentanediol. Cis dihydroxylation was accomplished by the Upjohn method.[23] The product was purified by column chromatography to afford the cis diol as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07(s, 1H), 3.65 (m, 1H), 3.43 (s, 2H), 3.29 (s, 2H), 2.67 (d, 1H, J = 10.8), 1.89 (dd, 1H, J_1 = 13.5, J_2 = 7.2), 1.74 (d, 1H, J = 14.7), 1.66 (d, 1H, J = 14.4), 1.60 (dd, 1H, J_1 = 13.7, J_2 = 8.9), 1.23 (s, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.11 (s, 6H), 0.02 (s, 6H).

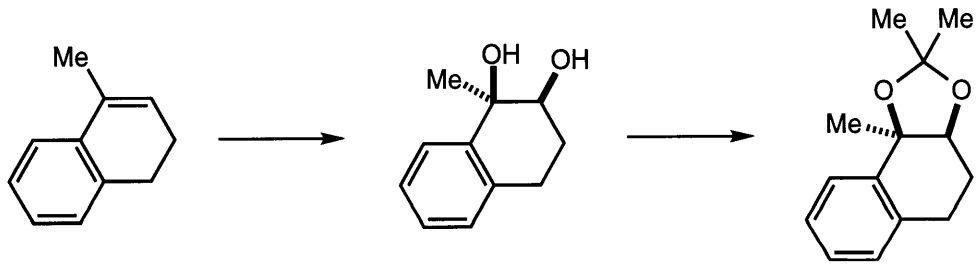


4,4-bis-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-hydroxy-2-methylcyclopentanone. To a solution of the diol (78 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) was added powdered 4A molecular sieves (100 mg), NMO (34 mg, 0.29 mmol), and TPAP (~4 mg, ~0.01 mmol). After stirring for 12 h at room temperature, the reaction mixture was passed through a pad of Celite and purified by flash chromatography,

which afforded the oxidative cleavage product as the major compound and 19 mg (24%) of the hydroxy ketone as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 1H), 3.62 (d, 1H, J = 9.0), 3.56 (d, 1H, J = 9.9), 3.45 (d, 1H, J = 9.9), 3.41 (d, 1H, J = 9.6), 2.42 (dd, 1H, J_1 = 18.6, J_2 = 1.1), 2.33 (d, 1H, J = 18.3), 1.99 (d, 1H, J = 14.7), 1.92 (dd, 1H, J_1 = 14.7, J_2 = 1.2), 1.28 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H).

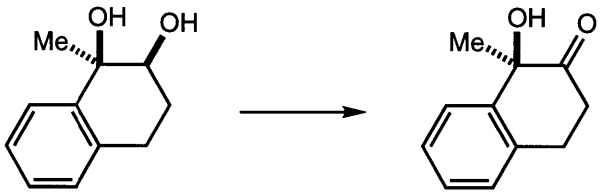


cis- and **trans-4,4-bis-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1-methyl-1,2-cyclopentanediol.** The hydroxyketone was reduced with $NaBH_4$ to afford a 2.5 : 1 (trans : cis) mixture of diols.

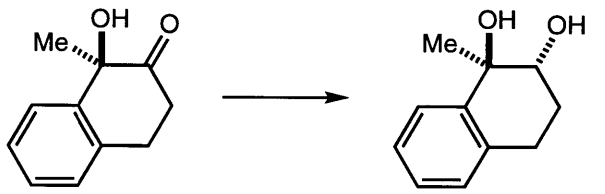


***cis*-1,2,3,4-Tetrahydro-1-methyl-1,2-naphthalenediol acetonide.** Cis dihydroxylation of the olefin[28] was accomplished by the Upjohn method,[23] followed by column chromatography. Treatment with 2,2-dimethoxypropane and catalytic PPTS, followed by column chromatography, afforded the acetonide as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, 1H, J_1 = 7.8, J_2 = 1.5), 7.22-7.11 (m, 2H), 7.03 (d, 1H, J = 7.2), 4.15 (dd, 1H, J_1 = 4.2, J_2 = 2.1), 3.04 (ddd, 1H, J_1 = 16.8, J_2 = 13.2, J_3 = 5.1), 2.60

(ddd, 1H, J_1 = 16.5, J_2 = 5.4, J_3 = 2.7), 2.29-2.20 (m, 1H), 1.99-1.87 (m, 1H), 1.56 (s, 3H), 1.42 (s, 3H), 0.96 (s, 3H).



3,4-Dihydro-1-hydroxy-1-methyl-2(1H)-naphthalenone [66405-14-9]. To a solution of the diol (20 mg, 0.11 mmol) in benzene (0.80 mL), was added $Bu_2Sn(OMe)_2$ (36 mg, 0.12 mmol). After 11 h of stirring at room temperature, 4A molecular sieves were added, and then a solution of Br_2 in CH_2Cl_2 was added dropwise until the color persisted. The solvent was removed in vacuo, and the white solid was subjected to flash chromatography, which afforded 15 mg (77%) of the hydroxy ketone as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, 1H, J_1 = 8.1, J_2 = 2.0), 7.35-7.23 (m, 2H), 7.17 (d, 1H, J = 7.5), 3.95 (s, 1H), 3.32 (ddd, 1H, J_1 = 15.6, J_2 = 7.8, J_3 = 7.8), 3.08 (ddd, 1H, J_1 = 15.6, J_2 = 7.5, J_3 = 3.6), 2.95 (ddd, 1H, J_1 = 18.0, J_2 = 7.2, J_3 = 3.3), 2.65 (ddd, 1H, J_1 = 18.0, J_2 = 9.3, J_3 = 7.2), 1.56 (s, 3H).



***trans*-1,2,3,4-Tetrahydro-1-methyl-1,2-naphthalenediol.** The hydroxyketone was reduced with $NaBH_4$ to afford the trans diol as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, 1H, J_1 = 7.2, J_2 = 2.4), 7.24-7.16 (m, 2H), 7.07 (d, 1H, J = 7.5), 3.93 (br

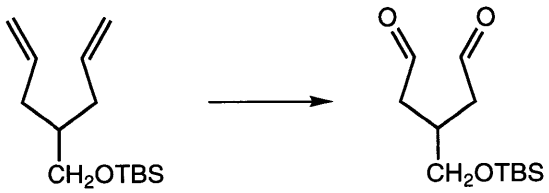
dd, 1H, J_1 = 11.7, J_2 = 2.4), 2.99-2.92 (m, 2H), 2.38 (br s, 1H), 2.11 (m, 1H), 2.01 (br s, 1H), 1.88 (m, 1H), 1.45 (s, 3H).

Preparation of Dicarbonyl Substrates

Note: Glutaraldehyde has been shown to oligomerize upon standing or in the presence of a variety of catalysts, including Lewis and protic acids.[29,30] This process has been reported to be reversible, and the monomer can be regenerated upon heating. We have found that chromatography of a glutaraldehyde derivative on silica gel initially yields the oligomer (vide infra), but that the monomer is accessed upon distillation.

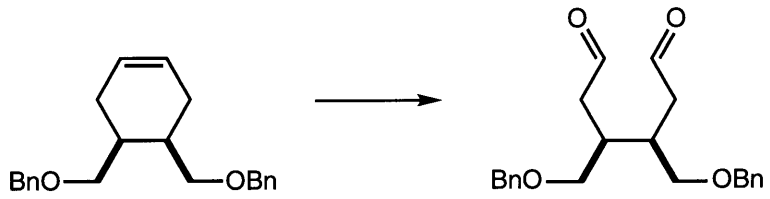
1,6-Dialdehydes have been reported to be unstable toward silica gel and difficult to isolate.[31,32] We have found that an adipaldehyde derivative can be purified by chromatography, albeit at the expense of partial decomposition (vide infra).

All preparations are unoptimized, since our primary objective was simply to obtain pure substrates for the pinacol cyclizations.

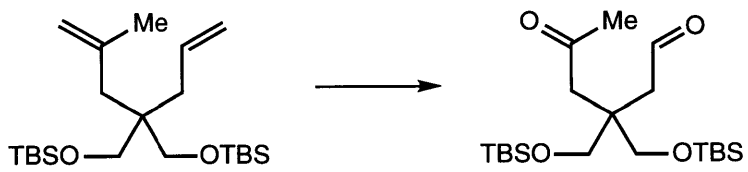


3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-pentanedial. The diene (prepared by TBS protection of the known alcohol)[33] (1.20 g, 5.00 mmol) was dissolved in a 1 : 1 solution of EtOAc and CH_2Cl_2 and cooled to -78 °C under a stream of O_2. The reaction mixture was ozonized until the solution was blue, and then it was purged with

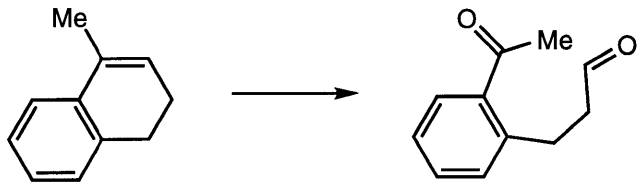
O_2. The solvent was removed in vacuo, and the residue was dissolved in EtOAc (75 mL). After addition of 5% Pd/C (300 mg), the reaction mixture was subjected to one atmosphere of H_2 for 48 h at room temperature. The resulting solution was filtered through a pad of Celite, concentrated, and purified by flash chromatography. The product, which elutes as a streak on silica gel, was collected and concentrated to a highly viscous oil (oligomeric; see Note above). Distillation (bulb-to-bulb) afforded 435 mg (35%) of the dialdehyde as a nonviscous colorless oil. ^1H NMR indicated that the material was about 90% monomeric. ^1H NMR (300 MHz, C_6D_6) δ 9.28 (t, 2H, J = 1.5), 3.23 (d, 2H, J = 5.4), 2.40 (heptet, 1H, J = 6.4), 1.96 (ddd, 2H, J_1 = 17.4, J_2 = 7.0, J_3 = 1.8), 1.81 (ddd, 2H, J_1 = 17.4, J_2 = 6.3, J_3 = 1.5), 0.90 (s, 9H), 0.04 (s, 6H).



(R*, S*)-3,4-bis[(phenylmethoxy)methyl]-hexanedial. The olefin[25] (3.12 g, 9.68 mmol) was dissolved in a 5 : 1 mixture of CH_2Cl_2 and MeOH. $NaHCO_3$ (350 mg) was added to prevent acetal formation,[34] and the resulting solution was cooled to -78 °C under a flow of O_2. The substrate was ozonized until TLC showed no starting material. After purging with O_2 and argon, methyl sulfide (6.2 g, 100 mmol) was added. The solution was allowed to stir at room temperature for 21 h, at which time the solvent was removed in vacuo. The product, which partially decomposes on silica gel, was purified by repeated flash chromatography to afford 366 mg (11%) of the dialdehyde as a clear, colorless oil.

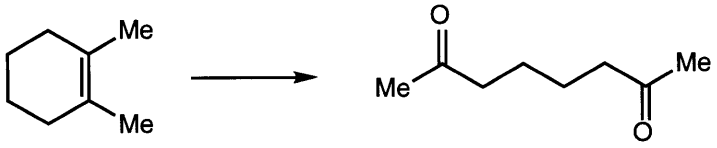


3,3-bis[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5-oxo-hexanal. The diene (vide supra) (4.00 g, 10.0 mmol) was dissolved in EtOAc (100 mL) and cooled to -78 °C under a flow of O_2. The heterogeneous reaction mixture was ozonized until the solution turned blue and no more solid remained. After purging with O_2 and argon, 5% Pd/C (100 mg) was added, and the mixture was then subjected to one atmosphere of H_2 for 43 h at room temperature. The resulting solution was filtered through a pad of Celite, and the solvent was removed in vacuo. The residue was purified by flash chromatography, which afforded 1.6 g (40%) of the ketoaldehyde as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, 1H, J = 2.3), 3.57 (s, 4H), 2.59 (s, 2H), 2.55 (d, 2H, J = 2.3), 2.12 (s, 3H), 0.87 (s, 18H), 0.01 (s, 12H).

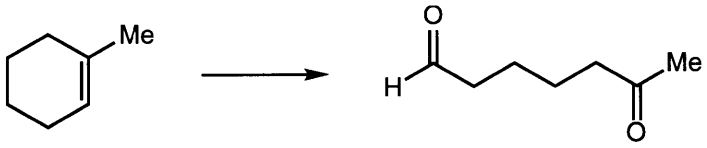


2-Acetyl-benzenepropanal. The olefin[28] (4.33 g, 30.0 mmol) was dissolved in a 5 : 1 mixture of CH_2Cl_2 and MeOH. $NaHCO_3$ (1 g) was added to prevent acetal formation.[34] The solution was cooled to -78 °C under a flow of O_2, and then ozonized until no starting material remained by TLC. After purging with O_2 and argon, methyl sulfide (19 g, 300 mmol) was added. The solution was allowed to stir at room temperature for 20 h, at which time the solvent was removed in vacuo. The orange residue was purified

by flash chromatography, which afforded 2.87 g (54%) of the ketoaldehyde as a pale yellow oil.



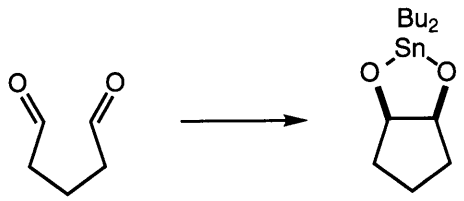
2,7-Octanedione. [1626-09-1]. The olefin (1.10 g, 10.0 mmol) was dissolved in a 5 : 1 solution of CH_2Cl_2 : MeOH and cooled to -78 °C under a flow of O_2. The material was ozonized until the solution turned blue. After purging with O_2, methyl sulfide (9.3 g, 150 mmol) was added, and the reaction mixture was stirred at room temperature for 37 hours. The solvent was removed in vacuo, and the residue was purified by flash chromatography, which afforded 1.17 g (82%) of the diketone as a white solid.



6-Oxoheptanal. [19480-04-7]. The olefin (9.62 g, 100 mmol) was dissolved in EtOAc (200 mL) and cooled to -78 °C under a flow of O_2. The material was ozonized and then purged with O_2. 5% Pd/C (0.50 g) was added, and the reaction was subjected to one atmosphere of H_2 for 35 h at room temperature. After filtration through Celite and concentration in vacuo, the residue was distilled (47-50°C/0.06 mm Hg) twice to obtain 4.1 g (32%) of the ketoaldehyde as a pale yellow oil.

Pinacol Coupling Reactions

Note: The yields reported below may differ slightly from those reported in Table 1, since the latter are the average of two runs.



***cis*-2,2-Dibutyltetrahydro-4H-cyclopenta[d]-1,3,2-dioxastannole. Table 1.1, entry 1.** Commercially available glutaric dialdehyde (50 wt. % solution; 5-6 mL) was dissolved in benzene (75 mL) and dried with $MgSO_4$. After filtration and concentration, the viscous, colorless oil was distilled bulb-to-bulb to afford the anhydrous dialdehyde as a clear, colorless oil which remained predominantly monomeric for at least 48 h (see Note above).

A solution of the dialdehyde (200 mg, 2.00 mmol), Bu_3SnH (699 mg, 2.40 mmol), and AIBN (33 mg, 0.20 mmol) in benzene (80 mL) was heated to reflux. Additional AIBN (33 mg, 0.20 mmol) was added every three hours. After 12 h, the reaction mixture was cooled to room temperature, and an aliquot was removed for GC analysis. The reaction mixture was concentrated, and the resulting white solid was washed with ice-cold toluene (3 x 5 mL) and pumped to dryness to afford 313 mg (47%) of the dioxastannolane as a white solid. The ^1H NMR spectrum was identical to the published[2] and the authentic (vide supra) spectra.

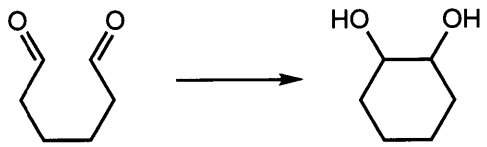
GC analysis of the bisacetate derivative (comparison with authentic products

prepared from commercially available cis and trans diols (Aldrich)) indicated that the cis : trans ratio was 98 : 1.

4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1,2-cyclopentanediol. Table 1.1, entry 2. A solution of the dialdehyde (218 mg, 0.890 mmol), Bu_3SnH (311 mg, 1.07 mmol), and AIBN (15 mg, 0.089 mmol) in benzene (36 mL) was heated to reflux in an oil bath. Additional AIBN (15 mg, 0.089 mmol) was added at 3 h intervals. After 12 h, the reaction mixture was cooled to room temperature, then concentrated to a cloudy, colorless oil and purified by flash chromatography, which afforded 147 mg (67%) of a mixture of diastereomeric cis diols as a clear, colorless oil. The ^1H NMR of the mixture was identical to that of authentic compounds prepared independently (vide supra). **Less polar diastereomer:** ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (br t, 2H), 3.54 (d, 2H, J = 3.0), 3.25 or 2.80 (br s, 2H), 2.24 (m, 1H), 2.03 (m, 2H), 1.49 (dt, 2H J_1 = 14.3, J_2 = 5.5), 0.93 (s, 9H), 0.09 (s, 6H). **More polar diastereomer:** ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (m, 2H), 3.43 (d, 2H, J = 5.1) 3.25 or 2.80 (brs, 2H), 2.42 (m, 1H), 1.77 (m, 2H), 1.64 (m, 2H), 0.09 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.2, 74.0, 66.6, 66.4, 36.8, 35.8, 34.1, 33.4, 25.8, 18.3, 18.2, -5.4, -5.5. IR (neat) 3383, 2928, 2885, 2857, 1472, 1463, 1439, 1406, 1388, 1361, 1338, 1256, 1190, 1096, 1005, 969, 939, 911, 836, 814, 775, 734, 667, 647. HRMS: Calcd for $C_{12}H_{27}O_3Si$ $[M+H]^+$: 247.1729. Found: 247.1727.

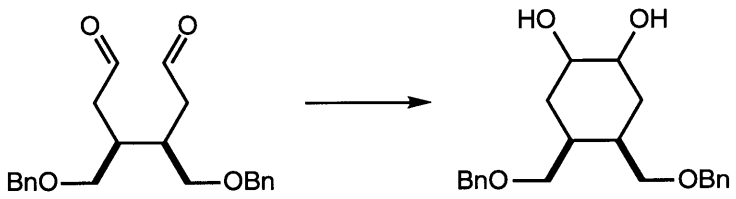
GC analysis of an acetylated aliquot of the unpurified reaction mixture (comparison with authentic products prepared independently, vide supra) indicated a product ratio

of 1.0 : 1 for the diastereomeric cis diols and a ratio of >99 : 1 for the cis : trans diols.



1,2-Cyclohexanediol. Table 1.1, entry 3. A solution of the dialdehyde (114 mg, 1.00 mmol), Bu_3SnH (349 mg, 1.20 mmol), and AIBN (16 mg, 0.10 mmol) in 10 mL benzene was heated to reflux for 1 h. Upon cooling to room temperature, the 1,3,2-dioxastannolane precipitated as a white solid. CH_2Cl_2 was added until a homogeneous reaction mixture was obtained, and an aliquot was then removed for GC analysis. The reaction mixture was concentrated to a white solid/colorless oil and purified by flash chromatography, which provided 97 mg (84%) of a mixture of cis and trans diols as a white solid. The ^1H NMR and ^{13}C NMR spectra were identical to those of the authentic products (Aldrich).

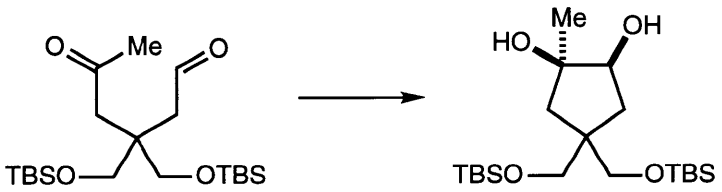
GC analysis of an acetylated aliquot (comparison with authentic products prepared from commercially available cis and trans diols (Aldrich)) indicated that a 2.4 : 1 (trans : cis) mixture of diols was present.



4,5-bis[(phenylmethoxy)methyl]-1,2-cyclohexanediol. Table 1.1, entry 4. A solution of the dialdehyde (172 mg, 0.486 mmol), Bu_3SnH (170 mg, 0.583 mmol), and

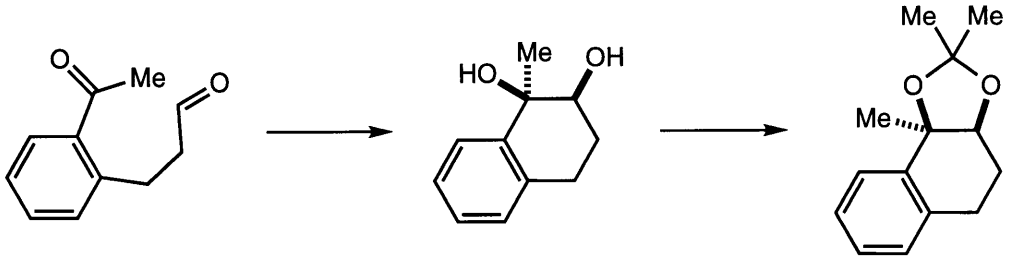
AIBN (16 mg, 0.097 mmol) in 4.9 mL of benzene was heated to reflux in an oil bath. After 3 h, AIBN (8 mg, 0.05 mmol) was added, and the reaction was refluxed for one additional hour. The reaction mixture was concentrated to a cloudy, colorless oil and purified by flash chromatography, which provided 152 mg (88%) of diols as a colorless oil which solidified on standing. ^{1}H NMR and ^{13}C NMR spectra were identical to those of the authentic products prepared independently (vide supra). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 10H), 4.45-4.39 (m, 4H), 3.90-3.31 (m, 6H), 3.15 (br s, OH), 2.85 (br s, OH), 2.60 (br s, OH), 2.34-1.23 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.3, 138.2, 137.4, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.65, 127.60, 127.5, 75.1, 73.4, 73.1, 73.08, 73.02, 72.2, 71.9, 71.8, 70.7, 69.6, 69.2, 68.5, 37.9, 35.1, 34.4, 33.4, 31.9, 30.6. IR (neat) 3385, 3062, 3029, 2924, 2864, 1718, 1603, 1496, 1453, 1365, 1274, 1206, 1095, 1071, 1028, 736, 697. HRMS: Calcd for $C_{22}H_{29}O_4$ $[M+H]^+$: 357.2066. Found: 357.2068.

GC analysis of an acetylated aliquot of the unpurified reaction mixture (comparison with authentic products prepared independently, vide supra) indicated that a 20 : 17 : 63 (cis : cis : trans) mixture of diols was obtained.



cis-4,4-bis-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1-methyl-1,2-cyclopentanediol. Table 1.1, entry 5. To a refluxing solution of the ketoaldehyde (101 mg, 0.250 mmol) in benzene (0.50 mL) was added a solution of Bu_3SnH (218 mg, 0.750 mmol), and AIBN (16 mg, 0.10 mmol) in benzene (1 mL) over 36 h via syringe pump. The reaction was cooled to room temperature, and an aliquot was passed through a plug of silica gel and analyzed by ^{1}H NMR. No trans diol was detectible (>20 : 1 cis

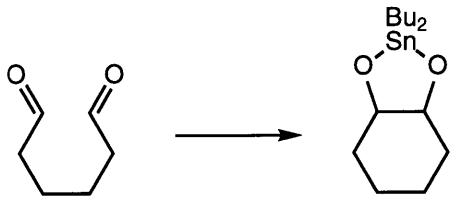
selectivity). The reaction mixture was concentrated to a pale yellow oil and subjected to flash chromatography to afford 64 mg (63%) of the cis diol as a colorless oil. The ^1H NMR spectrum was identical to that of the authentic product prepared independently (vide supra). ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 1H), 3.64 (m, 1H), 3.42 (s, 2H), 3.28 (s, 2H), 2.68 (d, 1H, J = 10.8), 1.88 (dd, 1H, J_1 = 13.7, J_2 = 7.4), 1.72 (d, 1H, J = 14.4), 1.65 (d, 1H, J = 14.1), 1.59 (dd, 1H, J_1 = 13.4, J_2 = 8.9), 1.22 (s, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.10 (s, 6H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.1, 77.7, 69.0, 68.5, 45.2, 43.4, 37.2, 25.9, 25.7, 23.4, 18.4, 18.1, -5.61, -5.64. IR (neat) 3412, 2955, 2929, 2885, 2857, 1472, 1438, 1406, 1388, 1361, 1256, 1188, 1086, 1006, 938, 839, 815, 777, 744, 669. HRMS: Calcd for $C_{20}H_{45}O_4Si_2$ $[M+H]^+$: 405.2856. Found: 405.2845.



***cis*-1,2,3,4-Tetrahydro-1-methyl-1,2-naphthalenediol acetonide. Table 1.1, entry 6.** A solution of the ketoaldehyde (176 mg, 1.00 mmol), Bu_3SnH (437 mg, 1.50 mmol), and AIBN (33 mg, 0.20 mmol) in benzene (100 mL) was heated to reflux in an oil bath. Additional AIBN (33 mg, 0.20 mmol) was added at 3 h intervals. After nine hours, the reaction mixture was cooled to room temperature, concentrated to a yellow oil, and passed through a pad of silica gel. Treatment of the crude diol with 2,2-dimethoxypropane (1.0 g, 10 mmol) and catalytic PPTS, followed by aqueous workup and flash chromatography, afforded 116 mg (53%) of the acetonide as a colorless oil. The ^1H NMR spectrum was identical to that of the authentic product prepared independently (vide supra). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J_1 = 7.4, J_2 =

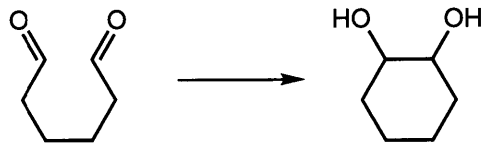
1.4), 7.24-7.13 (m, 2H), 7.06 (d, 1H, J = 7.1), 4.17 (dd, 1H, J_1 = 4.2, J_2 = 2.1), 3.06 (ddd, 1H, J_1 = 17.1, J_2 = 12.7, J_3 = 5.4), 2.62 (ddd, 1H, J_1 = 16.5, J_2 = 5.4, J_3 = 2.4), 2.31-2.22 (m, 1H), 2.01-1.89 (m, 1H), 1.58 (s, 3H), 1.44 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 134.9, 127.8, 127.7, 126.8, 126.4, 107.9, 79.04, 79.00, 27.5, 27.2, 27.1, 24.1, 23.6. IR (neat) 2982, 2931, 2870, 1492, 1439, 1378, 1367, 1295, 1237, 1201, 1159, 1107, 1090, 1063, 1002, 918, 871, 847, 762, 742, 710. HRMS: Calcd for $C_{14}H_{19}O_2$ $[M+H]^+$: 219.1385. Found: 219.1378.

An aliquot of the unpurified reaction mixture of the pinacol coupling was passed through a plug of silica gel and analyzed by GC (comparison with authentic products prepared independently, vide supra), which indicated a 20 : 1 ratio (cis : trans) of diastereomers.

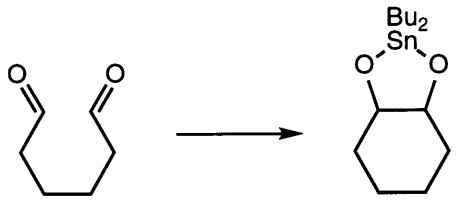


cis- and **trans-2,2-Dibutylhexahydro-1,3,2-benzodioxastannole. UV-initiated pinacol cyclization.** A solution of the dialdehyde (114 mg, 1.00 mmol) and Bu_3SnH (349 mg, 1.20 mmol) in toluene (10 mL) was placed in a sealable Pyrex Schlenk tube under an atmosphere of nitrogen. After irradiation for 10 h at room temperature without stirring, the 1,3,2-dioxastannolane had crystallized as white needles. The reaction mixture was concentrated, and the crystals were washed with cold benzene (3 x 5 mL). After pumping to dryness, 258 mg (74%) of a mixture of cis and trans 1,3,2-dioxastannolanes was isolated as a white solid. The ^{1}H NMR,[21] ^{13}C NMR,[35] and ^{119}Sn NMR[35] spectra were identical to the published spectra. ^{1}H NMR (300 MHz, $CDCl_3$) δ

3.63, 2.97 (br s, 2H), 1.87-1.24 (m, 20H), 0.92-0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.7, 71.7, 34.1, 32 (br), 27.5, 26.9, 25.1, 23 (br), 13.6. ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ -126 (br), -140 (br). Anal. Calcd for $C_{14}H_{28}O_2Sn$: C, 48.45; H, 8.13. Found: C, 48.59; H, 8.35.

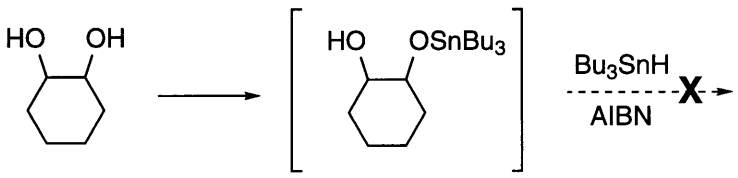


1,2-Cyclohexanediol. UV-initiated pinacol cyclization (eq 1.3). A solution of the dialdehyde (114 mg, 1.00 mmol) and Bu_3SnH (349 mg, 1.20 mmol) in toluene (10 mL) was placed in a sealable Pyrex Schlenk tube under an atmosphere of nitrogen. After irradiation for 15 h at room temperature without stirring, the 1,3,2-dioxastannolane had crystallized as white needles. The reaction was made homogeneous by addition of CH_2Cl_2, and an aliquot was removed for acetylation. GC analysis indicated a 2.6 : 1 (trans : cis) ratio of diols. The solvent was removed in vacuo, and the white solid was subjected to flash chromatography, which provided 93 mg (80%) of a mixture of cis and trans diols. The ^1H NMR spectrum was identical to that of commercially available cis and trans diols (Aldrich).

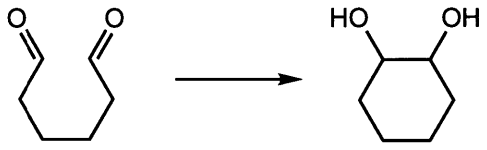


cis- and **trans- 2,2-Dibutylhexahydro-1,3,2-benzodioxastannole. Eq 1.2**. A solution

of the dialdehyde (114 mg, 1.00 mmol), Bu_3SnH (349 mg, 1.20 mmol), and AIBN (16 mg, 0.10 mmol) in 10 mL benzene was heated to reflux for 1 h. Stirring was stopped, and the reaction mixture was permitted to slowly cool to room temperature, allowing the 1,3,2-dioxastannolane to crystallize as white needles. After 34 h, the solvent was removed, and the crystals were washed three times with cold benzene. After pumping to dryness, 199 mg (60%) of the 1,3,2-dioxastannolane was obtained as white crystals. The ^1H NMR spectrum was identical to the published spectrum.[21]

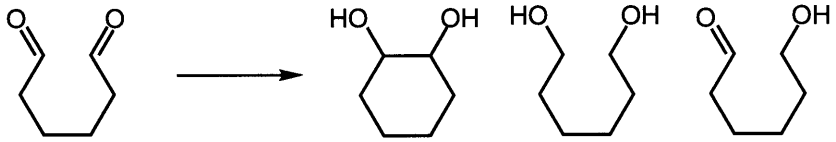


Eq 1.2. To a suspension of trans-1,2-cyclohexanediol (1.16 g, 10.0 mmol) in benzene (10 mL) was added Bu_3SnOEt (3.35 g, 10.0 mmol). The reaction was stirred under vacuum until no ethoxy peaks remained in the ^1H NMR spectrum, to afford a pale yellow oil/white solid. The ^1H NMR spectrum indicated that a mixture of tin alkoxides was present. To a solution of this mixture (32.4 mg, 0.080 mmol) in C_6D_6 (800 μL) in a J Young tube were added AIBN (1.0 mg, 0.008 mmol) and Bu_3SnH (27.9 mg, 0.096 mmol). The reaction was heated in an oil bath maintained at 80 °C for 2.5 h. ^1H NMR indicated that no 1,3,2-dioxastannolane had been formed. $PhSiH_3$ (9 mg, 0.08 mmol) was added, and after 105 min at ambient temperature, no Bu_2SnH_2 was observed, only Bu_3SnH.



1,2-Cyclohexanediol. TTMS-mediated pinacol cyclization. A solution of the

dialdehyde (228 mg, 2.00 mmol), TTMS (597 mg, 2.40 mmol), AIBN (33 mg, 0.20 mmol), and tetradecane (198 mg, 1.00 mmol, internal GC standard) in 20 mL benzene was heated to reflux for 3 h. GC analysis indicated that 5% of the dialdehyde remained, and 1.11 mmol of the TTMS had been consumed. ^{1}H NMR analysis revealed polymeric material in the carbinol, aliphatic, and TMS regions. An aliquot was treated with an excess of TBAF, acetylated, and analyzed by GC. 1,2-Cyclohexanediol was found to be present in a 71% yield (1.42 mmol, 1.4 : 1 trans : cis) as determined by integration versus the internal standard. In addition, acyclic reduction products were present in a 4% yield.

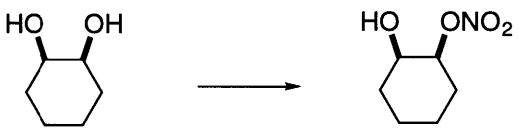


Bu_3GeH-mediated pinacol cyclization. A solution of the dialdehyde (9.1 mg, 0.08 mmol), Bu_3GeH (23.5 mg, 0.096 mmol), AIBN (1.5 mg, 0.01 mmol), and tetradecane (8.0 mg, 0.040 mmol, internal GC standard) in 0.800 mL benzene containing *n*-butyl methyl ether (0.0133 mmol, internal ^{1}H NMR standard) was heated to 80°C in a J. Young tube. Additional AIBN (2 mg) was added after 9.3 and 24.3 h. The reaction was monitored by ^{1}H NMR. After 35 h, 10% of the dialdehyde remained as evidenced by integration versus the internal standard. The reaction mixture was acetylated and analyzed by GC. 1,2-Cyclohexanediol was found to be present in a 27% yield (1.4 : 1 trans : cis) as determined by integration versus the internal standard. In addition, 1,6-hexanediol and 6-hydroxyhexanal were present in yields of 16% and 21% respectively.

Demonstration of Reversible Cyclization (Figure 1.5)

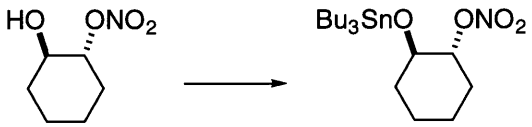
General. Nitrate esters have been shown to afford oxygen-centered radicals when treated with Bu_3SnH under free radical conditions.[18] Unfortunately, they do so neither rapidly nor cleanly.[10] In the following stereochemical tests for reversible cyclization, we regard the presence of*any* isomerization, in conjunction with the formation of *both* 1,3,2-dioxastannolane isomers to be sufficient evidence of reversibiltiy. The GC ratios, however, are not intended to reflect the degree of isomerization.

***trans*-1,2-Cyclohexanediol mononitrate.** To a suspension of *trans*-1,2-cyclohexanediol (4.64 g, 40.0 mmol) in Ac_2O (25 mL) at 0 °C was added a solution of fuming HNO_3 (2.52 g, 40.0 mmol) in Ac_2O (5 mL). The reaction was allowed to warm to room temperature over 2.5 h, and the Ac_2O was destroyed by slow addition of 700 mL saturated $NaHCO_3$ at 0 °C. After stirring at room temperature for 24 h, the product was exctracted from the aqueous layer with Et_2O, dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by flash chromatography, followed by bulb-to-bulb distillation to afford *trans*-1,2-cyclohexanediol mononitrate as a white solid. The ^1H and ^{13}C NMR spectra were identical to the published spectra.[36]



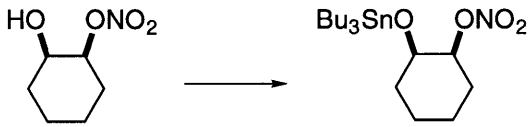
***cis*-1,2-Cyclohexanediol mononitrate.**[37] This material was prepared as above from

cis-1,2-cyclohexanediol (667 mg, 5.74 mmol) and fuming HNO_3 (362 mg, 5.74 mmol) in Ac_2O (20 mL). Flash chromatography afforded *cis*-1,2-cyclohexanediol mononitrate as a clear, colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (m, 1H), 4.03 (m, 1H), 2.05-1.98 (m, 1H), 1.83-1.65 (m, 6H), 1.46-1.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.4, 68.0, 30.7, 25.5, 22.0, 20.6.



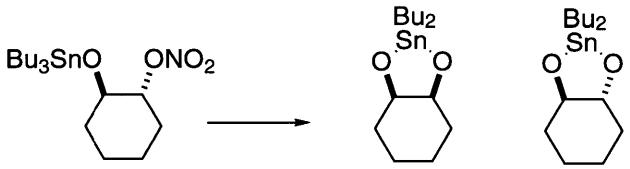
1.1

1.1. To a solution of the *trans*-1,2-cyclohexanediol mononitrate (676 mg, 4.19 mmol) in pentane (4 mL) was added Bu_3SnOEt (1.41 g, 4.19 mmol). The reaction was stirred under vacuum until no ethoxy peaks remained in the ^1H NMR spectrum. ^1H NMR (300 MHz, C_6D_6) δ 4.87 (m, 1H), 3.58 (m, 1H), 1.90-1.80 (m, 2H), 1.64-1.56 (m, 6H), 1.40-1.28 (m, 9H), 1.13-0.90 (m, 18H). ^{13}C NMR (75 MHz, C_6D_6) δ 89.1, 74.1, 37.0, 29.0, 28.6, 27.8, 24.4, 24.1, 15.5, 14.2. ^{119}Sn NMR (112 MHz) δ 100.2.

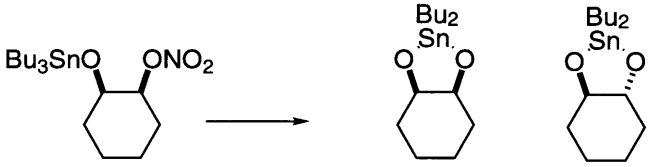


1.2

1.2. This material was prepared as above from *cis*-1,2-cyclohexanediol mononitrate (161 mg, 1.00 mmol) and Bu_3SnOEt (335 mg, 1.00 mmol). ^1H NMR (300 MHz, C_6D_6) δ 4.76 (m, 1H), 3.98 (m, 1H), 2.01-1.95 (m, 1H), 1.78-1.53 (m, 8H), 1.45-1.26 (m, 8H), 1.13-0.89 (m, 18H). ^{13}C NMR (125 MHz, C_6D_6) δ 86.5, 70.5, 34.8, 28.6, 27.8, 25.4, 23.9, 20.7, 15.5, 14.3.



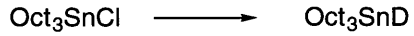
cis- and **trans- 2,2-Dibutylhexahydro-1,3,2-benzodioxastannole.** To a solution of **1.1** (450 mg, 1.00 mmol) and AIBN (16 mg, 0.10 mmol) in C_6H_6 (10 mL) was added Bu_3SnH (349 mg, 1.20 mmol). The reaction was heated to reflux for 5.5 h, addtional AIBN (16 mg, 0.10 mmol) was added, and the reaction was refluxed for an additional 7 h. GC analysis of an acetylated aliquot indicated a mixture of *trans* and *cis*-1,2-cycohexanediol bisacetates (3.9/1 trans/cis). The bulk reaction mixture was concentrated to a white solid/colorless oil. The solid was washed with pentane (3 x 1 mL), dried under vacuum, and analyzed by ^1H and ^{119}Sn NMR. Both *cis* and *trans*-1,3,2-dioxastannolanes were observed.



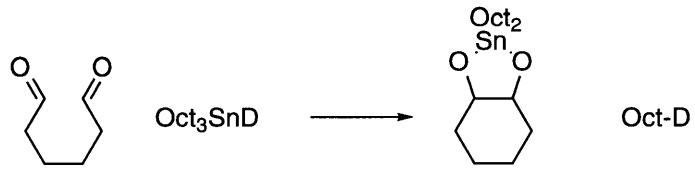
cis- and **trans- 2,2-Dibutylhexahydro-1,3,2-benzodioxastannole.** To a solution of **1.2** (37.4 mg, 0.083 mmol) and AIBN (1.3 mg, 0.008 mmol) in C_6D_6 (800 mL) in a J. Young tube were added Bu_3SnH (29.1 mg, 0.10 mmol) and methyl butyl ether (internal ^1H NMR standard). The reaction was heated in an oil bath maintained at 80 °C for 4 h, and 73% of the starting material remained, as determined by integration versus the internal standard. GC analysis of an acetylated aliquot indicated a mixture of *trans* and *cis*-1,2-cyclohexanediol bis acetates (1.3/1 trans/cis). The tube was immersed in an ice bath, and the resulting white solid was washed with C_6H_6 (1 x 1 mL), and dried under vacuum. The solid was dissolved in $CDCl_3$, and ^1H and ^{119}Sn NMR spectra were

recorded. Both cis and trans-1,3,2-dioxastannolanes were observed.

Determination of Octane/Deuterium Labelling Experiment (Scheme 1.2)



Trioctyltin deuteride. To a solution of $LiAlD_4$ (80.6 mg, 1.92 mmol) in Et_2O (2 mL) was added Oct_3SnCl (948 mg, 1.92 mmol) as a solution in Et_2O (4 mL) at 0 °C. After stirring at room temperature for 90 min, the reaction was filtered under an atmosphere of nitrogen, concentrated to a moist solid, and filtered through celite, washing with C_6H_6. Concentration under vacuum, followed by filtration through an Acrodisk, followed by concentration afforded trioctyltin deuteride as a slightly cloudy, colorless oil. No Oct_3SnH was oberved by ^1H NMR. ^1H NMR (300 MHz, C_6D_6) δ 1.68 (m, 6H), 1.43-1.52 (m, 30H), 1.04 (m, 6H), 0.94-0.90 (m, 9H). ^{13}C NMR (75 MHz, C_6D_6) δ 35.0, 32.8, 30.2, 30.1, 28.6, 23.5, 14.7, 9.1. ^{119}Sn NMR (111.9 MHz, C_6D_6) δ -90.5 (t, J = 243). ^2H NMR (46 MHz, C_6H_6) δ 5.14 (s, ^1J ($^{119}Sn/^2H$) = 243, ^1J ($^{117}Sn/^2H$) = 232). IR (neat) 2918, 2850, 1465, 1378, 1340, 1300, 723, 698, 666.



cis- and **trans-2,2-Dioctylhexahydro-1,3,2-benzodioxastannole** and **1-deuterioctane.** To a solution of adipaldehyde (127 mg, 1.11 mmol) and AIBN (18 mg, 0.11 mmol) in C_6H_6 were added Oct_3SnD (613 mg, 1.33 mmol), nonane (142 mg, 1.11 mmol; internal GC standard), and tetradecane (220 mg, 1.11 mmol; internal GC standard). The reaction was heated to reflux for 75 min, and an aliquot was analyzed by GC. An 82% yield of

octane was observed by integration versus the internal standard (nonane). Analysis by GC-MS indicated that the octane was 97.1% deuterated. GC analysis of an acetylated aliquot indicated an 80% yield of acetylated pinacol products (2.3 *trans/cis*).

After standing at room temperature for 16 h, the supernatent was removed from the resulting white solid, and the solid washed with ice cold toluene (3 x 2 mL) to afford 168 mg (37%) of the 1,3,2-dioxastannolane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63, 2.99 (br s, 2H), 1.88-1.27 (m, 36H), 0.88 (t, 6H, J = 6.6). ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.9, 72.0, 34.3, 32.1, 29.5, 29.4, 25.6, 25.4, 22.9, 14.3. ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ -126 (br), -141 (br), -288 (br). Additional support for the proposed structure was obtained via a chemical test: a sample of the white solid was acetylated and analyzed by GC; a mixture of *cis* and *trans* 1,2-cyclohexanediol bisacetates was observed.

Pinacol cyclization competition experiment (Figure 1.6). A solution containing the dialdehyde (114 mg, 1.00 mmol), ketoaldehyde (128 mg, 1.00 mmol), diketone (142 mg, 1.00 mmol), Bu_3SnH (349 mg, 1.20 mmol), and tetradecane (65 μL; as an internal standard) in benzene (10 mL) was prepared and analyzed by GC. AIBN (16 mg, 0.10 mmol) was added, and then the solution was heated to reflux for 90 min. Upon cooling to room temperature, a white precipitate formed. The reaction mixture was made homogeneous by addition of CH_2Cl_2, and then analyzed by GC. The amount of each dicarbonyl compound which remained, as a percentage of its original amount, was found to be: dialdehyde: 9%; ketoaldehyde: 87%; diketone: 100%.

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Chapter 2. Development of Organotin Hydride-Catalyzed Processes I. Synthetic Transformations Involving Sn-O Intermediates

2.1. Introduction

The vast body of literature pertaining to the use of organotin reagents in organic synthesis serves as a testimony to their importance.[1,2] Much of this literature has grown around Bu_3SnH[3] and the free radical chain reactions which it can undergo, despite serious concerns about the toxicity of some organotin species.[4-6] To exacerbate the toxicity issue, organotin reagents are notoriously difficult to remove from reaction mixtures at the purification stage,[7] thus rendering them unattractive for use in the preparation of drug substances.[8]

A variety of strategies have been recently advanced to address these concerns, many of which involve the development of alternative reagents to Bu_3SnH.[7] Rather than forsake Bu_3SnH altogether, and the often unique chemistry it can undergo, we have chosen to pursue the development of free radical synthetic methods which require *catalytic* quantities of organotin reagents.[9,10] The current chapter describes successful efforts towards this end, first with the development of a catalytic carbon-carbon bond-forming reaction (Section 2.2) followed by a catalytic variant of the Barton-McCombie deoxygenation (Section 2.3).

2.2. Organotin Hydride Catalyzed Carbon-Carbon Bond Formation: Radical-Mediated Reductive Cyclization of Enals and Enones.

Background

The stoichiometric Bu_3SnH-mediated reductive cyclization of enals and enones by a free radical chain process has been reported by several groups (Figure 2.2.1).[11-15] The mechanism proceeds first by addition of a tributyltin radical to the carbonyl group to produce a tin ketyl. Addition of this ketyl to a tethered olefin affords a new radical, which undergoes hydrogen atom abstraction from Bu_3SnH to generate the

reductive cyclization product (**1**).

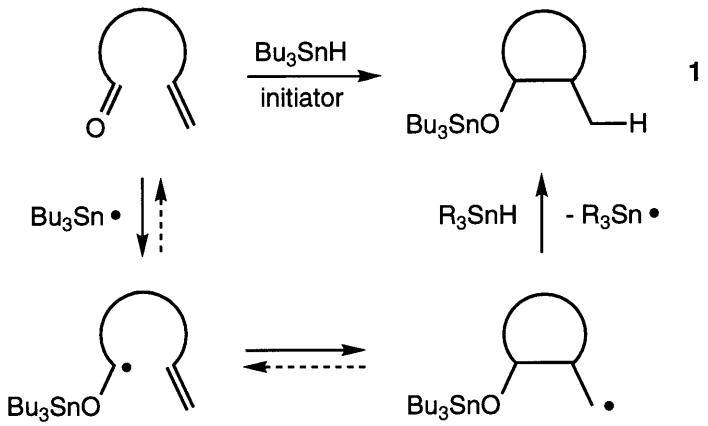
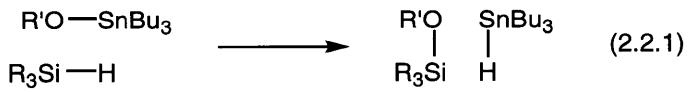


Figure 2.2.1. Reductive Cyclization with Stoichiometric Bu_3SnH

Employing only *catalytic* quantities of Bu_3SnH for this transformation requires the use of a stoichiometric amount of a second metal hydride capable of regenerating Bu_3SnH from tributyltin alkoxide **1**.[16,17] Silicon hydrides have been independently reported by several workers to react with tin alkoxides to afford tin hydrides and silyl ethers (eq 2.2.1).[16-22] Two known reactions, run in sequence, thus provide the basis for a new catalytic process (Figure 2.2.2).



(2.2.1)

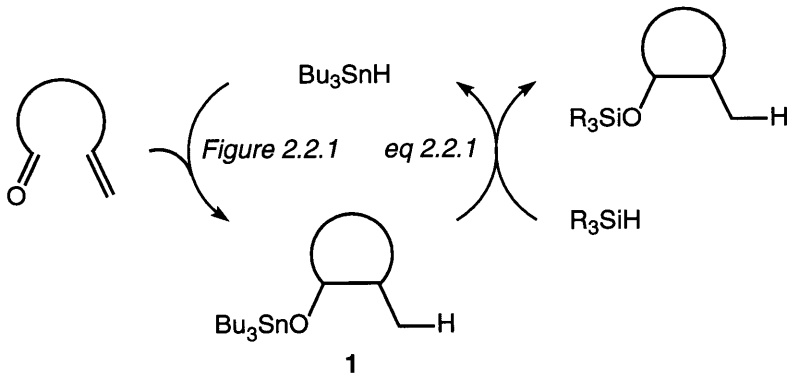


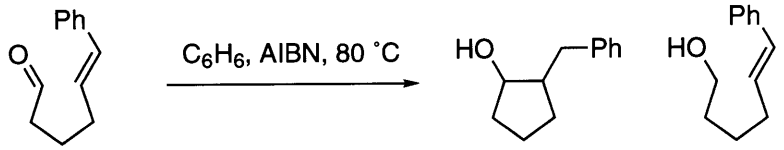
Figure 2.2.2. Proposed catalytic cycle for tin hydride-catalyzed, silicon hydride-mediated reductive cyclization.

Results and Discussion

However, when this catalytic proposal was put to the test, a puzzling result was obtained. Reaction of **2.2.1** with Bu_3SnH according to the stoichiometric Enholm conditions[14] afforded, as expected, complete conversion to the cyclic reduction products, and no acyclic material was detected (eq 2.2.2, >185/1 cyclic/acyclic). However, when subjected to the proposed catalytic conditions (10 mol % Bu_3SnH, $PhSiH_3$), a mixture of the cyclic and acyclic reduction products was observed in varying ratios (eq 2.2.3, ca. 1-13/1 cyclic/acyclic). This is the *opposite* trend expected for changing to lower concentrations of Bu_3SnH and cannot be explained by a simple background reduction with $PhSiH_3$, as we have found **2.2.1** to be inert towards $PhSiH_3$ (eq 2.2.5). When a less reactive silane (PMHS) was employed as the stoichiometric reductant, the cyclic/acyclic ratio was found to be even worse (eq 2.2.4, 0.1-0.3/1 cyclic/acyclic).

In addition to the observation of enhanced 1,2-reduction under catalytic conditions, we repeatedly noticed the formation of what appeared visually to be tin metal in the reaction vessels. This suggested that our catalyst (Bu_3SnH) was

somehow losing alkyl groups under the reaction conditions.



2.2.1

Bu_3SnH (1.5 equiv)	>185	1	(2.2.2)
Bu_3SnH (0.10 equiv) $PhSiH_3$ (stoichiometric)	1-13	1	(2.2.3)
Bu_3SnH (cat.) PMHS (stoichiometric)	0.1-0.3	1	(2.2.4)
$PhSiH_3$ (stoichiometric)	-	-	(2.2.5)

We reasoned that both of these observations (enhanced 1,2-reduction and tin metal formation) could be explained by a single postulate: small quantities of Bu_2SnH_2 are being generated under our catalytic reaction conditions. Dialkyltin dihydrides have been shown to be quite active catalysts for the simple, polar reductions of aldehydes and ketones in the presence of stoichiometric silanes.[23] In addition, numerous adventitious impurities are known to promote their decomposition to tin metal.[24,25] Thus, our catalyst (Bu_3SnH) is being converted by some unknown process to Bu_2SnH_2 in a manner competitive with its desired function. This competition gets worse when a less reactive silane (PMHS) is employed.

The solution to this problem seemed to require a means by which the turnover step could be accelerated. To our knowledge, $PhSiH_3$ is the most reactive silane for reducing Sn-O bonds to Sn-H bonds, so variation of the stoichiometric reductant was not an option.

Two facts from the literature suggested an alternative means by which we could accelerate the turnover step: (1) exchange of alcohols with tin alkoxides is rapid at

room temperature,[1] and (2) primary tin alkoxides are more readily reduced by silanes than are secondary or tertiary tin alkoxides.[18] So the incorporation of primary alcohol additives in the reaction mixture might sufficiently accelerate the turnover step (Figure 2.2.3), and the unknown Bu_2SnH_2-forming pathway may be suppressed.

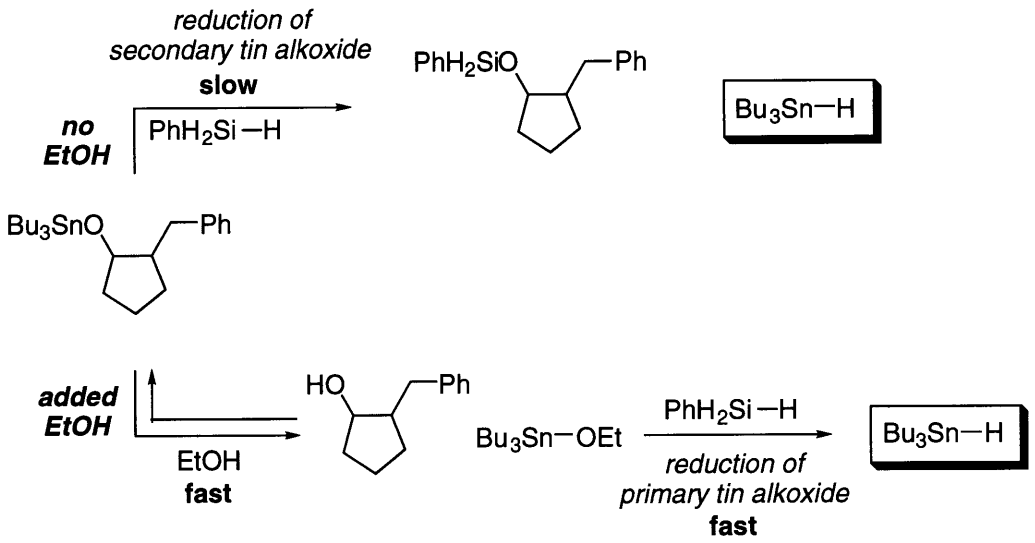
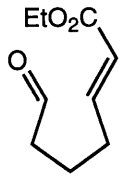
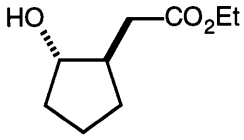
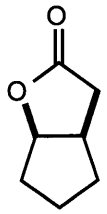
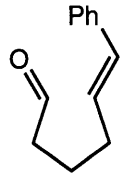
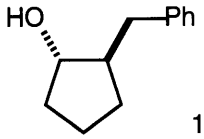
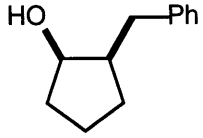
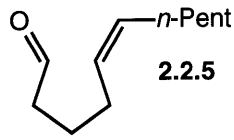
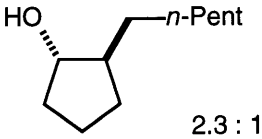
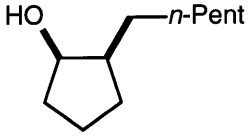
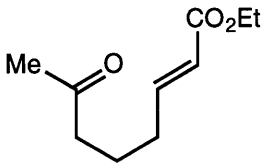
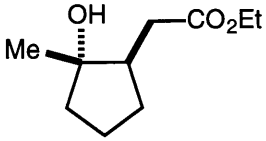
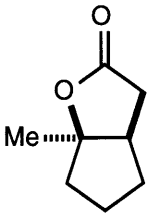
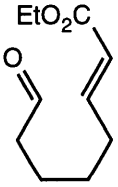
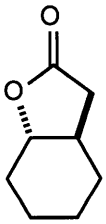
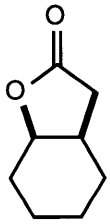
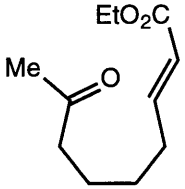
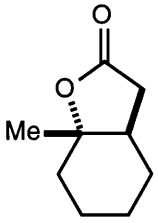
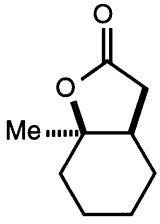


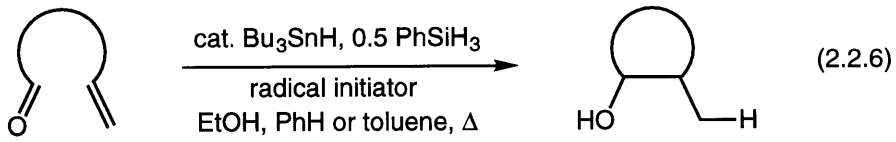
Figure 2.2.3. A proposed method for accelerating the turnover step: primary alcohol additives.

After additional optimization, as illustrated in Table 2.2.1, we established the viability of this strategy, and Bu_3SnH does indeed effectively catalyze the silicon hydride-mediated reductive cyclization of enals and of enones in the presence of a primary alcohol additive (eq 2.2.6). Thus, treatment of unsaturated aldehydes or ketones with 5-15 mol% $(Bu_3Sn)_2O$[26,27] and 0.5 equiv $PhSiH_3$ (radical initiator, 2 equiv EtOH, refluxing benzene or toluene) affords the desired cyclic products in good yields. Contrary to our earlier findings, we observe no acyclic reduction product derived from **2.2.1** (Table 2.2.1, entry 2).

Table 2.2.1. Bu_3SnH-Catalyzed Reductive Cyclization of Enals and Enones

Entry	Substrate	Products[a]	Yield[b]
1		 1.6 : 1 	71
2	 **2.2.1**	 1.2 : 1 	85
3	 **2.2.5**	 2.3 : 1 	67[c]
4		 1.0 : 1 	75
5	 **2.2.4**	 1.1 : 1 	76
6		 1.1 : 1 	66

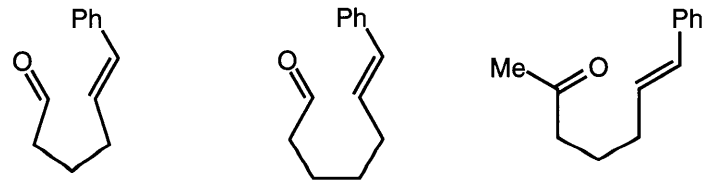
[a] Product ratios are based on analysis by capillary gas chromatography and/or ^1H NMR. [b] Yields refer to isolated mixtures of the cis and trans products and are the average of two runs [c] 29% 1,2-reduction is observed.



(2.2.6)

Both five- (Table 2.2.1, entries 1-4) and six-membered rings (entries 5-6) are efficiently generated by this new catalytic carbon-carbon bond-forming process. Cyclization proceeds more readily when the terminus of the olefin bears a radical-stabilizing substituent (e.g., ester or phenyl, entries 1 and 2); otherwise, a significant quantity of uncyclized alcohol resulting from 1,2-reduction of the aldehyde is produced (29%; entry 3).[14,28] Essentially the same diastereoselectivities are observed when we conduct the reactions under the catalyzed conditions as when we run them with stoichiometric Bu_3SnH,[14] a result consistent with the catalytic reaction proceeding by the pathway outlined in Figure 2.2.2.

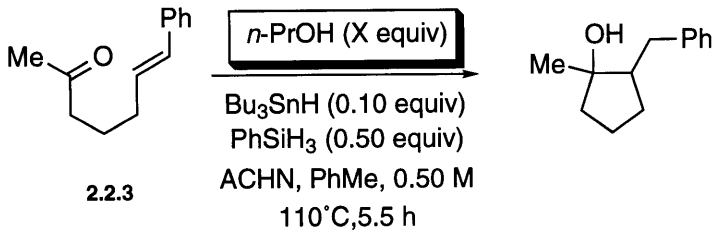
In order to probe the role of the EtOH additive, we examined the catalytic cyclization of three representative substrates (**2.2.1**, **2.2.2**, **2.2.3**) in the presence and absence of a primary alcohol additive.



2.2.1 **2.2.2** **2.2.3**

In the presence of the a primary alcohol additive, 79% of the enone (**2.2.3**) was found to be consumed after 5.5 h, and the corresponding cyclic products were generated in a 71% yield (eq 2.2.7). However, when no primary alcohol additive is present in the reaction mixture, 28% of the substrate is consumed in the same time period, and only an 8% yield of cyclic products is obtained (eq 2.2.8). Thus it appears

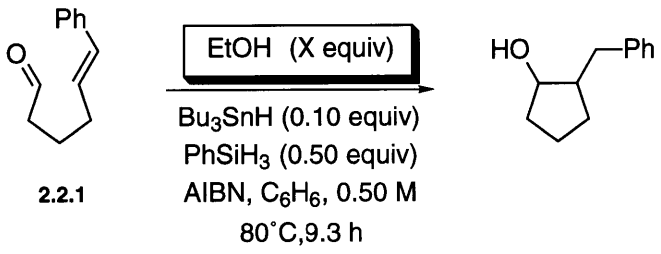
that *no* turnover events are observed from the bulky tertiary tin alkoxide intermediate unless a primary alcohol additive is present in the reaction mixture.



2.2.3

X = 2.0	71%	(2.2.7)
X = 0	8%	(2.2.8)

The next substrate, **2.2.1**, fared better than the ketone **2.2.3**, but in the absence of the EtOH additive, the reaction stalled out at ca. 40% conversion (40% yield of cyclic products, eq 2.2.10). However, in the same time period, complete conversion (>99%) was achieved in the presence of the EtOH additive (92% yield of cyclic products, eq 2.2.9). Thus, the secondary tin alkoxide intermediate turns over better than the tertiary tin alkoxide intermediate derived from **2.2.3**, but not well enough to allow for complete consumption of starting material (Figure 2.2.4). Contrary to the early optimization studies, no acyclic reduction product (<1%) was observed with or without EtOH.



2.2.1

X = 2.0	92%	(2.2.9)
X = 0	40%	(2.2.10)

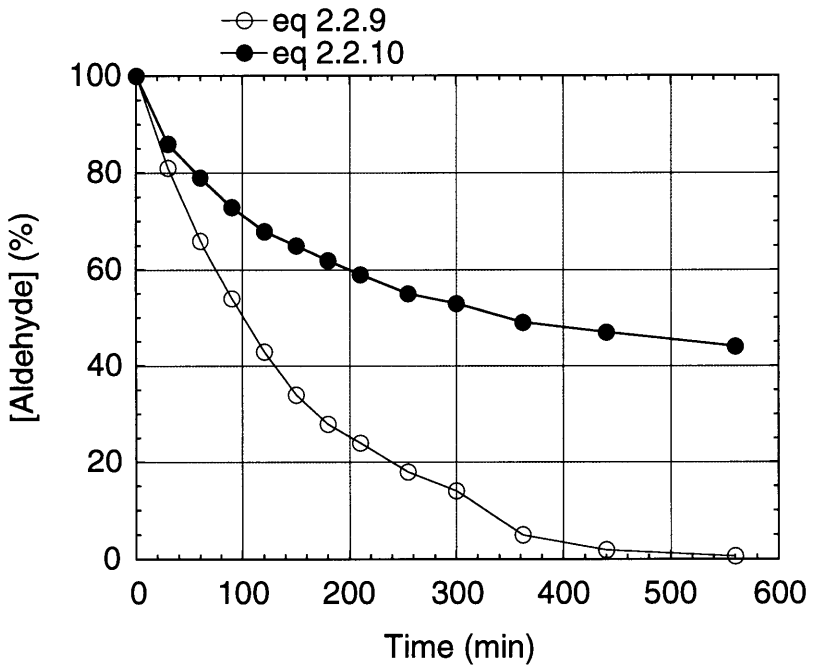
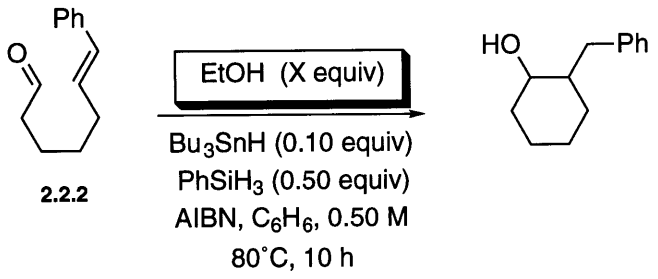


Figure 2.2.4. Plot of [**2.2.1**] versus time for eq 2.2.9 and eq 2.2.10. The discontinuity at 300 min is the result of more initiator being added.

The final substrate, **2.2.2**, displayed behavior similar to its enal counterpart **2.2.1** in that EtOH was required to achieve complete conversion (Figure 2.2.5). Only a 27% yield of cyclic products was achieved without EtOH (eq 2.2.12), whereas a 74% yield of cyclic products was achieved in the presence of the EtOH additive (eq 2.2.11).

No acyclic reduction product was observed in either case.



X = 2.0	74%	(2.2.11)
X = 0	27%	(2.2.12)

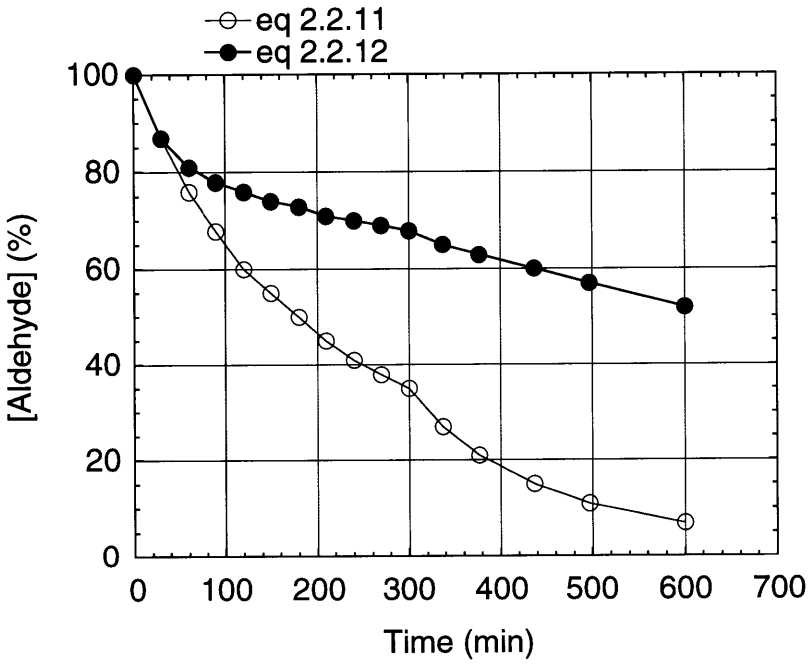
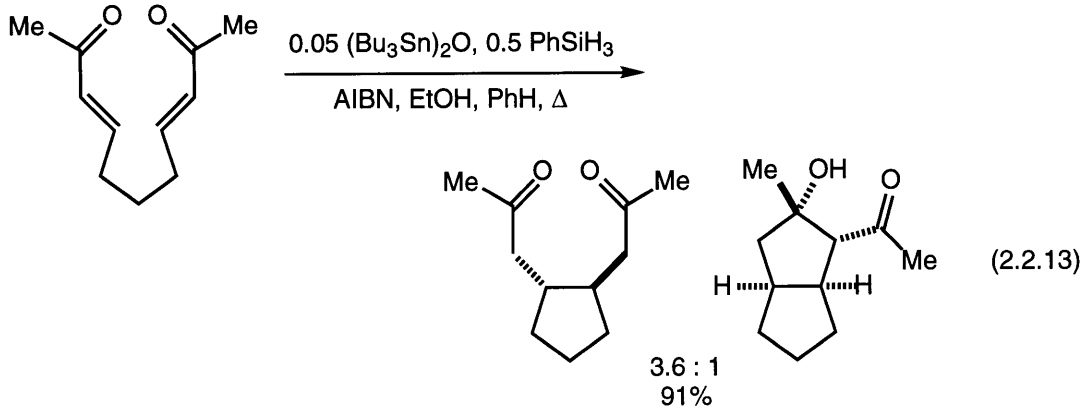


Figure 2.2.5. Plot of [2.2.2] versus time for eq 2.2.11 and eq 2.2.12. The discontinuity at 300 min is the result of more initiator being added.

A related system was also found to be susceptible to our catalytic strategy. Specifically, Enholm has reported that activated dienes undergo intramolecular

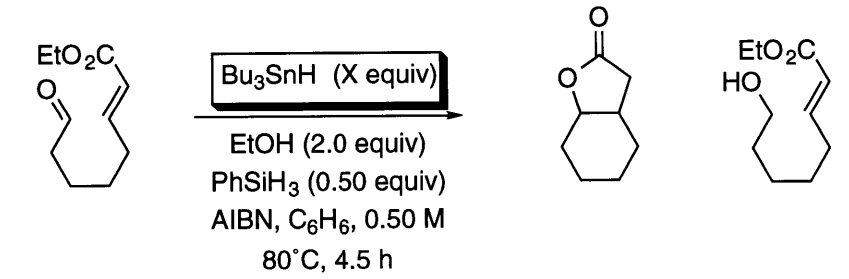
coupling upon treatment with three equivalents of tributyltin hydride.[29,30] We have found that this reaction can be effected with 5 mol% $(Bu_3Sn)_2O$ and 0.5 equiv $PhSiH_3$ in comparable yield and stereoselectivity (eq 2.2.13).



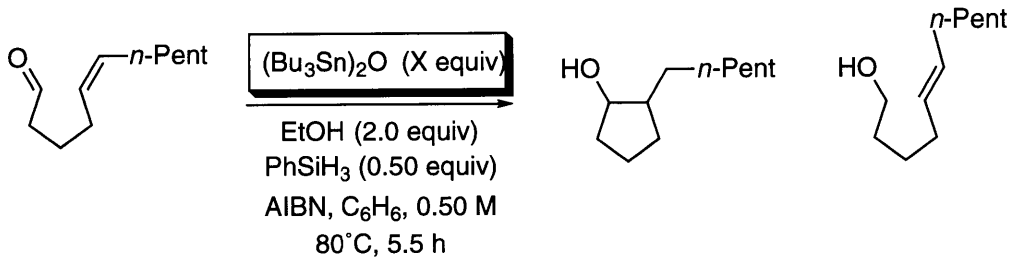
(2.2.13)

Previously, we noted that during the early stages of optimization (vide supra), anomalous levels of acyclic reduction products were sometimes observed in the catalytic cyclization of **2.2.1**. We postulated that the EtOH additive accelerates the turnover step (Figure 2.2.3) and maximizes the steady-state concentration of Bu_3SnH. By doing so, the formation of unwanted Bu_2SnH_2 is suppressed. Under the optimized conditions, however, the problem of enhanced 1,2-reduction (with or without the EtOH additive) was not observed with **2.2.1**, but it did manifest itself in two other substrates.

Thus, when the enal **2.2.4** was cyclized with 10 mol% Bu_3SnH, a 38% yield of the acyclic reduction product was observed (eq 2.2.14). Changing to 30 mol% catalyst loading under otherwise identical conditions afforded significantly less (16%) of the acyclic reduction product (eq 2.2.15). Similar behavior was displayed by **2.2.5** (eqs 2.2.16, 2.2.17). Thus, once again, a surprising trend is evident: lower Bu_3SnH concentrations afford more acyclic reduction products. If Bu_2SnH_2 is the culprit, what is the source of the Bu_2SnH_2?



X = 0.10	51%	38%	(2.2.14)
X = 0.30	78%	16%	(2.2.15)



X = 0.050	43%	52%	(2.2.16)
X = 0.15	68%	30%	(2.2.17)

We believe the ultimate source of the Bu_2SnH_2 is an intermolecular Bu_3SnH-mediated reductive coupling of aldehydes to form dioxastannolanes. As shown in Figure 2.2.6, following addition of the Bu_3Sn radical to an aldehyde, the tin ketyl **A** is proposed to add to the carbonyl carbon of another substrate molecule **B**. In a known process, intramolecular S_H2 attack by the oxygen radical **C** is expected to form a 1,3,2-dioxastannolane **D** via ejection of a butyl radical.[31] Subsequent reaction of the 1,3,2-dioxastannolane **D** with the silane is expected to generate Bu_2SnH_2.

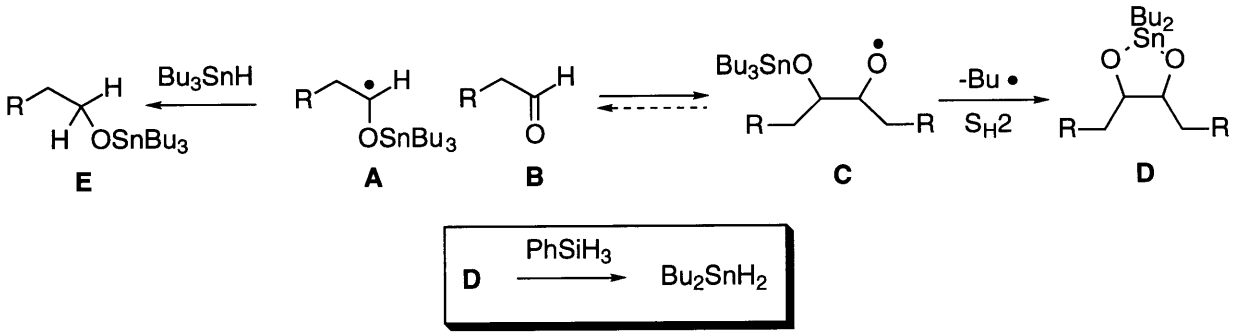
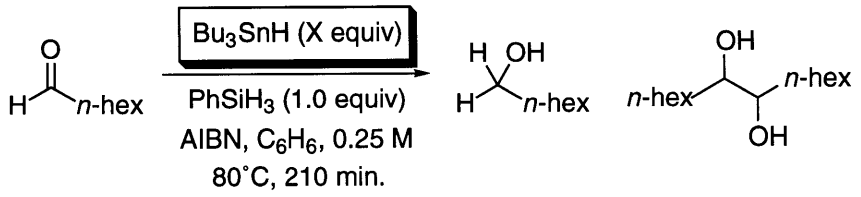


Figure 2.2.6. A proposed mechanism for Bu_2SnH_2 formation.

The reduction of unfunctionalized aldehydes by *stoichiometric* Bu_3SnH according to a free radical chain process is a well-known, synthetically useful procedure (Figure 2.2.4, **A**→**E**),[1] and to our knowledge, there is no literature precedent for competing dioxastannolane formation in these systems. But in order to cause problems in our reductive cyclizations of enals, only a catalytic quantity of dioxastannolane (and hence, Bu_2SnH_2) is required.[32] Furthermore, the yield of dioxastannolane should increase as the Bu_3SnH equivalents are decreased, that is, as we change from stoichiometric to catalytic conditions.

In order to test the feasibility of our proposed intermolecular pinacol coupling of aldehydes, we chose to examine the interaction of heptanal with Bu_3SnH under free radical conditions. Thus, we ran two side-by-side reactions which differed *only* in Bu_3SnH equivalents (eq 2.2.18, stoichiometric Bu_3SnH; eq 2.2.19, catalytic Bu_3SnH) and measured the rate of aldehyde consumption. The stoichiometric reaction appears to proceed according to a well-behaved decay curve (Figure 2.2.7), but the catalytic reaction displays a pronounced induction period. Following this induction period, the rate of aldehyde consumption increases dramatically, and the catalytic reaction actually *overtakes* the stoichiometric reaction!



Stoichiometric	X = 1.0	<0.04%	(2.2.18)
Catalytic	X = 0.05	3.1%	(2.2.19)

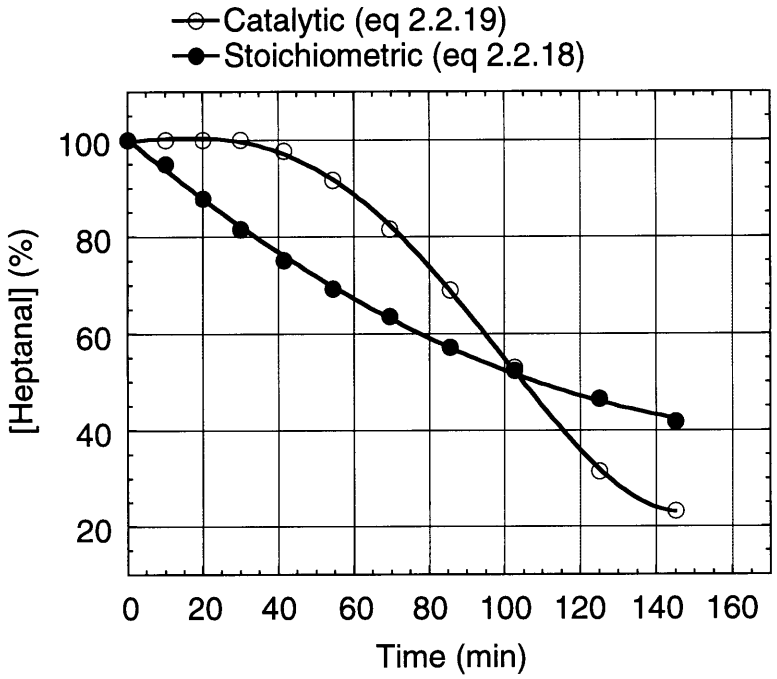


Figure 2.2.7. Plot of [heptanal] versus time for eq 2.2.18 and eq 2.2.19.

We interpret this rate behavior as evidence for the build-up of a new, highly reactive catalytic species. As evidenced by the intersection of the two decay curves, more of this new species is formed under the catalytic conditions than the stoichiometric conditons. Furthermore, 3% of the intermolecular pinacol product was formed in the catalytic reaction, but no detectible quantity was found in the stoichiometric reaction. All of these observations are consistent with the generation of Bu_2SnH_2 according to our proposed intermolecular pinacol coupling reaction.

To return to the question of how higher catalyst loadings suppress an intermolecular pinacol coupling reaction in some of our ketyl-olefin cyclizations, we require a scenario in which the rate of the undesired Bu_2SnH_2 formation becomes significant at low Bu_3SnH concentrations, but remains insignificant when the concentration of Bu_3SnH is high. A mechanistic hypothesis which meets these requirements is shown in Figure 2.2.8.

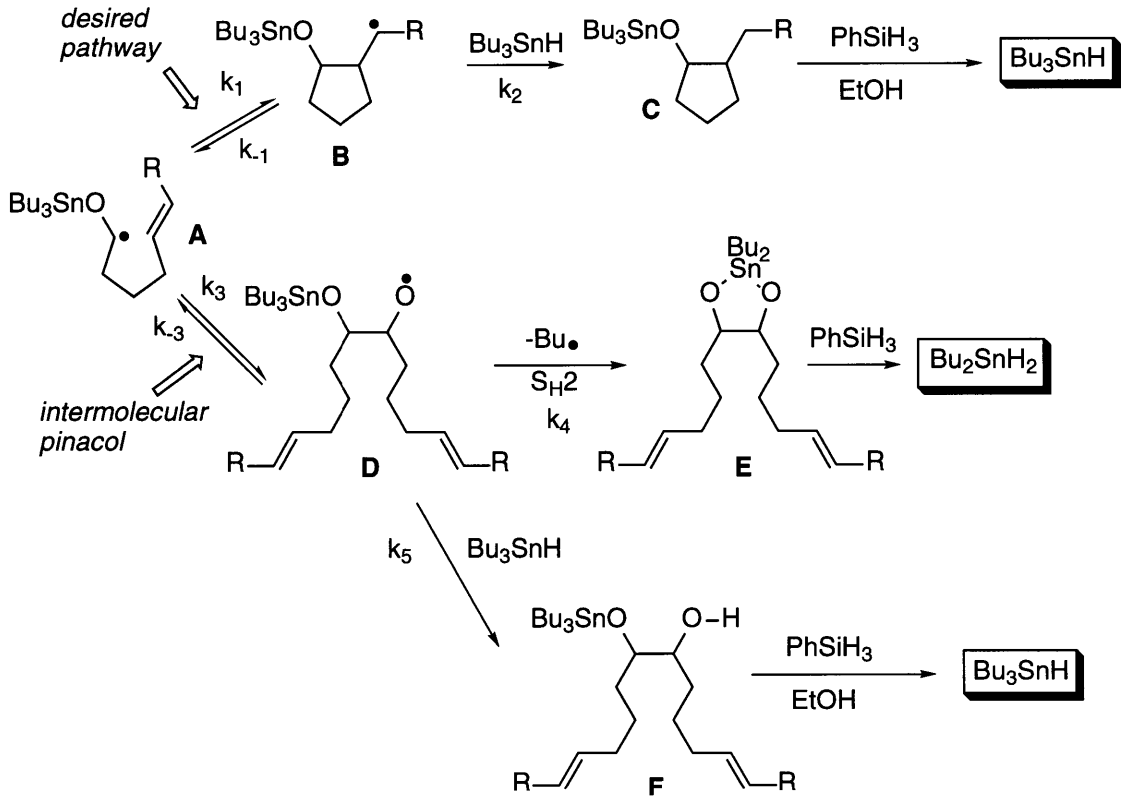


Figure 2.2.8. A proposed mechanistic explanation for the observation that higher catalyst loadings suppress Bu_2SnH_2 formation.

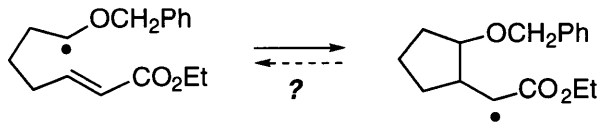
Thus, the tin ketyl **A** can react in at least two fashions. If the ketyl follows the desired pathway, the carbon-centered radical **B** requires a significant concentration of Bu_3SnH in order to irreversibly proceed to the right. That is, the product-determining step (**B**→**C**) is Bu_3SnH dependent, and this is reflected in the rate

expression (eq 2.2.20, d[**C**]/dt).

$$\frac{d[\mathbf{C}]}{dt} = \frac{k_1 k_2 [Bu_3SnH][\mathbf{A}]}{k_{-1} + k_2[Bu_3SnH]} \qquad \frac{d[\mathbf{E}]}{dt} = \frac{k_3 k_4 [\text{aldehyde}][\mathbf{A}]}{k_{-3} + k_4} \qquad (2.2.20)$$

The competing pathway, however, does not require Bu_3SnH in the product determining step. Therefore, at low [Bu_3SnH], the rate at which the ketyl **A** is converted to dioxastannolane **E** remains unchanged, and the ratio of the desired/undesired pathway is decreased. According to this scenario, catalytically relevant quanitities of Bu_2SnH_2 are believed to form when the concentration of Bu_3SnH is low.

The assumption that cyclization of **A** could become reversible at low Bu_3SnH concentrations (i.e. $k_{-1} \sim k_2[Bu_3SnH]$ at low concentrations) is believed to be valid based on a recent report by Curran.[2] Thus, in a system similar to the tin ketyl-olefin cyclizations, the diastereoselectivity in the cyclization of an α-benzyloxy radical was observed to exhibit a concentration dependence, and interconversion of the cis and trans isomers by means of reversible ring closure was suggested as a possible explanation (eq 2.2.21).



(2.2.21)

An alternative explanation by which higher catalyst loadings suppress Bu_2SnH_2 formation that does not require the assumption that cyclization of **A** is reversible can also be formulated. Thus, at high [Bu_3SnH], formation of **E** can be minimized by competition from H-atom abstraction (**D**→**F**), that is $k_5[Bu_3SnH] > k_4$.

In summary, we have developed a reductive cyclization of enals and enones

mediated by catalytic quantities of Bu_3SnH. The keys to the success of this strategy are: 1) the inclusion of EtOH as an additive in order to accelerate the turnover step, and 2) overcoming the formation of small amounts of a very active catalyst for aldehyde reduction: Bu_2SnH_2. A novel mechanism for Bu_2SnH_2 formation (intermolecular pincacol coupling followed by silane reduction) was shown to be valid in unfunctionalized aldehydes (heptanal). We believe the same mechanism can be operative in our catalytic reductive cylization of enals and was the source of enhanced 1,2-reduction in the early stages of optimization of **2.2.1**. Under the optimized conditions, we found that the lower limit on catalyst loadings for the enal substrates is determined by the propensity of a given aldehyde to undergo intermolecular pinacol coupling at a rate competitive with its desired cyclization.

Experimental

General

AIBN was obtained from Eastman and used without purification. Bis(tributyltin) oxide was obtained from Gelest and distilled prior to use. Absolute ethanol was obtained from Pharmco and distilled from magnesium turnings according to the literature procedure[33] prior to use. Phenylsilane and heptanal were obtained from Aldrich and distilled prior to use. (Carbethoxymethylene)triphenylphosphorane, cinnamyl bromide, allylmagnesium chloride, 9-BBN dimer, DME (anhydrous), 1,1'-azobis(cyclohexanecarbonitrile), and tetrabutylammonium fluoride (TBAF; 1.0 M in THF) were obtained from Aldrich and used without purification.

Solvents were distilled from the indicated drying agents: benzene (sodium/benzophenone); toluene (molten sodium); THF (sodium/benzophenone).

Analytical thin layer chromatography was performed using EM Reagents 0.25 mm silica gel 60 plates, and visualization was accomplished with anisaldehyde/H_2SO_4/EtOH/HOAc or with ethanolic phosphomolybdic acid. Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh).

^1H, and ^{13}C nuclear magnetic resonance spectra were recorded on Varian XL-300 or Unity-300 NMR spectrometers at ambient temperature. ^1H 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, and coupling constant (Hz). ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). All ^{13}C spectra were determined with complete proton decoupling.

Gas chromatography was performed on a Hewlett Packard 5890 Series II instrument utilizing a DB-1 capillary column (J & W Scientific).

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 or argon. Cyclization reactions were carried out in sealed 10 mL Schlenk tubes under an atmosphere of nitrogen, and reaction temperatures refer to those of the oil bath.

The yields reported below may differ slightly from those reported in Table 1, since the latter are the average of two runs.

Cyclization Reactions

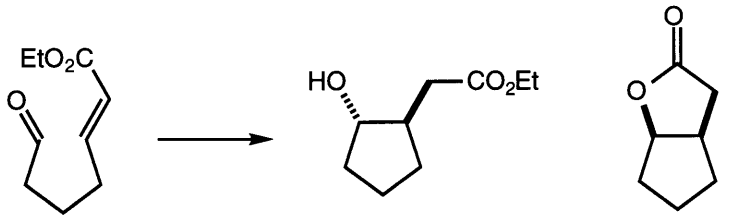


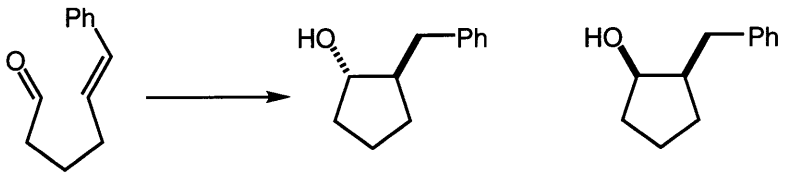
Table 2.2.1, entry 1. To a solution of the enal (170 mg, 1.00 mmol) in benzene (2.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (25 μL, 0.050 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol) and AIBN (16 mg, 0.10 mmol in 200 μL of benzene). The container was sealed, shaken and placed in an oil bath at 80 °C. After 6 h, TLC and GC analyses indicated that no starting material was present. The reaction mixture was treated with TBAF (3.0 mL, 3.0 mmol), and after stirring for 2 h, the material was subjected to aqueous workup with 2 N HCl (15 mL) and ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography, which provided 108 mg (70%) of a mixture of cis lactone and trans hydroxy ester as a colorless oil. The mixture was silylated,

separated by flash chromatography, and desilylated according to the literature procedure[34] to afford the trans hydroxyester and cis lactone as colorless oils.

***trans*-2-Hydroxycyclopentaneacetic acid ethyl ester.** The ^{1}H NMR spectrum was identical to the partial data reported in the literature.[35] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, 2H, J = 7.2), 3.83 (q, 1H, J = 6.4), 2.86 (br s, 1H), 2.43 (dd, 1H, J_1 = 16.2, J_2 = 6.6), 2.35 (dd, 1H, J_1 = 16.2, J_2 = 8.1), 2.13-2.00 (m, 1H), 1.99-1.86 (m, 2H), 1.79-1.51 (m, 3H), 1.24 (t, 3H, J = 7.2), 1.26-1.13 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 78.8, 60.6, 44.4, 38.5, 34.2, 30.6, 21.8, 14.1.

***cis*-Hexahydro-2*H*-cyclopenta[b]furan-2-one.** The ^{1}H NMR spectrum was identical to that reported in the literature.[36] ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 86.3, 37.8, 35.9, 33.5, 33.4, 23.3.

GC analysis of an aliquot taken from the unpurified reaction mixture, as well as ^{1}H NMR integration of the purified material, indicated that a 1.5 : 1 (trans : cis) mixture of compounds was present.



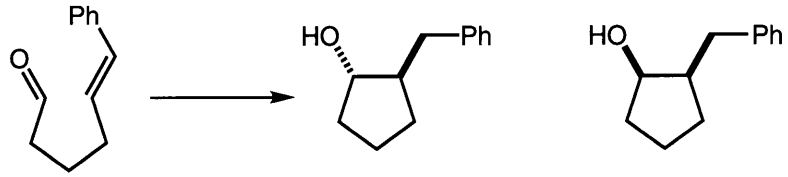
2.2.1

Table 2.2.1, entry 2. To a solution of the enal (174 mg, 1.00 mmol) in benzene (2.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (25 μL, 0.050 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol) and AIBN (16 mg, 0.10 mmol in 200 μL of benzene). The container was sealed, shaken and placed in an oil bath at 80 °C. After 5 h, more AIBN was added (16 mg, 0.10 mmol in 200 μL of benzene). After 7 more h, TLC indicated that no starting material was present. The reaction mixture was treated with TBAF (3.0 mL, 3.0 mmol), and after stirring for 1

h, the material was subjected to aqueous workup with 2 N HCl (15 mL) and ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography, which provided 149 mg (85%) of a mixture of cis and trans cyclopentanols as an analytically pure, colorless oil.

cis- and ***trans*-2-(Phenylmethyl)-cyclopentanol.** The ^1H and ^{13}C NMR spectra of the mixture were identical to those reported in the literature.[37] IR (neat) 3374, 3061, 3026, 2956, 2872, 1494, 1453, 1071, 1030, 747, 700. Anal. calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.55; H, 9.21.

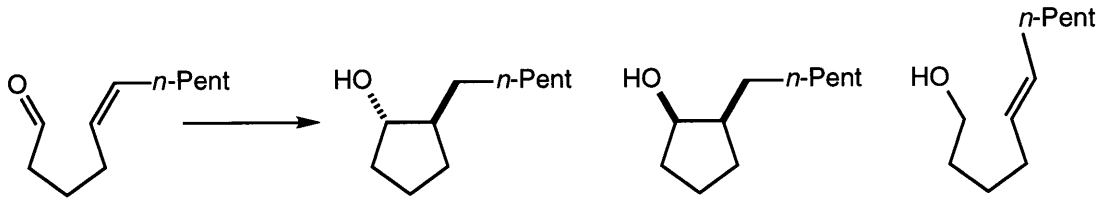
GC analysis of an aliquot taken from the unpurified reaction mixture, as well as ^1H NMR integration of the purified material, indicated that a 1.3 : 1 (trans : cis) mixture of cyclopentanols was present.



2.2.1

Catalytic cyclization of 2.2.1 with and without EtOH (eqs 2.2.9, 2.2.10). To a mixture of the enal (348 mg, 2.00 mmol), heptadecane (240 mg, 1.00 mmol; internal GC standard), and tetradecane (42.1 mg, 0.212 mmol; internal GC standard) was added AIBN (33 mg, 0.20 mmol) in 4 mL benzene. Bu_3SnH (58 mg, 0.20 mmol) and $PhSiH_3$ (108 mg, 1.00 mmol) were added, and an aliquot was removed for GC analysis. The solution was divided evenly between 2 sealable Schlenk tubes. EtOH (92 mg, 2.0 mmol) was added to one of the solutions, and both tubes were heated in the same oil bath at 80 °C. Aliquots were removed for GC ananlysis at regular intervals under a flow of Ar in order to determine consumption of aldehyde. Additional AIBN (0.10 equiv) was added to each tube after 300 min of heating. After

560 min, an aliquot from each reaction was analyzed by GC, and an additional aliquot was treated with TBAF and then acetylated for GC analysis. Product composition was determined from this acetylated aliquot, correcting the amount of acyclic reduction product for the amount generated from the aldehyde by reduction with TBAF/$PhSiH_3$.



2.2.5

Table 2.2.1, entry 3, eq 2.2.17. To a solution of the enal (168 mg, 1.00 mmol) in benzene (2.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (76 μL, 0.15 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol) and AIBN (16 mg, 0.10 mmol in 200 μL of benzene). The container was sealed, shaken and placed in an oil bath at 80 °C. After 12.5 h, TLC analysis indicated that no starting material was present. The reaction mixture was treated with TBAF (3.0 mL, 3.0 mmol), and after stirring for 1 h, the material was subjected to aqueous workup with 2 N HCl (15 mL) and ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography, which provided 167 mg (98%) of a mixture of cis and trans cyclopentanols and the simple reduction product as an analytically pure, colorless oil. Anal. calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.95; H, 12.86. The mixture was separated by flash chromatography to afford the three isomers as colorless oils.

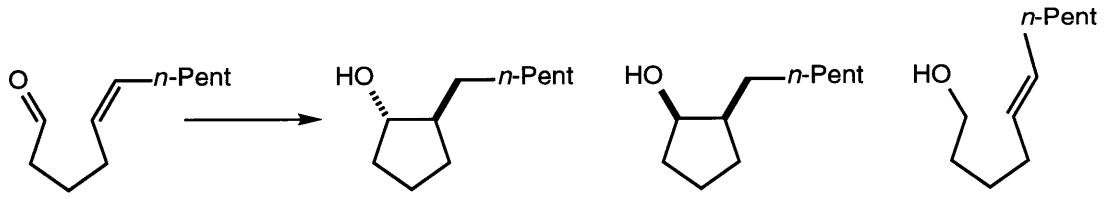
***cis*-2-Hexylcyclopentanol.** ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (td, 1H, J_1 = 4.0, J_2 = 1.2), 1.87-1.25 (m, 18H), 0.88 (t, 3H, J = 6.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.9, 45.8, 34.8, 31.9, 29.7, 29.2, 28.8, 28.6, 22.7, 21.8, 14.1. IR (neat) 3374, 2956, 2925, 2856, 1466,

1378, 1302, 1136, 1028, 988, 891, 724. HRMS: Calcd. for $C_{11}H_{22}O$: 170.1671. Found: 170.1669.

***trans*-2-Hexylcyclopentanol.** ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (q, 1H, J = 5.7), 1.96-0.99 (m, 18H), 0.88 (t, 3H, J = 6.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.4, 48.4, 34.6, 33.9, 31.8, 30.0, 29.6, 28.2, 22.6, 21.8, 14.1. IR (neat) 3333, 2922, 2854, 1464, 1456, 1378, 1344, 1078, 1022, 972, 724. HRMS: Calcd. for $C_{11}H_{22}O$: 170.1671. Found: 170.1669.

***E*- and *Z*-5-Undecen-1-ol.** ^1H NMR (300 MHz, $CDCl_3$) δ 5.46-5.29 (m, 2H), 3.66-3.61 (m, 2H), 2.09-1.93 (m, 4H), 1.63-1.20 (m, 11H), 0.90-0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.9, 130.4, 129.7, 129.3, 62.9, 32.5, 32.4, 32.3, 32.2, 31.5, 31.4, 29.4, 29.3, 27.2, 26.9, 25.8, 25.7, 22.5, 22.5, 14.0. IR (neat) 3331, 3004, 2926, 2856, 1458, 1378, 1061, 968, 726. HRMS: Calcd. for $C_{11}H_{22}O$: 170.1671. Found: 170.1669.

^1H NMR integration of the purified material indicated that a 2.3 : 1 (trans : cis) mixture of cyclopentanols was present. The stereochemistry was determined by oxidation of the cyclopentanol to the cyclopentanone by the literature procedure[38] followed by reduction with Li(*sec*-Bu_3BH). The latter reaction is known to yield the cis isomer in the reduction of 2-alkylcyclopentanones.[39] Furthermore, ^1H NMR integration indicated that 30% of the purified material was 5-undecen-1-ol (3.6 : 1 E : Z), as estimated by the relative intensities of the vinyl signals in the ^{13}C NMR.



2.2.5

Eq 2.2.16. The reaction was run as above, but with $(Bu_3Sn)_2O$ (29.8 mg, 0.0500 mmol). After 5.5 h, TLC indicated that no starting material remained. Workup and purification as above afforded 162 mg (95%) of the reduction products which were

collected together and analyzed by ^1H NMR. A 1.2 : 1 (acyclic : cyclic) mixture was observed. The cyclic products displayed a diastereomeric composition of 2.2 : 1 (trans : cis).

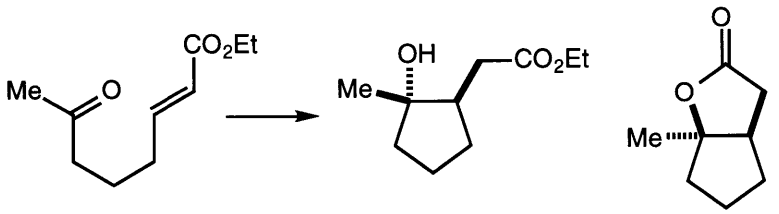


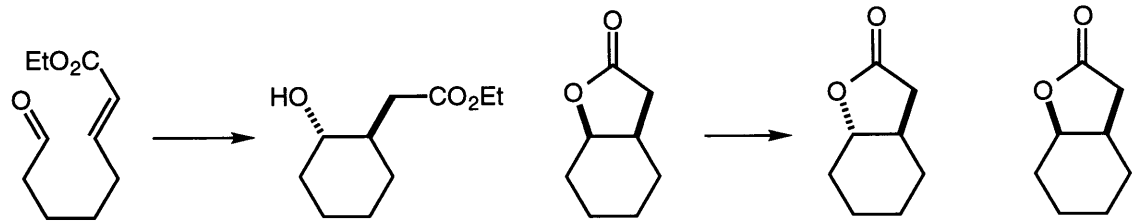
Table 2.2.1, entry 4. To a solution of the enone (184 mg, 1.00 mmol) in toluene (1.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (25 μL, 0.050 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (24 mg, 0.10 mmol in 200 μL of toluene). The container was sealed, shaken and placed in an oil bath at 110 °C. After 3.5 h, more initiator was added (24 mg, 0.10 mmol in 200 μL of toluene). After 3.5 more h, GC analysis indicated that only a small amount of starting material remained. The reaction mixture was treated with TBAF (3.0 mL, 3.0 mmol), and after stirring for 1 h, the material was subjected to aqueous workup with 2 N HCl (15 mL) and ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography, which provided 130 mg (80%) of a mixture of trans hydroxyester and cis lactone as a colorless oil. The mixture was separated by column chromatography to afford the two compounds as colorless oils.

***trans*-2-Hydroxy-2-methylcyclopentaneacetic acid ethyl ester.** ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, 2H, J = 7.1), 2.54 (br s, 1H), 2.47-2.15 (m, 3H), 2.00-1.89 (m, 1H), 1.81-1.47 (m, 4H), 1.29-1.15 (m, 1H), 1.24 (t, 3H, J = 7.1), 1.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 79.3, 60.6, 46.4, 41.1, 35.3, 30.3, 23.1, 20.5, 14.1. IR (neat) 3433, 2965, 2874, 1735, 1374, 1329, 1306, 1201, 1153, 1097, 1033. HRMS: Calcd. for $C_{10}H_{18}O_3$: 186.1256.

Found: 186.1258.

***cis*-Hexahydro-6a-methyl-2*H*-cyclopenta[b]furan-2-one.** The ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[40]

GC analysis of an aliquot taken from the unpurified reaction mixture (corrected for the response factor), as well as ^{1}H NMR integration of the purified material, indicated that a 1.0 : 1 (trans : cis) mixture of compounds was present.

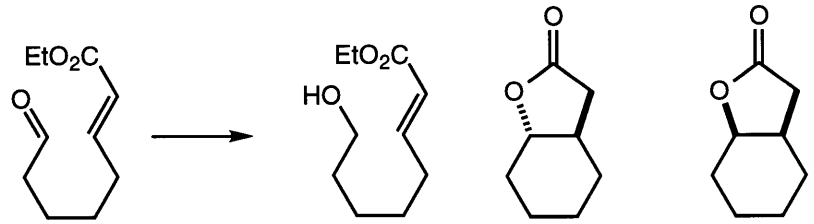


2.2.4

Table 2.2.1, entry 5. To a solution of the enal (184 mg, 1.00 mmol) in benzene (2.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (76 μL, 0.15 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol) and AIBN (16 mg, 0.10 mmol in 200 μL of benzene). The container was sealed, shaken and placed in an oil bath at 80 °C. After 6.5 h, TLC analysis indicated that no starting material remained. The reaction mixture was treated with TBAF (3.0 mL, 3.0 mmol), and after stirring for 1 h, the material was subjected to aqueous workup with 2 N HCl (15 mL) and ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and dissolved in CH_2Cl_2 (10 mL). A catalytic quantity of *p*-toluenesulfonic acid monohydrate was added, and the solution was stirred for 20 h. GC analysis indicated that all of the initially formed trans hydroxyester had been converted to the lactone. The solution was concentrated and purified by flash chromatography to afford 103 mg (74%) of an analytically pure mixture of cis and trans lactones as a colorless oil.

cis- and ***trans*-Hexahydro-2(3*H*)-benzofuranone.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (q, cis carbinol resonance, J = 4.2), 3.75 (td, trans carbinol resonance, J_1 = 10.9, J_2 = 3.7), 2.62-1.16 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 176.4, 85.0, 79.0, 44.6, 37.3, 35.7, 34.7, 30.0, 28.1, 27.6, 27.0, 25.2, 23.9, 22.6, 19.7. IR (neat) 2936, 2861, 1770, 1448, 1225, 1212, 1173, 1142, 1076, 1029, 989, 942, 931. Anal. calcd. for $C_8H_{12}O_2$: C, 68.55, H; 8.63. Found: C, 68.65; H, 8.62.

^{1}H NMR integration of the purified material indicated that a 1.1 : 1 (trans : cis) mixture of lactones was present. The stereochemistry was assigned by noting which carbinol signal grew in over the course of the acid catalyzed lactonization. This resonance was assigned to the trans isomer.



2.2.4

Eqs 2.2.14, 2.2.15. To a mixture of the enal (368 mg, 2.00 mmol), heptadecane (240 mg, 1.00 mmol), and tetradecane (41.7 mg, 0.210 mmol) was added AIBN (33 mg (0.20 mmol) in benzene (4.0 mL). $PhSiH_3$ (108 mg, 1.00 mmol) and EtOH (184 mg, 4.0 mmol) were added, and an aliquot was removed for GC analysis. The solution was divided between two sealable Schlenk tubes. To one was added Bu_3SnH (29 mg, 0.10 mmol) and to the other was added Bu_3SnH (87 mg, 0.30 mmol). The tubes were heated in the same oil bath at 80 °C for 4.5 h, at which time GC analysis indicated no aldehyde was left in either reaction. The reactions were treated with TBAF (3 mL of a 1 M solution in THF), stirred for 3 h, and then worked up with 2 N HCl and Et_2O. The combined organic layers were dried ($MgSO_4$), and an aliquot was acetylated and

analyzed by GC for the acyclic reduction product. The ether layers were filtered, concentrated, and dissolved in CH_2Cl_2 (10 mL). A catalytic quantity of *p*-toluenesulfonic acid monohydrate was added, and the solution was stirred for 20 h. GC analysis of an aliquot allowed for determination of the cyclic products.

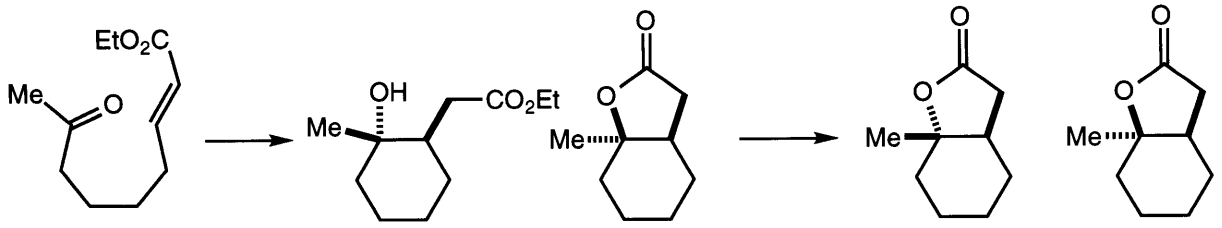
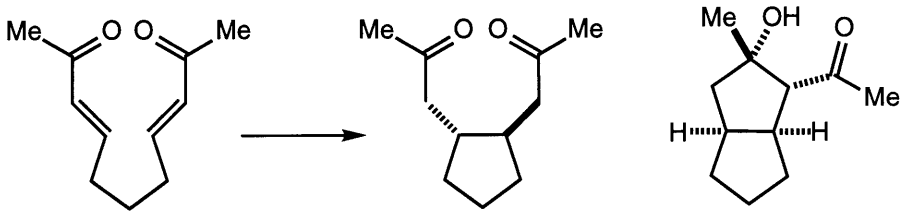


Table 2.2.1, entry 6. To a solution of the enone (198 mg, 1.00 mmol) in toluene (1.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (51 μL, 0.10 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (24 mg, 0.10 mmol in 200 μL of toluene). The container was sealed, shaken and placed in an oil bath at 110 °C. More initiator was added after 5.5 h (24 mg, 0.10 mmol in 200 μL of toluene) and after 9.5 h (12 mg, 0.050 mmol in 200 μL of toluene). After a total reaction time of 12 h, TLC analysis indicated that very little starting material remained. The reaction mixture was treated with TBAF (3.0 mL, 3.0 mmol), and after stirring for 1 h, the material was subjected to aqueous workup with 2 N HCl (15 mL) and ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and dissolved in CH_2Cl_2 (10 mL). A catalytic quantity of *p*-toluenesulfonic acid monohydrate was added, and the reaction was stirred until equilibrium was reached. The solution was concentrated and redissolved in CH_2Cl_2 (2x) in order to drive the lactonization to completion. The solution was concentrated and purified by flash chromatography to afford 102 mg (66%) of an analytically pure mixture of cis and trans lactones as a colorless oil. Anal. calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.13; H, 9.46.

***cis*-Hexahydro-7a-methyl-2(3*H*)-benzofuranone.** The signals assigned to the cis isomer in the ^{1}H and ^{13}C NMR spectra of the mixture were identical to those reported in the literature.[40]

***trans*-Hexahydro-7a-methyl-2(3*H*)-benzofuranone.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 85.9, 46.7, 36.8, 33.2, 25.4, 24.7, 22.9, 17.4.

GC analysis of an aliquot taken from the crude material indicated that a 1.1 : 1 (trans : cis) mixture of lactones was present.

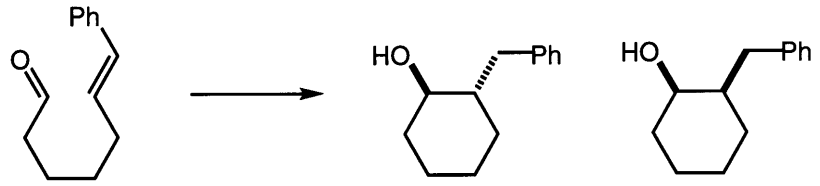


***trans*-1,1'-(1,2-Cyclopentanediyl)bis-2-propanone** and **(1.alpha., 2.alpha., 3a.alpha., 6a.alpha.)]-1-(Octahydro-2-hydroxy-2-methyl-1-pentalenyl)-ethanone. eq 3.** To a solution of the enone (180 mg, 1.00 mmol) in benzene (2.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (25 μL, 0.050 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol) and AIBN (16 mg, 0.10 mmol in 200 μL of benzene). The container was sealed, shaken and placed in an oil bath at 80 °C. After 7.5 h, TLC analysis indicated that no starting material was present. The solution was concentrated and purified by flash chromatography to afford 164 mg (90%) of a mixture of the two products as an analytically pure, colorless oil. The ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[30] Anal. calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.18; H, 9.99.

GC analysis of an aliquot taken from the crude material after being passed through a plug of SiO_2 indicated that a 3.6 : 1 (trans : cis) mixture of isomers was

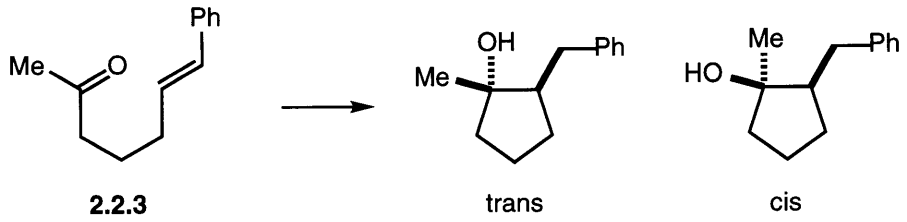
present.

Control reactions. Each of the seven substrates was submitted to the conditions described in the corresponding cyclization procedure, but in the absence of $(Bu_3Sn)_2O$. In every case, little (<3%) or no cyclized product was observed by GC analysis.



2.2.2

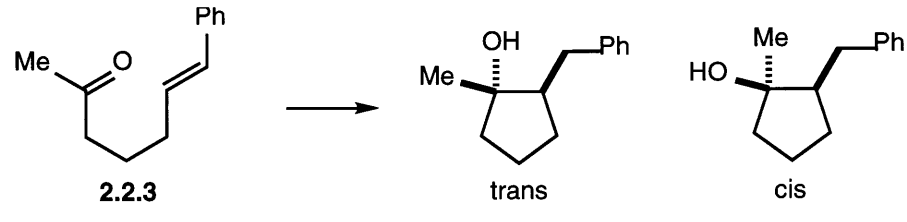
cis- and ***trans*-2-(Phenylmethyl)-cyclohexanol. eqs 2.2.11, 2.2.12.** To a mixture of the enal (377 mg, 2.00 mmol), heptadecane (240 mg, 1.00 mmol; internal GC standard), and tetradecane (42.1 mg, 0.212 mmol; internal GC standard) was added AIBN (33 mg, 0.20 mmol) in 4 mL benzene. Bu_3SnH (58 mg, 0.20 mmol) and $PhSiH_3$ (108 mg, 1.00 mmol) were added, and an aliquot was removed for GC analysis. The solution was divided evenly between 2 sealable Schlenk tubes. EtOH (92 mg, 2.0 mmol) was added to one of the solutions, and both tubes were heated in the same oil bath at 80 °C. Aliquots were removed for GC ananlysis at regular intervals under a flow of Ar in order to determine consumption of aldehyde. Additional AIBN (0.10 equiv) was added to each tube after 300 min of heating. After 600 min, an aliquot from each reaction was analyzed by GC, and an additional aliquot was treated with TBAF and then acetylated for GC analysis. Product composition was determined from this acetylated aliquot, correcting the amount of acyclic reduction product for the amount generated from the aldehyde by reduction with TBAF/$PhSiH_3$.



2.2.3 trans cis

***cis*- and *trans*-1-Methyl-2-(phenylmethyl)-cyclopentanol. (eqs 2.2.7, 2.2.8).** To a solution of the enone (47.1 mg, 0.250 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (6.1 mg, 0.025 mmol) in d_8-toluene (0.250 mL) in a J. Young tube were added Bu_3SnH (7.3 mg, 0.025 mmol), $PhSiH_3$ (13.5 mg, 0.125 mmol), *n*-PrOH (30 mg, 0.50 mmol), tetradecane (5.1 mg, 0.026 mmol; internal GC standard), and hexadecane (26.3 mg, 0.116 mmol; internal GC standard). An identical reaction was assembled without the *n*-PrOH, and both were heated in an oil bath maintained at 110 °C. After 2.5 h, additional initiator (0.10 equiv) was added to each reaction, and after 5.5 h, both reactions were analyzed by GC for consumption of starting material, and then treated with TBAF (0.75 mL of a 1 M solution in THF). After stirring for 45 min, the reactions were worked up with 2 N HCl and Et_2O, dried ($MgSO_4$), filtered, and analyzed by GC for product formation.

Preparation of Authentic Products



2.2.3 trans cis

***cis*- and *trans*-1-Methyl-2-(phenylmethyl)-cyclopentanol.** To a solution of the

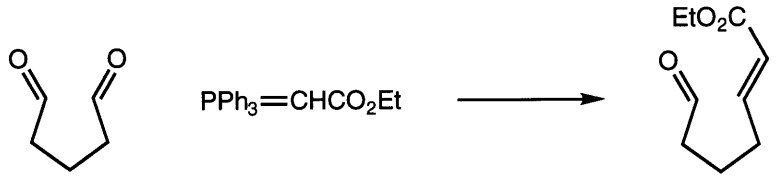
enone (102 mg, 0.542 mmol) in benzene (5.0 mL) were added Bu_3SnH (189 mg, 0.65 mmol) and AIBN (8 mg, 0.05 mmol). The reaction was heated to reflux for 6 h, at which time additional AIBN (4 mg in 0.10 mL benzene) was added. After an additional 18 h at reflux, the reaction mixture was concentrated, and the diastereomers were separated by flash chromatography.

GC analysis of the crude reaction mixture exhibited a 4.0 : 1 (trans : cis) mixture of diastereomers. The stereochemistry was determined by comparison of the ^1H NMR spectrum and GC retention time with a sample of the authentic trans isomer prepared by ring opening of the corresponding epoxide with BnMgCl.

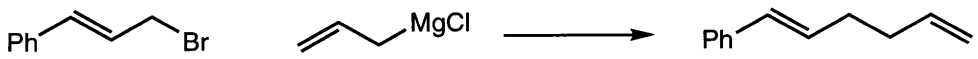
***trans*-1-Methyl-2-(phenylmethyl)-cyclopentanol (more polar diastereomer).** ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.21-7.16 (m, 3H), 2.89 (dd, 1H, J_1 = 13.2, J_2 = 4.5), 2.30 (dd, 1H, J_1 = 13.1, J_2 = 11.0), 2.10-2.00 (m, 1H), 1.84-1.50 (m, 5H), 1.43 (brs, 1H), 1.35-1.23 (m, 1H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 128.7, 128.3, 125.7, 80.5, 52.0, 41.0, 36.5, 29.1, 23.0, 20.0. IR (neat) 3372, 3084, 3061, 3026, 2959, 2872, 1603, 1494, 1453, 1375, 1324, 1301, 1270, 1206, 1133, 1095, 1076, 1047, 1030, 1005, 949, 912, 728, 699, 586, 564. HRMS: Calcd. for $C_{13}H_{18}O$: 190.1358. Found: 190.1358.

***cis*-1-Methyl-2-(phenylmethyl)-cyclopentanol (less polar diastereomer).** ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.21-7.15 (m, 3H), 2.89 (dd, 1H, J_1 = 13.2, J_2 = 4.2), 2.48 (dd, 1H, J_1 = 13.5, J_2 = 10.5), 1.85-1.62 (m, 5H), 1.60-1.44 (m, 2H), 1.32 (s, 3H), 1.14 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 128.8, 128.2, 125.6, 80.0, 51.3, 41.7, 35.2, 30.2, 26.3, 20.8. IR (neat) 3426, 3061, 3026, 2960, 2871, 1603, 1494, 1453, 1375, 1221, 1147, 1079, 1053, 1031, 934, 908, 858, 729, 698. HRMS: Calcd. for $C_{13}H_{18}O$: 190.1358. Found: 190.1358.

Preparation of Substrates

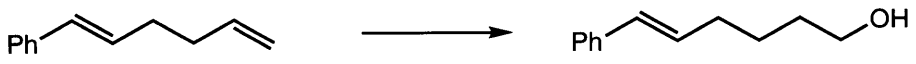


(*E*)-7-Oxo-2-heptenoic acid ethyl ester. To a solution of (carbethoxymethylene)triphenylphosphorane (10.5 g, 30.0 mmol) in anhydrous DME (250 mL) was added anhydrous glutaraldehyde[31] (3.0 g, 30 mmol). The reaction was heated to reflux for 1 h, then allowed to stand at room temperature for 19 h. The solution was concentrated and purified by flash chromatrography, followed by distillation (bulb-to-bulb) to afford the enal as a clear, colorless oil. The ^1H NMR and infrared spectra were identical to those reported in the literature.[41] ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 166.3, 147.4, 122.1, 60.1, 42.8, 31.1, 20.2, 14.1. HRMS: Calcd. for $C_9H_{14}O_3$: 170.0943. Found: 170.0944.

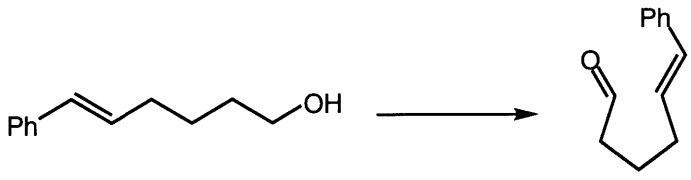


(*E*)-1,5-Hexadienylbenzene. To a solution of cinnamyl bromide (35.7 g, 181 mmol) in THF (300 mL) at 0 °C was added a 2 M solution of allylmagnesium chloride in THF (100 mL, 200 mmol). The reaction was allowed to warm to room temperature over 2 h, at which time TLC analysis indicated that no starting material was present. The reaction was quenched by the addition of a saturated solution of NH_4Cl (100 mL). After aqueous workup with brine and *tert*-butyl methyl ether (TBME), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Distillation (65-68 °C/40 mtorr) afforded 26.7 g (93%) of the diene as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.19 (m, 5H), 6.43 (d, 1H, J = 15.6), 6.26 (dt, 1H, J_1 = 15.6, J_2 = 6.5), 5.96-5.83 (m, 1H), 5.09 (dq, 1H, J_1 = 17.1, J_2 = 1.8), 5.02 (dd, 1H, J_1 = 10.1, J_2 = 1.5), 2.38-2.22 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.8, 130.2, 130.0, 128.4, 126.8, 125.9, 114.9, 33.5, 32.4.



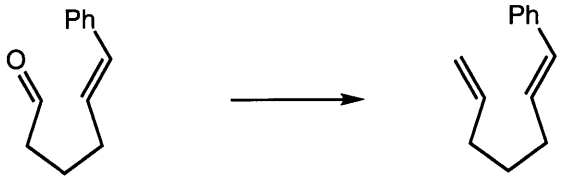
(*E*)-6-Phenyl-5-hexen-1-ol. To a solution of crystalline 9-BBN dimer (19.3 g, 79 mmol) in THF (300 mL) was added (*E*)-1,5-hexadienylbenzene (25 g, 158 mmol) via syringe. The reaction was stirred for 5 h, cooled in an ice bath, and a 1 : 1 solution of THF and ethanol was added (400 mL), followed by 1 M NaOH (160 mL) and 30% H_2O_2 (160 mL). After allowing to warm to room temperature and stirring for 12 h, the solution was subjected to aqueous workup with brine and TBME. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and passed through a pad of SiO_2. The material was then purified batchwise as needed by flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 5H), 6.38 (d, 1H, J = 16.3), 6.20 (dt, 1H, J_1 = 15.5, J_2 = 6.9), 3.64 (q, 2H, J = 6.4), 2.23 (q, 2H, J = 6.2), 1.67-1.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 130.5, 130.1, 128.4, 126.8, 125.9, 62.7, 32.7, 32.2, 25.5. IR (neat) 3355, 3058, 3024, 2934, 2860, 1494, 1448, 1070, 965, 746, 693.



2.2.1

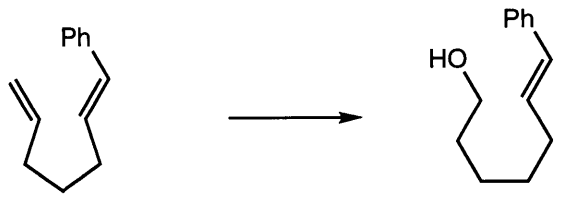
(*E*)-6-Phenyl-5-hexenal (2.2.1). (*E*)-6-phenyl-5-hexen-1-ol (2.83 g, 16.1 mmol) was

oxidized with PCC according to the literature procedure.[42] Purification by flash chromatography afforded 2.06 g (73%) of the aldehyde as a colorless oil. The material was further purified by bulb-to-bulb distillation (60 °C/20 mtorr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, 1H, J = 1.6), 7.38-7.20 (m, 5H), 6.42 (d, 1H, J = 15.9), 6.18 (dt, 1H, J_1 = 15.9, J_2 = 6.9), 2.49 (td, 2H, J_1 = 7.3, J_2 = 1.6), 2.27 (qd, 2H, J_1 = 8.2, J_2 = 1.2), 1.83 (pentet, 2H, J = 7.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 137.4, 130.9, 129.3, 128.4, 127.0, 125.9, 43.1, 32.1, 21.5. IR (neat) 3025, 2934, 2828, 2721, 1723, 1492, 1448, 1390, 967, 744, 694. HRMS: Calcd. for $C_{12}H_{14}O$: 174.1045. Found: 174.1046.

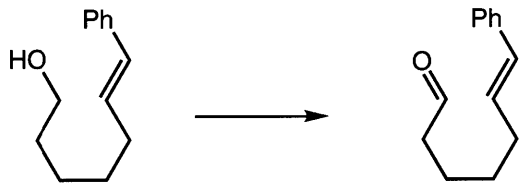


2.2.1

(*E*)-1,6-Heptadienylbenzene. To a solution of $NaN(TMS)_2$ (5.20 g, 28.3 mmol) in THF (200 mL) was added methyltriphenylphosphonium bromide (11.7 g, 32.6 mmol). After stirring for 1 h, the reaction mixture was cooled to 0 °C, and the aldehyde (**2.2.1**, 3.79 g, 21.8 mmol) was added as a solution in THF. After 15 min, TLC indicated that no aldehyde remained, so the reaction was treated with a saturated solution of NH_4Cl (50 mL), followed by extraction with hexanes. The organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by flash chromatography to afford 3.57 g (95%) of (*E*)-1,6-heptadienylbenzene as a clear, colorless oil. The ^{1}H NMR spectrum was identical to that published in the literature.[43]



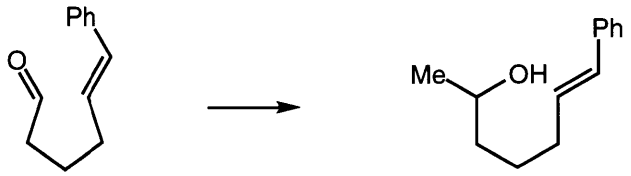
(*E*)-7-Phenyl-6-hepten-1-ol. To a solution of crystalline 9-BBN dimer (2.52 g, 10.3 mmol) in THF (30 mL) was added (*E*)-1,6-heptadienylbenzene (3.55 g, 20.6 mmol) via syringe. The reaction was stirred for 4.5 h, cooled in an ice bath, and a 1 : 1 solution of THF and ethanol was added (50 mL), followed by 1 M NaOH (21 mL) and 30% H_2O_2 (21 mL). After allowing to warm to room temperature and stirring for 10 h, the solution was subjected to aqueous workup with brine and Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography to afford 3.66 g (93%) of (*E*)-7-phenyl-6-hepten-1-ol as a clear, colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.29 (m, 2H), 7.19 (m, 1H), 6.38 (d, 1H, J = 16.5), 6.22 (dt, 1H, J_1 = 16.0, J_2 = 7.0), 3.66 (m, 2H), 2.23 (qd, 2H, J_1 = 7.3, J_2 = 1.5), 1.61 (pent, 2H, J = 7.0), 1.51 (pent, 2H, J = 7.5), 1.45-1.39 (m, 2H), 1.27 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 130.7, 129.8, 128.4, 126.8, 125.8, 62.8, 32.9, 32.6, 29.1, 25.3. IR (neat) 3345, 2928, 1598, 1494, 1448, 1071, 1053, 964, 744, 692. HRMS: Calcd for $C_{13}H_{18}O$ $[M+H]^+$: 191.1436. Found: 191.1435.



2.2.2

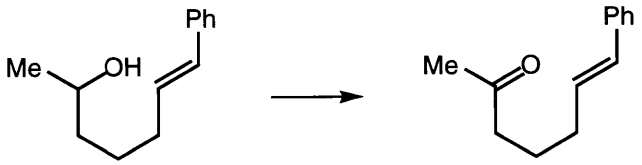
(*E*)-7-Phenyl-6-heptenal (2.2.2). (*E*)-7-Phenyl-6-hepten-1-ol (2.43 g, 12.8 mmol) was oxidized with PCC according to the literature procedure.[42] Purification by flash

chromatography afforded 1.52 g (63%) of the aldehyde as a pale yellow oil. The material was further purified by bulb-to-bulb distillation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, 1H, J = 1.8), 7.35 (d, 2H, J = 7.0), 7.30 (t, 2H, J = 7.5), 7.20 (t, 1H, J = 7.3), 6.40 (d, 1H, J = 15.5), 6.28 (dt, 1H, J_1 = 16.0, J_2 = 7.0), 2.47 (td, 2H, J_1 = 7.3, J_2 = 2.0), 2.25 (qd, 2H, J_1 = 7.2, J_2 = 1.0), 1.70 (m, 2H), 1.52 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 137.6, 130.3, 130.1, 128.5, 126.9, 125.9, 43.7, 32.7, 28.8, 21.6. IR (neat) 3058, 3024, 2932, 2857, 2720, 1724, 1598, 1493, 1459, 1448, 1409, 1390, 1072, 966, 745, 694. HRMS: Calcd. for $C_{13}H_{16}O$: 188.1201. Found: 188.1202.



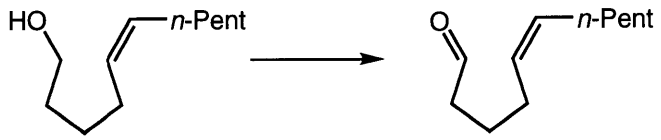
2.2.1

(*E*)-7-Phenyl-6-hepten-2-ol. To a solution of (*E*)-6-phenyl-5-hexenal (1.05 g, 6.00 mmol) in Et_2O (20 mL) at 0 °C was added a 3.0 M solution of MeMgBr in Et_2O (2.40 mL). After 1 h, the reaction was quenched by the addition of saturated NH_4Cl and worked up with brine and TBME. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by column chromatography to afford (*E*)-7-phenyl-6-hepten-2-ol as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.34 (m, 2H), 7.31-7.28 (m, 2H), 7.21-7.18 (m, 1H), 6.40 (d, 1H, J = 16.0), 6.22 (dt, 1H J_1 = 15.5, J_2 = 6.8), 3.83 (hex, 1H, J = 6.0), 2.24 (m, 2H), 1.63-1.47 (m, 4H), 1.35 (brs, 1H), 1.21 (d, 3H, J = 6.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 130.6, 130.0, 128.4, 126.8, 125.8, 67.9, 38.7, 32.9, 25.4, 23.5. IR (neat) 3354, 2930, 1494, 1449, 1373, 1131, 964, 745, 692. HRMS: Calcd for $C_{13}H_{18}O$ $[M+H]^+$: 191.1436. Found: 191.1435.



2.2.3

(*E*)-7-Phenyl-6-hepten-2-one (2.2.3). (*E*)-7-Phenyl-6-hepten-2-ol (1.07 g, 5.62 mmol) was oxidized with NMO/TPAP/CH_2Cl_2 according to the literature procedure.[44] Purification by flash chromatography afforded 809 mg (77%) of the ketone as a pale yellow oil. The material was further purified by bulb-to-bulb distillation to afford a white solid which melted to a clear, colorless oil upon warming to room temperature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 4H), 7.23-7.18 (m, 1H), 6.39 (d, 1H, J = 15.9), 6.17 (dt, 1H, J_1 = 15.9, J_2 = 6.9), 2.48 (t, 2H, J = 7.4), 2.23 (qd, 2H, J_1 = 7.2, J_2 = 1.5), 2.14 (s, 3H), 1.77 (pent, 2H, J = 6.8). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 137.5, 130.6, 129.7, 128.4, 126.9, 125.9, 42.8, 32.2, 30.0, 23.1. IR (neat) 2936, 1714, 1493, 1447, 1365, 1157, 966, 746, 693. HRMS: Calcd for $C_{13}H_{16}O$ $[M+H]^+$: 189.1279. Found: 189.1279.

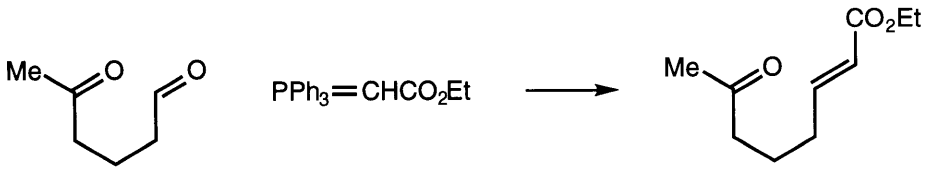


2.2.5

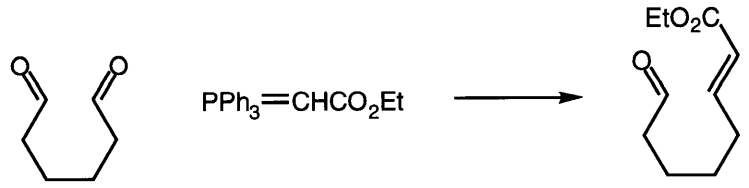
(*Z*)-5-Undecenal (2.2.5). (Z)-5-undecen-1-ol[45] (2.82 g, 16.6 mmol) was oxidized with PCC by the literature procedure.[42] Flash chromatography followed by bulb-to-bulb distillation (40-43 °C/40 mtorr) afforded the aldehyde as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, J = 1.8), 5.46-5.26 (m, 2H), 2.43 (dd, 2H, J_1 = 7.5, J_2 = 1.8), 2.08 (q, 2H, J = 7.5), 1.99 (q, 2H, J = 6.9), 1.69 (pentet, 2H, J = 7.2), 1.36-1.24 (m, 6H), 0.88 (t, 3H, J = 6.9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 131.3, 128.1, 43.2, 31.4, 29.2,

27.1, 26.4, 22.5, 22.0, 13.9. IR (neat) 3006, 2927, 2857, 2716, 1727, 1458, 1409, 1389. HRMS: Calcd. for $C_{11}H_{20}O$: 168.1514. Found: 168.1511.

The Z : E ratio was estimated to be 93 : 7 based on the relative heights of the vinyl signals in the ^{13}C NMR.



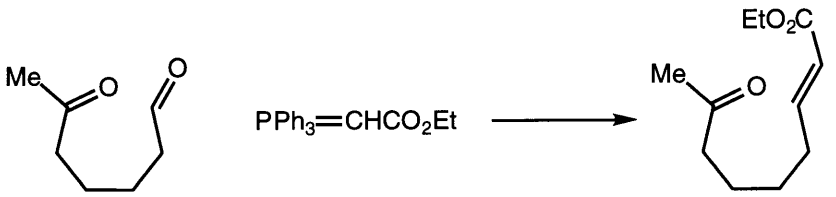
(*E*)-7-Oxo-2-octenoic acid ethyl ester. To a solution of (carbethoxymethylene)triphenylphosphorane (7.68 g, 22.0 mmol) in anhydrous DME (100 mL) was added 5-oxo-hexanal[46] (2.52 g, 22.0 mmol). The reaction was stirred for 54 h, at which time TLC analysis indicated that very little starting material was present. The solution was concentrated and purified by flash chromatography to afford 2.86 g (71%) of the enone as a colorless oil. The material was degased (freeze-thaw) with Ar (1x) and stored under an atmosphere of nitrogen. The ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[47]



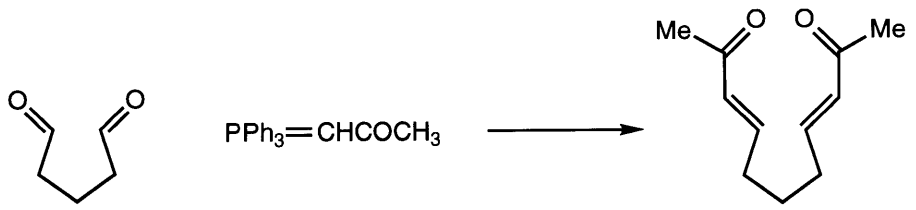
2.2.4

(*E*)-8-Oxo-2-octenoic acid ethyl ester (2.2.4). To a solution of adipaldehyde[48] (3.42 g, 30.0 mmol) in anhydrous DME (250 mL) was added (carbethoxymethylene)triphenylphosphorane (10.5 g, 30.0 mmol). The reaction was allowed to stir for 43 h, at which time it was concentrated and purified by flash

chromatography to afford 2.26 g (41 %) of the enal as a pale yellow oil. Prior to use, the material was distilled bulb-to-bulb (70-75 °C/50 mtorr) to afford a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, 1H, J = 1.5), 6.92 (dt, 1H, J_1 = 15.6, J_2 = 6.9), 5.81 (dt, 1H, J_1 = 15.6, J_2 = 1.6), 4.16 (q, 2H, J = 7.1), 2.44 (td, 2H, J_1 = 7.1, J_2 = 1.7), 2.21 (qd, 2H, J_1 = 7.1, J_2 = 1.6), 1.67-1.60 (m, 2H), 1.54-1.46 (m, 2H), 1.27 (t, 3H, J = 7.2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 166.4, 148.1, 121.7, 60.0, 43.5, 31.7, 27.4, 21.4, 14.1. IR (neat) 2982, 2938, 2864, 1710, 1654, 1368, 1311, 1268, 1187, 1154, 1043, 984. HRMS: Calcd. for $C_{10}H_{16}O_3$: 184.1099. Found: 184.1101.



(*E*)-8-Oxo-2-nonenoic acid ethyl ester. To a solution of 6-oxoheptanal[31] (2.56 g, 20.0 mmol) in anhydrous DME (100 mL) was added (carbethoxymethylene)triphenylphosphorane (7.0 g, 20 mmol). The reaction was stirred for 45 h, concentrated, and purified by flash chromatography to afford 3.2 g (81%) of the enone as a colorless oil. The material was degased (freeze-thaw) with Ar (2x) and stored under an atmosphere of nitrogen. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dt, 1H, J_1 = 15.6, J_2 = 6.9), 5.78 (dt, 1H, J_1 = 15.6, J_2 = 1.6), 4.15 (q, 2H, J = 7.1), 2.42 (t, 2H, J = 7.2), 2.18 (qd, 2H, J_1 = 7.2, J_2 = 1.4), 2.11 (s, 3H), 1.62-1.53 (m, 2H), 1.48-1.38 (m, 2H), 1.25 (t, 3H, J = 7.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 166.5, 148.5, 121.6, 60.1, 43.3, 31.9, 29.8, 27.5, 23.1, 14.2. IR (neat) 2983, 2934, 1715, 1652, 1446, 1367, 1267, 1182, 1097, 1043, 983. HRMS: Calcd. for $C_{11}H_{18}O_3$: 198.1256. Found: 198.1258.



(*E*,*E*)-3,8-Undecadiene-2,10-dione. The dienone was prepared according to the literature procedure.[30]

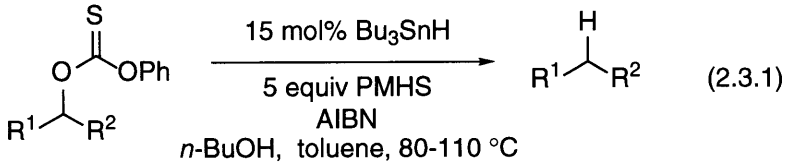
Test for Bu_2SnH_2 Formation in Reduction of Hepatanal (Eq 2.2.8, 2.2.9)

Eq 2.2.18, 2.2.19. To a solution of heptanal (228 mg, 2.00 mmol) and AIBN (33 mg, 0.20 mmol) in C_6H_6 was added decane (142 mg, 1.00 mmol; internal GC standard), heptadecane (120 mg, 0.500 mmol; internal GC standard) and $PhSiH_3$ (216 mg, 2.00 mmol). The solution was split evenly between two 20 mL sealable Schlenk tubes. To one was added Bu_3SnH (14.7 mg, 0.0500 mmol; eq 2.2.9), and to the other was added Bu_3SnH (291 mg, 1.00 mmol; eq 2.2.8). Each reaction was analyzed by GC and then immersed in the same oil bath maintained at 80 ± 1 °C. Aliquots were removed at regular intervals under Ar and analyzed by GC for aldehyde consumption as determined by integration versus decane. After 214 min of heating, each reaction was treated with THF (5 mL) and 4 N NaOH (5 mL), and stirred for 12 h. The reaction mixtures were partitioned with brine and Et_2O, the organic layer was removed, and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with 2 N HCl (1x) and brine, and dried ($MgSO_4$). GC analysis of an acetylated aliquot from eq 2.2.9 indicated that 0.031 mmol of the pinacol coupled product (7,8-tetradecanediol)[49] had formed (5.7/1 d,l/meso), whereas an acetylated aliquot from eq 2.2.8 showed no detectible amount of the pinacol product (<0.0004 mmol).

2.3. Discovery and Optimization of the Bu_3SnH-Catalyzed Barton-McCombie Deoxygenation of Alcohols.

Background

The Barton-McCombie procedure for the deoxygenation of alcohols (Figure 1)[50-52] is a useful tool for synthetic organic chemists.[53] This free-radical chain process typically employs 1.5-3 equivalents of Bu_3SnH as the reducing agent. As part of our program directed towards the development of organic transformations which call for *substoichiometric* quantities of organotin hydride, we endeavored to devise a protocol for a Bu_3SnH-catalyzed, silicon hydride-mediated variant of this reaction. In this section, we report the successful realization of this goal (eq 2.3.1).



(2.3.1)

The mechanism for the Barton-McCombie deoxygenation is known to proceed as in Figure 2.3.1.[54] Bu_3Sn radical first adds to the carbon-sulfur double bond, followed by β-fragmentation to afford a secondary carbon-centered radical. Finally, abstraction of a hydrogen atom from Bu_3SnH liberates the deoxygenated product. Initially, the tin is in the form of $Bu_3SnC(O)X$, but under the reaction conditions, this intermediate eliminates COS to afford Bu_3SnX. As a turnover step, we thus proposed regenerating the Bu_3SnH from Bu_3SnX by means of a silicon hydride used in stoichiometric quantities (Figure 2.3.2).

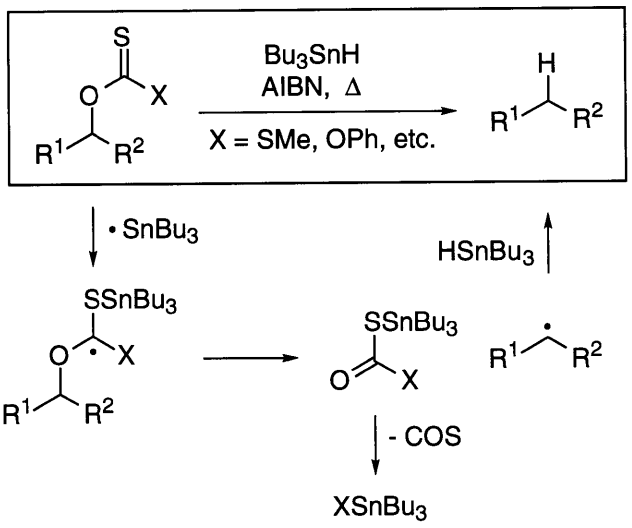


Figure 2.3.1. The Barton-McCombie Deoxygenation Reaction.

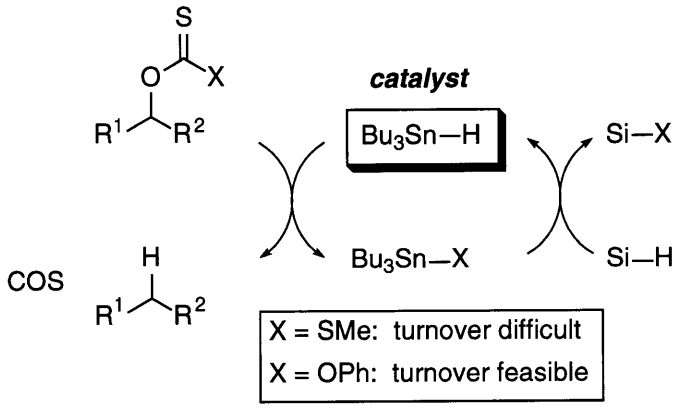


Figure 2.3.2. Proposed Bu_3SnH-catalyzed silicon hydride-mediated Barton-McCombie deoxygenation.

Results and Discussion

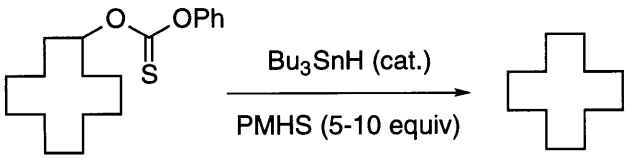
The classical Barton-McCombie procedure involves derivatization of a secondary alcohol as the methyl xanthate (Figure 2.3.1, X = SMe) prior to the deoxygenation.[50] The tin-containing product, after loss of COS, is Bu_3SnSMe. Unfortunately, the reduction of Sn-S bonds to Sn-H bonds, to our knowledge, has not been reported. On thermodynamic grounds, the reduction of a Sn-S bond to a Sn-H bond via *silane* reducing agents is calculated to be endothermic by ca. 1 kcal/mol (in contrast, the analogous reduction of Sn-O bonds to Sn-H bonds is calculated to be exothermic by ca. 10 kcal/mol).[55]

We therefore turned our attention to deoxygenation precursors in which X ≠ SMe, and chose to focus instead on the phenyl thionocarbonates (Figure 2.3.1, X = OAr) pioneered by Robins.[51,52] These auxilliaries have numerous advantages over the analogous methyl xanthate derivatives from the standpoints of safety (no CS_2 required), convenience (phenyl chlorothionoformate is commercially available), and reactivity.[56] The tin-containing product now is predicted to be $Bu_3Sn(OPh)$, and a previous report from this group has demonstrated that Sn-O intermediates are indeed efficient precursors to Bu_3SnH in tin-catalyzed, silicon hydride-mediated transformations (see Section 2.2).[57]

We selected PMHS ($TMSO-(SiHMeO)_n-TMS$) as the stoichiometric reductant for our tin-catalyzed Barton-McCombie process, based on the report of Itoi that PMHS can reduce $Bu_3Sn(OPh)$ to Bu_3SnH.[18,19] Furthermore, PMHS possesses the attributes of being non-toxic,[58] easily handled,[59] and inexpensive.[60]

As a test substrate, we chose *O*-cyclododecyl-*O*-phenylthionocarbonate (**2.3.1**, eq 2.3.2) and subjected it to 10 mol % Bu_3SnH and 5 equiv PMHS (AIBN, refluxing benzene). While the stoichiometric deoxygenation proceeds to completion in ≤ 1 h (Table 2.3.1, entry 1), we observed a disappointing 22% yield of cyclododecane after 20

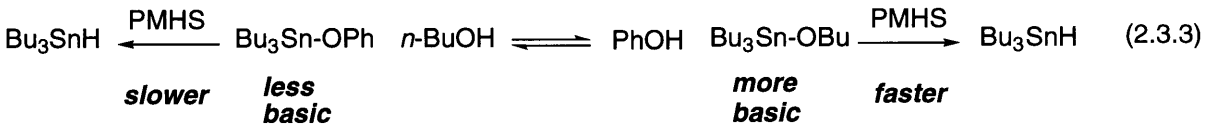
h under catalytic conditions (Table 2.3.1, entry 2).



(2.3.2)

2.3.1

Consistent with an early study by Itoi that $Bu_3Sn(OPh)$ reacts more slowly than $Bu_3Sn(OBu)$ with PMHS,[19] Pereyre reported that the rate of reduction of tin alkoxides depends strongly on the basicity of the alkoxy fragment.[22] Concerned that $Bu_3Sn(OPh)$ was not being turned over rapidly enough to support a catalytic cycle, we proposed that by adding a primary alcohol to the catalytic deoxygenations, the turnover step might be accelerated, and *overall* rate acceleration might be observed (eq 2.3.3).



(2.3.3)

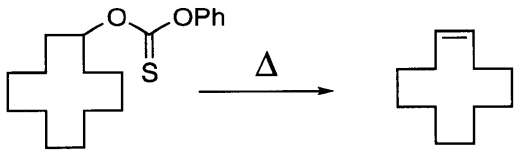
This proposal was borne out by experiment, and treatment of **2.3.1** with 10 mol % Bu_3SnH and 5 equiv PMHS (AIBN, refluxing benzene) in the presence of 2 equiv EtOH afforded a 56% yield of the deoxygenated product after 22 h (Table 2.3.1, entry 3). The background reaction (no Bu_3SnH) was found to proceed ≤6% in the same time period (Table 2.3.1, entry 4). A secondary alcohol additive, however, was found to be inferior to EtOH (Table 2.3.2, entry 5; 45% versus 74%).[61]

Table 2.3.1. Yields in the Deoxygenation of **2.3.1** as a Function of EtOH Additive

entry	tin source (equiv)	PMHS equiv	additive (equiv)	time (h)	yield (%)
1	Bu_3SnH (1.1)	0	none	1	quant
2	Bu_3SnH (0.1)	5	none	20	22
3	Bu_3SnH (0.1)	5	EtOH (2.0)	20	56
4	none	5	EtOH (2.0)	19	≤6

Conditions: radical initiator, C_6H_6, (0.10 M in substrate), 80 °C

Since our proposed catalytic cycle employs only 10 mol % Bu_3SnH, the rate was found to be significantly slower than the stoichiometric version (Table 2.3.1, entry 3 versus entry 1). We were therefore concerned that Chugaev elimination[62] of the thionocarbonates to afford cyclododecene (eq 2.3.4) might become competitive with the desired deoxygenation. In fact, upon heating **2.3.1** to 100 °C in toluene, 9% olefin is observed after 2 h. In order to minimize this side reaction, we selected high concentrations in the subsequent stages of the optimization to favor the desired pathway (bimolecular) over the undesired elimination (unimolecular).



2.3.1

(2.3.4)

Thus, treatment of **2.3.1** with 10 mol % Bu_3SnH and PMHS (10 equiv) in 1/1 EtOH/benzene (2 M), at 100 °C (radical initiator) reproducibly afforded the deoxygenated product in 69-75% yield (Table 2.3.2, entries 2-3). $(Bu_3Sn)_2O$ was found to be interchangeable with Bu_3SnH (Table 2.3.2, entries 3-4; see Section 2.2 for a discussion of $(Bu_3Sn)_2O$ as an efficient source of Bu_3SnH in the presence of silane

and primary alcohol).

Table 2.3.2. Optimization of the Deoxygenation of **2.3.1** as a Function of Solvent and Tin Source

entry	tin source (equiv)	solvent (conc/M)	time (h)	yield (%)
1	none	1/1 EtOH/C_6H_6 (2.0)	1	0
2	Bu_3SnH (0.10)	1/1 EtOH/C_6H_6 (2.0)	7	69
3	Bu_3SnH (0.10)	1/1 EtOH/C_6H_6 (2.0)	5	75
4	$(Bu_3Sn)_2O$ (0.050)	1/1 EtOH/C_6H_6 (2.0)	5	74
5	$(Bu_3Sn)_2O$ (0.050)	1/1 *sec*-butanol/C_6H_6 (2.0)	5	45
6	Bu_3SnH (0.10)	EtOH (0.33)	3	71
7	$(Ph_3Sn)_2O$ (0.050)	1/1 EtOH/C_6H_6 (2.0)	4	70

Conditions: 10 equiv PMHS, radical initiator, 100 °C

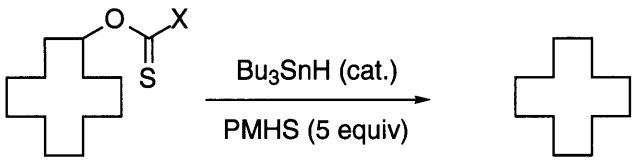
Although these initial results appeared promising, the yields were still inferior to the stoichiometric version (Table 2.3.1, entry 1), so we undertook further optimization. Changing to only EtOH as the solvent, at the maximum concentration which solubility would allow (0.33 M), afforded no improvement, and a yield of 71% was observed (Table 2.3.2, entry 6).

Replacing $(Bu_3Sn)_2O$ with $(Ph_3Sn)_2O$ likewise afforded little or no change in yield, and 70% deoxygenation was observed (Table 2.3.2, entry 7).

We suspected that the problem might be attributable to catalyst decomposition. To test this hypothesis, two catalytic reactions were run side-by-side, and after 1 h, the yields were 61% and 58%. To the first reaction was added an additional 10 mol

% Bu_3SnH, and both catalytic reactions were heated for an additional 4 h. The yields for the two catalytic reactions were now observed to be 78% and 72% respectively. These results suggested that catalyst decomposition is *not* the major problem, although it may be a factor in the less-than-optimal yields.

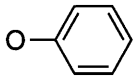
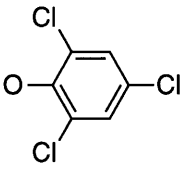
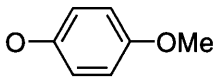
Next, under the assumption that substrate decomposition might be the problem, we explored alternative auxiliaries in the catalytic deoxygenation of cyclododecanol (eq 2.3.5). Thus, an electron-rich and an electron-poor aryl thionocarbonate were prepared. Unfortunately, both were inferior to the unsubstituted aryl ring (Table 2.3.3, entries 1-3). Likewise, when X = imidazole, disappointing results were observed (Table 2.3.3, entry 4).



(2.3.5)

A primary alkyl thionocarbonate (eq 2.3.5, X = OEt) was then prepared in anticipation that the intermediate tin species (Bu_3SnOEt) would rapidly turn over, and the need for primary alcohol additives could be supplanted. This substrate, however, was inferior under *stoichiometric* condtions to **2.3.1** and was not pursued further.

Table 2.3.3. Optimization of the Catalytic Deoxygenation of Cyclododecanol as a Function of the Auxilliary (eq 2.3.5)

Entry	X	Yield (%)
1		77
2		56
3		63
4		40

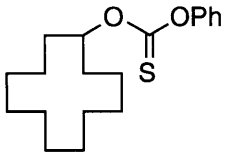
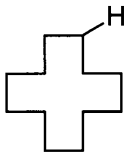
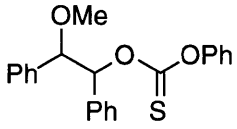
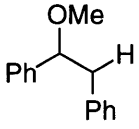
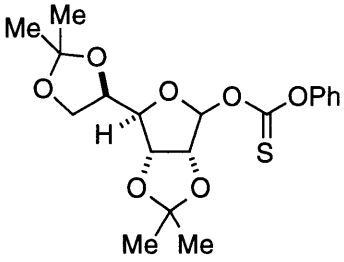
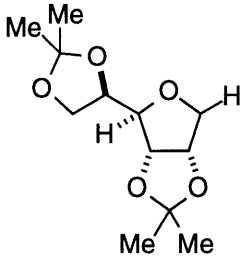
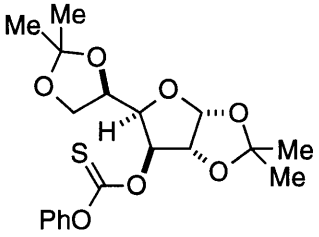
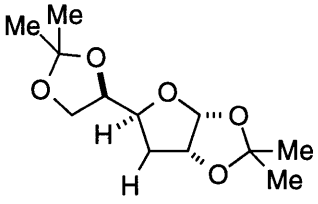
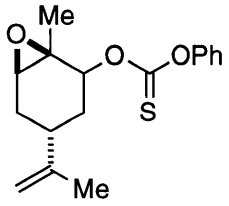
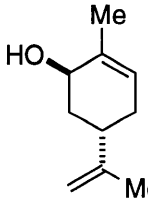
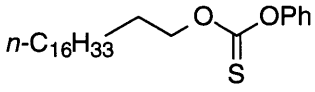
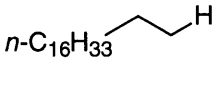
Conditions: 10 mol% Bu_3SnH, 5.0 PMHS, In•, *n*-BuOH, 100°C

At this point, a postdoctoral associate in our lab, Dr. Rosa Lopez took over the project. She performed additional optimization and produced a table of substrates (Table 2.3.4). In addition, she confirmed our hypothesis that $Bu_3Sn(OPh)$ would turnover faster in the presence of primary alcohol additives (eq 2.3.6).[63]

$$\underset{\text{1 equiv}}{Bu_3Sn\text{-}OPh} \quad \underset{\text{excess}}{\text{PMHS dimer}} \quad \xrightarrow[\text{toluene}]{\text{80 °C, 1 h}} \quad Bu_3SnH \qquad (2.3.6)$$

without *n*-BuOH, < 5% conversion
with *n*-BuOH, 43% conversion

Table 2.3.4. Bu_3SnH-Catalyzed Barton-McCombie Deoxygenation of Alcohols (Performed by Dr. Rosa Lopez)

Entry	Substrate	Product	Isolated Yield (%) Catalyzed[a]	Stoichiometric
1			66	68
2			70	65
3			63	72
4			75	79
5			68	61
6			66[b]	68

[a]Average of two runs. [b]12 mol % $(Bu_3Sn)_2O$ was used.

In summary, we have developed a novel Bu_3SnH-catalyzed, PMHS-mediated variant of the Barton-McCombie deoxygenation reaction; the reduction of

Bu_3SnOPh to Bu_3SnH in the presence of *n*-BuOH provides the critical turnover step for the catalytic cycle. Compared with the original procedure, which requires stoichiometric Bu_3SnH, this catalytic process is superior from the standpoints of decreased cost and tin waste, as well as increased ease of product purification.

Experimental

Solvents were distilled from the indicated drying agents: benzene (sodium/benzophenone); THF (sodium/benzophenone); CH_2Cl_2 (calcium hydride); EtOH (Mg^0).

Anhydrous *n*-butanol and pyridine were purchased from Aldrich. Bu_3SnH, $(Bu_3Sn)_2O$, and $(Ph_3Sn)_2O$ were distilled prior to use. PMHS was degassed under vacuum. Other reagents were used as received.

Analytical thin layer chromatography was performed using EM Reagents 0.25 mm silica gel 60 plates, and visualization was accomplished with potassium permanganate, ethanolic phosphomolybdic acid, or 5% H_2SO_4/EtOH. Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh).

^1H (300 MHz), and ^{13}C (75 MHz) nuclear magnetic resonance spectra were recorded on a Varian XL-300 or a Varian Unity 300 NMR spectrometer at ambient temperature. ^1H data are reported as follows: chemical shift in parts per million downfield from $SiMe_4$ (δ scale), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz), and integration. ^{13}C chemical shifts are reported in ppm downfield from $SiMe_4$ (δ scale). All ^{13}C spectra were determined with complete proton decoupling.

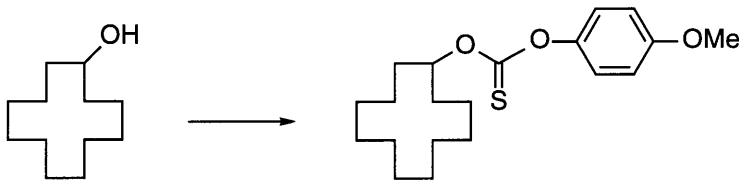
Gas chromatographic analysis was carried out on a Hewlett Packard 5890 Series II instrument using a DB-1 capillary column (J & W Scientific; 30 m length, 0.25 mm inner diameter, 45.5 cm/min helium flow rate).

Infrared spectra were obtained on a Perkin-Elmer Series 1600 FT-IR spectrophotometer (cm^{-1}). High resolution mass spectra were recorded on a Finnegan MAT System 8200 spectrometer.

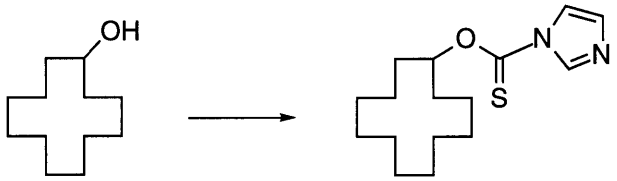
All reactions were prepared under an atmosphere of nitrogen in a Vacuum Atmospheres glove box and run under nitrogen or argon in oven-dried glassware.

O-Cyclododecyl-*O'*-phenylthionocarbonate (**2.3.1**),[56] *O*-cyclododecyl-*O*'(2,4,6-trichlorophenyl)thionocarbonate (Table 2.3.3, entry 2),[56] and carbonochloridothioic acid *O*-(4-methoxyphenyl) ester[64] were prepared by the literature methods.

The experimental details regarding Table 2.3.4 and eq 2.3.6 have been published.[63]

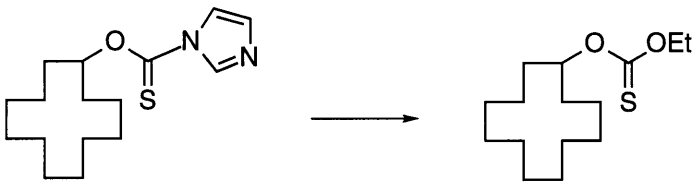


***O*-Cyclododecyl-*O*'(4-methoxyphenyl)thionocarbonate.** This material was prepared according to the general procedure in the literature[56] from cyclododecanol (3.69 g, 20.0 mmol), carbonochloridothioic acid *O*-(4-methoxyphenyl) ester (4.05 g, 20.0 mmol), and pyridine (1.90 g, 24 mmol) in CH_2Cl_2 (40 mL). Flash chromatography, followed by recrystallization (hot hexane) afforded *O*-cyclododecyl-*O*'(4-methoxyphenyl)thionocarbonate as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (dt, 2H, J_1 = 9.5, J_2 = 3.0), 6.91 (dt, 2H, J_1 = 9.5, J_2 = 3.0), 5.50 (m, 1H), 3.81 (s, 3H), 1.87 (m, 2H), 1.78-1.72 (m, 2H), 1.51-1.33 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 157.5, 147.0, 122.7, 114.3, 83.9, 55.5, 28.6, 23.9, 23.7, 23.3, 23.2, 20.9. IR (neat) 2931, 2862, 1597, 1505, 1469, 1444, 1281, 1201, 1179, 1157, 1101, 1037, 997, 830. HRMS: Calcd for $C_{20}H_{30}O_3S$ $[M+H]^+$: 351.1994. Found: 351.1994.



1H-Imidazole-1-carbothioic acid, O-cyclododecyl ester. This material was

prepared according to the general procedure in the literature from cyclododecanol (3.00 g, 16.4 mmol) and thiocarbonyl diimidazole (4.38 g, 25 mmol) in refluxing THF. Flash chromatography, followed by recrystallization (hot hexane) afforded 3.8 g (79%) of the product as white needles. The ^{1}H NMR spectrum was identical to the literature spectrum.[65]



***O*-Cyclododecyl-*O*'(ethyl)thionocarbonate.** To the thiourethane (1.18 g, 4.00 mmol) was added a solution of NaOEt (272 mg, 4.00 mmol) in 15 mL of 1/1 EtOH/CH_3CN. After stirring for 15 min, the reaction was worked up with 2 N HCl and hexane. The organic layers were dried ($MgSO_4$), filtered and concentrated, and the residue was purified by flash chromatography to afford 1.00 g (92%) of *O*-cyclododecyl-*O*'(ethyl)thionocarbonate as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (m, 1H), 4.47, (q, 2H, J = 7.0), 1.83-1.76 (m, 1H), 1.70-1.63 (m, 1H), 1.51-1.31 (m, 23H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 82.0, 68.7, 28.8, 23.8, 23.5, 23.4, 23.2, 21.0, 13.8.. IR (neat) 2933, 2863, 1470, 1446, 1369, 1278, 1235, 1188, 1153, 1070, 1040, 989, 922, 887, 847, 719. HRMS: Calcd for $C_{15}H_{28}O_2S$ $[M+H]^+$: 273.1888. Found: 273.1889.

Discovery and Optimization of the Catalytic Deoxygenation

Tables 2.3.1, 2.3.2, 2.3.3. In a J. Young tube (Wilmad) were placed the thionocarbonate or thiourethane (0.10-0.30 mmol), PMHS, heptadecane (internal GC standard), the tin source, the radical initiator (0.10 equiv; Table 2.2.1 AIBN; Table 2.3.2 and 2.3.3 1,1'-azobis(cyclohexanecarbonitrile), the alcohol additive (if employed), and solvent. The tube was sealed, and the reaction was heated in an oil

bath maintained at the specified temperature for the specified time period. The progress of the reactions was monitored by GC analysis of aliquots removed in the glove box. Yields were determined by integration of the cyclododecane versus the internal standard, and the yield from Table 2.3.1, entry 1 was defined as 100%. The remainder of the yields are normalized to this value.

2.4. References

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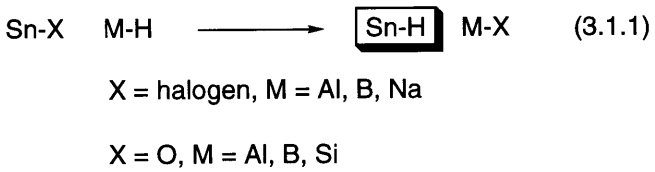
Chapter 3. Development of Organotin Hydride-Catalyzed Processes II. Synthetic Transformations Involving Sn-N Intermediates.

3.1. Introduction

The generation of a tin-hydrogen bond by the reaction between metal hydrides and compounds containing Sn-X bonds (X = halide, O) represents the primary means of synthesizing organotin hydrides (eq 3.1.1).[1] In addition, this transformation has been utilized as the turnover step in a number of catalytic tin hydride reactions of synthetic importance.



(3.1.1)

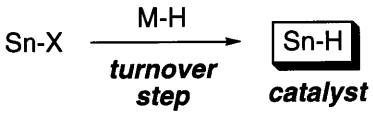
Thus, in tin-catalyzed alkyl halide reductions[2] (Table 3.1.1, entry 1) and alkyl radical cyclizations[3] (Table 3.1.1, entry 2), a borohydride which is employed in stoichiometric quantities reduces a tributyltin halide to the active catalyst (Bu_3SnH) in the turnover step. Furthermore, the polar reduction of carbonyls using catalytic dibutyltin dilaurate[4] or DBATO[5] in conjunction with stoichiometric PMHS (Table 3.1.1, entry 3) is believed to involve the reduction of an intermediate tin alkoxide to a tin hydride by the silane reducing agent in the turnover step.[5]

Work from this group has demonstrated the utility of organotin hydride catalysts in a series of free radical synthetic transformations, all of which require the reduction of a Sn-O bond to a Sn-H bond by means of a silane used in stoichiometric quantities. These include catalytic reductive cyclizations of enals/enones,[6] catalytic conjugate reductions of enones,[7] a catalytic version of the Barton-McCombie deoxygenation,[8] and catalytic reductions of nitroalkanes to alkanes (Table 3.1.1, entry 4).[9]

Encouraged by the success of these catalytic synthetic transformations, we wished to extend the scope of tin catalysis to include reactions involving intermediates in which

the identity of the tin-bound heteroatom is neither halide nor oxygen and decided to explore nitrogen. In order to realize this goal, a metal hydride for reducing *tin amides* to tin hydrides had to be chosen, and a suitable synthetic transformation had to be found (Table 3.1.1, entry 5).

Table 3.1.1. Previous Examples of Tin Hydride-Catalyzed Transformations

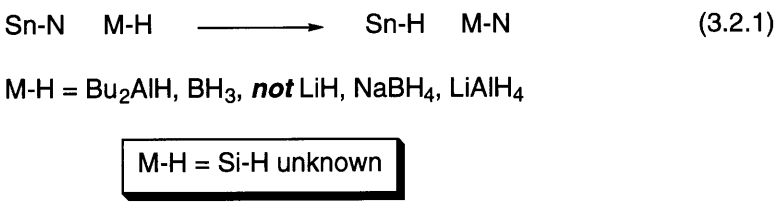


entry	X	M-H	synthetic transformation	
1	Br, I	$NaBH_4$	Radical Dehalogenations	***Corey***
2	I	$NaBH_3CN$	Radical Cyclization	***Stork***
3	O	PMHS	Polar Reductions of Carbonyls	***Nitzsche/Wick Lipowitz***
4	O	Si-H	Reductive Cyclizations of Enals/Enones Conjugate Reductions of Enones Barton-McCombie Deoxygenations Reductions of Nitroalkanes to Alkanes	***Fu***
5	N	*?*	*?*	***Fu??***

3.2. A New Method for Generating Sn-H Bonds: Reactions of Tin Amides with Silicon Hydrides

Background

Although less common than the Sn-Cl and Sn-O analogs, the metal-hydride reduction of Sn-N species to tin hydrides has been reported in the literature. Thus, Kula found that tin amides afforded tin hydrides upon treatment with Bu_2AlH and BH_3, while LiH, $NaBH_4$, and $LiAlH_4$ were unsuccessful (eq 3.2.1).[10] However, if a metal hydride is to be employed as the stoichiometric reducing agent in a tin-catalyzed organic transformation, then it must be unreactive toward sensitive functional groups, a requirement not met by the aforementioned reducing agents. Encouraged by our previous successes with silicon hydride reducing agents in tin-catalyzed transformations involving Sn-O intermediates (Table 3.1.1, entry 4), we chose to investigate their utility in the reduction of tin amides.



Unfortunately, little was known in the literature with respect to this matter. On thermodynamic grounds, the reaction is expected to be exothermic by ca. 9 kcal/mol,[11] (Figure 3.2.1). For comparison, the analogous Sn-O system[12-15] is calculated to be exothermic by 11 kcal/mol.[11] Despite favorable thermodynamics, however, Et_3SiH and Ph_3SiH are known to be unreactive towards tin amides.[16,17]

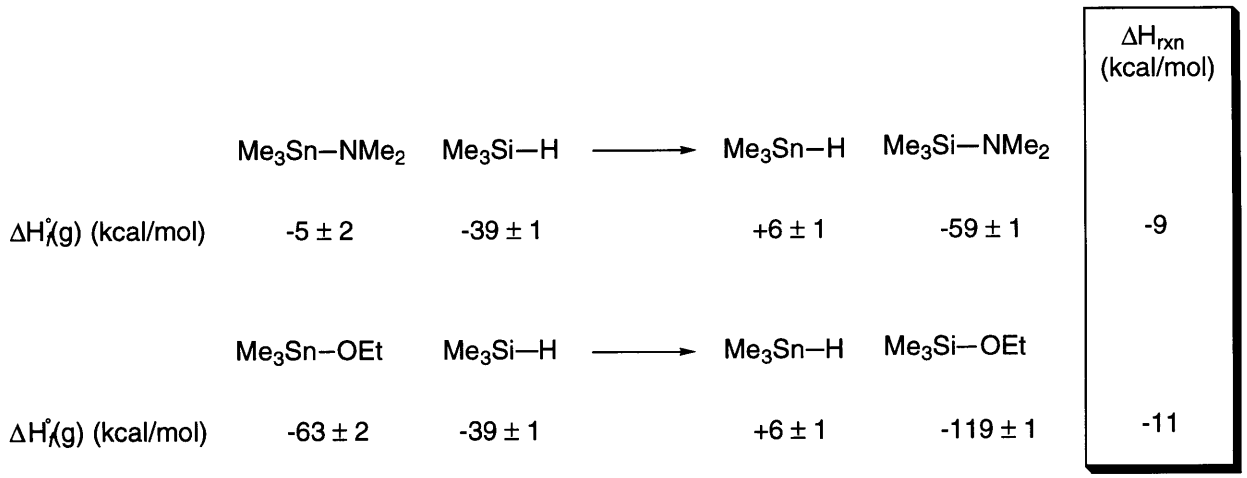


Figure 3.2.1. Calculated reaction enthalpies for the reductions of Me_3SnNMe_2 and Me_3SnOEt to Me_3SnH with Me_3SiH.

One early study by Creemers reports that Et_3SnNEt_2 in the presence of Ph_2SiH_2 or $PhSiH_3$ affords $Et_3SnSnEt_3$, but no experimental details are provided.[18] The intermediacy of Et_3SnH is *postulated* but not directly demonstrated (see below). Thus, prior to our work, the goal of generating useful quantities of tin hydrides from silanes and aminostannanes remained unrealized.

Two modes of reactivity between tin amides and Group 14 M-H species have been established and, *a priori*, either seemed equally plausible (Figure 3.2.2). In the first mode, the M-H can serve as a "proton donor" and liberate the free amine plus a new M-Sn bond. Such reactivity has been demonstrated for M = Ge[19] and Sn.[20]

Alternatively, the group 14 M-H can behave as a "hydride donor" and provide a tin hydride plus a new M-N bond, as desired. This latter mode of reactivity has also been observed in limited cases when M = Ge[19] or Sn.[21]

Figure 3.2.2. Two documented modes of reactivity between tin amides and group 14 M-H species.

Results and Discussion

We found that by reacting Bu_3SnNMe_2 with a series of silicon hydrides in benzene at 25°C or 80°C, Bu_3SnH is indeed observed in varying yields (Table 3.2.1). Consistent with previous reports, Et_3SiH and Ph_3SiH do not react with Bu_3SnNMe_2, even at elevated temperatures.[16,17] In contrast, PMHS dimer, PMHS, Et_2SiH_2, $OctSiH_3$, Ph_2SiH_2, and $PhSiH_3$ react with Bu_3SnNMe_2 to afford Bu_3SnH with varying degrees of effectiveness.

The other tin-containing product ($Bu_3SnSnBu_3$) is formed by the well-precedented hydrostannolysis of Bu_3SnNMe_2.[20] Thus, in the case of the most reactive silane ($PhSiH_3$), the desired process (eq 3.2.2, Sn-H bond formation) is much faster than the undesired reaction (eq 3.2.2, Sn-Sn bond formation), and Bu_3SnH is observed as the predominant tin-containing product. However, with less reactive silanes, the undesired pathway becomes competitive with the desired process. Thus, Et_2SiH_2 and the PMHS derivatives (Table 3.2.1, entries 3-6) afford $Bu_3SnSnBu_3$ as the exclusive tin-containing product.

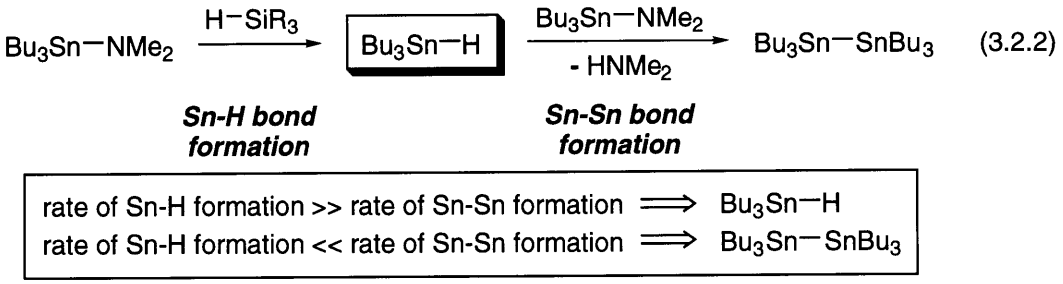


Table 3.2.1. Reaction of Bu_3SnNMe_2 with Silicon Hydrides in Benzene

entry	silane	equiv	temp (°C)	$t_{1/2}$ (min)	yield of Bu_3SnH (%)	yield of $Bu_3SnSnBu_3$ (%)
1	**Et_3SiH**	1.5	80	no reaction after 28 hours	0	0
2	**Ph_3SiH**	1.5	80	no reaction after 28 hours	0	0
3	**PMHS Dimer**	0.50	80	260	0	90
4	**PMHS**	1 H-equiv	80	89	0	96
5	**Et_2SiH_2**	0.50	80	48	0	90
6		1.0	80	21	0	90
7	**$OctSiH_3$**	0.33	25	47	1	90
8		1.0	25	17	21	73
9		5.0	25		60	35
10	**Ph_2SiH_2**	0.5	25	6.4	0	90
11		1.0	25	2.5	58	40
12		5.0	25		89	3
13	**$PhSiH_3$**	0.33	25	2.9	35	61
14		1.0	25	~ 1	83	14
15		5.0	25	< 1	99	

The rate of the desired reaction can be enhanced by simply adding more silane, and when 5 equiv of $PhSiH_3$ are employed (Table 3.2.1, entry 15), a quantitative yield of Bu_3SnH is obtained. This situation (lots of silane, little tin) mimics the conditions in a catalytic reaction, thus favoring the formation of Sn-H over Sn-Sn.

By comparing the $t_{1/2}$ values for the loss of Bu_3SnNMe_2, the following order of

silane reactivity is obtained:

$$PhSiH_3 > Ph_2SiH_2 > OctSiH_3 > Et_2SiH_2 > PMHS > \text{"PMHS Dimer"}$$

Consistent with earlier reports, reactions of Bu_3SnNMe_2 with Ph_2SiHCl and $PhSiHCl_2$ afford Bu_3SnCl immediately at room temperature, and no Bu_3SnH is observed.[22]

The amine-catalyzed dehydrogenative coupling of tin hydrides to afford Sn-Sn bonds is a well-precedented reaction[23] and could be the source of $Bu_3SnSnBu_3$ in our system (eq 3.2.3). However, this process is found *not* to be operative under our conditions to a significant extent as determined by integration in the ^1H NMR spectra. Thus, at the end of the reactions, one equivalent of amine is present for every one equivalent of $Bu_3SnSnBu_3$.

$$\begin{matrix} Bu_3Sn{-}H \\ Bu_3Sn{-}H \end{matrix} \xrightarrow{R_3N\ (cat.)} \begin{matrix} SnBu_3 \\ | \\ SnBu_3 \end{matrix} \quad H_2 \qquad (3.2.3)$$

$PhSiH_3$ and $OctSiH_3$ potentially bear three reactive hydrides per silicon, whereas Ph_2SiH_2 and Et_2SiH_2 contain two potentially reactive hydrides per silicon. In practice, however, complete replacement of hydride by nitrogen in these reagents is never observed.

Thus, $PhSiH_3$ was found to react with Bu_3SnNMe_2 as shown in Figure 3.2.3. In the first step, $PhSiH_3$ reacts with Bu_3SnNMe_2 to afford Bu_3SnH and $PhSiH_2NMe_2$ (Figure 3.2.3, eq 1). The second step then proceeds at a *faster* rate than the first step, i.e. by replacement of one hydride on $PhSiH_3$ by nitrogen, *enhancement* of the donating ability

of the remaining hydrides is observed (Figure 3.2.3, eq 2). This observation can be attributed to a beneficial electronic effect imparted by the nitrogen substituent. However, the third reaction is *never* observed under any reaction conditions which we evaluated (Figure 3.2.3, eq 3). Replacing all three hydrides on $PhSiH_3$ by nitrogen, therefore, is presumably prevented on steric grounds.

Reactions 1 and 2 (Figure 3.2.3) constitute a set of competitive consecutive second-order reactions. McMillan has analyzed this situation mathematically and has expressed the ratio of k_2 to k_1 as an implicit function of any two simultaneous concentrations.[24] Thus, by reacting $PhSiH_3$ with Bu_3SnNMe_2 under conditions in which reaction 4 can be neglected, the final concentrations of $PhSiH_3$ and $PhSiH_2NMe_2$ can be used to determine a value for k_2/k_1. (Control experiments demonstrate that no disproportionation of the aminosilanes occurs under our conditions.) In practice, this is achieved by using a large excess of $PhSiH_3$ (ca. 10 equiv) such that no $HNMe_2$ (and hence, no reaction 4) is observed. In this manner, k_2/k_1 was found to be 4/1.

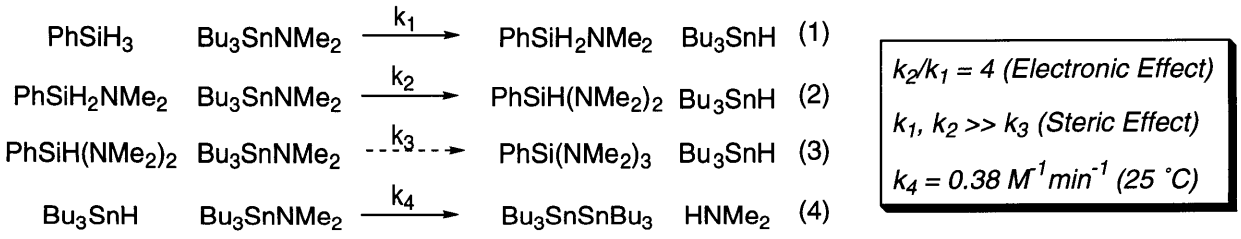


Figure 3.2.3. Kinetic analysis of the reaction between $PhSiH_3$ and Bu_3SnNMe_2.

Reaction 4 is observed to be second order overall (first order in Bu_3SnH and Bu_3SnNMe_2) with a rate constant of 0.38 $M^{-1}min^{-1}$ at 25 °C in benzene.[18] An alternative method for investigating the *absolute* values for k_1 and k_2 is to consider reaction 4 as an internal clock with a known rate constant. A kinetic simulation of the reaction between Bu_3SnNMe_2 and $PhSiH_3$ (Table 3.2.1, entry 14) using the software package HopKINSIM

(Figure 3.2.4) afforded values of 1.6 and 4.9 $M^{-1}min^{-1}$, respectively, for k_1 and k_2 (k_2/k_1 = 3/1).

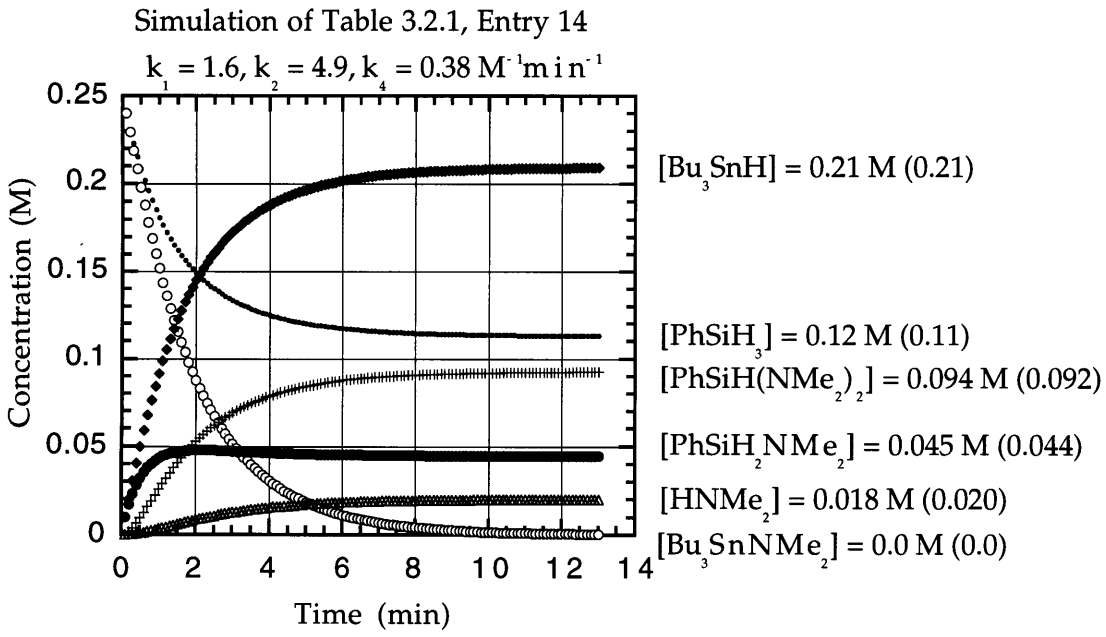
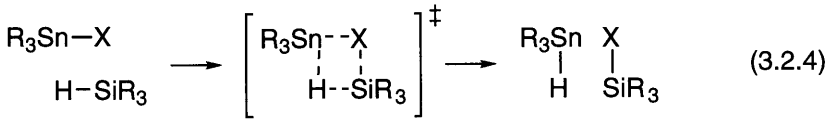


Figure 3.2.4. Kinetic simulation of the reaction between $PhSiH_3$ and Bu_3SnNMe_2 (Table 3.2.1, entry 14). Concentrations to the right of the graph are the final observed values, followed by the simulated values in parentheses.

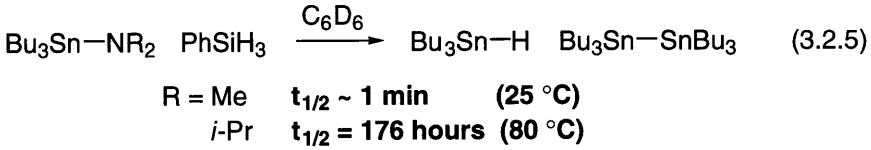
Similar behavior is exhibited by $OctSiH_3$ (i.e., $k_2 > k_1 >> k_3$), but an actual value for k_2/k_1 is experimentally difficult to obtain according to the method of McMillan since reaction 4 cannot be neglected in the case of this less reactive silane. Ph_2SiH_2 and Et_2SiH_2 likewise demonstrate less than exhaustive replacement of hydride by nitrogen, and $Ph_2SiHNMe_2$ and $Et_2SiHNMe_2$ are the only silicon-containing products observed.

Previous mechanistic studies on the silicon hydride mediated reduction of Sn-O bonds to Sn-H bonds have reported pronounced effects on the reaction rates as a function of the steric and electronic components of the alkoxy fragment.[25] We have

observed identical behavior in the Sn-N to Sn-H system, and by varying the amide fragment, the effects of sterics and basicity were probed. Thus, bulky $Bu_3SnNiPr_2$ reacts with $PhSiH_3$ with a $t_{1/2}$ of 176 h at 80°C as compared to <1.2 min for Bu_3SnNMe_2 at 25°C (eq 3.2.5). Furthermore, the rate is highly dependent on the basicity of the amide fragment: $Bu_3SnN(Me)Ph$ reacts with a $t_{1/2}$ of 153 h whereas $Bu_3SnN(Me)(p\text{-}C_6H_4\text{-}OMe)$ reacts with a $t_{1/2}$ of 24 h at 80°C (eq 3.2.6). Thus, in direct analogy with the tin alkoxide counterpart,[25] we propose a four-centered transition state mechanism (eq 3.2.4).

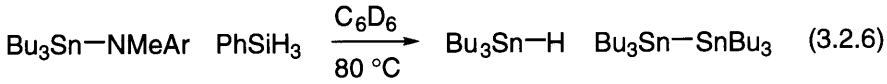


(3.2.4)



(3.2.5)

R = Me $t_{1/2}$ ~ 1 min (25 °C)
i-Pr $t_{1/2}$ = 176 hours (80 °C)



(3.2.6)

Ar = p-OMe-C_6H_4 $t_{1/2}$ = 24 hours
Ph $t_{1/2}$ = 153 hours

Bu_3Sn-pyrrole and Bu_3SnNPh_2 proved entirely unreactive towards $PhSiH_3$ under our conditions, presumably due to unfavorable electronic characteristics.

In the reaction between $Bu_3SnNMePh$ and $PhSiH_3$, an additional tin-containing product ($Bu_3Sn\text{-}SiH_2Ph$) is observed in yields ranging from 3-12% (eq 3.2.7). Three mechanisms for its formation can be envisioned.

The first mechanism (eq 3.2.8) can be ruled out by the following experiment: $Bu_3SnNMePh$ (1 equiv) is mixed with $PhSiH_3$ (2 equiv) in a sealed tube, and the mixture is heated to 100°C. After 33 h, no $Bu_3SnNMePh$ remains, and the $Bu_3Sn\text{-}SiH_2Ph$ comprises ca. 1% of the total silane. After an additional 45 h of heating, the Bu_3Sn-

SiH_2Ph has grown in to comprise ca. 16% of the total silane. Therefore, $Bu_3SnNMePh$ cannot be involved in the formation of the Sn-Si bond. We currently have no data to distinguish between the second two mechanisms (eq 3.2.9, 3.2.10).

$Bu_3SnNMePh$	$PhSiH_3$	⟶	$Bu_3SnNMePh$	Bu_3SnH	$Bu_3SnSnBu_3$	Bu_3SnSiH_2Ph	(3.2.7)
200 μmol	200 μmol		17 μmol (8.5%)	129 μmol (65%)	48 μmol (24%)	6 μmol (3%)	

$Bu_3SnNMePh$	$PhSiH_3$	⟶	Bu_3SnSiH_2Ph	HNMePh (3.2.8)
Bu_3SnH	$PhSiH_3$	⟶	Bu_3SnSiH_2Ph	H_2 (3.2.9)
Bu_3SnH	$PhSiH_2NMePh$	⟶	Bu_3SnSiH_2Ph	HNMePh (3.2.10)

In summary, we have demonstrated that aminostannanes afford tin hydrides upon treatment with suitably reactive silicon hydrides. In the presence of an excess of $PhSiH_3$, Bu_3SnNMe_2 is converted to Bu_3SnH in quantitative yield.

Experimental

General

The following compounds were used without purification: LDA (Aldrich, 97%); $LiNMe_2$ (Aldrich, 95%); $PhSiCl_3$ (Aldrich); $OctSiCl_3$ (Aldrich); $HNMe_2$ (Aldrich, 2.0 M in THF); hexamethylbenzene (Aldrich); $Bu_3SnSnBu_3$ (Aldrich); Bu_3SnCl (Aldrich); Ph_3SiH (United Chemical Technologies).

The following compounds were distilled prior to use: Et_3SiH (Aldrich); *n*-butyl methyl ether (Aldrich; from NaK/benzophenone); *N*-methylaniline (Aldrich; from CaH_2); *N*-methyl-*p*-anisidine (Aldrich; from CaH_2); NEt_3 (Aldrich; from CaH_2); $HN(i\text{-}Pr)_2$ (Aldrich; from CaH_2); Ph_2SiH_2 (PCR); Et_2SiH_2 (PCR); $OctSiH_3$ (United Chemical Technologies); Ph_2SiCl_2 (United Chemical Technologies); Ph_2SiHCl (United Chemical Technologies); $PhSiH_3$ (Fluka); 1,3-bis(trimethylsiloxy)-1,3-dimethyldisiloxane (Gelest); Bu_3SnH (Gelest); Bu_3SnNMe_2 (Gelest).

All chlorosilanes that were not obtained from commercial vendors were prepared by the method of Ishikawa.[26]

Bu_3Sn-pyrrole[27] and Bu_3SnNPh_2[28] were prepared by the literature methods.

Solvents were distilled from the indicated drying agents: benzene (sodium/benzophenone); toluene (molten sodium); THF (sodium/benzophenone); Et_2O (sodium/benzophenone); C_6D_6 (NaK/benzophenone).

^1H, ^{13}C, ^{119}Sn, and ^{29}Si nuclear magnetic resonance spectra for characterization purposes were recorded on Varian XL-300 or Unity-300 NMR spectrometers at ambient temperature. ^1H NMR data from kinetic runs were recorded on a Varian Unity-300 NMR spectrometer by collecting one transient per data point. The probe temperature was calibrated with neat ethylene glycol to within ±2 °C. ^1H 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, and coupling constant (Hz). ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). All ^{13}C spectra were determined with complete proton decoupling. ^{119}Sn chemical shifts are reported in ppm downfield from $SnMe_4$ (neat, external reference, δ scale) and were determined with pulse intervals of 25 s. Broad band ^1H NMR decoupling was only applied during acquisition. ^{29}Si chemical shifts are reported in ppm downfield from tetramethylsilane (external reference in C_6D_6, δ scale) and were determined with pulse intervals of 25 s. Broad band ^1H NMR decoupling, when employed, was only applied during acquisition. Coupling constants between all nuclei are reported in Hz.

High resolution mass spectra were recorded on a Finnegan MAT System 8200 spectrometer (EI at 70 eV).

All reactions were carried out under an atmosphere of nitrogen in a Vacuum Atmospheres glove box or under an atmosphere of argon using standard Schlenk techniques.

Preparation of Tin Amides

1,1,1-Tributyl-*N*-methyl-*N*-phenylstannanamine. To a flask containing dimethylaminotri-*n*-butyltin (15.0 g, 45.0 mmol) was added N-methylaniline (7.8 g, 73 mmol). The reaction was stirred under vacuum for 24 h, then fractionally distilled to afford 1,1,1-tributyl-*N*-methyl-*N*-phenylstannanamine as a clear, colorless oil (140-142 °C/70 mtorr). ^1H NMR (300 MHz, C_6D_6) δ 7.33-7.28 (m, 2H), 6.80-6.74 (m, 3H), 2.89 (s,

3H), 1.57-1.47 (m, 6H), 1.27 (sextet, 6H, J = 7.5), 1.12-1.07 (m, 6H), 0.89 (t, 9H, J = 7.2). ^{13}C NMR (75 MHz, C_6D_6) δ 156.1, 129.7, 115.9, 114.7, 37.5, 29.0, 27.9, 14.3, 14.2. ^{119}Sn (111.9 MHz, C_6D_6) δ 48.4.

Bu_3SnNMe_2 $HNMe(p\text{-}C_6H_4\text{-}OMe)$ ⟶ $Bu_3SnNMe(p\text{-}C_6H_4\text{-}OMe)$

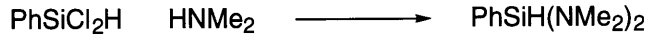
1,1,1-Tributyl-*N*-(4-methoxyphenyl)-*N*-methylstannanamine. To a solution of dimethylaminotri-*n*-butyltin (14 g, 42 mmol) in pentane (10 mL) was added *N*-methyl-*p*-anisidine (6.9 g, 50 mmol). The reaction was stirred under vacuum for 15 h, then fractionally distilled to afford 1,1,1-tributyl-*N*-(4-methoxyphenyl)-*N*-methylstannanamine as a yellow oil (145-155 °C/70 mtorr). ^1H NMR (300 MHz, C_6D_6) δ 6.99-6.93 (m, 2H), 6.74-6.68 (m, 2H), 3.46 (s, 3H), 2.94 (s, 3H), 1.60-1.49 (m, 6H), 1.29 (sextet, 6H, J = 7.3), 1.13-1.08 (m, 6H), 0.87 (t, 9H, J = 7.2). ^{13}C NMR (75 MHz, C_6D_6) δ 151.8, 150.5, 115.6, 115.5, 55.9, 38.1, 29.1, 27.8, 14.2, 14.1. ^{119}Sn (111.9 MHz, C_6D_6) δ 46.9.

Bu_3SnCl $LiN(i\text{-}Pr)_2$ ⟶ $Bu_3SnN(i\text{-}Pr)_2$

1,1,1-Tributyl-*N*,*N*-bis(1-methylethyl)stannanamine. To lithium diisopropylamide (6.07 g, 56.7 mmol) in Et_2O (40 mL) at 0 °C was added Bu_3SnCl (19.4 g, 59.5 mmol). The reaction was allowed to warm to rt, and the LiCl was removed by filtration under N_2. The filtrate was concentrated, and the residue was fractionally distilled to afford 1,1,1-tributyl-*N*,*N*-bis(1-methylethyl)stannanamine as a clear, colorless oil (103 °C/70 mtorr). ^1H NMR (300 MHz, C_6D_6) δ 3.27 (sept, 2H, J = 6.6), 1.68-1.58 (m, 6H), 1.40 (sextet, 6H, J = 7.2), 1.16 (d, 12H, J = 6.6), 1.08-1.02 (m, 6H), 0.95 (t, 9H, J = 7.4). ^{13}C NMR (75 MHz, C_6D_6) δ 50.1, 29.6, 28.2, 27.2, 14.8, 14.3. ^{119}Sn (111.9 MHz, C_6D_6) δ 24.0.

Independent Preparation of Reaction Products

For the authentic reaction products prepared in this section, spectroscopic data were obtained on the unpurified products; consequently, in certain instances definitive assignments of all resonances could not be made (compounds with partial peak listings are specifically noted).

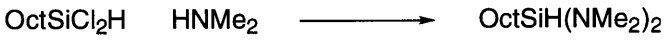


***N,N,N′,N′*-Tetramethyl-1-phenylsilanediamine.** To a solution of $PhSiCl_2H$ (531 mg, 3.00 mmol) in THF (2 mL) was added a 2.0 M solution of dimethylamine in THF (12 mL, 24 mmol). After stirring for 24 h, the reaction was filtered and concentrated to afford *N,N,N′,N′*-tetramethyl-1-phenylsilanediamine as a yellow oil. ^1H NMR (300 MHz, C_6D_6) δ 7.65-7.61 (m, 2H), 7.25-7.23 (m, 3H), 5.08 (s, 1H), 2.51 (s, 12H). ^{13}C NMR (75 MHz, C_6D_6) δ 137.1, 135.2, 130.3, 128.6, 38.2.

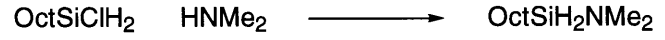
***N,N,N′,N′,N″,N″*-Hexamethyl-1-phenylsilanetriamine.** To $LiNMe_2$ (153 mg, 3.00 mmol) in Et_2O (2 mL) was added $PhSiCl_3$ (212 mg, 1.00 mmol). After stirring for 26 h, the reaction was filtered and concentrated to afford *N,N,N′,N′,N″,N″*-hexamethyl-1-phenylsilanetriamine as a clear, yellow oil. ^1H NMR (300 MHz, C_6D_6) δ 7.71-7.68 (m, 2H), 7.30-7.23 (m, 3H), 2.54 (s, 18H).

***N,N*-Dimethyl-1-phenylsilanamine.** To a solution of $PhSiClH_2$ (428 mg, 3.00 mmol) in THF (3 mL) was added a 2.0 M solution of dimethylamine in THF (4.5 mL, 9.0 mmol).

After stirring for 1 h, the reaction was filtered and concentrated to afford *N,N*-dimethyl-1-phenylsilanamine as a pale yellow oil. Partial spectroscopic data: ^{1}H NMR (300 MHz, C_6D_6) δ 7.59-7.56 (m, 2H), 7.21-7.18 (m, 3H), 5.08 (s, 2H), 2.43 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 135.4, 130.6, 128.7, 39.9.



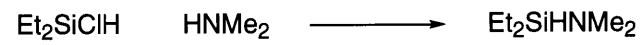
***N,N,N′,N′*-Tetramethyl-1-octylsilanediamine.** To a solution of $OctSiCl_2H$ in THF was added an excess of dimethylamine as a 2.0 M solution in THF. After stirring for 1 h, the reaction was filtered and concentrated to afford *N,N,N′,N′*-tetramethyl-1-octylsilanediamine as a pale yellow oil. ^{1}H NMR (300 MHz, C_6D_6) δ 4.62 (t, 1H, J = 2.1), 2.51 (s, 12H), 1.50-1.29 (m, 12H), 0.91 (t, 3H, J = 6.8), 0.72 (td, 2H, J_1 = 8.1, J_2 = 2.3). ^{13}C NMR (75 MHz, C_6D_6) δ 38.3, 34.1, 32.7, 30.2, 30.1, 24.1, 23.5, 14.7, 13.9.



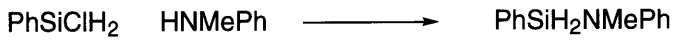
***N,N*-Dimethyl-1-octylsilanamine.** To a solution of $OctSiClH_2$ (536 mg, 3.00 mmol) in THF (5 mL) was added a 2.0 M solution of dimethylamine in THF (4.5 mL, 9.0 mmol). After stirring for 24 h, the reaction was filtered and concentrated to afford *N,N*-dimethyl-1-octylsilanamine as a pale yellow oil. ^{1}H NMR (300 MHz, C_6D_6) δ 4.62 (t, 2H, J = 3.0), 2.44 (s, 6H), 1.47-1.27 (m, 12H), 0.91 (t, 3H, J = 6.8), 0.74-0.67 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 40.0, 33.7, 32.7, 30.2, 30.1, 24.7, 23.5, 14.7, 13.5.

***N,N*-Dimethyl-1,1-diphenylsilanamine.** To a solution of Ph_2SiClH (656 mg, 3.00 mmol) in THF (5 mL) was added a 2.0 M solution of dimethylamine in THF (4.5 mL, 9.0 mmol). After stirring for 24 h, the reaction was filtered and concentrated to afford *N,N*-

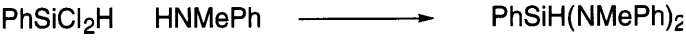
dimethyl-1,1-diphenylsilanamine as a pale yellow oil. ^{1}H NMR (300 MHz, C_6D_6) δ 7.66-7.60 (m, 4H), 7.23-7.16 (m, 6H), 5.53 (s, 1H), 2.52 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 135.8, 130.5, 128.7, 39.5.



1,1-Diethyl-*N,N*-dimethylsilanamine. To a solution of Et_2SiClH (491 mg, 4.00 mmol) in THF (5 mL) was added a 2.0 M solution of dimethylamine in THF (6.0 mL, 12 mmol). The reaction was filtered under argon, and the solvent was removed by distillation under argon at atmospheric pressure to afford 1,1-diethyl-*N,N*-dimethylsilanamine as a yellow oil. ^{1}H NMR (300 MHz, C_6D_6) δ 4.42 (pent, 1H, J = 2.7), 2.45 (s, 6H), 1.00 (td, 6H, J_1 = 7.9, J_2 = 1.9), 0.65-0.56 (m, 4H). ^{13}C NMR (75 MHz, C_6D_6) δ 39.4, 8.1, 5.6.

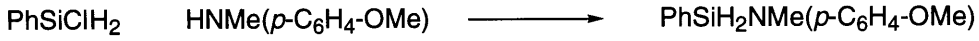


***N*-Methyl-*N*-phenyl-1-phenylsilanamine.** To a solution of HNMePh (321 mg, 3.00 mmol) in hexane was added $PhSiClH_2$ (428 mg, 3.00 mmol) and Et_3N (760 mg, 7.50 mmol). After stirring for 40 h, the mixture was filtered and concentrated to afford *N*-methyl-*N*-phenyl-1-phenylsilanamine as a cloudy oil. ^{1}H NMR (300 MHz, C_6D_6) δ 7.49-7.46 (m, 2H), 7.14-7.10 (m, 5H), 6.95-6.92 (m, 2H), 6.82-6.77 (m, 1H), 5.26 (s, 2H), 2.73 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 150.4, 135.0, 133.2, 130.9, 129.7, 128.9, 119.5, 116.4, 36.8.

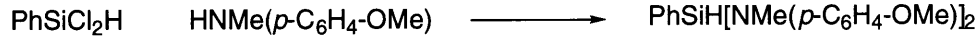


Bis(*N*-methyl-*N*-phenyl)-1-phenylsilanediamine. To a solution of HNMePh (643 mg, 6.00 mmol) in hexane was added $PhSiCl_2H$ (531 mg, 3.00 mmol) and Et_3N (1.52 g, 15.0 mmol). After heating to reflux for 24 h, the reaction was filtered and concentrated

to afford bis(*N*-methyl-*N*-phenyl)-1-phenylsilanediamine as a cloudy oil. Partial spectroscopic data: ^{1}H NMR (300 MHz, C_6D_6) δ 5.82 (s, 1H), 2,70 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 150.1, 135.4, 131.1, 129.7, 129.1, 120.1, 117.0, 34.4.



***N*-(4-Methoxyphenyl)-*N*-methyl-1-phenylsilanamine.** To a solution of HNMe(*p*-C_6H_4-OMe) (274 mg, 2.00 mmol) in hexane (5 mL) was added Et_3N (506 mg, 5.00 mmol) and $PhSiClH_2$ (285 mg, 2.00 mmol). After stirring for 1 h, the reaction was filtered and concentrated to afford *N*-(4-methoxyphenyl)-*N*-methyl-1-phenylsilanamine as a clear, colorless oil. ^{1}H NMR (300 MHz, C_6D_6) δ 7.54-7.50 (m, 2H), 7.16-7.11 (m, 3H), 6.88 (dt, 2H, J_1 = 9.3, J_2 = 2.4), 6.76 (dt, 2H, J_1 = 9.3, J_2 = 2.7), 5.30 (s, 2H), 3.34 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 154.2, 144.2, 135.1, 133.7, 130.8, 128.9, 118.1, 115.3, 55.6, 37.4.



Bis(*N*-(4-methoxyphenyl)-*N*-methyl)-1-phenylsilanediamine. To a solution of HNMe(*p*-C_6H_4-OMe) (137 mg, 1.00 mmol) in hexane was added Et_3N (253 mg, 2.50 mmol) and $PhSiCl_2H$ (88.6 mg, 0.500 mmol). After stirring for 15 h, the reaction was filtered and concentrated to afford bis(*N*-(4-methoxyphenyl)-*N*-methyl)-1-phenylsilanediamine as a cloudy oil. Partial spectroscopic data: ^{1}H NMR (300 MHz, C_6D_6) δ 7.59-7.56 (m, 2H), 7.19-7.16 (m, 3H), 6.97-6.94 (m, 4H), 6.80-6.76 (m, 4H), 5.78 (s, 1H), 3.34 (s, 6H), 2.77 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 154.6, 144.0, 135.6, 130.9, 129.0, 119.1, 115.3, 55.5, 35.2.

***N,N*-Bis(1-methylethyl)-1-phenylsilanamine.** To a solution of HN(*i*-Pr)$_2$ (760 mg,

7.50 mmol) in hexane was added $PhSiClH_2$ (428 mg, 3.00 mmol). After stirring for 54 h, the reaction was filtered and concentrated to afford *N*,*N*-bis(1-methylethyl)-1-phenylsilanamine. ^1H NMR (300 MHz, C_6D_6) δ 7.70-7.67 (m, 2H), 7.24-7.19 (m, 3H), 5.19 (s, 2H), 3.07 (sept, 2H, *J* = 6.7), 1.07 (d, 12H, *J* = 6.6). ^{13}C NMR (75 MHz, C_6D_6) δ 137.2, 135.3, 130.2, 128.6, 48.2, 24.8.

Reactions of Bu_3SnNMe_2 with Silicon Hydrides

General. All manipulations were performed under a nitrogen atmosphere in a Vacuum Atmospheres glove box. All reactions were run in duplicate.

To a J. Young tube (Wilmad) containing Bu_3SnNMe_2 (66.8 mg, 0.200 mmol) was added a 0.250 M solution of *n*-butyl methyl ether (internal standard) in C_6D_6 (800 μL), and an initial ^1H NMR spectrum was recorded. The silane was then added (t = 0), and the tube was immediately placed in the NMR probe, which was maintained at 25 °C (calibrated with neat ethylene glycol).

For $OctSiH_3$, $PhSiH_3$, and Ph_2SiH_2, the first data points were collected at t ~ 2.5 min. The progress of the reaction was monitored by ^1H NMR (integration versus *n*-butyl methyl ether) until ≤2% of the Bu_3SnNMe_2 remained.

For Et_2SiH_2 and 1,3-bis(trimethylsiloxy)-1,3-dimethyldisiloxane, and PMHS, the reactions were heated in an oil bath maintained at 80±2°C and monitored by ^1H NMR at regular intervals at 25°C until ≤4% of the original Bu_3SnNMe_2 remained.

At the conclusion of each reaction, a ^{13}C and a ^{119}Sn NMR spectrum were recorded, and all peaks were identified by comparison with authentic materials, which were purchased or prepared independently (see above). Yields were determined by integration versus the internal standard in the ^1H NMR spectra.

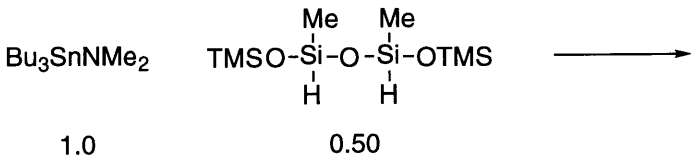
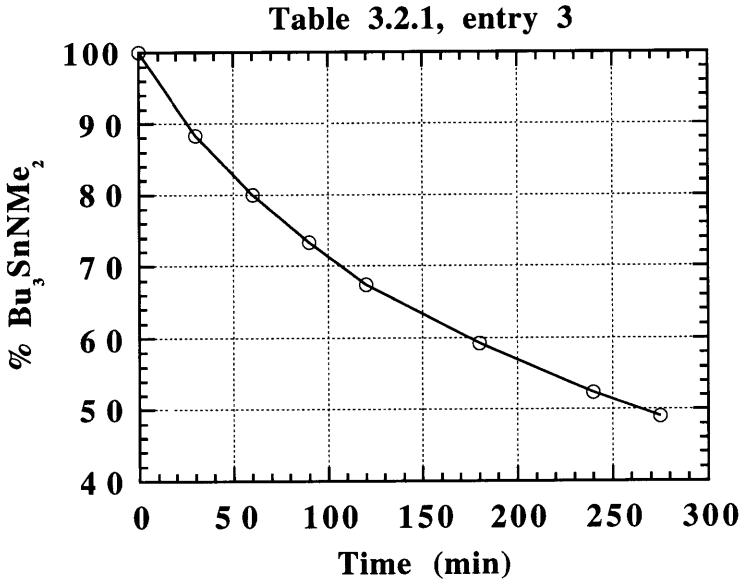


Table 3.2.1, entry 3. The aminostannane was allowed to react with 1,3-bis(trimethylsiloxy)-1,3-dimethyldisiloxane (28.3 mg, 0.100 mmol) and was consumed with a $t_{1/2}$ of 260 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	ΣSi-H	ΣSi-NMe_2	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
7	110	91	<2	90	200	190	190
3	95	96	<2	84	190	170	180



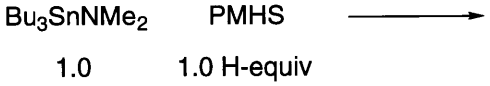
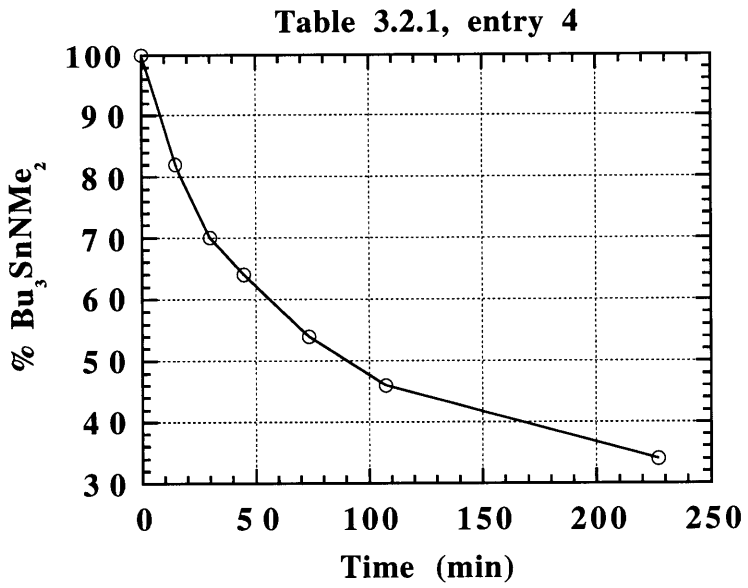


Table 3.2.1, entry 4. The aminostannane was allowed to react with PMHS (12 mg, 0.200 mmol of hydride) and was consumed with a $t_{1/2}$ of 89 min. The only tin-containing product was found to be $Bu_3SnSnBu_3$ in a 96% yield.

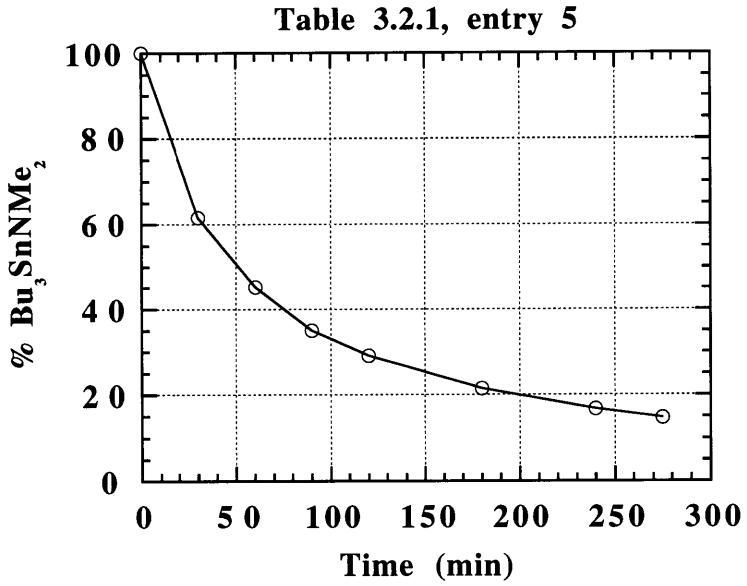


Bu_3SnNMe_2 Et_2SiH_2 ⟶

1.0 0.50

Table 3.2.1, entry 5. The aminostannane was allowed to react with Et_2SiH_2 (8.8 mg, 0.10 mmol) and was consumed with a $t_{1/2}$ of 48 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	Et_2SiH_2	$Et_2SiHNMe_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
5	5	93	<2	89	98	180	190
5	6	93	<2	89	99	180	190

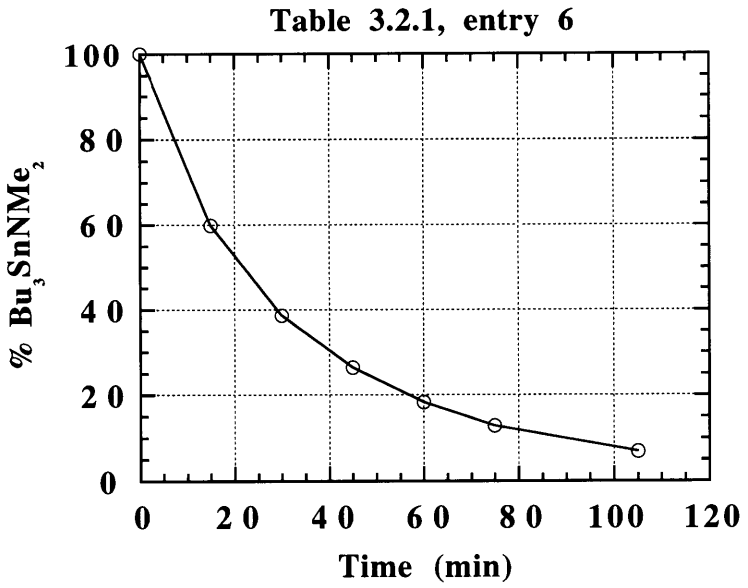


Bu_3SnNMe_2 Et_2SiH_2 ⟶

1.0 1.0

Table 3.2.1, entry 6. The aminostannane was allowed to react with Et_2SiH_2 (17.6 mg, 0.200 mmol) and was consumed with a $t_{1/2}$ of 21 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	Et_2SiH_2	$Et_2SiHNMe_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
<2	82	97	<2	91	180	180	190
<2	100	97	<2	92	200	180	190

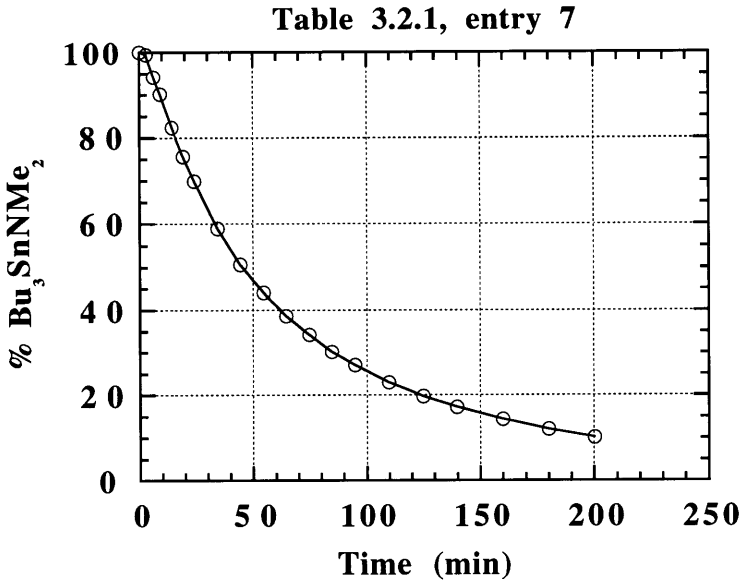


Bu_3SnNMe_2 $OctSiH_3$ ⟶

1.0 0.33

Table 3.2.1, entry 7. The aminostannane was allowed to react with $OctSiH_3$ (9.6 mg, 0.067 mmol) and was consumed with a $t_{1/2}$ of 47 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	$OctSiH_3$	$OctSiH(NMe_2)_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
3	14	47	4	90	60	190	190
<2	18	48	<2	89	66	180	190

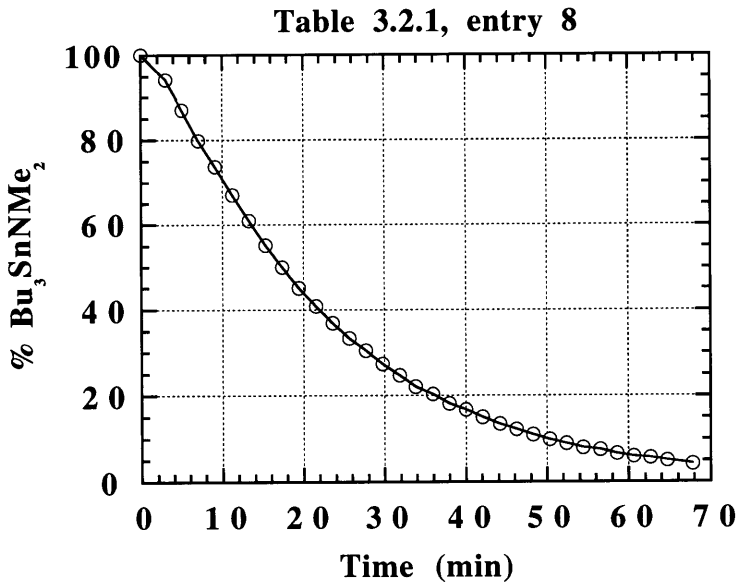


Bu_3SnNMe_2 $OctSiH_3$ ⟶

1.0 1.0

Table 3.2.1, entry 8. Bu_3SnNMe_2 was allowed to react with $OctSiH_3$ (28.9 mg, 0.200 mmol) and was consumed with a $t_{1/2}$ of 17 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	$OctSiH_3$	$OctSiH_2NMe_2$	$OctSiH(NMe_2)_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
2	140	9	53	42	72	202	192	187
2	140	9	53	43	73	202	191	188



Bu_3SnNMe_2 $OctSiH_3$ ⟶

1.0 5.0

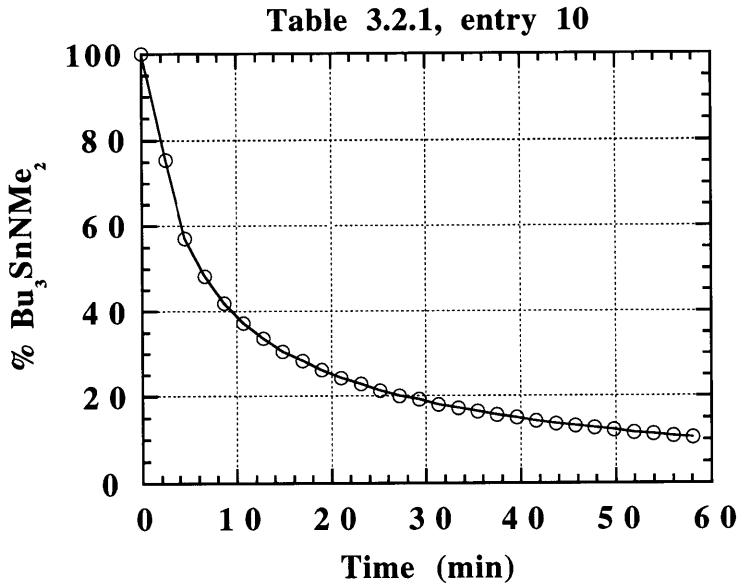
Table 3.2.1, entry 9. Bu_3SnNMe_2 was allowed to react with $OctSiH_3$ (144 mg, 1.00 mmol) and 119 μmol (60%) of Bu_3SnH were observed.

Bu_3SnNMe_2 Ph_2SiH_2 ⟶

1.0 0.50

Table 3.2.1, entry 10. The aminostannane was allowed to react with Ph_2SiH_2 (18.4 mg, 0.100 mmol) and was consumed with a $t_{1/2}$ of 6.4 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	Ph_2SiH_2	$Ph_2SiH(NMe_2)_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
<2	<2	98	<2	90	98	180	190
<2	<2	95	<2	89	95	180	190

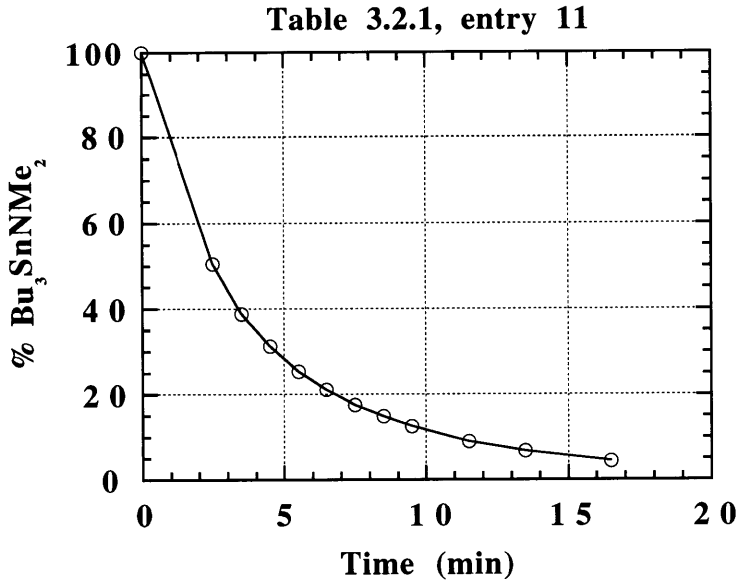


Bu_3SnNMe_2 Ph_2SiH_2 ⟶

1.0 1.0

Table 3.2.1, entry 11. Bu_3SnNMe_2 was allowed to react with Ph_2SiH_2 (36.9 mg, 0.200 mmol) and was consumed with a $t_{1/2}$ of 2.5 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	Ph_2SiH_2	$Ph_2SiHNMe_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
<2	45	150	110	39	195	188	189
<2	47	150	120	41	197	202	191



Bu_3SnNMe_2 + Ph_2SiH_2 ⟶

1.0 5.0

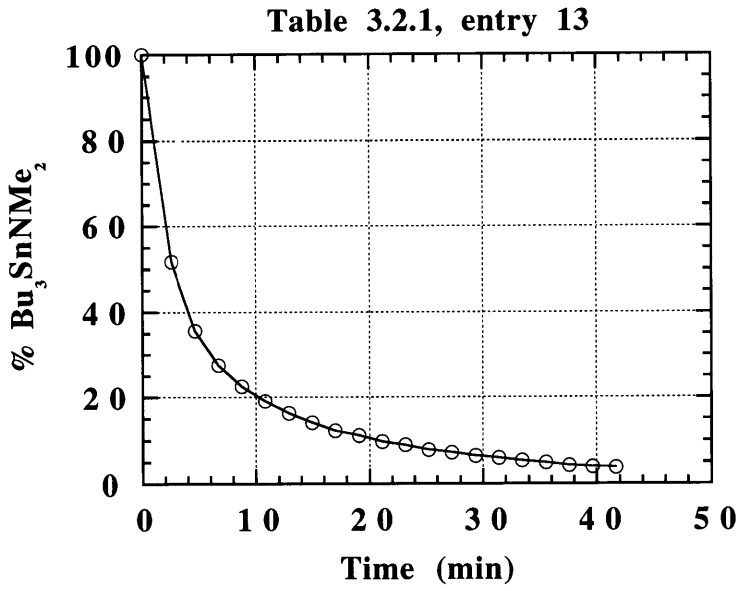
Table 3.2.1, entry 12. Bu_3SnNMe_2 was allowed to react with Ph_2SiH_2 (184 mg, 1.00 mmol), and yields of Bu_3SnH were found to be 177 μmol (88%) and 181 μmol (90%) for 2 runs as determined by ^1H NMR. Because of overlapping peaks in the ^1H NMR spectra, a third yield (88%) was obtained by GC analysis versus tetradecane as an internal standard.

Bu_3SnNMe_2 + $PhSiH_3$ ⟶

1.0 0.33

Table 3.2.1, entry 13. The aminostannane was allowed to react with $PhSiH_3$ (7.2 mg, 0.067 mmol) and was consumed with a $t_{1/2}$ of 2.9 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	$PhSiH_3$	$PhSiH_2NMe_2$	$PhSiH(NMe_2)_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
<2	<2	<2	64	73	62	64	200	190
<2	<2	<2	64	68	60	64	190	190



Bu_3SnNMe_2 $PhSiH_3$ ⟶

1.0 1.0

Table 3.2.1, entry 14. Bu_3SnNMe_2 was allowed to react with $PhSiH_3$ (21.6 mg, 0.200 mmol) and was consumed with a $t_{1/2}$ of ~1 min. The yields of all detectable species were found to be (μmol):

Bu_3SnNMe_2	$PhSiH_3$	$PhSiH_2NMe_2$	$PhSiH(NMe_2)_2$	Bu_3SnH	$HNMe_2$	ΣSi	ΣSn	ΣNMe_2
<2	94	36	75	170	14	205	198	200
<2	91	36	74	160	14	201	188	198

Bu_3SnNMe_2 $PhSiH_3$ ⟶

1.0 5.0

Table 3.2.1, entry 15. Bu_3SnNMe_2 (66.8 mg, 0.200 mmol) was allowed to react with $PhSiH_3$ (108 mg, 1.00 mmol). The yield of Bu_3SnH was found to be 203 μmol (102%) by integration versus the internal standard. A duplicate run afforded 195 μmol (97%).

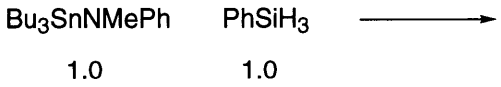
Reactions of Bu_3SnNRR' with $PhSiH_3$

General. All manipulations were performed under a nitrogen atmosphere in a Vacuum Atmospheres glove box. All reactions were run in duplicate.

To a J. Young tube (Wilmad) containing the tin amide (0.200 mmol) was added a 0.0208 M solution of hexamethylbenzene in C_6D_6 (800 μL), and an initial ^1H NMR spectrum was recorded. $PhSiH_3$ (21.6 mg, 0.200 mmol) was then added, and the tube was immersed in an oil bath maintained at 80±2 °C (t = 0). The progress of the reaction was monitored by ^1H NMR at regular intervals.

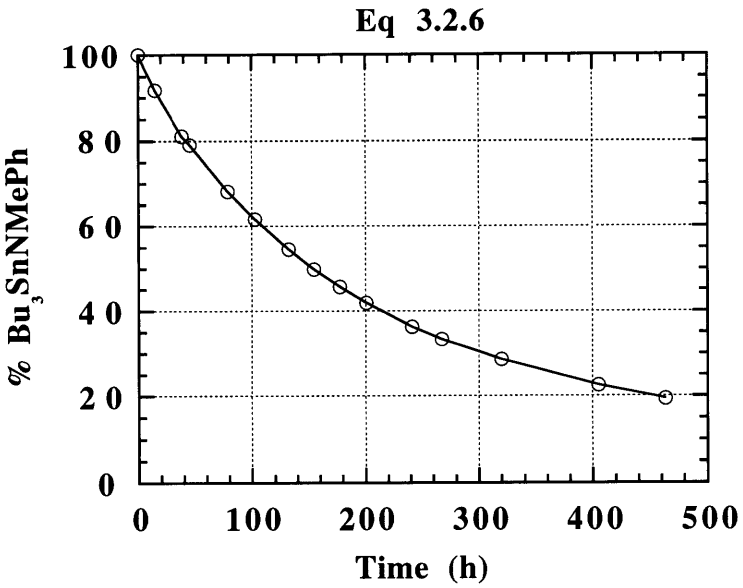
At the conclusion of each reaction, a ^{13}C and a ^{119}Sn NMR spectrum were recorded, and all peaks were identified by comparison with authentic materials, which were purchased or prepared independently (see above). Yields were determined by integration versus the internal standard in the ^1H NMR spectra.

Reactions between Bu_3SnNRR' and $PhSiH_3$



Eq 3.2.6. $Bu_3SnNMePh$ (79.2 mg, 0.200 mmol) was allowed to react with $PhSiH_3$ (21.6 mg, 0.200 mmol) and was consumed with a $t_{1/2}$ of 153 h. The yields of all detectable species were found to be (μmol):

$Bu_3SnNMePh$	$PhSiH_3$	$PhSiH_2NMePh$	$PhSiH(NMePh)_2$	Bu_3SnH	HNMePh	ΣSi	ΣSn	ΣNMePh
21	27	130	13	118	22	170	183	199
17	42	134	13	129	24	189	194	201



In addition, 24 μmol and 6 μmol of Bu_3SnSiH_2Ph were formed in the two reactions, respectively:

Bu_3SnSiH_2Ph

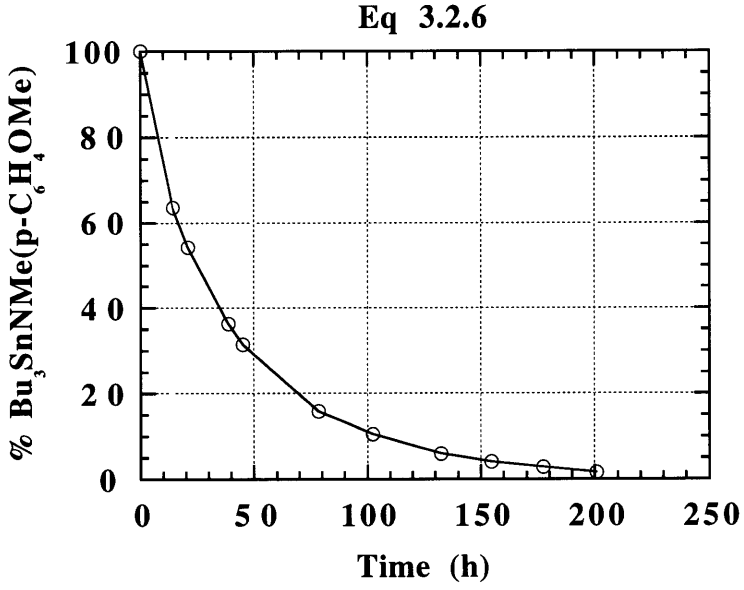
Characterization of Phenyl(tributylstannyl)silane. To $Bu_3SnNMePh$ (594 mg, 1.50 mmol) in a J. Young tube was added $PhSiH_3$ (325 mg, 3.00 mmol). The tube was sealed and placed in an oil bath maintained at 100 °C. After 33 h, no $Bu_3SnNMePh$ remained according to ^1H and ^{119}Sn NMR, and the stannylsilane comprised ca. 1% of the total silane. After heating for an additional 45 h at 100 °C, Bu_3SnSiH_2Ph had grown in to comprise ca. 16% of the total silane. Partial spectroscopic data were obtained on this mixture. ^1H NMR (300 MHz, C_6D_6) δ 7.61-7.58 (m, 2H), 4.79 (s, 2H, ^2J ($^{119}Sn/H$) = 67, ^1J (Si/H) = 188). ^{13}C NMR (75 MHz, C_6D_6) δ 30.9 (^2J ($^{119}Sn/C$) = 19), 28.1 (^3J ($^{119}Sn/C$) = 51), 9.7 (^1J ($^{119}Sn/C$) = 282). ^{119}Sn NMR (111.8 MHz, C_6D_6) δ -103.5. ^{119}Sn NMR (111.8 MHz, neat) δ -102.8 (^1J (Si/Sn) = 499, ^1J (C/Sn) = 281, ^2J (C/Sn) = 20, ^3J (C/Sn) = 52). ^{29}Si NMR (59.6 MHz, C_6D_6, proton coupled) δ -62.0 (t, ^1J (H/Si) = 190). ^{29}Si NMR (59.6 MHz, neat, proton decoupled) δ -62.4 (^1J ($^{119}Sn/Si$) = 499). HRMS (EI, *m/e*) calcd for $C_{18}H_{34}SiSn$ (M+) 398.1452; found 398.1451.

$Bu_3SnNMe(p\text{-}C_6H_4\text{-}OMe)$ $PhSiH_3$ ⟶

1.0 1.0

Eq 3.2.6. $Bu_3SnNMe(p\text{-}C_6H_4\text{-}OMe)$ (85.2 mg, 0.200 mmol) was allowed to react with $PhSiH_3$ (21.6 mg, 0.200 mmol) and was consumed with a $t_{1/2}$ of 24 h. The yields of all detectable species were found to be (μmol):

$Bu_3SnNMeAr$	$PhSiH_3$	$PhSiH_2NMeAr$	$PhSiH(NMeAr)_2$	Bu_3SnH	HNMeAr	ΣSi	ΣSn	ΣNMeAr
<2	35	127	20	117	30	182	177	197
<2	35	126	21	123	31	182	185	199

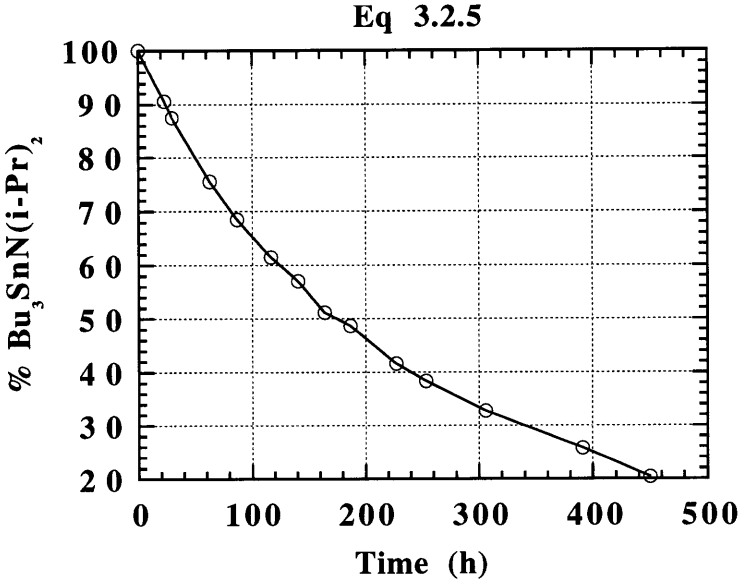


$Bu_3SnN(i\text{-}Pr)_2$ $PhSiH_3$ ⟶

1.0 1.0

Eq 3.2.5. $Bu_3SnN(i\text{-}Pr)_2$ (78.0 mg, 0.200 mmol) was allowed to react with $PhSiH_3$ (21.6 mg, 0.200 mmol) and was consumed with a $t_{1/2}$ of 176 h. The yields of all detectable species were found to be (μmol):

$Bu_3SnN(i\text{-}Pr)_2$	$PhSiH_3$	$PhSiH_2N(i\text{-}Pr)_2$	$PhSiH[N(i\text{-}Pr)_2]_2$	Bu_3SnH	$HN(i\text{-}Pr)_2$	ΣSi	ΣSn	$\Sigma N(i\text{-}Pr)_2$
19	105	91	<2	<2	95	196	209	205
16	108	87	<2	<2	96	195	208	199



Determination of k_2/k_1 for the reaction of $PhSiH_3$ with Bu_3SnNMe_2

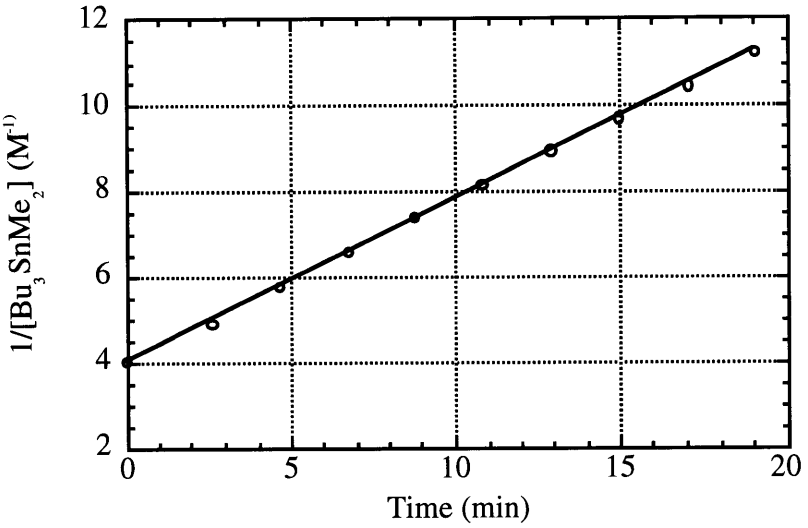
Figure 3.2.3. To a flask containing $PhSiH_3$ (54.1 mg, 0.500 mmol), was added a 0.500 M solution of *n*-butyl methyl ether in C_6D_6 (800 μL) under an atmosphere of N_2. Bu_3SnNMe_2 was added dropwise while stirring at ambient temperature. The reaction was transferred to an NMR tube, and the product ratios were determined by integration in the ^1H NMR versus the internal standard. Following the method of McMillan,[24] k_2/k_1 was calculated to be 4.5. No $PhSi(NMe_2)_3$ was observed. Thus, $k_1, k_2 >> k_3$. When the reaction was repeated in a sealed tube, a negligible amount of $HNMe_2$ was observed and k_2/k_1 was found to be 4.3. Therefore, reaction (4) can be neglected under these conditions.

Test for Disproportionation of Aminosilanes

To Bu_3SnNMe_2 (66.8 mg, 0.200 mmol) in a J. Young tube was added a 0.500 M solution of *n*-butyl methyl ether in C_6D_6 (800 μL) under an atmosphere of N_2. $PhSiH_3$ (21.6 mg, 0.200 mmol) was added, the tube was sealed, and after no Bu_3SnNMe_2 remained (ca. 45 min), the concentrations of $PhSiH_2NMe_2$, and $PhSiH(NMe_2)_2$ were determined by integration versus the internal standard in the ^1H NMR. Additional $PhSiH_3$ (21.6 mg, 0.200 mmol) was added, and after standing at ambient temperature for 84 h, followed by heating to 80 °C in an oil bath for 3 h, no significant changes in aminosilane concentrations were observed. $PhSi(NMe_2)_3$ (11.9 mg, 0.050 mmol) was then added, and after 10 min, the concentrations of all four silanes were measured by ^1H NMR. No significant changes in $PhSiH_3$, $PhSiH_2NMe_2$, or $PhSiH(NMe_2)_2$ concentrations were observed. Thus, no significant disproportionation among the four potential silane species occurs under our reaction conditions.

$$Bu_3SnNMe_2 \quad Bu_3SnH \longrightarrow Bu_3SnSnBu_3 \quad HNMe_2$$

To Bu_3SnNMe_2 (66.8 mg, 0.200 mmol) in a J. Young tube was added a 0.250 M solution of *n*-butyl methyl ether in C_6D_6 (800 μL) under an atmosphere of N_2. An initial ^1H NMR spectrum was recorded, and Bu_3SnH (58.2 mg, 0.200 mmol) was added. The progress of the reaction was monitored by ^1H NMR, maintaining a probe temperature of 25°C. By calculating an overall second order rate constant[18] of 0.38 $M^{-1}min^{-1}$, a $t_{1/2}$ of 10.5 min was found.


12
10
8
6
4
2
0
5
10
15
20
Time (min)
1/[Bu3SnMe2] (M-1)

3.3. Bu_3SnH-Catalyzed, Silicon Hydride-Mediated Reduction of Azides to Amines

Background

After having demonstrated that silanes indeed reduce tin amides to tin hydrides,[29] we turned our attention to the development of a tin-catalyzed transformation which exploits this novel reactivity as the turnover step. To test the feasibility of this strategy, we sought out a synthetic transformation which 1) affords tin amides, and 2) currently requires a stoichiometric quantity of organotin hydride. The reduction of azides to primary amines (eq 3.3.1) meets these requirements.[30-36]

$$R\text{–}N_3 \xrightarrow[\text{AIBN}\\ \text{benzene, }\Delta]{Bu_3SnH\ (\text{excess})} R\text{–}NH_2 \qquad (3.3.1)$$

via "$R\text{–}\underset{\displaystyle H}{N}\text{–}SnBu_3$"

Results and Discussion

Analogous to our catalytic methods involving Sn-O intermediates (Table 3.1.1, entry 4), we anticipated that a Bu_3SnH-catalyzed, silicon-hydride mediated azide reduction would proceed according to the pathway illustrated in Figure 3.3.1. In the first step, Bu_3SnH would react with RN_3 to afford $RNHSnBu_3$. Then, in the turnover step, the silane would regenerate the catalyst (Bu_3SnH) by reaction with $RNHSnBu_3$.

Unfortunately, this proposal did not stand up to the rigors of experiment. Thus, treatment of 2-azidododecane with 5 mol % Bu_3SnH and 0.67 equiv $PhSiH_3$ (AIBN, refluxing benzene) afforded a $\leq$ 12% yield of 2-aminododecane. We suspected that, although the postulated turnover step is known to be *chemically competent*,[29] it may not

occur rapidly under our reaction conditions, and Bu_3SnH is not being regenerated at a rate sufficient to sustain a catalytic cycle. To circumvent this problem, we chose to depend not on the reduction of Sn-N to Sn-H for the turnover step, but rather on the reduction of Sn-O to Sn-H[12-15] (Figure 3.3.2).

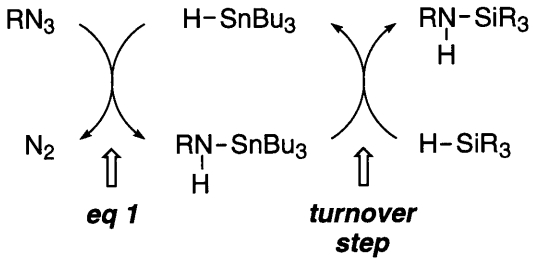


Figure 3.3.1. Bu_3SnH-catalyzed, silicon hydride-mediated reduction of azides: an initial approach.

We thus reasoned that by adding an alcohol (ROH) to the reaction mixture, the initially formed $RNHSnBu_3$ would be converted to $ROSnBu_3$ (Figure 3.3.2, Sn exchange).[37-39] Tributyltin alkoxides, in turn, have been shown to serve as Bu_3SnH precursors in a manner sufficient to support a catalytic cycle (Figure 3.3.2, turnover step).[6,8]

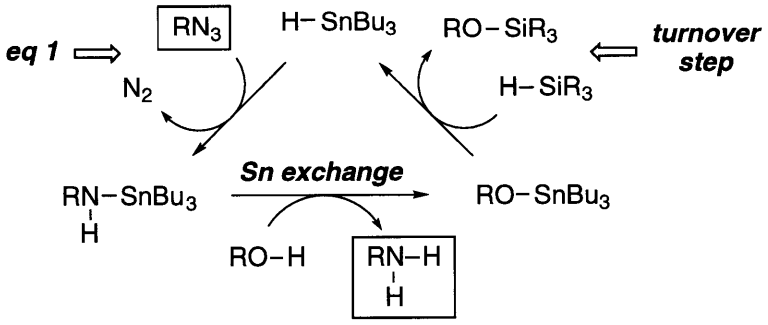
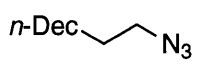
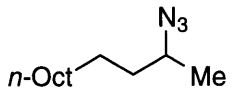
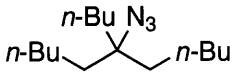
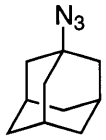
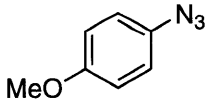


Figure 3.3.2. Bu_3SnH-catalyzed, silicon hydride-mediated reduction of azides: an alternate approach.

We chose primary alcohols as additives because the rate of reduction of $ROSnBu_3$ to Bu_3SnH is known to be quite sensitive to the steric paramaters of the alkoxide fragment.[12,25] We find that this modified catalytic cycle is indeed efficient, and a series of azides can be reduced to the corresponding primary amines in high yields. Thus, treatment of a primary, secondary, tertiary, or aryl azide with $(Bu_3Sn)_2O$ (2.5 mol%)[40] and $PhSiH_3$ (0.6 equiv) in the presence of *n*-PrOH (2 equiv) in refluxing benzene (AIBN) provides the primary amine in excellent yield (92-99%; Table 3.3.1, $PhSiH_3$).

Table 3.3.1. Bu_3SnH-Catalyzed Reduction of Azides to Amines

Entry	Substrate	Yield (%)[a]	
		$PhSiH_3$	PMHS
1		94[b]	95[b]
2		92[b]	94[b]
3		96	94
4		99[b]	96[b]
5		94	91

[a] Isolated yield, average of two runs.
[b] Isolated as the amine hydrochloride salt.

We have established that inexpensive PMHS (TMSO-$(SiHMeO)_n$-TMS) can also be used as the stoichiometric reductant in this Bu_3SnH-catalyzed transformation. Reaction of an organic azide with $(Bu_3Sn)_2O$ (2.5 mol%), PMHS (3 equiv), and *n*-PrOH (2 equiv) at 80 °C (AIBN) affords the desired amine in uniformly high yield (91-96%; Table 3.3.1,

PMHS). With either set of reaction conditions (PMHS or $PhSiH_3$), little or no reduction of the azide (<10%) is observed in the absence of Bu_3SnH, silane, or of *n*-PrOH. Alkynes, esters, and alkyl chlorides are compatible with both of the reduction conditions, but aldehydes, ketones, nitro groups, and alkyl bromides are not.

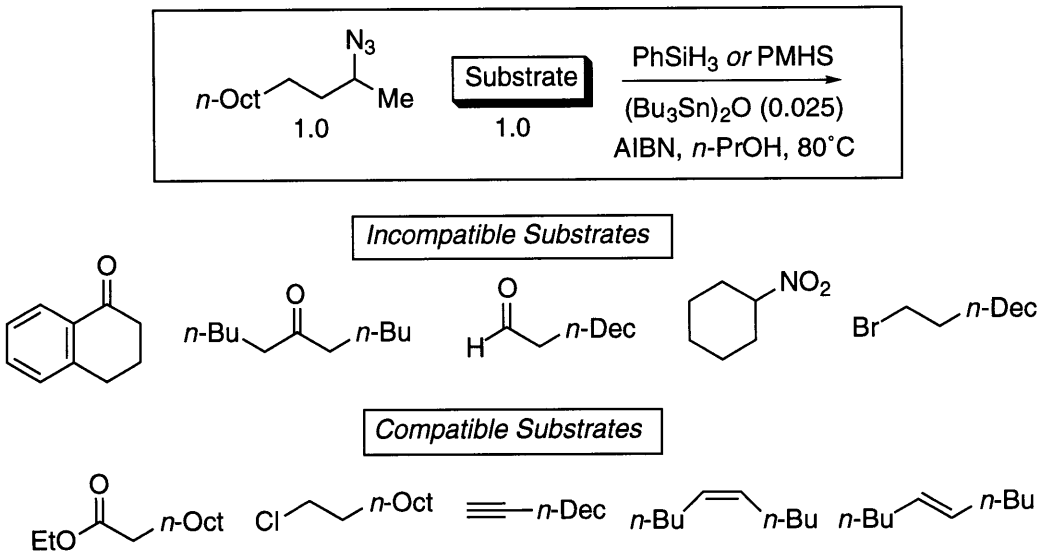
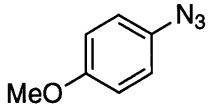
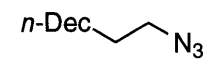
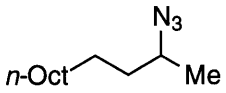
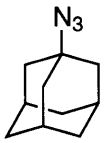
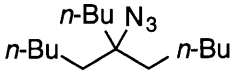


Figure 3.3.3. Functional group compatibility survey.

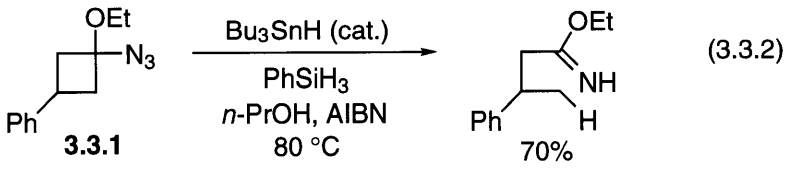
A modest dependence of the reaction rate on sterics and electronics of the azide is observed (Table 3.3.2). Thus, the relative rate of azide reduction for both the catalytic and the stoichiometric versions is found to obey the following sequence:

Aryl > Primary > Secondary > Tertiary

Table 3.3.2. Relative Rates for Azide Reduction Normalized to 1-Azidoadamantane.

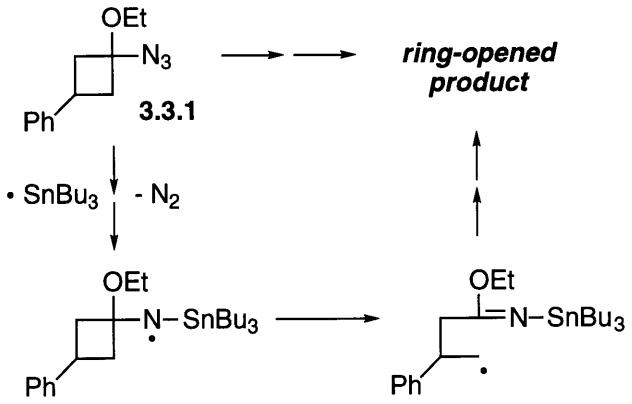
Entry	Substrate	Relative Rate vs. 1-Azidoamantane	
		Catalytic	Stoichiometric
1		26	14
2		1.6	1.4
3		1.1	1.1
4		1	1
5		0.70	0.80

In order to provide evidence for radical-mediated N-N bond cleavage in these Bu_3SnH-catalyzed reductions, we examined the reaction of azide **3.3.1** (Scheme 3.3.1). As demonstrated by Kim, if the reduction of this substrate follows a radical pathway, then a ring-opened product should be observed.[41] We have established that under our Bu_3SnH-catalyzed azide reduction conditions, ring opening does indeed occur to generate an acyclic imino ester (eq 3.3.2).



(3.3.2)

Scheme 3.3.1



The failure of our original catalytic proposal, in conjunction with the subsequent success according to our alternate strategy, has prompted a mechanistic investigation of the catalytic cycle. Thus, ^{119}Sn NMR has allowed for the examination of the elementary steps in the azide reduction.

First, we examined the reaction under stoichiometric conditions (Figure 3.3.4). When 2-azidodocecane was reacted with 1 equiv Bu_3SnH (AIBN, refluxing benzene) for 1 h, the ^{119}Sn NMR spectrum indicated that most of the tin had been converted to a mixture of two tin amides: the mono- and bis-stannylated derivatives of 2-aminododecane ($RNHSnBu_3$ and $RN(SnBu_3)_2$, **3.3.2**, Figure 3.3.4a). Treatment of this mixture with ca. 1.2 equiv of EtOH immediately afforded Bu_3SnOEt by ^{119}Sn NMR (Figure 3.3.4b). ^{1}H NMR analysis indicated that 2-aminododecane had been formed in 94% yield. Addition of ca. 1.4 equiv $PhSiH_3$ to the solution containing Bu_3SnOEt afforded 98% recovery of the Bu_3SnH (by ^{1}H NMR). The ^{119}Sn NMR spectrum showed the only tin-containing products to be $Bu_3SnSnBu_3$ (minor) and Bu_3SnH (major) (Figure 3.3.4c). Therefore, each of the steps in the revised catalytic cycle are observed to occur cleanly in a stepwise manner.

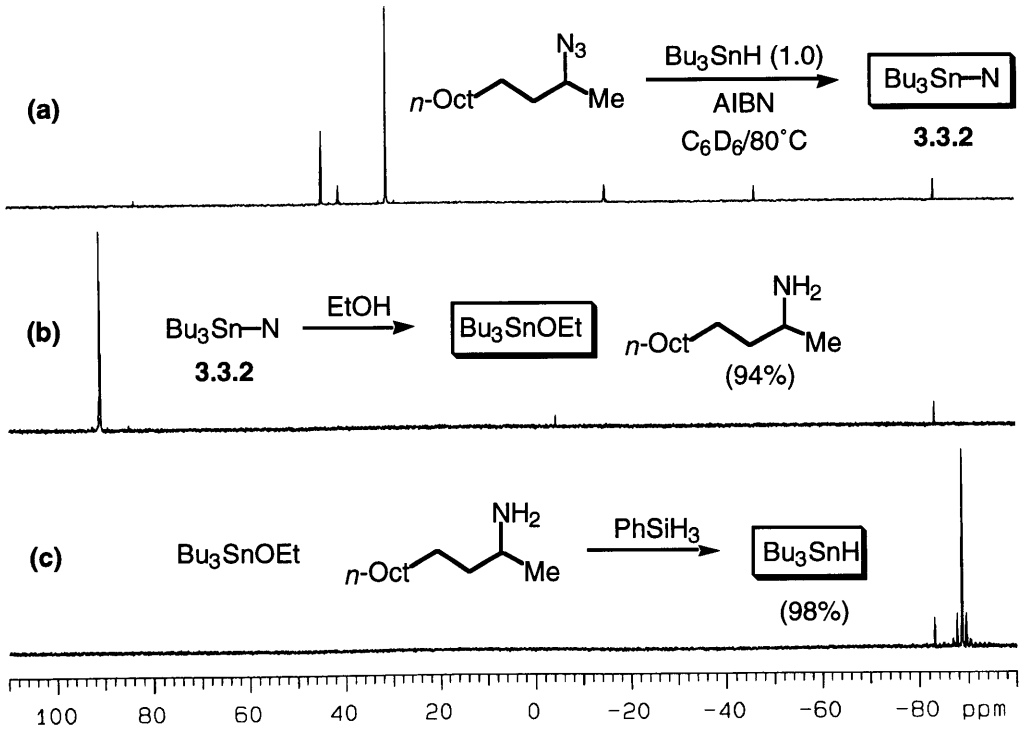


Figure 3.3.4. ^{119}Sn NMR spectra demonstrate that (a) Reduction of 2-azidododecane under stoichiometric Bu_3SnH conditions affords a mixture consisting predominantly of two tin amides **3.3.2**. (b) Treatment of tin amides **3.3.2** with EtOH cleanly affords Bu_3SnOEt and liberates the amine product in 94% yield. (c) Treatment of the resulting Bu_3SnOEt with $PhSiH_3$ regenerates the Bu_3SnH in 98% yield.

Next, we examined the reduction according to the original proposal (no primary alcohol additive) (Figure 3.3.5). Thus, 2-azidododecane was reacted with 5 mol % Bu_3SnH and 0.67 equiv $PhSiH_3$ (AIBN, refluxing benzene) for 2 h. Only 12% of the azide had been consumed by ^1H NMR analysis, and after standing at room temperature for 51 h, ^{119}Sn NMR revealed only a small amount of Bu_3SnH along with ≥ 7 unidentified species (Figure 3.3.5b). Upon addition of EtOH, immediate and clean conversion to Bu_3SnH was observed by ^{119}Sn NMR (Figure 3.3.5c). Therefore, in the

absence of a primary alcohol additive, the tin resting state appears to be in the form of a complex mixture of compounds which does not efficiently react with $PhSiH_3$ to regenerate the Bu_3SnH catalyst.

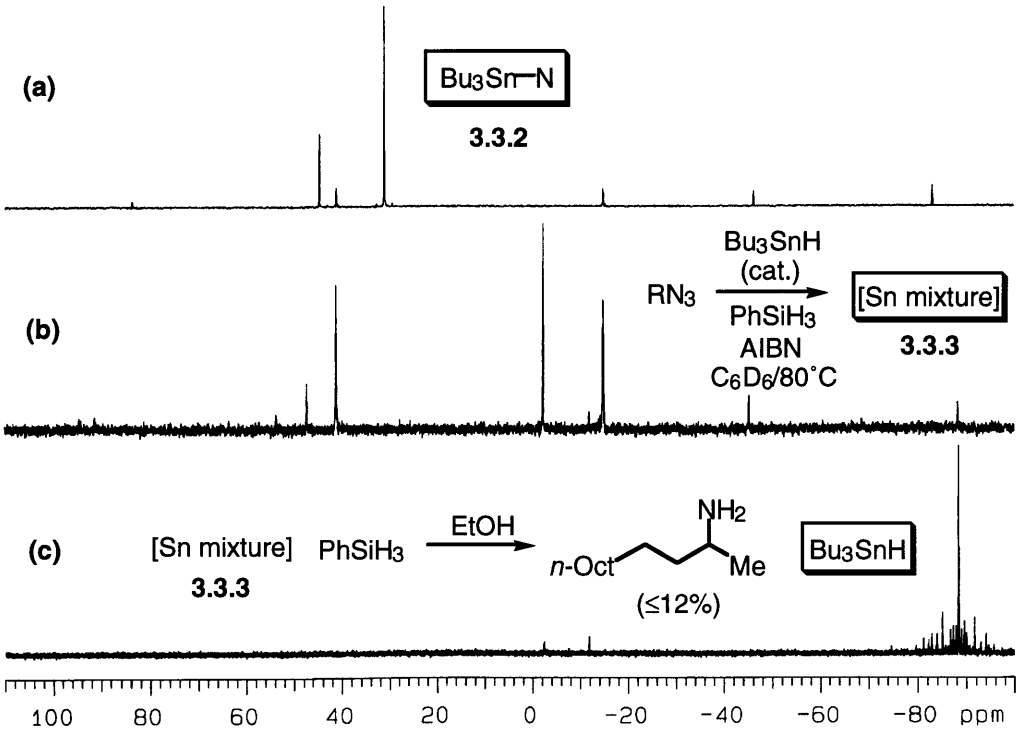


Figure 3.3.5. ^{119}Sn NMR spectra: (a) Mixture of tin amides **3.3.2** from the stoichiometric azide reduction is provided for comparison. (b) Attempted catalytic azide reduction according to the original plan (no primary alcohol additive). A complex tin mixure **3.3.3** which reacts only slowly with $PhSiH_3$ is obtained; R = 2-dodecyl. (c) Tin mixture **3.3.3** is immediately converted to Bu_3SnH upon treatment with EtOH. Only 12% of the azide has been consumed.

Finally, to investigate the revised catalytic protocol, 2-azidododecane was reacted with 5 mol % Bu_3SnH, 2 equiv *n*-PrOH, and 0.67 equiv $PhSiH_3$ (AIBN, refluxing benzene) for 2 h. At this time, ^{119}Sn NMR analysis revealed Bu_3SnH as the only tin-

containing species (Figure 3.3.6), and GC analysis indicated a 96% recovery of the Bu_3SnH. ^1H NMR revealed a 95% yield of 2-aminododecane. Therefore, we believe the revised catalytic cycle proceeds as drawn in Figure 3.3.2.

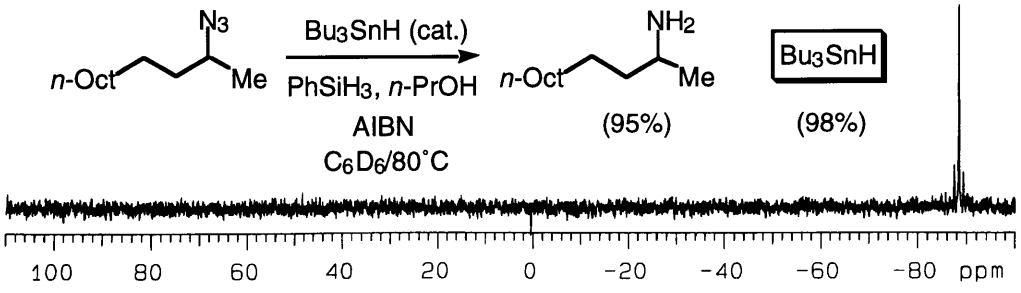


Figure 3.3.6. ^{119}Sn NMR spectrum demonstrates that catalytic azide reduction according to the optimized conditions (2 equiv *n*-PrOH) affords Bu_3SnH as the only tin-containing product.

In conclusion, we have developed a new Bu_3SnH-catalyzed process, the reduction of azides to amines. Although we were not able to effect this transformation according to our original plan (Figure 3.3.1), we have established the viability of an alternate strategy for catalysis that requires primary alcohols as additives (Figure 3.3.2). Mechanistic studies have shown that the reduction proceeds by a free radical cleavage of the N-N bond and that a primary alcohol additive is required in order to facilitate the regeneration of the Bu_3SnH catalyst via the reduction of Sn-O intermediates.

Experimental

General

The following materials were used without purification: AIBN (Eastman Kodak); HCl (Aldrich, 1.0 M in Et_2O); 1-azidoadamantane (Aldrich); 1-butanol (Aldrich, anhydrous); 1-adamantanamine (Aldrich); dodecylamine (Aldrich); $Bu_3SnSnBu_3$ (Aldrich); triethyl orthoformate (Aldrich); TsOH (Aldrich); TMS-N_3 (Aldrich); $SnCl_4$ (Aldrich, 99%); Et_3N (EM Science); NaN_3 (Aldrich); MsCl (Aldrich); *p*-anisidine (Aldrich); 1-dodecanol (Aldrich); 2-dodecanol (Aldrich).

The following materials were distilled prior to use: $(Bu_3Sn)_2O$ (Gelest); $PhSiH_3$ (Fluka); *n*-PrOH (Mallinkrodt, from Mg); EtOH (Pharmco, from Mg); benzyl ether (Aldrich); benzyl methyl ether (Pfaltz & Bauer); α-tetralone (Aldrich); 6-undecanone (Aldrich); dodecyl aldehyde (Aldrich); 1-dodecyne (Aldrich); ethyl caprate (Aldrich); *trans*-5-decene (Aldrich); *cis*-5-decene (TCI); 1-chlorodecane (Aldrich); 1-bromododecane (Aldrich); nitrocyclohexane (Aldrich); Bu_3SnH (Gelest); Bu_3SnOEt (Gelest).

PMHS (Aldrich) was stirred under full vacuum for 30 min and stored under nitrogen.

3-Phenylcyclobutanone was prepared according to the literature procedure.[42]

Solvents were distilled from the indicated drying agents: benzene (sodium/benzophenone); CH_2Cl_2 (CaH_2); C_6D_6 (NaK/benzophenone); THF (sodium/benzophenone).

^1H, ^{13}C, and ^{119}Sn nuclear magnetic resonance spectra were recorded on Varian XL-300, Unity-300, or VXR-500 NMR spectrometers at ambient temperature. ^1H 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, and coupling constant (Hz). ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). All ^{13}C spectra were determined with complete proton decoupling. ^{119}Sn chemical shifts are reported in ppm downfield from $SnMe_4$ (neat, external reference, δ scale) and were determined with pulse intervals of 1.5-5 s. Broad band ^1H NMR decoupling was only applied during acquisition.

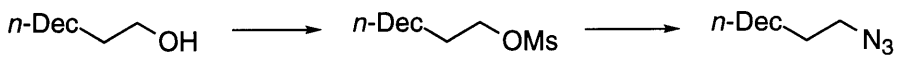
Analytical thin layer chromatography was performed using EM Reagents 0.25 mm silica gel 60 plates, and visualization was accomplished with anisaldehyde/H_2SO_4/EtOH/HOAc or with ethanolic phosphomolybdic acid. Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh).

Gas chromatography was performed on a Hewlett Packard 5890 Series II instrument utilizing a DB-1 or DB-1701 capillary column (J & W Scientific).

Infrared spectra were obtained on a Perkin-Elmer Series 1600 FT-IR spectrophotometer. High resolution mass spectra were recorded on a Finnegan MAT System 8200 spectrometer.

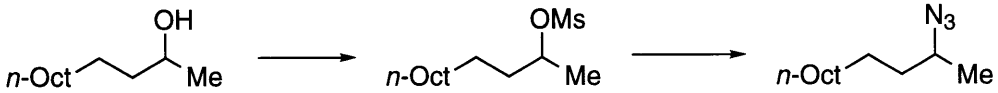
All reactions were carried out under an atmosphere of nitrogen in a Vacuum Atmospheres glove box or under an atmosphere of argon using standard Schlenk techniques.

Preparation of Azides

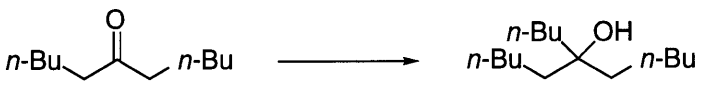


1-Azidododecane. To a solution of 1-dodecanol (5.59 g, 30.0 mmol) and Et_3N (6.1 g, 60 mmol) in CH_2Cl_2 at 0 °C was added MsCl (3.78 g, 33.0 mmol). The cooling bath was removed, and after 3 h, the reaction was subjected to aqueous workup with 1 M HCl

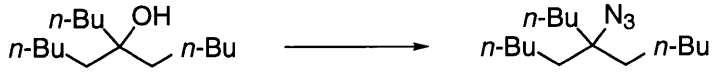
and CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in DMF, and NaN_3 (3.9 g, 60 mmol) was added. After stirring for 36 h, the reaction mixture was diluted with hexanes and washed with brine (3x). The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the residue was subjected to flash chromatography to afford 5.63 g (88%) of 1-azidododecane as a clear, colorless oil. The material was further purified by bulb-to-bulb distillation. ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (t, 2H, J = 6.6), 1.60 (pent, 2H, J = 7.2), 1.26 (m, 18H), 0.88 (t, 3H, J = 6.6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5, 31.9, 29.6, 29.5, 29.5, 29.3, 29.1, 28.9, 26.7, 22.6, 14.0. IR (neat): 2924, 2854, 2096, 1466, 1377, 1349, 1258, 1126. HRMS: Calcd. for $C_{12}H_{25}N$ $[M-N_2]^+$: 183.1987. Found: 183.1986.



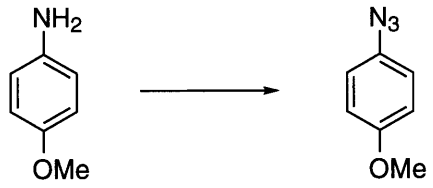
2-Azidododecane. To a solution of the mesylate of 2-dodecanol (prepared on a 50 mmol scale as above) in DMF (100 mL) was added NaN_3 (6.5 g, 100 mmol). The reaction was stirred at room temperature for 14 h, heated to 60 °C for 8 h, then stirred at room temperature for an additional 36 h. Workup and purification as above afforded 9.0 g (85%) of 2-azidododecane as a clear colorless oil. The material was further purified by bulb-to-bulb distillation (54-74 °C (oven temperature)/80 mtorr). ^1H NMR (300 MHz, $CDCl_3$) δ 3.42 (hex, 1H, J = 6.4), 1.55-1.23 (m, 21H), 0.88 (t, 3H, J = 6.6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.0, 36.2, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 26.1, 22.6, 19.3, 14.0. IR (neat): 2924, 2855, 2100, 1466, 1379, 1328, 1249, 628. HRMS: Calcd. for $C_{12}H_{25}N$ $[M-N_2]^+$: 183.1987. Found: 183.1985.



6-Butyl-6-undecanol. To a solution of 6-undecanone (13.6 g, 800 mmol) in THF (100 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes) until no ketone remained by TLC. The reaction was quenched with saturated NH_4Cl (200 mL) and extracted with Et_2O (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford 6-butyl-6-hydroxyundecane as a yellow oil. The residue was purified by flash chromatography portionwise as needed. ^1H NMR (300 MHz, $CDCl_3$) δ 1.44-1.20 (m, 22H), 1.09 (s, 1H), 0.93-0.87 (m, 9H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 74.4, 39.2, 39.0, 32.5, 25.7, 23.3, 23.1, 22.7, 14.1, 14.0. HRMS: Calcd for $C_{12}H_{27}O_3Si$: 228.2453. Found: 228.2452.



6-Azido-6-butylundecane. This reaction was run according to the general procedure in the literature[43] on a 28 mmol scale. The product was purified by flash chromatography, which provided 858 mg (12%) of 6-azido-6-butylundecane as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.51-1.45 (m, 6H), 1.36-1.26 (m, 16H), 0.94-0.88 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.8, 36.5, 36.2, 32.2, 25.7, 23.2, 23.1, 22.5, 14.0. IR (neat): 2935, 2863, 2096, 1466, 1257. HRMS: Calcd. for $C_{15}H_{31}N$ $[M-N_2]^+$: 225.2457. Found: 225.2456.

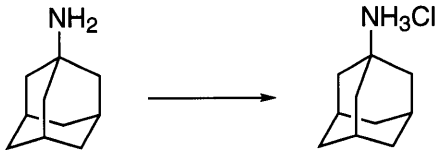


1-Azido-4-methoxybenzene. This material was prepared according to the procedure in the literature[44] on a 100 mmol scale. The product was purified by flash chromatography, which provided 9.0 g (60%) of 1-azido-4-methoxybenzene as a yellow

solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98-6.86 (m, 4H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 132.3, 119.9, 115.0, 55.4.

Preparation of Authentic HCl Salts: General

To a solution of the amine in Et_2O was added an excess of HCl (1.0 M solution in Et_2O). The white solid was collected by filtration, washed with Et_2O, dissolved in MeOH, and the resulting solution was concentrated to afford the HCl salt as a white solid.



1-Adamantanamine hydrochloride. ^{1}H NMR (300 MHz, CD_3OD) δ 4.88 (s, 3H), 2.18 (br s, 3H), 1.89 (d, 6H, J = 2.7), 1.76 (q, 6H, J = 13.1). ^{13}C NMR (75 MHz, CD_3OD) δ 53.2, 41.6, 36.6, 30.6.

1-Aminododecane hydrochloride. ^{1}H NMR (300 MHz, CD_3OD) δ 4.80 (br s, 3H), 2.91 (m, 2H), 1.66 (pent, 2H, J = 7.5), 1.30 (m, 18H), 0.90 (t, 3H, J = 6.8). ^{13}C NMR (75 MHz, CD_3OD) δ 41.0, 33.1, 30.8, 30.7, 30.6, 30.5, 30.3, 28.6, 27.6, 23.8, 14.6.

Bu_3SnH-Catalyzed Reductions of Azides to Amines: $PhSiH_3$

General Procedure (Table 3.3.1, entries 1, 2, 4): To a solution of the alkyl azide (2.00 mmol) and AIBN (16 mg, 0.10 mmol) in benzene (2.0 mL) were added $(Bu_3Sn)_2O$ (29.8 mg, 0.0500 mmol), $PhSiH_3$ (108-144 mg, 1.00-1.33 mmol), and *n*-PrOH (240 mg, 4.00 mmol). The reaction was heated to reflux for 90-120 min in an oil bath maintained at 90 °C. After cooling to r.t., pentane (10 mL) was added, followed by anhydrous HCl (5-7 mL of a 1.0 M solution in Et_2O). The resulting white solid was collected by filtration and then dissolved in MeOH. Removal of the solvent afforded the product amine as a white hydrochloride salt. The ^1H and ^{13}C NMR spectra of the hydrochloride salt were identical to spectra for material prepared by protonation of the commercially available amine.

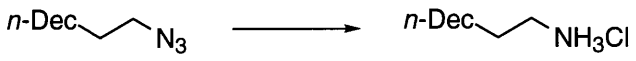


Table 3.3.1, entry 1. 1-Azidododecane (423 mg, 2.00 mmol) was reduced according to the general procedure using $PhSiH_3$ (144 mg, 1.33 mmol) for 2 h. Treatment with HCl (7 mL of a 1.0 M solution in Et_2O) afforded 426 mg (96%; second run: 91%) of the HCl salt of 1-aminododecane.

Control Reaction: no $(Bu_3Sn)_2O$. In side-by-side reactions, in the time required for 93% of 1-azidododecane to be consumed in a catalytic reaction, only 3% of 1-azidododecane was consumed in an otherwise identical run lacking $(Bu_3Sn)_2O$ (GC analysis versus an internal standard).

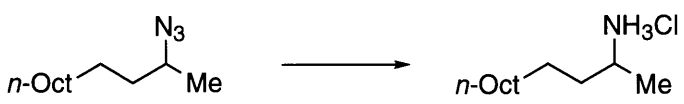


Table 3.3.1, entry 2. 2-Azidododecane (423 mg, 2.00 mmol) was reduced according to the general procedure using $PhSiH_3$ (144 mg, 1.33 mmol) for 2 h. Treatment with HCl (7 mL of a 1.0 M solution in Et_2O) afforded 406 mg (91%; second run: 94%) of the HCl salt of 2-aminododecane. ^1H NMR (300 MHz, CD_3OD) δ 4.90 (s, 3H), 3.25 (hex, 1H, J = 6.7), 1.69-1.45 (m, 2H), 1.42-1.27 (m, 19H), 0.90 (t, 3H, J = 6.8). ^{13}C NMR (75 MHz, CD_3OD) δ 49.3, 35.9, 33.1, 30.8, 30.8, 30.6, 30.5, 26.6, 23.8, 18.8, 14.6.

The HCl salt (207 mg, 0.933 mmol) was treated with 1 M NaOH (40 mL) and extracted with Et_2O (3x). The combined organics were dried (Na_2SO_4) and concentrated to afford a two-phase oil. Additional drying was effected by azeotropic removal of benzene on a rotary evaporator (3x) to afford 167 mg (97%) of 2-aminododecane as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 2.85 (m, 1H), 1.25 (br s, 18H), 1.12 (br s, 2H), 1.04 (d, 3H, J = 6.3), 0.87 (t, 3H, J = 6.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.8, 40.2, 31.8, 29.7, 29.5, 29.2, 26.3, 24.0, 22.5, 13.9. IR (neat) 4331, 4259, 3676, 3360, 2956, 2921, 2853, 1603, 1466, 1377, 1148, 803, 721. HRMS: Calcd for $C_{12}H_{27}N$: 185.2144. Found: 185.2144.

Control Reaction: no $(Bu_3Sn)_2O$. In the time required for 100% of 2-azidododecane to be consumed in a catalytic reaction (2 h), an otherwise identical reaction lacking $(Bu_3Sn)_2O$ lost only 3% of the azide, as evidenced by GC analysis versus an internal standard.

Control Reaction: no AIBN. An otherwise identical reaction run on a 1 mmol scale, lacking AIBN, exhibited a 42% loss of azide and a 36% yield of amine as evidenced by integration versus an internal standard in the ^1H NMR spectrum of the crude reaction mixture.

Control Reaction: no *n*-PrOH. An otherwise identical reaction run on a 1 mmol scale, lacking *n*-PrOH, exhibited a 14% loss of azide and a 9% yield of amine as evidenced by integration versus an internal standard in the ^1H NMR spectrum of the

crude reaction mixture.

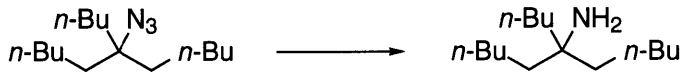


Table 3.3.1, entry 3. To a solution of 6-azido-6-butylundecane (253 mg, 1.00 mmol) and AIBN (8 mg, 0.05 mmol) in benzene (1.0 mL) were added $(Bu_3Sn)_2O$ (15 mg, 0.025 mmol), $PhSiH_3$ (54 mg, 0.50 mmol), and *n*-PrOH (120 mg, 2.00 mmol). The reaction was heated to reflux for 30 min in an oil bath maintained at 90 °C. After cooling to r.t., the reaction mixture was purified by flash chromatography, which afforded 219 mg (96%; second run: 97%) of 6-amino-6-butylundecane as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34-1.19 (m, 22H), 0.99 (br s, 2H), 0.92-0.86 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0, 40.2, 40.0, 32.6, 25.7, 23.4, 23.1, 22.6, 14.0, 13.9. IR (neat) 3362, 2956, 2929, 2859, 1612, 1466, 1378, 1342, 1160, 1020, 812, 727. HRMS: Calcd for $C_{15}H_{34}N$ $[M+H]^+$: 228.2691. Found: 228.2692.

Control Reaction: no $(Bu_3Sn)_2O$. In the time required for 97% of the azide to be consumed in a catalytic reaction (30 min), an otherwise identical run, lacking $(Bu_3Sn)_2O$, lost only 3% of the azide as evidenced by GC analysis versus an internal standard.

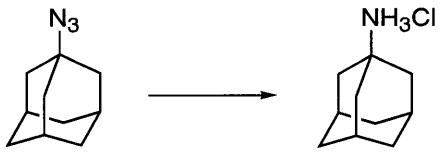


Table 3.3.1, entry 4. 1-Azidoadamantane (355 mg, 2.00 mmol) was reduced according to the general procedure using $PhSiH_3$ (108 mg, 1.00 mmol) for 1.5 h. Treatment with HCl (5 mL of a 1.0 M solution in Et_2O) afforded 366 mg (98%; second run: 100%) of the HCl salt of 1-aminoadamantane.

Control Reaction: no $(Bu_3Sn)_2O$. In the time required for 97% of 1-

azidoadamantane to be consumed in a catalytic reaction (38 min), an otherwise identical run, lacking $(Bu_3Sn)_2O$, lost only 5% of the azide as evidenced by GC analysis versus an internal standard.

Scale-up. When run on a 20 mmol scale, a yield of 3.81g (102%) was obtained.

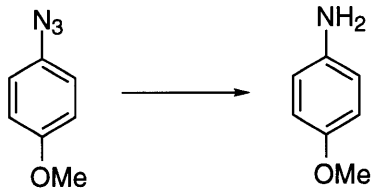


Table 3.3.1, entry 5. To a solution of 4-methoxy-1-azidobenzene (298 mg, 2.00 mmol) and AIBN (16 mg, 0.10 mmol) in benzene (2.0 mL) were added $(Bu_3Sn)_2O$ (29.8 mg, 0.0500 mmol), $PhSiH_3$ (108 mg, 1.00 mmol), and *n*-PrOH (240 mg, 4.00 mmol). The reaction was heated to reflux for 3 h in an oil bath maintained at 90 °C. After cooling to r.t., pentane (10 mL) was added, followed by anhydrous HCl (5 mL of a 1.0 M solution in Et_2O). The resulting purple solid was subjected to aqueous workup with 1 M NaOH and Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated to afford an orange oil. Chromatography afforded 230 mg (93%; second run: 96%) of *p*-anisidine as an orange solid. The ^1H and ^{13}C NMR spectra were identical to those obtained from the commercially available material.

Control Reaction: no $(Bu_3Sn)_2O$. An otherwise identical reaction, lacking $(Bu_3Sn)_2O$, lost only 3% of the azide after 3 h, as evidenced by ^1H NMR.

Functional Group Compatibility Survey: $PhSiH_3$ Method

Figure 3.3.3. To a solution of 2-azidododecane (211 mg, 1.00 mmol) and AIBN (8 mg, 0.05 mmol) in C_6D_6 (1.0 mL) were added $(Bu_3Sn)_2O$ (14.9 mg, 0.0250 mmol), $PhSiH_3$

(73 mg, 0.67 mmol), an internal standard (benzyl methyl ether or benzyl ether), *n*-PrOH (120 mg, 2.00 mmol), and the functional group-containing substrate (1.00 mmol). An aliquot was removed for an initial ^{1}H NMR spectrum, and the reaction was then heated in an oil bath maintained at 90 °C for 2 h. After cooling to r.t., an aliquot was removed for ^{1}H NMR analysis. A substrate was judged to be compatible if the yield of amine was ≥85% and the loss of substrate was ≤6%, based on integration versus the internal standard.

Bu_3SnH-Catalyzed Reductions of Azides to Amines: PMHS

General Procedure (Table 3.3.1, entries 1, 2, 4): To a mixture of the alkyl azide (2.00 mmol) and AIBN (16 mg, 0.10 mmol) were added $(Bu_3Sn)_2O$ (29.8 mg, 0.0500 mmol), PMHS (360 mg, 6.00 mmol), and *n*-PrOH (240 mg, 4.00 mmol). The reaction was heated in an oil bath maintained at 80 °C. After 1-2 h, the residue was cooled to r.t. and treated with anhydrous HCl (5 mL of a 1.0 M solution in Et_2O). Hexane was added if needed to facilitate precipitation. The resulting white solid was collected by filtration and then dissolved in MeOH. If insoluble material appeared upon standing, the solution was filtered prior to concentrating, which afforded the amine as a white hydrochloride salt. The ^{1}H and ^{13}C NMR spectra of the hydrochloride salt were identical to spectra for material prepared by protonation of the commercially available amine.

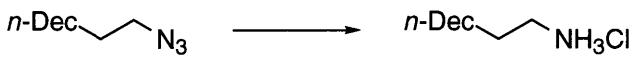


Table 3.3.1, entry 1. 1-Azidododecane (423 mg, 2.00 mmol) was allowed to react for 2 h according to the general procedure to afford 431 mg (97%; second run: 93%) of the HCl salt of 1-aminododecane.

Control Reaction: no $(Bu_3Sn)_2O$. An otherwise identical reaction run for 3.5 h, lacking $(Bu_3Sn)_2O$, still contained azide according to TLC and afforded no precipitate upon addition of hexane and HCl.

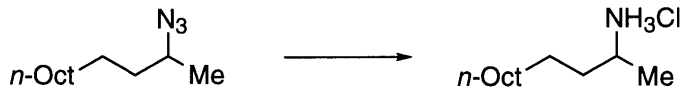


Table 3.3.1, entry 2. 2-Azidododecane (423 mg, 2.00 mmol) was allowed to react for 2 h according to the general procedure to afford 427 mg (96%; second run: 93%) of the HCl salt of 2-aminododecane.

Control Reaction: no $(Bu_3Sn)_2O$. An otherwise identical reaction, lacking $(Bu_3Sn)_2O$, still contained azide according to TLC and afforded no precipitate upon addition of hexane and HCl.

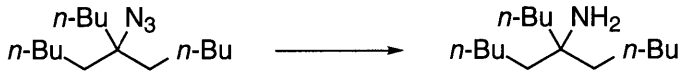


Table 3.3.1, entry 3. To a mixture of 6-azido-6-butylundecane (127 mg, 0.500 mmol) and AIBN (4 mg, 0.03 mmol) were added $(Bu_3Sn)_2O$ (7.5 mg, 0.013 mmol), PMHS (90 mg, 1.5 mmol), and *n*-PrOH (60 mg, 1.0 mmol). The reaction was heated in an oil bath maintained at 80 °C. After 5 h, the reaction mixture was cooled to room temperature and subjected to column chromatography. The product amine (contaminated by an insoluble white solid) was filtered, washed with pentane, and concentrated to afford 108 mg (95%; second run: 93%) of 6-amino-6-butylundecane as a clear, colorless oil. The ^1H and ^{13}C NMR spectra were identical with those obtained with $PhSiH_3$ as the stoichiometric reductant.

Control Reaction: no $(Bu_3Sn)_2O$. An otherwise identical reaction, run for 3.5 h and lacking $(Bu_3Sn)_2O$, proceeded to 1% conversion, as evidenced by GC analysis.

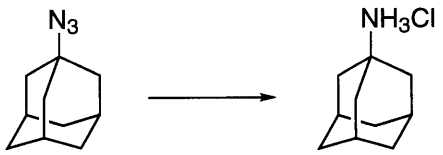


Table 3.3.1, entry 4. 1-Azidoadamantane (355 mg, 2.00 mmol) was allowed to react for 1 h according to the general procedure to afford 354 mg (94%; second run: 98%) of the HCl salt of 1-aminoadamantane.

Control Reaction: no $(Bu_3Sn)_2O$. An otherwise identical reaction, lacking $(Bu_3Sn)_2O$, still contained azide according to TLC and afforded no precipitate upon addition of hexane and HCl. Treatment with excess 1 M NaOH followed by extraction with Et_2O provided no amine product (^1H NMR).

Control Reaction: no *n*-PrOH. An otherwise identical reaction, run on a 1 mmol scale and lacking *n*-PrOH, still contained azide according to TLC and afforded 4 mg (2%) of precipitate upon addition of hexane and HCl.

Control Reaction: no AIBN. An otherwise identical reaction, run on a 1 mmol scale and lacking AIBN, still contained azide according to TLC and afforded 42 mg (22%) of precipitate upon addition of hexane and HCl.

Control Reaction: no PMHS. An otherwise identical reaction, run on a 1 mmol scale and lacking PMHS, still contained azide according to TLC and afforded no precipitate upon addition of hexane and HCl.

Scale-up. When run on a 20 mmol scale in a 1L round-bottom flask, the reaction began foaming vigorously after 25 min, and a rapid exotherm (CAUTION) accompanied by an immediate color change to black ensued. Isolation of the product as above afforded 3.82 g of the amine hydrochloride salt (102%).

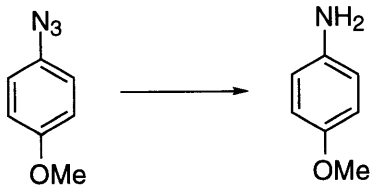


Table 3.3.1, entry 5. To a mixture of 4-methoxy-1-azidobenzene (298 mg, 2.00 mmol) and AIBN (16 mg, 0.10 mmol) were added 1-butanol (296 mg, 4.00 mmol), $(Bu_3Sn)_2O$ (29.8 mg, 0.0500 mmol), and PMHS (360 mg, 6.00 mmol). The reaction was heated in an oil bath maintained at 100 °C. After 5.5 h, the reaction was cooled to r.t. and treated with hexane (5 mL) and anhydrous HCl (5 mL of a 1.0 M solution in Et_2O). The resulting solid was collected by filtration and subjected to aqueous workup with 1 M NaOH and Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography afforded 225 mg (91%; second run: 91%) of *p*-anisidine as an orange solid. The ^1H and ^{13}C NMR spectra were identical to those obtained from the commercially available material.

Control Reaction: no $(Bu_3Sn)_2O$. An otherwise identical reaction, lacking $(Bu_3Sn)_2O$, contained azide and exhibited no amine product according to ^1H NMR of the crude reaction mixture.

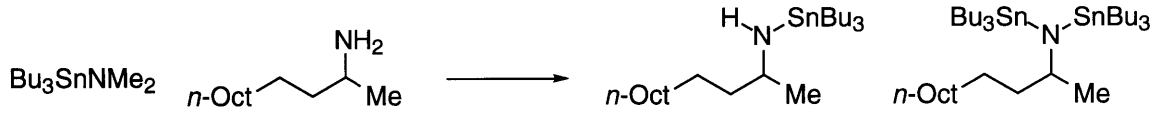
Functional Group Compatibility Survey: PMHS Method

Figure 3.3.3. To a mixture of 2-azidododecane (211 mg, 1.00 mmol) and AIBN (8 mg, 0.05 mmol) were added *n*-PrOH (120 mg, 2.00 mmol), $(Bu_3Sn)_2O$ (14.9 mg, 0.0250 mmol), PMHS (180 mg, 3.00 mmol), an internal standard (benzyl ether), and the functional group-containing substrate (1.00 mmol). An aliquot was removed for an initial ^1H NMR spectrum, and the reaction was then heated in an oil bath maintained at 80 °C for 2 h. After cooling to r.t., an aliquot was removed for ^1H NMR analysis. A

substrate was judged to be compatible if the yield of amine was ≥78% and the loss of substrate was ≤9%, based on integration versus the internal standard.

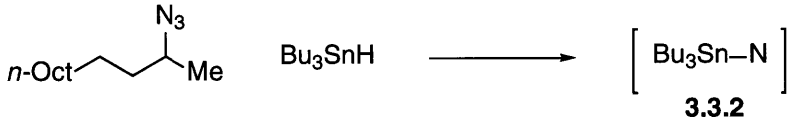
Investigation of Bu_3SnH-Catalyzed Azide Reduction by ^{119}Sn NMR

General. All manipulations were carried out under an atmosphere of nitrogen or argon. All yields were determined by integration versus the internal standard in the ^1H NMR spectrum. When possible, the identities of species observed in the ^{119}Sn NMR spectra were confirmed by comparison to authentic materials which were either prepared or purchased.



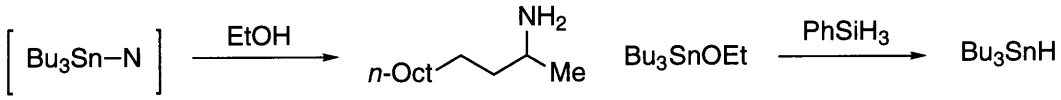
1,1,1-Tributyl-*N*-(1-methylundecyl)stannanamine and 1,1,1-tributyl-*N*-(1-methylundecyl)-*N*-(tributylstannyl)stannanamine. A mixture of Bu_3SnNMe_2 (297 mg, 0.890 mmol) and 2-aminododecane (165 mg, 0.890 mmol) was stirred under vacuum for 30 min. After standing at r.t. for 45 h, ^{119}Sn NMR analysis indicated that no Bu_3SnNMe_2 remained. The two new peaks that were observed were assigned to 1,1,1-tributyl-*N*-(1-methylundecyl)stannanamine and 1,1,1-tributyl-*N*-(1-methylundecyl)-*N*-(tributylstannyl)stannanamine. ^{119}Sn NMR (112 MHz, C_6D_6) δ 44.6, 31.2.

A. Stoichiometric Azide Reduction (Figure 3.3.4)



3.3.2

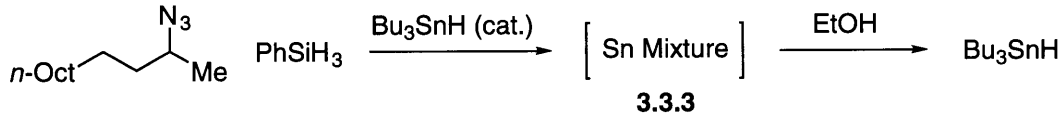
Generation of Tin Amides (3.3.2). To a solution of 2-azidododecane (634 mg, 3.00 mmol) and AIBN (25 mg, 0.15 mmol) in C_6D_6 (3.00 mL) were added Bu_3SnH (873 mg, 3.00 mmol) and benzyl ether (149 mg, 0.752 mmol, internal standard). The reaction was heated to reflux for 1 h in an oil bath maintained at 90 °C. After cooling to r.t., an aliquot was transferred to a J. Young tube and analyzed by ^{119}Sn NMR (**3.3.2**, Figure 3.3.4a). Six tin-containing products were observed, three of which were identified: $Bu_3SnSnBu_3$ (δ -83.1), $RNHSnBu_3$, and $RN(SnBu_3)_2$ (δ 44.6 and 31.1).



3.3.2

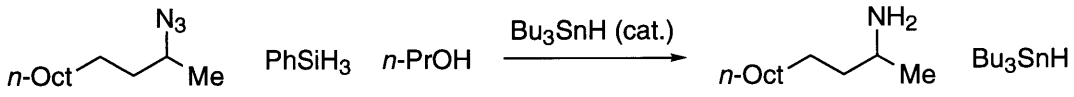
Treatment of Tin Amides (3.3.2) with EtOH, Followed by $PhSiH_3$. To a J. Young tube containing 1.7 mL of a solution of **3.3.2** (prepared as described in the preceding paragraph) was added EtOH (~1.2 equiv). An aliquot was analyzed by ^1H NMR, which revealed that 2-aminododecane had formed in 94% yield. The remainder of the reaction mixture was immediately analyzed by ^{119}Sn NMR (Figure 3.3.4b). Nearly complete conversion to Bu_3SnOEt (δ 91.1) was observed. $PhSiH_3$ (~1.4 equiv) was added, and after gas evolution had ceased (1 h), an aliquot was analyzed by ^1H NMR, which revealed that Bu_3SnH had formed in 98% yield. The remainder of the reaction mixture was analyzed by ^{119}Sn NMR (Figure 3.3.4c). Complete conversion to Bu_3SnH (δ -88.6) (major) and $Bu_3SnSnBu_3$ (minor) was observed.

B. Attempted Bu_3SnH-Catalyzed Azide Reduction in the Absence of *n*-PrOH (Figure 3.3.5)



Generation of Sn Mixture (3.3.3), Followed by Treatment with EtOH. To a solution of 2-azidododecane (317 mg, 1.50 mmol) and AIBN (12 mg, 0.075 mmol) in C_6D_6 (1.50 mL) were added Bu_3SnH (21.8 mg, 0.0750 mmol), $PhSiH_3$ (108 mg, 1.00 mmol), and benzyl ether (74 mg, internal standard). An aliquot was removed for ^1H NMR analysis. After heating to reflux for 2 h, ^1H NMR of an aliquot indicated a 12% loss of azide. After standing at room temperature for 51 h, the remainder of the reaction mixture was analyzed by ^{119}Sn NMR, which revealed a small amount of Bu_3SnH, along with ≥7 unidentified tin compounds (Figure 3.3.5b). EtOH (10 μL) was added, and the reaction was immediately analyzed by ^{119}Sn NMR (Figure 3.3.5c), which revealed nearly complete conversion to Bu_3SnH.

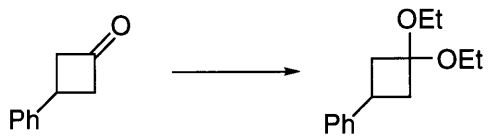
C. Bu_3SnH-Catalyzed Azide Reduction in the Presence of *n*-PrOH (Figure 3.3.6)



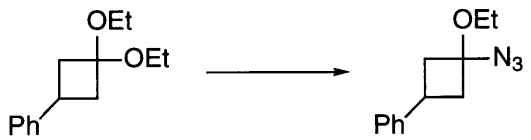
Quantitative Regeneration of Bu_3SnH Catalyst. To a solution of 2-azidododecane (211 mg, 1.00 mmol), AIBN (8 mg, 0.05 mmol), and tetradecane (2.7 mg, internal GC standard) in C_6D_6 (1.00 mL) were added $(Bu_3Sn)_2O$ (14.9 mg, 0.0250 mmol), $PhSiH_3$ (73 mg, 0.67 mmol), benzyl ether (99 mg, internal ^1H NMR standard), and *n*-PrOH (120 mg, 2.00 mmol). An aliquot was removed for ^1H NMR and GC analysis. After heating to

reflux for 2 h, ^{1}H NMR analysis indicated a 95% yield of 2-aminododecane, and GC analysis indicated a 96% recovery of Bu_3SnH. ^{119}Sn NMR analysis (Figure 3.3.6) revealed Bu_3SnH as the only observable tin-containing species.

Evidence for a Radical Pathway: Cyclobutane Ring-Opening



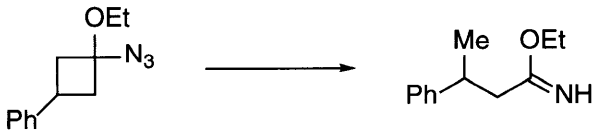
(3,3-Diethoxycyclobutyl) benzene. To a solution of 3-phenylcyclobutanone (2.00 g, 13.7 mmol) in absolute EtOH (5.0 mL) were added $(EtO)_3CH$ (4.1 g, 28 mmol) and a catalytic quantity of TsOH. After stirring for 3 h at r.t., TLC analysis indicated that no starting material remained. The reaction mixture was treated with a flake of KOH, and after stirring for 10 min the material was subjected to workup with hexanes and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford a pale yellow oil. Purification by flash chromatography afforded two portions of (3,3-diethoxycyclobutyl)benzene as clear, colorless oils weighing 1.87 g (homogeneous by TLC) and 690 mg (slightly impure by TLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.16 (m, 5H), 3.52 (q, 2H, J = 7.2), 3.47 (q, 2H, J = 7.2), 3.32 (pent, 1H, J = 8.9), 2.73-2.65 (m, 2H), 2.28-2.19 (m, 2H), 1.26 (t, 3H, J = 7.2), 1.21 (t, 3H, J = 7.2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 128.3, 126.7, 125.9, 99.4, 56.8, 56.4, 40.4, 30.5, 15.5, 15.3.



3.3.1

(3-Azido-3-ethoxycyclobutyl)benzene (3.3.1). The reaction was run according to the

published procedure.[45] To a mixture of (3,3-diethoxycyclobutyl)benzene (1.81 g, 8.23 mmol) and TMS-N_3 (948 mg, 8.23 mmol) at -78 °C was added $SnCl_4$ (~4 mg) via syringe. The cooling bath was removed, and after stirring for 1 h, TLC analysis indicated that no starting material was present. The reaction mixture was subjected to aqueous workup with hexanes and saturated $NaHCO_3$, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography, which afforded (3-azido-3-ethoxycyclobutyl)benzene in 2 portions weighing 1.18 g (homogeneous by TLC; clear, colorless oil; 2.1/1 mixture of diastereomers by ^1H NMR) and 515 mg (slightly impure by TLC; pale yellow oil). ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 3.63 (minor diastereomer, q, 2H, J = 7.2), 3.59 (major diastereomer, q, 2H, J = 7.2), 3.47 (minor diastereomer, pent, 1H, J = 8.7), 3.36 (major diastereomer, pent, 1H, J = 9.0), 2.87-2.68 (m, 2H), 2.46-2.35 (m, 2H), 1.31 (minor diastereomer, t, 3H, J = 7.2), 1.27 (major diastereomer, t, 3H, J = 6.9). ^{13}C NMR (75 MHz, $CDCl_3$) Major diastereomer: δ 143.6, 128.4, 126.5, 126.4, 91.5, 59.0, 41.3, 30.2, 15.2. Minor diastereomer: δ 143.9, 128.5, 126.5, 126.4, 91.7, 59.4, 40.4, 31.0, 15.4. IR (neat) 2980, 2104, 1268, 1230, 1196, 1140, 1046, 753, 698. HRMS: Calcd. for $C_{12}H_{15}NO$ $[M-N_2]^+$: 189.1154. Found: 189.1154.



3.3.1

Ethyl 3-phenylbutanimidate. To a solution of (3-azido-3-ethoxycyclobutyl)benzene, **3.3.1**, (109 mg, 0.500 mmol), AIBN (4 mg, 0.02 mmol), and benzyl ether (24.8 mg, 0.125 mmol; internal ^1H NMR standard) in C_6D_6 (500 μL) were added $(Bu_3Sn)_2O$ (7.5 mg, 0.013 mmol), $PhSiH_3$ (36 mg, 0.34 mmol), and *n*-PrOH (60 mg, 1.0 mmol). After heating the reaction to reflux for 90 min, ^1H NMR analysis indicated that ethyl 3-

phenylbutanimidate had been formed in 66% yield. A duplicate run afforded a yield of 75%. A portion of the reaction mixture was subjected to flash chromatography, which provided ethyl 3-phenylbutanimidate as a clear colorless oil. ^{1}H NMR (300 MHz, C_6D_6) δ 7.13-6.89 (m, 6H), 4.19 (q, 2H, J = 7.0), 2.92 (hex, 1H, J = 7.3), 2.29 (dd, 1H, J_1 = 14.4, J_2 = 7.5), 2.13 (dd, 1H, J_1 = 14.1, J_2 = 7.8), 1.11 (t, 3H, J = 7.2), 1.06 (d, 3H, J = 6.9). ^{13}C NMR (75 MHz, C_6D_6) δ 170.9, 146.4, 129.1, 127.4, 127.0, 61.5, 45.3, 37.9, 22.1, 14.7. IR (neat): 3326, 2967, 1650, 1604, 1494, 1480, 1453, 1402, 1376, 1338, 1094, 1036, 835, 763, 700. HRMS: Calcd. for $C_{12}H_{17}NO$: 191.1310. Found: 191.1311.

Determination of relative reactivity for azide substrates (Table 3.3.2)

Table 3.3.2 catalytic. To a solution of 1-adamantyl azide (89 mg, 0.50 mmol) and the azide in question (0.50 mmol) in benzene (2 mL) were added AIBN (8 mg, 0.050 mmol), $PhSiH_3$ (18 mg, 0.17 mmol), *n*-PrOH (40 mg, 0.67 mmol), and heptadecane (internal GC standard). The mixture was analyzed by GC and heated to reflux until the ratio of azides remained constant (i.e., until all the hydride was consumed). The percentage of the azide in question which was consumed was divided by the percentage of 1-adamantyl azide which was consumed in order to obtain relative rate values.

Table 3.3.2 stoichiometric. To a solution of 1-adamantyl azide (89 mg, 0.50 mmol) and the azide in question (0.50 mmol) in benzene (2 mL) were added AIBN (8 mg, 0.050 mmol) and heptadecane (internal GC standard), and the mixture was analyzed by GC. Bu_3SnH (146 mg, 0.500 mmol) was addded, and after heating to reflux until the ratio of azides remained constant, the relative rate values were obtained as in the preceeding paragraph.

3.4. Organotin-Catalyzed, Silicon-Hydride Mediated Room Temperature Reduction of Azides

Introduction

The previous section described two new tin-catalyzed methods for reducing azides to primary amines. We explored this transformation in the hopes of extending a new reaction of tin amides (the reduction to tin hydrides by silanes) to a novel catalytic process. Unfortunately, the Sn-N to Sn-H reduction was not fast enough to support a catalytic cycle, and we were forced to rely instead on the Sn-O to Sn-H couple for the turnover step (Figure 3.3.2). This observation, however, that tin exchange/reduction, is faster than the simple reduction of Sn-N to Sn-H, suggested a new set of possible tin-catalyzed reactions which exploits the reactive nature of tin amides.[46] Motivated by the ever-present need for new catalytic *asymmetric* methods in organic synthesis,[47] we proposed an enantioselective route to nitrogen heterocycles catalyzed by chiral tin reagents (Figure 3.4.1).

Thus, in the first step, the tin reagent would react with the azide to form a tin amide.[30-36] Then, intramolecular acyl transfer (the stereochemistry-determining step) would liberate Sn-OR and a chiral lactam. Finally, the silane reagent would reduce Sn-OR to Sn-H in the turnover step.[12-15]

One potential drawback of our aforementioned Bu_3SnH-catalyzed free-radical chain approaches to azide reductions, in the context of the proposed asymmetric transformation, is that they require radical initiators. The current arsenal of *reliable* radical initiators consists largely of peroxides and azoalkanes, and most of these require elevated temperatures (limited success with Et_3B[48] as a low temperature initiator in tin-catalyzed reductions has been experienced by the author). Thus, we wished to find a set of conditions for tin-catalyzed azide reductions which does not require elevated

temperatures, and we focused our efforts on two strategies.

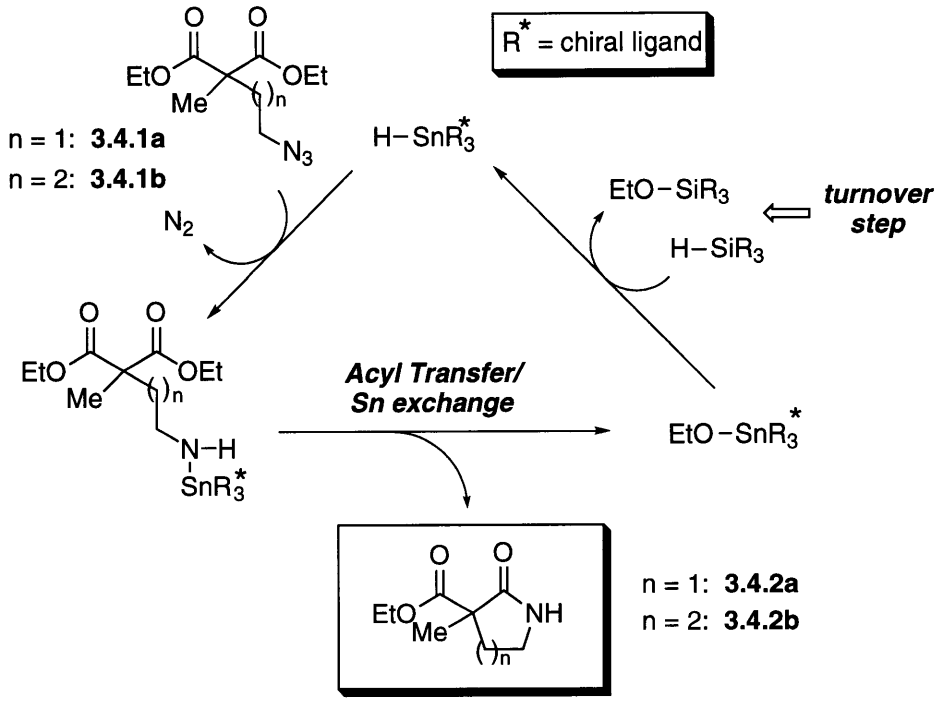
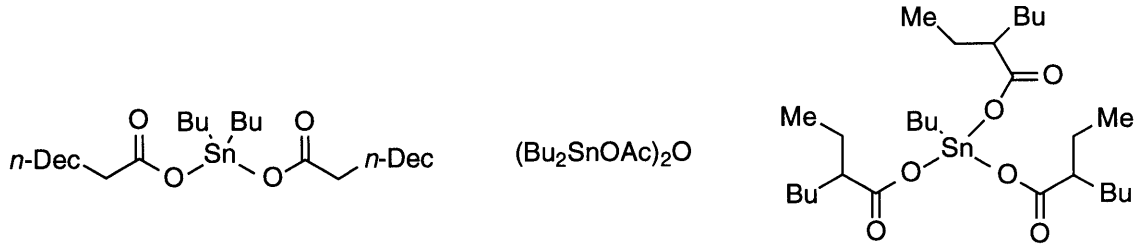


Figure 3.4.1. A proposed asymmetric synthesis of lactams catalyzed by chiral tin hydrides.

The first strategy builds upon two previous reports from the literature. Thus, Nitzsche and Wick[4] published a dibutyltin dilaurate catalyzed method for the reduction of carbonyls mediated by PMHS. Lipowitz at subsequently found that bis(dibutylacetoxytin) oxide (DBATO, the stable hydrolysis product of dibutlyltin diacetate) afforded superior results, and he provided evidence for the intermediacy of tin hydrides.[5]

Dibutyltin dilaurate and DBATO belong to a family of catalysts known as room temperature vulcanization (RTV) agents for silicones, and many are inexpensive, stable to atmospheric conditions, non-toxic, and commercially available.[49-52] Since the

Lipowitz publication, however, several new RTV tin catalysts have become readily available, and we anticipated that they, in turn, might exhibit new catalytic properties with respect to the reduction of organic functionalized substrates, specifically of azides.



dibutyltin dilaurate
Nitzsche/Wick
Carbonyl Reductions

DBATO
Lipowitz
Carbonyl Reductions

3.4.3
Hays/Fu
Azide Reductions

Figure 3.4.2. Three examples of RTV catalysts which have found use in tin-catalyzed, silicon mediated reductions.

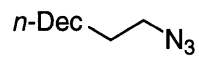
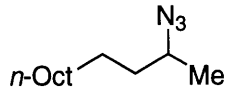
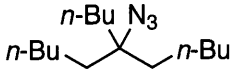
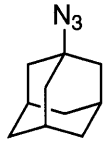
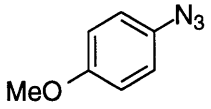
Results and Discussion

A series of organotin RTV catalysts were surveyed for activity in the simple reductions of azides to primary amines, and **3.4.3** emerged as the most reactive. Thus, treatment of a series of azides with 10 mol % **3.4.3**, PMHS (3 equiv), and *n*-PrOH (4 equiv) at room temperature affords the corresponding primary amines in high yields (eq 3.4.1, Table 3.4.1). No reduction is observed to occur in the absence of tin or of propanol.

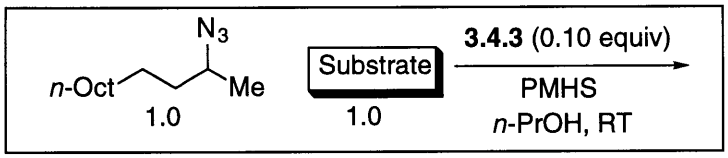
$$R\text{–}N_3 \xrightarrow[\text{PMHS}\\ n\text{-PrOH, RT}]{\textbf{3.4.3 (cat.)}} R\text{–}NH_2 \quad \textbf{\textit{76-90\%}} \qquad (3.4.1)$$

Alkynes, olefins, esters, alkyl chlorides, and alkyl bromides, are compatible with the reduction conditions, but ketones and nitro groups are not.

Table 3.4.1. Room Temperature PMHS-Mediated Reduction of Azides Catalyzed by **3.4.3.**

Entry	Substrate	Yield (%)[a]
1		82
2		86
3		76
4		82
5		90

[a] Isolated yield, average of two runs.



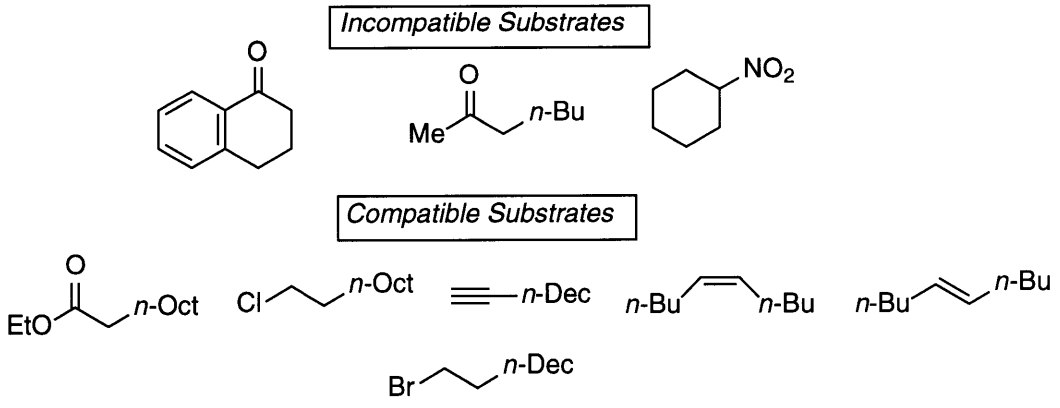
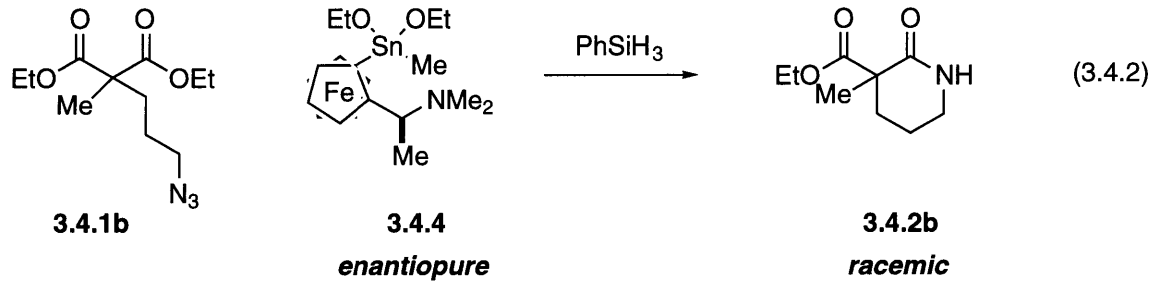


Figure 3.4.3. Functional group compatibility survey.

The second strategy to accomplish room temperature tin-catalyzed azide reductions focused on the enhanced reducing ability of tin dihydrides over the corresponding monohydrides.[23] Thus, treatment of **3.4.1a** with $Bu_2Sn(OMe)_2$ (10 mol %) and 1.5 equiv $PhSiH_3$ at room temperature afforded an 84% yield of the corresponding lactam **3.4.2a**. The 6-membered ring lactam **3.4.2b** was likewise cleanly formed. Unfortunately, replacing $Bu_2Sn(OMe)_2$ by the enantiopure tin bisalkoxide **3.4.4**[53] afforded the lactam **3.4.2b** in racemic form (eq 3.4.2).



3.4.1b **3.4.4** ***enantiopure*** **3.4.2b** ***racemic*** (3.4.2)

In conclusion, we have developed two *room temperature* organotin-catalyzed azide reductions in order to lay the groundwork for a possible asymmetric transformation which exploits the reactivity of the intermediate tin amide (Figure 3.4.1). The first strategy focused on the commerically available RTV catalysts (Figure 3.4.2), and the second strategy focused on the reactive tin dihydrides. Unfortunately, the only enantiopure tin catalyst available to the author afforded no asymmetric induction.

Experimental

General

n-Butyltris(2-ethylhexanoate)tin (**3.4.3**) and the remaining tin catalysts screened in this section were obtained from Gelest, Inc. and used without purification, with the exception of **3.4.4**, which was prepared by Jack Liang in these laboratories.

3.4.1a and **3.4.1b** were prepared by the literature method.[54]

The remaining materials and methods were described in the Experimental Section of 3.3.

The RTV catalysts which were found to be inferior to **3.4.3** for the catalytic reduction of azides were: bis(2-ethylhexanoate)tin, *n*-butyltin hydroxide oxide, di-*n*-butylbis(2,4-pentanedionate)tin, and di-*n*-butyldilauryltin.

Reductions of Azides to Amines Catalyzed by 3.4.3

General Procedure (Table 3.4.1): A mixture of the azide (1.00 equiv), *n*-butyltris(2-ethylhexanoate)tin (0.10 equiv), PMHS (3.0 equiv), and *n*-PrOH (4.0 equiv) was allowed to stir under N_2 until no starting material remained by ^1H NMR spectroscopy. The reaction mixture was purified by flash chromatography to afford the amines which were identical by ^1H and ^{13}C NMR to the authentic materials (Section 3.3).

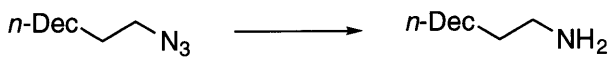


Table 3.4.1, entry 1. 1-Azidododecane (423 mg, 2.00 mmol) was reduced according to the general procedure for 27 h. Flash chromatography on the orange reaction mixture, followed by bulb-to-bulb distillation afforded 303 mg (82%; second run 82%) of

1-aminododecane as a white solid.

Control Reaction: no Sn. After 54 h, an identical reaction, but lacking in **3.4.3**, exhibited ≤5% reduction as evidenced by ^{1}H NMR spectroscopy.

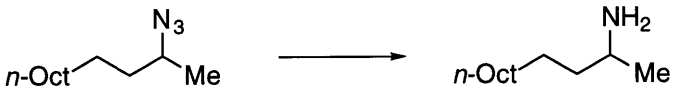


Table 3.4.1, entry 2. 2-Azidododecane (423 mg, 2.00 mmol) was reduced according to the general procedure for 46 h. Flash chromatography on the orange reaction mixture, followed by bulb-to-bulb distillation afforded 314 mg (85%; second run 86%) of 2-aminododecane as a clear, colorless oil.

Control Reaction: no Sn. After 56 h, an identical reaction, but lacking in **3.4.3**, exhibited ≤5% reduction as evidenced by ^{1}H NMR spectroscopy.

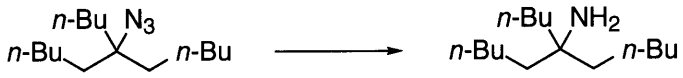


Table 3.4.1, entry 3. 6-Azido-6-butylundecane (127 mg, 0.500 mmol) was reduced according to the general procedure for 70 h. Flash chromatography afforded 84 mg (74%; second run 78%) of 6-amino-6-butylundecane as a clear, colorless oil.

Control Reaction: no Sn. After 9 days, an identical reaction, but lacking in **3.4.3**, exhibited ≤5% reduction as evidenced by ^{1}H NMR spectroscopy, and the azide stretch remained in the infrared spectrum.

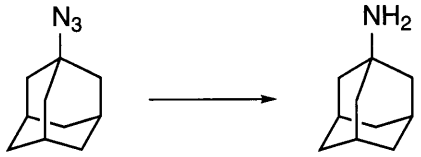


Table 3.4.1, entry 4. 1-Azidoadamantane (355 mg, 2.00 mmol) was reduced according to the general procedure. After 43 h, ^{1}H NMR analysis of the white, milky mixture, indicated that the reaction had progressed 89% to completion. Additional PMHS (240 mg, 4.0 mmol) was added, and after 1 h, the orange reaction was complete as evidenced by ^{1}H NMR. Flash chromatography afforded a white solid, which was taken up in Et_2O, filtered to remove insoluble materials, and concentrated to afford 254 mg (84%; second run 80%) of 1-aminoadamantane as a white solid.

Control Reaction: no Sn. After 54 h, an identical reaction, but lacking in **3.4.3**, exhibited ≤5% reduction as evidenced by ^{1}H NMR spectroscopy.

Control Reaction: no *n*-PrOH. After 45 h, an identical reaction, but lacking in *n*-PrOH, exhibited ≤5% reduction as evidenced by ^{1}H NMR spectroscopy.

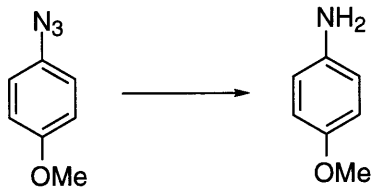


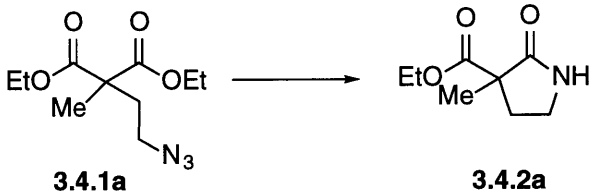
Table 3.4.1, entry 5. 4-Methoxy-1-azidobenzene (298 mg, 2.00 mmol) was reduced according to the general procedure for 72 h. The orange reaction mixture was concentrated, taken up in hexane, treated with HCl (5 mL of a 1 M solution in Et_2O), and the white precipitate was collected by filtration. Extraction of the free base from 40 mL of 1 N NaOH with Et_2O, followed by drying (Na_2SO_4) and flash chromatography afforded 236 mg (96%; second run 85%) of *p*-anisidine as an orange solid.

Control Reaction: no Sn. After 54 h, an identical reaction, but lacking in **3.4.3**, exhibited ≤5% reduction as evidenced by ^{1}H NMR spectroscopy.

Functional Group Compatibility Survey

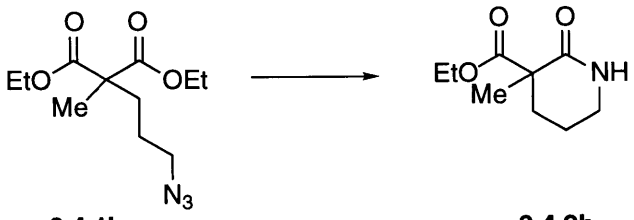
Figure 3.4.3. A mixture of 2-azidododecane (211 mg, 1.00 mmol), and the functional group containing substrate (1.00 mmol) was subjected to the standard reduction conditions. An aliquot was removed for an initial ^1H NMR spectrum, the reaction was then allowed to stir at room temperature under N_2, and an additional aliquot was removed for ^1H NMR analysis. A substrate was judged to be compatible if the yield of amine was ≥78% and the loss of substrate was ≤8%, based on integration versus the internal standard (benzyl methyl ether).

Tin Catalyzed Formation of Lactams via Azide Redcuction/Acyl Transfer



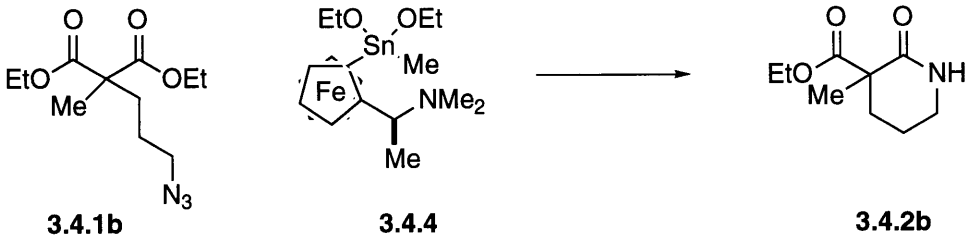
3.4.1a **3.4.2a**

3-Methyl-2-oxo-3-pyrrolidinecarboxylic acid ethyl ester (3.4.2a). To a mixture of $PhSiH_3$ (162 mg, 1.50 mmol) and $Bu_2Sn(OMe)_2$ (29 mg, 0.10 mmol) was added **3.4.1a** (243 mg, 1.00 mmol). The reaction was stirred at ambient temperature, and after 4 h, GC analysis indicated that the reaction had progressed 95%. Concentration, followed by flash chromatography afforded 144 mg (84%) of **3.4.2a** as a clear, colorless oil.[55] ^1H NMR (300 MHz, $CDCl_3$) δ 6.8 (brs, 1H), 4.19 (m, 2H), 3.46 (m, 1H), 3.34 (m, 1H), 2,62 (m, 1H), 2.00 (m, 1H), 1.43 (s, 3H), 1.26 (t, 3H, J = 7.1).



3.4.1b **3.4.2b**

3-Methyl-2-oxo-3-piperidinecarboxylic acid ethyl ester (3.4.2b). To a mixture of $PhSiH_3$ (81.2 mg, 0.750 mmol) and $Bu_2Sn(OMe)_2$ (14.8 mg, 0.050 mmol) was added **3.4.1b** (129 mg, 0.500 mmol). The reaction was stirred at ambient temperature, and after 20 h, GC analysis indicated that the reaction had progressed to completion. Hexane (1 mL) was added, the mixture was cooled on an ice bath, and the supernatent was removed from the resulting white solid. After washing with hexane (3x) and drying under vacuum, (**3.4.2b**) was obtained as a white solid, which was identical by ^{13}C NMR to the published material.[56]



3.4.1b **3.4.4** **3.4.2b**

3-Methyl-2-oxo-3-piperidinecarboxylic acid ethyl ester (Eq 3.4.2). To a mixture of $PhSiH_3$ (68 mg, 0.63 mmol) and **3.4.4** (20 mg, 0.042 mmol) was added **3.4.1b** (108 mg, 0.42 mmol). The reaction was stirred at ambient temperature, and after 11 h, GC analysis indicated that the reaction had progressed to completion. Hexane (1 mL) was added, the mixture was cooled on an ice bath, and the supernatent was removed from the resulting black solid. After washing with hexane (2x), the solid was passed through a pad of silica, eluting with EtOAc, and concentrated to afford **3.4.2** as a clear, colorless oil. Chiral GC analysis indicated an enantiomeric excess of 2%.

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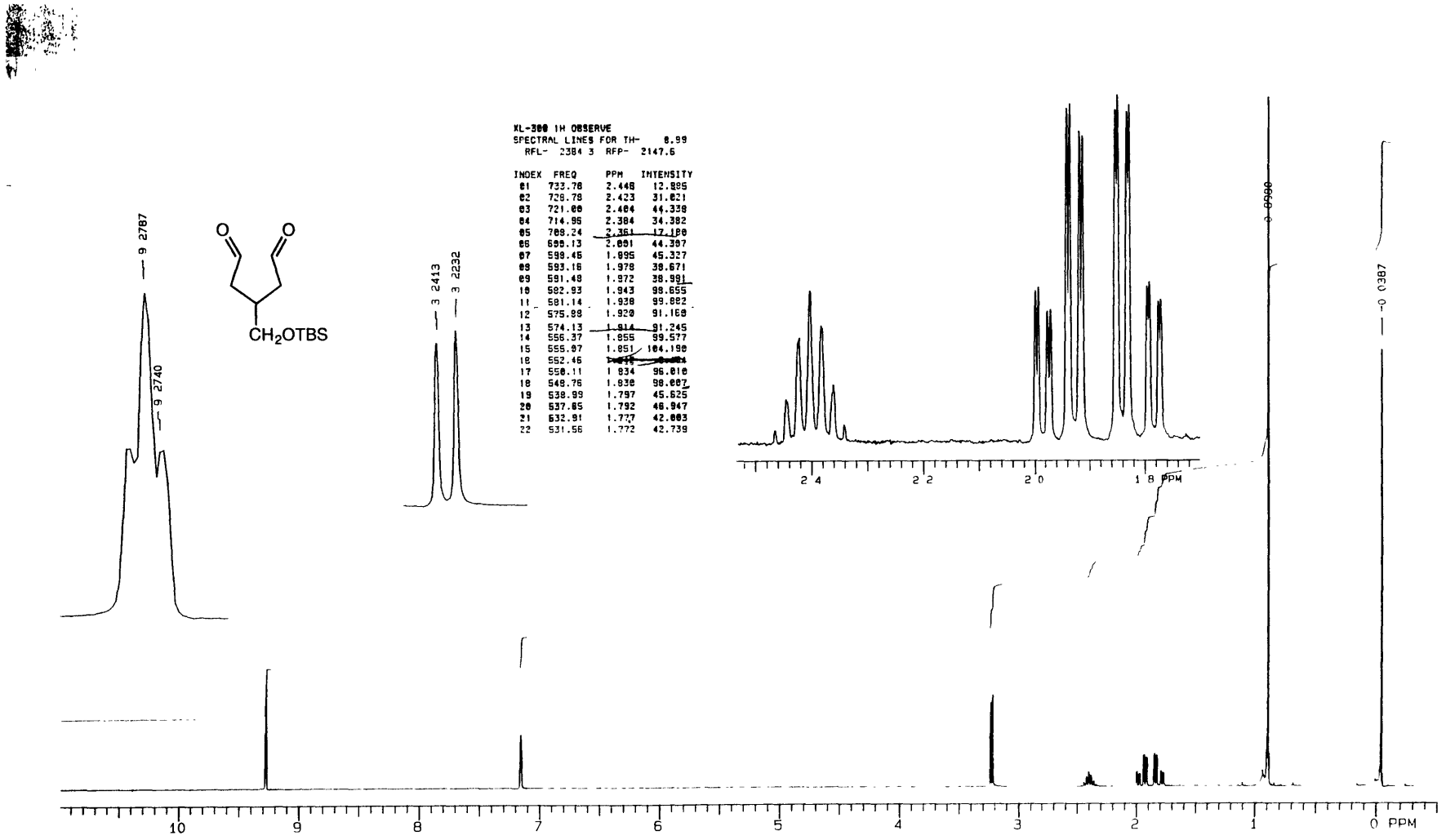
Appendix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02 728.78 2.423 31.621
03 721.00 2.404 44.338
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06 698.13 2.001 44.307
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09 591.48 1.972 38.981
10 582.93 1.943 98.655
11 581.14 1.938 99.882
12 575.88 1.920 91.168
13 574.13 1.914 91.245
14 556.37 1.855 99.577
15 555.97 1.851 104.198
16 552.46
17 550.11 1.834 96.810
18 548.76 1.830 98.007
19 538.99 1.797 45.525
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21 532.91 1.777 42.003
22 531.56 1.772 42.739
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9 2740
3 2413
3 2232
CH2OTBS
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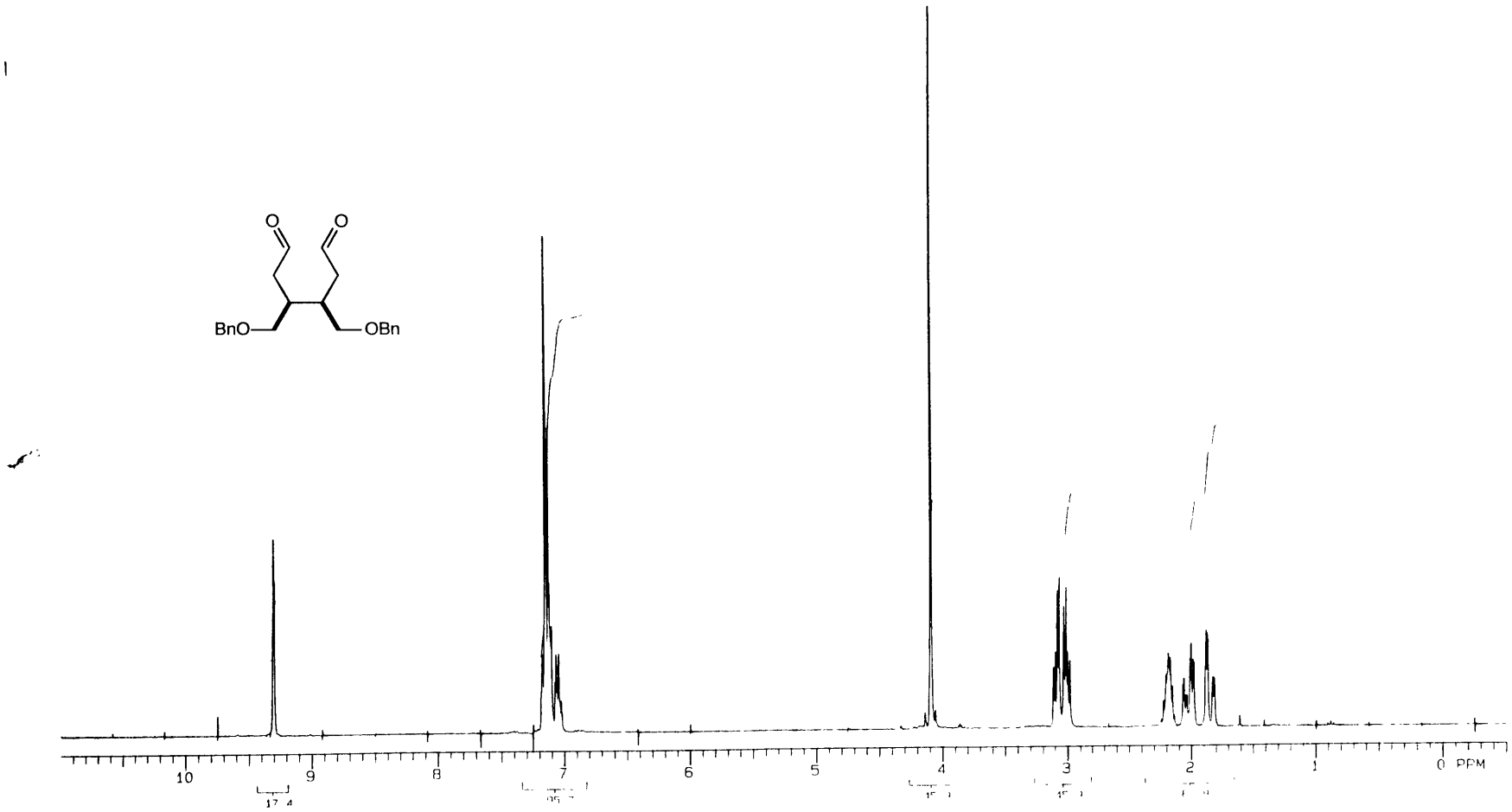
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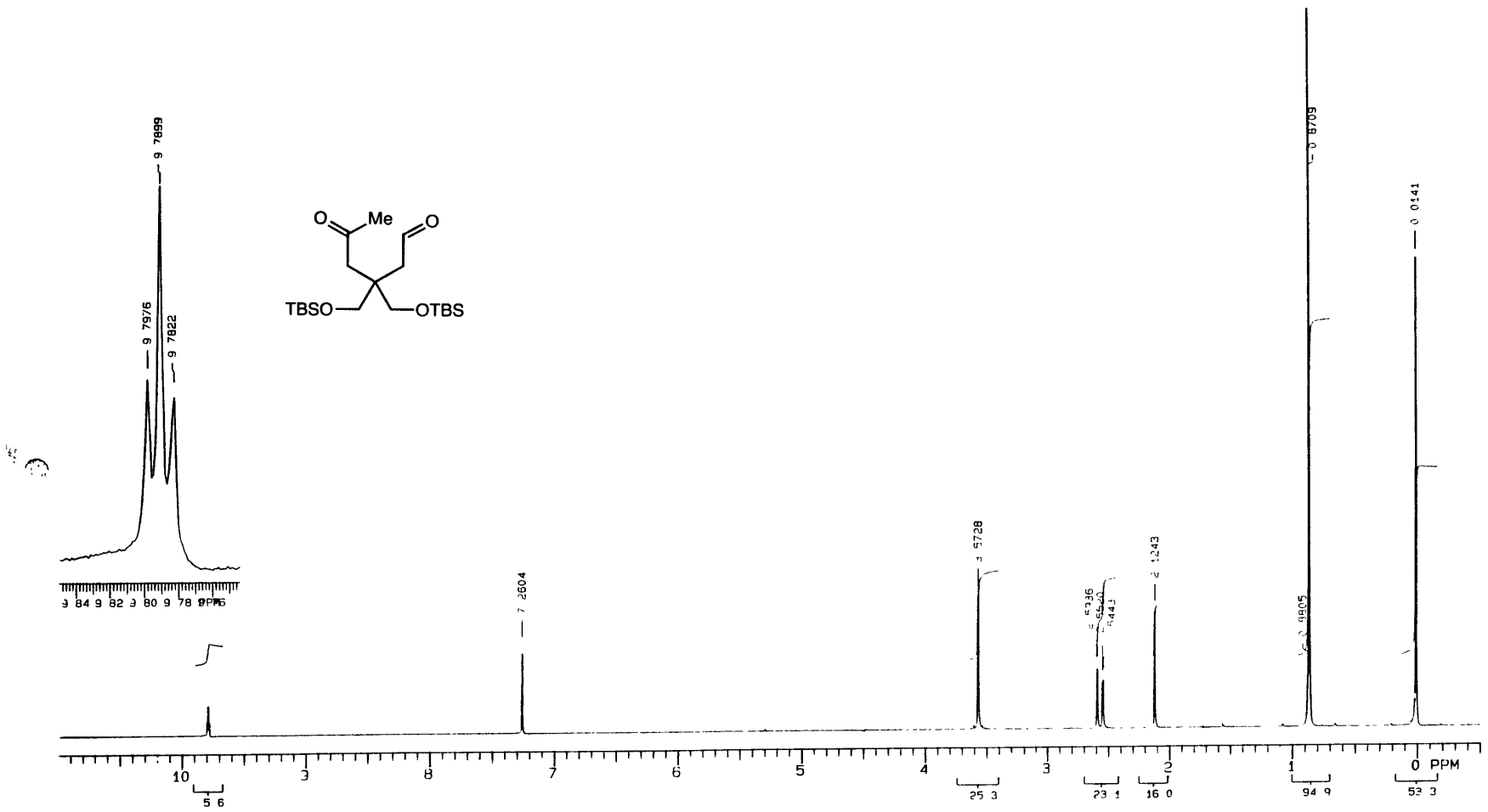
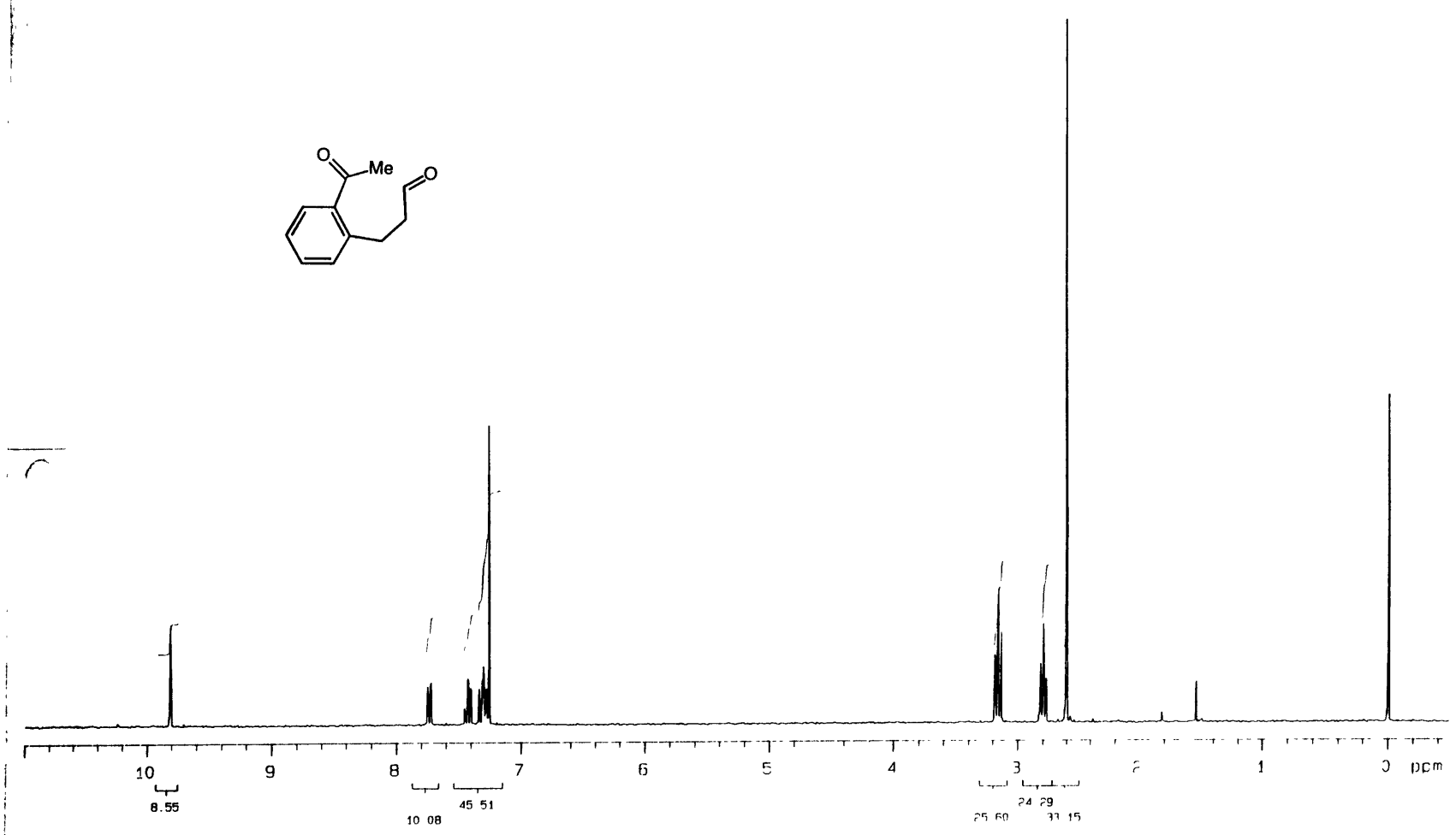
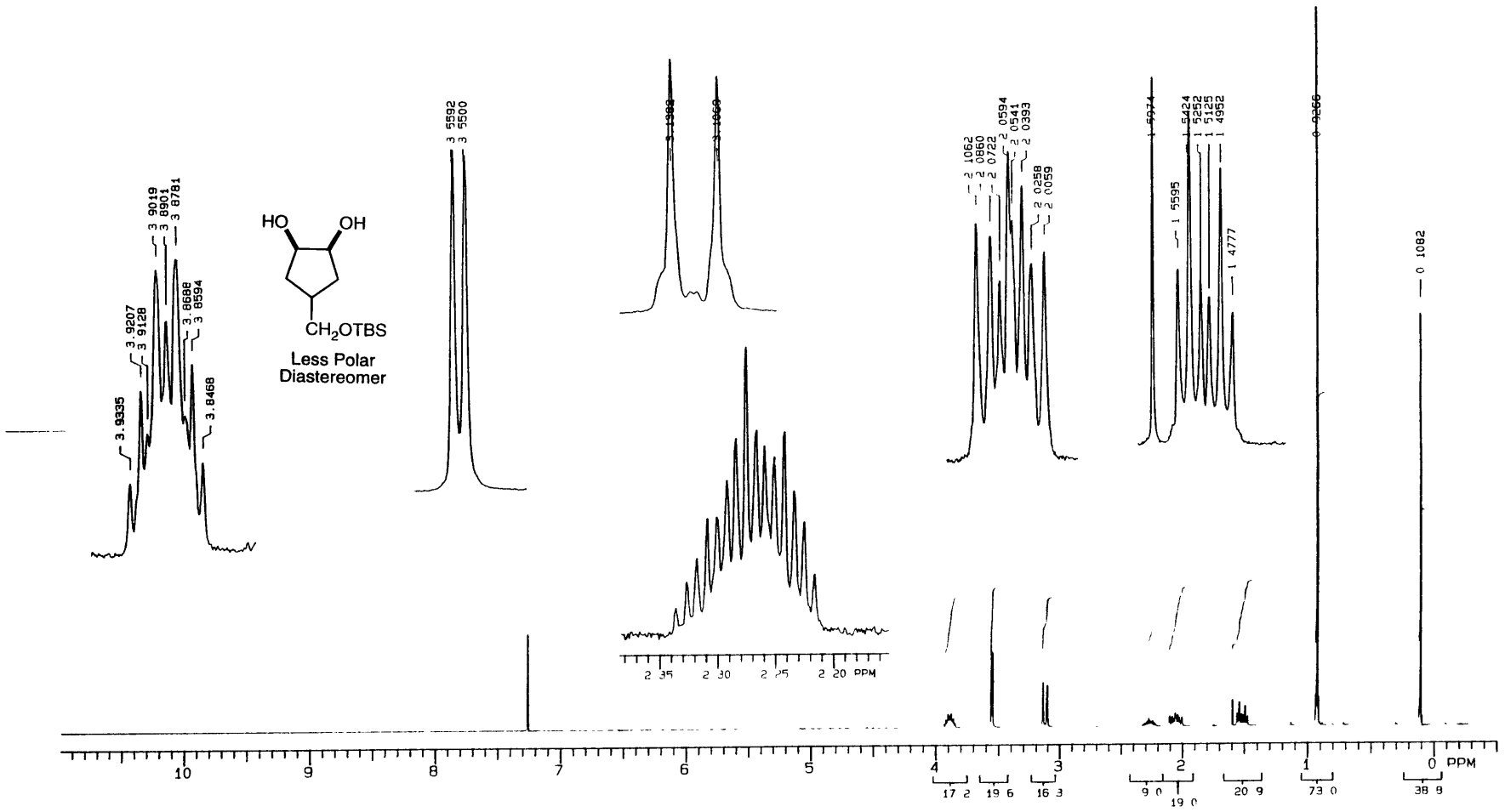
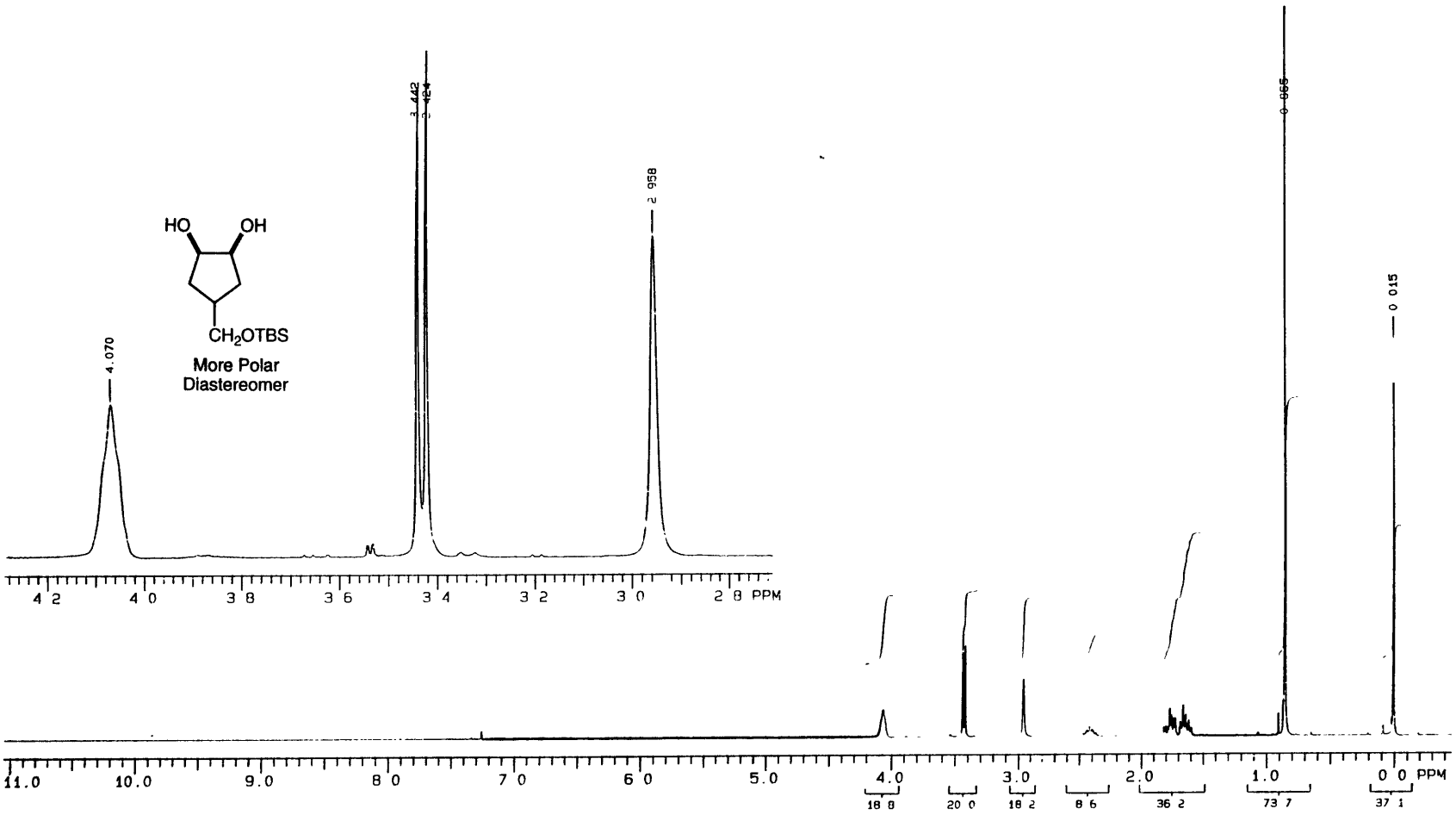
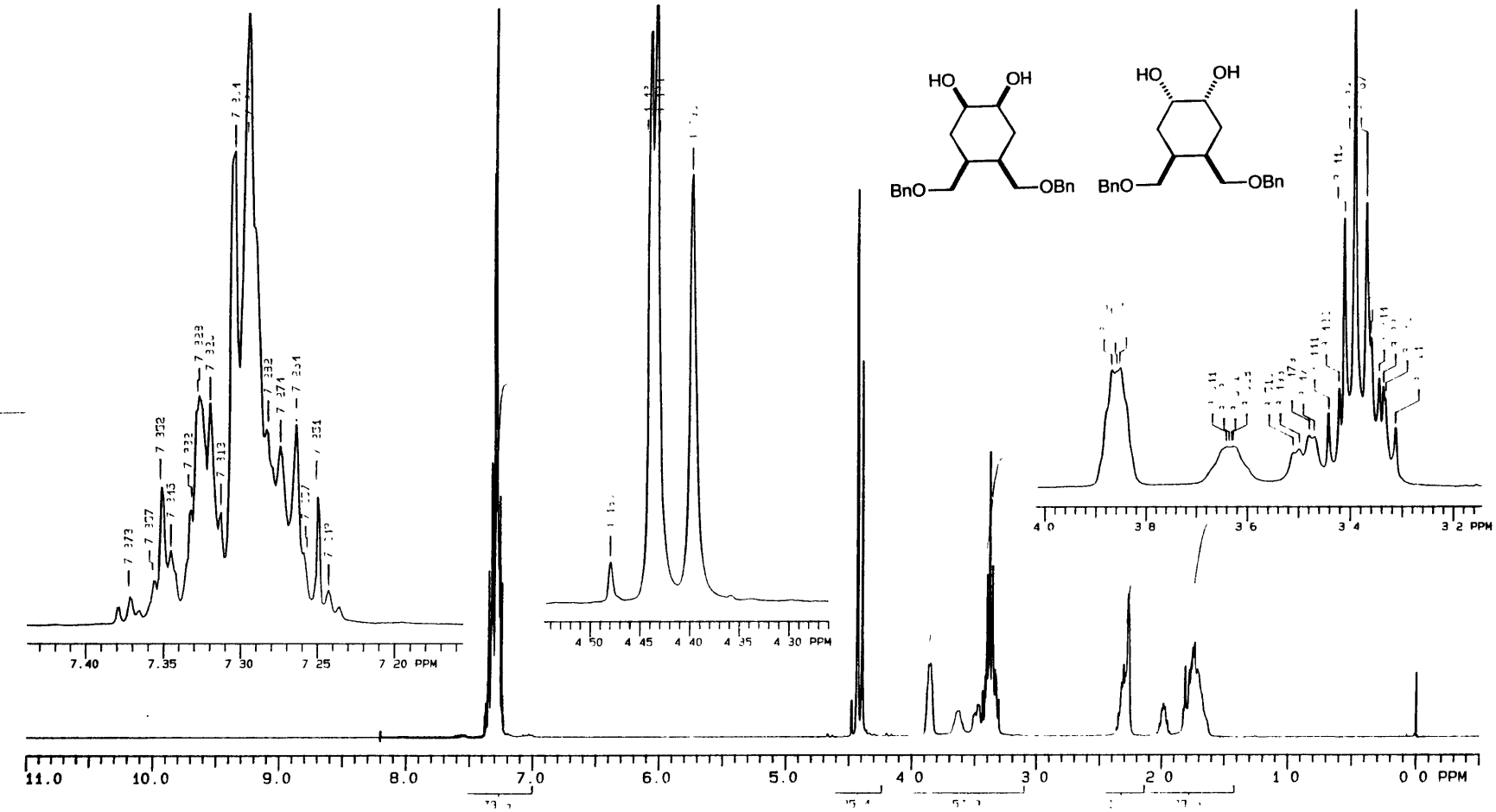
1
0 PPM

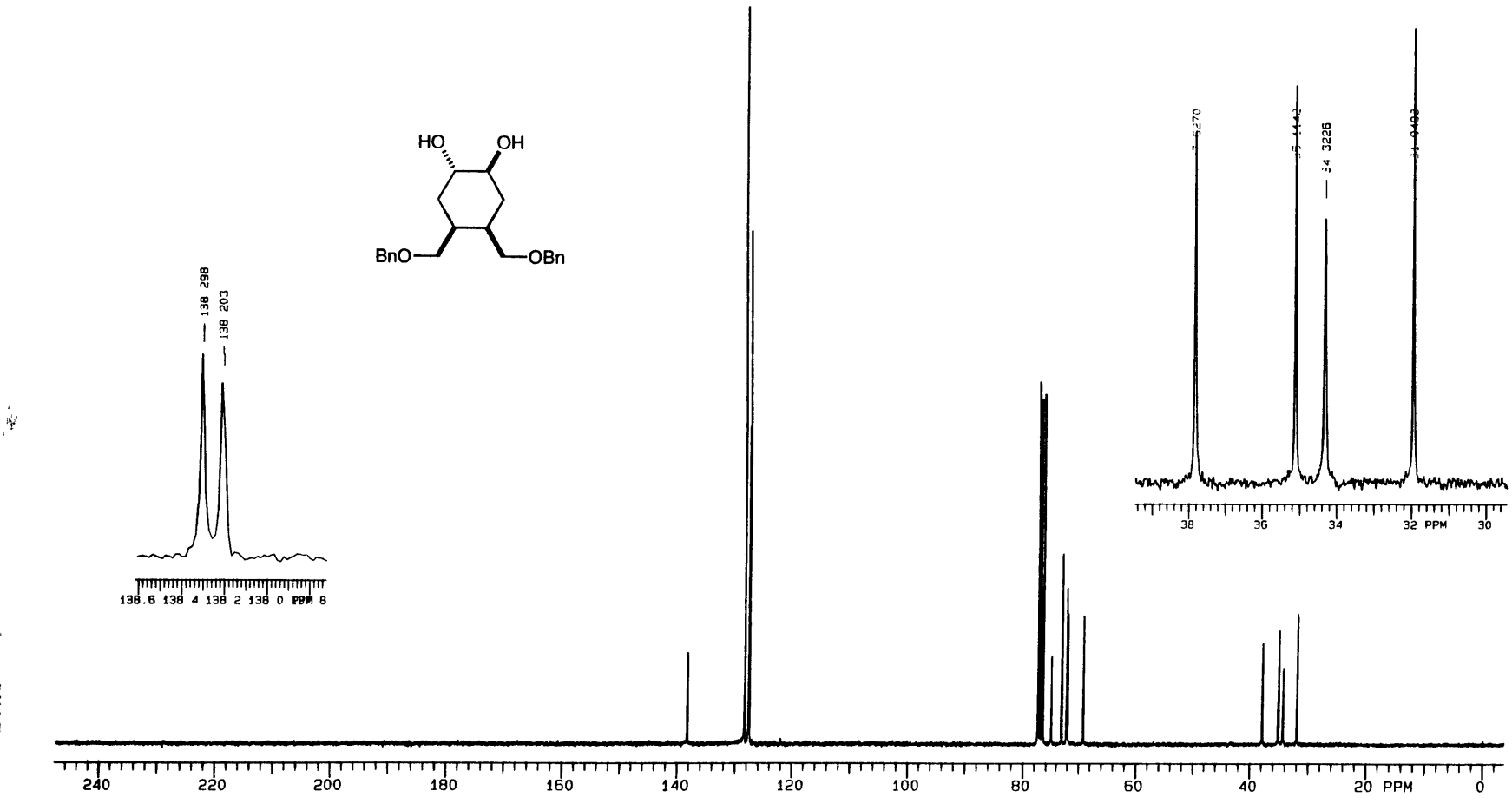

O
Me
O
TBSO
OTBS
9.7899
9.7976
9.7822
7.2604
5.5728
5.5436
5.5290
5.5143
2.1243
0.8709
0.8605
0.0141
PPM
5.6
25.3
23.1
16.0
94.9
53.3

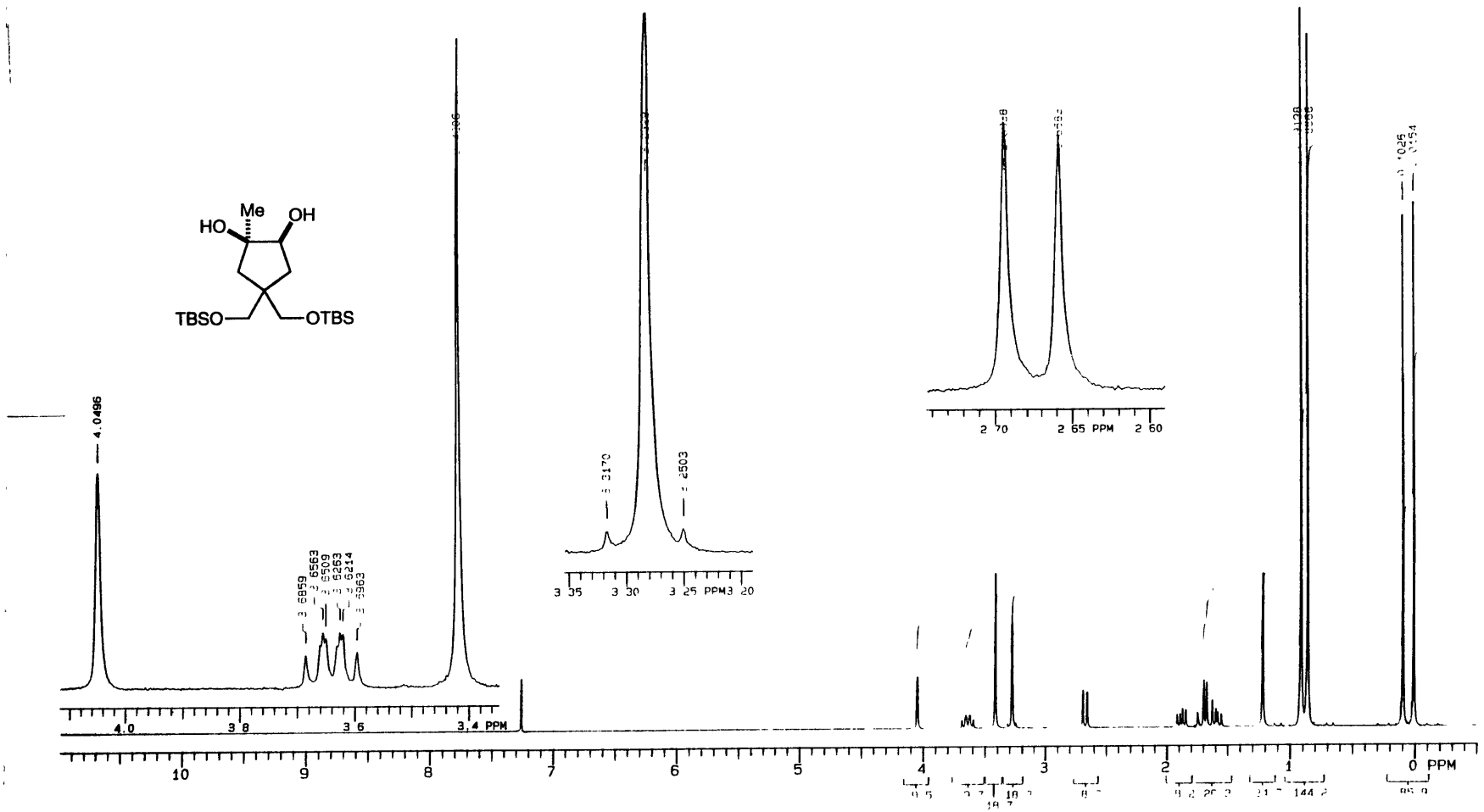

O
Me
O
10
9
8
7
6
5
4
3
2
1
0 ppm
8.55
10.08
45.51
25.60
24.29
33.15

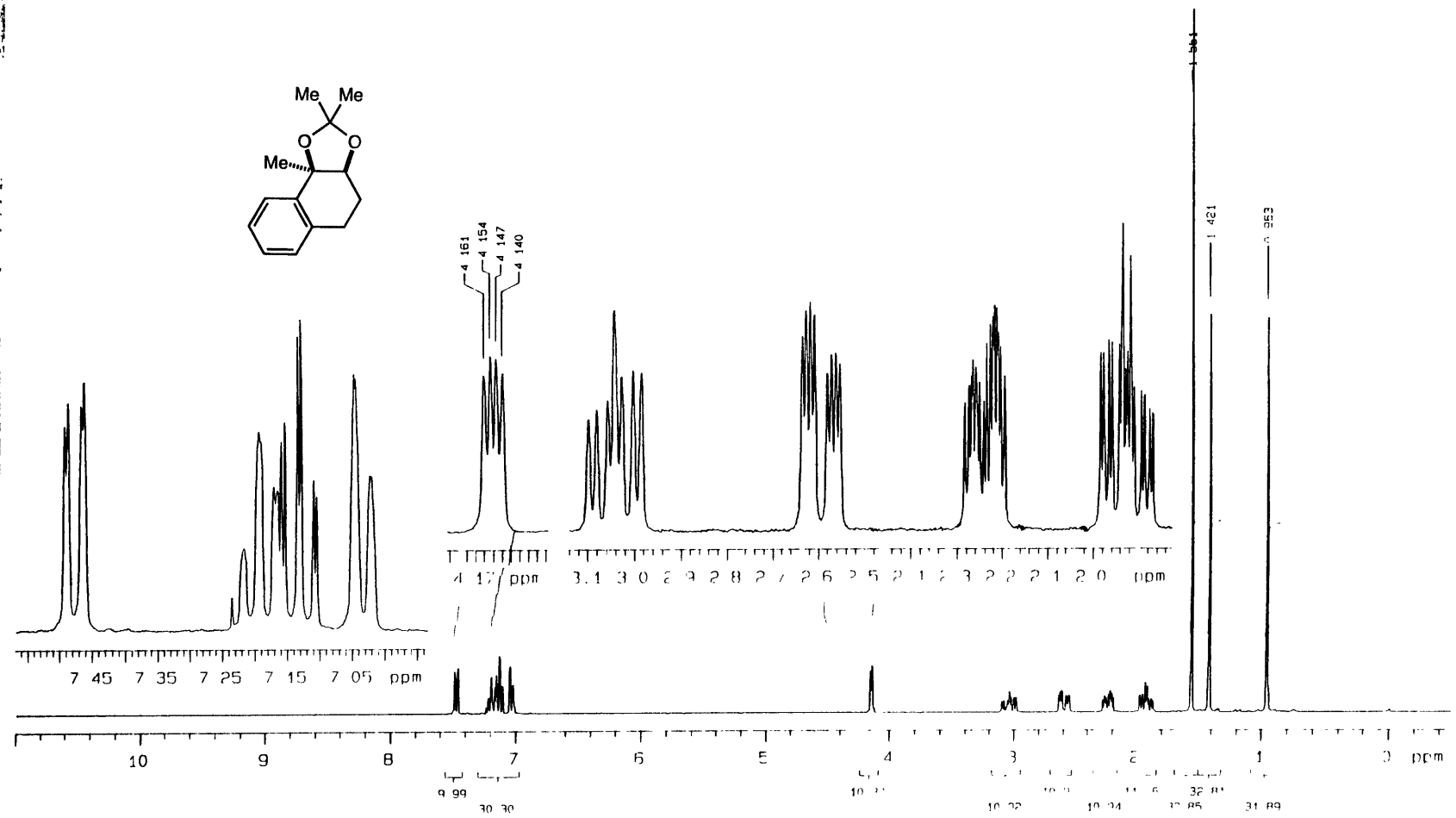

HO
OH
CH2OTBS
Less Polar
Diastereomer
3.9335
3.9207
3.9128
3.9019
3.8901
3.8781
3.8688
3.8594
3.8468
3.5592
3.5500
2.1062
2.0860
2.0722
2.0594
2.0541
2.0393
2.0258
2.0059
1.5974
1.5595
1.5424
1.5252
1.5125
1.4952
1.4777
0.9266
0.1082
2.35
2.30
2.25
2.20 PPM
10
9
8
7
6
5
4
3
2
1
0 PPM
17.2
19.6
16.3
9.0
19.0
20.9
73.0
38.8

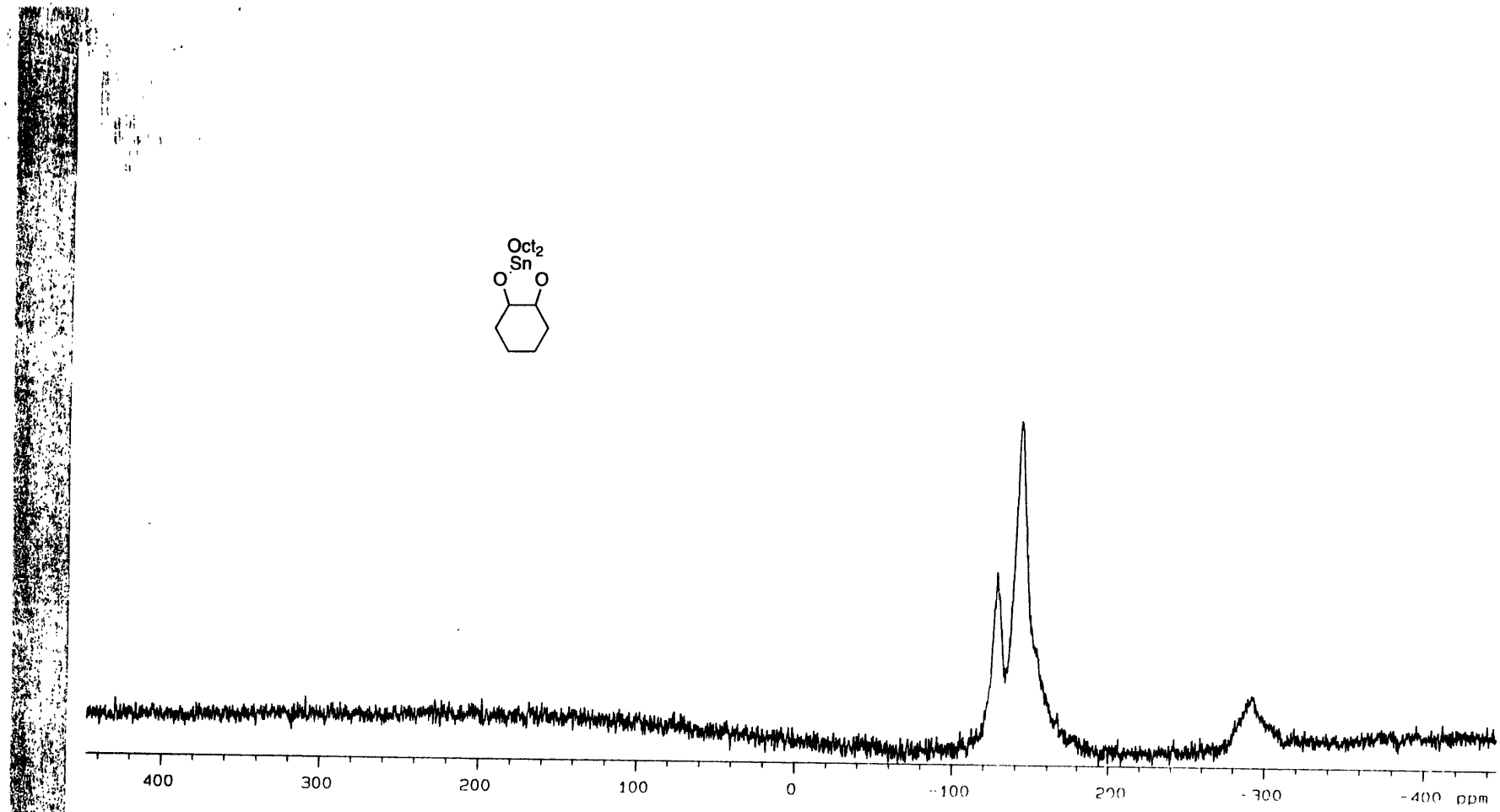

HO
OH
CH2OTBS
More Polar
Diastereomer
4.070
3.442
3.424
2.958
0.865
0.015
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8 PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
18.8
20.0
18.2
8.6
36.2
73.7
37.1

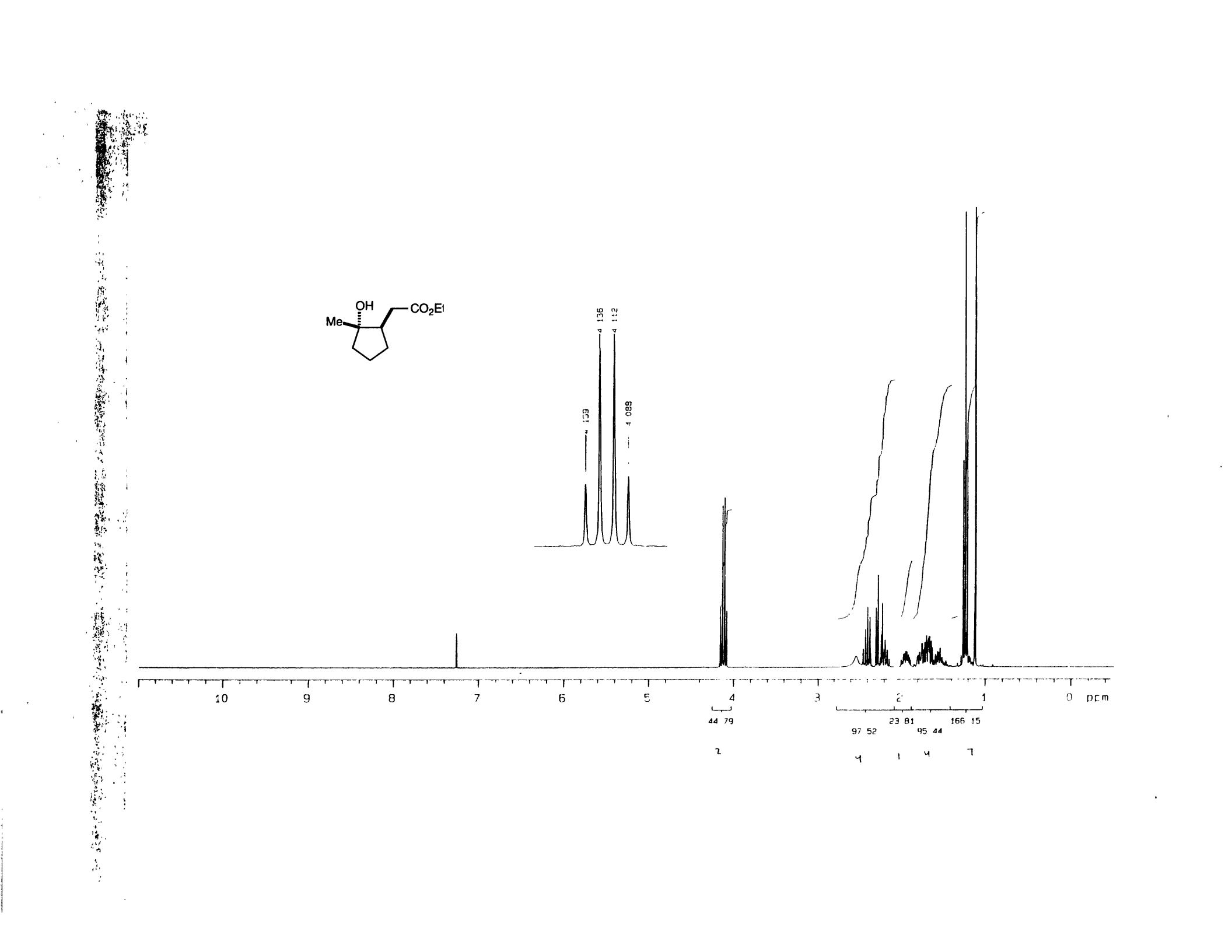

HO
OH
BnO
OBn
HO
OH
BnO
OBn
7.40
7.35
7.30
7.25
7.20 PPM
4.50
4.45
4.40
4.35
4.30 PPM
4.0
3.8
3.6
3.4
3.2 PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

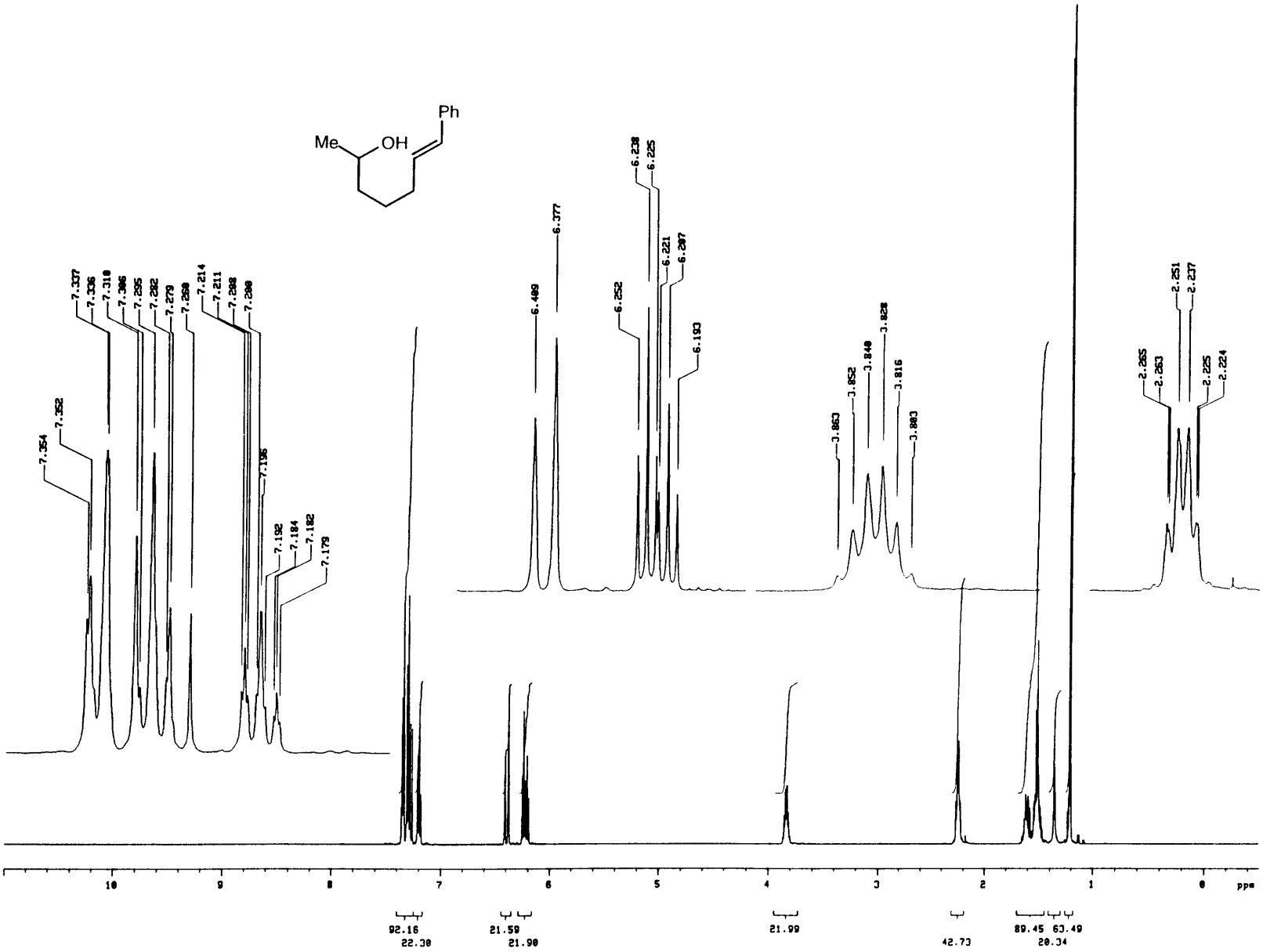

HO
OH
BnO
OBn
138.298
138.203
34.3226
240
220
200
180
160
140
120
100
80
60
40
20 PPM
0
38
36
34
32 PPM
30

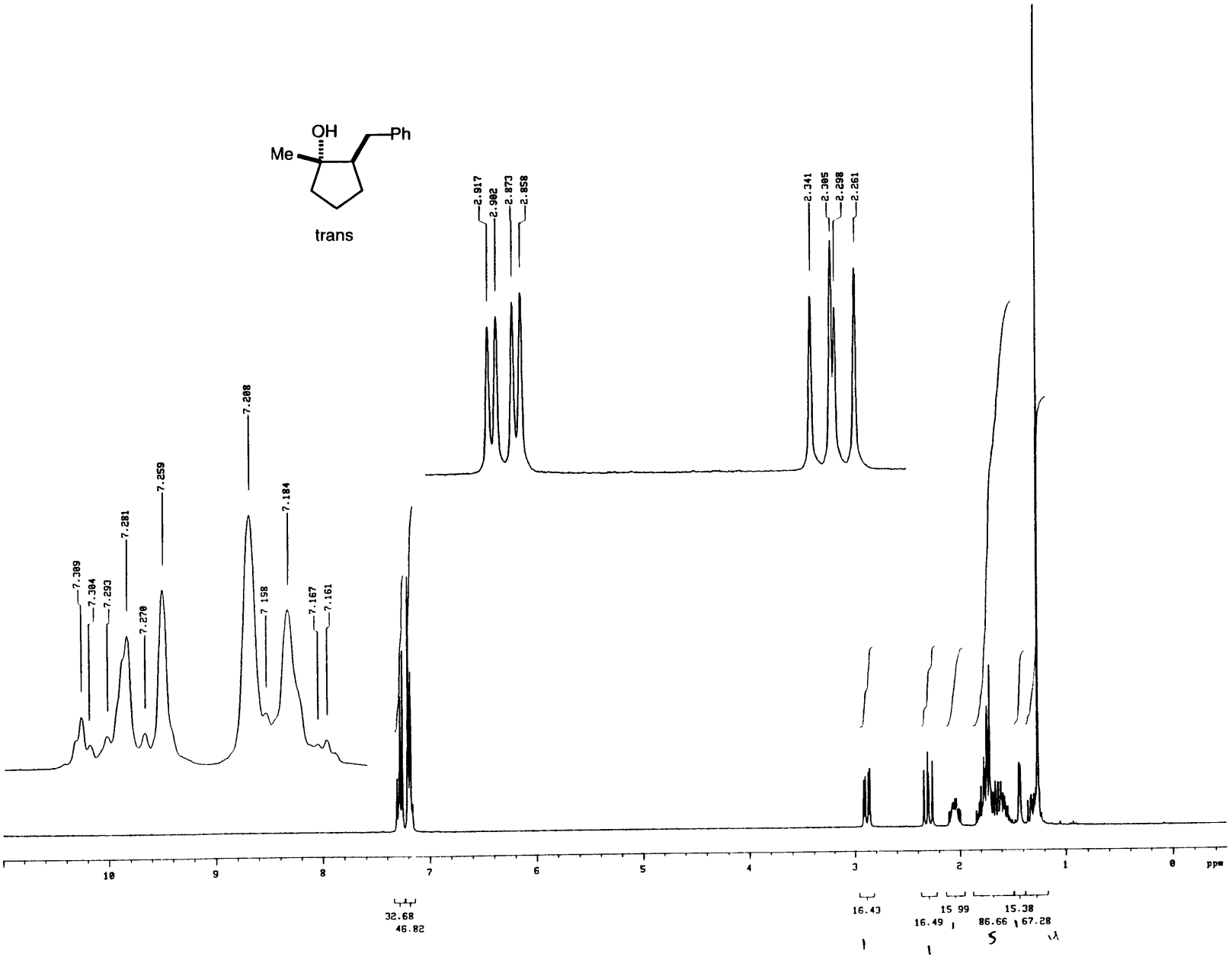

Me
HO
OH
TBSO
OTBS
4.0496
3.6859
3.6563
3.6509
3.6263
3.6214
3.5963
3.3170
3.2503
2.70
2.65 PPM
2.60
4.0
3.8
3.6
3.4 PPM
3.35
3.30
3.25 PPM
3.20
10
9
8
7
6
5
4
3
2
1
0 PPM

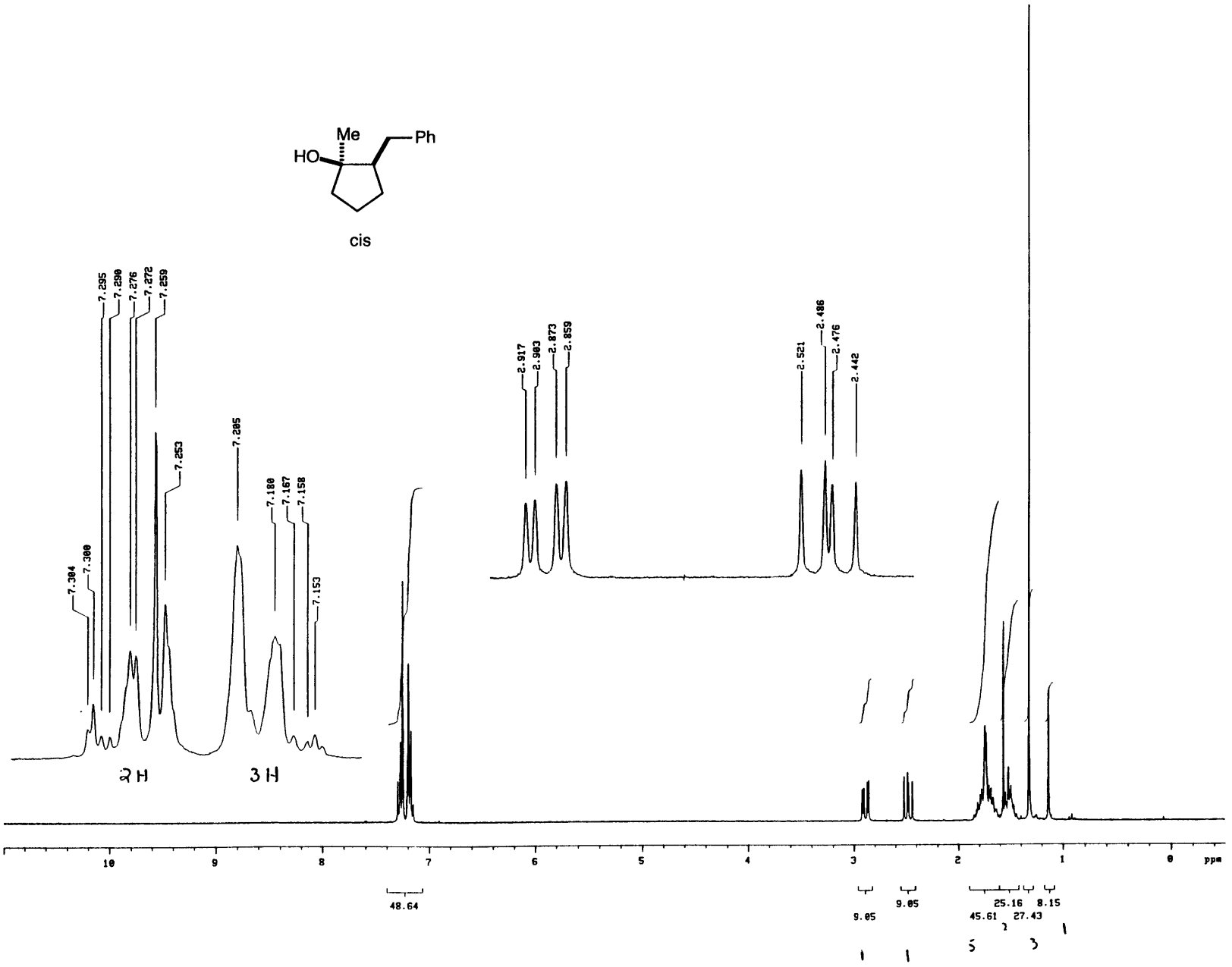

Me
Me
O
O
Me
4.161
4.154
4.147
4.140
1.561
1.421
0.953
7.45 7.35 7.25 7.15 7.05 ppm
4.17 ppm
3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.1 2.3 2.2 2.2 2.1 2.0 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm

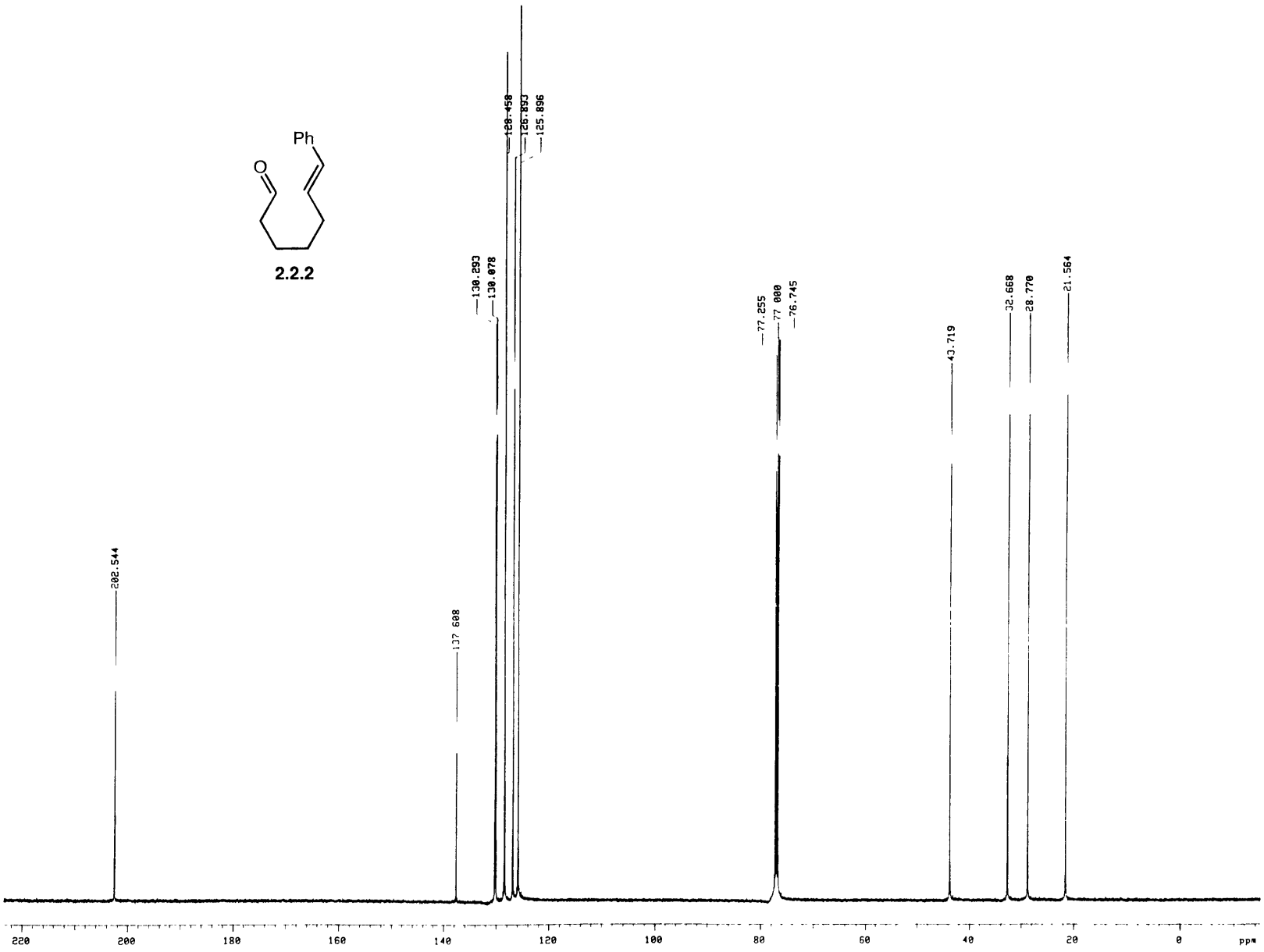

Oct2
Sn
O
O
400
300
200
100
0
-100
200
-300
-400 ppm

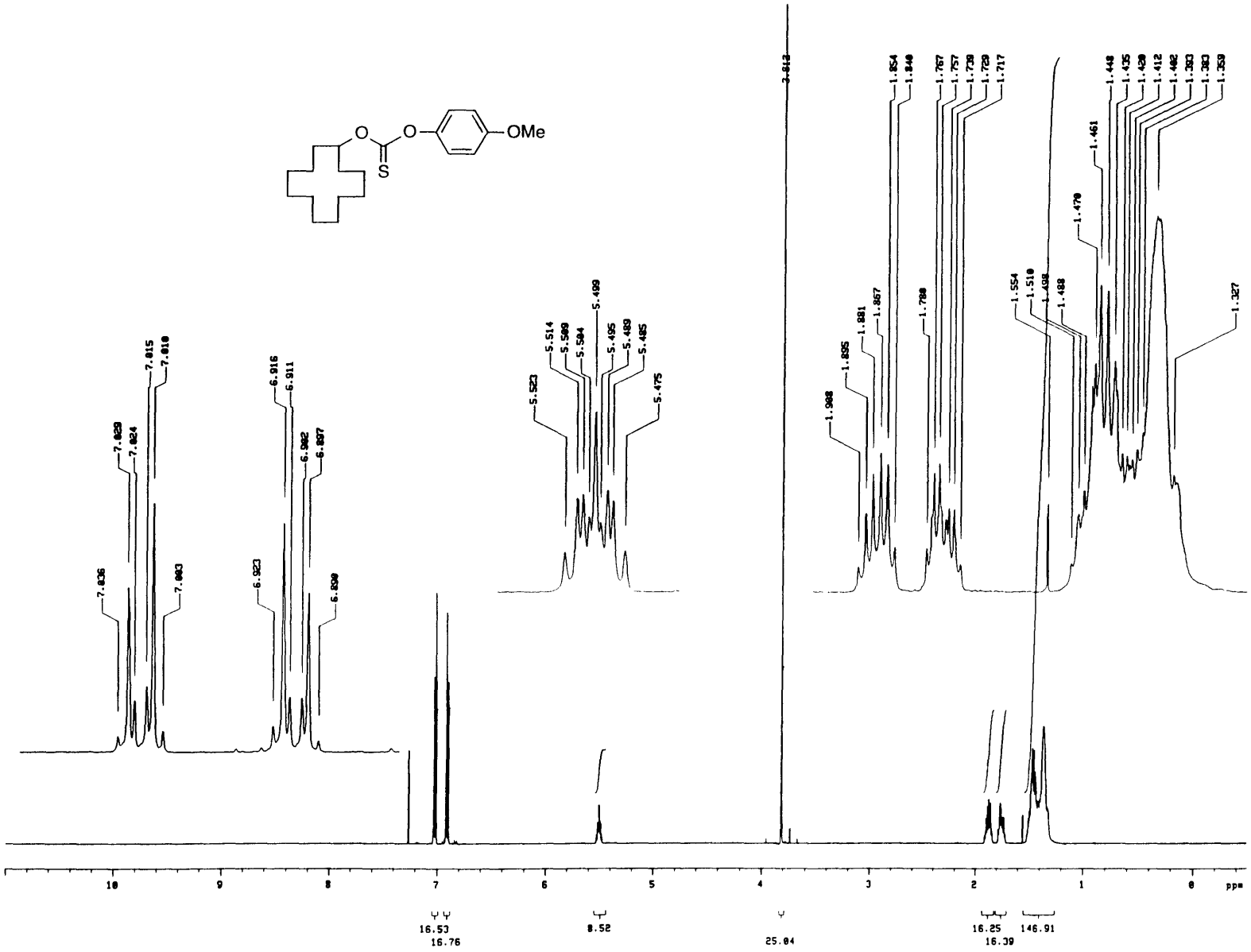

OH
Me
CO2Et
10
9
8
7
6
5
4
3
2
1
0
ppm
44 79
97 52
23 81
95 44
166 15

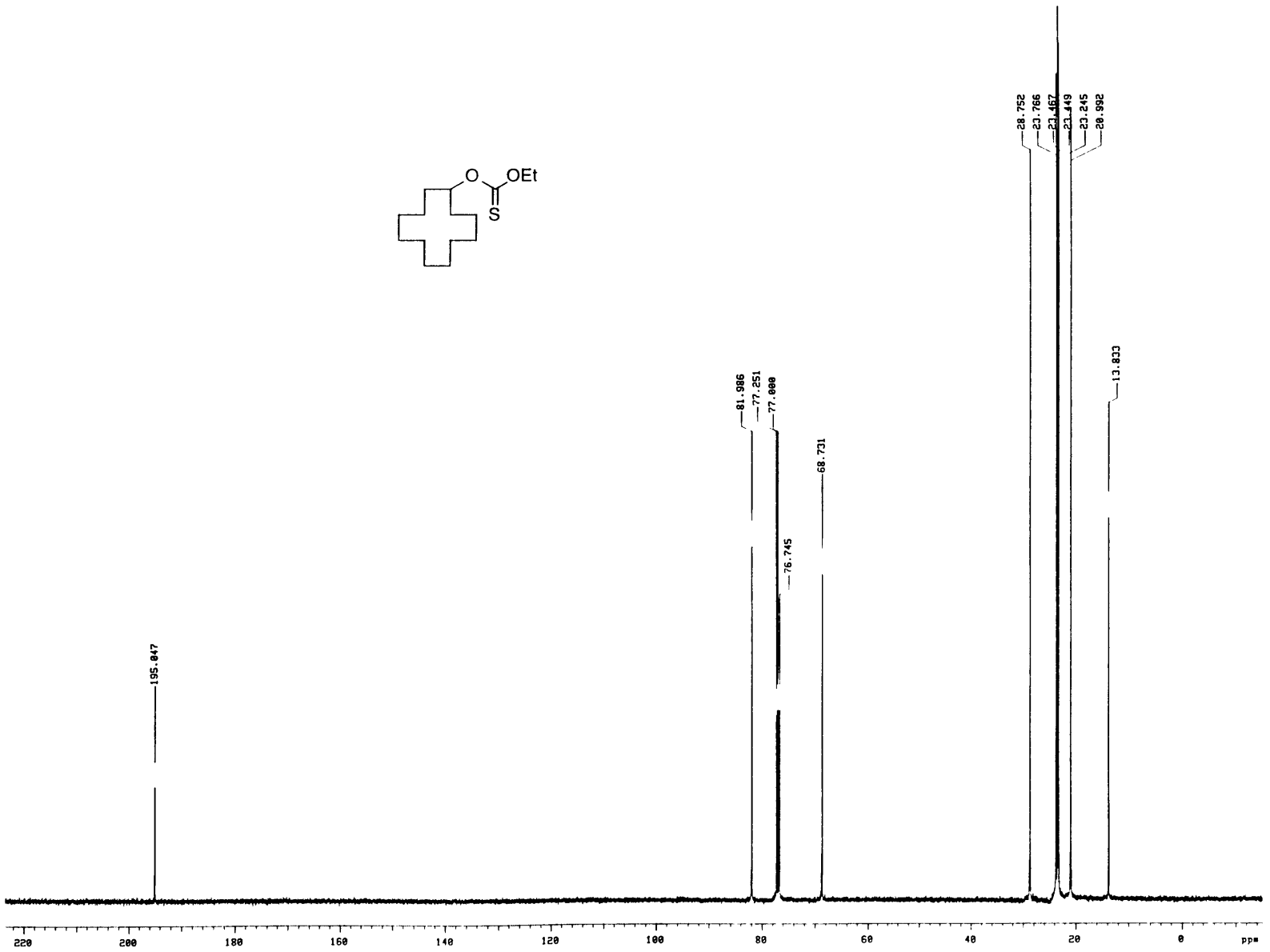

Ph
Me
OH
7.354
7.352
7.337
7.336
7.310
7.306
7.295
7.282
7.279
7.258
7.214
7.211
7.208
7.200
7.196
7.192
7.184
7.182
7.179
6.409
6.377
6.252
6.238
6.225
6.221
6.207
6.193
3.863
3.852
3.840
3.828
3.816
3.803
2.265
2.263
2.251
2.237
2.225
2.224
10
9
8
7
6
5
4
3
2
1
0
ppm
92.16
22.30
21.59
21.90
21.99
42.73
89.45
63.49
20.34

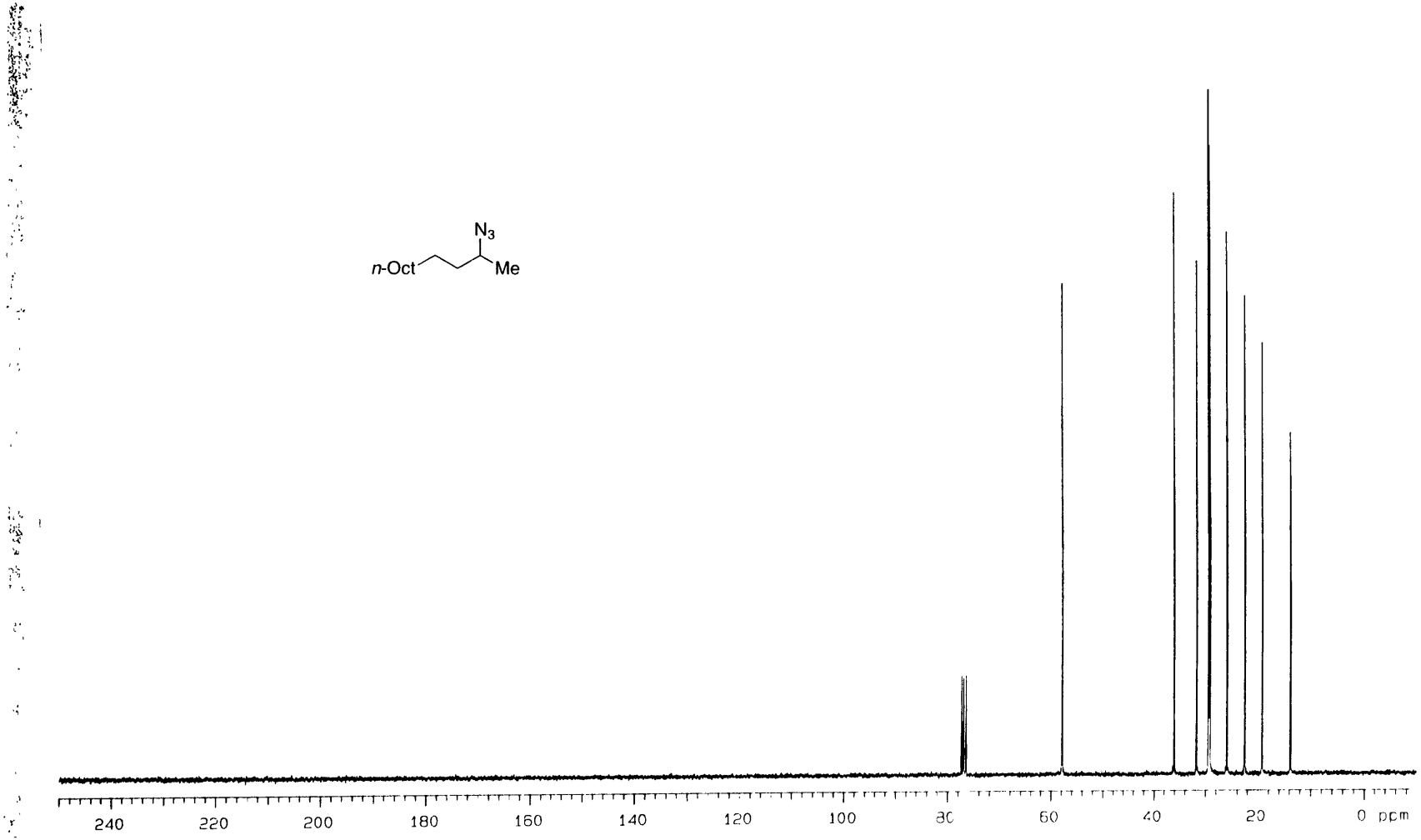

OH
Ph
Me
trans
2.917
2.902
2.873
2.858
2.341
2.305
2.298
2.261
7.309
7.304
7.293
7.281
7.270
7.259
7.208
7.198
7.184
7.167
7.161
10
9
8
7
6
5
4
3
2
1
0
ppm
32.68
46.82
16.43
15.99
16.49
15.38
86.66
67.28

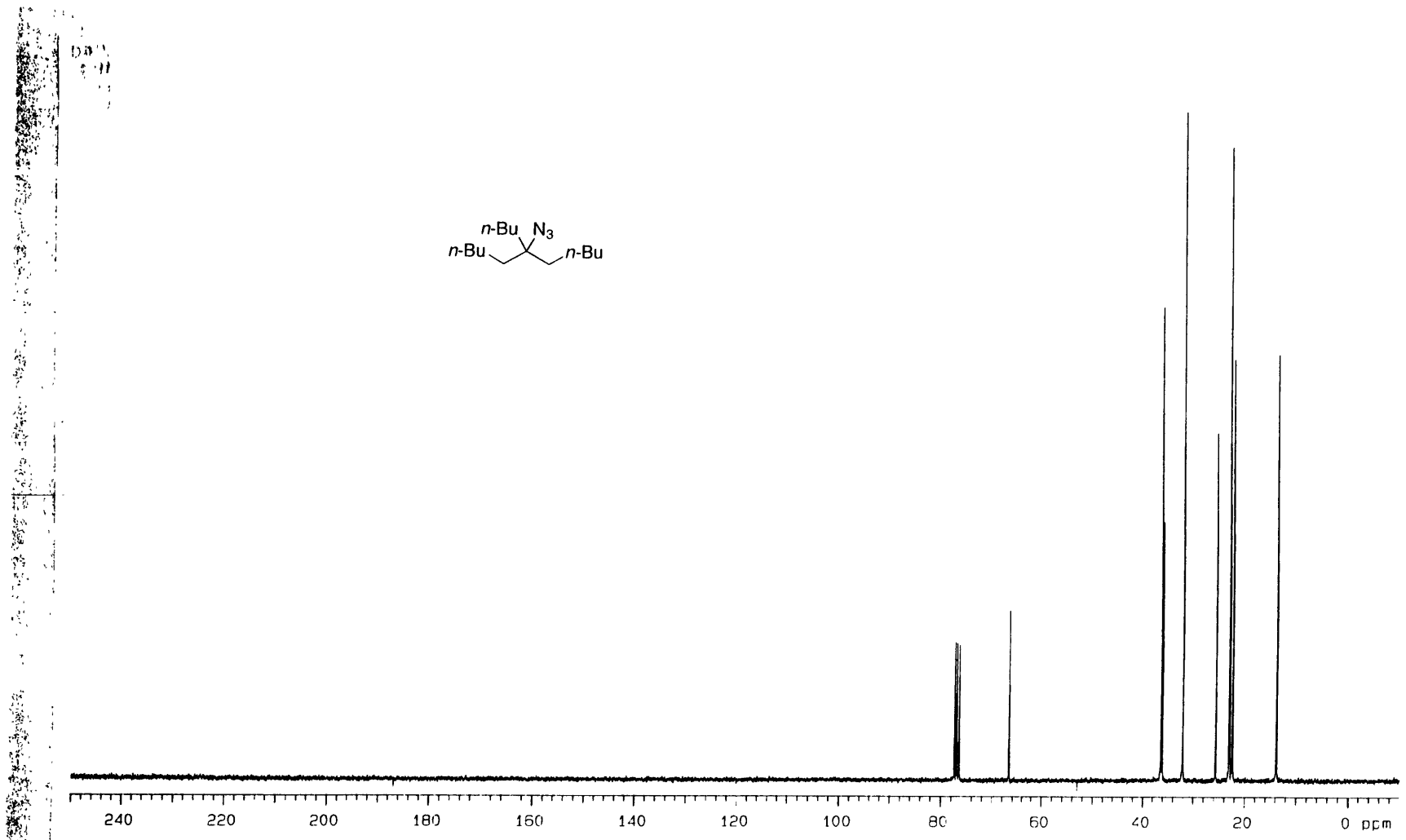

Me
Ph
HO
cis
7.304
7.300
7.295
7.290
7.276
7.272
7.259
7.253
7.205
7.180
7.167
7.158
7.153
2.917
2.903
2.873
2.859
2.521
2.486
2.476
2.442
2H
3H
10
9
8
7
6
5
4
3
2
1
0
ppm
48.64
9.05
9.05
45.61
25.16
27.43
8.15
1
1
5
3
1

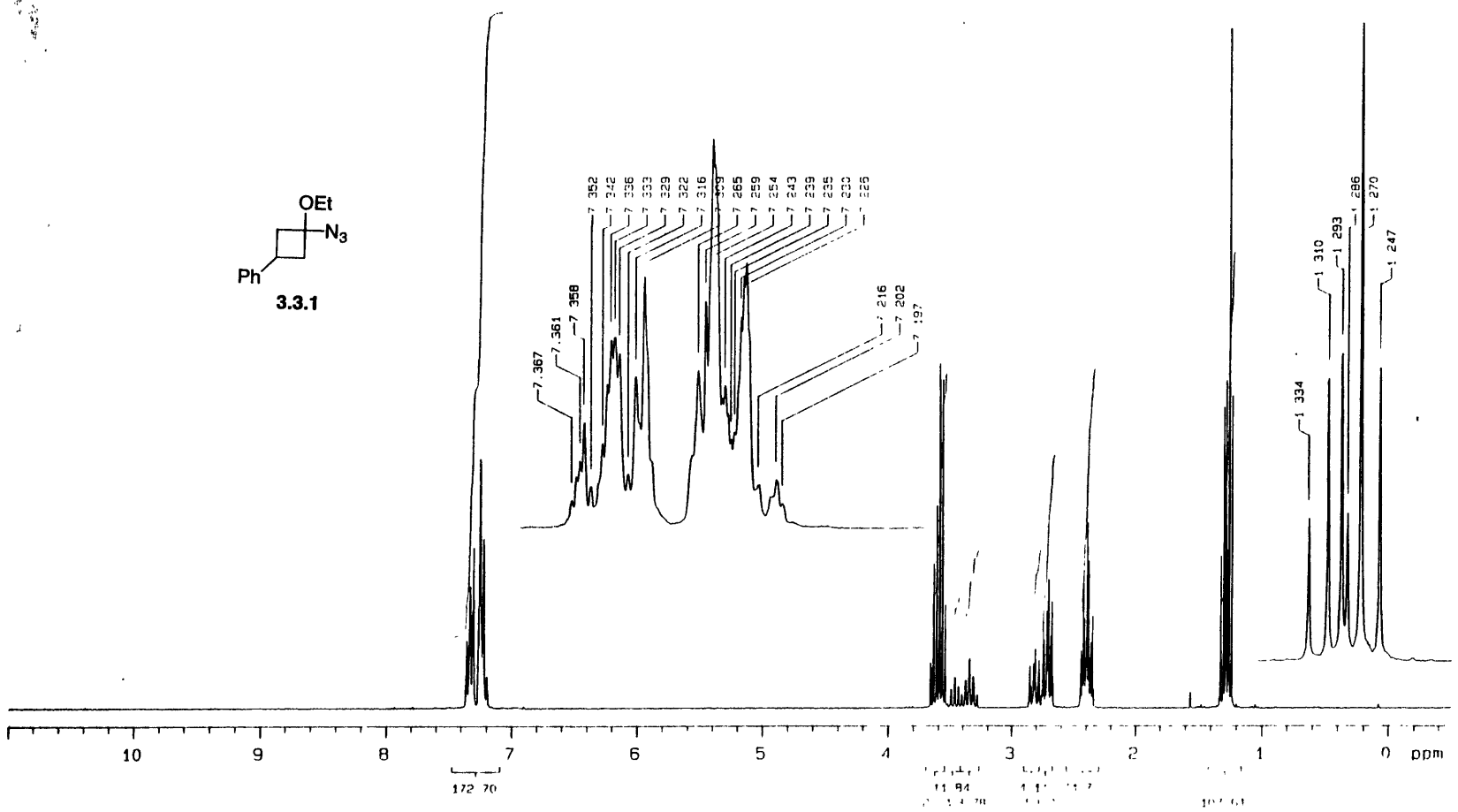

Ph
O
2.2.2
202.544
137.608
130.293
130.078
128.458
126.893
125.896
77.255
77.000
76.745
43.719
32.668
28.770
21.564
220
200
180
160
140
120
100
80
60
40
20
0
ppm

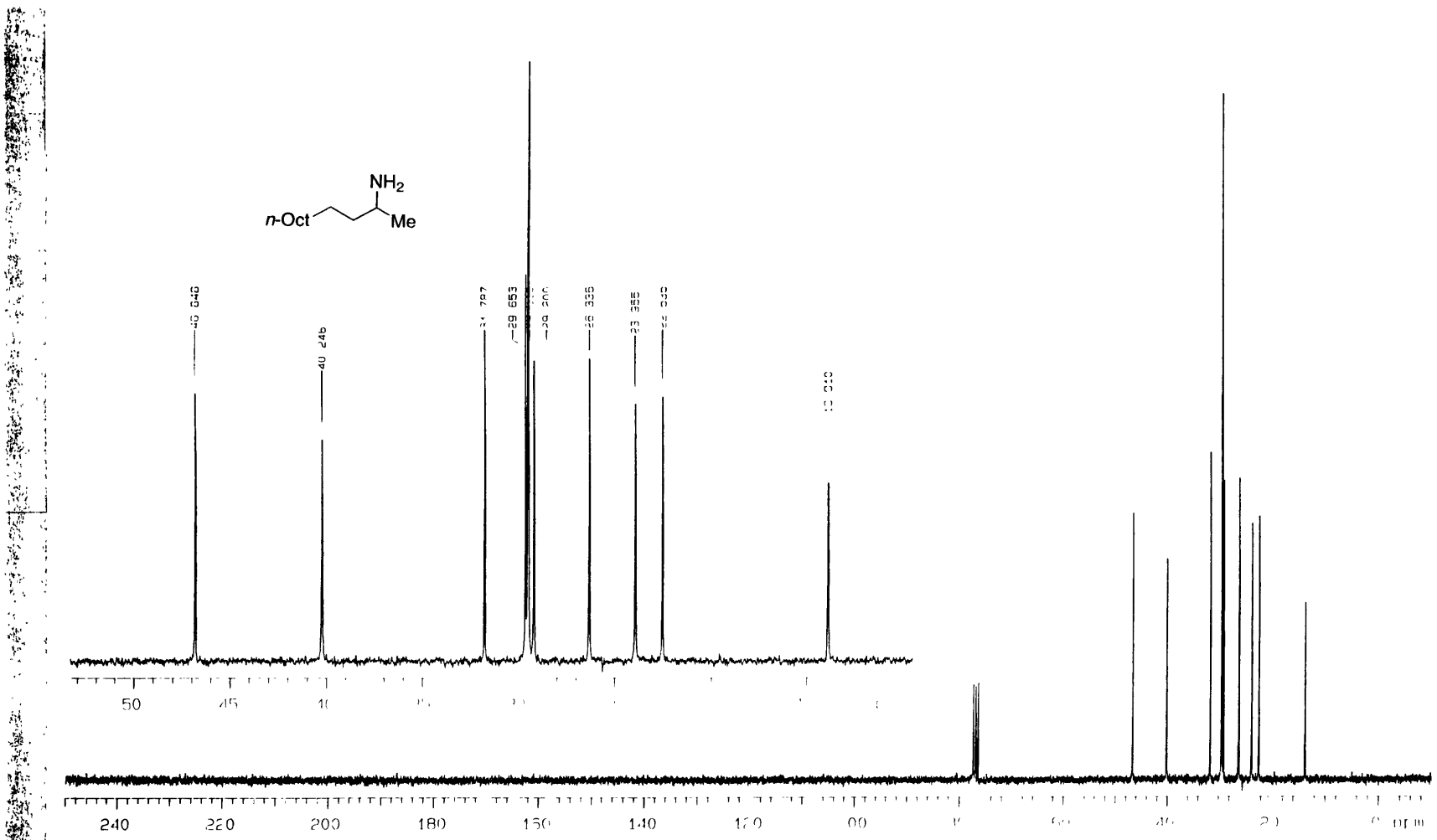

OMe
O
O
S
7.836
7.829
7.824
7.815
7.810
7.803
6.923
6.916
6.911
6.902
6.897
6.890
5.523
5.514
5.509
5.504
5.499
5.495
5.489
5.485
5.475
3.812
1.988
1.895
1.881
1.867
1.854
1.840
1.788
1.767
1.757
1.739
1.729
1.717
1.554
1.518
1.498
1.488
1.470
1.461
1.448
1.435
1.429
1.412
1.402
1.383
1.363
1.359
1.327
10
9
8
7
6
5
4
3
2
1
0
ppm
16.53
16.76
8.52
25.04
16.25
16.39
146.91

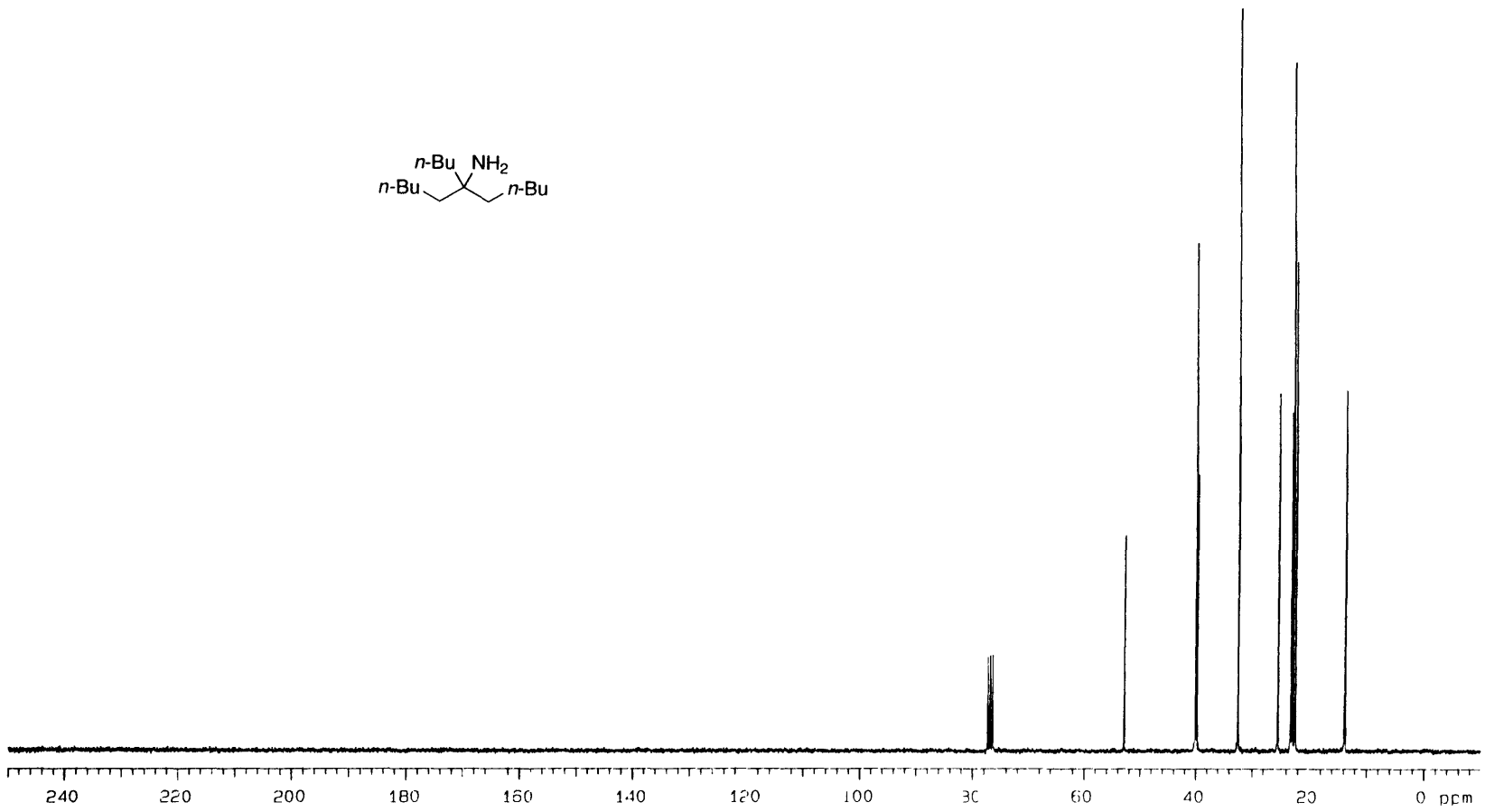

O
OEt
S
195.047
81.986
77.251
77.000
76.745
68.731
28.752
23.766
23.467
23.449
23.245
20.992
13.833
220
200
180
160
140
120
100
80
60
40
20
0
ppm


N3
n-Oct
Me
240
220
200
180
160
140
120
100
80
60
40
20
0 ppm


n-Bu
N3
n-Bu
n-Bu
240
220
200
180
160
140
120
100
80
60
40
20
0 ppm


OEt
N3
Ph
3.3.1
7.367
7.361
7.358
7.352
7.342
7.336
7.333
7.329
7.322
7.316
7.265
7.259
7.254
7.243
7.239
7.235
7.216
7.202
7.197
1.334
1.310
1.293
1.286
1.270
1.247
10
9
8
7
6
5
4
3
2
1
0
ppm
172.70


NH2
n-Oct
Me
40.246
31.797
29.653
26.335
23.355
19.319
50
240
220
200
180
140


n-Bu
NH2
n-Bu
n-Bu
240
220
200
180
160
140
120
100
80
60
40
20
0 ppm