FLUORODEMETALATION REACTIONS OF ORGANOGERMANIUM, -TIN AND LEAD COMPOUNDS.

By

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FOREWORD

In accordance with guideline number 7 of "Guidelines Concerning Thesis Preparation" (Faculty of Graduate Studies and Research, McGill University), the following text is cited:

"The candidate has the option, subject to the approval of the Department, of including as part of the thesis the text, or duplicated published text (see below), of an original paper, or papers. In this case the thesis must still conform to all other requirements explained in Guidelines Concerning Thesis Preparation. Additional material (procedural and design data as well as descriptions of equipment) must be provided in sufficient detail (e.g. in appendices) to allow a clear and precise judgement to be made of the importance and originality of the research reported. The thesis should be more than a mere collection of manuscripts published or to be published. It must include a general abstract, a full introduction and literature review and a final overall conclusion. Connecting texts which provide logical bridges between different manuscripts are usually desirable in the interests of cohesion.

It is acceptable for thesis to include as chapters authentic copies of papers already published, provided these are duplicated clearly on regulation thesis stationery and bound as an integral part of the thesis. Photographs or other materials which do not duplicate well must be included in their original form. In such instances, connecting texts are mandatory and supplementary explanatory material always necessary.

The inclusion of manuscripts co-authored by the candidate and others is acceptable but the candidate is required to make an explicit statement on who contributed to such work and to what extent, and supervisors must attest to the accuracy of the claims, e.g. before the Oral Committee. Since the task of the Examiners is made more difficult in these cases, it is in the candidate's interest to make the responsibilities of authors perfectly clear. Candidates following this option must inform the Department before it submits the thesis for review."

This thesis is written in the form of six papers: four communications and two full papers. Five papers have already been accepted and published. A specific statement is written in the beginning of each chapter citing where the original journal reference can be found. The reader should be aware that some papers might contain some minor modifications compared to the actual papers published due to the editor's revision. However, the manuscripts herein reflect the original versions when they have been accepted for publication.

For a better reading, tables, graphs and structures have been inserted within the text where it has been possible. At the beginning of chapters 2 to 5, some links between the different chapters have been included for a better cohesion. In the same sections, my personal contributions to this thesis have been well explained. The reader should also be aware that I sometimes used a style where the personal pronoun is utilized, especially in these sections. I wanted to make it clear what was my specific contribution in this thesis. In fact, all of the work has been done by the author of this thesis, excepting the normal supervision given by Dr David N. Harpp and Dr. T. H. Chan. However, the section 2.0 in chapter 2 has been a collaborative effort of Dr Aida and I, as specifically stated in this chapter.

For permitting the Examiners to have a clear idea of the experimental work, some appendices were included at the end of this manuscript.

REACTIONS DE FLUORODEMETALATION DES COMPOSES ORGANOMETALLIQUES DU GERMANIUM, DE L'ETAIN ET DU PLOMB

Résumé

Les ions fluorures attaquent de façon douce les oxides, sulfures et sélénures d'organoétains pour libérer des espèces extrêmement nucléophiles ("S^{2-}", RS^-, RO^-, RSe^-, etc.). Egalement, les premiers agents de transfert nucléophiles des ions "O^{2-}" et "Se^{2-}" sont présentés. L'atome d'étain agis ainsi comme un "agent de transfert du groupe 16 (VIB)". Avec la présence d'éther-couronnes ou de sels d'ammonium, ce procédé constitue une nouvelle voie pour générer des anions "nus". De nouveaux systèmes anhydres de fluoruration (CsF et éther-couronnes) faisant appel à la catalyse de transfert de phase solide-liquide ont été conçus et étudiés. En plus, des réactions de fluorodéstannylation pour former des liens C-C ont été tentées. Pour complémenter ces résultats, des réactions de fluorodégermanylation et de fluorodéplumbylation sont présentées. En résumé, l'ion fluorure peut réagir avec tous les atomes du goupe 14 pour libérer des espèces nucléophiles. Des intermédiaires pentacoordinés ont été observés par la RMN des noyaux ^{19}F et ^{119}Sn pour la fluorodéstannylation, confirmant ainsi le modèle de substitution nucléophile sur l'étain et le silicium. Des aspects mécanistiques ont été discutés ainsi qu'un effet possible d'accroissement de la nucléophilicité d'un anion causé par l'effet de proximité d'un atome métallique. Finalement, avec la présence de sels d'argent, l'oxide de tributylétain agis comme un agent de transfert d'oxygène doux dans la transformation d'iodures ou de bromures organiques primaires en alcools.

FLUORODEMETALATION REACTIONS OF ORGANOGERMANIUM, -TIN AND -LEAD COMPOUNDS

Abstract

Fluoride ions smoothly destannylate organotin oxides, sulfides and selenides to liberate highly nucleophilic species ("S^{2-}", RS^-, RO^-, RSe^-, etc.). Also, the first nucleophilic oxide "O^{2-}" and selenide "Se^{2-}" transfer agents are reported. The tin atom thus serves as a general "group 16 (VIB) transfer agent". In the presence of crown ethers or ammonium salts, this process results in a new way to generate "naked" nucleophiles. Novel anhydrous fluorinating systems (CsF and crown ethers) involving solid-liquid phase transfer catalysis have been designed and studied. In addition, C-C bond forming reactions have been investigated by fluorodestannylation. As an extension of these results, fluorodegermanylation and fluorodeplumbylation reactions are reported. As a generalization, fluoride ion demetalates the whole group 14 for releasing nucleophilic species. Some pentacoordinated intermediates have been observed by ^{19}F and ^{119}Sn NMR spectroscopy in fluorodestannylation, thus confirming the model of nucleophilic substitution at tin and silicon. Mechanistic aspects are discussed along with a possible metal proximity effect in the enhancement of the nucleophilicity of an anion. Finally, in the presence of silver salts, bis(tributyltin) oxide acts as a mild oxygen transfer agent in converting primary organic iodides and bromides to alcohols.

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CHAPTER 1: INTRODUCTION

1.0 The First Organometallics of Germanium, -Tin and Lead.

The birth of several classes of organometallic compounds dates from the nineteenth century. Among these groups were the first preparations and tentative characterization of some organogermanium, organotin, and organolead compounds.

Diethyltin diiodide was the first organotin to be synthesized by Lowig and recognized as such in 1852.[1] However, most of the other references mention that diethyltin diodide was prepared in 1849 by Sir Edward Frankland.[2]

Mendeleev predicted the existence of germanium (named "ekasilicium") in 1871,[3] before its discovery by Winkler in 1886.[4] This latter chemist synthesized the first organogermane, namely tetraethylgermane, in 1887.[5]

In 1853, the first organolead compound, hexaethyldilead, was reported.[6] Organolead research continued in 1915-1925 in several important investigations by Krause and Grosse.[7] However, the most important landmark came from Midgley and Boyd in 1922, with the discovery of tetraethyllead as an excellent antiknocking agent.[8] It definitively put organolead chemistry on the map and contributed to the development of the automobile industry after the first World War.

1.1 A Brief History of the Development of the Organogermanium, -Tin and -Lead Chemistry.

One of the most useful approach for defining and observing the development of a field is certainly through the careful analysis of the various published works from the past to the present. This section will thus emphasize the major developments in fundamental research through the compilation and the citation of numerous publications in organogermanium, -tin and -lead chemistry. Industrial contributions will be briefly indicated when necessary.

After these prelimary findings within group 14 from 1849 to 1887, publications on their chemistry appeared sporadically until about 1920. A slow but regular increase of publications followed that period till 1940. At this time, an exponential increase of this organometallic chemistry required a comprehensive compilation. It led to the publication of

numerous dictionaries and reviews presenting lists of compounds, their physical properties and references for their preparation and/or characterization. I am tempted to qualify the period between 1920 and 1960 as being merely descriptive and compilative, but it was a necessary step in the modern development of organometallic chemistry of this group.

Despite their early recognition, it was not until 1940 when a renaissance period of tin chemistry appeared in from the United States by the first commercial use of diorganotins to inhibit the thermal and photolytic degradation of polyvinyl chloride (PVC).[9] Before that, most of the attention was focussed on organolead (because of tetraethyllead) and on organoarsenic chemistry. Later on, the arrival of organosilicon chemistry and the famous organomagnesium chemistry, propelled by the early work of Grignard, attracted many chemists. It was not until 1960, that organotins were first compiled in an extensive review by some of the pioneers in organotin chemistry: Ingham, Rosenberg and Gilman.[10] Afterwards, in the nineteen seventies, several complete volumes on tin were published at almost the same time by Poller[11], Neumann[12] and Sawyer.[13] Several specialized reference books and series of volumes were also published under the name: "Gmelin Handbuch der Anorganischen Chemie".[14] Slowly, the general trend in the chemical reactivities of similar functional groups provided a more rationalized classification. However, the works focussed mainly on the preparation of organotins and their elementary reactivities during this period.[15] Some general treatises also appeared at the end of the 1970s.[16] Recently, an excellent encyclopedia gave a general overview about organotins;[17] a modern dictionary can also be found.[18]

From 1960 to 1970, the use of organotins in organic chemistry was sporadic. In the nineteen seventies the references accumulated rapidly. The first review of tin chemistry dedicated to organic synthesis appeared in 1971 in a Japanese journal.[19] Other reviews were also published in 1972[20] and in 1976[21]. In the 1980s, several other surveys were added.[22] Some specialized reports dealt with Sn-H, Sn-O, Sn-N, Sn-C, Sn-S, Sn-alkali metal and Sn-X (X=halide) bonds.[23] However, it was not until 1987 when an excellent book gathered the possible applications of tin in organic synthesis.[24] Annual surveys of the literature in organotin chemistry can be found in the Journal of Organometallic Chemistry (Organometallic Chemistry Reviews) published by Elsevier Science Publishers and in the Specialist Periodical Reports from the Royal Society of Chemistry (London).

With germanium, essentially the same historical development occurred. These compounds were finally compiled in an important book by Lesbre, Mazerolles and Satge.[25]

Again, the emphasis was put on the preparation and the fundamental reactivities of organogermanium compounds without a direct link with organic synthesis. An excellent general overview can also be found in an encyclopedia of organometallic chemistry;[26] a modern dictionary is currently available.[18]

The references on organolead chemistry are more limited. Nevertheless, an entire chapter in the encyclopedia *Comprehensive Organometallic Chemistry* is devoted to organolead compounds and their reactivities.[27] A recent dictionary of organolead compounds was published in 1985.[18] Other interesting sources of information are comprised in the annual survey on lead of the Journal of Organometallic Chemistry.[28]

These two latter classes of organometallics are less well developed than organotin chemistry in their applications in organic synthesis. Practical reasons may contribute to limit the use of these organometallics; the cost of the organogermanium starting materials are prohibitive and organoleads are highly toxic. The natural abondance of tin, the low cost of the starting materials and its relatively low toxicity, compared to lead, has certainly encouraged the development of this field in academic research as well as in industry (especially the PVC industry).

The expansion of these three fields in organometallic chemistry is such that a periodical named "Review of Silicon, Germanium, Tin and Lead Compounds" has been created. The "International Conference on the Organometallic and Coordination Chemistry of Germanium, Tin and Lead" usually held in European countries can also account for increasing developments involving those elements.

1.2 Industrial Uses of Organogermanium, -Tin and Lead.

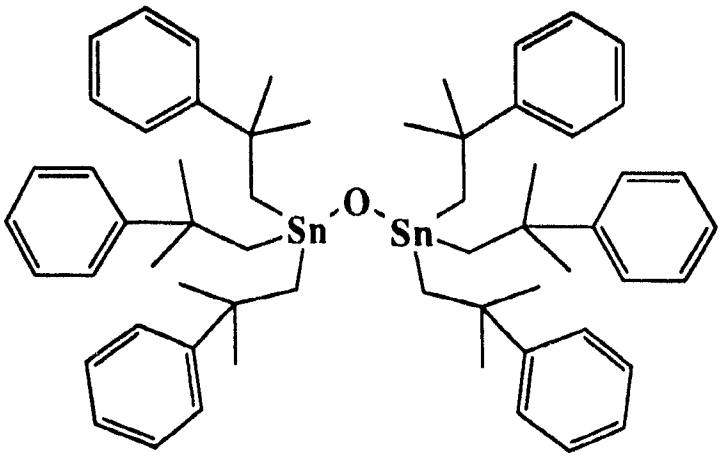
1.2.1 Applications of Organotins.

The most versatile and widely used class of organometallics in the series is without doubt the organotins. The world annual chemical production of organotins was estimated to be 40,000 tons around 1985. Globally, there are two general uses: as biocides and as PVC stabilizers. The biocides are characterized by a chemical structure having three organic substituents on tin whereas the PVC stabilizers usually involve one or two organic ligands. Some of the uses of organotin compounds will be described here but the reader is referred to other works for further details.[29] From the Internationational Tin Research Institute[30]

several publications are also available,[9] including the journal "Tin and its Uses", published monthly.

In the biological field, organotins have found broad applications as agrochemicals because of their highly selective fungicidal, insecticidal, herbicidal and bactericidal properties (see Table 1).[31] An annual production of 5,000 tons is estimated. During the course of this thesis research, I directly or indirectly used several well-known triorganotins produced in bulk quantities in industry. For instance, bis(tributyltin)oxide (**1**) is widely employed as a wood preservative.[17] However, because of its low solubility in water (0.001% w/v at 25°C), quaternary ammonium chlorides are usually added in order to render it water-dispersible.[32] A new and promising method described tributyltin methane- or ethanesulphonate (**2**) and (**3**) (Bu_3SnSO_3Me or Bu_3SnSO_3Et) as water-soluble biocides for wood preservation.[9] The so called "pretreated wood", sold in usual woodshops, probably contains some or a combination of these preservatives cited above against fungi. Tributyltin and triphenyltin fluoride (**4**) and (**5**), were originally employed as antifouling agents in marine paints to prevent the agglomeration of algae and other marine organisms on structures immersed in seawater.[17] Active research is presently being carried out on marine paints because of the potential economic value. For instance, it has been estimated that a ship can consume 40% more fuel after six months at sea when the fouling processes occurred.[33] Bis(trineophyltin)oxide (**6**) investigated in my research projects as new "O^{2-}" transfer agent (unpublished results) is a known acaricide sold by E. I. Dupont de Nemours & Co.

Why did agrochemists develop and use organotins? The reasons are: their highly selective mode of action in living organisms (see Table 2); their low phytotoxicity and especially their facile biodegradability by microorganisms and UV light to non-toxic monoorganotins and metallic tin.[17] As a global view of their range of toxicity, it is amazing to know that some organotins are currently used in the production of plastic drinking bottles whereas others can directly kill mammals.[17] Biological tests have indicated that triorganotins are generally more toxic than diorganotins and monoorganotins.[34] Apparently, the toxicity pattern can be roughly displayed as follows: the decrease of the chain length of the organic ligand on tin provokes a more acute toxicity. The biological selectivity mainly arises from these organic ligands. For instance, methyl groups are highly toxic to mammals and insects but butyl and propyl groups are more toxic to bacteria.[17] For tributyltins, a careful evaluation of their toxicity on mammals was undertaken and one important point found is that the effect of the "anionic part" of tin was almost negligible compared to the



Bis(Trineophyltin)oxide

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Table 1: List of Common Triorganotins and Their Uses

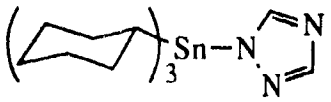
Structure	Commercial Name	Main Uses
$Bu_3SnOSnBu_3$	—	Fungicide in wood and stone preservation
Bu_3SnSO_3Me, Bu_3SnSO_3Et	—	Fungicide in wood preservation
Bu_3SnF	—	Antifouling agent
Ph_3SnF	—	Antifouling agent
Ph_3SnCl	Tinmate	Fungicide, antifouling agent
Ph_3SnOH	Du-Ter	Fungicide, antifouling agent

Table 2: Dependence of the Biological Activity While Varying the Substituents on Triorganotins.

Toxicity	Substituent on R_3SnX Compounds
Insects and mammals	Me
Mammals	Et
Gram-negative bacteria	Pr
Gram-positive bacteria	Bu
Fish, fungi and molluscs	Ph
Mites	Cyclohexyl, Trineophyl

Taken from reference 17, p. 608.

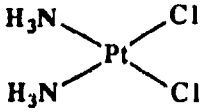
Table 3: List of Common Agrochemicals

Structure	Commercial Name	Use
$[(Ph(Me)_2CCH_2)_3Sn]_2O$	Vendex or Torque	Miticide, acaricide
	Plictran	Miticide, acaricide
	Peropal	Miticide
Ph_3Sn-OAc	Brestan	Fungicide
Ph_3Sn-Cl	Tinmate	Fungicide

kind of organic ligands.[35] No mutagenic, carcinogenic or neurotoxic effects were detected in studies on rats; although an acute dermal toxicity and a loss of weight were shown.[36] However, the lower alkyl ligands, like methyl or ethyl, are known to attack the central nervous system in mammals.[36]

Table 3 reports some common agrochemicals along with chemical structure and their use. The triphenyltin moiety has been preferred in agrochemicals because of its low phytotoxicity. Triphenyltin acetate (**7**) (Ph_3SnOAc) has been the first agrochemical produced in industry by Hoechst AG in the early 1960s. The trademark name is "Brestan". It is mainly used as fungicide against fungal organisms infesting potato, bean, carrot, celery, cacao, coffee, onion and rice plants.[9] Other compounds include triphenyltin chloride (**8**) (Ph_3SnCl) with the trademark name "Tinmate" and triphenyltin hydroxide (**9**) (Ph_3SnOH) under the name "Du-Ter".[9] A large, bulky, non-aromatic group on tin seems to be a common structural feature of active miticides and acaricides. Tricyclohexyltin hydroxide (**10**) ($(c\text{-hexyl})_3SnOH$), from Dow Chemical Co., is commonly referred to as "Plictran" on the market.[9] It prevents mites and insects from destroying crops of apples, pears, peaches, hazelnuts, tea, tomatoes, peppers, cotton and soybeans.[9] Other chemicals used for the same purpose are bis(trineophyltin)oxide (**6**), already mentioned, and 1-tricyclohexylstannyl-1,2,4-triazole (**11**) ($(c\text{-hexyl})_3SnN_3C_2H_2$) named as "Peropal".[9] The mammalian toxicity of the cyclohexyl groups have been shown to be tolerable.[36]

Another important biological application of diorganotins came from recent studies establishing the potential use of diorganotins as chemotherapeutic agents in cancer.[37] The importance of tin-based anti-tumour drugs in medicinal chemistry is such that special international conferences have been held in Europe on that specific topic, i.e. the "International Symposium on the Effect of Tin Upon Malignant Cell Growth". It is generally thought that the structural resemblance of some hexavalent diorganotins complexes (**13**) to the platinum complex "cisplatin" ($cis\text{-}Pt(NH_3)_2Cl_2$) (**12**), with respect to the presence of a cis dihalometal moiety, accounts for their physiological activities.[37]



"Cisplatin"

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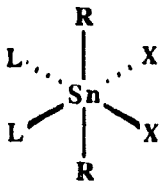

X = F, Cl, Br, I, NCS
L = Pyridine, monodentate ligand or bidentate ligand.
R = alkyl or Phenyl

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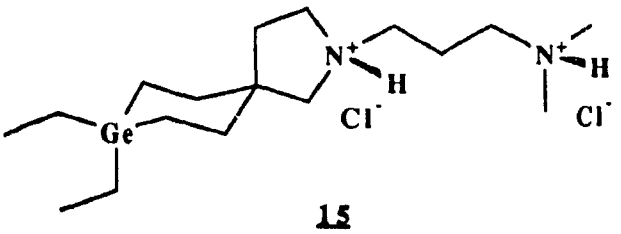
Many tin compounds inhibited cancer in animals from their antiproliferative properties (especially against P388 leukemia) and presented less harmful side effects on the kidney.[9] Further studies showed that they had limited activity against many experimental tumor systems.[37] For these reasons, no organotin has yet reached human clinical studies.[9] Organotins have also been used as general disinfectants. For instance, a formulation named Incidin* (trademark name) containing a mixture of tributyltin benzoate and formaldehyde are employed in some particular locations, like hospitals.[38]

It was mentioned at the beginning that dialkyl and monoalkyltins are used as stabilizers for the PVC industry. It is the largest single application for the organotins. Over 20,000 tons of material per year is used in major industrialized countries. What is a stabilizer and how does it work? The stabilizer is an additive (1-1.5%) in the polymerization process that prevents loss of HCl through dehydrohalogenation of the polymer during processing at high temperature (180-200°C). The corrosion of some equipment is also minimized. Additionally, it prevents the degradation of PVC caused by sunlight. The most effective diorganotins are those called "thiotins" or diorganotin dithiolates ($R_2Sn(SR)_2$). The Sn-S bond appears to be crucial for a better thermal stabilization of the polymer. Another class includes the bis(carboxylates) when long exposure of PVC to light is required. A synergetic effect is usually obtained when mixing mono and diorganotins as stabilizers. Several procedures presented in this thesis show the use of tin sulfur reagents like bis(triaralkyltin)sulfides ($R_3Sn\text{-}S\text{-}SnR_3$) and dibutyltin sulfide (Bu_2SnS). It is no surprise that several organotin sulfides discussed here are currently sold by various American companies. However, what is surprising is that they were never really used as general and mild sulfur transfer agents despite their early recognition (often before or in the 1940s). Bis(trimethyltin)sulfide was prepared as early as 1920 but remained unexploited as a reagent for organic synthesis.[39] It has thus been the purpose of part of this academic work to develop these organotin sulfides as reagents.

1.2.2 Applications of Organogermaniums

An excellent and brief overview on the uses of organogermaniums was written in 1985.[40] This section will not be exhaustive; only the important applications of the titled organometallics will be described here. As with tin, several organogermaniums present biocidal properties; but unlike diorganotins, diorganogermaniums are active against fungi.[41] However, in contrast to triorganogermaniums, they exhibit limited antibacterial activity.[42] An order of relative fungicidal power established that the "anionic part" of the diorganogermaniums is important.[40]

Some biological applications were found. One of the most interesting is surely a patent on 3-(trihydroxygermyl)propionic acid (**14**) and its salts as blood-pressure depressants in hypertension.[43] Some diorganogermaniums have also found some uses as antitumor drugs in lymphocytic leukemia[44] and cancer,[45] in a similar way as with diorganotins. Again, a structural resemblance of an active organogermanium compound (**15**) with the platinum complex (**16**) is obvious in the spiro system. Organogermaniums were the first anti-cancer drugs used in the group 14.[37] They were active against numerous experimental tumors but their limited value in clinical studies did not permit them to be used in routine medical treatment. At present, they are studied as biological response modifiers in the activation of interferon.[37]



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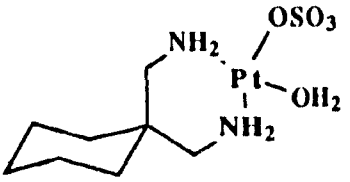

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Finally, in material and surface chemistry, volatile hydrogermanes have been used in high-temperature superconductor systems[46] and germanium complexes of phtalocyanine have been investigated as semiconductors.[47] Despite some attempts to find some industrial uses, the cost of the starting materials prohibited any major application in industry.

1.2.3 Applications of Organoleads

As stated previously, the main use for an organolead compound has been as an antiknocking additive in motor gasoline. In 1979, the total worldwide production of tetraethyllead (excluding the Eastern bloc countries) was 650,000 tons despite the enormous environmental problems caused by its use.[27] In 1989, some gasoline still contains this harmful additive! Their properties as biocides have been found to be powerful, much more than tin, but due to the environmental hazards, they are not likely to be exploited commercially.[27] Lead poisoning in birds and ducks is a convincing case. Overexposure to organoleads by inhalation, ingestion or direct contact with skin caused various symptoms in humans. The primary effects concern the central nervous system (C.N.S.). It may cause mental aberrations, spasmodic muscular contractions and nausea.[48] In addition, some

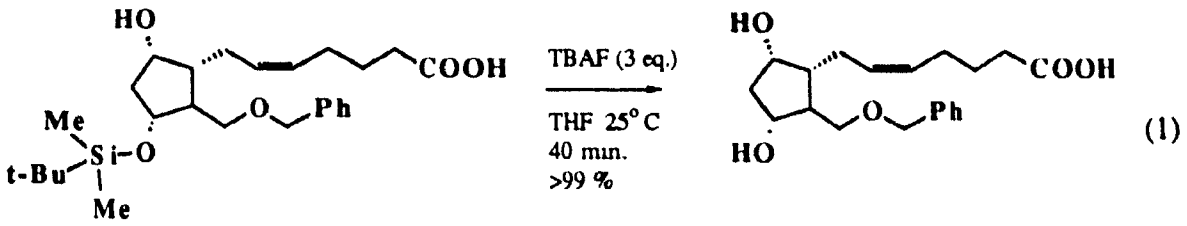
organoleads cause birth defects or other reproductive disorders.[49] Their decomposition in nature seems to involve degradation by U.V. radiation by a radical pathway.

Other limited applications include the use of organoleads as polymerization catalysts and as stabilizers for polymers.[27] For more information, the reader is referred to a general review.[27]

In the next sections, a literature survey of fluorodesilylation techniques is reported. In addition, some fluoride-induced reactions of organogermanium, -tin and -lead compounds will also be shown (especially on fluorodestannylation).

1.3 Organosilicon Chemistry in Organic Synthesis.

Organosilicon chemistry is now well anchored in organic synthesis. Several books have emerged during the last ten years.[49] The usefulness of organosilicon compounds in synthesis can be ascribed to several features: the β-effect for the stabilization of a positive charge;[50] the reluctance to form stable double bonds, in contrast to carbon;[51] the ability of silicon to stabilize a negative charge in the alpha position of this atom[52] and the ability to increase its coordination number from four to five or six.[53] This last property permits the existence of well-defined pentacoordinated or hexacoordinated complexes which were characterized by Frye and co-workers from the reaction of silica gel with catecholate anions.[54] Later, Muller,[55] Muetterties,[56] Corriu,[53] Martin[57] and Holmes[58] contributed their studies in this area. At this point, it is interesting to observe a parallel development in organic synthesis initiated by the use of the triaralkylsilyl ether as protective group.[59] In this instance, fluoride anions were utilized to deprotect a silyl ether functionality. Hypervalent silicon species are thought to be involved as intermediates. Silyl ethers have been found in various publications and a volume reserved a whole section on that topic in 1981.[60] Chan and Lalonde wrote a complete review of silyl ethers as protective groups in 1985.[61] Organic chemists soon recognized the mildness for introducing those protecting groups and their easy removal, under nearly neutral conditions. The birth of the fluorodesilylation methodology really began with the use of fluoride ions (such as tetrabutylammonium fluoride) in the deprotection of silyl ethers, as first shown by Corey and Vankateswarlu in 1972 in the synthesis of prostaglandin synthons (Eq. 1).[59]



(1)

The affinity of fluoride for silicon is the major driving force in this type of reaction (Si-F bond energy is about 140 kcal/mol in SiF_4).[62] Considerable research is still going on in various reactions such as fluorodesilylation-protonation, fluorodesilylation-alkylation, fluorodesilylation-elimination, generation of reactive species (such as ylides) and fluoride-induced rearrangements or fragmentations.

1.3.1 Fluorodesilylation-Protonation

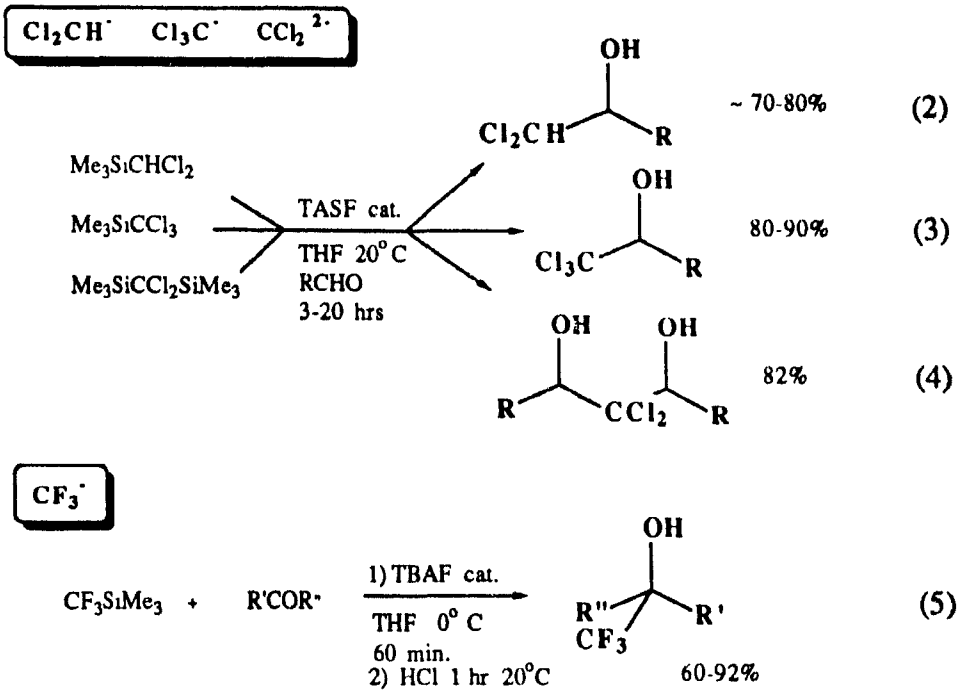
Since the work of Corey,[59] the fluorodesilylation-protonation reactions are well established for the cleavage of the oxygen-silicon bond. It is also possible to proto-desilylate benzyltrialkylsilanes,[63] allylsilanes,[64] alkynylsilanes[65] but unactivated vinyl trialkylsilanes are more problematic. However, Chan and Mychaijlowskij demonstrated that vinylsilanes having a β-hydroxy functionality, relative to the silicon group, can be desilylated by fluoride ion (the β-hydroxy effect).[66] In 1983 and 1985, the flurodesilylation of vinyl silanes was reinvestigated and it was found that some ligands on silicon (such as phenyl, allyl and alkoxy) favor the Si-C bond cleavage.[67] The desilylation of oxiranylsilanes was first reported by Chan and co-workers in 1974[68] followed later by numerous other investigations.[69] It has been demonstrated that retention of configuration at the epoxide is due to a slow carbanion inversion relative to a proton abstraction.[68] Many other fluorodesilylation-protonation reactions of the trialkylsilyl groups have been grouped in a section of an extensive review written by several Russian chemists in 1988.[70]

Instead of trapping the carbanion or carbanion-like intermediate derived from fluorodesilylation with a proton, it might also be interesting to use other kind of electrophiles such as ketones, aldehydes or organic halides. Therefore, the next section will report some fluorodesilylation-alkylation reactions.

1.3.2 Fluorodesilylation-Alkylation

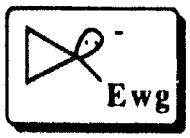
The formation of C-C bonds in organic chemistry has been part of this challenge in 1975, with the first quaternary ammonium enolate prepared from the reaction of an enol silylether with benzyltrimethylammonium fluoride (BTAF).[71] However, the benzyltrimethylammonium enolates reacted poorly with aldehydes or ketones and in moderate yields with organic halides. Nevertheless, the use of quaternary ammonium enolates was deemed to be advantageous, because before that time, problems of polyalkylation, regiospecifity of alkylation and competing of O-alkylation were often observed in reactions of metal enolates (especially with organic halides).[72] The use of fluoride ions with silicon was reinforced when TBAF[73] or TASF (tris(diethylamino)sulfur difluorotrimethylsilicate)[74] were utilized to generate enolate anions, which have a non-metal counterion and are able to react with carbonyl compounds as well as with alkyl halides. Later, an extensive work described the influence of the cation in the aldol-type reactions of enol silylethers catalysed by fluoride ions.[75] By the end of the 1970's and the beginning of the 1980's, benzyl,[76] ethynyl,[77] allyl,[78] oxiranyl,[79] $ArCOCH_2^-$,[80] propargyl,[81] acyl[82] and vinyl anions stabilized by an electron-withdrawing or stabilizing groups (CN, CO_2R, F, SPh)[83] were produced from fluorodesilylation and trapped with electrophiles (very often ketones or aldehydes). It led to a new way of forming C-C bonds under mild and almost neutral conditions. There are still controversies on the exact nature of the nucleophilic species; they can be considered as free carbanions in some cases due to the non-dependance of aralkyl ligands on silicon in the rate determining step and/or in the product formation. In other cases, a hypervalent silicate complex as the nucleophilic source was more probable. A complete review of the publications on fluorodesilylation-alkylation up to 1986 is available.[84] Recent publications in 1987-1989 will thus be presented in the following sections.

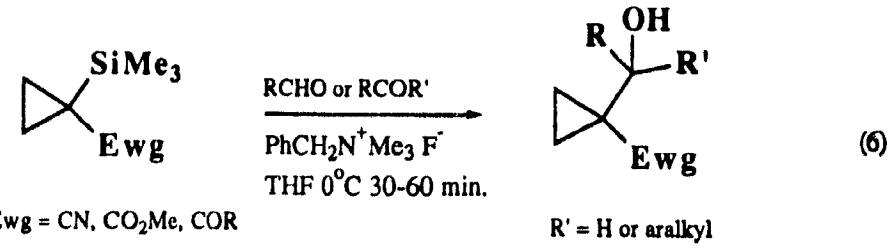
Many useful synthetic equivalents of halogenated carbanions appeared in 1988-1989; Scheme 1 outlines these procedures. It is now possible to cleanly generate synthetic equivalents of Cl_2CH^-, Cl_3C^- and CCl_2^{2-} with the help of the fluorodesilylation reaction (Eq. 2 to 4).[85] Unfortunately, the results with chloromethyltrimethylsilane (Me_3SiCH_2Cl), as a synthetic equivalent of $ClCH_2^-$, were poor. For comparison, the formation of carbanions derived from the reaction of an organolithium with dichloromethane or chloroform at low temperature (usually -90°C) was sluggish. Carbenes were also formed as side-products. No report of the CCl_2^{2-} anion equivalent existed before. In addition, Olah and co-workers just published a simple procedure for generating a CF_3^- anion equivalent, a matter of some interest in fluorine chemistry (Eq. 5).[86]



Other synthetic equivalents of the activated cyclopropyl anion,[87] β-keto anion[88] or fluorinated oxiranyl anion[89] were reported in 1988, as shown in Scheme 2. Paquette and co-workers demonstrated that it is possible to generate the corresponding anion from the 1-trimethylsilyl derivatives of methyl cyclopropanecarboxylate, cyanocyclopropane and acetylcyclopropane, and to trap them with aldehydes or ketones (Eq. 6).[87] The use of strong bases instead of TBAF produced undesired products. The coupling of an allyl chloride with trimethylsilyloxycyclopropane derivatives in the presence of silver fluoride produced δ,ε-unsaturated ketones (Eq. 7).[88] The ring opening of the cyclopropane followed by the attack of the electrophile give rise to a product derived from a synthetic equivalent of a β-metalloketone. Finally, an oxiranyl anion equivalent was generated from some fluorosilyloxiranes in the presence of a catalytic amount of TBAF and then reacted with various ketones or aldehydes (Eq. 8).[89]

Other articles focussed on the fluorodesilylation-alkylation reactions at carbon alpha to a nitrogen atom. Equations 9 and 10 demonstrate typical reactions where the fluoride ion serves to generate a carbanion-like species that will eventually react with an electrophile such as aldehydes or ketones. The term "carbanion-like" species is appropriate here. As shown in equation 9, N-(trimethylsilyl)methyl pyridone reacts with ketones when a catalytic amount of fluoride is used.[90] Equation 10 shows that vinyltriazoles can be easily obtained with this method.[91]

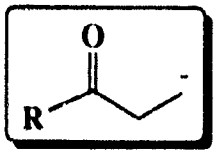


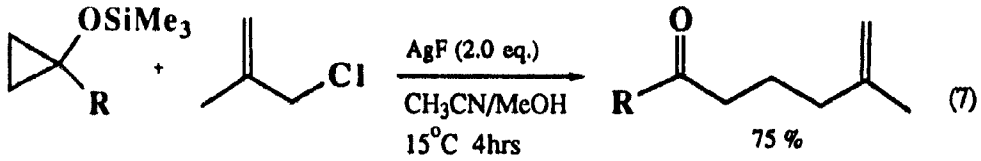


Ewg = CN, CO_2Me, COR

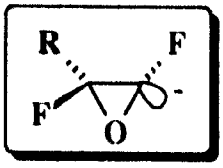
R' = H or aralkyl

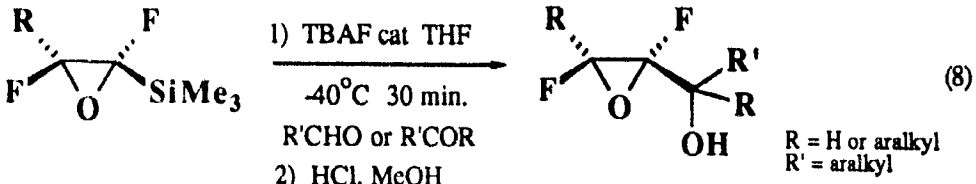
(6)





(7)

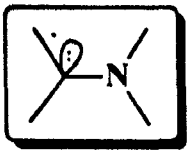


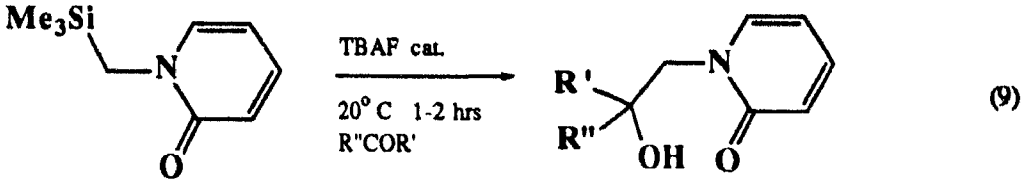


R = H or aralkyl
R' = aralkyl

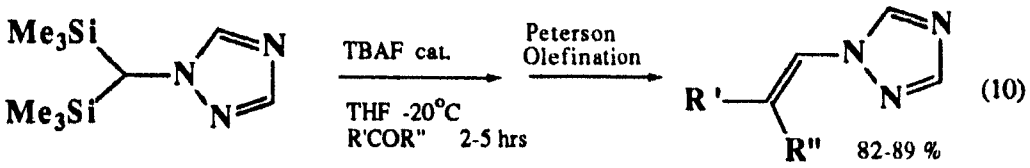
(8)

Ketone: ~ 48%
R'CHO: 65-85%
Enal: 61-63% (1,2-addition)
Retention of stereochemistry



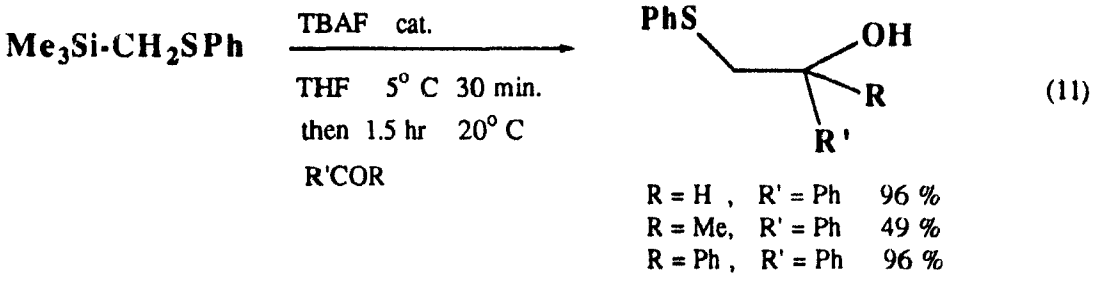


(9)



(10)

In a similar way, it is possible to alkylate at carbon alpha to a sulfur atom while using the fluorodesilylation technique (Eq. 11). For instance, phenylthiomethyltrimethylsilane reacted with fluoride ion to generate a nucleophilic species able to react with aldehydes or ketones.[92] The yields were moderate with some ketones and 1,2 addition took place with enones.



(11)

Some interesting applications of the fluorodesilylation reaction were encountered in some intramolecular cyclization reactions. Majetich and his group exploited the use of allylsilanes in a clever way from 1986-1989. An example is given below in Scheme 1, where an eight-membered ring compound is produced in excellent yield.[93] The formation of such a ring is usually considered to be difficult and the yields are often moderate. Other bicyclic compounds involving 5-5, 5-6, 5-7, and 6-7 membered rings were also demonstrated.[94] Several other publications involving intramolecular cyclizations were known, albeit for making the usual 5-, 6-ring systems.[95] A three-carbon ring expansion led to the synthesis of muscone with the help of allylsilanes.[96] These reactions induced by fluoride ions well complement similar reactions with strong Lewis acids ($SnCl_4$, $TiCl_4$, $EtAlCl_2$, etc.).

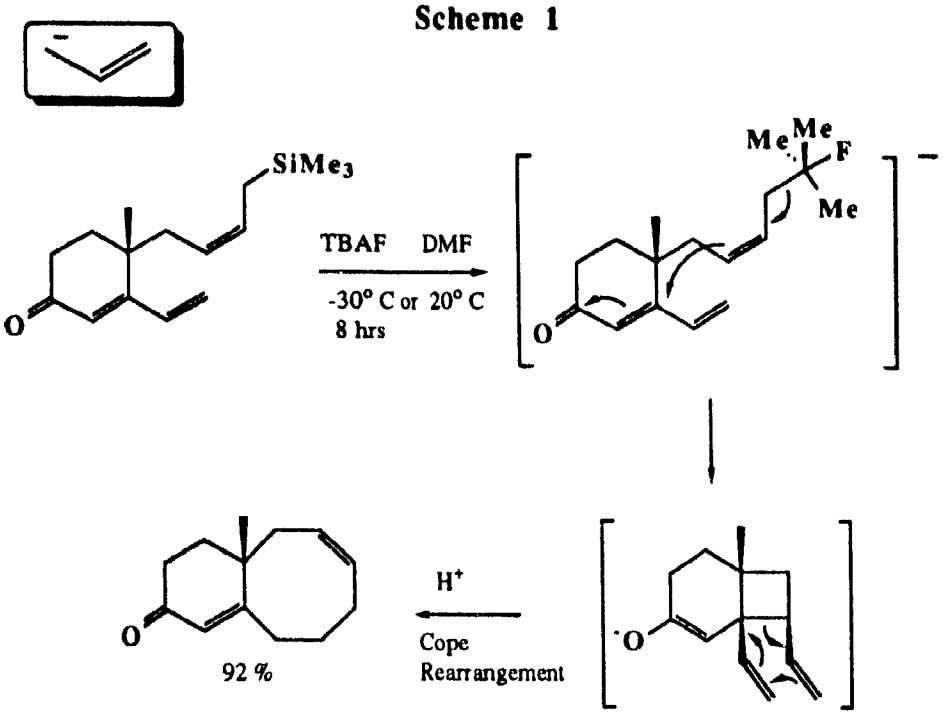
In 1987, allyltrifluorosilanes appeared as novel reagents for allylation.[97] The regiospecific and highly stereoselective reactions with aldehydes are worthy of mention. To account for such results, the authors proposed a cyclic chair-like transition state where the silicon atom is hexavalent, as shown in Scheme 2. The regiospecificity of these reactions contrast with the allyltrimethylsilane/CsF system where the regioselectivity usually varies from good to low. Interestingly, the results with crotylsilanes (See scheme 2) showed high threo and erythroselectivity, from E and Z isomer respectively.

The reader should be aware that the possible use organotin analogs have not been demonstrated for most of the cases shown above in this section. The overall effects (kinetic, thermodyanmic, etc.) upon changing silicon to tin in the fluorodestannylation-alkylation methodology are still unknown .

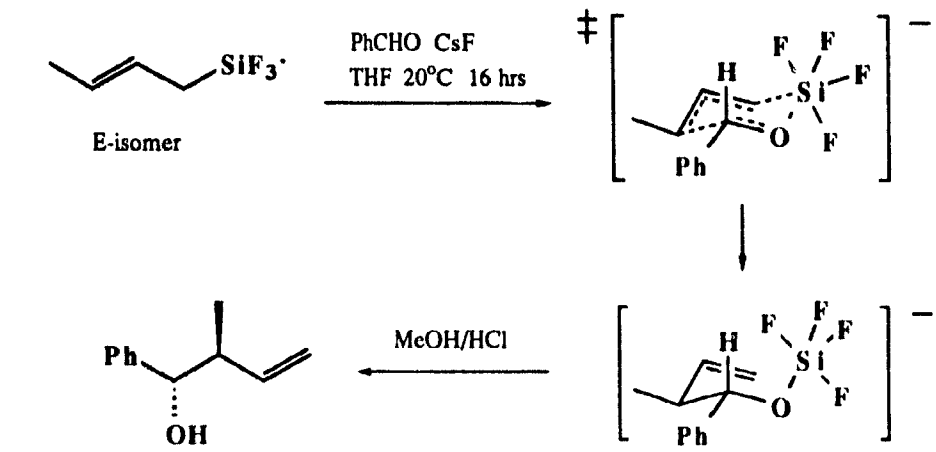
Many other nucleophiles from the group 16 have been released from fluorodesilylation. Sulfur , oxygen and selenium anions have been delivered in the presence of fluoride anions.[70] In 1987, it was shown possible to desilylate and alkylate protected silyl ethers of phenols in one step under mild and almost neutral conditions (Eq. 12).[98] To attain the same target, it usually requires two steps: deprotection and then alkylation with a mild base and an organic halide. However, in this example, it has not been possible to use this sequence of reactions.

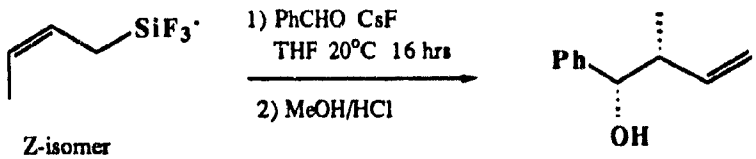
During the synthesis of subunits of ionomicin, an intramolecular reaction permitted to directly form an epoxide from a protected silyl ether having a mesylate group β to it, as shown in equation 13.[99] The main feature of this manipulation was to invert the configuration at a stereogenic center. In 1977, several anions of sulfur were produced from thiosilanes and fluoride ions. The reaction with aldehydes gave a mixed acetal of the general form R'-$CH(OSiMe_3)SR$ (R, R' = aralkyl).[100] No reaction was found with ketones but a 1,4-

Scheme 1



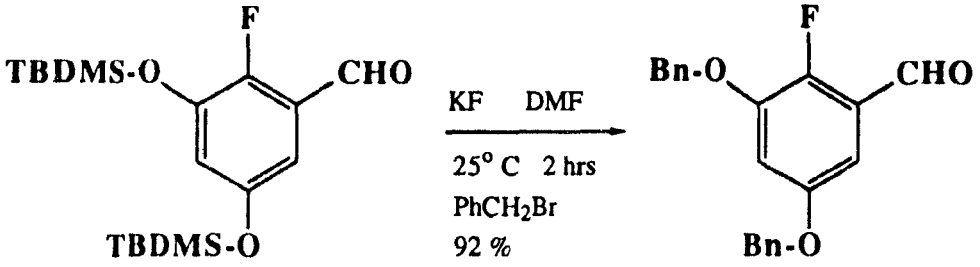
Scheme 2



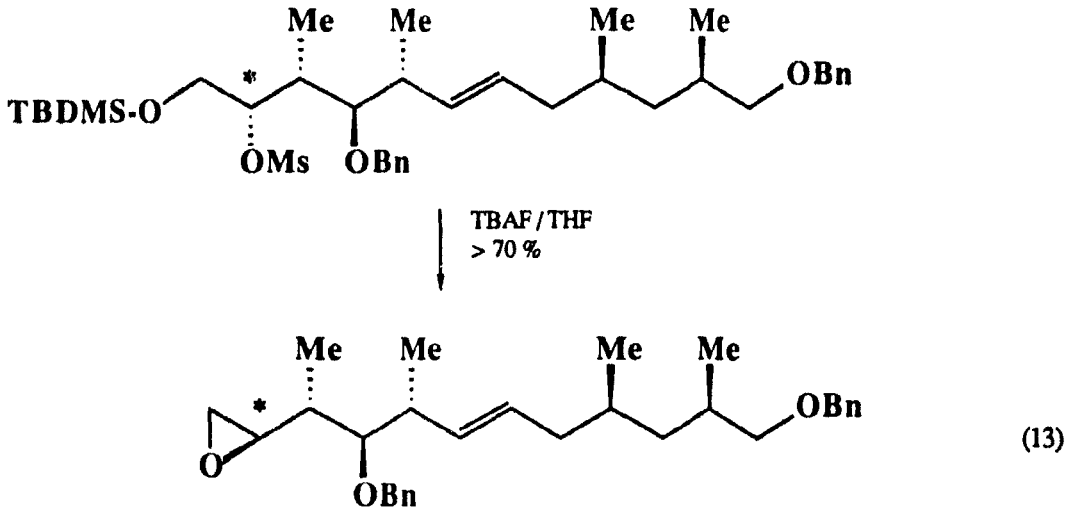


additon resulted with enals. In 1978, Liotta and coworkers presented similar reactions, induced by fluoride anions, with phenyl trimethylsilyl selenide and enals or epoxides.[101]

Alkoxide Anions



(12)

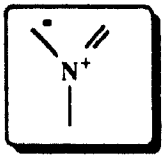


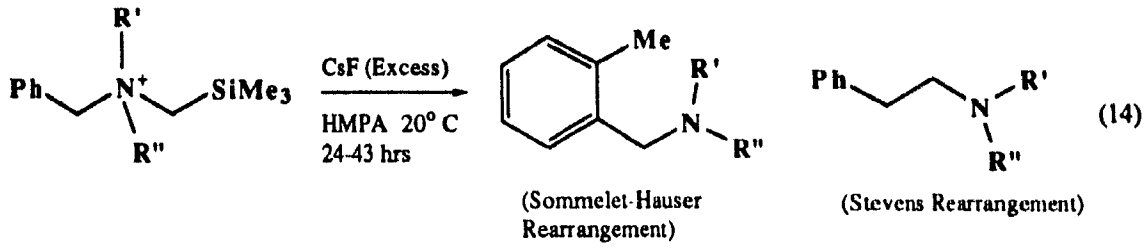
(13)

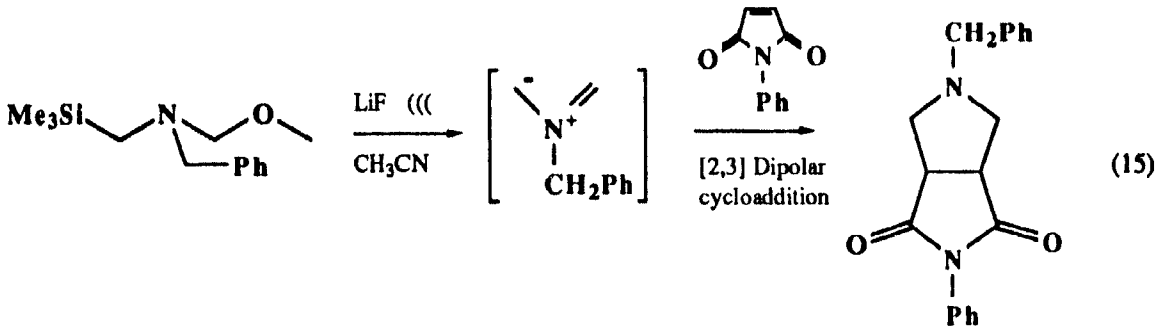
1.3.3 Generation of Reactive Species by Fluorodesilylation

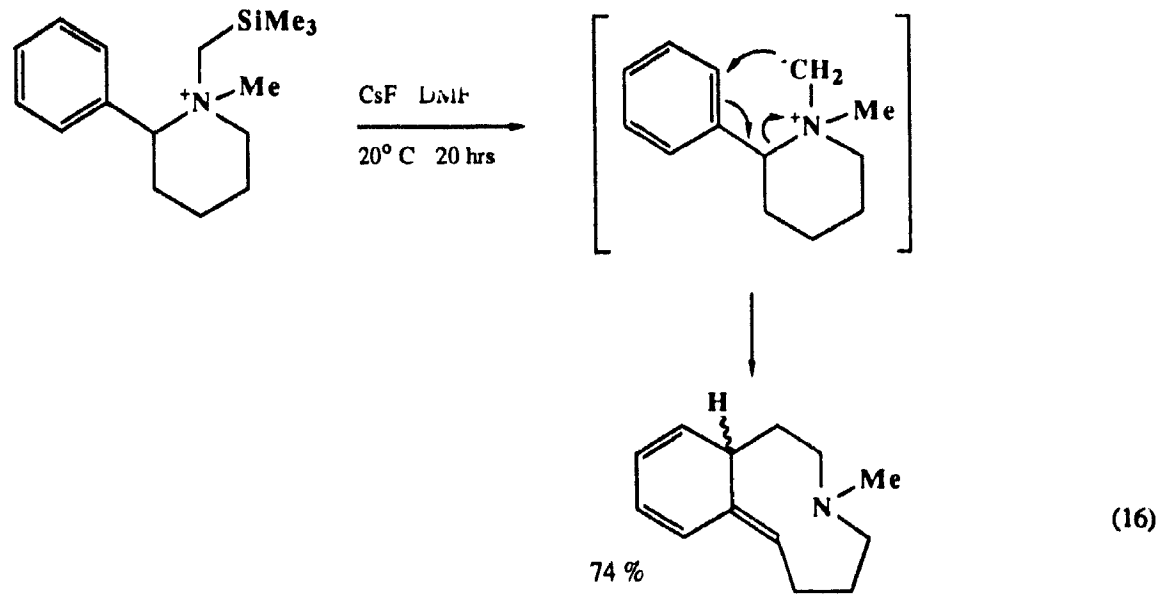
Several methods are known for making ylides of nitrogen, sulfur and phosphorus. Among them, fluorodesilylation represents one of the mildest way to generate ylides under almost neutral conditions, without the need of bases. Vedejs and Martinez were the pioneers in this area.[102] Padwa and his group also developed and used extensively this methodology for sulfur and nitrogen ylide formation.[103] These reactive intermediates are well known for undergoing [2,3] sigmatropic rearrangements. The Sommelet-Hauser rearrangement is a good example. Equations 14 and 15 in Scheme 3 present some typical work on nitrogen ylide

Scheme 3

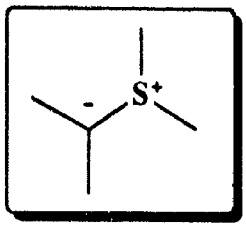


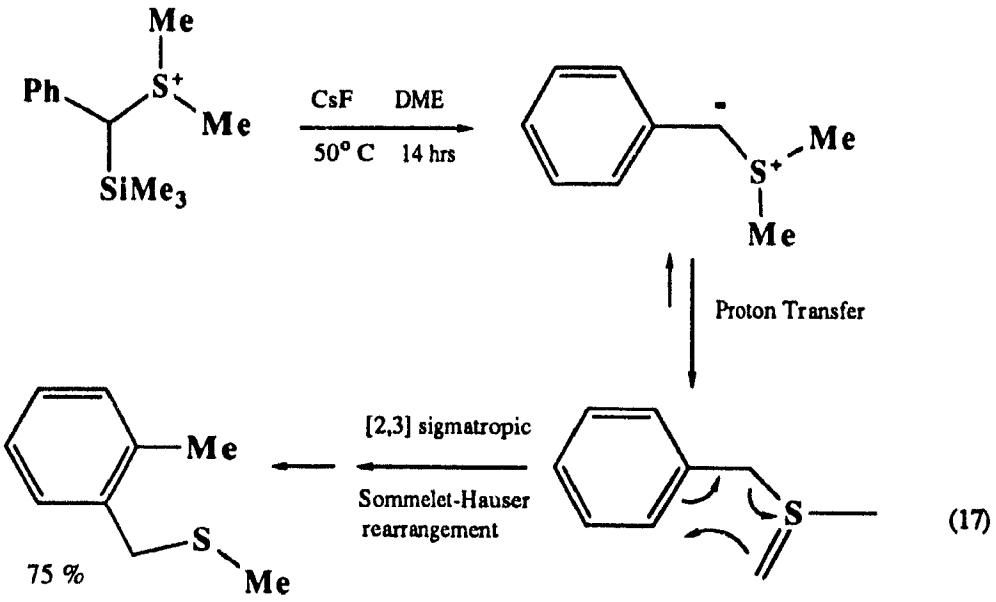

R'
Ph
N+
SiMe3
R"
CsF (Excess)
HMPA 20° C
24-43 hrs
Me
R'
N
R"
(Sommelet-Hauser Rearrangement)
Ph
R'
N
R"
(Stevens Rearrangement)
(14)

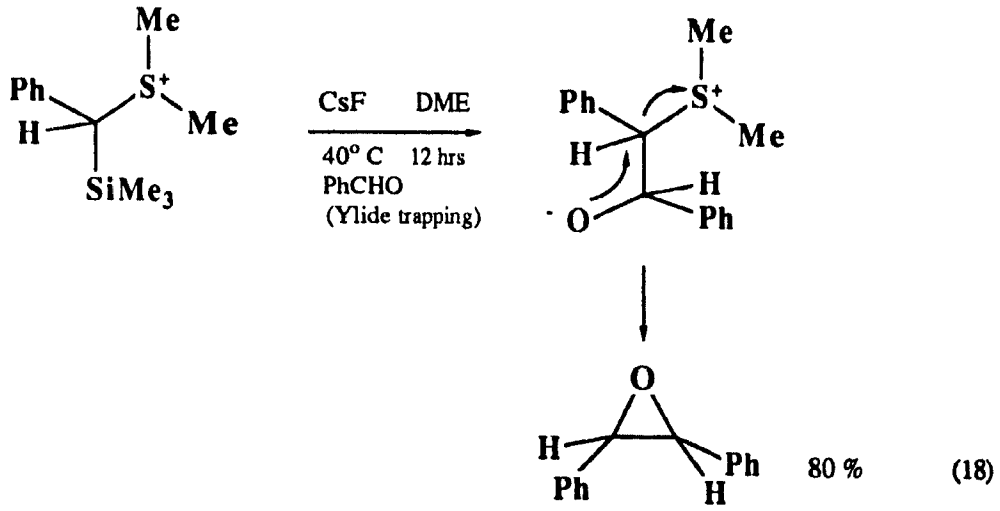

Me3Si
N
O
Ph
LiF (((
CH3CN
N+
CH2Ph
O
N
O
Ph
[2,3] Dipolar cycloaddition
CH2Ph
N
O
O
N
Ph
(15)


SiMe3
+N
Me
CsF DMF
20° C 20 hrs
CH2
+N
Me
H
Me
N
74 %
(16)

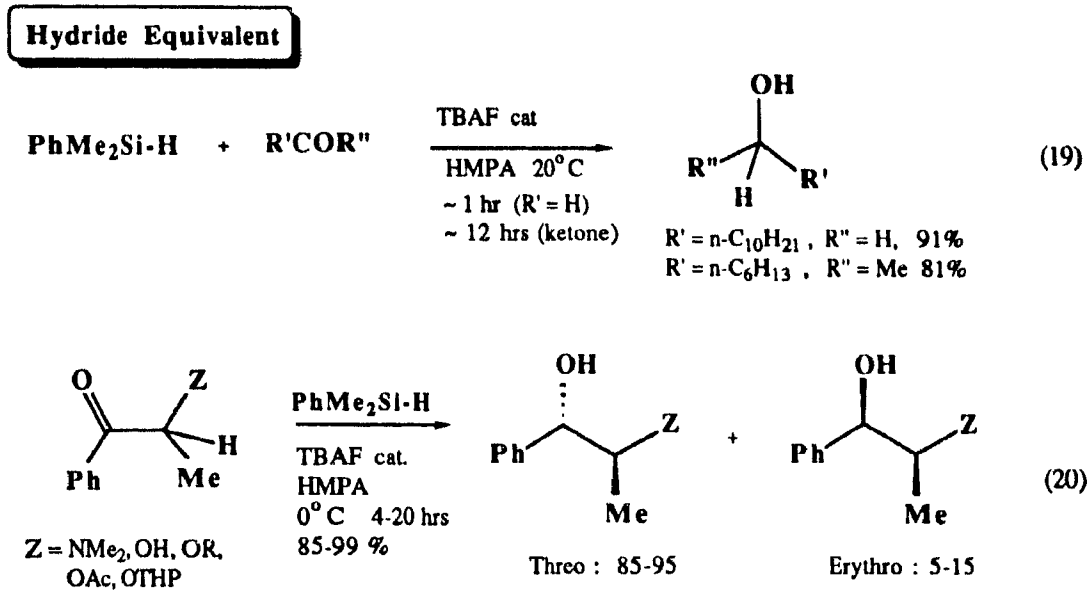
Scheme 4




Me
Ph
S+
Me
SiMe3
CsF DME
50° C 14 hrs
Me
S+
Me
Proton Transfer
[2,3] sigmatropic
Sommelet-Hauser
rearrangement
Me
S
Me
75 %
S
(17)


Me
Ph
S+
Me
H
SiMe3
CsF DME
40° C 12 hrs
PhCHO
(Ylide trapping)
Me
Ph
S+
Me
H
H
O
Ph
O
H
Ph
Ph
H
80 %
(18)

chemistry by Sato and Shirai (Eq. 14)[104] and by Padwa and Dent (Eq. 15).[105] In 1988, a method for making an unusual macrocyclic amine was reported using a stable intermediate in the Sommelet-Hauser rearrangement (eq. 16).[106] Some sulfur ylides were also reported in 1987-88, as shown in equations 17[107] and 18[107] (Scheme 4).



Another interesting class of nucleophilic species are the hydrides. The silanes (very often trialkylsilanes) have been used extensively in the reduction of ketones and aldehydes in the presence of fluoride ions in HMPA. Fujita and Hiyama presented complete kinetic studies on these reductions.[108] It appears that a solvent dependence (HMPA) was first order and the nucleophilic species involved were ionic hexavalent silicon complexes of the form $[R_3SiH(F).HMPA]^- Bu_4N^+$. In 1988, Fujita and Hiyama demonstrated that the reduction proceeded with high threoselectivity in a non-cyclic transition state.[109] This threoselectivity is in sharp contrast to most of the reductions known, which usually proceed in an erythroselective way (Eq. 19 and 20).[109]

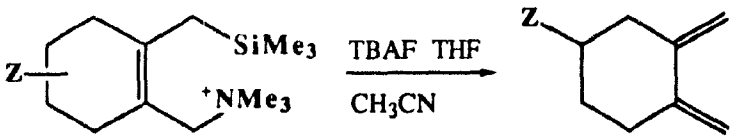
For more details about reactions involving anions or anion-like species implied in the fluorodesilylation technique, the reader should consult a general review.[70]

1.3.4 Fluorodesilylation-Eliminations.

A number of publications have appeared on fluorodesilylation-elimination. A brief summary will only be given here since a general review is available.[70] The use of such reactions has been well documented in the synthesis of strained cyclic (cyclopropene[110] and

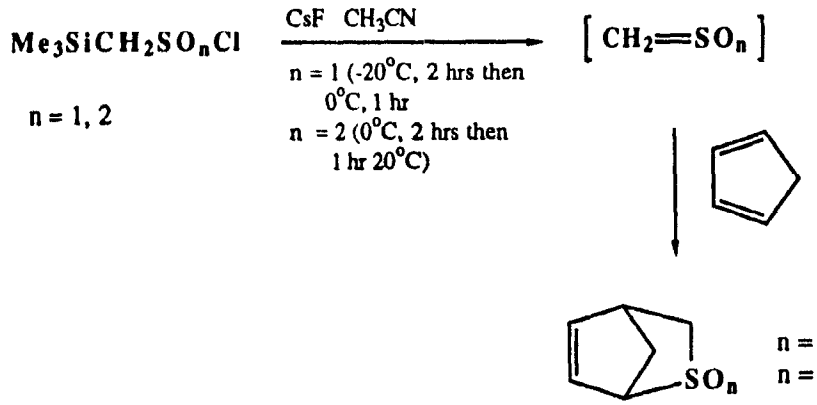
allene oxide[111]) or bicyclic molecules[112] possessing highly reactive double-bonds. In 1988, interest in this area continued, as described below in equations 21[113] and 22[114] .

Fluoride-Induced Eliminations



(21)

Diene for Diels-Alder Reaction



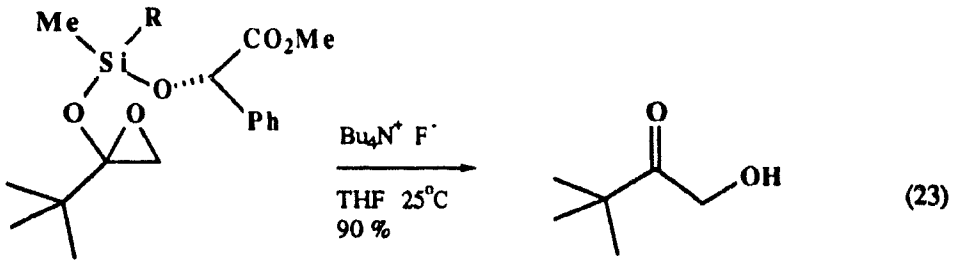
(22)

1.3.5 Fluoride-Induced Rearrangements or Fragmentations.

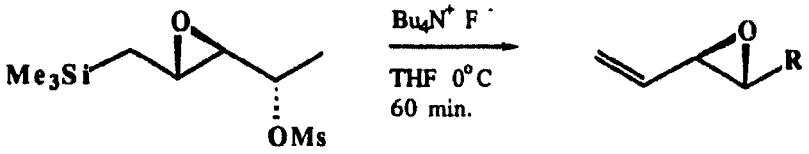
Triorganosilyl groups have also been involved in many reactions of fragmentation or rearrangement induced by fluoride ions. I collected here the most important publications since 1987 in order to give a brief overview about the recent research. For a more complete literature survey, the reader is referred to the books on silicon[49] and to some reviews.[70] In many cases, these reactions can be schematized by an elimination leading to a transient nucleophile followed by a fast intramolecular S_N2 reaction. Equations 23[115] , 24[116] and 25[116] represent well these processes. Most of the time, the rearrangements are conducted under mild and almost neutral conditions, especially with epoxides. They offer an interesting

method to invert the configuration at a stereogenic center while complementing the well-known Payne rearrangement of chiral α-epoxy alcohols, easily obtained from the Sharpless epoxidation.

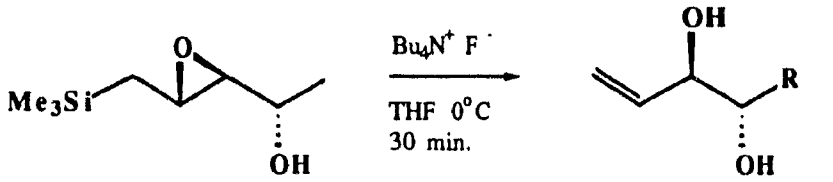
Rearrangements With Epoxides



(23)



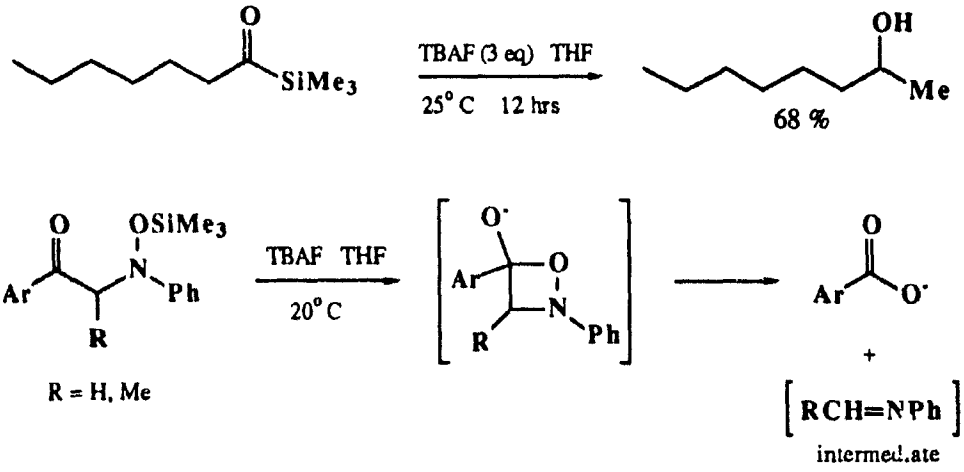
(24)



(25)

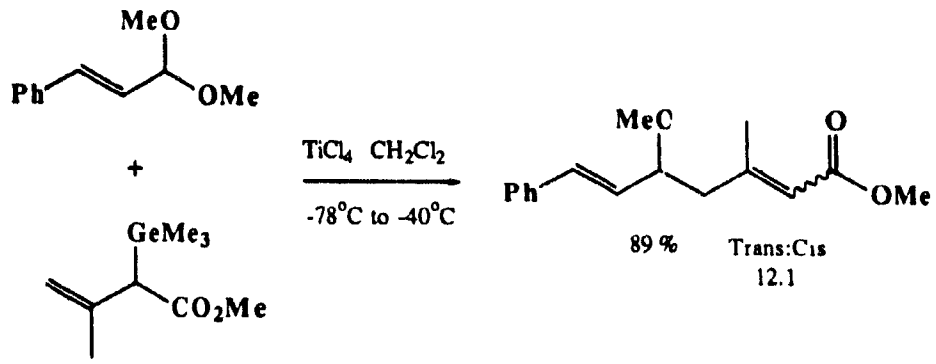
Another type of interesting rearrangement came from the treatment of acyl silanes with fluoride ions. An alkyl ligand on silicon is able to migrate to the carbonyl group when the silicon atom is hypervalent (Eq. 26).[117] Finally, an example of fragmentation was demonstrated in 1987, as shown in equation 27.[118]

Fluoride-Induced Rearrangement



1.4 Organogermanium Chemistry in Organic Synthesis.

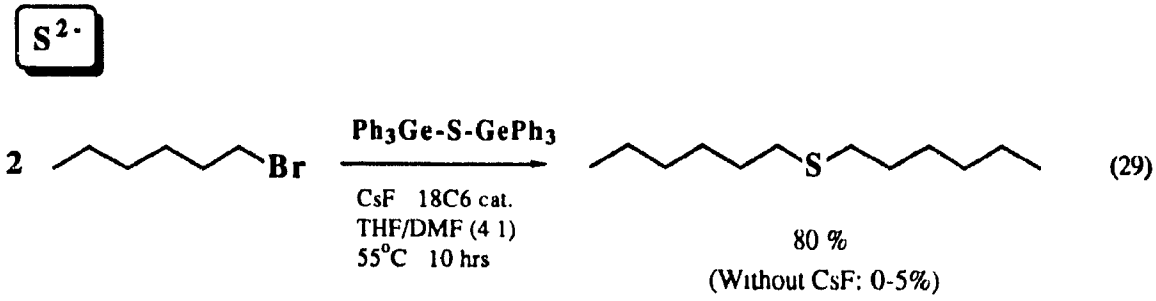
Only a few reactions are known where organogermanium reagents are used in organic synthesis even though considerable work has been published on organogermaniums and with heterocycles containing a germanium atom in the ring.[119] In the past, triphenylgermane (Ph_3GeH) has been briefly used in radical cyclizations.[120] In 1988, some publications involving germanium enolates can be found. The acyclic stereoselection in aldol-type reactions of germanium enolates with benzaldehyde was recently studied.[121] Another publication showed a masked form of germanium dienolate where alkylation predominates at the δ-position of the carboalkoxy group in the presence of various ketals or allyl halides and titanium tetrachloride (see Eq. 28).[122] These reactions complement those of the corresponding silyl ketene acetals where the alkylation proceeds α to the carboalkoxy group.



(28)

1.4.1 Fluorodegermanylation

In this thesis, the first fluorodegermanylation reactions applied to organogermanium sulfides will be described. Equation 29 demonstrates a new "S^{2-}" tranfer agent developed in our laboratory. Without fluoride ions, bis(triphenylgermanium)sulfide did not react at a useful rate and only some traces of the corresponding thioether were observed. More details will be given in chapter 4.

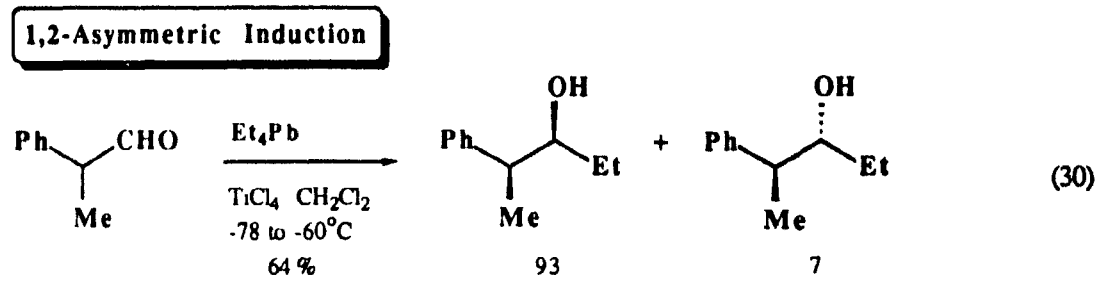


(29)

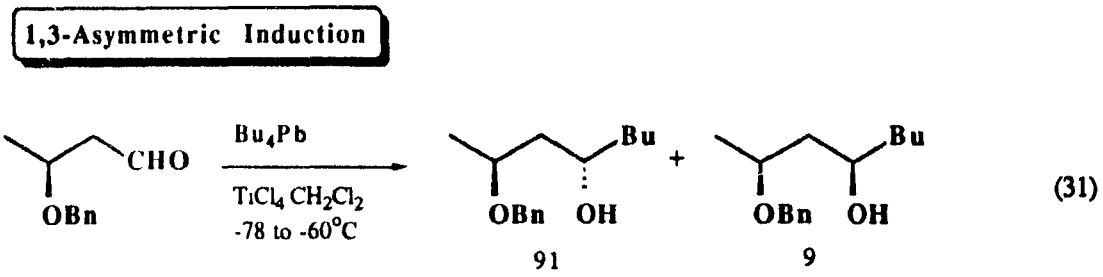
1.5 Organolead Chemistry in Organic Synthesis.

Due to their toxicity, their heat and light sensitivity, only a few compounds containing lead have appeared as practical reagents in organic synthesis. Lead thiocyanate ($Pb(SCN)_2$) was used in some reactions with organic halides for making organic thiocyanates.[123] The most popular reagent is certainly lead tetraacetate ($Pb(OAc)_4$).[124] In the past, allyllead reagents,[125] ((triphenylplumbyl)methyl) lithium and (bis(triphenylplumbyl)methyl)lithium[126] have also been used in organic synthesis. In 1987, Yamamoto and Yamada reported some

useful diastereoselective alkylation reactions involving aldehydes where excellent 1,2- and 1,3-asymmetric inductions were observed, as shown in equations 30 and 31.[127]



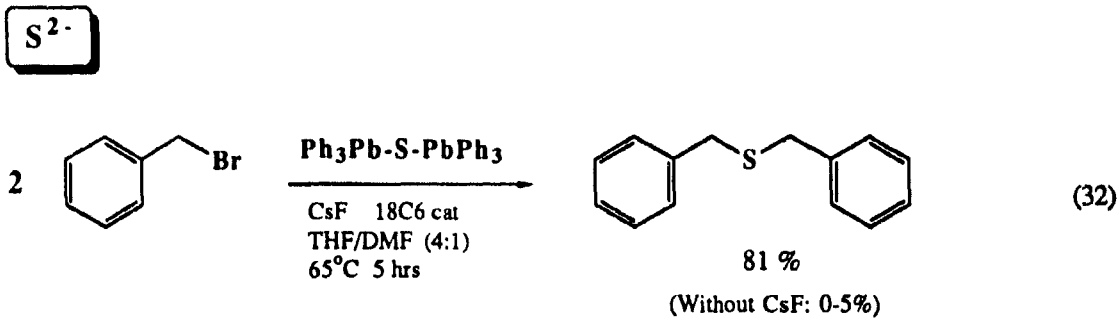
(30)



(31)

1.5.1 Fluorodeplumbylation

In this thesis, will be presented the first fluorodeplumbylation reaction applied to the release of sulfur anions. Equation 32 shows a brief overview of a new "S^{2-}" transfer agent. We demonstrated the strong fluoride effects on the reaction rate with bis(triphenyllead)sulfide and alkyl halides. More details will be given in chapter 4.



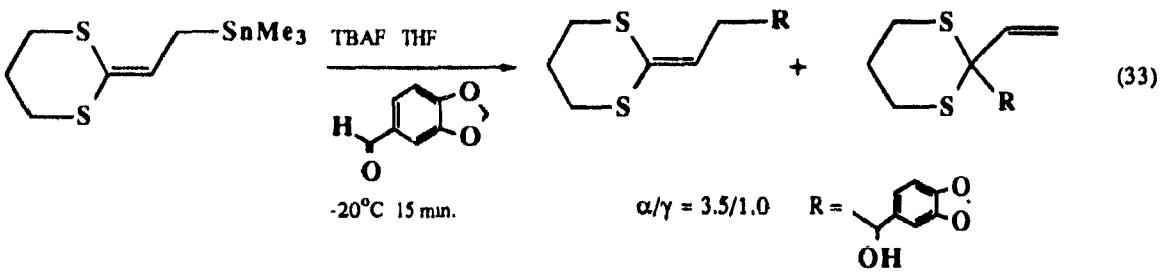
(32)

1.6 Organotin Chemistry in Organic Synthesis.

Overall, several different fields or divisions in organotin chemistry can be delineated. The transition-metal catalysed reactions for C-C bonds or carbon-heteroatom bonds formation is one of the most flourishing in the 1980's. Palladium-catalysed coupling reactions of vinyl, allyl, benzyl or aryl halides with organotins are certainly one of the most popular due to the mild conditions required and access to some unusual couplings, not easily obtained from classical organic chemistry. Clark Still and J. K. Stille and their respective research groups should be considered as the pioneers in this field. Another area is the use of Lewis acids in order to effect chemical transformations of organotins. Some of these reactions are similar to those found in organosilicon chemistry.[128] Finally, the recent explosion of radical chemistry, especially in intramolecular cyclizations, has mainly derived from the use of trialkyltin hydride (usually triphenyl or tributyltin hydride). An excellent view on that topic is presented in a book written by Giese, a pioneer in that area.[129]

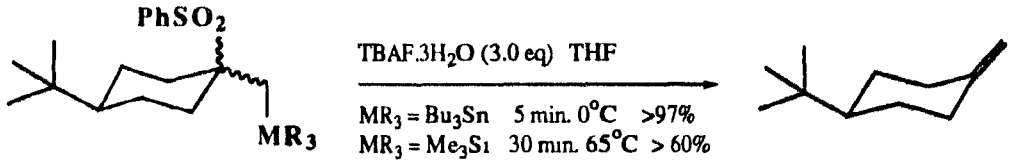
1.6.1 Fluorodestannylation.

An obvious question when one compares organotin to organosilicon chemistry is: is it possible to develop fluorodestannylation reactions? For over twenty years, organotins have been used in organic synthesis but no one had reported fluorodestannylation reactions . I was tempted to investigate these reactions in order to clarify the scope, the kinetic aspects and the mechanisms implied. It is the purpose of this thesis to examine all these questions and to investigate new reactions where the parallel and differences with the silicon chemistry will be compared. In 1987, the first complete volume dealing with "Tin in Organic Synthesis"[25] appeared; but only one reference was made to the process we now call fluorodestannylation.[130a] Here, Andersen and co-workers briefly reported the coupling of (1,3-dithian-2-yl) trimethylallylstannane with piperonal induced by fluoride anions. This example as shown below in equation 33 is the only synthetically useful reaction presented. Results were often poor and no generalization of these couplings was demonstrated.

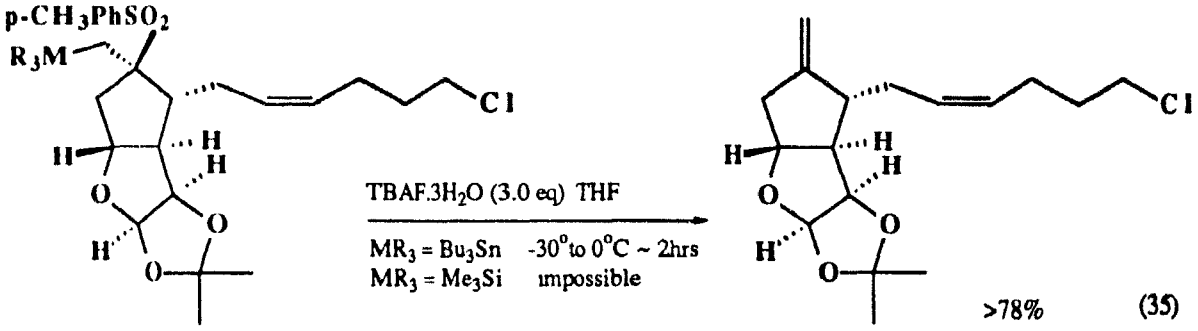


(33)

It was not until 1985 when Pearlman, Putt and Fleming from the Upjohn Company published the first promising article on fluorodestannylation.[130b] They clearly demonstrated an advantage in using the fluorodestannylation-elimination reaction for achieving the methylenation of moderately hindered sulfones, sometimes unavailable from a fluorodesilylation-elimination reaction (eq. 35). The most interesting results came from the observation of a significant increase of the reaction rate in the elimination process compared to the silicon analogs (Eq. 34).[130] They briefly tried to explain their kinetic data by either a greater kinetic affinity of the fluoride ion for tin rather than silicon or to the fact that the Sn-C bond is weaker than the Si-C bond. However, no experiment was made for elucidating the exact mechanism.

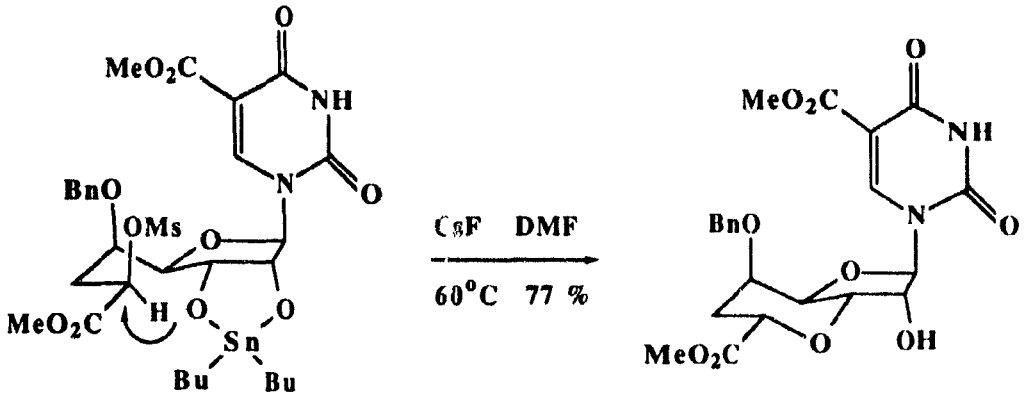


(34)



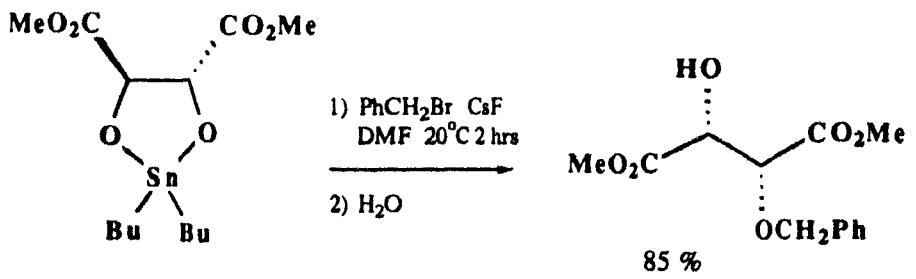
(35)

In 1986, the first fluorodestannylation-alkylation appeared in a communication from Danishefsky and Hungate.[131] A regioselective intramolecular O-alkylation was produced when the fluoride ion attacked the tin atom of a cyclic stannylene acetal for activating the oxygen atom, followed by an S_N2 reaction with a mesylate group (Eq. 36). The fact that there was no need to protect the non-participating oxygen atom was an advantage here. This key step led to the total synthesis of octosyl acid. In 1988, they published the full paper of that work;[132] they reported that the reaction proceeded under almost neutral conditions. In our work, as described in Chapter 3, we found some reactions of elimination in similar alkylations, proving some basicity of the reaction conditions. One should be aware that this intramolecular reaction might proceed under different conditions than for bimolecular reactions.



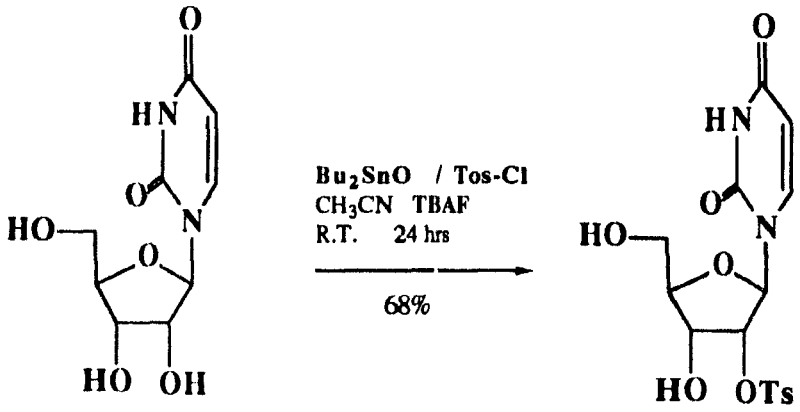
(36)

In 1987, a Japanese group reported the first study of fluoride sources along with the various electrophiles such as alkyl bromides or iodides that can be used in the regioselective O-monoalkylation of optically active O-stannylene acetal of dimethyl L-tartrate (Eq. 37).[133] A pentacoordinate complex of tin is thought to be responsible for the enhancement of the oxygen nucleophilicity. However, they also stated that the cesium cation might activate the alkyl halides through the interaction of this ion with the halogen atom of the electrophile. It seems highly questionable as the cesium cation is considered to be a poor Lewis acid.



(37)

In a very similar way, a French group used cyclic stannylene acetals for regioselective monotosylation of some nucleosides (uridine and adenosine) .[134] They obtained good to high regioselectivity when using TBAF in acetonitrile or CH_2Cl_2, compared to tetrabutylammonium bromide or chloride (Eq. 38).



(38)

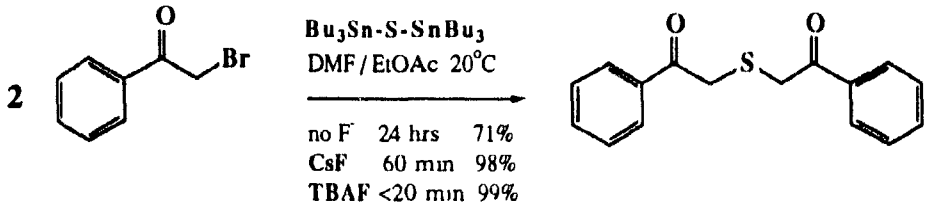
The rate enhancement of the O-alkylation with organotin oxides in the presence of the fluoride ions is significant. Without the use of fluoride, Ogawa and his group showed that regioselective benzylation and methylation of carbohydrates required strong heating for many hours in DMF or in the organic halide itself as the solvent.[135] In contrast, reactions with fluoride ion proceed smoothly at room temperature. We demonstrated similar fluoride effects in our own work, as shown in Chapter 3.

1.7 Fluorodemetalation Reactions Within Group 14.

In 1985, when I began this research, the original purpose was to develop a new sulfur transfer agent using bis(tributyltin)sulfide (or bis(tributylstannyl)sulfide). At about the same time, Steliou and Corriveau published one trial with this reagent in a paper focussing mainly

on the reaction of bis(trimethylsilyl)sulfide with alkyllithiums in order to release "Li_2S" salts in THF.[136] In 1987, we reported a communication dealing with the chemistry of bis(tributyltin)sulfide describing the strong importance of a donor solvent (DMF or CH_3CN) in its reactions.[137] This is presented in Chapter 2 of this thesis.

Due to the limited success with bis(tributyltin)sulfide and because of the strong and prolonged heating required to achieve thioether formation (~ 120-140°C for 12 to 24 hrs),[137] I had the idea to utilize some external nucleophiles in order to help the reaction, after having observed some strong solvent donor effects. I thought that if a nucleophile could complex on tin, the increase of the electronic density on this atom would help to release the sulfur anions. In November 1985, I thus decided to use fluoride or cyanide anions in view of their low nucleophilicity in S_N2 type reactions. When mixing bis(tributyltin)sulfide and phenacyl bromide in DMF/EtOAc (6.5:1.0 v/v), without heating (at 20°C), only a relatively slow reaction was previously observed (after 24 hours, the isolated yield was 71%) . When cesium fluoride was added, a strong yellow-orange color immediately appeared at the surface of the undissolved cesium fluoride crystals. The reaction was entirely completed within 60 minutes with an isolated yield of 98% (see equation 39). At that time, no report of fluoro or cyanodestannylation had been published. The same day, I confirmed that TBAF was even more effective: the reaction was almost instantaneous and a strong yellow-orange color persisted. Later, I also demonstrated that tetrabutylammonium cyanide (TBACN) was also useful in this reaction.



(39)

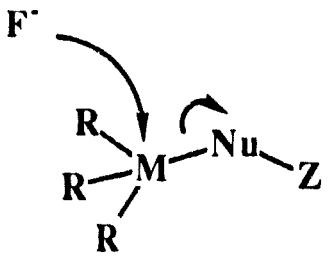
During 1987, we published these findings where we introduced the term fluorodestannylation.[138] As described in equation 39 above, several new sulfur transfer agents based on this idea were presented. Due to the problem of finding highly nucleophilic anhydrous fluorinating agents, we developed and studied the combination of crown-ethers with cesium fluoride.[139] A relative rate study in fluorodestannylation as well as in fluorination of organic halides led to the conclusion that edge or sandwich complexes of cesium cations with 18-crown-6 is almost as effective as in the usual 1:1 complex where the cation fits inside the cavity of the crown-ether. This is presented in detail in Chapter 2.

Last year, we reported the work where triorganotins act as general "group 16 transfer agents". The anions of oxygen, sulfur, selenium and carbon were released in the presence of fluoride ions from the corresponding organotins.[140] A careful choice of the cations (like cesium or tetraalkylammonium) in the medium can favor highly nucleophilic species due to weak ion-pairing processes between the nucleophile and the counterion. In addition, the mildness and neutrality of the reactions led to promising use in synthesis. Synthetic equivalents of "O^{2-}" and "Se^{2-}" were also discussed, along with a working hypothesis about the mechanisms involved in the fluorodestannylation reactions. Chapter 3 will present more details.

In Chapter 4 of this thesis, the general concept of fluorodemetalation within group 14 is presented (see Scheme 5). As with the idea of fluorodesilylation and fluorodestannylation, it appears interesting to observe the effect of the variation of the metal (or the metalloid) within the whole group 14.[141] The fluorodegermanylation and fluorodeplumbylation reactions have been demonstrated for the first time and compared to the two other known methods. In addition, the kinetic and mechanistic aspects of fluorodemetalation (especially the fluorodestannylation reactions) will be discussed with the help of multinuclear NMR experiments (^{119}Sn, ^{19}F, ^{13}C, ^{1}H NMR spectroscopy).[141]

Scheme 5

The Fluorodemetalation Concept



M = Si, Ge, Sn, Pb
Nu = O, S, Se, C, N, P nucleophiles
Z = Si, Ge, Sn, Pb, aralkyl etc.

In Chapter 5, other interesting uses of bis(tributyltin)oxide, as a mild oxygen tranfer agent in the presence of silver salts for the conversion of primary organic halides into alcohols, will be presented.[142] Claims to original work can be found immediately after this chapter.

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CHAPTER 2

TOWARD THE FLUORODESTANNYLATION METHODOLOGY

The section 2.0 will present the synthesis of organic sulfides from bis(tributyltin)sulfide and organic halides. The text has been published as a communication (Harpp, D. N.; Gingras, M.; Aida, T.; Chan, T. H. *Synthesis* **1987**, 1122). The original idea of using organotin sulfides as sulfur transfer agents belonged to professor Harpp and his post-doctoral fellow (named Aida) who investigated some reactions with this reagent. My contribution to this article has been to repeat some reactions and to bring some generalities while trying other possible halogenated substrates. I investigated half of the reactions shown in the Table in section 2.0 and I demonstrated a large solvent effect in these reactions. At this point, the prolonged heating of several hours (often at 110°-140°C for 12 to 24 hours) required for the reactions did not permit wide use of this method in organic synthesis, especially with sensitive substrates. Some improvements were necessary in order to bring about a mild and powerful sulfur transfer agent, as the nucleophilicity of bis(tributyltin)sulfide itself is very poor. In 1985, I thought about using fluoride and cyanide ions in order to help the reactions, as previously explained.

The section 2.1 of this chapter will introduce the concept of fluoro and cyano-destannylation applied to the release of powerful sulfur anions having cesium and tetrabutylammonium as counterion. This section has appeared as a published work (Harpp, D. N.; Gingras, M. *Tetrahedron Lett.* **1987**, *28*, 4373). This new methodology now permit the use of organotin sulfides as sulfur transfer agents under mild, neutral and anhydrous conditions. For further experimental details, Chapter 4 presents complete procedures on fluorodestannylation reactions involving organotin sulfides.

To overcome original problems with the formation of thiols as side-products in the fluorodestannylation reactions of organotin sulfides, I developed an anhydrous source of nucleophilic fluoride ions. I investigated the use of crown-ethers with cesium fluoride in order to improve the nucleophilicity of these ions. These results described in a communication published on this topic (Gingras, M.; Harpp, D. N. *Tetrahedron Lett.* **1987**, *29*, 4669) constitutes section 2.2. Further experimental details are available in the Appendix 1.

The literature search for references and the original writing of all of the publications described in chapter 2 were all my own work. The revision of these manuscripts were done with the excellent help of professor Harpp.

2.0 BIS(TRIBUTYLTIN)SULFIDE: AN EFFECTIVE AND GENERAL SULFUR TRANSFER REAGENT[1].

Abstract: *Bis(tributyltin) sulfide 1 acts efficiently to transfer the sulfur atom as S^{2-} to a variety of halide substrates to afford the corresponding thioether derivatives in very good overall yield.*

Many synthetic reagents, including sodium sulfide nonahydrate ($Na_2S.9H_2O$), are known to transfer S^{2-} for making organic sulfides[2]. Only a few of them however, deliver the sulfur atom in a precise amount under anhydrous, neutral and homogeneous conditions[3].

We wish to report that bis (tributyltin) sulfide (**1**) possesses all these characteristics and is commercially available[4] or easily made[5]. A general reaction scheme for making sulfides is presented in equation 1.

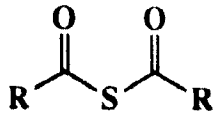
$$2\ R\text{-}X + \underset{\mathbf{1}}{Bu_3Sn\text{-}S\text{-}SnBu_3} \text{ -------> } R\text{-}S\text{-}R + 2\ Bu_3Sn\text{-}X \qquad \textbf{Eq.1}$$

The scope of this chemical process was investigated with numerous substrates and found to be quite general (see Table 1). Some success with (**1**) has been previously reported using sodium iodide in refluxing 2-butanone, however only with reactive halides[2c]. With our methodology, for many halides, the reaction usually takes place near room temperature within 24 hours, giving modest to excellent yields. For less reactive substrates, such as 1-iodopropane, a sealed tube containing chloroform is heated at 140°C for 12 to 24 hours, providing almost quantitative yield of product.

A solvent effect is noted for reactive substrates. Indeed, the rate of the reaction increases as the polarity and the ability to coordinate with tin increases[6], suggesting an ionic mechanism[7].

The water sensitivity[8] and the thermal decomposition[9] of thioanhydrides (**2**) make them a difficult class of compounds to prepare. We report here that yields obtained are among the best in the literature to date[10] (entries 1-3, Table 1). Substrates halogenated in the α-position of a carbonyl group form sulfides that were used in the preparation of some

heterocycles (thiophene, thiolene)[11a], or as dienophilic thioaldehydes in the Diels-Alder reaction[11b] or in carbohydrate derivatives[11c]. Thus, our method produces these useful sulfide intermediates under neutral and mild conditions.



2

Among the most interesting sulfides obtained are the carbonic acid derivatives (entries 4 to 6). Although bis(alkoxycarbonyl)sulfide has received attention recently[12], only one method giving high yield of products (>90%) is known[13]. Surprisingly, little information is available in the literature on bis((alkylthio)carbonyl)- or bis(dialkylaminocarbonyl)sulfides. No general method appears to be known for making these classes of compound in one step; thus, we present the first practical way to obtain them[14]. In addition to these sulfur derivatives, trisulfides (entry 7), sulfur transfer reagents (entry 8) and other thioethers (entries 9-22) are readily prepared.

The major limitation of this method consists of the purification of sulfides unstable on silica gel. Despite this drawback, this methodology remains quite general as discussed above. The preparation of reagent (**1**) according to slight modification of a published procedure[5] is described below. A typical experimental procedure for making sulfides with (**1**) is also summarized.

Bis(tributyltin) Sulfide (1): Sodium sulfide nonahydrate ($(Na_2S.9H_2O)$; 72.05 g., 0.200 mol) is dissolved in distilled H_2O (60 ml) at 35°C and this solution is added to a stirred solution of tributyltin chloride (97.64 g.; 0.300 mol) in THF (300 mL) in a 1000 mL flask. [The use of this solvent mixture appears to aid significantly to obtain good yields]. Extra H_2O (30 mL) is used to aid in the complete transfer of the Na_2S. The mixture is heated at reflux (65°C) for 4 hrs with vigorous stirring. After cooling, the phases are separated and the organic phase is evaporated. The residue (the crude reagent (**1**)) is extracted with dry Et_2O (4 x 50 mL) and the extract is dried ($MgSO_4$) with stirring (30 min.). After filtration and the solvent evaporation, the crude product is placed under vacuum to remove traces of solvent; yield: 88.18 g. (96%); pale yellow, viscous liquid Further purification is achieved by distillation in vacuum; yield of pure (**1**): 85.15 g. (93%); b.p. 225°C/0.4 Torr; purity (GLC):~99%.

Table 1: Formation of Sulfides Using Reagent 1 and Organic Halides

Entry No.	Halide (mol-eq)	1	Solvent	Temperature (°C)	Time (Hr)	Sulfides[d]	Yield (%)
1	CH_3COCl	1.00	$CHCl_3$	20	5	$(CH_3CO)_2S$	99a
2	CH_3COCl	1.05	CH_2Cl_2	20	24	$(CH_3CO)_2S$	86b
3	PhCOCl	1.00	$CHCl_3$	20	5	$(PhCO)_2S$	98a
4	EtOCOCl	1.00	$CHCl_3$	110	12	$(EtOCO)_2S$	94a
5	EtSCOCl	1.00	$CHCl_3$	110	12	$(EtSCO)_2S$	97a
6	Me_2NCOCl	1.00	$CHCl_3$	110	12	$(Me_2NCO)_2S$	92a
7	$PhCH_2SCl$	1.00	$CHCl_3$	0	0.2	$(PhCH_2S)_2S$	100b
8	NCS[e]	1.00	$CHCl_3$	0	0.5	$(Suc)_2S$	100b
9	$PhCH_2Br$	1.00	$CHCl_3$	110	12	$(PhCH_2)_2S$	99a
10	$PhCH_2Br$	1.00	CH_2Cl_2	40	28	$(PhCH_2)_2S$	25b
11	$PhCH_2Br$	1.00	$CHCl_3$	61	120	$(PhCH_2)_2S$	93b
12	n-PrI	1.00	$CHCl_3$	140	24	$(n\text{-}Pr)_2S$	97a
13	Allyl-Br	1.00	$CHCl_3$	110	12	$(Allyl)_2S$	98a
14	$PhCOCH_2Br$	1.00	$CHCl_3$	110	12	$(PhCOCH_2)_2S$	98a
15	$PhCOCH_2Br$	1.20	CH_2Cl_2	20	43	$(PhCOCH_2)_2S$	trace
16	$PhCOCH_2Br$	1.05	D/E[f]	20	24	$(PhCOCH_2)_2S$	71b
17	$PhCOCH_2Br$	1.20	D/E[f]	45	3	$(PhCOCH_2)_2S$	94b
18	$EtCOCH_2Br$	1.10	D/E[f]	20	22	$(EtCOCH_2)_2S$	56b
19	$EtCOCH_2Br$	1.10	D/E[f]	20	60	$(EtCOCH_2)_2S$	69b
20	$EtCOCH_2Br$	1.10	D/E[f]	55	2	$(EtCOCH_2)_2S$	29b
21	CH_3COCH_2Cl	1.10	D/E[f]	45	3	$(CH_3COCH_2)_2S$	trace
22	$CH_3COCHCH_3$ Br	1.05	$CHCl_3$	61	78	$(CH_3COCH)_2S$ CH_3	nil

a) yields were determined by gas chromatography using an internal standard; b) isolated product; c) sealed tube method; d) identified by nmr, ir, gc/ms and compared to authentic material; e) NCS is the abbreviation of N-chlorosuccinimide; Suc for succinimide; f) D/E= DMF/EtOAc (5:1).

When the above procedure is carried out on a smaller scale (5 g. of tributyltin chloride and 2 equiv. of $Na_2S.9H_2O$) reagent (**1**) is produced in 97% yield and 99% purity. This product could be used directly without purification by distillation. ^1H NMR ($CDCl_3/TMS_{int}$, 200 MHz): δ= 0.91 (t, 18H, 6 CH_3); 1.08 (t, 12H, 6 CH_2Sn); 1.34 (sext, 12H, 6 $CH_3\mathbf{CH_2}CH_2CH_2$); 1.56 (m, 12H, 6 $CH_3CH_2\mathbf{CH_2}CH_2$). ^{119}Sn NMR ($CDCl_3/Me_4Sn_{ext}$, 200 MHz): δ = 82.69.

Preparation of Diphenacyl Sulfide; Typical Procedure. A solution of α-bromoacetophenone (1.00 g., 5.02 mmol) and bis(tributyltin) sulfide (1; 1.85 g.,3.02 mmol) in DMF/EtOAc (5:1 v/v, 25 mL) is placed in a 50 mL flask. The mixture is kept under nitrogen and heated with an oil bath at 45°C while stirring vigorously. The reaction is monitored by TLC (silica gel, 5% acetone/95% hexane, UV visualization). After 6 h, the solvent is removed under high vacuum; purification is carried out on silica gel using hexane as first eluent (to remove non-polar organotin) followed by gradually increase the EtOAc content to 30% of the solvent mixture. The eluate is evaporated and the residue is recrystallized from hexane to give diphenacyl sulfide as a colorless solid; yield: 0.637 g. (94%); mp 75°C (sharp) (lit.[15] 67-68°C); ^1H NMR: δ= 3.98 (s, 4H); 7.22-7.62 (M, 6H); 7.86-8.05 (m, 4H); MS: M^+ (270); 77; 105.

For non-moisture sensitive products, EtOAc is added and a solution of $Zn(OAc)_2$ in H_2O can be employed to destroy any excess tin sulfide[16]. A solution of KF in H_2O with a catalytic amount of tetrabutylammonium fluoride trihydrate suffices to remove most organotin by-products[17]. Filtration of the whole mixture followed by a second filtration on silica gel for the organic phase only affords a pure product. For volatile sulfides, a Kugelrohr distillation is carried out.

Acknowledgements

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2.1 CYANO AND FLUORODESTANNYLATION: A NEW METHODOLOGY USING SOME POWERFUL SULFUR TRANSFER REAGENTS, THE ORGANOTIN SULFIDES[1]

Abstract: *Fluoride and cyanide ions destannylate bis(aralkyl)tin sulfides [R_3Sn-S-SnR_3] and trialkyltin sulfides [R_3Sn-S-R' (R = alkyl)] giving, in the presence of a variety of alkyl and activated halides, the corresponding thioether derivatives in excellent yield. The conditions are mild, neutral and anhydrous; a strong solvent effect is noted. Special comments are made concerning work-up procedures.*

Fluorodesilylation techniques have been recognized to be very important as applied to the cleavage of silyl ethers[2], in aldol condensations[3] as well as a variety of elimination reactions.[4] We felt that a parallel procedure could be developed using fluoride or cyanide ions to destannylate various tin-protected functionalities such as alcohols, amines and thiols.

Fluoride ion and many tin compounds are found to associate strongly to form "polymers".[5a] Indeed, while carrying out this work, the first examples of fluorodestannylation (elimination, alkylation) were published.[6]

We wish to report that sulfur transfer reagent bis(tributyltin) sulfide **1**[1,7] combines with a "naked" fluoride ion to release a powerful sulfur nucleophile; the counterion is a quaternary ammonium, or a cesium complexed with a crown-ether. In the presence of alkyl halides, sulfides are formed in excellent yield.[8] Cyanide ion was also successful as a destannylating agent although it is less reactive than fluoride, it represents the first example of this type of reaction.

R_3Sn-S-SnR_3

1

The process was found to be general (Eq. 1, Table 1) with a variety of organotin sulfides (readily available).[9]

$$2\,R\text{-}X + R'_3Sn\text{-}S\text{-}SnR'_3 + 2\,Z^- \text{-----> } R\text{-}S\text{-}R + 2\,R'_3Sn\text{-}Z + 2\,X^- \quad \text{(Eq. 1)}$$

R = alkyl; R' = Me, Ph, Bu, or $[Bu_2Sn\text{-}S]_3$; X = Cl, Br, I; Z = CN-, F-

Also, unsymmetrical sulfides have been prepared starting from trialkyltin mercaptides (R''_3SnSR') and an organic halide. The yields are good and the conditions anhydrous, mild and neutral (Eq. 2, Table 2).

$$R\text{-}X + R''_3Sn\text{-}SR' + Z^- \text{------> } R\text{-}S\text{-}R' + R''_3Sn\text{-}Z + X^- \quad \text{(Eq. 2)}$$

R = alkyl; R' = R" = alkyl; X = Cl, Br, I; Z = CN-, F-

Several common sources of fluoride ion (usually commercially available) were evaluated including tetrabutylammonium fluoride trihydrate ($TBAF.3H_2O$), the "anhydrous" version[10], cesium fluoride (complexed with 18-crown-6 or not)[11] and potassium fluoride (complexed with 18-crown-6 or not).[12] Only reactions with TBAF and cesium fluoride were effective.

Fluoride ion was employed in a catalytic amount as with some desilylations for highly reactive halides.[4] The choice of fluoride source varies with the organic halide used. For activated halides or where a 6-membered ring is formed (entries 9-19) either $TBAF.3H_2O$ or CsF can be used. Where the reactions are slow (as with 1-bromohexane) the use of $TBAF.3H_2O$ produces significant amounts of thiol. For these as well as the other substrates CsF with 18-crown-6 would appear to be the reagents of choice.

The effect of the tin substituent was found to be negligible compared to that of the source of the fluoride ion. Thus, various organotin sulfides, easily made or commercially available, were used in this study with little difference except for the toxicity[13] and purification.[14,15]

The following is a typical procedure for the preparation of thioethers such as di-*n*-hexyl sulfide In a 50 ml flask 1-bromohexane (409 mg; 2.48 mmol) bis(trimethyltin)sulfide (445 mg; 1.24 mmol) and a catalytic amount of 18-crown-6 (132 mg; 0.50 mmol). Ten mL of acetonitrile (dried over CaH_2 and P_2O_5) is added. Cesium fluoride (800 mg; 5.27 mmol, dried at 110°C for 2 days at 5mm Hg) is added in one portion. The mixture is stirred vigorously under nitrogen and heated at 75°C for 75 min. After cooling, the solvent is

Table 1 : Formation of Symmetrical Sulfides Using Organotin Sulfides and Alkyl Halides

Entry	Halide	Organotin	Solvent[i]	T°C	Time(hr)	F⁻ or CN⁻(mol)	Sulfide	Yield[a,c]
1	CH_3COCH_2Cl	$(Bu_3Sn)_2S$[f]	A	20	0.8	TBAF.3H$_2$O(1.0)	$(CH_3COCH_2)_2S$	93[e]
2	$PhCOCH_2Br$	$(Bu_3Sn)_2S$[f]	B	20	1.0	CsF(xs)	$(PhCOCH_2)_2S$	98
3	$PhCOCH_2Br$	$(Bu_3Sn)_2S$[f]	B	20	0.3	TBAF.3H$_2$O(2.2)	$(PhCOCH_2)_2S$	99
4	$PhCH_2Br$	$(Bu_3Sn)_2S$[f]	B	20	0.8	TBAF.3H$_2$O(4.6)	$(PhCH_2)_2S$	95[e]
5	$PhCH_2Br$	$(Bu_3Sn)_2S$[g]	A	20	0.3	TBAF.3H$_2$O(4.0)	$(PhCH_2)_2S$	99[b]
6	$PhCH_2Br$	$(Bu_3Sn)_2S$[h]	A	20	1.0	TBAF.3H$_2$O(2.1)	$(PhCH_2)_2S$	86[e]
7	$CH_3COCH(CH_3)Br$	$(Bu_3Sn)_2S$[h]	B	20	24	TBAF.3H$_2$O(1.0)	$(CH_3COCH(CH_3))_2S$	75[e]
8	$CH_3COCH(CH_3)Br$	$(Bu_3Sn)_2S$[h]	B	20	7	TBAF.3H$_2$O(2.0)	$(CH_3COCH(CH_3))_2S$	84[e]
9	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[g]	A	20	0.5	TBAF.3H$_2$O(2.0)[j]	thiane	99[e]
10	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[g]	A	42	0.5	TBAF.3H$_2$O(2.0)	thiane	99[e]
11	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[g]	A	20	0.8	TBAF.3H$_2$O(2.0)	thiane	99[e]
12	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[g]	B	60	0.5	TBAF.3H$_2$O(2.0)	thiane	96[e]
13	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[g]	A	40	0.5	TBAF(anh.,2.0)	thiane	26[e]
14	$Br(CH_2)_5Br$	$(Me_3Sn)_2S$[g]	A	40	5	TBAF.3H$_2$O(2.0)	thiane	91[e]
15	$Br(CH_2)_5Br$	$(Me_3Sn)_2S$[g]	A	50	0.5	TBAF.3H$_2$O(2.4)	thiane	90[e]
16	$Br(CH_2)_5Br$	$(Bu_2SnS)_3$	A	50	0.8	TBAF.3H$_2$O(2.4)[j]	thiane	99[e]
17	$Br(CH_2)_5Br$	$(Ph_3Sn)_2S$[g]	B	60	2	TBAF.3H$_2$O(2.0)	thiane	99[e]
18	$Br(CH_2)_5Br$	$(Ph_3Sn)_2S$[g]	B	60	0.5	TBAF.3H$_2$O(2.0)	thiane	88[e]
19	$Br(CH_2)_5Br$	$(Ph_3Sn)_2S$[g]	B	60	1.0	TBAF.3H$_2$O(2.0)	thiane	91[e]
20	$EtCH(CH_3)CH_2Br$	$(Me_3Sn)_2S$[h]	A	80	2.5	CsF.18C6(xs)	$(EtCH(CH_3)CH_2)_2S$	63[e]
21	$CH_3(CH_2)_5Br$	$(Bu_3Sn)_2S$[h]	A	20	2.5	TBAF(anh.,3.0)	$(CH_3(CH_2)_5)_2S$	13
22	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[h]	A	75	1.0	CsF.18C6(xs)	$(CH_3(CH_2)_5)_2S$	99
23	$PhCH_2Br$	$(Bu_3Sn)_2S$[h]	A	20	1.1	TBAC.N(2.1)	$(PhCH_2)_2S$	81

a) isolated yields except if noted NMR or GC yield, identified by NMR, IR, MS and compared to authentic material b) ^{1}H NMR yield, c) GC yield without internal standard, d) cyclic trimer, e) not optimized, f) 1.1 mol, g) 2.0 mol, h) 1.05 mol, i) A = acetonitrile, B = DMF/EtOAc (5:1), j) 2.0 mol of tetrapropylammonium iodide added

Table 2 : Formation of Unsymmetrical Sulfides from Organotin Sulfides and Alkyl Halides

Entry	Halide	Organotin[e]	Solvent[d]	T°C	Time(hr)	F⁻ or CN⁻(mol)	Sulfide	Yield[a,d]
1	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	2	CsF.18C6(xs)	$PhCH_2S(CH_2)_5CH_3$	87[b]
2	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	2	CsF.18C6(xs)	$PhCH_2S(CH_2)_5CH_3$	[c]
3	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	12	CsF(xs)	$PhCH_2S(CH_2)_5CH_3$	[c]
4	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	20	2.3	TBAC.N(2.2)	$PhCH_2S(CH_2)_5CH_3$	80[e]

a) isolated yields except if noted as NMR or GC yield. Identified by NMR, IR, MS and compared to authentic material b) ^{1}HNMR yield. c) GC yield without internal standard. d) A = acetonitrile. e) 1.05 mol

removed and 50 ml of ethyl acetate is added. After stirring for 5 min, the mixture is filtered over celite and then silica gel using ethyl acetate as eluent. Ethyl acetate is the preferred solvent to use to insure maximum removal of "polymeric" fluoride[5] especially when using silica gel purification. Di-*n*-hexyl sulfide is obtained as a colorless liquid (250 mg, quant.; ^{1}H NMR ($CDCl_3$, TMS_{int}, 200 MHz): 2.50 (t,4H); 1.58 (m,4H); 1.30 (m,12H); 0.89 (t,6H); MS (EI): 202(M^+, 40), 117(100), 84(86), 69(45), 61(77), 56(63), 55(65), 43(72), 42(67), 41(69), 28(66).

A strong solvent effect suggests an ionic mechanism. Polar aprotic solvents such as acetonitrile (CH_3CN) or dimethylformamide (DMF) are the best to effect an efficient reaction, but acetonitrile is preferred in that purification is easier. In solvents like methylene chloride or chloroform, the reaction is very slow and mostly incomplete even using higher temperatures.

Volatile R'S units such as CH_3SH, can be handled easily if they are converted to the triorganotin mercaptide (R_3SnSR'; R' = R = alkyl); such tin derivatives have high boiling points[16], thus, the unpleasant odor of the thiol is greatly attenuated. Many synthetic pathways are available to make these tin mercaptides;[17] thus, using the fluorodestannylation reaction for sulfur-deprotection combined with an appropriate electrophile (halides used here or those reported elsewhere)[1] give access to symmetrical (Table 1) or unsymmetrical sulfides (Table 2). In sum, this method provides a new and simple procedure for cleaving the sulfur-tin bond and in this case a means of preparing sulfides in high yield under mild, neutral and anhydrous conditions.

Acknowledgements

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2.2 NEW ANHYDROUS FLUORINATING SYSTEMS: THE COMBINATION OF CROWN-ETHERS AND CESIUM FLUORIDE. A RELATIVE RATE STUDY.

Abstract: *New anhydrous fluorinating systems are presented. 18-Crown-6 or dibenzo-24-crown-8 act as solid-liquid phase transfer catalysts with cesium fluoride. A catalytic amount of these crown ethers with CsF increased the rate of fluorodestannylation of trialkyltin mercaptides (used as a good fluoride probe) by a factor of 5-7. In addition, alkyl bromides, such as benzyl bromide, reacted in a similar way. Kinetic evidence for "sandwich" or "edge" complexes with the cesium cation and 18-crown-6 is presented.*

Although numerous fluorinating agents have been developed since 1970[1], only a few of them are effective enough to be used in a totally anhydrous medium[2]. This lack of a simple, practical and anhydrous S_N2 type fluorinating agent appears to be mainly caused by strong hydrogen bonding of the fluoride ion with water.[3]

Recent work by Clark[4a] and Ichihara[4b] has focussed on calcium fluoride-supported alkali metal fluoride (including cesium fluoride) in order to enhance fluorinations. While developing our fluorodestannylation procedure[5] we have made a systematic study of several fluoride sources. We found that cesium fluoride is not very efficient as a destannylating agent. In a similar fashion, we found that addition of a catalytic amount of 18-crown-6 (0.20 eq.) or dibenzo-24-crown-8 (0.20 eq.) resulted in a significant increase in reaction rate at room temperature for the generation of sulfide from bis(tributyltin) sulfide (**1**). Although these are not well known reagents, we demonstrated in a previous publication that organotin sulfides (including **1**), act as excellent probes to assign the relative nucleophilicity of the fluorinating agent.[4] While the idea of using 18-crown-6 with metal fluorides (NaF, KF) is not new[6], this simple crown-ether with cesium fluoride[7] appears not to have been investigated.

Bu_3Sn-S-$SnBu_3$

1

Indeed, it is expected that the large diameter of cesium (3.34 Å, revised version[8]) makes it impossible to fit perfectly in the cavity of 18-crown-6 (2.6-3.2 Å, revised version[8]) to form a flat 1:1 complex as described by Pedersen in 1967[9]. Later, he found that some 2:1 or 3:2 complexes are possible with cesium[8]. Recently, Kellogg[7a] demonstrated by using ^{133}Cs NMR that some 1:1 and higher complexes with 18-crown-6 were indeed possible (although not shown with CsF). In our case, it is also possible that cesium fluoride and 18-crown-6 complex together to make a "sandwich" or a "club-sandwich" complex as proposed by Pedersen[8] or a 1:1 "edge" complex. Thus, this fluorodestannylation constitutes evidence of the existence of these sandwich or edge complexes[10].

In Figure 1, the rate of fluorodestannylation of benzyl(tributyltin) sulfide (**2**) with cesium fluoride with or without 18-crown-6 is displayed. Using the initial rate method[11], the reaction rate increased by a factor of five at room temperature when using 18-crown-6 (Eq. 1).

$$Bu_3Sn\text{-}S\text{-}CH_2Ph + CH_3(CH_2)_5Br \xrightarrow{CsF} PhCH_2\text{-}S(CH_2)_5CH_3 + Bu_3Sn\text{-}F \quad (1)$$

In addition, we investigated the same reaction with dibenzo-24-crown-8 as catalyst (0.20 eq.). We obtained a rate increase of seven, roughly equivalent as with 18-crown-6 (factor of 5). From this, we conclude that "sandwich " or "edge" complexes have a similar efficiency as with a "usual" and flat 1:1 guest/host ratio complex (Fig. 2). Furthermore, the low solubility of cesium fluoride in acetonitrile[12] suggests that 18-crown-6 and dibenzo-24-crown-8 act as solid-liquid phase transfer catalysts (PTC)[13]. An evaluation of the nucleophilicity of these fluorinating systems thus give this qualitative order: TBAF "anhydrous"[2] > CsF.24-crown-8 ~ CsF.$(18\text{-crown-6})_n$> KF.18-crown-6.

These fluorinating systems demonstrate a useful approach towards an anhydrous fluorinating source. Indeed, 18-crown-6 can be dried in acetonitrile according to Gokel and Cram[14] and dibenzo-24-crown-8 is much less hygroscopic than the former.[15] Also, it should be pointed out that these catalysts are used in catalytic amounts, hence the water associated with their presence should be negligible when dried. To confirm this, we never observed a significant amount of thiol in these fluorodestannylation reactions.[5]

As previously mentioned, the recent reports[4] on the fluorination of benzyl bromide and other organic substrates indicated a rate enhancement by the use of CsF or KF supported on CaF_2. We carried out experiments to see if fluorinations would be increased by the use of CsF with 18C6. The result is displayed in Figure 3. There is an approximate rate enhancement of a factor of five for the production of benzyl fluoride from benzyl bromide. Thus, this system of CsF with crown ethers has applicability for the destannylation/alkylation reaction as well as a classic fluorination procedure.

Finally, these kinetic enhancements with the complexation of CsF and crown-ethers could certainly modify to some extent, pioneering works with this reagent in macrocyclic lactone ring closure reactions[16] and macrocyclic sulfide formation (including cyclophanes and related compounds).[17]

Acknowledgements

We thank the National Science and Engineering Research Council of Canada and the Ministère de l'Education du Québec for financial support.

Figure 1: Rate Effect of Crown Ethers on Equation 1.
Formation of n-Hexyl Benzyl Sulfide Vs Time

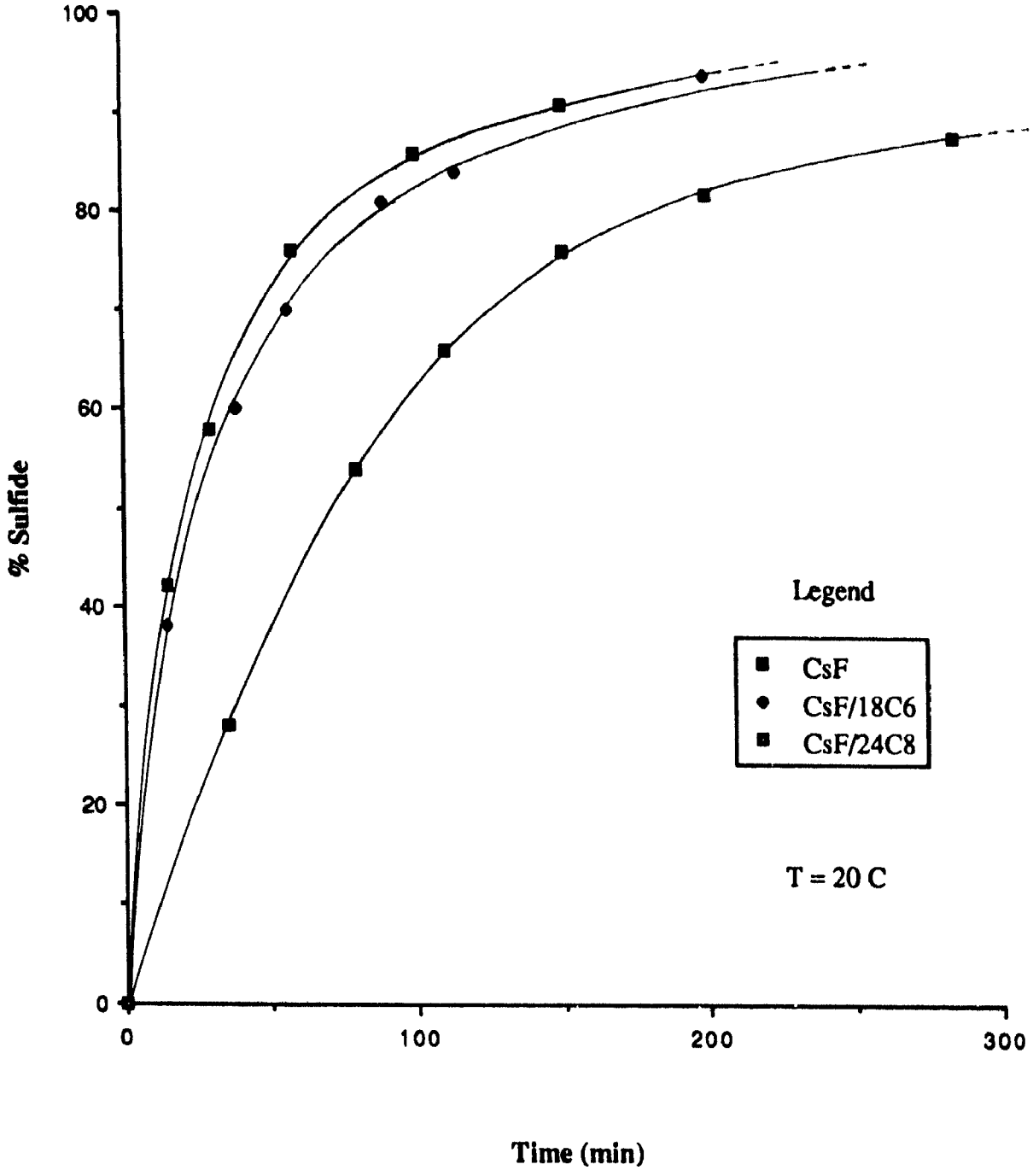
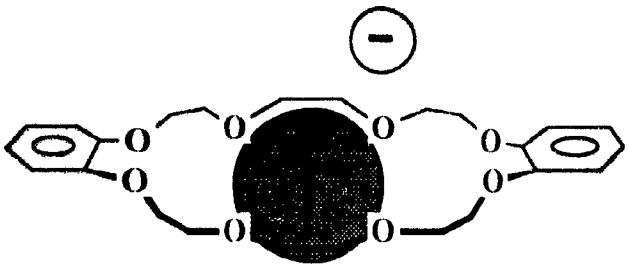
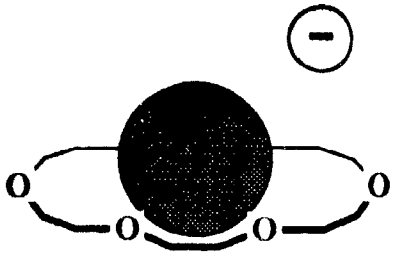


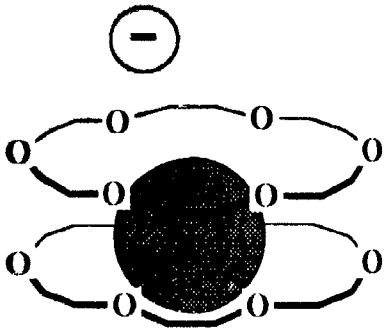
Figure 2



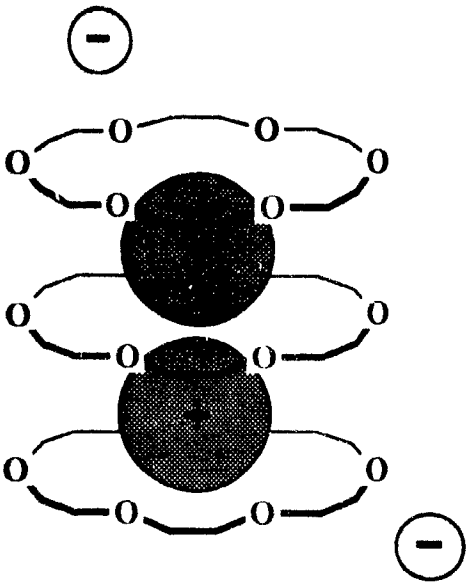
Classic 1:1 complex



Edge complex



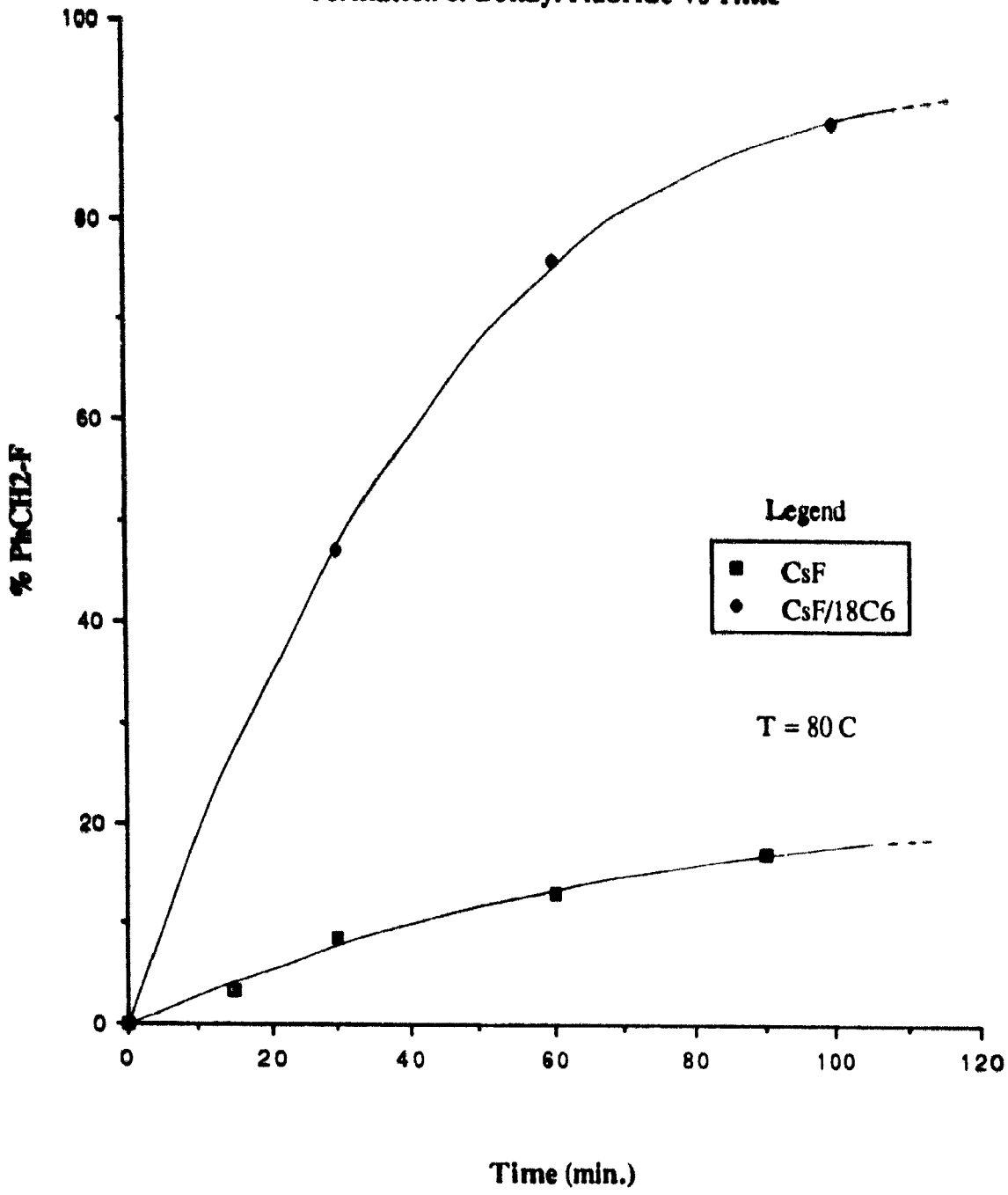
Sandwich complex



Club-sandwich complex

Figure 3

Formation of Benzyl Fluoride Vs Time



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CHAPTER 3

FLUORODESTANNYLATION

In chapter 2, the reader has been introduced to the first fluorodestannylation reactions. The fluorodestannylation methodology was successful when applied to organotin sulfides; new, practical and powerful sulfur transfer agents were generated and found to be useful for the synthesis of sulfides. The term fluorodestannylation was reported for the first time. Furthermore, I developed a new and effective fluorinating system of use in this methodology.

At this point, it was logical to extend the fluorodestannylation methodology and especially determine the scope and generality of this technique. In the following chapter, complete details about this new methodology will thus be reported where organotin oxides and organotin selenides act as new oxygen and selenium transfer agents. We will demonstrate that organotins can be seen as a general "group 16 transfer agent". The main features of this chapter are certainly the first presentations of practical "O^{2-}" and "Se^{2-}" transfer agents. Bis(tributyltin)oxide, a commercially available compound produced in bulk quantities, can thus be utilized as a synthetic equivalent of "O^{2-}" in the presence of fluoride ions. In a similar manner, bis(triphenyltin)selenide was found to be a very stable compound that should be considered as a practical synthetic equivalent of "Se^{2-}" in the presence of fluoride ions.

A new concept for generating naked anions will also be discussed. Synthetic equivalents of many unusual salts like cesium oxide (Cs_2O), cesium sulfide (Cs_2S) and cesium selenide (Cs_2Se) along with the corresponding tetraalkylammonium salts: $(Bu_4N)_2O$, $(Bu_4N)_2S$ and $(Bu_4N)_2Se$ will be demonstrated

Furthermore, discussions about the possible mechanisms are included with the help of ^{119}Sn NMR spectroscopy. It is the first time that possible mechanistic considerations are presented based on working hypothesis.

The analogies and differences with the fluorodesilylation methodology are encompassed in this chapter. From our experience thus far, it seems that fluorodestannylation complements well the fluorodesilylation techniques. On many

occasions, we demonstated the strong advantage of using tin instead of silicon due to low reactivity and/or instability of the silicon reagents.

Finally, we verified that Sn-C bond can be cleaved to release a carbanion-like species that could be trapped with carbonyl compounds, in a similar way as with silicon (see Chapter 1).

The next chapter was mainly taken from a published article (Harpp, D. N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, *110*, 7737). The writing of the original manuscript, the entire research work in the laboratory plus the literature search for references directly are solely my own contribution. Professor Harpp, as supervisor, assisted in the complete revision of this manuscript.

3.0 FLUORODESTANNYLATION. A POWERFUL TECHNIQUE TO LIBERATE ANIONS OF OXYGEN, SULFUR, SELENIUM AND CARBON.[1]

Abstract: *Fluoride ions smoothly destannylate organotin chalcogenides to liberate nucleophilic chalcogenide ions; hence the first nucleophilic oxide (O^{2-}) and selenide (Se^{2-}) transfer agents are reported where the tin atom serves as a "group 16(VIB) transfer agent". In the presence of crown ethers or ammonium salts, this process results in a new way to generate "naked" nucleophiles. Ethers, and selenides are formed in good-excellent yield In addition, a useful C-C bond forming reaction has been developed using alkyltins with aldehydes and acid chlorides in the presence of fluoride ion Aspects concerning reactivity and mechanism are presented. Finally, the generality of the fluorodestannylation procedure and the differences with parallel silicon chemistry are detailed.*

3.1 Introduction

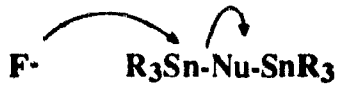
Considerable effort has been focused on desilylation reactions over the past decade[2]; far less attention has been accorded parallel work on organotin compounds. In 1985, Pearlman reported that fluoride ion could induce the formation of exocyclic double bonds from stannylated and hindered sec-alkyl sulfones[3]. The next year Danishefsky and Hungate published a fluorodestannylative procedure applied to a cyclic stannylene of use in an intramolecular O-alkylation[4]. Later in 1987, Ohno described selective O-monoalkylations of an O-stannylene acetal derived from a tartrate ester, using fluoride ion to promote the reaction[5]. None of the above procedures were extended beyond their specific synthetic context.

Our own work during this period involved the discovery of a fluorodestannylation reaction of organotin sulfides (**1**) permitting the preparation of a host of organosulfides in high yield under mild and neutral conditions[1] (Eq. 1). In addition, we found that cyanide ion performed comparably (cyanodestannylation).

$$\underset{\mathbf{1}}{R_3Sn\text{-}S\text{-}SnR_3} + 2\,R'\text{-}Br \xrightarrow[(or\ CN^-)]{F^-} R'\text{-}S\text{-}R' + 2\,R_3Sn\text{-}F \qquad \text{(Eq.1)}$$

We wish to report that fluoride ion combines with organotin oxides, -sulfides, -selenides and organotins in general to liberate the corresponding anion (Scheme 1, Table 1). In the presence of appropriate electrophiles, ethers, thioethers, organic selenides and carbon-carbon bonds are produced. Most of these reactions take place in neutral media in contrast with many known procedures using strong bases[6]. The generality of these fluoride and cyanide effects demonstrates a significant new dimension in organotin chemistry.

SCHEME 1



Nu = O, S, Se

Nu = OR, SR, SeR, C nucleophiles

Tin is a larger atom than silicon and while being considered hard, should be softer than silicon[7]. Hence, like silicon, it has a tendency to associate with the hardest atom, namely fluoride. While the analogy with fluorodesilylation is very close, experimentally, different results and reactivities from organotin to silicon analogs encouraged us to develop this general concept. For example, we found that hexamethyldisilthiane (**2**) when treated with fluoride ion in the presence of 1-bromohexane formed a 2.3:1 mixture of monosulfide *and* disulfide (Eq. 2), whereas the tin analog gave a near-quantitative yield of pure monosulfide (Eq 3).

Table 1. Tin Substrates Under Investigation.

Oxides	Sulfides	Selenides	Organostannanes
$R_3Sn\text{-}O\text{-}SnR_3$	$R_3Sn\text{-}S\text{-}SnR_3$	$R_3Sn\text{-}Se\text{-}SnR_3$	R''_4Sn
$R_3Sn\text{-}OR'$	$R_3Sn\text{-}SR'$	$R_3Sn\text{-}SeR'$	$Bu_3Sn\text{-}R''$
	R_2SnS		$Bu_3Sn\text{-}C{\equiv}CH$
R = aryl, alkyl; R' = alkyl; R" = allyl			

$$2\ CH_3(CH_2)_5Br + Me_3Si\text{-}S\text{-}SiMe_3 \xrightarrow{F^-} \underset{2}{\text{-S-}} + \underset{(2.3:1)}{\text{-S-S-}} \qquad \text{(Eq. 2)}$$

$$2\ CH_3(CH_2)_5Br + Me_3Sn\text{-}S\text{-}SnMe_3 \xrightarrow{F^-} \underset{1\quad (99\%)}{\text{-S-}} \qquad \text{(Eq. 3)}$$

In addition, hexamethyldisiloxane (3) does not generate a significant amount of ether in the presence of fluoride ion and simple organic halides, whereas the tin analog does (Eq. 4,5).

$$2\ CH_3(CH_2)_5I + Me_3Si\text{-}O\text{-}SiMe_3 \xrightarrow{F^-} \underset{3\quad (trace)}{\text{-O-}} \qquad \text{(Eq. 4)}$$

$$2\ CH_3(CH_2)_5I + Bu_3Sn\text{-}O\text{-}SnBu_3 \xrightarrow{F^-} \underset{4\quad (54\%)}{\text{-O-}} \qquad \text{(Eq. 5)}$$

We will present a new, general concept for generating *in situ* synthetic equivalents of cesium and quaternary ammonium salts containing oxygen, sulfur and selenium ions as "naked" nucleophiles; their effective nucleophilicities will be discussed. Finally, a possible mechanism for the fluorodestannylation reaction will be proposed as a working hypothesis.

3.2 Results and Discussion

3.2.1 Comparison of Fluorodestannylation with Fluorodesilylation

As indicated above, fluorodestannylation can be applied to a host of organotin derivatives (Table 1). Thus, tin can carry chalcogens as the synthetic equivalent of O^{2-}, S^{2-}, Se^{2-}, RO^-, RS^- and RSe^-. These organotins act as general "Group 16 (VIB) transfer agents" when combined with fluoride ion. The physical properties of most of these chalcogen-containing organotins are suitable for the synthetic chemist; they are usually high-boiling liquids, or solids with definite melting points . Their stability permits them to be manipulated without special precaution (e.g bis(triphenyltin)selenide (**5**) is stable to the ambient atmosphere for several days without turning red)[8]. Their solubility in many organic solvents makes them excellent substitutes for their chalcogens salt analogs (e.g. Na_2S, Na_2Se, etc.).

The general reactivity of organotins differs significantly from that of organosilicons due to the different bond energies of tin and the various chalcogens compared with silicon. Although the Sn-F bond energy is not known for triaralkyltin fluorides, a comparison can be made between some values obtained for the tin tetrahalide series (including SnF_4)[9,10]. The poor overlap of orbitals between large chalcogens like selenium and sulfur with silicon makes these compounds extremely unstable; tin however, accommodates these chalcogens much better. Also, oxygen strongly prefers to be bound with silicon rather than tin (although the latter type of compound is sufficiently stable). A qualitative explanation is provided by application of the concept of HSAB theory[7a] or the recent density functional theory[7b].

Several exchange reactions with a variety of silicon, germanium and tin derivatives lead to the qualitative evaluation of their bond energies and affinities toward some ligands containing oxygen and sulfur moieties[11]. These reactions help to rationalize the relative stability of Sn-O, Sn-S, Sn-Se bonds as compared to the Si-O, Si-S and Si-Se bonds. From these results, it has been demonstrated that tin is softer than silicon in trialkyltin mercaptides

or oxides even though the tin compounds used here should still be considered as hard Lewis acids.

3.2.1.1 Sulfur

We have already demonstrated the efficacy of the fluoro and cyanodestannylation procedure as applied to organotin sulfides **11**. At moderate temperatures (20-80°C) under essentially neutral solvent conditions, using combinations of CsF, CsF with 18-crown-6 (18C6) and tetrabutylammonium fluoride (TBAF) and cyanide (TBACN) with **1**, a variety of aliphatic halides can be converted in excellent overall yields (averaging over 90%) to the corresponding acyclic and cyclic sulfides. In sharp contrast, the silicon analog hexamethyldisilthiane (**2**) gives *di*sulfide as a significant product, showing the higher lability of the silicon-sulfur bond[12].

3.2.1.2 Oxygen

Although the methodology is still evolving, our results indicate that bis(tributyltin)oxide (**4**) combined with fluoride ion can deliver[13] the equivalent of O^{2-},thus providing a useful alternative to the well-known Williamson ether synthesis.[14] In addition, using this fluorodestannylation procedure, we are able to generate *in situ* a synthetic equivalent of cesium oxide (Cs_2O) complexed with a crown-ether. With hexamethyldisiloxane (**3**), the reaction failed; presumably the energy of silicon-oxygen bond is too strong to displace the oxide ion. To our knowledge, only trimethylsilanolate salts of lithium, sodium and potassium (see compound **13**) have been described as being synthetic equivalents of "O^{2-}" in the literature. This was however in a different context involving the conversion of carboxylic acid derivatives into their corresponding anhydrous acid salts[15]

Thus, we present the first "O^{2-} transfer agent" (**4**) involved in substitution reactions. This commercial reagent possesses significant nucleophilicity to counter-balance many elimination processes usually observed in the Williamson reaction. To test the basicity of the medium, we employed several iodo-compounds (well-known for giving a high degree of elimination under basic conditions[14c]) as shown in Tables 2 and 3. In contrast to the report of Danishefsky and Hungate[3] showing the neutrality of the process in an intramolecular O-alkylation using an organostannylene, we found that tributylstannyl oxide provoked some elimination as indicated by the alcoholic and alkene side products isolated or observed by gas chromatography. This basicity increases when the solvent was changed to DMSO or CH_3CN. A slow addition of the organotin oxide or variation in the number of equivalents of

Table 2. Formation of Symmetrical Ethers.

Entry	Substrate[a]	Organotin	Solvent[b]	T°C	Time(Hr)	Fluoride[c]/CN⁻	Product	Yield(%)
1	$PhCH_2Br$	$(Bu_3Sn)_2O$	A	70	6	TBAF $3H_2O$	$(PhCH_2)_2O$	41[g]
2	$PhCH_2Br$	$(Bu_3Sn)_2O$	A	50	2	TBAF $3H_2O$	$(PhCH_2)_2O$	50[g]
3	$PhCH_2Br$	$(Bu_3Sn)_2O$	A	55	7	CsF 18C6	$(PhCH_2)_2O$	71
4	n Hex I	$(Bu_3Sn)_2O$	A	90	36	CsF.18C6	$(n\text{-}Hex)_2O$	25[g]
5	n Hex I	$(Bu_3Sn)_2O$	B	52	5	CsF 18C6	$(n\text{-}Hex)_2O$	50[e]
6	n Hex-I	$(Bu_3Sn)_2O$	B	20	96	CsF	$(n\text{-}Hex)_2O$	53[g]
7	n-Hex I	$(Bu_3Sn)_2O$	C	52	5	CsF 18C6	$(n\text{-}Hex)_2O$	54[g]
8	n Hex-I	$(Bu_3Sn)_2O$	C	20	16	CsF 18C6	$(n\text{-}Hex)_2O$	50[g]
9	n Hex I	$(Bu_3Sn)_2O$	E	20	9	CsF 18C6	$(n\text{-}Hex)_2O$	5[e]
10	n Hex-I	$(Bu_3Sn)_2O$	C	20	144	TBACN[f]	$(n\text{-}Hex)_2O$	nil
11	n Hex I	$(Me_3Si)_2O$	B	50	28	CsF.18C6	$(n\text{-}Hex)_2O$	nil
12	n Decyl I	$(Bu_3Sn)_2O$	A	80	24	CsF 18C6	$CH_3(CH_2)_7CH=CH_2$	90

a) The molar ratio of substrate to organotin is 2.00 1.05, b) A = acetonitrile, B = DMF, C = 1-N-methyl-2 pyrrolidinone, D = DMSO, E = DMF/TMEDA, cesium fluoride was used in 1.3-1.5 fold excess unless otherwise noted, TEAF = tetraethylammonium fluoride, d) Isolated yields unless otherwise noted, e) G.C. yield, f) tetrabutylammonium cyanide g) benzyl alcohol or 1 hexanol as side product was observed by NMR and GC

Table 3. Formation of Unsymmetrical Ethers.

Entry	Substrate[a]	Organotin	Solvent[b]	T°C	Time(Hr)	Fluoride	Product	Yield[c](%)
1	Allyl-Br	$PhCH_2OSnBu_3$	A	100	2	CsF 18C6	$PhCH_2O$-Allyl	90
2	*n* Hex-I	$PhCH_2OSnBu_3$	A	75	2	AgF 24C8[d]	$PhCH_2O$-*n*-Hex	17
3	*n* Bu I	$PhCH_2OSnBu_3$	A	80	24	CsF 18C6	$PhCH_2O$-*n*-Bu	20
4	*n* Hex-I	$PhCH_2OSnBu_3$	NMP	20	24	CsF 24C8	$PhCH_2O$ *n*-Hex	69

a) The molar ratio of substrate to organotin is 1.00 1.05, b) A = acetonitrile, NMP = N methyl-2-pyrrolidinone c) isolated yields, not optimized, d) 24C8 = dibenzo-24-crown-8

cesium fluoride did not change the results; in the same way, the addition of crown-ethers increased the rate of the reaction but gave the same yield of ether.

Synthetic Equivalent of " O^{2-} "

$$2\ PhCH_2Br + Bu_3Sn\text{-}O\text{-}SnBu_3 \xrightarrow{F^-} PhCH_2\text{-}O\text{-}CH_2Ph + 2\ Bu_3Sn\text{-}F \quad \text{(Eq. 7)}$$

4 — 71%

$$2\ n\text{-}Hex\text{-}I + Bu_3Sn\text{-}O\text{-}SnBu_3 \xrightarrow{F^-} [n\text{-}hex]_2O + 2\ Bu_3Sn\text{-}F \quad \text{(Eq. 8)}$$

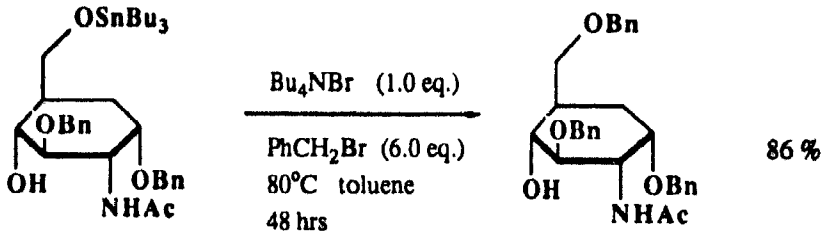
4 — 54%

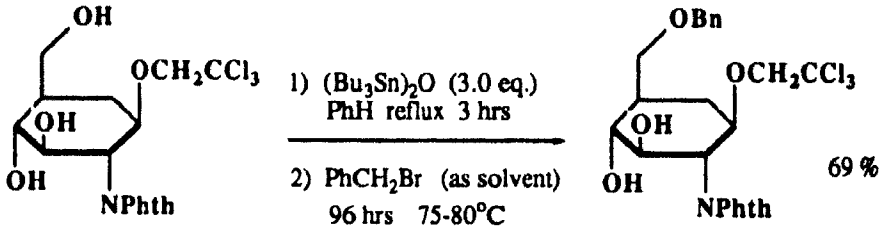
In addition to symmetrical aliphatic ethers which were formed in modest yield (*ca.* 50%, Table 2), unsymmetrical ethers have been prepared in better yield using this method (Table 3). In general, ethers can be prepared under mild conditions at room temperature. Furthermore, we have demonstrated a new strategy for directly introducing a benzyl ether group starting from an organic halide. In conclusion, the fluorodestannylation-alkylation procedure makes it possible to employ substrates having ß-hydrogens without causing too much elimination; in contrast, the Williamson conditions are usually reserved for phenols or compounds having no ß-hydrogens[14c] due to the strong basicity of the medium.

Considering the pioneering work of Ogawa and Veyrieres[16] in their regioselective stannylation-alkylation process on carbohydrate substrates, we thought it appropriate to give a clear representation of the reaction conditions found here compared to the usual or classical procedures[16]. As shown in Scheme 2, the reaction time is diminished to 2-3 hours when an organotin oxide is treated with fluoride ion in DMF or NMP (N-methyl-2-pyrrolidinone) in the presence of benzyl bromide. This is in sharp contrast to the few examples of parallel alkylations on simple monosaccharides[16]. These conditions require heating (80°C) for 2-3 days with reactive halides such as benzyl bromide. This suggests that our conditions can successfully be applied with monosaccharides; we are presently investigating this aspect in our laboratories.[17]

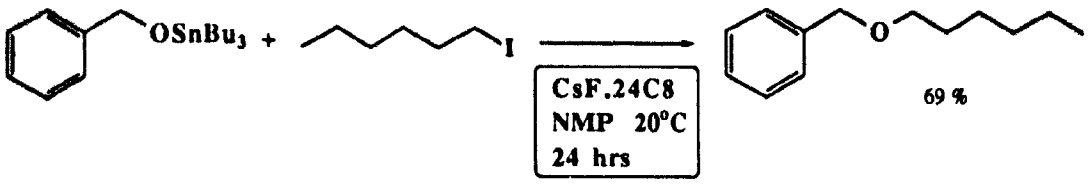
SCHEME 2

Classical Conditions for Alkylation





Conditions for Fluorodestannylation-Alkylation



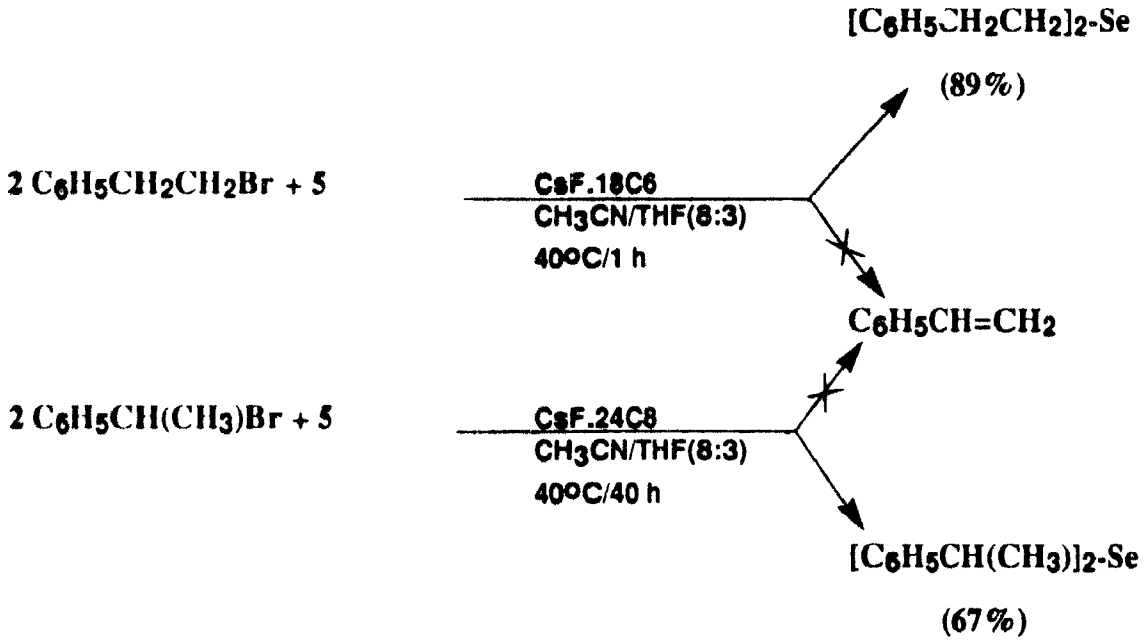
3.2.1.3 Selenium

For the preparation of organoselenides, up to now, the most prominent methods in the literature are certainly those developed by Gladysz[18] using lithium triethylborohydride with metallic selenium or the procedure of Klayman[19] using sodium borohydride with selenium pellets. However, in both cases the supersaturated selenide salt formed must be used immediately, as it tends to precipitate in time, losing its reactivity. Yields of organoselenides are *ca.* 50-60% using non-activated halides such as 1-bromohexane[18,19]. The silicon carrier of Se^{2-}, hexamethyldisilselenane[20] (**8**), is a highly reactive and difficult substance to work with; H_2Se is immediately liberated upon contact in air.

In contrast, organotin selenides are relatively stable; bis(triphenyltin)selenide (**5**) is not significantly odorous, can easily be prepared in substantial quantities (40g, 83% yield) and stored in a refrigerator for up to 1 year without any appreciable decomposition (verified by ^{119}Sn NMR). In the presence of alkyl halides this material is smoothly destannylated under neutral solvent conditions and mild reaction temperatures (*ca.* 40°C) (Table 4) to deliver organoselenides in excellent isolated yield.

Our method takes place in totally neutral, anhydrous conditions, whereas the two cited procedures have tendency to be basic by the slight excess of hydride reagent used or the difficulty associated with the titration or the weighing of such hydrides. This latter problem of standardization of hydride can also give rise to some undesired organic diselenides as by-products. As shown in Scheme 3, the neutrality of the medium appears responsible for the high yield preparation of di-1 and 2-phenethyl selenide (entries 1,2 in Table 4) without the formation of styrene. In the case 1-phenethyl bromide, it is a clear demonstration that hindered secondary organic selenides are readily obtainable (in this case as a dl/meso mixture).

Scheme 3. Demonstration of Reaction Neutrality for the Preparation of Bis 1- and 2- Phenethyl Selenides



3.2.1.4 Carbon

Our preliminary results indicate that the reactivity of organotins in the presence of fluoride ion is slightly less than with the corresponding silicon analogs with aldehydes[21]. Since the strength of the Sn-F bond is unclear in the literature (*ca.* 99 kcal/mol)[10] it is presently difficult to quantify and to compare accurately the thermodynamic effects in these systems.[22] However, the importance of carbon-carbon bond formation in organic synthesis led us to explore the use of fluorodestannylation in this field. Tetraallyltin, without fluoride assistance, has been a successful reagent for that purpose as demonstrated in 1980 by Daude and Pereyre[23]. However, long reaction times were required and only poor to good yields were obtained with ketones and some aldehydes (often less than 60% yield). Using allyl tributyltin, poor yields and strong heating were required to react with aldehydes.

As shown in Table 5, we are able to transfer allylic groups to aldehydes and an acid chloride using fluoride ion to promote coupling (entries 1,4). For example, using tetraallyltin (9) with fluoride ion, the reaction time decreased to 3 h at RT (85% yield) compared to 18 h at RT (82% yield) using the method of Daude and Pereyre[23]. In the

Table 4. Formation of Organic Selenides.

Entry	Substrate[a]	Organotin	Solvent[b]	T°C	Time(Hr)	Fluoride[c]	Product	Yield[d](%)
1	$PhCH_2CH_2Br$	$(Ph_3Sn)_2Se$	A	40	1 0	CsF 18C6	$(PhCH_2CH_2)_2Se$	89
2	$PhCH(CH_3)Br$	$(Ph_3Sn)_2Se$	A	40	40	CsF 24C8	$((PhCH(CH_3))_2Se$	67
3	$CH_3COO(CH_2)_3Br$	$(Ph_3Sn)_2Se$	A	36	2.0	CsF 24C8	$(CH_3COO(CH_2)_3)_2Se$	97
4	$CH_3(CH_2)_5Br$	$(Ph_3Sn)_2Se$	A	48	1 5	CsF 18C6	$(CH_3(CH_2)_5)_2Se$	96
5	$CH_3(CH_2)_5OTs$	$(Ph_3Sn)_2Se$	A	20	3 0	CsF 18C6	$(CH_3(CH_2)_5)_2Se$	70[e]
6	$CH_3(CH_2)_5Br$	$(Ph_3Sn)_2Se$	A	55	48	TBACN[f]	$(CH_3(CH_2)_5)_2Se$	nil

a) The molar ratio of substrate to organotin is 2 00 1 05, b) A = acetonitrile THF (8 3), c) a 5 fold excess was used, d) isolated yields, not optimized, e) 30% of diselenide was formed. f) tetrabutylammonium cyanide

Table 5. C-C Bond Formation.

Entry	Substrate[a]	Organotin	Solvent[b]	T°C	Time(Hr)	Fluoride	Product	Yield[c](%)
1	PhCH(Me)CHO	$(Allyl)_4Sn$	DMF	20	3	CsF(5 1)	PhCH(OH) Allyl	85
2	PhCH(Me)CHO	Bu_3Sn-Allyl	DMF	85	72	CsF(4 6)	PhCH(OH)-Allyl	7
3	PhCH(Me)CHO	$Bu_3SnC\equiv CH$	NMP	44	90	CsF(3 7)	$PhCH(OH)C\equiv CH$	nil
4	$PhCH_2COCl$	$(Allyl)_4Sn$	NMP	20	20	CsF(2 3)	$PhCH\overset{O}{\overset{\|}{C}}CH_2CH=CH_2$	76
5	$PhCH_2COCH_3$	$(Allyl)_4Sn$	A	55	200	CsF(4 5)	$PhCH_2C(CH_3)OH$-Allyl	16
6	Cyclo-$(CH_2)_{12}CO$	$(Allyl)_4Sn$	DMF	55	24	CsF(4 9)	$cyclo(CH_2)_{12}C(OH)(Allyl)$	2

a) The molar ratio of organotin to carbonyl compounds is 1 05 1 00, b) A = acetonitrile DMF (5 1) NMP = N-methyl-2-pyrrolidinone c) isolated yields not optimized

Table 6. List of Synthetic Equivalents of Various Salts of Cesium and Quaternary Ammonium Ions[a].

Cesium		Quaternary Ammonium			
Cs_2O	CsOR	TBA_2O	TBAOR	TEA_2O	TEAOR
Cs_2S	CsSR	TBA_2S	TBASR	TEA_2S	TEASR
Cs_2Se		TBA_2Se			

a) TBA = tetrabutyl ammonium; TEA = tetraethyl ammonium

This constitutes a real improvement over the usual salts of sodium or potassium complexed with crown-ethers. It should be noted that cesium salts like Cs_2S and Cs_2Se are found in the literature however with no clear application to organic synthesis[28]. Cs_2O has been used extensively in ceramics, glass additives, conductivity materials and as a co-catalyst in aromatization[29]. We present the first real application of it as a reagent in organic synthesis as well as for Cs_2Se and Cs_2S.

Although the magnitude of the nucleophilicity of several anions is enhanced, it is possible that these anions coordinate somewhat with the organotin fluoride formed in the medium (organotin halides usually tend to increase their coordination sphere to 5 ligands[30]). For this reason, we feel that comparison of the expected nucleophilicity for a pure "naked" anion to the experimental one obtained differs somewhat. Fortunately, to alleviate this negative effect, an excess of fluoride ions compete with the anion formed for the fifth coordination site on tin. Knowing that organotin fluoride prefers to form "polymers" with pentacoordinated tin[31], it supports that this competition for the fifth ligand favors fluoride ion rather than the "naked" anion.

Another important factor to consider here should be the "alpha effect" of the tin. For instance, if we assume that the reaction pathway proceeds with intermediates as shown below (**10**, **11**, **12**); the metal effect on the displacement reaction is not entirely clear. A silicon analog **13** of the tin oxide has been used recently as a synthetic equivalent of hydroxide or "O^{2-}"[15]. This salt demonstrated good solubility in organic solvents. It seems that trimethylsilanolates prefer to attack directly a carbomethoxy or an acyl chloride rather than abstracting α-protons. This supports the idea that the "alpha effect" on tin should enhance the nucleophilicity of the charged oxygen atom thus favoring S_N2 reaction.

R_3Sn-O-	R_3Sn-S-	R_3Sn-Se-	Me_3Si-O-
10	**11**	**12**	**13**

3.2.3 Fluoride Ion Study

As a general rule with transfer reagents **1** (R = Bu, phenyl), **4** and **5**, we found that tetrabutylammonium fluoride trihydrate (TBAF.$3H_2O$) is the most reactive source of fluoride ion but its water content limits its use only with activated electrophiles such as α-bromoketones. Benzyl bromide appears to be the limiting case where the TBAF.$3H_2O$ fluoride source can be used without too much formation of thiol[32] with reagent **1** (or alcohol with **4**); as side products. With non-activated alkyl halides such as 1 bromohexane, the preferred method for S^{2-} transfer employs our anhydrous fluorinating system: cesium fluoride complexed with a catalytic amount of 18-crown-6.[1]

This overall system appears to be general and very effective with activated alkyl halides. A qualitative scheme of reactivities associated with fluoride can be summarized as TBAF.$3H_2O$ > CsF.18C6 > CsF. This trend was determined with organotin oxides, organotin sulfides and organotin selenides; we are studying this effect with organostannanes containing labile C-Sn bonds.

3.2.4 Cyanide Study

Tetrabutylammonium cyanide (TBACN) was investigated mostly with activated organic halides such as benzyl bromide; we found that its reactivity did not permit us to use it with non-activated electrophiles without involving some forcing conditions as compared to the fluoride case. For example, treatment of benzyl bromide and bis(tributyltin)sulfide (**14**) in the presence of TBACN gives only a 42% yield of dibenzyl sulfide. The same reaction with TBAF.$3H_2O$ gave sulfide in 85% yield[1]. Finally, TBACN did not initiate alkylation in

either the reaction of bis(tributyltin)oxide (**4**) with 1-iodohexane or in the reaction of bis(triphenyltin)selenide (**5**) with 1-bromohexane.

3.2.5 Solvent Effects and Complexation on Tin

While studying the organotin sulfides[1], we observed that these kinds of reactions were highly sensitive to the solvent used. We established an order of reactivity associated with the choice of the solvents involved[33]. From this study, we found that non-polar and non-complexing solvents work poorly, whereas those having high dielectric constants (associated with a high level of complexing ability on tin) were the best to use[1]. These findings parallel our work with the organotin oxides and selenides; however, organotin oxides are more sensitive to the solvent used than the other systems studied. For example, both acetonitrile and DMF work very well with organotin sulfides (**1**) but the yield is halved (using more forcing conditions) in alkylating with organotin oxide (**4**) when DMF (E^o = 38.8)[34] was replaced by acetonitrile (E^o = 36.7)[34] (compare entries 4 and 5 in Table 2).

Even if both solvents have about the same dielectric constant, it seems that the complexation of DMF on organotin oxides is strongly required. It has been reported that this system is sensitive to the solvent used and DMF was found in many instances as the best solvent with organotin oxides[35] (especially in alkylations). In general, we found that the efficiency of the solvents in these systems (organotin oxides, sulfides and selenides as well as organostannanes) follows roughly the following trend: NMP > DMF >> CH_3CN >> EtOAc ~ CH_2Cl_2

We have shown by a ^{119}Sn NMR study[36] with organotin sulfides that fluoride ion complexed to a modest degree on tin at room temperature. However, at lower temperatures (-50 to -60°C), we were able to detect several new ^{119}Sn signals from TBAF and bis(tributyltin) sulfide (**14**) and can conclude that a complexation on tin had taken place. A labile complex is proposed at room temperature based on the broad signal observed[35].

3.2.6 Effect of Substituents on Tin

In general, triorganotins containing group 16 as a ligand do not show a significant variation in reaction rates with different substituents on tin. We already demonstrated this feature in a previous article on organotin sulfides **1**[1]. However, it appears that organotin oxides are more sensitive to the substituents. Qualitatively, we found significant differences in reactivity from phenyl to butyl groups on tin; the butyl group being more reactive.

Selenides should follow the same tendency as sulfides. Generally, for common alkyl halides involved in a S_N2 reaction, the substituent effects on tin are negligible compared to the fluoride and cyanide effects. Finally, the solvent effect usually takes priority over the substituent effects.

Substituent effects can be important where solubility problems slow the reaction rate; e.g. using bis(triphenyltin)selenide **5** in acetonitrile as solvent[37]. Steric hindrance combined with electronic effects can be an important consideration as demonstrated in the case of tetraallyltin (**9**) This is an unstable molecule and decomposes to a white solid at ambient atmosphere, whereas allyltributyltin is sufficiently stable to be manipulated without special precautions. As mentioned earlier, bis(triphenyltin)selenide (**5**) does not decompose easily to elemental selenium when exposed to the atmosphere for several hours or days but when the substituents offer less steric bulk, selenium formation is more rapid. Finally, the general mechanism of these reactions does not seem to be influenced by the substituents on tin.

3.2.7 Mechanistic Considerations

It is clear that fluorodestannylation is different from fluorodesilylation and we are investigating the characteristics of the former and trying to understand the general mechanism. From our results on sulfide formation[1] we proposed that the organotin sulfide is ionized to some extent prior to attack by fluoride and that this ionization facilitates the rate and extent of reaction. This speculation derives from a solvent and a ^{119}Sn NMR study of complexation on tin at room temperature, and that a trace of water catalyses the reaction[1]. Further support for ionization of organotins has already been described[38].

In organosilicon chemistry, a hypervalent silicon species has been implicated where fluoride attacks the silicon first, prior to the ionization of the Si-X bond[39]. Thus, from a mechanistic point of view, fluorodestannylation could proceed by a different pathway. It seems that the ionization process for tin could be generalized for organotin oxides and organotin selenides since the bond energy of these latter compounds are considered to be equal or lower for selenium and definitely lower for oxygen, compared to the tin-sulfur bond. This ionization could also provoke an increase in hardness for tin compounds and favor a better attack of fluoride or cyanide ion.

Based on the complexation study of fluoride ion on bis(tributyltin)sulfide (**14**) at room temperature using ^{119}Sn NMR[36], it could be suggested that fluoride ion does not directly attack the tin atom prior to liberating the chalcogenide ion. Instead, we propose a

solvent ionization process where an intermediate cationic triorganotin is formed and is temporarily stabilized by the solvent. Subsequently, fluoride ion could attack this positively charged intermediate; this pathway qualitatively explains the strong coordinative solvent effect observed. The counterion effect observed (from cesium to tetrabutylammonium) is also consistent with this mechanism.[1]

On the other hand, we recently found some spectroscopic evidence for a complex formation between TBAF and bis(tributyltin)sulfide (**14**) at low temperature[36]. Thus, we cannot exclude the existence of some negatively charged organotin fluoride complexes, in low concentration, acting as initiators of the reaction instead of the proposed ionization mechanism. The exact structure of these organotin fluoride complexes are unknown.

Bis(tributyltin)oxide (**4**) and bis(tributyltin)sulfide (**14**) reacted with benzyl bromide in the presence of TBAF.$3H_2O$ to produce tributyltin benzyl ether (**15**) and tributyltin benzyl sulfide (**16**), respectively. Their presence in the reaction mixture was confirmed (^{1}H NMR and ^{119}Sn NMR) by comparison with authentic samples independently prepared.[40]

Bu_3Sn-O-CH_2Ph **15**

Bu_3Sn-S-CH_2Ph **16**

Assuming that bis(triphenyltin)selenide (**5**) will follow the same reaction pathway, we then propose as a working hypothesis that the chalcogen atom is released in a stepwise manner. Two consecutive displacement steps should constitute the most probable mechanism and one of them should involve the nucleophile corresponding to a tributyltin chalcogenide ion (Scheme 5). This stepwise mechanism is also consistent with the predominant formation of thiols from bis(tributyltin)sulfide (**14**), 1-bromohexane and TBAF.$3H_2O$ in the presence of water; the intermediate tributyltin hexyl sulfide (**17**) being trapped or hydrolyzed.

Scheme 5. Suggested Mechanism

$$Bu_3Sn\text{-}Nu\text{-}SnBu_3 \text{ ------> } Bu_3Sn\text{-}Nu^- + [Bu_3Sn\text{-}Solvent]^+$$

$$[Bu_3Sn\text{-}Solvent]^+ + F^- \text{ ------> } Bu_3Sn\text{-}F$$

$$Bu_3Sn\text{-}Nu^- + PhCH_2Br \text{ ------> } PhCH_2\text{-}Nu\text{-}SnBu_3$$

$$PhCH_2\text{-}Nu\text{-}SnBu_3 \text{ ------> } PhCH_2\text{-}Nu^- + [Bu_3Sn\text{-}solvent]^+$$

$$[Bu_3Sn\text{-}solvent]^+ + F^- \text{ ------> } Bu_3Sn\text{-}F$$

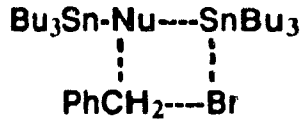
$$PhCH_2\text{-}Nu^- + PhCH_2Br \text{ ------> } PhCH_2\text{-}Nu\text{-}CH_2Ph$$

Nu = O, S, Se; solvent = DMF, CH_3CN; Bu_3SnF = "polymer"

The non-dependence of the substituents on tin on the reaction rate can be interpreted if the second alkylation step is the rate determining step. This step proceeds in the absence of tin substituents and without the help of an "activating effect" from the adjacent tin atom It is consistent with the predominant formation of thiols under aqueous conditions. As the concentration of the tnaralkyltin thiolate intermediates increases, because of the slower rate of the second alkylation, the intermediates are readily hydrolyzed. However, the slight dependance of the substituent on organotin oxides seems to justify a more complexe mechanism with oxygen as nucleophile.

A concerted mechanism appears unlikely because of the solvent polarity effect observed on the rate of the reaction (Scheme 6) and the fluoride effect. Furthermore, this mechanism, without the use of fluoride, has been ruled out by Kozuka and Ohya[41].

Scheme 6. Concerted Mechanism



A mechanism involving a doubly charged anion (Scheme 7) analogous to the findings in a recent paper by Steliou, Corriveau and Salama[42] (MeLi + $Me_3SiSSiMe_3$ ----> Li_2S) is less likely in this case because of the formation of products **15** and **16** in the presence of excess fluoride ion. In addition, the Sn-F bond (99 kcal/mol) is not as strong as the Si-F

bond (139 kcal/mol). Thus, a second attack of fluoride ion on the organotin Bu_3Sn-Nu- should be more difficult. The increase of the softness of tin with a negative charge in the alpha position and the natural repulsion of two negative charged species such as F- and Bu_3Sn-Nu- should also discourage this mechanism. A solvent assisted ionization process for making a doubly charged nucleophile (Nu^{2-}) seems to us less likely than the proposed mechanism.

Scheme 7. Doubly Charged Anion (direct attack of F-)

$$Bu_3Sn\text{-}Nu\text{-}SnBu_3 + F^- \longrightarrow Bu_3Sn\text{-}Nu^- + Bu_3Sn\text{-}F$$

$$Bu_3Sn\text{-}Nu^- + F^- \longrightarrow Nu^{2-} + Bu_3Sn\text{-}F$$

3.2.8 Comments About the Purification

The difficulty associated with the purification of products in some reactions involving organotin compounds has been accorded special attention[31,43] (especially with tributyltin hydride as reagent) The usual purification consists of treating the organotin formed as by-product with fluoride ion to generate the "polymeric" organotin fluoride, insoluble in many solvents However, in our hands this method failed to remove completely the organotin by-products. Here, we determined with the aid of ^{119}Sn NMR that the usual treatment of a reaction mixture with fluoride ion containing organotin bromide quantitatively forms polymeric organotin fluoride but the problem remained as these "polymeric" organotin fluorides are partially soluble in organic solvents We found that a simple filtration through a short column of silica gel using only ethyl acetate as eluent gave satisfactory results to remove "polymeric" organotin fluoride. A strong advantage of this methodology is a kind of "auto-purification" of the mixture with fluoride ion. As the reaction proceeds, fluoride ion removes the tin moiety as a precipitate, directly eliminating this extra step as is often done in the purification of organotins[31]

3.3 Conclusion

We have demonstrated that fluoride ion can attack organotin chalcogenides to liberate powerfully nucleophilic chalcogenide ions This process provides a new way to form "naked" nucleophiles; using this concept, ethers, sulfides and selenides can be generated smoothly under essentially neutral conditions. This method appears to be among the best in

the literature considering factors such as yield, temperature and short reaction time. The most important parameters found in these reactions were the fluoride or cyanide effects followed by a strong solvent effect. An order of reactivity has been established for the various fluoride sources used. A general mechanism has been postulated based on ^{119}Sn NMR and ^{1}H NMR. Organotins can act as general "Group 16 (IV) transfer agents", further, a new way for making carbon-carbon bonds has been demonstrated here by use of fluorodestannylation.

3.4 Experimental Part

Chemicals: All of the organotin compounds, organic halides, aldehydes, ketones, TBAF.$3H_2O$, CsF, selenium and crown-ethers were purchased from Aldrich Chemical Co and used as such, unless noted otherwise. Reagent grade acetonitrile, DMF and N-methyl-2-pyrrolidinone (NMP) were distilled over calcium hydride. THF was dried over metallic sodium wire using the benzophenone ketyl radical as an indicator. When some water was involved in the medium, spectroscopic grade DMF and acetonitrile were used without purification. Diethyl ether, hexane and ethyl acetate involved in the purification steps were reagent grade solvents. All of the reactions were carried out under a nitrogen atmosphere except when using TBAF.$3H_2O$. Cesium fluoride was dried under vacuum (2-5 mm Hg) at 110°C (pistol dryer) for 1 to 2 days.

Instrumentation: ^{119}Sn, ^{13}C and ^{1}H NMR spectra were recorded on a Varian XL-200 or XL-300 and the chemical shifts (in ppm) reported in reference to tetramethyltin, chloroform and tetramethylsilane respectively. All of the samples were dissolved in deuterated chloroform. For ^{119}Sn and ^{13}C NMR, a 10 mm B.B. or 5 mm B.B. probe was used and the spectra recorded using a decoupler. In the description of NMR spectra, the abbreviations s, d, t, q, and m signify singlet, doublet, triplet quartet and multiplet respectively. The uncorrected melting points were recorded in capillary tubes on a Gallenkamp apparatus. Infrared spectra were recorded on an Analect AQS-20 FTIR spectrometer using neat liquid between two blank sodium chloride cells or in solution with 0.1 mm sodium chloride cells with chloroform as solvent. Low resolution electron impact mass spectra were taken on a DuPont 21-492B mass spectrometer with a direct insertion probe 70 ev at 250°C. Chemically induced (C.I.) mass spectra were recorded with a source of 70 ev at 210°C with isobutane on a Hewlett Packard 5980A mass spectrometer.

Gas chromatography was performed on a Hewlett Packard Model 5890 combined with a Hewlett Packard integrator model 3390A or a Varian GC model 3700. A FID

detector was employed on both instruments. A capillary column with methyl silicone as adsorbent on the Hewlett Packard GC was used to monitor some reactions, to check purity and specifically to evaluate the yield of some reactions involving organotin oxide. The progress of the reactions and the purity of final products were monitored by TLC on aluminum sheet precoated with 0.2 mm silica gel 60 F254 (E. Merck 5554). Most of the thin-layer chromatograms were visualized using iodine absorbed on silica gel or with a molybdic acid solution or using a U.V.lamp. Flash chromatography was carried out using silica gel from E. Merck: Kieselgel 60 no. 9385, particle size: 0.040 - 0.063 mm.

Fluorodesilylation with Hexamethyldisilthiane (2). 1-Bromohexane (409 mg., 2.48 mmol), dried cesium fluoride (1.88 g., 12.4 mmol), a catalytic amount of 18-crown-6 (65 mg., 0.25 mmol) and dried acetonitrile (10 mL) were combined in a 25 mL flask. Commercial hexamethyldisilthiane from Petrarch Systems Ltd. (232 mg., 1.30 mmol., 0.27 mL) was injected over 10 min using a syringe (fumehood, odor). Upon addition at r.t., a blue color persisted and when the rate of addition increased, a green color appeared. After 2 h, the solvent was evaporated and 20 mL of n-hexane plus 10 mL of water were added. The organic layer was evaporated to give 266 mg. of a mixture of di-*n*-hexyl sulfide and di-*n*-hexyl disulfide in a ratio of 2.3:1.0 as determined by ^1H NMR: sulfide; 2.52 ppm (t, CH_2SCH_2) and disulfide; 2.70 ppm (t, CH_2SSCH_2).

Fluorodesilylation with Hexamethyldisiloxane (3). In a 50 mL flame-dried flask was placed 1-iodohexane (1.00 g., 4.72 mmol), 18-crown-6 (150 mg., 0.58 mmol), cesium fluoride (2.00 g., 13.2 mmol) and DMF (15 mL). Hexamethyldisiloxane (**3**, 0.766 g., 4.72 mmol 1.00 mL) was added slowly over 15 min at 50°C and the mixture was stirred vigorously. The formation of di-*n*-hexyl ether was followed by G.C. Only traces of the desired ether were detected (2-3% yield) after 28 h. The retention time of the product was identical to authentic di-*n*-hexyl ether under several conditions.

Formation of Symmetrical Ethers.

Dibenzyl Ether with TBAF.3H$_2$O (general procedure). Freshly distilled benzyl bromide, (504 mg., 2.95 mmol), bis(tributyltin)oxide (**4**, 1.04 g., 1.74 mmol), tetrapropylammonium iodide (230 mg. 0.73 mmol; this reagent can be omitted without drastically changing the results) and acetonitrile (12 mL) were placed in a flask closed with a stopper. After the mixture had been stirred for 5 min, tetrabutylammonium fluoride trihydrate (1.11 g., 3.50 mmol) was added in one portion. The reaction was stirred for 6 h at R.T.; the mixture became cloudy, indicating the presence of tributyltin fluoride.

Evaporation of the solvent and addition of ethyl acetate may result in the formation of a precipitate that can be filtered on celite. Filtration of the residue through a short column of silica gel (using pure ethyl acetate) followed by a solvent gradient of 100% hexanes to 10% EtOAc/hexanes gave 120 mg. of dibenzyl ether (0.61 mmol; 41% yield). ^{1}H NMR (60 MHz,) 7.27 (s, 10 H); 4.52 (s, 4 H). M.S. (m/z rel. intensities) 107 (17), 105 (13), 93 (10), 92 (100), 91 (62), 90 (7), 89 (9), 79 (18), 77 (10), 65 (14), 51 (11), 39 (95); I.R. ($CHCl_3$) 3000, 2860, 1495, 1450, 1355, 1085, 1065, 690.

Dibenzyl Ether with Cesium Fluoride. In a 100 mL flask was added freshly distilled benzyl bromide (1.00 g., 5.84 mmol), bis(tributyltin) oxide (**4**, 1.74 g., 2.92 mmol), a catalytic amount of 18-crown-6 (80 mg., 0.30 mmol) and acetonitrile (24 mL) An excess of cesium fluoride (2.0 g., 13.2 mmol) was added in one portion. The reaction mixture was stirred vigorously at 55°C for 7 to 9 h; ^{1}H NMR showed >95% conversion. After cooling at R.T., the solvent was evaporated Ethyl acetate (50 mL) and a saturated solution of potassium fluoride (25 mL) were added and stirred for 45 min at R.T. Finally, the organic layer washed with water (~25 mL) and dried over Na_2SO_4. A simple filtration on silica gel (short column) using pure ethyl acetate afforded pure dibenzyl ether (408 mg , 2.06 mmol, 71% yield). The spectral data were the same as above.

Di-*n*-hexyl Ether (General Procedure). A flask was charged with 1-iodohexane (1.00 g., 4.72 mmol), bis(tributyltin) oxide (**4**, 1.48 g., 2.48 mmol), 18-crown-6 (150 mg., 0.57 mmol) and N-methyl-2-pyrrolidone (15 mL). An excess of cesium fluoride (3.0 g., 19.7 mmol) was added in one portion while stirring vigorously at 52°C for 5h The reaction progress was monitored by G.C. After cooling, diethyl ether (40 mL) and water (40 mL) were added; the aqueous layer was discarded and the ethereal phase washed with water (4 x 20 mL) and dried over $Na_2SO_4/MgSO_4$. The precipitate of tributyltin fluoride was filtered on celite. The ether was evaporated and the residue dissolved in pure ethyl acetate. A simple filtration on a short column using the latter solvent removed the remaining tributyltin fluoride. Flash chromatography using 5% ethyl acetate/hexane ensures the removal of hexyl alcohol formed as side-product. Di-*n*-hexyl ether was obtained as a colorless liquid (236 mg., 1.27 mmol 54% yield). ^{1}H NMR, 3.40 (t, 4 H), 1.58 (m, 4 H), 1.30 (m, 12 H), 0.90 (t, 6 H). The sample was found to be identical to authentic material by G.C. under several conditions of operations (high and low temperature of the capillary column).

The procedure was extended to 1-tosylhexane, 1-bromohexane and 1-iodohexane while using acetonitrile or DMF instead of 1-methyl-2-pyrrolidinone with the conditions

specified in Table 2. In some instances, cesium fluoride was used in an equivalent amount compared to organotin oxide or the crown-ether was omitted.

Formation of Unsymmetrical Ethers

Allylbenzyl Ether with Cesium Fluoride. In a high pressure metal cylinder was placed tributyltin benzyl ether (**14**, 1.00 g., 2.50 mmol)[44] , allyl bromide (393 mg., 3.25 mmol), 18-crown-6 (200 mg., 0.76 mmol), an excess of cesium fluoride and acetonitrile (15 mL). It was stirred while heating at 100°C in the cylinder for 2 h. After cooling at R.T. the mixture was transferred to a flask and the solvent evaporated. Ethyl acetate (25 mL) was added and stirring continued for 5 min. A simple filtration through silica gel afforded 401 mg of an impure liquid product (a second more polar spot was detected by TLC). Flash chromatography afforded 330 mg of pure material ($PhCH_2OCH_2CH{=}CH_2$, 90%); ^1H nmr gave: 7.35 (m, 5H, **Ph**), 5.98 (m, **=CH**), 5.32 (d, **$=CH_2$**), 5.22 (d, **$=CH_2$**), 4.55, 4.05 (d, **CH_2**).

***n*-Hexylbenzyl Ether with Silver(I) Fluoride.** A flask was charged with 1-iodohexane (348 mg., 1.65 mmol), tributyltin benzyl ether (**15**, 590 mg., 1.48 mmol), silver(I) fluoride (dried at 50°C overnight under vacuum, 0.5 mm Hg), dibenzo-24-crown-8 (95 mg., 0.21 mmol) and acetonitrile (15 mL). The flask was heated at 75°C for 2 days. The solvent was removed and the mixture filtered on a short column of silica gel using pure ethyl acetate as eluent. An impure product (366 mg.) was flash chromatographed with 10% EtOAc/ 90% hexane. Finally, 47 mg of slightly impure *n*-hexyl benzyl ether (as determined by ^1H NMR) was obtained. ^1H NMR revealed the major signals of *n*-hexylbenzyl ether 7.36 (m), 4.5 (s), 3.47 (t), 1.6 (m), 1.3 (m), 0.90 (t).

***n*-Hexylbenzyl Ether with Cesium Fluoride.** Cesium fluoride (856 mg., 5.64 mmol) was flame-dried under high vacuum in a flask and cooled at r.t. under a stream of argon. Dibenzo 24-crown-8 was added in a catalytic amount (19 mg., 0.042 mmol) followed by 1-methyl 2-pyrolidinone (15 mL) and tributyltin benzyl ether (**15**, 1.00 g., 2.52 mmol); 1-iodohexane (588 mg., 2.77 mmol, 0.41 mL) was injected in the flask using a syringe. After stirring at R.T., a yellow color appeared within 10 to 15 min. Stirring continued for 24 h. Finally, ether (100 mL) and water (100 mL) were added; the ethereal phase was washed further with 3 x 30 mL of water. If needed, a filtration on celite could be carried out to remove insoluble organotin fluoride. The organic phase was dried using $Na_2SO_4/MgSO_4$. A filtration through a short column of silica gel using EtOAc as eluent was carried out followed by a flash chromatography using a gradient of hexane (100%) increasing to 10%

EtOAc. The product can be visualized on TLC while heating using a spray mixture developed in our lab: 30% H_2SO_4/5% HNO_3 in water; ^1H NMR 7 34 (m, 5 H); 4.51 (s, 2 H); 3.48 (t, 2 H); 1,62 (quintuplet, 2 H); 1.31 (m, 6 H); 0.89 (t, 3 H).

Formation of Symmetrical Selenides

Preparation of bis(Triphenyltin)selenide (5). A 250 mL flask, flamed and cooled under a nitrogen stream, was charged with a commercial solution of lithium borohydride 1.0 M in THF (105 mL., 0.105 mol). The flask was placed in an ice-bath and finely crushed selenium pellets (3.95 g., 0.050 mol) were added in small portions. A brown-red color appeared upon addition and hydrogen was liberated to finally give a white milky mixture The reaction mixture was stirred for 5 min and then warmed up to R.T. Stirring was continued for 2.5 h. Up to this point, this procedure is essentially that reported by Gladysz [18]. Triphenyltin chloride (36.62 g., 0.095 mol) was added in one portion followed by anhydrous THF (90 mL). The reaction was stirred vigorously overnight wrapped with an aluminum foil to prevent light-induced reactions. This sequence is similar to that reported by Detty with some silicon analogs[45]. *n*-Hexane (100 mL) was added in order to precipitate lithium chloride; the mixture was filtered on a pad of celite (under a vigorous flow of nitrogen from a funnel). Caution! highly toxic H_2Se is immediately liberated in contact with air. The solvent evaporation was carried out in a fumehood. The crude bis(triphenyltin)selenide (**5**) was dissolved in THF (60 mL) and absolute ethanol (200 mL) was added slowly to crystallize the white product. A filtration under atmospheric conditions afforded white crystalline (not highly odorous) bis(triphenyltin)selenide (**5**, 28.33 g., 0.036 mol) m.p. 147.0-147.5 °C (lit. 148°C [45]); ^{119}Sn NMR 79.13 (s); ^{13}C NMR 136.54; 129.29; 128.52. The mother liquors were evaporated to dryness and triturated with absolute ethanol to give 2.32 g. of additional bis(triphenyltin)selenide (**5**); combined yield: 83%

Di-(2-phenethyl) Selenide[46]. A 50 mL flask was charged with (2-bromoethyl)benzene (153 mg., 0.83 mmol), bis(triphenyltin)selenide (**5**, 345 mg., 0.44 mmol), 18-crown-6 (50 mg., 0.19 mmol), tetrahydrofuran (3.0 mL) and acetonitrile (8.0 mL). The mixture was stirred for 5-10 min.; cesium fluoride was added in one portion (1.0 g., 6.6 mmol) and the foil-wrapped reaction stirred vigorously for 1 h at 40°C. The solvent was evaporated and the mixture taken up in pure ethyl acetate. The insoluble impurities were filtered on celite. A flash chromatography using 5% EtOAc in hexane gave a colorless liquid corresponding to di(2-phenethyl) selenide (107 mg., 0.37 mmol; 89% yield)homogeneous on TLC (5% EtOAc/hexane); ^1H NMR 7.23 (m, 10 H), 2.88 (A_2B_2

system, 8 H); M.S. (C.I. based on ^{80}Se) 291 (M+1); ^{13}C NMR 128.57, 128.46, 37.30, 25.10; TLC showed one major spot (R_f= 0.70 in 10% acetone/90% hexane).

Di-*n*-hexyl Selenide from 1-Bromohexane. 1-Bromohexane (347 mg , 2.10 mmol), 18-crown-6 (30 mg., 0.11 mmol), cesium fluoride (1.26 g , 8 29 mmol) and acetonitrile (1o mL) were placed in a 50 mL flask A solution containing bis(triphenyltin)selenide (5, 779 mg., 1.00 mmol) and tetrahydrofuran (6.0 mL) was injected slowly over 45-50 min using a glass syringe. The reaction mixture was heated at 48°C during the addition To ensure maximum conversion, the reaction mixture was stirred for an additional 45 min. Evaporation of the solvent followed by a filtration through a short column of silica gel using pure ethyl acetate as eluent afforded 239 mg of a colorless liquid corresponding to di-*n*-hexyl selenide (96% yield) ^1H NMR 2,53 (t, 4 H); 1,65 (quintuplet, 4 H); 1.30 (m, 12 H), 0.87 (t, 6 H), M S (m/z rel intensities) 250 (^{80}Se, M+, 15), 248 (^{78}Se, M+, 4) 166 (19), 165 (24), 164 (7), 163 (8), 85 (31), 84 (25), 83 (22), 69 (14), 57 (34), 56 (34), 55 (31), 44 (7), 43 (100), 42 (17), 41 (43), 39 (16), 32 (24), 29 (47), 28 (61), 27 (45). TLC showed one major spot (R_f= 0.85 in 5% EtOAc/95% hexane).

Di-(4-acetoxybutyl) Selenide from 4-Bromobutyl Acetate. This is essentially the same procedure as described for di-*n*-hexyl selenide from 1-bromohexane but using the following chemicals: 4-bromobutyl acetate (400 mg., 2.05 mmol), bis(triphenyltin)selenide (5, 779 mg., 1.00 mmol), cesium fluoride (1 04 g., 6 85 mmol) and acetonitrile (15 mL). Dibenzo-24-crown-8 (90 mg , 0.20 mmol) was used as phase transfer catalyst The slow addition of the organotin selenide reagent dissolved in THF (6 0 mL) took 70 min at 36°C and the reaction mixture was further stirred for 50 min to ensure maximum conversion of the starting material. Di-(4-acetoxybutyl) selenide was obtained as a colorless liquid after filtration through a short column of silica gel (300 mg , 97 % yield). ^1H NMR 4 07 (t, 4 H); 2.58 (t, 4 H); 2 05 (s, 6 H); 1.73 (m, 8 H) M S. (m/z rel. intensities) 136 (13), 135 (10), 115 (17), 85 (4), 73 (8), 71 (15), 61 (5), 57 (5), 56 (17), 55 (35), 54 (10), 43 (100), 41 (15), 39 (11), 29 (17), 28 (24), 27 (10); ^{13}C NMR 170.98, 63 79, 28.78, 27 14, 23 29, 20 91, TLC on silica gel using 10% acetone/90% hexane showed one major spot (R_f - 0 25).

Di-*n*-hexyl Selenide from 1-(p-Toluenesulfonyl)-*n*-hexane. A dried 50 mL flask was charged with bis(triphenyltin) selenide (5, 922 mg., 1 18 mmol), 1-(p-toluenesulfonyl)-*n*-hexane (607 mg., 2.37 mmol) prepared in the standard way[47], 18-crown-6 (30 mg., 0.11 mmol), acetonitrile (16 mL) and THF (6.5 mL). Cesium fluoride was added in one portion (546 mg., 3.59 mmol) giving a bright yellow color. After being stirred for 3 h at R.T., the

solvent was evaporated and ethyl acetate (30 mL) was poured into the flask. Stirring was continued for a few more min at R.T., then filtered through celite, then on a short column of silica gel using ethyl acetate as eluent. A flash chromatography on silica gel using 3% EtOAc/97% hexane afforded 90 mg. (0.27 mmol) of di-*n*-hexyl diselenide; ^{1}H NMR 2.92 (t, 4 H); 1.73 (quintuplet, 4 H); 1.32 (m, 12 H); 0,90 (t, 6 H); M.S. (m/z rel. intensities) 166 (17), 164 (4), 85 (30), 84 (20), 69 (20), 57 (53), 56 (49), 55 (37), 43 (100), 42 (44), 41 (67), 39 (35), 32 (22), 29 (63), 28 (85), 27 (56) and di-*n*-hexylselenide in 70 % yield based on the 1H NMR signal at 2.52 ppm compared to the diselenide signal at 2.92 ppm.

Di-(1-phenethyl) Selenide from (1-Bromoethyl)benzene. Cesium fluoride (582 mg; 3.83 mmol) was added to a flask and the latter was flame-dried and cooled under a stream of argon. Dibenzo 24-crown-8 was added in a catalytic amount (39 mg., 0.087 mmol), followed by acetonitrile (16 mL) and the injection of (1-bromoethyl)benzene (379 mg., 2.05 mmol, 0.28 mL). With the use of a syringe pump, a solution of bis(triphenyltin)selenide (779 mg., 1.00 mmol) in THF (6.0 mL) was added over 1 h. The mixture was heated to 40°C during this addition and then for 40 h; 70 min after the addition of the bromide, a sample taken from the mixture indicated a 42% conversion of starting material by ^{1}H NMR. After 40 h, the solvent was evaporated and pure ethyl acetate was added. The residue was passed through a short column of silica gel using only ethyl acetate as eluent. ^{1}H NMR indicated 67% conversion into di-(1-phenethyl)selenide as a pair of diastereoisomers: ^{1}H NMR 7.26 (m, phenyl); 3.89 (q, Se-CH); 3.84 (q, Se-CH); 1.72 (d, CH_3), 1.60 (d, CH_3)

C-C Bond Formation

D,L 2-phenylpropionaldehyde with Tetraallyltin (9). d,l-2-Phenylpropionaldehyde (538 mg., 4.01 mmol), DMF (10 mL) and cesium fluoride (3.38 g., 22.3 mmol) were placed in a 50 mL flask. Tetraallyltin (**9**, 1.25 g., 4.35 mmol, 1.04 mL) was injected using a syringe within 5 min. After being stirred for 3 h at R.T., T.L.C. (20% EtOAc:80% hexane) showed almost complete conversion. After 3.7 h, diethyl ether (60 mL) and brine (45 mL) were added and the precipitate formed was filtered through celite, and the ethereal phase washed further with water (3 x 20 mL) and dried with Na_2SO_4. Flash chromatography on silica gel (using 20% EtOAc/ 80% hexane) afforded pure 4-phenyl-1-penten-3-ol (602 mg., 3.42 mmol) in 85% yield based on the aldehyde as a pair of diastereoisomers (determined by H^1 NMR); homogeneous on TLC; ^{1}H NMR 7.27 (m, 5 H), 5.83 (m, 1 H), 5.15 (m, 2 H), 3.75 (m, 1 H), 2.80 (q, 1 H), 2.13 (m, 2 H), 1.38 and 1.32 (2 pairs of doublets (2.4:1.0)), 3 H) MS (m/z rel. intensity) 176 (M+, 1), 135 (24), 117 (21), 107 (24), 106 (100), 105 (66), 104

(9), 103 (9), 92 (10), 91 (60), 79 (35), 78 (27), 77 (36), 71 (23), 65 (6), 57 (29), 51 (32), 43 (89), 41 (27), 39 (41), 29 (24), 28 (72), 27 (23).

1-Phenyl 2-methyl 4-pentene 2-ol from Phenylacetone and Tetraallyltin[48]. A flask was charged with cesium fluoride (1.20 g, 7.90 mmol) and then flame-dried under high vacuum. After cooling with a stream of argon, acetonitrile (9.5 mL) and DMF (0.5 mL) were added. Then freshly distilled phenylacetone (216 mg, 1.61 mmol, 0.22 mL) was injected followed by tetraallyltin (500 mg, 1.77 mmol, 0.42 mL). The reaction mixture was heated at 55-60°C for 8 days under argon. Acetonitrile was evaporated and DMF removed using high vacuum. Ethyl acetate was added to the residue which was then filtered through a short column of silica gel. Flash chromatography using 10% acetone/ 90% hexane provided d,l 1-phenyl 2-methyl-4-pentene 2-ol (45 mg; 16% yield based on phenylacetone), I.R. (neat) 3600-3250, 3060, 3030, 2975, 2930, 2900, 1640, 1495, 1450, 1010, 1000, 910, 760, 700. ^{1}H NMR 7.27 (m, 5 H), 5.95 (m, 1 H); 5.20-5.10 (m, 2 H), 2.77 (d, 2 H), 2.25 (d, 2 H); 1,15 (s, 3 H); M.S. (m/z rel. intensities) 176 (M+ ,0.2), 158 (0.3), 135 (40), 117 (26), 115 (16), 107 (20), 106 (100), 105 (59), 104 (37), 103 (26), 92 (29), 91 (87), 79 (24), 78 (36), 77 (44), 71 (26), 65 (17), 57 (41), 51 (24), 43 (76), 41 (43), 39 (30), 29 (25), 28 (20), 27 (28). TLC gave a single spot using acetone/hexane or ethyl acetate/hexane systems as eluents.

1-Phenyl 4-pentyne-3-ol from d,l Phenylpropionaldehyde and Ethynyltributyltin. Cesium fluoride (885 mg., 5.83 mmol), and NMP (8.0 mL) were placed in a 25 mL flask. Ethynyltributyltin (500 mg., 1.59 mmol) and d,l phenylpropionaldehyde (200 mg, 1.49 mmol, 0.20 mL) were added by syringe in one portion. The mixture was stirred at 44°C for 90 h. A bright yellow color appeared first and turned to orange over time. Ether (50 mL) and water (50 mL) were finally added. The ethereal phase was washed with 3 x 15 mL of water and dried on Na_2SO_4. Flash chromatography using 20% ethyl acetate in hexane gave no significant amount of the desired alcohol as determined by ^{1}H NMR. Several fractions revealed the presence of the tributyltin moiety as well as the consumption of the aldehyde; however, no attempt was made to hydrolyze the possible intermediate tin oxide.

1-Phenyl-4-penten-2-one from Phenylacetyl Chloride and Tetraallyltin. Cesium fluoride (613 mg., 4.04 mmol) was placed in a 25 mL flask and flame-dried and cooled under vacuum. Then 1-methyl pyrrolidinone (8.0 mL) was added, followed by phenyl acetyl chloride (0.21 mL; 249 mg., 1.61 mmol) and tetraallyltin (0.42 mL, 500 mg., 1.77 mmol). The reaction was stirred vigorously at R.T. for 20 h. A milky appearance denoted the

formation of organotin fluoride after a few hours. Ether (100 mL) was added followed by brine (75 mL). The ethereal phase was washed further with brine (3 x 25 mL) and dried on $Na_2SO_4/MgSO_4$. Flash chromatography on silica gel using 15% acetone in hexane as eluent gave pure 1-phenyl-4-penten-2-one (196 mg.; 76% yield) existing mainly as the enol form as indicated by I.R. (neat) 3560-3400, 3075, 3030, 2920, 1640, 1495, 1455, 1365, 1080, 1030, 1000, 914, 700, ^1H NMR 7 29 (m, 5 H); 5.87 (m, 1 H); 5.2-5.1 (m, 2 H); 2,80 (s, 2 H); 2.24 (d, 2 H), M.S. (m/z rel. intensity) 160 (M^+,8), 129 (1), 105 (15), 92 (28), 91 (100), 77 (12), 69 (23), 41 (41). ^{13}C NMR 137.18, 133.79, 130.73, 128.23, 126.54, 118,86, 73.49, 45.41, 43.50. Single spot on TLC using acetone/hexane or ethyl acetate/hexane systems as eluent.

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37. We failed to obtain a reaction with 1-bromohexane and bis(triphenyltin)selenide (**5**) in the presence of CsF/18-crown-6 in pure acetonitrile. In a mixture of THF/CH_3CN (8·3), the reaction proceeded rapidly.

38. In analogy with trialkyltin chlorides that are known to exist in the form of a diaquo cationic trialkyltin, it seems reasonable to extend this property to organotin oxides, sulfides and selenides based on the Sn-O, Sn-S and Sn-Cl bond energies; see reference 29 p 557. A recent ^{119}Sn NMR study demonstrated the formation of a stable stannonium cation at -78°C using HSO_3F, Wasylishen, R. E.; Leighton, K. L. *Can. J Chem.* **1987**, *65*, 1469.

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CHAPTER 4

FLUORODEMETALATION REACTIONS

The scope and mechanistic considerations of the fluorodestannylation methodology have been reported in chapter 3 for organotin oxides and selenides. In chapter 2, we briefly introduced the fluorodestannylation reactions applied to organotin sulfides It is now the purpose of this chapter to extend this reaction to other group 14 metals and to report the full scope and limits of this method with organotin sulfides.

As an extension of the fluorodestannylation technique, it is appropriate to investigate similar reactions with fluoride ions while changing tin to germanium or lead. This chapter will thus introduce the fluorodemetalation concept within the group 14 (Si, Ge, Sn and Pb). Organogermanium, -tin and -lead sulfides will be used as probe to investigate the general approach of using fluoride ions for releasing anions (sulfur anions here). This section will show the first fluorodegermanylation and fluorodeplumbylation reactions

Several questions still remain unanswered about the mechanism of the fluorodestannylation reaction. This chapter will thus bring new insights about the mechanistic aspects with the aid of variable-temperature ^{119}Sn and ^{19}F NMR spectroscopy.

Although pentacoordinated intermediates have been thought to be involved in substitution at tin, the results presented in this chapter are among the first spectroscopic proofs of their existence.

The chapter 4 was mainly taken from a manuscript sent for publication (Gingras, M.; Chan, T. H.; Harpp, D. N. submitted for publication). Again, the whole literature search of references, the writing of this article plus the laboratory work are the results of my personal efforts in this thesis. Professors Chan and Harpp assisted in the revision of the manuscript.

4.0 NEW METHODOLOGIES: FLUORODEMETALATION OF ORGANOGERMANIUM, -TIN AND -LEAD. APPLICATIONS WITH ORGANOMETALLIC SULFIDES TO PRODUCE HIGHLY ACTIVE ANIONS AND SPECTROSCOPIC EVIDENCE FOR PENTAVALENT INTERMEDIATES IN SUBSTITUTION AT TIN.

Abstract: *The general concept of fluorodemetalation is illustrated with three novel methodologies. Fluoride ion smoothly demetalates organogermanium, tin and lead sulfides under mild and neutral conditions to liberate some of the most active nucleophilic sulfur species known to date. More interestingly, their high reactivity seems to be a driving force for preparing sensitive macrocyclic sulfides where usual methods fail. Seven different sulfur transfer agents derived from group 14 are used to demonstrate fluorodemetalation. The reactions of fluorodeplumbylation and fluorodegermanylation are presented for the first time along with a discussion of their potential uses in chemistry. The study of fluoride sources as demetalating agents, solvents, substituents and substrates variation is reported. Mechanistic and kinetic aspects of fluorodemetalation are also discussed. In addition, we present a spectroscopic evidence for a pentacoordinated intermediate involved in the mechanism of substitution at tin by the use of low temperature ^{19}F and ^{119}Sn NMR spectroscopy. This reinforces the widely proposed model for reaction of substitution in group 14. Furthermore, we propose that the metal proximity effect on a charged anion will increase the nucleophilicity of the latter in the absence of severe steric hindrance by substituents on the metal.*

4.1 Introduction

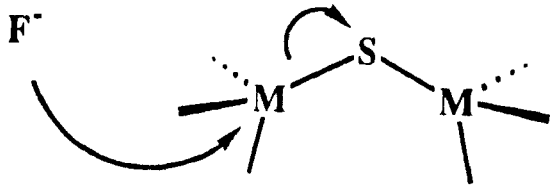
Organotins are widely used for industrial applications[1]. While there have been some investigations on organotin sulfides, their detailed chemistry has not been significantly explored. Early in this century, bis(trimethyltin)sulfide (**1**) was discovered[2] but remained unexploited. In 1982, Steliou and Mrani were the first to use bis(tributyltin)sulfide (**2**) as a potential reagent for making thioketones.[3] Later in 1985, they reported preliminary results for making thioethers.[4] In the same year, Kosugi discovered a palladium-catalyzed reaction with this reagent.[5]

Recently, we reported that (**2**) is useful as a general sulfur transfer agent for the high-yield synthesis of thioethers and related derivatives, albeit under forcing conditions.[6] Finally, we briefly communicated that fluoride and cyanide ions attack organotin sulfides and smoothly liberate the corresponding sulfur ligand as one of the most powerful

nucleophilic sulfur species known to date.[7] This reaction was achieved in *mild and neutral conditions*, without the need of any kind of base. Despite the fact that several methods are known for making sulfides, fluorodestannylation represents a real improvement in this area because of the neutrality of the medium, the mildness of the conditions and interestingly, the high reactivity of the sulfide ion released. This intriguing reactivity has been exploited by two different groups using this methodology since classic procedures had failed.[8] The fast rate of these reactions favors the formation of macrocyclic sulfides and the mild and neutral conditions could open new synthetic routes to thiacrown-ethers[9], cyclophanes[10] and sensitive organic sulfurated products such as penicillins, thienamycins and other carbapenems. This new sulfur transfer agent might also find some uses in the synthesis of the sensitive esperamicin A1 and neocarzinostatin chromophore-A. These antitumor and DNA cleaving agents are current, popular synthetic targets.[11]

We were among the first groups to report the reaction of fluorodestannylation[12,13,14,15]. This article will focus mainly on the technique of three novel methodologies of fluorodemetalation and on the special reactivity of the sulfur ions released. The sulfur chemistry and the products of the reactions will mainly serve to evaluate the usefulness and the potential of the fluorodemetalation concept. A complete study of fluoride sources, solvents and substituent effects (especially with organotins) are reported. We already demonstrated the general and wide aspect of this new technique for liberating naked anions from organotin oxides, organotin selenides and tetraorganotins.[15]

Scheme 1: Fluorodemetalation



M= Si, Ge, Sn, Pb

Due to the importance of organotins acting as a "group 16 (VIB) transfer agents" in the presence of fluoride ions,[15] we want to generalize the methodology of fluorodemetalation by reporting the first use of fluorodegermanylation and fluorodeplumbylation. In organic synthesis, organogermanium reagents are practically

nonexistent.[16] Only triphenylgermane is a well known reagent in radical reactions[17]; their use is relatively rare in industry as well.[18] In organolead chemistry there are a few important reagents[19]: lead tetraacetate,[20] allyl trialkyllead,[21] some lead salts,[22] triphenylplumbyl methyllithium or bis(triphenylplumbyl)methane.[23] They constitute the limited number of organolead tools available in organic synthesis.

For practical purposes, the handling of highly hygroscopic, smelly and much less reactive $Na_2S.9H_2O$ is avoided since most of these organometallic sulfides used in our study (Figure 1) are not odorous, they are often solid or liquid with high boiling point and are easily made or commercially available *(vide infra)*.[24] A further advantage is that they are soluble in many organic solvents, in contrast to the insoluble and less reactive $Na_2S.9H_2O$.

Figure 1: List of Sulfur Transfer Agents

Me_3Sn-S-$SnMe_3$	**Bu_3Sn-S-$SnBu_3$**	**Me_3Si-S-$SiMe_3$**
1	**2**	**3**
Ph_3Ge-S-$GePh_3$	**Ph_3Pb-S-$PbPh_3$**	**Ph_3Sn-S-$SnPh_3$**
4	**5**	**7**

$(Bu_2SnS)_3$
8

Mechanistic aspects of fluorodemetalation and partial rate studies (especially with tin) aided by a low temperature multinuclear NMR studies using ^{119}Sn, ^{13}C, ^{19}F and ^{1}H NMR are included, since not much is known about these reactions. Several kinetic studies have led to the assumption that pentacoordinated species are involved as intermediates in many organotin reactions.[25] We will then present spectroscopic evidence for a pentacoordinated intermediate involved in the substitution at tin as deduced by low temperature ^{19}F and ^{119}Sn NMR spectroscopy thus confirming the proposed model of substitution at tin.[25] Conclusions drawn on fluorodemetalation will have general implications on other chemistry involving group IV metals.

4.2 Results and Discussion

4.2.1 Synthesis of Organotin, Organogermanium and Organolead Sulfides.

There are numerous, well-established procedures for the preparation of organotin sulfides.[26] From a practical point of view, we selected only those that are the most convenient to carry out. Bis(tributyltin)sulfide (**2**) was synthesized according to a modification of the procedure of Midgal.[27] Other organotin sulfides are prepared in the same way using the appropriate organotin chloride (all commercially available). The simple and practical procedure shown in equation 5 was also reasonably successful with organogermanium chloride (53% yield) and organolead acetate (80-90% yield).

Tributyltin benzyl sulfide (**9**) was prepared using Wilkinson's catalyst in the presence of tributyltin hydride and benzyl mercaptan with excellent yield and purity.[28]

$$2\ R_3MX + Na_2S.9H_2O \text{ -------> } R_3M\text{-}S\text{-}MR_3 + 2\ NaX \qquad \textbf{(Eq. 5)}$$

M= Ge, Sn, Pb **X= Cl (or OAc with M= Pb)**

4.2.2 Fluoride Effects.

As can be seen in Table 1, the fluoride effect in fluorodestannylation provides a general decrease in reaction time and an increase in yields compared to the same reaction without fluoride ion. The magnitude of the difference in the rate is significant and becomes the most important reaction parameter to be considered in this work. Without fluoride, we previously demonstrated that high temperatures and long reaction times (100°C, 24 h) are required to achieve a good conversion of sulfide while using poorly or non-activated halides with bis(tributyltin)sulfide (**2**).[6] The addition of fluoride reduced the reaction time to 1 hour or less for most of the substrates. The low nucleophilicity of the fluoride ion makes it excellent to use in S_N2 type reactions, avoiding any competition with the nucleophilic ligand liberated from tin.

This strong fluoride effect was also observed for organolead sulfides where in the absence of fluoride ion, the reaction rates are usually too slow to be useful for synthetic purposes. As an example, bis(triphenyllead) sulfide (**5**) is relatively inert toward benzyl bromide after 4 days at 20°C in DMF (see Table 1). However, a drastic change resulted when cesium fluoride was added: after only 5 h, it was possible to isolate the corresponding sulfide in 67% yield. Bis(triphenylgermanium) sulfide (**4**) showed a similar fluoride effect.

Table 1 : Fluoride Effect in Fluorodemetalation

	Without fluoride		With fluoride		
Substrates	Time(h)	Yield(%)[b]	Time(h)	Yield(%)[b]	Fluoride
$(Bu_3Sn)_2S$[a]					
$PhCOCH_2Br$	24	71	<0.3	100	$TBAF.3H_2O$
$PhCOCH_2Br$	"	"	1.0	98	CsF
$PhCH_2Br$[c]	22	17	0.8	85	$TBAF.3H_2O$
$CH_3COCH(Br)CH_3$	78	0[c]	24	75	$TBAF.3H_2O$
$(Ph_3Pb)_2S$					
$PhCH_2Br$	96	5	9.5	67[d]	CsF
$(Ph_3Ge)_2S$					
$CH_3(CH_2)_4CH_2Br$	24	>1	10.0	60[e]	CsF

a) Reaction conditions. 20°C, DMF/EtOAc (5:1), halide (2.00 mmol), bis(tributyltin)sulfide (**2**, 1.10 mmol), fluoride. CsF (excess) or $TBAF.3H_2O$ (2.10 mmol), same concentration of each reagent for all different reactions; b) Isolated yields; c) not usual reactions conditions: $CHCl_3$ reflux (61°C), d) reaction conditions: 20°C, DMF, halide (2 00 mmol), bis(triphenyllead)sulfide (1.05 mmol), cesium fluoride (4 80 mmol) and 18C6 (catalytic), e) reaction conditions. 55°C, DMF/THF (1.4) bis(triphenylgermanium) sulfide (**4**, 1 00 mmol), 1-bromohexane (2 00 mmol, 18C6 (cat), CsF (5 8 mmol).

In the case of 1-bromohexane and fluoride ion, the symmetrical sulfide was isolated in 80% yield in 10 h.

In the organosilicon case, it has already been shown by Abel and co-workers[29] that strong heating at 160°C for 100 h was required to react 1-bromooctane with bis(trimethylsilyl)sulfide (**3**) for the formation of di-*n*-octyl sulfide (72% yield). In our methodology, the reaction took place at 20°C within a few minutes with cesium fluoride.

For example, we found that hexamethyldisilthiane (3) formed a 2.3:1 mixture of monosulfide and disulfide when treated with fluoride in the presence of halide whereas the tin analog gave a quantitative yield of monosulfide under the same conditions.

$$2\,CH_3(CH_2)_5Br + Me_3Si\text{-}S\text{-}SiMe_3 \xrightarrow{F^-} \text{-S-} + \text{-S-S-} \qquad \text{(Eq.1)}$$

3 (2.3:1)

$$2\,CH_3(CH_2)_5Br + Bu_3Sn\text{-}S\text{-}SnPh_3 \xrightarrow{F^-} \text{-S-} \qquad \text{(Eq. 2)}$$

2 (99%)

Fluorodegermanylation gives exclusively monosulfide when the reaction parameters are controlled properly (Eq. 3). Fluorodeplumbylation gave an isolable intermediate triphenyllead hexyl sulfide (**6**) that is slowly transformed into di-*n*-hexyl sulfide (Eq. 4).

$$2\,CH_3(CH_2)_5Br + Ph_3Ge\text{-}S\text{-}GePh_3 \xrightarrow{F^-} \text{-S-} \qquad \text{(Eq. 3)}$$

4 (80%)

$$2\,CH_3(CH_2)_5Br + Ph_3Pb\text{-}S\text{-}PbPh_3 \xrightarrow{F^-} Ph_3Pb\text{-}S\text{-}(CH_2)_5CH_3 + \text{-S-} \qquad \text{(Eq. 4)}$$

5 6

ratio: 5.7:1

From these results with sulfur, it appears to us that the fluorodemetalation reactions of germanium and lead could open wide fields of totally new synthetic procedures involving Ge-O, Ge-Se, Ge-Te, Ge-C, Pb-O, Pb-Se, Pb-Te and Pb-C bond cleavage reactions under mild and neutral conditions, in the presence of fluoride ions. New ways for generating nucleophiles could be envisaged because of the high affinity of fluorine for these metals.[30]

Cyanide ion also decreases the reaction time for the formation of sulfides from organotin sulfides. Although the magnitude of this effect is less pronounced than for fluoride, it is useful where fluoride cannot be used in a synthesis, e.g. if a silyl ether is present as a protective group in a specific step. Thus, with cyanide, slightly higher temperatures are required to attain a good yield of sulfide. For activated substrates, it appears to be as useful as fluoride (see entry 4 in Table 6 and entry 3 in Table 3). Because the best results were obtained with fluoride in the tin case, we did not study cyanodemetalation with germanium and lead.

4.2.3 Solvent Effects.

In general, the second most important parameter with fluorodestannylation appears to be the solvent used. The rate of formation of sulfide using bis(tributyltin)sulfide (**2**) without fluoride under various solvent conditions follows the following qualitative order: DMF/EtOAc (5:1) > CH_3CN > CH_2Cl_2 (cat. DMF) > EtOAc = CH_2Cl_2 = $CHCl_3$. Essentially the same order is followed when fluoride is employed.

Without fluoride ion, a qualitative rate effect has been deduced from the reaction time for identical substrates under identical conditions (reference synthesis). We concluded previously that the reaction is sensitive to the ionic strength of the medium.[6] Although DMF and acetonitrile have roughly the same dielectric constant (DMF: 37D CH_3CN: 39D at 25°C)[31], we observed different rates with various organotins. This can be rationalized if we assume that solvent coordination on tin is important; this was demonstrated by a ^{119}Sn NMR study. When bis(tributyltin)sulfide (**2**) ($CHCl_3$, 20°C) is used as a standard reference with the concentration mentioned, we obtained a slightly different shift of the ^{119}Sn signal in DMF and in CH_3CN for an identical number of mmol added to the reference system; DMF complexes or solvates bis(tributyltin)sulfide (**2**) more strongly than CH_3CN at the same concentration. A broad ^{119}Sn NMR signal or signal enlargement resulted when adding DMF to the reference sample demonstrating a labile DMF-Sn complex formation.

The complexation effect with solvents is consistent with the observed reaction rates using fluoride of cyanide ions in acetonitrile or DMF. It should be noted that the trend of the solvent effect on the rate of sulfide formation with and without fluoride favors DMF over CH_3CN. The solvent is still very important even in the presence of a potential complexing agent such as fluoride ion.

For organogermanium and organolead sulfides, we briefly investigated the role of solvent and found that DMF still has a strong effect on the reaction rate even if used as a minor co-solvent with THF. Because of the insolubility of the triphenyllead or triphenylgermanium groups in many solvents (such as acetonitrile, hexane, acetone) coupled with the more difficult work-up usually associated with DMF, we used tetrahydrofuran as the main solvent with success. This latter solvent was chosen by Gladysz in the reaction of triethylborohydride with elemental sulfur for generating Li_2S.[32]

4.2.4 Substituent Effects.

Several organotin sulfides of the form $R_3SnSSnR_3$ were investigated where R represents a phenyl, butyl or methyl substituent. Table 2 demonstrates that for identical reaction conditions, the substituent effects can be considered to be negligible compared to the solvent and the fluoride effects. The observation of a slight substituent effect is described qualitatively as: $(Bu_2SnS)_3 > = (Me_3Sn)_2S = (Bu_3Sn)_2S > (Ph_3Sn)_2S$. It should be noted that this effect can be caused by a problem of solubility for some organotin sulfides such as bis(triphenyltin)sulfide (7) when used in DMF. Most of the others are soluble to some extent in acetonitrile and DMF; ethyl acetate was added for better homogeneity. For organolead sulfides or organogermanium sulfides such as $R_3M\text{-}S\text{-}MR_3$ (where M= Pb, Ge), only R = phenyl was studied; the phenyl substituents give thermally stable, crystalline solids.

4.2.5 Fluoride and Cyanide Study

Several sources of fluoride ion are known, however, only a few of them are strictly anhydrous because of the strong hydrogen bonding of fluoride with water.[33] This problem has been described by Kuwajima and Nakamura in the enol silylether chemistry.[34] In some of our reactions with non-activated halides such as 1-bromohexane, we had to use an anhydrous source of fluoride ion to avoid competing thiol formation.[35] None of the well-known fluoride sources were especially effective with this type of substrate. As a consequence, we developed a new fluorinating system involving crown-ethers (18-crown-6) with dried cesium fluoride.[36] The crown-ethers are usually very hygroscopic but only a

Table 2: Substituent Effect on Tin vs Reaction Rate

$$Br(CH_2)_5Br + (R_3Sn)_2S \xrightarrow{F^-} \text{thiane} + 2\,R_3SnF$$

R	Yield(%)[b]	T(°C)	Time(min)	Solvent
Bu	100	42	1200	DMF/EtOAc(5:1)
Ph	100	42	720	DMF/EtOAc(5:1)
Bu	96	60	30	DMF/EtOAc(5:1)
Ph	88	60	30	DMF/EtOAc(5:1)
Bu	97	60	60	DMF/EtOAc(5:1)
Ph	94	60	60	DMF/EtOAc(5:1)
Me	75	20	<20	CH_3CN
Bu	100	20	45	CH_3CN
Me	90	50	45	CH_3CN
Bu_2SnS	100	50	45	CH_3CN

a) $Br(CH_2)_5Br$: (1.00 mol), $(R_3Sn)_2S$ (1.00 mol), fluoride: $TBAF.3H_2O$ (1.00 mol); b) G.C. yield.

catalytic amount is needed and they can be dried by a published procedure.[37] We have already shown that 18-crown-6 can complex a large ion like cesium.[36]

Table 3 lists the fluoride and cyanide sources that were examined. Among the ammonium fluoride salts used were: tetrabutylammonium fluoride (trihydrate or anhydrous version[38]), this same compound adsorbed on silica gel[39], benzyltrimethylammonium fluoride dried using the method of Kuwajima and Nakamura[40], benzyltrimethylammonium fluoride combined with tetrabutylammonium iodide, tetraethylammonium fluoride trihydrate combined with molecular sieves 3 Å and finally 2,4,6-trimethylpyridinium hydrogen fluoride.[41] Among the metal fluoride salts examined starting with the most active ones are: cesium fluoride complexed with 18-crown-6,[36] cesium fluoride alone, cesium fluoride combined with tetrabutylammonium iodide and finally, potassium fluoride complexed with 18-crown-6.[42] The latter is usually not very effective in our conditions.

Other fluoride ion sources used were: diethylaminosulfur trifluoride(DAST)[43] and tris(dimethylamino)sulfur- (trimethylsilyl) difluoride (TASF)[44]; TASF gave moderate success. We investigated more fluorides than cyanides for the reasons already explained. Nevertheless, we found that tetrabutylammonium cyanide was also very efficient, however the salt appears to be highly hygroscopic.

The qualitative effectiveness of the fluoride and cyanide sources in the fluorodestannylation procedure of organotin sulfide follows the trend: TBAF.3H_2O > CsF.18C6> CsF > BTAF > TEAF.3H_2O/sieves > TASF > TBAF anh. > KF.18C6. This order of reactivity has been determined by comparing the qualitative reaction rates and yields of different fluorides or cyanides under similar conditions as noted in Table 3.

As a general rule, we found that tetrabutylammonium fluoride trihydrate is the most reactive fluoride but its water content limits its use only with an activated electrophile such as α-bromoketones. Benzyl bromide appears to be the limiting case where this fluoride can be used without too much formation of thiol as a side product[35]. Furthermore, the reagent is decomposed to H_2S, hence the yield of sulfide is diminished. With non activated alkyl halides such as 1-bromohexane, the anhydrous fluorinating system cesium fluoride complexed with a catalytic amount of 18-crown-6[36] is employed. The latter system was found to be general and also very effective with activated alkyl halides. Tetrabutylammonium cyanide (TBACN) was investigated mostly with activated organic halides such as benzyl bromide but its reactivity did not permit us to use it with non-

Table 3 : Fluoride Study in Fluorodestannylation

Entry	Halide[a]	Organotin	Solvent[i]	T°C	Time(hr)	F^- or CN^- (mol)[h]	Sulfide	Yield%[f]
1	$PhCOCH_2Br$	$(Bu_3Sn)_2S$[c]	B	20	1 0	CsF 18C6(xs)	$(PhCOCH_2)_2S$	98
2	$PhCOCH_2Br$	$(Bu_3Sn)_2S$[c]	B	20	<0 3	TBAF $3H_2O$(2 2)	$(PhCOCH_2)_2S$	100
3	$PhCH_2Br$	$(Bu_3Sn)_2S$[c]	A	20	0 8	TBACN(2 1)	$(PhCH_2)_2S$	41
4	$PhCH_2Br$	$(Bu_3Sn)_2S$[c]	A	20	1 0	TBAF $3H_2O$(2 1)	$(PhCH_2)_2S$	86
5	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[d]	A	40	0 5	TBAF(anh 2 2)	thiane	26[g]
6	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[d]	A	40	<0 5	TBAF $3H_2O$(2 0)	thiane	100[g]
7	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[d]	A	20	0 5	TBAF(anh 2 0)	thiane	25[g]
8	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$[d]	A	20	0 8	TBAF $3H_2O$(2 0)	thiane	100[g]
9	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[c]	A	20	1 0	KF 18C6(xs)	$(CH_3(CH_2)_5)_2S$	0[g]
10	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[b]	A	75	1 0	CsF 18C6(xs)	$(CH_3(CH_2)_5)_2S$	99
11	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[b]	A	50	5 5	TBAF $3H_2O$(2 0) on SiO_2	$(CH_3(CH_2)_5)_2S$	2-5[g]
12	$CH_3(CH_2)_5Br$	$(Ph_3Sn)_2S$[d]	A	50	21	Me_3PyrHF/Na_2CO_3	$(CH_3(CH_2)_5)_2S$	0[g]
13	$CH_3(CH_2)_5Br$	$(Ph_3Sn)_2S$[c]	A	50	5 0	TBAI/CsF(3 0)		
14	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[c]	A	20	5 5	TEAF $3H_2O$(2 0) sieves 3Å	$(CH_3(CH_2)_5)_2S$	56
15	$CH_3(CH_2)_5Br$	$(Bu_3Sn)_2S$[c]	A	20	2 5	TBAF(anh 2 0)	$(CH_3(CH_2)_5)_2S$	13[g]
16	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[b]	A	20	1 0	DAST(2 0)	$(CH_3(CH_2)_5)_2S$	0[g]
17	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[c]	A	20	24	BTAF(anh 2 0) TBAI	$(CH_3(CH_2)_5)_2S$	70[g]
18	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S$[c]	A	20	12	TASF(2 1)	$(CH_3(CH_2)_5)_2S$	40[g]

a) 1 00 mol, b) 1 00 mol, c) 1 05 mol, d) 2 00 mol, e) 4 00 mol; f) isolated yields except if noted GC yield, identified by NMR and compared to authentic material, g) GC yield, h) TBAF tetrabutylammonium fluoride, BTAF benzyltributylammonium TBACN tetrabutylammonium cyanide, TBAI tetrabutylammonium iodide, TEAF tetraethylammonium fluoride, diethylaminosulfur trifluoride, TASF tris(dimethylamino)sulfonium trimethylsilyl difluoride, i) A = acetonitrile, B = DM (5 1)

activated electrophiles, for making symmetrical sulfides (see entry 3 in Table 3). However, TBACN is useful in the reaction of tributyltin benzyl sulfide with 1-bromohexane for making an unsymmetrical sulfide (see entry 4 in Table 6).

Surprisingly, tetrabutylammonium fluoride dried accordingly to Cox, Terpinski and Lawrynowicz[38] was not very reactive in the fluorodestannylation procedure. This is contrary to the reaction of fluorodesilylation where this "naked" fluoride ion plays a major role and has a high nucleophilicity.[34] Experimentally, we found that the hydrated compound was more effective (see Table 3: entries 5 and 6 or 7 and 8) than the "anhydrous" version (it is not possible to remove all the water content[38]). It should also be noted that a "slightly wet" fluoride ion has been demonstrated to have a higher nucleophilicity in some special cases.[45] However, we feel that a different mechanism is taking place in our fluorodestannylation procedure *(vide infra)*.

4.2.6 Applications of Fluorodemetalation.

4.2.6.1 Organotin Sulfides. For organotin sulfides, each differently substituted reagent reacted with most of the usual electrophiles (alkyl halides used here) likely by an S_N2 mechanism to give the appropriate thioether in the presence of "naked" fluoride or cyanide ions. We have previously described[6] that for highly activated substrates such as an acyl chloride or their related analogs, the reaction proceeds rapidly. No real assistance was needed for such compounds, however, while working with non-activated substrates such as 1-iodopropane, we used more forcing conditions to liberate the sulfur ligand on tin (140°C, 24 h). Thus, the concept of fluoro and cyanodestannylation provides a new an useful method for these reactions under *mild and neutral conditions*.

While applying this concept to organotin sulfides, where the appropriate counterion of the sulfide anion formed *in situ* is carefully chosen, we are able to generate powerful "naked" nucleophiles as have been demonstrated.[15] Thus, we generate synthetic equivalents of cesium sulfide Cs_2S complexed with 18 crown-6 or tetrabutylammonium sulfide $(Bu_4N)_2S$.

Table 4 : Formation of Symmetrical Sulfides From Fluorodestannylation

Entry	Halide	Organotin	Solvent[i]	T°C	Time(hr)	F^- or CN^-(mol)	Sulfide	Yield%[a]
1	CH_3COCH_2Cl	$(Bu_3Sn)_2S$[f]	A	20	0.8	TBAF.$3H_2O$(1.0)	$(CH_3COCH_2)_2S$	83[e]
2	$PhCOCH_2Br$	$(Bu_3Sn)_2S$[f]	B	20	1.0	CsF(xs)	$(PhCOCH_2)_2S$	98
3	$PhCOCH_2Br$	$(Bu_3Sn)_2S$[f]	B	20	0.3	TBAF.$3H_2O$(2.2)	$(PhCOCH_2)_2S$	99
4	$PhCH_2Br$	$(Bu_3Sn)_2S$[f]	B	20	0.8	TBAF.$3H_2O$(4.6)	$(PhCH_2)_2S$	85[e]
5	$PhCH_2Br$	$(Bu_3Sn)_2S$[g]	A	20	0.3	TBAF.$3H_2O$(4.0)	$(PhCH_2)_2S$	99[b]
6	$PhCH_2Br$	$(Bu_3Sn)_2S$[h]	A	20	1.0	TBAF.$3H_2O$(2.1)	$(PhCH_2)_2S$	86[e]
7	MeCOCH(Me)Br	$(Bu_3Sn)_2S$[h]	B	20	24	TBAF.$3H_2O$(1.0)	$(MeCOCH(Me))_2S$	75[e]
8	MeCOCH(Me)Br	$(Bu_3Sn)_2S$[h]	B	20	7	TBAF.$3H_2O$(2.0)	$(MeCOCH(Me))_2S$	57[e]
9	$EtCH(Me)CH_2Br$	$(Me_3Sn)_2S$[h]	A	80	2.5	CsF.18C6(xs)	$(EtCH(Me)CH_2)_2S$	63[e]
10	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2$[h]	A	75	1.0	CsF.18C6(xs)	$(CH_3(CH_2)_5)_2S$	99
11	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$	A	20	0.8	TBAF.$3H_2O$(2.1)	thiane	99[c]
12	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S$	A	20	0.5	TBAF.$3H_2O$(2.1)[f]	thiane	99[c]
13	$(ClCH_2)_2CO$	$(Bu_3Sn)_2S$	A	20	0.5	TBAF.$3H_2O$(2.2)	cyclo $(SCH_2COCH_2)_2$	16

a) isolated yields except if noted NMR or GC yield; identified by NMR, IR, MS and compared to authentic material b) ^1H NMR yield; c) GC yield without internal standard; d) cyclic trimer; e) not optimized; f) 1.1 mol; g) 2.0 mol; h) 1.05 mol; i) A = acetonitrile; B = DMF/EtOAc (5:1); j) 2.0 mol of tetrapropylammonium iodide added.

$R_3Sn\text{-}S\text{-}SnR_3 + 2\ CsF.18C6 \text{ -----> } "Cs_2S" + 2\ R_3SnF$ (Eq. 6)

$R_3Sn\text{-}S\text{-}SnR_3 + 2\ n\text{-}Bu_4NF \text{ -----> } "(n\text{-}Bu_4N)_2S" + 2\ R_3SnF$ (Eq. 7)

The methodology can be considered as a general one as no disulfide is formed (see Table 4). The yield is usually higher than 90% when the reaction parameters are optimized. The temperature required is relatively low and the reaction time is about 1 hour for non-activated halides such as 1-bromohexane.

A rough comparison of the methods available for achieving symmetrical sulfide formation can be divided in two general groups: one that operates under anhydrous conditions and the other in non-anhydrous conditions (Table 5). Our method belongs to the first category; a comparison in this group shows that, our method is the fastest way to obtain sulfides under anhydrous conditions because of the high reactivity of the sulfur released. A general overview of both groups indicates that only the method involving hexadecyltributyl phosphonium bromide as phase transfer catalyst, competes effectively [46] In terms of yield and general purity in an anhydrous medium, only the method involving hexamethyldisilthiane (**3**)/MeLi competes but under more forcing conditions than ours.[47] The method using the phosphonium catalyst can be comparable to ours (although in aqueous medium). No other method can generate synthetic equivalent of Cs_2S under *anhydrous and neutral* conditions; the closest procedure uses insoluble $Na_2S.9H_2O$ along with Cs_2CO_3/C_6H_6-EtOH under basic conditions and relies on cation exchanges in the vicinity of sulfide ion.[48]

The commercial availability of several organotin sulfides[24] plus the special reactivity of the nucleophilic sulfur ions released make this fluorodestannylation as one of the most powerful methodologies available.[49] A recent paper by Gleiter and Rittinger confirmed this.[8a] They succeeded in the thiacyclization of a ten-membered cyclodiyne (**11**) from the dichlorodiyne (**10**) while using our procedure (see Scheme 2). The use of ammonium sulfide $(NH_4)_2S$ did not give satisfactory results.[50]

Recently, our method has also been found successful for closing a 13-membered ring[8b] whereas the classic procedures such as sodium sulfide ($Na_2S.9H_2O$) or sodium hydrosulfide ($NaSH.xH_2O$) with a base in ethanol at reflux or hydrogen sulfide trapped in triethylamine failed. As shown in Scheme 4, the diacetylenic diiodo compound (**12**) reacted with bis(tributyltin)sulfide (**2**) in the presence of cesium fluoride with 18-crown-6 at 60°C

Table 5 : Generation of Sulfur Anions and Their Reactivities

AQUEOUS MEDIUM

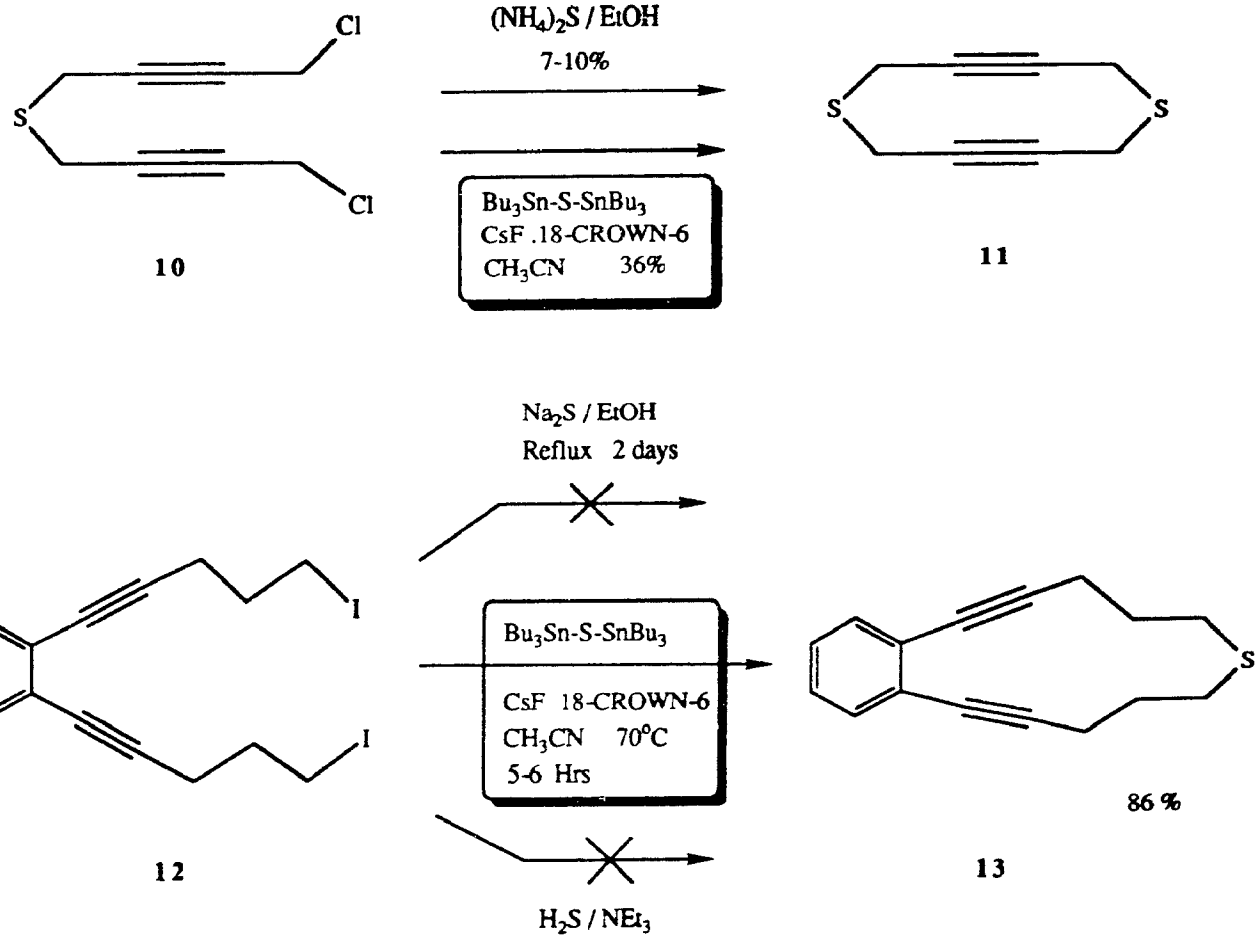
Reagents	Solvent	T°C	Time(h)	Base	Yield(%)[a]	Ref.
$Na_2S.9H_2O$	EtOH	20	20	neutral	89	47[a]
$Na_2S.9H_2O$[b]	H_2O	70	0.3	neutral	91	47[a]
R-SH	H_2O/org. solv.	20	20	NaOH	>70	47[b]
$CH_3C=SR(NH_2)^+$[c]	$CHCl_3$	20	7-10	KOH(s)	<70	47[c]

ANHYDROUS MEDIUM

Reagents	Solvent	T°C	Time(h)	Base	Yield(%)[a]	Ref.
S_8	THF	20	5	$LiEt_3BH$	71	47[d]
$(Me_3Si)_2S$	THF	65	8	MeLi	>95	47[e]
R-OH/R-SH/ $Ph_3PN(CH_3)Ph^+ I^-$	DMF	20	>8	NaH	52-90	47[f]
R_3Sn-S-SnR_3/F^-	CH_3CN/DMF	20-65	<1.0	neutral	>95	47[g]
Ph_3Ge-S-$GePh_3/F^-$	THF/DMF	55	10	neutral	80	--
Ph_3Pb-S-$PbPh_3/F^-$	THF/DMF	65	5	neutral	81[d]	--

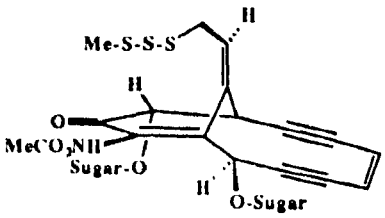
a) Average yields, b) catalytic addition of hexadecyl tributyl phosphonium bromide, c) catalytic amount of tribenzylmethyl ammonium chloride, d) yield from benzyl bromide

SCHEME 2

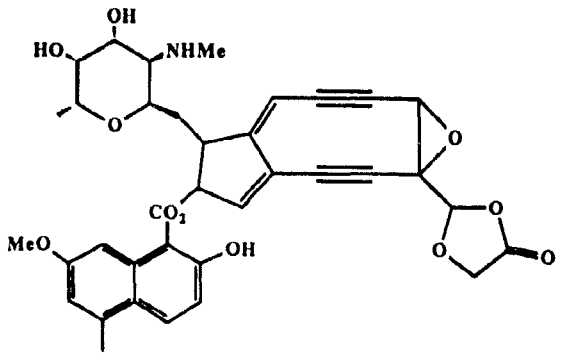

Cl
S
Cl
10
(NH4)2S / EtOH
7-10%
Bu3Sn-S-SnBu3
CsF .18-CROWN-6
CH3CN 36%
S
S
11
Na2S / EtOH
Reflux 2 days
I
I
12
Bu3Sn-S-SnBu3
CsF 18-CROWN-6
CH3CN 70°C
5-6 Hrs
S
86 %
13
H2S / NEt3

for achieving the ring closure to (**13**) in 86% yield. In summary, these examples demonstrate unambiguously the special reactivity of the sulfur ion released by this methodology.

One of the reasons for the failure of the classical procedures is that solutions containing Na_2S or HS^- cannot be made easily with organic solvents due to their low solubility, hence the simultaneous slow addition of both Na_2S (or SH^-) and the diiodo substrate (**12**), as required for intramolecular reaction under pseudo high dilution is more difficult. Secondly, even if sodium sulfide is used under high dilution techniques, its low reactivity associated with a lack of solubility in organic solvent, favors a build up of the concentration of both unreacted sulfide ion and the substrate directly encouraging polymerization. The cyclizations are helped by the "cesium effect" (a kinetic effect from "loose" ions pairing of the anionic nucleophile with the cation) reported by Kellogg in macrocyclization.[51] Also, the mildness of this reaction avoids most secondary products with these acetylenic compounds Although a similar cyclization, but with much less degree of freedom in the starting material, was successful with Na_2S for the synthesis of the bicyclic core of neocarzinostatin chromophore A, Wender and co-workers clearly mentioned the instability of such acetylenic derivatives.[11] As shown in Scheme 2a, we feel that our methodology should find a major use in the key ring closure reaction leading to the strained diacetylenic ring core of esperamicin A and neocarzinostatin chromophore A after the appropriate sulfur extrusion reaction.

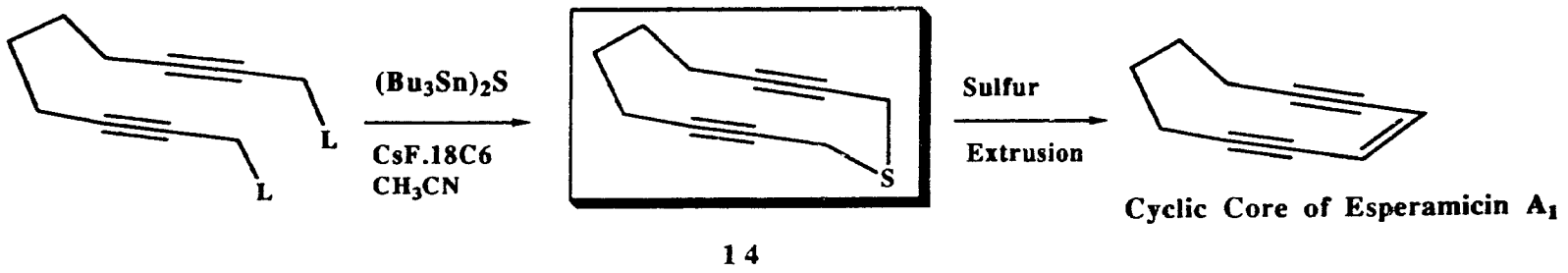


Esperamicin A_1



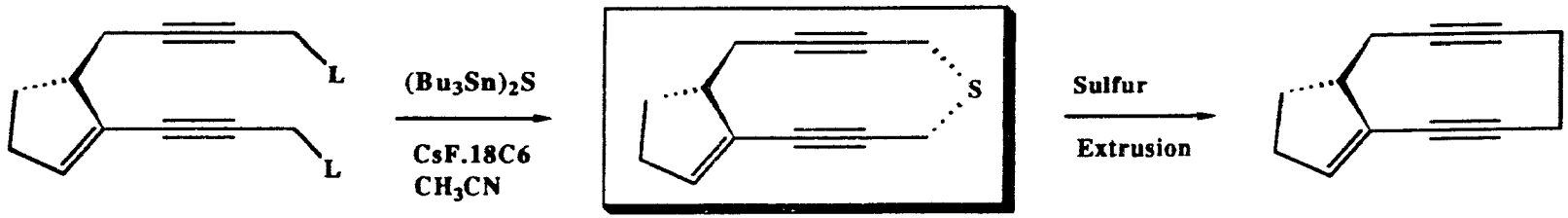
Neocarzinostatin Chromophore A

Scheme 2a



14

Cyclic Core of Esperamicin A_1



15

L= Leaving Group

Bicyclic Core of Neocarzinostatin Chromophore A

Nicolaou[11] and co-workers have already demonstrated the feasibility of the route involving (**14**) but no details were given for its preparation. In a similar way, Wender and co-workers[11] essentially showed the possibility of using an intermediate similar to (**15**).

A substrate study with simple organic halides indicates that fluorodestannylation of organotin sulfides can be considered to be sufficiently general by an examination of the number of different substrates reported in Table 5. The procedure is compatible with hydroxyl[52], nitrile, amide and α-ketone groups. From highly activated α-haloketones to benzylic and alkyl halides, the methods developed work very well, rapidly giving high yields of thioethers and related derivatives under neutral and anhydrous conditions.

Unsymmetrical sulfide formation can also be grouped into two divisions: the anhydrous and the aqueous. Our method gives yields comparable to the classic way of deprotonation and alkylation of thiols in a basic aqueous mixture or the modern method involving cesium carbonate in a polar aprotic solvent with DMF.[51] The thioiminium 53, and aminophosphonium salts[54] as well as the amide acetal procedures[55] are less versatile and the yield usually varies with the substrate used (see Table 5).

Most of the usual methods involve a base in some stage in the preparation of unsymmetrical sulfides. A strong feature of our fluorodestannylation procedure favors the *neutrality of the conditions*, both in the coupling step and in the preparation of the triorganotin mercaptide (see Table 6), only a few reagents have been developed for transferring mercaptides in a neutral medium. One of them makes the use of fluoride ion with a recently developed silicon reagent.[56] Another showed a S_NAr reaction on a fluorinated phenyl ring.[57] A disadvantage involves the numerous steps required to attain these silicon-sulfur reagents compared to the method presented here.

We can conclude that the fluoro/cyanodestannylation procedure represents a *mild, neutral, anhydrous and highly reactive way* to obtain unsymmetrical sulfides without the need of manipulating odorous material[28]. Furthermore, the tin substituent on sulfur can be viewed as a protective group. Using fluoride ion in wet solvent for the deprotection affords thiols after 24 h at room temperature.[35]

Table 6 : Formation of Unsymmetrical Sulfides from Destannylation

Entry	Halide	Organotin[e]	Solvent[d]	T°C	Time(hr)	F^- or CN^- (mol)	Sulfide	Yield%[a]
1	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	2	CsF.18C6(xs)	$PhCH_2S(CH_2)_5CH_3$	82[b]
2	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	2	CsF.18C6(xs)	$PhCH_2S(CH_2)_5CH_3$	76
3	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	12	CsF(xs)	$PhCH_2S(CH_2)_5CH_3$	55
4	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	20	2.3	TBACN(2 2)	$PhCH_2S(CH_2)_5CH_3$	84[c]

a) isolated yields except if noted as NMR or GC yield. Identified by NMR, IR, MS and compared to authentic material; b) ^1H NMR yield, c) GC yield without internal standard; d) A = acetonitrile; e) 1.05 mol.

Table 7 : Formation of Sulfides From Fluorodegermanylation and Fluorodeplumbylation

Entry	Halide	Organometal	Solvent[a]	T°C	Time(hr)	Fluoride(mol)	Sulfide	Yield%[b]
1	$PhCH_2Br$	$(Ph_3Pb)_2S$[c]	D	20	9.5	CsF(4.6)	$(PhCH_2)_2S$	67
2	$PhCH_2Br$	$(Ph_3Pb)_2S$	D	65	5 0	CsF(5 2)	$(PhCH_2)_2S$	81
3	$PhCOCH_2Br$	$(Ph_3Pb)_2S$	D	20	3.0	CsF(6.5)	$(PhCOCH_2)_2S$	95
4	$CH_3(CH_2)_5Br$	$(Ph_3Pb)_2S$	D	65	8.0	CsF(7.5)	$(CH_3(CH_2)_5)_2S$	11
5	$CH_3(CH_2)_5Br$	$(Ph_3Ge)_2S$	D	60	10.0	CsF(5 8)	$(CH_3(CH_2)_5)_2S$	80

a) D = DMF/THF 1·4 v/v; b) isolated yield; c) 1.05 mol-eq used.

4.2.6.2 Organogermanium and Organolead Sulfides.

As shown in Table 7, an investigation with bis(triphenyllead)sulfide (**5**) in the presence of cesium fluoride and activated organic halides gave excellent yields of thioethers. For instance, benzyl bromide or α-bromo acetophenone (entries 2,3) afforded 81 and 95% yield respectively. However, unactivated organic halides such as 1-bromohexane produced low yield of thioethers and gave mainly triphenyllead alkyl sulfides (entry 4). No organic disulfides were detected in any cases. Bis(triphenyllead) sulfide (**5**) represents a useful and soluble synthetic equivalent of sulfide ion (S^{2-}) and one of the rare organolead reagents. Thus, this is the first reaction of fluorodeplumbylation reported. Bis(triphenylgermanium) sulfide (**4**) was as successful as the tin derivative for making thioethers (Table 7). Both bis(triphenyllead)sulfide (**5**) and bis(triphenylgermanium)sulfide (**4**) are odorless and non-hygroscopic crystalline solids. This is in sharp contrast to the odorous and highly hygroscopic $Na_2S.9H_2O$.

4.2.7 Comparison of the Reactivities of Organic Silicon, Germanium, Tin and Lead Sulfides in Fluorodemetalation.

Hexamethyldisilthiane or bis(trimethylsilyl)sulfide (**3**) is the only sulfur transfer reagent that gives disulfide as a side-product. Germanium and tin analogs react similarly with organic halides to afford thioethers in excellent yield. The reactivity of the Ge-S bond is similar to Sn-S bond in fluorodemetalation. Germanium resembles tin rather than silicon in its behavior. Organolead (**5**) gives mainly an intermediate of lead alkyl sulfide with unactivated halides but generates thioethers with the activated ones. The Pb-S bond is less reactive in the fluorodemetalation.

Based on product formation, it appears that the Si-S bond is very labile under these conditions. For achieving the formation of organic disulfides, stable transient species such as (**16**) appear to be generated in some way. The question of the existence of free sulfide ion S^{2-} derived from (**3**) in the mixture, being responsible for this reaction, has not been ruled out. Also, S_N2 displacement with sulfide ion S^{2-} on the sulfur atom of the starting material could be possible.

$$S^{2-} + R_3Si\text{-}S\text{-}SiR_3 \text{ -----> } R_3Si\text{-}S\text{-}S^- + \text{"}R_3SiS^-\text{"} \qquad \text{(Eq. 8)}$$

3

$$R_3Si\text{-}S^- + R_3Si\text{-}S\text{-}SiR_3 \text{ -----> } R_3Si\text{-}S\text{-}S\text{-}SiR_3 + \text{"}R_3Si^-\text{"} \qquad \text{(Eq. 9)}$$

$Me_3Si\text{-}S\text{-}S^-$

16

The other sulfur metal bonds do not show this lability. It appears that the Si-S bond is more reactive than other metal sulfur bonds in the group 14. In terms of stability, disilthiane (3) decomposes rapidly in air, liberating H_2S. Other organometallics did not show this tendency. However, we noted that the pale yellow lead reagent (6) changes its color slowly to a dark orange with time. The most important thermodynamic driving force of these fluorodemetalations is certainly the metal fluoride bond energy formed, a factor in designing this general concept of flurorodemetalation.[16]

The high reactivity of the sulfur species liberated came from the "cesium effect" first described by Kellogg.[51] In generating the synthetic equivalent of cesium sulfide (Cs_2S), the "loose ion pairing" of sulfur anions combined with the help of a complexation of the cesium cations with crown-ethers provides one of the most powerful nucleophilic sulfur anions known. However, the metal (or metalloid) effect is another parameter to consider. The different complexing ability of the metal centers with the free sulfur anion released is probably responsible for the different activity while varying the metal.

$$R_3M\text{-}S\text{-}MR_3 + CsF \text{ ------> } \text{"}Cs_2S\text{".}R_3MF \quad (M = Si,Ge,Sn,Pb) \qquad \text{(Eq. 10)}$$

4.2.8 Spectroscopic Evidence for Pentavalent Intermediates in Reactions of Substitution at Tin.

For all bis(triorganotin)sulfides listed in Figure 1, we observed that a labile pentacoordinated complex was formed at 20°C with TBAF.$3H_2O$ or TBAF "anhydrous" in CD_2Cl_2. A rapid fluorine nucleus exchange, relative to the NMR time scale, provoked a

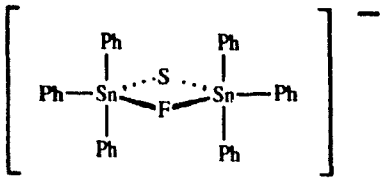
large broadening of the original signals and an upfield shift of a few ppm in the ^{119}Sn NMR spectra. Tetrabutylammonium cyanide produced the same effect on (**2**) but the complexation seemed to be weaker based on the signal broadening and the change in the chemical shift. A strong evolution of H_2S took place in most cases when using TBAF.$3H_2O$. The organotin sulfides were decomposed in the presence of this fluoride for giving some pentacoordinated anionic tin complexes (Eq. 11). Using low temperature ^{119}Sn NMR and ^{19}F, we observed trans and cis tetrabutylammonium difluorotrialkylstannate [n-Bu_4N]+ [R_3SnF_2]- (R= alkyl).[58] However, (**7**) produced only trans complexes. Low temperature ^{13}C NMR with (**1**) also showed an extra signal for the anionic complex. We never observed hexacoordination at higher field in the ^{119}Sn NMR spectra.

R_3Sn-S-SnR_3 + 2 TBAF.$3H_2O$ ------> [n-Bu_4N]+ [R_3SnF_2]$^-$ + H_2S (Eq. 11)

Obviously, the water content in our reactions destroys the reagent itself and explain our poor yields with unactivated halides when employing TBAF.$3H_2O$. However, the most interesting results came from a scanning of the ^{119}Sn spectral window from 400 ppm to -550 ppm. It demonstrated a clear triplet at -339 ppm (^1J [^{119}Sn-^{19}F]= 1958 Hz) and a doublet at -288 ppm (see Fig. 2) when using a ratio of 4:1 "dried" TBAF[38] /organotin (mol/mol) at 20°C in CD_2Cl_2. The first triplet signal corresponds to difluorotriphenylstannate anion (**17**). This was also confirmed independently with the synthesis of the same anion (**17**) from triphenyltin fluoride with TBAF.$3H_2O$ in a 1:1 ratio.[58]

The second doublet signal has the chemical shift in the range of pentavalent tin species from the ^{119}Sn NMR. We assigned these data to complexes (**18a**) and (**18b**). We ruled out doubly charged complexes because they should have their ^{119}Sn resonance frequencies at much higher field due to a large increase and spread of electron density through the whole molecule and especially on the ^{119}Sn nucleus. Furthermore, we are unaware of reports of doubly charged pentavalent triorganotin complexes. The coupling constant ^1J [^{119}Sn-^{19}F] is 1730 Hz. This value is in the range of our observed ^1J [^{119}Sn-^{19}F] couplings (1958 Hz) for the difluorotriarylstannate anion[58] (**17**); the lower value is clearly indicative of a different species. From an initial observation (^{119}Sn NMR alone) structure (**19**) appears valid however, it is inconsistent with the ^{19}F NMR of Figure 3 *(vide infra)*.

18a 18b



19

A ^{19}F NMR study at -80°C in CD_2Cl_2 also confirmed the presence of difluorotriphenylstannate anion (**17**) plus the presence of complexes (**18a** or **18b**). As shown in Figure 3, the signal at -100.7 ppm corresponds to difluorotriphenylstannate anion (**17**) with its ^{119}Sn and ^{117}Sn satellites at -97.2 ppm and -104.1 ppm. The broad signal at -79.9 ppm indicated an organotin-fluoride complex as judged from the broad ^{119}Sn and ^{117}Sn satellites centered at -77.01 and -83.00 ppm. We did not clearly observe other pentavalent intermediates from (**1**) and (**2**) with "dried" TBAF due to the lower stability of such anionic complexes having alkyl groups.

Assuming a doublet signal coming from (**18a** or **18b**) and centered at -79.9 ppm from both tin satellites, a rough evaluation of ^1J [^{119}Sn-^{19}F] and ^1J [^{117}Sn-^{19}F] gives a value of 1680 Hz (from the peak center of both signals). A previous evaluation of ^1J [^{119}Sn-^{19}F] established a slightly higher coupling constant than ^1J [^{117}Sn-^{19}F] (~ 87 Hz).[58] Adding a correction of ~ 44 Hz (87 Hz/2) to the centered ^1J [Sn-F] found, gives ^1J [^{119}Sn-^{19}F] = 1722 Hz. This value is close to 1730 Hz found with ^{119}Sn NMR. We can conclude that we observed the same species as with ^{119}Sn NMR (See Fig. 2). A symmetrically bridged structure (**19**), would be expected to give a triplet signal and a ^1J [Sn-F] coupling constant much different than a normal value of ~1958 Hz for ^1J [^{119}Sn-^{19}F] but no data are available for such exotic coupling constants. Finally, as the signal is broad even at -80°C, we concluded that a slow exchange between (**18a**) and (**18b**) took place.

Figure 2

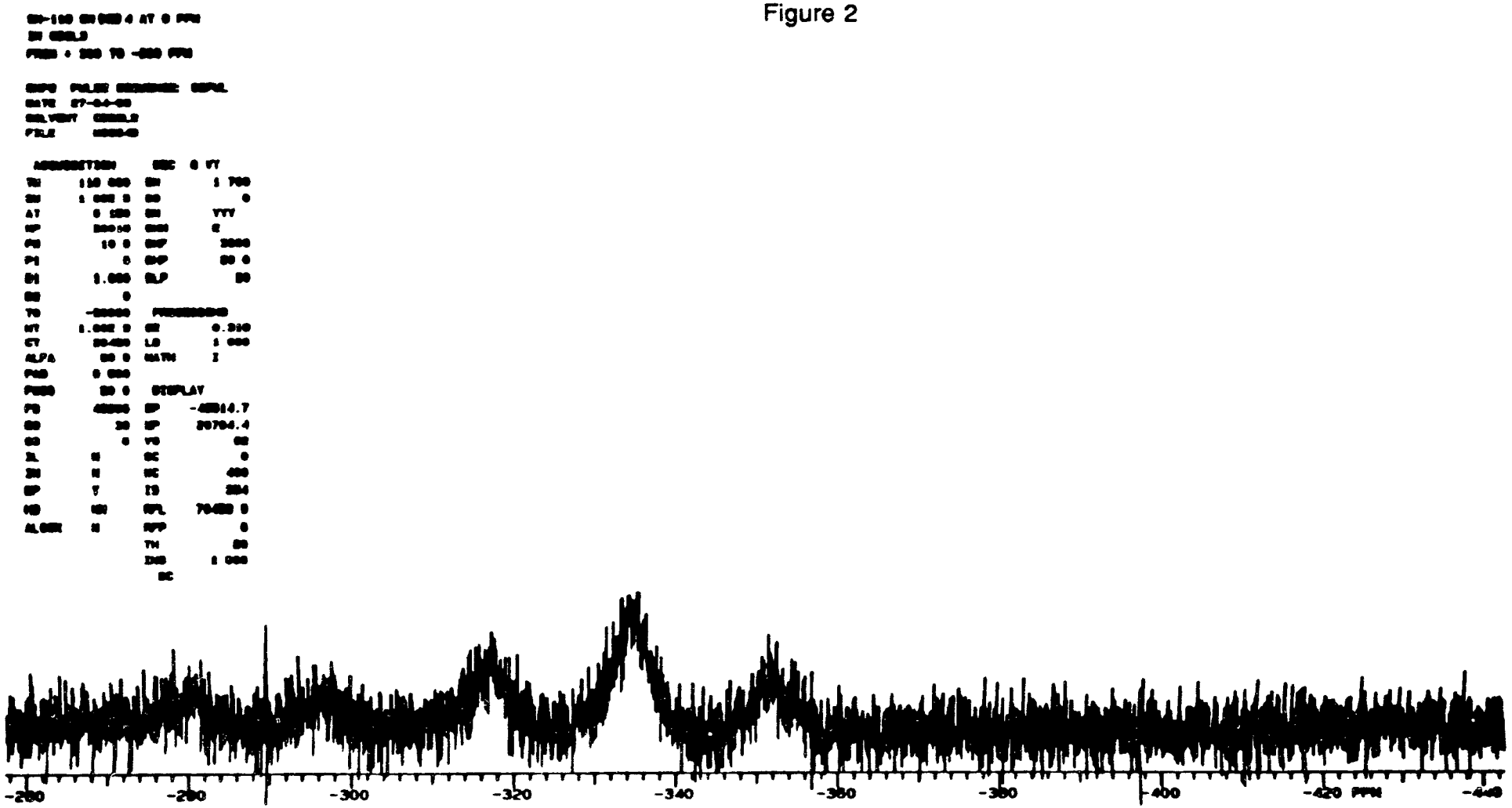


Fig.2: ^{119}Sn NMR spectra (200 MHz) of $(Ph_3Sn)_2S$ + TBAF "anhydrous" in a 1:4 ratio at 20°C in CD_2Cl_2 showing the triphenyltin difluoride anion along with the proposed complexes (19) or (20) having a sulfur ligand.

FIGURE 3

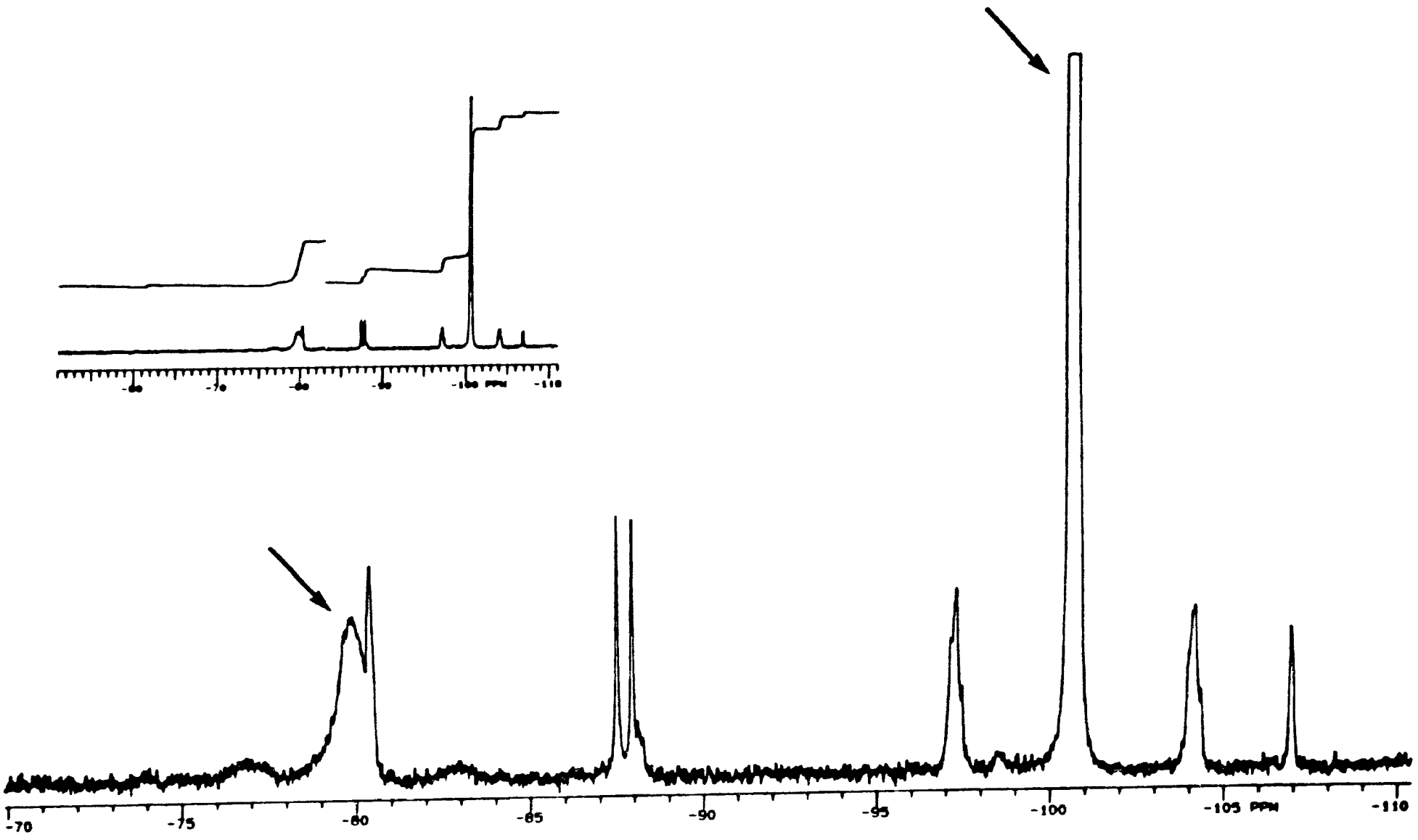


Fig.3: ^{19}F NMR spectra (300 MHz) of $(Ph_3Sn)_2S$ + TBAF "anhydrous" in 1.3/1.0 ratio at -80°C in CD_2Cl_2 showing the triphenyltin difluoride anion (right arrow) and the proposed complexes (19) or (20) with its tin satellites (left arrow). Other signals not mentioned in the text are impurities.

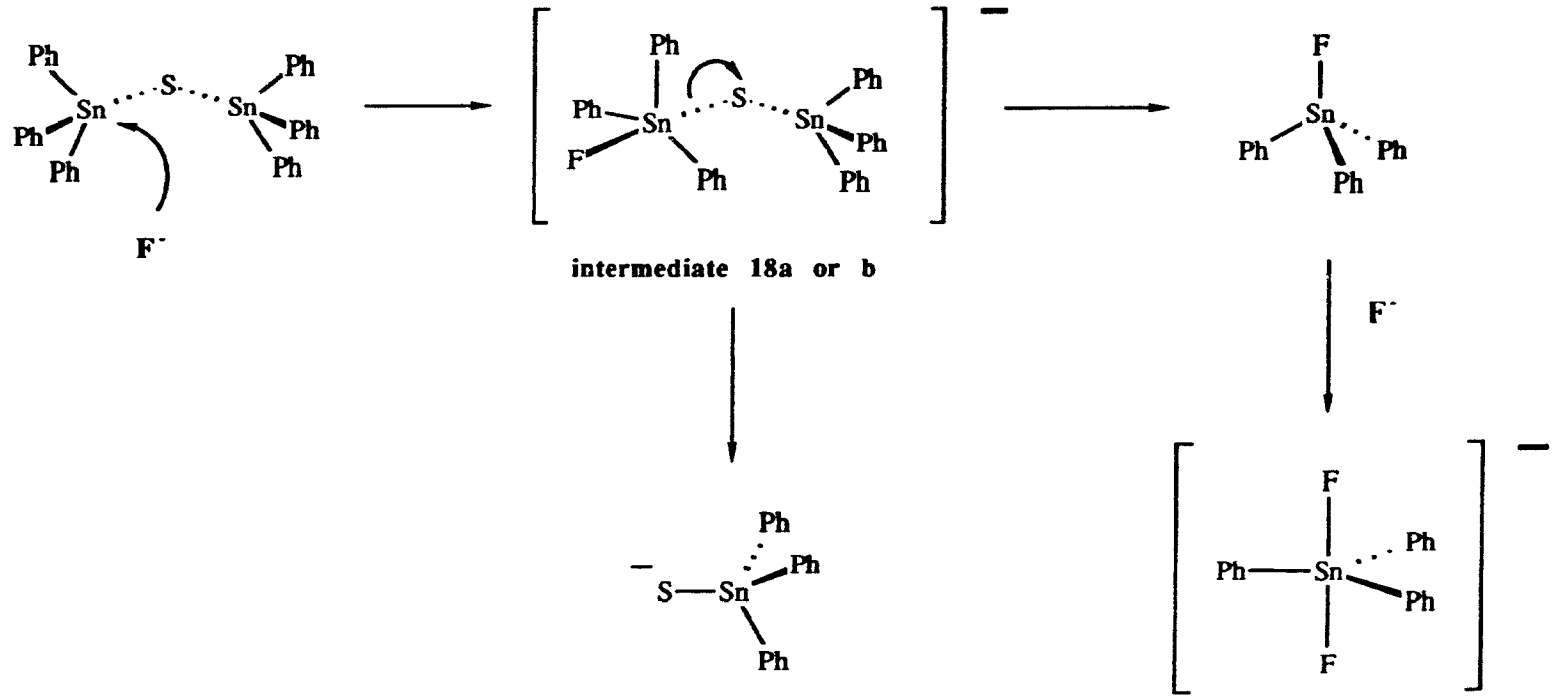
In summary, the combined results of tin and fluorine NMR studies indicate that there is a species in addition to $Ph_3SnF_2^-$. This species shows coupling between one fluorine and one tin atom with a coupling constant of about 1730 Hz. An equilibrium between structures (**18a**) and (**18b**) would appear to best satisfy the above data. From the publication of Holmes, Sau and Carpino, it is well described that the triphenyltin moiety gives stable and isolable crystalline pentacoordinated tin complexes at 20°C.[58] We took advantage of this higher complex stability in our study. *We thus present spectroscopic evidence that substitution at tin proceeds through pentacoordinated tin species.* This substitution is best represented in Scheme 3. A sulfur ligand on tin is replaced by a fluorine ligand through a pentacoordinated intermediate. This latter strongly activates the release of the highly nucleophilic sulfur anion in our fluorodestannylation. These results confirmed the model of substitution at tin.[25] To date, this model was fully described in some racemization processes at tin where kinetic evidence stated or assumed the existence of a pentavalent species as intermediate; however, to the best of our knowledge, only one spectroscopic evidence was reported.[25] Some intramolecular complexations on tin with a bidentate ligand were also used to model substitution derived from an external nucleophile.[59] As an extension of our work, it might also reinforce the model for the substitution at silicon where the racemization process has been well studied.[60]

4.2.9 Toward the Mechanism of Fluorodemetalation.

We first used organotin sulfides in order to have some working hypothesis about the possible mechanisms involved. Only a few mechanistic studies have been described with triaralkyltin mercaptides and organic halides. The work of Ohya and Kozuka in 1978,[61] proposed a sulfonium salt intermediate to explain the formation of several sulfides in non-polar and non-coordinating solvent. We determined that the most important parameter in this kind of reaction in the absence of fluoride or cyanide ion is the solvent effect[6]; this seems to be in agreement with the sulfonium salt mechanism proposed.

However, the fluoride and cyanide effects became crucial when these ions were incorporated in the mixture, followed by the usual solvent effect. We determined by ^{119}Sn NMR that bis(triphenyltin) sulfide (**7**) reacted with TBAF (anh.) to form a pentacoordinated tin complex corresponding to difluorotriphenylstannate anion [$Ph_3SnF_2^-$] (**17**) in CD_2Cl_2 plus some nucleophilic sulfur species (**18a** or **18b**). In an anhydrous medium, the liberation of hydrogen sulfide should be minimized and we feel that a slightly different complexation should take place in polar coordinating solvents. To explain the strong solvent effects in

Scheme 3


Ph
Sn
S
Sn
Ph
Ph
Ph
Ph
Ph
F⁻
Ph
Ph
Sn
S
Sn
Ph
F
Ph
Ph
Ph
intermediate 18a or b
F
Sn
Ph
Ph
Ph
F⁻
Ph
S
Sn
Ph
Ph
F
Ph
Ph
Sn
Ph
F

these reactions (with DMF, CH_3CN), we propose the formation of hexacoordinated complexes in low concentration having as ligands a solvent molecule (DMF, CH_3CN), a fluorine and a sulfur atom. We think that other substituents on tin (like butyl and methyl) should act in a similar way.

A first possible mechanism derived from our complexation study (CD_2Cl_2) with fluoride ion is shown in Scheme 4. We describe most of the pentavalent triorganotin complexes having trans ligands. Although some cis complexes could be present in solution, it is well known that trans triorganotin complexes are more stable and this stereochemistry usually predominates for triaralkyltin complexes.[62] For hexacoordination, the major stereochemistry is difficult to predict. Such penta or hexacoordination with fluoride in order to enhance the nucleophilicity of a ligand has precedents in the silicon literature: for an example among many others, a kinetic study with trimethylsilane and TBAF supported the existence of a hexacoordinated silicon atom in a reaction where a hydride was transferred to a carbonylated compound.[63]

Our preliminary observations focussed on a possible stepwise release of the sulfur atom from tin to halides. We observed the formation of an intermediate triorganotin alkyl sulfide on TLC using 1-bromohexane and bis(tributyltin) sulfide (**2**). With the same organic halide, we were able to trap this intermediate by adding a small amount of water to the mixture. We thus obtained the corresponding 1-hexanethiol in 59% yield along with some thioether.[35] Initially, it appeared that the fluorodestannylation reaction proceeded in a stepwise mechanism involving one fast S_N2 type reaction giving the intermediate tributyltin hexyl sulfide (**20**) followed by a slow step involving a second nucleophilic substitution with the free hexylthiolate anion (see Scheme 4).

Using benzyl bromide as halide, we obtained different results. We followed the reaction of bis(tributyltin)sulfide (**2**) (1.1 mol-eq) with benzyl bromide (2.0 mol-eq) and TBAF.$3H_2O$ (1.4 mol-eq) at -20°C by ^1H NMR with slow increase of the temperature to 20°C (CD_3CN as solvent). The CH_2 signal of benzyl bromide at 4.63 ppm decreased gradually as a new signal increased at 3.63 ppm corresponding to the CH_2 of dibenzyl sulfide. We noted a small peak at 3.75 ppm remaining during the whole reaction. This peak corresponded exactly to tributyltin benzyl sulfide (**9**) prepared independently.[28] Similarly, a ^{119}Sn NMR study also confirmed the formation of this product (see Fig. 4);[9] it should be an intermediate existing at low concentration during the reaction. It should be noted that this reaction was carried out under such conditions to favor a high concentration of the possible

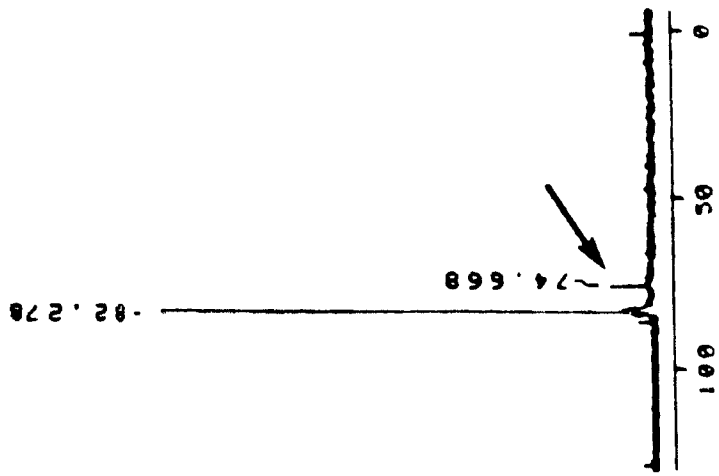
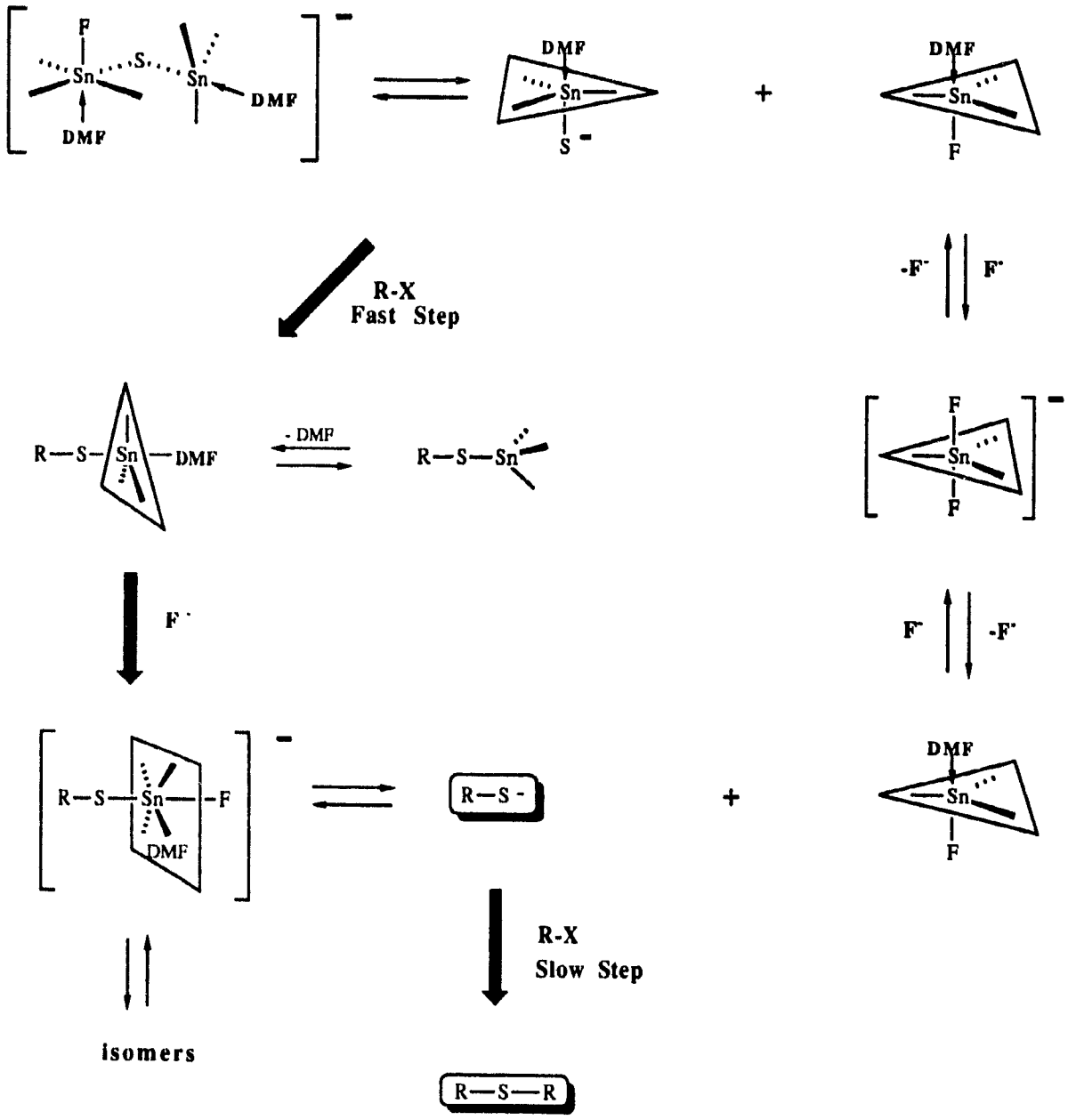


Fig. 4. ^{119}Sn NMR spectra (200 MHz) of possible intermediate $PhCH_2SnBu_3$.

SCHEME 4


F
Sn
S
Sn
DMF
DMF
DMF
Sn
S
DMF
Sn
F
R-X
Fast Step
-F
F
R—S—Sn—DMF
- DMF
R—S—Sn
F
Sn
F
F
-F
R—S—Sn—F
DMF
R—S -
DMF
Sn
F
R-X
Slow Step
isomers
R—S—R

intermediate; i.e. TBAF.$3H_2O$ was used in 1.4 mol-eq instead of 2.0 mol-eq. With benzyl bromide, the second nucleophilic substitution seemed to be the slowest step because of this observed tin intermediate.

Considering these intermediates, it is obvious that the sulfur atom is not liberated in the form of a sulfide "S^{2-}" ion. This form of sulfur anion release is characteristic of the methods developed by Steliou (hexamethyldisilthiane (**3**) and methyllithium)[4] and Gladysz[32] ($LiBHEt_3$ and elemental sulfur) in anhydrous media. Thus, fluorodestannylation appears to be a new method for releasing mercaptides. There remains a tin substituent bound to the sulfur atom until the last step of the reaction, thus the transformation is stepwise. Whatever the exact sulfur nucleophile, with organic halides such as 1-bromohexane, we propose the following general mechanism in an anhydrous medium, Scheme 4.

To explain the relative rates of the two nucleophilic substitutions, we thought that the rate of the first alkylation with the sulfur anion should be favored by the proximity of the tin atom. It should increase the electron density on sulfur, hence facilitate the S_N2 reaction (while lowering the energy of the transition state with a polarizability and delocalization of the electronic cloud through the tin atom). To our knowledge, the metal proximity effect of anions in S_N2 reactions has not been clearly delineated in the literature. The second step, is likely slower because of the lack of this metal proximity effect.

The choice of the counter-ion was critical in our work for achieving a powerful and fast S_N2 reaction. The explanations for the different reactivities observed with the different fluoride sources come from the cations associated with the fluorides. These cations become the counter-ions of sulfur anions in some step in the mechanism. It is well known that these ion pairs directly affect the alkylation rate. For example, tetrabutylammonium cation makes the sulfur anion more "loose" or free than the cesium cation. As proof of this hypothesis, the effect of the complexation of 18-crown-6 with cesium fluoride provoked an initial rate enhancement of five for the formation of benzyl-*n*-hexyl sulfide while reacting tributyltin benzyl sulfide (**9**), 1-bromohexane, cesium fluoride and 18-crown-6 in CD_3CN.[36]

A second but less probable mechanism from that depicted in Scheme 4 would be a solvent-assisted ionization of the organotin sulfide prior to attack by fluoride or cyanide ion. This ionization would generate nucleophilic species like $R_3Sn\text{-}S^-$ where R = triaralkyl group, although we do not have any rigorous experimental proof of it. The strong solvent effects

reported in our previous work (especially with polar coordinating solvents) is suggestive of this process.[6] Among the strongest points in favor of this ionization is the observation that anhydrous TBAF was not as effective as the hydrated form for synthesizing thiane (cf Table 3, entries 5 to 8). From the literature, it has been suggested that triaralkyltin halides can produce cationic diaquo-triorganotin ion in water.[64] One of these studies involved trimethyltin chloride in water and its corresponding diaquo triorganotin cation. Also, some ionization occurred with the butyl group as a substituent.[65] The weakness in the ionization approach is the absence of active pentacoordinated tin incorporating a sulfur ligand as observed with (7) using ^{119}Sn and ^{19}F NMR. We thus prefer the mechanism involving anionic fluorothiostannate complexes (**18a** and **18b**) as shown in Scheme 4.

As an extension of the proposals above, bis(triphenylgermanium)sulfide (**4**) reacted in a stepwise manner as with organotin sulfides. While reacting 1-bromohexane with this reagent and cesium fluoride, we followed the reaction by TLC using 5% EtOAc/95% *n*-hexane as eluent. Bis(triphenylgermanium)sulfide (**4**) (R_f= 0.40) disappeared slowly in favor of a new spot slightly less polar (Rf= 0.65). This spot also disappeared and a new, even less polar spot (Rf= 0.80) was formed corresponding to di-*n*-hexyl sulfide. We believe that the intermediate spot corresponds to triphenylgermanium-*n*-hexyl sulfide but we did not characterize it.

With bis(triphenyllead)sulfide (**5**), we essentially obtained the same chromatographic results as with bis(triphenylgermanium)sulfide (**4**). The intermediate spot corresponding to triphenyllead-*n*-hexyl sulfide (**6**) has been isolated and characterized by ^1H NMR; it decomposed slowly at room temperature. The fluorodeplumbylation also proceeded in a stepwise manner by appropriate TLC-detected spots.

The rate of the first S_N2 attack as proposed in the mechanism seems to be fast for silicon and tin but slightly slower with germanium and lead (as observed by TLC). However, the second alkylation offered several differences between the rates: for silicon and tin, it is fast; slower for germanium and very slow for lead. The tendency of lead to easily complex the free thiolate ligands prevent them from further alkylation. As triorganogermanium fluorides do not generally form polymeric pentacoordinated chains like triorganotin fluorides, it is a better Lewis acid for the thiolate anions released; this might explain the slower rates of alkylation in the last step in the fluorodegermanylation. From our results, we can make a generalization: we always observed a fast nucleophilic substitution in the first step of the fluorodemetalation reactions but a slower substitution in the second one.

We propose that a metal or a metalloid atom of group 14 directly attached to an anion R_3M-Nu⁻ will increase the nucleophilicity of the latter if the organic groups R on the metal do not sterically interfere for inhibiting the reactivity of this anion (M= Si,Ge,Sn,Pb and R= aralkyl group). Work on the trimethylsilanolate anion Me_3Si-O⁻ is also in full agreement with this statement.[66]

4.3 Conclusion

We reported three novel general methodologies: fluorodestannylation, fluorodegermanylation and fluorodeplumbylation. We presented the first reactions of fluorodemetalation of germanium and lead. Following these successful preliminary results with sulfur it could be envisaged that totally new fields of reactions involving fluorodeplumbylation could be opened where fluoride could induce the cleavage of Pb-O, Pb-Se, Pb-Te, Pb-C, Pb-N bonds for releasing the corresponding ligands. Lead could thus act as a new "group 16 transfer agent" in a similar way as we showed with organotins.[15] A new field of reactions can also be pictured with fluorodegermanylation. For the first time, a thorough study of fluorodestannylation was presented along with direct comparisons with three other fluorodemetalations. We reported the study of eight different new sulfur transfer agents that reacted in mild, neutral and anhydrous conditions. Some of them released one of the most active sulfur anion known to date. These particular reactivities have been well-defined in interesting thiamacrocyclization reactions.

As a second contribution to the understanding of the fluorodemetalation mechanism implied here, we have shown a spectroscopic evidence for a pentacoordinated intermediate involved in the substitution at tin from low temperature ^{19}F and ^{119}Sn NMR spectroscopy. It directly confirmed the substitution model at tin and lead to a reinforcement of the same model on silicon. A mechanistic proposal has been demonstrated for such fluorodemetalations based on some results from organotin chemistry.

We proposed that the metal proximity effect on a charged anion will increase the nucleophilicity of the latter in the absence of major steric hindrance coming from the organic ligands on the metal.

Finally, the global concept of flurorodemetalation, relying on the particular energetic metal-fluorine bond energies and the poor nucleophilicity of fluoride ion, might encourage other kinds of nucleophilic reactions with metals not presented here.

4.4 Experimental Part

Chemicals: Bis(tributyltin)sulfide (**2**) was purchased from Pfaltz and Bauer or prepared as previously described.[27] All organotin chlorides, triphenylgermanium chloride, trimethylgermanium bromide, tributyltin hydride, tetrabutylammonium cyanide, tetrabutylammonium fluoride trihydrate, 18-crown-6, DAST, TASF and sodium sulfide nonahydrate were purchased from Aldrich Chemical Co. and used without further purification. Triphenyllead acetate, dibutyltin sulfide (**7**) and tetramethylgermanium were bought from Morton Thiokol (Alfa Products). Bis(trimethylsilyl)sulfide (**3**) was purchased from Petrarch Systems. Most organic halides or thiols were used as received from Aldrich excepted benzyl bromide, which was distilled prior to use. Cesium fluoride was treated (110°C) in a pistol dryer for 2 days at 5 mm Hg. Acetonitrile (reagent grade) was refluxed several days over calcium hydride and distilled prior to use. Dimethylformamide (reagent grade) was distilled over calcium hydride and kept over molecular sieves 3Å (dried in an oven at 180°C for several weeks) under a nitrogen atmosphere. When some water was involved in the medium, spectroscopic grade DMF and CH_3CN were used without purification.

Instrumentation: ^{119}Sn, ^{1}H, ^{19}F, ^{73}Ge and ^{13}C NMR spectra were recorded on a Varian XL-200 (4.75 teslas) or XL-300 (7.05 teslas) spectrometer. The NMR shifts are reported in ppm in reference to tetramethyltin, tetramethylsilane, benzotrifluoride, tetramethylgermanium and $CDCl_3$ or CD_2Cl_2 respectively. In the description of NMR spectra, the abbreviations s, d, t, and m signify singlet, doublet, triplet and multiplet respectively. The uncorrected melting points were recorded in capillary tubes on a Gallenkamp apparatus. Infrared spectra were recorded on an Analect AQS-20 FTIR spectrometer using neat liquid between two blank sodium chloride cells or in solution with 0.1 mm sodium chloride cells with chloroform as solvent. Low resolution electron impact mass spectra were taken on a DuPont 21-492B mass spectrometer with a direct insertion probe (70 ev at 250°C). Chemically induced mass spectra were recorded with a source of 70 ev at 210°C (isobutane) on a Hewlett Packard 5980A mass spectrometer. GC-MS was recorded on Finnigan Mat 800 linked to GC Varian model 3500 using a capillary column as described below. An ionization source of 70 eV was used.

Gas chromatography was performed on a Hewlett Packard Model 5890 combined with a Hewlett Packard integrator model 3390A or a Varian GC model no 3700. A capillary column with methylsilicone as adsorbent on the Hewlett Packard GC was used to monitor

some of the reactions, especially the conversion of 1,5-dibromopentane to pentamethylene sulfide. The progress of the reactions and the purity of final products were monitored by TLC on aluminum sheets precoated with 0.2 mm silica gel 60 F254 (E Merck 5554). Most of the thin-layer chromatograms were visualized using iodine absorbed on silica gel, with a molybdic acid solution, using a U.V.lamp or an acidic solution of p-anisaldehyde. Flash chromatography was carried out using silica gel from E. Merck: Kieselgel 60 no 9385, particles size: 0.040-0.063 mm. Finally, bis(triaralkyltin) sulfides react with an aqueous solution of zinc acetate ($Zn(OAc)_2$) to give a precipitate of zinc sulfide (ZnS) at room temperature.[67] Thus, we sometimes used this finding in our method of purification to remove any excess of bis(triaralkyltin) sulfide when needed. A large excess of zinc acetate ($Zn(OAc)_2$) should be used because the residual fluoride ions also react with this reagent for giving zinc difluoride (ZnF_2).

Bis(triphenyltin) sulfide (7). A 50 mL flask was charged with triphenyltin chloride (10.53 g., 2.73 mmol) and reagent grade tetrahydrofuran (27 mL). A solution of sodium sulfide nonahydrate (6.56 g., 2.73 mmol) in 8 mL of water was added to this in one portion. The mixture was stirred vigorously while refluxing for 2 h at 65°C, (ratio THF/H_2O: 3.3/1). The reaction was followed by TLC (UV detector). When completed, THF was evaporated and 150 mL of ethyl acetate was added and the mixture surred a few minutes to completely dissolve the bis(triphenyltin)sulfide. The organic phase was separated, washed with 2 x 30 mL of water and dried over sodium sulfate. The mixture was filtered, and the solvent evaporated. Crude bis(triphenyltin)sulfide (10.05 g., 99.8 %, m.p 139-140°C, lit.[68] 141.5-143°C) is obtained as colorless crystals. The solid was recrystallized from hexane; m.p. 144-145°C; ^1H NMR (200 MHz) 7.15-7.40 (m); ^{119}Sn NMR (200 MHz) -54.70 (s)

Bis(trimethyltin)sulfide (1). A 250 mL flask was charged with trimethyltin chloride (30.0 g., 0.150 mol), sodium sulfide nonahydrate (36 g., 0.150 mol) and absolute ethanol (100 mL). The mixture was heated at reflux (77-80°C) for 5 h and monitored by GC. The solvent was evaporated and *n*-hexane (~150 mL) added and washed with water (~75 mL). The aqueous phase was kept and extracted more with diethylether (3 x 50 mL). The *n*-hexane and ether phases were dried separately over sodium sulfate; the last traces of solvent were removed with a vacuum pump. The *n*-hexane phase afforded 14.72 g of bis(trimethyltin)sulfide (1) and the ethereal phase gave 6.36 g (21.08, 78%) of pure liquid (99% by GC): ^1H NMR 0.45 (s); ^{119}Sn NMR 91.54 (s). The use of THF/H_2O (3.3/1) as solvent gave 70% yield; caution! trimethyltin chloride is highly toxic.

Tributyltin benzyl sulfide (9). This compound was made in a similar way as reported by Talley and Colley.[28]

Bis(triphenylgermanium)sulfide (4) In 50 mL flask was placed triphenylgermanium chloride (2.00 g.; 5.89 mmol) and sodium sulfide nonahydrate (0.780 g.; 3.25 mmol) partly sponged with a paper for removing water and then crushed. Finally, absolute ethanol was added (25 mL) and the mixture was refluxed for 2.5 h. The completion of the reaction was indicated by the disappearance of triphenylgermanium chloride on TLC using 20% EtOAc/ 80% *n*-hexane as eluent. Ethanol was evaporated and the residual yellowish solid taken up in chloroform (30 mL). A filtration on porous glass for removing sodium chloride and evaporation of the liquid afforded a stable, odorless, pale-yellowish solid corresponding to bis(triphenylgermanium) sulfide (**4**, 1.740 g. 46%); m.p. 118-119°C . The solid was redissolved in dichloromethane, filtered through a short column of silica gel (dichloromethane as eluent) and the solvent was partly evaporated. The product was recrystallized with the addition of *n*-hexane; m.p. 126-127°C (804 mg). A trituration of the solid in 25 mL of *n*-hexane (repeated twice) followed by a filtration afforded a pure product; m.p. 129-130°C (lit.[69] 138°C). A flash chromatography using 30% toluene/ 70% *n*-hexane or 10% EtOAc/ 90% *n*-hexane failed due to the insolubility of bis(triphenylgermanium)sulfide (**4**) ; ^{13}C NMR (300 MHz) 136.74, 134.63, 129.27, 128.02; M.S. (E.I.) (m/z rel. intensity) 643 (0.35); 642 (0.68); 641 (0.72); 640 (0.61); 638 (0.78); 637 (0.22); 636 (0.34) [M$^{\pm}$]; 549 (47.4); 548 (31.2); 547 (61.2); 545 (56.1) [M^{+} - H_2S and Ph$^{\cdot}$]; 471 (10.7); 469 (12.9); 467 (12.5) [M$^{\pm}$ - H_2S and 2 Ph$^{\cdot}$]; 379 (4.1); 377 (4.3); 375 (5.8) [M$^{\pm}$ - H_2S and 3 Ph$^{\cdot}$]; 307 (22.4); 305 (100); 304 (35.7); 303 (72.9); 301 (55.3) [Ph_3Ge^{+}]; 227 (15.2); 225 (11.8) ; 151 (38.3); 149 (28.4); 147 (22.4) [$PhGe^{+}$].

Bis(triphenyllead)sulfide (5). A 250 mL flask was charged with triphenyllead acetate (10.00 g.; 20.10 mmol), sodium sulfide nonahydrate sponged with paper for removing excess water (2.53 g.; 10.53 mmol) and 50 mL of absolute ethanol. The reaction was stirred for 2 days at r.t. As the ethanol was added, a dark brownish color took place. Ethanol was evaporated and chloroform (100 mL) was poured in the flask. The solution was stirred for a few min. and then filtered on a pad of celite. The solvent was evaporated and to the oily residue was added a few mL of *n*-hexane in order to induce the crystallization of the solid. All of the solvent was then evaporated under reduced pressure. Bis(triphenyllead)sulfide (**5**) was obtained as an odorless, pale-yellowish solid (8.94 g.; 94% yield); m.p. 133-134°C (lit.[70] 137-139°C). This solid was pure as shown by TLC and was used without further purification (TLC, 10% EtOAc/90% *n*-hexane; I_2 or U.V.). An attempt

to recrystallize the solid in hot ethanol failed and decomposed it giving some dark insoluble impurities. Dissolution of the solid in chloroform followed by a filtration through a short column of silica gel using chloroform as eluent and the trituration with *n*-hexane afforded a better purity; m.p. 136-137°C; ^{13}C NMR (CD_2Cl_2, 200 MHz) 137.02, 129.96, 129.24, 129.03; M.S. (E.I.) (m/z rel. intensity) 833 (0.3); 832 (0.3); 831 (0.25) [M^+ - Ph·]; 440 (17.5); 439 (91.1); 438 (42.3); 437 (40.1) [Ph_3Pb^+]; 285 (68.6); 284 (29.6); 283 (32.3) [PhPb+]; 208 (100): 207 (42.5); 206 (50.5) [Pb+]

***n*-Hexyl Triphenyllead Sulfide (6)** Into a 25 mL flask was placed 1-bromohexane (0.363 g.; 2.20 mmol), bis(triphenyllead)sulfide (**5**, 1.00 g.; 1.10 mmol), an excess of dried cesium fluoride (1.10 g.; 7.24 mmol) and 18-crown-6 (0.195 g.; 0.74 mmol) and 10 mL of THF and 2.5 mL of DMF. The reaction was stirred at r.t. for 2.0 h and then heated at 60°C for 23 h. The completion of the reaction was indicated by the disappearance of bis(triphenyllead)sulfide on TLC (10% EtOAc/ 90% *n*-hexane; Rf = 0.33) and the formation of a less polar spot (Rf = 0.52). ^1H NMR (200 MHz) 7.67 (H ortho; 6 H; d, d, J [H ortho-H meta] = 8 Hz; J [H ortho-H para] = 1.5 Hz); J [^{207}Pb-H ortho] = 44 Hz) 7.44 (H meta + H para; m, 9 H); 2.78 (CH_2-S; 2 H, t) ^{207}Pb satellite: 2.78; d, t, J [CH_2-^{207}Pb] = 30 Hz; J [CH_2-CH_2-S] = 7.6 Hz); 1.50 (CH_2-CH_2-S; 2 H, q, J = 6.8 Hz); 1.18 (m, 6 H); 0.81 (CH_3; 3 H; t, J = 6.6 Hz).

Benzyl Triphenyllead Sulfide. This compound was isolated as an intermediate from the reaction of benzyl bromide and bis(triphenyllead) sulfide at r.t.. A flash chromatography using 5% EtOAc/ 95% n-hexane as eluent afforded a pale yellowish solid 25 mg. (0.024 mmol; 1% yield); ^1H NMR (200 MHz) 7.58 (H ortho; 6 H; d, d, J [H ortho-H meta] = 8 Hz; J [H ortho-H para] = 1.5 Hz. [^{207}Pb satellites = 7.58; d, d, d, J [Pb-H ortho] = 44 Hz; J [H ortho-meta] = 8 Hz; J [H ortho- H para] = 1.5 Hz); 7.40 (H meta + H para; 9 H; m.); 7.14 (Ph of benzyl; 5 H); 3.98 (CH_2, 2 H, s); satellites = 3.98, d. J [^{207}Pb-CH_2] = 28 Hz).

Formation of Sulfides With Organotin Sulfides.

Without Fluoride or Cyanide Ion.

Diphenacyl Sulfide. α-Bromoacetophenone (1.20 g. 1.96 mmol) was dissolved in 10 mL DMF (spectrograde). To this solution, was added another solution consisting of bis(tributyltin)sulfide (**1**, 0.78 g., 3.92 mmol) in 10 mL of DMF and 3 mL ethyl acetate (spectrograde, to solubilize completely). The mixture was stirred at room temperature for 24 h; a yellow color usually appears. The ethyl acetate was evaporated and *n*-hexane was

injected slowly; the product precipitated and a simple filtration gave 309 mg of diphenacyl sulfide (1.14 mmol, 58 % yield) as a pure product; m.p. 74-75°C. Another recrystallization in *n*-hexane gave a sulfide with a sharp m.p. of 75°C. A second crop of sulfide from the initial reaction mixture afforded a further 71 mg., total: 380 mg, 71% yield: ^{1}H NMR (60 MHz) 8.10-7.80 (m, 4 H), 7.65-7.35 (m, 6 H), 4.00 (s, 4 H); M.S. (m/z rel. intensity) 270 (M†,7), 238 (9), 237 (16), 166 (6), 165 (19), 164 (6), 120 (13), 106 (18), 105 (100), 91 (19), 78 (21), 77 (44), 51 (18), 50 (13), 43 (13), 28 (28).

Dibenzyl Sulfide. In a flask of 50 mL was placed 1.00 g. of bis(tributyltin)sulfide (**2**, 1.63 mmol), 15 mL DMF (spectrograde), 5 mL ethyl acetate (spectrograde) and then freshly distilled benzyl bromide (560 mg, 3.27 mmol). The mixture was stirred for 22 h at 45°C and taken up in 100 mL of ethyl acetate. The organic phase was washed with 5 x 60 mL with water to remove DMF. A solution of potassium fluoride was added and stirred vigorously for a few min. The precipitate was collected and the organic phase washed with water and then dried over sodium sulfate. The evaporation of the solvent gave a residue that was purified by a flash chromatography on silica gel using a mixture of cyclohexane:hexane (1:1) and afforded 60 mg of benzyl sulfide (17% yield): ^{1}H NMR (60 MHz) 7.20 (s,10 H) 3.58 (s, 4 H); MS m/z rel. intensity 215 (15), 214 (48), 123 (25), 122 (18), 121 (18), 92 (31), 91 (100), 77 (11), 65 (25), 63 (10), 51 (10), 45 (17), 39 (11), 28 (26).

General Procedure for the Formation of Symmetrical Sulfides Using Tetrabutylammonium Fluoride Trihydrate.

The halide (2.00 mmol), the bis(triaralkyltin) sulfide (1.05 mmol) are placed in the same flask and a volume of acetonitrile or DMF/EtOAc (5:1 v/v) (spectrograde) was added to obtain a concentration of ca. 0.15 to 0.20 M. based on the halide. Then tetrabutylammonium ammonium fluoride trihydrate (2.10 to 2.20 mmol) was added to the flask and the mixture was stirred vigorously at room temperature for the appropriate time (very often a yellow to orange color appeared). For acetonitrile, the work-up consisted of evaporating the solvent, adding ethyl acetate and finally washing the organic phase with water (at this stage triaralkytin fluoride often had precipitated). The mixture was filtered through a pad of celite and the organic phase dried over sodium sulfate and filtered. The entire solution of ethyl acetate was passed through a short column of silica gel using only ethyl acetate in all steps of this procedure. With DMF, some ethyl acetate was added and the organic phase washed with water to get rid of the DMF before continuing the treatment in the same way as described with acetonitrile. For a better purification, a flash chromatography was carried out only for some sulfides. The yield obtained was excellent in

many cases. Only pure ethyl acetate should be used in the purification to get rid completely of residual tin derivatives. In some cases, the filtration through a short column of silica gel was not necessary and a usual flash chromatography was sufficient. However, for a safer purification, the short column method with ethyl acetate is strongly suggested (especially with non-polar products). For hydrophilic sulfides such as diacetonyl sulfide we avoided the use of water in the work-up. After acetonitrile was evaporated, the mixture was filtered through a short column of silica gel and continued as above.

Diacetonyl Sulfide ($CH_3COCH_2SCH_2COCH_3$). In a 25 mL flask was added bis(tributyltin)sulfide (2, 1.38 g., 2.26 mmol), 6 mL of reagent grade acetonitrile, 2-chloropropanone (380 mg, 4.10 mmol). A dropping funnel was filled with a solution of TBAF.3H2O (711 mg, 2.23 mmol) in 6 mL of acetonitrile. The addition was spread over 15 min. and stirring was continued for 30 min. Evaporation of the solvent and a flash chromatography over silica gel using first hexane as eluent, followed by adding gradually ethyl acetate to attain 30% v/v, afforded 248 mg (1.70 mmol, 83%) of a white solid (m.p. 46.0-46.5oC sharp; IR (CHCl3) max 3010, 2940, 1705, 1415, 1355, 1225, 1155; 1H NMR (60 MHz) 3.30 (s, 4 H), 2.7 (s, 6 H).

Diphenacyl Sulfide. α-Bromoacetophenone (250 mg, 1.26 mmol), bis(tributyltin)sulfide (2, 420 mg, 0.70 mmol) and 8 mL of DMF/EtOAc (5:1) were combined; $TBAF.3H_2O$ (442 mg, 1.40 mmol) was added in one portion and the mixture stirred for 20 min. at r.t. An orange color appeared; ethyl acetate (25 mL) and water were added. The organic phase was washed with more water (5 x 10 mL) and dried over sodium sulfate. A flash chromatography as described for diacetonyl sulfide was carried out; it was recrystallized in hexane. The reaction gave 171 mg of a crystalline thioether (100% yield, m.p. 75°C); the spectral data was identical with that of an authentic sample.

Dibenzyl Sulfide. A 50 mL flask was charged with freshly distilled benzyl bromide (428mg, 2,50 mmol), bis(tributyltin)sulfide (2, 803 mg, 1.31 mmol), acetonitrile (12 mL) and $TBAF.3H_2O$ (830 mg, 2.63 mmol). The mixture was stirred at r.t. for 1 h and the solvent evaporated. The residue containing tin derivatives was purified by flash chromatography using hexane as eluent. A filtration over celite with ethyl acetate as solvent may be needed prior to a direct chromatography; 230 mg of dibenzyl sulfide was obtained (86% yield). The spectral data was identical to an authentic sample.

4-Thia-3,5-dimethyl-2,6-heptanedione [$(CH_3COCH(CH_3))_2S$]. In a 25 mL flask was added 3-bromo-2-butanone (400 mg, 2.65 mmol), bis(tributyltin)sulfide (1, 850 mg, 1.39 mmol) and a solution of DMF/EtOAc (5:1) (12 mL). TBAF.$3H_2O$ (440 mg, 1.39 mmol) was added and the mixture stirred for 24 h at r.t. The reaction was dissolved in 30 mL of ethyl acetate and washed with water (10 mL). A filtration over celite was needed to remove the precipitate. The organic phase was washed again with water (3 x 10 mL), more TBAF.$3H_2O$ (430 mg) in water solution was added and then stirred for 30 min. The phases were separated and the organic layer dried over sodium sulfate. The residue was passed through a short column of silica gel using ethyl acetate as eluent; this was followed by a flash chromatography using EtOAc:hexane (2:8) as eluent. This afforded 160 mg of thioether (75%); one spot on TLC (EtOAc:hexane 2:8): ^1H NMR (60 MHz) 3.43 (q, 2 H), 2.25 (s, 6 H), 1,40 (d, 6 H); MS 174 (M^+, 21), 131 (29), 114 (26), 113 (25), 87 (34), 72 (47), 71 (34), 69 (27), 60 (25), 59 (38), 57 (41), 55 (37), 45 (31), 43 (100), 41 (32), 29 (26), 28 (89), 27 (25).

3,7-Dithiacyclooctane-1,5-dione. 1,3-Dichloroacetone (300 mg, 2.36 mmol), bis(tributyltin)sulfide (2, 60 g., 2.61 mmol) and acetonitrile (30 mL) were mixed together. To this was slowly added a solution of TBAF.$3H_2O$ (825 mg in 20 mL acetonitrile) over a period of 15 min., while stirring vigorously for another 15 min. The solvent was evaporated and a flash chromatography on silica gel was performed by using hexane first, followed by gradually adding EtOAc to 30% EtOAc in hexane. A white solid was obtained (33 mg, 16% yield), IR ($CHCl_3$) max 2945, 2920, 2865, 2850, 1700, 1395, 1260, 1175 (large band); ^1H NMR (60 MHz) 3,58 (s); MS 176 (M^+, 23), 133 (22), 103 (32), 101 (21), 98 (26), 92 (33), 91 (28), 74 (31), 71 (29), 61 (39), 60 (62), 59 (31), 58 (33), 57 (29), 56 (28), 55 (33), 49 (21), 47 (23), 46 (62), 45 (65), 43 (100), 42 (38), 41 (27), 39 (44), 29 (41), 28 (55), 27 (45), 26 (31).

Thiane: General procedure. A 10 mL test tube was filled with 1,5-dibromopentane (60 mg, 0.26 mmol), the appropriate organotin sulfide (0.52 mmol), 2.0 mL of acetonitrile or DMF/EtOAc (5:1) and finally TBAF.$3H_2O$ (168 mg, 0.53 mmol). The mixture was stirred for the appropriate time at the temperature in the Tables. The reaction was monitored by GC and the yields assigned by the area of the signal. The formation of thiane was confirmed by comparison with authentic material and GC-MS.

General Procedure for the Formation of Symmetrical Sulfides Using Cesium Fluoride Complexed with 18-crown-6 in Anhydrous Medium.

The halide (2.00 mmol), the bis(triaralkyltin)sulfide (1.05 mmol) and a catalytic amount of 18-crown-6 (~ 0.2 mmol) were added together and a volume of dried acetonitrile was injected using a syringe to give a concentration of about 0.20 to 0.25 M. based on the halide. An excess of dried cesium fluoride (~ 4 mmol) was added. The mixture was heated (if needed) and then cooled to r.t., the solvent evaporated and taken up with ethyl acetate. Water was added and organotin fluoride precipitated. The mixture was filtered through a pad of celite and passed through a short column of silica gel. Only ethyl acetate must be used here; if needed a flash chromatography can be carried out.

Typical Procedure: Preparation of di-*n*-Hexyl Sulfide. In a 50 mL flask was added 1-bromohexane (409 mg, 2.48 mmol), bis(trimethyltin)sulfide (**1**, 445 mg, 1.24 mmol) and a catalytic amount of 18-crown-6 (132 mg, 0.50 mmol) under a nitrogen atmosphere. Ten mL of acetonitrile (dried over calcium hydride and P_2O_5) was added with a syringe. Cesium fluoride (800 mg, 5.27 mmol, (dried at 110°C for 2 days at 5 mm Hg) was added in one portion. The mixture was stirred vigorously under nitrogen and heated at 75°C for 75 min. in an oil bath. After cooling, the solvent was removed and 50 mL of ethyl acetate was added. After stirring 5 min., the mixture was filtered over celite and then passed through a short column of silica gel using only ethyl acetate as eluent.

Di-*n*-hexyl Sulfide. (250 mg, quantitative yield) was obtained as a colorless liquid in a pure state, as confirmed by GC: ^{1}H NMR (200 MHz) 2.50 (t, 4 H), 1.58 (m, 4 H), 1.30 (m, 12 H), 0.89 (t, 6 H); MS (m/z rel. intensity) 202 (M^+, 40), 117 (100), 84 (86), 69 (45), 61 (77), 56 (63), 55 (65), 43 (72), 42 (67), 41 (69), 28 (66).

5-Thia-3,7-dimethylnonane. This was prepared by the same procedure as above using S(+)-bromo-2-methylbutane (773 mg, 5.12 mmol), bis(trimethyltin)sulfide (**1**, 1.08 g., 2.91 mmol), a catalytic amount of 18-crown-6, an excess of dried cesium fluoride and 22 mL of dried acetonitrile. The mixture was heated at 80oC for 2.5 h in an oil bath. Same work-up as above: 63% yield; ^{1}H NMR (200 MHz) 2.50 (d, d, 1J = 20 Hz; 2J = 5.6 Hz; 2H); 2.33 (d,d, 1J = 20 Hz; 2J = 7.0 Hz; 2H); 1.52 (m, 4H); 1.22 (m, 2H); 0.97 (d, 6H); 0.89 (t, 6H).

Formation of Symmetrical Sulfides with Tetrabutylammonium Cyanide (TBACN).

Dibenzyl Sulfide. In a 25 mL flask was placed freshly distilled benzyl bromide (428 mg, 2.50 mmol), bis(tributyltin)sulfide (**2**, 803 mg, 1.31 mmol), dried acetonitrile (12 mL) and TBACN (706 mg, 2.63 mmol). The reaction mixture was kept under nitrogen and stirred for 50 min. at r.t. The acetonitrile was evaporated and replaced with ethyl acetate (25 mL); a solution saturated with zinc acetate was then added to destroy any excess of organotin sulfide and stirring was continued for 15-30 min. The white precipitate that formed (ZnS) was collected and the organic phase washed with water (~ 20 mL). A saturated solution of potassium fluoride and TBAF.3H_2O (~200 mg) was added and stirring continued for 15-30 min. The phases were separated or filtered (if a precipitate was formed). The organic phase was washed with water (20 mL) and dried over sodium sulfate. A flash chromatography on silica gel (hexane as eluent) afforded 109 mg of a semi-solid with a low melting point corresponding to dibenzyl sulfide (41%): Spectral data were identical to those obtained in other synthesis mentioned before.

Other Fluorides Used in this Study.

Anhydrous Tetrabutyl Ammonium Fluoride (TBAF) was prepared as usual.[38] TBAF.3H_2O adsorbed on silica gel was made by following the procedure of Clark[71] except that silica gel having particles size of 0.040-0.063 mm was used.

TEAF.3H_2O with 3Å Sieves. TEAF.3H_2O (555 mg, 3.72 mmol), 7.0 mL of dried THF, and 1-1.5 g of molecular sieves (3Å) were placed in a flask under a nitrogen atmosphere. The mixture was stirred overnight and then the solvent evaporated to dryness with a strong flow of nitrogen while warming the flask slightly over a hot water bath. 1-Bromohexane (585 mg, 3.54 mmol), bis(trimethyltin)sulfide (**1**, 667 mg, 1.86 mmol) and acetonitrile (10 mL) were added to the flask and stirring at r.t. was continued for 5.5 h. The solvent was evaporated and ethyl acetate added, followed by a filtration through a short column of silica gel using ethyl acetate as eluent. The crude product showed good purity by ^{1}H NMR (202 mg, 56% yield): ^{1}H NMR (200 MHz) 2.51 (t, 4 H), 1.58 (quintuplet, 4 H), 1.48-1.20 (m, 12 H), 0.90 (t, 6 H).

Anhydrous Benzyl Trimethyl Ammonium Fluoride (BTAF). BTAF.H_2O (2.49 g.), dried THF and spherical molecular sieves 3Å (12.8 g.) were placed in a flask and stirred gently for 10 h under nitrogen. The whole mixture was filtered through a strainer under a

stream of nitrogen and the solvent evaporated with the same technique as used for TEAF.3H_2O. 1-Bromohexane (409 mg, 2.48 mmol), bis(trimethyltin)sulfide (**1**, 467 mg, 1.30 mmol), BTAF dried as above (419 mg, 2.48 mmol) and dried acetonitrile (10 mL) were placed in the same flask under nitrogen. Tetrabutyl ammonium iodide (350 mg) was added to ensure a better solubility of BTAF while increasing the ionic strength of the medium. The mixture was stirred at r.t. for 12 h ; the yield of di-n-hexyl sulfide was determined to be 70% by GC. The properties of the product formed were identical to those of di-*n*-hexyl sulfide previously made.

Cesium Fluoride and Tetrabutylammonium Iodide. Bis(triphenyltin)sulfide (**7**, 362 mg., 0.494 mmol), 1-bromohexane (84 mg, 0.25 mmol), cesium fluoride (200 mg) and tetrabutylammonium iodide (100 mg) were placed in the same flask under nitrogen. Acetonitrile (5 mL) was added and the reaction stirred for 5 h at 50-52°C. GC showed incomplete conversion of the halide and an approximate yield of 70-80% of di-*n*-hexyl sulfide.

2,4,6-Trimethylpyridine.HF. Bis(triphenyltin)sulfide (**6**, 2.50 g., 3.41 mmol), 1-bromohexane (563 mg, 3.41 mmol), 2,4,6-trimethylpyridine.HF (722 mg, 5.12 mmol) and acetonitrile were mixed together and heated at 50°C for 21 h. Only some small traces of di-*n*-hexyl sulfide were detected by TLC.

Potassium Fluoride and 18-crown-6. 1-bromohexane (409 mg, 2.48 mmol), bis(trimethyltin)sulfide (**1**, 445 mg, 1.24 mmol), acetonitrile (10 mL), potassium fluoride (excess) and 18-crown-6 (cat. amount) were placed in a flask and stirred at r.t. under nitrogen for 1 h. A sample was taken and analysed by GC; no sulfide was detected.

Formation of Unsymmetrical Sulfides: Benzyl-*n*-Hexyl Sulfide.

General Procedure with Cesium Fluoride. 1-Bromohexane (277 mg, 1.68 mmol), tributyltin benzyl sulfide (727 mg, 1.76 mmol) and dried acetonitrile (12 mL) were placed into a flask. Cesium fluoride (800 mg, 5.28 mmol) alone or complexed with 18-crown-6 (96 mg, 0.36 mmol) were added. The mixture was stirred vigorously at r.t. for 2 h under nitrogen with CsF /18C6 and for 12 h with CsF alone. The reaction was monitored by GC and ^1H NMR; the yields were recorded as described in Table 7. The purification involved evaporation of the acetonitrile, addition of ethyl acetate (30 mL) and addition of a saturated aqueous solution of potassium fluoride (~15 mL); the mixture was stirred for 30-45 min. A filtration was carried out if needed at this stage or later (to remove organotin fluoride) and

the phases were separated. The organic phase was washed with water and dried over sodium sulfate. A flash chromatography using hexane as eluent was carried out if needed. Benzyl-*n*-hexyl sulfide was obtained as a colorless liquid (260 mg, 76%). Some traces of unreacted starting material were observed by ^{1}H NMR prior to purification; ^{1}H NMR (60 MHz) 7.27 (s, 5 H), 3.70 (s, 2 H), 2.43 (t, 2 H), 1.7-1.03 (m, 8 H), 0.85 (t, 3 H); MS 208 (M^+, 14), 207 (22), 181 (19), 180 (10), 179 (11), 149 (12), 117 (14), 105 (12), 103 (12), 92 (19), 91 (100), 65 (15), 57 (12), 56 (13), 55 (13), 43 (13), 41 (22), 29 (16), 28 (21).

With TBACN: 1-Bromohexane (139 mg, 0.84 mmol), tributyltin benzyl sulfide (364 mg, 0.88 mmol), acetonitrile (5 mL) and TBACN (245 mg, 0.91 mmol) were mixed together and stirred at r.t. for 2.3 h under nitrogen to give benzyl-*n*-hexyl sulfide in 84% yield by GC. The retention time was compared to the isolated and characterized product obtained before.

Formation of Sulfides with Bis(triphenylgermanium)sulfide. With Fluoride

Di-*n*-Hexyl Sulfide. In a 25 mL flask were placed 1-bromohexane (165 mg, 1.00 mmol), bis(triphenylgermanium) sulfide (**4**, 320 mg, 0.50 mmol) and a catalytic amount of 18-crown-6 (26 mg;0.1 mmol). THF (4.0 mL) and DMF (1.0 mL) were added. Flamed-dried cesium fluoride (440 mg, 2.90 mmol) was added to the main flask while stirring for 45 min. at R.T. and then at 55°C for 10 h. THF was evaporated and to the remaining residue was poured ether (~25 mL) and water (~ 25 mL). The ethereal phase was further washed with water (3 x 20 mL) and then dried over $Na_2SO_4/MgSO_4$. A flash chromatography using 2% EtOAc/98% *n*-hexane as eluent afforded di-*n*-hexyl sulfide (80 mg, 80% yield) of a colorless liquid. The spectral data were as described before

Formation of Sulfides with Bis(triphenyllead)sulfide Without Fluoride Ion.

Dibenzyl Sulfide. Benzyl bromide (171 mg; 1.00 mmol), bis(triphenyllead)sulfide (477 mg) and DMF (5.0 mL) were mixed together and stirred at r.t. for 4 days. A black precipitate took place immediately. Finally, diethyl ether (30 mL) was added and the solution was filtered. Water (20 mL) was added and then discarded. The organic phase was washed further with water (3 x 20 mL) and dried over $Na_2SO_4/ MgSO_4$. ^{1}H NMR did not show any significant amount of dibenzyl sulfide.

With Cesium Fluoride

Diphenacyl Sulfide. a-Bromoacetophenone (199 mg; 1.00 mmol), bis(triphenyllead)sulfide (**5**, 477 mg; 0.55 mmol), cesium fluoride (547 mg; 3.60 mmol) and

18-crown-6 (15 mg) were placed in a 50 mL flask. THF (8.0 mL) was added *via* a syringe and the mixture was stirred at r.t for 1 to 2 min.. Then DMF (2.0 mL) was added into the flask. A yellow-orange color appeared immediately. The reaction was stirred at R.T for 3.0 h and followed by TLC using 30% EtOAc/70% *n*-hexane as eluent (U. V visualization) After 1.5 h, most of the starting material had disappeared. THF was evaporated and the reaction taken up in ethyl acetate (30 mL). A filtration on a pad of celite removed the remaining inorganic salts and most of the triphenyllead fluoride. Brine (20 mL) was added and the aqueous phase discarded. The organic phase was washed further with brine (3 x 15 mL). A flash chromatography using 25% EtOAc/ 75% *n*-hexane as eluent afforded diphenacyl sulfide (129 mg.; 0.60 mmol) in 95% yield. The compound was identical to a reference sample on TLC.

Dibenzyl Sulfide. In a 50 mL flask was placed benzyl bromide (171 mg; 1.00 mmol) and bis(triphenyllead)sulfide (**5**, 478 mg; 0.53 mmol). THF (8.0 mL) and DMF (2.0 mL) were added (a black color appeared immediately) *via* a syringe, followed by cesium fluoride (416 mg; 2.77 mmol) and 18-crown-6 (66 mg; 0.25 mmol) The flask was heated at 65°C for 5 h. The black color resulting from a complex formation between the organolead and DMF became pale gray after a few min. in the presence of fluoride. After only 1.5 h, most of the starting material (Rf = 0.40) reacted as determined by TLC (10% EtOAc/ 90% *n*-hex.) and was transformed in a more polar product corresponding to benzyl triphenyllead sulfide (Rf = 0.50). After evaporation of the solvent and addition of diethyl ether (30 mL), the mixture was filtered through a pad of celite and the content poured in a separating funnel. Water (30 mL) was added and then discarded. The ether phase was washed further with 3x15 mL of water and dried on $Na_2SO_4/MgSO_4$. A flash chromatography (using the same eluent as above) gave pure dibenzyl sulfide (69 mg, 0.32 mmol; 81% yield) with the same spectral data as before. The product was compared to authentic material, the purity was excellent as verified by ^1H NMR and TLC.

Dibenzyl Sulfide. In a similar way to the above procedure, dibenzyl sulfide was prepared with benzyl bromide (342.1 mg; 2.00 mmol), bis(triphenyllead)sulfide (**5**, 955 mg; 1.05 mmol), cesium fluoride (730 mg; 4.80 mmol), 18-crown-6 (53 mg; 0.20 mmol) and DMF (10 mL). The reaction turned black while adding the solvent. It was stirred at r.t. for 5 h then diethyl ether (30 mL) was poured in the flask and the work-up was similar to the above procedure. Dibenzyl sulfide (143 mg; 67% yield) obtained had the same spectroscopic properties as above and the purity was excellent on TLC.

Di-*n*-Hexyl Sulfide. In a 50 mL flask, put bis(triphenyllead)sulfide (**5**, 950 mg; 1.05 mmol), 1-bromohexane (336 mg; 2.04 mmol), cesium fluoride (1.20 g; 7.90 mmol), 18-crown-6 (30 mg; 0.11 mmol) were combined. Then THF (11 mL) were added and stirred for a few min. DMF was added (2.4 mL)and stir for a few min. then more DMF was added (2.4 mL) and the solution stirred at reflux for 8 h. TLC showed bis(triphenyllead)sulfide (**5**) (eluent: 10% EtOAc/ 90% *n*-hexane , I_2). After cooling, THF was evaporated and diethylether (25 mL) was added and the mixture filtered on a pad of celite. Saturated NaCl solution (20 mL) was poured in a dropping funnel along with the ethereal phase. After shaking, the aqueous phase was discarded and the organic one was washed further with brine (15 mL) followed by water (2 x 15 mL). The ethereal phase was dried over $Na_2SO_4/MgSO_4$ A flash chromatography using 3% EtOAc/97% n-hexane afforded di-*n*-hexyl sulfide as a minor component (22 mg, 0.11 mmol, 11% yield) along with triphenyllead-*n*-hexyl sulfide (326 mg; 0.63 mmol) as the major component (decomposed slowly); the same spectral data as previously indicated was observed for both compounds.

^{19}F and ^{119}Sn Complexation Study of Bis(triphenyltin) Sulfide with "Dried" TBAF. In a 5 mm NMR tube was placed bis(triphenyltin) sulfide (50 mg, 0.068 mmol) and CD_2Cl_2 (0.30 mL). A solution of "anhydrous: TBAF in CD_2Cl_2 was prepared according to Cox[38]. In a small flask, TBAF.$3H_2O$ (539 mg, 1.708 mmol) was dried overnight under high vacuum while heating at 40-45°C. Deuteromethylenechloride (1.00 mL) was added and the solution kept under N_2; 0.160 mL was transferred to an NMR tube containing the organotin sulfide. A weak evolution of H_2S resulted along with a yellowish color. ^{19}F and ^{119}Sn NMR spectra were recorded immediately. All of the manipulations were executed under nitrogen. In the presence of water, complex **18a** or **18b** is not observed.

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CHAPTER 5

ORGANOTIN OXIDES AS MILD OXYGEN TRANSFER AGENTS IN THE PRESENCE OF LEWIS ACIDS.

In the previous chapters, some nucleophilic species were released from organometallic reagents of group 14 when fluoride ions attacked the metal (Si, Ge, Sn, Pb) and cleave the metal-ligand bond. We now turn our attention to the possibility of using a mild Lewis acid in order to promote the reaction of a nucleophilic ligand attached to tin with halogenated substrates. In this instance, the activation of the electrophile is reported instead of activating the organotin oxide reagent itself, as previously shown in the fluorodestannylation methodology.

This chapter depicts the use of silver salts with commercial bis(tributyltin)oxide and primary alkyl halides for making alcohols. Although the halide to alcohol conversion is simple, there were few practical and general procedures in the literature.

Chapter 5 was taken from a recent publication (Gingras, M.; Chan, T. H. *Tetrahedron Lett.* **1989**, *30*, 279). Professor Chan provided some help from discussions and in the revision of this manuscript. The main writing of this article, the full literature search of references along with the laboratory work were the result of my efforts. Appendix 2 presents further details on the experimental procedures and a possible mechanism based on a working hypothesis.

5.0 SILVER-ASSISTED REACTIONS OF ORGANOTIN OXIDES. A MILD, NEUTRAL AND ANHYDROUS ONE-STEP CONVERSION OF PRIMARY ORGANIC HALIDES TO ALCOHOLS.

Abstract: *Bis(tributyltin)oxide acts as a mild oxygen transfer agent in converting primary organic iodides and bromides to give alcohols in good to excellent yields. The less reactive chlorides can be converted into alcohols when they are first transformed into bromides or iodides using the Finkelstein reaction. Silver salts are required for this one step conversion.*

Bis(tributyltin)oxide (**1**) is currently produced in bulk quantity and used as wood preservative, as killer of algae in anti-fouling paint and as general desinfectant.[1] It was first synthesized in 1941[2] and has since been considered as one of the major starting material for making organotin derivatives. In organic chemistry, it has been utilized widely in carbohydrate chemistry in the regioselective activation of hydroxyl groups toward alkylations and acylations.[3] More recently, we found that (**1**) acts as a general "O^{2-}" transfer agent via the methodology of fluorodestannylation.[4]

We would like to report that bis(tributyltin)oxide (**1**) reacts smoothly with organic iodides and bromides in the presence of silver salts to give the corresponding alcohols. To the best of our knowledge, this is the first example that an organotin compound is used in tandem with silver salts.

$Bu_3Sn\text{-}O\text{-}SnBu_3$

1

Although it has been well known that a tin atom attached to an oxygen atom enhances the nucleophilicity of the latter without increasing its basicity,[3,5] no one tried to use this finding in alkylations of organotin oxides in the presence of silver salts. Indeed, the usual alkylation of organotin oxides by organic halides required extensive heating (often near 200°C) for achieving C-O bond formation.[5] Similar vigorous conditions were required in

the alkylation reactions in carbohydrates even with the use of reactive benzyl bromide, allyl bromide or mem-chloride with tetrabutylammonium salts, as catalysts.[6]

In our case, we found that non-activated organic iodides such as 1-iodohexane (1.00 mol) reacted at room temperature with bis(tributyltin)oxide (**1**) (1.10 mol) in the presence of silver tosylate or silver nitrate (1.10 mol) in DMF, under anhydrous conditions. It gave at least 76% yield of 1-hexanol after 1.5 hr of reaction time, followed by an aqueous work-up (see Eq.1 and Table 1,entry 2). We found later that the organotin oxide and the silver salt should be used in ratio of 2.20 and 2.00 mol for optimal yields. The intermediate tributyltin hexyl oxide is unstable and easily hydrolysed (even in moist atmosphere or on silica gel). In a similar way, 1-bromohexane (1.00 mol) reacted with bis(tributyltin)oxide (**1**) (2.20 mol) and silver tosylate or silver nitrate (1.10 mol) at 90°C for 20-23 hrs (Eq.1). It afforded 74% yield of 1-hexanol (entry 3). The method seems general for usual primary bromides or iodides. Some starting material could be recovered which accounted for the non-quantitative conversions. Primary chlorides, such as 1-chlorooctane, did not react at all even under forcing conditions (entry 8). However, we found that a primary chloride, first converted to the iodide using the Finkelstein reaction (NaI/acetone), followed by our usual treatments for iodides, provided 1-nonanol in moderate overall yield (entry 9).

A strong coordinating solvent like DMF was crucial in this method. We used indifferently silver tosylate and silver nitrate for non-easily ionizable organic halides. However, we observed some traces of 1-tosylhexane when using silver tosylate with 1-iodohexane (~ 8% yield). It is probably better to use silver nitrate in many cases. When using organic bromides no tosylates were detected.

$$CH_3(CH_2)_5X + (Bu_3Sn)_2O \xrightarrow{Ag(I)} CH_3(CH_2)_5OSnBu_3 \xrightarrow[\text{or work-up } H_2O]{SiO_2} CH_3(CH_2)_5OH \quad (1)$$

X= Br, I

Interestingly, the reaction did not give any significant amount of ethers even if the appropriate ratio of 1-iodohexane (2.00 mol) and bis(tributyltin)oxide (1.00 mol) were used (entry 1). The result was a clean conversion of the organotin oxide to form the alcohol (84% yield based on organotin oxide). This clearly demonstrates that the first nucleophilic substitution took place easily but the second alkylation is kinetically less favored.

Table 1: Conversion of Organic Halides to Alcohols

Entry	Halide	Organotin[a]	Solvent	T(°C)	Time(hr)	Ag^+	Alcohol	Yield(%)[b]
1	$CH_3(CH_2)_5I$	$(Bu_3Sn)_2O$[c]	DMF	20	2	AgTos	$CH_3(CH_2)_5OH$	84
2	$CH_3(CH_2)_5I$	$(Bu_3Sn)_2O$[d]	DMF	20	2	AgTos	$CH_3(CH_2)_5OH$	76
3	$CH_3(CH_2)_5Br$	$(Bu_3Sn)_2O$	DMF	90	22	AgTos	$CH_3(CH_2)_5OH$	74
4	$CH_3(CH_2)_5Br$	$(Bu_3Sn)_2O$	DMF	90	14	Ag_2O	$CH_3(CH_2)_5OH$	71
5	$CH_3(CH_2)_5Br$	nil	DMF	90	22	Ag_2O	$CH_3(CH_2)_5OH$	12
6	$CH_3(CH_2)_8Br$	$(Bu_3Sn)_2O$	DMF	80	23	AgTos	$CH_3(CH_2)_8OH$	47
7	$CH_3(CH_2)_5Cl$[e]	$(Bu_3Sn)_2O$	DMF	20	2	AgTos	$CH_3(CH_2)_5OH$	74[f]
8	$CH_3(CH_2)_7Cl$	$(Bu_3Sn)_2O$	DMF	125	36	$AgNO_3$	$CH_3(CH_2)_7OH$	nil
9	$CH_3(CH_2)_8Cl$[e]	$(Bu_3Sn)_2O$	DMF	20	3.0	$AgNO_3$	$CH_3(CH_2)_8OH$	50[f]
10	$CH_3COO(CH_2)_4Br$	$(Bu_3Sn)_2O$	DMF	90	24	$AgNO_3$	$CH_3COO(CH_2)_4OH$	28
11	$CH_3COO(CH_2)_4Br$[e]	$(Bu_3Sn)_2O$	DMF	20	5	$AgNO_3$	$CH_3COO(CH_2)_4OH$	91[f]
12	$CH_3COO(CH_2)_4I$	$(Bu_3Sn)_2O$[h]	DMF	20	5.5	AgTos	$CH_3COO(CH_2)_4OH$	96
13	$PhCH_2CH_2I$	$(Bu_3Sn)_2O$[i]	DMF	20	0.5	$AgNO_3$	$PhCH_2CH_2OH$	70
14	$PhCH_2CH_2Br$[e]	$(Bu_3Sn)_2O$	DMF	20	0.5	$AgNO_3$	$PhCH_2CH_2OH$	63[f]
15	c-$C_6H_{10}CH_3(Br)$[g]	$(Bu_3Sn)_2O$	DMF	20	4	$AgNO_3$	c-$C_6H_{10}CH_3(OH)$	0-5
16	c-C_6H_{11}-I	$(Bu_3Sn)_2O$	DMF	75	28	AgTos	c-C_6H_{11}-OH	0-5

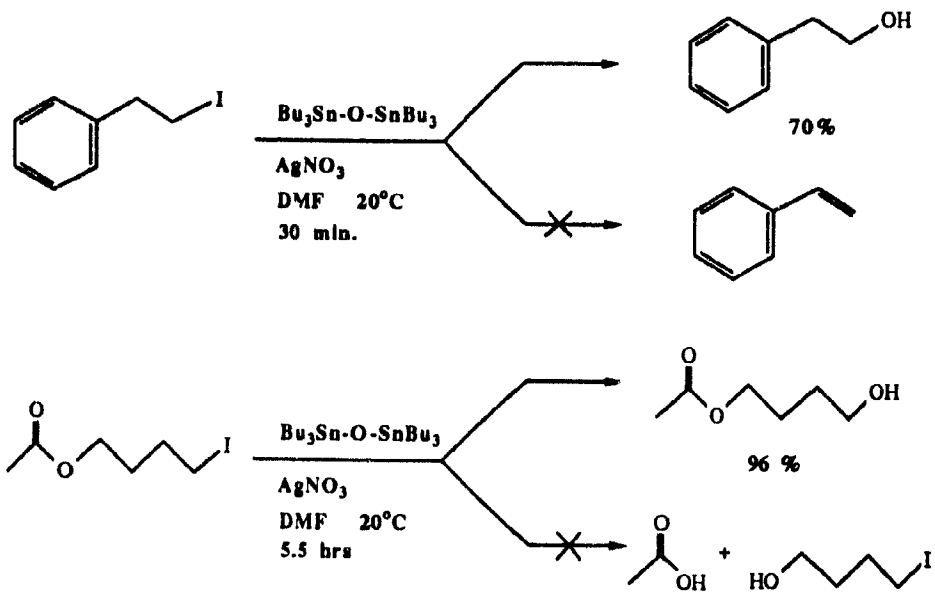
a) For organic bromides or chlorides: ratio $(Bu_3Sn)_2O$/Ag+/bromide = 2.2/1.1/1.0 (mol) b) Isolated yields, non optimized; products characterized by ^1H NMR (200 MHz), T.L.C.; G.C. and by comparison to authentic material. c) Ratio $(Bu_3Sn)_2O$/Ag+/iodide = 2.2/2.0/1.0 (mol). d) Ratio $(Bu_3Sn)_2O$/Ag+/iodide = 1.1/1.1/1.0 (mol) e) 2 steps: prior conversion to the iodide (NaI 3 0 eq /1.0 eq organic bromide or chloride/acetone, reflux) then conditions as described in the table. f) Overall yields. g) 1-bromo-1-methyl cyclohexane. h) Ratio $(Bu_3Sn)_2O$/Ag+/iodide = 2.0/1.3/1.0 (mol) i) Ratio $(Bu_3Sn)_2O$/Ag+/iodide = 2.2/2.0/1.0 (mol).

An excess of (**1**) is desirable in the case of organic bromides because (**1**) reacts directly with silver salts at R.T. to produce silver oxide (Ag_2O). It is a parallel and competitive reaction which diverts the reagent (**1**). This process is amplified when heating. Indeed, a black precipitate took place immediately in CH_3CN or DMF. It is conceivable that Ag_2O is the activating agent in the bromide case since silver tosylate, nitrate, triflate and Ag_2O (entry 4) are equally effective despite their different Lewis acidity. However, we ruled out the possibility of Ag_2O alone acting as the oxygen transfer agent in our method by a control experiment under similar conditions without (**1**). Silver (I) oxide accounted for less than 12% yield of alcohol as shown in entry 5, proving that (**1**) is the major oxygen transfer agent.

Although simple, this halide to alcohol conversion had been rare despite its potential usefulness. No practical method exists for converting non-activated organic halides to alcohols in one step in a neutral medium; the existing ones often involve basic hydrolysis or silver-assisted hydrolysis of reactive benzyl or allyl halides.[7] Other common procedures involve at least two steps by using the acetate anion as nucleophile which is usually a difficult displacement and often gives rise to some elimination. The acetate formed has to be hydrolyzed (usually under basic conditions) in the second step.[8] An alternative method involves the transformation of halides into hydroperoxides or peroxides with the use of silver triflate and hydrogen peroxide.[9] Then a reduction of the peroxide or hydroxiperoxide is required.

An advantage of the present reactions is that elimination reaction which often accompanies subtitution reaction of halides is minimized. As an ultimate proof, the base-sensitive (2-iodoethyl)benzene was readily converted to 2-phenethyl alcohol instead of giving styrene (scheme 1 and entry 13). Furthermore, ester groups remain unchanged in the reaction. Thus, 4-iodobutyl acetate was converted smoothly to the corresponding alcohol in nearly quantitative yield (scheme 1 and entry 12). On the other hand, secondary (iodocyclohexane, entry 16) or tertiary (1-bromo-1-methylcyclohexane, entry 15) halides did not afford significant yield of the corresponding alcohols. Elimination reactions predominated in these cases.

SCHEME 1: Neutrality of Reaction



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CHAPTER 6

GENERAL DISCUSSION

6.0 GENERAL CONCLUSION.

6.0.1 Practical View.

We have seen many industrial uses of organotin compounds in the introduction of this thesis (chapter 1). They are currently utilized in major industrial fields: as agrochemicals, as desinfectants, as wood preservatives, as potential drugs against cancer, as antifouling agents in marine paints and as general biocides. Finally, the PVC industry used them for many years as stabilizers. Unfortunately, many organotins produced in bulk quantities from the industry remained relatively unexploited in organic synthesis. One of the practical goals of this thesis was certainly to bring about some contributions in this area by employing well-known commercial compounds such as bis(tributyltin) sulfide [$(Bu_3Sn)_2S$], dibutyltin sulfide [Bu_2SnS] or bis(tributyltin) oxide [$(Bu_3Sn)_2O$] as sulfur and oxygen transfer agents. In addition, the successful phase transfer catalysis using the commercially available 18-crown-6 and cesium salts has been demonstrated. From simple and commercial reagents, it was shown that it is possible to obtain improved anhydrous nucleophilic fluorinating systems with metal fluorides (here cesium as metal).

6.0.2 Fundamental Research.

6.0.2.1 Fluorodestannylation.

It has been clearly demonstrated in this thesis that fluorodestannylation reactions can be useful tools for organic chemists. In fact, they complement well the known fluorodesilylation reactions. We therefore presented some examples where siloxanes could not act as oxygen transfer agent whereas organotin oxides could. A second advantage of the organotin reagents is certainly their higher stability compared to silicon analogs, especially when sulfur and selenium atoms are involved. On the other hand, preliminary results with

allyl and ethynyltins do not seems to present any advantage compared to allyl and ethynyl silanes in C-C bond formation in the presence of fluoride ions.

New ways for generating synthetic equivalents of cesium and tetraalkylammonium salts from fluorodestannylation of organotin oxides, sulfides and selenides are worthy of mention due to their high nucleophilicity ("naked anions").

Probably the most interesting contribution of this work to organic synthesis is the generality of these reactions within the whole group 16. Thus organotins acted as "group 16 transfer agents".

6.0.2.2 Fluorodegermanylation and Fluorodeplumbylation.

As an extension of the development of fluorodestannylation, some reactions involving lead and germanium were also successful. The variation of the metal atom within group 14 has been well described in this thesis. An important point that should be clear is that fluoride ion can not only attack silicon, but also the whole group 14 Fluoride ions combined with lead and germanium represents a successful combination unexploited until now.

6.0.2.3. Kinetic and Mechanistic Aspects.

In Chapter 4, we discussed about some working hypothesis about the reaction mechanism in fluorodemetalation. Overall, it seems that "S^{2-}" tranfer agents from organogermanium, -tin and -lead sulfides release sulfur in two steps. Consequently, sulfide ion S^{2-} is not usually observed in these fluorodemetalation reactions but the existence of anions of the general form $R_3Sn\text{-}S^-$ are more probable. One important point here is that we explained our kinetic results (relative rates) of this stepwise process by a α metal proximity effect which enhances the rate of nucleophilic reaction of the anion. To the best of our knowledge, no study has previously been made on this topic. From the work presented in Chapter 4, we also described some pentacoordinated intermediates in our reactions. Those intermediates were characterized by spectroscopic means. Finally, the mechanism of substitution at tin implying pentavalent tin species has been reinforced by those observations.

6.0.3 Fluorodemetalation Concept and Future Perspectives.

Due to the large bond energy of fluoride with many non-transition metal or metalloid, it seems that most of the reactions presented in this thesis with silicon, germanium, tin and lead compounds were favored thermodynamically. In other words, the relatively high Si-F, Ge-F,

compounds were favored thermodynamically. In other words, the relatively high Si-F, Ge-F, Sn-F and Pb-F bond energies seem to be the driving force of these reactions.

In the future, it might also be interesting to find out if the concept of fluorodemetalation developed here can be applied to transition metal chemistry. Knowing that several fluorine-metal bond energies are relatively high and in a similar way as with group 14, can it be possible to generalize fluorodemetalation with transition metals? Is it possible to generate anions from the attack of fluoride ion on transition metal complexes having a potential nucleophilic ligand as leaving group? Bond energies of several transition metals atoms with fluorine atom are relatively high and *a priori* some future projects in this area seem promising.

6.0.4. Fluorine and Crown-Ether Chemistry.

Beside the work related to fluorodemetalation reactions, it has been possible to develop in parallel some studies of new anhydrous fluorinating systems. These studies showed that edge or sandwich complexes implying cesium cation and crown-ethers provide similar rate enhancement in nucleophilic substitutions S_N2 by solid-liquid phase transfer catalysis. Finally, new anhydrous fluorinating systems were reported based on the combinations of crown-ethers (18-crown-6 and 24-crown-8) with cesium fluoride. However, it appears that a highly active anhydrous nucleophilic fluorinating agent would be very valuable in chemistry. As a future perspective, the finding of such a reagent will certainly find some uses in fluorodemetalation reactions and would be a valuable tool for organic chemists.

6.1 CONTRIBUTIONS TO KNOWLEDGE.

In chapter 2, we presented the use of bis(tributyltin)sulfide as new "S^{2-}" sulfur transfer agent. Among the main features of bis(tributyltin)sulfide are: its solubility in most organic solvents, its commercial availability, its stability in usual atmospheric conditions, its non-hygroscopicicity and the neutral, anhydrous conditions used for achieving sulfide formation In summary, we presented a reagent possessing many practical advantages compared to the classic salt "Na_2S".

I clearly demonstrated the flurorodestannylation concept with organotin sulfides as a novel method for releasing one of the most nucleophilic sulfur anions known to date. Five new different organotin sulfides were shown to be powerful sulfur transfer reagents in the presence of fluoride or cyanide ions Cyanodestannylation was also briefly introduced in organotin chemistry. Professor Harpp and I introduced the term fluorodestannylation in chemistry.

To overcome the lack of active but anhydrous nucleophilic fluorinating agents, I developed some new anhydrous fluorinating systems: the combination of crown-ethers with cesium fluoride in a solid-liquid phase transfer catalysis. I demonstrated that edge or sandwich complexes of the cesium cations with 18-crown-6 produced a relative rate increase of fluorination comparable to 24-crown-8. New insights were thus provided about the relative rates of nucleophilic substitutions in these phase-transfer catalysis, sandwich or edge complexes produced almost the same overall effect in these reactions compared to a classic 1:1 host-guest ratio where the cation fits well in the cavity of the crown-ether.

In chapter 3, I demonstrated the wide applications and generality of the fluorodestannylation methodology. It showed that highly active oxygen, sulfur, selenium anions can be released from the treatment of organotin oxides, sulfides and selenides with fluoride ions Practical, stable and powerful synthetic equivalents of "O^{2-}", "S^{2-}","Se^{2-}", "R-O^{-}", "R-S^{-}" anions were thus presented. Previously, there was no real report on nucleophilic "O^{2-}" and "Se^{2-}" transfer agents In addition, I investigated the possibility of using some tetraalkyltins for making C-C bond formation while employing the fluorodestannylation idea. Tetraallyltin was shown to react with aldehydes in a mild way. In summary, we clearly demonstrated that organotins act as "group 16 transfer agents" under mild and almost neutral conditions in the presence of fluoride ions.

In chapter 4, the broader concept of fluorodemetalation was introduced. The whole group 14 (excepted carbon) can be fluorodemetalated for releasing anions For instance, it was showed that organosilicon, -germanium,-tin and lead sulfides can release sulfur anions in the presence of fluoride ions. The first reactions of fluorodegermanylation and

fluorodeplumbylation were reported. In addition, we provided insights into the mechanism of these reactions. I showed from ^{19}F and ^{119}Sn NMR spectroscopy that pentacoordinated species having sulfur and fluoride ligands are present in these processes. I contributed by showing the first spectroscopic evidences of pentacoordinated intermediates in the substitution mechanism at tin. Finally, I proposed that a metal or metalloid atom of group 14 directly attached to an anion of the form $R_3M\text{-}Nu^-$ will increase the nucleophilicity of the latter in abscence of severe steric hindrance coming from the ligands on the metal (R= aralkyl group; M= Si, Ge, Sn, Pb).

In chapter 5, I demonstrated a new way to convert primary organic halides into alcohols in one step, under mild and almost neutral conditions. Despite the simplicity of this conversion, only rare methodologies exist for achieving this transformation. This procedure uses silver salts, the commercial bis(tributyltin)oxide (produced in bulk quantities) and the organic halide (bromide or iodide) in order to achieve this process. Again, bis(tributyltin) oxide acted as an oxygen transfer agent. It was the first investigation of a reaction with silver salts used in tandem with organotins.

APPENDIX I

EXPERIMENTAL DETAILS RELATED TO COMPLEXATION OF CROWN-ETHERS AND CESIUM FLUORIDE.

In addition to Section 2.2 , we thought it was appropriate to give more experimental details than those presented in the communication entitled : "New Anhydrous Fluorinating Systems: the Combination of Crown-Ethers and Cesium Fluoride. A Relative Rate Study." This appendix will clarify some procedures and techniques used to publish this article.

1.0 Chemicals.

Most chemicals reported have been previously made and the procedures for synthesizing and purifying them are known. Literature related to those compounds and their purification are provided in section 2.2. However, it seems appropriate to describe the preparation of benzyl (tributyltin) sulfide by the procedure of Talley and Colley[1].

Benzyl (tributyltin) Sulfide [$PhCH_2SSnBu_3$]: In a well ventilated fume-hood, to benzylmercaptan (3.73 g.; 30 mmol) is added freshly distilled THF from sodium/benzophenone (75 mL), followed by tributyltin hydride (8.73 g.; 30 mmol). At 20°C, the addition of a catalytic amount of chlorotris(triphenylphosphine) rhodium (36 mg; 0.10 mol%) immediately produces a dark red colored solution from which a large amount of hydrogen is released. After 10 min., the evolution of gas is almost stopped but the mixture is further stirred for 2 hrs at 20°C for ensuring completion of the reaction. THF is evaporated and the crude liquid is recovered (12.35 g.). A distillation under vacuum (0.25 mm Hg) provides a colorless liquid. The first fractions are discarded and the main fraction having a boiling point of 190°C (0.25 mm Hg) is kept (lit.[1] 145°C/0.15 mm Hg). Pure benzyl (tributyltin) sulfide is obtained as a colorless liquid (7.08 g.), followed by less pure fractions (4.31 g.). ^1H NMR ($CDCl_3$, TMS_{int}, 200 MHz). δ= 7.30 (Ph, m., 5 H), 3.76 ($PhCH_2$, s, 2 H); 1.50 ($CH_3CH_2CH_2CH_2Sn$, m., 6 H), 1.31 ($CH_3CH_2CH_2CH_2Sn$, quintuplet, 6 H), 1.02 (CH_2Sn, t., 6 H), 0.87 (CH_3, t., 9 H) ppm; ^{119}Sn NMR ($CDCl_3$, $Me_4Sn_{int.}$, 200

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1. Talley, J. J.; Colley, A. M. *J. Organomet. Chem* **1981**, *215*, C38.

MHz): δ= 75.65 ppm ; I.R. (neat, max.): 3060, 2955, 2920, 2870, 2845, 1600, 1490, 1460, 1450, 1375.

2.0 Relative rate study in the fluorination of benzyl bromide.

2.0.1. Selection of the analytical method.

Two distinct analytical methods were used in order to verify the accuracy of our results: gas chromatography and ^1H NMR spectroscopy (200 MHz).

Procedure: In a 50 mL flask, is placed freshly distilled benzyl bromide (0.987 g.; 0.686 mL; 5.77 mmol) and flame-dried cesium fluoride (1.519 g.; 10.0 mmol) plus dried acetonitrile (on CaH_2). To this mixture is added dried 18-crown-6 (0.320 g.; 1.21 mmol).[2] The reaction mixture is refluxed at 80°C with the use of an heating mantle. A small portion of the liquid is extracted after different period of time and analyzed by gaz chromatography and ^1H NMR. Our preliminary results indicated that both methods gave essentially the same results but we noted a small decomposition of benzyl bromide on the GC column at 90°C (retention time: $PhCH_2Br$ (6.2 min.); $PhCH_2F$ (2.2 min.) and impurity (4.2 min.). The description of the GC instrument was previously reported in the experimental section 3.4. We therefore decided to investigate the rate of these reactions from ^1H NMR spectroscopy while evaluating the integration area under the benzylic proton signals of benzyl bromide ($CDCl_3$, 4.67 ppm, singlet) and benzyl fluoride ($CDCl_3$, 5.34 ppm, doublet). No side reaction was apparent from ^1H NMR. Each sample taken from the mixture was diluted with $CDCl_3$ in order to get the lock signal on the spectrometer; no evaporation or other manipulations that could change the ratio of the two major products (benzyl fluoride and bromide) were done. Tables 1 and 2 present the results.

2.0.2. Relative rate study by ^1H NMR spectroscopy.

The above procedure was repeated but without any crown-ether. The stirring of this mixture and the heating were carefully reproduced. Again, some samples were extracted from the flask and analyzed by ^1H NMR. Table 1 shows the data obtained with and without 18-crown-6, as catalyst Finally, figure 1 demonstrates the change of the relative concentrations

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[2] Dried accordingly to. Gokel, G. W., Cram, D. J. *J. Org. Chem.* **1974**, *39*, 2445.

of benzyl bromide and fluoride with time in the presence of 18-crown-6. The example below shows how the percentage of conversion to the benzyl fluoride was evaluated:

$$\% \text{ conversion} = [\text{area } PhCH_2F / \text{area } PhCH_2Br + \text{area } PhCH_2F] \times 100$$

In Figure 3 (p. 55), the formation of benzyl fluoride vs time is reported. The slope of the curve at the origin gave the initial reaction rate. In this evaluation, we assumed no loss of any material, no side products and that the absolute NMR sensitivity of both benzylic proton $PhCH_2F$ and $PhCH_2Br$ signals are approximately equal at equal concentrations.

2.1 Relative rate study in fluorodestannylation.

As the results with the ^1H NMR technique previously used was satisfactorily, we decided to utilize it again with rate studies in a fluorodestannylation reaction.

Procedure: Benzyl (tributyltin) sulfide (317 mg; 0.767 mmol), 1-iodohexane (168 mg; 0.792 mmol) and CD_3CN (1.80 mL) are added to a flask under nitrogen atmosphere at 20°C. After stirring with flame-dried cesium fluoride (966 mg; mmol), small amounts of sample are taken at different time intervals, diluted with $CDCl_3$ and NMR spectra recorded. In these rate studies, the conversion into n-hexyl benzyl sulfide is followed by the integration of the benzylic proton signals of benzyl (tributyltin) sulfide (3.78 ppm; singlet) and n-hexyl benzyl sulfide (3.71 ppm; singlet). The same procedures are repeated but with an addition of 18-crown-6 (25 mg; 0.095 mmol)[2] or dibenzo 24-crown-8 (42 mg, 0.094 mmol). No significant side-product is observed in these reactions. Table 2 is a compilation of these data.

The example below shows how the percentage of conversion to n-hexyl benzyl sulfide is evaluated:

$$\% \text{ conversion} = [\text{area } PhCH_2\text{-S-Hex} / \text{area } PhCH_2SSnBu_3 + \text{area } PhCH_2\text{-S-hex}] \times 100$$

In Figure 1 (p. 53), the formation of benzyl n-hexyl sulfide vs time is reported. The slope of the curve at the origin gave the initial reaction rate. In this evaluation, we assumed no loss of any material, no side products and that the absolute NMR sensitivity of both benzylic proton signals of the two compounds are approximately equal at equal concentrations. Figure 2 shows the variation of the relative concentrations of n-hexyl benzyl sulfide, benzyl (tributyltin) sulfide and 1-iodohexane with time in the presence of CsF. Finally, figure 3

shows the variations while adding a catalytic amount of 18-crown-6. In Figure 1, p. 53, the slope of the curve at the origin give the initial rate of the reaction.

Table 1: Fluorination of Benzyl Bromide with CsF. Relative Rate Studies by ^{1}H NMR

Without 18-crown-6

Time (min.)	Conversion (%)
0	0.0
15	3.4
30	8.6
60	13.0
90	17.0

With 18-crown-6

Time (min.)	Conversion (%)
0	0
30	47
60	76
100	90

Table 2: Formation of n-Hexyl Benzyl Sulfide by Fluorodestannylation. Relative Rate Studies by ^{1}H NMR.

Without 18-crown-6

Time (min.)	Conversion (%)
0	0
36	28
79	54
110	66
150	76
200	82
285	88

With 18-crown-6

Time (min)	Conversion (%)
0	0
15	38
39	60
56	70
89	81
114	84
200	94

With dibenzo 24-crown-8

Time (min)	Conversion (%)
0	0
15	42
30	58
58	76
100	86
150	91

Figure 1: ^{1}H NMR Rate Study With Dried CsF, 18-crown-6 and Benzyl Bromide.

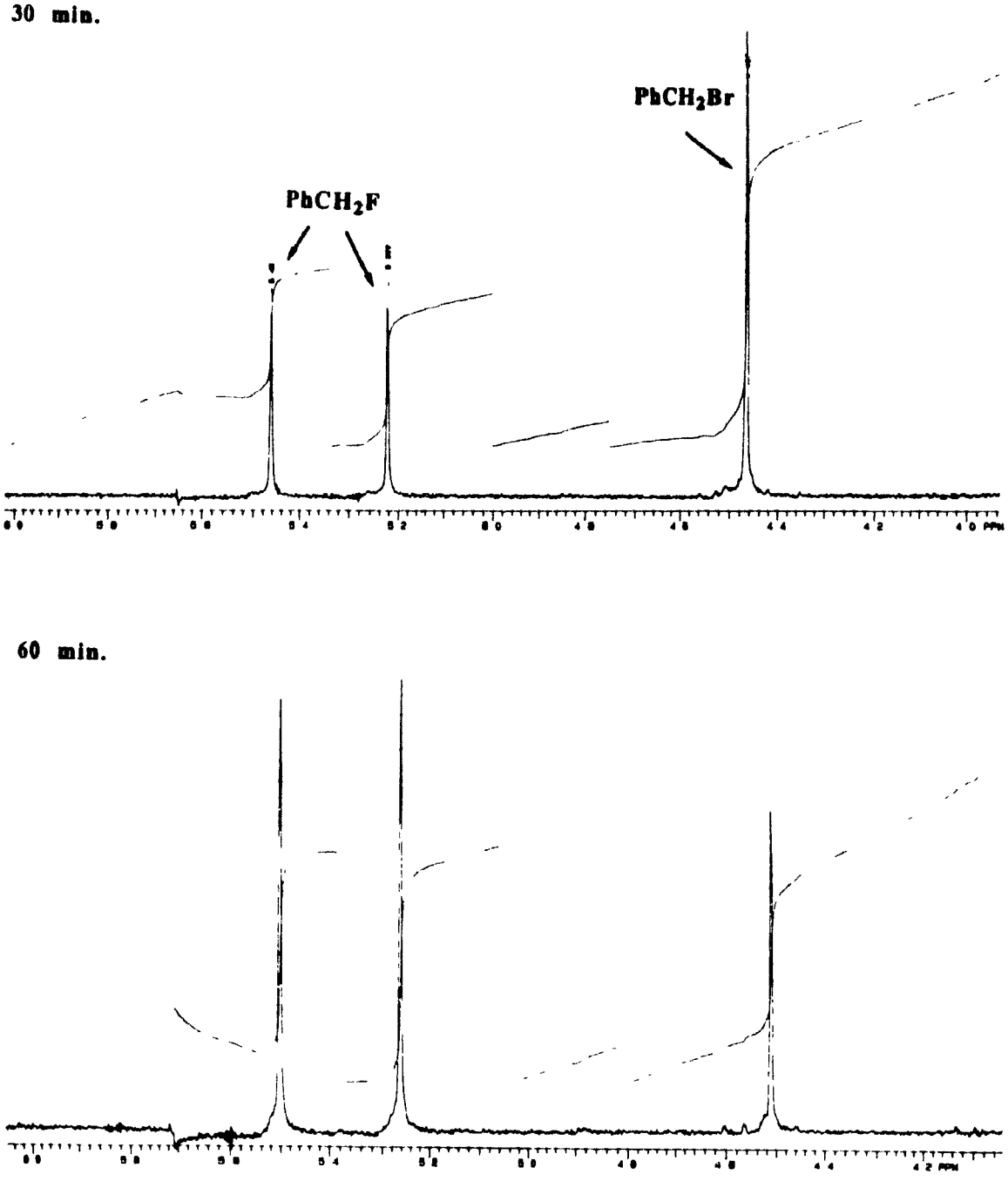


Figure 1: ^{1}H NMR Rate Study With Dried CsF, 18-crown-6 and Benzyl Bromide.

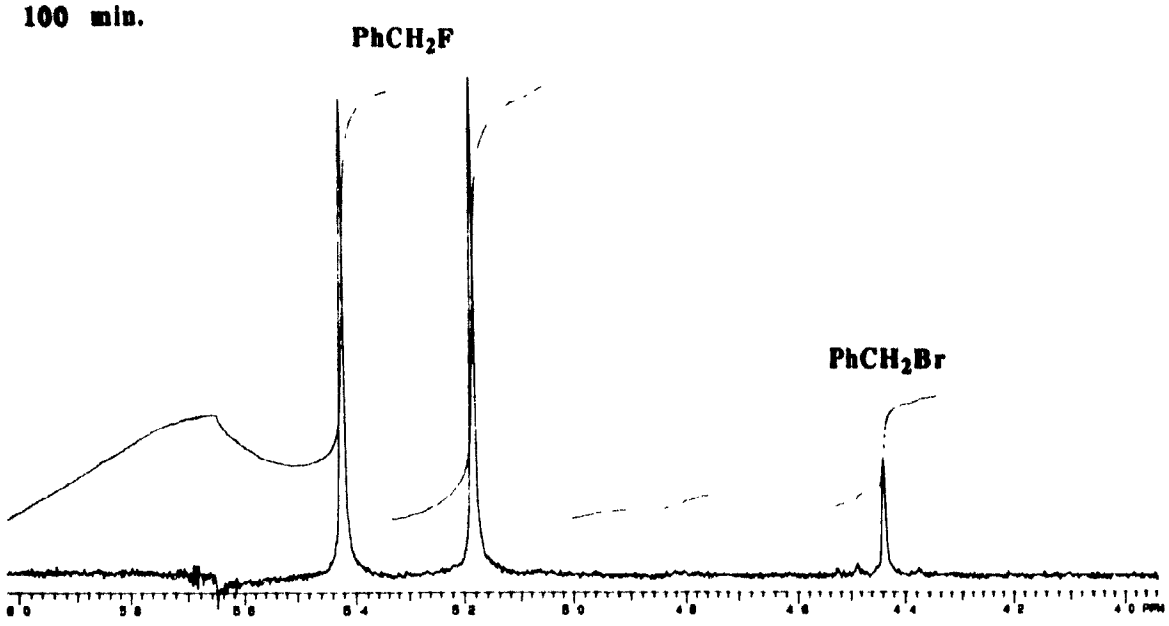


Figure 2: ^1H NMR Rate Study With Dried CsF, $PhCH_2SSnBu_3$ and 1-iodohexane.

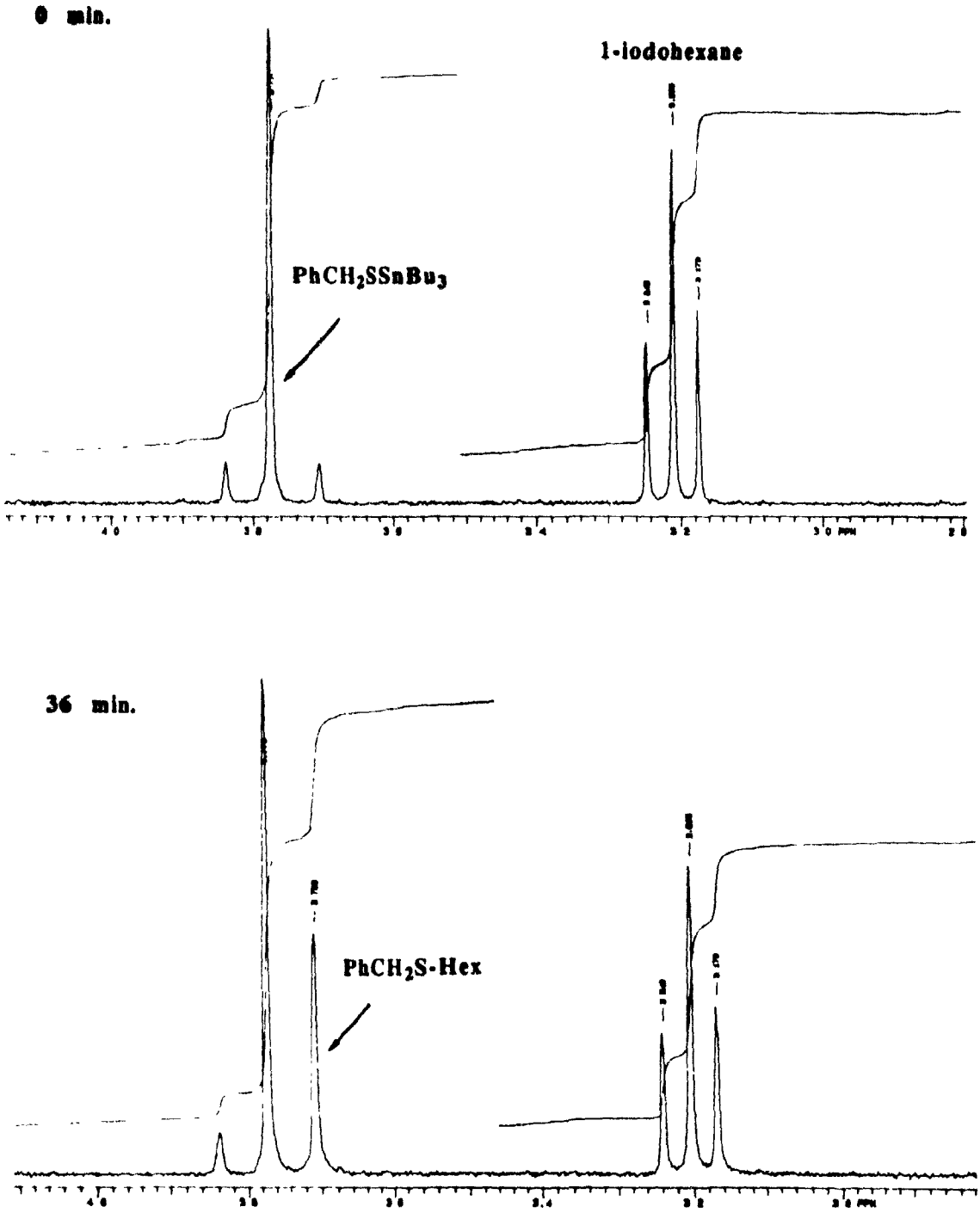


Figure 2: ^{1}H NMR Rate Study With Dried CsF, $PhCH_2SSnBu_3$ and 1-iodohexane.

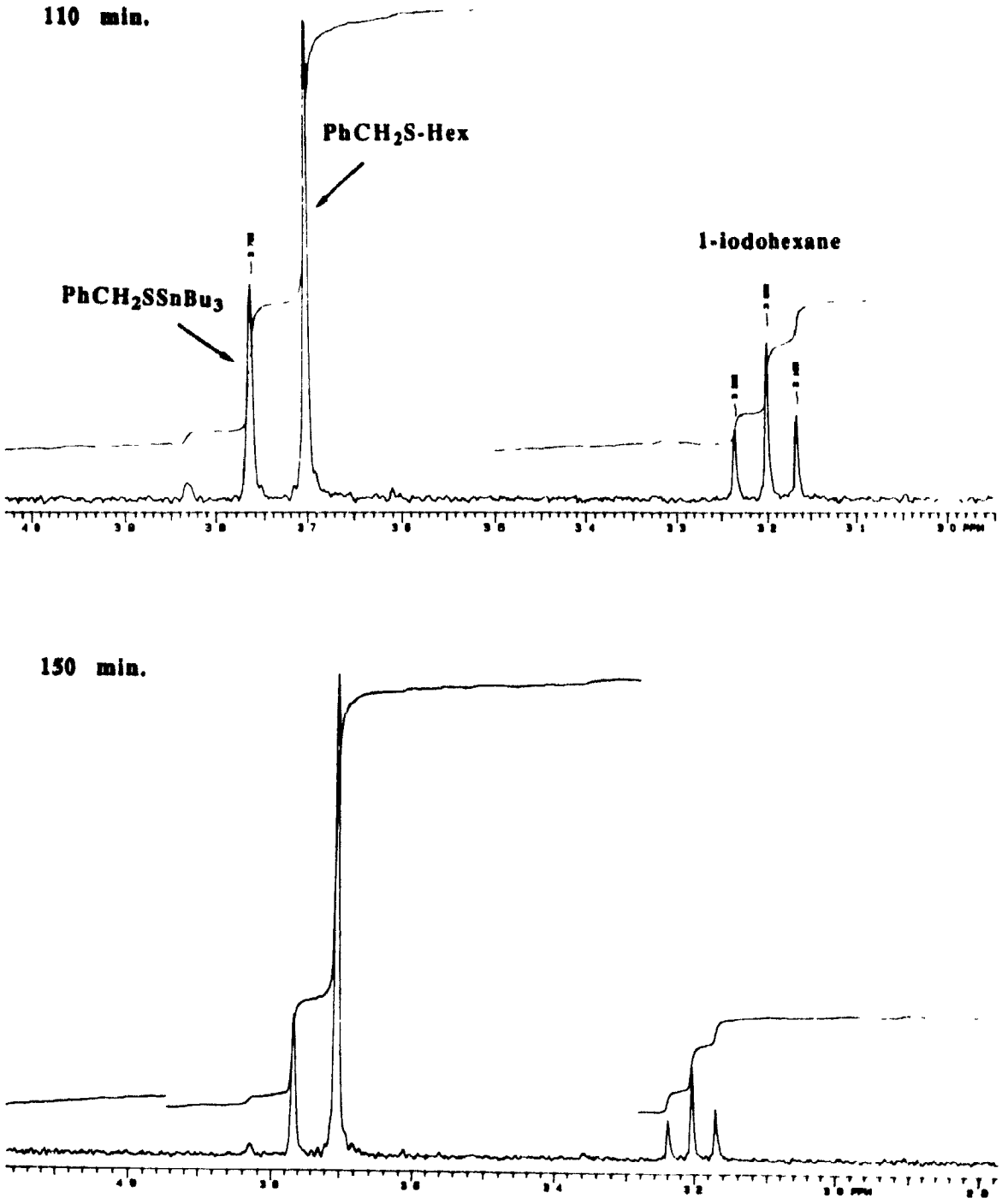


Figure 2: ^{1}H NMR Rate Study With Dried CsF, $PhCH_2SSnBu_3$ and 1-iodohexane.

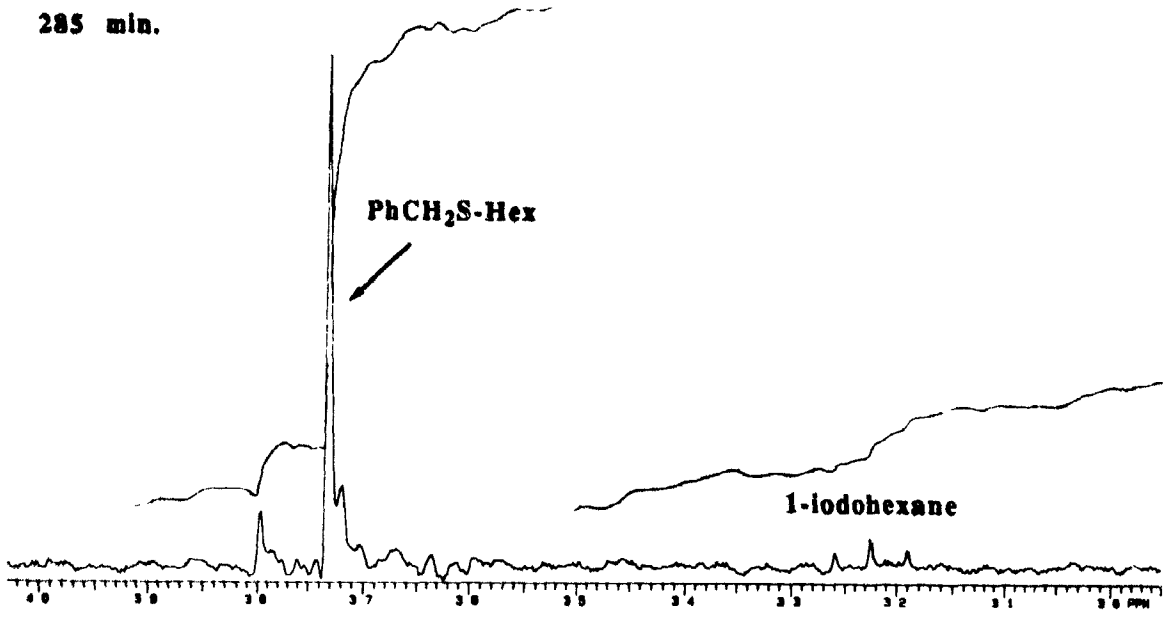


Figure 3: ^{1}H NMR Rate Study With CsF, 18-Crown-6, $PhCH_2SSnBu_3$ and 1-iodohexane.

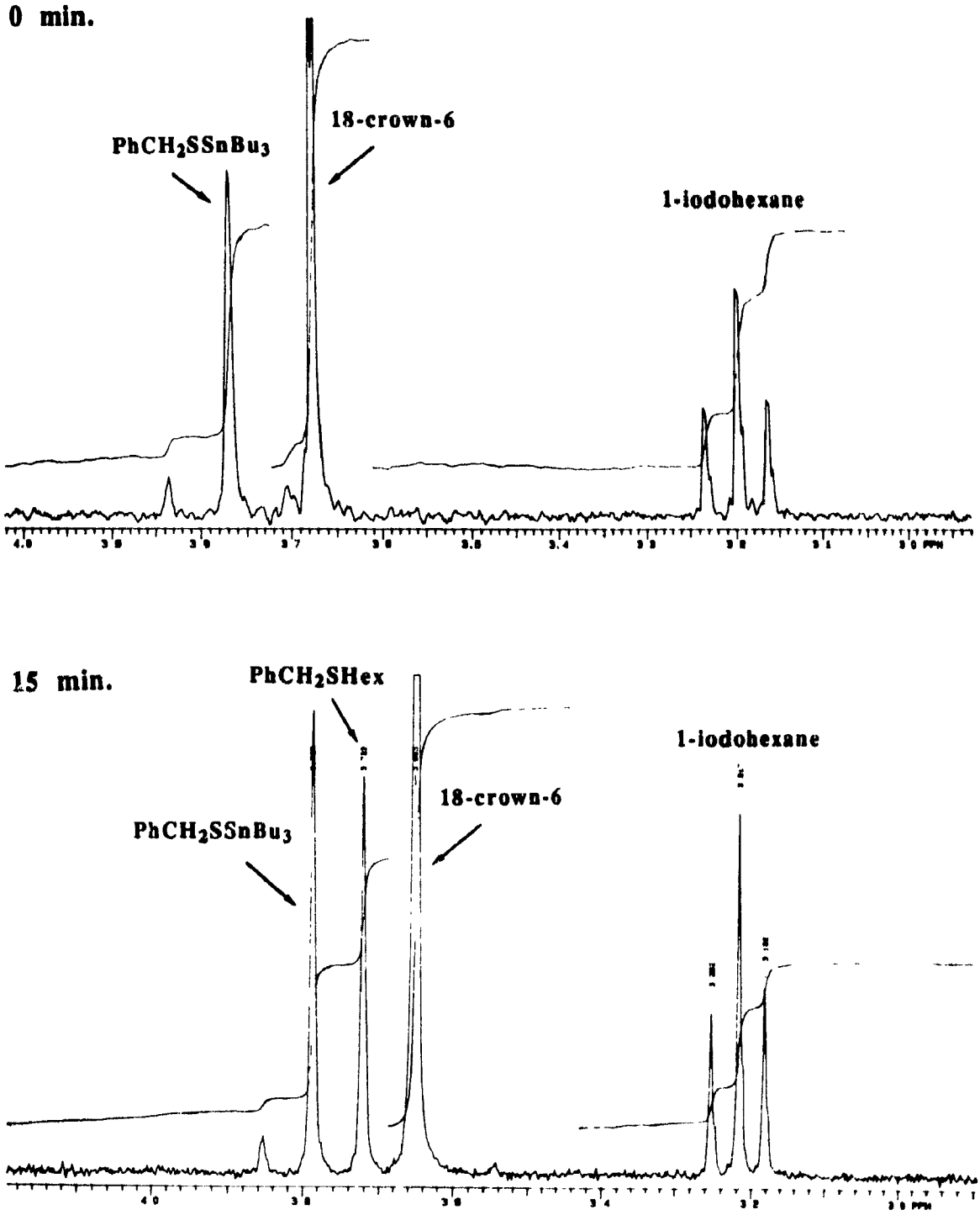


Figure 3: ^{1}H NMR Rate Study With CsF, 18-Crown-6, $PhCH_2SSnBu_3$ and 1-iodohexane.

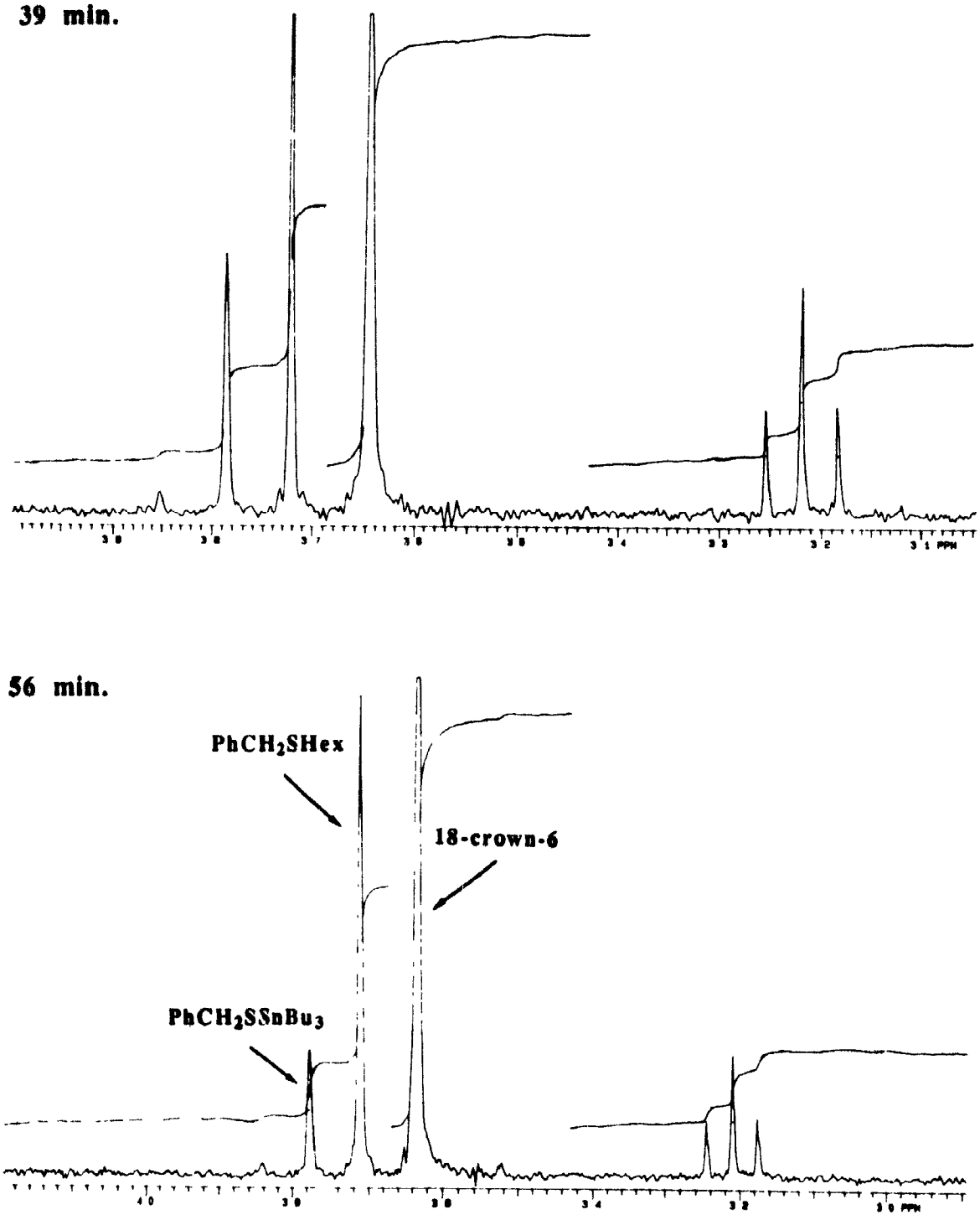
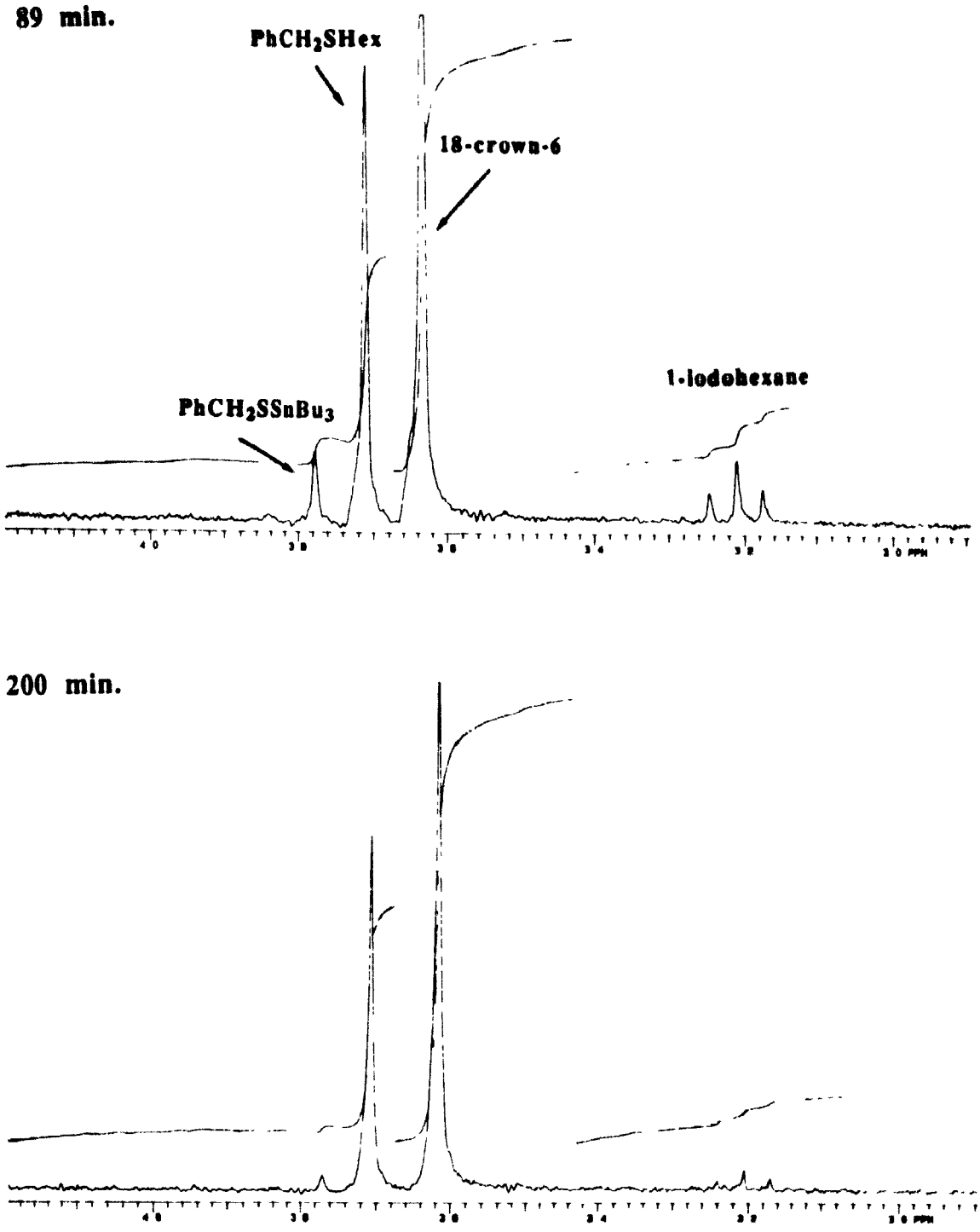


Figure 3: ^{1}H NMR Rate Study With CsF, 18-Crown-6, $PhCH_2SSnBu_3$ and 1-iodohexane.



APPENDIX II

SUPPLEMENTAL PROCEDURES AND DETAILS RELATED TO THE CONVERSION OF ORGANIC HALIDE TO ALCOHOL PROMOTED BY SILVER SALTS AND BIS(TRIBUTYLTIN) OXIDE.

In addition to section 5.0, we would like to give supplemental experimental details related to some procedures used in the publication of this communication. We also thought that it is appropriate to delineate a possible mechanism for the conversion of organic halides into alcohols, based on working hypothesis.

1.0 Chemicals.

Most chemicals mentioned as starting materials in this study where commercially available and utilized as received. For instance, bis(tributyltin) oxide, the various silver salts and most organic halides were bought from Aldrich Chemical Co. However, (2-iodoethyl) benzene is prepared from the corresponding bromide from the Finkelstein reaction. The procedure is described below:

(2-iodoethyl)benzene: In a 50 mL flask is placed (2-bromoethyl)benzene (2.00 g.; 10.8 mmol), sodium iodide (5.51 g ; 32.4 mmol) and dried acetone spectrograde quality (30 mL). The reaction is refluxed (45-50°C) under nitrogen atmosphere. The mixture turns deep yellow within a few min.. After 1 hour, the mixture is cooled and the solvent evaporated. A filtration on silica gel (short column) with hexane as eluent and evaporation of the solvent gives a colorless liquid. Complete removal of solvent under high vacuum yields (2-iodoethyl)benzene (1.850 g; 7.97 mmol; 74 % yield). ^{1}H NMR (200 MHz) shows complete conversion of the bromide into the iodide and excellent purity. ^{1}H NMR ($CDCl_3$, $TMS_{int.}$, 200 MHz): δ= 7.33 (H_{ortho} + H_{para}, m., 3 H), 7.23 (H_{meta}, m, 2 H); 3.37 ($PhCH_2$, t., 2 H); 3.23 (CH_2I, t , 2 H). TLC (SiO_2, hex. as eluent, I_2 or U.V.): 1 spot. R_f= 0.67.

2.0 Typical procedures.

2.0.1 Conversion of Primary Alkyl Iodides Into Alcohols.

1-hexanol: A 50 mL flask is charged with 1-iodohexane (683 mg; 3.22 mmol), bis(tributyltin)oxide (2.11 g.; 3.54 mmol; 1.80 mL) and DMF (10 mL) dried on CaH_2. Silver tosylate is added by small portions over 5 min. (988 mg; 3.54 mmol) while stirring vigorously at 20°C. After 2.0 hrs, GC showed 74% conversion and some organic iodide remains unreacted. A black precipitate is formed in the mixture. After 5.5 hrs, the reaction is unchanged. The whole mixture is filtered through a pad of celite; water (30 mL) and ether (30 mL) are added. After stirring for 5 min., the phases are separated and the organic one washed with water (3 x 20 mL) and dried on $Na_2SO_4/MgSO_4$. A flash chromatography using 10% acetone/90% hexane as eluent is initially done. The acetone content is increased slowly to 20%. 1-Hexanol is obtained in good purity (249 mg; 2.44 mmol, 76% yield) ^1H NMR ($CDCl_3$, $TMS_{int.}$, 200 MHz). 3.66 (CH_2OH, t, 2 H), 1.60 ($\mathbf{CH_2}CH_2OH$, quintuplet, 2H), 1.30 ($\mathbf{CH_2CH_2CH_2}CH_2CH_2OH$, m., 6 H); 0.90 ($CH_3$, t., 3H). It was identical as with authentic material (GC and ^1H NMR); note: 2 2 eq. of bis(tributyltin)oxide increased the yields of many reactions.

2.0.2 Conversion of Primary Alkyl Bromides Into Alcohols.

1-hexanol: A 50 mL flask is charged with 1-bromohexane (529 mg; 3 22 mmol), bis(tributyltin)oxide (3.83, 6.44 mmol), dried DMF on CaH_2 (10 mL) and silver tosylate (988 mg; 3.54 mmol). The mixture is immediately heated at 90°C for 22.5 hrs. After cooling, some ether is added (40 mL) and the mixture filtered on a pad of celite. The organic phase is washed with water (4 x 20 mL). An aqueous KF solution is added and the mixture stirred vigorously for 15 at R.T.. Filtration on a pad of celite followed by the separation of the phases, drying of the organic one on Na_2SO_4 and evaporation of the solvent afforded crude 1-hexanol. A filtration of the product on silica gel while using pure EtOAc, followed by a flash chromatography (10% acetone/90% hexane as eluent) afforded pure 1-hexanol (241 mg, 74% yield). ^1H NMR ($CDCl_3$, TMS_{int}, 200 MHz). same data as the above procedure GC (T° column 60°C; retention time= 4.7 min.) shows an excellent purity Comparisons with authentic material gives the same results by GC and ^1H NMR.

2.0.3 Conversion of Primary Organic Halides Into Alcohols.

A direct conversion of primary organic chlorides into alcohols is found to be almost impossible with the usual metods. We will thus describe a preliminary conversion of the chloride into the iodide from the Finkelstein reaction, followed by the usual method for converting organic iodide into alcohols (with silver salts and bis(tributyltin)oxide).

2.0.4 Conversion of Primary Organic Chlorides Into Iodides.

1-iodononane: In a 100 mL flask is added 1-chlorononane (961 mg; 5.90 mmol; 1.10 mL), NaI (2 66 g., 17.7 mmol) and dried acetone (spectrograde) (50 mL). The mixture is refluxed under nitrogen for 21.5 hrs. At this time, GC shows good conversion (86% yield) but after 42 hrs, the conversion is almost complete (98% yield). Acetone is evaporated and ether is added. A filtration on a plug of silica gel followed by evaporation of ether affords a colorless liquid corresponding to pure 1-iodononane. GC shows excellent purity and only a tiny amount of 1-chlorononane is observed as impurity. ^1H NMR ($CDCl_3$, $TMS_{int.}$, 200 MHz): δ= 3.18 (CH_2I, t., 2 H); 1.82 ($\mathbf{CH_2}CH_2I$, quintuplet, 2 H); 1.26 (m., 12 H); 0.90 (CH_3, t., 3 H).

1-iodononane into 1-nonanol: Without any further purification, 1-iodononane (419 mg; 1 65 mmol) as prepared above, is added to bis(tributyltin)oxide (2.16 g.; 3.63 mmol; 1.85 mL) and dried DMF (6.0 mL). Silver nitrate (561 mg; 3.30 mmol) is added to the main flask in small portions while stirring vigorously at 20°C. After 3 hrs, GC showed 51% conversion. Despite some prolonged heating at 55-60°C, the reaction does not proceed further. The alcohol was not isolated but GC and crude NMR spectra clearly demonstrate the presence of 1-nonanol. GC data are identical with authentic 1-nonanol.

Note: For converting bromides into alcohols, this alternative procedure can be utilized instead of a direct conversion of bromides into alcohols as previously demonstrated above.

3.0 Ag_2O as Possible Oxygen Transfer Agent in These Reactions.

In order to determine to which extent both oxygen transfer agents, bis(tributyltin)oxide and silver oxide, could contribute to form alcohols, we investigated some specific reactions. First, we carried out a trial under essentially the same conditions as in above but in the presence of Ag_2O and in the abscence of bis(tributyltin)oxide. The following procedure is reported:

In a 50 mL flask is added 1-bromohexane (531 mg; 3.22 mmol), Ag_2O (820 mg; 3.54 mmol) and DMF dried on CaH_2 (10 mL). The mixture is heated with an oil bath at 90°C while stirring vigorously. After 22 hrs, GC shows a small amount of alcohol formed. After cooling, the same work-up procedure as in section 2.0.2 is followed. 1-Hexanol is obtained in very low yield as an impure product (< 40 mg.; < 12% yield).

A second reaction definitively demonstatrates that bis(tributyltin)oxide is the major oxygen transfer agent in these reactions and that Ag_2O promotes this process:

In a 50 mL flask is added 1-bromohexane (531 mg, 3.22 mmol), dried DMF on CaH_2, Ag_2O (820 mg; 3.54 mmol) and bis(tributyltin)oxide (2.110 g; 3.54 mmol, 1.80 mL). The mixture is stirred vigorously while heating at 90°C for 14.5 hrs. After cooling, the same work up procedure is applied as in section 2.0.2. 1-hexanol is obtained as a colorless liquid (234 mg; 71%). ^1H NMR ($CDCl_3$, TMS_{int}, 200 MHz) indicates the same spectra as already reported in section 2.0.1..

4.0 Mechanistic Considerations.

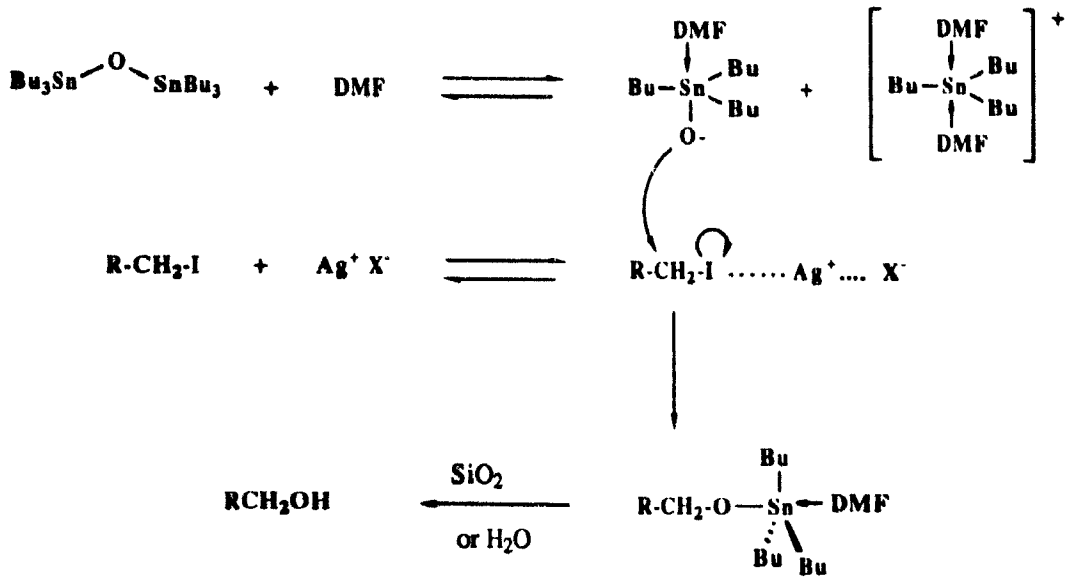
We described several indices about the reaction mechanism in section 5.0. First, a strong donor solvent effect (e.g. DMF) supposes penta or hexacoordinated organotin oxides as possible nucleophilic species. Secondly, silver salts seem to be involved in two different processes: a direct reaction with bis(tributyltin)oxide for giving Ag_2O and as Lewis acid (as Ag^+ species) that slightly coordinate the halide atom. Thirdly, bis(tributyltin)oxide also participates in two distinct processes: the reagent acts as an oxygen transfer agent but is also destroyed by silver salts for forming Ag_2O;. the latter compound beeing must less acid than Ag^+ ions.

Several arguments hold in favor of the third statement. With most organic iodides, the reactions are fast and do not require heat. Consequently, Ag_2O formation is probably slower than the transfer of oxygen from bis(tributyltin)oxide to the halide In contrast, organic bromides react slowly and as a consequence, bis(tributyltin)oxide tends to react with silver salts for giving Ag_2O. To confirm this, all different silver salts were equally effective with organic bromides. It might also be possible that Ag_2O is formed in both cases with iodides and bromides but that the rate of oxygen substitution with iodides is simply faster than with bromides. However, this assumption is not valid because we observed good yield of alcohol formation with only 1.1 equivalent of bis(tributyltin)oxide In this case, if Ag_2O is formed, we should not observe a significant yield because Ag_2O is not a good oxygen transfer agent. Although the reaction of bis(tributyltin)oxide and silver salts is almost spontaneous at R.T. in DMF, it is probable that Ag_2O is not the main Lewis acid with iodides but "free silver cations" (Ag^+) are present in sufficient concentration.to promote iodide-alcohol conversion prior to react with bis(tributyltin)oxide. In contrast, Ag_2O seems to be the main Lewis acid with

organic bromides A control experiment while using Ag_2O as Lewis acid instead of AgTos gave almost the same results (see entries 3 and 4; Table 1 in section 5.0).

Scheme 1 and 2 picture possible mechanism for organic iodides and bromides based on a working hypothesis.

Scheme 1: Possible Mechanism With Organic Iodides



Scheme 2: Possible Mechanism With Organic Bromides.