INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

New Aspects of

Organochalcogen Chemistry

Erwin Schultz

A thesis Submitted to the Faculty of Graduate Studies and Research in

Partial Fulfillment of the Requirements for the of Degree of

Doctor of Philosophy

Department of Chemistry
McGill University
Montreal, Quebec, Canada

© Erwin Schultz, August 1999

National Library of Canada
Bibliothèque nationale du Canada

Acquisitions and Bibliographic Services
Acquisitions et services bibliographiques

395 Wellington Street
Ottawa ON K1A 0N4
Canada

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-64663-7

Canada

I dedicate this thesis to the

memory of Valerie Parsons.

Valerie you will always be a part of me,

Thanks for the three wonderful years

you have given me.

To my parents Wolfgang and Alice Schultz,

for all their love and support.

For my sister Sonja.

"Results! Why man, I have gotten a lot of results. I know several thousand things that won't work."

Thomas A. Edison

"If I have a thousand ideas and only one turns out to be good, I am satisfied."

Alfred Nobel

ABSTRACT

The potential of chalcogen containing reagents in organic synthesis was investigated. More specifically, the efficiency of bis(triphenylstannyl) selenide (**105**) and bis(*tert*-butyldimethylsilyl) telluride (**95**) in the reductive dehalogenation of α-halocarbonyl compounds was illustrated. The mechanism of the dehalogenation process was also examined. The intermediacy of a transitional enolate species was established by the successful isolation of the chalcone condensation product, resulting from reaction with benzaldehyde. A difference in the reactivity of bis(triphenylstannyl) selenide (**105**) and bis(*tert*-butyldimethylsilyl) telluride (**95**) in the dehalogenation process was discerned.

An investigation directed at the elaboration of a system capable of generating a diatomic selenium unit was carried out. The thermal decomposition of titanocene pentaselenide (**177**), in the presence of diene trap 2,3-diphenyl-1,3-butadiene (**153**), was demonstrated to generate the monoselenide adduct 2,5-dihydro-2,3-diphenylselenophene (**207**). In the process, ^{1}H NMR evidence was obtained for the formation of diselenide **180**, indicative of the generation of a diatomic selenium species. Extensive refluxing of a reaction mixture composed of titanocene pentaselenide (**177**) and 2,3-diphenyl-1,3-butadiene (**153**) was shown to ultimately result in the formation of 3,4-diphenylselenophene (**181**). Mechanisms were proposed to account for these processes.

RÉSUMÉ

Le potentiel de réactifs contenant des chalcogènes pour la synthèse organique a été étudié. Plus précisemment, l'efficacité du bis(triphénylstannyl) sélénide (**105**) et du bis(*tert*-butyldiméthylsilyl) telluride (**95**) lors de la déhalogénation réductive de composés α-halocarbonylés a été démontrée. Le mécanisme de cette réaction de déhalogénation a également été examiné. L'existence d'un intermédiaire énolate a été établie grâce à l'isolation d'une chalcone, produit de condensation formé lors de la réaction avec du benzaldehyde. Une différence au niveau de la réactivité du bis(triphénylstannyl) sélénide (**105**) et du bis(*tert*-butyldiméthylsilyl) telluride (**95**) lors de la réaction de déhalogénation a été décelée.

Une étude dirigée vers l'élaboration d'un système capable de générer du sélénium diatomique a été entreprise. La décomposition thermique du titanocène pentasélénide (**177**) en présence d'une diène de piègeage, le 2,3-diphényl-1,3-butadiène (**153**), a permis de former le monosélénide 2,5-dihydro-2,3-diphénylsélénophène (**207**). Lors de ces réactions, la formation du disélénide (**180**) a été mise en évidence par RMN du ^{1}H. Ceci indique clairement la formation de sélénium diatomique. Le reflux prolongé d'un mélange réactionel composé de titanocène pentasélénide (**177**) et de 2,3-diphényl-1,3-butadiene (**153**) a démontré la formation de 3,4-diphénylsélénophène (**181**) comme composé final. Des mécanismes ont été proposés pour expliquer ces procédés.

ACKNOWLEDGEMENTS

First of all, I would like to express my deepest gratitude to Dr. David Harpp for giving me the opportunity of pursuing my graduate studies in his research group. His enthusiasm and dedication to both research and teaching has greatly inspired me. I cannot say enough about his remarkable human qualities and his support in some difficult times.

I would like to thank Christopher Parsons for his friendship and for some really great trucking trips. You have done a lot for me Chris, thanks!

A special thanks to Mia and Fons Houben who have always been like parents to me and whose enduring friendship is very important to me.

Pierre Lesté-Lasserre for the great many interesting discussions (both in and outside of the lab), ranging from chemistry to covering the wide world of sports. I'll miss your detailed baseball analyses and when France has a national baseball team I expect to see you do the play by play analysis. Thanks for always being there.

Ravi, what can I say. Thanks for the many outings on the town.

Thank you to all my colleagues past and present who made Room 240 a fun place to be: Sylvie Tardif, Ron Priefer, Cathy Bsilis, Charles Abrams, Andrzej Rys, Eli Zysman-Coleman and Imad Abu-Yousef.

Dr. Françoise Sauriol for assistance in NMR experiments, Dr. Anne-Marie Lebuis for the X-ray analysis and Dr. Orval Mamer and Mr. Nadim Saadeh for the recording of mass spectra.

Discussions with Dr. Farrell and Dr. Gleason were very much appreciated.

Ms. Renée Charron for her help in administrative matters.

GLOSSARY OF ABREVIATIONS

α	alpha
δ	chemical shift
γ	gamma
%	percent
A. D.	anno Domini
Ag	silver
Ar	argon
Au	gold
Bp.	boiling point
b	broad (in NMR)
ca.	circa
^{13}C NMR	carbon NMR
°C	degrees Celsius
$CDCl_3$	deuterated chloroform
Ce	cerium
CH_2Cl_2	methylene chloride
CI	chemical ionization
2-D	two-dimensional
d	doublet (in NMR)
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et_2O	diethyl ether

EtOAc	ethyl acetate
EtOH	ethanol
EI	electron impact
eV	electron volt
FAB	Fast Atom Bombardment
g	gram
h	hour, heptet (in NMR)
^{1}H NMR	proton NMR
Hg	mercury
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
^{o}K	degrees Kelvin
Ir	iridium
IR	infrared
j	coupling constant
K_2CO_3	potassium carbonate
kcal	kilocalories
Kr	krypton
$LiAlH_4$	lithium aluminum hydride
lit.	literature
M	molarity
M^+	molecular ion
m	meter, multiplet (in NMR)

mg	milligram
$MgSO_4$	magnesium sulfate
mm	millimeter
MHz	megahertz
ml	milliliter
mm	milimeter
mmol	millimole
Mn	manganese
mol	mole
m.p.	melting point
MS	mass spectrometry
N	normality
NBA	4-nitrobenzyl alcohol
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
Na_2Se	sodium selenide
Na_2SO_4	sodium sulfate
Na_2Te	sodium telluride
NaHSe	sodium hydrogen selenide
NaHTe	sodium hydrogen telluride
NMR	nuclear magnetic resonance
o-	ortho
PBr_3	phosphorus tribromide

Ph_3SnCl	triphenyltin chloride
ppm	parts per million
pK_a	negative logarithm of acidity constant K_a
q	quartet (in NMR)
s	singlet (in NMR)
t	tertiary
^{77}Se NMR	selenium NMR
Si	silicon
S_N2	substitution, nucleophilic, bimolecular
t	triplet (in NMR)
t-BuOH	*tert*-butanol
Th	thorium
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
Z	Zusammen

TABLE OF CONTENTS

CHAPTER 2: REDUCTIVE DEHALOGENATIONS OF α-HALOKETONES

CHAPTER 3: THE CHALCOGEN DIATOMICS

CHAPTER 4: EXPERIMENTAL

CHAPTER 1: INTRODUCTION TO ORGANOSELENIUM CHEMISTRY

1.1 Elemental Selenium and Tellurium.

Selenium and tellurium are part of a group of elements generally known as the chalcogens. Both are located in Group VI of the periodic table along with the better known elements, oxygen and sulfur. Selenium has the electronic structure [Ar] $3d^{10}4s^{2}4p^{4}$ and an atomic number of 34 whereas tellurium has the electronic structure [Kr] $4d^{10}5s^{2}5p^{4}$ and an atomic number of 52.

The Austrian chemist Franz Joseph von Reichenstein was the first to isolate tellurium in 1782,[1] a few years after J. Priestly and C. W. Scheele had independently discovered oxygen in 1773-4. The first traces of tellurium were discerned in ores mined in the gold districts of Transylvania.

The Swedish chemist J. J. Berzelius (discoverer of Si, Ce and Th) and J. G. Gahn (discoverer of Mn) are both credited with the discovery of selenium in 1817, about 35 years after the isolation of tellurium.[1]

The scarcity of both elements is reflected by their crustal abundance.[1] The earth's crust contains approximately 0.05 ppm of selenium which is similar to the contributions from Ag and Hg at about 0.08 ppm each. Selenium is ranked 66th in crustal composition.

---

[1] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, Pergamon Press: **1984**, New York; Chapter 16.

Tellurium is ranked 73rd in crustal composition and contributes approximately 0.002 ppm to its make up. Au and Ir show similar contributions at 0.004 ppm and 0.001 ppm respectively. Many of the selenium and tellurium minerals appear in association with the sulfides of the chalcophilic metals.

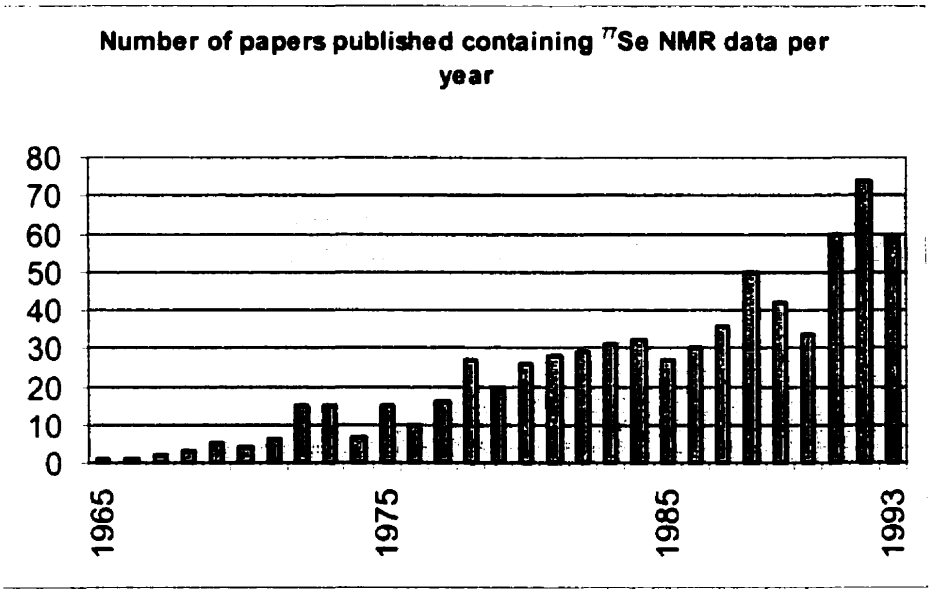
The anode slime that accumulates during the electrolytic refining of copper constitutes the main source of selenium and tellurium.[1] The sparseness of their minerals makes direct recovery not an economically viable option. Selenium finds good use in many industrial applications, of which the decolorization of glass is the largest single one. Xerography and photoconductors are other important industries in which selenium plays a central role. The main application of tellurium can be found in iron and steel production where it serves as an additive for improving machineability.[1] Other minor applications can be found in the production of fuses for explosives and in the development of semiconducting compounds.[2]

Selenium exists in three distinct forms or allotropes.[1] The first form, "red selenium", consists of Se_8 rings, the second form "grey metallic", is made up of helical polymeric chains and finally the third form, "vitreous black", which is also the common commercial form of the element, consists of an extremely complex and haphazard structure of large polymeric rings having up to a thousand atoms per ring. The grey metallic allotrope is the thermodynamically most stable form of selenium and can be obtained by warming the other allotropes.

[2] Cooper, W. C. *Tellurium*, Van Nostrand Reinhold Company: **1971**, New York; Chapter 1, p 1-2.

Tellurium on the other hand possesses only one crystalline form and this constitutes a labyrinth of spiral chains comparable to those in grey metallic selenium.[1]

Selenium has six immutable isotopes of which the most abundant is ^{80}Se (49.6 %).[1] They all have zero nuclear spin with the exception of the 7.6 % abundant ^{77}Se (I=1/2). This isotope has a sensitivity of 0.693 % relative to that of the proton. The low sensitivity, combined with the associated low abundance, causes the detectability of this nucleus to be 5.2×10^{-4} relative to that of the proton. As a consequence, studying this nucleus by magnetic resonance techniques was from the outset a formidable task.[3] The chemical shift range for ^{77}Se is in the range of ~ 3000 ppm.[4] As depicted in the diagram below, the literature containing ^{77}Se NMR data was few and far between prior to the 1980s.[5]



[3] Klayman L. K.; Gunther, W. H. H. *Organic Selenium Compounds: Their Chemistry and Biology*, John Wiley & Sons: **1973**, New York; Chapter 15, p 933.
[4] Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*, Volume 1, John Wiley & Sons: **1986**, New York; Chapter 6, p 190-191.
[5] Dudeck, H. *Progress in NMR Spectroscopy*, **1995**, 27, 1.

The enduring sensitivity problem associated with ^{77}Se NMR was finally resolved with the development of pulse Fourier transform spectrometers. This is reflected by the steady increase in the number of publications that have appeared from the 1970s to the 1990s.[5]

Tellurium can be observed in eight naturally occurring isotopic forms of which ^{130}Te (33.8 %) and ^{128}Te (31.7 %) are the two most abundant.[1] Again, as was the case for selenium, they all have zero nuclear spin except ^{123}Te and ^{125}Te which have spin ½, and a natural abundance of 0.91 % and 7.14 % respectively. The detectability of the latter is 2.2×10^{-3} relative to that of the proton and the chemical shift range is ~ 7000 ppm.[4] Because tellurium is located in the same group in the periodic table as selenium, it was prevalent among researchers to assume that what had been discovered for selenium must also apply to tellurium. This may have been an indirect cause for the lingering advances in ^{125}Te NMR spectroscopy relative to those made in ^{77}Se NMR spectroscopy.[6]

1.2 Biological Relevance of Selenium.

Organic compounds containing selenium not only have a reputation for being of explicit objectionable smell but also for being inherently very toxic. Their toxicity is believed to stem from selenium's facility to substitute for sulfur in proteins.[5] Once ingested, they are gradually eliminated from the body over extended periods of time causing foul-smelling breath and perspiration.

---

[6] Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*; John Wiley & Sons: **1986**, New York; Chapter 6, p 221.

The organic compounds seem nonetheless to be less dangerous than the salts which can be readily dissolved in water and hence are easier for the body to take up. The gases hydrogen selenide (H_2Se) and hydrogen telluride (H_2Te), are particularly dangerous as illustrated by the maximum permissible limits for air-borne concentrations which are set at 0.1 mg m^{-3} (cf. 10 mg m^{-3} for HCN).[1] Hydrogen sulfide (H_2S) is similar in toxicity to hydrogen cyanide causing, death and paralysis at 100 ppm.

Selenium is on the other hand a crucial trace element and micronutrient Selenium is said to protect vitamin E.[7] Vitamin E and selenium are both antioxidants and radical scavengers. Both play a key role in the protection of cells. In other words they protect the cell membrane from free-radical attack by combining with them.[8] As for all trace elements (with the exception of iodine) selenium is adequately supplied by any normal diet.[9] Care has to be taken however, since its biogenic range is very narrow. We are protected from an excess consumption of selenium by limiting its intake to natural food sources. Selenium supplementation in the form of pills or other sources is entirely unneeded and contrary to popular belief carries a real and considerable danger. Iron and iodine are the only trace minerals prescribed by doctors to supplement a diet.

---

[7] Greenwood, J. K. *The IBD Nutrition Book*, John Wiley & Sons, Inc., New York, **1992**; p 9.
[8] *Prevention Magazine's the Complete Book of Vitamins and Minerals the Latest Facts about Using Nutrition as a Powerful Force for Health and Healing*, Wings Books, New York, **1992**; p 153, 306 and 403.
[9] Deutsch, R. M. *The Family Guide to Better Food and Better Health*, Creative Home Library, **1971**, Des Moines; p 92-93.

A daily dietary intake of 50 to 200 μg of selenium, substantiated from animal studies, has been suggested to be optimal. Note however that there is no proof of greater benefit at the upper limit.[10] A very large amount, in fact close to a 100% of our required selenium intake, is provided from the consumption of cereal grains, fish (by far the richest source, and tuna being one of the best), meat and poultry. Selenium-comprising proteins such as glutathione peroxidase, which is associated with fat metabolism, have been discovered.[1,5]

There are particular places in the world in which selenium deficiency syndromes can be discerned. One of the better studied ones is known as "Keshan Disease". It is commonplace to certain areas of China and is a selenium-responsive endemic cardiomyopathy.[11] The disease is directly related to very low levels of selenium in the environment. Indeed soil sample analysis from Keshan disease areas showed depressed selenium levels.

An inverse correspondence between the average per capita intake of dietary selenium and the total cancer mortality as well as fatalities from leukemia, cancers of the colon, breast, ovary and lung was established in 27 countries. Arsenic, cadmium and mercury poisonings, in addition to certain cancers, routinely involve treatment with selenium based drugs. Finally, as is the case with vitamin E, selenium is believed to stimulate the immune system.

---

[10] *The Surgeon General's Report on Nutrition and Health*, Prima Publishing and Communications, **1988**; Rocklin, p 219.

[11] *Trace elements in human nutrition and health*, World Health Organization, Geneva, **1996**; Chapter 6, p 105.

Dr. Gerhard N. Schrauzer, pioneer and leader in selenium research summarizes the biological importance of selenium:[12]

"Selenium is probably one of the least-thought-about trace elements there is. But the evidence keeps piling up that selenium is important in preventing a whole list of conditions and at the top of the list is cancer. A lot of people worry about their intakes of calcium and iron but in a few years selenium will also be a common concern."

1.3 Selenium / Tellurium in Organic Chemistry.

Sulfur has been known since ancient times and can be found in many areas of the world in its elemental, unassociated form. Ancient man's familiarity with sulfur has been well documented throughout history and many references to its existence can be found in the bible.[13] The only other non-metallic element enjoying some mention from primeval history is carbon. The French chemist, A. L. Lavoisier, was the first to propose the elemental character of sulfur in 1777 and which was subsequently firmly established by J. L. Gay Lussac and L. J. Thenard in 1809.

---

[12] *Prevention Magazine's the Complete Book of Vitamins and Minerals the Latest Facts about Using Nutrition as a Powerful Force for Health and Healing*, Wings Books, New York, **1992**; Chapter 28.
[13] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, Pergamon Press: **1984**, New York; Chapter 15, p 757-760.

Lavoisier who is said to be the father of French chemistry modernized his science with the benchmark publication "Traité élémentaire de chimie" in 1789. He did not survive the French Revolution and was guillotined in 1794. W. C. Zeise from Denmark is one of the pioneers of modern organosulfur chemistry. He discovered the xanthates in 1822 and "mercaptan" (ethanethiol) in 1834. A great many of the distinctive sulfur containing organic functional groups had been discovered by 1865 in large part due to the comprehensive studies that were launched in response to Zeise's ground breaking work.[14]

It wasn't long until the organic compounds containing selenium or tellurium made their appearance. Loewig is credited with the preparation of the first organoselenium compound in 1836.[14] He synthesized diethyl selenide mingled with the diselenide. Approximately 30 years went past until the first pure compounds were isolated by Rathke in 1869.[14] Woehler was the first to report the synthesis of an organotellurium compound, diethyl telluride, in 1840.[14] Numerous other organoselenium and tellurium compounds were prepared in Woehlers's laboratory such as ethaneselenol (1847), diethyl telluroxide (1851), dimethyl telluride and dimethyl selenide (1856). The selenoxides were not brought to light until 1893 and selenophene itself was not synthesized until 1927. The synthesis of tellurophene had to wait until 1972.

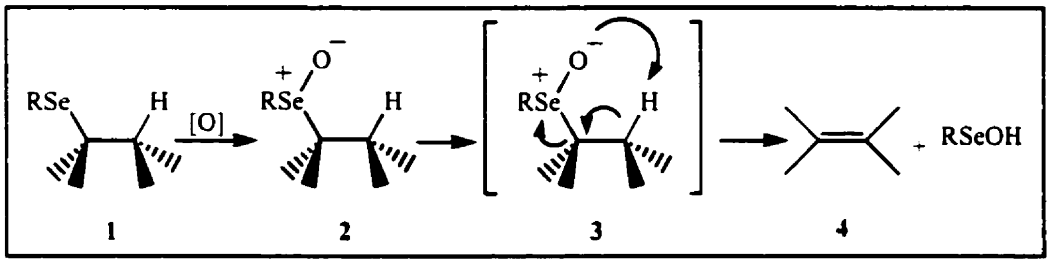
[14] Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*; Volume 1, John Wiley & Sons: **1986**, New York; Chapter 1, p 5.

When much of the groundwork had been laid down and after the initial flurry of activity had passed, further advances in the domain of organic selenium and tellurium chemistry were sluggish at best. The characteristic foul-smell, toxicity and sensitivity to air and light of organoselenium and tellurium compounds, were all major stumbling stones impeding further progress. Also, due to a lack of efficient isolation techniques, many of the molecules prepared were of low purity, which interfered with their subsequent study. Numerous papers reporting the isolation of new compounds were often erroneous. The advent of the 1950s brought about major developments, both in laboratory equipment and laboratory techniques and hence made it feasible to synthesize organic selenium and tellurium compounds in higher yields and purity. In addition compounds of fleeting stability were isolated. Much of the initial interest in this class of compounds was catalyzed by biological interest.

The organic compounds of selenium and tellurium generally tend to be less stable than the corresponding organosulfur compounds. The following decline in thermal stability of the hydrides is observed: $H_2O > H_2S > H_2Se > H_2Te$.[1] Both selenium and tellurium have a reduced disposition for multiple bond formation (*e.g.* to C, N, O). There seems to exist an inverse correlation between the stability of a double bond and an increase in the atomic number of one of the components going down a group. Double bond formation between two carbon atoms or between carbon and oxygen is a common occurrence and is easily accomplished in the laboratory. Formation of an analogous bond between carbon and sulfur is less common and one between carbon and selenium even more so.

There has been no report of a well characterized telluroketone. Simple molecules such carbon dioxide (O=C=O) and carbon disulfide (S=C=S) are stable whereas carbon diselenide (Se=C=Se) is mostly found in polymerized form. The corresponding carbon ditelluride (Te=C=Te) is unknown. A similar observation can be made about sulfur dioxide (SO_2), which is a stable gaseous molecule and selenium dioxide (SeO_2) which is a chain polymer. From these observations we can conclude that ease of double bond formation and increase in electronegativity difference between the two elements constituting the double bond, are inversely related.[1]

By the early 1970s, the organic chemistry of selenium had been extensively studied and reviewed. Nonetheless, only very little selenium-based methodology had been published and even less found widespread acceptance. However in 1973, Sharpless, Reich and Clive were all able to independently demonstrate the inherent potential of the selenoxide *syn*-elemination reaction (Scheme 1).[15]



Scheme 1

[15] Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*; Volume 2, John Wiley & Sons: **1986**, New York; Chapter 3, p 94-95.

This reaction has endured as one of the most efficient olefin forming reactions and did much to rid organoselenium chemistry of its stigma as an esoteric science. This discovery spurred a renewed interest in organic selenium research, which ultimately led to the development of numerous other selenium-based transformations of broad synthetic utility and ultimately to the genesis of a new area within the realm of organic chemistry. In the next few sections some of the many applications of selenium-based reagents will be briefly reviewed and will further demonstrate their usefulness to the synthetic organic chemist.

Organotellurium chemistry on the other hand remains at the periphery of modern organic chemistry and continues to struggle to gain acceptance. Sporadic reviews seem to indicate an increasing interest, which has resulted in the appearance in recent years of some useful tellurium-based methodology. When reagents are developed, capable of useful synthetic transformations (otherwise difficult by classical methods), organotellurium chemistry will emerge from obscurity.

1.4 Organoselenium Chemistry Today.

1.4.1 A Broad Range of Applications for Selenium Reagents in Modern Organic Chemistry.

One of the main driving forces in organic chemistry, aside from the synthesis of structurally interesting and complex natural compounds, is the quest for new reagents capable of new and interesting synthetic transformations.

This search has led to the development of reagents previously not considered as being part of the traditional sphere of organic chemistry. It is from such a quest that organoselenium chemistry, as an independent field, has emerged.

Prior to the 1970s, organoselenium reagents were considered as having only very limited synthetic value and hence their full potential remained largely unexplored. The discovery of the selenoxide *syn*-elimination reaction contributed largely to a new surge of interest, such that presently organoselenium reagents constitute an importance in the greater scheme of organic chemistry.

As will be shown in these following sections, workers carrying out organoselenium chemistry have contributed to synthetic progress in the form of highly selective reagents permitting effective functional group manipulations, otherwise difficult to carry out. There are electrophilic, nucleophilic and radical selenium reagents; in addition there exist organoselenium-based ring closures and organoseleno [2,3] sigmatropic rearrangements. These are but a few of the major areas in which organoselenium reagents have been particularly effective.

1.4.1.1 Electrophilic Selenium Reactions.

There exists a vast variety of electrophilic selenium reagents that are common-place in most synthetic laboratories. Elemental selenium is considered to be moderately electrophilic and can be induced to react with strong nucleophiles such as Grignard reagents or organolithium reagents.[16]

[16] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 1, p 1-6.

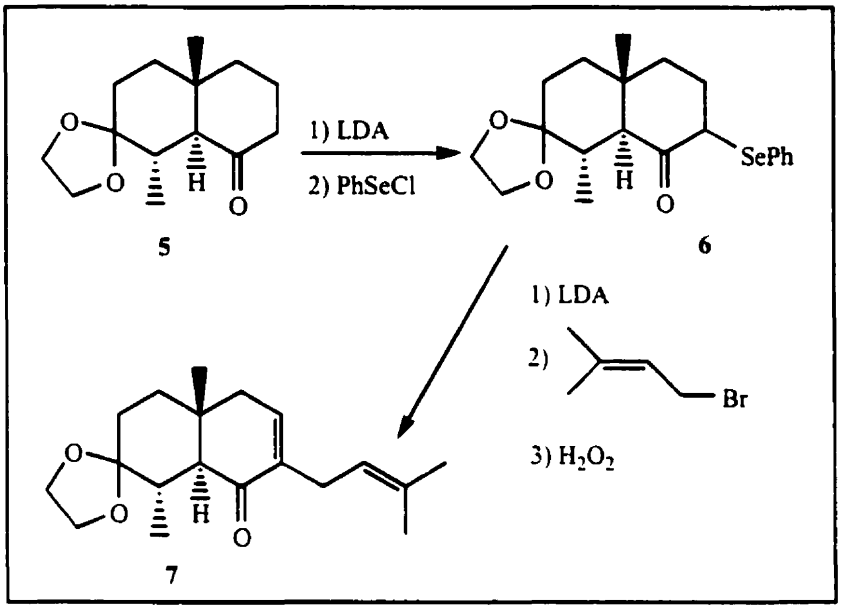
The most common electrophilic selenium reagents are Se (II) species and these are better known as selenenic reagents. As a result of extensive studies on the selenenyl halides (PhSeX) and the selenenyl pseudohalides where X is a nonhalide leaving group (OAc, SO_2Ar or SCN), it has become common practice to use the aryl instead of the alkyl derivatives. As a general observation, the aryl derivatives tend to be more stable and are less susceptible to cause unpleasant odors. Among the most prevalent electrophilic reagents, we can discern benzene selenenyl bromide, benzene selenenyl chloride and diphenyl diselenide. All are commercially available and are sufficiently stable to be stored for extended periods of time.

The selenenyl pseudohalides' reactivity in electrophilic reactions is contingent largely on the stability of the non-halide leaving group. Most of the pseudohalide reagents can be readily prepared from their corresponding halides *via* nucleophilic displacement. The aryl selenocyanates on the other hand are most easily obtained by reaction of a diazonium salt with potassium selenocyanate.

Some representative examples of reactions involving elctrophilic selenium reagents are:

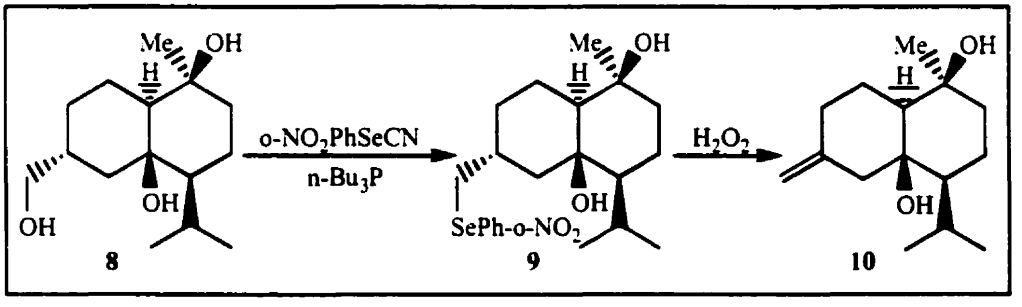
a) α-Selenenylation of carbonyl compounds; an efficient route to α,β-unsaturated carbonyls (Scheme 2).[17, 18]

[17] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 1, p 7-21.
[18] Nishizawa, M.; Grieco, P. A.; Burke, S. D.; Metz, W. *J. Chem. Soc., Chem. Commun.* **1978**, 76.



Scheme 2

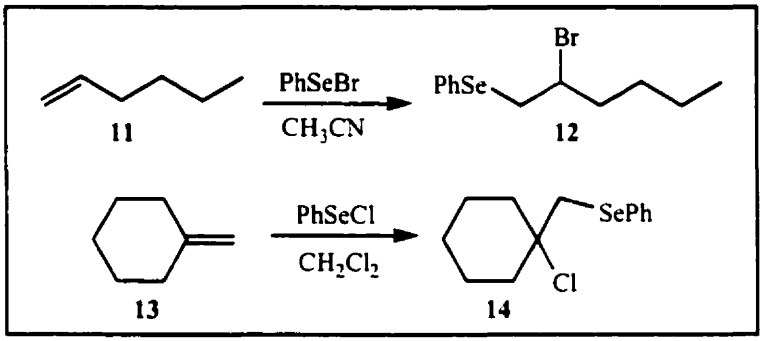
b) The reaction of selenium electrophiles with phosphorus nucleophiles is an effective method permitting the conversion of primary and secondary alcohols into aryl selenides. This procedure has proven to be particularly useful for the introduction of the *exo*-methylene functionality from hydroxymethylene substituents (Scheme 3).[19, 20]



Scheme 3

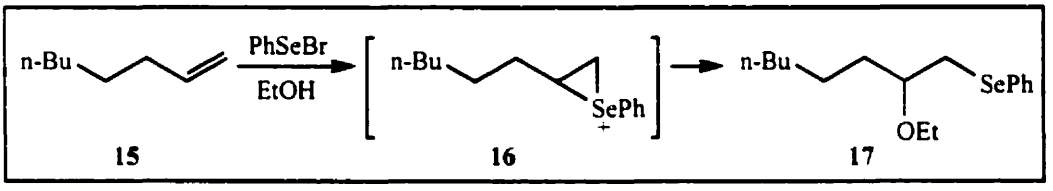
[19] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 1, p 48-53.
[20] Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, 45, 367.

c) Addition of selenenic electrophiles to olefins is a convenient method to form β-functionalized selenides (Scheme 4).[21, 22, 23, 24, 25, 26, 27]



Scheme 4

Note however that when these electrophilic addition reactions are carried out in the presence of other nucleophiles, the latter can intercept the intermediate "selenonium ion" **16** and hence become incorporated in the final product. This is often the case when alcohols, amines or water is present in the reaction mixture (Scheme 5).[28]



Scheme 5

---

[21] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 1 pp 56-64.
[22] Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, 19, 4977.
[23] Denis, J. N.; Vicens, J.; Krief, A. *Tetrahedron Lett.* **1979**, 20, 2697.
[24] Raucher, S. *J. Org. Chem.* **1977**, 42, 2951.
[25] Ho, P. T.; Kolt, R. J. *Can. J. Chem.* **1982**, 60, 663.
[26] Garratt, D. G.; Kabo, A. *Can. J. Chem.* **1980**, 58, 1030. [29] Schmid, G. H.; Garratt, D. G. *Tetrahedron* **1978**, 34, 2869. [28] Takahashi, T.; Nagashima, H.; Tsuji, J. *Tetrahedron Lett.* **1979**, 20, 799.
[27] Schmid, G. H.; Garratt, D. G. *Tetrahedron* **1978**, 34, 2869. [28] Takahashi, T.; Nagashima, H.; Tsuji, J. *Tetrahedron Lett.* **1979**, 20, 799. [28] Takahashi, T.; Nagashima, H.; Tsuji, J. *Tetrahedron Lett.* **1979**, 20, 799.
[28] Takahashi, T.; Nagashima, H.; Tsuji, J. *Tetrahedron Lett.* **1979**, 20, 799.

1.4.1.2 Nucleophilic Selenium Reactions.

Sodium phenyl selenide is the most commonly encountered selenium nucleophile. It is frequently used as part of a total synthesis and its efficacy is directly related to the method of preparation.[29] It can typically be generated by treatment of diphenyl diselenide with $NaBH_4$ in EtOH [30] (eq. 1), by reacting diphenyl diselenide with sodium or potassium metal in THF [31, 32] (eq. 2) or by reacting diphenyl diselenide with sodium or potassium hydride.[33] (eq. 3). An alternate pathway for the preparation of selenolates involves the deprotonation of the corresponding selenols with a metal hydride [34] (eq. 4).

$$2\ NaBH_4 + PhSeSePh \xrightarrow{EtOH} 2\ PhSe^-Na^+.BH_3 + H_2 \qquad (1)$$

$$PhSeSePh \xrightarrow{Na\ or\ (K)\ /\ THF} 2\ PhSe^-Na^+ \qquad (2)$$

$$PhSeSePh \xrightarrow{NaH\ or\ (KH)\ /\ THF} 2\ PhSe^-Na^+ + H_2 \qquad (3)$$

$$PhSeH \xrightarrow{NaH\ or\ (KH)\ /\ THF} 2\ PhSe^-Na^+ + H_2 \qquad (4)$$

---

[29] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**. New York. Chapter 4, pp 207-211.
[30] Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, 95, 2697.
[31] Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 18, 4365.
[32] Liotta, D *Acc. Chem. Res.* **1984**, 17, 28.
[33] Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, 11, 935.
[34] Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, 46, 2605.

Selenolates can also be generated starting from the corresponding selenocynates by reduction with $NaBH_4$, as demonstrated in Grieco's total synthesis of Deoxyvernolepin[35] or with superhydride as illustrated by Salama.[36] When superhydride is used, 2 equivalents of the hydride reagent are required to obtain the selenolate.

Lithium alkyl selenides are other useful selenium nucleophiles. They are available through the reaction of selenols with alkyl lithium reagents.[37] When elemental selenium is reacted in the presence of lithium enolates, β-keto lithium selenides are obtained, that can subsequently be alkylated.[38] This is an alternative method to the previously described electrophilic methodology, for the introduction of the phenyl or alkyl selenium functionality α to the carbonyl moiety.

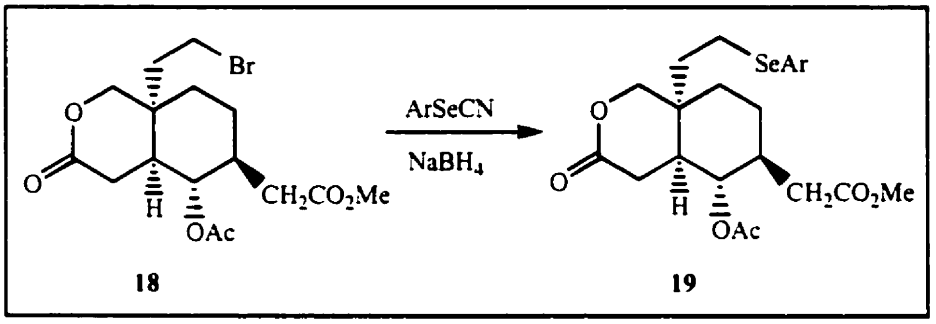
The following prevailing observations concerning the reactivity of metal phenyl selenolates can be drawn:

1) The reactivity is directly proportional to the ionic character of the species.
2) Aprotic solvents, in contrast to protic solvents, have an enhancing effect on the nucleophilicity of the selenium species.
3) The addition of reagents that selectively complex with the counterion, hence generating what is termed a "naked anion", will have a rate enhancing effect by increasing the reactivity of the nucleophile.

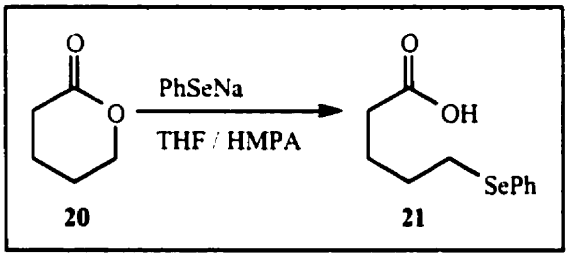
---

[35] Grieco, P. A.; Noguez, J. A.; Masaki, Y. *Tetrahedron Lett.* **1975**, 16, 4213.
[36] Salama, P.; Bernard, C. *Tetrahedron Lett.* **1995**, 36, 5711.
[37] Smith, A. B. III; Scarborough, R. M. Jr. *Tetrahedron Lett.* **1978**, 19, 1649.
[38] Liotta, D.; Saindane, M.; Barnum, C.; Ensley, H.; Balakrishnan, P. *Tetrahedron Lett.* **1981**, 22, 3043.

The following two examples clearly demonstrate the effectiveness of selenium nucleophiles, both in synthesis as well as in methodology. A synthetic application, (Scheme 6), can be found in Grieco's synthesis of *Deoxyvernolepin*.[35] The chemoselective S_N2 cleavage of esters and lactones, (Scheme 7), demonstrates both the usefulness and importance of selenium based methodology.[34]



Scheme 6



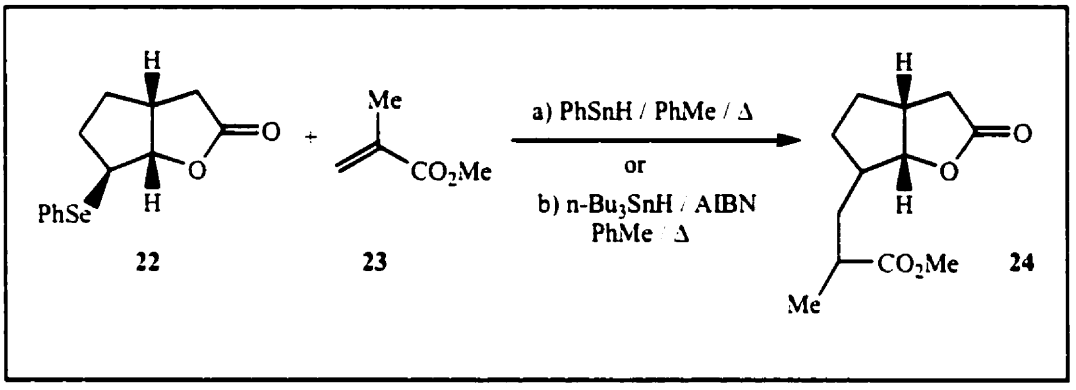
Scheme 7

1.4.1.3 Reactions Involving Selenium Radicals.

Organoselenium radicals have received considerably less attention than their nucleophilic or electrophilic counterparts. The field remains therefore largely unexplored and leaves the opportunity for considerable experimentation and development.

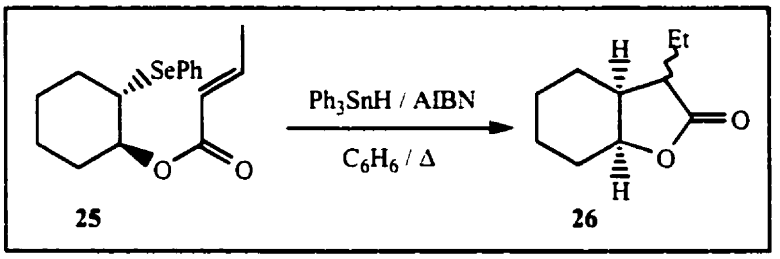
The chemistry of the organosulfur radicals, on the other hand, has been well studied and documented, as demonstrated by the extensive literature coverage.[39] Despite this lack of investigation, some important radical organoselenium-based methodologies have emerged that have subsequently found wide spread acceptance in the synthetic community. Among the more important ones that will be briefly examined in the next section are the tin-hydride mediated deselenizations and the selenosulfonation of olefins. The impact of these reactions is further amplified when carried out in conjunction with other functional group transformations.

Some illustrative examples include the capture of the intermediate carbon centered radical by a functionalized olefin in an intermolecular fashion (Scheme 8) as demonstrated by Burke or in an intramolecular fashion (Scheme 9) as demonstrated by Clive.[40, 41]



Scheme 8

[39] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 7, p 326.
[40] Burke, S. D.; Fobare, W. F.; Armistead, D. M. *J. Org. Chem.* **1982**, 47, 3348.
[41] Clive, D. L. J.; Beaulieu, P. L. *J. Chem. Soc., Chem. Commun.* **1983**, 307.



Scheme 9

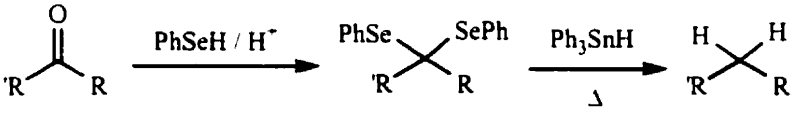
Not only do these reactions lead to new carbon-carbon bond formation and in the intramolecular example to cyclization, they also allow for the simultaneous insertion of a new additional functionality into the substrate. Selenides can be chemoselectively reduced in the presence of sulfides and the yields of deselenized product generally surpass the ones obtained employing more conventional reagents such as Raney nickel or alkali metals.

The reductive dehydroxylation of alcohols can be effectively carried out using selenium-based methodology. The process involves the transformation of the alcohol into a selenide, using an electrophilic selenium reagent, followed by the subsequent treatment with a tin hydride reagent (equation 5). This is an easy two-step sequence that is very effective for generating hydrocarbons from the corresponding primary or secondary alcohols.[42]

$$RCH_2OH \xrightarrow[n\text{-}Bu_3P]{ArSeCN} RCH_2SeAr \xrightarrow{Ph_3SnH} RCH_3 \qquad (5)$$

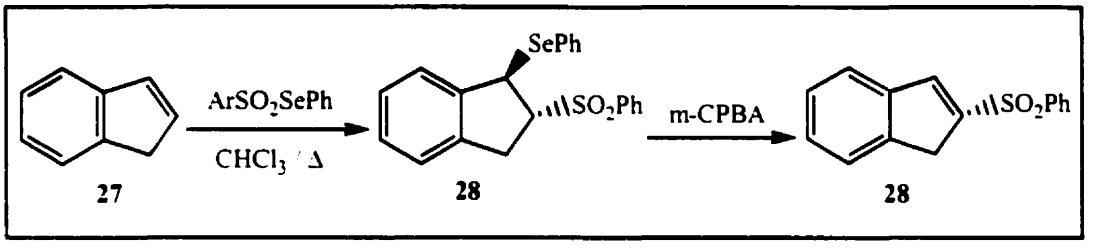
[42] Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, 102, 4438.

The reduction of aldehydes or ketones to their respective hydrocarbons is effectively accomplished by the Wolff-Kishner reaction, the Clemmensen reduction or by the desulfurization of thioacetals / thioketals with Raney nickel. Correspondingly, selenoketals / acetals are effectively reduced using the tin hydride mediated deselenization (equation 6).[43] This is another example of the plethora of selenium mediated functional group transformations that are possible.



(6)

The selenosulfonation of olefins is an other interesting functional group transformation that takes place *via* seleno-radical species (Scheme 10). The intermediate seleno-sulfone adducts can be rapidly transformed into vinyl sulfones *via* an oxidation-elemination reaction. Overall, this sequence allows for the expedient conversion of olefins into vinyl sulfones.[44]



Scheme 10

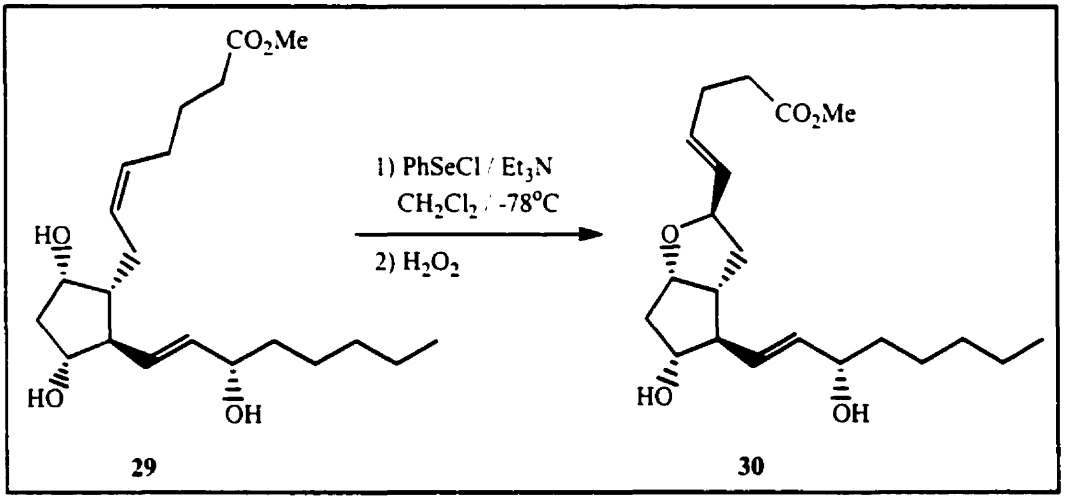
[43] Clive, D. L. J.; Chittattu, G.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1978**, 41.
[44] Back, T. G.; Collins, S. *J. Org. Chem.* **1981**, 46, 3249.

The last two aspects of modern organoselenium chemistry that will be briefly examined in this short synopsis are the organoselenium-mediated ring closure reactions and [2,3] sigmatropic rearrangements of organoselenium compounds.

1.4.1.4 Organoselenium-Based Ring Closure Reactions.

One of the singularly most important tasks frequently encountered in organic synthesis is the construction of carbocycles or heterocycles. Numerous ring-forming methodologies have been developed over the years, but the most useful ones have proven to be those in which a nucleophilic functionality reacts intramolecularly with an electrophilic moiety.[45] Organoselenium chemistry has made significant contributions in this important enterprise as depicted in the following examples.

Phenylseleno-etherification reactions (Scheme 11).[46]

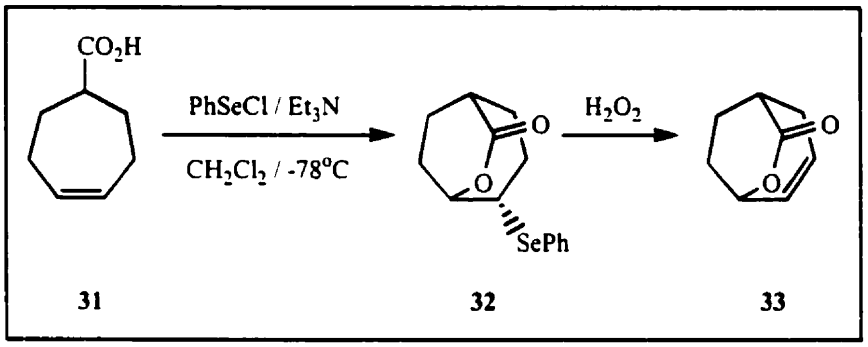


29 30

Scheme 11

[45] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 2, pp 127-129.
[46] Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, 103, 3480.

Phenylseleno-lactonization reactions (Scheme 12).[47]



Scheme 12

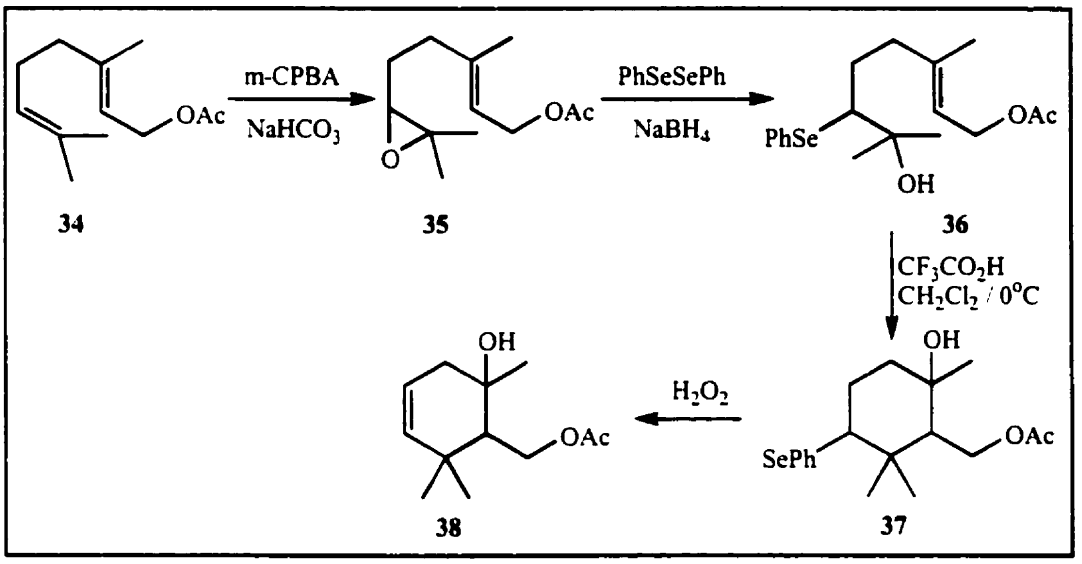
The phenylseleno-mediated ring closure reactions were also found to be pertinent to the synthesis of sulfur or nitrogen containing heterocycles. Nicolaou and co-workers have prepared various S-heterocycles whereas Clive and co-workers prepared various N-heterocycles.[48, 49]

Phenylseleno-carbocyclization reactions.

Kametani and co-workers have illustrated that an olefinic bond can be induced to participate as the nucleophile in the intramolecular ring opening of an episelenonium ion, hence leading to the formation of a new carbon-carbon bond and new carbocycle (Scheme 13).[50] This procedure is complementary to the radical organoselenium prompted cyclization described previously.

---

[47] Nicolaou, K. C.; Lysenko, Z. *J. Am. Chem. Soc.* **1977**, 99, 3185.
[48] Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1978**, 100, 2567.
[49] Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, 45, 2120.
[50] Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1128.



Scheme 13

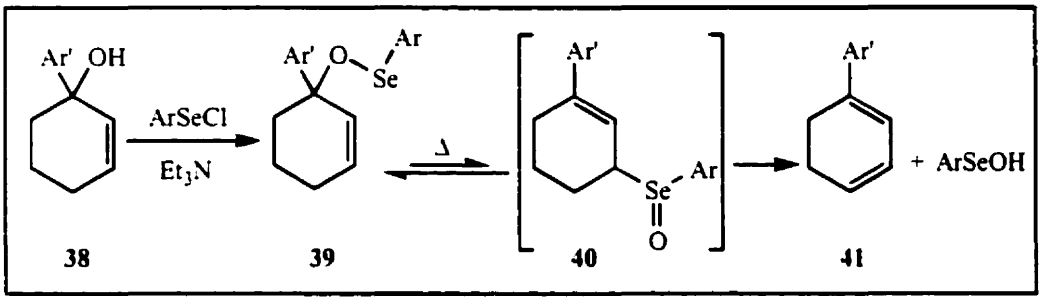
1.4.1.5 [2,3] Sigmatropic rearrangements involving selenium compounds.

The [2,3] sigmatropic rearrangement of allylic selenoxides is one of the most practical methods for the generation of allylic alcohols. Sharpless and Lauer were the first to describe this reaction as a result of their investigations on the oxidation of olefins with selenium dioxide.[51] The allyl selenide precursor is easily prepared and the subsequent oxidation to the selenoxide is invariably accompanied by the rearrangement to the selenenate ester, which in turn is readily hydrolyzed to the alcohol.[52] Reich was able to demonstrate the existence of an equilibrium between the selenoxide and the selenenate ester resulting from the [2,3] sigmatropic rearrangement.[53, 54]

---

[51] Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, 94, 7154.
[52] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 8, pp 365-372.
[53] Reich, H. J.; Reich, I. L.; Wollowitz, S. *J. Am. Chem. Soc.* **1978**, 100, 5981.
[54] Reich, H. J.; Wollowitz, S.; *J. Am. Chem. Soc.* **1982**, 104, 7051.

As demonstrated in Scheme 14, when selenenate ester **39** was refluxed in dichloromethane, diene **41** was slowly formed. This observation was explained by the conversion to a selenoxide which under the reaction conditions underwent a *syn* elimination.

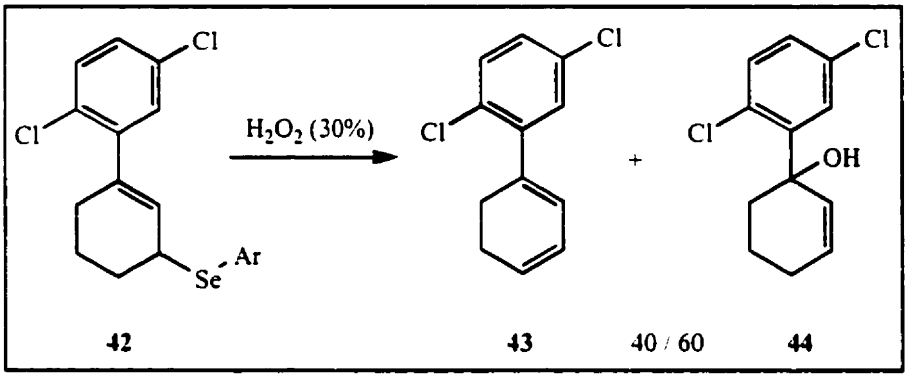


Scheme 14

The equilibrium is generally in favor of the selenenate ester to such an extent, that the [2,3]sigmatropic rearrangement is considered as being essentially irreversible. The energy difference between the selenoxide and the selenenate ester was estimated as ~11 kcal/mol. For the most part, there exists a temperature difference of approximately 100°C between selenenate ester formation and its conversion back to the selenoxide.

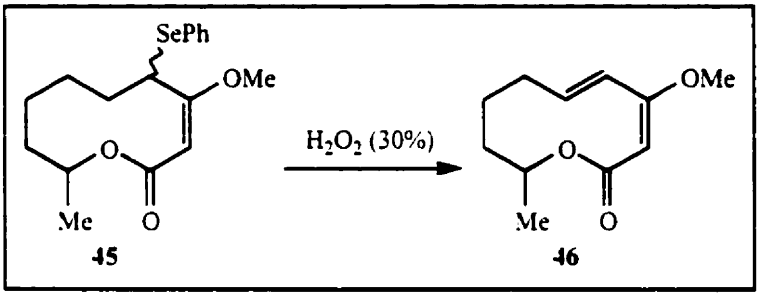
When both a [2,3]sigmatropic rearrangement and a selenoxide-*syn* elimination reaction are possible, the former is inherently favored. However, it is not uncommon to observe mixtures of allylic alcohol and diene as demonstrated in Scheme 15.[54, 55]

[55] Reich, H. J.; Reich, I. L. *J. Org. Chem.* **1981**, 46, 3721.



Scheme 15

A few reactions have been reported where the [2,3]sigmatropic rearrangement was completely suppressed in favor of the selenoxide *syn*-elimination (Scheme 16).[56]



Scheme 16

The chemistry of the selenoxide functionality, more specifically its applications as a synthon for [2,3]sigmatropic rearrangements and *syn*-eliminations, is at present very well documented. Low temperatures (~ -78°C) will generally prevent either from taking place. In the absence of β-hydrogens the selenoxide functionality is relatively stable and can be isolated.

[56] Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, 44, 2008.

In those systems where β-hydrogens are present, but the required conformation for *syn* elimination can not be attained or when the double bond formation imparts excessive ring strain, no fragmentation will occur.[57] Dialkyl selenoxides can be readily isolated whereas phenyl primary alkyl selenides fragment upon heating.

1.4.2 Selenium Containing Functional Groups.

Selenium analogs exist for all of the traditional oxygen and sulfur containing functional groups but the stabilities are remarkably different as illustrated by the frailty of the selenols (RSeH). They are extremely air sensitive and are readily oxidized to the corresponding diselenides by mere traces of oxygen. They are also extremely malodorous and are considerably more acidic than their oxygen counterparts.[58] Selenenic acids (RSeOH), the by-products resulting from the selenoxide *syn*-elimination, are also relatively unstable. They are very electrophilic and can potentially cause undesired side reactions in the course of the *syn*-elimiation reactions by adding across the newly generated double bond.[58] Selenenic acids are usually prepared in *situ* because of their instability and tendency to disproportionate to the diselenide and the seleninic acid, as illustrated in equation 5.[59]

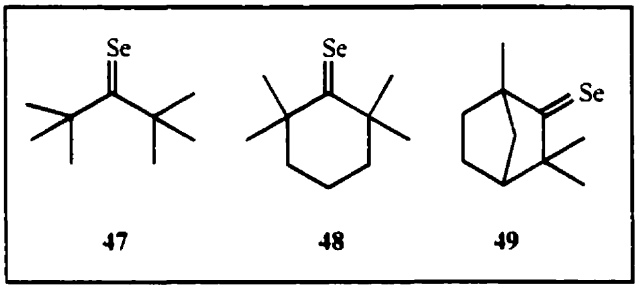
$$3\ \mathrm{ReSeOH} \rightleftharpoons \mathrm{RSeSeR} + \mathrm{RSeO_2H} + \mathrm{H_2O} \qquad (5)$$

---

[57] Clive, D. L. J. *Tetrahedron* **1978**, 34, 1049.
[58] Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*, Volume 1, John Wiley & Sons: **1986**, New York; Chapter 16, pp 620-628.
[59] Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, 97, 5434.

The seleninic acids ($RSeO_2H$), resulting from the disproportionation, are stable compounds and have pKa values similar to those of the carboxylic acids.

The selenium analogue of the carbonyl functionality has received a considerable amount of attention over the last two decades. The selenoaldehydes and ketones (selones) are considerably less stable then their oxygen or sulfur containing counterparts. They tend to be very sensitive to both light and moisture and will rapidly deposit red selenium when handled.[60] Some sterically hindered selones have been prepared and studied (Scheme 17).[61, 62, 63]



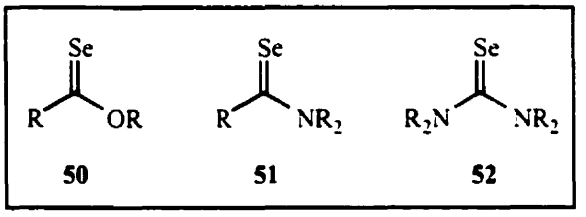
Scheme 16

Sterically hindered selones all exhibit a characteristic deep blue color, and tend to be stable compounds when kept in an inert atmosphere. When kept under a nitrogen or argon atmosphere, they can be heated up to 150°C for extended periods of time or exposed to ultraviolet light without any trace of decomposition.

---

[60] Liotta D. *Organoselenium Chemistry*; John Wiley & Sons: **1987**, New York, Chapter 6, pp 277-280.
[61] Back, T. G.; Barton, D. H. R.; Britten-Kelly, M. R.; Guziec, Jr. F. S. *J. Chem. Soc., Chem. Commun.* **1975**, 539.
[62] Back, T. G.; Barton, D. H. R.; Britten-Kelly, M. R.; Guziec, Jr. F. S. *J. Chem. Soc.,Perkin Trans. 1.*, **1976**, 19, 2079.
[63] Guziec, Jr. F. S.; Moustakis, C. A. *J. Org. Chem.* **1984**, 49, 189.

In the air however, they undergo rapid oxidation to the corresponding ketone and elemental selenium. The stability of the selenocarbonyl functionality is greatly enhanced when a heteroatom is attached to the carbonyl carbon (Scheme 17). The increased stability is imparted by the resonance delocalization of the heteroatom lone pair onto selenium.[64]



50 **51** **52**

Scheme 17

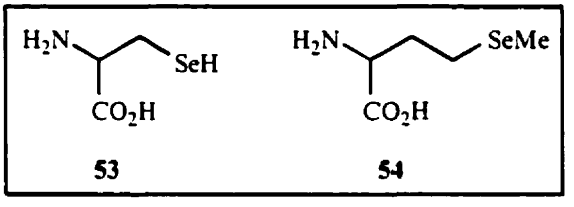
The selenoesters (**50**) are typically yellow liquids for the aliphatic series, and deep red oils for the aromatic series. Decomposition slowly occurs at room temperature with the concomitant deposition of red selenium. The generally colorless selenoamides (**51**) are more stable than the corresponding esters and can be kept for several months under refrigeration, without any trace of decomposition.[65] The selenoureas (**52**) are the most stable and, not surprisingly, the most studied of the compounds depicted in Scheme 18. They can be stored in the absence of air and light without decomposition.[66]

[64] Segi, M.; Kojima, A.; Nakajima, T.; Suga, S. *Synlett*, **1991**, 105.
[65] Cohen, V. I. *J. Org. Chem.* **1977**, 42, 2645.
[66] Klayman, D. L.; Shine, R. J.; *J. Org. Chem.* **1969**, 34, 3549.

A good proportion of the organoselenium literature that has appeared in the last 10 years, is concerned with the generation of selenoaldehydes and ketones. Subsequently, numerous new and more efficient methodologies have been developed, that allow for the synthesis of this highly unstable functionality. Once formed, they are trapped *via* a Diels-Alder reaction, which leads to interesting new selenium containing heterocycles.

1.5 Conclusions.

There exist numerous other selenium containing functional groups and many more synthetic transformations that involve selenium based reagents. Books and review papers reexamining the subject continue to appear periodically. Selenium-containing natural products are beginning to attract attention, in particular those that are found in garlic, onions and related plants.[67] A few representative examples are the selenoamino acids selenocystine (**53**) and selenomethionine (**54**) (Scheme 18).



53 **54**

Scheme 18

The total synthesis of such compounds will be an endeavor in which organoselenium based reagents and methodology will most certainly be put to the test.

[67] Block, E.; Cai, X. J.l Uden, P. C.; Zhang, X.; Quimby, B. D.; Sullivan, J. J. *Pure & Appl. Chem.* **1996**, 68(4), 937.

Hopefully, this brief synopsis was able to convey the idea that organoselenium chemistry is an active and vibrant field that has firmly established itself as an integral part of the larger domain known as "Organic Chemistry".

In the next chapter, the reductive dehalogenation of α-haloketones will be discussed. This constitutes one more functional group transformation that is easily accomplished using an organoselenium reagent.

CHAPTER 2 : REDUCTIVE DEHALOGENATION OF α-HALOKETONES.

2.1 Literature Survey.

The reductive dehalogenation of α-halocarbonyl compounds is a thoroughly researched area of organic chemistry and numerous methods have been developed capable of such transformations.

Goto and Kishi were able to demonstrate that α-bromoketones could be effectively reduced to the corresponding ketones by the action of sodium borohydride in the presence of catalytic amounts of either $Pb(OAc)_2$, $Ni(OAc)_2$ or $Hg(OAc)_2$.[68] Similarly, Borowitz was able to effect the reductive dehalogenation by using triphenylphosphine in refluxing benzene-methanol.[69, 70, 71] A few years later, Borowitz illustrated that the same transformation could also be accomplished with diphenylphosphine.[72] Townsend and Spencer demonstrated that treatment of α-haloketones with lithium iodide and boron trifluoride, was another effective dehalogenation procedure.[73] Organotin hydrides and zinc-acetic acid were also shown to be effective reducing reagents.[74, 75]

---

[68] Goto, T.; Kishi, Y. *Tetrahedron Lett.* **1961**, 513.
[69] Borowitz, I. J.; Grossman, L. I. *Tetrahedron Lett.* **1962**, 471.
[70] Borowitz, I. J.; Virkhaus, R. *J. Am. Chem. Soc.* **1963**, 85, 2183.
[71] Borowitz, I. J.; Kirby, K. C.,Jr.; Virkhaus, R. *J. Org. Chem.* **1966**, 31, 4031.
[72] Borowitz, I. J.; Kirby, K. C., Jr.; Rusek, P. E.; Lord, E. *J. Org. Chem.* **1969**, 9, 2687.
[73] Townsend, J. M.; Spencer, T. A. *Tetrahedron Lett.* **1971**, 137.
[74] Kuivilla, H. G.; Menapace, L. W.; *J. Org. Chem.* **1963**, 28, 2165.
[75] Sauers, R. R.; Hu, C. K. *J. Org. Chem.* **1971**, 36, 1153.

Since the initial period of intense activity, lasting about 10 years, groups continued to search for effective reagents capable of the selective reduction of halogens positioned α to the carbonyl functionality. More importantly, reagents were sought that could accomplish the above mentioned transformation chemoselectively, without affecting the carbonyl group. Ultimately, in keeping with a trend in organic chemistry, reagents were sought that could reduce the halogen even while in the presence of a wide variety of other functionalities.

This renewed interest again led to the development of new methodologies. Dubois illustrated that lithium diisopropylamide (LDA) could be used to reduce the bromine of α-haloketones.[76] Even though effective, LDA is nonetheless a strong base and will therefore cause undesired side reactions if sufficiently acidic protons are present elsewhere on the molecule.

The effectiveness of metal halides as potential and selective reducing agents for the α-halocarbonyl functionality, has been extensively examined. Titanium trichloride was shown by Ho to be an efficient dehalogenating agent.[77] The reaction is not suitable for heat and moisture-sensitive substrates. It is carried out in a 2 phase system (acetonitrile / water) and refluxed for a period of 18 hours in order to complete the reaction.

[76] Dubois, J. E.; Lion, C.; Dugast, J. Y. *Tetrahedron Lett.* **1983**, 24, 4207.
[77] Ho, T. H.; Wong, C. *Synth. Commun.* **1973**, 3, 237.

Fuji established that aluminum trichloride in the presence of ethanethiol, efficiently converts α-bromo and α-iodoketones into the corresponding dithioketals of the dehalogenated ketones.[78, 79] The dehalogenated carbonyl compounds could be directly obtained by substituting ethanethiol for diethylsulfide.

The use of lanthanides as reducing agents was investigated by Molander, and was found to be very effective for a wide variety of α-heterosubstituted ketones.[80] Not only were halogens effectively reduced, but α-oxygenated and α-thiosubstituted compounds (-OAc, $-OSiMe_3$, $-OCOCH_2Ph$, -OTs, -SPh, -S(O)Ph and $-SO_2Ph$) could also be reduced in high yield. The lanthanide reagent has also proven to be chemoselective as other functionalities such as carbonyl groups and primary iodides (at other places in the molecule) are readily accommodated under the reaction conditions. The reaction is also extremely mild, taking place at neutral conditions at $-78^{\circ}C$.

Divalent tin hydride, formed in *situ* from the reaction of stannous chloride with 2 equivalents of diisobutylaluminum hydride, was also shown to be an effective reagent for the reductive dehalogenations of α-bromo ketones.[81] Ono used the combination of metal chlorides such as tin (II) and tin (IV) chloride, iron (II) and iron (III) chloride, chromium (III) chloride or aluminum (III) chloride with sodium hydrogen sulfide, to reduce α-halocarbonyl substrates.[82]

---

[78] Fuji, K.; Node, M.; Kawabata, T.; Fujimoto, M. *Chem. Lett.* **1984**, 1153.
[79] Fuji, K.; Node, M.; Kawabata, T.; Fujimoto, M. *J. Chem. Soc., Perkin Trans. I* **1987** 1043.
[80] Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, 51, 1153.
[81] Oriyama, T.; Mukaiyama, T. *Chem. Lett.* **1984**, 2069.
[82] Ono, A.; Fujimoto, E.; Ueno, M. *Synth. Commun.* **1986**, 16, 653.

In a subsequent publication by the same authors, the hydro-dehalogenations were also observed to be effective with sulfur salts such as sodium sulfide, sodium sulfite, sodium hydrogen sulfite and sodium thiosulfite.[83] The authors also established that aromatic compounds such as benzene, aniline and pyridine could be induced to participate in the dehalogenation process when put in the presence of the above mentioned metal salts. In yet another paper, Ono described the use of sodium halides and sodium pseudohalides, in combination with the same metal halides, as useful dehalogenating procedures.[84] All of the procedures developed by Ono, are carried out by heating the reaction mixtures under reflux for 2 hours in aqueous THF. Heat and moisture-sensitive substrates should therefore not be dehalogenated under these conditions.

The use of aluminum triiodide is yet another example illustrating the intense scrutiny that metal halides have received as reagents in the dehalogenation process.[85] Under strictly anhydrous conditions, the authors were able to demonstrate the intermediacy of an aluminum enolate by trapping it with benzaldehyde in a crossed aldol condensation

The use of iodide ion has also received attention. Gemal and Luche illustrated the use of NaI in aqueous acid-THF, as being an efficient system for the dehalogenation of α-haloketones.[86] However, aqueous and acid-sensitive substrates should not be used under these conditions.

---

[83] Ono, A.; Maruyama, T.; Kamimura, J. *Synthesis* **1987**, 1093.
[84] Ono, A.; Kamimura, J.; Suzuki, N. *Synthesis* **1987**, 406.
[85] Borah, H.; Boruah, R. C.; Sandhu, J. S. *J. Chem. Soc., Chem. Commun.* **1991**, 154.
[86] Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1980**, 21, 3195.

Mandal, subsequently illustrated that iodide ion could be used in catalytic amounts in the presence of phosphorous acid to effect the dehalogenation of α-haloketones. This system was also effective for the dehalogenation of α-haloesters, acids and nitriles.[87] Penso was able to effect the reductive dehalogenation of α-haloketones by using hydroiodic acid in the absence of solvent.[88]

Iodotrimethylsilane was illustrated by Ho to be effective for the reductive removal of halogen atoms in the α-position of ketones.[89] The system was shown to be effective at room temperature. Reaction times could be accelerated by raising the temperature leading to complete reaction usually within an hour, as demonstrated by the disappearance of starting material. The hydrolytic sensitivity and its decomposition on prolonged storage are some of the drawbacks in using of iodotrimethylsilane. Olah demonstrated that the reagent system composed of chlorotrimethylsilane / sodium iodide in acetonitrile could be effectively employed to bring about the reductive dehalogenation of α-haloketones.[90]

In an ensuing paper, Olah illustrated that a mixture made of trichloromethylsilane and 3 equivalents of sodium iodide in dry acetonitrile, was not only effective for the cleavage of ethers, esters and lactones, but also for the reductive dehalogenation of α-haloketones.[91] Ono described the use of sodium iodide in combination with a metal salt, for the dehalogenation of α haloketones.[92]

---

[87] Mandal, A.; Nijasure, A. M. *Synlett* **1990**, 554.
[88] Penso, M.; Mottadelli, S.; Albanese, D. *Synth. Commun.* **1993**, 23, 1385.
[89] Ho, T. L. *Synth. Commun.* **1981**, 11, 101.
[90] Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *J. Org. Chem.* **1980**, 45, 3531.
[91] Olah, G. A.; Husain, A.; Sing, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, 48, 3667.
[92] Ono, A.; Fujimoto, E.; Ueno, M. *Synthesis* **1986**, 570.

The reaction of sodium iodide with chlorotrimethylsilane followed by the addition of samarium metal generates a samarium iodide equivalent, which has shown to be effective in the dehalogenation of α-haloketones and esters.[93]

Inorganic phosphorus compounds such as PI_3 and P_2I_4 have also been used in the reductive dehalogenation process.[94] The reactions readily take place at room temperature and require a stoichiometric amount of the phosphorus reagent.

Molybdenum and palladium catalysts have also been investigated as potential dehalogenating systems for the α-halocarbonyl functionality. Keinan described reductive dehalogenations using a system that was comprised of $PhSiH_3$, triphenylphosphine (Ph_3P) and catalytic amounts of molybdenum haxacarbonyl [$Mo(CO)_6$].[95] Suzuki and Moro-Oka were able to accomplish the reductive dehalogenations using a hexamethyldisilane ($Me_3SiSiMe_3$) / tetrakis(triphenylphosphine) palladium [$(Ph_3P)_4Pd$] system.[96]

Nickel boride, formed *in situ* from the reaction of sodium borohydride and nickel chloride, is yet another reagent that can be employed for the reductive dehalogenations of α-halocarbonyls.[97] The system was shown to be compatible with numerous other functionalities such as esters, lactones, alcohols and olefins.

---

[93] Akane, N.; Kanagawa, Y.; Nishiyama, Y.; Ishi, Y. *Chem. Lett.* **1992**, 12, 2431.
[94] Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1981**, 22, 1431.
[95] Perez, D.; Greenspoon, N.; Keinan, E. *J. Org. Chem.* **1987**, 52, 5570.
[96] Urata, H.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *J. Organomet. Chem.* **1982**, 234, 367.
[97] Sarma, J.C.; Borbaruah, M.; Sharma, R. P. *Tetrahedron Lett.* **1985**, 26, 4657.

Finally, various metal carbonyls as prospective dehalogenating agents have also been investigated. Alper illustrated the potential of the dicobalt octacarbonyl [$Co_2(CO)_8$], NaOH (5N) and benzyltriethylammonium chloride system by effectively reducing various α-halogenated carbonyls to their corresponding ketones.[98] In a subsequent paper, Alper described dehalogenations carried out by molybdenum hexacarbonyl [$Mo(CO)_6$] adsorbed on alumina (Al_2O_3).[99] Luh and Tam described the use of an iron pentacarbonyl [$Fe(CO)_5$] system to effect reductive dehalogenations.[100]

From the great number of methodologies that have been developed to accomplish the reductive dehalogenation α-haloketones, it becomes clear that it indeed constitutes an important functional group transformation. The topic continues to attract attention, and as will be discussed in the next section, organoselenium-tellurium reagents have also appeared that are capable of effecting this transformation.

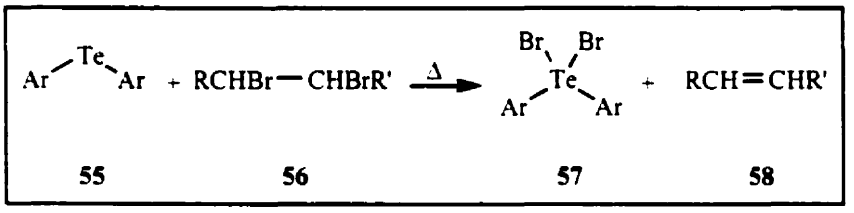
2.2 Project Rationale.

Research directed at the dehalogenation of organic substrates has encouraged many scientists to take a closer look at the potential of organoselenium / tellurium compounds.

[98] Alper, H.; Logbo, K. D.; des Abayes, H. *Tetrahedron Lett.* **1977**, 2861.
[99] Alper, H.; Pattee, L. *J. Org. Chem.* **1979**, 44, 2568.
[100] Luh, T. Y.; Lai, C. H.; Lei, K. H.; Tam, S. W. *J. Org. Chem.* **1979**, 44, 641.

As a direct result, a number of reagents have been developed that have subsequently proven effective in the above-mentioned functional group transformation. An interesting observation is that some of the so-called new selenium and tellurium reagents, found to be effective in the dehalogenation process, had been previously developed to accomplish other transformations.

The relative ease at which diaryltellurides can be transformed into their corresponding diaryl tellurium dihalides, led Campos to study their potential as dehalogenating agents.[101] He subsequently observed that refluxing a solution composed of a vicinal dihalide and a diarylditelluride, produced the alkene product mixed with the diaryl telurium dihalide (Scheme 19).



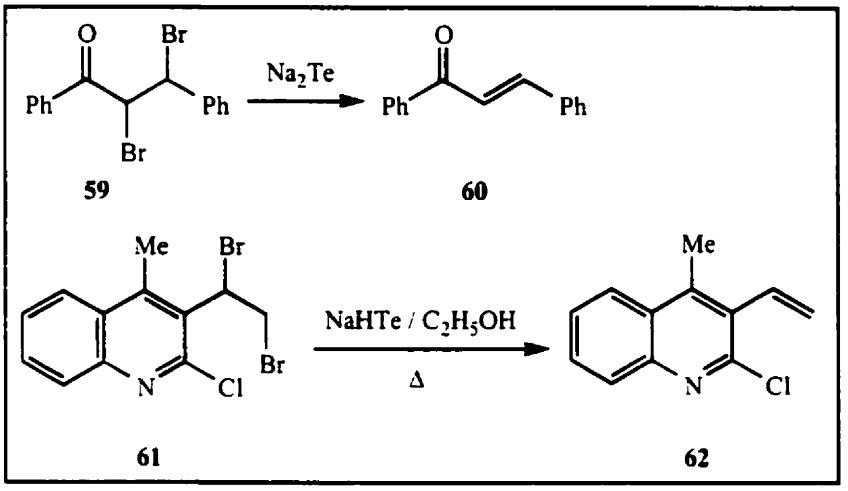
55 **56** **57** **58**

Scheme 19

It is well-known that inorganic species such as NaHSe, NaHTe, and Na_2Te function as highly effective reducing agents for the transformation of vicinal dihalides into olefins (Scheme 20).[102, 103, 104, 105] These reagents are relatively unstable and are usually prepared *in situ*, prior to use.

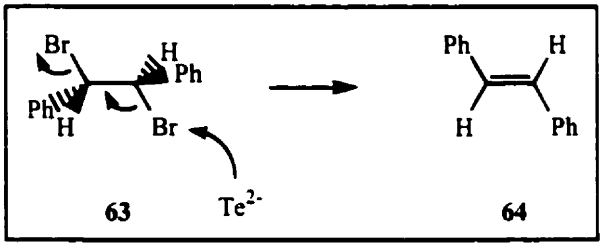
---

[101] de Moura Campos, M.; Petragnani, N. *Tetrahedron Lett.* **1960**, 5.
[102] Raja, T. K.; *Indian J. Chem.* **1980**, 19B, 812.
[103] Inouye, M. Suzuki, H. *Chem. Lett.* **1985**, 225.
[104] Ramasamy, K.; Kalyanasundaram, S. K.; Shanmugam, P. *Synthesis* **1978**, 311.
[105] Ramasamy, K.; Kalyanasundaram, S. K.; Shanmugam, P. *Synthesis* **1978**, 545.



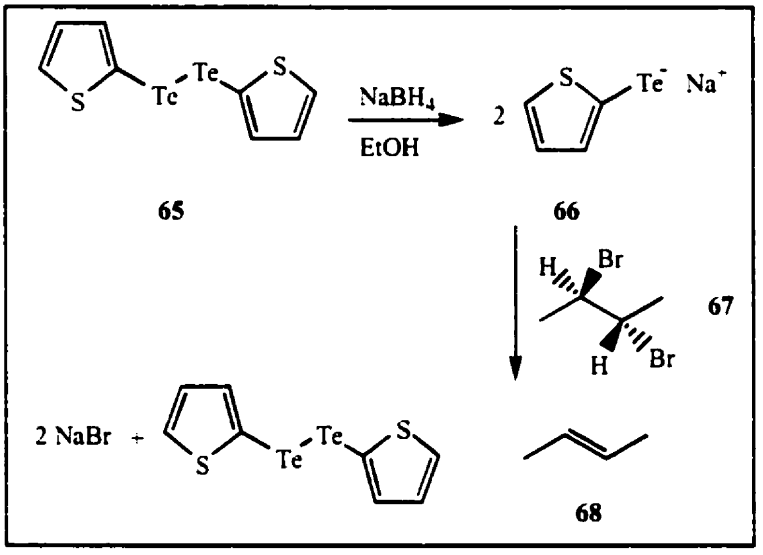
Scheme 20

The reduction with Na_2Te was found to be of particular synthetic interest, since it could support other reducible functionalities such as carbonyl, carboxyl, ester and nitro groups, which remain unaffected during the dehalogenation process. The reductions, when carried out in the presence of 2 equivalents of NaHTe, were shown to lead to the formation of the completely reduced alkane product. Hence, this reagent can also potentially be used for the hydrogenation of olefins. The elimination reaction is highly stereospecific, and appears to take place through a concerted *anti*-periplanar process (Scheme 21).



Scheme 21

Engman demonstrated that the reaction of sodium borohydride with a catalytic amount of bis(2-thienyl)ditelluride (**65**), generates a highly potent tellurium nucleophile that readily debrominates vicinal dibromides to olefins (Scheme 22).[106] This constitutes the first catalytic procedure for the dehalogenation of vicinal dihalides.

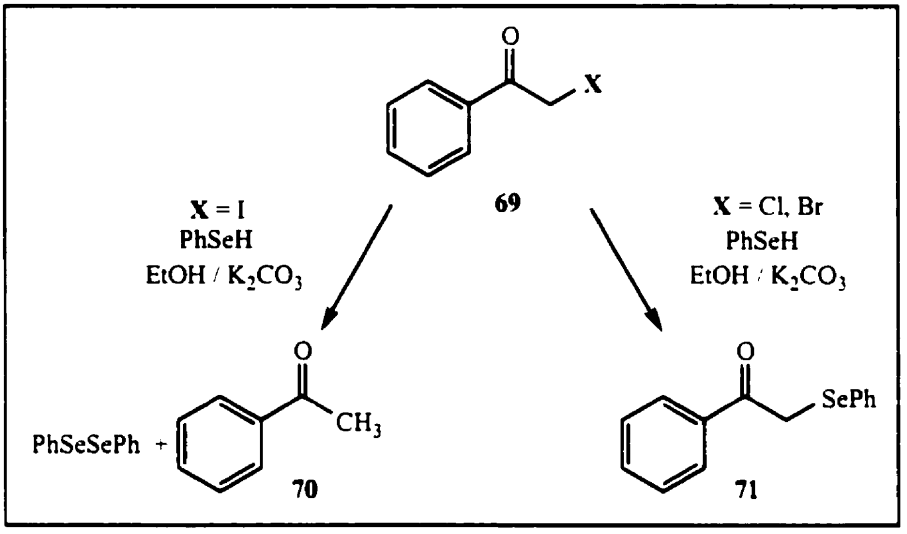


Scheme 22

Again, where this can be observed, the debromination reactions occur through an anti-periplanar transition state. Meso-2,3-dibromobutane (**67**) gives trans 2-butene (**68**) as the only product, upon dehalogenation. Also, due to the characteristic deep red color of the ditelluride, the reaction can be conveniently employed as a "titration" of the dibromide. The reaction mixture will become colorless when all of the dibromide has been consumed.

[106] Engman, L. *Tetrahedron Lett.* **1982**, 23, 3602.

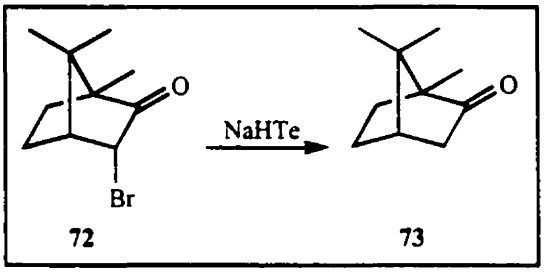
The reductive dehalogenation of α-haloketones using selenium and tellurium-based reagents, has also been investigated. Israel and co-workers observed that the reaction of α-chloro and α-bromoketones with selenols (or thiols), yields exclusively the substitution product whereas, the corresponding α-iodo compounds underwent exclusive reduction (Scheme 23).[107]



Scheme 23

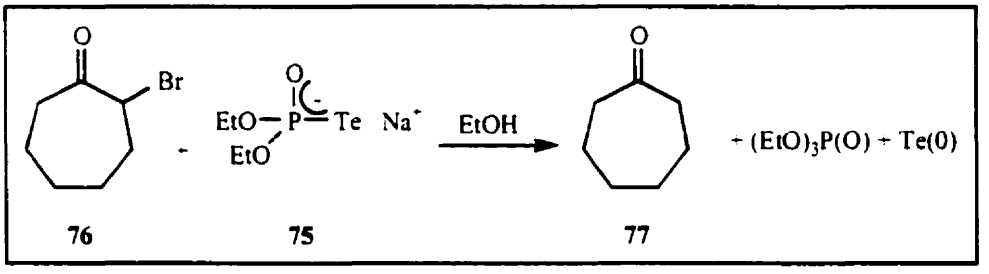
Osuka and Suzuki reported on the efficiency of NaHTe in reducing of α-halocarbonyl compounds (Scheme 24).[108] The dehalogenations occurred chemoselectively at room temperature and in good yield for all the substrates tried. The chemoselectivety is explained by a greater affinity for reaction of the tellurium ion at the halide than at the carbonyl functionality.

[107] Seshadri, R.; Pegg, W. J.; Israel, M. *J. Org. Chem.* **1981**, 46, 2596.
[108] Osuka, A.; Suzuki, H. *Chem. Lett.* **1983**, 119.



Scheme 24

Sodium O,O-diethyl phosphorotelluroate (**75**), was previously reported as being an effective reagent for the conversion of epoxides into olefins.[109] Clive subsequently illustrated that was also a mild and effective reagent for the reductive removal of halogens, positioned α to the carbonyl functionality (Scheme 25).[110]



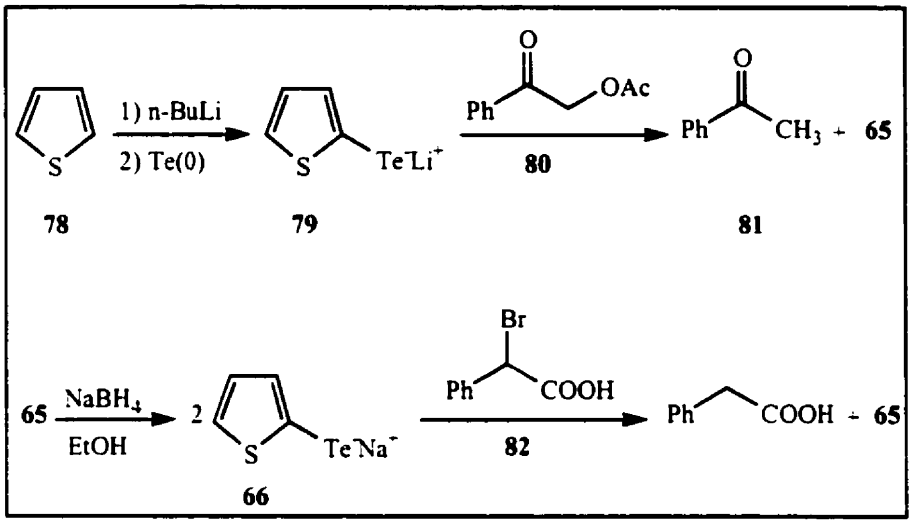
Scheme 25

Under identical reaction conditions, the selenium ester of **75** could not be observed to give rise to dehalogenated products.

Engman and Cava illustrated that lithium and sodium 2-thiophenetellurolates (the latter, **66** was previously desrcribed by Engman), were also highly efficient for the reductive removal of electronegative substituents other than halides, positioned α to the carbonyl functionality. They also illustrated the potential of these reagents for the dehalogenation of α-haloacids (Scheme 26).[111]

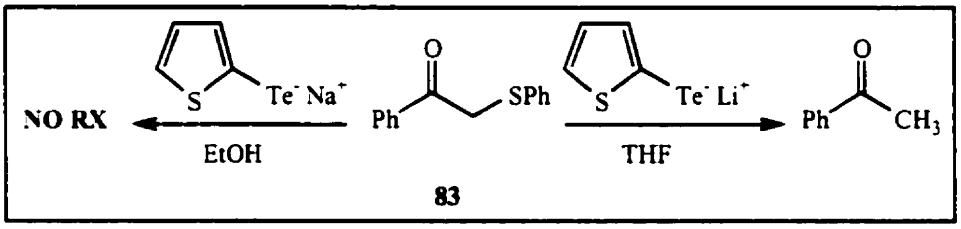
---

[109] Clive, D. L. J.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1977**, 658.
[110] Clive, D. L. J.; Beaulieu, P. L. *J. Org. Chem.* **1982**, 47, 1124.
[111] Engman, L.; Cava, M. P. *J. Org. Chem.* **1982**, 47, 3946.



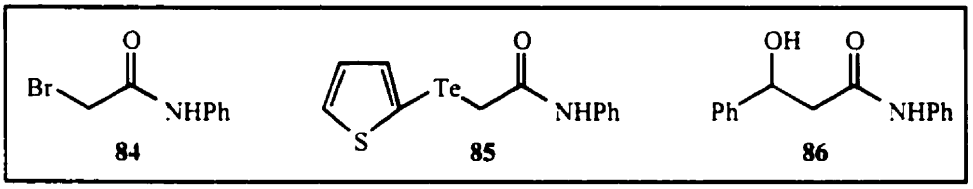
Scheme 26

Acetoxy, mesyloxy, and phenylthio groups, positioned in the α-position of acetophenone, have all been successfully removed. Again, the reaction with sodium 2-thiophenetellurolate (**66**) can be carried out using a catalytic amount of bis (2-thienyl) ditelluride (**65**). In the presence of functional groups susceptible of being reduced by $NaBH_4$, the lithium-thiophenyltellurolate (**79**) procedure should be used. The authors observed a lower nucleophilicity for the $NaBH_4$-generated tellurolate when compared to the lithium tellurolate, as can be seen in the reaction with phenacyl phenyl sulfide (Scheme 27).



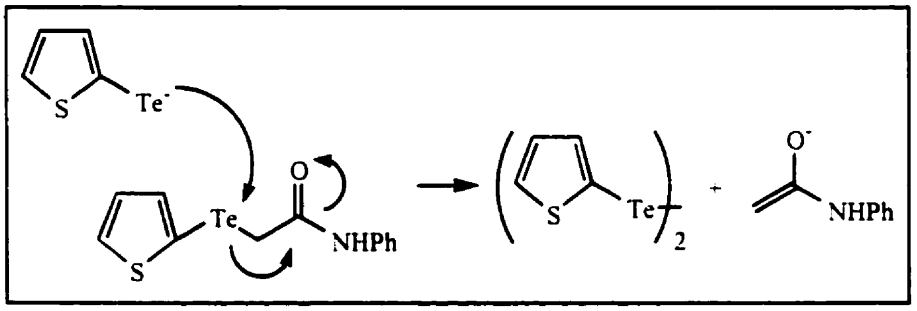
Scheme 27

The isolation of α-(2-thienyltelluro)acetanilide (**85**), generated from the corresponding α-bromoacetanilide (**84**), supports the supposition that α-telluroketones are in fact intermediates in the dehalogenation reactions. Evidence for the formation of an enolate intermediate in the subsequent step was provided by its successful trapping with benzaldehyde, generating hydroxyamide **86** (Scheme 28).



Scheme 28

Enolate formation supports a mechanism in which a second tellurium nucleophile attacks the tellurium atom in **85** hence regenerating the ditelluride starting material which in turn enables the process to become catalytic (Scheme 29).



Scheme 29

Our interest in the dehalogenation of α-haloketones, stemmed from the observation that the previously described procedures had some obvious synthetic limitations. The use of selenols or thiols is only effective for α-iodo substrates.[107]

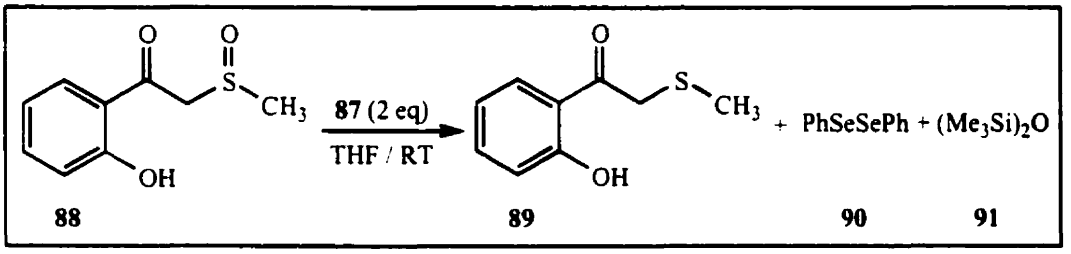
Inorganic species such as NaHSe or NaHTe are relatively unstable and have to be prepared *in situ*, prior to use.[108] Their preparation, as is the case for the formation of the sodium tellurolate described by Engman and Cava,[111] involves the reaction of elemental selenium or tellurium with an excess amount of sodium borohydride in ethanol, which makes the reagent mixture both a strong base and a strong reducing agent. This system should therefore not be used with complicated, polyfunctional substrates, in which side reactions could very easily result. The lithium tellurolates reported by Engman and Cave are also generated *in situ via* a two-step procedure, that requires the use of a strong base such as *n*-BuLi followed by a reaction with elemental tellurium.[111]

The sodium O,O-diethyl phosphorotelluroate, described by Clive[110] also requires prior, *in situ* formation, from the reaction of elemental tellurium and sodium diethyl phosphite in ethanol. Finally, the presence of ethanol as the solvent or co-solvent in these systems, is not always optimal since it tends to cluster around the reactant nucleophile hence diminishing its reactivity.

It was our intention to develop a new class of reagents that could overcome some or all of the above limitations. Ideally, these reagents should be easily prepared and stored over extended periods of time without decomposition. Also, they should be both mild and easy to use on any scale and tolerated by a wide array of functional groups.

2.3 Chalcogenides as Reducing Agents for the α-Halocarbonyl Functionality.

Detty observed that (phenylseleno)trimethylsilane [$PhSeSiMe_3$] **87** is an effective reagent for the reduction of sulfoxides, selenoxides and telluroxides into their corresponding sulfides, selenides and tellurides (Scheme 30).[112]



Scheme 30

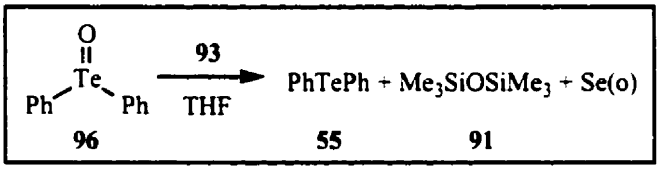
The reduction reactions with **87** were shown to be compatible with a variety of other functionalities such as alcohols, ketones, nitro groups, sulfones and olefins. The solubility and chromatographic properties of diphenyldiselenide **90**, also produced in the course of these reductions, complicated the isolation of the desired product in certain cases.

In a subsequent paper, Detty and Seidler reported on the improved efficiency for the reduction of the group 6A oxides, with bis(trialkylsilyl) chalcogenides **92-95**.[113]

$Me_3SiSSiMe_3$	$Me_3SiSeSiMe_3$	$Me_3SiTeSiMe_3$	t-$BuMe_2SiTeSiMe_2$t-Bu
92	**93**	**94**	**95**

[112] Detty, M. R. *J. Org. Chem.* **1979**, 44, 4528.
[113] Detty, M. R.; Seidler, M. D. *J. Org. Chem.* **1982**, 47, 1354.

The reductions carried out with these compounds are also compatible with numerous other functional groups (alcohols, ketones) and generate reaction mixtures (as illustrated with **93**) which are considerably easier to purify when compared to the reactions carried out with **87** (Scheme 31).

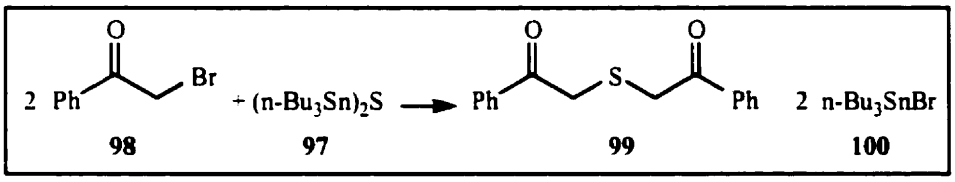


Scheme 31

The elemental chalcogen produced was removed by filtration and hexamethyldisiloxane **91** was readily removed by distillation or by column chromatography.

The sensitivity of compounds **93** and **94** however, constitutes a serious drawback. The former is an air-sensitive colorless oil that has to be stored at –20°C under an argon atmosphere in order to avoid decomposition. The latter is extremely sensitive to both air and light and decomposes within 24 hours, even when stored in the dark at –20°C under an argon atmosphere. The stability of these compounds can be markedly improved by incorporating bulkier side groups. This is demonstrated by bis(*tert*-butyldimethylsilyl)telluride **95**, which can be stored for several weeks when kept in the absence of light at –20°C and under an argon atmosphere. The above reactions are remarkably efficient and chemospecific. In addition, chalcogen nucleophiles appear to be intermediates in the process.

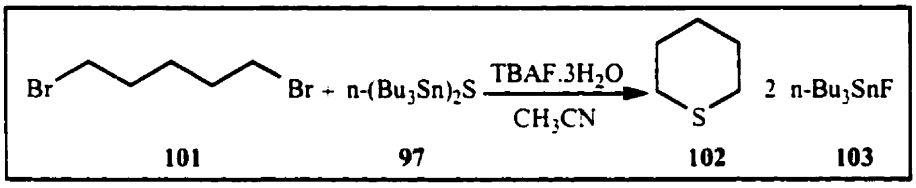
From earlier studies in our laboratory, we demonstrated that bis(tributylstannyl) sulfide **97** effectively functions as a sulfur transfer reagent to a variety of activated organic halides, including α-halocarbonyls, to generate the corresponding sulfides (Scheme 32).[114]



Scheme 32

It was assumed that since the rate of these reactions increased with an increase of solvent polarity and ability to coordinate with tin, that an ionic mechanism was most likely involved.

It was subsequently reported that in the presence of a fluoride ion, this reagent readily generates a potent sulfur nucleophile which rapidly reacts with organohalides, producing the corresponding sulfides in high yield (Scheme 33).[115]

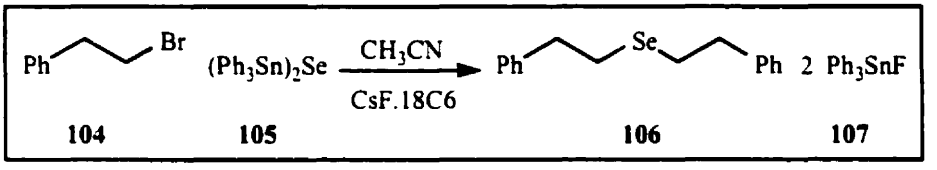


Scheme 33

Again a strong solvent effect was observed in which polar aprotic solvents such as acetonitrile were found to be optimal for an efficient reaction.

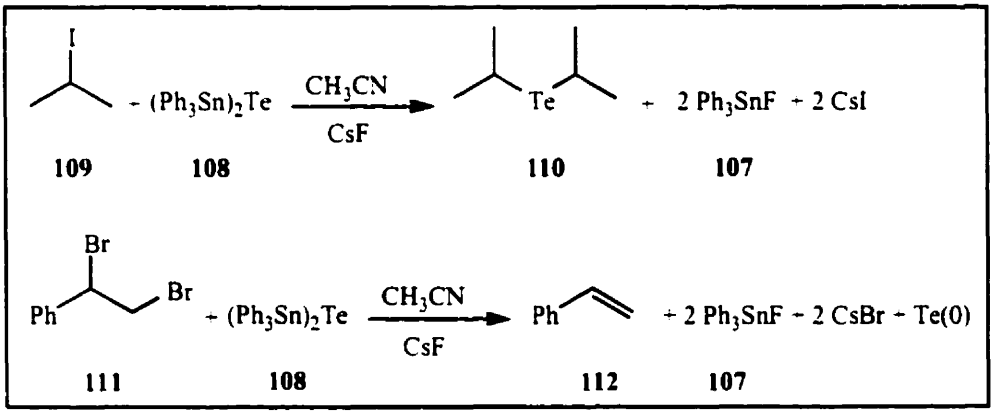
[114] Harpp, D. N.; Gingras, M.; Aida, T.; Chan, T. H. *Synthesis*, **1987**, 1122.
[115] Harpp, D. N.; Gingras, M. *Tetrahedron Lett.* **1987**, 38, 4373.

This methodology has also proven to be efficient for the preparation of a variety of selenides (70-90% yield), using bis(triphenylstannyl) selenide **105** as the selenium transfer reagent (Scheme 34).[116]



Scheme 34

Li was subsequently able to demonstrate that the fluorodestannylation reactions using bis(triphenylstannyl)telluride (**108**), were not only efficient for the synthesis of diorganotellurides, but also for the debromination of vicinal dibromides generating the corresponding olefins (Scheme 35).[117]

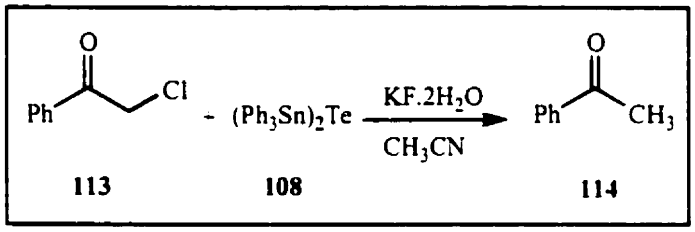


Scheme 35

[116] Harpp, D. N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, 110, 7737.
[117] Harpp, D. N.; Li, C. J. *Tetrahedron Lett.* **1990**, 44, 6291.

An interesting observation was made by Li when these reactions were carried out using 2-bromoacetophenone as the substrate. Not only was the telluride produced, but unexpectedly, significant amounts of the reduced product acetophenone were also generated. In the absence of a fluoride source, the amount of acetophenone diminished dramatically. These observations suggested that this reaction could possibly constitute a new methodology for the reductive removal of α-halocarbonyl substrates.

Following up on these results, Li was subsequently able to demonstrate that **108** in the presence of potassium fluoride dihydrate, indeed constitutes an effective procedure for the reductive dehalogenation α-haloketones (Scheme 36).[118]



113 **108** **114**

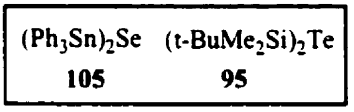
Scheme 36

2.4 Bis(triphenylstannyl) selenide (105) and Bis(*tert*-butyldimethylsilyl) telluride (95) as Dehalogenation Agents for α-Halo Carbonyl Compounds.

The scope and limitations of the fluoride induced dehalogenation of α-haloketones, using chalcogenide reagent **108**, remained relatively unestablished. Enolates were proposed as possible intermediates in these reactions, but attempts at trapping them with benzaldehyde remained unsuccessful.[119]

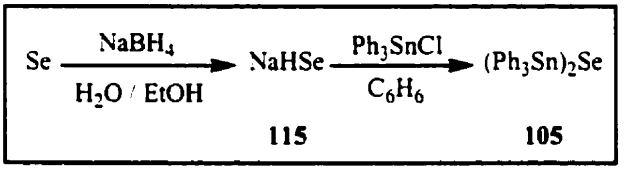
[118] Harpp, D. N.; Li, C. J. *Tetrahedron Lett.* **1991**, 32, 1545.
[119] Li, C. J. Ph. D. Thesis, McGill University, Montreal, Canada, **1991**.

In order to address these aspects, we investigated the potential of two related molecules, bis(triphenylstannyl) selenide **105** and bis(*tert*-butyldimethylsilyl) telluride **95** in the dehalogenation process.



2.4.1 Preparation and Physical Properties of 105 and 95.

Compound **105** was prepared according to a modified literature procedure by Einstein, *via* the addition of a benzene solution of triphenyltin chloride to an aqueous ethanol solution, containing *in situ* generated sodium hydrogen selenide **115** (Scheme 37).[120]



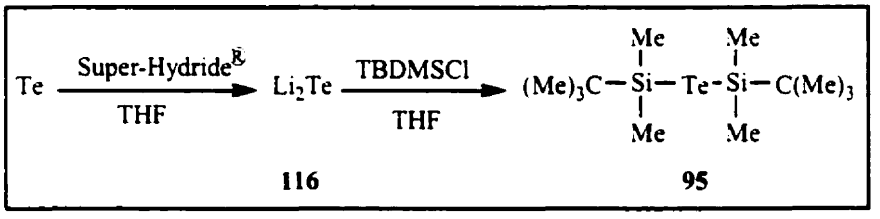
Scheme 37

Einstein's purification procedure requires several recrystallizations from a diethyl ether / hexane mixture, whereas we found that a very pure product (fine white needles) could be obtained from a single recrystalliztion from an ethanol / chloroform solvent system.

[120] Einstein, F. W. B.; Jones, C. H. W.; Sharma, R. D. *Can. J. Chem.* **1983**, 61, 2611.

The product obtained after purification possesses a sharp melting point at 141-142 °C (Lit. 148°C)[120] and was verified by ^1H, ^{13}C NMR and by MS. The compound displays a remarkable stability in that it can be freely handled in the atmosphere and has no distinct odor. It can be stored in the refrigerator for periods up to over a year without any detectable trace of decomposition as confirmed by ^1H NMR analysis. These characteristics, including its ease of preparation on small or large scale, are appropriate for use in organic synthesis.

Compound **95** was prepared according to a procedure developed by Detty which involved the addition of *tert*-butyldimethylsilyl chloride to a THF solution of lithium telluride **116** generated *in situ* from the reaction of elemental tellurium with lithium triethylborohydride or "Super Hydride" (Scheme 38).[113]



Scheme 38

The product was purified by distillation, directly from the reaction mixture. Bis(*tert*-butyldimethylsilyl)telluride **95** is a gray-white solid after initial vacuum distillation from the reaction mixture as an oil at 105 °C / 4.5 Torr. (Lit. 90-95°C at 5.5 Torr).[113] The compound is extremely foul smelling, air and moisture sensitive and is collected in a round bottomed flask, placed in a dry-ice bath. It can be stored for several days in the freezer with no noticeable decomposition.

Exposure to the air results in rapid decomposition with concomitant deposition of elemental tellurium within a few minutes.

2.4.2 Application of 105 and 95 in the Dehalogenation Process.

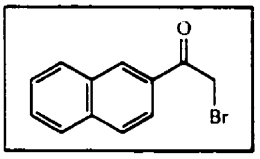
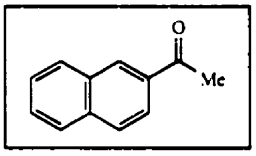
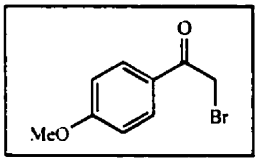
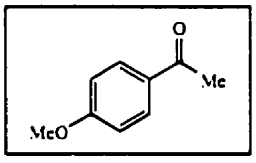
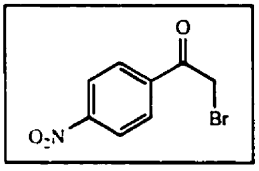
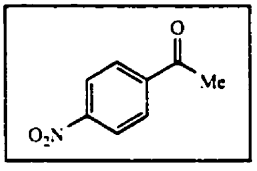
We were able to successfully carry out the reductive dehalogenation of various α-halo ketones with a reagent mixture that was composed of either compound **105** or **95** and potassium fluoride dihydrate (Table 1).

As can be observed from the results in Table 1, the reactions were carried out for 24 hours at room temperature to permit them to go to completion, as TLC analysis over shorter reaction times indicated persistent starting material. All the reactions, with the exception of entry 8, were completed after 24 hours as confirmed by ^{1}H NMR analysis of the crude reaction mixtures.

The inconsistent low yield of entry 6, as compared to the generally good yields obtained for all other substrates, was caused by difficulties in the purification procedure. A trace of starting material remained, that persistently co-eluted from the column with the desired product.

Although the reactions were carried out in essentially neutral and very mild conditions, a significant observation concerning the reaction times was made. We noted that under refluxing conditions, the reactions could be completed in only 2 hours. This is an important finding since it allows us to discern between simple and complicated substrates, by selecting the appropriate reaction conditions.

Table 1 Dehalogenation of α-haloketones with bis(triphenylstannyl) selenide **105** and bis(*tert*-butyldimethylsilyl)telluride **95**.

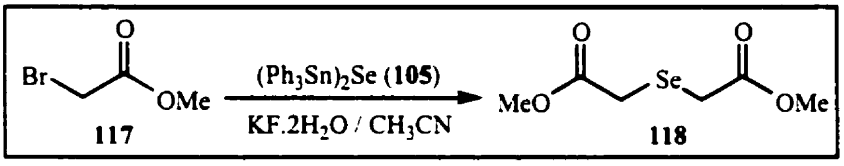
Entry	α-Haloketone	Time (h)	Product	Yield[b] (**105**)	Yield[c] (**95**)
1	$PhCOCH_2Br$	24	$PhCOCH_3$	(94)[d] 65	72
2	$PhCOCH_2Br$	2[e]	$PhCOCH_3$	(92)[d]	
3	$PhCOCH_2Cl$	24	$PhCOCH_3$	(89)[d]	75
4	$PhCOCH_2Cl$	2[e]	$PhCOCH_3$	(84)[d]	
5	$PhCOC(CH_3)_2Br$	24	$PhCOCH(CH_3)_2$	75	81
6	$PhCOCH(CH_3)Br$	24	$PhCOCH_2CH_3$	48	65
7		24		81	72
8		48		71	82
9		24		89	79

[a] Unless otherwise specified, all reactions were carried out at room temperature in CH_3CN with the haloketone / selenide **2** or telluride **3** / $KF.2H_2O$ in a 1:1:3 (mole ratio). [b] Isolated yields with selenide reagent **2**. [c] Isolated yields with telluride reagent **3**. [d] ^1H NMR yields. [e] Refluxing solvent.

A final but equally meaningful observation involves the selective reduction of the α-bromo functionality of entry 9, without affecting the nitro group. This is particularly interesting given the ease of the nitro-amine interconversion as demonstrated by the wide variety of reagents capable of this transformation. Note that an aromatic nitro functionality can be reductively removed upon treatment with $NaBH_4$ and a tertiary nitro functionality by treatment with NaHTe.

In all the dehalogenation reactions, the deposition of elemental chalcogen could be easily discerned. The yields illustrate the effectiveness of both reagents for the reductive dehalogenation of the α-haloketone functionality. Even though equally effective, compound **105** is the reagent of choice because it is considerably easier to handle and manipulate. The tellurium reagents **95** and **108** were observed to stain all the glassware they came in contact with, which imposed extensive glassware washing upon completion of the reactions.

The reaction of **105** with α-haloester **117** did not yield the anticipated dehalogenated product, but instead produced the symmetrical selenoester **118** (Scheme 39).



Scheme 39

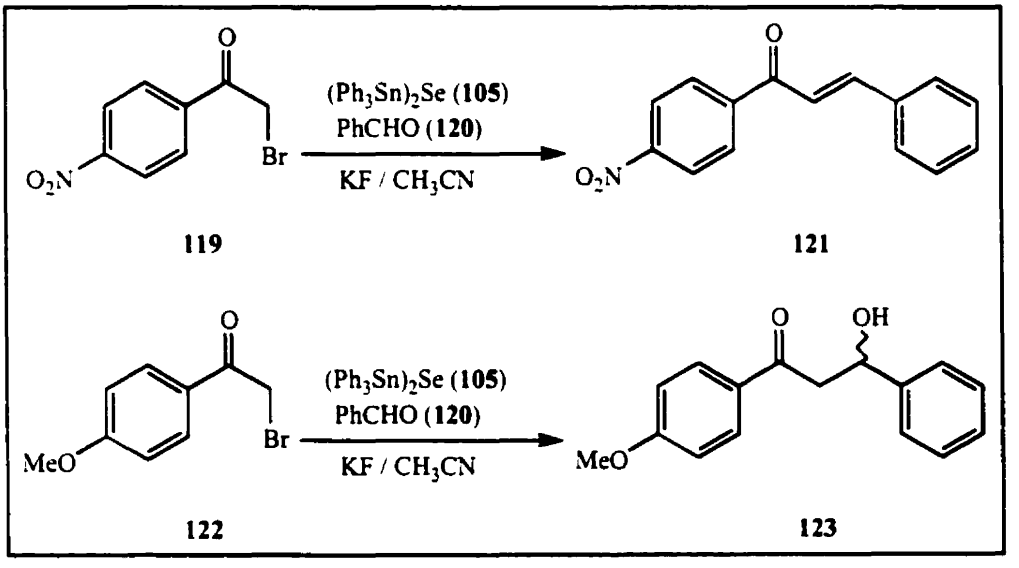
This observation was not entirely unexpected, in view of similar results previously reported from our laboratory describing the formation of symmetrical telluroesters

from the reaction of **108** and α-haloesters.[121] The selenoester **118** was obtained in very good yield (98%), after purification by column chromatography on silica gel. Compound **118**, as was the case for the telluroesters, displayed excellent stability when exposed to the atmosphere.

2.4.3 Trapping of Enolate Intermediates with Benzaldehyde.

In earlier work in our laboratory, mechanisms were postulated in which enolates were suggested as likely intermediates in a similar dehalogenation process. However, attempts at trapping this transitional species with benzaldehyde remained ineffective since none of the expected aldol condensation product could be observed.

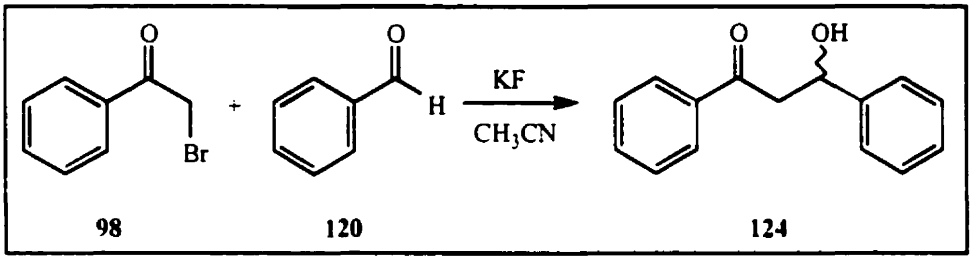
Here, we were able to successfully isolate compounds **121** and **123** (Scheme 40). The formation of these chalcone condensation products constitutes direct evidence for the enolate hypothesis.



Scheme 40

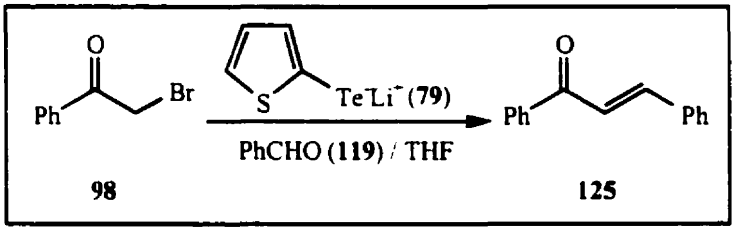
[121] Harpp, D. N.; Li, C. J. *Sulfur Letters* **1991** 13(3), 139.

Even though a large (10 fold) excess of benzaldehyde **120** was used in these reactions, it is likely that once optimized, the reaction could potentially find use as the Reformatsky analogue for the condensation of α-haloketones. We subsequently observed that the trapping reactions could also be effectively carried out using a 3:1 ratio of benzaldehyde to α-haloketone. When substrate **98** was reacted with **120** in a 1:3 ratio, **124** was obtained in 52% isolated yield (58% was obtained using a 10:1 reactant ratio). However, only 31% of **124** was obtained using a 1.5:1 reactant ratio (Scheme 41).



Scheme 41

Cava and Engman were able to make a similar observation, when they successfully isolated compound **125**, resulting from the reaction of benzaldehyde with the enolate of **98** (Scheme 42).[111]



Scheme 42

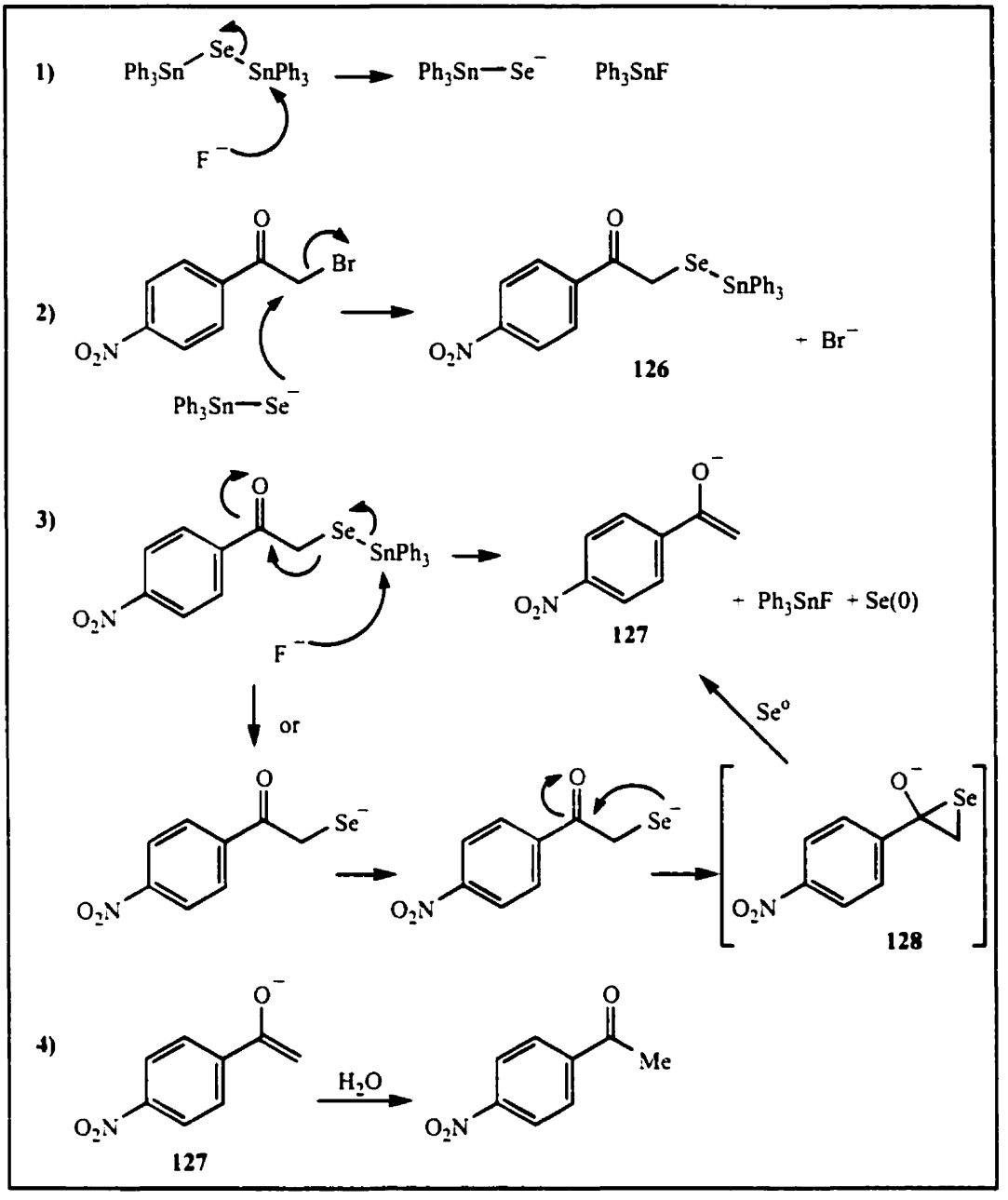
2.4.4 Mechanistic Aspects.

We propose a stepwise mechanism (Scheme 43), which is initiated by the attack of the very hard fluoride nucleophile at the site of higher partial positive charge, represented by the tin atom.[122] In orbital terms, this first step of the reaction should be very fast because it is charge driven. In other words, there exists a large Coulombic attraction between the fluoride anion and the electropositive tin atom. Bond energies are most certainly another important factor. Based on the bond strength, a much stronger bond is generated between fluoride and tin (111.5 kcal / mol) than between fluoride and selenium (81 kcal / mol).[123] Finally, after the displacement reaction, the negative charge resides on the more electronegative selenium atom.

In the second step, the newly generated selenium nucleophile displaces the halide located on the α-carbon in an S_N2 reaction, leading to the formation of **126**. It is well-established that carbon atoms undergoing S_N2 reactions are soft centers and that carbonyl groups are hard centers.[124] Because the selenium-based anion is a soft nucleophile, it will preferably attack the α carbon and in the process displace the halide.[125] A similar mechanism involving displacement of a halide located in the α position of a carbonyl with tellurium nucleophiles, was proposed separately by Clive and Cava.[110, 111]

---

[122] Harpp, D. N. H.; Schultz, E. K. V. *Synthesis* **1998**, 1137.
[123] Weast, C. R.; *CRC Handbook of Chemistry and Physics*, CRC Press, Inc. **1982-3**, 63rd edition, Boca Raton, Florida.
[124] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons: **1990**, New York; Chapter 3.
[125] Smith, M. B.; *Organic Synthesis*, McGraw-Hill: **1994**, New York; Chapter 2, pp-114-119.



Scheme 43

The third step involves attack of another fluoride ion on the tin atom of **126**, with the concomitant deposition of elemental selenium and formation of an enolate (**127**). Clive has postulated the intermediacy of epitellurides in the dehalogenation process.[110]

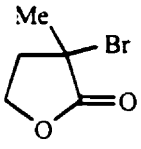
It is possible that an episelenide (**128**) could have been generated in our reactions. This highly unstable species would readily collapse with the extrusion of elemental selenium, which accounts for the formation of a gray solid in the reaction mixture, to generate the corresponding enolate.[126]

The fourth and final step likely involves protonation of the enolate by a water molecule to form the reduced and final product **127**.

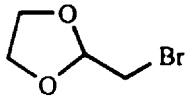
This mechanism accounts for the presence of enolate intermediates, which was confirmed by the formation of the chalcone products **121** and **123**.

2.5 Dehalogenation of Related Substrates.

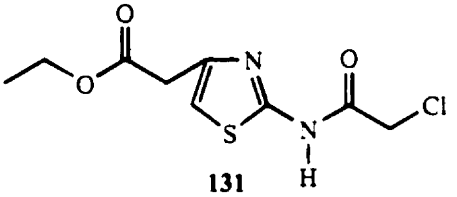
In an attempt to further explore the utility and limitations of chalcogenide reagents for the reduction of the α-halocarbonyl functionality, compounds **129**, **130**, and **131** were subjected to the dehalogenation process.



129



130

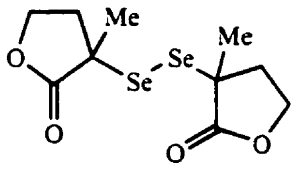


131

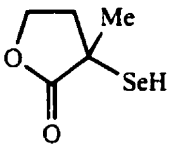
When the halogenated lactone **129**, was reacted in the presence of bis(triphenylstannyl) selenide (**105**) no reduced product could be isolated. Instead a coupling reaction was observed to occur which led to the formation of diselenide **132** as a pair of diastereomers in 54% isolated yield.

---

[126] Clive, D. L. J.; Denyer, C. V. *J. Chem. Soc.; Chem. Commun.* **1973**, 253.



132



133

This observation was not entirely unexpected since in a previous reaction with α-haloester **117** we also observed a coupling reaction. The formation of a diselenide instead of a monoselenide was however a little surprising and could possibly have occurred *via* the air oxidation of selenol **133**.

The formation of the monoselenide was most likely impeded by steric factors that would have been generated by the proximity of the methyl substituents. The formation of a selenol intermediate, invokes the presence of a relatively stable transitional selenium anion that is sufficiently long lived to be protonated and subsequently air oxidized to the diselenide.

It is well known that esters constitute a less acidic class of compounds than ketones, as illustrated by a difference of approximately five pK_a units between the corresponding α protons. This decreased acidity leads to an abated tendency for esters containing a selenium anion in the α-position, to expel the heavy element and form the corresponding enolate as compared to the analogous ketones.

The increased stability of selenium anions located in the α-position of the ester functionality could then explain why these anions form the observed chalcogen containing coupling products whereas those located in the α position of ketones readily extrude the heavy element and ultimately generate the reduced product.

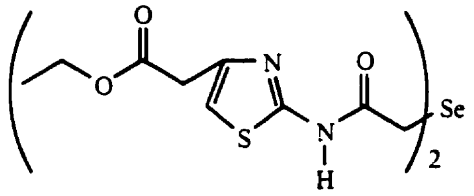
When substrate **129** was reacted with bis(triphenylstannyl) telluride (**108**) or bis(*tert*-butyldimethylsilyl) telluride (**95**) a complex reaction mixture was obtained that seemed to be composed of unreacted starting material, some reduced product, an alkene product that could have resulted from the elimination of HBr and other unidentified compounds.

The halogenated dioxolane **130** displayed no reactivity when combined with reagent **105**. The reaction mixture was monitored over a period of four days by ^{1}H NMR, which indicated that no reaction was taking place as illustrated by the presence of starting material only. Likewise, when **130** was reacted with either reagent **95** or **108**, no product formation could be observed. The deactivation of the α position of the dioxolane when compared to the α position of a ketone, is a probable cause for the observed lack of reactivity.

A similar observation was previously made in our laboratory, in which the ease of telluride formation was directly related to the nature of the halide substrate. Li found that while activated halides such as benzylic halides rapidly reacted with **108**, alkyl halides needed the activation of cesium fluoride in order to undergo the desired transformation.[117]

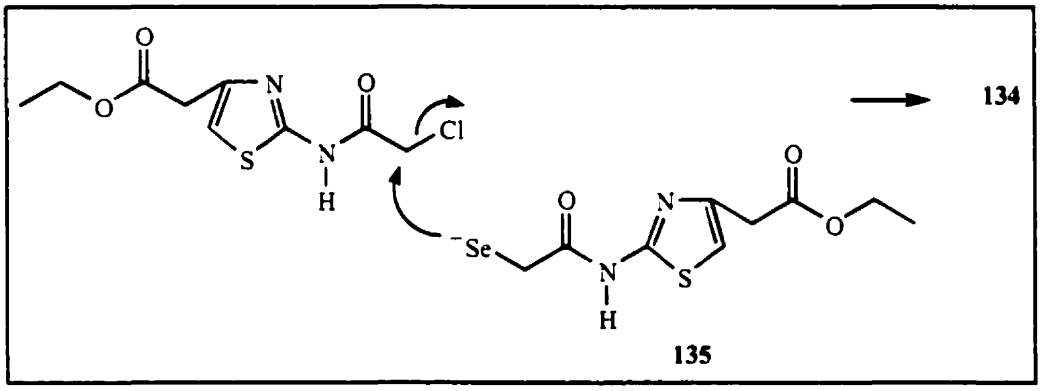
We could have tried the use of a more powerful fluoride source such as CsF for this reaction, but based on results obtained by Gingras, this would have likely resulted in the formation of a monoselenide.[116]

The reaction of **105** with polyfunctional substrate **131** did not yield the expected reduction product, but instead, generated monoselenide **134** in 59% yield.



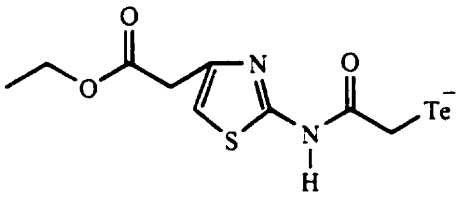
134

The formation of this product, in contrast to substrate **129**, can be accounted for by an S_N2 displacement of the chlorine atom by selenium nucleophile **135** (Scheme 44).

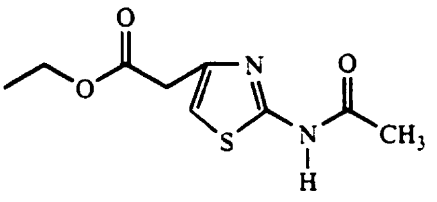


Scheme 44

Interestingly, when substrate **131** was reacted with either of the two tellurium reagents, **95** or **108**, reductive dehalogenation was effectively observed in 74% and 91% respectively. The larger size and decreased nucleophilicity of the tellurium anion **136** could make the extrusion of elemental tellurium, leading to the formation of the reduced product **137**, the preferred process.



136



137

2.6 Concluding Remarks.

We can conclude that both bis(triphenylstannyl) selenide (**105**) and bis(*tert*-butyldimethylsilyl) telluride (**95**), as was previously observed for telluride reagent **108**, are useful reagents for the reductive dehalogenation of the α-haloketone functionality. The reductions were carried out under essentially neutral and mild conditions whereas the option of refluxing exists with uncomplicated substrates.

The difference in reactivity between the selenium and tellurium based reagents, as demonstrated by the contrasting results obtained with substrates **129** and **131**, seems to indicate the possibility of selecting a reagent for a given substrate.

The compatibility of these chalcogenide reagents with other functionalities was further accentuated in their reactions with polyfunctional substrate **131**.

2.7 Contributions to Knowledge.

1. The potential of bis(triphenylstannyl) selenide **105** and bis(*tert*-butyldimethylsilyl) telluride **95** for the reductive dehalogenation of the α-haloketone functionality was illustrated and represents two new contributions to this area of organic chemistry.
2. We were able to ascertain the presence of enolates, postulated as reactive intermediates in the dehalogenation process, by their successful trapping with benzaldehyde. This successful trapping constitutes a new modification on the well known Reformatski reaction.
3. We were able to establish a difference in reactivity between the selenium and tellurium based reagents in the dehalogenation process.

Chapter 3: THE CHALCOGEN DIATOMICS

3.1 Introduction.

Symmetrical diatomic molecules such as H_2, N_2 and O_2, have been known to exist for over 200 years. Although hydrogen gas is the most abundant element in the universe, its recognition as an element was not firmly established until 1776, when Cavindish was credited with its first isolation.[127] The discovery of nitrogen, which constitutes 78.1% by volume of the Earth's atmosphere was attributed to Rutherford in 1772.[128] Oxygen, which was co-discovered by Scheele and Priestly in 1773-4, is equally abundant and makes up 23% by volume of our planet's atmosphere.[129]

The discovery of the halogen diatomics followed soon thereafter.[130] Even though the elemental nature of chlorine was not recognized until 1810, Scheele was the first to isolate and study the gas in 1772. The purple-black metallic luster of crystalline iodine was first perceived in 1811 by Courtois, following the acid treatment of the ash of calcinated seaweed. Elemental bromine, the only non-metallic element existing in liquid form at room temperature, was first isolated from the waters of the Montpellier salt marshes by Balard in 1826.

---

[127] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, Pergamon Press: **1984**, New York; Chapter 3, p 38-39.
[128] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, Pergamon Press: **1984**, New York; Chapter 11, p 466-468.
[129] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, Pergamon Press: **1984**, New York; Chapter 14, p 698-699.
[130] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, Pergamon Press: **1984**, New York; Chapter 17, p 920-926.

Fluorine gas, after more than 70 years of unsuccessful attempts by others, was first isolated in 1886 by Henri Moisan. For this benchmark achievement, he was awarded the Nobel Prize for Chemistry in 1906.

There exist a large number of unsymmetrical diatomic molecules, of which the most common are the hydrogen halides. Hydrochloric acid, formerly known as muriatic acid is probably the oldest unsymmetrical diatomic known to man. Reference pertaining to its existence can be found dating back as far as ~900 A. D. when the Arabian alchemist Rhazes is said to have prepared it in dilute concentrations. In the thirteenth century it was used in combination with nitric acid and was known as *aqua regia* for its use in the dissolution of gold.[130]

Nitric oxide (NO) is in all likelihood the most studied diatomic molecule of recent years.[131] Research in the bioinorganic chemistry of nitric oxide, has led to many important contributions and has established it as a fundamental component in mammals and other animals. In 1995 alone, more than 3500 publications referring to NO have appeared and in 1998 the Nobel Prize in Medicine was awarded to Furchgott, Ignarro and Murad for their work on the role of nitric oxide as a signaling molecule in the cardiovascular system.

This simple, yet vital biological molecule, is known to play an essential role in the transmission of nerve impulses, the regulation of blood pressure and in the immune response to bacterial infections.[132] Nitric oxide is also at the origin of a cascade of biochemical reactions, leading to erection in males.[133]

---

[131] Williams, L. H.; *J. Chem. Soc.; Chem. Commun.* **1996**, 1085.
[132] Rawls, R. *Chem. & Eng. News* **1996**, May 6, 38.
[133] Wilson, E. K. *Chem. & Eng. News* **1998**, June 29, 29.

The chemical and biological properties of S-nitrosothiols have been the subject of considerable research because this class of compounds is thought to be intrinsically connected to both the storage and transport of nitric oxide *in vivo*.[131]

The effectiveness of NO-donor drugs, such as nitroglycerine in the treatment of angina is well documented. Presently the potential of diazeniumdiolates as a source of nitric oxide and their use in the treatment of patients undergoing angioplasty is being investigated.

Finally, this simple yet inherently interesting diatomic inspired renowned chemist Carl Djerassi's latest novel entitled "NO".[134]

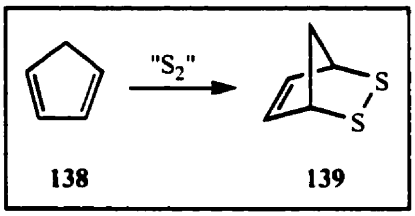
3.2 Diatomic Sulfur.

Other than sulfur atoms, diatomic sulfur which is extremely labile and reactive, is the simplest form of molecular sulfur. When a sample of elemental sulfur, which is composed of mainly S_8 rings, is heated at temperatures above 500°C, S_2 molecules are the prevailing species. At temperatures exceeding 800°C, the concentration of diatomic sulfur reaches its maximum.[135] Diatomic sulfur has been reported as being a blue violet gas, which is very stable at high temperatures.[136] At temperatures greater than 1400°C, it begins to dissociate into free sulfur atoms. The predisposition of diatomic sulfur to tetramerize, has rendered fruitless all attempts at its isolation.

---

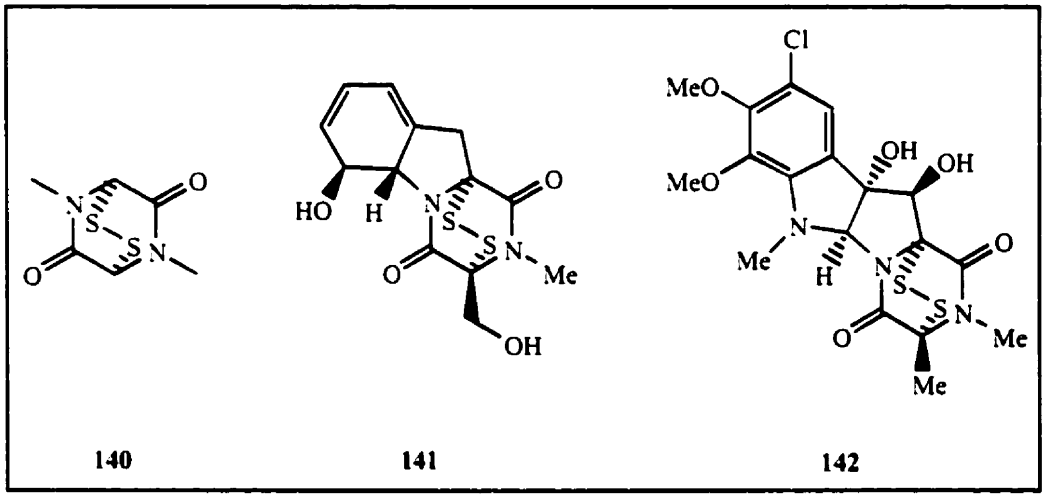
[134] Djerassi, C. *NO*, University of Georgia Press, **1998**, Athens, Georgia.
[135] Voronko, M. G.; Vyazankin, N. S.; Deryagina, E. N.; Nakhmanovich, A. S.; Usov, V. A. *Reactions of Sulfur with Organic Compounds*; Consultants Bureau: **1987**, New York, p16.
[136] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, Pergamon Press: **1984**, New York; p 775.

This illusive, highly reactive species, can however be effectively trapped *via* a Diels-Alder reaction as illustrated with diene **138**, with the concomitant formation of the corresponding cyclic 1,2 dithiine **139** (Scheme 45).[137]



Scheme 45

Numerous natural products incorporating a disulfide moiety have been discovered in the last 30 years. One such class of compounds, coming from the family of fungal toxins, is characterized by the epidithiodioxapiperazine (ETP) system **140**. Illustrative examples are gliotoxin **141** and sporidesmin **142**.[137]

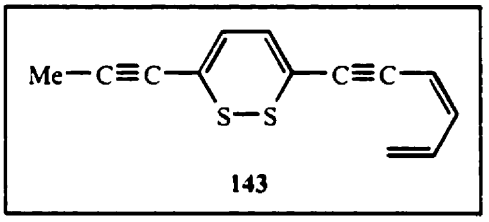


The bridged bicyclic disulfide unit seems to be at the origin of the antiviral, antibacterial and antifungal properties of these compounds.

[137] Block, E. *Advances in Sulfur Chemistry*; Jai Press Inc.: **1994** Greenwich, pp 97-133.

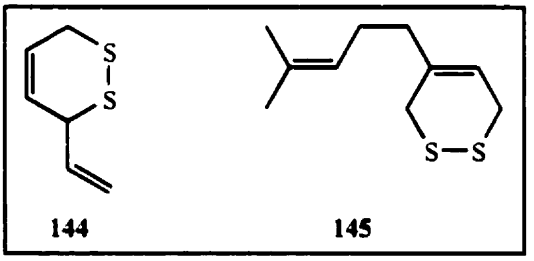
Recent studies have established the immunosuppressive properties of ETP compounds. However, their extreme toxicity to mammalian cells have however precluded their use in therapeutic applications.[137]

Thiarubrine C (**143**) is a representative of another class of biologically active compounds, generally known as the "thiarubrines", in which a 1,2-dithiin functionality is incorporated. These compounds were not only shown to possess antibacterial, antifungal and antiviral properties but also to have anticancer activity.[138]



143

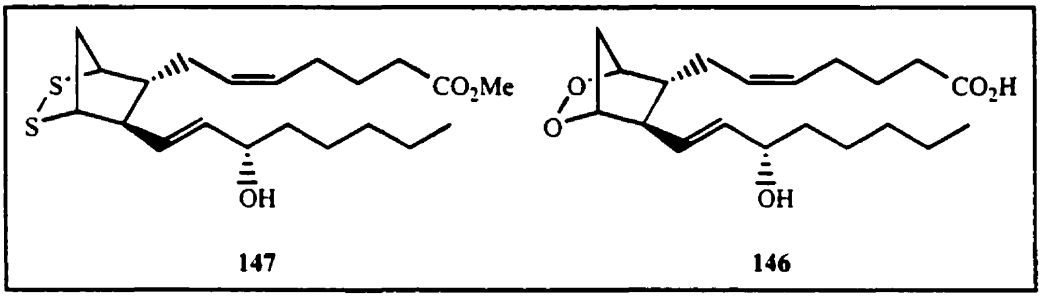
Other naturally occurring 1,2-dithiines include **144**, which has been isolated from garlic extracts and **145**, isolated from steamed distilled hops.[137]



144 **145**

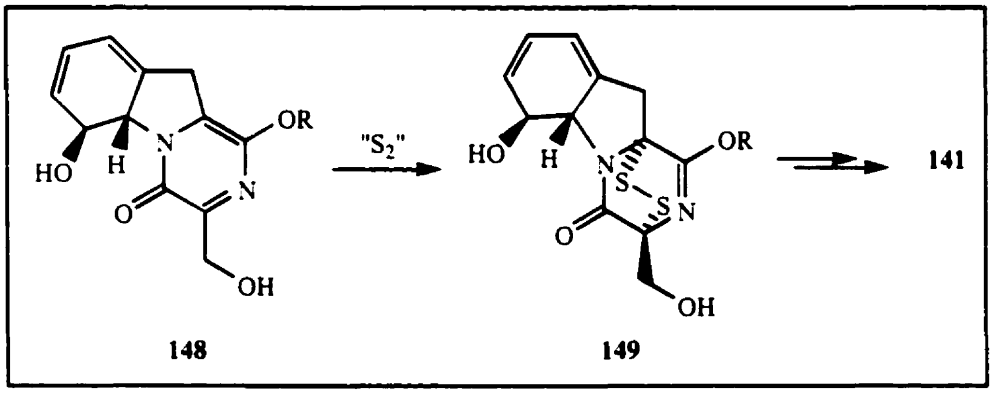
[138] Koreeda, M.; Wang, Y. *J. Org. Chem.* **1998**, 63, 8644.

The disulfide analogue **147** of the prostaglandin endoperoxide PGH_2 **146** has been synthesized. This compound was subsequently shown to be very effective in contracting the aorta strips and to cause rapid and irreversible aggregation of platelets, mimicking the natural prostaglandin thromboxane A_2.[139, 140]



147 **146**

The use of diatomic sulfur for the incorporation of the disulfide functionality, is an attractive synthetic alternative to the commonly employed oxidative coupling of two mercapto ends. Diene **148** could in essence react with an S_2 unit, *via* a Diels-Alder reaction, directly producing gliotoxin precursor **149** (Scheme 46).[141]



148 **149**

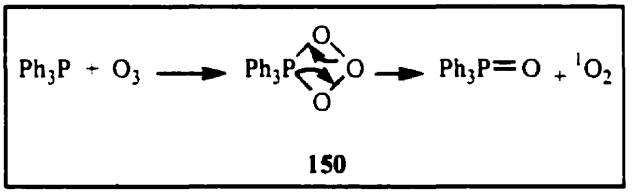
Scheme 46

[139] Hayashi, M.; Itoh, H.; Iguchi, S.; Miyake, H. *J. Am. Chem. Soc.* **1977**, 99, 3536.
[140] Greene, A. E.; Padilla, A.; Crabbe, P. *J. Org. Chem.* **1978**, 43, 4377.
[141] Steliou, K *Acc. Chem. Res.* **1991**, 24, 341.

The apparent synthetic potential of S_2 has led many groups, including our own, to establish research programs aimed to develop methodologies capable of generating this illusive sulfur allotrope. Until recently, the only source of diatomic sulfur (spectroscopic evidence) was from the pyrolysis of elemental sulfur; however, this method is synthetically unproductive.

3.3 Methods Used to Generate Diatomic Sulfur.

The generation of singlet oxygen ($^1O_2$) is easily accomplished by the thermal decomposition of a phosphine ozone adduct **150**, formed from the reaction of ozone with a phosphine reagent (Scheme 47).[142]

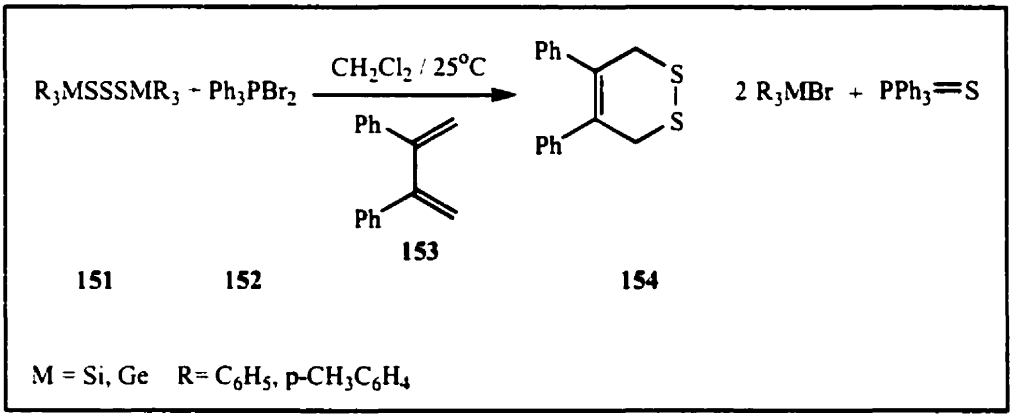


150

Scheme 47

Steliou established that a similar approach for the generation of $^1S_2$ was possible, with silyl and germanium protected trisulfides serving as latent sources of S_3 in analogy to the process in Scheme 47.[143] This represented the first synthetically useful method for the generation and trapping of singlet diatomic sulfur. Thus, the reaction of trisulfide **151** with triphenylphosphine dibromide (**152**) in the presence of a conjugated diene **153**, led to the formation of disulfide adduct **154** (Scheme 48).

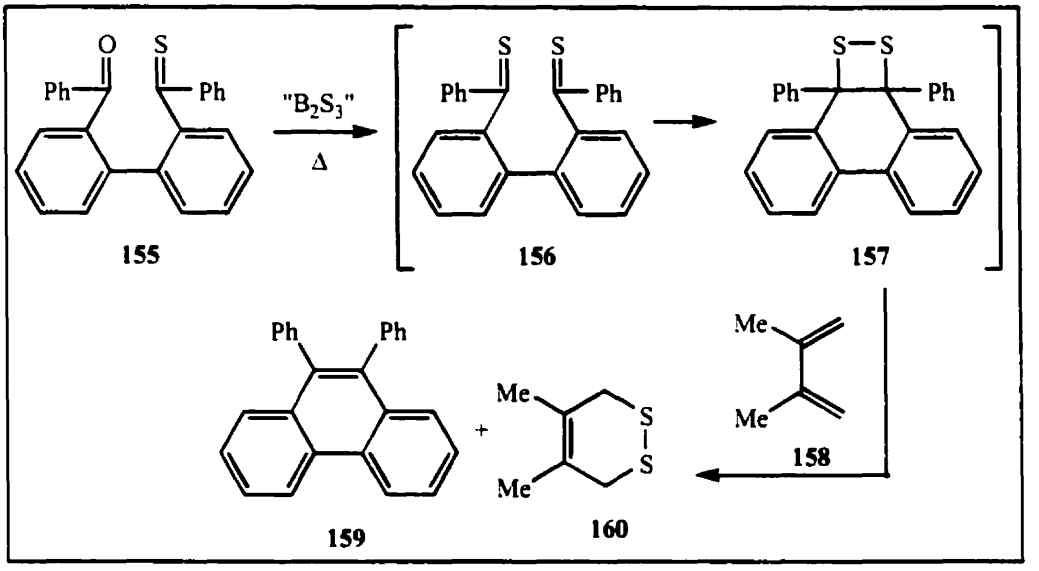
[142] Bartlett, P. D.; Lonzetta, C. M. *J. Am. Chem. Soc.* **1983**, 105, 1984.
[143] Steliou, K.; Gareau, Y.; Harpp, D. N. *J. Am. Chem. Soc.* **1984**, 106, 799.



Scheme 48

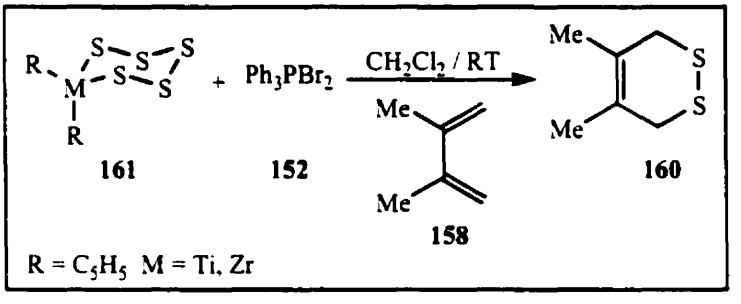
Steliou subsequently developed a very efficient method for the generation of this highly reactive dienophile *via* an unprecedented intramolecular carbon-carbon bond forming reaction.[144] He illustrated that monothione **155**, upon treatement with boron trisulfide, B_2S_3, is converted to dithione **156**, which spontaneously ejects S_2 presumably through disulfide intermediate **157** to give the 9,10-biphenylsubstituted phenanthrene derivative **159** (Scheme 49). Evidence for the generation of diatomic sulfur is again obtained by the isolation of dithiin **160**, formed by Diels-Alder trapping with 2,3-dimethylbutadiene **158**.

[144] Steliou, K.; Salama, P.; Brodeur, D.; Gareau, Y. *J. Am. Chem. Soc.* **1987**, 109, 926.



Scheme 49

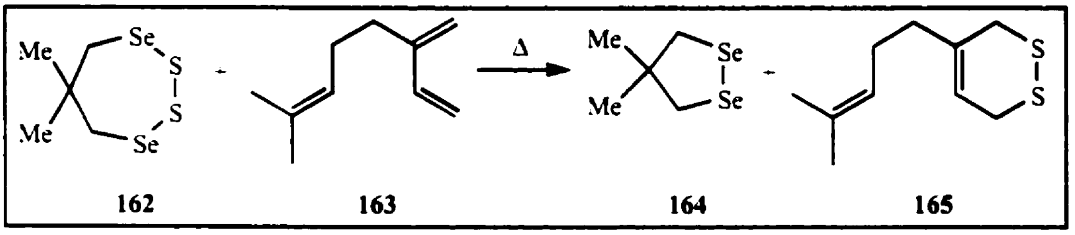
Harpp and MacDonald soon thereafter illustrated the use of organometallic pentasulfides **161**, as alternate sources for S_2. These compounds were shown to generate diatomic sulfur upon fragmentation with triphenylphosphine dibromide (**152**), as illustrated by the successful isolation of cycloadduct **160** (Scheme 50).[145]



Scheme 50

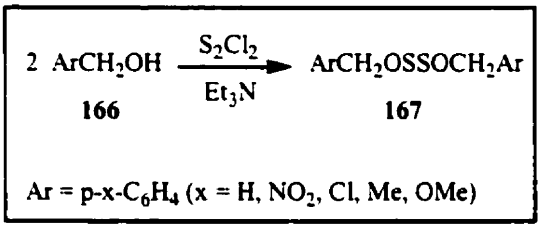
[145] Harpp, D. N.; MacDonald, J. G. *J. Org. Chem.* **1988**, 53, 3812.

A chalcogen ring contraction, developed by Schmidt and Gorl, was also shown to be useful for the generation of diatomic sulfur.[146] The authors were able to illustrate that cyclic 5,5-dimethyl-1,2-dithia-3,7-diselenacycloheptane (**162**), upon heating, undergoes a ring contraction leading to the formation of 4,4-dimethyl-1,2-diselenacyclopentane (**164**). The concomitantly formed S_2 was detected through the isolation of adduct **165**, formed in a Diels-Alder reaction with diene **163** (Scheme 51).



Scheme 51

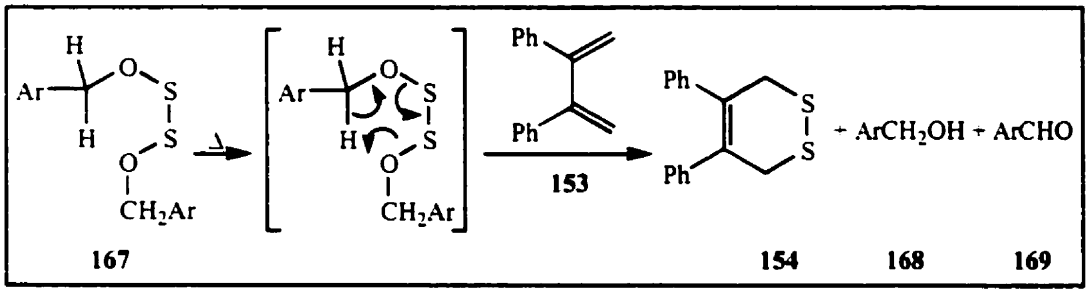
Another effort from our laboratory described the use of alkoxy disulfides **167**, as diatomic sulfur transfer reagents.[147] These compounds are readily prepared from the reaction between the alcohol precursor **166** and S_2Cl_2 (Scheme 52).



Scheme 52

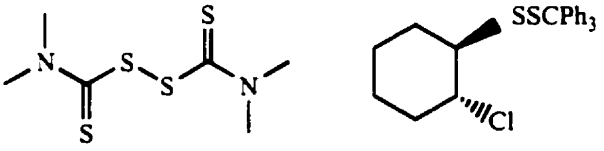
[146] Schmidt, M.; Gorl, U. *Angew. Chem., Int. Ed. Engl.* **1987**, 25, 887.
[147] Tardif, S. L.; Williams, C. R.; Harpp, D. N. *J. Am. Chem. Soc.* **1995**, 117, 9067.

These compounds upon heating were shown to undergo decomposition to form a benzyl alcohol derivative **168**, a benzaldehyde derivative **169** and diatomic sulfur, which was trapped as the corresponding dithiin **154** (ca. 60-80% overall conversion) in a Diels-Alder reaction with diene **153** (Scheme 53).



Scheme 53

Other substrates, studied or developed in our laboratories, which have shown potential as a diatomic sulfur transfer reagents are thiuram disulfide **170** and substrate **171**, formed from the addition of triphenylmethanethiosulfenyl chloride (Ph_3CSSCl) to cyclohexene.[148, 149]



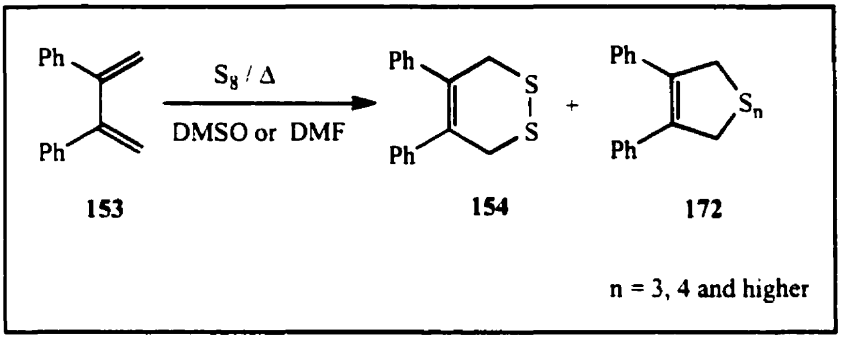
170 **171**

More recently, Andrzej Rys (in our laboratory) illustrated that elemental sulfur (S_8) reacts with conjugated dienes in polar solvents such as DMSO and DMF, to deliver cyclic di-and polysulfides **172** (Scheme 54).[150]

---

[148] Chew, W.; Harpp, D. N. *Sulfur Letters* **1993**, 16, 19
[149] Abu-Yousef, I.; Harpp, D. H. *Tetrahedron Lett.* **1994**, 35, 7167.
[150] Rys, A. Z.; Harpp, D. N. *Tetrahedron Lett.* **1997**, 38, 4931.

The polysulfides can be converted almost quantitatively to the corresponding disulfides upon treatment with triphenylphosphine. The exact mechanism of sulfur transfer in these systems has not been clearly delineated.



Scheme 54

Rys subsequently demonstrated that the efficiency of the trapping reactions with elemental sulfur could be significantly improved when carried out in the presence of catalytic amounts of metallocene polysulfides **173**, **174**, **175**, **176**.[151]

Cp_2MoS_4	Cp_2WS_4	Cp_2TiS_5	Cp_2ZrS_5
173	**174**	**175**	**176**

The nature of this catalytic influence is not fully understood, but appears to involve the resulfurization of a Cp_2MS_{n-2} species.

The search and development of alternate sources of S_2, remains one of the primary interests of a number of research groups including our own.

[151] Rys, A. Z.; Harpp, D. N. *Tetrahedron Lett.* **1998**, 39, 9139.

Next to the diatomic sulfur precursors that were briefly presented in the previous section, there have been numerous other publications on the subject (see references 141, 147 and references sited therein). In addition, two review articles on the chemistry of the chalcogen diatomics were recently published by Harpp.[152, 153] The remarkable structural variety of substrates, capable of delivering a diatomic sulfur unit, suggests that there will be many more discovered in the future.

3.4 Diatomic Selenium, A Literature Survey.

The synthetic generation of diatomic selenium represents a substantial challenge to the organic chemist. Even though this illusive diatomic has been known to exist for about 30 years as illustrated by ample spectroscopic studies, a literature survey reveals no reported method alluding to its successful generation and trapping.

A recent study has illustrated that selenium vapor in the temperature-pressure range of up to 1600°C and 150 bar consists mainly of Se_2.[154] Fourier-transform IR spectra of Se_2 and even of Te_2 were obtained in rare gas matrixes at 4°K.[155] The existence of other selenium allotropes such as Se_5 and Se_6 and Se_7 was established when their UV-photoelectron spectra were recorded.[156]

---

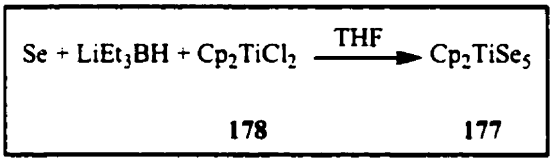
[152] Harpp, D. N. *Phosphorus, Sulfur, and Silicon* **1997**, 120 & 121, p41.
[153] Tardif, S. L.; Rys, A. Z.; Abrams, C. B.; Abu-Yousef, I. A.; Leste-Lasserre, P. B. F.; Schultz, E. K. V.; Harpp, D. N. *Tetrahedron* **1997**, 53, 12225.
[154] Hosokawa, S.; Tamura, K.; Inui, M; Endo, H. *Jpn. J. appl. Phys., Part I* **1993**, 32.
[155] Li, S.; Van Zee, R. J.; Weltner, W., Jr. *J. Chem. Phys.* **1993**, 99(1), 762.
[156] Becker, J.; Rademann, K.; Hensel, F. *Z. Naturforsh., A: Phys. Sci.* **1991**, 46(5), 453.

In anticipation that some of the methods developed for the generation of diatomic sulfur could be employed, or aid in the elaboration of systems conceivably capable of delivering a diatomic selenium entity, we decided to explore this synthetic venture.

3.5 Titanocene Pentaselenide 177 as a Possible Se_2 Precursor.

3.5.1 Synthesis of 177.

Titanocene pentaselenide was conveniently prepared in modest yield by the addition of commercially available titanocene dichloride **178**, to a solution of lithium polyselenides, generated from the reaction of elemental selenium with lithium triethylborohydride (Super-Hydride$^{©}$) (Scheme 55).[157, 158]



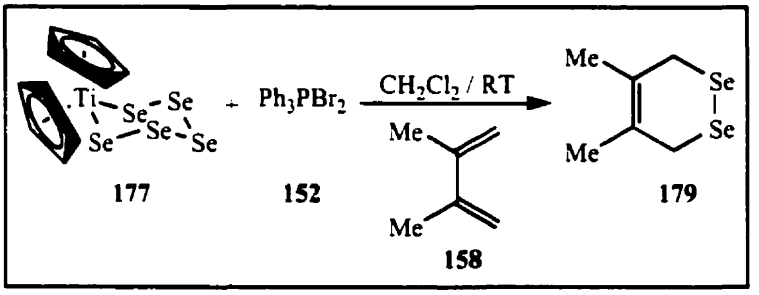
Scheme 55

3.5.2 Chemically Induced Fragmentation of 177.

Our first investigations at the generation of diatomic selenium were carried out by MacDonald who attempted to induce titanocene pentaselenide (**177**) to fragment in the presence of a diene trap (**155**) by treatment with triphenylphosphine dibromide (**152**) (Scheme 56).[159]

---

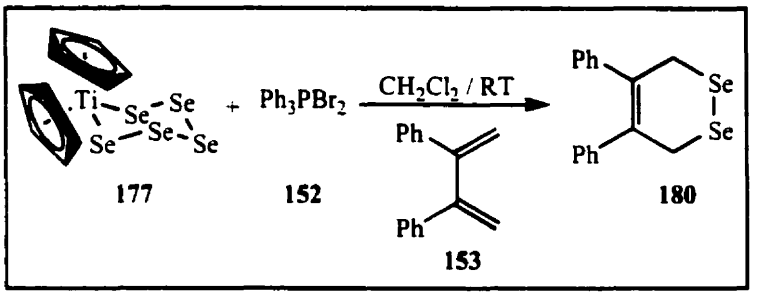
[157] McCall, J. M. Ph.D. Thesis, McGill University, Montreal, Canada **1983**.
[158] Kopf, H.; Block, B.; Schmidt, M. *Chem. Ber.* **1968**, 101, 272.
[159] Harpp, D. N.; MacDonald, J. G. unpublished results.



Scheme 56

Evidence that this system may have generated a diatomic selenium unit was provided by a ^{1}H NMR analysis of the crude reaction mixture. A signal at *ca.* 4.1 ppm. was observed which was assumed to belong to the methylene protons of diselenide **179**, but no firm conclusions were able to be made as to the structure. MacDonald observed a rapid decomposition of the product within one hour, with the concomitant deposition of elemental selenium (as confirmed by mass spectrometry) and the formation of a product which seemed to be a polymer of 2,3-dimethylbutadiene **158.** Subsequent purification attempts by chromatography on silica gel were unsuccessful and led to the isolation of a compound which slowly deposited elemental selenium. Ensuing ^{1}H NMR analysis produced a spectrum of a compound identified by MacDonald as being a polymer of cyclic diselenide **179**.

We attempted a modified repeat of this earlier work using 2,3-diphenyl-1,3-butadiene (**153**) as the diene trap, hoping that this would provide more stable trapping adducts (Scheme 57).



Scheme 57

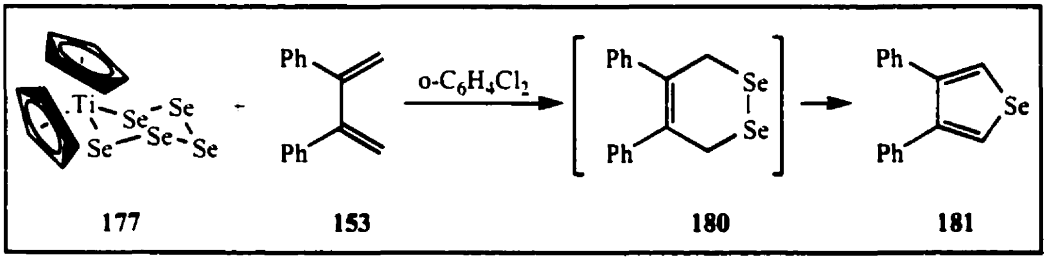
Repeated extractions of the crude reaction mixture with pentane, described as a good extraction procedure by MacDonald in which side products such as Ph_3PSe, Ph_3PBr_2 and titanium containing compounds are relatively insoluble, generated a bright yellow solution. Subsequent ^1H NMR analysis produced a spectrum in which a signal at 4.2 ppm and a considerably smaller one at 4.5 ppm. were detected. Signals corresponding to triphenylphosphine selenide (Ph_3PSe) and diene **153** were also observed. We assumed the signal at 4.2 ppm to be associated with trapped diselenide adduct **180**, due to its proximity to the signal previously observed by MacDonald. However, no conclusions could be drawn as to the identity of the small signal observed at 4.5 ppm, but it was assumed to correspond to the tetraselenide adduct in analogy to the diatomic sulfur trapping reactions. Within one hour, a red precipitate was observed in the NMR tubes, which was again identified by mass spectrometry as being elemental selenium. A TLC analysis of the reaction mixtures revealed a complex reaction mixture which impeded further purification attempts. Earlier, related work in our laboratory on the corresponding sulfur analogue **161** proved however to be more successful (Scheme 50).[145]

3.5.3 Thermal Fragmentation of 177.

Rys demonstrated that metalocene pentasulfides could be thermally induced to fragment and to transfer a 2-sulfur unit.[151] We anticipated that the analogous thermal decomposition of pentaselenide **177** could also lead to the transfer of a 2-selenium fragment that could subsequently be intercepted by a diene trap. We expected that the thermal decomposition reaction, since it is carried out in the absence of triphenylphosphine dibromide (**152**), would generate less complicated reaction mixtures that could be more easily purified.

3.6 Results and Discussion.

A solution containing titanocene pentaselenide (0.4 mmol) (**177**) and 2,3-diphenyl-1,3-butadiene (1.77 mmol) (**153**) in o-chlorobenzene (5 ml) was refluxed and repeatedly analyzed by ^{1}H NMR (Scheme 58).



Scheme 58

Based on the results previously obtained by MacDonald, we again expected to observe a signal at ~ 4.1 ppm., which hopefully would correspond to diselenide **180**. Since no signal could be observed in this region, even after 6 days of refluxing, the reaction was stopped and the residue purified.

To our surprise, the product actually isolated was selenophene **181** as confirmed by X-ray crystallography. The ^{1}H NMR, and ^{77}Se spectra were also consistent with this structure. We believed that this product was actually formed as a direct result from the loss of a molecule of H_2Se from **180**.

3.6.1 Attempted Synthesis of 1,2-Diselenins.

To verify the hypothesis that selenophene **181** could be directly formed from diselenide **180**, (which would also provide indirect evidence of a trapping reaction involving diatomic selenium) we next attempted its synthesis.

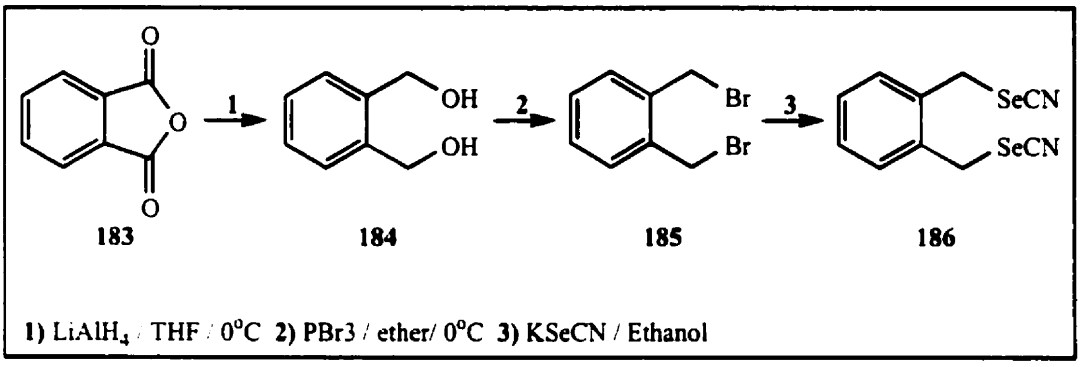
3.6.1.1 Synthesis of 1,4-dihydro-2,3-Benzodiselenin (182).

Prior to synthesizing diselenin **180**, which involves a very expensive starting material, we tried to optimize the reaction sequence by first preparing compound **182**.

The proposed reaction scheme starts with the $LiAlH_4$ reduction of commercially available phthalic anhydride (**183**) yielding 1,2-benzenedimethanol (**184**).[160] The diol was then treated with PBr_3 providing the corresponding dibromide **185** which was then reacted with KScCN to produce the diselenide precursor 1,2-benzenedimethylselenocyanate (**186**) (Scheme 59).[161, 162]

---

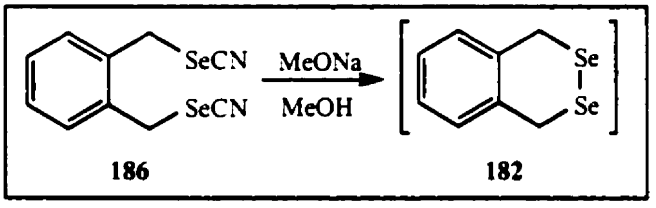
[160] Anderson, W. K.; Kinder, F. R., Jr. *J. Heterocyclic Chem.* **1990**, 27, 975.
[161] Drew, J.; Letelier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987**, 52, 4047.
[162] Otsubo, T, Ogura, F.; Yamaguchi, H. *Synth. Commun.* **1980**, 10 (8), 595.



Scheme 59

3.6.1.2 Sodium Methoxide Induced Cyclization of 186.

We attempted the cyclization of compound **186** by reacting it with sodium methoxide in methanol (Scheme 60).[163]



Scheme 60

A solution of sodium methoxide in methanol was slowly added *via* double tip to a colorless methanolic solution of **186**. When the addition was completed, a clear yellow reaction mixture was obtained in which a yellow precipitate slowly started to form. Upon completion of the reaction, the precipitate was collected. Ensuing ^{1}H NMR analysis revealed the presence of two products, which was confirmed by TLC analysis. Aside from the signals in the aromatic region, a singlet at 4.5 ppm and another at 3.9 ppm could be discerned.

[163] Rabelo, J. J.; Van Es, T. *Carbohydrate Research* **1973**, 30, 381.

The mother liquor was analyzed by TLC, and revealed the presence of faint amounts of additional product. It was subsequently concentrated under reduced pressure and yielded a negligible amount of extra yellow solid.

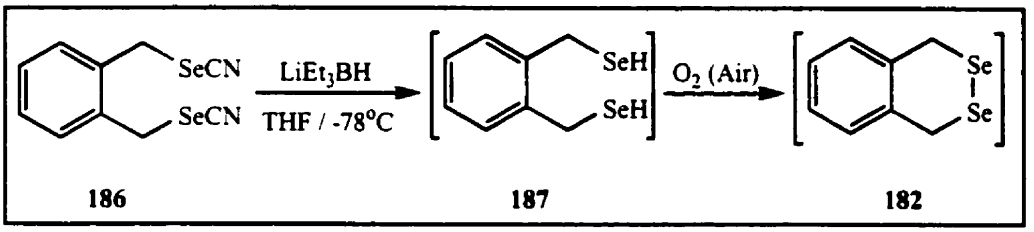
All efforts at the purification of the reaction mixture were unsuccessful and no clear picture could be obtained as to its composition. We suspected that the two products might be readily interconverting.

This hypothesis was subsequently corroborated when we tried to purify the reaction mixture by preparative TLC. We were able to isolate the two bands corresponding to the two products in the mixture which when removed and re-analyzed, reproduced a mixture of two products. Note however, that this may have been caused by the accidental co-removal of some of the other product. Additional support for an interconversion was obtained when a 2-D TLC analysis was carried out on the crude reaction mixture. A TLC plate spotted with the crude reaction mixture was developed (y-axis), which revealed the presence of the now customary two products. The TLC plate was then removed from the container and allowed to dry. It was then replaced in the container and this time developed along the x-axis. Each of the previous two spots could be observed to regenerate a mixture of two products identical to crude.

3.6.1.3 Super-Hydride© Induced Cyclization of 186.

We subsequently attempted the cyclization of **186** using the Super-Hydride© (lithium triethylborohydride) procedure developed by Salama (Scheme 61).[164]

[164] Salama, P.; Bernard, C. *Tetrahedron. Lett.* **1995**, 32, 5711.



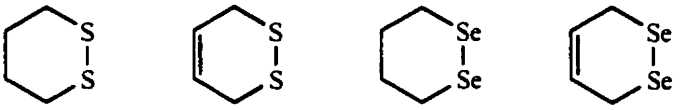
Scheme 61

Salama illustrated that the action of $LiEt_3BH$ on the selenocyanate function followed by air oxidation is an efficient means of generating a diselenide bond. Treatment of **186** in dry THF at –78°C with 2 equivalents of the hydride reagent, resulted in the formation of a clear yellow solution. The reaction vessel was then exposed to the atmosphere and allowed to slowly reach room temperature. Removal of the solvent under reduced pressure produced a yellow residue which was readily soluble in chloroform. A small amount of a yellow gum-like material remained; this required vigorous shaking in order for it to pass into solution. When analyzed by ^1H NMR, a spectrum was obtained which was practically identical to the one obtained from the sodium methoxide procedure. Again, all subsequent attempts at purifying the crude mixture were unsuccessful.

3.6.2 Stability of Selenium Containing Small Ring Systems.

It is well known that 1,2 dithiane **188** and 1,2-dithiin derivatives **189** are generally stable liquid or solid compounds.[165] Because the desired diselenide **182** could not be isolated, we decided to have a closer look at the stability of the analogous 1,2-diselenane **190** and 1,2-diselenin **191** systems.

[165] Freeman, F.; Kim, D. S. H.; Rodriguez, E. *Sulfur Rep.* **1989**, 9, 207.



188 **189** **190** **191**

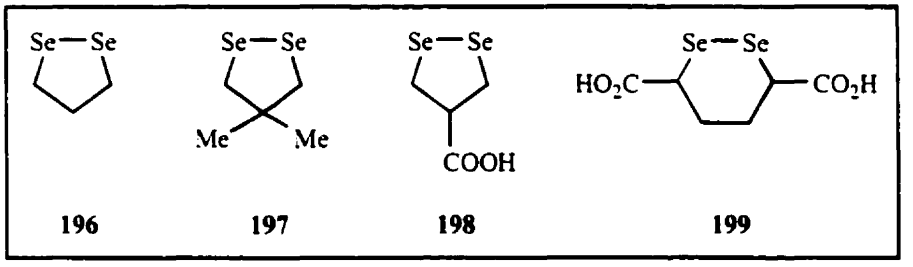
Selenacycloalkanes containing one selenium atom in the ring, show increased stability with increasing ring size.[166] Seleniranes or episelenides **192** have never been isolated but have been observed or proposed as transient intermediates in the reaction between selenium compounds and olefins. Selenetane **193**, is a labile compound that can be stored only under cool, dark conditions and has a great tendency to polymerize. The corresponding 3,3-dimethyl substituted derivatives are however reported to be considerably more stable. Ring sizes of five atoms and larger such as selenolane **194** and selenane **195** are stable.

192 **193** **194** **195**

Cyclic unsubstituted 1,2-diselenides constitute a very unstable class of compounds. These ring systems have a pronounced tendency for polymerization and are known to exist only in solution.[166] The corresponding substituted derivatives are however considerably more stable.

[166] Klayman, L. K.; Gunther, W. H. *Organic Selenium Compounds: Their Chemistry and Biology*, John Wiley & Sons: **1973**, New York; Chapter 11, p 379-426.

1,2-diselenolane **196** has never been prepared in the pure form whereas various 4-substituted derivatives such as **197** and **198** have been prepared and isolated. 1,2-Diselenane **190** is not known in the free form and exits in low molecular weight polymeric form. The dicarboxylic acid **199** is one of the very few known derivatives. An attempt at its preparation by the direct introduction of the diselenide moiety by using potassium diselenide failed and yielded only the 5-membered cyclic monoselenide.[166]

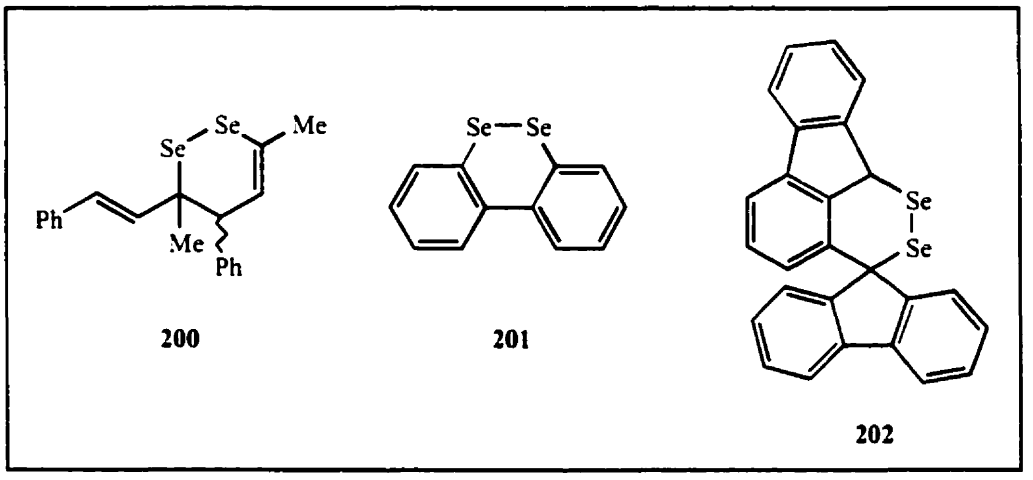


196 **197** **198** **199**

Unsaturated cyclic compounds such as the 1,2-diselenins, in contrast to their sulfur analogues, represent an even more unstable class of ring system. Literature reports in which this type of system was actually isolated, are scarce at best.[167,168,169,170] As was the case for the 1,2-diselenanes, the vast majority exist as low molecular weight polymers except for a few examples such as **200**, **201**, **202**. This inherent instability is consistent with our inability to successfully isolate diselenide **182**. It would also account for the presence of a small amount of a yellow gum like material, observed with the Super-Hydride© reaction, as a polymer of **182**.

---

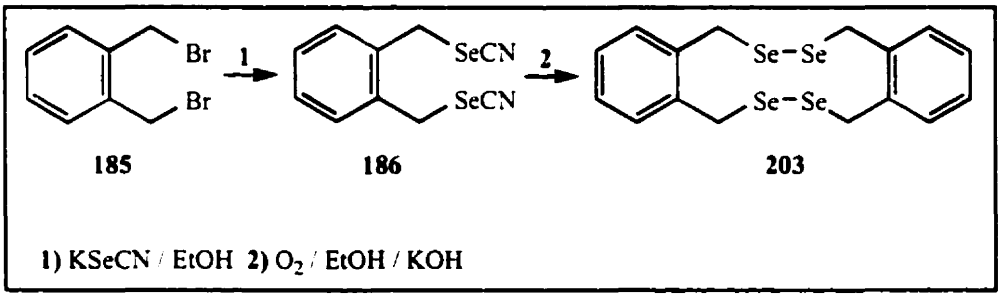
[167] Li, G. M.; Niu, S.; Segi, M.; Zingaro, R. A.; Yamamoto, H.; Watanabe, K.; Nakajima, T.; Hall, M. B. *J. Org. Chem.* **1999**, 64, 1565.
[168] Li, G. M.; Segi, M.; Nakajima, T.; *Tetrahedron Lett.* **1992**, 33, 3515.
[169] Murata, S.; Suzuki, T.; Yanagisawa, A.; Suga, S. *J. Heterocycl. Chem.* **1991**, 28(2), 433.
[170] Meinke, P. T.; Krafft, G. A. *J. Am. Chem. Soc.* **1988**, 110 8679.



200 **201** **202**

3.6.3 Composition of the Reaction Mixtures.

Considerable insight into our reaction system was gained by a publication by Sato, in which he concluded that diselenin **182** was not formed but that instead a dimer **203** was obtained (Scheme 62).[171]



Scheme 62

The ^{1}H NMR spectrum of **203** as reported by Sato, displayed the expected signals in the aromatic region and a singlet at δ 4.51 whereas the ^{77}Se NMR spectrum was reported to exhibited a signal at δ 357.0.

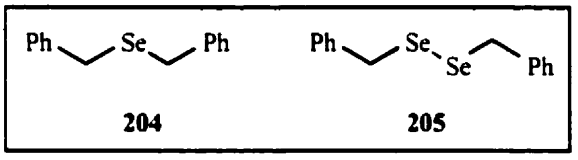
[171] Ogawa, S.; Ohara, S.; Kawai, Y.; Sato, R. *Heterocycles* **1994**, 38, 491.

The ^{13}C chemical shift of the four methylene carbons was reported at δ 32.7 whereas the signals at δ 128.3; 130.9, 136.9 were associated with the aromatic carbons. Finally, an analysis by mass spectrometry, was described by Sato as not producing the expected molecular ion peak, but instead produced an ion corresponding to $M^+/2$.[171]

With all this data in hand, we tried once again to cyclize selenocyanate **186** by using sodium methoxide in methanol as depicted in Scheme 60. A yellow solid was once more obtained whose ^1H NMR again displayed a signal at δ 3.9 and another at δ 4.5. At this point we were fairly certain that the signal observed at δ 4.5 in fact corresponds to the dimer, whereas the signal at δ 3.9 is associated with the monomer. This was subsequently corroborated by ^{13}C NMR analysis, which produced a signal at δ 32.7 corresponding to the dimer and a second at δ 24.3 associated with the monomer. In the aromatic region, the signals at δ 128.3, 130.9 and 136.9 correspond exactly with those reported by Sato. The other signals at δ 127.8, 128.2 and 137.1 would again be due to the monomer. Further proof for the presence of both dimer and monomer in the crude solid precipitate was obtained from ^{77}Se NMR analysis. Two signals, the first at δ 361.3 and the second at δ 308.4 were observed. The former is associated with the dimer (very close to the value of 357.0 reported by Sato and the latter with the monomer. Finally, the crude yellow solid was analyzed by mass spectrometry. Since selenium exists in six immutable isotopes we were not surprised to observe that the molecular fragment described by Sato [264 ($M^+/2$)] is in fact the most intense signal of an isotopic distribution.

This observed isotopic partition, corresponding to both monomer and fragmented dimer ($M^+/2$), matches very well with a calculated partition for $C_8H_8Se_2$. Upon enlargement, a considerably more complex isotopic distribution could observed, of which 526 (M^+) is the most intense. The increased complexity is due to the increased number of permutations possible with four selenium atoms.

Some additional information about the chemical shift of the methylene protons and the methylene carbons adjacent to a selenium atom was obtained by analyzing dibenzyl selenide (**204**) and dibenzyl diselenide (**205**).



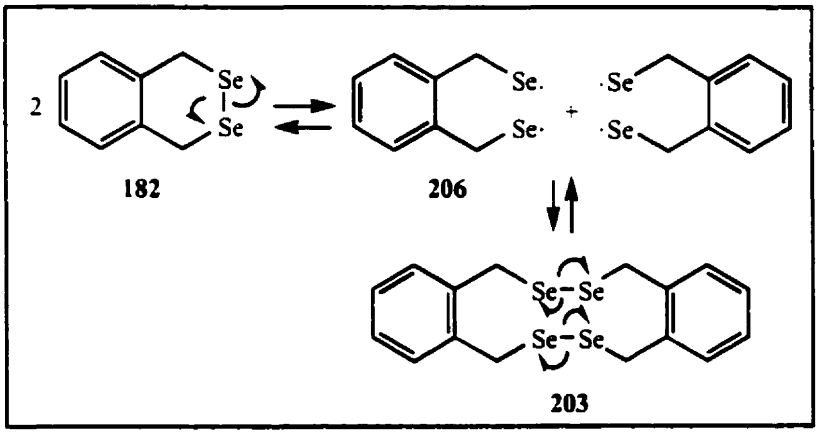
204 **205**

The signals for the methylene protons and methylene carbon of **204** were observed at δ 3.74 and δ 27.6 whereas the analogous signals for the diselenide **205** appear slightly more downfield, at δ 3.83 and δ 32.6 respectively. A downfield shift was also observed for the methylene protons and carbons in going from the monomer to the dimer, which provides some additional support for their presence in the reaction mixture.

3.6.4 Interconversion Between 182 and 203.

We had previously postulated that the reaction mixtures obtained from the sodium methoxide and Super-Hydride[c] promoted cyclizations of diselenocyanate **182** are composed of two compounds which would be both structurally and energetically similar in order to account for an interconversion to occur between them.

Based on our spectroscopic results and on the information reported by Sato,[171] we are confident that the reaction mixtures are actually composed of **182** and **203**. Both these compounds contain a Se-Se bond, which as shown previously, constitutes a labile functionality when part of a ring system. We can therefore conceive a homolytic cleavage of the Se-Se bond in **182** generating a selenium centered diradical **206** that can subsequently recyclize to form the original product, or combine with another diradical to form the dimer. Similarly, the dimer **203** could cleave into two monomeric diradicals **206**, which could then either recombine, or cyclize to form two monomeric species (Scheme 63).



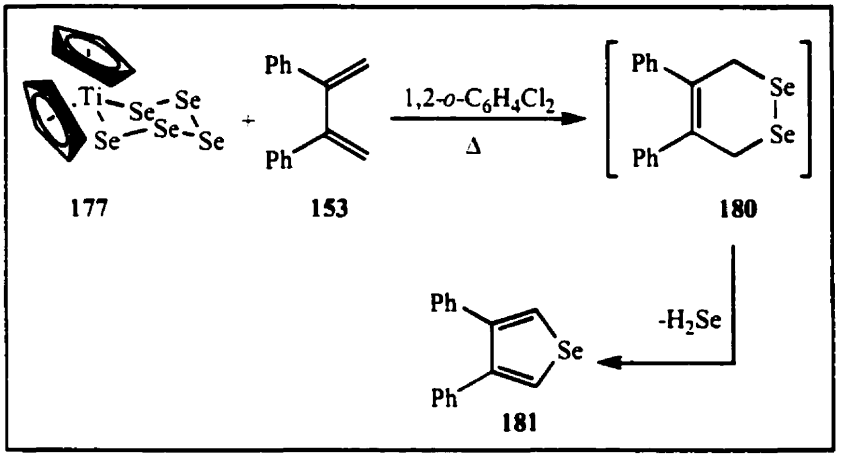
Scheme 63

This rapid interconversion would account for our unsuccessful attempts at the separation and purification of the individual components. These results therefore substantiate those previously obtained from a 2-D TLC analysis of the crude reaction mixtures from which the possibility of an interconversion was postulated. Note that a recent Chemical Abstracts structure search for diselenides **180** and **182** yielded no structures, suggesting that these molecules have not been previously synthesized or characterized.

3.6.5 Detailed Thermal Decomposition Study of 177.

In a recent publication we described our initial results at the generation and trapping of diatomic selenium (Scheme 58).[153] Rather than isolating diselenide **180**, which would have resulted from a Diels-Alder reaction between diatomic selenium and diene **153**, we obtained selenophene **181** whose structure was subsequently confirmed by X-ray crystallography.

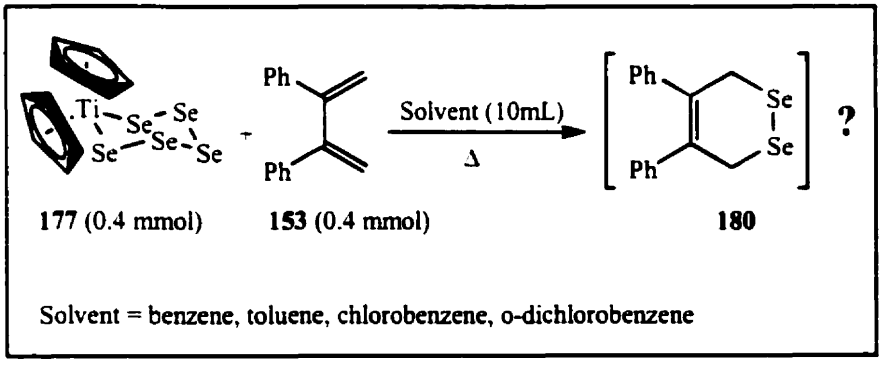
Aware of the inherent instability of ring systems such as **180** and as a result of the rather harsh reaction conditions involved (refluxing at 180°C) we suspected that the formation of selenophene **181** could have resulted from the loss of a molecule of H_2Se from intermediate diselenide **180** (Scheme 64).



Scheme 64

With the spectroscopic data obtained for diselenide **182** and the subsequent experimental results, we can now reasonably postulate the formation of diselenide **180**, in the crude reaction mixtures resulting from the trapping reactions.

Because of the conditions used during the first times this reaction was carried out, the diselenide if formed, could very well have been degraded before it could be detected by ^{1}H NMR. We therefore decided to carry out a more detailed study of this trapping reaction. Thus the reactions were first carried out with the reagents in a 1:1 ratio, in a variety of solvents encompassing a wide temperature range (Scheme 65).



Scheme 65

The reaction mixtures were analyzed by ^{1}H NMR for a characteristic diselenide signal expected at ~ δ 3.90. If present, this would constitute the first evidence, however indirect, for the generation of diatomic selenium.

^{1}H NMR analysis (sampling carried out every hour, for the first 5 hours) of the reactions carried out in refluxing benzene (Bp. 80°C) and toluene (Bp. 110°C), showed no trace of product formation. An identical conclusion was reached following overnight refluxing.

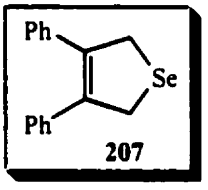
The reaction carried out in refluxing chlorobenzene (Bp. 132°C) remained clear of any product formation in the first five hours. However, analysis of the reaction mixture following overnight refluxing revealed a very small signal at δ 4.28.

Two very small signals, similar in intensity, the first at δ 3.80 and the second at δ 4.28, were detected following 1 hour of refluxing in o-dichlorobenzene (Bp.180 °C). When the reaction mixture was reanalyzed an hour later only the latter signal remained, which after ensuing analyses following three, four and five hours, of reaction time is considerably more intense but constant. A small trace of selenophene **181** formation can however be detected after three hours of refluxing, but does not seem to become more conspicuous upon subsequent analyses of the reaction mixture. Overnight refluxing produced a fairly intense signal at δ 7.95 (selenophene) and caused an obvious decrease in the intensity of the signal at δ 4.28.

Since the signal at δ 4.28 is located significantly more downfield as compared to the one associated with presumed diselenide **182**, we had doubts as to its identity as desired diselenide **180**.

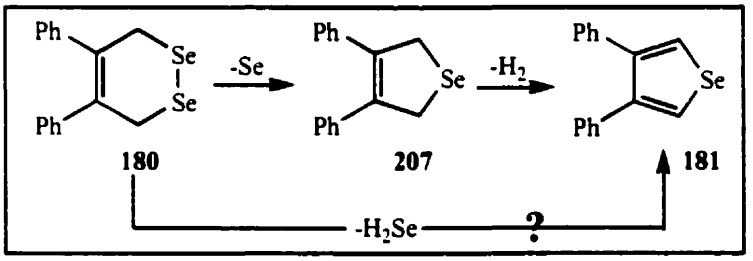
We believed that it was plausible to account for selenophene formation by a decomposition mechanism of the compound giving rise to the signal at δ 4.28. However, since the reaction mixture has also become considerably more complex following overnight refluxing, no clear conclusions could be drawn as to the value of this hypothesis. Indirect support was obtained when the reaction was carried out under identical reaction conditions but was allowed to reflux for 96 hours. Subsequent ^{1}H NMR revealed that none of the signal at δ 4.28 was present and that a very intense signal at δ 7.95 corresponding to selenophene **181** was the only detectable product present in the reaction mixture.

In order to identify the compound, giving rise to the signal at δ 4.28, the reaction was repeated under the same conditions but was stopped after 3 hours of refluxing. Its presence was subsequently confirmed by ^{1}H NMR analysis of the crude reaction mixture which, based on TLC analysis, was fairly complex. The crude mixture was then purified by column chromatography on silica gel, which yielded the desired compound in a relatively good state of purity. The identity of the compound, based on results obtained by mass spectrometry, was shown to be monoselenide **207**.



207

Based on these experimental observations, we propose a process in which diselenide **180** is indeed formed, but rapidly loses a selenium atom to generate **207**. The fleeting presence of **180** is postulated based on the brief appearance of a signal at δ 3.80 which is very close to the signal at δ 3.95 presumed to belong to diselenide **182**. Monoselenide **207**, in the presence of elemental selenium (Se_n) could be stripped of H_2, which then leads to the formation of selenophene **181** (Scheme 66).



Scheme 66

3.6.6 Trapping Reactions Carried out in o-Dichlorobenzene.

A summary of the trapping reactions that were carried out in o-dichlorobenzene, using a variety of different reactant ratios and reaction times, is displayed in Table 2.

Table 2: -Trapping reactions using different reactant ratios and reaction times.

Reaction	**Cp_2TiSe_5** (mmol)	**Diene (153)** (mmol)	**Time (h)** Refluxing	**Solvent (mL)** o-$C_6H_6Cl_2$
1	0.24	0.08	1	2
2	0.24	0.08	2	2
3	0.24	0.08	3	2
4	0.24	0.08	4	2
5	0.24	0.08	5	2
6	0.24	0.08	Overnight	2
7	0.08	0.24	3	2
8	0.08	0.24	5	2
9	0.08	0.24	7	2
10	0.08	0.24	Overnight	2
11	0.08	0.16	3	2
12	0.08	0.40	3	2

As indicated in Table 2, the first six reactions were carried using a 3-fold excess of titanocene pentaselenide (**177**) to 2,3-diphenyl-1,3-butadiene (**153**). ^{1}H NMR analysis of the crude reaction mixture resulting from one hour of refluxing (entry 1) displayed only a trace of compound **207** (signal at δ 4.28). Refluxing for two hours (entry 2) however provided a reaction mixture displaying a considerably more intense signal at δ 4.28. This signal becomes more intense following three hours of refluxing. Entries 4 and 5, give rise to signals comparable in intensity to the one obtained form entry 3. Overnight refluxing (entry 6) produced a still fairly intense signal at δ 4.28, however another signal (smaller than the former) can be clearly observed at δ 7.94, confirming the formation of some selenophene **181** product.

Entries 7-10 describe trapping reactions that were carried out with a 3-fold excess of the diene reagent. The reaction mixture refluxed for 3 hours (entry 7), produced a signal at δ 4.28 that was similar in intensity to the one obtained from entry 3. However, the latter reaction mixture, based on ^{1}H NMR analysis, seemed considerably cleaner. The ^{1}H NMR spectra obtained from the reaction mixtures resulting from 5 and 7 hours of refluxing respectively (entries 8 and 9), are very similar to entry 7. The impurities appear to have become slightly more pronounced following 7 hours of refluxing. When the reaction was refluxed overnight (entry 10), a signal estimated to be twice as intense as the one obtained from entry 6 was detected. Some selenophene was also produced, as demonstrated by the now characteristic signal at δ 7.94.

Interestingly, the intensity of the selenophene signal had not changed significantly when compared to entry 6 and furthermore, the ^{1}H NMR spectrum appears to be cleaner.

At this point it appeared to us that the trapping reactions carried out using a 3-fold excess of diene reagent constituted a more efficient means of generating monoselenide **207** as compared to the analogous reactions using a 3-fold excess of pentaselenide **177**. We carried out two additional reactions, the first using a 2-fold excess of diene (entry 11) and the second using a 5-fold excess (entry 12) to study whether a smaller or larger excess is beneficial to the formation of **207**.

Based on subsequent ^{1}H NMR analysis, the use of a 2-fold excess of diene appears to be less efficient for the generating **207**, whereas the use of a 5-fold excess does not seem to provide any additional benefits.

3.6.7 Trapping Reactions Carried out in 1,2,4-Trichlorobenzene (Bp. 214°C).

We next wanted to investigate the effect of a higher boiling solvent on the formation of monoselenide **207** and selenophene **181**. We hoped that the use of higher reaction temperatures and shorter reaction times could favorably affect the formation of **207** without the adverse formation of **181**. The reaction conditions used are summarized in Table 3.

Table 3: -Trapping reactions carried out in 1,2,4-trichlorobenzene.

Reaction	**Cp_2TiSe_5** (mmol)	**Diene (150)** (mmol)	**Time (h)** Refluxing	**Solvent (mL)** 1,2,4-$C_3H_3Cl_3$
1	0.08	0.24	3	2
2	0.08	0.24	2	2
3	0.08	0.24	1	2

The reactions were again carried out using a 3-fold excess of diene. A comparison of the ^{1}H NMR spectrum obtained from the reaction mixture following 3 hours of refluxing to the analogous reaction in o-dichlorobenzene (Table 2, entry 7) did indeed reveal a more intense signal at δ 4.28. Selenophene formation could however be observed in the former and the reaction mixture appeared more contaminated by impurities. Decreasing the reaction time by one hour does not seem to greatly affect the composition of the reaction mixture. Reducing the reaction time to one hour does however produce more **207** while only a little selenophene formation occurs. The monoselenide signal has become very intense, while the selenophene signal has become very small. Additionally, the reaction mixture seems considerably less contaminated by impurities.

We next carried out the reaction on a larger scale, in an attempt to reconfirm and fully characterize the product as monoselenide **207**. Hence, titanocene pentaselenide **(177)** (0.48 mmol) and 2,3-diphenyl-1,3-butadiene **(153)** (1.44 mmol) were refluxed for 1 hour in 1,2,4-trichlorobenzene (12 mL).

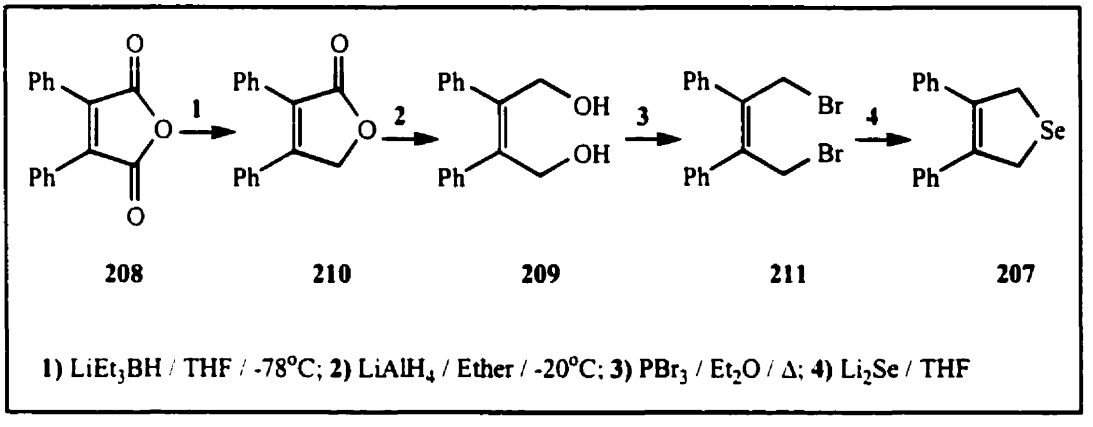
The reaction mixture was subsequently purified by column chromatography, which produced a relatively pure sample of **207** as confirmed by its ^{1}H NMR spectrum. An ensuing ^{13}C NMR displayed a signal at δ 35.2, corresponding to the methylene carbons and signals at δ 127.1; 128.2; 128.7; 137.6 and 138.1 corresponding to the aromatic and two olefinic carbons. In fact the four quaternary carbons in the molecule give rise to the signals at 137.6 and 138.1 respectively. Finally, mass spectrometry produced a molecular ion that again displays an isotopic distribution and whose most intense signal corresponds to M^{+} 286, consistent with **207**.

The reaction was repeated and the purified product analyzed for its carbon and hydrogen content. The results obtained revealed a 70.55% carbon and a 5.15 % hydrogen content, which differed in carbon percentage from our calculated value of 67.13% carbon; the 4.93 % hydrogen agreed with the theoretical values. The inherent difficulties associated with the purification process are accountable for these discrepancies. Even though the ^{1}H NMR spectrum of the crude reaction mixture appeared to be relatively simple, TLC analysis again exposed a complex picture that prevented the isolation of the monoselenide in a state of purity sufficient for an exact elemental analysis. The purification process was nonetheless efficient enough to ensure a product, whose ^{1}H NMR revealed only traces of contaminants and that could subsequently be analyzed by mass spectrometry. The same observations were made every time an attempt at the isolation of the monoselenide **207** was carried out.

3.6.8 Synthetic Approach to 207.

Even though monoselenide **207** was successfully identified as the product resulting from the reaction between titanocene pentaselenide **177** and diene **153**, we decided nonetheless to generate it again, this time using a stepwise approach. A spectral comparison can then be made and would constitute a final structural proof for monoselenide **207**.

Our synthetic strategy entailed the reduction of 2,3-diphenylmaleic anhydride (**208**) to the corresponding diol **209** via lactone **210**, followed by its conversion to dibromide **211**. Reaction of the dibromide with lithium selenide (Li_2Se) would then hopefully produce **207** (Scheme 67).



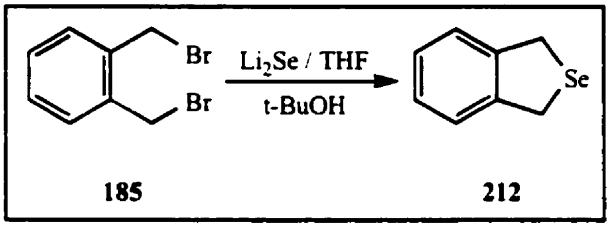
Scheme 67

The synthesis of 2,5-dihydro-2,3-diphenylselenophene (**207**) has been achieved only once, in a poor yield of only 16 %.[172] Our synthetic route, if successful, would constitute a useful addition towards the preparation of this heterocyclic ring system.

[172] Nakayama, J.; Ikuina, Y.; Murai, F.; Hoshino, M. *J. Chem. Soc.; Chem. Commun.* **1987**, 1072.

3.6.8.1 Synthesis of 2-Selenaindan (212).

Prior to attempting the synthetic sequence described in Scheme 67, we decided to first attempt the cyclization reaction on the more readily available dibromide **185** (Scheme 68).



Scheme 68

The lithium selenide reagent (Li_2Se) was readily prepared from the reaction of elemental selenium with 2.1 equivalents of Super-Hydride[c] in THF at 0°C under nitrogen.[173] The formation of a milky white reaction mixture is indicative of the successful generation of the selenide reagent. Note that the reagent was freshly prepared prior to every cyclization reaction.

$$Se\ (s) + 2\ LiEt_3BH \xrightarrow{THF} Li_2Se + 2\ Et_3B + H_2$$

Upon completion of the reaction, the crude reaction mixture was purified by column chromatography, which provided 2-selenaindan (**212**) in modest yield (36%). The ^1H NMR spectrum displayed a sharp signal at δ 4.32 corresponding to the four methylene protons. This corresponds very well with the value of δ 4.30 reported in the literature.[174]

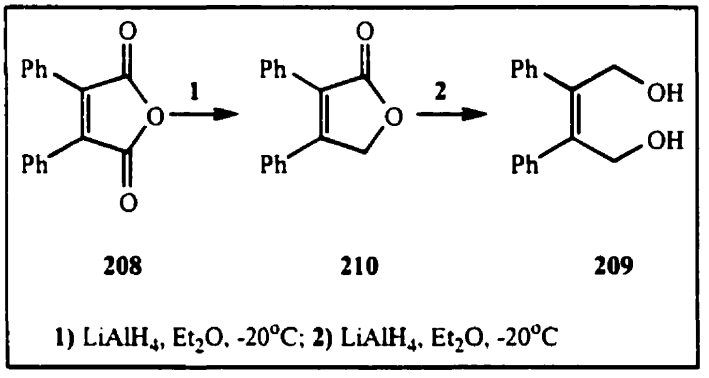
---

[173] Gladysz, J. A.; Hornby, J. L.; Garbe, J. E. *J. Org. Chem.* **1978**, 43, 1204.
[174] Higuchi, H.; Otsubo, T.; Ogura, F.; Yamaguchi, H.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* **1982**, 55, 182.

The ^{13}C NMR spectrum disclosed a signal at δ 29.8, corresponding to the methylene carbons and signals at 125.9, 126.4 and 141.6 associated with the aromatic carbons. Finally, mass spectrometry produced a molecular ion displaying the isotopic distribution associated with selenium containing compounds and whose most intense signal is M^+ 183.93 (calculated 183.98).

3.6.8.2 Synthesis of (Z)-2,3-Diphenyl-2-butene-1,4-diol (209).

The synthesis of (Z)-2,3-diphenyl-2-butene-1,4-diol (**209**) is described in the literature as being efficiently carried out, by a step wise reduction of 2,3-diphenylmaleic anhydride (**208**) (Scheme 69).[175, 176]



Scheme 69

In our hands, the $LiAlH_4$ reduction of anhydride **208** gave rise to a complex reaction mixture from which lactone **210** could be isolated in 48% yield. We found that a considerably cleaner reaction mixture is obtained when the reduction is carried out using $LiEt_3BH$ (Scheme 67).

[175] Urove, G. A.; Welker, M. E. *Organometallics* **1988**, 7, 1013.
[176] Urove, G. A.; Welker, M. E. *Journal of Organometallic Chemistry* **1990**, 384, 105.

Under the latter reaction conditions **210** was isolated in 71% yield, after purification.

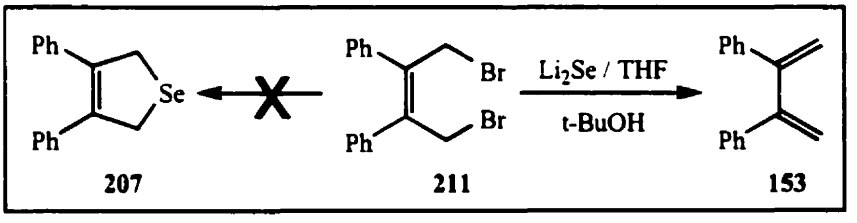
The reduction of lactone **210** was carried out as described in the literature.[175,176] A complex reaction mixture was obtained, from which the desired unsaturated diol **209** was isolated in 40% yield, after purification.

3.6.8.3 Synthesis of (Z)-2,3-Diphenyl-2-butene-1,4-dibromide (211).

(Z)-1,4-dibromo-2,3-diphenyl-2-butene (**211**) is readily obtained in good yield (86%), by reacting diol **209** with phosphorus tribromide (PBr_3) and traces of triethyl amine (Et_3N) in refluxing ether.[175,176] The melting point and ^1H NMR spectrum are consistent with the ones reported in the literature. The compound was subsequently further characterized by ^{13}C NMR and mass spectrometry. The latter displayed a molecular ion peak at M^+ 365.9 (calculated: 366.1) displaying the characteristic isotopic distribution of a molecule containing two bromine atoms.

3.6.8.4 Attempted Cyclization of 211 Using Li_2Se.

The attempted cyclization of dibromide **211** with Li_2Se, under conditions identical to those used for the successful formation of **212**, did not yield the expected product **207**, but instead generated diene **153** in 65% yield (Scheme 70).

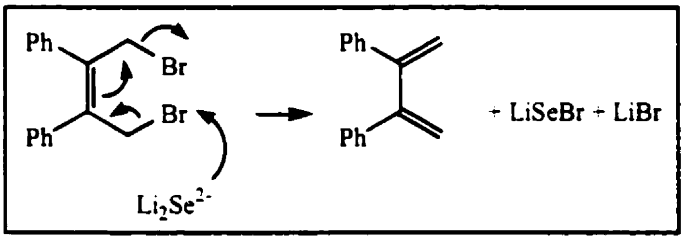


Scheme 70

Subsequent attempts, in which the addition of the dibromide **211** to the Li_2Se suspension was carried out at –78°C, or in which the amounts of t-BuOH were varied were unsuccessful. The major component of these reaction mixtures, as confirmed by ^1H NMR, was again diene **153**.

Given the observation that selenium and tellurium nucleophiles such as NaHTe, Na_2Te, NaHSe and Na_2Se have been described as efficient reagents for the dehalogenation of vicinal dihalides to give the corresponding olefins, the formation of diene **153** is not entirely unexpected.[102, 103, 104, 105]

In order to account for our observations, we propose a mechanism involving an attack of the selenium nucleophile on the first bromine atom, followed by the conjugate elimination of the second bromine atom (Scheme 71).

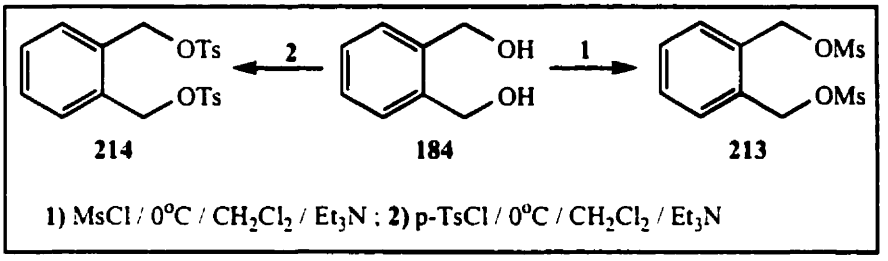


Scheme 71

3.6.8.5 Synthesis of Mesylate 213 and Tosylate 214.

We expected that the use of non-halide leaving groups, could potentially circumvent the elimination reaction from taking place. Both mesylates and tosylates are very effective leaving groups and have been frequently used in organic synthesis, in order to accomplish the displacement of a hydroxy functionality.

We once again first prepared the corresponding mesylate **213** and tosylate **214** in good yield (72 and 67% respectively) from the more readily available diol **184** (Scheme 72).

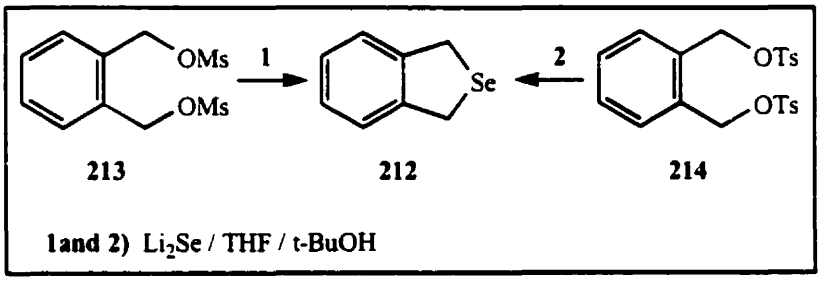


Scheme 72

A small amount of monochloride product (9%) was always observed to be present in the reaction mixtures resulting from the formation of **213**. This is explained by the displacement reaction of a mesylate group by the *in situ* generated chloride ion.

3.6.8.6 Attempted Cyclization of 213 and 214 Using Li_2Se.

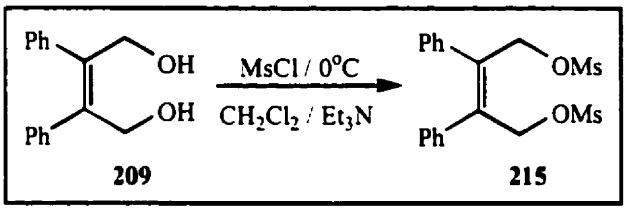
The addition of a THF solution of dimesylate **213** containing small amounts of t-BuOH to a freshly prepared THF suspension of Li_2Se, afforded the desired selenide **212** (as confirmed by ^1H NMR) in 70% isolated yield. When the reaction was carried out using ditosylate **214**, an isolated yield of 78% was obtained (Scheme 73).



Scheme 73

3.6.8.7 Synthesis of Mesylate 215.

A procedure identical to the one previously employed for the synthesis of **213** and **214**, was used to generate **215** in an isolated of 63% (Scheme 74).



209 **215**

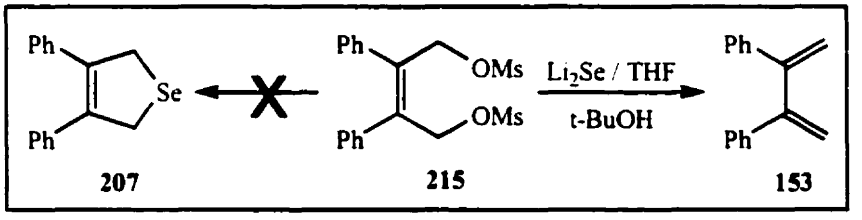
Scheme 74

Within a few hours following the isolation and purification of **215** (confirmed by ^{1}H NMR), a slow decomposition could be observed to occur. Dimesylate **215**, which was isolated as a white solid, slowly turned yellow upon prolonged exposure to the atmosphere. When left in a vial on the bench top for 24 hours, complete decomposition occurs, as demonstrated by the formation of a black solid. Subsequent TLC analysis confirms the complete disappearance of **215**. Due to its inherent instability, dimesylate **215** once purified, was immediately placed under nitrogen and stored at –20°C. Note that a gradual decomposition was also observed for compounds **213** and **214** but that complete decomposition only occurred after being stored on the bench for 5 days.

3.6.8.8 Attempted synthesis of 207 Using Li_2Se.

The addition of a THF solution of **215**, containing a small amount of t-BuOH to a freshly prepared THF suspension of Li_2Se, once again did not afford the desired monoselenide **207**.

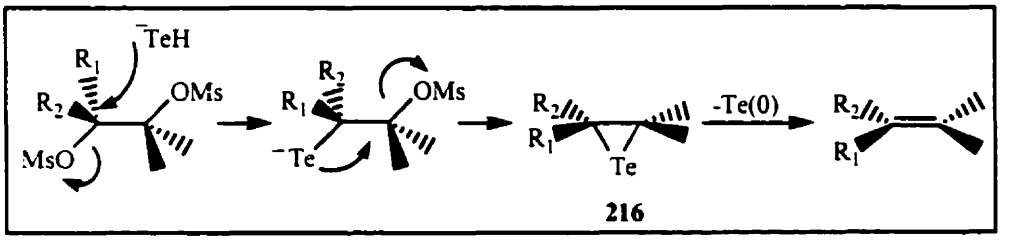
To our surprise, as was confirmed by ^{1}H NMR analysis, diene **153** was once again the main component of the reaction mixture (Scheme 75).



Scheme 75

A mechanism similar to the one proposed for the formation of diene **153** from dihalide **211** (Scheme 71) was assumed to be very unlikely, since this would imply attack of the selenium nucleophile on the mesylate oxygen.

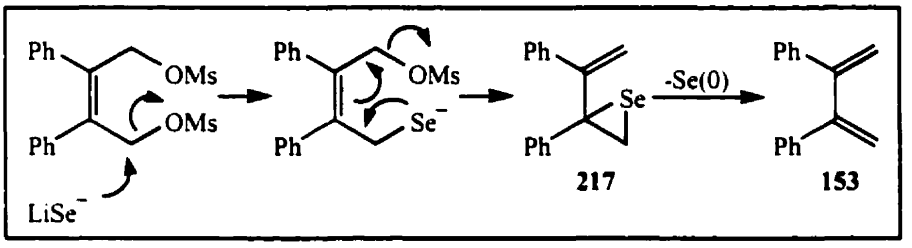
In a recent publication the NaHTe promoted elimination of vicinal disulfonates and dimesylates was reported.[177] A mechanism was proposed in which the tellurium nucleophile first displaces a mesylate (or tosylate) group, followed by the intramolecular displacement of the second mesylate group leading to the formation of an epitelluride **216**. The epitelluride then spontaneously extrudes tellurium, to afford the corresponding olefin (Scheme 76).



Scheme 76

[177] Bargues, V.; Blay, G.; Fernandez, I.; Pedro, J. R. *Synlett* **1996**, 655.

This mechanism supports our hypothesis, in which attack on the mesylate oxygen was judged unlikely. We therefore propose a mechanism in which the selenium nucleophile first displaces a mesylate group, followed by the concurrent formation of an episelenide **217** and the conjugate elimination of the second mesylate group. The episelenide then spontaneously extrudes elemental selenium to generate the observed diene **153** (Scheme 77).



Scheme 77

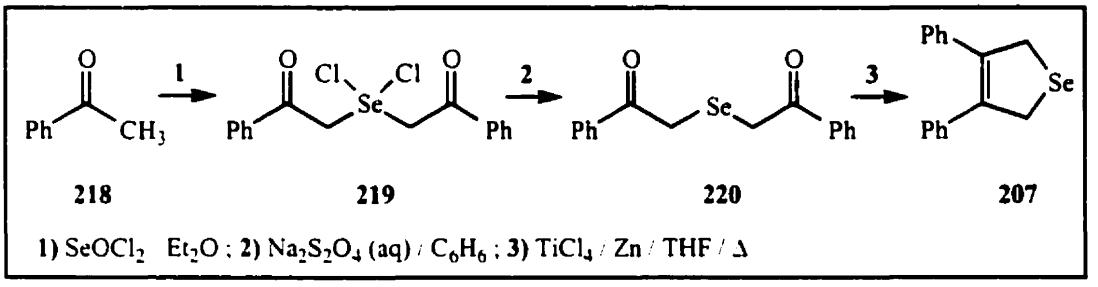
It has become clear that the 2,5-dihydroselenophene ring system is not accessible by a double nucleophilic displacement strategy. We have shown that substrates such as **211** and **215** prefer to generate a conjugated diene system which, when combined with the formation of elemental selenium, likely constitutes a thermodynamically more favorable process. The second displacement reaction, which would have led to the formation of the desired ring system, is therefore the slower of the two processes.

This is in contrast to systems such as **183**, **213** and **214** in which a similar mechanism would have resulted in the formation of a conjugated tetraene and subsequent loss of aromaticity. The second nucleophilic (intramolecular) displacement reaction therefore readily takes place.

We are however hopeful, that the use of electrophilic selenium species might provide the answer to the elaboration of new practical methods for the synthesis of 2,5-dihydroseleophenes.

3.6.8.9 Synthesis of 207 from Diketoselenides.

Since our attempts at the development of a new synthetic pathway to the 2,5-dihydroselenophene ring system remained unsuccessful, we decided to finally generate it *via* the only published literature procedure (Scheme 78).



Scheme 78

The reaction of acetophenone (**218**) with selenium oxychloride ($SeOCl_2$) effictively generates α, α'-diphenacyl selenide dichloride (**219**) in 91% isolated yield. The compound was subsequently added to a two-phase mixture of an aqueous solution of sodium dithionite ($Na_2S_2O_4$) and benzene, which produced diphenacyl selenide (**220**) in 73 % yield, after recrystallization from ethanol.[178, 179]

Nakayama reported that diphenacyl selenide, following a McMurry coupling reaction, produced a reaction mixture from which 2,5-dihydro-2,3-diphenylselenophene (**207**) was isolated in 16% yield.[172]

[178] Nakayama, J.; Shibuya, M.; Hoshino, M. *Heterocycles* **1987**, 26(4), 909.
[179] Nakayama, J.; Murai, F.; Hoshino, M.; Ishii, A.; *Tetrahedron Lett.* **1988**, 29, 1399.

Some of the reported side products were 2,3-diphenyl-1,3-butadiene (**153**) (31%) and 3,4-diphenylselenophene (**181**) (2%).[172] The crude reaction mixture was said to by purified by column chromatography, however the conditions used were not disclosed.

In our hands, the zinc/titanium promoted reductive cyclization produced a complex reaction mixture in which, following ^{1}H NMR analysis, the characteristic selenophene **181**, diene **153**, and 2,5-dihydro-2,3-diphenylselenophene (**207**) signals could be clearly observed.

After several attempts, we found that column chromatography using hexanes as the eluent, constitutes the best procedure to purify the reaction mixture. Even though the column requires approximately 8 hours to complete, an impure form of **207** (contains traces of diene **153**) is nonetheless obtained. A second column, using as the eluent system a mixture composed of hexanes and toluene (85/15) finally allowed the isolation of **207** in a very pure form. Both the ^{1}H and ^{13}C NMR correspond exactly to those previously obtained. The final piece of evidence characterizing 2,5-dihydro-2,3-diphenylselenophene (**207**) as the compound resulting from the reaction between diene **153** and pentaselenide **177** was provided by high resolution mass spectrometry from which a molecular weight of 286.02607 was obtained (the calculated molecular weight was 286.02605).

3.7 Concluding Remarks.

We can conclude that 2,5-dihydro-2,3-diphenylselenophene (**207**) is the product isolated from the reaction mixture, resulting from the thermal decomposition of titanocene pentaselenide (**177**) in the presence of diene **153**. Based on the inherent instability of small selenium containing ring systems, more specifically 1,2-diselenins, this result was not entirely unexpected. We did however obtain some ^{1}H NMR evidence, that the desired diselenide **180** was briefly present in the reaction mixture. It is very likely that the latter, under the reaction conditions, loses a selenium atom to finally form the more stable and isolated monoselenide **207**.

3.8 Contributions to Knowledge.

1 We have illustrated that the reaction of titanocene pentaselenide (**177**) and 2,3-diphenyl-1,3-butadiene (**153**) effectively leads to the formation of 2,5-dihydro-2,3-diphenylselenophene (**207**) instead of diselenide **180**.

2 We obtained ^{1}H NMR evidence for the formation of diselenide **180**, indicating that Se_2 may have been generated in the reaction mixture. This would constitute proof for the elaboration of the first system capable of generating this illusive selenium allotrope.

3 We have also shown that when the reaction mixture composed of pentaselenide **177** and diene **153** is refluxed for extended periods of time, selenophene **181** is formed.

CHAPTER 4: EXPERIMENTAL

4.1 Generalities

The commercial reagents were obtained from the Aldrich Chemical Company. Solid reagents were recrystallized when needed and distillation was performed on liquid reagents when required. Selenium (-100 mesh), tellurium (-200 mesh) and zinc (< 10 microns) were used directly without any previous treatment.

Different solvents were treated prior to use; methylene chloride (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled from phosphorous pentoxide (P_2O_5), hexanes were distilled from calcium hydride (CaH_2) and finally, tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketal).

Thin Layer Chromatography (TLC) was carried out on 0.25 mm Merck silica plates (60F-254) with polyester backing and visuallized with either UV light, a 10% aqueous sulfuric acid solution of ammonium molybdate-cerium sulfate dip or with a 1% aqueous potasium permanganate / 2% sodium carbonate dip followed by heating. Iodine adsorbed on silica gel was used for the detection of selenium containing compounds. Column Chromatography was carried out using Silicycle silica gel 60F-254 (230-400 mesh).

^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-200 MHz spectrometer. ^{77}Se NMR spectra were recorded on a Varian XL-300 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS). The abbreviations for the multiplicity assignments for the ^1H NMR spectra are as follows: "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "h" for heptet "m" for multiplet and "b" for broad.

Melting points (m.p.) were obtained using open end capillaries on a Gallenkamp K 8500 melting point apparatus and are uncorrected.

Low resolution electron impact (EI) and chemical ionization (CI) mass spectra were obtained using a Kratos MS 25RFA equipped wit a 70-eV ionizing energy source, used in direct-inlet mode and performed by Mr. Nadim Saadé. High resolution mass spectra were performed on a ZAB HS instrument at the Biomedical Mass Spectrometry Unit, McGill University by Dr. O. Mamer.

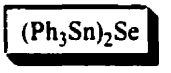
The elemental analysis for **207** was carried out at "Guelph Chemical Laboratories, Ltd." Guelph, Ontario.

The X-ray crystallography of compound **181** was determined by Dr. Anne-Marie Lebuis on a Rigaku AFC6S diffractometer at the Department of Chemistry, McGill University, Montreal, Quebec, Canada. The structure was solved using SHELXS-86 and SHELXL-93 system programs.

All air sensitive experiments were carried out under nitrogen (N_2) with freshly distilled dried solvents. All reactions involving anhydrous conditions were performed using glassware that was either flame dried and cooled under a steady stream of nitrogen or that was heated overnight in an oven at 140°C, then cooled in a desiccator containing Drierite.

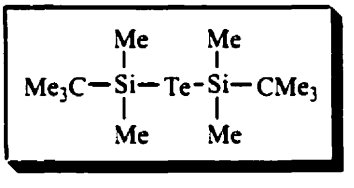
4.2 Experimentals for Chapter 2

1) Bis(triphenylstannyl)selenide (105)



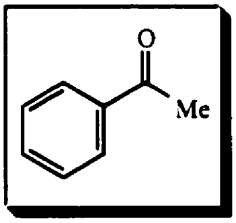
To a solution of selenium powder (2.21 g, 27.98 mmol) in ethanol (60 mL) and water (15 mL) was slowly added $NaBH_4$ (2.49 g, 66.10 mmol). The solution was then refluxed for 4 hours. The heating source was then removed and when the solution had sufficiently cooled down, a solution of Ph_3SnCl (21.57 g, 56.05 mmol) in benzene (70 mL) was then added over a period of 30 minutes using a dropping funnel. Once the addition was completed, the reaction was stirred a room temperature for 3 hours. The reaction mixture was then filtered using Celite and transferred to a separatory funnel. The organic layer was removed, dried using $MgSO_4$ and concentrated which yielded a gray colored solid. The crude product was subsequently purified by recrystallization from chloroform / ethanol to yield pure **105** (14.18 g, 65%); m.p. 141-142 °C (lit. m.p. 148 °C)[120]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.18 (m, 15H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 128.51, 129.27, 136.54, 138.73 ppm; MS (FAB, NBA matrix) m/z (%): 783 (2.6) $[M + H]^+$.

2) Bis(*tert*-butyldimethylsilyl)telluride (95)



A 50 mL three-necked, round bottomed flask was flamed and cooled under N_2. The flask was charged with a 1.0 M Super-Hydride[c] solution in THF (29 mL, 29.00 mmol). The flask was cooled in an ice bath and tellurium powder (1.78 g, 13.95 mmol) was added. The mixture was allowed to warm to room temperature and subsequently stirred for 2 hours. The reaction mixture was then again placed in an ice bath and *tert*-butylchlorodimethylsilane (4.87 g, 32.24 mmol) was added in one portion. The resulting mixture was then stirred for 2 hours at room temperature after which the low boiling volatiles were removed by distillation directly from the reaction vessel. The product was distilled at higher vacuum, again directly from the reaction vessel to yield **95** (1.78 g, 36%) as a gray solid after initial distillation from the mixture as an oil; b.p. 105 °C / 4.5 Torr (lit. b.p. 90-95 °C / 5.5 Torr.)[113]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (18 H, *t*-butyl), 0.53 (12 H, Si-CH_3) ppm.

3) <u>Acetophenone</u>



A mixture of 2-bromoacetophenone (0.25 g, 1.24 mmol), bis(triphenylstannyl)selenide (**105**) (0.97 g, 1.25 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.36 g, 3.79 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen.

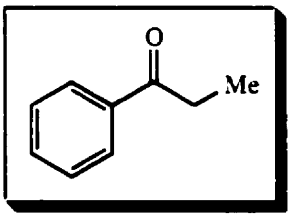
The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, toluene) to yield acetophenone (97.42 mg, 65%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97-7.93 (m, 2H), 7.48-7.44 (m, 3H), 2.53 (s, 3H, CH_3) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 197.84, 136.83, 132.86, 128.32, 128.05, 26.14 ppm; MS (EI) m/z (%): 120 (44).

A mixture of 2-chloroacetophenone (0.19 g, 1.24 mmol), bis(triphenylstannyl)selenide (**105**) (0.97 g, 1.25 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.36 g, 3.79 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. ^{1}H NMR analysis using toluene as the internal standard revealed that acetophenone was produced in 89% yield.

A mixture of 2-bromoacetophenone (0.31 g, 1.57 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.62 g, 1.74 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.47 g, 4.98 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, toluene) to yield acetophenone (0.13 g, 72%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97-7.92 (m, 2H), 7.49-7.45 (m, 3H), 2.59 (s, 3H, CH_3) ppm.

A mixture of 2-chloroacetophenone (0.21 g, 1.33 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.48 g, 1.34 mmol) and potassium fluoride dihydrate (KF $2H_2O$) (0.37 g, 3.90 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, toluene) to yield acetophenone (0.12 g, 75%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97-7.92 (m, 2H), 7.48-7.44 (m, 3H), 2.59 (s, 3H, CH_3) ppm

4) <u>Propriophenone</u>

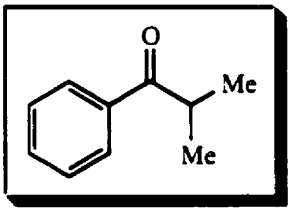


A mixture of 2-bromopropiophenone (0.78 g, 3.66 mmol), bis(triphenylstannyl)selenide (**105**) (2.85 g, 3.66 mmol) and potassium fluoride dihydrate (KF $2H_2O$) (1.03 g, 10.91 mmol) in acetonitrile (90 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL).

The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / toluene (1/1)) followed by a second column (benzene) to yield propiophenone (0.24 g, 48%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98-7.93 (m, 2H), 7.55-7.35 (m, 3H), 2.99 (q, 2H, j = 7.0 Hz, CH_2), 1.22 (t, 3H, J = 7.2 Hz, CH_3) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 200.82, 136.86, 132.85, 128.52, 127.95, 31.77, 8.22 ppm; MS (EI) m/z (%):134 (21).

A mixture of 2-bromopropiophenone (0.31 g, 1.45 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.58 g, 1.61 mmol) and potassium fluoride dihydrate (KF $2H_2O$) (0.45 g, 4.82 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, toluene) followed by a second column (toluene) to yield propiophenone (0.13 g, 65%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98-7.93 (m, 2H), 7.55-7.39 (m, 3H), 3.00 (q, 2H, j = 7.2 Hz, CH_2), 1.22 (t, 3H, J = 7.2 Hz, CH_3) ppm.

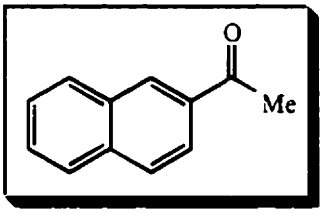
5) <u>Isobutyrophenone</u>



A mixture of 2-bromoisobutyrophenone (0.29 g, 1.28 mmol), bis(triphenylstannyl)selenide (**105**) (1.00 g, 1.28 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.36 g, 3.86 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / ethyl acetate (1/1)) to yield isobutyrophenone (0.14 g, 72%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.53-7.40 (m, 3H), 3.54 (h, 1H, J = 6.8 Hz, CH), 1.20 (d, j = 7.0 Hz, CH_3) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 204.35, 136.08, 132.68, 128.49, 128.19, 35.21, 19.03 ppm; MS (EI) m/z (%):148 (11).

A mixture of 2-bromoisobutyrophenone (0.31 g, 1.34 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.52 g, 1.44 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.41 g, 4.40 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, toluene) to yield isobutyrophenone (0.16 g, 81%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99-7.94 (m, 2H), 7.56-7.43 (m, 3H), 3.56 (h, 1H, J = 6.8 Hz, CH), 1.22 (d, j = 7.0 Hz, CH_3) ppm.

6) 2'Acetonaphthone

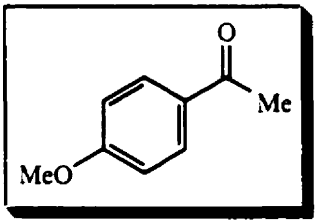


A mixture of 2-bromo-2'acetonaphthone (0.32 g, 1.29 mmol), bis(triphenylstannyl)selenide (**105**) (1.04 g, 1.33 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.38 g, 4.00 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / toluene (1/1)) followed by a second column (benzene) to yield 2'acetonaphthone (0.18 g, 81%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.05-7.81 (m, 4H), 7.61-7.49 (m, 2H), 2.68 (s, 3H, CH_3) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 197.90, 135.39, 134.28, 132.33, 130.03, 129.39, 128.30, 128.23, 127.61, 126.61, 123.70, 26.51 ppm; MS (EI) m/z (%):170 (54).

A mixture of 2-bromo-2'-acetonaphthone (0.32 g, 1.30 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.48 g, 1.34 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.37 g, 3.91 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL).

The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, benzene) followed by a second column (toluene) to yield 2'acetonaphthone (0.16 g, 72%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.03-7.81 (m, 4H), 7.65-7.49 (m, 2H), 2.72 (s, 3H, CH_3) ppm.

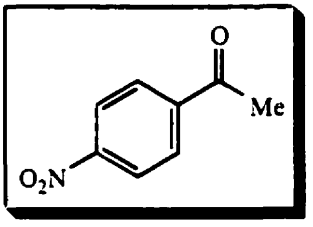
7) <u>4'-Methoxyacetophenone</u>



A mixture of 2-bromo-4'-methoxyacetophenone (0.30 g, 1.30 mmol), bis(triphenylstannyl)selenide (**105**) (1.02 g, 1.31 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.38 g, 4.00 mmol) in acetonitrile (30 mL) was stirred at room temperature for 48 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, benzene) to yield 4'methoxyacetophenone (0.14 g, 71%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93-7.88 (m, 2H), 6.92-6.87 (m, 2H), 3.83 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 196.77, 163.42, 130.53, 130.22, 113.61, 55.40, 26.29 ppm; MS (EI) m/z (%):150 (52).

A mixture of 2-bromo-4'-methoxyacetophenone (0.30 g, 1.30 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.48 g, 1.33 mmol) and potassium fluoride dihydrate ($KF{\cdot}2H_2O$) (0.38 g, 4.07 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, toluene) to yield 4'nitroacetophenone (0.16 g, 81%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94-7.90 (m, 2H), 6.94-6.89 (m, 2H), 3.85 (s, 3H, OCH_3), 2.54 (s, 3H, CH_3) ppm.

8) <u>4'-Nitroacetophenone</u>

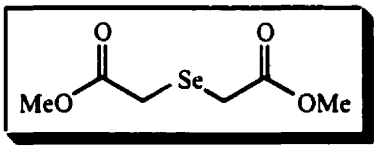


A mixture of 2-bromo-4'-nitroacetophenone (0.32 g, 1.30 mmol), bis(triphenylstannyl)selenide (**105**) (1.01 g, 1.30 mmol) and potassium fluoride dihydrate ($KF{\cdot}2H_2O$) (0.37 g, 3.93 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL).

The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, benzene) to yield 4'nitroacetophenone (0.19 g, 89%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31-8.27 (m, 2H), 8.11-8.07 (m, 2H), 2.66 (s, 3H, CH_3) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 196.26, 150.05, 141.31, 129.25, 123.79, 26.93 ppm; MS (EI) m/z (%):165 (24).

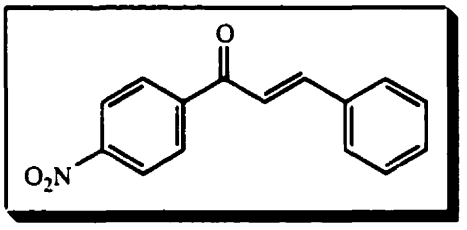
A mixture of 2-bromo-4'-nitroacetophenone (0.32 g, 1.30 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.47 g, 1.32 mmol) and potassium fluoride dihydrate (KF $2H_2O$) (0.37 g, 3.93 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, benzene) to yield 4'nitroacetophenone (0.17 g, 79%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31-8.27 (m, 2H), 8.11-8.07 (m, 2H), 2.66 (s, 3H, CH_3) ppm.

9) <u>Dimethyl selenodiacetate</u> (118)



A mixture of methyl bromoacetate (0.51 g, 3.31 mmol), bis(triphenylstannyl)selenide (**105**) (2.60 g, 3.33 mmol) and potassium fluoride dihydrate ($KF{\cdot}2H_2O$) (0.96 g, 10.20 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / ethyl acetate (4/1)) to yield dimethyl selenodiacetate (**118**) (0.37 g, 98%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.62 (s, 3H, CH_3), 3.28 (s, 2H, CH_2) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 171.00, 52.18, 23.08 ppm; ^{77}Se NMR (51 MHz, $CDCl_3$) δ: 248 ppm; MS (EI) m/z (%):226 (57).

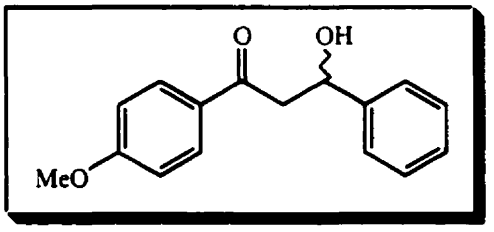
10) <u>Chalcone 121</u> (Benzylidene-4'-nitroacetophenone)



A mixture of 2-bromo-4'-nitroacetophenone (0.25 g, 1.03 mmol), bis(triphenylstannyl)selenide (**105**) (0.80 g, 1.27 mmol) potassium fluoride (KF) (0.18 g, 3.10 mmol) and benzaldehyde (1.11 mL, 10.93 mmol) in anhydrous acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite and the resulting filter cake washed washed with Et_2O.

The solution was concentrated and to the resulting crude residue was added Et_2O (30 mL) and water (5 mL).The organic layer was removed and the remaining aqueous layer re-extrated with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated and the resulting crude residue placed in the fume hood for several hours (to get rid of the excess benzaldehyde) and then purified by column chromatography (dry-pack, benzene) to yield compound **121** (0.15 g, 56%); ^1H NMR (200 MHz, $CDCl_3$) δ 8.37-8.32 (m, 2H), 8.16-8.12 (m, 2H), 7.89-7.35 (m, 7H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 189.02, 150.03, 146.82, 143.01, 134.24, 131.24, 129.40, 129.10, 128.70, 123.86, 121.24 ppm; MS (FAB, NBA matrix) m/z (%):254 (24) [M + H]$^+$.

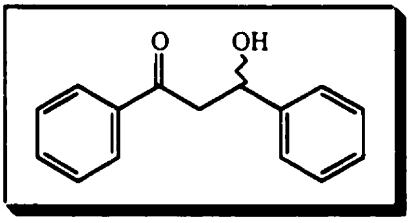
11) <u>Chalcone</u> 123



A mixture of 2-bromo-4'-methoxyacetophenone (0.24 g, 1.03 mmol), bis(triphenylstannyl)selenide (**105**) (0.80 g, 1.27 mmol) potassium fluoride (KF) (0.18 g, 3.10 mmol) and benzaldehyde (1.11 mL, 10.93 mmol) in anhydrous acetonitrile (30 mL) was stirred at room temperature for 48 hours under nitrogen.

The reaction mixture was then filtered using Celite and the resulting filter cake washed washed with Et_2O. The solution was concentrated and to the resulting crude residue was added Et_2O (30 mL) and water (5 mL).The organic layer was removed and the remaining aqueous layer re-extrated with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated and the resulting crude residue placed in the fume hood for several hours (to get rid of the excess benzaldehyde) and then purified by column chromatography (dry-pack, benzene / ethyl acetate (92/8)) to yield compound **123** (0.18 g, 67%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.95-7.90 (m, 2H), 7.43-7.26 (m, 5H), 6.94-6.86 (m, 2H), 5.31 (t, 1H, J = 6.0 Hz, CH), 3.86 (s, 4H, OH + OCH_3), 3.32-3.29 (m, 2H, CH_2, AB of AB-X system) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 198.65, 163.83, 143.02, 130.42, 129.53, 128.43, 127.50, 125.68, 113.75, 70.05, 55.42, 46.84 ppm.

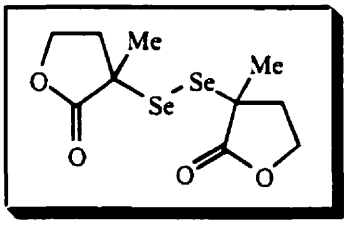
12) <u>Chalcone</u> 124



A mixture of 2-bromoacetophenone (0.20 g, 1.02 mmol), bis(triphenylstannyl)selenide (**105**) (0.80 g, 1.27 mmol) potassium fluoride (KF) (0.18 g, 3.10 mmol) and benzaldehyde (1.11 mL, 10.93 mmol) in anhydrous acetonitrile (30 mL) was stirred at room temperature for 24 hours under nitrogen.

The reaction mixture was then filtered using Celite and the resulting filter cake washed washed with Et_2O. The solution was concentrated and to the resulting crude residue was added Et_2O (30 mL) and water (5 mL). The organic layer was removed and the remaining aqueous layer re-extrated with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated and the resulting crude residue placed in the fume hood for several hours (to get rid of the excess benzaldehyde) and then purified by column chromatography (dry-pack, benzene / ethyl acetate (95/5)) to yield compound **124** (0.13 g, 58%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.97-7.93 (m, 2H), 7.59-7.29 (m, 8H), 5.35 (t, 1H, J = 6.0 Hz, CH), 3.39-3.36 (m, 2H, CH_2, AB of AB-X system) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 200.15, 142.91, 136.51, 133.63, 128.67, 128.54, 128.13, 127.65, 125.72, 69.99, 47.36 ppm; MS (FAB, NBA matrix) m/z (%):227 (9) $[M + H]^+$.

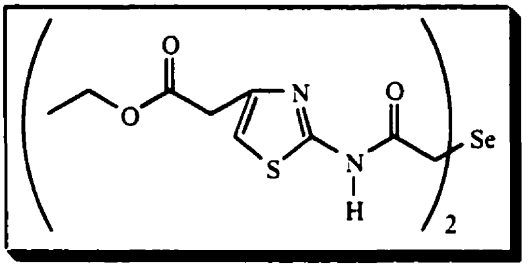
13) <u>Di-α-methyl-γ-butyrolactone-diselenide</u> 132



A mixture of (±)-α-bromo-α-methyl-γ-butyrolactone **129** (0.15 mL, 1.30 mmol), bis(triphenylstannyl)selenide (**105**) (1.02 g, 1.31 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.36 g, 3.80 mmol) in acetonitrile (30 mL) was stirred

at room temperature for 24 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / ethyl acetate (3/2)) to yield compound **132** as a pair of diastereomers (0.12 g, 54%); m.p. 82-87°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36-4.27 (m, CH_2, 4H), 2.60-2.32 (m, OCH_2, 4H), 1.73(s, CH_3, 6H), 1.69 (s, CH_3, 3H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 177.37, 177.27, 65.23, 65.18, 44.77, 44.47, 37.72, 37.62, 25.20, 25.17 ppm; ^{77}Se NMR (51 MHz, $CDCl_3$) δ: 537.82, 536.25 ppm; MS (EI) m/z (%):358 (6).

14) **Bis (Ethyl [2-(2-acetamido)thiazol-4-yl] acetate) selenide** 134



A mixture of ethyl [2-(2-chloroacetamido)thiazol-4-yl] acetate **131** (0.40 g, 1.52 mmol), bis(triphenylstannyl)selenide (**105**) (1.17 g, 1.50 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.43 g, 4.56 mmol) in acetonitrile (40 mL) was stirred at room temperature for 48 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with more acetonitrile or diethyl ether (2 x 10 mL).

The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / ethyl acetate (1/1)) to yield compound **134** (0.24 g, 59%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.4-9.0 (b, NH, 1H), 6.80 (s, C**H**S, 1H), 4.17 (q, OC**H**$_2$CH$_3$, 2H, j = 7.2 Hz), 3.70 (s, C**H**$_2$COO, 2H), 3.60 (s, C**H**$_2$Se, 2H), 1.25 (t, CH$_2$C**H**$_3$, j = 7.2 Hz, 3H) ppm, ^{13}C (50 MHz, $CDCl_3$) δ: 170.41, 168.28, 157.72, 143.10, 111.41, 61.23, 36.86, 25.30, 14.15 ppm; ^{77}Se NMR (51 MHz, $CDCl_3$) δ: 274.33 ppm; MS (FAB, NBA matrix) m/z (%):535 (43) $[M + H]^+$.

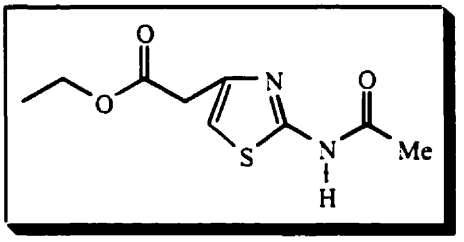
15) <u>Bis(triphenylstannyl)telluride</u> (108)

$(Ph_3Sn)_2Te$

To a solution of tellurium powder (3.57 g, 28.0 mmol) in ethanol (60 mL) and water (15 mL) was slowly added $NaBH_4$ (2.5 g, 66.0 mmol). The solution was then refluxed for 4 hours. The heating source was then removed and when the solution had sufficiently cooled down, a solution of Ph_3SnCl (21.6 g, 56.0 mmol) in benzene (70 mL) was then added over a period of 30 minutes using a dropping funnel. Once the addition was completed, the reaction was stirred a room temperature for 3 hours. The reaction mixture was then filtered using Celite and transferred to a separatory funnel. The organic layer was removed, dried using $MgSO_4$ and concentrated which yielded a gray colored solid.

The crude product was subsequently purified by recrystallization from chloroform / ethanol to yield pure **108** (13.5 g, 58%); m.p. 151-152 °C (lit. m.p. 150 °C)[120]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47-7.17 (m, 15H) ppm

16) <u>Ethyl [2-(2-acetamido)thiazol-4-yl] acetate</u> 137

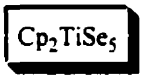


A mixture of ethyl [2-(2-chloroacetamido)thiazol-4-yl] acetate **131** (0.34 g, 1.30 mmol), bis(triphenylstannyl)telluride (**108**) (1.60 g, 1.95 mmol) and potassium fluoride dihydrate ($KF\cdot 2H_2O$) (0.38 g, 4.00 mmol) in acetonitrile (30 mL) was stirred at room temperature for 48 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with cloroform (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / ethyl acetate (2/3)) to yield compound **137** (0.18 g, 74%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.0-9.8 (b, NH, 1H), 6.80 (s, C**H**S, 1H), 4.15 (q, O**CH**$_2$CH$_3$, 2H, j = 7.2 Hz), 3.70 (s, **CH**$_2$COO, 2H), 2.21 (s, COC**H**$_3$, 3H), 1.23 (t, CH$_2$C**H**$_3$, j = 7.2 Hz, 3H) ppm.

A mixture of ethyl [2-(2-chloroacetamido)thiazol-4-yl] acetate **131** (0.26 g, 1.00 mmol), bis(*tert*-butyldimethylsilyl)telluride (**95**) (0.54 g, 1.52 mmol) and potassium fluoride dihydrate ($KF{\cdot}2H_2O$) (0.38 g, 4.00 mmol) in acetonitrile (30 mL) was stirred at room temperature for 48 hours under nitrogen. The reaction mixture was then filtered using Celite, and the reaction flask rinsed twice with cloroform (2 x 10 mL). The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes / ethyl acetate (2/3)) to yield compound **137** (0.21 g, 91%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.7-10.5 (b, NH, 1H), 6.77 (s, C**H**S, 1H), 4.12 (q, O**C**$\mathbf{H}_2$$CH_3$, 2H, j = 7.2 Hz), 3.66 (s, C$\mathbf{H}_2$COO, 2H), 2.19 (s, COC$\mathbf{H}_3$, 3H), 1.19 (t, CH_2C$\mathbf{H}_3$, j = 7.2 Hz, 3H) ppm.

4.3 Experimentals for Chapter 3

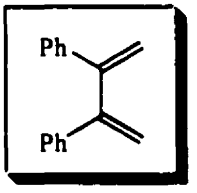
17) Titanocene pentaselenide (177)



To a solution of lithium polyselenide, prepared from the addition of a 1.0 M Super-Hydride[c] solution in THF (18.0 mL, 18.00 mmol) to powdered gray selenium (3.54 g, 44.80 mmol), was added a solution of bis(cyclopentadienyl)titanium dichloride (2.24 g, 9.00 mmol) in anhydrous THF (150 mL). The reaction mixture was subsequently stirred at room temperature for 5 hours.

Removal of the volatiles under reduced pressure provided a black residue, which was extracted with CH_2Cl_2 (5 x 200 mL). The resulting dark purple solution was then filtered using Celite and the filtrate concentrated to ~ 50 mL and subsequently stored at –20 °C overnight. Filtration provided **177** as a dark purple solid (1.5 g, 34%); m.p. 208-209 °C (lit. m.p. 211 °C)[157,158]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.38 (s, 5H), 5.96 (s, 5H) ppm; MS (EI) m/z (%):577 (2).

18) 2,3-Diphenyl-1,3-butadiene[180] (153)

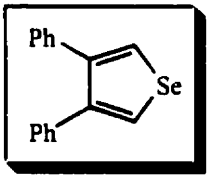


A flame dried 3-necked round bottomed flask, equipped with a reflux condenser and an addition funnel, was charged with magnesium powder (1.75 g, 71.98 mmol) and anhydrous diethyl ether (36 mL). The suspension was stirred vigorously and α-bromostyrene (8.5 mL, 65.58 mmol) was added to the addition funnel. α-Bromostyrene (15 – 20 drops) were then added to the magnesium suspension under vigorous stirring and the remaining α-bromostyrene diluted with anhydrous THF (15 mL). Once the reaction mixture started to reflux, the remaining α-bromostyrene was added dropwise. The reaction mixture was then refluxed for an additional hour.

[180] Fulcher, B.C.; Hunter, M.L.; Welker, M.E. *Synth. Commun.* **1993**, 23(2), 217.

The reaction was then allowed to cool to room temperature and was then transferred under nitrogen to a vigorously stirred solution of dichlorobis(triphenylphosphine)-nickel (II) [$(Ph_3P)_2NiCl_2$] (4.29 g, 6.56 mmol) and α-bromostryrene (6.8 mL, 52.46 mmol) in anhydrous diethyl ether (60 mL) at 0°C. Upon completion of the transfer, the solution was allowed to slowly reach room temperature and stirred overnight. The solution was then cooled to 0°C and HCl (1N, 100 mL) was slowly added. The organic layer was removed and the remaining aqueous layer extracted with ether (2 x 50 mL). The combined organic layers were then washed with $NaHCO_3$ (50 mL) and dried with $MgSO_4$. The solution was then concentrated and the resulting crude solid purified by column chromatography (dry-pack, hexanes) to yield **153** as a white solid (7.15 g, 66%); m.p. 46-47 °C (lit. m.p. 46-47 °C)[180]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.52-7.48 (m, 3H), 7.39-7.30 (m, 6H), 5.64 (d, j = 1.6 Hz, 2H), 5.42 (d, j = 1.6 Hz, 2H) ppm.

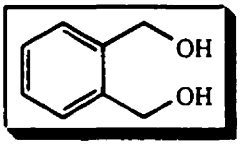
19) <u>Selenophene</u> 181



A solution of titanocene pentaselenide (**177**) (0.23 g, 0.40 mmol) and 2,3-diphenyl-1,3-butadiene (0.37 g, 1.77 mmol) in o-dichlorobenzene (5 mL) was refluxed for 6 days.

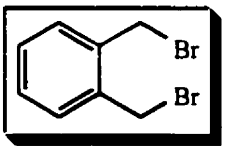
The solvent was removed under reduced pressure and the reaction flask extracted with pentane. The resulting red/orange solution was concentrated and the crude product purified by column chromatography (hexanes) to yield **181** as colorless crystals (33.00 mg, 29%); m.p. 106-108 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (s, 2H), 7.24-7.11 (m, 10H) ppm; ^{77}Se NMR (51 MHz, $CDCl_3$) δ: 584.46 ppm. The structure was subsequently confirmed by X-ray crystallography.

20) <u>1,2-benzenedimethanol</u> (184)



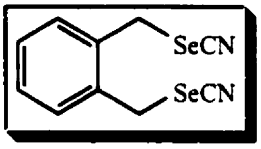
To a suspension of $LiAlH_4$ (5.12 g, 0.14 mol) in anhydrous THF (100 mL) at 0°C was transferred under nitrogen, a solution of phthalic anhydride (5.00 g, 33.75 mmol) in anhydrous THF (100 mL). The reaction was slowly warmed to room temperature and stirred overnight. The reaction mixture was then cooled to 0°C and consecutively treated with water and NaOH (15%). It was then filtered and the organic layer removed and concentrated. The resulting crude solid was purified by column chromatography (dry-pack, hexanes / ethyl acetate (1/1)) to yield **184** as a white solid (3.93 g, 84%); m.p. 62-63 °C (lit. m.p. 63-65 °C)[160]; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28 (s, 4H), 4.58 (s, 4H), 3.86 (s, 4H), ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 139.31, 129.66, 128.51, 63.88 ppm; MS (CI, NH_3) m/z (%):139 (28) $[M + H]^+$.

21) <u>1,2-bis(bromomethyl)benzene</u> (185)



To a solution of diol **184** (1.28 g, 9.26 mmol) in anhydrous ether (25 mL) at 0°C was added dropwise PBr_3 (1.85 mL, 19.62 mmol). The reaction mixture was then stirred at 0°C for 3 hours. The mixture was then poured onto ice and the organic layer removed, washed with $NaHCO_3$ and dried with $MgSO_4$. The organic layer was then concentrated which yielded **185** in a good state of purity (1.59 g, 65%); m.p. 90-91 °C (lit. m.p. 92-93 °C); ^1H NMR (200 MHz, $CDCl_3$) δ: 7.41-7.22 (m, 4H), 4.66 (s, 4H), ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 136.57, 131.10, 129.45, 30.00 ppm; MS (EI) m/z (%):264 (13).

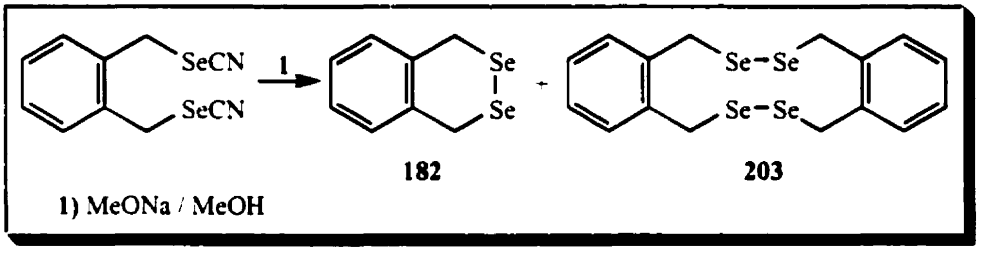
22) <u>1,2-benzenedimethylselenocyanate</u> (186)



To a solution of dibromide **185** (1.06 g, 4.02 mmol) in ethanol (30 mL) was added a solution of KSeCN (1.16 g, 8.05 mmol) in ethanol. The solution was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the crude residue extracted with benzene (100 mL).

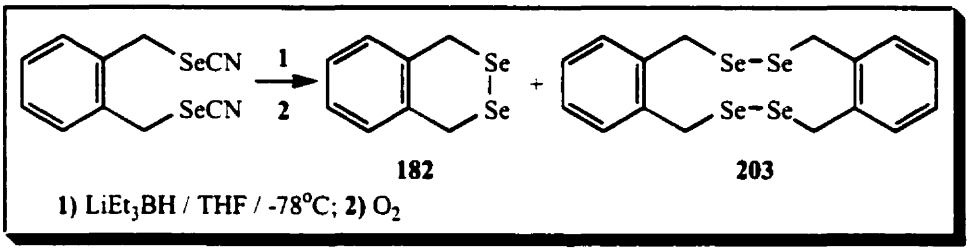
The crude product was subsequently purified by recrystallization from ethanol to yield pure **186** (0.82 g, 65%); m.p. 116-117 °C (lit. m.p. 112-113 °C)[171]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (s, 4H), 4.41 (s, 4H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 133.67, 131.60, 129.93, 101.21, 29.47 ppm; ^{77}Se NMR (51 MHz, $CDCl_3$) δ: 281.40 ppm; MS (CI, NH_3) m/z (%):334 (2) $[M + H + NH_3]^+$.

23) <u>Reaction of 186 with sodium methoxide</u>



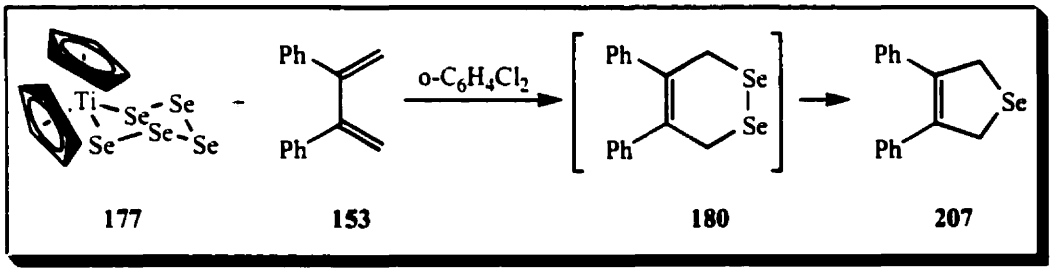
To a solution of 1,2-benzenedimethylselenocyanate (**186**) (0.16 g, 0.51 mmol) in anhydrous methanol (20 mL) was added under nitrogen a solution of sodium methoxide (86.0 mg. 1.59 mmol) in anhydrous methanol (20 mL). The reaction mixture was stirred at room temperature for 30 minutes and was then filtered to yield a yellow solid (94.00 mg) that was composed of two components (**182** and **203**) that could not be separated. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.31-7.22 (m, **182** and **203**), 4.51 (s, **203**, CH_2), 3.95 (s, **182**, CH_2) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 137.11 (**182**), 136.88 (**203**), 130.86 (**203**), 128.32 (**203**), 128.19 (**182**), 127.80 (**182**), 32.67 (**203**), 24.29 (**182**) ppm; ^{77}Se NMR (51 MHz, $CDCl_3$) δ: 361.3 (**203**), 308.4 (**182**) ppm; MS (EI) m/z (%):264 (41).

24) Reaction of 186 with Super-Hydride©



To a solution of 1,2-benzenedimethylselenocyanate (**186**) (0.16 g, 0.51 mmol) in anhydrous THF (20 mL) at –78°C was added under nitrogen a 1.0 M Super-Hydride© solution in THF (1.05 mL, 1.05 mmol). The solution was stirred at this temperature for 15 minutes. The reaction flask was then opened to the atmosphere and the cooling bath removed until room temperature was reached. Removal of the solvent under reduced pressure yielded a yellow solid that consisted of two components (**182** and **203**) that could not be separated. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.33-7.25 (m, **182** and **203**), 4.51 (s, **203**, CH_2), 3.95 (s, **182**, CH_2) ppm.

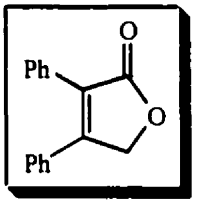
25) Formation of 2,5-dihydro-2,3-diphenylselenophene (207)



A solution of titanocene pentaselenide (**177**) (0.23 g, 0.40 mmol) and 2,3-diphenyl-1,3-butadiene (**153**) (83.00 mg, 0.40 mmol) in o-dichlorobenzene (10 mL) was refluxed for 3 hours. The heating source was removed and the solvent removed under vacuum. The crude reaction mixture was extracted with pentane (50 mL) and reconcentrated. The crude product was purified by column chromatography (dry-pack, hexanes (5 mL) / ether (2 drops)) to yield **207** (27.40 mg, 24%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20-7.05 (m, 10H), 4.26 (s, 4H) ppm; MS (EI) m/z (%):286 (59).

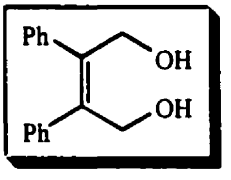
A solution of titanocene pentaselenide (**177**) (0.27 g, 0.48 mmol) and 2,3-diphenyl-1,3-butadiene (**153**) (0.30 g, 1.44 mmol) in 1,2,4-trichlorobenzene (12 mL) was refluxed for 1 hour. The heating source was removed and the solvent removed under vacuum. The crude reaction mixture was extracted with pentane (50 mL) and reconcentrated. The crude product was purified by column chromatography (dry-pack, hexanes (5 mL) / ether (2 drops)) to yield **207** (37.10 mg, 27%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21-7.02 (m, 10H), 4.27 (s, 4H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 138.11, 137.62, 128.70, 128.16, 127.07, 35.24 ppm; MS (EI) m/z (%):286 (46). Anal. Calcd. for $C_{16}H_{14}Se$: C, 67.13; H, 4.93; Found: C, 70.55; H, 5.15.

27) 3,4-diphenyl-2(5H)-furanone (210)



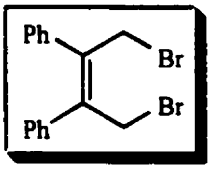
To a solution of 2,3-diphenylmaleic anhydride (5.00 g, 0.02 mol) in anhydrous THF (200 mL) at –78°C was added under nitrogen a 1.0 M Super-Hydride[c] solution in THF (100 mL, 0.10 mol). The solution was slowly warmed to room temperature and stirred overnight. The reaction mixture was treated with distilled water (20 mL) followed by treatment with a saturated NaCl (20 mL) solution. The organic layer was removed and the remaining aqueous layer extracted with Et_2O (100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. The resulting crude solid was purified by column chromatography (dry-pack, hexanes / ethyl acetate (7/3)) to yield compound **210** (3.37 g, 71%); m.p. 115-116 °C (lit. m.p. 115-116 °C)[176]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.29 (m, 10H), 5.16 (s, 2H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 173.41, 156.07, 130.57, 129.23, 128.98, 128.78, 128.66, 127.46, 70.54 ppm; MS (FAB, NBA matrix) m/z (%):237 (100) $[M + H]^+$.

28) (Z)-2,3-diphenyl-2-butene-1,4-diol (209)



To a solution of lactone **210** (0.46 g, 1.95 mmol) dissolved in anhydrous diethyl ether (20 mL) at –20°C was slowly added in small portions lithium aluminum hydride (0.11 g, 2.92 mmol). The solution was stirred at –20°C for 30 minutes and then allowed to warm to room temperature over 1 hour. Aqueous HCl (25 mL of a 1.0 M solution) was then added and the organic layer removed. The remaining aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The resulting crude solid was purified by column chromatography (dry-pack, hexanes / ethyl acetate (1/4)) to yield compound **209** (0.17 g, 35%); m.p. 82-84 °C (lit. m.p. 85-87 °C)[176]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.14-7.02 (m, 10H), 4.59 (s, 4H), 3.35-3.20 (b, 2H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 141.14, 140.98, 129.32, 127.93, 126.66, 64.11 ppm; MS (FAB, NBA matrix) m/z (%):241 (2) $[M + H]^+$.

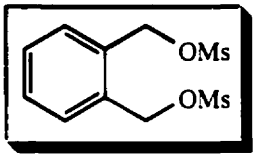
29) (Z)-1,4-dibromo-2,3-diphenyl-2-butene (211)



Diol **210** (0.10 g, 0.42 mmol) was dissolved in anhydrous diethyl ether (3 mL) and PBr_3 (0.04 mL; 0.42 mmol) was then added dropwise followed by the addition of 4 drops of triethyl amine. The solution was then refluxed for 1 hour. The reaction mixture was then cooled to 0°C and distilled water (1 mL) was added.

The organic layer was removed and the aqueous layer extracted with diethyl ether (3 x 4 mL). The combined organic layers were then dried with $MgSO_4$ and concentrated to yield **211** (0.13 g, 86%); m.p. 95-96 °C (lit. m.p. 98-100 °C)[176]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.18-7.09 (m, 10H), 4.53 (s, 4H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 140.53, 140.02, 129.83, 128.60, 128.07, 33.00 ppm; MS (FAB, NBA matrix) m/z (%):366 (8) $[M + H]^+$.

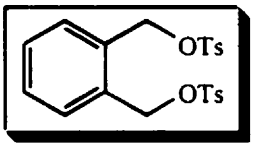
30) <u>Synthesis of mesylate</u> 213



To a solution of diol **184** (0.25 g, 1.81 mmol) and Et_3N (0.79 mL, 5.66 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0°C was added MsCl (0.35 mL, 4.53 mmol). The solution was stirred at 0°C for 10 minutes. The reaction mixture was then diluted with EtOAc (15 mL) and HCl (1M, 2.5 mL) was slowly added followed by the addition of a saturated solution of $NaHCO_3$ (5 mL). The organic layer was removed and the remaining aqueous layer extracted with EtOAc (2 x 5 mL). The combined organic layers were washed again with a saturated solution of $NaHCO_3$ (5 mL) and dried with Na_2SO_4. The solution was then concentrated and the crude product purified by column chromatography (dry-pack, hexanes / ethyl acetate (1/1)) to yield **213** (0.38 g, 72%).

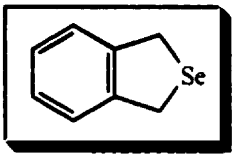
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49-7.39 (m, 4H), 5.31 (s, 4H), 2.94 (s, 4H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 132.64, 131.03, 130.21, 68.81, 37.99 ppm; MS (FAB, NBA matrix, NaCl) m/z (%):317 (9) $[M + Na]^+$.

31) <u>Synthesis of tosylate</u> 214



To a solution of diol **184** (0.25 g, 1.81 mmol) and Et_3N (0.79 mL, 5.66 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0°C was added TsCl (0.86 g, 4.53 mmol). The solution was stirred at 0°C for 30 minutes. The reaction mixture was then diluted with EtOAc (15 mL) and HCl (1M, 2.5 mL) was slowly added followed by the addition of a saturated solution of $NaHCO_3$ (5 mL). The organic layer was removed and the remaining aqueous layer extracted with EtOAc (2 x 5 mL). The combined organic layers were washed again with a saturated solution of $NaHCO_3$ (5 mL) and dried with Na_2SO_4. The solution was then concentrated and the crude product purified by column chromatography (dry-pack, hexanes / ethyl acetate (7/3)) to yield **214** (0.54 g, 67%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79-7.69 (m, 4H), 7.36-7.18 (m, 8H), 5.02 (s, 4H), 2.43 (s, 6H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 133.94, 132.45, 132.26, 130.29, 129.94, 129.60, 127.59, 68.98, 21.68 ppm; MS (FAB, NBA matrix) m/z (%):447 (7) $[M + H]^+$.

32) <u>2-selenaindan</u> (212)



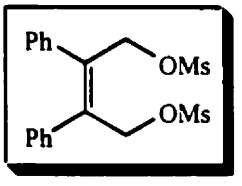
To a flame dried flask placed in an ice bath and charged with gray selenium (0.16 g, 2.03 mmol) was slowly added under nitrogen a 1.0 M Super-Hydride[c] solution in THF (4.00 mL, 4.00 mmol). The solution was then allowed to slowly reach room temperature and stirred for two hours after which an additional amount of anhydrous THF (3 mL) was added. A solution containing dibromide **185** (0.50 g, 1.90 mmol) and t-BuOH (1.40 mL, 14.6 mmol) in anhydrous THF (3 mL) was then added under nitrogen. The reaction mixture was stirred at room temperature for 3 hours and then concentrated. The crude residue was purified by column chromatography (dry-pack, hexanes / CH_2Cl_2 (4/1)) to yield compound **212** (0.13 g, 36%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.28-7.12 (m, 4H), 4.32 (s, 4H), ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 141.64, 126.43, 125.92, 29.67 ppm; MS (EI) m/z (%):183 (100).

To a flame dried flask placed in an ice bath and charged with gray selenium (0.13 g, 1.65 mmol) was slowly added under nitrogen a 1.0 M Super-Hydride[c] solution in THF (3.4 mL, 3.40 mmol). The solution was then allowed to slowly reach room temperature and stirred for two hours after which an additional amount of anhydrous THF (3 mL) was added. A solution containing dimesylate **213** (0.40 g, 1.36 mmol) and t-BuOH (1.00 mL, 10.5 mmol) in anhydrous THF (3 mL) was then added under nitrogen.

The reaction mixture was stirred at room temperature for 2 hours and then concentrated. The crude residue was purified by column chromatography (dry-pack, hexanes / CH_2Cl_2 (4/1)) to yield compound **212** (0.18 g, 70%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.28-7.13 (m, 4H), 4.33 (s, 4H), ppm.

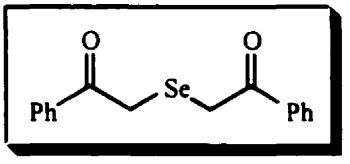
To a flame dried flask placed in an ice bath and charged with gray selenium (75.0 mg, 0.95 mmol) was slowly added under nitrogen a 1.0 M Super-Hydride[c] solution in THF (1.9 mL, 1.90 mmol). The solution was then allowed to slowly reach room temperature and stirred for two hours after which an additional amount of anhydrous THF (3 mL) was added. A solution containing ditosylate **214** (0.40 g, 0.90 mmol) and t-BuOH (0.69 mL, 7.2 mmol) in anhydrous THF (3 mL) was then added under nitrogen. The reaction mixture was stirred at room temperature for 2 hours and then concentrated. The crude residue was purified by column chromatography (dry-pack, hexanes / CH_2Cl_2 (4/1)) to yield compound **212** (0.13 g, 78%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.30-7.14 (m, 4H), 4.33 (s, 4H), ppm.

33) <u>Synthesis of mesylate</u> 215



To a solution of diol **209** (0.10 g, 0.42 mmol) and Et_3N (0.18 mL, 1.30 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0°C was added MsCl (0.08 mL, 1.04 mmol). The solution was stirred at 0°C for 30 minutes. The reaction mixture was then diluted with EtOAc (5 mL) and HCl (1M, 1.0 mL) was slowly added followed by the addition of a saturated solution of $NaHCO_3$ (4 mL). The organic layer was removed and the remaining aqueous layer extracted with EtOAc (2 x 5 mL). The combined organic layers were washed again with a saturated solution of $NaHCO_3$ (3 mL) and dried with Na_2SO_4. The solution was then concentrated and the crude product purified by column chromatography (dry-pack, hexanes / ethyl acetate (1/1)) to yield **215** (0.10 g, 63%). ^1H NMR (200 MHz, $CDCl_3$) δ 7.22-7.05 (m, 10H), 5.26 (s, 4H), 2.91 (s, 6H) ppm.

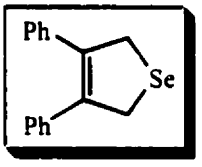
34) <u>Diphenacyl selenide</u> (220)



To a flame dried round bottomed flask charged with anhydrous diethyl ether (40 mL) was added under nitrogen, acetophenone (4.0 mL; 43.29 mmol) and selenium oxychloride ($SeOCl_2$) (1.18 mL, 17.32 mmol). The reaction mixture was then stirred overnight at room temperature and filtered. The gray white precipitate was washed with diethyl ether which provided α, α'-diphenacyl selenide dichloride (**219**) (6.06 g, 91%).

Compound **219** was added portion wise to a stirred two-phase solution of sodium dithionite ($Na_2S_2O_4$) (8.62 g, 49.51 mmol) in H_20 (100 mL) and benzene (100 mL) over a period of 30 minutes at room temperature. The benzene layer was removed and the remaining aqueous layer extracted with benzene (2 x 50 mL). The combined benzene layers were dried with Na_2SO_4 and concentrated. The crude product was subsequently purified by recrystallization from ethanol to yield pure **220** (3.81 g, 73%); m.p. 72-73 °C (lit. m.p. 72-73 °C)[178].

35) <u>2,5-dihydro-2,3-diphenylselenophene</u> (207)



A flame dried 3-necked round-bottomed flask, equipped with a reflux condenser and charged with zinc powder (0.62 g, 9.42 mmol), titanium tetrachloride (0.52 mL, 4.71 mmol) and anhydrous THF (12 mL) was refluxed for 15 minutes. A solution of diphenacyl selenium (**220**) (0.50 g, 1.57 mmol) in anhydrous THF was then added under nitrogen. The solution was then refluxed for 1 hour. The reaction mixture was then treated with a 10% K_2CO_3 solution (15 mL) and filtered. The filter cake was washed with diethyl ether (3 x 10 mL) and the organic layer removed and dried with Na_2SO_4. The crude product was purified by column chromatography (dry-pack, hexanes) followed by a second column (dry-pack, hexanes / toluene (85/15)) to yield pure **207** (0.44 g, 10%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20-7.02 (m, 10H), 4.28 (s, 4H), 2.91 (s, 6H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ: 138.15, 137.64, 128.69, 128.16, 127.07, 35.24 ppm; HRMS (EI) m/e Calcd for $C_{16}H_{14}Se$: 286.0260; Found: 286.0260.