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Organoselenium Chemistry

Modern Developments in Organic Synthesis

Volume Editor: Thomas Wirth

With contributions by
J. Drabowicz, M. Iwaoka, S. Kato, M. Mikołajczyk,
T. Murai, Y. Nishibayashi, C. Paulmier, S. Ponthieux,
P. Renaud, M. Tiecco, S. Tomoda, S. Uemura, T. Wirth

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Volume Editor

Dr. Thomas Wirth
Institut für Organische Chemie
Universität Basel
St. Johanns-Ring 19
4056 Basel, Switzerland
E-mail: thomas.wirth@unibas.ch

Editorial Board

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der Georg-August-Universität
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E-mail: ameijer1@uni-goettingen.de

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53121 Bonn, Germany
E-mail: voegtle@uni-bonn.de

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University of California
405 Higard Avenue
Los Angeles, CA 90024-1589, USA
E-mail: houk@chem.ucla.edu

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Institut de Chimie
Université de Strasbourg
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67008 Strasbourg Cedex, France
E-mail: lehn@chimie.u-strasbg.fr

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E-mail: sls@slsiris.harvard.edu

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Department of Chemistry
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Stanford, CA 94305-5080, USA
E-mail: bmtrost@leland.stanford.edu

Prof. Hisashi Yamamoto
School of Engineering
Nagoya University
Chikusa, Nagoya 464-01, Japan
E-mail: j45988a@nucc.cc.nagoya-u.ac.jp

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Preface

The pioneers of organoselenium chemistry realized that the chemistry of selenium-containing compounds offers multiple advantages over established methods. A wide range of reactions is possible, ranging from cationic, radical, and anionic transformations, to rearrangements and eliminations. Selenium-containing compounds can even be used as catalysts and ligands. The various findings in, and applications of, selenium chemistry has led, in recent years, to a tremendous growth which is reflected by the large number of publications in this field. However, the last comprehensive compilation of organoselenium chemistry appeared more than ten years ago. Embarking on a new millennium, we felt that there is a need for an update. I am grateful to the distinguished scientists who contributed, with their skill and expertise, the various chapters of this volume. By emphasizing the developments in organoselenium chemistry over the last number of years, this volume presents a comprehensive overview of the various facets, scope, and limitations of organic chemistry with selenium.

Basel, December 1999 Thomas Wirth

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Introduction and General Aspects

Thomas Wirth

Institut für Organische Chemie der Universität Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland. *E-mail: wirth@ubaclu.unibas.ch*

The development in organoselenium chemistry has been expanding rapidly over the last several years. The different reactivity of selenium-containing compounds in contrast to the sulfur analogs has led to versatile and new synthetic methods in organic chemistry. The principles of organoselenium chemistry are traced back to their origins. A survey on organoselenium compounds is combined with a short introduction to the various chapters of this book.

Keywords. New synthetic methods, NMR spectroscopy, Organoselenium chemistry, Selenium, Selenoenzymes

In 1817, Berzelius discovered the element selenium in the sludge of the lead chambers of the sulfuric acid chamber process of a plant at Gripsholm in Sweden [1]. He studied the properties and the inorganic compounds of this new element in detail. Organoselenium compounds have been known since 1847, when Wöhler and Siemens reported the first synthesis of ethyl selenol [2]. Therefore, selenium and its compounds are not exactly new for use in organic chemistry. In 1929 the first patent from I. G. Farbenindustrie AG for the use of selenium dioxide as oxidant in synthetic organic chemistry appeared [3]. Since that time, selenium dioxide has been known as a valuable reagent for oxidations and for the hydroxylation of slightly activated positions [4], and because of its volatility has been used in the purification process of elemental selenium [5]. A main source of selenium is the anode sludge deposited during the electrolytic refining of copper. Selenium is used in electronic devices as a photoconducting and semiconducting element, as a decolorizer of glass, in the pigments industry, in metallurgy, and as an essential micronutrient. Its production reaches several thousand tons per year.

In 1957 selenium was found to be an essential trace element [6]. Since that time, the biological properties of selenium have been investigated, and in 1973 the first selenoenzyme, glutathione peroxidase, was discovered [7]. This has led to a growing interest in the enzymology and the bioorganic properties of selenium [8].

It was not until 1970 that the formation of alkenes by decomposition of selenoxides was found to be a very versatile process proceeding under mild conditions [9]. Since that time, organoselenium chemistry has been focused on by organic chemists. The pioneering work of Sharpless et al. [10], Reich [11], and other research groups in the 1970s was accompanied first by reviews [12] and conference reports [13] on various aspects, followed by a rapid growth of organoselenium chemistry. This is reflected by a large number of publications

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dealing with organoselenium chemistry. Several books have been published in the 1980s on this topic as well [14] and a recent conference report highlighted the current activities in selenium chemistry [15, 16].

The various structures of organoselenium compounds are closely related to their sulfur analogs, but their properties are often quite different. Different bond lengths and bond strengths as well as a different electronic behavior lead to the difference in reactivity compared with homologous organochalcogen compounds. Reactions are possible which cannot be performed with organosulfur or organotellurium compounds.

Selenium forms weaker σ-bonds than sulfur and many reactions which involve the cleavage of such bonds are faster than for analogous sulfur compounds and proceed under milder reaction conditions. The *syn*-elimination of selenoxides was discovered in 1970 [9] and had a major impact on organoselenium chemistry. This reaction is about three orders of magnitude more rapid than the elimination of the corresponding less polar and less basic sulfoxides. Sigmatropic rearrangements proceed at markedly lower temperatures. These reactions are discussed in detail in Chap. 8 by Y. Nishibayashi and S. Uemura.

The homolytic cleavage of the carbon-selenium bond provides easy access to radicals, which can undergo various subsequent reactions. Radical chemistry using selenium-containing compounds is described by P. Renaud in Chap. 4.

The weak carbon-selenium bonds tune the reactivity of electrophilic selenium species as well. After the first publication in this area by Reich et al. in 1973 [17], intense activities can be recognized in this field of organoselenium chemistry. The versatility of electrophilic selenium species with respect to stereoselective synthesis is presented by M. Tiecco in Chap. 2.

The higher reactivity of organoselenium derivatives can also be observed in the various reactions of selenocarbonyl compounds which are described in detail by T. Murai and S. Kato in Chap. 7.

Selenium is more easily oxidized to Se(IV), but the oxidation stage Se(VI) is obtained with more difficulty than with the corresponding sulfur compounds. For example, selenuranes (tetracovalent selenium compounds) are more easily obtained than the sulfur analogs. The synthesis as well as the chemistry with selenium at higher oxidation stages is reviewed in Chap. 6 by M. Mikolajczyk and J. Drabowicz.

Organoselenium compounds are easily attacked by a nucleophile. Reaction with organolithium reagents allows a convenient synthesis of carbanionic species. C. Paulmier and S. Ponthieux describe this chemistry in Chap. 5.

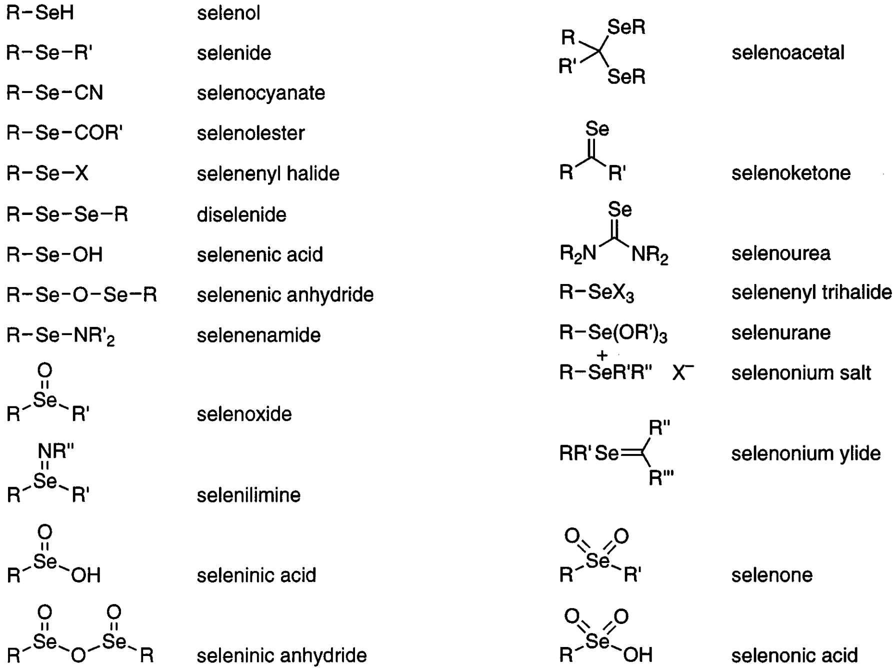
Selenides and selenolate anions are usually less basic and more nucleophilic than corresponding sulfur compounds. This unique property was recognized in 1973 by Sharpless and Lauer and used for the conversion of epoxides into allylic alcohols [18]. This publication can be regarded as another milestone in organoselenium chemistry. New aspects and a variety of other related reactions are summarized by M. Iwaoka and S. Tomoda in Chap. 3.

Because organoselenium compounds are more expensive than the corresponding sulfur compounds, there is an increasing use of only catalytic amounts of these compounds in a variety of reactions. This active area of research is summarized by Y. Nishibayashi and S. Uemura in Chap. 9.

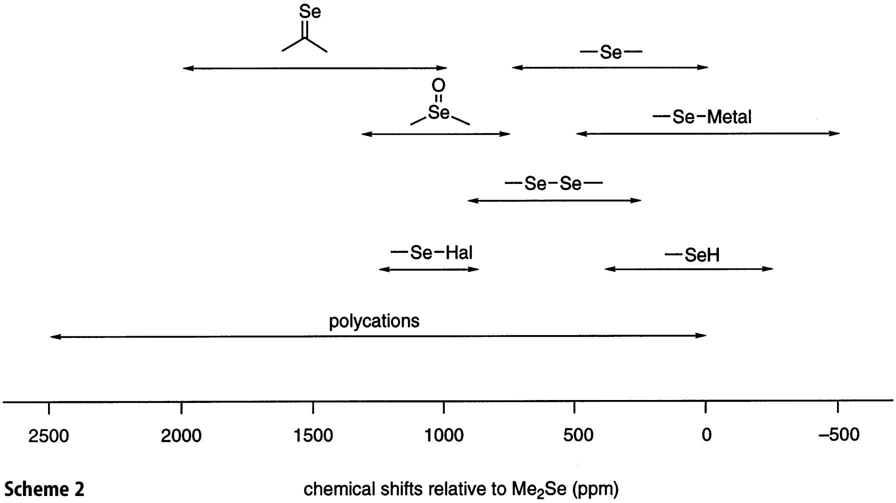
Organoselenium compounds can be efficiently introduced, manipulated, and removed in many different ways under mild conditions and usually in good yields. In Scheme 1 an overview is presented of different organoselenium compounds which are involved in the various transformations. Many of these organoselenium compounds and a variety of inorganic selenium compounds are commercially available. The synthesis of other reagents from commercially available starting materials is described in the respective chapters.

An important method for the characterization of selenium-containing compounds is ^{77}Se NMR spectroscopy. The ^{77}Se isotope has a natural abundance of 7.5% and its medium receptivity is about three times that of the ^{13}C nucleus. The first systematic NMR investigations on inorganic [19] and organic [20] selenium compounds were published about 30 years ago. The ^{77}Se resonances appear in a range of about 3000 ppm, making NMR spectroscopy a very sensitive tool for the analysis of selenium-containing compounds. Recently several compilations of ^{77}Se NMR data have been published [21]. In Scheme 2 some shifts of different selenium-containing compounds are indicated.

The several contributions to this volume focus on some selective aspects of organoselenium chemistry. Each contribution gives a critical survey discussing the most significant developments in the respective area over the last ten years. The conceptual presentation of the main principles as well as future research directions should also allow the non-specialist reader to understand the significant advantages of organoselenium chemistry over existing methodology.



Scheme 1



Scheme 2

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Electrophilic Selenium, Selenocyclizations

Marcello Tiecco

Istituto di Chimica Organica, Università degli Studi di Perugia, 06123-Perugia, Italy
E-mail: tiecco@unipg.it

The most important progress made in the last ten years in the production of new electrophilic selenium reagents as well as in their reactivity towards unsaturated compounds are presented and discussed. Several new selenium-promoted, ring-closure reactions are illustrated and the factors controlling the selectivity of the cyclization process are discussed. One-pot selenenylation-deselenenylation sequences, which occur using only catalytic amounts of the organoselenium reagents, are presented. Finally, the efficient asymmetric syntheses, which are carried out with the recently described chiral non-racemic electrophilic selenenylating agents, are also surveyed.

Keywords. Electrophilic selenium, Cyclization reactions, Catalytic processes, Chiral diselenides, Asymmetric syntheses

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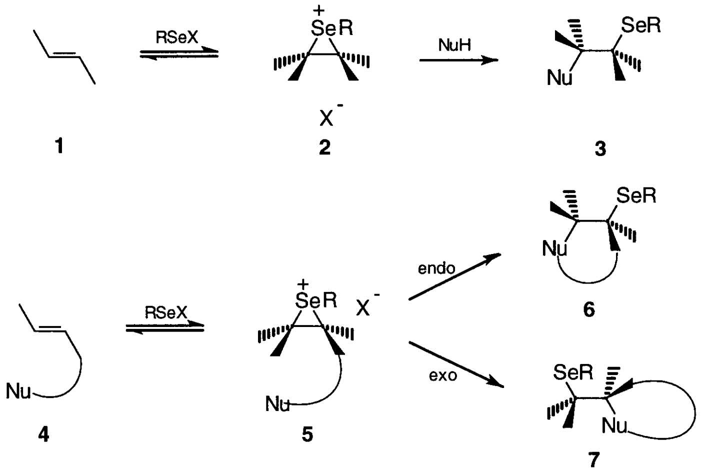
1
Introduction

Organoselenium compounds are now commonly employed as very useful and powerful reagents. They allow the chemo-, regio- and stereoselective introduction of new functional groups into complex organic substrates to be carried out under extremely mild experimental conditions. Selenium can be introduced as an electrophile, as a nucleophile or as a radical. Once incorporated, it can be directly converted into different functional groups or it can be employed first to favor further manipulation of the molecule and then eliminated in a later stage. In many respects the properties of organoselenium compounds are similar to those of the better known sulfur analogs. However, the introduction of the heteroatom, the manipulation of the resulting molecules and, in particular, the removal of the selenium containing functions occur under much simpler and milder conditions than those required for the corresponding sulfur compounds. The fundamental aspects of organoselenium chemistry have been described in excellent books and review articles that appeared some years ago [1–4]. Some review articles have also appeared more recently [5–8]. The scope of the present chapter is to illustrate the new aspects that have emerged in recent years in the field of addition reactions of electrophilic selenium reagents to carbon-carbon double bonds. The reactions of the electrophilic reagent RSeX with alkenes **1** (Scheme 1) are stereospecific *anti* additions which involve the formation of the seleniranium ion intermediates **2** and, in the presence of external nucleophiles NuH, afford compounds **3**. With unsymmetrical olefins the addition preferentially follows the thermodynamically favored Markovnikov orientation. In the case of alkenes **4**, holding suitably positioned nucleophilic groups, attack upon the seleniranium ion **5** takes place intramolecularly and the cyclic products **6** or **7** are thus formed.



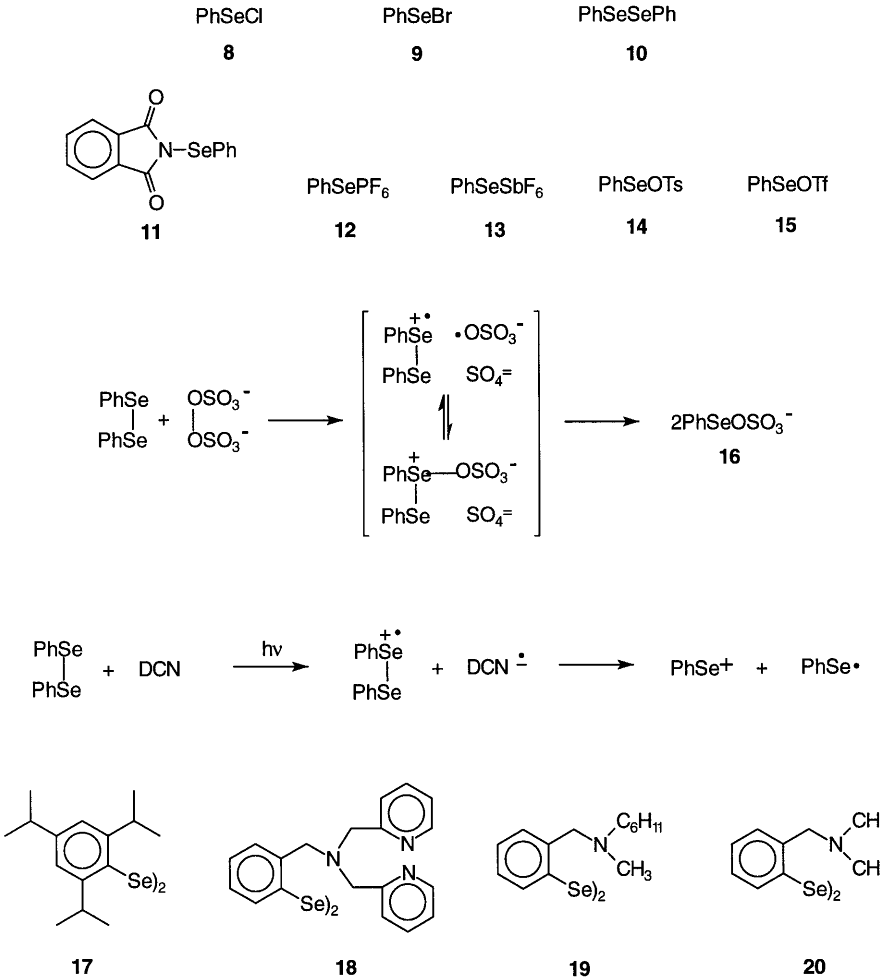
Scheme 1. Addition and Cyclization Reactions Promoted by Electrophilic Selenium Reagents

Several new procedures have been described for the production of the PhSeX which is the more commonly employed electrophilic reagent and which can be generated in the presence of different counterions. Moreover, more reactive and more selective electrophilic selenium reagents have also been prepared and investigated. Of particular interest are chiral, non-racemic selenium reagents that have been described recently and employed to effect asymmetric syntheses. In these cases, in fact, the stereochemistry of the new chiral carbon atoms which are generated in compounds **3**, **6** and **7** is controlled by the chiral reagent and diastereoselective addition and cyclization reactions are observed. The use of chiral selenium compounds in organic synthesis has been reviewed recently [9, 10].

Interesting new examples of stereospecific *anti* addition reactions across carbon-carbon double bonds have been described. However a considerably greater attention has been devoted to the study of the cyclization reactions. Factors governing the course of these reactions have been investigated and several new syntheses of important heterocyclic compounds have been described. A further interesting aspect, which emerged in recent years, concerns the possibility of effecting some functional group conversions with the use of only catalytic amounts of the electrophilic selenium reagent. The development of these catalytic processes and of the selenium promoted asymmetric syntheses probably represents the most important results, which have been reported recently in this field. Their conceptual and synthetic relevance considerably increases the importance of organoselenium chemistry.

2
The Production of the Electrophilic Reagents

The phenylselenyl moiety is the most common group used to introduce electrophilic selenium into an organic molecule. Most of the reagents employed are either commercially available, as for example PhSeCl **8** and PhSeBr **9**, or they can be easily produced either from **8** or from diphenyl diselenide **10**. Compounds **8** and **9** also are prepared from **10** by treatment with sulfuryl chloride or chlorine in hexane and with bromine in tetrahydrofuran, respectively. The appropriate choice of the reagent is necessary in order to ensure that a clean addition reaction can take place. In the cases of the addition reactions in the presence of external nucleophiles or in the selenium promoted cyclization reactions the use of phenylselenyl chloride or bromide give rise to some undesirable secondary processes such as the incorporation of the halide anions and the decrease in regioselectivity. For this purpose several new phenylselenenylating agents which do not contain nucleophilic counterions have been introduced (Scheme 2). Some of them were prepared from PhSeCl, like the *N*-(phenylseleno)phthalimide (*N*-PSP) **11** [11] or generated in situ, with silver salts, like the hexafluorophosphate **12** [12], the hexafluoroantimonate **13** [12], the tolylsulfonate **14** [13] or the triflate **15** [14]. In other cases the electrophilic reagent was produced in situ by the oxidation of diphenyl diselenide. Phenylselenyl sulfate (PSS) **16** is a very efficient electrophilic reagent, which is easily produced from the reaction of diphenyl diselenide with ammonium peroxodisulfate [15]. An electron transfer



Scheme 2. Common Electrophilic Selenenylating Agents

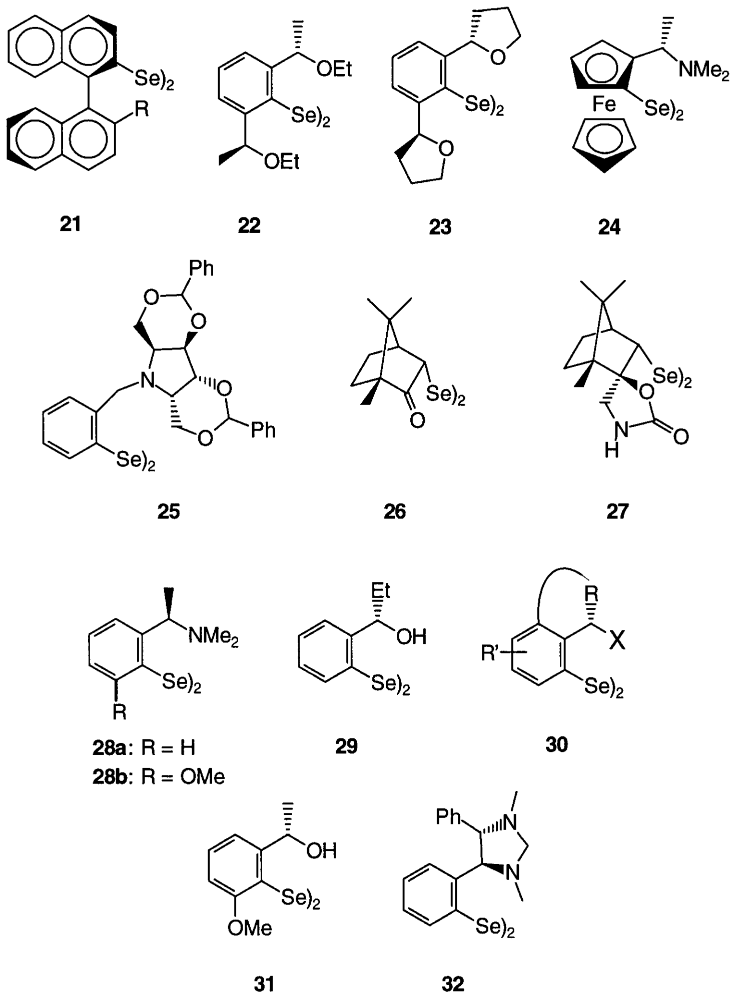
or an S_N2 reaction as suggested in Scheme 2 can initiate this process. The production of electrophilic phenylselenenylating agents from **10** can be effected with several other reagents. Thus, KNO_3 [15, 16], $CuSO_4$ [15], $Ce(NH_4)_2(NO_2)_6$ [15,17], and $Mn(OAc)_3$ [18] have all been successfully employed. Nitrogen dioxide [19], *m*-nitrobenzenesulfonyl peroxide [20], iodobenzene bis(trifluoroacetate) [21], iodobenzene diacetate [22] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [23] have also been proposed as oxidizing agents. The phenylselenyl cation (Scheme 2) can also be generated from the cleavage of the diphenyl diselenide radical cation produced by photosensitized single electron transfer from diphenyl diselenide to 1,4-dicyanonaphthalene [24]. The choice of one of these reagents is often dictated by the requirements of the particular addition reaction to be carried out. The two reagents which can be considered of general application for their efficiency and for the clean reactions to which they give rise are the phenylselenyl triflate **15** and sulfate **16**. This latter can be prepared more easily but it has the limitation that it cannot be employed at temperatures below –30 °C. An important and useful property of **16** is that it can be used to effect several conversions of functional groups using only catalytic amounts of diphenyl diselenide.

Diphenyl diselenides holding substituents in the phenyl ring have been prepared in order to alter the reactivity or the selectivity of the corresponding electrophilic reagents. Thus, (2,4,6-trisisopropylphenyl)selenium bromide, produced from the corresponding diselenide **17** by treatment with bromine, effected the ring closure of homoallylic alcohols to tetrahydrofurans with a stereoselectivity considerably higher than that observed with other phenylselenenylating agents [25]. The nitrogen containing diselenides **18**, **19** and **20** were employed to effect addition reactions to alkenes [26, 27] under catalytic conditions using copper nitrate and sodium persulfate as the oxidizing agents.

Very recently, using polystyrene beads, the preparation of some polymer-supported selenium reagents has been described by Nicolaou [28]. Polymer-bound selenium bromide and selenium phthalimide act as efficient selenenylating agents of alkenes. In view of their versatility and ease of handling these reagents can find useful applications in solid phase and combinatorial synthesis.

Several research groups have been deeply involved in the preparation of different types of optically active diselenides and in their in situ transformation into electrophilic selenenylating agents with one of the methods reported above. Examples of optically active diselenides are reported in Scheme 3. The first stereoselective electrophilic selenenylation reactions were reported by Tomoda [29] starting from the binaphthyl diselenide **21**. A few years later efficient selenenylating agents were produced from the C_2-symmetrical diselenides **22** and **23** which were described by Deziel [30]. The very interesting ferrocenyl diselenide **24** was prepared by Uemura [31] by metallation, treatment with elemental selenium and oxidative work-up. Compound **25** represents an example of a class of diselenides holding various chiral pyrrolidine moieties, which were prepared and employed in stereoselective syntheses by Tomoda [32]. Compound **26** was introduced by Back [33]. This is probably the most easily available chiral diselenide since it can be obtained on a large scale in a one-step preparation from camphor. Other camphor-based diselenides can be easily prepared from **26**. An efficient reagent is the diselenide **27** in which the carbonyl group has been converted into an oxazolidinone ring. A variety of structurally simpler diselenides were synthesized by Wirth [34]. Starting from the commercially available chiral precursors the diselenides **28** and **29** were simply prepared in a one-step synthesis consisting of the *ortho*-lithiation, reaction with elemental selenium and air oxidation. With this simple method a large number of diselenides having the general structure **30** ($X = NR''_2$, OR″) have been prepared. Particularly efficient electrophilic reagents were recently obtained from the diselenides **31** [35] and **32** [36] also described by Wirth.

A common characteristic of all these diselenides is the close proximity of a heteroatom (oxygen or nitrogen) to the selenium atom. It has been reported at several occasions that selenium can interact with nearby heteroatoms. In some

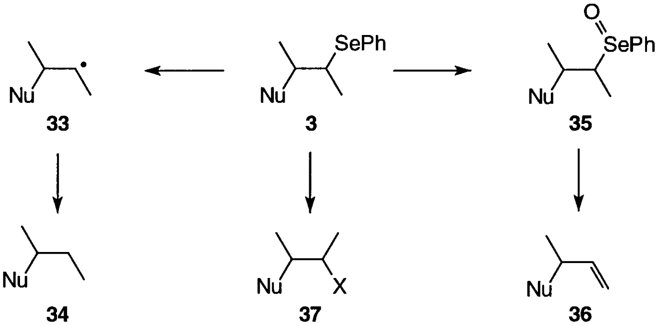


Scheme 3. Chiral Non-Racemic Diselenides

cases the existence of this interaction has been demonstrated by theoretical calculations as well as by crystal structure determinations and by NMR spectroscopic measurements [32e, 32f]. This interaction will force the chiral center to come close to the reaction center during the addition of the selenenylating agent to the alkene and this will result in asymmetric induction. Moreover, the same interaction should also dictate the structure of the active selenium reagent thus playing a fundamental role in forming the preferred diastereomer in the addition products 3.

3
Addition Reactions to Carbon-Carbon Double Bonds

There are relatively few direct applications of the additions of electrophilic phenylselenyl reagents to olefins. The great synthetic importance of these reactions is due to the fact that, because of the versatility of the selenium-containing moiety, the addition products **3** (Scheme 1) can be used as precursors for a series of useful transformations. In fact, the phenylseleno group can be removed in several ways leading to interesting derivatives in each case. By treatment with tin hydrides in the presence of AIBN, the homolytic cleavage of the carbon-selenium bond takes place and carbon radicals **33** are generated (Scheme 4). This opens the way to several interesting radical reactions. Alternatively, radicals **33** can effect hydrogen abstraction to afford the reduction products **34**. Oxidation of selenides **3** gives rise to selenoxides **35** from which the allylic products **36** are obtained by elimination. After conversion to selenones [37] by oxidation or to selenonium ions [38, 39] by treatment with PhSeX, the selenium moiety can react with various nucleophiles to afford the substitution products **37**. When optically active selenenylating agents are employed the addition products **3** are produced as a mixture of two diastereomers and their deselenenylation leads to enantioselective formation of compounds **34**, **36** and **37**. In some cases the two diastereomers can be separated and their deselenenylation thus produces enantiomerically pure compounds.



Scheme 4. Deselenenylation Reactions

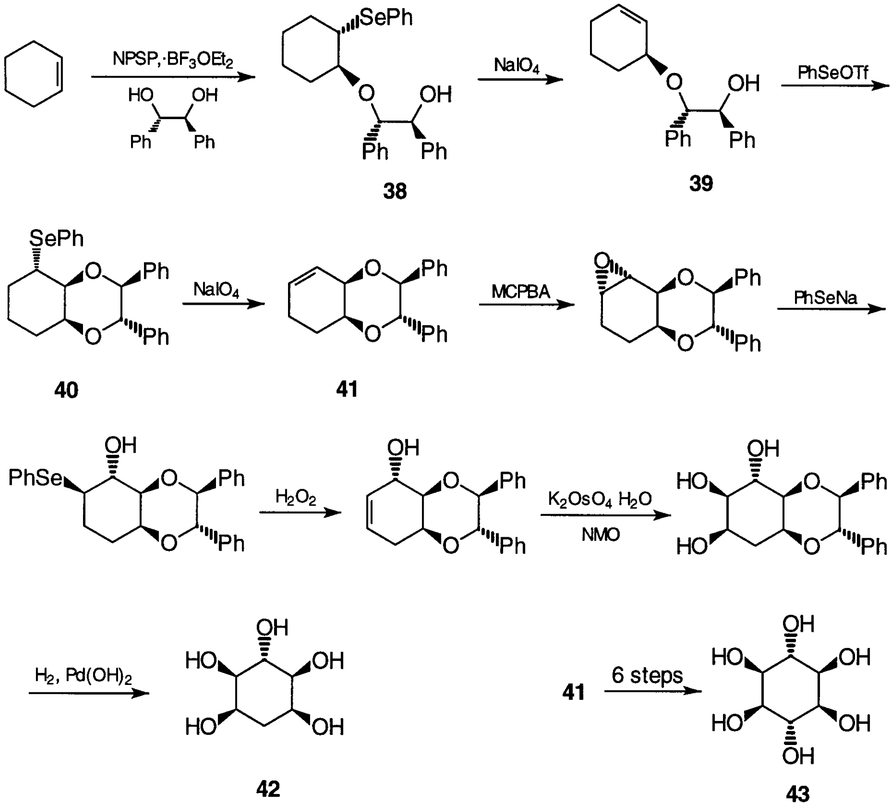
A limited number of new addition reactions has been described in recent years. These mainly concern reactions carried out in the presence of external oxygen (oxyselenenylation reactions) or nitrogen nucleophiles. On the other hand, oxyselenenylation reactions have been largely used as a probe to test the efficiency of the various chiral selenenylating agents.

3.1
Oxyselenenylation Reactions

The oxyselenenylation reactions, i.e. the stereospecific *anti* addition of an organoseleno group and of an oxygen nucleophile, such as an OH, OR, OCOR group, to an olefin are very useful and largely used procedures for the preparation of simple as well as complex molecules. Simple experimental conditions to effect efficient hydroxy-, alkoxy- or acetoxy-selenenylation of alkenes have already been described [1, 4] and are currently employed.

Engman reported that the acetoxyselenenylation of alkenes could be better carried out with PhSeBr in acetic acid in the presence of acetic anhydride and KNO_3 [40]. In the case of terminal olefins the addition proceeds with poor regiocontrol. However, when the chloroform solution of the two products was treated with catalytic amounts of boron trifluoride etherate, isomerization takes place and the anti-Markovnikov adduct was transformed into the Markovnikov product. The acetoxyselenenylation of alkenes can be cleanly effected also by oxidation of diphenyl diselenide with iodobenzene diacetate in acetonitrile [22].

An interesting application of sequential oxyselenenylation reactions was reported recently by Kim for the synthesis of biologically important cyclitols [41, 42]. Both, the stereochemistry and the regiochemistry of the sequential oxyselenenylation of cyclohexene, were controlled by the use of chiral diol hydrobenzoin as the nucleophile. Illustrated in Scheme 5 are the various steps employ-



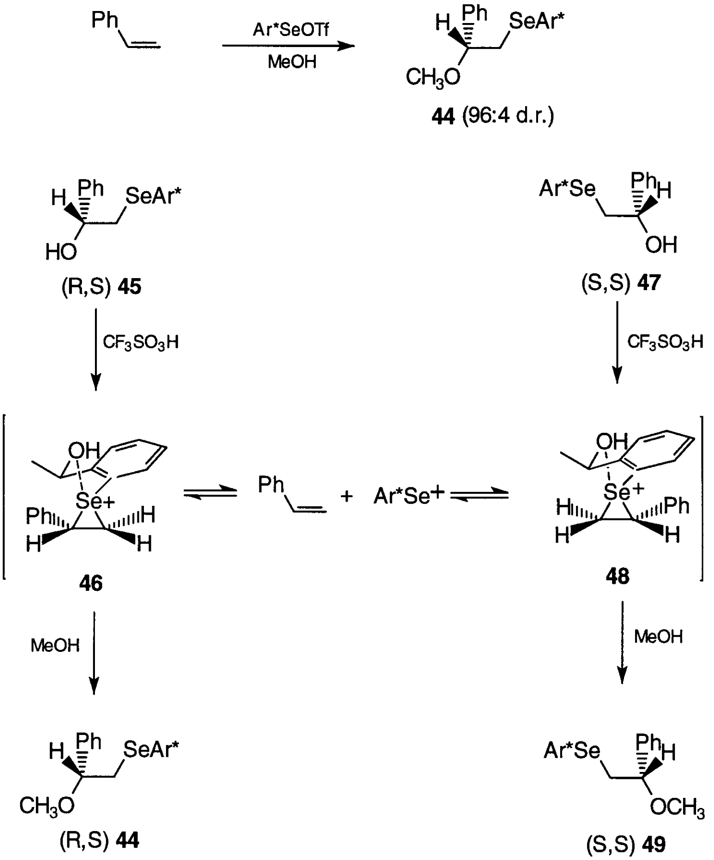
Scheme 5. Serial Oxyselenenylation Reactions. Synthesis of Cyclitols

ed for the synthesis of the important natural cyclitols *muco*-quercitol **42** and D-*chiro*-inositol **43** which shows physiological activity as an insuline mediator.

The reaction of cyclohexene with *N*-(phenylseleno)phthalimide in the presence of (*S*,*S*)-hydrobenzoin in methylene chloride afforded two diastereomeric oxyselenides (**38** and the (1*R*, 2*R*) diastereomer) in a 1:1 ratio. Compound **38** was separated and converted into the olefin **39** via selenoxide elimination. The second PhSeOTf promoted oxyselenenylation reaction gave only the *cis* fused bicyclic dioxane **40**. Oxidation and subsequent elimination provided the olefin **41**. This is the key intermediate for the syntheses of the cyclitols **42** and **43**, that were obtained from a series of classical reactions as indicated in the Scheme. Oxyselenenylation reactions have also been employed to promote glycosylation reactions [43].

3.1.1
Asymmetric Oxyselenenylation Reactions

Asymmetric oxyselenenylation reactions have been extensively employed to investigate the efficiency of the various chiral non-racemic selenenylating agents. In particular, the methoxyselenenylation of styrene has been studied with all the diselenides reported in Scheme 3. The mechanistic course of the methoxyselenenylation of styrene has been investigated in some detail by Wirth [44] using the selenyl triflate of diselenide **29**. Starting from the electrophilic reagent with the *S*-configuration, the two diastereomeric addition products were formed in a ratio of up to 96:4 and it was demonstrated that the newly generated stereocenter of the major diastereomer **44** (Scheme 6) has the (*R*)-configuration. This corresponds to a favored *re* attack of styrene. Since in the case of (*E*)-alkenes the formation of the seleniranium intermediates is the step determining the stereochemistry of the addition reactions [7, 29a] it can be said that the reaction of the alkene with the chiral selenium electrophile results in the preferential formation of one seleniranium intermediate. Competitive experiments demonstrated that the formation of the seleniranium intermediates is a reversible process; it follows that the preferential formation of one seleniranium intermediate over the other must reflect the difference of stability between them. Experimental evidences to support this interpretation were obtained by independently generating the seleniranium ions and by investigating their reactions with methanol. For this purpose the two optically active *β*-hydroxyselenides (*R*,*S*)-**45** and (*S*,*S*)-**47** were prepared [45] by reaction of the selenium anion produced from **29** with the (*R*)- or (*S*)-styrene epoxide. Protonation of **45** and **47** and a subsequent intramolecular S_N2 displacement by selenium generate the desired seleniranium intermediates. In the case of the intermediate **46**, corresponding to that formed by *re* attack of styrene, and which is assumed to be the more stable, the reaction with methanol gave the expected product (*R*,*S*)-**44**, without loss of stereochemical information at the benzylic carbon atom. In the case of the intermediate **48**, corresponding to the *si* attack of styrene, and assumed to be less stable, a mixture of (*S*,*S*)-**49** and (*R*,*S*)-**44** was obtained. This clearly indicates that some conversion of **48** into the more stable **46** occurred before reaction with methanol by a decomplexation-complexation mechanism as indicated in Scheme 6.



Scheme 6. Mechanism of Asymmetric Methoxyselenenylation of Styrene

The results obtained in the reactions of styrene with various electrophilic reagents derived from the diselenides indicated in Scheme 3 are illustrated in Table 1.

It can be observed that in several cases the addition reaction proceeds with excellent diastereomeric excesses. Although the reaction temperature, the solvent and the nature of the counter anion are different from case to case, nevertheless the data reported in the table can be used to have preliminary indications about the ability of the various electrophilic reagents to transfer the chirality to the newly generated stereocenters. The information gained from these experiments, however, must be used with caution since the stereoselectivity is also a function of the alkene employed and examples are known in which a reagent which gives unsatisfactory results with styrene can, in contrast, be efficient with other alkenes. This is clearly evident from the data reported in Table 2 in which the diastereomeric excesses measured for the reactions of the electrophilic reagents derived from the diselenides 24 and 26 with various alkenes are reported. In both cases the results obtained with other alkenes are much better than those observed with styrene.

Table 1. Asymmetric methoxyselenenylation of styrene

Diselenide	Counteranion	Conditions	*de* (%)	Yield (%)	Ref.
21	Br^-	MeOH, 25 °C	49	49	[29a]
22	TfO^-	Et_2O, –78 °C	77	88	[30a]
23	TfO^-	Et_2O, –78 °C	94	73	[30d]
24	TfO^-	CH_2Cl_2, –78 °C	35	97	[31d]
24	Br^-	CH_2Cl_2, 25 °C	97	21	[45]
25	PF_6^-	CH_2Cl_2, –78 °C	42	79	[32d]
26	SO_4^{2-}	CH_2Cl_2, 25 °C	30	91	[46a]
26	TfO^-	CH_2Cl_2, –78 °C	47	77	[33d]
28	TfO^-	Et_2O, 0 °C	10	64	[34b]
29	TfO^-	Et_2O, – 100 °C	89	81	[34b]
31	TfO^-	MeOH, –78 °C	98	55	[35]
32	TfO^-	Et_2O, – 100 °C	86	98	[36]
32	SO_4^{2-}	Et_2O, – 15 °C	86	74	[36]
32	SO_4^{2-}	Et_2O, 25 °C	76	95	[36]

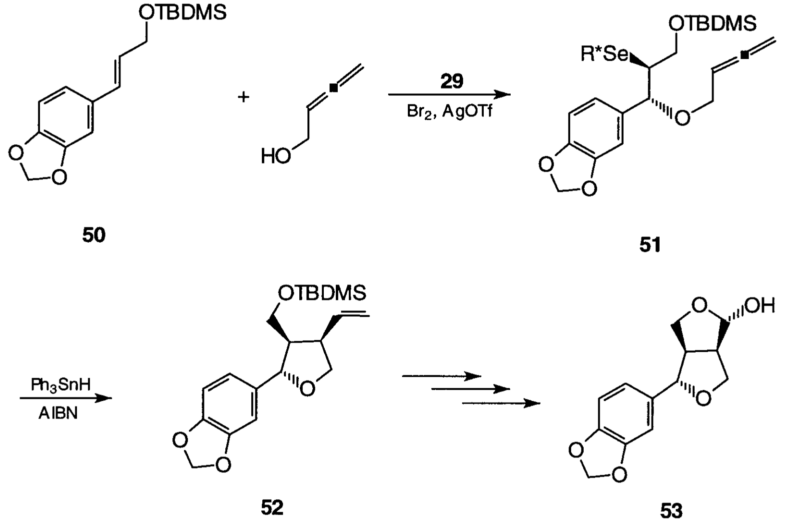
Table 2. Asymmetric methoxyselenenylation of alkenes

Alkenes	Diselenide **26**				Diselenide **24**			
	Anion	T °C	*de* (%)	Ref.	Anion	T °C	*de* (%)	Ref.
Styrene	SO_4^{2-}	25	30	[46a]	TfO^-	–78	35	[31d]
E-3-Octene	SO_4^{2-}	25	72	[46a]				
E-2-Butene	TfO^-	–78	74	[33d]	TfO^-	0	96	[31d]
β-Methylstyrene					TfO^-	0	96	[31d]
α-Methylstyrene	TfO^-	–78	66	[33d]	TfO^-	0	15	[31d]
Methyl styrylacetate	SO_4^{2-}	25	70	[46a]				
Methyl 3-hexenoate	SO_4^{2-}	25	80	[46a]				

Interestingly, the nature of the counter anion seems to have a considerable influence on selectivity and yield of the reactions. The effect of the counter anion on the course of the reactions of the electrophilic reagents derived from the diselenide **25** with *β*-methylstyrene, in methylene chloride and methanol at – 100 °C were investigated by Tomoda [32d]. The results obtained were as follows (counter anion, % yield and % *de* are given in the order): Br^-, 85, 52; ClO_4^-, 47, 80; TfO^-, 68, 89; BF_4^-, 67, 90; SbF_6^-, 64, 94; PF_6^-, 58, 95. On the basis of these results it was suggested that a decrease in the nucleophilicity of the counter anion, i. e. an increase in the electrophilicity of the selenium reagent, produces an enhancement of the *de* of the reactions. Similar observations were also made by Tiecco [46a] in the reactions of methyl styrylacetate, at room temperature in methanol, with the selenyl chloride, bromide, triflate and sulfate derived from **26** which gave the following yields and diastereomeric ratios: 49%, 40:60; 56%, 35:65; 77%, 42:58; 94%, 85:15. It is interesting to note that in the case of the sulfate the addition occurs with a facial selectivity different from that observed with the other counter anions. Similar changes in selectivity on passing from the bromide to the sulfate were also observed with styrene, α-methylstyrene, (*E*)-β-methylstyrene, (*E*)-4-octene and methyl (*E*)-3-hexenoate. No changes were observed with cyclohexene and cyclooctene.

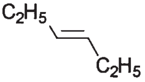
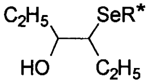
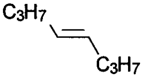
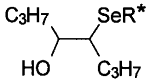
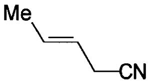
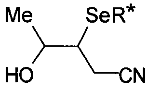
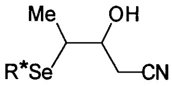
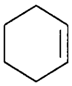
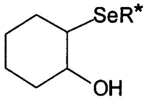
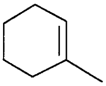
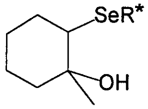
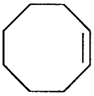
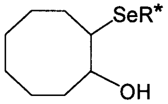
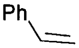
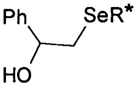
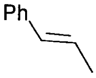
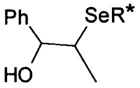
An interesting application of the asymmetric alkoxyselenenylation of alkenes to natural product synthesis was reported recently by Wirth, who described a short procedure to obtain some furofuran lignans [47]. The total synthesis of (+)-Samin **53** [47a] is shown in Scheme 7. The protected allylic alcohol **50** was treated with the selenyl triflate derived from diselenide **29** in the presence of 2,3-butadien-1-ol, and afforded the addition product **51** in 55% yield and with a diastereomeric ratio of 15:1. The favored *5-exo-trig* radical cyclization of the major isomer afforded the tetrahydrofuran derivative **52** from which the final product was obtained through few classical steps.

Quite recently, a new asymmetric addition reaction has been described by Tiecco. The oxidation of the diselenide **26** with ammonium persulfate produces the camphorselenyl sulfate, which reacts with alkenes in acetonitrile in the presence of water, to afford the hydroxyselenenylation products in good yields and with moderate to good diasteroselectivities [46b]. The results of these experiments are collected in Table 3. Moderate diastereomeric ratios were observed in the hydroxyselenenylation of cyclohexene, styrene and β-methylstyrene. Good facial selectivity was observed in all the other cases. The two diastereomeric addition products thus obtained could be separated in most cases. Enantiomerically pure saturated or allylic alcohols



Scheme 7. Total Synthesis of (+)-Samin

Table 3. Hydroxyselenenylation of alkenes with camphorselenyl sulfate, R^*SO_3H, in acetonitrile and water at 40 °C

Alkenes	Time (h)	Addition Products	Yield (%)	D. r.
	36		60	91:9
	39		89	94:6
	60		60	90:10
			10	90:10
	37		68	78:22
	31		75	90:10
	45		50	81:19
	28		68	65:35
	40		62	65:35

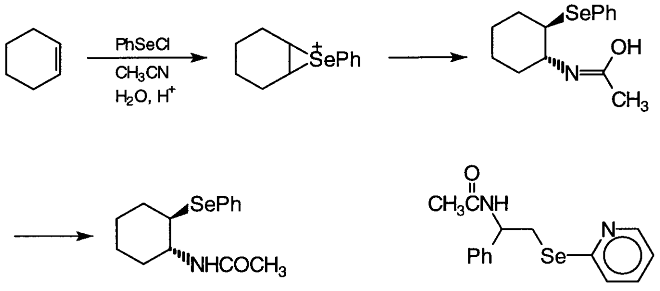
can be obtained by classical reductive or oxidative deselenenylation of the single isomers.

The behavior of the sulfate counter anion is noteworthy. A considerably important advantage in using sulfates is that the reactions can be effected at room temperature. From the data collected in Tables 1 and 2 it can be seen that in the methoxyselenenylation of alkenes the diastereomeric excesses thus obtained are comparable with those observed with other selenenylating agents, which, in contrast, required low reaction temperatures. The hydroxyselenenylation also was effected at 40 °C. This addition reaction represents a further advantage of the use of the sulfate counteranion. In fact, it seems rather difficult to find appropriate reaction conditions to obtain similar stereoselectivities with a selenenylating agent having a counteranion different from the sulfate. Finally, it will be shown in the following pages that with the use of the sulfate it is possible to effect several selenium catalyzed conversions. Of particular interest are the conversions catalyzed by chiral non-racemic selenium electrophiles.

3.2
Addition of Nitrogen Nucleophiles

Due to the important role of nitrogen functional groups, the addition reactions of an electrophilic selenium reagent and a nitrogen nucleophile to a carbon-carbon double bond represent a synthetically relevant process with potential practical applications. Among the reactions of this type which have been described already, perhaps the most important contribution is represented by the Ritter-type amide synthesis described by Toshimitsu and Uemura [48a, 48b]. The addition of a phenylselenyl and of an acylamino group to a mono or a 1,2-disubstituted olefin was accomplished by treating the olefin with PhSeCl in acetonitrile and water in the presence of trifluoromethanesulfonic acid.

The stereospecific conversion of cyclohexene into the corresponding amido selenide **54** is illustrated in Scheme 8. These amidoselenenylation reactions are commonly employed for the preparation of allylic and saturated amides by oxidative or reductive deselenenylation. Propionitrile, butyronitrile, benzonitrile and ethyl cyanoacetate may be used in place of acetonitrile. Styrene gave poor results and other electron-rich olefins such as 1-methylcyclohexene or 2,3-dimethylbut-2-ene did not give the amidoselenenylation products. The reaction can also be effected starting from the hydroxy- or methoxyselenenylation products of alkenes, in the presence of water and trifluoromethanesulfonic acid; in this case the nitriles are used in stoichiometric amounts [48c]. This methodology was employed to prepare the amidoselenenylation products of styrene, **55**, and of electron-rich olefins. It was necessary, however, to replace the phenyl-



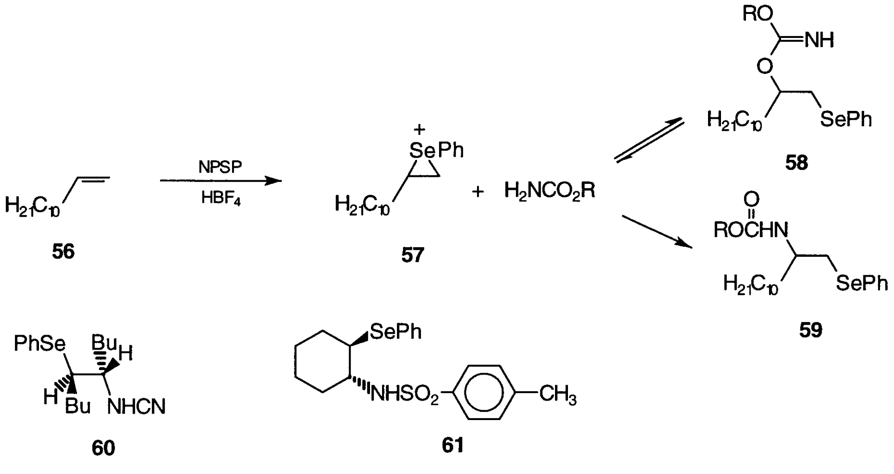
54 **55**

Scheme 8. Amidoselenenylation Reactions seleno with the 2-pyridylseleno group in order to increase the reactivity of the seleniranium intermediate [49].

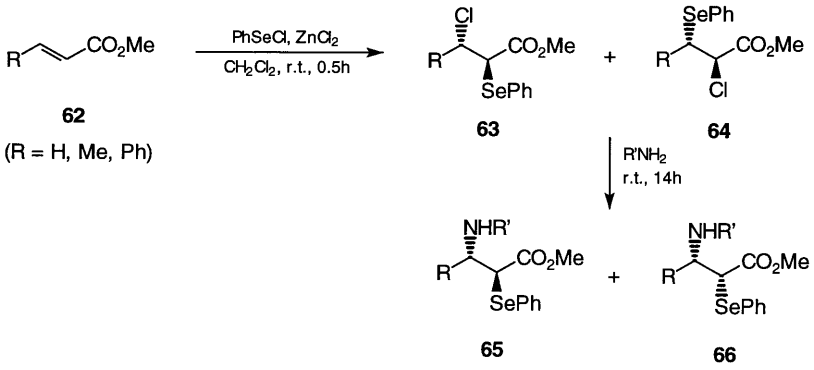
Other amidoselenenylation reactions have been described. Salazar [50] reported that the carbamatoselenenylation of alkenes can be effected using *N*-(phenylseleno)phthalimide, in the presence of tetrafluoboric acid, and ethyl carbamate as the nucleophile. The reaction is a stereospecific *anti* addition and works well with monosubstituted and 1,2-disubstituted alkenes. In the case of monosubstituted alkenes mixtures of regioisomers were obtained.

From a careful investigation of the reaction of dodec-1-ene **56** it was observed that, when the reaction temperature or the reaction time was diminished, the yields of the carbamatoselenenylation product **59** decreased and those of the oxyselenenylation product, derived from the hydrolysis of **58**, increased (Scheme 9). Owing to the ambident nature of the carbamate, compounds **58** and **59** can be formed by oxygen or nitrogen attack, respectively. The formation of the kinetically favored compound **58** seems to be reversible, whereas the nucleophilic attack by nitrogen on the seleniranium ion **57**, which produces the carbamatoselenenylation product **59** (and its regioisomer), seems to be an irreversible process under the reaction conditions employed. Similar good results were obtained when the same reactions were carried out with cyanamide as nucleophile. The cyanamidoselenenylation reaction worked well with mono-, di- and tri-substituted alkenes. Also in this case the addition was stereospecific and not regiospecific. Compound **60** was obtained from *trans*-dec-5-ene. It has also been reported that *p*-toluensulfonamide can be used as nucleophile in the reactions of alkenes with PhSeCl [51]. The reaction of cyclohexene afforded compound **61**.

Recently, Piancatelli has employed PhSeCl in the presence of zinc chloride to effect the stereospecific chloroselenenylation of electron-poor olefins such as ethyl maleate and fumarate, methyl acrylate and methyl vinyl ketone [52]. The addition occured with good regioselectivity also in the cases of the methyl esters of acrylic, crotonic and cynnamic acids **62** (Scheme 10). In the latter cases, if the



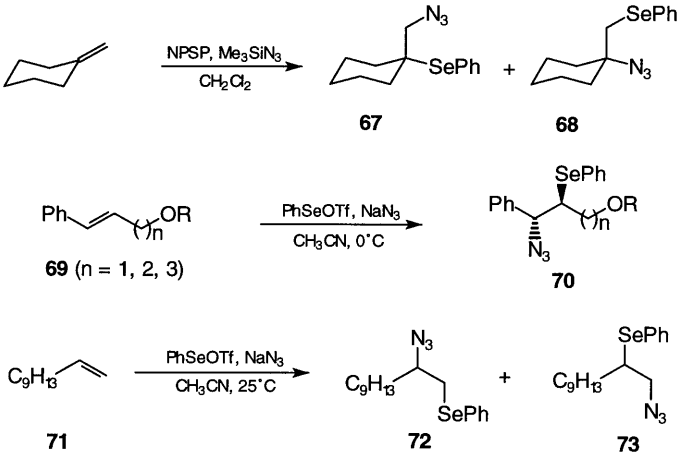
Scheme 9. Carbamato-, Cyanamido- and Sulfonamidoselenenylation of Alkenes



Scheme 10. Aminoselenenylation of Electron-poor Alkenes

reaction mixture was directly treated with a primary amine, the chloro derivatives **63** and **64** were directly converted into a *syn-anti* mixture of the two diastereomeric amino selenides **65** and **66** [53]. The entire process thus represents a convenient one-pot aminoselenenylation of alkenes.

One of the most important addition reactions which involves nitrogen nucleophiles is the azidoselenenylation of alkenes because both the azido and the phenylseleno group can give rise to several useful transformations. These compounds were first prepared by Krief from the reaction of alkenes with PhSeBr followed by sodium azide in DMF [54]. Direct azidoselenenylation of alkenes can be effected with PhSeCl and sodium azide in DMSO [55]. Under these conditions the reaction is stereospecific but it is not regiospecific. Similarly, the reaction of exocyclic alkenes with *N*-(phenylseleno)phthalimide and azidotrimethylsilane in methylene chloride (Scheme 11) gives rise to a 1:1 mixture of the regioisomers **67** and **68** [56].

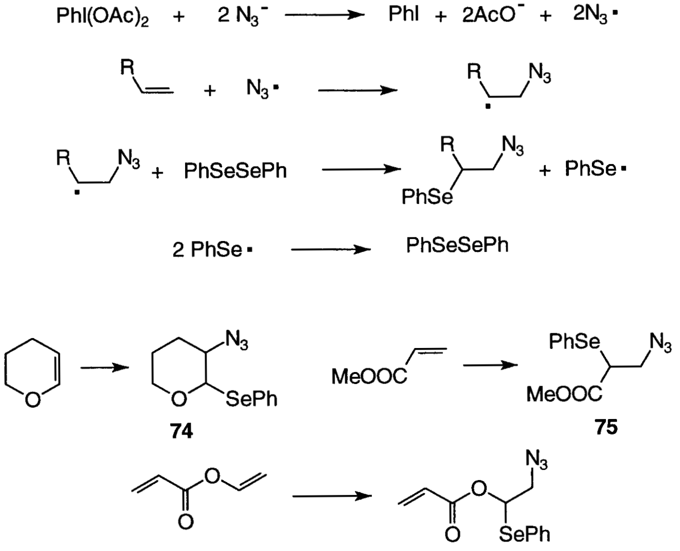


Scheme 11. Electrophilic Azidoselenenylation of Alkenes

Quite recently Tiecco reported that the electrophilic azidoselenenylation of alkenes can be effected with PhSeOTf and sodium azide in acetonitrile [57]. This reaction is a stereospecific *anti* addition in every case; the regiochemistry is instead determined by the structure of the starting alkene. Products **70** derived from phenyl substituted alkenes **69** were formed with complete regio- and stereoselectivity. Terminal alkenes gave, in contrast, a mixture of the two regioisomers; thus, for instance, 1-octene **71** afforded a 2:1 mixture of **72** and **73**.

The best experimental conditions to introduce a phenylseleno and an azido group to the alkene double bond are those which employ diphenyl diselenide, sodium azide and iodobenzene diacetate in methylene chloride. Under these conditions, however, the addition reaction occurs through the radical mechanism illustrated in Scheme 12 [58]. The addition therefore occurs with an anti Markovnikov orientation and it is not stereospecific. The reaction is initiated by the oxidation of the azido anion to the azido radical, which adds to the alkene to afford a carbon radical. This is trapped by the PhSeSePh to afford the final product and a PhSe radical, which dimerizes to give the diselenide.

Owing to its radical nature, this addition reaction can take place with different kind of alkenes. This is examplified in Scheme 12 in which the reaction products **74**, **75**, and **76** illustrate the regioselectivity and the chemoselectivity of the addition reaction with different substrates such as enol ethers, *α*,*β*-unsaturated esters and *α*,*β*-unsaturated vinyl esters.



74

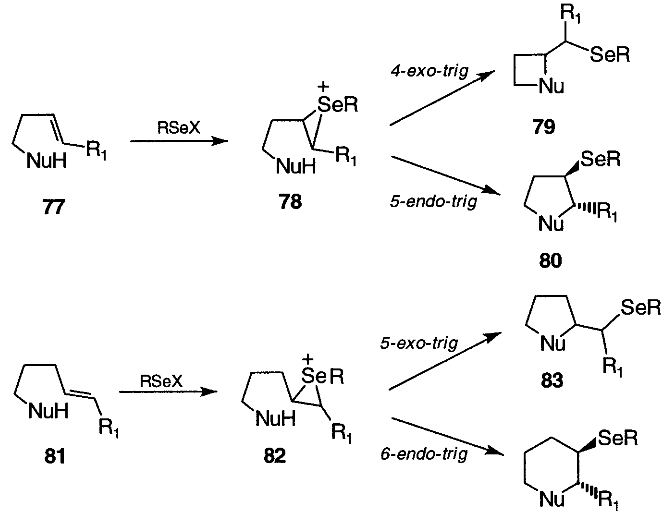
75

Scheme 12. Radical Azidoselenenylation of Alkenes **76**

4
Selenocyclizations

Owing to the great importance of heterocyclic compounds as final products or as reaction intermediates, several different methods have been described for their construction. Among the various kinds of ring forming reactions those based on the reaction of an electrophilic reagent with an alkene holding a suitably positioned nucleophilic group are certainly the most useful. The term of *cyclofunctionalization* was introduced by Clive [59] to describe this kind of process that can be promoted by several electrophilic reagents. The importance of the cyclofunctionalizations were outlined in an interesting and comprehensive review written by Cardillo some years ago [60]. The increasing popularity gained in recent years by selenium reagents to effect these ring closure reactions is due to the easy availability of the reagents, to the numerous chemical manipulations which can be effected on the selenium moiety before or during its removal, and to the mild reaction conditions required in the various steps. Selenium promoted cyclization reactions thus provide an easy access to a wide variety of heterocyclic compounds in general and to those containing oxygen and/or nitrogen heteroatoms in particular. Scheme 13 illustrates the possible ways of cyclization depending on the relative position of the nucleophile and of the double bond in the starting alkene. Optically active heterocyclic compounds can be prepared using electrophilic selenium reagents RSeX in which R is a chiral group.

Compounds of type **77**, passing through the seleniranium intermediates **78**, give rise to the four-membered cyclic compounds **79** which, according to Baldwin's rules [61], are the result of a *4-exo-trig* cyclization, or to the five-membered derivatives **80** as the result of a *5-endo-trig* cyclization. Only very few cases are known in which the cyclization affords a four-membered heterocyclic



Scheme 13. Selenium Induced Cyclofunctionalization Reactions

compound. Compounds **81** give rise to the seleniranium intermediate **82** from which a *5-exo-trig* or a *6-endo-trig* cyclization can form either **83** or **84**, respectively. The *4-exo-trig*, *5-exo-trig* and *6-endo-trig* cyclizations are favored, whereas the *5-endo-trig* is disfavored [61]. Nevertheless, several examples of *5-endo-trig* cyclization reactions, which occur with high stereoselectivity, have been reported recently in the literature. Knight [62] has suggested that the cationic nature of the reaction implies that this process should not be seen as a true exception to Baldwin's rules. The selenium promoted cyclofunctionalization process can also be applied to the synthesis of seven or larger membered heterocyclic compounds [63]. As indicated in Scheme 13, these ring closure reactions, like the intermolecular counterparts, are stereospecific *anti* additions.

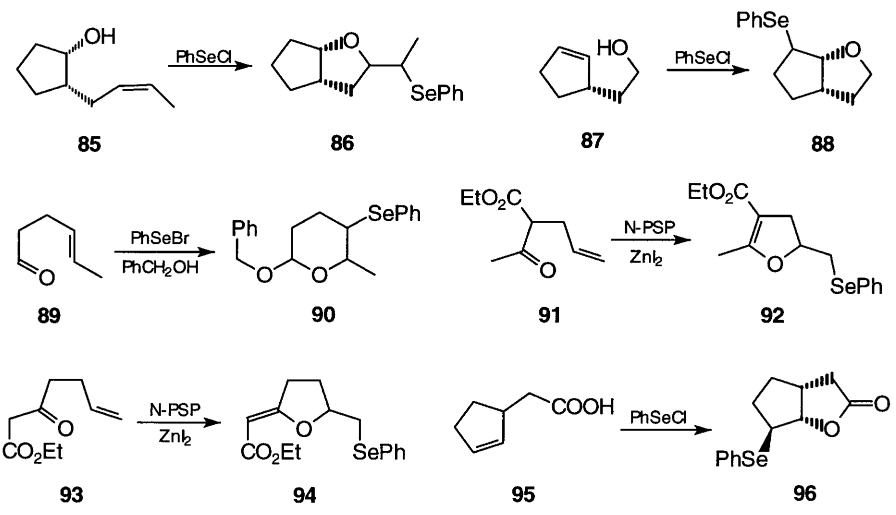
In the large majority of the examples reported in the literature the nucleophile tethered to the starting alkene is an oxygen or a nitrogen nucleophile and the cyclization process thus occurs through the formation of a carbon-oxygen or a carbon-nitrogen bond. Interesting competitive reactions can be observed when the nitrogen atom is incorporated in a functional group containing other nucleophilic atoms, which can also give rise to cyclization reactions. Examples are also known in which carbon nucleophiles can be used. These interesting ring closure reactions give rise to carbocyclic compounds.

4.1
Oxygen Nucleophiles

The cyclofunctionalizations of alkenes containing internal oxygen nucleophiles are the first and the most thoroughly investigated selenium promoted cyclization reactions. In the most common cases the oxygen atom can be that of an OH or of a COOH group. The corresponding cyclization reactions are usually referred to as selenoetherifications or selenolactonizations, respectively. These reactions have found wide application in synthesis, in particular in the construction of complex molecules and in the preparation of natural products. The results of the investigations carried out until about ten years ago have already been carefully described in some books and review articles [1–4, 60]. Some simple examples of these ring closure reactions are reported in Scheme 14.

The cyclizations of **85** to **86** and of **87** to **88** represent the simple cases in which the internal nucleophile is the OH group of an alcohol [64, 65]. An in situ generated hydroxy group, as in the addition of alcohols to carbonyl compounds, can also participate in phenylseleno-etherification reactions. This is examplified by the conversion of **89** into **90** in the presence of benzyl alcohol [66]. Another type of OH, which gives rise to these reactions is the enolic OH of β-dicarbonyl compounds. Thus, Ley reported that compounds like **91** and **93** can be transformed into the cyclic derivatives **92** and **94** by treatment with *N*-PSP **11** in the presence of zinc iodide [67]. The cyclization of **95** to **96** represents a simple example of the selenolactonization process [68, 69]. It is interesting to note that the various cyclization reactions indicated in Scheme 14, which require different electrophilic selenenylating agents, can all be effected with phenyselenyl sulfate [70].

A very interesting example of the synthetic utility of the selenoetherification reactions was reported by Metha [71] who described a very simple and

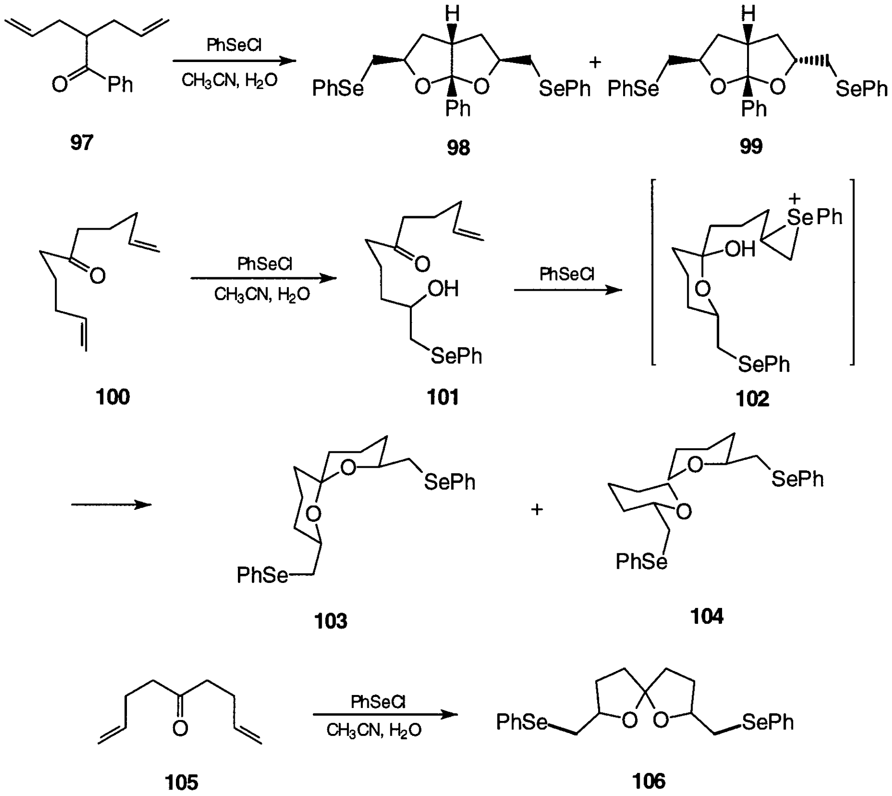


Scheme 14. Selenoetherification and Selenolactonization of Alkenes

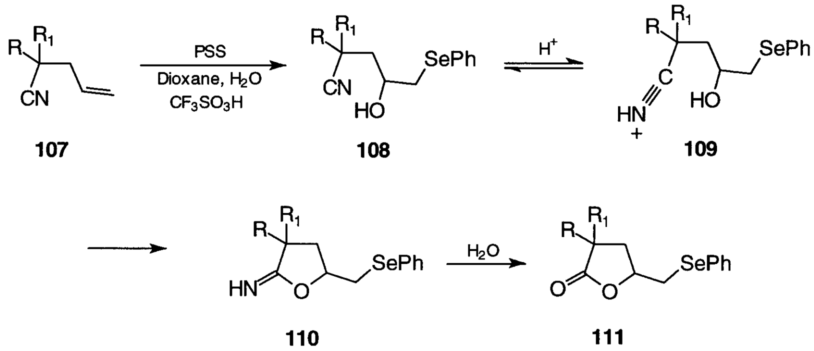
efficient conversion of dialkenyl ketones into several cyclic acetals of practical importance. Examples of these reactions are reported in Scheme 15. Treatment of compound **97** with PhSeCl in acetonitrile and water afforded a readily separable 1:1 mixture of **98** and **99** in good yields. The reaction conditions employed are those previously described by Toshimitsu [72] to effect the hydroxy-selenenylation of alkenes. Indeed, the cyclization reactions are proposed to proceed through an intermolecular and an intramolecular hydroxy-selenenylation in tandem. This is indicated in Scheme 15 for the cyclization of the undeca-1,10-dien-6-one **100**. The first step of the reaction produces the hydroxy selenide **101**. Intramolecular addition of the OH to the carbonyl group generates the nucleophile which traps the second seleniranium intermediate **102** and affords the spiroacetals **103** and **104** in a ratio of 30:70. Starting from the nona-1,8-dien-5-one **105** the five-membered spiroacetal **106** was obtained in good yield. The conversion of **97** into a 1:1 mixture of **98** and **99** was also effected by Pandey [24] by the photostimulated reaction of PhSeSePh with DCN in acetonitrile and water.

Also based on an intermolecular hydroxyselenenylation reaction followed by the addition of the OH to an unsaturated group is the selenium promoted conversion of alkenyl nitriles into lactones described by Tiecco [73]. Alkenyl nitriles **107** (Scheme 16) react with PSS **16**, generated from diphenyl diselenide and ammonium persulfate, in dioxane and water in the presence of trifluoromethanesulfonic acid, to afford the hydroxyselenenylation product **108** which is in equilibrium with the protonated molecule **109**. Intramolecular addition of the OH group give **110**, which is easily hydrolyzed to the final lactone **111**.

Electrophilic *5-endo-trig* cyclizations continue to be the subject of considerable research efforts by several groups. Interest has been focused on the stereoselectivity of the ring closure reactions of homoallylic alcohols to substituted



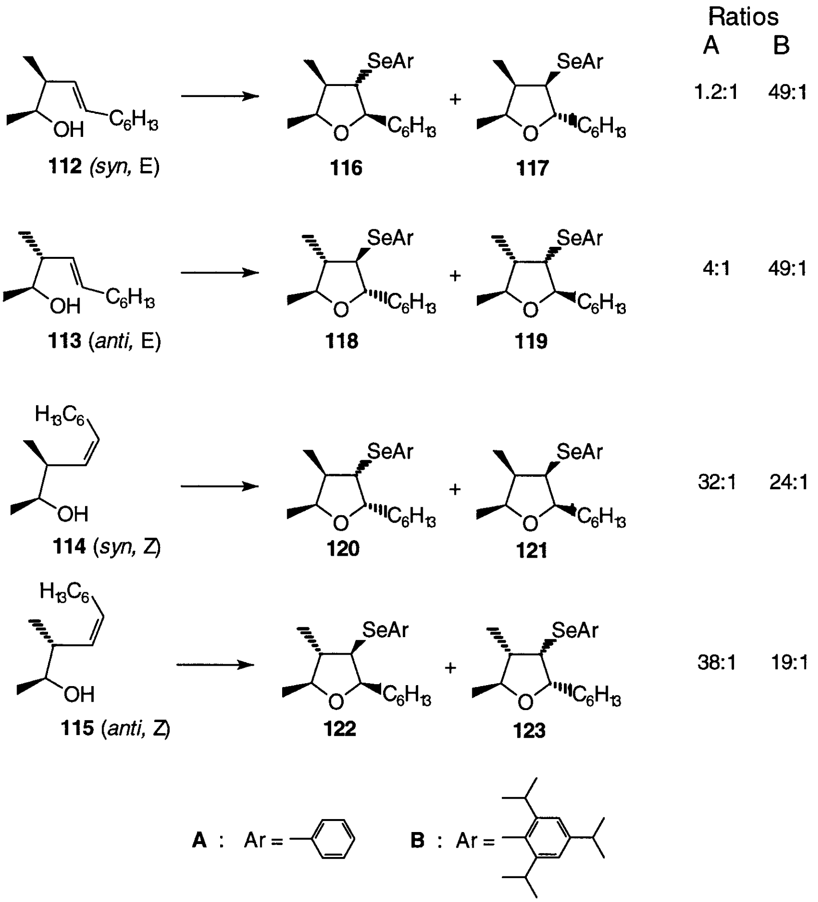
Scheme 15. Synthesis of Cyclic Acetals by Hydroxyselenenylation of Dialkenyl Ketones



Scheme 16. Selenolactonization of Alkenyl Nitriles

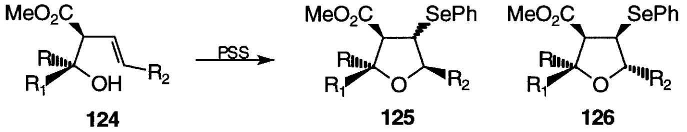
tetrahydrofurans [25, 74–77]. Scheme 17 summarizes the results obtained by Mihelich [74] in the cyclizations of the homoallylic alcohols **112**–**115** to the substituted tetrahydrofurans **116**–**123** carried out with *N*-(phenylseleno)phthalimide. Poor selectivities were observed in the cases of the (*E*)-olefins **112** or **113**, which afforded **116** and **117** or **118** and **119** in a 1.2:1 and 4:1 ratios, respectively. The cyclizations of the (*Z*)-olefins **114** and **115** were, in contrast, highly selective. The ratios of the two tetrahydrofurans **120** and **121** was 32:1 and that of **122** and **123** was 38:1. In all cases the favored product has an *anti* relationship of the phenyseleno group to the adjacent methyl.

With the aim of enhancing the stereoselectivity of this cyclization processes Lipshutz [25] used the (2,4,6-trisisopropylphenyl)selenium bromide derived from the diselenide **17**. The results of these reactions are also collected in Scheme 17. Interesting results were obtained with the (*E*)-olefins **112** and **113**,



Scheme 17. Stereoselectivity of the Cyclizations of Homoallylic Alcohols to Tetrahydrofurans Promoted by *N*-(Phenylseleno)phtalimide (A) and by (2,4,6-Trisisopropylphenyl)selenium Bromide (B)

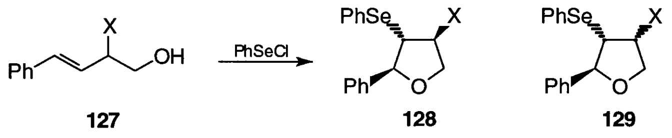
which now give the corresponding tetrahydrofurans with a ratio of 49:1 in both cases. The enhanced stereoselectivity realized with this new selenenylating agent has been explained on the basis of increased steric demands in the approach of the electrophile to the carbon-carbon double bond preferentially occurring away from the allylic substituent. A similar interpretation was also given by Tiecco [75] to explain the results obtained in the phenylselenyl sulfate promoted cyclizations of the 2-carbomethoxy-3-alkenols **124** into tetrahydrofuran derivatives **125** and **126** (Scheme 18). In all the cases investigated, the cyclization reactions preferentially gave compounds **125**, in which the phenylseleno group is in *anti* position with respect to the allylic carbomethoxy group. The ratios of the two stereoisomers varied from 10:1 to 19:1 depending on the nature of the substituents R, R_1, and R_2 as indicated in Scheme 18.



R	R_1	R_2	125:126
Me	Me	Et	13:1
Ph	Ph	Et	10:1
Ph	H	Et	11.5:1
Ph	H	H	11.5:1
Ph	H	Me	13:1
Me	H	Ph	19:1
H	Ph	Et	19:1
H	Ph	H	11.5:1
H	Ph	Me	13:1
H	Me	Ph	19:1

Scheme 18. Cyclizations of 2-Carbomethoxy-3-alkenols into Tetrahydrofuran Derivatives Promoted by Phenylselenyl Sulfate

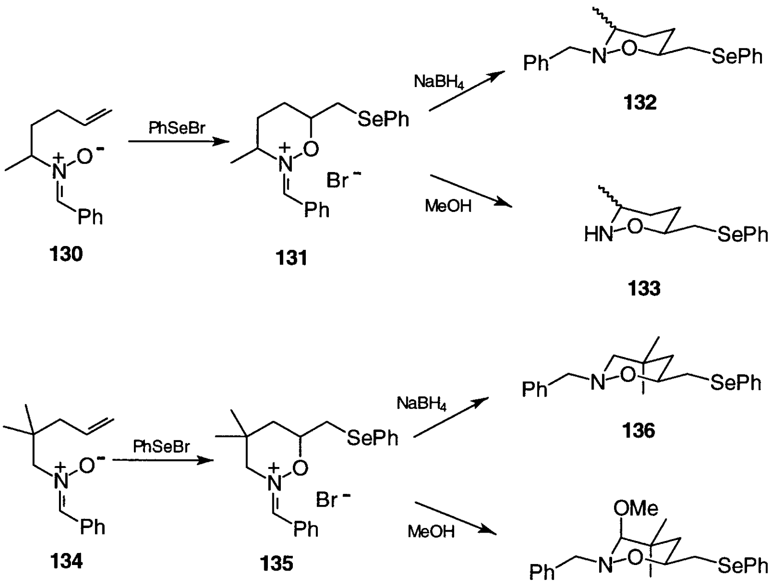
PhSeCl promoted cyclizations of several 2-substituted-3-alkenols **127** (Scheme 19) were investigated by Landais [76, 77] who found that the stereoselectivity of the ring closure reaction was strongly influenced by the nature of the substituents X. With substituents like OTIPS, NHPh, SPh or SO_2Ph the formation of the stereoisomers **128** was preferred, whereas compounds **129** were the major isomers when X was an OH, OEt, OCH_2CF_3 or an OPh group. It was suggested that steric and electronic effects of the substituents X determine the relative importance of the two conformations at the transition state leading to **128** or **129**. The experimental results can also be explained on the basis of a coordination which occurs between the incoming electrophile and the OH, OEt, OCH_2CF_3 and OPh groups favoring the formation of products **129**, in which the X and SePh groups have a *syn* relationship. Such a coordination has been suggested before to explain the selectivity observed in other *5-exo-trig* cyclizations [78].



X	128:129
OH	28:72
OEt	10:90
OCH_2CF_3	24:76
OPh	21:79
OTIPS	74:26
NHPh	74:26
SPh	73:27
SO_2Ph	87:13

Scheme 19. Cyclizations of 2-Substituted-3-alkenols into Tetrahydrofuran Derivatives Promoted by Phenylselenyl Chloride

A completely new cyclization reaction is the PhSeBr promoted conversion of alkenyl nitrones into 1,2-oxazines, which was recently reported by Tiecco [79]. This are the first examples to use alkenyl nitrones to effect ring closure reactions induced by electrophilic reagents. As indicated in Scheme 20, the nitrones **130** and **134** react with PhSeBr to give the cyclic iminium salts **131** and **135**, respectively. These intermediates suffer attack by nucleophilic reagents at the partially positive carbon atom. The nature of the final products depends on the structure of the starting nitrone and of the nucleophile employed. Thus, the intermediate



Scheme 20. Cyclization of Alkenyl Nitrones to 1,2-Oxazines **137**

131, in which the carbon-nitrogen double bond is exocyclic, reacts with sodium borohydride to afford the *N*-benzyl 1,2-oxazine **132**. On the contrary, treatment with methanol gives the 1,2-oxazine **133** and $PhCH(OMe)_2$ as the result of the methanolysis of the iminium salt. Compounds **132** and **133** were formed as a mixture of two stereoisomers in the ratio of 2:1 and 4:1, respectively. In both cases the major isomers were those in which the methyl group occupies an equatorial position. On the other hand, with intermediate **135**, in which the carbon-nitrogen double bond is endocyclic, the only reaction observed is the addition of the nucleophile at the positive carbon atom to afford compounds **136** and **137** which were formed as single stereoisomers.

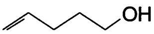
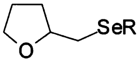
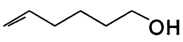
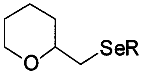
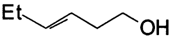
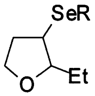
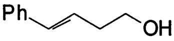
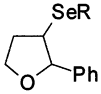
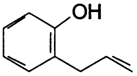
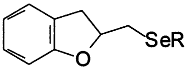
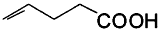
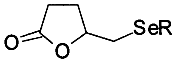
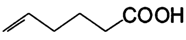
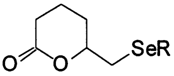
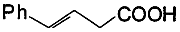
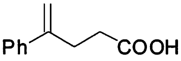
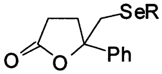
Asymmetric selenoetherification of unsaturated alcohols and selenolactonization of unsaturated carboxylic acids can be efficiently performed with chiral non racemic selenium electrophiles. This procedure represents a very convenient way to produce optically active heterocyclic compounds such as cyclic ethers and lactones. Nearly every research group working in the development of selenium promoted asymmetric syntheses has reported the use of these reagents in stereoselective selenocyclization reactions. Several selected examples of these cyclofunctionalization reactions, promoted by different selenium reagents, are reported in Table 4. This process seems to be of general application. Depending on the substituents linked to the carbon-carbon double bond and on the position of the nucleophilic OH and COOH groups, *5-endo-trig*, *5-exo-trig*, *6-endo-trig* as well as *6-exo-trig* ring closure reactions can all be easily effected. The cyclization reaction is a stereospecific process and its stereochemical course is similar to that described for the intermolecular oxyselenenylation reactions.

An examination of the data reported in the table indicates that excellent results can be obtained in most cases and that the nature of the nucleophile and the ring size of the formed heterocyclic compound have little influence on the facial selectivity observed. The last example reported in Table 4 refers to the interesting case of a 1,1-disubstituted alkene. The cyclization reaction proceeds with a good asymmetric induction to give a tetrasubstituted chiral carbon atom, which is not easily accessible by other methods [80].

4.2
Nitrogen Nucleophiles

The ring closure reactions of alkenes containing internal nitrogen nucleophiles, induced by electrophilic reagents, represent one of the best ways to produce nitrogen containing heterocyclic compounds [60]. The method is very versatile and allows a wide variety of heterocyclic structures to be constructed. Several new examples of this type of cyclofunctionalizations have been reported in recent years. The direct cyclizations of alkenyl primary amines have been rarely employed due to the side reactions usually associated with this process. Successful cyclizations can be effected starting from alkenyl amines which are *N*-protected with electron withdrawing substituents [70, 81–84, 62c] as indicated in Scheme 21 for the conversions of compounds **138** into the pyrrolidines **139**. The chiral pyrrolidine **141** was obtained by Wirth [80], in 40% and 45% *de*, from the asymmetric cyclization of **140** promoted by the selenenyl triflate deriving from

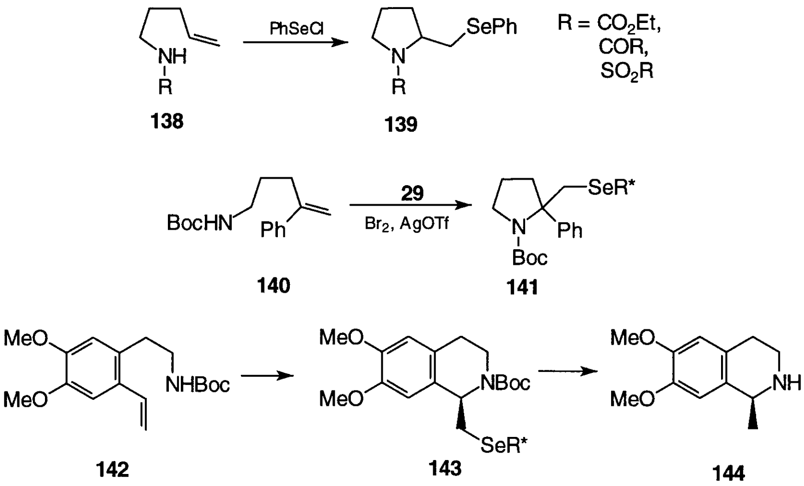
Table 4. % Yield and % *de* (in parentheses) of asymmetric selenoetherification and selenolactonization reactions using different diselenides

Alkene	Product	27^a $-95\,°C$, Cl^-	29^b $100\,°C$, TfO^-	24^c $-78\,°C$, Br^-	25^d $-100\,°C$ PF_6^-	23^e $-78\,°C$, TfO^-
		87 (68)		97 (95)	100 (22)	84 (91)
		96 (74)			80 (59)	
			60 (0)		86 (98)	
			87 (84)		88 (94)	92 (92)
		93 (84)		20 (95)	83 (13)	
		81 (90)		84 (95)	81 (57)	
		87 (82)		46 (87)	90 (39)	
			41 (72)		87 (92)	62 (99)
			58 (85)			

[a] Ref. [33c, 33e]. [b] Ref. [80]. [c] Ref. [31b]. [d] Ref. [32b, 32d]. [e] Ref. [30b,30d].

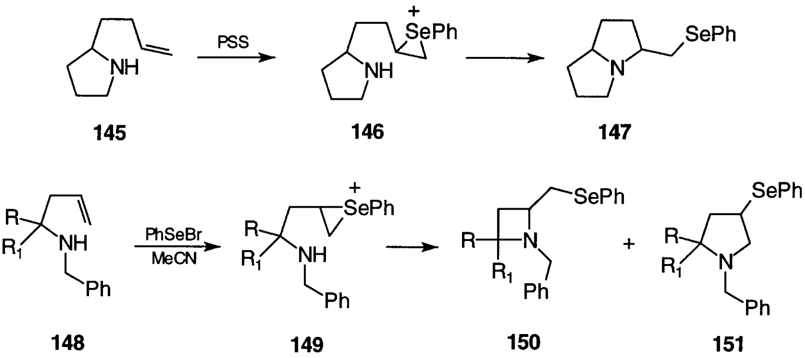
the diselenide **29**. The same reaction was applied by Wirth [85] to the synthesis of tetrahydroquinoline alkaloids. Cyclization of the Boc protected amine **142** afforded **143** with 90% *de*. Radical deselenenylation and deprotection of the nitrogen afforded (–)-salsolidine **144**.

Secondary alkenyl amines react normally with electrophilic selenium reagents and afford the expected cyclization products. The phenylselenyl sulfate promoted conversion indicated in Scheme 22 shows that alkenyl pyrrolidines



Scheme 21. Cyclization Reactions of Primary *N*-Protected Alkenyl Amines

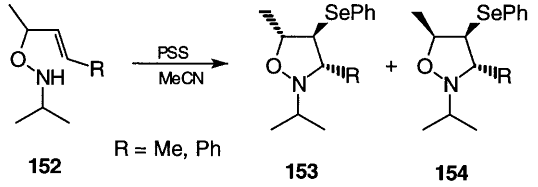
145 can be used to build up the pyrrolizidine nucleus 147 [23]. Quite recently, Paulmier [86] reported the first example of the formation of an azetidine ring from the PhSeBr or PhSeCl induced cyclization of homoallylic benzylamines 148 (Scheme 22). The seleniranium intermediate 149 can give rise to a *4-exo-trig* or to a *5-endo-trig* cyclization to afford the azetidine 150 or the pyrrolidine 151, respectively. As predicted by the Baldwin's rules [61], the *4-exo-trig* is favored over the *5-endo-trig* cyclization, but experimental evidence for the formation of 4-membered heterocycles is very scarce. The first clear-cut evidence is represented by the formation of 150. As the result of a detailed investigation carried out on several substituted homoallylic benzylamines and under different experimental conditions, it was found that 150 and 151 form through two competitive reactions and that the azetidine is favored by steric hindrance around the homoallylic carbon. As a matter of fact, when two substituents are present at the



Scheme 22. Cyclization Reactions of Secondary Alkenyl Amines

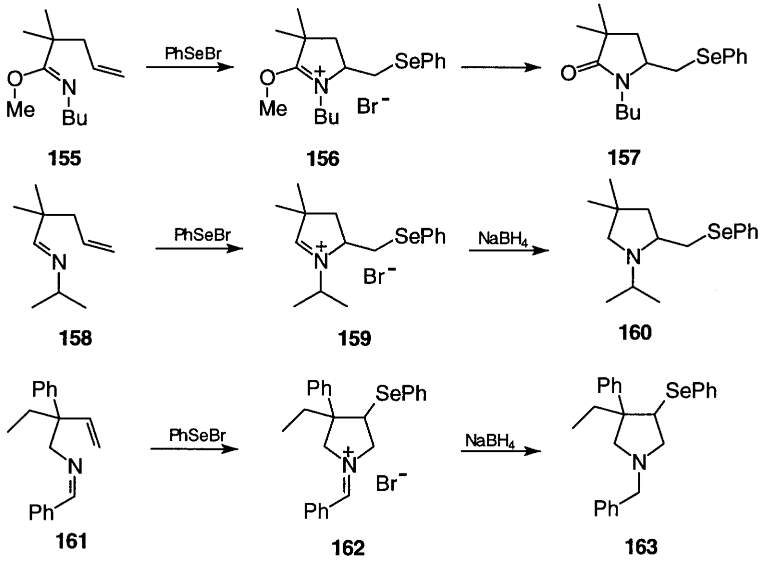
homoallylic carbon atom and the reaction is carried out in acetonitrile with PhSeBr, the azetidine **150** is the only reaction product.

Cyclization also occurs easily in the case of *O*-allyl hydroxylamines **152** (Scheme 23) which, on treatment with phenylselenyl sulfate **16**, afford *N*-alkyl isoxazolines in good yields [87]. The presence of a methyl group in the allylic position has no substantial effect on the stereochemical course of this *5-endo-trig* cyclization reaction, the two diastereomers **153** and **154** being formed in equal amounts.



Scheme 23. Cyclization Reactions of *O*-Allyl Hydroxylamines

The imino nitrogen atom is sufficiently nucleophilic to attack the carbon atom of the seleniranium intermediate. An interesting example of these reactions is the conversion of imidates into γ-lactams reported by Toshimitsu and Uemura [88–90] and by other authors [91, 92] which is illustrated in Scheme 24. The cyclization of **155** occurs through the formation of a carbon-nitrogen bond with the generation of the iminium salt **156**. The success of this reaction is due to the use of PhSeBr as the selenenylating agent. In this way, in fact, the bromine

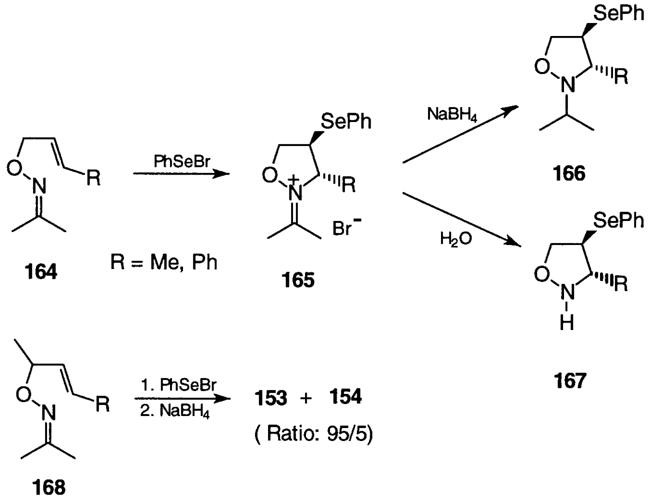


Scheme 24. Cyclization Reactions of Imidates and of Alkenyl Imines

anion can effect a nucleophilic substitution on the alkyl group of the iminium salt. The leaving group of this substitution is the molecule of the γ-lactam **157**.

Also reported in Scheme 24 are the PhSeBr promoted cyclization reactions of alkenyl aldimines described by De Kimpe [93, 94]. As indicated by the reactions of **158** and **161**, both, the *5-exo-trig* and the *5-endo-trig* cyclizations, can take place. The initially formed iminium salts **159** and **162** are converted into the corresponding pyrrolidines **160** and **163** by reduction with sodium borohydride. Compound **163** was obtained as an almost equimolecular mixture of two diastereomers.

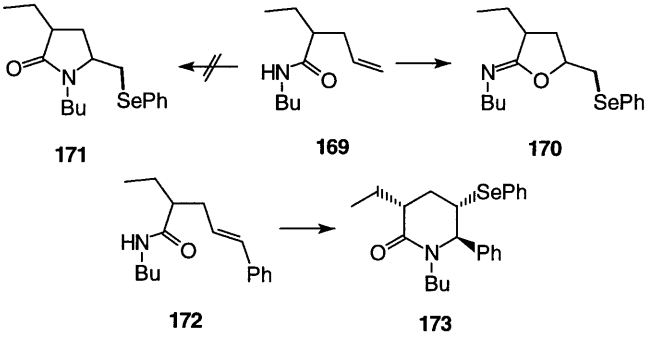
The same methodology was employed by Tiecco to effect the cyclizations of *O*-allyl oximes **164** indicated in Scheme 25. Treatment of the intermediate iminium salt **165** with sodium borohydride affords *N*-alkyl isoxazolidines **166** [95]. Alternatively, **165** can be treated with water to produce *N*-unsubstituted isoxazolidines **167** [96]. This synthesis of *N*-alkyl isoxazolidines represents a valid alternative to that described in Scheme 23. Moreover, the present cyclization reaction is much more stereoselective than the cyclization of *O*-allyl hydroxylamines. In fact, when the methyl derivative **168** was employed, the two isomeric isoxazolidines **153** and **154** were obtained in a ratio of 95:5. The same two products were, in contrast, formed in a 1:1 ratio when the reaction was carried out starting from the corresponding *O*-allyl hydroxylamines. Clearly, the steric requirements for the selenium-induced cyclization of the *O*-allyl oximes are much greater than those for the corresponding *O*-allyl hydroxylamines.



Scheme 25. Cyclization Reactions of *O*-Allyl Oximes

4.3
Competition Between Oxygen and Nitrogen

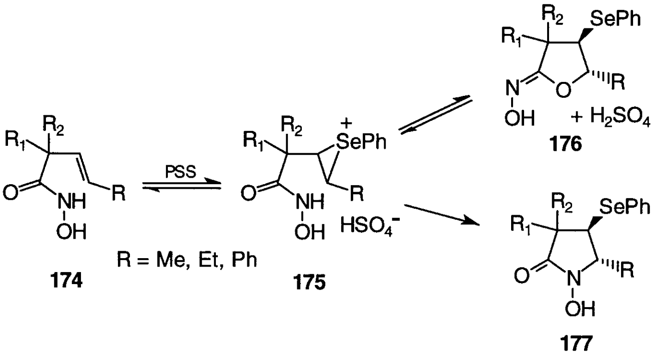
In all the examples reported so far, only the nitrogen atom can act as the nucleophile in the intramolecular capture of the seleniranium intermediates. We will now consider some interesting cases in which the nitrogen atom is incorporated in a functional group containing other nucleophilic atoms, which can give rise to competitive reactions leading to different heterocycles. In most cases, the course of the reaction is dictated by the structural properties of the starting unsaturated compounds. In several cases, however, a change in the experimental conditions can give rise to the formation of different products as the result of a kinetic or thermodynamic control of the reaction.



Scheme 26. Cyclization Reactions of Alkenyl Amides

The first class of compounds in which such a competition was observed is that of alkenyl amides. Toshimitsu [90] investigated the cyclization of the alkenyl amides promoted by PhSeCl or PhSeBr. Some of the results obtained are reported in Scheme 26. Compound **169** gave rise to a *5-exo-trig* ring closure reaction and afforded the imidate **170** derived from the trapping of the seleniranium intermediate by the oxygen atom. No evidences of the formation of the γ-lactam **171** were obtained. During work up, the imidate is easily transformed into the corresponding lactone. The presence of the phenyl group in **172** changes the regiochemistry of the addition reaction and a *6-endo-trig* cyclization takes place leading to the δ-lactam **173**. The reason is not clear why the *endo* cyclization of **172** proceeded by the nitrogen atom, while the *exo* cyclization of **169** proceeded by the oxygen atom. In general, however, in the cyclization reactions of unsaturated amides promoted by electrophilic reagents, the production of imidates like **170**, and hence of lactones, seem to be largely preferred. For the formation of lactams a strong electron-withdrawing group must be introduced on the nitrogen atom. Thus, carbamates, *N*-acyl amides, sulfonamides, etc. have all been employed. However, in order to facilitate cyclization by nitrogen atom attack, the use of a base is necessary in these cases. Another approach consists of the preliminary conversion of the amide into an imidate which, as we have already seen (Scheme 24), easily gives rise to the ring closure reaction using the non-bonding nitrogen electrons [60, 97]. Cyclizations of unsaturated amides promoted by several electrophilic reagents have been clearly described in a recent review [97].

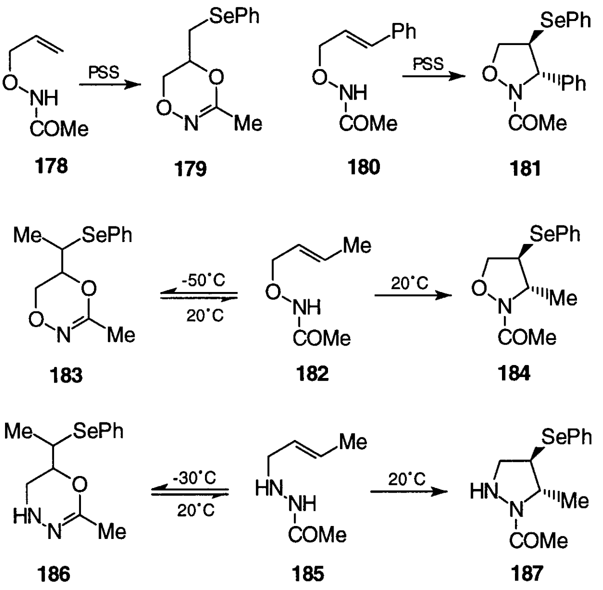
The phenylselenyl sulfate promoted cyclization of alkenyl hydroxamic acids reported by Tiecco [98], illustrates the interesting case in which the change of the experimental conditions has a substantial influence on the nature of the



Scheme 27. Kinetic and Thermodynamic Control in the Cyclization Reactions of Alkenyl Hydroxamic Acids

reaction products. As indicated in Scheme 27, the seleniranium intermediate **175**, derived from **174**, can be trapped by oxygen to afford the cyclic *N*-hydroxy imidates **176** or by nitrogen to afford *N*-hydroxy *γ*-lactams **177**. In the case in which R = Me or Et, the reaction at 20 °C gave **176**, while the reaction at 50 °C gave **177**. Moreover, the isolated compound **176** after warming at 50 °C for few hours, was completely transformed into **177**. The same kind of reactivity was observed with compounds **174** in which R = Ph. In this case, however, the reaction is faster and it was necessary to work at –20 °C or at 20 °C to cleanly obtain **176** or **177**, respectively. These data indicate that in these cyclizations the observed products can originate by the kinetic or the thermodynamic control of the reaction. The trapping of the seleniranium intermediate **175** by the more nucleophilic oxygen atom, leading to the imidates **176** is faster than the trapping by the nitrogen atom, which leads to **177**. However, under the conditions employed, the formation of the imidate is reversible. It is not unexpected that for the phenyl-substituted derivatives the reaction is faster than for the methyl or ethyl-substituted compounds.

A slightly different situation was encountered in the cyclizations of *O*-allyl hydroxamic acids [99]. The phenylselenyl sulfate induced ring closure reactions occur through the oxygen or the nitrogen atom as a function of the structure of the starting substrates and only in certain cases as a function of the experimental conditions employed. Thus, as indicated in Scheme 28, the unsubstituted *O*-allyl hydroxamic acid **178** in a *6-exo-trig* cyclization affords the 1,2,4-dioxazine **179**, whereas the phenyl derivative **180** in a *5-endo-trig* cyclization produced the *N*-acyl isoxazolidine **181**. The same two products were formed when the reactions were carried out at 50 °C or at –30 °C. Thus, in these cases the nature of the reaction products is governed by the structure of the starting products and the reactions take place with a Markovnikov orientation. On the contrary, the methyl derivative **182** gave the 1,2,4-dioxazine **183** at –50 °C and the *N*-acyl isoxazolidine **184** at 20 °C. This latter compound was also formed when the 1,2,4-dioxazine was warmed at 20 °C in the presence of acids. These data indicate that **183** is the product derived by kinetic control and that its



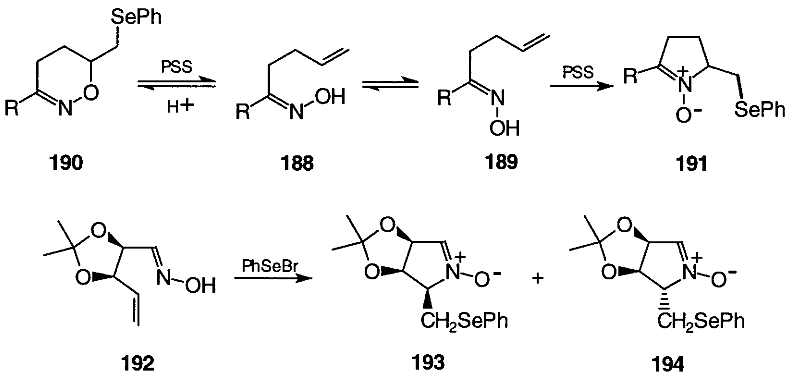
Scheme 28. Kinetic and Thermodynamic Control in the Cyclization Reactions of *O*-Allyl Hydroxamic Acids and of *N*-Allyl Acethydrazides

formation is reversible. Compound **184** is the product derived by thermodynamic control.

The reactions of the structurally related *N*-allyl acethydrazides **185** gave similar results [100]. As indicated in Scheme 28, at –30 °C the cyclization afforded the six-membered 1,3,4-oxadiazines **186** and at 20 °C gave the five-membered *N*-acetyl pyrazolidines **187**.

A different kind of competition is encountered in the selenium-induced cyclizations of alkenyl oximes, which were independently investigated by Grigg [101] and by Tiecco [15b]. In Scheme 29 it is indicated that, depending on the geometry of the starting oxime, one should obtain the 1,2-oxazines **190**, from **188**, or the cyclic nitrones **191**, from **189**. These experiments were carried out starting from a mixture of stereoisomeric oximes of known composition and it was observed that **190/191** ratios did not reflect the ratios of the starting isomeric oximes. The formation of the five-membered nitrones was preferred over the formation of the six-membered 1,2-oxazines and, if the reaction mixture was worked up after a few hours, the nitrones became the only reaction products. These data were explained on the basis of the observation that, under the experimental conditions employed, the formation of 1,2-oxazines is a reversible process and that the two starting oximes can interconvert [15b]. Thus, the whole process is shifted towards the formation of the thermodynamically more stable nitrones **191**.

This procedure has been used by Grigg as well as by other authors to synthesize nitrones as intermediates in the preparation of more complex molecules. An example is reported in Scheme 29. The oxime **192** was treated with PhSeBr and



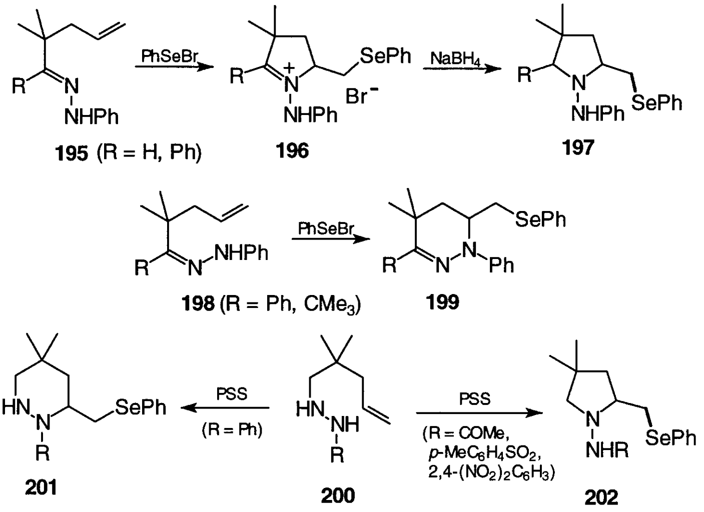
Scheme 29. Cyclization Reactions of Alkenyl Oximes

afforded a mixture of the two stereoisomeric nitrones **193** and **194** [102]. Nitrone **193** was employed in the synthesis of hydroxylated pyrrolizidines related to the natural alkaloid australine having important antiviral activity.

4.4
Competition Between Different Nitrogens

It was recently observed that the closely related alkenyl phenylhydrazones present a different behavior with respect to cyclization reactions [103]. An amino and an imino nitrogen are present in these molecules and it can be expected that both can give rise to cyclization leading to pyrrolidinamines (after reduction of the initially formed iminium salts) or to tetrahydropyridazines, respectively. The results obtained from the reactions carried out with PhSeBr are indicated in Scheme 30. In this case, under the conditions employed, no isomerization of the phenylhydrazone function takes place and the structure of the reaction products is strictly determined by the geometry of the starting alkenyl phenylhydrazone. Thus, in compounds **195** (R = H, Ph) it is the imino nitrogen atom which effects the trapping of the seleniranium intermediates and iminium salts **196** are produced. Reduction with sodium borohydride then gives the pyrrolidinamines **197**. In compounds **198** (R = Ph, CMe_3), on the contrary, cyclization occurs through the amino nitrogen atom and the tetrahydropyridazines **199** are produced.

Also summarized in Scheme 30 are the results of phenylselenyl sulfate promoted cyclizations of the alkenyl hydrazines **200** [104]. Depending on the nitrogen atom which acts as the nucleophile, the reaction can afford either the hexahydropyridazines **201** or the pyrrolidinamines **202**. It was expected that the substituent R could greatly influence the competition between the two nitrogen atoms in trapping the seleniranium intermediate. Starting from the alkenyl phenylhydrazine **200** (R = Ph) the cyclization afforded selectively the pyridazine derivative **201**. Substitution of the phenyl group with an electron-withdrawing substituent should decrease the nucleophilicity of this nitrogen atom thus

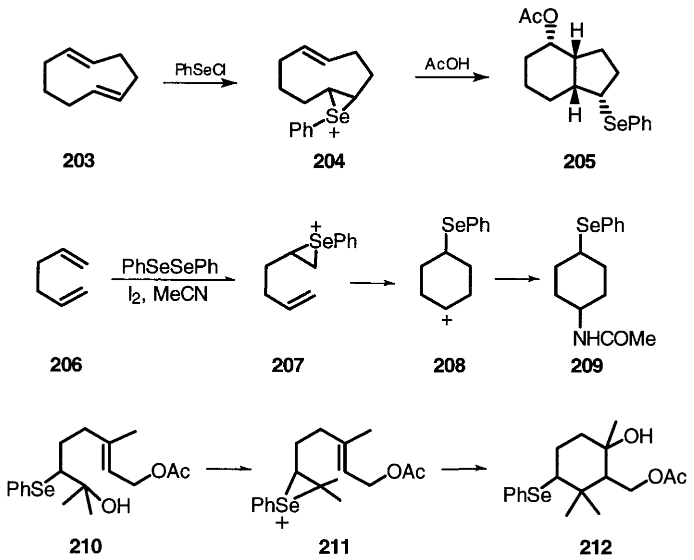


Scheme 30. Cyclization Reactions of Alkenyl Phenylhydrazones and of Alkenyl Phenylhydrazines

favoring the intervention of the other nitrogen atom and the formation of the pyrrolidinamine **202**. Indeed starting from the alkenyl acetylhydrazine **200** (R = COMe) the cyclization reaction afforded as the sole reaction product the pyrrolidinamine **202**. Similar results were also obtained with hydrazines in which R was a tosyl or a 2,4-dinitrophenyl group. With alkenyl ethoxycarbonyl hydrazines **200** (R = CO_2Et) the reaction was not selective and mixtures of the two cyclization products were obtained.

4.5
Carbon Nucleophiles

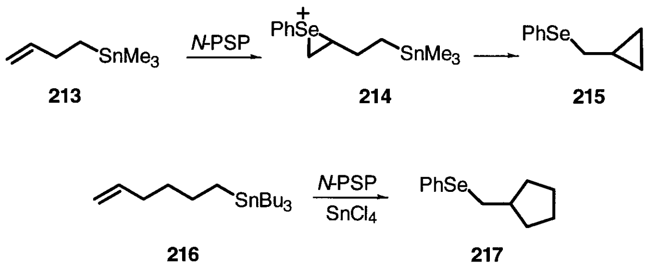
Carbocyclic compounds can be formed by the nucleophilic intramolecular capture of a seleniranium intermediate of an olefinic bond. The carbonium ion which is formed as intermediate can react with another nucleophile or with the solvent. The first examples of these carbocyclization reactions were observed with dienes. Clive [105] reported that the reaction of the diene **203** with phenylselenyl chloride in acetic acid afforded the intermediate **204** which reacted with the solvent to give the bicyclic compound **205** (Scheme 31). Carbocyclization reactions were efficiently promoted by phenylselenyl iodide produced by diphenyl diselenide and iodine. As indicated in Scheme 31, Toshimitsu reported that the reaction of 1,5-hexadiene **206**, in acetonitrile and water, afforded the acetamido cyclohexane derivative **209**, derived from the cyclization of the seleniranium intermediate **207** followed by the reaction of the carbocation **208** with acetonitrile [106]. In several cases, carbocyclization reactions can be more conveniently effected by independently generating the seleniranium intermediates. A simple procedure consists of the reaction of trifluoromethanesulfonic acid with β-hydroxyselenides, which can be easily obtained from the



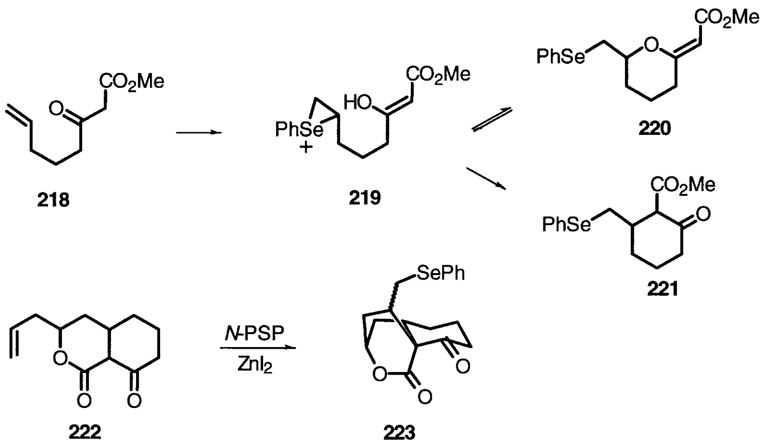
Scheme 31. Carbocyclizations of Dienes

nucleophilic opening of epoxides with sodium phenylselenolate [107]. Kametani [108] reported that the *β*-hydroxyselenide **210** (Scheme 31), deriving from the epoxide of the geranyl acetate, reacts with acids to give the seleniranium intermediate **211** which then affords the cyclization product **212**.

An interesting carbocyclization process was observed when alkenyl stannanes were treated with electrophilic selenenylating reagents containing a non-nucleophilic counterion. Thus, Nicolaou showed that compound **213** reacted with *N*-PSP **11** to form the intermediate **214** which then afforded the cyclopropane derivative **215** (Scheme 32) [109]. Further examples were reported by Herndon [110]. As indicated in Scheme 32, in the presence of tin tetrachloride, the stannane **216** was converted into the cyclopentane derivative **217**. This cyclization reaction proved to be quite general with respect to a variety of substitution patterns but it appears to be restricted to the formation of three- and five-membered ring.



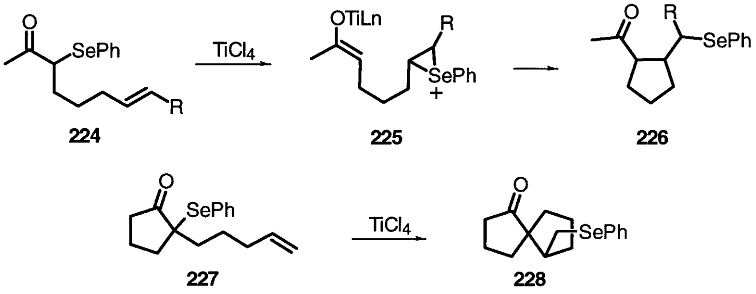
Scheme 32. Carbocyclizations of Alkenyl Stannanes



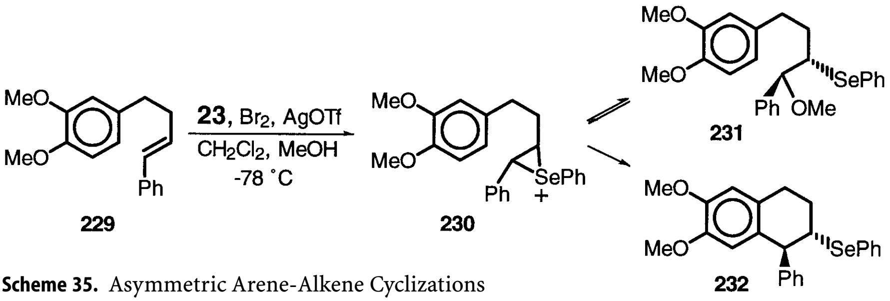
Scheme 33. Carbocyclization of Alkenyl 1,3-Dicarbonyl Compounds

Ley reported that selenium promoted carbocyclization reactions can also be effected by the enolic olefinic bonds of β-dicarbonyl compounds [111]. These reactions occur with *N*-PSP in the presence of zinc iodide, tin tetrachloride or aluminium trichloride. An example is reported in Scheme 33. In the intermediate **219**, derived from the β-ketoester **218**, cyclization through the oxygen atom to afford **220** is kinetically favoured. This reaction, however, is reversible, and upon prolonged reaction times and in the presence of strong acids the carbocyclization product **221** is formed. This procedure has been recently employed by Ley to effect the conversion of the alkenyl β-keto lactone **222** into the tricyclic selenide **223** (Scheme 33) which is a key intermediate in the preparation of model compounds with antifeedant activity [112].

In a related investigation Toru described carbocyclization reactions which occur by titanium tetrachloride promoted transfer of the phenylseleno group in α-phenylseleno alkenyl ketones [113]. As indicated in Scheme 34, the reaction of **224** with titanium tetrachloride produces the titanium enolate and the phenylseleno group adds to the carbon–carbon double bond. The intermediate **225** then



Scheme 34. Seleno-Transfer Carbocyclizations of α-Phenylseleno Ketones



Scheme 35. Asymmetric Arene-Alkene Cyclizations

gives rise to cyclization to afford the cyclopentane derivative **226**. Also reported in Scheme 34 is the reaction of the α-phenylseleno alkenyl ketone **227** that affords the spiro compound **228** with great stereoselectivity and in high yields.

An aromatic carbon atom of an electron rich benzene derivative can also trap seleniranium intermediates. Deziel has reported recently, that the reaction of **229** (Scheme 35) with the chiral selenyl triflate derived from the diselenide **23**, in methylene chloride and methanol, afforded a 1:1 mixture of compounds **231** and **232** [114]. These compounds are derived from the capture of intermediate **230** by methanol or by the aromatic carbon atom, respectively. The addition product **231** can be transformed into the cyclization product **232**, via the seleniranium intermediate **230**, by treatment with trifluoromethanesulfonic acid. The tetrahydronaphthalene derivative **232** was obtained with 70% yield in 98% diastereomeric excess.

5
Selenium Catalyzed Conversions

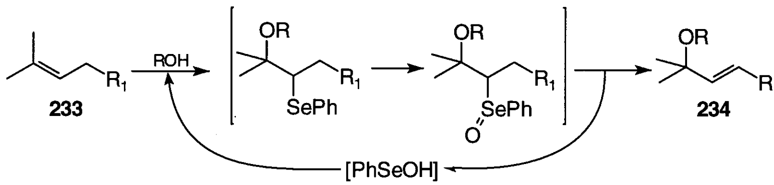
A typical conversion of functional groups, which is promoted by organoselenium reagents generally, requires several steps. Unless one of the few commercially available selenenylating agents is employed, the first step consists of the preparation of the appropriate reagent. Next, the reaction with an unsaturated compound, in the presence of an external or an internal nucleophile, affords the addition product which in most cases is not the final product but an intermediate which must be isolated and purified. Often the molecule is subjected to further manipulations that are favored by the presence of the selenium functionality. Moreover, since very few selenium containing compounds find practical applications, the deselenenylation of the molecule is required as the final step. The experimental conditions employed to effect this reaction are very important. In fact, depending on the method employed, the deselenenylation reaction can give rise to substitution or elimination products. In any case, if conditions can be found that the deselenenylation regenerates the electrophilic selenium reagent, which can restart the process, this multi-step conversion can be transformed into a one-pot procedure that, moreover, requires only catalytic amounts of the selenenylating agent or of its precursor. In recent years several research groups have investigated this important aspect of the organoselenium chemistry using different approaches. Several catalytic one-pot sequential selenenylation-deselenenylation reactions have been described already. The good results that have been obtained in most cases will certainly stimulate further research in this area.

5.1
One-pot Sequential Selenenylation and Deselenenylation Reactions

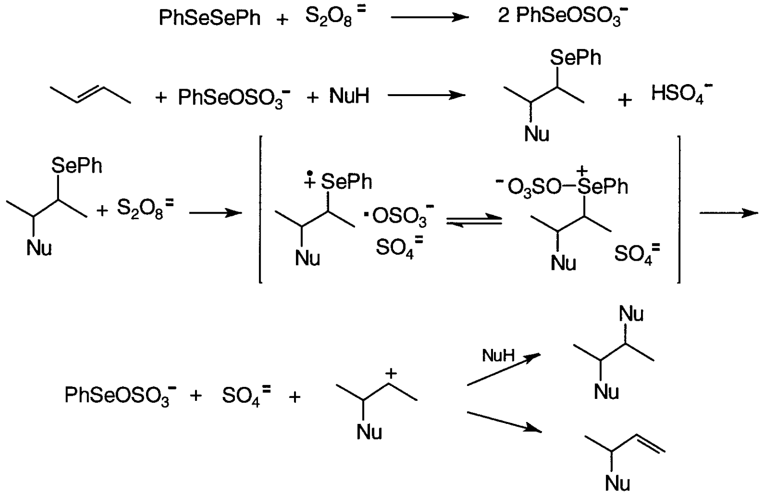
The first example of a catalytic approach to the selenium promoted conversion was reported by Torii, who described an oxyselenenylation-deselenenylation process using catalytic amounts of diphenyl diselenide [115]. The electrophilic species was produced from the diselenide by electrochemical oxidation in the presence of the alkene **233** in methanol or in water. As indicated in Scheme 36, the addition product is electrochemically oxidized to afford the selenoxide which by elimination gives the allylic ether or alcohol **234** and the phenylselenenic acid which continues the cycle by adding again to the alkene **233**.

A chemical method which does not involve selenoxides in the elimination step and which seems of more general application was introduced by Tiecco [116]. In the selenenylation reactions which were described previously and carried out with phenylselenyl sulfate, generated in situ by oxidation of diphenyl diselenide with ammonium persulfate, a small excess of diphenyl diselenide was always employed. It was observed that the alkyl phenyl selenides formed by intermolecular or intramolecular addition could react with ammonium persulfate suffering deselenenylation to afford the products of substitution or elimination and regenerate the phenylselenyl sulfate. It was suggested that, in a way similar to that proposed for the diphenyl diselenide and indicated in Scheme 2, by interaction with the persulfate, the alkyl phenyl selenides could give rise to the corresponding selenonium ions or selenium radical cations. These reactive species can suffer fragmentation to give the selenenylating species and a carbocation from which the substitution or the elimination products originate. It is also possible that, in some cases, carbocations are not involved and that the substitution or elimination products can be formed by the reaction of these intermediates with the nucleophile or with the base. On the basis of these observation Tiecco has developed a one-pot selenenylation-deselenenylation procedure using an excess of ammonium persulfate and only a

$$\mathrm{PhSeSePh} \xrightarrow[2\,\mathrm{ROH}]{-2e^-} 2\,\mathrm{PhSeOR} + 2\,\mathrm{H}^+ \quad (\mathrm{R} = \mathrm{Me, H})$$



Scheme 36. Electrochemical Catalytic Oxyselenenylation-Deselenenylation of Alkenes



Scheme 37. Sequential One-pot Selenenylation-Deselenenylation Reactions Catalyzed by Phenylselenyl Sulfate

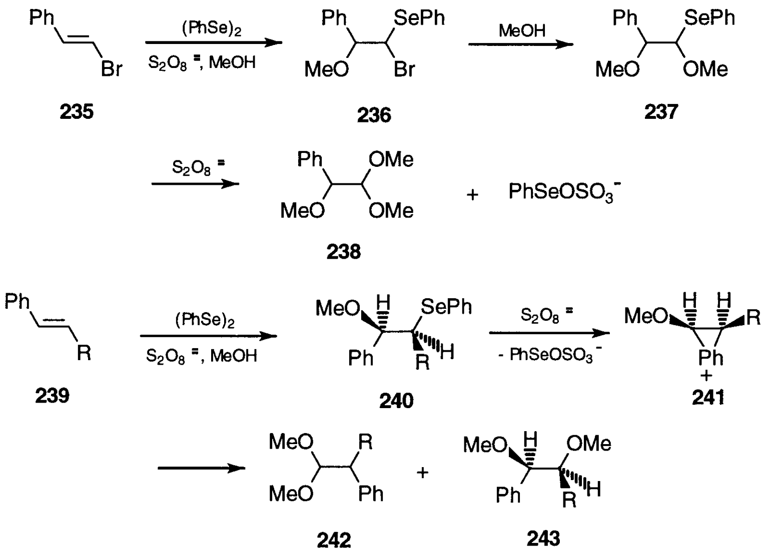
catalytic amount of diphenyl diselenide. The single steps of this procedure are reported in Scheme 37 in which carbocations are indicated as intermediates.

5.1.1
Deselenenylation with Substitution

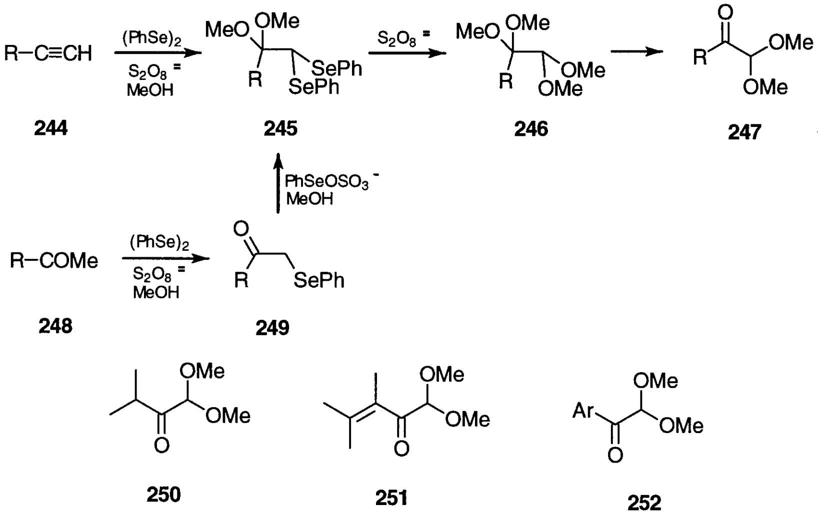
The first example of the use of the catalytic one-pot procedure described above, in which the deselenenylation occurs with substitution, is represented by the conversion of vinyl halides into α-alkoxy acetals [116]. This is illustrated in Scheme 38 in the case of β-bromostyrene **235**. The regioselective methoxyselenenylation affords the α-bromo selenide **236**, which undergoes a rapid solvolysis, through a selenium-stabilized carbocation to produce the selenide **237**. Oxidation of this alkyl phenyl selenide with ammonium persulfate produces an oxygen stabilized carbocation, which affords the final product **238**, and, at the same time, regenerates the selenenylating agent.

In a similar way, the styrene derivatives **239** were converted into the corresponding 1,1- and 1,2-dimethoxy alkanes, **242** and **243** (Scheme 38) [117]. The proposed formation of the intermediate phenonium ion **241**, from the reaction of the selenide **240** with the persulfate, explains the phenyl migration to give compounds **242** as well as the retention of configuration observed in 1,2-derivatives **243**.

A further interesting example is the conversion of the alkynes **244** (Scheme 39) into the α-ketoacetals **247** [118]. The reaction with phenylselenyl sulfate affords the product of double addition **245**, which is deselenenylated by the excess of persulfate to give the tetramethoxy alkane **246**. During work up deprotection occurs and compounds **247** are produced. The reaction occurs equally well with internal alkynes. Interesting enough, methyl ketones **248** reacted, under the same experimental conditions, to afford the same α-ketoacetals

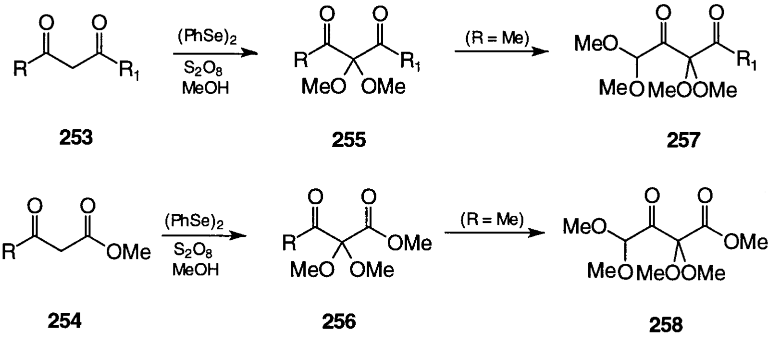


Scheme 38. Phenylselenyl Sulfate Catalyzed One-Pot Conversions of Vinyl Halides into Alkoxy Acetals and of Styrene Derivatives into 1,1- and 1,2-Dialkoxy Alkanes



Scheme 39. Phenylselenyl Sulfate Catalyzed One-Pot Conversions of Alkynes and of Methyl Ketones into Ketoacetals

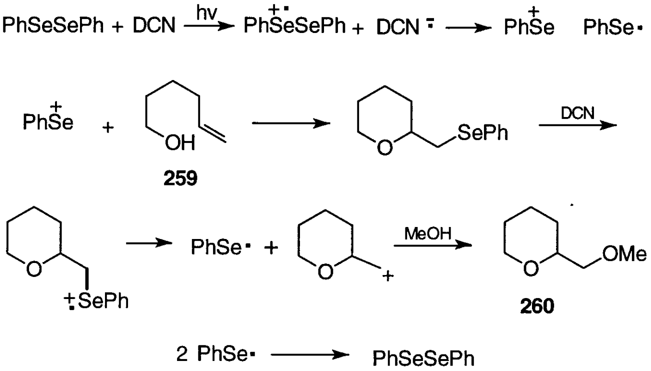
247 [119]. As indicated in Scheme 39, the initial process is the formation of the *α*-phenylseleno derivative **249** which gives a second addition reaction to afford products **245**, identical to those formed from terminal alkynes. This reaction seems to be of general application since alkyl, vinyl, and aryl methyl ketones give the *α*-ketoacetals of the type **250**, **251** and **252** with excellent results in every case.



Scheme 40. Phenylselenyl Sulfate Catalyzed One-Pot Conversions of Dicarbonyl Compounds into Vicinal Monoprotected Tricarbonyl and Diprotected Tetracarbonyl Compounds

β-Diketones 253 and *β*-keto esters 254, with the same procedure, were converted into the corresponding monoprotected vicinal tricarbonyl compounds 255 and 256, respectively (Scheme 40) [120]. Whenever the group linked to ketonic carbonyl was a methyl (R = Me), the diprotected vicinal tetracarbonyl compounds 257 and 258 were produced. The formation of these products represents a further example of the easiness with which the MeCO group is converted into the *α*-keto acetal under these experimental conditions.

As previously observed for the diphenyl diselenide (Scheme 2) [24], Pandey has found that the phenyl alkyl selenides also can be transformed into the corresponding radical cations by photostimulated single electron transfer to 1,4-dicyanonaphthalene (DCN). These intermediates, as proposed above, suffer fragmentation to afford diphenyl diselenide and a carbocation, which can be trapped by a nucleophile. On the basis of these observations Pandey [121] described a sequential one-pot selenenylation-deselenenylation of alkenes in methanol using only catalytic amounts of diphenyl diselenide. An example is reported in Scheme 41 which illustrates the single steps of this process



Scheme 41. Photostimulated Sequential One-Pot Selenenylation-Deselenenylation Reactions Catalyzed by Diphenyl Diselenide

applied to the conversion of the alkenol **259** into the tetrahydropyran derivative **260**.

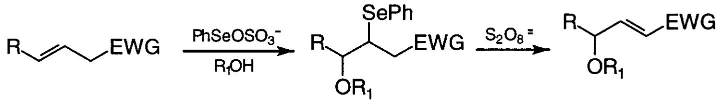
5.1.2
Deselenenylation with Elimination

The first example of this process is the electrochemical method described by Torii [115], which is illustrated in Scheme 36. Tomoda described a chemical method, which proceeds essentially in the same way, for a catalytic conversion of simple alkenes into allylic ethers and esters [122]. The catalytic oxyselenenylation-deselenenylation was effected with nitrogen substituted diselenides **18** or **19** using copper(II) nitrate as co-oxidant and sodium persulfate as oxidant [26]. Adding molecular sieves increased the efficiency of the process, which required seven days at room temperature. Selenoxides were proposed as the reactive intermediates responsible for the elimination reaction, which affords the final products. The selenenic acid thus formed then adds to the starting alkene. It was suggested that the selenenic acid is stabilized by intramolecular coordination with the tertiary nitrogen atom thus preventing its oxidation to the seleninic acid. Under identical experimental conditions, catalytic conversions of alkenes into allylic acetates were also effected using the diselenide **20**.

Tiecco described several examples of catalytic processes, in which the deselenenylation occurs with elimination. These reactions are suggested to proceed according to the general mechanism illustrated in Scheme 37 in which the reactive intermediates involved in the elimination step are not the selenoxides but the radical cations or the selenonium ions derived from the alkyl aryl selenide formed in the addition step. It has been observed that the elimination becomes greatly favored with respect to the substitution reaction whenever an electron-withdrawing group is present in the allylic position of the starting alkene so that a conjugate alkene can be obtained as the final product.

The first example of this type of a catalytic conversion is indicated in Scheme 42 [123]. This refers to β,γ-unsaturated esters and amides **261**, which, on treatment with an excess of ammonium persulfate and a catalytic amount of diphenyl diselenide, in methanol, ethylene glycol or in water, gave the addition products **262**. These, by reaction with persulfate, afforded the γ-alkoxy or the γ-hydroxy-α,β-unsaturated derivatives **263**, respectively.

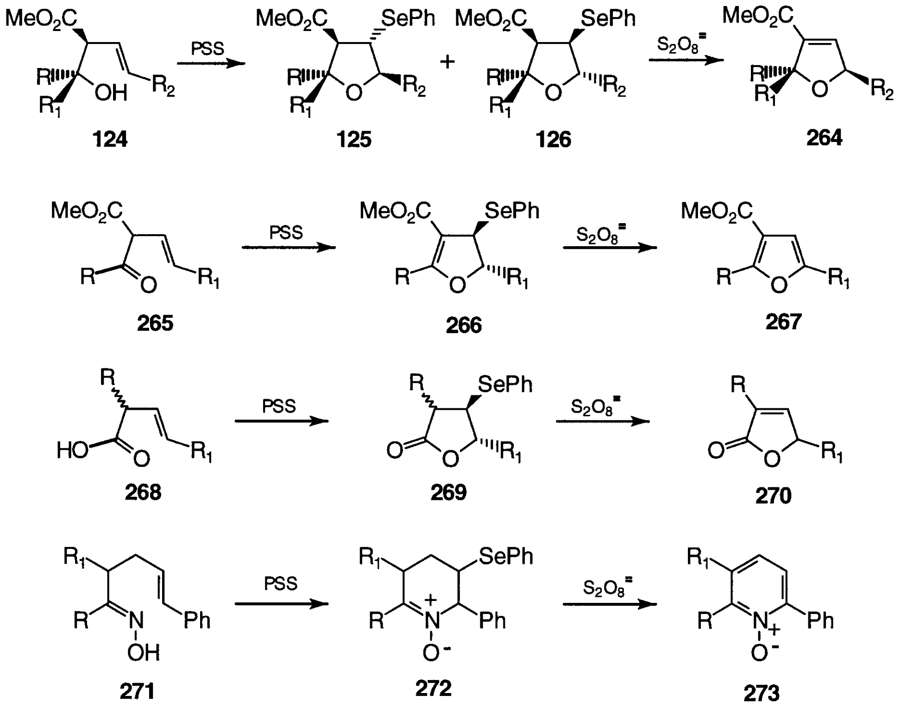
Other examples of this procedure refer to alkenes containing internal nucleophiles which react with phenylselenyl sulfate to afford the cyclization products.



261 **262** **263**

EWG = CO_2Me, $CONMe_2$ R = Me, Et, Ph R_1 = Me, CH_2CH_2OH, H

Scheme 42. Phenylselenyl Sulfate Catalyzed One-Pot Conversion of β,γ-Unsaturated Esters and Amides into the γ-Alkoxy or γ-Hydroxy-α,β-Unsaturated Derivatives



Scheme 43. Phenylselenyl Sulfate Catalyzed One-Pot Cyclization Reactions

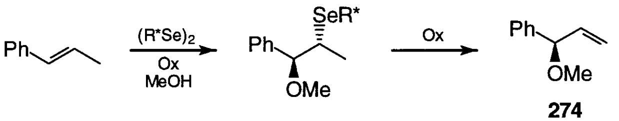
As reported in Scheme 18, the cyclization of 2-carbomethoxy-3-alkenols **124**, promoted by a stoichiometric amount of phenylselenyl sulfate, produces the corresponding tetrahydrofuran derivatives **125** and **126**. The formation of **125** was largely preferred and the stereoisomers **126** were formed in minute quantities. When the same reaction was repeated using a catalytic amount of diphenyl diselenide and an excess of ammonium persulfate (Scheme 43), the initially formed tetrahydrofurans suffered deselenenylation and afforded the 2,5-dihydrofurans **264**. The whole process was highly stereoselective [75]. The *erythro* alkenols **124** (R_1 = H) give the *trans* dihydrofurans, while the *threo* stereoisomers **124** (R = H) give the corresponding *cis* products both derived from the major isomers **125**. The minor isomers **126**, in fact, reacted with the persulfate to afford unidentified products. Probably the *cis* relationship between the phenyseleno and the methyl groups renders the approach of the persulfate anion to the selenium atom more difficult, so that the reaction takes a completely different course. Two further examples are reported in the Scheme 43. The first case refers to the direct conversion of α-vinyl β-dicarbonyl compounds **265** into the furans **267** [124] and the second to that of 3-butenoic acids **268** into the butenolides **270** [125]. In this latter reaction the carboxy group acts both as the internal nucleophile and as the electron-withdrawing group which facilitates the elimination step. The intermediate formation of the addition products **266** and **269** was demonstrated by independent experiments.

All the examples of the catalytic one-pot selenenylation-deselenenylation reactions reported above concern the use of oxygen nucleophiles. Also reported in Scheme 43 is the only available example in which a nitrogen nucleophile is involved in the addition step. Under the usual conditions, the oximes **271** react with phenylselenyl sulfate to afford the nitrones **272** which react with the persulfate to give pyridine *N*-oxides **273** by deselenenylation and dehydrogenation [126].

Several research groups have recently investigated the asymmetric version of the catalytic one-pot selenenylation-deselenenylation sequence described above. In particular, attention was devoted to the process in which the deselenenylation occurs with elimination. These experiments are simply carried out by replacing the diphenyl diselenide with a chiral diselenide and are suggested to proceed through a sequence of reaction steps similar to those proposed for the diphenyl diselenide by Tomoda [122] or by Tiecco [116] and indicated in the Schemes 36 and 37.

The first experiments concerned the conversion of the β-methylstyrene into the allylic ether **274** which was investigated by Tomoda [32a], Fukuzawa [31d] and by Wirth [127]. The results obtained are collected in Scheme 44. Good enantiomeric excesses were obtained by Wirth using the diselenides **28a** and **28b**, which were treated with potassium persulfate in the presence of nitrate ions.

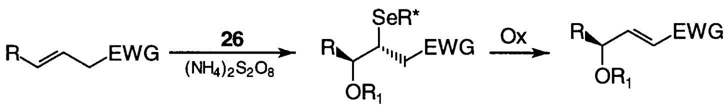
Quite recently, Tiecco [46a, 128] reported the asymmetric version of the one-pot conversion of β,γ-unsaturated esters and nitriles **261** (Scheme 42) into the enantiomerically enriched allylic ethers and alcohols **276** (Scheme 45). The reactions were effected with the selenenyl sulfate produced from the camphor diselenide **26**. Unfortunately, in the present case, this diselenide must be employed in stoichiometric amounts. However, it can be partially recovered at the end of the reaction. Good chemical yields and enantiomeric excesses (up to 86%) were obtained in the methoxyselenenylation-elimination reactions. Lower *ee* was observed when the reactions were run in ethylene glycol or in water. In the case of the hydroxyselenenylations, reaction yields were low because the addition products **275** gave rise to the lactones, which were then deselenenylated to the butenolides. These were isolated in about 30% yield.



274

(R*Se)$_2$	Oxidant	%Yield	%*ee*	Ref.
25	$Cu(NO_3)_2 + Na_2S_2O_8$	85	32	32a
24	$(NH_4)_2S_2O_8$	35	4	31d
28a	$K_2S_2O_8 + Ni(NO_3)_2$	35	56	117
28b	$K_2S_2O_8 + Ni(NO_3)_2$	23	75	117

Scheme 44. Catalytic Asymmetric Methoxyselenenylation-Elimination Reactions of β-Methylstyrene



261 275 276

		MeOH		$(CH_2OH)_2$		H_2O/MeCN		
R	EWG	%Yield	%*ee*	%Yield	%*ee*	%Yield	%*ee*	Conf.
Ph	CO_2Me	72	65	87	40	55	60	*R*
Et	CO_2Me	71	86	46	46	33	60	*S*
Me	CO_2Me	60	70					*S*
Me	CN	60	70	57	64	70	46	*S*

Scheme 45. Asymmetric Oxyselenenylation-Elimination Reactions of β,γ-Unsaturated Esters and Nitriles

Those described above are the first experiments in the field of the selenium catalyzed asymmetric syntheses. The results obtained from these new reactions are encouraging and justify further researches in order to develop more stereoselective and efficient reagents and reaction conditions.

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6
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Nucleophilic Selenium

Michio Iwaoka · Shuji Tomoda

Department of Life and Environmental Sciences, Graduate School of Arts and Sciences,
The University of Tokyo, Komaba, Meguro-ku, Tokyo 153–8902, Japan
E-mail: iwaoka@selen.c.u-tokyo.ac.jp · tomoda@selen.c.u-tokyo.ac.jp

Since Sharpless' application of a nucleophilic selenolate to the ring opening of epoxides, various nucleophilic selenium species have been widely used in organic synthesis. Advantages of the use of selenolates are rationalized in their high reactivity and selectivity as well as in the easy removal of the selenium moiety from the reaction products. In this chapter, the typical methods of preparing nucleophilic selenium species, their reactions with various organic substrates, and the utility of selenium reagents which have a selenium to main group element bond as an alternative source to the nucleophilic selenium are summarized. In addition, applications of nucleophilic selenium to asymmetric and solid-phase syntheses are presented separately. These new attempts are further increasing the intriguing utility of the nucleophilic selenium species.

Keywords. Selenium, Nucleophilic reactions, Selenium bonded to main group elements, Asymmetric synthesis, Solid-phase synthesis

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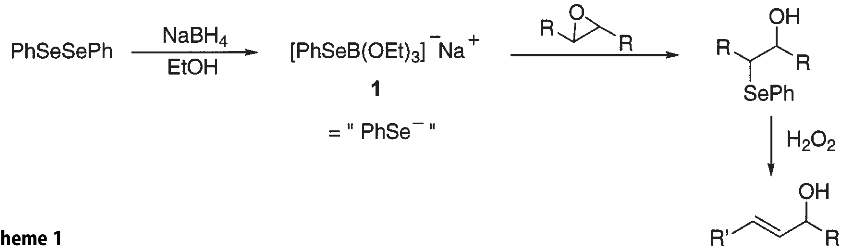
1
Introduction

The chemistry of nucleophilic selenium reagents began in 1973 when Sharpless et al. reported a simple method to prepare a benzeneselenolate equivalent **1** and its usefulness in the nucleophilic ring opening of various epoxides [1]. The subsequent oxidative elimination of the phenylseleno group led to allylic alcohols under mild conditions (Scheme 1). Sodium borohydride ($NaBH_4$) was employed as a reducing reagent to generate **1** from diphenyl diselenide (PhSeSePh) in ethanol. The structure of this mild nucleophilic selenium species is now known to be sodium phenylseleno(triethoxy)borate complex [$PhSeB(OEt)_3Na$] [2]. Since Sharpless' discovery, a number of nucleophilic reactions using **1** have been developed, including substitution reactions with halides, addition reactions to cyclic ethers, nucleophilic reductions of α,β-epoxy carbonyl compounds, etc. These reactions are potentially useful in organic synthesis as well as in the preparation of biologically active organoselenium compounds and diverse materials containing selenium (Sect. 3) [3].

To date a number of useful methods have been developed to prepare nucleophilic selenium species other than the Sharpless' method [1]. They involve



Scheme 1

insertion of selenium into lithium and Grignard reagents (Sect. 2.1) and reduction of diselenides, selenocyanates, and elemental selenium by several reducing reagents, such as alkali metals, alkali hydrides, hydrazines, and samarium reagents (Sect. 2.2). Electrochemical reduction has also been revealed to be effective (Sect. 2.2.5). Reactivity of the nucleophilic selenium species depends on the preparation method employed and the additives present in the solution. In general, these nucleophilic species are highly reactive and usually cannot be isolated.

Recently, a new class of more stable nucleophilic selenium reagents, which have a selenium bonded to main group elements, has been developed (Sect. 4). These selenium reagents have contributed to the wide expansion of the chemistry of nucleophilic selenium species. Novel applications to asymmetric synthesis (Sect. 5) and solid-phase synthesis (Sect. 6) have also been developed. These intriguing new attempts are further increasing the utility of the nucleophilic selenium species.

The nucleophilicity of selenolates is significantly higher than that of the corresponding thiolates. This property allows selenolates to be useful reagents in organic synthesis. Moreover, removal of the selenium moiety from the reaction products is easier because the selenium – carbon bond is weaker than the sulfur – carbon bond [3b].

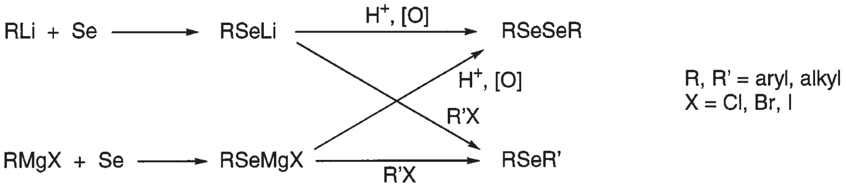
In the following sections, typical methods for the preparation of nucleophilic selenium species are described, followed by their general utility in various nucleophilic reactions. Subsequently described are unique reactions using selenium reagents having a selenium to main-group element bond as an alternative source to nucleophilic selenium species. Two recent topics, i.e. applications to asymmetric and solid-phase syntheses, are presented separately. Finally, the perspectives of nucleophilic selenium chemistry are discussed.

2
Preparation of Nucleophilic Selenium Species

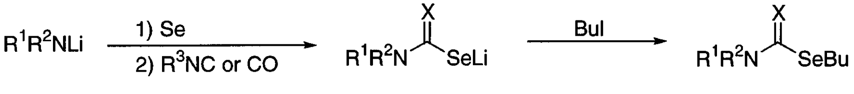
2.1
Insertion of Selenium into Organolithium or Grignard Reagents

Insertion of elemental selenium into alkyl- and aryllithium reagents or Grignard reagents is one of the useful and general methods to prepare nucleophilic selenium species [3]. The reaction is usually used for the synthesis of various diselenides or selenides as shown in Scheme 2 [4]. However, the applications are limited owing to the high reactivity of the lithium or Grignard reagents remaining in the reaction solution.

A similar selenium insertion proceeds with lithium amides of secondary amines. In the presence of an isocyanide, lithium selenocarbamidates **2** are produced, which can be trapped with butyl iodide to give the corresponding isoselenoureas **3** in good yields (Scheme 3) [5]. When the reaction is carried out under carbon monoxide atmosphere, the corresponding selenocarbamates are obtained [5].



Scheme 2



2 **3**

Scheme 3

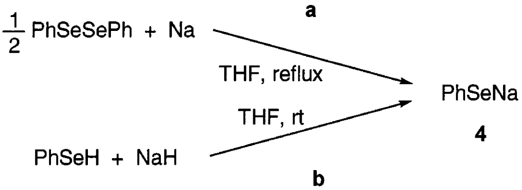
X = NR^3 or O

2.2
Reduction of Diselenides, Selenocyanates, and Elemental Selenium

2.2.1
Use of Alkali Metals and Hydrides

Reduction of diphenyl diselenide by sodium metal in refluxing THF produces copious precipitates of the salt of a benzeneselenolate anion **4** (Scheme 4a) [6]. This naked selenolate is more reactive than the one complexed with borane **1** [1]. For example, in the presence of HMPA, **4** undergoes an S_N2-type ester cleavage to produce the corresponding acids and alkyl phenyl selenides (Sect. 3.3) [6a]. Uncomplexed selenolate **4** can also be prepared by the reduction of benzeneselenol (PhSeH) with sodium hydride (NaH) (Scheme 4b) [6a].

Various diselenides can be reduced to the corresponding alkali selenolates by two equivalents of alkali hydrides (LiH, NaH, KH) in THF or DMF (Scheme 5) [7]. The yield significantly depends on the substrate structure and the reaction conditions. In general, the reactivity to the hydrides increases in the order



Scheme 4

$$\mathrm{RSeSeR + 2MH \xrightarrow[\text{THF or DMF}]{} 2RSeM} \qquad (\mathrm{M = Li, Na, K})$$

Scheme 5

LiH<NaH<KH and diaryl diselenides are more easily reduced than dialkyl diselenides. The reactions are faster in DMF than in THF [7a].

Reduction of selenocyanates **5** by alkali hydrides also produces the corresponding reactive selenolates **6**, but the mechanism is not simple. Krief et al. reported that the reduction of **5** with one equivalent of alkali hydride produces the diselenide **7**, whereas in the reduction using two equivalents of the alkali hydride the product is the selenolate **6** [8]. These results indicate that the reduction from **5** to **6** proceeds via the formation of diselenide **7** (Scheme 6). In this mechanism, air oxidation is not necessary to produce the diselenide from the selenocyanate when an equimolar amount of hydride is used.

Scheme 6

Sandman et al. [9] reported that elemental selenium is directly reduced to alkali metal selenides (Na_2Se, K_2Se) and diselenides (Na_2Se_2, K_2Se_2) by treatment with the appropriate amount of potassium or sodium in high-boiling polar solvents, such as DMF and HMPA. These inorganic selenium species are useful for the synthesis of various organic selenides and diselenides.

2.2.2
Use of Alkali Borohydrides

Reduction of diphenyl diselenides with sodium borohydride in alcohol is the most common and easiest method to prepare nucleophilic selenium species (Scheme 1) [1, 2]. The reaction is accompanied by vigorous evolution of gaseous hydrogen resulting in a colorless solution. The mild nucleophilic selenium species thus generated has been successfully applied to various types of synthetic reactions [3]. However, the real structure of the colorless selenium complex has been characterized only recently. Miyashita et al. measured the volume of the generated hydrogen gas to determine the reaction stoichiometry and characterized the complex structure unambiguously by ^{1}H NMR [2]. Thus, the structure of the complex is now revealed to be sodium phenylseleno(triethoxy)borate (**1**) (Scheme 7). This complex is slightly less nucleophilic compared with the naked selenolate anion **4** that is prepared by using alkali metals or hydrides (Scheme 4) [6]. Various diselenides and selenocyanates can also be reduced easily by $NaBH_4$ to the nucleophilic selenium species [3].

$$\mathrm{PhSeSePh} + 2\mathrm{NaBH_4} + 6\mathrm{EtOH} \xrightarrow{\mathrm{EtOH}} \underset{\mathbf{1}}{2\mathrm{Na[PhSeB(OEt)_3]}} + 7\mathrm{H_2}$$

Scheme 7

In aprotic solvents, such as dichloromethane and THF, potassium borohydride [10], lithium borohydride [8b], lithium triethylborohydride [8a, 11], and diisobutylaluminum hydride (DIBALH) [11] have been used instead of $NaBH_4$. $NaBH_4$ also reduces elemental selenium in alcohol or water to sodium hydrogen selenide or sodium diselenide (Na_2Se_2) depending on the stoichiometry of the reactants (Scheme 8) [12]. These anions are useful for the synthesis of selenides or diselenides, respectively, via nucleophilic substitution with various electrophiles.

$$4NaBH_4 + 2Se + 7H_2O \longrightarrow 2NaHSe + Na_2B_4O_7 + 14H_2$$

$$2NaHSe + Na_2B_4O_7 + 2Se + 5H_2O \longrightarrow 2Na_2Se_2 + 4H_3BO_3$$

Scheme 8

2.2.3
Use of Hydrazines

Reaction of diphenyl diselenide or dimethyl diselenide with hydrazine hydrate and sodium hydroxide generates the corresponding selenolates smoothly in solvents like DMF or diethyl ether and in the presence of tetrabutylammonium chloride as a phase-transfer catalyst [13]. The selenolates react with organic halides to give various selenides (Scheme 9). Similar conditions have been applied to the synthesis of aryl vinyl selenides from diaryl diselenides and acetylene [14].

$$\text{RSeSeR} \xrightarrow[\text{cat. } Bu_4NCl]{N_2H_4 \cdot H_2O/NaOH/DMF} \text{RSeNa} \xrightarrow{R'X} \text{RSeR'}$$

(R = Ph, Me)

Scheme 9

Similarly to $NaBH_4$, hydrazine reduces elemental selenium to sodium diselenide (Na_2Se_2), which is further reduced to sodium selenide (Na_2Se) by sodium dithionite (Scheme 10) [13]. Under phase-transfer conditions, the method has been successfully applied to the convenient synthesis of diselenides [15]. Phenylhydrazine also reduces elemental selenium in DMF [16].

$$4Se + N_2H_4 + 4NaOH \longrightarrow 2Na_2Se_2 + 4H_2O + N_2$$

$$Na_2Se_2 + Na_2S_2O_4 + 4NaOH \longrightarrow 2Na_2Se + 2Na_2SO_3 + 2H_2O$$

Scheme 10

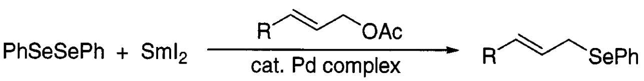
2.2.4
Use of Samarium Reagents

Samarium reagents are also useful for the preparation of nucleophilic selenium species from diselenides and elemental selenium [17]. Reduction of diphenyl diselenide with samarium diiodide in refluxing THF generates a benzeneselenolate which can react with *n*-butyl iodide to give *n*-butyl phenyl selenide in a good yield (Scheme 11) [17a]. Using this method, the ring-opening reaction of cyclic isopropylidene malonate derivatives was carried out [17b], and various benzotriazoles were transformed to unsymmetrical selenides [17c].

$$\frac{1}{2}\,\mathrm{PhSeSePh} + \mathrm{SmI_2} \xrightarrow[\text{THF, reflux}]{} \mathrm{PhSe^-} \xrightarrow[\text{HMPA}]{n\text{-BuI}} \mathrm{PhSe}\text{-}n\text{-Bu}$$

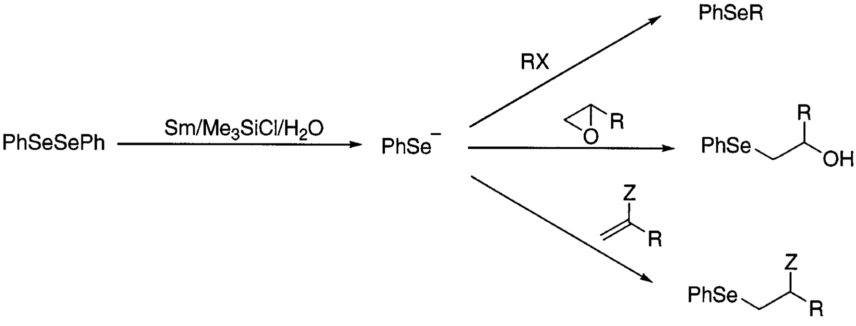
Scheme 11

It has been reported that, in the presence of a palladium catalyst, diphenyl diselenide and samarium diiodide react with allylic acetates to give allylic phenyl selenides under mild conditions (Scheme 12) [18]. In this case, however, the nucleophilic benzeneselenolate was not proposed as an intermediate of the reaction.



Scheme 12

Reduction of diphenyl diselenide with the Sm-Me_3SiCl-H_2O system also leads to a benzeneselenolate, which reacts with organic halides, epoxides, α,β-unsaturated esters or α,β-unsaturated nitriles to afford unsymmetrical phenyl selenides in good yields under mild and neutral conditions as shown in Scheme 13 [19]. This method is easier to handle than the use of air-sensitive SmI_2.



Scheme 13

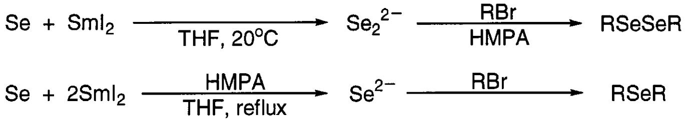
(Z = CN, CO_2Me)

On the other hand, the $TiCl_4$-Sm-THF system was applied for the preparation of selenol esters from diaryl diselenides and acid chlorides (Scheme 14) [20].

$$\text{RSeSeR} + \text{R'}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl} \xrightarrow[\text{THF, 50°C}]{\text{TiCl}_4\text{-Sm}} \text{R'}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{SeR}$$

Scheme 14

Reduction of elemental selenium with SmI_2 leads to the selective formation of Se^{2-} and Se_2^{2-} depending on the reaction stoichiometry, similar to the reduction with $NaBH_4$ and hydrazine (Sects. 2.2.2 and 2.2.3). These inorganic dianions react with alkyl bromides to produce dialkyl selenides and diselenides, respectively, in excellent yields (Scheme 15) [17a].



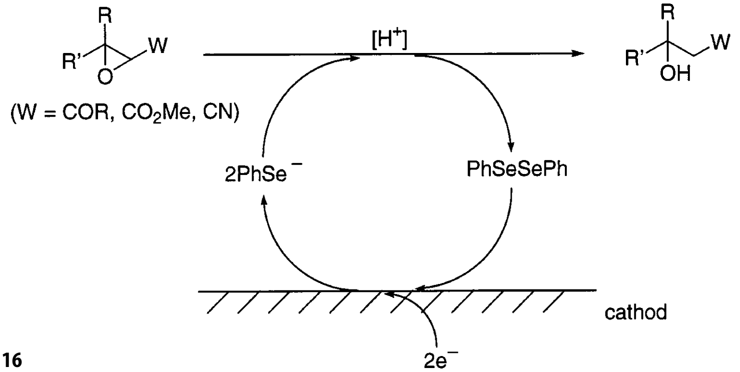
$$\text{Se} + \text{SmI}_2 \xrightarrow[\text{THF, 20°C}]{} \text{Se}_2^{2-} \xrightarrow[\text{HMPA}]{\text{RBr}} \text{RSeSeR}$$

$$\text{Se} + 2\text{SmI}_2 \xrightarrow[\text{THF, reflux}]{\text{HMPA}} \text{Se}^{2-} \xrightarrow{\text{RBr}} \text{RSeR}$$

Scheme 15

2.2.5
Electrochemical Reduction

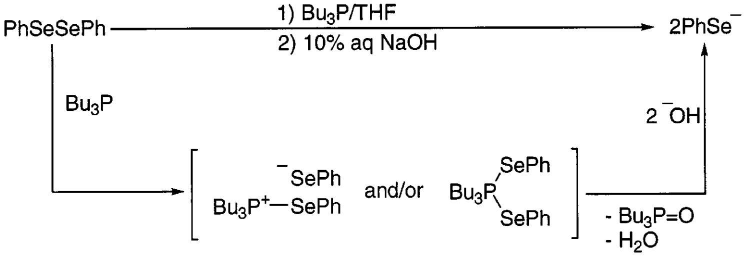
Cathodic reduction of diphenyl diselenide produces a benzeneselenolate, which catalyzes the reduction of α,β-epoxy carbonyl compounds into β-hydroxy carbonyl compounds in the presence of a proton source (Scheme 16) [21]. This electrochemical method is applicable to the selenation of haloalkanes, epoxides, and enones [22]. Electrochemical reduction of elemental selenium to diselenide dianion (Se_2^{2-}) and selenide dianion (Se^{2-}) is also possible [23].



Scheme 16

2.2.6
Other Methods

Treatment of diphenyl diselenide with tributylphosphine in an alkaline medium generates a benzeneselenolate anion [24], which reacts with various electrophiles, such as halides, epoxides, α,β-unsaturated ketones, to generate various selenides [24, 25]. The mechanism for the generation of the benzeneselenolate is proposed as shown in Scheme 17 [25]. A selenophosphonium ion and/or a pentavalent phosphorus species are initially formed in the reaction of diphenyl diselenide and tributylphosphine, and then the addition of sodium hydroxide liberates the benzeneselenolate and phosphine oxide.



Scheme 17

There are several other methods to reduce diselenides, selenocyanates, and elemental selenium. For example, sodium hydroxymethanesulfinate (rongalite) [26], carbon monoxide [27a], zinc powder [27b], hypophosphorous acid (H_3PO_2) [28], and sodium hydroxide (NaOH) under phase-transfer conditions [29] have been used to prepare nucleophilic selenium species.

3
Reactions of Nucleophilic Selenium Species

3.1
Reactions with Halides

Substitutions to halide compounds are the most typical reactions of nucleophilic selenium species (Scheme 18). Alkyl or aryl selenolates (R'SeM), which are prepared in situ by the methods described in Sect. 2, react with halides to give

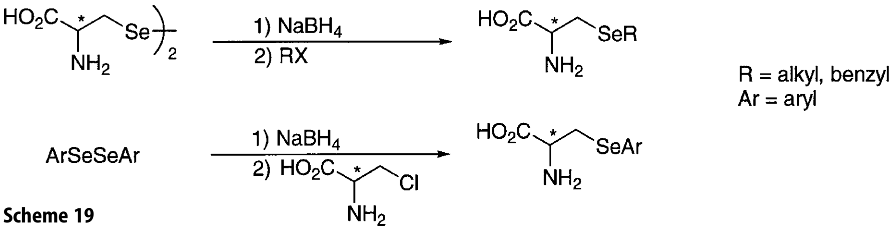
$$\mathrm{RX + R'SeM \longrightarrow RSeR' + MX}$$
$$\mathrm{2RX + M_2Se \longrightarrow RSeR + 2MX}$$
$$\mathrm{2RX + M_2Se_2 \longrightarrow RSeSeR + 2MX}$$
$$\mathrm{RX + KSeCN \longrightarrow RSeCN + KX}$$

X = Cl, Br, I
M = Li, Na, K, etc.

Scheme 18

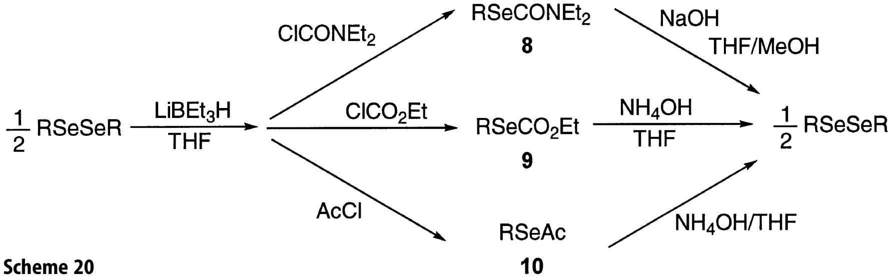
unsymmetrical selenides [7a, 10, 13, 17a, 19, 22, 25, 29]. Alkali metal selenides (M_2Se) and diselenides (M_2Se_2) also react with halides to produce symmetrical selenides and diselenides, respectively [12, 13, 15, 17a, 23]. Similarly, potassium selenocyanate is a good nucleophile to alkyl halides, leading to the corresponding alkyl selenocyanates [8b, 30].

Two interesting applications of this type of reaction are presented in Schemes 19 and 20. Selenium-substituted cysteine (selenocysteine) derivatives are synthesized by condensation between selenocysteine and the corresponding alkyl and benzyl halides or between areneselenolate and *β*-chloroalanine (Scheme 19) [31]. These compounds are considered as potential kidney selective prodrugs of biologically active selenol compounds.



Scheme 19

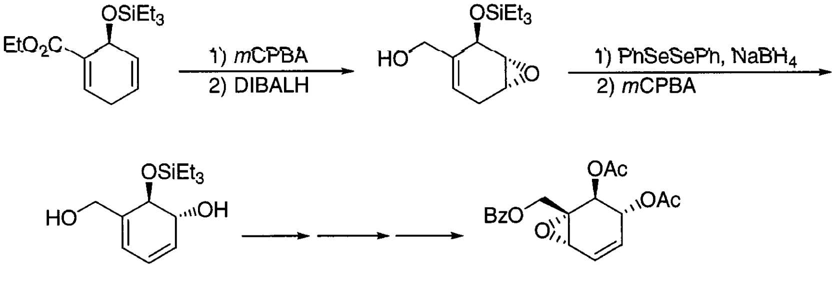
Nucleophilic selenium species, generated from diselenides by $LiBEt_3H$ in THF, react with diethylcarbamyl chloride, ethyl chloroformate, and acetyl chloride to yield the corresponding alkyl selenocarbamates **8**, selenocarbonates **9**, and selenoacetates **10**, respectively (Scheme 20) [32]. These compounds are stable against weak bases and reducing agents, such as $NaBH_4$, and can be good protecting groups of diselenides. Diselenides are easily regenerated by treating **8** with NaOH in THF/MeOH or by treating **9** or **10** with NH_4OH in THF [32].



Scheme 20

3.2
Ring Opening of Epoxides and Cyclic Ethers

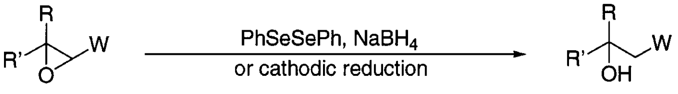
Ring opening of epoxides proceeds smoothly by the reaction with nucleophilic selenium species, whereas the opening of larger cyclic ethers, such as THF, does not proceed under normal conditions. As demonstrated in Scheme 1, ring opening of epoxides by nucleophilic selenium species and the subsequent oxidative elimination of the selenium moiety are useful and convenient procedures to obtain allylic alcohols [1]. This method has been widely applied in natural product synthesis [3a]. For example, the application in the synthesis of senepoxide (**11**) is shown in Scheme 21 [33].



Scheme 21 **11**

Ring opening of epoxides using selenolates that are generated by other methods, such as reduction with samarium reagents [19], electrochemical reduction [22], reduction with phosphine [25] or reduction with $NaBH_4$ under microwave irradiation [34], have also been reported.

The reaction with α,β-epoxy carbonyl compounds **12** leads to the corresponding reductive ring-opened products, β-hydroxy carbonyl compounds **13**, in good yields (Scheme 22). Electrochemically generated benzeneselenolate [21, 22] and sodium phenylseleno(triethoxy)borate (**1**) [35, 36], have been applied for this type of reaction as a nucleophilic selenolate. In the latter case, the reaction mechanism was suggested as shown in Scheme 23 [36]. Reaction of **1** with **12** first produces the ring-opened adduct **14**, which is then reacted with an excess amount of **1** to produce the final product **13**. This method is important as a simple synthetic procedure to aldols and β-hydroxy esters that are rather difficult to obtain by other methods. The reactions have been extended to the reduction of more functionalized α,β-epoxy carbonyl compounds [37] and have been successfully applied for the synthesis of several natural products [38].

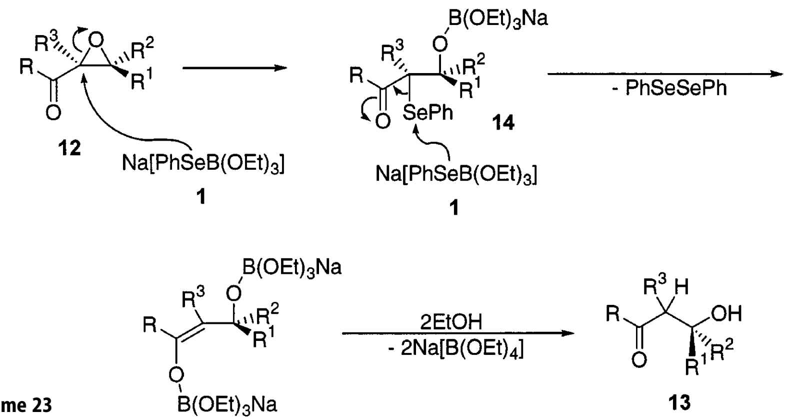


12 **13**

(W = COR, CO_2R, CN)

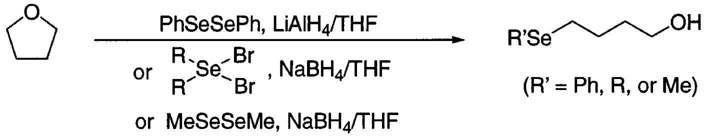
Scheme 22

Ring opening of larger cyclic ethers, such as THF, does not proceed normally by the reaction with selenolate **1** that is generated by the reduction with $NaBH_4$ in alcohol. However, the ring opening of THF takes place in good



Scheme 23

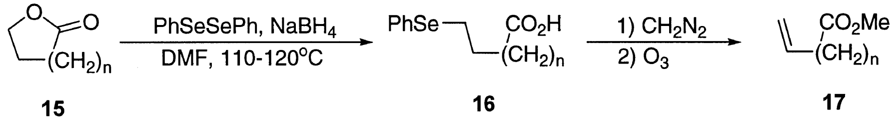
yields when diphenyl diselenide is reduced with $LiAlH_4$ in THF [39], diaryl- or dialkylphenylselenium dibromides are reduced with $NaBH_4$ in THF [40], or dimethyl diselenide is reduced with $NaBH_4$ in THF in the presence of $AlCl_3$ [41] (Scheme 24). In the second reaction [40], borane produced by the reduction of the dibromides with $NaBH_4$ [42] was claimed to play an important role in cleaving the ether bond. Similar ring-opening reactions of cyclic ethers proceed by treatment with tris(phenylseleno)borane [$B(SePh)_3$] [43].



Scheme 24

3.3
Reactions with Esters and Lactones

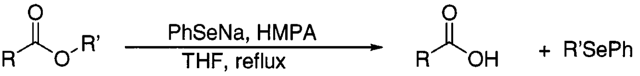
Selenolate **1** [1, 2], prepared from diphenyl diselenide by reduction with $NaBH_4$ in ethanol, is not reactive enough towards esters and lactones. However, application of more rigorous conditions, i.e. at 110–120 °C in dry DMF for lactones **15**, affords the corresponding ring-opened products, ω-phenylselenyl carboxylic acids **16**, in good yields [44]. Compounds **16** can be easily converted to ω-olefinic methyl esters **17** by treatment with diazomethane followed by oxidative elimination of the phenylseleno group (Scheme 25). By contrast, the uncomplex-



15 **16** **17**

Scheme 25

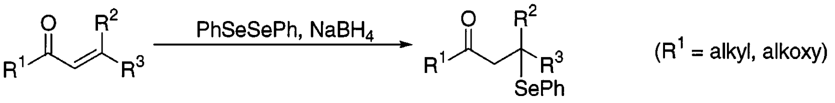
ed selenolate (PhSeNa), that is prepared by the reduction with sodium metal in refluxing THF, reacts with lactones under milder conditions in the presence of HMPA (at 67 °C) or 18-crown-6 (at 25 °C) [45]. By applying similar conditions, esters are converted to the corresponding acids and selenides through S_N2-type substitution reactions (Scheme 26) [6a].



Scheme 26

3.4
Michael Addition

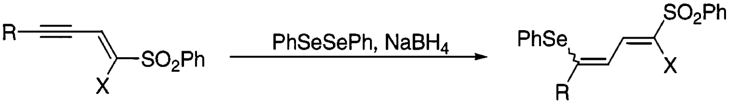
Treatment of α,β-unsaturated carbonyl compounds **18** with nucleophilic selenium species affords β-seleno carbonyl compounds **19** in good yields via Michael addition (Scheme 27) [46]. This reaction has been applied to protect α,β-unsaturated lactones [47], in natural product synthesis [48], and in asymmetric Michael additions in the presence of an alkaloid [49]. Michael addition also proceeds with selenolates that are prepared from diphenyl diselenide by cathodic reduction [22], reduction with the Sm-Me_3SiCl-H_2O system [19], and reduction with tributyl phosphine [25].



18 **19**

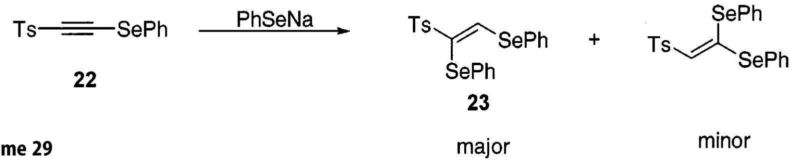
Scheme 27

Addition of the selenolate that is prepared from diphenyl diselenide by reduction with $NaBH_4$ to conjugate enyne sulfones **20** occurs at the δ-position of the sulfonyl group to give 4-phenylseleno-1-sulfonylbuta-1,3-dienes **21** regio- and stereoselectively (Scheme 28) [50]. On the other hand, addition of PhSeNa to the conjugated alkynyl sulfone **22** that has a β-phenylseleno substituent affords the *anti*-Michael adduct **23** preferentially (Scheme 29) [51].



20 **21**

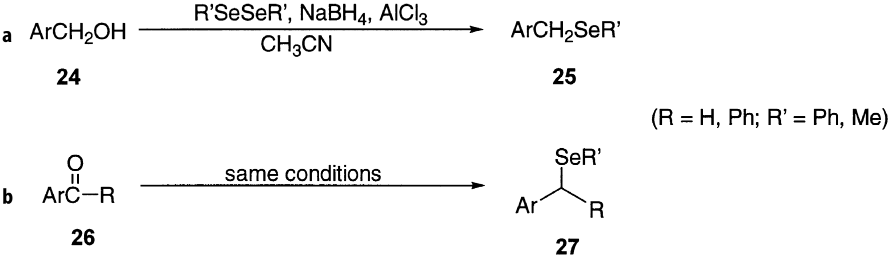
Scheme 28 (R = H, t-Bu, Ph; X = H, Cl, Br, SO_2Ph)



Scheme 29

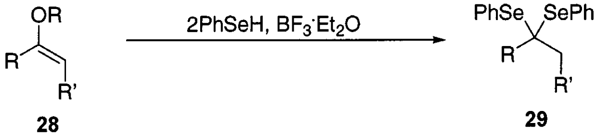
3.5
Miscellaneous

Selenolates prepared from diphenyl or dimethyl diselenide by reduction with NaBH$_4$ smoothly transform various benzylic alcohols **24** into the corresponding selenides **25** in the presence of aluminum chloride (Scheme 30a) [41]. AlCl$_3$ is considered to activate the alcohol substrate by coordinating to the oxygen. Similar transformations are possible by the reaction of alcohols with phenyl selenocyanate in the presence of tributyl phosphine [52]. When the selenolate is reacted with aromatic aldehydes or ketones **26** in the presence of AlCl$_3$, the corresponding benzylic selenides **27** are obtained in moderate yields (Scheme 30b) [41].



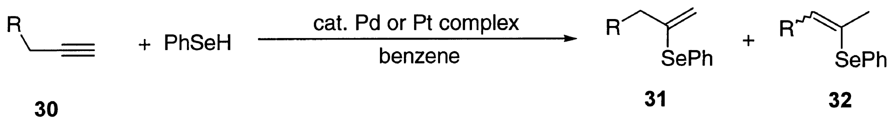
Scheme 30

Enol ethers **28** are easily converted to selenoacetals **29** by treatment with benzeneselenol in the presence of boron trifluoride etherate (Scheme 31) [53]. When cyclic enol ethers are employed, the corresponding open-chain products are formed. The selenoacetals obtained are considered to be important intermediates in organic synthesis [54].



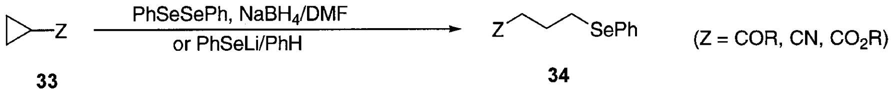
Scheme 31

Addition of benzeneselenol to terminal acetylenes **30** is catalyzed by a palladium complex to give Markovnikov adducts **31** preferentially [55]. The isomerized products **32** are also obtained depending on the catalyst employed (Scheme 32).



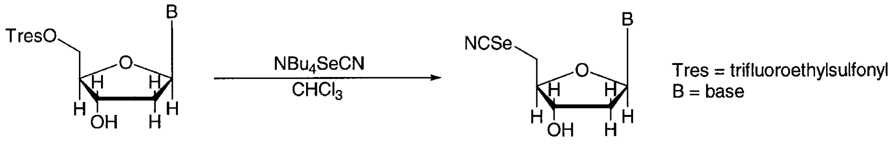
Scheme 32

Activated cyclopropanes **33** react with nucleophilic selenium species to give the ring-opened products **34** in moderate to good yields (Scheme 33) [56]. This reaction has been used for natural product synthesis [57].



Scheme 33

The selenocyanate ion ($SeCN^-$) is also a potentially useful nucleophilic selenium species [3]. Various organic electrophiles, such as halides [30], tosylates [58], diazonium salts [59], lactones [60], and sugars [61], react with $SeCN^-$ to produce organic selenocyanates. Usually commercially available potassium selenocyanate is employed as a source of the selenocyanate ion. However, this reagent is insoluble in nonpolar organic solvents, and this disadvantage sometimes causes limitations of its use. Recently, a soluble analogue to KSeCN, tetrabutylammonium selenocyanate, was prepared and successfully applied to the synthesis of various deoxynucleosides and sugars containing selenium (Scheme 34) [62]. These compounds are considered to be important as synthetic precursors of biologically significant compounds as well as potential analogues to enzyme substrates.



Scheme 34

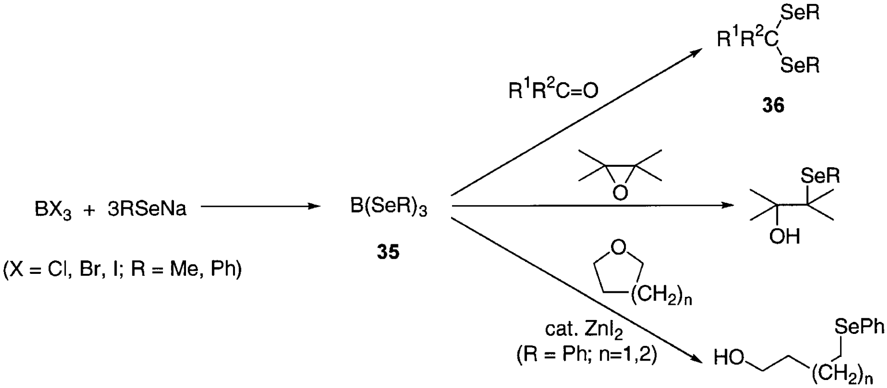
4
Selenium Bonded to Main Group Elements

Recently, selenium compounds with a selenium to main group element bond have attracted growing interest as a stable alternative (or source) to usually labile nucleophilic selenium species. In this section, the development of these reagents over the past decade is briefly presented from a synthetic point of view. A previous survey of organometallic compounds with a selenium atom bonded to main group elements is Zingaro's review from 1986 (see Chap. 11 in [3b]).

4.1
Group 13 Elements

4.1.1
Boron

Tri(organoseleno)boranes **35** are prepared from boron trihalides and organic selenolates as stable compounds (Scheme 35) [63]. These selenoboranes have been shown to be useful for the conversion of carbonyl compounds into selenoacetals **36** [64] and the selective ring opening of epoxides [65]. Recently, it was reported that tri(phenylseleno)borane reacts with cyclic ethers to produce ω-hydroxyalkyl phenyl selenides **37** in the presence of a catalytic amount of Lewis acid [43].

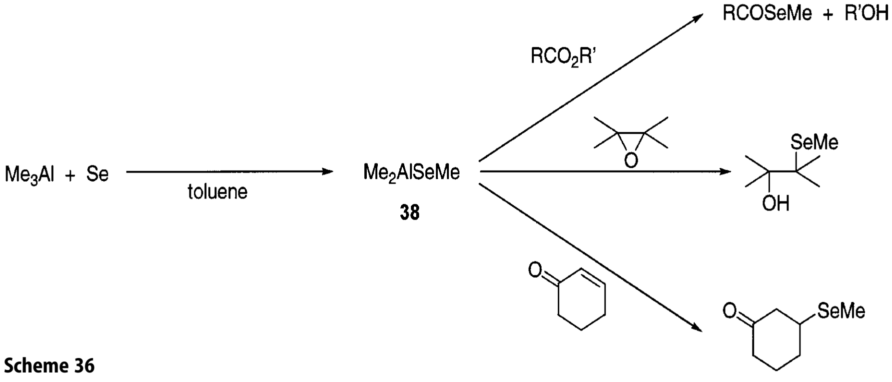


Scheme 35

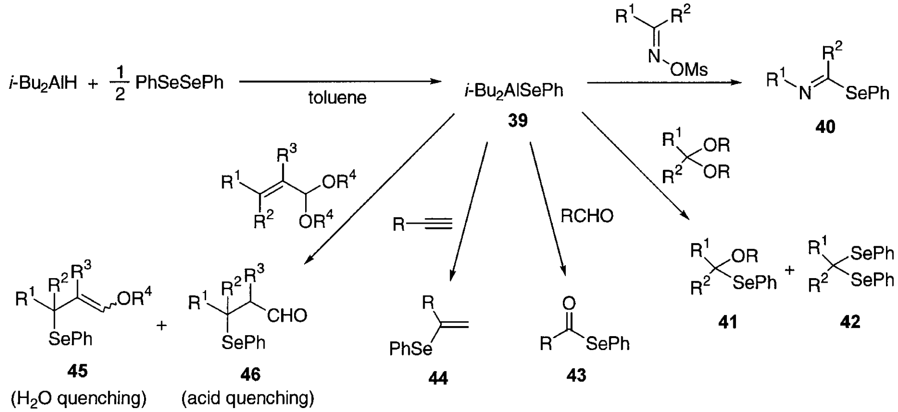
4.1.2
Aluminum

Dimethylaluminum methylselenolate (**38**) is prepared in situ by the reaction of trimethylaluminum with elemental selenium in refluxing toluene [66]. The yellow-colored solution can be used in various reactions, such as the conversion of esters to the corresponding selenol esters, the ring opening of epoxides, and Michael addition to cyclohexenone (Scheme 36) [66].

Diisobutylaluminum phenylselenolate (**39**), which is prepared in situ by the reaction between diphenyl diselenide and diisobutylaluminum hydride (DIBALH) [67], is also a useful nucleophilic selenium reagent (Scheme 37). For example, **39** reacts with oxime sulfonates to produce selenoimidic esters



Scheme 36

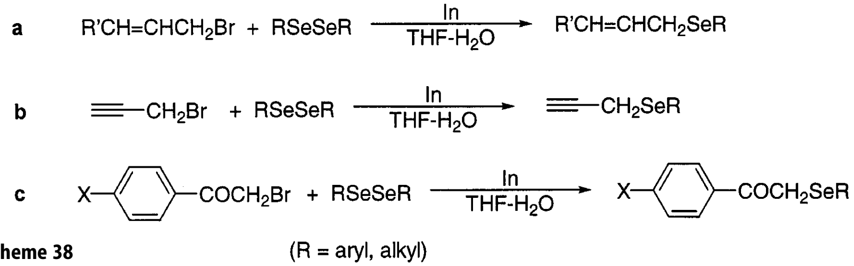


Scheme 37

40 via Beckmann rearrangement [67, 68]. Reaction of 39 with acetals produces monoselenoacetals 41 and diselenoacetals 42, depending on the stoichiometry [69]. Aldehydes are converted to the corresponding selenol esters 43 [70], and terminal acetylenes are transformed to 1-organo-1-phenylseleno ethenes 44 regioselectively [71]. The reaction with α,β-unsaturated acetals affords the corresponding 1-alkoxy-3-phenylseleno-1-alkenes 45 with neutral quenching and 3-phenylselenoalkanals 46 with acidic quenching in good yields [72]. Ganem applied this reagent in the total synthesis of bioactive quassinoids [73].

4.1.3
Indium

In the presence of indium, allyl bromides and propargyl bromides react smoothly with diselenides in aqueous media to give allyl and propargyl selenides, respectively, in moderate to good yields (Scheme 38a, b) [74]. By applying similar reaction conditions, α-selenocarbonyl compounds are synthesized by the reaction with α-halo ketones (Scheme 38c) [75]. These reactions do not need to be carried out under inert atmosphere. Although the reactive intermediates in these reactions have not yet been characterized, it seems that the reactions proceed via nucleophilic substitution of the halides with a selenolate equivalent, which might be generated by reduction with indium.

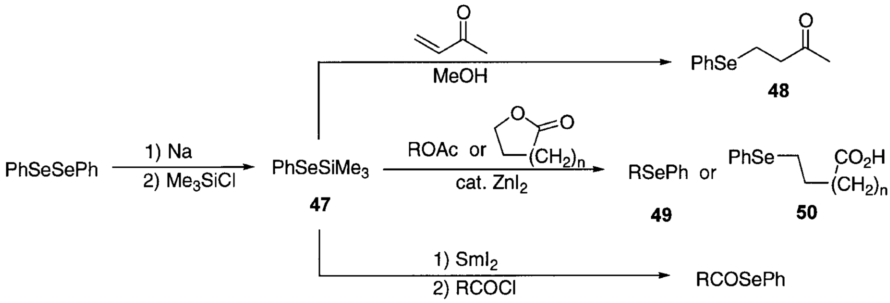


Scheme 38

4.2
Group 14 Elements

4.2.1
Silicon

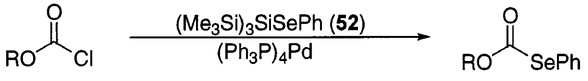
Phenyl trimethylsilyl selenide (47) is synthesized by sequential reaction of diphenyl diselenide with sodium and then trimethylsilyl chloride (Scheme 39) [76]. This colorless liquid reagent is somewhat sensitive to moisture, but stable under dry nitrogen atmosphere. Reagent 47 is a good nucleophilic selenium source. For example, the reaction with methanol produces benzeneselenol, which undergoes Michael addition with vinyl methyl ketone to give β-phenylseleno ketone 48 [76b]. Reaction with acetates or lactones in the presence of a catalytic amount of zinc iodide produces alkyl phenyl selenides 49 or ω-phenylselenenylcarboxylic acids 50, respectively [77]. Treatment of 47 with samarium diiodide in refluxing THF results in a reductive cleavage of the Se–Si bond to



Scheme 39

yield samarium phenylselenolate, which smoothly reacts with acyl halides to give selenol esters **51** [78].

A similar reagent, phenylselenotris(trimethylsilyl)silane (**52**), reacts with chloroformates in the presence of tetrakis(triphenylphosphine)palladium to produce (phenylseleno)formates **53** (Scheme 40) [79]. This reaction is also applicable to the preparation of selenol esters and selenol thionoformates [79].



Scheme 40

53

Bis(trimethylsilyl)selenide (**54**) [80] is another useful reagent as a source of a nucleophilic selenium species. This reagent has been shown to be useful for a convenient one-pot synthesis of unsymmetrical selenides **55** by stepwise treatment with *n*-butyllithium and the corresponding halides (Scheme 41) [81].

$$\underset{\mathbf{54}}{\mathrm{Me_3SiSeSiMe_3}} \xrightarrow[\mathrm{THF}]{n\text{-BuLi}} \mathrm{LiSeSiMe_3} \xrightarrow{\mathrm{R^1X}} \mathrm{R^1SeSiMe_3}$$

$$\xrightarrow{n\text{-BuLi}} \mathrm{R^1SeLi} \xrightarrow{\mathrm{R^2X}} \underset{\mathbf{55}}{\mathrm{R^1SeR^2}} \qquad (\mathrm{R^1, R^2} = \text{alkyl, acyl, etc.})$$

Scheme 41

4.2.2
Tin

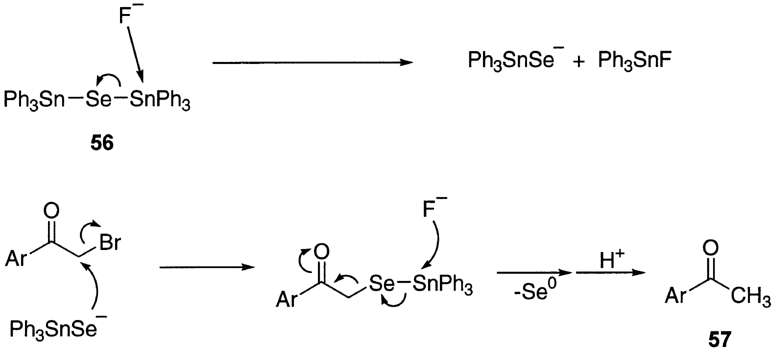
Organostannyl selenides undergo similar reactions to the corresponding organosilyl selenides. However, the stability and the reactivity are significantly different due to more favorable orbital overlaps between tin and selenium [82]. In general, organostannyl selenides are much more stable than organosilyl selenides.

Bis(triphenylstannyl) selenide (**56**), which is prepared by the reaction of NaHSe with triphenylstannyl chloride [82, 83], smoothly liberates a nucleophilic selenolate species with the aid of a fluoride ion [82]. The reaction conditions are neutral, producing the selenolate in a naked form. Therefore, in the reaction with halides, the corresponding symmetrical selenides are obtained in excellent yields without generating by-products (Scheme 42) [82]. When **56** is reacted

$$\underset{\mathbf{56}}{\mathrm{Ph_3SnSeSnPh_3}} + \mathrm{2RBr} \xrightarrow{\mathrm{F^-}} \mathrm{RSeR} + \mathrm{2Ph_3SnF}$$

Scheme 42

with α-halo ketones in the presence of fluoride, the dehalogenated products **57** are obtained under mild conditions [83b]. The proposed mechanism is shown in Scheme 43.

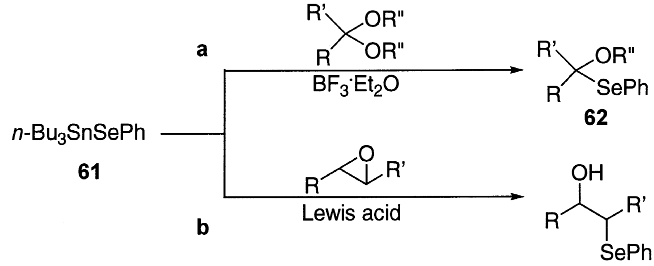


Scheme 43

Alkyl stannyl selenides are also useful nucleophilic selenium reagents. Trimethylstannyl or tributylstannyl methyl selenides **58** react with halides **59** to produce unsymmetrical selenides **60** in good yields in the presence of a fluoride ion or by treatment with *n*-butyllithium (Scheme 44) [84]. Tributylstannyl phenyl selenide (**61**) reacts smoothly with acetals to give monoselenoacetals **62** in the presence of boron trifluoride etherate (Scheme 45a) [85]. Similar reaction conditions were applied to the regioselective ring opening of epoxides (Scheme 45b) [86].

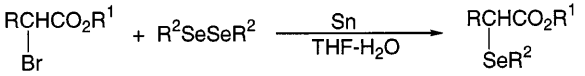
$$\underset{\textbf{58}}{R_3SnSeMe} + \underset{\textbf{59}}{R'X} \xrightarrow{F^- \text{ or BuLi}} \underset{\textbf{60}}{R'SeMe} \qquad (R = Me, Bu)$$

Scheme 44



Scheme 45

α-Bromo esters **63** react directly with diselenides in the presence of elemental tin to give α-seleno esters **64** in moderate to good yields, although the reaction mechanism is unclear (Scheme 46) [87].

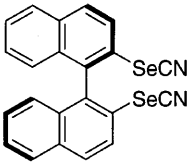


Scheme 46 **63** **64**

5
Applications to Asymmetric Ring Opening of Epoxides

Enantioselective ring opening of meso-epoxides is an important process in organic synthesis [88]. When a thiolate is employed as the nucleophile, moderate to good asymmetric induction is achieved [89]. Application of a selenolate to asymmetric ring opening of epoxides would have advantages, because a selenolate is more reactive than a thiolate. In addition, elimination of the selenium moiety from the ring-opened product is easier, allowing the reaction to be carried out under milder conditions.

The first attempt at enantioselective ring opening of meso-epoxides by using a chiral selenolate was reported in 1988 [90]. Enantiomerically pure selenobinaphthyl compounds **65**–**67** were synthesized and applied to the asymmetric ring opening of cyclohexene oxide (Scheme 47).



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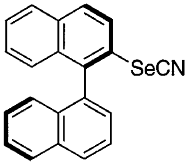

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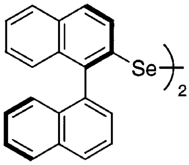

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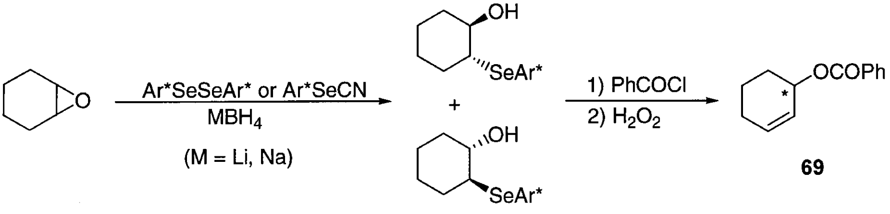
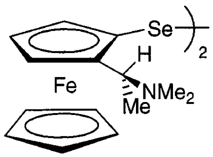


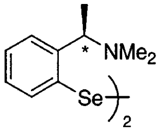
Scheme 47 **68**

The optical yield and stereoselectivity of the reaction were determined unambiguously by transforming the ring-opened products **68** into 2-cyclohexenyl benzoate (**69**). The obtained enantiomeric excess was up to 50% [90]. A similar protocol was employed by Nishibayashi et al., who synthesized a chiral diferrocenyl diselenide **70** and applied it to asymmetric ring opening of several meso-epoxides [91].



70

The obtained enantiomeric excess of compound **69** was up to 69% when the reduction conditions were $LiAlH_4$ in THF at –20 °C. Wirth applied diselenide **71** to a similar asymmetric ring opening, but the observed asymmetric induction was not so high (11% ee) [92].

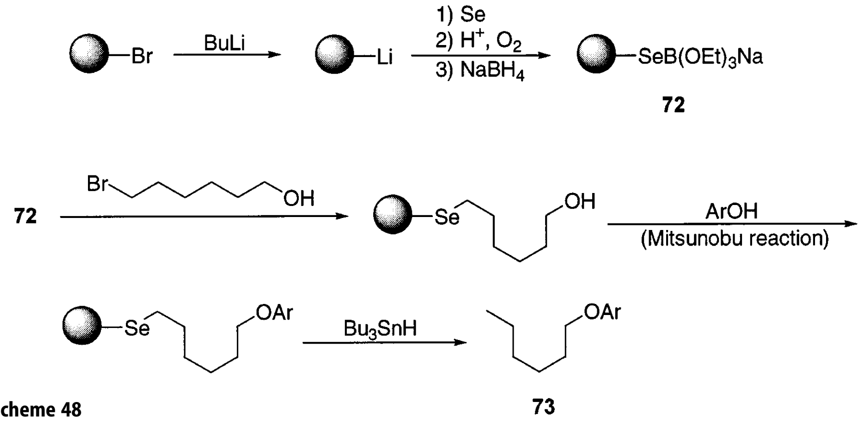


71

6
Applications to Solid-Phase Synthesis

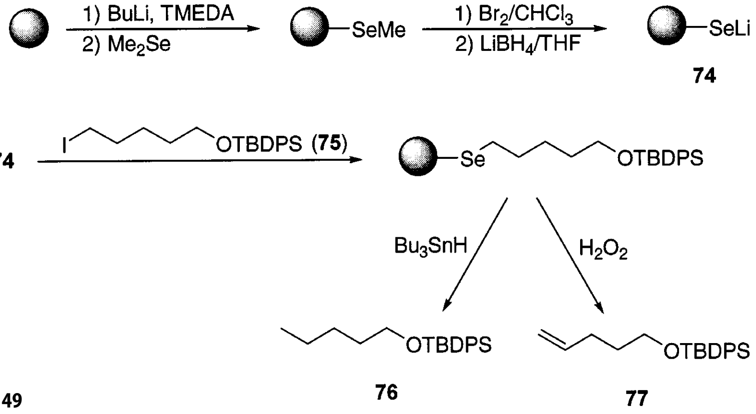
Polymer-supported reagents have attracted growing interest because they can be applied to combinatorial chemistry and solid-phase synthesis. Some newly developed selenium-containing polymers have been reported recently. These polymers show selective reactivity without forming toxic and odorous by-products in the form of low-molecular-weight selenium compounds.

Ruhland et al. synthesized polystyrene-bound selenium 72 and applied it to traceless solid-phase synthesis of a library of aryl alkyl ethers 73 (Scheme 48) [93].



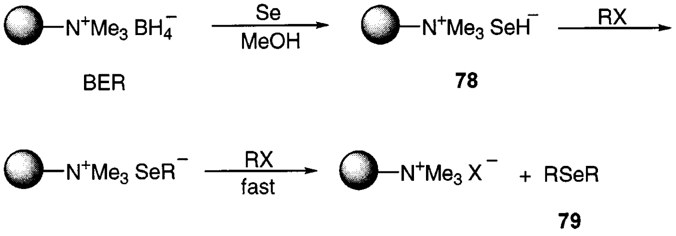
Scheme 48

Nicolaou et al. obtained a similar nucleophilic selenium bound to polystyrene 74 by a different method and demonstrated its usefulness in the transformation of alkyl iodide 75 into the corresponding alkane 76 and alkene 77 (Scheme 49) [94).



Scheme 49

Yanada et al. synthesized a new selenide exchange resin **78** by treatment of borohydride exchange resin (BER) with selenium. The subsequent reaction with alkyl halides or tosylates gives dialkyl selenides **79** selectively in a high yield (Scheme 50) [95].



Scheme 50

7
Perspectives

Nucleophilic selenium species have already been demonstrated to be very useful reagents for organic synthesis. However, their possibilities as useful synthetic reagents are still growing, as seen in the applications to asymmetric reactions and also solid-phase synthesis. These new attempts have only just begun to bud recently, and will bloom in the future. On the other hand, selenium reagents with a selenium to main group element bond exhibit unique nucleophilic reactivities depending on the main group element attached to the selenium, as decribed in Sect. 4. The design of new selenium reagents would be another interesting trial in the future. The chemistry of nucleophilic selenium will progress along these lines in the next decade.

8
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Radical Reactions Using Selenium Precursors

Philippe Renaud

Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg, Switzerland
E-mail: philippe.renaud@unifr.ch

Organoselenium compounds are very versatile radical precursors which are widely used. Due to their stability and ease of preparation, they offer unique advantages over organic halides as radical precursors. They can be utilized in tin mediated radical reactions as well as in group transfer reactions for the formation of carbon-carbon bonds and carbon-heteroatom bonds. Selenols and diselenides have found applications as reducing agents and radical traps, respectively. A survey of these different reaction types will be given. Information about new reactions based on electron and photoelectron transfers will also be provided.

Keywords: Radicals, Group transfer reactions, Photoelectron transfers, Selenosulfonation, Acyl radicals, Azidoselenenylation, Selenides, Selenol

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1
Introduction

Organoselenium compounds have played an important role in the development of radical reactions. The early radical chemistry of organoselenium compounds was reviewed in 1973 [1] and 1987 [2]. Some basic reactivity aspects of organoselenium compounds have played an important role in this development:

- First, the homolytic cleavage of carbon–selenium bonds and selenium–selenium bonds is an easy process that can be initiated thermally or photochemically. Sun lamp irradiation is usually sufficient to initiate a chain reaction involving organoselenium derivatives.
- Secondly, radical substitution at selenium is very effective with stannyl and silyl radicals. In some cases, carbon radicals are also able to make radical substitutions at selenium.
- Finally, divalent and tetravalent selenium can be involved in reductive and oxidative electron transfer processes.

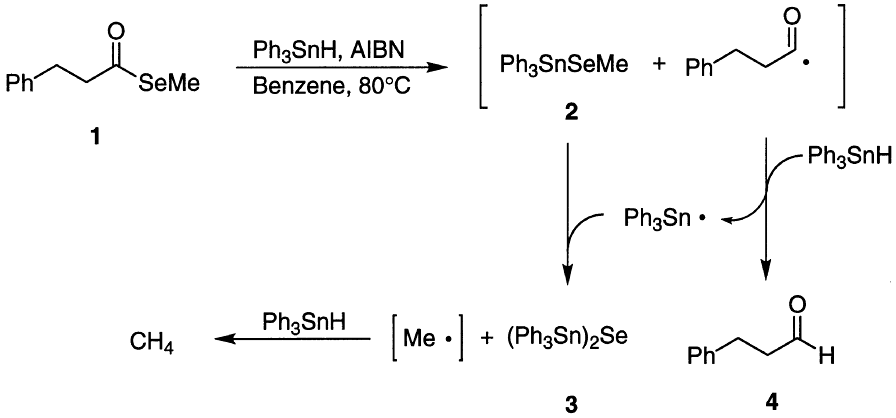
However, the attractiveness of selenium in radical reactions is not only caused by the above mentioned radical properties of organoselenium compounds. The rich chemistry of selenium has also been an important factor since it allows a facile preparation of stable radical precursors as well as attractive functional group transformations when the selenium moiety remains in the reaction products. The different sections of this chapter have been arranged according to reaction types.

2
Radical Precursors for Tin Mediated Reactions and Related Processes

Alkyl and aryl selenides are routinely applied as radical precursors for the generation of a wide range of radicals. They are very versatile radical precursors that are stable and easy to purify. The homolysis of the carbon-selenium bond is extremely easy (similar to a carbon-bromine bond). However, care should be taken when using organoselenium compound as radical precursors in tin mediated chain reactions. Indeed, two important factors have to be considered:

- First, small amount of impurities such as diphenyl diselenide can drastically enhance the rate of reduction by building phenylselenol in situ [3]. This can be a severe drawback, since direct reduction becomes more rapid than the desired radical reaction (usually and inter- or intramolecular carbon-carbon bond forming reaction). This effect is discussed in detail in Sect. 4.2.2.
- Second, methyl selenides may require two equivalents of tin derivatives for complete consumption of the starting material. This point has been demonstrated for acyl methyl selenides [4]. The reduction of the acylselenide **1** to the corresponding aldehyde **4** gave only a 1:1 mixture of **1** and **4** when the reaction was run with one equivalent of Ph_3SnH (Scheme 1). Addition of a second equivalent of tin hydride to the reaction mixture completely consumed the starting acyl selenide **1**. A preparative reaction with 2.2 equivalents of Bu_3SnH provided the aldehyde **4** in 85% yield. This behavior is rationalized by a competing reaction of the stannyl selenide **2** with stannyl radical producing the distannyl radical **3** and a methyl radical, which forms methane upon hydrogen abstraction from tin hydride. This behavior could also be of importance for other types of alkyl selenides as radical precursors. However, this has not been demonstrated experimentally. Therefore, utilizing aryl selenides instead of alkyl selenides as radical precursors is recommended. Indeed, the above mentioned side reaction does not take place with aryl selenides due to the instability of aryl radicals.

Among others, selenides have been used for the generation of alkyl, 1-EWG-substituted alkyl (EWG = electron withdrawing group), acyl, 1-alkoxyalkyl 1-aminoalkyl and 1-amidoalkyl radicals. Significant examples have been selected and are presented below. The availability of the starting selenides will be emphasized.



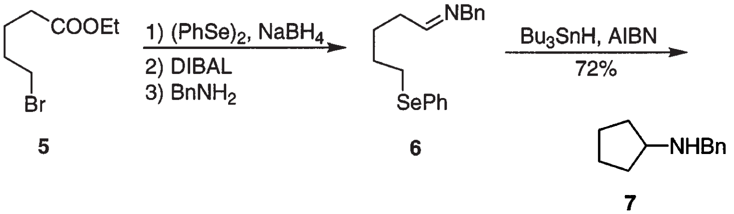
Scheme 1. Acyl methyl selenides require two equivalents of tin hydride for reduction to the corresponding aldehydes

2.1
Generation of Alkyl Radicals

Simple phenyl selenides have been widely used for this purpose. They are easily obtained from nucleophilic or electrophilic selenium reagents. Other reactions based on selenium stabilized carbanions and selenium containing building blocks will also be discussed.

2.1.1
Radical Precursors from Nucleophilic Selenolates

From halides. Halides are easily converted into selenides. Since halides are also suitable radical precursors, this transformation is usually done when side reactions of halides with nucleophiles can occur. An example of this type is reported in Eq. (1). The bromide **5** was converted into a phenyl selenide, which could stand DIBALH reduction and imine formation. Tin mediated cyclization of **6** afforded the cyclopentylamine **7** in 72% yield [5].

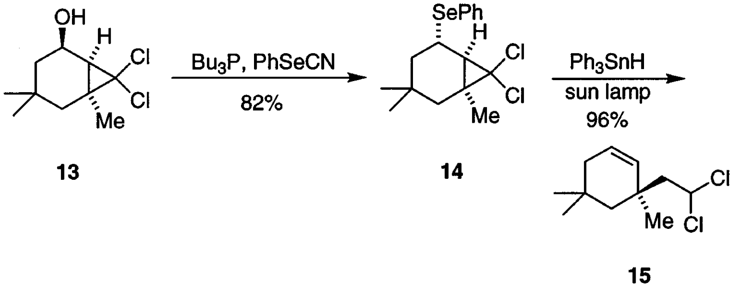


(1)

From alcohols. Alcohols can be transformed into phenylselenides in a stepwise manner via mesylation and reaction with lithium phenylselenolate. This procedure offers obvious advantages over the formation of the corresponding bromides or iodides when subsequent reaction with strong nucleophiles, such as organolithium compounds, are necessary to prepare the radical precursors. The diol **8** is converted to the bis(phenylselenide) **9** via the corresponding bis(mesylate) as shown in Scheme 2 [6]. Compound **9** is converted to the radical precursor **11** via reaction with lithium phenylacetylide followed by alkylation with allylbromide and a Pauson-Khand reaction. Such a reaction sequence would not be feasible with an alkyl halide. The cyclization afforded the expected tricyclic compound **12** in 95% yield.

Direct conversion of alcohols to phenylselenides is also possible. For example, treatment of **13** with $Bu_3P/PhSeCN$ affords the selenide **14** in 82% yield. Irradiation with a sun lamp in the presence of Ph_3SnH gives the monocyclic dichloride **15** [Eq. (2)] [7]. This example illustrates also the high chemoselectivity for the homolysis of the carbon-selenium bond relative to the carbon-chlorine bond of a *gem*-dichloride.

From lactones. Lactones can be opened with phenylselenolates in THF-HPMA. This reaction has been used to prepare a range of radical precursors as shown in Scheme 3 [8,9]. It is interesting to note that the selenide **17** furnishes the product



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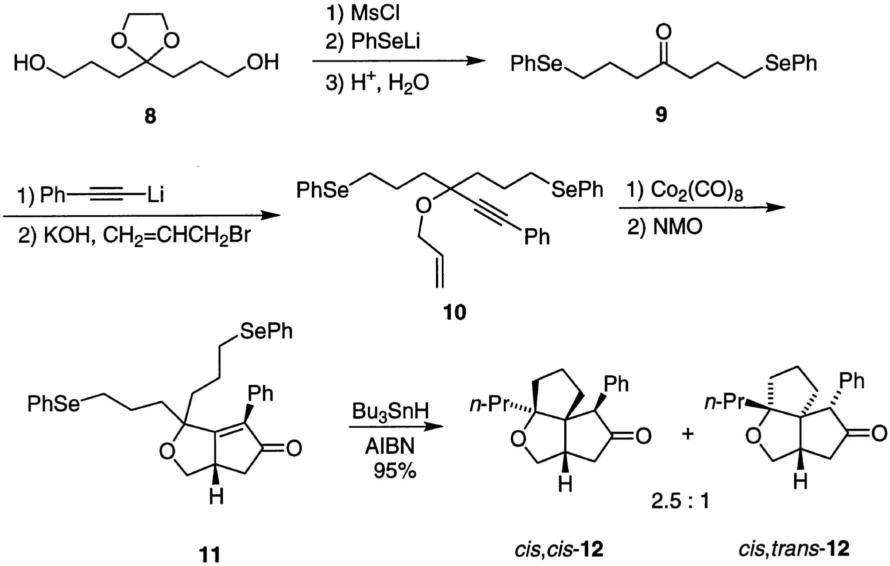
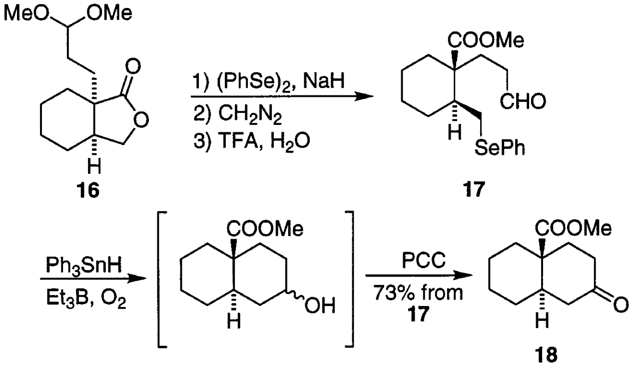


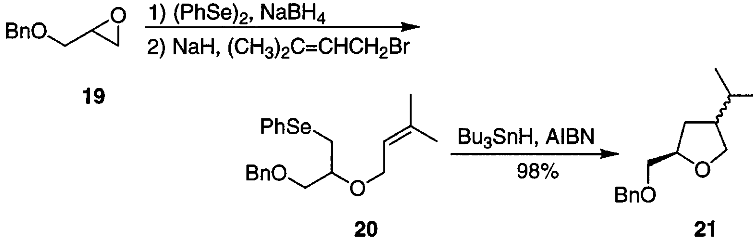
Scheme 2. Phenylselenyl groups are stable to many classical reaction conditions (organolithium, etherification, Pauson-Khand reaction)



Scheme 3. Preparation of selenide radical precursors from lactones

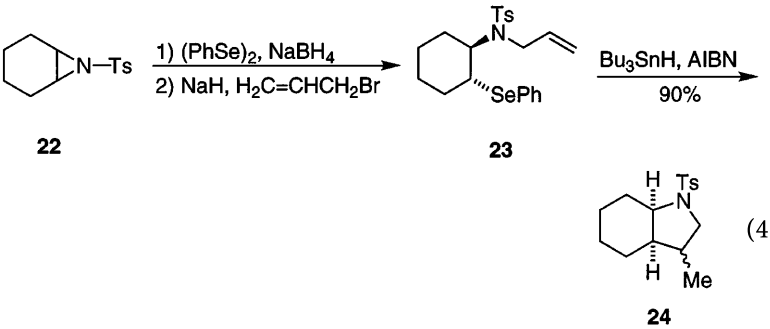
of cyclization onto an aldehyde in good yield when the reaction is initiated with triethylborane/oxygen [10].

From epoxides. A very efficient access to tetrahydrofuran derivatives has been developed based on ring opening of oxiranes with selenolates. For instance, preparation of 2,4-disubstituted tetrahydrofurans from epoxides is shown in Eq. (3) [11]. Opening of the epoxide **19** with diphenyldiselenide/$NaBH_4$ followed by prenylation gives the radical precursor **20** in excellent yield. Cyclization furnishes the tetrahydrofuran **21** in almost quantitative yield but with a modest stereocontrol. The oxirane opening approach described here competes with the electrophilic alkoxyselenenylation reported below (Sect. 2.1.2).



(3)

From aziridines. *N*-Tosylaziridines, easily obtained by aziridination of the corresponding alkenes, can be opened by selenolate reagents and furnish, after straightforward *N*-alkylation, radical precursors suitable for the preparation of pyrrolidine derivatives [12]. The preparation of octahydro-1*H*-indole **24** is shown in Eq. (4). A competing process involving radical azidoselenenylation of alkenes has also been developed and will be discussed later (Sect. 5.2).

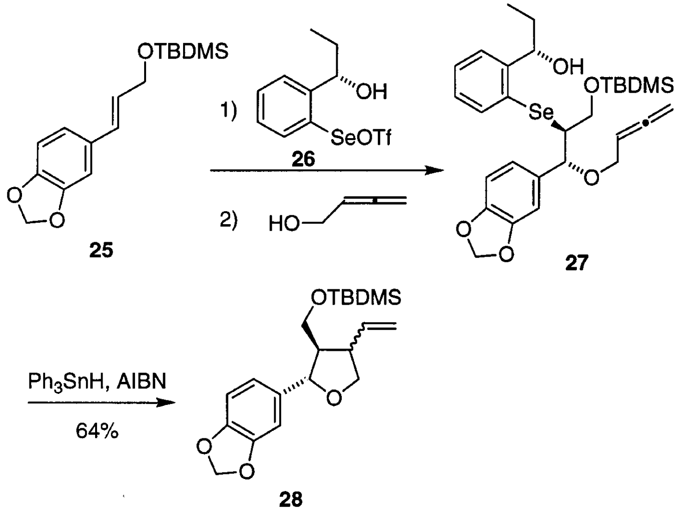


(4)

2.1.2

Radical Precursors from Electrophilic Selenium

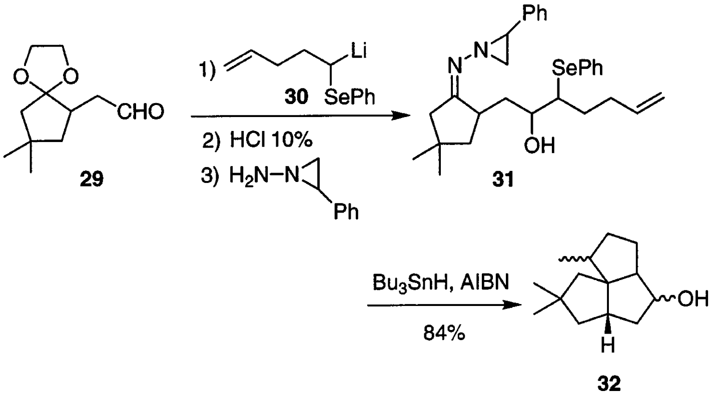
The very rich chemistry of electrophilic selenium has been used at many occasions for the preparation of alkyl radical precursors [13]. For instance, they have been used for the preparation of 2-deoxynucleosides [14, 15]. Recently, an elegant synthesis of (+)-samin was reported. The key reactions are the addition of the chiral selenium electrophile **26** to the alkene **25** in the presence of 2,3-butadien-1-ol and the radical cyclization of **27** leading to the tetrahydrofuran **28** [Eq. (5)] [16]. This example shows that even hindered aryl selenides are excellent radical precursors.



(5)

2.1.3
Radical Precursors from Selenium Stabilized Carbanions

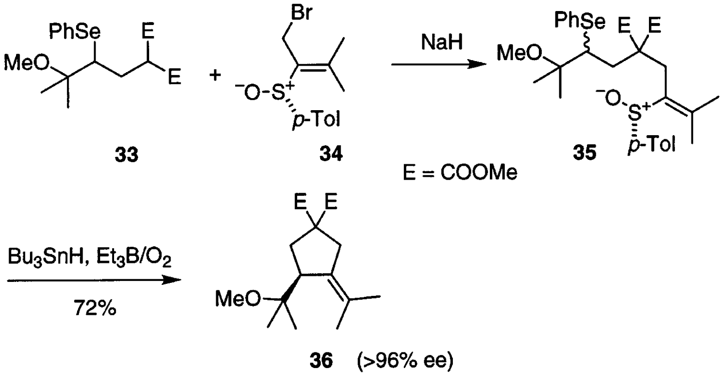
Selenium can act as a carbanion stabilizing group. This effect can be used for the facile generation of 1-selenosubstituted alkyllithium derivatives that are useful intermediates for the preparation of radical precursors. This strategy is demonstrated in Eq. (6) by the preparation of **31**, a radical precursor for the synthesis of the angular triquinane pentalenene [17]. The organolithium derivative **30** reacts with **29** to give **31** after subsequent acetal cleavage and hydrazone formation. Treatment of the hydrazone **31** with Bu_3SnH/AIBN affords the backbone of pentalenene in good yield.



(6)

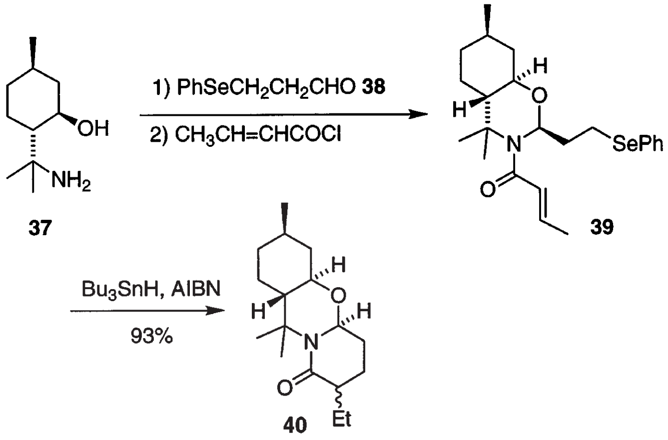
2.1.4
Selenides as Building Blocks

An efficient way of introducing selenium in a radical precursor is the use of selenium containing building blocks. The selenides are particularly appropriate when the reaction sequence involves reaction steps that are incompatible with halides or when the corresponding halides are not stable. In Eq. (7), preparation of the selenenylated alkenyl sulfoxide **35** by alkylation of malonate **33** with the bromide **34** is described [18]. This procedure is not feasible with the corresponding halide due to cyclopropane formation via intramolecular alkylation. Radical cyclization of **35** in a 5-*exo* mode affords, after elimination of the phenylsulfinyl radical, the methylenecyclopentane **36** in good yield and excellent enantioselectivity.



(7)

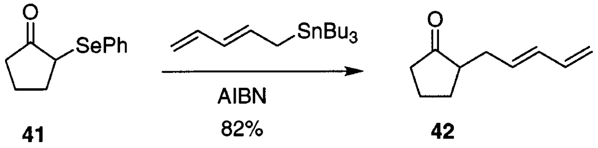
3-Phenylselenylpropanal **38** is a very good building block for the preparation of radical precursors since it is not prone to *β*-elimination [19, 20]. Condensation of the aminoalcohol **37** with **38** gives an *N*,*O*-acetal, which can be *N*-acylated with crotonyl chloride to afford the precursor **39**. Upon treatment with Bu_3SnH, **39** gives the tricyclic compound **40** in 93% yield [Eq. (8)] [20].



(8)

2.2
Generation of Carbonyl-Substituted and Related Alkyl Radicals

The preparation of α-selenoketones, esters, nitriles and related compounds can easily be performed via alkylation of the corresponding enolates or stabilized carbanions [21]. These compounds have found many synthetic applications in radical chemistry. In Eq. (9), a typical example involving a ketone is depicted [22]. The stability of α-selenoketones such as **41** is remarkable. Similar reactions with lactones have been performed. For instance, this approach has been applied to the stereoselective synthesis of oxygen-containing rings to either faces of a bicyclic structure [23]. The approach based on α-selenenylation/radical allylation compares favorably with classical enolate allylation procedures, which usually leads to mixture of mono- and diallylated compounds. Furthermore, this strategy is excellent for the preparation of quaternary carbon centers [24] as shown by the conversion of **43** to **45**, a key intermediate for the synthesis of fredericamycin A, [Eq. (10)] [25]. Similar reactions with sulfoxides [26] and phosphonates [27] have also been reported.



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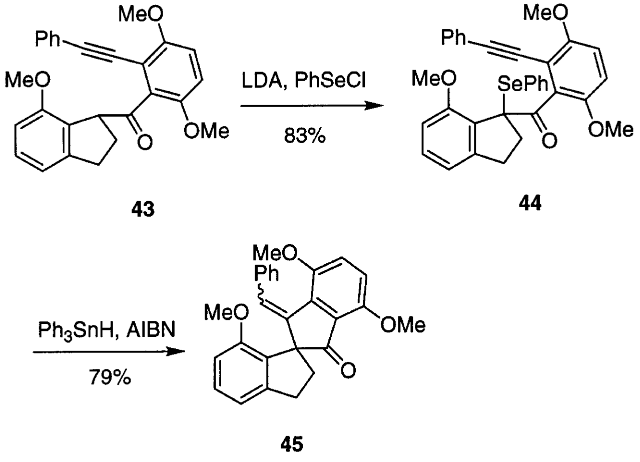
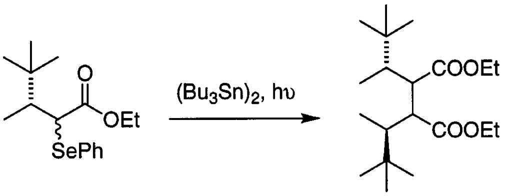
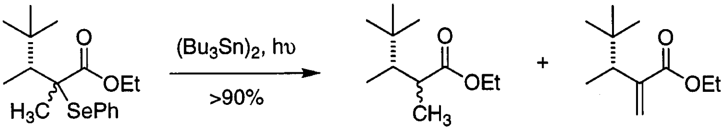


(10)

α-Selenoesters have also been used for radical dimerization [28]. For instance, the selenide **46** gives, upon irradiation in the presence of one equivalent of hexabutyldistannane, the dimer **47** [Eq. (11)] [29]. A competing process, i.e. the disproportionation of the radical intermediate is observed with tertiary radicals [Eq. (12)]. Similar disproportionation products have also been observed during the addition of sterically hindered radical to unreactive alkenes [30].



46 **47** (11)

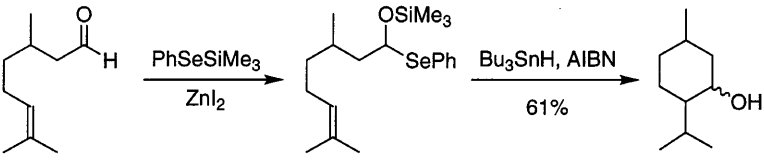


48 **49** **50** (12)

2.3
Generation of Alkoxy- and Amino-Substituted Alkyl Radicals

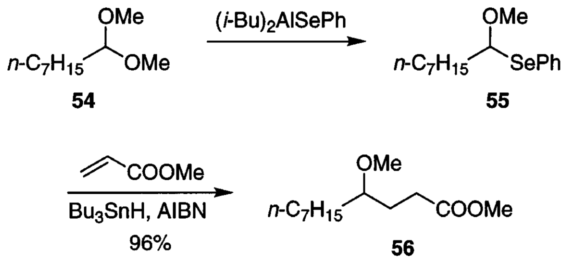
The generation of 1-alkoxy- and 1-aminoalkyl radicals from *O*,*X*- and *N*,*X*-acetals is a straightforward approach. However, this approach is seldom used due to the instability of these mixed acetals when X is an halide (Cl, Br, I) or due to the lack of reactivity when X is a phenylthio substituent. Selenium derivatives (X = SeR) are stable and can be purified by silica gel chromatography. As expected, they present excellent radical precursor properties. Moreover, different approaches to prepare the *O*,*Se*- and *N*,*Se*-acetals are reported in the literature.

Aldehydes can be converted directly into *O*,*Se*-acetals and used for radical cyclizations. This procedure is equivalent to a ketyl radical cyclization process, a typical example is shown in Eq. (13) [31]. Acetals such as **54** can also easily be converted into *O*,*Se*-acetals by treatment with (i-Bu)$_2$AlSePh. The selenide **55** is used for an efficient radical carbon-carbon bond formation [Eq. (14)] [32]. A very reliable route to *O*,*Se*-acetals from alcohols through the corresponding (tributylstannyl)methyl ethers has been used for the preparation of tetrahydrofuran derivatives [33].



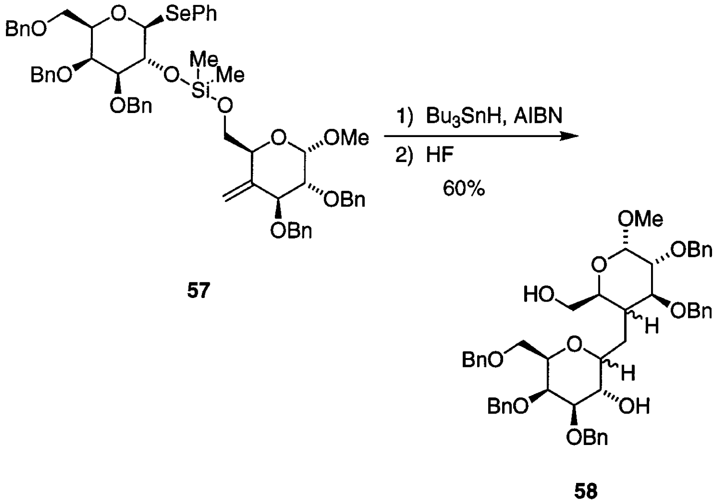
51 **52** **53** (13)

However, the most important applications of *O*,*Se*-acetals are related to sugar and nucleotide derivatives [34–36]. For instance, the generation of anomeric radicals from *O*,*Se*-acetals is a very popular approach. The preparation of C-disaccharides by an elegant 8-*endo*-trig cyclization involving two tethered monosaccharides has been reported [Eq. (15)] [37, 38]. In a related manner, a concise route to tunicamycin antibiotics has been developed: the key feature of



(14)

this approach is a silicon-mediated reductive coupling of aldehydes and allylic alcohols via the *O*,*Se*-acetal **59** [Eq. (16)] [39]. Radical cyclization followed by desilylation gives the coupling product **60** in 60% yield.



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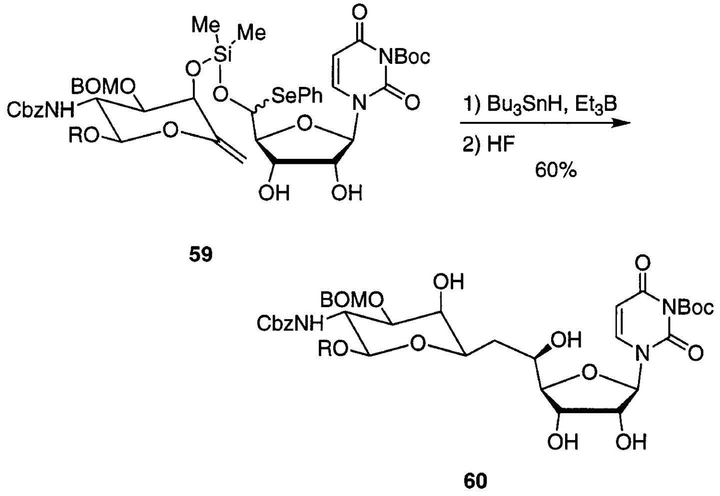
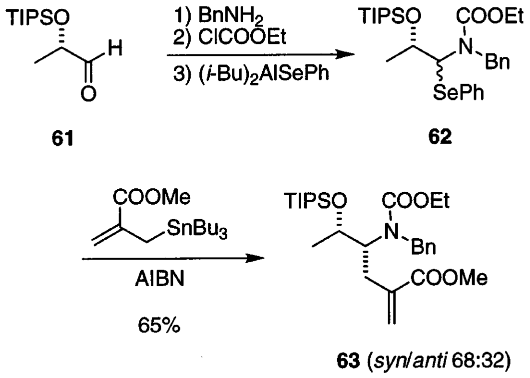


(16)

Other acetals such as *Se*,*Se*- [40], *S*,*Se*- [26] and *N*,*Se*-acetals [41, 42] have also been used to generate *Se*-, *S*- and *N*-substituted alkyl radicals. This strategy is one of the most efficient for the preparation of 1-amido substituted alkyl radicals from aldehydes [Eq. (17)]. Conversion of the aldehyde to an *N*,*Se*-acetal is achieved by conversion to the imine and treatment with ClCOOEt and $(i\text{-Bu})_2$AlSePh. Starting from lactaldehyde **61**, the *N*,*Se*-acetal **62** is prepared without racemization. Radical allylation affords the protected amine **63** in 65% yield [43].



61 **62**

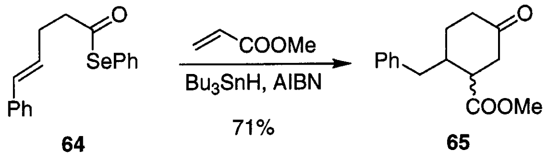
63 (*syn*/*anti* 68:32)

(17)

Other selenoacetals have been prepared by means of radical phenylseleno group transfer reactions and by trapping of radicals with diphenyl diselenide, these procedures will be discussed later in this chapter (Sects. 3.1 and 5.2).

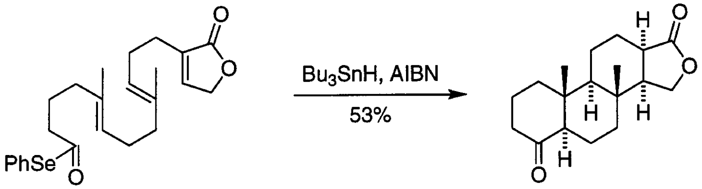
2.4
Acyl and Related Radicals

Acyl radicals are very useful synthetic intermediates. Their preparation is not simple since the corresponding halides are highly electrophilic and cannot be used as radical precursors. Organocobalt compounds were proposed as suitable source of acyl radicals [44]. However, the use of acyl selenides proved to be more general [45, 46]. These radical precursors can be efficiently prepared from the corresponding carboxylic acids and esters [47]. Acyl phenyl selenides should be preferred, when possible, relative to acyl methyl selenides due to the consumption of two equivalents of tin hydride with this last system (Scheme 1) [4]. Acyl selenides have found many applications in tandem radical additions to alkenes. Examples of intermolecular [Eq. (18)] [48, 49] and intramolecular reactions [Eq. (19)] [50a] are reported. The enoyl selenide **68** give the unsaturated acyl radicals **69**. This intermediate



64 **65**

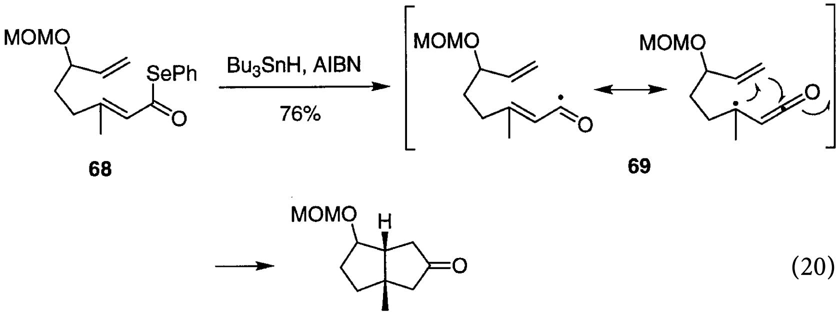
(18)



66 **67**

(19)

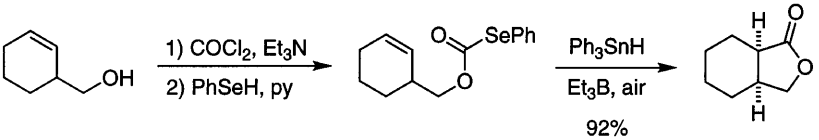
could react via its α-ketene alkyl radical form, by addition to a proximate double bond followed by tandem cyclization onto the ketene moiety, resulting in a neat one-pot synthesis of the diquinane **70** [Eq. (20)] [50b].



68 **69** **70**

(20)

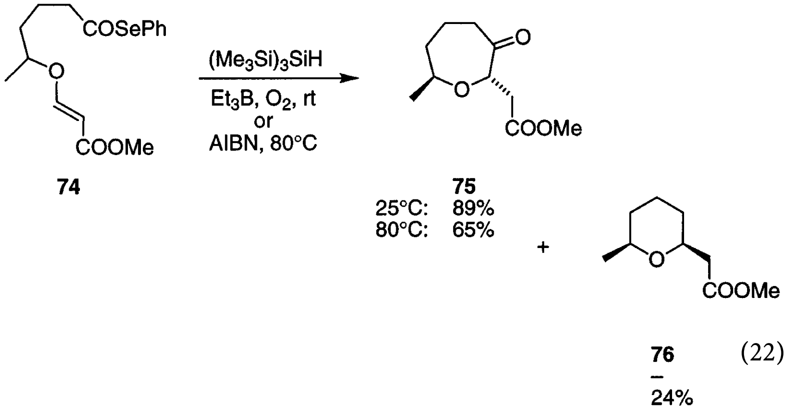
Starting from selenocarbonates, the synthesis of lactones could be achieved in an efficient manner as demonstrated by the conversion of **71** to **73** [Eq. (21)] [9,51]. The same strategy applied to selenocarbamates allows the preparation of lactams [52].



71 **72** **73**

(21)

Decarbonylation of acyl radicals is often an important side reaction, this is particularly true when the radical resulting from the decarbonylation is stabilized (secondary and tertiary alkyl radical, resonance stabilized radical, etc.). The decarbonylation can be partially avoided by running the reactions at lower temperature. The conversion of **74** to **75**/**76** [Eq. (22)] illustrates this fact [53]. At room temperature, with tris(trimethylsilyl)silane as reducing agent, the reaction gives the oxepan-3-one **75** in 89% yield. The same reaction in refluxing benzene gives **75** in 65% yield along with **76**, the product of decarbonylation/cyclization. Interestingly, the decarbonylation of acyl radical has been used to develop a decarboxylation procedure of carboxylic acids. This procedure is particularly efficient with α-heteroatom substituted acids such as α-hydroxy/alkoxy acids [54, 55] and α-amino/amido acids [56, 57]. For example, *N*-benzyl dehydroglutaric acid **77** could be allylated in a decarboxylative pathway via its selenoester **78** [Eq. (23)] [58]. This decarboxylation procedure compares favorably with the Barton decarboxylation procedure. Indeed, the acyl selenides are stable, easy to purify and produce the desired decarbonylated radicals in good to excellent yields.



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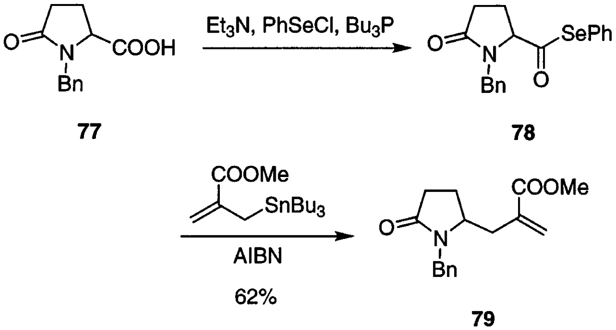
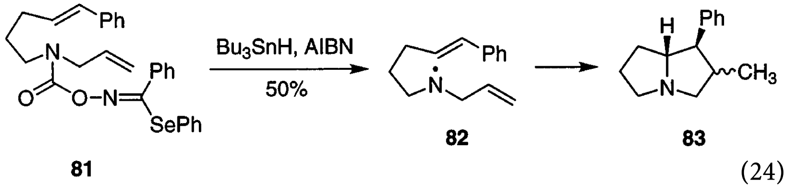


(23)

Finally, it is worth mentioning the rich chemistry of phenyl benzenecarbimidoselenoate **80**, easily prepared from the corresponding aldoxime by treatment with *N*-chlorosuccinimide followed by sodium phenylselenolate. This reagent can be used for generation of carbon, nitrogen or oxygen centered radicals according to Scheme 4 [59]. Examples illustrating the formation of an aminyl radical and of an alkoxy radical are depicted in Eqs. (24) and (25), respectively.



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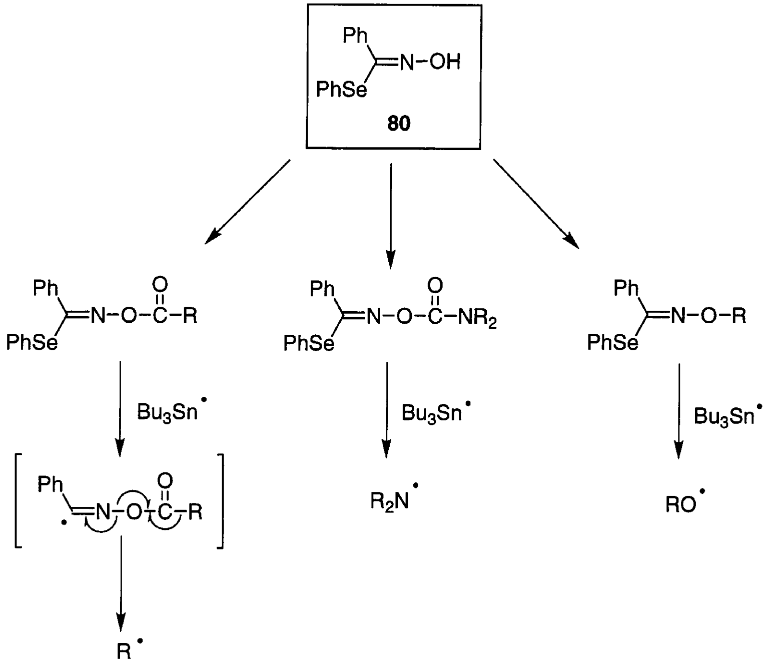
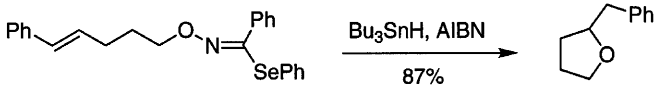


Scheme 4. The radical chemistry of phenyl benzenecarbimidoselenoate derivatives

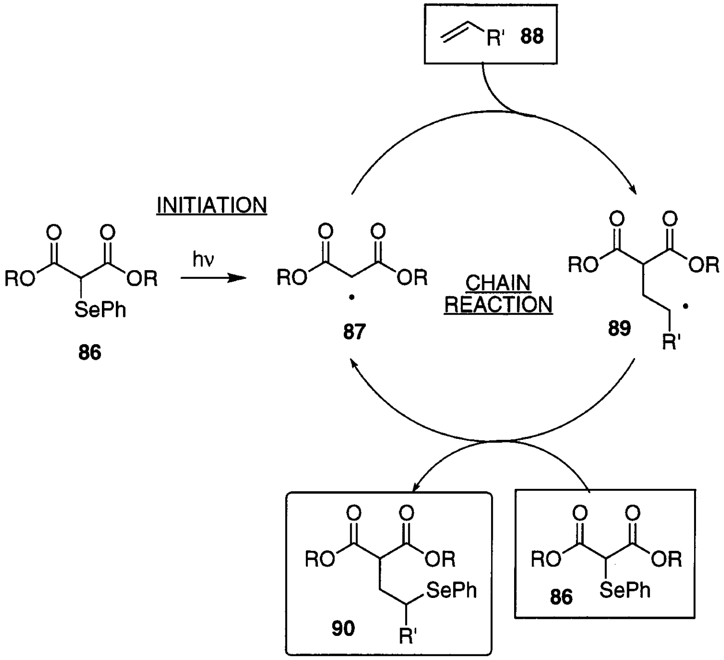


84 85 (25)

3
Seleno Group Transfer Reactions

3.1
Carbon-Centered Radicals

Following the pioneer work of Kharasch [60], methods involving radical transfer of halides have been developed. The atom transfer method has emerged in the 1980s as one of the best method for conducting intra- and intermolecular radical additions to olefins [61]. This approach is particularly appealing from an atom economy point of view since all atoms remains in the final product. The non-reductive nature of these reactions is also particularly important for the preparation of functionalized molecules. Halides transfers and more particularly iodine atom transfers have found nice applications for cyclizations, annulations and cascade reactions [62]. These reactions are based on exothermic radical steps, such as the addition of an alkyl radical to an olefin, followed by an exothermic atom transfer step. This exothermicity criteria limits the methods to starting halides leading to stabilized radicals. Such halides, particularly the iodides, are usually not very stable. Moreover, catalysis by transition metals or reactions in the presence of hexaalkyldistannane (to trap the undesired molecular iodine) are sometimes necessary to run halogen atom transfer reactions [63]. More recently, the transfer of a phenylseleno group from phenylselenomalonates has been reported [64]. The overall process is described in Scheme 5.



Scheme 5. Addition of phenylselenomalonate to alkenes under group transfer conditions

Irradiation of the selenomalonate **86** gives the malonyl radical **87**. This electrophilic radical adds efficiently to the olefin **88** to furnish the radical adduct **89**, this step (radical addition to an olefin) is exothermic. The abstraction of a phenylseleno group by **89** leads to the addition product **90** and to the starting malonyl radical **87**. This step is also exothermic due the high stabilization of the malonyl radical **87** relative to the radical adduct **89**. The rate constants for selenium transfer have been measured [65]. For the transfer from phenylselenomalonate to primary alkyl radicals, a rate constant of 8×10^5 $M^{-1}s^{-1}$ has been found. This constant is in the same order of magnitude as the reaction with the corresponding bromide and approximately 200–300 times slower than the corresponding iodides. Since the selenium transfer is a slow process, it is important to have a strongly exothermic group transfer step. Therefore, the selenium atom transfer under standard conditions works efficiently only when highly

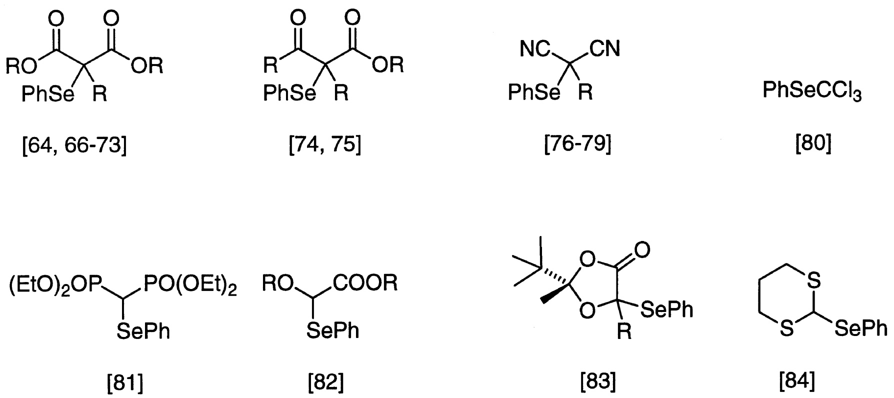
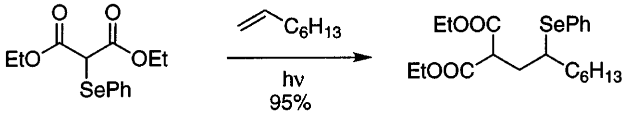


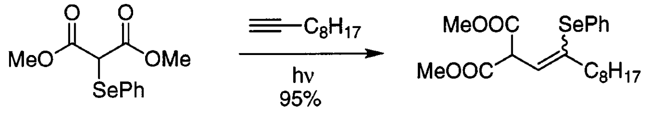
Fig. 1. Radical precursors for phenylseleno group transfer reactions

stabilized radicals are generated. A list of the main type of radical precursors used for selenium atom transfer is depicted in Fig. 1. Malonates [64, 66–73], *β*-ketoesters [74, 75], malononitriles [76–79], haloalkanes [80], diphosphonate [81], glycolate derivatives [82, 83] and dithianes [84]. More substrates such as *α*-seleno-esters, -nitriles, -ketones and -sulfones can also be used, however, the efficiency of the process is reduced [68].

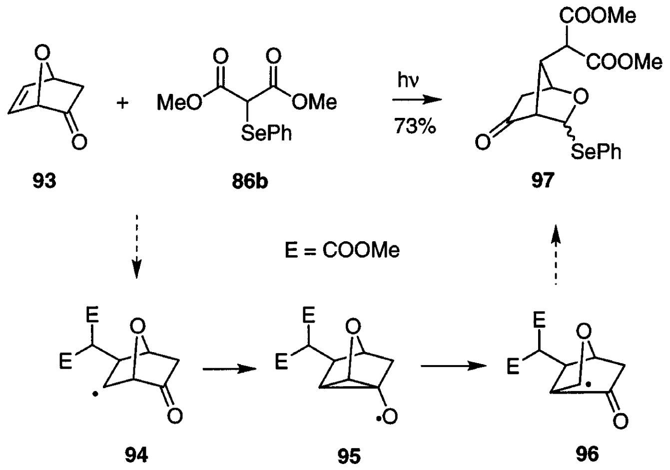
Typical examples involving the selenomalonate **86** are shown in Eqs. (26–28). Addition to simple unactivated alkenes [Eq. (26)] and alkynes [Eq. (27)] occur in good yield [64]. Transfer of a phenylseleno group is slow relative to iodine atom transfer, therefore, it is particularly useful when radical rearrangements are desired. For example, addition of **86b** to 7-oxanorbornenone **93** gives the rearranged product **97** [Eq. (28)] [71, 72, 85, 86]. The observed 1,2-acyl migration (**94** → **96**) is a slow process going presumably through the cyclopropyloxy radical **95**. This rearrangement is not observed when fast atom tranfer reactions are used. Indeed, addition of bromotrichloromethane via a bromine atom transfer to 7-oxanorbornenone **93** affords only the unrearranged product [79]. A second important point for the success of the rearrangement described in Eq. (28) is the stability of the final *O*,*Se*-acetal **97** (the equivalent bromide or iodide would not be stable).



86a **91** (26)

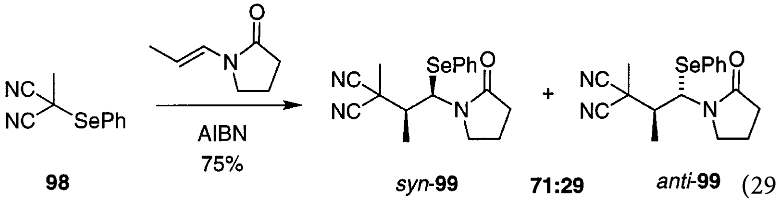


86b **92** (27)

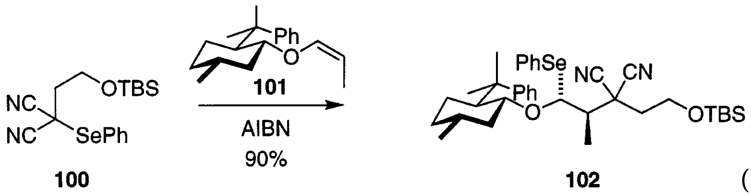


(28)

Malononitrile radicals could also be generated from the corresponding selenides and are excellent substrates for phenylseleno group transfer reactions. The reaction can either be initiated by sun lamp irradiation or using AIBN. Different examples illustrating the synthetic potential of these compounds are depicted in Eqs. (29–31). Again, the stability of the final products should be emphasized. Addition to enamides produces stable *N*,*Se*-acetals Eq. (29) [78]. By using the chiral enol ether **101** as radical trap, the *O*,*Se*-acetal **102** is obtained with good diastereoselectivity [Eq. (30)] [77]. Finally, related malononitriles such as **103** can be used for annulation and cyclization reactions [Eq. (31)]



(29)



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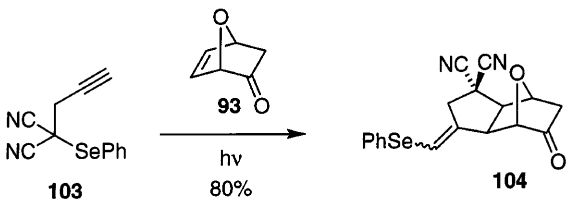
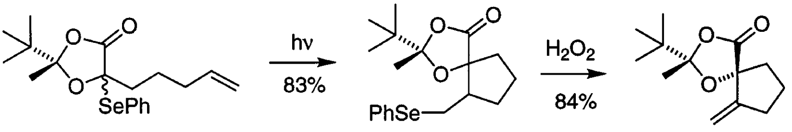


(31)

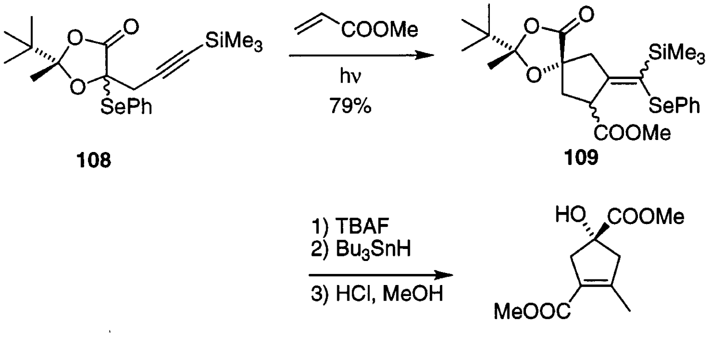
[76, 79]. Alkylative carbonylation of alkenes accompanied by a phenylselenyl group transfer has been used to prepare selenoesters via a three component coupling process [87].

The reaction with captodative stabilized radicals is also possible [82]. For instance, the preparation of 1-hydroxycyclopentanecarboxylic acid derivatives from a chiral glycolic acid equivalent is reported [83]. Cyclization and annulation procedures are depicted in Eqs. 32 and 33, respectively.



105 **106** **107**

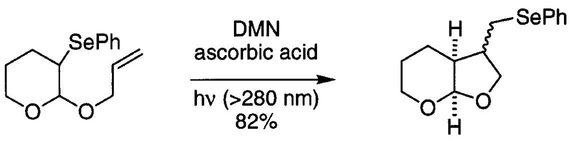
(32)



108 **109** **110**

(33)

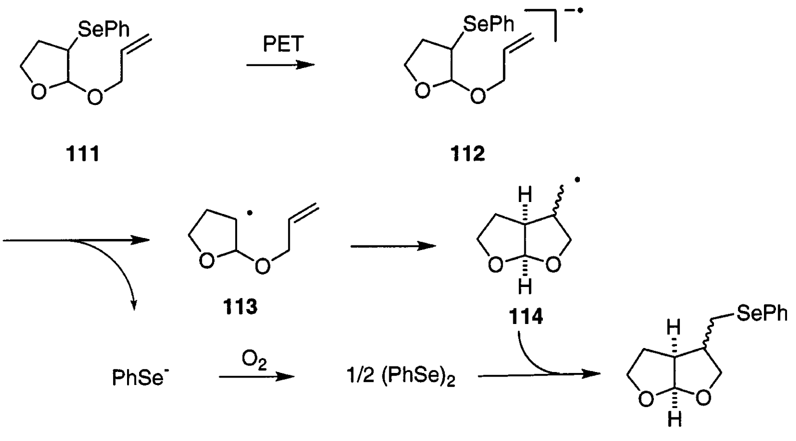
Recently, photosensitized activation of carbon-selenium bonds was used to achieve phenylseleno group transfer reactions starting with simple alkyl selenides [Eq. (34), Scheme 6)] [88]. The process involves a photosensitized electron transfer (PET) promoted reductive activation of the starting selenide **111** to the radical anion **112**. Fragmentation affords the radical **113** and the phenylselenolate anion. The selenolate dimerizes in the presence of oxygen to give diphenyl diselenide. After radical cyclization, **114** reacts with diphenyl diselenide to give the final selenide **115**. This procedure is expected to be general for intramolecular radical reactions such as cyclizations and radical rearrangements. So far, no intermolecular process has been reported.



111 **115**

(34)

DMN: 1,5-dimethoxynaphthalene



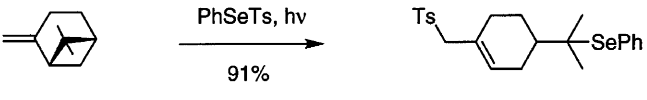
Scheme 6. PET induced phenylseleno group transfer cyclizations

3.2
Selenosulfonation

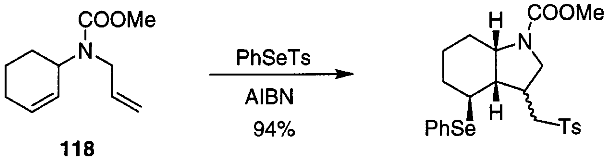
Arenesulfonyl selenides are known for a long time to be excellent radical precursors. They have been widely used for selenosulfonation of alkenes and related compounds. Reviews on this subject have already appeared [2, 89] and only selected examples with high synthetic potential will be given here.

3.2.1
Selenosulfonation of Alkenes

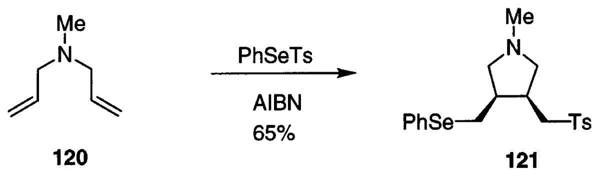
This reaction is particularly interesting when the intermediate radical adduct rearranges or forms a new carbon–carbon bond. In Eq. (35), ring opening of a cyclobutylmethyl radical derived from β-pinene **116** gives the cyclohexene derivative **117** [90]. Cyclization reactions have also been developed as demonstrated in Eqs. (36) and (37) [91–93]. The main interest of this approach is the high level of functionalization of the final products.



116 **117** (35)



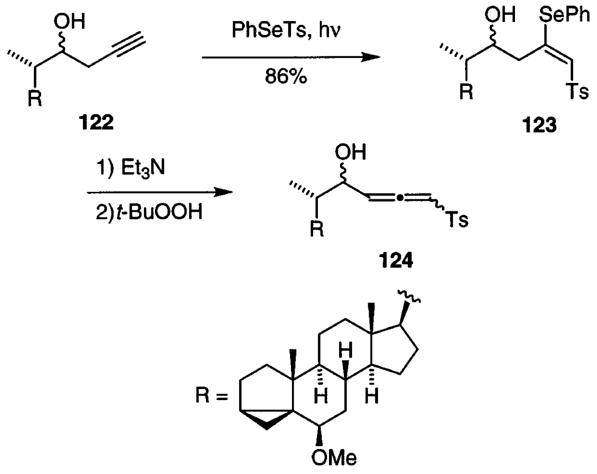
118 **119** (36)



(37)

3.2.2
Selenosulfonation of Alkynes

Radical selenosulfonation of alkynes leads to vinyl selenides that can be easily converted into allenes. Such an example is shown in Eq. (38) [94].



(38)

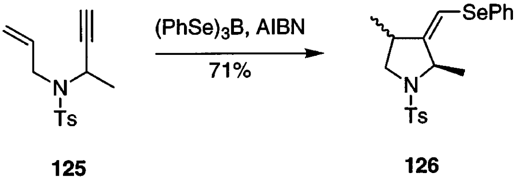
4
Phenylselenyl Radical Mediated Reactions

Phenylselenyl radicals can easily be generated by irradiation of diphenyl diselenide. However, due to their lack of reactivity towards non-activated alkenes and alkynes [95], this direct approach has rarely been used for synthetic purposes [96].

4.1
From Selenoboranes

Tris(methylseleno)borane and tris(phenylseleno)borane react with terminal alkynes in the presence of oxygen or in the presence of AIBN as radical initiator [97, 98]. The mechanism of this reaction is not completely elucidated, however, the generation of phenylselenyl radical intermediates is assumed by the authors. When applied to enynes, this reaction furnish cyclic compounds. An approach to the frameworks of kainoids is depicted in Eq. (39). Treatment of the enyne

125 with tris(phenylseleno)borane in the presence of AIBN yields the pyrrolidine **126**.



(39)

4.2
From Selenols

Phenylselenyl radicals are also formed when benzeneselenol is used as a reducing agent. These radicals are usually unable to propagate chain reactions since they dimerize rapidly. Two important exceptions are known: the propagation with acyl thiohydroxamates ("Barton esters") and the use of polarity reversal catalysis.

4.2.1
Picosecond Radical Kinetics with Benzeneselenol

Benzeneselenol is an extremely fast reducing agent for alkyl radicals. The rate constant for benzeneselenol trapping of alkyl radicals is $1.2 \times 10^9 s^{-1}$ at 20 °C [99]. This is faster than the coupling reaction of alkyl radicals with 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) [100]. This exceptionally large rate constant makes benzeneselenol a very useful radical clock for the measurement of very fast radical processes [99].

4.2.2
Polarity Reversal Catalysis with Benzeneselenol

The undesired effect. Minor amounts of diphenyl diselenide (or benzeneselenol) have a detrimental effect on stannane-mediated radical rearrangements. Selenides are often contaminated with diphenyl diselenide, due either to the use of diphenyl diselenide during the synthesis of the precursor or due to the (light induced) decomposition of the radical precursor itself. Diphenyl diselenide can suppress slow rearrangements and significantly lower the yields of even relatively rapid rearrangements [3]. To illustrate this point, the reaction of acetobromoglucose **127** with Bu_3SnH/AIBN affords the 2-deoxyglucopyranose **128** contaminated with 11% of the product of direct reduction **129**. In the presence of only 10 mol % diphenyl diselenide, the migration of the acetoxy group is completely suppressed and only the product of direct reduction **129** is formed [Eq. (40)]. The explanation of this effect is related to the well established polarity reversal catalysis (Scheme 7). The alkyl radical is reduced very efficiently with PhSeH (PhSeH reacts with alkyl radicals faster than Bu_3SnH by more than 3

$$\mathrm{R\bullet + PhSeH} \xrightarrow{\text{fast}} \mathrm{RH + PhSe\bullet}$$

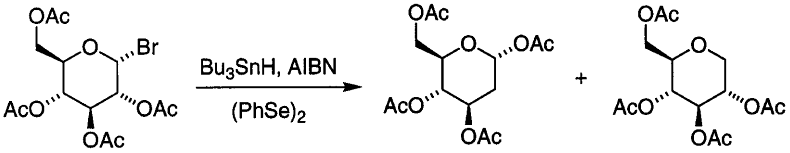
$$\mathrm{PhSe\bullet + Bu_3SnH} \xrightarrow{\text{fast}} \mathrm{PhSeH + Bu_3Sn\bullet}$$

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

$$\mathrm{(R\bullet + Bu_3SnH} \xrightarrow{\text{slow}} \mathrm{RH + Bu_3Sn\bullet)}$$

Scheme 7. Polarity reversal catalysis

orders of magnitude). The selenyl radical is unable to propagate a chain reaction but is rapidly reduced by tin hydride to regenerate the selenol and a tin radical that propagates the chain reaction. In summary, the slow reduction of alkyl radicals by tin hydride has been replaced by two very fast steps. The selenol acts as a catalyst for the reduction process. In conclusion, time spent in assuring rigorous absence of diselenides from the radical precursors will be rewarded by higher yields of rearranged products.

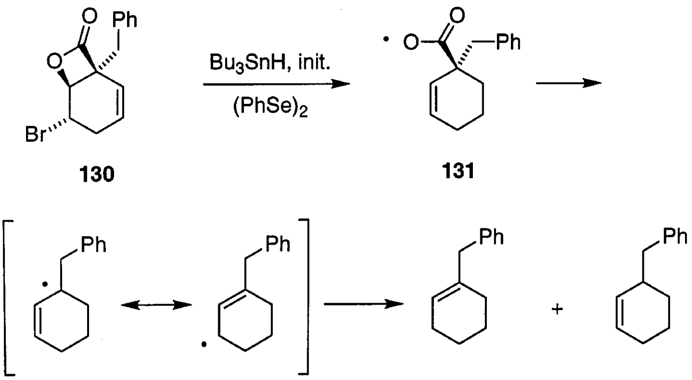


127 **128** **129**

no $(PhSe)_2$: 89 : 11

10 mol% $(PhSe)_2$: <5 : >95 (40)

Synthetic applications. Tin mediated radical chain reactions involving resonance-stabilized radicals such as allyl radicals are usually not efficient due to poor chain propagation. Indeed, the small exothermicity of the reaction of allylic radicals with Bu_3SnH makes this step slow and inefficient, radical dimerization becomes an important side reaction. This poor chain propagation could be overcome by the inclusion of a catalytic quantity of diphenyl diselenide that is reduced in situ to produce phenylselenol which, because of its exceptional hydrogen donating capacity, is able to reduce stabilized radicals [101]. This approach is illustrated by the example depicted in Eq. (41). Reduction of the bromolactone **130** with tin hydride affords the carbonyloxy radical **131**, which decarboxlyates to give the allylic radical **132**. In the presence of Bu_3SnH alone, a mixture of cyclohexenes **133** and **134** is isolated in 22% yield accompanied by dimeric products. When 10 mol % diphenyl diselenide is added to the reaction mixture, the conversion is faster and **133** is isolated as single reaction product in 85% yield. The same strategy has been used for the radical addition to arenes [102]. The diphenyl diselenide effect was also used for fine tuning of the 5-*exo*/6-*endo* product ratio in the stannane mediated cyclization of vinyl iodides [103].



130 **131** **132**

(41)

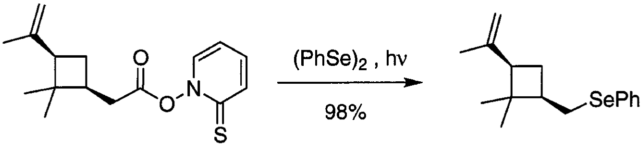
	133		134	yield
no $(PhSe)_2$:	88	:	12	22%
10 mol% $(PhSe)_2$:	100	:	0	85%

5
Diselenides as Radical Traps

Diphenyl diselenide reacts efficiently with alkyl radicals to give alkyl phenyl selenides. The rate of this reaction for primary alkyl radicals is $2.6 \times 10^7\,M^{-1}s^{-1}$ at 25 °C. The trapping reaction could be applied to many different types of radical reactions and deliver a selenide which is particularly suitable for further functionalization of the final product. Some typical examples are presented below.

5.1
Selenodecarboxylation

The decarboxylation of carboxylic acid via thiohydroxamate derivatives (often called "Barton esters") is an efficient procedure for the generation of radicals. When this reaction is performed in the presence of diphenyl diselenide, the corresponding selenides are obtained in excellent yield [Eq. (42)] [104]. For example, this reaction has been used for the preparation of *N*,*Se*-acetals from *α*-aminoacids [105, 106].

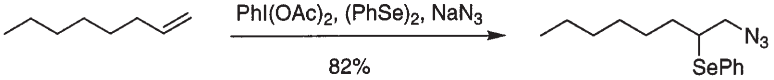


135 **136**

(42)

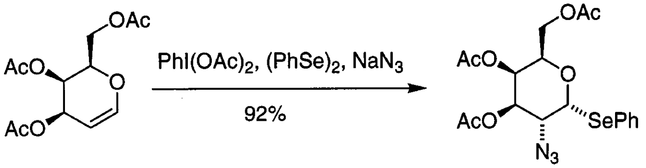
5.2
Azidoselenenylation

Radical azidoselenenylation of olefin is obtained upon treatment with diphenyl diselenide/(diacetoxy)iodobenzene/sodium azide [Eq. (43)] [107–109]. The unusual regiochemistry of this process, the azide is introduced at the least substituted position, is an indication of a possible radical mechanism. Reactions with radical probes such as 1,6-heptadiene and *β*-pinene corroborate this hypothesis [107]. The mechanism of the reaction is depicted in Scheme 8. Addition of the azide radical followed by trapping of the adduct with diphenyl diselenide afford the product of azidoselenenylation. This reaction has found very interesting applications in the field of carbohydrate chemistry [110, 111]. Treatment of glucals under azidoselenenylation conditions furnishes 2-azido-1-phenylselenoglycopyranosides which are precursors of a variety of aminosugars. For example, treatment of 3,4,6-tri-*O*-acetyl-D-glucal **139** under the same conditions affords the 2-azido sugar **140** in 92% yield (Eq. 44) [110].



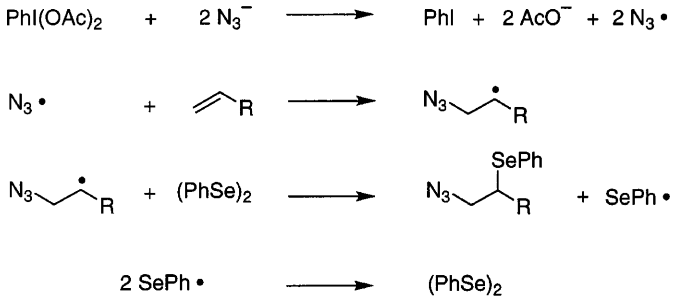
137 **138**

(43)



139 **140**

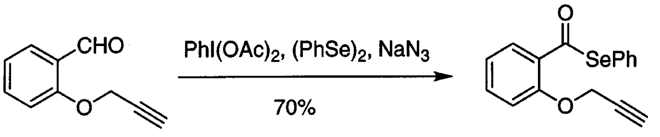
(44)



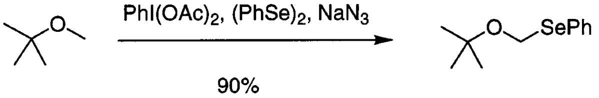
Scheme 8. Mechanism of the radical azidoselenenylation

5.3
Miscellaneous Reactions

The reagent of azidoselenenylation described above can also be applied to the conversion of aldehydes into selenoesters [Eq. (45)] and ethers into *O,Se*-acetals [Eq. (46)] [112]. The key step of this process is a hydrogen atom abstraction. Interestingly, the hydrogen abstraction step is faster than the azidoselenenylation of alkynes as demonstrated in Eq. (45).

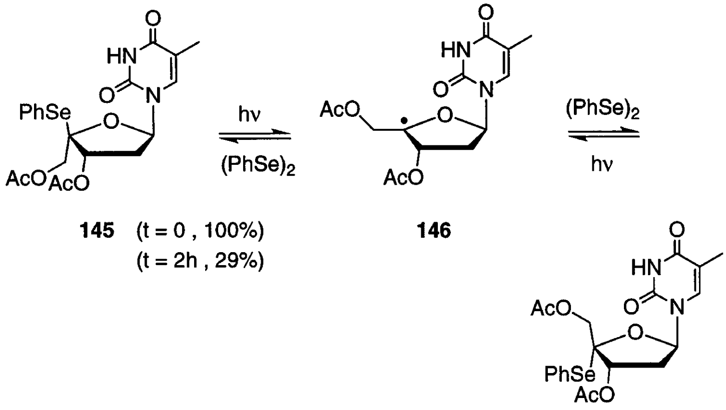


141 **142** (45)



143 **144** (46)

An elegant epimerization of 4′-phenylseleno deoxyribonucleosides **145** was achieved by irradiation of the selenoacetal in the presence of diphenyl diselenide with a Hg-high pressure lamp [Eq. (47)] [113]. This epimerization proceeds via the reversible formation of the 4′-C radical **146**. After 2 h of irradiation, the equilibrium mixture **145**/**147** = 29:71 is reached.



145 (t = 0 , 100%)
(t = 2h , 29%)

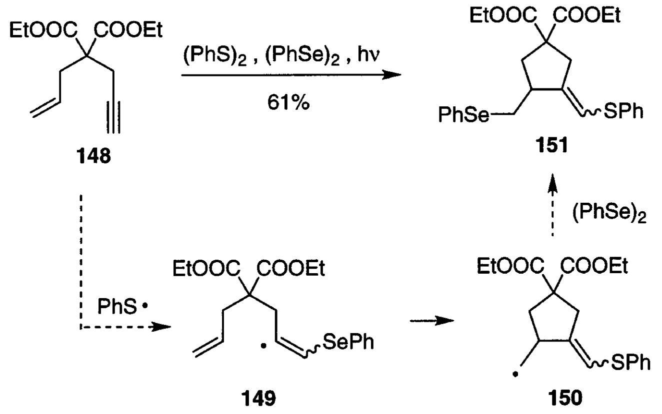
146

147 (t = 0 , 0%)
(t = 2h , 71%)

(47)

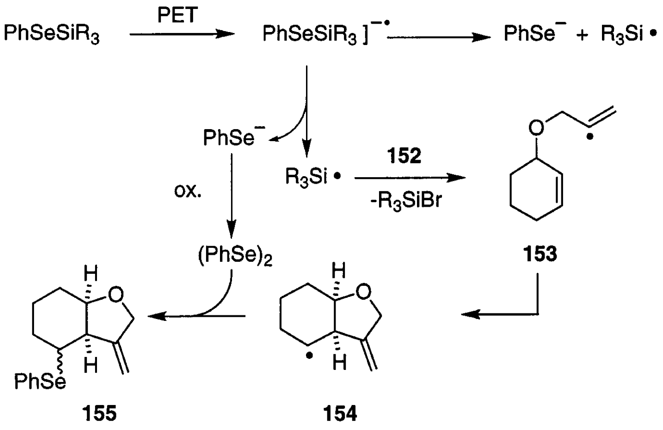
A regioselective thioselenenylation of alkynes has been developed [114]. The alkyne is irradiated in the presence of diphenyl diselenide and diphenyl disulfide. This has been used to perform cyclization reactions as shown in Eq. (48).

Upon irradiation, thiyl radicals are generated and add to the alkyne **148** (the corresponding selenyl radicals are also formed but are less reactive than the thiyl radicals). The vinyl radical **149** cyclizes to **150**. Finally, **150** reacts with diphenyl diselenide, the best radical trap present in the reaction mixture, to afford the product **151**.

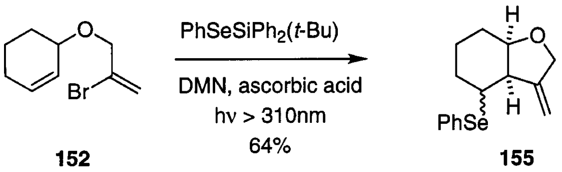


(48)

The photosensitized electron transfer (PET) activation of $PhSeSiPh_2(t\text{-}Bu)$ has been applied for cyclization reactions of halides [Eq. (49)] [115, 116]. The reaction sequence is depicted in Scheme 9. PET reductive activation of



Scheme 9. PET induced activation of $PhSeSiPh_2(t\text{-}Bu)$



(49)

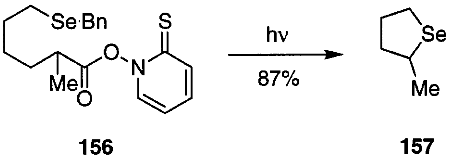
DMN = 1,5-dimethoxynaphthalene

$PhSeSiPh_2$(*t*-Bu) afforded a silyl radical that can abstract a bromine atom from **152** to give the radical **153**. Cyclization affords radical **154**, which react with diphenyl diselenide to give **155**. Diphenyl diselenide results from the oxidation of the phenylselenolate anion presumably by the oxygen present in the solvent.

6
Miscellaneous

6.1
Radical Substitution at Selenium

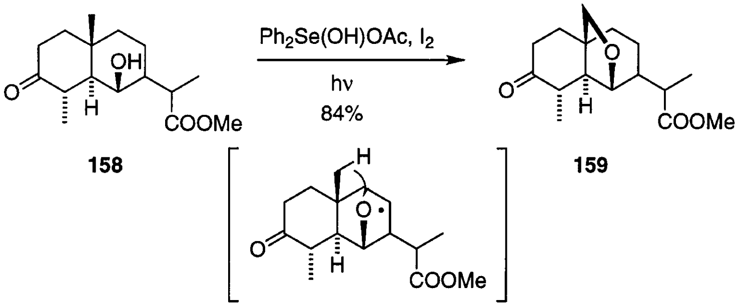
The radical substitution at selenium is efficient when the leaving radical is stabilized (e.g. benzyl, *tert*-butyl). This reaction has been used for the preparation of selenium containing heterocycles [117]. In Eq. 50, the conversion of the Barton ester **156** to the tetrahydroselenophene derivative **157** is described [118, 119]. Mechanistic studies and ab initio calculations indicate that the substitution does not involve hypervalent selenium derivatives.



(50)

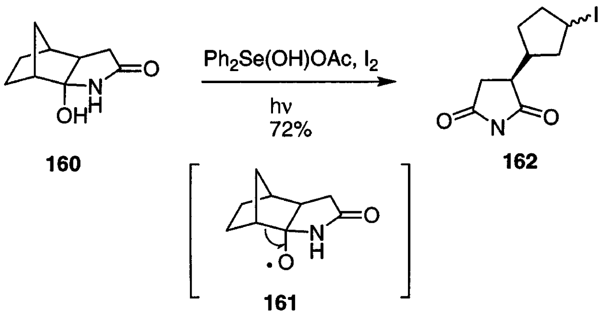
6.2
Alkoxyl Radicals from Tetravalent Selenium

The generation of alkoxyl radicals from alcohols is an important process which has been used for remote functionalization via hydrogen atom abstraction and for rearrangement via *β*-fragmentation. Hypervalent organoiodine compounds have been applied with success in this type of chemistry. More recently, tetravalent selenium compounds have been used for the same purpose [120]. An efficient way of making ether linkage from non-functionalized alcohols has been developed. The conversion of the alcohol **158** to the ether **159** is a key step in the synthesis of (+)-8-deoxyvernolepin [Eq. (51)] [121]. This transformation is best



(51)

achieved by using a mixture of $Ph_2Se(OH)OAc$ and iodine. For comparison, the use of $PhI(OAc)_2/I_2$ affords the desired ether **159** in lower yield. The same tetravalent selenium reagent was also used for fragmentation reactions [122, 123]. Treatment of the tricyclic compound **160** gives iodolactam **162** in 78% yield via the alkoxyl radical **161** [Eq. (52)].



(52)

7
Conclusions

Despite the toxicity of organoselenium compounds, they are routinely applied as precursors for radical reactions. This is due to the unrivaled quality of organoselenium compounds in term of stability, ease of preparation and ease of homolysis of the carbon–selenium bond. Their rich chemistry will continue to make them particularly attractive for the development of new radical processes. This is particularly true when complex systems are examined, such as radical precursors for cascade reactions. Moreover, processes where organoselenium derivatives are used in catalytic amounts will become more attractive and environmentally more friendly.

8
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Selenium-Stabilized Carbanions

Sylvain Ponthieux · Claude Paulmier

Laboratoire de Synthèse Thio et Sélénoorganique (IRCOF), Université de Rouen, UFR Sciences,
F-76821 Mont-Saint-Aignan Cedex, France
E-mail: claude.paulmier@univ-rouen.fr

This chapter presents the main results published during the last ten years, concerning the generation and the reactivity of selenium-stabilized carbanions. Their formation, by α-deprotonation of selenides, selenoxides and selenones or by Se/Li exchange reactions involving selenoacetals, are mentioned. Structural aspects and carbocyclization reactions are also reported.

In a second part, the reactivity of α-phenylselanyl enolates, derived from ketones, esters, lactones and α,β-unsaturated carbonyl compounds, is discussed. Alkylation, aldolisation and Michael reactions are considered as the use of selenium-stabilized carbanions in the natural product synthesis. Others α-functionalyzed species are also presented.

In the last section, the access to α-selanyl vinylmetals is considered. Besides the classical methods involving vinylic selenides and ketene selenoacetals, the hydrometallation (M = Sn, Zr, B) of acetylenic selenides constitutes an efficient method. These species can be considered as vinyl dianion equivalents. Some examples of cross-coupling reactions are presented.

Keywords. Selenium-stabilized carbanions, α-Selanyl enolates, Selenides, Selenoacetals, Alkylation, Aldolization, Carbocyclization, Michael addition

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1
Introduction

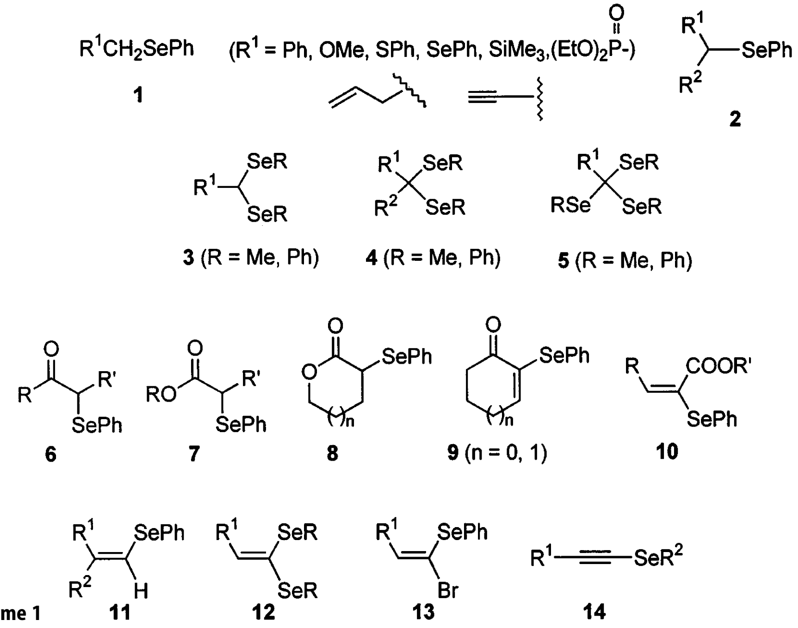
Selenium-stabilized carbanions are now recognized as very important intermediates in organic synthesis. Their formation and reactivity as nucleophilic reagents were studied over twenty years ago. Two general reviews on the organoselenium chemistry have assembled the main published results [1, 2]. More detailed descriptions and reactions of α-selanylalkyllithiums and potassium analogues can be found in two other publications [3, 4]. For their preparations, Li/Br exchange on α-bromo selenides and alkyllithium additions to vinyl phenyl selenides have been proposed but two principal methods are used. The first involves the lithium dialkylamide deprotonation of selenides having a geminal C–H bond sufficiently acidic. LDA is often used but stronger bases, such as potassium diisopropylamide (KDA), are also used in some particular cases (Scheme 1, structure **1**, **2**). The second general method is the alkyllithium cleavage of one C–Se bond of seleno acetals or ortho-triseleno esters (Scheme 1, structures **3**–**5**).

Before presenting the most recent results, we think that it is suitable to recall some features of the two methods cited. We will then discuss the reactivity of selenium-stabilized enolates and carbanionic species bearing another stabilizing group [CN, $PO(OEt)_2$, $ArSO_2$]. The last section of this chapter will be devoted to the generation and coupling reactions of α-selanylvinylmetal derivatives which can be formed from unsaturated selenides.

2
Generation and Reactivity of α-Selanylalkylmetals, α-Seleninyl and α-Selenonyl Analogues

One of the main properties of selenides is their aptitude for attack by various nucleophilic reagents. Alkyllithiums, which are not reactive with sulfides, have a marked selenophilic character. They form an "ate" complex on the selenium atom, which immediately decomposes with cleavage of one C–Se bond leading to the more stable carbanionic species.

Strong non-nucleophilic bases such as LDA, LiTMP, KDA, NaH, KH can deprotonate the α-carbon of selenides for which a substituent increases the acidity. Scheme 1 shows the structures **1** which are easily deprotonated by LDA in THF at – 78 °C. KDA is preferred for the deprotonation of selenides having the structure 2 (R^1, R^2 = alkyl groups).



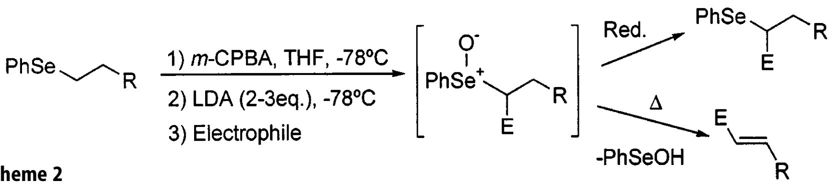
Scheme 1

The α-deprotonation of analogous methylselenides is more difficult, the MeSe group being less acidic that the PhSe one 1,1-Bis(methylselanyl)alkanes, for example, undergo extensive C–Se bond cleavage [4]. The addition of a coordinating cosolvent (TMEDA or HMPA) can improve the formation of the selenium-stabilized carbanion.

Because of the strong selenophilic character of alkyllithiums towards selenides, the treatment of selenoacetals with *n*-butyllithium in THF at –78 °C leads to the efficient formation of α-selanylalkyllithiums. The driving force of this reaction is the particular stability of these organometals compared with that of the alkyllithium used. Various methods have been proposed to prepare selenoacetals, ketene selenoacetals and *ortho*-triselenoalkanoates, which serve as substrates for Li/Se exchange [1–4] (Scheme 1, structures 3–5). Concerning the α-selanylvinyl carbanionic species, the different conditions for their generation are described in Sect. 6.

Selenium-stabilized carbanions behave as excellent nucleophiles and react with primary alkyl bromides or iodides, allylic and benzylic bromides, epoxides, oxetanes, disulfides, trialkylsilyl chlorides, aldehydes, ketones, carbon dioxide, dimethylformamide, acid chlorides or alkyl chloroformates. With conjugated enones, in the presence of HMPA as cosolvent, the 1,4-addition product is essentially obtained.

The carbanionic species formed by the α-deprotonation of sulfoxides and sulfones play an important role in synthesis. In contrast, the selenoxides are very



Scheme 2

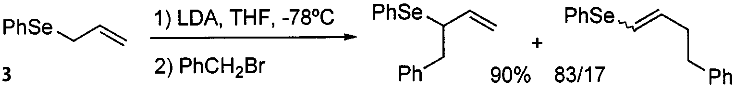
unstable at ambient temperature and undergo a *syn* elimination with formation of a selenenic acid (RSeOH) and olefinic compounds if a proton is present on a vicinal position. However, α-lithio selenoxides can be formed in THF, at −78 °C, by an in situ oxidation of the selenide, using *m*-CPBA, followed by deprotonation with LDA at the same temperature. After reaction with an electrophilic reagent, the selenoxide can be reduced to a selenide. At higher temperatures, the *syn*-elimination reaction occurs and the corresponding olefinic product is isolated [1,2] (Scheme 2).

As a consequence of the selenoxide instability, the oxidation into selenones is only possible if the *syn*-elimination reaction becomes difficult, as in the case of strained structures. Under these conditions, the selenone is deprotonated and the α-selenonylalkyllithiums formed can react as other selenium-stabilized carbanions. It must be added that the seleninyl [PhSe(O)-] and selenonyl [PhSe(O_2)-] substituents behave as very good leaving groups. Vinylic selenoxides and selenones can undergo an intramolecular displacement of the selenium moiety after nucleophilic addition to the double bond under basic conditions. Cyclopropanes and oxetanes have been synthesized in this way [1,2].

3
Recent Synthetic Applications

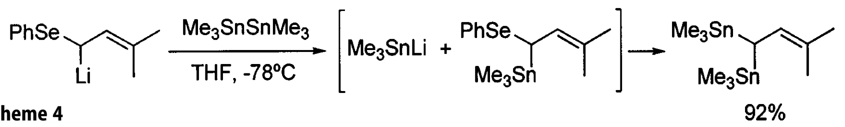
3.1
α-Deprotonation of Selenides, Selenoxides and Selenones

Reich et al. observed that the LDA treatment of an allyl selenide and subsequent alkylation with benzyl bromide afforded an isomeric mixture of allylic and vinylic selenides. The vinylic selenide, corresponding to the γ-attack of the allylic carbanion, was the minor product [5] (Scheme 3). After addition of 1-bromo-3-phenylpropane, instead of benzyl bromide, the allylic selenide was isolated in only 68% yield [6].



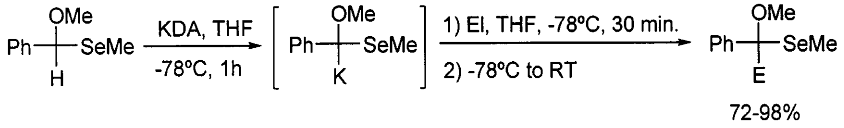
Scheme 3

The reaction of the lithiated allylic carbanion derived from prenyl selenide with hexamethyldistannane did not lead to the mono α-stannylated allylic selenide but to a bis-stannylated compound. A consecutive Se/Sn exchange, without allylic isomerization, occurred [5] (Scheme 4). The reaction involves a selenophilic attack by Me_3SnLi formed in the media.



Scheme 4

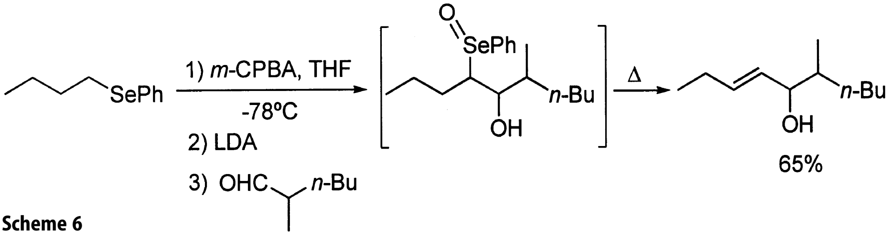
The mixed MeO, MeSe acetal derived from benzaldehyde was efficiently metalated by KDA in THF. The α-methoxy-methylselanyl benzylpotassium was stable at −78 °C and reacted with a large variety of electrophilic reagents including epoxides and alkyl halides leading to the corresponding O, Se mixed acetals in 72–98% yields [7] (Scheme 5).



Scheme 5

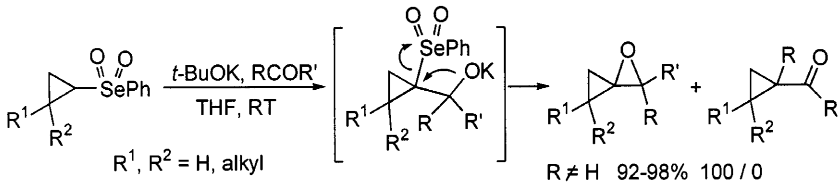
E = Me_3Si, $CH_3CH(OH)CH_2$, $PhCH_2$, $CH_2CH=CH_2$

α-Lithio selenoxides, easily prepared at −78 °C, as indicated in Sect. 2, were treated with aldehydes. The unstable selenoxides have been thermolyzed to give olefins. This strategy has been successfully used for the synthesis of (*E*)-6-methyl-dec-3-en-5-ol from butylphenyl selenide and 2-methylhexanal in 65% yield [8] (Scheme 6).



Scheme 6

α-Phenylselenonylcyclopropyl potassium derivatives were prepared by $KMnO_4$ or *m*-CPBA oxidation of the corresponding selenides followed by deprotonation with *t*-BuOK in THF at room temperature [9]. Krief et al. have shown that they react with aldehydes and ketones to give spiro[oxirane:cyclopentane] derivatives. The spiranes are produced in excellent yields when ketones are involved

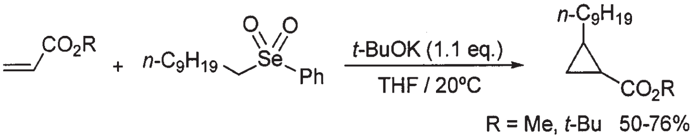


R ≠ H 92-98% 100 / 0

Scheme 7 R, R' = H, alkyl, aryl R = H 45-74% 3 / 1 to 1 / 2.3

whereas a mixture of spiro-oxirane and cyclopropyl ketone (~40:60 to 75:25) was obtained (45–74% total yield) when the reaction was performed with aliphatic aldehydes (Scheme 7).

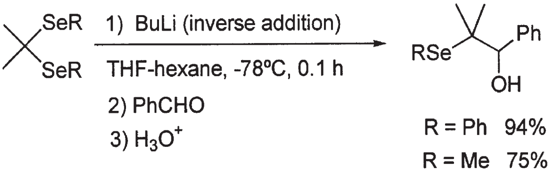
α-Selenonylalkylpotassium reagents, generated under the same conditions, reacted also with α,β-unsaturated esters and alkylidenemalonates to furnish alkyl cyclopropanecarboxylates in good yields [10] (Scheme 8). *tert*-Butyl esters were required to avoid transesterification of the substrate. The formation of one stereoisomer was observed. For the methyl ester a 2:1 mixture of geometric isomers was obtained whose stereochemistry was not assigned.



Scheme 8

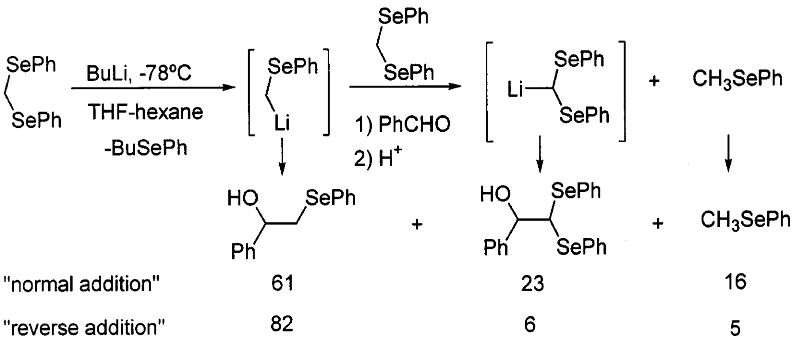
3.2
Se/Li Exchange Reactions

As mentioned in Sect. 2, α-selanylalkyllithiums are easily prepared by treatment of selenoacetals with alkyllithiums [1–4]. Krief et al. have shown that the efficiency of the reaction is dependent on the selenoacetal structure, the nature of the alkyllithium and the solvent used [11]. Two principle parameters govern the reaction. First, all structural features which allow a better stabilization of the carbanionic center greatly favor the reaction, enhancing the rate and also allowing the use of a less reactive organolithium reagent [11]. For example, the cleavage is more readily achieved on bis(phenylseleno)acetals than on methylseleno analogues. The α-selanylalkyllithium was trapped at low temperature with benzaldehyde to give a β-hydroxy selenide [11] (Scheme 9). The reaction did not go to completion with the methyl acetal.



Scheme 9

A THF or ethereal solution of selenoacetals derived from aldehydes must be added to *n*-BuLi or *s*-BuLi in hexane to avoid side reactions, i.e. their metalation is achieved not by the butyllithium but by the selanylalkyllithium produced in situ [11] (Scheme 10). Moreover, it was observed that selenoacetals formed from aromatic aldehydes and ketones, cyclopropanones are more reactive than those derived from aliphatic carbonyl compounds [11]. The second factor governing the reaction is the steric hindrance around the reactive site. Selenoacetals derived from aldehydes react in a few minutes but those derived from ketones

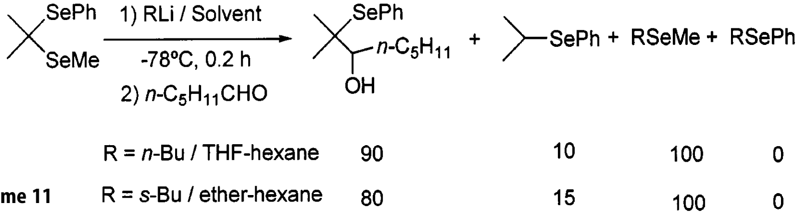


Scheme 10

require at least 5 h and those derived from hindered ketones, such as 7-tridecanone and adamantanone, must be treated with *s*-BuLi to obtain an efficient cleavage.

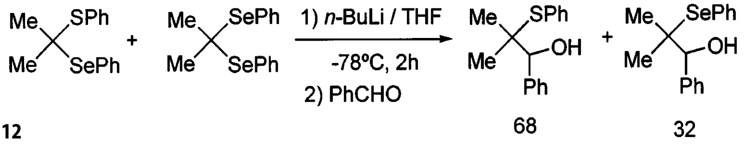
Whatever the nature of the substrate, the Se/metal exchange reaction proved to be more efficient when carried out in a THF/hexane mixture. Therefore, the following order of base/solvent systems was proposed : *t*-BuLi/THF-hexane ~ *s*-BuLi/THF-hexane > *n*-BuLi/THF-hexane ~ *s*-BuLi/ether-hexane > *n*-BuLi/ether-hexane >>> MeLi/THF-ether > *t*-BuLi/hexane ~ *n*-BuLi/hexane.

The treatment of mixed selenoacetals, such as 2-methylselanyl-2-phenylselanylpropane, with *n*-BuLi in THF/hexane or with *s*-BuLi in diethyl ether-hexane led, after addition of hexanal, to a mixture of a *β*-phenylselanyl alcohol and butyl methylselenide reflecting the exclusive cleavage of the C–SeMe bond [12] (Scheme 11)



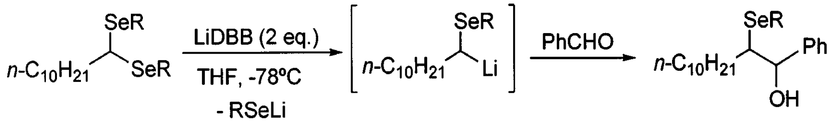
Scheme 11

The *n*-BuLi treatment of an equimolecular mixture of the bis(phenylseleno)acetal and the phenylseleno(phenylthio)acetal derived from acetone, followed by addition of benzaldehyde, led to the major formation of the *β*-phenylsulfanyl alcohol [12] (Scheme 12). This result is the consequence of a better stabilization of the negative charge by the phenylthio group.



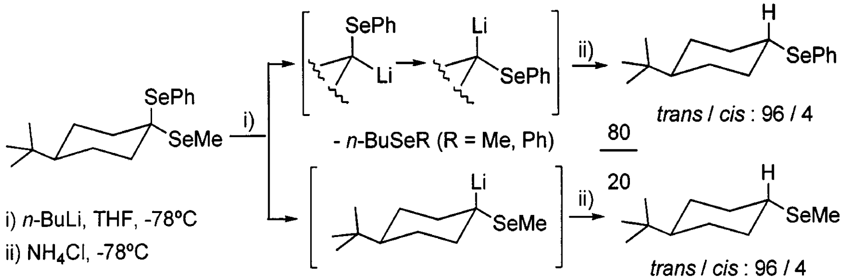
Scheme 12

The cleavage of the C–S bond by the treatment of sulfides with a lithium arenide is well known. Krief et al. have shown that selenoacetals of both the phenyl and the methyl series react with lithium di-*tert*-butylbiphenyl (LiDBB) to produce, after quenching with benzaldehyde, the corresponding *β*-hydroxy alkylselenides in good yields (53–72%) [13] (Scheme 13). Methylseleno derivatives are less prone than their phenylseleno analogues to react with lithium arenides. The presence of an additional stabilizing group, for example a phenyl substituent, facilitates the reductive cleavage of the C–Se bond.



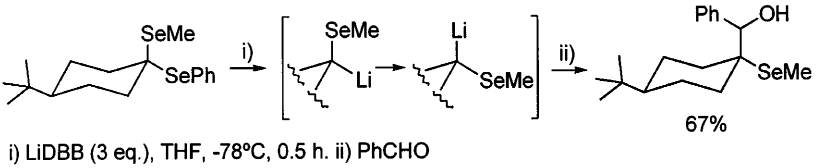
Scheme 13

The *n*-BuLi cleavage of the axial C–Se bond of bis(phenylseleno)acetals, derived from 4-*tert*-butylcyclohexanone, always occurs under kinetic control at –78 °C [14]. In the case of a mixed acetal, having respectively the phenylseleno and methylseleno groups in axial and equatorial positions, the cleavage of the equatorial C–SeMe bond was predominantly observed. The resulting stabilized carbanion rearranges almost instantaneously leading to the *α*-phenylselanylcyclohexyllithium with the C–Li bond in the axial position [14] (Scheme 14).



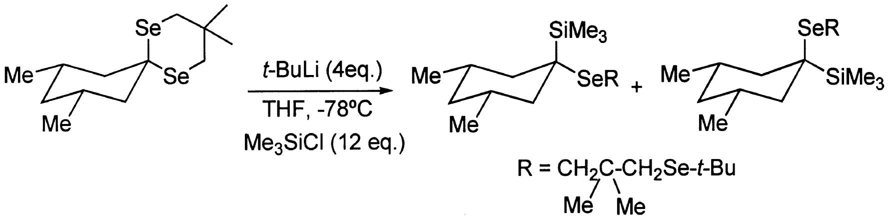
Scheme 14

The selective cleavage of the C–SePh bond of the axial MeSe, equatorial PhSe mixed acetal was observed when LiDBB was used. The less stable *α*-methylselanylalkyllithium with the C–Li bond in the equatorial position immediately epimerizes into its axial stereoisomer prior to reaction with benzaldehyde [13] (Scheme 15).



Scheme 15

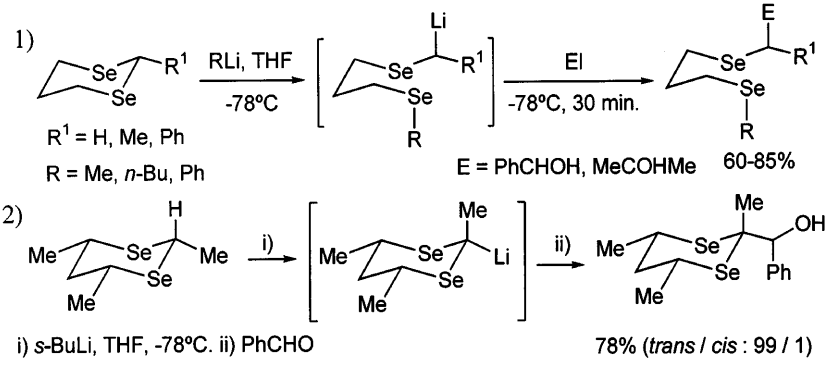
Reich et al. have shown that the equatorial C–Se bond of the 1,3-diselenane derived from *cis*-3,5-dimethylcyclohexanone can be cleaved kinetically by *t*-BuLi in THF and the resulting carbanion trapped by chlorotrimethylsilane. This high stereoselectivity was reversed in a sequential experiment. The Se_{ax}/Se_{eq} isomerization occurred at –78 °C leading to a 24:1 ratio in favor of the alkylselanyl group in the equatorial position [15] (Scheme 16). The half-life was estimated to be 7 min.



	time (min.)	$SeR_{eq.}$	$SeR_{ax.}$
- internal quench		3	97
- sequential addition	2	20	80
	8	55	45
	32	91	9
	60	96	4

Scheme 16

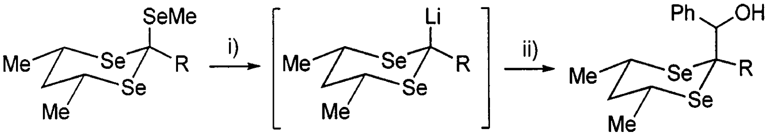
The nature of the substituents located at the 2-, 4-, and 6-positions of 1,3-diselenanes favors either C–Se bond cleavage or α-deprotonation. For R^1 = H, Me, Ph, in the 2-position, the action of *n*-BuLi, PhLi or MeLi afforded C–Se cleavage with formation of β-hydroxyalkyl-(3-butylselanylpropyl)selenides (60–85%) after reaction with benzaldehyde or acetone [16] (Scheme 17, reaction 1). With two methyl groups in *cis*-4,6-positions, the metalation by an alkyllithium is strongly dependent on the nature of the C-2 substituent. From a *cis*-C-2-methyl-substituted derivative, metalation requires the use of *s*-BuLi, no reaction being observed with *n*-BuLi or *t*-BuLi (Scheme 17, reaction 2). For *cis*- or *trans*-2-phenyl-1,3-diselenane, metalation can be performed with MeLi or PhLi and an unexpected C–Se



Scheme 17

bond cleavage was observed with *n*-BuLi. In both cases, epimerization occured at −78 °C, leading to a lithiated intermediate having the C–Li bond in equatorial position. A single stereoisomer was then isolated after quenching with benzaldehyde.

Organolithium derivatives bearing a C–Li axial bond, formed from cyclic *ortho*-triselenoalkanoate and *t*-BuLi, were trapped with benzaldehyde at −116 °C without inversion at the C-2 position [17] (Scheme 18).

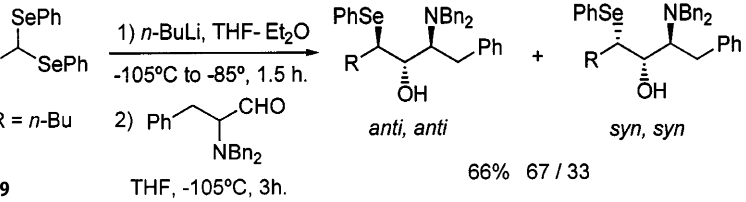


i) t-BuLi, THF, -116°C, 1h.
ii) PhCHO, -116°C, 0.5 h.

R = H 60% (d.e. 100%)
R = Me 68% (d.e. 99%)

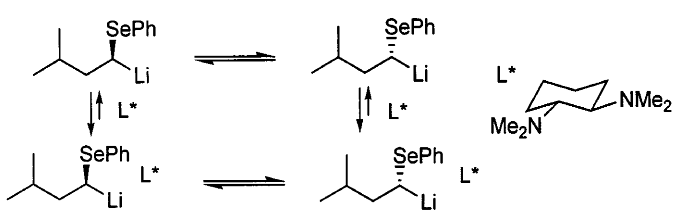
Scheme 18

α-Phenylselanylcyclohexyllithium derivatives are configurationally labile at −78 °C in THF [14, 15]. The configurational stability of secondary α-phenylselanylalkyllithiums is strongly temperature dependent. The diastereoselection in the Se/Li exchange process achieved from chiral 5-methyl-3-trimethylsilyloxypentanal has been studied. The trapping of these species with ketones or aldehydes occurred faster than their epimerization [18]. Therefore, the ratio of the products reflects the equilibrium ratio of the diastereoisomeric organometallic species. The slow enantiomeric equilibration, compared with the rate of the addition, was also observed in the reaction of α-phenylselanylpentyllithium with *N*,*N*-dibenzylphenylalaninal [19] (Scheme 19).



Scheme 19

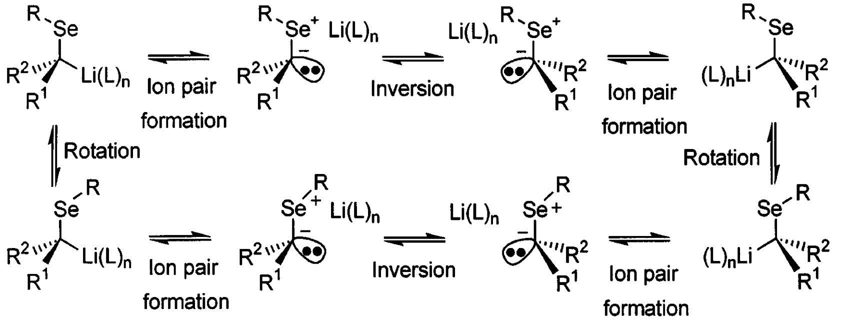
Complexation of an acyclic α-lithio selenide with a chiral diamine led to diastereoisomeric complexed lithium intermediates which reacted with aldehydes more rapidly than the uncomplexed forms [20] (Scheme 20). They were charac-



Scheme 20

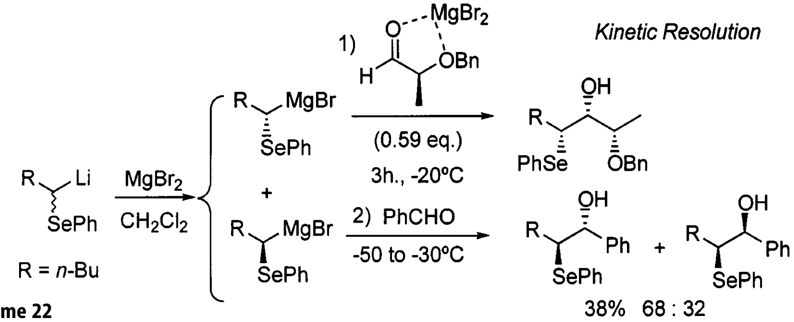
terized by ^{77}Se NMR spectroscopy and equilibrate themselves without dissociation [21].

The enantiomerization mechanism of racemic α-phenylselanylalkyllithiums has been studied. It seems that the rate limiting step is a reorganization with a contact ion pair formation [22, 23] (Scheme 21).



Scheme 21

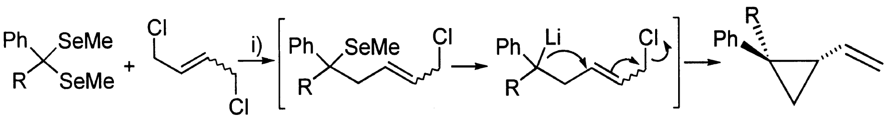
Selenenylated Grignard reagents, generated by transmetalation with magnesium bromide, have a higher stability than their lithium counterparts. They were enantiomerically enriched by kinetic resolution resulting from reactions with (*S*)-α-benzyloxypropionaldehyde and benzaldehyde successively [24] (Scheme 22).



Scheme 22

As discussed in Sect. 2, α-selanylalkyllithiums, generated from selenoacetals, can react with various electrophilic reagents, i.e. chloromethyl isopropyl ether for the synthesis of 1α-hydroxy vitamin D analogues [25] and with propargylic chloride derivatives for the preparation of alkynols [26]. A synthesis of vinylcyclopropane derivatives from 1,4-dichloro-but-2-ene was achieved with *trans* stereoselectivity (> 93%) in 68–89% yield. This one-pot cyclization, via an intramolecular allylic substitution, required the presence of two equivalents of *n*-BuLi [26] (Scheme 23).

Krief et al. [27–29] have carried out the synthesis of 1-arylbicyclo[3.1.0]hexanes and 1-arylbicyclo[4.1.0]heptanes via carbanionic cyclization of olefins

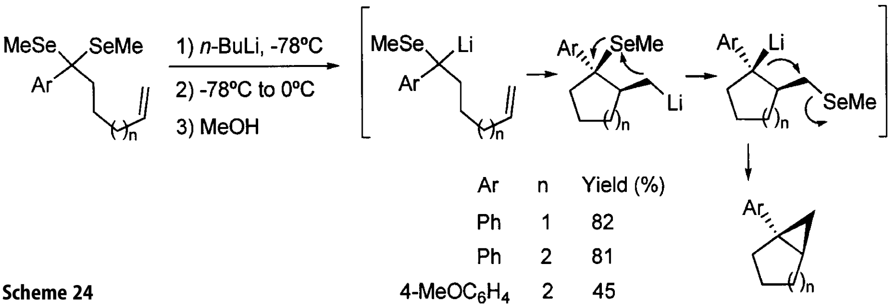


i) *n*-BuLi (2eq.), THF-hexane, -78°C

R	allyl chloride	Yield (%)	*trans* / *cis*
H	*E*	75	96 / 4
H	*Z*	89	93 / 7
Me	*E*	68	98 / 2

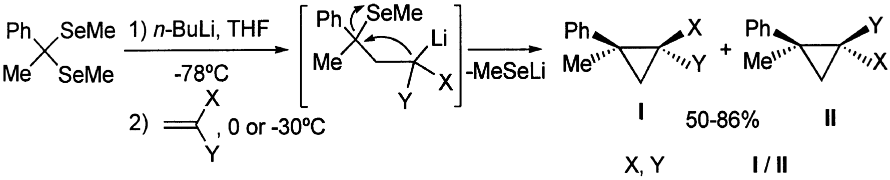
Scheme 23

(Scheme 24). A Li/SeMe exchange must be involved in the intermediate cycloalkylmethyllithium to explain the cyclopropane ring formation. This lithium methaneselenolate displacement has been extended to the stereoselective synthesis of functionalized arylcyclopropanes by reaction with olefinic substrates [30] (Scheme 25).



Ar	n	Yield (%)
Ph	1	82
Ph	2	81
4-MeOC$_6$H$_4$	2	45

Scheme 24



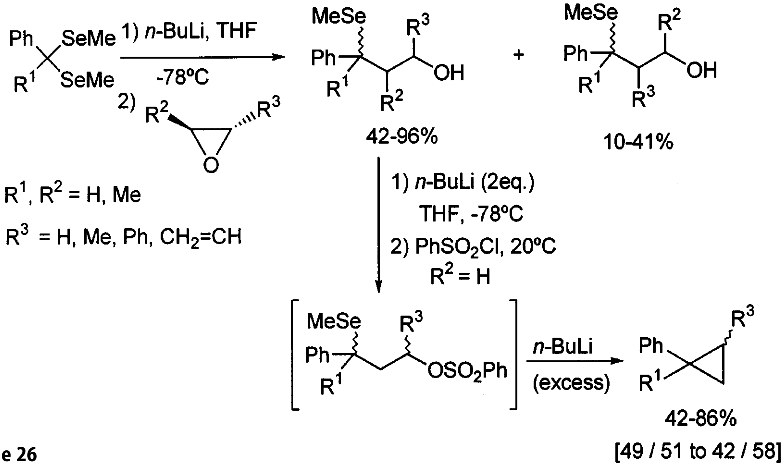
X = H, Ph, CH$_2$=CH, Me$_3$Si, PhS
Y = H, Me, SeMe

X, Y	I / II
Ph, H	97 / 3
CH$_2$=CH, H	3 / 97
Me$_3$Si, H	15 / 85
PhS, H	0 / 100
Ph, Me	0 / 100
Ph, SeMe	0 / 100

Scheme 25

The reaction of α-methylselanylbenzyllithiums and epoxides allows the synthesis of phenylcyclopropanes after displacement of a benzenesulfonyl group formed in situ from the intermediate γ-methylselanyl alcohol. The epoxide opening occurs with preferential attack of the less substituted carbon [31, 32] (Scheme 26).

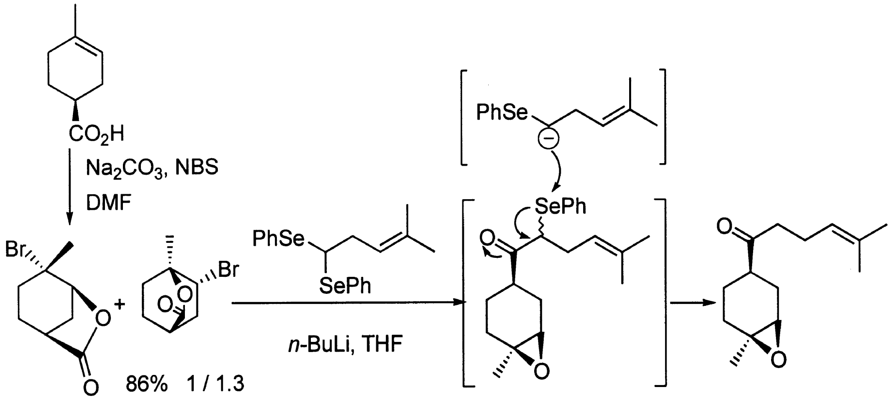
The formation of β-hydroxy selenides through reaction of a selenium-stabilized carbanion with a carbonyl compound has been extensively used, in particular for the synthesis of natural products [1–4, 33]. The most recent



Scheme 26

works concern the preparation of zizaene [34], khusimone [34] and pantalenene [35].

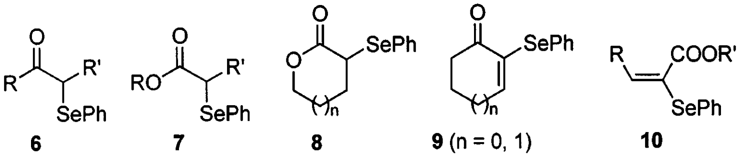
It is interesting to note that a side reaction, involving the cleavage of the PhSe group in an intermediate α-phenylselanyl ketone by the selenophilic α-phenylselanylalkyllithium, was observed in the synthesis of epoxybisaboladiene [36] (Scheme 27). The formation of the deselenenylated epoxide was observed.



Scheme 27

4
Reactivity of Lithium and Potassium α-Selanyl Enolates

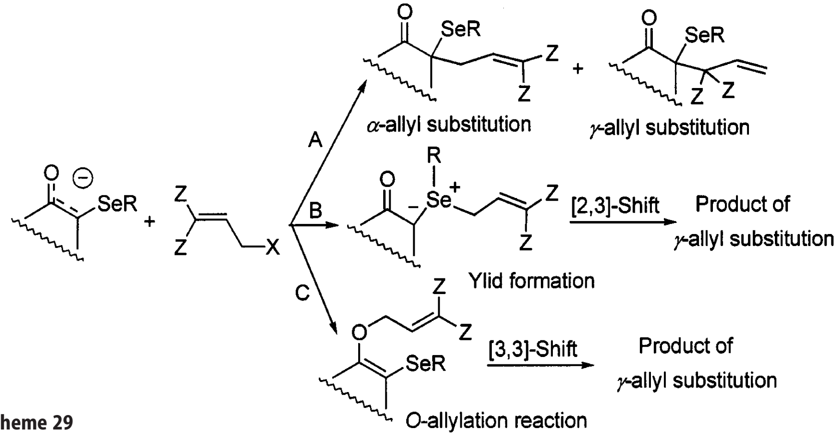
α-Phenylselanyl ketones, esters, lactones (Scheme 28, structures **6**–**8**) are easily deprotonated by LDA in THF at low temperature [1, 2]. Other bases can be used but the reaction is complicated by the increasing aptitude of the selenium atom to be attacked by various nucleophilic reagents leading to C–Se bond cleavage. The relative stability of the enolate formed becomes the driving force of the process. Enolates derived from α-selanyl ketones have a selenium affinity and the deselenenylation of the substrate is observed. The aim of this section is to present the recent observations concerning the reactivity of these intermediates, the formation and the reactivity of β-phenylselanyl enoxysilanes, some synthetic applications and properties of selenium-stabilized carbanions generated by nucleophilic addition on α,β-unsaturated structures such as **9** and **10** (Scheme 28).



Scheme 28

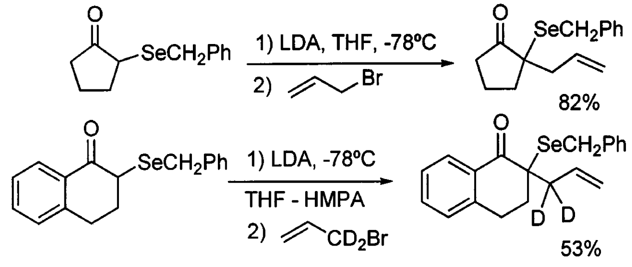
4.1
Mechanistic Aspects

The formation of α-allylated ketones through allylation of selenium-stabilized enolates, generated by deprotonation of α-selanylated ketones, can be explained by three general postulated mechanisms depending on the nature of the RSe substituent and the allyl halide used [37] (Scheme 29). The first explanation (pathway A) involves the direct allylation of the selenenylated α-carbon either by an S_N2 or an S_N2' process leading to two allylated α-selanyl ketones. The second process (pathway B) corresponds to the selenium alkylation giving an ylide, which undergoes a [2,3]-sigmatropic rearrangement, shifting the allyl group to the α-position. The third route (pathway C) requires an *O*-allylation reaction, followed by a [3,3]-sigmatropic rearrangement. The latter process is generally excluded because it needs elevated temperatures.



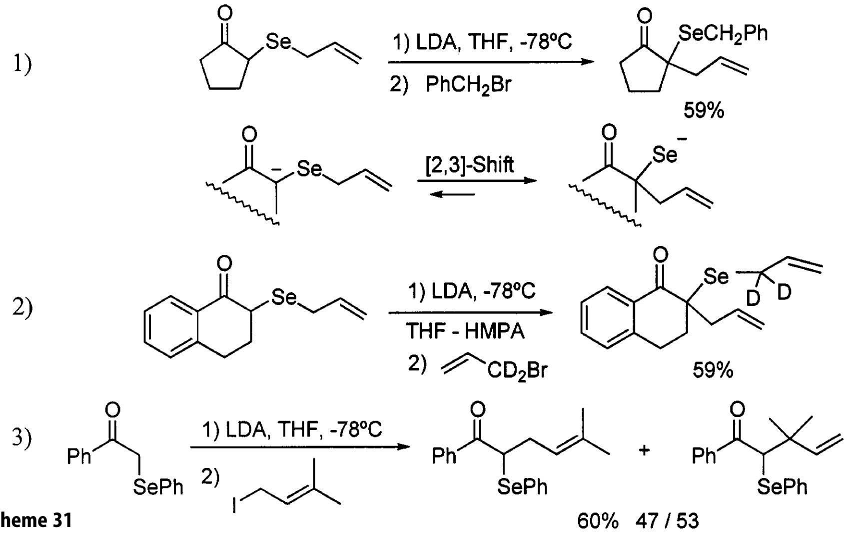
Scheme 29

The enolates derived from α-benzylselanylcyclopentanone and α-tetralone were treated with allyl bromide producing the corresponding α-allylcyclanones in 82 and 53 % yield, respectively. No scrambling reaction concerning the benzyl moiety was observed [37] (Scheme 30).



Scheme 30

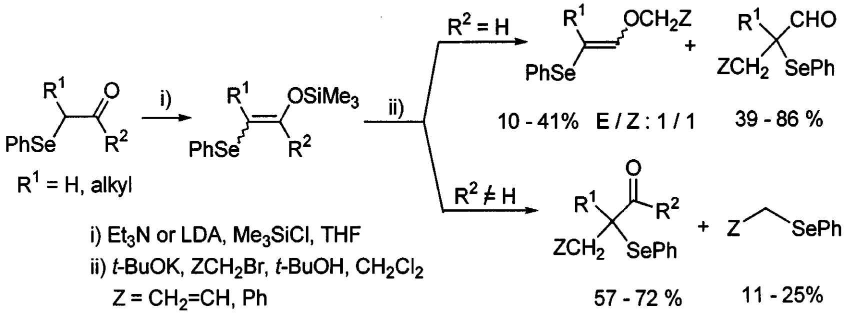
With an allylselanyl substituent under analogous conditions, however, it was observed that an α-allylated product was formed after reaction with benzyl bromide (Scheme 31, reaction 1). Pathway B could be invoked in this case but the reaction of allyl bromide-d_2 with the α-allylselanyl tetralone enolate gave the exclusive formation of allylselanyl-labeled product in 59% yield (Scheme 31, reaction 2). The migration ability of both allyl groups being identical, it was proposed that a [2,3]-sigmatropic rearrangement of the initially formed enolate had occurred leading to a lithium selenolate which was then allylated by the deuterated allylic bromide (Scheme 31). The prenylation of the enolate derived from phenylselanyl acetophenone led to the conclusion that the two isomeric unsaturated α-phenylselanyl ketones are formed by route A, after examination of the appropriate frontier orbitals of the enolate (HOMO) and allyl halide (LUMO) (Scheme 31, reaction 3).



Scheme 31

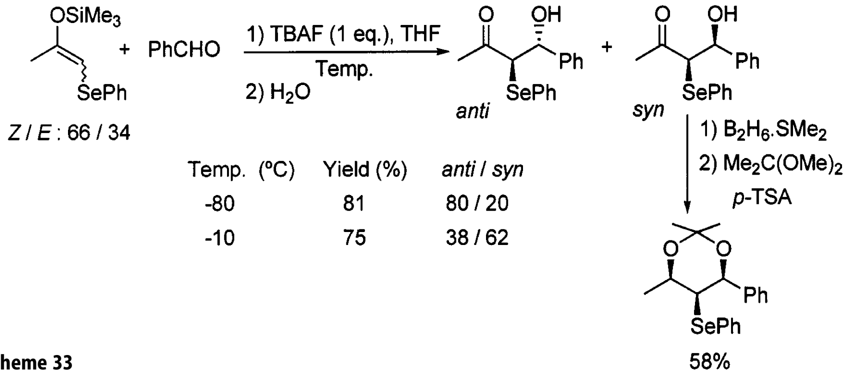
4.2
β-Phenylselanyl Enoxysilanes

We have shown that benzylation and allylation at the selenium atom can be partially operative and depend on the enolate structure [38] (Scheme 32). With silyl enol ethers, derived from α-phenylselanyl ketones as substrates, the formation of allyl or benzyl phenyl selenide was observed but the characterization of the carbene, which must be formed at the same time, was not achieved. In the course of the allylation or benzylation of phenylselanyl enolates, derived from α-phenylselanyl aldehydes, the amount of O-allylated products increased with the size of the R^1 substituent. In both reactions, phenylselanyl enolates were generated in situ by cleavage of the Si–O bond of β-selanyl enoxysilanes with t-BuOK in CH_2Cl_2 and t-BuOH as cosolvent.



Scheme 32

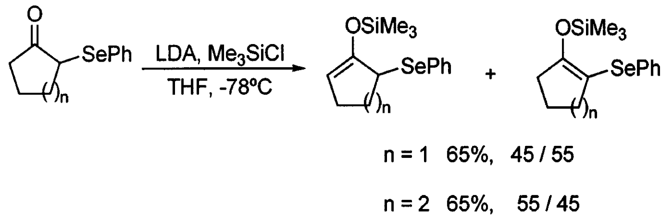
The enolate, generated by TBAF cleavage of the enoxysilane derived from phenylselanylacetone, was trapped with benzaldehyde [39] (Scheme 33). The *anti/syn* ratio of diastereoisomers, easily identified by ^1H and ^{77}Se NMR, was dependent on the temperature and the *E* or *Z* structure of the substrate. The borane reduction followed by a conventional acetonization led to a protected *syn*, *syn*-1,3-diol.



Temp. (°C)	Yield (%)	*anti* / *syn*
-80	81	80 / 20
-10	75	38 / 62

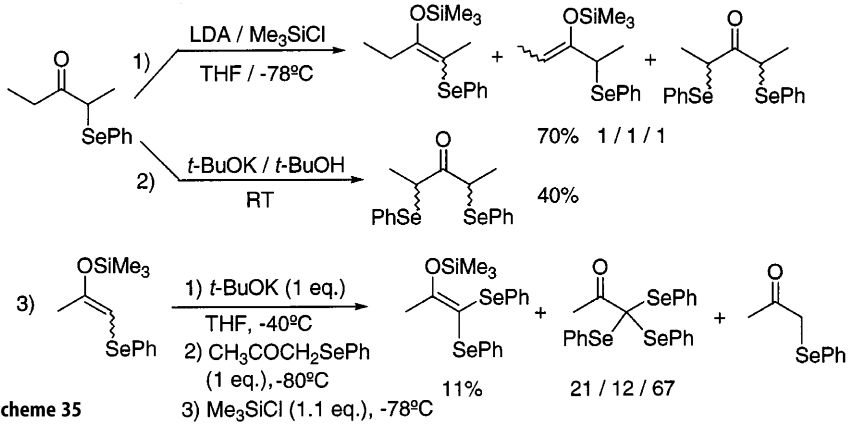
Scheme 33

It has been shown that the formation of β-phenylselanyl enoxysilanes, from α-phenylselanyl cyclanones, is not regioselective even by in situ quench of the enolate with chlorotrimethylsilane and despite the more acidic character of the C–H bond of the selenenylated carbon [40] (Scheme 34).



Scheme 34

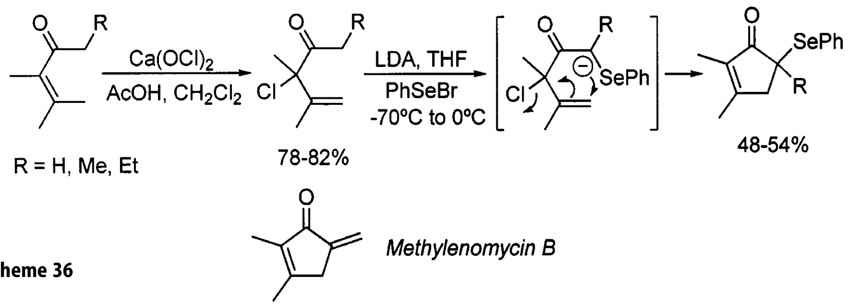
We have also observed that the silylation of the enolate derived from 2-phenylselanylpentan-3-one, generated under the same conditions, always afforded the α,α′-bis(phenylselanyl) ketone as well as the two regioisomeric enoxysilanes [40] (Scheme 35, reaction 1). Treatment of this ketone with *t*-BuOK in *t*-BuOH gave exclusively the α,α′-bis(phenylselanyl)pentanone [41] (Scheme 35, reaction 2). A selenophilic reaction occurred between the phenylselanylpropanone and its selenium-stabilized enolate. The enoxysilane derived from 1,1-bis (phenylselanyl)propanone was isolated albeit in poor yield (11%), besides the 1,1,1-tris(phenylselanyl)propanone and the unreacted phenylselanylpropanone [42] (Scheme 35, reaction 3).



Scheme 35

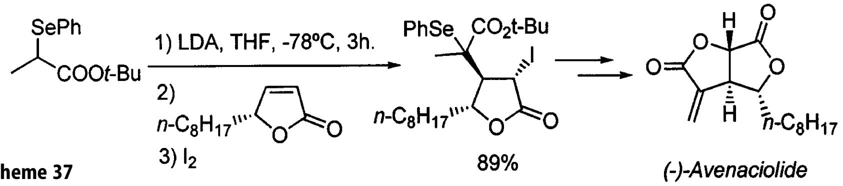
4.3
Synthetic Applications

An α-phenylselanyl enolate was formed as intermediate in the cyclization step leading to 5-phenylselanylcyclopent-2-enones prepared for the synthesis of methylenomycin B [43, 44] (Scheme 36). The author observed that the cyclization cannot take place in the absence of the PhSe group.



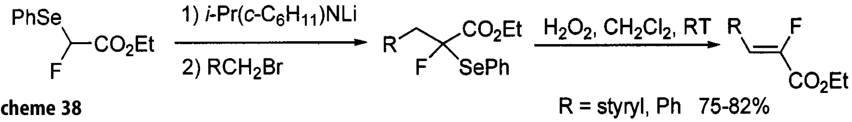
Scheme 36

Enolates derived from 2-phenylselanyl esters react with various electrophiles such as alkyl halides and benzeneselenenyl halides [45]. The Michael addition of the enolate, formed from *tert*-butyl 2-phenylselanyl propanoate, to *(R)*-5-*n*-octyl(5*H*)furan-2-one and subsequent iodination afforded a key intermediate for the total synthesis of (–)-Avenaciolide [46] (Scheme 37).



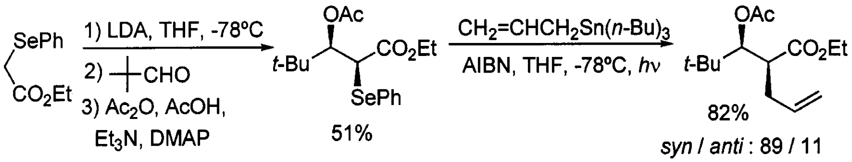
Scheme 37

The alkylation of the enolate derived from ethyl 2-fluoro-2-phenylselanyl propanoate, followed by an oxidative deselenenylation, allowed the stereoselective synthesis of (*E*)-α-fluoro-α,β-unsaturated esters [47] (Scheme 38).



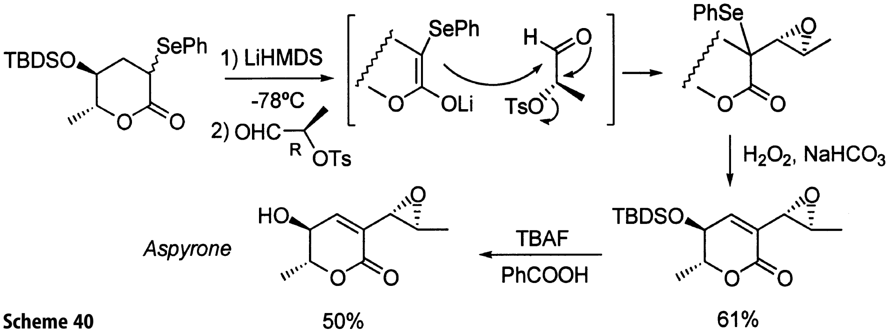
Scheme 38

The assignment of the diastereoisomers obtained in the aldol reaction of pivalaldehyde and ethyl phenylselanylacetate has been determined, after acetylation, from the ^{1}H NMR spectra to be 1 : 3 (*anti*/*syn*) [48] (Scheme 39). The radical allylation of the *syn*-isomer with tri-*n*-butylallylstannane displayed a good level of diastereoselectivity.



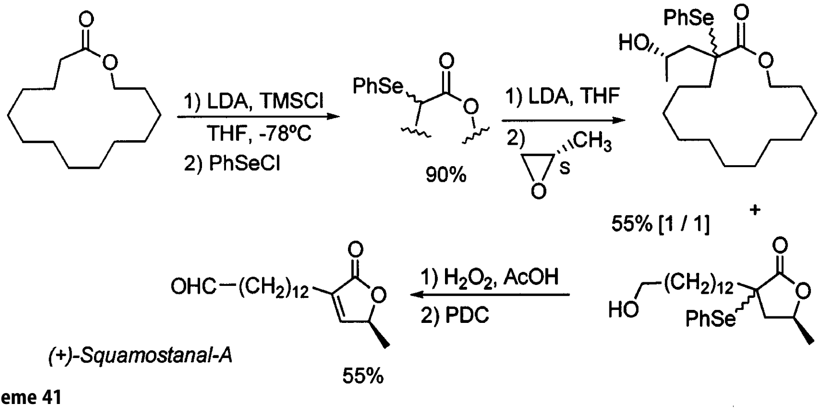
Scheme 39

The key step for the synthesis of aspyrone involves the reaction of an α-phenylselanyl δ-lactone enolate and (*R*)-2-tosyl propanal with subsequent stereospecific formation of epoxide [49] (Scheme 40).



Scheme 40

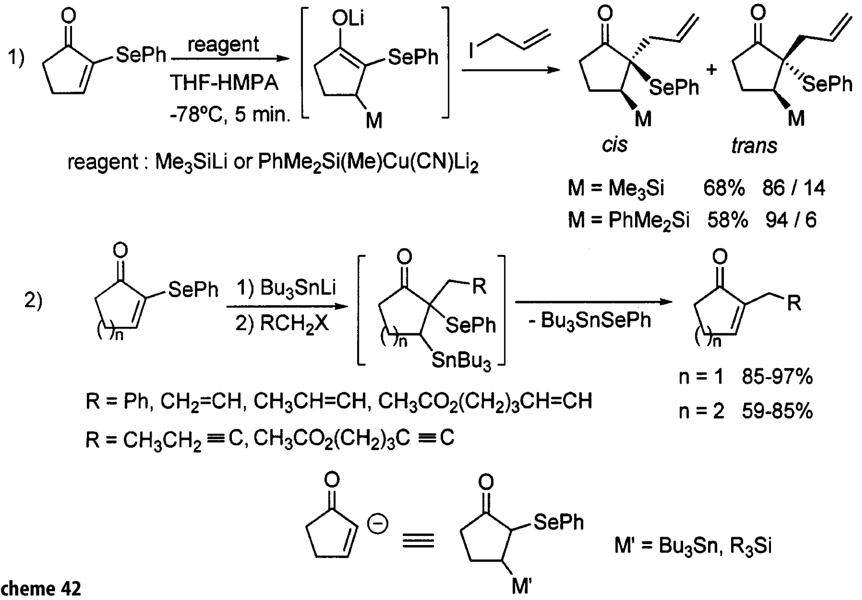
The reaction of a α-phenylselanyl enolate derived from 15-pentadecanolide and (*S*)-propylene oxide furnished a 1:1 mixture of lactones [50] (Scheme 41). The butyrolactone, resulting from a partial *trans* lactonization, led to (+)-Squamostanal-A in 55% yield after selenoxide *syn* elimination and PDC oxidation of the hydroxy group.



Scheme 41

4.4
Reactivity of α-Selanyl α,β-Unsaturated Carbonyl Compounds

Selenium-stabilized carbanions can also be generated by 1,4-addition of nucleophilic reagents to α-selanyl α,β-unsaturated carbonyl compounds. The addition of lithium dialkylcuprates to 2-phenylselanylcycloalk-2-enones has been widely used for the synthesis of natural products such as terrein [51] and for the construction of a prostanglandin skeleton [52]. No scrambling of an alkyl group between the selenium moiety and the cuprate was observed in contrast with the allylation of enolates derived from α-phenylselanyl ketones [37]. The conjugate addition of trialkylsilyllithiums or mixed silyl cuprates to 2-phenylselanylcycloalk-2-enones, followed by reaction with allyl iodide, afforded 2-allylcycloalkanones with high *cis* stereoselectivity (> 85%) [53] (Scheme 42, reaction 1).

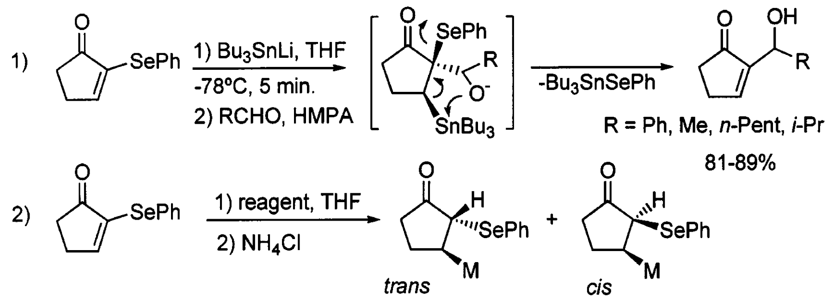


Scheme 42

The 1,4-addition of lithium tributylstannane to these enones, followed by the allylation of the resulting enolates, furnished 2-allylcycloalk-2-enones, in high yields, after subsequent elimination of $R_3SnSePh$ [54] (Scheme 42, reaction 2). The "$R_3SiSePh$" elimination was carried out by TBAF addition and those of "$R_3SnSePh$" can be successfully performed in a one-pot procedure under a variety of conditions: treatment with fluoride (TBAF, CsF), base (*n*-BuLi), Lewis acid ($TiCl_4$, $SnCl_4$, $MgCl_2$, $BF_3.OEt_2$) or silica gel, as well as under thermal or photochemical conditions. The PhSe and R_3Sn or R_3Si substituents in fact behave as an olefin masked group, allowing the substrates to be considered as α-keto vinyl anion equivalents.

Aldol reactions of aldehydes with the β-stannyl α-selanyl enolate generated from 2-phenylselanylcyclopent-2-enone directly produced 2-(1-hydroxyalkyl) cyclopenten-2-ones in high yields [55] (Scheme 43, reaction 1). The *n*-$Bu_3SnSePh$ elimination was explained by lithium aldolate assistance. The nature of the nucleophile has a dramatic effect on the stereochemistry of the 1,4-addition products isolated after protonolysis. The use of lithium dibutylcuprate afforded *cis*-compounds, whereas Me_3SiLi or, better, a mixed silylcuprate, furnished the *trans*-isomers as the major products [56] (Scheme 43, reaction 2).

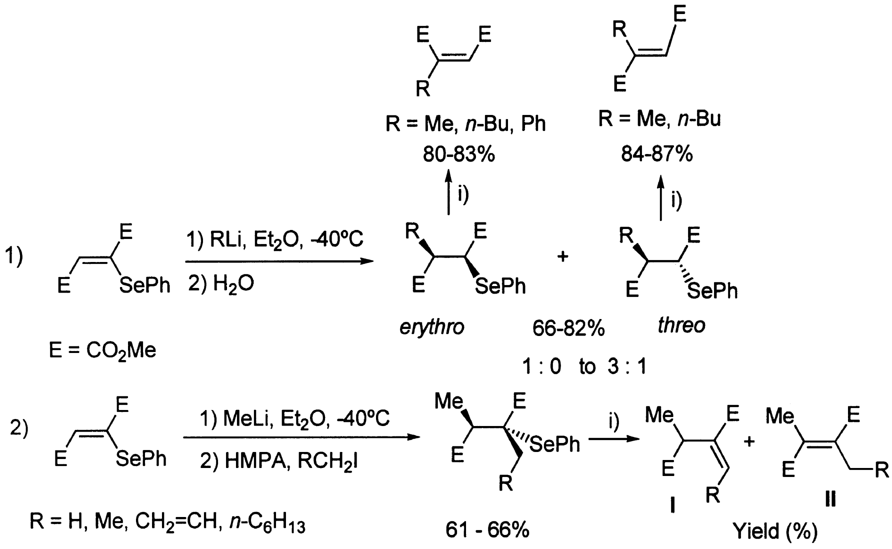
Dimethyl 2-phenylselanyl fumarate has also been used as a good Michael acceptor of organolithium reagents [57]. After hydrolysis of the resulting enolates, the addition products were isolated in good yields (66–82%) with the major formation of the *erythro*-isomer. The oxidative *syn* elimination of the selanyl



reagent	yield (%)	*trans* / *cis*
n-Bu_2CuLi	97	1 / 99
Me_3SiLi	67	84 / 16
$PhMe_2Si(Me)CuCNLi_2$	94	89 / 11

Scheme 43

group was then achieved on each diastereoisomer, providing either the maleate or the fumarate derivative in high yields (80–87%) (Scheme 44, reaction 1). When alkylation, with alkyl iodide or triflate, was carried out before hydrolysis, a complete diastereoselective addition giving the *threo*-isomer was observed (Scheme 44, reaction 2).



Yield (%)

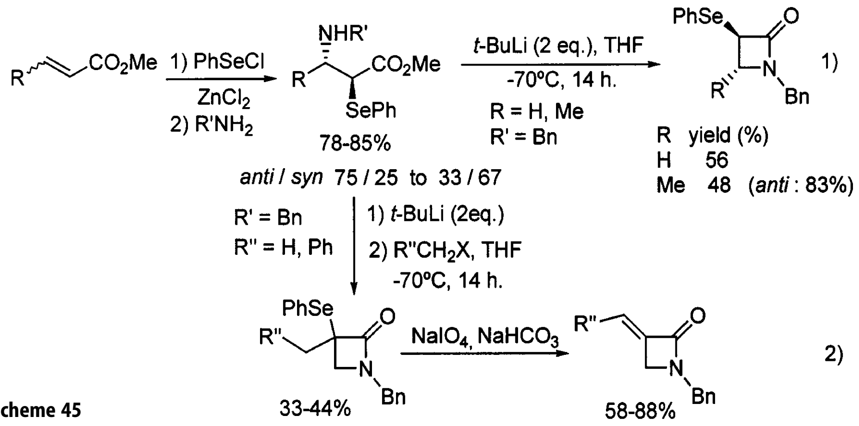
R	I	II
H	82	0
Me	21	66
$CH_2{=}CH$	83	0

i) $NaIO_4$, $NaHCO_3$, MeOH, H_2O

Scheme 44

Dimethyl 2-phenylselanyl fumarate also behaves as a good Michael acceptor for aliphatic amines leading to mixtures of *syn*- and *anti*-dimethyl 2-phenylselanyl-3-amino succinates in almost quantitative yield [58].

α-Phenylselanyl-β-amino esters, prepared by amino-selenenylation of α,β-unsaturated esters, were easily converted into α-phenylselanyl-β-lactams in fair yields (48–56%) by *tert*-butyllithium treatment [59] (Scheme 45, reaction 1). Starting from the *syn*- or *anti*-addition product, the cyclization was performed with *trans* stereoselectivity. Before hydrolysis, the enolate generated after lactamization could be trapped with alkyl halides to give α-alkyl α-phenylselanyl lactams in modest yields (33–44%) (Scheme 45, reaction 2). These compounds are then transformed into α-alkylidenes derivatives by the conventional oxidative *syn* elimination process.

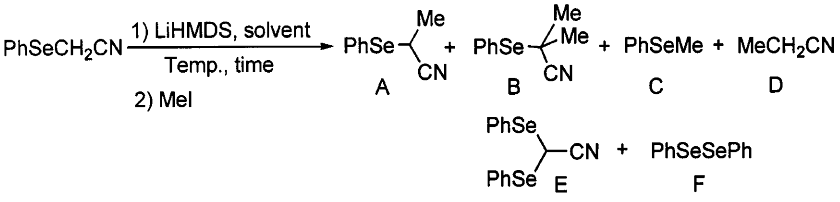


Scheme 45

5
Reactivity of Other α-Functionalized Selenium-Stabilized Carbanions

5.1
α-Cyano Selenium-Stabilized Carbanions

The outcome of the alkylation of the carbanion derived from phenylselanylacetonitrile with alkyl iodides is strongly dependent on the base (LiHMDS, NaHMDS, NaH and NaOH under phase-transfer conditions), the presence of



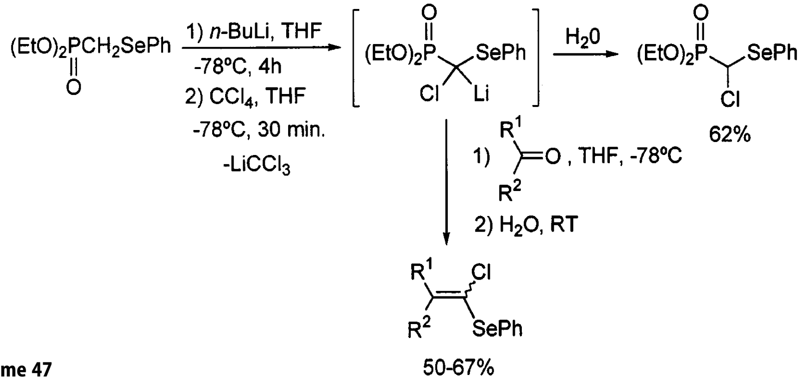
Temp.(°C)	Time (h.)	Solvent	Composition (A, B, C, D, E, F)
-78 to -20	1.5	THF	73 - 13 - 0 - 11 - 22 - 0
-78	5	THF / HMPA 10 : 1	36 - 54 - 1 - 0 - 7 - 0.2

Scheme 46

HMPA as cosolvent, the nature of the electrophilic reagent and the reaction time and temperature [60] (Scheme 46). It was discovered that the major side products formed besides the expected 2-phenylselanylalkanenitrile are bis(phenylselanyl)acetonitrile and propionitrile. The authors have proposed that the formation of bis(phenylselanyl)acetonitrile would result from the decomposition of an ate complex, the latter being formed by selenophilic attack of the carbanion derived from phenylselanylacetonitrile on the substrate. The α-selanyl nitriles behave as α-phenylselanyl ketones when treated with bases.

5.2
α-Phosphono Selenium-Stabilized Carbanions

Diethyl phenylselanylmethanephosphonate can be metalated with *n*-BuLi in THF at −78 °C. The lithiated phosphonocarbanionic species led to the corresponding α-chloro-α-phenylselanylphosphonate after treatment with carbon tetrachloride [61] (Scheme 47). The carbanion derived from the ethyl α-chloro-α-selanylphosphonate was used in a Horner-Emmons olefination with ketones to give α-chlorovinylphenyl selenides.

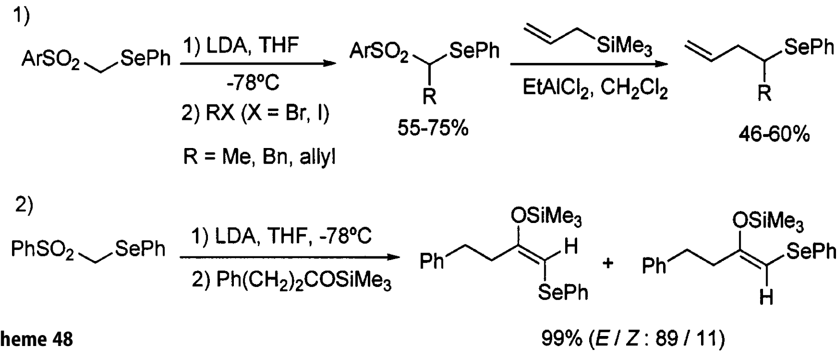


Scheme 47

5.3
α-Arenesulfanyl Selenium-Stabilized Carbanions

α-Phenylselanylmethyl sulfones were metalated with LDA, and then alkylated by various alkyl halides, leading to α-substituted sulfones [62] (Scheme 48, reaction 1). The modest yields observed were explained by the formation of byproducts, including methyl phenyl sulfone and bis(phenylselanyl)methylphenyl sulfone. The α-selenenylation of sulfones, via their carbanion, has furnished over-selenenylated products in appreciable amounts. The α-phenylselanylalkyl sulfones were easily converted into homoallylic selenides by coupling with allyltrimethylsilane in the presence of Et_2AlCl [62].

The reaction of the stabilized carbanion derived from α-phenylselanylmethyl phenyl sulfone with an acylsilane allowed the synthesis of *E*/*Z* mixtures of

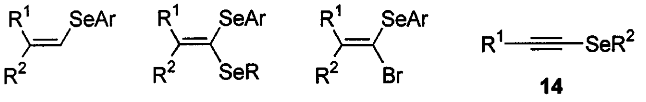


Scheme 48

β-phenylselanyl enoxysilanes in almost quantitative yield after Brook rearrangement [63] (Scheme 48, reaction 2).

6
Synthesis and Reactivity of α-Selanylvinylmetal Derivatives

In this concluding section, we will recall that α-selanylvinylmetal derivatives can be produced by α-deprotonation of vinylic aryl selenides **11**, cleavage of ketene selenoacetals **12** or bromine/lithium exchange of α-bromovinyl selenides **13** (Scheme 49). These strategies involve vinylic selenides whose syntheses are not simple. More recent works have used organocuprate additions, hydrometalations (M = Sn, Zr) or hydroborations of readily available acetylenic selenides **14** (Scheme 49). The process can be regio- and stereocontrolled and produce the α-selanylvinylmetal derivatives under mild conditions. The latter can be considered as vinyl dianion equivalents and are very useful intermediates for cross-coupling reactions.

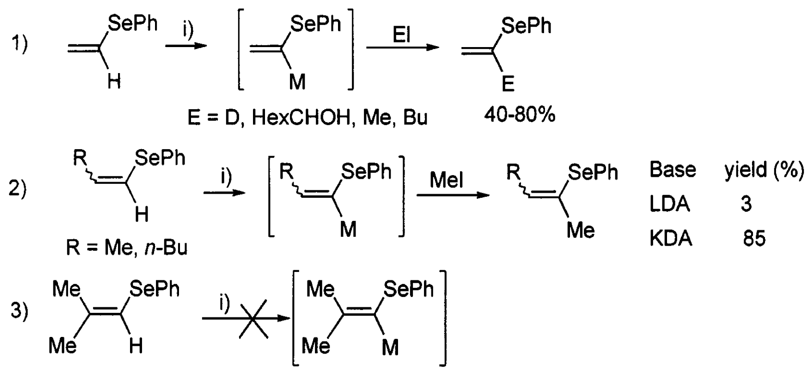


Scheme 49 **11** **12** **13** **14**

6.1
Generation from Vinylic Selenides and Ketene Selenoacetals

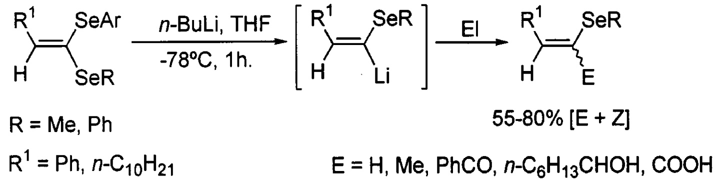
The α-deprotonation of vinylic aryl selenides is strongly dependent on the substituents [4]. For phenyl vinyl selenide, the reaction was successfully carried out with LDA or KDA at −78 °C in THF (Scheme 50, reaction 1). When a β-alkyl group is present, the use of LDA in THF leads to the abstraction of both vinyl and allyl protons. The α-deprotonation was improved using KDA in THF at −78 °C (Scheme 50, reaction 2). With two β,β'-alkyl groups, the metalation occurred only at an allylic position (Scheme 50, reaction 3).

α-Selanylvinyllithiums can be efficiently prepared by an Se/Li exchange reaction on ketene selenoacetals using n-BuLi at −78 °C in THF/hexane allowing the



Scheme 50 i) LDA or KDA, THF, -78°C

cleavage of a PhSe or a MeSe group. The stereochemistry of the products, obtained after reaction with an electrophilic reagent, seems to be dependent on the selanyl group cleaved [4] (Scheme 51).

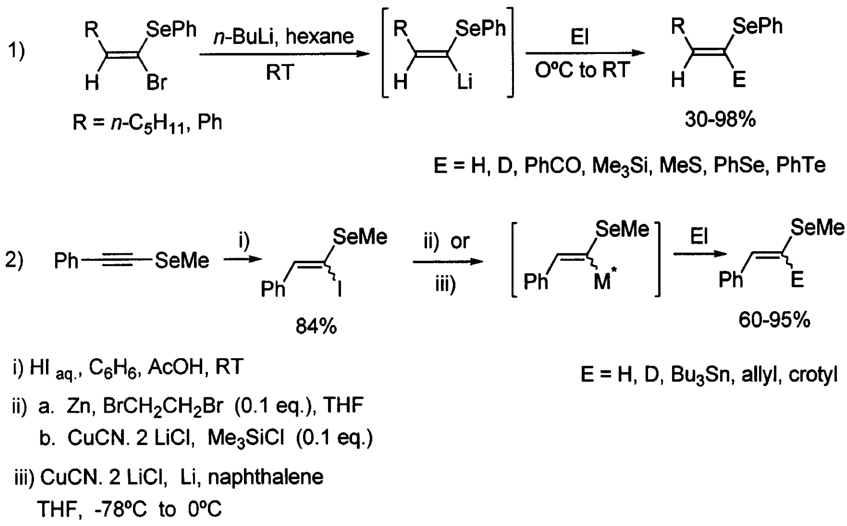


Scheme 51

α-Selanylvinyllithiums are also quantitatively formed by bromine/lithium exchange of α-bromovinyl selenides with butyllithium in hexane at room temperature. Addition of various electrophilic reagents afforded the corresponding vinylic selenides in good to high yields with retention of the double-bond configuration [64] (Scheme 52, reaction 1). 1-Iodo-2-phenylvinylmethyl selenide, prepared by HI addition to phenylethynyl methylselenide, was converted into vinylic organometallics (M=Zn, Cu) after specific activation, which were then reacted with electrophiles [65]. Successful reactions occurred with NH_4Cl, D_2O, allyl bromide or Bu_3SnCl, but no reaction took place with aldehydes, ketones or epoxides (Scheme 52, reaction 2). *Z*/*E* mixtures of olefinic compounds were always formed even with an isomerically pure starting material.

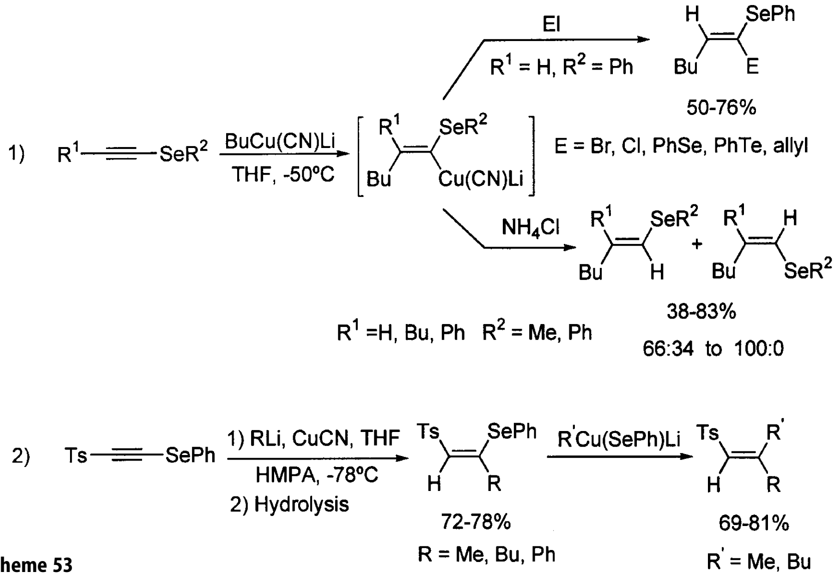
6.2
Cuprate Addition to Acetylenic Selenides

The reaction of various electrophiles with vinylcuprates, formed by addition of lithium *n*-butylcyanocuprate to acetylenic selenides afforded, α-substituted vinylic selenides in reasonable to good yields (50–76%) [66] (Scheme 53, reaction 1). Starting from phenylselanylacetylene, the two groups introduced have a *cis* configuration [67, 68]. A loss of stereoselectivity was observed after hydroly-



Scheme 52

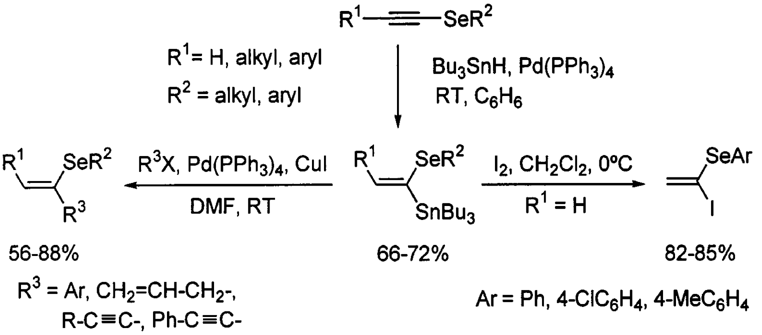
sis of the vinylic cuprate derived from substituted acetylenic selenides. Back et al. observed the opposite addition of alkylcuprates to phenylselanylethynyl tolyl sulfone [69, 70] (Scheme 53, reaction 2). The *syn* addition of the alkylcuprate was controlled by the sulfonyl group providing *β*-(phenylselanyl)vinyl sulfones in 72–78% yields. The deselenylative coupling reaction with a phenylselanyl-organocuprate, achieved on each geometric isomer of *β*-(phenylselanyl)vinyl sulfones, has allowed the stereocontrolled synthesis of *β*,*β*-disubstituted vinyl sulfones.



Scheme 53

6.3
Hydrostannylation of Acetylenic Selenides

(*E*)-(*α*-Phenylselanyl)vinylstannanes were regio- and stereoselectively obtained in good to high yields by palladium-catalyzed addition of tributyltin hydride to acetylenic selenides [71] (Scheme 54). From simple acetylenic selenides ($R^1 = H$), iodine treatment furnished 1-iodovinylaryl selenides in 82–85% yield after iododestannylation [71] (Scheme 54). These organometallics are also efficient precursors for the stereoselective synthesis of *α*,*β*-disubstituted vinyl selenides [72], 1,3-enynyl selenides [73] and 1,4-dienyl selenides [74] (Scheme 54). The cross-coupling reactions were catalyzed by tetrakis(triphenylphosphine)palladium in the presence of CuI in DMF at room temperature. The tributylstannyl group was always selectively replaced by a carbon-carbon bond with retention of configuration.

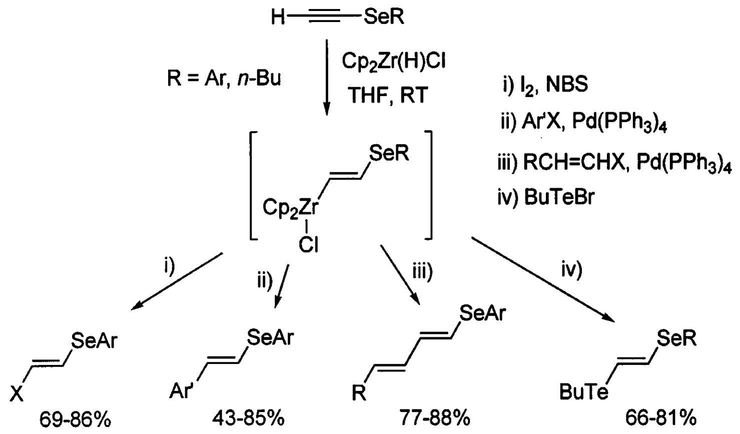


Scheme 54

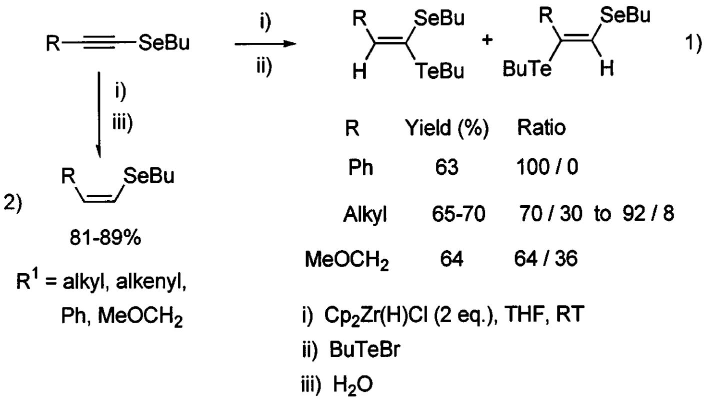
6.4
Hydrozirconation of Acetylenic Selenides

The regiochemistry of the hydrozirconation of acetylenic selenides with the Schwartz reagent [$Cp_2Zr(H)Cl$] is dependent on the nature of the substituents. For simple acetylenic selenides (R = Ar, *n*-Bu), *(E)*-*β*-zirconated vinyl selenides were formed exclusively. The reaction with electrophilic reagents has allowed the stereoselective synthesis of *(E)*-2-halovinylaryl selenides [75], *(E)*-2-arylvinyl aryl selenides [76], *(E,E)*-1-arylselanylbutadienes [77] and *(E)*-2-butyltelluranylvinyl selenides [78] (Scheme 55).

Dabdoud et al. have shown that the hydrozirconation of alkyn-1-ylbutyl selenides was complete with two equivalents of $Cp_2Zr(H)Cl$. The nature of the products, formed after reaction with BuTeBr, is dependent on the substituent R [78] (Scheme 56, reaction 1). With R=Ph, the ketene butylselanyl(butyltelluranyl)acetal was obtained exclusively. In the other cases (R = alkyl, $MeOCH_2$), small amounts of *(E)*-(2-butyltelluranyl)vinyl butyl selenides were also produced. The hydrozirconation of substituted acetylenic butyl selenides could be considered as a convenient approach for the synthesis of



Scheme 55



R^1 = alkyl, alkenyl, Ph, $MeOCH_2$

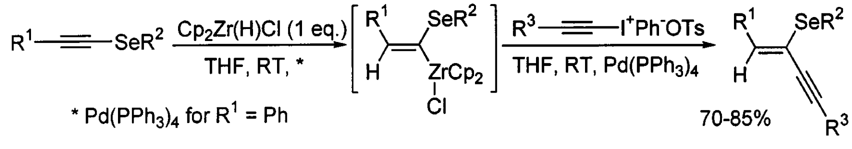
R	Yield (%)	Ratio
Ph	63	100 / 0
Alkyl	65-70	70 / 30 to 92 / 8
$MeOCH_2$	64	64 / 36

i) $Cp_2Zr(H)Cl$ (2 eq.), THF, RT
ii) BuTeBr
iii) H_2O

Scheme 56

(*Z*)-vinyl selenides after hydrolysis of the metallic intermediates (Scheme 56, reaction 2).

α-Zirconated vinyl selenides have been proposed as intermediates for the preparation of 2-phenylselanylbut-1-en-3-yne derivatives (1,3-enynyl selenides) by coupling reaction with alkynyliodonium tosylates in the presence of $Pd(PPh_3)_4$ [79] (Scheme 57). It must be noted that the authors used one equivalent of $Cp_2Zr(H)Cl$ in the presence of $Pd(PPh_3)_4$ (10 mmol %) for phenylethynyl selenides (R^1 = Ph).

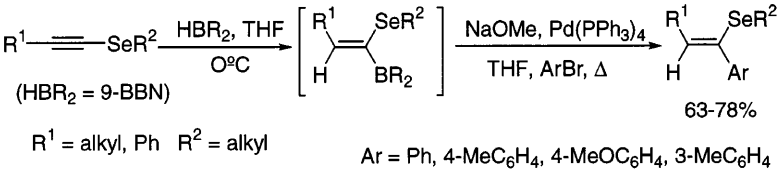


* $Pd(PPh_3)_4$ for R^1 = Ph

Scheme 57 R^1 = Bu, CH_2OMe, Ph R^2 = Me, Et R^3 = Ph, CH_2OMe

6.5
Hydroboration of Acetylenic Selenides

Hydroboration of acetylenic selenides with 9-BBN led to the regio- and stereoselective formation of α-selanylalkenyl boranes which were then converted into Z-α,β-disubstituted vinyl selenides by cross-coupling reaction with aryl bromides [80] (Scheme 58). With unsubstituted acetylenic selenides, an inversion of regioselectivity during the hydrozirconation was observed [81, 82].



Scheme 58

7
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Selenium at Higher Oxidation State

Józef Drabowicz · Marian Mikołajczyk

Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-363 Łódź, Sienkiewicza 112, Poland
E-mail: draj@bilbo.cbmm.lodz.pl · marmikol@bilbo.cbmm.lodz.pl

Until recently, selenium derivatives at a higher oxidation state had found rather limited use in organic synthesis. The last ten years, however, have shown that these species are valuable reagents and intermediates which allow clean and high-yielding transformations of a variety of functional groups even in very complex structures in a chemo- regio- and stereoselective manner, under rather mild reaction conditions. A comprehensive review of the synthetic utility of these compounds is presented here with particular emphasis on the stereochemical aspects of their use as reagents.

Keywords: Asymmetric synthesis, Oxidation, Selenium dioxide, Selenoxides, Selenuranes, Selenonium salts, Selones

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1
Introduction

The very rapid development of synthetic methodologies observed over the last three decades is based mainly on the introduction of a great number of heteroatom-containing derivatives as the reagents of choice. Due to the unique reactivity of these compounds it has become possible to introduce

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and/or interconvert different functional groups into very complex structures in a chemo-, regio- and stereoselective manner under rather mild reaction conditions [1]. During the past two decades it has been shown unequivocally that the selenium compounds (most often organic, but sometimes inorganic) react with a variety of organic substrates under neutral conditions. Therefore, they are commonly and effectively applied for the purposes mentioned above [2, 3].

Because selenium forms a very large number of inorganic and organic compounds showing different structural properties, the first question which should be answered in this chapter is the meaning of the term "selenium at higher oxidation state". A very useful criterion to classify all inorganic and organic selenium compounds, like other heteroatom-containing derivatives, is the formal oxidation state and the number (N) of ligands bonded to selenium. At present, a large number of stable selenium compounds with the formal oxidation state from 2 to 6 and with the ligand number from 1 to 6 can be prepared and, after isolation, handled under typical laboratory conditions.

Based on these criteria, selenium compounds can formally be divided into the following classes:

a. divalent, monocoordinated derivatives (selenocarbonyl compounds, selenides derived from tricoordinated, trivalent organophosphorus compounds)
b. divalent, dicoordinated derivatives (selenides, selenenyl compounds)
c. trivalent, tricoordinated derivatives (selenonium salts)
d. tetravalent, dicoordinated derivatives (selenium dioxide, diimidoselenium compounds)
e. tetravalent, tricoordinated derivatives (selenoxides, seleninic acid derivatives R,Se(O)X, selenilimines, selenites)
f. tetravalent, tetracoordinated derivatives (selenuranes)
g. pentavalent, tetracoordinated (selenoxonium salts $R_3Se^+ = O\ X^-$)
h. hexavalent, tetracoordinated derivatives (selones)
i. hexavalent, pentacoordinated derivatives (selenurane oxides)
j. hexavalent, hexacoordinated derivatives (perselenuranes)

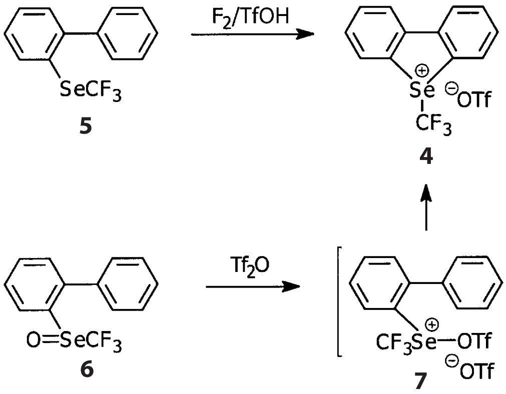
Looking at this list it is obvious that the selection of a borderline between selenium compounds which may be considered as the derivatives having lower oxidation state and their higher oxidation state analogues is to some extent a matter of formality and, as such, may always be considered as an arbitrary choice. After analysis of a preliminary outline of the chapters in this volume and taking into account the fact that pentavalent, tetracoordinated compounds have not yet been reported and that the first organic member of the selenurane oxide family has just been isolated [4] as a stable chemical species, we have decided to discuss here the recent synthetic application of selenium compounds from the classes c–f, h and j.

2
Trivalent, Tricoordinated Selenonium Salts

In spite of the fact that organic reactions proceeding via the three-membered, cyclic episelenonium ion intermediates have recently been widely used in organic synthesis [5], there are only a few publications in which application of the isolable cyclic and acyclic selenonium salts as synthetically useful reagents have been reported. The parent member of the selenonium salts family, trimethylselenonium hydroxide (**1**), was found [6] to have strong alkylating properties. This made possible the methylation of a wide range of nucleophilic substrates **2** to form the methylated products **3** in very high yields (Eq. 1).

$$\underset{\mathbf{1}}{Me_3Se^{\oplus}OH^{\ominus}} + \underset{\mathbf{2}}{NuH} \longrightarrow \underset{\mathbf{3}}{MeNu} + Me_2Se + H_2O \qquad (1)$$

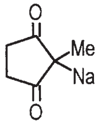
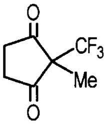
More recently, it has been reported [7] that similar properties were observed for Se-trifluoromethylated dibenzoselenonium salts. *Se*-(Trifluoromethyl) dibenzoselenophenium triflate (**4**) was successfully synthesized in high yield by the direct fluorination of an equimolar mixture of the selenide **5** and triflic acid (TfOH) with diluted molecular fluorine. The same salt was also obtained by cyclization of the selenoxide **6** with triflic anhydride (Tf_2O) – a reaction which probably occurs via the selenonium salt **7** (Scheme 1).

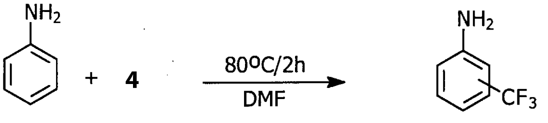


Scheme 1

As can be seen from Table 1, the trifluoromethylating agent **4** allowed the trifluoromethylations of some nucleophilic substrates which are otherwise impossible or difficult to achieve by more conventional ionic or free radical methods. It is interesting to note that the high reactivity of this reagent may be attributed to the additional driving force due to the restoration of lost aromaticity as the result of transformation of the central five-membered selenium-containing ring regarded as having 4π antiaromaticity to a 6π aromatic heterocycle as indicated by Kevill et al. [8] and Horak et al. [9]. Salt **4** was also successfully used for the trifluoromethylation of aniline (Eq. 2) giving *o*-(trifluoromethyl)aniline (**8a**) and *p*-(trifluoromethyl)aniline (**8b**).

Table 1. Trifluoromethylation of selected nucleophiles by *Se*-(trifluoromethyl) dibenzoselenophenium triflate **4**

Substrate	Conditions			Product [yield (%)]	
	Solvent	temp [°C]	time		
	DMF	-45↗rt	1 day		(76%)
$PhC{\equiv}C\text{-}Li$	THF	-78↗rt	1.25 h	$PhC{\equiv}CCF_3$	(89%)
$n\text{-}C_{12}H_{25}SNa$	THF	rt	0.5 h	$n\text{-}C_{12}H_{25}SCF_3$	(87%)
$2\text{-}Ph\text{-}C_6H_4SNa$	THF	0	0.5 h	$2\text{-}Ph\text{-}C_6H_4SCF_3$	(78%)



8a (38%)
b (19%)

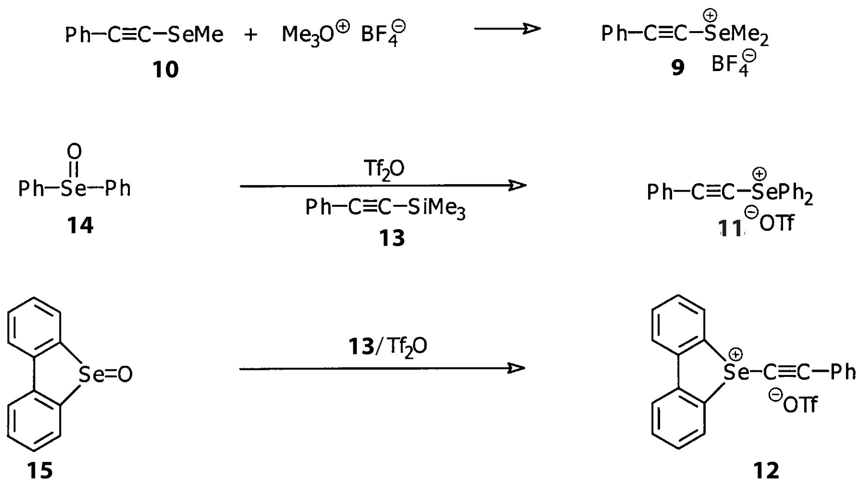
(2)

Although the first alkynylselenonium salt, ethylmethylphenylethynyl selenonium picrate, was prepared as early as 1965 [10], it is only very recently that the first reactions of selenonium salts have been reported [11]. Among these salts, acyclic dimethyl(phenylethynyl)selenonium tetrafluoroborate (**9**) was prepared by methylation of methyl phenylethynyl selenide (**10**) with Meerwein's reagent. The acyclic derivative **11** and the cyclic analogue **12** were synthesized by treatment of trimethyl(phenylethynyl)silane (**13**) and trifluoromethanesulfonic anhydride with diphenyl selenoxide (**14**) and dibenzoselenophene 5-oxide (**15**), respectively (Scheme 2).

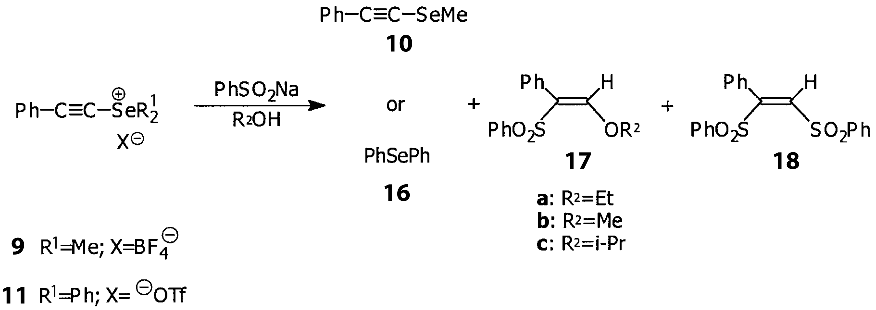
The selenonium salts **9** and **11** were found to react with one equivalent of sodium benzenesulfinate in an alcohol giving the products shown together with their ratio in Scheme 3. It is evident from the above data that the reaction of **9** and **11** with sodium benzenesulfinate gave (*Z*)-alkoxyvinyl sulfone **17a** and the reactions at room temperature or at 60 °C afforded (*Z*)-bis-(phenylsulfonyl)styrene (**18**) as a by-product. In contrast, the reactions of salts **9** and **11** with benzenesulfinic acid in isopropanol afforded (*Z*)-(*β*-phenylsulfonyl)vinylselenonium salts **19** and **20** in yields of 76 and 72%, respectively (Eq. 3). Neither the sulfone **17c** nor the vinylsulfone **18** was isolated from these reactions [11a].

(3)

19 R^1=Me; X=BF_4
20 R^1=Ph; X= $^{\ominus}$OTf



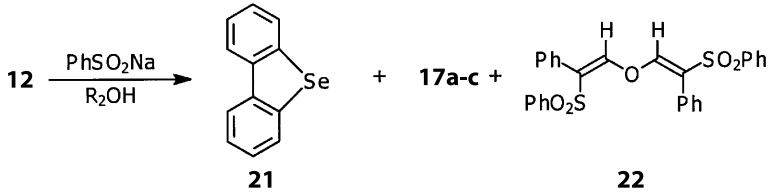
Scheme 2



Salt	Solvent	Temp [°C]	Products (% Yield) 10	16	17	18
9	EtOH	rt	(21)	-	**a** (74)	-
9	EtOH	60	(33)	-	**a** (25)	(20)
9	MeOH	rt	(25)	-	**b** (60)	-
9	*i*-PrOH	rt	(12)	-	**c** (68)	-
11	EtOH	rt	-	(73)	**a** (69)	(7)
11	EtOH	60	-	(73)	**a** (64)	(7)

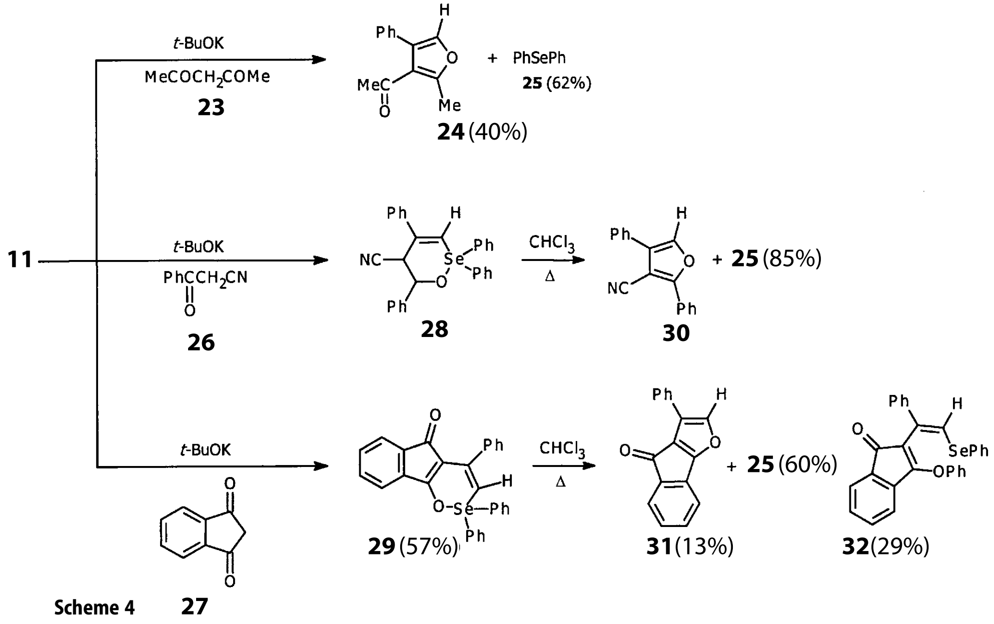
Scheme 3

It is interesting to note that the cyclic salt 12 did not react with benzenesulfinic acid; however, when treated with sodium benzenesulfinate in an alcohol, it gave dibenzoselenophene 21 and *Z*-alkoxyvinylsulfones 17a–c in moderate yields (51–77%). When the reaction was carried out in *t*-butyl alcohol, bis(phenylsulfonylvinyl)ether (22) was formed in 30% yield (Eq. 4).



(4)

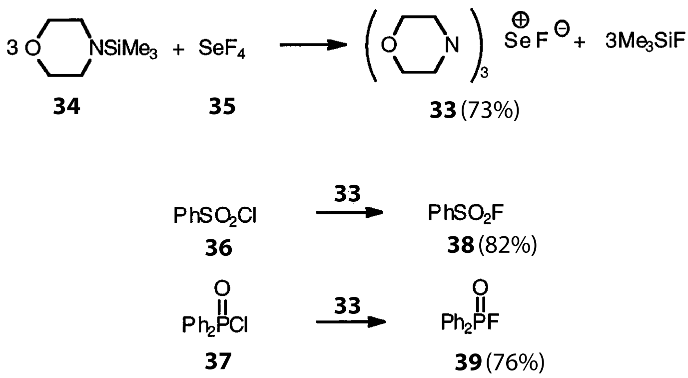
Reaction of the selenonium salt **11** with acetylacetone (**23**) and *t*-BuOK in THF gave the furan derivative **24** and diphenylselenide (**25**) in 40 and 62% yield, respectively. However, the reaction of this salt with benzoylacetonitrile (**26**) and 1,3-indandione (**27**) afforded the selenurane intermediates **28** and **29** in yields of 88 and 57%, respectively. These selenuranes gave after refluxing in chloroform the furan derivatives **30** and **31**, diphenyl selenide (**25**) and the structure **32** in the yields shown in Scheme 4.



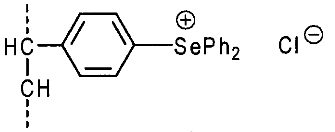
Scheme 4

Tris(morpholine)selenonium fluoride (**33**), easily prepared by the reaction of *N*-trimethylsilylmorpholine (**34**) with selenium tetrafluoride (**35**), is a very useful reagent for chloride/fluoride exchange reactions [12]. Thus, benzenesulfonyl chloride (**36**) and diphenylphosphinyl chloride (**37**) gave upon treatment with **33** the corresponding fluorides **38** and **39** in good yields (Scheme 5).

It was also found [13] that triphenylselenonium chloride and its polymer analogue **40** work as highly efficient phase-transfer catalysts even in the presence of a strong base, thus allowing, for example, the phenoxide substitution reaction of 1-bromooctane [13b].



Scheme 5



40

3
Tetravalent, Dicoordinated Derivatives

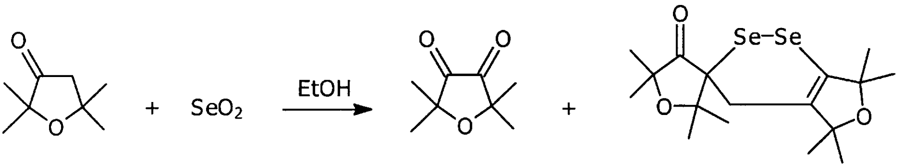
Within this class of selenium derivatives only selenium dioxide **41** alone, or in combination with other chemicals, and diimidoselenium reagents **42** are commonly used in organic synthesis. Because the use of these latter reagents is discussed in detail in Chap. 8 of this volume (devoted to rearrangements), our presentation will be limited to recent utilization of selenium dioxide as a reagent.

$O{=}Se{=}O$ **41**

$RN{=}Se{=}NR$ **42**

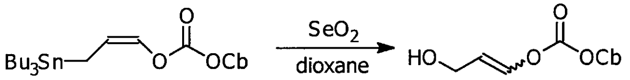
Earlier synthetic applications of selenium dioxide for the introduction of the carbonyl functionality at activated positions, to dehydrogenation of highly activated saturated sites, to hydroxylation of activated carbon-bearing positions, particularly at allylic(propargylic) sites, and to oxidative bond cleavage are presented in a few books devoted to selenium chemistry [2] or oxidation reactions [14]. These procedures are also permanently included in the Fieser & Fieser compendium of reagents [15].

A recent study of some parameters which influence the oxidation of 2- and 4-methylquinolines to aldehydes with selenium dioxide in dioxane has shown that the successful result of oxidation is dependent on the amount of the oxidant used, but not on its purity, and on neutralization of quinolinecarboxylic acid in the reaction product before isolation of an aldehyde [16]. When 2,2,5,5-tetramethyltetrahydrofuran-3-one (**43**) was oxidized with selenium dioxide in ethanol, the six-membered selenium-containing heterocycle **44** was formed along with the expected 3,4-furandione **45** [17] (Eq. 5).

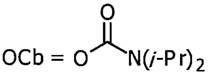


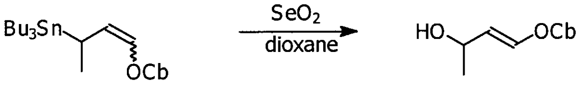
43 **45** **44** (5)

Allylic oxidation of olefins is a reaction of considerable value in organic synthesis [18] and selenium dioxide itself or in combination with other co-oxidants remains a highly predictable and reliable reagent to perform these reactions. Thus, selenium dioxide oxidation of (*Z*)-tributyltin 1-alkenylcarbamates **46** constitutes the first successful example of such a conversion ever reported with an element other than hydrogen [19]. Namely, it was found that with the allylic stannanes **46a** or **46b** oxidation occurred smoothly within 15 min to deliver in good yields the expected corresponding allylic alcohols **47a** and **47b**, respectively (Eqs. 6 and 7).



46a (*Z*/*E* >98:2) **47a** (83%) (6)





(7)

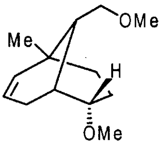
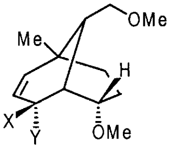
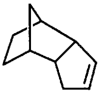
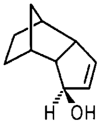
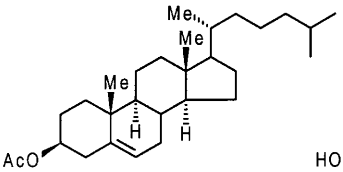
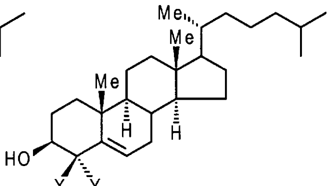
(*E*) or (*Z*) - **46b** [*Z*/*E*>98:2 or 16:84] **47b** (83%)

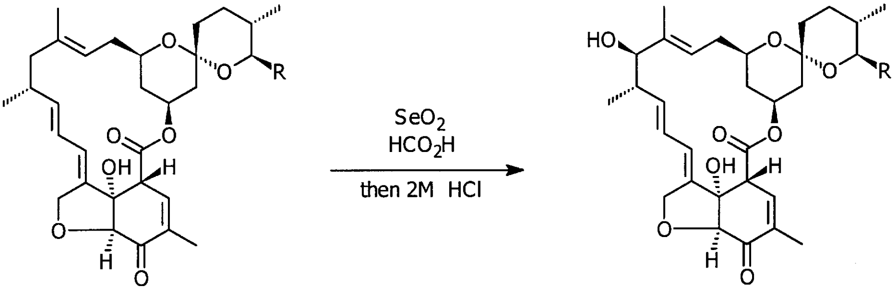
Interestingly, under these conditions, the oxidation appears to be highly stereoconvergent and both crotyl stannanes (*E*)- and (*Z*)-**46 b** led to the (*E*)-allylic alcohol **47 b** with an *E*/*Z* stereoselectivity better than 95%. This reaction has been extended to other more complex tributylstannyl-1-alkenylcarbamates which were oxidized with a stoichiometric amount of SeO_2 in the presence of formic acid. Good yields (59–82%) of the corresponding allylic alcohols were obtained.

In an earlier work, a combination of formic acid and selenium dioxide in dioxane was found to be an efficient system for the allylic oxidation of sterically hindered olefins leading to the corresponding allylic alcohols or formates (Table 2) [20].

13-*β*-Hydroxylation of milbemycins **54a–c**, 16-membered ring macrolides isolated from *Streptomyces hygroscopicus* and showing potent and broad spectrum activity as anthelmintics, acaricides and insecticides, was found to be relatively efficient (yields around 50%) by selenium dioxide oxidation in formic acid and subsequent acidic hydrolysis (Scheme 6) [21].

Table 2. Allylic oxidation of bicyclic olefins **48**–**50** with selenium dioxide/formic acid

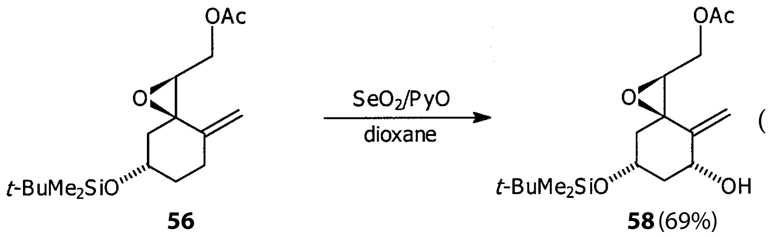
Substrate	Product	Yield (%) [Isomeric Ratio]
 **48**	 **51**	97% (**a**:**b**=92:8) **51a** X=OCHO, Y=H **51b** X=H, Y=OCHO
 **49**	 **52**	80%
 **50**	 **53**	57% (**a**:**b**=3:1) **53a** X=OCHO, Y=H **53b** X=H, Y=OCHO



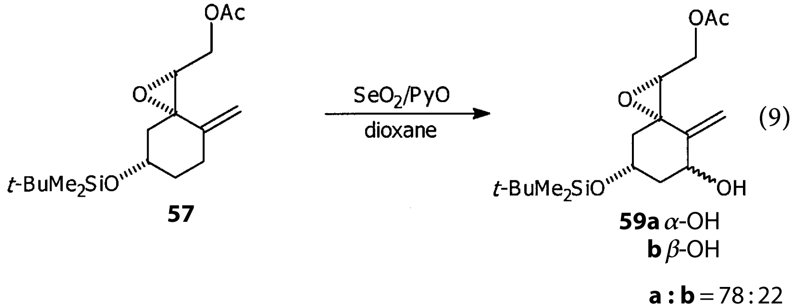
54 (R=Me, Et, *i*-Pr) **55** (45-49%)

Scheme 6

Hydroxylation of the allylic methylene group in *α*- and *β*-5,6-epoxides **56** and **57** was very effectively realized by a combination of selenium dioxide and pyridine *N*-oxide in dioxane [22a]. Starting from **56** the 1*β*-hydroxy isomer of **58** was obtained as a single product (Eq. 8) while, under the same conditions, the acetate **57** was converted to a 78:22 mixture of the 1*α*- and 1*β*-hydroxy isomers **59a** and **59b**, respectively (Eq. 9). In this context it is interesting to note that a similar hydroxylation procedure with



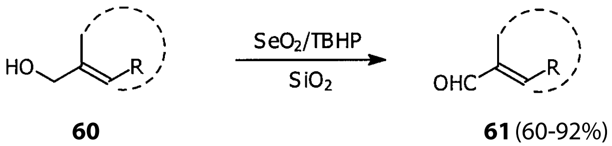
(8)



(9)

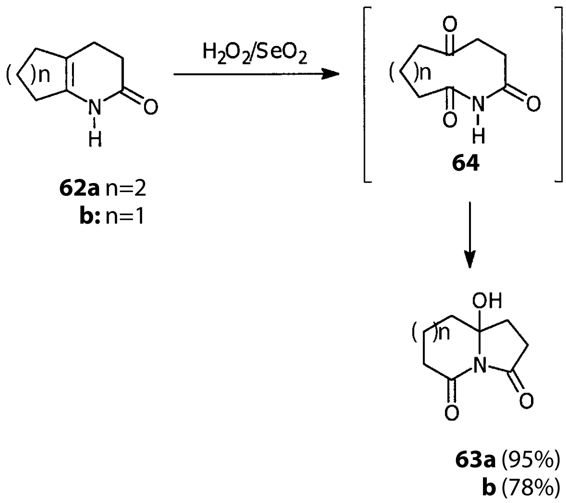
SeO$_2$ and *N*-methylmorpholine *N*-oxide [22b] failed to generate the desired products.

Considering the examples of allylic oxidation with the selenium dioxide derived reagents presented above it is of interest to note that the selective oxidation of primary allylic alcohols **60** to the corresponding α,β-unsaturated aldehydes **61** was achieved [23] using an SeO$_2$/(TBHP)/SiO$_2$ system, while secondary allylic, benzylic and saturated alcohols remained unaffected (Eq. 10).



(10)

Oxidation reactions with hydrogen peroxide catalyzed by selenium dioxide have been successfully applied to achieve a variety of basic functional group transformations such as oxidation of aldehydes and ketones and their azomethine derivatives into carboxy esters, phenols, nitriles and carboxylic acids [24] and sulfides to sulfoxides and/or to sulfones [25]. Very recently, oxidative cleavage of ene lactams **62** was efficiently performed [26] by SeO$_2$-catalyzed oxidation with H$_2$O$_2$ to give the corresponding ketoimides **63** (Scheme 7). The reaction was rationalized by assuming the transient formation of macrocyclic ketoimides **64** which are transformed into the final products via intramolecular nucleophilic attack of the nitrogen atom of the imido moiety on the carbonyl group. This procedure was suggested to be especially useful for the synthesis of indolizidine alkaloids which have received a lot of attention because of their potent enzyme inhibition properties.



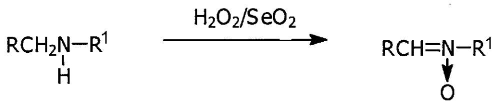
62a n=2
b: n=1

64

63a (95%)
b (78%)

Scheme 7

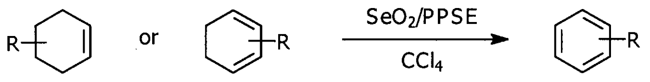
Secondary amines **65** were easily oxidized [27] to the corresponding nitrones **66** by hydrogen peroxide or urea hydrogen peroxide complex in the presence of SeO_2 as a catalyst (Eq. 11).



$$RCH_2N(H){-}R^1 \xrightarrow{H_2O_2/SeO_2} RCH{=}\overset{O}{\overset{\downarrow}{N}}{-}R^1 \qquad (11)$$

65 **66**

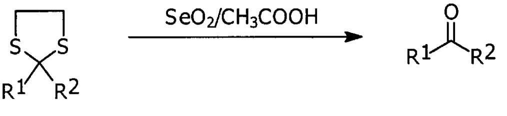
Early applications of SeO_2 as a dehydrogenation reagent were limited to compounds like 1,2-diarylethanes and 1,4-diketones which afforded conjugated unsaturated products [28]. Recently, the first aromatization of cyclohexenes **67** and cyclohexadienes **68** by selenium dioxide activated with trimethylsilylpolyphosphate (PPSE) has been reported [29]. It was found that the reaction described by Eq. (12) resulted in the formation of a variety of aromatics **69** in yields between 80 and 100% when substrates were refluxed in carbon tetrachloride for 16–22 h.



(12)

67 **68** **69**

It has also been reported [30] that a large number of 1,3-dithiolanes **70** were efficiently reconverted to the parent carbonyls **71** upon treatment with a 5-molar excess of selenium dioxide in acetic acid at room temperature for 1–2 h

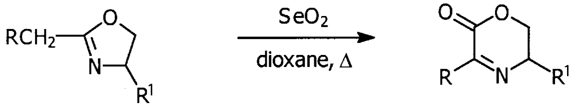


(13)

70 **71** (91-94%)

(Eq. 13). The method proved to be particularly effective with C-3 and C-17 dithiolane derivatives of steroid ketones which are usually deblocked under more vigorous conditions.

The selenium dioxide promoted oxidative rearrangement of 2-substituted oxazolines 72 unexpectedly gave [31] 3-substituted 5,6-dihydro-2*H*-1,4-oxazin-2-ones 73, useful chiral synthons for the synthesis of amino acid derivatives [32] (Eq. 14).

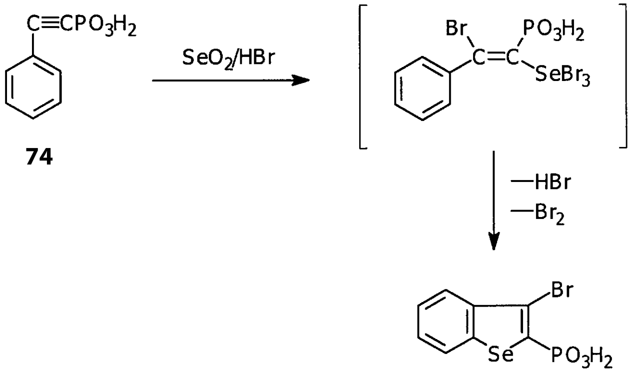


(14)

72 **73** (22-94%)

R = H, *i* Pr, *t*-Bu, Ph, Nph
R^1 = *i*-Pr, Ph, CH_2OBu

An oxidative heterocyclization of phenylethynylphosphonic acid (74) with selenium dioxide was reported to occur upon heating of both components in dioxane in the presence of 48% hydrobromic acid [33]. Phosphonic acid 75 functionalized with a benzoselenophene moiety was the single isolated reaction product (30% yield). It was suggested that this heterocyclization occurs as shown in Scheme 8.

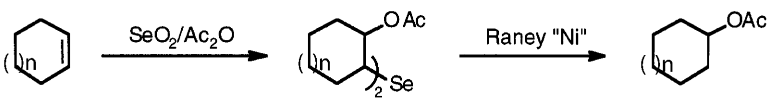


74

75

Scheme 8

Acetoxyselenylation of olefins 76 with a selenium dioxide/acetic anhydride system was found [34] to give the expected acetoxyselenylated derivatives 77. Their subsequent deselenylation with Raney nickel leads to the selenium-free acetates 78 (Scheme 9).



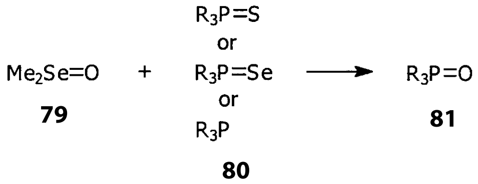
76 (n=0...5) **77** (44-60%) **78** (66%)

Scheme 9

4
Tetravalent, Tricoordinated Derivatives

Among tetravalent, tricoordinated selenium derivatives selenoxides have found the widest synthetic application. This is due to the fact that this group of seleninyl compounds undergo very mild and rather clean thermal elimination to form unsaturated products in high yields. Moreover, appropriate functionalized unsaturated selenoxides are very prone to thermal sigmatropic rearrangements and this property was the second foundation for the use of this type of selenoxides as important reagents in contemporary organic synthesis. Because both selenoxide reactions are discussed in detail in Chap. 8 of this volume, in our presentation these two aspects of selenoxide chemistry will be omitted. However, to cover this subject as comprehensively as possible, the use of selenoxides for a few other transformations are presented.

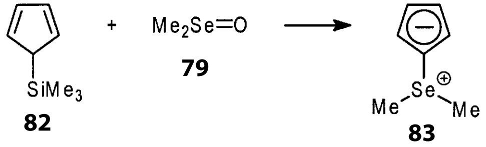
The first application of dimethyl selenoxide (**79**) as an oxidant to convert selected organophosphorus compounds **80** to their phosphoryl analogues **81** was reported as early as 1978 [35] (Eq. 15).



$$\underset{\mathbf{79}}{Me_2Se{=}O} + \underset{\mathbf{80}}{\begin{matrix} R_3P{=}S \\ \text{or} \\ R_3P{=}Se \\ \text{or} \\ R_3P \end{matrix}} \longrightarrow \underset{\mathbf{81}}{R_3P{=}O} \qquad (15)$$

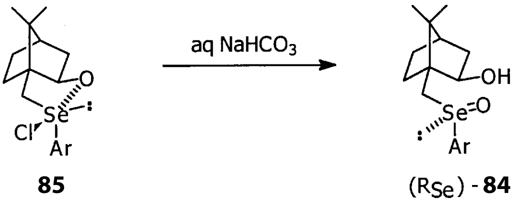
Simultaneously, **79** [36] and other selenoxides (dibenzyl [37], diphenyl [38] and bis(*p*-methoxyphenyl)selenoxide [39]) were applied as selective agents for the oxidation of various functional groups.

The reaction of 5-(trimethylsilyl)cyclopentadiene (**82**) with dimethyl selenoxide (**79**) was reported [40] to afford the selenoniocyclopentadiene **83** in almost quantitative yield (Eq. 16). The formation of the selenonium salts **7**, **11**, and **12** in the reaction of the appropriate selenoxide with triflic anhydride has been discussed earlier (see Sect. 2).



(16)

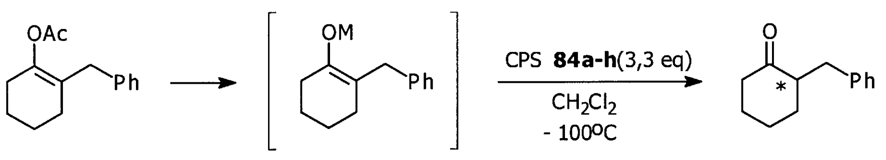
Very recently, the enantioselective protonation of simple enolates was developed [41] using diastereoisomerically pure γ-hydroxyselenoxides, derived from the 2-*exo*-hydroxy-10-bornyl group, as chiral compounds. The selenoxides **84**, containing various aryl groups, were prepared by treatment of the corresponding isomerically pure chloroselenuranes **85** with sodium hydrogen carbonate [41c] (Eq. 17).



85 (RSe) - **84**

a; Ar=Ph
b; Ar=2-Py
c; Ar=4-F-C_6H_4 (17)
d; Ar=4-Me-C_6H_4
e; Ar=4-MeOC_6H_4
f; Ar=2,4(MeO)$_2$$C_6H_3$
g; Ar=2-Me-4-MeOC_6H_3
h; Ar=2-MeC_6H_4

Using these selenoxides as a chiral proton source (CPS), the enantioselective protonation of the enolates of 2-benzylcyclohexane **86a,b** was found to be quite effective (Scheme 10).



86a M=Li
b M=ZnBr

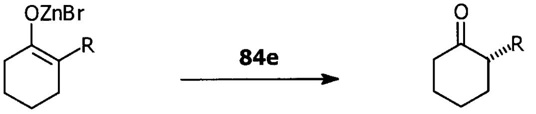
87 (35-82%)
0-89% ee

		87			
Enolate	Selenoxide	Yield [%]	[α]D	Abs. conf.	ee (%)
86a	(R)-**84a**	51	+13.3	R	29
86b	(R)-**84a**	57		S	40
86a	(R)-**84b**	76	+3.3	R	7
86a	(R)-**84c**	68	- 0.2		0
86a	(R)-**84d**	70	- 23.9	S	51
86a	(R)-**84e**	47	- 29.9	S	64
86a	(S)-**84e**	35		S	62
86b	(R)-**84e**	82		S	62
86b	(S)-**84e**	81		S	89
86a	(R)-**84f**	72	+12.3	R	26
86b	(R)-**84g**	51	+6.2	R	13
86b	(R)-**84h**	56	- 9.8	S	21

Scheme 10

The results indicate that the highest enantioselectivity of protonation was achieved using bromozinc enolate **86b** as the substrate and (*S*)-selenoxide **84e** as the CPS. Interestingly, the influence of the configuration of the seleninyl group on the enantioface differentiation is very small for the bromozinc enolate **86b** and negligible for the lithium enolate **86a**. This observation clearly shows that the chirality of the 2-*exo*-hydroxy-10-bornyl group chiefly determines the stereochemical outcome of the protonation process under consideration.

The results of the enantioselective protonation of some other enolates carried out under the optimal condititions with the selenoxide **84e** as the CPS are summarized in Eqs. (18) and (19).

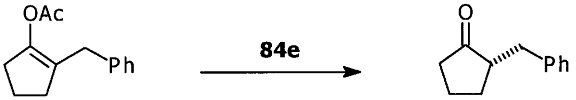


(18)

88a, R=PMB
b, R=*n*-Pr
c, R=*i*-Pr

89a, R=PMB 31%; 84% ee
b, R=*n*-Pr 78%; 88% ee
c, R=*i*-Pr 39%; 65% ee

PMB=4-$MeOC_6H_4CH_2$



(19)

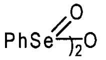
90

91 63%; 53% ee

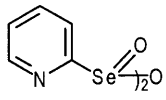
The oxidation of phenols, reported for the first time by the Barton group in 1975 [42], opened the way for extensive studies on the application of benzeneseleninic acid (**92**) and its anhydride **93** as specific oxidants for introducing a hydroxy or carbonyl group into various organic structures [43]. The basic drawback to the use of these reagents results from the fact that the reaction of phenolic substrates with **92** and **93** appears to form complex structures as was shown and rationalized earlier by the Barton group [44] and, recently, by Henriksen [45]. Continuing the search for more efficient seleninic derivatives, the Barton group found that oxidation reactions using 2-pyridineseleninic anhydride (**94**) are more efficient than those with benzeneseleninic anhydride (**93**) [46].

$PhSeO_2H$

92

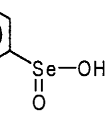

$(PhSe(=O))_2O$

93

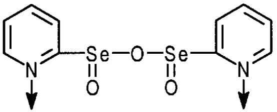


94

This may be attributed to the greater electron-withdrawing effect of the pyridine nucleus. Consequently, pentafluoroseleninic acid (**95**) and 2-(*N*-oxido)pyridineseleninic anhydride (**96**) were introduced [47] as the most efficient reagents in the oxidation of alcohols and in the allylic oxidation of olefins.

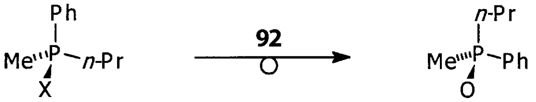


95



96

It is interesting to note that benzeneseleninic acid (**92**) was found [48] to behave as a very stereoselective oxidant of optically active methylphenyl-*n*-propylphosphine sulfide (**97a**) and methylphenyl-*n*-propylphosphine selenide (**97b**). The corresponding phosphine oxide **98** was formed with almost full inversion of configuration at the stereogenic phosphorus atom (Scheme 11).

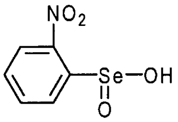


97a; X=S (ee=97.7%)
b; X=Se (ee=84%)

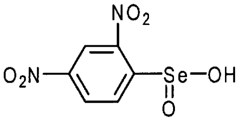
98 (ee=92%) from **97**
(ee=83%) from **97**

Scheme 11

Since the first observations reported in the late 1970s it has been known that seleninic acids can catalyze oxidative conversions with hydrogen peroxide [49]. This catalytic activity is due to the fact that seleninic acids react with hydrogen peroxide to produce the corresponding perseleninic acids. Thus, perbenzeneseleninic acid generated in such a way has been used as a convenient reagent for the oxidation of sulfides to sulfoxides or sulfones, aldehydes to carboxylic acids, alkenes to epoxides and in the Baeyer–Villiger reaction. More recently, the Baeyer–Villiger oxidation of aromatic aldehydes **99** and ketones **100** with hydrogen peroxide was found to give the highest yields of the corresponding aryl formates **101** or esters **102** when catalyzed by seleninic acids **103a** and **b** [50].



103a

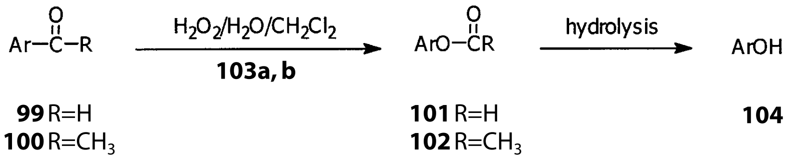


103b

Because the oxidation products **101** and **102** are easily hydrolyzed to the corresponding phenols **104**, the discussed procedure represents a convenient way to convert the carbonyl derivatives **99** and **100** to the corresponding phenols **104** (Scheme 12).

It should be mentioned that derivatives of acetophenone react much more slowly than the corresponding benzaldehyde derivatives. Therefore, to complete the reaction in a reasonable time, 90% hydrogen peroxide should be used. The nitro-substituted seleninic acids **103a,b** also manifested remarkable catalytic activity in the hydrogen peroxide oxidation of styrene to phenyloxirane [51].

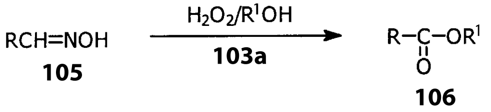
Oxidative conversion of aldoximes **105** into carboxylic esters **106** was effectively accomplished by treatment with an alcoholic solution of 30% hydrogen peroxide in the presence of catalytic amounts of 2-nitrobenzeneseleninic acid



	Carbonyls	Catalyst	Phenol, ArOH	
			No	Yield [%]
99a	2-$CH_3C_6H_4CHO$	**103b**	**104a**	94
99b	2,4,6-$(CH_3)_3C_6H_2CHO$	**103b**	**104b**	90
99c	4-PhC_6H_4CHO	**103b**	**104c**	77
100a	2,4-$(CH_3O)_2C_6H_3COCH_3$	**103a**	**104d**	65
100b	3,4-$(CH_3O)_2C_6H_3COCH_3$	**103b**	**104e**	67
100c	2,3,4-$(CH_3O)_3C_6H_2COCH_3$	**103a**	**104f**	86

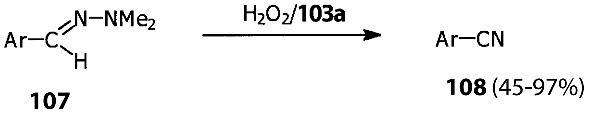
Scheme 12

(**103a**) (Eq. 20). Primary alcohols gave excellent to good yields, secondary ones – good to moderate, but with tertiary alcohols no ester formation was observed [52].



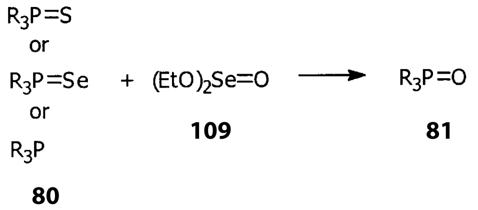
$$\underset{\mathbf{105}}{RCH{=}NOH} \xrightarrow[\mathbf{103a}]{H_2O_2/R^1OH} \underset{\mathbf{106}}{R{-}\overset{}{\underset{O}{\underset{\|}{C}}}{-}OR^1} \qquad (20)$$

The nitro-substituted seleninic acid **103a** was also found [53] to be an effective catalyst for the hydrogen peroxide mediated oxidative conversion of aromatic hydrazones **107** into nitriles **108** (Eq. 21). However, oxidation of hexanal dimethylhydrazone with this system gave only the parent aldehyde.



(21)

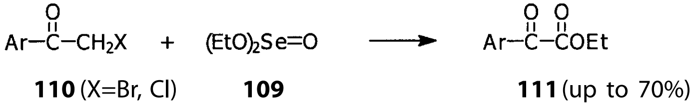
In addition to selenoxides and seleninic acids as oxidation agents, diethyl selenite (**109**) was reported as the first efficient oxygen transfer reagent. Namely, it was found [48] that diethyl selenite (**109**), easily prepared by the reaction of selenium dioxide with ethanol [54], is able to convert selected



$$\begin{matrix} R_3P{=}S \\ \text{or} \\ R_3P{=}Se \\ \text{or} \\ R_3P \\ \mathbf{80} \end{matrix} \; + \; \underset{\mathbf{109}}{(EtO)_2Se{=}O} \longrightarrow \underset{\mathbf{81}}{R_3P{=}O} \qquad (22)$$

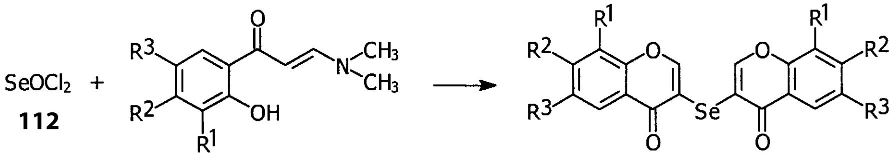
organophosphorus derivatives **80** into the corresponding phosphoryl compounds **81** (Eq. 22).

The oxidizing ability of diethyl selenite (**109**) was also tested in the oxidative conversion of the reactive halogenocarbonyls into the corresponding aldehydes (the so called Kornblum oxidation [55]). The model reactions with benzyl chloride and bromide as substrates have shown, however, that the expected conversion cannot be realized even after 244 h heating of both components in a sealed tube at between 120 and 140 °C [48, 56]. On the other hand, when phenacyl chlorides **110a** and bromides **110b** were used as substrates, the corresponding esters of phenylglyoxalic acid **111** were formed in yields approaching 70% [48, 56] (Eq. 23).



$$\underset{\mathbf{110}\,(X{=}Br,\,Cl)}{Ar{-}\overset{O}{\overset{\|}{C}}{-}CH_2X} \; + \; \underset{\mathbf{109}}{(EtO)_2Se{=}O} \longrightarrow \underset{\mathbf{111}\,(\text{up to } 70\%)}{Ar{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}OEt} \qquad (23)$$

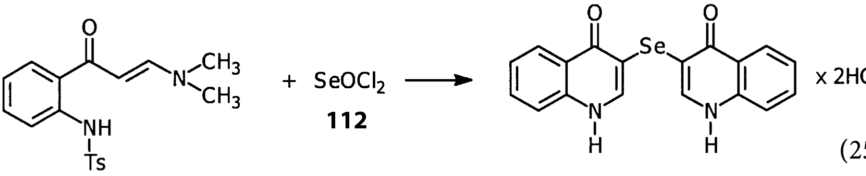
In contrast to thionyl chloride, which is commonly used as a reagent in organic synthesis, the application of seleninyl chloride (**112**) is limited to a few reactions. Thus, the new selenium-bridged chromanones **113** were prepared by the condensation of this chloride with enaminones of the 2-hydroxyphenylethanone type **114** [57] (Eq. 24).



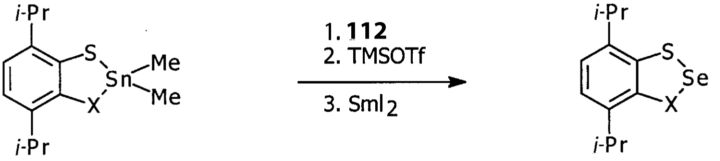
114 **113** (24)

A similar bisquinolone structure **115** was isolated in 72% yield when **112** was reacted with the *N*-tosylenaminone **116** (Eq. 25). The selenide **115** was further used for the preparation of novel selenium heterocycles [58].

Stable 4,7-disubstituted benzenotrichalcogenols **117** containing sulfur and selenium atoms in the five-membered ring were prepared by the reaction of the corresponding benzenodichalcogenostannoles **118** with seleninyl chloride (**112**) [59] (Eq. 26).



116 **115** (25)



118 (X=S, Se) **117** (X=S, Se) (26)

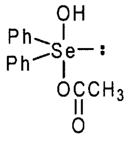
The literature reports a single paper on the synthetic application of selenilimines, the nitrogen analogues of selenoxides. It describes a novel carbonylation of selenilimines **119** to arylsulfonylisocyanates **120** catalyzed by palladium complexes like $PdCl_2(PhCN)_2$ or $PdCl_2(CH_3CN)_2$ [60] (Eq. 27).

$$\underset{\textbf{119}}{ArSO_2N{=}SePh_2} + CO \xrightarrow[35\text{ bar, }50^{\circ}C]{\text{Pd.complex}} ArSO_2NCO + Ph_2Se \qquad (27)$$

120 (52-78%)

5
Tetravalent, Tetracoordinated Derivatives

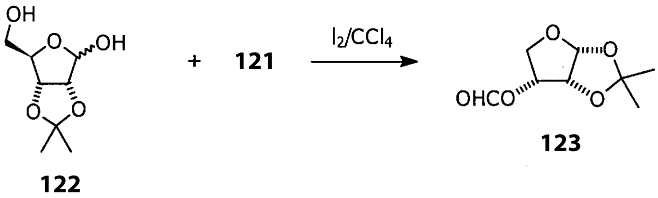
Tetravalent, tetracoordinated selenium compounds which contain a lone electron pair as a phantom ligand are commonly named selenuranes. Their chemistry, in contrast to the sulfur analogues (sulfuranes), is still in its infancy. In spite of this fact, the recent literature demonstrates that this class of high-coordinated organoselenium compounds constitutes a valuable addition to the list of selenium-containing reagents and intermediates with which it is possible to introduce and/or interconvert different functional groups even into very complex chemical structures in a chemo-, regio-, and stereoselective manner under rather mild reaction conditions. In 1988 the diphenylselenium hydroxyacetate **121**/iodine system was introduced as an efficient reagent to generate alkoxy radicals [61].



$$Ph_2\overset{OH}{\underset{OC(O)CH_3}{Se}}{-}:$$

121

For example, when carbohydrate derivatives with a suitably positioned hydroxyl group were reacted [62] with diphenylselenium hydroxyacetate (**121**) and iodine, the products resulting from a tandem β-fragmentation/cyclization

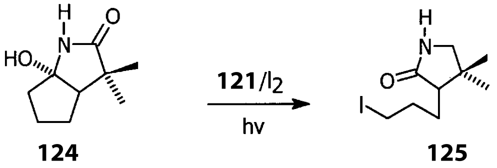


122 **123**

(28)

reaction were successfully obtained. Equation (28) shows this conversion for 2,3-*O*-isopropylidene-D-ribofuranose (**122**).

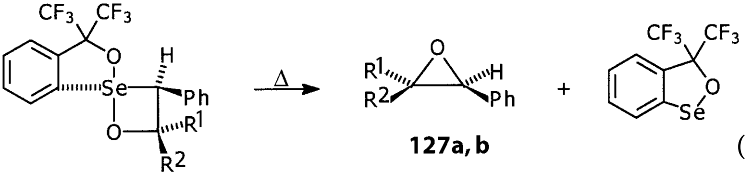
Similarly, the alkoxy radical intermediates generated by reacting carbinolimides **124** with the selenurane **121**/I_2 system under irradiation with visible light gave, after β-fragmentation, 3,5-substituted cyclic imides **125** in good yields [63] (Eq. 29).



124 **125**

(29)

Thermolysis of dialkoxyselenuranes **126a** and **b** was found to give oxiranes **127a** and **b** stereospecifically in high yield, although a small amount (2%) of an inverted product was obtained from **126b** [64] (Eq. 30).



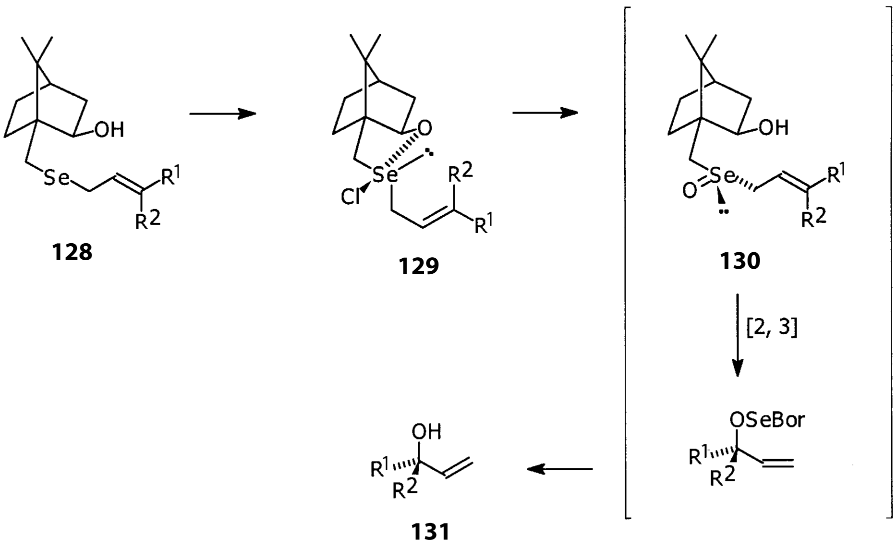
127a,b

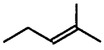
126a; R^1=CF_3; R^2=Ph
b; R^1=Ph; R^2=CF_3

(30)

Very recently, the Koizumi group has reported a very interesting application of diastereoisomerically pure chloroselenuranes containing the 2-*exo*-hydroxy-10-bornyl moiety as a chiral auxiliary. When chloroselenuranes **129**, prepared in situ from the corresponding allylic selenides **128**, were treated with aqueous $NaHCO_3$ at 0 °C, the corresponding allylic alcohols **131** were obtained in high chemical yields and in modest to high enantiomeric excess (ee) via the [2,3]-sigmatropic rearrangement of the allylic selenoxides **130** [65] (Scheme 13). A similar asymmetric [2,3]-sigmatropic rearrangement of allylic selenilimines prepared in situ from chloroselenuranes of type **129** was found to proceed in a highly stereoselective manner affording optically active *N*-protected allylic amines [66].

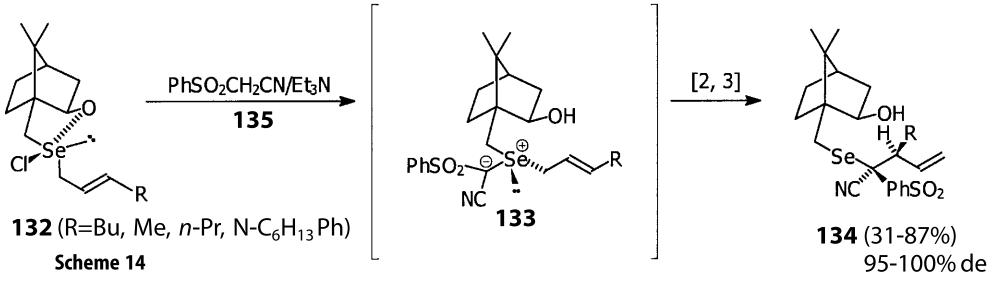
The same authors examined the [2,3]-sigmatropic rearrangement of the allylic selenonium ylides **133** generated in situ from chloroselenuranes **132** and (phenylsulfonyl)acetonitrile (**135**) in the presence of triethylamine as base



130				131	
No	R^1	R^2	E : Z	ee [%]	Abs. conf.
a	Ph	H	99 : 1	32	*R*
b	c-C_6H_{11}	H	95 : 5	26	*R*
c	n-C_6H_{13}	H	89 : 11	42	*S*
a	H	Ph	10 : 90	51	*S*
b	H	c-C_6H_{11}	16 : 84	80	*S*
c	H	n-C_6H_{13}	6 : 94	76	*R*
d		Me	99 : 1	88	*S*

Scheme 13

[67]. In this case also the corresponding, optically active diastereoisomerically pure homoallylic selenides **134** were isolated as a single product of this reaction (Scheme 14).



Scheme 14

Recent years have also witnessed an increasing interest in the use of halogenoselenuranes as reagents for interconversions of basic functional groups. As early as 1986 it was reported in a conference communication [68a] that the easily available dichloroselenuranes **137** react with alcohols **136** in the presence of equimolar amounts of triphenylphosphine with the clean formation of the corresponding chlorides **138** (Eq. 31).

$$\underset{\mathbf{136}}{R^1OH} + \underset{\mathbf{137}(R^2=\mathrm{Me,\ Ph})}{R^2_2SeCl_2} + Ph_3P \longrightarrow \underset{\mathbf{138}}{R^1Cl} + R^2_2Se + HCl + Ph_3P{=}O \quad (31)$$

A paper published recently [68b] provides a very detailed insight into the scope and mechanistic aspects of this reaction. Table 3 displays the relevant data whose salient features are as follows: (a) The reaction conditions are much milder than those using Ph_3P/CCl_4 [68c] or Ph_3PCl_2 [68d] as reagents; (b) the yields are very high and, in many cases, the crude reaction products can be used without further purification; (c) The carbon–carbon double-bond geometry is fully preserved in the unrearranged product (see cinnamyl chloride **138h**); and (d) There are no elimination by-products in the reaction with α-phenylethanol (**136g**) and adamantol (**136j**).

The usefulness of this new method for conversion of alcohols into chlorides was demonstrated by experiments with optically active substrates. It was found that both enantiomers of 2-octanol (**136k**) and (–)-menthol (**136l**) were converted to the corresponding chlorides **138k** and **138l** essentially with full inversion of configuration. However, (–)-cholesterol (**136m**) gave the corresponding chloride **138m** with full retention of configuration.

Table 3. Reaction of alcohols ROH **136** with dichloroselenurane **137** triphenylphosphine system

Alcohol **136**		Selenurane **137**	Solvent	Time (min)	Yield of **138** [%]
No	R	R^1			
a	n-C_8H_{17}	Me	CH_2Cl_2	20	100
a	n-C_5H_{17}	Me	C_6H_6	20	100
b	n-$C_{12}H_{25}$	Me	C_6H_6	60	92
c	n-$C_6H_5CH_2$	Me	$CHCl_3$	20	89
d	o-$CH_3OC_6H_4CH_2$	Me	CH_2Cl_2	20	95
e	m-$CH_3OC_6H_4CH_2$	Me	CH_2Cl_2	20	95
f	$C_6H_5CH_2CH_2$	Me	CH_2Cl_2	20	95
g	$C_6H_5(CH_3)CH$	Me	$CHCl_3$	10	95
h	$C_6H_5CH{=}CHCH_2$	Me	C_6H_6	2 days	66
i	4-t-Bu-cyclo-C_8H_{10}	Me	$CHCl_3$	20	92
j	adamantyl	Me	C_6H_6	10	93
k	(–) 2-octanol	Me	C_6H_6	4 h	64
l	(–)-menthol	Me	C_6H_6	24 h	96
m	(–)-cholesterol	Me	C_6H_6	20 h	84

Later, it was reported [69] that the alcohols **136a**, **136n**, **136o**, and **136p** gave upon treatment with di-(2-chloroethyl)dichloroselenurane (**139**) at 70 °C the corresponding chlorides **138a** and **138 n–p** in yields between 8 and 34% (Eq. 32).

$$\begin{array}{ccccc} \text{ROH} & + & (\text{ClCH}_2\text{CH}_2)_2\text{SeCl}_2 & \xrightarrow{\Delta} & \text{R–Cl} \\ \textbf{136a, n-p} & & \textbf{139} & & \textbf{138a, n-p}\ (8\text{-}34\%) \end{array} \qquad (32)$$

On the other hand, the reaction of alcohols **136a** and **136n–r** with di-(2-bromoethyl)dibromoselenurane (**140**) gave, under the same reaction conditions, the corresponding bromides **141 a–f** in moderate to high yields (Eq. 33).

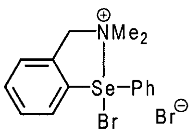
$$\begin{array}{ccccc} \text{ROH} & + & (\text{BrCH}_2\text{CH}_2)_2\text{SeBr}_2 & \longrightarrow & \text{R–Br} \\ \textbf{136} & & \textbf{140} & & \textbf{141} \end{array} \qquad (33)$$

Alcohol **136**		Bromide **141**	
No	R	No	Yield [%]
a	n-C_8H_{17}	**a**	98
n	n-C_5H_{11}	**b**	78
o	n-C_4H_9	**c**	96
p	n-$C_3H_7CH(CH_3)$	**d**	52
q	$C_2H_5CH(CH_3)$	**e**	50
r	$(CH_3)_3C$	**f**	41

Diphenyldibromoselenurane (**142**) and the ionic derivative **143** were found [70] to be efficient sources of positive bromine for bromolactonization of 4-pentanoic acid (**144**), bromocyclization of unsaturated alcohols and bromination of 1,3,5-trimethoxybenzene (**147**) (Eqs. 34 and 35).

Ph_2SeBr_2

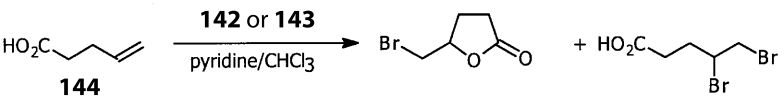
142



143

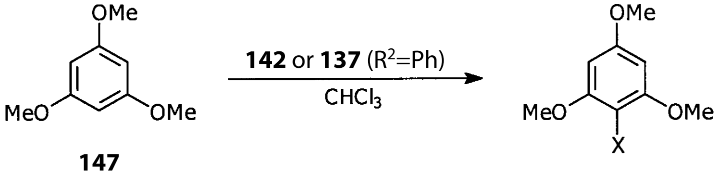
It should be noted that the use of diphenyldichloroselenurane (**137**, R^2 = Ph) failed to give detectable amounts of chlorination products in the reactions mentioned above. However, this selenurane gave 1-chloro-2,4,6-trimethoxybenzene (**148**, X = Cl) in quantitative yield when **147** was stirred with the reagent for 5 min in $CHCl_3$ solution.

In this context, it is also interesting to note that diphenyldichloroselenurane (**137**, R^2 = Ph) was found [71] to convert the silver salt of optically



144 **145** **146** (34)

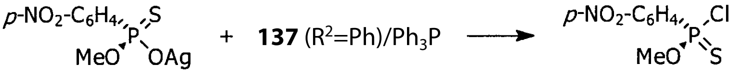
Reagent	**145/146** ratio
142	71:29
143	36:64



147 (35)

148 X=Br (80%)
X=Cl (92%)

active thioacid **149** to the corresponding thiophosphoryl chloride **150** with full stereoselectivity (Eq. 36).



149 **150** (36)

Moreover, the selenuranes **137** in the presence of a hydroxylic component were used [48, 71] for the conversion of organophosphorus derivatives **80** into the corresponding phosphoryl compounds **81** (Eq. 37).

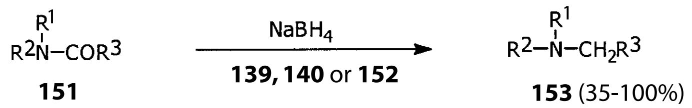
$$R_3P{=}X + \mathbf{137} \xrightarrow{H_2O \text{ or } MeOH} R_3P{=}O + R^1_2Se + HCl + X \qquad (37)$$

80 (X=S, Se; :) **81**

Treatment of tertiary amides **151** with a mixture of sodium borohydride and a dihalogenoselenurane (**139**, **140** or **152**) in THF gave the corresponding amines **153**. However, primary and secondary amides were not reduced under these conditions [72] (Scheme 15).

Similar treatment of several nitriles with a mixture of $NaBH_4$ and **139** in refluxing THF gave the corresponding primary amines [72b] (Scheme 16). It was suggested that the real reducing agent in the reaction under consideration could be the complex **156** of borane with the selenide initially formed from $NaBH_4$ and dihalogenoselenurane (Eq. 38).

Di-(2-bromoethyl)dibromoselenurane (**140**) has also been used as a selenium transfer reagent in the one-step alkoxyselenation of cyclohexene. It was found



$$\underset{\mathbf{151}}{R^2N(R^1)\text{-}COR^3} \xrightarrow[\mathbf{139}, \mathbf{140} \text{ or } \mathbf{152}]{NaBH_4} \underset{\mathbf{153}\ (35\text{-}100\%)}{R^2\text{-}N(R^1)\text{-}CH_2R^3}$$

R^1, R^2=Me, Et, Ph
R^3=H, Me

Et_2SeCl_2 **139** Et_2SeBr_2 **152** $(BrCH_2CH_2)_2SeBr_2$ **140**

151				Reducing agent	153
No	R^1	R^2	R^3		Yield [%]
a	Me	Me	H	**139**	82
a	Me	Me	H	**152**	82
b	Et	Et	Me	**139**	70
c	Me	Me	Me	**139**	35
c	Me	Me	Me	**152**	92
d	Ph	Ph	Me	**139**	89
e	Ph	Me	H	**139**	90
e	Ph	Me	H	**140**	100
e	Ph	Me	H	**152**	100

Scheme 15

$$\underset{\mathbf{154}}{RCN} \xrightarrow[\text{2. HCl}]{\text{1. NaBH}_4\text{ - }\mathbf{139}\text{/THF}} \underset{\mathbf{155}\ (35\text{-}72\%)}{RCH_2NH_2 \cdot HCl}$$

Scheme 16

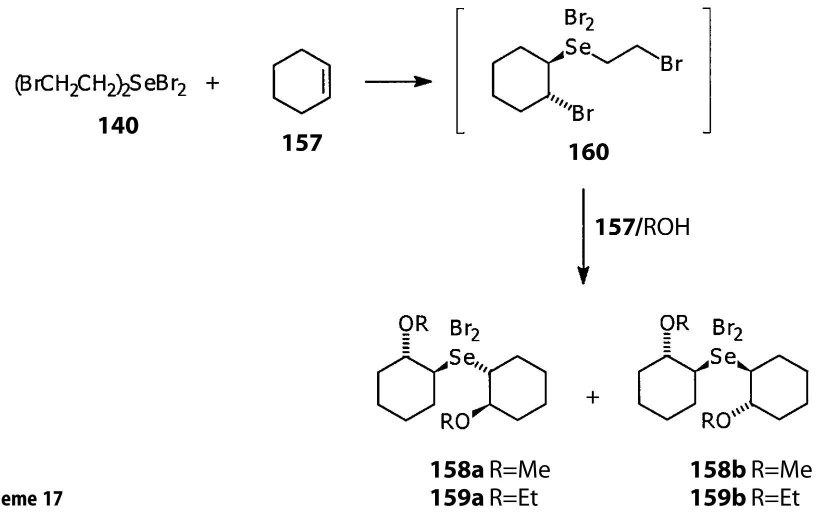
$$NaBH_4 + R_2SeX_2 \longrightarrow \underset{\mathbf{156}}{BH_3 \cdot R_2Se} \qquad (38)$$

that the reaction of this selenurane with cyclohexene (**157**) in alcohol under reduced pressure proceeds smoothly to give bis-(2-alkoxycyclohexyl)selenium dibromides **158** and **159** (11–75%) via 2-bromocyclohexyl-2′-bromoethylselenium dibromide (**160**) as an intermediate together with ethene [73] (Scheme 17).

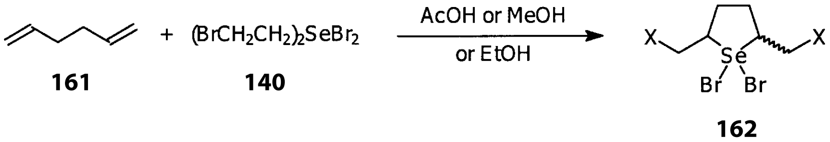
The reaction of dibromoselenurane **140** with 1,5-hexadiene (**161**) gave 2,5-bis(bromomethyl)tetrahydroselenophene-1,1-dibromide (**162a**) in 89% yield together with ethene. When this reaction was conducted in methanol or ethanol the corresponding alkoxy-substituted selenuranes **162b,c** were isolated [74] (Scheme 18).

The dibromoselenurane **140** was also applied as a selenium transfer reagent in the formation of trichalcogen bonds in metallocenophanes. Thus, 2-selena-1,3-dichalcogen[3]metallocenophanes **163** were obtained in high to moderate yields from the appropriate metallocene-1,1′-dithiols or -diselenols **164** upon treatment of **140** [75] (Scheme 19).

Dihalogenoselenuranes **165a,b**, derived from γ-phenylseleno α,β-unsaturated esters, were converted into α-halo β,γ-unsaturated esters **166a,b** by elimination of benzeneselenenyl halide [76] (Scheme 20).



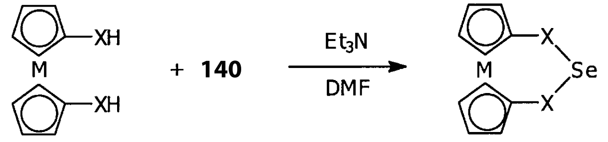
Scheme 17



162

Solvent	No	X	*cis* [%]	*trans* [%]
CH_3CO_2H	**a**	Br	36	53
MeOH	**b**	MeO	31	45
EtOH	**c**	EtO	19	29

Scheme 18



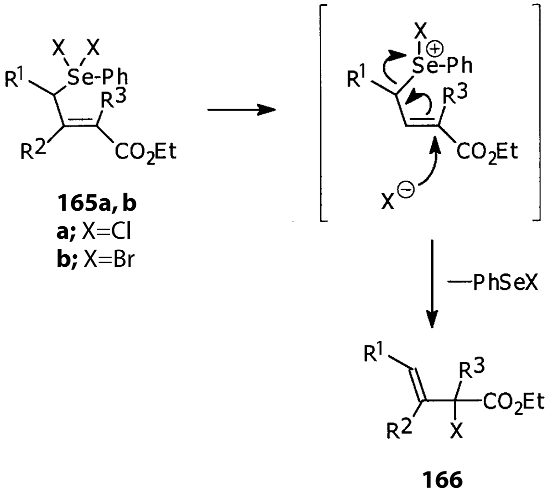
164 (M=Fe, Ru)
(X=S, Se)

163 (58-75%)

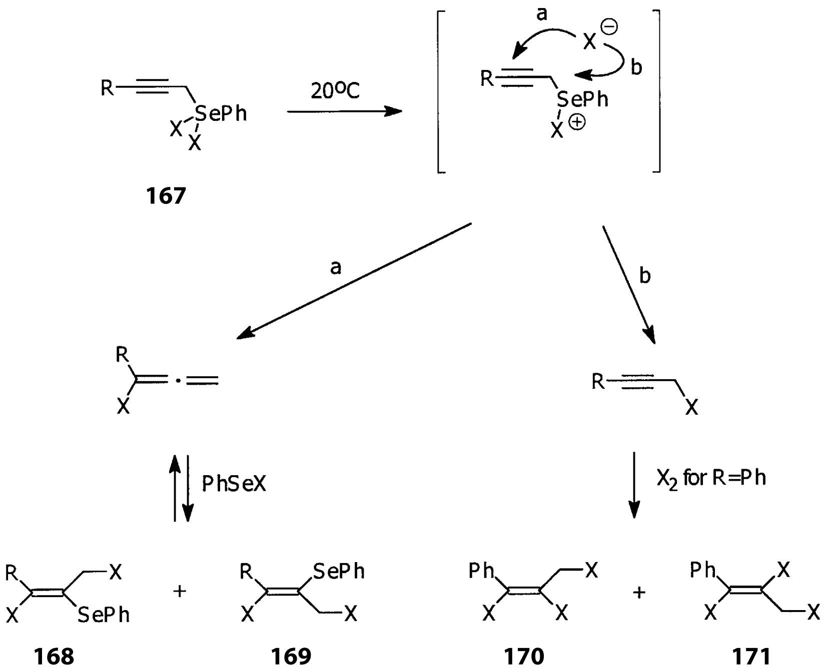
Scheme 19

Decomposition of dihalogenoselenuranes **167**, derived from propargylic selenides, resulted in the formation of 1,3-substituted 1,3-dihalo-2-phenylselenopropanes **168** and **169** as well as 1-substituted 1,2,3-trihalopropanes **170** and **171** as shown in Scheme 21 [77].

Among trihalogenoselenuranes only trichlorophenylselenurane (**172a**) has found wider application as a reagent in organic synthesis, in particular for for-



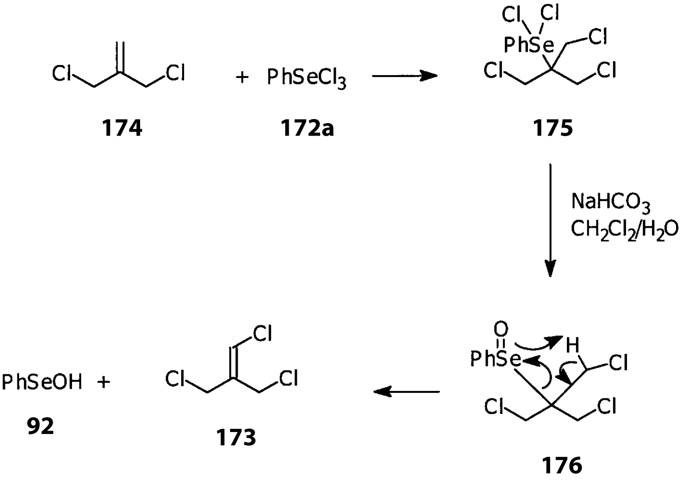
Scheme 20



Scheme 21

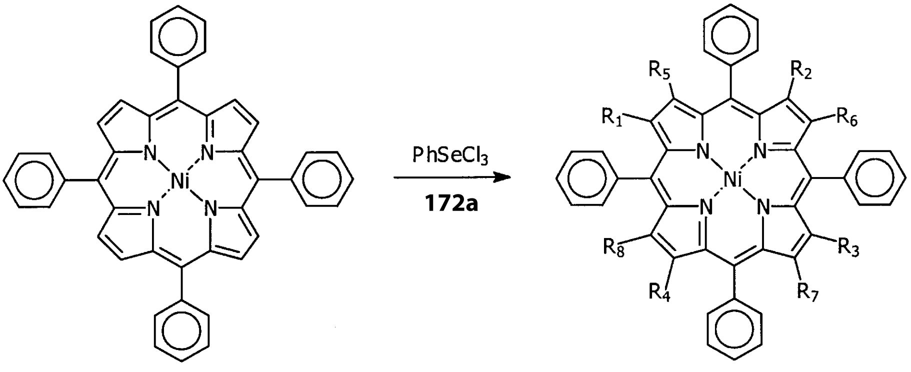
mation of new carbon–selenium bonds [78]. More recently, this selenurane has also been used as a selective chlorinating agent. Thus, vinylic chlorination using **172a** was thoroughly studied by Engman [79], who treated ketones and alkenes with **172a** and, after hydrolysis and cycloelimination, isolated in high yields the corresponding enones and chlorinated alkenes, respectively. 2-Chloromethyl-

1,3-dichloropropene (**173**), a useful and previously almost inaccessible synthon [80], was synthesized in the reaction of the commercially available precursor 3-chloro-2-chloromethyl-1-propene (**174**) with the trichloroselenurane **172a** [81]. The two-step synthesis of **173** in 50% overall yield is shown in Scheme 22.



Scheme 22

Of particular interest is that chlorination of Ni-mesotetraphenylporphyrin **177** was also conducted with this selenurane [82]. Thus, the reaction of **177** with **172a** used in a 1:3 molar ratio gave a mixture of di-**178** (30%), tri-**179** (50–55%), and polychlorinated products. When a 15-fold molar excess of $PhSeCl_3$ was used, compounds **180** and **181** containing six and seven chlorine atoms were obtained (Scheme 23).



177

178 R_1-R_2 = Cl; R_3-R_8 = H

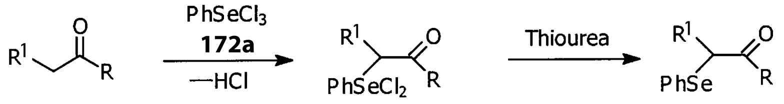
179 R_1-R_3 = Cl; R_4-R_8 = H

180 R_1-R_6 = Cl; R_7-R_8 = H

181 R_1-R_7 = Cl; R_8 = H

Scheme 23

A number of α-phenylselenenyl aldehydes **182** and ketones **183** were prepared on a large scale by treatment of the corresponding aldehydes **184** or ketones **185** with **172a** [83]. The intermediate adducts **186** or **187** formed were reduced by thiourea to give the final products (Scheme 24).



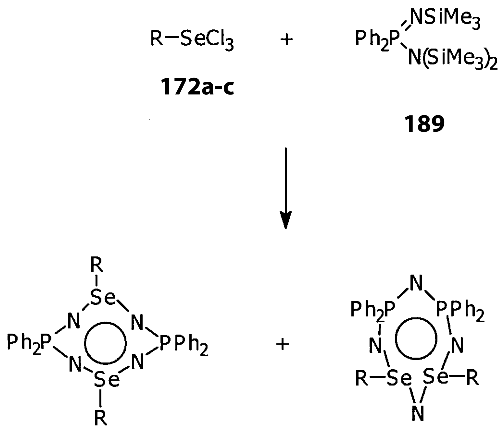
184 R=H
185 R#H

186 R=H
187 R#H

182 R=H (70-91%)
183 R#H (58-85%)

Scheme 24

A few diphosphadiselenatetrazocines **188a–c**, eight-membered heterocyclic rings, were synthesized by the cyclocondensation reaction of trichloroselenuranes **172a–c** with the iminophosphinamide **189** [84]. When methylselenurane (**172b**) and ethylselenurane (**172c**) were used in this reaction, the cyclic product **190** was also formed (Scheme 25). X-ray crystallography has shown that **188b** is an eight-membered chair with the two selenium atoms displaced on either side of the P_2N_4 plane by 107.3(2) Å.

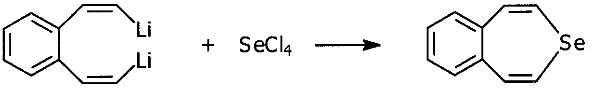


188a-c
a; R=Ph
b; R=Me
c; R=Et

190a, b
a; R=Me
b; R=Et

Scheme 25

The best known inorganic selenurane, selenium tetrachloride (**191**), has recently been used for the construction of various selenium-containing heterocyclic structures. For example, the first synthesis of 3-benzoselenoepine (**192**) was based on the reaction of 2,2-*o*-bis(β-lithiovinyl)benzene (**193**) with **191** [85] (Eq. 39).

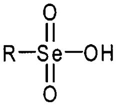


(39)

193 **191** **192**

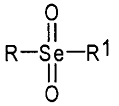
6
Hexavalent, Tetracoordinated Derivatives

Selenonic acids **194a** and selones **194b** belong to the best-known hexavalent, tetracoordinated organoselenium compounds. Moreover, they have found synthetic applications in recent years.



$$R-\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{Se}}}-OH$$

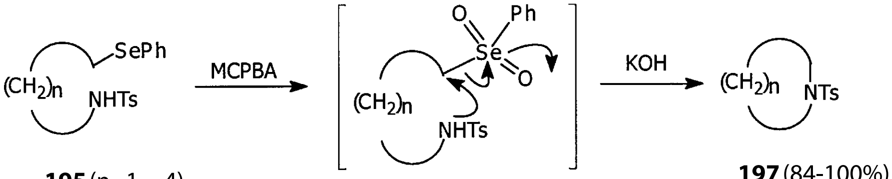
194a



$$R-\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{Se}}}-R^1$$

194b

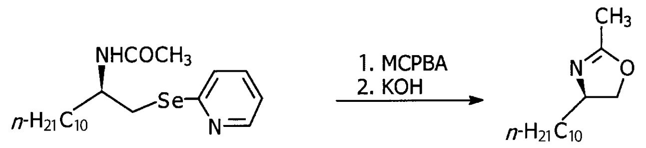
The synthetic utility of selones results from the fact that the selenonyl group has been recognized as an excellent leaving group and many substitution reactions have been reported using various kinds of nucleophiles [86]. The very recent reports more than justify this opinion. Thus, the selective synthesis of a few heterocyclic compounds was successfully carried out [87] through the intramolecular substitution of the phenylselonyl group by nitrogen or carbonyl oxygen in the appropriately functionalized *p*-toluenosulfonamides **196**. The latter compounds prepared in situ by the oxidation of *N*-[*ω*-(phenylseleno)]-*p*-toluene-sulfonamides **195** with *meta*-chloroperbenzoic acid (MCPBA) afforded the nitrogen heterocycles **197** through the intramolecular substitution of the resultant selonyl group by the nitrogen atom (Scheme 26).



195 (n=1...4) **196** **197** (84-100%)

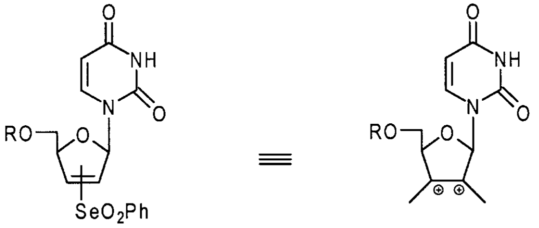
Scheme 26

Oxidation of the corresponding benzamides and subsequent cyclization gave heterocyclic derivatives depending on the number of carbon atoms between the attacking nucleophilic amide and the leaving selenonyl group. Application of this procedure to optically active amide **198** bearing a 2-pyridylselenonyl group on the *β*-carbon atom afforded optically active oxazoline **199** without loss of chiral information [87] (Eq. 40).



198 **199** (88%) (40)

At the end of the 1980s, the phenylselones derived from nucleosides were successfully exploited by Chattopadhyaya and co-workers for a variety of stereoselective conversions in this family of biologically active compounds [88]. They elaborated high-yield syntheses of a series of 2′,3′-ene-3′-phenylselones and 2′,3′-ene-2′-phenylselones **200** and showed their synthetic utility as synthetic equivalents of the dication **201** shown below.

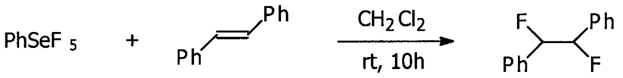


200 **201**

R = H
R = *p*-Toluoyl (Tol)
R = *t*-Butyldimethylsilyl
R = MMTr (Metamethoxytrytyl)

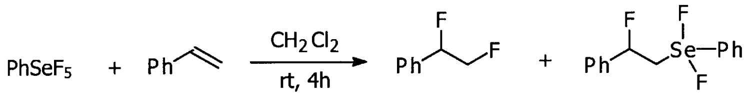
7
Hexavalent, Hexacoordinated Derivatives

To date there is only a single report on the synthetic utility of a perselenurane. Namely, it was found that phenylselenium pentafluoride (**202**) reacted smoothly with olefins such as **203** and **204** affording 1,2-difluorides **205**–**207** as shown in Eqs. (41) and (42) [89].



(41)

202 **203** **205** (90%; *erythro*/*threo* 4:1)



(42)

202 **204** **206** (16%) **207** (16%)

Because this type of perselenuranes can be easily prepared, and they are rather resistant to hydrolysis, this class of fluorides will undoubtedly be used more widely in the future as fluorinating agents.

8
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Selenocarbonyls

Toshiaki Murai · Shinzi Kato

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan
E-mail: mtoshi@cc.gifu-u.ac.jp · shinzi@apchem.gifu-u.ac.jp

Studies on the chemistry of selenocarbonyl compounds have been increasingly reported during the past decade. Initially, the focus had been mainly on the development of new synthetic methods for the preparation of selenocarbonyl compounds. The various achievements have allowed the evaluation of a wide range of applications. X-ray molecular structures of some derivatives have been disclosed. Selenocarbonyl compounds that are relatively stable but still retain high reactivity have exhibited unique reactions. The present review outlines the characteristic features of selenocarbonyl compounds. Their syntheses and reactions are classified on the basis of reaction patterns rather than the substituents adjacent to selenocarbonyl group. Several types of metal complexes having selenocarbonyl groups are described as well.

Keywords: Selenocarbonyl group, Selenoaldehydes, Selenoketones, Selenoamides, Selenoesters, Selenothioic acid S-esters, Diselenoesters, Selenourea, Selones

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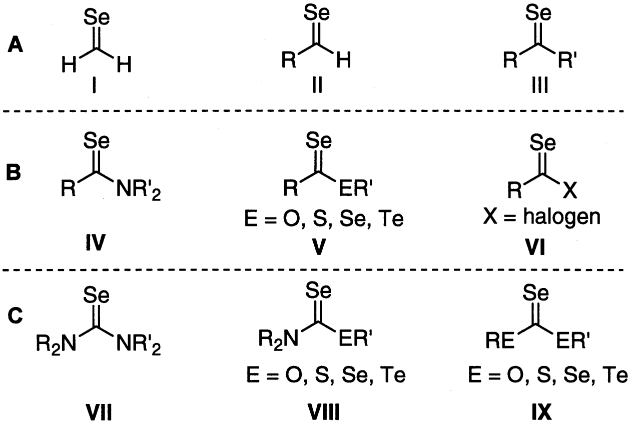
1
Overview

The carbonyl groups are one of the most ubiquitous and important functional groups in organic chemistry. The replacement of the oxygen atom with a heavier atom such as a sulfur or a selenium atom in the same row of the periodic table has attracted chemists from the fundamental point of view. In the initial stage of the research on such unnatural functional groups, focus is laid on the development of new approaches to isolate the compounds involving new functionalities. As for selenocarbonyl compounds, the number of reports on new methods for their synthesis has dramatically increased since the late 1980s. Several excellent reviews [1] have covered the results until the end of the 1980s. For the last ten years attention has been paid not only to new synthetic methodology but also to the wide variety of reactions and applications of selenocarbonyl compounds.

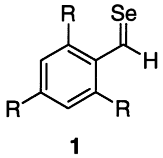
The selenocarbonyl compounds can be classified into three categories on the basis of the substituents adjacent to the carbon atom of the selenocarbonyl group (Scheme 1).



Scheme 1

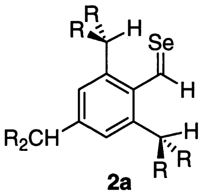
In category A (compounds **I**–**III**), only hydrogen atoms and carbon atoms are attached to the selenocarbonyl group. Second, one heteroatom-containing functional group is attached to the carbon atom of the selenocarbonyl group (category B, compounds **IV**–**VI**). Third, two heteroatom-containing functional groups are attached to the carbon atom of the selenocarbonyl group (category C, compounds **VII**–**IX**). The stability of selenocarbonyl compounds dramatically changes from the compounds in category A to those in category C. Generally, the derivatives in category A [2] are unstable. The protection of the selenocarbonyl group with sterically bulky substituents has enabled the isolation of selenoketones. Very recently, selenoaldehydes **1** [3] and **2** [4] were also synthesized as isolable derivatives. The importance of the steric protection has been proven by the different stability of two conformational isomers of **2**.

The conformer **2b** is stable even in air in the solid state, whereas it slowly isomerizes to the conformer **2a** in solution, then it dimerizes. However, the crystal analysis of selenoaldehydes has not yet been successful. In a series of selenoketones an aromatic derivative was successfully isolated by introducing methoxy group to the aromatic ring [5a], and the molecular structure was dissolved.



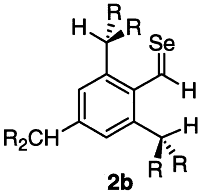
1

R = *tert*-Bu



2a

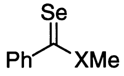
R = Me_3Si



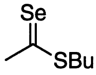
2b

R = Me_3Si

Among the compounds in category B, new synthetic methods for the preparation of selenoamides have been extensively developed [6]. At first, the stability of the compounds in category B seems to decrease in the order from E = N, O, S, and Se, but the tendency of the stability is not quite clear. For example, among methyl selenobenzoates **3**–**5** diselenoester **5** is more stable than *S*-ester **4** in air [7]. On the basis of these results, aliphatic derivatives of selenothioic acid *S*-esters were expected to be unstable. However, unlike this prediction, selenothioacetic acid *S*-esters **6** are stable enough to be handled on the bench and to be stored in a refrigerator for a long period. A variety of new reactions of **6** have also been realized since convenient synthetic methods are established [8]. On the other hand, much less study has been reported on the selenoesters, although they appear to be more stable, probably because of the lack of an easy method of synthesis [9]. The formation of the selenoxo form of selenoic acids **7** has been observed in a polar solvent at low temperatures for the first time [10].



3: X = O
4: X = S
5: X = Se



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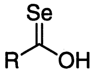

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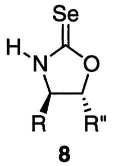
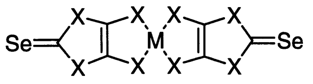


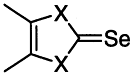
8

The compounds in the third category are generally more stable than those in categories A and B. The basic principles for synthesizing them were provided more than ten years ago [11]. However, several improved methods have been developed since increasing attention has been paid to the applications of the compounds in a variety of fields. For example, chemical properties, toxicity, and environmental impact of selenourea have been reported [12]. Chiral oxazoline-2-selones **8** have been used as new chiral derivatizing agents [13]. The compounds **9** have been tested as organic conducting molecules [14]. Furthermore, compounds **10** and **11** have been utilized as precursors of inorganic semiconductors [15] and organic conducting molecules [16].



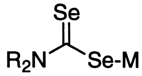
X = S, Se, M = transition metal

9



X = S, Se, Te

10

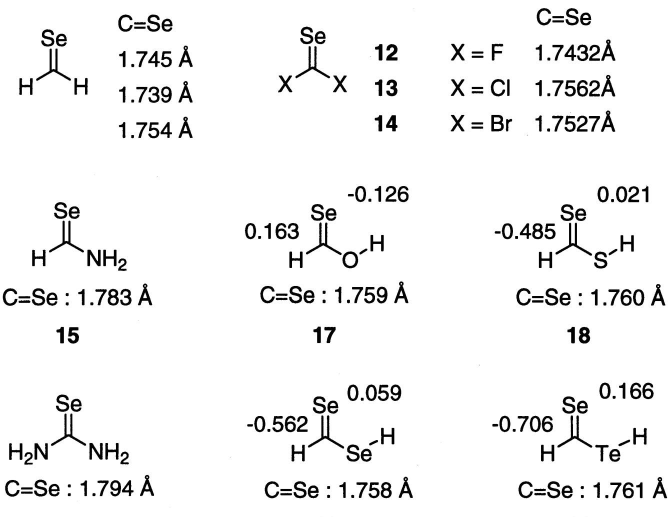


11

Additionally, carbon diselenide, selenoketenes [17] and isoselenocyanates (RN = C = Se) [18] in which the selenium atom is attached to the sp-carbon atom are also well known. They have often been used as key starting materials of the compounds in category C of Scheme 1.

2
Structures

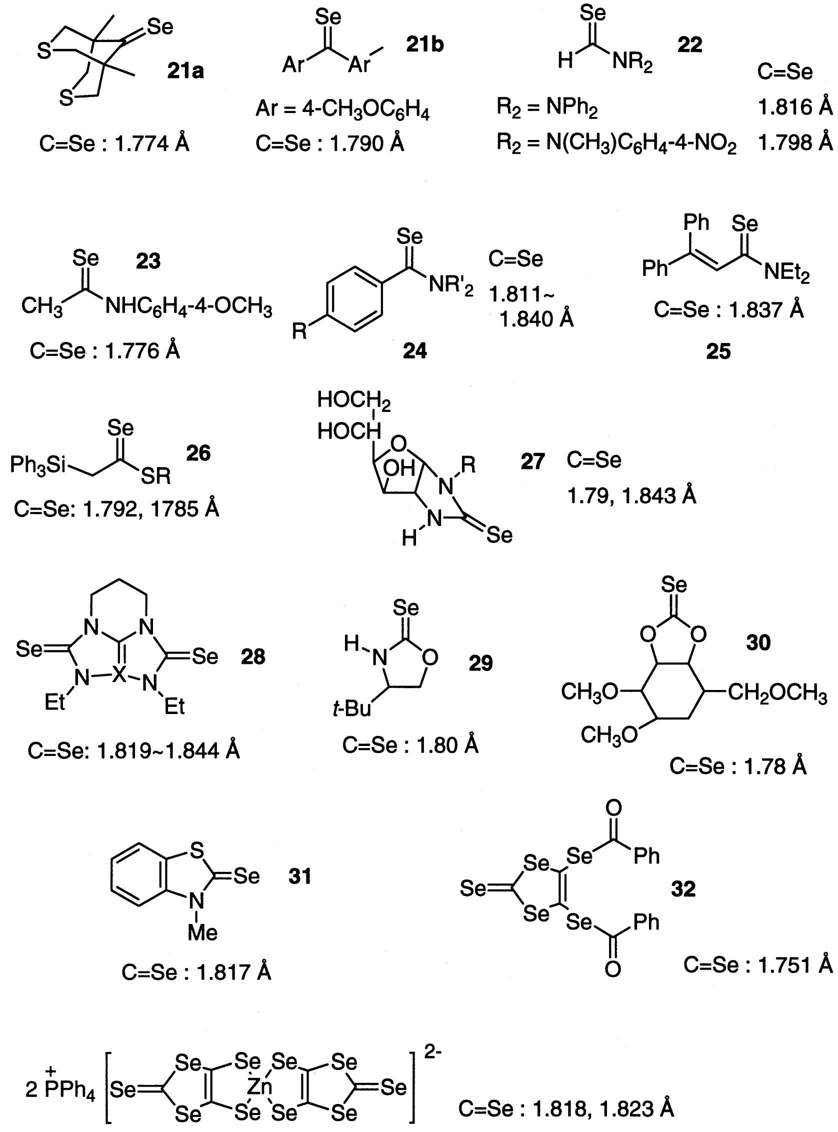
The molecular orbital calculations of selenocarbonyl compounds are still limited to the compounds having simple substituents, mainly because a large basis set is necessary for the selenium atom [19]. The bond lengths of C = Se calculated so far are within the range 1.74–1.79 Å (Scheme 2), although direct comparison of these data derived from different levels of theory is not appropriate. The introduction of a fluorine atom slightly shortens the lengths of carbon-selenium bonds in halogen-substituted selenoaldehydes **12**–**14** [19c]. The attachment of the nitrogen atom to the carbon atom of selenocarbonyl group caused the elongation of the C = Se bond as in the case of **15** and **16** [19d, e]. In the compounds **17**–**20**, tautomeric equilibrium is possible [19f]. Theoretical studies have suggested that tautomerization takes place more easily on going from **17** to **18**, **19**, and **20**. As for the compounds **17**–**20**, natural charge is also shown in Scheme 2. It should be noted that the carbon



Scheme 2

atom is more negative than the selenium atom in the selenocarbonyl groups of **18**–**20**.

X-ray molecular structure analyses of a wide range of selenocarbonyl compounds, in particular the compounds in category C in Scheme 1, have been studied (Scheme 3) [5, 8b, 20–27]. Representative bond lengths of C = Se are shown in Scheme 3. As for selenoketones **21a**, **b** [5], the bond lengths are less than 1.80 Å. In the nitrogen-substituted selenocarbonyl compounds,



Scheme 3 **33**

i.e., selenoformamides **22** [20a], selenoacetamide **23** [20b], selenobenzamides **24** [20c, d], α,β-unsaturated selenoamide **25** [20e,f], selenourea **27**, **28** [21, 22], oxazoline selone **29** [23], and thiooxazoline selone **31** [24], the bond lengths of C = Se are generally longer than 1.80 Å, whereas the introduction of oxygen, sulfur, and selenium atoms to selenocarbonyl groups (**26**, **30**, **32**, **33**) does not necessarily change the bond length of C = Se so clearly [8b, 24–27].

The hydrogen bonding interaction between the selenium atom of a selenocarbonyl group and a hydroxy group [23b] has been disclosed. The oxazoline selone **29** adopted dimeric structure through hydrogen bonding interaction via amide hydrogen and selenium atom [23a]. The formation of inclusion compounds of selenourea with ammonium chloride and adamantane has also been studied [28].

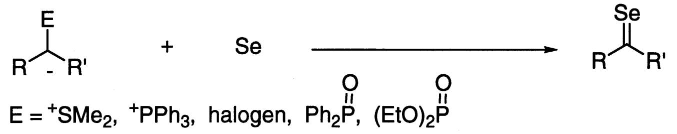
3
Syntheses

A variety of synthetic methods for preparing selenocarbonyl compounds have been developed, and recent reviews disclosed details of each compound in Scheme 1 [2b, 6, 8c, 9, 11]. Accordingly, the synthetic methods are classified based on the reaction patterns rather than the types of compounds in this review. In particular, attention has been paid to the step of the formation of the carbon-selenium bond. The selenium atom has generally been introduced electrophilically or nucleophilically to the organic molecules. Additionally, heterocumulenes involving selenium atoms have been used as a starting material.

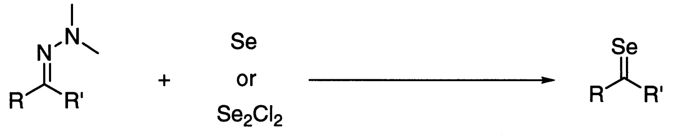
3.1
With Electrophilic Selenium

Elemental selenium can react with carbanions smoothly. The syntheses of selenocarbonyl compounds using elemental selenium are shown in Eqs. (1–13).

Sulfur ylides have been treated with elemental selenium to generate α-acyl selenoaldehydes and α,α'-diacyl selenocarbonyl compounds (Eq. 1) [29]. Staudinger chalogenation has been applied to the generation of aromatic selenoketones independently by Erker et al. [30] and Okuma et at. [31] at the same time. In these reactions dimethyl sulfide and triphenylphosphine work as a leaving group, and the generated selenocarbonyl compounds have been trapped with dienes. The reaction of carbanions having a good leaving group with elemental selenium proceeds smoothly. As a leaving group, halogen, phosphinoyl, and phosphonyl groups are known for the generation of 1,3-dicarbonyl selones **34** [32a], hexafluoro selenoacetone [32b], selenoamides [32c–f]. In the reaction of dihaloalkanes the intermediacy of selenoacyl halidies **35** has been postulated [33]. The reaction of hydrazone derivatives with elemental selenium, that was originally developed by Barton et al. [34] has continuously been tested for the new routes to hindered olefins via selenoketones [35]. The dihydrazone is reacted with diselenium dichloride to give selone **36a** and diselone **36b** as a blue oil [36]. The silyl stabilized carbanion is reacted with dicyano diselenide to give selenoaldehyde via silylmethylselenocyanate (Eq. 3) [3, 37].



(1)



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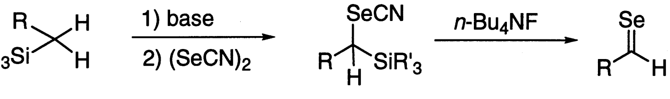
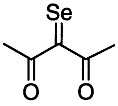
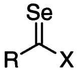


(3)

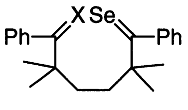


34



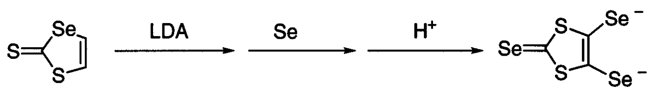
35

X = Cl, Br

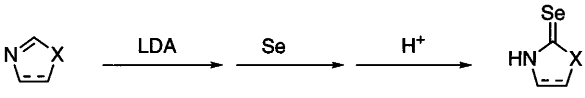


36a X = O
36b X = Se

The treatment of vinyl anions with elemental selenium also leads to selenocarbonyl compounds via eneselenolate anions (Eqs. 4–6). Deprotonation of 1,3-selenothio-2-thione with LDA followed by the reaction with elemental selenium proceeds accompanied with the rearrangement of vinylic skeleton to form 1,3-dithio-2-selone derivatives (Eq. 4) [38]. The vinyl anions from oxazolines and imidazoles were treated with elemental selenium to give the oxazoline selone and imidazoline selone after the aqueous workup (Eq. 5) [39]. The reaction of vinyl magnesium halides with elemental selenium and allyl bromide gives allyl vinyl selenides that undergo a seleno-Claisen rearrangement to generate γ,δ-unsaturated selenoaldehydes (Eq. 6) [40].

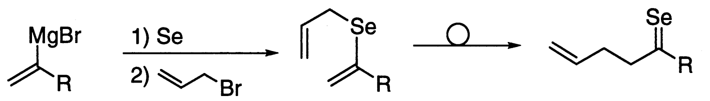


(4)

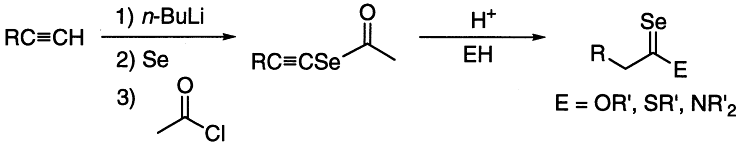


X = NMe, O

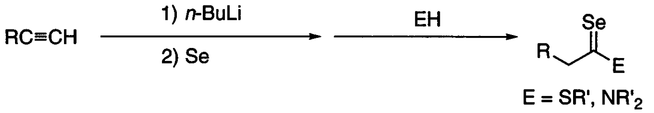
(5)



(6)

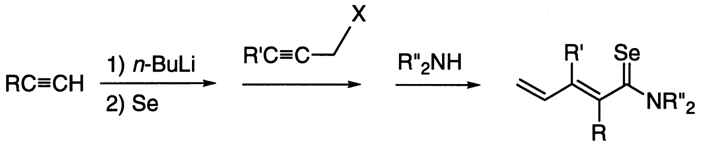


(7)



(8)

Alkynyl anions react smoothly with elemental selenium to form alkyneselenolates that have been used as key intermediates in the preparation of selenoamides, selenoesters, and selenothioic acid *S*-esters via selenoketene intermediates (Eqs. 7–10). The selenoacetic acid *Se*-alkynyl esters prepared via alkyneselenolates are converted to the selenocarbonyl compounds by reacting with amines, alcohols, or thiols under acidic conditions (Eq. 7) [8a, 41]. The direct conversion of alkyneselenolates to selenocarbonyl compounds is also successful in the reaction with amines [42] or thiols [8b, 43] (Eq. 8), whereas the reaction with alcohols only gives the dimerized products of alkyneselenolates, probably because of the low nucleophilicity of alcohols. The generation of selenoketene intermediates by trapping alkyneselenolates with propargyl bromide (Eq. 9) [44] or allylic bromides (Eq. 10) [45] and subsequent reaction with amines afford unsaturated selenoamides. A similar reaction using thiols also leads to the corresponding selenothioic acid *S*-esters, although the reaction pathway was not the same as that with amines [46].



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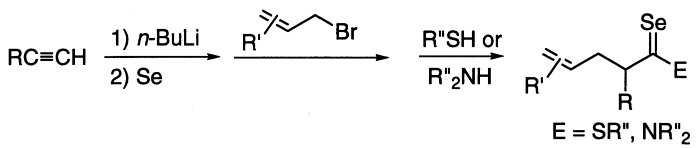
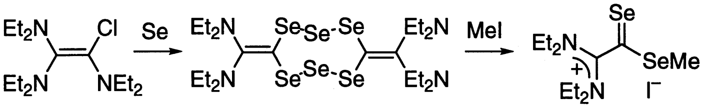


(10)

The electron-rich olefin (Eq. 11) [47] and alkyne (Eq. 12) [48] can react with elemental selenium to end up in the formation of diselenoesters and selenoamides. During the reaction of the former, several types of new species have been involved. As with the reaction of carbon monoxide with elemental selenium

[49], the coupling reaction of isonitrile with elemental selenium takes place (Eq. 13) [50]. The intramolecular trapping of the selenoisocyanate intermediate leads to the oxazoline selone as product.



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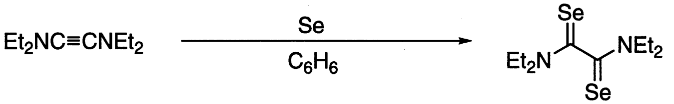

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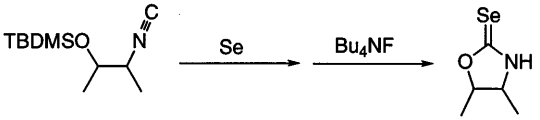
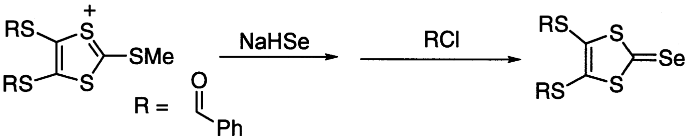


(13)

3.2
With Nucleophilic Selenium

Nucleophilic selenium reagents that can be described as Se^{2-} species have been used to construct carbon-selenium double bonds. They are generally prepared by the reduction of elemental selenium and used in situ or after isolation.

Hydrogen selenide (H_2Se) and sodium hydrogen selenide (NaHSe) which are efficiently generated by the reduction of elemental selenium with $NaBH_4$ react with sulfonium salts to form 1,3-dithiole-2-selones (Eq. 14) [15, 51]. The addition of NaHSe or H_2Se to imine [52] or iminonium salts [24] or silyl keteneacetals (Eq. 15) [53] gives cyclic selenoamide, selenocarbonates, selenothiocarbonates, or selenoesters, respectively. The nitriles have been known as good starting materials for aromatic primary selenoamides by reacting with H_2Se and NaHSe (Eq. 16). Several types of improved methods for the generation of H_2Se and NaHSe have been developed [6b, 54]. The use of potassium selenocarboxylate enabled the isolation of aliphatic primary selenoamides in good yields [54c]. The silylation of alkali metal selenocarboxylates has been found to give *O*-silyl selenoesters (Eq. 17) [55].



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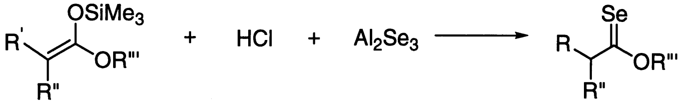

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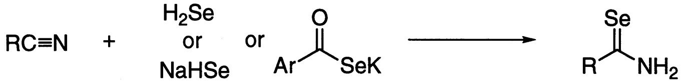

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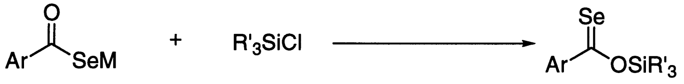
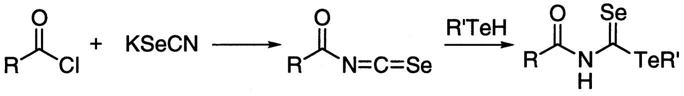


(17)

The formation of alkylselenocyanates by nucleophilic substitution at the sp^3 carbon atom with potassium selenocyanate (KSeCN) followed by the elimination of hydrogen cyanide or its equivalent has been used for the generation of selenoaldehydes [56, 57a, b], selenoketones [57c], and α-acyl selenoamides [58]. Alternatively, the acylation of KSeCN effectively takes place at the nitrogen atom to form acyl selenoisocyanates, that have been trapped with amines [59a] or tellurols (Eq. 18) [59b].

To convert carbonyl compounds to selenocarbonyl compounds, Lewis acidic selenium reagents such as $(Me_3Si)_2Se$/*n*-BuLi catalyst [60], $(Me_2Al)_2Se$ [61], $(Me_3Si)_2Se/BF_3 \cdot Et_2O$ [62], and $(9\text{-}BBN)_2Se$ [63] have been developed (Eq. 19). In the reaction with $(Me_2Al)_2Se$ acetals and orthoesters can be transformed into selenoaldehydes, selenoketones, and selenoesters with high efficiency [61e]. The generation of α,β-unsaturated selenoaldehydes and selenoketones is also successful with $(Me_2Al)_2Se$ [61d, g]. The selenoamides are synthesized by using $(Me_3Si)_2Se/BF_3 \cdot Et_2O$ from ordinary amides and nitriles [62b, c]. However, these reagents have to be prepared by at least two steps involving the reduction of elemental selenium. Very recently, more direct methods for the generation of aluminum selenolate from elemental selenium and *i*-Bu_2AlH and the reaction with amides have been reported [64].



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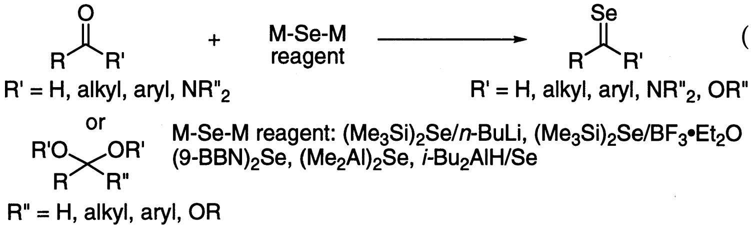
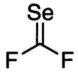


(19)

Lewis acid mediated reaction of $Hg(SeC_2F_5)_2$ [65] or flash vacuum pyro-lysis of $Me_3SnSeCF_3$ [66] leads to perfluoro-substituted selenoformaldehyde **37** and selenoacetaldehyde **38**. The reagent of $(Bu_3Sn)_2Se$ and Bu_4NF is reacted with α,α-dichloro carbonyl compounds to form selenoaldehydes bearing electron-withdrawing groups [67]. CuCl-catalyzed reaction of titanium selenide (Cp_2TiSe_5) with diazoalkane yields cyclic selenides followed by the extrusion of selenium atoms with PPh_3 and ends up in the formation of isolable selenoaldehydes [4]. Selenoxo phospholane **39** is applied as a selenating agent to the substitution of oxygen atoms of amides by selenium atoms [68].



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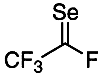

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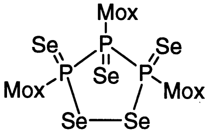
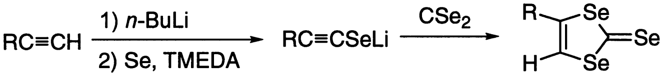


39

Mox = 2,4-di-*tert*-butyl-6-(methoxy)phenyl

3.3
With Carbon Diselenide

Carbon diselenide (CSe_2) has been used as a starting material for a long time. As a recent example, reduction of CSe_2 with Na followed by benzoylation gave 1,3-diselena-2-selone **32** [69]. The lithium alkyneselenolates generated as in Eqs. (7–10) are reacted with CSe_2 to afford 1,3-diselena-2-selones as a product in good to high yields (Eq. 20) [70].



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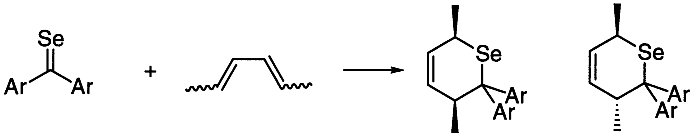
4
Reactions

The reactivity and reaction patterns of selenocarbonyl compounds vary considerably from the compounds in categories A–C in Scheme 1. The substituents adjacent to the selenocarbonyl group attenuate the polarity of the compounds. As a result, less polar selenoaldehydes and selenoketones behave as olefins, and the carbon selenium double bond of heteroatom-substituted selenocarbonyl compounds becomes more polar. In this section, a variety of transformations of selenocarbonyl compounds have been classified based on the reagents reacted with selenocarbonyl compounds.

4.1
With Olefins and Acetylenes

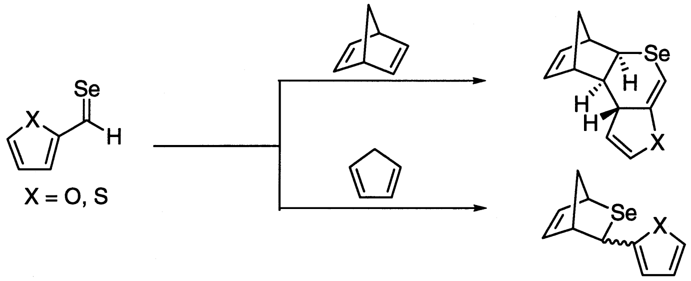
The selenoaldehydes and selenoketones generated in situ by a wide range of methods can generally be trapped with dienes [30, 31, 56, 57, 60–63]. Cyclopentadiene has often been used, and the hetero-Diels-Alder reaction proceeds to give *endo*-adducts as major products. The regioselectivity of the reaction with unsymmetrical dienes is high, the results being understood on the basis of the frontier orbital theory [57c]. In the reaction of diarylselenoketones with 2,4-hexadienes, *cis*-adducts are mainly obtained both from *trans*,*trans*- and *cis*,*trans*-hexadienes, whereas the reaction with *cis*,*trans*-hexadiene at about 12 kbar gives *trans*-adduct (Eq. 21) [71]. In these reactions, selenoaldehydes and selenoketones work as a dienophile. In contrast, α,β-unsaturated selenoaldehydes and heteroaryl selenoaldehydes can react both as dienes and dienophiles (Eq. 22) [61g].

The reaction of aryl selenoketones [72], selenothioacetic acid *S*-esters [73], and *N*-alkylidene selenoamides [74] with TCNE and acetylenes having electron-withdrawing groups have been carried out to afford cyclic selenides **40**–**42** and acyclic selenides **43**.



(21)

trans,trans-diene	85 °C	100	:	0
cis,trans-diene	80 °C	~98	:	2
	rt, 12 kbar	~85	:	15



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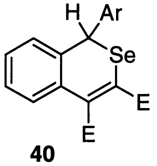

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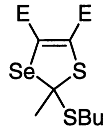

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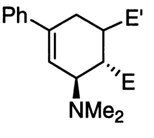

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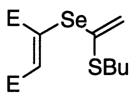
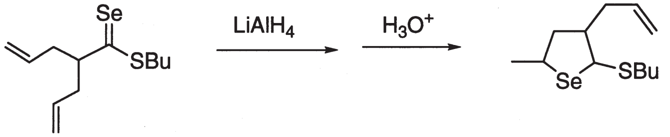


43

E : electron-withdrawing group

4.2
With Nucleophiles

The reduction of selenoketones [75] and selenoesters [76] has been known to give selenides. The reduction of selenothioic acid *S*-esters having allyl groups also proceeds smoothly accompanied with cyclization to afford tetrahydroselenophenes with high stereoselectivity (Eq. 23) [77].

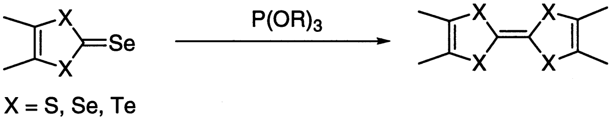

(23)

Neutral nitrogen nucleophiles can react with selenothioic acid *S*-esters [8a] and diselenoesters [20c] to afford selenoamides, whereas lithium salts of aromatic amines are reacted with selenoesters [78].

The Wittig-type olefination of selenoaldehydes with phosphonium ylides [79a] and diazonium salts are known [79b,c]. In these reactions the carbon nucleophiles initially attack the carbon atom of the selenocarbonyl group. The aromatic selenoketones undergo reductive dimerization with organolithium reagents probably via an electron transfer mechanism [80]. The addition of organolithium reagents takes place at the carbon atom of selenocarbonyl group of selenoformic acid *O*-esters [81] and selenoamides [82]. In the former case [81] a small amount of the products derived from the attack on the selenium atom of the selenocarbonyl group was also observed. α,α-Disubstituted selenoamides are converted to ketones with alkyllithium reagents [82b], whereas the Michael addition of alkyllithium to α,β-unsaturated selenoamides takes place selectively [83].

The addition of alcohols to *N*-alkylidene selenoamides generated in situ leads to *N*-alkoxyalkyl selenoamides [84]. The substitution reaction of alkoxy groups of selenoesters [RC(Se)OR′] with aluminum thiolates or selenolates proceeds smoothly to give the corresponding esters [RC(Se)SR′, RC(Se)SeR′] [7a, 85], whereas the addition of thiols to selenoaldehydes takes place at the selenium atom to afford selenenesulfides (RCH_2SeSR') [86].

The reaction of 1,3-dichalcogeno-2-selones with trialkyl phosphites has been used to synthesize perchalcogenofulvalenes, although the yields of the products are moderate (Eq. 24) [16, 87]. On the other hand, the treatment of selenothioic acid *S*-esters and diselenoesters with trialkylphosphites gives phosphoryl sulfides and selenides in good yields (Eq. 25) [88].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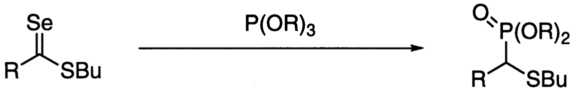
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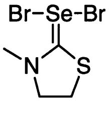
4.3
With Electrophiles

The alkylation and acylation of the selenium atom of selenoamides [89], selenourea [90], 1,3-dithia-2-selones, or 1,3-diselena-2-selones [91] with alkylating agents easily takes place to form selenonium salts in the first step, and then they are converted to diselenides, selenazoles, tetrathiafulvalenes, or cyclic selenides. The allylation of selenothioic acid *S*-esters with allylic bromides gives α-allylated esters. The introduction of three allyl groups at the α-carbon atom to the selenocarbonyl group is possible [92].

The condensation of two molecules of primary selenoamides proceeds with bromine under extrusion of selenium to give selenadiazoles [93]. The reaction of selenocarbonates, selenothiocarbonates [94], and selenourea [95] with bromine and iodine has been widely tested. The products depend on the amount of halogen used. For example, in the reaction of *N*-methylthiazoline-2(3*H*)-selone, the use of one equivalent of bromine gives hypervalent 10-Se-3 complexes **44**, whereas two equivalents of bromine cleave the carbon selenium double bond to give product **45**. A similar hypervalent compound is formed from 4-imidazolin-2-selone, but the iodination of bis(imidazolin-2-selone)methane gives iodinated product **46**. The availability of some of halogen adducts has been tested as a conducting material.



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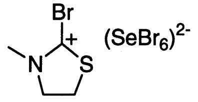

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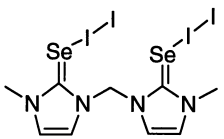
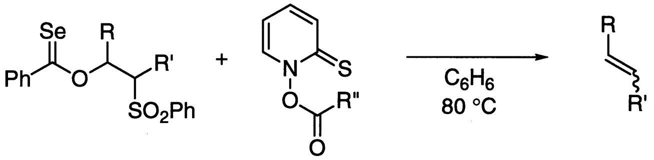


46

The oxidation of 4-imidazolin-2-selones with 7,7,8,8-tetracyanoquinodimethane [96] and electrochemical oxidation of benzthiazoline-2(3*H*)-selone has been carried out [97]. The properties of the former products have also been tested as semi-conducting molecules. The elimination of selenocarboxyl groups and sulfonyl groups mediated by *N*-acyloxypyridinethione gives olefins (Eq. 26) [98].

The reaction of selenoamides and selenourea with aldehydes and ketones has been known to take place via the nucleophilic attack of the selenium atom and end up in the formation of a variety of selenium- and nitrogen-containing heterocycles [99]. For example, selenourea was treated with β-keto ester in the presence of KOH to give selenouracil (Eq. 27) [100], and its biological activity has been tested [100b]. Very recently, Lewis acid mediated addition of primary selenoamides to α,β-unsaturated ketones has been reported to give 1,3-selenazines (Eq. 28) [99f].



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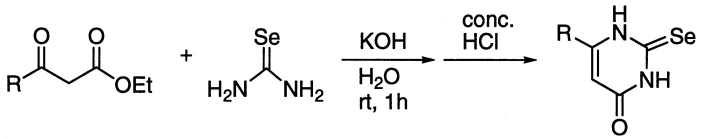

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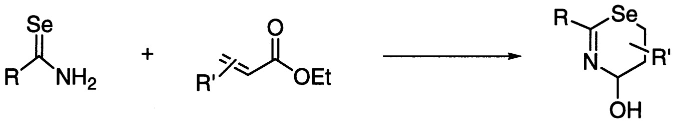
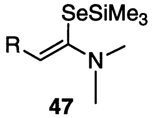


(28)

4.4
Via Eneselenolates

The selenium counterparts of enolate ions, i.e., eneselenolate ions, can be generated by the deprotonation of enolizable selenoamides [101], selenoesters [102], and selenothioic acid *S*-esters [103]. The generated eneselenolate ions are reacted with trimethylsilyl chloride, aldehydes, selenoesters, propargyl bromides, and oxiranes to give the products **47**–**52**.



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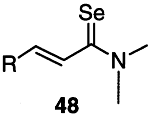

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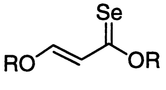

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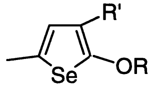

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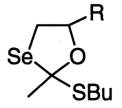

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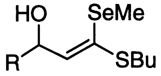

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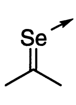
4.5
With Inorganic Metals and Metal Salts

The interaction of selenocarbonyl compounds with inorganic metals and metal salts has been examined for three different purposes. First, the reaction of selenoamides [104], selenothioacetic acid *S*-esters [105], and diselenoesters [85] with Cu, YbI_2/Yb, SmI_2/Sm, $NiCl_2$, or $Cd(OAc)_2$ proceeds with the extrusion of selenium atoms to form olefins or selenophenes. Second, the ability of selenocarbonyl compounds to trap toxic heavy metals such as Cd has been tested [106]. Finally, the treatment of selenourea with a wide range of metal salts, i.e., TeX_4 [107a], $Cd(NO_3)_2$, $Zn(NO_3)_2$ [107b], $SnCl_4$, $GeCl_4$ [107c], Cu^{2+}, Pd^{2+} [107d], and Se^{2+}[107e] has been reported. Additionally, the interaction of selenourea with gold thiolate and carboxylate has been studied [108].

5
Metal Complexes and Their Properties

The properties of three types of metal complexes **53**–**55** of selenocarbonyl compounds are briefly introduced in this section.



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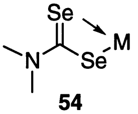

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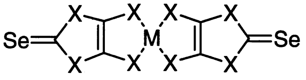
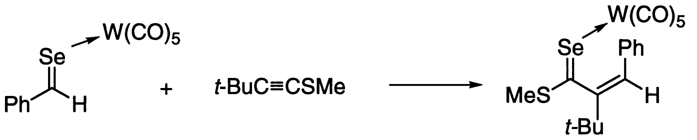


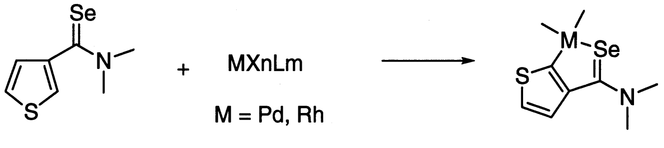
X = S, Se, Te **55**

One of the synthetic procedures of metal complexes of type **53** is the reaction of metal-carbene complexes with selenium sources such as alkyneselenolates [109]. The stability of selenobenzaldehyde is enhanced by coordinating to metal carbonyls, and the reactivity of the complexes has been studied [110]. For example, the selenobenzaldehyde complexes reacts with methylthiohexyne even at –30 °C to afford another type of complex where the selenium atom of the selenocarbonyl group is still coordinated to the metal (Eq. 29) [110d].

Alternatively, the reaction of isolated selenocarbonyl compounds with transition metal complexes has been applied to the synthesis of metal complexes of type **53**. The complexation of furanselenoamides and thiopheneselenoamides to Pd, Rh, and Ru halides is accompanied with cyclometallization (Eq. 30) [111]. The formation of Cu [112a], Ag, Au [112b,c], Zn, Cd [113], Co [114], Cr, Mo, and W [115] complexes has been attained by reacting selenourea or selenoamides with the corresponding metal halides or metal carbonyls.



(29)



(30)

Metal and ammonium diselenocarbamates of type **54** are already well known. Recently, NMR, Mössbauer, and EPR spectroscopic properties of bis(diselenocarbamate) selenide [116] and tris(diselenocarbamate) iron complexes [117] have been revealed. Zn, Cd [118], and In [119] diselenocarbamates are prepared as potential precursors of inorganic ternary materials.

^{77}Se NMR spectroscopy of various metal complexes of type **55** has been conducted [120]. The electric conductivity of Ni, Pd, Pt complexes of type **55** with several types of counter cations and their derivatives have been studied, discussed, and related to crystal structures of the complexes [14, 121]. The complexes **55** with Cu, Au [122], and W [123] have also been synthesized.

In summary, recent development of selenocarbonyl compounds has been reviewed. For the last ten years, a wide variety of synthetic procedures has been established, and some reactions have avoided the use of highly toxic hydrogen selenides and CSe_2. Recently, research fields concerning selenocarbonyl compounds and their metal complexes have begun to be shifted not only to their application to molecular conductors and magnets and but also to their use as key precursors of inorganic and organic conductors. The utilization of the selenocarbonyl compounds in biologically related chemistry as well as to the development of new synthetic reactions based on chiral selenocarbonyl compounds has been rather unexplored despite the impression that slight modification of the structures around the selenocarbonyl group is expected to attenuate highly the reactivity and sensitivity of the compounds. The theoretical approach to the nature of selenocarbonyl compounds is still basic, and the future progress of computational methods will also lead to new research fields in the chemistry of selenocarbonyl compounds. As a result, the selenocarbonyl group will become an important functional group in chemistry in the near future.

6
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Selenoxide Elimination and [2,3]Sigmatropic Rearrangement

Yoshiaki Nishibayashi[1] · Sakae Uemura[2]

[1] Department of Chemistry and Biotechnology, Graduate School of Engineering,
The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8656, Japan
[2] Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering,
Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
E-mail: uemura@scl.kyoto-u.ac.jp

Recent advances of the following four types of asymmetric reactions using organoselenium compounds are reviewed: selenoxide elimination, [2,3]sigmatropic rearrangement via selenoxides, [2,3]sigmatropic rearrangement via selenimides, and [2,3]sigmatropic rearrangement via selenium ylides. In all reactions, the preparation or the intervention of optically active organoselenium compounds having a chiral center on the selenium atom such as selenoxides, selenimides, and selenium ylides is shown to be essential to obtain the chiral organic compounds with high stereoselectivity.

Keywords: Selenoxide elimination, [2,3]Sigmatropic rearrangement, Selenoxide, Selenimide, Selenium ylide

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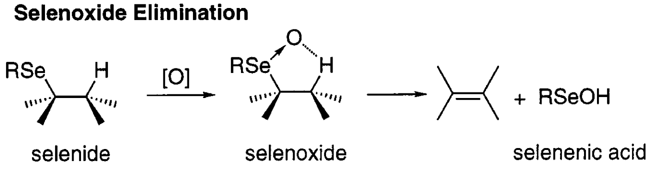
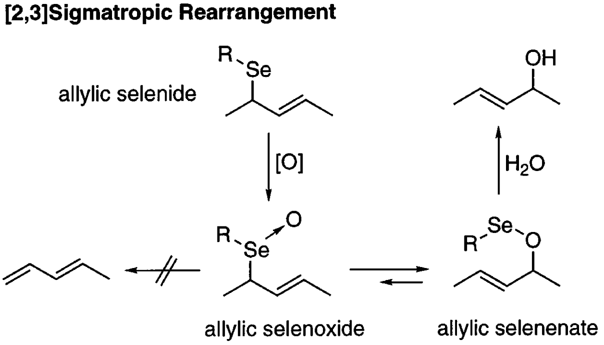
1
Introduction

Organoselenium reagents have provided useful intermediates to introduce new functional groups into organic molecules under mild conditions. For example, an organic selenide can easily be oxidized by various reagents to an organic selenoxide. When the resulting selenoxide bears a β-hydrogen atom, *syn* elimination occurs readily at room temperature giving an alkene together with a selenenic acid as by-product (Eq. 1):



(1)

For an allylic selenide, the oxidation does not lead to a conjugated diene, but rather a facile formation of an allylic alcohol via a selenenic ester (selenenate) takes place by [2,3]sigmatropic rearrangement even at low temperature (Eq. 2):



(2)

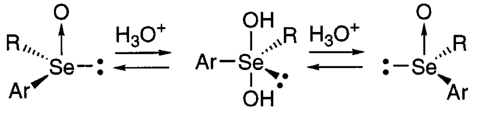
These two reactions are very useful in the field of synthetic organic chemistry and they are now regularly used for preparation of many compounds including natural products. Several reviews have already been published describing this chemistry [1a–c]. In comparison with the corresponding reactions of organosulfur compounds, the advantages of organoselenium compounds are that the activation energy for the above two reactions is much lower and hence the reactions proceed even at room temperature, suggesting that organoselenium compounds have a high potential for performing stereoselective reactions. However, their application to asymmetric organic synthesis was undeveloped until quite recently, in contrast to the corresponding organosulfur chemistry where the usefulness of the optically active organosulfur compounds has long been known for asymmetric synthesis. In this article, recent advances of asymmetric versions of these two reactions, i.e., selenoxide elimination and [2,3]sigmatropic rearrangement by using optically active organoselenium compounds, are reviewed [1d–f]. The results disclosed so far show that the followings are essential for achieving a high asymmetric induction in both reactions:

1. A highly stereoselective preparation of organoselenium compounds having a chiral center at the selenium atom
2. No or slow racemization of the resulting chiral organoselenium compounds
3. An efficient chirality transfer from the chiral selenium atom to the products

Asymmetric selenoxide elimination of the optically active vinyl selenoxides affords optically active allenes and cyclohexylidenes. On the other hand, asymmetric [2,3]sigmatropic rearrangement of allylic selenoxides, selenimides, and selenium ylides leads to the formation of the corresponding optically active allylic alcohols, amines, and homoallylic selenides, respectively.

2
Optically Active Selenoxides

The preparation of the highly optically active selenoxides is essential to achieve a high asymmetric induction in both selenoxide elimination and [2,3]sigmatropic rearrangement. At first, the preparation and the properties of chiral selenoxides, which are key intermediates in both reactions, are surveyed. Until recently, the chemistry of chiral selenoxides was little studied, and their preparation was first reported by Davis and co-workers in 1983 [2]. This is in sharp contrast to the chiral sulfoxides which have been known since the mid-1920s and which have played pivotal roles in the study of the origin of molecular recognition and asymmetric synthesis [3]. The principal difficulty in studying and preparing chiral selenoxides of a high enantiomeric purity is their configurational lability. In earlier studies, it was demonstrated that a chiral alkyl aryl selenoxide racemizes in the presence of moisture via the formation of an achiral hydrate, the racemization being much accelerated by the addition of acid but not basic media [4] (Eq. 3):

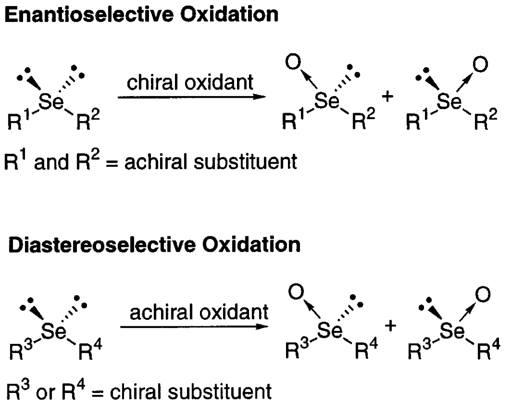


(3)

Bulky *ortho* substituents on an aryl group were shown to slow the rate of racemization by inhibiting sterically the formation of the achiral hydrate. Subsequent detailed studies by Kamigata and co-workers revealed that the rate-determining step is the protonation on the selenoxide oxygen [5]. They also succeeded in preparing an air stable enantiomerically pure (–)-4-(methoxycarbonyl)phenyl 2,4,6-triisopropylphenyl selenoxide by fractional crystallization of a diastereomeric menthyl ester followed by the removal of the chiral auxiliary [6]. The absolute configuration of this selenoxide was determined by X-ray crystallographic analysis of its diastereomer [6]. These results indicate that activation barriers for the racemization of the chiral selenoxides are considerably lower than those of the chiral sulfoxides, but it is possible to isolate the chiral selenoxides in the absence of water and acid.

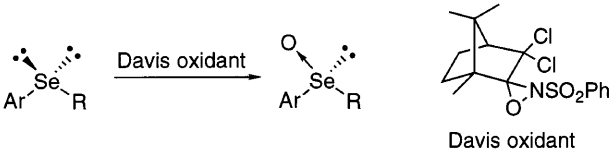
Another interesting example is the optical resolution of the selenoxides by complexation with an optically active binaphthol [7]. The resolution proceeded very efficiently owing to the facile racemization of the selenoxides and in some cases an optically pure selenoxide was obtained in more than 100% chemical yield based on the initial enantiomer [7].

There are two methods for obtaining the chiral selenoxides by direct oxidation of the corresponding selenides. One is the enantioselective oxidation of prochiral selenides, and the other is the diastereoselective oxidation of selenides bearing a chiral moiety (Eq. 4):



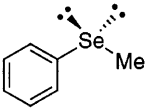
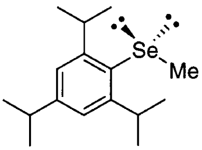
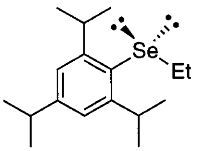
(4)

In the former case, almost complete stereoselective oxidation to the chiral selenoxides has been accomplished quite recently. The Davis oxidant, 3,3-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spirobicyclo[2.2.1]heptane-2,3′-oxaziridine, was found to be the most efficient reagent for the enantioselective oxidation of a variety of prochiral alkyl aryl selenides [8]. Asymmetric oxidation was accomplished by the treatment of the selenides with 1 molar equivalent of the Davis oxidant at 0 °C to afford the corresponding chiral alkyl aryl selenoxides in quantitative yields with 91–95% ee (Scheme 1). The oxidation of methyl phenyl selenide was complete within 1 min, whereas that of triisopropyl(a bulkier alkyl) phenyl selenide required a few hours. Typical results are



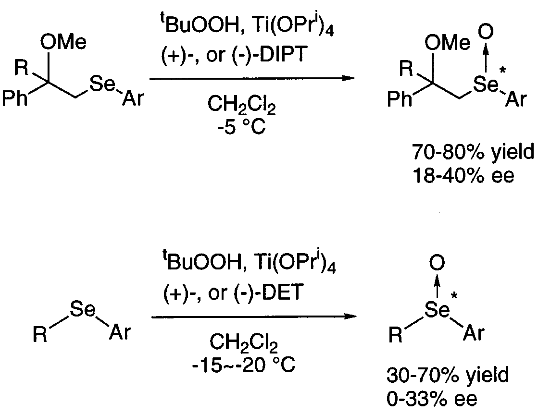
Scheme 1. Asymmetric oxidation of the prochiral selenides to the selenoxides using the Davis oxidant

Table 1. Asymmetric oxidation of the alkyl aryl selenides to the selenoxides using the Davis oxidant

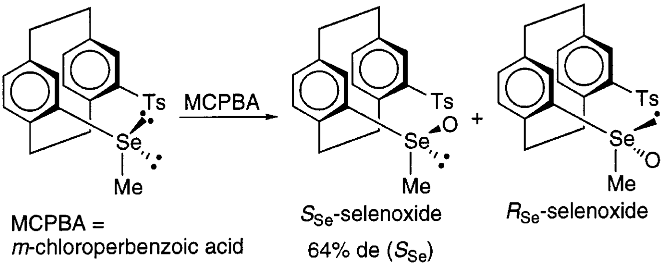
Selenide	Solvent	Reaction time (min)	Ee by NMR (%),[a] (config.)
	$CHCl_3$	<1	>95 (*S*)
	CCl_4	<1	94 (*S*)
	CH_2Cl_2	<1	64 (*S*)
	$CHCl_3$	90	>95 (*S*)
	$CHCl_3$	120	91 (*S*)

[a] Determined by using Eu(fod).

shown in Table 1. The Sharpless oxidant, which is a well known reagent for the asymmetric epoxidation of prochiral allylic alcohols, was less effective than the Davis oxidant for the asymmetric oxidation of prochiral alkyl aryl selenides [9]. Namely, the oxidation of β-methoxyalkyl aryl selenides and alkyl aryl selenides using *tert*-butylhydroperoxide (TBHP) in the presence of a tartrate and a titanium(IV) alkoxide gave the corresponding chiral selenoxides with moderate enantioselectivities (up to 40% ee) [9] (Scheme 2). On the other hand, the diastereomerically chiral selenoxides have been prepared first by the oxidation of the nonracemic [2.2]paracyclophane-substituted selenides as shown in Scheme 3 [10]. Specifically, the oxidation of 4-(methylseleno)-15-(*p*-toluenesulfonyl)[2.2]paracyclophane with *m*-chloroperbenzoic acid (MCPBA) at −60 °C for 3 min gave the corresponding chiral selenoxide, which had a new chiral center on the selenium atom, in quantitative yield with 64% de.



Scheme 2. Enantioselective oxidation of the alkyl aryl selenides to the selenoxides using the Sharpless oxidant

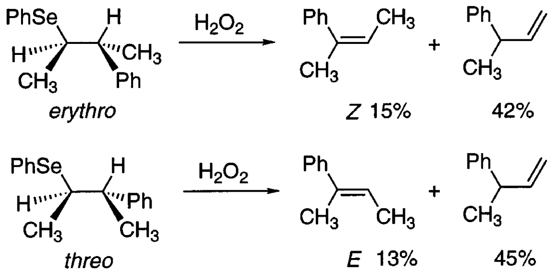


Scheme 3. Diastereoselective oxidation of methyl [2.2]paracyclophane selenide

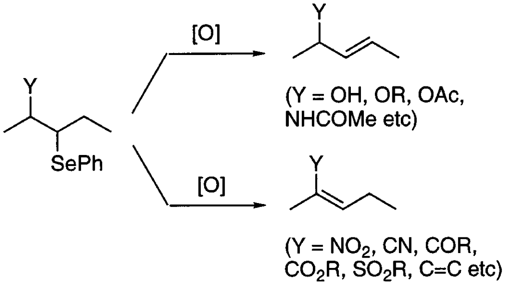
3
Selenoxide Elimination

Among the available methods for introducing an unsaturated carbon-carbon bond into organic molecules, selenoxide elimination reaction has been shown to be quite useful because of its simple procedure and its characteristic regioselectivity. Jones et al., who discovered the first selenoxide elimination, proposed an intramolecular mechanism entailing a five-membered ring structure to explain its *syn* nature [11]. This proposition was shown to be correct by Sharpless et al. who applied the method that was utilized by Cram to determine the stereochemistry of elimination in amine oxides [12]. Thus, the oxidation of *erythro*-selenide afforded only *Z*-olefin and that of *threo*-selenide gave only *E*-olefin (Scheme 4).

The regioselectivity in selenoxide elimination affording either allylic or vinylic products depends much on the nature of a *β*-substituent (Y) as shown in Scheme 5, making the reaction quite useful in organic synthesis [13]. Fujimoto's and Uemura's groups have recently carried out theoretical study of it by means of ab initio MO calculations [13]. The regioselectivity in the elimination was investigated by taking a simplified *β*-substituted selenoxide system,



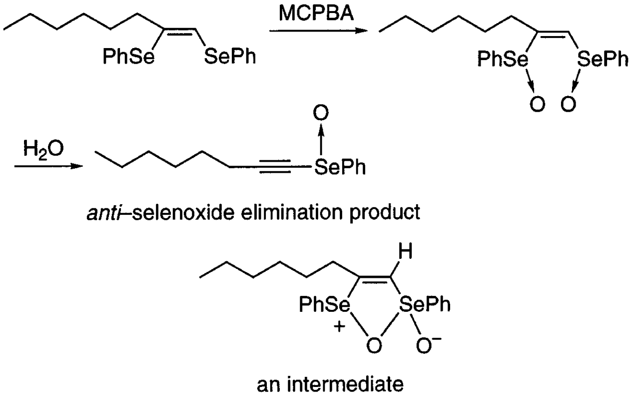
Scheme 4



Scheme 5

$CH_2(Y)CH(Se(O)CH_3)CH_3$ (Y = OCH_3, OH, CN, and Cl), as a model. The elimination occurs via a transition state with a five-membered ring structure, and the breaking of the C_β-H bond takes place earlier than that of the Se-C_α bond, in the favorable path. The experimental results obtained for the elimination of selenoxide showed a reasonable agreement with their theoretical results.

Sonoda and co-workers have found a novel selenoxide *anti*-elimination by oxidation of (*Z*)-1,2-bis(phenylseleno)-1-alkenes. The oxidation of (*Z*)-1,2-bis(phenylseleno)-1-octene with *meta*-chloroperbenzoic acid (MCPBA) and the subsequent work-up afforded the corresponding acetylenic phenyl selenoxide in 67% yield (Scheme 6). This result indicates that the *anti*-elimination of



Scheme 6. *anti*-Selenoxide elimination **I**

selenenic acid via an intermediate **I** took place. Although further investigations are required for understanding of the precise mechanism of this *anti*-elimination, the participation by the neighboring seleninyl group may conceivably cause this novel selenoxide *anti*-elimination [14].

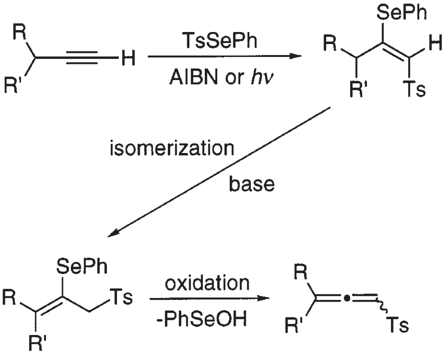
The asymmetric elimination has so far generally been carried out by enantioselective deprotonation using chiral bases [15]. Therefore, if an elimination from optically active selenoxides gave optically active alkenes, the reaction may provide a new methodology for asymmetric elimination to form a carbon-carbon double bond under mild conditions. A few examples of asymmetric selenoxide elimination are described below.

3.1

Enantioselective Selenoxide Elimination Producing Optically Active Allenes and α,β-Unsaturated Ketones

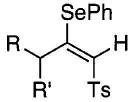
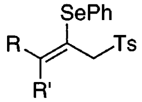
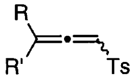
The first example of asymmetric selenoxide elimination was reported by Uemura and co-workers in 1992 [16a]. They envisaged applying the reaction to produce chiral allenic sulfones from some aryl vinyl selenides. The optically active allenes having an axial chirality are important synthetic intermediates for various biologically active compounds. However, the methods for asymmetric synthesis of axially chiral allenes reported so far have been limited to a few cases such as [3,3]Claisen and [2,3]Wittig rearrangements of optically active propargyl ethers and the copper-catalyzed alkylation of optically active propargyl compounds [17].

Previously, Back and co-workers reported the method for the preparation of allenic sulfones using selenoxide elimination as a key reaction [18]. The β-(phenylseleno)vinyl sulfones, which were readily obtained from the free-radical selenosulfonation of acetylenes, isomerized to the corresponding allylic sulfones under base-catalyzed conditions in nearly quantitative yield with high stereoselectivity favoring the *Z*-configuration. The allylic sulfones afforded allenic sulfones generally in high yields by oxidation with MCPBA or *tert*-butyl hydroperoxide, followed by selenoxide *syn*-elimination (Scheme 7). Numerous procedures exist for the preparation of allenes from various types of starting compounds. However, there are relatively few methods for converting unfunc-



Scheme 7

Table 2. Preparation of γ-substituted allenic sulfones

			
R	R′	*Z*/*E* ratio	Yield (%)
H	H	–	92
Cl	H	6:1	98
$^{n}C_7H_{15}$	H	>20:1	82
$CH_2OC(O)Ph$	H	>20:1	93
$-(CH_2)_5-$			50

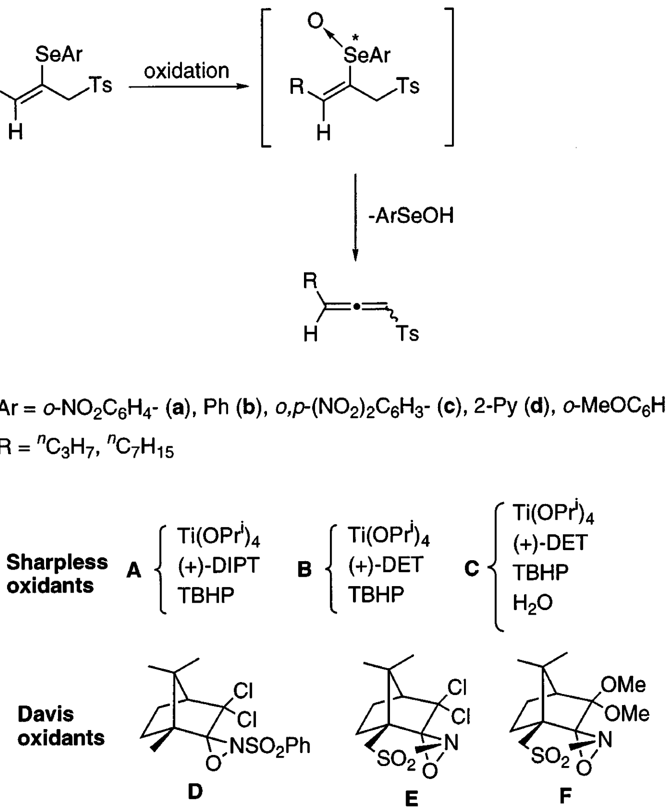
tionalized, simple acetylenes into the corresponding allenes. Thus, the selenosulfonation of acetylenes provides a new route for the synthesis of γ-substituted allenes as shown in Table 2.

When aryl vinyl selenides, prepared by the method described above, were oxidized with either the Sharpless (**A, B**), the modified Sharpless (**C**) or the Davis (**D, E, F**) reagent at −20 °C to around +30 °C for several days in CH_2Cl_2, the corresponding chiral allenic sulfones were obtained in high chemical yields with moderate enantiomeric excesses [16] (Scheme 8). Representative results are summarized in Table 3. The nature of the aryl group of the selenides had a remarkable effect upon the stereoselectivity of the products. The *o*-nitrophenyl group (**a**) was most effective for this asymmetric induction, the effectiveness being followed by the *o,p*-dinitrophenyl (**c**) and *o*-methoxyphenyl (**e**) groups, while the phenyl (**b**) and 2′-pyridyl (**d**) groups were not effective at all. This fact indicates that an *ortho*-substituent may stabilize the chiral selenoxide interme-

Table 3. Asymmetric synthesis of allenic sulfones[a]

Substrate		Oxidant	Conditions	Yield (%)	Ee (%)	Config.
Ar	R		Time/d (Temp./°C)			
o-$NO_2C_6H_4$-	$^{n}C_3H_7$	**A**	19 (0)	43	38	*R*
o-$NO_2C_6H_4$-	$^{n}C_3H_7$	**B**	16 (0)	72	21	*R*
o-$NO_2C_6H_4$-	$^{n}C_3H_7$	**C**	19 (0), then 4 (rt)	42	1	–
o-$NO_2C_6H_4$-	$^{n}C_3H_7$	**D**	15 (rt)	41	28	*R*
o-$NO_2C_6H_4$-	$^{n}C_3H_7$	**E**	15 (rt)	26	23	*R*
o-$NO_2C_6H_4$-	$^{n}C_3H_7$	**F**	15 (rt)	9	15	*S*
o-$NO_2C_6H_4$-	$^{n}C_7H_{15}$	**A**	19 (0)	59	38	*R*
Ph	$^{n}C_3H_7$	**B**	1 (−20), then 3 (rt)	73	1	–
o,p-$(NO_2)_2C_6H_3$-	$^{n}C_3H_7$	**A**	19 (0)	55	20	*R*
2-Py	$^{n}C_3H_7$	**B**	13 (0)	52	1	–
o-$MeOC_6H_4$-	$^{n}C_3H_7$	**A**	10 (0)	76	5	*S*

[a] All reactions were carried out in the presence of molecular sieves 4 Å.

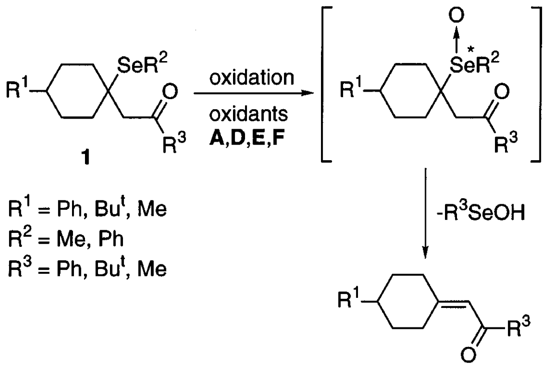


Scheme 8

diate sterically and the electron-withdrawing substituent may accelerate the elimination step preventing the racemization of the produced chiral selenoxide intermediate. As the oxidant, the Sharpless reagents (**A**, **B**) were more efficient than the Davis (**D**, **E**, **F**) and the modified Sharpless (**C**) reagents with respect to enantiomeric excess as well as chemical yield of the chiral allenes.

The effects of aryl groups were kinetically analyzed by comparing the rate constants of both steps (k_1 for oxidation step and k_2 for elimination step) which were determined by ^{1}H NMR analysis of the concentration of vinyl selenides, the intermediate selenoxide, and allenic sulfones [16b]. This kinetic study indicates that the rates of both oxidation and elimination steps were accelerated by the introduction of an electron-withdrawing group. Such acceleration has been known in the overall selenoxide elimination as well as in the selenoxide elimination step of alkyl aryl selenides. As a result, it was disclosed that the ratio of these rate constants (k_1/k_2) was closely related to the enantiomeric excess of the products; the smaller the ratio, the larger the enantiomeric excess becomes. Thus, the introduction of *o*-nitrophenyl group as an aryl moiety, which suppresses sterically the racemization of the intermediate chiral selenoxide and accelerates the selenoxide elimination step, is necessary to achieve a higher asymmetric induction.

As a further work of asymmetric selenoxide elimination, Uemura and coworkers applied this reaction to the preparation of axially chiral alkyl and aryl cyclohexylidenemethyl ketones starting from the substituted-cyclohexyl methyl and phenyl selenides [19]. Chiral cyclohexylidene compounds have attractive chiroptical properties, and their highly stereoselective preparation has been reported. Thus, various benzylidenecyclohexane or alkylidenecyclohexane derivatives were synthesized with a high stereoselectivity using chiral Wittig reagents [20]. For chiral cyclohexylidenemethyl carbonyl compounds, the carboxylic acid derivatives were prepared either by optical resolution or by asymmetric dehydrohalogenation with chiral lithium amides [21], while the ketone, ester, and aldehyde derivatives were mainly derived from chiral carboxylic acids [22]. The synthesis of chiral ketone derivatives from cyclohexylideneacetic acids was difficult because of a facile isomerization to the thermodynamically more stable *endo* olefins. Therefore, this new approach using asymmetric selenoxide elimination may provide a useful method for the preparation of the chiral cyclohexylidenemethyl ketones (Scheme 9).



Scheme 9

Thus, when cyclohexyl selenides **1**, prepared from the corresponding 4-substituted cyclohexanone via the selenoketals, were oxidized with various Davis and Sharpless oxidants, the chiral alkyl aryl 4-substituted cyclohexylidenemethyl ketones were obtained in excellent chemical yields with high enantiomeric excesses. Typical results are summarized in Table 4. In this asymmetric induction, R^2 of the substrate and the chiral oxidant employed were revealed to show a remarkable effect upon the enantioselectivity of the product. The use of a methyl moiety as R^2 instead of a phenyl moiety gave a higher ee value, probably due to the steric difference between the two groups bonded to the selenium atom of the substrate. The results indicate that the titanium complex of the Sharpless oxidant may promote the racemization of the chiral selenoxide intermediate by acting as a Lewis acid catalyst, whereas the racemization in the case of the Davis oxidant, which is aprotic in nature, is slow.

Table 4. Asymmetric synthesis of cyclohexylidenemethyl ketones[a]

Substrate 1			Oxidant	Solvent	Reaction time (h)	Yield (%)	Ee (%)	Config.
R^1	R^2	R^3						
Ph	Me	Ph	**D**	CH_2Cl_2	3.5	92	74	*R*
Bu^t	Me	Ph	**D**	$CHCl_3$	4	96	83	*R*
Bu^t	Me	Ph	**E**	CCl_4	4	56	24	*S*
Bu^t	Me	Ph	**F**	CCl_4	4	95	6	*R*
Bu^t	Me	Ph	**A**	CH_2Cl_2	4	100	2	–
Bu^t	Me	Bu^t	**D**	$CHCl_3$	5	70	82	*R*
Bu^t	Me	Me	**D**	$CHCl_3$	5	97	74	*S*
Bu^t	Ph	Ph	**D**	CH_2Cl_2	72	66	7	*R*
Bu^t	Ph	Ph	**A**	CH_2Cl_2	72	64	0	–
Me	Me	Ph	**D**	CH_2Cl_2	4	91	81	*R*

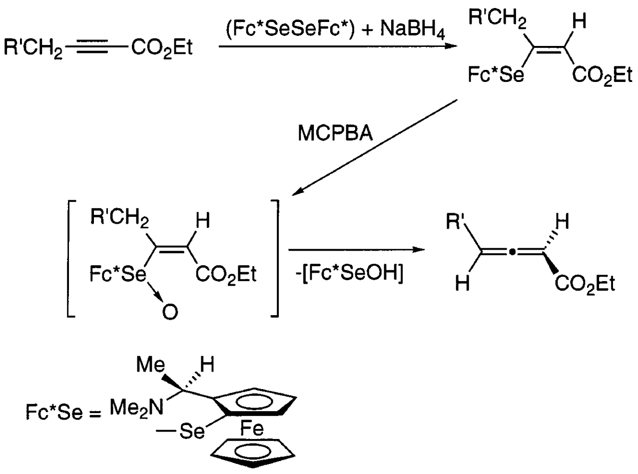
[a] At –20 °C.

3.2
Diastereoselective Selenoxide Elimination Producing Optically Active Allenecarboxylic Esters

Asymmetric selenoxide elimination via a diastereomeric chiral selenoxide as a key intermediate was also achieved by Uemura and co-workers [23]. They prepared new optically active diferrocenyl diselenides from the corresponding chiral ferrocenes and used the optically active ferrocenyl group as a chiral aryl moiety since an arylselenium moiety can easily be introduced into organic molecules.

The oxidation of the chiral ferrocenyl vinyl selenides, prepared from the optically active diferrocenyl diselenides and ethyl propiolate derivatives, with 1 molar equivalent of MCPBA under various conditions afforded the corresponding chiral selenoxides. The chiral selenoxides suffered in situ selenoxide elimination to afford the axially chiral allenecarboxylic esters in moderate chemical yields with high enantioselectivities (Scheme 10). Typical results are shown in Table 5. The reaction temperature had a remarkable effect upon stereoselectivity and the lower temperature gave better results. The addition of molecular sieves (4 Å) to the reaction system improved the stereoselectivity. Dichloromethane was revealed to be the solvent of choice. In other words, reaction conditions to suppress the racemization of a diastereomeric selenoxide intermediate were required. Asymmetric selenoxide elimination provides a new method for the preparation of the chiral allenecarboxylic esters which have so far been prepared by optical resolution of the corresponding racemic acids.

The high degree of diastereoselection in the oxidation of chiral ferrocenyl vinyl selenides was supported by the oxidation of the chiral *p*-tolyl ferrocenyl sulfide, instead of the selenide, with MCPBA at low temperature. Thus, an almost complete diastereoselective oxidation occurred either at –20 °C or –78 °C to give the corresponding chiral sulfoxide (Scheme 11). On the other hand, the oxidation of *p*-tolyl 1-(*N*,*N*-dimethylamino)ethylphenyl sulfide with MCPBA afforded



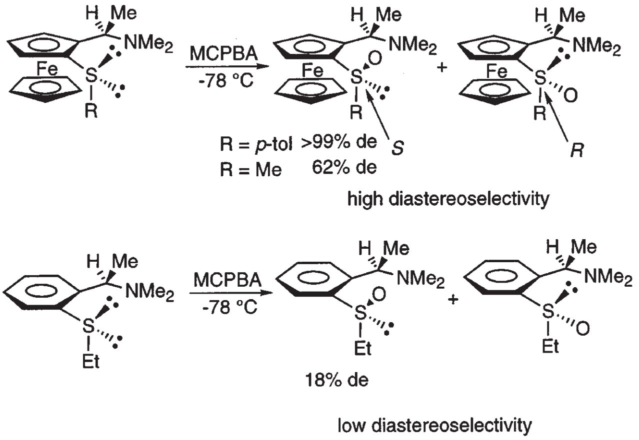
Scheme 10

Table 5. Asymmetric synthesis of allenecarboxylic esters

R′	Solvent	Conditions time/h (temp/°C)	Yield (%)	Ee[a] (%)
CH_3	MeOH	19 (0)	35	30
CH_3	Et_2O	22 (0)	21	16
CH_3	CH_2Cl_2	24 (0)	52	39
CH_3	CH_2Cl_2	45 (−20)	33	43
CH_3	CH_2Cl_2	1 (−78) ⟶ 46 (−20)	48	70
CH_3	CH_2Cl_2[b]	1 (−78) ⟶ 70 (−20)	43	89
C_2H_5	CH_2Cl_2[b]	1 (−78) ⟶ 70 (−20)	59	82
C_3H_7	CH_2Cl_2[b]	1 (−78) ⟶ 70 (−20)	52	85

[a] Configuration of the products is all *S*.

[b] In the presence of molecular sieves 4 Å.



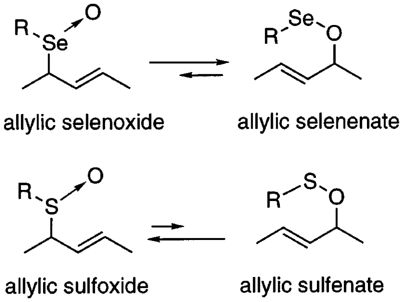
Scheme 11

the corresponding sulfoxide with low diastereoselectivity as also shown in Scheme 11, suggesting that the high diastereoselectivity observed here is not due to the chirality of the substituent on the ferrocene ring, but rather to the planar chirality of the ferrocene [23b].

4

[2,3]Sigmatropic Rearrangement via Allylic Selenoxides

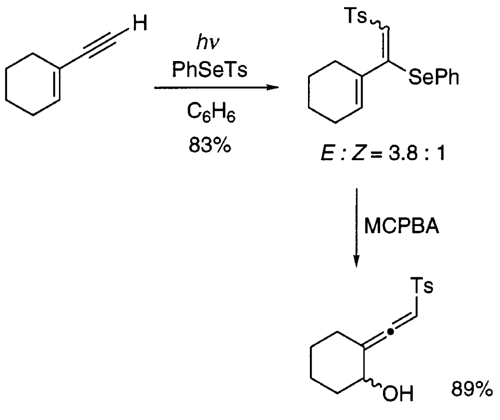
A typical [2,3]sigmatropic rearrangement involves a transfer of oxygen from the selenium atom to the carbon atom of an allylic selenoxide to produce the corresponding allylic selenenate and then an allylic alcohol after hydrolysis (Eq. 2). As described above, the rearrangement of the allylic selenoxides proceeds much faster than that of the allylic sulfoxides due to the lower activation energy of the former process [24]. Moreover, the equilibrium favors the selenenate in the Se series, but the sulfoxide in the S series (Eq. 5). Detailed kinetic and thermodynamic studies of [2,3]sigmatropic rearrangements of allylic selenoxides have been reported by Reich and co-workers [24].



(5)

A synthetically useful method to prepare the allenic alcohols via [2,3]sigmatropic rearrangement has been reported by Back and co-workers [25]. The selenosulfonation reaction, where a selenosulfonate undergoes an electrophilic or free-radical addition to unsaturated organic substrates, provides a convenient method for the preparation of organoselenium compounds such as vinylic and allylic selenides. A conjugated enyne can undergo a free-radical selenosulfonation by the attack of a sulfonyl radical at the terminal carbon atom of the triple bond (1,2-addition) as shown in Scheme 12 with ethynylcyclohexene as the substrate. The reaction is not very stereoselective, but favors *anti* addition. The adduct is an allylic selenide and reaction with MCPBA afforded the allenic alcohol in 89% yield via a [2,3]sigmatropic rearrangement of the intermediate vinylic selenoxide (Scheme 12). This rearrangement is stereospecific and, when a pure (*E*)-isomer was oxidized with MCPBA, only one isomer of the allenic alcohols was formed.

If the chiral allylic selenoxides were obtained by enantioselective or diastereoselective oxidation of the allylic selenides, the formation of the corresponding chiral allylic alcohols is expected after the hydrolysis of the intermediate chiral allylic selenenates obtained by chirality transfer in the rearrangement



Scheme 12

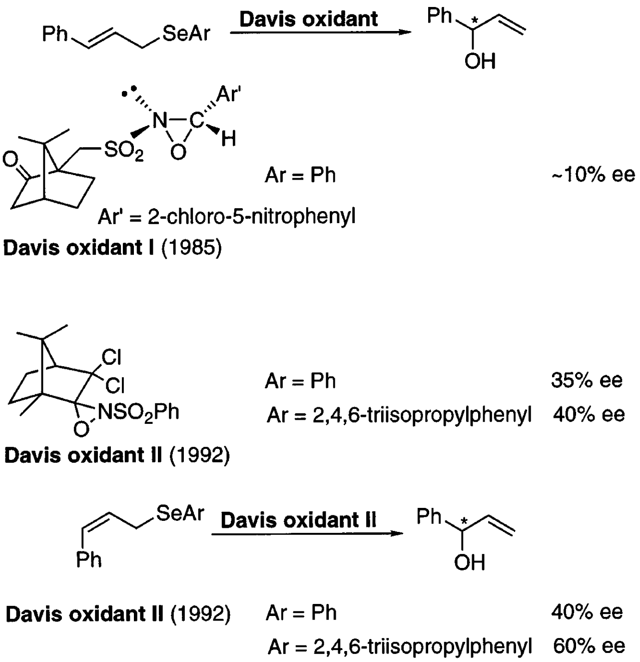
step. In fact, several asymmetric reactions via this process have recently been reported for the preparation of chiral allylic alcohols. In this section, typical results of asymmetric [2,3]sigmatropic rearrangement via chiral allylic selenoxides to afford the corresponding chiral allylic alcohols are described.

4.1

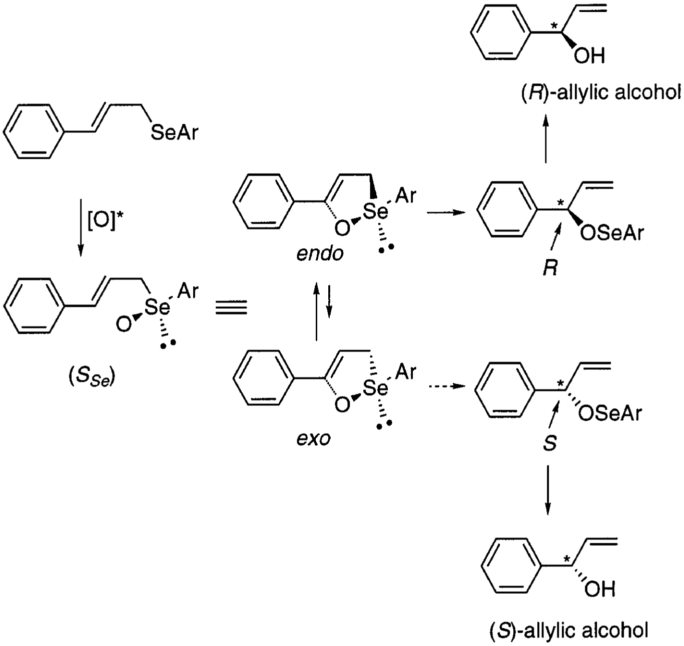
Enantioselective [2,3]Sigmatropic Rearrangement Producing Optically Active Allylic Alcohols

The first example of asymmetric [2,3]sigmatropic rearrangements via allylic selenoxides was reported by Davis and co-workers in 1985 [4]. They generated in situ a chiral cinnamyl phenyl selenoxide by oxidation of the corresponding prochiral selenide with the **Davis oxidant I** in $CHCl_3$ to give 1-phenyl-2-propen-1-ol after hydrolysis with only ~10% ee. However, the enantiomeric excess of the allylic alcohol product rose from ~10% ee to 60% ee using the more effective **Davis oxidant II** developed by themselves (Scheme 13) [8]. The oxidation of (*E*)- and (*Z*)-cinnamyl phenyl selenides was complete within 5 min at –60 °C whereas more hindered selenides required a higher reaction temperature (0 °C) for several hours. As the rearrangement of the allylic selenoxides to the allylic alcohols is extremely fast, it is reasonable to assume that the racemization of the chiral allylic selenoxides did not occur. In fact, it was clear that the presence of water, which accelerates the racemization of chiral selenoxides via hydration, had no influence on the chirality transfer of the chiral allylic selenoxides to the corresponding selenenates [8]. The selectivity of the allylic alcohols produced may be dependent on the free energy difference of the two possible transition states (*exo* and *endo*), from which the allylic alcohols having opposite configuration are obtained as shown in Scheme 14, and, therefore, it is concluded that rational modification of the aryl part of the allylic selenides is required for significant improvement of the ee value of allylic alcohols.

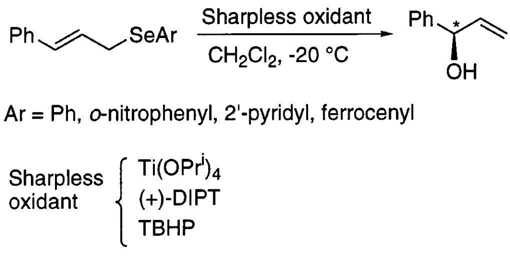
More recently, Uemura and co-workers have carried out the asymmetric oxidation of several aryl cinnamyl selenides using Sharpless oxidants [26] (Scheme 15). Typical results are shown in Table 6. They showed a strong corre-



Scheme 13



Scheme 14



Scheme 15

Table 6. Asymmetric oxidation of aryl cinnamyl selenides using the Sharpless oxidant

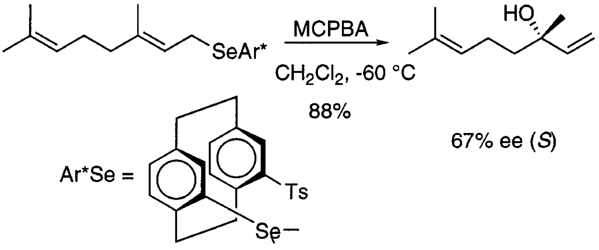
Ar	Yield (%)	Ee[a] (%)
Ph	41	69
o-nitrophenyl	42	92
2′-pyridyl	10	31
ferrocenyl	10	25

[a] Configuration of the product is *R*.

lation between the aryl group and the ee value of the allylic alcohol product. The introduction of an *o*-nitro group to an arylselenium moiety remarkably enhanced the enantioselectivity, while the use of either phenyl-, 2′-pyridyl-, or ferrocenyl-selenium moiety resulted in moderate to low ee value. The large steric and/or electronic effect of an *o*-nitro group to stabilize the chiral selenoxide intermediate is important for obtaining a high enantioselectivity. Thus, a large energy difference between the two possible transition states should be formed by introduction of the *o*-nitro group into the phenyl ring of the selenide.

4.2
Diastereoselective [2,3]Sigmatropic Rearrangement Producing Optically Active Allylic Alcohols

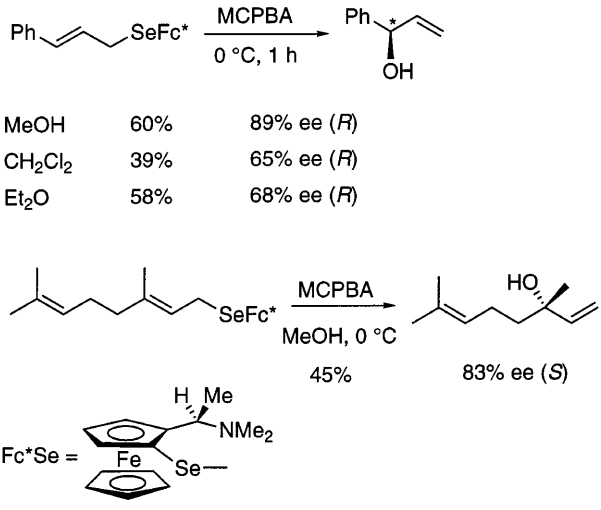
In 1991, Reich and Yelm reported the diastereoselective oxidation of the optically active geranyl [2.2]paracyclophanyl selenide with MCPBA in $CHCl_3$ at −60° C to give linalool with 67% ee via [2,3]sigmatropic rearrangement of the corresponding selenoxide [10] (Scheme 16). The result proved that the [2,3]sigma-



Scheme 16

tropic rearrangement of the γ,γ-dialkylallylic selenoxide proceeds through an *endo* transition state. Since an almost similar selectivity (64% de) was observed by oxidation of methyl [2.2]paracyclophanyl selenide (see above), a chirality transfer should occur at the rearrangement step of the chiral allylic selenoxide.

Uemura and co-workers applied the optically active diferrocenyl diselenide into asymmetric [2,3]sigmatropic rearrangement to produce chiral allylic alcohols [23b]. The oxidation of cinnamyl selenide bearing a chiral ferrocenyl group with MCPBA at −78 °C to around −20 °C in various solvents afforded the optically active 1-phenyl-2-propen-1-ol in moderate yields with a high enantiomeric excess (Scheme 17). The chiral linalool was also obtained with a higher enantiomeric excess than that of the above system using [2.2]paracyclophanyl selenide. The fact that methanol could be used for obtaining a high ee value indicates quite a fast sigmatropic rearrangement of the intermediate chiral ferrocenyl selenoxides, since it is known that the racemization of the optically active selenoxides occurs readily in methanol. The oxidation will give the chiral allylic selenoxides, which may rearrange via *endo*- and *exo*-transition states to the corresponding selenenates. In this case, the *endo*-transition state leading to (*R*)-allylic alcohol should be more stable than the *exo*-one because the steric repulsion between the styryl and chiral ferrocenyl moieties is larger in the *exo*-transition state.

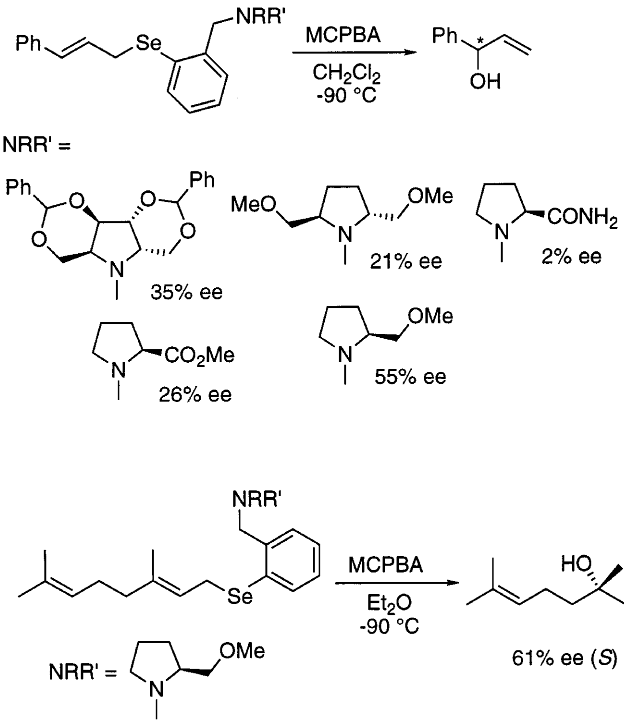


MeOH	60%	89% ee (*R*)
CH_2Cl_2	39%	65% ee (*R*)
Et_2O	58%	68% ee (*R*)

Scheme 17

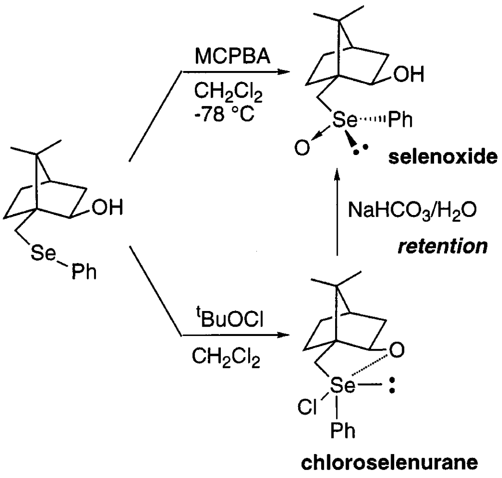
The asymmetric [2,3]sigmatropic rearrangement of several other allyl aryl selenides has been reported, but only moderate selectivities are observed [27] (Scheme 18). The oxidation of cinnamyl and geranyl selenides derived from L-prolinol with MCPBA at −90 °C afforded the chiral 1-phenyl-2-propen-1-ol and linalool with moderate enantiomeric excess, respectively.

The most important step of the above [2,3]sigmatropic rearrangement is the enantio- or diastereoselective oxidation of the allylic selenides and the transfer of the chirality of the selenium atom to C-3 of the resulting allylic alcohols. As



Scheme 18

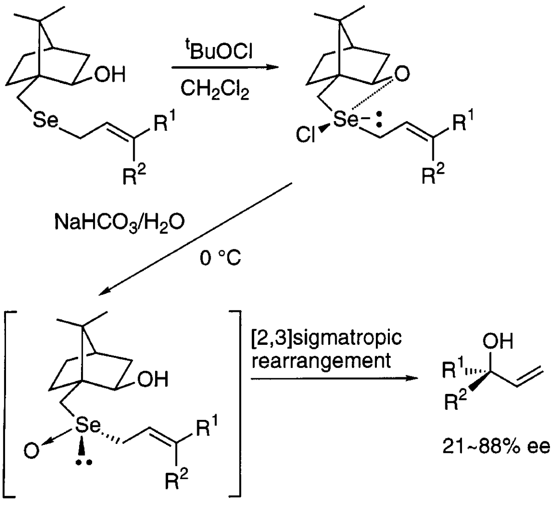
another approach to obtain the chiral selenoxides, Koizumi and co-workers used selenuranes (tetrasubstituted selenium(IV) compounds) bearing a 2-*exo*-hydroxyl-10-bornyl group as a chiral moiety [28]. An optically pure selenoxide was prepared by the following two methods using 2-*exo*-hydroxyl-10-bornyl phenyl selenide (Scheme 19). One is the direct diastereoselective oxidation of



Scheme 19

the selenide with MCPBA at –78 °C. The other is the nucleophilic substitution of a chloroselenurane, which was readily obtained by the diastereoselective oxidation of the selenide with *t*-BuOCl at 0 °C. The absolute configuration of the chloroselenurane and the selenoxide was unequivocally determined by X-ray crystallography. The alkaline hydrolysis of the (R_{Se})-chloroselenurane proceeded with retention of configuration to give the (R_{Se})-selenoxide as the sole product. In the latter case, the oxidation of the selenides with *t*-BuOCl was complete within 10 min at 0 °C to give the chloroselenurane as a single diastereomer in 80–90% yields. The addition of aqueous $NaHCO_3$ to the chloroselenurane at 0 °C instantaneously resulted in a complete hydrolysis, leading to the selenoxide as a single diastereomer in 90–100% yields. This selenoxide is stable at room temperature due to the bulkiness of the bornyl group and to an intramolecular hydrogen bond between the seleninyl oxygen and the secondary hydroxyl group.

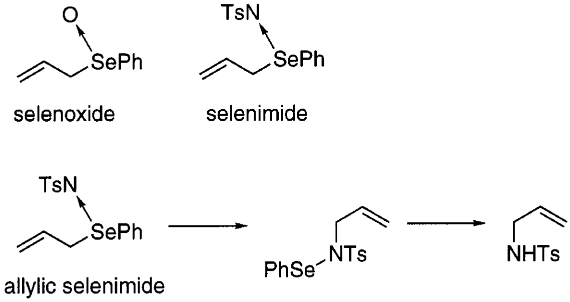
The stereoselective alkaline hydrolysis of the selenurane to afford a single diastereomer of the selenoxide was applied to asymmetric [2,3]sigmatropic rearrangement of an allylic selenoxide [29] (Scheme 20). The treatment of allylic chloroselenuranes with aqueous $NaHCO_3$ at 0 °C gave the corresponding allylic alcohols with moderate to high enantiomeric excess (up to 88% ee). The absolute configuration of the resulting allylic alcohols suggested that the [2,3]sigmatropic rearrangement of allylic selenoxides progresses predominantly via the *endo* transition state.



Scheme 20 R^1 = Ph, R^2 = H; R^1 = cyclohexyl, R^2 = H; R^1 = *n*-hexyl, R^2 = H; R^1 = H, R^2 = Ph; R^1 = H, R^2 = cyclohexyl; R^1 = H, R^2 = n-hexyl

5
[2,3]Sigmatropic Rearrangement via Allylic Selenimides

The nitrogen analogues of the selenoxides, the selenimides, should in principle be capable of [2,3]sigmatropic transformations similar to those of the selenoxides (Eq. 6):



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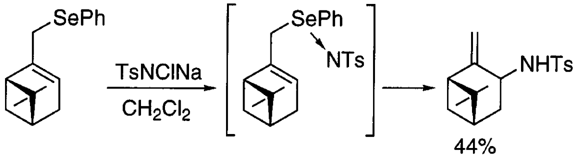
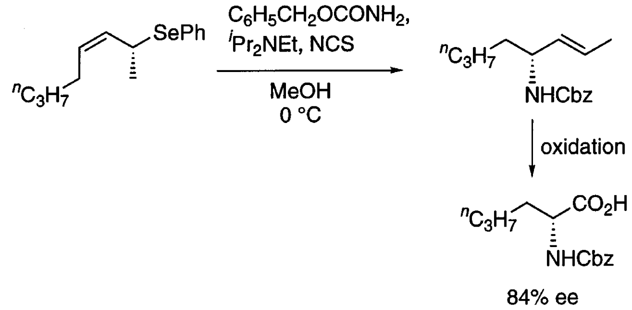
Two decades ago, Hori and Sharpless reported the reaction of 10-(phenylseleno)-*β*-pinene with Chloramine T (TsNClNa) to afford the corresponding allylic amine [30] (Scheme 21).



Scheme 21

Improved experimental procedures have been developed for this purpose [31]. Thus, anhydrous Chloramine T in methanol was revealed to be a highly effective reagent for the conversion of allylic selenides to the corresponding rearranged *N*-allylic-*p*-toluenesulfonamides (*N*-tosyl allylic amines) [31]. This reaction presumably proceeds by way of the corresponding allylic selenimide intermediate, which undergoes [2,3]sigmatropic rearrangement to the selenamide followed by methanolysis, to afford the observed allylic amine product. In place of hazardous anhydrous Chloramine T, which may decompose violently if heated above 130 °C, a mixture of *N*-chlorosuccinimide (NCS) and an amine can also be used for a similar purpose [32]. Thus, a one-step procedure for the preparation of *t*-butoxycarbonyl (Boc)- or carbobenzyloxy (Cbz)-protected primary allylic amines is shown in Scheme 22 [32, 33]. When the reaction starts from optically active allylic selenides, optically active allylic amines are produced [33]. More recently, *N*-(*p*-tolylsulfonyl)imino(phenyl)iodinane (PhI = NTs) was found to be a convenient reagent for imidation of sulfides [34] and selenides [35] to generate the corresponding sulfimides and selenimides, respectively.

In a previous section, the asymmetric [2,3]sigmatropic rearrangement of chiral selenoxides, prepared by diastereoselective oxidation or enantioselective



Scheme 22

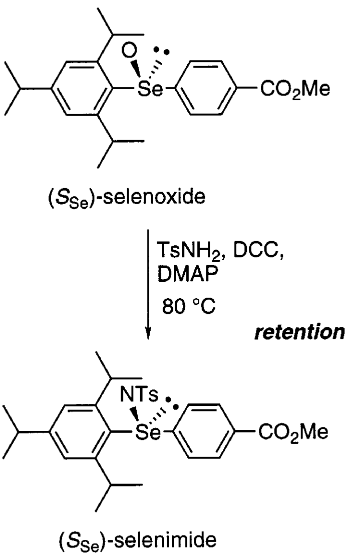
oxidation of the prochiral selenides, was described. If the chiral selenimides were obtained as intermediates by imidation of the selenides enantioselectively or diastereoselectively, the chirality transfer should in principle be expected to occur in the intermediates. Compared with the well-established preparative method for the synthesis of optically active allylic alcohols, procedures for the generation of optically active allylic amines which are very important compounds in organic synthesis are still quite limited [36]. In this section, some examples of [2,3]sigmatropic rearrangement via the chiral allylic selenimides to produce the chiral allylic amines are described.

5.1
Optically Active Selenimides

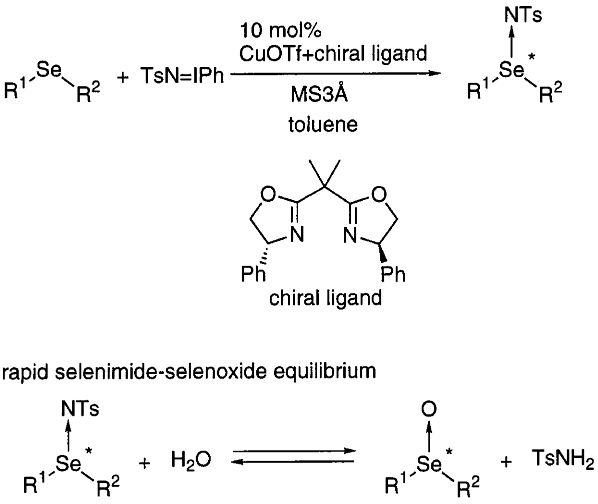
Selenimides are tricoordinate tetravalent compounds and are expected to be isolated in the optically active form since the optically active sulfonium imides are known. In 1981, Krasnov and co-workers reported the first synthesis of optically active selenimides starting from dialkyl- and diaryl-selenium dichlorides, but the scope of this reaction has not been fully developed, probably because of low yields of the products as well as their quite low optical activities [37]. Recently, Kamigata and co-workers isolated an optically pure selenimide by optical resolution of a diastereomeric selenimide and they studied its stereochemistry and the kinetics of epimerization by pyramidal inversion [38]. The detailed studies showed that the selenimide was more stable towards epimerization by pyramidal inversion than the sulfimide with the same substituents. Accordingly, a higher reaction temperature or a higher activation energy is required for the pyramidal inversion of the selenimide than of the corresponding sulfimide.

Furthermore, Kamigata and co-workers have shown an example of the conversion of a chiral selenoxide, obtained by the optical resolution of a diastereomeric mixture, into the corresponding enantiomerically pure selenimide, ascertaining the detailed stereochemistry of this compound [39] (Scheme 23). The transformation of the selenoxide into the selenimide proceeded with an overall retention of configuration at the selenium center in the presence of dicyclohexylcarbodiimide (DCC).

Very recently, Uemura and co-workers have reported the direct enantioselective imidation of prochiral selenides with PhI = NTs in the presence of a cata-



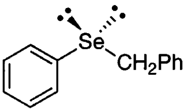
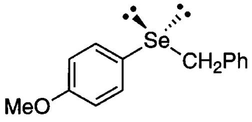
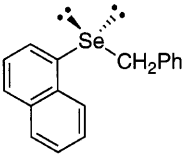
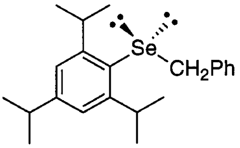
Scheme 23



Scheme 24

lytic amount of CuOTf and a chiral bis(oxazoline) in toluene to produce the corresponding chiral selenimides with moderate enantiomeric excesses [35] (Scheme 24). In the absence of molecular sieves, no enantioselectivity was observed. This is probably due to the interference of the rapid selenimide-selenoxide equilibrium by the removal of water present in the reaction mixture. Typical results are shown in Table 7. The enantioselectivities of the produced chiral selenimides are low (up to 36% ee), but this direct catalytic imidation of prochiral selenides may be a potentially useful method for the preparation of optically active chiral selenimides.

Table 7. Asymmetric imidation of the prochiral selenides

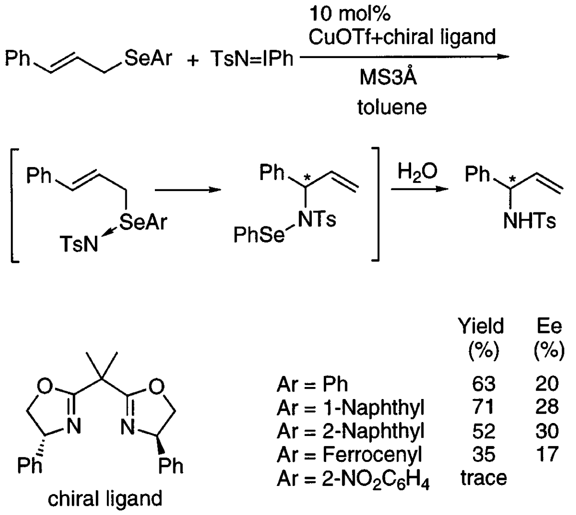
Selenide	Temp.[a] (°C)	Yield (%)	Ee[a] (%)
	25[b]	40	0
	25	53	32
	0	18	33
	25	37	20
	25	23	29
	25[c]	64	36
	25	0	

[a] For 24 h.
[b] Without MS 3 Å.
[c] MS 4 Å, for 48 h.

5.2
Enantioselective [2,3]Sigmatropic Rearrangement Producing Optically Active Allylic Amines

The enantioselective [2,3]sigmatropic rearrangement of allylic selenimides has been achieved by application of the asymmetric synthesis of selenimides [35]. When this reaction was applied to various aryl cinnamyl selenides, the expected optically active allylic amines were obtained in good yield with moderate enantioselectivity via [2,3]sigmatropic rearrangement of the intermediate chiral allylic selenimides (Scheme 25).

Almost the same selectivity as that of the selenimides by direct imidation of prochiral selenides (see Sect. 5.1) indicates that the chirality is not lost in the rearrangement step.



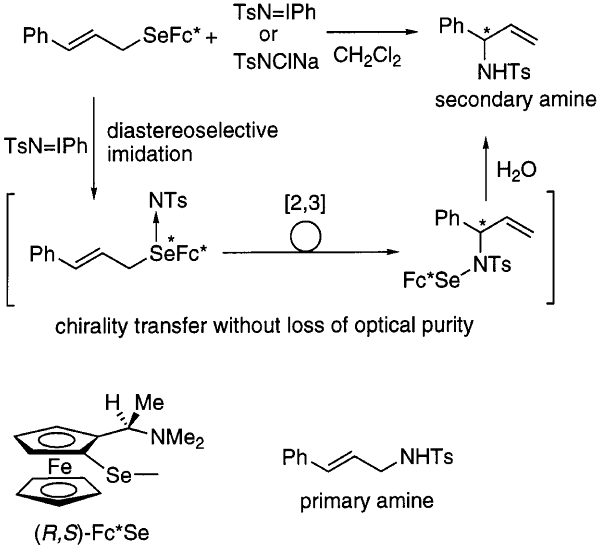
	Yield (%)	Ee (%)
Ar = Ph	63	20
Ar = 1-Naphthyl	71	28
Ar = 2-Naphthyl	52	30
Ar = Ferrocenyl	35	17
Ar = 2-$NO_2C_6H_4$	trace	

Scheme 25

5.3

Diastereoselective [2,3]Sigmatropic Rearrangement Producing Optically Active Allylic Amines

Uemura and co-workers have succeeded in diastereoselective imidation of optically active allylic ferrocenyl selenides to give the corresponding optically active allylic amines [40]. Thus, the treatment of optically active cinnamyl ferrocenyl selenides with TsN = IPh or TsNClNa in dichloromethane at 0 °C afforded the allylic amines in moderate yields with high enantiomeric excesses (Scheme 26).



Scheme 26

Table 8. Diastereoselective imidation of optically active allylic ferrocenyl selenides

Reagent	Temp. (°C)	Time (h)	Yield (%) (Ee[a] (%))	
			secondary amine	primary amine
TsNClNa	25	1	29 (13)	23
TsNClNa	0	20	13 (45)	27
TsN = I Ph	25	1	52 (49)	0
TsN = I Ph	0	20	52 (80)	0
TsN = I Ph	0	20	42 (87)[a]	0

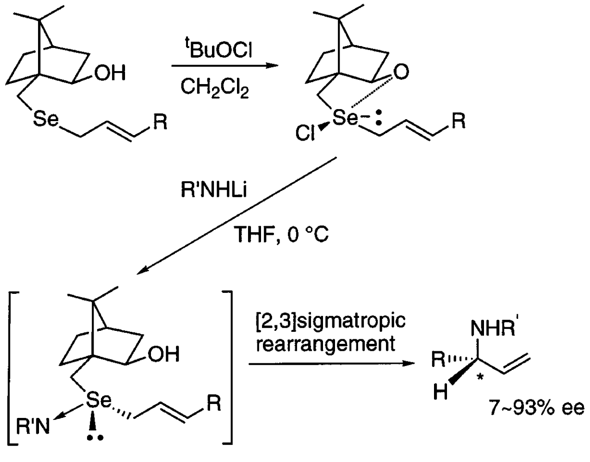
[a] (*S*,*R*)-Fc*Se was used in place of (*R*, *S*)-Fc*Se.

As shown in Table 8, TsN = IPh is a more effective reagent than TsNClNa in both product selectivity and enantioselectivity (up to 87% ee). The result of the high ee values of the produced allylic amines provided the basis for the following speculations concerning the present asymmetric reaction:

1. The initial imidation step proceeds with high diastereoselectivity.
2. The chirality transfer via [2,3]sigmatropic rearrangement occurs almost without loss of optical purity.

Compared with the case of the chiral selenoxides, the epimerization of chiral selenimides is known to be quite slow [38].

Koizumi and co-workers used the optically active allylic chloroselenuranes bearing the 2-*exo*-hydroxyl-10-bornyl group to obtain optically active allylic amines [41]. The treatment of allylic selenides with *t*-BuOCl gave the corresponding allylic chloroselenuranes as the only product. Benzyl carbamate, *t*-butyl carbamate, *p*-tosylamide, and diphenylphosphinamide were selected as the *N*-protected amines for selenimide formation. The nucleophilic reaction of



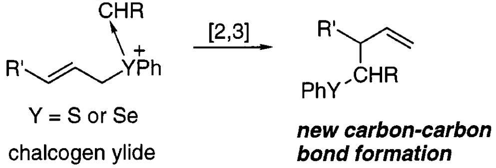
R = Ph or *i*Pr

Scheme 27 R' = Cbz, Boc, *p*-Ts or $Ph_2P(O)$

allylic chloroselenuranes with lithium *N*-protected amides afforded optically active allylic selenimides in situ with retention of configuration. The [2,3]sigmatropic rearrangement of these allylic selenimides gave *N*-protected allylic amines in high yields and with high enantiomeric excesses (up to 93% ee) (Scheme 27). From the absolute configuration of the resulting *N*-protected allylic amines, as well as from their high enantiomeric excesses, it was concluded that the [2,3]sigmatropic rearrangement of allylic selenimides proceeded predominantly via an *endo* transition state.

6
[2,3]Sigmatropic Rearrangement via Allylic Selenium Ylides

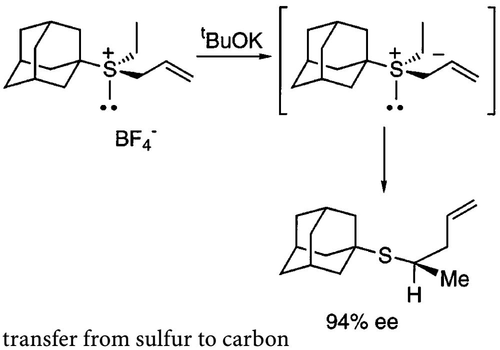
The [2,3]sigmatropic rearrangement of allylic chalcogen ylides provides a useful method for carbon-carbon bond formation (Eq. 7):



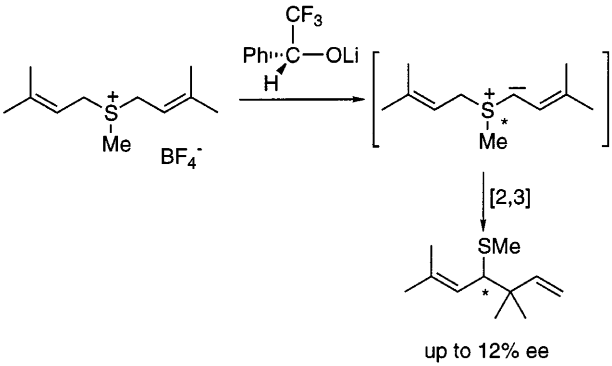
(7)

In sharp contrast to the well-studied [2,3]sigmatropic rearrangement of allylic sulfur ylides [42], the study of allylic selenium ylides is quite limited [43]. Furthermore, its asymmetric version using optically active allylic selenium ylides has not been developed until quite recently. In this section, some examples of the asymmetric [2,3]sigmatropic rearrangement via optically active allylic selenium ylides are described.

At first, the asymmetric [2,3]sigmatropic rearrangement of allylic sulfur ylides is surveyed. The first successful asymmetric [2,3]sigmatropic rearrangement involving sulfur ylides by Trost and Hammen appeared in 1973 [44]. The treatment of optically active sulfonium salt afforded the corresponding homoallylic sulfide with 94% enantiomeric excess, in which the chiral information has been transferred from the sulfur atom to the carbon atom with excellent control (Scheme 28). Trost and Biddlecom also reported another approach to generate



Scheme 28. Chirality transfer from sulfur to carbon

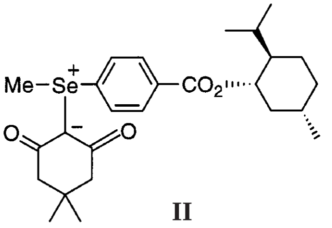


Scheme 29

chiral sulfur ylides [45]. Thus, asymmetric deprotonation of the diallylic sulfonium salt with a chiral base in a chiral solvent produced the corresponding sulfide via the optically active allylic sulfur ylide with low enantiomeric excess (up to 12% ee) (Scheme 29).

6.1
Optically Active Selenium Ylides

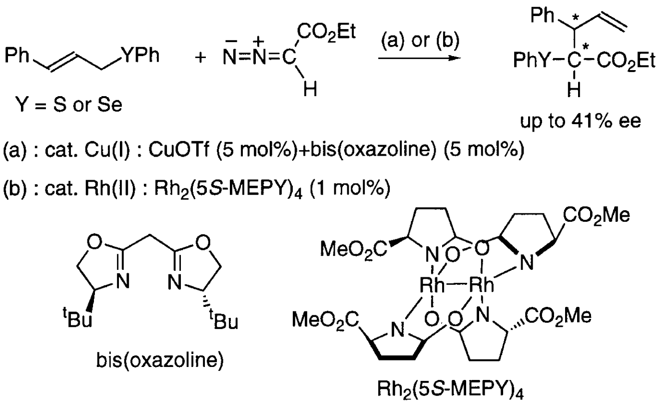
After the first preparation of a selenium ylide by Hughes and Kuriyan in 1935 [46], only a few papers on the synthesis of optically active selenium ylides have appeared until recently [47]. However, their optical purities were low. The synthesis of an optically pure selenium ylide by fractional recrystallization of single diastereomeric selenium ylides was first reported by Kamigata and co-workers in 1992 [48]. They designed a selenium ylide (II) with an electron-withdrawing group on the selenium atom to stabilize the chirality of selenium center thermodynamically. The fractional recrystallization of the diastereomeric selenium ylides possessing a menthyl group as a chiral source gave optically pure **II** as stable crystals. The absolute configuration around the selenium atom was determined by X-ray crystallographic analysis. The rate of racemization of the optically active selenium ylide was studied by heating a solution of a diastereomeric excess selenium ylide. This result indicated that the selenium ylide is not simply racemized thermally but it also decomposes at temperatures higher than 100 °C. The conclusion is that the selenium ylide is extremely stable towards thermal inversion (racemization by pyramidal inversion) in comparison with similar sulfur ylides [48].



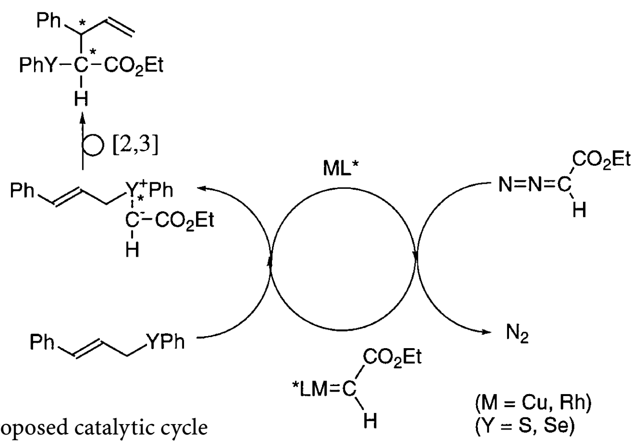
II

6.2
Enantioselective [2,3]Sigmatropic Rearrangement Producing Optically Active Homoallylic Chalcogenides

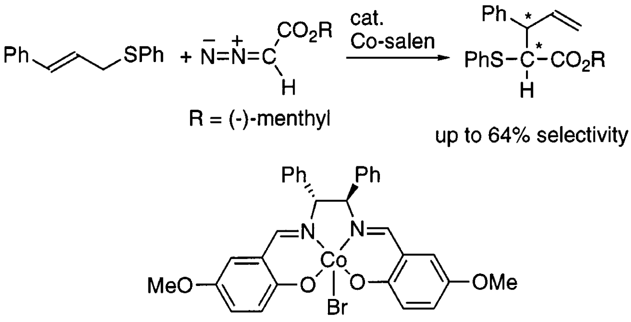
The method for the preparation of highly enantio- or diastereomerically enriched chiral selenium ylides from the corresponding selenides has not yet been developed. However, only one example of asymmetric [2,3]sigmatropic rearrangement via allylic selenium ylides has appeared in 1995 [49], where the asymmetric catalytic carbenoid addition to chalcogen atoms such as selenium and sulfur was employed in the first step. The reaction of cinnamyl phenyl selenide or sulfide with ethyl diazoacetate in the presence of a catalytic amount of Cu(I)-bis(oxazoline) or Rh_2(5*S*-MEPY)$_4$ afforded a diastereomeric mixture (around 3:2 to 2:1) of ethyl 2-phenylchalcogeno-3-phenylpent-4-enoates with moderate enantioselectivities (up to 41% ee) (Scheme 30). The enantiomeric excess in the reaction of the cinnamyl selenide was slightly higher than that of the cinnamyl sulfide under the same reaction conditions. The plausible reaction pathway of this catalytic reaction is shown in Scheme 31. Since it is



Scheme 30



Scheme 31. Proposed catalytic cycle



Scheme 32

known that the chirality transfer from the sulfur to the carbon in a sulfur ylide via [2,3]sigmatropic rearrangement proceeds without loss of optical purity and also the racemization does not occur at a chiral selenium ylide, the observed enantioselectivity of the products might depend on the initial step of carbenoid addition to the chalcogen atom. This reaction may provide a new method for the carbon-carbon bond formation with chiral induction at both carbon centers.

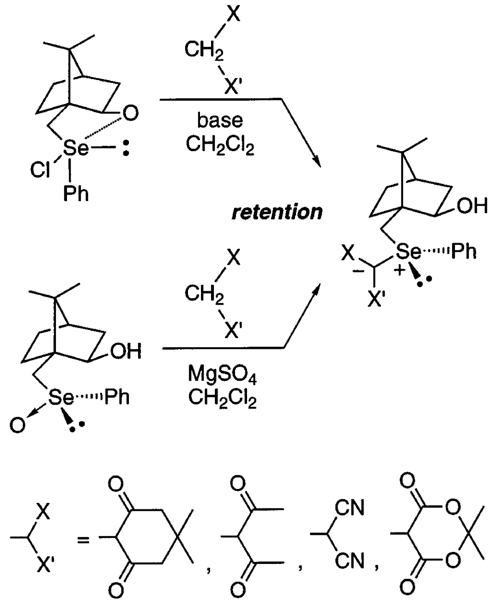
In 1997, Katsuki and Fukuda reported a higher selectivity (up to 64% ee) in a similar system using allylic sulfides in the presence of a chiral cobalt(III) salen catalyst [50] (Scheme 32).

It is worth noting that Doyle and co-workers have reported quite recently a Rh-catalyzed highly enantioselective [2,3]sigmatropic rearrangement of allylic oxonium ylides in place of the allylic chalcogen ylides [51].

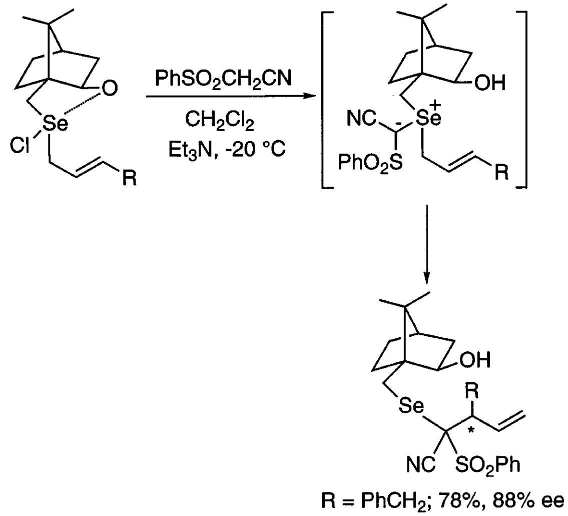
6.3
Diastereoselective [2,3]Sigmatropic Rearrangement Producing Optically Active Homoallylic Chalcogenides

Koizumi and co-workers used optically active allylic chloroselenuranes bearing a 2-*exo*-hydroxyl-10-bornyl group to produce optically active allylic selenium ylides in situ [52]. The nucleophilic reaction of the corresponding chiral chloroselenurane and selenoxide with an active methylene compound occurs in a highly stereoselective manner to give the corresponding chiral selenium ylides with retention of configuration [53] (Scheme 33).

The treatment of allylic chloroselenuranes with (phenylsulfonyl)acetonitrile and triethylamine afforded the corresponding homoallylic selenides in high yields along with their minor diastereomers and diastereomeric deselenenylated compounds [52] (Scheme 34). These results indicated that the [2,3]sigmatropic rearrangement of the resulting allylic selenium ylides proceeded in a highly stereoselective manner to give homoallylic selenides. From the absolute configuration of the resulting homoallylic selenides, as well as from their high diastereomeric excess, the [2,3]sigmatropic rearrangement of the intermediate allylic selenium ylides was revealed to proceed predominantly via an *endo* transition state.

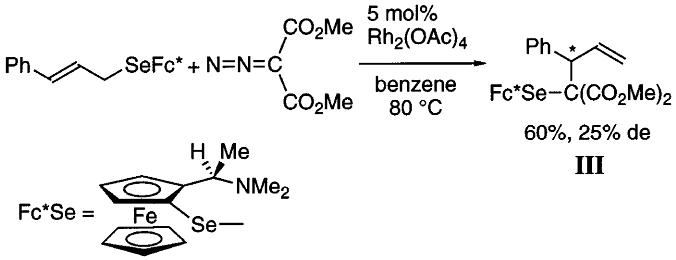


Scheme 33



Scheme 34

Nishibayashi and Uemura attempted the diastereoselective [2,3]sigmatropic rearrangement via a chiral selenium ylide bearing an optically active ferrocenylselenium moiety, but the selectivity was low (up to 25% de) [54]. The treatment of an allylic chiral ferrocenyl selenide with ethyl diazoacetate in the presence of a catalytic amount of $Rh_2(OAc)_4$ afforded a diastereomeric mixture (around 2:1) of ethyl 2-ferrocenylseleno-3-phenylpent-4-enoates (III) with low diastereoselectivity (Scheme 35).



Scheme 35

7
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Selenium Compounds as Ligands and Catalysts

Yoshiaki Nishibayashi[1], Sakae Uemura[2]

[1] Department of Chemistry and Biotechnology, Graduate School of Engineering,
The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8656, Japan
[2] Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering,
Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
E-mail: uemura@scl.kyoto-u.ac.jp

Recent advances of the preparation of novel optically active organoselenium compounds, mainly organic diselenides, and their application as chiral ligands to some transition metal-catalyzed reactions and also as procatalysts for asymmetric diethylzinc addition to aldehydes are reviewed. Recent results of catalytic reactions using some organoselenium compounds such as allylic oxidation of alkenes and its asymmetric version as well as epoxidation of alkenes are also summarized.

Keywords: Chiral ligand, Hydrosilylation, Diethylzinc addition, Allylic oxidation, Epoxidation

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1
Introduction

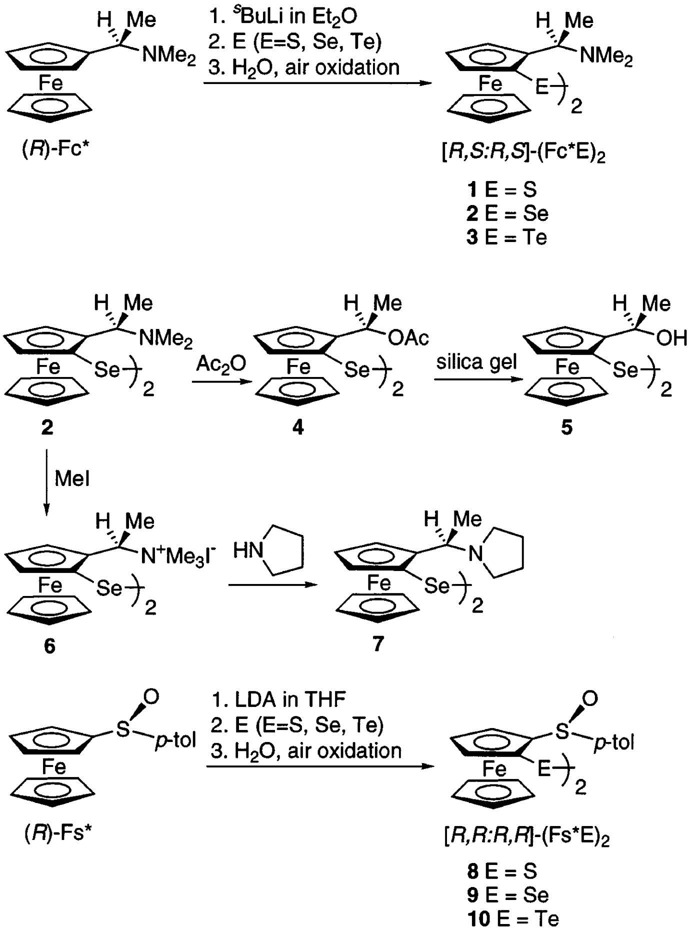
A variety of organoselenium compounds have proved to be quite useful for organic synthesis over several decades [1]. Organoselenium species can work as either nucleophiles or electrophiles to be introduced to other organic molecules, producing organoselenium compounds which are useful intermediates for organic synthesis as reviewed elsewhere in this book. Synthesis of optically active organoselenium compounds and their application to highly selective asymmetric synthesis are also of current interest. In this article, recent advances in the preparation of novel optically active organoselenium compounds and their application as chiral ligands and catalysts to asymmetric reactions are reviewed.

2
Diselenides as Chiral Ligands for Asymmetric Hydrosilylation of Ketones and Related Reactions

Transition metal-catalyzed asymmetric hydrosilylation of ketones is one of the most extensively studied asymmetric reactions, where phosphine ligands were used as chiral ligands until the early 1980s [2]. More recently, nitrogen-containing organic molecules have attracted much attention as chiral and achiral ligands [3]. On the other hand, it has been known for some time that many organochalcogen compounds interact with transition metal salts to afford coordination compounds which were thought to be unsuitable for transition metal-catalyzed reactions [4]. Previously, Uemura and co-workers reported the preparation of optically active [*R*,*S*;*R*,*S*]- and [*S*,*R*;*S*,*R*]-bis[2-[1-(dimethylamino)ethyl]ferrocenyl] dichalcogenides and their stoichiometric use for asymmetric selenoxide elimination, [2,3]sigmatropic rearrangement, nucleophilic ring-opening of *meso*-epoxides, and intermolecular- and intramolecular-electrophilic selenenylation [5]. With further study they have found that these diferrocenyl dichalcogenides, especially diselenides, work effectively as chiral ligands for the Rh(I)- and Ir(I)-catalyzed asymmetric hydrosilylation [6] and transfer hydrogenation [7] of several alkyl aryl ketones. The results of these catalytic reactions are described below.

2.1
Diselenides as Chiral Ligands for Asymmetric Hydrosilylation of Ketones and Imines

As chiral ligands for transition metal complex-catalyzed asymmetric reactions, a variety of novel chiral ferrocenylchalcogen compounds, which possess a planar chirality due to the 1,2-unsymmetrically disubstituted ferrocene structure, have been prepared from chiral ferrocenes (Scheme 1). Thus, chiral diferrocenyl dichalcogenides bearing an optically active dimethylaminoethyl or *p*-tolylsulfoxide moiety **1**–**10** were prepared by lithiation of the corresponding chiral ferrocenes, highly diastereoselectively, in moderate to high chemical yields.

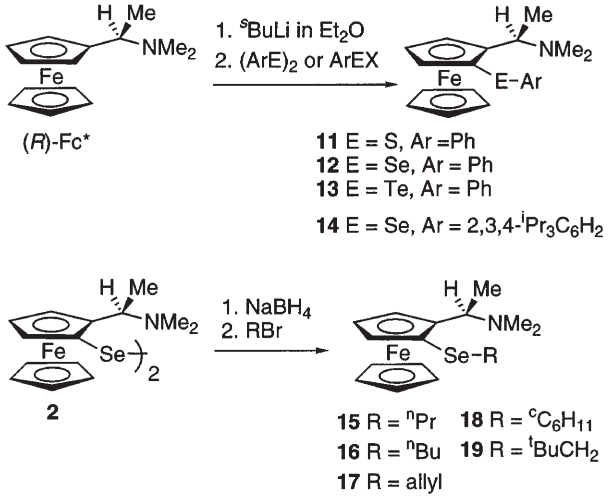


Scheme 1

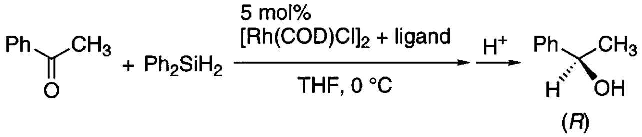
Several organoselenium and tellurium compounds having a chiral ferrocenylchalcogeno moiety **11–19** were also prepared as shown in Scheme 2.

These di- or mono-chalcogenides were revealed to be effective as chiral ligands in the Rh(I)-catalyzed hydrosilylation of acetophenone with diphenylsilane (Scheme 3, Table 1). The chiral substituent at the ferrocene ring had a remarkable effect upon the enantioselectivity of the alcohol produced. The results indicate that the dichalcogenides are generally more effective than the monochalcogenides and that the presence of a dimethylaminoethyl moiety on the ferrocene ring is most important for achieving a highly enantioselective hydrosilylation. Thus, the diselenide **2** was the best chiral ligand for asymmetric hydrosilylation of acetophenone (85% ee), while the analogues disulfide **1** and ditelluride **3** afforded the product with lower enantioselectivity (31% and 50% ee).

Table 2 summarizes typical results of the Rh(I)-catalyzed asymmetric hydrosilylation of a variety of alkyl aryl ketones in the presence of a catalytic amount



Scheme 2



Scheme 3

Table 1. Asymmetric hydrosilylation of acetophenone catalyzed by variety of Rh(I)-chiral ligands

Chiral ligand	Time (h)	Yield (%)	Ee (%)	Chiral ligand	Time (h)	Yield (%)	Ee (%)
1	70	46	31	**9**	190	36	26
2	40	31	85	**11**	20	51	16
3	70	67	50	**12**	20	26	40
4	20	90	5	**13**	20	30	18
5	70	50	12	**15**	20	81	16
7	70	37	31	**17**	20	25	35
8	90	81	0	**18**	20	81	16

of **2** (Scheme 4). The highest enantioselectivity (88% ee) was observed in the case of α-chloroacetophenone.

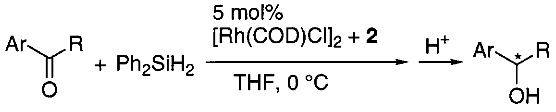
Compared to the rhodium-catalyzed asymmetric reactions, studies on the iridium-catalyzed ones have been limited until recently [8]. Hydrosilylation of acetophenone in the presence of a catalytic amount of Ir(I) complex and the ligand **2** proceeded smoothly to give 1-phenylethanol in good yield, but with a much lower enantioselectivity (up to 23% ee) than the case of Rh(I) complex [6]. It is noteworthy that the alcohol of the opposite configuration was obtained when the metal is changed from Rh(I) to Ir(I) [6] as has been also observed in similar reactions using chiral oxazolinylferrocenylphosphines as ligands [8].

Table 2. Asymmetric hydrosilylation of alkyl aryl ketones catalyzed by Rh(I)-(2)

Ketone		Time (h)	Alcohol (*R*)	
Ar	R		GLC yield (%)	Ee (%)
Ph	Me	24	31	85
Ph	Et	70	14	58
Ph	CH_2Cl	120	85	88[a]
Ph	CO_2Me	25	31	60
Ph	^tBu	240	5	85
indanone		240	5	42
4-NO_2-C_6H_4	Me	72	45	76[b]
4-Cl-C_6H_4	Me	72	41	74[a]
2-thienyl	Me	96	100	78

[a] The absolute configuration of the product is *S*.

[b] The absolute configuration was not determined.

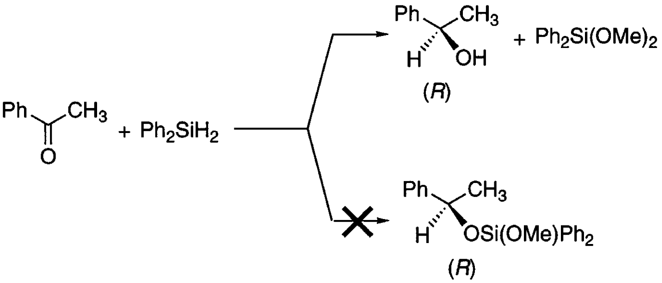


Scheme 4

Asymmetric hydrosilylation of imines affords synthetically useful optically active *sec*-amines, but study on this subject is still quite limited [8c]. Uemura and co-workers applied their Rh(I)-**2** catalytic system to two imines [6]. A good result was obtained from *N*-phenyl-1-phenylpropanimine (up to 53% ee), but the reaction with the *N*-benzyl analogue gave low selectivity (up to 11% ee).

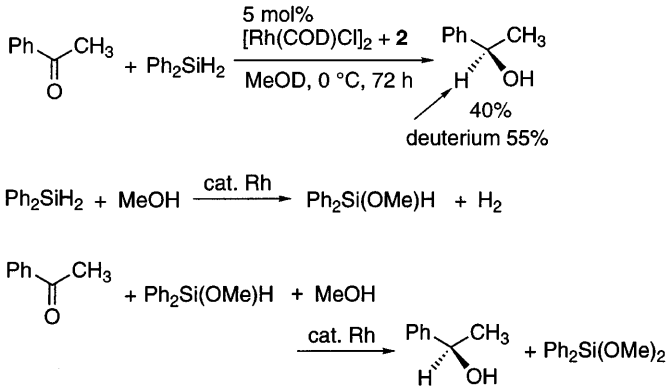
2.2
Diselenides as Chiral Ligands for Asymmetric Transfer Hydrogenation of Ketones

It was described earlier that the diselenide **2** acted as chiral ligand for the Rh(I)-catalyzed asymmetric hydrosilylation of unfunctionalized alkyl aryl ketones with diphenylsilane in tetrahydrofuran [6]. When the reaction was carried out in methanol as solvent, it gave directly a chiral alcohol, not a hydrosilylated product [7] (Scheme 5).



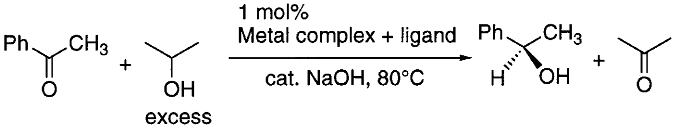
Scheme 5

1-Phenylethanol was obtained in good yield with a moderate enantioselectivity together with diphenyldimethoxysilane $Ph_2Si(OMe)_2$. A closer examination revealed that the reaction proceeded via a transfer hydrogenation under very mild and neutral conditions, not via hydrogenation by the evolved dihydrogen gas and also not via hydrosilylation by some silane species. It is worth noting that the reaction did not proceed at all in other alcohols such as ethanol or 2-propanol, probably because the Rh(I) complex cannot catalyze the reaction between diphenylsilane and ethanol or 2-propanol affording alkoxysilanes and hydrogen under the reaction conditions. When the ferrocene having a dimethylamino group and a diphenylphosphino group was used in place of **2**, this transfer hydrogenation did not occur, showing the utility of chiral diferrocenyl dichalcogenides. The partial transfer of hydrogen from methanol to the resultant alcohol was confirmed by the experiment using deuterated methanol (CH_3OD). Thus, when acetophenone was treated in CH_3OD, nearly equal amounts of deuterated and non-deuterated (at carbon) 1-phenylethanols were obtained, indicating that the introduced hydrogen in this reduction comes from both methanol and diphenylsilane (Scheme 6). In the transfer hydrogenation of a variety of alkyl aryl ketones, the enantioselectivity was generally moderate (22 ~ 48% ee).



Scheme 6

Uemura and co-workers have also investigated asymmetric transfer hydrogenation using the well-known 2-propanol/base system in the presence of an Rh(I), Ir(I), or Ru(II) complex and a diferrocenyl dichalcogenide (Scheme 7) [7], but the enantioselectivity was not satisfactory in all cases (7 ~ 35% ee).

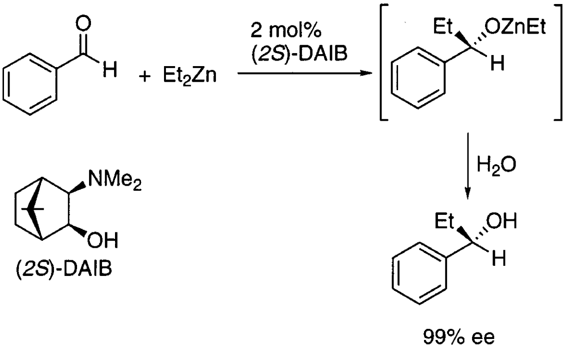


Scheme 7 Metal complex = $[Rh(COD)Cl]_2$, $[Ir(COD)Cl]_2$, $[Ru(COD)Cl_2]_n$

3
Chiral Diselenides and Selenides as Procatalysts for Diethylzinc Addition to Aldehydes

Asymmetric addition of diorganozincs to aldehydes catalyzed by chiral *β*-amino alcohols provides a general method for the preparation of chiral secondary alcohols. Oguni, Noyori, and co-workers found that the aminoalcohol, (2*S*)-3-*exo*-(dimethylamino)isobornenol ((2*S*)-DAIB), acts as a particularly efficient promoter for this asymmetric reaction [9, 10]. Reaction of benzaldehyde with diethylzinc in the presence of 2 mol% of (2*S*)-DAIB gives, after aqueous workup, (*S*)-1-phenylpropanol in high yield with 99% ee as shown in Scheme 8. Detailed mechanistic and theoretical studies of the (2*S*)-DAIB-promoted asymmetric addition have been reported [11].

Diols and diamines were also found to be highly efficient catalysts for this reaction. Recently it was shown that sulfur compounds containing amines are able to catalyze the diethylzinc addition to aldehydes [12].

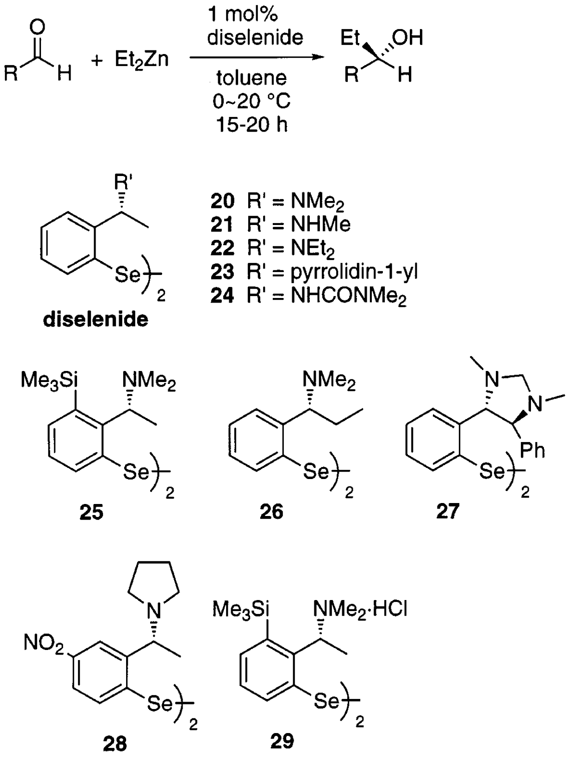


Scheme 8

3.1
Chiral Diselenides as Procatalysts in Diethylzinc Addition to Aldehydes

Quite recently, Wirth has found that the nitrogen-containing chiral diselenides of type **20**–**29** can be used as very efficient procatalysts for the addition of diethylzinc to arylaldehydes [13]. Such chiral diselenides can be prepared in a few steps from both enantiomers of the commercially available 1-phenylethylamine. The diselenides having a pyrrolidin-1-yl group **23** and a stereogenic center in the five-membered ring **27** were the most effective in this asymmetric addition to benzaldehyde (Scheme 9). Only 1 mol% of the diselenide is necessary in this catalytic addition yielding the secondary alcohols with high enantiomeric purity. Diethylzinc is added to various substituted benzaldehydes in the presence of the catalyst **23**. Regardless of the electronic nature of the aromatic ring of benzaldehydes, excellent yields and high enantiomeric excesses were obtained. Typical results are shown in Table 3.

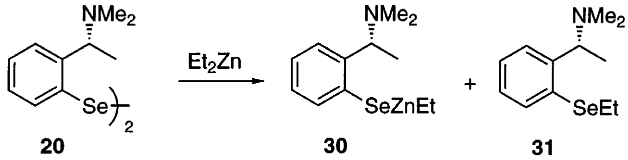
A more detailed investigation of this reaction revealed that the diselenide acts as procatalyst in the addition reaction. By the reaction of diethylzinc with the



Scheme 9

Table 3. Asymmetric addition of diethylzinc to benzaldehydes in the presence of diselenide

Diselenide	R	Yield (%)	Ee (%)
20	Ph	87	92
21	Ph	48	82
22	Ph	57	91
23	Ph	91	97
24	Ph	50	4
25	Ph	98	96
26	Ph	95	91
27	Ph	89	97
28	Ph	78	41
29	Ph	20	10
23	4-CF_3-C_6H_4	98	98
23	4-MeO-C_6H_4	77	93
23	4-^{t}Bu-C_6H_4	67	98
23	2-Br-C_6H_4	78	91
23	2-Br-3-Me-C_6H_3	79	92
23	3,5-$(CF_3)_2$-C_6H_3	90	98
23	2,3,4,5-F_4-C_6H	95	97

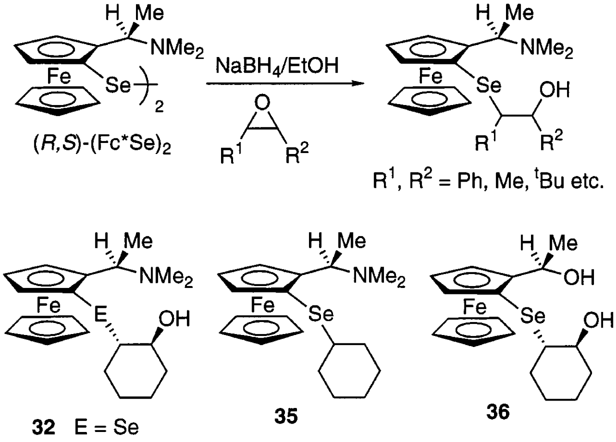


Scheme 10

diselenide **20**, the selenium-selenium bond of **20** is cleaved rapidly and the catalytically active zinc selenolate **30** and the ethylselenide **31** are formed (Scheme 10). Detailed NMR analysis showed an aggregation of the selenolate **30** which exchanges dynamically with other species. In analogy to previous observations [9–11], Wirth et al. assigned the aggregated mixtures as the catalytically inactive *meso* dimeric species and the chiral dimeric species, the latter of which are in equilibrium with the catalytically active monomers. Related to this result, an asymmetric amplification in this addition, i.e., a positive nonlinear relationship between the optical purity of the catalyst and the product was observed [13b].

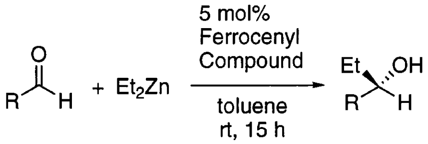
3.2
Chiral Ferrocenylselenium Aminoalcohols as Procatalysts in Diethylzinc Addition to Aldehydes

The chiral ferrocenylselenium reagents were found to act as the effective ligands for Rh(I)-catalyzed asymmetric hydrosilylation and transfer hydrogenation (see Sects. 2.1 and 2.2, respectively). Fukuzawa and Tsudzuki have found that the chiral ferrocenylselenium-based amino alcohols (DASF), prepared by treatment of the chiral diferrocenyl diselenide with $NaBH_4$ in ethanol followed by the addition of epoxides (Scheme 11), efficiently catalyzed the diethylzinc addition to aldehydes to provide the corresponding secondary alcohols with up to 99% ee



32 E = Se
33 E = S
34 E = Te

Scheme 11



Scheme 12

Table 4. Asymmetric addition of diethylzinc to aldehydes in the presence of chiral ferrocenyl compounds

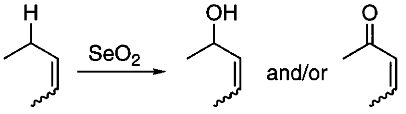
Ferrocenyl Compound	R	Yield (%)	Ee (%)
32	Ph	98	94
33	Ph	~90	52
34	Ph	~90	46
35	Ph	52	0
36	Ph	7	0
32	4-Me-C_6H_4	93	91
32	4-MeO-C_6H_4	95	99
32	4-Cl-C_6H_4	98	87
32	$PhCH_2CH_2$	96	86
32	1-Naphthyl	88	74
32	C_6H_{13}	91	71

[14]. The reaction of benzaldehyde with Et_2Zn in the presence of 5 mol% of DASF in toluene at room temperature for 15 h gave 1-phenylpropanol in good to excellent yields with up to 94% ee (Scheme 12). Typical results are shown in Table 4.

Among DASF derivatives examined, the compound **32** prepared from the diselenide **2** and cyclohexene oxide was revealed to be the best catalyst for this addition, giving up to 94% ee. It is noteworthy that the sulfur (**33**) and tellurium analogues (**34**) of **32** also catalyzed the reaction to afford the alcohol, but with lower enantioselectivity (52% and 46% ee, respectively). Related compounds **35** and **36** do not act at all as a catalyst for the reaction, indicating that the presence of both hydroxyl and dimethylamino groups in **32** are indispensable to act as an efficient asymmetric catalyst. Typical results of enantioselective addition of diethylzinc to aldehydes other than benzaldehyde catalyzed by **32** are also summarized in Table 4.

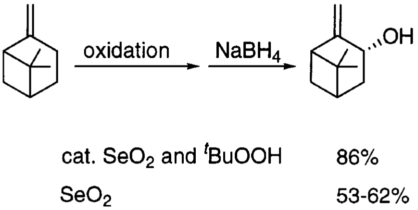
4
Catalytic Reactions Using Organoselenium Compounds

The long-known inorganic selenium compound in organic synthesis is selenium dioxide, SeO_2, which has been used traditionally as an oxidizing reagent for alkenes, ketones, and other substrates. One of the unique properties of selenium dioxide is its ability to introduce an oxygen at the allylic position of alkenes. Depending on the reaction conditions, the major products are either the allylic



Scheme 13

alcohols or the corresponding α,β-unsaturated carbonyl compounds (Scheme 13). The mechanism of the reaction has been studied extensively. Sharpless and Umbreit utilized catalytic amounts of selenium dioxide in the presence of *t*-butyl hydroperoxide (TBHP) for allylic oxidation of alkenes [15]. When alkenes were oxidized with TBHP in the presence of a catalytic amount of SeO_2 (1.5–2 mol%), the corresponding allylic alcohols were produced in yields comparable to, or better than, those obtained in the stoichiometric reaction with SeO_2 alone. For example, the reaction of β-pinene with TBHP in the presence of a catalytic amount of SeO_2 gave *trans*-pinocarveol in 86% yield. However, the stoichiometric oxidation of β-pinene with SeO_2 afforded the same allylic alcohol in 53–62% yield (Scheme 14).



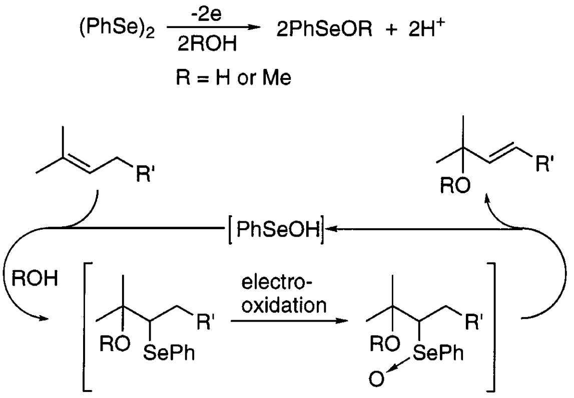
Scheme 14

Peroxyseleninic acid ($RSeO_3H$), obtained by oxidation of seleninic acid ($RSeO_2H$) with oxidants, was revealed to be an effective reagent for the epoxidation of alkenes. Sharpless and Reich reported independently the epoxidation of alkenes with hydrogen peroxide or TBHP in the presence of a catalytic amount (0.5–5 mol%) of arylseleninic acid ($ArSeO_2H$) [16]. The most effective catalysis was observed with the nitro-substituted $ArSeO_2H$. In order to avoid the toxicity of selenium compounds, even in its catalytic use, polystyrene-bound phenylseleninic acid has been used to avoid the contamination of the reaction products from selenium compounds [17]. Although organic transformations using a catalytic amount of selenium compounds have so far been limited to the above, some catalytic reactions using organoselenium compounds have been developed quite recently, and a few asymmetric reactions using a catalytic amount of chiral diselenides have been reported. Some catalytic organic transformations using organoselenium compounds are described below.

4.1
Catalytic Allylic Oxidation of Alkenes Using Diselenides

Oxyselenenylation-oxidative deselenenylation (oxyselenenylation-selenoxide elimination) sequence provides the double-bond transpositioned allylic alcohols and ethers from alkenes. Oxyselenenylation of alkenes and its asymmetric version are reviewed in Chap. 2, and selenoxide eliminations are described in Chap. 8. This useful method for organic synthesis involves two steps; oxyselenenylation with PhSeX (X=Cl, Br, OR, and NR_2) followed by oxidation with O_3, $NaIO_4$, or peroxides. In the former step a stoichiometric amount of PhSeX, and in the latter a large excess amount of oxidants, are generally required.

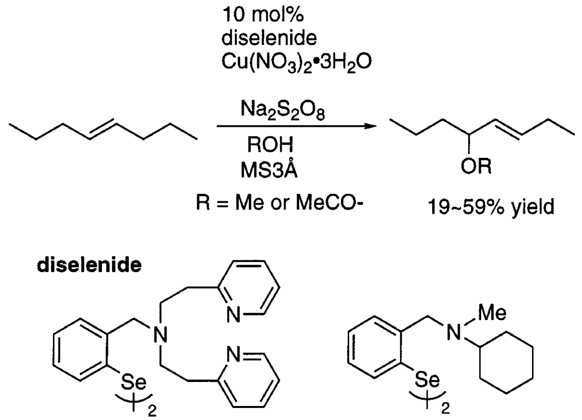
As an electrochemical reaction, Torii and co-workers demonstrated that the facile transformation of alkenes into allylic alcohols and ethers proceeded in the presence of a catalytic amount (10 mol%) of diphenyl diselenide (Scheme 15) [18]. Most of terminal ω double bonds of isoprenoids undergo regioselective oxyselenenylation-deselenenylation to give *trans*-allylic alcohols in aqueous acetonitrile and methyl ethers in methanol. The addition of SO_4^{2-} salts improves chemical yields since SO_4^{2-} salts prevent the conversion of phenylselenenic acid (PhSeOH) into the inert phenylseleninic acid ($PhSeO_2H$) by both disproportionation and electro-oxidation. This method was also applied to intramolecular reaction to form β-lactone in high yield.



Scheme 15

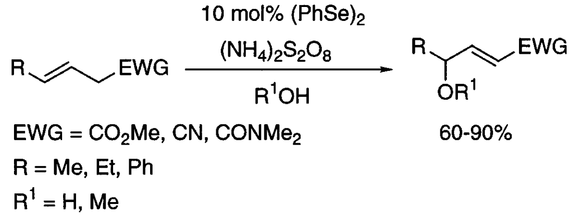
In 1992, Tomoda and Iwaoka reported the chemical process of a catalytic conversion of alkenes into allylic ethers and esters using organic diselenides bearing tertiary amines. The reaction of alkenes with $Na_2S_2O_8$ in the presence of a catalytic amount (10 mol%) of a diselenide and copper(II) nitrate trihydrate ($Cu(NO_3)_2 \cdot 3H_2O$) in MeOH or AcOH gave the corresponding allylic ethers and esters, respectively, in moderate yields (Scheme 16) [19]. The highest turnover number is 5.95 based on the diselenide employed. The most efficient conversion was achieved when molecular sieves (3 Å) were added to the reaction mixture. This may suggest that the removal of water, formed as the reaction proceeds, seems to be essential for the smooth addition of selenenic acid to the alkene. When the diselenide **38** was used as a catalyst instead of the diselenide **37**, the efficiency of the reaction increased. It was considered that the strong interaction between an electrophilic selenium and an internal tertiary amine would interrupt the disproportionation of a selenenic acid intermediate.

On the other hand, Tiecco and co-workers reported the use of peroxodisulfate ions for the transformation of diselenides into the corresponding selenenyl



37 38

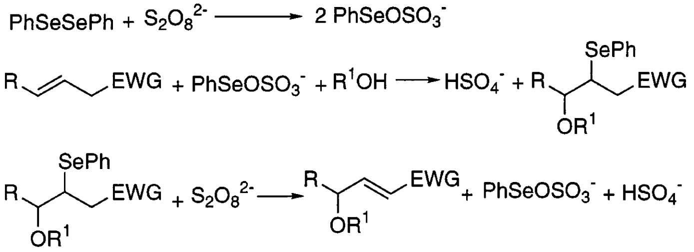
Scheme 16



Scheme 17

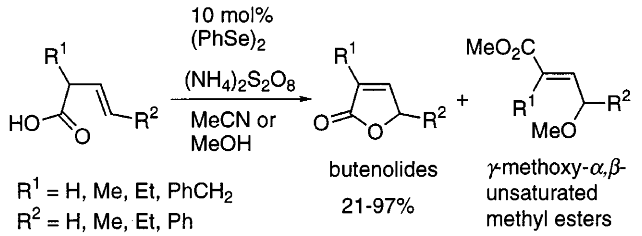
sulfates. The catalytic conversion of β,γ-unsaturated esters, amides, and nitriles into γ-alkoxy or γ-hydroxy α,β-unsaturated derivatives was achieved by persulfate anion oxidation of diphenyl diselenide (Scheme 17) [20]. Good yields of α,β-unsaturated compounds are obtained in all cases.

Under the same experimental conditions, simple unsubstituted alkenes gave rise to a mixture of several products. Thus, the presence of an electron-withdrawing group seems to be essential for the success of these reactions. The proposed course of this reaction is indicated in Scheme 18. The phenylselenenyl sulfate, produced from the reaction of diphenyl diselenide with ammonium persulfate $(NH_4)_2S_2O_8$, reacts with alkenes to give the alkoxy or hydroxy selenenylation products. The reaction of these addition products with the persulfate $S_2O_8^{2-}$ affords the corresponding products via selenoxide elimination and regenerates an electrophilic phenylselenenyl sulfate $PhSeOSO_3^-$.



Scheme 18

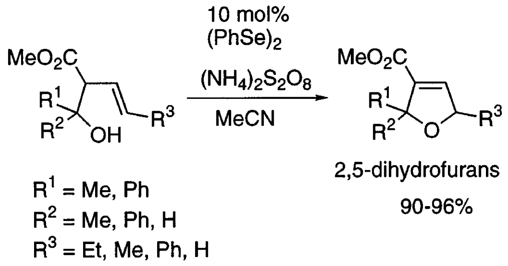
They also carried out the intramolecular version of the above catalytic oxidation to produce butenolides in good yields [21]. A variety of butenolides were obtained from the reaction of the easily available β,γ-unsaturated acids with a catalytic amount of diphenyl diselenide and an excess amount of ammonium persulfate in acetonitrile (Scheme 19). In this case, the carboxy group acts both as an internal nucleophile and as an electron-withdrawing group. Thus, a high regioselectivity of these reactions was attributed to the presence of an electron-withdrawing group in the α position of the starting compounds so that the conjugated alkenes can be formed by the elimination reaction. They also carried out the reaction using a stoichiometric amount of diphenyl diselenide and the results show that, in some cases, better yields of butenolides were obtained in the catalytic reaction than in the stoichiometric reaction. The reactions of β,γ-unsaturated acids in methanol afforded the γ-methoxy-α,β-unsaturated methyl esters in moderate yields together with the formation of butenolides.



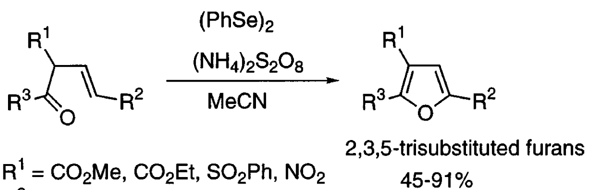
Scheme 19

Furthermore, Tiecco and co-workers have reported the conversion of β,γ-unsaturated alcohols into 2,5-dihydrofurans with a catalytic amount of diphenyl diselenide and an excess amount of ammonium persulfate in acetonitrile (Scheme 20) [22]. In all cases, excellent yields of 3-methoxycarbonyl-2,5-dihydrofurans were obtained (90–96%) without any by-products. The cyclization-elimination process of those β,γ-unsaturated alcohols capable of giving rise to stereoisomeric 2,5-dihydrofurans proceeds with high stereoselectivity. Thus, the *erythro*-unsaturated alcohols gave the *trans*-2,5-dihydrofurans, whereas the *threo*-unsaturated alcohols gave the *cis* derivatives.

In addition, the transformation of β,γ-unsaturated ketones containing an electron-withdrawing group in the α position into 2,3,5-trisubstituted furans was investigated (Scheme 21) [23]. Since the starting ketones react with ammonium persulfate to give several undesirable unidentified products, the catalytic reac-



Scheme 20



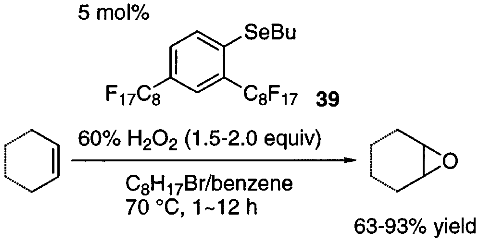
$R^1 = CO_2Me, CO_2Et, SO_2Ph, NO_2$
R^2 = Et, Me, Ph
R^3 = Ph, Et, 2-thienyl, 3-thienyl

Scheme 21

tion could not be carried out and it was necessary to use stoichiometric amounts of diphenyl diselenide. However, the diphenyl diselenide employed was almost quantitatively recovered, indicating that it acts only as a catalyst. A variety of 2,3,5-trisubstituted furans were obtained in moderate to high chemical yields (45–91%).

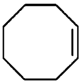
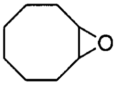
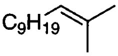
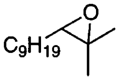
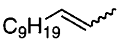
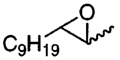
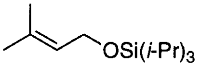
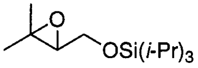
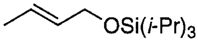
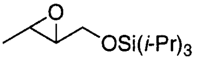
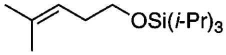
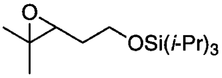
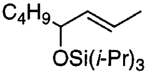
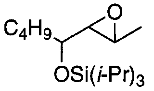
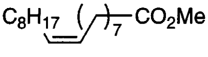
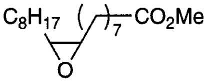
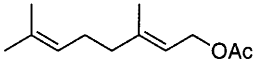
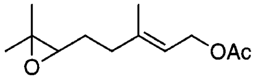
4.2
Catalytic Epoxidation of Alkenes

As described above, $PhSeO_2H$ has been revealed to be a good catalyst for epoxidation of alkenes with H_2O_2 or TBHP [16]. Quite recently Knochel and coworkers have reported the efficient organoselenium-catalyzed epoxidation of various alkenes with 60% hydrogen peroxide in a fluorous biphasic system [24]. A novel aryl butyl selenide **39** bearing perfluoroalkyl substituents was prepared and used where such substituents are necessary for selective solubilization in perfluorinated solvents. With 5 mol% of the catalyst **39**, various polysubstituted alkenes are oxidized in a biphasic system of benzene and bromoperfluorooctane using hydrogen peroxide to afford the corresponding epoxides in good isolated yields (Scheme 22). Typical results are shown in Table 5. In the cases of cyclododecene and octahydronaphthalene, the corresponding *trans*-diols were obtained in 63% and 68% yields, respectively. The catalyst is selectively soluble in perfluorinated solvents and can easily be recovered simply by phase separation. Furthermore, the catalysts can be reused several times without a decrease of yield and an increase of reaction time.



Scheme 22

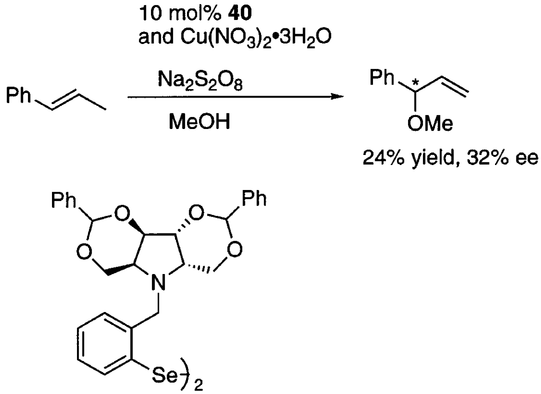
Table 5. Selenium-catalyzed epoxidation of alkenes with hydrogen peroxide in perfluorinated solvents

Alkene	Epoxide	Yield (%)
		92
		93
		80
		81
		81
		97
		97
		84
		63

4.3
Asymmetric Catalytic Allylic Oxidation of Alkenes Using Chiral Diselenides

If the optically active organoselenium compounds can be used for Tomoda's or Tiecco's catalytic system using diselenide and persulfate (see Sect. 4.1), a catalytic asymmetric oxidation reaction should be possible. The enantioselectivity of the produced allylic compounds may depend on the stereoselectivity of the oxyselenenylation step of chiral selenium electrophiles with prochiral alkenes. Several groups have reported diastereoselective oxyselenenylation using a variety of chiral diselenides in moderate to high diastereoselectivity [5f, g, i, 25]. The detailed results are reviewed in Chap. 2.

The first catalytic asymmetric oxyselenenylation-oxidative deselenenylation reaction was reported by Tomoda and co-workers in 1994 [26]. The treatment of

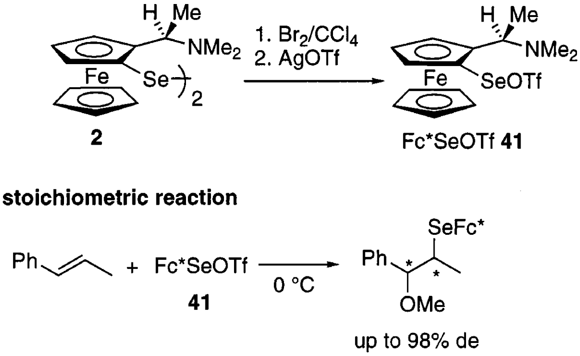


Scheme 23 **40**

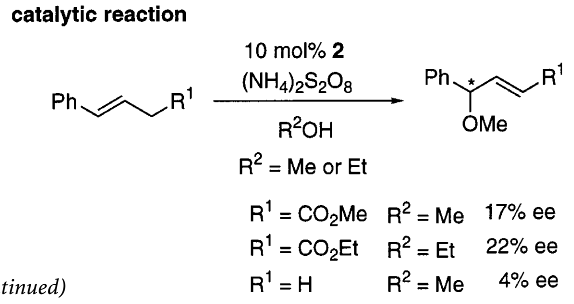
trans-β-methylstyrene with ammonium persulfate and a catalytic amount of diaryl diselenide **40** having a chiral pyrrolidine ring with C_2 symmetry in methanol gave rise to the formation of the optically active allylic ethers in 241% yield based on the selenium catalyst with 32% ee (Scheme 23). The ee value was the same level as that observed in the stoichiometric methoxyselenenylation [26].

The highest diastereoselectivity of asymmetric methoxyselenenylation of alkenes was achieved using the ferrocenylselenium triflates in excellent chemical yields [5g]. For example, the stoichiometric reaction of the chiral ferrocenylselenium triflate **41**, prepared from the chiral diferrocenyl diselenide **2**, with *trans*-β-methylstyrene afforded the corresponding methoxyselenenylated product in high chemical yield with excellent diastereoselectivity (up to 98% de). Fukuzawa and co-workers employed the diferrocenyl diselenide **2** for the catalytic asymmetric oxidation of β,γ-unsaturated esters and *trans*-β-methylstyrene to the corresponding optically active allylic methyl ethers with moderate enantioselectivity (Scheme 24) [27]. The allylic ethers were produced from 4-phenyl-3-butenoic acid esters in 70–78% yield with 17–22% ee.

Similarly, Tiecco and co-workers carried out the catalytic one-pot conversion of a β,γ-unsaturated ester into the corresponding allylic methyl ether using the

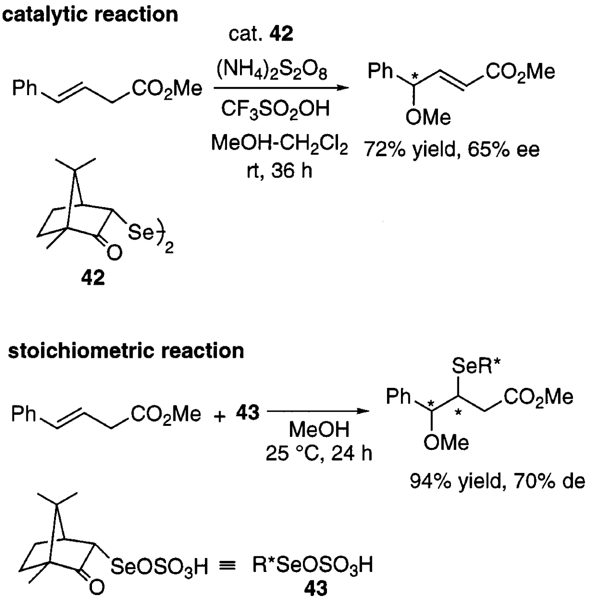


Scheme 24



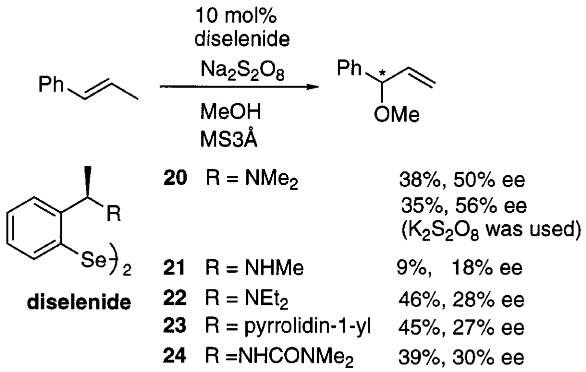
Scheme 24 *(continued)*

chiral dicamphor diselenide **42** [28] which was prepared by Back and co-workers [25e, 29]. The reaction proceeded slowly, and after 36 h at room temperature the allylic ether was obtained in 72% yield with 65% ee, which is in good agreement with the diastereomeric ratio observed by the stoichiometric reaction with the camphorselenenyl sulfate **43** (Scheme 25) [28].



Scheme 25

Wirth and co-workers used various chiral nitrogen-containing diselenides **20**–**24**, which worked effectively as procatalysts for diethylzinc addition to aldehydes (see Sect. 3.1) [13] and for the catalytic oxyselenenylation-elimination reaction of *trans*-β-methylstyrene (Scheme 26) [30]. Under the reaction conditions reported by Iwaoka and Tomoda [19], the diselenide **20** yields the product with highest enantioselectivity (up to 56% ee). Potassium peroxodisulfate seems to be superior to sodium and ammonium analogues. Effect of metal salts on stereoselectivity in the catalytic reaction using the diselenide **20** was investigated since it is known that metal ions can accelerate the decomposition of peroxo-



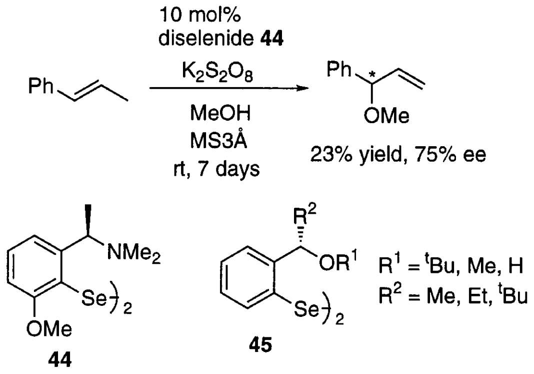
Scheme 26

Table 6. Effect of metal salts on stereoselectivity[a]

Metal salt (10 mol%)	Ee (%)	Metal salt (10 mol%)	Ee (%)
none	51	$ZnSO_4$	59
$Cu(NO_3)_2 \cdot 3H_2O$	56	$PdCl_2$	65
$CuCl_2$	46	$AgNO_3$	66
CuCl	41	$Zn(NO_3)_2 \cdot 6H_2O$	69
$CuSO_4$	50	$Ni(NO_3)_2 \cdot 6H_2O$	71

[a] The reaction in Scheme 26 using **20** at rt for 7 days.

disulfate. Typical results are shown in Table 6. Nickel nitrate, $Ni(NO_3)_2 \cdot 6H_2O$, was found to be the most effective salt for obtaining a higher stereoselectivity (up to 71% ee). With the diselenide **44** the stereoselectivity was improved to 75% ee in the same reaction (Scheme 27) [30]. Although the turnover number in this catalytic reaction is still low, this seems to be the highest enantioselectivity for the catalytic oxyselenenylation-elimination reaction so far obtained. It is noteworthy that the chiral oxygen-containing diselenides **45** developed for stoichiometric alkoxyselenenylation [31] proved to be less efficient in this catalytic reaction.



Scheme 27

5
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